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Comparative effectiveness of exercise training program in patients with heart failure: protocol for a systematic review of randomised controlled trials and network meta-analysis

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ABSTRACT

Introduction Heart failure (HF) is an end-stage of numerous heart diseases including hypertension, coronary heart disease and arrhythmia, in which the heart is unable to perform its circulatory function with sufficient efficiency due to structural or functional dysfunction (systolic or diastolic alterations). Strategies such as exercise rehabilitation may improve cardiac function, exercise capacity and health-related quality of life and reduce anxiety and depression in patients with HF. However, the relative effectiveness as well as the hierarchy of exercise interventions have not been well established, although various exercise options are available. Therefore, this protocol proposes to conduct a network meta-analysis (NMA) aiming to compare the effectiveness of different types of exercise training in patients with HF.

Methods and analysis PubMed, Embase and the Cochrane Library will be searched from inception to March 2021 for relevant randomised controlled trials. Other resources, such as Google Scholar and Clinical Trials.gov will also be considered. Studies assessing exercise rehabilitation in patients with HF will be selected. Two independent reviewers will identify eligible trials. The PEDro risk of bias assessment tool will be used to assess the quality of the included studies. Bayesian NMA will be used when possible to determine the comparative effectiveness of the different exercise interventions. The mean ranks and surface will estimate the ranking probabilities for the optimal intervention of various treatments under the cumulative ranking curve. Subgroup, sensitivity and meta-regression will be conducted to explain the included studies' heterogeneity if possible. We will also use the Grading of Recommendations, Assessment, Development, and Evaluation system to assess the strength of evidence.

Ethics and dissemination This systematic review and NMA will synthesise evidence on the effectiveness of the different exercises in patients with HF. The results will be submitted to a peer-reviewed journal. No ethical approval will be required because the data used for the review will be exclusively extracted from published studies.

PROSPERO registration number CRD42020165870.

Strengths and limitations of this study

- This will be the first systematic review to use network meta-analysis to compare various types of exercise rehabilitation programme in patients with heart failure.
- This network meta-analysis will integrate direct evidence with indirect evidence from different types of exercise mode comparisons to estimate the interrelations across all exercise interventions.
- The overall quality of evidence will be assessed with the Grading of Recommendations Assessment, Development and Evaluation, allowing for the assessment of certainty of evidence for the network meta-analysis.
- The findings of this study will provide practitioners and policymakers with tailored evidence to guide their decision-making.
- Due to the diversity in exercise rehabilitation interventions or methodological characteristics, high heterogeneity is possible.

INTRODUCTION

Heart failure (HF) is a complex chronic condition with increasing incidence and prevalence.[1] It is regarded as a rapidly growing public health issue, with a worldwide prevalence of approximately 38 million individuals, which causes a substantial economic burden, currently estimated at US$108 billion per year.[2 3] Aside from the economic burden, HF is also a leading cause of death, hospitalisation and rehospitalisation worldwide.[3] Patients with HF experience numerous symptoms, including fatigue, fluid retention, dyspnoea and inferior exercise tolerance, the latter leading to a decrease in their exercise capacity and health-related quality of life.[4]

Despite advancements in treatment, such as left ventricular assist device therapy and spironolactone, the condition still has high morbidity and mortality remains high.[1 5–8] Exercise therapy (ET) as a rehabilitation strategy in patients with HF is seen as a diagnostic and prognostic tool as well

as a therapeutic intervention.[9] This recognition stems from studies reporting that ET could improve clinical outcomes such as haemodynamics, skeletal muscle mass and psychological factors.[10] The findings of a Cochrane review also described the benefits of exercise-based rehabilitation, which include probable reductions in the risk of all-cause mortality, frequency of hospitalisation and improved health-related quality of life compared with patients receiving no exercise rehabilitation.[4]

Moreover, ET is increasingly regarded as an effective measure in the management of HF and is recommended by the Scottish Intercollegiate Guidelines Network, the National Institute for Health and Care Excellence, and other national guidelines.[11–15]

Exercise prescriptions can be complex and with varied component movements, duration and intensity as well as treatment setting, but they all show beneficial effects in patients with HF. Three randomised controlled trials (RCTs) have shown a positive effect of moderate-intensity interval aerobic exercise in exercise capacity and health-related quality of life.[16–18] Likewise, five RCTs have concluded that moderate-intensity continuous exercise improved exercise capacity, health-related quality of life and physical function, and reduced depression severity.[19–23] Similarly, an RCT found that individuals in HF enroled in low-intensity exercise can improve health-related quality of life and physical function.[24] Furthermore, a systematic review of 35 RCTs reported that the practice of aerobic and resistance exercise improved peak VO_2, muscle strength and health-related quality of life.[25] Another systematic review of 11 RCTs concluded that high-intensity interval exercise has a beneficial effect in improving peak VO_2.[26] Finally, evidence from a meta-analysis (two RCTs) showed that flexibility exercise (eg, yoga) could improve peak VO_2 and health-related quality of life.[27] In addition to the above, other forms of exercise, such as inspiratory training[28 29] and neuromuscular electrical stimulation,[30] have also been proposed for improving symptoms and functions of patients with HF. Consequently, a growing number of exercise options are being advocated.

However, there are no recent systematic reviews which can provide clinicians with information regarding which forms of exercise interventions yield the largest treatment effect, as traditional pairwise meta-analyses cannot provide comparisons of multiple interventions in a cohesive analysis. Network meta-analysis (NMA) allows for simultaneous consideration of the relative effectiveness of all available treatment alternatives, by pooling evidence from direct and indirect comparisons of multiple treatments.[31]

Hence, this protocol describes the methodology for a systematic review and NMA that will determine the comparative effectiveness of different forms of exercise interventions and provide supporting evidence for policymakers and practitioners who may desire to know which exercise intervention is the best and for whom.

According to the transitivity and similarity among the included studies and the randomisation of preservation, the precision of the estimated effect size and the ability to compare treatments that have not been directly compared in any trial will be improved.[32 33] Specifically, this research will integrate direct and indirect evidence to synthesise all available evidence regarding the effect of different types of exercise intervention in patients with HF.

METHODS AND ANALYSIS

This systematic review and NMA protocol has been registered with PROSPERO (registration number: CRD42020165870). The protocol will be conducted according to the Cochrane Collaboration Handbook[34] and will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement.[35]

Inclusion/exclusion criteria for study selection

Types of participants

The inclusion criteria for participants will be as follows: (1) age ≥18 years; (2) diagnosed with HF but with no limitation on gender, nationality, ethnicity and ejection fraction; the exclusion criteria will be as follows (1) if they had suffered heart shock or heart arrest; (2) impaired mobility; (3) diagnosis of major depression, cognitive functioning disorder; or (4) unstable vital signs.

Types of interventions

Eligible studies will report the following type of exercise rehabilitation: aerobic (low-intensity continuous exercise, low-intensity interval exercise, moderate-intensity continuous exercise, moderate-intensity interval exercise, high-intensity interval exercise), resistance exercise, flexibility exercise, inspiratory training, neuromuscular electrical stimulation or a combination of two or more of the above exercise forms, such as moderate-intensity continuous exercise combined with resistance exercise. We refer to Carvalho's research[36] to define whether the aerobic exercise intensity in patients with HF is high, moderate or low. An exercise intervention is defined as a type of physical rehabilitation that is planned, structured, and consists of repeated bouts over time with a duration of at least 4 weeks. However, studies that incorporate exercise with other health-related interventions, such as psychotherapy and nutritional intervention, will be excluded when data on physical activity cannot be extracted separately. Other intervention-related characteristics, such as supervision, will be acquired from each included study.

Comparator

General exercise or no exercise or usual care control compared with exercise interventions will be included.

Types of outcome measures

Our primary outcome measure will be mortality (all-cause and HF related), hospitalisation (all-cause or HF-related hospitalisation) and rehospitalisation. Secondary outcome measures will be peak oxygen consumption (Peak VO_2), peak work rate (Peak WR), VE/VCO_2 slope,

Table 1 Search terms

Search block	Search items
Participants	'Heart Failure' OR 'Heart Decompensation' OR 'Congestive Heart Failure' OR 'Congestive Heart Failure' OR 'Chronic heart failure' 'Cardiac Failure' OR 'diastolic heart failure' OR 'heart failure with normal ejection fraction' OR 'heart failure with preserved ejection fraction' OR 'heart failure with reduced ejection fraction' OR 'Ventricular dysfunction' OR 'LV dysfunction' 'LV dysfunction' OR 'Left ventricular diastolic dysfunction' OR HFNEF OR HFNEF OR HFNEFOR 'HF NEF' OR 'HF NEF' OR 'HF REF'
Intervention	Exercise OR Exercise Therapy OR Exercis* OR 'Physical Activit*' OR 'Physical Exercis*' OR 'Aerobic Exercis*' OR Train* OR 'Exercise Train*' OR 'High-Intensity Interval Training*' OR 'High-Intensity Interval Exercis*' OR 'Resistance Training*' OR 'Cardiac Rehabilitation' OR 'inspiratory muscle training' OR 'respiratory muscle training' OR 'inspiratory training' OR 'neuromuscular electrical stimulation' OR 'NMES'
Study design	'Randomised Controlled Trials' OR 'Random allocation' OR 'Controlled Clinical Trials' OR 'Control groups' OR 'Clinical trials' OR 'clinical trials, phase i' OR 'clinical trials, phase ii' OR 'clinical trials, phase iii' OR 'clinical trials, phase iv' OR 'Clinical Trials Data Monitoring Committees' OR 'Double-blind method' OR 'Single-blind method' OR Placebos OR 'Placebo effect' OR 'Cross-over studies' OR 'Multicenter Studies'

left ventricular ejection fraction (LVEF), the 6 min walk distance (6MWD), health-related quality of life (validated generic or disease-specific psychometric instrument), depression (all validated instruments), exercise adherence (defined as percentage of total prescribed sessions completed) and ET-related adverse events.

Type of studies

Eligible studies will be limited to RCTs with no restriction on the year of publication or language, assessing the effect of exercise interventions in patients with HF. Studies other than RCTs, duplicate reports, pilot studies, observational cohort studies, case–control studies, and reviews will be excluded. Only peer-reviewed publications will be included.

Data sources and search strategy

Electronic searches

A comprehensive search in literature will be conducted in the following electronic databases from inception to March 2021, with no limitation on the date of publication or the publication status of study: PubMed, the Cochrane Library and Embase. No language limitations will be imposed. Search terms are grouped into three blocks (table 1).

Other sources

In addition, we will also search the following sources to identify clinical trials, either in progress or completed: reference lists of identified articles for inclusion, Google Scholar, Baidu Scholar and Clinical Trials.gov.

Selection of studies

Two independent reviewers (YH and MG) will identify eligible studies by screening titles, abstracts and full texts sequentially. Disagreements will be resolved by the third reviewer (GS). If necessary, methodological experts will be consulted to reach consensus. The process of selecting studies will be shown using the PRISMA-compliant flow chart (figure 1).

Data extraction

Reviewers will extract the following data from RCTs: first author, country, recruitment dates, group (I/C), age, gender, LVEF(%), exercise intensity, mode, frequency (days/week), duration (minutes), programme length (weeks) and supervision (table 2). In case of insufficient information, the article author will be contacted through email or telephone to provide the missing information. Disagreement will be solved through discussion, and a third reviewer will adjudicate discrepancies.

Risk of bias in included studies

The methodological quality of eligible studies will be assessed by two reviewers (YH and MG) using the Physiotherapy Evidence Database (PEDro) scale (maximum score of 10) to assess the risk of potential bias.[37] Any disagreement will be resolved by a third reviewer (QW). The tool includes 11 domains: (1) eligibility criteria specified, (2) random allocation to groups, (3) concealed allocation, (4) baseline similarity, (5) subject blinding, (6) therapist blinding, (7) assessor blinding, (8) <15% attrition, (9) intention-to-treat analysis, (10) between-group statistic and (11) point estimates and variability of data reported (table 3). Trial quality is defined using the PEDro scale as follows: 'good' 6–8 points, 'fair' 4–5 points, 'poor' ≤ three points and points are only awarded when a criterion is satisfied.

Rating the confidence in the estimate of the effect in the NMA

Once the NMA is completed, we will then evaluate the quality of evidence of the included studies using the Grading of Recommendations Assessment, Development and Evaluation criteria.[38] Risk of bias, imprecision, indirectness, inconsistency and publication bias will be used to rate the quality of evidence from direct and indirect comparisons. This will inform our confidence in the quality of evidence and will be classified as follows: high, moderate, low or very low.

Statistical analysis

Before conducting NMA, a traditional pairwise meta-analysis will be performed. Weighted mean difference or

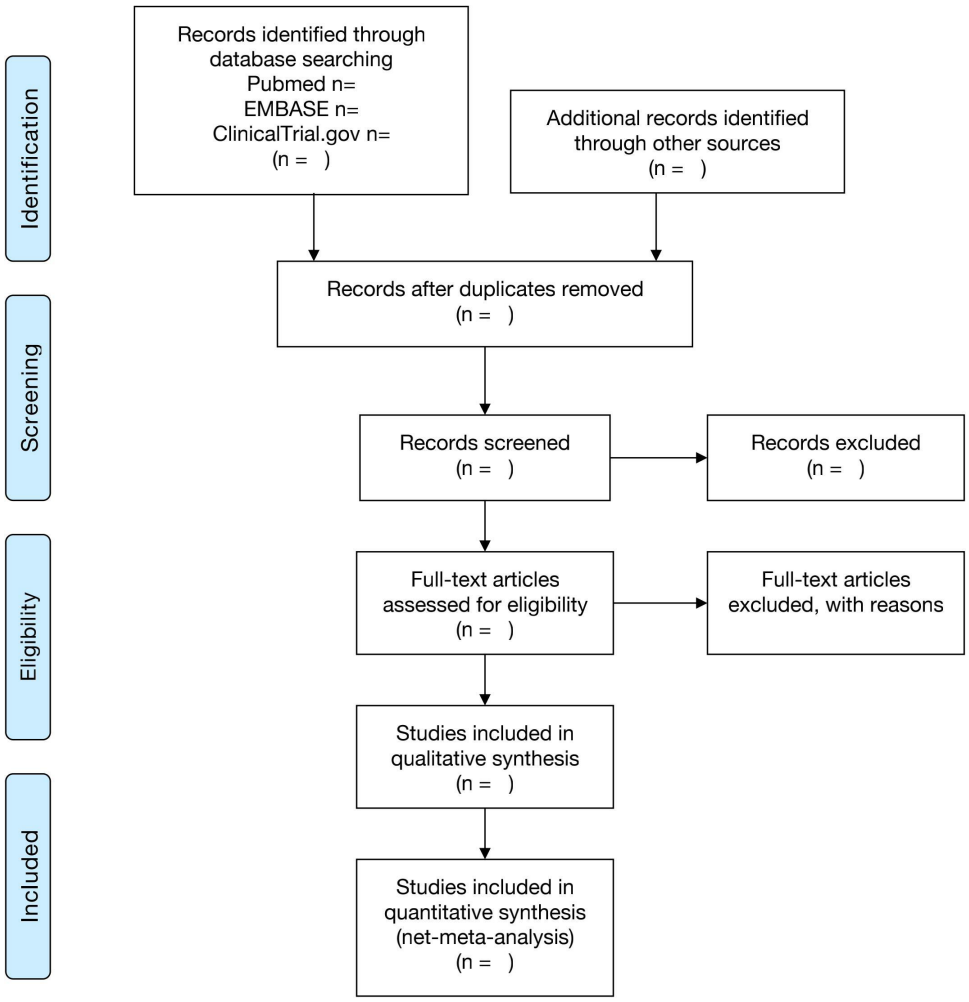

Figure 1 Flow diagram of the study selection process.

standardised mean difference (SMD) with 95% CI will be calculated for continuous data (Peak VO_2, Peak WR, VE/VCO_2 slope, LVEF, 6MWD, MLHFQ and depression score). In general, when the same measurement unit is used among studies for our outcomes of interest, the mean difference will be considered as treatment effects to analyse the results, or the SMD will be considered. For dichotomous outcomes, ET-related adverse events and relative risks of disease remission will be calculated for each study. Data will be pooled if at least three studies report comparable outcomes. If the data cannot be used for quantitative analysis, the evidence will be described and summarised. We plan to explore sources of statistical heterogeneity if there are 10 or more trials available per comparison. The I^2 statistic will quantify the degree of heterogeneity of each pairwise meta-analysis. An $I^2 \leq 50\%$ indicates negligible statistical heterogeneity, and the fixed-effects model (Mantel-Haenszel method) will be employed for meta-analysis.[39] While an $I^2 > 50\%$ will represent significant heterogeneity, the random-effects model (DerSimonian and Laird method) will be used to pool the results.[40] To ensure that findings are as robust as possible, sensitivity analyses will be performed by deleting each study separately to analyse the influence of each study on the overall results. Additionally, sources of heterogeneity will be explored by considering possible factors independently in a metaregression model. Potential effect moderators could be (but will not be limited to) the age of participants, gender distribution, risk of bias, sample size, ejection fraction and duration of intervention. If a significant moderator is found, further subgroup analyses will then be conducted to assess this moderator's effect.

Table 2 Summary of the included RCTs

Characteristics of studies included in the meta-synthesis of evidence												
Study	Group (n)	NYHA	Age	Sex	Intervention				Programme duration	Setting	Supervision	Adherence	Outcome measures
					Type	Time	Intensity	Frequency					

RCTs, randomised controlled trials.

Table 3 RCT quality assessment according to the PEDro scale

Study	1*	2	3	4	5	6	7	8	9	10	11	Total (0–10)
Example	+	–	+	+	+	–	+	–	+	+	+	7

Note : +, Met criteria; –, criteria not met; 1: eligibility criteria and source of participants; 2: random allocation; 3: concealed allocation; 4: baseline comparability; 5: blinded participants; 6: blinded therapists; 7: blind assessors; 8: adequate follow-up; 9: intention-to-treat analysis; 10: between-group comparisons; 11: point estimates and variability.
*Item 1 does not contribute to the total score.
PEDro, Physiotherapy Evidence Database; RCT, randomised controlled trial.

As such, subgroup analyses will be difficult to determine in advance. Subsequently, we will use the Markov Chain Monte Carlo algorithm by applying JAGS V.4.2.0, through the 'gemtc' package in R language (V.3.6.1) to conduct the NMA in a Bayesian hierarchical framework. NMA methods are extensions of the standard pairwise meta-analysis model that enable a simultaneous comparison of multiple interventions while preserving the internal randomisation of each individual trial. By contrasting the effect sizes of comparisons with a common comparator, the effect measures for treatments that have not been compared in a pairwise RCT can be compared indirectly. The convergence of the simulation will be checked with the Gelman-Rubin-Brooks method.[41] In the presence of evidence from direct and indirect comparisons, it is essential to assess whether the direct and indirect evidence is consistent. A node-splitting analysis will be used to judge inconsistency between direct and indirect evidence estimates separately for each intervention comparison, often shown as p values. The consistency model would be used if p values are more than 0.05, which indicate no significant inconsistency.[42 43] The available evidence would be summarised using a network diagram in which each node will represent a class of intervention (as categorised in the inclusion criteria), with node size being proportional to the number of patients receiving the treatment. The effect of pairwise comparisons of two interventions will be shown as edges interconnecting the nodes, where the thickness of the edge lines will represent the weight of pairwise comparisons. A contribution matrix will be presented to show the influence of individual comparisons and direct and indirect evidence on the overall summary of effects. To obtain a rank order, we will use Stata software (V.15.1) to calculate the surface under the cumulative ranking curve (SUCRA). SUCRA for each intervention will be calculated from a cumulative ranking probability that an intervention is above a certain ranking, taking values between 0 (indeed the worst intervention) and 1 (certainly the best intervention).[44] Each relative intervention effect estimate will result from the combination of the direct evidence between the two intervention arms and the indirect evidence derived from the NMA, which is assumed to be coherent. When a direct connection between the two treatment arms is unavailable, the result will be only indirect evidence. If 10 or more trials will be available for one comparison, publication bias for standard meta-analysis would be examined by detecting the funnel plot's visual asymmetry and assessment by Egger's test.[45]

DISCUSSION

HF is a long-term condition with many symptoms (dyspnoea, fatigue, chest pain). Exercise rehabilitation in patients with HF is directly related to the health-related quality of life, frequency of hospitalisation and economic burden.[46] Therefore, we will conduct this study to help clinicians guide their prescription of exercise type concerning treatment outcomes.

Traditional meta-analysis approaches are effective for exploring sample interventions but are unable to decide which types of exercise in patients with HF are best.[4 47 48] For example, a recent meta-analysis of 25 RCTs assessed the effect of exercise training intensity on health-related quality of life in patients with HF.[49] However, this study only reported the effects of different exercise intensities on health-related quality of life in patients with HF and failed to address the criteria for selecting which type of exercise is most suitable for patients with HF .

A comprehensive NMA approach that allows the analysis of head to head evidence and indirect evidence, achieving comparison of exercise rehabilitation which has not been evaluated direct. As such, this NMA is likely the best method to address the present research problem.

To the best of our knowledge, this will be the first comprehensive review to evaluate the effects of different types of exercise on patients with HF. This protocol summarises an organised procedure for optimal data extraction relevant to the topic. The findings will provide practitioners and policymakers with tailored evidence to guide their decision-making.

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Contributors MG conceived the study design. The first version of the protocol was drafted by MG, YH and was revised by GS, QW and ZG. The search strategy was developed by MG and will be performed by YH. MG, YH and QW will screen references for study selection and collect data from the included studies. MG will perform data synthesis and analysis. All authors drafted and critically reviewed this manuscript and approved the final version.

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