Cochrane Library

Cochrane Database of Systematic Reviews

Exercise-based cardiac rehabilitation for people with implantable ventricular assist devices (Review)

Yamamoto S, Hotta K, Ota E, Matsunaga A, Mori R

Yamamoto S, Hotta K, Ota E, Matsunaga A, Mori R.
Exercise-based cardiac rehabilitation for people with implantable ventricular assist devices.
Cochrane Database of Systematic Reviews 2018, Issue 9. Art. No.: CD012222.
DOI: 10.1002/14651858.CD012222.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Exercise-based cardiac rehabilitation for people with implantable ventricular assist devices

Shuhei Yamamoto[1], Kazuki Hotta[2], Erika Ota[3], Atsuhiko Matsunaga[4], Rintaro Mori[5]

[1]Department of Rehabilitation, Shinshu University Hospital, Matsumoto, Japan. [2]Department of Biomedical Sciences, Florida State University College of Medicine, Tallahassee, Florida, USA. [3]Global Health Nursing, Graduate School of Nursing Sciences, St. Luke's International University, Tokyo, Japan. [4]Department of Rehabilitation Sciences, Graduate School of Medical Sciences, Kitasato University, Minami-ku, Sagamihara, Japan. [5]Department of Health Policy, National Center for Child Health and Development, Tokyo, Japan

Contact address: Rintaro Mori, Department of Health Policy, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo, Tokyo, 157-0074, Japan. rintaromori@gmail.com.

Editorial group: Cochrane Heart Group.
Publication status and date: New, published in Issue 9, 2018.

Citation: Yamamoto S, Hotta K, Ota E, Matsunaga A, Mori R. Exercise-based cardiac rehabilitation for people with implantable ventricular assist devices. *Cochrane Database of Systematic Reviews* 2018, Issue 9. Art. No.: CD012222. DOI: 10.1002/14651858.CD012222.pub2.

ABSTRACT

Background

Heart failure is the end stage of heart disease, and the prevalence and incidence of the condition is rapidly increasing. Although heart transplantation is one type of surgical treatment for people with end-stage heart failure, donor availability is limited. Implantable ventricular assist devices (VADs) therefore offer an alternative treatment to heart transplantation. Although two studies reported the beneficial effects of exercise-based cardiac rehabilitation (CR) on functional capacity and quality of life (QOL) by performing systematic reviews and meta-analyses, both systematic reviews included studies with limited design (e.g. non-randomised, retrospective studies) or participants with implantable or extracorporeal VADs.

Objectives

To determine the benefits and harms of exercise-based CR for people with implantable VADs.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, Embase, PsycINFO, Conference Proceedings Citation Index-Science (CPCI-S) on Web of Science, CINAHL, and LILACS on 3 October 2017 with no limitations on date, language, or publication status. We also searched two clinical trials registers on 10 August 2017 and checked the reference lists of primary studies and review articles.

Selection criteria

Randomised controlled trials (RCTs) regardless of cluster or individual randomisation, and full-text studies, those published as abstract only, and unpublished data were eligible. However, only individually RCTs and full-text publications were included.

Data collection and analysis

Two review authors independently extracted outcome data from the included studies. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. We had no dichotomous data to analyse and used mean difference or standardised mean difference with 95% confidence intervals (CIs) for continuous data. Furthermore, we assessed the quality of evidence as it relates to those studies that contribute data to the meta-analyses for the prespecified outcomes, using GRADEpro software.

Main results

We included two studies with a total of 40 participants in the review. Exercise-based CR consisted of aerobic or resistance training or both three times per week for six to eight weeks. Exercise intensity was 50% of oxygen consumption (VO_2) reserve, or ranged from 60% to 80% of heart rate reserve. Two serious adverse events were observed in one trial, in which participants did not complete the study due to infections. Furthermore, a total of four participants in each group required visits to the emergency department, although these participants did complete the study. Summary scores from the 36-item Short Form Health Survey (SF-36) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) were measured as quality of life. One trial reported that the KCCQ summary score improved by 14.4 points in the exercise group compared with 0.5 points in the usual care group. The other trial reported that the SF-36 total score improved by 29.2 points in the exercise group compared with 16.3 points in the usual care group. A large difference in quality of life was observed between groups at the end of follow-up (standardised mean difference 0.88, 95% CI -0.12 to 1.88; 37 participants; 2 studies; very low-quality of evidence). However, there was no evidence for the effectiveness of exercise-based CR due to the young age of the participants, high risk of performance bias, very small sample size, and wide confidence intervals, which resulted in very low-quality evidence. Furthermore, we were not able to determine the effect of exercise-based CR on mortality, rehospitalisation, heart transplantation, and cost, as these outcomes were not reported.

Authors' conclusions

The evidence is currently inadequate to assess the safety and efficacy of exercise-based CR for people with implantable VADs compared with usual care. The amount of RCT evidence was very limited and of very low quality. In addition, the training duration was very short term, that is from six to eight weeks. Further high-quality and well-reported RCTs of exercise-based CR for people with implantable VADs are needed. Such trials need to collect data on events (mortality and rehospitalisation), patient-related outcomes (including quality of life), and cost-effectiveness.

PLAIN LANGUAGE SUMMARY

Exercise-based cardiac rehabilitation for people with implantable ventricular assist devices

Background

People with heart failure have a decreased capacity to undertake physical exercise, which has a negative impact on their health and quality of life. Recent research has shown that exercise-based cardiac rehabilitation (CR) may improve exercise capacity and quality of life in people with implantable ventricular assist devices (VADs), which are a type of mechanical pump that supports heart function. It was therefore considered important to systemically review randomised controlled trials (a type of study in which participants are assigned to a treatment group using a random method) to determine the benefits and harms of exercise-based CR in people with implantable VADs.

Purpose

To assess the effects of exercise-based CR in people with implantable VADs.

Methods

We searched the scientific literature for randomised controlled trials that assessed the effectiveness of exercise in people with heart failure who have implantable VADs by comparing participants receiving the exercise intervention with those receiving usual care, where the intervention consisted of a single type of exercise or more. We excluded participants with total artificial hearts. The evidence is current to 3 October 2017.

Results

We included only two randomised controlled trials and a total of 40 participants in this review. Exercise-based CR consisted of aerobic or resistance training or both three times per week for six to eight weeks. Two serious adverse events (i.e. participants who did not complete the study due to infections) occurred in one of the two trials. Furthermore, four participants in each study group required visits to the emergency department, although these participants did complete the study. Neither study evaluated the outcomes of death, rehospitalisation, heart transplantation, and cost. Due to the very low quality of the evidence, the effectiveness of exercise-based CR on quality of life was uncertain.

Quality of the evidence

We assessed the quality of the evidence for quality of life as very low due to the young age of the participants, Insufficient blinding, small number of participants, and imprecision because of wide range of confidence intervals. The effects of exercise-based CR for people with implantable VADs were not clear.

Conclusion

The current evidence is inadequate to assess the benefits and harms of exercise-based CR for people with implantable VADs compared with usual care. The amount of randomised controlled trial evidence was very limited and of very low quality. In addition, the training duration was very short term. High-quality randomised controlled trials are needed to collect data on events (death and rehospitalisation), patient-related outcomes (including quality of life), and cost.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Exercise-based cardiac rehabilitation compared to usual care for people with implantable ventricular assist devices

Patient or population: people with implantable ventricular assist devices
Setting: in hospital and home-based
Intervention: exercise-based cardiac rehabilitation
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with usual care	Risk with exercise-based cardiac rehabilitation				
Mortality due to all causes - not reported	-	-	-	-	-	
Mortality due to cardiovascular event - not reported	-	-	-	-	-	
Rehospitalisation due to cardiovascular event - not reported	-	-	-	-	-	
Serious adverse events: infection	-	-	-	-	⁻	1 trial reported no adverse events. The other trial reported 2 serious adverse events: 1 participant in the cardiac rehabilitation group had a driveline infection, and 1 participant in the usual care group had an in-

						fection. These 2 participants did not complete the study. A total of 2 serious adverse events were observed across the 1 trial
Health-related quality of life assessed with: 36-item Short Form Health Survey or Kansas City Cardiomyopathy Questionnaire (points) Scale from 0 to 100 points Follow-up: range 6 to 8 weeks	-	SMD 0.88 SD higher (-0.12 lower to 1.88 higher)	-	37 (2 RCTs)	⊕◯◯◯ very low [123]	A higher score means better quality of life.
Heart transplantation - not reported	-	-	-	-	-	
Cost - not reported	-	-	-	-	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __RCT:__ randomised controlled trial; __SD:__ standard deviation; __SMD:__ standardised mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1]Blinding of participants and personnel, or other potential sources bias (not intention-to-treat analysis) were poorly described in the included studies, therefore quality of evidence was downgraded by one level for risk of bias.

[2]The mean age of participants was a little younger compared with previous data, therefore quality of evidence was downgraded by one level for indirectness.

[3]The sample size was very small (n = 37), and 95% confidence intervals were very wide, therefore quality of evidence was downgraded by two levels for imprecision.

BACKGROUND

Description of the condition

Heart failure is the end stage of heart disease. The global prevalence of heart failure was reported at approximately 40 million by the Global Burden of Disease study (Vos 2016). Ischaemic heart disease is a major cause of heart failure, and the most common cause of death in the world, with an incidence of 8.76 million deaths in 2015 according to Global Health Observatory data reported by the World Health Organization (WHO 2017). In many countries, 1% to 2% of adults and more than 10% of elderly people have heart failure (Mosterd 2007), with a one-year survival rate of only 30% to 40% (Mozaffarian 2015). Furthermore, the number of people with heart failure has rapidly increased in the past few decades, and is estimated to continue increasing until 2035 (Mozaffarian 2015; Okura 2008). People with heart failure have symptoms such as fatigue, exertional breathlessness, and lethargy (McMurray 2012). In addition, these symptoms may induce a vicious cycle of deconditioning that leads to decreased quality of life (QOL) and increased disability (Hatta 2009). The classification of severity in heart failure is based on these symptoms and exercise capacity, and can be determined using tools from the New York Heart Association (NYHA) (ranging from class I to IV) and the American Heart Association (AHA)/American College of Cardiology (ACC) stages (ranging from stage A to D) (Fletcher 2001; Hunt 2005). End-stage heart failure is evaluated as NYHA IV or AHA/ACC stage D, which describes people who have severe symptoms at rest, despite maximal medical therapy. People with end-stage heart failure therefore have very low QOL and high disability (Hatta 2009).

Although heart transplantation is one type of surgical treatment for people with end-stage heart failure, donor availability is limited (AST and ASTS 2012). Ventricular assist devices (VADs) offer an alternative treatment to heart transplantation. Often used as a bridge to recovery, cardiac transplantation or destination therapy, VADs consist of a surgically implanted mechanical pump that increases cardiac output and maintains sufficient blood flow to the peripheral organs (Heart Failure Society of America 2010; Peura 2012). The majority of people with end-stage heart disease are managed with medications and devices (cardiac resynchronisation therapy pacemakers), and only the minority get transplants or VADs; indeed, these are particularly scarce outside wealthy health economies such as the United States (Kirklin 2018; Stehlik 2013). However, it is possible that the use of VADs may grow in time as the technology improves and costs fall.

There are two types of flow in VADs: continuous flow or pulsatile flow. While pulsatile-flow VADs are physically large with a short battery life, continuous-flow VADs are lightweight with better durability (Hrobowski 2013; Slaughter 2009). A large-scale prospective non-randomised observational study of VAD implantation therapy (ROADMAP trial) showed that VAD implantation dramatically increased survival rate, and improved QOL and NYHA classes of people with end-stage heart failure (Starling 2017). The ROADMAP study reported a two-year survival rate of 70% and 41% (70% versus 63% in intention-to-treat survival rate) in people with VADs versus optimal medical management, respectively. However, the following challenges still remain in the use of VAD implantation therapy (Starling 2017). First, although the QOL scores are significantly better in people with VADs than in people with optimal medical management, the QOL of people with VADs is lower than that of healthy people living in the community (Rose 2001; Ware 1993). Previous studies have suggested that lower QOL was closely correlated with impaired physical function and emotional status (Hoekstra 2013; Oh 2014). Second, the frequency of adverse events in people with VADs is approximately twice as high as that in people with optimal medical management. In particular, the rate of neurological events in people with VADs is approximately four times higher than that of optimal medical management. The ROADMAP study reported that 12% of people experienced pump thrombus and 11.7% experienced neurological events after VAD implantation (Starling 2017). People with VADs therefore require anticoagulant therapy to prevent potential embolism after VAD implantation (Peura 2012). However, such therapy could increase the risk of cerebral haemorrhage.

Description of the intervention

The AHA strongly recommends cardiac rehabilitation (CR) for people with heart failure to improve functional capacity and QOL and to reduce mortality (Yancy 2017). According to several guidelines, exercise-based CR decreases cardiovascular events (ACSM 2009; Canadian Cardiovascular Society 2014; Fletcher 2013). Furthermore, CR for people with VADs is safe and effective according to two previous systematic reviews and meta-analyses (Ganga 2017; Mahfood 2017). This type of therapy includes exercise training, risk-factor education, behaviour change, and psychological support for the purpose of primary or secondary prevention of disease. Exercise training consists of 30- to 60-minute exercise sessions on a treadmill or bicycle ergometer, which are performed more than 3 times per week over a period of 6 to 12 months, at a training intensity of 50% to 80% of peak oxygen consumption. Resistance training, such as weight training or machine training, is also performed as a type of CR for people with heart failure (Taylor 2014).

How the intervention might work

A Cochrane Review found that exercise-based CR was associated with a 25% reduction in mortality and a 39% reduction in hospital readmission for people with heart failure (Taylor 2014). Well-established evidence shows that exercise training improves physi-

cal function and emotional status in people with heart failure, resulting in improved QOL (Taylor 2014). It has been reported that exercise training can reduce coagulation potential and enhance fibrinolytic potential in both healthy people and people with heart disease (Womack 2003). Furthermore, exercise-based CR has been shown to improve the risk factor parameter of neurological events such as triglycerides, high-density lipoprotein cholesterol, and nitric oxide in people with heart disease (Rankovic 2012). However, there is little evidence describing the effects of exercise training on mortality, morbidity, or QOL in people with implantable VADs (Allen 2010).

Why it is important to do this review

The European Society of Cardiology does not provide guidance on whether exercise-based CR is likely to be an effective intervention for people with VADs (Ponikowski 2016). Recently, two studies reported the beneficial effects of exercise-based CR on functional capacity and QOL by performing systematic reviews and meta-analyses (Ganga 2017; Mahfood 2017). However, these two systematic reviews have some limitations relating to study design. First, both systematic reviews included studies with study designs that produce inherent limitations (e.g. non-randomised, retrospective studies). Second, the participants were people with implantable or extracorporeal VADs, which need to be considered separately. A meta-analysis of RCTs was therefore needed to examine the effects of exercise-based CR in people with implantable VADs. As the use of VADs will continue to rise due to the growing number of people with end-stage heart failure, it is necessary to clarify the effectiveness of exercise-based CR for people with VADs (Corra 2012). This review aimed to determine the benefits and harms of exercise-based CR for people with implantable VADs.

OBJECTIVES

To determine the benefits and harms of exercise-based cardiac rehabilitation (CR) for people with implantable ventricular assist devices (VADs).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) regardless of cluster or individual randomisation were eligible, but only individually randomised trials were included, as no relevant cluster RCTs were identified. In addition, full-text studies, those published as abstract only, and unpublished data were eligible. However, the only relevant studies identified were full-text publications.

Types of participants

We included participants 18 years of age or older, with a diagnosis of heart failure with an implantable VAD. We excluded participants with an extracorporeal VAD or total artificial heart.

Types of interventions

We included trials comparing exercise-based CR with usual care. Exercise-based CR is defined as a supervised or unsupervised inpatient, outpatient, community- or home-based intervention that includes some form of exercise training applied to a cardiac patient population. The intervention could be exercise training alone or exercise training in addition to psychosocial and/or educational interventions (i.e. 'comprehensive CR'). Usual care could include standard medical care such as drug therapy, but without any form of structured exercise training or advice.

Types of outcome measures

Primary outcomes

1. Mortality: all-cause and cardiovascular
2. Rehospitalisation: all-cause and cardiovascular events
3. Serious adverse events: defined as participants who could not complete the study due to device- and non-device-related adverse events
4. Heart transplantation

Secondary outcomes

1. Exercise capacity: peak oxygen consumption (peak VO_2: mL/kg/min) or other measures, e.g. 6-minute walking distance (6MWD: m)
2. Health-related QOL assessed by validated questionnaires, e.g. 36-item Short Form Health Survey (SF-36) (points), Minnesota Living with Heart Failure Questionnaire (points)
3. Cost

The reporting of one or more of the outcomes listed here in the trial was not an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We identified trials through systematic searches of the following bibliographic databases on 3 October 2017.

1. Cochrane Central Register of Controlled Trials (CENTRAL) Issue 9 of 12, 2017 in the Cochrane Library
2. Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE (Ovid, 1946 to 3 October 2017)
3. Embase (Ovid, 1980 to 2017 Week 40)
4. PsycINFO (Ovid, 1806 to September Week 4 2017)
5. Conference Proceedings Citation Index-S (CPCI-S) on the Web of Science (Thomson Reuters, 1990 to 3 October 2017)
6. CINAHL (Cumulative Index of Nursing and Allied Health Literature) (EBSCO, 1937 to 3 October 2017)
7. LILACS (Latin American and Caribbean Health Sciences Literature) (BIREME, 1982 to 3 October 2017)

The search strategy for MEDLINE (Ovid) (Appendix 1) was adapted for use in the other databases. The Cochrane sensitivity-maximising RCT filter was applied to MEDLINE (Ovid) (Lefebvre 2011), and adaptations of the filter were applied to the other databases, except CENTRAL. See Appendix 1 for all of the search strategies used.

We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (apps.who.int/trialsearch/) on 10 August 2017.

We searched all databases from their inception to the present, and we imposed no restriction on the language of publication or publication status.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We furthermore contacted experts in the field to ask if they knew of any ongoing or unpublished trials.

Data collection and analysis

Selection of studies

Two review authors (SY and KH) independently screened the titles and abstracts of all potentially relevant studies identified as a result of the search, and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. In case of disagreements, other review authors were asked to arbitrate (EO and RM). SY and KH retrieved the full-text reports/publications, and independently screened the full texts and identified studies for inclusion. SY and KH also identified and recorded reasons for the exclusion of ineligible studies. Any disagreements were resolved through discussion or by consulting other review authors (EO and RM) when necessary. The review authors identified and excluded duplicates, and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table.

Data extraction and management

A data collection form that had been piloted on at least one study in the review was used to record study characteristics and outcome data. Two review authors (SY and KH) extracted characteristics from the included studies, as follows.

1. Methods: study design, total duration of study, details of any 'run-in' period, number of study centres and location, study setting, and date of study.
2. Participants: the number of people randomised, the number of people completing treatment, the number of people who withdrew or were lost to follow-up, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (SY and KH) independently extracted outcome data from the included studies and checked each other's data extraction. One review author (SY) transferred data into the Review Manager 5 file (RevMan 2014). SY and KH double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (KH) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (SY and KH) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion, by involving other review authors (EO and RM), or by contacting the authors of the included studies. We assessed risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias, e.g. industry funding

We graded each potential source of bias as high, low, or unclear risk, and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We

summarised the 'Risk of bias' judgements across different studies for each of the domains listed. Where information on risk of bias was related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.
When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol (Yamamoto 2016a).

Measures of treatment effect

We planned to analyse dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs) but no such data was available to analyse.
We analysed continuous data as mean difference (MD) or standardised mean difference (SMD) with 95% CIs. The MD was the absolute difference between the mean value in two groups in a trial. The SMD was used as a summary statistic in the meta-analysis when the studies all assessed the same outcome but measured it in a variety of ways. We entered data presented as a scale with a consistent direction of effect. When the standard deviation (SD) for change from the baseline was not available, we calculated the SDs using the Review Manager 5 calculator. Where appropriate, we combined the results from included studies for each outcome to give an overall estimate of treatment effect.

Unit of analysis issues

We included only individually randomised trials and synthesised the relevant information.

Dealing with missing data

We planned to contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we would have explored the impact of including such studies in the overall assessment of results by sensitivity analysis. However, this was not applicable to this review. The denominator for each outcome in each study was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We used I^2 and Chi^2 statistics to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (e.g. I^2 score of > 50% and P < 0.05), we reported it and explored possible causes using prespecified subgroup analysis. However, we did not perform subgroup analyses because all results of I^2 scores were less than 50%.

Assessment of reporting biases

We planned that if we were able to pool more than 10 trials, we would create and examine a funnel plot to explore publication bias by assessing funnel plot asymmetry visually. However, we did not perform this analysis due to the small number of included trials.

Data synthesis

We undertook meta-analyses only where this was meaningful, that is if the treatments, participants, and the underlying clinical questions were similar enough for pooling to make sense. We pooled data from each study using random-effects modelling where appropriate, as we needed to consider the difference between the interventions in the two studies.

'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes.

1. Mortality due to all causes
2. Mortality due to cardiovascular event
3. Rehospitalisation due to cardiovascular event
4. Serious adverse events
5. Health-related QOL
6. Heart transplantation
7. Cost

One author (SY) used the five GRADE domains (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of evidence as it relates to those studies that contribute data to the meta-analyses for the prespecified outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro software (GRADEproGDT 2017). We justified all decisions to downgrade the quality of studies using footnotes, and made comments to aid readers' understanding of the review where necessary. A second review author (KH) checked the assessment.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses for primary outcomes if we obtained an I^2 score of greater than 50%.

1. Length of follow-up (< 12 months or $\geq$ 12 months)
2. Types of VAD (continuous flow or pulsatile flow)
3. Exercise setting (hospital only, home only, or both settings)
4. Type of rehabilitation (exercise only or comprehensive CR)
5. Year of publication (before 2000, or in or after 2000)
6. Prospective trial registration (there is proof that trials actually took place, or none).

We planned to use the formal test for subgroup interactions in Review Manager 5 (RevMan 2014), as well as adding the year of publication in order to assess the influence of usual care. The standard of usual care has changed with the times: beta-blockers, angiotensin-receptor blockers, and angiotensin-converting enzyme inhibitors became standard therapy for heart failure after the year 2000 according to a meta-analysis, Shekelle 2003, and guideline (Hunt 2001). We furthermore checked if the trial was prospectively registered or obtained registration information from the ethics committee that approved the trial. We thereafter planned to conduct a subgroup analysis according to whether the trial was registered/approved or not. However, we did not perform subgroup analyses because all results of I^2 scores were less than 50%.

Sensitivity analysis

We planned to carry out a sensitivity analysis for primary outcomes if the high risk of bias of some of the included studies affected the results. We defined 'high risk' as a study having: a high risk in terms of random sequence generation; inadequate allocation concealment; and greater than 20% of data missing (Tierney 2005). We planned to carry out the following sensitivity analyses.

1. Only including studies with a low risk of bias
2. Excluding trials with 10 or fewer events

However, trials were not at high risk of bias (i.e. random sequence generation: low; inadequate allocation concealment: low; and less than 20% of data missing). Furthermore, there were no adverse events in one trial, and two serious adverse events in the other trial. We therefore did not perform a sensitivity analysis.

RESULTS

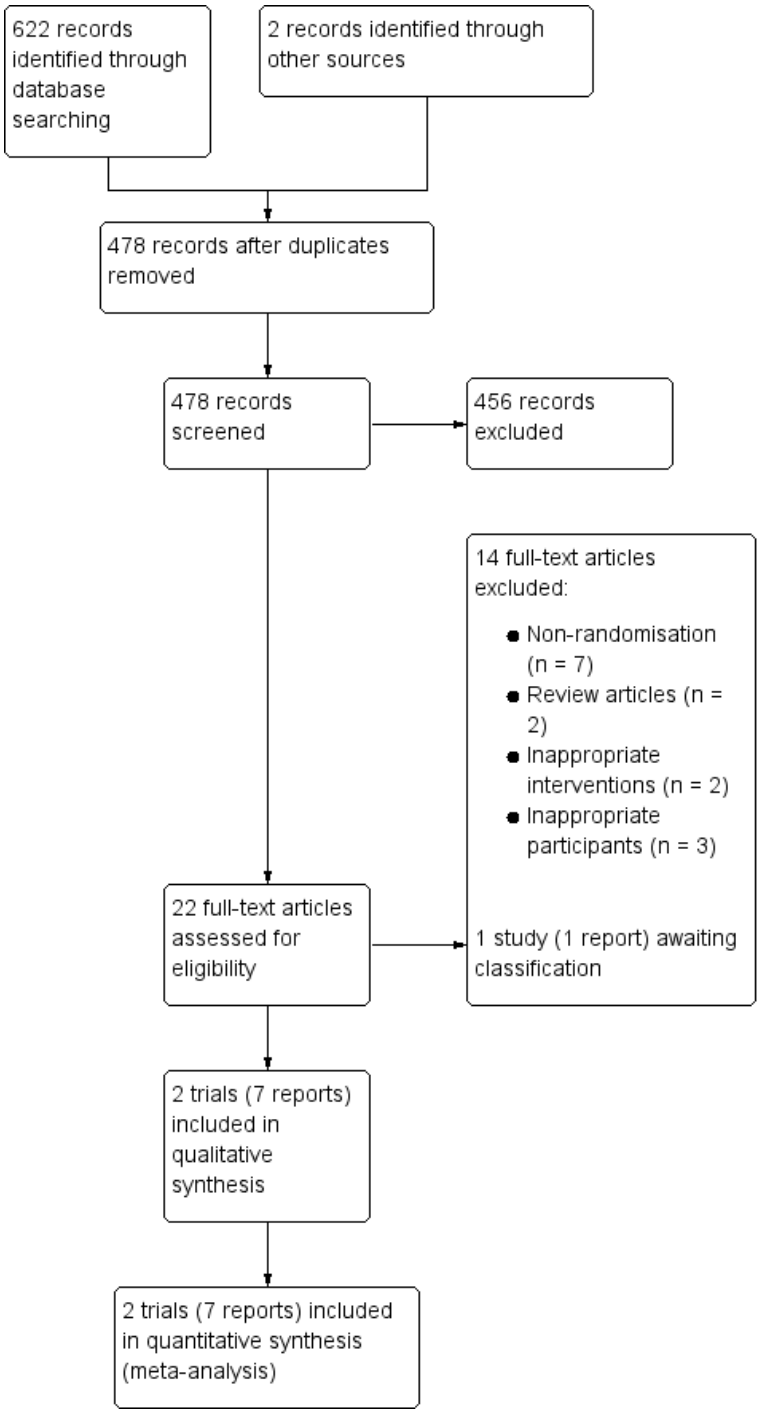
Description of studies

See: Characteristics of included studies and Characteristics of excluded studies.

Results of the search

We identified a total of 478 records after removal of duplicates, and retrieved the full texts of 22 records after screening titles and abstracts (Figure 1). Of the remaining records, we excluded a further 14 after full-text review: 7 studies were non-randomised; 2 studies were review articles; 2 studies had inappropriate interventions; and 3 studies had inappropriate participants. One of the remaining records was an RCT (Adamopoulos 2013), however it was not clear which types of VAD (i.e. implantable or extracorporeal) were assessed, and the details of the results were unclear. We tried to contact the author, but were unable to obtain the author's address. We therefore classified this trial as awaiting classification (see Characteristics of studies awaiting classification). We included a total of two trials (seven reports) in this review.

Figure 1. Study flow diagram.



Included studies

We included two studies with a total of 40 participants in this review. Both trials had small sample sizes and were single-centre studies. The duration of follow-up was six to eight weeks. One trial included people with Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) levels 1 and 2 (Hayes 2012), and the other trial included levels 1 to 4 (Kerrigan 2014). INTERMACS levels of 1 to 7 describe people who have severe symptoms at rest before VAD implantation. Although one trial was undertaken in the United States and the other in Australia, neither trial provided details on the ethnicity of participants. The mean age of participants in the included studies ranged from 40 to 60 years. Seventy-five per cent of recruited participants were men. Both trials evaluated exercise capacity (e.g. peak VO_2 or 6MWD) and QOL, although neither reported mortality and major adverse cardiovascular events (MACE). Exercise-based cardiac rehabilitation was aerobic exercise training using a treadmill, in Hayes 2012, or treadmill and cycle ergometer, in Kerrigan 2014, and one study also included resistance training (Hayes 2012). Exercise-based training was performed approximately three times per week for six to eight weeks. Exercise intensity was 50% of VO_2 reserve, or ranged from 60% to 80% of heart rate reserve. In one trial (Kerrigan 2014), usual care did not include an individualised exercise prescription, but participants were told to continue to follow their physician's instructions regarding care, including daily walking. In the other trial (Hayes 2012), usual care included a prescribed exercise regimen of regular walking. Details of the included studies are provided in the Characteristics of included studies table. Both trials were
supported by internal grants.

Excluded studies

We excluded 14 studies for the reasons provided in the Characteristics of excluded studies table. Many studies were excluded because they were not RCTs.

Risk of bias in included studies

'Risk of bias' assessments are indicated in Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

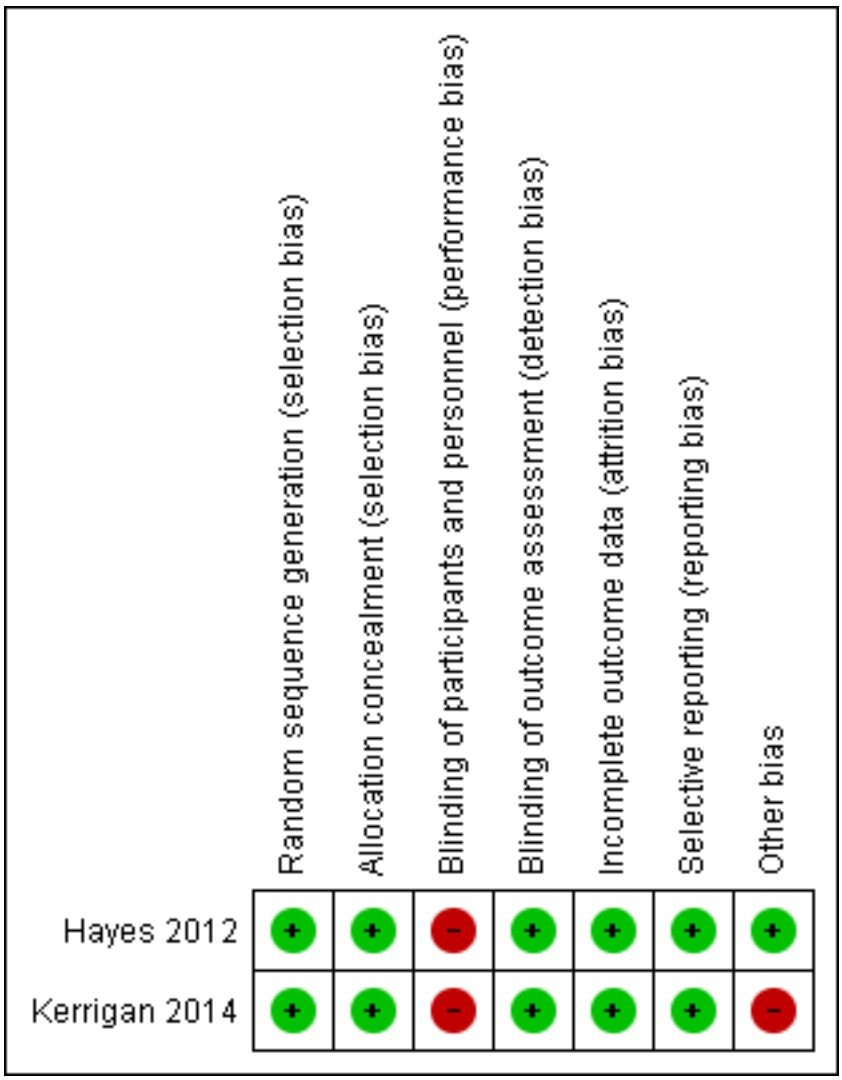
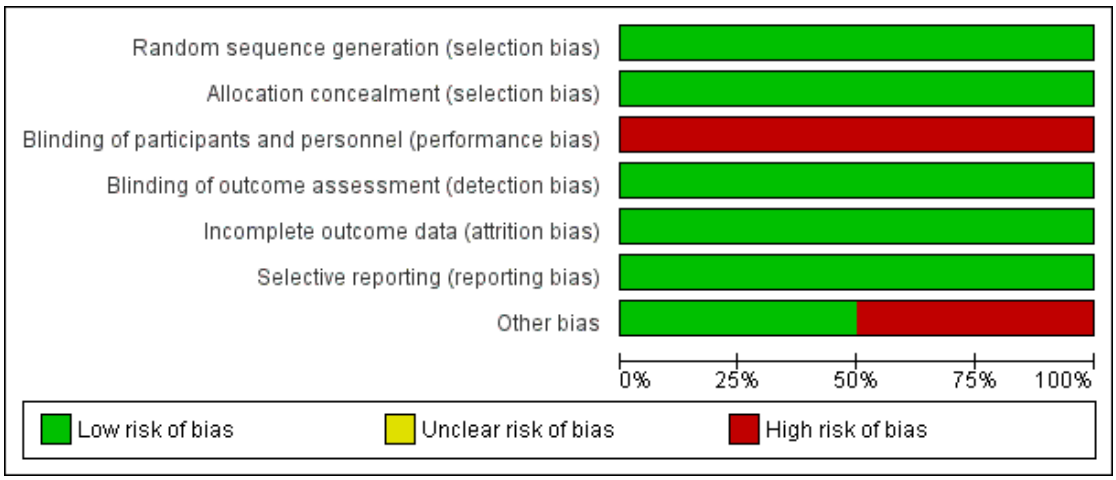


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Both trials reported that a computerised algorithm was used to randomly assign participants, and the allocation sequence was concealed using opaque envelopes.

Blinding

All participants were divided into an exercise group and a usual care group, and were instructed not to discuss their intervention. Due to the nature of the exercise intervention, blinding was not possible. However, as assessors were blinded in both trials, we considered the risk of detection bias to be low.

Incomplete outcome data

One trial reported no loss to follow-up or missing data in the study (Hayes 2012). The other trial reported that two participants in the exercise group did not complete the study: one participant moved away and the other experienced a driveline infection (dropout rate 11%), and one participant in the usual care group did not complete the study due to an infection (dropout rate 13%) (Kerrigan 2014).

Selective reporting

Both trials were registered with a clinical trial registry and reported on all outcomes.

Other potential sources of bias

There were no significant differences between the groups at baseline in both trials. However, one trial underwent analysis against only included participants whose results were known (Kerrigan 2014). The other trial underwent analysis against all participants (no dropouts) (Hayes 2012).

Effects of interventions

See: **Summary of findings for the main comparison** Exercise-based cardiac rehabilitation compared to usual care for people with implantable ventricular assist devices
See Summary of findings for the main comparison.
Data from 2 trials involving a total of 40 participants were available for assessing the effects of interventions.

Primary outcomes

Mortality

Neither trial reported on mortality.

Rehospitalisation

Neither trial reported on rehospitalisation.

Serious adverse events

One trial reported no adverse events (Hayes 2012). The other trial reported two serious adverse events: one participant in the exercise group had a driveline infection after a case of acute cholecystitis, and one participant in the usual care group had an infection (Kerrigan 2014). These two participants did not complete the

study. A total of two serious adverse events were observed across the one trial. Furthermore, a total of four participants in each group required visits to the emergency department, although these participants did complete the study. One participant was transferred to the emergency department due to a syncopal episode immediately after an exercise session. Three other participants in the exercise group visited the emergency department more than three hours after completing their last exercise session, and one of them required overnight hospitalisation due to epistaxis. Four participants in the usual care group visited the emergency department, three of whom required overnight hospitalisation due to oedema, infection, and anaemia.

Heart transplantation

No trial reported on heart transplantation.

Secondary outcomes

Exercise capacity

Peak VO_2 and 6MWD were measured to assess exercise capacity in both trials. In both trials, peak VO_2 was measured using a respiratory gas analyser, and 6MWD was performed using the American Thoracic Society guidelines (ATS Committee 2002).
For peak VO_2, we included 2 studies involving 37 participants in the analysis. Exercise capacity was measured at baseline and at six weeks in one trial (Kerrigan 2014), and baseline and eight weeks in the other trial (Hayes 2012). One trial reported that the increase in peak VO_2 was significant in the exercise group only (Kerrigan 2014), and the other trial reported a significant increase in peak VO_2 in both groups (Hayes 2012). In a pooled analysis of the two studies, there was no evidence of a difference in peak VO_2 at the end of follow-up between the groups when comparing the exercise group with usual care (mean difference (MD) 2.05 mL/kg/min, 95% confidence interval (CI) -1.72 to 5.82) (Analysis 1.1). Similarly, one trial reported that the increase in 6MWD was significant in the exercise group only (Kerrigan 2014), and the other trial reported a significant increase in 6MWD in both groups (Hayes 2012). In a pooled analysis of the two studies, there was no evidence of a difference in 6MWD at the end of follow-up between groups when comparing the exercise group with the usual care group (MD 45.56 m, 95% CI -6.72 to 97.85) (Analysis 1.2).

Health-related quality of life

Summary scores from the SF-36 and the Kansas City Cardiomyopathy Questionnaire (KCCQ) were measured as QOL. We included 2 trials involving 37 participants in this analysis. One trial reported that the KCCQ summary score improved by 14.4 points in the exercise group compared with 0.5 points in the usual care group (Kerrigan 2014). The other trial reported that the SF-36 total score improved by 29.2 points in the exercise group compared with 16.3 points in the usual care group (Hayes 2012). We calculated the SDs using the Review Manager 5 calculator because we did not obtain the SDs for changes from baseline for one study (Kerrigan 2014). In a pooled analysis of the two studies, there was a large difference in QOL between groups when comparing the exercise group with usual care (standardised mean difference (SMD) 0.88, 95% CI -0.12 to 1.88; 37 participants; 2 studies; very low-quality evidence; Analysis 1.3). This SMD size is considered to be a large effect according to the Cohen paper (Cohen 1988), as cited in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). However, the young age of the participants, high risk of performance bias, small sample size, and wide confidence intervals resulted in an assessment of very low-quality evidence for this outcome (Summary of findings for the main comparison).

Cost

Neither trial reported on cost analysis.

Subgroup analysis

We did not perform subgroup analyses because all results of I^2 scores were less than 50%.

DISCUSSION

Summary of main results

We included 2 RCTs involving a total of 40 participants in this review. Exercise-based CR consisted of aerobic or resistance training or both three times per week for six to eight weeks. The studies were conducted in the United States, Kerrigan 2014, and Australia, Hayes 2012. One trial showed improvements in exercise capacity (peak VO_2 and 6MWD) and QOL in the exercise group but not in the usual care group (Kerrigan 2014). The other trial reported that exercise capacity and QOL were improved in both groups (Hayes 2012). Pooled analyses of the two studies showed no evidence that CR improved exercise capacity, and a large difference in QOL between groups. However, the evidence for QOL was limited due to the young age of the participants, high risk of performance bias, small sample size, and wide confidence intervals, which resulted in very low-quality evidence.
Furthermore, we identified several problems in these trials. First, the period of exercise for people with implantable VADs was very short at 1.5 to 2 months compared with other systematic reviews on exercise-based cardiac rehabilitation that included studies of more than 3 months' duration (Anderson 2016; Taylor 2014; Yamamoto 2016). Second, the usual care group in one trial did not receive an individualised exercise prescription (Kerrigan 2014),

but were told to continue to follow their physician's instructions regarding care including daily walking. In the other trial (Hayes 2012), the usual care group received an exercise programme. The frequency of exercise sessions or adherence in the Kerrigan study might therefore be lower than that in the Hayes study (Hayes 2012; Kerrigan 2014), although both control groups received similar care. Third, the CR group was prescribed a bicycle training programme in the gym, whereas the usual care group received a walking programme (Hayes 2012). It was possible that the method of measuring the peak VO_2 by bicycle ergometer is biased towards showing improvement in the CR group (Hayes 2012). Furthermore, a total of two serious adverse events associated with infection was observed in one of the two trials (CR group: 1/25 (4%) versus usual care: 1/15 (7%)) (Kerrigan 2014). In addition, a total of four participants in each group required visits to the emergency department. Although exercise-based CR might have no effect on adverse events, we could not show that exercise-based CR is safe for people with implantable VADs because the quality of the evidence for serious adverse events was very low. Furthermore, due to a lack of data we were not able to assess the effect of exercise-based CR on our primary outcomes of mortality and rehospitalisation, and the secondary outcome of cost.

Overall completeness and applicability of evidence

The generalisability of this review is limited by the low average age and the very low number of participants. Data from the Centers for Medicare & Medicaid Services in the United States reported that the mean age of people with VADs was 61.8 years, and males accounted for 80.2% of people with VADs (Khazanie 2014). In our meta-analysis, one trial set in Australia reported the mean age of participants as less than 50 years, with males making up 85% of people with implantable VADs (Hayes 2012). The other trial set in the United States reported that the mean age of participants was 55 years, and 73% of participants were male (Kerrigan 2014). Participants in these studies were therefore a little younger compared with previous data. Types of intervention (aerobic and resistance training) in trials was properly prescribed according to AHA guidelines (Fletcher 2013). However, the term of exercise-based CR was very short compared with previous studies (Anderson 2016; Taylor 2014; Yamamoto 2016). For this reason, it is possible that the effect of the intervention is not sufficiently shown in this meta-analysis.

Quality of the evidence

Both of the included trials reported sequence generation, allocation concealment, and outcomes according to the registered protocol, and were judged to be at low risk of bias.

However, as the blinding of participants and personnel, or other potential sources of bias (not intention-to-treat analysis), were poorly described, we downgraded the quality of evidence by one level for the study limitations domain in serious adverse events and QOL outcomes. We judged the consistency of the effect domain as non-serious due to low heterogeneity in both outcomes. For the indirectness domain, we downgraded the quality of evidence by one level in both outcomes because the mean age of participants was a little younger compared with previous data. For the imprecision domain, we downgraded the quality of evidence by two levels in both outcomes because the sample size was very small, and 95% CIs were very wide in both outcomes. In addition, serious adverse events were not reported in one trial. Lastly, as there were only two trials, we could not assess the publication bias domain. For these reasons, we judged the quality of evidence to be very low.

Potential biases in the review process

The number of people with VADs has increased rapidly in recent years, with a relative increase of 324% from 2006 to 2011, and a 460% increase among elderly people (Khazanie 2014; Lampropulos 2014). For this reason, further systematic reviews and meta-analysis could be utilised in this field.

We conducted this review according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Furthermore, we undertook a comprehensive electronic search to identify published and unpublished studies, and synthesised and analysed data according to our review protocol (Yamamoto 2016a). We also searched conference abstracts. However, most abstracts focused on the same trials, or lacked sufficient data including authors' contact information (Adamopoulos 2013). It is therefore possible that we did not obtain all relevant data.

Agreements and disagreements with other studies or reviews

Our findings demonstrated that the effectiveness of exercise-based CR was very uncertain due to very low-quality evidence. The previous meta-analysis of exercise-based CR for people with implantable VADs reported that exercise-based CR significantly increased peak VO_2 by 3.00 mL/kg/min and 6MWD by 60.06 meters, and improved QOL (Mahfood 2017). The other review also reported similar results (Ganga 2017). However, some problems existed in these previous reviews, which included participants with either implantable or extracorporeal VADs, or that they were not RCTs. Furthermore, in our review the length of the training period was very short (i.e. from six to eight weeks). Future research therefore needs to address the long-term benefits of exercise training after VADs implantation. In addition, only one trial in this analysis featured an exercise-based CR of both aerobic training and resistance training (Hayes 2012). Resistance training alone

has been found to improve exercise capacity (i.e. peak VO_2 and 6MWD) (Jewiss 2016; Yamamoto 2016).

AUTHORS' CONCLUSIONS

Implications for practice

This review revealed a lack of evidence on the benefits of exercise-based cardiac rehabilitation (CR) for people with implantable ventricular assist devices (VADs), although the current European Society of Cardiology guidelines recommend exercise-based CR for people with heart failure (Ponikowski 2016). There was inadequate evidence to assess the safety and efficacy of exercise-based CR for people with implantable VADs compared with usual care, and evidence on improved QOL in exercise-based CR was of very low quality. However, the training period of the included studies in our meta-analysis was from six to eight weeks, which is much shorter than the three-month period used in previous studies for people with coronary heart disease or heart failure (Anderson 2016; Taylor 2014; Yamamoto 2016). An increase in exercise capacity is primarily determined by the level of exercise intensity and the length of the training period (Vromen 2016). For this reason, we consider that the short training period does not allow a correct understanding of the magnitude of the effects of exercise-based CR in people with implantable VADs. In addition, the effects of exercise-based CR on mortality were unclear. Further evidence on mortality and cost-effectiveness is needed to justify the promotion of exercise training for people with implantable VADs.

Implications for research

This review included only two trials and a very small sample size. Future larger randomised controlled trials for people with implantable VADs are required before findings can be regarded as robust and conclusive. Furthermore, as the frequency, intensity, time, and type (FITT) differed between the trials, future studies need to collect common intervention data. In addition, longer follow-up data are needed, as the duration of follow-up in these two trials was much too short. In recent years, many types of VAD have been released, and the type of VAD has a great influence on the survival rate (Acharya 2016; Peura 2012). In fact, treatment with continuous-flow VADs has significantly improved the probability of the survival rate and decreased the incidence of stroke and device failure over two years compared with pulsatile-flow VADs (Slaughter 2009). Subgroup analyses are therefore needed on types of VAD or year of publication. Furthermore, as the average age of people with VADs is increasing (Khazanie 2014), we also need to verify the effects of exercise-based CR on elderly people with implantable VADs.

ACKNOWLEDGEMENTS

The authors thank Ms Emma Barber for her editorial support. We also thank the Information Specialist of the Cochrane Heart Group for providing support with searching. The Methods section of this review is based on a standard protocol template provided by the Cochrane Heart Group.

REFERENCES

References to studies included in this review

Hayes 2012 *{published data only}*

ACTRN12609000742279. Can exercise training improve cardiovascular fitness and quality of life in patients with a left ventricular assist device (LVAD)?. anzctr.org.au/Trial/Registration/TrialReview.aspx?id=308009 (first received 2 June 2009).

Hayes K, Leet AS, Bradley SJ, Holland AE. Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device (LVAD): a randomised controlled trial. *Journal of Heart and Lung Transplantation* 2012;**31**(4):S82.

* Hayes K, Leet AS, Bradley SJ, Holland AE. Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: a preliminary randomized controlled trial. *Journal of Heart and Lung Transplantation* 2012;**31**(7):729–34.

Kerrigan 2014 *{published data only}*

* Kerrigan DJ, Williams CT, Ehrman JK, Saval MA, Bronsteen K, Schairer JR, et al. Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: the Rehab-VAD randomized controlled trial. *JACC Heart Failure* 2014;**2**(6):653–9.

Kerrigan DJ, Williams CT, Ehrman JK, Saval MA, Bronsteen K, Schairer JR, et al. Cardiac rehabilitation improves functional capacity in patients with continuous flow left ventricular assist devices. *Circulation* 2013;**128** (Suppl 22):A15438.

NCT01584895. Cardiac rehabilitation in patients with continuous flow left ventricular assist devices: Rehab VAD trial. clinicaltrials.gov/ct2/show/record/NCT01584895 (first received 23 April 2012).

Williams CT, Kerrigan D, Ehrman JK, Saval MA, Bronsteen K, Schairer JR, et al. Cardiac rehabilitation improves health status and six minute walk distance in patients with continuous flow left ventricular assist devices. *Circulation* 2013;**128**(Suppl 22):A15524.

References to studies excluded from this review

Alsara 2014 *{published data only}*

Alsara O, Perez-Terzic C, Squires RW, Dandamudi S, Miranda WR, Park SJ, et al. Is exercise training safe and beneficial in patients receiving left ventricular assist device therapy?. *Journal of Cardiopulmonary Rehabilitation & Prevention* 2014;**34**(4):233–40.

Cinar 2016 *{published data only}*

Cinar E, Karapolat H, Capaci K, Engin C, Yagdi T, Ozbaran M, et al. The effect of cardiac rehabilitation on functional capacity, psychological symptoms and quality of life in patients with a left ventricular assist device. *Journal of Heart and Lung Transplantation* 2016;**35**(4):S395.

Foray 1996 *{published data only}*

Foray A, Williams D, Reemtsma K, Oz M, Mancini D. Assessment of submaximal exercise capacity in patients with left ventricular assist devices. *Circulation* 1996;**94**(9 Suppl): II222–6.

Humphrey 1998 *{published data only}*

Humphrey R, Buck L, Cahalin L, Morrone T. Physical therapy assessment and intervention for patients with left ventricular assist devices. *Cardiopulmonary Physical Therapy Journal (American Physical Therapy Association, Cardiopulmonary Section)* 1998;**9**(2):3–7.

Karapolat 2013 *{published data only}*

Karapolat H, Engin C, Eroglu M, Yagdi T, Zoghi M, Nalbantgil S, et al. Efficacy of the cardiac rehabilitation program in patients with end-stage heart failure, heart transplant patients, and left ventricular assist device recipients. *Transplantation Proceedings* 2013;**45**(9):3381–5.

Kugler 2012 *{published data only}*

Kugler C, Malehsa D, Schrader E, Tegtbur U, Guetzlaff E, Haverich A, et al. A multi-modal intervention in management of left ventricular assist device outpatients: dietary counselling, controlled exercise and psychosocial support. *European Journal of Cardio-Thoracic Surgery* 2012; **42**(6):1026–32.

Laoutaris 2009 *{published data only}*

Laoutaris ID, Dritsas A, Adamopoulos S, Manginas A, Gouziouta A, Koulopoulou M, et al. Benefits of chronic exercise training on aerobic capacity and NT-proBNP plasma levels in patients with ventricular assist devices. *European Heart Journal* 2009;**30**:466.

Laoutaris 2010 *{published data only}*

Laoutaris ID. Training patients with ventricular assist devices. *Heart Surgery Forum* 2010;**13**:S35–6.

Laoutaris 2010a *{published data only}*

Laoutaris ID, Dritsas A, Adamopoulos S, Manginas A, Gouziouta A, Kallistratos MS, et al. Benefits of physical training on functional status in patients with ventricular assist devices long-term postimplantation. *Heart Surgery Forum* 2010;**13**:S92–3.

Laoutaris 2011 *{published data only}*

Laoutaris ID, Dritsas A, Adamopoulos S, Manginas A, Gouziouta A, Kallistratos MS, et al. Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term postimplantation. *European Journal of Cardiovascular Prevention & Rehabilitation* 2011;**18**(1): 33–40.

Marko 2015 *{published data only}*

Marko C, Danzinger G, Kaferback M, Lackner T, Muller R, Zimpfer D, et al. Safety and efficacy of cardiac rehabilitation for patients with continuous flow left ventricular assist devices. *European Journal of Preventive Cardiology* 2015;**22** (11):1378–84.

Pamboukian 2015 *{published data only}*

Pamboukian SV, Pagani FD, Naftel DC, Myers SL, Hollifield KA, Kirklin JK. Improvements in six minute walk distance after continuous flow ventricular assist device placement: comparison of pre-implant ambulatory and non-ambulatory patients. *Journal of Heart and Lung Transplantation* 2015;**34**(4):S333–4.

Staveski 2010 *{published data only}*

Staveski SL, Roth SJ, Rosenthal D, Wright GE. Comprehensive interdisciplinary care coordination for Berlin Heart VAD patients. *Cardiology in the Young* 2010; **20**:120.

Workowski 2014 *{published data only}*

Workowski AA, Bartsch P, Stuhr H, Willemsen D, Bjarnason-Wehrens B. Resistance training in patients with an intracorporal ventricular assist device (VAD) of the third generation during phase II cardiac rehabilitation (CR). *European Journal of Preventive Cardiology* 2014;**21**(1):S6.

References to studies awaiting assessment

Adamopoulos 2013 *{published data only}*

Adamopoulos S, Gouziouta A, Mantzouratou P, Kostakou E, Laoutaris ID, Dritsas A, et al. Exercise training up-regulates physiological growth signalling in the myocardium of patients with mechanical circulatory support: relevance to functional recovery. *Journal of the American College of Cardiology* 2013;**61**(10):E666.

Additional references

Acharya 2016

Acharya D, Loyaga-Rendon RY, Pamboukian SV, Tallaj JA, Holman WL, Cantor RS, et al. Ventricular assist device in acute myocardial infarction. *Journal of the American College of Cardiology* 2016;**67**(16):1871–80.

ACSM 2009

American College of Sports Medicine. In: Walther RT editor(s). *ACSM's Guidelines for Exercise Testing and Prescription*. Lippincott Williams & Wilkins, 2009.

Allen 2010

Allen JG, Weiss ES, Schaffer JM, Patel ND, Ullrich SL, Russell SD, et al. Quality of life and functional status in patients surviving 12 months after left ventricular assist device implantation. *Journal of Heart and Lung Transplantation* 2010;**29**:278–85.

Anderson 2016
Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. *Cochrane Database of Systematic Reviews* 2016, Issue 1. DOI: 10.1002/14651858.CD001800.pub3

AST and ASTS 2012
American Society of Transplantation and the American Society of Transplant Surgeons. Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients 2010 data report. *American Journal of Transplantation* 2012;**12 Suppl 1**:1–156.

ATS Committee 2002
ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *American Journal of Respiratory and Critical Care Medicine* 2002;**166**(1):111–7.

Canadian Cardiovascular Society 2014
Canadian Cardiovascular Society Heart Failure Management Primary Panel, Moe GW, Ezekowitz JA, O'Meara E, Howlett JG, Fremes SE, et al. The 2013 Canadian Cardiovascular Society heart failure management guidelines update: focus on rehabilitation and exercise and surgical coronary revascularization. *Canadian Journal of Cardiology* 2014;**30**:249–63.

Cohen 1988
Cohen J. *Statistical Power Analysis in the Behavioral Sciences*. 2nd Edition. Hillsdale: Lawrence Erlbaum Associates, Inc, 1988.

Corra 2012
Corra U, Pistono M, Piepoli MF, Giannuzzi P. Ventricular assist device patients on the horizon of cardiovascular prevention and rehabilitation. Can we convert challenges into opportunities?. *European Journal of Preventive Cardiology* 2012;**19**:490–3.

Fletcher 2001
Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. *Circulation* 2001;**104**:1694–740.

Fletcher 2013
Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation* 2013;**128**(8):873–934.

Ganga 2017
Ganga HV, Leung A, Jantz J, Choudhary G, Stabile L, Levine D J, et al. Supervised exercise training versus usual care in ambulatory patients with left ventricular assist devices: a systematic review. *PLoS ONE* 2017;**12**(3): e0174323.

GRADEproGDT 2017
GRADEproGDT. GRADEproGDT Guideline Development Tool [software]. Version accessed 10 May 2017. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015:gradepro.org (accessed 13 July 2017).

Hatta 2009
Hatta M, Joho S, Inoue H, Origasa H. A health-related quality of life questionnaire in symptomatic patients with heart failure: validity and reliability of a Japanese version of the MRF28. *Journal of Cardiology* 2009;**53**:117–26.

Heart Failure Society of America 2010
Heart Failure Society of America, Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, et al. HFSA 2010 comprehensive heart failure practice guideline. *Journal of Cardiac Failure* 2010;**16**(6):e1–194.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hoekstra 2013
Hoekstra T, Jaarsma T, van Veldhuisen DJ, Hillege HL, Sanderman R, Lesman-Leegte I. Quality of life and survival in patients with heart failure. *European Journal of Heart Failure* 2013;**15**(1):94–102.

Hrobowski 2013
Hrobowski T, Lanfear DE. Ventricular assist devices: is destination therapy a viable alternative in the non-transplant candidate?. *Current Heart Failure Reports* 2013;**10**:101–7.

Hunt 2001
Hunt SA, Baker DW, Chin MH, Cinquegrani MP, Feldman AM, Francis GS, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *Journal of the American College of Cardiology* 2001; **38**(7):2101–13.

Hunt 2005
Hunt SA, American College of Cardiology, American Heart Association Task Force on Practice Guidelines. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). *Journal of the American College of Cardiology* 2005;**46**:e1–82.

Jewiss 2016
Jewiss D, Ostman C, Smart NA. The effect of resistance training on clinical outcomes in heart failure: a systematic review and meta-analysis. *International Journal of Cardiology* 2016;**221**:674–81.

Khazanie 2014
Khazanie P, Hammill BG, Patel CB, Eapen ZJ, Peterson ED, Rogers JG, et al. Trends in the use and outcomes of ventricular assist devices among Medicare beneficiaries,

2006 through 2011. *Journal of the American College of Cardiology* 2014;**63**(14):1395–404.

Kirklin 2018

Kirklin JK, Xie R, Cowger J, de By TMMH, Nakatani T, Schueler S, et al. Second annual report from the ISHLT Mechanically Assisted Circulatory Support Registry. *Journal of Heart and Lung Transplantation* 2018;**37**(6):685–91.

Lampropulos 2014

Lampropulos JF, Kim N, Wang Y, Desai MM, Barreto-Filho JA, Dodson JA, et al. Trends in left ventricular assist device use and outcomes among Medicare beneficiaries, 2004-2011. *Open Heart* 2014;**1**(1):e000109.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Mahfood 2017

Mahfood Haddad T, Saurav A, Smer A, Azzouz MS, Akinapelli A, Williams MA, et al. Cardiac rehabilitation in patients with left ventricular assist device: a systematic review and meta-analysis. Journal of Cardiopulmonary Rehabilitation 2017; Vol. 37, issue 6:390–6. DOI: 10.1097/HCR.0000000000000254

McMurray 2012

McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm 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. *European Heart Journal* 2012;**33**:1787–847.

Mosterd 2007

Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007;**93**:1137–46.

Mozaffarian 2015

Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics - 2015 update: a report from the American Heart Association. *Circulation* 2015;**131**(4):e29–322.

Oh 2014

Oh B, Cho B, Choi HC, Son KY, Park SM, Chun S, et al. The influence of lower-extremity function in elderly individuals' quality of life (QOL): an analysis of the correlation between SPPB and EQ-5D. *Archives of Gerontology and Geriatrics* 2014;**58**:278–82.

Okura 2008

Okura Y, Ramadan MM, Ohno Y, Mitsuma W, Tanaka K, Ito M, et al. Impending epidemic: future projection of heart failure in Japan to the year 2055. *Circulation Journal* 2008;**72**(3):489–91.

Peura 2012

Peura JL, Colvin-Adams M, Francis GS, Grady KL, Hoffman TM, Jessup M, et al. Recommendations for the use of mechanical circulatory support: device strategies and patient selection: a scientific statement from the American Heart Association. *Circulation* 2012;**126**:2648–67.

Ponikowski 2016

Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**(27): 2129–200.

Rankovic 2012

Rankovic G, Djindjic N, Rankovic-Nedin G, Markovic S, Nejic D, Milicic B, et al. The effects of physical training on cardiovascular parameters, lipid disorders and endothelial function. *Vojnosanitetski Pregled* 2012;**69**:956–60.

RevMan 2014 [Computer program]

The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration, 2014.

Rose 2001

Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *New England Journal of Medicine* 2001;**345**(20):1435–43.

Shekelle 2003

Shekelle P, Morton S, Atkinson S, Suttorp M, Tu W, Heidenreich P, et al. Pharmacologic management of heart failure and left ventricular systolic dysfunction: effect in female, black, and diabetic patients, and cost-effectiveness. Evidence Report/Technology Assessment (Summary) 2003; Vol. 82:1–6.

Slaughter 2009

Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *New England Journal of Medicine* 2009;**361** (23):2241–51.

Starling 2017

Starling RC, Estep JD, Horstmanshof DA, Milano CA, Stehlik J, Shah KB, et al. Risk assessment and comparative effectiveness of left ventricular assist device and medical management in ambulatory heart failure patients: The ROADMAP study 2-year results. *JACC Heart Failure* 2017; **5**(7):518–27.

Stehlik 2013

Stehlik J, Hosenpud JD, Edwards LB, Hertz MI, Mehra MR. ISHLT International Registry for Heart and Lung Transplantation - into the fourth decade, from strength to strength. *Journal of Heart and Lung Transplantation* 2013; **32**(10):941–50.

Taylor 2014

Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, et al. Exercise-based rehabilitation for heart failure.

Cochrane Database of Systematic Reviews 2014, Issue 4. DOI: 10.1002/14651858.CD003331.pub4

Tierney 2005

Tierney JF, Stewart LA. Investigating patient exclusion bias in meta-analysis. *International Journal of Epidemiology* 2005;**34**:79–87.

Vos 2016

Vos T, Allen C, Arora M, Barber RM, Bhutta ZA, Brown A, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016;**388**(10053):1545–602.

Vromen 2016

Vromen T, Kraal JJ, Kuiper J, Spee RF, Peek N, Kemps HM. The influence of training characteristics on the effect of aerobic exercise training in patients with chronic heart failure: a meta-regression analysis. *International Journal of Cardiology* 2016;**208**:120–7.

Ware 1993

Ware JE, Snow K, Kosinski M, Gandek B. *SF-36 Health Survey: Manual and Interpretation Guide*. Boston: The Health Institute, New England Medical Center, 1993.

WHO 2017

World Health Organization. WHO methods and data sources for country-level causes of death 2000-2015. www.who.int/healthinfo/global_burden_disease/GlobalCOD_method_2000_2015.pdf (accessed prior to 12 September 2018).

Womack 2003

Womack CJ, Nagelkirk PR, Coughlin AM. Exercise-induced changes in coagulation and fibrinolysis in healthy populations and patients with cardiovascular disease. *Sports Medicine* 2003;**33**(11):795–807.

Yamamoto 2016

Yamamoto S, Hotta K, Ota E, Mori R, Matsunaga A. Effects of resistance training on muscle strength, exercise capacity, and mobility in middle-aged and elderly patients with coronary artery disease: a meta-analysis. *Journal of Cardiology* 2016;**68**(2):125–34.

Yancy 2017

Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017;**136**(6):e137–61.

References to other published versions of this review

Yamamoto 2016a

Yamamoto S, Hotta K, Ota E, Matsunaga A, Mori R. Exercise-based cardiac rehabilitation for people with ventricular assist devices. *Cochrane Database of Systematic Reviews* 2016, Issue 6. DOI: 10.1002/14651858.CD012222

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hayes 2012

Methods	Study design: Single-centre RCT Country: Australia Date of study: August 2009 and February 2011
Participants	Inclusion criteria: implanted LVAD, and age older than 18 years Exclusion criteria: people who declined to participate, had comorbidities that precluded exercise training, or had contraindications to exercise testing Number of randomised: N total = 14 (CR 7, usual care 7) Mean age (years, mean ± SD): CR 48.7 ± 14.5, usual care 45.9 ± 14.6 Sex: Total: Men 12, Women 2 CR: Men 6, Women 1 Usual care: Men 6, Women 1 Numbers lost to follow-up: 0
Interventions	Ergometer: 50% VO_2 reserve, 15 min. Treadmill: 60% of average speed during 6MWD, 15 min. If Borg RPE < 13, workload was progressed by 10%. Strength training: 3 upper limb and 3 lower limb exercises using free weights and machines. 2 sets of 10 repetitions (weight determined on an individual basis). 3 days per week for 8 weeks.
Outcomes	Peak VO_2, peak workload, 6MWD, QOL questionnaire (SF-36)
Notes	Funding sources: internal grant from Alfred Health

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised algorithm
Allocation concealment (selection bias)	Low risk	Sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding is impossible because of exercise-based intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded.

Hayes 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes were reported according to a registered protocol (ACTRN12609000742279)
Other bias	Low risk	There were no significant differences between the groups at baseline. Furthermore, this study performed an intention-to-treat analysis

Kerrigan 2014

Methods	Study design: Single-centre RCT Country: United States Date of study: June 2011 and September 2012
Participants	Inclusion criteria: recently implanted continuous-flow LVAD (1 to 6 months from surgery date), age older than 18 years, and participants had to be free of any major comorbidities or limitations that might interfere with exercise training Exclusion criteria: people who declined to attend CR or who attended a CR programme outside of the Henry Ford Health System Number of randomised: N total = 26 (CR 18, usual care 8) Mean age (years, mean ± SD): CR 53 ± 13, usual care 60 ± 12 Sex: Total: Men 19, Women: 7 CR: Men 11, Women 7 Usual care: Men 7, Women 1 Numbers lost to follow-up: 3 (CR 2, usual care 1)
Interventions	Treadmill + cycle ergometer, arm ergometer or recumbent stepper: 60% of heart rate reserve, 30 min. 3 sessions per week for 6 weeks.
Outcomes	Treadmill time, peak VO_2, VO_2 at AT, respiratory exchange ratio, minutes ventilation, VE/VCO_2 slope, 6MWD, leg isokinetic strength, QOL questionnaire (Kansas City Cardiomyopathy Questionnaire (KCCQ)), rest/submaximal/peak heart rate, heart rate recovery, rest/submaximal/peak mean arterial pressure
Notes	Funding sources: internal grant from the Edith and Benson Ford Heart and Vascular Institute

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Kerrigan 2014 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computerised algorithm
Allocation concealment (selection bias)	Low risk	Sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding is impossible because of exercise-based intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants in the training group did not complete study: 1 moved away, and the other had a driveline infection (dropout rate 11%). 1 participant in the usual care group did not complete the study due to an infection (dropout rate 13%)
Selective reporting (reporting bias)	Low risk	All outcomes were reported according to a registered protocol (NCT01584895)
Other bias	High risk	All participants who dropped out and were lost to follow-up were reported. However, the analysis included only those participants whose results were known

6MWD: 6-minute walking distance
AT: aerobic threshold
CR: cardiac rehabilitation
LVAD: left ventricular assist device
QOL: quality of life
RCT: randomised controlled trial
RPE: rating of perceived exertion
SD: standard deviation
SF-36: 36-item Short Form Health Survey
VO_2: oxygen consumption

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alsara 2014	Review article
Cinar 2016	This trial compared the effects of hospital-based interventions
Foray 1996	Non-RCT design (observational study)
Humphrey 1998	Non-RCT design (review article)
Karapolat 2013	Retrospective study (non-RCT design)
Kugler 2012	Non-RCT design
Laoutaris 2009	Included participants with extracorporeal VAD
Laoutaris 2010	Review article
Laoutaris 2010a	Included participants with extracorporeal VAD
Laoutaris 2011	Included participants with extracorporeal VAD
Marko 2015	Non-RCT design
Pamboukian 2015	Non-RCT design
Staveski 2010	Participants were paediatric patients. Not exercise-based cardiac rehabilitation
Workowski 2014	Non-RCT design

RCT: randomised controlled trial
VAD: ventricular assist device

Characteristics of studies awaiting assessment *[ordered by study ID]*

Adamopoulos 2013

Methods	Participants with VAD were randomised to a training group or a usual care group
Participants	Country and setting: unclear Nunber of randomised: N total = 32 (CR 16, usual care 16)

Adamopoulos 2013 (*Continued*)

Interventions	Aerobic training for 45 min at Borg scale 12 to 14 for 3 to 4 times a week High-intensity inspiratory muscle training, initially at the hospital (12 weeks) and then at home with confirmation of adherence until heart transplantation
Outcomes	Peak VO_2 and LVEF
Notes	Lacked sufficient data including authors' contact information

LVEF: left ventricular ejection fraction
VAD: ventricular assist device
VO_2: oxygen consumption

DATA AND ANALYSES

Comparison 1. Exercise-based cardiac rehabilitation versus usual care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exercise capacity: peak VO_2 (mL/kg/min)	2	37	Mean Difference (IV, Random, 95% CI)	2.05 [-1.72, 5.82]
2 Exercise capacity: 6-minute walking distance (m)	2	37	Mean Difference (IV, Random, 95% CI)	45.56 [-6.72, 97.85]
3 Quality of life	2	37	Std. Mean Difference (IV, Random, 95% CI)	0.88 [-0.12, 1.88]

Analysis 1.1. Comparison 1 Exercise-based cardiac rehabilitation versus usual care, Outcome 1 Exercise capacity: peak VO_2 (mL/kg/min).

Review: Exercise-based cardiac rehabilitation for people with implantable ventricular assist devices

Comparison: 1 Exercise-based cardiac rehabilitation versus usual care

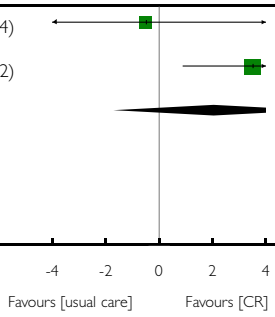
Outcome: 1 Exercise capacity: peak VO_2 (mL/kg/min)

Study or subgroup	Exercise N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hayes 2012	7	14.8 (4.9)	7	15.3 (4.4)		36.2 %	-0.50 [-5.38, 4.38]
Kerrigan 2014	16	15.3 (4.4)	7	11.8 (2)		63.8 %	3.50 [0.88, 6.12]
Total (95% CI)	**23**		**14**			**100.0 %**	**2.05 [-1.72, 5.82]**

Heterogeneity: Tau^2 = 4.01; Chi^2 = 2.01, df = 1 (P = 0.16); I^2 =50%

Test for overall effect: Z = 1.07 (P = 0.29)

Test for subgroup differences: Not applicable

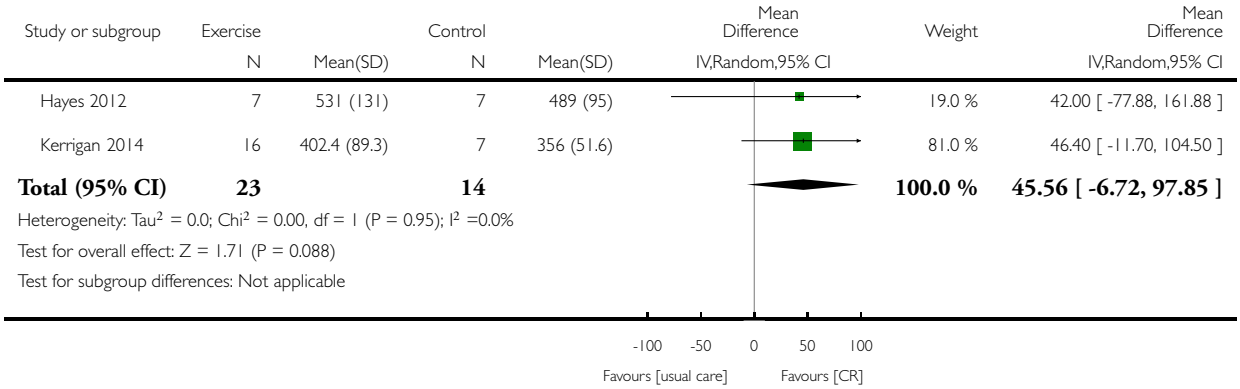


Analysis 1.2. Comparison 1 Exercise-based cardiac rehabilitation versus usual care, Outcome 2 Exercise capacity: 6-minute walking distance (m).

Review: Exercise-based cardiac rehabilitation for people with implantable ventricular assist devices

Comparison: 1 Exercise-based cardiac rehabilitation versus usual care

Outcome: 2 Exercise capacity: 6-minute walking distance (m)

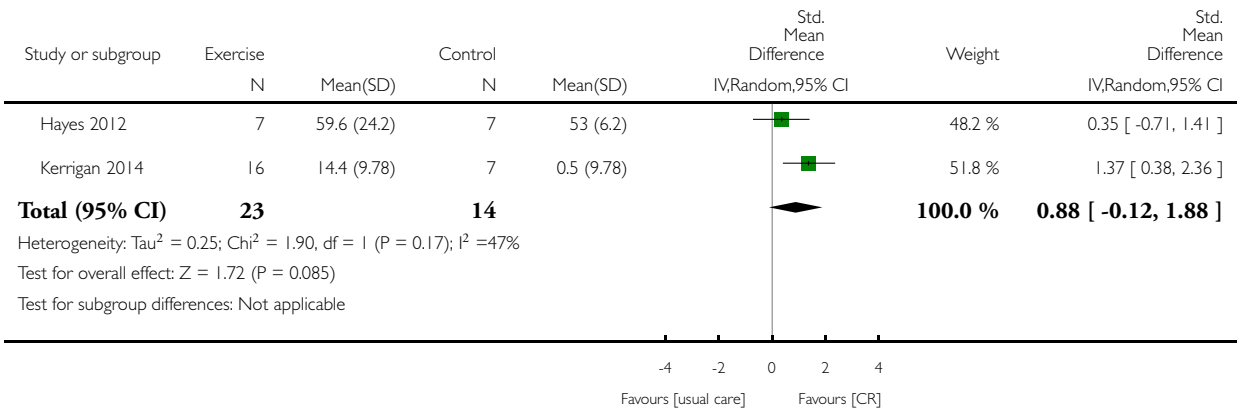


Analysis 1.3. Comparison 1 Exercise-based cardiac rehabilitation versus usual care, Outcome 3 Quality of life.

Review: Exercise-based cardiac rehabilitation for people with implantable ventricular assist devices

Comparison: 1 Exercise-based cardiac rehabilitation versus usual care

Outcome: 3 Quality of life



APPENDICES

Appendix 1. Search strategies

CENTRAL

#1 MeSH descriptor: [Exercise Therapy] explode all trees
#2 MeSH descriptor: [Sports] this term only
#3 MeSH descriptor: [Physical Exertion] this term only
#4 rehabilitat*
#5 (physical* near/5 (fit* or train* or therap* or activit*))
#6 MeSH descriptor: [Exercise] explode all trees
#7 (train* near/5 (strength* or aerobic* or exercise*))
#8 ((exercise* or fitness) near/3 (treatment or intervent* or program*))
#9 mobili*
#10 MeSH descriptor: [Rehabilitation] explode all trees
#11 kinesiotherap*
#12 MeSH descriptor: [Physical Education and Training] this term only
#13 (run* or walk* or jog* or danc*)
#14 (("lifestyle" or life-style) near/5 (physical* or activ*))
#15 MeSH descriptor: [Dance Therapy] explode all trees
#16 MeSH descriptor: [Patient Education as Topic] this term only
#17 (patient* near/5 educat*)
#18 ((lifestyle or life-style) near/5 (interven* or program* or treatment*))
#19 (motivat* near/5 (intervention or interv*))
#20 MeSH descriptor: [Health Education] this term only
#21 (health near/5 educat*)
#22 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 MeSH descriptor: [Heart-Assist Devices] this term only
#24 (ventric* near/2 assist*)
#25 VAD
#26 (ventric* near/2 device*)
#27 #23 or #24 or #25 or #26
#28 #22 and #27

MEDLINE

1. exp Exercise Therapy/
2. Sports/
3. Physical Exertion/
4. rehabilitat*.tw.
5. (physical* adj5 (fit* or train* or therap* or activit*)).tw.
6. exp Exercise/
7. (train* adj5 (strength* or aerobic* or exercise*)).tw.
8. ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw.
9. mobili*.tw.
10. exp Rehabilitation/

11. kinesiotherap*.tw.
12. "Physical Education and Training"/
13. (run* or walk* or jog* or danc*).tw.
14. (("lifestyle" or life-style) adj5 (physical* or activ*)).tw.
15. Dance Therapy/
16. Patient Education as Topic/
17. (patient* adj5 educat*).tw.
18. ((lifestyle or life-style) adj5 (interven* or program* or treatment*)).tw.
19. (motivat* adj5 (intervention or interv*)).tw.
20. Health Education/
21. (health adj5 educat*).tw.
22. or/1-21
23. Heart-Assist Devices/
24. (ventric* adj2 assist*).tw.
25. VAD.tw.
26. (ventric* adj2 device*).tw.
27. or/23-26
28. 22 and 27
29. randomized controlled trial.pt.
30. controlled clinical trial.pt.
31. randomized.ab.
32. placebo.ab.
33. drug therapy.fs.
34. randomly.ab.
35. trial.ab.
36. groups.ab.
37. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. exp animals/ not humans.sh.
39. 37 not 38
40. 28 and 39

Embase

1. exp kinesiotherapy/
2. sport/
3. exp exercise/
4. rehabilitat*.tw.
5. (physical* adj5 (fit* or train* or therap* or activit*)).tw.
6. (train* adj5 (strength* or aerobic* or exercise*)).tw.
7. ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw.
8. mobili*.tw.
9. exp rehabilitation/
10. kinesiotherap*.tw.
11. physical education/
12. (run* or walk* or jog* or danc*).tw.
13. (("lifestyle" or life-style) adj5 (physical* or activ*)).tw.
14. dance therapy/
15. patient education/
16. (patient* adj5 educat*).tw.
17. ((lifestyle or life-style) adj5 (interven* or program* or treatment*)).tw.
18. (motivat* adj5 (intervention or interv*)).tw.
19. health education/
20. (health adj5 educat*).tw.
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. exp heart assist device/

23. (ventric* adj2 assist*).tw.
24. VAD.tw.
25. (ventric* adj2 device*).tw.
26. 22 or 23 or 24 or 25
27. 21 and 26
28. random$.tw.
29. factorial$.tw.
30. crossover$.tw.
31. cross over$.tw.
32. cross-over$.tw.
33. placebo$.tw.
34. (doubl$ adj blind$).tw.
35. (singl$ adj blind$).tw.
36. assign$.tw.
37. allocat$.tw.
38. volunteer$.tw.
39. crossover procedure/
40. double blind procedure/
41. randomized controlled trial/
42. single blind procedure/
43. 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 38 or 39 or 40 or 41 or 42
44. (animal/ or nonhuman/) not human/
45. 43 not 44
46. 27 and 45

PsycINFO

1. exp Exercise/
2. SPORTS/
3. Physical Activity/
4. rehabilitat*.tw.
5. (physical* adj5 (fit* or train* or therap* or activit*)).tw.
6. (train* adj5 (strength* or aerobic* or exercise*)).tw.
7. ((exercise* or fitness) adj3 (treatment or intervent* or program*)).tw.
8. mobili*.tw.
9. exp REHABILITATION/
10. kinesiotherap*.tw.
11. Physical Education/
12. (run* or walk* or jog* or danc*).tw.
13. (("lifestyle" or life-style) adj5 (physical* or activ*)).tw.
14. Dance Therapy/
15. Client Education/
16. (patient* adj5 educat*).tw.
17. ((lifestyle or life-style) adj5 (interven* or program* or treatment*)).tw.
18. (motivat* adj5 (intervention or interv*)).tw.
19. Health Education/
20. (health adj5 educat*).tw.
21. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. (ventric* adj2 assist*).tw.
23. VAD.tw.
24. (ventric* adj2 device*).tw.
25. 22 or 23 or 24
26. 21 and 25
27. random$.tw.
28. factorial$.tw.

29. crossover$.tw.
30. cross-over$.tw.
31. placebo$.tw.
32. (doubl$ adj blind$).tw.
33. (singl$ adj blind$).tw.
34. assign$.tw.
35. allocat$.tw.
36. volunteer$.tw.
37. control*.tw.
38. "2000".md.
39. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40. 26 and 39

CPCI-S

18 #17 AND #16 AND #12
17 TS=(random* or blind* or allocat* or assign* or trial* or placebo* or crossover* or cross-over*)
16 #15 OR #14 OR #13
15 TS=(ventric* NEAR/2 device*)
14 TS=VAD
13 TS=(ventric* NEAR/2 assist*)
12 #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
11 TS=(health NEAR/5 educat*)
10 TS=(motivat* NEAR/5 (intervention or interv*))
9 TS=((lifestyle or life-style) NEAR/5 (interven* or program* or treatment*))
8 TS=(patient* NEAR/5 educat*)
7 TS=(("lifestyle" or life-style) NEAR/5 (physical* or activ*))
6 TS=(run* or walk* or jog* or danc*)
5 TS=(mobili* or kinesiotherap*)
4 TS=((exercise* or fitness) NEAR/3 (treatment or intervent* or program*))
3 TS=(train* NEAR/5 (strength* or aerobic* or exercise*))
2 TS=(physical* NEAR/5 (fit* or train* or therap* or activit*))
1 TS=rehabilitat*

CINAHL

S40 S22 AND S27 AND S39
S39 S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38
S38 TX allocat* random*
S37 (MH "Quantitative Studies")
S36 (MH "Placebos")
S35 TX placebo*
S34 TX random* allocat*
S33 (MH "Random Assignment")
S32 TX randomi* control* trial*
S31 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S30 TX clinic* n1 trial*
S29 PT Clinical trial
S28 (MH "Clinical Trials+")
S27 S23 OR S24 OR S25 OR S26
S26 (ventric* N2 device*)
S25 VAD
S24 (ventric* N2 assist*)
S23 (MH "Heart Assist Devices")
S22 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21

S21 (health N5 educat*)
S20 (MH "Health Education")
S19 (motivat* N5 (intervention or interv*))
S18 ((lifestyle or life-style) N5 (interven* or program* or treatment*))
S17 (patient* N5 educat*)
S16 (MH "Patient Education")
S15 (MH "Dance Therapy")
S14 (("lifestyle" or life-style) N5 (physical* or activ*))
S13 (run* or walk* or jog* or danc*)
S12 (MH "Physical Education and Training")
S11 kinesiotherap*
S10 (MH "Rehabilitation+")
S9 mobili*
S8 ((exercise* or fitness) N3 (treatment or intervent* or program*))
S7 (train* N5 (strength* or aerobic* or exercise*))
S6 (MH "Exercise+")
S5 (physical* N5 (fit* or train* or therap* or activit*))
S4 rehabilitat*
S3 (MH "Exertion")
S2 (MH "Sports")
S1 (MH "Therapeutic Exercise+")

LILACS

(exercise$ OR rehabilitat$ OR sport$ or physical$ OR fitness OR activit$ or run$ or walk$ or jog$ or danc$ or train$ or mobili$ or kinesiotherap$ or motivat$ or (patient$ educat$) or (health educat$) or lifestyle) [Words] and ((ventric$ assist$) OR (VAD) OR (ventric$ device$) OR (heart assist$)) [Words]

WHO International Clinical Trials Registry Platform (ICTRP) Search Portal

"ventricular assist device" AND "exercise"
"ventricular assist device" AND "rehabilitation"

ClinicalTrials.gov

"ventricular assist device" AND "exercise"
"ventricular assist device" AND "rehabilitation"

CONTRIBUTIONS OF AUTHORS

Shuhei Yamamoto prepared the drafts of the protocol and full review with support from Kazuki Hotta and Erika Ota. Atsuhiko Matsunaga, Rintaro Mori, and all the other authors provided critical comments on the draft and agreed on the submitted version of this review.

DECLARATIONS OF INTEREST

Shuhei Yamamoto: None known.

Kazuki Hotta: None known.

Erika Ota: None known.

Atsuhiko Matsunaga: None known.

Rintaro Mori: None known.

SOURCES OF SUPPORT

Internal sources

- National Center for Child Health and Development, Japan.

Grant 26A-5

External sources

- Japan Agency for Medical Research and Development, Japan.

AMED No.27300101

- National Institute for Health Research, UK.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Heart Group. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service (NHS), or the Department of Health.

- This work was supported by Japan Society for the Promotion of Science (JSPS), KAKENHI Grant Number JP16H06835, Japan.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.