

Exercise-based cardiac rehabilitation for adults with atrial fibrillation

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[Intervention Review]

Exercise-based cardiac rehabilitation for adults with atrial fibrillation

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ABSTRACT

Background

Exercise-based cardiac rehabilitation may benefit adults with atrial fibrillation or those who had been treated for atrial fibrillation. Atrial fibrillation is caused by multiple micro re-entry circuits within the atrial tissue, which result in chaotic rapid activity in the atria.

Objectives

To assess the benefits and harms of exercise-based rehabilitation programmes, alone or with another intervention, compared with no-exercise training controls in adults who currently have AF, or have been treated for AF.

Search methods

We searched the following electronic databases; CENTRAL and the Database of Abstracts of Reviews of Effectiveness (DARE) in the Cochrane Library, MEDLINE Ovid, Embase Ovid, PsycINFO Ovid, Web of Science Core Collection Thomson Reuters, CINAHL EBSCO, LILACS Bireme, and three clinical trial registers on 14 July 2016. We also checked the bibliographies of relevant systematic reviews identified by the searches. We imposed no language restrictions.

Selection criteria

We included randomised controlled trials (RCT) that investigated exercise-based interventions compared with any type of no-exercise control. We included trials that included adults aged 18 years or older with atrial fibrillation, or post-treatment for atrial fibrillation.

Exercise-based cardiac rehabilitation for adults with atrial fibrillation (Review)

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Data collection and analysis

Two authors independently extracted data. We assessed the risk of bias using the domains outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. We assessed clinical and statistical heterogeneity by visual inspection of the forest plots, and by using standard Chi^2 and I^2 statistics. We performed meta-analyses using fixed-effect and random-effects models; we used standardised mean differences where different scales were used for the same outcome. We assessed the risk of random errors with trial sequential analysis (TSA) and used the GRADE methodology to rate the quality of evidence, reporting it in the 'Summary of findings' table.

Main results

We included six RCTs with a total of 421 patients with various types of atrial fibrillation. All trials were conducted between 2006 and 2016, and had short follow-up (eight weeks to six months). Risks of bias ranged from high risk to low risk. The exercise-based programmes in four trials consisted of both aerobic exercise and resistance training, in one trial consisted of Qi-gong (slow and graceful movements), and in another trial, consisted of inspiratory muscle training.

For mortality, very low-quality evidence from six trials suggested no clear difference in deaths between the exercise and no-exercise groups (relative risk (RR) 1.00, 95% confidence interval (CI) 0.06 to 15.78; participants = 421; $I^2 = 0\%$; deaths = 2). Very low-quality evidence from five trials suggested no clear difference between groups for serious adverse events (RR 1.01, 95% CI 0.98 to 1.05; participants = 381; $I^2 = 0\%$; events = 8). Low-quality evidence from two trials suggested no clear difference in health-related quality of life for the Short Form-36 (SF-36) physical component summary measure (mean difference (MD) 1.96, 95% CI -2.50 to 6.42; participants = 224; $I^2 = 69\%$), or the SF-36 mental component summary measure (MD 1.99, 95% CI -0.48 to 4.46; participants = 224; $I^2 = 0\%$). Exercise capacity was assessed by cumulated work, or maximal power (Watt), obtained by cycle ergometer, or by six minute walking test, or ergospirometry testing measuring VO_2 peak. We found moderate-quality evidence from two studies that exercise-based rehabilitation increased exercise capacity, measured by VO_2 peak, more than no exercise (MD 3.76, 95% CI 1.37 to 6.15; participants = 208; $I^2 = 0\%$); and very low-quality evidence from four studies that exercise-based rehabilitation increased exercise capacity more than no exercise, measured by the six-minute walking test (MD 75.76, 95% CI 14.00 to 137.53; participants = 272; $I^2 = 85\%$). When we combined the different assessment tools for exercise capacity, we found very low-quality evidence from six trials that exercise-based rehabilitation increased exercise capacity more than no exercise (standardised mean difference (SMD) 0.86, 95% CI 0.46 to 1.26; participants = 359; $I^2 = 65\%$). Overall, the quality of the evidence for the outcomes ranged from moderate to very-low.

Authors' conclusions

Due to few randomised patients and outcomes, we could not evaluate the real impact of exercise-based cardiac rehabilitation on mortality or serious adverse events. The evidence showed no clinically relevant effect on health-related quality of life. Pooled data showed a positive effect on the surrogate outcome of physical exercise capacity, but due to the low number of patients and the moderate to very low-quality of the underpinning evidence, we could not be certain of the magnitude of the effect. Future high-quality randomised trials are needed to assess the benefits and harms of exercise-based cardiac rehabilitation for adults with atrial fibrillation on patient-relevant outcomes.

PLAIN LANGUAGE SUMMARY

Exercise-based cardiac rehabilitation for patients with atrial fibrillation

Background

Atrial fibrillation (AF) is the most common irregular heart beat a person can experience. It affects the heart by 'taking over' and sending out electric pulses that makes the heartbeat irregular and inefficient. Symptoms can include irregular heartbeat, shortness of breath, weakness, dizziness, and fainting. Exercise-based cardiac rehabilitation aims to restore health in people with atrial fibrillation or those who have been treated for atrial fibrillation, through regular exercise.

Review question

This systematic review assessed the benefits and harms of exercise-based cardiac rehabilitation in adults with atrial fibrillation.

Study characteristics

We included six randomised trials with a total of 421 participants. The evidence is current to July 2016.

Key results

There were two deaths and eight serious adverse events (harmful side effects) reported in the six trials, therefore, we had insufficient data to conclude whether exercise-based cardiac rehabilitation improved outcomes that matter the most to patients, such as death and serious adverse events (e.g. hospitalisation). Exercise-based rehabilitation was not found to have a clinically relevant impact on quality of life for the patient group, but may increase exercise capacity.

Quality of the evidence

The quality of the evidence ranged from moderate to very low for all outcomes. It was possible for people in the trials to know to which intervention group they were randomised, the reporting of the results was not complete in many trials, and for some outcomes, the results varied across trials. These considerations limit our confidence in the overall results of the review.

Conclusions

Further randomised clinical trials that are conducted with low risks of bias and low risks of the play of chance, in a broader population of patients with AF, are needed to assess the impact of exercise-based interventions.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Exercise compared to No exercise for adults with atrial fibrillation						
Patient or population: adults with atrial fibrillation Setting: in hospital, in municipalities ¹ , and home-based Intervention: Exercise Comparison: No exercise						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with No exercise	Risk with Exercise				
Mortality follow-up: 8 weeks to 6 months	Study population		RR 1.00 (0.06 to 15.78)	421 (6 RCTs)	⊕○○○ VERY LOW ²	Trial sequential analysis (TSA) showed that only 0.15% of the required information size (141,997) was reached
	5 per 1000	5 per 1000 (0 to 76)				
Serious adverse events Follow-up: 8 weeks to 6 months	Study population		RR 1.01 (0.98 to 1.05)	381 (5 RCTs)	⊕○○○ VERY LOW ²	TSA showed that only 1.48% of the required information size (23,723) was reached
	26 per 1000	27 per 1000 (26 to 28)				
Quality of life assessed with SF-36 PCS Scale: 0 to 100 Higher = better Follow-up: 20 weeks to 6 months	The mean quality of life in the control groups ranged from 47.9 to 49.5 points			224 (2 RCTs)	⊕⊕○○ LOW ³	TSA showed that the required information size of 185 participants was reached. This led us to conclude that any possible intervention effect, if any, was less than 7 points
	The mean quality of life in the exercise groups was 1.96 points higher (2.5 lower to 6.42 higher)					
Quality of life assessed with SF-36 MCS Scale: 0 to 100	The mean quality of life in the control groups was 51.9 points			224 (2 RCTs)	⊕⊕○○ LOW ³	TSA showed that the required information size of 57 participants was reached. This led us to
	The mean quality of life in the exercise groups was 1.99 points higher (0.48 lower to 4.46					

Higher = better Follow-up: 20 weeks to 6 months		higher)			conclude that any possible intervention effect, if any, was less than 7 points
Exercise capacity measured by different tools Follow-up: 8 weeks to 4 months		The standardised mean mean difference for exercise capacity was 0.86 more in the exercise groups (0.46 higher to 1.26 higher)	359 (6 RCTs)	⊕○○○ VERY LOW ⁴	Exercise capacity assessed with VO ₂ peak in two trials, 6-minute walking test in three trials, and by cycle ergometer test in one trial
Exercise capacity assessed with VO ₂ peak Higher = better Follow-up: 4 months to 5 months.	The mean exercise capacity in the control groups ranged from 20.7 to 32.1 mL/kg/min	The mean exercise capacity was 3.76 mL/kg/min higher in the exercise groups (1.37 higher to 6.15 higher)	208 (2 RCTs)	⊕⊕⊕○ MODERATE ⁵	TSA showed the alpha-spending boundaries for benefit were crossed, indicating that sufficient information was obtained, and the result was not due to random error
Exercise capacity assessed with 6-minute walking test Higher = better Follow-up: 12 weeks to 4 months	The mean exercise capacity ranged from 406.38 to 602 meters	The mean exercise capacity was 76.76 meters higher in the exercise group (14 higher to 137.53 higher)	272 (4 RCTs)	⊕○○○ VERY LOW ³	TSA showed that the required information size (3392) was not reached when assessing a minimal relevant difference of 25 meters

*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; RR: Risk ratio; OR: Odds ratio;

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

SF-36 = Short Form-36

PCS = physical component summary measure

MCS = mental component summary measure

¹ Training centres could be located in the municipalities (outside the hospitals), they were run by physiotherapists hired by the municipalities.

² Downgraded by 3 levels because of serious limitations in study design (1 level) and very serious risk of imprecision (2 levels).

³ Downgraded by 2 levels because of a very serious limitation in study design (risk of bias due to lack of blinding and incomplete outcome data).

⁴ Downgraded by 3 levels because of very serious limitations in study design (2 levels) and serious risk of imprecision (1 level).

⁵ Downgraded by 1 level because of a serious limitation in study design (1 level).

BACKGROUND

Description of the condition

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia (irregular heart beat). It affects 1.5% to 2% of the population in Europe and North America (Ball 2013; Kirchhof 2016; Nguyen 2013). The incidence of AF is increasing, mainly due to the ageing population (Ball 2013; Camm 2012; Go 2001; Ruigomez 2005; Stewart 2001). Atrial fibrillation is associated with increased mortality, heart failure, stroke, and other thromboembolic events (Camm 2010; Kirchhof 2016; Kirchhof 2007; Stewart 2002). As such, AF has now become a health, social, and economic burden (Brenyo 2011), and is expected to worsen over the coming decades (Camm 2012).

Patients with AF can experience palpitations, shortness of breath, fatigue, dizziness, and syncope (fainting) (Kirchhof 2016). An American observational study of 655 individuals found that AF symptoms are a negative predictor for patients' physical capacity (Atwood 2007). Symptoms and duration of AF episodes vary within the individual, and from individual to individual (Kirchhof 2016). Five different types of AF exist: first-diagnosed AF, paroxysmal AF, persistent AF, long-standing persistent AF, and permanent AF (Kirchhof 2016). First-diagnosed AF is the term given to the condition when a patient presents with AF for the first time, regardless of the duration of the arrhythmia, or the presence and severity of AF-related symptoms. Paroxysmal AF is self-limited, and usually the rhythm converts spontaneously to sinus rhythm within 48 hours. In persistent AF, the AF episode lasts longer than seven days, or requires cardioversion to end the episode. When the duration of AF exceeds one year, AF is considered to be long-standing persistent. Finally, permanent AF is when AF is accepted without further attempts of conversion, or these attempts have been shown to be unsuccessful or short-lasting (Kirchhof 2016; Lafuente-Lafuente 2012).

Treatment of AF focuses on re-establishing and maintaining sinus rhythm (so-called rhythm control) and protecting the patient against thromboembolic complications (Kirchhof 2016). When AF is longer-lasting (as in persistent AF, long-standing persistent AF, and permanent AF), an additional therapeutic goal is to control the heart rate in the range of 60 to 80 beats/minute at rest, and 90 to 115 beats/minute when active (rate control). This is achieved by treatment with antiarrhythmic drugs, which block the function of the atrioventricular node (Brenyo 2011; Kirchhof 2016). Treatment should also aim at reducing symptoms and discomfort related to AF (Brenyo 2011).

Acute management of patients with AF includes acute conversion to sinus rhythm, protection against thromboembolic events, and acute improvement of cardiac function. However, AF recurrence is common despite administration of antiarrhythmic drugs to maintain normal sinus rhythm after cardioversion (Kirchhof 2016).

Radiofrequency ablation is sometimes used to treat AF. It is an invasive treatment developed to cure AF. In a Cochrane systematic review, Chen and colleagues found that ablation had a better effect in inhibiting recurrence of AF compared with medical therapies, but there was limited evidence demonstrating that sinus rhythm was maintained after ablation and after long-term follow-up (Chen 2012). Despite the results of the systematic review, ablation seems to have an increasingly accepted role in the treatment of AF (Brenyo 2011; Calkins 2009; Kirchhof 2016).

Studies have found that quality of life is impaired in individuals with AF compared to healthy controls, the general population, or patients with coronary heart disease in the western world (Dabrowski 2010; Kang 2004; Thrall 2006). Studies have suggested that maintaining sinus rhythm improves quality of life, and may be associated with improved survival (Dabrowski 2010; Dorian 2000; Dorian 2002; Kang 2004; McCabe 2011; Thrall 2006). If patients lack self-management skills, they can experience distress when trying to handle symptoms of AF, such as palpitations, dyspnoea, and fatigue. Some patients with AF report that they have not received education or help from health professionals regarding how to live with AF (McCabe 2011; Lane 2015).

Description of the intervention

Cardiac rehabilitation provides beneficial effects in patients following myocardial infarction and percutaneous coronary intervention and in those with heart failure, by improving physical, mental, cognitive, and social function; and reducing the risk of mortality, hospitalisation, and healthcare costs (Anderson 2016; Piepoli 2014; Taylor 2014). While there are many definitions of cardiac rehabilitation, the following presents the combined key elements: "The coordinated sum of activities required to favourably influence the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that patients may, by their own efforts, preserve or resume optimal functioning in their community, and through improved health behaviour, slow or reverse progression of disease" (BACPR 2012). According to this definition, cardiac rehabilitation is a complex, comprehensive intervention that should include not only exercise training, but also education and psychosocial management, and a behavioural modification programme designed to improve the physical and emotional well-being of patients with heart disease (Piepoli 2014). Cardiac rehabilitation can include patient assessments, nutritional counselling, and risk factor management focusing on lipids, blood pressure, weight, diabetes mellitus, and smoking cessation (Piepoli 2014).

Studies of exercise training for patients with AF have used various protocols, indicating the uncertainty of what should be the precise exercise advice for patients with AF. A review of exercise rehabilitation for AF that included 36 studies (six randomised clinical trials) in 1512 patients, made the following recommendations for exercise training: (1) include three or more weekly sessions of

moderate intensity whole-body aerobic activities (such as walking, jogging, cycling, or rowing); (2) each session should be at least 60 minutes long; continue the sessions for at least three months; and (3) sessions should include stretching, balance exercises, resistance training, and callisthenics (Giacomantonio 2013). The review included studies with a variety of different designs, and did not consider rehabilitation components other than exercise training. Current recommendations for rehabilitation following myocardial infarction, percutaneous coronary intervention, heart valve replacement, and heart failure recommend that psychosocial or educational support, or both, should be offered to patients, in addition to exercise training (National Board of Health 2013). However, no such national or international recommendation for rehabilitation is currently provided for patients with AF. A systematic review including 30 studies of mixed designs exploring rehabilitation for patients living with permanent AF, reported that no studies had included psychosocial support, education, or both, with the aim of improving the patient's self-management skills (Lowres 2011).

How the intervention might work

At present, the effect of exercise-based cardiac rehabilitation on total mortality, serious adverse events, and health-related quality of life for patients with AF remains uncertain. Existing evidence from both randomised clinical trials and observational studies indicates that exercise-based interventions positively affect heart rate control, exercise capacity, symptom burden, improves symptom and disease management, decrease rates of anxiety and depression, and increases quality of life for patients with AF (Giacomantonio 2013; Hegbom 2006; Osbak 2011; Reed 2013).

The general cardiovascular mechanisms of physical exercise in the healthy individual include an increase in heart rate, blood pressure, whole body oxygen uptake, facilitated by brainstem cardiovascular activation (Hambrecht 2000). Cardiovascular adaptation to dynamic physical exercise increases cardiac chamber size, facilitating an increased stroke volume, lowers blood pressure, lowers resting heart rate, and improves endurance training, by promoting volume hypertrophy due to increased wall stretch and increased venous return (Hawley 2014). Physical exercise also increases activity in the parasympathetic nervous system, resulting in an increase in heart rate variability, a blunted arterial baroreflex response, and an impaired heart rate response to atropine, which independently decreases the risk of death (Levy 1998). Overall, physical inactivity is an independent predictor of morbidity and all-cause cardiovascular mortality (Blair 1996; Myers 2002).

Evidence shows that exercise training for cardiac patients, has benefits on the heart and coronary vasculature, including myocardial oxygen demand, endothelial function, autonomic tone, coagulation and clotting factors, inflammatory markers, and the development of coronary collateral vessels (Clausen 1976; Hambrecht 2000). A randomised trial including 30 patients with permanent

AF showed that exercise capacity and heart rate variability improved after two months of exercise training, compared with no exercise training (Hegbom 2006). A prospective uncontrolled pilot study in 10 patients with AF, found that among older individuals with AF, exercise training decreased the ventricular rate at rest and during exercise, and increased exercise capacity following regular moderate physical activity (Plisiene 2008). Similarly, a pre-post study of 20 patients showed increases in physical capacity (a 15% increase measured by maximum oxygen uptake (VO₂ max)) after exercise (Mertens 1996). In a randomised clinical trial including 49 patients with permanent AF, Osbak and colleagues concluded that exercise capacity measured by VO₂ peak improved significantly after 12 weeks of exercise training compared to no exercise (Osbak 2011).

We might anticipate the same, or similar effects of exercise-based cardiac rehabilitation, as seen in other cardiac populations who typically receive cardiac rehabilitation, i.e., those with myocardial infarction, post percutaneous intervention, and heart failure. Two Cochrane reviews have shown that exercise-based cardiac rehabilitation has a number of positive effects in these latter populations that include reductions in deaths and hospitalisation, and improvements in health-related quality of life (Anderson 2016; Taylor 2014).

Possible harmful effects of exercise-based cardiac rehabilitation for patients with AF could include increased risk of adverse events (e.g. arrhythmias) or serious adverse events like hospitalisation because of exercise-induced AF. A review reported serious adverse events to be 2/560 (2 events of Ischaemic chest pain in 560 patients with AF), and non-serious adverse events to be 43/560 (43 events of exercise-induced AF), which the authors considered to be a low risk (Giacomantonio 2013).

We have not been able to find examples of integrated rehabilitation programmes for patients with AF, or guidelines outlining recommendations for rehabilitation for patients with AF, but Hendriks and colleagues found, in a randomised trial, that follow-up in a nurse-led AF clinic significantly reduced cardiovascular hospitalisations and mortality compared with usual care (Hendriks 2012; Hendriks 2014). They also found that the AF-related knowledge level was higher in the nurse-led group at one year follow-up, compared with the control group that received usual care (Hendriks 2014).

In summary, studies show that exercise training has some positive effects on patients with AF. However, few studies have included psycho-educational interventions, which may offer further benefit to AF patients, such as improvements in mental health. Evidence exploring mortality and re-hospitalisation is lacking.

Why it is important to do this review

Three reviews have sought to assess the effects of exercise training for patients with AF (Giacomantonio 2013; Lowres 2011; Reed 2013). In terms of informing rehabilitation practice for AF pa-

tients, these reviews have a number of limitations: lack of published protocol before being conducted (Giacomantonio 2013; Lowres 2011; Reed 2013); focused solely on exercise training (Giacomantonio 2013; Reed 2013); included observational studies (Giacomantonio 2013; Lowres 2011; Reed 2013); and none of the reviews presented potential harms (Reed 2013). This Cochrane review aims to overcome these limitations by assessing the evidence from randomised trials, and investigating both the benefits and harms of exercise-based rehabilitation in patients with AF. We will consider not only trials of exercise training alone, but also trials that include a psycho-educational interventional component, based on our published protocol (Risom 2013).

OBJECTIVES

To assess the benefits and harms of exercise-based rehabilitation programmes compared with no exercise training controls in adults who currently have AF, or have been treated for AF. We will consider programmes that include exercise training alone or with another intervention (such as a psycho-educational component).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised clinical trials regardless of language, publication year, publication type, and publication status.

Types of participants

Adult patients (18 years old or older) of both sexes and of all ethnicities, who currently have AF, or who have been treated for AF. We included patients regardless of the type of AF, and the treatment of the arrhythmia.

Types of interventions

Experimental intervention

The rehabilitation programme had to include exercise training. Exercise-based interventions were defined as: any rehabilitation programme in an inpatient, outpatient, or community- or home-based setting that was provided for a patient with AF. The rehabilitation programme must have included an exercise training component; it may also have included a psycho-educational component.

The exercise component had to focus on strengthening the patient's exercise capacity, and preferably improve their rate control (i.e. reduced maximum heart rate during exercise). The psycho-educational component had to focus on psychosocial support or education, aiming to improve the patient's self-management skills. There were no restrictions in the length, intensity, or content of the training programme.

Control intervention

We included the following control interventions:

- Treatment as usual (e.g. standard medical care, such as drug, and ablation therapy).
- No intervention.
- Any other type of cardiac rehabilitation programme, as long as it did not include a physical exercise element.

The last point was added after the protocol was published to include a comprehensive answer to the objectives in the review.

Co-interventions

We included trials with co-interventions other than rehabilitation as long as they were equally delivered in the experimental and control groups. Co-interventions could include: drugs, ablation techniques, or dietary interventions.

Types of outcome measures

We assessed all outcomes at two time points:

- end of intervention (as defined by the trialists); and
- longest available follow-up.

There was no minimum length of follow-up for the studies that were eligible for the review.

Primary outcomes

1. Mortality: all-cause mortality and cardiovascular mortality.
2. Serious adverse events: defined as any untoward medical occurrence that was life threatening, resulting in death, or that was persistent or leading to significant disability; any medical event, which had jeopardised the patient or required intervention to prevent it; any hospital admission, or prolongation of existing hospital admission (ICH-GCP 2015).
3. Health-related quality of life using generic or disease-specific validated instruments, e.g. Short Form-36 (SF-36), or Minnesota Living with Heart Failure questionnaire.

Secondary outcomes

1. Exercise capacity: any measure of exercise capacity, including direct measurement of oxygen uptake (VO₂ peak or VO₂ max), or indirect measures such as exercise time, walking distance, etc.

2. Symptoms including palpitations, dyspnoea, dizziness, and episodes of AF during the intervention period (Kirchhof 2016).
3. Return to work, or loss of employment.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases from their inception to 14 July 2016, to identify reports of relevant randomised clinical trials:

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 6) in the Cochrane Library (searched 14 July 2016);
2. The Database of Abstracts of Reviews of Effectiveness (DARE; 2015, Issue 2) in the Cochrane Library (searched on 14 July 2016);
3. Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE Ovid (1946 to 14 July 2016);
4. Embase Classic, Embase Ovid (1947 to 2016 week 28);
5. PsycINFO Ovid (1806 to July week 2 2016);
6. Web of Science Core Collection Thomson Reuters (1990 to 14 July 2016);
7. CINAHL EBSCO (1937 to 14 July 2016);
8. LILACS Bireme (1987 to 14 July 2016).

The search strategy for MEDLINE Ovid was adapted for use in the other databases (Appendix 1). The Cochrane sensitivity-maximising randomised clinical trial filter for MEDLINE was applied and adapted for the other databases where applicable (Lefebvre 2011).

We also conducted a search for adverse effects in the following databases, from their inception to 14 July 2016.

1. Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE Ovid (1946 to 14 July 2016);

2. Embase Classic, Embase Ovid (1947 to 2016 week 28). The search strategies are in Appendix 1. An adverse effects filter was applied using terms as recommended in the *Cochrane Handbook of Systematic Reviews of Interventions* (Loke 2011).

Searching other resources

We searched the following clinical trial registries on 16 September 2016, to identify ongoing trials. See the search strategy in Appendix 1:

1. ClinicalTrials.gov (www.clinicaltrials.gov);
2. Controlled-trials.com (www.controlled-trials.com);
3. The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; apps.who.int/trialsearch/).

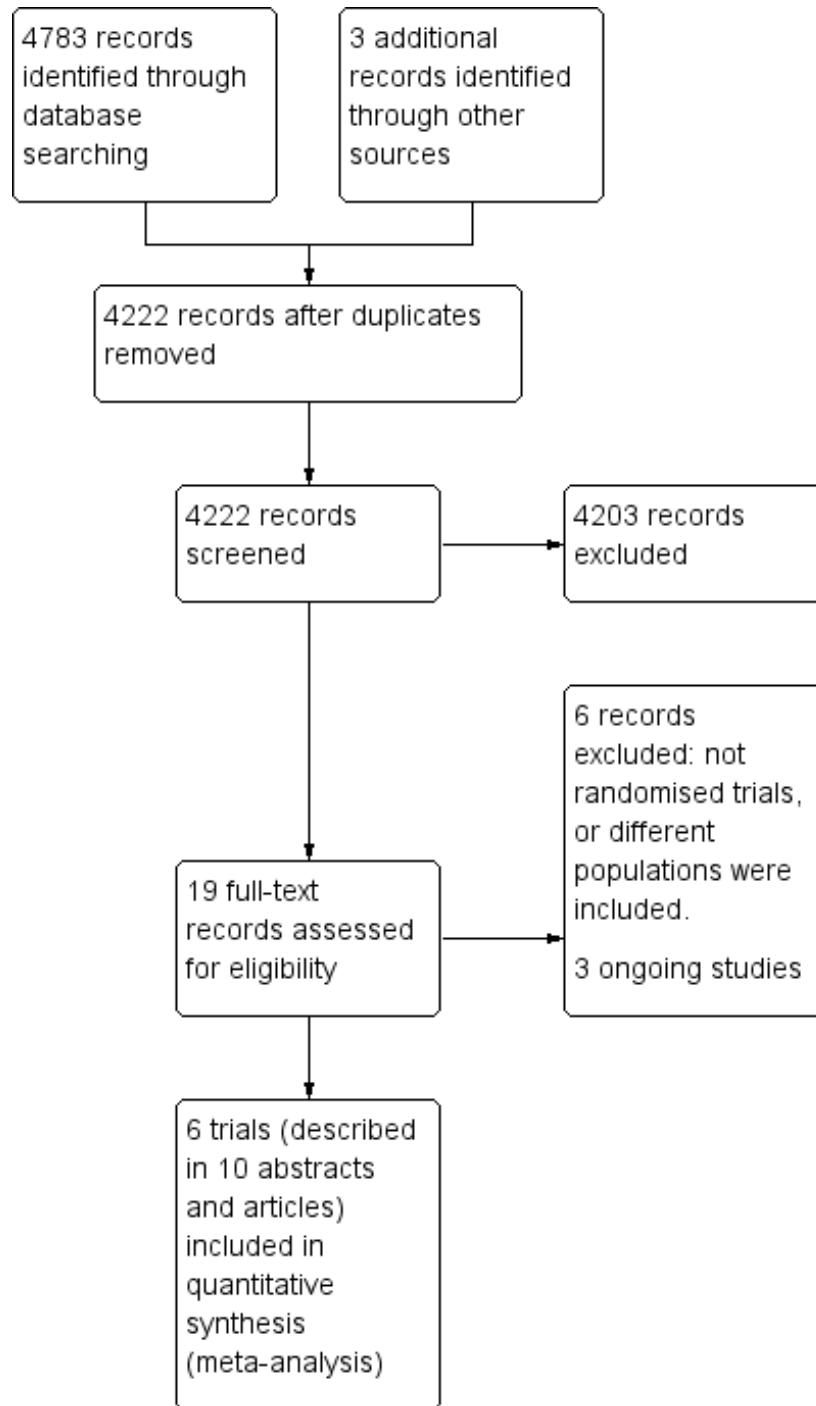
We checked the reference lists of publications for included studies for any unidentified randomised trials. We did not impose any language restrictions.

Data collection and analysis

Selection of studies

Two authors (SSR and PPJ) independently read titles and abstracts of all publications identified from searches and excluded studies that did not meet the inclusion criteria. We retrieved full-text copies of all potentially relevant studies, and the same two authors independently assessed them for eligibility, based on the defined inclusion criteria. The authors resolved disagreements by discussion, and when necessary, a third author (SKB) was asked to mediate. The study selection process was documented using a PRISMA study selection flow chart (Figure 1); excluded studies with reasons for their exclusion were detailed in the [Characteristics of excluded studies](#) table.

Figure 1. Study flow diagram



Data extraction and management

Two authors (SSR and PPJ) independently extracted data from the identified trials using standardised data extraction forms. For the trial conducted by some of the authors in this review, data were extracted by RST, who was not involved in the trial (Risom 2016). Where data were presented both numerically (in tables or text) and graphically (in figures), we used numeric data, because of possible measurement error when estimating from graphs. A third author (SKB) confirmed all numeric calculations and extractions from graphs or figures. We resolved any discrepancies by consensus. SSR entered data into Cochrane's statistical software Review Manager 5 (RevMan 5 2014). In those cases where there were not sufficient data or data were unclear in the published trial reports, we contacted authors, then them to clarify the missing information.

We extracted the following data.

1. General information: published or unpublished, title, authors' names, source, country, contact address, language of publication, year of publication, duplicate publication, funding.
2. Study characteristics: design, duration of follow up.
3. Interventions: type and dose of exercise training, other rehabilitation interventions, setting (i.e. inpatient, outpatient, or home), time after hospitalisation, and type of control (e.g. intervention or conventional care).
4. Participants: inclusion and exclusion criteria, number of participants in intervention and control group, patient demographics (including sex and ethnicity), clinical characteristics (including type of AF), and losses to follow-up.
5. Outcomes: mortality (all-cause mortality, cardiovascular mortality), serious adverse events defined above, health-related quality of life (using generic or disease-specific validated instruments), exercise capacity, symptoms (including palpitations, dyspnoea, dizziness, and attacks during the intervention period), return to work or loss of employment.
6. Risk of bias: see [Assessment of risk of bias in included studies](#) below.

We sought to compare data from each intervention group of each parallel group trial; for cross-over trials, we had planned only to use data from the first phase of the trial (i.e. before cross-over).

Assessment of risk of bias in included studies

Two authors (SSR and PPJ) independently assessed the risk of bias of the included trials using Cochrane's tool for assessing risk of bias (Higgins 2011a). Disagreements were resolved by discussion.

Overall risk of bias

We categorised a trial as being at low risk of bias if the trial was rated at low risk in all the domains listed below. We categorised a trial as being at high risk of bias if the risk of bias was rated as either uncertain or high in any of the domains listed below. We expected all trials to be categorised at an overall high risk of bias, as it is not possible to blind participants and personnel (Savovic 2012; Wood 2008). Therefore, we also categorised trials as being at a lower risk of bias, if a trial was rated low risk of bias in all the domains listed below except blinding of participants and personnel. For viewing the bias risk domains see [Appendix 2](#).

Measures of treatment effect

Dichotomous outcomes were expressed as a risk ratio (RR) with 95% confidence intervals (CI). Continuous outcomes were expressed as a mean difference (MD) between intervention groups. We preferred not to calculate effect size measures (standardised mean difference (SMD)), however, when studies used different instruments to assess the same outcome (e.g. quality of life or exercise capacity), we calculated and pooled effect sizes using the SMD and transformed the effect back to the units of one or more of the specific instruments (Higgins 2011).

Unit of analysis issues

For cluster-randomised trials, we had planned to contact the trial authors to obtain an estimate of the intra-cluster correlation (ICC) when appropriate adjustments for the correlation between participants within clusters had not been made, or impute it using estimates from the other included trials, or from similar external trials. We included one trial that used a cross-over design, from which we only included participants in the analysis before the cross over.

Dealing with missing data

We obtained missing data by contacting the authors of the trials, if possible. When data remained unavailable, we assessed and discussed the impact of the missing data.

We analysed dichotomous outcomes according to the intention-to-treat method, which included all participants regardless of compliance or follow-up (Higgins 2011b; Sterne 2011). For the primary analyses, we assumed that participants lost to follow-up were alive, had no serious adverse events, and did not experienced loss of employment. We conducted sensitivity analyses (see below). For continuous outcomes, we analysed available patient data and only included data of those for whom results were known (Sterne 2011). Where mean (M) and standard deviations (SD) were missing, we obtained those directly from the authors. We had also planned to obtain SDs by calculation, or by imputing SDs from

other included trials, specifically trials with a low risk of bias, however, that was not necessary in this review.

Assessment of heterogeneity

We explored clinical heterogeneity by comparing the population, experimental intervention and control intervention. We observed statistical heterogeneity in the trials both by visual inspection of a forest plot and by using a standard Chi^2 value with a significance level of $P = 0.10$. We assessed heterogeneity using the I^2 statistic. We interpreted an I^2 estimate of at least 50% and a statistically significant Chi^2 statistic as evidence of a substantial problem with heterogeneity (Higgins 2011).

Assessment of reporting biases

Small study (publication) bias

We had planned to construct funnel plots for each outcome for which there were at least ten trials, or all trials were of similar sizes, to establish the potential influence of small study effects and potential publication bias (Furukawa 2006). Therefore, due to the limited number of included studies (six studies), we were not able to construct funnel plots.

Data synthesis

We performed data synthesis according to recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and statistical analyses using the latest version of Review Manager 5 (RevMan 5 2014), and Trial Sequential Analysis software (TSA 2011). We used both random-effects and fixed-effect models for meta-analyses (Deeks 2011; DeMets 1987; DerSimonian 1986). We presented results from the random-effects model when heterogeneity was high and from fixed-effects when heterogeneity was low. When different measuring scales were used (e.g. exercise capacity) to measure the same outcome, we reported data from each measuring scale, and finally calculated a SMD.

Trial Sequential Analysis

Trial sequential analysis was the planned application to control risks of random errors, because cumulative meta-analyses are at risk of producing such errors due to sparse data and repetitive testing on the accumulating data (Thorlund 2009a; Thorlund 2009b; TSA 2011; Wetterslev 2008; Wetterslev 2009). The underlying assumption of trial sequential analysis is that testing for significance may be performed each time a new trial is added to the meta-analysis. To minimise random errors, we calculated the required information size (i.e. the number of participants needed in a meta-analysis to detect or reject a certain intervention effect (Wetterslev

2008)). We adjusted the required information size with the diversity (D-square) of the meta-analysis (Wetterslev 2009). We added the trials according to the year of publication, and if more than one trial was published in a year, we added trials alphabetically, by the last name of the first author (Wetterslev 2008).

In our meta-analysis, the diversity-adjusted required information size for binary outcomes was based on the assumption of a plausible relative risk reduction (RRR) of 20% from the proportion with the outcome in the control group (Wetterslev 2008). For continuous outcomes, we had planned to assess a minimal relevant difference of 0.5 SDs, using the SD in the control group. However, instead, we used a minimal relevant difference of seven points for the SF-36 physical and mental component scales (Berg 2015; Dorian 2000), 3 mL/kg/min for VO_2 peak (Mertens 1996), and 25 meters for the six-minute walking test (ATS statement 2002; Wise 2005; Gremeaux 2011). These differences were decided before the TSAs were conducted. As a default, we used a type I error of 5%, a type II error of 20%, and diversity-adjusted required information size, unless otherwise stated (Wetterslev 2008; Wetterslev 2009).

We constructed trial sequential monitoring boundaries on the basis of the required information size and the risks for type I and type II errors (TSA 2011; Wetterslev 2008). These boundaries determine the statistical inference that may be drawn regarding the cumulative meta-analysis. If the monitoring boundaries for benefits or harms are crossed before the diversity-adjusted required information size is reached, it is possible that firm evidence may be established, and further trials may turn out to be superfluous, at least for the postulated intervention effect. On the other hand, if the boundaries are not surpassed, it would most probably be necessary to continue conducting trials in order to detect or reject a certain intervention effect.

Subgroup analysis and investigation of heterogeneity

We had planned to perform subgroup analyses on the primary outcomes using stratified meta-analysis. However, due to the small number of included trials and participants, small number of events, and poor reporting within the trials, this was not possible. In the future, we plan to perform subgroup analyses on the following.

- Trials including women compared to trials including men.
- Trials including younger patients compared to trials including older patients, defined by the trialists or by mean age.
- Trials with exercise intervention only, compared to trials with exercise intervention plus any other co-intervention, such as psycho-educational intervention.
- Participants with persistent AF compared to participants with paroxysmal AF.
- Hospitalisation after rehabilitation because of AF compared to no hospitalisation because of AF.

Sensitivity analysis

In the future, for the primary outcomes, we plan to perform sensitivity analyses on the following:

- Trials with overall low risk of bias. If no trials are categorised as overall low risk of bias, we will analyse trials with overall lower risk of bias separately.

Dichotomous outcomes

Best-worst case scenario

For this analysis, we assumed that all participants lost to follow-up in the experimental group had not experienced the outcome (e.g. death), and all those with missing outcomes in the control group had experienced the outcome (e.g. death).

Worst-best case scenario

For this analysis, we assumed that all participants lost to follow-up in the experimental group had experienced the outcome (e.g. death), and all those with missing outcomes in the control group had not experienced the outcome (e.g. death).

Continuous data

Assumptions for lost data

It was not necessary to make any assumptions for lost continuous data in this review (see [Dealing with missing data](#)). However, had it been necessary, we would have compared the findings from our assumptions with data only from those participants who completed the trials.

Summary of findings

We developed a 'Summary of findings' table, which incorporates GRADE methods to assess the quality of the body of evidence supporting each of the major outcomes in our review; please see [Summary of findings for the main comparison](#) (Guyatt 2008). For our assessments, we evaluated the risk of bias, inconsistency, imprecision, directness, and risk of publication bias. We used GRADEpro GDT software to create 'Summary of findings' table (GRADEpro GDT 2014). Our decisions were guided by the GRADE guidelines (Andrews 2013a; Andrews 2013b; Balshem 2011; Brunetti 2013; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2011h; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Mustafa 2013).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

Our electronic searches for this review yielded a total of 4222 titles (following removal of duplicates). After reviewing titles and abstracts, we retrieved 19 records for possible inclusion. After examining the texts, six articles and three ongoing studies were excluded, and ten records (abstracts and full-text articles) on six randomised clinical trials were included. The study selection process is summarised in the PRISMA flow diagram shown in [Figure 1](#). The information on the three ongoing trials can be found in the [Characteristics of ongoing studies](#) table.

Included studies

We included six trials, with a total of 421 patients, described in ten abstracts and papers, which compared exercise-based rehabilitation versus no intervention or treatment as usual for patients with AF or patients who had been treated for AF (Hegbom 2006; Malmo 2016; Osbak 2011; Pippa 2007; Risom 2016; Zeren 2016). Details of included trials are provided in the [Characteristics of included studies](#) tables.

One trial had a cross-over design, where the patients in the control group received the intervention after the control period (Hegbom 2006). We have only included the patient data from the first part of the trial (intervention N = 15; control N = 15).

One trial was conducted in Norway (Hegbom 2006), two in Denmark (Osbak 2011; Risom 2016), one in Italy (Pippa 2007), one in Sweden (Malmo 2016), and one in Turkey (Zeren 2016).

All trials reported outcomes at the end of the intervention, which was either eight weeks (Hegbom 2006), 12 weeks (Osbak 2011; Zeren 2016), 16 weeks (Pippa 2007), 20 weeks (Malmo 2016), or six months post-randomisation (Risom 2016).

All six trials compared an exercise training programme with no additional interventions; one trial included two hours of education on best practices for cardiovascular risk management for both the intervention and the control groups (Pippa 2007), and one trial included psycho-educational consultations as a supplement to the physical exercise (Risom 2016).

The exercise training interventions differed in duration (8 weeks to 16 weeks), frequency (from twice a day, seven days a week, to two or three sessions per week), and session length (15 minutes, to 90 minutes per session). The exercise training sessions were supervised or non-supervised home-based sessions. In four of the trials, the intervention consisted of aerobic training and cool down and warm-up periods (Hegbom 2006; Malmo 2016; Osbak 2011;

Risom 2016). The aerobic training was undertaken at an intensity corresponding to 70% of maximal exercise capacity (Osbaek 2011), 70% to 90% of maximum heart rate (Hegbom 2006), or up to 85% to 95% of peak heart rate (Malmo 2016). In one trial, the Borg scale was used and intensity was progressively increased during the weeks (Borg 11 to 17 (Risom 2016)), another trial used 85% to 90% of maximal heart rate and Borg 6 to 20 in four-minute intervals (Malmo 2016).

In the one trial, the intervention consisted of Qi-gong, which is slow and graceful movements with a focus on breathing, with the aims of inducing emotional control, increasing muscle tone, and enhancing body flexibility and strength (Pippa 2007). Another trial included an intervention that consisted of inspiratory muscle training at 30% of maximal inspiratory pressure (Zeren 2016).

All six trials recruited adult patients with, or treated for, AF. Three trials included patients with permanent AF (Hegbom 2006; Osbaek 2011; Zeren 2016); in one trial, the patients were diagnosed with AF at least three months prior to the start of the trial and were taking anticoagulant treatment for at least two months (Pippa 2007). Another trial recruited patients who had had an ablation for

paroxysmal or persistent AF (Risom 2016), and one trial recruited patients with nonpermanent AF (Malmo 2016).

Excluded studies

After review of the full-text reports, six publications of six studies were excluded from the review. One abstract was excluded since no intervention was applied (Angergard K 2015), and one was excluded because the control group also received the experimental intervention (Borland 2015). Two studies were excluded since patient groups other than patients with AF were included (Kim 2014; Frederix 2015), and two studies were excluded as no randomisation was performed (Mertens 1996; Vanhees 2000). The three ongoing studies were excluded since no results were presented (see Ongoing studies).

Risk of bias in included studies

See Figure 2 for overview of risk of bias in the included trials. The six trials demonstrated various risks of bias across the domains.

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Groups balanced at baseline	Groups received same intervention (performance bias)	For-profit-bias	Intention-to-treat
Hegbom 2006	?	?	?	?	+	?	+	?	?	-
Malmo 2016	?	?	-	+	+	+	+	-	+	+
Osbak 2011	+	+	-	?	+	+	+	?	+	+
Pippa 2007	+	+	?	?	+	?	+	?	?	+
Risom 2016	+	+	-	+	-	+	+	+	+	+
Zeren 2016	+	+	-	+	-	+	+	+	+	-

Allocation

Randomisation was adequately reported in four trials. In one trial, random sequence generation was generated by a random numbers table (Pippa 2007), one was generated by a random list (Osbaek 2011), one was computer-generated (Risom 2016), and one used pre-filled envelopes (Zeren 2016). Allocation concealment was secured by computer-generated allocation in three trials, and sealed envelopes in one trial, as previously described. Two trials did not describe their method of allocation (Hegbom 2006; Malmo 2016).

Blinding

It is not possible to blind patients, clinicians or carers in studies of exercise-based cardiac rehabilitation. However, outcome assessment should be blinded to patient allocation. Four of the trials stated that they took measures to blind outcome assessment (Malmo 2016; Osbaek 2011; Risom 2016; Zeren 2016).

Incomplete outcome data

We judged all trials to be at low risk for incomplete outcome data. Information about all patients was available, and the number and reasons for dropouts and withdrawals were properly described in all trials. In the trial by Risom and colleagues, a larger number of patients did not complete all assessments, which is described in the trial (Risom 2016).

Selective reporting

All outcomes described in the method sections were reported in all trials. One trial had documented the hierarchy of outcomes in a published design article (Risom 2013).

Other potential sources of bias

Groups balanced at baseline

In all trials, the intervention groups appeared to be balanced at baseline.

Groups received same intervention (performance bias)

One trial used a cross-over design, which meant that we only used the before cross-over data (Hegbom 2006). In the trial by Pippa and colleagues, both groups received two hours of cardiovascular disease training, but they did not describe what kind of standard care the control group received otherwise (Pippa 2007). Osbaek and colleagues described that the patients in the control group were advised to continue a habitual physical activity, but they did not

describe if the groups received any standard care (Osbaek 2011). Patients in the control groups received standard medical treatment in two trials (Risom 2016; Zeren 2016), and in one trial, patients continued their previous exercise habits (Malmo 2016).

For-profit-bias

Three trials described their funding sources as being from independent private sources or grants from national government funds (Malmo 2016; Osbaek 2011; Risom 2016). Two trials did not describe funding sources (Hegbom 2006; Pippa 2007). One trial did not receive any funding to conduct the trial (Zeren 2016).

Intention-to-treat analysis

Although not stated, three trials appeared to undertake an intention-to-treat analysis as groups were analysed according to the initial random allocation (Malmo 2016; Osbaek 2011; Pippa 2007); one trial used intention-to-treat analysis (Risom 2016); and one trial did not use intention-to-treat in the analysis (Zeren 2016). The impact of loss to follow-up was not examined in the trials.

Small-trial bias

There were insufficient trials to assess for small trial effects, or to assess whether the effect estimated varied systematically according to sample size.

Effects of interventions

See: [Summary of findings for the main comparison Exercise compared to No exercise for adults with atrial fibrillation](#)

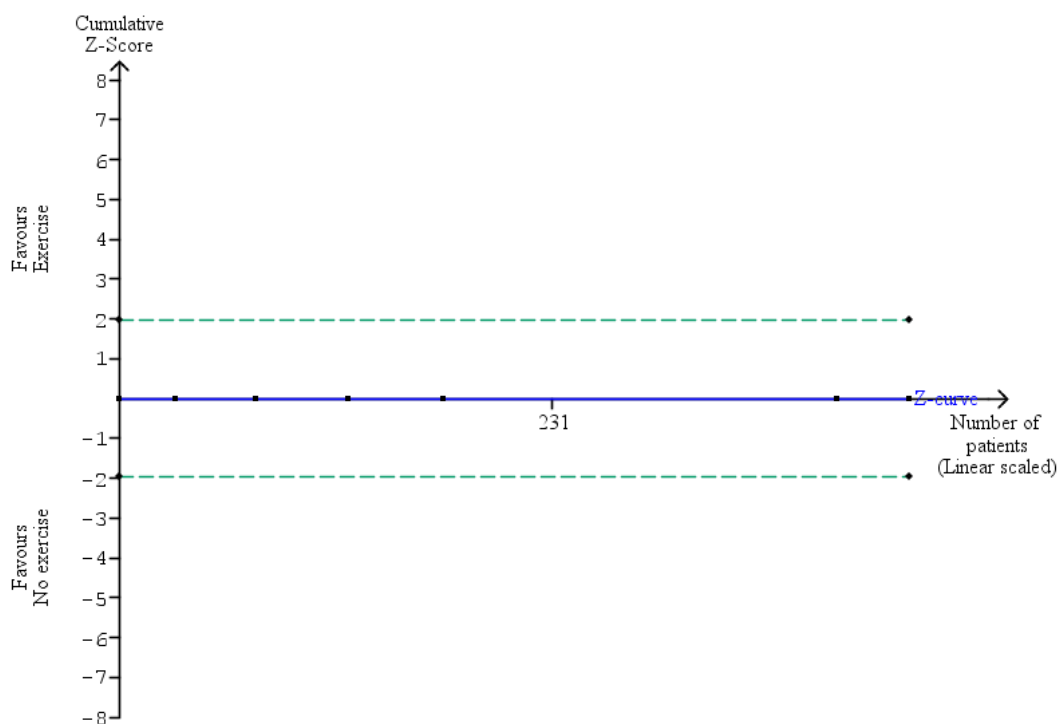
Primary outcomes

Mortality (all-cause mortality and cardiovascular mortality)

Two deaths were reported in one of the six trials, one death in each group (Risom 2016). A trial physician judged both deaths to be unrelated to the intervention or the trial. Very low-quality evidence from pooled results showed no clear difference between groups (RR 1.00, 95% CI 0.06 to 15.78; participants = 421; studies = 6; $I^2 = 0\%$; Analysis 1.1).

Trial sequential analysis (TSA) showed that the diversity-adjusted required information size of 140,645 participants was not reached, as the accrued number of participants was only 421 (0.3%). We assumed a control event proportion of 0.5% (as observed in the control group), and used an empirical continuity correction of 0.01 for zero event trials (Figure 3).

Figure 3. Mortality. Trial Sequential Analysis on mortality in the six trials was performed based on the proportion with mortality in the control group set at 0.5%, a relative risk reduction of 20%, a type I error of 5%, a type II error of 20% (80% power), and diversity of 1%. The diversity-adjusted required information size was 140,645 participants. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of P = 0.05. The cumulative Z-curve (blue line) does not cross the conventional statistical boundaries. The trial sequential monitoring boundaries and the diversity-adjusted required information size are not shown as the accrued number of participants only amounted to 421/140,645 (0.3%).



Sensitivity analysis

We performed sensitivity analysis to assess the possible impact of data loss on death. Taking the worst-best case assumption that all patients lost to follow-up in the exercise group died, and the patients with missing outcomes in the no-exercise control group survived, there was no clear difference between groups in mortality (RR 0.83, 95% CI 0.26 to 2.65; participants = 421; studies = 6; $I^2 = 0\%$; [Analysis 1.2](#)); we also found no clear difference when taking the best-worst case assumption (lost to follow-up in exercise group

survived and lost to follow-up in the control group died (RR 0.59, 95% CI 0.08 to 4.35; participants = 421; studies = 6; $I^2 = 0\%$; [Analysis 1.3](#))).

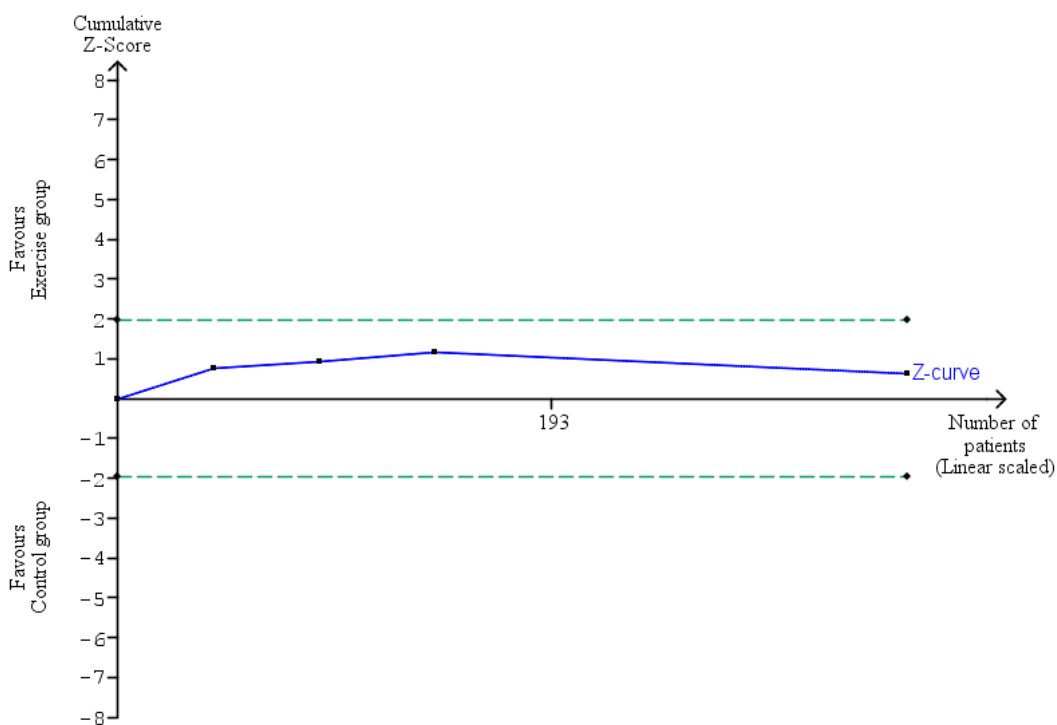
Serious adverse events

Only one of the trials stated that they formally collected serious adverse events as an outcome ([Risom 2016](#)). Nevertheless, five trials did report a total of eight serious adverse events; see additional [Table 1](#) ([Hegbom 2006](#); [Malmo 2016](#); [Osbaek 2011](#); [Pippa 2007](#);

Risom 2016). We found very low-quality of no clear difference between groups in the number of patients with serious adverse events (exercise-based rehabilitation: 3/192 (1.56%) versus control: 5/189 (2.65%); the RR for non-events was 1.01, 95% CI 0.98 to 1.05; participants = 381; studies = 5; $I^2 = 0\%$; Analysis 1.4).

Trial sequential analysis showed that the diversity-adjusted information size of 23,723 participants was not reached. We assumed a control event proportion of 2.9% (as observed in the control group), and used an empirical continuity correction of 0.01 for zero event trials (Figure 4).

Figure 4. Serious adverse events. Trial Sequential Analysis on serious adverse events in four trials was performed based on the proportion with serious adverse events in the control group set at 2.9%, a relative risk reduction of 20%, a type I error of 5%, a type II error of 20% (80% power), and diversity of 0%. The diversity-adjusted required information size was 23,723 participants. The blue line represents the cumulative Z-score of the meta-analysis. The light blue lines represent the conventional statistical boundaries of $P = 0.05$. The trial sequential monitoring boundaries and the diversity-adjusted required information size are not shown as the accrued number of participants only amounted to 351/23723 (1.48%).



Sensitivity analysis

We found no clear differences in the risk of serious adverse events in the sensitivity analyses; worst-best case scenario (assuming all rehabilitation group drop-outs experienced a serious adverse event, and all control group drop-outs did not (RR 1.46, 95% CI 0.54 to 3.97; participants = 383; studies = 5; $I^2 = 0\%$; Analysis 1.5)); and best-worst case scenario (assuming rehabilitation group drop-outs did not experience a serious adverse event, and all control drop-outs did (RR 0.65, 95% CI 0.19 to 2.24; participants = 383; studies = 5; $I^2 = 0\%$; Analysis 1.6)).

Health-related quality of life (HRQL)

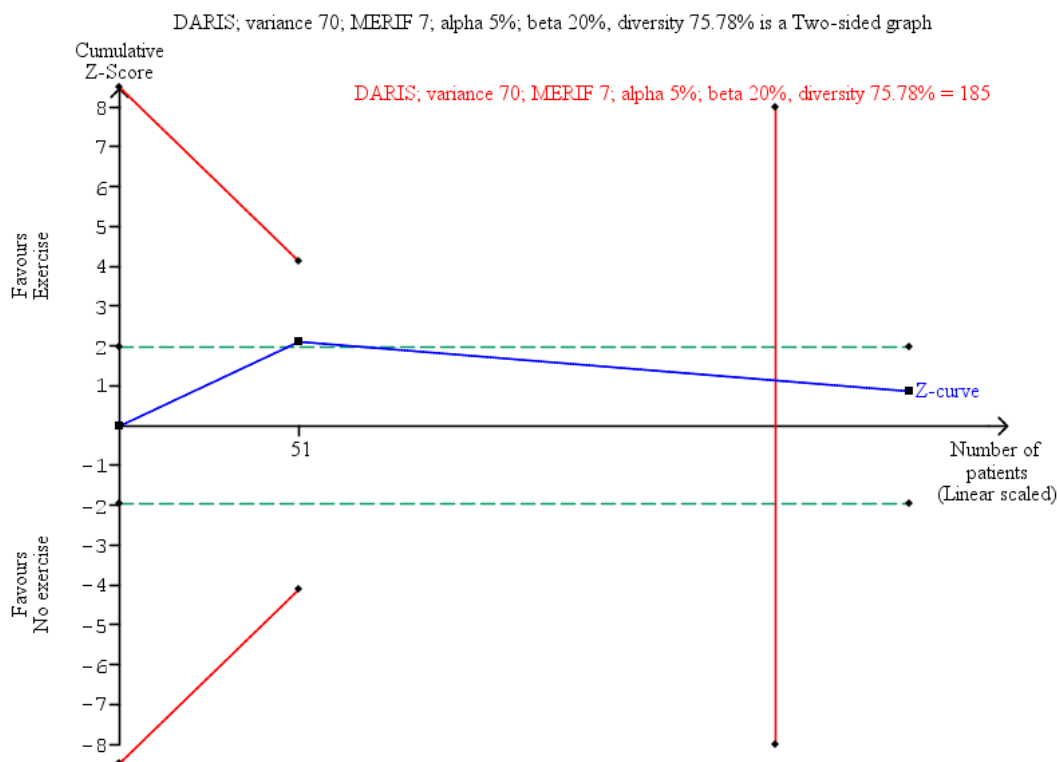
We have provided an overview of the tools used to measure HRQL in Table 2. Four trials reported HRQL measured by SF-36 (Hegbom 2006; Malmo 2016; Osbak 2011; Risom 2016).

Hegbom 2006 only reported combined results for the intervention and control groups, therefore, we were unable to include those results in the meta-analysis (Hegbom 2006).

SF-36 physical component summary measures (PCS)

Malmo 2016 and Risom 2016 reported results for the mental (MCS) and physical component summary measures (PCS). When we pooled results from the PCS, we found low-quality evidence of no clear difference between groups (MD 1.96, 95% CI -2.50 to 6.42; participants = 224; studies = 2; $I^2 = 69\%$; Analysis 1.7). We performed TSA on these two trials (Figure 5). We found that the cumulative Z-score crossed the diversity-adjusted required information size, indicating that sufficient information was provided. Thus, we could conclude that a possible intervention effect, if any, was less than seven points.

Figure 5. Quality of life, SF-36 physical component score. Trial sequential analysis on quality of life assessed with SF-36 physical component score assessing a minimal relevant clinical difference of 7 points, and variance of 70 points (empirical data), was performed based on a type I error of 5%, a type II error of 20% (80% power), and diversity of 75.78%. The diversity-adjusted required information size was 175 participants. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of $P = 0.05$. The red inward sloping lines represent the trial sequential monitoring boundaries. The cumulative Z-curve crossed the diversity-adjusted required information size (red vertical line), indicating that sufficient information was provided.

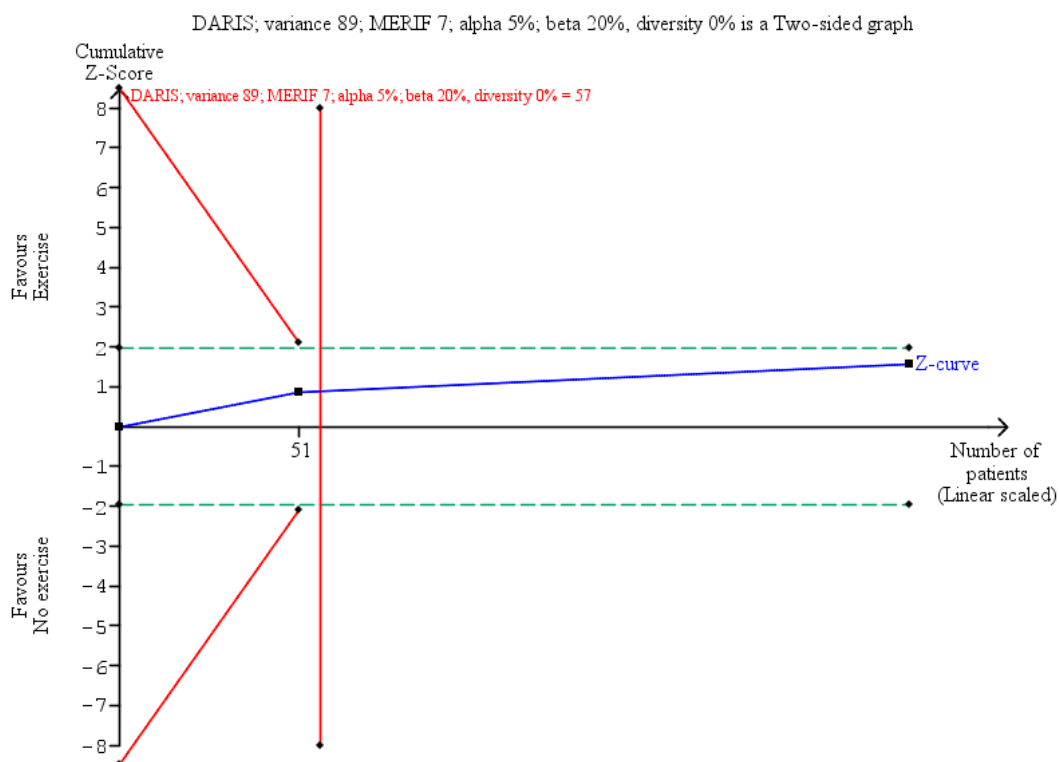


SF-36 mental component summary measures (PCS)

We found low-quality evidence of no clear difference between groups for the MCS, (MD 1.99, 95% CI -0.48 to 4.46; participants = 224; studies = 2; $I^2 = 0\%$; Analysis 1.8 (Malmö 2016; Risom 2016)).

We performed TSA on these two trials (Figure 6). We found that the cumulative Z-score crossed the diversity-adjusted required information size, indicating that sufficient information was provided. Thus, we could conclude that a possible intervention effect, if any, was less than 7 points.

Figure 6. Quality of life, SF-36 mental component score. Trial sequential analysis on quality of life assessed with SF-36 mental component score assessing a minimal relevant clinical difference of 7 points, and variance of 89 points (empirical data), was performed based on a type I error of 5%, a type II error of 20% (80% power), and diversity of 0%. The diversity-adjusted required information size was 57 participants. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of $P = 0.05$. The red inward sloping lines represent the trial sequential monitoring boundaries. The cumulative Z-curve (blue line) did not cross the trial sequential monitoring boundaries for benefit or harm (red inward sloping lines). The cumulative Z-curve crossed the diversity-adjusted required information size (red vertical line) indicating that sufficient information was provided.



SF-36 subscale summary measures

Three trials reported results for the eight subscales for SF-36 (Malmö 2016; Osbak 2011; Risom 2016). We found low-quality evidence from pooled data of the subscales (Analysis 1.12; Analysis 1.13):

- Physical function: MD 1.46, 95% CI -1.26 to 4.18; participants = 274; studies = 3; I² = 0%;
- Role physical: MD 2.79, 95% CI -0.52 to 6.10; participants = 274; studies = 3; I² = 0%;
- Bodily pain: MD 0.73, 95% CI -3.99 to 5.45; participants = 274; studies = 3; I² = 23%;
- General health: MD 7.11, 95% CI 3.46 to 10.77; participants = 273; studies = 3; I² = 0%;
- Vitality: MD 6.10, 95% CI 1.91 to 10.30; participants = 274; studies = 3; I² = 0%;
- Social functioning: MD 2.85, 95% CI -0.72 to 6.41; participants = 274; studies = 3; I² = 0%.
- Role emotional: MD 2.91, 95% CI -1.69 to 7.50; participants = 275; studies = 3; I² = 0%;
- Mental health: MD 2.09, 95% CI -1.08 to 5.26; participants = 274; studies = 3; I² = 0%;

Minnesota Living with Heart Failure questionnaire (MLHF-Q)

One study used the MLHF-Q questionnaire to measure self-rated quality of life, and reported a statistically insignificant difference between groups in the global score (MLHF-Q total potential) in favour of the exercise group, measured at post-intervention follow-up (exercise group mean 15 points, SD 17 points versus no exercise group mean 23 points, SD 21 points, $p=0.13$) (Osbak 2011). The trialists did not report if this difference was clinically relevant.

Hospital Anxiety and Depression scale (HADS)

One study also reported a statistical insignificant difference between groups at follow-up in the HADS-anxiety scale (exercise group 3.85 points versus no exercise group 3.8 points, $p=0.09$) and in the HADS-depression scale (exercise group 2.92 points versus no exercise group 2.36 points, $p=0.41$) (Risom 2016).

Exercise capacity

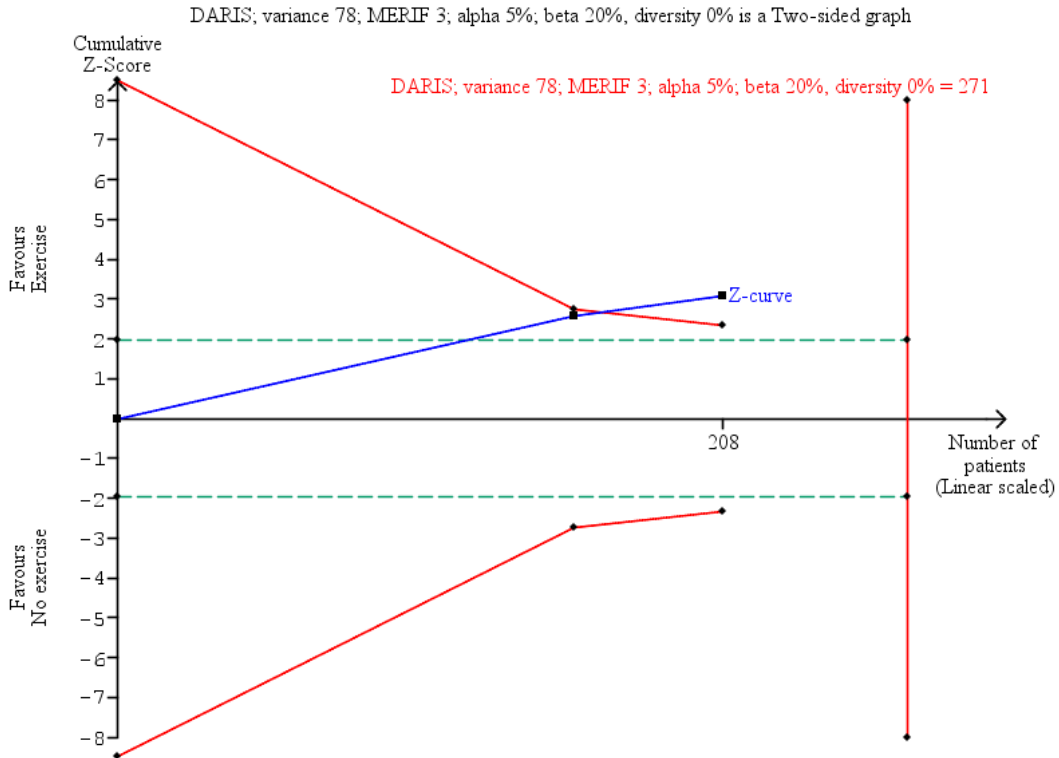
Exercise capacity was assessed by measuring cumulated work (Hegbom 2006), or maximal power (Watt (Osbak 2011)), obtained with a cycle ergometer; a six-minute walking test (6MWT (Osbak 2011; Pippa 2007; Risom 2016; Zeren 2016)), or ergospirometry testing that measured VO₂ peak (Malmö 2016; Risom 2016).

VO₂ peak

We found moderate-quality evidence from pooled data that exercise-based rehabilitation increased exercise capacity compared with no exercise, measured at the end of intervention (MD 3.76, 95% CI 1.37 to 6.15; participants = 208; studies = 2; I² = 0%; Analysis 1.17).

We performed TSA on exercise capacity, assessed with VO₂ peak with a minimal relevant clinical difference of 3 mL/kg/min, variance of 78 mL/kg/min (empirical data), based on a type I error of 5%, a type II error of 20% (80% power), and diversity of 0% (Figure 7). The diversity-adjusted required information size of 271 participants was not met. However, the cumulative Z-curve crossed the trial sequential monitoring boundaries for benefit, indicating that sufficient information had been obtained, and the result was not due to random error.

Figure 7. Exercise capacity, VO2 peak. Trial sequential analysis on exercise capacity assessed with VO2 peak assessing a minimal relevant clinical difference of 3 mL/kg/min, and variance of 78 mL/kg/min (empirical data), was performed based on a type I error of 5%, a type II error of 20% (80% power), and diversity of 0%. The diversity-adjusted required information size was 271 participants. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of P = 0.05. The red inward sloping lines represent the trial sequential monitoring boundaries. The cumulative Z-curve (blue line) crosses the trial sequential monitoring boundaries for benefit, indicating that sufficient information was obtained.



Six-minute walking test (6MWT)

We found very low-quality evidence from pooled data that exercise-based rehabilitation increased exercise capacity, measured by 6MWT, compared with no exercise at the end of the intervention (MD 75.76, 95% CI 14.00 to 137.53; participants = 272; studies = 4; I² = 85%; [Analysis 1.18](#)). The TSA showed that there was not enough information to confirm or reject a difference of 25 meters ([Figure 8](#)).

Figure 8. Physical capacity, 6-minute walking test. Trial sequential analysis on exercise capacity assessed with 6-minute walking test assessing a minimal relevant clinical difference of 25 meters, and variance of 8280 m (empirical data), was performed based on a type I error of 5%, a type II error of 20% (80% power), and diversity of 87.74%. The diversity-adjusted required information size was 3392 participants. The blue line represents the cumulative Z-score of the meta-analysis. The green lines represent the conventional statistical boundaries of $P = 0.05$. The cumulative Z-curve (blue line) crosses the conventional statistical boundaries. However, the trial sequential monitoring boundaries and the diversity-adjusted required information size are not crossed, indicating that insufficient information is obtained.



Cumulated work

One study reports that exercise-based rehabilitation increased exercise capacity statistically significant compared with no exercise at post intervention follow-up (exercise group mean 2,077 watts (SD 753 watts) versus no exercise group mean 1,152 watts (SD 341 watts), $p < 0.001$) (Hegbom 2006).

Maximal power

One study reports that exercise-based rehabilitation increased exercise capacity statistically significantly compared with no exercise at post-intervention follow-up (exercise mean 174 watt (SD 56 watt) versus no exercise mean 127 watt (SD 37 watt), $p = 0.002$) (Osbaek 2011).

Standardised mean difference estimate of effect

We combined the results from the three different assessment tools in a meta-analysis to determine a pooled estimate of effect, and found very low-quality evidence that exercise-based rehabilitation increased exercise capacity compared with no exercise at the end of intervention (SMD 0.86, 95% CI 0.46 to 1.26; participants = 359; studies = 6; $I^2 = 65\%$; Analysis 1.19).

AF symptoms

Three trials reported AF symptoms (Hegbom 2006; Malmo 2016; Risom 2016). One study measured AF symptoms at post-intervention follow-up with the Symptom and Severity Checklist questionnaire (Malmo 2016). They found a larger decrease in the exer-

cise group compared to the no exercise group in AF frequency (exercise mean 11.5 points (SD 5.3 points) versus no exercise mean 16.7 points (SD 5.2 points); and AF severity (exercise mean 8.1 points (SD 6.1 points) versus no exercise mean 14.1 points (SD 3.5 points), however the authors did not report if the difference was statistically or clinically significant. One study reported post-intervention AF symptoms on the entire population (including cross-over data), therefore, the data are observational (Hegbom 2006). It reported no change in AF symptom frequency measured on the Symptom and Severity Checklist at baseline (mean 14 points (SD 5 points) and after exercise training (mean 12 points (SD 7 points). No data were reported for the control group. One study reported self-reported AF symptoms related to physical exercise (exercise group n = 2, no exercise group n = 1) and not related to physical exercise (exercise group n = 1, no exercise group n = 2) (Risom 2016).

Employment loss or return to work

None of the trials reported employment loss or return to work.

Subgroup analyses

There were insufficient trials to undertake subgroup analyses.

Summary of findings tables

We found very low-quality evidence for mortality, serious adverse events, exercise capacity assessed with 6MWT, and exercise capacity estimated with SMD. We found low-quality evidence for quality of life assessed with the SF-36 physical and mental component summary measures, and moderate-quality evidence for exercise capacity assessed with VO₂ peak (Summary of findings for the main comparison).

DISCUSSION

Summary of main results

This systematic review identified six randomised clinical trials with a total of 421 patients that compared exercise-based cardiac rehabilitation with a no exercise control. The exercise-based programmes in four trials consisted of both aerobic exercise and resistance training or joint movements (Hegbom 2006; Malmö 2016; Osbak 2011; Risom 2016); the exercise-based programme in (Pippa 2007) consisted of Qi-gong (slow and graceful movements that is reported to increase muscle tone and enhance body flexibility and strength; and in (Zeren 2016), the exercise-based programme consisted of inspiratory muscle training at 30% of maximal inspiratory pressure. All six trials complied with the European Society of Cardiology recommendation for physical activity

for secondary prevention (Piepoli 2014)). There were inadequate data to assess the impact of exercise-based cardiac rehabilitation on the primary outcomes of mortality and serious adverse events. Regarding health-related quality of life, the trial sequential analysis showed that there were adequate data to make conclusions for the SF-36 mental and physical component summary measures, but the pooled data showed no beneficial effects of exercise training on these measures. The quality of evidence was low for those outcomes.

We found moderate to very low-quality of evidence from pooled estimates that exercise training led to short-term improvements in exercise capacity, measured at the end of intervention. This effect could have been due to the high risks of bias and imprecision, as the trial sequential analysis showed that the required information size was not reached. Due to lack of data, we could not assess the impact of exercise-based cardiac rehabilitation on the other secondary outcomes of this review: symptoms including palpitations, dyspnoea, dizziness, and AF episodes during the intervention period, return to work, or loss of employment (Kirchhof 2016).

Because of the overall low quality of evidence, exercise should still only be provided in randomised clinical trials and tested against no intervention. From more trials, we can achieve adequate information on patients with AF, so we can assess the risk of important, patient-relevant, primary outcomes.

Overall completeness and applicability of evidence

The generalisability of this review is limited by the low number of randomised clinical trials, the low number of patients with AF included, and the few patients with outcomes. The included trials all recruited highly selected study populations. In three of the trials, the participants had permanent AF (Hegbom 2006; Osbak 2011; Zeren 2016), in one trial, the patients had to be symptomatic, and have non-permanent AF to be included (Malmö 2016), another trial required the patients to have had AF for at least three months (Pippa 2007), and one trial included patients if they had been treated with an ablation for paroxysmal or persistent AF (Risom 2016). The patients were primarily younger men, who were willing to participate in an exercise training programme.

Only one of the trials included two centres for recruitment (Risom 2016); the other five trials were single-centre trials (Hegbom 2006; Malmö 2016; Osbak 2011; Pippa 2007; Zeren 2016). Taken together, these factors potentially limit the applicability of this review to the broader group of AF patients. However, given the potential safety considerations in this population, recruitment to trials of exercise-based rehabilitation is likely to be limited to highly selected study populations. Larger multi-centre trials of exercise-rehabilitation with a broader population of patients with AF are warranted.

Quality of the evidence

The overall risk of bias summary shows that in some trials, lack of reporting of methods in the included randomised trials, especially blinding of patients, personnel, and outcome assessment, made it difficult to assess their methodological quality and thereby judge their risk of bias. Other trials described their methodology in more depth and therefore, we classified some of the bias domains as low risk of bias. Using the GRADE methodology and 'Summary of findings' table, we assessed the quality of the evidence to range from moderate to very low across the outcomes. We were able to judge the minimal clinically important difference for the major predefined outcomes but not the minor outcomes.

Potential biases in the review process

We conducted the review according to the recommendations provided in the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2011a).

We followed our peer-reviewed and pre-published protocol in order to avoid biases during the conduct and write-up of the review. In addition, we performed a comprehensive literature search to identify published and unpublished trials. We contacted study authors for further information.

Our review has some limitations. As already stated, the majority of included trials were relatively small and were all of short-term follow-up, therefore, the numbers of reported events were small. Only one of the trials sought to formally collect data on mortality and serious adverse events as outcomes. Therefore, inclusions of these outcomes in this review have been based on our judgments of the descriptions of losses to follow-up, and data provided by the authors on request.

Agreements and disagreements with other studies or reviews

Our findings are broadly in accord with three reviews of exercise-training for AF (Giacomantonio 2013; Lowres 2011; Reed 2013). All three reviews included randomised trials plus other studies of various designs. Some of the same randomised clinical trials that we included in this systematic review were identified in the reviews (Hegbom 2006; Osbak 2011; Pippa 2007).

Similar to our findings, mortality was not reported in most reviews. One review (Lowres 2011) looked for mortality in their included studies and found that only one trial reported deaths (Vanhees 2000) - two cardiac-related deaths and one death from stroke during the intervention period or at least 48 hours after participating in exercise training. Other Cochrane reviews evaluating rehabilitation for patients with heart failure and coronary heart disease have reported that mortality is the same or lower in the cardiac rehabilitation group compared with the control group (Anderson 2014; Anderson 2016; Taylor 2014).

One review (Giacomantonio 2013) found that out of 560 patients with AF in their systematic review, there were two life-threatening events reported in the included studies. We find that out of the six trials we included, five trials reported few serious adverse events. Cochrane reviews exploring re-hospitalisation among patients who have participated in cardiac rehabilitation because of heart failure or coronary heart disease, found a trend towards lower hospitalisation rates in patients who participated in cardiac rehabilitation compared with patients in the control group (Anderson 2016; Taylor 2014). Taken together, it seems likely that it is safe for patients with AF to participate in exercise-based cardiac rehabilitation programmes. However, firm evidence is lacking.

In (Lowres 2011) and (Reed 2013), they reported that health-related quality of life was measured in few studies in their systematic reviews. They found that health-related quality of life was improved on some of the SF-36 domains, and that the physical component summary was significantly improved ($P < 0.05$) in two trials (Lowres 2011). As described in the results, we did not find a beneficial effect of rehabilitation on health-related quality of life measured on the SF-36. The SF-36 is designed to measure general health and physical function rather than disease-specific symptoms and challenges related to life with AF, and therefore, it can be discussed how well the SF-36 measures health-related quality of life among patients with AF or those who have been treated for AF (Aliot 2014).

Our finding that exercise-based cardiac rehabilitation may increase physical capacity in the short term is consistent with the previous systematic reviews by Lowres and colleagues and Reed and colleagues (Lowres 2011; Reed 2013). (Lowres 2011) included randomised trials and prospective cohort studies published in English, and found a statistically significant increase in physical capacity in most trials after participating in cardiac rehabilitation. (Reed 2013) found that exercise capacity improved in all included trials after exercise intervention. However, neither review followed a pre-published protocol, they were limited to English literature only, and included studies of various designs.

Studies have suggested that maintaining sinus rhythm improves quality of life (Dabrowski 2010; McCabe 2011; Thrall 2006), and patients can experience distress when trying to handle symptoms of AF such as palpitations, dyspnoea, and fatigue (McCabe 2011). Therefore, we wanted to assess these issues in this review. We found that only two of the included trials assessed symptom severity as an outcome (Hegbom 2006; Malmo 2016). Hegbom 2006 found that symptom frequency did not change statistically before and after a physical exercise intervention. However, they did find a statistically significant difference in symptom severity. Hegbom had chosen an incomplete cross-over study design, where patients served as their own controls. Because of that and the small sample size, it was not possible to draw a conclusion based on this trial. Malmo 2016 found that patients in the exercise group experienced fewer symptoms after the physical exercise program compared to the patients in the no exercise group.

Adherence to the rehabilitation programme was discussed in three of the six included trials. [Pippa 2007](#) described how three participants did not participate in the full rehabilitation programme due to lack of interest (two participants), and to retinal embolism (one participant), but since they all participated in more than half of the intervention sessions, they were included in the final analysis. [Malmo 2016](#) described six patients who completed less than 80% of the exercise programme due to intercurrent infections and musculoskeletal symptoms. [Risom 2016](#) also described adherence to the programme, defined as at least 75% adherence; 44% of the patients adhered to both the exercise and psycho-educational programme. There is a need for more focus on adherence in future rehabilitation research to be able to analyse the effect of the rehabilitation programmes in more detail, and to know if lack of effect is due to low adherence to the programme ([Anderson 2014](#)).

As the trials in this review reported few deaths and only few serious adverse events in the short follow-up, we cannot judge the possible long-term harms of exercise-based cardiac rehabilitation for adults with AF. Therefore, future research needs to address long-term harms of exercise training. In [Giacomantonio 2013](#), they reported serious adverse events and adverse events among all the patients with AF in the studies they had included (N = 1120) and found that two patients experienced a life-threatening event and 43 patients experienced a non-life-threatening event per 13,628 exercise sessions (an estimated total 519,412 minutes of exercise). In summary, the findings of this review are broadly in accord with previous systematic reviews of exercise-training for AF ([Giacomantonio 2013](#); [Lowres 2011](#); [Reed 2013](#)). However, all three reviews included non-randomised studies, which are associated with increased risk of selection bias, overestimation of benefits, and underestimation of harms ([Jakobsen 2013](#)). Reporting bias cannot be ruled out if studies do not explicitly report having had a protocol. Also, when including non-randomised studies, we need to consider how potential confounders are addressed, and consider the likelihood of increased heterogeneity resulting from residual confounding and from other biases that vary across studies.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review shows that there was limited and low-quality evidence that assessed the impact of exercise-based cardiac rehabilitation for adults with AF or those who were treated for AF. There was insufficient evidence to decide if exercise-based rehabilitation should be provided for patients with AF. Furthermore, the

trials were conducted primarily in younger males, therefore, these potential benefits may not be generalisable to the wider community of patients with AF or those who were treated for AF. Our findings were in line with the European Society of Cardiology guidelines that do not recommend exercise-based cardiac rehabilitation for patients with AF because of lack of evidence ([Kirchhof 2016](#)). In particular, the impact of exercise-based cardiac rehabilitation on mortality and serious adverse events remains unclear, with low- to very low-quality evidence.

Implications for research

Adequately powered randomised trials, conducted with low risk of bias are needed to determine whether the effects of exercise-based cardiac rehabilitation reported in small short-term trials can be confirmed for outcomes that matter most to patients (i.e. mortality, serious adverse events, and health-related quality of life). Multi-centre trials that include comprehensive cardiac rehabilitation that test not only exercise training, but also risk-factor education and counselling, and psychosocial interventions should be the focus of future trials of exercise-based rehabilitation in patients with AF. Future trials should be designed according to the SPIRIT guidelines and reported according to the CONSORT statements for non-pharmacological trials ([Chan 2013](#); www.consort-statement.org).

Patients included in exercised-based cardiac rehabilitation studies are typically highly selected. We still do not know if cardiac rehabilitation for patients with AF is safe, due to a small number of non-serious and serious adverse events reported by the trials identified in this review. Also, criteria and predictors to identify the patients who benefit most from rehabilitation are still lacking. Until more trials providing higher quality evidence exist, exercise-based cardiac rehabilitation should be tailored and adjusted throughout as necessary.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Hegbom 2006

Methods	RCT cross-over design, Single centre Norway	
Participants	<p>N = 30 (Intervention N = 15; control N = 15). Numbers of participants lost to follow up: 2. Number of early drop outs: 1. Number with complications:1 (respiratory infection). Sex: male 87.5%. Age: Intervention 62 years (SD 7); control: 62 years (SD 7.) Diagnosis; AF type: Permanent AF. Ethnicity: Not reported. Inclusion: Permanent AF, age younger than 75 years, and willing to participate in a 2-month training program Exclusion: Patients who already participated in exercise training more than twice weekly, who had medical contraindications to exercise, or those unable to participate for any logistic reason Time after hospitalisation: Not reported.</p>	
Interventions	<p>Intervention: Duration: 1.25 hr class, 3 sessions/week for 8 weeks. Consisting of 5 minutes of warm-up, three 15-minute periods of aerobics at HRmax, interrupted by strengthening exercise for the back, thighs, and stomach. The session ended with a 5-minute cool down followed by 15 minutes of stretching and relaxation. intensity: 70% to 90% of maximum heart rate. Modality: Not reported. The sessions were supervised and held at one of two rehabilitation centres Control: Controls did not perform physical exercise. Other: Patients were also encouraged to be generally physically active during the training period</p>	
Outcomes	<p>Relevant outcomes: QoL by SF-36, exercise testing by cycle ergometer test, measured by cumulated work that was calculated by adding the workload every minute, symptoms severity checklist Other outcomes: 24-hour Holter recording, activities of daily living</p>	
Notes	follow up 8 weeks.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not described.
Allocation concealment (selection bias)	Unclear risk	not described.

Hegbom 2006 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% of the participants were not analysed.
Selective reporting (reporting bias)	Unclear risk	We could not identify any protocol published before the trial was conducted. All outcomes described in the method section of the paper were reported
Groups balanced at baseline	Low risk	Groups were balanced at baseline according to the authors.
Groups received same intervention (performance bias)	Unclear risk	Both groups received an exercise training programme, but one group worked as control group
For-profit-bias	Unclear risk	Not described.
Intention-to-treat	High risk	Intention-to-treat not used.

Pippa 2007

Methods	RCT; Single centre, Italy; 16-week follow-up
Participants	<p>N = 43 (Intervention N = 22; control N = 21). Numbers of participants lost to follow up: 0. Number of early drop outs: 3. Number with complications: 2 (one with retinal embolism and one had deep vein thrombosis) Sex: male Intervention 63.6%; control 76.2%. Age: Intervention 68.3 years (SD 7.2); control 67.8 years (SD 9.1) Diagnosis; AF type: Permanent AF defined as at least 3 months with AF Ethnicity: 100% Caucasian. Inclusion: diagnosed with AF at least 3 months prior, and were taking anticoagulant treatment for at least 2 months Exclusion: ejection fraction < 30%, New York Heart Association class III-IV, or both, history or suspicion of a recent thromboembolic event, recent heart rate instability, or other indication for electrocardiographic monitoring during exercise training, chronic systemic diseases in the acute phase, bone or joint conditions limiting exercise training, major logistic impairments, involvement in regular training programs, and inability to give informed consent</p>

Pippa 2007 (Continued)

	Time after hospitalisation: Not reported.	
Interventions	<p>Intervention: program consisted of two sessions/week (90 min) for 16 weeks of qigong. Qigong consist of slow and graceful movements with a focus on breathing. All classes were assisted by a physician and a therapist. Qigong is reported to induce emotional control, increase muscle tone, and enhance body flexibility and strength</p> <p>Control: No intervention.</p> <p>Other: All patients: before the start of the study, all participants revised 2 hours of training on best practices for cardiovascular risk management</p>	
Outcomes	<p>Relevant outcomes: 6-minute walking test, serious adverse events</p> <p>Other outcomes: Ejection fraction, Body mass index, biochemical markers</p>	
Notes	follow-up at 16 weeks.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table.
Allocation concealment (selection bias)	Low risk	The randomisation was computer-generated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analyses were carried out on all 43 participants.
Selective reporting (reporting bias)	Unclear risk	We could not identify any protocol published before the trial was conducted. All outcomes described in methods section of the paper were reported
Groups balanced at baseline	Low risk	Groups were balanced at baseline, according to the authors.
Groups received same intervention (performance bias)	Unclear risk	Both Intervention and control groups received two hours of cardiovascular disease training, but did not describe what else the control group received

Pippa 2007 (Continued)

For-profit-bias	Unclear risk	Not described.
Intention-to-treat	Low risk	The term intention-to-treat (ITT) was not stated, but it was clear from the paper that the results were analysed according to ITT analyses

Osbak 2011

Methods	RCT; single centre, Denmark	
Participants	<p>N = 49, (Intervention N = 25; control N = 24). Numbers of participants lost to follow up: 0. Number of early drop outs: 2. Number with complications: 2 (one had influenza and one needed surgery) Sex: male 74.5%. Age: Intervention 69.5 years (SD 7.3); control 70.9 years (SD 8.3) Diagnosis: AF type: permanent AF. Ethnicity: not reported. Inclusion: adults with permanent AF who were willing to participate in a training program and able to give informed consent for participation Exclusion: severe CHF (New York Heart Association classes III-IV), severe refractory hypertension, previous heart valve surgery, moderate to severe pulmonary disease, low life expectancy, and lack of ability to exercise time after hospitalisation: Not reported.</p>	
Interventions	<p>Intervention: duration: 3 sessions/week; 1-hour classes for 12 weeks; including aerobic training, cool down and warm-up periods, at least 30 min by Borg 14 to 16 corresponding to 70% of maximal exercise capacity. The exercise was carried out by ergometer cycling, walking on stairs, running, fitness training on physioballs, and interval training. The exercise sessions were carried out in groups of five lead by a physiotherapist Other: exercise component was based on the ETICA trial. Encouraged to do light exercise for 30 min daily Standard care group: They were advised to continue their habitual physical activity</p>	
Outcomes	<p>Relevant outcomes: Ergometer testing, 6-minute walking test, health-related quality of life measured by SF-36 and Minnesota Living with Heart Failure questionnaire Other outcomes: CO measure by cardioScreen, blood samples - natriuretic peptides (ANP, NT, BNP) Data on serious adverse events were obtained directly from authors</p>	
Notes	follow-up 12 weeks	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Generated by a random list.
Allocation concealment (selection bias)	Low risk	Randomisation was carried out by envelopes containing either the text 'control' or 'active'. There was no information about the distribution of the envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Ergometer test: "A physician and a research assistant blinded to the group allocation status of the patients were present. However, remarks were sometimes made by the patient hinting to their trial status. In an exercise study, it is not possible to keep the study double blinded. Obviously, the patients knew which group they belonged to, but we have tried to maintain blinding as far as possible for the examiner."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs and all participants were included in the analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in methods were reported, but adverse events and safety were added
Groups balanced at baseline	Low risk	Judging from the baseline tables, groups were balanced at baseline
Groups received same intervention (performance bias)	Unclear risk	Not clear. The control patients were advised to continue a habitual physical activity. Standard care not described
For-profit-bias	Low risk	The study was supported by grants from the Danish Medical Association Research Foundation, Hvidovre Hospital Research Foundation, and Lundbeck Foundation
Intention-to-treat	Low risk	The term 'intention-to-treat' was not stated, but it was clear from the paper that the results were analysed according to ITT

Methods	RCT; two centres, Denmark.
Participants	<p>N = 210, (Intervention N = 105; control N = 105).</p> <p>Numbers of participants lost to follow up: 3.</p> <p>Number of early drop-outs: N = 17 (Intervention N = 10; control N = 7)</p> <p>Number with complications: 2 deaths not related to the trial (Intervention = 2; control = 1); 1 serious adverse event (Intervention) related to the trial; 23 adverse events (Intervention = 16; control = 7) related to the trial</p> <p>Sex: male 70% intervention; 73% control.</p> <p>Age: Intervention 60 years (SD 9); control: 59 years (SD 12.25)</p> <p>Diagnosis: AF type: paroxysmal or persistent AF.</p> <p>Ethnicity: not reported.</p> <p>Inclusion criteria: consecutive patients planned for treatment with radiofrequency catheter ablation for AF were screened for inclusion. Patients ≥ 18 years of age, Danish speaking, and providing oral and written informed consent</p> <p>Exclusion criteria: unable to understand trial instructions, pregnant or breastfeeding, reduced ability to follow the planned programme due to other physical illness, prior to RFA had been engaged in intense physical exercise or sports at a competitive level several times a week, did not wish to participate, or were enrolled in a clinical trial that prohibited participation in additional trials.</p> <p>Time after hospitalisation: patients were approached by the trial nurse for information about the trial after ablation procedure</p>
Interventions	<p>Physical exercise Intervention: duration: 3 sessions/week, 1-hour classes for 12 weeks; The training program consisted of graduated cardiovascular training based on intensity prescription using the Borg 15-point scale and strength exercises altered stepwise during training sessions. Training intensity was progressively increased during the 12 weeks</p> <p>The program was initiated with one mandatory training session at the hospital; the continuing physical exercise program was then offered in three locations according to the patient's preference: (1) supervised training at hospital; (2) local trial protocol-certified, supervised facility; or (3) home-based training with physiotherapist contact when needed</p> <p>Psycho-educational intervention: duration: 4 consultations/6 months; Education and information were provided about AF to prepare the patients for expected symptoms, and a consultation guide was developed to ensure that certain areas were discussed, e. g. the ablation and fear of AF recurrence. The psycho-educational consultations were inspired by R.R. Parse's Human becoming practice methodologies theory. Furthermore, the consultations complied with recommendations on the use of patient education and psychosocial support in secondary prevention. Two cardiac care nurses were trained in the theory and conducted the consultations, a physician could be contacted if needed. Consultations were performed face-to-face or by telephone</p> <p>Standard care group: The usual care group followed usual care for patients treated for AF with RFA, which included a 3- to 6-month follow-up consultation with a physician at the treating hospital and no further rehabilitation or after-care. Usual care was the same in both included hospitals</p>
Outcomes	<p>Relevant outcomes: mortality, serious adverse events, and adverse events, physical capacity measured by VO₂ testing, health-related quality of life measured by Short Form-36, and anxiety and depression measured by Hospital Anxiety and Depression scale, 6-minute walking test, sit-to-stand test</p> <p>Raw data on quality of life and 6-minute walking test were obtained directly from authors</p>

Notes	follow-up 6 months.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomised 1:1 to comprehensive cardiac rehabilitation plus usual care versus usual care alone, using a computer-generated allocation sequence with a varying block size of 6, 8, and 12
Allocation concealment (selection bias)	Low risk	Randomization was carried out centrally by a computer, and was obtained by telephone
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients were not blinded to which intervention group they were in. Outcome assessment staff were blinded to which group patients were allocated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Outcome assessment including ergospirometry testing, data management, and analyses were undertaken by research staff masked to group allocation."
Incomplete outcome data (attrition bias) All outcomes	High risk	17 drop-outs (10 intervention, 37 control), were handled by using intention-to-treat analyses
Selective reporting (reporting bias)	Low risk	A protocol describing the trial was published. All outcomes described in the methods section were reported in the results section of the paper. Other outcomes were described in the protocol and will be reported elsewhere
Groups balanced at baseline	Low risk	Judging from the baseline table, groups were balanced at baseline
Groups received same intervention (performance bias)	Low risk	Patients in the experimental cardiac rehabilitation group followed a comprehensive programme consisting of exercise training and psycho-educational consultations plus usual care. The usual care consisted of a 3- to 6-month follow-up consultation with a physician at the treating hospital, and no further rehabilitation or after-care. Usual care was the same in both included hospitals
For-profit-bias	Low risk	"This trial was supported by the Danish Strategic Research Council, The Heart Centre, Rigshospitalet, Copenhagen, Denmark, Metropolitan University College, Copenhagen, Denmark, The Copenhagen Trial Unit, Denmark and The Lundbeck Foundation, Denmark."

Risom 2016 (Continued)

Intention-to-treat	Low risk	ITT was used in the analyses.
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Malmö 2016

Methods	RCT; single centre, Norway.
Participants	<p>N = 51, (Intervention N = 26; control N = 25). Numbers of participants lost to follow up: 0. Number of early drop outs: 0. Number with complications: 1 in the control group (1 stroke) Sex: male 77% intervention; 88% control. Age: Intervention 56 years (SD 8); control 62 years (SD 9). Diagnosis; AF type: symptomatic, ECG-documented, non-permanent AF Ethnicity: not reported. Inclusion: symptomatic, ECG-documented, non-permanent AF who were referred for first AF ablation, or to the outpatient clinic Exclusion: performing endurance training at high intensity > 2 times a week or at moderate intensity for > 3 times a week, previous open heart surgery, left ventricular ejection fraction < 45%, significant cardiac valve disease, implanted cardiac pacemaker, coronary artery disease without complete revascularization, or inability to accomplish the exercise programme Time after hospitalisation: Patients were recruited when referred for first AF ablation or to the outpatient clinic</p>
Interventions	<p>Intervention: duration: 3 sessions/week for 12 weeks; including aerobic training, warm-up and cool down periods, with four 4-minute intervals at 85% to 90% of maximal heart rate and Borg 6 to 20. The exercise was walking or running on a treadmill. The exercise sessions were carried out in a facility with the option of one additional exercise session at home when trained in using the heart monitor Standard care group: continued their previous exercise habits</p>
Outcomes	<p>Relevant outcomes: Change in time in AF from baseline to follow-up, AF symptoms, exercise capacity measured as peak oxygen uptake (VO₂ peak), health-related quality of life measured by SF-36 and AF symptoms and severity checklist, and number of cardioversions and hospital admissions resulting from AF Other outcomes: lipid status, cardiac volumes, level of physical activity</p>
Notes	follow-up 20 weeks.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not described.
Allocation concealment (selection bias)	Unclear risk	not described.

Malmö 2016 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients were not blinded to which intervention group they were in. "The investigators performing the data analyses were blinded for intervention identity, and none of the study investigators were involved in treatment of the patients."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The investigators performing the data analyses were blinded for intervention identity."
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs and all participants were included in the analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in methods were reported, adverse events and safety were added
Groups balanced at baseline	Low risk	Judging from the baseline tables, groups were balanced at baseline, only differences in patients age were reported
Groups received same intervention (performance bias)	High risk	The control patients were advised to continue their habitual physical activity. Standard care not described
For-profit-bias	Low risk	The study was supported by grants from the Norwegian Council of Cardiovascular Disease (Oslo, Norway), Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (Trondheim, Norway), K.G. Jebsen Foundation, and SINTEF Unimed (Trondheim, Norway)
Intention-to-treat	Low risk	All patients completed the intervention and were included in the analysis

Zeren 2016

Methods	RCT; single centre, Turkey.
Participants	<p>N = 38, (Intervention N = 19; control N = 19).</p> <p>Numbers of participants lost to follow up: 3.</p> <p>Number of early drop outs: 2.</p> <p>Number with complications: not reported.</p> <p>Sex: male 47% intervention, 56% control.</p> <p>Age: Intervention 66.18 years (SD 8.76); control 67.06 years (SD 6.39)</p> <p>Diagnosis: AF type: permanent AF.</p> <p>Ethnicity: not reported.</p> <p>Inclusion: clinically stable, left ventricular ejection fraction above 40% and New York Heart Association Class I (cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs, etc.), and</p>

	Class II (mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity) Exclusion: chronic obstructive lung disease, rheumatic valvular heart disease, previous heart valve surgery, recent coronary bypass surgery (three months prior to study), acute myocardial infarction, hypertrophic obstructive cardiomyopathy, and having a pacemaker time after hospitalisation: not reported.	
Interventions	Intervention: duration: 15 minutes twice a day, 7 days a week, for 12 weeks. Once a week patients in the training group came to the department, had their maximal inspiratory pressure measured again, and received a supervised inspiratory muscle training session. Intervention: threshold inspiratory muscle trainer (Threshold IMT) device (Respironics, U.S.) was used for inspiratory muscle training. The training group received inspiratory muscle training at 30% of maximal inspiratory pressure. Patients were instructed to maintain diaphragmatic breathing with the device for five breaths and rest for 5 to 10 seconds before the next five breaths. All patients wore nose-clips during training Standard medical treatment of permanent atrial fibrillation was based on the ventricular rate control and antithrombotic therapy, for the purpose of preventing atrial fibrillation-related complications and thromboembolism	
Outcomes	Relevant outcomes: functional capacity measured by 6-minute walking test Other outcomes: pulmonary function, respiratory muscle strength	
Notes	follow-up 12 weeks.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A numbered series of 38 prefilled envelopes specifying group assignment were used
Allocation concealment (selection bias)	Low risk	Randomisation was carried out by a computer-based program.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Patients were not blinded to which intervention group they were in. "Patients' assessments and inspiratory muscle training were performed by different and blinded physiotherapists."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The physiotherapist that collected the data was not aware of which patients belonged to the training group or the control group. Patients' assessments and inspiratory muscle training were performed by different physiotherapists."
Incomplete outcome data (attrition bias) All outcomes	High risk	5 drop-outs (2 intervention group, 3 control group); they were not included in the analysis

Zeren 2016 (Continued)

Selective reporting (reporting bias)	Low risk	All outcomes described in the methods were reported.
Groups balanced at baseline	Low risk	Judging from the baseline table, groups were balanced at baseline
Groups received same intervention (performance bias)	Low risk	“Standard medical treatment of permanent atrial fibrillation was based on the ventricular rate control and antithrombotic therapy, for the purpose of preventing atrial fibrillation-related complications and thromboembolism.”
For-profit-bias	Low risk	The researchers were not financially supported to conduct the trial
Intention-to-treat	High risk	ITT was not used in the analysis.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Angergard K 2015	No intervention was applied.
Borland 2015	The control group also received the intervention.
Frederix 2015	The study evaluated the cost-effectiveness of a comprehensive cardiac telerehabilitation programme for various patients with different heart diseases who had participated in cardiac rehabilitation
Kim 2014	The study evaluated the influence of atrial fibrillation on the clinical characteristics and rehabilitation outcomes of patients with cerebral infarction
Mertens 1996	The study was not randomised
Vanhees 2000	The study was not randomised

Characteristics of ongoing studies [ordered by study ID]

NCT01673139

Trial name or title	Effect of 3 years of exercise in patients with atrial fibrillation
Methods	RCT
Participants	150 70 to 75 year-old persons with atrial fibrillation included in the “Generation 100 study”

NCT01673139 (Continued)

Interventions	3 years of interval or moderate exercise
Outcomes	Primary outcome measures: change in burden of atrial fibrillation (timeframe: At baseline and 3 years); burden of atrial fibrillation measured by Holter monitor and the patient Secondary outcome measures: size of left ventricle, quality of life, endothelial function, diameter of brachial artery measured by ultrasound, maximal oxygen uptake, atrial extra systoles, number of hospitalisations with atrial fibrillation as main diagnosis, total number of electrical cardioversions, number of electrical cardioversions because of atrial fibrillation, size of left atrium, function of left atrium, function of left ventricle,
Starting date	September 2012
Contact information	Jan Paal Loennechen, Norwegian University of Science and Technology, Trondheim
Notes	Norway

NCT01721863

Trial name or title	Effects of exercise training in patients with permanent atrial fibrillation
Methods	RCT
Participants	58 patients with permanent atrial fibrillation
Interventions	Progressive aerobic exercise training with 40% to 85% maximal oxygen consumption for 40 minutes, 3 sessions per week for 12 weeks versus treatment as usual
Outcomes	Primary outcome measures: exercise capacity Secondary outcome measures: heart rate variability, change values of head-up tilt test, endothelial function, and quality of life
Starting date	2010
Contact information	Ying-Tai Wu, National Taiwan University Hospital, Department of Health
Notes	Taiwan

NCT01817998

Trial name or title	Atrial fibrillation (AF) and physical exercise (EXAF)
Methods	RCT
Participants	60 patients older than 18 years with ECG-documented paroxysmal or persistent AF
Interventions	Moderate to severe (80% to 85% of maximum capacity) or low intensity (50% of max capacity) training

NCT01817998 (Continued)

Outcomes	1. The effect of physical exercise on AF burden. 2. The effect of physical exercise on the risk of cardiovascular hospitalisation
Starting date	November 2012
Contact information	Ane Katrine Skielboe: a.k.skielboe@gmail.com Ulrik Dixen, Consultant: ulrik.dixen@regionh.dk
Notes	Denmark