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Exercise-based cardiac rehabilitation improves exercise capacity and health-related quality of life in people with atrial fibrillation: a systematic review and meta-analysis of randomised and non-randomised trials

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ABSTRACT

Objective The aim of this study was to undertake a contemporary review of the impact of exercise-based cardiac rehabilitation (CR) targeted at patients with atrial fibrillation (AF).

Methods We conducted searches of PubMED, EMBASE and the Cochrane Library of Controlled Trials (up until 30 November 2017) using key terms related to exercise-based CR and AF. Randomised and non-randomised controlled trials were included if they compared the effects of an exercise-based CR intervention to a no exercise or usual care control group. Meta-analyses of outcomes were conducted where appropriate.

Results The nine randomised trials included 959 (483 exercise-based CR vs 476 controls) patients with various types of AF. Compared with control, pooled analysis showed no difference in all-cause mortality (risk ratio (RR) 1.08, 95% CI 0.77 to 1.53, p=0.64) following exercise-based CR. However, there were improvements in health-related quality of life (mean SF-36 mental component score (MCS): 4.00, 95% CI 0.26 to 7.74; p=0.04 and mean SF-36 physical component score: 1.82, 95% CI 0.06 to 3.59; p=0.04) and exercise capacity (mean peak VO$_2$: 1.59 ml/kg/min, 95% CI 0.11 to 3.08; p=0.04; mean 6 min walk test: 46.9 m, 95% CI 26.4 to 67.4; p<0.001) with exercise-based CR. Improvements were also seen in AF symptom burden and markers of cardiac function.

Conclusions Exercise capacity, cardiac function, symptom burden and health-related quality of life were improved with exercise-based CR in the short term (up to 6 months) targeted at patients with AF. However, high-quality multicentre randomised trials are needed to clarify the impact of exercise-based CR on key patient and health system outcomes (including health-related quality of life, mortality, hospitalisation and costs) and how these effects may vary across AF subtypes.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia and associated with

Key questions

What is already known about this subject?
► Previous meta-analyses have shown that exercise-based cardiac rehabilitation (CR) targeted at patients with atrial fibrillation (AF) can improve short-term (up to 6 months) exercise capacity.
► However, given the lack of high-quality evidence, exercise-based CR is not formally recommended in current international guidelines for the management of AF.

What does this study add?
► This contemporary review confirms that exercise-based CR for AF improves exercise capacity in the short term compared with a no exercise control.
► This review also shows improvements in health-related quality of life, cardiac function and symptom burden.

How might this impact on clinical practice?
► Additional evidence is needed to inform the clinical and cost-effectiveness of the provision of exercise-based CR specifically targeted for those with AF.

increased risks of stroke, heart failure, dementia and death.[1] AF has a prevalence of approximately 2% in adults and increasing incidence, mainly due to the ageing population.[2][3] AF is a highly heterogeneous condition split in to five diagnostic categories: first-diagnosed AF (patient presents with AF for the first time), paroxysmal AF (self-limiting and usually the rhythm converts spontaneously to sinus (normal) rhythm within 48 hours), persistent AF (AF episode lasts longer than 7 days, or requires cardioversion), long-standing persistent AF (duration of AF exceeds 1 year) and permanent AF (accepted

by the patient (and physician) and no rhythm control interventions are used).[4] Patients with AF can experience palpitations, shortness of breath, fatigue, dizziness and syncope (fainting), depression, anxiety and reduced exercise capacity.[3–6]

Current AF management mainly focuses on rate and rhythm control and reducing stroke risk and its associated morbidity and mortality.[4] However, although effective in managing symptoms and stroke risk, current treatments do not focus on patients' exercise capacity, ability to self-manage and mental health.[7–9] Poor health-related quality of life (HRQoL) therefore remains a common and important problem of patients with AF receiving conventional medical therapy. HRQoL in patients with AF has been shown to be lower than age and sex-matched members of the general population and other cardiac groups, including coronary heart disease (CHD).[9] Beyond medical management, evidence suggests AF may be controlled by improving lifestyle.[10 11] One aspect of lifestyle therapy that is poorly understood, with respect to AF, is regular exercise.[12]

Mechanisms by which exercise may improve health outcomes for patients with AF include atrial remodelling, antiarrhythmic effects via changes in autonomic control, reduced blood pressure, reduced bodyweight and reduced lipids.[13] For example, a study evaluated the long-term impact of weight loss on rhythm control of 355 obese patients (body mass index (BMI) $\geq 27 \, \text{kg/m}^2$) with AF. Long-term sustained weight loss ($\geq 10\%$) was associated with significant reduction of AF burden and maintenance of sinus rhythm.[14] Exercise has also been shown to stimulate improvements in mental health through improvements in self-efficacy and reduced inflammation.[15 16]

A substantive body of evidence supports the benefits of exercise-based cardiac rehabilitation (CR) for CHD (post-myocardial and post-revascularisation)[17 18] and heart failure populations.[12] A recent meta-analysis of 33 randomised trials found that exercise-based CR reduced the risk of overall and heart failure-specific hospitalisation and resulted in improvements in HRQoL compared with usual medical care.[19] AF is a common comorbidity in patients with CHD and heart failure referred to exercise-based CR. However, given the sparse evidence for CR specifically targeted for patients with AF, the 2012 European Society of Cardiology and 2011 American College of Cardiology/American Heart Association guidelines for the management of AF do not formally recommend rehabilitation.[4 20 21]

Since these guidelines were published, a Cochrane review in 2017 has found that exercise-based rehabilitation programmes targeted at AF patients significantly increased their exercise capacity (standardised mean difference (SMD): 0.86, 95% CI 0.46 to 1.26) compared with no exercise control. However, only a small volume of evidence (six randomised trials in 421 patients with AF) of moderate to very low-quality and of short-term follow-up (up to 6 months) was identified and little or no data were available on the impact on HRQoL or clinical events, such as mortality and hospitalisation.

Aware that a number of trials have been published since this 2017 Cochrane review, we sought to undertake a de novo systematic review and meta-analysis to provide a contemporary summary of the impact of exercise-based CR specifically aimed at patients with AF.

The specific aims of this review were to: (i) investigate if exercise-based CR reduces the risk of mortality and hospitalisation of patients with AF; (ii) to identify if markers of cardiac function and AF risk are altered with exercise-based CR; (iii) and to confirm whether exercise-based CR increases exercise capacity and HRQoL in patients with AF.

METHODS
Search strategy
Potential studies were identified by conducting systematic searches of PubMed, EMBASE and the Cochrane Library of Controlled Trials up until 30 November 2017. Searches included a mix of MeSH and free text terms related to the key concepts of exercise-based CR, atrial fibrillation, arrhythmia, heart rate and heart rate variability. In addition, systematic reviews, meta-analyses and reference lists of papers were hand searched for additional studies. One reviewer (NAS) conducted the search and full articles were assessed for eligibility by two reviewers (NK and NAS) using the inclusion criteria. A sample search strategy is presented in online supplementary files. Authors were contacted and asked to provide clarification of study information if needed.

Study type and participants
Randomised controlled trials (RCTs) and non-RCTs of exercise training in adult patients with AF were included. Abstracts and non-English language studies were excluded.

Intervention
Exercise-based CR was defined to allow for inclusion of a broad range of physical activities, including aerobic, resistance exercise training, combined training (aerobic and resistance), yoga, pilates, Tai Chi and hydrotherapy. Additionally, the physical therapies of Functional Electrical Stimulation and Inspiratory Muscle Training were included in the definition of exercise-based CR for the purpose of this review. To be included in the review, studies had to compare an exercise-based CR intervention to no exercise or usual care, or 'other exercise' control groups and the duration of the exercise-based CR had to be a minimum of 4 weeks. We also included trials that included exercise-based CR with other interventions including education and psychological support as many contemporary rehabilitation programmes use all three components.

Outcomes

Primary

i. All-cause mortality and all-cause hospitalisation.

ii. HRQoL: any validated HRQoL questionnaire was included.

iii. Exercise capacity, for example, peak VO$_2$ or 6 min walk distance.

Secondary

i. Measures of cardiac function, for example, resting heart rate.

ii. Other clinical risk factors associated with AF, for example, AF burden or AF symptoms.

Data extraction

Two reviewers (NAS, NK) extracted the following information for each study: (1) author, year of publication and study design; (2) AF patient demographic and clinical characteristics (eg, age or type of AF); (3) exercise intervention characteristics (eg, duration, modality, frequency, intensity); (4) number of patient events (binary outcomes), or mean and SD (or SE, p value or 95% CIs) (continuous outcomes); (5) characteristics of assessment methodology for AF and (6) reporting of adverse events and intervention compliance.

Data synthesis

Statistical analyses were performed using Revman V.5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark). For meta-analysis of binary data, risk ratios (RRs) were calculated. Individual meta-analyses were completed for continuous data by using the mean baseline follow-up change and SD. Where the mean change and SD were not reported, this was calculated by subtracting the follow-up mean from the baseline mean, and Revman V.5.3 enabled calculations of SD using number of participants in each group, within-group or between-group p values or 95% CI. In cases where exact p values are not provided, we used default values, for example, p<0.05 becomes p=0.049, p<0.01 becomes p=0.0099 and p=not significant becomes p=0.051. Where data were reported as median, the median was assumed to equal the mean. Data not provided in main text or tables were extracted from figures. For continuous data, MD was used where outcome measures were homogenous. Where outcome measures were measured by different methods, SMD was used. Statistical heterogeneity was quantified using the I^2 test. Values ranged from 0% (homogeneity) to 100% (high heterogeneity).[22] A fixed effects meta-analysis model was used when there was evidence of no statistical heterogeneity (ie, I^2 statistic ≤50%) and a
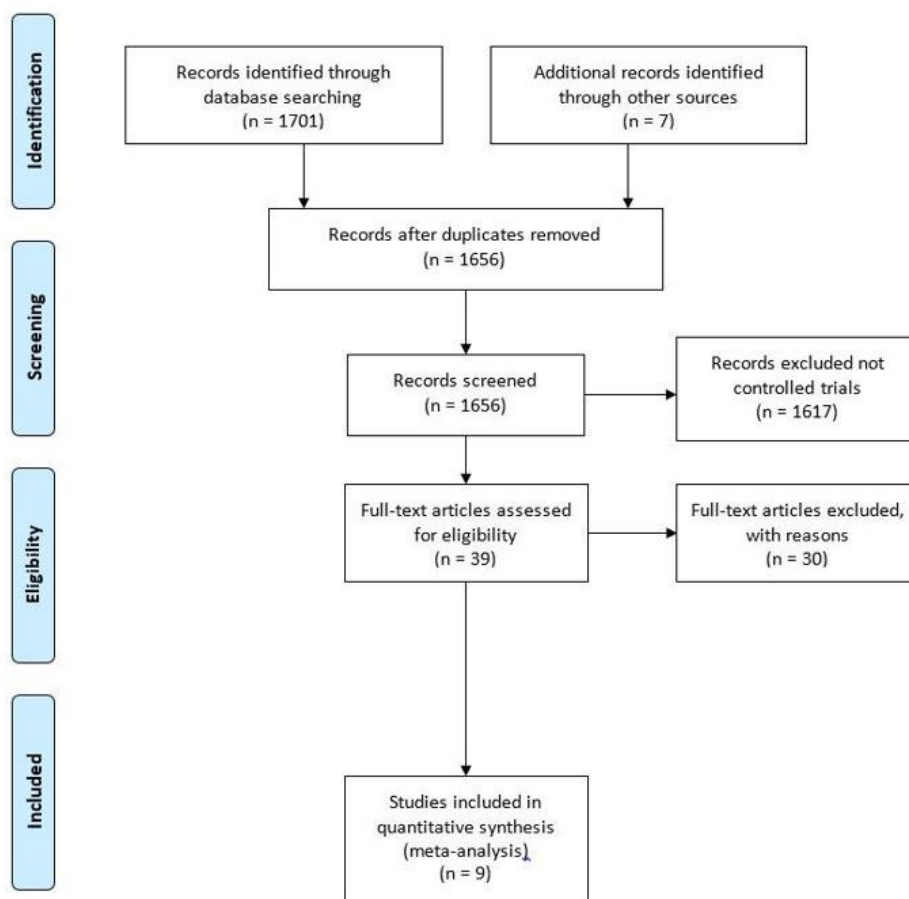
Figure 1 PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Table 1 Included studies

Study	Inclusion criteria	Intervention: control	Exercise/control	Outcomes
Hegbom [25]	Patients with chronic AF,<75 years.	*Exercise* 8 weeks, three sessions/week. Supervised, 1.25 hours, aerobic exercise: 5 min warm-up, 3×15 min periods of aerobics @ 70%–90% HR_{max} interrupted by strengthening exercise (back, thighs and stomach), followed by a 5 min cool-down and 15 min of stretching. Sessions completed @ one of two rehabilitation Centres. *Control* Usual care.	15/15 randomised 13/15 analysed	Heart rate variability Maximal heart rate Resting heart rate Cumulated workload (W) Exercise time max. (min) QoL (SF-36)
Luo [2]	Heart failure patients with LVEF <35%. Sub-analysis of those with AF from HF ACTION trial.	*Exercise* 12 weeks, three sessions/week. Supervised aerobic exercise (walking, treadmill, or cycle ergometer), followed by transition to a home-based exercise programme for an additional 2 years. *Control* Usual care.	193/189 randomised and analysed	6MWD Peak VO_2 QoL (KCCQ) All-cause mortality/ hospitalisation Cardiovascular mortality/HF hospitalisation
Malmo [26]	Patients with non-permanent AF (paroxysmal or persistent)	*Exercise* 12 weeks, three sessions/week. Aerobic (walking/running), 10 min warm-up @ 60%–70% H_{Rpeak}, then 4×4 min intervals @ 85%–95% of HR_{peak} with 3 min of active recovery @ 60%–70% H_{Rpeak} between intervals. *Control* Usual care.	26/25 randomised and analysed	Time in AF AF symptoms and severity Blood pressure Resting heart rate Peak heart rate Cardiac volumes (ejection fraction) QoL (SF-36) Peak VO_2 lipid status (TC, HDL, LDL, TG) hsCRP BMI, weight activity
Osbak [27]	Adults with permanent AF.	*Exercise* 12 weeks, three sessions/week, @ 70% maximal exercise capacity (Borg scale scores 14–16). Total exercise duration was 60 min 3, minimum 30 min @ 70% maximal exercise capacity. *Control* Usual care.	25/24 randomised 24/23 analysed	CO (maximal and resting) Maximal heart rate Resting heart rate Blood pressure Heart rate reserve 6MWD Maximal power (W) QoL (MLHF-Q and SF-36) ANP, NT-pro-BNP Adverse events
Pippa [28]	Patients diagnosed with AF at least 3 months prior, and taking anticoagulant treatment for at least 2 months.	*Exercise* 16 weeks, two sessions/week. 90 min sessions of qi gong training. Qi gong refers to a set of static exercises. *Control* Usual Care.	22/21 randomised and analysed	6MWD BMI Lipids (TC, HDL) Homocysteine Ejection fraction Adverse events
Risom [29]	Consecutive patients planned for treatment with radiofrequency catheter ablation,≥18 years. Paroxysmal or persistent AF.	*Exercise* 12 weeks, three sessions/week, graduated cardiovascular training based on Borg 15-point scale and strength exercises. *Control* Usual care.	105/105 randomised*	Peak VO_2 Maximal power (W) STS Max. blood pressure QoL (SF-36, HADS) EHRA score Mortality, adverse events

Continued

Table 1 Continued

Study	Inclusion criteria	Intervention: control	Exercise/control	Outcomes
Skielboe [10]	Patients with paroxysmal/persistent AF.	*Exercise* 12 weeks, two sessions/week, 60 min/session, high Intensity – (80% of maximal RPE). *Comparator* 12 weeks, two sessions/week, 60 min/session, low Intensity (50% of maximal RPE).	38/38 randomised† 26/29 analysed†	Burden of AF (time spent in AF) Peak VO$_2$ Hospital admissions Adverse events
Wahlstrom [31]	Patients with paroxysmal AF, necessitating pharmacological treatment.	*Exercise* 12 weeks, one session a week, 60 min group session of yoga (Mediyoga) and encouraged to practice at home. *Control* Usual care.	40/40 randomised 33/36 analysed	QoL (SF-36, EuorQoL-5D) Resting heart rate Blood pressure
Zeren [30]	Patients with permanent AF, LVEF >40%.	*Exercise* 12 weeks, 2×15 min sessions, 7 days/week. Inspiratory muscle training a@ 30% MIP. *Control* Usual care.	19/19 randomised 17/16 analysed	Pulmonary function Respiratory muscle strength Adverse events

*Different numbers for analysis at different time points for different outcomes.
†Performed ITT analysis and per protocol analysis.
ACR, Albumin: Creatinine ratio; AF, Atrial Fibrillation; ANP, Atrial Natriuretic Peptide; BMI, Body mass index; ERHA, European Heart Rhythm Score; HADS, Hospital anxiety and depression score; HD, High density lipoprotein; HF, Heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LDL, Low density lipoprotein; MLHF-Q, Minnesota living with heart failure questionnaire; 6MWD, 6 minute walk distance; NT-Pro-BNP, N-terminal Pro-Brain Natriuretic Peptide; QoL, Quality of life; RPE, Rate of Perceived Exertion; SF-36, Short form-36; STS, Sit-to stand test; TC, Total cholesterol; TG, Triglycerides; eGFR, estimated Glomerular Filtration Rate; hsCRP, high-sensitive C-reactive protein.

random effects inverse variance model was used when the I^2 statistic >50%. We judged statistical significance based on 5% level of significance and reported pooled mean results with 95% CIs. Where a study included multiple intervention groups and a control group, each intervention group was considered separately and the sample size of the control group was divided by the number of intervention groups to eliminate over inflation of the sample size. If data were reported for multiple time points during the intervention, only the data at the end of the intervention were extracted as long as data were available for both the intervention and control group. Where two publications referred to the same study population, the publication with the highest number of participants was used. Visual inspection of funnel plots[23] was used to assess risk of publication bias.

Study quality

Study quality was assessed using the TESTEX; the Tool for assessment of study quality and reporting, designed specifically for use in exercise training studies.[24] This is a 15-point scale that assesses study quality (maximum 5 points) and reporting (maximum 10 points). Two reviewers (RST and NAS) independently conducted quality assessment. A study quality score <10 was considered low quality. If relevant subanalyses were conducted by removing low-quality studies from pooled analyses.

RESULTS

Our initial search identified 1701 titles, and hand searching a further 7 potential studies for inclusion. Fifty-two duplicate studies were removed, and a further 1617 papers excluded as they were not RCTs or non-RCTs. Thirty studies were excluded at full text screening as they were not studies of exercise-based CR in adults with AF. Also, 13 were acute (single exercise session) studies, 16 were not AF studies and 1 was a paediatric study. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram (figure 1) describes the selection process. Nine studies (nine publications) were included in this analysis[2 10 25–31] (see table 1).

Trial and patient characteristics

Eight RCTs compared exercise-based CR with control participants, while one RCT compared high-intensity exercise training versus exercise at lower intensity.[10] The total number of participants in the nine included studies yielded 959 participants, 483 allocated to exercise training and 476 to control. One study, in addition to the exercise component, also included a psycho-educational part of the intervention.[29]

Study quality and risk of bias

Median TESTEX score was 12 out of 15. Monitoring of physical activity in the control group (3/9 studies) and assessment of energy expenditure during training (4/9 studies) were the only two items not performed by at

Table 2 Assessment of study quality and reporting using Tool for the assessment of Study quality and reporting in Exercise (TESTEX)

Study	Eligibility criteria specified	Randomisation details specified	Allocation concealed	Groups similar at baseline	Assessors blinded	Outcomes measures assessed >85% participants*	Intention to treat analysis	Reporting between-group statistical comparison†	Point measures and measures of variability	Activity monitoring in control group	Relative exercise intensity constant	Exercise volume and energy expenditure	Overall TESTEX (/15)
Hegbom [25]	1	0	0	1	0	3	0	2	1	0	0	0	8
Luo [2]	1	1	1	0	1	3	1	2	1	1	0	1	13
Malmo [26]	1	0	0	0	1	2	0	2	1	1	1	1	10
Osbak [27]	1	1	1	1	1	2	1	2	1	0	1	0	12
Pippa	1	1	1	1	0	3	1	2	1	0	0	0	11
Risom [29]	1	1	1	1	1	2	1	2	1	0	1	1	13
Skielboe [10]	1	1	1	1	1	2	1	2	1	1	1	1	14
Wahlstrom [31]	1	1	0	1	0	1	0	2	1	0	0	0	7
Zeren [30]	1	1	1	1	1	2	1	2	1	0	1	0	12
Total	9	7	6	7	6	9	6	9	9	3	5	4	

*Three points possible—one point if adherence >85%, one point if adverse events reported, one point if exercise attendance is reported.
†Two points possible—one point if primary outcome is reported, one point if all other outcomes reported. 0 awarded if no mention was made of this criteria or if it was unclear.
Key: total out of 15 points.

least 50% of studies; see table 2. Two studies produced a TESTEX score <10.

Primary outcomes
Mortality and hospitalisation
Evidence from pooled analysis of eight studies[2 25–31] showed 52 deaths in 445 (11.7%) exercising participants and 47 deaths in 438 (10.7%) control participants. There was no significant difference in pooled RR between exercise-based CR and control groups (RR 1.08, 95% CI 0.77 to 1.53, p=0.64, I^2=0%) (figure 2). There were 156 occurrences of either all-cause mortality or hospitalisation reported in 386 (40.4%) intervention participants and 147 occurrences in 379 (38.7%) control participants (RR 1.04, 95 CI% 0.93 to 1.16, p=0.51, I^2=0%) (figure 3).

HRQoL
Five studies reported on HRQoL using SF-36; however, Hegbom et al[25] only reported combined intervention and control data and therefore could not be pooled. Three studies reported SF-36 MCS[26 29 31]; pooled analyses showed a significant improvement in MCS in exercise-based CR versus control participants (MD 4.00, 95% CI 0.26 to 7.74; p=0.04, I^2=62%) (figure 4). Three studies reported SF-36 physical component scores (PCS)[26 29 31]; pooled analyses showed a significant improvement in PCS in exercise-based CR versus control participants (MD 1.82, 95% CI 0.06 to 3.59; p=0.04, I^2=26 %) (figure 5). Analyses also demonstrated a significant improvement in the SF-36 subscale of vitality in exercise-based CR versus control (MD 8.33, 95% CI 2.15 to 14.52 p=0.008, I^2=54%) (see online supplementary file), and SF-36 general health (MD 7.54, 95% CI 4.63 to 10.44, p<0.001, I^2=50%) (see online supplementary file). One study[2] measured self-reported HRQoL using the Kansas City Cardiomyopathy Questionnaire (KCCQ) with only minimal improvements observed from exercise-based CR.

Exercise capacity
Three studies reported peak VO_2 (2, 26, 29) and pooled analysis showed a significant improvement in intervention vs control participants for peak VO_2 (MD 1.59 ml/kg/min, 95% CI 0.11 to 3.08; p=0.04 I^2=82%) (figure 6). Five studies reported 6 min walk distance and pooled analysis showed a significant improvement in intervention versus control participants (MD 46.93 m, 95% CI 26.44 to 67.42; p<0.001, I^2=66%) (figure 7).

Secondary outcomes
Cardiac function
Four studies reported resting heart rate[25–27 31]; however, Hegbom et al[25] only provided combined intervention and control data. Pooled analysis of available data from three studies[26 27 31] showed resting heart rate to be reduced in exercising versus control participants (MD −4.61 beats/min, 95% CI −7.42 to −1.80, p=0.001); I^2=45% (see online supplementary file). Maximal heart rate was reduced in exercising versus control participants; (MD −2.95 beats/min, 95% CI −5.31 to −0.59, p=0.01; I^2=50%) (see online
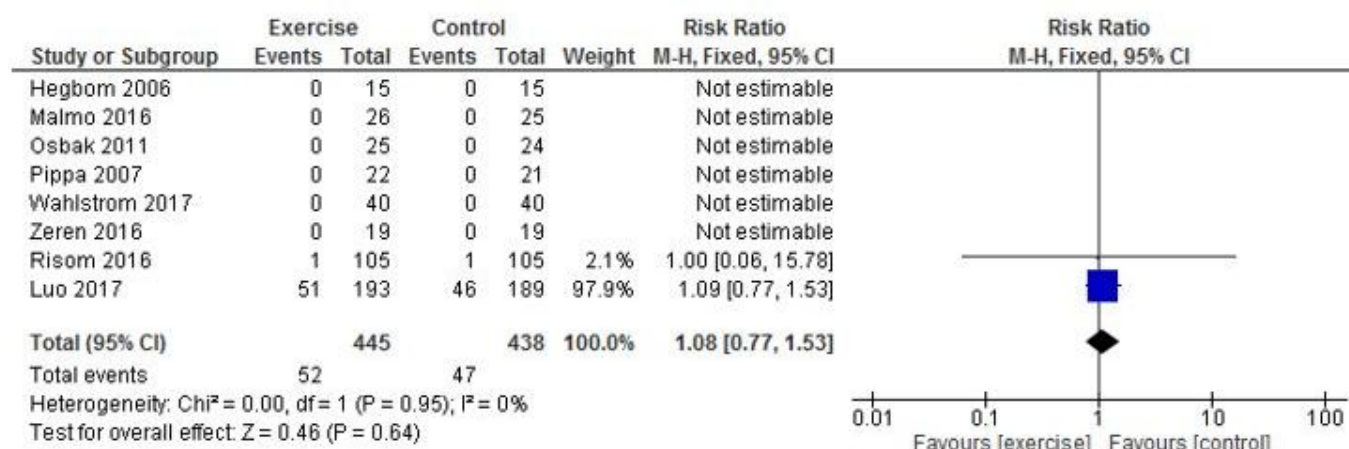
Figure 2 All-cause mortality.

supplementary file). Left ventricular ejection fraction was assessed by measuring the volume of blood ejected from the left ventricular chamber using MRI[26] and two-dimensional echocardiography.[28] Left ventricular ejection fraction was significantly increased by exercise-based CR versus control (MD 4.31%, 95% CI 2.12 to 6.51, p<0.001; I²=0%) (see online supplementary file). One study reported left atrial volume to be unchanged after exercise-based CR versus control (MD 0.0 cm³, 95% CI-6.49 to 6.49, p=1.00).

AF burden and symptoms

Two studies reported time spent in AF.[10 26] Malmo et al[26] observed a decrease in mean time spent in AF from 8.1% to 4.8% in the exercise-based CR group, which was significantly different from controls (MD 7.6%, 95% CI 2.0 to 13.0, p=0.001). Three studies reported on AF symptoms[25 26 29]; however, Hegbom only reported combined intervention and control data. Malmo et al[26] reported changes in AF symptoms, assessed by the AF Symptoms and Severity Checklist, with significant reductions in symptom frequency and severity, compared with controls (p<0.01). Risom et al[29] reported

no significant difference in European Heart Rate Association (EHRA) scores between exercise-based CR and control groups.

Clinical risk factors

Pooled data from three studies[26–28] indicated a decrease in systolic and diastolic BP; however, this was not statistically significant (see online supplementary file). Two studies reported BMI changes. A statistically significant change in BMI compared with controls was observed by Malmo et al[26], while no change was observed by Pippa et al.[28] Similarly, in patients with permanent AF, Osbak et al[27] failed to observe any changes between groups for lean body mass or fat percentage. Malmo et al observed significant decreases in total cholesterol, low-density lipoprotein and triglycerides compared with controls. In contrast, Pippa et al reported no change in total cholesterol.

Analyses of high-intensity versus lower-intensity exercise training

Skielboe et al[10] reported no significant differences between groups exercising at higher versus lower intensities for any of the outcome measures.
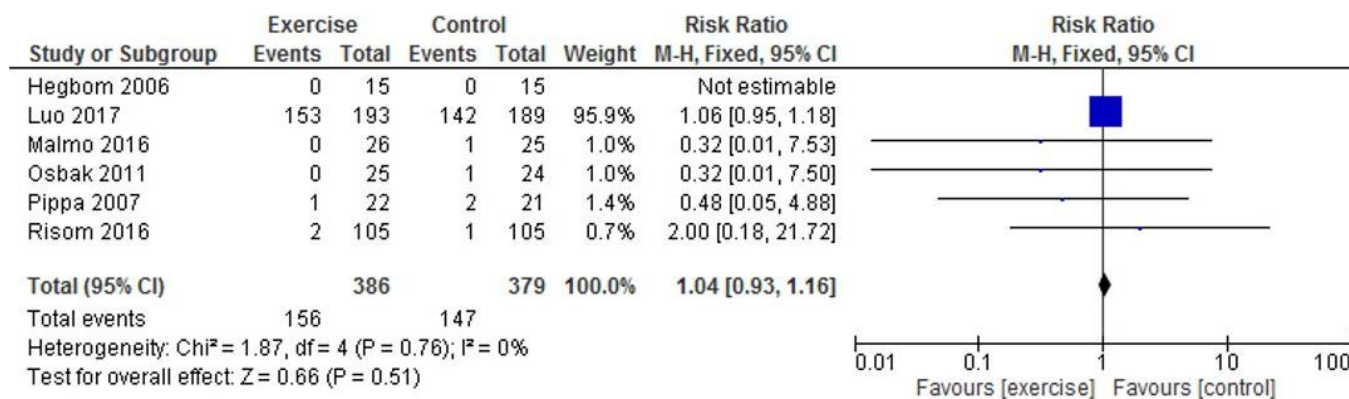
Figure 3 All-cause mortality or hospitalisation.
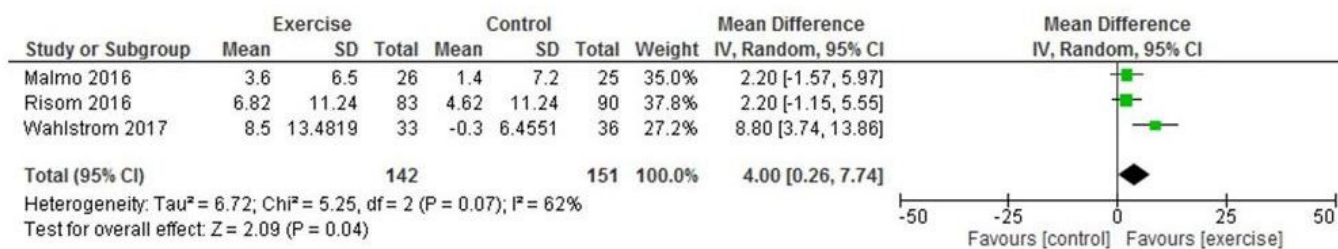
Figure 4 Change in SF-36 mental component score.

Publication bias
Examination of funnel plots showed no evidence of publication bias.

DISCUSSION

This updated systematic review and meta-analysis provides a contemporary summary of the impact of exercise-based CR aimed at patients with AF.[12] We included data from nine randomised trials in a total of 959 patients with various types of AF. Our study shows improvements in exercise capacity, HRQoL and various measures of cardiac function, and AF symptom burden in the short term (up to 6 months) following exercise-based CR compared with no exercise control. However, there was insufficient evidence to determine if the benefits of exercise-based CR vary across types of AF, to assess the impact of CR on the risk of mortality or hospitalisation or to determine the optimal exercise training intensity to elicit beneficial health outcomes.

Comparison with previous studies

Compared with the 2017 Cochrane review, our study included an additional three randomised trials and an additional 538 patients with AF. Our pooled analysis failed to show a reduction in mortality and hospitalisation due to insufficient evidence, consistent with the previous Cochrane review.[12] However, our findings of the positive impact of exercise-based CR on exercise capacity are consistent with this previous Cochrane review. Our analysis showed that mean peak VO_2 was improved by about 1.6 ml/kg/min after exercise-based CR which corresponds to ~0.5 METs in people with AF. These findings correspond with a meta-analysis of 41 trials of people with CHD and heart failure which

found a pooled MD of 3.3 ml/kg/min for VO_2 in favour of CR[32] (corresponding to ~1.0 METs). It would take a typically deconditioned cardiac patient with AF with a peak VO_2 value of ~13 ml/kg/min to a value >14 ml/kg/min.[33 34] This is clinically meaningful as it would reduce the mortality and morbidity risk of such a patient[35] and represents an absolute change of 4%–5% which would be noticeable in terms of associated symptoms, for example, dyspnoea. The observed mean improvement in 6 min walk distance of 47 m is also above the minimally clinically important difference of 41.8 m previously reported.[36] Importantly this updated review provides additional evidence of the potential benefit on HRQoL.

Our analyses showed that exercise-based CR can impact on the various subscales of HRQoL. Both the MCS and PCS of the SF-36 demonstrated significant improvements.[12] It is has been proposed that compared with disease-specific measures generic HRQoL measures (such as the SF-36) may lack the sensitivity to AF-specific symptoms and specific barriers unique to AF.[37] However, given that we were able to see improvements using a generic HRQoL instrument other factors may also be relevant here. For example, non-specific factors such as depression, anxiety and fear of social isolation associated with the risk of a stroke are likely to a major concern for people with AF.[38]

Resting heart rate was reduced in exercising participants possibly reflecting better rate control which is important in AF.[39 40] Previous work has shown a j-shaped relationship between heart rate and mortality in people with AF.[39] Maximal heart rate was also reduced by about 1.7 beats per minute less than resting heart rate reduction. However, heart rate reserve (the difference
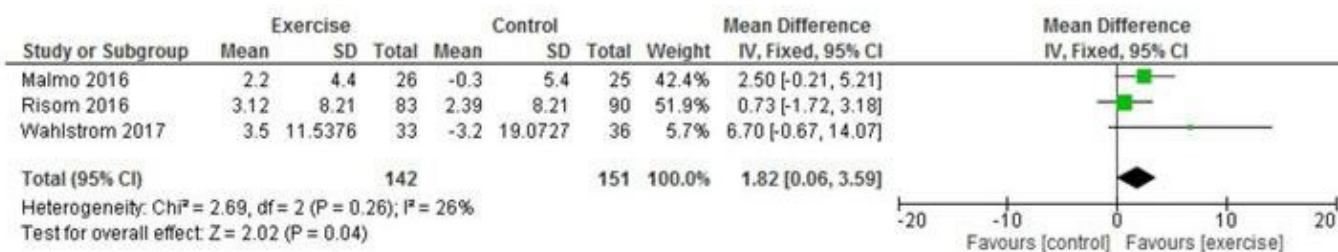
Figure 5 Change in SF-36 physical component score.
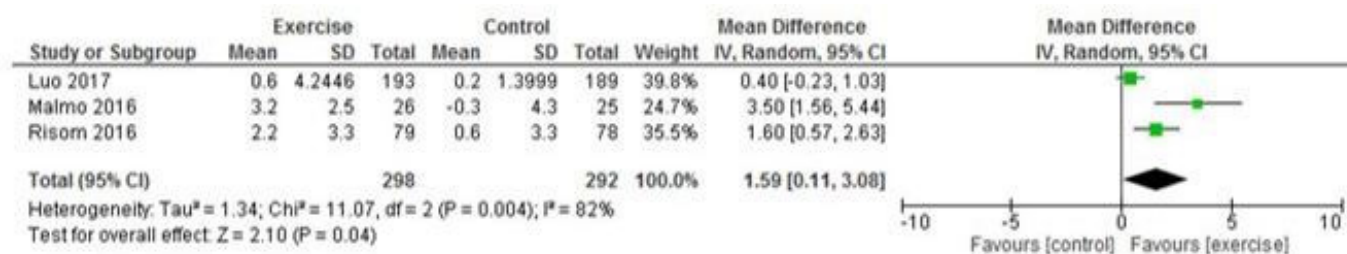
Figure 6 Change in VO$_2$ peak.

between resting and maximum heart rate) was not reported in any of the included studies. Impaired heart rate reserve in patients with permanent AF treated according to a strict rate-control strategy is associated with an increased risk of hospitalisation for patients with heart failure.[41] It is important to note that there is no defined clinical end point for heart rate control. For example, the RACE-II trial compared lenient rate control (target resting heart rate <110 bpm) to strict rate control (target resting heart rate <80 bpm) and found no differences in mortality, hospitalisation, stroke, systemic embolism, major bleeding and arrhythmic events (HR 0.84; 90% CI 0.58 to 1.21).[42]

Our analysis showed left ventricular ejection fraction was significantly increased by exercise-based CR versus control participants. This is especially important in people with AF who derive great benefit from improved systolic function.[43] Limited data from only one study[26] in this analysis reported left atrial volume to be unchanged after exercise-based CR versus control. Larger left atrial size is a strong predictor of AF initiation and propagation, and therefore, any reduction in this parameter is likely to increase the likelihood of a rhythm control strategy.[44] Data on ejection fraction were collected using MRI[26] and two-dimensional echocardiography.[28] Both of these approaches use Simpson's rule to calculate ventricular volume, which brings some consistency. However neither study mentioned, number of beats nor HR at time of recording which given the heterogeneous nature of AF in any given patient could have been a limitation. Finally, it is important to recognise that diastolic function is being recognised as an important risk factor for AF.[45] Left ventricular diastolic function has been shown to be able to predict the occurrence

of AF even when other cardiovascular risk factors are controlled for.[46] However, there were insufficient data in the included studies to allow meaningful analyses.

Strengths and limitations

We believe this to be the most comprehensive systematic review of exercise-based CR for AF to date and found no evidence of publication bias. However, we recognise this study had a number of limitations. First was the small number of eligible studies and considerable variability in terms of their interventions, participants and outcomes. As a result, data pooling was limited to small patient numbers and to small number of common outcomes. The exercise-based CR programmes varied greatly between studies with respect to exercise intensity, duration, frequency and modality. Second, AF burden is difficult to measure due to its heterogeneous nature, and the fact that frequency of symptom severity varies between different AF subtypes. Finally, given the lack of studies and lack of availability of individual patient data no subgroup analyses in relation to the clinical sub-types of AF (ie, first-diagnosed AF, paroxysmal AF, persistent AF, long-standing persistent AF and permanent AF) could be carried out.

Implications for clinical practice and future research

Exercise-based CR represents a promising intervention for people with AF. However, due to insufficient evidence, we believe it is premature to recommend exercise-based CR targeted at patients with AF. Future large-scale trials with well-developed and delivered interventions should be conducted to understand if exercise-based CR can elicit long-term effects on HRQoL and other important clinical outcomes in people with
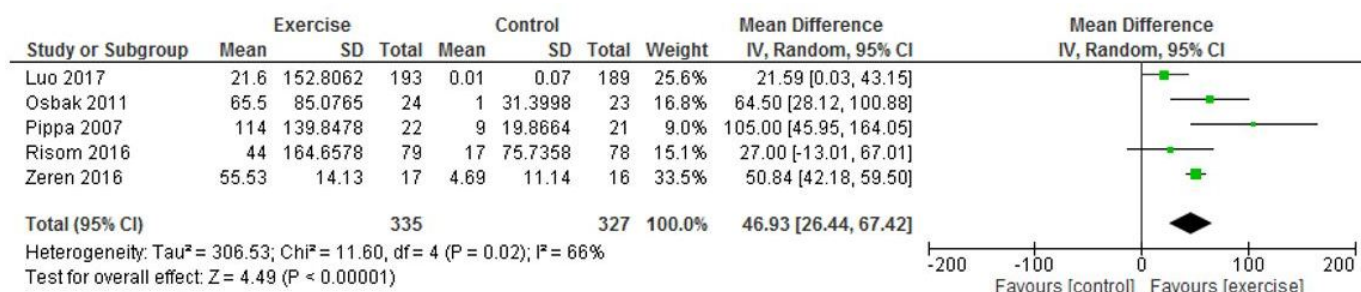
Figure 7 Six-minute walk test.

AF. Such trials should also be adequately powered to investigate potential variations in the impact of exercise-based CR across the various clinical subtypes of AF.

CONCLUSION

Exercise capacity, measures of cardiac function, AF symptom burden and HRQoL were seen to improve in the short term (up to 6 months) with exercise-based CR in people with AF compared with no exercise control. There appeared to be no differences in outcomes between exercise at high and lower intensity. Further high-quality randomised trials which target the specific subtypes of AF are needed to definitively assess the impact of exercise-based CR on key patient and healthcare system outcomes, including HRQoL, clinical events and costs.

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