Buckley, BJ, Long, L, Lane, DA, Risom, S, Fitzhugh, CJ, Berg, SK, Palm, P, Sibilitz, KL, Svendsen, JH, Gluud, C, Zwisler, A-D, Lip, GYH, Neubeck, L and Taylor, RS

Exercise based cardiac rehabilitation for atrial fibrillation: Cochrane systematic review, meta-analysis, meta-regression and trial sequential analysis

Exercise-Based Cardiac Rehabilitation for Atrial Fibrillation: A Cochrane Systematic Review, Meta-Analysis, Meta-Regression, and Trial Sequential Analysis

Benjamin JR Buckley PhD[1,2*] Linda Long PhD[3] Deirdre A Lane PhD[1,4] Signe S Risom PhD[5,6] Charlotte Fitzhugh MSc[2] Selina K Berg PhD [6,7,8,9] Christian Gluud PhD[10,11] Pernille Palm PhD[6] Kirstine L Sibilitz PhD[6] Jesper H Svendsen PhD[6,7] Ann-Dorthe Zwisler PhD[12] Lis Neubeck PhD[13] Gregory YH Lip PhD[1,4] Rod S Taylor PhD[3,9]

[1] Liverpool Centre for Cardiovascular Science, University of Liverpool, Liverpool John Moores University, and Liverpool Heart and Chest Hospital, Liverpool, UK
[2] Cardiovascular Health Sciences, Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK
[3] MRC/CSO Social and Public Health Sciences Unit & Robertson Centre for Biostatistics, Institute of Health and Well Being, University of Glasgow, Glasgow, UK
[4] Department of Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Science, University of Liverpool, Liverpool, UK
[5] Institute of Nursing and Nutrition, University College Copenhagen, Copenhagen, Denmark
[6] Department of Clinical Medicine, Faculty Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[7] Department of Cardiology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark
[8] University of Southern Denmark, Odense, Denmark
[9] National Institute of Public Health & Department of Psychology, University of Southern Denmark, Copenhagen, Denmark
[10] Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Centre for Clinical Intervention Research, The Capital Region, Copenhagen University Hospital – Rigshospitalet , Copenhagen, Denmark
[11] Department of Regional Health Research, The Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
[12] REHPA, The Danish Knowledge Centre for Rehabilitation and Palliative Care, Odense University Hospital, Nyborg, Denmark
[13] Centre for Cardiovascular Health, Edinburgh Napier University, Edinburgh, UK

Corresponding author
Benjamin JR Buckley
Liverpool Centre for Cardiovascular Science,
Liverpool John Moores University, University of Liverpool, and Liverpool Heart and Chest Hospital, Liverpool, UK
B.J.Buckley@ljmu.ac.uk

Word count ~3000

Abstract

Objective To undertake a contemporary review of the impact of exercise-based cardiac rehabilitation (ExCR) for patients with atrial fibrillation (AF).

Data sources CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, WoS Core Collection, LILACS and trial registers were searched from inception to 24 March 2024.

Eligibility criteria Randomised clinical trials (RCTs) comparing ExCR with any non-exercise control.

Design Random-effect meta-analysis was presented as effect estimates and 95% confidence intervals (CIs). Meta-regression examined study level effect modification. Cochrane risk of bias, GRADE, and trial sequential analysis (RTSA) were applied.

Results Twenty RCTs (n=2,039) with mean follow up of 11 months showed ExCR did not impact all-cause mortality (8.3% vs 6.0%, relative risk (RR) 1.06, 95% CI: 0.76 to 1.48) or serious adverse events (2.9% vs 4.1%, RR 1.30, 95% CI 0.66 to 2.56) but did reduce AF symptom severity (mean difference (MD) -1.61, 95%CI: -3.06 to -0.16), AF burden (MD -1.61, 95% CI -2.76 to -0.45), episode frequency (MD -0.57, 95% CI -1.07 to -0.07), episode duration (MD -0.58, 95% CI -1.14 to -0.03), AF recurrence (RR 0.68, 95% CI 0.53 to 0.89), and improved exercise capacity (VO_2 peak: MD 3.18, 95% CI: 1.05 to 5.31 $ml^{-1}.kg^{-1}.min$). There was benefit for the mental component but not the physical component of HRQoL. No differential effects across AF sub-type, ExCR dose, or mode of delivery were seen.

Conclusion Meta-analyses of RCT evidence for ExCR for patients with AF demonstrate several clinical benefits without an increase in serious adverse events or mortality. GRADE and RTSA assessments indicate that further high-quality and adequately powered RCTs are needed.

What is already known

Exercise-based cardiac rehabilitation (ExCR) has shown improvements in functional capacity and quality of life in other cardiac conditions, such as heart failure and coronary artery disease.
Previous studies on atrial fibrillation (AF) have been inconclusive, and ExCR is not currently indicated for AF patients.
The 2017 Cochrane review identified limited RCT evidence, showing some improvements in exercise capacity for AF patients but uncertainty about broader benefits.

What are the new findings

This updated Cochrane review with 20 RCTs shows that ExCR reduces AF recurrence, symptom severity, burden, and episode frequency.
ExCR improves exercise capacity (VO2 peak) and the mental component of health-related quality of life (HRQoL), but not the physical component.
No significant impact of ExCR on all-cause mortality or serious adverse events was found and further well-powered studies are needed for these outcomes.

Introduction

Atrial fibrillation (AF) is the most frequent cardiac arrhythmia. It has been estimated that 6 to 12 million people will develop this condition in the United States by 2050 and 17.9 million in Europe by 2060.[1] AF is a major risk factor for ischaemic stroke and constitutes an important economic burden along with significant morbidity and mortality.[1]

While current medical treatments are effective in controlling symptoms and stroke risk in AF, the addition of patient self-management interventions are potentially key to the management of arrhythmia progression, maintaining functional capacity and health-related quality of life (HRQoL).[2, 3] Exercise-based cardiac rehabilitation (ExCR) is a complex, comprehensive intervention that includes exercise training alongside personalised lifestyle risk factor management, psychosocial intervention, medical risk management, and health behaviour education.[4-6] Based on a strong body of randomised clinical trial (RCT) evidence demonstrating improvements in functional capacity, HRQoL, and reductions in the risk of hospitalisation and associated healthcare costs, ExCR has level I, grade A recommendation for patients following myocardial infarction, percutaneous coronary intervention, and heart failure.[7-9] As the benefits of exercise for people with AF have been unclear, current international guidelines for management of AF do not recommend participation in ExCR.[2, 10]

Our Cochrane review published in 2017, identified six RCTs of ExCR vs. no exercise controls across 421 participants with AF.[11] Whilst showing improvements in functional capacity, the impact of ExCR on participant-reported outcomes and clinical events was uncertain and further trials were needed. Since this review, several additional RCTs have been published.[12] The aim of this study was to undertake a contemporary systematic review with meta-analysis and trial sequential analysis (RTSA) to update the evidence base on the impact of ExCR for participants with AF.

Methods

This systematic review with meta-analyses, meta-regression, and trial sequential analysis was conducted and reported in accordance with the Cochrane Handbook for Interventional Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[13, 14]

Data Sources and Search Strategy The following electronic databases were searched from inception to 24 March 2024, to identify reports of relevant RCTs: Cochrane Central register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, CINAHL, Web of Science Core Collection, and LILACS. The full search strategy is provided in the supplementary file (S1). Reference lists of included studies were checked for any unidentified RCTs. No language restrictions were imposed.

Study Selection

Reviewers (BJRB, LL, SSR, DAL and RT) independently screened all titles, abstracts, and full-text material in duplicate to select studies that met the following eligibility criteria: (1) RCTs regardless of language, publication year, type, or status. (2) Adult participants with AF, or treated for AF (i.e., cardioversion, catheter ablation, etc) were considered for inclusion. (3) Exercise-based interventions were defined as: any rehabilitation programme in an inpatient, outpatient, community, or home-based setting. The rehabilitation programme must have included an exercise training component and may also have included a psycho-educational component (comprehensive rehabilitation). There were no restrictions in the length, intensity, or content of the exercise training programme. (4) Controls could include treatment as usual (e.g., standard medical care, such as drug, cardioversion, and ablation therapy), no intervention, or any other type of cardiac rehabilitation programme or risk factor management, if it did not include exercise training. (5) Trials with co-interventions other than rehabilitation (e.g., drug treatment, ablation, diet) were permitted if they were delivered equally in the experimental and control groups. (6) Primary outcomes included clinical events: all-cause and cardiovascular mortality, serious adverse events as defined in the individual trials which typically included any untoward medical occurrence, any medical event, which had jeopardised the patient or required intervention to prevent it, any hospital admission, or prolongation of existing hospital admission. AF recurrence and burden (recurrence or amount of AF measured via ECG, Holter, smart wearable, or hand-held device). AF symptom severity and burden: the impact of AF on individuals with AF was measured with validated questionnaires, e.g., the European Heart Rhythm Association (EHRA) score and Atrial Fibrillation Severity Scale (AFSS). Secondary outcomes included HRQoL (using generic or disease-specific validated instruments, e.g., Short Form-36 (SF-36), AF Effect on Quality of life quesTionnaire (AFEQT)), and exercise capacity (any measure of exercise capacity, including direct measurement of oxygen uptake (VO_2 peak), or indirect measures such as sub-maximal exercise capacity tests and walking distance (e.g., 6-minute walk test (6MWT)). Full-text copies of all potentially relevant studies were retrieved, and independently assessed for eligibility. The authors resolved disagreements by discussion, and when necessary, a third author mediated. The study selection process was documented using a PRISMA flow chart.

Data Extraction and Quality Appraisal

Two authors (from BJRB, LL, SSR and DAL) independently extracted data and assessed risk of bias from the identified trials using standardised data extraction forms. Data were transferred

into Cochrane's Review Manager (RevMan Web) and R.[15] When insufficient data were published, authors were contacted to provide missing data. 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 eligibility criteria. Risk of bias was assessed using Cochrane's RoB 1 tool plus four additional domains (supplementary file; S2).[13] As all trials would be categorised as having an overall high risk of bias given it is not possible to blind participants and personnel to ExCR, trials were categorised as lower risk of bias if rated low risk in all domains except blinding of participants and personnel.[16, 17]

Statistical analysis

Dichotomous outcomes were expressed as a relative risk (RR) with 95% confidence intervals (CI). Continuous outcomes were expressed as a mean difference (MD) between intervention groups. When studies used different instruments to assess the same outcome (e.g., quality of life or exercise capacity), pooled effect sizes using standardised mean difference (SMD) were calculated. Where mean and standard deviations (SD) were missing, they were sought directly from the trial authors. Where SDs were not presented, they were calculated from 95% confidence intervals or interquartile range following Cochrane guidance. Clinical heterogeneity was explored by comparing the population, experimental intervention and control arm. Statistical heterogeneity was investigated by visual inspection of forest plots, Chi^2 (significance level P=0.10), and I^2 statistic (≥50% and a statistically significant Chi^2 statistic were deemed evidence of a substantial heterogeneity).[13] Funnel plots and Egger tests were used to assess potential small-study effects and publication bias.[13] Data were pooled from each study using random-effect models, which provide more conservative effect estimates. Where trial size permitted, univariate meta-regression was used to explore between trial heterogeneity. All statistical analyses were performed using R.[15] GRADE (Grading of Recommendations Assessment, Development and Evaluation)[18] and trial sequential analysis (RTSA: https://CRAN.R-project.org/package=RTSA)[19] were employed to interpret certainty of results.

Equity, Diversity, and Inclusion Statement

In this Cochrane review, we included participants from a variety of geographic regions, including Europe, Asia, Australia, North and South America. However, most trials were conducted in Europe, and the majority of participants were male (73%), with a mean age of 63 years. This may limit the generalisability of the findings to more diverse populations, particularly underrepresented ethnic groups and women.

The investigator team consisted of researchers from multiple countries and included individuals with diverse academic backgrounds and career stages. We did not specifically aim to recruit investigators based on gender or other characteristics but aimed to bring together a multidisciplinary and geographically diverse team to enhance the breadth of perspectives.

In the meta-regression analysis, we explored any impact on in outcomes by sex, age, geographic region, AF subtype and found no significant impact of these covariates. Future research should prioritise the collection of such data to allow for a more equitable and comprehensive analysis of outcomes.

Results

Study selection

The electronic searches for this update yielded a total of 6063 titles and abstracts, of which, 4538 unique records were eligible for screening resulting in 51 full-text reports assessed for inclusion. A total of 30 studies were excluded. In this review update, we included 14 new RCTs (represented by 15 reports) and one new report of a previously included trial, resulting in 20 RCTs (26 reports). The study selection process is summarised in Figure 1. A summary of included trial characteristics is presented in Table 1. Detail of excluded trial characteristics can be found within the Cochrane review.[11]

Characteristics of included trials and participants

The 20 included trials randomised 2039 participants with AF. All trials were conducted between 2006 and 2024 and most were small and of single centre design. Ten trials were conducted in Europe,[20-29] four in Asia,[30-33], two in Australia,[34, 35], one each in Brazil,[36] Canada,[37] and Russia,[38] and one multi-country trial.[39]

Follow-up periods ranged from 8-weeks to 5 years; nine trials reported follow-up <6-months,[22-25, 27-29, 31, 36] six trials reported follow-up between 6 to 12-months,[21, 30, 32, 33, 35, 37, 38] and four trials reported follow-up >12-months.[20, 26, 34, 39] Four trials included participants with paroxysmal AF,[27, 28, 37, 38] nine trials included persistent or sustained (paroxysmal and persistent) AF,[20, 21, 23, 26, 30, 32, 34, 35, 40] six trials included permanent AF,[22, 24, 25, 29, 31] and one trial was mixed/not defined.[39] Seven trials included participants with symptomatic AF.[23, 26, 27, 30, 34, 35, 38] The mean percentage of male participants across studies was 73% (range 46-100%) and the mean age was 63 years (range 56-71 years).

Five trials assessed comprehensive ExCR, which included educational and/or psychological intervention components,[20, 21, 26, 34, 37] with the remaining 15 RCTs comparing exercise only CR vs. control. All trials employed a 'no formal exercise training' control arm with a range of active components including education, psychological intervention, and usual medical care (i.e., pharmacology and ablation procedures). Eight trials tested purely centre-based rehabilitation,[22-25, 33, 34, 36, 39] seven were remote,[20, 21, 27-29, 31, 38] and five were hybrid (combination of centre and remote).[26, 30, 32, 35, 37]

The exercise training interventions differed in duration (8 to 24 weeks), frequency (1 to 7 sessions per week), session length (15 to 90 minutes per session), and intensity. Intensity of aerobic exercise training was prescribed in a variety of ways including percentage heart rate max, percentage peak exercise capacity, and rating of perceived exertion. Five trials were of overall light aerobic intensity,[25, 27-29, 34] 11 moderate intensity,[20, 22, 24, 26, 30-32, 36-39] and three vigorous intensity.[21, 23, 35] Six of the trials included aerobic and resistance-based exercise training,[22, 26, 30, 32, 36, 37] while the remaining 15 trials included aerobic exercise training only. Of the aerobic-based exercise training interventions, one trial consisted of Qi-gong (slow and graceful movements with a focus on breathing),[25] one inspiratory muscle training,[29] and two were yoga-based interventions.[27, 28]

Risk of bias and GRADE assessment

The overall risk of bias was mixed for included trials (supplementary file; Figures S1 and S2). Details of random sequence generation, allocation concealment, and use of intention to treat analyses were typically poorly reported. However, reporting bias, groups balanced at baseline, performance bias, and for-profit bias were typically well reported and at low risk of bias. Due to the nature of ExCR trials, participant blinding was not possible. Weak evidence of funnel plot asymmetry may be present for exercise capacity measures (VO_2peak and 6MWT). No other outcomes demonstrated clear asymmetry or significant Egger's tests (supplementary file; S2 Figures S3-S13).

Outcomes

A summary of the findings up to 12-months follow-up is presented in Table 2. GRADE assessments for certainty of evidence across all outcomes ranged from very low-to-moderate certainty. Evidence for downgrading of each outcome is presented in Table 2. Results from RTSA are provided throughout the results and summarised in Table 3. RTSA figures are provided in supplement 4 (Figures S17-S26).

All-cause mortality

Nine trials (n=1173 participants) reported all-cause mortality as an outcome. [20, 22-26, 29, 33, 35, 39] Three trials contributed to the effect estimate [20, 26, 39] as the remaining studies reported zero events in each arm. There was no difference in mortality between ExCR vs controls (RR 1.06, 95% CI: 0.76 to 1.48; RTSA CI: 0.03 to 31.43; studies = 9; I^2 = 0%; Figure 2a). We assessed the evidence for mortality to be of low certainty using GRADE.

Serious adverse events

Ten trials (n=825 participants) reported serious adverse events [21-26, 30, 33, 35, 36, 41]. Six trials contributed to the effect estimate [23-26, 30, 35, 37], as the remaining four studies reported zero events in each arm. There was no difference in serious adverse events between ExCR and controls (RR 1.30, 95% CI: 0.66 to 2.56; RTSA CI: 0.00 to >100; studies = 10; I^2 = 0%; Figure 2b). Evidence for serious adverse events was assessed as very low certainty.

AF recurrence

Four trials (n=378) reported AF recurrence dichotomously, measured with Holter monitors worn for various lengths of time [30, 34, 35, 38]. Moderate certainty of evidence demonstrated a benefit of ExCR vs controls (RR 0.68, 95% CI 0.53 to 0.89; RTSA CI: -0.33 to 1.29; I^2 = 0%; Figure 3).

AF symptom severity

Five trials reported the AFSS [20, 23, 34, 35, 37], although not all trials contributed to all components. AF symptom severity (GRADE: low certainty of evidence), demonstrated a benefit for ExCR vs controls (MD -1.61, 95% CI: -3.06 to -0.16; RTSA CI: -3.94 to 0.76; participants = 600; studies = 5; I^2 =61%; Figure 4a); AF burden – moderate certainty of evidence, demonstrated a benefit for ExCR vs controls (MD -1.61, 95% CI -2.76 to -0.45; RTSA CI: -2.74 to -0.44; participants = 317; studies = 3; I^2 =0%; Figure 4b); AF episode frequency – low certainty of evidence, demonstrated a benefit for ExCR vs controls (MD -0.57, 95% CI -1.07 to -0.07; RTSA CI: CI -1.27 to -0.13; participants

= 368; studies = 3; I^2 =0%; Figure 4c); AF episode duration – moderate certainty of evidence, demonstrated a benefit for ExCR vs controls (MD -0.58, 95% CI -1.14 to -0.03; RTSA CI: -1.36 to 0.19; participants = 317; studies = 3; I^2 =0%; Figure 4d).

HRQoL

Fourteen trials included a validated HRQoL measure (supplementary file; S3). Eleven trials reported the SF-36, four reported the Minnesota Living with Heart Failure questionnaire, two reported the disease specific AF Effect on QoL questionnaire (AFEQT), one reported the Kansas City Cardiomyopathy Questionnaire (KCCQ), one reported the disease specific AF-QoL, one reported the EQ-VAS, and one reported the EQ-5D. As most trials reported the SF-36, this measure was meta-analysed. SF-36 mental component summary measure (MCS) – moderate certainty of evidence demonstrated a benefit of ExCR vs controls, (MD 2.67, 95% CI 0.89 to 4.45; RTSA Naïve CI: 1.14 to 4.14; participants = 504; studies = 6; I^2 = 2%; Figure 5a). SF-36 physical component summary measure (PCS) – very low certainty of evidence demonstrated no clear difference between ExCR vs controls (MD 1.77, 95% CI -0.17 to 3.71; RTSA CI: −2.46 to 5.96; participants = 504; studies = 6; I^2 = 52%; Figure 5).

Exercise capacity

Exercise capacity was reported as VO_2peak and six-minute walk test (6MWT), measured up to 12-months follow up. Low certainty of evidence demonstrated a benefit of ExCR on VO_2peak vs controls (MD 3.18, 95% CI 1.05 to 5.31; RTSA CI: -24.52 to 29.66; participants = 791; studies = 7; I^2 = 91%; Figure 6). Meta-analyses for 6MWT and the pooled standardised mean difference (SMD) effect estimate of VO_2 peak and 6MWT are presented in the supplementary file (S4). The SMD for exercise capacity was used for meta-regression due to having the largest sample size.

Meta-regression

Due to limitations in the number of included trials and outcomes reported, we were only able to investigate potential trial level moderators of ExCR effects for serious adverse events and exercise capacity (SMD) up to 12-months follow-up. The only significant associations were in exercise capacity, where smaller improvements were seen in trials with longer follow up (P=0.019) and larger improvements were seen in trials conducted in South America (p=0.029) (Table 4 and Figure S16, supplementary file)).

Discussion

This Cochrane systematic review and meta-analysis including meta-regression and RTSA incorporated data from 20 RCTs in 2,039 participants with AF. Compared with controls, ExCR resulted in reduced AF severity, burden, and recurrence and improvements in mental components of HRQoL, and exercise capacity. The effects of ExCR were consistent across trials irrespective of AF subtype, participant characteristics, and the nature of ExCR intervention (including dose and setting). Whilst there was no significant difference between ExCR vs controls in the risk of all-cause mortality and the composite outcome of serious adverse events, the number of events across trials was low and therefore underpowered.

Studies have suggested that maintaining sinus rhythm improves HRQoL and patients can experience distress when trying to handle symptoms of AF such as palpitations, dyspnoea, and fatigue.[42, 43] As AF recurrence was not available in previous meta-analyses, we are unable to compare our AF recurrence findings with previous systematic reviews. However, recent observational evidence has reported ExCR to be associated with a lower risk of AF progression compared to matched non-exercise controls (OR 0.74, 95% CI 0.66 to 0.83).[44] This effect size is consistent with our pooled reduction in AF recurrence following ExCR (RR 0.68, 95% CI 0.53 to 0.89). Given that recurrent AF is associated with increased healthcare utilisation, greater AF burden, and higher rates of progression to persistent AF, this reduction is clinically meaningful.[45] A relative risk reduction of 32% suggests that structured exercise interventions may play a key role in improving symptom control, reducing the need for additional medical interventions (e.g., repeat cardioversion or ablation), and ultimately enhancing long-term disease management in AF patients.

Although we found an improvement in HRQoL in terms of the mental health component of the SF-36, the improvement in physical health component was not statistically significant. This may reflect that as a generic tool, the SF-36 may be less sensitive to clinically important, disease-specific changes in HRQoL This hypothesis is supported by the observed improvements seen in various AFSS domains in our present analyses, particularly of note are improvements in symptom severity and burden following ExCR. A recent non-Cochrane systematic review with 12 studies demonstrated that aerobic exercises (aerobic interval training, Qigong, yoga, and
ExCR) were all associated with improvements in sub-components of in HRQoL measured via SF-36 tool.

Although we observed an improvement in the mental health component of the SF-36, the change in the physical health component did not reach statistical significance. This may suggest that, as a generic tool, the SF-36 is less sensitive to clinically meaningful, disease-specific changes in HRQoL. .[46, 47] This interpretation is supported by the improvements noted in several AFSS domains in our current analysis, particularly symptom severity and AF burden following ExCR. A recent non-Cochrane systematic review of 12 studies further supports this finding, showing that aerobic interventions such as aerobic interval training, Qigong, yoga, and ExCR were associated with only small improvements in mental and physical components of SF-36 for patients with AF.[48]

The findings of this review provide an important update on the evidence seen previously in the 2017 Cochrane systematic review including 6 RCTs in 421 participants [11] and the 2018 Smart et

al. review and meta-analysis with 9 RCTs in 959 participants.[49] Consistent with the present update, both these previous reviews reported improvements in exercise capacity, as expected. However, with access to a larger body of evidence, our meta-analysis results show greater precision of exercise capacity effects following ExCR. Our results have clinical significance. For example, the demonstrated improvement in mean pooled VO_2 peak of 3.18 $ml.kg^{-1}.min^{-1}$ is not only statistically significant (95% CI: 1.05 to 5.31) but also clinically important, given a 1 $ml.kg^{-1}.min^{-1}$ improvement has traditionally been accepted as a clinically meaningful change.[50, 51]

Various mechanisms have been proposed for how exercise-based interventions can lead to improvement in AF participant outcomes.[12, 52] While improvements in traditional cardiovascular risk factors likely account for a substantial proportion of the benefit, additional mechanisms may directly impact AF burden and recurrence. Exercise training promotes favorable atrial remodeling, including reduced atrial stiffness and fibrosis, which may help limit AF substrate development, though further research is needed.[53] Enhanced vagal tone, a well-documented adaptation to endurance training, has been implicated in both AF promotion and suppression, depending on the extent of autonomic remodeling.[52, 54] Moderate-intensity exercise within ExCR programs may optimise autonomic balance, preserving heart rate variability and parasympathetic benefits. Additionally, exercise-induced improvements in vascular function and hemodynamics, including enhanced endothelial function, arterial compliance, and left atrial hemodynamics, may reduce AF morbidity by improving overall cardiovascular efficiency.[53, 55, 56]

While the mechanisms underlying benefits of ExCR are multifaceted, they may also extend beyond improvements in physiological measures. Exercise training is known to have psychological benefits, including reductions in anxiety and depression, which are prevalent in individuals with AF and can exacerbate symptom perception. Collectively, these adaptations provide plausible mechanisms through which ExCR not only supports general cardiovascular health and wellbeing but also yields AF-specific benefits, including reductions in AF recurrence post-treatment and improvements in self-reported AF burden and severity.

While regular physical activity and exercise training reduces AF risk, a U-shaped relationship has been observed, with ‘excessive’ endurance exercise potentially increasing AF prevalence, particularly among master athletes.[52] The mechanisms underlying this phenomenon may include atrial remodeling, heightened vagal tone, and exercise-induced inflammation.[52] However, it is important to note that this subgroup represents a very small fraction of the overall AF population. Although we don’t expect this subgroup to be attending ExCR, the ESC Sports Cardiology Guidelines recognise the need for individualised exercise prescriptions in this context.[57] The guideline recommends that if no AF recurrence occurs within 1 month of an ablation procedure, sports activity may be resumed. However, it is unknown whether continuation of sports after successful ablation might progress the disease process. And therefore, no firm recommendation can be made about the ‘safe’ dose of activity level following ablation. Thus, ExCR may provide safe and effective physical activity for AF patients across the spectrum, but more tailored support is needed with those who have developed ‘athletic AF’.

Strengths and Limitations

This is to our knowledge the most comprehensive contemporary review to date of RCT evidence assessing the impact of ExCR. However, our review has several potential limitations. Risk of bias varied substantially, with several trials inadequately reporting trial methods of random sequence generation, allocation concealment, and intention-to-treat analysis. The number of trials reporting primary outcomes of interest were few. Furthermore, given the nature of ExCR, participant blinding is impossible and therefore patient-reported outcomes such SF-36 and AFSS are subject to reporting bias. Most included trials were relatively small and had short-term follow-up. The number of reported deaths and serious adverse events were small, which substantially reduced certainty. There was considerable clinical heterogeneity across trials both in terms of patient population and nature of ExCR. Most participants were male, and better female representation is needed in future trials. We considered heterogeneity by undertaking more conservative random-effects meta-analyses. There was potential evidence of publication bias with funnel plot asymmetry for exercise capacity measures.

Implications

Although GRADE and RTSA assessment indicated that additional trials would improve certainty and precision, there is now a body of evidence showing the beneficial impact of ExCR in terms of AF severity, burden, and recurrence, as well as HRQoL and exercise capacity. Although further research is needed, meta-regression indicated that effects were consistent across a range of patient and intervention characteristics (for exercise capacity). AF management guidelines should reflect this updated evidence base by recommending ExCR alongside drug and ablation therapies for patients with AF. The commissioning and funding of future evidence generation for ExCR should prioritise well-conducted large multicentre RCTs, recruiting representative AF populations and adequately powered for AF-specific outcomes, including recurrence and clinical events.

Conclusions

This comprehensive systematic review with meta-analysis, meta-regression, and trial sequential analysis of RCTs demonstrates participation in ExCR reduces disease recurrence, severity and burden and improves exercise capacity and HRQoL for participants with AF.

Acknowledgements
We thank Charlene Bridges for running the initial database searches.

Contributions of authors
BJRB is the guarantor. BJRB and RT drafted the manuscript. Meta-analysis, meta-regression, and trial sequential analysis (RTSA) were completed in R by BJRB. BJRB, LL, DAL, SSR, CF and RT identified the included trials, extracted data and assessed bias from the trials in duplicate. All authors have reviewed, revised, and approved the final version of the review for publication.

Competing interests
Ben Buckley - has received investigator-initiated research grants from BMS/Pfizer, Huawei EU and consultancy fees from Huawei EU.
Deirdre Lane - has received investigator-initiated educational grants from Bristol-Myers Squibb (BMS) and Pfizer, has been a speaker for Bayer, Boehringer Ingelheim, and BMS/Pfizer and has consulted for BMS and Boehringer Ingelheim.
Christian Gluud – No known conflicts of interests.
Lis Neubeck has received investigator-initiated grants from BMS Pfizer and Daiichi Sankyo
Signe Stelling Risom – No known conflicts of interests
Pernille Palm – No known conflict of interests
Jesper Hastrup Svendsen – has received institutional research grant from Medtronic outside this work, speaker fee from Medtronic and he is a member of a Medtronic advisory board
Charlotte Fitzhugh – No known conflicts of interests

Funding
Not applicable
Ethical approval
Not applicable
Data sharing statement
Not applicable
Patient involvement
No

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Figure legends

Figure 1. PRISMA flow diagram.

Figure 2. Forest plot: Effects of exercise-based cardiac rehabilitation vs. control on all-cause mortality (a) and serious adverse events (b) in patients with AF.

Figure 3. Forest plot: Effects of exercise-based cardiac rehabilitation vs. control for AF recurrence measured via Holter monitoring in patients with AF.

Figure 4. Forest plot: Effects of exercise-based cardiac rehabilitation vs. control ExCR vs. control for AFSS Symptom Severity (a), AF Burden (b), Episode Frequency (c), and Episode Duration (d) in patients with AF.

Figure 5. Forest plot: Effects of exercise-based cardiac rehabilitation vs. control for SF-36 Mental Component Score (a) and SF-36 Physical Component Score (b) in patients with AF.

Figure 6. Forest plot: Effects of exercise-based cardiac rehabilitation vs. control for cardiorespiratory fitness presented as VO_2peak ($ml \cdot kg^{-1} \cdot min^{-1}$) in patients with AF. Except for Luo 2019 where pre-post change scores are presented.

Tables

Table 1. Summary of trial, population, and intervention characteristics of included trials.

Characteristics	**Number of studies (%) or median of study means (range)**
Trial	
Publication year	
2000-2009	2 (10%)
2010-2019	10 (50%)
2020 onwards	8 (40%)
Study continent	
Europe	11 (55%)
Asia	4 (20%)
America	2 (10%) (1 North, 1 South)
Australia	2 (10%)
Other/Mixed	1 (5%)
Single centre	17 (85%)
Sample size	68 (30-382)
Follow-up duration	6 (2-12)
Population characteristics	
% Male	72 (46-100)
Age (years)	63 (56-71)
AF subtype	
Paroxysmal	4 (20%)
Persistent	2 (10%)
Sustained (Paroxysmal + Persistent)	7 (35%)
Permanent	6 (30%)
Mixed/NR	1 (5%)
Received catheter ablation + ExCR	6 (30%)
Intervention characteristics	
Intervention type	

Exercise only	15 (75%)
Comprehensive programme	5 (25%)
Intervention dose	
Duration	12 weeks (8-52)
Frequency	3 sessions/week (1-7)
Length	40 mins/session (15-90)
Intensity	
Light	5 (25%)
Moderate	11 (55%)
Vigorous	4 (20%)
Setting	
Centre-based only	8 (40%)
Home-based only	7 (35%)
Hybrid (combination of centre and home-based)	5 (25%)

Table 2. Summary of Findings.

Primary Outcomes						
Patient or population: adults with atrial fibrillation **Setting:** in hospital, community centres, and home-based **Intervention:** ExCR **Comparison:** Non-exercise controls						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Quality of evidence (GRADE)**	**Comments**
	Risk with No exercise	**Risk with Exercise**				
Mortality Follow-up: 2 to 60 months	80 per 1000	88 per 1000 (63 to 124)	RR 1.06 (0.76 to 1.48)	1173 (9 RCTs)	⨁⨁⨀⨀ LOW[1]	ExCR has little to no impact on all-cause mortality. Several studies had no events in either the intervention arm or the control arm. Studies were downgraded due to risk of bias and imprecision.
Serious adverse events Follow-up: 2 to 12 months	30 per 1000	41 per 1000 (20 to 85)	RR 1.30 (0.66 to 2.56)	825 (10 RCTs)	⨁⨁⨀⨀ LOW[2]	ExCR has little to no impact on serious adverse events. Several studies had no events in either the intervention arm or the control arm. Studies were downgraded due to risk of bias, inconsistency, and imprecision.
AF recurrence assessed with Holter monitors Follow-up: 3 to 12 months	460 per 1000	322 per 1000 (258 to 405)	RR 0.68 (0.53 to 0.89)	378 (4 RCTs)	⨁⨁⨁⨀ MODERATE[3]	ExCR likely reduces AF recurrence in the short-term (up to 12 months). Studies were downgraded due to risk of bias.

AF symptom severity assessed with AFSS Lower = better Follow-up: 3 to 12 months	The mean AF symptom severity in the control groups was 7.1 points	The mean AF symptom severity in the exercise groups was 1.6 points lower (3.0 to 0.2 lower)		600 (5 RCTs)	⨁⨁⊖⊖ LOW[4]	ExCR may reduces AF symptom severity in the short-term (up to 12 months). Studies were downgraded due to risk of bias and inconsistency.
AF burden assessed with AFSS Lower = better Follow-up: 3 to 12 months	The mean AF burden in the control groups was 14.3 points	The mean AF burden in the exercise groups was 1.6 points lower (2.8 to 0.5 lower)		317 (3 RCTs)	⨁⨁⨁⊖ MODERATE[5]	ExCR likely reduces AF burden in the short-term (up to 12 months). Studies were downgraded due to risk of bias.
Quality of life assessed with SF-36 MCS Scale: 0 to 100 Higher = better Follow-up: 20 weeks to 12 months	The mean quality of life in the control groups was 48.5 points	The mean quality of life in the exercise groups was 2.7 points higher (1 to 4.5 higher)		504 (6 RCTs)	⨁⨁⨁⊖ MODERATE[6]	ExCR probably improves the mental components of health-related quality of life in the short-term (up to 12 months). Studies were downgraded due to risk of bias.
Quality of life assessed with SF-36 PCS Scale: 0 to 100 Higher = better Follow-up: 20 weeks to 12 months	The mean quality of life in the control groups was 42.5	The mean quality of life in the exercise groups was 1.8 points higher (0.2 lower to 3.7 higher)		504 (6 RCTs)	⨁⊖⊖⊖ VERY LOW 7	It is very unclear about the effect of ExCR on the physical components of health-related quality of life in the short-term (up to 12 months). Studies were downgraded due to risk of bias, inconsistency, and imprecision.

*__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, __ExCR__; Exercise-based cardiac rehabilitation, __RR__; Risk ratio, __GRADE__; Grading of Recommendations Assessment, Development and Evaluation (a systematic approach to rating the certainty of evidence), __AFSS__; Atrial Fibrillation Symptom Severity questionnaire.
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
1 Downgraded by 1 level for serious risk of bias (most weighted trial (97%) was deemed high risk of intention to treat) and by 1 level for serious imprecision (low event rate for precision (<300 events; n=101) and wide 95% CIs including both benefit and harm).
2 Downgraded by 1 level for serious risk of bias, and by 1 level for serious imprecision. Largest (and most influential trial) has crucial attrition bias. Low event rate for precision (<300 events; n=38) and wide 95% CIs including both benefit and harm.
3 Downgraded by 1 level for serious risk of bias. The largest (and hence most influential) trial has attrition bias with >20% dropout in the control arm.
4 Downgraded by 1 level for serious risk of bias and by 1 level for inconsistency. Crucial risk of bias for at least one criterion across all trials (participant blinding). Outcome measure is a PRO. Substantial statistical heterogeneity (Chi2 p=0.04, I2=61%).
5 Downgraded by 1 level for serious risk of bias. Crucial risk of bias for at least one criterion across all trials (participant blinding). Outcome measure is a PRO.
6 Downgraded by 1 level for serious risk of bias. Crucial risk of bias for at least one criterion across all trials (participant blinding). Outcome measure is a PRO.
7 Downgraded by 1 level for serious risk of bias, by 1 level for serious inconsistency, and by 1 level for serious imprecision. Crucial risk of bias for at least one criterion across all trials (participant blinding). Outcome measure is a PRO. Substantial statistical heterogeneity (Chi2 p=0.06, I2=52%). Summary effect estimate is largely positive, though includes no effect. Therefore, imprecision may be a serious issue.

Table 3. RTSA: Trial Sequential Analysis findings.

Primary outcomes						
Analysis	Method	AIS	DARIS (D^2)	Random effects CI	RTSA adjusted CI	Conclusion
1.1 All-cause mortality	20% RRR Random effects Alpha 1.25% Beta 10% 2 sided analytic RTSA	1,173	13 354 (0%)	0.76 to 1.48	0.03 to 31.43	More trials warranted
1.2 Serious adverse event	20% RRR Random effects Alpha 1.25% Beta 10% 2 sided analytic RTSA	825	35 191 (0%)	0.66 to 2.56	0.00 to >100	More trials warranted
1.3 AF recurrence	RRR 20% Random effects Alpha 1.25% Beta 10%	378	1 636 (0%)	0.53 to 0.89	0.33 to 1.29	More trials warranted
1.4 AFSS Symptom Severity	MCID 2 (SD 5) Random effects Alpha 1.25% Beta 10% 2 sided analytic RTSA	600	952 (68%)	-3.06 to -0.16	−3.94 to 0.76	More trials warranted
1.5 AFSS Burden	MCID 2 (SD 5) Random effects Alpha 1.25% Beta 10% 2 sided analytic RTSA	317	365 (0%)	-2.76 to -0.45	−2.74 to −0.44 (SW adjusted)	More trials warranted

1.6 HRQoL MCS	MCID 3 (SD 12) Random effects Alpha 1.25% Beta 10%	504	455 (7%)	0.89 to 4.45	1.21 to 4.14 (RTSA Naïve CI)	More trials warranted
1.7 HRQoL PCS	MCID 3 (SD 12) Random effects Alpha 1.25% Beta 10%	504	1 153 (65%)	-0.17 to 3.71	−2.46 to 5.96	More trials warranted
Secondary outcomes						
1.8 AFSS Episode Frequency	MCID 3 (SD 6) Random effects Alpha 1.25% Beta 10% 2 sided analytic	317	365 (0%)	-1.07 to –0.07	−1.27 to 0.13	More trials warranted
1.9 AFSS Episode Duration	MCID 3 (SD 6) Random effects Alpha 1.25% Beta 10% 2 sided analytic	317	365 (0%)	-1.14 to -0.03	−1.36 to 0.19	More trials warranted
1.10 Cardiorespiratory fitness (VO_2 peak)	MCID 2 (SD 6) Random effects Alpha 1.25% Beta 10%	791	10 749 (98%)	1.05 to 5.31	-24.52 to 29.66	More trials warranted

RTSA was conducted in RStudio using the meta-analytical data conducted using meta and metafor packages. RTSA was conducted using the RTSA package in RStudio with the following protocol; type = analysis, outcome = RR, two-sided alpha corrected via modified Bonferroni adjustment, beta = 0.1, alpha and beta spending boundaries = Lan & DeMets version of O'Brien-Fleming boundaries, minimum clinically important difference = 0.8 for binary outcomes (mortality, serious adverse event, AF recurrence), 3 points for AFSS, 5 points for HRQoL, and 2 $ml \cdot kg^{-1} \cdot min^{-1}$ for VO_2peak. It was not possible to calculate RTSA adjusted CIs for several measures.

AIS; Achieved information size, **RRR**; Relative risk reduction, **DARIS**; Diversity adjusted required information size, **CI**; Confidence interval, **RTSA**; RStudio Trial Sequential Analysis, **AFSS**; Atrial Fibrillation Symptom Severity questionnaire, **HRQoL**; Health-related quality of life, **MCS**; mental component scale, **PCS**; Physical component scale.

Table 4. Meta-regression results.

Regression variable	**Serious adverse events** ***P*-value**	**Exercise capacity** ***P*-value**
Publication year	0.291	0.395
Continent	0.781	0.0053 (South America; 0.029)
Exercise only vs comprehensive rehabilitation	0.838	0.137
Risk of bias	0.525	0.189
Sample size	0.345	0.077
Mean age	0.799	0.910
% male	0.969	0.147
AF subtype	0.217	0.540
Catheter ablation	0.279	0.099
DOACs (published 2013 onwards after release of DOACs in 2010)	0.287	0.104
Exercise type (aerobic, resistance, mixed, IMT)	0.577	0.295
Exercise duration	0.546	0.231
Exercise frequency	0.488	0.938
Exercise programme length	0.597	0.695
Aerobic exercise dose	0.662	0.154
Setting (home, centre, hybrid)	0.195	0.127
Longest follow-up (months)	0.380	0.019
Aerobic exercise intensity (light, moderate, vigorous)	0.675	0.416

Univariate meta-regression was completed in R using meta and metafor packages. Studies with NAs / zero events were omitted from model fitting.
DOACs; direct oral anticoagulant, **AF**; atrial fibrillation, **IMT**; inspiratory muscle training.