**Exercise-based cardiac rehabilitation and all-cause mortality among patients with atrial fibrillation**

Benjamin J.R. Buckley, PhD1,2\*, Stephanie L. Harrison, PhD1,2, Elnara Fazio-Eynullayeva, MA3, Paula Underhill4, Deirdre A. Lane, PhD1,2,5, Dick H.J. Thijssen, PhD6,7, Gregory Y.H. Lip, MD1,2,5

1Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom

2Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, United Kingdom

3TriNetX LLC., Cambridge, MA, United States

4TriNetX LLC., London, United Kingdom

5Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

6Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, UK

7Research Institute for Health Science, Department of Physiology, Radboud University Medical Centerum, Nijmegen, The Netherlands

**Date** April 14th, 2021

**Manuscript wordcount** 2,761

**\*Corresponding author** Benjamin Buckley PhD, Liverpool Centre for Cardiovascular Science, University of Liverpool, William Henry Duncan Building, Liverpool, L7 8TX United Kingdom

Email: Benjamin.Buckley@liverpool.ac.uk.

Phone: +44 (0)151 794 2000

**Abstract**

**Background**

There is limited evidence of long-term impact of exercise-based CR on clinical endpoints for patients with AF. We therefore compared 18-month all-cause mortality, hospitalisation, stroke, and heart failure in patients with AF and an electronic medical record (EMR) of exercise-based CR to matched controls.

**Methods and Results**

This retrospective cohort study included patient data obtained on February 3, 2021 from a global federated health research network. AF patients undergoing exercise-based CR were propensity score matched to AF patients without exercise-based CR by age, sex, race, co-morbidities, procedures, and medication. We ascertained 18-month incidence of all-cause mortality, hospitalisation, stroke, and heart failure.

Of 1,366,422 patients with AF, 11,947 patients had an EMR of exercise-based CR within 6-months of incident AF who were propensity score matched with 11,947 AF patients without CR. Exercise-based CR was associated with 68% lower odds of all-cause mortality (odds ratio 0.32, 95% confidence interval (CI) 0.29-0.35), 44% lower odds of hospitalisation (0.56, 95% CI 0.53-0.59), and 16% lower odds of incident stroke (0.84, 95% CI 0.72-0.99) compared to propensity score matched controls. No significant associations were shown for heart failure at 18-months (0.93, 95% CI 0.84-1.04). The beneficial association of exercise-based CR on all-cause mortality was independent of sex, older age, comorbidities, and AF subtype.

**CONCLUSIONS**

Exercise-based CR among patients with incident AF was associated with lower odds of all-cause mortality, hospitalisation, and stroke at 18-months follow-up, supporting the provision of exercise-based CR for patients with AF.

**Key words**: Preventive Cardiology; Arrhythmia; Cardiovascular Disease; Multimorbidity; Cohort Study

**Abbreviations**

ACC; American College of Cardiology

AF; Atrial fibrillation

AHA; American Heart Association

BMI; Body mass index

CR; Cardiac rehabilitation

CRF; Cardiorespiratory fitness

CDC; Centers for Disease Control and Prevention

EMR; Electronic medical record

ESC; European Society of Cardiology

GEMs; General equivalence mappings

HF; Heart failure

ICD-10-CM; Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification

MET; Metabolic equivalent

PSM; Propensity score matching/matched

**Clinical Perspective**

**What is new?**

* In the present study, we investigated the association of exercise-based cardiac rehabilitation (CR) on all-cause mortality, hospitalisation, stroke, and heart failure in patients with atrial fibrillation (AF).
* In this retrospective cohort study of 23,894 patients with incident AF, exercise-based CR was associated with 68% lower odds of all-cause mortality, 44% lower odds of hospitalisation, and 16% lower odds of incident stroke, compared to matched controls at 18-months follow-up.

**What are the clinical implications?**

* Exercise-basedCR may be beneficial for patients with AF on important clinical endpoints, supporting the inclusion of patients with incident AF for exercise-based CR.

**Introduction**

Cardiac rehabilitation (CR) and exercise promote secondary prevention of cardiovascular disease and associated adverse events. Exercise-based CR is therefore an essential component of routine care for patients with acute coronary syndrome, those undergoing revascularisation (coronary artery bypass graft or percutaneous coronary intervention), and those with heart failure.1, 2 In patients with coronary heart disease, exercise-based CR has been shown to improve exercise capacity, health-related quality of life, reduce hospitalisations, and depending on the source of evidence, reduce all-cause or cardiovascular-related mortality.3

Regular exercise has been shown to have potent protective effects in the primary and secondary prevention of atrial fibrillation (AF).4 For example, exceeding 500 MET-mins/week (metabolic equivalents) has been associated with reduced risk of incident AF.5 In addition, greater cardiorespiratory fitness (CRF) was associated with increased freedom of AF and for every 1 MET increase in CRF, AF recurrence was reduced by 9%.6, 7 One randomised controlled trial compared CR to usual care for 210 patients treated with catheter ablation for AF.8 Findings revealed a significantly higher (~1 MET) CRF at 4-months in CR compared to usual care. Despite such promising evidence for the beneficial effect of exercise as secondary prevention for patients with AF, exercise-based CR is not part of any routine care pathways for patients with AF. In addition, there is currently no evidence of the long-term impact of exercise-based CR on important clinical endpoints for patients with AF.9

Utilising a large online database, we explored the hypothesis that exercise-based CR is associated with reduced all-cause mortality, hospitalisation, and cardiovascular morbidity in patients with AF. Therefore, the aim of the present study, using a global federated health research network, was to compare 18-month all-cause mortality, hospitalisations, stroke, and heart failure in patients with AF and an electronic medical record (EMR) of exercise-based CR to propensity score matched patients with AF and no EMR of exercise-based CR.

**Methods**

Data Availability Statement: To gain access to the data in the TriNetX research network, a request can be made to TriNetX (https://live.trinetx.com), but costs may be incurred, a data sharing agreement would be necessary, and no patient identifiable information can be obtained.

Study Design and Participants

This retrospective observational study was conducted with data provided by TriNetX, a global federated health research network with access to EMRs from participating academic medical centres, specialty physician practices, and community hospitals, predominantly in the United States. Patients with AF were identified in TriNetX based on Centers for Disease Control and Prevention (CDC) coding.10 AF was identified from International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification (ICD-10-CM) codes in patient EMRs: I48 (Atrial fibrillation and flutter), I48.0 (Paroxysmal atrial fibrillation), I48.1 (Persistent atrial fibrillation), and I48.21 (Permanent atrial fibrillation). Exercise-based CR was identified from ICD-10-CM codes Z71.82 (Exercise counselling), Healthcare Common Procedure Coding System (HCPCS) code S9472 (CR program, non-physician provider, per diem), or Current Procedures Terminology (CPT) code 1013171 (Physician or other qualified health care professional services for outpatient CR). Diagnoses in TriNetX are represented by ICD-10-CM codes. If a healthcare organization provided data in ICD-9-CM, TriNetX uses a 9-to-10-CM mapping based on general equivalence mappings (GEMs) plus custom algorithms and curation to transform data from ICD-9-CM to ICD-10-CM. These exercise-based CR codes were used as exclusion criteria in the propensity score matched control cohorts. This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and the checklist can found as a supplement (eTable 1).11

As a federated network, research studies using the TriNetX network do not require ethical approval or patient informed consent as no patient identifiable information is received.

Data Collection

The TriNetX network was searched on February 3, 2021 and an anonymised dataset from 2009 to 2020 of patients with incident AF was analysed. The exercise-based CR cohort were aged ≥18 years with CR and/or exercise programmes recorded in EMRs within 6-months of an incident AF diagnosis. Controls were aged ≥18 years with a diagnosis of AF and no history of exercise-based CR in EMRs. For both the exercise-based CR cohort and controls, patients with AF were identified in EMRs from at least 18-months prior to the search date to ensure a minimum follow-up of 18-months from AF diagnosis (12-months from CR). At the time of the search, 41 participating healthcare organisations had data available for patients who met the study inclusion criteria. Thus, following propensity score matching, the cohort consisted of patients with AF who either were referred for exercise-based CR (due to cardiovascular disease) within 6-months of an incident AF diagnosis (intervention) or were not referred for exercise-based CR (control).

Statistical Analysis

All statistical analyses were completed on the TriNetX online platform. Baseline characteristics were compared using chi-squared tests for categorical variables and independent-sample t-tests for continuous variables. Current CR provision is typically reserved for cardiovascular patients following an acute coronary syndrome, those undergoing a revascularisation procedure (coronary artery bypass graft or planned percutaneous coronary intervention), and patients with heart failure. Thus, propensity score matching (PSM) was used to control for these differences in the two cohorts. Exercise-based CR patients and controls were 1:1 PSM using logistic regression for age at AF diagnosis, sex, race, hypertensive diseases, ischaemic heart diseases, heart failure, cerebrovascular diseases, diabetes mellitus, chronic kidney disease, respiratory diseases, nervous system diseases, neoplasms, cardiovascular procedures (e.g. cardiography, echocardiography, cardiac catheterisation, revascularisation (e.g., percutaneous coronary intervention or coronary artery bypass graft), cardiac devices, electrophysiological procedures), and cardiovascular medications (e.g. beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, ACE inhibitors). These variables were chosen because they are established risk factors for AF and/or mortality or were significantly different between the two cohorts.12 The TriNetX platform uses ‘greedy nearest-neighbour matching’ with a caliper of 0.1 pooled standard deviations. Following PSM, logistic regressions produced odds ratios with 95% confidence intervals (CIs) for 18-month incidence of all-cause mortality, hospitalisation, stroke, and heart failure, comparing exercise-based CR with controls. These outcomes were based on ICD-10-CM codes in patient EMRs. Additional sub-analyses (following PSM) were conducted to produce odds ratios with 95% CIs to explore the effect of some population subgroups (sex, body mass index (BMI), history of cardiovascular events, and AF subtype) on the odds of all-cause mortality between the exercise-based CR cohort and controls. Statistical significance was set at *P*<0.05.

**Results**

Patient characteristics

In total, 1,366,422 patients from 41 healthcare organisations had a diagnosis of AF at least 18-months before the search date of which, 12,315 (0.9%) had an EMR of exercise-based CR within 6-months of diagnosis. The exercise-based CR cohort was distributed between the four large Census Bureau designated regions of the United States as follows: 6% (*n*=739) in the Northeast, 30% (*n*=3,695) in the Midwest, 33% (*n*=4,064) in the South, 27% (*n*=3,325) in the West, and 5% (*n*=616) were unknown. The control cohort was also distributed between the four large Census Bureau designated regions of the United States as follows: 17% (*n*=230,198) in the Northeast, 19% (*n*=257,280) in the Midwest, 43% (*n*=582,266) in the South, 8% (*n*=108,329) in the West, 1% (*n*=13,541) non-United States, and 12% (*n*=162,493) were unknown.

Compared to controls, the exercise-based CR cohort was younger, had a lower proportion of females, had a higher proportion of people identified as white, and had a higher proportion of patients with health conditions, history of cardiovascular procedures, and use of cardiovascular medications. These variables were included in subsequent PSM analyses. Table 1 shows the characteristics of the exercise-based CR cohort and controls both before and following 1:1 PSM. Following 1:1 PSM, there were 11,947 patients in each cohort (*n*=23,894 patients included in analyses), which were overall well balanced.

*Clinical outcomes*

Following PSM, 18-month all-cause mortality was 6.1% (*n*=721 of 11,909 patients) in the exercise-based CR cohort and 16.8% (*n*=1,965 of 11,713 patients) in the matched controls (*P*<0.0001). Logistic regression models showed 68% lower odds of all-cause mortality (odds ratio 0.32, 95% CI: 0.29-0.35) in the exercise-based CR cohort compared to controls. 18-month hospitalisation rate was 33.3% (*n*=3,974 of 11,947 patients) in the exercise-based CR cohort and 47.0% (*n*=5,616 of 11,947 patients) in the matched controls (*P*<0.0001). Logistic regression models showed exercise-based CR was associated with 44% lower hospitalisations (odds ratio 0.56, 95% CI 0.53-0.59) compared to controls. 18-month incident stroke rate was 2.8% (*n*=310 of 11,071 patients) in the exercise-based CR cohort and 3.3% (*n*=351 of 10,638 patients) in the matched controls (*P*=0.003). Logistic regression models showed 16% lower odds of incident stroke (odds ratio 0.84, 95% CI 0.72-0.99) in the exercise-based CR cohort compared to controls. No significant difference was found between the exercise-based CR cohort and controls for new onset heart failure (odds ratio 0.93, 95% CI 0.84-1.04: Table 2).

*Subgroup analyses*

Following PSM, subgroup logistic regression analyses demonstrated that exercise-based CR was associated with lower all-cause mortality compared to controls for all included subgroups: female, male; aged >75 years, aged <75 years; obese, not obese; history of stroke, no history of stroke; history of acute myocardial infarction (AMI), no history of AMI; and paroxysmal AF, persistent AF, and permanent AF (Figure 1).

**Discussion**

This is the first study to demonstrate that exercise-based CR was associated with lower odds of all-cause mortality, hospitalisation, and stroke in a large cohort of patients with AF. Primarily, the present study of 23,894 patients with incident AF demonstrated that exercise-based CR was associated with 68% lower odds of all-cause mortality compared to PSM controls. Second, the beneficial association of exercise-based CR with lower all-cause mortality was independent of sex, older age, obesity, history of stroke, history of AMI, and AF subtype. Collectively, this retrospective analysis represents the first follow-up data set of its kind for incident AF, strongly supporting the clinical value of exercise-based CR following an AF diagnosis, and highlighting the need for controlled clinical trials on this topic.

*Cardiac rehabilitation and all-cause mortality*

Not specific for AF patients, exercise-based CR is recommended (with the highest level of scientific evidence - class I) by the European Society of Cardiology (ESC),13 the American Heart Association (AHA) and the American College of Cardiology (ACC).14 These global recommendations are supported by studies that find CR-related improvements in exercise capacity, health-related quality of life, and reductions in hospital admissions.15, 16 Findings related to all-cause mortality, however, are less clear. In contrast to earlier Cochrane meta-analyses,15, 17 the most recent Cochrane systematic review and meta-analysis of 63 studies (14,846 participants)16 did not observe a statistically significant reduction in all-cause mortality following exercise-based CR in coronary heart disease patients compared to no-exercise controls. However, real-world data studies have found exercise-based CR to be associated 32% to 90% lower odds of all-cause mortality when compared to PSM controls.18-20

Importantly, the previously discussed studies focussed on patients other than those with AF. Indeed, exercise-based CR is not part of routine care for patients diagnosed with AF. It is therefore important to note that the exercise-based CR cohort in the present study presented with a high proportion of patients with multiple cardiovascular comorbidities. This is due to the fact that current exercise-based CR provision is reserved for patients following an acute coronary syndrome, those undergoing a revascularisation procedure (coronary artery bypass graft or planned percutaneous coronary intervention), and heart failure. Thus, PSM was used to control for these differences in the two cohorts. The findings of the present study are therefore the first encouraging evidence for the provision of exercise-based CR for patients newly diagnosed with AF for lower odds of all-cause mortality, hospitalisation, and stroke (Table 2 and Figure 1).

*AF-specific cardiac rehabilitation*

The relationship between physical activity and AF has been somewhat counterintuitive, with some evidence supporting an association between exercise training and the occurrence of AF 4. Nonetheless, given exercise provides a promising first line treatment for individuals diagnosed with AF, associated with enhanced quality of life,21 AF-specific outcomes,22 reduced secondary cardiovascular events,23 and more recently lower odds of AF subtype progression,24 one may expect a reduction in all-cause mortality following exercise-based CR. However, two previous systematic reviews and meta-analyses, Risom et al 9 and Smart et al 25 did not find a reduction in all-cause mortality following CR for patients with AF. Smart et al 25 did however report improvements in AF symptom burden, health-related quality of life, exercise capacity, and cardiac function. Given the small number of available intervention studies (9 randomised controlled trials with 959 participants) and heavy weighting on one trial for mortality outcome analyses (97.9%), it may not be surprising that no effects for all-cause mortality were found.

One previous large multicentre observational study (EuroObservational Research Programme AF Long term General Registry) analysed the relationship between physical activity and major adverse outcomes in 2,442 patients with AF 26. Aligned with the findings of the present paper, not only was all-cause mortality lower in “regular” and “intense” physical activity cohorts, but all patient subgroups were associated with lower all-cause mortality compared to no physical activity.

Older patients are typically underrepresented in CR despite a higher disease prevalence 27. Given the heightened risk of mortality in older patients, it is promising exercise-based CR was associated with a significantly lower all-cause mortality (61%) for patients aged >75 years in the present study. This magnitude is largely agreeable with previous real-world data in a more broad cardiovascular patient cohort.18-20 This is particularly important in patients with AF, given prevalence increases from 2% to 20% in people over 80 years.28 Similarly, female patients are less likely to be referred to CR 29 and our findings are promising given both male and female patients with AF were associated with reduced all-cause mortality with exercise-based CR. This is particularly important given females with AF have a 2 fold increased risk of mortality compared to non-AF comparisons, higher than that attributable to males (1.5 fold increased risk).30 It is therefore vital access to CR and exercise programmes is equitable, regardless of sex and age.

Finally, our findings are the first to demonstrate significant associations of lower all-cause mortality following exercise-based CR, stratified for AF subtype. Although a non-linear relationship between AF and exercise seems likely (with guideline exercise levels associated with reduced incident AF and chronic excessive endurance exercise associated with increased AF prevalence)4, the 2020 ESC guidelines for AF encourage patients to undertake moderate-intensity exercise and remain physically active to prevent AF incidence or recurrence.31 However, the effect of exercise-based CR on major adverse cardiovascular events is uncertain31. Our findings are therefore the first promising evidence suggesting exercise-based CR is associated with lower odds of mortality and serious adverse events in patients with incident AF. Interventional research via appropriately powered randomised controlled trials investigating the effects of exercise-based CR is therefore warranted.

**Limitations**

A number of limitations are noteworthy. First, the data were collected from health care organization EMR databases and some co-morbidities may be underreported, and ethnicity was not available for all participants. Indeed, recording of ICD codes in administrative datasets may vary by factors such as age, number of comorbidities, severity of illness, length of hospitalization, and whether in-hospital death occurred.32 In particular, an EMR of CR and exercise does not necessarily provide information as to whether a participant attended, the intervention type and dose, or intervention adherence – this is an important limitation to this type of data. Nor do we have patient physical activity levels following the intervention, which would be an interesting outcome. Second, the data were from multiple healthcare organizations in the United States but may not be representative of the wider population. Third, despite efforts to control for several important patient characteristics using PSM, residual confounding may have impacted our results, including lifestyle factors (such as baseline fitness and physical activity levels), socioeconomic status, disease severity, and quality of care, which are not obtainable from EMRs. For more information on this, please refer to the linked reference.33 Fourth, it was not possible to factor for multiple comparisons in the subgroup analyses within the online database. Finally, the observed benefit of exercise-based CR in the present study is a potential function of improved management and outcomes related to cardiovascular comorbidity, rather than improvement to the AF substrate itself. However, given prior work by our group has also demonstrated lower odds of progression from paroxysmal to sustained AF with exercise-based CR compared to matched controls,24 it is promising that such substantial benefits may be realised via exercise-based CR in a real-world cohort of AF patients with substantial cardiovascular comorbidity. Nevertheless, subsequent randomised controlled trials are needed to further investigate the impact of exercise-based CR on AF more directly.

**Conclusions**

Using a global federated health research network, we found that participation in exercise-based CR in 21,250 patients with incident AF was associated with a reduction in all-cause mortality, hospitalisation, and stroke at 18-month follow-up post AF diagnosis. The survival benefit associated with exercise-based CR was also observed in all patient subgroups and AF subtypes. The findings of the present study therefore support the provision of exercise-based CR for patients with incident AF.

FUNDING/SUPPORT

There was no specific funding received for this study.

ROLE OF FUNDER/SPONSOR STATEMENT

TriNetX LLC funded the acquisition of the data used through use of the database.

ACCESS TO DATA AND DATA ANALYSIS

The first author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ORIGINALITY OF CONTENT

All information and materials in the manuscript are original.

DISCLOSURES

Benjamin JR Buckley has received funding from Bristol-Myers Squibb (BMS)/Pfizer. Stephanie L Harrison has received funding from BMS. Elnara Fazio-Eynullayeva and Paula Underhill are employees of TriNetX LLC. Deirdre A Lane has received investigator-initiated educational grants from BMS, has been a speaker for Boehringer Ingeheim, and BMS/Pfizer and has consulted for BMS, Boehringer Ingelheim, and Daiichi-Sankyo. Gregory YH Lip: consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

**References**

1. Piepoli MF, Corrà U, Benzer W, Bjarnason-Wehrens B, Dendale P, Gaita D, McGee H, Mendes M, Niebauer J, Zwisler A-DO, Schmid J-P, Rehabilitation CRSotEAoCPa. Secondary prevention through cardiac rehabilitation: From knowledge to implementation. A position paper from the cardiac rehabilitation section of the european association of cardiovascular prevention and rehabilitation. *European J Cardiovasc Prev Rehabili*. 2010;17:1-17

2. Price KJ, Gordon BA, Bird SR, Benson AC. A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus? *Eur J Prev Cardiol*. 2016;23:1715-1733

3. Anderson LJ, Taylor RS. Cardiac rehabilitation for people with heart disease: An overview of cochrane systematic reviews. *Int J Cardiol*. 2014;177:348-361

4. Buckley BJR, Lip GYH, Thijssen DHJ. The counterintuitive role of exercise in the prevention and cause of atrial fibrillation. *Am J Physiol-heart C*. 2020

5. Elliott AD, Linz D, Mishima R, Kadhim K, Gallagher C, Middeldorp ME, Verdicchio CV, Hendriks JML, Lau DH, Gerche AL, Sanders P. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: Evidence from the uk biobank cohort. *European Heart Journal*. 2020;41:1479-1486

6. Pathak RK, Middeldorp ME, Lau DH, Mehta AB, Mahajan R, Twomey D, Alasady M, Hanley L, Antic NA, McEvoy RD, Kalman JM, Abhayaratna WP, Sanders P. Aggressive risk factor reduction study for atrial fibrillation and implications for the outcome of ablation: The arrest-af cohort study. *J Am Coll Cardiol*. 2014;64:2222-2231

7. Pathak RK, Elliott A, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Hendriks JM, Twomey D, Kalman JM, Abhayaratna WP, Lau DH, Sanders P. Impact of cardiorespiratory fitness on arrhythmia recurrence in obese individuals with atrial fibrillation: The cardio-fit study. *J Am Coll Cardiol*. 2015;66:985-996

8. Risom SS, Zwisler AD, Rasmussen TB, Sibilitz KL, Madsen TL, Svendsen JH, Gluud C, Lindschou J, Winkel P, Berg SK. Cardiac rehabilitation versus usual care for patients treated with catheter ablation for atrial fibrillation: Results of the randomized copenheartrfa trial. *Am Heart J*. 2016;181:120-129

9. Risom SS, Zwisler AD, Johansen PP, Sibilitz KL, Lindschou J, Gluud C, Taylor RS, Svendsen JH, Berg SK. Exercise-based cardiac rehabilitation for adults with atrial fibrillation. *Cochrane Database Syst Rev*. 2017;2:CD011197

10. Centers for Disease Control and Prevention. International classification of diseases, tenth revision, clinical modification (icd-10-cm). 2020

11. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (strobe) statement: Guidelines for reporting observational studies. *Journal of clinical epidemiology*. 2008;61:344-349

12. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, Abdelalim A, et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980&#x2013;2017: A systematic analysis for the global burden of disease study 2017. *The Lancet*. 2018;392:1736-1788

13. Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I, Iliou MC, Pedretti RFE, Schmid J-P, Vigorito C, et al. Secondary prevention through comprehensive cardiovascular rehabilitation: From knowledge to implementation. 2020 update. A position paper from the secondary prevention and rehabilitation section of the european association of preventive cardiology. *Eur J Prev Cardiol*. 2020:204748732091337

14. Drozda J, Messer JV, Spertus J, Abramowitz B, Alexander K, Beam CT, Bonow RO, Burkiewicz JS, Crouch M, Goff DC, et al. Accf/aha/ama–pcpi 2011 performance measures for adults with coronary artery disease and hypertension: A report of the american college of cardiology foundation/american heart association task force on performance measures and the american medical association–physician consortium for performance improvement. *Circulation*. 2011;124:248-270

15. Oldridge NB, Guyatt GH, Fischer ME, Rimm AA. Cardiac rehabilitation after myocardial infarction. Combined experience of randomized clinical trials. *JAMA*. 1988;260:945-950

16. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. *J Am Coll Cardiol*. 2016;67:1-12

17. Heran BS, Chen JMH, Ebrahim S, Moxham T, Oldridge N, Rees K, Thompson DR, Taylor RS. Exercise-based cardiac rehabilitation for coronary heart disease (review). *Cochrane Db Syst Rev*. 2011:CD001800

18. Doimo S, Fabris E, Piepoli M, Barbati G, Antonini-Canterin F, Bernardi G, Maras P, Sinagra G. Impact of ambulatory cardiac rehabilitation on cardiovascular outcomes: A long-term follow-up study. *European Heart Journal*. 2019;40:678-685

19. Eijsvogels TMH, Maessen MFH, Bakker EA, Meindersma EP, van Gorp N, Pijnenburg N, Thompson PD, Hopman MTE. Association of cardiac rehabilitation with all-cause mortality among patients with cardiovascular disease in the netherlands. *Jama Netw Open*. 2020;3:e2011686-e2011686

20. de Vries H, Kemps HM, van Engen-Verheul MM, Kraaijenhagen RA, Peek N. Cardiac rehabilitation and survival in a large representative community cohort of dutch patients. *Eur Heart J*. 2015;36:1519-1528

21. Osbak PS, Mourier M, Kjaer A, Henriksen JH, Kofoed KF, Jensen GB. A randomized study of the effects of exercise training on patients with atrial fibrillation. *Am Heart J*. 2011;162:1080-1087

22. Rienstra M, Hobbelt AH, Alings M, Tijssen JGP, Smit MD, Brugemann J, Geelhoed B, Tieleman RG, Hillege HL, Tukkie R, Van Veldhuisen DJ, Crijns H, Van Gelder IC, Investigators R. Targeted therapy of underlying conditions improves sinus rhythm maintenance in patients with persistent atrial fibrillation: Results of the race 3 trial. *Eur Heart J*. 2018;39:2987-2996

23. Garnvik LE, Malmo V, Janszky I, Ellekjaer H, Wisloff U, Loennechen JP, Nes BM. Physical activity, cardiorespiratory fitness, and cardiovascular outcomes in individuals with atrial fibrillation: The hunt study. *Eur Heart J*. 2020;41:1467-1475

24. Buckley BJR, Harrison SL, Fazio-Eynullayeva E, Underhill P, Lane DA, Thijssen DHJ, Lip GYH. Association of exercise-based cardiac rehabilitation with progression of paroxysmal to sustained atrial fibrillation. *Journal of Clinical Medicine*. 2021;10

25. Smart NA, King N, Lambert JD, Pearson MJ, Campbell JL, Risom SS, Taylor RS. 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. *Open Hear*. 2018;5:e000880

26. Proietti M, Boriani G, Laroche C, Diemberger I, Popescu MI, Rasmussen LH, Sinagra G, Dan GA, Maggioni AP, Tavazzi L, Lane DA, Lip GYH, Investigators E-AGPR. Self-reported physical activity and major adverse events in patients with atrial fibrillation: A report from the eurobservational research programme pilot survey on atrial fibrillation (eorp-af) general registry. *Europace*. 2017;19:535-543

27. Deaton C. Addressing the paradox of age and participation in cardiac rehabilitation. *Eur J Prev Cardiol*. 2019;26:1050-1051

28. Lloyd-Jones Donald M, Wang Thomas J, Leip Eric P, Larson Martin G, Levy D, Vasan Ramachandran S, D’Agostino Ralph B, Massaro Joseph M, Beiser A, Wolf Philip A, Benjamin Emelia J. Lifetime risk for development of atrial fibrillation. *Circulation*. 2004;110:1042-1046

29. Colella TJ, Gravely S, Marzolini S, Grace SL, Francis JA, Oh P, Scott LB. Sex bias in referral of women to outpatient cardiac rehabilitation? A meta-analysis. *Eur J Prev Cardiol*. 2015;22:423-441

30. Benjamin Emelia J, Wolf Philip A, D’Agostino Ralph B, Silbershatz H, Kannel William B, Levy D. Impact of atrial fibrillation on the risk of death. *Circulation*. 1998;98:946-952

31. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, Boriani G, Castella M, Dan G-A, Dilaveris PE, et al. 2020 esc guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the european association of cardio-thoracic surgery (eacts): The task force for the diagnosis and management of atrial fibrillation of the european society of cardiology (esc) developed with the special contribution of the european heart rhythm association (ehra) of the esc. *European Heart Journal*. 2020

32. Chong WF, Ding YY, Heng BH. A comparison of comorbidities obtained from hospital administrative data and medical charts in older patients with pneumonia. *BMC Health Serv Res*. 2011;11:105-105

33. Nørgaard M, Ehrenstein V, Vandenbroucke JP. Confounding in observational studies based on large health care databases: Problems and potential solutions - a primer for the clinician. *Clin Epidemiol*. 2017;9:185-193

|  |
| --- |
| **Table 1.** Baseline characteristics %(*n*)\* of the AF populations with and without CR and exercise before and after propensity score matching.  |
|  | **Initial populations** | **Propensity score matched populations** |
|  | AF without CR (n=1,354,107) | AF with CR (n=12,315) | *P*-value | AF without CR (n=11,947) | AF with CR (n=11,947) | *P*-value |
| Age (years) at diagnoses; mean (SD) | 70.4 (13.4) | 67.4 (12.1) | <0.0001 | 67.5 (12.4) | 67.6 (12.0) | 0.45 |
| White | 78.9 (1,068,111) | 83.8 (10,320) | <0.0001 | 84.1 (10,047) | 83.6 (9,992) | 0.33 |
| Male | 55.9 (757,103) | 70.8 (8,715) | <0.0001 | 70.7 (8,443) | 70.3 (8,395) | 0.50 |
| Female | 44.1 (596,688) | 29.2 (3,600) | <0.0001 | 29.3 (3,502) | 29.7 (3,552) | 0.48 |
| Black or African American | 7.8 (105,877) | 7.3 (894) | <0.0001 | 7.8 (930) | 7.4 (885) | 0.27 |
| Unknown | 11.7 (158,502) | 6.9 (852) | 0.021 | 6.3 (754) | 7.0 (836) | 0.033 |
| Asian | 1.3 (17,910) | 1.4 (172) | <0.0001 | 1.2 (147) | 1.4 (167) | 0.26 |
| Ischaemic heart diseases | 11.9 (161,368) | 78.8 (9,703) | 0.47 | 80.2 (9,578) | 78.2 (9,342) | <0.001 |
| Hypertensive diseases | 24.8 (335,777) | 78.1 (9,614) | <0.0001 | 77.3 (9,234) | 77.6 (9,270) | 0.58 |
| Diseases of the respiratory system | 16.1 (217,935) | 66.6 (8,203) | <0.0001 | 64.7 (7,726) | 65.8 (7,864) | 0.06 |
| Diseases of the nervous system | 15.1 (204,010) | 54.1 (6,659) | <0.0001 | 51.3 (6,134) | 53.2 (6,355) | 0.004 |
| Heart Failure | 7.6 (103,547) | 48.7 (6,001) | <0.0001 | 48.8 (5,826) | 47.8 (5,709) | 0.13 |
| Diabetes Mellitus | 10.8 (146,298) | 35.0 (4,312) | <0.0001 | 33.8 (4,043) | 34.8 (4,152) | 0.14 |
| Chronic Kidney Disease | 6.0 (81,454) | 23.1 (2,841) | <0.0001 | 22.7 (2,717) | 23.0 (2,745) | 0.67 |
| Cerebrovascular diseases | 5.2 (70,372) | 22.0 (2,707) | <0.0001 | 20.5 (2,450) | 21.7 (2,587) | 0.030 |
| Neoplasms | 10.9 (147,783) | 20.7 (2,551) | <0.0001 | 18.8 (2,249) | 20.9 (2,491) | <0.001 |
| Cardiovascular Procedures† | 22.8 (308,994) | 90.3 (11,118) | <0.0001 | 89.7 (10,711) | 90.0 (10,750) | 0.40 |
| Cardiovascular Medications‡ | 35.7 (482,867) | 91.8 (11,311) | <0.0001 | 90.9 (10,865) | 91.6 (10,943) | 0.07 |
| \*Values are % (n) unless otherwise stated. Baseline characteristics were compared using a chi-squared test for categorical variables and an independent-sample t-test for continuous variables. Data are taken from structured fields in the electronic medical record systems of the participating healthcare organizations, therefore, there may be regional or country-specific differences in how categories are defined. †Cardiovascular procedures include cardiography, echocardiography, catheterization, cardiac devices, electrophysiological procedures. ‡Cardiovascular medications include beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, ACE inhibitors. AF; atrial fibrillation, CR; cardiac rehabilitation and exercise programmes, SD; standard deviation. |

|  |
| --- |
| **Table 2.** Major adverse events and new onset health conditions at 18-month follow-up from incident AF diagnosis; comparing AF patients who received exercise-based CR (*n*=11,947) to AF patients who received usual care only (*n*=11,947).  |
|  | Odds Ratio | 95% CI | *P*-value |
| Major adverse events |  |  |  |
|  All-cause mortality | 0.32 | 0.29-0.35 | <0.0001 |
|  Hospitalisation | 0.56 | 0.53-0.59 | <0.0001 |
|  Stroke | 0.84 | 0.72-0.99 | 0.032 |
| New onset conditions |  |  |  |
|  Heart failure | 0.93 | 0.84-1.04 | 0.20 |
| AF; atrial fibrillation, CR; cardiac rehabilitation, 95% CI; 95% confidence interval.  |