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ORIGINAL RESEARCH

Exercise-Based Cardiac Rehabilitation and All-Cause Mortality Among Patients With Atrial Fibrillation

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BACKGROUND: There is limited evidence of long-term impact of exercise-based cardiac rehabilitation (CR) on clinical end points for patients with atrial fibrillation (AF). We therefore compared 18-month all-cause mortality, hospitalization, stroke, and heart failure in patients with AF and an electronic medical record 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. Patients with AF undergoing exercise-based CR were propensity-score matched to patients with AF without exercise-based CR by age, sex, race, comorbidities, cardiovascular procedures, and cardiovascular medication. We ascertained 18-month incidence of all-cause mortality, hospitalization, stroke, and heart failure. Of 1 366 422 patients with AF, 11 947 patients had an electronic medical record of exercise-based CR within 6-months of incident AF who were propensity-score matched with 11 947 patients with AF without CR. Exercise-based CR was associated with 68% lower odds of all-cause mortality (odds ratio, 0.32; 95% CI, 0.29–0.35), 44% lower odds of rehospitalization (0.56; 95% CI, 0.53–0.59), and 16% lower odds of incident stroke (0.84; 95% CI, 0.72–0.99) compared with propensity-score matched controls. No significant associations were shown for incident heart failure (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, rehospitalization, and incident stroke at 18-month follow-up, supporting the provision of exercise-based CR for patients with AF.

Key Words: arrhythmia ■ cardiovascular disease ■ cohort study ■ multimorbidity ■ preventive cardiology

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 revascularization (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 hospitalizations, 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 metabolic equivalent mins/week (METs) has been associated with reduced risk of incident AF.[5] In addition, greater cardiorespiratory fitness was associated with increased freedom of AF and for every 1 MET increase in cardiorespiratory fitness, AF recurrence was reduced by 9%.[6,7] One randomized

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CLINICAL PERSPECTIVE

What Is New?

- We investigated the association of exercise-based cardiac rehabilitation on all-cause mortality, rehospitalization, incident stroke, and incident heart failure in patients with atrial fibrillation.
- In this retrospective cohort study of 23 894 patients with incident atrial fibrillation, exercise-based cardiac rehabilitation was associated with 68% lower odds of all-cause mortality, 44% lower odds of rehospitalization, and 16% lower odds of incident stroke, compared with propensity-matched controls at 18-month follow-up.

What Are the Clinical Implications?

- Exercise-based cardiac rehabilitation may be beneficial for patients with atrial fibrillation on important clinical end points, supporting the inclusion of patients with incident atrial fibrillation for exercise-based interventions.

Nonstandard Abbreviations and Acronyms

CR	cardiac rehabilitation
EMR	electronic medical record
PSM	propensity-score matching

controlled trial compared CR to usual care for 210 patients treated with catheter ablation for AF.[8] Findings revealed a significantly higher (≈1 MET) cardiorespiratory fitness at 4 months in CR compared with 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 end points for patients with AF.[9]

Using a large online database, we explored the hypothesis that exercise-based CR is associated with reduced all-cause mortality, rehospitalization, 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, rehospitalization, stroke, and heart failure in patients with AF and an electronic medical record (EMR) of exercise-based CR to propensity-score matched (PSM) 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 centers, 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 coding.[10] AF was identified from *International Classification of Diseases, Ninth and Tenth Revisions, Clinical Modification* (*ICD-9-CM* and *ICD-10-CM*) codes in patient EMRs: I48 (atrial fibrillation and flutter), I48.0 (paroxysmal AF), I48.1 (persistent AF), and I48.21 (permanent AF). Exercise-based CR was identified from *ICD-10-CM* codes Z71.82 (exercise counseling), Healthcare Common Procedure Coding System code S9472 (CR program, non-physician provider, per diem), or Current Procedures Terminology code 1013171 (physician or other qualified healthcare 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 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 PSM control cohorts. This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology guidelines and the checklist can be found as a supplement (Table S1).[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 anonymized data set from 2009 to 2020 of patients with incident AF was analyzed. The exercise-based CR cohort were aged ≥18 years with CR and/or exercise programs 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 before 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 organizations had data available for patients who met the study inclusion criteria. Thus, following PSM, the cohort consisted of patients with AF who either were referred for exercise-based CR (because of 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 revascularization procedure (coronary artery bypass graft or planned percutaneous coronary intervention), and patients with heart failure. Thus, PSM was used to control for these differences in the 2 cohorts. Patients with exercise-based CR and controls were 1:1 PSM using logistic regression for age at AF diagnosis, sex, race, hypertensive diseases, ischemic heart diseases, heart failure, cerebrovascular diseases, diabetes mellitus, chronic kidney disease, respiratory diseases, nervous system diseases, neoplasms, cardiovascular procedures (eg, cardiography, echocardiography, cardiac catheterization, revascularization [eg, percutaneous coronary intervention or coronary artery bypass graft], cardiac devices, electrophysiological procedures), and cardiovascular medications (eg, beta-blockers, antiarrhythmics, diuretics, antilipemic agents, antianginals, calcium channel blockers, angiotensin-converting enzyme inhibitors). These variables were chosen because they are established risk factors for AF and/or mortality or were significantly different between the 2 cohorts.[12] The TriNetX platform uses "greedy nearest-neighbour matching" with a caliper of 0.1 pooled SDs. Following PSM, logistic regressions produced odds ratios (ORs) with 95% CIs for 18-month incidence of all-cause mortality, hospitalization, 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 ORs with 95% CIs to explore the effect of some population subgroups (sex, body mass index, 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 organizations 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 4 large Census Bureau designated regions of the United States as follows: 6% (n=739) in the Northeast, 30% (n=3695) in the Midwest, 33% (n=4064) in the South, 27% (n=3325) in the West, and 5% (n=616) were unknown. The control cohort was also distributed between the 4 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 with 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=1965 of 11 713 patients) in the matched controls ($P<0.0001$). Logistic regression models showed 68% lower odds of all-cause mortality (OR, 0.32; 95% CI, 0.29–0.35) in the exercise-based CR cohort compared with controls; 18-month hospitalization rate was 33.3% (n=3974 of 11 947 patients) in the exercise-based CR cohort and 47.0% (n=5616 of 11 947 patients) in the matched controls ($P<0.0001$). Logistic regression models showed exercise-based CR was associated with 44% lower hospitalizations (OR, 0.56; 95% CI 0.53–0.59) compared with 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 (OR, 0.84; 95% CI, 0.72–0.99) in the exercise-based CR cohort compared with controls. No significant difference was found between the exercise-based CR cohort and controls for new onset heart failure (OR, 0.93; 95% CI, 0.84–1.04; Table 2).

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 (y) at diagnoses; mean (SD)	70.4 (13.4)	67.4 (12.1)	<0.0001	67.5 (12.4)	67.6 (12.0)	0.45
Sex						
Male	55.9 (757 103)	70.8 (8715)	<0.0001	70.7 (8443)	70.3 (8395)	0.50
Female	44.1 (596 688)	29.2 (3600)	<0.0001	29.3 (3502)	29.7 (3552)	0.48
Race						
White	78.9 (1 068 111)	83.8 (10 320)	<0.0001	84.1 (10 047)	83.6 (9992)	0.33
Black	7.8 (10 877)	7.3 (894)	<0.0001	7.8 (930)	7.4 (885)	0.27
Asian	1.3 (17 910)	1.4 (172)	<0.0001	1.2 (147)	1.4 (167)	0.26
Unknown	11.7 (158 502)	6.9 (852)	0.021	6.3 (754)	7.0 (836)	0.033
Comorbidities						
Ischaemic heart diseases	11.9 (161 368)	78.8 (9703)	0.47	80.2 (9578)	78.2 (9342)	<0.001
Hypertensive diseases	24.8 (335 777)	78.1 (9614)	<0.0001	77.3 (9234)	77.6 (9270)	0.58
Diseases of the respiratory system	16.1 (217 935)	66.6 (8203)	<0.0001	64.7 (7726)	65.8 (7864)	0.06
Diseases of the nervous system	15.1 (204 010)	54.1 (6659)	<0.0001	51.3 (6134)	53.2 (6355)	0.004
Heart failure	7.6 (103 547)	48.7 (6001)	<0.0001	48.8 (5826)	47.8 (5709)	0.13
Diabetes mellitus	10.8 (146 298)	35.0 (4312)	<0.0001	33.8 (4043)	34.8 (4152)	0.14
Chronic kidney disease	6.0 (81 454)	23.1 (2841)	<0.0001	22.7 (2717)	23.0 (2745)	0.67
Cerebrovascular diseases	5.2 (70 372)	22.0 (2707)	<0.0001	20.5 (2450)	21.7 (2587)	0.030
Neoplasms	10.9 (147 783)	20.7 (2551)	<0.0001	18.8 (2249)	20.9 (2491)	<0.001
Cardiovascular care						
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

AF indicates atrial fibrillation; and CR, cardiac rehabilitation and exercise programmes.

*Values are % (n) unless otherwise stated. Baseline characteristics were compared using a χ^2 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, angiotensin-converting enzyme inhibitors.

Subgroup Analyses

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

DISCUSSION

This is the first study to demonstrate that exercise-based CR was associated with lower odds of all-cause mortality, rehospitalization, 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 associates with 68% lower odds of all-cause mortality compared with 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 acute myocardial infarction, 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 patients with AF, exercise-based CR is recommended (with the highest level of scientific evidence—class I) by the European Society of

Table 2. Major Adverse Events and New Onset Health Conditions at 18-Month Follow-Up From Incident AF Diagnosis; Comparing Patients With AF Who Received Exercise-Based CR (n=11 947) With Patients With AF 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
Hospitalization	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 indicates atrial fibrillation; and CR, cardiac rehabilitation.

Cardiology,[13] the American Heart Association, and the American College of Cardiology.[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 patients with coronary heart disease compared with 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 with PSM controls.[18–20]

Importantly, the previously discussed studies focused 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 because current exercise-based CR provision is reserved for patients following an acute coronary syndrome, those undergoing a revascularization procedure (coronary artery bypass graft or planned percutaneous coronary intervention), and heart failure. Thus, PSM was used to control for these differences in the 2 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, rehospitalization, and stroke (Table 2 and Figure).

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

Subgroup	*n*=participants	Odds Ratio	95% CI	*P*-value
Total cohort	**21,250**	**0.36**	**0.33-0.40**	**<0.0001**
Female	6,282	0.39	0.33-0.46	<0.0001
Male	14,962	0.34	0.31-0.38	<0.0001
Aged ≥75 years	9,202	0.39	0.35-0.45	<0.0001
Aged <75 years	12,756	0.32	0.28-0.36	<0.0001
BMI ≥30	5,892	0.38	0.32-0.45	<0.0001
BMI <30	7,824	0.47	0.41-0.54	<0.0001
History of stroke	816	0.39	0.25-0.61	<0.0001
No history of stroke	20,436	0.35	0.32-0.39	<0.0001
History of AMI	2,560	0.28	0.21-0.37	<0.0001
No history of AMI	18,690	0.37	0.34-0.41	<0.0001
Paroxysmal AF	8,954	0.32	0.27-0.37	<0.0001
Persistent AF	2,728	0.43	0.34-0.54	<0.0001
Permanent AF	3,226	0.48	0.39-0.58	<0.0001

Sample size is number of patients in analysis with and without post-incident AF diagnosis CR , following propensity score matching.
CR; cardiac rehabilitation and exercise programmes, AF; atrial fibrillation, 95% CI; 95% confidence interval, BMI; body mass index, AMI; acute myocardial infarction.

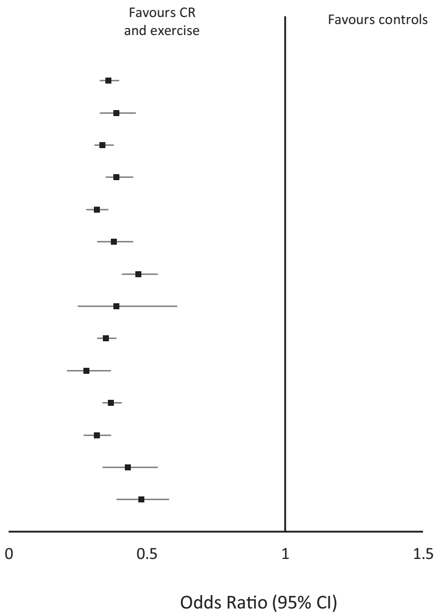

Figure. Subgroup-specific odds ratios for all-cause mortality at 18-month follow-up from incident atrial fibrillation diagnosis; comparing patients with atrial fibrillation who received exercise-based cardiac rehabilitation with matched patients with atrial fibrillation who received usual care only (controls).
Sample size is number of patients in analysis with and without post-incident atrial fibrillation diagnosis cardiac rehabilitation, following propensity-score matching. AF indicates atrial fibrillation; AMI, acute myocardial infarction; BMI, body mass index; and CR, cardiac rehabilitation and exercise programs.

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, 2 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 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 randomized 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 multicenter observational study (EuroObservational Research Programme AF Long term General Registry) analyzed 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 with 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 that 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 >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 women with AF have a 2-fold increased risk of mortality compared with non-AF comparisons, higher than that attributable to men (1.5-fold increased risk).[30] It is therefore vital that access to CR and exercise programs are equitable, regardless of sex and age.

Finally, our findings 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 European Society of Cardiology 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 uncertain.[31] To our knowledge, 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 randomized-controlled trials investigating the effects of exercise-based CR is warranted.

Limitations

A number of limitations are noteworthy. First, the data were collected from healthcare organization EMR databases and some comorbidities may be underreported, and ethnicity was not available for all participants. Indeed, recording of *ICD* codes in administrative data sets 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 with matched controls,[24] it is promising that such substantial benefits may be realized via exercise-based CR in a real-world cohort of patients with AF and substantial cardiovascular comorbidity. Nevertheless, subsequent randomized-controlled trials are needed to further investigate the impact of exercise-based CR on AF substrate and underlying mechanisms more directly.

CONCLUSIONS

Participation in exercise-based CR in 23 894 patients with incident AF was associated with a reduction in all-cause mortality, rehospitalization, and incident stroke at 18-months following AF diagnosis. The survival benefit associated with exercise-based CR was consistent across 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 and warrant further prospective research.

ARTICLE INFORMATION

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Supplementary Material

Table S1

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SUPPLEMENTAL MATERIAL

Table S1. STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page/section information can be found
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2; abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2; abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 5; introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5; end of introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5 onwards; methods (study design and participants)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5; methods (data collection)
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 5 onwards; methods (study design and participants)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Page 5 onwards; methods (statistical analysis)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5 onwards; methods (study design and participants), (data collection), and statistical analysis)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Page 5 onwards; method, page 6; results, and Table 1*
Bias	9	Describe any efforts to address potential sources of bias	Page 6; methods (statistical analysis)
Study size	10	Explain how the study size was arrived at	Page 6; methods (data collection)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6; methods (statistical analysis)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 6; methods (statistical analysis)
		(*b*) Describe any methods used to examine subgroups and interactions	Page 6; methods (statistical analysis)
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A

		(*e*) Describe any sensitivity analyses	Page 6; methods (statistical analysis)
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 7; results (patient characteristics)
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 7; results (patient characteristics)
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	Page 7; results (patient characteristics)
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 7; results (clinical outcomes)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 7; results (clinical outcomes)
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Page 7 onwards; results
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 7; results (subgroup analyses)
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 8; discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 10; limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 11; conclusions
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 11; conclusions
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups. **Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.