Jin et al. International Journal of Arrhythmia (2022) 23:31
https://doi.org/10.1186/s42444-022-00082-y

International Journal of Arrhythmia

RESEARCH

Association of physical activity with the risk of major adverse cardiac and cerebrovascular events and mortality in patients with concomitant atrial fibrillation and coronary artery disease

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Abstract

Background: Although regular physical activity benefits cardiovascular health, there is a concern that intense exercise is linked to the promotion of atrial fibrillation (AF) and coronary plaque rupture. However, the impact of physical activity on the outcomes of patients with concomitant AF and coronary artery disease (CAD) remains unclear. This study aimed to evaluate the association with clinical outcomes according to the level of physical activity in patients with concomitant AF and CAD.

Methods: We assessed 551 patients with AF and CAD (mean age, 67.1 ± 9.8 years) who completed a self-reported questionnaire for physical activity from 2015 to 2020 in a single tertiary-care hospital. Physical activity levels were converted into metabolic equivalent of task (MET) per week and categorized to correspond with multiple public health recommendations. We examined the association between physical activity, all-cause mortality, and major adverse cardiac and cerebrovascular events (MACCE).

Results: The risks of all-cause mortality (P for linear trend = 0.017) and MACCE (P for linear trend = 0.05) appeared inverse trend with a greater level of physical activity. Compared with inactive patients, patients who met the recommended target range of physical activity (500–1,000 MET-min/week: unadjusted hazard ratio [HR] = 0.58, 95% confidence interval [CI] = 0.36–0.99) and highly active patients who exceeded the minimum recommended level (≥ 1,000 MET-min/week: unadjusted HR = 0.47, 95% CI = 0.25–0.88) had a lower risk of all-cause mortality in the unadjusted model; however, these associations did not remain significant after adjusting for the model. There was no evidence of increased risk of all-cause mortality and MACCE at levels of physical activity above the recommended target range, even with vigorous-intensity physical activity exceeding the recommended target range.

Conclusions: There appears to be an inverse trend between physical activity levels and all-cause mortality and MACCE in patients with concomitant AF and CAD. No excess risk of mortality or MACCE was found at exercise levels

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above the recommended target range. Further large-scale studies are warranted to create an improved evidence base concerning the effects of physical activity in patients with AF and CAD.

Keywords: Atrial fibrillation, Coronary artery disease, Physical activity, Exercise, Mortality

Introduction

Physical activity clearly benefits cardiovascular health. In fact, regular physical activity is an important component of therapy for most cardiovascular diseases and is associated with reduced cardiovascular mortality [1]. However, physical activity may paradoxically trigger sudden cardiac arrest in individuals with cardiovascular disease [2]. Although the promotion of physical activity is more important following cardiovascular disease diagnosis, physicians' consultations need to maintain a balance between the multiple benefits of exercise and adverse risks such as sudden cardiac arrest.

Atrial fibrillation (AF) is the most common heart rhythm disorder and coronary artery disease (CAD) is the most common type of heart disease [3, 4]. The coexistence of AF and CAD is rising rapidly and is a frequent condition in clinical practice, making it challenging for consulting physicians to promote appropriate physical activity. Physical activity has been shown to provide numerous health benefits to patients with CAD and AF [5–8]. However, there is concern regarding a temporary increase in exercise-related cardiac events, including sudden cardiac arrest and acute myocardial infarction, among individuals with structural cardiac disease [9]. AF could cause the heart to beat faster than usual; therefore, AF with a rapid ventricular response could occur during exercise. With an increased heart rate, increased wall stress may provoke plaque rupture and increase oxygen demand, accelerating the apoptosis of myocardial cells [10]. In the current guidelines, physical activity below the ischemic thresholds may be considered in chronic coronary artery disease. And, excessive endurance exercise maybe avoided to prevent AF incidence or recurrence. What remains unknown is precisely how much exercise is required to produce these beneficial effects and, more controversially, if excessive exercise can cause harm in patients with AF and CAD. However, research on the association between physical activity and adverse cardiovascular events in patients with concomitant AF and CAD is lacking.

This study aimed to evaluate the impact of physical activity on clinical outcomes in patients with concomitant AF and CAD. We conducted analyses of categorical dose–response relationships between different volumes of physical activity, major adverse cardiac and cerebrovascular events (MACCE), and all-cause mortality.

Methods

Study population

The participants were consecutive patients diagnosed with concomitant AF and CAD who underwent coronary angiography at the Inje University Sanggye Paik Hospital between 2015 and 2020. AF was defined as an episode of irregular heart rhythm without detectable P waves lasting more than 30 s [11], and CAD was defined as the presence of at least 50% luminal diameter stenosis in at least one major coronary artery or a history of previous percutaneous coronary intervention [12, 13]. In this study, CAD was confirmed by interventional cardiologist, only using coronary angiogram. The exclusion criteria were as follows: (1) Physically incapacitated patients, (2) Patients who underwent valve surgery or coronary artery bypass graft, and (3) Hypertrophic cardiomyopathy, arrhythmogenic ventricular cardiomyopathy, and hereditary channelopathies. The participants were prospectively enrolled in a longitudinal registry, and the analysis was performed retrospectively. This registry recruited the patients who have undergone coronary angiogram and were diagnosed coronary artery disease and be referred for cardiac rehabilitation. The questionnaire for physical activity was used to obtain baseline physical activity. This study was performed on 551 patients with atrial fibrillation out of a total of 2250 patients. The study was approved by the Institutional Review Board of Inje University Sanggye Paik Hospital in Seoul, Republic of Korea, and complied with the Declaration of Helsinki.

Assessment of physical activity

Physical activity data were collected by a trained study coordinator using a standardized form and protocol after each participant had undergone coronary angiography. Each participant was asked about the average weekly time spent performing the following intensities of physical activity, with several examples of physical activity types under three intensity categories: vigorous, moderate, and light. Vigorous-intensity physical activity was defined as intense exercise that causes severe shortness of breath, such as running. Moderate-intensity physical activity was defined as exercise that causes mild shortness of breath, such as brisk walking and cycling at each participant's usual speed. Light-intensity physical activity was defined as easy to breathe, carrying a conversion during exercise, such as slow or leisure-pace walking. Each type of activity was assigned a metabolic equivalent task

(MET) score based on energy cost [14, 15]. We computed the energy expended in each activity by multiplying the associated MET score by the length of the activity (minute) and summed the energy expended across the light-, moderate-, and vigorous-intensity activities to estimate the total energy expenditure per week.

The participants were stratified on the basis of their weekly physical activity levels as follows: 1) inactive group, no physical activity beyond basic movements from daily life activities; 2) insufficiently active group, having less than the key guideline target range (1–500 MET-min/week); 3) active group, meeting the key guideline target range (500–1,000 MET-min/week); and 4) highly active group, exceeding the key guideline target range (> 1,000 MET-min/week) [16, 17].

Study outcomes

The primary outcomes were all-cause mortality and major adverse cardiac and cerebrovascular events (MACCE), including cardiovascular death, acute myocardial infarction, ischemic stroke, repeat revascularization, and hospitalization for heart disease. Myocardial infarction was defined as the presence of ischemic symptoms, electrocardiographic changes, abnormal angiographic findings indicative of myocardial infarction, an increase in creatine kinase–myocardial band fraction above the normal upper limit, or an increase in troponin above the 99th percentile of the normal upper limit [18]. Repeat revascularization included target vessel revascularization—regardless of whether the procedure was clinically or angiographically driven—or nontarget vessel revascularization. Stroke, as indicated by neurological deficits, was confirmed by a neurologist using imaging modalities. All events were diagnosed by experienced attending physicians and the patients were reviewed by cardiologists.

Statistical analysis

Descriptive statistics were used to assess the participants' baseline characteristics and comorbidities. We used Cox proportional hazards regression stratified by cohort to generate hazard ratios (HRs) and their 95% confidence intervals (CIs) for physical activity and study outcomes. Models for clinical variable adjustments were used to assess the associations. Multivariable models were adjusted for age, sex, body mass index (BMI), heart failure, hypertension, diabetes, previous myocardial infarction (MI), prior stroke or transient ischemic attack, AF, chronic kidney disease, dyslipidemia, smoking, and alcohol intake. These covariates were selected based on their previously established roles as predictive factors for sudden cardiac arrest and coronary heart disease-related death [19, 20]. We further examined physical activity levels by separating vigorous-intensity and non-vigorous-intensity activities and creating mutually adjusted models. We also compared insufficient physical activity group (0 and 1–500 MET-min/week) to sufficient physical activity group (> 500 MET-min/week). Kaplan–Meier curves were generated using a log-rank test to show differences in primary outcomes among the different physical activity levels. Statistical significance was set at $P < 0.05$. Statistical analysis was performed using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

In total, 551 participants (mean age, 67.1 ± 9.8; women, 183 [33%]) were included in the analysis. The baseline characteristics of the study participants, stratified according to their physical activity levels, are presented in Table 1. With regard to physical activity level, 31.3% of the participants were inactive, 25.6% performed insufficiently active physical activity (1–500 MET-min/week), 23.2% performed active physical activity (500–1,000 MET-min/week), and 19.9% performed highly active physical activity (> 1,000 MET-min/week).

Association of physical activity with mortality and MACCE

Patients were followed for a median of 48 months (interquartile range, 36–60 months). When meeting and exceeding the recommended guidelines, physical activity was associated with a reduced risk of all-cause mortality in an unadjusted Cox regression model (500–1,000 MET-min/week: unadjusted HR = 0.58, 95% CI = 0.36–0.99, and ≥ 1,000 MET-min/week: unadjusted HR = 0.47, 95% CI = 0.25–0.88) (Table 2). This association did not remain significant after adjusting for the model (Table 2). However, the risk of all-cause mortality was inversely trend with a greater level of physical activity (Fig. 1A, P for linear trend = 0.017).

The risk of MACCE was also inversely trend with a greater level of physical activity (Fig. 1B, P for linear trend = 0.05). However, we did not observe a significant reduction in MACCE risk for those who met or exceeded the guideline-recommended physical activity (Table 2).

Kaplan–Meier analysis demonstrated a gradually decreased cumulative incidence of all-cause mortality and MACCE with increasing physical activity levels (all-cause mortality: log rank $p = 0.007$, MACCE: log rank $p = 0.05$) (Fig. 2).

We also categorized two groups (insufficient physical activity group ([0 and 1–500 MET-min/week]) and sufficient physical activity group [> 500 MET-min/week]) to compare sufficient physical activity group to insufficient physical activity group. The adjusted hazard

Table 1 Baseline characteristics stratified by the physical activity level

Characteristic	Physical activity level, MET-min/week				P for trend
	None	1 to < 500	500 to < 1000	≥ 1000	
Participants	172 (31.3%)	141 (25.6%)	128 (23.2%)	110 (19.9%)	
Age	69.3 ± 10.0	66.0 ± 10.8	67.0 ± 9.3	65.3 ± 8.1	0.04
Male	113 (65.8%)	91 (64.5%)	87 (68.0%)	77 (70.0%)	0.12
BMI (kg/m^2)	24.3 ± 3.7	24.6 ± 3.4	24.4 ± 2.9	24.7 ± 2.9	0.56
Medical history					
Persistent AF	54 (31.4%)	37 (26.2%)	36 (28.1%)	28 (25.5%)	0.17
Heart failure	19 (11.0%)	13 (9.2%)	13 (10.2%)	9 (8.2%)	0.13
Hypertension	132 (76.7%)	106 (75.2%)	98 (76.6%)	81 (73.6%)	0.14
Diabetes	86 (50.0%)	63 (44.7%)	62 (48.4%)	46 (41.8%)	0.23
History of stroke/TIA	23 (13.4%)	16 (11.3%)	17 (13.3%)	10 (9.1%)	0.25
Chronic kidney disease	18 (10.4%)	12 (8.5%)	12 (9.4%)	8 (7.3%)	0.17
Previous MI	14 (8.1%)	7 (5.0%)	10 (7.8%)	6 (5.5%)	0.36
Previous PCI	22 (12.8%)	16 (11.3%)	15 (11.7%)	11 (10.0%)	0.07
Beta blocker use	84 (48.8%)	68 (48.2%)	61 (47.7%)	55 (50.0%)	0.29
N-CCB use	28 (16.3%)	26 (18.4%)	19 (14.8%)	19 (17.2%)	0.89
Class I AAD use	11 (6.4%)	11 (7.8%)	9 (7.0%)	9 (8.2%)	0.68
Class III AAD use	12 (7.0%)	11 (7.8%)	10 (7.8%)	10 (9.1%)	0.58
Intervention following coronary angiogram					
PCI	54 (31.4%)	36 (25.5%)	29 (22.7%)	21 (19.1%)	0.06
CABG	3 (1.7%)	1 (0.7%)	2 (1.6%)	2 (1.8%)	0.64
Echocardiogram					
Left ventricular EF (%)	55.6 ± 12.5	57.5 ± 12.8	56.8 ± 13.2	58.7 ± 14.5	0.18
LAVI (mL/m^2)	32.3 ± 15.5	31.1 ± 15.6	31.7 ± 17.2	30.8 ± 16.8	0.09
Smoker (Ex- or current)	61 (35.5%)	48 (34.0%)	50 (39.1%)	44 (40.0%)	0.15
Alcohol (1 or more per week)	81 (47.1%)	65 (46.1%)	63 (49.2%)	56 (50.9%)	0.12
Total cholesterol (mg/dL)	186.1 ± 38.1	183.7 ± 37.1	185.6 ± 36.9	182.8 ± 37.1	0.53
Triglyceride (mg/dL)	132.0 ± 82.5	130.8 ± 82.6	131.7 ± 73.1	128.9 ± 80.5	0.26
LDL (mg/dL)	117.5 ± 35.4	116.1 ± 37.5	116.5 ± 39.6	115.6 ± 39.1	0.09
HDL (mg/dL)	52.6 ± 30.5	53.2 ± 31.1	52.9 ± 28.7	55.5 ± 30.2	0.41

Values are expressed as n (%) or means ± standard deviations

AAD antiarrhythmics, *AF* atrial fibrillation, *BMI* body mass index, *CABG* coronary artery bypass graft surgery, *EF* ejection fraction, *HDL* high-density lipoprotein, *LAVI* left atrial volume index, *LDL* low-density lipoprotein, MET: metabolic equivalent task, *MI* myocardial infarction, *N-CCB* non-dihydropyridine calcium channel blocker, *PCI* percutaneous coronary intervention, *TIA* transient ischemic attack

ratio of all-cause mortality and MACCE were 0.72 (95% CI = 0.47–1.11, $p = 0.14$) and 0.76 (95% CI = 0.51–1.14, $p = 0.18$), respectively.

Physical activity intensity and outcomes

We employed separate vigorous and non-vigorous (light to moderate) intensity physical activity categories ranging from 0 to > 1000 MET-min/week, and the analysis models were mutually adjusted for both physical activity intensities. There was no relationship between physical activity intensity and outcomes and no significant increased risk of mortality and MACCE in those who engaged in vigorous-intensity exercise (Additional file 1: Supplementary Tables 1 and 2). We did not observe a significant association between high-volume or vigorous-intensity physical activity and adverse cardiovascular outcomes in this study.

Types of atrial fibrillation and outcomes

The association between physical activity level and AF risk was not different across the subgroup of paroxysmal and persistent AF, and there was no evidence of harm at the any level of physical activity across the subgroups paroxysmal and persistent AF (Additional file 1: Supplementary Table 3).

Table 2 Risk of all-cause mortality and MACCE in relation to physical activity level

Physical activity (MET-hour/week)	None	1 to < 500	500 to < 1000	≥ 1000
All-cause mortality	172 (31.3%)	141 (25.6%)	128 (23.2%)	110 (19.9%)
Event, No. (%)	25 (14.5%)	16 (11.3%)	12 (9.4%)	8 (7.3%)
Incidence (1,000 person-years)	42	32	25	20
Hazard ratio (95% CI)				
Unadjusted	1.00 (ref.)	0.73 (0.44–1.18)	0.58 (0.36–0.99)	0.47 (0.25–0.88)
Age and sex adjusted	1.00 (ref.)	0.87 (0.53–1.43)	0.68 (0.39–1.17)	0.63 (0.33–1.20)
Fully adjusted†	1.00 (ref.)	0.90 (0.55–1.47)	0.71 (0.41–1.23)	0.68 (0.36–1.30)
MACCE				
Event, No. (%)	26 (15.1%)	18 (12.8%)	14 (10.9%)	10 (9.1%)
Incidence (1,000 person-years)	42	33	28	24
Hazard ratio (95% CI)				
Unadjusted	1.00 (ref.)	0.81 (0.50–1.30)	0.67 (0.40–1.13)	0.62 (0.35–1.08)
Age and sex adjusted	1.00 (ref.)	0.93 (0.58–1.49)	0.74 (0.44–1.24)	0.71 (0.40–1.26)
Fully adjusted†	1.00 (ref.)	0.96 (0.59–1.55)	0.75 (0.44–1.27)	0.77 (0.43–1.38)

† Multivariable adjusted hazard ratio: age, sex, body mass index, heart failure, hypertension, diabetes, previous myocardial infarction, prior stroke or transient ischemic attack, chronic kidney disease, dyslipidemia, smoking, and alcohol intake

CI confidence interval, *MACCE* major adverse cardiac and cerebrovascular event, *MET* metabolic equivalent task

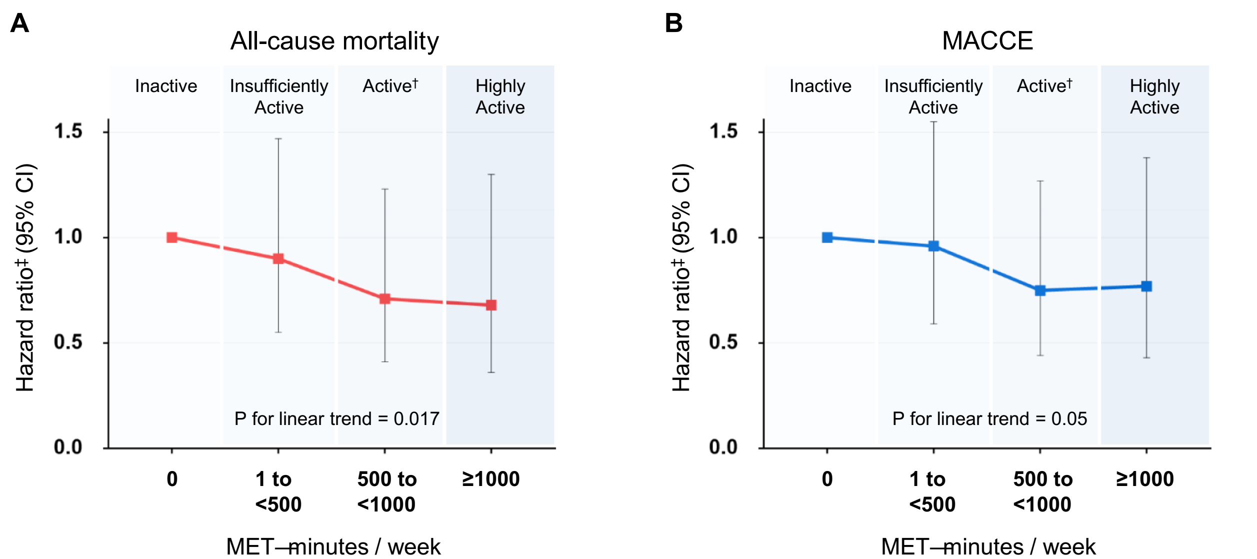
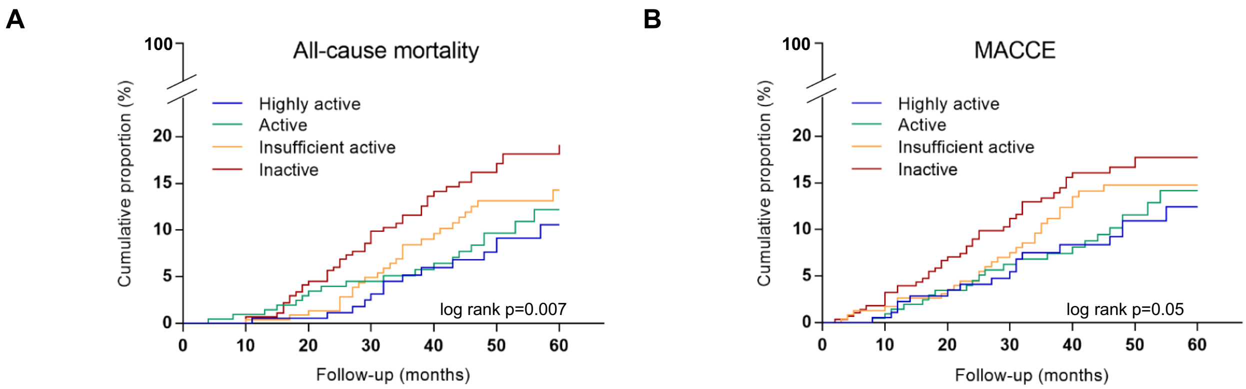


Fig. 1 Multivariable adjusted relative risk of all-cause mortality (**A**) and MACCE (**B**) according to physical activity levels as classified in the Physical Activity Guidelines. †Minimum key guidelines target range in Physical Activity Guidelines for Americans by the U.S. Department of Health and Human Services (2018): Doing the equivalent of 500–1,000 MET-min/week of physical activity. ‡Multivariable adjusted hazard ratio: age, sex, body mass index, heart failure, hypertension, diabetes, previous myocardial infarction, prior stroke or transient ischemic attack, chronic kidney disease, dyslipidemia, smoking, and alcohol intake. CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; MET, metabolic equivalent task

Discussion

The present study investigated the association between physical activity and the risk of all-cause mortality and MACCE in patients with concomitant AF and CAD. The risk of all-cause mortality and MACCE was inversely trend with a greater level of physical activity, although there was no statistically significant reduction in all-cause mortality and MACCE risk with physical activity.



A — No. at risk

	0	10	20	30	40	50	60
Inactive	173	173	158	134	105	54	53
Insufficient active	141	141	135	118	98	46	44
Active	128	128	121	108	91	46	43
Highly active	110	110	109	91	73	39	38

B — No. at risk

	0	10	20	30	40	50	60
Inactive	173	169	151	126	97	49	48
Insufficient active	141	139	132	113	90	43	40
Active	128	126	118	102	84	43	40
Highly active	110	109	99	88	68	38	36

Fig. 2 Kaplan–Meier cumulative incidence of all-cause mortality (**A**) and MACCE (**B**) in different physical activity levels as classified in the Physical Activity Guidelines. MACCE, major adverse cardiac and cerebrovascular events

There was no evidence of an increased risk of mortality and MACCE at levels of physical activity above the recommended minimum key target range, even with vigorous-intensity physical activity exceeding the key target range.

Physical activity is a widely accepted means of reducing the risk of mortality and morbidity in patients with cardiovascular disease [21]. Exercise has been shown to reduce the risk of cardiovascular mortality and percutaneous coronary intervention in patients with established CAD [22], and physical activity is associated with a lower risk of cardiovascular mortality and morbidity in patients with AF [8]. However, paradoxically, exercise has long been known to transiently increase the risk of acute myocardial infarction and sudden cardiac arrest [23–25], and high volumes of endurance exercise increase AF risk [26].

The number of patients with concomitant AF and CAD is progressively increasing, and physicians are encouraged to promote exercise in all of these patients. However, it is a complex condition to precisely determine the amount of physical activity required for beneficial effects and whether potential harm is associated with a high volume of vigorous exercise. The concern among physicians in such settings is MACCE onset; however, evidence for the impact of physical activity on clinical events and mortality is sparse. The present study showed the beneficial impact of physical activity on MACCE, and mortality was maintained, with no excess risk of MACCE or mortality in coexisting AF and CAD.

Atrial fibrillation has been consistently associated with increased rates of mortality and morbidity [27, 28] as well as worse prognosis in patients with CAD [29]. There is a need for cost-effective preventive measures and long-term management strategies to combat the future burden on these patients. However, no physical activity guidelines have been established for patients with concomitant AF and CAD. Our research suggests that public physical activity guidelines might be equally applied to patients with AF and CAD to slow the progression of cardiovascular disease. Patients are also advised to do 150 min a week of moderate-intensity activity such as cycling and brisk walking or 75 min a week of vigorous-intensity activity such as jogging and running, or an equivalent combination. However, very high intensive exercise such as competitive sports may be restricted in patients with symptomatic myocardial ischemia or uncontrolled tachycardia despite medical therapy [1].

Limited data are available regarding the association between physical activity and outcomes in patients with coexisting AF and CAD. To the best of our knowledge, this is the first study to evaluate the impact of physical activity on clinical outcomes, particularly in patients with concomitant AF and CAD. However, this study has some considerable limitations. The limitations of this study include its reliance on self-reported physical activity, which was reported at a single time point. The conditions at the time of questionnaire completion may not represent actual physical activity conditions throughout life. Nevertheless, the self-reported physical activity questionnaire used has been confirmed in several studies and has yielded valuable results to date [15, 17]. In addition, there was no data about the heart rate of the patients at the events. It was not known from our study whether exercise is associated with an excessive increase in heart rate and consequently and AF with rapid ventricular rate-induced MACCE. This study was based on a single-center experience and a retrospective, non-randomized control study, which could have caused site-specific bias and selection bias. We reduced this bias by performing appropriate adjusted statistical analyses. However, the small sample size may have reduced the power of the study and increased the margin of error, which may render the study meaningless. Therefore, further randomized controlled studies with larger populations and longer follow-up periods are warranted.

Conclusions

Physical activity was inversely trend with all-cause mortality and MACCE in patients with concomitant AF and CAD. No excess risk of all-cause mortality and MACCE was found at levels of physical activity above the recommended target range, even with vigorous-intensity physical activity exceeding the key target range. Further multicenter randomized studies that use larger populations with longer follow-up periods are therefore needed to establish an improved evidence base concerning the effects of physical activity in patients with concomitant AF and CAD.

Abbreviations

AF: Atrial fibrillation; BMI: Body mass index; CAD: Coronary artery disease; CI: Confidence interval; HR: Hazard ratio; MACCE: Major adverse cardiac and cerebrovascular event; MET: Metabolic equivalent of task; MI: Myocardial infarction.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s42444-022-00082-y.

Additional file 1: Supplemental Table 1. Risk of all-cause mortality according to the intensity of physical activity; **Supplemental Table 2.** Risk of MACCE according to the intensity of physical activity; **Supplemental Table 3.** Risk of all-cause mortality and MACCE in relation to physical activity level according to type of atrial fibrillation; **Supplementary Appendix.** Physical activity questionnaire Korean form in the study.

Acknowledgements

None.

Author contributions

M-NJ contributed to the concept and design of the study, performed the analysis of data, and drafted the manuscript. JS, BGK, GSK, HYL, YSB, and BOK contributed to acquisition and interpretation of data for the study.

Funding

This study is supported by a grant from the Korean Heart Rhythm Society (2020–06).

Availability of data and materials

Data are available from the authors upon reasonable request with permission of Institutional Review Board of Inje University Sanggye Paik Hospital.

Declarations

Ethics approval and consent to participate

The study protocol was authorized by the Institutional Review Board of Inje University Sanggye Paik Hospital (2022-01-029-004). This is a retrospective study and informed consent was waived.

Consent for publication

All authors have permitted the publication.

Competing interests

The authors declare that there is no conflict of interest.

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Received: 8 September 2022 Accepted: 10 November 2022
Published online: 19 December 2022

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