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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

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ABSTRACT

Aims: Physical activity is protective against cardiovascular (CV) events, both in general population as well as in high-risk CV cohorts. However, the relationship between physical activity with major adverse outcomes in atrial fibrillation (AF) is not well-established. Our aim was to analyse this relationship in a 'real-world' AF population. Second, we investigated the influence of physical activity on arrhythmia progression.

Methods and Results: We studied all patients enrolled in the EURObservational Research Programme on AF (EORP-AF) Pilot Survey. Physical activity was defined as 'none', 'occasional', 'regular' and 'intense', based on patient self-reporting**.** Data on physical activity were available for 2,442 patients: 38.9% reported none, 34.7% occasional, 21.7% regular and 4.7% intense physical activity. Prevalence of the principal CV risk factors progressively decreased from none to intense physical activity.

Lower rates of CV death, all-cause death and composite outcomes were found in AF patients who reported regular and intense physical activity ($p<0.0001$). Increasing physical activity was inversely associated with CV death/Any thromboembolic event (TE)/bleeding in the whole cohort, irrespective of gender, paroxysmal AF, elderly age or high stroke risk. Any level of physical activity intensity was significantly associated with lower risk of CV death/Any TE/Bleeding at 1-year follow-up. Physical activity was not significantly associated with arrhythmia progression.

Conclusions: Atrial fibrillation patients taking regular exercise were associated with a lower risk of all-cause death, even when we considered various subgroups, including gender, elderly age, symptomatic status and stroke risk class. Efforts to increase physical activity amongst AF patients may improve outcomes in these patients.

Keywords: atrial fibrillation, physical activity, exercise, adverse outcomes, all-cause death.

WHAT'S NEW

- Atrial fibrillation (AF) patients taking regular exercise had a lower rates of major adverse outcomes;
- Exercise levels in AF patients are inversely associated with composite outcomes at 1-year follow-up;
- Compared with patients taking no physical activity, all AF patients who regularly exercised had a tendency towards lower risk of all-cause death at 1-year follow-up.

INTRODUCTION

Sedentary lifestyle is a major risk factor for cardiovascular (CV) disease[1]. Accordingly, implementation of regular physical activity has been identified as one of the principal public health promotion strategies in order to reduce the impact of risk factors on CV risk[2,3]. Indeed, regular physical activity has been associated to a reduction in incident CV disease, CV and all-cause death, possibly through various physiological mechanisms[4,5]. Moreover, the influence of physical activity on CV morbidity and mortality seems to go beyond intensity, with the same beneficial effect also with light physical activity[6].

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia and is a major contributor to CV mortality and morbidity, especially from thromboembolism and heart failure. A relationship between AF-related adverse outcomes and physical activity has not been established. Data investigating the effect of exercise rehabilitation or chronic exercise training show that AF patients undergoing structured physical activity intervention programmes reported better exercise tolerance, quality of life and less intensive clinical management[7,8]. However, the influence of physical activity on major adverse events occurring in the long-term follow-up of AF patients are limited and inconclusive[7].

For years, physical activity has been reported as an important risk factor for developing AF both in athletes and general population and regardless of its intensity[9]. On the basis of the available evidence, this issue seems to be controversial. A large comprehensive systematic review and meta-analysis reported that athletes, exercising in several different sports, have a higher risk of developing AF, with a more than five-fold greater risk of incident AF

compared with controls[10]. Furthermore, observational data about intensively exercising athletes (as long-distance skiers or professional cyclists) seem to corroborate the idea that intensive exercise could be a risk factor for arrhythmias, in particular AF[11–13].

Conversely, one large observational study found that better cardiorespiratory fitness (CRF) was strongly associated with a reduced risk of incident AF (hazard ratio [HR]: 0.92, 95% confidence interval [CI]: 0.91-0.93, p<0.001 after all adjustments) throughout all patient subgroups and with a clear dose-effect response[14]. Another large cohort study on structured weight-management in AF obese patients, found that both higher baseline CRF level and a better CRF improvement were associated with a reduced risk of AF recurrence[15]. Other observational studies on physical activity and the risk of incident AF demonstrated that this risk was different across gender and age subgroups[16,17]. In male subjects, exercise is associated with a higher risk of developing AF in young age, while is inversely associated with AF risk in the elderly[16]. In women, however, exercise did not increase the risk of incident AF in younger subjects; among elderly females, the association between exercise and AF remains[17].

The aim of this study was to explore the relationship between self-reported physical activity and major adverse events in AF patients prospectively enrolled in the EURObservational Research Programme on AF (EORP-AF) Pilot Survey. Second, we explored the relation of physical activity to arrhythmia progression from paroxysmal AF to more established patterns. Third, we assessed the impact of physical activity in relation to outcomes by sex, elderly age (age ≥75), paroxysmal AF and high thromboembolic risk.

METHODS

The EORP-AF Pilot study was an observational prospective study enrolling consecutive AF patients managed by cardiologists, conducted by the European Society of Cardiology in nine European countries[18]. Details about study procedures[18] and main results[19] have been previously published.

Patients eligible for the study were both AF inpatients and/or outpatients referred to cardiology services (either hospital or office-based centres). Across the entire enrolment period, all patients consecutively presenting at every site were considered for eligibility. AF had to be recorded as a primary or secondary cardiovascular disease. Qualifying events were recorded by any electrocardiographic documentation occurring within the 12 months before the enrolment. Follow-up data were recorded 1 year after the enrolment date. Over 13 months of enrolment, a total of 3,119 AF patients were collected. All patients for whom the intensity of physical activity was reported were considered for these analyses.

During the enrolment interview, patients self-reported their level of physical activity. According to patients' reports, physical activity over the preceding 2 years was defined according to its intensity, irrespective of type of activity, as follows: (i) 'None' if no exercise or exercise was for <3 hours/week for <2 years; (ii) 'Occasional' if exercise <3 hours/week for ≥2 years; (iii) 'Regular' exercise if exercise was ≥3 hours/week for ≥2 years); (iv) 'Intense' exercise if physical activity was reported for >7 hours/week for ≥2 years. Thromboembolic risk was assessed according to the Congestive Heart Failure-Hypertension-Age ≥75 years-Diabetes Mellitus-Stroke/transient ischemic attack (TIA)/thromboembolism-Vascular

Disease-Age 65-74 years-Sex category (CHA_2DS_2-VASc) score. A "high-risk" AF patient was defined as a CHA_2DS_2-VASc score ≥2[20].

Symptomatic status at the baseline was defined according to European Heart Rhythm Association (EHRA) score[21]. Accordingly, patients with EHRA I were considered as asymptomatic, while EHRA score from II to IV described patients progressively more symptomatic and unable to attend their usual daily activities[21].

During the pre-specified 1-year follow-up period, the occurrence of major adverse events was recorded with office-based follow-up visits according to patients' self-reports, physicians' letters or hospital discharge summaries. According to the study protocol, the following events were recorded: CV death; all-cause death; stroke/ TIA; any bleeding; any thromboembolic event (TE) (defined as the occurrence of any stroke, TIA, acute coronary syndrome, coronary intervention, cardiac arrest, peripheral or pulmonary embolism). Composite outcomes of the major adverse events previously specified were also considered.

In order to evaluate the influence of physical activity on AF progression, we evaluated how many patients with paroxysmal AF at baseline progressed to persistent, long-standing persistent or permanent AF subtypes based on clinical examination, and ECGs performed during the follow-up period. All patients with paroxysmal AF who at the 1-year follow-up visit were defined as persistent, long-standing persistent or permanent AF were categorized as "AF progression"; conversely, all patients still classified as paroxysmal AF at 1-year were defined as "AF non-progression".

Statistical Analysis

Continuous variables were reported as mean±SD or as median and interquartile range (IQR). Among-group comparisons were made using a non-parametric test (Kruskal–Wallis test). Categorical variables were reported as percentages. Among-group comparisons were made using a chi-square test or Fisher's exact test (if any expected cell count was less than five). For qualitative variables with more than two possibilities, the Monte Carlo estimates of the exact p-values are used.

Plots of the Kaplan-Meier curves for time to all-causes death in relation to physical activity intensity categories were performed. The survival distributions have been compared using the log-rank test. A logistic regression analysis was performed in order to establish the clinical factors significantly associated with AF progression. All variables considered of clinical relevance underwent a univariate analysis and those predictors with a level significance of $p<0.10$ were inserted into the model. A significance level of 0.05 is required to allow a variable into the model (SLENTRY=0.05), and a significance level of 0.05 is required for a variable to stay in the model (SLSTAY=0.05). No interaction was tested. A Hosmer and Lemeshow Goodness-of-Fit Test was used to verify that the model was optimal. In addition, univariate logistic regression analysis on the effect of physical activity categories on major adverse events was performed, with associations expressed as odds ratios with 95% confidence intervals, comparing the categories of physical activity with 'no physical activity' category as the reference. This analysis was also performed stratified according to gender, elderly patients (age≥75 years), paroxysmal AF and high thromboembolic risk (CHA_2DS_2-VASc score ≥2). A two-sided p value <0.05 was considered statistically significant.

All analyses were performed using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

From the original study population, data on physical activity intensity were available for 2,442 patients (78.5%). Self-reported physical activity was as follows: 38.9% reported none physical activity, whilst 34.7% reported occasional, 21.7% regular and 4.7% intense physical activity (Table 1). Of the selected cohort, 979 (40.1%) were female and median [IQR] age was 70 [62-77] years (34.2% were aged ≥75 years); 42.3% were overweight and 28.5% of patients were obese. Paroxysmal AF was more frequently recorded in patients with intense physical activity ($p<0.0001$). High thromboembolic risk (CHA_2DS_2-VASc score ≥2) was found in 81.6% (1,993 patients).

With increasing physical activity intensity categories, there was a decrease in mean age and proportion of females, as well as in those with hypertension, diabetes (all $p<0.0001$) and hypercholesterolemia ($p=0.019$). Conversely, smoking habit was less prevalent in patients who reported no physical activity ($p=0.033$). The proportion of obese patients was lower in the intense physical activity group ($p=0.008$). Patients with intense physical activity had a mean higher left ventricular ejection fraction ($p=0.0420$).

Taking into account co-morbidites conditions, patients with intense physical activity reported a lower prevalence of coronary artery disease ($p=0.0024$), chronic heart failure ($p<0.0001$) and valvular heart disease ($p=0.0007$). Both patients with regular and intense physical activity had a significant lower rate of previous stroke ($p=0.0010$).

Accordingly, CHA_2DS_2-VASc score progressively decreased, as did the proportion at 'high-risk' of stroke/TE (p<0.0001) across the physical activity categories. Patients who reported no physical activity had a lower proportion of EHRA class I (asymptomatic AF) while patients who had a progressively more intense physical activity were more likely to be symptomatic at EHRA class II-IV (p<0.0001). At 1-year follow-up pharmacological cardioversion (Table 2) was progressively more used across the four physical activity categories (p=0.0013). Electrical cardioversion and catheter ablation were more likely used in patients with regular and intense physical activity (both p<0.0001).

There were no differences in the proportion of patients receiving oral anticoagulants in relation to physical activity (p=0.619), but non-vitamin K antagonist oral anticoagulants were more often used in the intense physical activity group (p=0.005). Patients who reported regular and intense physical activity were more frequently treated with at least one antiarrhythmic drug (p=0.001), particularly a Class I antiarrhythmic drug (p<0.001). AF patients reporting intense physical activity were less frequently treated with statins (p=0.002), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (p<0.001), diuretics (p<0.0001), aldosterone blockers (p<0.001) and digoxin (p=0.004).

Arrhythmia Progression and Physical Activity

Of the 632 (26.3%) paroxysmal AF patients at baseline, data on AF subtype at 1-year were available in 603 patients (96.8%). Of these, 88 patients (14.6%) were defined as "AF progression" and their clinical characteristics were similar to AF non-progression patients (Table S1). "AF progression" patients were older (p=0.0226) and more frequently underweight (p=0.008). The proportion of "AF progression" patients progressively

decreased according to increasing categories of physical activity intensity, from 17.7% in patients reporting no physical activity to 6.8% with intense physical activity, although if this difference was not found to be statistically significant (p=0.306). Logistic regression found that only the 'underweight' category was independently associated with AF progression, while intense physical activity showed an inverse trend for an association with "AF progression" (Table 3).

Follow-up Analysis

During the 1-year follow-up (Table 4), patients in the regular and intense physical activity categories had a lower prevalence of CV death and all-cause death separately (both p<0.0001), as well as the composite endpoint of "all-cause death/any TE" (p<0.0001). Meanwhile rates for the composite outcome of "CV death/any TE/bleeding" progressively decreased throughout the physical activity categories (p<0.0001). There was no significant difference in rates of stroke/TIA or bleeding by self-reported physical activity level.

Univariate logistic regression analysis for the whole cohort (Table 5) found that all intensity levels of physical activity were *inversely* associated with the composite outcome of 'CV death/any TE/bleeding' (Figure 1). Survival analysis demonstrates that patients reporting any physical activity intensity level had lower risk for all-cause death when compared to patients reporting none physical activity (p<0.0001) (Figure 2).

Subgroup Analyses

A gender-stratified analysis showed similar results, compared to the overall cohort. Both male and female patients in the 'none' physical activity category reported higher event rates

for CV death ($p<0.0001$ and $p<0.001$, respectively), all-cause death ($p<0.0001$) and the composite outcomes (Table S2). Similar results were obtained for elderly (age≥75 years) patients, paroxysmal AF and high thromboembolic risk (CHA_2DS_2-VASc score ≥2) patients (Table S2).

On logistic analysis (Table S3), occasional physical activity in all subgroups was inversely associated with the composite outcome of CV death/Any TE/Bleeding. This inverse association was significant also for regular physical activity in all subgroups, except for elderly patients. Intense physical activity was significantly inversely associated with the composite outcome only for male patients ($p=0.025$), while in the other subgroups this was non-significant. Similar to the overall population, survival analysis in the various subgroups showed that the none physical activity conferred a higher risk for all-cause death compared to patients reporting any intensity level of physical activity ($p<0.0001$).

DISCUSSION

Our study provides the *first* evidence that AF patients exercising at any level of intensity have a lower risk of all-cause death compared to AF patients with no physical activity on a long-term follow-up observation. Second, the composite outcome of CV death/any TE/bleeding was inversely proportional to intensity of self-reported physical activity. Third, the proportion of "AF progression" decreased as the intensity of physical activity increased but not significantly, with no significant evidence that more intensive physical activity was associated with less arrhythmia progression. Last, the association between physical activity and the reduced risk of all-cause death was significant regardless of gender, older age (≥75 years), presence of paroxysmal AF and high thromboembolic risk (CHA_2DS_2-VASc score ≥2).

The beneficial effect of physical activity on CV death and all-cause death in the general population has been shown. For example, the Framingham Heart Study reported that among 4,729 free from CV disease at baseline, long-term physical activity was inversely associated with lower all-cause death (rate ratio 0.81, 95% CI 0.71-0.93) and CVD-attributable mortality (rate ratio 0.83, 95% CI 0.72-0.97) over 40 years follow-up[22]. A large prospective, observational cohort, the Aerobics Center Longitudinal Study demonstrated that leisure-time running was associated with a reduced risk for both all-cause and CV death in 55,137 subjects followed for a mean follow-up of 15 years[6]. Reduced risks were evident across the different classes of running categories (running distance, running frequency, total amount of running and running speed)[6].

Our data show fo*r the first time* in a large European AF population that occasional, regular or intense physical activity was associated with a reduced risk of all-cause death and inversely associated with the composite outcome of CV death/any TE/bleeding. This evidence supports previous data of the impact of physical activity on secondary CV prevention[5]. Both observational and randomized controlled trials have shown that physical activity, as well as structured rehabilitation programmes, are associated with improvements in all CV associated risk factors, and also in reductions in CV morbidity and mortality[5]. Indeed, our findings underline the important role of physical activity in the management of CV risk, and specifically, in patients with AF.

The inverse association between progressively more intensive physical activity and reduced outcomes rates, as long as its hypothesized beneficial effect, as shown by our data could be simply explained by the exercise effect in reducing CV risk. Recently, improved cardiorespiratory fitness (CRF) has been related to reduced incidence of CV events, CV death and all-cause death, beyond the physical activity itself and weight reduction[23]. In the Aerobics Center Longitudinal Study, the incremental value of CRF was associated with a progressive decrease in all-cause and CV death, regardless of both body weight and body fat reductions[23]. The role of CRF may be considered as crucial in the relationship between physical activity, body weight and CV risk, both in the general population and high-risk CV patients[4]. Our data demonstrating a similar relationship between physical activity and reduced adverse events in all subgroups considered, also strengthens the possible role of physical activity in reducing adverse events in AF patients, regardless of their clinical characteristics and presentation. Conversely, physical activity could represent a major marker of health status in AF patients, and indeed, those undertaking intense physical

activity had less risk factors and comorbidities, as well as a lower thromboembolic risk overall. Therefore, healthier subjects (with a lower risk of major adverse events) would be more easily prone to taking more exercise.

Evidence about the relationship between physical activity and AF has largely been controversial. Several studies report a direct association between physical activity and the occurrence of incident AF[9,16,17]; conversely, some large well-controlled trials suggest that physical activity seems to be protective both in terms of incident AF[14], recurrence of AF[15] and AF burden. One national cohort observational study examining about the role of physical activity in the occurrence of both vascular events and arrhythmias, found that over a long term follow-up of 26.3 years, high exercise capacity was associated both with reduced vascular events (HR: 0.67, 95% CI 0.65-0.70) and the occurrence of arrhythmia episodes (HR: 0.92, 95% CI: 0.88-0.97)[24]. However, no significant association was found in regard to the occurrence of AF episodes. In a recent interventional randomized trial, aerobic interval activity reduced AF burden in patients with non-permanent AF, at least over short-term follow-up [25]. In the present study, our results show that despite a gradual reduction in the proportions of AF progression across the categories of physical activity intensity, this difference in proportions was not statistically significant. Also, our analyses were not able to document an independent association between any physical activity intensity category and AF progression.

Interestingly, patients with intense physical activity were more frequently diagnosed with paroxysmal AF. They were also more symptomatic, more frequently treated with at least one antiarrhythmic drug or interventions aimed to restore sinus rhythm. Even if these

findings seem to be inconsistent with previous findings showing that physical activity helps improve symptoms [7,15], perhaps with a dose-response relationship [15], this could reflect a protective action of physical activity in preventing AF recurrence and burden[15,25]. Indeed, even if non-significant, there was a trend for an inverse association between intense physical activity and AF progression. On the other hand the higher prevalence of paroxysmal AF in patients with intense physical activity could simply reflect that being more frequently in sinus rhythm, those patients were more easily prone to increased exercise.

Strengths and Limitations

The strength of our data is the "real world population" of AF patients who were consecutively recruited by European cardiologists. Conversely, the latter may not completely represent the AF population managed by non-cardiologists. One major limitation is clearly represented by the self-reported nature of the data on physical activity. Moreover, the lack of specific details about the type and frequency of physical activity further underlines this limitation. Likewise, given the observational nature of the study, more reliable quantification of physical activity as the metabolic equivalents were not available. Furthermore, the relatively short follow-up period and generally low rate of major adverse events could have limited power to associate physical activity with events, in particular to detect survival differences in patient subgroups. Lastly, EORP-AF was an observational study and was not powered to detect survival differences in different patient subgroups; moreover, we cannot imply a causal relationship between physical activity and event rates. Thus, our data are not intended to be as a proof of the "protective effect" of physical activity in AF patients, but to be considered as hypothesis-generating. Further

interventional trials in the AF population, with adequate recording of physical activity and properly powered to detect differences in survival, are needed.

CONCLUSIONS

Patients with AF taking regular exercise seem to report a significant tendency in lower risk of all-cause death, regardless of gender, elderly age, clinical presentation and stroke risk class. Physical activity was not independently associated with AF progression. Efforts to increase physical activity amongst AF patients may improve outcomes in these patients.

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G Boriani: small speaker's fees from Boehringer, Medtronic Inc, St.Jude and Boston Scientific. GA Dan: small speaker-fees from Boehringer-Ingelheim, Bayer and Pfizer. L Tavazzi: Trial Committee member and member of the speakers' bureau for Servier at present, and trial Committee member for Boston Scientific in the previous 36 months. DA Lane: investigator-initiated educational grants from Bayer Healthcare, Boehringer Ingelheim, and Bristol-Myers-Squibb and has served as a speaker for Boehringer Ingelheim, Bayer, and Bristol-Myers- Squibb/Pfizer. She is also a member of the AEGEAN study Steering Committee. GYH Lip: guideline membership/reviewing for various guidelines and position statements from ESC, EHRA, NICE etc. Steering Committees/trials: Includes steering

committees for various Phase II and III studies, Health Economics & Outcomes Research, etc. Investigator in various clinical trials in cardiovascular disease, including those on antithrombotic therapies in atrial fibrillation, acute coronary syndrome, lipids, etc. Consultant for Bayer/Jensen J&J, Astellas, Merck, Sanofi, BMS/Pfizer, Biotronik, Medtronic, Portola, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo.
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Table 1: Baseline Characteristics of Patients According to Physical Activity Intensity

	None	**Occasional**	**Regular**	**Intense**	
	n=949	*n=848*	*n=530*	*n=115*	***p***
Demographics					
Age *years*, Median (IQR)	74 (66-80)	69 (62-77)	65 (58-72)	64 (56-72)	<0.0001
Age ≥75 years, n (%)	453 (47.7)	276 (32.5)	85 (16.0)	21 (18.3)	<0.0001
Female Gender, n (%)	462 (48.7)	349 (41.2)	140 (26.4)	28 (24.3)	<0.0001
BMI, n (%) *2,389*					0.008
Underweight	16 (1.7)	9 (1.1)	2 (0.4)	0	
Normal	271 (29.6)	216 (25.8)	145 (27.7)	40 (35.4)	
Overweight	373 (40.7)	348 (41.6)	235 (44.9)	54 (47.8)	
Obese	257 (28.0)	263 (31.5)	141 (27.0)	19 (16.8)	
LVEF *%*, Mean±SD	52.5±14.4	52.0±13.0	52.6±13.0	55.8±12.2	0.0420
AF Subtypes, n (%) *2,403*					<0.0001
First Detected	311 (33.1)	235 (28.4)	169 (32.4)	25 (21.9)	
Paroxysmal	202 (21.5)	240 (29.0)	146 (28.0)	44 (38.6)	
Long-Standing Persistent	32 (3.4)	55 (6.6)	16 (3.1)	6 (5.3)	
Persistent	175 (18.6)	173 (20.9)	126 (24.1)	21 (18.4)	
Permanent	219 (23.3)	125 (15.1)	65 (12.5)	18 (15.8)	
Cardiovascular Risk Factors, n (%)					
Diabetes Mellitus *2,430*	226 (24.0)	178 (21.1)	77 (14.6)	15 (13.2)	<0.0001
Hypertension *2,431*	694 (73.5)	643 (76.1)	335 (63.3)	57 (50.4)	<0.0001
Current Smoker *2,407*	84 (8.9)	101 (12.1)	71 (13.6)	13 (11.7)	0.033

	None	Occasional	Regular	Intense	
	n=949	*n=848*	*n=530*	*n=115*	***p***
Hypercholesterolemia *2,398*	466 (50.2)	423 (50.7)	230 (43.9)	45 (40.5)	0.019
Alcohol ≥2-3 units/day *2,356*	64 (7.0)	59 (7.2)	56 (11.0)	14 (13.0)	0.010
Concomitant Conditions, n (%)					
Coronary Artery Disease *2,117*	329 (39.2)	271 (37.3)	145 (31.8)	22 (23.2)	0.0024
Chronic Heart Failure *2,324*	453 (49.0)	416 (51.1)	200 (41.4)	28 (27.2)	<0.0001
Valvular Heart Disease *2,299*	620 (67.9)	524 (64.9)	282 (58.4)	52 (54.2)	0.0007
Dilated Cardiomyopathy *2,311*	106 (11.5)	107 (13.2)	50 (10.4)	5 (5.0)	0.0750
HCM *2,315*	32 (3.5)	39 (4.8)	18 (3.7)	3 (3.0)	0.5125
Previous Stroke *2,429*	77 (8.1)	53 (6.3)	15 (2.9)	6 (5.3)	0.0010
Previous TIA *2,421*	48 (5.1)	29 (3.5)	17 (3.2)	5 (4.4)	0.2363
PVD *2,310*	130 (14.0)	88 (11.2)	58 (11.7)	6 (5.9)	0.0610
CHA_2DS_2-VASc score					
Mean score ± SD	3.79 ±1.74	3.31 ±1.73	2.44 ±1.68	2.17 ±1.78	<0.0001
CHA_2DS_2-VASc class, n (%)					<0.0001
Class 0	22 (5.8)	35 (4.1)	65 (12.3)	19 (16.5)	
Class 1	76 (8.0)	103 (12.1)	101 (19.1)	29 (25.2)	
Class ≥2	851 (89.7)	710 (83.7)	364 (68.7)	67 (58.3)	
EHRA score, n (%)					<0.0001
EHRA I	479 (50.5)	319 (37.6)	173 (32.6)	34 (29.6)	
EHRA II-IV	470 (49.5)	529 (62.4)	357 (67.3)	81 (70.4)	

	None	Occasional	Regular	Intense	
	n=949	*n=848*	*n=530*	*n=115*	***p***
Drug Therapy at Discharge/After Consultation					
Antithrombotic therapy, n (%)					
At least one *2,438*	911 (96.1)	823 (97.2)	498 (94.3)	110 (95.7)	0.071
Antiplatelet *2,438*	296 (31.2)	312 (36.8)	179 (33.9)	30 (26.1)	0.025
Oral anticoagulant *2,437*	761 (80.4)	697 (82.3)	430 (81.4)	97 (84.3)	0.619
NOACs *2,439*	63 (6.6)	60 (7.1)	45 (8.5)	18 (15.7)	0.005
Antiarrhythmic drugs, n (%) *2,441*					
At least one	289 (30.5)	306 (36.1)	215 (40.6)	45 (39.1)	<0.001
Antiarrhythmic Class I	73 (7.7)	80 (9.4)	68 (12.8)	19 (16.5)	0.001
Antiarrhythmic Class III	217 (22.9)	224 (26.4)	152 (28.7)	26 (22.6)	0.066
Other treatments, n (%)					
Statins *2,437*	443 (46.7)	453 (53.5)	243 (46.1)	45 (39.1)	0.002
ACEi/ARBs *2,438*	609 (64.4)	587 (69.3)	324 (61.1)	60 (52.2)	<0.001
Beta blockers *2,437*	637 (67.3)	611 (72.2)	379 (71.5)	76 (66.1)	0.0870
Diuretics *2,439*	564 (59.6)	458 (54.1)	221 (41.7)	30 (26.1)	<0.0001
Aldosterone blockers *2,439*	269 (28.4)	209 (24.7)	121 (22.8)	12 (10.4)	<0.001
DHP calcium-channel blockers *2,439*	118 (12.4)	125 (14.8)	75 (14.2)	7 (6.1)	0.053
Non-DHP calcium-channel blockers *2,439*	75 (7.9)	43 (5.1)	28 (5.3)	7 (6.1)	0.064

	None	Occasional	Regular	Intense	
	n=949	*n=848*	*n=530*	*n=115*	***p***
Digoxin *2,440*	208 (21.9)	169 (20.0)	86 (16.2)	12 (10.4)	0.004
DRI Aliskiren *2,439*	2 (0.2)	0	2 (0.4)	0	0.358*
Oral anti-diabetics *2,441*	157 (16.5)	121 (14.3)	59 (11.1)	10 (8.7)	0.011
Insulin *2,441*	58 (6.1)	44 (5.2)	17 (3.2)	4 (3.5)	0.085
Thyroid-suppressing drugs *2,441*	22 (2.3)	17 (2.0)	16 (3.0)	6 (5.2)	0.169
Beta-2 agonists *2,441*	21 (2.2)	11 (1.3)	6 (1.1)	1 (0.9)	0.274
Anticholinergic agents *2,441*	34 (3.6)	15 (1.8)	5 (0.9)	0	0.001

Legend: ACEi= angiotensin-converting enzyme inhibitors; ARBs= angiotensin receptor blockers; BMI= body mass index; DHP= dihydropyridine; DRI= direct renin inhibitor; HCM= hypertrophic cardiomyopathy; IQR= interquartile range; LVEF= left ventricular ejection fraction; NOACs= non-vitamin k antagonist oral anticoagulants; PVD= peripheral vascular disease; SD= standard deviation; TIA= transient ischemic attack. *Fisher's exact test.

Table 2: Interventions at 1-year Follow-up According to Physical Activity Intensity

	None *n=949*	**Occasional** *n=848*	**Regular** *n=530*	**Intense** *n=115*	***p***
Pharmacological Cardioversion	52 (6.3%)	78 (9.6)	58 (11.2)	17 (15.3)	0.0013
Electrical Cardioversion	32 (4.0)	30 (3.8)	34 (6.8)	14 (12.8)	<0.0001
Catheter Ablation	18 (2.2)	29 (3.6)	36 (6.9)	8 (7.1)	<0.0001

Table 3: Logistic Regression Analysis for AF Progression Occurrence

	Univariate Analysis			Multivariable Analysis		
	Odds Ratio	***95% CI***	***p***	***Odds Ratio***	***95% CI***	***p***
Age *(in years)*	1.021	[1.000-1.043]	0.046	-	-	-
Female Gender	0.943	[0.596-1.493]	0.803	-	-	-
BMI *(ref. Normal)*						
Underweight	13.400	[1.347-133.325]	0.022	13.832	[1.377-138.979]	0.026
Overweight	0.671	[0.394-1.142]	-	0.657	[0.384-1.122]	0.124
Obese	0.578	[0.308-1.087]	-	0.531	[0.281-1.003]	0.051
Diabetes	0.635	[0.316-1.276]	0.202	-	-	-
Hypertension	1.266	[0.759-2.110]	0.366	-	-	-
Current smoker	1.105	[0.569-2.145]	0.768	-	-	-
Hypercholesterolemia	1.295	[0.819-2.046]	0.269	-	-	-

Physical Activity *(ref. None)*						
Occasional	0.761	[0.448-1.293]	0.327	0.720	[0.417-1.241]	0.237
Regular	0.757	[0.412-1.390]	-	0.700	[0.374-1.313]	0.267
Intense	0.341	[0.099-1.169]	-	0.310	[0.089-1.078]	0.066

Legend: CI= confidence interval; ref= reference.

Table 4: Major Adverse Events During 1-year Follow-up According to Physical Activity Categories

	None n=949	**Occasional** n=848	**Regular** n=503	**Intense** n=115	***p***
Major Adverse Events, n (%)					
Stroke/TIA	9 (1.1%)	9 (1.2%)	2 (0.4%)	1 (1.0%)	0.426*
Bleeding	13 (1.7%)	9 (1.2%)	3 (0.6%)	0	0.235*
Any TE	34 (4.3%)	25 (3.4%)	21 (4.2%)	3 (2.9%)	0.733*
CV death	53 (5.8%)	12 (1.4%)	2 (0.4%)	1 (0.9%)	<0.0001*
All-cause death	116 (12.2%)	33 (3.9%)	7 (1.3%)	3 (2.6%)	<0.0001*
All-cause death/Any TE	150 (16.6%)	58 (7.5%)	28 (5.5%)	6 (5.6%)	<0.0001
CV death/Any TE/Bleeding	99 (12.0%)	45 (6.1%)	26 (5.2%)	4 (3.8%)	<0.0001*

Legend: CV= cardiovascular; TE= thromboembolic event; TIA= transient ischemic attack;

*Fisher's exact test.

Table 5: Effect of Physical Activity Categories on Major Adverse Events

Physical Activity	**1-year outcome**	**Whole Cohort**		
		Odds Ratio*	**95% CI**	***p***
Occasional	Stroke/TIA	1.07	[0.42-2.71]	0.885
	Any TE	0.78	[0.46-1.32]	0.353
	Bleeding	0.72	[0.51-1.03]	0.07
	CV death/Any TE/Bleeding	0.48	[0.33-0.69]	**<0.0001**
Regular	Stroke/TIA	0.35	[0.07-1.62]	0.159
	Any TE	0.97	[0.56-1.70]	0.923
	Bleeding	0.75	[0.47-1.19]	0.218
	CV death/Any TE/Bleeding	0.40	[0.26-0.63]	**<0.0001**
Intense	Stroke/TIA	0.83	[0.10-6.65]	0.864
	Any TE	0.65	[0.20-2.17]	0.484
	Bleeding	0.49	[0.17-1.37]	0.169
	CV death/Any TE/Bleeding	0.29	[0.10-0.80]	**0.011**

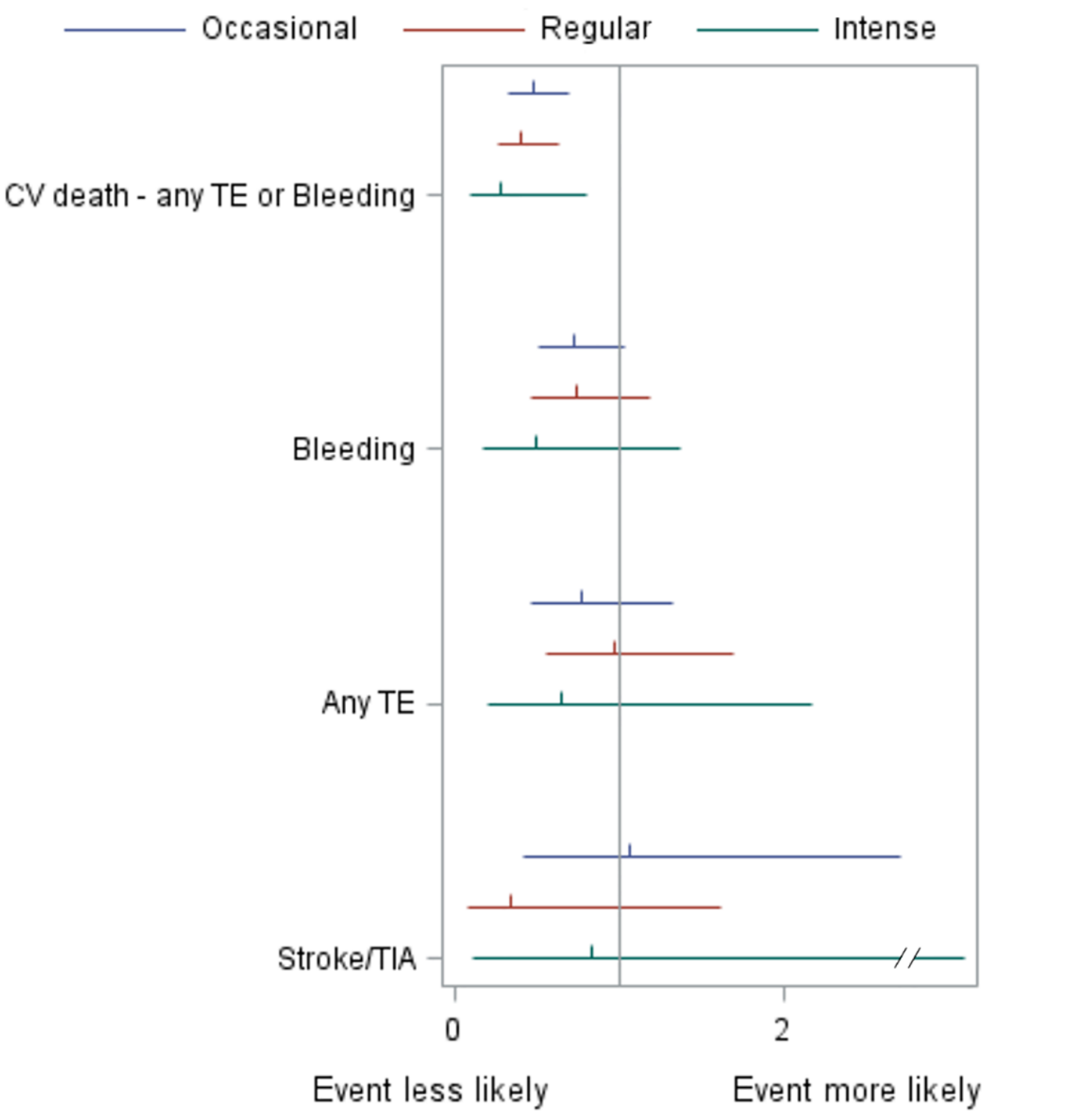
Legend: *Analysis presented is unadjusted univariate logistic analysis. CI= confidence interval; CV= cardiovascular; NA= not available; TE= thromboembolic event; TIA= transient ischemic attack.

FIGURE LEGENDS

Figure 1: Univariate Logistic Analysis for Major Adverse Events

Legend: TE: thromboembolic event; TIA= transient ischemic attack.

Figure 2: Kaplan-Meier Curves for All-Cause Death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Regular
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CV death - any TE or Bleeding
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Stroke/TIA
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Event less likely
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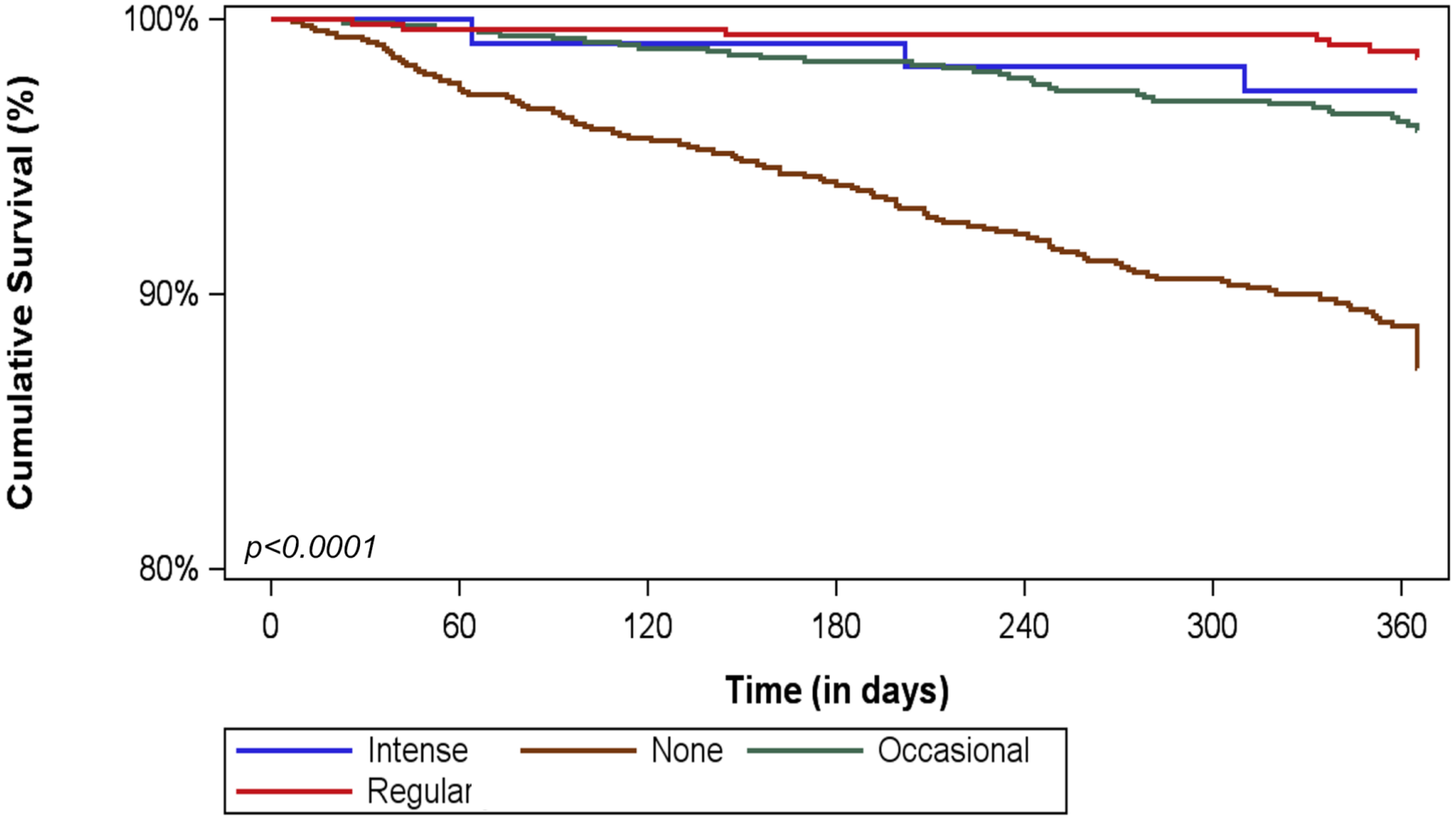

Number of Subjects at risk

Intense	115		114		113		97
None	947	924	905	888	867	839	693
Occasional	847	844	837	828	820	804	688
Regular	530	528	527	525	524	519	467

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

Supplementary Material

Table of Contents

Table S1: Baseline Characteristics of Patients According to AF Progression

	AF Progression	**AF Non-Progression**	
	n=88	**n=515**	***p***
Demographics			
Age in years Median (IQR)	70 (62-76)	66 (59-74)	0.023
Age ≥75 years, n (%)	29 / 88 (33.0)	120 / 515 (23.3)	0.052
Female gender, n (%)	36 / 88 (40.9)	218 / 515 (42.3)	0.803
BMI, n (%)			0.008
Underweight	3 / 86 (3.5)	1 / 507 (0.2%)	
Normal	30 / 86 (34.9)	134 / 507 (26.4%)	
Overweight	35 / 86 (40.7)	233 / 507 (46.0%)	
Obese	18 / 86 (20.9)	139 / 507 (27.4%)	
Cardiovascular Risk Factors, n (%)			
Diabetes Mellitus	10 / 88 (11.4)	86 / 512 (16.8)	0.199
Hypertension	65 / 88 (73.9)	355 / 514 (69.1)	0.365
Current Smoker	12 / 86 (14.0)	65 / 508 (12.8)	0.767
Hypercholesterolemia	45 / 86 (52.3)	234 / 510 (45.9)	0.268
Alcohol ≥2-3 units/day	6 / 86 (7.0)	24 / 503 (4.8)	0.423*
CHA_2DS_2-VASc score			0.306
Mean score ± SD	2.9 ±1.6	2.7 ±1.8	
CHA_2DS_2-VASc class, n (%)			0.025
Class 0	6 / 88 (6.8)	45 / 515 (8.7)	
Class 1	9 / 88 (10.2)	111 / 515 (21.6)	

	AF Progression n=88	AF Non-Progression n=515	*p*
Class ≥2	73 / 88 (83.0)	359 / 515 (69.7)	
Drug Therapy at Discharge/After Consultation			
Antithrombotic Therapy, n (%)			
At least one	84 / 88 (95.5)	490 / 515 (95.1)	>0.999
Antiplatelet	19 / 88 (21.6)	178 / 514 (34.6)	0.016
Oral anticoagulant	75 / 88 (85.2)	397 / 514 (77.2)	0.092
NOACs	5 / 88 (5.7)	39 / 515 (7.6)	0.529
Antiarrhythmic Drugs, n (%)			
At least one	45 / 88 (51.1)	252 / 515 (48.9)	0.702
Antiarrhythmic class I	15 / 88 (17.0)	98 / 515 (19.0)	0.659
Antiarrhythmic class III	29 / 88 (33.0)	155 / 515 (30.1)	0.591
Other Treatments, n (%)			
Statins	46 / 88 (52.3)	259 / 514 (50.4)	0.744
ACEi/ARBs	63 / 88 (71.6)	317 / 512 (61.9)	0.082
Beta blockers	58 / 88 (65.9)	352 / 514 (68.5)	0.632
Diuretics	33 / 88 (37.5)	185 / 514 (36.0)	0.786
Aldosterone blockers	10 / 88 (11.4)	55 / 514 (10.7)	0.853
DHP calcium-channel blockers	11 / 88 (12.5)	76 / 514 (14.8)	0.573
Non-DHP calcium-channel blockers	5 / 88 (5.7)	21 / 514 (4.1)	0.567*
Digoxin	3 / 88 (3.4)	27 / 514 (5.3)	0.602*

	AF Progression n=88	AF Non-Progression n=515	*p*
Oral anti-diabetics	8 / 88 (9.1)	61 / 515 (11.8)	0.453
Insulin	2 / 88 (2.3)	18 / 515 (3.5)	0.753*
Thyroid-suppressing drugs	4 / 88 (4.5)	11 / 515 (2.1)	0.254*
Beta-2 agonists	-	2 / 515 (0.4)	>0.999*
Anticholinergic agents	-	4 / 515 (0.8)	>0.999*

Legend: ACEi= angiotensin-converting enzyme inhibitors; ARBs= angiotensin receptor blockers; BMI= body mass index; DHP= dihydropyridine; DRI= direct renin inhibitor; IQR= interquartile range; NOACs= non-vitamin k antagonist oral anticoagulants. *Fisher's exact test.

Table S2: Major Adverse Events Rate According to Physical Activity in Subgroups at 1-Year FU

	None	**Occasional**	**Regular**	**Intense**	***p***
Male Patients					
N° of patients	487	499	390	87	
Major Adverse Events, n (%)					
Stroke/TIA	4 (1.0%)	4 (0.9%)	2 (0.5%)	1 (1.2%)	0.750
Bleeding	8 (2.0%)	6 (1.4%)	2 (0.5%)	0	0.277
Any TE	15 (3.7%)	16 (3.7%)	20 (5.3%)	2 (2.5%)	0.497
CV death	28 (6.0%)	9 (1.8%)	1 (0.3%)	1 (1.2%)	**<0.0001**
All-cause death	65 (13.3%)	24 (4.8%)	4 (1.0%)	2 (2.3%)	**<0.0001**
All-cause death /Any TE	80 (17.0%)	40 (8.7%)	24 (6.3%)	4 (4.8%)	**<0.0001**
CV death/Any TE/Bleeding	51 (12.0%)	30 (6.9%)	23 (6.2%)	3 (3.7%)	**0.004**
Female Patients					
N° of patients	462	349	140	28	
Major Adverse Events, n (%)					
Stroke/TIA	5 (1.3%)	5 (1.6%)	0	0	0.611
Bleeding	5 (1.3%)	3 (1.0%)	1 (0.8%)	0	0.927
Any TE	19 (4.9%)	9 (3.0%)	1 (0.8%)	1 (4.2%)	0.110
CV death	25 (5.6%)	3 (0.9%)	1 (0.7%)	0	**<0.001**
All-cause death	51 (11.0%)	9 (2.6%)	3 (2.1%)	1 (3.6%)	**<0.0001**
All-cause death/Any TE	70 (16.1%)	18 (5.8%)	4 (3.1%)	2 (8.0%)	**<0.0001**
CV death/Any TE/Bleeding	48 (12.0%)	15 (4.9%)	3 (2.4%)	1 (4.2%)	**<0.001**

Elderly Patients					
N° of patients	453	276	85	21	
Major Adverse Events, n (%)					
Stroke/TIA	7 (1.9%)	3 (1.3%)	0	0	0.749
Bleeding	8 (2.2%)	3 (1.3%)	0	0	0.693
Any TE	17 (4.7%)	7 (3.0%)	5 (6.4%)	1 (5.3%)	0.451
CV death	30 (7.0%)	4 (1.5%)	1 (1.2%)	0	**0.002**
All-cause death	74 (16.3%)	17 (6.2%)	3 (3.5%)	1 (4.8%)	**<0.0001**
All-cause death/Any TE	91 (20.9%)	24 (9.7%)	8 (9.9%)	2 (10.0%)	**<0.001**
CV death/Any TE/Bleeding	54 (14.0%)	16 (7.0%)	6 (7.8%)	1 (5.3%)	**0.032**
Paroxysmal AF					
N° of patients	202	240	146	44	
Major Adverse Events, n (%)					
Stroke/TIA	2 (1.2%)	1 (0.4%)	0	0	0.590
Bleeding	1 (0.6%)	0	1 (0.7%)	0	0.433
Any TE	9 (5.3%)	5 (2.2%)	7 (4.9%)	0	0.179
CV death	11 (5.6%)	1 (0.4%)	0	0	**<0.001**
All-cause death	20 (9.9%)	4 (1.7%)	1 (0.7%)	0	**<0.0001**
All-cause death/Any TE	29 (15.3%)	9 (4.0%)	8 (5.6%)	0	**<0.0001**
CV death/Any TE/Bleeding	21 (11.8%)	6 (2.7%)	8 (5.6%)	0	**<0.001**
High Risk (CHA_2DS_2-VASc≥2)					
N° of patients	851	710	364	67	
Major Adverse Events, n (%)					

	None	Occasional	Regular	Intense	*p*
Stroke/TIA	9 (1.3%)	8 (1.3%)	2 (0.6%)	1 (1.8%)	0.575
Bleeding	11 (1.6%)	9 (1.5%)	3 (0.9%)	0	0.819
Any TE	32 (4.6%)	23 (3.8%)	18 (5.4%)	3 (5.3%)	0.723
CV death	51 (6.3%)	11 (1.6%)	2 (0.6%)	1 (1.5%)	**<0.0001**
All-cause death	114 (13.4%)	32 (4.5%)	6 (1.6%)	3 (4.5%)	**<0.0001**
All-cause death/Any TE	146 (18.0%)	55 (8.7%)	24 (7.0%)	6 (10.0%)	**<0.0001**
CV death/Any TE/Bleeding	93 (12.7%)	42 (7.0%)	23 (6.9%)	4 (6.9%)	**<0.001**

Legend: CV= cardiovascular; TE= thromboembolic event; TIA= transient ischemic attack.

Table S3: Multivariable Effect of Physical Activity on Major Adverse Events According to Subgroups

PA	1-year Outcome	Male Patients			Female Patients			Elderly Patients		
		OR*	**95% CI**	***p***	**OR***	**95% CI**	***p***	**OR***	**95% CI**	***p***
Occasional	Stroke/TIA	0.93	[0.23-3.75]	0.922	1.27	[0.36-4.43]	0.706	0.66	[0.17-2.60]	0.555
	Any TE	0.99	[0.48-2.04]	0.990	0.59	[0.26-1.32]	0.193	0.63	[0.26-1.55]	0.321
	Bleeding	0.67	[0.41-1.10]	0.109	0.78	[0.47-1.31]	0.346	0.45	[0.26-0.76]	**0.003**
	CV death/ Any TE/Bleeding	0.55	[0.34-0.88]	**0.011**	0.38	[0.21-0.69]	**0.001**	0.46	[0.26-0.83]	**0.008**
Regular	Stroke/TIA	0.54	[0.10-2.96]	0.470	NA	NA	-	NA	NA	-
	Any TE	1.47	[0.74-2.91]	0.269	0.15	[0.02-1.15]	0.036	1.39	[0.49-3.88]	0.215
	Bleeding	0.65	[0.35-1.21]	0.177	0.93	[0.45-1.90]	0.840	0.91	[0.36-2.27]	0.532
	CV death/ Any TE/Bleeding	0.48	[0.29-0.81]	**0.005**	0.18	[0.05-0.58]	**0.001**	0.52	[0.21-1.25]	0.139
Intense	Stroke/TIA	1.25	[0.14-11.36]	0.841	NA	NA	-	NA	NA	-
	Any TE	0.66	[0.15-2.94]	0.581	0.84	[0.11-6.54]	0.866	1.12	[0.14-8.92]	0.912
	Bleeding	0.34	[0.08-1.46]	0.131	0.99	[0.23-4.36]	0.993	0.73	[0.09-5.56]	0.761

PA	1-year Outcome	Male Patients			Female Patients			Elderly Patients		
	CV death/ Any TE/Bleeding	0.28	[0.08-0.92]	**0.025**	0.32	[0.04-2.41]	0.244	0.34	[0.04-2.61]	0.278

Legend: *Analysis presented is unadjusted univariate logistic analysis. CI= confidence interval; CV= cardiovascular; NA= not available; OR= odds ratio; TE= thromboembolism; TIA= transient ischemic attack.

Table S3 (Continued): Multivariable Effect of Physical Activity on Major Adverse Events According to Subgroups

PA	1-year Outcome	Paroxysmal AF			High Risk (CHA_2DS_2-VASc≥2)		
		OR*	**95% CI**	***p***	**OR***	**95% CI**	***p***
Occasional	Stroke/TIA	0.38	[0.03-4.18]	0.408	1.03	[0.39-2.68]	0.953
	Any TE	0.41	[0.13-1.24]	0.103	0.82	[0.48-1.43]	0.491
	Bleeding	0.58	[0.25-1.35]	0.200	0.64	[0.44-0.92]	**0.017**
	CV death/ Any TE/Bleeding	0.21	[0.08-0.52]	**<0.001**	0.51	[0.35-0.75]	**<0.001**
Regular	Stroke/TIA	NA	NA	-	0.46	[0.10-2.13]	0.308
	Any TE	0.92	[0.33-2.54]	0.875	1.18	[0.65-2.13]	0.588
	Bleeding	2.73	[0.87-8.57]	0.074	0.96	[0.60-1.55]	0.975
	CV death/ Any TE/Bleeding	0.45	[0.19-1.04]	0.056	0.51	[0.31-0.82]	**0.005**
Intense	Stroke/TIA	-	-	-	1.37	[0.17-10.98]	0.768
	Any TE	-	-	-	1.16	[0.34-3.90]	0.815
	Bleeding	-	-	-	0.85	[0.30-2.43]	0.771

PA	**1-year Outcome**		**Paroxysmal AF**			**High Risk (CHA_2DS_2-VASc≥2)**	
	CV death/ Any TE/Bleeding	-	-	**-**	0.51	[0.18-1.44]	0.196

Legend: *Analysis presented is unadjusted univariate logistic analysis. CI= confidence interval; CV= cardiovascular; NA= not available; OR= odds ratio; TE= thromboembolism; TIA= transient ischemic attack.