The AFLETES study – Atrial Fibrillation in veteran athLETEs and the risk of stroke.

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KEY WORDS

Atrial fibrillation, veteran athletes, athlete's heart, stroke.

ABSTRACT

Objectives

Endurance athletes are at an increased risk of atrial fibrillation (AF) when compared to the general population. However, the risk of stroke in athletes who develop AF is not known. We aimed to assess this using a widely distributed online survey.

Methods

A questionnaire was broadcasted through social media and sports clubs. Individuals that have competed in at least one competitive event and were ≥40 years old were included. Self-reported demographic, past medical history and training history data were captured and a CHA_2DS_2-VASc was calculated. Binary logistic regression was used to assess variables associated with AF and stroke.

Results

The survey achieved 1002 responses from 41 countries across Africa, Australasia, Asia, Europe, North America, and South America and 942 were included in the final analysis. The average age was 52.4±8.5 years and 83.7% were male. The most common sports were cycling (n=677,71.9%), running (n=558,59.2%) and triathlon (n=245,26%). There were 190 (20.2%) individuals who reported AF and 26 (2.8%) reported stroke. Lifetime exercise dose (OR:1.02, 95%CI:1.00-1.03, p=0.02) and swimming (OR:1.56, 95%CI:1.02-2.39, p=0.04) were associated with AF in multivariable analysis independent of other risk factors. AF (OR:4.22, 95%CI:1.81-9.60, p<0.01) was associated with stroke, even in individuals with a CHA_2DS_2-VASc of 0 or 1 (OR:4.15, 95%CI:1.79-9.60, p<0.01).

Conclusions

This survey provides early evidence that veteran endurance athletes who develop AF may be at an increased risk of developing stroke, even in those deemed to be at low risk by CHA_2DS_2-VASc score.

SUMMARY BOX

What is already known on this topic?

- Veteran endurance athletes are at an increased risk of AF, but their risk of stroke is unknown.

What this study adds.

- We provide evidence of self-reported stroke risk in a moderately large sample of veteran endurance athletes.

- Lifetime dose of exercise was associated with an increased risk of AF.

- AF was associated with an increased risk of stroke, even in individuals considered to be at low-risk.

How this study might affect research, practice or policy.

- Current risk scores that are used to inform anticoagulation therapy may not appropriately risk stratify athletes with AF. Further prospective studies are needed and in the interim clinicians seeing veteran athletes with AF may need to consider anticoagulation therapy at lower thresholds than currently recommended.

INTRODUCTION

The benefits of exercise for cardiovascular health are well recognised. However, exercise may have a U-shaped dose response curve(1). Some of the strongest evidence for adverse cardiovascular consequences is in the development of atrial fibrillation (AF); where both professional and non-professional athlete populations appear to be at an increased risk when compared to the general population (2-5).

Thromboembolic events, such as stroke, are well-known complications of untreated AF(6). Physical activity is thought to lessen the risk of stroke; attributable to a reduction in cardiovascular risk factors associated with exercise participation in addition of the direct effects of exercise(4, 7).

CHA_2DS_2-VASc is a clinical tool used to assess the annual risk of thromboembolic events in AF and to inform anticoagulation therapy(8). However, CHA_2DS_2-VASc, is not validated in athletes and many will have a score of 0 or 1 (gained by female sex), indicating no need for anticoagulation. Mechanisms of AF pathophysiology may be different in athletes. Furthermore, athletes demonstrate cardiac phenotypes such as atrial dilatation that are associated with an increased risk of stroke. It may be that athletes who

develop AF are not appropriately risk-stratified by CHA_2DS_2-VASc(9). Studies are yet to investigate this risk.

The aim of this study was to estimate the risk of stroke in veteran endurance athletes (≥40 years old) who develop AF compared to those who remain in sinus rhythm.

METHODS

Study design and participants

This study was approved by the ethics committee at the University of Leicester. Participants were recruited through advertising on social media and relevant sporting organisations were asked to circulate the questionnaire to their members. The survey link remained open between 17th March 2021-27th September 2021.

Participants were linked to a webpage that contained information of the study where individuals were required to confirm informed consent. Participants completed a self-administered questionnaire (Jisc Online Surveys, University of Leicester licence) that contained 27 questions (Supplementary document). The readability of the questionnaire was calculated using the Simple Measure of Gobbledygook (SMOG) index through an online readability checker to ensure the reading age was between class years 5-7 (10, 11). Basic demographic data, past-medical history was collected as well as data on health-related behaviours, estimated lifetime exercise dose (weekly dose multiplied by 52 and years of training), exercise participation characteristics and health data on atrial fibrillation and stroke. CHA_2DS_2-VASc was calculated for each participant.

Statistical analysis

For continuous variables, normality was assessed using the Kolmogorov-Smirnov test and visual inspection of histograms (12). Normal variables are presented as mean and standard deviation (SD). Parametric variables are presented as median and interquartile range (IQR). The cohort was divided into two groups: those without AF and those with AF. Categorical differences between groups were assessed using Chi-squared test and Fisher's exact test (when ≤5 measures were expected). Continuous variables were assessed using independent samples t-test (parametric data) and Mann-Whitney U test (non-parametric data). Mean difference (MD) and 95% confidence intervals (95%CI) were calculated between these groups and Levene's Test for Equality was used to assume equal variance. Individuals with AF were further sub-stratified by CHA_2DS_2-VASc status. Individuals with AF and CHA_2DS_2-VASc of 0 or 1 (AFC0/1) made one group, and ≥2 (AFC2) another to reflect the clinical

risk that governs when anticoagulation is often recommended(*13*). Associations with AF and stroke were assessed using binary logistic regression to calculate an odds ratio (OR). A theoretical multivariable model was constructed and a p-value of <0.05 was considered significant.

Patient and public members had significant involvement in dissemination as the study was widely shared on social media platforms. The Global Cycling Network, a YouTube channel with 2.6 million subscribers featured this study in a video: (https://www.youtube.com/watch?v=Fo0j94ODPiA).

RESULTS

Demographics, exercise, and cardiovascular risk factors

Overall, 1002 individuals from 41 countries across Africa, Australasia, Asia, Europe, North America and South America completed the survey (Supplementary document). Figure 1 shows how the final analysis dataset was derived and reasons for exclusion.

Figure 1 – Flow diagram depicted reasons for exclusion and final analysis cohort

Demographic data is shown in Table 1. The final analysis dataset contained 942 individuals (94.2% completion rate), with the majority being male (83.7%) and White (96.3%) from English speaking countries. Cycling was the most frequently reported sport (n=677,71.9%) followed by running (n=558,59.2%) and triathlon (n=245,26%)). More than half of participants reported that local events (54.4%) were their highest level of competition, however, 237(25.2%) individuals competed at national level or above. On average, individuals exercised 9.3 hours per week (SD:5.2), over 20.0 years (SD:13.4). While rates of diabetes mellitus, congestive heart failure, thromboembolism, vascular disease, and pre-existing cardiovascular disease and cardiomyopathy were low, around one in ten participants reported hypertension and high cholesterol.

Table 1 – Characteristics of participants overall and stratified by AF status.

Variable	Overall	Individuals without AF	Individuals with AF	Mean difference (95%CI) p or p for chi-squared/Fischer's exact
N	942	752	190	-
Sex n(%) Male Female	 788 (83.7) 154 (16.3)	 613 (81.5) 139 (18.5)	 75 (92.1) 15 (7.9)	<0.01
Age, years	52.4 (8.5)	51.3 (8.0)	56.6 (8.9)	5.28 (3.97-6.59) p<0.01)

Ethnicity n(%) φ White Non-white	910 (96.6) 32 (3.4)	727 (96.7) 25 (3.3)	183 (96.3) 7 (3.7)	0.81
Profession n(%) White/Blue Collar Manual labourers Full time athlete Unemployed	842 (89.4) 65 (6.9) 4 (0.4) 31 (3.3)	677 (90.0) 50 (6.6) 3 (0.4) 21 (2.8)	163 (85.8) 15 (7.9) 1 (0.5) 10 (5.3)	White/Blue collar vs others = 0.12
Smoking n(%) Current Previous Never smoked	7 (0.6) 239 (25.4) 696 (73.9)	6 (0.8) 190 (25.3) 555 (73.8)	0 49 (25.8) 141 (74.2)	Smoking history vs never smoked = 0.91
Alcohol: Units per week n(%) 0 <8 units 8-15 units >15 units Not stated	138 (14.8) 426 (45.2) 250 (26.5) 124 (13.2) 4 (0.4)	104 (13.8) 341 (45.3) 203 (27.0) 100 (13.3) 3 (0.4)	32 (16.8) 85 (44.7) 47 (24.7) 24 (12.6) 1 (0.5)	Never drink vs drinking = 0.24
Binge drinking n(%) Never Up to once per month More than once per month	436 (46.3) 329 (34.9) 177 (18.8)	326 (43.4) 270 (35.9) 154 (20.5)	108 (56.8) 59 (31.1) 23 (12.1)	Never vs binge drinking <0.01
Exercise type n(%)φ Cycling Running Triathlon Swimming Other	677 (71.9) 558 (59.2) 245 (26.0) 156 (16.6) 170 (18.0)	531 (70.6) 447 (59.4) 200 (26.6) 113 (15.0) 140 (18.6)	146 (76.8) 111 (58.4) 45 (23.7) 43 (22.6) 30 (15.8)	0.09 0.80 0.41 0.01
Highest level of competition n(%) Local Regional National International Professional	514 (54.6) 199 (21.1) 120 (12.7) 109 (11.6) 8 (0.8)	419 (55.7) 168 (22.3) 90 (12.0) 75 (10.0) 4 (0.5)	95 (50.0) 31 (16.3) 30 (15.8) 34 (17.9) 4 (2.1)	International + professional vs others = <0.01
Hours exercising per week	9.3 (5.2)	9.0 (4.6)	10.5 (7.1)	1.47 (0.64-2.30, p<0.01)
Training years	20.0 (13.4)	18.8 (12.7)	24.8 (15.3)	6.03 (3.64-8.41, p<0.01)
Lifetime exercise dose (per 1000 hours)	10.1 (10.9)	9.2 (9.2)	14.0 (15.1)	4.8 (2.56-7.08, p<0.01)
Competitions per year	5 (3-12)	5 (3-12)	6.5 (2-20)	0.05
Resting heart rate (beats per minute)	52.0 (9.4)	52.2 (9.56)	51.5 (8.9)	0.66 (-2.17-0.86, p=0.40)
Diabetes Mellitus (type 1 or 2) n(%)	12 (1.3)	9	3	0.68
Hypertension n(%)	101 (10.7)	73	28	0.045
Thromboembolism n(%)	18 (1.9)	11	7	0.046
Congestive heart failure n(%)	5 (0.5)	1	4	<0.01
Vascular disease n(%)	13 (1.4)	8	5	0.098
High cholesterol n(%)	104 (11.0)	81	23	0.60
Stroke n(%)	26 (2.8)	12 (1.6)	14 (7.4)	<0.01
Age of first stroke	48.1 (12.5)	43 (13.4)	52.4 (10.3)	9.43 (-0.48-19.33, p=0.06)

φindicates that participants could chose multiple options.
Final column compares individuals with AF versus individuals without AF.
Parametric variables presented as mean(SD) and non-parametric variables presented as median (IQR).

Atrial Fibrillation

There were 190 (20.2%) individuals who reported a history of AF, and more than half of these were paroxysmal (n=116(61.1%))(Table 1). Most individuals were diagnosed after reporting symptoms (n=136(71.6%)) but 11(5.8%) individuals were diagnosed after a stroke.

Associations with atrial fibrillation

Individuals with AF were older (MD:5.28, 95%CI:3.97-6.59, p<0.01), showed lower rates of binge drinking behaviours, more likely to be swimmers (p=0.01) and included a higher number of international and professional athletes (p<0.01) (Table 1). The number of hours exercised per week (MD:1.47, 95%CI:0.64-2.30, p<0.01), years trained (MD:6.03, 95%CI:3.64-8.41, p<0.01) were higher in those that had AF, although the number of competitions per year was marginally non-significant (p=0.05). There were higher rates of both hypertension (p<0.05) and congestive heart failure (p<0.01) in individuals with AF.

Univariable associations with AF can be seen in Supplementary Table 1. All measures of exercise dose were associated with AF but female sex (OR:0.38, 95%CI:0.22-0.66, p<0.01) and, surprisingly, binge drinking more than once per week (OR:0.54, 95%CI:0.33-0.86, p=0.01) were associated with a reduced odds of AF. In multivariable models (Table 2), age (OR:1.06, 95%CI:1.04-1.09, p<0.01), lifetime exercise dose (OR:1.02, 95%CI:1.00-1.03, p=0.02) and swimming (OR:1.56, 95%CI:1.02-2.39, p=0.04) remained significantly associated with AF and female sex remained associated with a decreased risk of AF(OR:0.43, 95%CI:0.24-0.77, p<0.01) (Figure 2).

Table 2 – Multivariable model assessing associations with AF (left), stroke (middle) and AFC0/1(right)

	AF		Stroke		Stroke and AFC0/1
Co-variables	Odds ratio (95%CI, p)	Co-variables	Odds ratio (95%CI, p)	Co-variable	Odds ratio (95%CI, p)
Age	1.06 (1.04-1.09, p<0.01)	Age	1.03 (0.99-1.08, p=0.19)	Age	1.05 (1.00-1.10, p=0.07)
Female sex	0.40 (0.23-0.72, p<0.01)	Female sex	1.36 (0.44-4.16, p=0.59)	Female sex	1.44 (0.46-4.45, p=0.53)
Non-white	1.37 (0.57-3.33, p=0.48)	Non-white	1.23 (0.15-9.72, p=0.85)	Non-white	1.13 (0.14-9.01, p=0.91)
DM	0.98 (0.25-3.86, p=0.98)	DM	6.73 (1.29-35.26, p=0.02)	DM	7.96 (1.51-42.02, p=0.01)
Hypertension	1.29 (0.78-2.13, p=0.33)	Hypertension	0.8 (0.23-2.84, p=0.73)	Hypertension	1.04 (0.30-3.65, p=0.95)
Smoking history	1.05 (0.72-1.55, p=0.8)	Smoking history	0.68 (0.25-1.86, p=0.45)	Smoking history	0.73 (0.27-2.00, p=0.55)
Swimming	1.56 (1.02-2.39, p=0.04)	AF	4.22 (1.81-9.85, p<0.01)	AFC0/1	4.15 (1.79-9.60, p<0.01)
Lifetime exercise dose	1.02 (1.00-1.03, p=0.02)				

Stroke

There were 26 (2.8%) individuals who reported stroke at the average age of 48.1±12.5 years. Most strokes occurred in individuals with CHA_2DS_2-VASc of 0 (n=14, 53.8%) or 1 (n=8, 30.8%). More than half of the strokes occurred in individuals with AF (n=14, 53.8%) and most of these occurred in individuals with AFC0/1 (n=12 (46.2% of all strokes)) (Table 3). There were only 2 in those with AFC2 (Table 3). Anticoagulation stratified by AFC0/1 and AFC2 can be seen in Supplementary Table 2. Interestingly, only half those with AFC2 reported taking anticoagulation therapy . Three individuals had a subsequent stroke, two of whom were anticoagulated.

Table 3 – Characteristics of participants with a diagnosis of AF, with and without stroke.

Variable	AF with no stroke	AF with stroke	P
N	176	14	
Sex n(%) Male Female	162 (92.0) 14 (8.0)	13 (92.9) 1 (7.1)	0.49
Age	56.5 (8.9)	57.6 (9.0)	-1.16 (-6.03-3.71) p=0.64
Ethnicity n(%) White Non-white	170 (96.6) 6 (3.4)	13 (92.9) 1 (7.1)	0.39
Profession n(%) White/Blue Collar Manual labourers Full time athlete Unemployed	153 (86.9) 12 (6.8) 1 (0.6) 10 (5.7)	11 (78.6) 3 (21.4) 0 0	White collar vs others = 0.18
Smoking n(%) Current Previous Never smoked	0 47 (26.7) 129 (73.3)	0 2 (14.3) 12 (85.7)	Never smoked vs others = 0.31
Alcohol, Units per week n(%) 0 <8 units 8-15 units >15 units	29 (16.7) 80 (45.5) 45 (25.6) 24 (13.6)	4 (28.6) 5 (35.7) 2 (14.3) 2 (14.3)	Nil alcohol vs others = 0.14
Binge drinking n(%) Never Up to once per month More than once per month	99 (56.3) 57 (32.8) 20 (11.5)	9 (64.3) 2 (14.3) 3 (21.4)	Never binge vs others = 0.19
Exercise type n(%)φ Cycling Running Triathlon Swimming Other	140 (79.5) 103 (58.5) 39 (22.2) 37 (21.0) 26 (14.9)	6 (42.9) 8 (57.1) 6 (42.9) 6 (42.9) 4 (28.6)	0.02 0.87 0.15 0.01 0.30
Highest level of competition n(%) Local Regional National International Professional	89 (51.1) 29 (16.7) 28 (15.9) 30 (17.0) 3 (1.7)	6 (42.9) 2 (14.3) 2 (14.3) 4 (28.6) 1 (7.1)	National, international, and professional versus others = 0.10

Exercise dose per week (hours)	10.4 (7.4)	10.8 (3.5)	-0.27 (-4.35-3.78) p=0.48
Training years (years)	24.4 (15.1)	30.4 (17.6)	-5.96 (-14.34-2.42) p=0.16
Lifetime exercise dose per 1000 hours	13.8 (15.4)	14.9 (10.9)	-1.02 (-9.31-7.28) p=0.81
Competitions per year	6 (2-20)	7.5 (3.5-25)	0.92
Resting heart rate (beats per minute)	51.4 (8.4)	54.1 (14.4)	-2.84 (-7.73-2.05) p=0.25
Diabetes Mellitus (type 1 or 2) (%)	1 (0.6)	2 (14.3)	0.01
Hypertension (%)	26 (14.9)	2 (14.3)	0.66
Thromboembolism (%)	7 (4.0)	0	NA
Congestive heart failure (%)	4 (2.3)	0	NA
Vascular disease (%)	5 (2.9)	0	NA
High cholesterol (%)	20 (11.5)	3 (21.4)	0.19
AF n(% of group) Paroxysmal (% of AF) Persistent (% of AF) Permanent (% of AF) Unknown	109 28 (16.1) 31 (17.8)	6 (42.9) 4 (28.6) 3 (21.4)	<0.01 <0.01 <0.01
Age of AF diagnosis (SD)	48.6 (12.7)	48.4 (13.5)	0.17 (-6.81-7.15) p=0.96
Diagnosis of AF (% of those with AF)ϕ Symptoms Incidentally from heart rate monitor Athlete screening Diagnosed after stroke/TIA	125 (71.0) 37 (21.0) 24 (13.6) 0	9 (64.3) 0 1 (7.1) 10 (71.4)	<0.01 NA 0.32 NA
Cardiac disease prior to AF diagnosis (% of those with AF) Pacemaker Myocardial infarction Cardiomyopathy	7 (4.0) 3 (1.7) 2 (1.1)	0 0 0	NA NA NA
CHA_2DS_2VASc n(%) 0 1 2 3	107 (60.8) 45 (25.6) 19 (10.8) 5 (2.9)	9 (64.3) 3 (21.4) 1 (7.1) 1 (7.1)	0.28
Medications taken for AF Apixaban Rivaroxaban Edoxaban Warfarin Dabigatran Other medication Unknown medication	16 (9.2) 14 (8.0) 4 (2.3) 3 (1.7) 0 5 (2.9) 4 (2.3)	6 (42.9) 2 (14.3) 2 (14.3) 1 (7.1) 0 1 (7.1) 0	<0.01 <0.01 <0.01 <0.07 NA 0.01 NA

Associations with stroke

Within those with AF, there were no differences in all measures of exercise dose between those with and without stroke (Table 3). Those with AF and stroke had a greater proportion of swimmers and runners, and a significantly larger number of individuals were anti-coagulated (Table 3). There were 11 individuals who reported having AF diagnosed following stroke and the majority of these individuals had a CHA_2DS_2-VASc of 0 or 1 (Supplementary Table 3)

Univariable analysis can be seen in Supplementary Table 4. AF was associated with stroke (OR:4.71, 95%CI:2.14-10.37, p<0.01), and this was true for all AF types. Individuals with AFC0/1 was associated with stroke (OR:4.15, 95%CI:1.88-9.16, p<0.01), but not individuals with AFC2 (OR: 2.96, 95%CI: 0.66-13.25, p=0.16). In the multivariable models, diabetes mellitus (OR: 6.73, 95%CI: 1.29-35.26, p=0.02) and AF (OR: 4.22, 95%CI:1.81-9.85, p<0.01) remained associated with stroke (Table 2). When stratifying, individuals with AFC0/1(OR:4.15, 95%CI:1.79-9.60, p<0.01) remained associated with stroke (Table 2). Due to the theoretical risk of overfitting, each co-variable were added consecutively, and the model was assessed using the NagelKerke's pseudo R^2 to aim for an increase <0.05 from univariable to multivariable models (Supplementary Table 5) (14). The Bayesian information criterion (BIC) are also presented (Supplementary Table 5). A multivariable analysis of AFC2 was not conducted due to the low number of events.

DISCUSSION

Atrial fibrillation is associated with an increased risk of stroke in athletes

AFLETES aimed to estimate the risk of stroke in endurance athletes who have engaged in competitive sport and developed AF. To our best knowledge, it is not only the first study to assess this risk, but also amongst the largest and most widely distributed of its kind.

The most significant and novel result from this survey is that AF appears to be associated with stroke in athletes. Traditionally, these individuals are unlikely to be offered anticoagulation as many would have a CHA_2DS_2-VASc of 0 or 1. This was consistent with our results, where most individuals with or without AF had a CHA_2DS_2-VASc of 0 or 1 (n=884, 93.8%).

This association between AF and stroke not only remained when adjusting for known cardiovascular risk factors, but also when assessing individuals deemed to be low risk by clinical risk scores (AFC0/1). This is an important finding, as it suggests that current methods of risk stratification in AF, namely CHA_2DS_2-VASc, may not appropriately capture this risk in athletes, even though it is thought to perform better in individuals at lower risk of stroke compared to the older CHADS score(13). Furthermore, there were no reported histories of cardiomyopathy, myocardial infarction or pacemaker, emphasising that this may be a low-risk group. There were 11 individuals diagnosed AF following a stroke. This describes a significant proportion of those with AF who had a stroke (78.6%) and brings into question how many athletes may have subclinical or undiagnosed AF that future prevalence studies may wish to investigate.

Within the limitations of the survey design, inferring causality is not justified. However, there may be biological plausibility for the observed risk of stroke. First, left atria are more dilated in athletes (*15*). In the general population, meta-analyses have shown left atrial enlargement is associated with a graded risk of stroke(*16, 17*). Fibrosis, oxidative stress and inflammation may lead to myopathic states of the atria(*18*). Atrial myopathy is associated with endothelial dysfunction and haemodynamic stasis, which in turn may favour a pro-thrombotic state(*18*). During exercise, there is increased reliance on the atrial contractile-booster function, but this can be reduced in individuals with AF, which could promote deranged atrial flow(*19*). Individuals who engage in exercise frequently develop sinus bradycardia. While traditionally considered a benign phenotype of cardiorespiratory fitness, bradycardic patterns may by a sign of atrial dysfunction that can cause haemodynamic stasis, which is a component of Virchow's Triad(*20*). While numerous studies have investigated structural and functional adaptations within the Athlete's Heart syndrome, there is no data using novel flow phenotyping methods, such as 4D flow(*21*).

Dose-response of exercise and the risk of atrial fibrillation

There was evidence of a dose-response of exercise to the risk of AF. Individuals with AF had a higher training volume per week, had been training for longer and marginally completed more events per year. Lifetime exercise dose remained associated with AF in multivariable models. This finding is fits well with other published literature(*1, 3, 5*). We show a dose-dependent risk of AF within individuals who are competing, and not only against the general population which other literature have reported(*22*). This suggests that the risk of AF is not homogenous amongst athletes, but those competing at the highest levels may be the most at risk.

Swimming is associated with AF

Swimming remained associated with AF, even when adjusting for lifetime exercise dose. This is a novel finding as this compares swimmers to other sport types. The most comparable existing study found that competitive swimming was associated with an increased risk of AF when compared to individuals from a general internal medicine clinic(*23*). Swimming varies from sports such as cycling and running in two parameters. One, individuals perform in a horizontal or prone position and so the characteristics of haemodynamic homeostasis may vary when compared to sport conducted in orthostasis. Orthostatic intolerance in swimmers has been previously described(*24*). Autonomic dysregulation that accompanies this effect, may have some implication in arrhythmogenesis. Two, cold water submersion is known to evoke antagonist physiological responses(*25*). The cold shock response can upregulate sympathetic autonomic mediated tachycardia and, conversely, the diving response can stimulate parasympathetic mediated bradycardia. This 'autonomic conflict' may predispose swimmers to arrhythmogenesis (*25*).

Pathophysiology of atrial fibrillation in athletes

The pathophysiological processes that cause exercise-induced AF are not clear. As described by Coumel's triangle of arrhythmogenesis, there are substrate, modulator and trigger factors that a mechanism should satisfy(26). Endurance exercise evokes a volume overload-like-state and so the left atria is subject to periods of high sheer wall stress(27). This is accompanied by the acute phase response and atrial stretch(27). Inflammatory markers that rise acutely following physical exertion are also associated with an increased risk of AF (18, 28, 29). Over time, repetitive bouts of insult to the left atria may lead to irreversible remodelling(27). Fibrosis has been observed to a larger degree in exercised animals and human athletes when compared to controls(30, 31). However, the type of fibrosis may be different to that seen in disease states such as heart failure as observed by transcriptomic analysis in animal models(32). Fibrosis could provide a mechanical substrate that can alter conduction and promote arrhythmia(31). As the atria have less capacity to increase wall thickness, wall stress is proportionally higher when compared to the ventricles, and this may explain the predominance of fibrosis in the atria(33). There is little evidence that suggest athletes are at a higher risk of developing ventricular arrythmias, suggesting that fibrosis may have some role in arrhythmogenesis in athletes(33). A high vagal tone is a common finding in athletes and may act as a modulator(33, 34). High vagal tone can shorten the refractory period, increasing susceptibility to re-entry arrhythmia(27, 33-35). In animal models, exercised rats with high vagal tone were more likely to have inducible AF(36). This phenotype is observed in athletes with exercise induced AF, where AF is typically bought on during periods of high vagal tone such as sleeping and eating(33). Triggers may arise from atrial ectopy, which may be more frequent and common with increasing lifetime exercise dose (31, 33, 35). Altogether, the substrate, modulation and trigger related evidence provide biologically plausible mechanism of arrhythmogenesis in athletes, but further histological and electrophysiological evidence is needed.

Clinical implications

Establishing risks of thromboembolic events is important as the decision of anticoagulation is complicated in athletes(37). In this study, the number of individuals receiving anticoagulation for AF was 30.5%, and only 53.8% in AFC2. Typically, anticoagulation is offered to individuals with CHA_2DS_2-VASc scores ≥2 and suggests that there is a lower rate of treatment in this group. Clinician or athlete reluctance for anticoagulation may have several drivers. One, there may be significant bleeding risks associated with exercise participation. Two, in many cases, anticoagulation may mandate the individual to refrain from their sporting activities or career altogether(2, 9). Three, as participatinon in competitive exercise is

viewed as a positive health-related behaviour, it may sway clinicians and patients away from anticoagulation due to perceptions of low-risk. These considerations are still appropriate for veteran athletes, with evidence to suggests that those who participate in sport at a young age continue to do so later in life(*38*). The results from this study suggest the risk in athletes with AF is not negligible; an important consideration when informing decisions around anticoagulation. Longitudinal studies of the risk of stroke in athletes with AF and without a previous history of stroke are required to accurately determine clinical risk and the need for anticoagulation.

Strengths and limitations

This study has strengths. One, this was an international survey, with a high response rate from 41 countries and to our best knowledge, it is the largest and most widely participated study of its kind. Two, we captured risk factors and were able to calculate a self-reported CHA_2DS_2-VASc score. Three, we used several dissemination methods, which may have improved both reach and engagement. Four, the quantification of exercise dose is challenging as it is determined by frequency, intensity, training history and exercise type. While the use of metabolic equivalents (METS) has gained popularity, it comes with limitations, particularly in the context of self-reported data. Our study used several measures of quantifying exercise dose, which may be more applicable given the survey design. Finally, the use of an online questionnaire helped retain engagement considering the face-to-face confines posed by the pandemic.

This study has limitations, the most significant of which comes from the design. Surveys are subject to several types of bias, including: sampling, response and volunteer bias. This study was advertised as 'assessing heart health' in individuals who participate in high levels of exercise. This might explain the high rates of AF seen when compared to the general population as individuals with existing AF were more like to engage. However, this response bias does not explain the dose-response of exercise and AF seen in our results. This survey was conducted on an online platform. This may have discouraged engagement in some groups including individuals with higher executive dysfunction, a complication attributed to stroke thus underrepresenting true stroke prevalence. However, the SMOG index of the study was calculated to be school years 5-7, increasing the readability for many users, including individuals without fluency in English and those with higher executive dysfunction (*10*). Furthermore, underreporting does not explain the association of AF with stroke. The survey used self-reported outcomes which may be unreliable, particularly from lay audiences. A large proportion of the participants were White and Male and from English speaking countries. More data are needed from other countries and ethnicities. This a recognised issue in cardiovascular research in exercise, and

limits applicability of our findings (39). However, as the absolute number of females that participated was 154, some analysis may have remained adequately powered. We did not capture data on banned substances, many of which can influence stroke risk. Although this was an anonymised questionnaire, the investigators deemed that it was unlikely that participants would readily share this information. Finally, as the number of stroke events was 26, there may be a theoretical risk of over-fitting in the multivariable model. However, several precautions were taken. One, the Nagelkerke pseudo R^2 value showed an increase of <0.05 between adjusted and unadjusted analysis. Two, the results were consistent in univariable and different iterations of the multivariable model, including on addition of each co-vairable (Supplementary Table 5). Three, all included variables and the results have biological rationale in line with wider literature. Four, the other co-variables did not demonstrate correlation between them. Finally, there was a limited increase in BIC criteria within the multivariable model from 2 towards 7 co-variables (Supplementary Table 5).

CONCLUSIONS

This study provides early, cautious evidence that veteran individuals who engage in competitive exercise that develop AF may be at an increased risk of stroke that is not appropriately elucidated CHA_2DS_2-VASc. Future research requires larger studies specifically addressing the risk of stroke in athletes with AF to determine whether this is risk is higher than for the general population which may require amendment of threshold for anticoagulation.

CONTRIBUTORSHIP

As per the International Committee of Medical Journal Editors (ICMJE).
SP, CR, VB, AJS, MPMG-B, TR, AS and GPM contributed to:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of dada from the work.
2. Drafting the work or revision it critically for important intellectual content
3. Final approval of the version to be published.
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

COMPETING INTERESTS AND FUNDING

DATA SHARING

Individual data cannot be shared, as permission was not sought from participants.

ETHICAL APPROVAL

This study received formal approval from the independent ethics approval committee at the University of Leicester.

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Total number of survey responses **(n = 1002)**

Excluded:
- Did not consent to participation **(n = 1)**
- Under the age of 40 **(n = 1)**

Not analysable:
- Factor that contribute to CHA$_2$DS$_2$VASc not stated **(n = 58)**
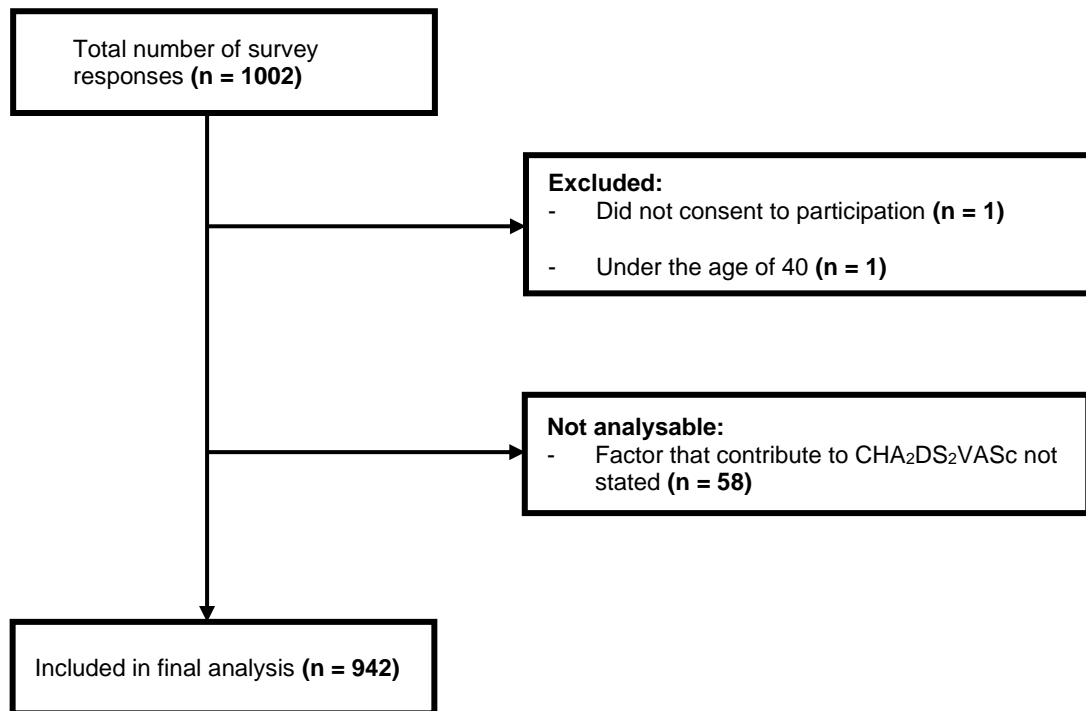
Included in final analysis **(n = 942)**

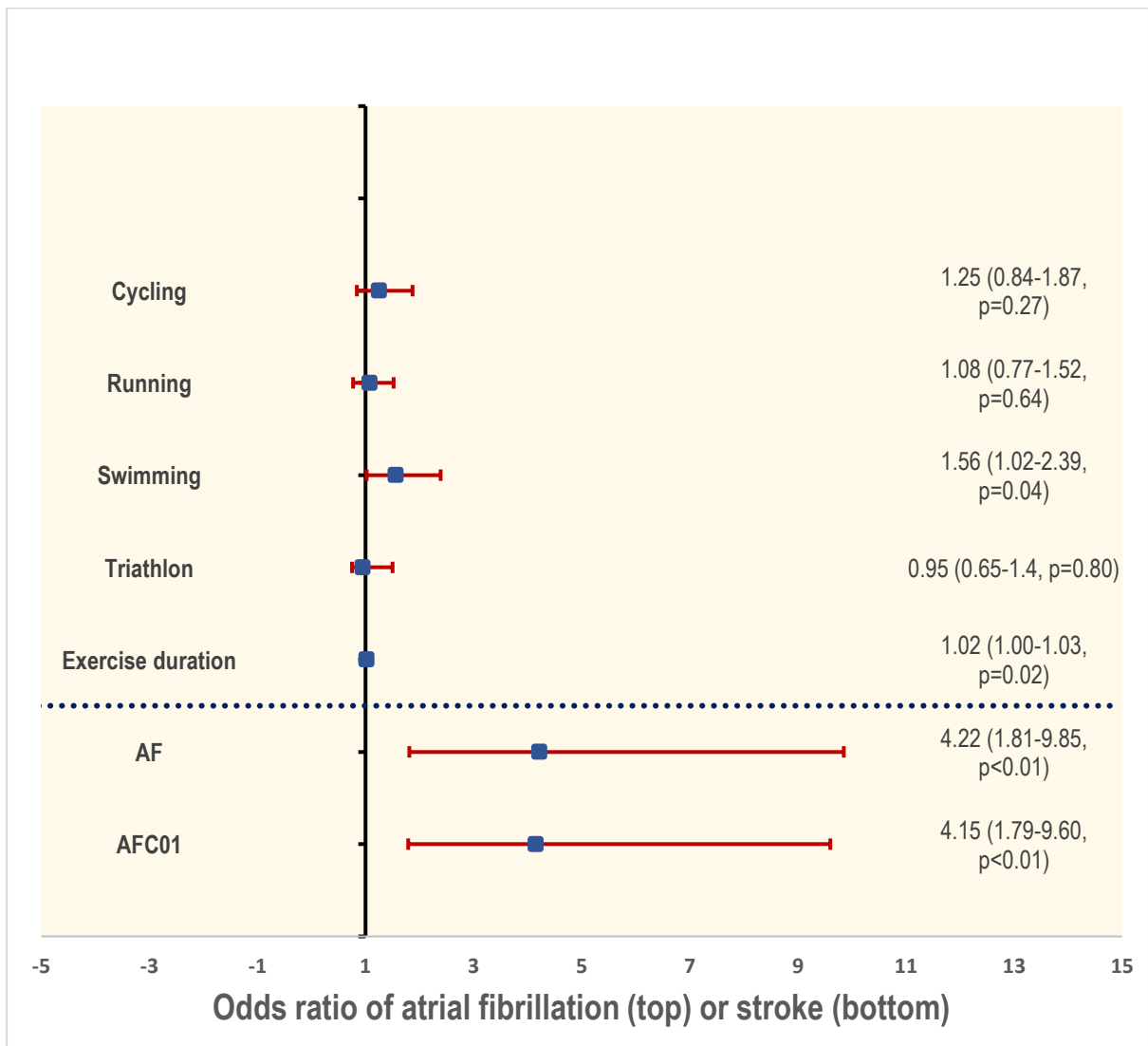*Figure 1 – Flow diagram depicted reasons for exclusion and final analysis cohort*

Figure 2 – Forest plot demonstrating the odds ratios for selected variables associated with AF (top) and stroke (bottom).

Indicates statistically significant OR.

Supplementary document

1. I understand that my participation is voluntary. I have read and understand the participant information and I agree to participate in this survey.

2. Have you competed in at least one competitive sporting event? *this is defined as an event where you were placed and ranked on performance against other competitors in an organised event. This can be at any level.

3. Are you at least 40 years old?

4. Please tell us how old you are.

5. Where are you completing this survey from?

6. What was your sex at birth?

7. What is your ethnicity?

8. Please tell us what your main job is. If you have had multiple job roles, please state the job that you have spent the most time in.

9. How would you best describe your smoking status?

10. How many units of alcohol would you say that you have consumed on average PER WEEK in the last 20 years? (Pint of beer/lager or cider = 2 Units, Pint of premium beer or larger or cider = 3 Units, Alcopop or can/bottle of regular lager = 1.5 units, Can of premium lager or strong beer = 2 units, Glass of wine 175ml = 2 units, Large glass of wine 250ml = 3 units, single measure of spirits = 1.5 units).

11. How many times on average over the last 20 years would you binge drink PER MONTH? (more than 8 units in one session for males OR more than 6 units in one session for females) (Pint of beer/lager or cider = 2 Units, Pint of premium beer or larger or cider = 3 Units, Alcopop or can/bottle of regular lager = 1.5 units, Can of premium lager or strong beer = 2 units, Glass of wine 175ml = 2 units, Large glass of wine 250ml = 3 units, single measure of spirits = 1.5 units).

12. Please tell us what sport(s) you have competed in. Tick all that apply.

12.a. If you selected Other, please specify:

13. What is/was the highest level you competed at?

14. Were you a professional or non-professional athlete in your respective sport? *professional is defined by a regular salary given to you through your employer for your competition in sport. Prize money alone is not considered professional

15. How many hours on average PER WEEK, have you trained in sport?

16. How many years have you trained for? (to the nearest whole year)

17. How many competitive events did/do you do on average PER YEAR?

18. Do you/have you suffered with any of these conditions? Please tick all that apply

19. What is your resting heart rate?

20. Have you ever been told you have an irregular heart rhythm called atrial fibrillation?

21. How would you best describe the AF that you had?

22. What age were you when you were first diagnosed with AF? Please state

23. Did you have heart disease before your diagnosis with AF?

24. How did you get diagnosed with AF?

25. Do you take blood thinning medication as a result of your AF?

26. Have you ever been told you have had a stroke or mini-stroke (also called a TIA)?

27. How old were you at the time of your first stroke?

28. Since your first stroke or mini stroke have you had any further strokes despite being on blood thinning medication?

29. If you would like the results of the study emailed to you, or you are happy to be contacted to participate in future studies related to this project, then please leave your email below. Leaving your email does not mean that you are obliged to participate in future studies.

List of countries from where participants completed the survey

Australia - 46
Austria – 3
Belgium – 2
Bulgaria – 1
Canada – 21
Colombia – 1
Croatia – 2
Denmark – 2
Dominican Republic – 1
Finland – 1
France – 6
Germany – 7
Hong-Kong - 1
Hungary - 2
India – 1
Ireland – 8
Italy – 2
Japan – 3
Malaysia – 3
Mexico – 1
Netherlands – 6
New Zealand – 12
Norway – 2
Philippines – 1
Poland – 2
Portugal – 1
Saudi Arabia – 1
Serbia – 1
Singapore – 1
Slovakia – 1
Slovenia – 2
South Africa – 9
Spain – 4
Sri Lanka – 1

Sweden – 8
Switzerland – 3
Thailand – 2
Turkey – 1
UAE – 1
United Kingdom – 676
USA – 116

Supplementary Table 1: Univariable associations with AF

Variable	Odds ratio (95%CI, p)
Female sex	0.38 (0.22-0.66, p<0.01)
Age (SD)	1.07 (1.05-1.10, p<0.01)
Non-white	1.11 (0.47-2.61, p=0.81)
Profession	White/Blue Collar = 0.69 (0.43-1.11, p=0.13) Manual labourers = 1.20 (0.66-2.19, p=0.55) Full time athlete = 1.32 (0.14-12.77, p=0.81) Unemployed = 1.93 (0.90-4.18, p=0.09)
Smoking	Current/Previous = 0.98 (0.68-1.41, p=0.91) Never smoked = 1.02 (0.71-1.47, p=0.91)
Alcohol	0 = 1.30 (0.84-1.99, p=0.24) <8 units = 0.98 (0.71-1.34, p=0.88) 8-15 units = 0.89 (0.62-1.28, p=0.53) >15 units = 0.94 (0.59-1.52, p=0.81)
Binge drinking	Never = 1.70 (1.24-2.35, p<0.01) Up to once per month = 0.80 (0.57-1.13, p=0.21) More than once per month = 0.54 (0.33-0.86, p=0.01)
Exercise type	Cycling = 1.38 (0.95-2.00, p=0.09) Running = 0.96 (0.69-1.32, p=0.80) Swimming = 1.65 (1.12-2.45, p=0.01) Triathlon = 0.86 (0.59-1.24, p=0.41)
Highest level of competition	Local = 0.80 (0.58-1.09, p=0.16) Regional = 0.68 (0.45-1.03, p=0.07) National = 1.38 (0.88-2.16, p=0.16) International/Professional = 3.45 (1.46-8.15, p<0.01)
Exercise dose per week (hours)	1.05 (1.02-1.08, p<0.01)
Training years (years)	1.03 (1.02-1.04, p<0.01)
Lifetime exercise dose (per 1000 hours)	1.04 (1.02-1.05, p<0.01)
Competitions per year	1.02 (1.01-1.04, p<0.01)
Resting heart rate (beats per minute)	0.99 (0.98-1.01, p=0.40)
Diabetes Mellitus (type 1 or 2)	1.32 (0.36-4.94, p=0.68)
Hypertension	1.61 (1.01-2.57, p=0.047)
Thromboembolism	2.58 (0.99-6.74, p=0.05)
Congestive heart failure	-
Vascular disease (peripheral artery disease aortic plaques)	2.51 (0.81-7.77, p=0.11)
High cholesterol	1.14 (0.70-1.87, p=0.60)

Supplementary Table 2 – Distribution of anticoagulation amoungst individuals with atrial fibrillation stratified by CHA$_2$DS$_2$VASc score.

	AFC0/1 (n=164) (%)	AFC2 (n=26) (%)
Warfain	2 (1.2)	2 (7.7)
DOAC	33 (20.1)	11 (42.3)
Other medication	5 (3.0)	1 (3.8)
Unknown medication	4 (2.4)	0

Supplementary Table 3 – Chracteristics of individuals diagnosed with AF after their stroke.

Variable	
N (% of overall, of those with AF, of those with stroke)	11 (1.2, 5.8, 42.3)
Sex	Male = 10 (10.9)
	Female = 1 (9.1)
Age (SD)	56.55 (9.63)
Ethnicity (%) φ	White = 10
	Asian = 0
	Black = 0
	Mixed = 0
	Other = 1
Profession (%)	White/blue collar = 9
	Manual labourers = 2
Smoking (%)	Current smoker = 0
	Ex-smoker = 2
	Never smoked = 9
Alcohol units (%)	0 = 3
	<8 units = 4
	8-15 units = 2
	≥15 units = 1
Binge drinking (%)	Never = 6
	Less than once a month = 2
	More than once a month = 3
Exercise type *φ	Cycling = 4
	Running = 8
	Swimming = 6
	Triathlon =5
	Other = 2
Highest level of competition (%)	Local = 1 (9.1)
	Regional = 2 (18.2)
	National = 2 (18.2)
	International =4 (36.4)
	Professional = 1 (9.1)
	Missing = 1(9.1)
Exercise dose per week (hours) (SD)	10.7 (3.95)
Training years (years) (SD)	32.3 (17.2)
Lifetime exercise dose (per 1000 hours) (SD)	15.2 (10.8)
Competitions per year (median (IQR))	8 (5-25)
Resting heart rate (beats per minute) (SD)	54.5 (16.0)
Diabetes Mellitus (type 1 or 2) (%)	1 (9.1)
Hypertension (%)	1 (9.1)
Thromboembolism (%)	1 (9.1)
Congestive heart failure (%)	0
Vascular disease (%)	0
High cholesterol (%)	2 (18.2)
Paroxysmal	3 (27.3)
Persistent	3 (27.3)
Permanent	3 (27.3)
Unknown	2 (18.2)
Stroke	
Age of first stroke	

CHADSVASC	0=7 (63.6)
	1=2 (29.3)
	2=1 (9.1)
	3=1 (9.1)

φ indicates that participants could chose multiple options.

Supplementary Table 4: Univariable associations with stroke

Variable	Odds ratio (95%CI, p)
Female sex	0.95 (0.32-2.80, p=0.92)
Age	1.05 (1.01-1.10, p=0.02)
Non-white	1.17 (0.15-8.93, p=0.88)
Profession	White/Blue Collar = 0.47 (0.17-1.27, p=0.14)
	Manual labourers = 1.84 (0.54-6.32, p=0.33)
	Full time athlete = -
	Unemployed = 2.73 (0.61-12.16, p=0.19)
Smoking	Current/Previous = 0.67 (0.25-1.79, p=0.42)
	Never smoked = 1.50 (0.56-4.03, p=0.42)
Alcohol	0 = 2.18 (0.90-5.28, p=0.09)
	<8 units = 0.76 (0.34-1.70, p=0.51)
	8-15 units = 0.65 (0.24-1.74, p=0.39)
	>15 units = 0.86 (0.25-2.90, p=0.80)
Binge drinking	Never = 1.36 (0.62-2.97, p=0.44)
	Up to once per month = 0.68 (0.28-1.65, p=0.40)
	More than once per month = 1.03 (0.38-2.77, p=0.96)
Exercise type φ	Cycling = 0.53 (0.24-1.17, p=0.12)
	Running = 0.95 (0.43-2.08, p=0.89)
	Swimming = 2.84 (1.24-6.49, p=0.01)
	Triathlon = 1.86 (0.83-4.15, p=0.13)
Highest level of competition	Local = 0.49 (0.22-1.10, p=0.08)
	Regional = 0.94 (0.35-2.51, p=0.89)
	National = 0.90 (0.27-3.05, p=0.87)
	International + Professional = 3.45 (1.46-8.15, p<0.01)
Exercise dose per week	1.04 (0.99-1.09, p=0.09)
Training years (years)	1.05 (1.02-1.07, p<0.01)
Lifetime exercise dose (per 1000 hours)	1.03 (1.00-1.05, p=0.02)
Competitions per year	1.01 (0.97-1.04, p=0.82)
Resting heart rate (beats per minute)	1.01 (0.97-1.05, p=0.71)
Diabetes Mellitus (type 1 or 2)	7.23 (1.50-34.78, p=0.01)
Hypertension	1.05 (0.31-3.56, p=0.94)
Thromboembolism	2.30 (0.29-18.09, p=0.43)
Congestive heart failure	-
Vascular disease (peripheral artery disease aortic plaques)	2.88 (0.36-23.04, p=0.32)
High cholesterol	1.96 (0.72-5.32, p=0.19)
AF	Overall = 4.71 (2.14-10.37, p<0.01)
	Paroxysmal = 2.94 (1.10-7.89, p=0.03)
	Persistent = 7.78 (2.39-25.39, p<0.01)
	Permanent = 5.27 (1.43-19.45, p=0.01)
	CHA_2DS_2VASc 0/1 = 4.15 (1.88-9.16, p<0.01)
	CHA_2DS_2VASc ≥2 = 2.96 (0.66-13.25, p=0.16)
Age of AF diagnosis	1.00 (0.96-1.04, p=0.95)
CHA_2DS_2VASc (all group)	0/1= 0.35 (0.12-1.06, p=0.06)
	≥2= 2.83 (0.94-8.50, p=0.06)

φ indicates that participants could chose multiple options.

Co-variable	Odds ratio (95%CI, p)	Co-variable	Odds ratio
2 co-variables			
Age	1.03 (0.99-1.08) p=0.16	Age	1.05 (1.00-1.10) p=0.04
AF	3.97 (1.74-9.06) p<0.01	AFC0/1	3.72 (1.68-8.24) p<0.01
3 co-variables			
Age	1.03 (0.99-1.08) p=0.16	Age	1.05 (1.00-1.10) p=0.04
Female sex	1.33 (0.44-4.03) p=0.62	Female sex	1.42 (0.46-4.36) p=0.54
AF	4.09 (1.77-9.47) p<0.01	AFC0/1	3.91 (1.73-8.84) p<0.01
4 co-variables			
Age	1.03 (0.99-1.08) p=0.20	Age	1.05 (1.00-1.10) p=0.06
Female sex	1.34 (0.44-4.10) p=0.60	Female sex	1.43 (0.46-4.41) p=0.54
DM	6.72 (1.30-34.75) p=0.02	DM	8.13 (1.55-42.56) p=0.01
AF	4.18 (1.80-9.72) p<0.01	AFC0/1	4.20 (1.83-9.66) p<0.01
5 co-variables			
Age	1.03 (0.99-1.08) p=0.18	Age	1.05 (1.00-1.10) p=0.06
Female sex	1.34 (0.44-4.09) p=0.61	Female sex	1.43 (0.46-4.42) p=0.54
DM	6.82 (1.31-35.48) p=0.02	DM	8.13 (1.55-42.54) p=0.01
Hypertension	0.76 (0.22-2.69) p=0.67	Hypertension	1.03 (0.30-3.59) p=0.97
AF	4.22 (1.81-9.82) <0.01	AFC0/1	4.21 (1.82-9.72) p<0.01
6 co-variables			
Age	1.03 (0.99-1.08) p=0.19	Age	1.05 (1.00-1.10) p=0.07
Female sex	1.36 (0.44-4.15) p=0.60	Female sex	1.43 (0.46-4.44) p=0.53
DM	6.74 (1.28-35.38) p=0.02	DM	7.98 (1.51-42.13) p=0.04
Hypertension	0.81 (0.23-2.85) p=0.74	Hypertension	1.05 (0.3-3.65) p=0.94
Smoking	0.68 (0.25-1.86) p=0.45	Smoking	0.73 (0.27-1.99) p=0.54
AF	4.23 (1.81-9.87) p<0.01	AFC0/1	4.16 (1.80-9.61) p<0.01
7 co-variables			
Age	1.03 (0.99-1.08, p=0.19)	Age	1.05 (1.00-1.10, p=0.07)
Female sex	1.36 (0.44-4.16, p=0.59)	Female sex	1.44 (0.46-4.45, p=0.53)
Non-white	1.23 (0.15-9.72, p=0.85)	Non-white	1.13 (0.14-9.01, p=0.91)
DM	6.73 (1.29-35.26, p=0.02)	DM	7.96 (1.51-42.02, p=0.01)
Hypertension	0.8 (0.23-2.84, p=0.73)	Hypertension	1.04 (0.30-3.65, p=0.95)
Smoking history	0.68 (0.25-1.86, p=0.45)	Smoking history	0.73 (0.27-2.00, p=0.55)
AF	4.22 (1.81-9.85, p<0.01)	AFC0/1	4.15 (1.79-9.60, p<0.01)
Variables were added at each step. Nagelkerke pseudo R^2 for 7 co-variables = 0.10 Nagelkerke pseudo R^2 for 2 co-variables = 0.08 Nagelkerke pseudo R^2 for 1 variable = 0.07	Bayesian information criterion (BIC) for 7 co-variables = 621.3 BIC 6 co-variables = 611.96 BIC 5 co-variables = 592.97 BIC 4 co-variables = 578.4 BIC 3 co-variables = 566.21 BIC 2 co-variables = 546.78 BIC for AF univariable = 22.3 No evidence of correlation between the co-varibles (excluding AF).	Nagelkerke pseudo R^2 for 7 co-variables = 0.097 Nagelkerke pseudo R^2 for 2 co-variables = 0.07 Nagelkerke pseudo R^2 for 1 variable = 0.054	Bayesian information criterion (BIC) for 7 co-variables = 633.79 BIC 6 co-variables = 624.56 BIC 5 co-variables = 605.54 BIC 4 co-variables = 593.51 BIC 3 co-variables = 578.93 BIC 2 co-variables = 558.62 BIC for AF univariable = 22.3