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Atrial flutter – clinical risk factors and adverse outcomes in the Framingham Heart Study

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Abstract

Background—Few epidemiological cohort studies have evaluated atrial flutter (flutter) as an arrhythmia distinct from atrial fibrillation (AF).

Objective—To examine the clinical correlates of flutter and its associated outcomes to distinguish them from those associated with AF in the Framingham Heart Study.

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DISCLOSURES

None

Methods—We reviewed and adjudicated electrocardiograms previously classified as flutter or AF/flutter and another 100 electrocardiograms randomly selected from AF cases. We examined the clinical correlates of flutter by matching up to 5 AF and 5 referents to each flutter case using a nested case-referent design. We determined the 10-year outcomes associated with flutter with Cox models.

Results—During mean follow-up of 33.0±12.2 years, 112 participants (mean age 72±10 years, 30% women) developed flutter. In multivariable analyses, smoking (odds ratio [OR] 2.84; 95% confidence interval [CI], 1.54 to 5.23), increased PR interval (OR 1.28 per SD; 95% CI, 1.03 to 1.60), myocardial infarction (OR 2.25; 95% CI, 1.05 to 4.80) and heart failure (OR 5.22; 95% CI, 1.26 to 21.64) were associated with incident flutter. In age- and sex-adjusted models, flutter (vs. referents) was associated with 10-year increased risk of AF (hazard ratio [HR] 5.01; 95% CI, 3.14 to 7.99), myocardial infarction (HR 3.05; 95% CI, 1.42 to 6.59), heart failure (HR 4.14; 95% CI, 1.90 to 8.99), stroke (HR 2.17; 95% CI, 1.13 to 4.17), and mortality (HR 2.00; 95% CI, 1.44 to 2.79).

Conclusions—We identified the clinical correlates associated with flutter and observed that flutter was associated with multiple adverse outcomes.

Keywords

Atrial flutter; atrial fibrillation; risk factors; outcomes; epidemiology

Introduction

Atrial flutter (flutter) has often been combined with atrial fibrillation (AF) in major epidemiological studies including the Framingham Heart Study (FHS),[1] Atherosclerosis Risk in Communities (ARIC),[2] and Rotterdam Study,[3] as well as in clinical trials such as of anticoagulation[4] and antiarrhythmic agents.[5] One likely reason for combining the arrhythmias is that flutter is far less common than AF,[6] and may be misdiagnosed by physicians.[7] Flutter has a distinct underlying electrophysiological mechanism, and may be more difficult to pharmacologically rate control than AF.[8] In addition, flutter and AF may occur in the same individual over time.[9]

Flutter is classified as typical or atypical. Typical flutter describes a macro-reentry circuit around the tricuspid annulus characterized by organized atrial activity.[10,11] Atypical flutter describes a wide-variety of re-entry circuits in either the left or right atrium (not involving the cavotricuspid isthmus) and can be difficult to diagnose on electrocardiogram alone.[8,12] In comparison, disorganized, uncoordinated atrial activity is seen in AF. We hypothesized that although there would be overlap between risk factors for typical flutter and AF, there would also be differences due to the varying underlying electrophysiological mechanisms. In addition, we postulated that flutter is associated with significant adverse clinical outcomes. Identifying such variation may contribute towards developing targeted treatment to modify flutter risk and prevent associated adverse events. Thus, we sought to determine the clinical correlates and outcomes associated with typical flutter in the FHS.

Methods

The FHS is a longitudinal community-based epidemiological cohort study initiated in 1948. The designs of the FHS Original and Offspring cohorts have been well described.[13,14] Briefly, 5,209 individuals between 28–62 years of age were enrolled in 1948 to join the Original cohort. In 1971, 5,124 children of the Original cohort and their spouses were recruited into the Offspring cohort. Participants were followed from their initial examinations through December 2002 for the identification of atrial arrhythmias. All participants provided informed consent. The study protocol was approved by the Institutional Review Board of the Boston University Medical Center.

Atrial Flutter

Electrocardiograms were obtained from routine FHS clinic examinations, and ambulatory and hospital records. We reviewed all (n=465) ECGs from FHS inception up to December 2002 of Original and Offspring cohorts that had been previously confirmed as flutter or AF/flutter along with 100 random ECGs previously diagnosed as AF. Three cardiologists (P.T.E., S.A.L., P.A.L., E.J.B., or J.W.M.), blinded to the original interpretation, independently adjudicated and classified each ECG individually as typical flutter, AF, or other arrhythmia. AF was defined by the absence of regular, organized atrial activity and an irregular ventricular response.[8] Typical flutter was defined by discrete, organized atrial activity defined by the presence of sawtooth pattern F waves at a rate of 240 to 340 beats per minute.[8] We excluded individuals with prevalent AF or flutter (n=3). Possible atypical flutter (n=18) cases were excluded from our analyses due to distinct underlying electrophysiological mechanisms from typical flutter, the more common type of flutter.[12] All 100 ECGs previously diagnosed as AF were confirmed to be AF. Any disagreement between the cardiologists was resolved by joint review of the ECG.

Case referent design

For each flutter case, up to 5 AF and 5 referent cases were matched by age (±2 years) and sex at the same baseline examination in a nested case-referent design (Supplemental Figure 1). Therefore, we did not evaluate age and sex as risk factors, or sex-dependent differences in outcomes. The nested case-referent design was chosen to allow for better accounting for the confounding influences of age, sex, and decade of occurrence such as the changes in the prevalence of AF risk factors over the decades.[15] When identifying AF cases to be matched, we also required that the diagnosis of AF to be approximately at the same time (±2 years) as the flutter cases from the same baseline exam. Cases were described by the first recorded ECG of incident flutter or AF. Hence, Framingham participants with AF who later developed flutter were categorized into the AF group, and not in the flutter group. No individuals with prevalent AF were included in the flutter group. The referents included individuals without either flutter or AF at the time of the diagnosis of the case. The baseline examination for clinical covariates was the most proximal prior examination but no more than 10 years earlier than the date of incident flutter. There was no major difference in the time interval from baseline examination and event date between the groups (flutter 2.4±2.0 years; AF 2.9±2.0 years; referent 2.4±2.0 years). When matching AF to flutter cases we required the difference in the time interval to be less than 2 years.

Clinical variables

Participants in the FHS have undergone routine follow-up examinations biennially for the Original cohort and every 4–8 years for the Offspring cohort. In addition, cardiovascular, neurological, and death records from outpatient visits or hospitalizations between examination cycles are routinely sought and reviewed. At each examination, participants' medical history, physical examination, 12-lead ECG and blood tests were obtained.

Height and weight were measured directly and used to calculate the body mass index (weight [in kilograms] divided by height [in meters] squared). Systolic blood pressure and self-reported use of anti-hypertensive medication were recorded. Moderate-to-heavy alcohol use was self-reported as consuming ≥7 drinks/week for women or ≥14 drinks/week for men as defined by the Centers for Disease Control and Prevention.[16] One drink is equivalent to approximately 12 grams of alcohol. Current smoking (yes/no) was defined as self-reported use of ≥1 cigarette/day within the year prior to the FHS examination. Diabetes mellitus was diagnosed if the participant used insulin or an oral hypoglycemic agent, had a fasting glucose level ≥126mg/dl, or a random blood glucose ≥200mg/dl. Myocardial infarction and heart failure (HF) were diagnosed by review of hospital records and physician reports, and adjudication by three FHS investigators.[17] Valvular heart disease was defined as ≥grade III/VI systolic murmur or any diastolic murmur auscultated at an FHS examination. Heart rate was obtained from the ECG. The PR interval was measured from the beginning of the P-wave deflection to the end of the PR-segment at the junction with the QRS complex. All covariates were obtained from the most proximal FHS examination cycle preceding the identification of AF or flutter.

We studied clinical outcomes during a follow-up period of 10 years. Outcomes evaluated included AF, myocardial infarction, HF, stroke, and all-cause mortality. Ten-year follow-up began from the date of incident flutter for flutter case and matched referent cases, and from the date of incident AF for AF cases. Myocardial infarction, HF, and stroke were diagnosed by review of hospital records, physician reports, imaging and laboratory data, and adjudicated by three FHS investigators as has been described previously.[17–19]

Statistical analyses

We related clinical covariates smoking, moderate-to-heavy alcohol use, body mass index, heart rate, PR interval, diabetes, systolic blood pressure, hypertension treatment, valvular heart disease, and history of myocardial infarction or HF to flutter using a) age- and sex-adjusted, and b) multivariable-adjusted conditional logistic regression models, including all covariates noted above. We also compared the selected risk factors in individuals in the flutter group with the referent and AF groups using conditional logistic regression models.

We examined matching sets stratified Cox proportional hazard models to relate flutter to clinical outcomes including subsequent AF, myocardial infarction, HF, stroke, and all-cause mortality with adjustment for age and sex. Analyses for mortality also were adjusted for prevalent cardiovascular disease. Analyses of incident outcomes were performed after exclusion of the specified disease (i.e. those with prevalent disease myocardial infarction, HF, or stroke, were excluded in analyses of myocardial infarction, HF, or stroke,

respectively). Ten-year cumulative incidence graphs were adjusted for competing risk of death. Clinical outcomes in the flutter group were compared with the referent and AF groups in separate analyses. Within each matching set, the follow-up for outcomes started from the flutter cases' date of diagnosis. For all outcomes except AF, the follow-up ended at outcome event, or was censored at 10-years, AF diagnosis, last contact or death, whichever came first. With AF as the outcome, the observations were censored at the earliest of 10-years, last contact, or death. We used SAS version 9.3 (SAS Institute, Cary, NC) for analyses. We considered a 2-sided $P<0.05$ statistically significant.

Results

During the cohorts' mean follow-up of 33.0±12.2 years of 10,330 individuals (346,301 person-years), 126 participants developed flutter of which 112 met inclusion criteria (14 excluded with incomplete baseline examination) and 2,003 individuals developed AF. The incidence rate of flutter was 36/100,000 person-years and the incidence rate of AF was 578/100,000 person years. The mean age of individuals at flutter diagnosis was 72±10 (range 53–92) years and 30% were women. Baseline characteristics of the study participants included in the analyses are presented in Table 1.

In age- and sex-adjusted conditional logistic regression models smoking, moderate-to-heavy alcohol use, higher mean PR interval, history of myocardial infarction, and history of HF were associated with incident flutter compared to referents (Table 2). In multivariable analyses, smoking (odds ratio [OR] 2.84; 95% confidence interval [CI], 1.54 to 5.23; $P<0.001$), higher mean PR interval (OR 1.28, per 1 standard deviation (equal to 32 ms); 95% CI, 1.03 to 1.60; $P=0.03$), history of myocardial infarction (OR 2.25; 95% CI 1.05 to 4.80; $P=0.04$), and history of HF (OR 5.22; 95% CI, 1.26 to 21.64; $P=0.02$) remained statistically significantly associated with an increased risk of incident flutter compared to referents (Table 2). Compared with the AF group, individuals with flutter were less likely to have valvular heart disease (OR 0.16; 95% CI, 0.05 to 0.55; $P=0.004$), and had a longer PR interval (OR 1.38, per 1 standard deviation (equal to 36 ms); 95% CI, 1.06 to 1.80; $P=0.02$) in multivariable analyses (Supplemental Table 1).

Outcomes

During 10-year follow-up among participants with flutter, 40 developed incident AF, 12 had a myocardial infarction, 13 developed HF, 14 had a stroke, and 64 died. Table 3 shows the incidence rate per 1000 person-years for each outcome in those with flutter, AF, and referents. Although based on small numbers in age- and sex-adjusted analyses, the 10-year hazard ratios for AF was increased 5-fold, myocardial infarction was increased 3-fold, HF was increased 4-fold, and stroke and all-cause mortality were increased 2-fold in participants with flutter compared with matched referents (Table 4). In comparison to participants with AF, there was no significant difference in HF, stroke, or mortality risk but participants with flutter had an increased risk of MI (Table 4). Figures 1 and 2 show the 10-year cumulative incidence of AF, myocardial infarction, HF, stroke, and mortality.

Discussion

We distinguished flutter from AF to determine putative risk factors and define 10-year outcomes associated with flutter in the FHS, a large, community-based cohort. In the present study, smoking, prolonged PR interval, history of myocardial infarction, and history of HF were associated with increased risk of flutter compared to referents. In contrast with AF, flutter compared to referents was not associated with body mass index, diabetes or hypertension. Our findings expand on previously reported flutter predictors from the Marshfield Epidemiologic Study Area[6,20] which found sex, HF and chronic pulmonary disease as risk factors for flutter and no association with diabetes or hypertension.

In our study, there was no significant difference in the association of clinical correlates and the development of incident flutter and AF except for valvular heart disease and PR interval. Previously demonstrated AF risk factors - prolonged PR interval,[21,22] smoking,[23] history of myocardial infarction,[24] and history of HF[14] – were associated with flutter in our study. However, valvular heart disease, a strong AF risk factor,[14] was not associated with flutter. Since the predominance of valvular disorders detected on physical examination are left-sided, major left atrial structural and electrical remodeling from valvular disease may promote AF without promoting typical flutter, a right-sided arrhythmia.[25] Additionally, individuals with flutter were more likely to have a prolonged PR interval, which might promote the atrial anatomic or functional conduction delay that is a prerequisite for a macro-reentrant arrhythmia such as flutter.[12] Nevertheless, the overlap of risk factors of flutter and AF may partially explain why patients with flutter have a high risk of AF.[26,27]

In our analyses, we identified significantly increased risks for AF, myocardial infarction, HF, stroke, and mortality in FHS participants who developed flutter compared to referents. Comparing flutter with AF, the risk of HF, stroke, and mortality were not different. Our findings support previous studies demonstrating that the occurrence of AF in follow-up is common in individuals with a history of flutter.[27,28] Similarly, the presence of left atrial appendage thrombus[29] and increased risk of stroke associated with flutter also has been previously described,[27,30] and professional management guidelines[8] for anticoagulation in flutter and AF are similar. The underlying pathology of stroke in flutter is complicated, given that atrial thrombus formation is believed to be due to lack of organized atrial activity in AF. The organized atrial activity seen in flutter is associated with higher blood flow velocity in the left atrial appendage,[31] and thus supposedly lower risk of thrombus formation.[32] It is possible that flutter increases stroke risk by potentiating atrial or appendage dysfunction.[31] It is also possible that the increased stroke risk attributed to flutter is related to the high likelihood of future or concomitant AF,[33] which may go undiagnosed.[34]

Our data show that flutter is associated with an increased risk of myocardial infarction and HF compared with referents. A previous smaller study of flutter (n=37) reported an association with coronary artery disease.[35] Despite the exclusion of preexisting HF and myocardial infarction in our analyses of outcomes, the sequence of causality is difficult to determine for flutter, and myocardial infarction or HF. The interrelations may represent a cycle, in which the presence of either flutter or myocardial infarction/HF leads to the

development of the other. One hypothesis may be that asymptomatic/subclinical atherosclerosis promotes the development of the functional line of conduction block[36] or slowed conduction[11] that generates flutter. Flutter in turn may result in localized myocardial ischemia, inflammation, and endothelial dysfunction promoting coronary artery disease. Other possible explanations may be the overlap of risk factors between flutter and myocardial infarction, or the presence of undiagnosed AF, which is also associated with a higher risk for myocardial infarction.[37] Interestingly, in our study we observed an increased risk of myocardial infarction in flutter compared to AF. Further investigation needs to confirm the findings, given the limited number of FHS participants with flutter and myocardial infarction or HF. Furthermore, we excluded a significant number of participants with prevalent myocardial infarction in examining the association of flutter with this outcome.

The strengths of our study include the use of a large community-based sample, rigorous ascertainment of clinical risk factors, long-term follow-up and surveillance for adverse events, and consistent event adjudication. However, there are several limitations of our investigation. The limited number of cases may constrain the statistical power of our analyses of both risk factors and 10-year outcomes, particularly regarding null findings. The findings in our study will need to be confirmed in larger data sets. FHS participants are mainly white, middle-aged and older adults; our findings may not be representative of individuals from other ethnicities, younger individuals or other geographic areas. This is especially true since atrial arrhythmias relate to atrial size, a factor known to vary among different racial and ethnic groups.[38] AF is a common arrhythmia that is underdiagnosed in the population, often due to its paroxysmal and sometimes minimally symptomatic nature.[34] Cases identified here as referent or flutter may have had unrecognized AF resulting in possible misclassification bias. Our diagnosis of valvular heart disease was based on clinical criteria, thus there is a possibility of misclassification. Further, due to the observational study design and small numbers of cases we did not evaluate if anticoagulation, electrical cardioversion, or ablative therapies modified prospective 10-year outcomes following flutter onset. In addition, anticoagulation in AF and flutter is known to affect prognosis.[8] However during the study period, rates of anticoagulation have been previously demonstrated to be low, and we do not have complete data on anticoagulation to evaluate its effects.

Additional studies should identify if our data can be applied to other ethnicities and if there are sex-dependent differences in risk factors and outcomes. Consolidation of data with other cohorts may allow identification of additional risk factors for flutter. Future studies could also evaluate if there are differences in clinical characteristics between individuals with flutter who develop AF compared to those who do not.

Conclusion

In a community-based sample, we identified risk factors associated with flutter and found that flutter, similar to AF, was associated with multiple adverse outcomes, including AF, myocardial infarction, HF, and all-cause mortality. Although several common clinical factors were shared between flutter and AF, our findings demonstrate differences between flutter and AF consistent with a potential distinct epidemiology of flutter. Future studies

with larger number of cases may help confirm these findings and study how treatment of flutter may reduce adversity and improve its prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AF	atrial fibrillation
ECG	electrocardiogram
FHS	Framingham Heart Study
HF	heart failure

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Clinical Perspectives

Atrial flutter has often been combined with atrial fibrillation (AF) in large epidemiological studies despite having different electrophysiological mechanisms. In this study, we examine the clinical correlates of flutter and its associated adverse outcomes during a 10-year follow-up. In our study, compared with referents, participants who develop flutter are more likely to have been smokers, have a longer PR interval, history of myocardial infarction, and history of heart failure. Compared with AF, participants who develop flutter were less likely to have valvular heart disease and had a longer PR interval. Over the subsequent 10-years after diagnosis of flutter there is an increased risk of developing AF, having a myocardial infarction, developing heart failure, having a stroke and dying. Identification of putative risk factors may lead to developing targeted treatment strategies to reduce the risk of flutter and associated adverse outcomes. Future studies should study if different treatment strategies, such as medical therapy versus electrophysiological ablation, for flutter modifies prognosis.

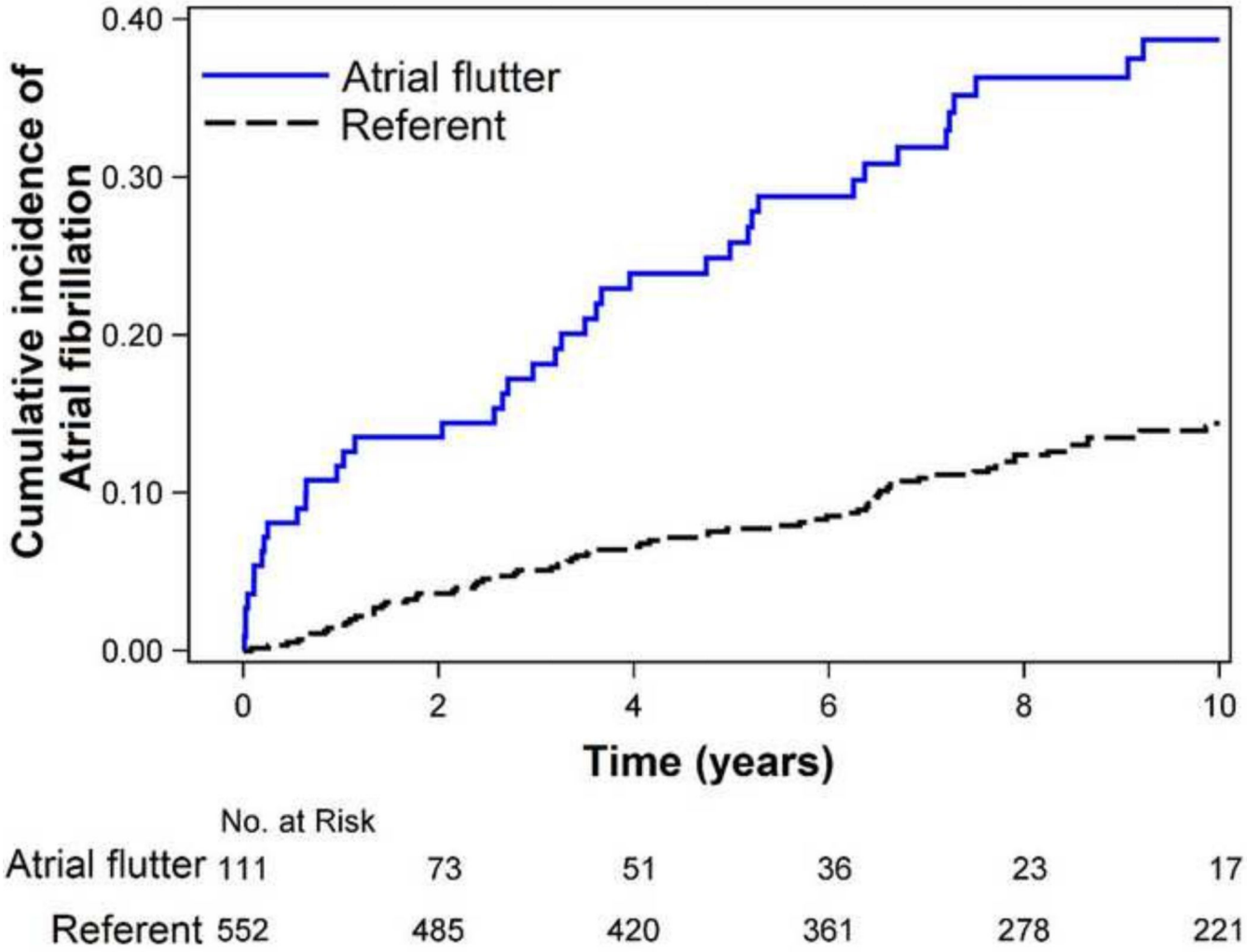

Figure 1.

Ten-year cumulative incidence of atrial fibrillation in the atrial flutter and referent groups. Graph adjusted for competing risk of death.

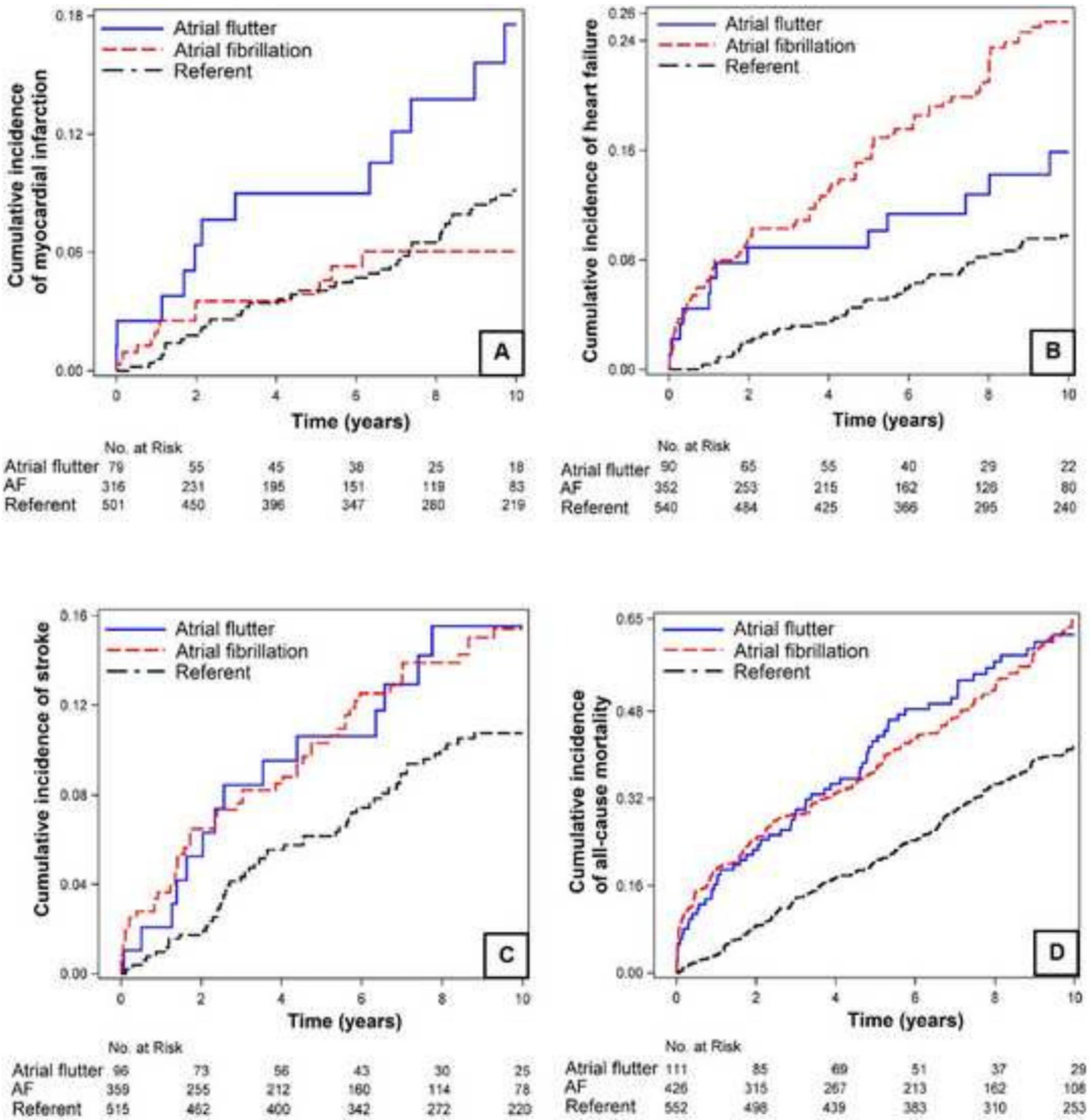

Figure 2.

Ten-year cumulative incidence of (A) myocardial infarction, (B) heart failure, (C) stroke, and (D) all-cause mortality in Framingham Heart Study participants with atrial flutter, atrial fibrillation (AF), and referents. Graphs adjusted for competing risk of death (except for all-cause mortality).

Table 1

Baseline characteristics of the study sample.

Clinical characteristics	Flutter (n=112)	AF (n=426)	Referents (n=552)
Age, years	72±10	72±9	71±10
Women	34 (30)	125 (29)	170 (31)
Current smoking	29 (26)	69 (17)	68 (12)
Moderate-to-heavy drinking	11 (10)	29 (7)	25 (5)
BMI, kg/m^2	27.0±4.6	28.0±5.2	27.3±4.3
ECG heart rate	69±15	66±13	67±13
ECG PR interval, ms	184±40	175±35	174±30
Systolic blood pressure, mmHg	138±20	141±21	139±20
Hypertensive treatment	50 (45)	240 (57)	230 (42)
Diabetes	12 (11)	69 (16)	61 (11)
Significant murmur†	4 (4)	53 (13)	33 (6)
Heart failure	9 (8)	20 (5)	8 (1)
Myocardial infarction	20 (18)	68 (16)	43 (8)
Stroke	13 (12)	39 (9)	26 (5)

AF = atrial fibrillation; Flutter = atrial flutter; ECG = electrocardiographic;

Values are presented as mean ± standard deviation, or number (%)

†Defined as any diastolic murmur or systolic murmur of grade ≥3 of 6

Table 2

Risk factors for the development of incident atrial flutter compared with referents.

Variables	Age- and sex-adjusted OR (95% CI)	P-value	Multivariable-adjusted† OR (95% CI)	P-value
Smoking	2.83 (1.66–4.81)	0.0001	2.84 (1.54–5.23)	0.0008
Moderate-to-heavy alcohol use	2.73 (1.25–5.98)	0.01	2.20 (0.92–5.25)	0.08
Body mass index	0.94 (0.76–1.16)	0.56	0.91 (0.71–1.15)	0.43
Heart rate	1.11 (0.90–1.37)	0.35	1.13 (0.87–1.47)	0.35
PR interval	1.28 (1.05–1.55)	0.01	1.28 (1.03–1.60)	0.03
Systolic blood pressure	0.97 (0.78–1.20)	0.78	0.98 (0.76–1.27)	0.88
Hypertension treatment	1.11 (0.72–1.73)	0.63	1.21 (0.74–1.97)	0.44
Diabetes mellitus	0.95 (0.49–1.83)	0.87	0.99 (0.46–2.11)	0.98
Valvular heart disease	0.60 (0.21–1.71)	0.34	0.43 (0.12–1.54)	0.19
History of myocardial infarction	2.44 (1.36–4.38)	0.003	2.25 (1.05–4.80)	0.04
History of heart failure	5.40 (1.95–14.98)	0.001	5.22 (1.26–21.64)	0.02

CI = confidence interval; OR = odds ratio

Odds ratios are expressed per 1 standard deviation increase for continuous variables.

†Adjusted for all covariates: smoking, moderate-to-heavy alcohol use, body mass index, heart rate, PR interval, systolic blood pressure, hypertension treatment, diabetes, valvular heart disease, history of myocardial infarction, and history of heart failure. Analyses were performed using conditional logistic regression models.

Table 3

Atrial flutter and adverse outcomes, 10-year incidence rate per 1000 person-years.

Outcome†	Event Number/Number at risk			Event rates per 1000 person-years (95% CI)		
	Atrial flutter	Atrial Fibrillation	Referents	Atrial flutter	Atrial fibrillation	Referents
Atrial Fibrillation	40/111	--	74/552	101 (81–121)	--	21 (12–30)
Myocardial infarction	12/79	18/316	42/501	33 (22–45)	14 (7–22)	12 (5–19)
Heart Failure	13/90	82/352	49/540	36 (24–48)	55 (41–70)	14 (7–21)
Stroke	14/96	51/359	52/515	28 (17–38)	32 (21–42)	15 (8–23)
Death	64/111	250/426	212/552	126 (104–147)	120 (98–141)	57 (43–72)

CI = confidence interval; Referents = individuals without atrial fibrillation or atrial flutter

†Participants with prevalent disease were excluded from the specific outcome analysis.

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Table 4

Atrial flutter and age- and sex-adjusted 10-year outcomes.

	Atrial flutter versus referents‡		Atrial flutter versus atrial fibrillation	
Outcome	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Atrial fibrillation	5.0 (3.1–8.0)	<0.001	--	--
Myocardial infarction	3.1 (1.4–6.6)	0.004	4.5 (1.5–32.4)	0.008
Heart Failure	4.1 (1.9–9.0)	<0.001	0.9 (0.4–1.7)	0.67
Stroke	2.2 (1.1–4.2)	0.02	0.9 (0.5–1.7)	0.70
Death†	2.0 (1.4–2.8)	<0.001	0.9 (0.7–1.3)	0.58

HR = hazard ratio; CI = confidence interval;

†Also adjusted for the presence or absence of prevalent cardiovascular disease.

‡Referents defined as participants without AF or atrial flutter.