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Death and thrombo-embolic risk after ablation of atrial flutter compared with atrial fibrillation: a nationwide cohort study

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Aims The aim of this study was to investigate whether there is a similar mortality and thrombo-embolic risk, after an atrial ablation procedure, compared with an atrial fibrillation (AF) procedure.

Methods and results Using data from nationwide Danish health registries, we identified patients aged 18–75 years undergoing a first-time atrial flutter or an AF ablation procedure in the period 2000–13. Cox proportional hazards regression was used to calculate hazard ratios (HRs) after 5 years of follow-up, adjusting for concomitant risk factors. A total of 1096 and 2266 patients underwent an ablation for atrial flutter or AF, respectively. Age distribution was similar in the two, but atrial flutter patients had more co-morbidities. During 5 years of follow-up, we observed 38 and 36 deaths in the atrial flutter and AF groups, corresponding to an almost two-fold higher mortality rate among atrial flutter patients [crude HR 1.92, 95% confidence interval (CI) 1.22–3.03]. The higher mortality rate persisted after adjustment for age, sex, diabetes mellitus, and hypertension (adjusted HR 1.68, 95% CI 1.05–2.69). The rate of thrombo-embolic events was similar in the two groups (crude HR 1.34, 95% CI 0.71–2.56; adjusted HR 1.22, 95% CI 0.62–2.41).

Conclusion In this observational study, patients with atrial flutter had a significantly higher all-cause mortality rate compared with those with AF after an ablation procedure, but similar thrombo-embolic event rates. Future studies should elucidate the reason for this difference in mortality.

Keywords Atrial flutter • Ablation • Death • Thromboembolism • Epidemiology

Introduction

Atrial flutter confers a higher mortality and thrombo-embolic risk compared with a healthy population, and this risk is considered to be similar to that seen in atrial fibrillation (AF).[1–5] Current guidelines[6] recommend that patients with atrial flutter are managed the same way as those with AF, with regard to thrombo-embolic prevention. Contrary to ablation of AF, ablation of atrial flutter is often offered as a first-line treatment for typical atrial flutter and due to the high procedural success rate (~95%) and the low annual recurrence rate (5–10%);[7] ablation is often considered as a curative treatment. Indeed, it has been suggested that a cavotricuspid isthmus ablation procedure could reduce the risk of stroke and mortality in patient with atrial flutter;[8] however, there are only few studies that have investigated long-term mortality after an atrial flutter ablation procedure.[8–10]

In the present study, we hypothesized that there is a similar mortality and thrombo-embolic risk following stand-alone atrial flutter ablation compared with an AF ablation. To investigate this hypothesis, we used data from nationwide Danish health registries to assess and compare the long-term risk of mortality and thrombo-embolic events in patients with atrial flutter compared with those with AF following an ablation procedure.

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What's new?

- Patients with atrial flutter have a significantly higher all-cause mortality rate compared with those with atrial fibrillation after an ablation procedure.

Methods

Data sources

Study data were obtained by merging three nationwide Danish health registries. Using the unique Danish personal identification number that is assigned to all Danish residents, we linked data from the Danish Civil Registration System, the Danish National Patient Registry, and the National Prescription Registry. The Danish Civil Registration System holds information on date of birth, sex, migration, vital status, and date of death of all Danish inhabitants. The National Prescription Registry has recorded data on all prescriptions dispensed from Danish pharmacies since 1994, coded according to the Anatomic Therapeutic Chemical (ATC) Classification System. The Danish National Patient Registry has registered all hospital admissions along with discharge diagnoses since 1977 [using since 1994 the 10th version of the International Classification of Diseases (ICD)]. The Danish National Patient Registry also contains information on surgical procedures, coded according to the Danish version of the Nordic Classification of Surgical Procedures.

Study population and clinical variables

The study population comprised of Danish patients, between 18 and 75 years old, registered with an incident atrial flutter or AF ablation procedure code, between 1 January 2000 and 1 January 2014. Baseline was defined as the date that the ablation procedure was registered. To reduce confounding, patients with a previous atrial flutter or an AF ablation procedure code, or ICD-10 codes for heart failure, ischaemic heart disease, pacemaker, valvular heart disease, and/or prior thrombo-embolic events were excluded from the study population. To ensure that we only included patients treated according to the guidelines for ablation procedure, we excluded those who were not warfarin users at baseline (defined as not having redeemed a prescription for warfarin in a 90-day period before baseline and as sensitivity analysed with cut-off at 180 and 360 days before baseline).

Comorbid conditions were identified in the Danish National Patient Registry based on ICD-10 codes (see Supplementary material online, *Table S1*). The National Prescription Registry was used to obtain information on medication according to ATC codes (see Supplementary material online, *Table S1*).

Outcomes

The primary outcome was all-cause death, as obtained from The Danish Civil Registration System. Secondary outcomes were a combined endpoint of thrombo-embolic events (ischaemic stroke, ICD-10 I63; transient ischaemic attack, ICD-10, G45; pulmonary embolism, ICD-10, I26), as obtained from the Danish National Patient Registry.

Statistical analysis

Time-to-event analysis was used to describe and compare event rates in the two arrhythmia groups. Time-to-event was measured from the ablation procedure until death, combined thrombo-embolic event, emigration, or end of follow-up 1 January 2014, whichever came first.

Kaplan–Meier curves were used to describe survival in each of the two arrhythmia groups. Event rates and hazard ratios (HRs) based on Cox proportional hazard regression models were calculated for 5 years of follow-up. HR was adjusted for baselines differences using following variables: age (continuous; cubic spline), sex (binary), hypertension (binary), and diabetes mellitus (binary). In an additional adjusted analysis, we also adjusted for time since the diagnosis of atrial flutter or AF (continuous; cubic spline) and anticoagulant therapy (time-varying covariate: $<$90 days since last warfarin prescription redemption).

We performed a sensitivity analysis excluding all patients with a prior diagnosis/procedure code for chronic obstructive pulmonary disease, previous heart valve operation, heart arrhythmia operation, and/or congenital heart disease.

Data were analysed using Stata (StataCorp, College Station, TX, USA).[11]

Ethical considerations

No ethical approval is required for anonymous registry-based studies in Denmark. The study has been approved by the Danish Data Protection Agency (File No. 2012-41-0633).

Results

We identified 8170 patients with an incident atrial flutter or an AF ablation procedure. A total of 4809 patients did not fulfil the inclusion criteria and were excluded, mainly due to the lack of anticoagulant treatment ($n = 2044$) at baseline (*Figure 1*). The study population consists of 3361 patients and 1096 (33%) had an incident atrial flutter ablation procedure. Baseline characteristics of the study population are summarized in *Table 1*. In both arrhythmia groups, patients were predominantly male (79.2 vs. 72.6%) with similar age (mean: 59.3 vs. 57.4 years). The most common co-morbidity in both groups was hypertension (26.5 vs. 27.0%). There was a higher frequency of patients with congenital heart disease (3.3 vs. 0.8%), prior heart arrhythmia operation (2.3 vs. 1.4%), and heart valve operation (1.2 vs. 0.4%) in the atrial flutter group. The use of antiarrhythmic medication was evenly distributed between the two groups. Mean time with diagnosis was lower in the atrial flutter group compared with the AF group (mean: 2.0 vs. 2.8 years).

Kaplan–Meier survival curves for the two arrhythmia groups are shown in *Figure 2* and indicate a higher mortality risk in the atrial flutter group compared with the AF group. There was no clear difference in short-term mortality between the two arrhythmia groups.

Event rates and HR for 5-year follow-up are presented in *Table 2*. We observed an almost two-fold higher crude mortality rate after atrial flutter ablation, when compared with AF ablation [crude HR 1.92, 95% confidence interval (CI) 1.22–3.03]. This higher rate persisted after multivariable adjustment (HR 1.68, 95% CI 1.05–2.69). After additional adjustment for time with diagnosis and (time-varying) anticoagulant therapy, we found similar effect size estimates, although they were no longer statistically significant (HR 1.50, 95% CI 0.92–2.45). Of note after 3 months, the proportion of patients still in anticoagulant therapy was 83% for atrial flutter patients compared with 87% for the AF patients (see Supplementary material online, *Figure S1*). The rate of thrombo-embolic events was similar in the atrial flutter group compared with the AF group (crude HR 1.34, 95% CI 0.71–2.56; adjusted HR 1.22, 95% CI 0.62–2.41; *Table 2*). In a univariate analysis, only age was a predictive factor

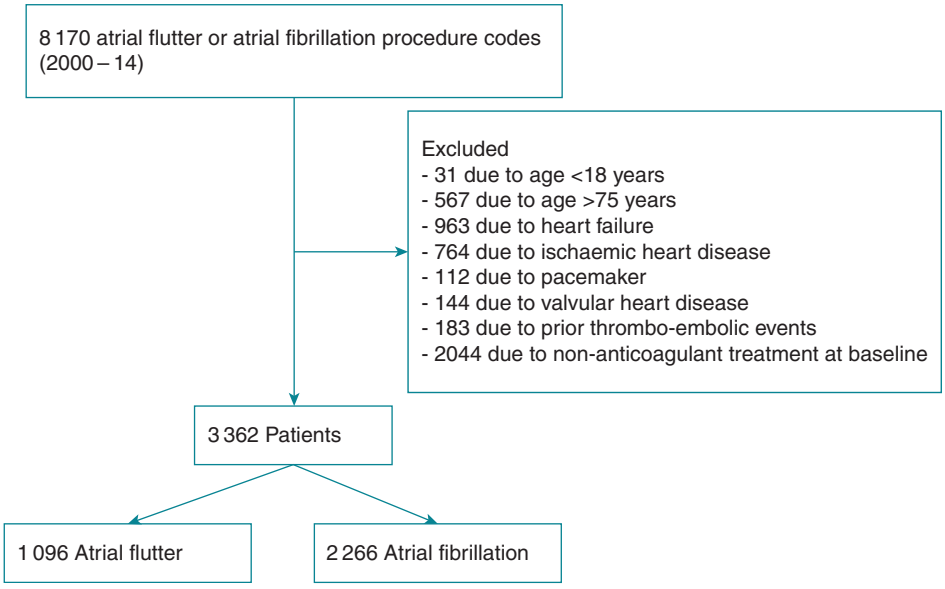

Figure 1 Flow chart of the study population.

Table 1 Patient characteristics

	Atrial flutter (*N* = 1096)	Atrial fibrillation (*N* = 2266)	Baseline difference *P*-value
Procedures			
2000–06	327	385	<0.001
2007–14	769	1881	
Male sex	868 (79.2%)	1645 (72.6%)	<0.001
Mean age, years (range)	59.3 (18–75)	57.4 (22–75)	<0.001
Mean time with diagnosis, years (SD)	2.0 (2.9)	2.8 (3.5)	<0.001
Hypertension	290 (26.5%)	612 (27.0%)	0.73
Diabetes mellitus	61 (5.6%)	82 (3.6%)	0.009
Obesity	51 (4.6%)	86 (3.8%)	0.24
Thyrotoxicose	29 (2.6%)	76 (3.3%)	0.27
Alcoholism	13 (1.2%)	15 (0.6%)	0.12
Renal disease	13 (1.2%)	15 (0.6%)	0.12
Chronic obstructive pulmonary disease	35 (3.2%)	38 (1.7%)	0.005
Anti-arrhythmic medication[a]	391 (35.7%)	835 (36.8%)	0.51
Heart arrhythmia operation	25 (2.3%)	32 (1.4%)	0.07
Heart valve operation	13 (1.2%)	10 (0.4%)	0.01
Congenital heart disease	36 (3.3%)	19 (0.8%)	<0.001

SD, standard deviation.
[a]Combined digoxin, amiodarone, sotalol, flecainide, verapramil, or dronedarone.

for death (HR 1.08, 95% CI 1.05–1.11), but similar for both arrhythmias (see Supplementary material online, *Table S2*).

In the sensitivity analysis excluding patients with prior heart arrhythmia operation, heart valve operation, and congenital heart disease, we still observed a higher mortality rate in the atrial flutter group compared with the AF group, although this was no longer statistically significant (crude HR 1.83; 95% CI 1.14–2.93) and adjusted HR 1.33, 95% CI 0.79–2.22). These results did not change if we excluded renal impairment and chronic obstructive pulmonary disease. In the sensitivity analysis using alternative definitions for warfarin usage at baseline (prescription redemption <180 and 360 days, respectively), the mortality rate remains elevated (crude HR 1.81, 95% CI 1.17–2.80 and crude HR 1.80, 95% CI 1.16–2.78).

Discussion

In this large-scale study using Danish nationwide registry data, we found that patients with atrial flutter had a significantly higher all-cause mortality rate compared with those with AF after an ablation procedure, but a similar or trend against a possibly modestly higher thrombo-embolic risk.

To our knowledge, there are no long-term studies investigating mortality after an atrial flutter ablation procedure. However, observational studies[3,4] have suggested that atrial flutter confers a similar mortality risk as patients with AF in a non-ablated population and that atrial flutter ablation is associated with a 45% lower all-cause mortality risk compared with non-ablated atrial flutter patients.[8] Our study extends these observations by indicating a higher mortality rate after atrial flutter ablation compared with AF ablation.

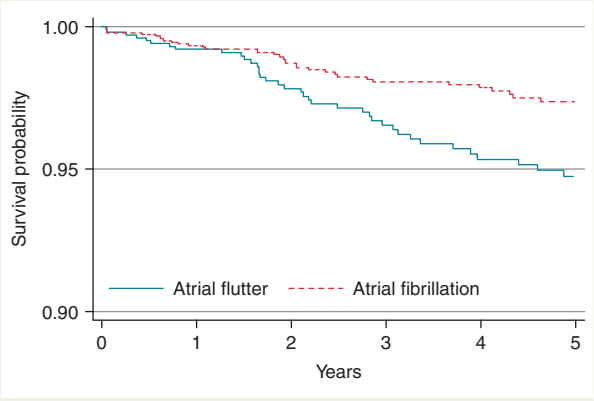

Figure 2 Kaplan–Meier survival plot. Kaplan–Meier survival probability plots for atrial flutter and atrial fibrillation after an ablation procedure with 5 years follow-up.

The overall mortality rates were quite low in both groups, with an absolute risk difference being 1.9% over a 5-year follow-up period, but this finding was very surprising to us. In this study, death occurred in 38 patients (3.5%) with atrial flutter which is lower than the 18.5% reported in the study by Seara *et al.*[10] Indeed, Seara *et al.* found that in patients without transition to AF after an atrial flutter ablation, age (HR 1.05, 95% CI 1.01–1.09), chronic pulmonary disease (HR 2.85, 95% CI 1.39–5.83), and heart failure (HR 2.72, 95% CI 1.15–6.40) were predictive factors for death. In contrast to Seara *et al.*, we excluded patients with prior heart failure, ischaemic heart disease, prior thrombo-embolic events, and those who were non-anticoagulated at baseline. This means that our study population is a relatively healthy one compared with Seara *et al.* However, even after adjustment of age, we still found that the higher mortality risk persisted. As expected, the mean time with diagnosis was higher in the AF group compared with the atrial flutter group (2.8 vs. 2.0 years), consistent with guideline recommendations that an atrial flutter ablation procedure could be offered as a first-line treatment. Conversely, AF ablation is usually recommended following unsuccessful treatment with an anti-arrhythmic drug. After adjustment for time with diagnosis and anticoagulant therapy during follow-up, HR of death remained comparable with those from the main analysis, although they were no longer statistically significant.

The incidence of thrombo-embolic events was similar in the groups (HR 1.22, 95% CI 0.62–2.41) and cannot explain the higher mortality rate. The stroke rate of 4.6 strokes per 1000 person-years is lower than in a study from the Philadelphia Veterans Affairs Medical Center[12] that reported an incidence of 21 strokes per

Table 2 Event counts, rates, and Cox hazard ratios after 5 years of follow-up

	Ablation procedure	
	Atrial fibrillation	**Atrial flutter**
Death		
Events (*n*)	36	38
Rate, per 100 person-years (95% CI)	0.56 (0.41–0.78)	1.08 (0.78–1.48)
HR (95% CI)		
Crude	1.00 (reference)	1.92 (1.22–3.03)
Adjusted[a]	1.00 (reference)	1.68 (1.05–2.69)
Adjusted[b]	1.00 (reference)	1.50 (0.92–2.45)
Thrombo-embolic events		
Events (*n*)	22	16
Rate, per 100 person-years (95% CI)	0.35 (0.23–0.53)	0.46 (0.28–0.75)
HR (95% CI)		
Crude	1.00 (reference)	1.34 (0.71–2.56)
Adjusted[a]	1.00 (reference)	1.32 (0.69–2.55)
Adjusted[b]	1.00 (reference)	1.22 (0.62–2.41)

HR, hazard ratio; CI, confidence interval; TE, stroke, transient ischaemic attack, and pulmonary embolisms.
[a]Adjusted for: age (restricted cubic spline), sex, hypertension, and diabetes mellitus.
[b]Adjusted for: age (restricted cubic spline), sex, hypertension, diabetes mellitus, time with diagnosis (restricted cubic spline) and anticoagulant therapy (time-varying: <90 days since last warfarin prescription redemption).

1000 person-years after a successful ablation procedure for typical atrial flutter. All patients in the present study were on anticoagulant treatment at the time of the ablation procedure, and the higher mortality rate persisted even after adjustment for anticoagulant therapy during follow-up.

One major concern after an successful atrial flutter ablation procedure is the development of incident AF, which in some studies has been reported as high as 25[13] and 33.4%.[10] Unfortunately, we have no information on the development of incident AF after the atrial flutter ablation procedure. In contrast to our results, one population-based study[4] found a similar mortality risk in patients with both atrial flutter and AF compared with those with only AF (47 vs. 45%).

One plausible explanation for the differences in mortality would be that the co-morbidity among atrial flutter ablation patients is of a multifactorial nature not easily captured by simple regression adjustment, as performed in our study. Indeed, our findings for baseline co-morbidities suggest that atrial flutter ablation patients were uniformly slightly more ill than AF ablation patients. As an alternative explanation, one could also speculate that the higher mortality rate be driven by the clinician's perception that an atrial flutter ablation procedure is more 'curative' than an AF ablation procedure, so that post-ablation follow-up in atrial flutter patients may be insufficient. Undertreated atrial tachyarrhythmias could lead to heart failure and thereby a higher mortality rate. Although there were no overwhelming differences between the atrial flutter and the AF group at baseline characteristics, progressive co-morbidity, repeated ablation procedures, or pacemaker implantation could perhaps explain the higher mortality and the higher mortality rate could thus be multifactorial. Also, the development of AF post-ablation could lead to more fatal strokes in the atrial flutter group.[6] Future studies should elucidate the patient history following the initial ablation procedure.

Limitations

There are several important limitations to the present study. Most importantly, our study is based on registry data which leaves open the possibility of residual and unmeasured confounding, in addition to a misclassification and ascertainment error. It is plausible that atrial flutter ablation is offered to a more elderly and possibly more sick population for which the relevant co-morbidities are not captured by the registries. In particular, we had no information on time in therapeutic range among warfarin users, and the warfarin prescription criteria were based on a strict definition; nor did we have information on laboratory, anthropometric, or socioeconomic data. We also did not have information on cause of death.

Another limitation, a prior history of AF, may have been underestimated in the atrial flutter ablation group, as it is sometimes asymptomatic and therefore may not have been documented. Finally, the study is performed on an ethnically and socioeconomically relatively homogeneous population. It is therefore important to reassess our findings in more diverse study populations.

Conclusion

Patients with atrial flutter had a significantly higher all-cause mortality rate compared with those with AF after an ablation procedure. Future studies are needed to better understand the reasons for this higher mortality.

Supplementary material

Supplementary material is available at *Europace* online.

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Conflict of interest: G.Y.H.L. has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim and has served as a speaker for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Sanofi Aventis. T.B.L. has been on the speaker bureaus for Bayer, BMS/Pfizer, Janssen Pharmaceuticals, Takeda, Roche Diagnostics, and Boehringer Ingelheim.

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