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Risk of arterial and venous thromboembolism in patients with atrial fibrillation or flutter: A nationwide population-based cohort study

Jens Sundbøll [a,b,*], Erzsébet Hováth-Puhó [a], Kasper Adelborg [a,b], Anne Ording [a], Morten Schmidt [a,b], Hans Erik Bøtker [b], Henrik Toft Sørensen [a]

[a] Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark
[b] Department of Cardiology, Aarhus University Hospital, Skejby, Palle Juul-Jensens Blvd. 99, DK-8200 Aarhus N, Denmark

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ABSTRACT

Background: Patients with atrial fibrillation or flutter (AFF) are at increased risk of ischemic stroke, but their risk of other thromboembolic events remains less clear.
Methods: During 2004–2013, we conducted a nationwide population-based cohort study using Danish medical registries. We identified all patients with first-time AFF and sampled a sex-, age-, and calendar year-matched general population comparison cohort without AFF. For myocardial infarction, peripheral embolism, ischemic stroke, hemorrhagic stroke, deep venous thrombosis, and pulmonary embolism, we computed cumulative risks and adjusted incidence rate ratios (aIRRs) adjusted for comorbidity and medication.
Results: The study population consisted of 103,989 patients with AFF and 519,935 individuals without AFF from the general population. Ten-year cumulative risks in the AFF cohort were 3.5% for myocardial infarction, 0.5% for peripheral embolism, 6.7% for ischemic stroke, 1.3% for hemorrhagic stroke, 1.0% for deep venous thrombosis, and 1.3% for pulmonary embolism. During the first 30 days following AFF, aIRRs were markedly (4 to 16-fold) increased for all outcomes and similarly elevated for myocardial infarction (aIRR = 8.0, 95% confidence interval (CI): 6.8–9.5) and ischemic stroke (aIRR = 9.9, 95% CI: 8.5–11.5). Thereafter, aIRRs decreased gradually, reaching unity after 5 years for myocardial infarction, deep venous thrombosis, and pulmonary embolism, but remained 1.6 to 3.5-fold increased for peripheral embolism, ischemic stroke, and hemorrhagic stroke.
Conclusions: AFF was a risk factor for all arterial and venous outcomes during the first year of follow-up, but only for peripheral embolism, ischemic stroke, and hemorrhagic stroke thereafter.

1. Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, with a lifetime prevalence of approximately 25% [1,2]. It is associated with a 3- to 4-fold increased risk of ischemic stroke and a 2-fold increased risk of death [3]. Known risk factors for atrial fibrillation include advanced age and age-related diseases such as hypertension, myocardial infarction (MI), and valvular heart disease [4,5]. With an ongoing demographic shift in age in Western populations and improved survival following predisposing cardiac diseases like MI [6], a >2-fold increase in the prevalence of atrial fibrillation during 2010–2060 is expected [7]. Thus, atrial fibrillation is emerging as a major public health concern [8,9], and identifying the risk of cardiovascular complications has become increasingly important to target preventive strategies.

Atrial fibrillation or flutter (AFF) creates an intra-atrial stasis with the potential to cause thrombus formation and embolization [10]. Beyond increasing the risk of ischemic stroke [3,11–15], AFF has been linked to an elevated risk of other arterial and venous events. Despite the clinical relevance, however, the literature does not provide information on how risks of cardiovascular events after AFF evolve during follow-up and whether risks are sustained during long-term follow-up. AFF has been associated with a ≈1.7-fold increased risk of MI [16–18]. One study has examined the risk of peripheral embolism, reporting a ≈5-fold increased risk [19] while AFF has been associated with a ≈3-fold increased risk of hemorrhagic stroke [20]. Risk of venous thromboembolism was investigated in two studies reporting an 8-fold increased risk < 6 months [21] and a 28-fold increased risk < 3 months after a first-time AFF diagnosis [22]. Studies on long-term risk of venous

Abbreviations: MI, myocardial infarction; AFF, atrial fibrillation or flutter; DVT, deep venous thrombosis; PE, pulmonary embolism; DNPR, Danish National Patient Registry; ICD, International Classification of Diseases; ED, emergency department; IRR, incidence rate ratio; CI, confidence interval.

* Corresponding author at: Department of Clinical Epidemiology, Aarhus University Hospital, Olof Palmes Allé 43-45, DK-8200 Aarhus N, Denmark.
E-mail addresses: jens.sundboll@clin.au.dk (J. Sundbøll), ep@clin.au.dk (E. Hováth-Puhó), kade@clin.au.dk (K. Adelborg), ao@clin.au.dk (A. Ording), morten.schmidt@clin.au.dk (M. Schmidt), heb@dadlnet.dk (H.E. Bøtker), hts@clin.au.dk (H.T. Sørensen).

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thromboembolism following AFF are equivocal with reports of no increased risk [22] and of moderately increased risk [21,23].

We examined the risk of MI, peripheral embolism, ischemic stroke, hemorrhagic stroke, deep venous thrombosis (DVT), and pulmonary embolism (PE) among patients with first-time AFF compared with a matched general population cohort.

2. Methods

2.1. Setting and design

We conducted this population-based cohort study in Denmark, which had a cumulative population of 6,567,382 inhabitants during the study period. The Danish National Health Service provides universal tax-supported health care, guaranteeing unfettered access to general practitioners and hospitals. Accurate and unambiguous linkage of all registries is possible at the individual level in Denmark using the unique central personal registry number assigned to each Danish citizen at birth and to residents upon immigration [24].

2.2. Patients with atrial fibrillation or flutter

We used the Danish National Patient Registry [25] (DNPR) to identify all patients with a first-time diagnosis of AFF during the study period between 1 July 2004 and 1 July 2013. The DNPR has recorded information on dates of admission and discharge from all Danish non-psychiatric hospitals since 1977 and from emergency room and outpatient clinic visits since 1995 [25]. Each hospital discharge or outpatient visit is recorded in the DNPR with one primary diagnosis and one or more secondary diagnoses classified according to the *International Classification of Diseases*, *Eighth Revision* (ICD-8) through 1993 and *Tenth Revision* (ICD-10) thereafter [25]. We identified AFF patients using both primary and secondary inpatient, outpatient, and emergency department (ED) diagnoses. We excluded patients with a previous or concurrent inpatient or outpatient diagnosis of MI, peripheral embolism, stroke, transient ischemic attack, or venous thromboembolism. Since <0.4% of all patients in our cohort were coded specifically as either atrial fibrillation or atrial flutter, we collapsed the codes into one disease entity. More than 90% of patients registered with these codes had atrial fibrillation [26]. Considering atrial fibrillation and flutter one disease entity is reasonable because they share risk factors and to some degree pathophysiology [27,28]. Furthermore, data from observational and echocardiographic studies suggest that risk of thromboembolism following atrial flutter is comparable to that of atrial fibrillation and that spontaneous echo contrast and left atrial thrombi are prevalent also in patients with atrial flutter [10]. The index date was defined as the hospital admission date of AFF (for inpatients) or the date of the first visit for AFF (for outpatients/ED patients). ICD and Anatomical Therapeutic Chemical classification system codes used in the study are provided in Supplemental Table 1.

2.3. General population comparison cohort

We created a population-based comparison cohort from the general population using the Danish Civil Registration System [24]. For each patient in the AFF cohort, up to 5 individuals from the general population were randomly selected from the Danish Civil Registration System and matched on sex, single year of age, and calendar year of the patient's AFF diagnosis. We used matching with replacement (*i.e.*, individuals from the general population comparison cohort could be matched with more than one AFF patient) [29]. Each comparison cohort member was assigned an index date corresponding to the date of admission or outpatient/ED visit for the corresponding AFF patient. All comparison cohort members were required to be alive on the date the corresponding AFF patient was first hospitalized or seen in an outpatient clinic/ED for AFF. We included only comparison cohort members without a previous hospital-based diagnosis of MI, peripheral embolism, stroke, transient ischemic attack, or venous thromboembolism and without any previous AFF diagnosis. Individuals from the comparison cohort diagnosed with AFF during follow-up joined the AFF cohort at that point and follow-up was discontinued in the comparison cohort.

2.4. AFF risk factors, comorbidity, and comedications

From the DNPR, we obtained information on AFF risk factors and comorbid conditions diagnosed at any time from 1977 until the index date. These consisted of all inpatient and outpatient hospital diagnoses of chronic pulmonary disease (as a measure of long-term smoking), heart failure, valvular heart disease, intermittent claudication, diabetes mellitus, hypertension, hypercholesterolemia, obesity, hyperthyroidism, hypothyroidism, and alcoholism-related disorders. To increase the sensitivity of hypertension, diabetes mellitus, and chronic pulmonary disease, we used both hospital-based diagnoses and any redeemed prescriptions of disease-specific medication using data from the National Health Service Prescription Database [30] (Supplemental Table 1).

Moreover, we obtained information on concurrent use (*i.e.*, ≤90 days before admission) of nitrates (if ≥2 prescriptions were registered), statins, aspirin, clopidogrel, amiodarone, and non-steroidal anti-inflammatory drugs from the prescription database [30].

2.5. Outcomes

Outcomes were all first-time hospitalizations (primary and secondary inpatient diagnoses) registered in the DNPR for MI, peripheral embolism, ischemic stroke, hemorrhagic stroke, DVT, and PE following the index date [25].

To distinguish cases of venous thromboembolism with and without known predisposing conditions, we separately analysed the risks of provoked and unprovoked venous thromboembolism (Supplemental Table 2). Since approximately two thirds of all unspecified strokes are known to be ischemic strokes [31], we classified unspecified strokes as ischemic strokes.

2.6. Statistical analysis

We characterized the AFF and comparison cohorts according to age, sex, CHA_2DS_2-VASc score, comorbidities, and comedications (Table 1). In each analysis, we followed all AFF patients and comparison cohort members from the index date until occurrence of an outcome, emigration, death, or 31 November 2013, whichever came first.

Table 1
Characteristics of patients with atrial fibrillation or flutter and members of the general population comparison cohort.

	Atrial fibrillation or flutter cohort n = 103,989	Comparison cohort n = 519,935
Median age, years (25th–75th percentiles)	72.6 (63.0–81.7)	72.6 (63.0–81.7)
Age groups, years		
<55	12,412 (11.9)	61,944 (11.9)
55–64	18,662 (17.9)	93,754 (18.0)
65–74	27,582 (26.5)	137,785 (26.5)
≥75	45,333 (43.6)	226,452 (43.6)
Male	54,879 (52.8)	274,389 (52.8)
CHA_2DS_2-VASc score		
0	21,144 (20.3)	129,767 (25.0)
1	13,008 (12.5)	66,808 (12.8)
2	24,240 (23.3)	124,874 (24.0)
>3	45,597 (43.8)	198,486 (38.2)
Comorbidity		
Chronic pulmonary disease	26,055 (25.1)	85,445 (16.4)
Heart failure	6794 (6.5)	11,046 (2.1)
Valvular heart disease	6023 (5.8)	8272 (1.6)
Intermittent claudication	1504 (1.4)	4871 (0.9)
Diabetes mellitus	11,460 (11.0)	41,212 (7.9)
Hypertension	41,627 (40.0)	133,902 (25.8)
Hypercholestolemia	4020 (3.9)	12,733 (2.4)
Obesity	4584 (4.4)	10,838 (2.1)
Hyperthyroidism	2698 (2.6)	9181 (1.8)
Hypothyroidism	1435 (1.4)	6149 (1.2)
Alcoholism-related disorders	3251 (3.1)	9720 (1.9)
Comedication use before the index date		
Nitrates	4430 (4.3)	9515 (1.8)
Statins	16,019 (15.4)	65,510 (12.6)
Aspirin	23,452 (22.6)	71,246 (13.7)
Clopidogrel	880 (0.8)	2171 (0.4)
Amiodarone	541 (0.5)	160 (0.0)
Non-steroidal anti-inflammatory drugs	14,920 (14.3)	57,282 (11.0)
Oral anticoagulants and aspirin use 30 days after the index date		
Oral anticoagulants	34,535 (33.2)	2082 (0.4)
Aspirin	17,838 (17.2)	30,370 (5.8)

Table values are numbers (%) unless otherwise specified.

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