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# New-onset atrial fibrillation among patients with infection in the emergency department: A multicentre cohort study of one-year stroke risk

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## Conflicts of interest

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## Contributors

TGH, AL, AP and AB designed the study and interpreted the results and TGH drafted the paper. AP analyzed the data. All authors critically reviewed the paper, assisted with interpretation of the results, and have approved the final edition. TGH assumes responsibility for the final paper.

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## ABSTRACT

**Background:** Patients with new-onset atrial fibrillation in relation to infection are frequent in emergency departments (ED) and may require antithrombotic therapy due to increased risk of stroke. Our objective was to describe the one-year risk of stroke in ED patients with infection, new-onset atrial fibrillation and no antithrombotic therapy.

**Methods:** Population-based cohort study at four EDs in Denmark and Sweden. Atrial fibrillation was identified by ECG upon arrival at the ED and infection was identified by discharge diagnosis. Patient history was followed for 12 months or until initiation of oral anticoagulant therapy, ischemic stroke or death. Primary outcome was stroke within 12 months compared to patients with infection and no atrial fibrillation.

**Results:** 15,505 patients were included in analysis. 48.7% were male and the median age was 71 (IQR, 56 – 83). Among the included patients, 2,107 (13.6%) had atrial fibrillation of any kind and 822 (39.0%) of these had new-onset atrial fibrillation with a median CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3 (IQR 2 – 4).

New-onset atrial fibrillation during infection showed an absolute post-discharge one-year risk of stroke of 2.7% (95% CI 1.6 – 4.2), corresponding to a crude HR of 1.4 (95% CI 0.9 – 2.3), a sex and age adjusted HR of 1.0 (95% CI 0.6 – 1.6) and a CHA<sub>2</sub>DS<sub>2</sub>-VASc adjusted HR of 1.1 (95% CI, 0.7 – 1.8) compared to patients with infection, but no atrial fibrillation.

**Conclusions:** ED patients with infection and new-onset atrial fibrillation without current OAC therapy had a 2.7% absolute one-year risk of stroke. Stroke events were mainly related to sex and age and risk factors identified by the CHA<sub>2</sub>DS<sub>2</sub>-VASc score.

## INTRODUCTION

Patients with atrial fibrillation have a significantly increased risk of stroke [1] which can be reduced by oral anticoagulant (OAC) therapy [2]. Congestive heart failure, hypertension, age > 75, diabetes, previous stroke/TIA/thromboembolism, vascular disease, age 65-74 and sex category (CHA<sub>2</sub>DS<sub>2</sub>-VASc) in patients with atrial fibrillation are identified to calculate the CHA<sub>2</sub>DS<sub>2</sub>-VASc score [3], which is recommended to be used as guidance for whether to start OAC. The European Society of Cardiology recommends initiating OAC treatment in patients with atrial fibrillation and a moderate or high risk of stroke (CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 1$ ) [4], whereas US guidelines recommend OAC treatment for atrial fibrillation patients at high risk of stroke [5].

Both atrial fibrillation and infection can each lead to serious adverse outcomes. Concomitantly, they have been associated with poor short- and long-term outcomes, with increased risk of ischemic stroke and with heart failure and death [6,7].

An emergency department (ED) study found that 16 % of acute patients presenting with infection had atrial fibrillation and that these patients had a four-fold increased risk of major adverse cardiovascular events including stroke within 90 days [8].

As atrial fibrillation can be completely asymptomatic, [9] it can be unclear whether infected patients with atrial fibrillation diagnosed in the ED have preexisting atrial fibrillation or new-onset atrial fibrillation related to the infection. Furthermore, it is unknown if these patients should be treated by OAC.

The aim of the present study was to investigate the one-year post-discharge risk of stroke for ED patients with infection, new onset atrial fibrillation and no current OAC treatment.

## **MATERIALS & METHODS**

### **Study design and setting**

We conducted a multi-centre cohort study in adult ED patients at 1) Odense University Hospital, Odense, Denmark, 2) the Hospital of South West Jutland, Esbjerg, Denmark, 3) Helsingborg Hospital, Sweden and 4) Skåne University Hospital, Lund, Sweden. We included patients admitted to the ED at Lund and Helsingborg from 1 January 2010 to 31 December 2014, and patients admitted to the ED in Odense and Esbjerg between 13 March 2013 and 30 April 2014.

### **Participants**

We included all adult ED patients ( $\geq 18$  years) with an ECG performed within 4 hours of arrival. Only the first ECG taken upon arrival and only the first contact with an ECG in the study period were included.

### **Data sources**

ECGs were retrieved from the digital central ECG database for the Region of Southern Denmark and the Region of Skåne. Triage, main diagnoses, time of arrival, and time of discharge were retrieved from the logistic systems for EDs in the Region of Southern Denmark and the Region of Skåne [10].

All Swedish and Danish residents are, at birth or immigration, issued a permanent and unique civil registration number, enabling individual-level linkage between administrative registries. With the use of such registry data, we identified and linked data concerning comorbidity, prescription drug use, and discharge diagnoses, and followed patients with respect to death or emigration [11–16].

Further details on these registries are provided in Supplement 1.

## Definitions

The diagnosis of atrial fibrillation was based on the ECG algorithms described in Supplement 2. A previous ECG diagnosis of atrial fibrillation in the regional ECG databases or an atrial fibrillation diagnosis within the last five years in the Danish National Patient Registry or Skåne Healthcare Register, determined whether included patients with atrial fibrillation were classified as having known atrial fibrillation. Patients with atrial fibrillation who had redeemed one or more prescriptions of OAC (see Supplement 3) within the 90 days prior to ED contact were also classified as patients with known atrial fibrillation. Patients who presented with atrial fibrillation but had no previous diagnosis of atrial fibrillation in the regional ECG database or in the Danish National Patient Registry or Skåne Health Register and no redeemed prescriptions of OAC in the 90 days prior to the ED contact were classified as having new onset atrial fibrillation.

All discharge diagnoses were extracted from the Danish National Patient Registry or Skåne Healthcare database. Infection was defined using ICD-10 discharge diagnosis codes (see Supplement 3) from the ED or the subsequent hospitalization.

Ischemic stroke was identified by diagnoses (Supplement 3) made from the date of hospital discharge up to 365 days following the ED visit, excluding discharge diagnoses from the index contact.

Date of death was extracted from the Danish Civil Registration System or the Swedish Population Register, examining the period from arrival at the ED until 365 days after ED arrival.

Charlson Comorbidity Index scores [17] were calculated for a 5-year period ending on the day of ED contact.

CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were calculated based on registration of ICD-10 codes (Supplement 3) for congestive heart failure, hypertension, age  $\geq 75$ , diabetes, previous stroke/TIA/thromboembolism, vascular disease, age 65 – 74, and female sex, all during the 5 years previous to ED contact in the

Danish National Patient Registry or the Skåne Healthcare database [18]. Hypertension and diabetes were also based on redeemed prescriptions for antihypertensive or antidiabetic medication within 90 days (Supplement 3).

### **Validation of atrial fibrillation diagnosis-algorithm**

We validated the atrial fibrillation diagnosis algorithm by manually assessing 500 ECGs from the Danish MUSE® database. Two researchers, TGH and AL, blinded and independently evaluated all 500 ECGs. Disagreements were settled by an arrhythmia specialist (AB). The kappa value between the manual evaluation and the MUSE® Marquette 12SL algorithm was then calculated and found to be 0.86 (95% CI, 0.78 – 0.95). The sensitivity of the Marquette 12SL algorithm was 81% (95% CI 67% – 92%), the specificity 99% (95% CI 98% – 99%), the negative predictive value 98% (95% CI 97% – 99%), and the positive predictive value 95% (95% CI 82% – 99%).

### **Exposure and outcome**

The primary exposure was new-onset atrial fibrillation during infection compared to unexposed patients defined as having infection without atrial fibrillation and without redeemed prescriptions for OAC in the 90 days preceding ED contact. Primary outcome was one-year stroke risk, excluding diagnoses from the index contact. Secondary outcomes were 30-day stroke risk, 30-day and one-year mortality for patients with new-onset atrial fibrillation, as well as 30-day and one-year stroke risk and mortality for patients with known atrial fibrillation, either -with or without redeemed prescriptions for OAC in the 90 days prior to index contact.

## Statistics

Continuous data are presented as medians (IQR: interquartile range) and categorical data as proportions with 95% confidence intervals based on a binominal distribution.

All patients with a discharge diagnosis of infection were divided into four mutually exclusive groups: 1) No atrial fibrillation and no current OAC treatment; 2) New-onset atrial fibrillation and no current OAC treatment; 3) Previously known atrial fibrillation and no current OAC treatment; and 4) Previously known atrial fibrillation and a current OAC treatment.

In the analysis of stroke risk, patient history was followed from the ED contact for 30/365 days or until a diagnosis of stroke (after hospital discharge), a redeemed prescription of OAC among patients without OAC before index admission, or death, whichever came first. In the analysis of mortality risk, patients were followed from the ED visit until death or 30/365 days, whichever came first, i.e., without censoring upon OAC initiation.

The association between new-onset atrial fibrillation during infection and stroke or death was evaluated using Cox regression analyses controlling for (i) sex and age, or (ii) CHA<sub>2</sub>DS<sub>2</sub>-VASc score. The analysis of stroke risk includes death as a competing risk. Absolute risk estimates were calculated based on cumulative incidence in the relevant group taking in consideration competing risk of death.

To evaluate the validity of the definitions of ischemic stroke used, we calculated 30-day and one-year HR for ischemic stroke restricted to ICD10 codes I63.0-6 (Supplement 4), also including death as a competing risk.

Statistical analysis was performed using STATA version 15 (StataCorp LP, College Station, Texas).

The study was approved by the Danish Data Protection Agency (No. 2008-58-0035, Journal nr.

15/21632) and the Danish Health Authority (No. 3-3013-1031). In accordance with Swedish law,

the study was approved by the regional ethics review board at Lund and by Region Skåne; this level of review was not required in Denmark.

## RESULTS

### Baseline characteristics

A total of 113,989 individuals had an ECG recorded within 4 hours of ED contact, and after exclusions, 15,505 patients with infection were included in the analysis (Figure 1), of which 48.7% were males. Their median age was 71 years (IQR 56-83).

Atrial fibrillation on the first ECG was found in 2,107 patients (13.6%), of which 822 (39.0%) had new-onset atrial fibrillation without current OAC therapy. Of the patients with infection 1,285 (61.0%) had previously known atrial fibrillation, and 719 (56.0%) of them were not currently on OAC therapy (Table 1). Patients with new-onset atrial fibrillation had a median CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 3 (IQR 2 – 4).

### Stroke risk and mortality

The absolute one-year post-discharge risk of stroke in patients without atrial fibrillation was 2.0% (95% CI 1.7 – 2.2) taking in consideration competing risk of death. Patients with new-onset atrial fibrillation had an absolute one-year stroke risk of 2.7% (95% CI 1.6 – 4.2), an age- and sex-adjusted HR of 1.0 (95% CI 0.6 – 1.6) and a CHA<sub>2</sub>DS<sub>2</sub>-VASc-adjusted one-year stroke HR of 1.1 (95% CI 0.7 – 1.8) compared to patients with infection alone (Table 2). In the new-onset atrial fibrillation group, 190 (23.1%) patients were censored during the one-year follow-up period due to initiation of OAC therapy.

Among patients with known atrial fibrillation, the one-year post-discharge risk of stroke was 6.2% (95% CI 4.3 – 8.6) for patients without OAC treatment before ED contact, and 5.2% (95% CI 3.4 –

7.5) for patients with OAC treatment before ED contact. A Kaplan-Meier plot presents time to stroke in Figure 2, including death as a competing risk.

30-day mortality in patients with no atrial fibrillation or current OAC was 6.5% (95% CI 6.1 – 7.0) and one-year mortality in this group was 17.3% (95% CI 16.7 – 18.0). Mortality for patients with new-onset atrial fibrillation and no current OAC was 14.6% (95% CI 12.3 – 17.2) at 30 days and 29.6% (95% CI 26.5 – 32.8) at one year. Patients with infection and known atrial fibrillation had a 30-day mortality risk of 17.9% (95% CI 15.2 – 21.0) without current OAC therapy and 12.2% (95% CI 9.6 – 15.2) with current OAC therapy, whereas one-year mortality for these groups was 39.5% (95% CI 35.9 – 43.2) and 28.8% (95% CI 25.1 – 32.7), respectively. Crude and adjusted HRs are presented in Table 2.

## DISCUSSION

In this multicentre study we found that ED patients with infection and new-onset atrial fibrillation had a 2.7% absolute one-year stroke risk, but the adjusted HR was not significantly increased compared to infected patients without atrial fibrillation.

Similarly, other studies have researched the association between new-onset atrial fibrillation in patients with infection and ischemic stroke [6–8]. Comparison to other studies remains challenging as setting, exposure and endpoints are different. Previous studies have primarily focused on in-hospital or long-term outcome in sepsis patients. One study focused on the ED and concluded that atrial fibrillation in infected patients was an independent risk factor for major adverse cardiovascular events (MACE) [8]. However this study has not included OAC status in analysis, and MACE included not only ischemic stroke.

Unsurprisingly, stroke risk was closely related to CHA<sub>2</sub>DS<sub>2</sub>-VASc score, and confounder control by CHA<sub>2</sub>DS<sub>2</sub>-VASc, eliminated the small crude increased stroke risk among patients with new-onset atrial fibrillation and infection.

According to European and US guidelines, OAC should be considered in patients with stroke risk factors [4,5]. This was later supported by a study of atrial fibrillation patients that found infection did not affect the base stroke risk [19].

Among patients with infection and known atrial fibrillation, more than 50% were not on OAC.

Unfortunately, we were unable to identify reasons why some patients with known atrial fibrillation did not receive OAC therapy. A UK study [20] showed that patients coded as “resolved atrial fibrillation” remain at a higher risk of stroke than patients without atrial fibrillation. A previous study demonstrated that cumulative atrial fibrillation burden while not on OAC treatment increases

the risk of ischemic stroke [21]. Patients with known atrial fibrillation not receiving OAC had the highest one-year stroke risk and mortality in our study, possibly due to intermittent atrial fibrillation and a relatively high cumulative atrial fibrillation burden. In the present study, we included the first ECG at the ED and there was no information regarding the duration of atrial fibrillation or bleeding risk, which could be a relevant factor when considering OAC initiation.

The clinical significance of the present study is that 13.6% of infected patients had atrial fibrillation in the ED and that almost 40% of these had new-onset atrial fibrillation, yet only 23.1% of the new-onset 40% initiated OAC therapy initiated during follow-up. We do not know if the atrial fibrillation resolved spontaneously before discharge from the hospital. If it did, it is a possible explanation for the low prevalence of OAC treatment.

An ICU-based study reported significantly higher mortality than the present study, with a 30-day and one-year absolute mortality of 35% and 61% for patients with sepsis and new-onset atrial fibrillation [22]. A study based on US claims data also reported a 46.2% one-year absolute mortality in patients with sepsis and new-onset atrial fibrillation [7], which is considerably higher than our one-year mortality of 31.8% for patients with infection and new-onset atrial fibrillation. The variability in mortality risk estimates may reflect the different patient populations at different hospitals, as well as different comorbidities. It may perhaps also reflect differences in case and outcome definitions, especially regarding the severity of infection.

## **Strengths & limitations**

In this multicentre study from two countries, we had a large population size including two academic and two community EDs, increasing the study's generalizability.

Because of the unique personal identification numbers utilized in Scandinavia, we can link data on an individual level between different national registers, achieving complete follow-up including prescriptions and co-morbidities, allowing for confounder control.

The discharge diagnoses of atrial fibrillation, ischemic stroke and infection from the Danish National Patient Register have previously been validated [23–25], with positive predictive values of 93% for atrial fibrillation, 88% for ischemic stroke, and 78% for infection. As false-positive categorizations of infection and stroke occur, a misclassification bias – despite limited numbers – will tend to drive risk estimates towards 1. Manual validation, especially of the stroke cases, would have minimized this risk, but we were unable to perform this due to mandatory anonymization of the data.

When validating the atrial fibrillation diagnosis algorithm, we reached a positive predictive value of 95%, which was similar to previous studies [26], indicating the reliability of computer-based diagnosis of atrial fibrillation. However, the sensitivity was 81%, which means some atrial fibrillation patients were overlooked. This possible misclassification could mean increased risk in our control group and the possibility of falsely reduced risk in our exposure groups.

The design of this study was observational and retrospective, and therefore we can not be certain about the causality between the different entities, and existing residual or unmeasured confounders

cannot be excluded. Since validating our conclusions in a randomized trial would not necessarily be achievable due to ethical concerns, more information is needed to enrich and extend the findings of our study.

We cannot know if patients with new-onset atrial fibrillation had been suffering from an undetected atrial fibrillation prior to their first contact, but this reflects daily clinical life and conditions for decision-making in the ED. Considering that atrial fibrillation is often asymptomatic [27], an underestimation of preexisting atrial fibrillation is possible.

The sensitivity analysis did not significantly change the distribution of events, and it reduced the risk of cerebral hemorrhagic events for those with an I63.9 diagnosis. Infection site was proportionally similar across our groups. The role of infection site and severity regarding outcome could be explored in future studies, but was not the focus of the present study.

## **Conclusion**

In this study, we found that ED patients with infection and new onset atrial fibrillation without current OAC therapy had a 2.7% absolute one-year stroke risk. Stroke events were mainly related to sex and age and risk factors identified by the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, and thus the adjusted HR was not increased in patients with new-onset atrial fibrillation.

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