

BMJ Open Is atrial fibrillation a risk factor for in-hospital cardiac arrest?: a Swedish retrospective cohort study

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ABSTRACT

Introduction Atrial fibrillation (AF) is associated with increased morbidity and mortality. Recent findings suggest that AF is also associated with out-of-hospital cardiac arrest. However, whether that association can be generalised to in-hospital cardiac arrests (IHCA) is still unknown.

Aims To examine whether there is a stronger association with IHCA among hospitalised patients with AF compared with patients without AF.

Materials and methods All adult patients admitted to the Karolinska University Hospital, Stockholm, Sweden during 2014–2015 were included. Data were drawn from their medical file and matched against the Swedish Registry for Cardiopulmonary Resuscitation. Patients who were documented as ever having the International Classification of Diseases, 10th revision code I48 prior to the current hospitalisation were categorised to the AF group and the remaining were categorised to the non-AF group. The primary outcome was occurrence of an IHCA.

Results In all, 102 416 patients were included. Among these, 10% had been diagnosed with AF and <1% (n=326) suffered from an IHCA, only 42 (13%) had a VF/VT. In a multivariable model adjusting for sex, age, CharlsonComorbidity Index score and whether the patients had been admitted electively or urgently, having AF was significantly associated with IHCA (OR 1.760; 95% CI 1.356 to 2.269; p<0.001).

Conclusions Within this observational cohort study, patients with AF had a stronger association with IHCA than patients without AF. AF might be an independent risk factor for IHCA.

INTRODUCTION

Atrial fibrillation (AF) is the most commonly sustained cardiac arrhythmia, estimated to occur in 33.5 million people worldwide, and the prevalence of AF is at least 3% of the adult population in Sweden.^{1 2} Beyond its impact on quality of life, AF is associated with increased morbidity and mortality and is perhaps most known as a risk factor for stroke.^{3–5} But, in patients with AF, stroke/peripheral embolism only accounted for 7% of deaths.⁶ Evidence of the association between AF and sudden cardiac death (SCD) such as out-of-hospital cardiac arrest (OHCA) in the general population has emerged in recent years.^{5 7 8} Cardiac arrest that occurs in-hospital (IHCA) only has

Strengths and limitations of this study

- A strength of the current study relates to the large study population of 100 000 patients ranging from 18 to over 100 years of age and with a wide variety of conditions.
- Strength is the use of International Classification of Diseases, 10th revision (ICD-10) codes to identify exposure and comorbidities and the linkage to validated national registries, which facilitates a complete follow-up.
- Limitations relate to lack of information of ICD-10 codes for 'Diabetes with chronic complications'.

an overall survival of 15%–30%, so preventing it from happening is crucial, yet not an easy task.⁹ Thus, the European Resuscitation Council have adopted a 'chain of prevention' in their Guidelines for Resuscitation,¹⁰ highlighting the areas that hospitals need to focus on in order to better prevent and detect IHCA. One way to prevent IHCA is to monitor patients by using technology such as continuous ECG monitoring, or telemetry. Telemetry was initially used mainly in critically ill patients,¹¹ but today is used to monitor patients with a wide variety of conditions, including AF.¹² However, due to limited resources, not every patient can be monitored and clinically useful criteria for better selection of high-risk patients that benefit from monitoring are needed especially since most emergency response team activations are preceded by cardiac rhythm and rate changes.¹³ While there is evidence of patients with AF having an independently increased risk of OHCA,⁵ to the best of our knowledge, no clinical studies have investigated this relationship in a hospitalised population.

AIM

The primary objective was to examine whether there was an association with IHCA

among patients with AF compared with patients without AF.

METHOD

Study design and settings

This observational cohort study took place at the Karolinska University Hospital in Stockholm, Sweden. Karolinska University Hospital has two sites, Solna and Huddinge, which are about 30 km apart, and host about 750 beds each. Together they have about 50 000 urgent and elective, adult, unique inpatient admissions per year. Inpatient data were retrieved from the electronic patient record database, Karolinska University Hospital's database (KARDA), and were matched against the Swedish Registry for Cardiopulmonary Resuscitation (SRCR). The SRCR is a nationwide, population-based registry that has been collecting data according to Utstein on IHCA from almost all hospitals in Sweden since 2005.^{14 15} Personal identification numbers were used to link information between KARDA and the SRCR. Ethical approval for this study has been granted by the Stockholm Regional Review Board (Dnr 2016/1340-31/2).

Patient and public involvement

The research question and outcome measure was developed in order to guide future clinical practice and public management. No patients were involved in the study design, recruitment to or conduct of the study. Patients admitted to Karolinska University Hospital can assess results of the hospital's studies via internet website and posters on the hospital walls.

Participants

All patients admitted to the Karolinska University Hospital between 1 January 2014 and 31 December 2015 were eligible for this study. Patients under the age of 18 were excluded. In cases where individual patients had been admitted to the hospital on multiple occasions during the study period, only the first occasion was included. The definition of IHCA used by SRCR was used, that is, a hospitalised patient who is unresponsive with apnoea (or agonal, gasping respiration) where cardiopulmonary resuscitation (CPR) and/or defibrillation is initiated.¹⁶ For patients with multiple IHCAs during the same admission, only the first episode was included. Patients who had ever received the diagnosis AF (International Classification of Diseases, 10th revision (ICD-10) code I48) before the admission were defined as cases, and those who had not were defined as controls.

Data collection and categorisation

From KARDA, the following patient characteristics were retrieved: exposure ICD-10 I48 (yes or no), sex, age (in years), whether the admission was elective or urgent, whether the admission came through the emergency department (yes or no), date of death (if any) and dates of admission and discharge. The dates of admission

and discharge were used to calculate the length of stay (in days). In addition, to account for comorbidities, patients were scored using the updated Charlson Comorbidity Index (CCI).¹⁷ This index is a well-established tool for assessing disease burden by assigning weighted points based on the presence of 12 chronic conditions.¹⁷ To calculate this score, information about whether patients had been given any of the diagnoses in the CCI during the 10 years prior to the admission was also retrieved from KARDA. Patients were then matched against the hospital's own reporting to SRCR to get data on whether they have had an IHCA at the Karolinska University Hospital during the study period, and if so, the date of the event and whether the primary rhythm was shockable (ventricle tachycardia (VT) or ventricle fibrillation (VF)) was also recorded. The date of the IHCA and the date of death were used to calculate the 30-day survival.

Statistical analyses

Descriptive statistics with mean/SD and median/IQR were used to describe numerical variables, and proportions for categorical variables. Pearson's χ^2 test was used to test for statistical significance of comparisons between the case group and the control group. To evaluate the association between AF and IHCA, logistic regression models were used to compute ORs with 95% CIs. A univariable logistic regression model with IHCA as the dependent variable and AF as the independent variable was first used to calculate a crude OR with 95% CI, and a multivariable model with AF, sex, age (in years, as a continuous variable), CCI score (as a continuous variable) and the type of admission as the independent variables was then used to calculate an adjusted OR with 95% CI. A sensitivity analysis for heart failure was done with adjustments including age, sex and type of admission. A p value of <0.01 was considered significant. Missing data were kept missing, that is, not imputed. All data processing and analyses were conducted using R V.3.3.2.¹⁸

RESULTS

Study participants

A total of 102 416 unique patients were included in this study. The mean age was 55 years (SD \pm 21; range 18–105) and 58% were women (table 1). Regarding comorbidity, according to the CCI, the median score was 0 (IQR 0–2). Patients were most often admitted urgently (67%). The median length of stay was 2 days (IQR 1–4). Of all patients, 10% (n=10 039) had been diagnosed with AF, that is, included as cases. Although the largest number of patients with AF was found within the age category 70–79 years (n=3224), the proportion of patients with AF increased with age, ranging from <1% among those 18–49 years old to 34% among those aged 90 years or more (figure 1).

Table 1 Characteristics of 102 416 adult patients hospitalised at Karolinska University Hospital 1 January 2014 to 31 December 2015 divided based on if they had or had not had atrial fibrillation defined as ever having received the International Classification of Diseases, 10th revision code I48

	Patients with atrial fibrillation n (%) 10 039 (100)	Patients without atrial fibrillation n (%) 92 377 (100)	P values*
Sex			<0.001
Male	4243 (42)	55 601(60)	
Female	5793 (58)	36 633 (40)	
Unknown	3 (0)	143 (0)	
Age category			<0.001
18–49	337 (3)	41 863 (45)	
50–59	701 (7)	12 055 (13)	
60–69	1875 (19)	15 337 (17)	
70–79	3224 (32)	13 883 (15)	
80–89	2865 (29)	7151 (8)	
≥90	1035 (10)	2031 (2)	
Unknown	2 (0)	57 (0)	
Charlson Comorbidity Index¹⁷			<0.001
Low 0–4 points	9036 (90)	86 179 (93)	
Medium 5–7 points	467 (5)	1326 (1)	
High ≥8 points	536 (5)	4872 (5)	
Type of admission			
Elective	2994 (30)	30 858 (33)	
Urgent	7045 (70)	61 519 (67)	
Length of stay (in days)			<0.001
<10	8689 (87)	85 721 (93)	
10–30	1200 (12)	6065 (7)	
>30	150 (1)	590 (1)	
Unknown	0 (0)	1 (0)	
In-hospital cardiac arrest			
Yes	93 (1)	233 (0)	<0.001
VT/VF	14 (15†)	28 (12†)	0.330
Did not survive to 30 days	58 (62†)	155 (67†)	0.569

*P value assessed with χ^2 test.

†Percentage of in-hospital cardiac arrests.

Differences between those with and those without atrial fibrillation

The majority of patients with AF were men in contrast to the majority of those without AF who were women (table 1, $p<0.001$). Patients with AF had a considerably higher mean age than those without AF (75 years, SD ± 12 and 53 years, SD ± 20 , respectively; $p<0.001$). Moreover, women in the AF group were on average older than men (78 years, SD ± 11 and 73 years, SD ± 12 , respectively, $p<0.001$). As for comorbidities, those with AF had higher CCI scores than those without AF (median CCI scores were 1 (IQR 0–2) and 0 (IQR 0–2), respectively, table 1). Studying each group of comorbidities individually, the

most common group was ‘Any malignancy’, which was prevalent in 25% of those with AF and in 19% of those without (table 2, $p<0.001$). In patients with AF, ‘Heart failure’ and ‘Chronic pulmonary disease’ were second and third most common (present in 25% and 13%, respectively) while ‘Metastatic solid tumour’ and ‘Chronic pulmonary disease’ were corresponding second and third most common once in those without AF (present in 6% and 6%, respectively) (table 2). Regarding heart failure, it was present in 25% of those with AF compared with 3% among those without AF. Furthermore, patients with AF stayed in hospital for slightly longer (median 3 days, IQR 1–6 vs 2 days, IQR 1–4).

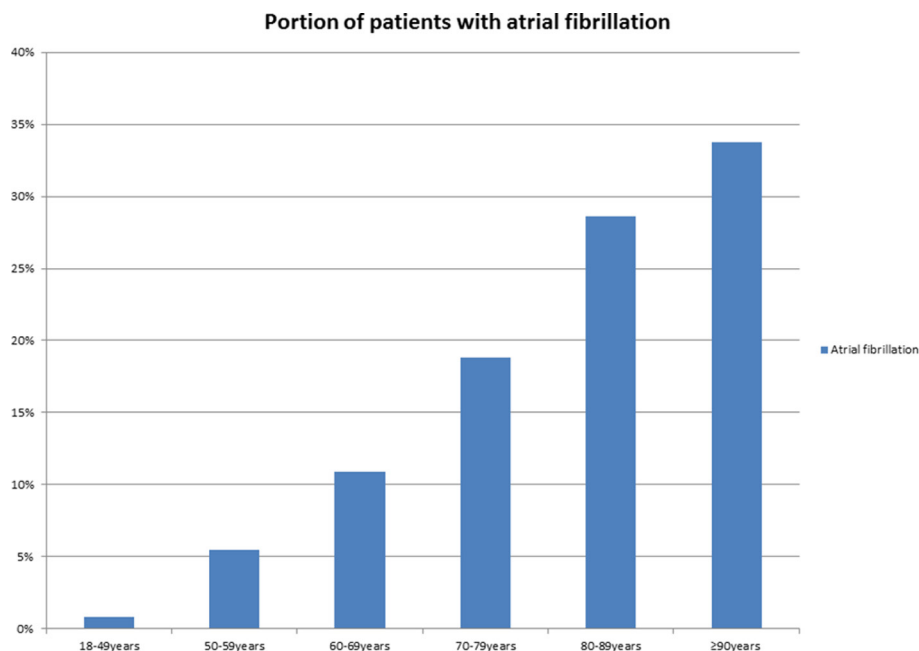


Figure 1 Portion of patients with atrial fibrillation (International Classification of Diseases, 10th revision code I48) among adult hospitalised patients at Karolinska University Hospital 1 January 2014 to 31 December 2015.

Association between atrial fibrillation and in-hospital cardiac arrests

In total, IHCA occurred in <1% (n=326) of the patients during the study period. Almost a third of the patients had AF (29%). The primary rhythm was shockable (VT

or VF) in 15% of those with AF and 12% of those without (p=0.33, table 1). No significant difference regarding 30-day survival after the IHCA was found between those with compared with without AF. Patients with AF had a crude and adjusted significantly higher association with

Table 2 Charlson Comorbidity Index among hospitalised patients at Karolinska University Hospital during 2014–2015

Disease/disease group	ICD-10 code	Points	Atrial fibrillation	
			Yes 10039	No 92377
AIDS/HIV	B20, B21, B22, B23, B24	4	13 (<1)	399 (<1)
Any malignancy, including leukaemia and lymphoma	C0, C1, C2, C3, C40, C41, C43, C45, C46, C47, C48, C49, C5, C6, C70, C71, C72, C73, C74, C75, C76, C80, C81, C82, C83, C84, C85, C883, C887, C889, C900, C901, C91, C92, C93, C940, C941, C942, C943, C9451, C947, C95, C96	2	2464 (25)	17795 (19)
Metastatic solid tumour	C77, C78, C79, C80	6	514 (5)	5098 (6)
Dementia	F00, F01, F02, F051	2	229 (2)	747 (<1)
Hemiplegia or paraplegia	G041, G81, G820, G821, G822	2	94 (1)	717 (<1)
Congestive heart failure	I50	2	2459 (25)	2453 (3)
Chronic pulmonary disease	J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67	1	1310 (13)	5899 (6)
Mild liver disease	K702, K703, K717, K73, K740, K742, K743, K744, K745, K746	2	146 (<1)	895 (<1)
Moderate or severe liver disease	K721, K729, K766, K767	4	158 (<1)	1011 (<1)
Rheumatological disease	M050, M051, M052, M053, M058, M059, M060, M063, M069 M32, M332, M34, M353	1	453 (5)	3280 (4)
Renal disease	N01, N03, N052, N053, N054, N055, N056, N072, N073, N074, N18, N19, N25	1	866 (9)	3314 (4)

ICD-10, International Classification of Diseases, 10th revision.

Table 3 Association between atrial fibrillation and in-hospital cardiac arrest among hospitalised patients at Karolinska University Hospital during 2014–2015

	Crude OR (95% CI)	Adjusted OR (95% CI)*
Atrial fibrillation		
No	1.00 (reference)	1.00 (reference)
Yes	3.70 (2.89 to 4.69)	1.76 (1.36 to 2.27)

*Adjusted for sex, age, Charlson Comorbidity Index¹⁷ and type of admission.

IHCA compared with those without AF (crude OR 3.70, 95% CI 2.89 to 4.69 and adjusted 1.76 (1.36 to 2.27), table 3). A sensitivity analysis for heart failure was done with adjustments including age, sex and type of admission (OR 1.79, 95% CI 1.37 to 2.34).

DISCUSSION

In this observational study of adult hospitalised patients at a large university hospital in Sweden, we found an association with IHCA almost twice as strong in patients with AF compared with those without AF.

To the best of our knowledge, no previous studies have been published investigating the association between AF and cardiac arrest in a hospitalised population. However, several studies have shown AF and its association with cardiac arrest or SCD in various other out-of-hospital populations. In line with our results, Chen *et al*⁸ analysed data from two population-based cohorts and showed that patients with new-onset or incident AF were found to suffer from SCD twice as often as patients without AF. Likewise, in another community-based study, AF has been suspected to predispose for OHCA due to VF.⁷ Regarding IHCA with VF as first rhythm, in our study only a minority suffered such an event, which is in line with earlier findings from Sweden.¹⁴ While not statistically significant due to the small number of patients, this difference may, if found in larger material, be an indication of an inherent proarrhythmic effect of AF. Interestingly and even more sparsely studied is the association to IHCA with pulseless electric activity as first rhythm in patients with AF, and it is possible that tachycardia or bradycardia might be causal. Finally, in line with our study, Odotayo *et al*¹ conducted a systematic review of seven studies on the association between AF and SCD and found an almost doubled pooled relative risk even though there was considerable heterogeneity among the study populations, which supports our finding of an independent association between AF and cardiac arrest.

Though evidence of an association between AF and cardiac arrest has been found in the present study as well as others,^{4 7 8} the association is complex and may be caused by several mechanisms. AF may just be a marker of the presence (or severity) of another cardiovascular condition, with a greater extent of underlying structural

heart disease. The association may also be caused by proarrhythmic side effects of some of the drugs used in AF treatment; however, such data are lacking in our dataset. Another possible explanation is that AF is inherently proarrhythmic and in itself a cause of cardiovascular death.

If the association between AF and cardiac arrest is confounded by another cardiovascular disease, heart failure might very well be the culprit. Coexisting heart failure has been stated as an important confounder and predictor of SCD^{6 19}; in line with previous studies,^{7 8} our results remained after adjustments and our sensitivity analysis for heart failure did not change main outcome. Still, the relationship between AF, heart failure and cardiac arrest is interesting, given that in the present study, heart failure occurred in more than twice as many patients with AF than in those without AF among all who had an IHCA. More studies, especially large prospective ones, are needed in the future to explore this relationship further. Regarding other comorbidities, all the groups of comorbidities included in this study were more commonly found in patients suffering an IHCA than in the entire study population. One important finding from our study is that only about 10% of patients dying while in hospital receive CPR since do-not-attempt-resuscitation decisions such as allow natural death are common.²⁰ Therefore, patients with AF likely do not have a higher general burden of disease to such degree that a cardiac arrest is expected. Interestingly though, in the group of patients with AF, the prevalence of malignancies was higher in the entire group than in those who had an IHCA, which may indicate that more cardiac arrests were triggered by something else, such as AF.

Moreover, some drugs used in the treatment of AF have been reported as having proarrhythmic effects. In a large Cochrane review, some older antiarrhythmic drugs used to convert AF to sinus rhythm and to maintain sinus rhythm, such as sotalol, disopyramide, flecainide and even metoprolol, which also has an opposite association, were associated with an increased risk of mortality and/or an increased rate of proarrhythmic events.²¹ It is also possible that the overuse of some drugs, such as beta-blockers, may cause hypotension, which in turn leads to cardiac arrest. Hypotension has been shown to be the cause of about 7% of IHCAs.¹⁴ The evidence for these links is poor though, and no significant effect has been seen in studies adjusting for drug use.^{7 8 22}

Strengths of the current study relate to the large study population of all hospitalised patients at two physical hospitals totalling to more than 100 000 patients, ranging from 18 to over 100 years of age and with a wide variety of conditions. Other strengths were the use of ICD-10 codes to identify exposure and comorbidities and the linkage to validated national registries, which facilitates a complete follow-up.²³

Limitations relate to first because of a mishap during the retrieval of our data; for one of the conditions, ‘Diabetes with chronic complications’, information was

missing and we were unable to re-retrieve data from KARDA. Hence, the CCI scores in our data are lower than the actual score for some patients (weighted point for the condition diabetes was 1). However, this was a non-differential misclassification since the same was present for both patients with and without AF. Still, diabetes mellitus is a risk factor for AF and they frequently coexist because of associations with other risk factors.¹² Second, AF has been shown to be asymptomatic in many people,²⁴ and so as with every study on the prevalence of AF, our proportion of AF may be underestimated. It was not possible for us to verify the AF diagnoses by ECG recordings. Finally, because of the low number of VT/VF arrests, we were unable to conclude whether the association between AF and IHCA is present in the subgroup of IHCA with VT/VF.

CONCLUSION

In conclusion, within this observational study, patients with AF have a stronger association with in-hospital cardiac arrest than patients without AF. Future studies need to distinguish between paroxysmal, persistent and permanent AF, find the underlying causes of the association as well as further identify risk factors in order to narrow down the population at an increased risk of cardiac arrest.

Contributors AR, JE, AC, PN, MR, JH and TD have directly participated in the planning, execution and analyses of the study. AR and TD designed the study. AR and TD performed acquisition of data. AR and TD performed statistical analysis. AR, JE, AC, PN, MR, JH and TD interpreted the data. AR, JE and TD drafted the manuscript. AR, JE, AC, PN, MR, JH and TD critically revised the manuscript and have read and approved the final version of the submitted manuscript. TD obtained funding. TD supervised the study.

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Competing interests None declared.

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