Hospitalisation patterns change over time in patients with atrial fibrillation

Janne Fristrup Qvist[1], Pernille Høgh Sørensen[2] & Ulrik Dixen[3]

ABSTRACT

INTRODUCTION: Atrial fibrillation (AF) is a cardiac epidemic. In this study, we aimed to describe the causes of hospitalisation in an AF population over time and to study how different AF treatment strategies affected hospitalization.

MATERIAL AND METHODS: This was an observational study in which long-term follow-up data were collected from hospital records, discharge papers and diagnostic codes. The study population (n = 156) was observed over a total period of ten years which was divided into two successive observation periods (OP), OP1 and OP2. Fourteen endpoints of cardiovascular hospitalisations were evaluated.

RESULTS: The causes of hospitalisation shifted over time. We observed a lower proportion of admissions due to AF in OP2 (63%) than in OP1 (87%) and a higher proportion of admissions due to congestive heart failure (16% versus 3%) and of days of inpatient care due to ischaemic stroke (25% versus 7%). Persistent AF where sinus rhythm was pursued was associated with a four-fold increase in the risk of hospitalisation (multivariate Poisson analysis, rate ratio 3.97, 95% confidence interval 2.73-5.76, p < 0.0001) compared with accepted permanent AF.

CONCLUSION: Over time, the causes of hospitalisation in an AF population shifted from AF relapse to the most frequent complications of AF, ischaemic stroke and congestive heart failure. In this observational study, patients treated with rhythm control were more frequently hospitalised than patients treated with rate control.

TRIAL REGISTRATION: not relevant.

FUNDING: not relevant.

Atrial fibrillation (AF) is the most commonly sustained arrhythmia. In Denmark, it is expected that the number of patients with AF will more than double in the 2000-2020 period, and that 1.9% of the entire population will have an AF diagnosis by the year 2020 [1]. The lifetime risk of AF in people over the age of 40 years reaches 25% [2], and the prevalence of AF in 2050 is estimated to increase three-fold due to improved treatment of other heart diseases, better health care and an aging population [3]. AF is associated with excess mortality independently of other cardiovascular diseases [4, 5] and the disease burden is considerable, both for the patients and in terms of health-care costs.

Hospital admissions associated with AF are costly, and one survey estimated that they accounted for more than half of the costs associated with treatment of AF patients [6]. Not many studies have investigated the causes of hospitalisation in an AF population over time. We therefore set out to examine the cardiovascular causes of hospitalisation in a well-described AF population over a ten-year period. Our aims were to describe any change in the causes of hospitalisation over time and to determine if treatment strategy had any influence on this pattern.

MATERIALS AND METHODS

Study sample and design

The study was designed as a ten-year follow-up observational study of a well-characterised group of AF patients. The patient population has been described previously [7]. Patients with electrocardiography (ECG)-documented AF and restored sinus rhythm (SR) at the time of enrollment were included. Patients were accepted for inclusion with successful elective cardioversion of long-lasting (> 48 h) AF to SR, earlier episodes of paroxysmal AF lasting longer than 30 sec. and short-lasting (< 48 h) acute AF with spontaneous, pharmacological or electrical cardioversion to SR. Some patients were included from the outpatient clinic, others after hospitalisation. The exclusion criteria were Parkinson's disease, other neuromuscular disease with tremor causing a high noise level in the signal-averaged ECG-recording measured in the original study [7], pacemaker, psychiatric disease or inability to communicate in Danish or English.

Patients were enrolled in the original study between 1999 and 2001 and received a follow-up visit in 2002 or 2003 (**Figure 1**). The ten-year follow-up was conducted in 2010 and consisted of two observation periods: observation period 1 (OP1) from the first enrollment (1999-2001) to the first follow-up (2002-2003) and observation period 2 (OP2) from the first follow-up (2002-2003) to later follow-up (2010). Patients were only included in the ten-year follow-up study if they had participated in the first follow-up study performed from late 2002 to early 2003 when all patients who were still alive were invited to a follow-up visit with clinical examination. At first follow-up, AF classification was re-evaluated by examination of hospital records and patient interviews. We registered if the patient was treated with

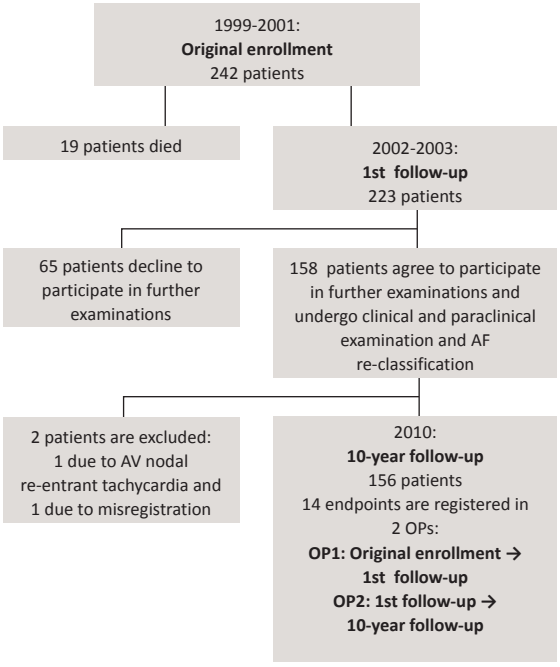
ORIGINAL ARTICLE

1) Department of Cardiology, Herlev Hospital
2) Department of Internal Medicine, Amager Hospital
3) Department of Cardiology, Hvidovre Hospital

Dan Med J 2014;61(1):A4765

FIGURE 1

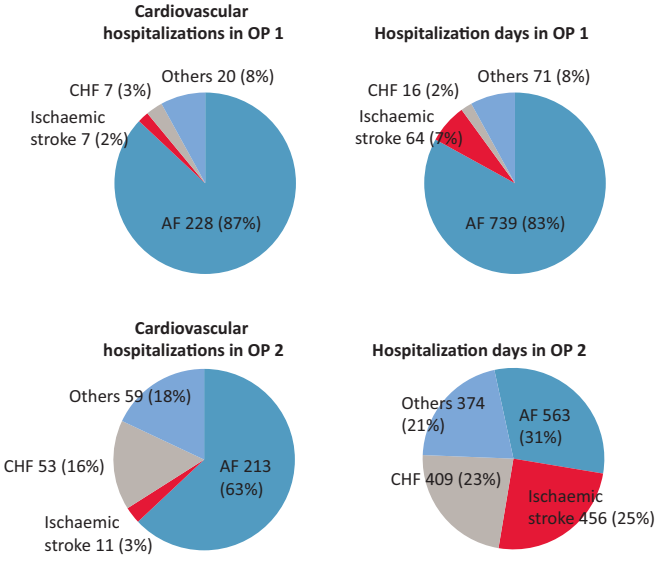
Patients were enrolled in the original study between 1999 and 2001 and received a follow-up visit in 2002 or 2003.



AF = atrial fibrillation; AV = atrioventricular; OP = observation period.

FIGURE 2

The number and length of hospitalisations.



AF = atrial fibrillation; CHF = congestive heart failure; OP 1 = observation period 1; OP 2 = observation period 2.

rhythm control where SR was pursued with antiarrhythmic medical therapy (specific drugs or dosages were not registered), electrical cardioversion or ablation (persistent AF), or if AF was accepted as a permanent condition with no further attempt to restore the sinus rhythm (permanent AF). The enrollment date was the exact date the patient entered the original study; the end of OP1 was the exact date of the first follow-up visit; and the end of OP2 was the date we examined the patient's files or the date at which the patient died or emigrated.

Our data sources included hospital records, discharge papers and diagnostic codes (International Classification of Diseases (ICD)-10 codes). All patients gave written informed consent. The project was a priori approved by the local Ethics Committee and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Clinical evaluations

Paroxysmal AF was defined as AF with spontaneous cardioversion to SR; persistent AF was defined as AF with pursued SR through treatment with antiarrhythmic drugs or electrical cardioversion; and permanent AF was defined as the acceptance of AF without further attempts to restore SR. Endpoints were defined prior to study start and were hospitalisation due to paroxysmal AF, persistent AF, permanent AF, AF of unknown type, ischaemic stroke that included in-hospital rehabilitation, acute myocardial infarction, congestive heart failure, dysregulated anticoagulant treatment without bleeding, dysregulated anticoagulant treatment with bleeding, ablation of AF, pulmonary embolism, pacemaker implantation or pacemaker control and complications to antiarrhythmic treatment of AF and, in addition, we registered cardiac death, non-cardiac death and death of unknown cause. The number of days in hospital for each hospitalisation was registered. Only primary admission diagnoses were considered and only admissions with an overnight stay in hospital and admissions that covered at least two consecutive dates were registered. Two investigators carefully screened data for these endpoints. In case of concomitant admission causes, the most clinically significant diagnosis was registered. Patients with alternating atrial flutter and AF were registered as AF. No patients in this study sample had atrial flutter only.

Statistical analysis

Continuous data are reported as means and standard deviations if normally distributed, and as medians and ranges if non-normally distributed. Discrete data are presented as counts and percentages. Comparisons of groups were performed using t-tests. Univariate and multivariate regression analyses of count data were performed as Poisson regressions. Using backward stepwise regression the multivariate analyses were controlled for AF classification, gender, age, congestive heart failure, ischaemic heart disease, diabetes mellitus, renal insuffi-

ciency (judged from creatinine level), body mass index and hypertension. Data regarding the pharmacological treatment over time for each patient, including anticoagulant treatment, were not available. The dates of enrollment and file examination/death were used to compute time of risk for each patient, and this time of risk was used as an offset in Poisson regressions. To compensate for different lengths of follow-up periods (OP1 and OP2), endpoints are reported as number per 1,000 patient years. A p-value < 0.05 was considered statistically significant. All analyses were performed with the SAS 9.1 statistical package programmes (SAS Institute, Cary, NC, USA).

Trial registration: not relevant

RESULTS

Patient characteristics

The study population is described in **Table 1**. The mean duration of OP1 (from enrollment to first follow-up) was 2.9 years (0.7). All types of co-morbidity were more common at first follow-up than at enrollment (Table 1). Patients were only included in this study if they had participated in the first follow-up visit. These patients did not differ from the original larger cohort (242 patients) on any characteristic. Progression to permanent AF at the first follow-up had occurred in 29% of patients (Table 1). At the first follow-up, patients with persistent AF and permanent AF were comparable on many variables and differed only in age (patients with persistent AF were younger) and the prevalence of diabetes mellitus and congestive heart failure (diabetes mellitus was more common and congestive heart failure was less common in patients with persistent AF than in patients with permanent AF, Table 1).

TABLE 1

The characteristics of 156 patients who were included in original enrollment in 1999-2001 and the first follow-up in 2002-2003 and the characteristics of the subgroups of these patients with persistent and permanent atrial fibrillation (AF) at the first follow-up.

	Original inclusion 1999-2001 (N = 156)	1st follow-up 2002-2003 (N = 156)	Persistent AF 2002-2003 (N = 92)	Permanent AF 2002-2003 (N = 45)	p-value[a]
Hypertension, n (%)	54 (35)	70 (45)	40 (43)	19 (42)	0.79
Congestive heart failure, n (%)	37 (24)	47 (30)	21 (23)	23 (50)	< 0.05
Ischaemic heart disease, n (%)	28 (18)	29 (19)	16 (17)	8 (18)	0.96
Diabetes mellitus, n (%)	10 (6)	18 (12)	14 (15)	2 (4)	< 0.05
Chronic obstructive pulmonary disease, n (%)	11 (7)	14 (9)	8 (9)	5 (11)	0.65
Gender, male/female, n (%)	107 (69) /49 (31)	107 (69) /49 (31)	62 (71) /27 (29)	31 (69) /14 (31)	–
AF classification, paroxysmal/ persistent/ permanent, n (%)	20 (13) /136 (87) /0 (0)	19 (12) /92 (60) /45 (29)	–	–	–
Age, yrs, mean (± SD)	64 (± 12)	66 (± 11)	64 (± 11)	70 (± 9)	< 0.05
Time with AF diagnosis, yrs, mean (± SD)	2.1 (± 2.9)	–	–	–	–

SD = standard deviation.
a) t-test, persistent AF vs permanent AF.

Observation periods

The mean (± standard deviation (SD)) duration of the entire observation period (OP1 and OP2) was 9.2 (2.0) years. Overall, 598 endpoints were registered (262 in OP1 and 336 in OP2).

Descriptive analysis – changes over time

The mean (± SD) duration of OP1 and OP2 was 2.9 (0.7) years and 6.3 (1.8) years, respectively. With a cohort of 156 patients, the total time of risk in the two observation periods was 1,428 patient years: 445 patient years in OP1 and 983 patient years in OP2. The number and length of hospitalisations are illustrated in **Figure 2**. There were 2,692 hospitalisation days in the entire period: 890 days in OP1 and 1,802 days in OP2. There were 472 admissions per 1,000 patient years in OP1 and 341 admissions per 1,000 patient years in OP2.

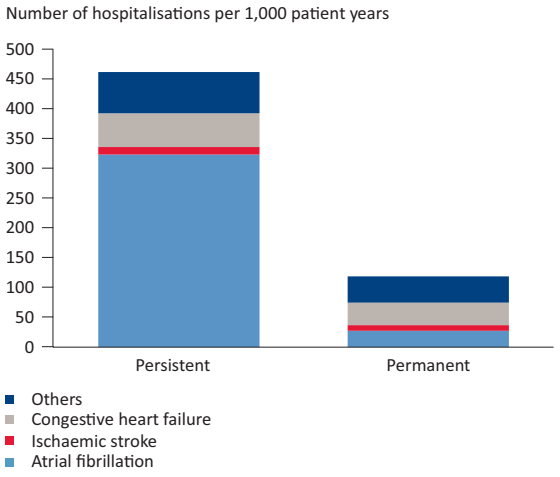
There was a shift in the cause of hospitalisation from OP1 to OP2 (Figure 2). In OP1, AF accounted for 87% of hospitalisations, but this was reduced to 63% in OP2. Hospitalisations due to congestive heart failure increased from 3% in OP1 to 16% in OP2, and hospitalisations due to ischaemic stroke increased from 2% in OP1 to 3% in OP2 (Figure 2). The proportion of days spent in hospital after admission due to AF decreased from 83% in OP1 to 31% in OP2, and the proportion of days spent in hospital due to congestive heart failure and ischaemic stroke increased from 2% to 23% and from 7% to 25%, respectively (Figure 2).

The causes of hospitalisation in OP2 were different in patients with persistent and permanent AF, respectively (**Figure 3**). Among patients with persistent AF, there were 461 hospitalisations per 1,000 patient years; and in patients with permanent AF, there were 120 hospitalisations per 1,000 patient years (Figure 3). The number of hospitalisations due to AF was 323 per 1,000 patient years in patients with persistent AF, and 29 per 1,000 patient years in patients with permanent AF and the number of hospitalisations due to congestive heart failure was 54 per 1,000 patient years in patients with persistent AF and 40 per 1,000 patient years in patients with permanent AF (Figure 3).

Multivariate Poisson analyses showed that persistent AF was associated with a higher risk of admission due to all types of AF (paroxysmal, persistent, and permanent) than permanent AF (rate ratio 10.08, 95% confidence interval 4.94-20.58, p < 0.0001) and a higher risk of admission due to all endpoints (rate ratio 3.97, 95% confidence interval 3.73-5.76, p < 0.0001).

FIGURE 3

Cardiovascular hospitalisations in observation period 2 in patients with persistent and permanent atrial fibrillation.



DISCUSSION

Our main finding is that the causes of hospitalisation in AF patients change over time and that the risk of hospitalisation is significantly affected by treatment strategy.

We observed a decrease in the number of hospitalisations and the number of days spent in hospital from OP1 to OP2, and a marked shift from hospitalisations due to AF relapse towards hospitalisations caused by the complications of the arrhythmia, primarily ischaemic stroke, and congestive heart failure. To our knowledge, no other studies have described hospitalisation patterns in an AF population over this length of time with such detailed hospitalisation data.

The Framingham Heart Study reported that mortality was higher in AF patients and that stroke occurred more often in AF patients than in non-AF patients [8, 9]. Other studies have focused on decreased quality of life in AF patients [10-12]. However, hospitalisation is also important, both for the patient and in terms of healthcare costs. It has been argued that the number of hospitalisations and the number of days spent in hospital are more relevant endpoints in AF trials than whether or not SR is maintained [13]. Furthermore, cardiovascular hospitalisation is a valid surrogate endpoint for mortality [14].

With an increasing AF population, the hospitalisation pattern in AF patients is of significant economic importance. The hospitalisation pattern in our study population changed from relapsing AF towards AF complications over time. Notably, one of four days spent in hospital in OP2 was caused by ischaemic stroke. In OP1, there were seven hospital admissions due to computed tomography-verified ischaemic strokes; and in OP2, there were 11, and these led to 64 and 456 days in hospital, respectively. These data are in line with the data reported by Petty et al who established that AF patients with stroke had a worse prognosis than non-AF patients with stroke [15].

The other serious complication of AF is congestive heart failure, although it has been debated whether AF or congestive heart failure is the first to appear, i.e. the chicken-and-egg debate. The more severe the congestive heart failure, the more likely patients are to develop AF [16]. We observed a minor increase in the prevalence of congestive heart failure over time, from 24% at original enrollment to 30% at the first follow-up, without a rise in the proportion of patients with ischaemic heart disease. This supports the hypothesis that AF itself begets congestive heart failure in some patients. Patients with persistent AF were hospitalised more often with congestive heart failure in OP2 than patients with permanent AF, even though the diagnosis of congestive heart failure was more common in patients with permanent AF. More patients with persistent AF developed congestive heart failure during OP2.

Patients who debut with congestive heart failure are more often hospitalised than patients already diagnosed with congestive heart failure for whom anti-congestive treatment is already well established.

The ongoing debate as to whether rate control or rhythm control is the optimal AF treatment strategy has taken many turns. In most patients, SR will be pursued if the patient has symptoms during arrhythmia. Conversely, in patients with acceptable symptoms or no symptoms at all after regulation of the ventricular rate, permanent AF is accepted and only the ventricular rate is treated. In this observational design, we found increased admission rates in patients with persistent AF compared with patients with accepted permanent AF. Counting the admissions, the risk of hospitalisation rate was equal to one hospitalisation every second year for patients with persistent AF versus one hospitalisation every tenth year for patients with permanent AF.

This is in accordance with data from large-scale randomised studies such as the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study and other clinical trials that have investigated the effect of treatment strategy on hospitalisation rates in AF patients [17, 18]. In the present study, patients with persistent AF were younger and had a lower prevalence of concomitant congestive heart failure than patients with permanent AF at the first follow-up visit in 2002 and 2003, and they would therefore be expected to have fewer hospital admissions. Although the present study was limited by its observational design, the increased frequency of hospitalisations due to AF in the setting of

pursued SR appears to be caused by the treatment strategy.

The primary limitation of this study is its observational design. Lack of data on specific pharmacologically treatment is also a study limitation. In addition, the reduced use of electrical cardioversion and rhythm control in general after publication of the AFFIRM study and similar AF strategy studies [19, 20] within our observation period might have affected the hospitalisation pattern.

In conclusion, the causes of hospitalisation within an AF population changed over time from primarily being relapses of arrhythmia towards a more prominent role for the most feared AF complications, namely ischaemic stroke and congestive heart failure. This underlines the importance of prophylactic anticoagulation. Our observational study confirmed previous results from randomised studies reporting a reduced risk of hospitalisation when permanent AF was accepted.

CORRESPONDENCE: *Janne Fristrup Qvist,* Kardiologisk Afdeling, Herlev Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark. E-mail: janneqvist@gmail.com

ACCEPTED: 6 November 2013

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk.

ACKNOWLEDGEMENTS: We would like to extend our gratitude to *Steen Ladelund* for theoretical development of statistical models and supervision of the statistical analyses.

LITERATURE

1. Koch MB, Davidsen M, Juel K. Hjertekarsygdomme i Danmark, forekomst og udvikling 2000-2009: National Institute of Public Health, University of Southern Denmark. www.hjerteforeningen.dk/files/Rapporter_mm/Hjertekarsygdomme%20i%20Danmark.%20Forekomst%20og%20udvikling%202000-2009.pdf (1 May 2013).
2. Lloyd-Jones DM, Wang TJ, Leip EP et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. Circulation 2004;110:1042-6.
3. Stefansdottir H, Aspelund T, Gudnason V et al. Trends in the incidence and prevalence of atrial fibrillation in Iceland and future projections. Europace 2011;13:1110-7.
4. Benjamin EJ, Wolf PA, D'Agostino RB et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946-52.
5. Miyasaka Y, Barnes ME, Gersh BJ et al. Coronary ischemic events after first atrial fibrillation: risk and survival. Am J Med 2007;120:357-63.
6. Le Heuzey JY, Paziaud O, Piot O et al. Cost of care distribution in atrial fibrillation patients: the COCAF study. Am J Med 2004;147:121-6.
7. Dixen U, Ravn LS, Soeby-Rasmussen C et al. Raised plasma aldosterone and natriuretic peptides in atrial fibrillation. Cardiology 2007;108:35-9.
8. Benjamin EJ, Wolf PA, D'Agostino RB et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946-52.
9. Wolf PA, Abbott RD, Kannel WB et al. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983-8.
10. Steg PG, Alam S, Chiang CE et al. Symptoms, functional status and quality of life in patients with controlled and uncontrolled atrial fibrillation: data from the RealiseAF cross-sectional international registry. Heart 2012;98:195-201.
11. Dąbrowski R, Smolis-Bąk E, Kowalik I et al. Quality of life and depression in patients with different patterns of atrial fibrillation. Kardiol Pol 2010;68:1133-9.
12. Reynolds MR, Morais E, Zimetbaum P et al. Impact of hospitalization on health-related quality of life in atrial fibrillation patients in Canada and the United States: results from an observational registry. Am Heart J 2010;160:752-8.
13. Le Heuzey JY. Hospitalization: a relevant endpoint in atrial fibrillation management? Europace 2011;13:1061-2.
14. Friberg L, Rosenqvist M. Cardiovascular hospitalization as a surrogate endpoint for mortality in studies of atrial fibrillation: report from the Stockholm Cohort Study of Atrial Fibrillation. Europace 2011;13:626-33.
15. Petty GW, Brown RD Jr, Whisnant JP et al. Ischemic stroke subtypes : a population-based study of functional outcome, survival, and recurrence. Stroke 2000;31:1062-8.
16. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91:2D-8D.
17. Wyse DG, Slee A, Epstein AE et al. Alternative endpoints for mortality in studies of patients with atrial fibrillation: the AFFIRM study experience. Heart Rhythm 2004;1:531-7.
18. Roy D, Talajic M, Nattel S et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358:2667-77.
19. Wyse DG, Waldo AL, DiMarco JP et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33.
20. Van Gelder IC, Hagens VE, Bosker HA et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002;347:1834-40.