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Atrial Fibrillation at an Internal Medicine Ward: Clinical and Prognostic Implications

Miriam Shteinshnaider [1], Dorit Almoznino-Sarafian [1], Irena Alon [1], Irma Tzur [1], Sylvia Berman [2], Natan Cohen [1], Oleg Gorelik [1]

[1] Department of Internal Medicine "F", and [2] Research & Development Division and Department of Nephrology, Assaf Harofeh Medical Center (affiliated to Sackler School of Medicine, Tel Aviv University), Zerifin, Israel

Abstract

Background: Little is known about atrial fibrillation (AF) appearing during hospitalization in an Internal Medicine ward.
Purpose: We aimed to investigate characteristics and prognostic significance of in-hospital onset AF.
Methods: We studied 249 consecutive unselected patients admitted to this medical department with paroxysmal or persistent AF (out-of-hospital group) or AF developed during hospitalization (in-hospital group). Demographic, clinical, laboratory, electrocardiographic and echocardiographic data and all-cause mortality following discharge were recorded and compared between the groups
Results: Diabetes mellitus (p=0.05), renal dysfunction (p<0.001), chronic lung disease (p=0.03) and history of stroke (p=0.01) were found more common in the in-hospital group (56 patients), compared to the out-of-hospital group (193 patients). Patients from the in-hospital group were more likely to have recurrent episodes of AF during hospitalization (p=0.002), were more frequently treated with amiodarone (p<0.001), discharged in sinus rhythm (p=0.04) and with medications for rhythm control (p=0.04). Time from onset to termination of AF (p<0.001) and hospital stay (p<0.001) were longer in the in-hospital group. On a median of 39-months follow-up, survival rate was lower in the in-hospital vs. out-of-hospital group (69.6% vs. 81.3%, p=0.025). Older age was significantly associated with shorter survival in the in-hospital group [odds ratio (OR)=1.87, 95% confidence interval (CI) 1.15–3.03, p=0.009]. In the out-of-hospital group, advanced age (OR=2.17, 95%CI 1.51–3.10, p<0.001), no prior AF episode (OR=3.41, 95%CI 1.56–7.46, p=0.002), diabetes mellitus (OR=2.22, 95%CI 1.12–4.39, p=0.006) and renal dysfunction (OR=2.44, 95%CI 1.10–5.38, p=0.049) were significantly associated with shorter survival.

Conclusion: Patients developing in-hospital AF differed from subjects hospitalized for AF with respect to the severity of the clinical profile and prognosis.

Key words: Atrial fibrillation; Hospital; Prognosis; Survival

Corresponding Address : Department of Internal Medicine "F", Assaf Harofeh Medical Center, 70300 Zerifin, Israel.

Introduction

Atrial fibrillation (AF) is the most common significant cardiac rhythm disorder in clinical practice.[1–5] Hemodynamic impairment and thromboembolic events in AF result in significant morbidity and mortality.[1–5] AF occurs more frequently in the presence of concomitant cardiovascular and non-cardiovascular illnesses, and its clinical presentation is heterogeneous.[2–5]

A number of previously published studies describe increased morbidity and mortality in a variety of patient populations developing AF during hospitalization, including those after cardiac or non-cardiac surgery,[6–8] as well as those admitted with acute coronary syndromes and heart failure (HF).[9–12]

AF is a common reason for admission to an internal medicine department for appropriate evaluation and treatment. However, AF may also appear following hospital admission for various comorbidities. Such patients characteristically have multiple risk factors for onset of AF during hospitalization. These may include advanced age, cardiovascular diseases, electrolyte abnormalities and other acute medical conditions. Surprisingly, the detailed clinical profile of patients developing AF during hospitalization at an internal medicine ward, as well as the prognostic significance of AF in this context, has not been sufficiently investigated. The single available retrospective study recently published, describes increased short-term mortality in 24 male patients who developed AF during hospitalization in internal medicine ward.[13]

In the present investigation we prospectively evaluated various clinical and prognostic aspects associated with in-hospital development of AF in patients admitted to our medical department for various acute medical illnesses. This patient cohort was compared to a group of patients specifically admitted with AF initially developed out of the hospital setting.

Methods

Study Design

Study population included 249 adult patients. They were admitted to the Emergency Department due to a variety of medical disorders and then randomly selected to be hospitalized in our department, one of the six Departments of Internal Medicine in our Medical Center. All patients having paroxysmal or persistent AF at the time of admission, irrespective of reason for admission, were included in the out-of-hospital group (193 patients). The other group (56 patients) developed AF during hospitalization (in-hospital group). Patients with unknown AF duration and permanent AF were excluded from this study. Informed consent was obtained from each patient. The study was carried out in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee.

Data Collection

Demographic, clinical, electrocardiographic (ECG), chest X-ray and laboratory data of the patients were recorded following admission. During hospitalization, echocardiographic data were also collected from standard color two-dimensional and Doppler echocardiographic recordings. On discharge, additional data, including the main underlying cause of AF, recurrent in-hospital AF episodes, time from AF onset to conversion to sinus rhythm, ECG rhythm, duration of hospital stay, recommended medications and in-hospital mortality, were registered. Following discharge, all-cause mortality was recorded and death was confirmed by hospital or outpatient death certificates. At the end of follow-up period extending up to 5 years, the collected data were subjected to statistical analysis.

Definitions

Anemia, according to the World Health Organization criteria, was defined as a hemoglobin concentration of <13 g/dl in men and <12 g/dl in women. Renal function was assessed by estimating glomerular filtration rate (GFR) using the Modification of Diet in Renal Disease (MDRD) equation.[14] Renal dysfunction (RD) was defined as GFR <60 ml/min/1.73m^2. Cardiac conduction disturbances included bundle-branch blocks. Valvular disorder was defined as a moderate or severe insufficiency and/or stenosis of any cardiac valve.

Table 1 Characteristics of the patients enrolled in the study

Variable	Entire group (n=249)	In-hospital group (n=56)	Out-of-hospital group (n=193)	p[a]
Age (years)	69.9 ± 15	71.3 ± 13.4	67.8 ± 14	0.09
Male sex	50.2%	50%	50.5%	1.0
Main reasons for admission				
AF	55.8%	0%	72%	**<0.001**
Infection	15.6%	48.2%	6.2%	
Exacerbation of heart failure	11.6%	17.8%	9.8%	
Acute coronary syndrome	10.4%	16%	8.8%	
Stroke	2.4%	8.9%	0.5%	
Other	4.2%	9.1%	2.7%	
Chronic conditions				
Prior episodes of AF	48.5%	48.2%	48.5%	1.0
Hypertension	62.2%	60.7%	67.5%	0.3
Dyslipidemia	60%	64%	59.3%	0.5
Coronary artery disease	32.9%	30.4%	33.7%	0.6
Diabetes mellitus	31.7%	42.9%	28.4%	**0.05**
Anemia	22.5%	30.4%	20.1%	0.1
Heart failure	20%	26.8%	18.6%	0.2
Renal dysfunction	42%	64.3%	36.3%	**<0.001**
Current smoking	15.2%	16.1%	15%	0.8
Chronic lung disease	14.8%	25%	12.4%	**0.03**
History of stroke	12.4%	23.2%	9.8%	**0.01**
Medications prescribed before admission				
ACE-inhibitors/angiotensin receptor blockers	45.3%	46.4%	44.8%	0.9
β-receptor blockers	45.3%	50%	44.3%	0.5
Calcium channel blockers	29.7%	28.6%	30.4%	0.9
Anti-arrhythmic drugs	20.4%	25%	20%	0.4
Statins	38.5%	39.3%	38.9%	1.0
Furosemide	20.8%	28.6%	19.1%	0.1
Thiazide diuretics	16.4%	8.9%	19.1%	0.1
Anti-platelet agents	57.8%	55.4%	58.8%	0.6
Anticoagulants	13.2%	19.6%	11.9%	0.2
Clinical data on admission				
Body temperature (°C)	36.7 ± 0.6	36.9 ± 0.7	36.6 ± 0.5	**0.004**
Heart rate (beats/min)	113 ± 28	121 ± 25	111 ± 29	**0.02**
Respiratory rate (breaths/min)	18 ± 5	20.8 ± 6	17.2 ± 4	**<0.001**
Oxygen saturation (%)	96 ± 5	94.8 ± 7	96.8 ± 4	0.1

Blood pressure (mm Hg)				
Systolic	136.6 ± 26	136.2 ± 31	136.7 ± 25	0.9
Diastolic	78 ± 17	75.1 ± 16	79.2 ± 16	0.09
Laboratory data on admission				
Serum glucose (normal 75-110 mg/dl)	131.1 ± 50	134.9 ± 59	130 ± 47	0.5
Serum sodium (normal 136-146 mmol/l)	138.5 ± 4	138.1 ± 4	138.6 ± 4	0.4
Serum potassium (normal 3.3-5.1 mmol/l)	4.1 ± 0.5	4.2 ± 0.5	4.1 ± 0.5	0.7
Serum magnesium (normal 1.7-2.55 mg/dl)	2.01 ± 0.2	2.0 ± 0.3	2.0 ± 0.2	0.8
Serum creatinine (normal 0.5-0.9 mg/dl)	1.04 ± 0.4	1.12 ± 0.4	1.02 ± 0.4	0.07
Estimated GFR (normal >60 ml/min/1.73m2)	70.1 ± 27.2	66.0 ± 34.8	71.3 ± 24.6	0.2
Serum albumin (normal 40-53 g/l)	39.8 ± 5	37.6 ± 7	40.4 ± 4	**0.007**
Serum cholesterol (normal 140-200 mg/dl)	179.2 ± 50	164.7 ± 51	184.3 ± 47	**0.01**
Serum triglycerides (normal 30-150 mg/dl)	142.7 ± 97	138.8 ± 99	143 ± 97	0.7
Serum C-reactive protein (normal 0.2-5.0 mg/l)	29.8 ± 53	41.9 ± 67.3	26.2 ± 47.2	**0.02**
ESR (normal 0-30 mm/h)	33.3 ± 26	46 ± 29	30.2 ± 24	**0.006**
Blood hemoglobin (normal 13.0-16.2 g/dl)	13.1 ± 1.7	12.6 ± 1.7	13.3 ± 1.7	**0.003**
White blood cell count (normal 4.0-11.0x109/l)	8.9 ± 3.6	10.0 ± 3.8	8.6 ± 3.3	**0.01**
TSH (normal 0.3-4.2 mIU/l)	1.87 ± 1.6	1.9 ± 1.8	1.9 ± 1.6	0.9
Treatment for AF during hospitalization				
Amiodarone	52.6%	75%	46.4%	**<0.001**
Propafenone	11.6%	10.4%	12.4%	**0.8**
Calcium channel blockers	23.2%	19.6%	24.7%	**0.5**
Digoxin	14.8%	14.3%	15.5%	1.0
β-receptor blockers	14.4%	10.7%	16%	0.4
Electric cardioversion	4.4%	5.4%	4.6%	0.7
Electrocardiographic data Cardiac conduction disturbances during AF				
Right bundle branch block	16.9%	18.2%	16.5%	0.8
Left bundle branch block	7.6%	10.9%	6.7%	0.4
Recurrent AF during hospitalization	10.8%	23.2%	7.2%	**0.002**
Rhythm on discharge				
Sinus rhythm	88.1%	96.1%	85.9%	**0.04**
AF	11.9%	3.9%	14.1%	
Echocardiographic data				
LVEF (%)	55.7 ± 9.0	56.7 ± 7.5	55.4 ± 9.4	**0.4**
Decreased (<50%) LVEF	14.4%	10.2%	15.6%	**0.5**
Preserved (≥50%) LVEF	85.6%	89.2%	84.4%	0.5
Left atrial diameter (mm)	41 ± 6.1	41 ± 6.2	40.8 ± 5.8	0.8
Segmental wall motion abnormalities	25.9%	25%	27%	0.8
Significant valvular disorders	19.3%	19.6%	19.2%	0.8
Time from onset to termination of AF (h)	36 ± 46	58.4 ± 47.0	25.5 ± 28.8	**<0.001**
Duration of hospital stay (days)	5.6 ± 4.6	8.7 ± 5.5	4.7 ± 4.0	**<0.001**

Medications prescribed on discharge				
Anti-arrhythmic drugs	77.5%	90%	76.7%	**0.04**
β-receptor blockers	36.5%	24%	41.7%	**0.02**
Calcium channel blockers	27.7%	36%	27.1%	**0.2**
Digoxin	2.1%	2%	2.6%	0.5
ACE-inhibitors/angiotensin receptor blockers	39%	44%	37.5%	0.4
Statins	44.9%	46.2%	46.1%	1.0
Diuretics	42.1%	48%	42.7%	0.5
Anti-platelet agents	65.3%	58%	67.2%	0.2
Anticoagulants	31.9%	38%	30%	0.3

Data are presented as Mean ± SD or percentages of presenting cases. a Statistical comparison between groups of patients with in-hospital vs. out-of-hospital AF. AF: atrial fibrillation, ACE: angiotensin-converting enzyme, GFR: glomerular filtration rate, ESR: erythrocyte sedimentation rate, TSH: thyroid-stimulating hormone, LVEF: left ventricular ejection fraction

Statistical Analysis

Statistical evaluation of the results was performed by comparing the data obtained for the entire AF patient group with those separately obtained for the in-hospital and for the out-of-hospital AF groups. Univariate analysis was applied using Pearson's chi-square or Fisher's exact tests, as appropriate, for statistical comparison of discrete variables. Analysis of Variance (ANOVA) was adopted for continuous variables. To determine the prognostic significance of the variables, survival curves were plotted using the Kaplan-Meier estimate. Mantel-Cox and Breslow tests were applied to evaluate the differences between the curves. Variables significantly associated with survival when using the Kaplan-Meier estimate ($p<0.1$) were reevaluated by Cox proportional-hazards model, to identify the variables most significantly associated with mortality. A p-value ≤0.05 was considered statistically significant. The data were analyzed using BMDP Statistical Software.[15]

Results

Characteristics of the patients

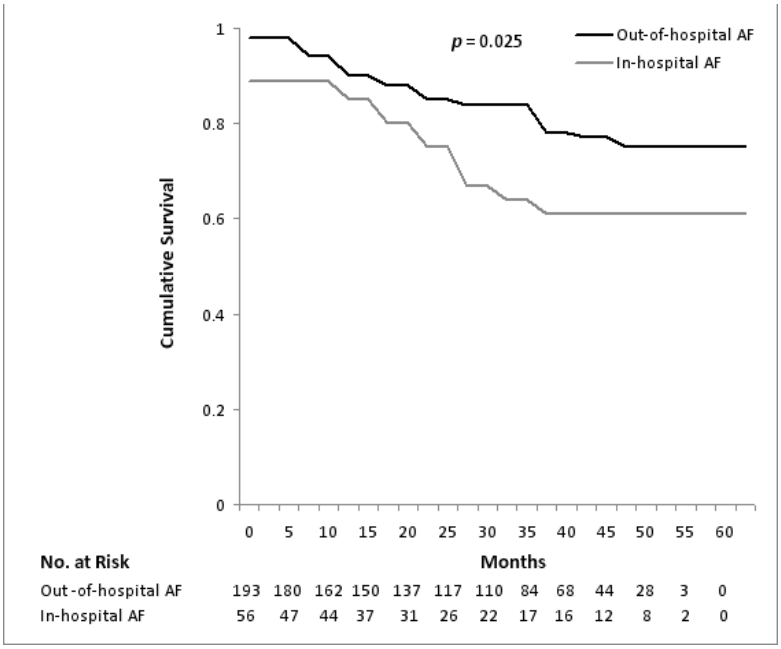
Demographic, clinical, laboratory, electrocardiographic and echocardiographic data of the patients with acute onset (paroxysmal or persistent) AF are presented in Table 1. Out of the total of 249 patients, 193 (77.5%) belonged to the out-of-hospital group and 56 (22.5%) constituted the in-hospital group. No significant differences in mean age or sex between the study groups were recorded.

Infection, exacerbated HF, acute coronary syndrome and stroke were more frequent reasons for admission in the in-hospital compared to the out-of-hospital group. Clinical profiles of the patients were also diverse. Thus, diabetes mellitus (DM), chronic lung disease, RD and history of stroke were found more common in the in-hospital group compared to the out-of-hospital group [42.9% vs. 28.4% ($p=0.05$), 25% vs. 12.4% ($p=0.03$), 64.3% vs. 36.3% ($p<0.001$), and 23.2% vs. 9.8% ($p=0.01$), respectively]. Patients in the in-hospital group had higher mean body temperature, heart and respiratory rates on admission [36.9 ± 0.7 vs. 36.6 ± 0.5 °C ($p=0.004$), 121 ± 25 vs. 111 ± 29 beats/min ($p=0.02$), and 20.8 ± 6 vs. 17.2 ± 4 breaths/min ($p<0.001$), respectively]. The relevant treatments before admission were not significantly different between the groups.

Significant differences between the two groups were also observed with respect to some laboratory data. Thus, patients in the in-hospital group had lower mean levels of blood hemoglobin (12.6 ± 1.7 vs. 13.3 ± 1.7 g/dl, $p=0.003$), serum albumin (37.6 ± 7 vs. 40.4 ± 4 g/l, $p=0.007$) or serum cholesterol (164.7 ± 51 vs. 184.3 ± 47 mg/dl, $p=0.01$), and higher mean values of serum C-reactive protein (CRP, 41.9 ± 67.3 vs. 26.2 ± 47.2 mg/l, $p=0.02$), erythrocyte sedimentation rate (46 ± 29 vs. 30.2 ± 24 mm/h, $p=0.006$) or white blood cell count (10.0 ± 3.8 vs. 8.6 ± 3.3 x109/l, $p=0.01$).

Patients from the in-hospital group had more frequent episodes of recurrent AF during hos-

Figure 1: . The Kaplan-Meier estimates of survival it the in-hospital vs. out-of-hospital AF groups. AF: atrial fibrillation



pitalization (23.2% vs. 7.2%, p=0.002). However, they were more likely to be discharged with sinus rhythm (96.1% vs. 85.9%, p=0.04) or with medications for rhythm control (90% vs. 76.7%, p=0.04). Mean time from the onset to termination of AF was significantly longer in the in-hospital group (58.4 ± 47 vs. 25.5 ± 25.8 hours, p<0.001). Mean time elapsing from the admission to the onset of AF in the in-hospital group was 27.8 ± 41.4 hours. The in-hospital AF patient group also needed prolonged mean hospital stay (8.7 ± 5.5 vs. 4.7 ± 4 days, p<0.001). Among the anti-arrhythmic drugs administered for treatment of AF, amiodarone was more frequently prescribed to the in-hospital patients compared to the out-of-hospital group (75% vs. 46.4%, p<0.001).

Survival

Mean and median follow-up periods in whole patient group were 56.7 and 39 months, respectively. Eight patients died during hospitalization (6 of them of sepsis or pneumonia, one of ischemic stroke and one of advanced malignancy). During the follow-up period, 53 out of 249 (22.3%) patients died. Survival rates for the first three years were 90%, 85% and 78%, respectively.

Fig.1 illustrates the survival rate curves for the two investigation groups. It can be seen that in-hospital AF was associated with decreased long-term survival (p=0.025). The mean respective survival time and survival rate were, respectively, 39.6 months and 69.6% in the in-hospital group vs. 47.1 months and 81.3% in the out-of-hospital group.

Variables Associated with Survival: Univariate Analysis

Variables associated with decreased survival in the entire group were: older age, DM, RD and decreased left ventricular ejection fraction (LVEF) (p=0.01, 0.025, 0.007 and 0.005, respectively). Treatment with statins (p=0.025) and recurrent AF prior to admission (p=0.02) were associated with better survival [Table 2].

When the two groups were analyzed separately, mortality in the in-hospital group was associated with older age and male sex (Table 2, p=0.001 and 0.02, respectively). In the out-of-hospital group [Table 2], shorter survival was associated with older age (p=0.002), DM (p=0.025), RD (p=0.012) and decreased LVEF (p=0.006). By contrast, treatment with statins and prior epi-

sodes of AF predicted better survival (p=0.03 and 0.04, respectively).

Variables most significantly associated with survival

When Cox proportional-hazards model was applied to scrutinize the entire patient group [Table 3], the following variables were most significantly associated with poor survival: older age, no history of recurrent AF and DM. By contrast, treatment with statins predicted better survival.

Variables most significantly associated with survival in in-hospital AF differed from those in out-of-hospital AF [Table 3]. In the in-hospital group, older age was most significantly associated with poor prognosis. In the out-of-hospital group, advanced age, a new-onset AF, DM and RD were more significantly associated with shorter survival, while treatment with statins predicted better survival.

Discussion

Characteristics of the patients

The present investigation was designated to verify statistical methods of our previous observations. Our experience tended us to suggest that patients admitted to the hospital with AF and those developing AF while already staying in a medical department due to other acute conditions, substantially differ with respect to their clinical profile and prognosis. Thus far, this issue has been poorly investigated. Our present results reveal that such difference does exist, implicating that these two patient groups require distinction in their bedside management.

The present study design differed from that of a single similar publication available in the literature in which patients who were hospitalized for acute medical illness and developed AF during hospitalization were compared with those hospitalized for acute medical condition but did not develop AF during hospitalization, or with patients referred to the emergency room with the new-onset AF being their sole complaint.[13] Unlike the retrospective data collection in the mentioned publication, the majority of our data were collected prospectively. Our patient populations were much larger and included both genders, unlike the above mentioned study comprising only 24 patients of male sex in each group. Selection of the analyzed clinical variables was more extensive and the follow-up period was longer.

In the present investigation, the two study groups substantially differed with respect to their comorbidities as well as their clinical characteristics and laboratory analyses. Thus, patients from the in-hospital group were statistically more likely to have DM , RD, chronic lung disease or history of stroke, compared to the out-of-hospital group, confirming the previous observation that patients developing AF during hospital stay are more severely ill.[13] Patients of the in-hospital AF group had higher body temperature as well as higher heart and respiratory rates when compared to the out-hospital AF population. Furthermore, these patients demonstrated lower levels of serum albumin and blood hemoglobin. Inflammatory markers, such as serum CRP, erythrocyte sedimentation rate and white blood cell count, were significantly elevated in the in-hospital AF population.

Some aspects regarding the AF characteristics of the in-hospital group patients from our study are novel and as such might be of clinical importance. Thus, contrary to our out-of- hospital group, the in-hospital group had higher frequency of episodes of AF occurring during hospitalization, despite the fact that higher proportion of these patients returned to sinus rhythm on discharge. This would tend to suggest that the trigger for AF remained active up to amelioration of those clinical conditions which had been the reason for the patient's admittance in the first place. It is plausible that, in addition to routine anti-arrhythmic treatment, any effective treatment of concurrent acute illness also had a positive impact on successful cardioversion. We are not aware of any data regarding the recurrence rates of AF during hospitalization in patients similar to those comprised in our study. As stated before, elevation of various inflammatory markers in the in-hospital group indicates a significant association between

Table 2 Variables associated with survival in the entire, in-hospital and out-of-hospital AF groups (univariate analysis)

	Entire group (n=249)		In-hospital group (n=56)		Out-of hospital group (n=193)	
	Mean survival duration (months)	P	Mean survival duration (months)	P	Mean survival duration (months)	P
Age group (years)		**0.01**		**0.001**		**0.002**
<70	50.6		52.5		50.1	
≥70	41.0		30.6		43.9	
Gender		0.4		0.02		0.5
Male	45.7		33.6		48.8	
Female	45.5		42.2		45.3	
Prior episode of AF		**0.02**		0.4		**0.04**
Yes	48.2		41.8		49.6	
No	43.2		37.3		44.5	
Renal dysfunction		**0.007**		0.5		**0.012**
Yes	38.2		36.2		38.9	
No	47.7		40.3		49.0	
Diabetes mellitus		**0.025**		0.5		**0.025**
Yes	41.2		37.2		42.1	
No	47.3		40.8		48.7	
Hypertension		0.1		0.7		0.06
Yes	43.1		37.8		44.1	
No	46.6		40.6		50.9	
LVEF		**0.005**		0.17		**0.006**
Decreased (<50%)	37.7		30.5		38.4	
Preserved (≥50%)	49.1		43.7		50.3	
Recurrent AF during hospitalization		0.1		0.5		0.3
Yes			31.2		43.9	
No	39.5		40.7		46.9	
Treatment with statins	45.8	**0.025**		0.7		**0.03**
Yes			43.0		50.3	
No	49.4		41.9		45.4	
Treatment with ACE-inhibitors/ angiotensin receptor blockers	44.9	0.2		0.3		0.7
Yes	44.7		31.4		46.2	
No	49.0		41.8		48.0	

AF: atrial fibrillation, ACE: angiotensin-converting enzyme, LVEF: left ventricular ejection fraction

inflammation and development of AF, as well as between successful treatment of inflammation and conversion of AF to normal rhythm. According to the literature, high levels of CRP are associated with increased risk of AF recurrence.[16–18]

The additional interesting finding is the observed longer mean time elapsing from the AF onset up to conversion to sinus rhythm in the in-hospital compared to the out-of-hospital group (59 h and 26 h, respectively). We also have demonstrated that patients with AF onset during hospitalization needed a significantly prolonged hospital stay, compared to patients from the out-of-hospital group. Lengthening of hospital stay has been previously reported in AF patients with HF,[11] acute myocardial infarction[9] and after surgery.[7,8] There is no data regarding the length of hospital stay for patient populations similar to ours. The data provided herein allow us to conclude that patients with the in-hospital onset AF developed the latter at the later stages of their hospital stay. Consequently, their hospital stay was prolonged as a result of such complication. However, it is also possible that in a given patient severity of the clinical profile was predictive both of the prolongation of hospital stay and conversion of AF to normal rhythm.

We also observed that longer time period was needed for cardioversion in our entire study group, as compared to drug-oriented trials.[19–21] Nevertheless, it was comparable with study performed on unselected patient population.[22] Time of pharmacologically achieved conversion to sinus rhythm appears to vary depending on the anti-arrhythmic drug choice.[19–21] Among the prescribed anti-arrhythmic drugs used in our study, amiodarone was the one most frequently applied both during hospitalization and on discharge. We applied amiodarone so extensively since it is one of the most effective anti-arrhythmic agents which is also commonly used in clinical practice as a drug of choice for treatment of patients with AF in the presence of coronary artery disease and/or HF,[3,5,19–21,23,24] the latter conditions being common in our patients. However, amiodarone is known to exert its effects more slowly than other anti-arrhythmic drugs[19–21] Thus, despite the fact that amiodarone administration was associated with relative prolongation of time elapsing from the AF onset to conversion to normal rhythm, successful cardioversion was achieved in the majority of our patients.

Survival

We conducted a long-term follow-up on our study groups, including survival and the variables associated with the latter. In accordance with previously published data,[11,12,22,25] the fol-

Table 3 Variables most significantly associated with low survival (Cox proportional-hazards model)

Variable	p	Odds ratio	95% confidence interval
Entire group			
Age[a]	<0.001	2.05	1.56–2.71
New onset atrial fibrillation	0.002	2.25	1.22–4.16
Diabetes mellitus	0.012	2.04	1.15–3.65
Treatment with statins	0.035	0.51	0.27–0.98
In-hospital atrial fibrillation group			
Age[a]	0.009	1.87	1.15–3.03
Out-of-hospital atrial fibrillation group			
Age[a]	<0.001	2.17	1.51–3.10
New-onset atrial fibrillation	0.002	3.41	1.56–7.46
Diabetes mellitus	0.006	2.22	1.12–4.39
Renal dysfunction	0.049	2.44	1.10-5.38
Treatment with statins	0.061	0.49	0.22–1.07

[a]For each 10 years increment

lowing variables were found to be significantly associated with poor prognosis: older age, DM, RD, reduced LVEF and first episode of AF. Moreover, we observed decreased long-term survival in patients with the onset of AF during hospitalization, compared to those admitted to the hospital with AF. Furthermore, significant predictors of death were found to be different for the two study groups: in the in-hospital group - older age and male gender, whereas in the out-of-hospital group - older age, RD, DM, reduced LVEF and new-onset AF. Treatment with statins was associated with prolonged survival only in the out-of-hospital group.

Of interest, the first episode of AF (compared with diagnosed paroxysms of AF prior to admission) was significantly associated with lower survival. Similar observations have been reported in other studies performed on AF patients hospitalized with acute coronary syndromes and HF or admitted for cardioversion.[11,12,22] Our results support the hypothesis that first episode of AF should always be considered a risk factor for the presence of previously unknown and, most probably, severe underlying disease.[22] It is possible that increased mortality after the acute event of AF is due to these adverse consequences of new-onset AF on cardiac function. The intrinsic mechanisms leading to increased mortality shortly after the new-onset AF are probably of hemodynamic origin, whereas in the recurrent forms of arrhythmia mortality most probably results from stroke, progressive electrical remodeling, etc.[11,12] Noteworthy, since patients with recurrent episodes of AF are likely to be already pharmacologically treated after their previous cardiovascular evaluations, this alone might be predictive of a better long-term prognosis.[11,22]

As already mentioned, in the present study treatment with statins was associated with prolonged survival of both the entire patient population and the out-of-hospital group. Beneficial effects of statins on AF have been previously reported in several studies. Data from different observational trials have shown that statins may decrease the incidence of different types of AF, including the new-onset AF after electrical cardioversion, cardiac surgery, acute coronary syndrome and/or left ventricular dysfunction.[26–30] The anti-arrhythmic mechanisms of statin-induced AF prevention in HF patients are not fully understood. Positive effects of statins on AF appear to be independent of their cholesterol-reducing properties, but might be related to their pleiotropic anti-inflammatory and antioxidant effects, as well as to atrial remodeling attenuation and ion channel stabilization.[28] Inflammation, documented by higher levels of CRP, which may be a pathogenic component of AF, appears to be involved in the early phase of electrical remodeling (as early as within 24 h after AF initiation) and to promote the persistence of AF.[4,27,28]

Study limitations

The main limitation of the present study was the relatively small number of patients within the in-hospital group, which might have compromised our ability to define any other variables predictive of lower survival. In addition, it was difficult to accurately estimate the onset, and therefore the total duration of AF in the out-of hospital group. With respect to the period preceding the hospitalization, we could only rely on the clinical records of the patient, if available, or on the complaints and symptom descriptions provided by the patient. It is also possible that our results were limited by inclusion of patients from only one internal medicine department from a single medical center as well as by the specificity of local medical services.

Conclusions

The results of the present study confirmed that, expectantly, the bedside clinical variables and survival prediction significantly differ between the patients developing AF during hospitalization and those hospitalized with AF appearing prior to admission. These results may be clinically important. They indicate that patients with in-hospital AF onset require more optimal management and monitoring in order to reduce their time of the hospital stay and to decrease their risk of mortality. Improved management of relevant comorbidites, including RD and/or DM as well as prescription of statins, may be found beneficial for death prevention in patients with AF.

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