ORIGINAL ARTICLE

Clinical profile and management in non-valvular atrial fibrillation and heart failure patients

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Abstract: Introduction – Heart failure (HF) and atrial fibrillation (AF) coincide in many patients. The bond between these two conditions is sealed by the shared similar risk factors and common pathophysiology. **Purpose –** The objective of our study is to assess the prevalence, clinical characteristics and to determine in-hospital mortality of non-valvular AF in HF patients. Methods: A total of 434 patients admitted consecutively in our clinic with diagnosis of AF and HF were evaluated during hospitalization. Baseline characteristics and clinical outcomes were extracted. The patients were divided in two gropus: valvular and non-valvular AF. **Results –** The mean age of our studied group (263 eligible patients with non-valvular AF and HF) was 73.79 years with a SD of 10.487 (p=0.000). Comorbidities found among our patients were: anxiety disorders (37.3%), chronic kidney disease (31.2%), diabetes mellitus (28.1%), arthrosis (28.1%), hepatic disorders (25.5%), obesity (24.0%), malignancy (22.5%), left bundle branch (12.2%), Parkinson disease (9.9%), hemorrhagic events (8.7%), stroke (8.4%), peripheral vascular disease (7.2%), anemia (6.8%), and right bundle branch (5.3%). **Conclusion –** The presence of non valvular AF in HF patients is associated with a high number of risk factors, comorbidities and high in-hospital mortality.
Keywords: atrial fibrillation; heart failure; anticoagulants; comorbidities; mortality

Rezumat: Introducere – Insuficiența cardiacă (IC) și fibrilația atrială (FA) reprezintă patologii frecvent întâlnite la mulți pacienți. Legătura dintre aceste două condiții este subliniată și prin factorii de risc comuni. Scopul acestui studiu este de a evalua prevalența, caracteristicile clinice și de a determina mortalitatea intraspitalicească a FA non-valvulare la pacienții cu IC. **Material și metode –** Un total de 434 de pacienți internați consecutiv în clinica noastră, cu diagnosticul FA și IC au fost evaluați în timpul spitalizării din punctul de vedere al profilului clinico-biologic. Pacienții au fost împărțiți în două grupuri: cu FA valvulară și non-valvulară. **Rezultate –** Vârsta medie a pacienților incluși în studiu (263 de pacienți eligibili cu FA non-valvulară și IC) a fost 73,79 ani cu DS de 10,487 ani (p = 0,000). Printre comorbiditățile pacienților din lotul de studiu, cele mai frecvent întâlnite au fost: anxietatea (37,3%), boli cronice de rinichi (31,2%), diabet zaharat (28,1%), artroze (28,1%), afectare hepatică (25,0% (8,2%), boală Parkinson (9,9%), evenimente hemoragice (8,7%), accident vascular cerebral (8,4%), boală vasculară periferică (7,2%), anemia (6.8%) și blocul de ramura dreaptă (5,3%). **Concluzie –** Prezența FA non-valvulară la pacienții cu IC este asociată cu un număr mare de factori de risc, comorbidități și o mortalitate crescută intraspitalicească.
Cuvinte cheie: fibrilație atrială; insuficiență cardiacă; anticoagulante; comorbidități; mortalitate

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia worldwide. AF is still one of the leading causes of heart failure, stroke, sudden death, and cardiovascular morbidity in the world[1], although major progresses were made in the management of patients with this arrhythmia.

It is estimated that its prevalence is 3% in adults aged 20 years or older[2,3], with a greater value in elderly patients[4]. AF is independently associated with a two-fold increased risk of all-cause mortality in women compared to men[5] (a 1.5-fold increase) and has increased morbidity[6,7]. In developing countries, the age-adjusted incidence and prevalence of AF are lower

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in women, while the risk of death in women with AF is similar to or higher than that in men[8,9].

Heart failure (HF) and AF coincide in many patients. The bond between these two conditions is sealed by the shared similar risk factors and common pathophysiology. Structural cardiac remodling, activation of neurohormonal mechanisms, and rate-related impairment of left ventricular (LV) function are some of the incriminated causes and exacerbation between these two nexus[10]. Both conditions interact with each other causing increased mortality rates.

AF and HF are cardiovascular disease epidemics that have grown worldwide in the past 2 decades[11].

The interaction between HF and AF has been a quest for many researchers[12-14].

AF has many underlying cardiovascular diseases and can be precipitated by concomitant conditions. In order to prevent AF burden, an important keystone, is treating, preventing and certifying[15,16] these factors.

It is a challenge to diagnosis AF, especially silent episodes, before it's redoubtable complications are installed (stroke and decompensated heart failure). The major goals of AF imply rate and rhythm control, stroke prevention therapy, acute management, treatment of underlying and concomitant cardiovascular conditions. In the last years a great effort throughout countless research and studies[17] were made, but nevertheless, there are still gaps to be covered concerning treatment options, and AF management.

Due to high prevalence and important impact, HF prevention requires tilted attention towards affected AF patients. Therefore, it is extremely important to identify clinical aspects of AF and HF patients. A common group of patient encountered in daily practice is the one that combines heart failure and atrial fibrillation.

AIM

The objective of our study is to assess the prevalence, clinical characteristics and to determine in-hospital mortality of non-valvular AF in HF patients.

METHOD

Study population

We conducted a retrospective observational study among adult patients, who have the clinical diagnosis of AF and HF. A total of 263 patients admitted consecutively in our hospital between January 2016 and December 2016, were evaluated. Baseline characteristics and clinical outcomes were extracted. The main inclusion criteria for study participation was documented AF and HF. Patients admitted in another clinic or department and transferred to ours, were also included. Patients with exclusively short, temporary AF episodes (e.g. AF following cardiac surgery) were excluded. Patients suffering from an acute disease, other than the cardiac one (e.g. general surgery), or patients that were transferred from our clinic to another were not enrolled.

Assessments

Data were obtained from the patient's medical charts; the demographic information, as well as clinical assessment and comorbidities were noted. Laboratory findings in conjunction with physician notes as well as medication from the patient's medical charts, were used to determine whether or not they have a specific comorbidity. CHA_2DS_2-VASC and HAS-BLED scores were assessed for each patient and noted.

Patients were divided in two groups: valvular and non-valvular AF. Valvular AF according to the *European Society of Cardiology Guidelines* definition includes patients with moderate to severe mitral stenosis or prosthetic heart valves (and valve repair in North American guidelines), and thus they should be treated with VKA. Valvular heart diseases, such as mild mitral stenosis, mitral regurgitation, aortic stenosis and aortic insufficiency, do not alter the low flow in the left atrium, and it seems they do not increase the risk of cloth (induced by AF).

Arterial hypertension was defined on the basis of clinical history or by the use of antihypertensive medication at admission. Congestive heart failure and cardiomyopathy were diagnosed according to the *European Society of Cardiology* (ESC) definition. The diagnosis of ischemic heart disease was made on the patient's history of significant coronary artery disease revealed by coronary angiography or on the basis of chest pain associated with elevated level for cardiac markers (troponin I or high sensitivity troponin I) / echocardiography changes consistent with the validated ischemia on the electrocardiography, or a positive non-invasive stress test. The diagnosis of valvular heart disease was established by moderate or severe valvular stenosis or regurgitation. Diabetes was ascertained by a fasting serum glucose value greater than 126 mg/dl, a HbA1c greater than 6.5% or the use of glucose lowering agents or insulin. The diagnosis of chronic kidney disease was determined by a creatinine clearance calculated by MDRD study equation lower than 60 ml/min/m^2. Ischemic or hemorrhagic stroke

were certified by a cerebral computer tomography scan (performed during admission or in emergency department) and neurological assessments. Chronic obstructive pulmonary disease was set out by abnormal pulmonary function tests or current treatment with an inhaled long acting bronchodilator and/or an inhaled corticosteroid. Endocrine disorders assessed were: pituitary, thyroid disorders (estimated throughout TSH level, free T4 and/or T3 value); adrenal disorder (searched in patients that hade an intake of ≥7.5 mg prednisone equivalent); pheocromocitoma (take into consideration in patients with high levels of catecholamines); primary aldosteronism (considered in patients with high aldosterone levels). Anemia was considered as a reducing amount of red blood cells (RBCs) per mm^3 of blood, or a decrease in hemoglobin value (below 13 g/dL in men and under 12 g/dL in women). Patients who met the inclusion criteria but died during the specified observation range were also included in the study.

Statistical analysis

All statistical analyses were conducted using SPSS 21. Results are presented as mean ± standard deviation SD (for numerical variables) or percentages. Continuous variables were reported as the mean±SD or as the median and interquartile range (IQR). Categorical variables were reported as percentages. Continuous variables were analyzed for normalization and compared using the *t* Student test; they were expressed by mean value ± standard and/or median deviation. For comparison of parameter averages the Mann-Whitney U method and the Wilcoxon method W are used. The degree of correlation (r) between the studied parameters was evaluated by calculating the correlation coefficient Pearson. On multivariate analysis, logistic regression model was used. A cut-off value of $p < 0.05$ was considered statistical significant. Intergroup comparisons were made using a Chi-square test.

RESULTS

From a total of 434 patients admitted within one year into our hospital, a group of 92 patients were excluded from the study due to missing data or they were lost-to follow-up. Patients were divided in two groups: valvular (79 patients with a SD of 0.294) and non-valvular (263 patients with a SD of 0.299) AF. Both groups of patients presented HF. All the following assessments and characteristics refer to the non-valvular AF group. The mean age of our studied group (non-valvular AF) was 73.79 years with a SD of 10.487 (p=0.000), as seen in (Table 1), with slight male predominance (54.4% vs. 45.6%).

Demographic data and baseline characteristics are shown in (Table 2). In our study group of non-valvular AF and HF patients, we found 3.8 % first detected AF, 28.9% paroxysmal AF, 17.1% persistent AF, 25.1% long standing persistent AF, and 25.1% permanent AF. A third (86 SD 0.294) of our patients presented HF with preserved ejection fraction (HFpEF), almost a quarter of our study group (64 SD 0.337) were included in HF mid-range ejection fraction (HFmrEF), and the majority have HF with reduces ejection fraction HFrEF.

Between the risk factors found in our study group we specify: hypertension (54.3%), dilative cardiomyopathy (47.1%), ischemic heart disease (44.9%), dyslipidemia (38.0%), chronic obstructive pulmonary disease (36.1%), endocrine disorders (6.1%), and valvular heart disease (72.62%), and pacemakers (4.9%). In our study group, 66.2% patients presented at echography mitral regurgitation. A percentage of 31.7% have mild regurgitation, 22.8 % have moderate and 11.8 % have severe mitral regurgitation. Aortic regurgitation was encountered in 20.5% patients, most of them have mild aortic regurgitation (SD 0.291). Tricuspid regurgitation was noted in 39.5% patients, almost half of theme presented mild tricuspid regurgitation. Aortic stenosis was found in 16.8% patients, and mitral stenosis in 4.2% patients. A number of 19 (SD 0.263), patient presented with native heart valve involvement. Pulmonary hypertension was found in 22.8% patients most of them presenting moderate or severe pulmonary hypertension.

Comorbidities found among our patients were: anxiety disorders (37.3%), chronic kidney disease (31.2%), diabetes mellitus (28.1%), arthrosis (28.1%), hepatic disorders (25.5%), obesity (24.0%), malignancy (22.5%), left bundle branch (12.2%), Parkinson disease (9.9%), hemorrhagic events (8.7%), stroke (8.4%),

Table 1. Student *t* test for mean age of our study group

One-Sample Test						
	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
Vârsta	114.105	263	.000	73.787	72.51	75.06

Table 2. Baseline characteristics in our study group

Baseline characteristics				
Main Criteria	**Specific criteria**		**Value**	**SD**
Statistical consideration	Male (n=143)/Female (n=120)		54.4 / 45.6	0,477
	Urban (n=135) / Rural (n=128)		51.3 / 48.7	0,294
	Age (%)	20-34 yo.	0.4	0,262
		35-44 yo.	0.4	0,338
		45-54 yo.	4.1	0,293
		55-64 yo.	12.2	0,366
		65-74 yo.	31.2	0,274
		75-84 yo.	40.3	0,288
		>85 yo.	11.4	0,226
	Deceased patients (n=34)		12.9	0,247
Clinical considerations	Heart rate, BPM		84.3±22	0,302
	Mean arterial pressure, mmHg		109.3±17.2	0,351
	Body mass index (BMI), kg/m^2		27.4±4.9	0,405
	NYHA class	Class I	10(3.8)	0,299
		Class II	56(21.3)	0,315
		Class III	108(38.0)	0,262
		Class IV	89(31.2)	0,293
Lab differences	NT-proBNP pg/ml		14 320±14 201	0,366
	TnI, ng/mL		2.92±2.43	0,275
	D-dimers,µg/mL		2.71±1.83	0,483
Ecocardiographical parameter	LVEF, %		37±26	0,282
	Left atrial volume, ml		108±24	0,314
	Mitral regurgitation volume, ml		34.5±18	0,263
	Left atrium surface, 173/m^2		36.8±19.1	0,376
	Systolic pressure in pulmonary artery, mmHg		41±14	0,169

yo: years old; BPM: beats per minute; BMI: body mass index; TnI: troponine I; LVEF: left ventricular ejection fraction.

peripheral vascular disease (7.2%), anemia (6.8%), and right bundle branch (5.3%) All the associated comorbidities and risk factors are highlighted in (Table 3).

At discharge, in the non-valvular AF group, 50.2% have beta-blockers prescribed, 42.6% angiotensin converting enzyme inhibitors, 23.6% angiotensin II receptor blockers, 31.9% on digoxin, 20.9% on calcium antagonists, 81.4% on diuretics, 32.3% on aspirin, 45.6% statins, 29.7% antiarrhythmic agents. More than one third of the patients in our study group have a non-vitamin K antagonist oral anticoagulant (NOAC) prescription: 15.6% used Dabigatran, 14.1% take Apixaban, and 8.4% are on Rivaroxaban, proving once more the underutilization of NOAC.

In (Figure 1) we emphasize the thromboembolic risk profile estimated throughout the CHA2DS2 – VASC score, whose median in our study was 5.19 SD 1.337 the majority of the cases having a score ≥2.

Figure 2 highlights the hemoragic risk profile estimated throughout the HAS-BLED score, whose median in our study was 3.08 SD 1.5, the majority of the cases having a score ≥3.

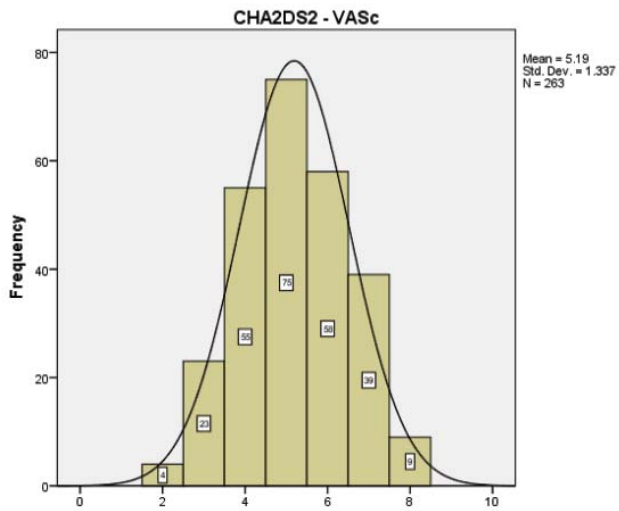

Figure 1. The thromboembolic risk profile estimated in our study group throughout the CHA_2DS_2-VASC score.

In our study group, we had an in-hospital mortality rate of 12.9% (sudden cardiac death were also included in these numbers), compared to an in-hospital

Table 3. Prevalence of comorbidities found in AF patients in our study group

Prevalence of associated conditions with non-valvular AF			
Comorbidities		**n**	**SD**
Hypertension		143	0.302
Dilative cardiomyopathy		124	0.447
Ischemic heart disease		118	0.413
Dyslipidemia		100	0.196
Anxiety disorders		98	0.350
Chronic obstructive pulmonary disease		95	0.200
Chronic kidney disease		82	0.216
Diabetes mellitus		74	0.275
Arthrosis		74	0.414
Hepatic disorders		67	0.318
Obesity		63	0.353
Malignancy		58	0.302
Left bundle branch block		32	0.229
Parkinson		26	0.262
Hemorrhagic event		23	0.277
Stroke		22	0.338
Peripheral vascular disease		19	0.304
Anemia		18	0.483
Endocrine disorders		16	0.351
Right bundle branch block		14	0.291
Pacemakers		13	0.316
Mitral regurgitation	1st degree	14	0.000
	2nd degree	69	0.169
	3rd degree	60	0.376
	4th degree	31	0.301
Aortic regurgitation	1st degree	6	0.262
	2nd degree	40	0.294
	3rd degree	4	0.283
	4th degree	4	0.314
Tricuspid regurgitation	1st degree	5	0.200
	2nd degree	46	0.196
	3rd degree	33	0.229
	4th degree	20	0.447
Mitral stenosis	mild	7	0.413
	moderate	4	0.232
Aortic stenosis	mild	12	0.196
	moderate	15	0.216
	severe	17	0.353
Pulmonary hypertension	mild	10	0.196
	moderate	31	0.318
	severe	19	0.000
Tricuspid stenosis		1	0.229

mortality rate of 24.3% in the other group (valvular AF) (p= 0.02).

DISCUSSION

This study targets a specific group of population and assess several aspects related to non-valvular AF in patients hospitalized with HF. The results confirm a high prevalence of non-valvular AF in HF in our clinic, with a high thromboembolic risk profile and low rate of use of NOAC. Atrial fibrillation was associated with several comorbidities, implying a high mortality rate.

Compared with international registries, the age of our study group, was similar with that reported in the following registries: EORP-AF Pilot survey[14] (71.2 years), EHFS (71.3 years)[18]; ADHERE (72.5 years)[19]; and almost 5 years younger than in OPTIMIZE-HF trial (78 years)[20].

Differences as the subtypes of AF can be noted mainly regarding the first diagnosed AF, which in our study was little encountered (3.8%) compared to other registries like EORP-AF Pilot survey[14] (35%). The same observation can be made concerning long

Tabel 4. Prevalence of therapeutical agents used in our study group

Therapeutical agents	Value	SD
ACEI, n (%)	112 (42.6)	0,187
Other antiplatelets*, n (%)	43 (16.3)	0.294
Antiarrhythmic agents, n (%)	77 (29.7)	0,366
ARB, n (%)	62 (23.6)	0.247
ASA, n (%)	85 (32.3)	0,302
Calcium channel blocking agents (dihydropyrines) n (%)	48 (18.3)	0.316
Calcium channel blocking agents (non- dihydropyrines) n (%)	7 (2.6)	0.337
Digoxin, n (%)	84 (31.9)	0.285
Diuretic, n (%)	214 (81.4)	0.351
NOAC, n (%)	100 (38.1)	0.294
Statins, n (%)	120 (45.6)	0,262
VKAs, n (%)	163 (62.0)	0.376
Beta blockers, n (%)	132 (50.2)	0,301

ACEI: Angiotensin converting enzymes inhibitors; ASA: acetylsalicylic acid; ARB: Angitensin II receptor blockers; VKAs: vitamin K antagonists; NOAC: new oral anticoagulants.
* Other antiplatelets: clopidogrel, prasugrel, ticagrelor.

standing persistent AF which represented a quarter of our patients, but in the EORP-AF Pilot survey[14] it was only found in 5.3% of the patients. These could be explained by the fact that in our study we only presented the non-valvular AF patients, not all AF patients like in other registries. Non-valvular AF was not a pre-specified subgroup in the specified studies.

Only a few studies have assessed the subtype of HF (according to the last classification) in cases of AF. Differences can also be noticed between these types of HF: we found a higher prevalence of HFrEF (43.0%), compared to HFpEF (32.7%) and HFmrEF (24.3%). In the AF registries were HFrEF can be found in a quarter of the patients and HFpEF in 45.1%. These facts could be explained due to the emergency profile of our clinic and the limited admission of HF in the cardiology clinic, resulting in more severe and decompensated cases and the poorer clinical status of our patients. Clinical trials, such as CHARM study[21] state a much higer prevalence of HFpEF than in our study, but these could be explained throughout the introduction of HFmrEF.

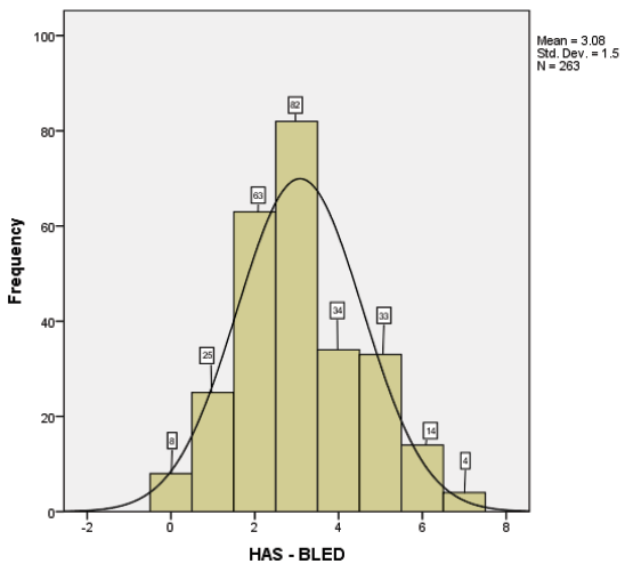

Figure 2. The hemoragic risk profile estimated in our study group throughout the HAS-BLED score.

We could identify differences betwen our group and other registries concerning some risk factors like hypertension and endocrine disorders. We found hypertension in more than half of our group (54.3%), compared to a percentage of 73.9% in the EORP-AF Pilot survey[14], 77% in the ADHERE study[22], 52% in the *Swedish Heart Failure Registry*[23] (that included 7.392 patients with HFrEF and AF) and 46% in the AATAC trial[24]. Smaller published studies[25] reported simillar prevalence to ours. The association of the remaining risk factors for AF-HF found in the present study has been reported similarly, in other studies.

Similarly, the association of comorbidities found in our patients has been reported in the international literature.

In terms of therapeutical agents used, we could find some diferences between our group and the other registries concerning the prescription of beta-blockers and diuretics. A percentage of 50.2% patients in our study received betablockers compared to 77.4% in the EORP-AF Pilot survey[14] 78% in the AATAC trial[24], and 79% in AF-CHF trial[26]. This is interesting given that beta-blockers are now a standardized part of treatment in AF and FH following numerous randomized clinical trials reporting a substantial reduction in all-cause mortality[27], cardiovascular death and hospitalization. The undepriscription of beta-blockers could be expla-

ined by the frailty of our patients and could reflect the severity of HF[26].

Non-valvular AF was mostly assesd in the cohorts enrolled in trials on NOAC[28-31], based on highly-selected patients. The *European Heart Rhythm Association* position paper states that the currently unique contraindications to NOAC are patients with mechanical heart valves and those with moderate-to-severe mitral stenosis. Patients with native heart valve involvement, regardless of their severity, are suitable for NOAC therapy. Patients with bioprosthetic heart valves and mitral valve repair may be suitable for NOAC except for the first 3-6 months postoperatively. Patients with transaortic valve implantation or percutaneous transluminal aortic valvuloplasty are also considered as being eligible for NOAC, but future studies are required to prove the level of evidence for NOAC use, particularly in these patients[32]. The bleeding risk, for the last population (often requiring a combination with antiplatelet therapy), has to be carefully asseed and it's ultimately the decision of the physician who assesses the risk and benefit.

Despite the limitations on NOAC usage due to their cost, the proportion of patients treated with NOAC are progressively increasing, proving their effectiveness and safety. In our study NOAC were more commonly prescribed (38.1%) than in other reported studies: 7.2% in EORP-AF Pilot survey[14], 14.1% in ORBIT-AF[33] registry, 23% in GLORIA-AF[34] trial. This suggests a much better adherence to evidence and guidlines recommendation, but familiarity with prescribing NOAC may still be a challenge.

There is growing interest on assessing if the trombembolic risk, as well as the risk of death, reagarding clinical presentation is related to the type of AF, as investigated by numerous clinical trials[35]. In our study, the CHA_2DS_2-VASc score showed an elevated thromboembolic risk profile: median of 5.19 with a SD of 1.337, and most of the patients have a score ≥2. The results obtained suggest that there is still a underutilization of NOAC in these patients, mainly those at higher thromboembolic risk, which might have an important impact on mortality after hospital discharge, as shown in the ADHERE Study[22]. Underutilization of NOAC in patients with AF and HF has also been reported in the literature. Our findings are in concordance with specification of the EORP-AF Pilot survey[36] which states that estern countries have a tendency in underuntilizaton of NOAC. Stroke and bleeding risks were higher in AF patients with HF.

Probably only the physicians individual experience coroborated with a better knowledge on these direct oral anticoagulants (and on their effect) might help to increase the anticoagulation use rate in these patients. The lack of a heart failure unit prones in selecting more severely ill patients to be hospitalized in the general cardiology or internal medicine department. Greater complexity of these cases, requiring a longer length of stay (in hospital) for clinical compensation just underlines the importance of a specialized heart team and unit that could alleviate these patients.

In the present study, in-hospital mortality was 9.26%, greater than that reported in the international literature, such as the ADHERE Registry[22] (4%), once again suggesting the more severe profile of the patients in this study. Our numbers obtained are higher, but these could be explained due to the emergency profile of the hospital and because of the presence of a stroke unit (a high addressability from all the nearby counties).

LIMITATIONS OF THE STUDY

This is a small single-center retrospective non-randomized study, without a control group. This makes interpretation of data difficult. The data shown in this study represent the clinical practice in our center, so they cannot be generalized. However, compared with the data in the literature the prevalence of AF comorbidities is quite similar with the general data. We did not perform echocardiographic assessment of the left atrial strain and of the left atrial functions.

CONCLUSION

We found in our study, that the presence of non valvular AF in HF patients is associated with a high number of risk factors, comorbidities and high in-hospital mortality. Knowledge of the underlying factors and their management is the cornerstone for optimal treatment in AF patients.

Despite the extensive amount of literature that treats these conditions (HF and AF) individually and combined, there is still a demanding need for further research.

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