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Research Article

Cardiovascular Risk Factors in Atrial Fibrillation Associated with Ischaemic Heart Disease

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ABSTRACT

Objective: To describe cardiovascular risk factors in Atrial Fibrillation (AF) in relation with ischaemic diseases in an emergency service.**Methodology:** Cross-sectional study of patients with AF attended in the (ES) of the HUAV during 2016. Epidemiological and clinical data and their CVRF were analysed. The statistical association was made through the Chi-Square or Mann-Whitney test. The risk factors associated with AF were adjusted with logistic regression models, calculating OR.**Results:** We evaluated 552 patients with 46% men and (54%) women with an average age of 72.9 years. In 57 patients (10.3%), the detection of AF was coincidental. The younger patients presented with more frequent palpitations ($p < 0.05$) and the older patients had dyspnea ($p < 0.05$). The older patients are the ones that take longer to consult ($p < 0.05$). 17% (94) of patients with AF have a heart attack before, during or after the episode of AF, with a higher prevalence among men ($p < 0.05$). The probability of diagnosing ischaemic heart disease in a male patient with AF, hypertensive and diabetic is 71%.**Conclusion:** In men with hypertension and DM a correct diagnostic and therapeutic management, should consider the diagnostic possibility that AF is related to the presence of ischaemic disease. AF can be considered as an anginal equivalent in patients who meet the three conditions: being male, with hypertension and DM.

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Introduction

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population. Sufferers also have higher morbidity and mortality [1]. The prevalence of AF in the general population, both in the US and Europe, is around 1-2% [2, 3]. This percentage increases significantly with age, especially after 65 years [2]. The association with age and sex has been demonstrated in several

studies. AF incidence is higher in men than in women, at any age range [4, 5]. This feature, given the increasingly ageing population, predicts an increase of this disease in the coming years. In Spain, the data available point towards a similar evolution to that of US populations and those of other European countries [6].

Besides the epidemiological data, its serious medical consequences would suggest that we are facing a serious health problem. AF doubles the risk of death in women and increases it 1.5 times in men. It is one of

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the leading causes of heart failure (HF), stroke, sudden death and cardiovascular morbidity worldwide and a greater number of hospitalizations [7]. Heart failure is present in 30% of patients with AF, and AF appears in 30-40% of patients with HF, especially in those with a lower functional class. Both diseases are enhanced, increasing cardiovascular morbidity and all-cause mortality in patients presenting them [8]. High blood pressure (HBP), present in 60-80% of patients with AF, and Diabetes Mellitus (DM), present in 20%, are independent risk factors for the onset and progression of this arrhythmia [8, 9]. The relationship between AF and ischaemic heart disease (IHD) is well known. Between one-third and one-quarter of patients with AF suffer from coronary heart disease [8]. AF is the most common arrhythmia presented by patients with acute myocardial infarction, worsening their prognosis [10]. This is confirmed by Jabre *et al.* in a large study including 278,854 patients [11]. The study by GUSTO III and the OACIS confirmed increased mortality at one year of AMI in patients with peri-AMI AF [12, 13]. The clinical presentation of AF varies. Between 15 and 30% of these patients are asymptomatic, their arrhythmia being detected coincidentally. In elderly patients, where chronic forms of AF predominate, symptoms decrease or even disappear. In 15-20% of patients, stroke is the initial presentation of this arrhythmia [14]. Palpitations are typical of paroxysmal forms of AF [15].

Chest Pain (CP) occurs in episodes of AF, even in the absence of structural heart disease. This may be due to decreased myocardial perfusion, independent of heart rate. It should be noted that in AF, coronary vascular resistance increases due to the irregularity of the ventricular response and the action of the sympathetic and renin-angiotensin-aldosterone nervous system [16]. A recent study in patients with FA versus patients without, highlights a greater presence of subclinical coronary disease, whether obstructive or not, by conducting multislice CT, with similar demographic and clinical characteristics [17]. Hospital emergency departments (ED) play a key role in the management of this disease since it is where the first therapeutic measures are taken. It is essential to have a thorough understanding of these patients in order to develop a suitable therapy, thus preventing serious clinical consequences arising from inadequate therapeutic management [18]. Hence, we approached this study with the aim of ascertaining when to suspect or detect the presence of ischaemic heart disease in patients attending for AF.

Materials and Methods

I Type of Study

We conducted a cross-sectional observational epidemiological study, collecting clinical information on all patients seen at the ED of the HUAV where AF is one of the reasons for consultation, during 2016.

II Exclusion Criteria

Patients for whom it was not possible to complete the necessary data for the study were excluded.

III Final Sample

After applying the exclusion criteria, from a total of 588 patients, 552 were included.

IV Study Variables

Sociodemographic variables (age and sex) were collected. Clinical variables included the reason for consultation, the duration of the episode upon admission, the presence of CRF (DM, HBP, CKD, and levels of total cholesterol, LDL-C and HDL-C) and the existence of IHD, both its chronic and its acute forms in the episode.

V Statistical Analysis

First, qualitative variables were described by absolute frequency and percentages, and quantitative variables using the mean and standard deviation or the median and quartiles 25 and 75, as deemed appropriate by evaluating the normality of these variables, according to the Shapiro-Wilks test. Bar charts were plotted to represent percentages or means. Second, for different statistical association analyses, the chi-square or the Mann-Whitney test was used, as appropriate, calculating the p-value for assessing significance. Third, to evaluate the association of risk factors of AF with IHD, logistic regression models were adjusted, calculating the corresponding odds ratios, 95% confidence intervals and p-values. Also, we included the sex variable in the logistic regression models as an adjustment variable and a multivariate model was also performed using a Backwards Stepwise algorithm to select the one with the best goodness of fit. All statistical analyses were performed using the R program version 3.4.3 R (2018) setting a level of significance of $\alpha=0.05$.

Results

The mean age of the study population was 72.9 years (± 13 years). We obtained a sample of 552 patients: 254 men (46%) and 298 women (54%). The prevalence of AF in women was seen to increase with age ($p<0.05$), whereas no clear trend was observed for men.

I Clinical Manifestations

For 57 patients (10.3%), detection of AF was coincidental. In 44.7% (247) of cases, patients suffered palpitations and 19.5% (108) had chest pain. Dyspnea was manifested by 26% (144). Other reasons for attending the ED were syncope, asthenia, unsteadiness or dizziness, which were present in 20% of cases. This distribution is shown in (Figure 1). Younger patients more frequently presented with palpitations ($p<0.05$) and older patients had dyspnea ($p<0.05$).

In (Table 1), we describe patient characteristics depending on the time of onset of the first symptom and consultation at the ED. Older patients take longer to attend the ED ($p<0.05$).

Table 1: Sample characteristics according to duration of symptoms.

	<48h N=267	>48h N=285	p-value
Sex:			0.031
Male	136 (53.5%)	118 (46.5%)	
Female	131 (44.0%)	167 (56.0%)	
Age:			<0.001
[18-65]	100 (70.9%)	41 (29.1%)	
[65-80]	109 (54.0%)	93 (46.0%)	
[>80]	58 (27.8%)	151 (72.2%)	
Mean age	70.0 [60.0;78.0]	80.0 [70.0;85.0]	<0.001

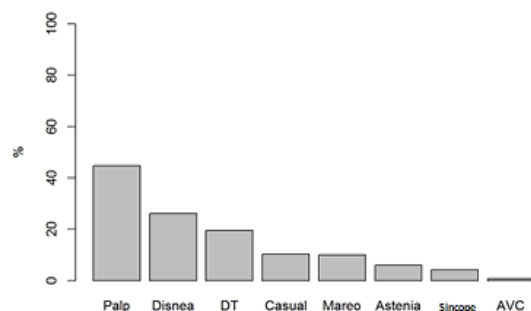


Figure 1: Reasons for consultation for atrial fibrillation.

II Cardiovascular Risk Factors

In our sample, HBP, DM and CKD are associated with older age ($p < 0.05$). Women have higher levels of total cholesterol, HDL-C and LDL-C ($p < 0.05$ in all cases). In addition, for total cholesterol and LDL-C, statistical interaction between sex and age is observed, revealing that for ages below 65 years there is no difference between cholesterol levels, while at older ages women have higher values.

III Atrial Fibrillation and Ischaemic Heart Disease

In (Table 2), we performed a description of the cardiovascular risk factors of the sample, and the presence of ischaemic heart disease. 17% (94) of patients with AF have IHD before, during or after the AF episode, with a higher prevalence among men ($p < 0.05$). Univariate analyses were performed adjusted for sex and multivariate analysis associating CRF with IHD in AF patients.

Elevated levels of HDL-C act as a protective factor for IHD ($OR = 0.97$).

The prevalence of IHD increases to 21.6% ($OR = 5.51$; $p < 0.05$) in patients with HBP. It increases to 24.7% ($OR = 1.80$, $p < 0.05$) in CKD and to 30.6% in diabetic patients ($OR = 3.19$; $p < 0.05$). This association preserves statistical significance after adjusting for sex.

Figure 2 shows that the likelihood of detecting ischaemic heart disease in a male patient with AF, hypertension and diabetes is 71%.

Table 3 summarizes the multivariate and univariate logistic regression performed in the study.

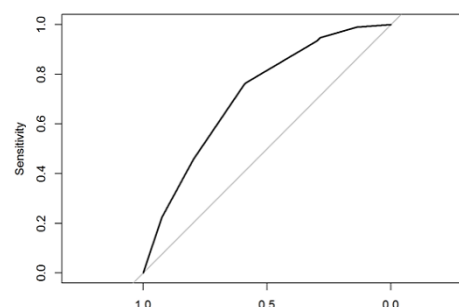


Figure 2: Likelihood of detecting ischaemic heart disease in a male patient with AF, hypertension and diabetes. ROC curve: The area under the curve (AUC) is 0.71.

Table 2: Sample characteristics.

	Total Sample N=552	N
Sex:		552
Female	298 (54.0%)	
Male	254 (46.0%)	
Age	72.9 (13.5)	552
HBP		550
no HBP	147 (26.7%)	
HBP	403 (73.3%)	
DM:		550
no DM	403 (73.3%)	
DM	147 (26.7%)	
Cholesterol	212 (41.1)	467
LDL	131 (34.7)	411
HDL	55.2 (14.7)	412
CKD:		547
no CKD	454 (83.0%)	
CKD	93 (17.0%)	
Age:		552
[18-65)	141 (25.5%)	
[65-80)	202 (36.6%)	
[>80)	209 (37.9%)	
CI:		552
no IHD	458 (83.0%)	
IHD	94 (17.0%)	

HBP: High blood pressure; DM: Diabetes Mellitus II; CKD: Chronic Kidney Disease; IHD: Ischaemic Heart Disease.

Table 3: Univariate and Multivariate Logistic Regression.

	Univariate Logistic Regression			Adjusted for gender p-value	Multivariate Logistic Regression		
	Beta (SD)	OR (95% CI)	p-value		Beta (SD)	OR (95% CI)	p-value
HBP	1.706 (0.41)	5.51 (2.66 - 13.37)	0.00003	0.00001	1.53 (0.42)	4.62 (2.18 - 11.39)	0.0002
DM	1.159 (0.24)	3.19 (2.01 - 5.06)	<0.00001	<0.00001	0.97 (0.25)	2.64 (1.63 - 4.27)	0.00007
CKD	0.589 (0.27)	1.80 (1.04 - 3.05)	0.03	0.03			
Cholesterol	-0.003 (0.00)	1.00 (0.99 - 1.00)	0.33	0.55			
LDL	-0.003 (0.00)	1.00 (0.99 - 1.00)	0.49	0.67			
HDL	-0.034 (0.01)	0.97 (0.95 - 0.99)	0.0009	0.003			
Sex	0.555 (0.23)	1.74 (1.11 - 2.74)	0.02		0.73 (0.24)	2.08 (1.30 - 3.36)	0.002
Age	0.012 (0.01)	1.01 (1.00 - 1.03)	0.17				

HBP: High blood pressure; DM: Diabetes Mellitus II; CKD: Chronic Kidney Disease; OR: Odds Ratio; SD: Standard deviation; CI: Confidence Interval.

Discussion

For men with HBP and DM, for proper diagnostic and therapeutic management we believe the diagnostic possibility that AF is related to the presence of IHD should be considered. Our work confirms that age is a factor which significantly determines the prevalence of AF, with an increase in older ages, especially among women [1, 19, 20]. Such association is not so patent among men. Contrary to other studies, women predominate in our sample, thanks to the number of patients over 80 years of age.

I Clinical Manifestations

The clinical presentation of AF varies greatly and can range from the asymptomatic patient to the critically ill, passing through a variety of symptoms such as palpitations, shortness of breath, chest discomfort/pain, asthenia [7, 14]. Both men and women, in any age range, show the same clinical behaviour accompanying AF motivating their visit to the emergency department.

In our study, the most common symptoms were palpitations, whose cause has not yet been clarified [14]. This is significantly the predominant presenting symptom in younger people, which we associate to the natural history of AF, since it is they who suffer episodes of paroxysmal AF, typical of the early stages of this arrhythmia. Typically, patients with paroxysmal AF are more symptomatic than those with persistent or permanent AF [16].

We know that in the absence of serious structural diseases or accessory pathways, AF is unlikely to cause significant adverse haemodynamic effects [14]. In our study, dyspnea and syncope are significantly the main reasons for older patients attending the ED. We believe this is due to higher associated pathology and increased myocardial functional impairment. In addition, the most frequent forms of AF are persistent/permanent AF, a cause of silent myocardial function impairment. It has been described that in this population, symptoms decrease or even disappear [14]. This alerts us to the need for a routine search for AF, especially among the older population.

In patients aged between 65 and 80 years, dizziness and instability as the presentation of AF appears significantly. This may be due to these patients' lower myocardial function impairment, in comparison to older patients. For this reason, it is important in this group of patients to take measures to prevent myocardial function impairment due to AF or its precipitating factors.

Unspecific symptoms in patients aged over 65 years, with a greater likelihood of developing complications, causes a delay in visiting the ED and consequently a greater delay in AF diagnosis. This point reinforces the need, for the population over the age of 65 manifesting symptoms like dizziness/unsteadiness, asthenia, dyspnea or syncope, to rule out AF, looking for irregularities in the arterial pulse, to facilitate its diagnosis before the onset of serious medical conditions [14].

In our sample, the coincidental detection of AF or its detection in the context of other diseases occurs in 10-12% of patients, both women and men and in any age range, which is a lower proportion than the 15-30% described elsewhere. These patients have the same risk of acute complications as symptomatic patients [14]. Detecting AF in the context

of an AVCA only occurs in four patients belonging to the older age group. This confirms that checking for AF should be routine for any patient attending the emergency department, especially if presenting cardiovascular risk factors.

One problem the emergency physician is posed with is the diagnosis of a patient who consults for chest pain and AF is detected. In our sample, this occurs in 19.7% of patients, both men and women and at any age. Chest pain can occur in AF, even in the absence of structural heart disease, poor myocardial perfusion and an increase in coronary vascular resistance [14, 16]. Furthermore, it is proved that patients with AF have a higher prevalence of heart disease whether obstructive or not, that AF is the arrhythmia that most complicates AMI and it is also present in patients with chronic heart disease, worsening their prognosis [17, 21, 22]. The two pathologies, IHD and AF, share cardiovascular risk factors that predispose their development. These data should lead emergency physicians to consider the possibility that AF is presented in the context of acute or chronic heart disease.

II Cardiovascular Risk Factors

HBP, an independent factor for the development of AF, is the most frequently found CRF in AF (60-80%). In our sample it is present in 73.27% of patients. Its presence increases with age and is more common especially in older patients ($p < 0.05$), with a predominance among elderly women ($p < 0.05$). DM is present in 20% of patients with AF and is an independent risk factor for its development [17]. In our sample it is present in 26.7% of patients. It occurs equally in both sexes and is significantly more common in older patients ($p < 0.05$). CKD, present in 15-20% of patients with AF, is present in 17% of our patients [19]. Its behaviour is similar to that of HBP, i.e., it is more common in older patients ($p < 0.05$), with increasing prevalence among the most elderly women.

Regarding total cholesterol, LDL-C and HDL-C, the current study shows that total cholesterol and LDL-C are high, especially in the population where AF is most prevalent, that is, among older women. Conversely HDL-C, a protective factor for cardiovascular disease, is higher in younger women with AF. There are studies in which no relationship has been established between dyslipidemia and the development of AF [8, 23].

III Atrial Fibrillation and Ischaemic Heart Disease

Since AF and IHD share important CRF as risk factors for their occurrence, it is important to know which patients with AF may suffer from some form of IHD, regardless of the clinical presentation, and if when attending for chest pain the diagnosis of "haemodynamic angina" is correct. We should consider that 90% of cases of imbalance between O₂ delivery and requirements of the myocardium is due to atherosclerotic lesions of the coronary arteries. There are other factors that increase myocardial oxygen demand, such as tachyarrhythmias, which can cause angina in IHD [24]. In AF, we know that chest pain can occur even with a normal heart rate [14]. Also, one of the problems of patients with chest pain attending the ED is inappropriate discharge, which occurs as the source of the pain is deemed non-heart-related, being an AMI. This is estimated to occur in between 2 and 10% of cases [25]. Such patients are not given due medical care and have twice the mortality rate of those

admitted for the same reason. In view of the results of our study, we believe that this group might include patients with AF.

Seventeen percent of our sample were diagnosed with IHD. In these patients, suffering a CRF significantly increases the possibility of having IHD. In the univariate analysis of CRF, HBP very significantly increases the likelihood that AF is associated with the presence of coronary artery disease, with an odds ratio of 5.51. Diabetic patients also have a very significantly increased likelihood of AF and IHD occurring together with an OR of 3.19. Also, suffering from CKD also increases this likelihood (OR 1.80). Being male, according to the present study, is also an independent risk factor of suffering AF together with IHD (OR 1.74).

This study reflects the protective role of HDL-C in the development of cardiovascular disease. Higher levels of HDL-C offer greater protection against the development of IHD. Multivariate analysis shows that being a man, suffering from HBP and DM very significantly increase AF manifesting as a complication of coronary heart disease. In these patients, we must consider the diagnostic possibility that AF behaves like an anginal equivalent. We believe that we must deepen the study into these patients. As a line of future research, we plan to investigate the possible relationship of the clinical manifestations of AF with CRF and the presence of IHD. Also, given the close relationship between AF and CRF, there is the possibility that microvascular disease might play an important role in the emergence and development of AF.

As conclusions of our study, we believe that routine checking for AF in the older population, especially in the presence of dyspnea or syncope, should be a priority. Furthermore, atrial fibrillation can be considered as an anginal equivalent, as our study shows that the likelihood of an AF patient suffering coronary heart disease increases significantly in males suffering from hypertension or DM.

Ethical Approval

The study was approved by the Ethics Committee of the Lleida Biomedical Research Institute. Data confidentiality and anonymity were preserved under the 2018 European Data Protection Act.

Conflicts of Interest

None.

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