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Atrial Fibrillation And Coronary Heart Disease: Fatal Attraction

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Abstract

In this manuscript, the profile and clinical management of hypertensive patients with chronic ischemic heart disease and atrial fibrillation (AF) is examined and whether high heart rate is associated with a different profile is determined. CINHTIA was a cross-sectional and multicenter survey aimed to define the clinical profile of hypertensive patients with chronic ischemic heart disease daily attended in Spain. Blood pressure, LDL-cholesterol and diabetes control rates were established according to ESHESC 2003, NCEP-ATP III and ADA 2005 guidelines, respectively. Out of the 2024 patients, 338 (16.7%) exhibited AF. The group of patients with AF was older and with higher prevalence of diabetes, organ damage and cardiovascular disease. Blood pressure (41.8% vs 34.5%, p=0.014) and diabetes (28.5% vs 20.9%,p=0.044) were worse controlled in patients with AF, with a trend to a lower control of LDL-cholesterol (31.2% vs 26.8%, p=0.093). When distributing patients with AF according to heart rate, except for smoking, left ventricular hypertrophy and peripheral arterial disease that were more frequent in those with higher heart rate, no significant differences were found in other risk factors or organ damage between groups. Blood pressure, glycemia and LDL-cholesterol were worse controlled in the subgroup with highest heart rate. In clinical practice, hypertensive patients with chronic ischemic heart disease and AF have a bad prognosis not only due to a worse clinical profile, but also due to lower risk factors control rates. In contrast with patients at sinus rhythm, higher heart rate was less related with a worse clinical profile in subjects with AF.

Key words: **atrial fibrillation; hypertension; chronic ischemic heart disease; heart rate.**

Introduction

Atrial fibrillation (AF) is the most common arrhythmia found in clinical practice. It has been estimated that about 2.3 million people in North America and 4.5 million people in the European Union have paroxysmal or persistent AF.[1] Moreover, this condition will likely increase in the following years due to the ageing of the population and a rising prevalence of chronic heart disease.[2] AF doubles the mortality rate in affected patients and this condition is associated with a greater risk of stroke and heart failure.[3,4] Some years ago, the AFFIRM trial reported that the management of AF with the rhythm-control strategy offered no survival advantage over the rate-control strategy, and that there were potential advantages, such as a lower risk of adverse drug effects, with the rate-control strategy. This study also emphasized the need of anticoagulation regardless the strategy used in high-risk pa-

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tients.[5] The results of AFFIRM were in some way surprising. Since the restoration of sinus rhythm improves the hemodynamic disturbances associated with AF,[6] one might expect that this would reduce cardiovascular outcomes in this population. As a consequence of the AFFIRM trial, many patients that would be suitable for electrical or pharmacological cardioversion were damned to persist on AF. Moreover, it is likely that some physicians have underestimated the true risk of AF, even with an underuse of anticoagulant therapy.[7] On the other hand, several epidemiologic studies have shown that high heart rate is an independent factor of cardiovascular and all-cause mortality in patients with hypertension or coronary artery heart disease.[8-10] However, in patients with AF, the relationship between heart rates and adverse outcomes is less established.[11,12]

CINHTIA (Cardiopatía Isquémica cróNica e HiperTensIón Arterial en la práctica clínica en España) was a cross-sectional and multicenter survey aimed to define the clinical profile of hypertensive patients with chronic ischemic heart disease attended in daily practice across Spain. In this manuscript, the profile and clinical management of the patients with AF is examined. Moroever, whether high heart rate is associated with a different clinical profile is also determined.

Methods

The methods and design of the study have been previously described.[13,14] Briefly, a total of 112 investigators, all of them cardiologists, participated in the study. Each investigator was asked to include consecutively patients ≥18 years, male or female, with an established diagnosis of hypertension and chronic ischemic heart disease. Patients with an acute coronary syndrome within the three previous months were excluded. Chronic ischemic heart disease was defined as the presence of stable angina, evidence of myocardial ischemia assessed by stress tests, history of myocardial infarction for >3 months or previous revascularization (surgery or percutaneous). The definitions of risk factors, organ damage and associated clinical conditions were performed according to ESH-ESC 2003 guidelines.[15] The presence of organ damage or associated clinical conditions was recorded from the patients´ clinical history. Sedentary lifestyle was defined as the physical activity shorter than a 30 minute daily walk. The diagnosis of atrial fibrillation was made with the baseline electrocardiogram that all patients should have done to be included in the study. Adequate blood pressure, LDL-cholesterol and glycemic control rates were defined according to ESH-ESC 2003, NCEP-ATP III and ADA 2005 guidelines, respectively.[15-17] Regarding heart rate, Diaz et al demonstrated that in the intervals <63 bpm; 63-82 bpm and >82 bpm, the differences in mortality rates were more important, being more relevant in those with > 82 bpm.[18] As a result, we compared those patients with sinus rhythm >82 bpm vs those with the same heart rate but at AF and the clinical management of patients with AF according to the predefined intervals of heart rate.

Statistical analysis

The Chi-square test was used to analyze the relationship between categorical variables. Comparison of continuous variables between groups was performed using the Student's t-test. A p-value <0.05 was used as the level of statistical significance. Database recording was subjected to internal consistency rules and ranges to control inconsistencies/inaccuracies in the collection and tabulation of data (SPSS version 12.0, Data Entry).

Results

Sinus Rhythm vs Atrial Fibrillation (Table 1):

Of the 2024 patients, 1686 (83.3%) were at sinus rhythm and 338 (16.7%) had AF. Patients with atrial fibrillation were older, with more diabetes, organ damage and cardiovascular disease, while dyslipidemia were more frequent in patients with sinus rhythm. More than a half of patients with AF were male, and this proportion was clearly inferior to those subjects at sinus rhythm. Diastolic blood pressure and heart rate were higher in patients with AF. In this group, there was a trend to increased systolic blood pressure values. Concerning to risk factors control rates, blood pressure (41.8% vs 34.5%, p=0.014) and diabetes (28.5% vs 20.9%, p=0.044) were worse controlled in patients with AF, with a trend to a lower control in LDL-cholesterol (31.2% vs 26.8%, p=0.093). Regarding treatments, a higher number of drugs were pre-

Table 1 Clinical characteristics of the overall study population (n=2024).

	SR (n=1686; 83.3%)	AF (n=338; 16.7%)	P
Biodemographic data			
Age (years)	65.9±10.2	71.3±8.1	<0.001
Gender (male) (%)	71.0	54.7	<0.001
BMI (kg/m2)	28.2±3.8	28.6±4.2	0.083
LVEF (%)	58.4±11.3	55.7±12.1	0.001
Cardiovascular risk factors			
Dyslipidemia (%)	79.5	72.2	0.02
Current smoker (%)	12.1	12.3	NS
Diabetes (%)	30.1	44.6	<0.001
Sedentary lifestyle (%)	27.4	39.5	<0.001
Organ damage			
Left ventricular hypertrophy (%)	45.7	65.4	<0.001
Heart failure (%)	13.6	42.9	<0.001
Peripheral arterial disease (%)	14.6	22.2	0.001
Renal impairment (%)	9.9	25.3	<0.001
Stroke (%)	6.9	16.3	<0.001
Physical examination			
SBP (mmHg)	142.3±17.7	144.3±18.7	0.061
DBP (mmHg)	81.5±11.2	82.9±11.4	0.042
Heart rate (bpm)	68.7±10.9	89.7±6.6	<0.001
Treatment (%)			
≥4 drugs	88.2	93.6	0.02
Antihypertensive drugs	100	100	NS
Beta blockers	67.9	62.6	0.072
Calcium channel blockers	43.6	48.0	NS
ACEI	43.1	46.2	NS
Diuretics	29.8	62.3	<0.001
ARB	31.6	38.9	0.012
Alpha-blockers	3.9	7.0	0.018
Lipid lowering drugs	76.2	68.1	0.001
Antidiabetic drugs	25.9	39.8	<0.001
Antiplatelets	95.2	53.8	<0.001
Anticoagulants	2.7	70.5	<0.001
Control rates			
Blood pressure (%)	41.8	34.5	0.014
LDL cholesterol (%)	31.2	26.8	0.093
Diabetes (%)	28.5	20.9	0.044

SR: sinus rhythm; AF: atrial fibrillation; BMI: body mass index; VEF; left ventricular ejection fraction; SBP: systolic blood pressure; DBP: iastolic blood pressure; ACEi: angiotensin- converting enzyme inhibitors; ARB: angiotensin receptor blockers

scribed in subjects with AF (93.6% of patients with AF vs 88.2% of patient at sinus rhythm were taking at least 4 drugs). Although the total number of antihypertensive agents was similar in both groups, diuretics, angiotensin receptor blockers and alpha blockers were more frequently prescribed in patients with AF. There was a trend to a higher use of beta blockers in subjects without AF. Lipid lowering drugs and antiplatelets were more frequent in the population without AF and antidiabetics and anticoagulants in those with AF. One third of the patients with AF were not taking anticoagulants.

Sinus Rhythm vs Atrial Fibrillation in Patients with a Heart Rate >82 bpm (Table 2)

Out of the 2024 patients, 228 (11.3%) had a heart rate >82 bpm. Of these, 174 (74.6%) were at sinus rhythm and 58 (25.4%) in AF. Patients with AF were older, with higher prevalence of diabetes, organ damage and cardiovascular disease. Diastolic blood pressure was higher in the group with AF. Contrary, dyslipidemia was more frequent in the group at sinus rhythm. Interestingly, heart rates values were similar in both groups. Concerning to risk factors control rates, blood pressure (20.9% vs 15.3%, p=0.03) and glycemia (20.3% vs 11.5%, p=0.01) were worse controlled in patients with AF, while no differences were found regarding rates of LDL-cholesterol control (19.8% vs 21.6%, p=NS). There was a trend to a use of more drugs in subjects with AF, with no differences between groups in the number of antihypertensive drugs, but with significant differences in the classes of antihypertensive agents. Accordingly with the higher proportion of dyslipidemia in patients with sinus rhythm, these patients were taking more lipid lowering drugs. Since there was a higher proportion of diabetics in the patients with AF, antidiabetics were more frequently prescribed in this subgroup. Once again, about one third of the patients with AF were not taking anticoagulants.

Clinical Characteristics of Patients with Atrial Fibrillation According to Heart Rate Values (Table 3)

Out of the 338 patients with AF, 63 (18.6%) had a heart rate <63 bpm, 217 (64.2%) 63-82 bpm and 58

Table 2 Clinical characteristics of the study population with a heart rate >82 bpm (n=228)

	SR (n=170; 74.6%)	AF (n=58; 25.4%)	P
Biodemographic data			
Age (years)	66.8±10.8	69.4±8.3	0.02
Gender (male) (%)	66.4	48.9	0.005
BMI (kg/m2)	29.0±3.9	29.7±5.4	NS
LVEF (%)	55.9±12.8	56.1±13.4	NS
Cardiovascular risk factors			
Dyslipidemia (%)	78.5	69.1	0.01
Current smoker (%)	16.8	20.3	NS
Diabetes (%)	36.5	45.5	0.02
Sedentary lifestyle (%)	63.1	67.0	NS
Organ damage			
Left ventricular hypertrophy (%)	53.8	76.9	0.005
Heart failure (%)	26.4	44.0	0.02
Peripheral arterial disease (%)	18.7	26.4	0.02
Renal impairment (%)	12.2	25.5	0.02
Stroke (%)	6.8	16.7	0.03
Physical examination			
SBP (mmHg)	151.2±17.9	153.4±18.0	NS
DBP (mmHg)	86.7±12.1	89.9±11.3	0.03
Heart rate (bpm)	89.9±6.6	89.7±6.6	NS
Treatment (%)			
≥4 drugs	86.9	93.2	0.08
Antihypertensive drugs	100	100	0.999
Beta blockers	58.4	60.3	NS
Calcium channel blockers	38.5	60.0	0.001
ACEI	49.7	43.6	NS
Diuretics	36.6	61.8	0.001
ARB	32.9	45.5	0.03
Alpha-blockers	3.7	3.6	NS
Lipid lowering drugs	72.7	63.6	0.01
Antidiabetic drugs	31.1	43.6	0.01
Antiplatelets	94.4	47.3	
Anticoagulants	1.9	72.7	
Control rates			
Blood pressure (%)	20.9	15.3	0.03
LDL cholesterol (%)	19.8	21.6	NS
Diabetes (%)	20.3	11.5	0.01

(17.2%) >82 bpm. Patients with higher heart rate were more frequently women and obese. Except for smoking, left ventricular hypertrophy and peripheral arterial disease that were more frequent in those with higher heart rate, no significant differences were found in the other cardiovascular risk factors and organ damage between groups. Systolic and diastolic blood pressure were higher in those with a heart rate > 82 bpm. Concerning to risk factors control rates, blood pressure (51.7% vs 34.6% vs 15.3%, p<0.001), glycemia (41.7% vs 18.4% vs 11.5%, p=0.02) and LDL-cholesterol (36.4% vs 25.2% vs 21.6%, p=0.03) were worse controlled in patients with highest heart rate.

With regard to treatments, except for beta blockers that were more frequently prescribed in those with lower heart rate and calcium channel blockers in those with higher heart rates, no significant differences were found between groups.

Discussion

Hypertension and cardiomyopathies are conditions that markedly increase the risk of AF; and the concomitance of AF with any of them rises cardiovascular outcomes.[19-21] The initial analysis of AFFIRM trial reported that treatment of patients with AF and a high risk for stroke or death with a rhythm-control strategy offered no survival advantage over a rate-control strategy. Although the information provided from this study is important, post-hoc analyses of the AFFIRM data have shown new and valuable information. Thus, it has been reported that sinus rhythm was either an important determinant of survival or a marker for other factors associated with survival that were not recorded, determined, or included in the survival model and that warfarin use improved survival.[21] In this context, the results of our survey provide current information about the clinical profile of the patients with ischemic heart disease and hypertension according to the presence of AF.

On the other hand, unfortunately, in some way, the initial reports of AFFIRM trial could provoke that some physicians diminished the perception of risk for AF, as the underuse of anticoagulation denotes.[7] In fact, our data, recorded some years after the AFFIRM publication, showed that about a third of the study population were not taking anticoagulants. All these data suggest that the information provided from clinical trials, cannot always directly translate to every patient attended in daily

Table 2 Clinical characteristics of the study population with atrial fibrillation according to the different intervals of heart rate (n=338).

	<63 bpm (n=63; 18.6%)	63-82 bpm (n=217; 64.2%)	>82 bpm (n=58; 17.2%)	P
Biodemographic data				
Age (years)	71.4±8.7	71.6±7.9	69.4±8.3	NS
Gender (male) (%)	70.7	51.0	48.9	0.02
BMI (kg/m2)	27.3±3.4	28.7±3.9	29.7±5.4	0.004
LVEF (%)	54.0±11.6	56.2±11.9	56.1±13.4	NS
Cardiovascular risk factors				
Dyslipidemia (%)	64.9	73.9	69.1	NS
Current smoker (%)	7.0	12.1	20.3	0.001
Diabetes (%)	43.9	44.4	45.5	NS
Sedentary lifestyle (%)	60.3	61.5	67.0	NS
Organ damage				
Left ventricular hypertrophy (%)	53.4	67.0	76.9	0.018
Heart failure (%)	36.2	45.9	44.0	NS
Peripheral arterial disease (%)	13.8	22.8	26.4	0.030
Renal impairment (%)	27.6	25.1	25.5	NS
Stroke (%)	15.5	16.6	16.7	NS
Physical examination				
SBP (mmHg)	135.0±18.9	144.8±17.8	153.4±18.0	<0.001
DBP (mmHg)	76.2±10.2	82.9±10.7	89.9±11.3	<0.001
Heart rate (bpm)	58.2±4.2	72.7±4.9	89.7±6.6	<0.001
Treatment (%)				
≥4 drugs	89.7	94.7	93.2	NS
Antihypertensive drugs	100	100	100	NS
Beta blockers	79.3	57.7	60.3	0.011
Calcium channel blockers	39.7	48.6	60.0	0.041
ACEI	48.3	45.7	43.6	NS
Diuretics	55.2	64.9	61.8	NS
ARB	41.4	36.5	45.5	NS
Alpha-blockers	10.3	6.7	3.6	NS
Lipid lowering drugs	60.3	69.7	63.6	NS
Antidiabetic drugs	34.5	39.9	43.6	NS
Antiplatelets	58.6	53.4	47.3	NS
Anticoagulants	70.7	71.6	72.7	NS
Control rates				
Blood pressure (%)	51.7	34.6	15.3	<0.001
LDL cholesterol (%)	36.4	25.2	21.6	0.03
Diabetes (%)	41.7	18.4	11.5	0.02

BMI: body mass index; LVEF; left ventricular ejection fraction; SBP: systolic blood pressure; DBP: diastolic blood pressure; ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers

clinical practice, since the population included in these studies is somehow selected.[22-24] The present survey shows that AF is associated with a worse clinical profile, with more cardiovascular risk factors and organ damage. Moreover, despite a higher number of drugs prescribed in this population, cardiovascular risk factors control rates were lower. This is in accordance with studies that have reported that coronary artery disease is associated with an increased mortality in patients with AF.[21]

Although the cross-sectional studies cannot determine whether AF is the cause or the consequence of the worse clinical profile found in patients with hypertension and ischemic heart disease, its presence indicates that these patients should be treated more aggressively that patients at sinus rhythm.

It has been reported that high heart rate is an independent risk factor for cardiovascular disease.[8-10] A recent manuscript analyzed the influence of heart rate from the CINHTIA database, including only those patients at sinus rhythm.[14] Interestingly, this study reported that patients with high heart rate exhibited a poorer prognosis not only due to a worse clinical profile, but suggestively because despite the use of a similar number of drugs, patients with higher heart rate were associated with lesser risk factors control. We performed the same analysis in those patients with AF. Remarkably, although left ventricular hypertrophy and peripheral arterial disease were more frequent in those with higher heart rate, the other cardiovascular risk factors and organ damage did not differ according to heart rate.

This means that although high heart rate is a cardiovascular risk factor for those patients at sinus rhythm, this seems to be different in the subjects with AF. In fact, a substudy of AFFIRM trial showed that after controlling for covariates, there were no significant relation between either achieved heart rate at rest or achieved exercise heart rate and event-free survival.[12] However, in the present survey there was a clear relationship between cardiovascular risk factors control and higher heart rate; higher heart rate, worse control. It is likely that this lower control found in patients with AF and higher heart rate may increase the risk of adverse events. This is in accordance with Cooper et al that showed that patients with AF and higher initial ventricular rate presented an increased risk of cardiovascular hospitalization.[25] As a result, although heart rate is a weaker predictor of cardiovascular outcomes in patients with AF compared with those at sinus rhythm, it should not be ignored since it is associated with poorer risk factors control. The cross-sectional design of the study was chosen to best represent the "real world" of the clinical practice.

Consequently, a large population of hypertensive patients achieved by consecutive sampling was included in the trial. This methodology has its limitations since it reduces the level of control that can be exercised to reduce variation and bias. However, the large number of patients included in the study
minimizes this theoretical limitation. On the other hand, although this kind of design is useful to generate hypothesis, it cannot provide information about clinical outcomes. As a result, it is necessary to perform prospective trials to confirm that the findings obtained from our study translate into a worse cardiovascular prognosis. Since this survey was carried out in a population attended by cardiologists in Spain, the data could be generalized probably only to those countries with the same health care delivery and cardiovascular risk profile. In conclusion, in daily clinical practice, hypertensive patients with chronic ischemic heart disease and AF exhibit a worse clinical profile, with more concomitant cardiovascular risk factors and organ damage, and lower risk factors control. In contrast with patients at sinus rhythm, higher heart rate was less related with a worse clinical profile in subjects with AF.

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