

## Structural heart disease in anticoagulated patients with nonvalvular atrial fibrillation: prevalence and clinical profile in a spanish sample

*Cardiopatía estructural en pacientes anticoagulados con fibrilación auricular no valvular: prevalencia y perfil clínico en una muestra nacional*

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### To the Editor,

Although the definition of nonvalvular atrial fibrillation (NVAF) varies,<sup>1 and 2</sup> it generally does not exclude patients with structural heart disease (SHD), such as certain valve diseases. However, there is limited information on the frequency of this association in Spain. The objective of this article was to report the prevalence and clinical profile of patients with SHD and well as the prevalence of heart failure in a broad Spanish nationwide sample of patients with NVAF.

Data from the FANTASIIA registry<sup>3</sup> were used. This registry included 2178 outpatients with NVAF who were receiving anticoagulation (according to protocol, the ratio of vitamin K antagonists to direct anticoagulants was 4:1). We excluded individuals younger than 18 years, those with prosthetic cardiac devices, those with any grade of mitral stenosis, and those with moderate or severe mitral regurgitation. Participants were enrolled consecutively between June 1, 2013, and October 15, 2014, in 50 Spanish centers selected by the investigators to ensure representation from throughout the country, with the primary objective of assessing the effectiveness of anticoagulation in patients with NVAF by type and quality of treatment. The diagnoses of SHD were taken from the medical records and included the following: coronary artery disease, hypertensive heart disease, dilated cardiomyopathy, hypertrophic cardiomyopathy, significant valve disease (aortic valve, tricuspid valve, or pulmonary valve disease of at least moderate intensity), and other heart diseases. Patients with coronary artery diseases and other concurrent heart diseases were classified as having coronary artery disease. The presence of heart failure was recorded independently. Overall, 47.15% of the sample had SHD (Table 1). The most frequent type of SHD was coronary artery disease (18.14%), followed by hypertensive heart diseases (11.43%), and dilated cardiomyopathy (6.01%). Hypertrophic cardiomyopathy was reported in 2.06% and significant valve diseases in 1.79%. Only 34 patients (1.56%) had isolated NVAF (age < 65 years, with no heart disease or embolic risk factor). Among patients with SHD, there were fewer women and there was a higher rate of cardiovascular risk factors, comorbidities, heart failure, permanent atrial fibrillation, and severe symptoms, and greater embolic and hemorrhagic risk. These patients also had worse left ventricular ejection fractions and renal function, as well as lower hemoglobin levels. Most of the drug classes were more frequently prescribed in patients with SHD, except for angiotensin receptor blockers (prescribed with a similar frequency) and antiarrhythmics and direct anticoagulants (prescribed less often). Overall, 27.23% of the patients had heart failure, with differential characteristics with respect to the sample, similar to patients with SHD, with a few exceptions (Table 2). Studies in Spain have reported a prevalence of coronary artery disease of between 10% and 20% in anticoagulated patients with NVAF,<sup>4, 5 and 6</sup> a similar prevalence to that reported in our study. The CALIFA registry is the only one of these

studies to report frequencies of hypertensive heart failure (15.7%) and valve disease (4%) in Spain.<sup>4</sup> These frequencies are similar to those reported in our registry (11.4% and 2%, respectively). It is possible that exclusion of patients with moderate or severe mitral regurgitation could partly explain this low frequency of heart disease. In the case of heart failure, previous studies have reported frequencies between 22% and 24%,<sup>4, 5 and 6</sup> which are similar to those observed in this series. A limitation of the present study is that several design features (anticoagulation in the 6 months prior to inclusion, exclusion of hospitalized patients, the willingness of the physicians involved in the registry, etc) could have resulted in a biased sample, and so extrapolation of our results to the overall population with NVAF should be made with caution. Furthermore, classification of heart disease was performed using medical records, which, although a true reflection of everyday clinical practice, may have heterogeneous application of diagnostic criteria. Nevertheless, our results, obtained in a large Spanish sample of consecutive patients with NVAF, suggest that almost half have SHD and more than quarter have heart failure. These patients had a different clinical profile to the other patients with NVAF and they received direct anticoagulants less frequently.

**Table 1.** General Characteristics of the Patients Included in the Study by Presence and Type of Structural Heart Disease

Variable	All	No SHD	SHD	P <sub>1</sub>	Coronary artery disease	HTHD	DCM	HCM	Valve disease	Others <sup>a</sup>	P <sub>2</sub>
Patients, n	2178	1151	1027		395	249	131	45	39	79	
<b>Demographic data</b>											
Age, y	73.78 ± 9.42	73.58 ± 9.23	74 ± 9.62	.239	74.37 ± 8.91	75.86 ± 9.08	69.49 ± 10.55	68.36 ± 11.89	79.1 ± 6.61	73.61 ± 10.21	< .001
Female sex, %	43.85	48.74	38.36	< .001	26.33	54.22	21.37	24.44	58.97	48.1	< .001
<b>Cardiovascular risk factors and concurrent disease</b>											
Hypertension	80.39	77.85	83.25	.002	86.33	96.39	63.36	68.89	76.92	74.68	< .001
Hyperlipidemia	52.3	46.57	58.71	< .001	71.9	50.6	54.2	51.11	28.21	41.77	< .001
Diabetes mellitus	29.57	22.76	37.2	< .001	44.56	36.55	32.82	13.33	20.51	27.85	< .001
Current smoker	5	6.08	3.8	.015	3.8	3.21	6.87	4.44	0	3.8	.189
Exsmoker	32.05	26.76	37.98	< .001	49.87	26.9	48.09	22.22	30.77	26.58	< .001
COPD/OSA	17.54	14.07	21.42	< .001	22.53	24.1	19.85	15.56	17.95	17.72	< .001
Renal failure	18.92	13.21	25.32	< .001	29.37	22.09	25.19	13.33	28.21	21.52	< .001
Liver dysfunction	1.1	1.04	1.17	.779	1.52	0.8	0	0	2.56	2.53	.533
Previous CVA	17.13	16.42	17.92	.355	20.76	14.46	15.27	20	17.95	16.46	.427
Modified Charlson comorbidity index	1.14 ± 1.15	0.73 ± 0.92	1.6 ± 1.21	< .001	1.72 ± 1.28	1.46 ± 1.07	1.85 ± 1.15	1.33 ± 1.13	1.46 ± 1.33	1.34 ± 1.15	< .001
<b>Cardiac history</b>											
Heart failure	27.23	0	57.74	< .001	50.63	56.62	95.89	51.11	41.02	51.89	< .001
Preserved ejection fraction (>45%)	14.97	0	31.74	< .001	21.77	45.78	7.63	51.11	38.46	44.3	< .001
Depressed ejection fraction (<45%)	12.26	0	26		28.86	10.84	86.26	0	2.56	7.59	
ODAC	24.49	27.91	20.68		20.3	20.88	16.79	17.78	23.08	22.78	

**AF-related information**

Permanent AF <sup>b</sup>	49.42	43.94	55.56	< .001	51.65	57.43	64.12	51.11	51.28	67.09	< .001
EHRA functional class III-IV <sup>b</sup>	8.06	4.01	12.57	< .001	11.9	13.29	9.16	11.11	20.51	12.66	< .001
CHADS <sub>2</sub> scale	2.25 ± 1.25	1.86 ± 1.11	2.69 ± 1.25	< .001	2.78 ± 1.26	2.82 ± 1.19	2.6 ± 1.32	2.11 ± 1.17	2.54 ± 1.25	2.39 ± 1.19	< .001
CHA <sub>2</sub> DS <sub>2</sub> -VAsC scale	3.7 ± 1.59	3.23 ± 1.42	4.23 ± 1.62	< .001	4.68 ± 1.57	4.28 ± 1.46	3.53 ± 1.66	3.07 ± 1.54	4.21 ± 1.47	3.71 ± 1.59	< .001
HAS-BLED scale	2.01 ± 1.05	1.89 ± 0.96	2.14 ± 1.11	< .001	2.39 ± 1.15	2.15 ± 0.98	1.72 ± 1.15	1.6 ± 1.12	2.28 ± 1.17	1.86 ± 1	< .001

**Examination and diagnostic procedures at initial visit**

Left bundle branch block	7.25	3.55	11.37	< .001	11.28	8.13	23.62	11.11	8.11	7.69	< .001
Ejection fraction, %	58.72 ± 11.09	61.8 ± 7.28	55.34 ± 13.35	< .001	52.57 ± 14.04	60.4 ± 9.59	42.6 ± 13.53	65.91 ± 6.98	61.51 ± 6.99	60.92 ± 7.92	< .001
Hemoglobin, g/dL	13.66 ± 1.71	13.82 ± 1.65	13.48 ± 1.75	< .001	13.49 ± 1.76	13.49 ± 1.6	13.78 ± 1.74	14.26 ± 1.61	12.34 ± 1.81	13.27 ± 1.81	< .001

**Pharmacological therapy**

Diuretics	57.38	47.33	68.59	< .001	61.93	75.5	77.86	60	64.1	75.95	< .001
Aldosterone antagonist	13.88	6.56	22.05	< .001	21.57	17.67	51.91	13.33	10.26	15.19	< .001
ACEI	31.18	24.06	39.12	< .001	42.64	33.33	57.25	26.67	20.51	35.44	< .001
ARB	40.13	39.98	40.29	.883	39.34	53.01	29.01	33.33	20.51	39.24	< .001
Statins	54.57	45.58	64.59	< .001	87.82	52.21	55.73	46.67	35.9	40.51	< .001
Antiplatelet agents	10.42	4.46	17.07	< .001	39.09	2.41	4.58	0	7.69	1.27	< .001
Beta-blockers	60.29	52.06	69.46	< .001	72.59	63.45	85.5	82.22	48.72	51.9	< .001
Digoxin	18.04	14.26	22.24	< .001	17.51	19.68	41.22	20	25.64	24.05	< .001

**Calcium antagonists**

Dihydropyridines	13.65	12.95	14.44		17.51	18.07	3.82	8.89	15.38	8.86	
Verapamil	2.4	2.71	2.05	.003	1.02	3.21	0.76	6.67	0	2.53	< .001
Diltiazem	8.03	9.97	5.85		7.11	6.43	4.58	2.22	7.69	5.06	
Antiarrhythmics	24.82	28.35	20.88	< .001	19.8	22.49	16.79	37.78	20.51	13.92	< .001
VKA	75.51	72.09	79.32		79.7	79.12	83.21	82.22	76.92	77.22	
ODAC	24.49	27.91	20.68	< .001	20.3	20.88	16.79	17.78	23.08	22.78	.006

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ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; COPD/OSA, chronic obstructive pulmonary diseases/obstructive sleep apnea syndrome; CVA, cerebrovascular accident; DCM, dilated cardiomyopathy; EHRA, European Heart Rhythm Association; HCM, hypertrophic cardiomyopathy; HTHD, hypertensive heart disease; ODAC, oral direct anticoagulants; SHD, structural heart disease; VKA, vitamin K antagonist.  $P_1$ , comparison between patients with SHD and without SHD (Mann-Whitney test for continuous variables and chi-square test for categorical variables);  $P_2$ , comparison between patients without SHD, coronary artery diseases, HTHD, DCM, HCM, valve diseases, and others (Kruskal-Wallis test for continuous variables and chi-square test for categorical variables).

<sup>a</sup> Congestive heart disease, congenital heart disease, pericardial disease, others.

<sup>b</sup> According to the European Society of Cardiology.<sup>1</sup>

<sup>c</sup> Flecainide, propafenone, amiodarone, dronedarone, or sotalol.

Quantitative data expressed as mean  $\pm$  standard deviation and qualitative data as percentages.

**Table 2.** General Characteristics of the Patients Included in the Study by Presence and Type of Heart Failure

Variable	All	Without HF	With HF	$P_1$	HF conserved	HF impaired	$P_2$
Patients, n	2178	1585	593		326	267	
<b>Demographic data</b>							
Age, y	73.78 $\pm$ 9.42	73.7 $\pm$ 9.15	73.99 $\pm$ 10.1	.541	75.42 $\pm$ 9.84	72.23 $\pm$ 10.15	< .001
Female sex	43.85	45.68	38.95	.005	53.07	21.72	< .001
<b>Cardiovascular risk factors and concurrent disease</b>							
Hypertension	80.39	79.87	81.79	.317	88.04	74.16	< .001
Hyperlipidemia	52.3	49.15	60.71	< .001	55.21	67.42	.003
Diabetes mellitus	29.57	25.3	40.98	< .001	44.79	36.33	.044
Current smoker	5	5.43	3.88	.14	2.45	5.62	.055
Exsmoker	32.05	29.38	39.96	< .001	29.45	52.81	< .001
COPD/OSA	17.54	15.33	23.44	< .001	23.01	23.97	.846
Renal failure	18.92	14.64	30.35	< .001	27.61	33.71	.127
Liver dysfunction	1.1	1.14	1.01	.805	0.92	1.12	1
Previous CVA	17.13	16.85	17.88	.57	15.64	20.6	.132
Modified Charlson comorbidity index	1.14 $\pm$ 1.15	0.78 $\pm$ 0.94	2.11 $\pm$ 1.12	< .001	2.11 $\pm$ 1.07	2.11 $\pm$ 1.18	1

**Cardiac history**

No heart disease	55.10	74.50	0.00		0.00	0.00	
Coronary artery disease	18.91	12.62	36.76		30.39	43.68	
Hypertensive heart diseases	11.92	6.99	25.92		40.28	10.34	
Dilated cardiomyopathy	6.27	0.52	22.61	< .001	3.53	43.30	< .001
Hypertrophic cardiomyopathy	2.15	1.42	4.23		8.13	0.00	
Valve disease	1.87	1.49	2.94		5.30	0.38	
Other heart diseases <sup>a</sup>	3.78	2.46	7.54		12.37	2.30	

**AF-related information**

Permanent AF <sup>b</sup>	49.42	45.13	60.88	< .001	60.12	61.8	.827
EHRA functional class III-IV <sup>b</sup>	8.06	4.56	17.37	< .001	18.09	16.47	.332
CHADS <sub>2</sub> scale	2.25 ± 1.25	1.92 ± 1.1	3.12 ± 1.2	< .001	3.24 ± 1.09	2.99 ± 1.3	.013
CHA <sub>2</sub> DS <sub>2</sub> -VASC scale	3.7 ± 1.59	3.35 ± 1.43	4.63 ± 1.65	< .001	4.87 ± 1.49	4.34 ± 1.77	< .001
HAS-BLED scale	2.01 ± 1.05	1.93 ± 1	2.2 ± 1.14	< .001	2.24 ± 1.03	2.15 ± 1.25	.346

**Examination and diagnostic procedures at initial visit**

Complete left bundle branch block	7.25	3.8	16.47	< .001	9.97	24.43	< .001
Ejection fraction, %	58.72 ± 11.09	61.68 ± 7.65	51.17 ± 14.45	< .001	60.29 ± 8.3	40.14 ± 12.48	< .001
Hemoglobin, g/dL	13.66 ± 1.71	13.75 ± 1.67	13.41 ± 1.78	< .001	13.2 ± 1.75	13.67 ± 1.78	.001

**Pharmacological therapy**

Diuretics	57.38	49.46	78.41	< .001	78.22	78.65	.920
Aldosterone antagonist	13.88	6.73	32.88	< .001	19.63	49.06	< .001
ACEI	31.18	26.29	44.18	< .001	36.2	53.93	< .001
ARB	40.13	40.51	39.12	.558	42.94	34.46	.042
Statins	54.57	51.49	62.73	< .001	58.28	68.16	.013
Antiplatelet agents	10.42	8.51	15.51	< .001	13.5	17.98	.139
Beta-blockers	60.29	54.6	75.38	< .001	69.02	83.15	< .001
Digoxin	18.04	14.41	27.66	< .001	21.78	34.83	< .001

**Calcium antagonists**

Dihydropyridines	13.65	14.41	11.64		15.34	7.12	
Verapamil	2.4	2.6	1.85	.006	2.15	1.5	.001
Diltiazem	8.03	8.95	5.56		7.36	3.37	
Antiarrhythmics <sup>c</sup>	24.82	26.86	19.39	< .001	21.47	16.85	.175
VKA	75.51	73.46	80.94	< .001	80.06	82.02	
ODAC	24.49	26.54	19.06		19.94	17.98	.599

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ACEI, angiotensin converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; COPD/OSA, chronic obstructive pulmonary diseases/obstructive sleep apnea syndrome; CVA, cerebrovascular accident; EHRA, European Heart Rhythm Association; HF, heart failure; ODAC, oral direct anticoagulants; SHD, structural heart disease; VKA, vitamin K antagonist.  $P_1$ , comparison between patients with HF and without HF (Mann-Whitney test for continuous variables and chi-square test for categorical variables);  $P_2$ , comparison between patients with HF and conserved systolic function and patients with HF and depressed systolic function (Kruskal-Wallis test for continuous variables and chi-square test for categorical variables).

<sup>a</sup> Congestive heart diseases, congenital heart diseases, pericardial disease, others.

<sup>b</sup> According to the European Society of Cardiology.<sup>1</sup>

<sup>c</sup> Flecainide, propafenone, amiodarone, dronedarone, or sotalol.

Quantitative data expressed as mean  $\pm$  standard deviation and qualitative data as percentages.

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