

# Atrial Fibrillation in Decompensated Heart Failure: Associated Factors and In-Hospital Outcome

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#### **Abstract**

Background: Studies on atrial fibrillation (AF) in decompensated heart failure (DHF) are scarce in Brazil.

Objectives: To determine AF prevalence, its types and associated factors in patients hospitalized due to DHF; to assess their thromboembolic risk profile and anticoagulation rate; and to assess the impact of AF on in-hospital mortality and hospital length of stay.

Methods: Retrospective, observational, cross-sectional study of incident cases including 659 consecutive hospitalizations due to DHF, from 01/01/2006 to 12/31/2011. The thromboembolic risk was assessed by using CHADSVASc score. On univariate analysis, the chi-square, Student t and Mann Whitney tests were used. On multivariate analysis, logistic regression was used.

Results: The prevalence of AF was 40%, and the permanent type predominated (73.5%). On multivariate model, AF associated with advanced age (p < 0.0001), non-ischemic etiology (p = 0.02), right ventricular dysfunction (p = 0.03), lower systolic blood pressure (SBP) (p = 0.02), higher ejection fraction (EF) (p < 0.0001) and enlarged left atrium (LA) (p < 0.0001). The median CHADSVASc score was 4, and 90% of the cases had it  $\ge$  2. The anticoagulation rate was 52.8% on admission and 66.8% on discharge, being lower for higher scores. The group with AF had higher in-hospital mortality (11.0% versus 8.1%, p = 0.21) and longer hospital length of stay (20.5  $\pm$  16 versus 16.3  $\pm$  12, p = 0.001).

Conclusions: Atrial fibrillation is frequent in DHF, the most prevalent type being permanent AF. Atrial fibrillation is associated with more advanced age, non-ischemic etiology, right ventricular dysfunction, lower SBP, higher EF and enlarged LA. Despite the high thromboembolic risk profile, anticoagulation is underutilized. The presence of AF is associated with longer hospital length of stay and high mortality. (Arq Bras Cardiol. 2014; 103(4):315-322)

Keywords: Atrial Fibrillation; Heart Failure; Ventricular Dysfunction, Left; Inpatients; Hospital Mortality.

#### Introduction

Atrial fibrillation (AF) is a very important health problem. It is the most frequent arrhythmia in patients with chronic heart or lung diseases, affects 1% of the population, and is associated with an increase in the risk for stroke and with a double-fold increase in mortality<sup>1,2</sup>. Heart failure (HF) is considered a severe public health problem worldwide due to its elevated prevalence, increasing incidence and high costs. In addition, it has a high hospitalization rate, being one of the major causes of morbidity and mortality in industrialized countries<sup>3</sup>. Decompensated HF (DHF) is the major cause of hospitalization of patients older than 65 years in the Brazilian

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Unified Health Care System (SUS) and has an elevated in-hospital mortality<sup>4</sup>. Approximately 50% of the patients are readmitted in six months due to DHF<sup>5</sup>.

The concomitance of AF and HF can be explained because both share similar risk factors and mechanisms, or because there is a causal relationship between the entities. Considering that the morbidity and mortality attributed to each of those comorbidities are significant, the concomitance of AF and HF identifies individuals at higher mortality risk. Most studies on AF and HF have been conducted with outpatient cohorts, and studies on patients with DHF are rare<sup>6,7</sup>.

Brazilian data on AF and HF are still scarce, and no Brazilian study has assessed in a representative population the prevalence of associated factors, the thromboembolic risk profile and the influence of AF on in-hospital mortality and on hospital length of stay of patients with DHF.

The present study had the following objectives: to determine the prevalence of AF and its types in patients hospitalized due to DHF at the university-affiliated Clementino Fraga Filho hospital (HU); to define the independent risk factors associated with AF; to analyze the thromboembolic

risk profile and anticoagulation rate of those patients; and to assess the impact of AF on in-hospital mortality and on hospital length of stay.

## Method

This retrospective, observational, cross-sectional study of incident cases included 659 consecutive hospitalizations due to DHF, from 01/01/2006 to 12/31/2011, at HU. The patients were identified by using the search tool of the HU's electronic medical record, and both electronic and printed medical records were used to identify the variables of interest.

Based on the electronic medical record, all index hospitalizations of DHF cases were assessed, in the search for any supraventricular arrhythmia reported. The medical records with the following terms were selected: atrial fibrillation; atrial flutter; supraventricular tachycardia; atrial tachycardia; atrial rhythm. From that selection, all printed medical records with those terms were obtained, and the presence of AF on electrocardiogram (ECG) was assessed. All ECGs with AF since the beginning of the patient's follow-up at HU were scanned or photographed and analyzed according to the definitions. Other supraventricular tachycardias were not considered. Occasional doubts were clarified with an experienced examiner.

Heart failure was defined according to the criteria of the European Society of Cardiology published in 20058: presence of HF symptoms at rest or during exertion in addition to evidence of cardiac dysfunction at rest, and, in case of doubt, the additional criterion of response to specific treatment for HF was used. On cardiac function assessment, the echocardiography performed at the index-hospitalization (performed in 64% of the cases) or data of previous echocardiographies were considered. Heart failure with preserved ejection fraction (HFPEF) was diagnosed based on those criteria when ejection fraction (EF) was greater than 40%.

The criterion used to diagnose DHF was the appearance of new symptoms or recent worsening of functional class, requiring urgent hospitalization for compensation. Atrial fibrillation was diagnosed based on the definition of the European Society of Cardiology<sup>9</sup>: irregular rhythm with RR intervals with no repeated pattern; absence of sinus P waves, and possible visualization of atrial electrical activity on some leads, mainly V1, in which case, the atrial cycle length should be variable and shorter than 200 ms.

Atrial fibrillation was classified according to the European Society of Cardiology<sup>9</sup> as follows:

- paroxysmal, when AF episodes ended spontaneously, requiring neither drugs nor electrical cardioversion, lasting usually less than seven days, and frequently less than 24 hours, with or without recurrences;
- persistent, when AF episodes did not end spontaneously, requiring pharmacological and/or electrical cardioversion to sinus rhythm reversion;
- permanent, when AF was always present, and attempts to sinus rhythm reversion failed or when arrhythmia reversion was not attempt by any means.

The thromboembolic risk of patients with AF was estimated by use of the CHADSVASc score, which attributes 1 point to the presence of HF or EF < 40%, systemic arterial hypertension (SAH), age between 65 and 74 years, diabetes mellitus (DM), vascular disease, and female sex; and 2 points to age  $\geq$  75 years, ischemic stroke, transient ischemic attack or thromboembolism.

The outcomes assessed were as follows: in-hospital all-cause mortality and hospital length of stay.

For the purpose of statistical analysis, data were stored in a specific data bank, elaborated in the SPSS software, version 15.0. In descriptive analysis, the categorical variables were described as frequency and percentage, and the continuous variables as mean and standard deviation or median and interquartile interval, according to the distribution pattern. On univariate analysis, to compare categorical variables, the chi-square test was used, and, for continuous variables, Student *t* test or Mann-Whitney U test, as indicated. On multivariate analysis, logistic regression model was used.

To assess intra- and interobserver reliability in the diagnosis of AF, 100 electrocardiographic tracings were randomly selected and blindly reviewed by the study's author and by a specialist in arrhythmia. Kappa statistics was used to measure agreement between the observers. Those indices were high: intraobserver, 0.96, and interobserver, 0.84.

The significance level adopted was 5%.

The present study was approved by the Committee on Ethics and Research (065/09). Because this was a retrospective study without intervention, informed written consent was not required by that committee.

#### Results

Table 1 shows the general characteristics of the cases of DHF included in this study, such as the type of HF. Of those cases, 426 (64.6%) underwent echocardiography during hospitalization, and Table 2 shows the results. The presence of AF was assessed in 4,013 ECG, and that arrhythmia was identified during hospitalization in 264 cases (40.1%) as follows: permanent AF, in 194 cases (73.4%); and paroxysmal and persistent AF, in 35 cases each (13.3%).

Table 3 shows the comorbidities and demographic, clinical and laboratory variables in the groups with and without AF. Atrial fibrillation was associated with the following: older age; reduced systolic blood pressure (SBP); higher prevalence of non-ischemic and valvar etiologies; previous hospitalization; lower prevalence of DM; previous stroke; smoking habit; HFPEF; less frequent use of resynchronization therapy; and left bundle-branch block (LBBB). Table 4 compares the echocardiographic variables between the groups with and without AF. Atrial fibrillation was associated with the following: more preserved systolic function; lower left ventricular dilatation; larger left atrium; and higher prevalence of right ventricular dysfunction and of moderate to severe mitral regurgitation.

The multivariate model included variables with p < 0.10 in the comparison between the groups with and without AF. Table 5 shows the variables that maintained an independent

Table 1 – Demographic, clinical and laboratory characteristics of the hospitalizations due to DHF in this study

Variables *	Result
Age (years) †	64 (54-75)
SBP (mm Hg) †	120 (100-130)
HR (bpm) †	80 (70-96)
Hemoglobin (mg/dL) †	12.6 (11.2 – 14.0)
Urea (admission) †	53.0 (36.5 – 82)
Creatinine (admission) †	1.2 (0.9 – 1.7)
Sodium (mEq/L) †	137 (134 – 140)
Male sex ‡	54.6
HFPEF ‡ 16.1	
Ischemic etiology ‡	41.0
Previous hospitalization due to DHF ‡	57.6
DM‡	30.9
SAH‡	69.7
CKF ‡	22.8
Previous stroke ‡	8.2
COPD ‡	9.3
PVD ‡	7.6
Smoking habit ‡	22.9
Pacemaker ‡	10.0
Resynchronization ‡	3.9
ICD ‡	3.6
LBBB ‡	35.2

DHF: decompensated heart failure; SBP: systolic blood pressure; HR: heart rate; HFPEF: heart rate with preserved ejection fraction; DM: diabetes mellitus; SAH: systemic arterial hypertension; CKF: chronic kidney failure; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; LBBB: left bundle-branch block; ICD: implantable cardioverter defibrillator. (\*) n of 659 hospital admissions; (†) median (IQ); (‡) percentage.

association with AF after logistic regression. Figure 1 shows the thromboembolic risk profile estimated by use of the CHADSVASc score, whose median in this study was 4, with 90% of the cases having a score  $\geq 2$ .

The warfarin sodium use rate on hospital admission was 52.8%, increasing to 66.8% on hospital discharge. Figure 2 shows the anticoagulation rate on hospital admission and on discharge for each CHADSVASc score.

Regarding the outcomes, the mean hospital length of stay of patients with DHF was  $18.0 \pm 14$  days. Patients with AF had longer hospital length of stay than those without AF (means of  $20.5 \pm 16$  days and  $16.3 \pm 12$  days, respectively; p = 0.001). The in-hospital mortality of patients with DHF was 9.3%, being 11.0% in those with AF and 8.1% in those without AF (p = 0.21). Mortality did not statistically differ according to the types of AF as follows: paroxysmal, 8.6%; persistent, 17.1%; and permanent, 10.3% (p = 0.44).

Table 2 – Echocardiographic variables on hospital admission in this study

Variables *	Result
EF (%)†	33 (26 – 45.5)
LVd (mm) †	61 (53 – 70)
LVs (mm) †	51 (41 – 59)
LA (mm) †	47 (42 – 52)
PASP (mm Hg) †	46 (38 – 55)
Normal ventricular function ‡	69 (17.1)
Mild ventricular dysfunction ‡	20 (5.0)
Moderate ventricular dysfunction ‡	61 (15.1)
Severe ventricular dysfunction ‡	253 (62.8)
Right ventricular dysfunction ‡	185 (50.5)
Moderate or severe MR ‡	240 (60.2)

EF: ejection fraction; LVd: diastolic left ventricle; LVs: systolic left ventricle; LA: left atrium; PASP: pulmonary artery systolic pressure; MR: mitral regurgitation; (\*) n of 426 hospital admissions; (†) Median (IQ); (‡) n (%).

### **Discussion**

This is the first Brazilian study to assess several aspects related to AF in patients hospitalized due to DHF. The results confirm a high prevalence of AF in DHF in Brazil, mainly of the permanent type, with a high thromboembolic risk profile and low rate of use of anticoagulants. Atrial fibrillation was associated with several factors, implying longer hospital length of stay and higher mortality, although with no statistical significance.

The present study used the same methodology of international registries of DHF, with consecutive cases, in which each hospitalization is considered one case<sup>10</sup>. Thus, one patient can contribute with more than one hospitalization. However, the analysis of the general characteristics of the case series shows important differences as compared with international registries, mainly regarding age, which was on average 10 years younger than that reported in the following registries: EHFS, 71.3 years<sup>11</sup>; ADHERE, 72.5 years<sup>10</sup>; and OPTIMIZE-HF, 78 years<sup>12</sup>. Another important difference is the much lower prevalence of HFPEF in our study population (16%) as compared with that of international registries (50%)11. In addition to younger age, underdiagnosis of HFPEF in Brazil might be the major cause of that difference. Such data have already been reported in a previous study of our group<sup>13</sup>, are in accordance with the public health network profile reported in the EPICA study<sup>14</sup>, and show the importance of Brazilian studies for proper knowledge about the Brazilian reality.

The prevalence of AF was 40% during hospitalization, being in accordance with that reported in the literature as follows: 41% in the EHFS II Registry, and 33% in the ADHERE Registry<sup>15</sup>. The study by Latado et al<sup>16</sup>, assessing patients with DHF admitted to intensive care units, has reported a 22% prevalence of AF, similar to that reported in the study by Villacorta et al<sup>17</sup> (22.3%).

Table 3 - Demographic, clinical, laboratory variables and comorbidities in the groups with and without atrial fibrillation

Variables	AF *	No AF †	p Value
Age (years) ‡	66.8 (13.5)	62.2 (14.2)	< 0.0001
SBP (mm Hg) §	110 (100-130)	120 (106-140)	< 0.0001
HR (bpm) §	84 (70-98)	80 (70-96)	0.07
Hemoglobin (mg/dL) §	12.6 (11.5-14)	12.5 (11-14)	0.52
Urea §	56 (39-85)	50.5 (35-80)	0.12
Creatinine §	1.2 (0.9-1.6)	1.2 (0.9-1.7)	0.77
Sodium §	136 (133-139)	137 (134-140)	0.06
Male sex //	56.4	53.4	0.45
Ischemic etiology //	30.6	47.8	< 0.0001
Valvar etiology *4	16.2	4.8	< 0.0001
Previous hospitalization due to HF //	64.5	52.6	0.004
DM //	22.1	36.8	< 0.0001
SAH //	66.6	71.8	0.17
CKF //	19.8	23.8	0.46
Previous stroke //	11.8	5.7	0.005
Smoking habit //	17.2	26.8	0.004
COPD //	9.5	9.1	0.84
PVD //	8.8	6.7	0.33
HFPEF //	16.8	9.5	0.008
Pacemaker //	12.6	17.6	0.16
ICD //	6.7	5.2	0.53
Resynchronization //	1.5	5.5	0.011
LBBB //	28.4	39.9	0.032

AF: atrial fibrillation; SBP: systolic blood pressure; HR: heart rate; HF: heart failure; HFPEF: heart rate with preserved ejection fraction; DM: diabetes mellitus; SAH: systemic arterial hypertension; CKF: chronic kidney failure; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; LBBB: left bundle-branch block; ICD: implantable cardioverter defibrillator. (\*) n of 264 hospital admissions; (†) n of 395 hospital admissions; (‡) mean (SD); (§) median (IQ); (//) percentage.

Table 4 – Echocardiographic variables in the groups with and without atrial fibrillation

Variables	AF*	No AF†	p Value	
EF (%) ‡	42.4 (19.5)	35.1 (15.4)	0.003	
LVd (mm) ‡	59.3 (12.3)	62.5 (11.3)	0.02	
LVs (mm) ‡	46.9 (14.8)	51.6 (13.1)	0.004	
LA (mm) ‡ 50.9 (9.9)		45.0 (9.2)	< 0.0001	
PASP (mm Hg) ‡	47.9 (14.8)	47.9 (15.0)	0.78	
Normal ventricular function §	27.3	10.8		
Mild ventricular dysfunction §	4.5	5.2		
Moderate ventricular dysfunction §	9.7	18.5	0.0004	
Severe ventricular dysfunction §	58.4	65.5	< 0.0001	
Right ventricular dysfunction §	57.7	47.3	0.06	
Moderate or severe MR §	e or severe MR § 66.9		0.03	

AF: atrial fibrillation; EF: ejection fraction; LVd: diastolic left ventricle; LVs: systolic left ventricle; LA: left atrium; PASP: pulmonary artery systolic pressure; MR: mitral regurgitation; (\*) n of 154 hospital admissions; (†) n of 249 hospital admissions; (‡) mean (SD); (§) percentage.

Table 5 - Logistic regression model: variables associated with atrial fibrillation

Variables	В	p Value	OR	95% CI
Age	0.05	< 0.0001	1.053	1.03-1.08
Ischemic etiology	-0.77	0.023	0.46	0.24-0.90
Right ventricular dysfunction	0.76	0.03	2.13	1.09-4.20
SBP	-0.02	0.02	0.98	0.97-1.00
EF	0.05	< 0.0001	1.05	1.03-1.08
LA	0.10	< 0.0001	1.11	1.06-1.16

B: regression constant; OR: Odds Ratio; CI: confidence interval; SBP: systolic blood pressure; EF: ejection fraction; LA: left atrium.

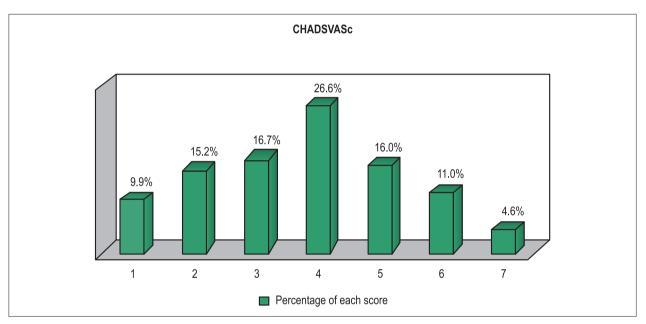


Figure 1 – Percentage distribution of hospitalizations of patients with atrial fibrillation according to CHADSVASc scoring.

Permanent AF was the most frequent type (73.5%), followed by the paroxysmal and persistent types (at equal proportions). Only a few studies have assessed the type of AF in cases of DHF. Some studies have only reported the occurrence of a new episode of AF or permanent AF during hospitalization. A Polish study with 99 patients published in 2008<sup>18</sup> described results similar to those of the present study, with permanent AF in 62% of the cases and paroxysmal or persistent (not differentiated) in 38%.

Similarly to ours, some studies have demonstrated an association of AF with more advanced age<sup>19-21</sup>. That might be explained by the fact that the conditions predisposing to AF are common among the elderly.

Similarly, the association of AF with higher EF and HFPEF found in the present study has been reported in the international literature. In the GWTG-HF<sup>21</sup>, the echocardiogram performed during hospitalization has also shown greater frequency of HFPEF and higher EF in the group with AF. A Canadian study published in 2006<sup>22</sup>, assessing

2,802 patients with their first episode of DHF, has shown that the group with HFPEF had a significantly higher proportion of AF. Those data are in accordance with those of other clinical trials, such as the CHARM study<sup>23</sup>.

An enlarged left atrium was strongly associated with AF. That was already expected, because left atrial enlargement is related to atrial cardiac remodeling and to the pathophysiology of AF in patients with HF24. Several studies have shown an association between lower SBP and AF. Our case series had a median SBP of 110 mm Hg versus 120 mm Hg in patients without AF. In the GWTHF<sup>21</sup>, the result was similar, but with higher absolute levels as compared with those of the present study (143 mm Hg for sinus rhythm versus 135 mm Hg with AF). In the Cardiovascular Research Network, published in 2013<sup>25</sup>, the differences in SBP were smaller, when analyzed into the following three groups: 132 mm Hg for sinus rhythm; 129 mm Hg for previous AF; and 132 mm Hg for new-onset AF. Reduced SBP is an important prognosis predictor in DHF, according to the ADHERE Registry<sup>10</sup>, and its association with AF emphasizes the potential severity of the patients.

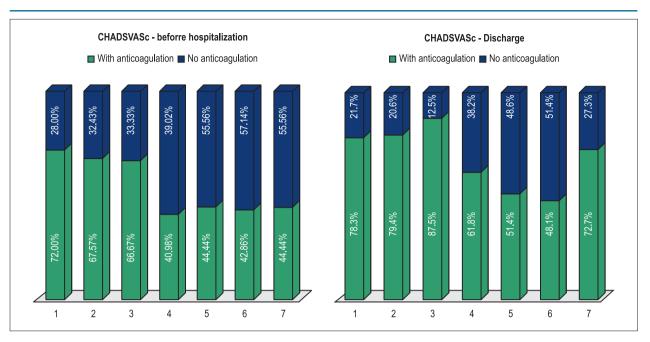


Figure 2 – Percentage of anticoagulation according to the CHADSVASc score on hospital admission and discharge

In the present study, the CHADSVASc score of patients with AF showed an elevated thromboembolic risk profile: median of 4, and 90% of the cases with a score  $\geq 2$ . However, the anticoagulation rate prior to hospital discharge was only 66%. Underutilization of anticoagulants in patients with AF and DHF has also been reported in the international literature. The ADHERE Registry Linked to Medicare Claims<sup>26</sup> has shown that 79% of hospitalized patients eligible for anticoagulation have been discharged with no anticoagulants, even at a high risk for stroke. Not receiving warfarin sodium was independently associated with a higher risk of death one year after hospital discharge.

The present study showed an additional interesting and paradoxical finding: the use of anticoagulants decreased with a higher thromboembolic risk score. This might reflect the concern with hemorrhagic complications of the anticoagulant therapy, because elevated thromboembolic risk scores, such as CHADSVASc score, are associated with also higher bleeding risk scores, such as HASBLED score. Our data did not allow assessing the bleeding risk profile of the cases with AF by using the HASBLED score, and not even the percentage of patients with absolute contraindications to anticoagulants, so that those results could be better interpreted. Nevertheless, the figures strongly suggest that there is significant underutilization of anticoagulation in those patients, mainly those at higher thromboembolic risk, which might have an important impact on morbidity and mortality after hospital discharge, as shown in the ADHERE Study<sup>15</sup>.

The higher future availability of new anticoagulants, in addition to better knowledge on those new drugs and experience with them, might help to increase the anticoagulation use rate in those patients, because part of that underutilization might be explained by the difficulties and limitations of traditional coumarin anticoagulation.

The mean hospital length of stay in the present study was very high (18 days), much higher than that obtained in the SUS data bank (DATA-SUS), around 6 days<sup>27</sup>. A study assessing hospitalizations due to HF in São Paulo from 1992 to 2010 has reported a mean hospital length of stay of 10 days ( $\pm$  1.0)<sup>28</sup>. The hospital length of stay of patients with DHF at public and private health care institutions reported in the EPICA project<sup>14</sup> was the closest to that found in the present study. At private health care institutions, the mean hospital length of stay was 8 days, while at public health care institutions, that figure increased to 12.6 days. According to international studies, that hospital length of stay tends to be shorter. The analysis of Medicare data<sup>29</sup>, assessing hospitalizations due to HF, has shown a mean hospital length of stay of 5.5  $\pm$  5.4 days. The ADHERE Registry<sup>30</sup> has reported a hospital length of stay of 4.3 days.

The longer hospital length of stay of our case series suggests greater severity of the cases, requiring a longer length of stay for clinical compensation. The difficulty of having access to beds at a tertiary hospital tends to select more severely ill patients. In addition, the functioning characteristics of the university-affiliated hospital might contribute to increase the hospital length of stay of those patients.

In our study, the presence of AF was associated with a significant increase in the hospital length of stay, on average from 14 to 20 days, which is in accordance with other articles published. In GWTG-HF²¹, the hospital length of stay was significantly longer in patients with AF (mean of 5 days in the presence of AF versus 4 days with sinus rhythm). In the study by Rivero-Ayerza et al³¹, patients with AF of recent onset had a longer length of stay at the intensive care unit (2.6  $\pm$  5.3 days) as compared with those with previous AF (1.2  $\pm$  3.5 days) and those without AF (1.5  $\pm$  4.1 days). Similarly to hospitalization due to DHF, in the present study, hospitalizations due to AF were much longer. No Brazilian study has assessed the difference in the hospital length of stay due to DHF between the groups with and without AF.

In the present study, in-hospital mortality was 9.26%, greater than that reported in the international literature, such as the ADHERE Registry (4%), once again suggesting the more severe profile of the patients in this study, as shown by Gripp et al<sup>13</sup>.

The comparison with Brazilian studies shows similar results. Barreto et al<sup>32</sup> have reported an 8.8% in-hospital mortality of patients admitted due to DHF at the Cotoxó hospital, while the EPICA study<sup>14</sup> has reported a 9% in-hospital mortality, both very similar to that of the present study.

Those results show that the presence of AF was associated with a 35% higher mortality (from 8.1% to 11%), but without reaching statistical significance, probably because the sample lacks statistical power (type II error). International registries with much larger samples have shown similar results: the EHFS, assessing new-onset AF<sup>31</sup>, has reported mortality due to DHF of 7% without AF and of 8% with AF, and significant difference only for new-onset AF (12%); the GWTG-HF has reported mortality of 4% in the presence of AF and of 2.6% without AF.

The major limitations of this study result from its retrospective characteristic, depending on information extracted from medical records. Current criteria for the HFPEF diagnosis could not be used, because they were not available in the medical records consulted. Finally, echocardiography was not performed at all hospitalizations, the use of previous tests being required to assess the type of HF.

## Conclusion

Atrial fibrillation is very common in DHF, the most prevalent type being permanent AF. Atrial fibrillation is associated with more advanced age, non-ischemic etiology, right ventricular dysfunction, lower SBP, higher EF and enlarged left atrium. Although the thromboembolic risk profile is high, anticoagulation is underutilized and tends to be less frequent in the highest risk scores. The presence of AF is associated with longer hospital length of stay and high in-hospital mortality.

#### **Author contributions**

Conception and design of the research: Mendes FSNS, Atié J, Garcia MI, Sousa AS, Feijó LA, Xavier SS; Acquisition of data: Mendes FSNS, Gripp EA, Xavier SS; Analysis and interpretation of the data: Mendes FSNS, Atié J, Gripp EA, Xavier SS; Statistical analysis: Xavier SS; Writing of the manuscript: Mendes FSNS; Critical revision of the manuscript for intellectual content: Atié J, Garcia MI, Sousa AS, Feijó LA, Xavier SS.

#### Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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#### **Study Association**

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