ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical characteristics and prognostic impact of atrial fibrillation in patients with chronic heart failure

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Informed consent statement: All patients signed an informed consent and approved the utilization of their anonymized clinical information for medical research purposes.

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Data sharing statement: Statistical code and dataset are available from the corresponding author at his email address. All data are anonymized and there is no risk of patients' identification.

Abstract

AIM

To assess the prevalence, clinical characteristics and independent prognostic impact of atrial fibrillation (AF) in chronic heart failure (CHF) patients, and the potential protective effect of disease-modifying medications, particularly beta-blockers (BB).

METHODS

We retrospectively reviewed the charts of patients referred to our center since January 2004, and collected all clinical information available at their first visit. We assessed mortality to the end of June 2015. We compared patients with and without AF, and assessed the association between AF and all-cause mortality by

RESULTS

A total of 903 patients were evaluated (mean age 68 ± 12 years, 73% male). Prevalence of AF was 19%, ranging from 10% to 28% in patients ≤ 60 and ≥ 77 years, respectively. Besides the older age, patients with AF had more symptoms (New York Heart Association II-III 60% *vs* 44%), lower prevalence of dyslipidemia (23% *vs* 37%), coronary artery disease (28% *vs* 52%) and left bundle branch block (9% *vs* 16%). On the contrary, they more frequently presented with an idiopathic etiology (50% *vs* 24%), a history of valve surgery (13% *vs* 4%) and received overall more devices implantation (31% *vs* 21%). The use of disease-modifying medications (*i.e.*, BB and ACE inhibitors/angiotensin receptor blockers) was lower in patients with AF (72% *vs* 80% and 71% *vs* 79%, respectively), who on the contrary were more frequently treated with symptomatic and antiarrhythmic drugs including diuretics (87% *vs* 69%) and digoxin (51% *vs* 11%). At a mean follow-up of about 5 years, all-cause mortality was significantly higher in patients with AF as compared to those in sinus rhythm (SR) (45% *vs* 34%, *P* value < 0.05 for all previous comparisons). However, in a multivariate analysis including the main significant predictors of all-cause mortality, the univariate relationship between AF and death (HR = 1.49, 95%CI: 1.15-1.92) became not statistically significant (HR = 0.98, 95%CI: 0.73-1.32). Nonetheless, patients with AF not receiving BB treatment were found to have the worst prognosis, followed by patients with SR not receiving BB therapy and patients with AF receiving BB therapy, who both had similarly worse survival when compared to patients with SR receiving BB therapy.

CONCLUSION

AF was highly prevalent and associated with older age, worse clinical presentation and underutilization of disease-modifying medications such as BB in a population of elderly patients with CHF. AF had no independent impact on mortality, but the underutilization of BB in this group of patients was associated to a worse long-term prognosis.

Key words: Atrial fibrillation; Chronic heart failure; Beta-blockers; Digoxin; Prognosis

Core tip: In this retrospective analysis atrial fibrillation (AF) was diagnosed in 1 out of 5 patients with chronic heart failure. The arrhythmia was associated with older age, worse clinical presentation and underutilization of disease-modifying medications, particularly beta-blockers (BB) and ACE inhibitors/angiotensin receptor blockers. At a mean follow-up of about 5 years, mortality was significantly higher in patients with AF, and patients with AF not receiving BB treatment were found

to have the worst prognosis. However, in a multivariate analysis including main significant predictors of all-cause mortality, such as age, gender, blood pressure, coronary artery disease, comorbidities and medications, the univariate relationship between AF and death became not statistically significant.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia and frequently coexists with chronic heart failure (CHF)[1]. It is commonly held that CHF decompensated by a transient AF episode has better prognosis than CHF with permanent AF[2]. However, the real prognostic impact of permanent AF in patients with CHF remains poorly understood[3-6] and a matter of current debate[7,8]. Conflicting data also exist on medical treatment of CHF patients with AF, particularly in the elderly. Indeed, although beta-blockers (BB) are a corner-stone therapy of CHF, their value when AF coexists has recently been questioned[9]. Thus, the aim of this study was to investigate the prevalence, clinical characteristics and prognostic impact of permanent AF in a cohort of unselected CHF patients referred to a single tertiary outpatient clinic. In particular, we assessed whether a diagnosis of permanent AF was independently associated with increased all-cause mortality, and whether this association was influenced by medical therapy with BB.

MATERIALS AND METHODS

Study population

The study population was drawn from a tertiary CHF outpatient clinic; all patients with a diagnosis of CHF, New York Heart Association (NYHA) functional class between I and III and a readable rest ECG were considered eligible. Data were retrospectively collected by reviewing all available complete records of the first visit at the clinic between January 1st 2004 and May 31st 2015. A total of 941 unique patients were originally included; 23 patients were subsequently excluded because they did not have a readable ECG, and another 10 patients because the heart rhythm was not clearly definable due to pacemaker stimulation. Mortality was ascertained by consulting hospital and administrative databases and death registers. Follow-up was censored at June 30, 2015; survival status was not retrievable

in five patients, leaving a final study sample of 903 patients.

All patients signed an informed consent allowing the utilization of their anonymized clinical information for medical research purposes, as approved by the local Institutional Review Board.

Variables of interest

Permanent AF (subsequently indicated solely as AF) was defined as a documented history of AF that had persisted for more than 6 mo and was confirmed by a surface ECG at first visit. A diagnosis of coronary artery disease (CAD) was ascertained by coronary angiography, and patients without any luminal stenosis > 50% were considered without CAD. Information regarding previous percutaneous and/or surgical revascularization and previous valve surgery was also routinely collected. The remaining patients with other CHF etiology (including hypertensive cardiac disease, valve disease, tachycardiomyopathy, idiopathic cardiomyopathy) were all incorporated in a single group. Implanted devices were divided as follows: Mono/bicameral pacemakers (PM), biventricular pacemakers (CRT-D/CRT-P) and implantable-cardioverter defibrillators (ICD). Hypertension was defined by a blood pressure $\geq$ 140/90 and/or the use of antihypertensive medications. Diabetes mellitus was defined by history of diabetes mellitus and/or a random plasma glucose $\geq$ 200 mg/dL and/or fasting plasma glucose $\geq$ 126 mg/dL and/or an HbA1c $\geq$ 7% and/or use of antidiabetic treatments. Dyslipidemia was defined by history of high cholesterol levels and/or a total cholesterol $\geq$ 200 mg/dL. Present or former smoking was ascertained by medical interview, and patients who had smoked > 100 cigarettes/year were considered as smoker. Cancer history was defined by a previous or current malignancy, regardless of disease status at the time of medical interview. A clinical diagnosis of chronic obstructive pulmonary disease (COPD) was made during the visit based on the presence of a history of COPD, and/or signs and/or symptoms suggestive of COPD including chronic productive cough, chronic wheezing, emphysema or bronchitis.

Lab tests completed within 3 mo from the study visit were considered to identify anemia (hemoglobin levels < 13.5 g/dL in male and < 12.5 g/dL in female patients) and chronic kidney disease (CKD: Estimated glomerular filtration rate < 60 mL/min per 1.73 m^2 as calculated from creatinine using the CKD-EPI formula).

The following variables were collected from a basal 12-lead standard ECG: Heart rhythm, heart rate, and presence of a right or left bundle branch block. Left ventricular ejection fraction (LVEF) was derived from a transthoracic echocardiogram obtained within 3 mo from the first visit, and patients with a LVEF > 45% were considered as having a preserved LVEF.

Information regarding ongoing medications was ascertained for each patient, and included CHF-modifying drugs (*i.e.*, BB, ACE inhibitors and/or angiotensin receptor antagonists (ACEi/ARB) and aldosterone antagonists)], diuretics (both loop diuretics and thiazides), other blood pressure lowering drugs (such as calcium channel blockers and alpha blockers), digoxin, amiodarone, lipid-lowering drugs (*i.e.*, statins) antiplatelet drugs (including aspirin, clopidogrel and - for very few patients - ticagrelor), and anticoagulants (*i.e.*, warfarin and very few patients with direct factor X or thrombin inhibitors).

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentages. Characteristics of patients with AF *vs* sinus rhythm (SR) were compared using student's *t* test and χ^2 test as appropriate. To define univariate predictors of all-cause mortality, we compared characteristics of dead *vs* alive patients at the end of follow-up. Univariate and multivariate predictors of mortality were also investigated by Cox regression analysis. Variables with a *P* value < 0.10 in univariate analysis were selected based on clinical and statistical criteria (*i.e.*, to ease the interpretation of the analysis and to avoid multicollinearity) and introduced into a multivariate model. A backward elimination of variables with a *P* value > 0.05 was performed to obtain the final multivariate reduced model. Kaplan-Meyer curves were obtained for all-cause mortality in patients with AF *vs* SR, and also based on the use of BB medications. All analyses were performed using SAS for Windows (version 9.2; SAS Institute Inc, Cary, NC). The statistical review of the manuscript was performed by a biomedical statistician.

RESULTS

Study population

From January 2004 to May 2015, a total of 903 patients were evaluated who satisfied our inclusion criteria (mean age 68 ± 12 years, 73% male). Prevalence of AF was 19%, ranging from 10% to 28% in patients $\leq$ 60 and $\geq$ 77 years of age, respectively (*P* < 0.0001). Characteristics of study population by the presence of AF or SR are summarized in Table 1. Patients with AF were significantly more symptomatic in comparison to patients with SR (NYHA class II-III 60% *vs* 44%). CAD was less common in patients with AF than in those with SR (28% *vs* 52%), as were previous coronary revascularization (21% *vs* 37%) and dyslipidemia (23% *vs* 37%). By contrast, a non-ischemic etiology was more frequent in the AF group (50% *vs* 24%), as well as a history of previous valve surgery (13% *vs* 4%). Patients with AF received overall more devices implantation (31% *vs* 21%). ECG data showed a lower prevalence of left bundle branch block (9% *vs* 16%) and a higher mean heart rate (80 ± 19 *vs* 70 ± 13) in patients with AF. Patients with AF were more frequently diagnosed with CHF with preserved LVEF (29% *vs* 21%).
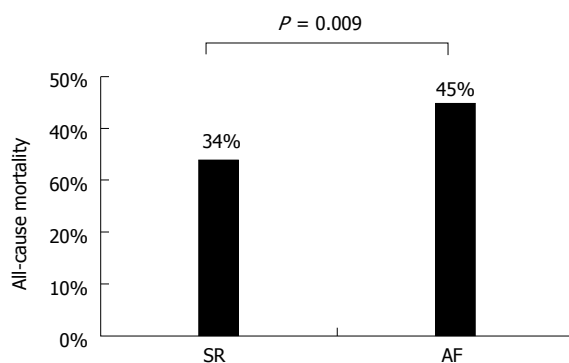
Figure 1 All-cause mortality in patients with atrial fibrillation and in patients with sinus rhythm. SR: Sinus rhythm; AF: Atrial fibrillation.

Treatment differences in patients with AF

When AF was present, there was a significant lower percentage of treatment with disease-modifying medications, including BB (72% *vs* 80%) and ACEi/ARB (51% *vs* 66%), as well as a less frequent use of calcium channel blockers (6% *vs* 13%), statins (28% *vs* 49%), amiodarone (6% *vs* 13%) and antithrombotic treatment (19% *vs* 63%). On the contrary, treatment with diuretics (87% *vs* 69%), aldosterone blockers (46% *vs* 37%), digoxin (87% *vs* 69%) and oral anticoagulants (82% *vs* 16%) was lower in patients with SR (Table 1).

Mortality in the study population

At a mean follow-up of 59 ± 40 mo (range 1 to 137 mo), all-cause mortality was significantly higher in patients with AF as compared to those in SR (45% *vs* 34%, Figure 1). Patients with AF were more likely to die during the course of our extended follow-up (Figure 2). Table 2 shows univariate associations of variables listed in Table 1 with all-cause mortality. At univariate analysis, patients who died had more frequently a diagnosis of AF than those who survived (23% *vs* 16%), were significantly older at baseline (71 ± 10 years *vs* 66 ± 12 years), had lower systolic and diastolic blood pressure (127 ± 19 mmHg *vs* 130 ± 19 mmHg, 72 ± 10 mmHg *vs* 76 ± 10 mmHg, respectively) and had more often NYHA class II-III (60% *vs* 40%), idiopathic etiology of CHF (32% *vs* 26%), implantable devices (29% *vs* 19%), PM stimulation (14% *vs* 9%) and a history of ventricular tachycardia (7% *vs* 4%). Moreover, diabetes mellitus (32% *vs* 24%), cancer history (14% *vs* 8%), COPD (18% *vs* 10%), chronic anemia (11% *vs* 8%), CKD (10% *vs* 6%), and use of diuretics (82% *vs* 67%), digoxin (26% *vs* 14%) or aldosterone blockers (45% *vs* 35%) was more frequent in the group of patients who died at follow-up. On the contrary, variables associated with survival were the presence of dyslipidemia (27% *vs* 39%), a preserved LVEF (19% *vs* 24%), and the use of BB (72% *vs* 82%) and ACEi/ARB (75% *vs* 79%) (Table 2).

In a multivariate analysis including the main significant predictors of all-cause mortality, the univariate relationship between AF and death (HR = 1.49, 95%CI:

Table 1 Characteristics of study population by presence of atrial fibrillation or sinus rhythm at baseline

	Atrial fibrillation (*n* = 173)	Sinus rhythm (*n* = 730)	*P* value
Demographics and physical examination			
Age (yr)	72 ± 11	66 ± 12	< 0.0001
Age ≥ 65 yr (%)	81	60	< 0.0001
Male gender (%)	70	73	0.42
SBP (mmHg)	127 ± 18	130 ± 19	0.10
DBP (mmHg)	74 ± 10	75 ± 10	0.47
NYHA II-III (%)	60	44	0.0002
Aetiology			
CAD (%)	28	52	< 0.0001
Previous CABG/PCI (%)	21	37	< 0.0001
Without CAD (%)	22	24	0.58
Others/idiopathic (%)	50	24	< 0.0001
Valve surgery (%)	13	4	< 0.0001
Device			
Any PM (%)	30	19	0.001
CRT-P/CRT-D (%)	10	7	0.14
ICD (%)	11	16	0.07
Any Device (%)	31	21	0.005
History of VT (%)	2	5	0.06
Risk factors			
Hypertension (%)	61	60	0.81
Diabetes mellitus (%)	24	28	0.39
Dyslipidaemia (%)	23	37	0.0004
Ever smoke (%)	27	41	0.001
Comorbidities			
Cancer history (%)	12	10	0.47
COPD (%)	14	13	0.55
Anaemia (%)	6	10	0.11
CKD (eGFR < 60) (%)	7	8	0.57
ECG			
Heart Rate (bpm)	80 ± 19	70 ± 13	< 0.0001
PM stimulation (%)	24	8	<0.0001
Right Bundle Branch Block (%)	7	5	0.65
Left Bundle Branch Block (%)	9	16	0.01
Echocardiogram			
Preserved LVEF (> 45%) (%)	29	21	0.022
LVEF (%)	38 ± 14	35 ± 12	0.05
Medications			
Beta-blockers (%)	72	80	0.01
ACEi/ARB (%)	71	79	0.02
Beta-blockers and ACEi/ARB (%)	51	66	0.0003
Aldosterone blockers (%)	46	37	0.02
Diuretics (%)	87	69	< 0.0001
Calcium channel blockers (%)	6	13	0.01
Alfa-blockers (%)	6	8	0.55
Digoxin (%)	51	11	< 0.0001
Statin (%)	28	49	< 0.0001
Amiodarone (%)	6	13	0.01
Antithrombotic treatment (%)	19	63	< 0.0001
OAT (%)	82	16	< 0.0001
DAPT (%)	2	16	< 0.0001
OAT and antithrombotic (%)	8	2	0.0006
Antithrombotic only (%)	11	61	< 0.0001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NYHA: New York Heart Association; CAD: Coronary artery disease; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; PM: Pacemaker; CRT-P/D: Cardiac resynchronization therapy pacing/defibrillator; ICD: Internal cardioverter defibrillator; VT: Ventricular tachycardia; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate (obtained by CKD-EPI formula); LVEF: Left ventricular ejection fraction; ACEi: ACE inhibitors; ARB: Angiotensin receptor blockers; OAT: Oral anticoagulant treatment; DAPT: Dual anti-platelet therapy.
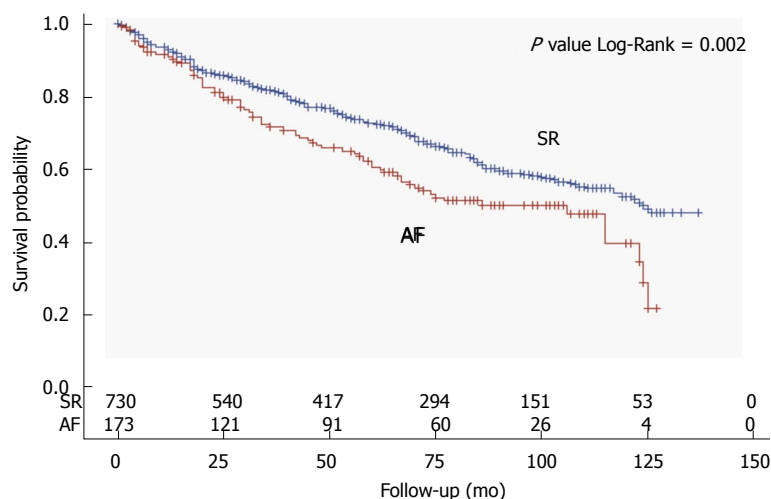
Figure 2 Kaplan-Meier curves of overall survival according to the presence of atrial fibrillation or sinus rhythm. SR: Sinus rhythm; AF: Atrial fibrillation.
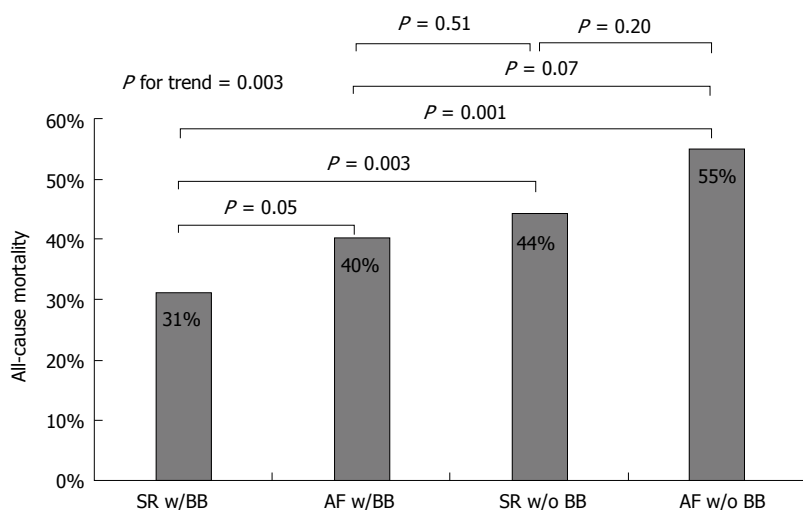

Figure 3 All-cause mortality in patients with atrial fibrillation as compared to patients with sinus rhythm based on the use of beta-blocker medications. SR: Sinus rhythm; AF: Atrial fibrillation; BB: Beta-blocker.

1.15-1.92) became not statistically significant (HR = 0.98, 95%CI: 0.73-1.32, Table 3). In the final reduced multivariate model, independent predictors at baseline of all-cause mortality were the following: Older age, male gender, lower systolic blood pressure, NYHA class Ⅱ-Ⅲ, presence of CAD at coronary angiography, presence of an implanted device, diagnosis of diabetes mellitus, COPD or anemia, history of cancer, non-use of ACEi/ARB and statins, and use of diuretics and digoxin (Table 3).

Mortality differences by BB medications
All-cause mortality was studied also through a comparison between patients with SR and patients with AF based on the presence or absence of BB treatment. Patients with AF not receiving BB treatment were found to have the worst prognosis, followed by patients with SR not receiving BB therapy and patients with AF receiving BB therapy, who both had similarly worse survival when compared to patients with SR

receiving BB therapy (Figure 3). During the course of follow-up, patients with AF not receiving BB treatment had the worst prognosis, followed by patients with SR not receiving BB therapy together with patients with AF receiving BB therapy, and finally patients with SR receiving BB therapy (Figure 4).

DISCUSSION
Overall, our data demonstrates that in ambulatory patients with CHF, the presence of permanent AF is associated with worse clinical presentation, underuse of disease-modifying medications including BB, and possibly worse prognosis. After accounting for confounders, we found no independent association between AF and all-cause mortality; nonetheless, we found a significantly worse prognosis in AF patients with CHF not receiving BB treatment.

Patients with AF in our study population were older and had a higher NYHA functional class at presentation,
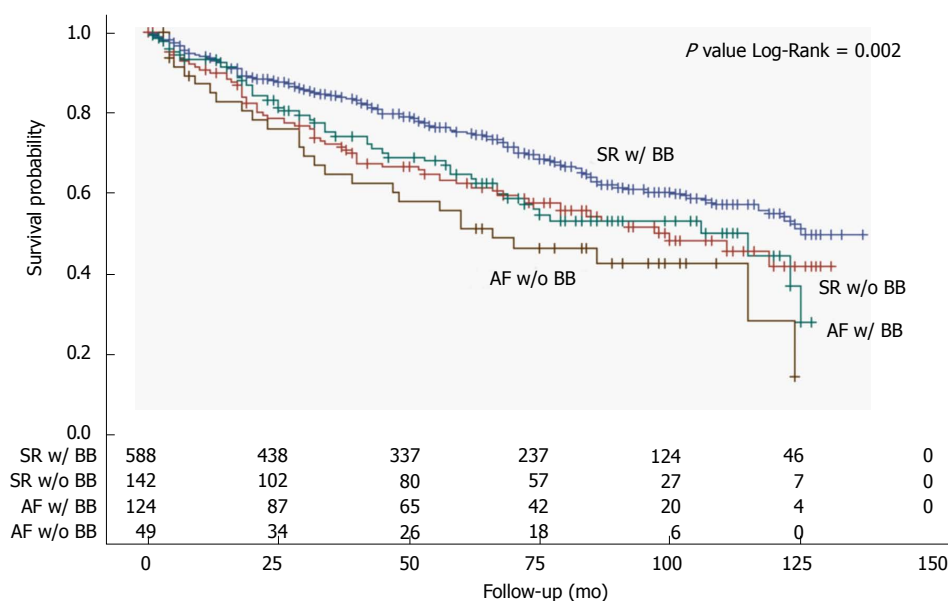
Figure 4 Kaplan-Meier curves of overall survival according to the presence of atrial fibrillation or sinus rhythm and the use of beta-blocker medications.
SR: Sinus rhythm; AF: Atrial fibrillation; BB: Beta-blocker.

Table 2 Characteristics of study population by survival or death

	Death (*n* = 324)	Alive (*n* = 579)	*P* value	HR (95%CI)	*P* value
Atrial fibrillation (%)	23	16	0.0085	1.48 (1.14-1.92)	0.0028
Demographics and physical examination					
Age (yr)	71 ± 10	66 ± 12	< 0.0001	1.05 (1.04-1.06)	< 0.0001
Male gender (%)	25	29	< 0.0001	2.4 (1.85-3.07)	< 0.0001
SBP (mmHg, 10)	127 ± 19	130 ± 19	0.0238	0.93 (0.88-0.99)	0.0228
DBP (mmHg, 10)	72 ± 10	76 ± 10	< 0.0001	0.76 (0.67-0.85)	< 0.0001
NYHA II-III (%)	60	40	< 0.0001	1.7 (1.35-2.10)	< 0.0001
Aetiology					
CAD (%)	51	46	0.18		
Previous CABG/PCI (%)	33	35	0.57		
Without CAD (%)	17	27	0.0002	0.53 (0.4-0.71)	< 0.0001
Others/idiopathic	32	26	0.049	1.29 (1.02-1.63)	0.0302
Valve surgery (%)	5	6	0.57		
Device					
Any PM (%)	28	17	0.0003	1.64 (1.29-2.1)	< 0.0001
CRT-P/CRT-D (%)	8	7	0.32		
ICD (%)	20	13	0.0027	1.45 (1.1-1.9)	0.0074
Any device (%)	29	19	0.0006	1.57 (1.23-2.00)	0.0002
History of VT (%)	7	4	0.0258	1.53 (1.01-2.32)	0.0439
Risk factors					
Hypertension (%)	58	61	0.2619		
Diabetes mellitus (%)	32	24	0.0053	1.72 (1.36-2.17)	< 0.0001
Dyslipidaemia (%)	27	39	0.0003	0.68 (0.53-0.87)	0.0023
Ever smoke (%)	32	41	0.0055	0.92 (0.72-1.16)	0.4668
Comorbidities					
Cancer history (%)	14	8	0.0044	1.89 (1.37-2.60)	< 0.0001
COPD (%)	18	10	0.0006	1.84 (1.4-2.40)	< 0.0001
Anaemia (%)	11	8	0.0521	2.22 (1.57-3.13)	< 0.0001
CKD (eGFR < 60) (%)	10	6	0.0551	2.807 (1.85-4.25)	< 0.0001
ECG					
Heart rate (bpm, 10)	72 ± 15	70 ± 15	0.1026	1.06 (0.99-1.14)	0.0805
PM stimulation (%)	14	9	0.0438	1.56 (1.14-2.14)	0.0057
Right bundle branch block (%)	7	5	0.0866	1.38 (0.9-2.1)	0.1321
Left bundle branch block (%)	12	16	0.0761	0.75 (0.53-1.05)	0.0958
Echocardiogram					
Preserved LVEF (> 45%) (%)	19	24	0.056	0.74 (0.56-0.98)	0.0345
LVEF (%)	34 ± 12	36 ± 11	0.0015	0.98 (0.97-0.99)	0.0008
Medications					
Beta-blockers (%)	72	82	0.0003	0.67 (0.53-0.85)	0.0012
ACEi/ARB (%)	75	79	0.0994	0.69 (0.53-0.88)	0.0032

Beta-blockers and ACEi/ARB (%)	32	68	0.003	0.66 (0.53-0.83)	0.0002
Aldosterone blockers (%)	45	35	0.0033	1.57 (1.26-1.95)	< 0.0001
Diuretics (%)	82	67	< 0.0001	2.5 (1.87-3.31)	< 0.0001
Calcium channel blockers (%)	14	11	0.1588		
Alfa-blockers (%)	8	7	0.8049		
Digoxin (%)	26	14	< 0.0001	1.6 (1.25-2.05)	0.0002
Statin (%)	39	48	0.0088	0.8 (0.64-1.00)	0.0513
Amiodarone (%)	12	12	0.8421		
Antithrombotic treatment (%)	56	54	0.5669		
OAT (%)	31	27	0.2374		
DAPT (%)	10	15	0.0282	0.89 (0.62-1.29)	0.5394
OAT and antithrombotic (%)	3	4	0.4946		
Antithrombotic only (%)	53	50	0.4149		

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NYHA: New York Heart Association; CAD: Coronary artery disease; CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention; PM: Pacemaker; CRT-P/D: Cardiac resynchronization therapy pacing/defibrillator; ICD: Internal cardioverter defibrillator; VT: Ventricular tachycardia; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate (obtained by CKD-EPI formula); LVEF: Left ventricular ejection fraction; ACEi: ACE inhibitors; ARB: Angiotensin receptor blockers; OAT: Oral anticoagulant treatment; DAPT: Dual anti-platelet therapy.

Table 3 Univariate and multivariate predictors of all-cause mortality

	Univariate		Multivariate full		Multivariate reduced	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Atrial fibrillation	1.48 (1.14-1.92)	0.0028	0.98 (0.73-1.32)	0.8896		
Age (1 yr)	1.05 (1.04-1.06)	< 0.0001	1.04 (1.03-1.05)	< 0.0001	1.04 (1.03-1.05)	< 0.0001
Male gender	2.4 (1.85-3.07)	< 0.0001	1.45 (1.11-1.90)	0.0068	1.48 (1.13-1.93)	0.0045
SBP (10 mmHg)	0.93 (0.88-0.99)	0.0228	0.92 (0.86-0.98)	0.0084	0.91 (0.86-0.97)	0.0057
NYHA II-III	1.7 (1.35-2.10)	< 0.0001	1.3 (1.03-1.65)	0.0265	1.32 (1.05-1.66)	0.0195
Without CAD	0.53 (0.4-0.71)	< 0.0001	0.61 (0.44-0.84)	0.0023	0.58 (0.43-0.80)	0.0008
Any device	1.57 (1.23-2.00)	0.0002	1.65 (1.19-2.29)	0.0028	1.57 (1.23-2.02)	0.0004
Dyslipidaemia	0.68 (0.53-0.87)	0.002	0.8 (0.60-1.06)	0.1151		
Diabetes mellitus	1.72 (1.36-2.17)	< 0.0001	1.63 (1.27-2.08)	0.0001	1.59 (1.25-2.04)	0.0002
Cancer history	1.89 (1.37-2.60)	< 0.0001	1.82 (1.31-2.54)	0.0004	1.84 (1.33-2.56)	0.0003
COPD	1.84 (1.4-2.4)	< 0.0001	1.33 (0.98-1.80)	0.0707	1.38 (1.02-1.86)	0.0359
Anaemia	2.22 (1.57-3.13)	< 0.0001	1.82 (1.23-2.69)	0.0027	1.95 (1.37-2.79)	0.0002
CKD (eGFR < 60)	2.81 (1.85-4.25)	< 0.0001	1.42 (0.87-2.29)	0.1577		
Preserved LVEF (> 45%)	0.74 (0.56-0.98)	0.034	0.91 (0.68-1.22)	0.5369		
PM stimulation	1.56 (1.14-2.14)	0.006	0.91 (0.59-1.40)	0.6561		
Beta-blockers	0.67 (0.53-0.85)	0.001	0.83 (0.64-1.09)	0.1903		
ACEi/ARB	0.69 (0.53-0.88)	0.003	0.77 (0.59-1.01)	0.0634	0.73 (0.56-0.94)	0.0169
Aldosterone blockers	1.57 (1.26-1.95)	< 0.0001	1.11 (0.86-1.43)	0.429		
Diuretics	2.5 (1.87-3.31)	< 0.0001	1.51 (1.09-2.10)	0.0134	1.58 (1.17-2.15)	0.0031
Digoxin	1.6 (1.25-2.05)	0.0002	1.29 (0.97-1.73)	0.0807	1.31 (1.00-1.72)	0.0482
Statin	0.8 (0.64-1.00)	0.051	0.8 (0.60-1.05)	0.1108	0.71 (0.55-0.90)	0.0057

Any device included any pacemaker or internal-cardioverter defibrillator. SBP: Systolic blood pressure; NYHA: New York Heart Association; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate by CKD-EPI formula; LVEF: Left ventricular ejection fraction; PM: Pacemaker; ACEi: ACE inhibitors; ARB: Angiotensin receptor blocker.

in agreement with other data reported in the literature[10,11]. The presence of AF was also associated with an increased use of symptomatic medications, such as diuretics and digoxin, and a less frequent use of CHF-modifying medications, such as BB and ACEi/ARB. In addition, CAD was less represented among AF patients, whereas the prevalence of valve disease and non-cardiovascular comorbidities was greater in this group of patients, who interestingly also had a higher mean LVEF and more frequently a preserved LVEF (here LVEF > 45%). Recent literature emphasizes the stronger correlation of AF with CHF with preserved LVEF as compared to reduced LVEF[12], though this association was rather weak in our population, possibly because it mainly included CHF patients with reduced LVEF. CHF patients with AF are usually characterized by the presence of multiple comorbidities, and it is still unknown whether the adverse outcomes associated with AF are related to the arrhythmia itself, or to the burden of comorbidities associated with this diagnosis[8].

Contrasting findings have been published regarding a potential independent contribution of AF to increased mortality in patients with CHF. Some studies found AF to be an independent predictor of worse outcomes[13,14] whereas others found no independent association after accounting for confounders[4-6]. Two meta-analyses reported a 30%-40% increased risk of mortality when CHF is associated with a diagnosis of AF[7,8], irrespective of LVEF. In our study population, the coexistence of CHF and permanent AF resulted in a worse outcome,

as shown by the Kaplan-Meyer survival curve in Figure 2. However, after adjusting for other significant predictors (including older age, male sex, systolic blood pressure, NYHA class II-III, ischemic etiology, pacemaker implanted, diabetes mellitus, history of cancer, COPD, anemia), AF did not show an independent impact on overall mortality (Table 3). This finding is in accordance with the abovementioned analyses from the COMET[5] and the V-HeFT study[4]. Advanced age and CHF severity have been shown to largely explain the association between AF and mortality in CHF patients, and this was also true in our study population, in which beyond age and NYHA functional class, we demonstrated a significant and independent contribution of non-cardiovascular comorbidities to mortality, including COPD, anemia and a history of cancer.

Although the use of BB in the setting of CHF has recently been disputed[9], we observed the worst prognosis in AF patients not receiving BB medications, while patients with AF receiving BB presented a significant survival benefit similar to those with SR not receiving BB but still lower than those with SR receiving BB treatment (Figures 3 and 4). It is still uncertain whether BB therapy reduces morbidity and mortality in patients with AF, but a class IA indication is given for these medications in patients with CHF and AF to control ventricular rate[15]. Our present results support this recommendation and point against the underuse of BB medications that is generally observed in CHF with AF as compared to those with SR[9].

The contribution of treatment with digoxin to the worse outcome in patients with CHF and AF is a matter of current debate[16]. We observed that digoxin was used in half of our patients with AF, and in only 1 out of 10 patients with SR. These percentages refer to the use of digoxin at first study visit, which happened some years ago starting in 2004, and probably do not reflect the current use of this medication in our clinical practice. Trends in the use of digoxin for AF have been steadily decreasing in the recent years, at least in the American population[17], and this drug has class IIa/B recommendations for rate control treatment of AF in most recent European[15] and American[18] HF guidelines. This is because of an overall neutral effect of this drug on mortality[19], and some observational studies showing an independent association with increased mortality[20]. Accordingly, its utilization was a strong and independent predictor of mortality at multivariate analysis in our retrospective analysis (Table 3).

The presence of implantable devices was associated with increased mortality in our final multivariate model. This finding appears counterintuitive at first, but may have different explanations. In particular, the presence of a device may be representative of a sicker CHF patient, for which the implantation of a device is generally indicated. In addition, when we distinguished patients with only pacing devices from patients with a resynchronizing device (either CRT-P or CRT-D) and patients with an ICD, only patients with a pacing device

and an ICD implanted showed a statistically significant worse prognosis (Table 2). Treatment of LV dyssynchrony with CRT device is expected to improve EF and symptoms over time, which in turn has a major positive impact on outcomes, including survival[15]. This is also at least partially reflected by the positive prognostic association of the presence of a left bundle branch block that we found in our study population (Table 2), which is likely indicative of the effect of CRT in patients that were implanted with a resynchronizing device after the first study visit at our clinic.

In contrast to what would be expected, dyslipidemia was associated with a reduction of mortality. In the setting of CHF, the presence of low cholesterol levels is known to identify patients with more advanced cardiac disease (*i.e.*, with sarcopenia and possibly cachexia), and low concentrations of low-density lipoproteins have been associated with worse prognosis[15]. Patients with advanced cardiac disease are also less likely to receive lipid-lowering medications such as statins, for which the indication in CHF patients without active CAD is lacking[15]. Thus, the presence of dyslipidemia and the use of statins in our CHF population of advanced age probably indicate a healthier patient, which explain the associations of both these variables with a better prognosis.

Our analysis has several limitations that should be acknowledged. First, this is a retrospective analysis, thus our findings can only be interpreted with the intrinsic limits of this methodology. Second, cardiac rhythm was defined at first study visit, and we cannot exclude subsequent rhythm modifications. Third, we assessed mortality from all causes and could not obtain clear information specifically on cardiovascular and non-cardiovascular mortality. Because a history of cancer was a significant predictor of increased mortality, in an attempt to remove deaths due to malignancy, we performed sensitivity analysis excluding patients with a positive history of cancer. This analysis included 812 patients, of whom 659 with SR (81%) and 153 with AF (19%), and a total of 279 deaths out of the original 324. In this subsample, final results of independent predictors of mortality were substantially unchanged (data not shown). Finally, due to the low number of patients with preserved LVEF, we could not explore the interaction between LVEF and AF on mortality.

Our retrospective cohort study investigating a real-world population of elderly ambulatory CHF patients confirmed the association of AF with older age and worse clinical presentation previously reported in the literature. It further highlighted how a diagnosis of AF also led to an underutilization of disease-modifying medications such as BB and ACEi/ARBs, and to a more frequent use of symptomatic and antiarrhythmic drugs, particularly diuretics and digoxin, which in turn were independently associated with worse prognosis. In multivariate analysis, AF had no independent impact on all-cause mortality, which nonetheless was found to be the highest in AF patients not receiving BB medications.

Further prospective randomized studies are needed investigating the independent prognostic impact of BB treatment in CHF with AF.

COMMENTS

Background

Atrial fibrillation (AF) frequently coexists with chronic heart failure (CHF). Conflicting data exist on the prevalence, clinical characteristics and medical treatment of HF patients with AF, particularly in the elderly. The independent prognostic impact of AF in these patients also remains unknown, as well as the potential protective effect of disease-modifying medications, particularly beta-blockers (BB).

Research frontiers

The independent prognostic impact of AF in patients with CHF is a current matter of debate, and many have argued that this association is solely explained by other conditions associated to this arrhythmia, particularly comorbidities and underuse of disease-modifying medications.

Innovations and breakthroughs

This analysis confirmed the relevant clinical impact of AF in patients with CHF, although like other previous studies in the literature found no independent prognostic impact of this arrhythmia on overall mortality at long-term follow-up after accounting for several important confounders which are frequently found in these elderly CHF patients.

Applications

The study findings highlight the underuse of disease-modifying medications in CHF patients with coexisting AF, particularly BB. This is a matter of current debate in the clinical arena, with international guidelines giving a strong recommendation for the use of BB as a first-line treatment to control ventricular rate in euvolemic patients with New York Heart Association class I-III CHF. Efforts need to be done in order to increase the appropriate use of these medications in CHF with AF in the real world.

Peer-review

This interesting study by Gigli *et al* examined the impact of AF on outcomes in patients with CHF. The authors conclude that AF did not have an independent impact on mortality, but BB use appeared to affect this relationship.

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