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Age-Dependent Prognostic Significance of Atrial Fibrillation in Outpatients with Chronic Heart Failure: Data from the Italian Network on Congestive Heart Failure Registry

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Key Words
Atrial fibrillation · Heart failure · Elderly · Prognosis

Abstract
Objectives: The role of atrial fibrillation (AF) in older patients with heart failure (HF) is controversial because many variables seem to influence their outcome. We investigated the predictivity of AF in 3 age groups of outpatients with HF. ***Methods:*** We analyzed 8,178 outpatients enrolled in the Italian Network on Congestive Heart Failure Registry with HF diagnosed according to the European Society of Cardiology criteria. A trained cardiologist established the diagnosis of AF and HF at the entry visit at each center. We stratified the population into 3 age groups, as follows: group A, ≤65 years; group B, 66–75 years, and group C, >75 years. ***Results:*** Group A was composed of 4,261 patients, 683 with AF (16.0%); in group B there were 2,651 patients, 638 with AF (24.1%), and group C was composed of 1,266 patients, 412 with AF (32.5%). The 1-year mortality rate was higher in AF patients in all groups. In a multivariate model, AF remained an independent risk factor for death in groups A and B, but not in group C [group A: hazard ratio (HR) 1.42, 95% confidence interval (CI) 1.10–1.81; group B: HR 1.29, 95% CI 1.00–1.67; group C: HR 1.05, 95% CI 0.78–1.43]. ***Conclusion:*** The prevalence of AF increased with age and was associated with a higher mortality rate. However, AF independently predicted all-cause mortality only in patients aged ≤75 years.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in patients living in industrialized countries [1], and heart failure (HF) has to be considered the prevalent cardiovascular disease in the 21st century [2]. Both diseases are frequently diagnosed in the elderly, in whom they often coexist because one predisposes the patient to

[1] See the Appendix for a complete list of the centers and investigators participating in the Italian Network on Congestive Heart Failure.

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the other [3–5]. This frequent association markedly worsens symptoms and increases morbidity and hospitalizations in older patients, with an elevated cost for health care services [6]. The pathophysiological correlations between these two cardiac disorders have already been clarified [7–9] and are partially related to the same risk factors as those relevant for ischemic heart disease and hypertension [8, 9] or the same precipitating factors (e.g. pulmonary infections or decompensated chronic obstructive pulmonary disease) [10, 11]. Alteration of sympathetic activation, neurohormonal pathway overexpression and enlargement of the heart chambers [12, 13] are some of the pathophysiological mechanisms that link these two disorders and that are responsible for their progressive clinical deterioration. The hemodynamic and clinical consequences of the presence of AF in patients with HF are well known and are correlated with the lack of atrial synchrony and contribution to left ventricular filling, irregular ventricular rate, increase in mean diastolic pressure in the atria and decrease in the cardiac index [12, 14]. Negative hemodynamic effects of AF are highly deleterious in older patients because atrial contribution to the diastolic filling volume is greater than in younger patients [15].

On the basis of these hemodynamic and clinical findings, many studies have attempted to clarify the prognostic role of AF in patients with HF, but the data are quite conflicting, sometimes also for the same authors [9].

The aim of the present study was to verify the prognostic role of AF in different age groups of patients with HF enrolled in the Italian Network on Congestive Heart Failure Registry [16].

Methods

Study Design, Collected Data and Definitions

Data for the present analysis originate from the database of the Italian Network on Congestive Heart Failure Registry [16], a permanent registry designed by an ad hoc committee of the Italian Association of Hospital Cardiologists (Associazione Nazionale Medici Cardiologi Ospedalieri, Florence, Italy) in 1995. 150 cardiology centers actively participated in the study, which was a good representation of the cardiology centers existing in our country. Short training sessions were organized to prepare clinicians to collect and enter data into the registry. Using an ad hoc designed software, patients' data were recorded at each center by trained cardiologists and were then pooled into a database at the Italian Association of Hospital Cardiologists Research Center. A requirement for entry into the database was that patients had a diagnosis of HF based on the European Society of Cardiology guideline criteria [17]. Data on demographic, clinical, instrumental and biohumoral variables and therapies were collected for each patient. At baseline, a 12-lead ECG was recorded and coded by a single cardiologist at each participating center, using a standardized format outlined in the database. Patients were followed according to the routine clinical practice of the participating centers. In this context, patients underwent standard chest X-ray, 24-hour Holter ECG monitoring to confirm the presence of persistent or permanent AF, two-dimensional echocardiography and blood sampling for the most common laboratory tests, and others if the attending cardiologists deemed them necessary. Cardiologists at the participating centers were responsible for confirming the diagnosis of AF and classifying it as persistent or permanent, for defining the etiology of congestive HF and the NYHA class, reporting whether a third heart sound was audible and computing the cardiothoracic ratio. Left ventricular ejection fraction was calculated from a 4-chamber apical echocardiographic view. Ventricular tachycardia was defined as an episode of tachycardia with widened QRS that lasted longer than 3 beats with a heart rate >100 beats/min, as revealed by 24-hour Holter ECG monitoring. Renal insufficiency was defined as serum creatinine >2.5 mg/dl, hypokalemia as a serum potassium value <3.5 mEq/l and anemia as hemoglobin <11 mg/dl for women and <12 mg/dl for men. Previous hospitalizations for congestive HF in the year before the entry visit were also recorded. After the baseline visit, patients were followed up for at least 1 year. In the case of death occurring outside the hospital, the event was confirmed by a telephone interview with the patient's relatives, using a standard questionnaire aimed at determining the type of death (sudden vs. nonsudden).

Study Population

A total of 8,178 consecutive patients with HF were followed for 1 year, and available data on AF were considered for the present analysis, excluding patients on a waiting list for heart transplantation. Patients were stratified into 3 age groups as follows: group A, ≤65 years; group B, 66–75 years, and group C, >75 years.

Statistical Analyses

Continuous variables are reported as means ± standard deviation and compared by t test, while categorical variables are reported as percentages and compared by χ^2 test. Patients with AF were compared to patients without AF in each of the 3 age groups. Multivariate analyses (Cox models) were used to determine the independent predictors of 1-year all-cause mortality, 1-year sudden death and 1-year all-cause hospitalization in each age group. Variables statistically significant in univariate analysis and variables considered of relevant clinical interest, even though not statistically significant, were used in the models. The following variables were considered: gender (female vs. male), NYHA class (III–IV vs. I–II), ischemic etiology, systolic blood pressure (continuous), heart rate (continuous), hospitalization for HF in the previous year, creatinine (>2.5 vs. ≤2.5 mg/dl), cardiothoracic ratio (>0.55 vs. ≤0.55), ejection fraction (≤30 vs. >30%), third heart sound, AF (yes vs. no) and use of angiotensin-converting enzyme (ACE) inhibitors and β-blockers (no vs. yes). Firstly, a Cox model was performed for the 3 end-points in the total population of patients, introducing age as a continuous variable, in order to evaluate the prognostic role of age. Also, Kaplan-Meier curves according to the presence or absence of AF were calculated for the above-mentioned 3 end-points in each age group and compared by log-rank test. A p value <0.05 was considered statistically significant. All data were analyzed using SAS® software (version 8.2) [18].

Table 1. Clinical and hemodynamic characteristics in the 3 groups of patients according to the presence or absence of AF

	Group A: age ≤65 years (n = 4,261)			Group B: age 66–75 years (n = 2,651)			Group C: age >75 years (n = 1,266)		
	AF (n = 683)	no AF (n = 3,578)	p	AF (n = 638)	no AF (n = 2,013)	p	AF (n = 412)	no AF (n = 854)	p
Mean ± SD age, years	57 ± 7	54 ± 10	<0.0001	71 ± 3	70 ± 3	0.006	81 ± 4	80 ± 4	0.010
Females, %	19.9	21.1	0.48	32.5	27.2	0.011	50.2	42.7	0.012
NYHA class III–IV, %	36.6	25.5	<0.0001	42.5	29.3	<0.0001	41.3	34.5	0.020
Etiology of HF, %									
Ischemic	17.6	37.0		28.1	52.1		32.5	48.8	
Valvular	22.1	6.0		27.3	8.1		20.4	11.9	
Hypertensive	12.0	9.1	<0.0001	16.9	13.6	<0.0001	22.6	20.1	<0.0001
Idiopathic	39.4	42.3		22.9	23.4		17.0	14.9	
Other	8.9	5.6		4.8	2.8		7.5	4.3	
Third heart sound, %	20.9	27.6	0.0003	18.0	21.3	0.073	17.5	17.2	0.91
Previous hospitalization, %	59.2	53.9	0.012	63.0	55.5	0.0009	65.8	57.6	0.005
Ejection fraction, %[1]									
>40%	26.6	21.1		35.0	22.7		41.4	33.5	
30–40%	37.2	40.1	0.044	41.5	46.1	<0.0001	42.7	44.2	0.047
<30%	36.2	38.8		23.5	31.2		15.9	22.3	
Potassium <3.5 mEq/l, %[2]	2.4	1.6	0.26	3.7	2.0	0.070	4.2	1.4	0.029
Creatinine >2.5 mg/dl, %[3]	1.4	2.1	0.37	2.3	3.6	0.22	1.8	5.4	0.026
Ventricular tachycardia, %[4]	36.0	27.0	0.029	33.9	30.0	0.43	37.7	30.1	0.33
Anemia, %[5]	13.6	12.4	0.54	15.2	15.2	1.00	21.5	26.5	0.22
LBBB, %	17.4	25.1	<0.0001	15.0	25.5	<0.0001	13.8	22.6	0.0002
Cardiothoracic ratio >0.55, %[6]	64.3	51.3	0.029	74.4	62.6	0.060	74.5	62.5	0.14

Previous hospitalisation was defined as one or more hospitalizations in the year prior to entry in the registry. LBBB = left bundle branch block. [1] 4,977 patients with data available (group A = 2,692 patients; group B = 1,571 patients; group C = 714 patients). [2] 4,589 patients with data available (group A = 2,481 patients; group B = 1,467 patients; group C = 641 patients). [3] 4,682 patients with data available (group A = 2,506 patients; group B = 1,499 patients; group C = 677 patients). [4] 1,730 patients with data available (group A = 1,039 patients; group B = 525 patients; group C = 166 patients). [5] 3,557 patients with data available (group A = 1,919 patients; group B = 1,125 patients; group C = 513 patients). [6] 968 patients with data available (group A = 513 patients; group B = 300 patients; group C = 155 patients).

Results

Baseline Characteristics

In table 1, the clinical characteristics of the study population compared according to the presence of AF in each age group are reported. There were significant differences in the mean age between patients with AF and those without AF in each group. An increasing proportion of females among patients with AF was observed moving from group A to group C (19.9 vs. 32.5 vs. 50.2%). Advanced NYHA class (III–IV) was prevalent in patients with AF in all 3 groups.

The etiology of HF differed substantially between patients with AF and without AF in all 3 groups; dilated cardiomyopathy was the most frequent cause of HF in group A, while ischemic etiology was more frequent in groups B and C. A greater percentage of patients with AF had had a previous hospitalization compared with those without AF in all age groups.

As expected, the proportion of HF patients with preserved ejection fraction (>40%) increased with increasing age; in all age groups, the proportion of patients with AF was higher in the group of patients with preserved ejection fraction. Hypokalemia was associated with AF in all age groups, although only in group C was there a significant difference compared to patients in sinus rhythm (4.2 vs. 1.4%; p = 0.03). In contrast, renal insufficiency was prevalent in patients without AF in all age groups, with a significant difference only in group C (5.4 vs. 1.7%; p = 0.03). Considering the prevalence of other electrical disturbances, we found that ventricular tachycardia was more frequent in patients with AF in all 3 groups, although data on this arrhythmia were available only for a relatively small number of patients; the difference between patients with and without AF was significant only in group A (36.0 vs. 27.0%; p = 0.03). Anemia progressively increased across the 3 age groups without reaching statistical significance in any of them. Left bun-

Table 2. Rates of drug prescriptions in the 3 groups of patients according to the presence or absence of AF

	Group A: age ≤65 years (n = 4,261)			Group B: age 65–75 years (n = 2,651)			Group C: age >75 years (n = 1,266)		
	AF (n = 683)	no AF (n = 3,578)	p	AF (n = 638)	no AF (n = 2,013)	p	AF (n = 412)	no AF (n = 854)	p
β-Blockers, %	18.3	25.3	<0.0001	11.1	17.0	0.001	5.3	8.1	0.07
ACE inhibitors, %	84.0	85.9	0.20	77.3	80.4	0.08	71.1	74.1	0.25
Digoxin, %	89.0	59.1	<0.0001	84.3	57.3	<0.0001	84.2	56.3	<0.0001
Oral anticoagulant, %	71.6	23.7	<0.0001	58.0	16.9	<0.0001	26.7	9.1	<0.0001
Aspirin, %	12.5	33.6	<0.0001	22.6	43.0	<0.0001	37.1	43.4	0.03
Other antiarrhythmics, %[1]	29.0	24.4	0.011	24.5	25.7	0.52	19.9	22,6	0.28
Diuretics, %	91.5	78.3	<0.0001	92.2	84.6	<0.0001	89.8	84.5	0.011

[1] This includes the following drugs: antiarrhythmics class Ia-Ib-Ic, class III and class IV.

Table 3. One-year outcomes in the 3 age groups according to the presence or absence of AF

	Group A: age ≤65 years (n = 4,261)			Group B: age 65–75 years (n = 2,651)			Group C: age >75 years (n = 1,266)		
	AF (n = 683)	no AF (n = 3,578)	p	AF (n = 638)	no AF (n = 2013)	p	AF (n = 412)	no AF (n = 854)	p
1-year all-cause mortality, %	13.0	8.5	0.0002	15.2	11.3	0.008	17.5	15.2	0.31
1-year sudden death, %	6.3	3.7	0.002	4.9	5.4	0.62	5.3	4.9	0.75
1-year hospitalization, %	28.6	22.1	0.0002	23.8	23.8	0.99	21.4	18.2	0.17

dle branch block was systematically more frequent in patients without AF. Cardiac enlargement (defined as cardiothoracic ratio >0.55), data for which were available only in a small percentage of patients (12%), was seen to be associated with AF in all age groups.

Pharmacological Treatment

Table 2 reports the prescription patterns of the most relevant drugs for HF in each age group according to the presence of AF (mean prescription rate across the 5 years of the registry enrolment, i.e. 1995–1999). AF was associated with a lower use of both ACE inhibitors and β-blockers with increasing age. As expected, digoxin and warfarin therapy were more frequently prescribed in patients with AF, although in patients over 75 years, oral anticoagulant therapy was markedly underused. In contrast, the utilization of antiplatelets increased with age and in the absence of AF. Diuretics were systematically used more frequently in patients with AF than in those without AF.

One-Year Outcomes

Univariate Analysis

The results of univariate analysis of 1-year outcomes are reported in table 3. The all-cause mortality rate increased with age both in patients with AF and in those without AF. In groups A and B, AF was statistically significantly associated with a higher total mortality rate (13.0 vs. 8.5%, p = 0.0002, and 15.2 vs. 11.3%, p = 0.008, respectively) while it was not in the older patients (group C: 17.5 vs. 15.2%; p = 0.31). Sudden death was significantly more frequent in patients with AF only in younger patients (group A: 6.3 vs. 3.7%; p = 0.002), whereas in older patients, we did not find any significant difference in the incidence of sudden death among patients with AF and those in sinus rhythm (group B: 4.9 vs. 5.4%, p = 0.62; group C: 5.3 vs. 4.9%, p = 0.75). Similarly, only younger patients with AF had significantly higher hospitalization rates (group A: 28.6 vs. 22.1%; p = 0.0002), while in the 2 older groups of patients, no significant differences were detected among those with AF and those in sinus rhythm

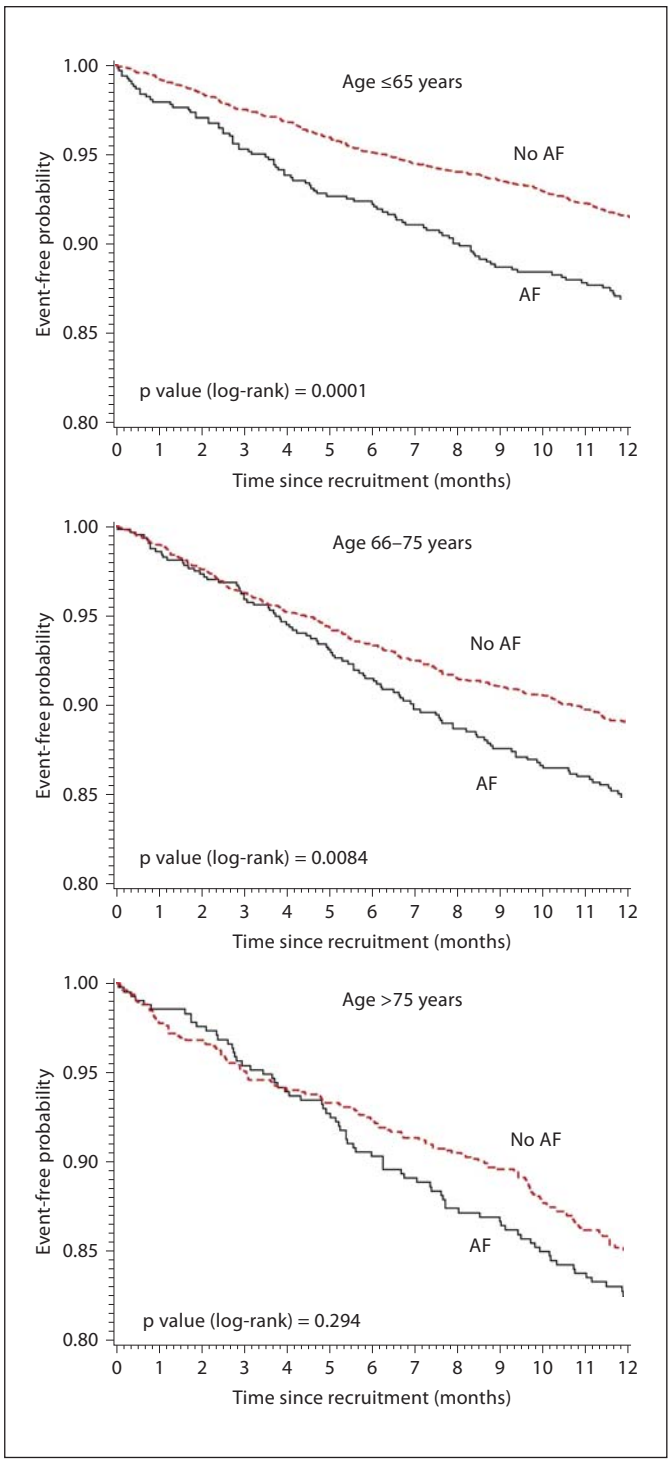

Fig. 1. Kaplan-Meier curves of 1-year total mortality in the 3 age groups according to the presence or absence of AF.

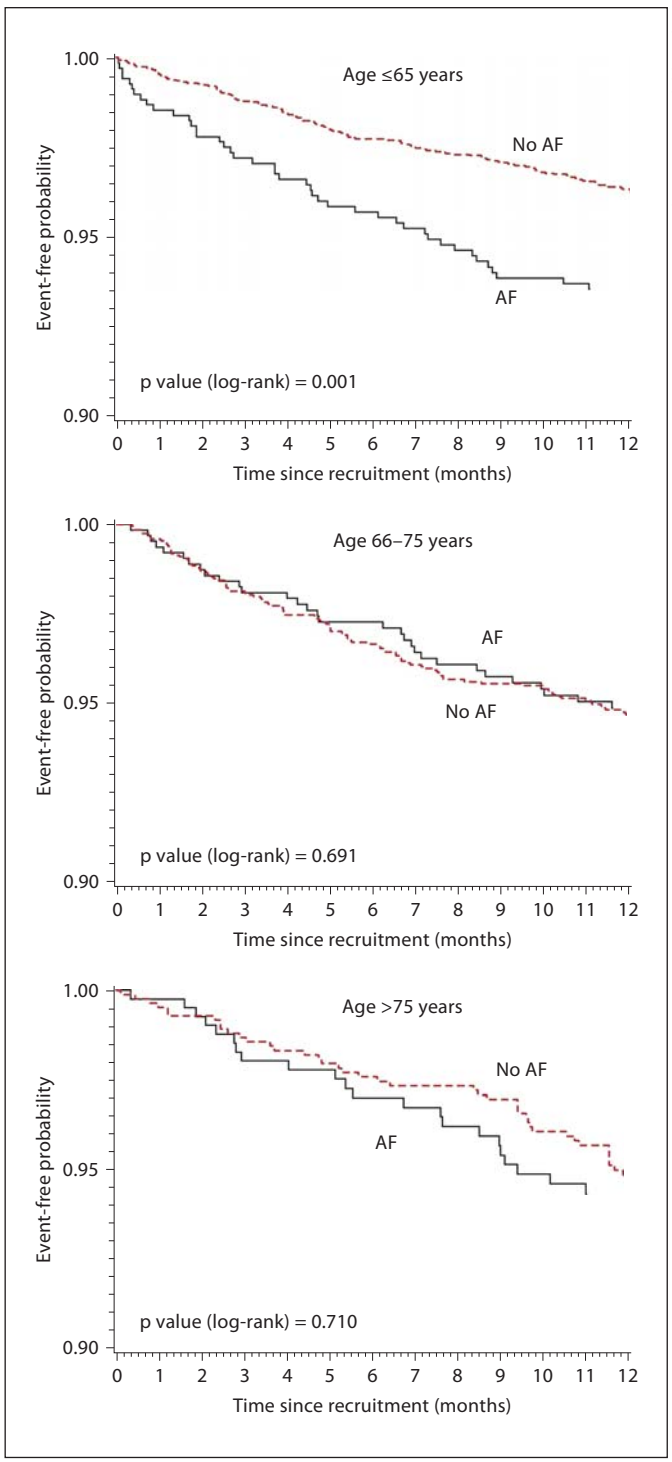

Fig. 2. Kaplan-Meier curves of 1-year sudden death in the 3 age groups according to the presence or absence of AF.

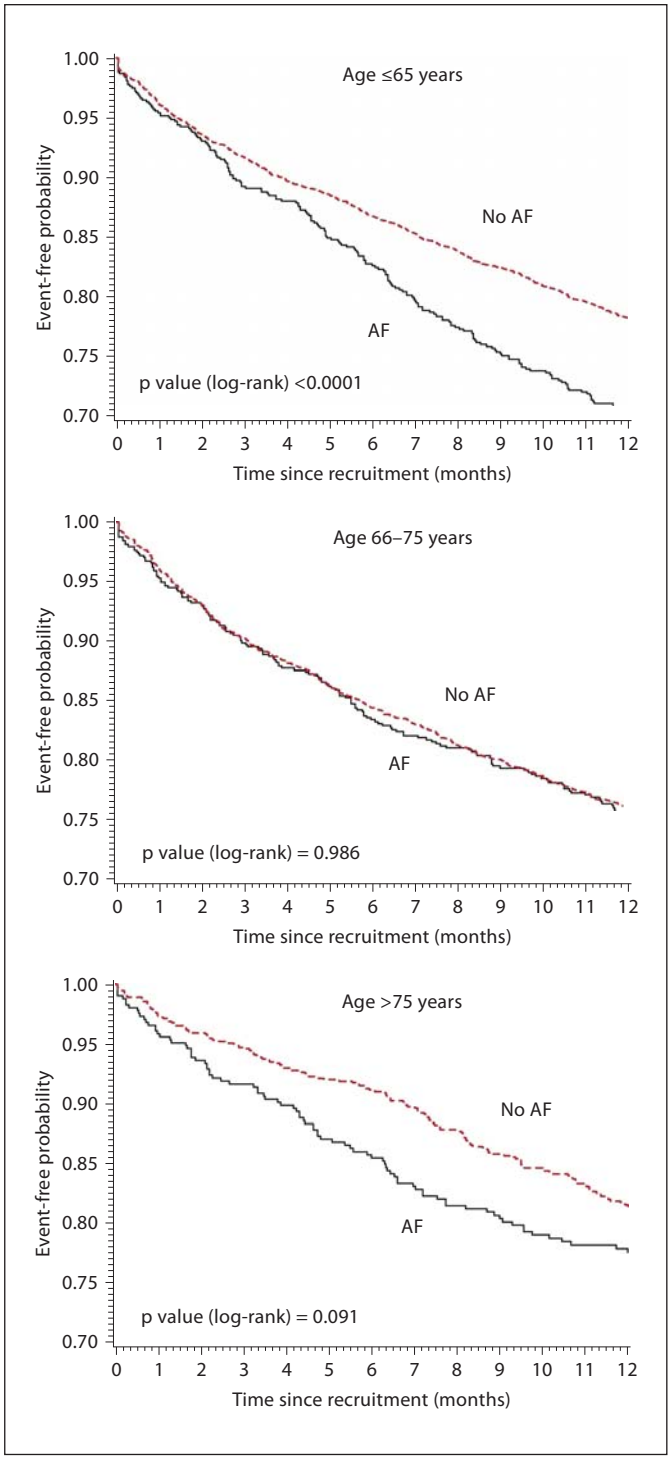

Fig. 3. Kaplan-Meier curves of 1-year hospitalization in the 3 age groups according to the presence or absence of AF.

Color version available online

(group B: 23.8 vs. 23.8%, p = 0.99; group C: 21.4 vs. 18.2%, p = 0.17). Kaplan-Meier curves according to the presence/absence of AF for 1-year all-cause death, sudden death and hospitalization are shown in figures 1–3.

All-cause mortality curves were significantly different between patients with AF and those without AF in groups A and B (p = 0.0001 and p = 0.0084, respectively); sudden death and hospitalization curves diverged significantly between patients with AF and those without only in group A (p = 0.001 and $p < 0.0001$, respectively). In all other cases, the difference between the curves was not statistically significant.

Multivariate Analysis

In the models in which age was included as a continuous variable, both AF and age were independent predictors of all-cause mortality [hazard ratio (HR) 1.22, 95% confidence interval (CI) 1.04–1.42, and HR 1.03, 95% CI 1.02–1.03, respectively]. With regard to sudden death, age still maintained its independent predictive value (HR 1.02, 95% CI 1.01–1.03), while neither AF nor age were independent predictors of all-cause hospitalization.

The results of the multivariate analyses with regard to 1-year all-cause mortality, sudden death and hospitalization in each age group are shown in figure 4. The presence of AF was an independent predictor of 1-year outcomes in younger patients (group A), whereas it predicted only 1-year all-cause mortality in group B. In group C, AF was not confirmed to be an independent predictor of outcome.

Discussion

General Considerations

It is well known how AF negatively modifies the hemodynamic and clinical profile of patients affected by HF [7]. It seems reasonable to postulate that these negative effects may affect prognosis, particularly in the elderly, in whom the loss of atrial contribution greatly limits cardiac reserve [15] and predisposes to thromboembolism [19]. The incidence and prevalence of AF increases with age and worsening HF [12, 20], and our data also confirm the elevated prevalence of AF in patients of advanced age and NYHA class. In all 3 groups of our study population, the presence of AF in patients with HF was strongly associated with previous hospitalizations, reinforcing the relationship between AF and a worse clinical profile of HF. With increasing age, AF is more frequently detected in females (in patients aged less than or equal to

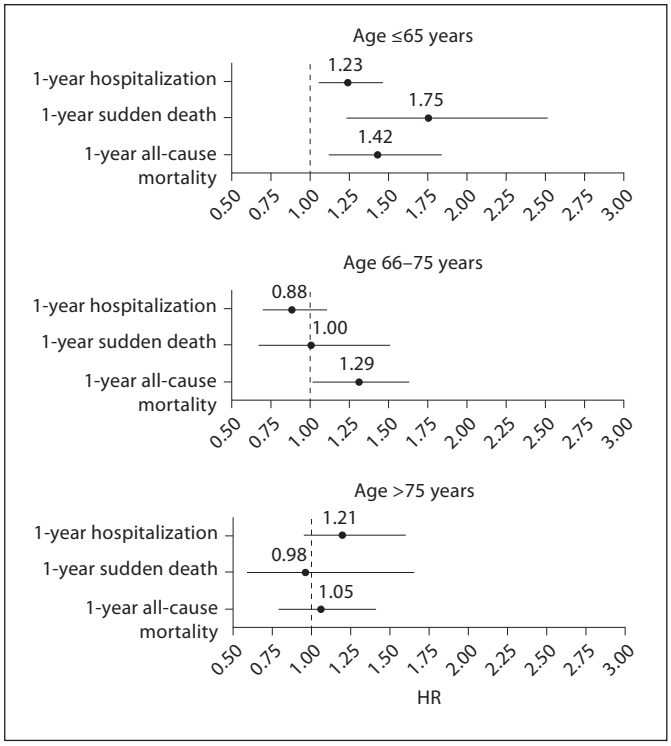

Fig. 4. Independent prognostic value of AF in the 3 groups of patients. Multivariate Cox regression models adjusted for gender, NYHA class, ischemic etiology, systolic blood pressure, heart rate, previous hospitalization for HF, creatinine (>2.5 mg/dl), cardiothoracic ratio (>0.55), ejection fraction (≤30%), third heart sound, ventricular arrhythmias, β-blockers and ACE inhibitor therapy.

65 years, females were prevalent among those without AF) and also in patients with preserved left ventricular ejection fraction [21]. Ischemic and hypertensive etiology were the main causes of HF in our older group, both in patients with and without AF, as previously reported in the Framingham Heart Study [4].

Analyzing our data concerning electrolyte disturbances, we found that patients affected by AF presented lower levels of serum potassium compared to those in sinus rhythm, but these differences were statistically significant only in the older group; this finding could be explained by the fact that an aged kidney is more prone to potassium dispersion during diuretic therapy [22]. Interestingly, renal insufficiency, defined as serum creatinine >2.5 mg/dl, was observed at a higher rate in patients without AF in all 3 age groups, and the difference was significant in group C. We might hypothesize that the presence of renal insufficiency, with its tendency to hyperkalemia, might be protective against developing a hypokalemic state, which is known to be a risk factor for the onset of AF as well as for other cardiac arrhythmias [23].

Pharmacological Approach

First of all, we must underline the general underuse of β-blockers in our study population; this clinical approach is most evident in the older group with AF. This finding is in accordance with data derived from another Italian registry [24], demonstrating the substantial difference in the utilization of β-blockers between randomized trials [25, 26] and routine clinical practice, particularly in elderly patients, even though the efficacy of β-blockers in older patients with HF has been confirmed [27]. However, we must underline that this finding is probably justified on the basis of two significant considerations. Firstly, it represents the mean prescription rate of this drug over a long period of enrolment, as the registry started in 1995, and secondly, the first large clinical trial which tested the efficacy of β-blockers was the US carvedilol trial [26], published in 1996, and it is known that the transfer of evidence derived from randomized clinical trials is a process that usually takes several years. The underuse of β-blockers in the 3 age groups with AF in the present study was probably also related to the high rate of prescription of digoxin; in fact, this drug was prescribed in all 3 groups of AF patients at a significantly higher rate than in those patients in sinus rhythm. ACE inhibitors were prescribed at a high rate in all groups, with an overall rate of more than 80%, in accordance with the results of the Study of Patients Intolerant of Converting Enzyme Inhibitors registry [28].

There are clear indications that patients with AF should be treated with oral anticoagulation therapy in the presence of one or more other risk factors for systemic embolism and in the absence of hemorrhage risk [29]. Our data demonstrate that a deep-seated caution exists also in the cardiology care setting, particularly in regard to the elderly, in whom the greatest benefit has already been documented [29].

Prognostic Implications

The prognostic role of AF in patients affected by HF has been debated for a long time, with controversial findings [12]. Two large trials [30, 31] with a total of 14,000 patients reported that the all-cause mortality rate was significantly higher in the presence of AF. Middlekauff et al. [32] demonstrated the negative prognostic role of AF in patients with HF, even though, interestingly, in this study the authors underlined that AF lost its predictive power in patients with a worse hemodynamic profile. In the Veterans Affairs Vasodilator-Heart Failure Trial, AF was not

found to be a negative predictive variable in patients with AF and NYHA class II–III [33], and Crijns et al. [34], in patients with more advanced NYHA class (III–IV), demonstrated that there was no significant difference in the mortality rate after adjustment for age and for clinical and hemodynamic variables. More recently, data derived from the Valsartan Heart Failure Trial [20] showed that the occurrence of AF in patients with chronic HF independently increases the risk of all-cause mortality and combined mortality and morbidity by 40 and 38%, respectively. Regarding this controversy, data available in the literature seem to underline how the clinical relevance of AF could change depending on the different levels of cardiac dysfunction and clinical impairment of the patients [9].

Our data can contribute to defining the prognostic role of AF according to the age of the patients. In a cohort of outpatients followed by cardiologists, we observed that AF maintains its independent effect on 1-year all-cause mortality in those aged less than or equal to 75 years irrespective of left ventricular systolic function, confirming the results of Mamas et al. [35] and the ancillary analysis of the Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity study [36]. In our study, in the youngest subgroup of patients, the Kaplan-Meier curves diverged very early during the follow-up period; this finding could have important clinical consequences, suggesting a possible prognostic benefit of a timely aggressive approach to maintain or restore sinus rhythm in this young population of patients.

Our sample is different from the study population analyzed by Aronow et al. [37]; these authors found a significant association between AF and mortality in very old patients regardless of the presence of systolic dysfunction. In that study, the mean age of the population was over 80 years, all patients had a prior myocardial infarction and finally the differences in mortality rate between patients with AF and those without were related primarily to preserved systolic function [37].

The fact that AF is not an independent predictor for mortality and hospitalization in the oldest patients is an important finding but, in our opinion, is not sufficient to influence therapeutic choices in the very elderly population, because other relevant outcomes should be considered, such as the risk of disabling stroke, global functional impairment and the health-related quality of life [38]. So, in this aged population, therapeutic decisions must be individualized from a geriatric point of view.

Some limitations of our study must be acknowledged. ECG analysis and diagnosis of AF were not carried out in a single core laboratory using standardized, blinded methods and quality control techniques; the diagnosis was defined by each cardiologist on the basis of clinical history and ECG at entry into the registry. Further, no data are available regarding the duration of the electrical disturbance at the time of enrolment in the registry.

Finally, we must underline that our data are derived from outpatients managed in a cardiology ward. For this reason, these patients presented a low level of comorbidity compared to those usually treated in internal and geriatric medicine wards. Therefore, our results are surely not fully generalizable to all patients with AF and HF.

Conclusion

We found that the prevalence of AF increased with age and was associated with a worse clinical profile and a higher mortality rate. However, AF was able to predict all-cause mortality only in patients aged $\leq$75 years irrespective of left ventricular systolic function. Sudden death and all-cause hospitalization rates were predicted by the presence of AF only in the youngest group of patients.

Appendix

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