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Role of permanent atrial fibrillation (AF) on long-term mortality in community-dwelling elderly people with and without chronic heart failure (CHF)

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ABSTRACT

Permanent AF is characterized by an increased mortality in elderly subjects with CHF. Moreover, AF increased the risk of mortality also in elderly subjects without CHF. Thus, we examined long-term mortality in community-dwelling elderly people with and without CHF. A total of 1332 subjects aged 65 and older were selected from the electoral rolls of Campania, a region of southern Italy. The relationship between AF and mortality during a 12-year follow-up in 125 subjects with CHF and in 1.143 subjects without CHF were studied. Elderly subjects showed a higher mortality in those with respect to those without AF (72.1% vs. 51.8%; $p < 0.01$). Similarly, elderly subjects without CHF showed a higher mortality in those with respect to those without AF (61.8% vs. 49.8%; $p < 0.05$). In contrast, elderly subjects with CHF showed a similar mortality in those with respect to those without AF (74.7% vs. 82.4%; $p = 0.234$). Multivariate analysis shows that AF was predictive of mortality in all elderly subjects (Hazard Risk = HR = 1.39, 95% confidence interval (CI) = 1.25–2.82; $p < 0.001$). When the analysis was conducted considering the presence and the absence of CHF, AF was strongly predictive of mortality in elderly subjects without CHF (HR = 1.95, 95%CI = 1.25–4.51; $p < 0.001$) but not in those with CHF (HR = 1.12, 95%CI = 0.97–3.69; $p = 0.321$). We concluded that AF is able to predict long-term mortality in elderly subjects. Moreover, AF is strongly predictive of long-term mortality in the absence but not in the presence of CHF.

1. Introduction

AF is a peculiar arrhythmia of aging, with a prevalence of about 5% in people aged 65 years and older and it increases up to 10% of those over the age of 80 years (Wolf et al., 1991; Go et al., 2001; Aronow, 2008). AF is characterized by an age-related increase in morbidity and mortality (Fang et al., 2007).

Moreover, AF is frequently associated to CHF but the role of this relationship on mortality is still controversial (Benjamin et al., 1998; Miyasaka et al., 2007; Rivero-Ayerza et al., 2008; Bilato et al., 2009). Recently, data from the Italian Network on CHF Registry reported that AF was not an independent risk factor for death in patients oldest than 75 years (Baldasseroni et al., 2010).

In addition, AF in the absence of CHF is not considered as a benign entity. French middle-aged men with "lone atrial" fibrillation show a 4-fold increase in cardiovascular mortality and a 2-fold increase in all-cause mortality (Jouven et al., 1999). Recently, it has also been demonstrated that AF should be considered a possible marker of frailty, geriatric condition characterized by a high mortality (Fumagalli et al., 2010).

Thus the aim of the present study is to verify the role of AF on morbidity and mortality in community-dwelling elderly subjects with and without CHF.

2. Subjects and methods

The "Osservatorio Geriatrico Regione Campania" was a cross-sectional study performed in 1992 in Campania, a Region in Southern Italy (Cacciatore et al., 1997). To guarantee homogeneous sampling of the whole territory, and to reduce survey costs, a stratified multi-stage sampling design was used. The referendum

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electoral roll of 1991 was used as the population source. Municipalities (the lowest level of local government) were the primary sampling units and they were first organized within districts (the intermediate level) according to size, as reflected by the number of polling-stations. These data were supplied by district authorities. Two polling stations were randomly selected from each municipality, according to a planned target of 100 stations. Due to repeated sampling, the two largest municipalities had more than two polling stations (Salerno had 4 and Naples had 20). Forty municipalities from a total of 550 were involved in the survey. Subjects older than 65 years were randomly chosen within each polling station, allocation being stratified by sex and age, in order to preserve the same age and sex distribution of the target population. The information was gathered in 1992 in all subjects enrolled in a period of 6 months. The "Osservatorio Geriatrico Regione Campania" was a cross-sectional study performed in 1992 in Campania, a region of Southern Italy. The study design and population are described elsewhere (Cacciatore et al., 2005).

2.1. Study population

The study sample consisted of 1780 individuals aged 65 and older randomly selected from the electoral rolls, resident in the five municipalities of Campania, and stratified by a three-step procedure according to age, sex, and size of urban unit. The sample was constituted by 756 (42.5%) men and 1024 (57.5%) women. Of these, 448 (25.2%) individuals refused to participate in the study thus resulting in a study sample of 1332 subjects, which represents an overall participation rate of 74.8%. The sample was followed-up for 12 years, i.e., up to the end of 2003. Deaths were assessed by questioning general practitioners and confirmed by examination of death certificates. Of the 1332 subjects enrolled in 1992, data on mortality and on social support were missing for 35 (2.6%) and for 9 (0.06%) subjects, respectively, thus resulting in a sample of 1288 individuals (554 men and 734 women). Of these, 681 (52.9%) were deceased, 324 men (58.5%) and 357 women (48.6%). The CHF diagnosis was uncertain in 20/1288 individuals (1.6%), consequently 1268 were examined.

2.2. AF diagnosis

AF was diagnosed by electrocardiogram (ECG) recordings. ECGs were evaluated for presence of AF by 2 cardiologists and validated by a third cardiologist; all were blinded to clinical characteristics of participants. Inter-observer reliability was ≈99%. In case of discordance, the ECG was re-evaluated and consensus was reached. VVI pacemaker-induced rhythm was classified as AF. We considered AF only in the cases of longstanding AF (i.e., more than 1 year) which usually leads to permanent AF (Estes et al., 2008).

2.3. CHF diagnosis

The diagnosis of CHF was considered possible when participants reported that a physician had told them they had CHF, and/or they had received specific treatment with diuretics and digitalis or vasodilators. The diagnosis was subsequently confirmed by means of a physical examination and a review of medical records to identify cardiomegaly and pulmonary edema on chest X-ray, or evidence of dilated left ventricle and global or segmental wall motion abnormalities. Physical examination was performed to look for the following signs and symptoms: dyspnea, orthopnea, tachycardia, AF, jugular venous distension, abdomino-jugular reflux, pulmonary rales, third sound, and edema.

2.4. Social support

Social support consisted of three categories: social networks, social relationships and economic support. Social networks refer to everyday contacts including size, density, reciprocity, durability, intensity and frequency of contacts. Social relationships refer to the existence, quantity, and type of relationships. The score ranges from 0 to 17, in which the highest score corresponds to the lowest social support level (Mazzella et al., 2010).

2.5. Concomitant chronic morbidities, cognitive function, depression and disability

The presence of chronic co-morbidities was evaluated from the medical history and confirmed by a trained physician in a physical examination. The Italian version of the Mini-Mental State Examination (MMSE) was used to measure cognitive mental status (Measso et al., 1993). Cognitive impairment is defined as a score of less than 24 on the MMSE. The Geriatric Depression Scale (GDS) (Yesavage et al., 1983) was used to evaluate depressive symptoms. Data about drug consumption (class and administration) were recorded. Disability was evaluated by means of the Basic Activities of Daily Living (BADL) (Katz et al., 1963). BADL assesses the following domains: bathing or showering, dressing, eating, getting in and out of bed, transferring from bed to chair and using the toilet. For each item a four-point outcome score was assigned as follows: "uses no help to perform the activity", "uses a device to perform the activity", "uses assistance of another person to perform the activity", "does not perform the activity". Subjects who could not perform the function without help were considered disabled. Subjects were considered BADL disabled if they lost 1 or more functions ($\geq$1 lost).

2.6. Statistical analysis

Data were collected and analyzed using the SPSS 13.0 statistics package. The baseline characteristics of the sample are expressed as mean $\pm$ standard deviation. Subjects were stratified by the presence and absence of AF and by the presence and absence of CHF. Categorical variables were analyzed using Chi-square testing, and continuous variables using a one-way ANOVA. The Cox regression analysis was used to evaluate the effect of AF on long-term mortality in the absence and in the presence of CHF independently of the effect exerted by age, sex (female), heart rate (bpm), pulse blood pressure, number of concomitant diseases, number of drugs taken, MMSE, GDS and BADL ($\geq$1 lost). For a hazard ratio (HR) higher than 1, the independent variable was defined as having a "predictive" effect on the dependent variable whereas if the HR was less than 1, the independent variable was defined as having a "protective" effect on the dependent variable. Survival curves were constructed stratified by the absence and presence of CHF. Each HR was associate to 95%CI. p values less than 0.05 were considered significant.

3. Results

Demographic and clinical characteristics of elderly subjects in the presence and absence of AF are shown in Table 1. The prevalence of AF was 5.3% and the mortality in elderly subjects was 72.1% in the presence and 51.8% in the absence of AF ($p < 0.01$) (Table 1). Heart rate, number of diseases and drugs were higher in the presence than in the absence of AF. Interestingly MMSE score was lower and GDS was higher in the presence than in the absence of AF. More importantly, disability (BADL lost ≥ 1) was more evident in elderly subject with than in those without AF (13.8% vs. 6.4%; $p = 0.04$) (Table 1).

Table 1
Demographic and clinical characteristics of elderly subjects in the presence and absence of AF; *n* (%), mean ± S.D., or %.

Variables	All	AF no	AF yes	*p*
Number (%)	1288	1147 (94.7)	68 (5.3)	
Age (years)	74.2 ± 6.3	74.1 ± 6.3	75.1 ± 6.5	<0.229
Female sex, %	57.0	57.1	54.4	<0.660
Heart rate (bpm)	75.3 ± 10.2	75.1 ± 9.9	80.0 ± 13.9	<0.001
Pulse pressure (mmHg)	63.3 ± 16.	163.5 ± 16.1	59.7 ± 15.5	<0.060
Disease number	2.4 ± 1.3	2.4 ± 1.3	3.3 ± 1.5	<0.001
Drug number	2.2 ± 2.0	2.0 ± 1.8	4.7 ± 2.1	<0.01
Aspirin or warfarin (%)	7.3	7.1	10.3	<0.354
MMSE score	25.3 ± 4.8	25.4 ± 4.7	22.7 ± 5.5	<0.05
GDS score	11.4 ± 6.6	11.2 ± 6.6	13.4 ± 5.6	<0.011
BADL lost ≥ 1 (%)	6.8	6.4	13.8	<0.04
Social support score	13.1 ± 2.7	13.1 ± 2.6	14.0 ± 2.6	<0.193
Mortality (%)	52.9	51.8	72.1	<0.05

Table 2
Demographic and clinical characteristics of elderly subjects with and without CHF stratified for the presence and absence of AF; (%), mean ± S.D., or %.

Variables	CHF no		CHF yes	
	AF no	AF yes	AF no	AF yes
Number (%)	1113 (97.0)	34 (3.0)	87 (71.9)	34 (28.1)
Age (years)	73.9 ± 6.2	74.3 ± 6.2	75.9 ± 6.6	75.8 ± 6.8
Female sex %	56.3	55.9	63.2	52.9
Heart rate (bpm)	74.8 ± 9.7	80.9 ± 12.1	79.2 ± 12.1	79.1 ± 14.5
Pulse pressure (mmHg)	63.3 ± 15.9	58.3 ± 15.7	66.9 ± 18.2	61.1 ± 15.5
Disease number	2.2 ± 1.1	2.2 ± 1.1	4.9 ± 1.1	4.5 ± 1.0
Drug number	2.0 ± 1.1	2.9 ± 1.6*	4.6 ± 2.0	4.9 ± 2.2
Aspirin or warfarin %	6.9	8.8	11.5	11.8
MMSE score	25.5 ± 4.6	24.1 ± 4.7*	23.5 ± 5.5	23.0 ± 5.8
GDS score	10.8 ± 6.4	11.6 ± 5.2	16.6 ± 6.3	15.3 ± 5.5
BADL lost ≥ 1 (%)	5.1	6.3*	18.3	21.2
Social support score	12.9 ± 2.6	13.1 ± 2.7	14.3 ± 2.5	14.7 ± 2.3
Mortality (%)	49.8	61.8*	74.7	82.4

* $p < 0.05$ vs. absence of AF.

Table 2 shows demographic and clinical characteristics with and without CHF and stratified according to the presence and absence of AF. In elderly subject without CHF, the prevalence of AF was 3.0%. Moreover, elderly subjects without CHF but with AF were characterized by an increased of heart rate, drugs number and disability (BADL lost ≥ 1) and a reduced of MMSE score. When mortality was considered, elderly subjects without CHF showed a higher mortality in those with respect to those without AF (49.8% vs. 61.8%; $p < 0.05$) (Table 2). In elderly subject with CHF, the prevalence of AF was 28.1%. However, in the presence of CHF no differences were observed in the demographic and clinical characteristics considered in elderly subjects with and without AF. When mortality was considered, elderly subjects with CHF showed a similar mortality in those with respect to those without AF (74.7% vs. 82.4%; $p = 0.166$) (Table 2).

Multivariate analysis shows that AF was predictive of mortality in all elderly subjects (HR = 1.39, 95%CI = 1.25–2.82; $p < 0.001$) independently by the role of age, sex, heart rate, pulse pressure, number of diseases and drugs, MMSE and GDS score, BADL lost ≥ 1, social support and CHF (Table 3). When the analysis was conducted considering the presence and the absence of CHF, AF was strongly predictive of mortality in elderly subjects without CHF (HR = 1.95; 95%CI = 1.25–4.51; $p < 0.001$) (Table 3, Fig. 1A) but not in those with CHF (HR = 1.12; 95%CI = 0.97–3.69; $p = 0.321$) (Table 3, Fig. 1B).

4. Discussion

Our results demonstrate that the presence of AF is able to predict long-term mortality in elderly subjects. Subjects with AF

Table 3
Multivariate analysis on long-term mortality in all elderly subjects and in the presence and absence of CHF.

Variables	All subjects		CHF-no		CHF-yes	
	HR (95%CI)	*p*	HR (95%CI)	*p*	HR (95%CI)	*p*
Age (years)	1.14 (1.11–1.17)	<0.001	1.16 (1.13–1.20)	<0.001	1.03 (1.01–1.12)	<0.035
Female sex	0.38 (0.29–0.51)	<0.001	0.37 (0.27–0.50)	<0.001	0.34 (0.11–1.06)	<0.344
Heart rate (bpm)	0.99 (0.98–1.01)	<0.915	1.00 (0.98–1.05)	<0.952	0.98 (0.95–1.02)	<0.986
Pulse pressure (mmHg)	0.99 (0.99–1.01)	<0.168	1.00 (0.98–1.01)	<0.185	1.00 (0.97–1.03)	<0.838
Disease number	1.04 (0.92–1.17)	<0.511	1.02 (0.89–1.18)	<0.706	0.94 (0.60–1.46)	<0.785
Drug number	1.11 (1.03–1.20)	<0.001	1.09 (1.09–1.19)	<0.03	1.04 (0.78–1.39)	<0.763
Warfarin or aspirin	0.96 (0.93–1.02)	<0.145	0.98 (0.97–1.04)	<0.261	0.95 (0.91–1.03)	<0.111
MMSE score	0.97 (0.94–1.00)	<0.078	0.96 (0.92–0.99)	<0.03	1.02 (0.93–1.13)	<0.584
GDS score	1.02 (1.01–1.04)	<0.050	1.02 (1.01–1.03)	<0.04	0.95 (0.87–1.05)	<0.958
BADL lost ≥ 1 (%)	2.82 (1.21–6.63)	<0.016	4.11 (1.43–11.77)	<0.008	3.15 (0.53–18.6)	<0.206
Social support score	1.47 (1.16–1.86)	<0.001	1.49 (1.16–1.91)	<0.002	1.50 (0.57–3.90)	<0.405
CHF	1.92 (1.10–3.36)	<0.020	–		–	–
AF	1.39 (1.25–2.82)	<0.001	1.95 (1.25–4.51)	<0.001	1.12 (0.97–3.69)	<0.321

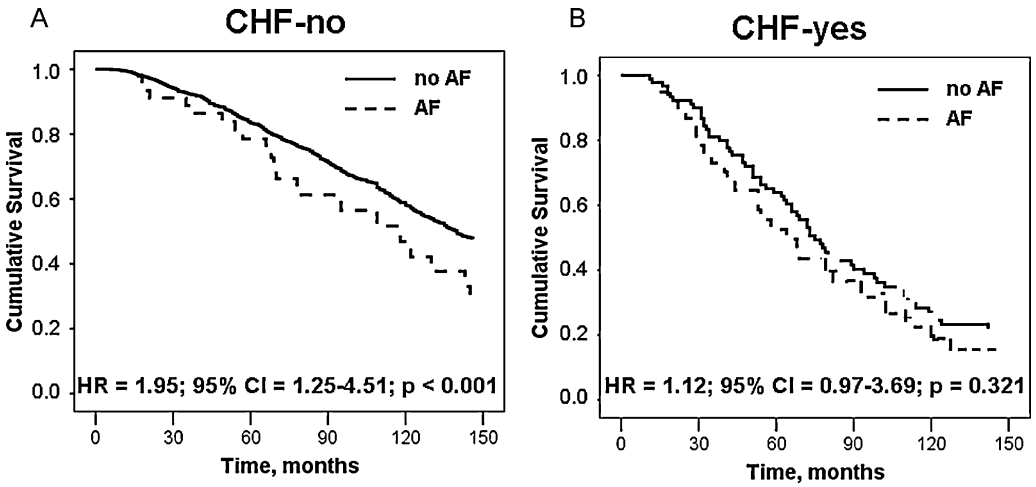

Fig. 1. Cox regression analysis of mortality in elderly patients stratified for the absence (CHF-no, panel A) and the presence of (CHF-yes, panel B) and permanent AF.

are characterized by several typical geriatric conditions such as cognitive decline, depression symptomatology and, more importantly, disability. AF is high prevalent in elderly subject with CHF. However, the presence of CHF seems to reduce the influence of AF on long-term mortality. In fact, AF is strongly predictive of long-term mortality in the absence of CHF but not in the presence of CHF.

4.1. AF, morbidity and mortality

In our study, the presence of AF is associate to high mortality and it is related to the presence of several findings, typical of geriatric clinical condition defined "frailty" (Fumagalli et al., 2010). In fact, the number of diseases and drugs, and depressive symptomatology are higher while MMSE was lower in the presence than in the absence of AF. More importantly, the disability was more marked in the presence than in the absence of AF.

In GIFA study when AF was considered as comorbid condition this subgroup present a higher number of diseases and, consequently, a higher number of drugs taken before hospitalization when compared to elderly patients in sinus rhythm and in those with AF as main diagnosis. More importantly in this study the prevalence of disabilities showed the highest values in the group of patient showing AF as comorbid condition (Fumagalli et al., 2010).

It has been demonstrated in an Older Italian Population (Pro.V.A. Study) that the prevalence of AF increased linearly with increasing severity of disability: 5% in nondisabled, 11% in moderately disabled, and 17% in severely disabled. This data strongly suggest a strong relationship between AF and disability (Bilato et al., 2009). Disability in AF may be due to both age-related hemodynamic changes, including diastolic impairment, and to a consequence of comorbility. In particular AF is highly associated with disability in patients with stroke (Sudlow et al., 1998; Tilvis et al., 2007).

An other important aspect of AF in the elderly is the strong association with cognitive decline. The relationship between AF and cognitive impairment is widely studied (Mead and Keir, 2001). Moreover, the relationship has been recently demonstrated in both case-control hospital (Jozwiak et al., 2006) and cross-sectional community studies (Bilato et al., 2009). Finally, depressive symptoms were also more frequent in the presence of AF both in the presence and the absence of CHF: among AF patients, symptoms of depression prevailed in a range between 32 and 38% (Thrall et al., 2007; Frasure-Smith et al., 2009).

Thus, in our AF cohort elderly subjects show several clinical characteristics of frailty which may justify the increased mortality risk observed in this group of subjects.

4.2. AF, morbidity and mortality in the presence and absence of CHF

CHF and AF are major cardiovascular disorders that are highly prevalent in the elderly and frequently associated with each other. However, the intricate relationship between CHF and AF is still unknown (Deedwania and Lardizabal, 2010).

In our study, at the end of follow-up, the mortality is significantly higher in the presence than in the absence of AF. When considering the presence and the absence of CHF, long-term mortality was not influenced by the presence of AF. Accordingly, AF is predictive of long-term mortality in the presence but not in the absence of CHF. Although the presence of CHF may apparently exacerbate the role of AF on mortality, the risk of long-term mortality seems to go to the opposite direction.

From the Insurance Industry's Medical Information Bureau, it was noted that among 126 subjects (mean age about 55 years) with chronic AF and no major associated condition, total mortality during 3.3 years of follow-up was about eight times higher than in the standard insurance table (Gajewski and Singer, 1981). In Framingham Heart Study in subjects 55–94 years of age (mean age = 73.7 years), AF was associated with a risk for death of 1.5 (95%CI = 1.2–1.8) in men and 1.9 (95%CI = 1.5–2.2) in women subjects who developed AF during 40 years of follow-up of the original. However, in secondary multivariate analyses, in subjects free of valvular heart disease and pre-existing cardiovascular disease, AF remained significantly associated with excess mortality, with about a doubling of mortality in both sexes (Benjamin et al., 1998). Interestingly, in the Olmsted County Study, 3288 subjects (mean age 71 ± 15 years) diagnosed with first AF and without CHF prior to or at AF diagnosis, there were no detectable changes over time with respect to the absolute or the relative mortality risk for AF after CHF diagnosis (Miyasaka et al., 2006). In the Italian Network on CHF Registry, 8178 outpatients with CHF and AF were stratified the population into 3 age groups of age ($\leq$65 years; 66–75 years, and $>$75 years). In a multivariate model, AF was an independent risk factor for death in $\leq$65 (HR = 1.42, 95%CI = 1.10–1.81) and 66–75 (HR = 1.29, 95%CI = 1.00–1.67) years groups but not in $>$75 years group (HR = 1.05, 95%CI = 0.78–1.43). Thus in CHF subjects, AF independently predicted all-cause mortality only in patients aged $\leq$75 years (Baldasseroni et al., 2010).

The higher mortality risk observed in AF subjects in the absence (HR = 1.95) than in the presence (HR = 1.12) may be explained in

different way. First of all, in our cohort AF subjects in the absence of CHF are characterized by the characteristics of "clinical frailty" which includes not only comorbidity and disability but also polipharmacy and relative adverse drug reactions, and lack of social support (Strandberg and Pitkälä, 2007). This condition is associated to higher long-term mortality alone and in association with chronic disease as CHF (Cacciatore et al., 2005; Kulminski et al., 2008). Secondly, it is possible that the severity of CHF may overcame the influence of AF on long term-mortality, or in alternative, AF in CHF subjects may be better treated in contrast to subjects in the absence of CHF in whom many times the therapy is under evaluated. Moreover, since supporting diagnostic information available is often limited, so that underlying cardiovascular disease might have been neglected or hidden in AF subjects. Finally, it should be taken into account that our results are obtained in a community-dwelling cohort and not in hospitalized or institutionalized AF patients.

4.3. Conclusions

We concluded that AF is related to high morbidity and mortality in elderly community-dwelling elderly people. More importantly, AF seems to influence mortality risk more in the absence than in the presence of CHF. Several hypothesis may explain this intriguing phenomenon. Clinical frailty conditions, highly prevalent in elderly subjects with AF without CHF, should be considered.

Conflict of interest statement

None.

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