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Mortality in patients with atrial fibrillation and common comorbidities – a cohort study in primary care

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Abstract

Objective: To study the association between cardiovascular co-morbidities and mortality risk in primary care patients with atrial fibrillation.

Methods: The study population included all adults (n=12,283) 45 years diagnosed with AF at 75 primary care centers in Sweden between 2001 and 2007. The outcome was mortality (until 2010) and data were explored for co-morbidities using Cox regression with Hazard Ratios (HRs). Analyses were performed stratified by sex and by age-group (45–64, 65–74 and 75 years of age) with adjustment for age, socio-economic factors and relevant comorbidities.

Results: During a mean of 5.8 years (standard deviation 2.4) of follow-up, 3,954 (32%) patients died (1,971 (35%) women, and 1,983 (30%) men). High HRs were found for congestive heart disease (CHF) and cerebrovascular diseases for all age-groups among men and women (except for the 45–64 year old women); for coronary heart disease among the oldest men; for diabetes among the 65–74 year old men and the 45–64 year old women. Low HRs were found for hypertension among women 75 years of age.

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Declaration of Interests

The authors report no conflicts of interest.

Conclusions: In this clinical setting, CHF and cerebrovascular diseases were consistently associated with mortality in all age-groups. The possible protective effect by hypertension among elderly women should be interpreted with caution.

Keywords

coronary heart disease; cerebrovascular disease; depression; congestive heart failure; gender; hypertension; diabetes

1. Introduction

Atrial fibrillation (AF) is the most prevalent arrhythmia worldwide (1). Two percent of Swedish adults have a history of AF (2). Atrial fibrillation is associated with an increased risk of cardiovascular morbidity and mortality (3). Important and validated risk factors or concomitant cardiovascular conditions for patients with AF include: older age, male sex, hypertension, heart disease (chronic heart failure (CHF), coronary heart disease (CHD) (4), myocardial infarction (MI) (5, 6), valvular heart disease, and hypertrophic and dilated types of cardiomyopathy (7)), and diabetes (2). Other important risk factors include genetics, overweight and obesity (8), higher amount of pericardial and visceral fat, sleep apnea, atrial dilatation and stretch, chronic kidney disease, smoking (9), high alcohol consumption (10), and thyroid dysfunction (11, 12). In addition, CHD and MI increase the risk of CHF and mortality in AF patients (6), and CHF in itself is also associated with increased mortality in patients with AF (13, 14).

Prevention of cerebrovascular diseases (i.e. stroke) is of particular importance in patients with AF as ischemic stroke (IS) is an important and highly studied complication (15); it is five times as common in individuals with AF compared to individuals without AF (16). CHA₂DS₂-VASc is the most used risk stratification instrument to assess the need for anticoagulant treatment to prevent IS among AF patients (17). In addition, it can also predict other outcomes associated with AF, such as resource utilization, readmissions, and mortality (18). CHA₂DS₂-VASc is also predictive for IS among patients without AF (19) and for predicting the onset of AF (20).

There are some relevant co-morbidities that are not included in the CHA₂DS₂-VASc score. For example, psychological distress is often present among patients diagnosed with AF (21), and depression and/or anxiety are linked to increased severity of AF symptoms (22–24). Depression among men with AF has also been shown to be associated with increased mortality (25).

Socio-demographic factors, such as age, gender and socioeconomic status are of importance for both relevant co-morbidities in patients with AF and for mortality, and should thus be accounted for. There are also gender differences, e.g. in the prevalence of AF (1, 2, 26), differences in age distribution (26–28), presence of relevant co-morbidities (26, 28, 29), including depression and anxiety (30), and the risks of both stroke and mortality (31), which is why men and women should be studied separately.

As most studies are performed in AF patients from hospitals, studies from primary care are needed to validate results from hospital patients in a clinical setting, i.e., primary care, where most AF patients are treated. In Sweden, 64 % of all AF patients are registered with an AF diagnosis in primary care (2).

Thus, our aim was to study the association between mortality and the following relevant co-morbidities after adjustments for age and socioeconomic factors: cardiovascular diseases, e.g., hypertension, CHD, CHF, and cerebrovascular disease, diabetes, and depression and anxiety, in men and women with AF treated in primary care.

2. Methods

2.1 Design

In this study, we used patient data from 75 primary health care centers (PHCCs), which were mostly located in Stockholm County (n=48 PHCCs). Individuals attending any of the participating PHCCs between 2001 and 2008 were included in the study. To extract individual electronic patient records (EPRs) we used *Extractor* software (http://www.sll.se/SLPOtemplates/SLPOPage1___10400.aspx; accessed September 19, 2010) was used. We also used data from the following national Swedish registers: the Total Population Register, the National Patient Register and the Swedish Cause of Death Register. The registers contain individual-level data on age, gender, education and hospital admissions for all residents registered in Sweden. The data in these registers were linked to clinical data from the patient records as well as to information on socioeconomic status on all individuals (n=1,098,420) registered at the 75 PHCCs. In order to ensure anonymity, the national identification numbers were replaced with new unique serial numbers. Ethical approvals were obtained from the regional boards at Karolinska Institutet and Lund University.

2.2 Study population

Patients diagnosed with AF were identified based on the presence of the ICD-10 code (10th version of the WHO's International Classification of Diseases) for atrial fibrillation (I48) in patients' medical records. In total, 12,283 individuals (6,646 men and 5,637 women), aged 45 years or older at the time of AF diagnosis at any of the 75 participating PHCCs from January 1, 2001, until December 31, 2007, were included in the study.

2.3 Exposure

Cardiovascular and psychiatric co-morbidities were identified both from the registered diagnoses from the 75 participating PHCCs and from registered hospital diagnoses among the 12,283 AF patients (i.e. the study population): hypertension (I10–15); coronary heart disease, including registered diagnoses of myocardial infarction, (CHD; I20–25); congestive heart failure (CHF; I50 or I110), cerebrovascular diseases, including registered diagnoses of ischemic or hemorrhagic stroke (I60–69); diabetes (E10–14); depression (F32–F34, F38–F39); anxiety disorders (F40–41), non-rheumatic valvular heart diseases (I34–38); and cardiomyopathy (I42). No diagnosis of rheumatic valvular heart diseases (I05–08) was recorded. Oral anticoagulant treatment was identified, with warfarin (ATC-code: B01AA03) being the only drug used during the time period.

The CHA₂DS₂-VASc score is used to assess the risk of stroke and is based on the following factors, with most factors giving one point in the score if not otherwise stated: female gender; congestive heart failure; hypertension; age between 65 and 74 years, age 75 years and above (two points); diabetes mellitus; a history of stroke or previous transient ischemic attacks and thromboembolism (two points); and the presence of any cardiovascular disease (recorded as myocardial infarction, peripheral artery disease or plaque in the aorta) (17).

2.4 Outcome variable

Data from the Cause of Death Register were used for the follow-up. Time to death from first AF diagnosis was registered (until December 31, 2010).

2.5 Socio-demographic factors

Educational level was categorized as 9 years (partial or complete compulsory schooling), 10–12 years (partial or complete secondary schooling) and >12 years (college and/or university studies).

Marital status was classified as married, unmarried, divorced or widowed.

Neighborhood socioeconomic status (SES) areas were categorized into three groups according to the neighborhood index score in the neighborhood of residence: more than one standard deviation (SD) below the mean (high SES or low deprivation level), more than one SD above the mean (low SES or high deprivation level), and within one SD of the mean (middle SES) (32).

2.6 Statistical analyses

Analyses were performed stratified by sex and divided by age-groups according to CHA₂DS₂-VASc.

Two types of follow-up analyses were performed. First, we used Cox regression to estimate hazard ratios (HRs) with 95% confidence interval (95% CI), where time to death was the outcome. Second, Laplace regression was used to calculate the difference in years until death for the first 25% of the participants (33). Different distributions and mathematical calculations are used to obtain results in Cox and Laplace regression. Thus, we considered the results to be more robust when findings were statistically significant with both methods. Regression models were used for men and women in three different age-groups: 45–64 years, 65–74 years and 75 years and above. We included adjustment for age, socio-demographic factors (educational level, marital status and neighborhood socio-economic status), comorbidities (hypertension, CHD, CHF, cerebrovascular diseases, diabetes, depression and anxiety) and oral anticoagulant treatment (warfarin). We did not include the covariates valvular heart disease and cardiomyopathy in the final models due to a low number of cases (excluding these factors in the models only changed the results marginally). Cox regression models were tested by Harrell's C-statistics (34). We tested models only including age, as this is a strong risk factor for mortality in itself, and in multivariate models.

A *p*-value for two-sided tests of <0.01 was considered statistically significant due to the multiple comparisons between men and women. A two-sided *p*-value of <0.05 was

considered statistically significant for variables in the Cox regression and Laplace regression analyses. All analyses were performed in STATA 14.1, with an amendment for Laplace regression as presented by Bottai et al. (33).

In the supplementary analyses, we classified subjects into survivors and deceased. Ageadjusted differences between distributions of variables were analyzed by using logistic regression (when dichotomized) or by ANCOVA (for variables with three or four categories). We also stratified survivors and deceased according to their CHA₂DS₂-VAsC scores. The incidence rates of mortality per 100 person-years at risk were estimated for men and women separately.

3. Results

Characteristics of the study population (n=12,283 individuals) are shown separately for men (n=6,646) and women (n=5,637) in the different age-groups (Table 1). A total of 1,983 men (29.8%) and 1,971 women (35.0%) died during the follow-up. The mean follow-up time was 5.8 years (standard deviation (SD) 2.4). HRs were calculated based on 71,602 person-years at risk (39,154 among men and 32,448 among women). Mortality rates per 100 person-years were 6.07 (95% CI 5.81–6.35) for women and 5.06 (95% CI 4.85–5.29) for men. Most variables were significantly different when comparing survivors and deceased after ageadjustments, with some exceptions (Supplementary Table 1). Among men, differences were non-significant for valvular heart disease and anxiety. For women, differences were nonsignificant for cardiomyopathy, depression, and anxiety.

Cox regression models for the association between different comorbidities and mortality risk are shown in Table 2, stratified by sex and age-group. In multivariable models among men, significantly higher HRs were found in all three age-groups for the association between CHF and mortality as well as for the association between cerebrovascular diseases and mortality. Among men, there were significant associations with mortality for diabetes and depression in the age-group 65–74 years and, for CHD, in the age-group 75 years among men. Among women, significantly higher HRs were found in all three age-groups for the association between CHF and mortality. In the age-group 45–64 years of age, there was an association between diabetes and mortality; in the age-groups 65–74 and 75 years of age, there was an association between cerebrovascular diseases and mortality in women. In the age-group 65–74 years, there was an association between depression and mortality. A significantly lower HR in the association between hypertension and mortality was found in the age-group 75 years in women. C-statistics indicated that the co-morbidities improved prediction of mortality beyond age, although not in the age-group 75 years.

The corresponding Laplace regression models are shown in Table 3. Among men, a shorter time period before the first 25% had died was found in all three age-groups for both CHF and cerebrovascular diseases. In the age-group 75 years, this was the case for CHD. In women, a shorter time period before the first 25% had died was found in all three age-groups for CHF. In the groups 65–74 and 75 years of age, this was the case for cerebrovascular diseases and, in the age-group 75 years, for diabetes. For hypertension and depression, a longer survival time was found in the age-group 75 years in women.

Stratification by CHA2DS2-VASc scores for survivors and deceased showed highly significant results for both men and women (Supplementary Table 2).

4. Discussion

The main finding of this study of patients with AF was the consistent association between CHF and mortality and cerebrovascular diseases and mortality in both men and women in all age-groups, with the exception of the youngest women for cerebrovascular diseases. In addition, we found an increased mortality associated with depression among men and women 65–74 years of age, and, for diabetes, among the youngest women. A decreased mortality risk was observed among men and women with hypertension in the oldest age-groups.

The findings of an increased mortality among patients with CHF are in line with earlier findings (13, 14, 35), as is the association with cerebrovascular diseases (35, 36). The increased mortality among patients with concomitant diabetes is also in line with earlier findings (37). On the other hand, the lower mortality associated with hypertension in the oldest age-group is somewhat surprising, as hypertension is a risk factor for both AF, CHD, CHF and cerebrovascular diseases. However, the finding of hypertension being protective among the oldest women must be interpreted with caution, as the C-statistics indicated that prediction of mortality did not improve when adding variables in addition to age. With this in mind, an effective antihypertensive treatment could actually be protective for both CHF and cerebrovascular diseases (38), diagnoses we found to be associated with a higher mortality.

Furthermore, the finding that the CHA2DS2-VASc scores were strongly associated with mortality is in line with earlier findings (18). CHA2DS2-VASc scores actually seem to be predictive, not only among AF patients but also in non-AF subjects, and could be regarded as a useful tool for predicting cardiovascular risk (18).

As regards to psychiatric co-morbidity, we found an increased mortality risk among both men and women with depression in the age-group 65–74 years of age, which is in line with previous research (25, 39). However, we found no statistically shorter survival in the corresponding Laplace models, but a marginally longer survival in the oldest age-group in women; a finding we recommend to be interpreted with caution as the corresponding Cox model showed no significant results. In contrast to depression, we found no association between anxiety and mortality (data not shown).

In the age-group ≥ 75 years, lower HRs were found for both CHF and cerebrovascular diseases. The mortality is higher among elderly, both in general, and also due to competing factors such as for instance cancer and dementia. C-statistics analyses indicated that all results in those above 75 years of age should be interpreted with caution, as the diagnoses did not improve C-statistics beyond age in this group. However, as AF is associated with cardiovascular co-morbidities such as CHD, MI, CHF and cerebrovascular diseases (4–6), to a larger extent than among non-AF subjects, the effect of these co-morbidities could be of importance even among the oldest. In addition, cardiovascular risk factors are of importance for the development of both vascular dementia and Alzheimer's disease (40).

To sum up, our study had an exclusive focus on AF patients treated in primary care examining how a comprehensive set of comorbidities and risk factors may affect the mortality in both women and men in all ages, which represents a novel contribution, where many new results emerged.

There are, however, several limitations of this study which must be kept in mind when interpreting the results. The study sample only included patients with AF registered in primary health care. In another study it was found that 36% of all registered AF patients in Stockholm County did not have a registered diagnosis of AF in primary health care (2). Silent AF is another problem and could represent up to 11% among patients with several risk factors (41). All these mentioned factors could have affected the results and yielded discrepant findings. We did not have access to data on criteria for diagnosis of CHF or on type of CHF. Besides, no data on severity of CHF and CHD were available. Patients treated in primary care may have had less severe CHF than patients treated in hospital care, and/or, to a higher extent, a preserved ejection fraction. Moreover, AF could not be classified as paroxysmal, persistent or permanent. Cardiomyopathy was not further specified regarding type. Additionally, we had no access to data on renal function. Anticoagulant treatment used during the time period included only warfarin and as the rate of patients treated with anticoagulants has increased after the introduction of new oral anticoagulants (NOACs) (42), the results could have been different if performed after the introduction of the NOACs.

A major strength of this study was that we were able to link clinical data from individual patient records to data from national hospital patient data as well as highly complete demographic and socioeconomic registers (less than 1% of information missing). While many previous follow-up studies of AF have used only hospital data, the current study used data from primary care as well as hospitals, which may better reflect the risks associated with AF in the population. Moreover, randomized controlled trials often exclude individuals with comorbidities, such as AF patients with concomitant diabetes and CHF. In the current study, we had the possibility to include these patients in the analyses, which means that the findings are more representative of the variety of patients encountered in clinical practice today. We also adjusted for socio-economic factors, i.e. educational level, marital status and neighborhood socio-economic status, which are important risk factors for mortality.

In this clinical setting of AF patients in primary care, we found that CHF and cerebrovascular diseases were consistently associated with mortality in both women and men. The potential beneficial effect from antihypertensive drugs on preventing CHF and pre-term mortality needs to be further investigated in patients with AF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key messages

1. We found congestive heart failure and cerebrovascular diseases to be consistently associated with mortality in both women and men
2. We found hypertension to be associated with lower mortality risk among women ≥ 75 years of age, although this finding must be interpreted with caution
3. Depression was found to be associated with increased mortality risk among men and women aged 65–74 years of age

Table 1

Descriptive data for patients aged ≥ 45 years with diagnoses of AF ($n=12,283$), for men and women divided by age-groups, in primary care attending the 75 PHCCs between January 1st 2001 and December 31st 2007

	Men			Women		
	45–64 years <i>n</i> =1,592	65–74 years <i>n</i> =2,042	75 years <i>n</i> =3,012	45–64 years <i>n</i> =626	65–74 years <i>n</i> =1,266	75 years <i>n</i> =3,745
Age (years), mean (SD)	58.0 (4.9)	69.9 (2.8)	81.1 (4.4)	58.9 (4.4)	70.3 (2.8)	82.4(4.9)
Mortality	143 (9.0)	399 (19.5)	1,441 (47.8)	43 (6.9)	188 (14.9)	1,740 (46.5)
Co-morbidity						
Hypertension	596 (37.4)	961 (47.1)	1,242 (41.2)	255 (40.7)	640 (50.6)	1,892 (50.5)
Coronary heart disease	246 (15.5)	505 (24.7)	971 (32.2)	86 (13.7)	273 (21.6)	1,153 (30.8)
Congestive heart failure	427 (26.8)	783 (38.3)	1,646 (54.7)	154 (24.6)	475 (37.5)	2,199 (59.7)
Valvular heart disease	50 (3.1)	74 (3.6)	170 (5.6)	25 (4.0)	63 (5.0)	189 (5.1)
Cardiomyopathy	37 (2.3)	15 (0.7)	8 (0.3)	9 (1.4)	8 (0.6)	13 (0.4)
Cerebrovascular diseases	171 (19.7)	372 (18.2)	734 (24.4)	81 (12.9)	231 (18.3)	977 (26.1)
Diabetes mellitus	292 (18.3)	492 (24.1)	528 (17.5)	113 (18.1)	293 (23.1)	687 (18.3)
Depression	108 (6.8)	107 (5.2)	197 (6.5)	79 (12.6)	136 (10.7)	412 (11.0)
Anxiety disorders	52 (3.3)	43 (2.1)	88 (2.9)	35 (5.6)	75 (5.9)	203 (5.4)
Anticoagulant treatment	909 (57.1)	1,331 (65.2)	1,476 (49.0)	333 (53.2)	762 (60.2)	1,596 (42.6)
Educational level						
Compulsory schooling	477 (30.2)	807 (40.1)	1,202 (44.5)	200 (32.3)	552 (45.0)	1,847 (59.5)
Secondary schooling	681 (43.2)	728 (36.2)	958 (35.5)	265 (42.8)	447 (36.4)	916 (29.5)
College and/or university studies	420 (26.6)	477 (23.7)	540 (20.0)	154 (24.9)	228 (18.6)	342 (11.0)
Marital status						
Married	896 (56.5)	1,325 (65.1)	1,729 (57.7)	333 (53.2)	565 (44.8)	765 (20.5)
Unmarried	284 (17.9)	167 (8.2)	179 (6.0)	79 (12.6)	90 (7.1)	230 (6.2)
Divorced	363 (22.9)	359 (17.6)	299 (10.0)	134 (21.4)	232 (18.4)	426 (11.4)
Widowed	44 (2.8)	184 (9.0)	792 (26.4)	80 (12.8)	373 (29.6)	2,304 (61.9)
Neighborhood SES						
High	649 (40.8)	836 (40.9)	1,171 (38.9)	218 (34.8)	461 (36.4)	1,269 (33.9)
Middle	680 (42.7)	914 (44.8)	1,436 (47.7)	274 (43.8)	593 (46.8)	1,910 (51.0)
Low	263 (16.5)	292 (14.3)	405 (13.5)	134 (21.4)	212 (16.8)	566 (15.1)

Information on educational level and marital status is missing for some individuals.

Table 2

Cox regression models (with hazard ratios (HRs) and 95% confidence interval (CI)) for mortality among patients aged ≥ 45 years with diagnoses of AF ($n=12,283$) in primary care attending the 75 PHCCs between January 1st 2001 and December 31st 2007;

Diagnosis	Men			Women		
	45–64 years	Men 65–74 years	75 years	45–64 years	Women 65–74 years	75 years
Hypertension	1.03 (0.72–1.46)	0.91 (0.74–1.12)	0.92 (0.81–1.03)	0.81 (0.41–1.57)	0.84 (0.62–1.15)	0.85 (0.76–0.94)
Coronary heart disease	1.26 (0.84–1.90)	1.07 (0.86–1.34)	1.19 (1.06–1.35)	0.69 (0.29–1.66)	1.15 (0.82–1.61)	1.12 (0.99–1.26)
Congestive heart failure	2.51 (1.76–3.58)	2.40 (1.94–2.96)	1.55 (1.37–1.75)	3.42 (1.77–6.59)	2.35 (1.70–3.25)	1.48 (1.31–1.68)
Cerebrovascular diseases	1.76 (1.14–2.71)	1.51 (1.21–1.89)	1.33 (1.18–1.51)	1.61 (0.78–3.33)	2.18 (1.58–3.00)	1.52 (1.36–1.71)
Diabetes mellitus	1.18 (0.79–1.77)	1.31 (1.05–1.63)	0.99 (0.85–1.14)	2.26 (1.14–4.45)	1.08 (0.76–1.52)	1.13 (0.99–1.30)
Depression	1.56 (0.87–2.81)	1.53 (1.08–2.19)	1.14 (0.92–1.41)	1.37 (0.52–3.61)	1.63 (1.07–2.49)	0.98 (0.82–1.17)
C-statistics, age- adjusted only	0.57	0.58	0.68	0.59	0.55	0.68
C-statistics, full model	0.73	0.70	0.66	0.83	0.71	0.69

Multivariate models include adjustment for age, all socio-economic factors (educational level, marital status and neighborhood socio-economic status), co-morbidities and anticoagulant treatment Model check revealed no significant interactions

C-statistics shown in univariate models including only age, and in multivariate models

Table 3

Laplace regression models (with years gained or lost until first 25 % deaths, and 95% confidence interval (CI)) among patients aged 45 years with diagnoses of AF ($n=12,283$) in primary care attending the 75 PHCCs between January 1st 2001 and December 31st 2007;

Diagnosis	Men			Women		
	45–64 years	65–74 years	75 years	45–64 years	65–74 years	75 years
Hypertension	-0.24 (-1.48; 1.01)	0.57 (-0.19; 1.33)	0.38 (-0.06; 0.83)	0.33 (-1.84; 2.50)	0.76 (-0.17; 1.69)	0.60 (0.21;1.00)
Coronary heart disease	-0.86 (-2.16; 0.44)	0.21 (-0.61; 1.02)	-0.51 (-0.99; -0.02)	0.59 (-2.76; 3.94)	-0.49 (-1.90; 0.92)	-0.15 (-0.56; 0.26)
Congestive heart failure	-2.72 (-3.86; -1.57)	-2.65 (-3.36; -1.93)	-0.78 (-1.29; -0.28)	-3.49 (-5.33; -1.67)	-2.48 (-3.56; -1.40)	-0.66 (-1.10; -0.23)
Cerebrovascular diseases	-1.62 (-2.99; -0.25)	-1.01 (-1.87; -0.15)	-0.69 (-1.19; -0.20)	-1.25 (-4.00; 1.51)	-1.88 (-3.04; -0.72)	-0.84 (-1.26; -0.42)
Diabetes mellitus	-0.18 (-1.41; 1.95)	-0.95 (-1.80; -0.11)	0.03 (-0.57; 0.63)	-1.24 (-3.22; 0.73)	0.26 (-0.96; 1.48)	-0.46 (-0.93; 0.02)
Depression	-1.60 (-4.07; 0.87)	-1.78 (-3.99; 0.42)	-0.19 (-1.36; 0.99)	-0.65 (-2.92; 1.62)	-1.73 (-3.63; 0.17)	0.48 (0.02; 0.93)

Multivariate models include adjustment for age, all socio-economic factors (educational level, marital status and neighborhood socio-economic status), co-morbidities and anticoagulant treatment.