

Gender-related differences in risk of cardiovascular morbidity and all-cause mortality in patients hospitalized with incident atrial fibrillation without concomitant diseases: A nationwide cohort study of 9519 patients[☆]

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ARTICLE INFO

Article history:

Received 12 February 2014

Received in revised form 10 September 2014

Accepted 20 September 2014

Available online 11 October 2014

Keywords:

Atrial fibrillation

Cardiovascular morbidity

Mortality

Cohort

Nationwide

ABSTRACT

Background: Previous studies of patients with “lone” and “idiopathic” atrial fibrillation (AF) have provided conflicting evidence concerning the development, management and prognosis of this condition.

Methods: In this nation-wide, retrospective, cohort study, we studied patients diagnosed with incidental AF recorded in national Swedish registries between 1995 and 2008. Controls were matched for age, sex and calendar year of the diagnosis of AF in patients. All subjects were free of any in-hospital diagnosis from 1987 and until patients were diagnosed with AF and also free of any diagnosis within one year from the time of inclusion. Follow-up continued until 2009. We identified 9519 patients (31% women) and 12,468 matched controls.

Results: Relative risks (RR) versus controls for stroke or transient ischemic attack (TIA) in women were 19.6, 4.4, 3.4 and 2.5 in the age categories <55, 55–64, 65–74 and 75–85, years respectively. Corresponding figures for men were 3.4, 2.5, 1.7 and 1.9. RR for heart failure were 6.6, 6.6, 6.3 and 3.8 in women and 7.8, 4.6, 4.9 and 2.9 in men. All RR were statistically significant with $p < 0.01$. RR for myocardial infarction and all-cause mortality were statistically significantly increased only in the two oldest age categories in women and 65–74 years in men.

Conclusions: Patients with AF and no co-morbidities at inclusion had at least a doubled risk of stroke or TIA and a tripled risk of heart failure, through all age categories, as compared to controls. Women were at higher RR of stroke or TIA than men.

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1. Introduction

Atrial fibrillation (AF) has been reported to be an independent risk factor of death and morbidity [1]. The mortality risk increases in the presence of co-morbidities, while AF in patients without co-morbidities has been considered relatively harmless, possibly because this arrhythmia is often found in younger individuals [1,2]. The number of patients with AF without co-morbidities is dependent on the definition of the study populations, but there is as yet no study on the

long-term course of a very large cohort of patients and controls with this condition.

Patients below 60 years of age have been considered to have lone AF if they have no evidence of cardiopulmonary disease, while idiopathic AF requires the absence of any other disease, irrespective of age [1,3]. However, the definitions of lone and idiopathic are heterogeneous, the age criterion has been questioned and the studied populations have been small or have lacked controls free from AF [4–12].

A statistically significant increase in all-cause mortality has only been found in one study of patients with lone or idiopathic AF (Table 1) [5,6,8,11,12]. Previous studies of heart failure in the general population have shown an increased prevalence in men compared to women and that patients with AF have an increased risk of heart failure [1,2,11,13–15]. However, studies with 41 to 76 patients with lone or idiopathic AF have not shown any statistically significantly increased

[☆] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Table 1
Studies of lone or idiopathic atrial fibrillation with controls.

First author	N	Controls	Age-mean (years)	Follow-up (years)	Stroke/TIA	Heart failure	Myocardial infarction	All-cause mortality	Combined endpoint
Brand et al [4]	43	Age–sex matched	70.6 (men) 68.1 (women)	30	0.9% vs 0.2% ^a (<i>p</i> < 0.01)	ns	ns (coronary heart disease)	–	
Jouven et al [5]	25	Age–sex matched	47.6	23	–	–	–	RR 1.95 (<i>p</i> = 0.02)	
Janghvir et al [6]	76	Age–sex specified incidence rates	44.2	30	0.9% vs 0.5% ^a (<i>p</i> = 0.004)	ns	–	ns	
Weijis et al [7]	41	Age–sex matched	58	5.5 (mean)	ns	ns	ns	ns	8.9% vs 3.6% ^{a,b} (<i>p</i> = 0.006)
Kopecky et al [8]	97	Life-table analysis and difference between isolated, recurrent and chronic AF	44.0	14.8 (mean)	Low ^c	–	Low ^c	ns	
Stewart et al [11]	15	Age–sex matched	^d	20	–	–	–	ns	ns ^e
Kopecky et al [12]	55	Age–sex matched	74	9.6 (median)	2.0% vs 0.2% ^a (<i>p</i> < 0.01)	–	2.6% vs 1.1% ^a (<i>p</i> = 0.02)	ns	5.0% vs 1.3% ^{a,f} (<i>p</i> < 0.01)

Abbreviations: N, numbers of patients; TIA, transient ischemic attack; ns, not statistically significant; RR, relative risk; vs, versus; y, years.

^a Annual rates in percentage.

^b Cardiovascular death, myocardial infarction, cerebrovascular accident, heart failure, coronary artery disease and new onset hypertension.

^c Confirmed low incidence.

^d Age not specified in subgroup of patients with lone atrial fibrillation.

^e Cardiovascular hospitalization and death.

^f Stroke, transient ischemic attack, myocardial infarction, valvular heart disease, coronary heart disease and cardiac surgery.

risk of heart failure while reports diverge on the risk of coronary heart disease in these patients [4,6,7,12]. Cohorts of 43 to 76 patients with lone or idiopathic AF had an increased risk of stroke with annual rates between 0.9% and 2.0%, and equal rates between in men and women have been found [4,6,12].

National health registries in Sweden record the discharge diagnoses of all hospitalized patients and provide high quality information [16,17]. Personal identification numbers allow comprehensive coverage of all non-emigrated patients throughout life. Due to the all-inclusive nature

of the information recorded in the registries, it is possible to obtain a national estimate of long-term cardiovascular risks. The registries are well established and allow researchers to make retrospective analyses in large patient cohorts, and they permit the performance of prospective nationwide randomized trials [2,18–20].

Our purpose was to estimate the risk of stroke or transient ischemic attack, heart failure, myocardial infarction and all-cause mortality in all patients hospitalized with incident AF as the only diagnosis and in matched controls in a comprehensive nation-wide study.

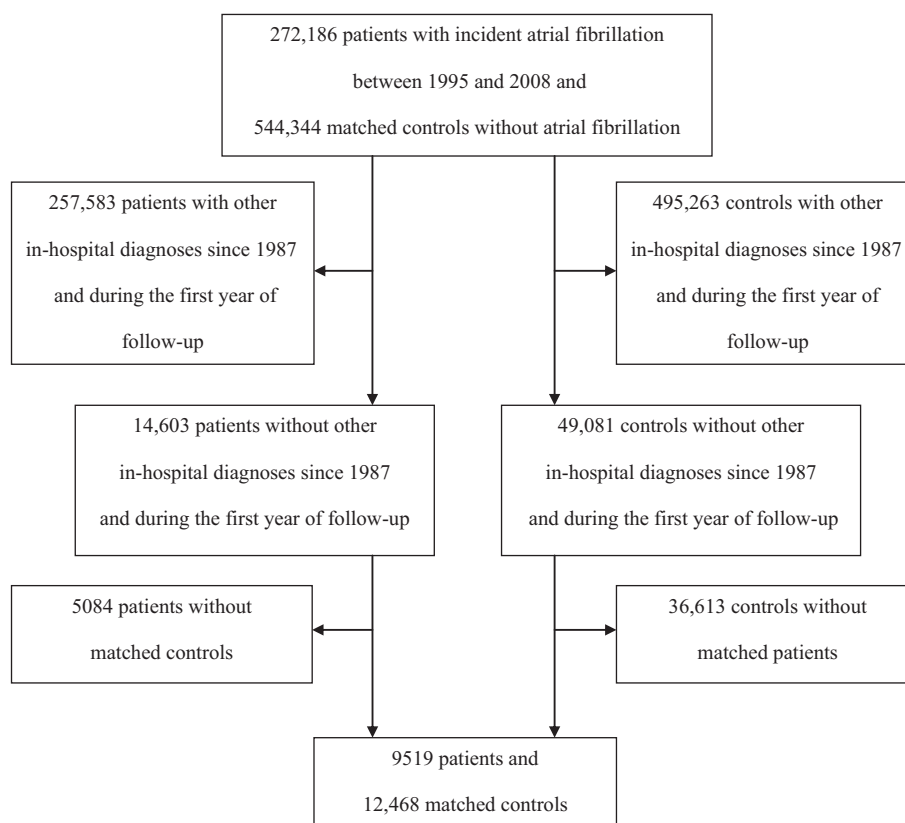


Fig. 1. Flowchart of patients with incident atrial fibrillation and matched controls without other diagnoses.

2. Methods

2.1. Study design and national registries

We conducted a nationwide, retrospective controlled cohort study using the Swedish National Patient Registry, the General Population Registry and the Cause of Death Registry. The study cohort was identified by the epidemiological centre at the Swedish National Board of Health and Welfare, and the matching procedure was carried out by Statistics Sweden. The Swedish National Patient Registry has a >99% coverage of hospital diagnoses from 1987 and onwards, and the diagnoses have a positive predictive value of 85–95% [16]. Although some conditions that are generally managed on an outpatient basis, such as hypertension, is known to be somewhat underreported, the validity of the registry is high and has therefore been proposed to be used for epidemiological studies by the National Board of Health and Welfare [16,17]. In Sweden, all inhabitants have a unique personal identification number, all have equal access to health care and hospital services, and hospitals are required to record all discharge diagnoses. This provides the possibility to record and track all non-emigrated patients in clinical registries and analyze morbidity and mortality in the entire Swedish population. This study complied with the Declaration of Helsinki, and the study protocol was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2009/273).

2.2. Study population and definitions of patients, controls, outcome and follow-up

Patients were eligible if they had a diagnosis of incident AF between 1995 and 2008 and no diagnosis of AF between 1987 and 1994, thus making it likely that the AF was truly incident. AF was defined according to the International Classification of Diseases (ICD): 427 D (DA, DB, DC, DD, DW) in ICD 9 (1987–1996) and I 48, I 48.9 and I 48.9 (A, B, C, D, E, F, P, X) in ICD 10 (1997–2011). No distinction could be made between paroxysmal, persistent or permanent AF, and atrial flutter. To identify patients with incident AF without other diseases, the National Patient Registry was used to exclude patients with other in-hospital diagnoses from 1987 until the time of inclusion. All diagnoses from ICD 9 (001–999) and ICD 10 (A00–Z99) were excluded: thus, included patients only had a single diagnosis of AF. In the event of re-hospitalization with any in-hospital diagnosis or death within one year from the time of the incident AF, such patients were excluded in order to increase the likelihood that subsequent events were due to AF and not to an undetected developing cardiovascular condition.

For each patient with AF, one or two controls with no hospital record of AF between 1987 and 2009 were selected and matched for age, sex and calendar year of the diagnosis of AF by linkage with the General Population Registry. First-degree relatives of patients with AF were not included as controls. Diagnoses that were excluded since 1987

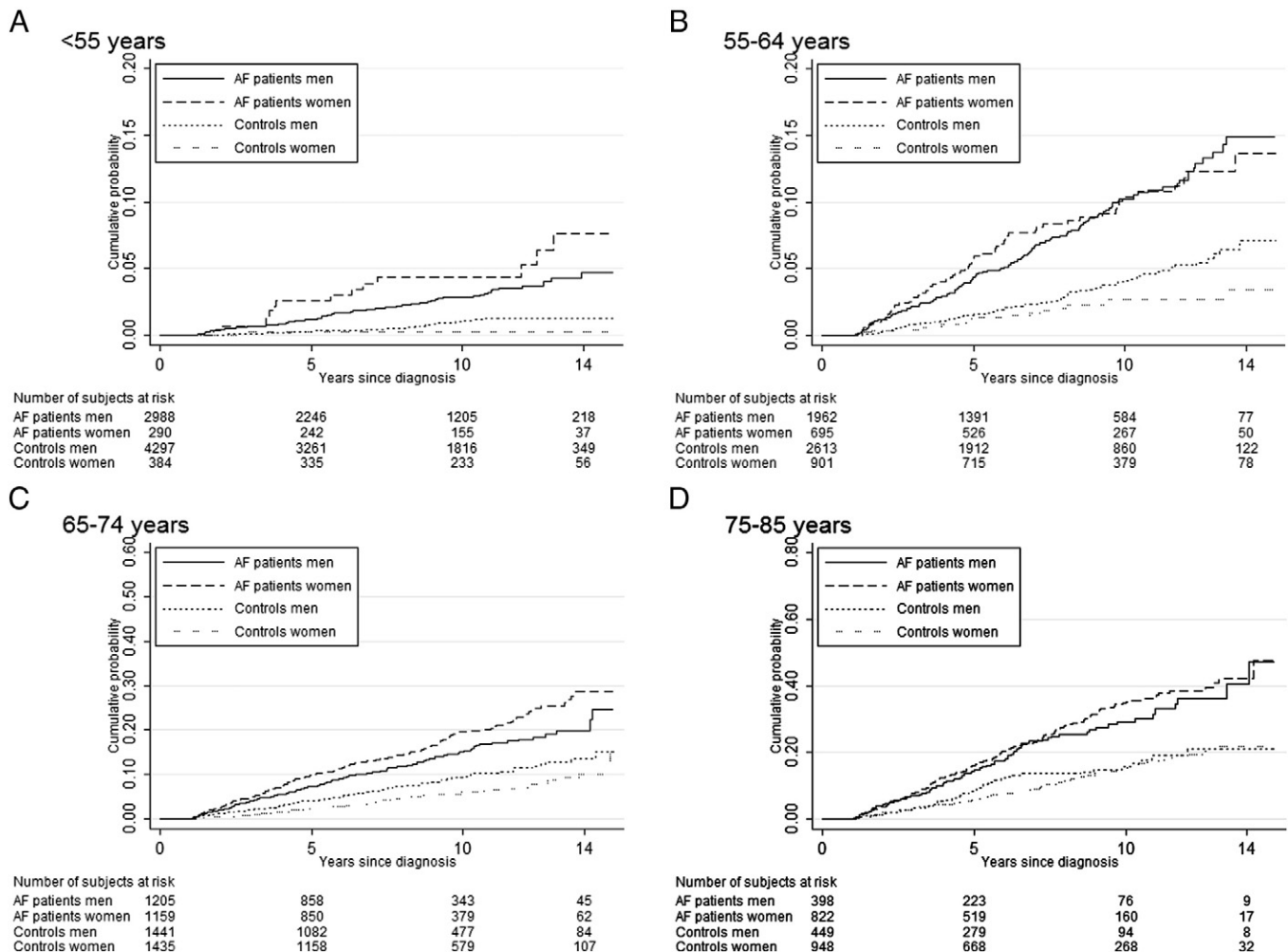


Fig. 2. A-2D Risk of stroke and transient ischemic attack in patients with atrial fibrillation and controls without other diagnoses in all age categories.

Table 2

Annual stroke and mortality rate in patients with atrial fibrillation and controls without other diagnoses with corresponding risk scores from CHA₂DS₂-VASc and CHADS₂ divided into sex and age categories.

CHA ₂ DS ₂ -VASc		CHADS ₂	Annual stroke rate (%)		Annual mortality rate (%)	
			Patients	Controls	Patients	Controls
<i>Women</i>						
<55	1	0	0.5	0.0	0.2	0.3
55–64	1	0	1.1	0.3	0.5	0.5
65–74	2	0	2.1	0.6	1.7	1.3
75–85	3	1	3.9	1.5	5.0	3.6
<i>Men</i>						
<55	0	0	0.3	0.1	0.2	0.2
55–64	0	0	1.0	0.4	0.7	0.7
65–74	1	0	1.6	0.9	2.3	2.0
75–85	2	1	3.3	1.7	5.9	5.1

Abbreviations: CHA₂DS₂-VASc = Cardiac failure, Hypertension, Age \geq 75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex category (female). CHADS₂ = Cardiac failure, Hypertension, Age \geq 75, Diabetes, and Stroke (doubled).

were the same in controls as in the patients with AF. All controls were alive on January 1st in the year of the diagnosis of the index patient. If a control person had died earlier related to the index patient during the first year, the time at risk was set to one day.

During follow-up, the classifications from the ICD 9 and 10 were: stroke and transient ischemic attack, 433 (A, B, C, D, W, X), 434 (A, B, X), 435, I 63 (0, 1, 2, 3, 4, 5, 6, 8, 9), I 64 and G 45 (0, 1, 2, 3, 4, 8, 9); heart failure, 428 (A, B, X) and I 50 (0, 1, 9); myocardial infarction, 410 (A, B, W, X), 411 (A, B, C, X), 412, I 21 (0, 1, 2, 3, 4, 9), I 22 (0, 1, 8, 9) and I 25.2. The risks of an in-hospital diagnosis were assessed from the date of inclusion to the date when such a diagnosis was registered, a patient died or emigrated, or to the end of follow-up on 31 December 2009.

The original cohort consisted of 272,186 patients with incident AF between 1995 and 2008. There were 9519 patients with incident AF

and 12,468 matched controls without in-hospital diagnoses since 1987 and during the first year after inclusion (Fig. 1).

2.3. Statistical analysis

Continuous variables were summarized with mean and standard deviations (SD) and categorical percentages. Unadjusted Kaplan–Meier plots were used to calculate the cumulative probability of stroke and transient ischemic attack, heart failure, myocardial infarction and all-cause mortality. Rates of diseases were defined as the number of persons with the specific disease and mortality rates as the number of deaths, which were divided by the number of person-years at risk. The annual rates were then calculated by dividing the ten-year rate with ten. Cox regression models were used to compare patients with AF and controls, adjusted by age at diagnosis and categorized into five-year age bands, with the first category younger than 55 years, and modelled as a categorical variable. Separate regression models were estimated for men and women combined with age categories at diagnosis of: younger than 55, 55–65, 65–74 and 75–85 years of age. Cox regression was also used to compare women and men with AF. To measure associations, we used hazard ratios as estimates of relative risks accompanied with 95% confidence intervals (CI). All statistical calculations were made with STATA release 11 software (StataCorp, College Station, TX, USA), and two-sided *P* values of <0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

There were 9519 patients and 12,468 matched controls in our study cohort (Fig. 1). The mean age was higher in women than men, 67.7 ± 10.4 years vs. 54.9 ± 13.4 years ($p < 0.01$). The proportion of women was 9% in the age category younger than 55 years, 26% at

Table 3

Rates, events and hazard ratios of cardiovascular morbidity and all-cause mortality in patients with atrial fibrillation without other diagnoses, specified in sex and age categories.

Age category	Women					Men					AF patients
	AF patients		Controls		AF patients vs. controls	AF patients		Controls		AF patients vs. controls	Women vs. men
	Rates ^a	Events	Rates ^a	Events	HR (95 % CI)	Rates ^a	Events	Rates ^a	Events	HR (95 % CI)	HR (95 % CI)
Stroke and TIA											
<55	5.0	14	0.2	1	19.6 (2.6–149.2)	2.9	74	0.9	32	3.4 (2.2–5.2)	1.67 (0.94–2.95)
55–64	10.5	61	2.4	19	4.4 (2.6–7.3)	10.1	151	4.1	84	2.5 (1.9–3.2)	1.00 (0.74–1.34)
65–74	21.1	194	6.2	78	3.4 (2.6–4.5)	16.1	147	9.7	112	1.7 (1.3–2.1)	1.25 (1.01–1.56)
75–85	38.3	210	15.6	111	2.5 (2.0–3.2)	33.7	85	17.5	53	1.9 (1.4–2.7)	1.11 (0.86–1.43)
Total ^b					3.1 (2.6–3.7)					2.2 (1.8–2.5)	1.16 (1.01–1.34)
Heart failure											
<55	5.0	14	0.8	3	6.6 (1.9–23.1)	2.9	74	0.4	14	7.8 (4.4–13.8)	1.60 (0.90–2.84)
55–64	10.4	61	1.6	13	6.5 (3.6–11.8)	8.5	130	1.9	39	4.6 (3.2–6.6)	1.15 (0.84–1.56)
65–74	19.9	186	3.3	42	6.3 (4.5–8.8)	20.7	191	4.4	52	4.9 (3.6–6.6)	0.88 (0.72–1.08)
75–85	40.2	222	11.4	84	3.8 (2.9–4.8)	45.6	113	16.1	50	2.9 (2.0–4.0)	0.84 (0.67–1.06)
Total ^b					4.8 (4.0–5.8)					4.4 (3.7–5.3)	0.94 (0.82–1.07)
Myocardial infarction											
<55	1.4	4	1.3	5	1.1 (0.3–4.2)	2.0	51	1.7	62	1.2 (0.8–1.7)	0.66 (0.24–1.84)
55–64	4.0	24	2.6	21	1.5 (0.8–2.7)	5.7	87	5.3	110	1.1 (0.8–1.4)	0.66 (0.42–1.04)
65–74	9.1	88	4.9	62	1.9 (1.4–2.6)	12.4	116	8.9	103	1.4 (1.1–1.8)	0.68 (0.51–0.90)
75–85	14.3	84	9.5	70	1.5 (1.1–2.1)	18.7	49	17.5	54	1.1 (0.7–1.6)	0.74 (0.52–1.06)
Total ^b					1.6 (1.3–2.0)					1.2 (1.0–1.4)	0.70 (0.57–0.84)
All-cause mortality											
<55	3.5	10	3.3	13	1.1 (0.5–2.4)	2.4	62	2.1	78	1.2 (0.8–1.6)	1.32 (0.68–2.58)
55–64	6.2	38	6.1	49	1.0 (0.7–1.6)	8.5	133	7.6	161	1.1 (0.9–1.4)	0.65 (0.45–0.93)
65–74	20.7	207	15.0	192	1.4 (1.2–1.7)	27.3	267	22.2	267	1.2 (1.0–1.5)	0.67 (0.56–0.81)
75–85	57.3	351	40.2	302	1.5 (1.3–1.7)	64.5	179	56.5	181	1.1 (0.9–1.4)	0.81 (0.68–0.97)
Total ^b					1.4 (1.3–1.6)					1.2 (1.0–1.3)	0.74 (0.66–0.84)

Abbreviations: AF, atrial fibrillation; HR, hazard ratio; Rates, incidence rates per 1000 person-years; Events, numbers of actual cases; TIA, transient ischemic attack.

^a Rates per 1000 person-years.

^b Hazard ratio adjusted by age at diagnosis in five year intervals from <55 years.

55–64 years, 49% at 65–74 years, 67% at 75–85 years and 33% in the total cohort.

3.2. The incidence and risk of stroke or transient ischemic attack during follow-up

The annual rates of stroke and transient ischemic attack in women were 0.5%, 1.1%, 2.1% and 3.9% in age categories <55, 55–64, 65–74 and 75–85 years and 0.0%, 0.3%, 0.6% and 1.5% in the corresponding controls (Fig. 2A–D). In men, the corresponding rates were 0.3%, 1.0%, 1.6% and 3.3% in patients with AF and 0.1%, 0.4%, 0.9% and 1.7% in controls (Table 2). AF was strongly associated with the occurrence of stroke and transient ischemic attack in all age categories and both sexes, and the difference versus matched controls was statistically significant (Table 3). The relative risk in patients versus controls was tripled in women and doubled in men. In female compared to male patients, the incidence rates were statistically significantly higher overall and in the age category 65–74 years.

3.3. The incidence and risk of heart failure during follow-up

The annual rates of heart failure in women were 0.5%, 0.9%, 1.8% and 3.7% in age categories <55, 55–64, 65–74 and 75–85 years and 0.0%, 0.1%, 0.3% and 1.0% in controls (Fig. 3A–D). In men, the corresponding

rates were 0.3%, 0.8%, 1.9% and 4.3% in patients and 0.0%, 0.2%, 0.4% and 1.5% in controls. AF was strongly associated with an increased risk of heart failure in all age categories and both sexes, and the risks were statistically significant compared with matched controls (Table 3). Overall, the relative risk was almost fivefold in women and at least fourfold in men. The incidence rates in patients with AF were comparable between women and men in all age categories.

3.4. The incidence and risk of myocardial infarction during follow-up

The annual rates of myocardial infarction in women were 0.2%, 0.4%, 0.8% and 1.4% in age categories <55, 55–64, 65–74 and 75–85 years and 0.1%, 0.2%, 0.5% and 0.9% in controls (Fig. 4A–D). In men, the corresponding rates were 0.2%, 0.5%, 1.2% and 1.9% in patients and 0.1%, 0.5%, 0.9% and 1.7% in controls. Myocardial infarction in patients with AF occurred less often than stroke and transient ischemic attack and heart failure, while the incidence in controls was higher than stroke and transient ischemic attack and heart failure (Table 3). The relative risk showed only a weak association, indicating a trend towards an increased risk of myocardial infarction, although this was statistically significant only in women older than 65 years and in men 65–74 years. In patients with AF, it was found that the incidence rates were statistically significantly increased in men overall and in the age category 65–74 years, when compared to women.

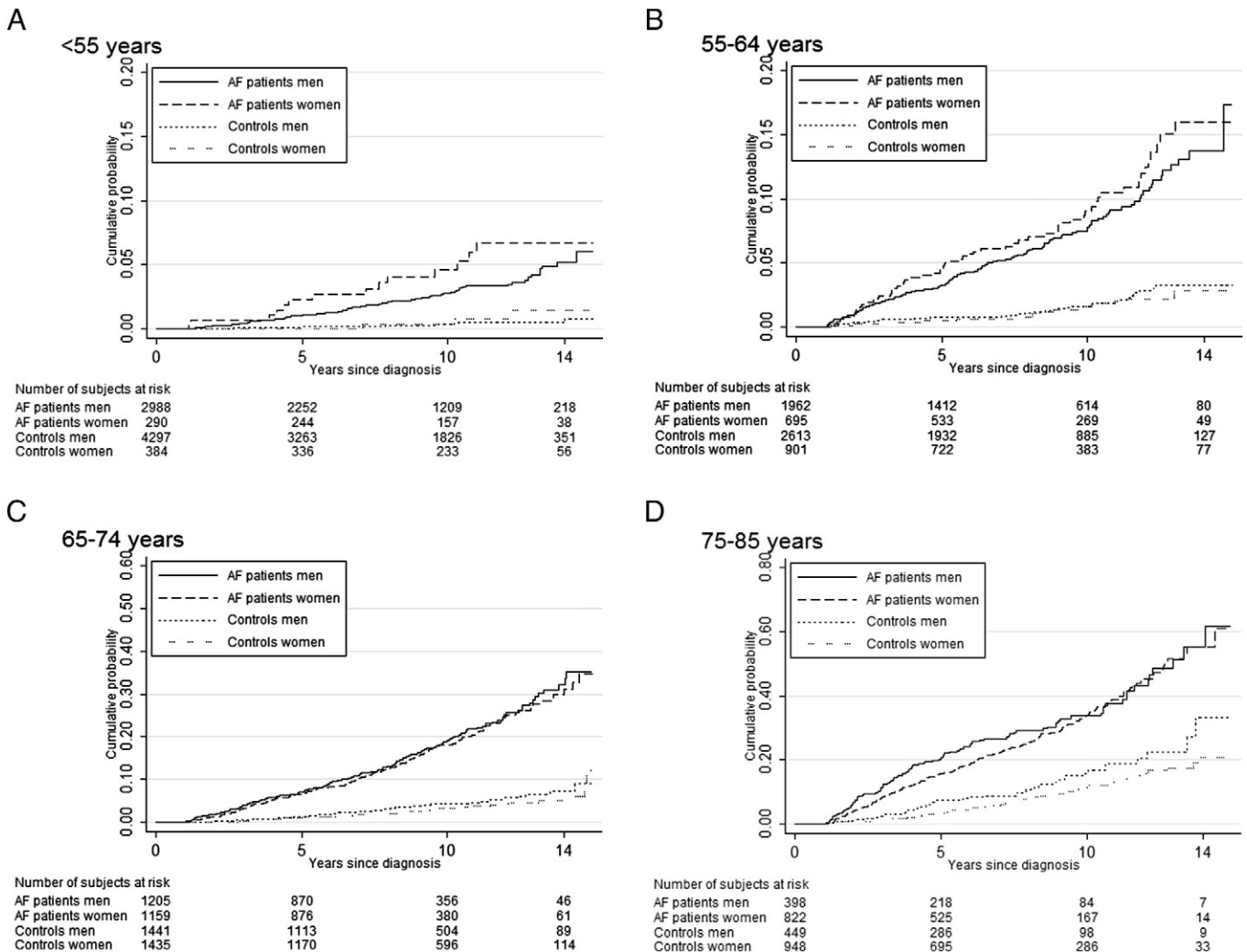


Fig. 3. A-3D risk of heart failure in patients with atrial fibrillation and controls without other diagnoses in all age categories.

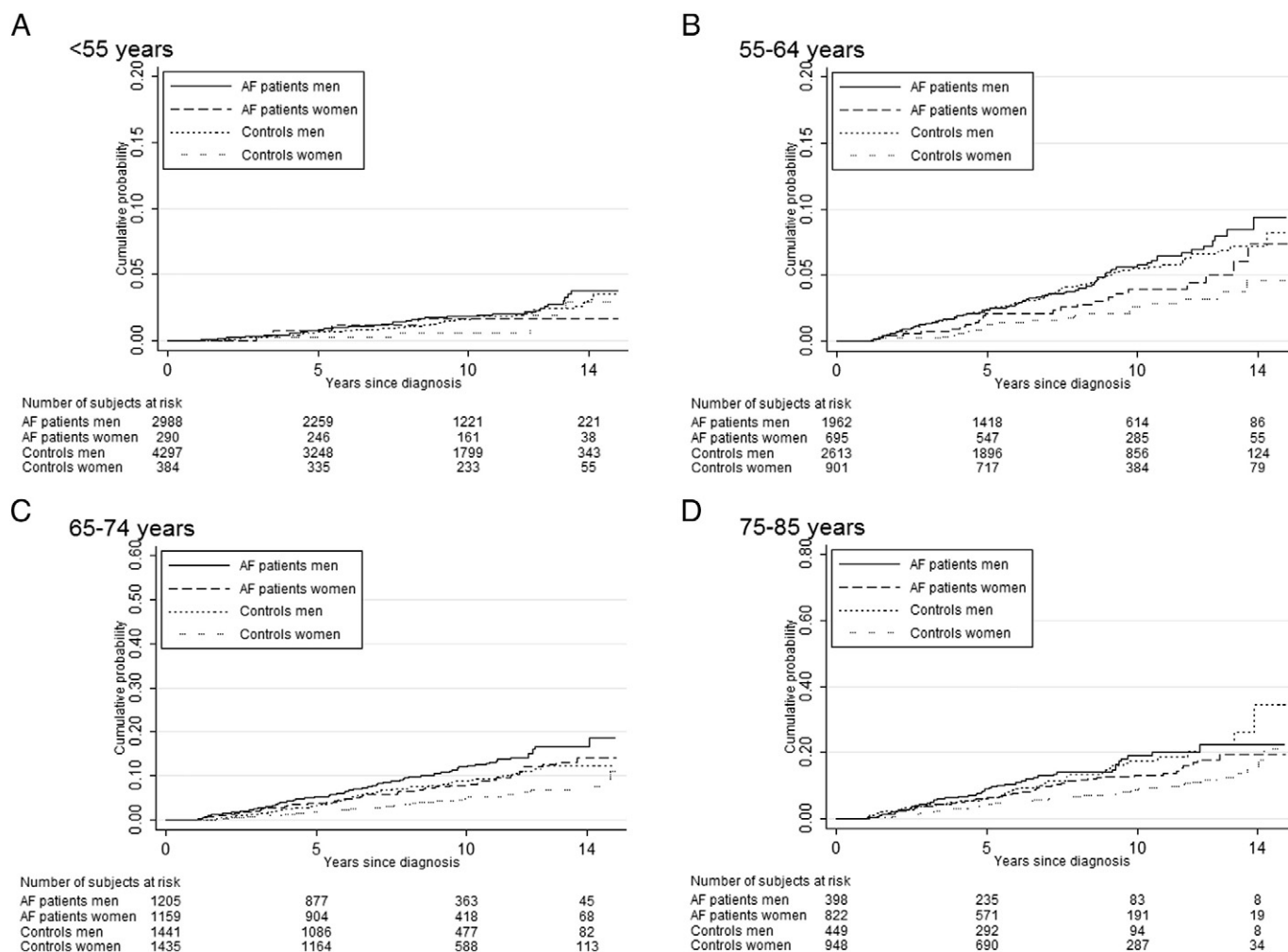


Fig. 4. A–D risk of myocardial infarction in patients with atrial fibrillation and controls without other diagnoses in all age categories.

3.5. The incidence and risk of all-cause mortality during follow-up

The annual rates of all-cause mortality in women were 0.2%, 0.5%, 1.7% and 5.0% in age categories <55, 55–64, 65–74 and 75–85 years and 0.3%, 0.5%, 1.3% and 3.6% in controls (Fig. 5A–D). In men, the corresponding rates were 0.2%, 0.7%, 2.3% and 5.9% in patients and in controls 0.2%, 0.7%, 2.0% and 5.1% (Table 2). In total, women had a relative risk versus controls of 1.4 (95% CI, 1.3 to 1.6) and men 1.2 (95% CI, 1.0 to 1.3) (Table 3). In the different age categories, the strongest association was seen in women in the age categories of 65–74 and 75–85 years. In male patients, the incidence rate was increased in all age categories and was statistically significant from age 55 and older, when compared to women.

4. Discussion

In this large and nation-wide matched control study, AF as the one and only diagnosis at inclusion was not a harmless condition and was over time associated with increased risk of subsequent cardiovascular morbidity that differed between age groups and sexes.

To the best of our knowledge, our study cohort represents by far the largest number of patients with incident AF and no other co-morbidity at the time of diagnosis. Moreover, this is the first study with complete national coverage of this diagnosis. Strikingly, we found an annual incidence of stroke or transient ischemic attack of 1.0–1.1% in the age category between 55 and 64 years in both sexes. While this does not

justify long-term warfarin treatment according to current guidelines, the comparative efficacy and lower risk of new oral anticoagulation might result in an advantageous benefit/risk ratio in this group and thus increase the number of candidates for treatment [21–33].

The two risk scores CHA₂DS₂-VASc and CHADS₂ are intended to discriminate patients with a high enough risk of stroke to justify anticoagulation [21,22]. The annual rate of stroke and transient ischemic attack in patients younger than 55 years of age was 0.5% in women and 0.3% in men and 0.0% and 0.1% in controls. The corresponding risks in patients and controls between 55 and 64 years of age were 1.1% and 0.3% in women and 1.0% and 0.4% in men. These patients had no diseases other than AF at the time of inclusion, which corresponds to zero points in CHADS₂ and zero points in men and one point in women in CHA₂DS₂-VASc. In the risk scores, one point is sufficient to suggest anticoagulation treatment, except when female sex is the only risk factor in the CHA₂DS₂-VASc [23]. In the CHA₂DS₂-VASc score, one point corresponds to an annual stroke rate with a range between 0.6% and 2.0% [22,24–28]. In CHADS₂ for a score of one point, the corresponding annual stroke rates are more pronounced and lie between 3.0% and 4.8% [26–28]. Eckman et al. suggested that an annual stroke rate of 0.9% would justify a change of treatment policy from warfarin to novel anticoagulation therapy [29]. The annual rates for intracranial bleeding in studies of novel anticoagulant are between 0.2% and 0.5% in cohorts where the median ages were between 70 and 73 years, and the mean values in the CHADS₂ score were between 2.1 and 3.5, which are significantly lower than for warfarin [30–32]. Taillandier et al. have pointed out that overtreatment occurred in patients with CHA₂DS₂-VASc

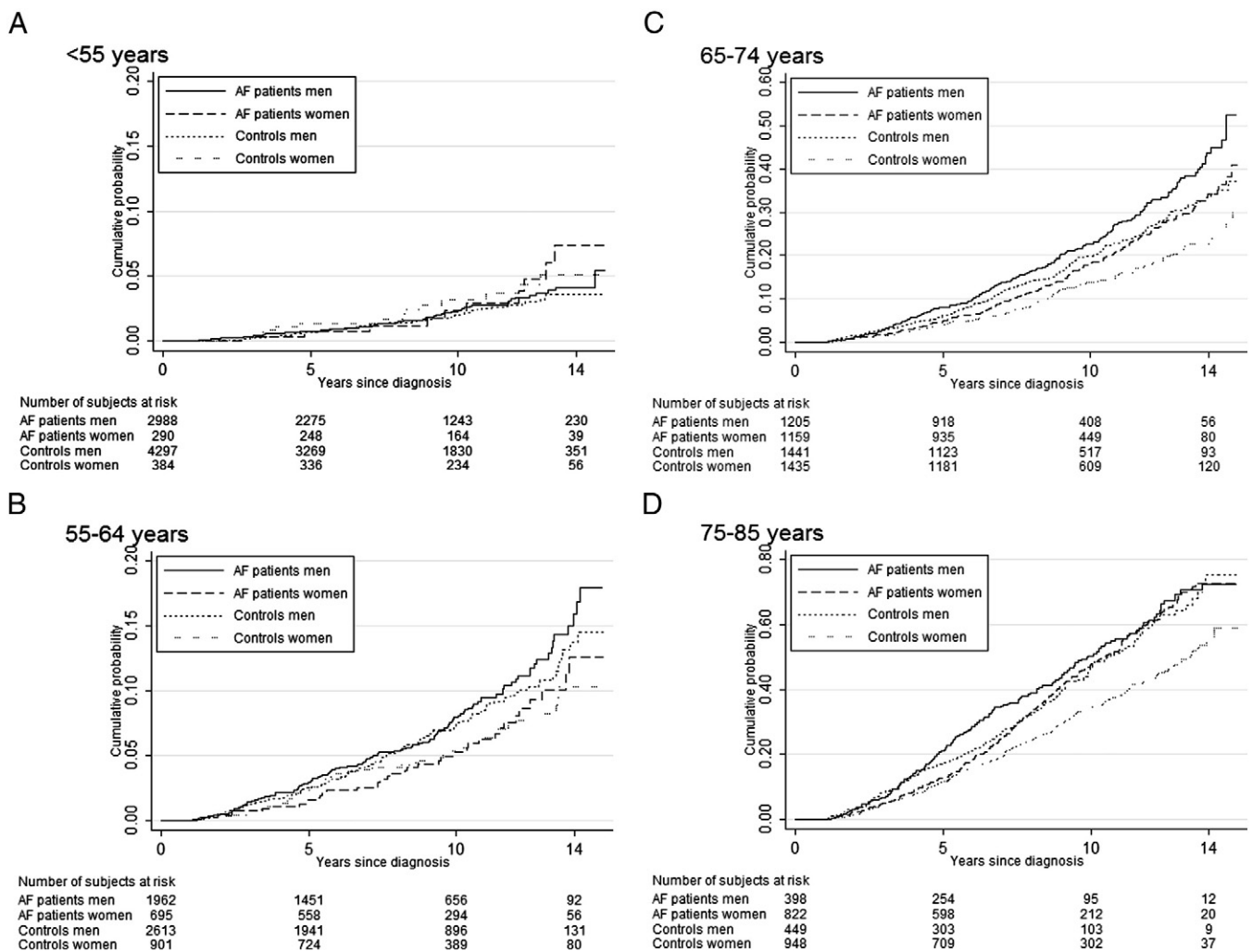


Fig. 5. A-5D risk of all-cause mortality in patients with atrial fibrillation and controls without other diagnoses in all age categories.

score = 0 and was as high as 44% [33]. They found no effect of anticoagulation treatment, and the yearly stroke rates were 0.64% in untreated (mean age 41 years) and 0.69% in treated patients (mean age 52 years) [33]. In patients with AF between 55 and 65 years of age and without other co-morbidities, the efficiency of preventive anticoagulation treatment and the risk for major bleedings are uncertain.

The relative risks and event rates of stroke or transient ischemic attack were increased in women compared to men and in all age categories. These findings are in line with previous studies and support that the female gender is given special attention in the risk assessment of stroke or transient ischemic attack, but they also imply that female gender alone is sufficient to identify subgroups of patients that could be candidates for anticoagulation [18,21].

Further, and in contrast to the previous studies, we found heart failure to be the most common cardiovascular disease in any of the age categories among patients and controls and observed that the risk of heart failure versus controls did not differ between women and men. Given our large cohort compared to earlier, smaller studies and that the diagnosis of heart failure has a high positive predictive value in the registries, these findings seem reasonable. Presumably, patients without other in-hospital diagnoses at the time of inclusion have a risk of developing tachycardia-induced heart failure during follow-up. Regarding myocardial infarction, we observed an increased risk in both sexes overall but, as concerns the different age categories, an association was seen only in women older than 65 years and in men between 65 and 74 years of age. This is similar to previous findings

where only one study, in which patients had a mean age of 74 years at inclusion, showed an increased risk of myocardial infarction (Table 1). In patients with AF in our study, the incidence rate of myocardial infarction was higher in men than in women, in line with findings in patients without atrial fibrillation [34,35]. For all-cause mortality, the relative risk was statistically significant overall in women and men. However, the relative risk in the various age categories was only increased in women older than 65 years and in men between 65 and 74 years of age. The increased all-cause mortality could reflect the increased risks we found for stroke and heart failure and needs more investigation.

We chose to include patients up to the age of 85 years and analyze data in four different age groups. Exclusion and inclusion criteria in earlier studies varied, and the rates of lone or idiopathic AF were between 1.6% and 30%, while the incidence of idiopathic AF was as high as 67% in the Paris Protective Study [4–6,8,36,37]. In our previously described study cohort of 272,186 patients with AF, from which the cohort of this study was derived, 5% had no other in-hospital diagnoses during at least the eight years prior to inclusion and one year after inclusion [2].

In our nationwide study population of patients hospitalized with incident AF, the patients in the 55 to 64 years segment amounted to 2657 individuals, which are 27.9% of the studied cases without other diseases or 1.0% of the original cohort. Considering that AF can most often be managed without hospitalization, we assume that the risk ratios in this study are an underestimation of potential new candidates for

anticoagulation and that a substantial number of patients were not hospitalized or not even detected owing to asymptomatic AF.

4.1. Limitations

The number of confounding factors was greatly reduced by exclusion of all in-hospital diagnoses except AF in patients and controls, but subjects who are exclusively managed in outpatient care are not registered in Swedish hospital registries. Especially the diagnosis of hypertension is suspected to be underestimated since many patients are only diagnosed and treated in primary care. This possible misclassification could also apply to controls. Most likely, we also underestimated the true national number of AF diagnoses in both patients and controls.

We have no access to echocardiography examinations due to our study design that uses the Swedish National Patient Registry. Most previous studies have not used echocardiography, however, and because that examination is part of the routine hospital work-up in Sweden, the majority of patients in our study were most likely examined, thus considerably reducing the risk of concomitant heart failure [4–8,11,12]. We have no data on medication records during the study period between 1995 and 2009. A number of patients may have been on anticoagulation medication despite a formal guideline recommendation, but our database does not provide information on this. Further, the use of antiarrhythmic drugs and the possible impact they may have is unknown to us. Other potential confounders such as smoking, educational level and socioeconomic status may have affected the relative risk for outcomes between patients and controls.

The various types of AF, i.e. paroxysmal, persistent or permanent, might have influenced the results, but the registry data did not allow for this differentiation. On the other hand, since the registry allowed us to identify incident AF, it is likely that a substantial proportion of patients were found in an early phase and that some of them progressed to persistent and permanent types during the 14 years of follow-up. In addition, we decided to include atrial flutter, since it often coexists in patients with AF and the differential diagnosis can be challenging.

5. Conclusions

The relative risk of a stroke or a transient ischemic attack and heart failure was significantly higher in patients with AF irrespective of age and sex. The association of AF with myocardial infarction and all-cause mortality was weaker. Women were at higher risk of stroke or transient ischemic attack than men. While agreeing with current guidelines on anticoagulant treatment in patients 65 years and older, our study results pointed out that the annual rate of stroke and transient ischemic attack in men and women between 55 and 64 years was 1.0% and 1.1% and in controls 0.4% and 0.3%, respectively. Our findings might justify prevention measures if new oral anticoagulant agents are found to have the same efficacy and sufficient safety at these ages.

Conflict of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: KMH is an employee of AstraZeneca and has an academic affiliation with Uppsala University. TA, AM, ILB, OF, NE and DP have nothing to declare. None of the supporting institutions were involved in the study concept, analysis or drafting of the manuscript. The lead author, TA, affirms that this manuscript is an honest, accurate and transparent account of the study reported, that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

Acknowledgments

Contributors: TA and DP had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis. TA wrote the first manuscript draft. AM and ILB participated in the statistical analysis. AM, ILB, OF, KMH, NE and DP participated in drafting the manuscript. Acquisition of data, study concept and design, analysis and interpretation of data: TA, AM, ILB, OF, KMH, NE and DP.

Funding: The study was supported by a grant from AstraZeneca R&D Mölndal, the Örebro Heart Foundation and the Research Committee of Örebro University Hospital (OLL 2012-265231).

Ethical approval: The study was approved by the ethics committee of the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2009/273).

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