Trends in mortality after first hospitalization with Atrial Fibrillation diagnosis in Sweden 1987 to 2006

Olsson LG[1, 2], Swedberg K[2], Lappas G[2], Stewart S[3], Rosengren A[2].

[1] Department of Medicine, Mora Hospital, Mora, Sweden

[2] Department of Molecular and Clinical Medicine, Sahlgrenska Academy

University of Gothenburg, Sweden

[3] Baker IDI Heart and Diabetes Institute, Melbourne, Australia

Corresponding author: Lars G Olsson

Address for correspondence: Department of Medicine, Sahlgrenska University Hospital/Östra, SE-416 85 Göteborg, Sweden. Telephone +46/31/3434086. E-mail: larsgustavo@hotmail.com

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Conflicts of interest

None to declare.

Keywords: Atrial fibrillation * Mortality * Epidemiology

Abstract:

Background: To examine trends in 3-year mortality after a first hospitalization for atrial fibrillation in a large cohort with and without important cardiovascular comorbidities.

Methods: The Swedish Hospital Discharge and Cause of Death Registries were linked to investigate trends in mortality for all patients 35 to 84 years hospitalized for the first time with a discharge diagnosis (principal or contributory) of atrial fibrillation in Sweden during 1987 to 2004. We performed an analysis of temporal trends in mortality stratified for presence or absence of co-morbidities affecting survival.

Results: Exactly 376000 patients (56 % male, mean age 72 years) with a first diagnosis of atrial fibrillation during 1987-2006 were identified and followed for 3 years. Patients with one or more of the prespecified comorbidities had the highest mortality and the largest absolute decline in mortality, but patients without these comorbidities had a slightly larger relative decline (absolute risk reduction in 3-year mortality (AAR) from 42.5 to 34.7%, Hazard Ratio (HR) 0.76; 95% confidence interval (95% CI) 0.74 to 0.77 versus ARR 16.2% to 11.7%, HR 0.71; 0.68 to 0.74. In patients below 65, with no comorbidities, there were no or small decreases in mortality, and they still had a 2 times increased mortality compared to the general population (SMR 2.00; 1.90 - 2.10).

Conclusions: Survival after a first hospitalization with an atrial fibrillation diagnosis improved regardless whether important comorbidities were present or absent. Patients < 65 years old without diagnosed comorbidities still had a poor prognosis compared to the general population.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia. Recent studies have shown an increased incidence and prevalence in western Europe and the US(1-5), and the prevalence is expected to rise in the foreseeable future. Atrial fibrillation is associated with an increased risk of premature mortality. Despite an increased number of deaths associated with incident and prevalent atrial fibrillation the case-fatality has decreased during the 80s and 90s in Europe(1, 6), but not in the US(7, 8). Atrial fibrillation is associated with comorbidities such as ischemic heart disease(9), chronic heart failure(10) and stroke(11, 12). All these conditions adversely affects prognosis and have shown a general, albeit not uniform decline in mortality during the last 30 years(13-17). Earlier studies have performed analyses adjusted for comorbidities and/or mortality rates in the general population or within the study cohort, but this approach gives little information regarding risks in different age groups and with different sets of comorbidities.

Objectives:

We examined the risk for all-cause mortality up to three years after a first atrial fibrillation diagnosis, with respect to trends over time and further, to which extent age, gender and co-morbidities were associated with prognosis. We utilized the Swedish hospital discharge registry together with cause-specific Death register.

Design:

Setting:

Sweden has a universal health care system that provides health care (including hospital care) to the Swedish population (population ranging from 8.4 to 9.0 million people during the period 1987 to 2006). Registration of principal and contributory discharge diagnoses for all patients is mandatory in the hospital discharge register. Diagnosis at discharge is coded with the International Classification of Diseases (ICD) system (ICD 8th revision until 1986, ICD 9th revision until 1996, ICD 10th revision thereafter). Each patient is given a principal diagnosis and up to five secondary

diagnoses. For the purpose of the present study, data from the national hospital discharge and cause-specific death registers were linked through the personal identification number (PIN), which is unique for all Swedish citizens. The hospital discharge register has been in existence since the 1960s and operating on a nationwide basis, with near-complete coverage, since 1987.

Subjects:

We identified all first hospital admissions with a principal or secondary discharge diagnosis of atrial fibrillation in men and women aged 35 to 84 years during the period 1987 to 2006. The discharge codes applied were 427.93 (ICD-8) (only used for exclusion of patients with AF before 1987), 427D (ICD-9), and I48 (ICD 10). To ascertain freedom from earlier hospitalizations and to ensure that patients from all years had the same chance to be identified as a new case we censored for hospitalizations with an atrial fibrillation diagnosis up to seven years before the index hospitalization. Significant co-morbidities during the preceding 7 years and including the index hospitalization were recorded. Patients who died during index hospitalization were excluded. Complete follow-up data were available from 1st January 1987 through 31st December 2007. Only patients with the possibility to experience 3-year survival within the observation period were included in the survival analysis.

Validity of the registers

In the period from 1987 to 1996, a primary discharge diagnosis was lacking in 0.8% of all admissions to Swedish departments of internal medicine (including admissions for cardiovascular reasons)(18). Register-based data diagnoses for heart failure and acute myocardial infarction in Sweden according to the hospital discharge register have been shown to have good validity (19, 20). In a random sample of 100 randomly selected patients with a hospital diagnosis of AF enrolled in the Malmö Diet and Cancer Study, 95 were verified by ECG while 2 probably had AF (ECG missing) yielding a 97% positive predictive value (21).

Statistical analysis

All analyses were carried out using the Statistical Analysis System (SAS), version 9.2, and the R statistical computing system, version 2.10.0. Means and proportions for continuous and categorical variables were calculated. We performed a co-variable adjusted analysis with all (relevant) comorbidities, age, gender and time periods (1987-1991; 1992-1996; 1997-2001 and 2002-2004) in order to extract comorbidities associated with an increased mortality. The independent association of each period of AF admission, age, gender and comorbidity with death was quantified as hazard ratios estimated through Cox regression.

We examined sex- and age-specified all-cause mortality from day 1 up to 1095 days (3 years) after hospital admission by time period and presence or absence of significant co-morbidities. We stratified by age with 65 years as the cut-off point because we wished to characterize a relatively young population (the conventional retirement age in Sweden is 65) while at the same time retaining reasonable statistical power. Also, several stroke prediction scores uses 65 years as an age cutoff-point (22,23). Cumulative incidence functions for death are presented graphically for each period. Mortality rates from the Swedish population were applied to the patient's evaluated person-years of exposed to risk to estimate the expected number of deaths and presented in a standardized mortality ratio (SMR).

The discharge codes used to define ischemic heart disease were 410-414 (ICD-8 and ICD-9), I20-I25 (ICD-10), chronic heart failure 427.00 (ICD-8), 428A, 428B, 428X (ICD-9) and I50 (ICD-10), stroke 430-434, 436 (ICD8 and ICD9) and I60-I64 (ICD10) for both ischemic and hemorrhagic strokes. Other co-morbidities were defined by the following discharge codes prior to and including the index hospitalization: diabetes: 250 (ICD-8 and ICD-9), E10, E11, E14(ICD-10); hypertension: 401-405 (ICD-8 and 9), I10–I15 (ICD-10); valvular disease: 394–396, 424 (ICD-8 and 9), I05–I09, I34–I35 (ICD-10); hyperthyreosis: 242 (ICD-8 and ICD-9), E05 (ICD10); chronic obstructive pulmonary disease 490-492 (ICD8 and ICD-9)J40-44 (ICD-10), asthma 493 (ICD-8 and ICD-9), J45 (ICD-10) and chronic kidney disease 585-586 (ICD-8 and ICD-9), N18 and N19 (ICD10)

Results

Baseline variables

The baseline variables are presented in **table 1**. Exactly 376000 patients were discharged with a first diagnosis of atrial fibrillation between 1987 and 2006, 56% were men. Women were older than men (74.4 vs 70.4 years). Chronic heart failure and ischemic heart disease were the most common comorbidities, present in 27.9 and 27.8% of the patients, respectively. Overall, 14.6 % had a previous stroke diagnosis and 12.3 % diabetes mellitus. Women more often had previous stroke, diagnosed hypertension and hyperthyroidism, while men more often had ischemic heart disease. Chronic heart failure, diabetes, cancer, pulmonary disease (chronic obstructive pulmonary disease and asthma) and chronic kidney disease were present to a similar degree in males and females.

Predictors of mortality in multivariable analysis

In the 328907 patients included up until 31st December 2004, a total of 90835 patients (27.6%) died. **Table 2** shows the results of the co-variable-adjusted analysis of 3-year mortality. Chronic heart failure, previous stroke, diabetes mellitus, ischemic heart disease, cancer, pulmonary disease, chronic kidney disease and valvular disease were all independent predictors of all-cause mortality and all subsequent analyses were stratified according to the presence or absence of any of these co-morbidities. Patients hospitalized during periods after 1987-91 had successively reduced mortality, with 3-year mortality for those hospitalized in 2002-04 30% lower than those hospitalized in the first period.

Survival trends

Figure 1 shows time trends in mortality. There was a decline in mortality during the observation period, regardless of patient category. The decline was more pronounced in the first three periods and slowed down between period 3 and 4. Patients with one or more of the prespecified co-morbidities had the highest mortality and the largest absolute decline in mortality, however patients without any of the pre-specified co-morbidities had a larger relative decline in mortality during the observation period (absolute risk reduction in 3-year mortality (AAR) from 42.5 to 34.7%, hazard ratio (HR)

0.76; 95% confidence interval (95% CI) 0.74 to 0.77 versus ARR 16.2% to 11.7%, HR 0.71; 0.68 to 0.74 (**fig 1**). Patients with prespecified comorbidities had an early steep increase in mortality. Patients without prespecified comorbidities had smaller early increase in mortality and more evenly distributed events.

Age and sex-specific survival trends

Table 3 and 4 demonstrates survival trends by age, sex and comorbidity. Older patients with comorbidities experienced declines in mortality, regardless of gender (HR 0.74; 0.73 – 0.76 and HR 0.79; 0.77 – 0.82, respectively). Men 35-64 years old had a 34% reduction in 3-year mortality rates after hospital discharge (HR 0.66; 0.61 – 0.72) while young women had virtually unchanged mortality rate. The initially higher mortality rates among younger men with comorbidities became more similar to the death rates in young women during 2002-04 while women retained their survival advantage in the older patients. In patients without any of the pre-specified comorbidities older men and women experienced significantly decreased mortality rates (HR 0.68; 0.64 - 0.73 and HR 0.73; 0.69 – 0.78, respectively). Among patients 35-64 year old men showed a small decline in mortality with a slightly larger one for women (HR 0.82; 0.70 - 0.96 and HR 0.51; 0.37 – 0.70, respectively). The death rates in the younger patients were however very low, thus an increased risk of chance variation.

Comparison with underlying population mortality rate

Atrial fibrillation was associated with increased risk of mortality, when compared to the underlying population mortality rate (**table 5**). Because comparisons over time are subject to variation due to population trends in mortality and therefore less meaningful to report we here present the average standardised mortality ratios (SMR´s) for the entire period.

Young patients with comorbidities had an almost 9-fold increased mortality compared to the general population (SMR 8.86; 8.64 – 9.09). However, despite the much lower absolute mortality in young AF patients without comorbidities, they still had a 2 times increased mortality compared to the general population (2.00; 1.90 – 2.10). Patients 65-84 years old with comorbidities had a 3-fold increased risk of mortality (3.36; 3.34 – 3.38), and those without comorbidities a 36% increased risk (1.36; 1.34 – 1.39).

Discussion:

In this large cohort of patients discharged from hospital with a first AF diagnosis during an 18-year period we found an overall decline in 3-year mortality rates, regardless of diagnosed comorbidities. This was most evident in older patients overall and young male patients with any of the pre-specified comorbidities. Young women showed, regardless of comorbidity, no decline in mortality rates. Regardless of presence or absence of prespecified comorbidities, patients with an AF diagnosis had an adverse prognosis compared with the general population. This was especially evident in the younger patients.

Earlier studies on trends in mortality after "first ever" atrial fibrillation with observation periods during the 80s and the 90s have showed divergent results. Two European analyses from the Danish and Scottish hospital discharge registries have shown declines in mortality over 8 and 20-year observation periods, respectively (1, 6). Two American studies, one from Olmsted county and one from the Medicare 5% cohort showed virtually unchanged mortality rates during 15 and 20-year follow-up, with or without adjustments for mortality rates in the general study population(7, 8). There might be several reasons for these differences. Both American studies included more women than the European studies. As opposed to the present analysis several of the studies had higher overall mortality for women, and both the European studies had, as we had, smaller declines in mortality over time in women than in men. The Medicare 5% sample study included older patients that were more ill than ours and the other European studies. Olmsted County study comprised of a relatively small and heterogeneous sample and may thus have a lack of statistical power compared with the other studies.

The main differences between our study and the earlier hospital registry studies are the later observation period in our study and the fact that we stratified for age and comorbidity. This approach allowed us to make some important observations. First, the poor prognosis associated with atrial fibrillation persists even in the absence of important comorbidities, especially in younger patients. Secondly, both patients with and without co-morbidities saw highly significant declines in mortality. The trends in

the two groups were similar, but with very different patient populations the reason for the changes may differ. In general, treatment for patients with AF has improved during the last 30 years with more patients receiving oral anticoagulants and a transition from rhythm-regulating to rate-regulating drugs, a trend started in the early 90s (34). Moreover, many of the important comorbidities have shown prognostic improvements during this time-period (15, 16, 17, 22). Thus, the decline in mortality seen in patients with comorbidities is probably a due to a combination of these two trends. The reasons for the marked declines in elderly patients without any of the pre-specified comorbidities are less clear. While the use of oral anticoagulants probably also have increased in this group of patients, there may be improvements in diagnosis and treatment of comorbidities not fully reflected in the present analysis. Hypertension is the most important treatable cardiovascular risk factor and an important risk factor for ischemic heart disease, stroke (29), and chronic heart failure (30-31), especially in conjunction with atrial fibrillation. While the prevalence of hypertension were equally low in the other hospital registries (1, 5), the prevalence ranged between 70 and 84% in the analysis from Olmsted County and 50% in the Stockholm Cohort of Atrial Fibrillation (SCAF) study (7, 28), so hypertension is most likely underreported in this cohort and its prognostic importance may be underestimated. Thirdly, as already mentioned, as opposed to both the American (8), the Danish (1) and the Scottish studies (5, 6), women in the present study had lower overall mortality rates, but smaller improvements in prognosis in general than men. This was most notable in younger women with any of the prespecified comorbidities. The reasons for this are unclear. This could be influenced by the mortality trends seen in patients with myocardial infarction, angina pectoris or a chronic heart failure diagnosis(15, 16, 22), or, probably less important, in patients with stroke after AF diagnosis, all diagnoses where women had smaller mortality reductions over time than did men (17). Women with heart failure more often have preserved systolic function, a syndrome with lower mortality overall but equal risk in the acute setting and with poorer treatment results (10, 23).

In younger patients without important comorbidities, males and females had similar mortality rates with no clinically important changes in risk over time. The high risk compared with age and sex-matched population is probably be due to the nature of this data, an unselected hospital cohort where we could stratify by the presence or absence

of diagnosed disorders with major impact on survival, but were unable to define a subpopulation with "true" lone AF. Despite a low probability for ischemic stroke in terms of diagnosed risk factors in this age group the patients may still be at risk and AF-related strokes are particularly malignant in the young. A growing body of evidence suggests that a more widespread use of oral anticoagulants may be beneficial, even in patients with risk levels for stroke earlier considered as low (32).

The prevalence of diagnosed valvular heart disease and chronic renal disease were also remarkably low compared with more well defined cohorts. As is the case with hypertension, both conditions are probably present but not accounted for in many patients with other diagnoses such as chronic heart failure and nephropatic diabetes mellitus.

In both groups the decline in mortality slowed down during the last two time periods. There are several possible reasons for this. First, this may in part mirror the trends seen in important comorbidities, such as chronic heart failure (16). Second, as mentioned before, the paradigm shift that transformed atrial fibrillation treatment began in the early 90s (34). The initial decline and the ensuing more modest change in mortality may be due to an initially increased utilization of oral anticoagulants that successively levelled off. Indeed, the use of oral anticoagulants has increased, but several studies still indicates under-utilization (32).

Limitations

The main strength of this analysis is the completeness of the data, with a nationwide unselected cohort of patients, and a large number of events that allowed detailed analyses by diagnosis, time period, gender and age group. Even so, these data were collected for administrative rather than research purposes and our diagnoses were not formally validated other than in small samples performed by another centres (18-21). However, given the high positive predicted value produced by the aforementioned study and two others from Denmark (99% positive predictive value in 174 patients and 92.6% positive predictive value for the AF or AFL diagnosis in 278 patients) (17, 33) we feel confident that only a minority of the patients in our study are misdiagnosed. As already mentioned, there is a probable underreporting of several important co-morbidities, most notably hypertension but also valvular heart disease and chronic renal disease and

no information is given about any disease severity. The true prognostic impact of co-morbidities in this context is therefore uncertain. Many patients with atrial fibrillation are diagnosed and treated entirely in primary care and most hospitals in Sweden perform acute or elective cardioversions on an outpatient basis only. The patients included in our analyses are thus most probably sicker than the total patient population with atrial fibrillation.

Changes in coding practices during the study may have occurred, due to an increased interest in atrial fibrillation and its risk factors or economic incentives, which may affect our results. Also, we did not have access to information on medical therapy in these patients. As already mentioned, atrial fibrillation-specific treatment has changed during the last 30 years with a marked reduction of the use of class I rhythm-regulating drugs and the increased use of OAC, together with treatment of associated conditions, the impact of these changes is unknown to us (34).

Conclusion

This analysis shows a decline in mortality rates in patients discharged from hospital with a first atrial fibrillation diagnosis. The declines may be both due to changes in important comorbidities and due to atrial fibrillation-specific factors. However, atrial fibrillation is associated with a high risk of premature mortality, especially in younger patients compared with the general population. Young women had no improvement in prognosis over the observation period. More effort must be put into identifying adverse prognostic factors in order to reduce the high mortality rates in patients with atrial fibrillation, with or without associated comorbidities.

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Figure legends:

Figure 1. Temporal trends in mortality up to three years after hospital discharge with "first-ever" atrial fibrillation diagnosis

Solid lines: **Patients without the prespecified comorbidities.**

Dashed lines: **Patients with the prespecified comorbidities**

Table 1. Baseline characteristics for patients with a first hospital diagnosis of atrial fibrillation in Sweden 1987 to 2004

	Men	*Women*	*All*
Number of patients	210696	165304	376000
Mean age (SD)	70.4 (10.3)	74.4 (8.3)	72.1 (9.7)
Medical history (including index admission)			
Previous stroke n (%)[1]	29199 (13.9)	25523 (15.4)	54722 (14.6)
Chronic Heart Failure n (%)	46395 (28.1)	58539 (27.8)	104934 (27.9)
Ischemic Heart Disease n (%)	64000 (30.4)	40604 (24.6)	104604 (27.8)
Diabetes mellitus n (%)	26013 (12,3)	20418 (12,4)	46431 (12,3)
Valvular disease n (%)	13677(6.5)	11755(7.1)	25432(6.8)
Hypertension n (%)	41939 (19.9)	38138 (23.1)	80077 (21.3)
Chronic Kidney Disease n (%)	2487 (1.2)	1423 (0.9)	3910 (1.0)
Hyperthyroidism n (%)	897 (0.4)	2695 (1.6)	3592 (1.0)
Pulmonary disease n (%)[2]	14507 (6.9)	11166(6.8)	25673 (6.8)
Cancer n (%)	25554 (12.1)	20297 (12.3)	45851 (12.2)

1. Includes stroke at hospital admission

2. Includes asthma and chronic obstructive pulmonary disease

Table 2. Multivariable analysis of risk for 3-year mortality in 328907 patients with a first hospital diagnosis of atrial fibrillation in Sweden 1987 to 2004.

Variables	*Hazard Ratio*	*95% Confidence Interval*
1987-1991	1 (reference)	
1992-1996	0.83	0.82 - 0.85
1997-2001	0.72	0.71 - 0.74
2002-2004	0.68	0.67 - 0.69
Female sex	0.80	0.79 - 0.81
Age at discharge (per decade increase)	1.89	1.88 - 1.91
Cancer	2.07	2.04 - 2.10
Chronic heart failure	1.72	1.70 - 1.74
Previous stroke	1.66	1.64 - 1.69
Diabetes mellitus	1.48	1.45 - 1.50
Chronic kidney disease	2.49	2.39 - 2.58
Pulmonary disease[2]	1.50	1.47 - 1.53
Ischemic heart disease	1.16	1.14 - 1.17
Valvular heart disease	1.10	1.07 - 1.12
Hypertension	0.94	0.93 - 0.96
Hyperthyroidism[1]	0.91	0.85 - 0.97
All p-values <0.0001 except 1. p=0.0044 2. Includes Asthma and Chronic Obstructive Pulmonary Disease		

Table 3. Temporal trends in mortality up to three years after first hospitalisation with a first atrial fibrillation diagnosis. Patients with prespecified diagnoses

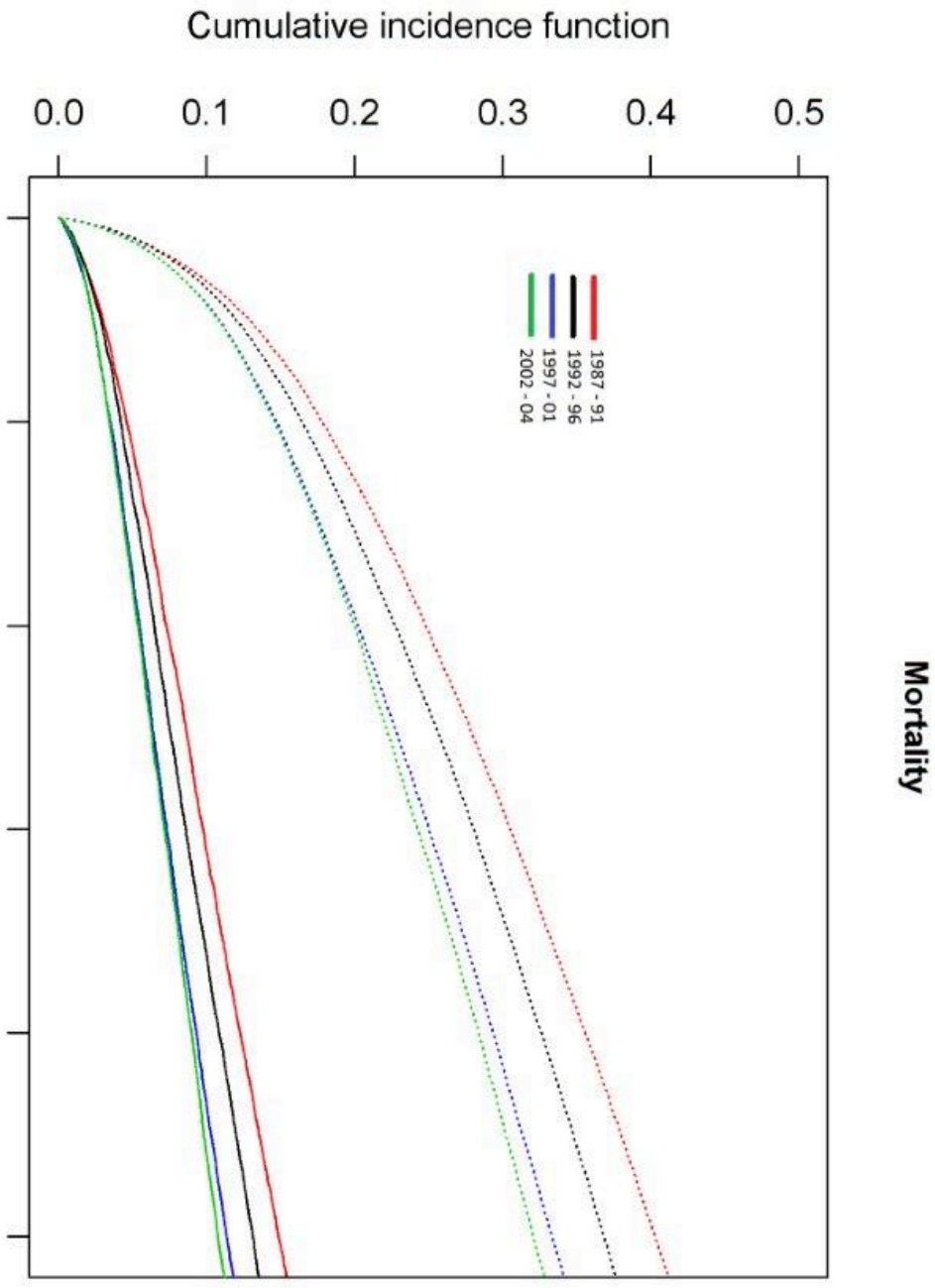
	n deaths	*Mortality rate/1000*	*Hazard Ratio*	*95% CI*	*p-value*	*n deaths*	*Mortality rate/1000*	*Hazard Ratio*	*95% CI*	*p-value*
35-64		**Males**					**Females**			
1987-1991	1000	94.3	1			277	67.5	1		
1992-1996	1050	75.1	0.80	0.74-0.88	<.0001	417	74.9	1.10	0.95 - 1.29	0.20
1997-2001	1052	65.0	0.70	0.64-0.76	<.0001	401	65.8	0.97	0.84 - 1.14	0.74
2002-2004	475	60.4	0.66	0.61-0.72	<.0001	169	61.2	0.91	0.78 - 1.05	0.20
65-84										
1987-1991	9954	232.3	1			8171	197.4	1		
1992-1996	13071	201.2	0.88	0.85-0.90	<.0001	10379	175.7	0.90	0.87-0.92	<.0001
1997-2001	11962	177.9	0.78	0.76-0.80	<.0001	9304	155.9	0.80	0.78-0.83	<.0001
2002-2004	5046	172.8	0.74	0.73-0.76	<.0001	3872	154.7	0.79	0.77-0.82	<.0001

Table 4. Temporal trends in mortality up to three years after first hospitalisation with a first atrial fibrillation diagnosis. Patients with no prespecified diagnoses

	n deaths	*Mortality rate/1000*	*Hazard Ratio*	*95% CI*	*p-value*	*n deaths*	*Mortality rate/1000*	*Hazard Ratio*	*95% CI*	*p-value*
35-64		**Males**					**Females**			
1987-1991	261	16.6	1			80	13.6	1		
1992-1996	288	15.2	0.92	0.78-1.09	0.32	69	9.3	0.68	0.49-0.94	0.02
1997-2001	294	12.3	0.74	0.63-0.87	0.0004	101	11.2	0.82	0.61-1.10	0.19
2002-2004	130	12.0	0.82	0.70-0.96	0.014	30	7.4	0.51	0.37-0.70	<.0001
65-84										
1987-1991	1742	91.9	1			1676	74.1	1		
1992-1996	1986	76.0	0.83	0.78-0.88	<.0001	1872	62.7	0.85	0.79 - 0.90	<.0001
1997-2001	2113	67.3	0.74	0.69-0.78	<.0001	1915	55.2	0.75	0.70 - 0.80	<.0001
2002-2004	876	63.4	0.68	0.64-0.73	<.0001	802	54.3	0.73	0.69 - 0.78	<.0001

Table 5. Standardised mortality ratios in patients hospitalized with AF in 1987-2004 by age group and presence or absence of comorbidities

Age group	***With comorbidities***			***Without comorbidities***		
	Observed deaths	*Expected deaths*	*SMR; 95% CI*	*Observed deaths*	*Expected deaths*	*SMR; 95% CI*
35-64	5902	666.1	8.86; 8.64 – 9.09	1546	771.7	2.00; 1.90 – 2.10
65-84	85149	25326.9	3.36; 3.34 – 3.84	15485	11373.1	1.36; 1.34 – 1.39


Cumulative incidence function
0.0
0.1
0.2
0.3
0.4
0.5
1987 - 91
1992 - 96
1997 - 01
2002 - 04
Mortality