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Trends in stroke incidence after hospitalization for atrial fibrillation in Sweden 1987 to 2006

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Background: To investigate recent trends in incidence of hemorrhagic and non-hemorrhagic strokes in patients with atrial fibrillation (AF).

Methods: The Swedish Hospital Discharge and Cause of Death Registries were linked to provide outcome data.

Results: 321,276 patients 35 to 84 years (56.5% male, mean age 71.5 years) free of prior stroke with a first AF diagnosis during 1987-2006 were included. Over 3 year follow-up 24,733 patients (7.7 %) were diagnosed with ischemic stroke and 2,292 (0.7 %) with hemorrhagic stroke. The 3-year incidence of ischemic stroke decreased from 8.7% for patients diagnosed in 1987-1991 to 6.6% for those diagnosed in 2002 to 2006. The corresponding incidence of hemorrhagic stroke increased from 0.38% for patients diagnosed in 1987-1991 to 0.57% for those diagnosed in 2002 to 2006. Covariable-adjusted risk of ischemic stroke was significantly reduced (HR 0.65; 0.63-0.68) while risk of hemorrhagic stroke was significantly increased (HR 1.19; 1.05-1.36). Compared to the general population, total stroke risk decreased more among AF patients.

Conclusion We found a considerable decrease in risk of ischemic stroke in Sweden in patients without prior stroke and with a first hospital diagnosis of AF. There was an increased risk of hemorrhagic stroke, but because hemorrhagic stroke represented only a small proportion of all strokes, the overall risk of stroke declined.

Keywords: Atrial fibrillation * Acute stroke * Epidemiology * Prevention

Introduction

Patients with atrial fibrillation (AF) have an increased risk of stroke. Up to 25% of all patients with acute stroke have AF on their admission ECG. Moreover, AF-related strokes tend to be more severe with more lasting disabilities and increased long and short-term mortality[1-4]. Cost-effective evidence-based strategies for stroke prevention in AF patients, such as monitored anticoagulation therapy, have been available for several decades[5], but under-utilization persists[6-9]. Given that several epidemiological studies show that the incidence and prevalence of AF have increased and will continue to increase in the foreseeable future the temporal trends of stroke in these patients is of particular interest[10, 11]. Analyses from North American studies show considerable declines in stroke incidence over time in AF patients[12, 13]. Equivalent results from European studies are more ambiguous[14, 15]. However, because the overall population incidence of stroke varies considerably over time, the AF specific component for the observed change against a background of a potential broader change in stroke incidence in the population is uncertain. Also, the temporal trends on incidence of hemorrhagic strokes in this patient category have not been widely studied[13, 15].

We wanted to examine trends in the incidence of ischemic and hemorrhagic stroke up to three years after an index admission for AF at the whole population level, during the period 1987 – 2006, by linking the Swedish hospital discharge registry to the national Swedish death registry. We then compared AF-specific trends over this 20-year period with those observed within the general population.

Methods

Patient population:

Sweden has a universal health care system that provides low-cost health care (including hospital care) to the Swedish population (population ranging from 8.4 to 9.1 million people during the

period 1987 to 2006). Registration in the hospital discharge register is mandatory for all hospitalized patients. 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.

Index hospitalization for AF:

We identified all first hospital admissions with a principal or secondary discharge diagnosis of AF in men and women aged 35 to 84 years during the period 1987 to 2006. In order to ascertain freedom from earlier hospitalizations and to ensure that patients from all years had the same chance to be identified as new cases, we censored for hospitalizations with a diagnosis of AF up to seven years before the index hospitalization. Patients with prior ischemic or hemorrhagic stroke within seven years were excluded in the same manner. The reason for this was to minimize the risk for ambiguity on timing of first AF hospital diagnosis and to minimize the inclusion of recurrent strokes, a common problem. The specific diagnose codes used to identify incident atrial fibrillation cases were: 427.92 (ICD-8) (only used for exclusion of patients with AF before 1987), 427D (ICD-9), and I48 (ICD-10). The discharge codes used to identify stroke cases were: Ischemic stroke: (432-434 (ICD-8 and ICD-9) and I63, I64 (ICD-10) and hemorrhagic stroke (430, 431 (ICD-8 and ICD-9), I60–I62 (ICD-10). The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology[16]

Comorbidity

Significant comorbidities during the preceding 7 years and index hospitalization were recorded. The specific discharge codes used were: Ischemic heart disease: 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); 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: 393–398, 424 (ICD-8 and ICD-9), I05–I09, I34–I35 (ICD-10); Hyperthyroidism: 242 (ICD-8 and ICD-9), E05 (ICD-10); Cancer: 140-207 (ICD-8 and ICD-9), C00-C97 (ICD-10); Chronic obstructive pulmonary disease 490-492 (ICD8 and ICD-9), J40-44 (ICD-10); Asthma 493 (ICD-8 and ICD-9), J45 (ICD-10).

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Follow-up:

We examined age- and sex-specific incidence of fatal and non-fatal ischemic and hemorrhagic stroke (as classified above) from day 1 up to 1095 days (3 years) after the index hospitalization by 5-year periods (1987-1991, 1992-1996, 1997-2001 and 2002-2006). We attempted to identify predictors of occurrence of ischemic strokes amongst baseline variables and time period of AF occurrence. We also examined the age and gender-adjusted stroke occurrence in this cohort and compared it that of the whole Swedish population.

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)[17]. 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)[18]. In a validation study of all first-ever strokes in the city of Örebro February 1999-January 2000, 333/377 of the diagnoses in the hospital discharge and cause of death registries were identified in the community-based registry, giving a sensitivity of 88% and specificity of 92%[4]. In an earlier study based on the Swedish MONICA material 3492/3562 of stroke cases in patients 25-

74 years old 1985-1989 were identified by the hospital discharge registry, yielding a 98% sensitivity, due to a 32% rate of false positives there was a positive predictive value of 68,5%[19].

Statistical analysis

All analyses were carried out using the Statistical Analysis System (SAS), version 9.2, and the R statistical computing system, version 2.9.0. Means and proportions for continuous and categorical variables were calculated. Estimates of the cumulative incidence of ischemic stroke with death or hemorrhagic stroke as competing risk, within 3 years were calculated, and are presented for each period of AF hospitalization, gender and age group. The estimates for hemorrhagic stroke were calculated in a similar manner. Additionally, the cumulative incidence function for stroke with death as a competing risk is illustrated graphically for the whole population within a 3-year interval from admission, for each period of AF hospitalization, and for men and women separately. When comparing men and women, age adjustment was done implicitly through comparison of age-matched subsets. The hazard ratios between the first period, 1987-1991, and all other periods of AF admission for total, ischemic and hemorrhagic stroke were estimated through Cox regression independently of age, gender and co-morbidity. To estimate the excess risk, when compared with a normal population, of stroke after AF hospitalization we used the age and sex standardised morbidity ratio (SMR), as calculated from the number of people with a first-time stroke (within 7 years) for each age-, sex- and year-specific cell.

Results

Baseline

A total of 321,276 patients with a first hospitalization for AF and no recorded history of stroke within 7 years were discharged from Swedish hospitals 1987-2006. Patient characteristics at hospital discharge are summarized in **Table 1**. Overall, 56.5 % were male and mean age was 71.5

years. Men were on average 4 years younger than women. Slightly less than a third had concurrent ischemic heart disease, with more men than women affected. A similar proportion of men and women (28.2 and 28.9%, respectively) had chronic heart failure. Valvular disease was diagnosed in 7.1% of cases and hyperthyroidism in only 0.4% of cases.

Time trends in 3-year stroke incidence

Between 1987 and 2006, 24,733 (7.7%) of this cohort were diagnosed with a fatal or non-fatal ischemic stroke and 2292 (0.7%) with a fatal or non-fatal hemorrhagic stroke within 3 years from the index hospitalization. There was a 27% relative reduction in the 3 year total stroke incidence (hazard ratio (HR) 0.73; 95% confidence interval (CI) 0.71 to 0.76) between 1987-1991 and 2002-2006, corresponding to an absolute decline from 9.1 to 7.2%. This was mainly driven by a 29% relative decrease in ischemic stroke incidence (HR 0.71; 0.68 to 0.73), in absolute percentages from 8.7 to 6.6% (**figure 1**), while there was a 32% relative increase in 3-year hemorrhagic stroke incidence (HR 1.32; 1.13-1.56) corresponding to an absolute change from 0.38 to 0.57% (**figure 2**). Between 1987-1991 and 1992-1996 there was a non-significant increase in incidence of total stroke; reflecting an increase in both ischemic and hemorrhagic strokes. Total stroke and ischemic stroke then decreased, while hemorrhagic strokes rose markedly between 1997-2001 and 2002-2006. With the exception of hemorrhagic strokes during 2002-2006, incidence rose evenly during the 3-year follow-up. Women had a higher 3-year stroke incidence (10.5% during 1987-1991 versus 7.7% during 2002-2006 than did men (7.2% versus 4.2%). This translated to a 26% relative decrease (HR 0.74; 95% CI 0.70-0.78) among women and a 30% relative decrease (HR 0.70; 95% CI 0.66-0.74) among men. The higher incidence of stroke in women was due to a persistent higher 3-year incidence of ischemic strokes among women while 3-year incidence of hemorrhagic stroke was similar for men and women.

Age and sex-specific trends in stroke rate

Table 2 and **3** shows the age and sex specific trends in 3-year stroke rate during the 20 year observation period. There was a decrease in total strokes during the observation period, regardless of sex and age. Men generally had bigger decreases than women and younger women had non-significant decreases in ischemic stroke rate. As opposed to the other age- and gender-specified groups women aged 35-64 and 65-74 had non-significant increases in total and ischemic stroke rate between 1987-1991 and 1992-1996.

Hemorrhagic stroke was far less common than ischemic stroke, with a greater chance of random variation, also, any misclassification of stroke cases will have large impact in this group. By and large, the lowest risk was found during 1987-91 (**Figure 2**) but with no marked difference over the first 2 years of follow-up between the periods. However, starting in the second year there was a visible increase in risk for those with AF in the last period (2002 to 2006), corresponding to a calendar period of 2004 to 2008 for the hemorrhagic strokes, particularly among older men. The quantitatively largest increases were seen among women aged 35 to 64 years and for older men, with the highest number of diagnosed cases. Of note, older men had relatively few diagnosed cases during 1987-1991.

Comparison with underlying population stroke rate

As shown in **figure 3**, during 1987-1996, AF patients had a stroke rate about 3.5 times that of the general population which decreased slowly to around 2.6 during 2002-2006 around the year 2000, and remained steady thereafter.

Predictors of stroke

When adjusted for age, sex and baseline co-morbidities, there was a 32% decrease in total stroke incidence from the first to the last study period (HR 0.68; 0.66 – 0.71; $p<0.0001$), driven by a 35% reduction in ischemic strokes and counter-balanced by a 19% increase in number of hemorrhagic

strokes (**table 4**). Only 2002-2006 showed a significant increase of hemorrhagic strokes compared with 1987-1991. Female sex was associated with an 11% excess risk of total stroke and 14% excess risk of ischemic stroke, while male sex was associated with a 17% excess risk of hemorrhagic stroke. In contrast, ischemic heart disease and chronic heart failure were only weakly associated with risk of ischemic stroke in this population and not associated with increased risk of hemorrhagic stroke.

Discussion

This analysis shows that the risk of ischemic stroke after first hospitalization for AF in Sweden has decreased over 20 years. There was a marked increase in hemorrhagic stroke, mainly after 2004, and predominantly among older men. Even so, because hemorrhagic stroke represented only a small proportion of all strokes the net effect was a marked decrease in overall stroke risk among patients with AF. This trend is over and beyond that found in the general population.

Earlier studies on this topic have shown a decreased stroke incidence over time in most[12-14] but not all cases[15]. Moreover, there were small or no changes in the incidence of hemorrhagic strokes in the two studies where this was reported, regardless whether use of anticoagulants increased[13] or remained low[15]. Our data does not comprise information on anticoagulant treatment on individual or group-wise basis. Studies on the use of anticoagulant therapy suggest continued underutilization, with many factors other than established risk factors influencing prescription patterns[6-9]. However, European and American studies show an increased use of anticoagulants during the last two decades[8, 12, 13].

The reason for the increase in hemorrhagic stroke rate seen in our study is unclear, but it coincides with the introduction and validation of clinically useful stroke risk prediction schemes, most notably the $CHADS_2$ criteria[20], and landmark trials highlighting the importance of oral anticoagulation in patients with AF[21, 22]. Still, if we surmise that both the increase in hemorrhagic

stroke and the decrease in ischemic stroke were due to increased use of anticoagulants, the reduced risk of ischemic stroke vastly overrides the increase in risk of hemorrhagic stroke.

Data from Swedish Hospital Discharge Registry and other, smaller Swedish cohorts indicate an increased stroke incidence in the general population 1985-1998[23-25]. With the small changes seen in our cohort during this period, this resulted in a decline in AF-related stroke incidence relative to that of the general Swedish population, something reflected in the standardized morbidity ratio. More recent data indicates a decline in stroke incidence in the general population after the mid-90s, while AF-related stroke incidence declined even more. The overall incidence of hemorrhagic strokes is decreasing, in Sweden and other western countries, likely due to improved treatment for hypertension[26]. With the exception of the relative increase in hemorrhagic strokes in younger women, a finding of unclear significance, the increase seen in our study was confined to the oldest patients potentially reflecting an increased use of anti-coagulants in this group.

Of the potential predictors for stroke in AF that we investigated, chronic heart failure was comparatively weakly linked to future stroke, as seen in other analyses[14, 27]. The reported prevalence of diabetes and hypertension was low in our study in comparison with smaller, more well-defined epidemiological study cohorts[12, 26, 28], but similar to other hospital cohorts[10, 14]. The lower risk for ischemic stroke among patients with valvular disease probably reflects a higher chance of being treated with anticoagulants, particularly since they also had a higher chance of cerebral bleeding. The increased risk for stroke associated with female sex has been seen in some[14, 29], but not all analyses[12 27]. Differences in other baseline variables, comorbidities and medications not fully reflected in the information available to us may have influenced the results. Female sex is incorporated as a risk factor for stroke in the recently devised CHA_2DS_2-VASc score[30].

Limitations

The main strength of our study was the nationwide unselected cohort of patients, with a large number of events that allowed detailed analyses by diagnosis, time period, gender and age group. Even so, there are a number of limitations, mostly reflecting that these data were collected for administrative rather than research purposes, with an ensuing lack of detail. First, as already discussed, there were no data on treatment, particularly anti-coagulation therapy. Second, there is a probable underreporting of several important comorbidities, so the true prognostic impact of co-morbidities in this context is therefore uncertain. Third, an inherent feature with our long follow-up time is that the handling of patients will change together with is that the possibility and propensity to diagnose AF may have changed over time, many patients with AF are diagnosed and treated entirely in primary care and acute or elective cardioversions may be performed on an outpatient basis. The patients included in our analysis are thus most probably more sick than the average patient with AF. Fourth, that is, AF may be more actively sought for due to increased knowledge about the risks associated, and economic incentives to include diagnosis may also play a role. This may lead to milder cases with a lower risk for stroke being included towards the end of the observation period. Lastly, even though the routine use of CT scans in stroke from the early 80s in Sweden means that the distinction between hemorrhagic stroke and ischemic stroke will be reliable, there are no means through which we differentiate cardio-embolic strokes from those of atherosclerotic origin. However, the distinctly different temporal trends of stroke in this patient cohort compared with the general population makes it likely that AF plays an important role for the development of stroke among these patients and that the (possible) inclusion of milder cases are less important for the results seen here.

Conclusions

Patients with AF had a high but declining risk of stroke in Sweden during 1987-2006. This decline was above and beyond that seen in the general population, a trend most apparent in the first 15

years of the observation period. We observed an increasing risk of hemorrhagic stroke over the last years of the study period, an increase that by far was outweighed by the reduced risk of ischemic stroke.

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Conflicts of interest:

None.

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Figure legends

1. Secular trends of ischemic stroke incidence after first hospitalization for atrial fibrillation in Sweden 1987-2006.

2. Secular trends of hemorrhagic stroke incidence after first hospitalization for atrial fibrillation in Sweden 1987-2006.

3. Standardized morbidity ratio (SMR) all strokes in patients hospitalized with first AF diagnosis 1987-2006 in comparison with the general Swedish population.

Table 1: Baseline characteristics

		Men	***Women***	***Total***
Number of patients		181,496	139,780	321,276
Age at discharge	*Mean*	69.7±10.6	73.9±8.6	71.5±10.0
Ischemic heart disease	*n (%)*	54871 (30.2)	34360 (24.6)	89231 (27.8)
Chronic heart failure	*n (%)*	51216 (28.2)	40450 (28.9)	91666 (28.5)
Diabetes mellitus	*n (%)*	20664 (11.4)	16037 (11.5)	36701 (11.4)
Hypertension	*n (%)*	33073 (18.2)	29855 (21.4)	62928 (19.6)
Valvular heart disease	*n (%)*	12315 (6.8)	10445 (7.5)	22760 (7.1)
Cancer	*n (%)*	22116 (12.2)	17567 (12.6)	39683 (12.4)
Hyperthyreosis	*n (%)*	804 (0.4)	2360 (1.8)	3164 (1.0)
Pulmonary disease[*]	n (%)	12867 (7.1)	9939 (7.1)	22806 (7.1)

[*] *Includes asthma and chronic obstructive pulmonary disease*

Table 2: Age specified stroke-rate in women within three years after a first hospitalisation for atrial fibrillation

		All strokes					**Ischemic strokes**					**Hemorrhagic strokes**				
Age group	*Period*	*N EVENTS*	*STROKE CASES PER 1000*	*Hazard Ratio*	*95% CI*	*p-value*	*N EVENTS*	*STROKE CASES PER 1000*	*Hazard Ratio*	*95% CI*	*p-value*	*N EVENTS*	*STROKE CASES PER 1000*	*Hazard Ratio*	*95% CI*	*p-value*
35-64	**1987-1991**	132	14.2	1			122	13.2	1			10	1.1	1		
	1992-1996	204	16.9	1.20	0.96-1.49	0.10	189	15.6	1.20	0.96-1.51	0.11	15	1.2	1.16	0.52-2.58	0.72
	1997-2001	213	15..2	1.10	0.88-1.36	0.40	187	13.4	1.04	0.83-1.31	0.71	26	1.9	1.74	0.84-3.61	0.14
	2002-2006	203	13.5	0.95	0.76-1.19	0.67	173	11.5	0.86	0.68-1.08	0.20	30	2.0	2.26	1.10-4.62	0.026
65-74	**1987-1991**	730	34.5	1			674	31.9	1			56	2.6	1		
	1992-1996	1057	38.1	1.09	0.99-1.19	0.08	975	35.2	1.09	0.98-1.20	0.10	82	3.0	1.10	0.78-1.55	0.58
	1997-2001	888	32.4	0.92	0.84-1.02	0.12	813	29.6	0.92	0.83-1.02	0.10	75	2.7	1.01	0.71-1.42	0.97
	2002-2006	652	26.3	0.75	0.68-0.84	<.0001	577	23.3	0.71	0.64-0.80	<.0001	75	3.0	1.30	0.92-1.85	0.13
75-84	**1987-1991**	2021	64.6	1			1918	61.3	1			103	3.3	1		
	1992-1996	2790	62.0	0.96	0.91-1.02	0.15	2631	58.5	0.95	0.90-1.01	0.12	159	3.5	1.06	0.83-1.36	0.64
	1997-2001	2658	52.7	0.82	0.78-0.87	<.0001	2479	49.2	0.81	0.76-0.86	<.0001	179	3.6	1.06	0.83-1,35	0.66
	2002-2006	2399	47.5	0.72	0.68-0.76	<.0001	2216	43.8	0.69	0.65-0.74	<.0001	183	3.6	1.25	0.98-1.59	0.07

Table 3: Age-specified stroke rate in men within three years after a first hospitalisation for atrial fibrillation

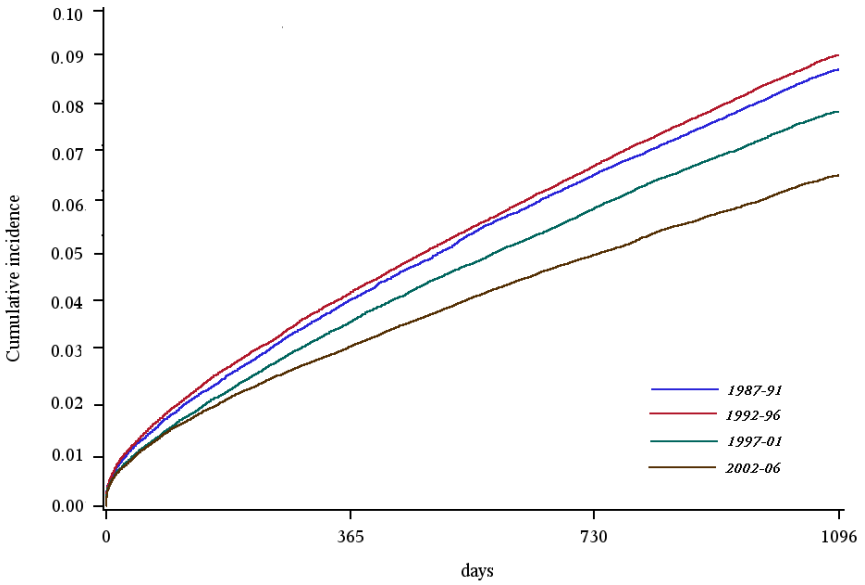
		All strokes					***Ischemic strokes***					***Hemorrhagic strokes***				
Age group	*Period*	*N EVENTS*	*STROKE CASES PER 1000*	*Hazard Ratio*	*95% CI*	*p-value*	*N EVENTS*	*STROKE CASES PER 1000*	*Hazard Ratio*	*95% CI*	*p-value*	*N EVENTS*	*STROKE CASES PER 1000*	*Hazard Ratio*	*95% CI*	*p-value*
35-64	**1987-1991**	349	14.2	1			302	12.2	1			47	1.9	1		
	1992-1996	409	13.4	0.95	0.83-1.10	0.52	351	11.5	0.95	0.81-1.11	0.52	58	1.9	1.00	0.68-1.46	0.98
	1997-2001	441	11.8	0.84	0.73-0.96	0.011	376	10.0	0.84	0.71-0.96	0.012	65	1.7	0.90	0.62-1.31	0.57
	2002-2006	420	10.5	0.73	0.63-0.84	<.0001	353	8.8	0.69	0.59-0.80	<.0001	67	1.7	1.03	0.71-1.49	0.88
65-74	**1987-1991**	961	35.3	1			869	31.9	1			92	3.4	1		
	1992-1996	1298	34.4	0.96	0.88-1.04	0.35	1170	31.0	0.96	0.88-1.05	0.34	128	3.4	0.98	0.75-1.29	0.91
	1997-2001	1123	29.2	0.82	0.75-0.89	<.0001	979	25.4	0.79	0.72-0.87	<.0001	144	3.7	1.07	0.83-1.39	0.60
	2002-2006	864	22.6	0.64	0.58-0.70	<.0001	744	19.5	0.60	0.54-0.66	<.0001	120	3.1	1.06	0.81-1.39	0.68
75-84	**1987-1991**	1286	54.1	1			1223	51.4	1	1.02-1.04		63	2.6	1		
	1992-1996	1999	54.2	1.00	0.94-1.08	0.89	1857	50.4	0.98	0.92-1.06	0.64	142	3.8	1.43	1.06-1.92	0.018
	1997-2001	2031	47.0	0.87	0.82-0.94	0.0002	1865	43.1	0.85	0.79-0.91	<.0001	166	3.8	1.39	1.04-1.85	0.027
	2002-2006	1897	40.8	0.75	0.70-0.80	<.0001	1690	36.3	0.69	0.64-0.74	<.0001	207	4.4	1.87	1.41-2.48	<.0001

Table 4. Independent predictors of stroke up to 3 years after first hospitalisation for atrial fibrillation

	Total stroke				Ischaemic stroke				Hemorrhagic stroke			
	Hazard Ratio	**95% Hazard Ratio Confidence Limits**		**p-value**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**p-value**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**		**p-value**
1987-1991	1	reference			1	Reference			1	reference		
1992-1996	0.98	0.95	1.02	0.32	0.98	0.94	1.01	0.19	1.08	0.94	1.22	0.28
1997-2001	0.84	0.81	0.87	<.0001	0.82	0.79	0.85	<.0001	1.05	0.93	1.20	0.42
2002-2006	0.68	0.66	0.71	<.0001	0.65	0.63	0.68	<.0001	1.19	1.05	1.36	0.0070
Age (per decade increase)	1.74	1.72	1.77	<.0001	1.79	1.76	1.82	<.0001	1.40	1.33	1.47	<.0001
Female versus male sex	1.11	1.09	1.14	<.0001	1.14	1.11	1.17	<.0001	0.83	0.77	0.91	<.0001
Diabetes Mellitus	1.45	1.40	1.50	<.0001	1.47	1.42	1.53	<.0001	1.20	1.06	1.36	0.0046
Hypertension	1.28	1.24	1.32	<.0001	1.25	1.22	1.29	<.0001	1.59	1.45	1.75	<.0001
Valvular Heart Disease	0.90	0.86	0.94	<.0001	0.86	0.82	0.91	<.0001	1.31	1.13	1.52	0.0003
Ischaemic Heart Disease	1.04	1.02	1.07	0.0016	1.06	1.04	1.09	<.0001	0.84	0.76	0.92	0.0004
Chronic Heart Failure	1.04	1.01	1.07	0.007	1.04	1.01	1.07	0.0121	1.04	0.95	1.14	0.43
Pulmonary Disease*	0.86	0.82	0.91	<.0001	0.86	0.81	0.90	<.0001	0.94	0.79	1.12	0.51
Hyperthyreosis	0.82	0.72	0.93	0.0024	0.79	0.69	0.91	0.0009	1.12	0.76	1.67	0.56
Cancer	0.97	0.93	1.00	0.068	0.95	0.92	0.99	0.022	1.10	0.97	1.25	0.15

*Includes Chronic Obstructive Pulmonary Disease and Asthma

Figure 1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0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
Cumulative incidence
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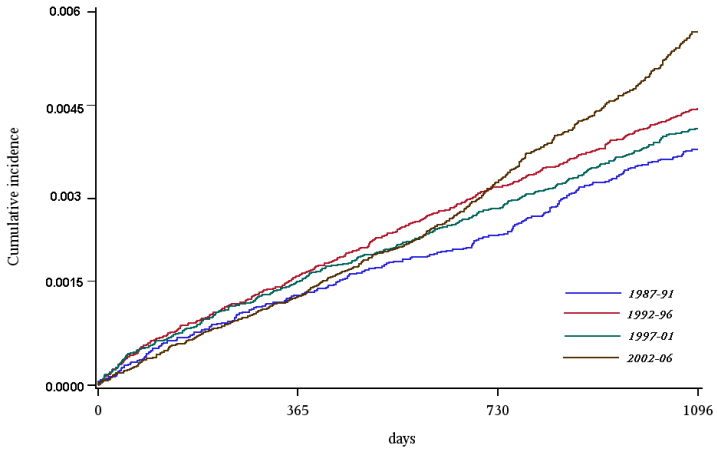
365
730
1096
days
1987-91
1992-96
1997-01
2002-06

Figure 2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Cumulative incidence
0
365
730
1096
days
1987-91
1992-96
1997-01
2002-06