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Seasonal variation and trend in hospital admissions for stroke in patients with atrial fibrillation in Denmark and New Zealand: analysis of hospital discharge data from 1977 to 2008

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Abstract:

Objectives: There are relatively few large studies of seasonal variation in the occurrence of stroke in patients with AF. We investigated the seasonal variation in incidence rates of hospitalizations with stroke in patients from Denmark and New Zealand.

Design: Cohort study.

Setting: Nationwide hospital discharge data from Denmark and New Zealand.

Participants: 248,103 (median age 75) subjects having a first-time hospitalization with AF in Denmark and 52,181 (median age 76) subjects in New Zealand constituted the study population. Subjects with previous hospitalization with stroke were excluded.

Primary and secondary outcome measures: Peak-to-trough ratio of the seasonal variation in weekly incidence rates of stroke in patients with AF adjusted for an overall trend was primary outcome measure and was assessed using a log-linear Poisson regression model. Secondary outcome measures were incidence rate ratios of AF and 30-days case fatality for stroke patients.

Results: Annual incidence rate ratio for AF in Denmark was 1.059% (95%CI: 1.057-1.060) for patients aged <65 and 1.054% (95%CI: 1.053-1.055) for patients aged ≥65, whereas 1.019% (95%CI: 1.006-1.013) for patients aged <65 and 1.043% (95%CI: 1.041-1.044) for patients aged ≥65 in New Zealand. In Denmark 37,444 subjects were hospitalized with stroke, and 7,794 subjects in New Zealand, both showing peaks during winter with peak-to-trough ratios equal 1.21 and 1.27, respectively and a decreasing trend. The annual 30-days case fatality risk for stroke patients is now (2000-08) about 20% in both countries.

Conclusions: Although incidence rates of hospitalizations with stroke in patients with AF have decreased in recent years, this remains a common AF complication with a high case fatality risk. The marked winter peak in incidence rates of hospitalization with AF related stroke suggests that there are opportunities to reduce this complication. Further studies are necessary to identify how to optimize treatment of AF and prevention of stroke.

Article Focus:

Estimate the peak-to-trough ratio of hospitalisations with stroke in atrial fibrillation patients in a cohort study design based on discharge data from Denmark and New Zealand using a log-linear Poisson regression model.

Explore trends in incidence rates of atrial fibrillation in the entire Danish and New Zealand population.

Estimate 30-days case fatality risks for stroke in atrial fibrillation patients in Denmark and New Zealand.

Key Messages:

Hospitalisations with stroke in atrial fibrillation patients show a peak during winter and trough during summer in countries in opposite hemispheres.

The incidence rates of atrial fibrillation in entire Danish and New Zealand population have increased since start of registration of hospitalisations until 2008.

The 30-days case fatality risk for stroke in atrial fibrillation patients seems to have been at a constant level during 2000-2008.

Strengths and limitations:

The main strength of this study is that study cohort is based on two entire national populations.

The main limitation of this study was inherent to its observational nature since the negative predictive value of discharge data may not be assessed.

The cohort study design indicates associations to be explored further to identify causality trough randomised controlled studies.

1. **Introduction**

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, and is associated with a substantial risk of mortality and morbidity from thromboembolism and especially thromboembolic stroke. Well-established risk factors for stroke in AF patients are prior stroke, advanced age, hypertension, diabetes mellitus, moderate-severe systolic dysfunction and vascular disease [1–3].

A seasonal variation in acute presentation with various cardiovascular disorders has been reported, with data on acute presentations with myocardial infarction, sudden death, rupture/dissection of aortic aneurysms, heart failure hospitalizations and venous thromboembolism [4–9] all showing a seasonal peak during winter. Acute stroke and transient ischemic attack show a similar pattern [10,11].

In addition, a seasonal variation in paroxysmal AF has been documented by 24-hour Holter electrocardiogram, with maximum and minimum incidences in autumn and summer, respectively [12]. It has been suggested that AF hospital admissions may also exhibit a seasonal variation, with the risk being modestly higher during the winter and inversely associated with outdoor temperature [13]. Nonetheless, this effect may be small and has been considered unlikely to be significant for policy or etiological research purposes [14]. However, this may reflect the limitations of relatively small single centre studies, and large "real world" population-based analyses may be needed. Indeed, using the linked Scottish Morbidity Record scheme between 1990 and 1996, there was a total of 33,582 male and 34,463 female AF hospitalizations, which showed a substantial seasonal variation in AF hospitalizations and deaths, particularly in the elderly [15].

Few studies exist on seasonal variation in occurrences of stroke and mortality risk after stroke in patients with AF. One analysis from the Danish National Registry of Patients has previously found a seasonal variation in stroke occurrence in patients with non-valvular AF but no effect of season on mortality after stroke [16]. One small series of approximately 300 Greek patients with first-ever cardio embolic acute stroke due to AF also revealed a seasonal peak during winter and a decline of stroke occurrence during summer [17].

Assuming a seasonal variation in hospital admissions with stroke in patients with AF, we would expect to see similar temporal patterns in countries from different parts of the world. However, we are unaware of any data comparing seasonal changes over a comparable time period between two countries, irrespective of seasonality shift by being in the northern or southern hemisphere. In this study we described the occurrences of hospitalizations with stroke in patients with AF, including

estimating the seasonal variation in the two countries investigating the temporal patterns from the northern and southern hemisphere. Furthermore, we described the overall trend in incidence rates of hospitalization admissions for both AF and stroke in patients with AF over a twenty year period. Differences in annual 30-days case fatality risks between countries were also assessed.

2. Material and methods

2.1 Study Period and Study Population

The study period in Denmark was from 1 January 1977 and in New Zealand from 1 January 1988, both to 31 December 2008. Incident non-valvular AF, stroke and mortality was recorded using the International Classification of Diseases (ICD). Both principal and additional diagnoses were included for analysis. No discrimination was made between ischemic or hemorrhagic strokes.

The Danish cohort was identified in the Danish National Registry of Patients, starting in 1977, using the Danish Personal Identification number. This is a unique and national identification number which is part of the personal information stored in the Civil Registration System. The Danish study population in the present study included Danish residents who developed incident AF from 1977 to 2008. ICD codes were used to extract admissions for AF. The 8th revision (ICD-8) was used until 1994, and after 1994 the 10th revision (ICD-10) was used. AF and atrial flutter were coded separately in ICD-8 (codes 427.93 and 427.94), whereas in ICD-10, AF and atrial flutter have a single ICD code (I48). Therefore, atrial flutter cases have also been included in the present study. In Denmark, incidences of stroke were found in the Danish National Registry of Patients, using ICD-8 (433, 434, and 436) and ICD-10 (I63, I64).

The cohort from New Zealand was identified from 1988 to 2008, using the National Minimum Dataset. The National Minimum Dataset, managed by the New Zealand Ministry of Health, holds information on all publicly funded hospitalizations in New Zealand. Each hospitalization is linked with the patient's National Health Index (NHI) number, which is a unique number provided to each person using health and disability support services in New Zealand. This index is stored in the NHI database along with demographic details of the person. In the National Minimum Dataset ICD 9th revision (ICD-9) was used until June 1999, and after that ICD-10 was used. Similar to the Danish data, AF and atrial flutter were coded separately in ICD-9 (codes 427.31 and 427.32), whereas in ICD-10, AF and atrial flutter have a single ICD code (I48). In New Zealand, incidences of stroke were found in the National Minimum Dataset using ICD-9 (433, 434, 436) and ICD-10 (I63, I64).

In Denmark annual population figures were obtained from Statistics Denmark, whereas in New Zealand only five-year population figures were available from Statistics New Zealand starting from 1996. Annual estimates for the New Zealand population from 1988 to 2008 were obtained by linear inter- and extrapolation.

2.2 Statistical analysis

Initial trend analysis of incidence rates of AF, ie the annual number of hospitalizations with AF divided by the annual population size, in the two countries were performed. A Poisson regression model was used to model annual incidence rates of first time hospitalizations with AF, assuming a log-linear trend. Incidence rates were estimated stratified on age groups (<65 and ≥ 65 years of age) and type of diagnosis (principal or additional diagnosis). Only annual incidence rates from 1988 to 2008 were analyzed. Statistical significance of interaction between trend and countries was assessed with a likelihood ratio test.

AF related stroke was defined as a first time hospitalization with stroke having previous hospital admissions for AF. A log-linear Poisson regression model was used to model the seasonal variation in weekly incidence rates of hospitalizations with AF related stroke adjusted for an overall trend. Weekly incidence rates of AF related stroke were defined as the weekly number of hospitalizations with AF related strokes divided by the weekly number of patients with AF in the entire population. The seasonal variation component was modeled as a sum of four sinusoids with frequencies one to four [18]. The overall trend was modeled using restricted cubic splines with five knots [19]. As a measurement of the seasonal variation we estimated the peak-to-trough ratio, which is an incidence rate ratio.

In addition, annual 30-days case fatality risks were calculated for both countries. For each year the total number of first time hospitalizations with AF related stroke was calculated, along with the number of death within 30 days of admission with stroke, with no discrimination on cause of death. The 30-days case fatality risk was estimated as the ratio between these annual numbers. A logit-linear logistic regression model was fitted to mortality data, assuming a logit-linear trend. Assessment on statistically significant interaction between trend and countries was performed by a likelihood ratio test.

P-values less than 5% were considered statistically significant. All analyses were performed in `R` version 2.13.1 [20] using the package `Peak2Trough` [21].

3. Results

Demographic descriptions of the two cohorts are found in Table 1. For the Danish cohort, we identified 248,103 incident hospitalizations with AF for the 32-year period from 1977 to 2008, of which 47.8% were females. For the New Zealand cohort 52,181 similar subjects were identified for the 21-year period from 1988 to 2008 (48.3% females). The median age at time of AF in the Danish cohort was 75.2 years, which was similar to the New Zealand cohort (75.8 years).

The distribution of ICD codes of AF was similar between the two cohorts, also stratified on sex (Table 1). By contrast, the distribution of diagnosis type differed in the two cohorts. In both cohorts more than half of AF diagnoses were given as a supplementary diagnosis to a principal diagnosis, with a higher proportion in New Zealand, than in Denmark. The median weekly count of AF hospitalizations in Denmark was 132, whereas in New Zealand the weekly count was 49. There was no significant sex difference in weekly counts between the cohorts.

Differences in comorbidities were apparent between Denmark and New Zealand. In Table 2, characteristics of the sub-group defined as all patients with AF having at least one comorbid disease. The distribution of age in the two countries was very similar, although congestive heart failure was more frequent in the New Zealand cohort and diabetes more frequent in the Danish cohort.

Annual incidence rates of AF hospitalizations in Denmark and New Zealand are shown in Figure 1. For both countries, the incidence rates for patients younger than 65 years of age were markedly lower than for patients above 65 years of age. A likelihood ratio test indicates a significant difference in increase over time in incidence rates between countries for both age groups. In Denmark, the incidence rates increased by 5.4% annually (95% CI: 5.3-5.5) for patients above 65 years of age compared with only an increase of 4.3% annually (95% CI: 4.1-4.4) for the same patients in New Zealand. For the younger patients the incidence rates increased by 5.9% annually (95% CI: 5.7-6.0) in Denmark and 1.9% (95% CI: 0.6-1.3) in New Zealand.

During follow-up 37,444 subjects were hospitalized with stroke (55.1% females) in the Danish cohort, which encompassed 15.1% of the entire cohort. In New Zealand the figures were 7,794 (54.3% females), which encompassed 15.0% of the cohort. The median weekly count of stroke in Denmark was 21 and 7 in New Zealand. Table 3 shows further follow-up characteristics of the two cohorts.

The seasonal variations for both countries estimated by fitting the Poisson regression model and adjusted for an overall trend are shown in Figure 2. Time for seasonal peak in both countries was winter and time for seasonal trough was summer. The peak-to-trough ratio in Denmark was 1.21, i.e.

the risk of being hospitalized with AF related stroke at peak time in winter is 21% higher compared to summer. In New Zealand the peak-to-trough ratio was 1.27.

Weekly incidence rates of AF related stroke hospitalizations were decreasing in both countries during the study period; see Figure 3 which shows the estimated trends. From 1980 to 1986 the incidence rates in Denmark decreased markedly reaching a plateau of approximately 4 hospitalizations per 100 person-years during the period from the late 1980s to 2002, followed by a further decline. Afterwards the incidence rates seem to decrease further. Similarly in New Zealand the incidence rates decrease markedly during the first five years from 1988 to 1992. In 1998 the incidence rate has decreased to the same level as in Denmark, though from 2004 the incidence rates increased slightly.

The annual 30-days case fatality risks for Denmark and New Zealand are shown in Figure 4. The analysis indicated that the odds ratio for death within 30 days after stroke decreased by 2.0% (95% CI: 1.4-2.4) annually in Denmark over the entire observation period. By contrast the odds ratio increased by 4.5% (95% CI: 3.3-5.8) annually in New Zealand. Overall, the case fatality risk converged in both countries towards a value of about 20% during the most recent period.

4. Discussion

This study shows that stroke remains a common complication of AF affecting around 15% of those hospitalized with AF in Denmark and New Zealand. AF associated stroke is serious with a 20% 30-day case fatality risk in recent years (2000-08). This study found evidence of a marked seasonal variation in incidence rates of hospitalizations with AF related stroke, with a peak in winter and a trough in summer in both countries. The analysis indicated a difference in overall trend in incidence rates of hospitalizations with AF related stroke between countries, Denmark tending to have lower incidence rates, compared to New Zealand. In contrast, we showed a highly significant increase in AF over time in both countries. Furthermore, we found differences in the distributions of ICD codes and type of diagnoses in the two countries.

The main limitation of this study was inherent to its observational nature. Even though the positive predictive value of the diagnosis of AF is very high in the Danish registry (93%) [22,23], the negative predictive value of such data sources is harder to assess. Consequently, studies based on hospital discharge registries may be affected by misclassification and inclusion bias - for example, by including only patients admitted to hospital with AF we might have increased the proportion of patients who were at higher risk of thromboembolic events and death. The incidence of stroke was defined by the Danish National Registry of Patients, and not all stroke diagnoses were defined by

cerebral imaging. The diagnosis of stroke has previously been validated in the Danish registry; with a positive predictive value of ischemic stroke of 97% [24]. Also, we are limited by the inability to differentiate between ischemic and hemorrhagic strokes, but from a Danish stroke registry we know that stroke in patients with AF is predominantly embolic [25]. AF related stroke by definition requires hospitalization and recorded diagnosis for two separate conditions, so trends in incidence rates are determined by factors that affect both of these events and may be complex to interpret. Misclassification or under-reporting of comorbidities, especially hypertension and diabetes, may have occurred [26], and we did not have data on the nature of AF in any of the cohorts. No data exist on the validity of diagnoses on AF and stroke from the National Minimum Dataset in New Zealand. Our study included patients from Denmark and New Zealand, who were treated in different settings and probably with different methods. However, the range of patients was similar regarding age and co-morbid conditions. The nature of exposures was comparable, and the definitions of outcomes were all defined by comparable ICD-coding in the two countries. The differences in health care systems in the two countries can hardly influence the referral pattern around AF. Furthermore, comparison of the two countries brings forward interesting questions when we compare with similar but smaller studies from other countries.

Consistent with another study we showed that the seasonal variation in incidence rates of hospitalizations with AF related stroke in both countries was characterized by a peak in winter and trough in summer [16]. This pattern is reported for several other cardiovascular diseases [4–12,15,17]. The previously reported peak-to-trough ratio from Denmark of 1.11 [16] is similar to the peak-to-trough ratio reported in this study, however slightly lower. This may be due to the difference in resolution of data. In the present study weekly incidence rates were analyzed as opposed to monthly incidence rates in Frost et al [16]. The finding that the characteristics of the seasonal variation in both countries are similar may be important in the search for identifying underlying risk factors causing AF related stroke. Such factors may be climate factors, e.g. temperature, humidity and hours of sunshine, as well as seasonal variation in occurrences of risk factors for both AF and stroke, e.g. hypertension [27,28] and infectious diseases [29]. The difference in peak-to-trough ratio between two countries, may also lead to the identification of causes that may explain the seasonality, by considering differences between the two countries, for instance climatic differences, housing conditions, and life style patterns [30,31].

The overall trend in weekly incidence rates of hospitalizations with AF related stroke in Denmark found in this study show a markedly decrease during the first seven years from 1977 to 1984. During the late eighties and early nineties several studies regarding AF and its potential increasing risk of stroke were published [32,33], which led to introduction of oral anticoagulant treatment

[34,35]. This concurrence reveals the prophylactic effects of anticoagulant treatment, preventing AF patients to develop stroke. However, the overall trend in incidence rates of AF related stroke in New Zealand indicates that the awareness of AF and its consequences was not as present until the early nineties. Furthermore, this study indicates that the trend in incidence rates in Denmark is decreasing further towards the end of the study period, whereas in New Zealand the trend seems to increase.

The risk of stroke is multi-factorial, and is affected by risk factors such as history of hypertension, current smoking, diet, physical activity, diabetes mellitus, alcohol intake, psychosocial stress and depression, cardiac causes (e.g. AF), and ratio of apolipoproteins B to A1 [36]. Indeed, greater awareness of some risk factors e.g. blood pressure control and smoking cessation may have contributed to a lowering of AF related stroke incidence over this period. Also, a managed care approach to high risk patients (e.g. recent transient ischemic attack) may have led to the reduction in stroke hospitalizations in more recent years [37]. This is clearly a positive observation, given that AF related strokes are associated with a higher mortality, as well as a greater morbidity and disability.

Whilst the annual incidence rates of hospitalizations with AF were lower in New Zealand compared with Denmark for both age groups there was still a highly significant increase over time in incidence rates for both countries and both age groups. This is consistent with reported increasing trends in hospitalization for AF in the United States, between 1985 and 1999 [38]. In the analysis by Wattigney et al, US hospitalizations for AF increased dramatically (2- to 3-fold) in the period 1985-1999. In their study, women were hospitalized with AF more often than men on an annual basis, although the age-standardized prevalence of hospitalizations was greater in men than women. Women hospitalized with AF tended to be older than men, which our results confirm.

Unsurprisingly we found the median age of both Danish and New Zealand cohorts to be similar (approximately 75 years). The incidence rates for patients younger than 65 years of age were much lower than for patients above 65 years of age. Indeed, these observations are consistent with other epidemiological data including analyses of hospitalization data [22,38–40]. There was no significant sex difference in weekly counts in either cohort. Of note, the median weekly count of AF hospitalizations and AF related strokes in Denmark were higher than in New Zealand. The reasons for this remain uncertain, but may reflect the different demographic profile, differences in referral patterns and awareness of the disease as well as differences in associated comorbidities. Taking into account the variation in distribution of types of diagnoses of AF, where in New Zealand nearly 70% of the AF diagnoses were in addition to another principal diagnosis, compared with nearly 60% in Denmark, the difference in incidence rates of hospitalizations with AF may be due to differences in the health system in the two countries. In Denmark the health system is funded by taxes, and all

contacts with the health system are free of charge for the patient. By contrast, in New Zealand only parts of the health system are fully funded by taxes, notably hospital care, whereas visits to the general practitioner are subject to a small user charge. Given the unspecific symptoms of AF, patients might be less likely to contact their general practitioner when experiencing symptoms with palpitations and shortness of breath. This is supported by the fact that AF patients with stroke often have non-recognized AF [25]. Consequently, a larger proportion of the New Zealand population may be undiagnosed with AF than in Denmark.

In the present study, we found significant differences in comorbidities (Table 2). Despite the similar age distribution between countries, congestive heart failure was more frequent in the New Zealand cohort and diabetes more frequent in the Danish cohort. This difference may reflect the fact that additional diagnoses for AF are used more frequently in the New Zealand cohort than in the Danish, and may be a random finding in patients referred with symptoms of congestive heart failure. The reason for the highly significant differences in all variables even in what seems very similar, e.g. hypertension, is the high number of observations in this study comprising more than three hundred thousand patients.

This study found that there was a minor decrease in the 30-days case fatality risk for AF related strokes during the study period in Denmark, but an evident increase in New Zealand. Our findings indicate that the 30-days case fatality risk in Denmark was higher than in New Zealand until the late nineties, whereas afterwards the difference does not seem evident. This may be due to differences in anticoagulant treatments between the two countries but this also remains tentative.

5. Conclusion

This is the first concurrent analysis of the epidemiology of AF related stroke in nationwide population data from two western countries, one in the northern hemisphere and one in the southern hemisphere. We showed that the incidence rates of hospitalization with stroke in patients with AF exhibit a marked seasonal variation in both countries, which is characterized by a peak in winter and a trough in summer. Both countries have also shown a downward trend in hospitalizations with stroke in patients with AF, despite a pronounced increase in AF hospitalizations. This trend, seasonal variation and differences in comorbidities and distribution of types of diagnoses between the two countries, merit further study. Such research could help us better understand the clinical epidemiology and public health impact of AF and its complications and identify opportunities for better prevention of AF and stroke.

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Table 1: Demographic description of patients with atrial fibrillation in Denmark and New Zealand

	Total		Women		Men	
Denmark						
Number of AF	248,103	(100%)	118,681	(47.8%)	129,422	(52.2%)
Age at AF, years (median (IQR))	75.2	(66.2-82.4)	78.4	(70.7-84.5)	72	(62.5-79.6)
AF						
427.31 (ICD-8)	80,076	(32.3%)	39,811	(33.5%)	40,265	(31.1%)
427.32 (ICD-8)	7,409	(3.0%)	2,978	(2.5%)	4,431	(3.4%)
I48 (ICD-10)	160,618	(64.7%)	75,892	(64.0%)	84,726	(65.5%)
Diagnosis type						
Principal	104,307	(42.0%)	47,807	(40.3%)	56,500	(43.7%)
Additional	143,796	(58.0%)	70,874	(59.7%)	72,922	(56.3%)
Weekly counts (median (IQR))	132	(94-205)	63	(46-96)	68	(48-108)
New Zealand						
Number of AF	52,181	(100%)	25,186	(48.3%)	26,995	(51.7%)
Age at AF, years (median (IQR))	75.8	(67.5-82.4)	78.1	(70.4-84.3)	73.6	(65.1-80.3)
AF						
427.93 (ICD-9)	18,367	(35.2%)	8,968	(35.6%)	9,399	(34.8%)
427.94 (ICD-9)	1,424	(2.7%)	529	(2.1%)	895	(3.3%)
I48 (ICD-10)	32,390	(62.1%)	15,689	(62.3%)	16,701	(61.9%)
Diagnosis type						
Principal	15,660	(30.0%)	7,876	(31.3%)	7,784	(28.8%)
Additional	36,521	(70.0%)	17,310	(68.7%)	19,211	(71.2%)
Weekly counts (median (IQR))	49	(32-61)	23	(15-30)	25	(16.75-32)

AF: Atrial fibrillation, ICD: International Classification of Diseases, IQR: Inter quartile range

12

Table 2: Comorbidities and age distribution among patients hospitalized with atrial fibrillation having at least one comorbid disorder in Denmark and New Zealand

	Denmark	New Zealand
Characteristics		
Percentage of all patients with AF having at least one comorbid disorder	32.2	53.1
Age, years (at time of AF)		
Age ≥75 years	55.8	56.3
Age 65-74	27.9	26.1
Women	46.7	46.5
Congestive heart failure	29.4	53.4
Hypertension	35.1	22.2
Diabetes	19.0	8.2
Acute myocardial infarction	31.5	29.0
Peripheral arterial disease	10.6	10.9
Coronary artery disease	34.7	31.3

The comorbid conditions were registered if they preceded an incident diagnosis of AF.

Data are percentages.

Table 3: Demographic description of patients with atrial fibrillation related strokes in Denmark and New Zealand

	Total		Women		Men	
Denmark						
Number of strokes	37,444	(100%)	20,612	(55%)	16,832	(45%)
Age at stroke, years (median (IQR))	79.4	(73-84.8)	81.5	(75.8-86.3)	76.7	(69.7-82.3)
Stroke						
433 (ICD-8)	2,960	(7.9%)	1,556	(7.5%)	1,404	(8.3%)
434 (ICD-8)	1,312	(3.5%)	642	(3.1%)	670	(4%)
436 (ICD-8)	8,949	(23.9%)	5,107	(24.8%)	3,842	(22.8%)
I63 (ICD-10)	9,771	(26.1%)	5,262	(25.5%)	4,509	(26.8%)
I64 (ICD-10)	14,452	(38.6%)	8,045	(39%)	6,407	(38.1%)
Diagnosis type						
Principal	28,010	(74.8%)	15,630	(75.8%)	12,380	(73.6%)
Additional	9,434	(25.2%)	4,982	(24.2%)	4,452	(26.4%)
Weekly counts (median (IQR))	22	(17-27)	12	(9-15)	10	(7-13)
Time to stroke, days (median (IQR))	332	(0-1508.2)	319	(0-1466.2)	348	(0-1563)
New Zealand						
Number of strokes	7,794	(100%)	4,232	(54.3%)	3,562	(45.7%)
Age at stroke, years (median (IQR))	79.8	(72.8-85.3)	81.6	(75.3-86.7)	77.6	(70.5-83.5)
Stroke						
433 (ICD-9)	115	(1.5%)	44	(1%)	71	(2%)
434 (ICD-9)	700	(9%)	358	(8.5%)	342	(9.6%)
436 (ICD-9)	1,512	(19.4%)	815	(19.3%)	697	(19.6%)
I63 (ICD-10)	3,581	(45.9%)	1,999	(47.2%)	1,582	(44.4%)
I64 (ICD-10)	1,886	(24.2%)	1,016	(24%)	870	(24.4%)
Diagnosis type						
Principal	6,150	(78.9%)	3,338	(78.9%)	2,812	(78.9%)
Additional	1,644	(21.1%)	894	(21.1%)	750	(21.1%)
Weekly counts (median (IQR))	7	(4-9)	4	(2-5)	3	(2-5)
Time to stroke, days (median (IQR))	584	(5-1724)	590	(9-1705.5)	576	(0-1745.8)

AF: atrial fibrillation, ICD: International Classification of Diseases, IQR: Inter quartile range

Figure 1: Observed annual incidence rates of first-time hospitalizations with a principal or additional diagnosis of atrial fibrillation per 1,000 person-years for the Danish and New Zealand population.

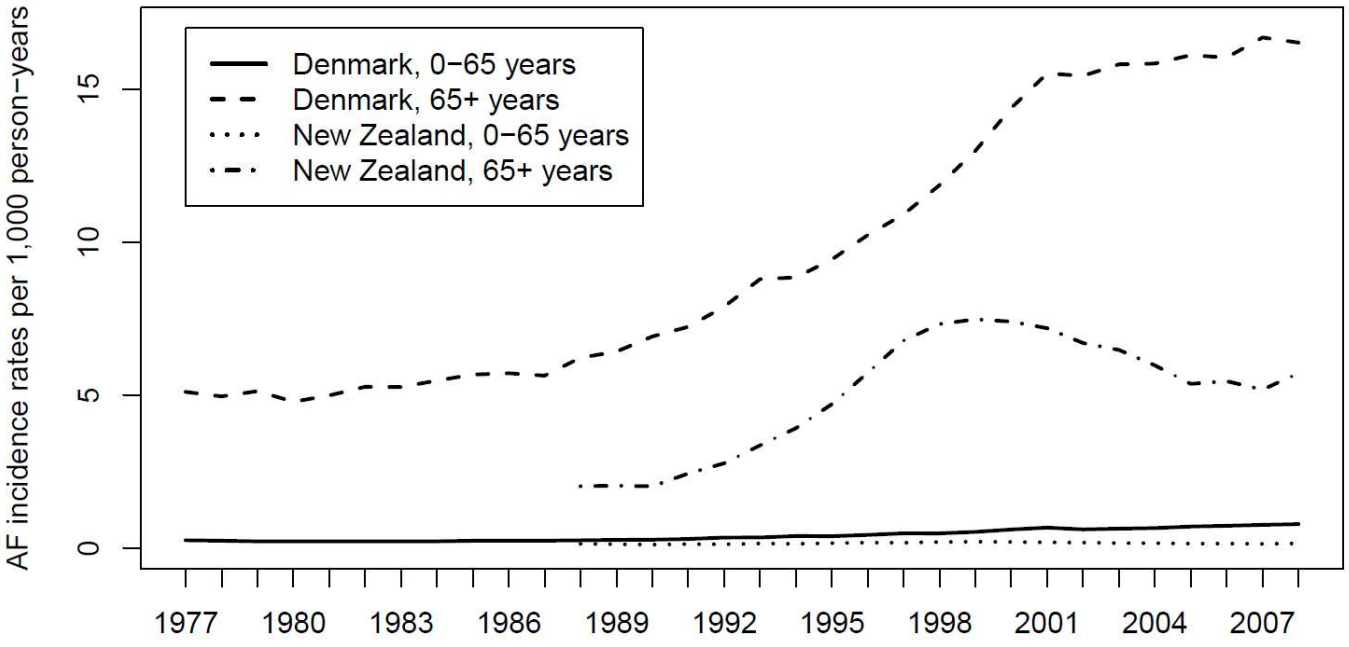


Figure 2: Estimated seasonal variation in incidence rates of hospitalisations with stroke in patients with atrial fibrillation in Denmark (solid line) and New Zealand (dashed line) adjusted for overall trend. The seasonal variation is represented as the percentual deviation in incidence rates from annual median, and incidence rates are aggregated to weekly observations. Shaded bands represent 95% confidence intervals.

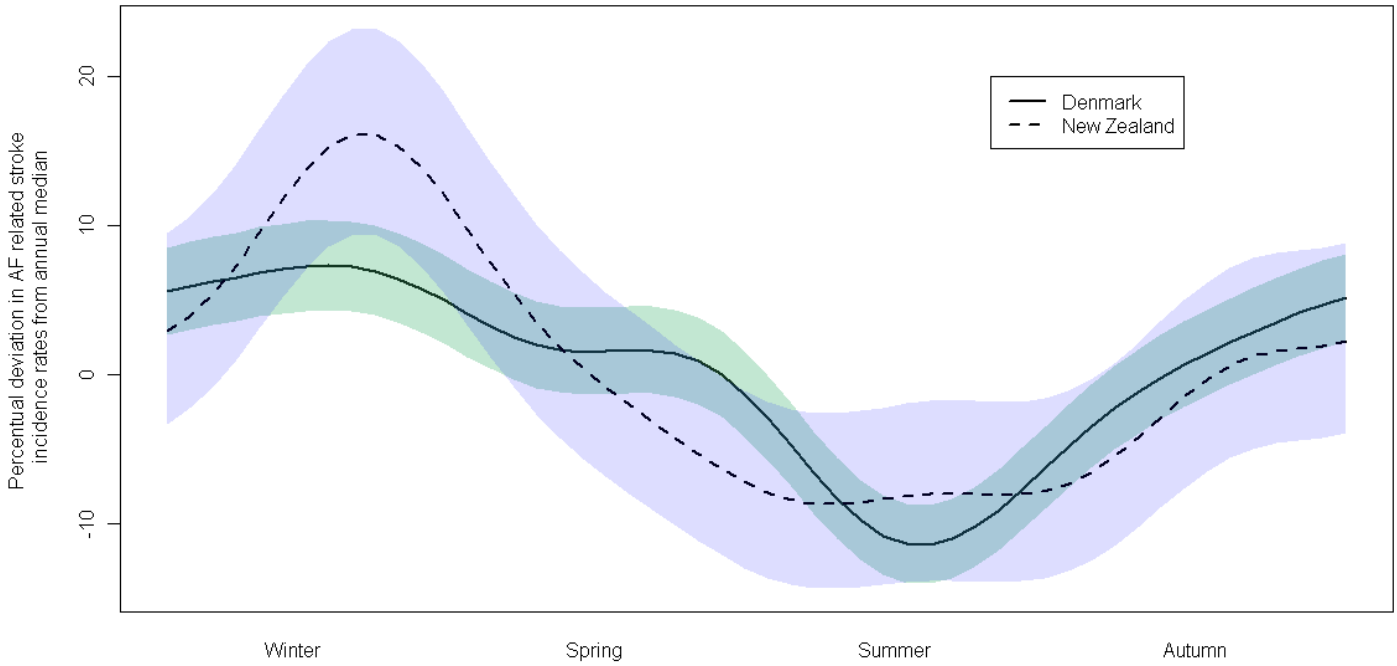


Figure 3: Estimated overall trend of Danish (solid line) and New Zealand (dashed line) weekly incidence rates of hospitalisations with atrial fibrillation related stroke per 100 person-years adjusted for seasonality. Shaded bands represent 95% confidence intervals.

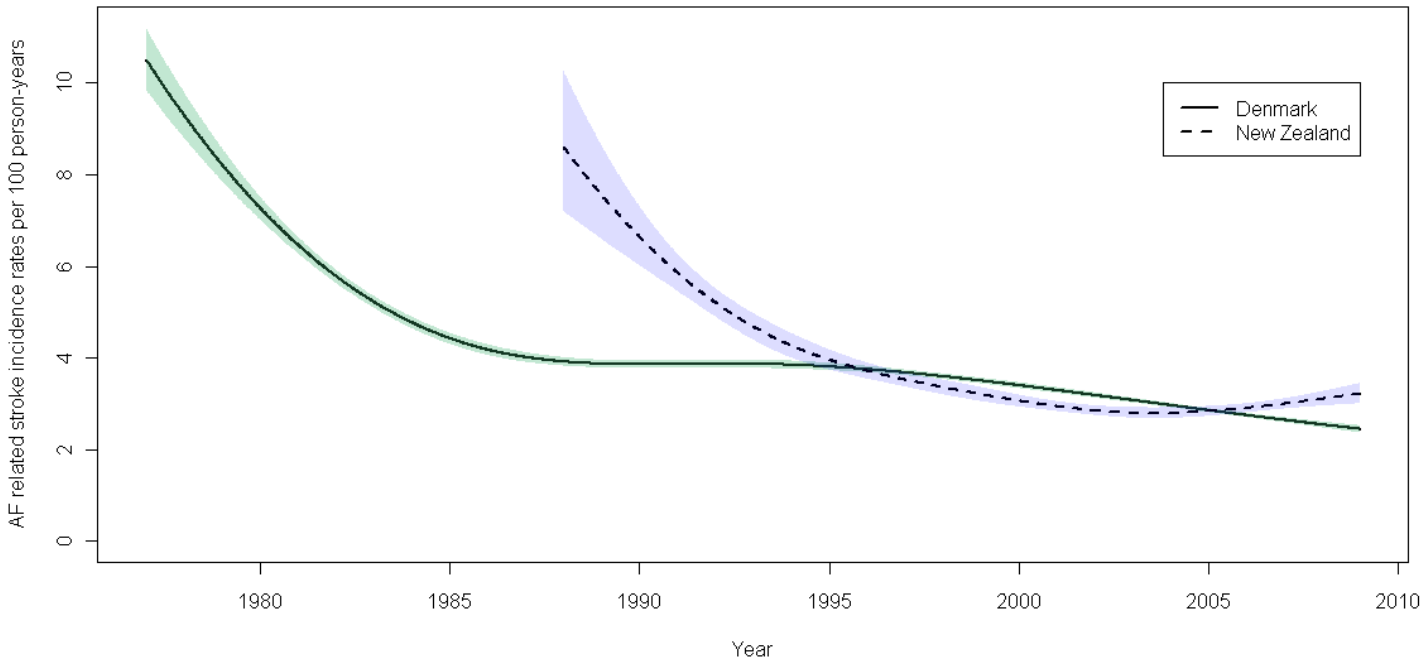
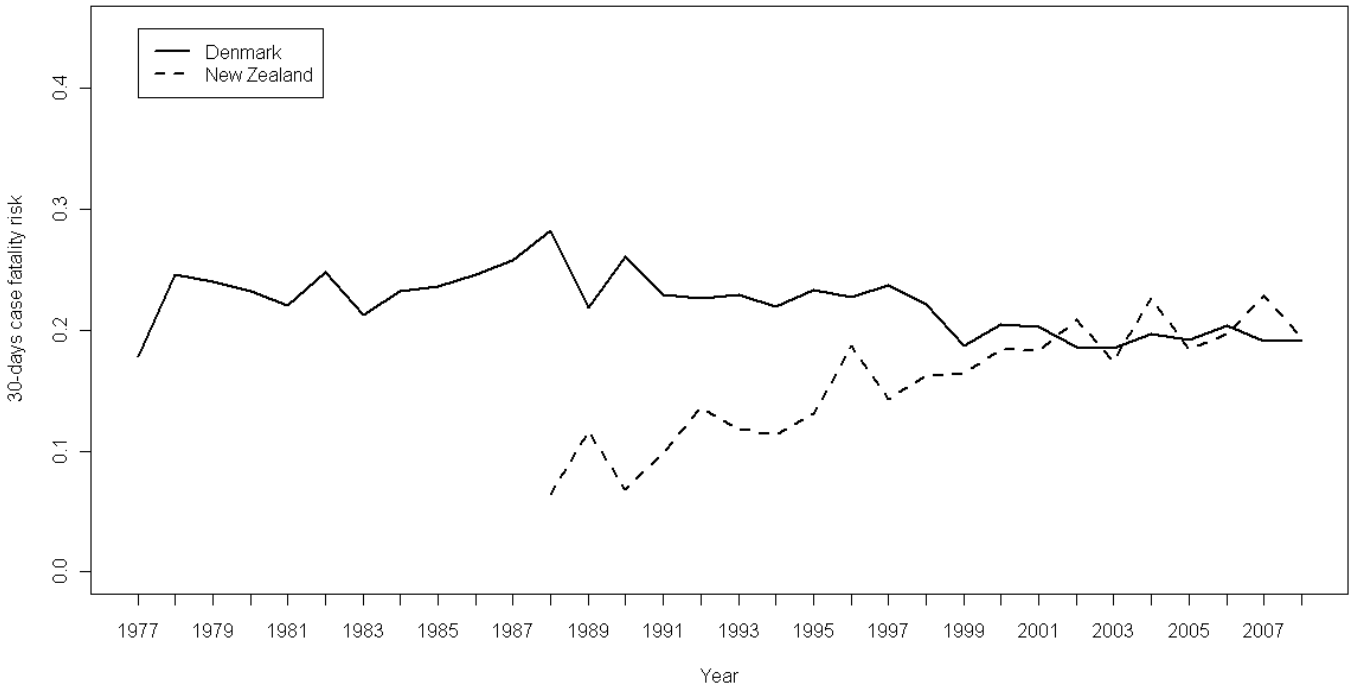


Figure 4: Estimated annual 30-days case fatality risk for atrial fibrillation related stroke patients in Denmark and New Zealand



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Seasonal variation and trend in hospital admissions for stroke in patients with atrial fibrillation in Denmark and New Zealand: analysis of hospital discharge data from 1977 to 2008

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Seasonal variation and trend in hospital admissions for stroke in patients with atrial fibrillation in Denmark and New Zealand: analysis of hospital discharge data from 1977 to 2008

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Keywords: Stroke, Atrial fibrillation, Seasonal variation, Epidemiology, Cardiology, Poisson regression

Word Count: 3614

Abstract:

Objectives: There are relatively few large studies of seasonal variation in the occurrence of stroke in patients with AF. We investigated the seasonal variation in incidence rates of hospitalizations with stroke in patients from Denmark and New Zealand.

Design: Cohort study.

Setting: Nationwide hospital discharge data from Denmark and New Zealand.

Participants: 243,381 (median age 75) subjects having a first-time hospitalization with AF in Denmark and 51,480 (median age 76) subjects in New Zealand constituted the study population. Subjects with previous hospitalization with stroke were excluded.

Primary and secondary effect measures: Peak-to-trough ratio of the seasonal variation in weekly incidence rates of stroke in AF patients adjusted for an overall trend was primary effect measure and was assessed using a log-linear Poisson regression model. Secondary effect measures were incidence rate ratios of AF and 30-days case fatality for stroke patients.

Results: Annual incidence rate ratio for AF in Denmark was 1.055% (95%CI: 1.053-1.057) for patients aged <65 and 1.050% (95%CI: 1.049-1.051) for patients aged ≥65, whereas 1.002% (95%CI: 0.998-1.006) for patients aged <65 and 1.026% (95%CI: 1.024-1.028) for patients aged ≥65 in New Zealand. In Denmark 36,088 subjects were hospitalized with stroke, and 7,518 subjects in New Zealand, both showing peaks during winter with peak-to-trough ratios equal 1.22 and 1.27, respectively and a decreasing trend. The 30-days case fatality risk for stroke patients is now (2000-08) about 20% in both countries.

Conclusions: Although incidence rates of hospitalizations with stroke in patients with AF have decreased in recent years, this remains a common AF complication with a high case fatality risk. The marked winter peak in incidence rates of hospitalization with stroke in AF patients suggests that there are opportunities to reduce this complication. Further studies are necessary to identify how to optimize treatment of AF and prevention of stroke.

Article Focus:

Estimate the peak-to-trough ratio of hospitalisations with stroke in atrial fibrillation patients in a cohort study design based on discharge data from Denmark and New Zealand using a log-linear Poisson regression model.

Explore trends in incidence rates of atrial fibrillation in the entire Danish and New Zealand population.

Estimate 30-days case fatality risks for stroke in atrial fibrillation patients in Denmark and New Zealand.

Key Messages:

Hospitalisations with stroke in atrial fibrillation patients show similar seasonal variation with a peak during winter and trough during summer in countries in opposite hemispheres.

The incidence rates of atrial fibrillation in entire Danish and New Zealand population have increased since start of registration of hospitalisations until 2008.

The 30-days case fatality risk for stroke in atrial fibrillation patients seems to have been at a constant level during 2000-2008.

Strengths and limitations:

The main strength of this study is that study cohort is based on two entire national populations.

The main limitation of this study was inherent to its observational nature since the negative predictive value of discharge data may not be assessed.

The cohort study design indicates associations to be explored further to identify causality trough randomised controlled studies.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, and is associated with a substantial risk of mortality and morbidity from thromboembolism and especially thromboembolic stroke. Well-established risk factors for stroke in AF patients are prior stroke, advanced age, hypertension, diabetes mellitus, moderate-severe systolic dysfunction and vascular disease [1–3].

A seasonal variation in acute presentation with various cardiovascular disorders has been reported, with data on acute presentations with myocardial infarction, sudden death, rupture/dissection of aortic aneurysms, heart failure hospitalizations and venous thromboembolism [4–9] all showing a seasonal peak during winter. Acute stroke and transient ischemic attack show a similar pattern [10,11].

In addition, a seasonal variation in paroxysmal AF has been documented by 24-hour Holter electrocardiogram, with maximum and minimum incidences in autumn and summer, respectively [12]. It has been suggested that AF hospital admissions may also exhibit a seasonal variation, with the risk being modestly higher during the winter and inversely associated with outdoor temperature [13]. Nonetheless, this effect may be small and has been considered unlikely to be significant for policy or etiological research purposes [14]. However, this may reflect the limitations of relatively small single centre studies, and large "real world" population-based analyses may be needed. Indeed, using the linked Scottish Morbidity Record scheme between 1990 and 1996, there was a total of 33,582 male and 34,463 female AF hospitalizations, which showed a substantial seasonal variation in AF hospitalizations and deaths, particularly in the elderly [15].

Few studies exist on seasonal variation in occurrences of stroke and mortality risk after stroke in patients with AF. One analysis from the Danish National Registry of Patients has previously found a seasonal variation in stroke occurrence in patients with non-valvular AF but no effect of season on mortality after stroke [16]. One small series of approximately 300 Greek patients with first-ever cardio embolic acute stroke due to AF also revealed a seasonal peak during winter and a decline of stroke occurrence during summer [17].

Assuming a seasonal variation in hospital admissions with stroke in patients with AF, we would expect to see similar temporal patterns in countries from different parts of the world. However, we are unaware of any data comparing seasonal changes over a comparable time period between two countries, irrespective of seasonality shift by being in the northern or southern hemisphere. In this study we described the occurrences of hospitalizations with stroke in patients with AF, including estimating the seasonal variation in the two countries investigating the temporal patterns from the northern and southern hemisphere. Furthermore, we described the overall trend in incidence rates of hospitalization admissions for both AF and stroke in patients with AF over a twenty year period. Differences in annual 30-days case fatality risks between countries were also assessed.

2. Material and methods

2.1 Study Period and Study Population

The study period in Denmark was from 1 January 1977 and in New Zealand from 1 January 1988, both to 31 December 2008. Hospitalisations with first time non-valvular AF and stroke were recorded using the International Classification of Diseases (ICD). Both principal and additional diagnoses were included for analysis. No discrimination was made between ischemic or hemorrhagic strokes.

The Danish cohort was identified in the Danish National Registry of Patients, starting in 1977, using the Danish Personal Identification number. This is a unique and national identification number which is part of the personal information stored in the Civil Registration System. The Danish study population in the present study included Danish residents who developed incident AF from 1977 to 2008. ICD codes were used to extract admissions for AF. The 8th revision (ICD-8) was used until 1994, and after 1994 the 10th revision (ICD-10) was used. AF and atrial flutter were coded separately in ICD-8 (codes 427.93 and 427.94), whereas in ICD-10, AF and atrial flutter have a single ICD code (I48). Therefore, atrial flutter cases have also been included in the present study. In Denmark, incidences of stroke were found in the Danish National Registry of Patients, using ICD-8 (433, 434, and 436) and ICD-10 (I63, I64). To avoid including prevalent cases of both AF and stroke in AF patients, identified cases before 1980 were excluded from the analyses for the Danish cohort.

The cohort from New Zealand was identified from 1988 to 2008, using the National Minimum Dataset. The National Minimum Dataset, managed by the New Zealand Ministry of Health, holds information on all publicly funded hospitalizations in New Zealand. Each hospitalization is linked with the patient's National Health Index (NHI) number, which is a unique number provided to each person using health and disability support services in New Zealand. This index is stored in the NHI database along with demographic details of the person. In the National Minimum Dataset ICD 9th revision (ICD-9) was used until June 1999, and after that ICD-10 was used. Similar to the Danish data, AF and atrial flutter were coded separately in ICD-9 (codes 427.31 and 427.32), whereas in ICD-10, AF and atrial flutter have a single ICD code (I48). In New Zealand, incidences of stroke were found in the National Minimum Dataset using ICD-9 (433, 434, 436) and ICD-10 (I63, I64). To avoid including prevalent cases of both AF and stroke in AF patients, identified cases before 1991 were excluded from the analyses for the New Zealand cohort.

In Denmark annual population figures were obtained from Statistics Denmark, whereas in New Zealand only five-year population figures were available from Statistics New Zealand starting from 1996. Annual estimates for the New Zealand population from 1988 to 2008 were obtained by linear inter- and extrapolation.

Comorbidities were assessed by identifying hospitalizations with either congestive heart failure (ICD8: 427.09, 428, ICD9: 428, ICD10: I11.09, I50), hypertension (ICD8: 400-404, ICD9: 401-405, ICD10: I10-I13, I15),

diabetes (ICD8: 249, 250, ICD9: 250, ICD10: E11, E14), acute myocardial infarction (ICD8: 410, ICD9: 410, ICD10: I21, I22), peripheral artery disease (ICD8: 440.2, 443, 444, ICD9: 440, 443, 444, ICD10: I70.2, I73.9, I74.5), or coronary artery disease (ICD8: 412, ICD9: 414, ICD10: I25.1). One subject may have more than one comorbidity.

2.2 Statistical analysis

We define three effect measures for analyses. First, incidence rates of AF, defined as the annual number of hospitalizations with AF divided by the annual population size. Second, weekly incidence rates of stroke in AF patients defined as the weekly number of first time hospitalizations with stroke having previous hospital admissions for AF divided by the weekly person-time at risk i.e. for a given week the number of AF patients with no previous stroke. Third, 30-days case fatality risk, defined as the annual number of death among stroke patients having AF divided by the annual number of stroke patients having AF.

A log-linear Poisson regression model was fitted to incidence rates of AF, adjusting for a linear trend and modeling an interaction between trend and country. The analysis was stratified on age groups (<65 and ≥ 65 years of age). Only annual incidence rates from 1991 to 2008 were analyzed.

A log-linear Poisson regression model was fitted to weekly incidence rates of stroke in AF patients adjusted for a non-linear trend and a seasonal variation component. The seasonal variation component was specified as a sum of four sinusoids with frequencies one to four [18]. The overall trend was specified as a restricted cubic spline with five knots [19]. As a measurement of the seasonal variation we estimated the peak-to-trough ratio, which is an incidence rate ratio.

A logit-linear logistic regression model was fitted to 30-days case fatality risks, adjusting for a linear trend and modeling an interaction between trend and country.

Assessments of statistically significant interaction between trend and countries were performed by a likelihood ratio test. Tests for overdispersion of Poisson models and goodness of fit, including tests for all models were performed.

P-values less than 5% were considered statistically significant. All analyses were performed in `R` version 2.15.1 [20] using the package `Peak2Trough` [21].

3. Results

Demographic descriptions of the two cohorts are found in Table 1. For the Danish cohort, we identified 243,381 incident hospitalizations with AF for the 29-year period from 1980 to 2008, of which 48% were females. For the New Zealand cohort 51,480 similar subjects were identified for the 18-year period from 1991 to 2008 (48%

females). The median age at time of AF in the Danish cohort was 75.2 years, which was similar to the New Zealand cohort (75.8 years).

The distribution of diagnosis type differed in the two cohorts (Table 1). In both cohorts more than half of AF diagnoses were given as a supplementary diagnosis to a principal diagnosis, with a higher proportion in New Zealand, than in Denmark. The median weekly count of AF hospitalizations in Denmark was 142, whereas in New Zealand the weekly count was 53. There was no significant sex difference in weekly counts between the cohorts.

Differences in comorbidities were apparent between Denmark and New Zealand. In Table 2, characteristics of comorbidities for all AF patients are given. In general, comordibities were more present in the New Zealand cohort compared with the Danish cohort except for diabetes.

Annual incidence rates of AF hospitalizations in Denmark and New Zealand are shown in Figure 1. For both countries, the incidence rates for patients younger than 65 years of age were markedly lower than for patients above 65 years of age. A likelihood ratio test indicates a significant interaction between trend and country, i.e. difference in increase over time in incidence rates between countries, for both age groups (both p-values less than 0.001). In Denmark, the incidence rates increased by 5.0% annually (95% CI: 4.9-5.1%) for patients above 65 years of age compared with only an increase of 2.6% annually (95% CI: 2.4-2.8%) for the same patients in New Zealand. For the younger patients the incidence rates increased by 5.4% annually (95% CI: 5.3-5.7%) in Denmark and 0.2% (95% CI: -0.2-0.58%) in New Zealand.

During follow-up 36,088 subjects were hospitalized with stroke (55.1% females) in the Danish cohort. In New Zealand the figures were 7,518 (54.6% females). The median weekly count of stroke in Denmark was 22 and 7 in New Zealand. Table 3 shows further follow-up characteristics of the two cohorts.

The seasonal variations for both countries estimated by fitting the Poisson regression model and adjusted for an overall trend are shown in Figure 2. Time for seasonal peak in both countries was winter and time for seasonal trough was summer. The peak-to-trough ratio in Denmark was 1.22, i.e. the risk of being hospitalized with stroke in AF patients at peak time in winter is 22% higher compared to summer. In New Zealand the peak-to-trough ratio was 1.27.

Weekly incidence rates of hospitalizations with stroke in AF patients were overall decreasing in both countries during the study period; see Figure 3 which shows the estimated trends. From 1985 to the end of study period the incidence rates in Denmark decreased markedly reaching a plateau of approximately 3.5 hospitalizations per 100 person-years during the period from the mid 1990s to 2000, followed by a further decline. Similarly in New Zealand the incidence rates decrease markedly during the first 14 years from 1991 to 2004.

The 30-days case fatality risks for Denmark and New Zealand are shown in Figure 4. The analysis indicated that the odds ratio for death within 30 days after stroke in AF patients decreased by 1.1% (95% CI: 0.83-1.4%) annually in Denmark. By contrast the odds ratio increased by 0.87% (95% CI: -0.31-2.07%) annually in New Zealand. A likelihood ratio test indicated strong evidence in favor of interaction between trend and country (p=0.002). Overall, the 30-days case fatality risk converged in both countries towards a value of about 20% during the most recent period.

All models were assessed for overdispersion and revealed no indication of such.

4. Discussion

This study shows that stroke remains a common complication of AF. Stroke in AF patients is serious with a 20% 30-days case fatality risk in recent years (2000-08). This study found evidence of a marked seasonal variation in incidence rates of hospitalizations with stroke in AF patients, with a peak in winter and a trough in summer in both countries. The analysis indicated a difference in overall trend in incidence rates of hospitalizations with stroke in AF patients between countries, Denmark tending to have lower incidence rates, compared to New Zealand. In contrast, we showed a highly significant increase in incidence rates of AF over time in both countries. Furthermore, we found differences in the type of diagnoses in the two countries.

The main limitation of this study was inherent to its observational nature. Even though the positive predictive value of the diagnosis of AF is very high in the Danish registry (93%) [22,23], the negative predictive value of such data sources is harder to assess. Consequently, studies based on hospital discharge registries may be affected by misclassification and inclusion bias - for example, by including only patients admitted to hospital with AF we might have increased the proportion of patients who were at higher risk of thromboembolic events and death. The incidence of stroke was defined by the Danish National Registry of Patients, and not all stroke diagnoses were defined by cerebral imaging. The diagnosis of stroke has previously been validated in the Danish registry; with a positive predictive value of ischemic stroke of 97% [24]. Also, we are limited by the inability to differentiate between ischemic and hemorrhagic strokes, but from a Danish stroke registry we know that stroke in patients with AF is predominantly embolic [25]. Stroke in AF patients by definition requires hospitalization and recorded diagnosis for two separate conditions, so trends in incidence rates are determined by factors that affect both of these events and may be complex to interpret. Misclassification or under-reporting of comorbidities, especially hypertension and diabetes, may have occurred [26], and we did not have data on the nature of AF in any of the cohorts. No data exist on the validity of diagnoses on AF and stroke from the National Minimum Dataset in New Zealand. Our study included patients from Denmark and New Zealand, who were treated in different settings and probably with different methods. However, the range of patients was similar regarding age and co-morbid conditions. The nature of exposures was comparable, and the definitions of outcomes were all defined by comparable ICD-coding in the two countries. The differences in health care systems in the two countries can hardly

influence the referral pattern around AF. Furthermore, comparison of the two countries brings forward interesting questions when we compare with similar but smaller studies from other countries.

Consistent with another study we showed that the seasonal variation in incidence rates of hospitalizations stroke in AF patients in both countries was characterized by a peak in winter and trough in summer [16]. This pattern is reported for several other cardiovascular diseases [4–12,15,17]. The previously reported peak-to-trough ratio from Denmark of 1.11 and pattern of seasonality [16] are similar to the results reported in this study, however the peak-to-trough ratio is slightly lower. This may be due to the difference in resolution of data. In the present study weekly incidence rates were analyzed as opposed to monthly incidence rates in Frost et al [16]. The finding that the characteristics of the seasonal variation in both countries are similar may be important in the search for identifying underlying risk factors causing stroke in AF patients. Such factors may be climate factors, e.g. temperature, humidity and hours of sunshine, as well as seasonal variation in occurrences of risk factors for both AF and stroke, e.g. hypertension [27,28] and infectious diseases [29]. The difference in peak-to-trough ratio between two countries, may also lead to the identification of causes that may explain the seasonality, by considering differences between the two countries, for instance climatic differences, housing conditions, and life style patterns [30,31].

The overall trend in weekly incidence rates of hospitalizations with stroke in AF patients in Denmark found in this study show a markedly decrease from late 1980s. During the late eighties and early nineties several studies regarding AF and its potential increasing risk of stroke were published [32,33], which led to introduction of oral anticoagulant treatment [34,35]. This concurrence reveals the prophylactic effects of anticoagulant treatment, preventing AF patients to develop stroke. However, the overall trend in incidence rates of stroke in AF patients in New Zealand indicates that the awareness of AF and its consequences was not as present until the early nineties. Furthermore, this study indicates that the trend in incidence rates in Denmark is decreasing further towards the end of the study period, whereas in New Zealand the trend seems to increase.

The risk of stroke is multi-factorial, and is affected by risk factors such as history of hypertension, current smoking, diet, physical activity, diabetes mellitus, alcohol intake, psychosocial stress and depression, cardiac causes (e.g. AF), and ratio of apolipoproteins B to A1 [36]. Indeed, greater awareness of some risk factors e.g. blood pressure control and smoking cessation may have contributed to a lowering of hospitalizations with stroke in AF patients over this period. Also, a managed care approach to high risk patients (e.g. recent transient ischemic attack) may have led to the reduction in stroke hospitalizations in more recent years [37]. This is clearly a positive observation, given that stroke in AF patients are associated with a higher mortality, as well as a greater morbidity and disability.

Whilst the annual incidence rates of hospitalizations with AF were lower in New Zealand compared with Denmark for both age groups there was still a highly significant increase over time in incidence rates for both countries and both age groups. This is consistent with reported increasing trends in hospitalization for AF in the United States, between 1985 and 1999 [38]. In the analysis by Wattigney et al, US hospitalizations for AF increased dramatically

(2- to 3-fold) in the period 1985-1999. In their study, women were hospitalized with AF more often than men on an annual basis, although the age-standardized prevalence of hospitalizations was greater in men than women. Women hospitalized with AF tended to be older than men, which our results confirm.

Unsurprisingly we found the median age of both Danish and New Zealand cohorts to be similar (approximately 75 years). The incidence rates for patients younger than 65 years of age were much lower than for patients above 65 years of age. Indeed, these observations are consistent with other epidemiological data including analyses of hospitalization data [22,38–40]. There was no significant sex difference in weekly counts in either cohort. Of note, the median weekly count of AF hospitalizations and stroke in AF patients in Denmark were higher than in New Zealand. The reasons for this remain uncertain, but may reflect the different demographic profile, differences in referral patterns and awareness of the disease as well as differences in associated comorbidities. Taking into account the variation in distribution of types of diagnoses of AF, where in New Zealand nearly 70% of the AF diagnoses were in addition to another principal diagnosis, compared with nearly 60% in Denmark, the difference in incidence rates of hospitalizations with AF may be due to differences in the health system in the two countries. In Denmark the health system is funded by taxes, and all contacts with the health system are free of charge for the patient. By contrast, in New Zealand only parts of the health system are fully funded by taxes, notably hospital care, whereas visits to the general practitioner are subject to a small user charge. Given the unspecific symptoms of AF, patients might be less likely to contact their general practitioner when experiencing symptoms with palpitations and shortness of breath. This is supported by the fact that AF patients with stroke often have non-recognized AF [41]. Consequently, a larger proportion of the New Zealand population may be undiagnosed with AF than in Denmark.

In the present study, we found some differences in comorbidities (Table 2). Despite the similar age distribution between countries, especially congestive heart failure was more frequent in the New Zealand cohort and diabetes more frequent in the Danish cohort. This difference may reflect the fact that additional diagnoses for AF are used more frequently in the New Zealand cohort than in the Danish, and may be a random finding in patients referred with symptoms of congestive heart failure.

This study found that there was a minor decrease in the 30-days case fatality risk for stroke in AF patients during the study period in Denmark, but an increase in New Zealand. Our findings indicate that the 30-days case fatality risk in Denmark was higher than in New Zealand until the late nineties, whereas afterwards the difference does not seem evident. This may be due to differences in anticoagulant treatments between the two countries but this also remains tentative.

5. Conclusion

This is the first concurrent analysis of the epidemiology of stroke in AF patients in nationwide population data from two western countries, one in the northern hemisphere and one in the southern hemisphere. We showed that the incidence rates of hospitalization with stroke in AF patients exhibit a marked seasonal variation in both countries, which is characterized by a peak in winter and a trough in summer. Both countries have also shown a downward trend in hospitalizations with stroke in AF patients, despite a pronounced increase in AF hospitalizations. This trend, seasonal variation and differences in comorbidities and distribution of types of diagnoses between the two countries, merit further study. Such research could help us better understand the clinical epidemiology and public health impact of AF and its complications and identify opportunities for better prevention of AF and stroke.

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Table 1: Demographic description of patients with atrial fibrillation in Denmark and New Zealand

	Total		Women		Men	
Denmark						
Number of AF	243,381	(100%)	116,395	(47.8%)	126,986	(52.2%)
Age at AF, years (median (IQR))	75.2	(70.7-84.6)	78.4	(62.4-79.5)	71.9	(62.4-79.5)
AF						
427.31 (ICD-8)	75,739	(31.1%)	37,680	(32.4%)	38,059	(30.0%)
427.32 (ICD-8)	7,050	(2.9%)	2,834	(2.4%)	4,216	(3.3%)
I48 (ICD-10)	160,592	(66.0%)	75,81	(65.2%)	84,711	(66.7%)
Diagnosis type						
Principal	103,846	(42.7%)	47,585	(40.9%)	56,261	(44.3%)
Additional	139,535	(57.3%)	68,810	(59.1%)	70,725	(55.7%)
Weekly counts (median (IQR))	142	(99-211)	69	(48-99)	74	(50-112)
New Zealand						
Number of AF	51,480	(100%)	24,883	(48.3%)	26,597	(51.7%)
Age at AF, years (median (IQR))	75.8	(70.4-84.3)	78.1	(65.0-80.3)	73.6	(65.0-80.3)
AF						
427.93 (ICD-9)	17,705	(34.4%)	8,682	(34.9%)	9,023	(33.9%)
427.94 (ICD-9)	1,389	(2.7%)	515	(2.1%)	874	(3.3%)
I48 (ICD-10)	32,386	(62.9%)	15,686	(63.0%)	16,700	(62.8%)
Diagnosis type						
Principal	15,501	(30.1%)	7,810	(31.4%)	7,692	(28.9%)
Additional	35,978	(69.9%)	17,073	(68.6%)	18,905	(71.1%)
Weekly counts (median (IQR))	53	(41-63)	25	(19-31)	27	(21-33)

AF: Atrial fibrillation, ICD: International Classification of Diseases, IQR: Inter quartile range

Table 2: Comorbidities and age distribution among patients hospitalized with atrial fibrillation having at least one comorbid disorder in Denmark and New Zealand

	Denmark	New Zealand
Characteristics		
Percentage of all patients with AF having at least one comorbid disorder	32.5	53.3
Age, years (at time of AF)		
Age ≥75 years	50.7	52.8
Age 65-74	26.6	27.1
Women	47.8	48.3
Congestive heart failure	9.6	28.4
Hypertension	11.5	11.9
Diabetes	6.2	4.4
Acute myocardial infarction	10.3	15.5
Peripheral arterial disease	3.5	5.8
Coronary artery disease	11.2	16.8

The comorbid conditions were registered if they preceded an incident diagnosis of AF.

Data are percentages.

Table 3: Demographic description of patients with stroke having atrial fibrillation in Denmark and New Zealand

	Total		Women		Men	
Denmark						
Number of strokes	36,088	(100%)	19,872	(55%)	16,216	(45%)
Age at stroke, years (median (IQR))	79.5	(76.0-86.4)	81.6	(69.8-82.4)	76.7	(69.8-82.4)
Stroke						
433 (ICD-8)	2,452	(6.8%)	1,279	(6.4%)	1,173	(7.2%)
434 (ICD-8)	1,139	(3.2%)	556	(2.8%)	583	(3.6%)
436 (ICD-8)	8,274	(22.9%)	4,730	(23.8%)	3,544	(21.9%)
I63 (ICD-10)	9,771	(27.1%)	5,262	(26.5%)	4,509	(27.8%)
I64 (ICD-10)	14,452	(40.0%)	8,045	(40.5%)	6,407	(39.5%)
Diagnosis type						
Principal	27,094	(75.1%)	15,110	(76.0%)	11,984	(73.9%)
Additional	8,994	(24.9%)	4,762	(24.0%)	4,232	(26.1%)
Weekly counts (median (IQR))	22	(14-31)	12	(8-17)	10	(6-14)
Time to stroke, days (median (IQR))	380	(0-1572)	365	(0-1528)	397	(0-1634)
New Zealand						
Number of strokes	7,518	(100%)	4,104	(54.6%)	3,414	(45.4%)
Age at stroke, years (median (IQR))	80.0	(75.5-86.7)	81.8	(70.8-83.7)	77.9	(70.8-83.7)
Stroke						
433 (ICD-9)	109	(1.4%)	43	(1%)	66	(1.9%)
434 (ICD-9)	654	(8.7%)	337	(8.2%)	317	(9.3%)
436 (ICD-9)	1,288	(17.1%)	709	(17.3%)	579	(17.0%)
I63 (ICD-10)	3,581	(47.6%)	1,999	(48.7%)	1,582	(46.3%)
I64 (ICD-10)	1,886	(25.1%)	1,016	(24.8%)	870	(25.5%)
Diagnosis type						
Principal	5,916	(78.7%)	3,227	(78.6%)	2,689	(78.8%)
Additional	1,602	(21.3%)	877	(21.4%)	725	(21.2%)
Weekly counts (median (IQR))	7	(5-10)	4	(2-6)	3	(2-5)
Time to stroke, days (median (IQR))	645	(14-1776)	641	(17-1749)	654	(10-1814)

AF: atrial fibrillation, ICD: International Classification of Diseases, IQR: Inter quartile range

Figure 1: Observed incidence rates of first-time hospitalizations with a principal or additional diagnosis of atrial fibrillation per 1,000 person-years for the Danish and New Zealand population.

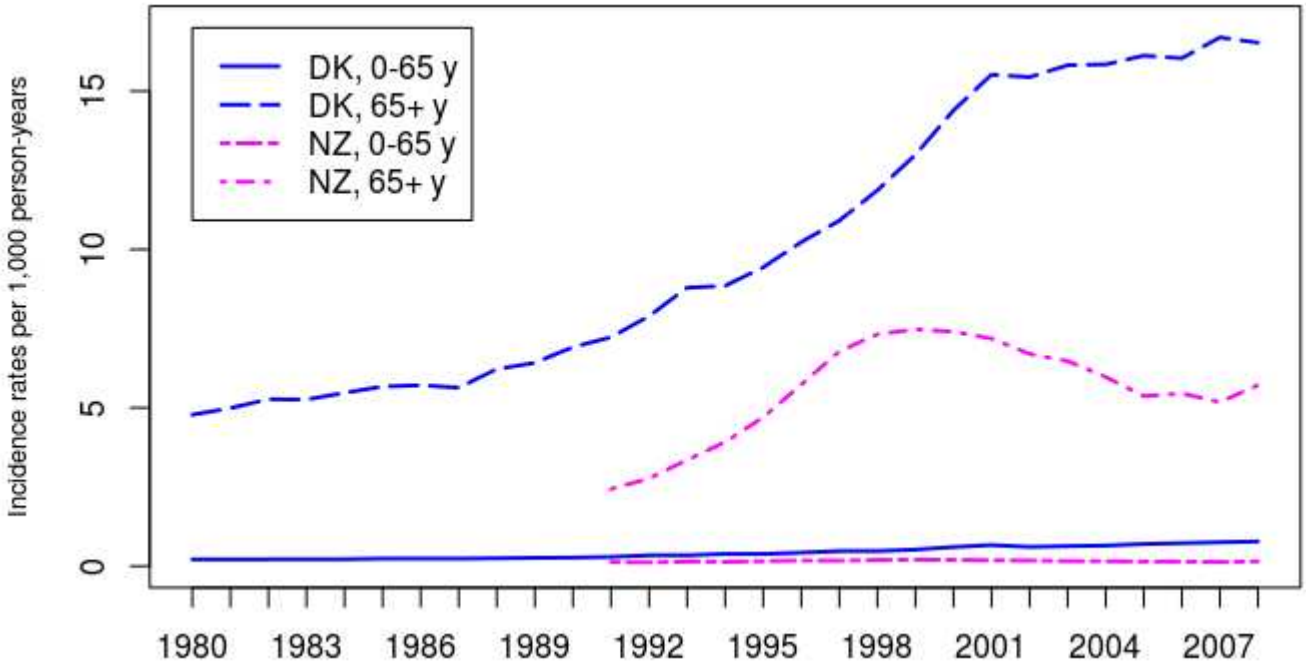


Figure 2: Estimated seasonal variation in incidence rates of hospitalisations with stroke in patients with atrial fibrillation in Denmark (solid line) and New Zealand (dashed line) adjusted for overall trend. The seasonal variation is represented as the percentual deviation in incidence rates from annual median, and incidence rates are aggregated to weekly observations. Shaded bands represent 95% confidence intervals.

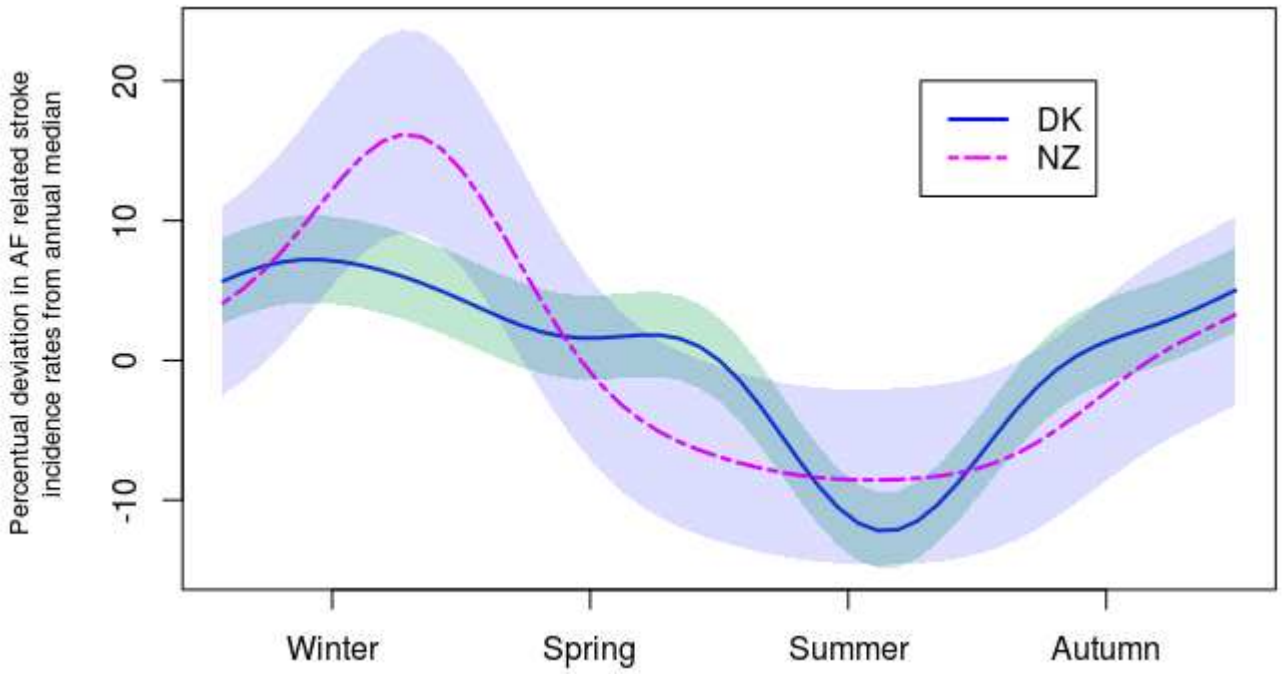


Figure 3: Estimated overall trend of Danish (solid line) and New Zealand (dashed line) weekly incidence rates of hospitalisations with stroke in atrial fibrillation patients per 100 person-years adjusted for seasonality. Shaded bands represent 95% confidence intervals.

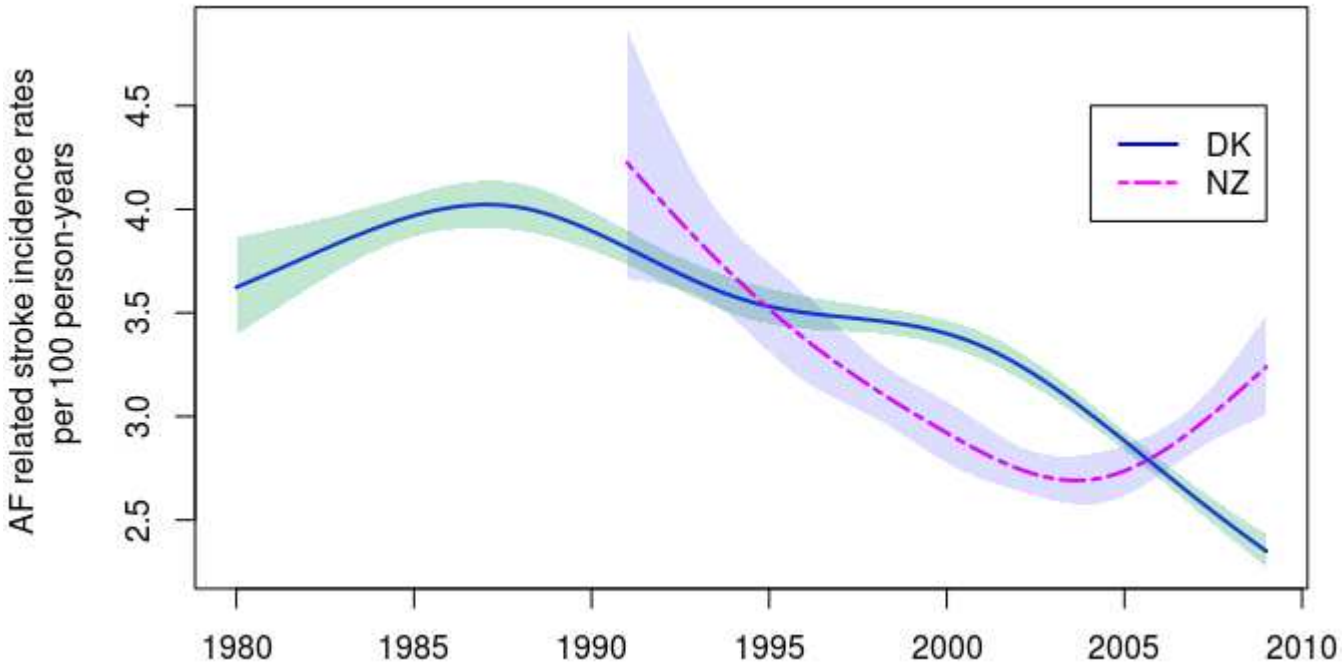
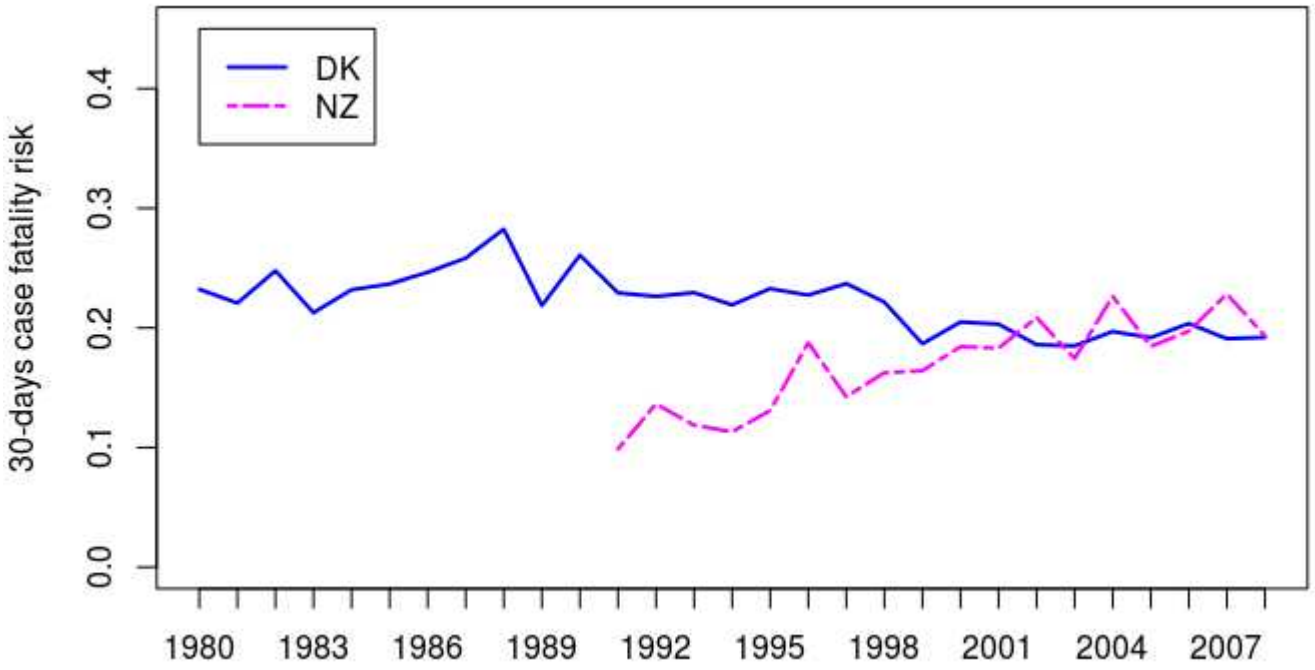


Figure 4: Observed 30-days case fatality risk for stroke in atrial fibrillation patients in Denmark and New Zealand



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Seasonal variation and trend in hospital admissions for stroke in patients with atrial fibrillation in Denmark and New Zealand: analysis of hospital discharge data from 1977 to 2008

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Seasonality, incidence and prognosis in atrial fibrillation and stroke in Denmark and New Zealand

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Abstract:

Objectives: There are relatively few large studies of seasonal variation in the occurrence of stroke in patients with AF. We investigated the seasonal variation in incidence rates of hospitalizations with stroke in patients from Denmark and New Zealand.

Design: Cohort study.

Setting: Nationwide hospital discharge data from Denmark and New Zealand.

Participants: 243,381 (median age 75) subjects having a first-time hospitalization with AF in Denmark and 51,480 (median age 76) subjects in New Zealand constituted the study population. Subjects with previous hospitalization with stroke were excluded.

Primary and secondary effect measures: Peak-to-trough ratio of the seasonal variation in weekly incidence rates of stroke in AF patients adjusted for an overall trend was primary effect measure and was assessed using a log-linear Poisson regression model. Secondary effect measures were incidence rate ratios of AF and 30-days case fatality for stroke patients.

Results: Incidence rates of AF per 1,000 person-years in Denmark increased by 5.4% (95%CI: 5.3-5.7%) for patients aged <65 and 5.0% (95%CI: 4.9-5.1%) for patients aged ≥65, whereas the increase was 0.2% (95%CI: -0.2-0.6%) for patients aged <65 and 2.6% (95%CI: 2.4-2.8%) for patients aged ≥65 in New Zealand. In Denmark 36,088 subjects were hospitalized with stroke, and 7,518 subjects in New Zealand, both showing peaks during winter with peak-to-trough ratios of 1.22 and 1.27, respectively and a decreasing trend. The 30-days case fatality risk for stroke patients having AF is now (2000-08) about 20% in both countries.

Conclusions: Although incidence rates of hospitalizations with stroke in patients with AF have decreased in recent years, this remains a common AF complication with a high case fatality risk. The marked winter peak in incidence rates of hospitalization with stroke in AF patients suggests that there are opportunities to reduce this complication. Further studies are necessary to identify how to optimize treatment of AF and prevention of stroke.

Article Focus:

Explore trends in incidence rates of atrial fibrillation in the entire Danish and New Zealand population.

Estimate the peak-to-trough ratio of hospitalisations with stroke in atrial fibrillation patients in a cohort study design based on discharge data from Denmark and New Zealand using a log-linear Poisson regression model adjusted for an overall trend.

Estimate 30-days case fatality risks for stroke in atrial fibrillation patients in Denmark and New Zealand.

Key Messages:

The incidence rates of atrial fibrillation in entire Danish and New Zealand population have increased since start of registration of hospitalisations until 2008.

Hospitalisations with stroke in atrial fibrillation patients show similar seasonal variation with a peak during winter and trough during summer in countries in opposite hemispheres.

The 30-days case fatality risk for stroke in atrial fibrillation patients seems to have been at a constant level during 2000-2008.

Strengths and limitations:

The main strength of this study is that study cohort is based on two entire national populations.

The main limitation of this study was inherent to its observational nature since the negative predictive value of discharge data may not be assessed.

The cohort study design indicates associations to be explored further to identify causality trough randomised controlled studies.

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, and is associated with a substantial risk of mortality and morbidity from thromboembolism and especially thromboembolic stroke. Well-established risk factors for stroke in AF patients are prior stroke, advanced age, hypertension, diabetes mellitus, moderate-severe systolic dysfunction and vascular disease [1–3].

A seasonal variation in acute presentation with various cardiovascular disorders has been reported, with data on acute presentations with myocardial infarction, sudden death, rupture/dissection of aortic aneurysms, heart failure hospitalizations and venous thromboembolism [4–9] all showing a seasonal peak during winter. Acute stroke and transient ischemic attack show a similar pattern [10,11].

In addition, a seasonal variation in paroxysmal AF has been documented by 24-hour Holter electrocardiogram, with maximum and minimum incidences in autumn and summer, respectively [12]. It has been suggested that AF hospital admissions may also exhibit a seasonal variation, with the risk being modestly higher during the winter and inversely associated with outdoor temperature [13]. Nonetheless, this effect may be small and has been considered unlikely to be significant for policy or etiological research purposes [14]. However, this may reflect the limitations of relatively small single centre studies, and large "real world" population-based analyses may be needed. Indeed, using the linked Scottish Morbidity Record scheme between 1990 and 1996, there was a total of 33,582 male and 34,463 female AF hospitalizations, which showed a substantial seasonal variation in AF hospitalizations and deaths, particularly in the elderly [15].

Few studies exist on seasonal variation in occurrences of stroke and mortality risk after stroke in patients with AF. One analysis from the Danish National Registry of Patients has previously found a seasonal variation in stroke occurrence in patients with non-valvular AF but no effect of season on mortality after stroke [16]. One small series of approximately 300 Greek patients with first-ever cardio embolic acute stroke due to AF also revealed a seasonal peak during winter and a decline of stroke occurrence during summer [17].

Assuming a seasonal variation in hospital admissions with stroke in patients with AF, we would expect to see similar temporal patterns in countries from different parts of the world. However, we are unaware of any data comparing seasonal changes over a comparable time period between two countries, irrespective of seasonality shift by being in the northern or southern hemisphere. In this study we described the occurrences of hospitalizations with stroke in patients with AF, including estimating the seasonal variation in the two countries investigating the temporal patterns from the northern and southern hemisphere. Furthermore, we described the overall trend in incidence rates of hospitalization admissions for both AF and stroke in patients with AF over a twenty year period. Differences in annual 30-days case fatality risks between countries were also assessed.

2. Material and methods

2.1 Study Period and Study Population

The study period in Denmark was from 1 January 1977 and in New Zealand from 1 January 1988, both to 31 December 2008. Hospitalisations with first time non-valvular AF and stroke were recorded using the International Classification of Diseases (ICD). Both principal and additional diagnoses were included for analysis. No discrimination was made between ischemic or hemorrhagic strokes.

The Danish cohort was identified in the Danish National Registry of Patients, starting in 1977, using the Danish Personal Identification number. This is a unique and national identification number which is part of the personal information stored in the Civil Registration System. The Danish study population in the present study included Danish residents who developed incident AF from 1977 to 2008. ICD codes were used to extract admissions for AF. The 8th revision (ICD-8) was used until 1994, and after 1994 the 10th revision (ICD-10) was used. AF and atrial flutter were coded separately in ICD-8 (codes 427.93 and 427.94), whereas in ICD-10, AF and atrial flutter have a single ICD code (I48). Therefore, atrial flutter cases have also been included in the present study. In Denmark, incidences of stroke were found in the Danish National Registry of Patients, using ICD-8 (433, 434, and 436) and ICD-10 (I63, I64). To reduce inclusion of prevalent cases of both AF and stroke in AF patients, identified cases before 1980 were excluded from the analyses for the Danish cohort.

The cohort from New Zealand was identified from 1988 to 2008, using the National Minimum Dataset. The National Minimum Dataset, managed by the New Zealand Ministry of Health, holds information on all publicly funded hospitalizations in New Zealand. Each hospitalization is linked with the patient's National Health Index (NHI) number, which is a unique number provided to each person using health and disability support services in New Zealand. This index is stored in the NHI database along with demographic details of the person. In the National Minimum Dataset ICD 9th revision (ICD-9) was used until June 1999, and after that ICD-10 was used. Similar to the Danish data, AF and atrial flutter were coded separately in ICD-9 (codes 427.31 and 427.32), whereas in ICD-10, AF and atrial flutter have a single ICD code (I48). In New Zealand, incidences of stroke were found in the National Minimum Dataset using ICD-9 (433, 434, 436) and ICD-10 (I63, I64). To avoid including prevalent cases of both AF and stroke in AF patients, identified cases before 1991 were excluded from the analyses for the New Zealand cohort.

In Denmark annual population figures were obtained from Statistics Denmark, whereas in New Zealand only five-year population figures were available from Statistics New Zealand starting from 1996. Annual estimates for the New Zealand population from 1988 to 2008 were obtained by linear inter- and extrapolation.

Comorbidities were assessed by identifying hospitalizations with either congestive heart failure (ICD8: 427.09, 428, ICD9: 428, ICD10: I11.09, I50), hypertension (ICD8: 400-404, ICD9: 401-405, ICD10: I10-I13, I15),

diabetes (ICD8: 249, 250, ICD9: 250, ICD10: E11, E14), acute myocardial infarction (ICD8: 410, ICD9: 410, ICD10: I21, I22), peripheral artery disease (ICD8: 440.2, 443, 444, ICD9: 440, 443, 444, ICD10: I70.2, I73.9, I74.5), or coronary artery disease (ICD8: 412, ICD9: 414, ICD10: I25.1). One subject may have more than one comorbidity.

2.2 Statistical analysis

We define three effect measures for analyses. First, incidence rates of AF, defined as the annual number of hospitalizations with AF divided by the annual population size. Second, weekly incidence rates of stroke in AF patients defined as the weekly number of first time hospitalizations with stroke having previous hospital admissions for AF divided by the weekly person-time at risk i.e. for a given week the number of AF patients with no previous stroke. Third, 30-days case fatality risk, defined as the annual number of death among stroke patients having AF divided by the annual number of stroke patients having AF.

A log-linear Poisson regression model was fitted to incidence rates of AF, adjusting for a linear trend and modeling an interaction between trend and country. The analysis was stratified on age groups (<65 and ≥ 65 years of age). Only annual incidence rates from 1991 to 2008 were analyzed.

A log-linear Poisson regression model was fitted to weekly incidence rates of stroke in AF patients adjusted for a non-linear trend and a seasonal variation component. The seasonal variation component was specified as a sum of four sinusoids with frequencies one to four [18]. The overall trend was specified as a restricted cubic spline with five knots [19]. As a measurement of the seasonal variation we estimated the peak-to-trough ratio, which is an incidence rate ratio.

A logit-linear logistic regression model was fitted to 30-days case fatality risks, adjusting for a linear trend and modeling an interaction between trend and country.

Assessments of statistically significant interaction between trend and countries were performed by a likelihood ratio test. Tests for overdispersion of Poisson models and goodness of fit, including tests for all models were performed.

P-values less than 5% were considered statistically significant. All analyses were performed in `R` version 2.15.1 [20] using the package `Peak2Trough` [21].

3. Results

Demographic descriptions of the two cohorts are found in Table 1. For the Danish cohort, we identified 243,381 incident hospitalizations with AF for the 29-year period from 1980 to 2008, of which 48% were females. For the New Zealand cohort 51,480 similar subjects were identified for the 18-year period from 1991 to 2008 (48%

females). The median age at time of AF in the Danish cohort was 75.2 years, which was similar to the New Zealand cohort (75.8 years).

The distribution of diagnosis type differed in the two cohorts (Table 1). In both cohorts more than half of AF diagnoses were given as a supplementary diagnosis to a principal diagnosis, with a higher proportion in New Zealand, than in Denmark. The median weekly count of AF hospitalizations in Denmark was 142, whereas in New Zealand the weekly count was 53. There was no significant sex difference in weekly counts between the cohorts.

Differences in comorbidities were apparent between Denmark and New Zealand. In Table 2, characteristics of comorbidities for all AF patients are given. In general, comordibities were more present in the New Zealand cohort compared with the Danish cohort except for diabetes.

Incidence rates of AF hospitalizations in Denmark and New Zealand per 1,000 person-years are shown in Figure 1. For both countries, the incidence rates for patients younger than 65 years of age were markedly lower than for patients above 65 years of age. A likelihood ratio test indicates a significant interaction between trend and country, i.e. difference in increase over time in incidence rates between countries, for both age groups (both p-values less than 0.001). In Denmark, the incidence rates increased by 5.0% annually (95% CI: 4.9-5.1%) for patients above 65 years of age compared with only an increase of 2.6% annually (95% CI: 2.4-2.8%) for the same patients in New Zealand. For the younger patients the incidence rates increased by 5.4% annually (95% CI: 5.3-5.7%) in Denmark and 0.2% (95% CI: -0.2-0.58%) in New Zealand.

During follow-up 36,088 subjects were hospitalized with stroke (55.1% females) in the Danish cohort. In New Zealand the figures were 7,518 (54.6% females). The median weekly count of stroke in Denmark was 22 and 7 in New Zealand. Table 3 shows further follow-up characteristics of the two cohorts.

The seasonal variations for both countries estimated by fitting the Poisson regression model and adjusted for an overall trend are shown in Figure 2. Time for seasonal peak in both countries was winter and time for seasonal trough was summer. The peak-to-trough ratio in Denmark was 1.22, i.e. the risk of being hospitalized with stroke in AF patients at peak time in winter is 22% higher compared to summer. In New Zealand the peak-to-trough ratio was 1.27.

Weekly incidence rates of hospitalizations with stroke in AF patients were overall decreasing in both countries during the study period; see Figure 3 which shows the estimated trends. From 1985 to the end of study period the incidence rates in Denmark decreased markedly reaching a plateau of approximately 3.5 hospitalizations per 100 person-years during the period from the mid 1990s to 2000, followed by a further decline. Similarly in New Zealand the incidence rates decrease markedly during the first 14 years from 1991 to 2004.

The 30-days case fatality risks for Denmark and New Zealand are shown in Figure 4. The analysis indicated that the odds ratio for death within 30 days after stroke in AF patients decreased by 1.1% (95% CI: 0.83-1.4%) annually in Denmark. By contrast the odds ratio increased by 0.87% (95% CI: -0.31-2.07%) annually in New Zealand. A likelihood ratio test indicated strong evidence in favor of interaction between trend and country (p=0.002). Overall, the 30-days case fatality risk converged in both countries towards a value of about 20% during the most recent period.

All models were assessed for overdispersion and revealed no indication of such.

4. Discussion

This study shows that stroke remains a common complication of AF. Stroke in AF patients is serious with a 20% 30-days case fatality risk in recent years (2000-08). This study found evidence of a marked seasonal variation in incidence rates of hospitalizations with stroke in AF patients, with a peak in winter and a trough in summer in both countries. The analysis indicated a difference in overall trend in incidence rates of hospitalizations with stroke in AF patients between countries, Denmark tending to have lower incidence rates, compared to New Zealand. In contrast, we showed a highly significant increase in incidence rates of AF over time in both countries. Furthermore, we found differences in the type of diagnoses in the two countries.

The main limitation of this study was inherent to its observational nature. Even though the positive predictive value of the diagnosis of AF is very high in the Danish registry (93%) [22,23], the negative predictive value of such data sources is harder to assess. Consequently, studies based on hospital discharge registries may be affected by misclassification and inclusion bias - for example, by including only patients admitted to hospital with AF we might have increased the proportion of patients who were at higher risk of thromboembolic events and death. The incidence of stroke was defined by the Danish National Registry of Patients, and not all stroke diagnoses were defined by cerebral imaging. The diagnosis of stroke has previously been validated in the Danish registry; with a positive predictive value of ischemic stroke of 97% [24]. Also, we are limited by the inability to differentiate between ischemic and hemorrhagic strokes, but from a Danish stroke registry we know that stroke in patients with AF is predominantly embolic [25]. Stroke in AF patients by definition requires hospitalization and recorded diagnosis for two separate conditions, so trends in incidence rates are determined by factors that affect both of these events and may be complex to interpret. Misclassification or under-reporting of comorbidities, especially hypertension and diabetes, may have occurred [26], and we did not have data on the nature of AF in any of the cohorts. No data exist on the validity of diagnoses on AF and stroke from the National Minimum Dataset in New Zealand. Our study included patients from Denmark and New Zealand, who were treated in different settings and probably with different methods. However, the range of patients was similar regarding age and co-morbid conditions. The nature of exposures was comparable, and the definitions of outcomes were all defined by comparable ICD-coding in the two countries. The differences in health care systems in the two countries can hardly

influence the referral pattern around AF. Furthermore, comparison of the two countries brings forward interesting questions when we compare with similar but smaller studies from other countries.

Consistent with another study we showed that the seasonal variation in incidence rates of hospitalizations stroke in AF patients in both countries was characterized by a peak in winter and trough in summer [16]. This pattern is reported for several other cardiovascular diseases [4–12,15,17]. The previously reported peak-to-trough ratio from Denmark of 1.11 and pattern of seasonality [16] are similar to the results reported in this study, however the peak-to-trough ratio is slightly lower. This may be due to the difference in resolution of data. In the present study weekly incidence rates were analyzed as opposed to monthly incidence rates in Frost et al [16]. The finding that the characteristics of the seasonal variation in both countries are similar may be important in the search for identifying underlying risk factors causing stroke in AF patients. Such factors may be climate factors, e.g. temperature, humidity and hours of sunshine, as well as seasonal variation in occurrences of risk factors for both AF and stroke, e.g. hypertension [27,28] and infectious diseases [29]. The difference in peak-to-trough ratio between two countries, may also lead to the identification of causes that may explain the seasonality, by considering differences between the two countries, for instance climatic differences, housing conditions, and life style patterns [30,31].

The overall trend in weekly incidence rates of hospitalizations with stroke in AF patients in Denmark found in this study show a markedly decrease from late 1980s. During the late eighties and early nineties several studies regarding AF and its potential increasing risk of stroke were published [32,33], which led to introduction of oral anticoagulant treatment [34,35]. This concurrence reveals the prophylactic effects of anticoagulant treatment, preventing AF patients to develop stroke. However, the overall trend in incidence rates of stroke in AF patients in New Zealand indicates that the awareness of AF and its consequences was not as present until the early nineties. Furthermore, this study indicates that the trend in incidence rates in Denmark is decreasing further towards the end of the study period, whereas in New Zealand the trend seems to increase.

The risk of stroke is multi-factorial, and is affected by risk factors such as history of hypertension, current smoking, diet, physical activity, diabetes mellitus, alcohol intake, psychosocial stress and depression, cardiac causes (e.g. AF), and ratio of apolipoproteins B to A1 [36]. Indeed, greater awareness of some risk factors e.g. blood pressure control and smoking cessation may have contributed to a lowering of hospitalizations with stroke in AF patients over this period. Also, a managed care approach to high risk patients (e.g. recent transient ischemic attack) may have led to the reduction in stroke hospitalizations in more recent years [37]. This is clearly a positive observation, given that stroke in AF patients are associated with a higher mortality, as well as a greater morbidity and disability.

Whilst the annual incidence rates of hospitalizations with AF were lower in New Zealand compared with Denmark for both age groups there was still a highly significant increase over time in incidence rates for both countries and both age groups. This is consistent with reported increasing trends in hospitalization for AF in the United States, between 1985 and 1999 [38]. In the analysis by Wattigney et al, US hospitalizations for AF increased dramatically

(2- to 3-fold) in the period 1985-1999. In their study, women were hospitalized with AF more often than men on an annual basis, although the age-standardized prevalence of hospitalizations was greater in men than women. Women hospitalized with AF tended to be older than men, which our results confirm.

Unsurprisingly we found the median age of both Danish and New Zealand cohorts to be similar (approximately 75 years). The incidence rates for patients younger than 65 years of age were much lower than for patients above 65 years of age. Indeed, these observations are consistent with other epidemiological data including analyses of hospitalization data [22,38–40]. There was no significant sex difference in weekly counts in either cohort. Of note, the median weekly count of AF hospitalizations and stroke in AF patients in Denmark were higher than in New Zealand. The reasons for this remain uncertain, but may reflect the different demographic profile, differences in referral patterns and awareness of the disease as well as differences in associated comorbidities. Taking into account the variation in distribution of types of diagnoses of AF, where in New Zealand nearly 70% of the AF diagnoses were in addition to another principal diagnosis, compared with nearly 60% in Denmark, the difference in incidence rates of hospitalizations with AF may be due to differences in the health system in the two countries. In Denmark the health system is funded by taxes, and all contacts with the health system are free of charge for the patient. By contrast, in New Zealand only parts of the health system are fully funded by taxes, notably hospital care, whereas visits to the general practitioner are subject to a small user charge. Given the unspecific symptoms of AF, patients might be less likely to contact their general practitioner when experiencing symptoms with palpitations and shortness of breath. This is supported by the fact that AF patients with stroke often have non-recognized AF [41]. Consequently, a larger proportion of the New Zealand population may be undiagnosed with AF than in Denmark.

In the present study, we found some differences in comorbidities (Table 2). Despite the similar age distribution between countries, especially congestive heart failure was more frequent in the New Zealand cohort and diabetes more frequent in the Danish cohort. This difference may reflect the fact that additional diagnoses for AF are used more frequently in the New Zealand cohort than in the Danish, and may be a random finding in patients referred with symptoms of congestive heart failure.

This study found that there was a minor decrease in the 30-days case fatality risk for stroke in AF patients during the study period in Denmark, but an increase in New Zealand. Our findings indicate that the 30-days case fatality risk in Denmark was higher than in New Zealand until the late nineties, whereas afterwards the difference does not seem evident. This may be due to differences in anticoagulant treatments between the two countries but this also remains tentative.

5. Conclusion

This is the first concurrent analysis of the epidemiology of stroke in AF patients in nationwide population data from two western countries, one in the northern hemisphere and one in the southern hemisphere. We showed that the incidence rates of hospitalization with stroke in AF patients exhibit a marked seasonal variation in both countries, which is characterized by a peak in winter and a trough in summer. Both countries have also shown a downward trend in hospitalizations with stroke in AF patients, despite a pronounced increase in AF hospitalizations. This trend, seasonal variation and differences in comorbidities and distribution of types of diagnoses between the two countries, merit further study. Such research could help us better understand the clinical epidemiology and public health impact of AF and its complications and identify opportunities for better prevention of AF and stroke.

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Table 1: Demographic description of patients with atrial fibrillation in Denmark and New Zealand

	Total		Women		Men	
Denmark						
Number of AF	243,381	(100%)	116,395	(47.8%)	126,986	(52.2%)
Age at AF, years (median (IQR))	75.2	(70.7-84.6)	78.4	(62.4-79.5)	71.9	(62.4-79.5)
AF						
427.31 (ICD-8)	75,739	(31.1%)	37,680	(32.4%)	38,059	(30.0%)
427.32 (ICD-8)	7,050	(2.9%)	2,834	(2.4%)	4,216	(3.3%)
I48 (ICD-10)	160,592	(66.0%)	75,81	(65.2%)	84,711	(66.7%)
Diagnosis type						
Principal	103,846	(42.7%)	47,585	(40.9%)	56,261	(44.3%)
Additional	139,535	(57.3%)	68,810	(59.1%)	70,725	(55.7%)
Weekly counts (median (IQR))	142	(99-211)	69	(48-99)	74	(50-112)
New Zealand						
Number of AF	51,480	(100%)	24,883	(48.3%)	26,597	(51.7%)
Age at AF, years (median (IQR))	75.8	(70.4-84.3)	78.1	(65.0-80.3)	73.6	(65.0-80.3)
AF						
427.93 (ICD-9)	17,705	(34.4%)	8,682	(34.9%)	9,023	(33.9%)
427.94 (ICD-9)	1,389	(2.7%)	515	(2.1%)	874	(3.3%)
I48 (ICD-10)	32,386	(62.9%)	15,686	(63.0%)	16,700	(62.8%)
Diagnosis type						
Principal	15,501	(30.1%)	7,810	(31.4%)	7,692	(28.9%)
Additional	35,978	(69.9%)	17,073	(68.6%)	18,905	(71.1%)
Weekly counts (median (IQR))	53	(41-63)	25	(19-31)	27	(21-33)

AF: Atrial fibrillation, ICD: International Classification of Diseases, IQR: Inter quartile range

Table 2: Comorbidities and age distribution among patients hospitalized with atrial fibrillation having at least one comorbid disorder in Denmark and New Zealand

	Denmark	New Zealand
Characteristics		
Percentage of all patients with AF having at least one comorbid disorder	32.5	53.3
Age, years (at time of AF)		
Age ≥75 years	50.7	52.8
Age 65-74	26.6	27.1
Women	47.8	48.3
Congestive heart failure	9.6	28.4
Hypertension	11.5	11.9
Diabetes	6.2	4.4
Acute myocardial infarction	10.3	15.5
Peripheral arterial disease	3.5	5.8
Coronary artery disease	11.2	16.8

The comorbid conditions were registered if they preceded an incident diagnosis of AF.

Data are percentages.

Table 3: Demographic description of patients with stroke having atrial fibrillation in Denmark and New Zealand

	Total		Women		Men	
Denmark						
Number of strokes	36,088	(100%)	19,872	(55%)	16,216	(45%)
Age at stroke, years (median (IQR))	79.5	(76.0-86.4)	81.6	(69.8-82.4)	76.7	(69.8-82.4)
Stroke						
433 (ICD-8)	2,452	(6.8%)	1,279	(6.4%)	1,173	(7.2%)
434 (ICD-8)	1,139	(3.2%)	556	(2.8%)	583	(3.6%)
436 (ICD-8)	8,274	(22.9%)	4,730	(23.8%)	3,544	(21.9%)
I63 (ICD-10)	9,771	(27.1%)	5,262	(26.5%)	4,509	(27.8%)
I64 (ICD-10)	14,452	(40.0%)	8,045	(40.5%)	6,407	(39.5%)
Diagnosis type						
Principal	27,094	(75.1%)	15,110	(76.0%)	11,984	(73.9%)
Additional	8,994	(24.9%)	4,762	(24.0%)	4,232	(26.1%)
Weekly counts (median (IQR))	22	(14-31)	12	(8-17)	10	(6-14)
Time to stroke, days (median (IQR))	380	(0-1572)	365	(0-1528)	397	(0-1634)
New Zealand						
Number of strokes	7,518	(100%)	4,104	(54.6%)	3,414	(45.4%)
Age at stroke, years (median (IQR))	80.0	(75.5-86.7)	81.8	(70.8-83.7)	77.9	(70.8-83.7)
Stroke						
433 (ICD-9)	109	(1.4%)	43	(1%)	66	(1.9%)
434 (ICD-9)	654	(8.7%)	337	(8.2%)	317	(9.3%)
436 (ICD-9)	1,288	(17.1%)	709	(17.3%)	579	(17.0%)
I63 (ICD-10)	3,581	(47.6%)	1,999	(48.7%)	1,582	(46.3%)
I64 (ICD-10)	1,886	(25.1%)	1,016	(24.8%)	870	(25.5%)
Diagnosis type						
Principal	5,916	(78.7%)	3,227	(78.6%)	2,689	(78.8%)
Additional	1,602	(21.3%)	877	(21.4%)	725	(21.2%)
Weekly counts (median (IQR))	7	(5-10)	4	(2-6)	3	(2-5)
Time to stroke, days (median (IQR))	645	(14-1776)	641	(17-1749)	654	(10-1814)

AF: atrial fibrillation, ICD: International Classification of Diseases, IQR: Inter quartile range

Figure 1: Observed incidence rates of first-time hospitalizations with a principal or additional diagnosis of atrial fibrillation per 1,000 person-years for the Danish and New Zealand population.

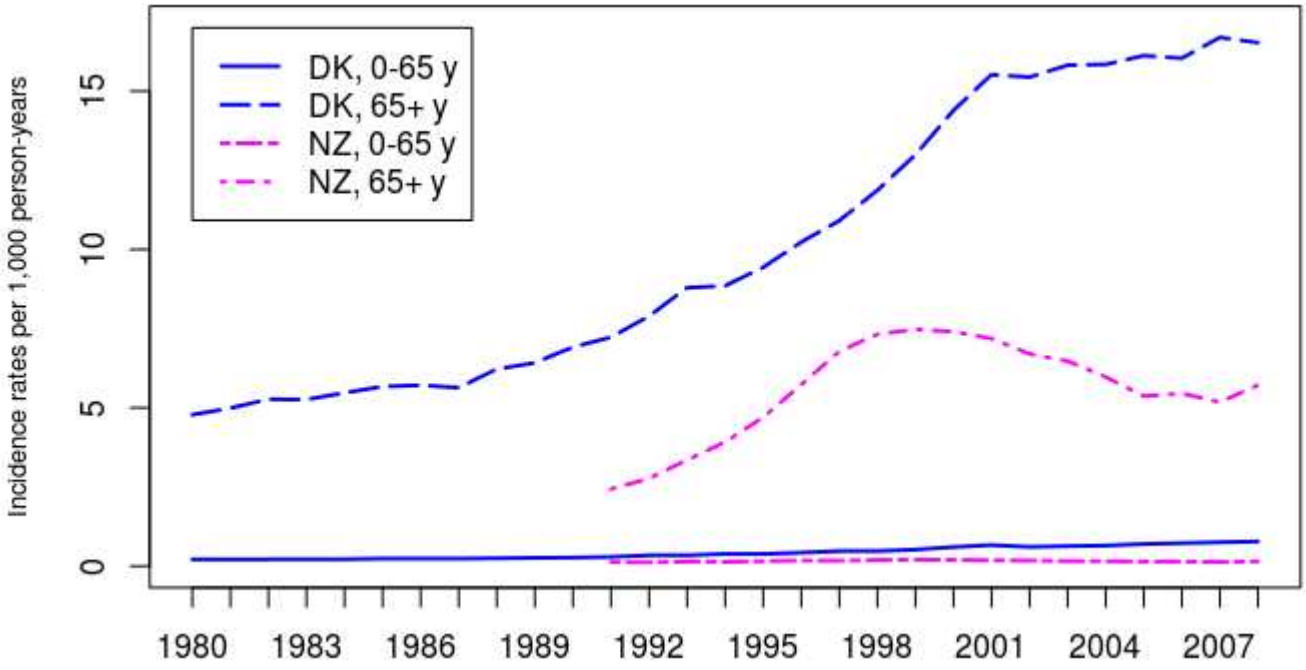


Figure 2: Estimated seasonal variation in incidence rates of hospitalisations with stroke in patients with atrial fibrillation in Denmark (solid line) and New Zealand (dashed line) adjusted for overall trend. The seasonal variation is represented as the percentual deviation in incidence rates from annual median, and incidence rates are aggregated to weekly observations. Shaded bands represent 95% confidence intervals.

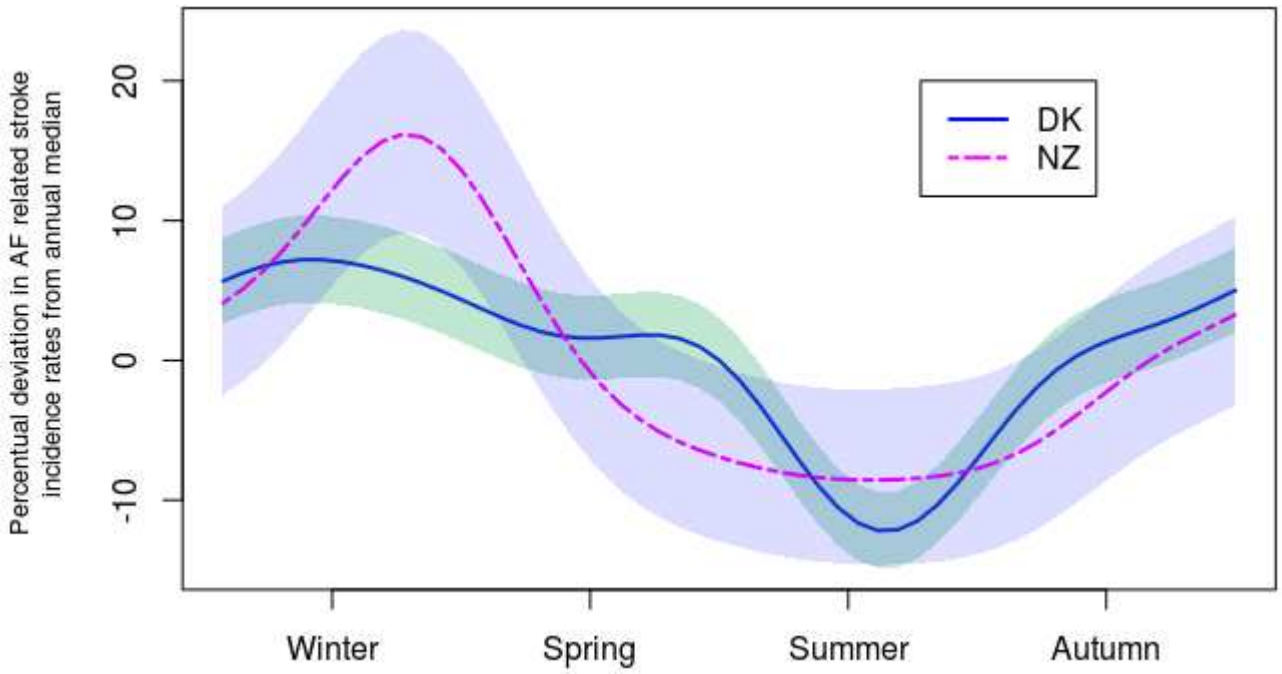


Figure 3: Estimated overall trend of Danish (solid line) and New Zealand (dashed line) weekly incidence rates of hospitalisations with stroke in atrial fibrillation patients per 100 person-years adjusted for seasonality. Shaded bands represent 95% confidence intervals.

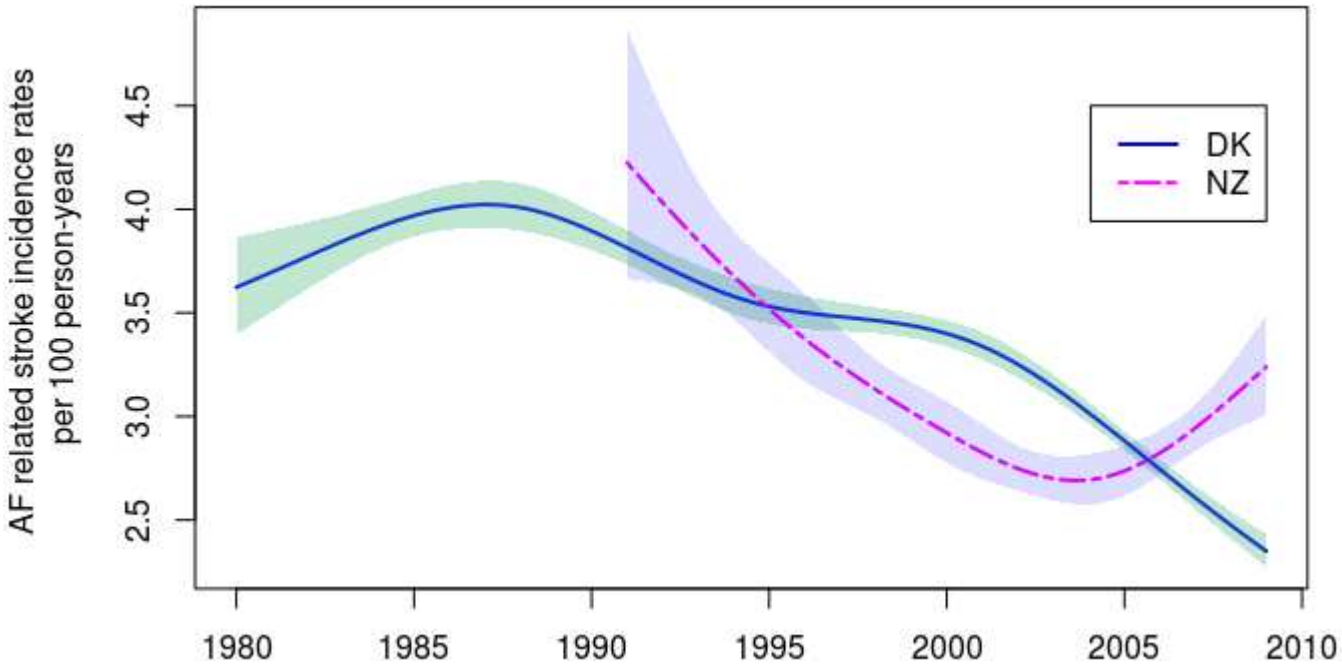
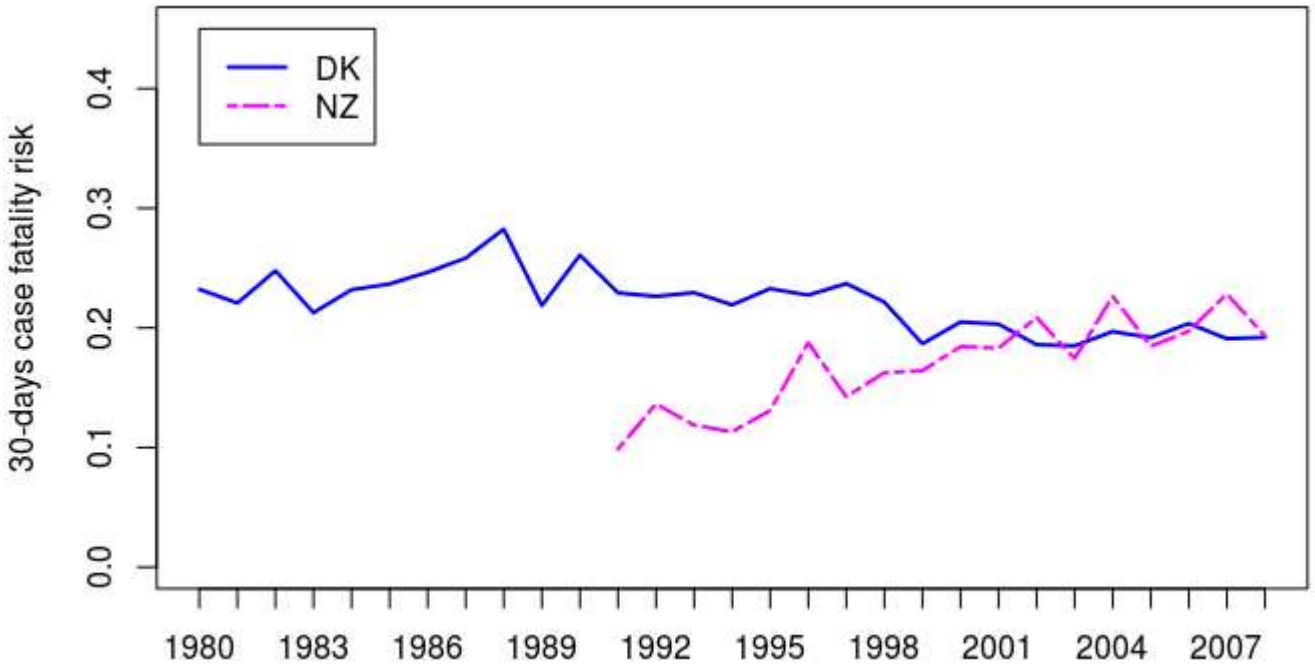


Figure 4: Observed 30-days case fatality risk for stroke in atrial fibrillation patients in Denmark and New Zealand



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.