Decrease in mortality in patients with a hospital diagnosis of atrial fibrillation in Denmark during the period 1980–1993

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Background Atrial fibrillation is associated with increased mortality. We hypothesized that the death rate in atrial fibrillation patients in Denmark has diminished during the period 1980–1993.

Methods In a random sample of half of the Danish population, 30 330 patients were found to have a diagnosis of incident atrial fibrillation in the Danish National Hospital Discharge Register 1980–1993. Information on previous and concomitant cardiovascular and metabolic diseases during the period 1977–1993 was sought in the register. The temporal trend in total and cardiovascular mortality in the cohort of atrial fibrillation patients was analysed.

Results A significant decrease in total and cardiovascular mortality was seen, 12–13% for total mortality and 17–18% for cardiovascular mortality. By adjusting for the decreasing cardiovascular mortality rate in the general population, a decrease in the relative risk of total mortality of 8–13% with time was seen for the atrial fibrillation cohort, compared with the population risk, while no reduction in the relative risk of cardiovascular death was seen.

Conclusion A significant decrease in mortality with calendar period occurred in the cohort of atrial fibrillation patients.

Key Words: Atrial fibrillation, epidemiology, prognosis.

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Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia seen in clinical practice. The arrhythmia is often caused by underlying cardiovascular or metabolic diseases: hypertension, ischaemic heart disease, heart valve disease, heart failure, thyrotoxicosis, or diabetes[1–3]. Atrial fibrillation in itself may cause reduction of physical capacity because of lack of atrial systole during ventricular filling, inappropriate control of heart rate during daily life activities or tachycardia induced cardiomyopathy[4]. Atrial fibrillation is associated with cerebrovascular thromboembolism[5–12] and excess mortality[12–15].

Improvements have occurred in cardiovascular medicine and surgery, for example, cessation-of-smoking programmes, diet-modification programmes, antihypertensive treatment, use of aspirin, anticoagulation, thrombolysis, beta-blockers, cholesterol-lowering drugs, ACE inhibitors, direct current cardioversion, echocardiography, invasive cardiology, heart surgery during cardiopulmonary bypass, and stroke rehabilitation programmes. This progress may have improved prognosis in atrial fibrillation patients.

We analysed changes in total and cardiovascular mortality in patients with a hospital diagnosis of incident atrial fibrillation during the period 1980–1993. Changes in mortality were analysed within the atrial fibrillation cohort and with external reference to the Danish population.

Methods

Study population

The general health and hospital care systems in Denmark are non-charge and non-profit systems that are tax financed. The cohort of patients with atrial fibrillation was found in the Danish National Hospital
Discharge Register within a nearly 50% random sample from the Danish population (all persons with one of 15 randomly selected birthdays a month).

Patients aged 50–89 years were included in the present analysis if they were discharged from hospital with an incident diagnosis of atrial fibrillation. Registrations with modification codes ‘not found’ or ‘under observation for’ were excluded, as were patients only seen in outpatient clinics. To avoid inclusion of individuals with prevalent atrial fibrillation, those who had a diagnosis of atrial fibrillation during the period 1977–1979 were not considered. Patients who died within the same month as a diagnosis of incident atrial fibrillation (n=2662) were excluded.

Month and year of the first registration (incidence) of atrial fibrillation was registered, together with age at diagnosis and gender. Previous or simultaneous diagnoses in The Danish National Hospital Discharge Register, during the period 1977–1993, of diseases disposing to atrial fibrillation[1–3] and cardiovascular mortality were recorded: hypertension, diabetes, hyperthyroidism, ischaemic heart disease, acute myocardial infarction, congestive heart failure, mitral valve disease, aortic valve disease, stroke, and peripheral atherosclerosis. A diagnosis of chronic obstructive pulmonary disease was included as a marker of smoking. Time and cause of death were sought in the National Death Register 1980–1993 for each person. If no death record was found, the person was followed until 31 December 1993. Follow-up was restricted to 1993 due to a change to ICD-10 in 1994. Coding of diseases was done by the discharging hospital’s medical staff according to the WHO ICD-8. Cause of death was coded by the Danish National Board of Health, according to WHO standards on the basis of causes of death noted in death certificates completed by doctors in hospitals, general practice or forensic medicine.

The definitions of diseases and causes of death by WHO ICD-8 codes for the present analysis are given in the appendix.

Statistical analysis

Gender-, age- and calendar-year-specific incidence rates of atrial fibrillation were calculated by dividing the number of incident cases by the corresponding person-years from the population.

Person-years at risk of dying in the atrial fibrillation cohort was calculated for each gender in 5-year age groups and the three calendar periods 1980–84, 1985–89 and 1990–93. The observed number of deaths was compared to that expected for the cohort. The expected number of deaths was calculated by multiplying person-years at risk with the corresponding gender-, age- and calendar-year-specific death rates from the Danish population. Standardized mortality ratios are defined as the observed divided by expected number of deaths. The relative risk, a generalization of the standardized mortality ratios, was analysed using multiplicative Poisson regression models[16]. These are log-linear regression models where the observed number of deaths is considered to be Poisson distributed. The logarithm of the expected number of deaths was used as an offset-variable (a constant in the linear regression model) and covariates (age and calendar time at atrial fibrillation diagnosis, and time since diagnosis and status of earlier or concomitant diseases) were multiplicative factors in the model. For each of the covariates, one of the categories was chosen as the reference and the reported parameters for the other categories were interpreted as relative risks compared to this reference category, standardized for the other factors in the model. In analysis of concurrent or previous diseases, the absence of disease was chosen as the reference level. This illustrates relative changes in risk for the cohort, relative to the population. The interpretation of an age parameter is the relative risk for the cohort for the reference category of covariates compared to the Danish population in that specific age group since no intercept was used in the regression model. Relative risk for atrial fibrillation patients with other categories of the covariates can be found by multiplying the shown relative risk for age by the relative risk for the other covariate categories. Separate analyses were made for men and women.

The rate of death in the cohort was analysed with Poisson regression models using the logarithm of the person-years under risk as the offset-variable. Such models illustrate the relative change in risk in the cohort itself. Poisson regression models were fitted using PROC GENMOD in SAS 6.12.

Results

Incidence, demographic and clinical data

The age-specific incidence rates of hospital diagnoses of atrial fibrillation increased in both males and females and in all age groups (Figs 1 and 2). The most pronounced increase was seen in persons aged 80–89 years. The crude male:female case ratio was 1:1 (Table 1), but the age-specific incidence rates were higher in men than in women (Figs 1 and 2). The age distribution is shown in Table 1. The fraction of patients aged 80–89 years was 21.7% in men and 38.5% in women.

The prevalence of a previous or concomitant hospital discharge diagnosis of hypertension, diabetes, hyperthyroidism, chronic obstructive pulmonary disease, ischaemic heart disease, congestive heart failure, mitral valve disease, aortic valve disease, stroke and peripheral atherosclerosis appears in Table 1.

Prognosis

Persons aged 50–59 years had at the reference levels for the other risk factors (calendar period 1980–84, 1–<2 year since atrial fibrillation diagnosis, and no history of
and/or presence of concomitant diseases) a four- to fivefold excess risk of death compared to the Danish population (Table 2). The elevated relative risk diminished with increasing age. Persons aged 80–89 years had a two- to threefold increase in relative death risk. The highest mortality risk was seen within the first year after incident atrial fibrillation diagnosis, thereafter, mortality risk declined.

Hypertension, diabetes, chronic obstructive pulmonary disease, ischaemic heart disease, congestive heart failure, cardiac valve disease, stroke and peripheral atherosclerosis were significantly associated with increased mortality (Table 3). For some of the diseases (diabetes, chronic obstructive pulmonary disease, ischaemic heart disease, congestive heart failure, and peripheral atherosclerosis), the relative death risk was highest in the younger patients, and a regular decreasing trend with increasing age was seen, but in Table 3, only the main effects of concomitant diseases are shown.

Two-thirds of the total mortality was caused by cardiovascular death. Cardiovascular mortality risk increased substantially with decreasing age. In persons aged 50–59 years at the standard level for the other risk factors, the mortality risks were increased by a factor of six in men and a factor of eight in women (Table 2). The cardiovascular mortality risk decreased with time since diagnosis of incident atrial fibrillation (Table 2).

The effect of calendar year on prognosis is shown in Table 4 and in Fig. 3. The risk of mortality, compared to the trend in the Danish population, decreased significantly by 8% in men and 12% in women from 1980–84 to 1990–93. No significant reduction in cardiovascular mortality was seen in comparison with the population trend.
However, when making an internal comparison of mortality rates within the cohort of atrial fibrillation patients, a 13% and 12% reduction in total mortality and an 18% and 17% reduction in cardiovascular mortality was seen during the period in men and women, respectively (Table 4). In the internal comparison of mortality rates, risk factor estimates for the other factors in the model, (time since diagnosis, and history or presence of concomitant diseases) were similar to the risk estimates for the relative risk of death comparing with the Danish population.
Incidence

The incidence rate of hospital diagnoses of atrial fibrillation in the Danish population increased substantially during the period 1980–1993. An increase in discharges from hospital with atrial fibrillation has also been noted in the U.S.A. where the number of annual discharges (incident cases as well as readmissions) with a primary diagnosis of atrial fibrillation doubled from 117 000 in 1982 to 252 000 in 1993[17].

We believe that the increasing focus on atrial fibrillation in both primary and secondary health care explains the increasing incident rates.

The incidence rate of patients discharged with atrial fibrillation at the age 80–89 years increased from 8/1000 person-years in 1980 to 13/1000 person-years in 1993. In the Framingham study, the incidence of atrial fibrillation in persons aged 75–85 years was 15–17/1000 person-years. For persons older than 85 years the Framingham incidence rate was 31–40/1000 person-years, depending on gender[1]. If these incidence rates can also be used for the Danish population, it means

Table 3  Effect of concomitant diseases on total mortality and cardiovascular mortality in the Danish atrial fibrillation cohort, 1980–93. Relative risk (RR) and 95% confidence intervals (95% CI)

<table>
<thead>
<tr>
<th>Previous or concomitant disease</th>
<th>Men RR (95% CI)</th>
<th>Women RR (95% CI)</th>
<th>Men RR (95% CI)</th>
<th>Women RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>1·26 (1·18–1·35)</td>
<td>1·24 (1·17–1·33)</td>
<td>1·26 (1·18–1·35)</td>
<td>1·24 (1·17–1·33)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1·40 (1·30–1·50)</td>
<td>1·46 (1·37–1·55)</td>
<td>1·34 (1·23–1·47)</td>
<td>1·39 (1·29–1·50)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>0·84 (0·70–1·00)</td>
<td>0·82 (0·75–0·90)</td>
<td>0·93 (0·74–1·16)</td>
<td>0·82 (0·73–0·92)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1·36 (1·28–1·44)</td>
<td>1·40 (1·31–1·50)</td>
<td>1·03 (0·95–1·11)</td>
<td>1·20 (1·08–1·33)</td>
</tr>
<tr>
<td>Ischaemic heart disease with myocardial infarction</td>
<td>1·44 (1·38–1·50)</td>
<td>1·35 (1·29–1·42)</td>
<td>1·67 (1·58–1·77)</td>
<td>1·48 (1·40–1·56)</td>
</tr>
<tr>
<td>Mitral valve disease</td>
<td>1·22 (1·03–1·45)</td>
<td>1·39 (1·23–1·57)</td>
<td>1·49 (1·23–1·81)</td>
<td>1·69 (1·47–1·95)</td>
</tr>
<tr>
<td>Aortic valve disease</td>
<td>1·32 (1·11–1·57)</td>
<td>1·23 (1·06–1·44)</td>
<td>1·60 (1·30–1·95)</td>
<td>1·38 (1·16–1·65)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1·34 (1·25–1·44)</td>
<td>1·47 (1·37–1·57)</td>
<td>1·54 (1·42–1·67)</td>
<td>1·65 (1·53–1·78)</td>
</tr>
<tr>
<td>Peripheral atherosclerosis</td>
<td>1·48 (1·35–1·63)</td>
<td>1·68 (1·51–1·86)</td>
<td>1·54 (1·38–1·73)</td>
<td>1·80 (1·60–2·03)</td>
</tr>
</tbody>
</table>

Concomitant diseases: diseases prior to or in the same hospital admission as incident diagnosis of atrial fibrillation. Relative risk estimates are adjusted for age and calendar period of atrial fibrillation, time since diagnosis, and the other diseases in the table. The analyses model the ratio between the observed and the expected numbers of deaths; expected numbers are based on mortality in the entire population. The models include interaction terms between age and some of the diseases.

Table 4  Effect of calendar period on total mortality and cardiovascular mortality in the Danish atrial fibrillation cohort, 1980–93. Adjusted for trend in the population (Model 1) and internal comparison in the cohort (Model 2). Relative risk and 95% confidence intervals (95% CI)

<table>
<thead>
<tr>
<th>Calendar period</th>
<th>Death, all causes</th>
<th>Cardiovascular death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men RR (95% CI)</td>
<td>Women RR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Men RR (95% CI)</td>
<td>Women RR (95% CI)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted for mortality trend in population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980–84 reference</td>
<td>1·00</td>
<td>1·00</td>
</tr>
<tr>
<td>1985–89</td>
<td>0·95 (0·90–1·02)</td>
<td>0·91 (0·85–0·97)</td>
</tr>
<tr>
<td>1990–93</td>
<td>0·92 (0·86–0·98)</td>
<td>0·87 (0·82–0·93)</td>
</tr>
<tr>
<td>Trend test $P=0·0004$</td>
<td>Trend test $P=0·0001$</td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal comparison in cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1980–84 reference</td>
<td>1·00</td>
<td>1·00</td>
</tr>
<tr>
<td>1985–89</td>
<td>0·92 (0·86–0·98)</td>
<td>0·90 (0·85–0·96)</td>
</tr>
<tr>
<td>1990–93</td>
<td>0·87 (0·82–0·93)</td>
<td>0·88 (0·83–0·94)</td>
</tr>
<tr>
<td>Trend test $P=0·0001$</td>
<td>Trend test $P=0·0005$</td>
<td></td>
</tr>
</tbody>
</table>

Risk estimates are adjusted for age and time since diagnosis of atrial fibrillation, and concomitant or previous diseases.
Model 1: The ratios between the observed and the expected number of deaths; expected numbers are based on mortality in the Danish population.
Model 2: The rate ratios in subgroups of the cohort.

Discussion

Incidence

The incidence rate of hospital diagnoses of atrial fibrillation in the Danish population increased substantially during the period 1980–1993. An increase in discharges from hospital with atrial fibrillation has also been noted in the U.S.A. where the number of annual discharges (incident cases as well as readmissions) with a primary diagnosis of atrial fibrillation doubled from 117 000 in 1982 to 252 000 in 1993[17].
that many patients with atrial fibrillation were not seen in hospital, or were not coded for atrial fibrillation when seen in hospital.

**Disposing morbidity**

Almost half of the patients had ischaemic heart disease, and one third of the patients had congestive heart failure. Hypertension was seen in 17–20% of the patients. This is in contrast with the Framingham study, where hypertension was seen more often and heart failure was seen less often\(^1\). This may indicate that the subgroup of atrial fibrillation patients seen in hospital carries a higher cardiovascular morbidity than atrial fibrillation patients detected in population surveys.

Rheumatic heart disease has almost disappeared in developed countries. Mitral or aortic valve disease was seen in up to 6% of the female patients. In the Framingham study\(^1\) valve disease was present in 17% of men and 30% of women with atrial fibrillation. It is possible that systematic echocardiographic screening of atrial fibrillation patients would have increased the number of patients with significant heart valve disease. However, Godtfredsen’s survey\(^18\) of 1212 patients with atrial fibrillation hospitalized from 1940–1967 demonstrated a transition in the aetiology of atrial fibrillation from predominantly rheumatic valve disease in the early part of the period to ischaemic heart disease in the later part. The Framingham study\(^1\) was initiated in 1948. This may explain why rheumatic valve disease was an important aetiology in the Framingham study, but not in our study.

**Prognosis**

A significant fall in relative risk of death after discharge with a diagnosis of atrial fibrillation was seen during the study period when compared with the mortality in the
Danish population. The decrease in mortality with calendar time was even more pronounced in the internal comparison in the atrial fibrillation cohort. This indicates that the mortality risk reduction seen in atrial fibrillation patients is partly caused by better treatment of the underlying cardiovascular diseases or a historical and nonspecific lowering of case-fatality rates in cardiovascular disease. This corresponds to the trend towards lower cardiovascular mortality rates with calendar time in the cohort of atrial fibrillation patients, while no significant reduction in excess cardiovascular mortality risk with calendar time was seen when compared with the general Danish population, in which the case-fatality rate in ischaemic heart diseases has diminished\(^\text{[10]}\). Thus, most of the prognostic improvement for cardiovascular death observed in the present cohort of atrial fibrillation patients may be explained by the lower case-fatality rates in ischaemic heart diseases seen in the general population.

For non-cardiovascular causes of death an improvement in prognosis was seen with increasing calendar time. It was not possible to identify a single group of diseases (e.g. cancer) that could explain this decrease in mortality risk.

**Possible bias**

Under-reporting of atrial fibrillation may have occurred due to the possibility that some patients with atrial fibrillation may not have been coded for atrial fibrillation at discharge. Such a misclassification will give rise to an underestimation of the excess risk of being diagnosed as an atrial fibrillation patient.

Under-reporting of co-morbidity may have occurred. The possibility of under-reporting co-morbidity is highest in patients with several concomitant diseases. In the present study, sampling of information on co-morbidity was possible from 0 to 17 years before the diagnosis of atrial fibrillation. A diagnosis of atrial fibrillation late in the study period was, therefore, associated with a higher probability of being coded for previous diseases. The estimation of the prognostic significance of the calendar year of atrial fibrillation diagnosis was adjusted for the presence of co-morbidity. We cannot exclude the possibility that the improvement in prognosis derives from a higher probability of under-reporting of concomitant diseases at the beginning of the study period. Such a differential misclassification may lead to a false (and too optimistic) conclusion regarding the calendar effect\(^\text{[20]}\). However, when the Poisson regression models were fitted, without inclusion of information on co-morbidity, the same estimates of risk reduction with calendar period were obtained.

We have no valid data on confounders such as family history, social class, level of education, diet, exercise habits, smoking, cholesterol levels and body mass index. Furthermore, no data on medication were available. We could not evaluate the prognostic significance of changes in antiarrhythmic treatment strategy (e.g. less use of class Ic antiarrhythmic agents), and the increasing use of coumarines with calendar time.

**Conclusions**

The age-standardized incidence of patients hospitalized with atrial fibrillation increased substantially during the period 1980–1993. A significant decrease in mortality with calendar time in atrial fibrillation patients occurred.

**References**


Appendix

Definitions of diseases by WHO ICD-8 codings used for the present analysis

**Atrial fibrillation**
427.93

**Hypertension**
400–404, 410.09, 411.09, 412.09, 413.09, 414.09, 430.00, 430.01, 430.08, 430.09, 431.00, 431.01, 431.08, 431.09, 432.00, 432.01, 432.02, 432.08, 432.09, 433.09, 434.09, 435.09, 436.00, 436.01, 436.09, 437.00, 437.01, 437.08, 437.09, 438.09

**Ischaemic heart disease**
410–414

**Acute myocardial infarction**
410

**Congestive heart failure**

**Mitral valve disease**
394, 396

**Aortic valve disease**
395, 396

**Peripheral atherosclerosis (atherosclerosis outside coronary and cerebral arteries)**
440, 445.00, 445.08, 445.09

**Stroke**
431, 433, 434, 436.01, 436.90

**Chronic obstructive pulmonary disease**
491, 492

**Hyperthyroidism**
242

**Diabetes**
249, 250

**Mortality caused by cardiovascular diseases**