Epidemiology of atrial fibrillation in the general population

Epidemiologie van atriumfibrilleren in de algemene populatie

Jan Heeringa

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Chapter 1

General introduction

Introduction

Atrial fibrillation is a common disease of the heart, characterized by an irregular and, if not treated, mostly fast heart rhythm. The origin of the disease is the atrial part of the heart. It is a rare disease before the age of 55, but the prevalence is sharply increasing with age. In many cases patients do not even notice that they have a rhythm disorder. But if they have complaints, they mention dyspnoea, chest pain, palpitations, dizziness, and sometimes syncope.[1] For many years, atrial fibrillation has been considered as an innocent bystander of old age, but it is nowadays generally accepted that atrial fibrillation is associated with impaired quality of life[2] and increased morbidity and mortality.[3-8] Treatment regimens evolved as a consequence, unfortunately sometimes introducing new potential harms to the patients with this disease. Atrial fibrillation is involved in pathological processes through the whole body and has through that inspired numerous investigators in internal medicine, cardiology, neurology, pathology, pharmacology, physiology and epidemiology. The disease concept has evolved as science evolved and often has been in the centre of intense dispute.

Landmarks and controversies in the history of atrial fibrillation

The famous William Harvey (1578-1657) was probably the first who recognized and described atrial fibrillation in 1628 (in : Exercitatio anatomica de motu cordis en sanguinis in animalibus).[9] In those ancient times it was generally believed that the heartbeat and the arterial pulse as an easy diagnostic tool were two independent mechanisms. He definitely concluded that the contraction of the left ventricle caused the arterial pulsation through the body, but his contemporaries did not follow him. Even Laennec in 1819 believed that the arteries had an own movement. He observed situations with discrepancies between the movements of the heart and the movements of vessels and this made him believe that the actions of the vessels were not dependent on the heart beat. He probably had observed atrial fibrillation, with the now well-known characteristics of the irregular pulse and the pulse-deficit. De Sénac who lived in France from 1693 to 1770 detected that the heart is an irritable organ and he was the first to describe palpitations of the heart caused by mitral stenosis. Remarkably, he described also that quinidine could relieve palpitations of the heart and he also stated that the causes of palpitations were not the causes of the natural heartbeat. During the 19th century graphical pulses of veins and arteries were intensively studied and thus also a state of delirium cordis or of pulsus irregularis perpetuus had been notified. Other investigators worked on the effect of electricity on tissues and MacWilliam reported the state of delirium cordis in which fibrillating

contractions in animal hearts, generated by faradic currents, could be observed.[10] At that moment two definitions of delirium cordis were known, but investigators were unaware of each other's findings until Hering in 1903 suggested that both descriptions were basically of the same process. Then the first electrocardiographic registration of atrial fibrillation by Lewis, inspired by sir Mackenzie, followed after the invention by Einthoven of the string galvanometer in 1901.[11] Thus, atrial fibrillation was in the midpoint of the discussion on the origin of blood circulation and stimulated later also the development of modern electrocardiography as a powerful instrument in cardiology.

In those early years of the 20th century started already the discussion on whether atrial fibrillation is caused by rapidly discharging, spontaneously active, atrial ectopic foci, by a single re-entrant re-entry circuit or by multiple functional re-entrant circuits.[12] This discussion is nowadays still ongoing despite the wealth of new information on the electrophysiological basis of atrial fibrillation. The work of Moe who presented his theory of the multiwavelet theory in 1959 has dominated the thinking about the background of atrial fibrillation for many years. He stated that atrial fibrillation could persist and propagate through a random fractionation of the wave front around islands of refractory tissue, independent of focal discharge. His theory has evolved under the influence of the work of Allessie in 1977[12] and gained further support. In 1998 Haissaguerre[13] presented his observations on the rapid firing focus, arising in the left atrium at the entrance of the pulmonary veins and so the theory on the electrophysiological background shifted again towards the very localized origin of atrial fibrillation. Another landmark in the electrophysiological field of atrial fibrillation has been formed by the work of Wijffels and Allessie who developed the concept that atrial fibrillation begets atrial fibrillation by processes of remodelling.[14] The knowledge on the basics of electro physiology may open the routes to new therapies of atrial fibrillation and these therapies are urgently needed.

The very early therapeutic arsenal of atrial fibrillation consisted of the treatment by digoxin[15] and quinidine.[16] In 1962 developed the promising therapy of electric cardioversion.[17,18] Also new drugs developed that could induce chemical cardioversion.[19] It turned out that even after successful cardioversion antiarrhythmic medication was needed to prevent recurrence of atrial fibrillation.[20] During many years the gold standard of therapy was that physicians primarily should restore sinus rhythm by electric or drug-induced cardioversion. Long-term antiarrhythmic medication was consequently needed to sustain sinus rhythm. In many cases this goal could not be reached and then rate control could be accepted as the second best therapy. The AFFIRM trial[21], the PIAF trial[22] and the RACE trial[23] showed that this gold standard needed re-evaluation. Contra intuitively, these trials established that a rate control strategy was not inferior to a rhythm control strategy. Probably the advantages of a restoration of sinus rhythm were neutralized by the disadvantages of the antiarrhythmics that were needed to preserve

sinus rhythm. These drugs had already shown that they were able to induce proarrhythmia, death, bradyarrhythmia and negative inotropy. The results of these trials greatly changed clinical practice but also stimulated the search for new and safer antiarrhythmic drugs. These are still under development.[24,25] It also changed thinking about pacing[26] and ablation therapy.[27]

In the 70s of the former century awareness grew that embolic stroke possibly was one of the greatest threats of atrial fibrillation.[28] Initially it was thought that mitral stenosis with atrial fibrillation was the culprit. In a landmark study of the Framingham Study in which sufferers from rheumatoid heart disease were excluded, it was shown that also non-valvular atrial fibrillation conferred a 5-fold increased risk of ischemic stroke.[8] A number of studies established that atrial fibrillation was a marker of larger strokes resulting in more pronounced disability and higher death rates compared to those who experienced stroke in sinus rhythm.[29,30] Several trials followed addressing the prophylactic capacity of anticoagulants and antiplatelets. It appeared that anticoagulant drugs indeed could reduce the risk of stroke by 64% and that antiplatelets could reduce this risk by 19%.[31,32] Unfortunately at the cost of a higher risk of major bleeding, with intracerebral bleeding with a 60% mortality as the greatest fear. Scepticism remained on the potential of antiplatelets because the results were not completely statistically significant. Risk stratification schemes based on clinical characteristics were developed to identify patients on lower risk in which antiplatelets would suffice and patients at a higher risk for whom anticoagulants are needed. Anticoagulants are difficult to use in practice. Frequent measurements of the INR are needed to provide a safe level of anticoagulation and the stability of levels of anticoagulation is easily disturbed by drug-drug interactions and by food-drug interactions.[33] Guidelines on the prescription of anticoagulants are insufficiently followed by physicians[34], based on the fear to induce lethal bleeding and on the knowledge that the results of the trials that provided these guidelines had major shortcomings.[35] Searches for newer and safer anticoagulants with the same efficacy as the current are frustrated at the short term by the occurrence of unexpected side effects of the promising Ximelagatran.[36] Surgical treatments are under study that could reduce stroke risk by closure of the left atrial appendage.[37] The current risk prediction schemes have at their best a fair performance.[38] In the light of this performance and of the drawbacks of the anticoagulant therapy additional measures are highly desirable to predict better who are at the highest risk of stroke.

Not only stroke, but also an increased risk of heart failure and an increased mortality in atrial fibrillation are heavily debated. Heart failure and atrial fibrillation are two highly interrelated conditions. Heart failure is the strongest predictor of atrial fibrillation.[39] Heart failure is also often diagnosed in the course of atrial fibrillation.[40] Questions remain, however, on the independent character of atrial fibrillation as a predictor of heart failure.[41] It is an old observation that atrial fibrillation patients are at a higher risk of death. Godtfredsen described

in his landmark study in 1975 the poor prognosis of 1212 atrial fibrillation patients in a Danish hospital-based study.[42] It remained unclear whether the poor prognosis in atrial fibrillation reflected the rhythm disorder per se or the prognosis of the risk factors of atrial fibrillation. The Framingham Study provided further evidence of an independent association of atrial fibrillation with death.[3] However the results of that study describe an older follow-up period, 1948-1988. Further, studies on the cause-specific mortality in atrial fibrillation are limited.

Rationale of this thesis

The majority of the investigations on atrial fibrillation are in selected populations. Recent population bases studies are scarce. Therefore, we aimed to investigate significant topics on atrial fibrillation in the population-based Rotterdam Study. This large study of elderly, 55 years and over, inhabitants of a suburb of Rotterdam, started in 1990 and continues until today.

Aims of the thesis

We aimed to describe prevalence and incidence of atrial fibrillation (Chapter 2). Population based figures from Western Europe are not available. The most reliable figures are obtained from the United States and are from earlier periods. Further we wanted to investigate a number of risk factors of incident atrial fibrillation, adding to what was already known from previous studies. We investigated omega-3 fatty acids and atrial fibrillation (Chapter 3.1), atherosclerosis and atrial fibrillation (Chapter 3.2), smoking and atrial fibrillation (Chapter 3.3) and the role of normal thyroid function as a risk factor of atrial fibrillation (Chapter 3.4). To investigate whether markers of the prothrombotic state could possibly help to predict better stroke and poor outcome in atrial fibrillation we examined markers of the prothrombotic state cross-sectionally (Chapter 4.1) and longitudinally with cardiovascular outcome (Chapter 4.2). Subsequently, we aimed to investigate the prognosis of atrial fibrillation with respect to heart failure (Chapter 5.1), to mortality (Chapter 5.2) and to stroke (Chapter 5.3).

Study population

The studies described in this thesis are embedded in the Rotterdam Study. That study started in 1990 in 7983 elderly (55 years and over) inhabitants of the Rotterdam suburb Ommoord. The study focuses on cardiovascular, neuro-geriatric and psycho-geriatric diseases and on diseases of the eye and of the locomotor system. Baseline measurements were between 1990-1993. The first follow-up examination started at July 1993 and ended December 31st 1994. The second follow-up examination was performed between April 1997 and December 31st 1999. The third follow-up measurement started January 1st 2002 and was completed in July 2004. A solid collaboration with the general practitioners and the pharmacies of Ommoord contributes substantially to the collection of the data and the validation of diagnoses of interest.

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Chapter 2

Prevalence, incidence and lifetime risk of atrial fibrillation

Abstract

Aims We aimed to investigate the prevalence and incidence of atrial fibrillation in a large European population-based study.

Methods The study is part of the Rotterdam Study, a population-based prospective cohort study among subjects aged 55 years and over. The prevalence at baseline was assessed in 6808 participants. Incidence of atrial fibrillation was investigated during a mean follow-up period of 6.9 years in 6432 persons.

Results We identified 376 prevalent and 437 incident cases. Overall prevalence was 5.5%, rising from 0.7% in the age group 55-59 years to 17.8% in those aged 85 years or over. The overall incidence rate was 9.9/1000 person-years. The incidence rate in age group 55-59 years was 1.1/1000 person-years, rose to 20.7/1000 person-years in age group 80-84 years and stabilized in those aged 85 years or over. Prevalence and incidence were higher in men than in women. The lifetime risk to develop atrial fibrillation at the age of 55 years was 23.8% in men and 22.2% in women.

Conclusion In this prospective study in a European population, the prevalence and incidence of atrial fibrillation increased with age and were higher in men than in women. The high lifetime risk to develop atrial fibrillation was similar to North American epidemiological data.

Introduction

Atrial fibrillation is associated with substantial mortality and morbidity from thrombo-embolism, heart failure and impaired cognitive function.[1-5] With populations aging, atrial fibrillation is likely to become a greater public health burden, and thus reliable prevalence and incidence figures are needed both for clinicians and policy-makers.[6]

The prevalence of atrial fibrillation has been investigated in several countries, but many epidemiological uncertainties still remain, in particular as to why the prevalence figures differ widely between studies.[7-17] Prevalence rates in the elderly are scarce. Incidence data on atrial fibrillation are also limited. Only two American population-based studies have presented data on incidence.[18,19] A Canadian study presented incidence figures in men only and one British population study presented the incidence of atrial fibrillation, based mainly on hospitalisations.[20,21] In this analysis, from the Rotterdam Study, we report the prevalence and incidence of atrial fibrillation, the prevalence of atrial fibrillation at three moments during follow-up and the lifetime risk of atrial fibrillation, in a large population-based epidemiological study.

Methods

Study population

The Rotterdam Study is a population-based prospective cohort study, which started in 1990 in Ommoord, a suburb of Rotterdam. The study design has been described in detail elsewhere.[22] In short, all inhabitants of this area aged 55 and over (N=10275) were invited to participate and 78% (N=7983) entered the study. They were interviewed at home and most (N=7151) were examined at the research center to enable the collection of baseline data (1990-1993), including a 10-second 12-lead resting ECG. Those who did not visit the research center were in general dependent or lived in nursing homes. The participants were re-examined in two follow-up rounds. The first examination round was performed between July 1993 and December 1994. The second follow-up round started in April 1997 and ended in December 1999. The Medical Ethics Committee of Erasmus University approved the study and participants gave informed consent.

Evaluation of atrial fibrillation

Three methods were used to assess cases of atrial fibrillation or atrial flutter.[23,24] (1) At baseline and during follow-up examinations 10-s 12-lead ECGs were recorded at the research center with an ACTA Gnosis IV ECG recorder (EsaOte, Florence, Italy), stored digitally and analyzed with the Modular ECG Analysis System (MEANS).[25,26] MEANS is characterized by

a high sensitivity (96.6%) and a high specificity (99.5%) in coding arrhythmias.[27] To verify the diagnosis of atrial fibrillation, all ECGs with a diagnosis of atrial fibrillation or atrial flutter or any other rhythm disorder were recoded independently by two physicians who were blinded to the MEANS diagnosis. The judgment of a cardiologist was asked and taken as decisive in case of persistent disagreement. (2) General practitioners participating in the Rotterdam Study sent computerized information on atrial fibrillation, based on their own records and on hospital discharge letters, to the researchers of the Rotterdam Study. Specially trained follow-up assistants verified this information. A senior physician examined all the information and coded the events according to the International Classification of Diseases (code I48 of the 10th revision). For a diagnosis of atrial fibrillation or atrial flutter we required an ECG that verified the diagnosis. (3) Hospital discharge diagnoses were also obtained from the LMR system (de Landelijke Medische Registratie). This national registration accumulates all hospital discharge diagnoses of Dutch inhabitants.

To ascertain atrial fibrillation at baseline we used ECGs as described above. In addition, the general practitioner files of all participants were screened for the presence of atrial fibrillation at or before baseline.

We did not consider a person as having atrial fibrillation if (1) atrial fibrillation occurred during the process of dying and was not the cause of death or if (2) transient atrial fibrillation occurred during a myocardial infarction or a cardiac operative procedure.

Information on vital status was obtained on a regular basis from the central registry of the Municipality of Rotterdam, from collaborating general practitioners and by obtaining information during follow-up rounds. For those participants whose information on vital status remained missing, the Central Registry of Genealogy of the Netherlands was consulted. This national institute receives population registry records of those inhabitants of the Netherlands who have died.

All participants were followed from the date of entry into the Rotterdam Study (1990-1993) to the date of onset of atrial fibrillation, the date of death or to January 1, 2000, whichever came first. The date of onset of atrial fibrillation was defined as the midpoint between the date of the follow-up round at which atrial fibrillation was detected and the date of the previous round at which atrial fibrillation had not yet been detected. If also or only information of a diagnosis of atrial fibrillation was available from either the general practitioner files and/or the LMR registry this date was taken as the date of onset. Follow-up by January 1, 2000 was complete for 99.1% of the total study population.

General baseline measurements

Information on current health status, medical history and smoking was obtained using a computerized questionnaire. Participants were classified as current or non-smokers. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured twice at the right upper arm with a random zero mercury sphygmomanometer in the sitting position. Systolic and diastolic blood pressures were calculated as the average of the two consecutive measurements. Hypertension was defined as a systolic blood pressure of 160 mmHg or over or a diastolic blood pressure of 100 mmHg or over, or the use of blood pressure lowering drugs prescribed for hypertension.[28] A history of myocardial infarction was defined as a self-reported myocardial infarction with hospital admission or the presence of a myocardial infarction on the ECG. A positive report of myocardial infarction was confirmed by reviewing the medical records of general practitioners and specialists for the presence of myocardial infarction. Left ventricular hypertrophy was diagnosed by the MEANS program with an algorithm that takes into account QRS voltages, with an age-dependent correction, and repolarization changes. Diabetes was defined as the use of antidiabetic medication or a random or post-load serum glucose level of 11.1 mmol/L or more. Heart failure at baseline was assessed as described previously.[29,30] In short, diagnosis of heart failure was based on a score of heart failure symptoms, on medication prescribed with the indication of heart failure, on hospital discharge diagnoses and on the information available in general practitioner files. Blood samples were drawn by venipuncture, and serum total cholesterol and HDL cholesterol were measured with an automated enzymatic method.

Population for analysis

For this study an ECG was not available for analysis of atrial fibrillation at baseline in 343 participants because of logistic reasons. The population for analysis consisted of 6808 participants for whom at baseline an ECG was available. In this population prevalence at baseline and at three consecutive moments during follow-up was measured. After exclusion of 376 participants with atrial fibrillation at baseline, the incidence and lifetime risk of atrial fibrillation were calculated in 6432 persons.

Statistical analysis

Prevalence of atrial fibrillation at baseline was calculated as the proportion of those who had atrial fibrillation in the study population at the time of the baseline measurements. Wilson's score method for a binomial proportion was used to calculate 95% confidence intervals. Prevalence estimates were calculated for the total study population, for men and women separately, and for different age categories. Crude incidence rates for atrial fibrillation were calculated by dividing

the number of incident cases of atrial fibrillation by the number of person-years accumulated in the population without atrial fibrillation at baseline. The 95% confidence intervals were calculated based on the Poisson distribution. Incidence rates were calculated for men and women separately and for 5-year age categories. To evaluate whether the prevalence became higher during follow-up we calculated prevalence figures at three moments during follow-up: at the end of the baseline measurements (July 1, 1993), at the end of the first follow-up round (January 1, 1995) and at the end of the second follow-up round (January 1, 2000). A logistic regression model was used to evaluate differences between the prevalence at July 1, 1993 and at January 1, 2000. In this analysis, observation 1 (1 July 1993) and observation 2 (1 January 2000) were considered as two independent observations. The lifetime risk of atrial fibrillation with 95% confidence intervals was calculated using a SAS macro from the Framingham Study.[31] This macro takes into account competing risk of death.[32] The risks of atrial fibrillation were calculated for men and women separately at the ages of 55, 60, 65, 70, 75, 80 and 85 years onwards. SPSS 11 for Windows (SPSS, Inc, Chicago, Illinois) and SAS 8.2 (SAS Institute Inc., Cary, NC, USA) were used for data analyses.

Results

Baseline characteristics of our study population are presented in table 1. In the study population, 209 cases had atrial fibrillation on the ECG at baseline. Investigation of general practitioner files identified another 167 participants who had no atrial fibrillation at the baseline examination, but had been diagnosed with atrial fibrillation in an earlier period. They were also included as atrial fibrillation cases. The total number of prevalent cases was therefore 376, including 169 men (44.9%) and 207 women (55.1%).

The overall prevalence of atrial fibrillation was 5.5%, 6.0% in men and 5.1% in women. The prevalence in the age stratum 55-60 years was 0.7% and increased with each successive stratum. In the stratum of 85 years and over, the prevalence was 17.8%. Prevalence in each age stratum was higher in men than in women (Table 2).

After exclusion of the prevalent atrial fibrillation cases, 437 participants developed new atrial fibrillation (198 men and 239 women) during a follow-up of 44175 person-years (mean 6.9 years); the overall incidence was 9.9/1000 person-years. There was a steep increase in the incidence with age, with the exception of those who were older than 85 years. The incidence was 1.1/1000 person-years at ages 55-60, rose to 20.7/1000 person-years in the age group 80-85 but stabilized (18.2/1000 person-years) in those who were 85 years or over (Table 3). The incidence was higher in men than in women across all age groups.

Prevalence figures during follow-up were calculated based on the prevalence at baseline, on the incidence figures of atrial fibrillation and on the mortality figures of the study population. The prevalence at July 1, 1993 was 6.1% (men 6.8%, women 5.5%). The prevalence increased to 6.7% (men 7.9%, women 5.9%) on January 1, 1995 and to 8.3% (men 9.5%, women 7.5%) on January 1, 2000. This increase, although substantial (OR 1.40: 95% CI 1.22-1.62) was not significant after adjustment for age at the date of the measurement of the concerning prevalence figures (OR 1.05; 0.91-1.22, prevalence at January 1, 2000 compared to the prevalence at July 1, 1993). Further adjustment for gender only minimally changed the age adjusted point estimate.

Period risk and lifetime risk at different ages for men and women separately are shown in table 4. At the age of 55 years, the lifetime risk of atrial fibrillation was 23.8% for men and 22.2% for women. Lifetime risks remained almost the same across age categories until the age of 75 years. After that, lifetime risks decreased in a pattern that was the same for men and women. Women and men did not differ substantially in lifetime risks. However, men constantly had a higher risk for future atrial fibrillation than women if limited time periods were considered, independent of the age group.

Table 1 Baseline characteristics of the study population (N=6808)
The Rotterdam Study, 1990-1993

Characteristic	
Age, years	69.3 ± 9.1
Gender, % women	59.5
Body Mass Index, kg/m^2	26.3 ± 3.7
Hypertension, %	21.4
Systolic blood pressure, mmHg	139.3 ± 22.5
Diastolic blood pressure, mmHg	73.6 ± 11.7
Total cholesterol, mmol/L	6.6 ± 1.2
HDL cholesterol, mmol/L	1.35 ± 0.36
Current smoking, %	22.8
Diabetes mellitus, %	10.5
History of myocardial infarction, %	12.8
Left ventricular hypertrophy, %	5
Heart failure, %	2.5

Numbers are mean ± SD for continuous variables and percentages for dichotomous variables.

Table 2 **Prevalence with 95% confidence interval of atrial fibrillation at baseline by gender and age** (N=6808)

The Rotterdam Study, 1990-1993

	All			Men			Women		
Age groups (years)	*N*	*Cases*	*Cases/N**	*N*	*Cases*	*Cases/N**	*N*	*Cases*	*Cases/N**
55-59	1161	8	0.7 (0.4-1.4)	485	4	0.8 (0.3-2.1)	676	4	0.6 (0.2-1.5)
60-64	1411	24	1.7 (1.2-2.5)	620	16	2.6 (1.6-.3.4)	791	8	1.0 (0.5-2.0)
65-69	1291	51	4.0 (3.0-5.2)	597	31	5.2 (3.7-7.3)	694	20	2.9 (1.9-4.4)
70-74	1130	68	6.0 (4.8-7.6)	464	32	6.9 (5.0-9.6)	666	36	5.4 (4.1-7.0)
75-79	855	77	9.0 (7.3-11.1)	330	43	13.0 (9.8-17.1)	525	34	6.5 (4.7-8.9)
80-84	533	72	13.5 (10.9-16.7)	164	25	15.2 (10.5-21.5)	369	47	12.7 (9.7-16.5)
≥85	427	76	17.8 (14.5-21.7)	95	17	17.9 (11.5-26.8)	332	58	17.5 (13.8-21.9)
All	6808	376	5.5 (5.0-6.1)	2590	165	6.0 (5.0-7.0)	4053	206	5.1 (4.5-5.8)

* Denotes % (95% CI)

Table 3 **Incidence rates of atrial fibrillation with 95% confidence intervals by gender and age** (N=6432)

The Rotterdam Study, 1990-1999

	All		*Men*		*Women*	
Age groups (years)	*Cases/py*	*Rate (95% CI)**	*Cases/py*	*Rate (95% CI)**	*Cases/py*	*Rate (95% CI)**
55-59	3/2741	1.1 (0.3-2.9)	3/1140	2.6 (0.7-7.0)	-	-
60-64	27/8361	3.3 (2.2-4.7)	17/3496	4.9 (2.9-7.6)	10/4821	2.1 (1.1-3.7)
65-69	54/9817	5.5 (4.2-7.1)	28/4269	6.6 (4.5-9.3)	26/5548	4.7 (3.1-6.8)
70-74	100/8662	11.5 (9.5-14)	45/3627	12.4 (9.2-16.4)	55/5035	10.1 (8.3-14.1)
75-79	101/6899	14.7 (12.0-17.7)	51/2566	19.9 (15.7-25.9)	50/4332	11.5 (8.7-15.1)
80-84	92/4445	20.7 (16.8-25.3)	36/1414	25.5 (18.1-34.8)	56/3031	18.2 (14.1-23.8)
≥85	60/3294	18.2 (14.0-23.3)	18/709	25.4 (15.6-39.2)	42/2585	16.2 (11.9-21.7)
All	437/44175	9.9 (9.0-10.9)	198/17223	11.5 (10.0-13.2)	239/26952	8.9 (7.8-10.2)

Py, person-years

* Denotes per 1000 person-years

CI, confidence interval

Table 4 Cumulative risk of atrial fibrillation in percentages at different ages in men and women (N=6432)

The Rotterdam Study, 1990-1999

Period risk (%) in 5-years intervals

Age (years)	5y	10y	15y	20y	25y	30y	Lifetime risk (95% CI)
Men							
55	0.8	2.8	5.4	9.6	15.2	20.1	23.8 (15.6-26.9)
60	2.1	4.7	8.9	14.6	19.6		23.3 (15.1-26.4)
65	2.8	7.3	13.4	18.7			22.7 (14.3-25.8)
70	5.0	11.6	17.5				21.9 (13.3-25.2)
75	7.9	14.9					20.2 (11.1-23.8)
80	9.2						16.1 (6.4-20.3)
>85							11.8 (1.3-17.2)
Women							
55	0	1.0	2.9	7.2	11.1	16.3	22.2 (14.7-24.8)
60	0.9	2.9	7.2	11.2	16.4		22.3 (14.8-24.9)
65	2.0	6.4	10.6	19.1			22.1 (14.6-24.8)
70	4.6	9.0	14.7				21.1 (13.4-23.8)
75	4.8	11.2					18.3 (10.2-21.2)
80	7.4						15.3 (7.4-18.9)
>85							11.8 (1.9-14.1)

Table 5 Incidence rates of atrial fibrillation in 3 population-based studies

	Framingham Study	Rotterdam Study	Cardiovascular Health Study
Men			
55-64		3.1	2.2
65-74		~9.0	9.9
65-69			12.3
70-74			22.8
75-84	~18	21.9	
75-79			34.8
≥80			58.7
≥85	38	25.4	
Women			
55-64	1.9	1.6	
65-74	~5.0	7.7	
65-69			10.9
70-74			9.1
75-84	~15	15.4	
65-69			23.1
≥80			25.1
≥85	31.4	16.2	

Rates are per 1000 person-years.

Discussion

In this large population-based study the prevalence of atrial fibrillation increased with age and was higher in men than in women in each age group. The incidence of atrial fibrillation was also higher in each successive age group, except for those who were older than 85 at baseline. The incidence rate was higher in men than in women. The lifetime risk of atrial fibrillation was high with only small differences between the sexes.

In the Rotterdam Study, we had, besides ECG data, the opportunity to survey general practitioner files over a considerable period before the start of the study and this may have helped us to obtain more reliable (but high) prevalence figures. The Cardiovascular Health Study reported prevalence figures that were lower in most age groups in comparison with our study.[8] A study in the Mayo Clinic reported relatively high prevalence figures in the elderly.[10] Also, Lake et al in Australia reported prevalence figures that were similar to the present study.[9]

Several problems in the assessment of atrial fibrillation may cause the differences between studies. Atrial fibrillation is characterized by its well-documented temporal pattern and many patients with atrial fibrillation have no hospital contact.[16] Furthermore, many patients are unaware of the presence of atrial fibrillation or periods of atrial fibrillation.[33] These problems indicate that assessment of atrial fibrillation indeed should be based on actual measurements by ECG, on information from general practitioners and on hospital records.

Our incidence rates are similar to those reported from the Framingham Study. In the age category 85 years and older, however, a higher incidence was reported in the Framingham Study, especially in women (Table 5). The Framingham Study started much earlier than the present study, and measurements in populations may have made participants and physicians more aware of health and disease resulting in interventions. This may have caused participants with diseases that facilitate atrial fibrillation to have a better survival in the Framingham Study. The incidence figures of the Cardiovascular Health Study were almost twice as high as in our study, but this cohort is older than the Rotterdam Study population. This alone cannot explain the difference, as in all age strata the incidence figures were still higher in the Cardiovascular Health Study. Furthermore, differences in racial demography and/or co morbidity between the cohorts may have lead to differences in the incidence figures. Other ascertainment methods in the Cardiovascular Health Study (e.g. self report of atrial fibrillation by participants) may also have played a role.

In the present study, prevalence figures were higher at two points during follow up than at baseline. In the Framingham Study, the prevalence over several biennial surveys rose, independent of changes in age and gender.[34,35] In general, the prevalence of a disease can rise over time due to more attention from clinicians and general practitioners for the disease of

interest in the course of time, leading to a smaller proportion that remains undetected, due to better survival of participants with atrial fibrillation and due to a better survival of those clinical conditions that are risk factors of atrial fibrillation. Our data however indicate that aging of the cohort was mainly responsible for the rise in prevalence in the Rotterdam Study in the time window 1990-2000.

We calculated lifetime risks of atrial fibrillation of 23.8% for men aged 55 years and 22.2% for women aged 55 years, which correspond very well with recent data on the lifetime risk of developing atrial fibrillation in the Framingham Study.[36] The difference between the sexes was small, and while risk in men was always higher over small time periods than in women, the similar lifetime risks probably reflect the better life expectancy of women. Lifetime risks of atrial fibrillation remained high and unchanged over a wide range of ages (55-75 years), indicating that there is equilibrium between rising death rate and rising incidence of atrial fibrillation. After the age of 75 years, lifetime risks declined in spite of the increasing incidence rate, through increasing death rates and decreasing life expectancy. However, our data from the Rotterdam Study is almost totally Caucasian, and extrapolation to other populations should be done with caution.

In conclusion, prevalence and incidence figures are presented from a large prospective, population-based Dutch study. These data are the first European data that enable a comparison between populations in Western Europe and in North America. The prevalence and incidence of atrial fibrillation are high, increase with age, are higher in men than in women and result in a very substantial lifetime risk.

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Chapter 3.1

Intake of very long-chain n-3 fatty acids from fish and incidence of atrial fibrillation

Abstract

Background Atrial fibrillation is the most common sustained cardiac arrhythmia. It is a major cause of morbidity and mortality through an increased risk of thromboembolic stroke. Experimental as well as observational evidence suggests that n-3 polyunsaturated fatty acids may have antiarrhythmic effects. The objective of this study was to examine whether high intakes of fish and its very long-chain n-3 fatty acids eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) are associated with risk of incident atrial fibrillation.

Methods We used data from the Rotterdam Study, a prospective cohort study. At baseline, dietary intake data were available for 5184 subjects free from atrial fibrillation. Dietary intake was assessed using a semi quantitative food-frequency questionnaire, and incidence of atrial fibrillation was continuously monitored during follow-up. Cox proportional hazards model (adjusted for lifestyle and disease factors) was used to examine the associations between intakes of EPA plus DHA and of fish with atrial fibrillation.

Results After a mean follow-up of 6.4 ($\pm$1.6) years, 312 subjects developed atrial fibrillation. Intake of EPA and DHA in the third textile compared with first was not associated with risk of atrial fibrillation (relative risk 1.18, 95% CI 0.88-1.57). Furthermore, no association was observed with intake of $\geq$20 g/d fish compared with no fish intake (relative risk 1.17, 95% CI 0.87-1.57).

Conclusion In this study, intakes of EPA and DHA and the consumption of fish were not associated with the onset of atrial fibrillation. This finding does not support that n-3 fatty acids have a general antiarrhythmic effect.

Introduction

Very long-chain n-3 polyunsaturated fatty acids (n-3 PUFAs) primarily occur in the diet in fish. Intakes of fish and fish products or its n-3 fatty acids may reduce cardiovascular mortality and sudden cardiac death.[1-4] Clinical trials show that only a few months of moderate intakes of n-3 PUFA are needed to decrease the risk of cardiac events.[5-7] This suggests an immediate effect of n-3 fatty acids on arrhythmia rather than a slow effect via reduced progression (or regression) of atherosclerosis. Moreover, observational studies show a strong relationship of eating fish and blood levels of n-3 fatty acids with fatal coronary heart disease and sudden cardiac death, but not with non-fatal heart disease.[2,4,8,9] In addition, in vitro and animal model experiments show that n-3 fatty acids increase the threshold for arrhythmias and almost totally prevent ventricular fibrillation.[10] Thus, experimental as well as observational evidence suggests that n-3 PUFA may have general antiarrhythmic effects that protect against sudden death. Atrial fibrillation is the most common sustained cardiac arrhythmia. It is a major cause of morbidity and mortality through an increased risk of thromboembolic stroke.[11-14] The prevalence of atrial fibrillation increases with advancing age, making atrial fibrillation a particular problem among elderly. It can be postulated that intake of n-3 fatty acids in humans not only influences ventricular arrhythmia, but also atrial arrhythmia. One recent study[15] found an inverse association of atrial fibrillation with intake of tuna or other broiled or baked fish, but not with intake of fried fish or fish sandwiches (fish burgers). The authors ascribe this difference to the different n-3 fatty acid content of various fishmeals. However, they did not actually assess intake of n-3 fatty acids. Another study showed no relationship between consumption of n-3 fatty acids from fish and atrial fibrillation. However, the authors could not exclude the possibility of residual confounding by intake of fish oil capsules.[16] In this prospective cohort study, we examined whether intakes of very long-chain n-3 fatty acids eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) from fish are associated with risk of atrial fibrillation in a population of men and women aged 55 years and older.

Methods

The Rotterdam Study

The Rotterdam Study is a large population-based prospective cohort study of the frequency and determinants of cardiovascular, neurological, locomotor, and ophthalmologic diseases in people aged 55 years and older. The Medical Ethics Committee of Erasmus University Rotterdam approved the study. All 10275 inhabitants from Ommoord, a suburb of Rotterdam,

the Netherlands, who were 55 years and older, were invited to participate in the study. Of these, 7983 subjects (response rate 78%) gave their written informed consent and participated in the study.[17] The participants were interviewed at their home and were examined during 2 visits at the research center for baseline data collection. The participants were reexamined twice during 2 follow-up rounds. The first round was performed between July 1993 and December 31, 1994. The second round started in April 1997 and ended December 31, 1999.

Baseline examinations

Information on current health status, medical history, and smoking behavior was obtained by a computerized questionnaire. Participants were classified as current or nonsmokers. Blood pressure was measured at the right upper arm with a random-zero sphygmomanometer with participants in sitting position. Systolic and diastolic blood pressures were calculated as the average of 2 consecutive measurements. Hypertension was defined as a systolic blood pressure of 160 mm Hg or higher or a diastolic blood pressure of 90 or higher, or the use of antihypertensive drugs. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Diabetes was defined as the use of antidiabetic medication or a post-load or preload serum glucose level equal to or higher than 11.1 mmol/L. A history of myocardial infarction was defined as a self reported myocardial infarction with hospital admission or the presence of myocardial infarction on the electrocardiogram (ECG); both were subsequently confirmed by a review of the medical records of general practitioners (GPs) and specialists for the presence of myocardial infarction.

Dietary assessment

Dietary assessment was performed in 2 stages at baseline. First, participants completed a checklist at home, on which they indicated all foods and drinks they had consumed at least twice a month during the preceding year. This checklist also contained questions on use of dietary supplements. Subsequently, a trained dietician at the research center interviewed the participants using an extensive, validated, semi quantitative food-frequency questionnaire.[18, 19] Participants were specifically asked to indicate the frequency, amount, and kind of fish eaten with the hot meal, on a sandwich, and in between meals. The food intake data were converted to energy and nutrient intake using the computerized Dutch Food Composition Table.[19,20] Intake of specific fatty acids was based on a food composition database derived from the TRANSFAIR study.[21,22] For this database, the 100 food items that contribute most to total fat intake in the Dutch dietary pattern were sampled and analyzed as methyl esters of the fatty acids present in the food. All fat intakes were calculated as grams per day.

Diagnosis of atrial fibrillation

Three methods were used to assess cases of atrial fibrillation or atrial flutter. (1) At baseline and during follow-up examinations, 10-second 12-lead ECGs were recorded at the research center with an ACTA Gnosis IV ECG recorder (EsaOte, Florence, Italy), stored digitally, and analyzed with the modular ECG analysis system (MEANS).[23,24] MEANS is characterized by a high sensitivity (96.6%) and a high specificity (99.5%) in coding arrhythmias.[25] To verify the diagnosis of atrial fibrillation, all ECGs with a diagnosis of atrial fibrillation or atrial flutter or any other rhythm disorder were recorded independently by 2 physicians who were blinded to the MEANS diagnosis. The judgment of a cardiologist was asked and taken as decisive in case of persistent disagreement. (2) GPs participating in the Rotterdam Study sent computerized information on atrial fibrillation, based on their own records and on hospital discharge letters, to the researchers of the Rotterdam Study. Specially trained follow-up assistants verified this information. A senior physician examined all the information and coded the events according to the International Classification of Diseases (code I48 of the 10th revision). For a diagnosis of atrial fibrillation or atrial flutter, we required an ECG that verified the diagnosis. (3) Hospital discharge diagnoses were also obtained from the Landelijke Medische Registratie system. This national registration accumulates all hospital discharge diagnoses of Dutch inhabitants.

To ascertain atrial fibrillation at baseline, we used ECGs as described above. In addition, the GP files of all participants were screened for the presence of atrial fibrillation at or before baseline. For the assessment of incident atrial fibrillation cases, we used ECGs obtained during the follow-up measurements, the information from the GP files and the information from the Landelijke Medische Registratie system. We did not consider a person as having atrial fibrillation if (1) atrial fibrillation occurred during the process of dying and was not the cause of death or if (2) transient atrial fibrillation occurred during a myocardial infarction or a cardiac operative procedure. All study participants were followed from the date of baseline examination (1990-1993) to the date of onset of atrial fibrillation, the date of entry into the second follow-up round, or the date of death, which ever came first. If atrial fibrillation had been detected by the MEANS computer system only during one of the follow-up investigation rounds, the midpoint between the date of the concerning investigation round and the date of the former investigation round was taken as the date of onset. Hereafter, the GP files and the hospital discharges data set were searched to register a more precise date of onset if possible. In those cases in which the atrial fibrillation cases had not been detected by the MEANS computer program only, but (in addition) by the inspection of the GP files and/or the hospital discharges database, the earliest date that could be recorded was taken as the date of onset. Follow-up by January 1, 2000, was completed in 99.1% of the total potential follow-up time up to that date.

Vital status

Information on vital status was obtained on a regular basis from the Central Register of population of the Municipality of Rotterdam and from collaborating GPs and by obtaining information during follow-up rounds. For those participants for whom information on vital status remained missing, the Central Registry of Genealogy of the Netherlands was consulted. This national institute receives population registry record of those inhabitants of the Netherlands who have died.

Population for analysis

Our study population consisted of 5184 participants in the Rotterdam Study who had no atrial fibrillation at baseline or in their medical history and for whom a completed food-frequency questionnaire was available. We excluded 209 participants with AF diagnosed at baseline and 167 participants with a history of AF.

Data analysis

EPA plus DHA intake was categorized in tertiles of intake per day, resulting in the following categories: $\leq$43 mg, >43 and <144 mg, and $\geq$144 mg EPA plus DHA. Fish intake was classified in 3 categories: 0 (reference), >0 to 20, and $\geq$20 g/d. Crude incidence rates were calculated for tertiles of EPA plus DHA and for the 3 categories of fish intake. Cox proportional hazards models were used to examine the associations of intakes of EPA plus DHA and the onset of atrial fibrillation, and between the intake of fish and the incidence of atrial fibrillation. Hazard ratios expressed as relative risks (RRs) were calculated with their 95% CIs, adjusted for age, sex, and energy intake. Additional adjustments were made for diabetes mellitus, myocardial infarction, intake of saturated fat, intake of alcohol, smoking status, blood pressure, high-density lipoprotein (HDL) cholesterol levels, and total cholesterol levels, all measured at baseline. The analyses were repeated with exclusion of those subjects who had been diagnosed at baseline with history of myocardial infarction. Data were analyzed using SPSS version 11.0 for Windows (SPSS Inc, Chicago, IL).

Results

The study population comprised 2105 men and 3079 women with a mean age of 67.4 ± 7.7 years; 29.5% of the population reported no intake of fish at baseline. The mean intake of EPA plus DHA was 146 ± 192 mg/d. The mean daily intake of fish in the total population was 15.7 ± 18.7 g/d, which is approximately 1 fishmeal per week. Less than 0.5% of the study population

used supplements containing n-3 fatty acids. Table 1 shows the general characteristics of the study participants by categories of EPA plus DHA. During the follow-up period, 799 subjects (15.4%) died, of which 233 (4.5%) were as a result of cardiovascular causes. The prevalence and incidence of atrial fibrillation in our study were as expected and in line with the results of other studies (data not shown).

After a mean follow-up of 6.4 (±1.6) years, 312 subjects developed atrial fibrillation. Figure 1 shows survival free of atrial fibrillation for the different tertiles of EPA plus DHA intake. Dietary intakes of EPA plus DHA were not related to incidence of atrial fibrillation. The RR after adjustment for age, sex, and energy intake was 1.25 (95% CI 0.95-1.67) for the highest compared with the lowest tertile of intake. Additional adjustment for diabetes mellitus, myocardial infarction, intake of saturated fat, intake of alcohol, smoking status, blood pressure, HDL cholesterol levels, and total cholesterol levels did not considerably change the results; the fully adjusted model yielded an RR for incidence of atrial fibrillation of 1.18 (95% CI 0.88-1.57) (Table 2). The incidence of atrial fibrillation was also not significantly associated with fish intake after adjustment for age, sex, and energy intake; the RR was 1.27 (95% CI 0.95-1.70) for intakes more than 20 g/d compared with intakes of 0 g/d fish. After further adjustment for additional risk factors (Model 2), the RR became 1.17 (95% CI 0.87-1.57) for intakes of 20 g/d versus no intake of fish (Table 3). Exclusion of subjects with a previous myocardial infarction (N = 600) had no considerable effect on the results (Tables 2 and 3). Only 0.5% of the subjects reported intake of fish oil capsules. Exclusion of these subjects did not alter our results.

Table 1 Baseline characteristics of the study population per category of fish intake (N=5184)

	Tertiles of EPA plus DHA intake		
	≤43 (Reference)	*43-144*	*≥144*
Age (y) 68.2 ± 8.0	67.5 ± 7.6	66.4 ± 7.3	
Sex (% men)	38.2	39.8	43.8
Body mass indexMI (kg/m^2)	26.2 ± 3.5	26.4 ± 3.8	26.3 ± 3.7
Smoking status			
Current	23.4	22.6	24.9
Former	39.7	43.0	45.4
Never	36.8	34.4	29.8
Diabetes mellitus (%)	9.0	8.8	9.3
History of Myocardial infarction(%)	11.3	12.7	11.2
Hypertension (%)	19.9	18.7	21.3
Systolic blood pressure (mm Hg)	139 ± 22	138 ± 22	139 ± 22
Diastolic blood pressure	73 ± 11	73 ± 11	74 ± 11
Total cholesterol	6.62 ± 1.19	6.68 ± 1.16	6.77 ± 1.19
HDL cholesterol	1.35 ± 0.36	1.35 ± 0.36	1.38 ± 0.37
Glucose 6.7 ± 2.5	6.8 ± 2.6	6.8 ± 2.5	
Total energy intake (kJ/d)	8100 ± 2020	8178 ± 2047	8495 ± 2231
Intake total fat (g/d)	79.5 ± 26.5	80.1 ± 27.2	82.1 ± 28.4
Intake saturated fat (g/d)	32.0 ± 11.5	31.5 ± 11.3	32.1 ± 12.5
Intake trans fatty acids (g/d)	2.7 ± 1.3	2.6 ± 1.3	2.5 ± 1.3
Alcohol intake (g/d)	8.4 ± 13.4	10.0 ± 14.8	13.0 ± 17.1
Fish intake (g/d)	1.0 ± 2.2	11.9 ± 8.4	34.3 ± 20.0
EPA plus DHA (mg/d)	19.4 ± 12.3	87.8 ± 29.3	330 ± 237

Table 2 RR of incident atrial fibrillation with intake of EPA and DHA in 5184 Dutch men and women aged 55 years and older

	Tertiles of EPA plus DHA intake		
	≤43 (Reference)	*43-144*	*≥144*
No. of subjects	1728	1728	1728
Median intake (mg/d)	18.5	84.5	258.3
All subjects			
No. of events	96	111	105
Person-years	11 202	11 108	11 013
Incidence/1000 y	8.6	10.0	9.5
Relative Risk, model 1	1	1.22 (0.93-1.61)	1.25 (0.95-1.67)
Relative Risk, model 2	1	1.22 (0.92-1.61)	1.18 (0.88-1.57)
Subjects without previous MI			
No. of events	76	86	79
Person-years	9835	9657	9712
Incidence/1000 y	7.7	8.9	8.1
Relative Risk, model 1	1	1.22 (0.89-1.66)	1.20 (0.88-1.65)
Relative Risk, model 2	1	1.23 (0.90-1.69)	1.15 (0.83-1.60)

RRs were obtained by Cox proportional hazard analysis, with 95% CI in parentheses.

Model 1: adjusted for age, sex, and energy intake.

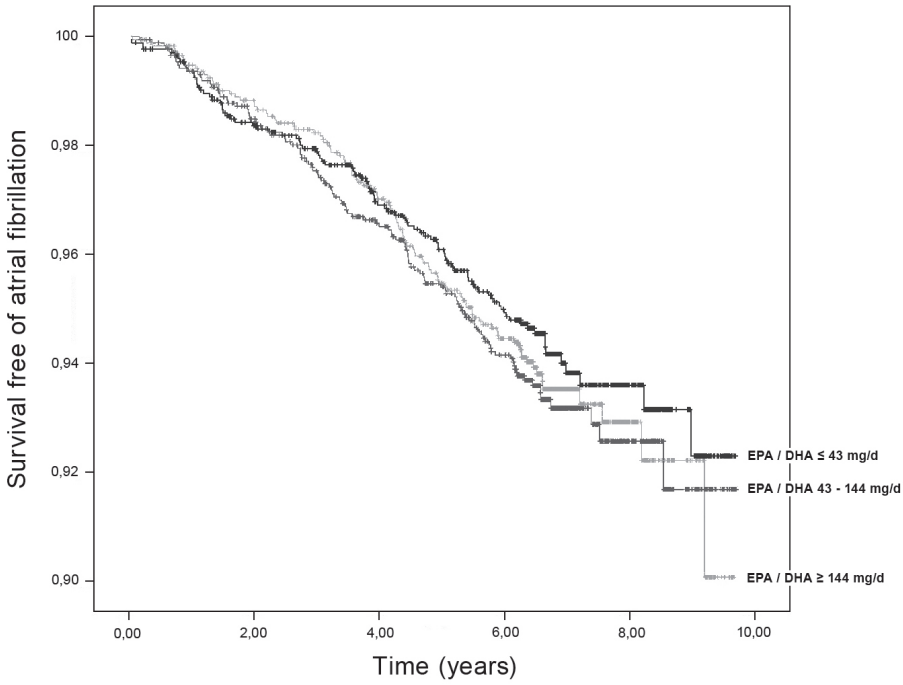
Model 2: adjusted age, sex, energy intake, diabetes mellitus, alcohol intake, systolic blood pressure, HDL and total cholesterol levels, intake of saturated fatty acids, smoking status, and previous myocardial infarction (except for subgroup analyses excluding subjects with a history of myocardial infarction).

Table 3 RR of incident atrial fibrillation with fish intake in 5184 Dutch men and women aged 55 years and older

	Categories of fish intake (g/d)		
	0 (Reference)	*>0 and <20*	*≥20*
No. of subjects	1527	2030	1627
Median intake (mg/d)	0	9.6	32.1
All subjects	All subjects		
No. of events	84	124	104
Person-years	9938	13 000	10 385
Incidence/1000 y	8.4	9.5	10.0
Relative Risk, model 1	1	1.17 (0.89-1.54)	1.27 (0.95-1.70)
Relative Risk, model 2	1	1.07 (0.81-1.42)	1.17 (0.87-1.57)
Subjects without previous MI			
No. of events	67	93	81
Person-years	8767	11220	9217
Incidence/1000 y	7.6	8.3	8.8
Relative Risk, model 1	1	1.14 (0.83-1.56)	1.24 (0.89-1.71)
Relative Risk, model 2	1	1.12 (0.81-1.53)	1.16 (0.84-1.62)

RRs were obtained by Cox proportional hazard analysis, with 95% CI in parentheses.
Model 1: adjusted for age, sex, and energy intake.
Model 2: adjusted age, sex, energy intake, diabetes mellitus, alcohol intake, systolic blood pressure, HDL and total cholesterol levels, intake of saturated fatty acids, smoking status, and previous myocardial infarction (except for subgroup analyses excluding subjects with a history of myocardial infarction).

Figure 1 Survival free of atrial fibrillation of subjects in the Rotterdam Study according to intake of EPA and DHA



Discussion

In our study population, higher intakes of EPA and DHA from fish were not inversely associated with the onset of atrial fibrillation. This finding is in line with Danish Diet, Cancer, and Health study, in which consumption of n-3 fatty acids from fish was not associated with the risk of atrial fibrillation.[16] However, in contrast, Mozaffarian et al[15] observed in their prospective cohort study an inverse association between the intake of tuna and other broiled and baked fish with the occurrence of atrial fibrillation.

Several factors may contribute toward a lack of association, including differences in age, potential confounding lifestyle factors, dietary changes during the follow-up period, and possible adverse effects of intake of fried fish. An important difference with the study of Mozaffarian et al. is that our participants were younger. Our population consisted of persons aged 55 years and older, with a mean age at baseline of 67 years, whereas the population of Mozaffarian et al consisted of persons aged 65 years and older, with a mean age of almost 73 years at baseline.[15]

Furthermore, adequate control for confounding by lifestyle factors is a major problem in studies of nutrients. It is possible that variables related to fish consumption are different between Europe and the United States. This may result in differences in residual confounding between studies.

Another explanation for not observing an association between n-3 and AF in our study is that subjects may have changed their diets as a consequence of disease. Therefore, we excluded subjects with previous atrial fibrillation from the analysis. We also repeated the analyses with exclusion of subjects who had a myocardial infarction. However, excluding these subjects did not materially affect the results. Therefore, we believe that it is unlikely that dietary changes as a consequence of disease can explain the absence of an association in our study.

Moreover, an association between intakes of n-3 fatty acids from fish and atrial fibrillation could also have been weakened by intake of fried fish, which is generally high in trans-fatty acids and relatively low in EPA and DHA. Intake of fried fish also often coincides with other unfavorable eating habits and lower socioeconomic class.[26] In addition, high levels of trans-fatty acids in the blood have been associated with a higher risk of a primary cardiac arrest.[27] We therefore repeated the analysis with exclusion of those subjects who reported intake of fried fish (N=1214). This resulted in an RR of 1.07 (0.76-1.49) for high versus low consumers of EPA plus DHA. Thus, consumption of fried fish consumers cannot explain the absence of an association in our study.

It has been suggested that a very modest to low intake of n-3 fatty acids from fish (200 mg/d) would be sufficient for the protective effect on heart disease risk, with little additional benefit of higher intakes.[2,4] Thus, a possible relationship between fish intake and heart disease could remain

undetected in populations in which almost all people already eat at least some fish. However, this does not apply to the Rotterdam study. As much as one third of the population reported no intake of fish at all. Furthermore, the range of fish intake in our study was sufficiently large to show an association if one would exist. In earlier analyses of the Rotterdam Study, associations between intake of n-3 fatty acids and mental diseases have been reported.[28,29] Thus, fish and n-3 fatty acids were measured accurate enough for detecting associations with health status. This makes errors in assessing fish intake or intake of n-3 fatty acids an unlikely explanation for the lack of association in our present analysis of risk of atrial fibrillation. Furthermore, Frost and Vestergaard[16] could not exclude the possibility of residual confounding caused by a lack of information on intake of fish oil tablets in their study. In our study, it is highly unlikely that residual confounding caused by intake of fish oil capsules has influenced our results.

Finally, the association could have been obscured because of misclassification of prevalent or incident atrial fibrillation. However, we believe that this explanation is highly unlikely. As described, we used 3 different methods to identify subjects with atrial fibrillation to ensure complete registration and not overlooking cases of atrial fibrillation. In addition, this approach enabled us to very precisely define the prevalent or incident status of atrial fibrillation cases. Furthermore, the prevalence and incidence of atrial fibrillation in our study were as expected and in line with the results of other studies.

Thus, in this prospective population-based study, we found no indication for a relationship between intake of either n-3 fatty acids from fish or fish itself and the incidence of atrial fibrillation. There is now a large body of evidence indicating that a higher intake of n-3 fatty acids reduces the risk of fatal heart disease.[1-4,30] The most plausible mechanism is that n-3 fatty acids reduce the risk of fatal heart disease through preventing cardiac arrhythmias. Indeed, there is evidence from cell, animal, and population studies supporting this hypothesis.[31] However, our current finding and the finding of Frost and Vestergaard[16] do not support a general antiarrhythmic effect of n-3 fatty acids. Nevertheless, we cannot exclude the possibility that n-3 fatty acids influence certain forms of cardiac arrhythmia, which are directly life-threatening, such as ventricular tachycardia and fibrillation. A more definitive answer will come from ongoing randomized controlled trials on clinically relevant end points.[32]

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Chapter 3.2

Subclinical atherosclerosis and atrial fibrillation

Abstract

Aims To investigate whether atherosclerosis affects the risk of atrial fibrillation in persons without overt coronary heart disease.

Methods The study was part of the Rotterdam Study, a population-based cohort study among subjects aged 55 years and over. The association between subclinical atherosclerosis and atrial fibrillation was examined in 4407 subjects without a history of myocardial infarction and/or angina pectoris and /or cardiac operative procedures and without atrial fibrillation at baseline. During a median follow-up of 7.5 years, 269 cases of atrial fibrillation were identified. Measures of atherosclerosis included intima-media thickness of the common carotid artery and the presence of carotid plaques. Relative risks (RR) were calculated with 95% confidence intervals (CI), adjusted for age, gender, body mass index, hypertension, systolic blood pressure, serum cholesterol level, smoking, diabetes mellitus, left ventricular hypertrophy on the ECG and the use of cardiac medication.

Results The risk of atrial fibrillation was associated with carotid intima-media thickness (RR 1.90; 95% CI 1.20-3.00), highest versus lowest quartile) and severity of carotid plaques (1.49; 1.06-2.10, severe versus absence). Risk estimates were stronger in women than in men.

Conclusion These data suggest that aggressive management of asymptomatic atherosclerotic vascular disease may help to prevent atrial fibrillation.

Introduction

Myocardial infarction is a strong predictor of atrial fibrillation, especially in men.[1] Myocardial damage, often in association with heart failure, contributes to the onset of atrial fibrillation in subjects with myocardial infarction. It is not known, however, whether the presence of coronary atherosclerosis without manifest myocardial infarction also causes atrial fibrillation. At a subclinical level, atherosclerotic vascular disease may cause some damage to myocardial tissue by a gradual reduction of the blood supply to the atrial tissues with ischemia/infarction and premature apoptosis of myocytes, fibrous tissue replacement and subsequent facilitation of re-entry processes.[2] The role of atherosclerosis in the development of atrial fibrillation is supported by results of studies in which atrial tissues were histologically investigated.[3-5]

Results of studies that examined the relation between atrial fibrillation and cardiac manifestations of atherosclerosis, such as angina pectoris in the absence of a myocardial infarction and angiographically demonstrated narrowing of coronary arteries without overt damage to the heart, are conflicting.[6-10] Studies dependent upon coronary angiographic documentation of coronary artery disease are also limited by the selected nature of the population studied and, by the very nature of this measurement, cannot be feasibly or ethically applied to large-scale population surveys. A non-invasive index of atherosclerosis using intima-media thickness and plaques measured by ultrasonography has been shown to be a good indicator of systemic atherosclerotic vascular disease, with a relation to the risk of stroke and myocardial infarction.[11] To our knowledge only one population-based study, the Cardiovascular Health Study, reported on the association between atherosclerosis and risk of atrial fibrillation. In that study, no significant associations were found between 2 measures of generalized atherosclerosis (carotid intima-media thickness and the ankle-arm index) and risk of atrial fibrillation.[7,10]

In the present population-based analysis from the Rotterdam study, we investigated the associations between intima-media thickness and plaques of the extracranial carotid arteries (as measured by ultrasonography) and the risk of atrial fibrillation in asymptomatic persons during a median follow-up of 7.5 years.

Methods

Study population

The Rotterdam Study is a population-based prospective cohort study aimed at assessing the occurrence and progression of and risk factors for chronic diseases in the elderly. Neurogeriatric, cardiovascular, locomotor and ophthalmologic diseases are the main areas of interest.[12] All

residents of the Rotterdam suburb Ommoord, aged 55 years and over, were invited to participate. Of the 10275 eligible individuals, 7983 (78%) responded. From 1990 to 1993, participants were interviewed at their home and 7151 were examined at the research center to obtain baseline measurements, including a 10-second 12-lead resting electrocardiogram (ECG). Those who did not visit the research center were in general dependent or lived in nursing homes. Participants were re-examined during two follow-up rounds. The first follow-up examination started July 1, 1993 and ended December 31, 1994. The second follow-up examination started April 1, 1997 and ended December 31, 1999. The medical ethics committee of the Erasmus University in Rotterdam approved the study and all participants gave informed consent.

Diagnosis of atrial fibrillation

Atrial fibrillation at baseline and during follow-up was ascertained using three methods, as described earlier.[13] In short, at baseline and during follow-up examinations 10-s 12-lead ECGs were recorded with an ACTA electrocardiograph (ESaOte; Florence; Italy), stored digitally and analyzed by the Modular ECG Analysis System (MEANS).[14-16] Additional information was obtained from the medical files of participating general practitioners, which included the results of their own work and those of physicians practicing in hospitals and outpatient clinics, and from a national registration of all hospital discharge diagnoses.

All study participants were followed-up from the day of entrance in the Rotterdam Study (1990-1993) to the date of onset of atrial fibrillation, the date of death or lost to follow-up or to January 1, 2000, whichever came first. Follow-up by January 2000 was complete for 99.1 % of the study population.

Measurements of atherosclerosis

The common carotid artery, the bifurcation and the internal carotid artery at both sides were visualized by ultrasonography using a 7.5 MHz transducer (ATL Ultramark IV, Advanced Technology Laboratories, Bethel, Washington, USA). Common carotid intima-media thickness was measured for a 1-cm length that was proximal to the bulbus. The anterior and posterior wall in the left and right common carotid artery were measured and averaged. The averages of the left and right side were added and divided by two, if measurements at both sides were available. When the result of one side was absent owing to poor visualization the result of the other side was used. A plaque was defined as a focal broadening of the intima-media relative to adjacent segments with protrusion into the lumen either composed of only calcified deposits or a combination of calcified and non-calcified material. The left and right common carotid arteries, left and right carotid bifurcation and left and right internal carotid arteries were examined for the presence of plaques. A weighted plaque score was obtained by counting the sites where a plaque

was visible and dividing this number by the total number of sites for which an ultrasonographic image was available. The result was multiplied by 6, the maximum number of sites. This score ranges from 0-6. Subjects were excluded from the analyses if visualization of more than 4 of the 6 sites had not been possible. All examinations were performed with the observer blinded to the clinical details of the participants.

Measurements of covariates

Information on current health status, medical history and smoking behavior was obtained using a computerized questionnaire. Participants were classified as current smokers, former smokers or never smokers. The body mass index was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured twice at the right upper arm with a random zero mercury sphygmomanometer in the sitting position. Systolic and diastolic blood pressures were calculated as the average of the two consecutive measurements. Hypertension was defined as a systolic blood pressure of 160 mmHg or higher or a diastolic blood pressure of 100 mmHg or higher or the use of blood pressure lowering drugs prescribed for hypertension. A history of myocardial infarction was defined as a self-reported myocardial infarction with hospital admission or the presence of a myocardial infarction on the ECG. A positive self-report of myocardial infarction was confirmed by reviewing the medical records of general practitioners and specialists. Angina pectoris was measured by the Rose questionnaire.[17] Left ventricular hypertrophy was diagnosed by the MEANS program with an algorithm that takes into account QRS voltages, with an age-dependent correction, and repolarization. Non-fasting blood samples were drawn by means of venipuncture. Serum total cholesterol levels were measured with an automated enzymatic method. Diabetes was defined as the use of anti-diabetic medication or a random or post-load serum glucose level of 11.1 mmol/L or higher. Cases of incident myocardial infarction were ascertained as described previously.[18]

Vital status

Information on vital status was obtained on a regular basis from the Central Register of Population of the municipality of Rotterdam, from collaborating general practitioners and by obtaining information during follow-up rounds. For those participants for whom information remained missing, the Central Registry of Genealogy of the Netherlands was consulted in The Hague. This national institute receives population registry records of those inhabitants of the Netherlands who have died.

Population for analysis

For the present study, an ECG was not available for analysis of atrial fibrillation in 343

participants who had visited the research center at baseline, mainly owing to logistic reasons. We additionally excluded 1666 participants belonging to at least one of the following categories: (1) Persons with a history of myocardial infarction (typical, silent or non-Q-wave) at baseline (N=871) or persons with insufficient data to exclude previous myocardial infarction (N=186). (2) Persons with angina pectoris as measured with the Rose questionnaire (N=454) and persons who had not completed the Rose questionnaire (N=103). (3) Participants with a history of a coronary artery bypass graft or a percutaneous transluminal coronary angioplasty (N=195). (4) Participants with atrial fibrillation at baseline (N=376). Thus, subjects for whom both an ECG was made at baseline and an ultrasonographic examination had been performed (N=4407) were included in the present study. Among these, 182 participants had missing information on the intima-media thickness measurement and 215 had missing information on carotid plaques. Measurements of the covariates in the population for analysis were complete for more than 99% of the study population, except for hypertension and body mass index (1.5% and 2% missing data, respectively). Participants with missing data on covariates were excluded in the analyses.

Statistical analysis

The distribution of the carotid intima-media thickness measurements was positively skewed. A natural logarithmic transformation was applied to obtain a more normal distribution. The natural log transformed intima-media thickness was categorized in quartiles based on the distribution of the population for analysis. Participants with a carotid plaque score of 0, 1, 2 and ≥3 were categorized as having no, mild, moderate and severe carotid atherosclerosis respectively. In the analyses, the lowest carotid intima-media thickness quartile and absence of carotid plaques were used as the reference categories. Age- and sex-adjusted hazard rate ratios, expressed as relative risks (RR) with their 95% confidence intervals (CI), were calculated using the Cox proportional hazards model with atrial fibrillation as the dependent variable and the atherosclerosis variables as the independent variables. Additional adjustments were made for body mass index, hypertension, systolic blood pressure, serum cholesterol level, smoking, diabetes mellitus, left ventricular hypertrophy on the ECG and the use of cardiac medication (digoxin, nitrates and anti-arrhythmic drugs). The analyses were further stratified by gender. In a secondary analysis we analyzed the associations after exclusion of those subjects in which incident myocardial infarction had preceded the onset of atrial fibrillation during the follow-up period. Data were managed and analyzed using SPSS for Windows, release 11.0. Population-attributable risks with 95% confidence intervals, adjusted for confounders, were calculated with IRAP, version 2.2.[19,20]

Results

The baseline characteristics are summarized in table 1. During a median follow-up of 7.5 years, 269 new cases (6.1%) of atrial fibrillation were identified. Of those, 44 cases (16.4%) were identified by the screening rounds only (N=38) or were identified by the screening process earlier than by any other method (N=6).

After adjustments for age and sex, statistically significant associations were found between carotid intima-media thickness and carotid plaques with the risk of atrial fibrillation. The associations were stronger for the higher quartiles of intima-media thickness and for increased severity of carotid plaques. After further adjustments for clinical features, the associations were somewhat attenuated, but remained statistically significant (table 2). The results for men and women separately are presented in table 3. In women, the associations between the atherosclerosis measures and the risk of atrial fibrillation were positive and statistically significant, and reflected a dose-response relationship. In men, however, the association between intima-media thickness and the risk of atrial fibrillation increased with increasing quartiles of intima media thickness, but this association was not statistically significant. No association was found between carotid plaques and the risk of atrial fibrillation in men. When we repeated the analyses excluding those new atrial fibrillation cases that developed following an incident myocardial infarction (N=13) the associations were not materially different (data not shown). The population-attributable risks associated with intima-media thickness and carotid plaques were 33% and 19% respectively.

Table 1 Baseline characteristics of the study population by gender

The Rotterdam Study, 1990-1999

Characteristic	Men N=1669 (37.9 %)	Women N=2738 (62.1%)
Age, y	67.1 ± 7.8	68.5 ± 8.8
Body mass index, kg/m^2	25.6 ± 2.9	26.6 ± 4.0
Hypertension, %	26.4	35.4
Systolic blood pressure, mm Hg	138.9 ± 22.0	139.4 ± 22.9
Diastolic blood pressure, mm Hg	75.3 ± 11.7	73.2 ± 11.5
Total cholesterol, mmol/L	6.3 ± 1.2	6.9 ± 1.2
HDL-cholesterol, mmol/L	1.24 ± 0.32	1.46 ± 0.36
Smoking, %		
Current	30.7	19.7
Former	60.9	28.3
Never	8.5	52.0
Diabetes mellitus, %	8.1	9.5
Left ventricular hypertrophy, %	4.4	3.8
Cardiac medication, %	3.2	5.0
Intima-media thickness, mm	0.84 ± 0.15	0.80 ± 0.14
Intima-media thickness, mm*	0.82 (0.73-0.92)	0.78 (0.70-0.88)
Carotid plaques, %		
No	40.1	47.0
Mild	15.8	17.9
Moderate	17.4	16.3
Severe	26.6	18.7

Numbers are mean ± SD for continuous variables and percentages for dichotomous variables.
Cardiac medication indicates the use of digoxin, nitrates or anti-arrhythmic drugs.
* Median value with interquartile range between ( ).

Table 2 Measures of atherosclerosis and risk of atrial fibrillation

The Rotterdam Study, 1990-1999

Characteristic	Cases/subjects	RR (95% CI) Model 1)	RR (95%CI Model 2
Carotid intima-media thickness			
1st quartile	30/1056	1 (Reference)	1 (Reference)
2nd quartile	42/1057	1.12 (0.70-1.79)	1.13 (0.70-1.83)
3rd quartile	86/1056	2.09 (1.36-3.20)	1.99 (1.28-3.10)
4th quartile	98/1056	2.12 (1.36-3.29)	1.90 (1.20-3.00)
Carotid plaques			
No	80/1860	1 (Reference)	1 (Reference)
Mild	47/718	1,29 (0.90-1.86)	1.33 (0.92-1.94)
Moderate	46/701	1.23 (0.85-1.78)	1.19 (0.81-1.73)
Severe	77/913	1.51 (1.09-2.09)	1.49 (1.06-2.10)

Model 1: adjusted for age and gender.
Model 2: adjusted for age, gender, body mass index, hypertension, systolic blood pressure, total serum cholesterol level, smoking, diabetes mellitus, left ventricular hypertrophy on the ECG and cardiac medication.
Abbreviations: RR, Relative risk; CI, Confidence interval.

Table 3 Measures of atherosclerosis and risk of atrial fibrillation, by gender

The Rotterdam Study, 1990-1999

Characteristic	Cases/subjects	RR (95%CI) Model 1	RR (95%CI) Model 2
	Men		
Carotid intima-media thickness			
1st quartile	12/317	1 (Reference)	1 (Reference)
2nd quartile	15/367	0.88 (0.41-1.89)	1.01 (0.46-2.21)
3rd quartile	30/417	1.48 (0.75-2.93)	1.67 (0.81-3.43)
4th quartile	40/498	1.48 (0.75-2.93)	1.61 (0.77-3.36)
Carotid plaques			
No	34/637	1 (Reference)	1 (Reference)
Mild	18/251	1.18 (0.67-2.10)	1.18 (0.66-2.12)
Moderate	10/270	0.57 (0.28-1.17)	0.55 (0.27-1.12)
Severe	32/425	1.19 (0.73-1.96)	1.12 (0.67-1.88)
	Women		
Carotid intima-media thickness			
1st quartile	18/739	1 (Reference)	1 (Reference)
2nd quartile	27/690	1.27 (0.70-2.33)	1.20 (0.65-2.20)
3rd quartile	56/639	2.54 (1.46-4.40)	2.26 (1.30-3.95)
4th quartile	77/913	2.63 (1.48-4.67)	2.14 (1.19-3.86)
Carotid plaques			
No	46/1223	1 (Reference)	1 (Reference)
Mild	29/467	1.38 (0.86-2.21)	1.46 (0.90-2.37)
Moderate	36/425	1.79 (1.15-2.80)	1.73 (1.09-2.76)
Severe	45/488	1.79 (1.16-2.76)	1.84 (1.17-2.90)

Model 1: adjusted for age.

Model 2: adjusted for age, body mass index, hypertension, systolic blood pressure, total serum cholesterol level, smoking, diabetes mellitus, left ventricular hypertrophy on the ECG and cardiac medication.

Abbreviations: RR, Relative risk; CI, Confidence interval.

Discussion

In this population-based study, we found that atherosclerosis was associated with new onset atrial fibrillation in subjects without a history of coronary heart disease. The indices of atherosclerosis used in this study have been shown to be measures of generalized atherosclerosis.[21,22] The results suggest that atherosclerosis may be a causal factor in the etiology of atrium fibrillation even when no overt coronary heart disease is present.

To our knowledge, the Cardiovascular Health Study is the only population-based study that previously investigated associations between measures of atherosclerosis and atrial fibrillation.[7,10] In that study carotid intima-media thickness and the ankle-arm index were not associated with incident atrial fibrillation. The reason for the discrepancy with our findings is not clear. There are, however, important differences in populations, ascertainment methods and analyses between the two studies. For example, the Cardiovascular Health Study included atrial fibrillation cases by self-report, and the proportion of those who had a history of a myocardial infarction in the Cardiovascular Health Study was lower than in the Rotterdam Study (9.2% versus 13.2%) in spite of the older mean age of the Cardiovascular Health Study population.[23] The older age of the study population of the Cardiovascular Health Study is notable, as one could speculate that associations between atherosclerosis variables and atrial fibrillation may be less at older age through competing vascular risks. In addition, associations in the Cardiovascular Health Study were adjusted for left atrial size, valvular disease and a coronary injury score based on ECG characteristics which may be highly correlated with atherosclerosis and thus could obscure a relation between atherosclerosis and atrial fibrillation. An analysis from the Manitoba Follow-up Study, where angina without myocardial infarction and ST-T wave changes without clinical evidence of ischemic heart disease were independently associated with the onset of atrial fibrillation, supports our hypothesis that atherosclerotic vascular disease is associated with atrial fibrillation.[9]

Associations of carotid intima-media thickness and risk of atrial fibrillation were weaker in men than in women, and the association between carotid plaques and atrial fibrillation was absent in men. We are unable to fully explain these differences between the sexes, but one possibility is that men with a high degree of atherosclerosis have died from cardiovascular disease before entering our study or before the development of atrial fibrillation.

Reliable associations strongly depend on accurate incidence figures. Population-based incidence figures of atrial fibrillation, however, are rare. Our incidence rates are similar to those reported by the Framingham Study. The incidence figures of the Cardiovascular Health Study, however, are twice as high, but this cohort is of participants older than 65 years and probably reflects the older age of that cohort and other ascertainment methods.

We could hypothesize that atherosclerosis, either gradually or abruptly, reduces the blood supply to the sinus node and the atrial tissues that affect the gradual spreading of the electrical impulse over the atria and a normal contraction of the atria. This reduced flow may result in fibrosis and microscopic scarring of the atrial wall,[2] inducing areas with reduced conduction or even blocked conduction. Areas in the atria with decreased conduction velocity have been shown to favor re-entry mechanisms, which can result in the development of atrial fibrillation.[24,25] Ischemia itself, however, may also shorten the refractory period and decrease the conduction velocity, potentially facilitating re-entry processes and the onset of atrial fibrillation.[26] These hypotheses are also supported by several pathology studies and experimental studies.[2,4,27] For example, in a study of subjects with longstanding atrial fibrillation, nodal artery stenosis was present without distinct lesions of the sinus node or the internodal tracts, suggesting that diminished blood flow may play a role in the origin of atrial fibrillation in these cases.[4] Also, in another large pathological study, approximately 16% of subjects with longstanding atrial fibrillation had moderate to severe coronary artery disease without any histological evidence of infarction.[3] Finally, it has been postulated that the sinus node artery plays an essential role in the synchronization of the numerous sites of automaticity within the sinus node. Dysfunction or rigidity of the sinus node artery could thus lead to a state of decreased rhythmic stability.[28]

Our study is limited by the assumption that measures of non-coronary atherosclerosis are a marker of the extent of coronary atherosclerosis. However, we previously found that the measures of non-coronary atherosclerosis, including carotid intima-media thickness and carotid plaques, were strongly associated with coronary calcification, as measured by electron beam computed tomography.[21] Not all participants of the Rotterdam Study who completed the baseline examinations had an ultrasonographic examination, due to a restricted availability of ultrasonographers at the end of 1992 and in 1993. Therefore, missing data on the ultrasonographic examinations were random and not based on disease status of participants. We did not distinguish between atrial fibrillation (paroxysmal or permanent) and atrial flutter when identifying cases, but these arrhythmias have the same risk factors and the same consequences.[29,30] Moreover, periods of atrial fibrillation in paroxysmal atrial fibrillation are much more common than is generally perceived by patients or their physicians and over time, paroxysmal atrial fibrillation in a very high proportion changes into chronic atrial fibrillation.[31,32]

In aging populations, as is the case in Western Europe, atrial fibrillation will become progressively more important as the prevalence of atrial fibrillation increases sharply with age.[13] Atrial fibrillation is associated with considerable morbidity and mortality, increasing numbers of hospital admissions and rising costs.[33-38] Our findings suggest that the impact of atherosclerosis on the development of atrial fibrillation may be larger than is commonly thought. The results indicate that management of atherosclerotic vascular disease and its risk factors in the general

population and aggressive treatment of participants with higher levels of atherosclerosis may contribute to a decrease in the incidence of atrial fibrillation, thereby lowering disease burden and costs. The population-attributable risks for intima-media thickness of 33% and for carotid plaques of 19% suggest that successful treatment of atherosclerosis may result in a considerable reduction of atrial fibrillation cases in the community.

In conclusion, in this prospective, population-based study, we found that measures of generalized atherosclerosis predict the onset of atrial fibrillation in persons without obvious coronary heart disease. The findings suggest that aggressive management of atherosclerotic vascular disease, including in asymptomatic subjects, may help to prevent atrial fibrillation.

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Chapter 3.3

Cigarette smoking and risk of atrial fibrillation

Abstract

Background Cigarette smoking is an important risk factor for cardiovascular disease but it is unknown whether it also contributes to the risk of atrial fibrillation.

Methods The study is part of the Rotterdam Study, a population-based cohort study among subjects aged 55 years and over. The association between cigarette smoking and the risk of atrial fibrillation was examined in 5668 subjects without atrial fibrillation at baseline. During a median follow-up of 7.2 years, 371 cases of atrial fibrillation were identified. Relative risks (RR) were calculated with 95% confidence intervals (CI) using the Cox proportional hazards model, adjusted for age, gender, body mass index, hypertension, systolic blood pressure, serum cholesterol level, diabetes mellitus, left ventricular hypertrophy on the ECG, prevalent and incident myocardial infarction, prevalent heart failure and the use of pulmonary medication.

Results After multivariate adjustment, current smokers and former smokers had increased risks of atrial fibrillation as compared to never smokers (RR 1.51; 95% CI 1.07-2.12 and 1.48; 1.12 -1.96, respectively). No differences were found between men and women.

Conclusions The results of this prospective, population-based study show that current and former smoking of cigarettes are associated with increased risk of atrial fibrillation.

Introduction

Tobacco smoking is the best-documented preventable risk factor for cancer[1] and cardiovascular disease.[2,3] Tobacco smoking harms the heart through several mechanisms. In general, smoking causes or aggravates endothelial dysfunction and atherosclerosis and causes cardiac rhythm disorders through the combined effects of nicotine, carbon monoxide and polycyclic aromatic hydrocarbons.[4-10] Tobacco smoking may thus change the myocardial substrate as well as action potentials. Both processes provoke and facilitate atrial fibrillation. Several case reports are presented on the onset of atrial fibrillation following the ingestion of nicotine,[11,12] but the results of population-based studies on the association between smoking and atrial fibrillation are conflicting.[13-18] Therefore, we investigated the association of cigarette smoking with the onset of atrial fibrillation in a large prospective population-based study, the Rotterdam Study.

Methods

Study population

The Rotterdam Study is a prospective population-based cohort study aimed at assessing the occurrence and progression of and risk factors for chronic diseases in the elderly. Neurogeriatric, cardiovascular, locomotor and ophthalmologic diseases are the main areas of interest.[19] All residents of the Rotterdam suburb Ommoord, aged 55 years and over, were invited to participate. Of the 10275 eligible individuals, 7983 (78%) responded. Between 1990 and 1993, participants were interviewed at their home and 7151 were examined at the research center to obtain baseline measurements, including a 10 second 12-lead resting electrocardiogram (ECG). Those who did not visit the research center were in general dependent or lived in nursing homes. Participants were re-examined during two follow-up rounds. Follow-up examinations were performed between July 1993 and December 31st 1994 and between April 1997 and December 31st 1999. The Medical Ethics Committee of the Erasmus University approved the study and all participants gave informed consent.

Assessment of smoking

Information on smoking behavior was obtained using a computerized questionnaire during the home visit. Participants were classified as current smokers, former smokers or never smokers. Current smokers were participants who answered yes to the question: “are you currently smoking?” Former smokers were participants who answered no to this question but who positively answered the question: “are you a former smoker?” Both current and former

smokers answered additional questions on smoking habits (cigarettes, pipes or cigars), amount of smoking, duration of smoking and on age of starting and of stopping, if applicable.

Diagnosis of atrial fibrillation

Atrial fibrillation cases were ascertained at baseline and during follow-up as described previously.[20] In short, ECGs were recorded with an ACTA electrocardiograph (ESaOte; Florence; Italy), stored digitally and analyzed by the Modular ECG Analysis System (MEANS).[21-23] Two research physicians and a cardiologist verified this information. Additional information was obtained from general practitioner files, from outpatient clinics and from a national registration system that accumulates all hospital discharge diagnoses of Dutch inhabitants. We did not distinguish between atrial fibrillation and atrial flutter when we identified cases.[24,25] Further, we did not discriminate between paroxysmal atrial fibrillation and chronic atrial fibrillation.[26,27] Those who developed atrial fibrillation during a serious disease resulting in death very shortly after the detection of atrial fibrillation, whilst atrial fibrillation was not the cause of the serious disease, were not considered as having atrial fibrillation. They were censored on the date of detection of atrial fibrillation. Furthermore, subjects with atrial fibrillation during myocardial infarction or during cardiac operative procedures who permanently recovered during the hospital admission were not included among the cases.

Measurement of covariates

Covariates were measured by a computerized questionnaire taken at the baseline home visit and by the investigations at the Rotterdam study research center during two visits including the current use of medication. The information on medication obtained from the home interview was completed by the computerized information from the collaborating pharmacies. Details have been described in detail elsewhere.[20] Of note, hypertension was defined as a systolic blood pressure of 160 mmHg or higher or a diastolic blood pressure of 100 mmHg or higher or the use of blood pressure lowering drugs prescribed for hypertension. A history of myocardial infarction was defined as a self-reported myocardial infarction with hospital admission or the presence of a myocardial infarction on the ECG, confirmed by reviewing the medical records of general practitioners and specialists. Myocardial infarction during follow-up was ascertained using ECGs obtained during the two follow-up rounds and using the information from participating general practitioners, from outpatient clinics and from hospital admissions. Left ventricular hypertrophy was diagnosed by the MEANS program with an algorithm that takes into account QRS voltages, with an age-dependent correction, and repolarization.[28] Diabetes was defined as the use of anti-diabetic medication or a random or post-load serum glucose level of 11.1 mmol/L or higher. Assessment of heart failure at baseline in the Rotterdam Study has been described in detail previously.[29]

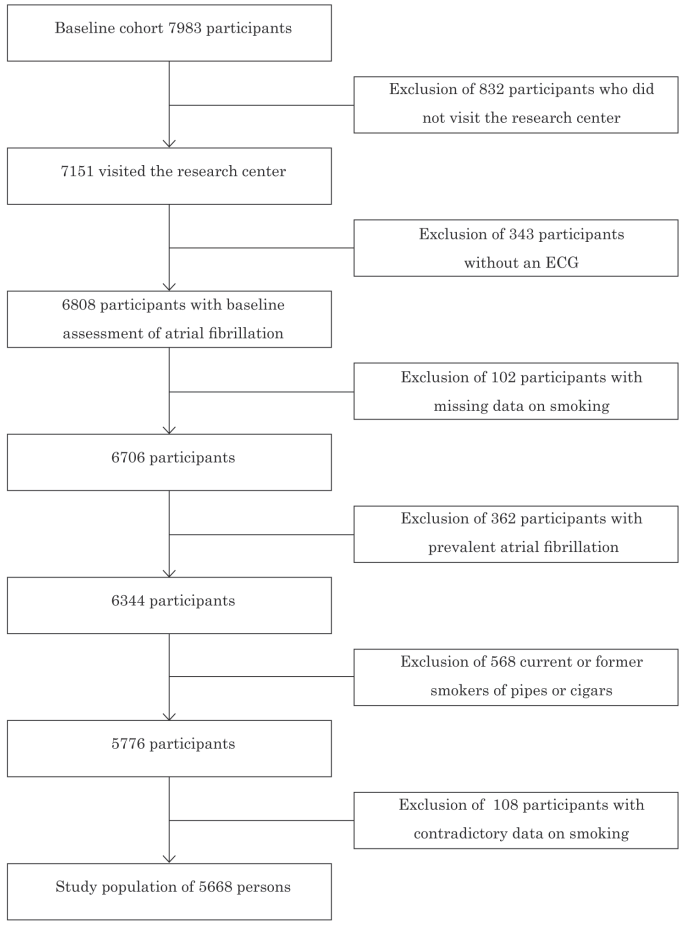
Vital status

Information on vital status was obtained on a regular basis from the Central Register of population of the municipality of Rotterdam, from collaborating GPs and by obtaining information during follow-up rounds. For those participants for whom information remained missing, the Central Registry of Genealogy of the Netherlands was consulted.

Population for analysis

Our study population consisted of 5668 participants who had no trial fibrillation at baseline and for whom reliable information on smoking was available. Former and current smokers of pipes or cigars were excluded. (Figure 1).

Figure 1 Selection of the study population



Statistical analysis

Current and former smokers were further categorized into tertiles based upon duration of smoking in years and upon the amount of smoking. Age and gender adjusted hazard rate ratios, expressed as relative risks (RR) with their 95% confidence intervals (CI), were calculated using the Cox proportional hazards model with incident atrial fibrillation as the dependent variable and categories of smoking as the independent variable. In all analyses, never smokers formed the reference category. Additional adjustments were made for prevalent and incident myocardial infarction, body mass index, hypertension, systolic blood pressure, serum cholesterol level, diabetes mellitus, left ventricular hypertrophy on the ECG, heart failure at baseline and the use of medication prescribed for obstructive pulmonary disease or emphysema. Smoking is associated with a higher risk of dying from several causes, which may obscure potential associations between smoking and atrial fibrillation through competing risk. Therefore we investigated in a secondary analysis the association between smoking and risk of mortality. In this analysis atrial fibrillation cases were censored on the date of onset. We additionally computed a Kaplan-Meier curve of death and atrial fibrillation by age. To investigate whether the risk of atrial fibrillation was different in men and women we added an interaction term to the final model for smoking and gender. In a secondary analysis we also evaluated the risks of smoking and atrial fibrillation in the age group 75 years and younger and in the age group older than 75 years. The p-value for significance for all analyses was 0.05. Complete, non-missing records were available in 94.4% of the participants. Missing values for cardiovascular risk factors were added using the expectation-maximization algorithm.[30] Data were managed and analyzed using SPSS for Windows, release 11.0.

Results

The baseline characteristics are presented in table 1. Those who had never smoked (N=2229) were in general slightly older than former smokers (N=2159) and considerably older than current smokers (N=1280). Never smokers consisted almost entirely of women (90.7%). Current smokers had been smoking a median number of 45 years (range 4-85 years). The median number of cigarettes per day in this group was 15 (range 1-50 cigarettes). Corresponding numbers for former smokers were 28 years (range 1-83 years) and 15 cigarettes per day (range 1-100). During a median follow-up of 7.2 years, 371 new cases of atrial fibrillation were identified. After adjustments for age and gender statistically significant associations were found of both current (RR 1.50 (95% CI 1.07-2.10)) and former smoking (1.49 (95% CI 1.14-1.97)) with risk of atrial fibrillation (Table 2). After additional adjustments, the associations did not change materially.

The results in men and women were not significantly different. The p-value for interaction current smoking*gender was 0.81 and the p-value for interaction former smoking*gender was 0.61. For this reason, and because of small numbers, we did not stratify our further analyses on amount and duration of smoking for gender. When we stratified by age we found that the relative risk estimates slightly decreased for current smoking and were close to one for former smoking in the oldest group (Table 3).

In current smokers, a significantly increased risk as compared to never smokers was only found for the first tertile of both duration of smoking and amount of smoking (Table 2). The associations were weaker and no longer statistically significant when participants in the second and third tertile were compared to never smokers.

In former smokers, however, we found that increasing duration of smoking was associated with the risk of atrial fibrillation in a way that is compatible with a dose-response relationship. This was also the case for the age and gender adjusted association of the amount of smoking with atrial fibrillation, but the dose-response relationship disappeared after additional adjustments (Table 2).

The results of the analysis of mortality are shown in table 4. In current smokers an increased risk of mortality was found in all categories of duration and amount of smoking. The risks were approximately equally high for the three tertiles of duration, with a tendency towards a lower risk in the highest tertile. The amount of current smoking was associated with the risk of mortality in a pronounced, dose-response relationship. Subjects who had stopped smoking had only a slightly and not statistically significant increased risk of mortality.

Table 1 Baseline characteristics by smoking behavior

The Rotterdam Study

Characteristic	Never smokers (N=2229)	Former smokers (N=2159)	Current smokers (N=1280)
Age (years)	71.2 (9.8)	67.4 (7.6)	65.8 (7.4)
Gender (% women)	90.7	45.8	52.9
Body mass index (kg/m^2)	26.8 (3.9)	26.5 (3.5)	25.5 (3.9)
Hypertension (%)	38.5	34.4	27.5
Systolic blood pressure (mm Hg)	142 (22.9)	138.2 (21.7)	136.2 (22.7)
Total serum cholesterol (mmol/l)	6.7 (1.2)	6.6 (1.2)	6.7 (1.2)
Diabetes mellitus (%)	10.3	8.5	9.7
History of myocardial infarction (%)	9.6	13.7	13.0
Left ventricular hypertrophy on the ECG (%)	5.7	4.2	3.1
Heart failure (%)	3.2	2.1	1
Anti-asthmatic medication (%)	3.5	6.1	5.9
Duration of smoking (years)*	Not applicable	28 (1-83)	45 (4-85)
Amount of smoking* (number of cigarettes)	Not applicable	15 (1-100)	15 (1-50)

Values are percentages or mean values with standard deviations between brackets.
* Median value with the range between brackets.

Table 2 Smoking and risk of atrial fibrillation

The Rotterdam Study

	Cases/subjects	Model 1	Model 2
Smoking		RR (95% CI)	RR (95% CI)
Current smoking*	78/1280	1.50 (1.07-2.10)	1.51 (1.07-2.12)
Former smoking*	160/2159	1.49 (1.14-1.97)	1.48 (1.12-1.96)
Duration of smoking			
Current smoking*			
Tertile 1: ≤41 years	24/441	1.84 (1.14-2.97)	1.84 (1.13-2.97)
Tertile 2: 41-48 years	23/421	1.58 (0.97-2.57)	1.52 (0.93-2.52)
Tertile 3: ≥49 years	31/418	1.24 (0.78-1.95)	1.28 (0.80-2.03)
Former smoking*			
Tertile 1: ≤20 years	44/756	1.30 (0.91-1.87)	1.39 (0.96-1.99)
Tertile 2: 20-34 years	49/642	1.65 (1.15-2.38)	1.58 (1.09-2.29)
Tertile 3: ≥35 years	67/761	1.59 (1.13-2.25)	1.51 (1.06-2.15)
Number of cigarettes per day			
Current smoking*			
Tertile 1: ≤10	28/345	1.74 (1.12-2.68)	1.74 (1.13-2.70)
Tertile 2: 10-20	26/508	1.23 (0.78-1.96)	1.22 (0.76-1.96)
Tertile 3: ≥20	24/427	1.57 (0.96-2.58)	1.61 (0.98-2.65)
Former smoking*			
Tertile 1: ≤7	57/736	1.48 (1.07-2.05)	1.56 (1.13-2.16)
Tertile 2: 7-20	60/834	1.47 (1.03-2.10)	1.41 (0.98-2.03)
Tertile 3: ≥20	43/589	1.57 (1.05-2.33)	1.41 (0.94-2.12)

* Never smoking is the reference category (133 cases/2229 participants).

Model 1: adjusted for age and gender.

Model 2: adjusted for age, gender, prevalent and incident myocardial infarction, body mass index, hypertension, systolic blood pressure, serum cholesterol level, diabetes mellitus, left ventricular hypertrophy on the ECG, heart failure at baseline and the use of medication prescribed for obstructive pulmonary disease or emphysema.

Table 3 Smoking and risk of atrial fibrillation, stratified by age

The Rotterdam Study

	Cases/subjects	Model 1 RR (95% CI)	Model 2 RR (95% CI)
Current smoking*			
Age ≤75 years, never smoking	59/1452	1 (Reference)	1 (Reference)
Age ≤75 years, current smoking	56/1108	1.46 (0.97-2.19)	1.54 (1.01-2.34)
Age >75 years, never smoking	74/777	1 (Reference)	1 (Reference)
Age >75 years, current smoking	22/172	1.47 (0.82-2.65)	1.45 (0.80-2.61)
Former smoking*			
Age ≤75 years, never smoking	59/1452	1 (Reference)	1 (Reference)
Age ≤75 years, former smoking	122/1795	1.69 (1.19-2.40)	1.65 (1.16-2.36)
Age >75 years, never smoking	74/777	1 (Reference)	1 (Reference)
Age >75 years, former smoking	38/364	1.13 (0.71-1.80)	1.21 (0.75-1.94)

* Never smoking is the reference category.

Model 1: adjusted for age and gender.

Model 2: adjusted for age, gender, prevalent and incident myocardial infarction, body mass index, hypertension, systolic blood pressure, serum cholesterol level, diabetes mellitus, left ventricular hypertrophy on the ECG, heart failure at baseline and the use of medication prescribed for obstructive pulmonary disease or emphysema.

Table 4 Smoking and risk of total mortality

The Rotterdam Study

	Cases/subjects	Model 1 RR (95% CI)	Model 2 RR (95% CI)
Smoking			
Current*	273/1280	1.90 (1.57-2.30)	1.84 (1.54-2.19)
Former*	365/2159	1.13 (0.95-1.38)	1.19 (0.99-1.42)
Duration of smoking			
Current smokers*			
Tertile 1: ≤41 years	56/441	2.19 (1.62-2.97)	2.09 (1.54-2.85)
Tertile 2: 41-48 years	68/421	2.19 (1.64-2.91)	2.18 (1.63-2.92)
Tertile 3: ≥49 years	149/418	1.68 (1.33-2.11)	1.61 (1.27-2.04)
Former smokers*			
Tertile 1: ≤20 years	96/756	1.07 (0.85-1.35)	1.20 (0.94-1.52)
Tertile 2: 20-34 years	89/642	1.06 (0.82-1.39)	1.13 (0.87-1.46)
Tertile 3: ≥35 years	180/761	1.19 (0.97-1.47)	1.21 (0.97-1.51)
Number of cigarettes per day			
Current smokers*			
Tertile 1: ≤10	82/345	1.71 (1.32-2.20)	1.60 (1.24-2.08)
Tertile 2: 10-20	105/508	1.86 (1.46-2.39)	1.84 (1.43-2.37)
Tertile 3: ≥20	86/427	2.32 (1.76-3.04)	2.31 (1.75-3.04)
Former smokers*			
Tertile 1: ≤7	135/736	1.13 (0.92-1.38)	1.23 (1.00-1.52)
Tertile 2: 7-20	124/834	1.05 (0.83-1.33)	1.05 (0.82-1.34)
Tertile 3: ≥20	106/589	1.28 (0.99-1.65)	1.28 (0.99-1.65)

* Never smokers are the reference category.

Model 1: adjusted for age and gender.

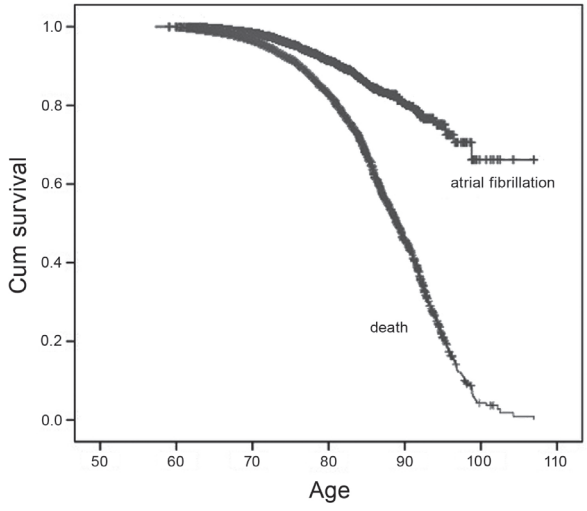
Model 2: adjusted for age, gender, prevalent and incident myocardial infarction, body mass index, hypertension, systolic blood pressure, serum cholesterol level, diabetes mellitus, left ventricular hypertrophy on the ECG, heart failure at baseline and the use of medication prescribed for obstructive pulmonary disease or emphysema.

Discussion

In this prospective, population-based study, both current and former smoking were associated with risk of atrial fibrillation. The results were independent of a history of myocardial infarction at baseline and myocardial infarction occurring during follow-up. The results were also independent of pulmonary disease at baseline.

Among current smokers, no dose-response relationship could be observed between measures of duration of smoking and amount of smoking and the risk to develop atrial fibrillation. Only subjects in the first tertile of duration and severity of smoking had a significantly higher risk to develop atrial fibrillation. Subjects in the second and third tertile had lower and non-significantly increased risks. Competing risk of mortality may explain this finding. Subjects with a long duration of smoking and heavy smokers who are susceptible to develop atrial fibrillation might have died from cardiovascular disease before entering the study or during the study before they could develop atrial fibrillation. Therefore, those heavily exposed subjects who are still alive and in the study may be more resistant to the effects of smoking and therefore exhibit lower risks of atrial fibrillation compared to subjects exposed to lower doses of exposure. Our results on smoking and total mortality showed that current smoking was still a strong risk factor for mortality in our cohort. The number died (N=979) was much larger than the number that developed atrial fibrillation (N=371) during follow-up. This supports the influence of mortality on our risk estimates for atrial fibrillation, especially because myocardial infarction and pulmonary cancer, the most frequent causes of death due to smoking, tend to occur at a younger age than atrial fibrillation, which generally develops at an older age. Figure 2 shows that from age 70 onwards the Kaplan-Meier curves of death and atrial fibrillation by age considerably diverge

Figure 2
Kaplan-Meier survival curve of atrial fibrillation and death by age
The Rotterdam Study



with a steeper curve for death indicating that a high risk of death relative to the risk of atrial fibrillation may play a role in the associations of smoking with atrial fibrillation.

Among former smokers a weak dose response relationship was seen between higher tertiles of duration and amount of smoking and the risk of atrial fibrillation. Selective mortality may also explain why the associations of current and former smoking in our population are comparable and why also among former smokers no strong trends were seen with duration and number of cigarettes. The same mechanism may explain our results that persons aged 75 years or younger have a higher risk to develop atrial fibrillation associated with former smoking than persons older than 75 years. Remarkably, former smoking remained a risk factor for atrial fibrillation, while it is only a weak predictor of death. Possibly former smokers susceptible to the fatal effects of smoking have died before entering the study.

The associations of smoking on risk of atrial fibrillation have been previously investigated in six longitudinal studies. In the Framingham Heart Study, cigarette smoking was a potential risk factor for atrial fibrillation in women but statistical significance could not be reached in multivariate analyses.[13] Current smoking was investigated in the Cardiovascular Heart Study as a risk factor for atrial fibrillation but an association was not found.[14] Smoking was also assessed in the Manitoba Follow-up Study, which investigated the onset of atrial fibrillation in a originally healthy male population (air crew recruits).[15] In this study, the age adjusted relative risk to develop atrial fibrillation was 1.37 (95% CI 1.00-1.87), but did not remain in the multivariate model. In the Copenhagen City Heart Study,[17] the Renfrew/Paisley Study[18] and in the Danish Diet Cancer and Health Study[16] no associations were found between smoking and atrial fibrillation. One explanation for the absence of independent associations in two of these studies may be the fact that current smoking was compared to never and former smokers together. This may have obscured associations in the Framingham Heart Study and in the Cardiovascular Health Study, as the results of our study suggest that both current and former smoking are associated with the risk of atrial fibrillation. Another explanation may be that the participants of the Rotterdam Study were heavier smokers during a longer period of time than the participants of the other studies. Further, smoking was not the main focus of these studies. Therefore, associations may be attenuated in multivariate models containing variables that may be in the causal pathway between smoking and atrial fibrillation. This may have played a role in the Cardiovascular Health Study, which focused on the role of echocardiography examinations as a predictor of atrial fibrillation, in the Copenhagen City Heart Study that studied reduced lung function ((FEV1) % predicted) as a risk factor of atrial fibrillation, but also in the Manitoba Follow-up Study, where several cardiac disease conditions and ECG disturbances were included in the final model. Further, the Copenhagen City Heart Study, the Renfrew/ Paisley Study and the Danish Diet, Cancer, and Health Study included participants with a much lower mean (10-

15 years lower) age than the Rotterdam Study. These three studies also based the diagnosis of atrial fibrillation mainly on hospital-derived data. This may have caused that in these studies small relative risks, as is the case for smoking in relation to atrial fibrillation, remained undetected.

In our study, we examined the association of smoking with atrial fibrillation beyond the well-known effects of smoking on myocardial infarctions by adjusting for myocardial infarctions at baseline but also myocardial infarctions occurring during follow-up. Several mechanisms may be involved in the associations of smoking with atrial fibrillation. Tobacco smoke is a mixture of more than 4000 gaseous chemicals.[9] From these, especially nicotine and carbon monoxide are very toxic to the heart. Carbon monoxide may both influence automaticity of the heart and reduce the exercise tolerance of the heart by reduction of the oxygen carrying capacity and oxygen release of hemoglobin.[31] Nicotine has many well-documented effects on the heart.[8,32] The main cardiovascular effect is sympathetic neural stimulation causing an increase in heart rate and blood pressure, but also regional myocardial hypo perfusion in those who have already coronary artery disease. It should be emphasized, however, that also oxidant substances and polycyclic aromatic hydrocarbons may cause short-lived or permanent damage to the conduction system of the heart.[33]

Atrial fibrillation is a rare disease beneath the age of 60 years and this means that the majority of atrial fibrillation cases occur in the elderly. The strengths of our study are its population-based character and the inclusion of participants above the age of 55 years. We were able to base the case finding upon our own baseline and follow-up measurements. Detailed additional information was available from general practitioners, out patient clinics and hospital admissions. This enabled us to define very accurately prevalent atrial fibrillation cases and subsequently incident atrial fibrillation cases.

Our study is limited by the fact that we have no echocardiographic data at baseline. Further, the assessment of chronic obstructive pulmonary disease and emphysema was based on medications prescribed for these conditions and not on pulmonary function tests. Thus, we may have missed cases belonging to the mildest categories of pulmonary disease. We have no information on those who were invited to participate, but did not respond (22% of those who were eligible to participate). This may have influenced the incidence of atrial fibrillation, but this has probably not changed the associations of smoking and atrial fibrillation. Finally, the observational character of our study precludes a judgment on causality.

The consequences of the results of our study for public health are twofold. First, a 50% increase in the risk of atrial fibrillation due to smoking is not very high, but we have to realize that the importance of the finding is great because former smoking and current smoking are so prevalent in the community. Further, the importance is even underestimated in our study,

because we adjusted for myocardial infarction at baseline and during follow-up. Second, quitting of smoking is one of the most important preventive measures for a series of diseases. In our study the associations with mortality of current and former smoking suggest this. However with respect to atrial fibrillation, not mediated by myocardial infarction, both current and former smoking have the same harmful effects, indicating that one should never start smoking.

Conclusion

The results of this prospective, population-based study indicate that smoking is associated with an increased risk of atrial fibrillation. Former smoking is an equally strong risk factor as current smoking.

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Chapter 3.4

High-normal thyroid function and risk of atrial fibrillation

Abstract

Background Overt and subclinical hyperthyroidism are both well-known independent risk factors for atrial fibrillation. We aimed to investigate the association of high-normal thyroid function with the development of atrial fibrillation in a prospective, population-based, study in the elderly, the Rotterdam Study.

Methods The association between thyroid stimulating hormone (TSH) and atrial fibrillation was examined in 1426 subjects with TSH in the normal range (0.4-4.0 mU/L) and without atrial fibrillation at baseline. In 1177 persons of this group we also examined the association between free thyroxin (FT4) within the normal range (11-25 pmol/L) and atrial fibrillation. During a median follow-up of 8 years, 105 new cases of atrial fibrillation were identified. Hazard ratios (HR) were calculated with 95% confidence intervals (CI) using Cox proportional hazards models, adjusted for age, sex, current smoking, former smoking, body mass index, systolic blood pressure, hypertension, history of a myocardial infarction, presence of heart failure, left ventricular hypertrophy on the electrocardiogram, diabetes mellitus, total cholesterol level and time of the drawing of blood samples.

Results The risk of atrial fibrillation was associated with the TSH level. The multivariate adjusted HR was 1.94 (95% CI 1.13-3.34, lowest versus highest quartile; P for trend 0.02). The multivariate adjusted level of FT4 showed a graded association with risk of atrial fibrillation (1.62; 95% CI 0.84-3.14, highest versus lowest quartile; P for trend 0.06).

Conclusion Within the normal range of thyroid parameters, persons with high-normal thyroid function are at an increased risk of atrial fibrillation.

Introduction

Atrial fibrillation is the most common cardiac arrhythmia in the elderly. The prevalence and incidence increase with advancing age.[1,2] The disease is associated with a higher risk of stroke,[3] peripheral embolism[4] and mortality.[5] The treatment of atrial fibrillation is not without danger as is illustrated by the increased risk of major bleeding and proarrhythmia.[6,7] Therefore, prevention of atrial fibrillation is highly preferable, indicating the need of knowledge of the risk factors of atrial fibrillation. Overt hyperthyroidism is a well-known risk factor for atrial fibrillation,[8,9] but subclinical hyperthyroidism, defined as a serum thyroid stimulating hormone (TSH) level below the normal range with free thyroxine (FT4) levels within the normal range, has also been identified as a predictor of atrial fibrillation.[10-14] Recently, a cross-sectional population-based study showed that the serum FT4 concentration is independently associated with atrial fibrillation in euthyroid persons with serum TSH levels in the normal range.[14] We prospectively investigated the role of parameters of thyroid function in the development of atrial fibrillation in euthyroid persons. The study is part of the population-based Rotterdam Study.

Methods

Study population

The Rotterdam Study is a prospective population-based cohort study that is aimed at assessing the occurrence and progression of and risk factors for chronic diseases in the elderly. Neurogeriatric, cardiovascular, locomotor and ophthalmologic diseases are the main areas of interest.[15] All residents of the Rotterdam suburb Ommoord, the Netherlands, aged 55 years and over, were invited to participate. Of the 10275 eligible individuals, 7983 (78%) responded. Between 1990 and 1993, these participants were interviewed at their home and 7151 were examined at the research center to obtain baseline measurements, including a 10 second 12-lead resting electrocardiogram (ECG). Those who did not visit the research center were in general dependent or lived in nursing homes. Participants were re-examined during two follow-up rounds. The first follow-up examination was performed between July 1, 1993 and December 31, 1994. The second follow-up examination started in April 1, 1997 and ended December 31, 1999. The Rotterdam Study collaborates with the general practitioners (GPs) and with the pharmacies in the area of Ommoord. The medical ethics committee of the Erasmus University approved the study and all participants gave informed consent.

Assessment of thyroid status

In 2002, we randomly selected 2000 participants of the Rotterdam Study cohort who visited the research center at baseline. In 1877 participants baseline serum samples stored at –80 degrees Celsius were available and TSH levels were measured with a commercial TSH assay (Lumitest (Henning, Berlin, Germany, currently Brahms, Berlin, Germany). In 2007, serum FT4 concentrations were measured (Vitros ECi Immunodiagnostic System (Ortho-Clinical Diagnostics, Amersham, United Kingdom) in 1544 participants for whom stored baseline blood samples were still available. The Spearman correlation coefficient of TSH between measurements three years apart, in different samples, was 0.71, P-value 0.01, suggesting reasonable stability over time. In 42 participants FT4 was measured twice, in 2000 and in 2007, in the same blood samples. The Spearman correlation coefficient was 0.81, P-value < 0.001, suggesting the limited effects of storage over time. The reference ranges of TSH (0.4-4.0 mU/L) and FT4 (11-25 pmol/L) were the same as those used in previous studies on thyroid function of the Rotterdam Study and were based on the normal range of the assays. The Spearman correlation coefficient between TSH and FT4 was –0.27, P-value 0.01.

Diagnosis of atrial fibrillation

New cases of atrial fibrillation were ascertained using three methods: (1) At baseline and during follow-up examinations ECGs were recorded with an ACTA electrocardiograph (ESaOte; Florence; Italy), stored digitally and analyzed by the Modular ECG Analysis System (MEANS). The reported sensitivity and specificity of the MEANS program in coding arrhythmias is high (96.6% and 99.5% respectively).[16-18] To verify the diagnosis of atrial fibrillation, all ECGs with a diagnosis of atrial fibrillation, atrial flutter or any other rhythm disorder were recoded independently by two research physicians who were blinded to the MEANS diagnosis. The judgment of a cardiologist was sought and taken as decisive in those cases in which disagreement persisted between the coding physicians. (2) General practitioners participating in the Rotterdam Study sent computerized information on selected diseases to the researchers of the Rotterdam Study on a weekly basis. Specially trained follow-up assistants verified the information using GP records and hospital discharge letters. A senior physician examined all the information and coded the events according to the International Classification of Diseases, 10th revision (code I48). (3) Data on atrial fibrillation were acquired from the LMR system (de Landelijke Medische Registratie). This national registration system accumulates all hospital discharge diagnoses of Dutch inhabitants. To ascertain atrial fibrillation at baseline we used ECGs as described above. Furthermore, the general practitioner files of all participants were screened for the presence of atrial fibrillation at or before baseline. We did not distinguish between atrial fibrillation and atrial flutter when we identified cases because both conditions are very similar with respect to

risk factors and the consequences.[19,20] Also, we did not discriminate between paroxysmal atrial fibrillation and chronic atrial fibrillation. It has been demonstrated that the frequency of periods of atrial fibrillation in paroxysmal atrial fibrillation as measured by continuous monitoring is much higher than the frequency perceived by patients and their physicians. In addition, paroxysmal atrial fibrillation changes into chronic atrial fibrillation over time in the majority of cases.[21,22] Those participants who developed atrial fibrillation during a serious disease resulting in death very shortly after the detection of atrial fibrillation, which was not the cause of the serious disease, were not considered as having atrial fibrillation. They were censored on the date of detection of atrial fibrillation. Furthermore, subjects with transitory atrial fibrillation during myocardial infarction or during cardiac operative procedures were not included among the cases. All study participants were followed up from the day of entrance in the Rotterdam Study (1990-1993) to the date of onset of atrial fibrillation, the date of death or to 01-01-2000, whichever came first. If atrial fibrillation had been detected exclusively by the MEANS computer system during one of the follow-up rounds, the midpoint between the date of the center visit of the concerning round and the date of the center visit of the former round was taken as the date of onset of atrial fibrillation. If atrial fibrillation was detected as well, or only, by the two other workup protocols the earliest date was taken as the date of onset. By January 1, 2000, follow-up was complete for 99.1% of the study population.

Measurement of covariates

Information on medical history, smoking and medication was obtained using the computerized questionnaire taken at the baseline home visit. The information on medication obtained from the home interview was completed by the computerized information from collaborating pharmacies. Participants were classified as current smokers, former smokers or never smokers. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured twice at the right upper arm with a random zero mercury sphygmomanometer in the sitting position. Systolic and diastolic blood pressures were calculated as the average of the two consecutive measurements. Hypertension was defined as a systolic blood pressure of 160 mm Hg or higher or a diastolic blood pressure of 100 mm Hg or higher or the use of blood pressure lowering drugs prescribed for hypertension, encompassing grade 2 and 3 hypertension, according to World Health Organization criteria. A history of myocardial infarction was defined as a self-reported myocardial infarction with hospital admission or the presence of a myocardial infarction on the ECG. A positive self-report of myocardial infarction was confirmed by a review of the files of general practitioners and specialists. Assessment of heart failure at baseline in the Rotterdam Study has been described in detail previously.[23] In short, heart failure cases were classified in accordance with the guidelines of the European Society of Cardiology based

on the presence of at least two symptoms of heart failure (shortness of breath, ankle swelling and pulmonary crepitations), or on the use of medication (diuretics, glycosides or angiotensin converting enzyme inhibitors), prescribed for the indication heart failure in combination with objective evidence of cardiovascular disease. Data from the hospital discharge diagnoses database and from the general practitioners files were used to complete this information. Left ventricular hypertrophy was diagnosed by the MEANS program with an algorithm that takes into account QRS voltages, with an age-dependent correction, and repolarization. Diabetes was defined as the use of antidiabetic medication or a random or post-load serum glucose level of 11.1 mmol/L or higher. Serum total cholesterol was measured with an automated enzymatic method.

Vital status

Information on vital status was obtained on a regular basis from the Central Register of Population of the municipality of Rotterdam, from collaborating GPs and by collecting information during follow-up rounds. For the participants for whom information remained missing, the Central Registry of Genealogy of the Netherlands was consulted. This national institute receives population registry records of those inhabitants of the Netherlands who have died.

Population for analysis

For the present study serum TSH samples were available from 1877 participants of the Rotterdam Study. We excluded 71 persons with prevalent atrial fibrillation and 79 participants for whom information on atrial fibrillation at baseline was missing. We also excluded 130 persons with a serum TSH level less than 0.4 mU/L, 177 persons with a serum TSH level greater than 4.0 mU/L and 55 persons who used thyrostatics (N=11) and/or thyreomimetics (N=40) and/or amiodarone (N=9). The population for analysis consisted of 1426 subjects. Serum FT4 measurements were available in 1196 out of the 1426 subjects. Based on serum FT4 levels outside the normal range (FT4 <11 pmol/l and >25 pmol/l), 19 subjects were excluded for analysis of FT4, resulting in a secondary study population of 1177 persons.

Statistical analysis

Age and sex adjusted hazard ratios (HRs) along with their 95% confidence intervals (CIs), were estimated using the Cox proportional hazards model with incident atrial fibrillation as the dependent variable and serum TSH and FT4 levels respectively as the independent variables. Serum TSH and FT4 levels were categorized into quartiles. In the analyses the highest quartile of TSH and the lowest quartile of FT4 were used as the reference categories. Additional adjustments were made for current smoking, former smoking, body mass index,

systolic blood pressure, hypertension, history of a myocardial infarction at baseline, presence of heart failure at baseline, left ventricular hypertrophy on the ECG, diabetes mellitus, total cholesterol level and the time of the drawing of the blood sample. We calculated P for trend using TSH and FT4 as continuous variables. The Grambsch-Therneau test was used to test the validity of the proportional hazards assumption in all models used (which was found to be the case). Calculations for this purpose were made with STATA statistical software (Stata Corp, College Station, Texas). The numbers of missing values of covariates were low (1% or less). Missing values for cardiovascular risk factors were imputed using the expectation-maximization algorithm. Because of low numbers we did not stratify the analyses by sex. Data were managed and analyzed using SPSS version 11.0 (SPSS Inc. Illinois) and STATA, version 8 SE.

Results

The characteristics of the study population are shown in table 1. In this population of euthyroid participants we identified 105 cases of atrial fibrillation (7.4%) based on the normal range of TSH during a median follow-up time of 8 years (range 0.3-10.5 years). After adjustments for age and sex, subjects in the first quartile of TSH had an increased risk of atrial fibrillation compared with subjects in the lowest quartile. (HR 1.97, 95% CI 1.15-3.38; P-value for trend 0.02; Table 2). Additional adjustments did not change the associations (Table 2). In participants with values in the normal range of TSH and FT4, a graded association of FT4 and the risk of atrial fibrillation was found. (HR 1.73, 95% CI 0.91-3.28, highest quartile compared with the lowest quartile; P for trend 0.05; Table 3). The associations were slightly lower after additional adjustments and the P-value for trend just lost statistical significance (HR 1.62, 95% CI 0.84-3.14; P for trend 0.06).

Table 1 Baseline characteristics of 1455 participants in the Rotterdam Study

Variable	Value (SD)
Age (years)	68.4 (7.5)
Proportion of men (%)	41
TSH (mU/L)	1.66 (0.81)
FT4 * (pmol/L)	16.3 (3.0)
Body mass index (kg/m^2)	26.4 (3.7)
Systolic blood pressure (mm Hg)	138 (21)
Serum total cholesterol level (mmol/l)	6.8 (1.2)
Smokers	
Never smokers (%)	32.9
Current smokers (%)	23.8
Former smokers (%)	43.3
Diabetes mellitus (%)	9.8
History of myocardial infarction (%)	12.3
Left ventricular hypertrophy on the ECG (%)	3.2
Hypertension (%)	32
Heart failure (%)	1.6

Values are percentages or mean values with standard deviations between brackets.
* Subjects (N=1177) with FT4 within the normal range (11-25 pmol/L).

Table 2 Serum thyroid simulating hormone (TSH) and risk of atrial fibrillation

The Rotterdam Study

Participants had serum TSH levels within the normal range of TSH (0.4-4.0mU/L) and did not use amiodarone and/or thyroid medication. N=1426

Characteristic	Cases/ subjects	HR (95% CI) Model 1	HR (95%CI) Model 2
TSH (mU/L)	105/1426		
1st quartile (0.4-1.04)	39/358	1.97 (1.15-3.38)	1.94 (1.13-3.34)
2nd quartile (1.05-1.51)	20/356	1.01 (0.54-1.87)	1.06 (0.57-1.99)
3rd quartile (1.52-2.16)	26/355	1.29 (0.72-2.31)	1.34 (0.75-2.41)
4th quartile (2.17-3.98)	20/357	1 (Reference)	1 (Reference)
P-value for trend		0.02	0.02

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, current smoking, former smoking, body mass index, systolic blood pressure, hypertension, history of a myocardial infarction at baseline, presence of heart failure at baseline, left ventricular hypertrophy on the ECG, diabetes mellitus, total cholesterol level and the time of drawing of the blood sample.
Abbreviations: HR, Hazard ratio; CI, Confidence interval.

Table 3 Serum free thyroxine (FT4) levels and risk of atrial fibrillation

The Rotterdam Study

Participants had normal levels of TSH (0.4-4.0 mU/L) and normal levels of FT4 (11-25 pmol/L) and did not use amiodarone and/or thyroid medication. N=1177.

Characteristic	Cases/ subjects	HR (95% CI) Model 1	HR (95%CI) Model 2
FT4 (pmol/L)	83/1177		
1st quartile (11.0-14.4)	15/297	1 (Reference)	1 (Reference)
2nd quartile (14.5-15.9)	20/289	1.40 (0.72-2.74)	1.29 (0.65-2.52)
3rd quartile (16.0-17.9)	23/296	1.58 (0.83-3.04)	1.51 (0.78-2.90)
4th quartile (18.0-25.0)	25/295	1.73 (0.91-3.28)	1.62 (0.84-3.14)
P-value for trend		0.05	0.06

Model 1: adjusted for age and sex.
Model 2: adjusted for age, sex, current smoking, former smoking, body mass index, systolic blood pressure, hypertension, history of a myocardial infarction at baseline, presence of heart failure at baseline, left ventricular hypertrophy on the ECG, diabetes mellitus, total cholesterol level and the time of drawing of the blood sample.
Abbreviations: HR, hazard ratio; CI, Confidence interval.

Discussion

We report the findings of the first (to our knowledge) prospective population-based study on the association between normal thyroid function and risk of atrial fibrillation. We found that participants in the lowest quartile of the normal range of serum TSH had an almost twofold increased risk of atrial fibrillation compared with those who were in the highest quartile. Furthermore, we found a graded association between levels of FT4 and risk of atrial fibrillation.

Overt hyperthyroidism is a well-known risk factor for atrial fibrillation.[8,9,24] Also, subclinical hyperthyroidism, defined as a low TSH ≤0.1 mU/L, with a serum FT4 concentration within the normal range has been identified as a causal condition for atrial fibrillation.[10-14] A recently published cross-sectional study revealed that in euthyroid persons, defined by TSH within the normal range, serum FT4, but not TSH, is associated with atrial fibrillation.[14] In our prospective study, we also found that, within the euthyroid range, those who have higher levels of thyroid function are at an increased risk of atrial fibrillation compared with those who have lower levels. In our study, in contrast with the study of Gammage et al., TSH levels within the normal range were clearly associated with the risk of atrial fibrillation. Higher levels of FT4 tended to be associated with an increased risk of atrial fibrillation, but the association lacked statistical significance. Together, the findings together support the hypothesis that within the normal range of thyroid function, higher thyroid function confers a higher risk of atrial fibrillation.

The level of serum FT4 is tightly regulated by the classical hypothalamic-pituitary-thyroid axis. Three pathways are involved in the effects of thyroid hormone on the heart. The active thyroid hormone triiodothyronine (T3) binds to the T3 nuclear receptors resulting in specific cardiac gene expression. Furthermore, T3 influences the sensitivity of the peripheral sympathetic system, and, finally, T3 affects the peripheral hemodynamic state, leading to increased cardiac filling which effects cardiac contraction patterns.[25] Excess of thyroid hormone causes arrhythmias, peripheral vasodilatation and changes in cardiac contractility. Each person probably has his or her own individual set point for thyroid function. Genetic factors play an important role in the set point of the hypothalamic-pituitary-thyroid axis.[26,27] In a Danish study the individual reference ranges for test results in a healthy group of young males were very narrow while the group reference for thyroid function test results was much wider.[28] The results of our study indicate that within the normal range of thyroid function certain persons are nonetheless at increased risk for developing atrial fibrillation.

It could be hypothesized that low levels of serum TSH have a nonthyroidal reason. It is known that critical illness may cause a decrease in the level of TSH. Chronic diseases of the elderly, causing both atrial fibrillation and a low TSH level, could have confounded the association of a

low TSH level with atrial fibrillation. We believe that this is not the case in our study. First, the participants were able to come to our research center and therefore belonged to the healthier part of the Rotterdam Study population. Second, the results of the secondary analysis revealed that both lower levels of TSH and higher levels of FT4 were associated with atrial fibrillation, indicating that the effect indeed is thyroidal as low levels of TSH in the case of critical illness go together with low levels of FT4.[29,30]

Based on the results of our study we are unable to conclude that high thyroid function is a risk factor for atrial fibrillation or that low thyroid function is protective against atrial fibrillation. To the best of our knowledge hypothyroidism has never been associated with atrial fibrillation, in contrast to hyperthyroidism. Therefore we believe that the best explanation of our results is that high thyroid function within the normal range is associated with atrial fibrillation.

The strengths of our study are the population based setting and its longitudinal character, through which we were able to give evidential value to earlier cross-sectional findings. Some weaknesses also need to be mentioned. When we measured FT4 in stored samples in 2007, we were unable to obtain samples from the same number of participants for whom TSH had been measured in 2002. The more limited availability of blood samples at a later time might reflect the mechanism that serum samples of participants who are not very healthy at baseline or at early follow-up are depleted owing to more intensive use for cross-sectional and case control studies. A selection of healthy participants for the analysis of FT4 could be the result. We analyzed the associations of TSH and risk of atrial fibrillation in the original TSH sample (N=1426) and in the sample for which a FT4 measurement was also available (N=1177) and concluded that the associations were almost identical. Therefore we believe that this potential selection has not influenced the results. In our study we measured FT4 as a marker of the active hormone. Measurements of T3 and free T3 need a considerable amount of serum and population-based studies are restricted in this respect.

It is generally believed that there are reasons to reconsider the normal range of TSH levels. Most discussion, however, is on the upper limit of TSH,[31-33] indicating that the upper normal limit should be decreased to 2.5 mU/l. The lower limit of TSH is less debated. Our data indicate that in persons whose thyroid function is within the normal range a subgroup may be found at higher risk of atrial fibrillation owing to increased thyroid function. The observational character of our study, however, precludes a judgment on causality, and whether the relationship is causal has to be determined in other studies. Of interest, in populations with normal thyroid function, associations of thyroid function with bone status and physical activity have been reported.[34-36]

It is known that atrial fibrillation resulting from overt hyperthyroidism is reverted in 60 to 75% of the patients if they receive a proper antithyroid treatment.[37] Whether patients with atrial fibrillation patients and high normal thyroid function also easily revert to sinus rhythm if

they are treated as if they were hyperthyroid also needs to be investigated.

In conclusion, within the normal range of serum thyroid function parameters, subjects with high-normal thyroid function are at an increased risk of atrial fibrillation. This finding requires confirmation in other studies.

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Chapter 4.1

Atrial fibrillation and the prothrombotic state in the elderly

Abstract

Background Atrial fibrillation (AF) is a major cause of stroke among the elderly. Evidence for a prothrombotic state in AF is controversial, and there is a lack of studies among the elderly. We studied the relationships between AF and 3 prothrombotic plasma markers - von Willebrand factor (vWf; a marker of endothelial damage/dysfunction), soluble P-selectin (sP-sel; a marker of platelet activation), and fibrinogen, a marker of rheology - in a matched case-control study nested within a large community-based study of an elderly population.

Methods We identified 162 elderly participants (mean age 78 years; 51% male) in the Rotterdam Study with documented AF and matched each case by age and sex to 2 population controls. vWf and sP-sel were measured by enzyme-linked immunosorbent assay; fibrinogen was measured with the Clauss method. We used conditional logistic regression analysis to assess the relationships between the markers and AF, adjusting for potential confounders.

Results There were no significant relationships between either fibrinogen (P=0.8) or sP-sel (P=0.6) and AF. However, a positive linear relationship between vWf level and presence of AF remained significant after adjustment for potential confounders among women (odds ratio [OR], 1.17; 95% CI, 1.02 to 1.34) per 10-IU/dL increase in vWf but not among men (OR, 1.06; 95% CI, 0.96 to 1.17).

Conclusions We observed a positive relationship between AF and plasma vWf (or endothelial damage/dysfunction) in our elderly population, which was most apparent among women. Fibrinogen and sP-sel levels were unrelated to AF. The prothrombotic state of AF may be subject to sex differences, but longitudinal studies are needed to determine the relationship between these plasma markers and stroke risk.

Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, is a major cause of morbidity and mortality through an increased risk of thromboembolic stroke.[1-3] The prevalence of AF and the thromboembolic risk associated with the arrhythmia increase with advancing age, making AF a particular problem among the elderly.[4] The mechanisms behind cerebral thromboembolism in AF are incompletely understood,[5] but abnormal levels of prothrombotic plasma markers have been found in AF patients compared with healthy control subjects,[6-9] leading to suggestions of a generalized prothrombotic state in AF. Although it has recently been suggested that it may be the presence of additional cardiovascular disease among AF patients rather than AF itself that is associated with the observed changes in prothrombotic markers,[10] the prothrombotic state in AF has not been adequately studied among the elderly.

To investigate the presence of a prothrombotic state in AF among the elderly, we studied the relationships between AF and 3 prothrombotic plasma markers - von Willebrand factor (vWf; a marker of endothelial damage/dysfunction), soluble P-selectin (sP-sel; a marker of platelet activation), and fibrinogen (the precursor to insoluble fibrin and an important rheological factor) - in a matched case-control study nested within a large community-based study of an elderly population.

Methods

Study Population

The Rotterdam Study is a population-based prospective cohort study of the occurrence and progression of chronic diseases of the elderly and its risk factors. The study primarily addresses neurological, cardiovascular, locomotor, and ophthalmological diseases. The design of the study has been described previously.[11] In brief, between 1990 and 1993, 7983 inhabitants of Ommoord, a suburb of Rotterdam, ≥55 years of age were extensively interviewed in their homes and examined at a specially equipped research center to allow collection of baseline data, including a resting 12-lead ECG. Two hundred four cases of AF were identified among 6808 participants for whom an ECG was available for analysis; ECGs were missing for 1175 subjects usually because of technical or logistical problems. Stored plasma samples were available for analysis for 162 of the AF cases. Each case was matched on the basis of sex and age within 5 years with 2 controls without AF from the cohort for whom plasma was available for analysis.

Baseline Examinations

Information on current health status, medical history, and smoking behavior was obtained from a computerized questionnaire. Participants were classified as current or nonsmokers. Blood pressure was measured twice on the right upper arm with a random-zero mercury sphygmomanometer in patients in the sitting position. Systolic and diastolic blood pressures were calculated as the average of 2 consecutive measurements. Hypertension was defined from the World Health Organization criteria of the time as systolic blood pressure of ≥160 mm Hg, diastolic blood pressure of ≥90 mm Hg, or the use of blood pressure-lowering drugs prescribed for hypertension. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Serum total cholesterol was measured with an automated enzymatic method. Diabetes was defined as the use of antidiabetic medication or a preload or postload serum glucose level of 11.1 mmol/L.

Ten-second 12-lead ECGs were recorded at the research center with an ACTA Gnosis IV ECG recorder (ESAOte), stored digitally, and analyzed with the Modular ECG Analysis System (MEANS).[12] This computer program has been shown to be highly reliable at ECG diagnosis.[13] ECGs that the MEANS program was not able to interpret because of poor ECG quality or pacemaker activity on the ECG were evaluated separately. Visual coding of these ECGs to determine the presence of a rhythm disorder was possible in 52 poor-quality ECGs. Because pacemaker implantation is often necessary in AF, information on the underlying rhythm disorder was obtained from general practitioner files for 25 subjects with pacemaker activity on the ECG. Of these participants, 12 had AF as the underlying rhythm disorder. Left ventricular hypertrophy (LVH) was diagnosed by the MEANS program with an algorithm taking into account QRS voltages with an age-dependent correction and repolarization. A history of myocardial infarction (MI) was defined as a self-reported MI with hospital admission or the presence of MI on the ECG. A positive report of MI was confirmed by a review of the medical records of general practitioners and specialists for the presence of MI. Peripheral venous blood samples were taken at the research center, with no stasis or minimal stasis applied if needed, and collected in CTAD collection tubes (0.11 mol/L citrate, 15 mmol/L theophylline, 3.7 mmol/L adenosine plasma, and 0.198 mmol/L dipyridamole). Samples were stored at –80°C until laboratory analysis. Measurements of sP-sel and vWf were performed with enzyme-linked immunosorbent assay (ELISA) with reagents from R&D Systems and Dako-Patts, respectively. The unit for vWf, IU/dL, was standardized by reference vWf from the National Institute for Biological Standards and Controls. Intra-assay coefficients of variation for all ELISA assays were <5%; interassay variances were <10%. Plasma fibrinogen (g/L) was measured with the Clauss technique on a Pacific Hemostasis coagulometer with bovine thrombin from Alpha Laboratories. Because of natural sample wastage over time, 1 control sample was unavailable for all analyses, and an

additional 10 samples produced unreliable results on fibrinogen analysis (concentration, <1 g/L) and thus were excluded from subsequent statistical analysis for this marker.

Statistical Analysis

Patient characteristics were compared between cases and matched controls by conditional logistic regression. Because fibrinogen and sP-sel were not normally distributed, we undertook analyses using the natural log transformation of these variables because this technique would result in a more normal distribution. The associations between AF and the 3 prothrombotic plasma markers were examined by calculating crude odds ratios (ORs) with their 95% confidence intervals (CIs) through conditional logistic regression. Stratified analyses were performed according to sex.

We undertook 2 separate approaches to examine the true relationships between AF and our 3 markers by removing the effects of possible confounding factors. First, indexes of blood pressure (systolic blood pressure, diastolic blood pressure, history of hypertension, LVH), history of MI, smoking status, serum cholesterol, diabetes, and BMI were considered potential confounding factors if a univariate value of $P < 0.25$ was found for the association with any prothrombotic marker and for AF. These potential confounding factors were tested in the conditional logistic regression model for AF with the relevant prothrombotic markers and were kept in the final conditional logistic regression model if $P < 0.05$ was met. If any index of blood pressure was significant, we entered all other blood pressure indexes into the final model because these markers represent different characteristics of hypertension, although diastolic and systolic blood pressures were never together in the models.

Second, we restricted our investigation to those free of cardiovascular disease (other than AF). Participants were considered free of cardiovascular disease if they had no previous history of MI, no hypertension, no LVH on the ECG, and no diabetes. Cases of AF without these additional features were considered 'lone' AF cases. Because the absence or presence of cardiovascular disease was not a matching variable, we performed an unmatched logistic regression analysis in this group. An additional justification for this procedure was that the estimates of both the matched and unmatched analysis did not differ substantially. The estimates of the unmatched analysis were generally closer to unity.

Results

Whole Group

The clinical features of the AF cases and non-AF controls are outlined in Table 1. Compared

with the control group, the AF group had a lower mean systolic blood pressure, a higher mean age and a lower mean serum cholesterol level. There were no significant differences with regard to sex (as expected from the matching process), presence of hypertension, diabetes mellitus, previous MI, LVH (by ECG criteria), and smoking status. Furthermore, there were no significant differences in natural log-transformed fibrinogen, vWf, or natural log-transformed sP-sel levels between the 2 groups. After adjustment for potential confounding factors (Table 2), no significant associations were found between natural log-transformed fibrinogen or natural log-transformed sP-sel and AF in our conditional logistic models. However, a significant positive association was found between vWf and AF (OR, 1.11; 95% CI, 1.03 to 1.20). When we stratified cases and controls according to sex, we found significant positive associations between vWf levels and AF among women (adjusted OR, 1.20; 95% CI, 1.04 to 1.39 per 10-IU/dL increase) but not men (adjusted OR, 1.08; 95% CI, 0.97 to 1.19; Table 2). Indeed, women with vWf levels in the fourth quartile of the range were 5.4 times as likely to be in AF than those with vWf levels in the lowest quartile, after adjustment for potential confounders (OR, 5.39; 95% CI, 1.53 to 18.97). In men, this result could not be found (OR, 1.98; 95% CI, 0.81 to 4.83; Table 2). No significant relationship was found between natural log-transformed sP-sel or natural log-transformed fibrinogen and AF among individual sexes. The proportion of men in the study >75 years of age was 54%, whereas 72% of women were >75 years of age. However, secondary analysis of the data by age stratification did not reveal any effect of age on the relationships between vWf, natural log-transformed sP-sel, or natural log-transformed fibrinogen and AF (data not shown).

Lone AF

We identified 66 cases with lone atrial fibrillation and 158 controls without cardiovascular disease. Table 3 summarizes the characteristics of this subpopulation by presence of lone atrial fibrillation. No significant differences were found in age, sex, smoking status, systolic blood pressure, cholesterol levels, BMI, and levels of vWf, natural log-transformed sP-sel, and natural log-transformed fibrinogen between lone AF cases and controls. In the logistic regression model (Table 4), no significant associations were found between prothrombotic markers and lone AF.

Table 1 Characteristics of the case-control study population by presence of atrial fibrillation

The Rotterdam Study, 1990-1993

Characteristic	AF cases N=162	Controls N=324	P
Percentages			
Male	51	51	1.0
Current Smoking	22	20	0.6
Diabetes	19	16	0.4
Hypertension	23	27	0.4
Left Ventricular Hypertrophy	12	8	0.2
Myocardial Infarction	21	14	0.06
Mean (SD)			
Age	78 (8)	77 (8)	0.003
Systolic Blood Pressure (mmHg)	140 (23)	145 (22)	0.007
Diastolic Blood Pressure(mmHg)	75 (13)	73 (11)	0.08
Cholesterol (mmol/l)	6.1 (1.2)	6.4 (1.4)	0.004
Body Mass Index (kg/m^2)	26 (4)	26 (3)	0.02
LN Fibrinogen (g/L)	0.80 (0.29)	0.79 (0.30)	0.8
vWf (IU/dl)	144 (32)	138 (32)	0.08
LN sP-sel (ng/ml)	3.39 (0.32)	3.41 (0.33)	0.6

P-values were obtained by conditional logistic regression.

LN = natural log transformation, vWf = von Willebrand factor, sP-sel = soluble P-selectin.

Table 2 Odds ratios with their 95% confidence intervals calculated by conditional logistic regression describing the relationship between prothrombotic plasma factors and AF

The Rotterdam Study, 1990-1993

			All	Men	Women
vWf*	Crude		1.06(0.99-1.12)	1.01(0.93-1.10)	1.11(1.01-1.22)
	Adjusted**		1.11(1.03-1.20)	1.08(0.97-1.19)	1.20(1.04-1.39)
VWf in	Crude	1	1 (Reference)	1 (Reference)	1 (Reference)
in quartiles		2-1	1.01 (0.85-1.75)	1.07 (0.50-2.32)	0.99 (0.44-2.21)
		3-1	1.15 (0.68-1.95)	1.01(0.49-2.08)	1.31 (0.49-2.08)
		4-1	1.78 (1.04-3.06)	1.25 (0.60-2.64)	2.61 (1.17-5.83)
	Adjusted**	1	1 (Reference)	1 (Reference)	1 (Reference)
		2-1	1.16 (0.59-2.27)	1.17 (0.52-2.90)	1.44 (0.48-4.36)
		3-1	1.28 (0.66-2.48)	1.31 (0.54-3.17)	1.53 (0.46-5.50)
		4-1	2.89 (1.46-5.71)	1.98 (0.81-4.83)	5.39 (1.53-18.97)
LN fibrinogen	Crude		1.1 (0.6-2.1)	1.4 (0.6-3.0)	0.9 (0.3-2.3)
	Adjusted***		1.1 (0.5-2.2)	1.5 (0.6-3.8)	0.6 (0.2-1.9)
LN sP-sel					
	Crude		0.8 (0.5-1.5)	0.7 (0.3-1.6)	1.1 (0.4-2.6)
	Adjusted****		0.9 (0.5-1.9)	0.7 (0.3-1.7)	1.3 (0.4-4.1)

* For von Willebrand factor odds ratios are presented per 10 iU/dl increase.

** Adjusted for age, systolic blood pressure, serum cholesterol level, history of hypertension, left ventricular hypertrophy (LVH) and BMI.

*** Adjusted for age, systolic blood pressure, history of hypertension and LVH.

**** Adjusted for age, serum cholesterol level, diastolic bloodpressure, history of hypertension and LVH.

LN = natural log transformation, vWf = von Willebrand factor, sP-sel = soluble P-selectin.

Table 3 Characteristics of the study population by presence of lone atrial fibrillation

The Rotterdam Study, 1990-1993

Characteristic	AF cases N=66	Controls N=158	P
Percentages			
Male	62.1	19.0	0.3
Current Smoking	27.7	19.0	0.2
Mean (SD)			
Age	76.4 (7.8)	76.1 (8.0)	0.8
Systolic Blood Pressure (mmHg)	132 (16.6)	135 (15.4)	0.3
Diastolic Blood Pressure (mmHg)	72.7 (10.3)	69.9 (9.0)	0.06
Cholesterol (mmol/l)	6.2 (1.0)	6.3 (1.3)	0.5
Body Mass Index (kg/m^2)	26.1 (3.3)	25.5 (3.5)	0.2
LN Fibrinogen (g/L)	0.78 (0.29)	0.81 (0.28)	0.4
vWf (IU/dl)	139 (32)	136 (32)	0.5
LN sP-sel (ng/ml)	3.4 (0.29)	3.4 (0.34)	1

P-values obtained by chi-square test for categorical variables and Student's t-test for continuous variables.

Lone atrial fibrillation cases are defined as cases with AF in the absence of hypertension, myocardial infarction, left ventricular hypertrophy and diabetes. Their controls have the same characteristics, in the absence of AF.

LN = natural log transformation, vWf = von Willebrand factor, sP-sel = soluble P-selectin.

Table 4 Odds ratios with their 95% confidence intervals calculated by logistic regression describing the relationship between prothrombotic plasma factors and lone AF

The Rotterdam Study, 1990-1993

		All	Men	Women
von Willebrand factor*	†	1.02 (0.93-1.12)	0.96 (0.86-1.07)	1.19 (1.00-1.43)
	**	1.02 (0.93-1.13)	1.00 (0.87-1.12)	1.13 (0.94-1.35)
LN fibrinogen	†	0.7 (0.3-1.9)	1.3 (0.4-4.6)	0.2 (0.02-1.2)
	***	0.7 (0.3-2.0)	1.4 (0.4-4.8)	0.2 (0.02-1.1)
LN sP-sel	†	0.88 (0.36-2.17)	0.81 (0.25-2.57)	1.00 (0.23-4.23)
	****	0.82 (0.32-2.09)	0.67 (0.20-2.24)	0.92 (0.20-4.22)

* For von Willebrand factor odds ratios are presented per 10 iU/dl increase.

† Adjusted for age and gender (if applicable).

** Additionally adjusted for serum cholesterol level, systolic blood pressure and BMI.

*** Additionally adjusted for systolic blood pressure.

**** Additionally adjusted for serum cholesterol level and diatolic blood pressure.

LN = natural log transformation, sP-sel = soluble P-selectin.

Lone atrial fibrillation cases are defined as cases with AF in the absence of hypertension, myocardial infarction, left ventricular hypertrophy and diabetes. Their controls have the same characteristics, in the absence of AF.

Discussion

Among an elderly community-based population, the presence of AF was significantly associated with increased vWf levels in women but not men. Indeed, after adjustment for potential confounding variables, the association between vWf and AF in women was more pronounced, becoming significant for the whole group despite the lack of a significant relationship in men alone. However, AF was not associated with increased fibrinogen or sP-sel levels among the whole group or among individual sexes, and the presence of lone AF was not associated with significantly altered vWf, sP-sel, or fibrinogen levels compared with controls free of cardiovascular disease.

Several previous studies, including those from our group, have described associations between AF and abnormal prothrombotic plasma markers, including fibrinogen, vWf, and sP-sel, suggesting AF itself to be the cause of a prothrombotic state.[6-9] However, these studies have usually compared AF cases with healthy controls and have failed to adequately adjust for the confounding presence of concomitant cardiovascular disease among AF cases. Furthermore, cases in such studies have been derived from a secondary care setting, and thus there may be important additional noncardiovascular differences between cases and controls. The Framingham Offspring Study addressed these problems in a community-based setting by comparing 47 subjects with prevalent AF (mean age, 62.0 years; 75% male) with 167 subjects without AF but matched for age, sex, BMI, smoking, blood pressure, and diabetes.[10] They found no differences in vWf, fibrinogen, plasminogen activator inhibitor-1, or plasma viscosity between the 2 groups, and although a marginal difference was found in level of tissue plasminogen activator, it became nonsignificant after adjustment for additional cardiovascular disease. No markers of platelet activation were measured.

The most important differences between our present study and the Framingham study are our larger sample size, older age group (with a higher proportion of women), and inclusion of a marker of platelet activation, sP-sel. These factors have allowed us, in an age group at greater risk of thromboembolic stroke, to more closely examine the relationship between AF and 3 potential mechanisms of thrombus formation: platelet activation, endothelial damage or dysfunction, and fibrinogen (as a direct contributor to both fibrin deposition and abnormal blood flow dynamics). In keeping with the results from the Framingham study,[10] the present study found no association between AF and fibrinogen or the platelet marker sP-sel. However, our finding of a significant relationship between AF and vWf, after adjustment for possible confounders, may be important because the relationship appears more pronounced among women than men.

It is unclear why there should be an independent association between AF and vWf in women

but not in men or in cases of lone AF compared with healthy controls. However, the case-control design of this study has potential for survival effects: If coexisting AF and raised prothrombotic markers reduce survival, the combination would be seen less frequently in our elderly population, and the association thus would be underestimated. Thus, it is also possible that sex differences in this survival effect, such as an increased early mortality in men with raised vWf, might lead to apparent sex differences in the relationship between AF and vWf in our cross-sectional study. Of note, in an earlier study sampled from the same community population, AF was significantly associated with dementia and impaired cognitive function in women but not men[14]; differences in antithrombotic therapy and coincident cardiovascular disorders were suggested as possible explanations. We chose fibrinogen, vWf, and sP-sel as prothrombotic markers because they appear to be unaffected by antithrombotic therapy.[7,15,16]

We did not take into account the possible presence of other cardiac arrhythmias (including paroxysmal AF because the diagnosis of AF was made on the basis of a single ECG) or noncardiovascular disease. Thus, it is possible that estimated associations between AF and fibrinogen, sP-sel, and vWf in both sexes might have been confounded by the unknown prevalence of these disorders in both groups. In addition to possible confounding by unmeasured disease states among the control group, the lack of any significant association between lone AF and our markers might also be due to reduced statistical power. Furthermore, we constructed our conditional logistic regression model using statistical methods to identify possible confounding factors within our population rather than identifying confounding factors using the available literature. In view of the high prevalence of cardiovascular disease among the control group, including higher systolic blood pressure and serum cholesterol than in AF cases, the control group may well have been far from healthy, which may have lead to underestimation of the relationship between AF and our markers.

We also considered that the age and condition of the plasma samples, some of which had been in storage for up to 10 years and thus were at risk of deterioration,[17] might have affected the relationships between AF and our prothrombotic markers. Indeed, because 10 samples produced unreliable fibrinogen values, the remaining samples used may also have deteriorated from their original state, which may explain why we found no significant relationship between this marker and any clinical feature on univariate analysis (data not shown), despite the known association between fibrinogen and cardiovascular disease. However, we did observe the expected strong association between sP-sel and smoking ($P<0.001$; data not shown) and between vWf and MI, diabetes mellitus, current smoking, LVH, and peripheral vascular disease (data not shown), suggesting that sample deterioration is unlikely to have significantly affected these 2 markers and is thus unlikely to have altered the relationship between either sP-sel or vWf and AF.

With the above caveats in mind, we must consider that raised vWf in AF, especially among

women, might have implications for the pathogenesis of thromboembolic disease in this group. Raised plasma vWf levels have previously been found to independently predict presence of left atrial appendage thrombus in patients with AF[18] and correlate with severity of ultrastructural changes to the left atrial appendage endocardium in mitral stenosis.[19] Furthermore, increased left atrial appendage endocardial expression of vWf has been described in AF[20] and appears to correlate with the presence of adherent platelet thrombus in the overloaded left atrial appendage.[21] If the relationship between AF and raised vWf is indeed stronger among women, it may represent, in part, a potential mechanism of the apparent excess stroke risk conferred by AF among women compared with men[22,23] and thus warrants further investigation. Indeed, even though we found no relationships between sP-sel or fibrinogen and AF, the cross-sectional nature of our analysis does not allow us to examine whether plasma fibrinogen, sP-sel, or vWf levels might relate to risk of subsequent stroke and thromboembolism in AF, a question that we intend to address in a future longitudinal study among the same cohort.

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Chapter 4.2

A longitudinal population-based study of prothrombotic factors in elderly subjects with atrial fibrillation

Abstract

Background A prothrombotic or hypercoagulable state in atrial fibrillation may contribute to stroke and thromboembolism. Results of longitudinal population-based studies in elderly persons with atrial fibrillation are not available yet.

Methods In the Rotterdam Study, a population-based prospective cohort study 162 participants with atrial fibrillation at baseline, aged 55 years and over, were matched on age and gender with 324 persons in sinus rhythm. Associations were examined between three coagulation factors and the risk of total and cardiac mortality and stroke. Hazard rate ratios were calculated with 95% confidence intervals using Cox's proportional hazards model, adjusted for potential confounders.

Results Plasma von Willebrand factor was, age and gender adjusted, associated with cardiac mortality in the total population (RR 1.16; 1.06-1.27, per 10 IU/dl increase), but statistical significance was lost after additional adjustments. A strong association (1.27; 1.08-1.50, per 5 units increase) was found between soluble P-selectin and cardiac mortality in atrial fibrillation patients but not in participants in sinus rhythm. Further, the expected association between fibrinogen and cardiac mortality was only observed in those in sinus rhythm (2.60; 1.69-4.01, per unit increase), and not in atrial fibrillation. No associations were found between coagulation factors and stroke.

Conclusions In this population-based study, plasma levels of soluble P-selectin predicted clinical adverse outcomes in atrial fibrillation, suggesting a role of platelets in the prothrombotic state associated with atrial fibrillation. Fibrinogen was a risk factor of cardiac and all-cause mortality in sinus rhythm, but not in atrial fibrillation.

Introduction

The prevalence, incidence and consequences of atrial fibrillation are greatest among the elderly.[1,2] Mortality is twice as high in persons with atrial fibrillation[3] and the risk of peripheral embolism[4] and stroke[1] is approximately five-fold higher than in those without atrial fibrillation. Although stroke risk may be reduced with appropriate use of antithrombotic therapy,[5,6] such therapy is often less well tolerated in older people.[7] Simple tools to identify atrial fibrillation cases at increased risk are therefore urgently needed. This would allow targeting of therapy to those at high risk, potentially avoiding harmful intervention in the lower risk groups.

Several small cross-sectional studies have suggested that atrial fibrillation is associated with a prothrombotic or hypercoagulable state.[8] Indeed, certain indices of a prothrombotic state have been shown to be associated with left atrial thrombosis[9] or to predict vascular events in atrial fibrillation cases receiving aspirin-based therapy.[10] However, population-based data are lacking.

Three potential pathways may confer a prothrombotic state and we chose one well-established representative of each pathway for our analyses, namely von Willebrand factor (vWf), an index of endothelial damage and dysfunction, fibrinogen, an index of rheology and clotting, and soluble P-selectin (sP-sel), mainly an index of platelet activation.[11]

The present study examines the associations between these three plasma indices and the risk of total and cardiac mortality and stroke among 162 persons with atrial fibrillation and 324 persons without atrial fibrillation at baseline who were matched for age and gender, nested within the Rotterdam Study, a population-based cohort study of the elderly.

Methods

Study population

The Rotterdam Study is a population-based prospective cohort study of the occurrence and progression of chronic diseases and its risk factors in persons aged 55 years and over. The study concentrates on neurological, cardiovascular, locomotor and ophthalmologic diseases.[12] In brief, between 1990 and 1993 all participants of the Rotterdam suburb Ommoord in this age category were invited to participate. Of these 7983 (78%) responded. The participants were interviewed at their home and were examined at the research center to allow for collection of baseline data. The study population was re-examined twice during two follow-up examinations. The first follow-up examination was performed between July 1993 and December 31st 1994. The second follow-up examination started in April 1997 and ended December 31st 1999.

The presence of atrial fibrillation at baseline was assessed with a 10-second 12 lead ECG. Two hundred four cases with atrial fibrillation were identified among 6808 participants for whom an ECG was available at baseline. Stored plasma samples were available for 162 of the atrial fibrillation cases. Each case was matched for age, within 5-year age strata, and gender with two cases without atrial fibrillation at baseline for whom plasma was available.

Baseline Examinations

Information on current health status, medical history, medication and smoking behavior was obtained by a computerized questionnaire. Participants were classified as current smokers, former smokers or never smokers. Blood pressure was measured at the right upper arm with a random-zero mercury sphygmomanometer with participants in sitting position. Systolic and diastolic blood pressures were calculated as the average of two consecutive measurements. Hypertension was defined as a systolic blood pressure of 160 mmHg and over and/or a diastolic blood pressure of 90 mmHg and over, or the use of anti-hypertensive drugs. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Serum total cholesterol was measured with an automated enzymatic method. Diabetes was defined as the use of anti-diabetic medication or a post or preload serum glucose level of $\geq$11.1 mmol/l.

The 10-second 12 lead ECGs were recorded at the research center with an ACTA Gnosis IV ECG recorder (ESAOte), stored digitally and analyzed with the Modular ECG Analysis System (MEANS).[13,14] Each MEANS diagnosis of atrial fibrillation was subsequently validated by two research physicians and a cardiologist. Left ventricular hypertrophy on the ECG was diagnosed with an algorithm that takes into account QRS voltages with an age-dependent correction and repolarization. A history of myocardial infarction was defined as a self-reported myocardial infarction with hospital admission or the presence of myocardial infarction on the ECG, subsequently confirmed by a review of the medical records of general practitioners and specialists for the presence of myocardial infarction.

Blood sample collection and analysis

Non-fasting peripheral venous samples were taken at the research center, with no stasis or minimal stasis applied if needed and collected in CTAD collection tubes containing 0.11 mmol/L citrate, 15 mmol/l theophylline, 3.7 mmol/l adenosine plasma and 0.198 mmol/l dipyridamole. Samples were stored at -80^0 C. Measurements of sP-sel and vWf were performed with enzyme-linked immunoabsorbent assay (ELISA) with reagents from R&D Systems and Dako-Patts, respectively. The unit for vWf, IU/dL, was standardized by reference from the National Institute for Biological Standards and Controls. Intra-assay coefficients of variation for all ELISA assays were <5%, inter-assay variances were <10%. Plasma fibrinogen (g/L) was measured with the

Clauss technique on a Pacific Haemostasis coagulometer with bovine thrombin from Alpha Laboratories. Because of natural sample wastage over time, 1 control sample was unavailable for all analyses. Ten additional samples produced unreliable results on fibrinogen analysis (concentration <1 gram/L) and were thus excluded from subsequent statistical analyses of this marker.

Follow-up

In the Rotterdam Study, information on disease status during follow-up is obtained from participating general practitioners, who send computerized information on diseases of interest and information on hospital admissions to the investigators of the Rotterdam Study. Follow-up assistants verify all information and try to obtain the optimal amount of information on each event. Subsequently, two research physicians independently code all reported events according to the International Classification of diseases, 10th edition (ICD10). In those cases in which consensus cannot be obtained, expert judgment of a specialist in cardiac diseases or neurological diseases is considered as final. Information on vital status is obtained from the central registry of the Municipality of Rotterdam, from collaborating general practitioners and by obtaining information during follow-up rounds. For those participants whose information on vital status remains missing, The Central Registry of Genealogy of the Netherlands is consulted.

For the present study all-cause mortality, cardiac mortality and stroke are the outcomes of interest. Cardiac mortality is defined as death due to myocardial infarction (ICD-10 code I21), other acute or chronic ischemic heart disease (I24-25), ventricular fibrillation (I49), congestive heart failure (I50), sudden cardiac death (I46) or sudden death cause unknown (R96). Stroke is defined as rapidly developing clinical signs of focal disturbance of cerebral function with no apparent other cause than a vascular origin. Strokes are classified as definite, probable and possible. A stroke is classified as definite if the diagnosis is based on typical clinical symptoms and neuro-imaging was performed to verify the diagnosis. A stroke is considered as probable if symptoms and signs are typical, but neuro-imaging was not performed. In all other cases, when symptoms are not typical and when neuro-imagining was not performed, a stroke is considered possible. Possible strokes were not used in the analyses. We only included cases of ischemic stroke. In the analyses cases with cerebral bleeds were censored. Subarachnoid haemorrhages were not included as cases in our analyses. In the analysis of mortality, participants were followed until January 1st 2000, the date of death or the date of the second follow-up examination (1997-1999). In our study (162 + 324) no participants were lost to follow-up. In the analysis of stroke, participants were followed to the date of initial stroke, date of death or the end of follow-up for stroke, namely January 1st 1999.

Statistical analysis

Univariate comparisons of prothrombotic markers and cardiovascular characteristics were made between participants with and without atrial fibrillation using conditional logistic regression. Standard deviations of continuous variables in the two controls per case were calculated considering the controls as two repeated measurements of one series of controls. Age and gender adjusted associations between the three prothrombotic markers and the three endpoints were evaluated with the Cox's proportional hazards model. All analyses were performed separately for those in atrial fibrillation and those in sinus rhythm. Hazard rate ratios were calculated with 95% confidence intervals, adjusted for age and gender. To adjust for other confounding factors two strategies were followed. First, we adjusted for covariates that are known to be potential confounders from previous studies investigating the associations between atrial fibrillation and prothrombotic markers, namely diabetes, myocardial infarction and smoking. Secondly, we evaluated the association between the prothrombotic markers and each event by entering all well-known cardiovascular factors and the use of cardiac medication (digoxin, nitrates or anti-arrhythmic drugs) or the use of diuretics as potential confounders. Missing values for cardiovascular risk factors were imputed using the expectation-maximization algorithm. SPSS 11 for Windows (SPSS, Inc, Chicago, Illinois) was used for data analysis.

Results

A description of the characteristics of those with atrial fibrillation and those in sinus rhythm is presented in table 1. Plasma levels of the vWf, sP-sel and fibrinogen were not significantly different between atrial fibrillation cases and controls. Persons with atrial fibrillation more often had a history of myocardial infarction, though the difference lacked statistical significance (P =0.06) and had a higher body mass index and a lower systolic blood pressure than those in sinus rhythm. Serum cholesterol levels were lower in those with atrial fibrillation. The atrial fibrillation cases were significantly older than the sinus rhythm cases, despite the matching on age within 5-year strata. Atrial fibrillation cases used more often cardiac medication (nitrates, digoxin or anti-arrhythmic drugs) and diuretics than sinus rhythm cases.

The total follow-up time for total and cardiac mortality was 2895 person-years and the average follow-up time was 6.0 years. During follow-up, 232 participants died: 94 of those with atrial fibrillation and 138 of those in sinus rhythm. In the atrial fibrillation group, 26 participants died from cardiac causes compared to 23 in the sinus rhythm group. In our study population, 54 strokes occurred: 24 in the atrial fibrillation group and 30 in the sinus rhythm group. Total follow-up time for stroke was 2528 person-years with a mean follow-up of 5.2 years.

All-cause mortality

A weak statistically significant association was observed between vWf and all-cause mortality in the total study population. This association was not present in the stratified analyses and totally disappeared after additional adjustments. Atrial fibrillation cases and sinus rhythm cases differed with respect to the association between fibrinogen and all-cause mortality and sP-sel and all-cause mortality. We found a strong age and gender-adjusted association between fibrinogen and all-cause mortality in the sinus rhythm group (1.58; 1.25-2.00), which was absent in the atrial fibrillation group (1.05; 0.76-1.44). Additional adjustments did not change these associations substantially. A weak, but significant association between sP-sel and all-cause mortality was found in the whole group, even after adjustments (1.07; 1.01-1.14, per 5 units increase in plasma level of sP-Sel), but statistical significance was lost in the stratified analyses (Table 3).

Cardiac death

A statistically significant association between vWf and cardiac death was observed in the total group (1.16; 1.06-1.27, per 10iU/dl increase in plasma vWf) and in the sinus rhythm group (1.17; 1.03-1.33). The associations became considerably weaker and statistically non-significant after adjustments for cardiovascular risk factors, resulting in equally weak and non-significant risk estimates in both cardiac rhythm groups. Higher levels of sP-sel were strongly associated with cardiac mortality (1.27; 1.08-1.50) among the atrial fibrillation participants, but not among those in sinus rhythm (1.04; 0.86-1.26). Additional adjustments did not change these associations substantially. Conversely, higher levels of fibrinogen were associated with higher cardiac mortality in participants in sinus rhythm (2.60; 1.69-4.01), but not among atrial fibrillation cases (1.06; 0.60-1.88). Additional adjustments did not change the associations significantly (Table 4).

Stroke

No associations were found between prothrombotic factors and stroke (Table 5).

Table 1 Characteristics of the study population by type of underlying cardiac rhythm

The Rotterdam Study, 1990-1999

	Atrial fibrillation (N=162)	Sinus rhythm (N=324)	P*
Characteristics			
Mean (SD)			
Age (years)	78 (8)	77 (10.9)	0.003
Systolic blood pressure (mmHg)	140 (23)	145 (27.6)	0.007
Serum cholesterol level (mmol/l)	6.1 (1.2)	6.4 (1.7)	0.004
Body mass index (kg/m^2)	26.4 (3.7)	25.7 (4.2)	0.02
Fibrinogen, g/L	2.32 (0.7)	2.32 (0.9)	0.8
Von Willebrand factor, IU/dl	144 (32)	138 (40.2)	0.08
Soluble P-Selectin, ng/ml	31.3 (10.1)	31.8 (13.1)	0.6
Percentages			
Male	51	51	1
Smoking			0.6
Current smoker	21.9	19.9	
Former smoker	40.0	44.2	
Never smoked	38.1	36.0	
Diabetes	19	16	0.4
Hypertension	23	27	0.4
Left ventricular hypertrophy	12	8	0.2
History of myocardial infarction	21	14	0.06
Cardiac medication	51.2	17.3	0.000
Diuretics	41.4	21.9	0.000
Betablocking agents	19.8	13.3	0.06

* P-values obtained by conditional logistic regression.

Cardiac medication indicates the use of nitrates, digoxin or anti-arrhythmic drugs.

Values are percentages or means with standard deviation between brackets.

Table 2 Crude incidence rates of all cause mortality, cardiac mortality and stroke by type of underlying cardiac rhythm

The Rotterdam Study, 1990-1999

	Total (N)	Person-years	Endpoints (N)
All-cause mortality			
All	484	2895	232
Atrial fibrillation	162	904	94
Sinus rhythm	324	1992	138
Cardiac mortality			
All	484	2895	49
Atrial fibrillation	162	904	26
Sinus rhythm	324	1992	23
Stroke			
All	484	2528	54
Atrial fibrillation	162	801	24
Sinus rhythm	324	1726	30

The figures of the person-years do not add due to rounding.

Table 3 Adjusted hazard rate ratios describing the association between each prothrombotic factor and all-cause mortality by type of underlying cardiac rhythm

The Rotterdam Study 1990-1999

	All	Atrial fibrillation	Sinus rhythm
Von Willebrand Factor*			
†	1.05 (1.01-1.10)	1.04 (0.97-1.11)	1.04 (0.98-1.10)
‡	1.04 (1.00-1.09)	1.03 (0.96-1.10)	1.04 (0.98-1.10)
§	1.02 (0.97-1.06)	1.00 (0.93-1.08)	1.02 (0.96-1.08)
Soluble P-Selectin**			
†	1.09 (1.03-1.16)	1.08 (0.98-1.20)	1.08 (1.00-1.17)
‡	1.09 (1.03-1.16)	1.11 (1.00-1.23)	1.07 (0.99-1.16)
§	1.07 (1.01-1.14)	1.08 (0.98-1.20)	1.06 (0.98-1.15)
Fibrinogen***			
†	1.35 (1.12-1.63)	1.05 (0.76-1.44)	1.58 (1.25-2.00)
‡	1.32 (1.09-1.62)	1.02 (0.73-1.43)	1.53 (1.20-1.96)
§	1.25 (1.03-1.53)	0.95 (0.68-1.32)	1.47 (1.15-1.89)

* For von Willebrand Factor hazard rate ratios are presented per 10 IU/dl increase.

** For soluble P-Selectin hazard rate ratios are presented per 5 ng/ml increase.

*** For fibrinogen hazard rate ratios are presented per 1 g/ml increase.

† Adjusted for age and sex.

‡ Adjusted for age, sex, diabetes, smoking and body mass index.

§ Adjusted for age, sex, body mass index, diabetes, hypertension, smoking, systolic blood pressure, serum total cholesterol level, history of myocardial infarction, left ventricular hypertrophy and the use of cardiac medication (nitrates, digoxin or anti-arrhythmic drugs) and/or diuretics.

Table 4 Adjusted hazard rate ratios describing the association between each prothrombotic factor and cardiac mortality by type of underlying cardiac rhythm

The Rotterdam Study, 1990-1999

	All	Atrial fibrillation	Sinus rhythm
Von Willebrand Factor*			
†	1.16 (1.06-1.27)	1.14 (0.99-1.30)	1.17 (1.03-1.33)
‡	1.16 (1.06-1.27)	1.14 (1.00-1.30)	1.15 (1.01-1.31)
§	1.09 (0.99-1.20)	1.08 (0.94-1.25)	1.10 (0.96-1.27)
Soluble P-Selectin**			
†	1.17 (1.03-1.33)	1.27 (1.08-1.50)	1.04 (0.86-1.26)
‡	1.17 (1.03-1.31)	1.27 (1.08-1.50)	1.02 (0.85-1.23)
§	1.12 (0.99-1.27)	1.19 (1.01-1.41)	0.98 (0.80-1.20)
Fibrinogen***			
†	1.79 (1.26-2.54)	1.06 (0.60-1.88)	2.60 (1.69-4.01)
‡	1.79 (1.25-2.54)	1.09 (0.62-1.94)	2.51 (1.63-3.91)
§	1.56 (1.08-2.34)	0.96 (0.55-1.66)	2.37 (1.47-3.83)

* For von Willebrand Factor hazard rate ratios are presented per 10 IU/dl increase.

** For soluble P-Selectin hazard rate ratios are presented per 5 ng/ml increase.

*** For fibrinogen hazard rate ratios are presented per 1 g/ml increase.

† Adjusted for age and sex.

‡ Adjusted for age, sex, diabetes, smoking and body mass index.

§ Adjusted for age, sex, body mass index, diabetes, hypertension, smoking, systolic blood pressure, serum total cholesterol level, history of myocardial infarction, left ventricular hypertrophy and the use of cardiac medication (nitrates, digoxin or anti-arrhythmic drugs) and/or diuretics.

Table 5 Adjusted hazard rate ratios describing the association between each prothrombotic factor and stroke by type of underlying cardiac rhythm
The Rotterdam Study, 1990-1999

	All	Atrial fibrillation	Sinus rhythm
Von Willebrand Factor*			
†	1.02 (0.93-1.11)	0.96 (0.84-1.09)	1.05 (0.94-1.18)
‡	0.99 (0.90-1.08)	0.92 (0.75-1.06)	1.02 (0.90-1.14)
§	0.98 (0.90-1.08)	0.91 (0.78-1.06)	1.01 (0.89-1.15)
Soluble P-Selectin**			
†	0.98 (0.85-1.12)	0.94 (0.76-1.16)	1.01 (0.84-1.16)
‡	0.96 (0.84-1.11)	0.92 (0.75-1.14)	0.98 (0.82-1.17)
§	0.95 (0.83-1.10)	0.90 (0.72-1.13)	0.97 (0.81-1.17)
Fibrinogen***			
†	0.97 (0.64-1.49)	0.62 (0.31-1.25)	1.31 (0.79-2.18)
‡	1.01 (0.66-1.54)	0.75 (0.39-1.44)	1.28 (0.76-2.16)
§	1.00 (0.65-1.92)	0.74 (0.38-1.41)	1.28 (0.76-2.17)

* For von Willebrand Factor hazard rate ratios are presented per 10 IU/dl increase.

** For soluble P-Selectin hazard rate ratios are presented per 5 ng/ml increase.

*** For fibrinogen hazard rate ratios are presented per 1 g/ml increase.

† Adjusted for age and sex.

‡ Adjusted for age, sex, diabetes, smoking and body mass index.

§ Adjusted for age, sex, body mass index, diabetes, hypertension, smoking, systolic blood pressure, serum total cholesterol level, history of myocardial infarction, left ventricular hypertrophy and the use of cardiac medication (nitrates, digoxin or anti-arrhythmic drugs) and/or diuretics.

Discussion

Among 162 atrial fibrillation cases and 324 age and sex matched persons in sinus rhythm participating in this population-based study of elderly subjects, statistically significant associations were observed between plasma indices of the prothrombotic state and subsequent mortality, especially cardiac mortality. Furthermore, relationships between some of the plasma indices and outcome differed between atrial fibrillation cases and those in sinus rhythm. However, no association was observed between plasma levels of vWf, sP-sel or fibrinogen and subsequent stroke, either among atrial fibrillation cases or persons in sinus rhythm.

The prognostic significance of plasma vWf for the development of cardiovascular disease among populations has been demonstrated previously.[15-18] In the present study, plasma vWf was a predictor of cardiac mortality among the whole study population. This relationship was not of statistical significance among either atrial fibrillation cases or persons in sinus rhythm, although the risk estimates were of a similar magnitude. This suggests that the prognostic importance of plasma vWf in atrial fibrillation may be similar to the prognostic importance of plasma vWf in the general population. We have previously shown that increased plasma vWf levels in this cohort are associated with the presence of atrial fibrillation, especially among women.[19] Plasma vWf (or endothelial damage/dysfunction) can therefore both be related to atrial fibrillation and to subsequent cardiac mortality in this study population.

The predictive value of sP-sel for cardiovascular events is still debated.[20,21] In the present study, plasma sP-sel predicted cardiac mortality among atrial fibrillation cases, suggesting a relationship between platelet activation and cardiac death in atrial fibrillation. It is unclear why this association was limited to atrial fibrillation cases and not seen among persons in sinus rhythm in this study. There are some discrepancies between studies investigating platelet activation in atrial fibrillation.[9,10,22,23] Atrial fibrillation itself was not associated with plasma sP-sel levels in our cohort,[19] suggesting that it is not atrial fibrillation itself that promotes platelet activation. It is possible, however, that the altered blood flow patterns that occur in the left atrium, the left atrial appendage and in arteries as a result of atrial fibrillation[24] might favor interaction between activated platelets and endothelium, neutrophils or other platelets, leading to thrombosis.

Plasma fibrinogen is well described as a predictor of cardiovascular events in population studies.[16,17,25-27] In the present study, plasma fibrinogen predicted cardiovascular and all-cause mortality among the non-atrial fibrillation group, but not among atrial fibrillation cases. Indeed, this is the second study to find no relationship between fibrinogen and vascular events in atrial fibrillation.[23] This finding may suggest reduced physiological importance of plasma fibrinogen level in atrial fibrillation, compared to sinus rhythm. The reasons for this are unclear, but

could once again reflect altered blood-flow patterns in atrial fibrillation, with the rheological effects of fibrinogen having greater importance upon thrombosis at high-shear blood flow within arterial tissue during sinus rhythm than upon low-shear left atrial thrombogenesis in atrial fibrillation.[24]

Blood was not available for analyses in 42 of the 204 atrial fibrillation cases, approximately 21%. In age and gender adjusted analyses, however, only body mass index was different in those selected for the analysis and those without available blood. We do not see how this may have influenced our results, the more so as we adjusted in the analyses for body mass index.

It is surprising that plasma vWf, sP-sel and fibrinogen did not predict stroke in this study, either among atrial fibrillation cases or those in sinus rhythm, since these indices have previously been shown to predict stroke.[16,28,29] A non-significant association, however, between fibrinogen and stroke in sinus rhythm (1.31; 0.79-2.18) and the absence of an association in atrial fibrillation (0.62 (0.31-1.25)) suggest similar mechanisms as discussed with respect to the associations between fibrinogen and cardiac death. Power problems in our small study may have attributed to this unexpected finding. Furthermore, the existence of a prothrombotic state in atrial fibrillation has been questioned[30] as many of the abnormal prothrombotic plasma indices described in atrial fibrillation[8] may be due to the presence of underlying cardiovascular disease.[30,31] Certainly there are some difficulties for statistical analyses to fully and completely account for all possible confounders.[30]

In conclusion, this study demonstrates the potential for plasma indices of the prothrombotic state to predict clinical outcome both in atrial fibrillation and in sinus rhythm, but the identification of a single reliable predictor of stroke in atrial fibrillation remains elusive. Although plasma vWf and sP-sel show some promise as markers of risk in atrial fibrillation, it may be that the measurement of single indices is insufficient to gauge thrombotic risk. Atrial fibrillation has been associated with raised levels of several prothrombotic indices other than vWf, sP-sel and fibrinogen.[8,24] Recently, increased plasma levels of tissue factor (TF), the initiator of coagulation in vivo, have been described in atrial fibrillation,[32,33] and can be related to levels of vascular endothelial growth factor[32] and interleukin-6.[33] A link between the prothrombotic state and inflammation may be of particular importance, since inflammatory indices may predict both atrial fibrillation[34] and cardiovascular events.[28] Further prospective studies are needed to establish the predictive value of other prothrombotic indices (such as TF) and indices of inflammation (such as C-reactive protein and interleukin-6), for the occurrence of stroke and cardiovascular events in atrial fibrillation.

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Chapter 5.1

Atrial fibrillation and the development of heart failure

Abstract

Background Heart failure is a known risk factor for atrial fibrillation and several studies found an association between atrial fibrillation and the development of heart failure. Atrial fibrillation and heart failure, however, are highly interrelated and uncertainties remain on the relationship between these diseases. We investigated the role of atrial fibrillation in the development of heart failure in a large longitudinal population-based study of elderly inhabitants of Rotterdam, the Netherlands.

Methods The association between atrial fibrillation and heart failure was examined in 6544 subjects without heart failure at baseline. Prevalent atrial fibrillation was present in 305 participants. During a median follow-up of 11.9 years, 600 cases of incident atrial fibrillation and 822 cases of incident heart failure were identified. Relative risks (RR) were calculated with 95% confidence intervals (CI) using time-dependent Cox proportional hazards models, adjusted for age, sex, baseline cardiovascular risk factors, baseline levels of left ventricular hypertrophy on the ECG and ankle-arm index and baseline and incident coronary heart disease. Subjects with heart failure diagnosed at the same date as incident atrial fibrillation were censored.

Results After multivariate adjustment, prevalent (RR 1.87; 95% CI 1.47-2.37) and incident (RR 3.22; 2.59-4.01) atrial fibrillation cases had increased risks of heart failure. The association was lower after exclusion of the heart failure cases within the time window of one year after incident atrial fibrillation (RR 1.98; 1.52-2.59). The risks were slightly higher in women than in men.

Conclusion The results of this population-based, longitudinal study provide further evidence that atrial fibrillation is an independent predictor of heart failure.

Introduction

Heart failure and atrial fibrillation are two highly related diseases. Both diseases become more prevalent with advancing age, have an equally high lifetime risk of 25-30%,[1-4] and share important determinants.[5] Heart failure is the strongest independent risk factor for the incidence of atrial fibrillation.[6] It is an old observation that atrial fibrillation impairs cardiac function[7] and the results of various studies indicate that atrial fibrillation may cause heart failure.[8,9] A rapid and irregular ventricular response in atrial fibrillation may cause a decrease in left ventricular function and cardiac output. Loss of atrioventricular synchrony may additionally result in impaired diastolic filling, also resulting in a reduction in stroke volume and cardiac output.[10-12] Until now, the relationship between atrial fibrillation and the development of heart failure has been investigated in three prospective population-based studies[13-15] and in a longitudinal study of male air crew recruits.[16] Two studies found an independent association between prevalent atrial fibrillation and heart failure. One study showed that incident atrial fibrillation was associated with heart failure in healthy young men. The Framingham Study showed that atrial fibrillation and heart failure are often found together and that atrial fibrillation precedes heart failure in the same proportion as heart failure precedes atrial fibrillation.

The evidence for an independent role of atrial fibrillation in the development of heart failure, however, is difficult to establish for several reasons. Atrial fibrillation and heart failure are often diagnosed at the same moment. It is probable that atrial fibrillation remains unnoticed for patients and their physicians for a considerable time[17] until symptoms of heart failure become manifest. On the other hand, asymptomatic left ventricular dysfunction has been shown to cause atrial fibrillation, making it difficult to assess which disease was the first to develop.[18]

In this longitudinal study, we describe the role of atrial fibrillation in the development of heart failure in persons aged 55 years and over in the population-based Rotterdam Study.

Methods

Study population

The Rotterdam Study is a population-based prospective follow-up study, aiming at the assessment of the occurrence of and progression of and risk factors for chronic diseases of the elderly. Neuro-geriatric, psycho-geriatric, cardiovascular, locomotor and ophthalmologic diseases are the main areas of interest.[19] At the start of the study, in 1989, all inhabitants aged 55 years and older of the Rotterdam suburb Ommoord were invited to participate. Of the 10,275 eligible subjects, 7,983 (78%) responded. The baseline measurements, consisting of a

home interview and two series of examinations at the research center, were carried out in the period 1990-1993. The first follow-up examination started at July 1993 and ended December 31st 1994. The second follow-up examination was performed between April 1997 and December 31st 1999. The third follow-up measurement started January 1st 2002 and was completed in July 2004. The Medical Ethics Committee of the Erasmus MC approved the study. All participants signed an informed consent.

The Rotterdam Study collaborates with the general practitioners in the area of Ommoord. Each Dutch inhabitant is assigned to one general practitioner. Dutch general practitioners record all disease events in their files, including information from hospitals and outpatient clinics. The general practitioners collaborating with the Rotterdam Study send all computerized information on diseases of interest to the researchers of the Rotterdam Study on a weekly basis. Trained research assistants verify this information and try to obtain the optimal amount of additional information. In addition, collaboration with the pharmacies in the Rotterdam Study area makes it possible to obtain detailed information on all drug prescriptions dispensed to participants of the study.

Assessment of atrial fibrillation

The assessment of atrial fibrillation at baseline and follow-up has been described in detail previously.[2] In short, three methods were used to identify cases of atrial fibrillation or atrial flutter. At baseline and at follow-up, 10 second 12-lead ECGs were recorded at the research center with an ACTA Gnosis IV ECG recorder (EsaOte, Florence, Italy), stored digitally and analyzed with the Modular ECG Analysis System (MEANS).[20-22] Additional information was obtained from the files of the collaborating general practitioners and from the LMR system (de Landelijke Medische Registratie). This national registration accumulates all hospital discharge diagnoses of Dutch inhabitants. Prevalent atrial fibrillation was defined based on the ECG measurement at baseline and on the information from general practitioners. Incident atrial fibrillation was evaluated with the ECG measurements during follow-up rounds, with the information from the collaborating general practitioners and with the information generated by hospital admissions. The date of onset of atrial fibrillation was defined as the midpoint between the date of the follow-up round at which atrial fibrillation was detected and the date of the previous round at which atrial fibrillation had not yet been detected. If also or only information of a diagnosis of atrial fibrillation was available from either the general practitioner files and/or the LMR registry this date was taken as the date of onset. Follow-up by January 1, 2005 was complete for 99% in person years of the total study population.

Ascertainment of heart failure cases

Assessment of heart failure at baseline in the Rotterdam Study has been described in detail previously.[23] In short, heart failure cases were classified in accordance with the guidelines of the European Society of Cardiology[24] based on the presence of at least two symptoms of heart failure (shortness of breath, ankle swelling and pulmonary crepitations), or on the use of medication (diuretics, glycosides or angiotensin converting enzyme inhibitors), prescribed for the indication heart failure in combination with objective evidence of cardiovascular disease. Information from the hospital discharge diagnoses database and the information from the general practitioners files were used to complete this information. Cases of incident heart failure were obtained by the continuous monitoring of the participants through the automated linkage to the general practitioner files.[1] Cases were classified as definite, probable, possible or unlikely according to the criteria of the European Society of Cardiology.[24] All available data on events were independently classified by two research assistants. A cardiologist verified all probable and possible cases of heart failure and all cases with persistent disagreement between the research assistants. Definite and probable cases of heart failure were included in the analyses. The date of incident heart failure was defined as the day of the first occurrence of symptoms suggestive of heart failure, obtained from the medical records, or the day of receipt of a first prescription for a loop diuretic or an ACE-inhibitor, whichever came first.

Vital status

Information on vital status was obtained on a regular basis from the central registry of the Municipality of Rotterdam, from collaborating general practitioners and by obtaining information during follow-up rounds. For those participants whose information on vital status remained missing, the Central Registry of Genealogy of the Netherlands was consulted. This national institute receives population registry records of those inhabitants of the Netherlands who have died.

Cardiovascular risk factors

Information on current health status, smoking behavior and the current use of medication was obtained during the home interview using a computerized questionnaire. The information on medication obtained from the home interview was completed by the computerized information from the collaborating pharmacies. Body Mass Index (BMI) was calculated as weight (kg)/ length (m^2). Blood pressure was measured in sitting position at the right brachial artery using a random-zero sphygmomanometer. Systolic and diastolic blood pressures were calculated as the average of two consecutive measurements. Blood samples were drawn by venipuncture. Serum total cholesterol, HDL-cholesterol and glucose were measured with an automated enzymatic

method. Diabetes mellitus was considered present when glucose levels exceeded 11.0 mmol/l and/or the use of antidiabetic medication was present. CRP was measured in serum samples kept frozen at –20^{0}C, using a high sensitivity rate near infrared particle immunoassay (NIPIA) method (Immage®, Beckman Coulter). The presence of atherosclerosis in the arteries of the lower extremities was evaluated by measuring the systolic blood pressure of the posterior tibial artery at both the left and right ankle, using an 8 MHz continuous Doppler-probe (Huntleigh 500 D, Huntleigh Technology, Bedfordshire, UK) and a random zero sphygmomanometer with the subject in supine position. Ankle brachial pressure indexes were calculated as the ratios of the systolic blood pressure at each ankle to that at the right arm. In the analyses the lowest of both measurements was used as a measure of generalized atherosclerosis. Left ventricular hypertrophy on the ECG was diagnosed by the MEANS program with an algorithm that takes into account QRS voltages, with an age-dependent correction, and repolarization. A history of myocardial infarction at baseline was defined as a self-reported myocardial infarction with hospital admission or the presence of a myocardial infarction on the ECG. A positive self-report of myocardial infarction was confirmed by reviewing the medical records of general practitioners and specialists for the presence of myocardial infarction. Cases of incident myocardial infarction were ascertained using information from ECGs during follow-up rounds, the information from collaborating general practitioners and information from the dataset of hospital discharge diagnoses. Information on coronary artery bypass grafts (CABG) and on percutaneous transluminal coronary angioplasty (PTCA) was obtained at baseline with the results of the home interview and during follow-up with the information from the baseline measurements and the results of the follow-up procedures in the practices of the collaborating general practitioners. Coronary heart disease at baseline and during follow-up was diagnosed if participants were diagnosed with a myocardial infarction or underwent PTCA or CABG.

Population for analysis

At baseline, 7151 persons were examined at the research center of the Rotterdam Study. For the present study, an ECG was not available for analysis of atrial fibrillation in 343 participants, mainly due to logistic reasons, resulting in 6808 persons who had a baseline assessment of atrial fibrillation. Of these we excluded 264 persons who had heart failure at baseline (N=228) or who had missing baseline data on heart failure (N=36) resulting in a population for analysis of 6544 persons.

Statistical analysis

Age and sex adjusted hazard rate ratios, expressed as relative risks (RR) with their 95% confidence intervals (CI), were calculated using the Cox proportional hazards model with

incident heart failure as the dependent variable and atrial fibrillation as the independent variable. Additional adjustments were made for baseline diabetes, diastolic blood pressure, systolic blood pressure, medication prescribed with the indication hypertension, body mass index, former and current smoking, serum total cholesterol level, serum HDL-cholesterol level, serum CRP level, left ventricular hypertrophy on the ECG, ankle to brachial pressure index and for coronary heart disease at baseline and during follow-up. Separate analyses were conducted stratified for sex.

First, we analyzed the association between prevalent atrial fibrillation and heart failure. Subjects were followed from baseline until one of the following: a diagnosis of incident heart failure, death, or loss to follow-up or the end of the study (January 1, 2005), whichever occurred first. Subsequently, we investigated the association between incident atrial fibrillation and heart failure. In those cases in which atrial fibrillation and heart failure were diagnosed at the same date, subjects were censored at that date. To increase the probability that atrial fibrillation indeed precedes heart failure, we reanalyzed the association between incident atrial fibrillation and heart failure including a time lag of 1 year between the date of diagnosis of atrial fibrillation and the onset of heart failure. Heart failure cases originating in this time window were censored at the date of onset of heart failure and not considered as case. Finally, we examined whether the concomitant presence of coronary heart disease affected the risk of heart failure. We constructed a time dependent variable of incident atrial fibrillation combined with the presence of coronary heart disease. This variable was then used as a categorical variable with the absence of both atrial fibrillation and coronary heart disease as the reference category. Missing values for covariates were added using the expectation-maximization algorithm. SPSS version 11 for Windows (SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results

Baseline characteristics of the study population are shown in table 1. The median follow-up duration was 11.9 years (range 0.04-15.5 years). Among the 6544 participants, 308 (4.7%) had atrial fibrillation at baseline and 600 (9.6%) subjects developed atrial fibrillation during follow-up. During follow-up, 822 (12.6%) were diagnosed with heart failure. During 62217 person years of follow-up in participants in sinus rhythm, 511 participants were diagnosed with heart failure (8 cases per 1000 person years) and during 1910 person years of follow-up in participants with incident atrial fibrillation 99 participants developed heart failure (52 cases per 1000 person years). In the participants who had been diagnosed with incident atrial fibrillation and incident heart failure, 38 participants had both diagnoses on the same day. These were not considered

as a case, but were censored on that day. Heart failure preceded atrial fibrillation in 94 cases and atrial fibrillation preceded heart failure in 99 cases. The median follow-up time in the participants with incident atrial fibrillation who developed heart failure following the diagnosis of atrial fibrillation was 571 days (range 2-3009 days). Of these, 36 persons developed heart failure within the time window of one year after the diagnosis of incident atrial fibrillation.

The results of the Cox proportional hazards analyses are presented in table 2. The age- and sex-adjusted relative risk to develop heart failure in subjects with prevalent atrial fibrillation was 1.90 (1.49-2.41). The relative risk after additional adjustments was 1.87 (1.47-2.37). The RRs in subjects with incident atrial fibrillation were almost twice as high (RR 3.64 (2.92-4.53) and RR 3.22 (2.59-4.01) respectively). The RRs associated with incident atrial fibrillation decreased to 2.25 (1.73-2.93) and 1.98 (1.52-2.59), respectively, when we censored the participants who developed heart failure within one year after the diagnosis of incident atrial fibrillation. The RRs were in all 3 analyses slightly higher in women than in men.

Table 3 presents the results of the analysis of the joint presence of atrial fibrillation and coronary heart disease. The multivariate adjusted RR to develop heart failure was 3.50 (2.65-4.62) for subjects with only atrial fibrillation, 2.76 (2.32-3.28) for subjects with only coronary heart disease and 7.39 (5.21-10.48) when both conditions were present, compared to those who had neither disease. The highest RR was found in men with both atrial fibrillation and coronary heart disease (8.12 (5.30-12.45)).

Table 1 Baseline characteristics of the study population

The Rotterdam Study, 1990-1993

Variable	
Age (years)	69 (9.0)
Proportion of men (%)	41
Prevalent atrial fibrillation (%)	4.7
Body mass index (kg/m^2)	26.3 (3.7)
Systolic blood pressure (mm Hg)	139 (22.4)
Serum total cholesterol level (mmol/l)	6.6 (1.2)
Serum HDL cholesterol level (mmol/l)	1.4 (0.4)
Smoking	
Never smokers (%)	35
Current smokers (%)	23
Former smokers (%)	41
Diabetes mellitus (%)	10
History of coronary heart disease (%)	13
Left ventricular hypertrophy on the ECG (%)	4.5
Hypertension (%)	33
Ankle to brachial pressure index	1.06 (0.23)
Serum CRP level (mg/L)	3.5 (7.0)

Values are percentages or mean values with standard deviations between brackets.

Table 2 The association between atrial fibrillation and incident heart failure

The Rotterdam Study, 1990-2005

Variable	No of Cases/Subjects	Model 1	Model 2
	RR (95% CI)	RR (95% CI)	
All			
Prevalent atrial fibrillation	822/6544	1.90 (1.49-2.41)	1.87 (1.47-2.37)
Incident atrial fibrillation	704/6239	3.64 (2.92-4.53)	3.22 (2.59-4.01)
Incident atrial fibrillation, time-lag 1 year*	668/6239	2.25 (1.73-2.93)	1.98 (1.52-2.59)
Men			
Prevalent atrial fibrillation	394/2658	1.87 (1.33-2.61)	1.65 (1.18-2.31)
Incident atrial fibrillation	338/2526	3.44 (2.52-4.68)	3.15 (2.31-4.30)
Incident atrial fibrillation, time-lag 1 year*	319/2526	2.07 (1.42-3.02)	1.88 (1.28-2.75)
Women			
Prevalent atrial fibrillation	428/3886	1.95 (1.39-2.74)	2.19 (1.56-3.07)
Incident atrial fibrillation	366/3713	3.85 (2.83-5.25)	3.41 (2.50-4.66)
Incident atrial fibrillation, time-lag 1 year*	349/3713	2.44 (1.69-3.54)	2.15 (1.48-3.13)

Model 1: adjusted for age and sex, if applicable.

Model 2: adjusted for age, sex, if applicable, baseline diabetes, diastolic blood pressure, systolic blood pressure, medication prescribed with the indication hypertension, body mass index, former and current smoking, serum total cholesterol level, serum HDL-cholesterol level, serum CRP level, left ventricular hypertrophy on the ECG, ankle to brachial pressure index and for coronary heart disease (myocardial infarction or coronary artery bypass grafting or percutaneous transluminal angioplasty) at baseline and during follow-up.

* Heart failure cases, developed within a time window of one year after the date of onset of atrial fibrillation, were excluded as a case and censored on the date of heart failure.

Abbreviations: RR, relative risk; CI, confidence interval.

Table 3 The association between the presence of atrial fibrillation and/or coronary heart disease and incident heart failure

The Rotterdam Study, 1990-2005

Variable*	Model 1	Model 2
	RR (95% CI)	RR (95% CI)
All		
Absence of atrial fibrillation and coronary heart disease	1 (Reference)	1 (Reference)
Coronary heart disease only	3.03 (2.55-3.61)	2.76 (2.32-3.28)
Atrial fibrillation only	3.97 (3.03-5.27)	3.50 (2.65-4.62)
Atrial fibrillation and coronary heart disease both present	7.64 (5.39-10.84)	7.39 (5.21-10.48)
Men		
Absence of atrial fibrillation and coronary heart disease	1 (Reference)	1 (Reference)
Coronary heart disease only	3.18 (2.51-4.02)	2.69 (2.12-3.42)
Atrial fibrillation only	3.54 (2.27-5.54)	3.05 (1.95-4.78)
Atrial fibrillation and coronary heart disease both present	7.93 (5.20-12.11)	8.12 (5.30-12.45)
Women		
Absence of atrial fibrillation and coronary heart disease	1 (Reference)	1 (Reference)
Coronary heart disease only	2.86 (2.21-3.70)	2.64 (2.05-3.42)
Atrial fibrillation only	4.32 (3.04-6.14)	3.83 (2.68-5.47)
Atrial fibrillation and coronary heart disease both present	7.07 (3.74-13.38)	6.29 (3.32-11.94)

* We constructed a time dependent variable of incident atrial fibrillation combined with the presence of coronary heart disease (myocardial infarction or coronary artery bypass grafting or percutaneous transluminal angioplasty). This variable was then used as a categorical variable with the absence of both atrial fibrillation and coronary heart disease as the reference category.
Model 1: relative risks are adjusted for age and sex, if applicable.
Model 2: relative risks are adjusted for age, sex, if applicable, baseline diabetes, diastolic blood pressure, systolic blood pressure, medication prescribed with the indication hypertension, body mass index, former and current smoking, serum total cholesterol level, serum HDL-cholesterol level, serum CRP level, left ventricular hypertrophy on the ECG and ankle to brachial pressure index.
Abbreviations: RR, relative risk; CI, confidence interval.

Discussion

This population-based cohort study of elderly persons showed a relationship between atrial fibrillation and subsequent heart failure, even after adjustment for a wide range of cardiovascular disorders and risk factors. We excluded those cases of atrial fibrillation and heart failure that were diagnosed on the same date. The association remained after exclusion of the heart failure cases that fell within the time window of one year after onset of atrial fibrillation. There was a tendency towards a higher risk in individuals who developed atrial fibrillation during follow-up compared to those who had atrial fibrillation at baseline. The results indicate that atrial fibrillation is an independent predictor of heart failure. Subjects with both atrial fibrillation and coronary heart disease had a sevenfold increased risk compared to persons who were free from both conditions.

Our findings support data from smaller clinical studies and case reports.[9,25-29] These studies suggest a causal relationship between atrial fibrillation and heart failure, based on the observation that left ventricular function improved after termination of the atrial arrhythmia. Three population-based studies and one study in occupationally recruited men only reported an association between atrial fibrillation and heart failure. The Renfrew-Paisley Study found that atrial fibrillation was associated with heart failure during a long follow-up period of twenty years.[13] However, that study only used prevalent atrial fibrillation cases and was performed in a younger population (45-64 years), which may have been a selected group. The Cardiovascular Health Study found that prevalent atrial fibrillation predicts heart failure in an elderly population.[14] The Manitoba follow-up study found an almost three-fold increase in risk for developing heart failure following atrial fibrillation.[16] That study only included men in the Royal Canadian Air Force with baseline age ranging from 18 to 62 years. Our study also included women and the baseline age was higher, but we found similar results. The Framingham Study focused in a cohort of participants with incident atrial fibrillation and incident heart failure on the temporal relationship between both conditions and on their influence on mortality.[15] They found that atrial fibrillation preceded heart failure with the same percentage as heart failure preceded atrial fibrillation. The results of our study thus confirm the already found association between atrial fibrillation and heart failure and strengthen the concept that there is a causal relationship between the arrhythmia and a poor performance of the heart.

Several mechanisms may cause a decrease in left ventricular function in atrial arrhythmias.[30-33] First, irregular ventricular responses may cause a decrease in cardiac output by beat-to beat changes in ventricular filling, influencing myocardial contractility through the Frank-Starling mechanism and the interval force relation. Second, loss of atrioventricular synchrony may impair diastolic filling, reduce stroke volume, increase mean diastolic pressure and reduce

cardiac output. Third, rapid atrial fibrillation, as well as other persistent supraventricular and ventricular tachyarrhythmias, may cause heart failure. The proposed mechanisms for this so-called tachycardia-induced cardiomyopathy include myocardial energy depletion and impaired energy utilization, myocardial ischemia, abnormal calcium handling and cellular and extra cellular matrix remodeling. In the case of atrial fibrillation, high heart rates may occur during minor exercise, while heart rate is controlled in rest. This 'concealed' form of tachycardia-induced cardiomyopathy may have long-term deleterious effects on left ventricular systolic function. Finally, rise of atrial natriuretic peptide as is seen in atrial fibrillation, may protect against heart failure. These systems may fail when atrial natriuretic peptide levels decrease with increasing loss of myocytes in the atria in the course of longstanding atrial fibrillation.

The concomitant presence of coronary heart disease and atrial fibrillation yielded a greater risk for developing heart failure. Apparently, a vulnerable myocardium, either caused by coronary heart disease or the burden of atrial fibrillation, becomes at higher risk for failure when the second condition emerges. This finding also confirms the independent role of atrial fibrillation in the development of heart failure. It has to be investigated whether this high risk of heart failure by the combined effect of coronary heart disease and atrial fibrillation can be converted to the risk of coronary heart disease only if atrial fibrillation is properly treated.

Some methodological issues need to be addressed. It is known that many cases of heart failure develop especially within the first year following atrial fibrillation.[34] This early clustering may be the result of pre-existing unrecognized heart failure at the time of diagnosis of atrial fibrillation. Our association remained after we excluded cases within this first year after the diagnosis of atrial fibrillation. All diagnoses of heart failure and atrial fibrillation were made using information derived from general practitioner's records and hospital discharge letters and available ECGs in case of atrial fibrillation. All available information on atrial fibrillation and heart failure was verified and checked, thus reducing misclassification. We included only clinically ascertained cases of heart failure. We did, however, not use echocardiography to assess cardiac function at baseline and we therefore missed subjects with asymptomatic left ventricular dysfunction and some of these cases could have preceded the development of atrial fibrillation. Finally, our study is observational and therefore the associations may not reflect causal relationships.

With the above caveats in mind, our results may have several implications for clinical practice. First, our results suggest that elderly patients with atrial fibrillation should be carefully monitored for the first signs of heart failure, especially if also coronary heart disease is involved. Second, investigations are needed to find the best strategies to prevent heart failure in atrial fibrillation. Based on several trials considering death, stroke and hospitalizations as endpoints, there is a tendency to judge rhythm control and rate control strategies equally

effective in the treatment of atrial fibrillation. Before the results of these trials were known, conversion to sinus rhythm was the best practice strategy and this has greatly changed since then.[35] It is not clear, however, whether this change in strategy is also preferable in the light of heart failure as a possible consequence of atrial fibrillation. Based on the mechanisms through which atrial fibrillation may cause heart failure it is possible that a rhythm control strategy is preferable above a rate control strategy in the fight against heart failure in atrial fibrillation. To our best knowledge, trials considering rhythm and rate control in atrial fibrillation with heart failure as the endpoint have not been performed yet.

In conclusion, our results give further support for the concept that atrial fibrillation is an independent predictor of heart failure.

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Chapter 5.2

All-cause and cause-specific mortality in persons with atrial fibrillation

Abstract

Background Atrial fibrillation is associated with an increased risk of death. Data from recent risk periods and data on cause specific mortality are sparse. We aimed to investigate the associations in the Rotterdam Study in the period 1990 to 2005.

Methods The study population consisted of 6432 participants who had no atrial fibrillation at baseline (1990-1993). During a median follow-up of 12 years, 630 persons developed atrial fibrillation and 2445 participants died. Relative risks (RR) were calculated with 95% confidence intervals (CI) using time-dependent Cox proportional hazards models, adjusted for age, sex, baseline cardiovascular risk factors and baseline and incident myocardial infarction and heart failure.

Results The multivariate adjusted RR of all-cause mortality associated with incident atrial fibrillation was 1.61 (95% CI 1.42-1.81), with only small differences between the sexes. Strong associations were found with death due to stroke and intracranial bleeding (2.28, 1.61-3.22), heart failure (3.00, 2.14-4.20), cardiac arrest (2.53, 1.71-3.74) and a miscellaneous group of cardiovascular death (2.78, 1.61-4.82). Death by pulmonary disorders (2.23, 1.07-4.65) and death by ischemic heart disease (2.11, 1.18-3.76) were strongly associated with atrial fibrillation in men but not in women. In women, but not in men, a strong association was found with death due to trauma and self-harm. (3.43, 1.50-7.87)

Conclusion Atrial fibrillation is still associated with a 60% increased risk of mortality, in spite of considerable improvements in the treatment of cardiovascular disorders in recent years. The most prevailing causes of death in atrial fibrillation are stroke, heart failure, sudden death, ischemic heart disease and emphysema.

Introduction

Atrial fibrillation is associated with increased mortality. Although this association has been shown by many studies[1-13], several questions still need to be answered.[13-21] Atrial fibrillation, myocardial infarction and heart failure become more prevalent with age and share important risk factors. Myocardial infarction and heart failure are also important risk factors for atrial fibrillation[22] and it is difficult to establish the independency of an association between atrial fibrillation and mortality. The Framingham Study[6] was the first study that found an independent association of atrial fibrillation with death. These results, however, were based on the findings from 1948 to 1988. Relevant co-morbid conditions associated with atrial fibrillation, such as myocardial infarction and heart failure, are better recognized and treated now and therefore a better clinical outcome and prognosis of atrial fibrillation could be expected in more recent risk periods. Prospective data from more recent periods, however, are lacking. Furthermore, there is a paucity of data on cause-specific mortality in atrial fibrillation.

In this study we investigated atrial fibrillation in relation to total and cause-specific mortality in a large prospective population-based study, the Rotterdam Study.

Methods

Study population

The Rotterdam Study is a population-based, prospective follow-up study, aiming at the assessment of the occurrence and progression of and risk factors for chronic diseases of the elderly. Neuro-geriatric, cardiovascular, locomotor, ophthalmologic and psycho-geriatric diseases are the main areas of interest.[23] At the start of the study, in 1989, all inhabitants aged 55 years and older of the Rotterdam suburb Ommoord were invited to participate. Of the 10275 eligible subjects, 7983 (78%) responded. The baseline measurements, consisting of a home interview and two series of examinations at the research center, were carried out in the period 1990-1993. The first follow-up examination started in July 1993 and ended on December 31st, 1994. The second follow-up examination was performed between April 1997 and December 31st 1999. The third follow-up round was between January 2002 and July 2004. The Medical Ethics Committee of the Erasmus MC approved the study. All participants signed an informed consent.

Follow-up procedures

Information on diseases of interest is obtained from the baseline measurements and from the follow-up examinations. To obtain additional information the Rotterdam Study collaborates with

the general practitioners and pharmacists in the area of Ommoord. In general Dutch inhabitants are assigned to one general practitioner and one pharmacy. General practitioners have a central position in the Dutch health care system, which means that all medical information, also on hospital admissions and hospital outpatient care is available in the files of Dutch general practitioners. The general practitioners who are affiliated to the Rotterdam Study send all computerized information on diseases of interest to the researchers of the Rotterdam Study on a weekly basis. Trained follow-up research assistants of the Rotterdam Study verify this information and try to obtain the optimal amount of additional information on these diagnoses.

Assessment of atrial fibrillation

The assessment of atrial fibrillation at baseline and follow-up has been described in detail previously.[24] In short, three methods were used to identify cases of atrial fibrillation or atrial flutter. At baseline and at follow-up 10 second 12-lead ECGs were recorded at the research center with an ACTA Gnosis IV ECG recorder (EsaOte, Florence, Italy), stored digitally and analyzed with the Modular ECG Analysis System (MEANS).[25-27] Prevalent atrial fibrillation was defined based on the ECG measurement at baseline and on the information from general practitioners. Incident atrial fibrillation was evaluated with the ECG measurements during follow-up rounds, with the information from the collaborating general practitioners and with information from the LMR system (de Landelijke Medische Registratie). This national registration accumulates all hospital discharge diagnoses of Dutch inhabitants. The date of onset of atrial fibrillation was defined as the midpoint between the date of the follow-up round at which atrial fibrillation was detected and the date of the previous round at which atrial fibrillation had not yet been detected. If also or only information of a diagnosis of atrial fibrillation was available from either the general practitioner files and/or the LMR registry this date was taken as the date of onset. Follow-up by January 1, 2005 was complete for 99% in person years of the total study population.

Vital status and cause of mortality

Information on vital status was obtained on a regular basis from the central registry of the Municipality of Rotterdam, from collaborating general practitioners and by obtaining information during follow-up rounds. For those participants whose information on vital status remained missing, the Central Registry of Genealogy of the Netherlands was consulted. Causes of death were classified according to the Tenth Revision of the International Statistical Classification of Diseases and Health Related Problems (ICD-10). We used the underlying cause of death, which is the disease or injury, which initiated the train of events leading directly to death. The diagnosis of death was assessed in four working groups, namely cancer, cardiovascular diseases, neurological diseases and a miscellaneous group considering internal medicine, pulmonary

diseases, trauma and ill-defined conditions. In each working group two physicians who were initially blinded to each other's diagnosis tried to obtain final agreement on the cause of death under consideration. The four groups were supervised by a specialist in cancer epidemiology, cardiovascular medicine, and neurological diseases and in diseases of internal medicine respectively. These supervisors finally checked the agreement of coders, if necessary corrected the cause of death and took the final decision in the case of persistent disagreement between coders. For the present study we used 13 groups of causes of mortality. *Sepsis, internal medicine:* A00-B99; D50-D89; E00-E88; G00-G09; J10-J18; J20-J22; K00-K92; L00-L99; M00-M36; N00-N99. *Neoplasms:* C00-D48. *Dementia:* F00-F03; G30-G32. *Other neurological disorders:* G12-G26; G31-G99. *Ischemic heart disease:* I20-I25. *Intracranial hemorrhage and stroke:* I60-I69. *Heart failure:* I42, I50. *Cardiac arrest:* I46.; R99. *Miscellaneous group of cardiovascular diseases:* I01-I15; I26-I28; I30-I41; I44-I45; I47-I49; I51-I52; I70-I99 *Unexpected death:* R96-R98. *Senility, cachexia and ill-defined conditions:* R54; R64; R99. *Pulmonary disease:* J39-J47; J69-J96. *Trauma and self-harm, complications of medical care:* S00-Y98.

Cardiovascular risk factors

Information on current health status, smoking behavior and the current use of medication was obtained during the home interview using a computerized questionnaire. Participants were classified as current smokers, former smokers or non-smokers. The information on medication obtained from the home interview was completed by the computerized information from the collaborating pharmacies. Body Mass Index (BMI) was calculated as weight (kg)/length $(m)^2$. Blood pressure was measured in sitting position at the right brachial artery using a random-zero sphygmomanometer. Systolic and diastolic blood pressures were calculated as the average of two consecutive measurements. Blood samples were drawn by venipuncture. Serum total cholesterol, HDL-cholesterol and glucose were measured with an automated enzymatic method. Diabetes mellitus was considered present when glucose levels exceeded 11.0 mmol/l and/or the use of antidiabetic medication was present. C-reactive protein (CRP) was measured in serum samples kept frozen at -20^0C, using a high sensitivity rate near-infrared particle immunoassay (NIPIA) method (Immage®, Beckman Coulter). The common carotid artery, the bifurcation and the internal carotid artery at both sides were visualized by ultrasonography using a 7.5 MHz transducer (ATL Ultramark IV, Advanced Technology Laboratories, Bethel, Washington, USA). Common carotid intima-media thickness was measured over a length of one cm proximal to the bulbus as described previously.[28,29] A history of myocardial infarction was defined as a self-reported myocardial infarction with hospital admission or the presence of a myocardial infarction on the ECG. A positive self-report of myocardial infarction was confirmed by reviewing the medical records of general practitioners and specialists for the presence of myocardial infarction.

Left ventricular hypertrophy was diagnosed by the MEANS program with an algorithm that takes into account QRS voltages, with an age-dependent correction, and repolarization. Cases of incident myocardial infarction were ascertained using information from ECGs during follow-up rounds, the information from collaborating general practitioners and information from the dataset of hospital discharge diagnoses. Assessment of heart failure at baseline and during follow/up in the Rotterdam Study has been described in detail previously.[30-32] Only definite and probable cases were included in the analyses.

Population for analysis

At baseline, 7151 persons were examined at the research center of the Rotterdam Study. For the present study, an ECG was not available for analysis of atrial fibrillation in 343 participants, mainly due to logistic reasons, resulting in 6808 persons who had a baseline assessment of atrial fibrillation. Of these, 376 were identified with atrial fibrillation at baseline. The population for analysis consisted of 6432 participants who had no atrial fibrillation at baseline

Statistical analysis

First, we examined the association of incident atrial fibrillation and all-cause mortality by calculating age and sex adjusted hazard rate ratios, expressed as relative risks (RR) with their 95% confidence intervals (CI), using time-dependent Cox regression analysis. Additional adjustments were made for baseline levels of systolic blood pressure, diastolic blood pressure, medication prescribed for hypertension, body mass index (BMI), former smoking, current smoking, total serum cholesterol level, serum HDL-cholesterol level, diabetes mellitus, left ventricular hypertrophy on the ECG, carotid intima-media thickness, serum CRP level, baseline myocardial infarction and heart failure, and incident myocardial infarction and heart failure before the onset of atrial fibrillation. Subjects were followed from baseline until one of the following: death, loss to follow-up or January 1, 2005. Separate analyses were conducted stratified for sex. In secondary analyses, we estimated the association of atrial fibrillation with mortality independent of myocardial infarction and heart failure by additionally adjusting the associations of atrial fibrillation with death for myocardial infarction and heart failure that evolved after the diagnosis of atrial fibrillation. We also analyzed the association of atrial fibrillation with death after the exclusion of those participants who died within the period of 30 days after the diagnosis of atrial fibrillation. Next, we examined atrial fibrillation in relation to cause-specific mortality. We calculated relative risks for the association of incident atrial fibrillation and categories of mortality, adjusted for the same confounders as used in the analysis of all-cause mortality. Missing values for cardiovascular risk factors were added using the expectation-maximization algorithm. SPSS version 15 for Windows (SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results

During a median follow-up of 12 years (range 0.05-15.5 years), 630 persons developed atrial fibrillation and 2445 participants (38 %) died, 1345 women (35 % of the 3846 women at risk) and 1100 men (42.5% of the 2586 men at risk). The baseline characteristics of the study population are presented in Table 1 and the causes of death are displayed in Table 2. After adjustments for age and sex, incident atrial fibrillation was associated with an 80% increased risk of death. (Table 3) After additional adjustments, a 60% increased risk remained. The associations were slightly higher in women than in men. Additional adjustment for myocardial infarction occurring after the diagnosis of atrial fibrillation did not change the estimates. However, when we adjusted for heart failure after atrial fibrillation, the risk of total mortality associated with atrial fibrillation decreased from 60% to 30%. When we repeated the analyses excluding those participants who died within 30 days after the diagnosis of atrial fibrillation, the association of atrial fibrillation with mortality was lower but remained statistically significant in both sexes (RRs 1.23, 1.02-1.48 and 1.31, 1.10-1.56 in men and women respectively). We next examined the relation of atrial fibrillation with cause-specific mortality. In general, similar relative risks for cause-specific mortality were found for men and women (Table 4). Strong associations were found with mortality due to intracranial bleeding and stroke, heart failure, cardiac arrest and the miscellaneous group of cardiovascular mortality diagnoses. Death by pulmonary disorders and death by ischemic heart disease, however, were strongly associated with atrial fibrillation in men but not in women. Atrial fibrillation was a strong predictor of death due to trauma and self-harm in women but not in men.

Table 1 Baseline characteristics of the study population

The Rotterdam Study, 1990-1993

Variable	
Age (years)	68.9 (8.9)
Proportion of men (%)	40.2
Heart failure (%)	2.5
History of myocardial infarction (%)	12.5
Left ventricular hypertrophy on the ECG (%)	4.7
Diabetes mellitus (%)	9.7
Smokers	
Never smokers (%)	35
Current smokers (%)	23.1
Former smokers (%)	41.9
Proportion on antihypertensive medication (%)	14.5
Systolic blood pressure (mmHg)	139 (22.4)
Diastolic blood pressure (mmHg)	74 (11.5)
Serum total cholesterol level (mmol/l)	6.6 (1.2)
Serum HDL cholesterol level (mmol/l)	1.4 (0.4)
Body mass index (kg/m^2)	26.3 (3.7)
Intima-media thickness (mm)	0.82 (0.15)
Serum CRP level (mmol/L)	3.3 (6.9)

Values are percentages or mean values with standard deviations between brackets.

Table 2 Causes of death

The Rotterdam Study, 1990-2005

Variable	All (%)	Men (%)	Women (%)
Sepsis, internal medicine	190 (3.0)	83 (3.2)	107 (2.8)
Neoplasms	669 (10.4)	356 (13.8)	313 (8.1)
Dementia	140 (2.2)	45 (1.7)	95 (2.5)
Other neurological disorders	52 (0.8)	28 (1.1)	24 (0.6)
Ischemic heart disease	153 (2.4)	84 (3.2)	69 (1.8)
Intracranial hemorrhage and stroke	241 (3.7)	76 (2.9)	165 (4.3)
Heart failure	181 (2.8)	69 (2.7)	112 (2.9)
Cardiac arrest	173 (2.7)	98 (3.8)	75 (2.0)
Miscellaneous group of cardiovascular diseases	89 (1.4)	45 (1.7)	44 (1.1)
Unexpected death	113 (1.8)	40 (1.5)	73 (1.9)
Senility, cachexia and ill-defined conditions	299 (4.6)	93 (3.6)	206 (5.4)
Emphysema, COPD and other pulmonary disease	79 (1.2)	53 (2.0)	26 (0.7)
Trauma, self-harm and complications of medical care	66 (1.0)	30 (1.2)	36 (0.9)
Total	2445	1100	1345

Table 3 Incident atrial fibrillation and all-cause mortality

The Rotterdam Study, 1990-2005

	RR (95%CI)	RR (95%CI)	RR (95%CI)
	All participants	Men	Women
Model A	1.81 (1.60-2.04)	1.78 (1.49-2.12)	1.84 (1.56-2.17)
Model B	1.61 (1.42-1.81)	1.54 (1.29-1.84)	1.62 (1.37-1.91)
Model C	1.58 (1.40-1.78)	1.51 (1.27-1.80)	1.60 (1.35-1.89)
Model D	1.32 (1.16-1.49)	1.26 (1.04-1.51)	1.33 (1.12-1.58)
Model E	1.29 (1.14-1.47)	1.23 (1.02-1.48)	1.31 (1.10-1.56)
Model F	1.45 (1.28-1.65)	1.35 (1.12-1.63)	1.50 (1.26-1.78)

Model A: Relative risks are adjusted for age and sex, if applicable.
Model B: Adjusted for age, sex (if applicable), baseline levels of systolic blood pressure, diastolic blood pressure, medication prescribed for hypertension, body mass index (BMI), former smoking, current smoking, total serum cholesterol level, serum HDL-cholesterol level, diabetes mellitus, left ventricular hypertrophy on the ECG, carotid intima-media thickness, serum CRP level, baseline myocardial infarction and heart failure, and incident myocardial infarction and heart failure before the onset of atrial fibrillation.
Model C: Adjusted for the confounders of model B, but additionally for myocardial infarction after the diagnosis of atrial fibrillation.
Model D: Adjusted for the confounders of model B, but next to it also for heart failure after the diagnosis of atrial fibrillation.
Model E: Adjusted for the confounders of model B, but additionally both myocardial infarction and heart failure after the diagnosis of atrial fibrillation.
Model F: participants who died within the time window of 30 days after the diagnosis of atrial fibrillation were excluded. Adjusted for all confounders of model B.

Table 4 Incident atrial fibrillation and risk of cause-specific death

The Rotterdam Study

1990-2005	Cases N	All participants RR (95%CI)		Cases N	Men RR (95%CI)		Cases N	Women RR (95%CI)	
		Model A	Model B		Model A	Model B		Model A	Model B
Sepsis, internal medicine	190	1.26 (0.80-2.00)	1.12 (0.70-1.77)	83	1.02 (0.50-2.05)	0.98 (0.48-1.98)	107	1.34 (0.72-2.49)	1.26 (0.68-2.35)
Neoplasms	669	1.22 (0.91-1.63)	1.18 (0.88-1.58)	356	1.13 (0.77-1.67)	1.11 (0.76-1.64)	313	1.28 (0.82-1.99)	1.22 (0.78-1.90)
Dementia	140	1.02 (0.57-1.81)	1.01 (0.56-1.80)	45	1.59 (0.67-3.80)	1.49 (0.62-3.61)	95	0.79 (0.36-1.72)	0.80 (0.36-1.75)
Other neurological diseases	52	1.00 (0.35-2.80)	0.94 (0.33-2.66)	28	1.18 (0.35-3.87)	1.16 (0.34-3.96)	24	0.63 (0.08-4.90)	0.63 (0.08-4.92)
Ischemic heart disease	153	2.50 (1.57-3.97)	1.80 (1.31-2.87)	84	2.84 (1.60-5.05)	2.11 (1.18-3.76)	69	1.62 (0.72-3.64)	1.28 (0.56-2.92)
Intracranial hemorrhage and stroke	241	2.51 (1.78-3.55)	2.28 (1.61-3.22)	76	2.11 (1.12-3.97)	1.84 (0.97-3.48)	165	2.56 (1.68-3.89)	2.42 (1.59-3.69)
Heart failure	181	4.47 (3.20-6.23)	3.00 (2.14-4.20)	69	4.74 (2.78-8.08)	3.54 (2.04-6.12)	112	3.70 (2.38-5.75)	2.73 (1.74-4.27)
Cardiac arrest	173	3.14 (2.12-4.63)	2.53 (1.71-3.74)	98	3.30 (1.99-5.47)	2.56 (1.54-4.26)	75	2.80 (1.40-5.24)	2.59 (1.38-4.84)
Miscellaneous group of cardiovascular diseases	89	3.46 (2.02-5.91)	2.78 (1.61-4.82)	45	3.20 (1.45-7.07)	2.35 (1.04-5.31)	44	3.75 (1.77-7.95)	3.24 (1.51-6.92)
Unexpected death	113	0.67 (0.29-1.53)	0.62 (0.27-1.42)	40	0.53 (0.13-2.22)	0.55 (0.13-2.30)	73	0.71 (0.25-1.97)	0.71 (0.26-1.99)
Senility, cachexia and ill-defined conditions	299	1.28 (0.89-1.85)	1.22 (0.84-1.76)	93	1.35 (0.73-2.49)	1.28 (0.69-2.40)	206	1.13 (0.71-1.79)	1.11 (0.70-1.77)
Emphysema, COPD and other pulmonary disease	79	1.98 (1.05-3.70)	1.75 (0.92-3.32)	53	2.41 (1.18-4.89)	2.23 (1.07-4.65)	26	0.89 (0.22-4.39)	0.94 (0.22-4.10)
Trauma, self-harm and complications of medical care	66	2.30 (1.19-4.46)	2.35 (1.20-4.59)	30	1.30 (0.39-4.33)	1.24 (0.37-4.24)	36	3.20 (1.38-7.44)	3.43 (1.50-7.87)

Model A: relative risks are adjusted for age and sex (if applicable).

Model B: additionally adjusted for baseline levels of systolic blood pressure, diastolic blood pressure, medication prescribed for hypertension, body mass index (BMI), former smoking, current smoking, total serum cholesterol level, serum HDL-cholesterol level, diabetes mellitus, left ventricular hypertrophy on the ECG, carotid intima-media thickness, serum CRP level, baseline myocardial infarction and heart failure, and incident myocardial infarction and heart failure before the onset of atrial fibrillation.

Discussion

In this large population-based follow-up study atrial fibrillation was associated with a 60% increased risk of all-cause mortality. This association was independent of cardiovascular risk factors and cardiac diseases. The differences in associations between men and women were very small. The main causes of death associated with atrial fibrillation were heart failure, intracranial hemorrhage and stroke, cardiac arrest and other cardiovascular death. In men, atrial fibrillation was additionally associated with death due to ischemic heart disease and pulmonary disorders and in women with death categorized as trauma and self-harm.

Results of several studies indicated that atrial fibrillation is associated with an increased risk of death.[1-5] The Framingham Study, was the first study that showed a convincing independent association of atrial fibrillation with death.[6] Subsequently, studies showed that also atrial flutter[12], paroxysmal atrial fibrillation[8] and idiopathic atrial fibrillation[9] were associated with increased risks of death. Our study is comparable to the Framingham Study in a number of characteristics. Both studies aim at the elderly in the general population, aged 55 years and over, but the Framingham Study excluded persons older than 94 years at each biennial examination. Lifetime risks of atrial fibrillation in both studies are almost identical[24,30] and both studies have no loss to follow-up with respect to total mortality. Therefore we believe that a comparison of mortality risks between these different studies is acceptable. In the Rotterdam Study we describe the associations in the period 1990-2005 and the Framingham Study reported associations for the time-window 1948-1988. In the Framingham Study, atrial fibrillation was associated with a multivariate adjusted 50% increased risk in men and a 90% increased risk in women. Our results were identical in men (a 50% increased risk) and lower in women (a 60% increased risk). These data indicate that the prognosis of atrial fibrillation with respect to mortality probably has not improved over time in men and became somewhat better in women. A better prognosis of atrial fibrillation over time has been described in a number of mainly hospital based studies[17-21], although in one study no evidence could be found of an improved mortality over the period 1980-2000.[13]

Heart failure is an important risk factor for both atrial fibrillation and death and is therefore an important confounder in our analyses. Atrial fibrillation, however, may also cause heart failure We found that heart failure after atrial fibrillation conferred an important proportion of the increased risk of mortality in atrial fibrillation. In both sexes the excess risk of death was 50% lower if the associations were adjusted for heart failure following the onset of atrial fibrillation. The most probable explanation is that an increased incidence of heart failure following atrial fibrillation and/or a more severe course of heart failure in atrial fibrillation patients compared to those who have sinus rhythm lead to a higher mortality. Undetected heart failure before the

diagnosis of atrial fibrillation, however, may also have played a role in some cases. The change in RR, however, when we adjusted for myocardial infarction following atrial fibrillation, was negligible. Further we could not reproduce the absence of an association with total mortality in men after excluding the 30-day mortality, as shown in the Framingham Study.

Although adjusted risks were highly comparable between the Framingham Study and the Rotterdam Study, important differences were found between the studies with respect to age adjusted relative risks (the age-adjusted relative increased risks were 240% in men and 350% in women in the Framingham Study and 78% in men and 84% in women in the Rotterdam Study). This indicates that, though the prognosis of atrial fibrillation probably remained equal, as indicated by the comparability of fully adjusted relative risks, the prognosis of atrial fibrillation patients has improved considerably over time through a better treatment of cardiovascular risk factors of atrial fibrillation or a change towards more benign risk factors of atrial fibrillation over time. Godtfredsen described in his hospital based series that in the period 1940-1967 atherosclerotic heart disease became much more important as the underlying condition for atrial fibrillation and that the prevalence of rheumatic heart disease in atrial fibrillation patients declined from 30% to 18%.[1] This shift towards a more benign condition has without doubt influenced the prognosis of atrial fibrillation patients. The incidence of rheumatic fever has declined further and it is now a rare disease in developed countries.[31]

Our study is the first that provides associations on cause-specific mortality in atrial fibrillation based on population-based study. We adjusted the associations for a wide range of cardiovascular risk factors and disorders. Therefore, these associations may help to identify the mechanisms that lead to a higher mortality in atrial fibrillation. Cause-specific mortality was reported in the AFFIRM study, but comparisons were not made between participants with and without atrial fibrillation but between treatment strategies in atrial fibrillation.[32,33] The Renfrew-Paisley Study presented cause-specific mortality in a restricted number of groups in prevalent and younger (45-65 years) atrial fibrillation participants.[11] The Framingham Study,[6] finally, presented cause-specific mortality percentages for atrial fibrillation participants and matched controls during the first year of follow-up.

Atrial fibrillation was strongly related to death by stroke and intracranial hemorrhage, reflecting the strong association of atrial fibrillation with stroke. Strokes in atrial fibrillation are in general larger and have a higher mortality than strokes in sinus rhythm. Further, anticoagulants or antiplatelets, prescribed in atrial fibrillation to prevent stroke, have a small but distinct risk of intracerebral hemorrhage. We found a strong association in our study between atrial fibrillation and death due to heart failure, even after adjustment for heart failure before the onset of atrial fibrillation. This may be due to atrial fibrillation causing heart failure, or undiagnosed heart failure before atrial fibrillation. Atrial fibrillation was also strongly associated

with cardiac arrest in our study. Several mechanisms may be responsible for sudden death in atrial fibrillation. Post-myocardial mortality is increased if myocardial infarction is complicated by the onset of atrial fibrillation.[34] Also, atrial fibrillation patients with heart failure are at a higher risk of cardiac arrest then patients with stand alone heart failure.[35] Modern implantable cardioverters/defibrillators (ICD) have considerable storage capabilities of ECG data preceding tachy-arrhythmic episodes. The analysis of these stored data has demonstrated that atrial fibrillation patients with an ICD are a greater risk of recurrent ventricular tachyarrhythmias than patients in sinus rhythm. We adjusted, however, in our analyses for myocardial infarction and heart failure. Therefore our data may indicate that atrial fibrillation patients without organic heart disease are also at a greater risk of ventricular tachycardia and/or ventricular fibrillation.[36,37] The proarrhythmic side effects of medication used to preserve rhythm and rate in atrial fibrillation, however, could also have played a role in our finding.[38] We included in the miscellaneous group of cardiac diseases several cardiac conditions that are associated with atrial fibrillation. Important contributors to this group are valve diseases and pulmonary embolism. This may explain the association of atrial fibrillation with mortality in this group.

We found several differences in cause-specific mortality associated with atrial fibrillation between men and women. In men, a strong association was found of atrial fibrillation with ischemic heart disease mortality. In women this association was lower and not statistically significant. We suggest that residual confounding by coronary atherosclerosis with the well-known difference between the sexes caused the sex difference. Also, an interaction between certain degrees of coronary atherosclerosis and the strong variation in beat-to-beat cardiac output that characterizes atrial fibrillation may have played a role. The higher risk of death due to pulmonary diseases in men and not in women with atrial fibrillation is likely to be explained by a greater damage of pulmonary tissue due to smoking in men than in women, resulting in more serious or more frequent emphysema in men, despite the adjustment for smoking within the gender categories.. An association was found with traumatic death in women only. Hip fractures, more frequent in women and with the well-known high mortality rate, may be responsible for this finding.[39] Death in hip fracture patients may be caused by heart failure that had remained unrecognized until that moment.

The strengths of our study are the population-based character with a long and nearly complete follow-up and the recent risk period. Due to the large number of atrial fibrillation cases and number of deaths we had the opportunity to examine associations with cause-specific mortality. Finally, we had precise data on vital status. The certainty of the diagnosis death is warranted in the Netherlands with a highly organized administration. A limitation is the uncertainty of data on cause of death. The cause of death is in the Netherlands almost always coded based on the clinical picture prior to death and not on autopsies. The Rotterdam Study

has extensive information on the disease history of participants prior to death and on the clinical picture and circumstances during death. Nevertheless, it is known that even in the most reliable situations autopsies substantially add to the diagnoses and death codes based only on the clinical picture.[40,41]

In conclusion, we found that that atrial fibrillation is still associated with an increased mortality. Improvements in the treatment of hypertension, myocardial infarction and heart failure that are important risk factors for atrial fibrillation have not improved the poor prognosis of atrial fibrillation. We investigated cause-specific mortality in atrial fibrillation and found that stroke, heart failure, sudden death, ischemic heart disease and emphysema contributed to the increased mortality in this high-prevalent disease of the elderly. These results may help clinicians to develop strategies to improve the poor prognosis of atrial fibrillation.

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Chapter 5.3

Atrial fibrillation and risk of stroke in the general population

Abstract

Background. The increased risk of stroke in atrial fibrillation can be prevented by the prescription of oral anticoagulants and, to a lesser degree, of platelet inhibitors. The evidence for the preventive effects of these drugs accumulates since 1989 but is mainly based on clinical trials. Recent population-based studies on the risk of stroke in atrial fibrillation are not available. Also, the effectiveness of anticoagulants and platelet inhibitors has hardly been studied in a population under everyday circumstances.

Methods The association of atrial fibrillation with stroke and stroke-subtypes was examined in 6577 subjects without stroke at baseline. Prevalent atrial fibrillation was present in 341 participants. During a median follow-up of 11.9 years, 605 cases of incident atrial fibrillation, 695 cases of incident stroke and 733 cases of incident transient brain attack were identified. Relative risks (RR) were calculated with 95% confidence intervals (CI) using Cox proportional hazards models, adjusted for age, sex, baseline cardiovascular risk factors and history of cardiovascular disease.

Results After multivariable adjustment, increased risks of stroke were found in prevalent (RR 1.59; 95% CI 1.21-2.09) and incident (RR 3.13; 2.59-4.01) atrial fibrillation. The highest risk was observed in women with ischemic stroke (RR 5.11; 3.64-7.18). Atrial fibrillation was also associated with transient brain attacks (incident atrial fibrillation, RR 2.65; 2.12-3.32). The inverse association of oral anticoagulant drugs (RR 0.27; 0.14-0.54) with stroke was stronger than the association of platelet inhibiting drugs with stroke (RR 0.94; 0.54-1.62).

Conclusion Atrial fibrillation is still a strong risk factor for stroke in the general population. The performance of oral anticoagulant drugs to prevent stroke in atrial fibrillation in this observational study in the general population is comparable to the results of clinical trials.

Introduction

Atrial fibrillation is the most common sustained rhythm disorder with a distinct age related incidence and prevalence.[1,2] Stroke is a common complication of atrial fibrillation.[3,4,5,6] Strokes due to atrial fibrillation are larger than strokes due to atherosclerosis and result in more pronounced disability and more often in death.[7,8] Evidence that anticoagulant drugs reduce stroke risk in atrial fibrillation with 60% and antiplatelets reduce the risk with 20%, became available from 1989 onward.[9-11] Subsequently, risk stratification schemes based on clinical characteristics, were constructed. These schemes predict which atrial fibrillation patients are at high risk of stroke and benefit from oral anticoagulants and which patients have a low risk for whom antiplatelets suffice.[9,12-15,16-19] Based on these risk stratification schemes, national and international guidelines to prevent stroke in atrial fibrillation have been developed. The adherence to these guidelines, however, is in general poor.[20-23] To our best knowledge, population-based studies on the association between atrial fibrillation and stroke are not available for recent risk periods. We investigated the associations between atrial fibrillation and risk of stroke in the Rotterdam Study, a population-based, prospective study of persons aged 55 years or older.

Methods

Study population

The Rotterdam Study is a population-based prospective follow-up study, aiming at the assessment of the occurrence and progression of and risk factors for chronic diseases of the elderly. Neuro-geriatric, psycho-geriatric, cardiovascular, locomotor and ophthalmologic diseases are the main areas of interest.[24] At the start of the study, in 1989, all inhabitants aged 55 years and older of the Rotterdam suburb Ommoord were invited to participate. Of the 10,275 eligible subjects, 7,983 (78%) responded. The baseline measurements, consisting of a home interview and two series of examinations at the research center, were carried out in the period 1990-1993. The first follow-up examination started in July 1993 and ended December 31st 1994. The second follow-up examination was performed between April 1997 and December 31st 1999. The third follow-up round was between January 2002 and July 2004. The Medical Ethics Committee of the Erasmus MC approved the study. All participants signed an informed consent.

Follow-up procedures

The Rotterdam Study collaborates with the general practitioners and pharmacists in the area of Ommoord. In general, Dutch inhabitants are assigned to one general practitioner and

one pharmacy. General practitioners have a central position in the Dutch health care system, which means that all medical information, also on hospital admissions and hospital outpatient care is available in the files of Dutch general practitioners. The general practitioners who are affiliated to the Rotterdam Study send all computerized information on diseases of interest to the researchers of the Rotterdam Study on a weekly basis. Trained follow-up research assistants of the Rotterdam study verify this information and try to obtain the optimal amount of additional information on these diagnoses. Information on vital status is obtained on a regular basis from the central registry of the Municipality of Rotterdam, from collaborating general practitioners and by obtaining information during follow-up rounds. For those participants whose information on vital status remains missing, the Central Registry of Genealogy of the Netherlands is consulted. This national institute receives population registry records of those inhabitants of the Netherlands who have died.

Assessment of stroke and transient ischemic attacks

The assessment of stroke at baseline has been described previously.[25] During follow-up, strokes were identified by the monitoring system as described above. Research physicians reviewed all information. An experienced stroke neurologist (P.J. Koudstaal) verified all diagnoses. A stroke was diagnosed if a participant had positive symptoms lasting longer than 24 hours. Strokes were sub classified as ischemic if a CT scan or a MRI scan, performed within 4 weeks after the onset of the stroke symptoms ruled out other diagnoses or when indirect evidence (deficit limited to 1 limb or completely resolved within 72 hours, or atrial fibrillation in the absence of anticoagulants or antiplatelets) pointed towards an ischemic origin of the stroke. Hemorrhagic strokes were diagnosed when a hemorrhage was visible on the scan or when indirect signs made the diagnosis plausible (the patient became permanently unconscious or died within hours after the onset of symptoms). If a stroke did not match these criteria it was called unspecified. Transient neurological attacks were defined as attacks of sudden neurological symptoms that completely resolved within 24 hours, with no clear evidence for the diagnosis of migraine, epilepsy, Ménière's disease, hyperventilation, cardiac syncope, hypoglycemia or orthostatic hypotension. If only focal brain symptoms were reported the event was classified as a focal transient neurological attack. If only non-focal brain symptoms were reported the event was classified as non-focal. A mixed transient neurological attack was diagnosed if for an attack both focal and non-focal signs were reported.

Assessment of atrial fibrillation

The assessment of atrial fibrillation at baseline and follow-up has been described in detail previously.[1] In short, three methods were used to identify cases of atrial fibrillation or atrial

flutter. At baseline and at follow-up 10 second 12-lead ECGs were recorded at the research center with an ACTA Gnosis IV ECG recorder (EsaOte, Florence, Italy), stored digitally and analyzed with the Modular ECG Analysis System (MEANS).[26-28] Prevalent atrial fibrillation was defined based on the ECG measurement at baseline and on the information from general practitioners. Incident atrial fibrillation was evaluated with the ECG measurements during follow-up rounds, with the information from the collaborating general practitioners and with information from the LMR system (de Landelijke Medische Registratie). This national registration accumulates all hospital discharge diagnoses of Dutch inhabitants. The date of onset of atrial fibrillation was defined as the midpoint between the date of the follow-up round at which atrial fibrillation was detected and the date of the previous round at which atrial fibrillation had not yet been detected. In the majority of cases, however, it was possible to obtain precise onset dates with the information from either the general practitioner files and/or the LMR registry. Follow-up by January 1, 2005 was complete for 99% in person years of the total study population.

Assessment of the prescription of platelet inhibiting drugs and the use of anticoagulants

Data on use of platelet inhibitors (i.e. acetylsalicylic acid and carbasalate calcium) were derived from 7 fully automated pharmacies in which nearly all participants (99.7%) were registered. These pharmacies continuously provided details on all filled prescriptions from January 1, 1991, including the product name, generic name, number of tablets, date of delivery, prescribed number of tablets and daily drug dosage. The use of anticoagulants was assessed using the INR measurements of the regional anticoagulation clinic. This clinic monitors all inhabitants of Ommoord with an indication for anticoagulant therapy. The choice of type of anticoagulant was made by the physician. The optimal target range of anticoagulant therapy, as recommended by the Federation of Dutch Thrombosis Centers, lies between 2.5 and 3.5 INR in the case of atrial fibrillation. Prothrombin times were monitored at 1-6-week intervals by reference to the INR. The duration of this interval is based on the stability of the anticoagulant level.

For all cases of stroke and participants from the remainder of the cohort, we assessed whether they were current users of coumarin anticoagulants or platelet inhibitors at the date of the stroke (defined as index day). Use of anticoagulants was defined as current if the index date fell within the time window of 42 days after a measurement of the INR. Current use of antiplatelets at the index-date was calculated based on the day of prescription, the prescribed number of units and the prescribed daily number of units. Participants who started antiplatelets were considered as current users as soon as they had used antiplatelets for 7 days. If participants stopped the use of antiplatelets they were still considered as current users until 7 days after the last intake of the drug.

Cardiovascular risk factors

Information on current health status, smoking behavior and the current use of medication was obtained during the home interview using a computerized questionnaire. The information on medication obtained from the home interview was completed by the computerized information from the collaborating pharmacies. Participants were classified as current smokers, former smokers or never-smokers. Body Mass Index (BMI) was calculated as weight (kg)/length $(m)^2$. Blood pressure was measured in sitting position at the right brachial artery using a random-zero sphygmomanometer. Systolic and diastolic blood pressures were calculated as the average of two consecutive measurements. Blood samples were drawn by venipuncture. Serum total cholesterol, HDL-cholesterol and glucose were measured with an automated enzymatic method. Diabetes mellitus was considered present when glucose levels exceeded 11.0 mmol/l and/or the use of antidiabetic medication was present. CRP was measured in serum samples kept frozen at -20^0C, using a high sensitivity rate near infrared particle immunoassay (NIPIA) method (Immage®, Beckman Coulter). The common carotid artery, the bifurcation and the internal carotid artery at both sides were visualized by ultrasonography using a 7.5 MHz transducer (ATL Ultramark IV, Advanced Technology Laboratories, Bethel, Washington, USA). Common carotid intima-media thickness was measured over a length of one cm proximal to the bulbus as described previously.[29,30] A history of myocardial infarction was defined as a self-reported myocardial infarction with hospital admission or the presence of a myocardial infarction on the ECG, confirmed by reviewing the medical records of general practitioners and specialists. Left ventricular hypertrophy was diagnosed by the MEANS program with an algorithm that takes into account QRS voltages, with an age-dependent correction, and repolarization. Assessment of heart failure at baseline in the Rotterdam Study has been described in detail previously.[31,32]

Population for analysis

At baseline, 7151 persons were examined at the research center of the Rotterdam Study. For the present study, an ECG was not available for analysis of atrial fibrillation in 343 participants, mainly due to logistic reasons, resulting in 6808 persons who had a baseline assessment of atrial fibrillation. We excluded 198 participants who had a history of stroke at baseline. We additionally excluded 33 participants for whom no information on stroke incidence was available, resulting in a study population of 6577 persons for the analyses including prevalent atrial fibrillation cases. In the analyses considering only incident atrial fibrillation, we excluded in addition 341 prevalent atrial fibrillation cases leaving a study population of 6236 persons.

Statistical analysis

In the first analysis, age and gender adjusted hazard rate ratios, expressed as relative

risks (RR) with their 95% confidence intervals (CI), were calculated using the Cox proportional hazards model with stroke and stroke-subtypes (ischemic, hemorrhagic and unspecified) as the dependent variables and prevalent atrial fibrillation as the independent variable. Separate analyses were conducted stratified for gender. In the second analysis, stroke and stroke subtypes were used as the dependent variables and incident atrial fibrillation, as a time-varying variable, was used as the independent variable. In the third analysis, the same procedure was performed with transient neurological attacks and subtypes (focal, non-focal and mixed) as endpoints. In the fourth analysis, we investigated the association between stroke or transient ischemic attack, whichever came first, and the subsequent onset of atrial fibrillation. In this analysis, a time-dependent composite variable was used describing the first presence of any stroke or transient neurological attack during follow-up as the independent variable. Cases were excluded when both stroke and atrial fibrillation were diagnosed on the same day. In the last analysis, in the atrial fibrillation participants only, we used time-dependent Cox models to compute hazard ratios for the association between stroke and current use at the index date of anticoagulants or antiplatelets, respectively. The reference was non-use of either drug at the index-date. All analyses were additionally adjusted for myocardial infarction and heart failure at baseline, baseline levels of systolic and diastolic blood pressure, medication prescribed for hypertension, body mass index, current smoking, former smoking, total cholesterol level, HDL-cholesterol level, diabetes mellitus, left ventricular hypertrophy on the ECG, intima-media thickness and serum CRP level. Subjects were followed from baseline until one of the following: death, loss to follow-up or January 1, 2005 Missing values for cardiovascular risk factors were added using the expectation-maximization algorithm. SPSS version 15 for Windows (SPSS Inc., Chicago, IL, USA) was used for data analysis.

Results

The baseline characteristics of the study population are presented in table1. We identified 344 prevalent atrial fibrillation cases. During a total follow-up of 64661 years (median follow-up of 11.9 years with a range from 0.5 to 15.5 years), we identified 605 participants with incident atrial fibrillation, 695 participants with incident stroke (410 ischemic strokes, 66 hemorrhagic strokes and 219 unspecified strokes, respectively 59%, 9.5% and 31.5%) and 733 participants with a transient brain attack (352 focal, 308 non-focal, 55 mixed, 18 isolated vertebrobasilar, 48%, 42%, 7.5% and 2.5% respectively). The absolute stroke risk in persons with incident atrial fibrillation was 29/1000 person years (80 cases in 2769 person years) and in persons without atrial fibrillation 9/1000 person years (555 strokes in 61892 person years).

The associations of prevalent atrial fibrillation with risk of stroke are presented in table 2. A strong and statistically significant association was found between prevalent atrial fibrillation and stroke of all types. The association was mainly found in women, with nearly absent and non-significant associations in men. The associations with ischemic strokes were not very outspoken and only statistically significant in women after additional adjustments. A strong association was found with hemorrhagic stroke. The associations with hemorrhagic stroke were not significant in the gender-stratified analyses, probably due to the low numbers of hemorrhagic stroke, although effect sizes were almost equal in men and women. The association with unspecified strokes was strong and statistically significant, notably in women.

The associations of incident atrial fibrillation with risk of stroke are presented in table 3. Strong and statistically significant associations with strokes of all types were found, both in men and women, with slightly higher risks in women. The highest risk was found in women for the risk of ischemic stroke (RR 5.11 (95%CI 3.64-7.18). The RR of incident atrial fibrillation with hemorrhagic stroke was 2.0, almost equally high in men and women, but not statistically significant. A 70% increased risk of unspecified stroke was found in women.

Incident atrial fibrillation was not only associated with focal transient brain attacks, but also with non-focal transient brain attacks, with no differences between the sexes (Table 4). No associations were found between incident atrial fibrillation and mixed transient brain attacks. An association was present with isolated vertebrobasilar brain attacks after adjustment for age and sex. Additionally adjusted analyses were not performed for this outcome due to the low number of events.

In table 5, the results are presented of the Cox proportional hazards analysis with stroke or transient ischemic attack; whichever came first, as the independent variable and the subsequent onset of atrial fibrillation as the dependent variable. In this analysis, stroke was a strong predictor of atrial fibrillation in both sexes.

Table 6 presents the associations of anticoagulants and platelet inhibiting drugs with risk of stroke in subjects with atrial fibrillation. Atrial fibrillation cases have a 73% reduced risk of ischemic stroke when they use anticoagulants and a three times increased risk of hemorrhagic stroke. The associations of antiplatelets with the risk of stroke were near 1 and statistically non-significant. At the time of diagnosis of stroke, 19% of the atrial fibrillation cases used anticoagulants, another 21% used antiplatelets and 60% used neither drug (data not shown in the tables).

Table 1 Baseline characteristics of the study population

The Rotterdam Study, 1990-1993

Variable	
Age (years)	69.1 (9.0)
Proportion of men (%)	40.2
Prevalent atrial fibrillation (%)	5.2
Heart failure (%)	3.2
History of myocardial infarction (%)	12.9
Left ventricular hypertrophy on the ECG (%)	4.8
Diabetes mellitus (%)	10.2
Smokers	
Never smokers (%)	35.3
Current smokers (%)	22.8
Former smokers (%)	41.9
Proportion on antihypertensive medication (%)	14.3
Systolic blood pressure (mm Hg)	139 (22.4)
Diastolic blood pressure	74 (11.6)
Serum total cholesterol level (mmol/l)	6.6 (1.2)
Serum HDL cholesterol level (mmol/l)	1.4 (0.4)
Body mass index (kg/m^2)	26.3 (3.7)
Intima-media thickness (mm)	0.83 (0.15)
Serum CRP level (mmol/L)	3.3 (6.9)

Values are percentages or mean values with standard deviations between brackets.

Table 2 Prevalent atrial fibrillation and the risk of stroke and stroke sub-types

The Rotterdam Study, 1990-2005

	Men and women			Men			Women		
	Cases	RR (95%CI) N=6577		Cases	RR (95%CI) N=2646		Cases	RR (95%CI) N=3935	
		Model A	Model B		Model A	Model B		Model A	Model B
All strokes	695	1.63 (1.24-2.14)	1.59 (1.21-2.09)	281	1.16 (0.73-1.85)	1.07 (0.67-1.72)	414	2.06 (1.48-2.88)	2.09 (1.48-2.94)
Ischemic strokes	410	1.28 (0.84-1.96)	1.29 (0.84-1.97)	181	0.97 (0.49-1.92)	0,82 (0,41-1.65)	229	1.61 (0.94-2.75)	1.80 (1.05-3.10)
Hemorrhagic strokes	66	2.76 (1.28-5.94)	2.37 (1.08-5.20)	25	2.12 (0.61-7.43)	2.43 (0.69-8.59)	41	3.27 (1.24-8.61)	2.40 (0.87-6.61)
Unspecified strokes	219	1.79 (1.19-2.70)	1.73 (1.14-2.62)	75	1.12 (0.52-2.37)	1.22 (0.56-2.67)	144	2.33 (1.43-3.78)	2.31 (1.40-3.83)

Model A: adjusted for age and gender.

Model B: adjusted for age, gender, body mass index, systolic blood pressure, diastolic blood pressure, medication prescribed for hypertension, serum total cholesterol level, serum HDL-cholesterol level, left ventricular hypertrophy on the ECG, history of myocardial infarction, heart failure, serum CRP level, diabetes, current smoking and former smoking.

Table 3 Incident atrial fibrillation and the risk of stroke and stroke sub-types

The Rotterdam Study, 1990-2005

	Men and women			Men			Women		
	Cases	RR (95%CI) N=6236		Cases	RR (95%CI) N=2492		Cases	RR (95%CI) N=3744	
		Model A	Model B		Model A	Model B		Model A	Model B
All strokes	635	3.37 (2.74-4.15)	3.13 (2.54-3.86)	261	2.99 (2.16-4.14)	2.86 (2.06-3.96)	374	3.71 (2.83-4.85)	3.36 (2.55-4.42)
Ischemic strokes	386	4.87 (3.80-6.25)	4.40 (3.42-5.66)	172	4.03 (2.77-5.87)	3.54 (2.42-5.17)	214	5.74 (4.13-7.00)	5.11 (3.64-7.18)
Hemorrhagic strokes	58	2.04 (0.91-4.57)	2.00 (0.88-4.52)	22	2.05 (0.59-7.14)	1.85 (0.52-6.57)	36	2.01 (0.70-5.80)	1.93 (0.66-5.68)
Unspecified strokes	191	1.72 (1.10-2.71)	1.60 (1.01-2.52)	67	1.44 (0.65-3.20)	1.36 (0.61-3.05)	124	1.90 (1.10-3.29)	1.77 (1.02-3.09)

Model A: adjusted for age and gender.

Model B: adjusted for age, gender, body mass index, systolic blood pressure, diastolic blood pressure, medication prescribed for hypertension, serum total cholesterol level, serum HDL-cholesterol level, left ventricular hypertrophy on the ECG, history of myocardial infarction, heart failure, serum CRP level, diabetes, current smoking and former smoking.

Table 4 Incident atrial fibrillation and the risk of transient neurological attacks and subtypes of transient neurological attacks

The Rotterdam Study, 1990-2005

	Men and women			Men			Women		
	Cases	RR (95%CI) N=6236		Cases	RR (95%CI) N=2492		Cases	RR (95%CI) N=3744	
		Model A	Model B		Model A	Model B		Model A	Model B
All transient neurological attacks	699	2.73 (2.19-3.14)	2.65 (2.12-3.32)	270	2.45 (1.72-3.50)	2.50 (1.75-3.58)	429	2.95 (2.22-3.92)	2.80 (2.10-3.73)
Focal transient attacks	332	2.94 (2.14-4.04)	2.80 (2.03-3.86)	129	2.44 (1.45-4.12)	2.43 (1.43-4.12)	203	3.33 (2.24-4.96)	3.21 (2.14-4.81)
Non-focal transient attacks	299	2.61 (1.85-3.68)	2.58 (1.82-3.65)	112	2.55 (1.48-4.38)	2.75 (1.59-4.76)	187	2.66 (1.70-4.16)	2.50 (1.59-3.93)
Mixed transient attacks	52	1.24 (0.44-3.48)	1.14 (0.40-3.24)	19	0.78 (0.10-5.91)	0.62 (0.08-4.87)	33	1.55 (0.47-5.16)	1.40 (0.41-4.72)
Isolated vertebrobasilar attacks ±	16	7.98 (2.62-24.4)		10	±		6	±	

A: adjusted for age and gender.

B: adjusted for age, gender, body mass index, systolic blood pressure, diastolic blood pressure, medication prescribed for hypertension, serum total cholesterol level, serum HDL-cholesterol level, left ventricular hypertrophy on the ECG, history of myocardial infarction, heart failure, serum CRP level, diabetes, current smoking and former smoking.

± Analysis only adjusted for age and gender and not for men and women separately due to small numbers.

Table 5 Stroke or transient ischemic brain attack, whichever came first, and the risk of atrial fibrillation

The Rotterdam Study, 1990-2005

	Men and women	Men	Women
Atrial fibrillation cases in the study population	603/6236	274/2492	329/3744
	RR (95%CI)	RR (95%CI)	RR (95%CI)
Unadjusted	2.34 (1.87-2.94)	2.52 (1.18-3.49)	2.18 (1.59-2.99)
Age and gender adjusted	1.80 (1.43-2.27)	1.96 (1.40-2.73)	1.67 (1.22-2.30)
Additionally adjusted ±	1.70 (1.35-2.14)	1.88 (1.35-2.63)	1.52 (1.10-2.10)

Cases were excluded when both stroke and atrial fibrillation were diagnosed on the same day.

± Additional adjustments are for body mass index, systolic blood pressure, diastolic blood pressure, medication prescribed for hypertension, serum total cholesterol level, serum HDL-cholesterol level, left ventricular hypertrophy on the ECG, history of myocardial infarction, heart failure, serum CRP level, diabetes, current smoking and former smoking.

Table 6 The associations between current use of antiplatelets or anticoagulants respectively and stroke subtypes in atrial fibrillation cases

The Rotterdam Study, 1990-2005

	Ischemic stroke RR (95%CI)		Hemorrhagic stroke RR (95%CI)		Unspecified stroke RR (95%CI)	
	Model A	Model B	Model A	Model B	Model A	Model B
Antiplatelets	1.02 (0.60-1.76)	0.94 (0.54-1,62)	1.50 (0.29-7.8)	±	0.95 (0.37-2.44)	±
Anticoagulants	0.32 (0.16-0.62)	0.27 (0.14-0.54)	4.3 (1.1-16.3)	±	1.14 (0.44-2.93)	±

Model A: associations are controlled for age and gender.

Model B: associations are controlled for age, gender, body mass index, systolic blood pressure, diastolic blood pressure, medication prescribed for hypertension, serum total cholesterol level, serum HDL-cholesterol level, left ventricular hypertrophy on the ECG, history of myocardial infarction, heart failure, serum CRP level, diabetes, current smoking and former smoking.

± Not additionally adjusted owing to the small number of events.

Discussion

The main finding of this population-based study is that atrial fibrillation is still an important predictor of stroke in the period 1990-2005. Atrial fibrillation was not only associated with the risk of focal but also with the risk of non-focal transient brain attacks. Anticoagulant use in atrial fibrillation was associated with a 70% reduced risk of stroke. The use of antiplatelets was not associated with risk of stroke. Finally, we found that atrial fibrillation was not only a predictor of stroke, but also that stroke predicted atrial fibrillation.

The observed association of incident atrial fibrillation with risks of stroke and transient brain attacks demonstrate that patients in atrial fibrillation are still at a high risk of brain damage. One explanation for this finding is that the first results of clinical trials on the preventive potential of anticoagulants were too close to the start of our observational study to have affected clinical practice. Another explanation may be the general problematic implementation of the guidelines on anticoagulants in elderly atrial fibrillation patients. It is known that physicians are reluctant to prescribe anticoagulants in atrial fibrillation. The threat to induce intracranial bleeding, characterized by a mortality risk of 60%, is perhaps the greatest barrier to prescribe adequate anticoagulation.[21] Our data show that these fears are not imaginary. The relative risk of intracranial hemorrhage in prevalent atrial fibrillation was 2.4 and the relative risk in incident atrial fibrillation was only slightly lower. Anticoagulants distinctly increased the risk of hemorrhagic stroke. The knowledge of physicians that they may cause an intracranial bleeding in healthy persons who have not yet suffered a stroke but who are, until the first prescription of an oral anticoagulant, only at a higher risk of ischemic stroke, poses a major ethical issue, even keeping in mind that the absolute numbers of hemorrhagic stroke are considerably lower than those of ischemic stroke. The ratio of hemorrhagic to non-hemorrhagic stroke was 1:7 in all strokes in our study. This ratio, however, may be underestimated. We found a high number of unspecified strokes and an unknown proportion of this sub-category will have had hemorrhagic stroke. The development of new and safer anticoagulants is delayed[33] and the risk of hemorrhagic stroke in anticoagulant treated atrial fibrillation patients can in the meantime probably only be assessed by very precisely monitoring the INR.

The association of atrial fibrillation with risk of non-focal neurological is new. Only recently it was established that in the general population not only focal neurological attacks are associated with a higher risk of stroke[34] but that also temporary disturbances with diffuse, non-localizing symptoms are characterized by a high risk of stroke.[35] Risk stratification schemes using clinical characteristics to predict risk of stroke in atrial fibrillation show that a previous stroke or transient focal neurological attacks in atrial fibrillation confers the highest risk of subsequent stroke. These patients always need anticoagulants to prevent stroke unless strict

contraindications prohibit the prescription of these drugs. Our results suggest that clinicians also should be aware of non-focal transient neurological symptoms in patients with atrial fibrillation as a marker of increased risk of subsequent stroke.

The 73% reduction of ischemic stroke risk by anticoagulants, as observed in the Rotterdam Study is comparable to the 64% reduction computed in a recent meta-analysis and the 68% reduction of the pooled analysis.[9] The results of our study therefore confirm the findings of other studies that the capacity of anticoagulants to reduce stroke risk in atrial fibrillation, which had been initially found in clinical trials, can be translated to the daily clinical practice.[36,37] Apparently, regular monitoring of the INR by anticoagulation clinics reduce the risk of non-compliance under everyday circumstances, which may be an important reason for the discrepancy between efficacy in clinical trials and in a real life setting. In our study no stroke reduction by antiplatelets could be observed in atrial fibrillation. This finding supports the ongoing concerns on the role of antiplatelets in the prevention of stroke in atrial fibrillation.[38]

Several years ago it has been documented that stroke may precede the diagnosis of atrial fibrillation.[39] This phenomenon has also been observed in the Framingham Study.[40] We were able to reproduce this finding. A likely explanation is that paroxysmal atrial fibrillation prior to chronic atrial fibrillation caused the stroke and was absent at the moment of the physical examination for stroke. It could also be hypothesized, however, that neurological disturbance causes atrial fibrillation, as has been described by Vingerhoets.[41] In that study, it was found that especially primary intracerebral bleeding was responsible for transient atrial fibrillation with a time interval of 3-77 days. In our study, 80 cases of incident stroke or transient neurological brain attack preceded the diagnosis of incident atrial fibrillation. The time interval, however, between stroke and atrial fibrillation was in general much larger than in the study of Vingerhoets, indicating that indeed paroxysmal atrial fibrillation in the onset to chronic atrial fibrillation could have been responsible for an incorrect diagnosis of non-atrial fibrillation related stroke.

The strengths of our study are its longitudinal character in a large population of the elderly with a long follow-up through which we were able to identify a large number of cases of atrial fibrillation, stroke and transient neurological attacks. Furthermore, we had the opportunity of monitoring antiplatelet and anticoagulant medication at a daily basis. An important limitation of our study is that not all strokes were evaluated with CT or MRI imaging, resulting in relatively large group of undefined stroke subtype. Finally, the observational character of our study prohibits definite statements on causality.

Conclusions

Stroke as a consequence of atrial fibrillation is still a major problem in the general elderly population. The finding of an inverse association of anticoagulants with stroke similar in size to the results of clinical trials supports the prescription of anticoagulants in elderly atrial fibrillation patients. We found that not only focal but also non-focal transient attacks were associated with atrial fibrillation.

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Chapter 6

General discussion

The aim of this study was the investigation of epidemiological aspects of atrial fibrillation in a general population of the elderly. Atrial fibrillation is a rare disease before the age of 55 years, but the prevalence increases steeply with advancing age. The prevalence almost doubles per decade.1 The disease is characterized by an increased morbidity and mortality.[2-7] Many medical disciplines are involved in the different aspects of this disease and each year 2000 new papers are published on atrial fibrillation. We investigated atrial fibrillation in the general population. It is known that only one third of patients with atrial fibrillation has hospital treatment.[8]

Main findings

Prevalence and incidence

In this thesis we described the prevalence and incidence of atrial fibrillation in 6808 participants of the Rotterdam Study for whom a baseline ECG was available.

Prevalence

Reliable knowledge on the prevalence of atrial fibrillation is especially needed for clinicians and public health officials to estimate the need for supplies for this disease and to estimate the costs. Knowledge on incidence figures related to age and sex helps to predict the prevalence in the future with changing population sizes and structures. The populations of Western Europe are aging and therefore it can be expected that the total prevalence of atrial fibrillation will rise. An age-adjusted rise has recently been suggested by the Framingham Study and in a study from England that described the prevalence of atrial fibrillation in a general practitioner's database.[9,10] In our study, we found that the prevalence sharply rose with advancing age in men and in women. We additionally calculated the prevalence at three moments during follow-up and established that in our cohort the age and sex adjusted prevalence did not increase during the time-window 1990-2000. An age adjusted rise, as found in the Framingham Study, could have resulted from a better survival of persons with important risk factors, e.g. myocardial infarction and heart failure, from an increased awareness for the disease by physicians in the course of time and from a better survival of subjects with atrial fibrillation. A lower age adjusted prevalence, on the other hand, could have been expected from better treatment of the risk factors for atrial fibrillation over time. The observations in the Framingham Study were from 1968-1989 and that study therefore started 20 years earlier than the Rotterdam study and stopped at the moment that the measurements in the Rotterdam Study started.[9] This could explain differences with the findings in the Rotterdam Study. The age and sex adjusted increase in prevalence in the general

practitioners population in England and Wales between 1994 and 1998 may be the result of different ascertainment methods.[10]

Incidence

We found that the incidence of atrial fibrillation markedly increased with age, comparable with the age-related increase in incidence rates from the Framingham Study. The lifetime risk to develop atrial fibrillation in our study was identical to the lifetime risk reported by the Framingham Study[11] and is about 1 in 4 for persons aged 55 years. Changes in incidence over time have not yet been reported.

Risk factors of atrial fibrillation

Atrial fibrillation can be described as an arrhythmia characterized by rapid asynchronous atrial electrical activation. The initiation needs fast ectopic activity, but the continuation requires a substrate in the atria. This substrate can be formed by local anatomic disturbances, or by spatial dispersion of atrial refractory periods.[12,13] Generally accepted risk factors are valvular disease, in particular mitral valve disease, heart failure, hypertension, diabetes mellitus, history of myocardial infarction, left ventricular hypertrophy[14], older age, male gender and hyperthyroid heart disease.[15-17] These clinical conditions promote atrial fibrillation mainly by increasing intra-atrial pressure or enlargement of the atria, thus disturbing a normal architecture of the atria or the electrical homogeneity in the atria. We studied the following potential risk factors of incident atrial fibrillation: 1) the intake of very long-chain n-3 fatty acids, 2) subclinical atherosclerosis, 3) normal thyroid function and 4) smoking of cigarettes. During the realization of our cohort of atrial fibrillation participants and completion of this thesis a number of new risk factors were found in other studies. The Cardiovascular Health Study identified high-sensitivity C-reactive protein (CRP) as a potential risk factor.[18] This association has been intensely studied since then and the view remains that atrial fibrillation may lead to increases in CRP and not viceversa.[19] The Framingham Study[20] and the Danish Diet, Cancer, and Health Study[21] reported both an association of body mass index with atrial fibrillation. The Framingham researchers also mentioned that pulse pressure may be a better predictor of atrial fibrillation than blood pressure.[22]

We discuss the findings of the possible risk factors for atrial fibrillation that were investigated in the framework of this thesis in the following sections.

Intake of very long-chain n-3 fatty acids

Fish consumption is associated with a decreased risk of coronary heart disease mortality,

as has been established in a meta-analysis of prospective cohort studies.[23] The effect has been attributed to the ingestion of n-3 polyunsaturated fatty acids, that probably reduce ventricular and life-threatening arrhythmia.[24] It was hypothesized that the effect on ventricular arrhythmia could be generalized to atrial arrhythmia. Indeed, the Cardiovascular Health Study found that consumption of tuna and other broiled or baked fish was associated with a 28% lower risk of atrial fibrillation.[25] No inverse association, however, was found between fried fish or fish burgers and atrial fibrillation.

We followed 5184 participants without atrial fibrillation at baseline for whom energy and nutrient intake data were available based on a food-frequency questionnaire during a mean follow-up of 6.4 years. In this period, 312 new atrial fibrillation cases were detected. Intake of eicosapentaenoic acid (EPA) and of docosahexaenic acid (DHA) and the intake of fish were not associated with risk of atrial fibrillation. In the Danish Diet, Cancer and Health study neither an inverse association with the consumption of fat fish was found.[26] On the other hand, it has been found that postoperative atrial fibrillation in cardiac surgery is diminished by the prescription of supplementary n-3 PUFA.[27] Thus, the role of n-3 polyunsaturated fatty acids in atrial fibrillation is controversial at this moment. It appears that also the effect of n-3 PUFA on fatal coronary heart disease is less convincing in later trials than in earlier observational studies.[28,29]

Subclinical atherosclerosis

Intima-media thickness and the presence of plaques, both measured by ultrasonography at the carotid arteries are widely used and thoroughly validated measures of generalized atherosclerosis.[30] Coronary calcification as assessed by electron beam computed tomography is a better measurement of coronary atherosclerosis, but is less widely available and suffers from a radiation burden. Invasive angiographic measurements are not applicable in screening of large populations. Because in a previous study of our group markers of non-cardiac atherosclerosis were strongly associated with the amount of coronary calcification, measurement of carotid atherosclerosis could be used to evaluate the relation between atherosclerosis and risk of atrial fibrillation.[31]

We hypothesized that generalized atherosclerosis, as an indicator of coronary atherosclerosis might be a risk factor of atrial fibrillation. The Cardiovascular Health Study is the only population-based study that had investigated atherosclerosis as a risk factor for atrial fibrillation earlier. No association was found in that study.[32,33] We excluded persons who had atrial fibrillation at baseline, but also persons who had angina as measured by the Rose questionnaire and participants with a history of myocardial infarction or cardiac surgery. We assessed atherosclerosis in 4407 participants, and after a median follow-up 7.5 years, in 269 participants with new-onset atrial

fibrillation occurred. We found that subclinical atherosclerosis is an independent risk factor of atrial fibrillation with a stronger association in women than in men.

Smoking of cigarettes

Smoking is a very powerful risk factor of cardiovascular disease[44,45], pulmonary disease[46] and cancer.[47] Both electrophysiological properties and the anatomical substrate of the atria may be altered by nicotine, carbon monoxide and polycyclic aromatic hydrocarbons from cigarette smoke.[48] Therefore, we hypothesized that smoking may cause atrial fibrillation, despite the knowledge that a number of studies had not identified smoking as a risk factor of atrialfibrillation.[14,21,33,49-51]

The association of smoking of cigarettes and atrial fibrillation was investigated in 5668 participants without atrial fibrillation at baseline. Besides age, sex and cardiovascular risk factors, the analysis was adjusted for medication prescribed for chronic obstructive pulmonary disease and emphysema. We identified 371 new cases of atrial fibrillation during a median follow-up of 7.2 years. Both former and current smoking were associated with a modest increased risk of atrial fibrillation.

We also investigated the association of the duration of smoking and the number of cigarettes smoked per day with the risk of atrial fibrillation. We did not find a dose-response relationship of current smoking with atrial fibrillation, in contrast to the findings in former smokers. This is probably caused by the strong relation of current smoking with death. This may have contributed to the lack of an association between smoking and atrial fibrillation in previous studies. Former smoking was still a risk factor for atrial fibrillation, while quitting of smoking reduces the risk for the most smoking related diseases.

Normal thyroid function

The association of hyperthyroidism and atrial fibrillation has been described for many years and also subclinical hyperthyroidism has a high suspicion of facilitating atrial fibrillation.[15,16,34-38] The close relationship between thyroid function and atrial fibrillation and the observations that bone metabolism[39] and physical activity[40] are associated with thyroid function in the normal range, led to the hypothesis that normal levels of TSH may be associated with atrial fibrillation. In 2007, a cross-sectional study was published that reported an association between serum free thyroxin level within the normal range and atrial fibrillation.[38]

We found in our longitudinal study that within the euthyroid range, participants who have higher levels of thyroid function are at a higher risk of atrial fibrillation compared to those who have lower levels. Based on our study it cannot be concluded whether low levels are protective or that high levels provoke atrial fibrillation, but the most obvious explanation is that high

normal function may be a risk factor for atrial fibrillation. Our study contributes to the ongoing discussion on the definition of the normal range of thyroid function.[41-43]

The prothrombotic state and atrial fibrillation

Atrial fibrillation is associated with an at least five-fold increased risk of stroke.[7] The stroke risk is not identical in all atrial fibrillation patients. A higher stroke risk is especially found in subjects with a prior stroke or transient ischemic brain attack, in females, in persons with hypertension, diabetes or heart failure, and in elderly patients.[52] Risk stratification schemes have been developed to predict those who are at a high risk of stroke and thus need preventive therapy with anticoagulants and those who have a lower risk for whom antiplatelet therapy is acceptable.[53] Currently, there is no agreement on these schemes and the discriminative ability of each scheme is only fair, with a c-statistic ranging from 0.56-0.62.[54] This underlines the need to find better strategies to predict stroke. Transesophageal echocardiography is an additional method to identify persons at a high risk of stroke. The invasive and time-consuming character of this procedure, however, interferes with application in larger populations. Therefore, we need simpler tools to predict stroke risk in atrial fibrillation. The concept of a generalized prothrombotic state in atrial fibrillation may help to develop these tools. Abnormal levels of prothrombotic markers have been found in atrial fibrillation patients compared with healthy controls,[55-58] but in one study (in younger participants) it was found that the difference between atrial fibrillation and sinus rhythm was the consequence of different patterns of cardiovascular risk factors.[59] Prothrombotic factors in atrial fibrillation had not been measured in the elderly.

In 162 participants of the Rotterdam study with confirmed atrial fibrillation and in 324 age and sex matched controls, we measured three prothrombotic plasma markers: von Willebrand factor, a marker of endothelial damage/dysfunction, soluble P-selectin (sP-sel), a marker of platelet activation and fibrinogen, a precursor to the insoluble fibrin and an important rheological factor. We investigated cross-sectionally the association of these factors with atrial fibrillation. We found that von Willebrand factor was positively associated with atrial fibrillation. The association was stronger in women than in men. No associations were found of sP-sel and fibrinogen with atrial fibrillation. It has been described that von Willebrand factor in atrial fibrillation patients is associated with the presence of left atrial appendage thrombus and with endocardial changes in the overloaded atrial appendage.[60] In a sub sample of the Framingham Offspring Study, no relation was found between von Willebrand factor and atrial fibrillation.[59]

Subsequently, we investigated the associations of these three factors with all-cause mortality, cardiac mortality and with stroke, stratified for sinus rhythm and atrial fibrillation. No associations were found of von Willebrand factor, sP-sel and fibrinogen with risk of stroke.

SP-sel was associated with cardiac mortality in atrial fibrillation but not in subjects in sinus rhythm. Fibrinogen was associated with all-cause mortality and with cardiac mortality in participants in sinus rhythm, but not in participants in atrial fibrillation.

In conclusion none of the three factors predicted stroke in subjects with atrial fibrillation. Our study, however, was small and thus a lack of power may have played a role. We analyzed only three markers out of the many possible markers of a prothrombotic state. However, also in other studies no indicative factor has been found up to date, thus leaving markers of a prothrombotic state as putative predictors of stroke in atrial fibrillation.

Prognosis

In this thesis we investigated heart failure, all-cause and cause-specific mortality and stroke as potential consequences of atrial fibrillation.

Heart failure

Heart failure and atrial fibrillation are two highly interrelated diseases. They share important risk factors as hypertension, diabetes and myocardial infarction.[61] Heart failure and atrial fibrillation are both more prevalent with advancing age, with a lifetime risk of 25%.[11,62] Heart failure is an important risk factor of atrial fibrillation[4] and atrial fibrillation often precedes heart failure.[63] Therefore, it can be hypothesized that atrial fibrillation is a risk factor of heart failure. The hypothesis is supported by the characteristic rapid and irregular ventricular response and the loss of atrioventricular synchrony in atrial fibrillation that may impair cardiac output below physiological requirements.[64] An independent association, however, between atrial fibrillation and heart failure, however, has been difficult to prove.[65]

We investigated the relationship between atrial fibrillation and the onset of heart failure in 6544 subjects without heart failure at baseline. In this study population, 305 participants had prevalent atrial fibrillation. During a median follow-up of 11.9 years, 600 cases of new atrial fibrillation and 784 cases of incident heart failure were identified. Participants who were diagnosed on the same day with atrial fibrillation and heart failure were censored at the day of onset and not considered as case. This is because if both diseases are diagnosed at the same day, it is impossible to conclude which disease preceded the other. In further analyses, we also excluded heart failure cases that developed within one year after the diagnosis of atrial fibrillation. Even with this restriction, incident atrial fibrillation cases had an almost 100% increased risk of heart failure, adjusted for a wide range of cardiovascular risk factors. We found that the joint presence of coronary heart disease and atrial fibrillation increased the risk

of heart failure with more than 700%.

Our results add to the knowledge that atrial fibrillation independently predicts heart failure. This may change the thinking with regard to therapy of atrial fibrillation. The current therapeutic possibilities are not without danger.[66] The uncertainty on the rhythm or rate control strategies stimulated the search for newer therapies.[67,68] The knowledge that atrial fibrillation indeed precedes and causes heart failure may enforce this search. Patients with coronary heart disease and atrial fibrillation belong to a group with a very high risk of heart failure and this group needs the highest attention to improve prognosis.

Mortality

It is known from several studies that atrial fibrillation patients have an increased risk of mortality.[2,3,49,69-77] The complicated cause-effect relationships between atrial fibrillation, heart failure and myocardial infarction pose major problems in the recognition of the independent effect of atrial fibrillation on mortality. The Framingham Study was the first study that found an independent association of atrial fibrillation with mortality. This study, however, described the association in the time-period 1948-1988. That period is characterized by rapid improvements in treatment of important cardiovascular risk factors for atrial fibrillation and this could have resulted in a better prognosis of atrial fibrillation in a later period. Further, there is a paucity of data on cause-specific mortality in atrial fibrillation. Therefore, we followed 6432 participants of the Rotterdam Study without atrial fibrillation at baseline from 1990 to 2005 and assessed the prognosis with respect to all-cause mortality and cause-specific mortality. During a median follow-up of 12 years, 630 participants developed atrial fibrillation and 2445 participants died.

Atrial fibrillation was associated with an independent 60% increased risk of all-cause mortality. Our study is comparable to the above-mentioned Framingham Study in a series of important characteristics. Therefore, we believe that it is acceptable to compare the results of our study with the results of the Framingham Study. The mortality risk adjusted for cardiovascular risk factors and relevant co-morbidities as found in our study does not differ from the relative risks observed in the Framingham Study, but the relative risks adjusted for age and sex only are very different between the studies: the age and sex adjusted mortality risk associated with atrial fibrillation was much higher in the earlier follow-up period of the Framingham Study as compared to the more recent period in the Rotterdam Study. This suggests that the prognosis of atrial fibrillation patients improved in the past decades, but that the independent effect of atrial fibrillation on mortality practically remained the same. We found that the development of heart failure following the diagnosis of atrial fibrillation considerably increased the risk of all-cause mortality. This suggests that part of the independent effect of atrial fibrillation on mortality may go through the development of heart failure.

We also investigated the causes of death in atrial fibrillation. Both men and women with atrial fibrillation had an increased risk of mortality by heart failure, intracranial hemorrhage and stroke, cardiac arrest and a miscellaneous group of cardiac causes of mortality. Death by pulmonary disorders and death by ischemic heart disease were strongly associated with atrial fibrillation in men but not in women. Atrial fibrillation was a strong predictor of death due to trauma and self-harm in women but not in men.

Stroke

Stroke as a consequence of atrial fibrillation has been intensively studied since its first observation in 1978. Powerful preventive measures became available in 1989 when the results from several clinical trials were published that indicated that anticoagulant drugs were capable to reduce the risk of stroke with more than 60%. Recent population-based estimates of the stroke risk in atrial fibrillation are not available.

We investigated the association between atrial fibrillation and stroke in 6577 participants of the Rotterdam Study without stroke at baseline. In this study population, 344 participants were diagnosed with prevalent atrial fibrillation. During a median follow-up of 11.9 years, 605 participants were identified with incident atrial fibrillation, 695 with incident stroke and 733 with incident transient brain attacks. In general, atrial fibrillation was a strong predictor of stroke and stroke subtypes. Also, strong associations were found of atrial fibrillation with transient neurological attacks. The associations were stronger in women than in men. Remarkably, a strong association was also found with non-focal transient brain attacks, strengthening the recently developed concept that these attacks have a pathological background rather than being innocent and ignorable. Anticoagulants, but not antiplatelets, were strongly and adversely associated with risk of stroke in our study. We observed that only 19% of our atrial fibrillation participants who suffered a stroke used anticoagulants, 21% used antiplatelets and 60% used neither drug at the time of stroke. An additional finding was that stroke or transient ischemic brain attacks also predicted atrial fibrillation. Probably, transitory atrial fibrillation sometimes causes stroke but remains undetected initially. We conclude that stroke as a consequence of atrial fibrillation is still a major problem in the general elderly population. The finding that the preventive performance of anticoagulants in our study of the elderly seems to be equal to the results from clinical trials may help clinicians to prescribe anticoagulants in elderly atrial fibrillation patients. It is known that the decision to use these drugs in the elderly is difficult to make. Based on our results, we also believe that clinicians should realize that not only focal but also non-focal transient attacks are associated with atrial fibrillation. This may have serious consequences for the application of already known risk prediction schemes. Finally, physicians treating patients with a stroke or transient neurological attack without atrial fibrillation should be aware of possibly undetected atrial fibrillation as the underlying diagnosis.

Methodological considerations

Study population

Our study was population-based, but potential selections have to be considered. Participants of a population-based study are generally healthier than non-responders. We included only those participants who were willing and who were able to come to the research center and for whom an ECG was available. Those who did not attend the research center were in general older and had more often a history of myocardial infarction. Thus, subjects with a high risk of atrial fibrillation or complications of atrial fibrillation may have been excluded from our study. This has probably generated an underestimation of our prevalence and incidence figures. It is unlikely that this has biased the estimates of associations between risk factors and atrial fibrillation and between atrial fibrillation and clinical outcomes in our study.

Loss to follow up

The Rotterdam Study is an observational, prospective cohort study with a long follow-up. Complete follow-up is challenging. In the Rotterdam Study, the percentage loss to follow-up is very low due to a series of measures to complete follow-up. Only participants moving abroad are in general considered as lost to follow-up. This is a low percentage and will not influence the validity of the study. Inevitably, however, differences in precision and completeness of followup originate in the case that participants move from the Rotterdam region to other parts of the country. Also precision of follow-up changes if participants are admitted to nursing homes. Especially in the case of admission to nursing homes this loss of precision is differential with respect to disease status.

Competing risk

In the analysis of smoking, we hypothesized that to fully understand the association of smoking with atrial fibrillation competing risk of death due to smoking has to be taken into account. Competing risk may occur when a risk factor for a certain disease is also a risk factor for death and when the number of deaths is considerable. In that case, a selected group of persons who are relatively insensitive to the effects of the risk factor of interest remains alive and is left in the study. This causes an attenuation of the relative risks. This may have been the case in the analysis of current smoking as a risk factor of atrial fibrillation. The same mechanism may cause differences in associations between men and women if the risk factor is associated with death different in men and women. This may have played a role in our study when we examined the association of atherosclerosis with atrial fibrillation. Atherosclerosis was a stronger risk factor in women than in men. It is known that atherosclerosis affects men earlier and more

aggressively than women. Atherosclerosis could thus become an important risk factor for atrial fibrillation in women but not in men, if atherosclerotic men died early, leaving men in the study population who were relatively insensitive to the effects of atherosclerosis.

Clinical implications

We found that atrial fibrillation was strongly associated with risk of heart failure (260% increase), all-cause mortality (30% increase) and stroke (240% increase). Stroke is considered as a major adverse event in atrial fibrillation and preventive measures in atrial fibrillation mainly focus on the prevention of this complication. Our data indicate that stroke in atrial fibrillation is not a negligible problem. It has to be examined why this still is the case. A recent study[78] showed that among patients who had atrial fibrillation, who had been prescribed anticoagulants and who were admitted for a first ischemic stroke, a sub-therapeutic INR (INR <2) was present in 75% of the cases. More discussion is needed in order to formulate realistic goals in the prevention of stroke in atrial fibrillation and measures to realize these goals probably need controlled implementation. Further, our data indicate that prevention of heart failure and mortality in atrial fibrillation need additional attention. The overwhelming focus on stroke prevention in atrial fibrillation in the past years may have resulted in a relatively underexposure of the risks of heart failure and death, and less attention for the development of measures to prevent these adverse outcomes. The data on the risks of atrial fibrillation are impressive and it could be argued that patients with atrial fibrillation need focused care. At present, focused care is common for heart failure and is implemented by specific outpatient clinics with specialized nurses, supervised by cardiologist or general practitioners with dedicated knowledge on heart disease. It has to be examined whether atrial fibrillation outpatient clinics analogous to heart failure outpatient clinics could help to improve the prognosis of atrial fibrillation.

In our study, we observed that only 16% of all new cases of atrial fibrillation had been detected singularly by ECG measurements at the research center. This indicates that the yield of prevention programs using ECG measurements to identify atrial fibrillation in an early stage might be low.

Future research

Etiology

The ongoing discussion on the potential causes of atrial fibrillation indicates that research on risk factors of atrial fibrillation is still needed. The finding of an association of CRP with new-onset atrial fibrillation raised the question whether CRP can be considered a new risk factor for atrial fibrillation. CRP is a sensitive marker of inflammation and elevated CRP could also be the consequence of increased levels of atherosclerosis, hypertension and the metabolic syndrome associated with atrial fibrillation. It has also been postulated that atrial fibrillation is not the consequence of inflammation, but that a rise in inflammation could be the consequence of the arrhythmia. Further investigations are needed to unravel this interplay of risk factors for atrial fibrillation. It has been found that men are at greater risk to develop atrial fibrillation than women. Until now, this finding remains unexplained. Gender differences in atrial fibrillation are not the aim of this thesis. However, differences between the sexes were frequently observed in the analysis of the studies presented in this thesis. Differences between sexes have been studied in detail in coronary artery diseases[79-81] but less is known on the background of the differences between men and women in atrial fibrillation.[82,83,84] It would be of interest to know whether differences in presentation and outcome between men and women in atrial fibrillation are related to differences in level of coronary atherosclerosis between men and women.

Hypertension as a risk factor for atrial fibrillation has been identified very early in epidemiological studies of atrial fibrillation. Later, an increased pulse pressure has been identified as an additional risk factor. Blood pressure is nowadays very intensely treated in the general population and it would be very interesting and relevant to evaluate the current role of hypertension in the onset of atrial fibrillation, taking into account all measurements and interventions that are common in the current management of hypertension.

A family history of atrial fibrillation has been observed in patients with atrial fibrillation for many years.[11,85,86] This suggests that atrial fibrillation is heritable. Several genetic loci have been identified for atrial fibrillation.[87-89] Mutations in the cardiac sodium channel,[90] potassium channels[91-95] and connexins[96] have been reported as rare causes of atrial fibrillation. Genome wide association (GWA) studies, in which hundreds of thousands common genetic variants are genotyped and analyzed for disease association, have been conducted in the past years. One of the first reported results was a strong association between two single nucleotide polymorphisms (SNPs) on chromosome 4q25 and atrial fibrillation in an Icelandic population, which was replicated in other studies.[97] A GWA study is currently performed in the Rotterdam Study in collaboration with other population-based studies.

Prognosis

Atrial fibrillation is not only associated with an irregular heart rhythm but also with beat-to-beat differences in cardiac output. If there is a fast rhythm, especially common in untreated atrial fibrillation cases, even a pulse deficit can be found at the radial artery. This means that many heartbeats are not vigorous enough to lead to peripheral pulsation. A compelling question is what the effect of this phenomenon is on the cardiac circulation and perfusion of the heart muscle. It could be hypothesized that this leads to a disturbance in oxygenation of the atrial tissues thus favoring remodeling, especially if also atherosclerotic obstruction, even unnoticed, plays a role. Mutatis mutandis, this phenomenon could also lead to hypoperfusion of the ventricular muscular mass with fibrosis and heart failure as a consequence. Further investigations are needed that focus on the coronary circulation and the effect of atrial fibrillation and different treatment strategies in atrial fibrillation. Results of these studies could lead to a better understanding of remodeling and heart failure in atrial fibrillation with better treatment strategies as a result.

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Chapter 7

Summary

The normal heartbeat is maintained by the sinus node and is regulated by the metabolic needs of the body. At rest the frequency is about 60-70 beats per minute, but at maximum exercise a frequency of 180-200 beats per minute can be observed. Atrial fibrillation is a disturbance of the rhythm of the heart. The normal pacemaker function of the sinus node is replaced by rapid electrical activity in different parts of the upper chambers of the heart, and as a consequence atria do not contract anymore. In this situation, the rhythm of the heart is now determined by the interaction of the fast electrical activity in the atria and the filtering function of the atrioventricular node. Thanks to this node, organisms with atrial fibrillation can stay alive and do not die immediately from ventricular fibrillation when atrial fibrillation begins. Atrial fibrillation is a rare disease in the general population, but is characterized by a sharply increasing incidence and prevalence with age from 55 years onwards. Many aspects of the etiology and management of atrial fibrillation are unknown or controversial. Further, patients with atrial fibrillation are unaware of their rhythm disorder in a considerable proportion of the cases and it is known that only a minority of the cases receives hospital treatment. Therefore, we investigated the epidemiology of atrial fibrillation in the general population of the elderly, the Rotterdam Study. This study started in 1990 with 7983 participants aged 55 years and over, living in the Rotterdam suburb Ommoord.

At baseline and during three follow-up rounds we assessed atrial fibrillation using 10 sec 12 lead resting ECGs, digitally stored and analyzed by the MEANS computer program. Two research physicians and a cardiologist who were blinded for the diagnosis of MEANS verified all ECGs with an arrhythmia diagnosis based on this computer program. This information was completed by information obtained from files from the general practitioners of Ommoord who participate in the Rotterdam Study. These files also include information from medical specialists who treated the subject. Hospital discharge diagnoses were also obtained from the LMR system. (de Landelijke Medische Registratie).

Findings

Incidence and prevalence

We calculated the prevalence and incidence of atrial fibrillation in the period 1990-2000. (Chapter 2). Overall prevalence was 5.5%, rising from 0.7% in the age group 55-59 years to 17.8% in those aged 85 years or over. The overall incidence rate was 9.9/1000 person-years. The incidence rate in the age group 55-59 years was 1.1/1000 person-years, the rate rose to 20.7/1000 person-years in age group 80-84 years, and stabilized in those aged 85 years or over. The prevalence and incidence were higher in men than in women. The lifetime risk to develop

atrial fibrillation at the age of 55 years was 23.8% in men and 22.2% in women, comparable to earlier presented North-American figures.

Risk factors

Generally accepted risk factors for atrial fibrillation are age, male sex, valvular heart disease, heart failure, hypertension, diabetes mellitus, left ventricular hypertrophy and hyperthyroid heart disease. We investigated longitudinally four potential risk factors for atrial fibrillation in the period 1990-2000 in participants who were free from atrial fibrillation and presented the results in chapter 3.

Fish consumption, mediated by the presumed protective effect of n-3 polyunsaturated fatty acids, has been shown to reduce ventricular arrhythmia. In our study no association could be found of the ingestion of fish or the intake of eicosapentaenoic acid and docosahexaenic acid as, measured by a food-frequency questionnaire, with the risk of atrial fibrillation (Chapter 3.1).

Myocardial infarction is a strong risk factor for atrial fibrillation. It is unknown, whether asymptomatic atherosclerosis is associated with atrial fibrillation. We assessed generalized atherosclerosis as a proxy of coronary atherosclerosis by measuring carotid intima-media thickness and the presence of carotid plaques. In our study population of participants without a history of myocardial infarction and without complaints suggestive for angina pectoris, we found that markers of generalized atherosclerosis were associated with the risk of atrial fibrillation (Chapter 3.2). These associations were stronger in women than in men.

Smoking of cigarettes is a well-recognized risk factor for cardiovascular disease, pulmonary disease and cancer. Nicotine, carbon monoxide and polycyclic aromatic hydrocarbons are the three noxious components of cigarette smoke. These components may alter electrophysiological properties and the anatomical substrate of atrial tissue. Therefore, we hypothesized that smoking of cigarettes may be associated with atrial fibrillation. This association had not been found in previous population-based studies. In our study, both former and current smoking of cigarettes were associated with atrial fibrillation (Chapter 3.3).

Overt hyperthyroidism and subclinical hyperthyroidism are known risk factors for atrial fibrillation. It is also known that bone metabolism and physical activity are associated with thyroid function within the normal range. Therefore, we investigated the associations of thyroid stimulating hormone and free thyroxin within the normal range with atrial fibrillation. Our study showed that thyroid function within the normal range was associated with atrial fibrillation (Chapter 3.4).

Prothrombotic state

Atrial fibrillation is associated with a five-fold increased risk of stroke. The stroke risk is not

identical in all patients, but depends on age, sex and cardiovascular co-morbidities. Stroke risk prediction schemes segregate patients in high-risk groups that need oral anticoagulants with potentially harmful side effects and patients with lower risks who can be treated with platelet inhibitors. These schemes, however, have only a modest performance. Better tools are needed to predict the individual stroke risk. The view of a generalized prothrombotic state in atrial fibrillation may help to develop these tools.

We measured three prothrombotic plasma markers in 162 participants with atrial fibrillation at baseline and 324 controls, matched 1:2 on age and sex. Von Willebrand factor is a marker of endothelial damage/dysfunction, soluble P-selectin is a marker of platelet activation and fibrinogen is a marker of rheology. We investigated cross-sectionally the associations of these markers with atrial fibrillation (Chapter 4.1). Only von Willebrand factor was associated with atrial fibrillation. Subsequently, we investigated longitudinally the associations of these markers with all-cause mortality, cardiac mortality and stroke, stratified for sinus rhythm and atrial fibrillation in the time period 1990-2000 (Chapter 4.2). Fibrinogen was associated with all-cause mortality and cardiac mortality in participants in sinus rhythm but not in participants with atrial fibrillation. In both strata no statistical significant associations were found of these markers with stroke.

Prognosis

We investigated the prognosis of prevalent and incident atrial fibrillation with respect to heart failure, all-cause and cause-specific mortality (only incident atrial fibrillation) and stroke in the time period 1990-2005.

Incident atrial fibrillation was associated with a 100% increased risk of heart failure, even after the exclusion of those heart failure cases that occurred within the time window of one year after the diagnosis of atrial fibrillation. This finding supports and strengthens the concept that atrial fibrillation is an independent predictor of heart failure. We found that the combined presence of coronary heart disease and atrial fibrillation increased the risk of heart failure with more than 700% compared to participants without coronary heart disease and without atrial fibrillation (Chapter 5.1).

It is known that atrial fibrillation is associated with an increased mortality. The Framingham Study showed that atrial fibrillation is an independent predictor of all-cause mortality. We compared the associations of atrial fibrillation with mortality as found in our study (1990-2005) with the associations found in the Framingham Study (1948-1988). We found that the independent association of atrial fibrillation with mortality has not changed over time, despite considerable improvements in the treatment of angina pectoris, hypertension, myocardial infarction and heart failure. Data on cause-specific mortality associations with atrial fibrillation

are rare and very limited in population-based studies. We found that both men and women with atrial fibrillation had increased risks of death by heart failure, intracranial hemorrhage and stroke, cardiac arrest and a miscellaneous group of cardiac mortality causes. In men, death by pulmonary disorders and death by ischemic heart disease were strongly associated with atrial fibrillation. In women strong associations were found with death by trauma and self-harm (Chapter 5.2).

Atrial fibrillation is a strong risk factor for stroke. Recent population-based risk estimates, however, are not available. Since 1989, it is known that oral anticoagulant drugs are able to reduce stroke risk in atrial fibrillation with more than 60%. Therefore, it can be hypothesized that the risk of stroke in atrial fibrillation is nowadays much lower. We found that in the period 1990-2005 atrial fibrillation was still associated with a five-fold increased risk of ischemic stroke. Atrial fibrillation was associated with focal but also with non-focal transient brain attacks. Anticoagulant use in atrial fibrillation was associated with a 70% reduction of strokes. The use of antiplatelets was not associated with reduction of stroke risk. Finally, we found that atrial fibrillation was not only a predictor of stroke, but also that stroke predicts atrial fibrillation (Chapter 5.3).

Considerations

In chapter 6 methodological considerations, clinical considerations and further research topics are discussed in relation to the main findings of this thesis.

Chapter 8

Samenvatting

De sinusknoop reguleert de normale hartslag en wordt aangestuurd door de eisen van de stofwisseling van het lichaam. In rust is de hartfrequentie ongeveer 60-70 slagen per minuut, maar bij maximale inspanning kan de frequentie oplopen tot 180-200 slagen per minuut. Bij atriumfibrilleren is er sprake van een verstoring van het normale hartritme. De normale pacemakerfunctie van de sinusknoop heeft plaatsgemaakt voor snelle elektrische activatie in verschillende delen van de atria, bovenin het hart. Daardoor contraheren de atria niet meer. Het hartritme wordt nu bepaald door de interactie tussen de snelle elektrische activatie en de filterende functie van de atrioventriculaire knoop. Dankzij deze knoop kunnen organismen met atriumfibrilleren overleven en sterven zij niet direct ten gevolge van ventrikelfibrilleren op het moment dat atriumfibrilleren ontstaat. Atriumfibrilleren is een zeldzame aandoening in de algemene populatie, maar neemt sterk toe met het ouder worden vanaf het 55e levensjaar. Veel aspecten van de etiologie en de therapie van atriumfibrilleren zijn onbekend of controversieel. Bovendien zijn veel patiënten met atriumfibrilleren niet op de hoogte van het feit dat zij deze aandoening hebben en slechts een klein gedeelte van de patiënten wordt in een ziekenhuis behandeld. Daarom onderzochten we de epidemiologie van atriumfibrilleren onder ouderen in de algemene praktijk, in de ERGO studie (The Rotterdam Study). Deze studie ging in 1990 van start onder 7983 oudere (55 jaar en ouder) inwoners van de Rotterdamse wijk Ommoord.

Tijdens het baseline onderzoek en tijdens 3 vervolgonderzoeken onderzochten we atriumfibrilleren met behulp van 10 seconden 12 afleidingen ECGs, die digitaal opgeslagen en beoordeeld werden door het MEANS computer programma. Alle ECGs met welke ritmestoornis dan ook op basis van het MEANS programma werden beoordeeld op de aanwezigheid van atriumfibrilleren door twee onderzoekers en een cardioloog die niet op de hoogte waren van de MEANS diagnose. Deze informatie werd aangevuld met informatie uit de statussen van de huisartsen uit Ommoord. Deze huisartsen werken samen met de ERGO studie. Huisartsen statussen bevatten naast de eigen verslaglegging, ook de informatie van specialistische behandelingen. Ziekenhuis ontslagdiagnosen werden tevens verkregen van het LMR systeem (de Landelijke Medische Registratie).

Resultaten

Incidentie en prevalentie

We berekenden de prevalentie en incidentie van atriumfibrilleren in de periode 1990-2000 (Hoofdstuk 2). De prevalentie in de gehele onderzoekspopulatie was 5,5%, toenemend van 0,7% in de leeftijdsgroep 55-59 jaar tot 17,8% in de groep die 85 jaar of ouder was. De incidentie berekend over de gehele studiepopulatie was 9,9/1000 persoonsjaren. De incidentie in de

leeftijdsgroep 55-59 jaar bedroeg 1,1/1000 persoonsjaren, oplopend tot 20,7/1000 persoonsjaren in de leeftijdsgroep 80-84 jaar waarna de incidentie niet verder toenam bij diegenen die 85 jaar of ouder waren. De prevalentie en incidentie waren hoger bij mannen dan bij vrouwen. Het lifetime risico om atriumfibrilleren te krijgen op 55 jarige leeftijd was 23,8% bij mannen en 22,2% bij vrouwen, vergelijkbaar met eerder gepubliceerde gegevens uit Noord-Amerika.

Risicofactoren

Leeftijd, mannelijk geslacht, klepafwijkingen van het hart, hartfalen, hypertensie, diabetes mellitus, linker ventrikel hypertrofie, en hartziekte gerelateerd aan hyperthyreoidie zijn algemeen aanvaarde risicofactoren voor atriumfibrilleren. Wij onderzochten longitudinaal vier potentiële risicofactoren voor atriumfibrilleren in de periode 1990-2000 bij deelnemers die geen atriumfibrilleren hadden tijdens de baseline meting. De resultaten staan vermeld in hoofdstuk 3.

Consumptie van vis bleek in het verleden gerelateerd te zijn aan een vermindering van ventriculaire ritme stoornissen, naar aangenomen werd door het beschermende effect van lange keten n-3 meervoudig onverzadigde vetzuren. Wij vonden in onze studie geen associatie van de inname van vis of eicosapentaeenzuur (EPA) en docosahexaeenzuur (DHA), gemeten met een voedingsvragenlijst, met het risico op het krijgen van atriumfibrilleren (Hoofdstuk 3.1).

Het optreden van een hartinfarct is een sterke risicofactor voor atriumfibrilleren. Het is onbekend in hoeverre asymptomatische atherosclerose geassocieerd is met atriumfibrilleren. Wij onderzochten gegeneraliseerde atherosclerose, als een proxy maat voor coronaire atherosclerose, door het meten van de dikte van de intima-media en het bestaan van plaques in de carotis arteriën. In onze studiepopulatie, bestaande uit deelnemers die nooit een hartinfarct hadden doorgemaakt en die geen klachten wijzend op angina pectoris hadden, stelden we vast dat gegeneraliseerde atherosclerose was geassocieerd met het krijgen van atriumfibrilleren (Hoofdstuk 3.2). Het risico was sterker onder vrouwen dan onder mannen.

Het roken van sigaretten is een bekende risicofactor voor cardiovasculaire aandoeningen, longziektes en kanker. Nicotine, koolstof monoxide en polycyclische aromatische koolwaterstoffen zijn de 3 schadelijke componenten van sigaretten rook. Deze stoffen kunnen de elektrofysiologische eigenschappen en het anatomische substraat van atrium weefsel veranderen. Daarom stelden wij de hypothese op dat het roken van sigaretten geassocieerd was met atriumfibrilleren. Deze associatie was nog niet in eerder populatie onderzoek gevonden. In onze studie hadden rokers, maar ook mensen die vroeger rookten, maar ondertussen gestopt waren, een hoger risico op atriumfibrilleren (Hoofdstuk 3.3).

Hyperthyreoidie en subklinische hyperthyreoidie zijn bekende risicofactoren voor atriumfibrilleren. Het was al bekend dat de botstofwisseling en lichamelijke activiteit geassocieerd zijn

met de normale schildklierfunctie. In onze studie bleek dat schildklierfunctie parameters in de normale range eveneens geassocieerd zijn met atriumfibrilleren (Hoofdstuk 3.4).

Prothrombotische staat

Atriumfibrilleren is geassocieerd met een 5 keer verhoogd risico op beroerte. Het risico op beroerte is niet gelijk bij alle patiënten met atriumfibrilleren, maar hangt af van de leeftijd, het geslacht en de aanwezigheid van cardiovasculaire risicofactoren. Er bestaan schema's om het risico op beroerte te voorspellen en zo patiënten met atriumfibrilleren in te delen in hoogrisico groepen die orale anticoagulantia met potentieel schadelijke bijwerkingen nodig hebben en in groepen met een lager risico die behandeld kunnen worden met plaatjesremmers. De voorspellende waarde van deze schema's is matig. Daarom zijn er betere predictoren van het risico op beroerte nodig. Vanuit de hypothese dat er bij atriumfibrilleren sprake is van een gegeneraliseerde prothrombotische staat is het misschien mogelijk betere predictoren te ontwikkelen.

We maten 3 prothromborische plasmamarkers in 162 deelnemers met atriumfibrilleren en 324 controles zonder atriumfibrilleren, 1:2 gematched op leeftijd en geslacht. Von Willebrand factor is een marker van endotheel beschadiging/disfunctie, soluble P-selectin is een marker van plaatjes activatie en fibrinogeen is een rheologische marker. We onderzochten cross-sectioneel de associaties van deze markers met atriumfibrilleren (Hoofdstuk 4.1). Alleen von Willebrand factor was geassocieerd met atriumfibrilleren. Vervolgens onderzochten we longitudinaal de associaties van deze markers met totale mortaliteit, cardiale mortaliteit en beroerte, in strata van sinus ritme en van atriumfibrilleren, in de periode 1990-2000 (Hoofdstuk 4.2). Fibrinogeen was geassocieerd met totale mortaliteit en cardiale mortaliteit in de deelnemers in sinus ritme, maar niet in de atriumfibrilleren groep. Er werden in beide strata geen associaties gevonden van deze markers met het optreden van beroerte.

Prognose

We onderzochten de prognose van prevalent en incident atriumfibrilleren met betrekking tot hartfalen, tot totale en oorzaak-specifieke mortaliteit en tot beroerte in de tijdsperiode 1990-2005.

Incident atriumfibrilleren was geassocieerd met een toename van 100% van het risico op hartfalen, zelfs nadat de hartfalen cases optredend binnen een jaar na het begin van atriumfibrilleren waren geëxcludeerd. Deze bevinding is een ondersteuning en versterking

van het concept dat atriumfibrilleren een onafhankelijke predictor is van hartfalen. De gecombineerde aanwezigheid van coronaire hartziekte en atriumfibrilleren verhoogde het risico van hartfalen met meer dan 700% vergeleken met deelnemers zonder coronaire hartziekte en zonder atriumfibrilleren (Hoofdstuk 5.1).

Het is bekend dat atriumfibrilleren geassocieerd is met een toegenomen sterfte. De Framingham Studie toonde aan dat atriumfibrilleren een onafhankelijke predictor is van totale sterfte. We vergeleken de associaties van atriumfibrilleren zoals gevonden in onze studie (1990-2005) met de resultaten van de Framingham Studie (1948-1988). We stelden vast dat de onafhankelijke associatie met totale sterfte niet veranderd was in de loop van de tijd, ondanks het feit dat er aanzienlijke verbeteringen waren opgetreden in de behandeling van angina pectoris, hypertensie, het hartinfarct en hartfalen. Oorzaakspecifieke mortaliteit in relatie met atriumfibrilleren is nauwelijks onderzocht in populatie studies tot nu toe. We stelden vast dat zowel mannen als vrouwen met atriumfibrilleren een verhoogd risico hadden op sterfte door hartfalen, intracraniële bloeding en beroerte, hartstilstand en meer zeldzame oorzaken van cardiale sterfte samengenomen in een restgroep. Onder mannen met atriumfibrilleren was er een sterke associatie met sterfte door ischemische hartziekte en door longziekten. Onder vrouwen met atriumfibrilleren vonden we sterke associaties met sterfte door trauma en door suïcide (Hoofdstuk 5.2).

Atriumfibrilleren is een sterke risicofactor voor het optreden van beroerte. Echter recente risicoschattingen in onderzoeken in de algemene populatie zijn niet voorhanden. Sinds 1989 is het bekend dat anticoagulantia het risico op beroerte in atriumfibrilleren met meer dan 60% kunnen terugbrengen. Daarom kan verondersteld worden dat het risico op beroerte nu veel lager is dan vroeger. We vonden dat atriumfibrilleren in de tijdsperiode 1990-2005 nog steeds geassocieerd was met een 5 maal verhoogd risico op ischemische beroerte. Atriumfibrilleren was niet alleen geassocieerd met focale maar ook met non-focale TIA's. Anticoagulantia gebruik bij atriumfibrilleren was geassocieerd met een reductie van het optreden van beroerte van 70%. Het gebruik van plaatjesremmers was niet geassocieerd met een reductie van het risico op beroerte. Ten slotte vonden we dat atriumfibrilleren niet alleen een predictor was van beroerte, maar dat beroerte ook een voorspeller was van het optreden van atriumfibrilleren (Hoofdstuk 5.3).

Overwegingen

In hoofdstuk 6 komen methodologische aspecten, klinische overwegingen en onderwerpen voor verder onderzoek aan de orde.

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About the author

Jan Heeringa was born in Ooster-Nijkerk, the Netherlands (Oktober 28th, 1950). He attended grammar school (Lyceum 'Oostergo' in Dokkum) and graduated in 1969. In the same year he started his medical studies in Groningen and graduated in 1976. In 1976 and 1977 he worked as an army medical officer of 43 Pantserinfanteriebataljon. He specialized in family medicine during 1977 and 1978. In 1978 he started to work as a general practitioner in the health center Ommoord until now. In 1989 his practice was one of the Ommoord general practitioner practices that participated in the Rotterdam Study. In 1999 he joined the department of Epidemiology of the Erasmus University in order to control the data on atrial fibrillation, resulting in this thesis on the epidemiology of atrial fibrillation. In 2002 he was appointed as coordinator of the Rotterdam Study. He is married to Anne Visser. They have two daughters, Nynke en Roos, and one granddaughter, Floor Anna.

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DE VERSTEKELING

Bij ieder schepsel dat geboren wordt
zijn reis begint, scheept in het ruim de dood
zich in. En maakt zich met het schip vertrouwd,
dringt door tot iedre vezel van het hout
de romp, de mast, de kabels en de touwen
de zeilen hurkend in de reddingsboot.

Het zijn de kleine kindren die hem kennen
en hem niet vrezen: zij zijn nog pas zo kort
geleden uitgevaren uit hun nacht
ze moeten aan het daglicht nog zo wennen.
Zoals schaduw bij het licht behoort
zo leeft de dood binnen het leven voort.

M. Vasalis