Atrial fibrillation and cause of death, sex differences in mortality, and anticoagulation treatment in low-risk patients
Atrial fibrillation and cause of death, sex differences in mortality, and anticoagulation treatment in low-risk patients
Abstract

Background: Atrial fibrillation (AF) is the most common arrhythmia but information on cause of death in patients with AF is sparse, and whether individuals at low risk of cerebral infarction (CVL) should receive anticoagulant medication is controversial. Studies of sex differences with respect to mortality risk have shown conflicting results.

Methods: Data were obtained from Swedish National Registers. In Study I, there were 272 186 AF patients and matched controls and in Studies II and III, 9519 AF patients and no other diagnosis and matched controls. Study IV compared treatment with warfarin to no treatment in 48 433 patients with AF. Hazard ratio (HR) was calculated with 95% confidence intervals and outcome rates as number per 1000 person-years.

Results: Ischemic heart disease (IHD) was the most common underlying cause of death and was present in 40.2% of AF patients at a HR of 1.7 (1.4-2.1). CVL/stroke was a cause of death in 13.1%, HR 2.7 (1.8-4.0). Among underlying and contributing causes of death, the most common diagnoses were IHD in 43.5%, HR 1.7 (1.4-2.0) and heart failure in 33.1%, HR 2.9 (2.2-3.7). The HRs for mortality in females with AF in age categories ≤65, 65-74, and 75-85 were 2.15, 1.72, and 1.44, and for males 1.76, 1.36, and 1.24. The rates of mortality in females with AF in age categories 55-64, 65-74, and 75-85 were 6.2, 20.7, and 57.3, and for males 8.5, 27.3, and 64.5. In patients 65-74 years, females with a CHA2DS2-VASc score of 2, and males with a score of 1 receiving warfarin treatment showed a significantly reduced risk of cerebral infarction/stroke, HR 0.46 (0.25-0.83) for females and for males, HR 0.39 (0.21-0.73).

Conclusions: Most common causes of death in AF patients were CVL/stroke, heart failure, and IHD. HR of mortality in patients with AF was higher in females than in males but absolute risk was higher in males with AF compared to females with AF. Anticoagulant therapy was beneficial in patients ≥65 years, regardless of the CHA2DS2-VASc score.

Keywords: Atrial fibrillation; Cerebral infarction; Anticoagulation; Cause of death; Mortality risk; Sex differences; CHA2DS2-VASc score

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Förmaksflimmer är den vanligaste rytmrubbningen som drabbar hjärtat. Vid 50 års ålder är knappt 1% drabbade och vid 75 års ålder cirka 14% vilket innebär att i befolkningen är förekomsten cirka 3%. Förmaksflimmer innebär ett elektriskt kaos i förmaken som därmed minskar hjärtats effektivitet att pumpa blodet. Detta kan innebära sytom, till exempel nedsatt ork, andfåddhet och hjärtklappning.

Förmaksflimmer har också visat sig öka risken för död, men det är inte helt klart hur detta sker. Är förmaksflimmer en direkt orsak till död eller är rytmrubbningen en markör för ökad sjuklighet som i sin tur leder till död? Det är visat att blodförtunnande behandling minskar risken för hjärnninfarkt och död men det finns risker med biverkningar i form av blödning. Därför ska patienter med förmaksflimmer och låg risk för hjärnninfarkt inte ges blodförtunnande behandling med anledning av att nytta är för liten i förhållande till riskerna.

Detta arbete försöker visa vilka diagnoser som orsakar död hos patienter med förmaksflimmer och vilka diagnoser som bara är kopplade till annan sjuklighet som leder till död. Även var gränsen går för nytta av blodförtunnande behandling undersöks samt skillnader mellan könen vad gäller risken för död.

Studierna är baserade på nationella svenska register där slutenvårdsregistret och dödsorsaksregistret ingått i alla fyra delarbeten. I delarbete I-III har populationsregistret använts för att skapa kontroller till fallen och i delarbete IV läkemedelsregistret för att dela in patienter med förmaksflimmer i de som medicinerar med waran och de som inte gör det.

Delarbete I undersökte 272 186 patienter och 544 344 kontroller och visade att förmaksflimmer var en oberoende riskfaktor för död. Den relativt riskökningen var högre hos kvinnor i jämförelse med män men den absoluta riskökningen var tvärtom högre hos män. Andra sjukdomar som bidrog mest till ökad dödlighet hos patienter med förmaksflimmer var tumörsjukdom, kroniskt obstruktiv lungsjukdom och kronisk njursvikt.

Delarbete II undersökte 9519 patienter med endast förmaksflimmer som diagnos och jämfördes med 12 468 kontroller utan diagnoser. Risken för stroke eller TIA för kvinnor med förmaksflimmer jämfört med kontroller var HR 3,1 (CI 95% 2,6-3,7) och hos män HR 2,2 (CI 95% 1,8-2,5) där även den absoluta risken var högre för kvinnor. För hjärtsvikt var risken för kvinnor HR 4,8 (CI 95% 4,0-5,8) och för män HR 4,4 (CI 95% 3,7-5,3) men inga skillnader sågs mellan könen av den absoluta risken.
För hjärtinfarkt var risken för kvinnor HR 1,6 (CI 95% 1,3-2,0) och HR 1,2 (CI 95% 1,0-1,4) för män där den absoluta risken var högre för män. Avseende dödlighet var risken HR 1,4 (CI 95% 1,3-1,6) för kvinnor och för män HR 1,2 (CI 95% 1,0-1,3) där den absoluta risken var högre hos män.

Delarbete III undersökte samma kohort som delarbete II och studerade underliggande orsak till död. Den enda grupp av sjukdomar som orsakade ökad risk för död hos patienter med förmaksflimmer var kardiovaskulära orsaker, HR 2,0 (CI 95% 1,8-2,3). Risken för död hos kvinnor var HR 2,3 (CI 95% 1,9-2,8) och HR 1,7 (CI 95% 1,4-2,0) för män. Diagnoser som var de vanligaste orsakerna till död hos både män och kvinnor med förmaksflimmer var kranskärllsjukdom och hjärninfarkt. I en utvidgad analys av underliggande och bidragande orsaker uppvisade diagnoserna hjärninfarkt, kranskärllsjukdom, hjärtsvikt och hjärtstopp de vanligaste dödsorsakerna hos patienter med förmaksflimmer i förhållande till kontrollerna.


Sammanfattningsvis påvisades att ökad risk för död hos patienter med förmaksflimmer orsakas av hjärninfarkt, hjärtsvikt och kranskärllsjukdom. Kvinnor hade högre relativa risker för död jämfört med män men de absoluta riskerna uppvisade dock det omvända förhållandet. Patienter 65 år och äldre, oavsett kön eller eventuell förekomst av andra riskfaktorer uppvisade skyddande effekt av behandling med waran.
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Errata

Study III

p.1077, 2.3
“The Chi-2 test and Fischer exact test were used when appropriate.” should be deleted.

p.1079, 3.2
“valvular diseases, cardiac arrest, atherosclerosis and heart failure” should be added in the last sentence.

p.1079, 3.3
“cerebral haemorrhage” should be deleted in the last sentence.

p.1081, 4.8
“heart failure” in line 5 should be deleted and replaced with “ischemic heart disease”.

Abbreviations

AF  Atrial fibrillation
AR  Absolute Risk
CHA2DS2-VASc  Congestive heart failure 1 point, Hypertension 1 point, Age ≥75 years 2 points, Diabetes Mellitus 1 point, Stroke or Transient ischemic attack 2 points, Vascular disease 1 point, Age 65-74 years 1 point and Female Sex 1 point

CHADS2  Congestive heart failure 1 point, Hypertension 1 point, Age ≥75 years 1 point, Diabetes Mellitus 1 point, Stroke or Transient ischemic attack 2 points

CI  Confidence Interval
CVL  Cerebrovascular lesion
ECG  Electrocardiogram
HR  Hazard Ratio

IHD  Ischemic Heart Disease
NOAC  Novel oral anticoagulant
OR  Odds Ratio
P-value  Probability value
RCT  Randomised controlled trials
RR  Relative Risk
SMR  Standardized mortality ratio
TIA  Transient Ischemic Attack
1. Introduction

Atrial fibrillation (AF) is the most commonly diagnosed cardiac arrhythmia in Sweden, with prevalence of approximately 3% in the general population and approximately 14% in individuals >75 years.\textsuperscript{1, 2} Annual cost associated with this disease in Sweden is estimated at €708 million, half of which is related to complications of stroke and heart failure.\textsuperscript{3} The goals of this research were to identify causes of, and contributors to, death in patients with AF and to determine the lowest threshold of the CHA\textsubscript{2}DS\textsubscript{2}-VASc risk score warranting prophylactic anticoagulant therapy.

1.1 History

The first description of AF based on electrocardiogram was published in 1906 by William Einthoven, who called it “pulsus inaequalis et irregularis”.\textsuperscript{4, 5} However, the condition had been described in the literature for centuries. The probably earliest recorded report of AF was from Huang Ti Nei Ching Su Wen, emperor physician of China believed to have ruled sometime between 1696 and 2598 BC: “When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades”.\textsuperscript{6} In 1909, Sir Thomas Lewis stated that AF was a common clinical condition.\textsuperscript{4}

1.2 Sinus rhythm and AF

Sinus rhythm is the normal heart rhythm. The conduction system of the heart consists of the sinus node, atrioventricular node, bundle of His, and the right and left fascicles. The cells in the sinus node have the highest rate of spontaneous depolarization in the conduction system and determine the heart rate. In normal rhythm, the ECG shows every QRS wave complex to be preceded by a consistent and regular P-wave that initiates contraction of the atria and optimizes ventricular filling (Figure 1).

Atrial fibrillation is an arrhythmia with uncoordinated activation of cells in the atria that leads to the absence of atrial contraction. Strong P-waves are replaced by fibrillatory waves in the atria that will be at a frequency of >300 beats per minute. The atrioventricular node retards conduction, leading to a slower frequency and irregular rhythm in the ventricles. Due to the lack of atrial contraction and synchrony between the atrium and the ventricle, cardiac output is reduced by 5-25\%.

\textsuperscript{7, 8}
1.3 Types of AF
In 2001, a consensus driven by clinical relevance recommended following classification where AF was defined into five classes depending on duration of the episodes and the presentation.\(^9\)

First-detected episode of AF. Bearing in mind that there may be uncertainty about duration and previous undetected episodes. Paroxysmal was defined as AF that terminates spontaneously within 7 days. Persistent was defined as sustained AF $\geq$7 days or $<7$ days if pharmacological treatment or electrical cardioversion was used to terminate AF. Long-standing persistent AF was defined as continuing AF for $>1$ year. Permanent was defined as continuous AF where cardioversion failed or not attempted.

In the latest guidelines from 2016, classification is similar, except AF that is cardioverted within 7 days should now be considered paroxysmal.\(^{10}\) In most patients, AF progresses from paroxysmal short episodes to more frequent and persistent episodes, and finally to become permanent.\(^9\) Few patients will be paroxysmal over decades.\(^{11}\)
1.4 Aetiology and pathophysiology

Several conditions increase the risk of acquiring AF. Hypertension is the most common cause and is present in at least 50% of patients with AF.\textsuperscript{12, 13} About 30% of AF patients have heart failure, and 10-20% exhibit coronary heart disease or chronic obstructive pulmonary disease.\textsuperscript{7, 14, 15} Other conditions, including diabetes mellitus, sleep apnoea, ageing, chronic renal disease, and a postoperative state increase the risk for AF.\textsuperscript{7, 16, 17} The mechanisms are unclear, but may depend on structural remodelling of the atria by activation of fibroblasts, enhanced connective tissue deposition, and fibrosis, leading to electrical dissociation and later to AF.\textsuperscript{18-22} In addition, up to 30% of patients show a genetic predisposition to developing AF from cardiomyopathies and dysfunction of ion channels in the cell membranes.\textsuperscript{23} Some patients develop AF without other known disease or conditions. Thus, conditions causing AF are multifactorial and, in individual cases, are often unknown.

1.5 Atrial fibrillation mortality and cause of death

Gajewski and Singer (1981) reported that patients with paroxysmal or chronic AF and mitral valve stenosis or coronary artery disease had a higher mortality than those without AF.\textsuperscript{24} Godtfredsen (1982) found higher mortality in a hospital-based cohort of patients with AF compared with the general population.\textsuperscript{25}

In 1998, the Framingham study showed an increased risk of death in patients with AF compared to those without, and acknowledged AF as an independent risk factor and cause of death.\textsuperscript{26} Subsequent observational studies have confirmed these results, but the basis for the increased mortality in patients with AF is unclear. Studies investigating cause of death in patients with AF have shown that cardiovascular causes are overrepresented (Table 2). Coronary artery disease, sudden cardiac death, and heart failure are the most common causes of death in patients with AF, and cerebral infarction is reported at an incidence of 6.0-10.9%.\textsuperscript{27-30} These results have been reported in cohorts of AF patients with known comorbidities, and AF free controls were not used.

This thesis investigated a cohort with AF with no other clinical diagnoses. Patients were also compared to controls with no clinical diagnoses. It is a challenge to determine whether AF per se is a cause of death or an associated factor. Investigation of causes of death is essential to developing potential interventions with the aim of reducing mortality.
Table 1  Studies of underlying and contributing causes of death in patients with AF

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<tr>
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<td>Number of deaths</td>
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<td>Underlying cause (U) or Contributing causes (C)</td>
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<td>U</td>
<td>U + C</td>
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<td>Causes of death - Cardiovascular</td>
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<td>Progressive Heart failure</td>
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<td>Stroke/Systemic embolism</td>
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<td>Hemorrhage</td>
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<td>6</td>
<td>4.1</td>
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<td>7</td>
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<td>Cerebrovascular disease</td>
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<tr>
<td>Cardiomyopathia</td>
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</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td>2.4</td>
<td>4.4</td>
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</tr>
</tbody>
</table>

| Causes of death - Non-Cardiovascular                |                  | Cancer              |                  | 11.8          | 3.2            | 17.6           | 2.7            | 6.0            |
| Respiratory                                         |                  | 5.8                |                  | 3.2           | 9.8            | 4.9            |
| Infection                                           |                  | 4.5                |                  | 11.8          | 9.1            | 13.9           |
| Trauma                                              |                  | 0.9                |                  | 1             | 9.4            |
| Other non-cardiovascular                             |                  | 10.8               |                  | 3.3           | 19.1           |
| Endocrine                                           |                  | 5.8                |                  | 9.2           |
| Digestive                                           |                  | 10.8               |                  | 4.8           |
| Genitourinary                                       |                  | 11.8               |                  | 6.3           |
| Mental disorders                                    |                  | 5.8                |                  | 6.3           |
| Nervous system                                      |                  | 4.5                |                  | 8.8           |
| Blood and blood forming                             |                  | 10.8               |                  | 9.4           |

Rates in percent.
1.6 Atrial fibrillation and sex differences in mortality

The first study to examine the relationship between sex and mortality in patients with AF was Benjamin in 1998 who found an odds ratio of 1.5 (1.2-1.8) in males and 1.9 (1.5-2.2) in females.26 Studies have shown conflicting results (Table 2). Sex differences in mortality in patients with AF are uncertain. Some studies have reported an increased risk of mortality for males compared to females, while other studies obtained the opposite result or no differences.26, 31-38

Table 2 Studies of all-cause mortality in men and women in patients with AF

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients and controls</th>
<th>Results and analysis</th>
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<tbody>
<tr>
<td>Benjamin</td>
<td>621 incident AF</td>
<td>M 1.5 (1.2-1.8)</td>
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<td></td>
<td>1242 controls</td>
<td>F 1.9 (1.5-2.2)</td>
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<tr>
<td></td>
<td></td>
<td>M versus F 1.2 (0.98-1.49)</td>
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<td></td>
<td></td>
<td>Odds Ratio</td>
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<tr>
<td>Wolf</td>
<td>13558 AF</td>
<td>Men</td>
</tr>
<tr>
<td></td>
<td>13195 controls</td>
<td>65-74 years 1.21 (1.00-1.46)</td>
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<td>75-84 years 1.07 (0.96-1.19)</td>
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<td>85-89 years 1.10 (1.04-1.16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
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<tr>
<td></td>
<td></td>
<td>65-74 years 1.20 (1.00-1.45)</td>
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<td></td>
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<td>75-85 years 1.20 (1.09-1.32)</td>
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<td>85-89 years 1.22 (1.14-1.29)</td>
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<tr>
<td></td>
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<td>Relative Risk</td>
</tr>
<tr>
<td>Stewart</td>
<td>100 prevalent AF</td>
<td>M 1.5 (1.2-2.2)</td>
</tr>
<tr>
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<td>15306 controls</td>
<td>F 2.2 (1.5-3.2)</td>
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</tr>
<tr>
<td>Ruigomez</td>
<td>1035 chronic AF</td>
<td>M 2.3 (1.8-3.0)</td>
</tr>
<tr>
<td></td>
<td>5000 controls</td>
<td>F 2.8 (2.2-3.6)</td>
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<td>Relative Risk</td>
</tr>
<tr>
<td>Friberg</td>
<td>276 AF</td>
<td>M 1.9 (1.4-2.5)</td>
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<tr>
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<td>29310 controls</td>
<td>F 3.9 (2.7-5.5)</td>
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<td>Stollerberger</td>
<td>409 AF</td>
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<td>Olsson</td>
<td>376000 AF SMR</td>
<td>F versus M 0.80 (0.79-0.81)</td>
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<td>Hazard Ratio</td>
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</table>

AF, atrial fibrillation; M, men; F, female; SMR, standardized mortality rate.
1.7 Atrial fibrillation, cerebral infarction, and anticoagulation

The first report of a positive effect of anticoagulation therapy on the risk of arterial embolism was from Szekely in 1964, who reported a five-fold incidence of embolism in patients with mitral valve stenosis and AF compared to those in sinus rhythm. Treatment of patients with AF with warfarin halved the risk of embolism.

Bjerkelund and Orning found in 1969 a stroke incidence of 0.8% in patients who underwent electrical cardioversion and were treated with anticoagulants compared to 5.3% in cardioversion patients not receiving anticoagulation therapy.

Until the 1980s, patients with valvular AF or a planned electrical cardioversion received anticoagulation treatment, but there was uncertainty regarding anticoagulation for non-valvular AF and the role of antiplatelet treatment. In 1989, the Atrial Fibrillation, Aspirin, Anticoagulation (AFASAK) study comparing no anticoagulation therapy, aspirin, and warfarin showed a significantly lower incidence of cerebral infarction in the warfarin group, a result that was confirmed by subsequent similar studies. Whether patients with AF and a low risk for stroke should receive anticoagulation or antiplatelet agents, or no treatment, was already in question at that time.

Risk scores have been developed to identify patients that would benefit from treatment. The first scoring system with broad global use, the CHADS2 score, was published in 2001, and implemented in European and US guidelines in 2006. The acronym refers to congestive heart failure, hypertension, age ≥75 years, and diabetes mellitus, with each factor assigned one point. The S2 indicates stroke or transient ischemic attack and was assigned two points. Patients with a score of 0 were recommended aspirin, a score ≥2 recommended warfarin, and in patients with one point, either aspirin or warfarin were considered.

To differentiate patients at low risk of stroke, the CHA2DS2-VASc score was proposed in 2010 and included in the European guidelines from 2012. The updated scoring system is comparable to the CHADS2 score with the addition of age 65-74 years, female sex, and vascular disease each assigned one point, and age ≥75 years given two points. In the 2016 guidelines an update came into effect when antiplatelet medication as treatment and the point for female sex were omitted. AF guidelines recommend that males with zero points and females with one point do not receive anticoagulation treatment. The question remains whether anticoagulation therapy is warranted for patients with one additional point in the risk
score, irrespective of sex; hence, for males with a score of 1 and females with two points, anticoagulation should be considered on an individual basis. Anticoagulation is recommended for males with two or more points and females with three or more points.
2. Aims

The overall aim of these studies was to investigate patients with AF and causes of death, sex differences in mortality and if individuals at low risk of cerebral infarction should receive warfarin.

Study I
To estimate the risk of mortality in patients with incident AF and the role of age, sex, and concomitant disease compared to matched controls in a nationwide cohort.

Study II
To estimate the risks of stroke or transient ischemic attack, heart failure, myocardial infarction, and all-cause mortality in patients with incident AF as the sole diagnosis at the time of AF diagnosis compared to matched controls in a nationwide cohort.

Study III
To describe the causes of death in patients with incident AF as the sole diagnosis at the time of AF compared to matched controls in a nationwide cohort.

Study IV
To compare risks of cerebral infarction according to the CHA2DS2-VASc score, age and sex in a nationwide cohort of patients with AF with and without warfarin therapy.
3. Subjects and Methods

All studies were based on Swedish National Registers. Atrial fibrillation was defined according to the International Classification of Diseases (ICD): 427 D (DA, DB, DC, DD, and DW) in ICD 9 (1987-96) and I 48, I 48.9, and I48.9 (A, B, C, D, E, F, P, and X) in ICD 10 (1997-present).

From 1987 through 2008 the National Board of Health and Welfare identified 567 171 individuals with AF, and Statistics Sweden identified 4 677 463 possible controls as individuals not diagnosed with AF. After defining the time-period from 1995 to 2008, age ≤ 85 years, and in-hospital diagnosed incident AF, a matching procedure was carried out by Statistics Sweden and assigned two controls without AF to each AF patient. Subjects were matched on age, sex, and year of the incident AF. The cohort consisted of 272 186 patients and 544 372 controls. Data used in studies I-IV are shown in Figure 2.

3.1 Data sources and national registers

The Swedish National In-patient Register (Studies I-IV)
The register, also called the Hospital Discharge Register, was first produced in 1964 by the National Board of Health and Welfare and reached national coverage in 1987. More than 99% of somatic and psychiatric diagnoses are registered. A validation study showed 85-95% of all diagnoses to be valid, reaching 97% for AF.47, 48 Diagnoses are coded according to the International Classification of Diseases, ICD 9 (1987-1996) and ICD 10 (1997-present) and consist of a single primary diagnosis and up to nine secondary diagnoses, along with admission and discharge dates.

The Total Population Register (Studies I-III)
This register has complete national coverage and contains data of age, sex, place of residence, date of emigration and/or immigration, and death. The register has covered all of by Statistics Sweden from 1968 to the present and is maintained Sweden.49
Figure 2. Flowchart

Study 1
- 272,186 patients with incident atrial fibrillation between 1995-01-01 and 2008-12-31
- 95,634 matched controls without atrial fibrillation
- 49,081 controls without other in-hospital diagnoses since 1987-01-01 and during the first year of follow-up
- 14,603 patients without other in-hospital diagnoses since 1987-01-01 and during follow-up
- 5,084 patients without matched controls

Study 2 and Study 3
- 9,519 patients and 12,468 matched controls

Study 4
- 48,453 patients with incident atrial fibrillation without warfarin during inclusion period
- 15,782 patients without warfarin
- 27,166 patients with warfarin
- 5,485 patients without warfarin

8,788 patients with warfarin started before incident atrial fibrillation
- 59,981 patients with incident atrial fibrillation between 2009-01-01 and 2009-12-31
- 27,603 patients with death, stroke or emigration from incident atrial fibrillation
- 36,613 controls with other in-hospital diagnoses since 1987-01-01 and during the first year of follow-up
- 38,413 controls without matched controls

8,788 patients with warfarin started before incident atrial fibrillation
- 2,760 patients with death, stroke or emigration from incident atrial fibrillation
- 495,263 controls with other in-hospital diagnoses since 1987-01-01 and during the first year of follow-up
- 5,485 patients without warfarin
- 15,782 patients without warfarin
- 27,166 patients with warfarin

257,583 patients with other in-hospital diagnoses since 1987-01-01 and during the first year of follow-up
- 495,263 controls with other in-hospital diagnoses since 1987-01-01 and during the first year of follow-up
- 5,084 patients without matched controls

495,263 controls without matched controls

Study 1
- 272,186 patients with incident atrial fibrillation between 1995-01-01 and 2008-12-31
- 54,344 matched controls without atrial fibrillation
- 54,344 matched controls without atrial fibrillation
- 49,081 controls without other in-hospital diagnoses since 1987-01-01 and during the first year of follow-up
- 14,603 patients without other in-hospital diagnoses since 1987-01-01 and during follow-up
- 5,084 patients without matched controls

Study 2 and Study 3
- 9,519 patients and 12,468 matched controls

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257,583 patients with other in-hospital diagnoses since 1987-01-01 and during the first year of follow-up
- 495,263 controls with other in-hospital diagnoses since 1987-01-01 and during the first year of follow-up
- 5,084 patients without matched controls
The Cause of Death Register (Studies I-III)
In Sweden, registration of death began in 1741, and from 1961 has been systematically implemented, covering all residents. Statistics Sweden maintained the register until 1994 when responsibility was assumed by the National Board of Health and Welfare. A single underlying cause of death and potentially up to 19 contributing causes may be stated in the death certificate. About 99% of deaths are registered, with cause of death coded according to the ICD. Validation of the register has shown inconsistencies in data with respect to the underlying cause. In approximately 80% of cases, underlying cause of death was shown to be correct, but is less accurate in patients with multiple possible causes. Identifying a single cause of death was initiated in an era of high premature mortality, in contrast to the present when people survive to advanced age and often develop more than one disease.

The Swedish Prescribed Drug Register (Study IV)
This registry was initiated in 2005 and comprises a record of drugs prescribed and dispensed to patients regardless the care was public or private. The date of every withdrawal is registered, and coverage is nearly complete for all prescriptions written in Sweden.

The Swedish Register of Education (Study IV)
The registry was initiated in 1985 by Statistics Sweden and is updated annually. It reports the highest education level and year of graduation of all residents from 16 to 74 years of age. Education is divided into seven levels from <9 years primary education to postgraduate. Information of education from 1960, 1970, and 1990 was added from the Population and Housing Register.

The Population and Housing Register (Study IV)
The registry was implemented in 1960 by Statistics Sweden, with information collected every five years until 1990. Variables include, for example, home ownership, number of household residents, profession, and income.

3.2 Study I
Study I was a retrospective cohort study of 272,186 patients with incident AF diagnosed from 1 January 1995 to 31 December 2008, along with 544,344 controls without AF from the general population (Figure 2). Out-
comes were all-cause mortality and confounding factors that were adjusted for were ischemic heart disease, acute myocardial infarction, heart failure, stroke, transient ischemic attack, hypertension, chronic obstructive pulmonary disease, diabetes mellitus, neoplasm, and chronic renal failure. AF patients and controls were stratified according to sex and the age categories <65, 65-74, and 75-85 years. Patients were tracked through 31 December 2009.

3.3 Study II
The study was a retrospective cohort study comprising 9,519 patients with the sole diagnosis of incident AF between 1 January 1995 and 31 December 2008 and 12,468 controls with no hospital diagnoses from 1987 to the date of AF diagnosis of an age- and sex-matched patient (Figure 2). Outcomes were stroke and transient ischemic attack, heart failure, myocardial infarction, and all-cause mortality. AF patients and controls were stratified according to sex and the age categories <55, 55-64, 65-74, and 75-85 years. Patients were tracked through 31 December 2009.

3.4 Study III
The study was a retrospective cohort study using the cohort designated in study II. Outcome was underlying cause of death, with analysis performed in two steps: first, the underlying cause of death was identified according to the relevant chapter (I-XX) in ICD 9/ICD 10. Second, any underlying cause of death from the chapter IX (Diseases of the circulatory system) was identified by diagnoses from I 10 to I 71. Analysis was performed for the entire cohort, as well as separately for males and females. Patients were tracked through 31 December 2008.

3.5 Study IV
This was a retrospective study of a cohort comprising 48,433 patients with incident AF diagnosed from 1 January 2006 through 31 December 2008 (Figure 2). Patients on warfarin were compared with patients not receiving anticoagulation therapy. For patients that started warfarin more than 30 days after diagnosis or who discontinued treatment during the studied period, a time-varying exposure analysis was conducted to include all eligible patients. Patients were classified according to age (<65, 65-74, or 75-85 years), sex, and CHA2DS2-VASc score (0, 1, 2, or ≥3). Primary
outcome was cerebral infarction and stroke, and secondary outcome was cerebral bleeding. Patients were tracked through 31 December 2009.

3.6 Ethics

The research methods complied with the declaration of Helsinki and were approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2009/273) on 7 October 2009.

Data used were anonymous, and informed consent was not required. Management of personal identification numbers and matching of patients and controls from different registries were carried out by Statistics Sweden and the Swedish National Board of Health and Welfare. Prior to being provided to our research group, data were anonymized, and identification of individual patients was not possible.
4. Statistical analysis

Continuous variables are presented as mean and standard deviation and categorical variables as percentage. Comparison between groups was expressed as hazard ratio (HR), considered significant with 95% confidence intervals (CI) for HR not including 1.0. The HR value was considered equivalent to relative risk. P values of <0.05 were considered significant. The software STATA version 11, 13, or 14 (STATA Corp, College Station, TX, USA) was used in all studies, and Study IV used SPSS version 22 (IBM Corp., NY, USA).

Kaplan–Meier estimate
The standard estimator of the survival function in time-to-event analysis is the Kaplan-Meier estimate, which shows the proportion of individuals in the studied group that has not yet experienced the event of interest, in a graphic curve over time.\(^56, 57\) In Studies II and IV, the Kaplan–Meier curve was inversed to compare patients and controls that suffered cerebral infarction, heart failure, myocardial infarction, or death during the study period.

Cox regression
Cox regression estimates the association between predictors and time-to-event.\(^58\) The advantage of the Cox regression compared to other regression models is that it takes censored observations into consideration, i.e. observations where it is unknown exactly when the event of interest occurs, or if it occurs at all. The most common type of censoring is right censoring, where all that is known is that the individual still has not experienced the event at the end of the study. Cox regression is based on a proportional condition assuming that the predictor affects the outcome at a consistent level during the studied period. Schoenfeld residuals were used to assess whether proportional hazards were present, i.e. to confirm that the effect of a change in a covariate is constant over time.\(^59\) Conditions of Studies I and IV were non-proportional, so the study period was divided into two time-segments to enable the use of Cox regression.\(^60\) In Study I, time was separated at one-year post-diagnosis, and in Study IV time was separated at six months.
Hazard ratio (HR), relative risk (RR), and absolute risk (AR)

Cox regression is used in time-to-event analysis to estimate the HR which represents the instantaneous risk of an event at any time during study period. HR is calculated by the hazard (risk) of an event in the exposed group divided with the hazard in the non-exposed group. Hazard can usually be thought of as incidence rate, which is the number of events per 100 or 1000 person-years and is interpreted as the AR when comparing females and males. RR is the cumulative risk of an event over a given time period and the HR is sometimes considered as RR in studies. In study I-III of this thesis, the HR was referred to as RR.

Time-varying exposure analysis

Study IV compared the outcomes in AF patients with and without warfarin treatment, which may have changed during the study period. One option was to analyse warfarin treatment as a fixed covariate, yes or no, at the time of patient inclusion in the study. To decrease misclassification and to include all patients, another option was to use a time-varying exposure analysis. Patients who began treatment 30 days or more after diagnosis, or who showed irregular withdrawals, were included in the warfarin arm of the study when receiving treatment and the non-warfarin arm when not receiving treatment.
5. Results

5.1 Study I

All-cause mortality in patients with AF
Risk for all-cause-mortality in patients with AF was increased compared to controls in all age categories (Table 3). HR was higher in females than in males, in the youngest age category, and within the first year after inclusion compared to 1-14 years of tracking. In AF patients, the incidence rates of mortality were lowest in the youngest females and highest in the oldest males. Concomitant diseases associated with the highest risk of mortality in patients with AF were chronic renal failure, chronic obstructive pulmonary disease, neoplasms, and heart failure.

Table 3 Hazard ratio of all-cause mortality in patients with a primary or secondary diagnosis of atrial fibrillation versus controls

<table>
<thead>
<tr>
<th></th>
<th>Female</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% confidence interval</td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>4.88 (4.17-5.72)</td>
<td>3.07 (2.82-3.35)</td>
</tr>
<tr>
<td>1-14 years</td>
<td>2.15 (1.99-2.32)</td>
<td>1.76 (1.69-1.84)</td>
</tr>
<tr>
<td>65-74 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>2.88 (2.69-3.09)</td>
<td>2.07 (1.97-2.16)</td>
</tr>
<tr>
<td>1-14 years</td>
<td>1.72 (1.67-1.78)</td>
<td>1.36 (1.33-1.40)</td>
</tr>
<tr>
<td>75-85 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>2.09 (2.04-2.15)</td>
<td>1.72 (1.68-1.76)</td>
</tr>
<tr>
<td>1-14 years</td>
<td>1.44 (1.42-1.46)</td>
<td>1.24 (1.22-1.26)</td>
</tr>
</tbody>
</table>

Follow-up <1 year and 1-14 years. Hazard ratio with 95% confidence interval.

5.2 Study II

Cardiovascular morbidity and all-cause mortality in patients with AF as sole diagnosis
Risk of stroke and transient ischemic attack and heart failure in patients with AF was higher than in controls in all age categories (Table 4). Risk of myocardial infarction and all-cause mortality relative to controls was greater in females > 65 years but lower in males. Annual rates of stroke and transient ischemic attack were three-fold in females and, in males, double that of controls (Table 5).
In patients with CHA2DS2-VASc scores of 0, 1, and 2 points, the annual rates of stroke ranged from 0.3-1.0%, 0.5-1.6%, and 2.1-3.3%, respectively. In AF patients, the incidence rates of mortality per 1000 person-years in age-categories 55-64, 65-74, and 75-85 years were for females 6.2, 20.7, and 57.3, and for males 8.5, 27.3, and 64.4.

Table 4 Hazard ratio of cardiovascular morbidity and all-cause mortality in patients with AF as sole diagnosis versus controls without diagnosis according to sex and age categories

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age category</th>
<th>Women AF patients vs. controls HR (95 % CI)</th>
<th>Men AF patients vs. Controls HR (95 % CI)</th>
<th>AF patients women vs. men HR (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke and TIA</td>
<td>&lt;55</td>
<td>19.6 (2.6-149.2)</td>
<td>3.4 (2.2-5.2)</td>
<td>1.67 (0.94-2.95)</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>4.4 (2.6-7.3)</td>
<td>2.5 (1.9-3.2)</td>
<td>1.00 (0.74-1.34)</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>3.4 (2.6-4.5)</td>
<td>1.7 (1.3-2.1)</td>
<td>1.25 (1.01-1.56)</td>
</tr>
<tr>
<td></td>
<td>75-85</td>
<td>2.5 (2.0-3.2)</td>
<td>1.9 (1.4-2.7)</td>
<td>1.11 (0.86-1.43)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>3.1 (2.6-3.7)</td>
<td>2.2 (1.8-2.5)</td>
<td>1.16 (1.01-1.34)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>&lt;55</td>
<td>6.6 (1.9-23.1)</td>
<td>7.8 (4.4-13.8)</td>
<td>1.60 (0.90-2.84)</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>6.5 (3.6-11.8)</td>
<td>4.6 (3.2-6.6)</td>
<td>1.15 (0.84-1.56)</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>6.3 (4.5-8.8)</td>
<td>4.9 (3.6-6.6)</td>
<td>0.88 (0.72-1.08)</td>
</tr>
<tr>
<td></td>
<td>75-85</td>
<td>3.8 (2.9-4.8)</td>
<td>2.9 (2.0-4.0)</td>
<td>0.84 (0.67-1.06)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>4.8 (4.0-5.8)</td>
<td>4.4 (3.7-5.3)</td>
<td>0.94 (0.82-1.07)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>&lt;55</td>
<td>1.1 (0.3-4.2)</td>
<td>1.2 (0.8-1.7)</td>
<td>0.66 (0.24-1.84)</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>1.5 (0.8-2.7)</td>
<td>1.1 (0.8-1.4)</td>
<td>0.66 (0.42-1.04)</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>1.9 (1.4-2.6)</td>
<td>1.4 (1.1-1.8)</td>
<td>0.68 (0.51-0.90)</td>
</tr>
<tr>
<td></td>
<td>75-85</td>
<td>1.5 (1.1-2.1)</td>
<td>1.1 (0.7-1.6)</td>
<td>0.74 (0.52-1.06)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1.6 (1.3-2.0)</td>
<td>1.2 (1.0-1.4)</td>
<td>0.70 (0.57-0.84)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>&lt;55</td>
<td>1.1 (0.5-2.4)</td>
<td>1.2 (0.8-1.6)</td>
<td>1.32 (0.68-2.58)</td>
</tr>
<tr>
<td></td>
<td>55-64</td>
<td>1.0 (0.7-1.6)</td>
<td>1.1 (0.9-1.4)</td>
<td>0.65 (0.45-0.93)</td>
</tr>
<tr>
<td></td>
<td>65-74</td>
<td>1.4 (1.2-1.7)</td>
<td>1.2 (1.0-1.5)</td>
<td>0.67 (0.56-0.81)</td>
</tr>
<tr>
<td></td>
<td>75-85</td>
<td>1.5 (1.3-1.7)</td>
<td>1.1 (0.9-1.4)</td>
<td>0.81 (0.68-0.97)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>1.4 (1.3-1.6)</td>
<td>1.2 (1.0-1.3)</td>
<td>0.74 (0.66-0.84)</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; HR, hazard ratio; CI, confidence interval; TIA transient ischemic attack.
Table 5 Annual stroke rate and mortality rate in patients with atrial fibrillation as sole diagnosis and controls without diagnosis with corresponding risk scores from CHA2DS2-VASc and CHADS2 in sex and age categories

<table>
<thead>
<tr>
<th></th>
<th>CHA2DS2-VASc</th>
<th>CHADS2</th>
<th>Annual stroke rate (%)</th>
<th>Annual mortality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>Female &lt;55</td>
<td>1</td>
<td>0</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>55-64</td>
<td>1</td>
<td>0</td>
<td>1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>65-74</td>
<td>2</td>
<td>0</td>
<td>2.1</td>
<td>0.6</td>
</tr>
<tr>
<td>75-85</td>
<td>3</td>
<td>1</td>
<td>3.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Men &lt;55</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>55-64</td>
<td>0</td>
<td>0</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>65-74</td>
<td>1</td>
<td>0</td>
<td>1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>75-85</td>
<td>2</td>
<td>1</td>
<td>3.3</td>
<td>1.7</td>
</tr>
</tbody>
</table>

5.3 Study III

Underlying cause of death in patients with AF as sole diagnosis
As an underlying cause of death, only cardiovascular diseases were associated with an increased risk of death in AF patients versus controls (Table 6). Specifically, a significant increased risk of death was seen with chronic ischemic heart disease, cerebral infarction or stroke, cerebrovascular disease, myocardial infarction, and hypertension (Table 7). No increased risk was observed as underlying cause of death from cardiac arrest, heart failure, or pulmonary embolism.

In a separate study (unpublished data), contributing causes of death were analysed in conjunction with the underlying causes (Table 8). A significant increased risk of death was seen with chronic ischemic heart disease, heart failure, cerebral infarction or stroke, cardiac arrest, atherosclerosis, hypertension, and cerebrovascular disease.
**Table 6 Underlying cause of death according to ICD-10 diagnosis chapters in patients with atrial fibrillation and controls without co-morbidities**

<table>
<thead>
<tr>
<th>Chapter</th>
<th>AF (N=9 519)</th>
<th>Controls (N=12 468)</th>
<th>HR</th>
<th>CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths (%)</td>
<td>Deaths (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>IX</td>
<td>589 55.6</td>
<td>372</td>
<td>35.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>II</td>
<td>243 22.9</td>
<td>356</td>
<td>34.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Respiratory</td>
<td>X</td>
<td>53 5.0</td>
<td>72</td>
<td>6.9</td>
<td>0.9</td>
</tr>
<tr>
<td>External</td>
<td>XX</td>
<td>33 3.1</td>
<td>51</td>
<td>4.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Mental</td>
<td>V</td>
<td>31 2.9</td>
<td>45</td>
<td>4.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Digestive</td>
<td>XI</td>
<td>27 2.6</td>
<td>40</td>
<td>3.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Symptom</td>
<td>XVIII</td>
<td>24 2.3</td>
<td>19</td>
<td>1.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Nervous</td>
<td>VI</td>
<td>19 1.8</td>
<td>38</td>
<td>3.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Endocrine</td>
<td>IV</td>
<td>17 1.6</td>
<td>17</td>
<td>1.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Infection</td>
<td>I</td>
<td>14 1.3</td>
<td>12</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>9 0.9</td>
<td>19</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td></td>
<td>1 059 100</td>
<td>1 041</td>
<td>100</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Hazard ratio with 95% confidence interval. P-value <0.05 considered statistically significant.

External (XX) includes accidental injuries. Symptom (XVIII) includes symptoms, signs, abnormal results of clinical investigation where no classifiable diagnosis is recorded. Other includes chapter III, VII-VIII, XII-XVII and XIX.
Table 7 Underlying cause of death according to ICD-10 diagnosis in patients without comorbidities at the time of AF diagnosis and matched controls

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>AF (N=9 519)</th>
<th>Controls (N=12 468)</th>
<th>HR</th>
<th>CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deaths (%)</td>
<td>Deaths (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>237</td>
<td>178</td>
<td>1.7</td>
<td>1.4-2.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>121</td>
<td>119</td>
<td>1.3</td>
<td>1.0-1.7</td>
<td>0.046</td>
</tr>
<tr>
<td>Chronic ischemic heart disease</td>
<td>108</td>
<td>55</td>
<td>2.5</td>
<td>1.8-3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic cardiac disease</td>
<td>8</td>
<td>4</td>
<td>2.5</td>
<td>0.6-8.4</td>
<td>0.131</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>90</td>
<td>4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cerebral infarction or stroke</td>
<td>77</td>
<td>36</td>
<td>2.7</td>
<td>1.8-4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>35</td>
<td>21</td>
<td>2.1</td>
<td>1.2-3.6</td>
<td>0.007</td>
</tr>
<tr>
<td>Heart failure</td>
<td>29</td>
<td>22</td>
<td>1.6</td>
<td>0.9-2.8</td>
<td>0.084</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>28</td>
<td>38</td>
<td>0.9</td>
<td>0.6-1.5</td>
<td>0.757</td>
</tr>
<tr>
<td>NOS</td>
<td>24</td>
<td>11</td>
<td>2.7</td>
<td>1.3-5.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>5</td>
<td>4.0</td>
<td>1.5-11.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>15</td>
<td>9</td>
<td>2.1</td>
<td>0.9-4.7</td>
<td>0.086</td>
</tr>
<tr>
<td>Aneurysm or dissection</td>
<td>13</td>
<td>22</td>
<td>0.7</td>
<td>0.4-1.5</td>
<td>0.387</td>
</tr>
<tr>
<td>Cardiomyopathia</td>
<td>9</td>
<td>6</td>
<td>1.9</td>
<td>0.7-5.4</td>
<td>0.211</td>
</tr>
<tr>
<td>Valve disorders</td>
<td>7</td>
<td>10</td>
<td>0.9</td>
<td>0.3-2.3</td>
<td>0.767</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>7</td>
<td>3</td>
<td>2.9</td>
<td>0.7-11.2</td>
<td>0.125</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2</td>
<td>7</td>
<td>0.4</td>
<td>0.1-1.7</td>
<td>0.196</td>
</tr>
<tr>
<td>Cardiovascular deaths</td>
<td>589</td>
<td>372</td>
<td>2.0</td>
<td>1.8-2.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NOS, not otherwise specified from cardiovascular deaths. NA, not applicable. Hazard ratio with 95% confidence interval. P-value <0.05 considered statistical significant.
Table 8 Underlying and contributing cardiovascular causes of death according to ICD-10 diagnosis in patients without comorbidities at the time of AF diagnosis and matched controls

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>AF (N=9,519) Deaths</th>
<th>(%)</th>
<th>Controls (N=12,468) Deaths</th>
<th>HR</th>
<th>CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease I20-I25</td>
<td>256</td>
<td>43.4</td>
<td>195</td>
<td>1.7</td>
<td>1.4-2.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic ischemic heart disease I25</td>
<td>164</td>
<td>27.8</td>
<td>116</td>
<td>1.8</td>
<td>1.4-2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Myocardial infarction I21-I23</td>
<td>125</td>
<td>21.2</td>
<td>126</td>
<td>1.3</td>
<td>1.0-1.6</td>
<td>0.066</td>
</tr>
<tr>
<td>Ischemic cardiac disease I20, I24</td>
<td>15</td>
<td>2.5</td>
<td>8</td>
<td>2.4</td>
<td>1.0-5.6</td>
<td>0.050</td>
</tr>
<tr>
<td>Atrial fibrillation I48</td>
<td>215</td>
<td>36.5</td>
<td>5</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Heart failure 150</td>
<td>195</td>
<td>33.1</td>
<td>84</td>
<td>2.9</td>
<td>2.2-3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebral infarction or stroke 163-164</td>
<td>142</td>
<td>24.1</td>
<td>48</td>
<td>3.7</td>
<td>2.7-5.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac arrest 146.1, 9</td>
<td>100</td>
<td>17.0</td>
<td>39</td>
<td>3.2</td>
<td>2.2-4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atherosclerosis 170</td>
<td>98</td>
<td>16.6</td>
<td>75</td>
<td>1.6</td>
<td>1.2-2.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension 110-115</td>
<td>83</td>
<td>14.1</td>
<td>44</td>
<td>2.4</td>
<td>1.7-3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebrovascular disease 167, 169</td>
<td>65</td>
<td>11.0</td>
<td>41</td>
<td>2.0</td>
<td>1.4-3.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebral hemorrhage 160-162</td>
<td>36</td>
<td>6.1</td>
<td>42</td>
<td>1.1</td>
<td>0.7-1.7</td>
<td>0.748</td>
</tr>
<tr>
<td>NOS</td>
<td>26</td>
<td>4.4</td>
<td>11</td>
<td>3.0</td>
<td>1.5-6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Valve disorders 134-137</td>
<td>19</td>
<td>3.2</td>
<td>12</td>
<td>2.0</td>
<td>1.0-4.1</td>
<td>0.064</td>
</tr>
<tr>
<td>Aneurysm or dissection 171</td>
<td>13</td>
<td>2.2</td>
<td>23</td>
<td>0.7</td>
<td>0.4-1.4</td>
<td>0.321</td>
</tr>
<tr>
<td>Cardiomyopathia 142</td>
<td>11</td>
<td>1.9</td>
<td>6</td>
<td>2.4</td>
<td>0.9-2.0</td>
<td>0.088</td>
</tr>
<tr>
<td>Pulmonary embolism 126</td>
<td>9</td>
<td>1.5</td>
<td>13</td>
<td>0.9</td>
<td>0.4-6.4</td>
<td>0.750</td>
</tr>
</tbody>
</table>

All cardiovascular causes of deaths 1,316 693
Cardiovascular deaths 589 372 2.0 1.8-2.3 <0.001

NOS, not otherwise specified from cardiovascular deaths. NA, not applicable. Hazard ratio with 95% confidence interval. P-value <0.05 considered statistical significant.


5.4 Study IV

Outcomes of cerebral infarction and cerebral haemorrhage in AF patients on warfarin versus no warfarin with respect to CHA2DS2-VASc, sex and age categories.

Patients ≥65 years receiving warfarin had a significantly lower risk of cerebral infarction and stroke compared to patients not receiving warfarin (Table 9). Also, warfarin therapy was associated with significantly lower incidence of cerebral infarct in patients ≤65 years with at least two of the risk factors hypertension, diabetes mellitus, heart failure, or vascular disease. Risk of cerebral haemorrhage was significantly higher in males <65 years with no other disease included in the CHA2DS2-VASc score receiving warfarin therapy than in those without warfarin (Table 10). In other risk categories, no difference was seen in cerebral haemorrhage in patients with or without warfarin.
Table 9 Hazard ratio of cerebral infarction and stroke stratified by sex, age and CHA2DS2-VASc score related to time-varying warfarin exposure

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>No warfarin</th>
<th>1-48 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>events</td>
</tr>
<tr>
<td><strong>Men</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 426</td>
<td>19</td>
</tr>
<tr>
<td>1</td>
<td>1 141</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>654</td>
<td>11</td>
</tr>
<tr>
<td>≥3</td>
<td>440</td>
<td>27</td>
</tr>
<tr>
<td>65-74 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 004</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>1 247</td>
<td>25</td>
</tr>
<tr>
<td>≥3</td>
<td>1 822</td>
<td>98</td>
</tr>
<tr>
<td>75-85 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>795</td>
<td>25</td>
</tr>
<tr>
<td>≥3</td>
<td>3 550</td>
<td>239</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>538</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>403</td>
<td>15</td>
</tr>
<tr>
<td>≥3</td>
<td>382</td>
<td>14</td>
</tr>
<tr>
<td>65-74 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>821</td>
<td>13</td>
</tr>
<tr>
<td>≥3</td>
<td>1 948</td>
<td>98</td>
</tr>
<tr>
<td>75-85 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>5 096</td>
<td>315</td>
</tr>
</tbody>
</table>

N, numbers; y, years of age.

Hazard ratio with 95% confidence interval. HR lower than 1 indicates protective effect of warfarin.
Table 10 Hazard ratio of cerebral haemorrhage stratified by sex, age and CHA2DS2-VASc score related to time-varying warfarin exposure

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n events</td>
<td>n events</td>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 436</td>
<td>10</td>
<td>2 890</td>
<td>4</td>
<td>4.60 (1.40-15.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 151</td>
<td>12</td>
<td>1 228</td>
<td>9</td>
<td>1.53 (0.62-3.78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>672</td>
<td>5</td>
<td>695</td>
<td>3</td>
<td>1.64 (0.39-6.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>472</td>
<td>8</td>
<td>443</td>
<td>6</td>
<td>0.98 (0.33-2.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1 020</td>
<td>11</td>
<td>1 240</td>
<td>11</td>
<td>1.08 (0.46-2.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 266</td>
<td>16</td>
<td>1 300</td>
<td>13</td>
<td>0.99 (0.47-2.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>1 874</td>
<td>23</td>
<td>2 062</td>
<td>24</td>
<td>0.83 (0.46-1.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-85 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>810</td>
<td>13</td>
<td>1 514</td>
<td>24</td>
<td>0.77 (0.38-1.55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>3 633</td>
<td>58</td>
<td>6 046</td>
<td>94</td>
<td>0.87 (0.62-1.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>546</td>
<td>4</td>
<td>1 435</td>
<td>4</td>
<td>2.63 (0.64-10.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>410</td>
<td>2</td>
<td>589</td>
<td>4</td>
<td>0.64 (0.12-3.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>398</td>
<td>6</td>
<td>402</td>
<td>7</td>
<td>1.00 (0.31-3.22)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>847</td>
<td>5</td>
<td>1 182</td>
<td>5</td>
<td>1.31 (0.37-4.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>2 016</td>
<td>20</td>
<td>2 039</td>
<td>16</td>
<td>1.28 (0.65-2.52)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75-85 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>5 254</td>
<td>54</td>
<td>8 777</td>
<td>95</td>
<td>0.89 (0.63-1.27)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

N, numbers; y, years of age.
Hazard ratio with 95% confidence interval. HR lower than 1 indicates protective effect of warfarin.
6. Discussion

6.1 Main findings
Firstly, this thesis showed that AF was an independent risk factor of all-cause mortality in patients with incident AF and the concomitant diseases that contributed most were found outside the thromboembolic risk score. Furthermore, causes of death in patients with AF as the sole diagnosis at inclusion time were cerebral infarction, heart failure and myocardial infarction when compared to controls. Additionally, associations of mortality were seen for chronic ischemic heart diseases, atherosclerosis, cardiac arrest and hypertension. Another finding was that absolute risk for mortality was higher in males with AF compared to females with AF. However, HR in patients with AF, as compared to controls, was higher in females than in males. Finally, warfarin treatment showed a benefit in reducing cerebral infarction in patients with AF ≥65 years, even if the CHA2DS2-VASc score was 1 point. AF patients with 1 point due to other risk factors than age showed no benefit from warfarin treatment. Males with ≥2 points and females with ≥3 points had a positive effect from warfarin and in patients with 0 points there was an increased risk for intracerebral bleeding.

6.2 Methodological considerations
The studies in this thesis are based on Swedish registers which have nationwide coverage. The personal identification number allows an individual to be tracked in different registers and enables long term follow up. The Swedish National In-patient Register offers almost complete coverage of hospital diagnoses, high validity, and the register is recommended by the National Board of Health and Welfare for use in epidemiological studies. However, diagnoses and causes of death might be inaccurate. Also, subjects only examined and treated in primary care are not included in the in-hospital register.

Based on the results from observational studies, causality cannot be inferred. Observational studies are used to generate new hypotheses and to search for associations for outcomes or treatments where results from randomised controlled trials (RCTs) are lacking. In RCTs, subjects are often younger and healthier and there might be a run-in period which can underestimate side effects. Observational studies allow the analysis of large data sets and to examine populations not studied in RCTs, as in
Study IV, where AF patients with 1 point from the CHA\textsubscript{2}DS\textsubscript{2}-VASc score were separated into different strata and then analysed. If differences in outcomes are found in observational studies, a natural next step would be to conduct a RCT, or if this is unrealistic, to verify findings in observational studies in other cohorts.

Instead of modelling time to an event as an outcome with Cox proportional hazard regression, an alternative could have been to use Poisson regression in which follow-up time is classified into bands and events per time unit called rates are used as the outcome.\textsuperscript{66} Poisson regression gives relative rates as association measures, which is very similar to hazard ratios under the assumption of proportional hazard in Cox regression and piecewise constant rate in Poisson regression. If there are non-proportional assumptions in a Cox regression, this can be solved by splitting the time periods to reach proportional assumption, as we did in study I. Cox regression is a common model and well known in medical research and was applied in this thesis.

An alternative matching procedure with propensity score could have been possible.\textsuperscript{67} The propensity score is a calculated probability for exposure or treatment intervention assignment conditional on observed baseline characteristics.\textsuperscript{68} This score could have been used to match AF exposed to unexposed (Studies I-III) and warfarin with non-warfarin treated AF patients (Study IV). However, if comorbidities or other predictors are absent, as far as we know, as in Studies II and III, the propensity score matching would not add any further information. In Study I, it might have been conceivable with a propensity score matching since there were differences in baseline characteristics of comorbidities between patients and controls. Whether this had any effect on outcome is unknown but the current matching on age, sex and time for incident AF are considered appropriately and all statistical evaluation was performed either by adjusting or stratifying for the matching variables. The propensity score matching is used increasingly frequently in medical research, but adjusting for confounding by ordinary regression technique appears to give similar results.\textsuperscript{69,70}

A retrospective study using national registers has strengths and limitations. The strengths include the large study population with matched controls and the nationwide coverage with almost complete follow-up. In contrast, the limitations are the internal validity, primarily confounding factors and detection bias.
External validity

Generalisability
Generalisability represents the level of confidence in extending the findings in a studied group to a larger population. These studies were based on national registers in Sweden and might not be applicable worldwide. In Asia, higher incidence rates of stroke are seen compared to Europe in individuals with the same CHA2DS2-VASc score.\textsuperscript{71} No primary care or outpatient register was available for our research, and all diagnoses stem from the Swedish In-hospital Register, which may imply that the patients included had more severe disease. However, complete national coverage and few losses to follow-up increases generalisability. The various types of AF: paroxysmal, persistent or permanent, might have influenced the results. Moreover, atrial flutter was included since it often coexists in patients with AF and it is likely that the incident AF has progressed during the 14 years of follow-up from paroxysmal or atrial flutter to a permanent AF.

Internal validity

Confounding Factors
Confounding occurs when unmeasured differences exist between an exposed and unexposed group.\textsuperscript{72} This might lead to the assumption of associations that do not exist or to overlooking valid associations. The effects of confounding factors can be reduced by matching, stratification, and statistical adjustments.

Confounding by indication is an inability to compensate for differences in patient characteristics between groups when an outcome is measured. Confounding by indication is likely in Study IV, where AF patients with warfarin treatment were compared with those without warfarin. The prescription of drugs may be influenced by factors other than known data from the register as different degree of diseases, biological age and drug abuse.

Randomising the patients, as in a prospective study, was not possible in this research, and matching was conducted to make the studied groups as comparable as possible. All patients were matched to controls with respect to sex, age, and year of diagnosis of AF in Studies I-III, and according to the CHA2DS2-VASc score in Study IV. To further reduce the effect of confounding, the study population was stratified and analysed into sex and age groups, and the results were calculated for each category.
In Study I, adjustment was made for multiple concomitant diseases, and, in Study IV, for neoplasm, chronic obstructive pulmonary disease, chronic renal failure, and education. In Studies II and III, adjustment was made only for age at time of diagnosis, since AF was the sole diagnosis in this population.

**Selection bias**
Selection bias was probably a minor issue in these studies. Inclusion of patients and controls was based on registers and not on informed consent or patient acceptance. There was no difference in the tracking of patients and controls, since the national registers are more than 99% complete. Participants who emigrated were excluded from the analysis, but the number of these cases was low and did not differ between patients and controls.

**Detection bias, Misclassification**
Detection bias may have occurred in Studies I-III in which patients with AF may have been more extensively examined than controls without AF. In Study IV, all participants had AF, but those taking warfarin were regularly monitored, which involved visits to medical care units and a higher likelihood of detecting concomitant disease, potentially leading to an overestimation of some associations. In Study III, in patients whose cause of death was cancer, AF patients showed almost lower mortality than patients without AF. This might have been an effect of frequent medical examinations in cancer patients and detection of AF in an early stage which led to anticoagulant medication and a decrease of cardiovascular complications as cerebral infarction. For the outcomes of cerebral infarction, myocardial infarction, and cerebral bleeding, detection bias would be a minor problem, since these diagnoses lead to hospital care rather than solely primary care in both AF subjects and controls.

The sensitivity of the diagnosis of AF in the National In-patient Register is high, however, some controls could have been misclassified due to undiagnosed AF. This was obvious in Study III, in which the Cause of Death Register identified AF in two of 207 males and in two of 165 females identified as non-AF in the National In-patient Register. These subjects had been managed only in outpatient care. Undiagnosed or unreported AF may have led to overestimation of the risk for outcomes in controls.
Random error
Risk of random error decreases with study population size. Study I included a large population, and the confidence intervals were narrow. The populations in Studies II, III, and IV were divided into subgroups with fewer subjects, resulting in wider confidence intervals and a higher risk that results may have been affected by chance or random error. Studies II and III, investigating patients with AF as the sole diagnosis at time of inclusion, with matched controls, included, to the best of my knowledge, the largest cohort of such patients to date and the risk of random error was lower than in previous smaller studies. Study IV, which only included patients with AF, also comprised a large cohort.

6.3 Causes of, and contributors to, mortality in patients with AF
Research has shown AF to be an independent risk factor for mortality, as was confirmed in Study I. However, a causal relationship or association of AF with mortality has been questioned. For AF patients, current guidelines suggest that diagnoses associated with higher risk of death are stroke, sudden cardiac death, and progressive heart failure. Those studies examined AF patients, but did not compare outcomes to those of AF-free controls. This study compared the rates of death from various causes in AF patients to those of the controls, and found cerebral infarct to have the highest HR as an underlying cause in AF subjects, while heart failure was the most frequent contributing cause. Chronic ischemic heart disease as an underlying cause of death, or an underlying plus contributing cause of death, showed a significantly higher association with mortality. Also, cardiac arrest as a contributing factor in AF patients compared to controls showed a significantly higher association with mortality.

6.3.1 Cerebral infarction (I63-I64)
The pathophysiology of thrombus development in left auricle of patients with AF and the increased risk of embolus are well-known. The majority of cerebral infarction in patients with AF can be prevented by anticoagulation therapy, which reduces the risk of embolus by about 66% and of mortality by about 25%. Cerebral infarction has, in former studies, been shown as a cause of death in 6% to 10.9% of AF patients. This study showed a mortality rate of 13.1% and the highest hazard ratio of the considered conditions with almost a tripled risk compared to controls, which confirms former studies and suggests cerebral infarct as the underlying cause of death having highest impact in patients with AF.
Cerebrovascular disease (I67, I69) was associated with a doubled risk of death. This condition may include residual effects of cerebral infarction (I69.3), one year or longer post-onset. Thus, data of cerebrovascular disease might underestimate the rate of cerebral infarction (I63-I64) as a contribution to death.

6.3.2 Heart failure (I50)
AF may lead to heart failure due to impairment of atrial systole which decreases left ventricle filling and cardiac output up to 25%. In addition, rapid and irregular ventricular conduction can lead to tachycardia-induced heart failure. In earlier studies, reports of progressive heart failure as underlying cause range from 15-29.2% of deaths. However, the definition of heart failure used in these studies was broad, and prescribed medication, for example beta blockers or diuretics, might have been sufficient to meet the criteria. Also, ischemic heart disease as a cause to heart failure or as a cause of death was not taken into account.

Study III showed heart failure as the underlying cause of death in 4.7% of patients with AF, similar to its prevalence in controls. However, it is recommended that heart failure not should be reported as an underlying cause of death on a death certificate, and instead should the aetiology of the heart failure be listed as the underlying cause.

Heart failure was involved in 33.1% of deaths as a contributing cause, and was associated with a tripled mortality risk in AF patients compared to controls. These findings are in agreement with Wattigney from 2002, who examined underlying and contributing causes of death in patients with AF, and reported heart failure to be involved in 32%. The most common aetiology of heart failure is chronic ischemic heart disease. In AF patients, 47% showed the combination of heart failure and chronic ischemic heart disease, comparable to earlier studies showing 51%. This suggests that approximately half of all deaths with heart failure as a contributing cause occur in the absence of ischemic heart disease, increasing the probability of AF-induced heart failure as a cause of death.

6.3.3 Ischemic heart disease (I20-I25), Atherosclerosis (I70)
Ischemic heart disease includes myocardial infarction (I21-I23), chronic ischemic disease (I25), and ischemic cardiac disease (I20, I24). Chronic ischemic heart disease was doubled and significantly higher as an underlying cause of death as well as in combination with contributing cause in subjects with AF compared to controls. Myocardial infarction was signifi-
cantly more prevalent as an underlying cause of death [HR 1.3 (CI 95% 1.0-1.7) P = 0.046], but not as an underlying and contributing cause [HR 1.3 (CI 95% 1.0-1.6) P = 0.066]. Ischemic cardiac disease demonstrated minimal impact on mortality, with few cases as an underlying cause of death in either AF patients or controls.

A meta-analysis of patients with AF found an annual risk of myocardial infarction of 0.4-2.5%, with higher rates when comorbidities were present. Atrial fibrillation may lead to myocardial infarction via an embolus from the left auricle entering the coronary arteries or by induction of tachycardia-induced ischemia. Our results indicated that myocardial infarction is a more common underlying cause of death in AF patients than in non-AF.

Systemic inflammation is associated with development of atherosclerosis and AF. Studies reported ischemic heart disease to be an underlying cause of death in 21.2 and 27.2% of patients with AF. This study found chronic ischemic heart disease to be an underlying cause of death in 18.3% of subjects, significantly more common in AF patients compared to controls. Systemic atherosclerosis affecting coronary arteries leads to chronic ischemic heart disease and promotes structural remodelling and fibrosis and an increased risk of worsening AF or developing other comorbidities. Whether AF may promote atheromatous lesions is not clear; therefore, atherosclerosis and chronic ischemic heart disease are suggested to be associated with the increased risk of death and not direct causes.

6.3.4 Cardiac arrest/Sudden cardiac death (I46.1, 9 and I49.0, 9)

Studies have shown 22.3% and 28% of deaths of patients with AF to be sudden cardiac death (Table 1). In these studies, sudden cardiac death was considered in cases of unexpected death within one hour of onset of cardiac symptoms, cardiac-related death during sleep, or cardiac-related death within 24 h of last being seen alive. Ischemic heart disease with myocardial infarction was not treated as a separate cause of death and was included in sudden cardiac death. A recent study of AF patients using similar criteria showed 31.7% of deaths to be sudden cardiac death. Notably, 72.9% of these patients exhibited congestive heart failure and 41.8% coronary heart disease in baseline characteristics, suggesting ischemia or progressive heart failure as a potential aetiology of the underlying cause of death.

Studies relying on death certificates as the source of cause of death have reported cardiac arrest as underlying cause in 3.3% and as underlying or
contributing cause of death in 15.6%, similar to this findings of 1.2% as an underlying cause and 17.0% as an underlying or contributing cause.29,30

The pathophysiological mechanisms underlying AF association with sudden cardiac death are unclear. It has been suggested that AF produces a pro-arrhythmic effect via reduction in ventricular refractoriness and electrical remodelling in ventricular myocytes, resulting in impaired calcium handling of the ventricle during tachycardia.83-85 Alternatively, AF may be a marker of cardiac arrest by other cardiovascular morbidity as heart failure or the use of antiarrhythmic drugs.86 In this study, patients with AF had no other clinical diagnoses at inclusion, and cardiac arrest as an underlying or contributing cause of death was significantly higher, and tripled compared to non-AF controls. Of the patients with cardiac arrest reported as an underlying or contributing cause of death, 56% had chronic ischemic heart disease or myocardial infarction as co-morbidity, which may have been the actual underlying cause of death. This means that the remaining 44% did not have ischemic heart disease at death, and cardiac arrest via electrical malfunction might have been the underlying cause of death. Due to differences in methods and definitions used in research, as well as to uncertain pathophysiology, the influence of sudden cardiac arrest as a cause of death in AF patients is still unclear.

6.3.5 Hypertension (I10-I15)
Hypertension as a sole diagnosis is a risk factor for cardiovascular morbidity and mortality.87-89 It is the most commonly associated condition, variously reported at 49% and 90% of AF patients exhibiting hypertension as concomitant disease.12,13 Hypertension may induce AF via increased sympathetic activity, renin-angiotensin-aldosterone system (RAAS) activation, and afterload, leading to left ventricular hypertrophy that increases the risk of AF.13, 90, 91 Studies have shown regression of left ventricular hypertrophy and a lower incidence of AF in patients treated with RAAS blockade.92-94

Study III included only patients with AF as sole hospital diagnosis, but may have underestimated hypertension in those who were managed out of hospital care. We found 2.7% of AF subjects to present hypertension as an underlying cause of death and in 14.1% of patients as an underlying or contributing cause of death, and both were significantly higher compared to controls. There is no pathophysiological evidence that AF, as a sole condition, induces hypertension, and these findings contribute to the hy-
hypothesis that hypertension shows an association with mortality in patients with AF.

6.3.6 Pulmonary embolism (I26), Cerebral haemorrhage (I60-I62), Cardiomyopathy (I42), Valve disorders (I34-I37), and Aneurysm or dissection (I71)

These diagnoses showed no increased risk as underlying or underlying and contributing causes of death in AF patients compared to controls. It has been suggested that thrombosis could develop in the right auricle, leading to pulmonary embolism.95 This study did not find higher incidence of pulmonary embolism in patients with AF compared to controls. Cerebral haemorrhage as a cause of death occurred at a similar rate in AF patients and controls. This is in agreement with studies investigating cerebral haemorrhage in AF with and without anticoagulation therapy.96 Cardiomyopathy as a cause of death has been reported to be associated with AF.97 This investigation did not bear this out, although the condition may have been reported as heart failure. Valve disorders, aneurysms, and dissection had low rates and showed no significant differences in risk of death in AF patients and controls.

6.3.7 Non-cardiovascular disease

When underlying cause of death was examined in AF patients who had no co-morbidities at the time of diagnosis, only cardiovascular disease demonstrated an increased risk. This does not exclude an association of other disease with mortality in patients with AF. For example, diabetes mellitus, chronic renal failure, and chronic obstructive pulmonary disease were shown in Study I, as well as by other researchers, to be associated with mortality in patients with AF.98-100

Results of this investigation support an increased risk of death caused by cerebral infarction, heart failure, and myocardial infarction in AF subjects compared to those without AF due to a known pathophysiology. The links among chronic ischemic heart disease, myocardial infarction, and atherosclerosis are atheromatous and showed an association to mortality in AF patients compared to controls. Cardiac arrest may be associated with acute myocardial infarction, and differences in diagnostic criteria of cardiac arrest may influence whether it is considered a cause of death through electrical malfunction alone or secondary to ischemic heart disease or heart failure.
6.4 Atrial fibrillation, sex, and mortality

In all age categories, female subjects with AF and comorbidities showed increased HR of mortality compared to males. However, absolute risk was higher for AF-males compared to AF-females in the same age category. Mortality rates of controls relative to patients with AF were lower. Hence, for a given age category, AF-males will have the highest rate of death, followed by AF-females, male controls, and finally female controls. This pattern is similar in other conditions, for example diabetes mellitus and heart failure: mortality, at a given age, will first affect males with disease, with longest life in females without disease.\(^1\)\(^2\) This is in agreement with the difference in life expectancy for males and females in the general population.\(^3\)\(^4\) Renoux showed in 2017 similar results of a lower absolute risk of mortality for females with AF compared to males [HR 0.81 (0.80-0.83)].\(^5\)

When underlying cause of death was studied in the groups without comorbidities at the time of AF diagnosis, death from cerebral infarction or stroke and chronic ischemic heart disease was significantly higher in both males and females with AF than in controls. In males, hypertension as a cause of death was significantly higher than in controls, while, in females with AF, atherosclerosis and cerebrovascular disease were significantly more frequent causes of death compared to controls. We found few cases of hypertension and atherosclerosis, and their impact on mortality was low. Rates of cerebrovascular disease (I 67, I 69) were slightly higher, but this might reflect complexity of diagnosis because of its interconnections with cerebral infarction or stroke (I 63, I 64). The conditions having the greatest impact on mortality in patients with AF as the underlying cause were cerebral infarction/stroke and chronic ischemic heart disease in both males and females.

6.5 Anticoagulation and AF

In this work, results in patients <65 years were reinforced current treatment guidelines, and showed a benefit of anticoagulation treatment in females with ≥3 points and males with ≥2 points in the CHA2DS2-VASc score. Patients ≥65 years exhibited a significantly lower rate of cerebral infarction with treatment versus no treatment, a result that may contribute to knowledge of risk factors of one point with most influence to be age 65-74 years.

Anticoagulation therapy guidelines are based on studies of the annual rate of cerebral infarction in patients without treatment, which have re-
ported rates ranging from 0.2% to 6.6% and conditions that add one point to the CHA$_2$DS$_2$-VASc score have not been independently analysed, study inclusion criteria have differed, and target outcomes have varied. In this work, the outcome was cerebral infarction and stroke and did not include transient ischemic attacks and systemic or pulmonary embolus. A quarantine period of 30 days post-diagnosis was used so that necessary diagnostics, for example echocardiography or newly discovered diabetes mellitus, were completed to determine the CHA$_2$DS$_2$-VASc score. AF was incident cases, and no subject used warfarin prior to the diagnosis.

Age 65-74 and ≥75 years has been determined to be stronger predictors of cerebral infarction than in diseases, providing one and two points in the CHA$_2$DS$_2$-VASc score. Therefore, the age categories of the CHA$_2$DS$_2$-VASc scale (<65, 65-74, and ≥75 years) were compared in this work. Female sex was added to the CHA$_2$DS$_2$-VASc score in 2010 and gives one point as a single risk factor. However, current guidelines state it has no added effect on cerebral infarction when compared with males. Our findings are in agreement with current recommendations; no differences were seen between sexes in risk for cerebral infarction.

In AF patients <65 years, no positive effect of warfarin on rate of cerebral infarction was observed in males with 0 or 1 point or in females with 1 or 2 points. The lack of evidence of benefit suggests that these categories should not be treated with warfarin.

Cerebral haemorrhage was more common in men <65 years with 0 points and warfarin treatment compared with no warfarin. In all other risk categories, the risk of cerebral haemorrhage was equal between patients treated or not treated with warfarin and in line with a recent study that indicated that patients with equal risk from the CHA$_2$DS$_2$-VASc score, irrespective of warfarin, have similar risks for cerebral haemorrhage. However, novel oral anticoagulants (NOAC) have shown lower risk of cerebral haemorrhage than warfarin and are equated in guidelines. This study investigated only warfarin since NOAC were not available at that time, but these results would be transferable to NOAC and patients with AF.

This work shows that, of factors providing one point from the CHA$_2$DS$_2$-VASc score, age category 65-74 years exhibited the highest risk for cerebral infarction and stroke. We investigated warfarin, and similar research including NOAC is needed. However, results of these studies suggest revision of the anticoagulation treatment regimen in patients with AF.
7. Conclusions

This thesis showed a benefit of treatment with warfarin in patients with AF ≥65 years in reducing cerebral infarction, independent of the CHA₂DS₂-VASc score. Patients <65 years having at least two risk factors from disease, as well as males with a CHA₂DS₂-VASc score of 2 and females with a score of 3, will benefit from warfarin treatment as recommended in current guidelines.

This research confirmed cerebral infarction, heart failure, and myocardial infarction as causes of death in patients with AF. Chronic ischemic heart disease, atherosclerosis, cardiac arrest, and hypertension are considered contributing factors to higher mortality in AF patients than in those without AF, due to the lack of evidence of a pathophysiological explanation.

The HR for mortality in patients with AF relative to controls was higher in females than in males. However, the absolute risks were higher in males. The source of this disparity is essentially that female controls, free of AF, had the lowest absolute risk of mortality, increasing the HR of AF females.
8. Clinical implications and future considerations

Every year, about 4000 individuals in Sweden are affected by cerebral infarction caused by AF where adequate anticoagulant treatment was not administered associated with annual costs of 3000 million SEK. One reason for undertreatment is uncertainties of how patients with AF and low risk for cerebral infarction should be treated. This study observed a possible benefit of warfarin treatment in patients ≥65 years, with or without other risk factors. These findings suggest a new algorithm for anticoagulant treatment for patients with AF, the AF 65² score (Figure 3).

Figure 3 AF 65² - Recommendations for anticoagulantia in patients with AF

- Diagnosis of atrial fibrillation
- Age ≥65 years
- At least two of following diagnoses:
  - Hypertension
  - Chronic heart failure
  - Diabetes Mellitus
  - Vascular disease
- Revaluation at least yearly
- or
- at the time of an addition of a risk factor from above
This study was retrospective and does not constitute a basis for causality and a study with NOAC is needed. Effect of age was analysed according the CHA₂DS₂-VASc score categories, <65, 65-74 and ≥75 years. In future research, age should be studied as a continuous variable in order to determine a potential cut-off for recommendation of treatment.

CHA₂DS₂-VASc is the recommended score but female sex (Sc) is omitted in the most recent guidelines since it does not increase risk of cerebral infarction adequately to justify anticoagulation when comparing to men.¹⁰ This newer recommendation was confirmed in this thesis and lead to the clinical conclusion that using a CHA₂DS₂-VA score is reasonable. In the future it may be relevant to evaluate different grades of heart failure and vascular disease by biomarkers such as troponin and NT-pro BNP for treatment guidance. This strategy has been presented in the ABC-score and may better predict patients with low risk for cerebral infarction.¹¹⁶

Anti-arrhythmic drugs with the purpose to secure sinus rhythm have not showed any reduction in mortality in AF patients when compared to a rate control strategy.¹⁰ AF ablation studies have showed varying results with respect to a potential reduction in mortality and two randomized controlled studies, CABANA and EAST have to be completed to bring more clarity in the area.¹¹⁷-¹²² In study III, cerebral infarction and heart failure were the diagnoses with the highest associations to death in AF patients. These causes of deaths correspond to those in ablation studies that showed lower mortality and point to targets for therapy to reduce mortality in the future. Findings in this thesis lead to a suggestion of causes, associations or no associations to mortality for AF patients (Table 11).
Table 11 AF and cause of death or association with mortality

<table>
<thead>
<tr>
<th>Cause</th>
<th>ICD-10 code</th>
</tr>
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<tbody>
<tr>
<td>Cerebral infarction</td>
<td>I63-I64</td>
</tr>
<tr>
<td>Heart failure</td>
<td>I50</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>I21-I23</td>
</tr>
<tr>
<td><strong>Association</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic ischemic heart disease</td>
<td>I25</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>I46.1, 9; I49.0, 9</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>I70</td>
</tr>
<tr>
<td>Hypertension</td>
<td>I10-I15</td>
</tr>
<tr>
<td><strong>No association</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>I26</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>I42</td>
</tr>
<tr>
<td>Aneurysm or dissection</td>
<td>I71</td>
</tr>
<tr>
<td>Cerebral haemorrhage</td>
<td>I60-I62</td>
</tr>
<tr>
<td>Valve disorders</td>
<td>I34-I37</td>
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However, with the current knowledge, anticoagulation is the only therapy which has been shown to reduce mortality in AF patients and rate control is equal to rhythm control strategy.\textsuperscript{10}

In this thesis, warfarin treatment was compared with no warfarin treatment in different risk categories. This means that some patients with AF were under treated and others over treated with warfarin and this is a known problem. About 60\% of patients between 80 and 89 years are not treated with anticoagulation and in those with a CHA\textsubscript{2}DS\textsubscript{2}-VASc score of 0 points about 25\% are treated.\textsuperscript{1, 123} If this depends on lack of knowledge at prescribing doctor or patient unwillingness are unclear and since 2013 anticoagulation treatment has improved in patients at risk but there is still room for improvement.\textsuperscript{115}

In the future, a great challenge might be patients with asymptomatic and undiagnosed AF. Screening of 75- and 76-year-olds individuals have shown that 3.0\%-5.2\% have undiagnosed AF implying that 30\% of all patients with AF in this age category can only be diagnosed with screening measures.\textsuperscript{2, 124} However, patients with asymptomatic AF are healthier than symptomatic patients and there is uncertainty on whether anticoagulation lead to a decrease in cerebral infarctions in this group of patients. Therefore, no evidence exists for health benefits and screening is not recommended.\textsuperscript{125} The StrokeStop study investigating this type of patients is ongoing and results are probably expected sometime during 2018.\textsuperscript{124}

AF is a disease that affect many individuals and much work has been done and more is needed in order to prevent and prohibit other diseases and death caused by AF.
9. Financial support

This work was supported from the Research Committee of Örebro University Hospital (OLL 2012-265231, OLL 2017-768021), AstraZeneca R&D Mölndal and the Örebro Heart Foundation.
10. Acknowledgements

Professor Ole Frøbert, my principal supervisor who have guided me through this work and encouraged me to watch the compass and to keep following the direction. Recurrent deadlines and rapid answers by email with seriousness have been a relaxing combination with the morning meetings while citing Johan Glans. You have put Örebro on the map for cardiovascular research. Thank you for being a part of your team.

Dritan Poçi, my co-supervisor is always positive and has an ability to move mountains. The energetic and tireless side of you is obvious when your emails are constantly sent at 01.35 AM. You see trouble as something that does not exist. Thank you for your invitation at the start of this work.

Nils Edvardsson, who has an enviable experience in this field and is always helpful with my questions.

Karin M Henriksson who initiated this project a decade ago and for all your support.

Anders Magnuson for important help explaining the statistical parts and for the enjoyable lunches talking about tennis.

Inge-Liss Bryngelsson who always encouraged me to move on. You have structured my knowledge of data and, during many phone-calls, we have discussed everything between life and death. I hope we will keep on discussing.

Stella Cizinsky, for your support and all your help through the years. Peter Lindell, Mentor 2, who have inspired me in the clinical work and whose knowledge in different areas has been enjoyable and educational to listen to. Espen Fengsrud, roommate and closest colleague during these years and thank you for all discussions about most things, especially cross-country skiing. Anna Björkenheim, it has been a pleasure to work with you. Usama Dhaha, for your kindness in letting me live in your apartment.
Anders Englund, one reason moving to Örebro in 2005. Peter Linde for bringing happiness to seriousness. Henrik Almroth for being a close colleague and friend.

Thanks to Lars Forsell, Marianne Werling and Annelie Berg for the easy and good cooperation with you about the technical aspects. Karin Johansson, Margit Qvist, Lena Svedberg and Lena Buske for many years of work with studies and patients. Lena Ikonen and Elisabeth Andersson for bringing order in many areas of the arrhythmia unit.

Colleagues and staff at the Department of Cardiology. 13 good years!

Mentor 1, Ulf Hurtig and Per Lundberg who was a prospect from the time when I was a hang-around. A clear clinical view of Cardiology, what is written and what is not? We had recurrent scientific sessions and deep studies of “Pistvakt”, which never will be forgotten.

Kurt Pettersson for all our discussions during the years in the neighborhood and in other places.

We have been friends for many years, Andreas Johansson and Martin Gunnarsson, and I am looking forward of many years in the future. My brother-in-law Per, for many entertaining meetings and discussions. As a son-in-law to Siw, of course I have to thank you too.

Mattias and Johan, I appreciate your phone calls and contact during the years and I am proud that you are my brothers!

My parents, Lars and Mait have always been a back-up and a support to my decisions.

Finally, my family Mia and Ida. Mia, you are one-of-a-kind and I am the lucky guy. Thank you for the former years and for the years to come. Ida, you are my everything – I am speechless!
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