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Studies of Risks Associated with Atrial Fibrillation

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Tomorrow never knows

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ABSTRACT

Aim: To investigate temporal trends in the risk of mortality and stroke associated with incident atrial fibrillation (AF) in Sweden. To investigate the risk of morbidity and mortality associated with prevalent and incident AF in patients with chronic heart failure with preserved (CHF-PEF) or reduced left ventricular ejection fraction (CHF-REF) enrolled in two large randomised trials.

Methods: In Papers I and II, we utilized Swedish National Hospital Discharge Registry linked with the cause-specific death registers. The hospital discharge registry has been in operation since the 1960s and has operated on a nation-wide basis since 1987. From this source all patients discharged from a Swedish hospital with a first diagnosis of AF were collected, and data regarding age, gender and registered comorbidities were obtained and compared by 5-year periods. Paper III utilized data from the Carvedilol Or Metoprolol European Trial (COMET). Paper IV utilized data from the Candesartan in Heart failure-Assessment of Reduction in Morbidity and mortality (CHARM) programme.

Results: The incidence of ischemic strokes up to 3-years after a first diagnosis of AF was 11.6% 1987-1991 (period 1) and 9.6% 2002-2006 (period 4), corresponding to a 17.5% relative decrease, the decrease mainly occurred during 1997-2001 (period 3), with small changes before and thereafter. The incidence of hemorrhagic strokes was 1.0% period 1 and 1.3% period 4, a 37.2% relative increase. The total number of strokes thus declined during the observation period. The decline in the total stroke incidence in AF patients was higher than that seen in the rest of the Swedish population. 3-year mortality was 34% during period 1 and 26% period 4, corresponding to a 23% relative decrease in mortality during the observation period. Patients diagnosed with any of previous stroke, chronic heart failure, acute coronary syndrome and diabetes mellitus had high but declining 3-year mortality rates during the observation period, regardless of age and sex. Patients without the prespecified comorbidities had lower case-fatality, especially in younger patients, but improvements in survival were smaller. Patients with CHF and AF had an increased risk of mortality and morbidity compared to patients in sinus rhythm, regardless of LVEF at baseline. Patients with CHF-REF had the highest absolute morbidity and mortality in CHARM trial, but patients with CHF-PEF had higher relative increase in morbidity and mortality with AF. New onset AF during the follow-up was a strong predictor of mortality and morbidity in both studies, regardless of baseline LVEF.

Conclusions: Patients discharged from a Swedish hospital with a first diagnosis of atrial fibrillation had moderate decreases in stroke incidence and mortality during a 20 year observation period. Although treatment and management of AF and its associating conditions, have improved dramatically during the last 30 years, AF is still associated with an excess morbidity and mortality. Even when patients with important comorbidities are excluded from the analysis, there is a considerable mortality among patients with AF. In a prespecified analysis of two large randomized trials with CHF and AF, AF was associated with increased morbidity and mortality both when present and when occurring during study follow-up, regardless of baseline EF.

Keywords: Atrial fibrillation, stroke, ischemic, hemorrhagic, mortality, temporal trends, ejection fraction, preserved, chronic heart failure, new onset, cohort study, randomised controlled trial.

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LIST OF ORIGINAL PAPERS

This thesis is based on the following papers, identified in the text by their roman numerals:

I Olsson LG, Swedberg K, Lappas G, Stewart S, Rosengren A. Trends in stroke incidence after hospitalization for atrial fibrillation in Sweden 1987 to 2006. *Manuscript*

II Olsson LG, Swedberg K, Lappas G, Stewart S, Rosengren A. Trends in mortality after hospitalization for atrial fibrillation in Sweden 1987 to 2006. *Manuscript*

III Swedberg K, Olsson LG, Charlesworth A, et al. Prognostic relevance of atrial fibrillation in patients with chronic heart failure on long-term treatment with beta-blockers: results from COMET. *Eur Heart J 2005;26:1303-8.*

IV Olsson LG, Swedberg K, Ducharme A, et al. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the candesartan in heart failure-assessment of reduction in mortality and morbidity (CHARM) program. *J Am Coll Card 2006;47:1997-2004.*

INNEHÅLL

ABBREVIATIONS AND ACRONYMS

ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
ASA	Acetyl-Salicylic Acid
CABG	Coronary Artery Bypass Graft
CHARM	Candesartan in Heart failure-Assessment of Reduction in Morbidity and mortality
CHF	Chronic heart failure
CHF-PEF	Chronic Heart Failure with Preserved Ejection Fraction
CHF-REF	Chronic Heart Failure with Reduced Ejection Fraction
CI	Confidence Interval
CV	Cardiovascular
COMET	Carvedilol Or Metoprolol Evaluation Trial
COPD	Chronic Obstructive Pulmonary Disease
DIAMOND	Danish Investigations of Arrhythmia and Mortality ON Dofetilide
DRG	Diagnosis Registration Group
ECG	Electrocardiogram
EpC	Epidemiologiskt Centrum
ESC	European Society of Cardiology
ECHOS	EchoCardiography and Heart Outcome Study
HR	Hazard Ratio
ICD	International Classification of Diseases
INR	International normalised ratio
LVEF	Left Ventricular Ejection Fraction
NT-proBNP	N-aminoTerminal pro B-type natriuretic peptide
NYHA	New York Heart Association classification
OAC	Oral Anticoagulant
OR	Odd´s ratio
PCI	Percutaneous Coronary Intervention
RR	Relative risk
SCAF	Stockholm Cohort-Study of Atrial Fibrillation
SMR	Standardised Morbidity/Mortality Ratio
TIA	Transient Ischemic Attack

INTRODUCTION

"When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades; when the pulse is slender (smaller than feeble, but still perceptible, thin like a silk thread), then the impulse of life is small."
Huang Ti Nei Ching Su Wen

The sentence above is perhaps the earliest description of atrial fibrillation, by Huang Ti Nei Ching Su Wen, physician to the Yellow emperor, (by legend ruler of China 2697–2597 BC or 2696-2598 BC), in his *"The Yellow Emperor's Classic of Internal Medicine"* [1, 2]. Physicians noted the irregular heart rhythm early, and its severe consequences in most but not all patients, but the first description of atrial fibrillation (or auricular fibrillation originally) was made in the 17th century (Table 1). When non-invasive blood pressure testing (sphygmometry) became available in the early 20th century researchers noted the highly irregular pulse curves in some patients. The pattern was called pulsus irregularis, inequalis, deficiens or mitralis, the latter due to its presence in many patients with advanced mitral disease[3]. One of the early pioneers, Mackenzie, postulated from the absence of auricular activity in polygraphic measurements of jugular vein pulsations, that the right auricula was paralyzed at all times, but this view was later changed when paroxysmal episodes of this phenomenon were found, in between which normal atrial contractions could be detected. When electrocardiography became available it was clear that the auricular contraction was substituted by an undulating baseline with irregular ventricular rhythm[4]. Lewis, Mackenzie's protégé, was the first to catch this arrhythmia on an ECG sheet and described it in 1909.

Table 1. Early history

1628	William Harvey describes "fibrillation of the auricles" in animals.
1816	René Laennec invents the stethoscope
1827	Robert Adams reports the association of irregular pulses with mitral stenosis
1863	Etienne Marey publishes a pulse tracing from a "pulsus mitralis" patient
1874	Alfred Vulpian observes atrial fibrillation in dog (in vivo)
1894	Theodor Engelman reports atrial fibrillation from multiple foci in the atria
1900	Willem Einthoven invents the electrocardiograph
1909	Lewis records atrial fibrillation with the electrocardiograph

Adapted from Lip GY, Beevers DG. ABC of atrial fibrillation. History, epidemiology, and importance of atrial fibrillation. BMJ. 1995[2].

"For when fibrillation sets in there is a complete cessation of coordinate contraction; if viewed directly the auricle is seen to be in a position of diastole and at first glance it may appear to be absolutely at rest. If carefully inspected, however, its surface is seen to be the seat of great activity; constant undulations are everywhere present. The appearance is somewhat similar to the very fine tremor sometimes observed in a protruded tongue or the fibrillary movements seen in skeletal muscles in some

nervous disorders, only the activity is very much greater. In place of giving rise to a single rhythmical impulse which is conveyed to the ventricle, the auricle gives rise to exceedingly numerous irregularly spaced impulses which are conveyed along the auriculo-ventricular bundle without any semblance of rhythmicity and to which 'the ventricle responds as best it may. Hence the rise in rate and the gross irregularity of the pulse." H W Allen, 1913.

It was early associated with rheumatic heart disease (the endocarditic group) and cardiac fibrosis (the sclerotic group). Its occurrence was coupled to palpitations, heart failure and dropsy (oedema).

Allen continues, *"Prognosis depends largely on two factors: our ability to maintain the heart beat at a moderate rate and the quality of the ventricular muscle."*

Main treatments were prolonged bedrest with elevated head and cardiac glycosides, which helped to unload the ventricle by improving diuresis and lower heart rate[5]. The two most common glycosides were digitalis or strophantin. While digitalis toxicity was common, it was not seen as a great problem. Although considered as more useful in the acute setting, the more fast-acting strophantin could cause sudden death so careful dosing was necessary. Strophantin was removed from the Swedish market in 1948 because of its liver- and cardiotoxicity[6].

Atrial fibrillation was for a long time considered in the context of the underlying cardiovascular disease and not as a risk factor in itself. The first case reports of arterial embolism in rheumatic heart disease and the benefits of treatment with oral anticoagulants were presented in the 1940s[7]. Excess risk of stroke associated with atrial fibrillation was thought to be confined to these patients or to patients with intermittent fibrillation. In the late 1970s-early 1980s the first analyses of atrial fibrillation from the Framingham study were published. In these publications the increased stroke risk in patients with atrial fibrillation and ischemic or hypertensive heart disease, as well as the relationship between age, incident atrial fibrillation and excess mortality were described[8-10]. Later analyses confirmed these findings[11-13] .

Definitions

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterised by uncoordinated atrial activation with subsequent deterioration of atrial mechanical function. On the electrocardiogram (ECG), AF is characterised by the replacement of regular P-waves by rapid oscillations or fibrillatory waves that vary in amplitude, shape and timing, associated with an irregular, frequently rapid ventricular response when atrioventricular (AV) conduction is intact.

The ESC guidelines for the management of atrial fibrillation provided the following consensus statement on a simple and clinically useful definition of atrial fibrillation[14]:

1. Paroxysmal atrial fibrillation. If the arrhythmia converts spontaneously within 7 days (mostly within 24 hours).

2. Persistent atrial fibrillation. If the arrhythmia lasts longer than 7 days but is converted either by pharmacological or direct-current cardioversion.

3. Permanent atrial fibrillation. Long-lasting arrhythmia, not responding to cardioversion or where it has not been attempted.

When a patient has had more than 2 episodes, AF is called recurrent. Both paroxysmal and persistent AF can be recurrent. Further categories of AF:

- Lone AF. No universal definition exists but usually AF in the absence of any clinical or echocardiographic evidence of cardiopulmonary disease, including hypertension and diabetes and any other known precipitating cause or illness. Usually afflicts younger patients, an age cut-off <60 has been employed by some[15] but not all researchers[16, 17].

- Non-valvular AF. AF in the absence of rheumatic mitral valve disease, prosthetic heart valve or mitral valve repair.

Lifetime risk, incidence and prevalence

AF is the most common arrhythmia treated in clinical practice. It is the cause of about one third of hospitalizations for cardiac dysrhythmias. Lifetime risk has been calculated in two studies. In Framingham at age 40 there was a 26% risk for men and a 23% risk for women and when patients without prior or concurrent CHF or MI was considered, there was a 16% lifetime risk[18]. In the Rotterdam city study there was a 23.8% risk for males and 22.2% risk for females in patients 55 years old[19] to develop AF.

The incidence of AF in European and American populations is low in young patients but increases steeply with age. The age-specific incidence is higher in men than in women, with diminishing differences in older patients. Incidence rates varied between 0.1-0.6 cases/1000 patient-years incidence in patients <55 years old up to 14.4-42.7 in patients 75-84 years old and as much as 17.5-60/1000 patient years in octogenarians. In general, North American cohorts had higher incidence rates than European[19-24]. Temporal trends in European and American cohorts show marked increases in age-specific incidence during the last decades with doubled to tripled numbers of "first ever" hospitalizations for AF[24-26]. The changes seen in the Swedish hospital registry between 1987-2006 are slightly more modest, with a steady increase in all age groups, with a maximum 84% increased incidence in patients 75-84 years old (Figure 1). Men had higher AF incidence than women, but the male disadvantage diminished with age (4 times increased incidence in 35-44 year olds and 1.1 times in patients 75-84 years old, data not shown).

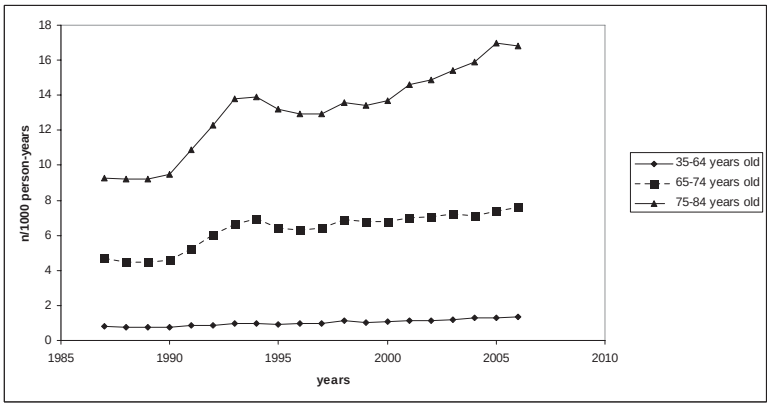

Figure 1. Incidence of hospitalizations with first AF diagnosis in Sweden 1987-2006. Data from the Swedish Hospital Discharge Registry.

In 2008 approximately 6 million Europeans and 2.3 million US citizens had an atrial fibrillation diagnosis[27]. Prevalence ranges between 1 to 2% in the general population in Europe and the US[28-30]. Prevalence increase with age and cardiovascular morbidity, age adjusted prevalence is for reasons largely unexplained higher in men than in women, but as already mentioned, lifetime risks are similar, probably because women live longer. In Europe the prevalence in patients >50 years old ranges between 1.5 and 5.5%, 5 to 15% in 80 years old and up to 18% in patients >85 years old[31]. Many AF episodes are asymptomatic and many patients do not seek care, so the true prevalence may be higher[32]. Several studies show an increased prevalence over time during the last decades, again with bigger increases in males than females[33-35]. Prevalence figures are likely to double during the next 50 years in Europe and projected prevalence figures for the US in 2050 ranges between 5.1 and 12.1 million, even figures up to 16 millions have been proposed[14, 29].

In more selected populations the prevalence varies more. In 82,565 patients discharged alive from Swedish hospitals after a first time AMI, 6275 were discharged with an AF diagnosis with 78% having AF at hospital admission[36]. In 106,780 Medicare patients age >65 discharged from hospital with an AMI, 11,510 (10.8%) had AF at baseline[37]. In patients with chronic heart failure the prevalence seems to increase with disease severity with up to 50% prevalence in NYHA IV patients[38]. The reason for the trend of increased incidence and prevalence is probably multi-factorial, with people living longer, more survivors of ischemic heart disease and chronic heart failure, more obesity and diabetes mellitus. Increased awareness of the risks associated with AF and economic incentives such as DRG coding may also play a role.

Both in Europe and in the US, an increased number of hospitalizations associated with atrial fibrillation has been reported[26, 39]. Some authors have suggested the cause of this increase is changed AF managing practices rather than increased AF morbidity[40]. In the US more deaths associated with atrial fibrillation have been noted[41].

Cost

An analysis from the UK estimated the cost of atrial fibrillation to around €350 million or 0.62% of NHS spending on medical care 1995, long-term nursing-home costs added €66 million[42]. The costs had increased to €655 million in 2000 or 0.92% of NHS health care spending. Cost for an AF admission in five European countries ranged between €1363 and €6445 and for an outpatient admission €68 to €540 with large variations regarding treatment traditions, labour and property costs[43]. In a recent analysis of costs associated with care for patients with AF during 2007 in Sweden total cost was estimated at €708 million in direct and indirect costs, with the biggest cost drivers complications (i.e. stroke or heart failure) followed by an increased number of hospital admissions[44]. These estimates are conservatively calculated, the real costs are probably higher and given the aging population, they are likely to increase in the future.

Risk factors for developing atrial fibrillation

As mentioned previously, atrial fibrillation is firmly associated with ageing, and male sex seems to confer an additional risk[27]. Hypertension and diabetes mellitus are the quantitatively most important risk factors among co-morbidities in terms of attributable risk, while patients with chronic heart failure, myocardial infarction or valvular disease may have a higher relative risk to develop AF. Several novel risk factors have emerged during the last years, many related to different stages of the above mentioned illnesses, but also related to habitus and lifestyle[27]. Acute atrial fibrillation can be caused by reversible conditions and may cease, when the precipitating causes are treated. Major risk factors are listed in Table 2. The main goal in preventing AF and/or halt its progression to a more sustained state is to prevent atrial dilatation and interstitial fibrosis which is proportional to the ease of maintaining sinus rhythm[45].

Table 2. Risk factors identified in prior studies for atrial fibrillation

Age
Male sex
Hypertension
Chronic heart failure
Valvular Heart Disease
Ischemic heart disease
Diabetes Mellitus
Hyperthyreosis

Adapted from Kannel WB, Benjamin EJ. Status of the Epidemiology of atrial fibrillation *Med Clin North Am* 2007[27]

Risks associated with atrial fibrillation

Atrial fibrillation and mortality

Atrial fibrillation is associated with an increased risk of premature death that seems to be coupled to co-morbidities and risk of stroke. In a retrospective analysis with a 25 year follow-up of 76 patients with lone AF the risk of CV morbidity and mortality was not significantly different from general population and when events occurred usually other cardiovascular morbidities had developed[15]. In more unselected populations the risk of mortality with AF present seems to remain approximately doubled after covariable adjustment[13, 46, 47]. New onset AF is a consistent predictor of mortality in patients with AMI[37, 48, 49], hypertensive heart disease[50] and heart failure regardless of ejection fraction[51-55]. Prevalent AF is a consistent predictor of excess mortality in patients with AMI[37], hypertensive heart disease[50] but not in patients with CHF[56-58].

Temporal trends in mortality associated with AF show a decline in most[26, 59, 60], but not all studies[47]. These trends are parallel with declines in mortality associated with coronary heart disease[61, 62], ischemic stroke[63] and chronic heart failure[64, 65] during the last 30 years.

Atrial fibrillation and stroke

AF increases the risk of stroke 4 to 5-fold[12]. In Framingham, there was a 41.5/ 1000 person-years stroke incidence in patients with new-onset non-rheumatic AF compared with 2.8/1000 person-years in patients free of AF[8]. In contrast to other stroke risk factors atrial fibrillation retained its ability to cause stroke even in octogenarians[12]. In a later analysis there was a 29/1000 person-years incidence of non-fatal stroke in patients not taking OAC[66]. In the SCAF study, the incidence of first-ever ischemic stroke in AF-patients was 21/1000 patient-years in paroxysmal and 25 in permanent AF during a 3.6 year follow-up[67]. Atrial fibrillation is the underlying cause in up to 25% of all strokes, and up to 50% of cardio-embolic strokes[68-70]. Stroke in patients with atrial fibrillation is often more severe, more often fatal and associated with more severe sequele[70-72]. The risk for stroke does not seem to differ much with type of atrial fibrillation, but there is a paucity of prospective data on stroke risk in paroxysmal or intermittent AF[67, 73, 74] . In a recent meta-analysis it was concluded that risk factors for ischemic stroke in patients with atrial fibrillation include previous stroke, increasing age, hypertension and diabetes mellitus[75]. These risk factors are also important for stroke in patients with sinus rhythm and patients with atrial fibrillation carry an increased risk of non-embolic strokes as well[76]. Female gender was a risk marker in some but not all studies and heart failure diagnosis and coronary heart disease were inconclusively associated with increased risk for stroke.

Four studies have evaluated trends in stroke risk over time. In two American studies, there was a halving of incident ischemic strokes over time. In both populations the number of patients given OAC increased considerably during follow-up[77, 78]. In contrast, the Dijon city stroke study showed a minute 1.5% reduction in number of cardio-embolic strokes despite an increased use of OAC during 22 years[79]. Lastly, a study on material from the Danish Hospital discharge registry, there was a more mod-

est 20% decrease over 22 years time when adjusted for co-morbidities, age and trends in general stroke incidence in the Danish population. No information about OAC was given[80].

Atrial fibrillation and heart failure

In the Framingham cohort, several AF patients developed CHF over time[54]. AF was associated with a tripled risk of CHF in the Manitoba study[20]. While this may reflection of reflect the progression of cardiovascular diseases such as AMI or hypertension[81, 82], AF can be the prime cause of acute heart failure. AF or other atrial and ventricular arrhythmias can sometimes cause tachycardia-induced cardiomyopathy. The mechanisms behind this are poorly understood, the prevalence is not known, and in the clinical setting it is often mistaken for a dilated cardiomyopathy presenting with a high ventricular rate. When the arrhythmia is treated, LVEF improves or even returns to normal within a relatively short time span[83-85]. Recent research shows that ventricular remodelling may persist even after the acute phase[84]. Repeated episodes may lead to progressive heart failure and even sudden death[83].

Treatments to reduce risk in atrial fibrillation

As already mentioned, the improvement of treatment and management of cardiovascular conditions associated with AF has been substantial during the last 30 years. For AF in itself, there are only two treatments that have proven efficacy on hard endpoints (that is, mortality, strokes and hospitalization). A previous meta-analysis shows that OAC is associated with a 64% reduction in stroke incidence and a 26% decrease in all-cause mortality in patients with AF[86]. The need for continuous monitoring and the fear of bleeding complications hampers the use of OAC[87, 88]. A study of a direct thrombin inhibitor has shown promising results in this context[89]. Recently dronedarone, a novel class III antiarrhythmic has shown beneficial effects on cardiovascular mortality, cardiovascular hospitalizations and ischemic stroke in patients with paroxysmal or persistent AF[90], unfortunately these results does not extend to patients with AF and severe CHF where mortality is increased[91]. Modifying AF substrate by way of pulmonary vein isolation and Cox-Maze procedure improves quality of life, exercise capacity and cardiac function[92]. Limited data on hard endpoints, other than quality of life, such as mortality and stroke, and long-term freedom of AF limits its use[92].

Several scores have been developed as a help and guide to which patients benefit most from OAC treatment (Appendix). $CHADS_2$ score, derived from clinical trial data constitutes an easy remembered and utilized stroke prediction score utilizing clinically available parameters and a division of patients into low risk (0 points, where no treatment or ASA is recommended), moderate risk (1-2 points, where OAC could be considered) and high risk (>2 points, where OAC is recommended)[93, 94]. The moderate predictive value of $CHADS_2$ (and other stroke scores), the clustering of cases with moderate stroke risk and the knowledge that patients with mild to moderate risk (i.e. 0-1) still may benefit from OAC treatment had lead to the development of the CHA_2DS_2-VaSC-score. This score, a development of the Birmingham stroke score[95], has added several risk factors to $CHADS_2$[96]. The pilot study indicates that it is of similar efficacy compared to other prediction schemes, but readily identified patients with

a very low stroke risk. HAS-BLED score is an attempt to identify patients at high risk of bleeding complications and thus not eligible for OAC treatment[97]. Both CHA_2DS_2-VaSC and HAS-BLED is currently being validated in different patient cohorts.

Atrial fibrillation is a very common condition and it is associated with significant morbidity and mortality. The incidence and prevalence of AF is rising and is projected to continue to rise. Managing patients with AF will be one of future's challenges and in order to be prepared for that we need to know more about the present and recent past. Treatment of AF and associated morbidities have undergone several changes during the last 30 years, we wanted to se whether this is reflected in time trends of stroke, ischemic and hemorrhagic, and mortality, the two most important risks associated with AF. Earlier studies in this research field are either small, had short observation periods or did not include important analyses, such as incidence hemorrhagic stroke and prognostic importance of comorbidities. We utilized the Swedish Hospital Discharge Registry coupled to Swedish Death registry for this purpose. Moreover, important patient subcategories with AF are poorly defined. CHF and AF is a common combination, where there is some uncertainty regarding whether it is AF in itself that is the risk factor or of it is a marker of a more severe underlying disease. Most of the earlier trials was smaller, had short follow-up and did not include patients on contemporary CHF treatment. Few trials have analysed risk of AF in patients with CHF and preserved ejection fraction, a very common condition. We utilised COMET and CHARM trial, two large clinical trials including CHF patients with a broad spectrum of ejection fractions with 5-year and 3.5 years follow-up time, respectively.

AIMS

- To investigate temporal trends in the risk of stroke associated with incident atrial fibrillation in a large cohort
- To investigate temporal trends of mortality associated with incident atrial fibrillation in a large cohort
- To investigate the risk of morbidity and mortality associated with prevalent and incident atrial fibrillation in patients with chronic heart failure and reduced or preserved ejection fraction enrolled in two large randomised trials

PATIENTS AND METHODS

Paper I and II

Patient population Paper I and II

Sweden has a universal health care system that provides low-cost health care (including hospital care) to the Swedish population (population ranging from 8.4 to 9.0 million people during the period 1987 to 2004). Registration of principal and up to five contributory or secondary discharge diagnoses for all patients is mandatory in the hospital discharge register. Diagnosis at discharge is coded with the International Classification of Diseases (ICD) system (ICD 8th revision until 1986, ICD 9th revision until 1996, ICD 10th revision thereafter). Each patient is given a principal diagnosis and up to five secondary diagnoses. For the purpose of the present study, data from the national hospital discharge and cause-specific death registers were linked through the personal identification number (PIN), which is unique for all Swedish citizens. The hospital discharge register has been in existence since the 1960s and operating on a nationwide basis, with near-complete coverage, since 1987.

Index hospitalization for AF

We identified all first hospital admissions with a principal or secondary discharge diagnosis of AF in men and women aged 35 to 84 years during the period 1987 to 2006. The discharge codes applied were 427.4 (ICD-8) (only used for exclusion of patients with AF before 1987), 427.3 (ICD-9), and I48 (ICD 10). Consistent with previous analyses using these data[65, 98], to ascertain freedom from earlier hospitalizations and to ensure that patients from all years had the same chance to be identified as new cases, we censored for hospitalizations with a diagnosis of AF up to seven years before the index hospitalization. In Paper I, patients with prior stroke, ischemic (432-434 (ICD8 and ICD9) and I63, I64 (ICD10) or hemorrhagic (430, 431 (ICD8 and ICD9), I60–I62 (ICD10), within seven years, were excluded in the same manner. The reason for this was to minimize the risk for ambiguity on timing of first AF hospital diagnosis and to minimize the inclusion of recurrent strokes, a common problem[96]. In Paper II we censored for AF in the same manner as in Paper I but previously diagnosed ischemic or hemorrhagic strokes up to seven years before and including admission day was allowed.

Comorbidity

Significant co-morbidities during the preceding 7 years and index hospitalization were recorded. Specific discharge codes used to define common forms of comorbidity were: ischemic heart disease: 410-414 (ICD-8 and ICD-9), I20-I25 (ICD-10); chronic heart failure 427.00 (ICD-8), 428A, 428B, 428X (ICD-9) and I50 (ICD-10); diabetes: 250 (ICD-8 and ICD-9), E10, E11, E14 (ICD-10); hypertension: 401-405 (ICD-8 and 9), I10-I15 (ICD-10); valvular disease: 393–398, 424 (ICD-8), I05–I09 (ICD-9), I34-I35 (ICD-10); hyperthyroidism: 242 (ICD-8 and ICD-9), E05 (ICD-10); cancer: 140-207 (ICD-8 and ICD-9), C00-C97 (ICD10); Chronic obstructive pulmonary disease 491,492 (ICD-9), 490-492 (ICD-8 and 9), J40-44 (ICD-10); asthma 493 (ICD-8 and 9), J45 (ICD10).

Follow-up Paper I

We examined age- and sex-specific incidence of fatal and non-fatal ischemic and hemorrhagic stroke (as classified above) from day 1 up to 1095 days (3 years) after the index hospitalization by 5-year periods (period 1; 1987-1991, period 2; 1992-1996, period 3; 1997-2001, period 4; 2002-2006). We attempted to identify predictors of occurrence of ischemic strokes amongst baseline variables and time period of AF occurrence. We also examined the age and gender-adjusted stroke occurrence in this cohort and compared it with that of the whole Swedish population.

Follow-up Paper II

Due to the known relationship between atrial fibrillation and several conditions, we first performed a co-variable adjusted analysis with all relevant comorbidities, age, gender and time periods (period 1; 1987-1991, period 2; 1992-1996, period 3; 1997-2001, period 4; 2002-2006) in order to extract relevant cardiovascular comorbidities. We examined sex- and age-specified all-cause mortality from day 1 up to 1095 days (3 years) after hospital admission by time period and performed a comorbidity-stratified analysis.

Validity of the registers Paper I and II

In the period from 1987 to 1996, a primary discharge diagnosis was lacking in 0.8% of all admissions to Swedish departments of internal medicine, including cardiology[99]. In an early manual control of hospitalizations due to heart failure, acute myocardial infarction, or AF in two large hospitals in Göteborg less than 3% of hospitalizations had been missed by the national register[100]. The overall validity of cardiovascular diagnoses (ischemic heart disease, angina pectoris, and cerebrovascular disease) in the hospital discharge register was analyzed in 1986 and 1990 by studying random samples of about 900 medical records. The percentages of false positives and false negatives were all below 4%[101].

Statistical analysis Paper I and II

All analyses were carried out using the Statistical Analysis System (SAS), version 9.2, and the R statistical computing system, version 2.9.0. Means and proportions for continuous and categorical variables were calculated. Estimates of the conditional probability of ischemic and hemorrhagic stroke within 365 days, and 3 years were calculated. In the analysis regarding ischemic stroke death and hemorrhagic stroke were considered as competing risks. In the analysis regarding hemorrhagic stroke death and ischemic stroke were treated as competing risks[102]. These are presented for each period of AF hospitalization, gender and age group. Additionally, the cumulative incidence function for stroke is illustrated graphically for the whole population within a 3-year interval from admission. Different curves are presented for each period of AF hospitalization, and for men and women separately. When comparing men and women, age adjustment was done implicitly through comparison of age-matched subsets. The independent association of each period of AF admission (the first period was the reference), age, gender and co-morbidity with the hazard for ischemic stroke are quantified by hazard ratios estimated through Cox regression. To estimate the excess

risk, when comparing with a normal population, of stroke after AF hospitalization we used the age and sex standardised morbidity ratio.

Paper III and IV

The study population in Papers III and IV consisted of patients enrolled in two prospective, randomised, double-blind clinical trials, Carvedilol Or Metoprolol Evaluation Trial (COMET)[103] and Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) programme[104].

Patient population Paper III

COMET was a randomized, double-blind comparison of carvedilol with metoprolol tartrate. A detailed description of study design and inclusion/exclusion criteria has been published earlier[105]. In summary, eligible patients had symptomatic CHF [New York Heart Association (NYHA) class II–IV] and at least one cardiovascular admission during the previous 2 years. Left-ventricular ejection fraction had to be ≤0.35 measured within the previous 3 months by echocardiography or radionuclide angiography. Patient demographics were obtained at randomization together with a 12-lead electrocardiogram (ECG) and further baseline assessments. Clinical follow-up investigations were performed in 4-month intervals and yearly 12-lead ECG's.

Analysis Paper III

On the basis of the presence of atrial fibrillation on the baseline ECG, patients were grouped as No AF or AF. Patients with a history of atrial fibrillation with sinus rhythm at baseline ECG were considered to have paroxysmal atrial fibrillation and included in the No AF group. Patients with sinus rhythm at baseline and ECG documented atrial fibrillation during follow-up were classified as new onset AF. The primary outcome of COMET was all-cause mortality. A co-primary outcome was all-cause mortality or all-cause hospital admission. Secondary outcomes included cardiovascular death, worsening heart failure, or the composite cardiovascular death or hospitalization for worsening heart failure. An endpoint committee consisting of three experienced cardiologists classified death as cardiovascular or non-cardiovascular.

Patient population Paper IV

The design of the CHARM program has been described in detail earlier[106]. In brief, 7599 patients with symptomatic CHF in New York Heart Association functional class II to IV were randomized to candesartan (target dose 32 mg once daily, mean dose 24 mg) or matching placebo. Patients were divided into one of the three component trials based on left ventricular ejection fraction (LVEF) and treatment with an angiotensin-converting enzyme inhibitor (ACE-I). The CHARM-Alternative study included patients with EF ≤0.40 not treated with ACE-I because of intolerance[107]. The CHARM-Added study included patients with LVEF ≤0.40 already treated with an ACE-I[108], and the CHARM-Preserved study evaluated patients with LVEF >0.40 regardless of ACE-I treatment[109]. Patients in CHARM-Preserved had to have had a hospital admission for a cardiac reason at some time in the past. In acknowledgment of the results of the HOPE trial inclusion criteria into CHARM Preserved trial was relaxed and treatment with ACE-inhibitors was allowed in high-risk patients[110].

The investigators were asked to complete a structured ECG report at the randomization visit. At the end of follow-up, investigators were asked to report whether or not a new diagnosis of AF had been made during follow-up and how it was diagnosed. In the present analysis, during the median follow-up of 37.7 months, all patients with new development of AF were included regardless of whether the episodes were symptomatic or whether they were paroxysmal or persistent.

Analysis Paper IV

The primary objective of this analysis was to examine the risk of cardiovascular (CV) events related to baseline AF (according to investigators interpretation of the baseline ECG) in CHF patients with a broad spectrum of ejection fractions. We also assessed the frequency of CV events in patients in whom new AF developed during follow-up. The exact timing of AF onset was not recorded. In a secondary analysis, we examined the influence of baseline rhythm (AF or other) on the effect of candesartan on outcomes and on the need for permanent withdrawal from study drug because of serious adverse effects. Patients in sinus rhythm at baseline but with a history of AF were categorized as no AF. Analyses were carried out for all patients, and stratified by EF. The CHARM-Added and CHARM-Alternative participants were considered the low EF group and CHARM-Preserved participants were considered the preserved EF group. The primary outcome of the component trials in the CHARM program was the composite of CV death or admission to hospital for worsening CHF. These events were adjudicated by a blinded committee. Pre-specified secondary outcomes included all-cause mortality, CV death, admission to the hospital for CHF, and fatal or nonfatal stroke. All deaths were classified as CV unless an unequivocal non-CV cause was established.

Statistical analysis Paper III

Differences between patients with or without atrial fibrillation were performed using $\chi 2$ tests for categorical data and t-tests for continuous parameters. Kaplan–Meier estimates of mortality were calculated and differences between the groups assessed using Cox proportional hazard models. In order to adjust for all significant prognostic factors that might affect outcome, we produced a multivariable Cox regression model using baseline variables presumed to be of prognostic importance: age, gender, ejection fraction, blood pressure, NYHA class, aetiology, previous angina, S-creatinine, S-sodium, and dose of furosemide. Decisions regarding whether to include continuous parameters as linear covariates or as multi category factors were based on the functional form of each variable as a predictor obtained from Martingale residual plots. Where the plot did not appear to be linear, and there was no appropriate transformation, cut points were chosen from the plot to create categorical variables. The prognostic significance of new onset AF was assessed using a time-dependent Cox regression analysis. The same sets of baseline variables were included, and new onset AF and the NYHA class were introduced as time-dependent covariates. It is noted that the results presented were identical when adjustment was made for all significant baseline predictors, obtained for each endpoint using forward and backward stepwise procedures (data not shown). All tests performed were two-sided and the significance level was 0.05. No attempt has been made to adjust the significance level of the data presented for multiple testing.

Statistical analysis Paper IV

All outcome variables were defined as the time to an event or censoring and were analyzed with the proportional hazards model. Both simple Cox regression models and multiple Cox regression models were fitted to data. The explanatory variables included in the multiple regression models were the same set of 33 variables that were adjusted for in the CHARM program[104], except for the variable ACE-I at baseline. All subgroups analyzed for the low EF group were stratified by component trial (CHARM-Added or CHARM-Alternative). When an analysis included new-onset AF as an explanatory variable, a logistic regression model was fitted to data because information on timing of occurrence of AF was lacking, and these analyses are therefore presented as odds ratios rather than hazard ratios (HR). In this analysis, the response was considered to be a binary variable, indicating whether or not a patient experienced a CV event. All p values were generated from the Wald test statistics.

RESULTS

Paper I

Baseline

A total of 321,276 patients aged 35 to 84 years, with a first hospitalization for AF and no recorded history of stroke were discharged from Swedish hospitals 1987-2006. Patient characteristics are summarized in Table 3. Overall, 56.5 % were male and mean age was 71.5 with men in average being 4 years younger than women. Overall, slightly less than a third had concurrent ischemic heart disease with more men than women affected overall. A similar proportion of males and females had chronic heart failure. Valvular disease was diagnosed in only 7.1% of cases and hyperthyroidism in only 0.4%.

Table 3. Baseline data for 321,276 Swedish patients aged 35 to 84 years and no prior stroke with a first-time hospitalization for atrial fibrillation

		Male	**Female**	**Total**
Number of patients		181496	139780	321276
Age at discharge	**mean**	69.7	73.9	71.5
Ischemic heart disease	n (%)	54871 (30.2)	34360 (24.6)	89231 (27.8)
Chronic heart failure	n (%)	51216 (28.2)	40450 (28.9)	91666 (28.5)
Diabetes mellitus	n (%)	20664 (11.4)	16037 (11.5)	36701 (11.4)
Hypertension	n (%)	33073 (18.2)	29855 (21.4)	62928 (19.6)
Cardiomyopathy	n (%)	3782 (2.1)	1216 (0.9)	4998 (1.6)
Valvular heart disease	n (%)	12315 (6.8)	10445 (7.5)	22760 (7.1)
Cancer	n (%)	22116 (12.2)	17567 (12.6)	39683 (12.4)
Hyperthyreosis	n (%)	804 (0.4)	2360 (1.8)	3164 (1.0)

Incidence of ischaemic stroke within 3 years

Between 1987 and 2006, 24733 (7.7%) of this cohort were subsequently diagnosed with a fatal or non-fatal ischemic stroke and 2292 (0.7%) with a fatal or non-fatal hemorrhagic stroke within 3 years from the index hospitalization. Overall, 30-day incidence of ischemic stroke remained unchanged over the study period. Alternatively, there was a 17.5% relative risk reduction in the incidence of ischaemic stroke within 3 years over the entire 20-year period; in absolute numbers stroke incidence fell from 11.6% during period 1 to 9.6% during period 4. As shown in Figure 2, there was little change in the incidence of stroke in the first two study periods (1987-1996), with a dramatic change in incidence during 1997-2001 that was sustained through 2002-2006.

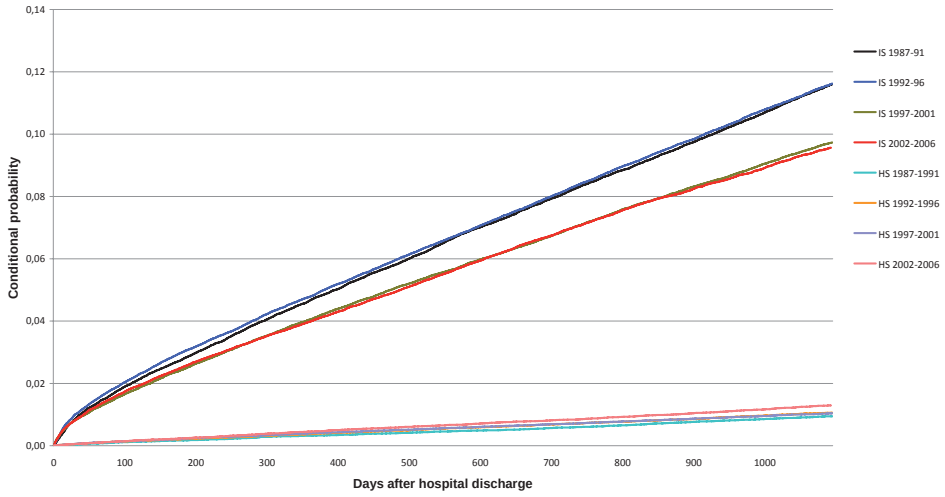

Figure 2. Time trends in stroke incidence after first hospital atrial fibrillation diagnosis in Sweden 1987-2006.

Table 4 compares the pattern of ischemic stroke events according to age composition of the study cohort. There was a clear age gradient in three-year rates of ischemic stroke during the entire study period with declining rates in all age-groups. Three-year rates of ischemic stroke in 1987 to 1991 was 38.4 per 1000 observation years among AF patients aged 35 to 64 years, 100.2 per 1000 in patients aged 65 to 74, and 178.5 per 1000 in patients aged 75 to 84 years. Corresponding figures in 2002 to 2006 were 33.8, 76.4, and 143.5 per 1000, or relative decreases by 12% ($p=0.29$), 24% and 20% (both $p<0.0001$).%. The decline was slightly more pronounced among men than among women in three-year rates of ischemic strokes during the entire study period (Table 5). Three-year rates of ischemic stroke in 1987-1991 were 133 versus 101 per 1000 observation years for women and men, respectively. Corresponding figures in 2002 to 2006 were 114 and 82 per 1000 observation years in women and men, respectively, a relative decrease by 15% and 19% (both $p<0.0001$).

Table 4. Ischemic stroke within one and three years after a first hospitalization for atrial fibrillation by age group

	N EVENTS	STROKE CASES PER 1000	N EVENTS	STROKE CASES PER 1000
35-64				
Days after AF	365		1095	
Period				
1987-1991	177	15.2	424	38.4
1992-1996	228	15.5	540	38.7
1997-2001	243	13.8	563	33.3
2002-2006	299	14.9	526	33.8
		-2% (p= 0.89)*		-12% (p= 0.29)*
65-74				
Days after AF	365		1095	
Period				
1987-1991	667	38,1	1543	100.2
1992-1996	952	40.3	2145	101.4
1997-2001	803	34.2	1792	83.6
2002-2006	725	31.1	1321	76.4
		-18% (p=0.0003)*		-24% (p<0.0001)*
75-84				
Days after AF	365		1095	
Period				
1987-1991	1528	72.4	3141	178.5
1992-1996	2160	69.8	4488	168.8
1997-2001	2048	59.0	4344	142.5
2002-2006	2219	59.5	3906	143.5
		-18% (p<0.0001)*		-20% (p<0.0001)*

*For difference period 4 vs period 1.

Table 5. Ischemic stroke within one and three years after a first hospitalization for atrial fibrillation by gender

	N EVENTS	STROKE CASES PER 1000	N EVENTS	STROKE CASES PER 1000
Female				
Days after AF	365		1095	
Period				
1987-1991	1265	55.6	2714	133.4
1992-1996	1768	56.7	3795	134.2
1997-2001	1570	47.3	3479	114.1
2002-2006	1669	48.7	2966	114.4
		-12% (p=0.001)*		-15% (p<0.0001)*
Male				
Days after AF	365		1095	
Period				
1987-1991	1107	40.3	2394	101.1
1992-1996	1572	41.3	3378	101.5
1997-2001	1524	35.8	3220	84.0
2002-2006	1574	33.9	2787	81.6
		-16% (p<0.0001)*		-19% (p<0.0001)*

*For difference period 4 vs period 1.

Incidence of hemorrhagic stroke within 3 years

As noted above, hemorrhagic strokes were far less common than ischemic strokes during three years after hospitalization for AF (Figure 2). However, in contrast to ischemic stroke, there was a 37.2% relative increase in the number of hemorrhagic stroke cases during the study period (Figure 3), but the overall result is still a net decrease of total number of strokes. As can be seen in Table 6, there was a clear age gradient in three-year rates of hemorrhagic stroke with increased rates in all age groups, however, only in patients 75-84 years old did changes reach statistical significance. Three-year rates of hemorrhagic stroke in 1987 to 1991 was 5.4 per 1000 observation years among AF patients aged 35 to 64 years, 10.6 per 1000 in patients aged 65 to 74, and 11.4 per 1000 in patients aged 75 to 84 years. Corresponding figures in 2002 to 2006 were 7.1, 12.2, and 17.1 per 1000, a relative increase by 33% (p=0.20), 15% (p=0.054), and 51% (<0.0001). As can be seen in Table 7, women and men had very similar incidence and relative increase of hemorrhagic strokes over the study period.

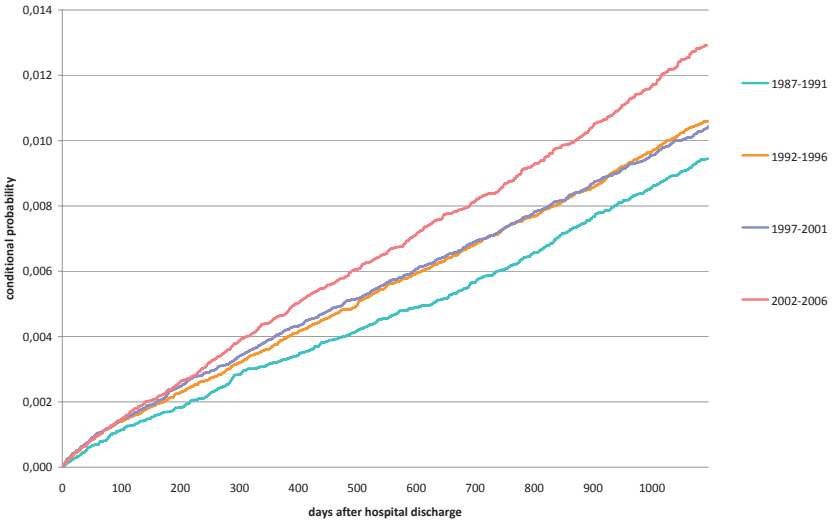

Figure 3. Time trends in hemorrhagic stroke incidence after first hospital atrial fibrillation diagnosis in Sweden 1987-2006.

Table 6. Hemorrhagic stroke within one and three years after a first hospitalization for atrial fibrillation by age group

	N EVENTS	STROKE CASES PER 1000	N EVENTS	STROKE CASES PER 1000
35-64				
Days after AF	365		1095	
Period				
1987-1991	177	1.9	424	5.4
1992-1996	228	2.3	540	5.4
1997-2001	243	1.6	563	5.5
2002-2006	299	2.3	526	7.1
		+23% (p=0.39)*		+33% (p=0.20)*
65-74				
Days after AF	365		1095	
Period				
1987-1991	667	3.5	1543	10.6
1992-1996	952	3.6	2145	10.9
1997-2001	803	4.2	1792	11.0
2002-2006	725	4.7	1321	12.2
		+33% (p=0.083)*		+15% (p=0.054)*
75-84				
Days after AF	365		1095	
Period				
1987-1991	1528	3.8	3141	11.4
1992-1996	2160	4.6	4488	13.4
1997-2001	2048	5.3	4344	13.0
2002-2006	2219	5.8	3906	17.1
		+54% (p=0.0009)*		+51% (p<0.0001)*

*For difference period 4 vs period 1.

Table 7. Hemorrhagic stroke within one and three years after a first hospitalization for atrial fibrillation by gender

	N EVENTS	STROKE CASES PER 1000	N EVENTS	STROKE CASES PER 1000
Female				
Days after AF	365		1095	
Period				
1987-1991	66	3.1	169	9.5
1992-1996	108	3.7	256	10.3
1997-2001	127	4.0	280	10.3
2002-2006	148	4.6	288	12.8
		+50% (p=0.006)*		+35% (p= 0.0004)*
Male				
Days after AF	365		1095	
Period				
1987-1991	89	3.4	202	9.4
1992-1996	141	3.8	328	10.8
1997-2001	169	4.1	375	10.6
2002-2006	204	4.6	394	13.0
		+38% (p=0.009)*		+38% (p=0.0003)*

*For difference period 4 vs period 1.

Comparison with underlying population incidence of stroke

As shown in Figure 4, during the first years of the study period, AF patients had a stroke rate about 4 times that of the general population which decreased slowly to around 3 around the year 2000, and remained steady thereafter.

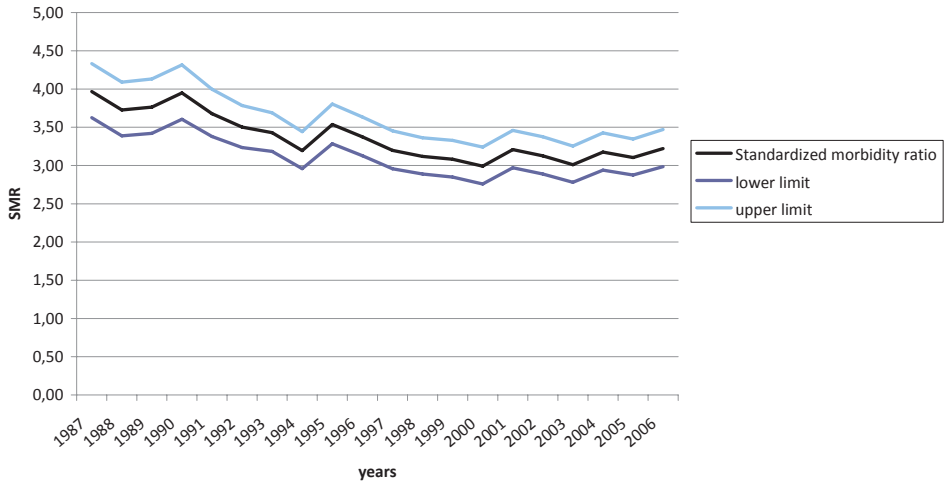

Figure 4. Standardized morbidity ratio all strokes in patients hospitalised with first atrial fibrillation diagnosis 1987-2006 compared with swedish population.

Predictors of stroke

When adjusted for age, sex and baseline co-morbidities, there was a 21% decrease in ischemic stroke risk from the first to the last period (Table 8). The association was non-linear, with period 3 but not period 2 having significantly lower risk of subsequent stroke compared with the first period and no further decrease between period 3 and 4. Age, female sex, diabetes mellitus, ischemic heart disease and hypertension were all predictors of stroke occurrence in this population. Chronic heart failure was not a predictor of ischemic stroke.

When adjusted for age, sex and baseline co-morbidities, age, male sex and hypertension were powerful predictors of hemorrhagic strokes. Time periods were not predictive of incident hemorrhagic strokes (data not shown). To further explore these results we repeated the analysis and included age and time periods as an interaction term. No significant interaction between age composition and time period was found (HR for interaction 1.01; 1.00–1.02; p=0.23 for period 4 versus period 1).

Table 8. Independent predictors of ischemic stroke up to 3 years after first hospitalization for atrial fibrillation

Parameter	Hazard Ratio	95%	Hazard Ratio Confidence Limits	p-value
Sex (female vs male)	1.14	1.11	1.17	<.0001
Age (per 10-year increase)	1.79	1.76	1.82	<.0001
Chronic heart failure	1.02	1.00	1.05	0.13
Diabetes mellitus	1.47	1.42	1.52	<.0001
Hypertension	1.27	1.23	1.31	<.0001
Valve disease	0.86	0.82	0.91	<.0001
Hyperthyreosis	0.79	0.68	0.90	0.0006
Cancer	0.95	0.92	0.99	0.017
Ischemic Heart Disease	1.06	1.03	1.09	<.0001
1987-1991	1			
1992-1996	0.98	0.94	1.01	0.23
1997-2001	0.82	0.80	0.86	<.0001
2002-2006	0.79	0.76	0.82	<.0001

Paper II

Multivariable analysis

Table 9 shows the results of the co-variable-adjusted analysis of death. All subsequent periods after 1987-91 were independently associated with reduced mortality. Chronic heart failure, previous stroke, acute coronary syndrome (unstable angina pectoris and myocardial infarction) and diabetes mellitus were all strong predictors of prognosis in this cohort ($p<0.0001$) and therefore we adjusted for the absence or presence of these comorbidities in the following analyses. Other important comorbidities were cancer, pulmonary disease (COPD and asthma). In contrast, a diagnosis of hypertension, angina pectoris or hyperthyreosis was, albeit weakly, associated with improved prognosis.

Table 9. Multivariable analysis on risk for mortality in patients hospitalized with first AF diagnosis 1987-2006 in Sweden

Parameter	Hazard ratio	95% HR Confidence limits	
Age (per decade increase)	1.89	1.88	1.91
Male sex	0.80	0.79	0.81
1987-1991	1 (reference)		
1992-1996	0.84	0.82	0.85
1997-2001	0.74	0.72	0.75
2002-2006	0.70	0.68	0.71
Chronic heart failure	1.73	1.71	1.76
Previous stroke	1.65	1.63	1.68
Diabetes Mellitus	1.50	1.47	1.52
Acute Coronary Syndrome[1]	1.43	1.41	1.46
Valvular heart disease	1.13	1.10	1.15
Angina pectoris	0.86	0.85	0.88
Hypertension[2]	0.98	0.96	0.99
Hyperthyreosis[3]	0.91	0.85	0.97
Pulmonary Disease[4]	1.52	1.49	1.55
Cancer	2.10	2.07	2.13

1. Myocardial infarction and unstable angina pectoris. All variables $p<0.0001$ except. 2. $p=0.0068$
3. $p=0.0032$ 4. Chronic Obstructive Pulmonary Disease and Asthma

Patient characteristics

The baseline variables are presented in Table 10. Exactly 376,000 patients were discharged with a diagnosis of first atrial fibrillation between 1987 and 2006, 56% were men. Women were older than men at discharge (74.4 vs 70.4 years). Chronic heart failure was the most common comorbidity with similar prevalence in men and women. Men had more ischemic heart disease and women had more previous stroke, hypertension and hyperthyreosis. Cancer and pulmonary disease (chronic obstructive pulmonary disease and asthma) were present to a similar degree in males and females. 200,593 patients (53.3% of total population, 53.8% of these patients were men) had any of the four diagnoses selected for subsequent stratified analysis.

Table 10. Baseline characteristics

		Female	Male	All
Number of patients		165,304	210,696	376,000
Mean age		74.4	70.3	72.1
Comorbidities				
Previous stroke	n (%)	25523 (15.4)	29199 (13.9)	54722 (14.6)
Acute coronary syndrome[1]	n (%)	28,173 (17.0)	46,025 (21.8)	74,198 (19,7)
Chronic heart failure	n (%)	46,395 (28.1)	58,539 (27.8)	104,934 (27.9)
Diabetes mellitus	n (%)	20,418 (12,4)	26,013 (12,3)	46,431 (12,3)
Any of the above	n (%)	87,249 (52.8)	113,344 (53.8)	200,593 (53.3)
Angina pectoris	n (%)	25,392 (15.4)	38,273 (18.6)	64,665 (17.2)
Hypertension	n (%)	38,138 (23.1)	41,939 (19.9)	80,077 (21.3)
Hyperthyreosis	n (%)	2695 (1.6)	897 (0.4)	3592 (1.0)
Valvular heart disease	n (%)	11,755(7.1)	13,677(6.5)	25,432(6.8)
Pulmonary disease[2]	n (%)	11,166(6.8)	14,507(6.9)	25,673(6.8)
Cancer	n (%)	20,297(12.3)	25,554(12.1)	45,851(12.2)

*Includes chronic obstructive pulmonary disease and asthma.

Survival trends

During the 20-year observation period, 107,972 patients (28.7%) died. Mortality rates declined overall from a three-year mortality of 34% period 1 vs 26% in period 4, corresponding to a 23% relative mortality decrease (8% absolute risk decrease; $p<0.0001$) (Figure 5). When divided by age and gender, there was a clear age-gradient in 3 year mortality (Tables 11-13). Men had higher mortality than women in all age groups, but also more pronounced decreases in mortality, which was more apparent in younger patients. Males and females 75-84 years old had similar decreases in mortality.

With respect to 3-year mortality rates in patients with the pre-specified co-morbidities, males had a 3-year mortality during period 1 of 263, 498 and 577 per 1000 patients in patients 35-64, 65-74 and 75-84 years old, respectively, with corresponding mortality rates for period 4 151, 250 and 446 per 1000 patients, giving Hazard Ratios (HR) 0.54;

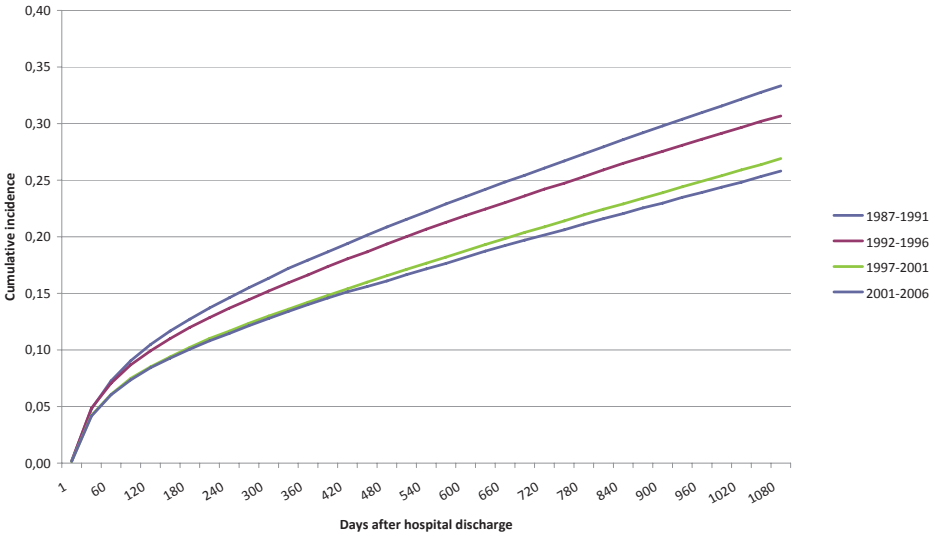

Figure 5. Mortality after first hospitalization with an atrial fibrillation diagnosis in Sweden 1987-2006.

Table 11. 3-year mortality by age and sex after first hospital AF diagnosis in Sweden 1987-2006 - all patients

		Women					***Men***			
days after hospital discharge	*1095*					*1095*				
35-64	n events	Mortality/1000 patient-years	Hazard ratio	HR 95% CI	p-value	n events	Mortality/1000 patient-years	Hazard ratio	HR 95% CI	p-value
1987-1991		100.7	1				132.0	1		
1992-1996		104.5	1.04	0.91-1.20			113.5	0.85	0.79-0.92	
1997-2001		93.5	0.93	0.81-1.06			94.7	0.70	0.65-0.76	
2002-2006		81.3	0.81	0.70-0.92			94.7	0.71	0.66-0.76	
Mean annual change, %		**-0.96%**			p=0.002		**-1.4%**			P<0.0001
65-74										
1987-1991		218.6	1				305.4	1		
1992-1996		207.9	0.95	0.90-1.01			268.8	0.86	0.83-0.90	
1997-2001		173.0	0.77	0.73-0.82			228.5	0.72	0.69-0.75	
2002-2006		169.2	0.76	0.71-0.80			205.9	0.64	0.61-0.67	
Mean annual change, %		**-1.14%**			p<0.0001		**-1.6%**			P<0.0001
75-84										
1987-1991		430.0	1				517.7	1		
1992-1996		386.1	0.87	0.85-0.90			464.2	0.86	0.82-0.89	
1997-2001		345.6	0.75	0.73-0.78			414.9	0.74	0.72-0.76	
2002-2006		332.9	0.72	0.70-0.75			402.8	0.71	0.69-0.74	
Mean annual change, %		**-1,13%**			P<0.0001		**-1.11%**			P<0.0001

95% CI 0.49-0.59), 0.57; 0.54-0.60 and HR 0.69; 0.67-72, p<0.0001 for all (Table 12). Females had a 3-year mortality during period 1 of 210, 319 and 509 per 1000 patients, respectively, corresponding mortality rates for period 4 was 152, 234 and 397 per 1000 patients, giving HR's 0.71; 0.59-0.85, 0.70 (0.65-0.75) and 0.72 (0.69-0.74), p=0.0002 for 35-64 year olds, p<0.0001 for the other age groups (Table 12).

In patients without the preselected comorbidities, 3-year mortality was, not unexpectedly, lower (Table 13). Males had a 3-year mortality during period 1 of 72, 198 and 410 per 1000 patients, with corresponding mortality rates for period 4 of 64, 152 and 327 per 1000 patients, giving HR's 0.89; 0.79-1.01, 0.76; 0.70-0.82 and 0.76; 0.72-0.81, p=0.052 for 35-64 year olds, p<0.0001 for the other age groups. Females had a 3-year mortality period 1 of 63, 130 and 302 per 1000, with corresponding figures for period 4 was 53, 115 and 242 per 1000 patients, giving HR's 0.86; 0.70-1.05 (p= 0.13), 0.89; 0.80-0.99 (p= 0.0262) and 0.78; 0.73-0.82 (p<0.0001).

Table 12. 3-year mortality by age and sex after first hospital AF diagnosis in Sweden 1987-2006 - patients with pre-specified comorbidities*

		Women				***Men***		
35-64	*n events*	*Mortality/1000 patient-years*	*Hazard ratio*	*HR 95% CI*	*n events*	*Mortality/1000 patient-years*	*Hazard ratio*	*HR 95% CI*
1987-1991	194	210,4	1		792	263,3	1	
1992-1996	274	211,9	1.01	0.84-1.22	795	205,9	0,75	0.68-0.83
1997-2001	246	165,0	0.76	0.63-0.92	806	163,0	0.58	0.53-0.64
2002-2006	281	151,8	0.71	0.59-0.85	922	151,4	0.54	0.49-0.59
Mean annual change, %		**-1.4%**		p=0.0002		**-2.1%**		p<0.0001
65-74								
1987-1991	1439	318,9	1		2859	398,2	1	
1992-1996	1784	300,4	0.93	0.87-1.00	3390	342,1	0.83	0.79-0.88
1997-2001	1379	243,1	0.73	0.67-0.78	2807	279,6	0.65	0.62-0.69
2002-2006	1277	234,1	0.70	0.65-0.75	2598	250,3	0.57	0.54-0.60
Mean annual change, %		**-1.3%**		p<0.0001		**-1.9%**		p<0.0001
75-84								
1987-1991	5673	508,7	1		5463	577,4	1	
1992-1996	7076	462,4	0.88	0.85-0.91	7506	525,7	0.87	0.84-0.90
1997-2001	6685	409,6	0.74	0.72-0.77	7385	525,7	0.73	0.71-0.76
2002-2006	6678	396,7	0.72	0.69-0.74	7823	445,9	0.69	0.67-0.72
Mean annual change, %		**-1.1%**		p<0.0001		**-1.1%**		p<0.0001

*Includes previous stroke, acute coronary syndrome, chronic heart failure and diabetes mellitus.

Table 13. 3-year mortality by age and sex after first hospital AF diagnosis in Sweden 1987-2006 - patients without pre-specified comorbidities*

		Women				***Men***		
35-64	*n events*	*Mortality/1000 patient-years*	*Hazard ratio*	*HR 95% CI*	*n events*	*Mortality/1000 patient-years*	*Hazard ratio*	*HR 95% CI*
1987-1991	163	62,5	1		469	71,6	1	
1992-1996	212	63,1	1.00	0.83-1.25	543	68,5	0.96	0.84-0.89
1997-2001	256	66,2	1.07	0.88-1.30	540	58,3	0.81	0.72-0.92
2002-2006	248	53,2	0.86	0.70-1.05	707	63,6	0.89	0.79-1.00
Mean annual change, %		**-0.75%**		p=0.13		**-0.56%**		p=0.052
65-74								
1987-1991	667	130,3	1		1232	198,2	1	
1992-1996	849	126,3	0.97	0.88-1.08	1463	179,6	0.90	0.83-0.97
1997-2001	700	110,3	0.84	0.76-0.94	1234	161,4	0.80	0.74-0.87
2002-2006	748	114,8	0.89	0.80-0.99	1298	151,7	0.76	0.70-0.82
Mean annual change, %		**-0.60%**		p=0.026		**-1.18%**		p<0.0001
75-84								
1987-1991	2068	301,9	1		2142	409,8	1	
1992-1996	2548	264,9	0.86	0.81-0.91	2698	350,3	0.82	0.78-0.87
1997-2001	2455	242,4	0.77	0.73-0.82	2649	317,8	0.69	0.69-0.78
2002-2006	2822	241,5	0.78	0.73-0.82	7823	326,7	0.76	0.72-0.81
Mean annual change, %		**-1.44%**		p<0.0001		**-1.01%**		p<0.0001

*Includes previous stroke, acute coronary syndrome, chronic heart failure and diabetes mellitus.

Paper III

Patient characteristics

There were 600 patients (19.8%) who presented with atrial fibrillation at the baseline ECG. Baseline demographic variables by the presence of atrial fibrillation are presented in Table 14. Patients with atrial fibrillation were older (65 vs.61 years; P=0.0001), more often males (88 vs. 78%; P=0.0001), had more severe heart failure symptoms as reflected by NYHA class, and had a longer duration of CHF. Ischaemic heart disease and dilated cardiomyopathy were the two most common aetiologies of CHF in both groups although the former was less common in the AF group (43 vs. 55%; P=0.0001). Accordingly aspirin and, although not frequently used, lipid lowering therapy were more common in patients with sinus rhythm, whereas baseline atrial fibrillation was more often associated with treatment with digitalis, anti-arrhythmics, and anticoagulants.

Table 14. Baseline characteristics by presence of atrial fibrillation in COMET

	AF at baseline (*n*=600)	**No AF at baseline (*n*=2429)**	**Total (*n*=3029)**	***P*-value**
Age (years) mean/SD	65.1/10.0	61.2/11.6	62.0/11.4	<0.0001
Gender (% male)	87.5	77.9	79.8	<0.0001
Race (% white)	99.7	98.8	99.0	0.3
Body mass index (kg/m^2) mean	27.5	26.7	26.9	0.0001
Systolic BP (mmHg) mean	127.3	125.8	126.1	0.085
Diastolic BP (mmHg) mean	78.0	76.9	77.1	0.037
Heart rate (bpm) mean	82.5	80.8	81.1	0.005
NYHA class				
% II	37.8	51.0	48.4	<0.0001
% III	57.5	45.4	47.8	
% IV	4.7	3.6	3.8	
Ejection fraction (%) mean	26.2	26.1	26.1	0.719
Duration CHF (months) mean/median	55.3/33.0	39.2/18.0	42.4/21.0	<0.0001
Aetiology CHF[a]				
% Ischaemic heart disease	43.0	54.9	52.5	<0.0001
% Hypertension	22.3	16.6	17.7	0.0010
Comorbidities				
Previous MI (%)	31.1	44.1	41.5	<0.0001
CAD (confirmed by angiography) (%)	52.8	60.1	58.9	0.016
Current angina (%)	20.6	21.9	21.6	0.494
Hypertension (%)	39.9	36.1	36.9	0.088
Diabetes (%)	24.8	24.0	24.2	0.675
Stroke (%)	8.6	6.7	7.1	0.112
ECG findings at baseline[a]				
% Sinus rhythm	0.8	92.8	74.6	<0.0001
% Atrial fibrillation/flutter	100.0	0.0	19.8	
% Paced rhythm	5.2	6.9	6.5	0.13
% LBBB	3.7	6.0	5.5	0.027
Concomitant medication at randomization				
Diuretics[b] (%)	99.0	98.6	98.7	0.485
ACE-inhibitors (%)	92.2	91.1	91.4	0.427
Angiotensin receptor antagonists (%)	6.2	6.6	6.5	0.682
Digitalis (%)	81.2	54.1	59.4	<0.0001
Anti-arrhythmics (%)	16.3	11.1	12.1	0.0005
Nitrates (%)	29.2	33.6	32.8	0.037
Aldosterone antagonists (%)	12.2	10.5	10.8	0.227
Beta-blockers[c] (%)	4.7	4.2	4.3	0.613
Anticoagulants (%)	74.5	38.6	45.7	<0.0001
Aspirin (%)	19.0	41.3	36.8	<0.0001
Lipid lowering agents (statins) (%)	10.5	23.7	21.1	<0.0001

MI, myocardial infarction; CAD, coronary artery disease. [a]More than one answer possible. [b]Inclusion criteria.
[c]Stopped prior to study start.

Outcomes

The presence of atrial fibrillation at baseline ECG compared with no atrial fibrillation was associated with significantly increased all-cause mortality over a 5 year follow-up period [relative risk (RR) 1.29: 95% CI 1.12–1.48; P=0.0004, Figure 6]. Patients with

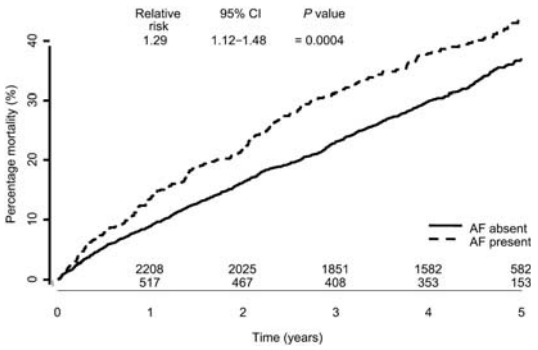

Figure 6. All-cause mortality by baseline atrial fibrillation in COMET.

atrial fibrillation also experienced higher all-cause death or all-cause hospitalization rate (RR 1.25: CI 1.13–1.38) as well as cardiovascular death or hospitalizations for worsening heart failure rate (RR 1.35: CI 1.20–1.52; both P=0.001) (Figures 7 and 8). A total of 11 pre-specified patient variables obtained at baseline including allocation group were included in a post-hoc regression analysis model. After adjustment for baseline covariates in the Cox regression analysis, presence of atrial fibrillation was no longer significantly associated with all-cause mortality (Table 15). However, for all-cause mortality or all-cause hospitalizations, atrial fibrillation had independent prognostic impact (RR 1.13: CI 1.02–1.26; P= 0.025). Furthermore, atrial fibrillation was of independent significant importance for all-cause mortality or hospitalization for worsening heart failure (RR 1.19: CI 1.05–1.35; P=0.007). After adjustment for age and gender only, atrial fibrillation was no longer of independent prognostic importance for mortality. Allocation to carvedilol therapy remained of independent beneficial importance for all-cause mortality in this model (RR 0.836: CI 0.74–0.94; P= 0.0042).

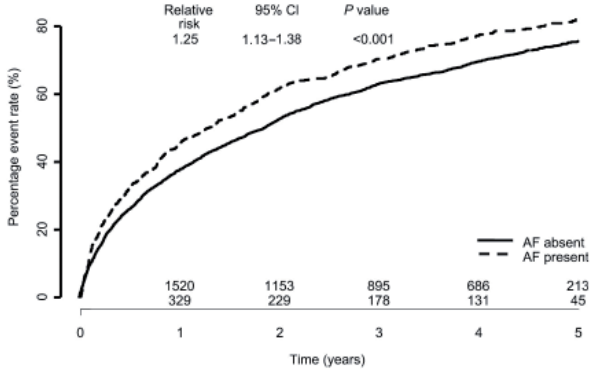

Figure 7. All-cause mortality and all-cause hospitalizations by baseline atrial fibrillation in COMET.

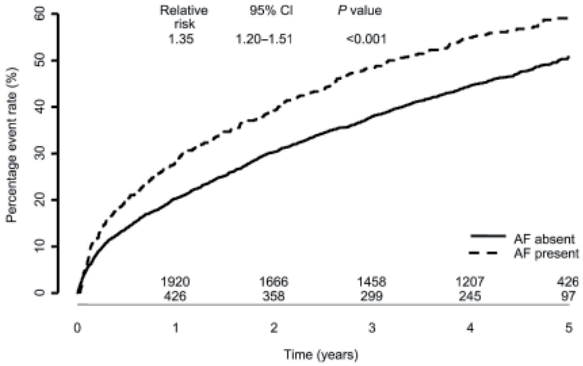

Figure 8. Cardiovascular mortality or hospitalization for worsening heart failure by baseline atrial fibrillation in COMET.

Table 15. Multivariable analysis of risk of all-cause mortality in patients with AF vs. No AF at baseline

	RR	95% CI	*P*-value
Carvedilol vs. Metoprolol	0.84	0.74, 0.94	0.0042
Increasing age (per 10 year increase)	1.42	1.33, 1.52	<0.001
Female vs. male	0.87	0.74, 1.02	0.0855
Increasing systolic BP (per 10 mm Hg increase)	0,92	0.89, 0.95	<0.001
Increasing LVEF (per 10 unit increase)	0.82	0.75, 0.89	<0.001
IHD vs. Rest	1.33	1.15, 1.52	<0.001
NYHA III vs. NYHA II	1.44	1.26, 1.64	<0.001
NYHA IV vs. NYHA II	1.83	1.39, 2.40	<0.001
Previous angina	0.94	0.81, 1.09	0.4078
Increasing sodium	0.94	0.92, 0.96	<0.001
Increasing creatinine	1.002	1.001, 1.003	<0.001
Diuretic dose 41–120 vs. ≤40 mg	1.37	1.18, 1.58	<0.001
Diuretic dose >120 vs. ≤40 mg	1.63	1.37, 1.94	<0.001
AF vs. No AF	1.07	0.92, 1.24	0.3811

AF=Atrial Fibrillation, BP=Blood Pressure, IHD=Ischaemic Heart Disease, LVEF=Left Ventricular Ejection Fraction, NYHA=New York Heart Association Classification

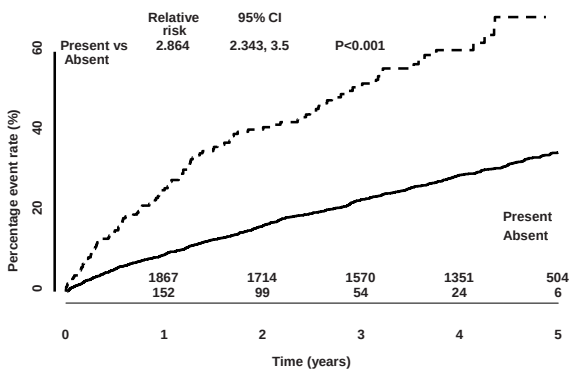

Figure 9. Mortality following new onset AF in patients with sinus rhythm at baseline.

Risk after new onset AF during follow-up

In 580 of 2429 patients with sinus rhythm at baseline, onset of atrial fibrillation were reported during the study. New onset atrial fibrillation remained an independent predictor of subsequent all-cause mortality when treated as a time-dependent variable (RR 1.90: CI 1.54–2.35; P= 0.0001) regardless of treatment allocation and changes in NYHA classification over time (Figure 9 and Table 16). Treatment allocation to carvedilol or metoprolol did not affect incidence of atrial fibrillation (RR 0.93; P= 0.2).

Table 16. Time dependent analysis in COMET trial of risk for all-cause mortality after new onset AF and NYHA class included in the model

	RR	95% CI	P-value
Carvedilol vs. Metoprolol	0.92	0.80, 1.06	0.2418
New-onset AF	1.90	1.54, 2.35	<0.0001
NYHA II vs. NYHA I	1.60	1.17, 2.17	0.003
NYHA III vs. NYHA I	3.41	2.50, 4.66	<0.0001
NYHA IV vs. NYHA I	8.62	5.92, 12.56	<0.0001
Baseline covariables			
Increasing age (per 10 year increase)	1.31	1.21, 1.41	<0.0001
Female vs. Male	0.84	0.70, 1.01	0.0615
Increasing systolic BP (per 10 mm Hg increase)	0.93	0.90, 0.97	0.0008
IHD vs. Rest	1.31	1.11, 1.55	0.0016
Increasing LVEF (per 10 unit increase)	0.81	0.73, 0.90	0.0001
Previous angina	1.01	0.85, 1.20	0.9136
Increasing sodium	0.947	0.929, 0.966	<0.0001
Increasing creatinine	1.002	1.001, 1.003	<0.0001
Diuretic dose 41–120 vs. ≤40 mg	1.38	1.17, 1.64	0.0001
Diuretic dose >120 vs. ≤40 mg	1.54	1.26, 1.89	<0.001

Paper IV

Baseline characteristics

A total of 7,601 patients were randomized to candesartan or placebo, 7,599 with available data. Baseline characteristics are summarized in Table 17. In general, patients with AF were older, had a higher baseline heart rate, more often had a cardiothoracic ratio of >0.5 and a history of hospitalization for heart failure. Patients with AF had similar EF to those in sinus rhythm but had a worse New York Heart Association functional classification. Patients with AF less frequently had a history of prior myocardial infarction, angina pectoris, or diabetes mellitus. Ischemic heart disease was the most common aetiology of heart failure regardless of presence or absence of AF, but it was a less common cause in patients with AF (43.5%) than without AF (64.8%). Hyperten-

sion was reported as the aetiology of CHF more commonly in patients with AF, much more commonly in patients with PEF, and most commonly in those with AF and PEF. Patients with AF were more often treated with digitalis, diuretic agents and OAC and less often with beta-blocker and acetylsalicylic acid. A small number of patients were treated with an antiarrhythmic drug in either group, regardless of AF, with more frequent use in patients with a low EF.

Table 17. Baseline variables by presence of AF in the CHARM program

Variable	Low EF		Preserved EF	
	AF	No AF	AF	No AF
N	670	3,906	478	2,545
Age (yrs)	68.1 (9.9)	64.7 (11.1)	71.4 (9.6)	66.4 (11.1)
DBP (mm Hg)	76.5 (10.9)	75.7 (10.7)	78.4 (11.1)	77.8 (10.6)
SBP (mm Hg)	127.3 (18.1)	127.4 (18.9)	134.3 (18.6)	136.5 (18.4)
HR (beats/min)	76.5 (15.6)	73.5 (12.8)	76.6 (14.5)	70.3 (11.8)
BMI	27.7 (5.0)	27.6 (5.1)	28.9 (5.9)	29.2 (5.8)
Ejection fraction	0.29 (0.08)	0.29 (0.08)	0.55 (0.09)	0.54 (0.09)
Cardiothoracic ratio >0.5	231 (34.5%)	942 (24.1%)	133 (27.8%)	361 (14.2%)
Male gender	523 (78.1%)	2,865 (73.3%)	277 (57.9%)	1,534 (60.3%)
Current smoker	81 (12.1%)	624 (16.0%)	57 (11.9%)	352 (13.8%)
Creatinine ≥2.0 mg/dl	16 (9.3%)	86 (6.1%)	6 (4.5%)	46 (4.8%)
NYHA functional class				
II	193 (28.8%)	1,387 (35.5%)	269 (56.3%)	1,567 (61.6%)
III	439 (65.5%)	2,406 (61.6%)	197 (41.2%)	943 (37.1%)
IV	38 (5.7%)	113 (2.9%)	12 (2.5%)	35 (1.4%)
Medical history				
Previous CHF hospitalization	539 (80.4%)	2,811 (72.0%)	390 (81.6%)	1,686 (66.3%)
Previous MI	294 (43.9%)	2,370 (60.7%)	115 (24.1%)	1,225 (48.1%)
Angina pectoris	293 (43.7%)	2,242 (57.4%)	187 (39.1%)	1,630 (64.0%)
Stroke	73 (10.9%)	322 (8.2%)	48 (10.0%)	220 (8.6%)
Hypertension	346 (51.6%)	1,897 (48.6%)	294 (61.5%)	1,649 (64.8%)
Diabetes mellitus	178 (26.6%)	1,128 (28.9%)	108 (22.6%)	749 (29.4%)
CABG	143 (21.3%)	994 (25.4%)	59 (12.3%)	595 (23.4%)
PCI	57 (8.5%)	645 (16.5%)	31 (6.5%)	495 (19.4%)
Implantable cardiac defibrillator	21 (3.1%)	147 (3.8%)	4 (0.8%)	19 (0.7%)
Pacemaker implanted	82 (12.2%)	334 (8.6%)	45 (9.4%)	176 (6.9%)
Etiology				
Ischemic heart disease	341 (50.9%)	2,634 (67.4%)	158 (33.1%)	1,548 (60.8%)
Idiopathic dilated cardiomyopathy	191 (28.5%)	873 (22.4%)	52 (10.9%)	211 (8.3%)
Hypertension	63 (9.4%)	234 (6.0%)	133 (27.8%)	551 (21.7%)
Atrial fibrillation	22 (3.3%)	10 (0.3%)	81 (16.9%)	53 (2.1%)
ECG findings at baseline				
Bundle branch block	181 (27.0%)	1,196 (30.8%)	78 (16.3%)	356 (14.1%)
Paced rhythm	64 (9.6%)	259 (6.7%)	31 (6.5%)	125 (4.9%)
Left ventricular hypertrophy	64 (9.6%)	632 (16.3%)	86 (18%)	358 (14%)
Concomitant medication				
Digitalis glycoside	533 (79.6%)	1,879 (48.1%)	313 (65.5%)	529 (20.8%)
Diuretics	632 (94.3%)	3,395 (86.9%)	430 (90.0%)	1,829 (71.9%)
Spironolactone	171 (25.5%)	749 (19.2%)	87 (18.2%)	265 (10.4%)
Beta-blocker	332 (49.6%)	2,187 (56.0%)	216 (45.2%)	1,468 (57.7%)
Calcium channel blocker	86 (12.8%)	512 (13.1%)	136 (28.5%)	808 (31.7%)
Antiarrhythmic agent	100 (14.9%)	493 (12.6%)	47 (9.8%)	253 (9.9%)
Lipid-lowering drug	184 (27.5%)	1,707 (43.7%)	112 (23.4%)	1,150 (45.2%)
Oral anticoagulant	513 (76.6%)	1,077 (27.6%)	350 (73.2%)	398 (15.6%)
Acetylsalicylic acid	179 (26.7%)	2,305 (59.0%)	107 (22.4%)	1,655 (65.0%)
ACE inhibitors	397 (59.3%)	2,152 (55.1%)	77 (16.1%)	499 (19.6%)

Outcomes in patients with AF on baseline ECG

Atrial fibrillation recorded on baseline ECG was associated with an increased risk of morbidity and mortality (Figures 10 and 11). Patients with AF and low EF had the highest absolute risk for adverse CV outcomes (e.g., 45% with CV death or CHF hospitalization) relative to those with low EF and sinus rhythm (37% with an event), PEF and AF (34% with an event), or PEF and sinus rhythm (21% with an event). However, AF was associated with a greater increase in the risk of CV death or hospitalization for worsening heart failure in patients with PEF (HR 1.72, 95% confidence interval [CI] 1.45 to 2.06) than in patients with low EF, (HR 1.29, 95% CI 1.14 to 1.46, p for interaction 0.008). The same was true for all-cause mortality: PEF HR 1.80 (95% CI 1.46 to 2.21) and low EF HR 1.38 (95% CI 1.21 to 1.59, p for interaction 0.041) (Figures 10 and 12). Similarly, for each of these adverse CV outcomes, with the exception of stroke, patients with low EF and AF at baseline had the highest absolute risk and patients with PEF and AF at baseline had a relative greater increase in risk than those with low EF and AF. When adjusted for 32 covariates in multiple regression analysis, baseline AF remained an independent risk factor for CV death or hospitalization for heart failure in patients with PEF (HR 1.32, 95% CI 1.06 to 1.65, p= 0.015) but not in those with low EF (HR 1.12, 95% CI 0.97 to 1.29, p= 0.12). After covariate adjustment, AF at baseline remained an independent predictor of all-cause mortality regardless of baseline EF: PEF HR 1.37 (95% CI 1.06 to 1.79) and low EF HR 1.22 (95% CI 1.04 to 1.43).

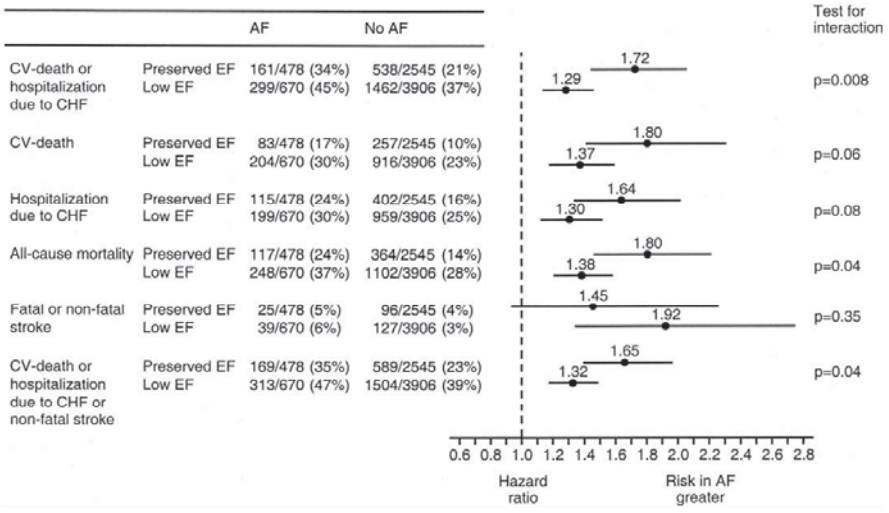

Figure 10. Risk of baseline atrial fibrillation (AF) for cardiovascular CV) events depending on ejection fraction (EF). CHF=Chronic Heart Failure.

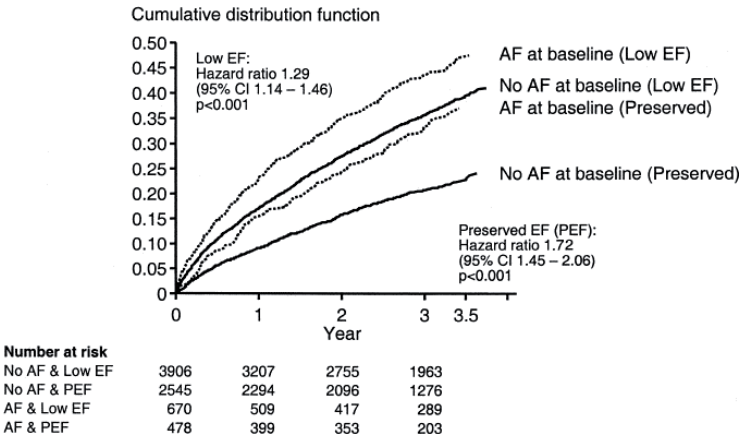

Figure 11. Time to cardiovascular death or hospitalization for heart failure in patients with or without atrial fibrillation (AF) and low or preserved ejection fraction (EF) in CHARM.

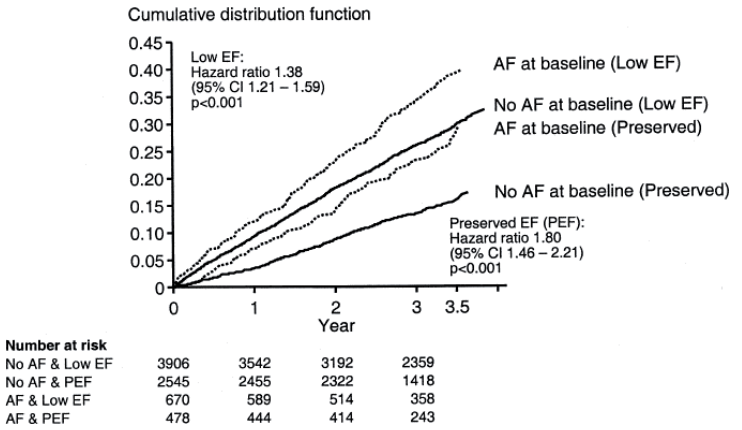

Figure 12. Time to all-cause mortality in patients with or without atrial fibrillation (AF) and low or preserved ejection fraction (EF) in CHARM.

Outcomes in patients with new onset AF

In 392 patients, AF developed during follow-up, 263 (7.8%) in the low EF group and 129 (4.9%) in the PEF group. Patients with new-onset AF experienced a higher risk of morbidity and mortality regardless of baseline EF. The odds ratio for CV death or hospitalization for worsening heart failure was 4.22 (95% CI 2.90 to 6.13) in the PEF group and 3.17 (95% CI 2.45 to 4.09) in the low EF group; p= 0.19 for interaction (Figure 13). For all-cause mortality the odds ratio was 2.57 (95% CI 1.70 to 3.90) in the PEF group and 1.85 (95% CI 1.44 to 2.37) in the low EF group; p= 0.18 for interaction. Again, the absolute risk of an adverse CV outcome was highest in the low EF-new AF patient group, but the patients with PEF and new AF had a greater relative

increase in risk than those with low EF and new AF. For example, the absolute risk of CV death or CHF hospitalization was 66% in the low EF-new AF group and was increased from 20% to 47% by the new development of AF in the PEF group.

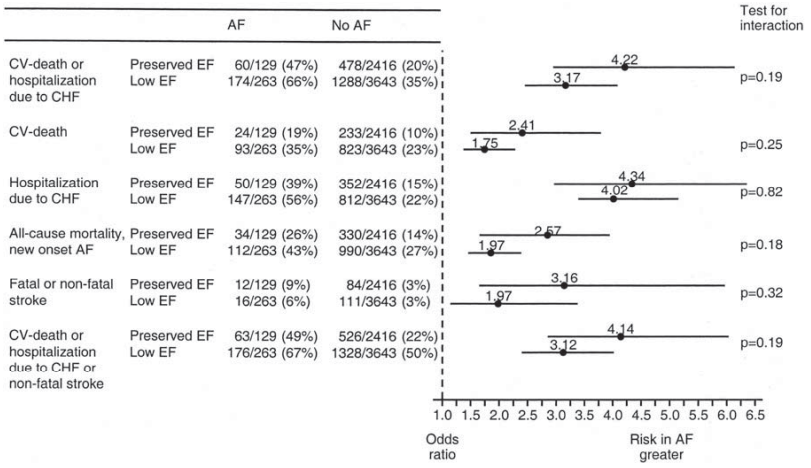

Figure 13. Risk of new-onset atrial fibrillation (AF) for cardiovascular (CV) events depending on ejection fraction (EF). CHF=Chronic Heart Failure.

Treatment effects

In the CHARM-Overall program, candesartan reduced the risk of the composite primary endpoint in both AF (HR 0.83, 95% CI 0.69 to 0.99) and non-AF groups (HR 0.84, 95% CI 0.77 to 0.92; p for interaction 0.80). There were also trends toward a reduced risk of all-cause mortality in both groups that did not reach statistical significance, HR 0.82 (95% CI 0.67 to 1.01) for AF and HR 0.94 (95% CI 0.85 to 1.04) for no AF, p for interaction 0.22. In the PEF group there was no significant effect of candesartan on the primary composite end point in the overall population and no difference in effect according to presence or absence of AF (p for interaction 0.82). In patients with low EF, candesartan reduced CV morbidity and mortality to a similar degree regardless of the presence of AF at baseline (Table 18).

Table 18. Treatment effects in CHARM Low-EF patients depending on heart rhythm

	Candesartan Events	Placebo Events	HR	95% CI	Interaction
Cardiovascular death or hospitalization because of heart failure					
AF	139/336 (41%)	160/334 (48%)	0.78	0.62–0.98	0.62
No AF	678/1,953 (35%)	784/1,953 (40%)	0.82	0.74–0.91	
All-cause mortality					
AF	109/336 (32%)	139/334 (42%)	0.70	0.55–0.90	0.05
No AF	533/1,953 (28%)	569/1,953 (29%)	0.92	0.82–1.04	
CV death or CHF hospitalization or nonfatal stroke					
AF	147/336 (44%)	166/334 (50%)	0.80	0.64–1.00	0.58
No AF	705/1,953 (36%)	799/1,953 (41%)	0.84	0.76–0.93	

DISCUSSION

Our findings indicate that the prognosis is improving in patients discharged from a Swedish hospital with a diagnosis of AF during 20 years observation period. However, AF still carries a considerable risk of stroke and mortality. AF in CHF was associated with a considerable morbidity and mortality regardless of baseline EF. Patients with CHF-REF had the highest absolute mortality, while patients with CHF-PEF had the biggest relative increase in mortality. New onset AF was a strong prognostic predictor regardless of EF.

We found that patients discharged from a Swedish hospital with a first AF diagnosis are old and have highly prevalent co-morbidities and that women develop AF at higher age and have a different medical background than men. A diagnosis of chronic heart failure had similar prevalence in men and women but the aetiology may differ as earlier studies have shown that ischemic origin is relatively more common in males, while hypertensive origin is more common in women[111, 112]. In epidemiological studies on CHF up to 50% have CHF-PEF where the aetiology more often is hypertension, patients are older and more often women[113, 114]. The age and gender composition and reported co-morbidities are similar to that seen in international hospital cohorts[59, 60].

Chronic heart failure was not an independent predictor of stroke incidence in our multivariable analysis. This is in accordance with a recent meta-analysis where a diagnosis of CHF or echocardiographic evidence of left ventricular systolic dysfunction were inconsistent predictors of stroke occurrence in patients with AF[75]. In a large cohort of hospitalised patients, CHF was an independent albeit weak predictor of stroke[80]. A recent literature review suggested LVEF ≤20, left ventricular aneurysm, pedunculated thrombus or previous stroke as high-risk markers for cardiac thromboembolism in patients with CHF and sinus rhythm[115]. In our analysis, patients with previous stroke were excluded and patients with these other risk markers were probably in a minority. Thus, in our study, patients with chronic heart failure in general probably constitute a low-risk population in terms of stroke risk other than the risk provided by the co-morbid atrial fibrillation. With a prevalence of 20% in our cohort, hypertension is probably underestimated, given the prevalence seen in other cohorts[13, 77, 116, 117]. Hypertension complicated with AF is associated with increased mortality and risk of CHF and stroke[81, 82]. Hypertension, as well as age, diabetes (and previous stroke/TIA that we censored for up to seven years before index hospitalization) have consistently been reported as risk predictors for stroke, in both atrial fibrillation and non-atrial fibrillation cohorts[75, 76].

The strong association between female sex and risk of stroke in the present study was seen in some[80, 118], but not all prior studies[75, 77]. Women develop stroke at higher ages than men and less often receive OAC as primary or secondary prevention[119, 120]. A stroke risk score including female gender as a risk factor has recently been proposed based on the Euroheart survey[96].

Stroke incidence has remained quite stable in Sweden during the 80's and 90's, but coinciding with the change seen in patients with AF there is a decrease in the general population from the mid90's and onwards. Our analysis shows a further decrease in patients with AF in addition to that seen in the rest of the Swedish population[121-123]. The incidence of hemorrhagic strokes in the general population has decreased, probably as a result of improved hypertensive treatment[117, 123]. We found an increased incidence of hemorrhagic strokes during the observation period, an increase related to the ageing in this patient group but probably also associated with an increased use of OAC.

Our results mirror those of two other large hospital cohorts. Frost et al found a 22% decrease in 3-year stroke incidence among men and a 20% decrease in women, after adjustment for age, co-morbidities and stroke incidence in the Danish population. In an age-specific analysis young patients had bigger improvements than older patients with AF[80]. As with our study, no information of medical treatment was available in this study, but another study showed increased use of OAC in Danish patients with AF between 1995 and 2004[124]. An analysis of the Medicare 5% sample showed a decreased stroke incidence from 46.3 stroke cases to 19.5 per 1000 patient-years between 1992 and 2002 while the use of OAC had increased from 24.5 to 56.3% in patients with atrial fibrillation[78]. The incidence rate for hemorrhagic strokes remained stable during the observation period. Two smaller studies showed marked[77] or only minor[79] decreases in stroke incidence. Case-fatality remained unchanged in both studies and the proportion of OAC-treated patients increased. Studies on the use of OAC suggests under-utilization and factors other than established risk factors seem to influence the prescription of OAC[87, 88, 119]. However, European and American studies show an increased utilization during the last two decades[35, 77, 78, 124, 125].

In addition to the general analysis of mortality our intention was to examine the role of co-morbidities in the prognosis of AF. Our analysis confirms the impact of comorbidities on AF mortality. When some of the most important prognostic indicators in patients with AF were excluded from analysis, the remaining patients had an adverse prognosis. We were unable to create a population absolutely free of concomitant heart or other diseases, but this was never our intention. Patients with lone atrial fibrillation in its proper form, i. e. patients without cardiovascular disease including diabetes mellitus and hypertension with no precipitating causes for AF occurrence, are relatively few and not representative of the general patient with AF[15]. Remaining excess mortality may be due to co-morbidities not fully reflected in baseline characteristics (e.g. hypertension), AF in itself or in conjunction with non-cardiac illnesses. Cancer and COPD (included in pulmonary diseases) are both independent predictors of new onset AF, patients with AF and these comorbidities of course have a poor prognosis, which is reflected in the present work[126]. The tendency towards more improvements in younger male patients with any the prespecified comorbidities may be due to improvements in background evidence-based treatments and management of ischemic heart disease[61, 62].

Four analyses on temporal trends have been published. Two analyses have been made on Scottish hospital cohorts (SMR)[26, 59], where short-and long-term case fatality was reduced. These analyses were not adjusted for trends in the corresponding general population. Frost et al adjusted for age, co-morbidities and for trends in the general

Danish population in their analysis, and found a 20% decrease of mortality in males and an 18% decrease in females, respectively 1995-1999 vs 1980-1984[60]. In an age and sex-matched comparison with the general Minnesota population, Miyasaka et al found an almost 10 time excess mortality risk within the four months after diagnosis of AF(HR 9.62; 95% CI 8.93 to 10.32 and a 66% excess risk thereafter (HR 1.66; 1.59 – 1.73)[47]. Mortality remained unchanged during the 22-year observation period.

As a contrast to the Swedish register studies, patients enrolled in the COMET and CHARM trials were younger, with a higher male preponderance, regardless of baseline heart rhythm. Most similar to the hospital population in terms of age and gender composition was, not surprisingly, the CHARM Preserved population. OAC was prescribed in about ¾ of patients with AF, well above the numbers from EuroHeart survey[127]. By design, patients in COMET were all treated with a beta-blocker. In the CHARM trial, beta-blockers were less often prescribed in patients with AF regardless of EF, a possible reflection of chronotropic incompetence in elderly, frail patients. Baseline heart rate was higher in patients with AF, regardless of LVEF. Knowing from COMET and other cohorts including subjects with CHF in sinus rhythm that heart rate is an independent risk factor for mortality and hospitalizations, these differences may be of importance[128, 129]. A recently published clinical trial on strict versus lenient rate control in patients with AF showed no difference on clinical outcomes. Patients enrolled in our studies had more advanced heart disease so the results may not be applicable[130].

The higher relative risk of AF in CHF-PEF than CHF-REF in the CHARM analysis may be a reflection of different stages of the disease. It is important to remember that LVEF is a strong albeit crude prognostic marker. When looking at the entire CHARM cohort, LVEF was an independent predictor of prognosis below 45%, while a LVEF above 45% did not contribute further prognostic information[131]. Diastolic dysfunction is present in both apparently healthy subjects and in a wide spectrum of patients, both with and without CHF, and the delineation between diastolic dysfunction and CHF-PEF is not entirely clear, especially since many patients with diastolic dysfunction may not have diagnosed CHF-PEF and vice versa[113]. Due to impaired passive (early) ventricular filling patients become more dependent on atrial systole to maintain adequate cardiac output. Onset of AF could lead to important hemodynamic consequences in these patients. In a previous pacing study irregular pacing patterns mimicking AF was responsible for reductions in cardiac output and increases in pulmonary wedge pressure *regardless* of heart rate[132]. New onset AF was a strong predictor of mortality, CHF and stroke in three large clinical trials on diabetes and hypertension with and without left ventricular hypertrophy, all patient groups where diastolic dysfunction is common[81, 82, 133]. As the diastolic dysfunction progresses, the relative importance of the late phase (atrial systole) may diminish. Advanced CHF, regardless of ejection fraction, is associated high but varying prevalence of restrictive left ventricular filling pattern, with little or no atrial contribution[134]. In fact, CHF-REF-patients may have more advanced diastolic dysfunction than CHF-PEF[135]. Diastolic dysfunction is an important prognostic indicator in both CHF-PEF and CHF-REF[134, 136, 137] and NT-proBNP, a strong prognostic indicator in patients with CHF-REF and PEF[136, 138], varies with the degree of diastolic dysfunction within the same LVEF strata both in patients with CHF-REF and PEF[139, 140]. In several trials enrolling patients with severe

CHF, AF did not predict prognosis[141, 142]. The prognostic importance of AF in relation to diastolic dysfunction in CHF-REF patients have been analysed in several trials. In a substudy of the ECHOS trial diastolic dysfunction was assessed by echocardiography. A restrictive filling pattern was associated with poor prognosis in AF as well as in sinus rhythm, but AF did not add any prognostic information beyond that of the filling pattern[143]. In an analysis of a smaller CHF cohort, markers of diastolic dysfunction outperformed AF as a prognostic marker in patients with mostly CHF-REF[137]. In one study a pulmonary wedge pressure above 16mm Hg was not predictive of prognostic importance with AF[144]. In a recent study consisting of 8931 consecutively admitted patients with AF and an echocardiographic examination made in a Californian centre, only patients with preserved or mildly impaired systolic function had worse prognosis with AF. After co-variable adjustment, only patients with AF and preserved systolic function carried worse prognosis relative SR[145]. Finally, in a study of 368 patients with severe CHF-PEF, AF was not a predictor of mortality[146]. Thus, the relative importance of AF may vary with the degree of systolic as well as diastolic dysfunction. This may explain some of variations in the prognostic importance of AF in CHF patients seen in earlier trials together with age, comorbidities and concomitant medications etc[56].

The discrepancies in patients with heart failure is even more puzzling with regards to the uniform behaviour of the trial regarding AF in the acute setting of a myocardial infarction with or without left ventricular dysfunction[48, 49, 147-149]. This led Danish investigators to perform separate analysis on patients with ischemic and non-ischemic origin, with data from the DIAMOND and ECHOS studies[150, 151], where prognostic importance was retained in patients with ischemic HF but not in non-ischemic HF. Preliminary results from the MAGGIC meta-analysis on individual patient data seem to offer supporting evidence. CHF with an ischemic origin was associated with impaired prognosis in both CHF-PEF and REF while CHF with a non-ischemic origin was associated with impaired prognosis in CHF-PEF but not CHF-REF. (K Swedberg, personal communication). The patophysiologic basis for these findings is not clear.

In contrast, in both studies, new onset AF was highly related to the subsequent risk of morbidity and mortality, something seen in most[51, 53-55], but not all earlier studies[142]. Deaths attributed to acute onset of atrial fibrillation may be attributed to acute deterioration of hemodynamics[132, 152], while long term mortality is maybe more related to structural and electrical remodelling and risk of stroke. Those at highest risk may die early, and after that a levelling off occurs due to deaths in both groups which reduce the prognostic impact of AF. Also, in patients with baseline AF, OAC and improved CHF treatment may have been employed after onset thereby contributing to an improved prognosis.

LIMITATIONS

Paper I and II

The main strength of Paper I and II is the completeness of the data, with a nationwide unselected cohort of patients, and a large number of events that allowed detailed analyses by diagnosis, time period, gender and age group. Even so, these data were collected for administrative rather than research purposes and our cases were not formally validated. However, register-based data diagnoses for heart failure and acute myocardial infarction in Sweden according to the hospital discharge register have been shown to have good validity[153, 154]. Similar hospital discharge diagnoses for atrial fibrillation from Denmark have been validated; in 174 retrieved records, evidence for atrial fibrillation was found in 99%[80]. However, there is a probable underreporting of several important co-morbidities, most notably hypertension, which has been demonstrated in other hospital populations[26, 80]. The true prognostic impact of co-morbidities in this context is therefore uncertain. Many patients with atrial fibrillation are diagnosed and treated entirely in primary care and most hospitals in Sweden do not admit patients for acute or elective cardioversions. The patients included in our analyses are thus most probably more sick than the average patient with atrial fibrillation.

Additional limitations to these studies include firstly that we cannot differentiate cardio-embolic strokes from those of atherosclerotic origin. Second, risk factors for stroke in AF patients are also risk factors for stroke in patients without atrial fibrillation. However, the distinctly different temporal trends of stroke in this patient cohort compared with the general population makes it likely that atrial fibrillation plays an important role in the outcome of these patients. Third, we do not have access to information on medication in these patients. AF-specific treatment has changed during the last 30 years with a marked reduction of the use of class I anti-arrhythmic agents and increased use of OAC, together with treatment of associated conditions, the impact of these changes are unknown to us.

Paper III and IV

Paper III and IV were retrospective analyses of the prognostic importance of atrial fibrillation. The presence of atrial fibrillation at the baseline ECG was used as definition of atrial fibrillation. We could therefore not evaluate the importance of paroxysmal compared with sustained atrial fibrillation in these trials. Incidence of new atrial fibrillation was assessed by adverse events reporting or presence at ECG at the final visit in Paper III and documented at the end of the study from investigator reports the latter of course only possible in survivors. New-onset AF was documented at the end of the study from investigator reports in Paper IV. In none of the studies, systematic recordings was performed, so episodes of AF may have been missed, particularly paroxysmal AF. These analyses therefore neglected the prevalence of and probably underestimated the incidence of paroxysmal and persistent AF. Though paroxysmal AF seem to be a prognostic marker in cohorts not generally consisting of CHF-patients, both in terms of stroke and other CV-morbidity and mortality[67, 74, 155], no such connection is seen in the few CHF cohorts where it has been evaluated[156, 157]. Also,

patients who died early did not have the opportunity to develop AF, so collectively the relationship reported here probably underestimates the true relationship of new-onset AF and mortality. Also, the relationship in time between an adverse CV outcome and new-onset AF in Paper IV was not possible to analyze because of lack of information when onset of AF occurred.

CONCLUSION

Atrial fibrillation is a common disorder, both in unselected hospital patients and in patients with chronic heart failure, regardless of the ejection fraction. There was a modest decrease in the number of ischaemic strokes after a first AF hospital diagnosis in Sweden between 1987 and 2006. The decrease was partly offset by an increased hemorrhagic stroke incidence but resulted in a net decrease of total stroke incidence during this time period, additional to the decline in stroke incidence seen in the general Swedish population. However stroke incidence and excess risk due to presence of AF remained high in this patient group. Patients with AF had an improved survival during the 20 year observation period, but high mortality rates persisted at end of follow-up. Patients with any of four cardiovascular comorbidities had the highest mortality, but also the biggest improvements. Even after the exclusion of patients with important cardiovascular morbidities, mortality remained high, especially in the oldest patients, and temporal trends indicated smaller improvements in survival.

In a prespecified analysis of two large clinical trials with CHF and AF, AF was associated with increased morbidity and mortality both when present and when occurring during study follow-up, regardless of baseline EF. This analysis indicates the need to implement evidence-based treatments and to intensify the efforts to identify and manage the causes of increased morbidity and reduced survival in patients with CHF and AF.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Bakgrund

Förmaksflimmer är den vanligaste rytmrubbningen i kliniskt vardag. Förekomsten varierar mellan 1-2% i olika studier. Förekomsten av förmaksflimmer är relaterat till ökande ålder och flera olika hjärt- och kärlsjukdomar, där hypertoni och diabetes mellitus verkar vara de riskfaktorer som orsakar flest antal förmaksflimmer medan patienter med hjärtsvikt och klaffsjukdom har större risk att få förmaksflimmer.

Förmaksflimmer är associerat med en dubblerad risk för förtida död, fyra-fem gångers ökad risk för stroke och tre gångers ökad risk för att utveckla hjärtsvikt i jämförelse med individer utan denna rytmrubbning. Då förbättrad behandling av utlösande faktorer och en allmänt förbättrad hälsa gör att vi lever längre, spås förekomsten av förmaksflimmer att öka. Detta kommer att vara en av sjukvårdens framtida utmaningar. Flera studier har gjorts angående tidstrender av risk för stroke och dödlighet efter förstagångsdiagnos av förmaksflimmer. Flera av dessa är antingen små, har kort uppföljningstid eller analyserar inte relevanta frågeställningar. Vidare är viktiga grupper av patienter med förmaksflimmer dåligt definierade. Vid kronisk hjärtsvikt är förmaksflimmer en vanlig komplikation som leder till förtida död, men huruvida det är flimret i sig som är farligt eller det är den underliggande sjukdomen som är orsaken är oklart. Vilken risk förmaksflimmer utgör hos patienter med hjärtsvikt med bevarad pumpfunktion är otillräckligt studerat.

Frågeställning

- Hur ser tidstrenderna ut för insjuknande i ischemisk och blödningsstroke efter utskrivning från sjukhus med förstagångsdiagnos förmaksflimmer?
- Hur ser tidstrenderna ut för död efter utskrivning från sjukhus med förstagångsdiagnos förmaksflimmer?
- Hur mycket ökar dödlighet och sjuklighet hos patienter med kronisk hjärtsvikt med nedsatt eller bevarad pumpfunktion vid samtidigt förmaksflimmer
- Hur mycket ökar dödlighet och sjuklighet hos patienter med kronisk hjärtsvikt med nedsatt eller bevarad pumpfunktion efter nydebuterat förmaksflimmer

Metoder

I arbete I och II använde vi oss av svenska slutenvårdsregistret, ett register som varit bruk sedan 60-talet och som sedan 1987 har data på alla patienter som skrivits ut från sjukhusvård i Sverige. Detta register länkades till dödsorsaksregistret. Vi hämtade upp information om samtliga individer som skrivits ut från sjukhus med en förstagångsdiagnos av förmaksflimmer mellan 1987-2006 i Sverige. Information inhämtades om när diagnosen ställdes, ålder, kön samt övriga diagnoser. Vi delade in observationsperioden i fyra stycken femårsperioder, och analyserade förändringar över tid i strokeinsjuknande och dödlighet upp till tre år efter förstagångsdiagnos av förmaksflimmer.

Då det är allmänt känt att dödlighet och sjuklighet hos patienter med förmaksflimmer till stor del är kopplat till annan sjuklighet, gjorde vi en analys för att identifiera sjukdomar särskilt associerade med risk för förtida död hos dessa patienter. Vi använde denna information för att dela upp patienterna efter förekomst av dessa diagnoser och på så sätt studera hur viktiga de är för dödligheten hos patienter med förmaksflimmer. För analysen av förmaksflimrets betydelse vid hjärtsvikt använde vi oss av två stora randomiserade, läkemedelsstudier. COMET studien inkluderade patienter med nedsatt pumpförmåga och följda i fem år. CHARM studien inkluderade patienter med hjärtsvikt uppdelade i tre delstudier, två studier utvärderade patienter med nedsatt pumpförmåga och en studie patienter med bevarad pumpförmåga. Uppföljningstiden var 3.5 år.

Resultat

321276 patienter utan tidigare strokediagnos skrevs ut med en förstagångsdiagnos förmaksflimmer under 20 års tid. 3-års insjuknandet i ischemisk stroke var under 1987-91 (period 1) 11.6% och sjönk till 9,6% under 2002-2006 (period 4), en 17,5% minskning. Huvuddelen av minskningen skedde under 1997-2001 (period 3) med små förändringar före och efter. Kvinnor hade högre risk att utveckla stroke, andra viktiga riskfaktorer var diabetes mellitus, hypertoni och ischemisk hjärtsjukdom. 3-årsinsjuknandet i hjärnblödningar steg under perioden från 1.0 till 1.3%, en ökning på 37.5% men resultatet blev ändå en minskning av totala antalet stroke. De minskningar vi fann förelåg utöver de minskningar i strokeinsjuknande man ser i resten av den svenska befolkningen under samma tid.

376000 patienter skrevs ut med en förstagångsdiagnos förmaksflimmer under 20 års tid (i denna analys var tidigare stroke tillåten). Dödligheten upp till 3 år efter flimmerdiagnos minskar från 34% period 1 till 26% period 4, en relativ minskning på 23%. När vi delade upp patienterna efter förekomst eller frånvaro av tidigare stroke, kronisk hjärtsvikt, diabetes mellitus och akut koronart syndrom (akut hjärtinfarkt och instabil angina pektoris), fyra diagnoser tätt associerade med ökad dödlighet hos patienter med förmaksflimmer, noterade vi hög dödlighet hos patienter med ovan nämnda sjukdomar, högre hos män och hos äldre. Minskad dödlighet över tid sågs hos bägge könen i alla åldersgrupper i denna kategori, mest uttalat hos män<75år. Hos patienterna utan dessa sjukdomar var dödligheten lägre, men steg snabbt med ålder, och minskningarna i dödlighet över tid var mindre.

I COMET studien var förmaksflimmer hos en hjärtsviktspatient förknippat med ökad risk för förtida död och sjukhusinläggning jämfört med hjärtsviktspatienter i sinusrytm. När vi justerade resultaten för andra kardiovaskulära riskfaktorer innebar förmaksflimmer inte längre en ökad risk för död, men däremot för död och sjukhusinläggning. Utveckling av förmaksflimmer under studien var däremot associerad med en klart ökad risk att dö under studietiden. I CHARM studien var förmaksflimmer hos en hjärtsviktspatient förenat med ökad risk för förtida död och sjukhusinläggning. Hjärtsviktspatienter med reducerad pumpförmåga och förmaksflimmer vid studiens start hade den högsta risken för död och sjuklighet, men patienter med hjärtsvikt och

bevarad pumpförmåga försämrades mer av sitt flimmer jämfört med patienter med bevarad pumpförmåga i sinusrytm. Patienter som utvecklade förmaksflimmer under studien hade klart ökad risk för förtida död och kardiovaskulär sjukdom, oavsett pumpförmåga.

Slutsats

Vi såg måttliga minskningar i strokeincidens och dödlighet hos sjukhusvårdade patienter med en förstagångsdiagnos av förmaksflimmer i Sverige under en 20-årig uppföljning. Trots förbättrad behandling av förmaksflimmer och utlösande sjukdomar under de 30 senaste åren är förmaksflimmer fortfarande associerat med hög dödlighet och sjuklighet. Även om patienter med de viktigaste kardiovaskulära diagnoserna exkluderade från analysen har patienter med förmaksflimmer fortfarande en ökad risk att dö, speciellt med stigande ålder. Patienter med kronisk hjärtsvikt komplicerad med förmaksflimmer har hög risk för sjuklighet och förtida död.

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Appendix

Selected clinical risk scores for the evaluation of risk for ischemic and hemorrhagic strokes in patients with atrial fibrillation

$CHADS_2$	1 Point each for the presence of C= Chronic heart failure, H= Hypertension, A= Age >75 years, D= Diabetes Mellitus and 2 points for S=Earlier Stroke or TIA. 0-1 point is considered low risk, 1-2 is considered moderate risk and >2 is considered high risk.
CHA_2DS_2-VaSC	C=Chronic heart failure/LV dysfunction (1 point), H=Hypertension (1 point), A_2=Age >75 (2 points), D=Diabetes Mellitus 1 point, S_2=Earlier Stroke/TIA/Other thromboembolic event (2 points), A=Age 65-74 (1 point), SC=Sex Category (i e female gender) (1 point)
HAS-Bled	H=Hypertension, A=abnormal renal/liver function, S=stroke, B=bleeding history or predisposition, l=labile INR, e=elderly (>65), d=drugs/alcohol concomitantly (1 point each)