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Paroxysmal Atrial Fibrillation

Prognostic Implications

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Stockholm MMVIII

Paroxysmal Atrial Fibrillation
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Published and printed by Elanders
ISBN: 978-91-7409-085-7

*“There is no ailment in which such success can be achieved,
no other cardiac disorder which may be so speedily benefitted,
as the well-managed case of auricular fibrillation”.*

Sir Thomas Lewis (1881-1945).

Clinical Disorders of the Heartbeat 1912.

To Inger, My, Agnes, Klara and Tore

ABSTRACT

This thesis is based on data from the Stockholm Cohort on Atrial Fibrillation (SCAF). This cohort consists of all 2912 patients with atrial fibrillation or flutter who were treated as in or outpatients at South Hospital in Stockholm or at Gustavsberg Primary Care Centre during 2002. The patients have been followed prospectively through medical records complemented by information from national registers of hospitalisations and mortality.

In *Study I* we evaluated the incidence of ischaemic and haemorrhagic stroke in 855 patients with paroxysmal atrial fibrillation (PxAF). We found that the stroke incidence was approximately twice as high as in the general population and similar to that of permanent atrial fibrillation (PermAF). Warfarin prophylaxis appeared to be as efficient in Px AF as in PermAF. The incidence of cerebral bleedings was low and not higher in patients using warfarin than in patients using aspirin.

In *Study II* we investigated the mortality among patients with PxAF and found it to be higher than expected from age and sex adjusted specific rates in the general population. The standardized mortality ratio (SMR) was 1.6. Patients with PxAF died more often than expected from myocardial infarction (SMR 2.4), heart failure (SMR 2.6) and cardiovascular disease in general (SMR 2.1). The increased mortality in PxAF appears to be present mainly in subjects with concomitant cardiovascular co-morbidity. Treatment with warfarin was found to be associated with improved survival in PxAF patients.

In *Study III* we studied how current guideline recommendations are translated into clinical practice. We found that approximately half of the patients who ought to have warfarin also had received such treatment. Undertreatment was particularly common in patients with PxAF and in patients aged >80 years. Important risk factors for stroke did not increase the likelihood of warfarin treatment.

In *Study IV* we investigated whether patients who remain in sinus rhythm after DC-cardioversion obtain any prognostic benefit from having normal sinus rhythm restored. From the SCAF-cohort 361 patients who had been DC-cardioverted were studied. Patients without known relapse to atrial fibrillation within three months after cardioversion had a lower incidence of all-cause mortality (HR 0.5, 95% C.I. 0.3-1.0) as well as a lower incidence of the composite end point consisting of death, ischaemic stroke, myocardial infarction or hospitalization for heart failure (HR 0.5, 95% C.I. 0.3-0.8) after multivariable adjustment.

Conclusions

PxAF is associated with increased morbidity and mortality which is similar to that of PermAF. Underlying cardiovascular disease seems to account for most of this. Therefore it is essential to diagnose and treat any underlying cardiovascular disease in PxAF-patients.

Warfarin seems to be helpful, not only against stroke but also against premature cardiovascular death. Therefore it is essential to provide PxAF-patients with adequate anticoagulant treatment unless there are clear contraindications for such therapy.

Our results suggest that restoration and maintenance of sinus rhythm may improve the prognosis in patients with atrial fibrillation. Therefore, we propose that eligible patients should be given an opportunity to be restored to sinus rhythm before atrial fibrillation is accepted as permanent.

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ABBREVIATIONS

AF	Atrial fibrillation
CI	Confidence interval
ECG	Electrocardiogram
HR	Hazard ratio
PermAF	Permanent atrial fibrillation
PersistAF	Persistent atrial fibrillation
PxAF	Paroxysmal atrial fibrillation
SIR	Standardized incidence ratio
SMR	Standardized mortality ratio
TIA	Transient ischaemic attack

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following studies, which will be referred to by their Roman numerals.

- I. Friberg L, Hammar N, Rosenqvist M.
Stroke Incidence in Paroxysmal Atrial Fibrillation:
-report from the Stockholm Cohort of Atrial Fibrillation (SCAF).
Submitted for publication.
- II. Friberg L, Hammar N, Pettersson H, Rosenqvist M.
Increased mortality in paroxysmal atrial fibrillation:
-report from the Stockholm Cohort-study of Atrial Fibrillation (SCAF).
Eur Heart J. 2007 Oct;28(19):2346-53.
- III. Friberg L, Hammar N, Ringh M, Pettersson H, Rosenqvist M.
Stroke prophylaxis in atrial fibrillation: who gets it and who does not?
Report from the Stockholm Cohort-study on Atrial Fibrillation (SCAF-study).
Eur Heart J. 2006 Aug;27(16):1954-64. Also published in European Heart Journal
Chinese Excerpts Edition 2007; 34-46. ISSN 1816-286X
房颤患者卒中的预防：哪些患者得到了治疗？
- IV. Friberg L, Hammar N, Edvardsson N, Rosenqvist M.
Restoration of Sinus Rhythm is Associated with Improved Prognosis in Patients
with Atrial Fibrillation
- report from the Stockholm Cohort of Atrial Fibrillation (SCAF).
Submitted for publication.

1. INTRODUCTION

This thesis is concerned with people whose hearts spontaneously alternate between normal rhythm and AF, i.e. patients with paroxysmal and persistent AF. According to my own clinical experience, their rhythm problems have been seen more as a disturbing nuisance than as something of prognostic importance.

In the past, when I met AF-patients in the emergency department who spontaneously reverted to sinus rhythm the result was alleviation. Luckily, it was just PxAF and therefore no need to ponder about anticoagulation. Then I would not have to go through lengthy explanations about warfarin treatment with a patient who often was elderly and in need of more of my scarce time than I had to spare. Many fellow physicians share similar experiences.

The idea that PxAF is more or less harmless may have sprung from an idea that less AF is less dangerous than more AF and that self-limited attacks of short duration therefore cannot do much harm, although no studies supported this. But is PxAF really harmless? The purpose of the studies in this thesis was to shed some light on this common clinical situation.

1.1 HISTORICAL PERSPECTIVE

In AF the pulse is typically irregular and the patient may experience palpitations. Such sensations of palpitations and irregularities of the pulse have naturally been a frequent matter of concern and alarm to mankind.

Some hold that the very first mentioning of AF was made in ancient China. The famous quotation reads;

“When the pulse is irregular and tremulous and the beats occur at intervals then the impulse of life fades”

The quotation is from the first book of the “Neijing”, often referred to as “The Yellow Emperor’s Canon of Internal Medicine”, where a lengthy chapter is devoted to the art of pulse palpation which should be performed at dawn before food and drink have been taken, *“before the breath of Yin has begun to stir, and the breath of Yang has not yet dispersed thoroughly”* (1-3).



Fig 1.
The Yellow Emperor Huangdi (2600 B.C.)

The authorship has been attributed to the mythical hero and taoist saint Huangdi, founder of the Chinese Han dynasty (approx 2600 B.C.). According to modern research, however, this textbook of traditional chinese medicine was probably compiled, completed and continuously revised by countless anonymous authors until it found its present form a couple of hundred years B.C. (3). Furthermore, the alleged description of AF is vague and could refer to any other cardiac arrhythmia.

Therefore it may as well be Hippocrates (approx 460-370 B.C.) who was the first to make observations about AF.

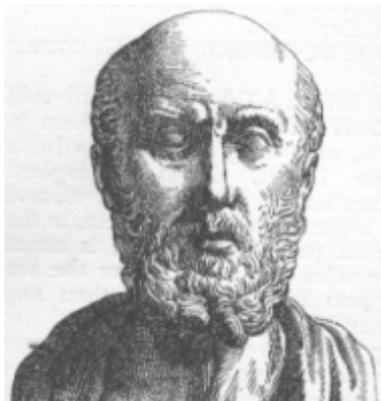


Fig 2.
Hippocrates (approx 460-370 B.C.)

Hippocrates considered “violent palpitations of the heart” to be a sign of a poor prognosis and also noted that persons “who suffer frequent and strong faints without any manifest cause, die suddenly” (4).

As with emperor Huangdi it may be objected that Hippocrates was not very precise in his description. Certainly, there are other irregular rhythms than AF, and cardiogenic syncope associated with sudden death is most likely not AF or the associated tachycardia syndrome but rather complete AV-block, ventricular tachycardia or ventricular fibrillation.

In the days of Hippocrates and Huangdi there was no ECG and even the role of the heart was poorly understood. At this time, the vessels were generally seen as originator of the pulse, not the heart. No one had yet discovered the meaning of the atria, or even less

what use one could have of the auricular appendages of the atria (5). (Indeed, one may still ask why we have these appendages)

It was not until the 17th century and the emergence of the new empirical natural sciences that the modern understanding of AF began to emerge. William Harvey (1578-1657) examined hearts of fishes, frogs, eels, birds, dogs and horses. In 1628 he showed that the heartbeat commenced in the atria “The movement is seen to begin from the auricles and to pass on to the ventricles” (5, 6). He also noticed “strange, undulating movements” of the right atrium in a dying experimental dog, thought to be the very first description of AF.

A hundred years later Jean-Baptiste Senac (1693-1770), physician to the French king Louis XV, confirmed Harvey’s observations. As a clinician he was interested in palpitations and found that mitral valve disease was a frequent cause;

“When the obstacles in the heart obstruct the entrance to the ventricles, blood accumulates in the cavities of the auricles and irritates the fibres of their wall. Their contractions become more lively” (5, 7, 8).

During the 19th century the understanding of AF increased (9-12) by means of animal experiments and post mortem examinations. Without the aid of the ECG it was almost impossible to tell with certainty whether a patient with an irregular rhythm had AF or some other arrhythmia. Terms used by different authors during this time were therefore typically descriptive ones; “frémissement fibrillaire”, “delirium cordis”, “pulsus irregularis perpetuus” or “rebellious palpitations”.

It was not until 1909 that Sir Thomas Lewis in London and Rothberger and Winterberg in Vienna established AF as a clinical entity by means of Willem Einthovens newly discovered electrocardiogram (9, 10, 13-15). Lewis named the arrhythmia “auricular fibrillation” while Rothberger and Winterberg named it “Vorhofflimmern”.

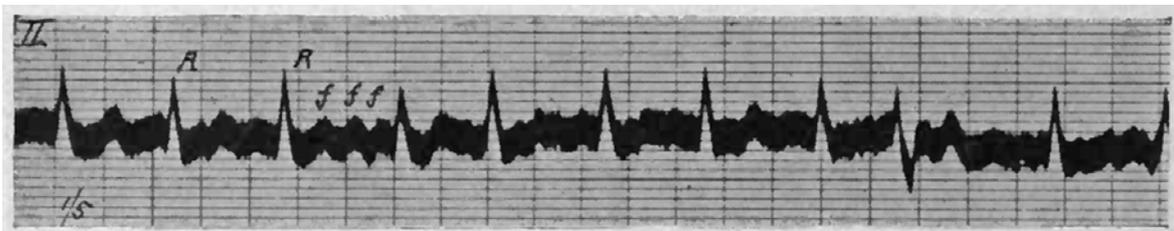


Fig 3.

AF recorded by Lewis 1909 in a patient with rheumatic heart disease

Atrial fibrillation was a serious condition a hundred years ago. It often lead to heart failure and death within a few years. Lewis considered AF to be an essentially chronic and terminal malady which in most cases “heralds cardiac failure so that few patients survive its onset for more than ten years”. From his autopsy studies he also came to suspect that AF could result in embolic stroke;

“If a series of diseased hearts be examined at autopsy, ante-mortem clots are found in much the heavier percentage in those auricles, which during life exhibited fibrillation. The virtual paralysis of the auricles, and the consequent stagnation of blood in them definitely predisposes to thrombosis in the appendices”(13).

Lewis also made observations specifically related to paroxysmal atrial fibrillation (PxAF) at a time when distinctions between different types of AF was unheard of.

“In paroxysmal fibrillation I have observed a coincidence between embolism of lungs and brain and the resumption of the normal auricular contractions. Presumably, clots, formed during the period of auricular fibrillation, were detached when the heart resumed its natural mode of beating”(13).

When Edvard Bell Krumbhaar published his thesis “Transient Auricular Fibrillation – an electrocardiographic study” at the University of Pennsylvania in 1916 he was probably the first ever to have made PxAF the topic of a scientific dissertation (16). In his thesis he concluded that PxAF was a rare condition, but that the newly invented string galvanometer probably would reveal many more cases. Krumbhaar noted with remarkable accuracy that paroxysms might be triggered by acute infection, acute alcohol intoxication, hyperthyroidism, underlying myocardial degeneration, valvular heart disease, pulmonary embolus or acute pericarditis.

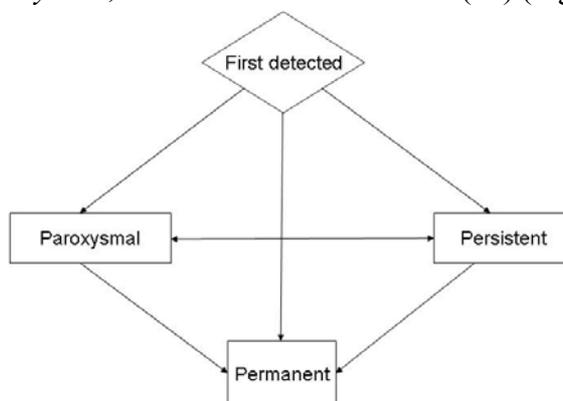
The present understanding of AF is that it involves two main processes; multiple self-sustaining reentrant wavelets, as originally proposed by Moe and Abildskov (17) and enhanced automaticity, with rapidly firing groups of cells especially round to the orifices of the pulmonary veins, as demonstrated by Jais, Haissaguerre and others(18).

1.2 DEFINITIONS

“Atrial fibrillation is”, according to the joint expert groups of the European and American Cardiological Societies, “a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. On the electrocardiogram (ECG), AF is characterized by the replacement of consistent 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” (19).

1.3 CLASSIFICATION OF AF

The currently recommended classification scheme for AF considers 4 different types of AF; *First detected, Paroxysmal, Persistent and Permanent* (19) (Fig 4).



*Fig 4
Patterns of atrial fibrillation*

When AF is detected for the first time it is generally not possible to determine whether it is intermittent or permanent. There is often uncertainty about the duration from onset of AF since AF often may be asymptomatic. When the patient has had at least two documented episodes of AF it is termed recurrent. Recurrent AF may either be self-terminating in which case it is called paroxysmal, or sustained in which case it is called persistent.

According to current international conventions on terminology, PxAF is characterized by self-terminating episodes of AF that last up to 7 days (most less than 24h) (19, 20). This definition does, however, not cover all situations. Difficulties arise in relation to:

- Patients with PxAF who occasionally may have longer episodes of PersistAF which may have to be terminated by cardioversion. Conversely, approximately 40% patients with PersistAF who had been successfully cardioverted showed multiple spontaneously terminating episodes of PxAF in a study using ambulant ECG-monitoring (21). There is no widely accepted agreement on how to distinguish between PxAF and PersistAF. Workers in this field tend to use their own definitions, which, however, rarely are presented in detail.
- Asymptomatic AF. The reported frequency and duration of episodes depends on how closely the patients are monitored. Thus, the number of patients with PxAF is likely to increase as more resources are allocated to discover AF.
- There is no widely accepted agreement on the minimum duration of AF to be counted as an episode of AF, or how many episodes of AF there has to be for AF to be of clinical and practical significance. The use of long time ECG-monitoring and monitoring by the expanded memory capacity of cardiac pacemakers have shown that brief asymptomatic episodes of AF are very common. Yet there is no consensus on how such episodes should be interpreted.

In the SCAF cohort study we determined the type each patient's AF from the accumulated information that was available by the end of the inclusion year. To avoid ambiguity in the classification of PxAF and PersistAF, we considered all patients who were cardioverted during the inclusion year as having PersistAF. During follow-up patients were analyzed according to the type of AF they had on the inclusion to the study, although the type of AF may later have changed (i.e. analogous to on-intention-to-treat design).

Patients were only eligible for inclusion if they had received a clinical ICD-10 diagnosis of AF. Thus, patients with very short episodes of PxAF were unlikely to be considered for inclusion.

The term "lone AF" is used to describe young individuals (<60 years) with no other concomitant cardiovascular disease (22, 23). These patients have low risk of embolic stroke and should for that reason not be treated with anticoagulants. The definition of lone AF varies, and its prevalence is in all probability inversely related to the thoroughness with which cardiovascular disease is looked for.

1.4 EPIDEMIOLOGY

PxAF is an elusive disease that may pass unnoticed. It is difficult to determine if and when someone who once has had an episode of PxAF is to be regarded as free of AF. It is difficult to distinguish PxAF from PersistAF in patients with episodes of both kinds. Any attempt to estimate the prevalence of PxAF therefore involves both difficulties with arbitration as well as some guesswork.

Current estimates of the prevalence of AF in any form are in the range of 2-5 % of persons aged 65 years, 5-10 % at age 75 years and 9-18 % at 85 years or older (24-28). Surprisingly little has been reported about the epidemiology of PxAF. Previous reports have estimated that PxAF constitute 18-62% of all AF (29-31). Patients with PxAF are generally younger than those with PermAF (32-34).

In AF of any type the debut of AF occurs at lower ages in men than in women. In the population, however, there are almost as many men as women suffering from AF because women live longer (26, 35-39). Whether this also applies to patients with PxAF has not been studied specifically.

In the SCAF-cohort study we investigated the prevalence of AF and PxAF in 2002 at the Gustavsberg Primary Care Centre. The results, which are presented below, have not been published previously (and thus not in any of the articles of this thesis). Details about how the study was done is explained below in the section on methodology.

During the year 2002 we found that a diagnosis of any kind of AF was given to 0.3 % of the population in the ages 18-64 years, 5.4 % in the ages 65-79 years and 12 % at 80 years or older. However, these figures are obviously too low since many patients with AF did not receive a diagnostic code of AF each year. We found that AF patients on average lacked an ICD-diagnosis of AF in their case records or in the National Hospital Discharge Register for one out of three years of follow up. Such gaps may arise when a patient has had all his or her contacts with the Primary Care Centre during one full year as diagnostic ICD codes are used less consequently in the primary care than in the hospital. The true prevalence of AF (all forms) could therefore be estimated to be 0.4% in the ages 18-64 years, 8.1 % in the ages 65-79 years and 18 % at 80 years or older. The prevalence of PxAF can be estimated to be 0.1% in the ages 18-64 years, 2.2 % in the ages 65-79 years and 3.9 % at 80 years or older (Fig 5).

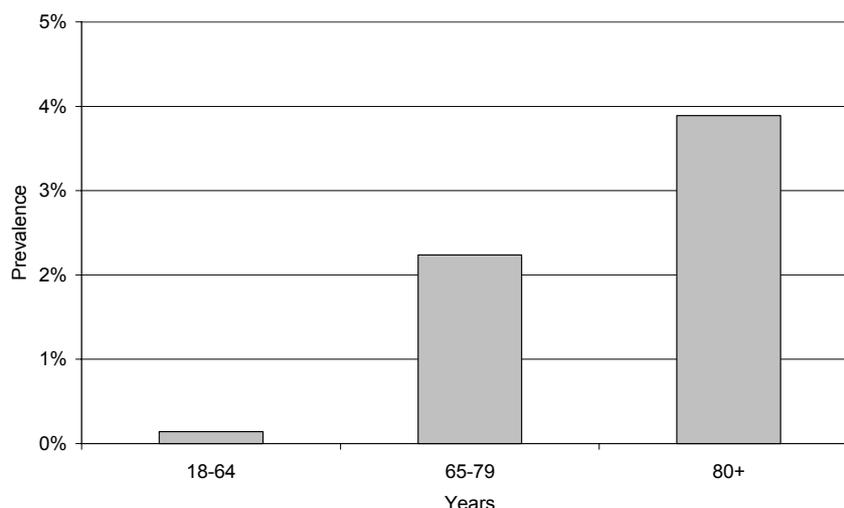


Fig 5.

Estimated prevalence of symptomatic PxAF in the Gustavsberg area 2002.

PxAF was relatively more common among younger persons. Of all patients with AF 36% in the ages 18-64 years had PxAF, 28 % in the ages 65-79 years and 22 % in the ages ≥ 80 years. Extrapolation of the data from Gustavsberg indicate that there may be 30-40 000 persons with symptomatic PxAF in Sweden which has a population of approximately 9 million inhabitants.

Among younger PxAF patients there was a dominance of men, whereas women dominated among patients 80 years and older (Fig 6).

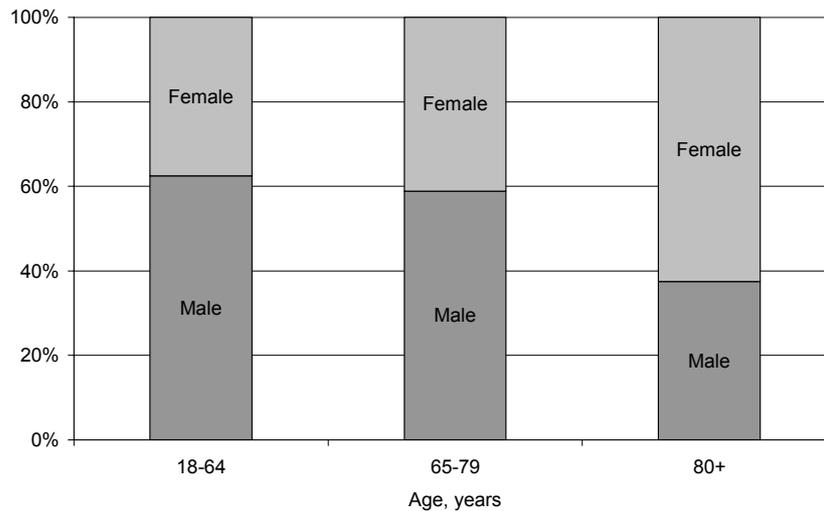


Fig 6.

Sex distribution in different age-groups in patients with PxAF in Gustavsberg 2002.

1.5 PROGNOSIS

Relatively little is known about the prognosis in PxAF specifically (40), although much is known about the prognosis in PermAF or AF in general. Current recommendations regarding the treatment of patients with PxAF (19) are therefore mostly based on evidence from studies primarily dealing with PermAF.

Mortality

There are few studies on mortality in PxAF specifically. In one of these no excess mortality was found in comparison to an age and sex matched sample from the general population (41). Other studies have shown that PxAF indeed is associated with increased mortality, but that cofactors are mainly responsible for this (42-45). Evidence is, accordingly, conflicting as to whether PxAF is an independent risk factor for premature death.

Other studies dealing with all forms of AF, such as the Framingham Heart Study, have shown that AF is associated with an increased risk of premature death. After adjustment for age and comorbidity, the reported relative risk in various studies has been in the range of 1.2-2.0 (46-48).

Ischaemic stroke

There are but a few studies directly addressing the risk of ischaemic stroke in PxAF. These studies indicate that the risk of ischaemic stroke in PxAF is substantial and not different from that in PermAF (33, 49, 50).

The risk of ischaemic stroke in PermAF and in non-specified AF is reported to be 2-7 times that in persons without AF (51-53). The risk of stroke varies widely depending on age and comorbidity. Recently a stroke risk classification scheme for patients with AF, known as CHADS₂, was adopted in the guideline document of the European and American Cardiological Societies (19, 54, 55). In this scheme one point is given for each of cardiac failure, hypertension, age>75 and diabetes mellitus. A previous stroke or TIA is given 2 points as such events are considered as major risk factors. According to this scheme the annual adjusted stroke rate varies between 2% and 18% with increasing CHADS₂- scores (Table 1).

CHADS ₂ -score	Stroke rate per 100 patient years	
	Unadjusted	Adjusted (CI)
0	1.2	1.9 (1.2-3.0)
1	2.8	2.8 (2.0-3.8)
2	3.6	4.0 (3.1-5.1)
3	6.4	5.9 (4.6-7.3)
4	8.0	8.5 (6.3-11.1)
5	7.7	12.5 (8.2-17.5)
6	44.0	18.2 (10.5-27.4)

Table 1.
Risk of Stroke stratified by CHADS₂-score. From Gage et al (54)

1.6 CLINICAL PRESENTATION

Clinical symptoms of PxAF may range from no symptoms to disabling symptoms. Patients may typically complain about palpitations, dyspnea and fatigue that prevents them from doing things they normally do, like climbing stairs or going for a walk. Occasionally symptoms include lightheadedness or syncope, especially in conjunction with the termination of an episode of AF if the arrhythmia is associated by sinus node disease. The first symptom may also be an embolic stroke (56).

Symptomatic and asymptomatic PxAF may coexist in the same patient. In patients with symptomatic PxAF asymptomatic episodes have been shown to be far more frequent than symptomatic episodes of AF (21, 57-60). Thus, the symptomatic episodes may be seen as the visible tip of an iceberg. There does not appear to be any difference between asymptomatic and symptomatic PxAF regarding the prognosis (61, 62).

As much as one third of all AF is clinically silent in the sense that it is discovered accidentally without the patient seeking medical attention for it (61, 62). The exact prevalence of silent PxAF remains unknown. However, patients may suffer from reduced vitality and fatigue not realizing that the reason for their lack of well-being is AF (63). Even if unaware of their arrhythmia, such patients may experience an improvement in quality of life if the arrhythmia is successfully treated.

1.7 MANAGEMENT

The overall aim for treating PxAF is to alleviate symptoms, prevent recurrences and to prevent stroke and other complications that follow PxAF. Available treatment modalities include antiarrhythmic medication, antithrombotic medication as well as non-pharmacological alternatives. The latter range from minimally invasive catheter ablation techniques to open heart surgery and generally aim at curative elimination of atrial fibrillation or flutter. The results are generally good and it is likely that non-pharmacological methods, especially catheter ablation techniques, will play an increasingly important role in the future. At present, however, curative treatment is only available for a small fraction of all patients with PxAF due to limited capacity to meet the potential demands.

Rhythm or rate control

A treatment strategy aimed at restoration and maintenance of stable sinus rhythm is called a rhythm control strategy. There is also a rate control strategy in which AF is accepted as permanent and efforts are aimed at minimizing symptoms by giving medication to keep heart rate within physiological limits at rest and during exercise. Adequate prevention of thromboembolic complications must be considered in both strategies.

Although PxAF is not a sustained arrhythmia, the distinction between rhythm and rate control strategies regarding PxAF-patients may still be resorted to in a broader sense. First, because patients may both have spontaneously terminating episodes of PxAF, and occasionally more protracted episodes of AF that have to be terminated by electrical or pharmacological cardioversion. Second, there may be differences in the aggressiveness of the choice of anti-arrhythmic agents and in when patients are to be considered for non-pharmacological interventions.

In the AFFIRM and RACE trials the rate and rhythm control strategies were evaluated and failed to show any difference in mortality or perceived quality of life (64-67). These studies were, however, troubled by massive crossover between treatment arms and are therefore difficult to evaluate regarding the prognostic importance of sinus rhythm for patients who actually remained in sinus rhythm.

In practice, the choice of strategy is largely depending on the severity of symptoms. A patient who is incapacitated and highly symptomatic during an episode of AF has more to gain, and is more motivated to endure the side effects of treatment or the hardships of non-pharmacological attempts, than a less symptomatic patient.

Prevention of stroke

Dose-adjusted oral anticoagulation with antagonists to vitamin K, in Sweden almost exclusively warfarin, has been shown to effectively prevent thromboembolic stroke in patients with AF. The reduction is in the order of 60 % compared with placebo treatment (68-72). Warfarin treatment has also been shown to reduce mortality in AF-patients (73). Whether any of this also is true for PxAF is not known. Most investigations showing this protective effect have been made on patients with PermAF exclusively, or with only a minority of patients with PxAF. It is possible that the results also are valid for patients with PxAF, but the evidence for this is relatively weak as only a few studies made on patients with PxAF have demonstrated a protective effect against stroke (50, 74).

INTRODUCTION

Acetylic acid (aspirin) 81-325 mg has been shown to provide a more modest protection against stroke, which is less efficient than warfarin (49, 68-71, 75).

Treatment with warfarin increases the frequency and severity of haemorrhages, including cerebral haemorrhages, compared to no treatment. The risk of bleeding depends on age and comorbidity, where several of the factors that signify an increased risk of ischaemic stroke also indicate an increased risk of a haemorrhagic stroke (76-78). The risk of bleeding is also related to the intensity of treatment, for which the optimal therapeutic range in most patients is 2.0-3.0 INR.

Current international guidelines recommend the use of oral anticoagulants (warfarin), unless contraindicated, for all patients with more than one moderate risk factor, or CHADS2-score ≥ 2 (19). For patients with CHADS2-score 1 the choice of oral anticoagulation (e.g. warfarin) or acetylic acid is optional. Patients without other risk factors for stroke than AF are recommended to use acetylic acid 81-325 mg unless they are younger than 60 years in which case the choice between acetylic acid and no treatment is optional. The use of oral anticoagulation in patients with lone atrial fibrillation is considered as contraindicated.

Risk Category	Recommended therapy	
No risk factors	Aspirin, 81 to 325 mg daily	
One moderate-risk factor	Aspirin, 81 to 325 mg daily, or warfarin (INR 2.0 to 3.0, target 2.5)	
Any high-risk factor or >1 moderate-risk factor	Warfarin (INR 2.0 to 3.0, target 2.5)	
Less validated or weaker risk factors	Moderate-risk factors	High-risk factors
Female gender	Age ≥ 75 years	Previous stroke, TIA or embolism
Age 65 to 74 years	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve
Thyrotoxicosis	LV ejection fraction $\leq 35\%$	
	Diabetes mellitus	

Table 2
Antithrombotic therapy for patients with atrial fibrillation
(from the ACC, AHA, ESC Guidelines of 2006)

2. AIMS OF THE THESIS

1. To evaluate the risk of ischaemic and haemorrhagic stroke in patients with PxAF.
2. To investigate mortality in patients with PxAF and to identify amenable contributing risk factors.
3. To assess how well ACC/AHA/ESC Guidelines regarding warfarin treatment in AF is translated into clinical practice, and to identify factors that are associated with warfarin treatment.
4. To investigate if successful restoration and maintenance of sinus rhythm has any prognostic implications.

3. MATERIAL AND METHODS

All studies in this thesis are based on a cohort of patients with a diagnosis of atrial fibrillation or flutter in 2002 who have been followed prospectively since then. The cohort is referred to as SCAF, which is an acronym for the Stockholm Cohort of Atrial Fibrillation.

Recruitment began with a computerized search in the local patient register at South Hospital in Stockholm, Sweden. South Hospital serves approximately 600 000 inhabitants and is one of the largest hospitals in Sweden. All patients with a diagnostic ICD-10 code used for atrial fibrillation or atrial flutter (I48.9 and I49.5 with or without optional specifying subcodes) treated as in or outpatients at the departments of Cardiology, Internal Medicine or at the Emergency Department during 2002 were identified. After exclusions of duplicates due to alternating use of ICD-codes on different occasion, the complete digitally stored information was examined and validated by two cardiologists according to a predefined protocol.

Only patients with a documented episode of atrial fibrillation or flutter during 2002 were included. Most of the exclusions were made among patients with ICD-code I49.5 (sinus node disease). This code, used without specifying subcode, harbours both patients with the tachybradycardia syndrome including PxAF, and patients with bradycardia only. In few patients another supraventricular arrhythmia had been mistaken for AF. In yet other patients documentation was lacking and the diagnosis could not be confirmed. Eleven patients were not included as they were temporary visitors to Sweden and not available for follow-up. All in all 2789 patients remained for study after examination of medical records and ECG tracings.

In addition, we identified all patients with AF or flutter at the Gustavsberg Primary Care Centre in 2002 in the same way as we did at the South Hospital. This was done in order to determine the prevalence of AF and PxAF in a geographically well-defined area. South Hospital in Stockholm was unsuitable for that purpose as it is a University Hospital which may receive patients from anywhere in the county or even beyond that. We chose Gustavsberg Primary Care Centre which has a well-defined catchment area of 33 000 inhabitants with a demographic profile similar to the Swedish mean. We also identified patients from Gustavsberg who had been treated at South Hospital which is the nearest large hospital serving the Gustavsberg area. In addition, patients from Gustavsberg were identified at four out-patient clinics in Stockholm (Nacka Hospital, Globen Heart, Stockholm Heart Center and Sophiahemmet). Many patients had been to several of these clinics during the inclusion year. In all we found 240 patients with AF who were living in Gustavsberg. Of these 123 patients had not been at the South Hospital during 2002. These

patients were added to the cohort whereby the total number of patients in the SCAF-cohort totalled 2912.

Background information about comorbidity and previous diseases was obtained from local medical records, and combined with information from the National Hospital Discharge Register going back to 1987 nationally and for Stockholm County to 1972. The cohort has been followed prospectively with re-examinations of medical records and through national registers of hospital discharges and mortality. In the analyses patients were classified according to the type of AF they had at the latest contact in 2002, although some patients may have changed type of arrhythmia since then, e.g. progressed from PxAF to PermAF. Information about medication was recorded from the latest contact each calendar year. If a patient suffered an ischaemic or haemorrhagic stroke, information about medication was also obtained from that occasion.

3.1 PATIENTS

All four studies in this thesis are based on the 2912 patients described above. However, the numbers of patients included in each one of the constituent studies varies as is explained below.

Study I

This study compared stroke incidence in PxAF with that in PermAF. We therefore excluded all patients with other forms of AF, i.e. patients with PersistAF (n=619) and patients whose type of AF could not be accurately determined from the accumulated information available at the end of the inclusion year (n=148). Also, patients could not be regarded as representative if the reason for their inclusion was that they were brought to hospital because of a stroke (which would mean that an endpoint event preceded the start of the observation period). We therefore excluded all patients who had a stroke in conjunction with the index-generating hospital contact (n=93), i.e. the hospital period when they got the diagnosis that made them enter the study. Whether they changed ward, clinic or hospital did not matter as long as hospital periods were immediately adjoining. For similar reasons we excluded patients who died (n=88) in conjunction with the first contact. A few patients were excluded because they fulfilled several of these criteria. The analysis was thus performed on 1981 patients representing approximately 5 500 patient years at risk. We also performed the same analyses after exclusion of another 313 patients with a history of a previous ischaemic stroke, TIA or cerebral bleeding (i.e. before the contact that caused the inclusion in the cohort). The rationale for this was that patients with an previous stroke are at particularly high risk of having another stroke. We wanted to see whether an exclusion of these high-risk patients affected the results in the multivariable analyses. In this reduced analysis 1668 patients were included, representing approximately 4 700 patient years.

Study II

For this study on mortality in PxAF we excluded 88 patients who died in conjunction with the index-generating contact. The reason for excluding these patients was that if a terminal disease made them enter the study, they would not be representative for AF patients in general. The analyses were thus performed on 2824 patients representing more than 7 300 patient years at risk.

Study III

In this investigation which addresses the question of which AF-patients receive prophylactic treatment against stroke, we only studied SCAF-patients who had been treated at South Hospital in Stockholm (n=2796). The reason why the patients from Gustavsberg were not included was that Study III was the first of the studies to be written. It was published before data regarding the patients from Gustavsberg were available. As we were only concerned with the circumstances of the index-generating contact no further exclusions were made.

Study IV

In this study on the prognostic implications of restoration of normal sinus rhythm we studied those patients in the cohort who had a DC-cardioversion during follow-up (n=415). Patients with predominantly paroxysmal AF after cardioversion (n=53) and one patient who died during the index-generating hospital period were excluded. The remaining 361 patients were followed from the date of the first DC cardioversion after inclusion in the cohort until the end of 2006 regarding all-cause mortality, and until the end of 2005 for a combined end point consisting of all-cause mortality, stroke, myocardial infarction or hospitalization for heart failure. The reason for the difference in follow-up time was that we had easy access to updated information about when patients died, but that the national register with information about hospitalizations lagged behind.

3.2 METHODS

Study I

For comparisons of stroke incidence in PxAF and PermAF with that of the general population in Stockholm County we calculated standardized incidence ratios (SIR) using sex and age specific official statistics from the general population in Stockholm County for the years of the study.

We also compared the stroke incidence between patients with PxAF and patients with PermAF. We made univariate comparisons of the annual incidence of stroke and used multivariable Cox regression to adjust for differences in age, comorbidity and medication.

Study II

In this investigation on mortality in PxAF we made both comparisons with the general population and comparisons within the cohort between patients with different forms of AF.

For comparisons with the general population we used standardized mortality ratios (SMR) where we compared mortality among patients with different types of AF with the mortality that would be expected from the general population using age and sex matched official population statistics. We also compared the incidence of death due to specific causes in the cohort, with the age and sex matched incidence of death in the general population. For this analysis we used data from the National Cause of Death Register, which, however, only was available for the years 2002 and 2003 at the time of writing.

For comparisons of mortality in PxAF with that in other forms of AF Cox Proportional Hazards analysis was used. Since warfarin use was strongly associated with a favourable outcome we wanted to further control for confounding factors that might have affected the choice to treat or not to treat with warfarin. Propensity scores for the likelihood of

receiving warfarin were therefore calculated using all available background information. We then matched patients on propensity scores and performed a multivariable analysis on a limited set of matched patients who had similar background characteristics but where half were treated with warfarin and half were not.

Study III

In this investigation we studied the anti-thrombotic medication patients had been prescribed for prophylaxis against stroke when they entered the cohort. Information about current and previous disease was obtained from local medical records and from the National Hospital Discharge Register. In order to identify factors associated with the likelihood of receiving warfarin we used multivariable logistic regression and the CHAID Tree analysis (see page 28). We also evaluated how the ACC/AHA/ESC Guidelines regarding stroke prophylaxis in AF were followed in clinical practice.

Study IV

Patients who had a DC cardioversion during follow-up were followed prospectively with regard to whether or not they relapsed into AF within the first 3 months after cardioversion. The primary end point was all-cause mortality. We also used a secondary composite end point consisting of all-cause mortality, hospitalization for ischaemic stroke, acute myocardial infarction or heart failure. Multivariable regression was used to adjust for cofactors.

3.3 ETHICS

Approval for the study was obtained from the Regional Ethics Committee (Reg Nr 2005/4:2).

3.4 STATISTICAL METHODS

For analyses of means and proportions we used Student's t-test (two-sided) and chi-square analysis. Standardized mortality ratios (SMR) were calculated for comparisons of observed numbers of deaths in AF-patients with that expected from the mortality in the general population. In these analyses sex, age (one-year age groups) and calendar year were taken into account. SMR was also calculated for specific causes of death. An analogous method to calculate standardised incidence ratios (SIR) for the incidence of stroke in AF patients compared with that in the general population was used in study I. For the SMR and the SIR we calculated confidence intervals assuming that the observed numbers of deaths/stroke events followed a Poisson distribution.

For multivariable analyses we used logistic regression. Logistic regression was also used in study II to calculate propensity scores for receiving treatment with warfarin based on the available information about patients comorbidities, previous diseases and other medication. In this analysis each patient was assigned a score indicating the likelihood of receiving warfarin treatment. Patients with equal propensity scores were then matched pairwise according to whether or not they were treated with warfarin. Finally, multivariable analyses were performed on this reduced set of patients where the impact of having been chosen for warfarin treatment had been minimised.

Survival analyses were performed using Kaplan Meier methods with log-rank tests. For multivariable adjustment of time dependent variables we used Cox regression.

MATERIAL AND METHODS

We also used a classification tree technique to identify variables associated with treatment of warfarin and to describe the patients who did and did not receive it. For this purpose we used the CHAID algorithm (CHi-squared Automatic Interaction Detection) (79). A CHAID analysis starts with all data in one group. Each possible split on each explanatory variable is executed in the search of the split that leads to the strongest association with the dependent variable.

P-values <0.05 were considered significant. 95 % confidence intervals (CI) were calculated. All analyses were performed in SPSS versions 13.0, 14.0 or 15.0

4. RESULTS

4.1.1 Study I: Stroke in Paroxysmal Atrial Fibrillation

The annual incidence of ischaemic stroke was 2.8% in PxAF and 3.0% in PermAF during a mean follow-up of 3.6 years. Stroke incidence remained similar in PxAF and PermAF after adjustment for cofactors. Using the stroke incidence in PermAF as reference, the hazard ratio for ischaemic stroke in PxAF patients was 1.2 (CI 0.7-1.6) compared with PermAF (Fig 8).

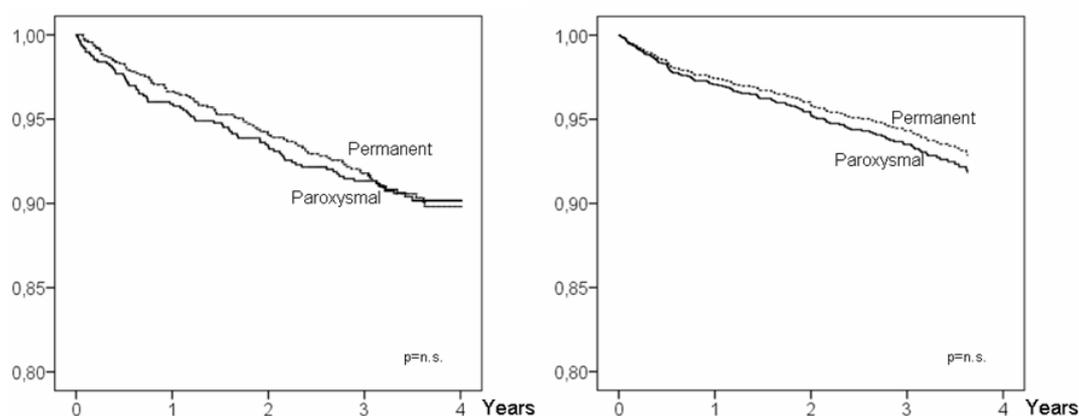


Fig 8.

Ischaemic stroke (163) in patients with PxAF and PermAF. Unadjusted incidence to the left, multivariably adjusted to the right. Observe abbreviation of scale.

The corresponding HR for all stroke combined (ischaemic, unspecified and haemorrhagic), was 0.9 (CI 0.6-1.3). Compared with the general population ischaemic stroke was twice as common in PxAF after standardization for age and sex (SIR 2.1, CI 1.5-2.7). Warfarin use was associated with 50% lower incidence of ischemic stroke in patients with PxAF. Cerebral bleedings was about as rare in PxAF-patients using warfarin as in the general population..

4.1.2 Study II: Mortality in Paroxysmal Atrial Fibrillation

During a mean follow-up of 4.6 years 267 out of 888 patients with PxAF died. This was more than was expected from sex and age standardized rates in the general population (SMR 1.6, CI 1.4-1.8). The excess mortality was found within the field of cardiovascular disease only. SMR for myocardial infarction as cause of death was 2.4 (CI 1.4-3.7) and for heart failure 2.6 (CI 1.3-5.2) in PxAF patients.

A comparison of the mortality in different forms of AF showed that PxAF was associated with a poorer prognosis than PersistAF but better than in PermAF (Fig 7). After adjustment for differences in age, sex, comorbidity and medication, the hazard ratio for

RESULTS

PxAF compared with PersistAF was 1.5 (CI 1.2-2.0). Compared with PermAF the risk was lower; hazard ratio 0.7 (CI 0.6-0.9). It did not appear to matter whether the arrhythmia was flutter or fibrillation.

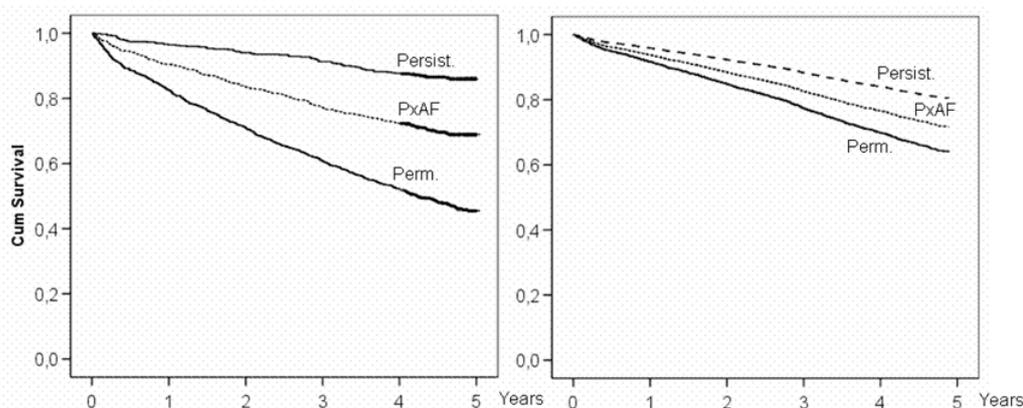


Fig 7.

Mortality in relation to AF type in 2824 patients during mean follow up time 4.6 years. Left: Unadjusted mortality in relation to type of atrial fibrillation. ($p < 0.0001$ between all curves) Right; Multivariable Cox analysis (p -value for difference between PxAF and PersAF = 0.0008, between PxAF and PermAF = 0.0001).

Survival was better in PxAF patients treated with warfarin than in those without warfarin. After adjustment for cofactors the hazard ratio in favour of warfarin was 0.5 (CI 0.3-0.9, $p = 0.016$). This finding remained unchanged after propensity score matching for factors that may have affected the choice to treat with warfarin. PxAF patients who used warfarin did not have higher mortality than the general population (SMR 1.1, CI 0.8-1.4) in contrast to patients who used aspirin (SMR 1.7, CI 1.4-1.9) or patients without any prophylactic treatment (SMR 2.2, CI 1.6-2.8)

4.1.3 Study III: Stroke Prophylaxis in Atrial Fibrillation; Who gets it?

Of 2796 patients with AF 41 % used warfarin, 35 % used aspirin and 18 % had nothing to protect against embolic stroke. Approximately two thirds of the patients ought to have been prescribed warfarin according to the guideline recommendations that were valid at the time of the study (80), i.e. they had indications and no contraindications for warfarin treatment. Of these about half received it.

We identified 679 patients with high risk of embolic stroke (CHADS₂-score ≥ 3) (54, 55) who were without contraindications to Warfarin. Only 56 % of them had been given warfarin. We also found that one out of four patients with lone AF was prescribed warfarin, although warfarin is contraindicated in lone AF according to the guidelines. Of the five risk factors for embolic stroke used in the CHADS₂-algorithm for risk stratification, only a prior stroke was associated with a greater likelihood to receive warfarin. Heart failure, hypertension, diabetes and age >75 years did not seem to improve the likelihood of treatment.

The classification tree analysis showed that the most important factor influencing the probability of warfarin treatment was whether the patient had PxAF or not. Of those PxAF patients who ought to have warfarin 36% actually got it, compared to 65 % of patients with PermAF or PersistAF. Accordingly, individual risk assessment appear to play a minor role for decisions regarding anticoagulation. Other circumstances, such as care by a specialist in cardiology or in internal medicine appeared to be of some importance.

4.1.4 Study IV Restored sinus rhythm – Improved Prognosis

In this study of 361 patients who were DC-cardioverted at least once during follow-up, 11% died and 20% reached a composite end point consisting of death or hospitalization for myocardial infarction, stroke or heart failure.

Recurrences of AF were frequent, especially during the first months after cardioversion. Patients who remained in sinus rhythm were generally younger and healthier than those who relapsed. Factors associated with early relapse were higher age, male sex, diabetes, chronic pulmonary disease, number of previous cardioversions and number of days at hospital during preceding years.

Successful cardioversion without known relapse of AF within three months was associated with lower all-cause mortality (HR 0.5, CI 0.3-1.0) as well as a lower incidence of the composite end point (HR 0.5, CI 0.3-0.8) after multivariable adjustment (Fig 9)

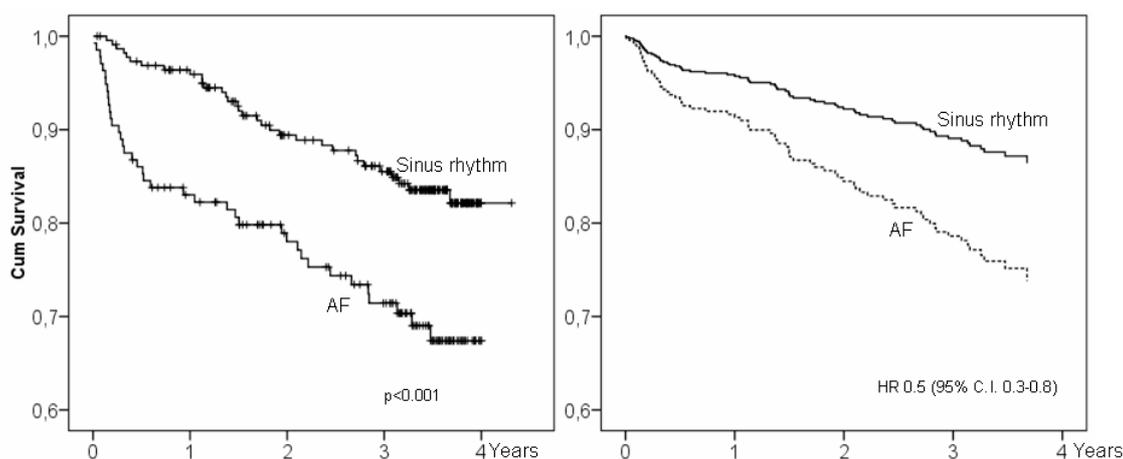


Fig 9.

Incidence of death, ischaemic stroke, myocardial infarction or hospitalisation for heart failure in relation to relapse or no relapse of atrial fibrillation within three months after DC cardioversion. Unadjusted (left) and multivariable adjusted (right).

Patients who were in sinus rhythm at the time of their latest hospital contact during follow-up had lower mortality than those who were in AF (8% vs. 15%, $p < 0.05$), although this difference was not significant in the multivariable analysis (Table 2). The composite end point was also reached less often by those who were in sinus rhythm at time of their latest contact (9% vs. 33%, $p < 0.0001$). This difference remained significant after multivariable adjustment (HR 0.4; 95% C.I. 0.2-0.6).

5. GENERAL DISCUSSION

PxAF is common. According to our estimates it afflicts 30 000-40 000 persons in Sweden which has a population of about 9 million inhabitants. The real prevalence is probably much higher since PxAF often is asymptomatic. Even symptomatic PxAF may pass unrecognized if the cause of the symptoms is not correctly recognised. A person with PxAF may suffer fatigue, dyspnea or dizziness and think it is the flue, too much smoking or something else. When such a person goes to the doctor, the latter may fail to make a correct diagnosis if no ECG is taken, which may occur especially in the primary care, or if the patient by chance happens to be in sinus rhythm when the ECG is recorded. Symptoms from PxAF may be mistaken for asthma, chronic bronchitis, obesity, heart failure, silent angina pectoris, lack of physical activity or just an effect of increasing age.

5.1 THE PROGNOSIS IN PxAF

The results of our studies based on the SCAF cohort show that PxAF is associated with a risk of stroke which appears to be similar to that of PermAF. It is also associated with an increased risk of premature death when compared with the general population. The excess mortality concerns cardiovascular disease in general, not just embolic stroke. PxAF appears to be a marker of persons with cardiovascular disease which may, or may not, have been diagnosed before.

A practical conclusion that may be drawn from this is that one should not only treat the arrhythmia, but also search for other underlying heart disease when a patient shows up with previously undiagnosed AF. It may be indicated to change present routines and include bicycle ergometer testing in the basic clinical evaluation of PxAF patients. Such test are presently not included in the basic work-up as recommended by the ACC/AHA/ESC guidelines (19). According to the current recommendations exercise tests are only recommended for PxAF patients to provoke suspected exercise-induced AF, or to exclude ischemia before starting treatment with a type 1C antiarrhythmic drug.

Whether the increased morbidity and mortality in PxAF is due to cofactors alone, or if PxAF in itself contributes, cannot easily be answered. In Study IV we addressed this issue by studying the long-term prognosis for DC-cardioverted patients in relation to if and when they relapsed into AF. In this study restored and maintained sinus rhythm was associated with a better prognosis than early relapse.

Cardioverted patients were generally the healthiest of all AF-patients. Within this healthy minority there were differences between those who relapsed and those who remained in sinus rhythm after cardioversion. After multivariable adjustment for the relatively small differences there were among cardioverted patients, sinus rhythm still appeared to be associated with a more favourable prognosis.

AFFIRM and RACE were two randomized prospective trials aiming to evaluate which treatment strategy is the best of rhythm control and rate control (66, 67). The results, that were published in 2002, did not show any survival benefit from the choice of either strategy. However, both studies were made on-intention-to-treat and patients were evaluated according to the strategy to which they had been randomized, irrespective of whether it was possible to keep patients in sinus rhythm or not. These studies were not designed to answer whether sinus rhythm is of any importance for prognosis. In clinical practice the results from the AFFIRM and RACE trials caused some confusion regarding the meaningfulness of cardioverting patients. The message that either treatment strategy was as good as the other, was at times taken as evidence that there was nothing to be gained from trying to restore sinus rhythm, except perhaps in highly symptomatic patients. Interestingly, however, a post-hoc analysis was made in the AFFIRM study which showed that the presence of sinus rhythm during follow-up was significantly associated with better survival (81).

5.2 DC-CARDIOVERSION – HOW MANY TIMES?

In patients with repeated cardioversions we saw that the chance to remain in sinus rhythm successively declined, and the time to relapse became increasingly shorter with each successive cardioversion (Fig 10).

Medication may have shifted slightly to more aggressive antiarrhythmic treatment with each successive DC-cardioversion, but the number of patients given other antiarrhythmic agents than betablockers and sotalol was too small to allow for separate analyses. Most of the patients remained on the same medication after DC-cardioversion as they had when they contracted their relapse. Unless antiarrhythmic therapy is changed the use and benefit of repeated DC-cardioversions beyond a second cardioversion may thus be questioned. Nonetheless, the findings in our studies makes in reasonable to propose that at least one or two attempts at restoring sinus rhythm should be contemplated in all patients with AF.

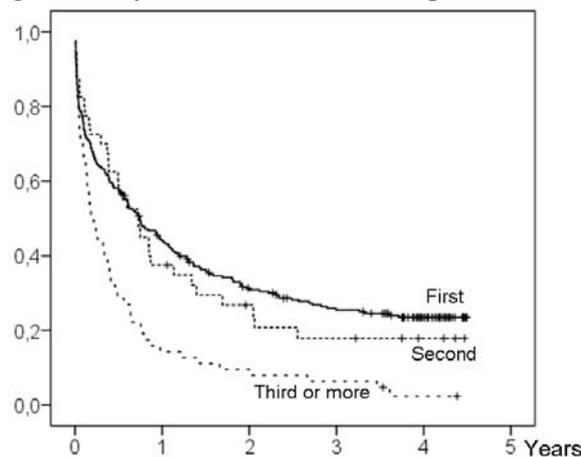


Fig 10.

Recurrence of atrial fibrillation among 361 patients undergoing DC cardioversion in relation to number of previous cardioversions.

Sinus rhythm is probably beneficial in AF patients who manage to remain in sinus rhythm after cardioversion. Although this is difficult to prove, as has been discussed above, I believe that patients ought to have the benefit of the doubt. This implies that more patients

than today should be offered DC-cardioversion, and that more patients should be referred for non-pharmacological treatment.

5.3 THE ROLE OF WARFARIN IN PxAF

Patients with PxAF who had been prescribed warfarin had a much better prognosis than patients using aspirin or those without prophylaxis against stroke. Interestingly, this beneficial effect was not only seen regarding stroke, but also regarding mortality. Our knowledge about how patients took warfarin is fragmentary. We had to rely on information as it became available when patients were in contact with the hospital. Our aim was, however, not to investigate if warfarin protects against stroke in AF, since we believe that this question already has been settled. Our aim was to investigate if patients with PxAF have the same benefit of warfarin as patients with other types of AF. The results of our study indicate that they do. A prospective, randomized, placebo-controlled trial would certainly give more definitive evidence but would be impossible to perform for ethical reasons.

In the near future it will be possible to increase the accuracy of these data with the help of two newly launched national registers in Sweden. The first of these is the Auricula Register, a register for the improvement of the quality of treatment of AF patients. The second is a national register of pharmacological prescriptions that shows exactly what medication each patient obtained from their pharmacy and on which date.

The current guidelines on the management of AF (19) recommend that patients with PxAF should have the same thrombotic prophylaxis as patients with PermAF. This recommendation primarily rests on the findings of high stroke rates in PxAF patients in the SPAF trial (49). Our results support the conclusions of the SPAF trial but are based on almost twice as many PxAF patients and who have been followed for almost twice as long. From the results of our studies of the SCAF cohort we are convinced that prescription of warfarin, after due consideration of indications and contraindications, is a most efficient way to save lives and to avoid cerebral catastrophes in patients with PxAF.

5.4 WARFARIN IN CLINICAL PRACTICE

Awareness of the need for efficient anticoagulation in AF is growing. Prescription habits have changed markedly over the last few decades. In the late 80s and early 90s not even patients with PermAF were usually treated with warfarin, unless there was significant mitral disease or perhaps also in patients with thyrotoxicosis. At that time thyrotoxicosis was considered as a highly thrombotic condition, although it now is counted as one of the “less validated or weaker risk factors”(19).

Ten years ago a study on warfarin use was performed at another Stockholm hospital (82) showing that only 40% of eligible patients aged < 80 years with PermAF and at least one risk factor received warfarin. The corresponding figure was 78% in our study of the prescription patterns in 2002, as presented in Study III.

The recommendation that patients with PxAF should be treated with anticoagulants in the same manner as patients with PermAF was relatively new when we investigated how recommendations on warfarin use had permeated into clinical practice. Hopefully, more PxAF patients without contraindications to warfarin get adequate prophylaxis now than they did in 2002 when only 36% of PxAF patients received warfarin.

Present studies show that PxAF patients have an increased morbidity and mortality that can be largely be neutralized with proper use of warfarin. Yet, the majority of PxAF patients are not given this possibility. Prescribing warfarin to patients with PxAF when there are no important contraindications will probably within a short time prevent many strokes and save many lives since the condition is so common. In a recent health economic study on the costs of AF in the County of Östergötland in Sweden (83) warfarin treatment of AF was not only seen as cost efficient but also as a way of saving money due to the extremely high costs for the disability caused by stroke.

6. METHODOLOGICAL CONSIDERATIONS

Patients cannot be assigned to neither sinus rhythm nor AF because they alternate between these rhythms in more or less unpredictable ways. The SCAF-study is therefore not a randomized study but an observational study, where the patients were identified retrospectively, but followed as a cohort prospectively from the index hospitalization.

It would have been preferable if we had examined all patients according to a standardized protocol at index and then arranged for follow-up visits at regular intervals. This, however, was not a realistic option considering that the cohort comprises approximately 3000 patients who have been followed for approximately 5 years.

An observational study based on records and registers have other merits. This includes assessment of actual treatment patterns and its consequences in terms of prognosis. In real life patients may not always be treated according to scientific evidence and the latest guideline recommendations. One example of this concerns patients who ought to have warfarin to protect from stroke but who do not get it. After what is already known about the efficacy of warfarin to protect from stroke in PermAF it would not be ethically acceptable to randomize PxAF patients to receive no prophylaxis in order to find out whether warfarin is beneficial in this patient group too.

Furthermore, observation of spontaneously occurring relapses, cardioversions or return of stable sinus rhythm gives complementary information to what is learned from randomized studies.

6.1 GENERALIZABILITY

6.1.1 A hospital based cohort

The majority of the patients in the cohort had been treated as in-patients at South Hospital during 2002 (78% of all patients). The remainder had been treated only as outpatients at South Hospital (n=520) or at Gustavsberg Primary Care Centre (n=123).

It is likely that patients treated at a hospital are more symptomatic or else of poorer general health than those who only seek medical help at an out-patient clinic. Indeed, patients who had only been treated as out-patients were younger (68 vs 76 years) and healthier (e.g. 5% had a previous myocardial infarction vs. 22 % among hospitalized patients).

The findings in a study of primarily hospital based patients may not be the same as it would have been if most of the patients were recruited in an out-patient clinic. It is,

however, uncertain whether it would have been possible to perform a study like ours on an out-patient basis since documentation is far less detailed in open clinics than in hospitals, and since there is no counterpart to the National Hospital Discharge Register from where information about previous and current diseases can be obtained.

6.1.2 Same treatment at South Hospital as elsewhere?

If medical treatment does not affect outcome, treatment would be more or less in vain. If treatment differs between hospitals, some hospitals probably present better results than others.

In order to achieve a good and uniform standard of treatment for all AF patients, irrespective of where they live, guideline recommendations have been issued both by the Swedish National Board of Health and Welfare (Socialstyrelsen) and by the major international cardiological societies.

The awareness of these guidelines is increasing but to what extent they permeate the clinical practice is largely unknown. In order to fill that information gap the Auricula register has recently been launched in Sweden. In this register information about treatment, diagnostic procedures and comorbidity is collected in a way as to give feedback to the participating hospitals as to how they perform in comparison with other units in the treatment of patients with AF. As yet, we have not been able to use this information to draw any conclusion as to how well South Hospital performs in comparison with other Swedish hospitals. For international comparisons, we know that hospitals all over the world confess to the same international guidelines, but we know very little about how these guidelines are adhered to.

6.2 SELECTION BIAS

6.2.1 Representativity of the South Hospital patients

Stockholm South Hospital primarily serves the population from the southern part of central Stockholm and the proximal southern suburbs. Compared with the northern and western parts of Stockholm this population has a lower mean income and a lower mean level of education. There are also differences in life expectancy between different districts in Stockholm County(84). Men in Skarpnäck, a district served by South Hospital, are for example expected to die 4 years earlier than men in the high-income district of Östermalm. For women life expectancy differed by approximately 2½ years between these areas. In view of this background we wanted to validate the findings from the SCAF-cohort and see to what extent our results were affected by regional differences in health and thus if our findings regarding risks associated with PxAF may have been exaggerated.

We obtained sex and age specific death rates for the population in 14 different districts of the City of Stockholm (approximately 780 000 inhabitants) for the years 2002-2006. We could not obtain death rates for the surrounding municipalities in Stockholm County (another 1.1 million inhabitants. Because of this we could not use the entire cohort for

METHODOLOGICAL CONSIDERATIONS

recalculation of SMR. The available statistics was rather coarsely stratified in age groups (ages 20-49 yrs, 50-64 yrs, 65-79 yrs, 80-90 yrs). For this end 422 patients with PxAF, 586 patients with PermAF and 306 with PersistAF were analyzed according to the postal code of the registered home adress.

In essence, the result of this analysis did not change our original results (Table 2)

	As published in Study II (n=2824) SMR (95% CI)	With geographically stratified deathrates (n=1370) SMR (95% CI)
Paroxysmal	1.6 (1.4-1.8)	1.7 (1.4-2.0)
Persistent	0.9 (0.7-1.1)	1.0 (0.8-1.3)
Permanent	2.3 (2.1-2.4)	2.4 (2.1-2.7)
All	1.8 (1.7-2.0)	1.9 (1.8-2.1)

Table 2.

Standardized mortality ratios as reported in Study II and also performed on a smaller set of patients with use of death rates from different geographical areas in Stockholm.

6.2.2 Patients lost to follow-up

Essentially no patients were lost to follow-up regarding all cause mortality. For stroke, myocardial infarction and hospitalization for heart failure there may have been some losses to follow-up due to diagnostic inaccuracies, miscoding of diagnosis and ‘silent’ cases. Diagnosed hospital treated cases were included in national registers of hospital discharges and deaths. Many patients had only few hospital contacts, or even just one single at the index hospitalization. For these patients information was lacking about changes in medication and about what rhythm they were in during the follow-up.

The quality of information regarding such matters is therefore uneven. There is obviously more information about those in poor health than about those who feel fine and stay away from the hospital. It is conceivable that less detailed information about healthier patients than about patients with more health problems may affect analyses.

6.3 MISCLASSIFICATIONS

6.3.1 Misclassifications regarding type of AF

Our classification of patients according to type of AF may contain errors due to incomplete information. When ICD-codes of AF were used, the additional letter used to specify the type of AF was rarely added. This information was often evident in the written text of the medical record, although the optional letter code had not been used. In other cases, however, we had to make out the type of AF with less information.

For the classification we used the internationally recommended definitions (presented above in chapter 1.3). In order to increase the accuracy of diagnosis we used the cumulative information available for each patient by the end of the year of inclusion rather

than what was known at the very first contact in 2002. The mean number of hospital contacts during the inclusion year was 2.4 ± 1.9 . This strategy resulted in a relatively small residual group of patients with unknown type of AF.

In order to avoid difficulties in differentiating between patients with PxAF and PersistAF we considered patients who were DC-cardioverted as having PersistAF although some of them rightly may have been classified as PxAF. In this way the PxAF group became smaller, but at the same time more homogenous.

We consequently analyzed patients in relation to the form of AF they had at the end of the year of inclusion without consideration to changes that may have occurred later during follow-up. After one year 12 % of PxAF-patients (alive and with a contact that year) had progressed to PermAF. After two years 20 % of PxAF patients were in PermAF. However, as information was lacking for many patients we decided not to use this information in the analyses.

6.3.2 Misclassifications regarding comorbidity

We did not examine the patients in the cohort according to a standardized protocol at index. This would certainly have been preferable but was not a realistic option. Instead, we tried to minimize the impact of inhomogeneous information in the medical records by applying a strict protocol for extracting information from the medical records, and by extending the reading of medical records from preceding years. We combined information from different sources, such as written records from different doctors and different clinics, laboratory tests, reports from physiological examinations and information from the National Hospital Discharge Register which carries information about which diagnoses patients were treated for up to over 30 years back.

Still, there may be factors that we have failed to record that are of importance for the general health of the patients.

6.3.3 Misclassifications regarding rhythm

Patients with intermittent forms of AF spend shorter or longer periods in AF. Keeping track of these changes for study purposes is difficult and would require continuous monitoring of rhythm, or at a minimum regular examinations of rhythm. Doing that with 3000 patients during 5 years was practically not possible. The documentation of heart rhythm for this study was solely derived from medical records, which were the result of the patients spontaneous contacts with the hospital or the primary care centre.

In Study IV on a subset of DC-cardioverted patients we used the information that was available 3 months after cardioversion and the latest available information during follow-up. We believe that the information about symptomatic relapses within the first three months after cardioversion is relatively reliable, since cardioverted patients are offered one or more return visits for a control ECG and possibly for a change of prophylactic regimen. The relapse rate may, however, still have been underestimated as patients may have been treated in primary care or in a private open clinic without contacting their hospital. Furthermore, they may also have had asymptomatic relapses. It is less likely that patients in sinus rhythm have been misclassified as being in AF. If, hypothetically, sinus rhythm has a

favourable effect on the prognosis, misclassifications about rhythm would most likely have resulted in an underestimation of this effect.

6.3.4 Misclassifications regarding medication

We have information about the medication of all patients for the inclusion year 2002, but during follow-up the information is incomplete for the same reasons as with the information about rhythm.

When we examined the medical records we documented what medication that was valid at the latest contact for each calendar year. If the patient had suffered a stroke or cerebral bleeding we also documented what medication was given at that time, provided that the patient was cared for at South Hospital where we had easy access to the medical records.

In the analyses we used information about the medication that was given when a stroke or a cerebral bleeding occurred, but for patients who had not suffered an event we used information about the medication as it was on the latest documented contact.

In the extreme case this could mean that the medication of a patient with a stroke late during follow-up is compared with baseline information for another patient who had not suffered an endpoint event and had not had a reason to visit a hospital for several years. The information about patients with few hospital contacts is likely to contain more errors and misclassifications than that of those with frequent hospitalizations.

Information about the real exposure to medications over time would have been preferable. This has recently become possible following an introduction of a new national register of dispensed prescriptions. In future studies emanating from the SCAF cohort this will be a most valuable tool, but for the present investigations this information was unavailable.

6.3.5 Misclassifications regarding stroke

When scrutinizing the medical records we tried to evaluate how well a diagnosis of ischaemic stroke was supported by clinical findings and results of CT and MR scans. We found that the number of stroke events varied depending on how strictly the condition was defined (Fig 11). We also found that there were patients who had stroke but who had not received a diagnostic code for it. In the National Hospital Discharge Register we found yet other patients who had suffered a stroke, but who had been treated at other hospitals than South Hospital.

Our conclusion is that absolute certainty about which patient has suffered a stroke is difficult to obtain. Partly this is because it is difficult to make a diagnosis when symptoms are vague and a CT/MR-scan is made too early for an infarction to show. We found that our own evaluation of diagnostic strength and accuracy, which was based on second-hand information, contained too much of personal judgement and therefore was unsuitable for a scientific study. Therefore, after having evaluated the documentation of stroke during the

first two years of the study, we decided to abandon these efforts. Instead, we chose to accept the impartial and binary information of the Hospital Discharge Register, fully aware that it not is the absolute truth.

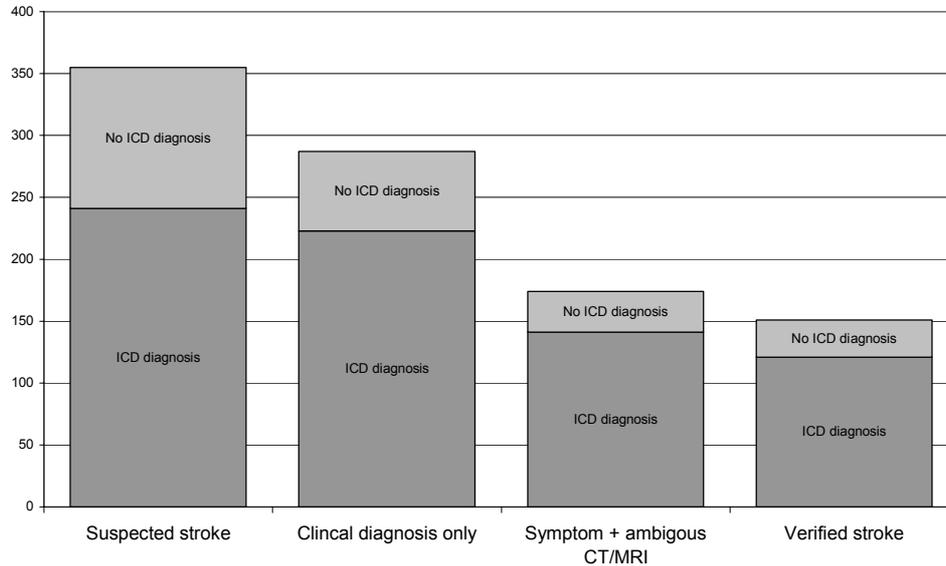


Fig 11.

Incidence of stroke during 2002 and 2003 varied depending on how strict criteria for diagnosis that were used. “No ICD diagnosis” means that although the medical records at South Hospital carried information indicating that a stroke or TIA had occurred no diagnostic code was used and the event was not listed in the national hospital discharge register.

6.4 CONFOUNDING

6.4.1 Comorbidity and other factors

In the studies in this thesis we have repeatedly compared subgroups of AF patients in order to investigate whether certain factors are associated with the outcome. In such comparisons it is vital to take into account and make adjustments for differences in baseline characteristics. We used information from various sources, including registers that goes back several decades in time in order to minimize the impact of differences in baseline characteristics. We also tried propensity score analysis in study II to minimize the effect of differences in comorbidity. Still there may be differences that we have failed to adjust for.

Randomization is the preferred method to neutralize differences in background characteristics. However, randomization was not an applicable technique for the purpose of these studies.

Differences that we have failed to adjust for include lifestyle factors. The documentation in the medical records is often unreliable regarding factors like

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smoking and drinking although they may be of great importance for health. Information is often fragmentary regarding factors like physical activity, eating habits, obesity and impaired glucose tolerance that also may have a profound impact on the prognosis.

In addition, it is likely that a patient who looks fit and healthy is treated differently than one who looks as if in poor general health even if there is no diagnosis attached. Someone who looks ill is more likely to be ill, than someone who looks fine, e.g. having a cancer disease that was not known at the time.

Thus, undocumented differences in health and lifestyle factors may have contributed to residual confounding in the analyses.

7. CONCLUSIONS

PxAF is associated with increased morbidity and mortality, which is similar to that of PermAF. Since underlying cardiovascular disease seems to account for most of this, and since warfarin treatment markedly improves prognosis, it is essential to diagnose and treat any underlying cardiovascular disease and to provide patients with adequate anticoagulant treatment unless there are substantial contraindications.

Our results furthermore suggest that restoration and maintenance of sinus rhythm may improve the prognosis in patients with atrial fibrillation. Therefore, we propose that eligible patients should be given an opportunity to be restored to sinus rhythm before atrial fibrillation is accepted as permanent.

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9. ACKNOWLEDGEMENTS

I would like to express my gratitude and appreciation to all those who helped and supported me during my work with this thesis. In particular I would like to thank:

Mårten Rosenqvist, my main supervisor and tutor, for your humour, genius and your truly humanitarian view of life. For your recognition of what really matters, in life as well as in medicine and in science (Always have the year of a thesis printed in roman numerals, never in arabic! Never let a meeting interfere with a parade with the Royal Horseguard!) Thank you for your guidance, your valuable ideas, your encouragement and for believing in me. And thank you for taking care of loads of red tape. Without your help I might have gone fishing instead!

Niklas Hammar, my brainy co-supervisor and co-tutor. Your sharp analytical mind was always on the watch for a foul confounder, a bothering bias or misclassification. I was confounded more than once, but finally learned that in epidemiology you really have to exercise your brain, not just juggle with significances and confidence intervals.

Nils Edvardsson, my co-author on study IV. I am truly honoured and find it a bit thrilling to have my name on the same paper as yours. During my education to become a cardiologist I was most impressed of your immense knowledge of cardiac arrhythmias. I still am.

Hans Pettersson, my co-author on study II and III for learning me how to muster the fearful SPSS, our statistical software used to bring about almost every little figure you find in this booklet apart from the pagination.

Mattias Ringh who helped me in the seemingly endless task of reading and extracting information from an almost endless quantity of medical journals in the beginning when it was difficult to see the point in doing it. For those of you who haven't tried it; imagine having spent a full day in front of the computer (all of your friends were out having fun), just having succeeded in reading 47 medical records (out of approximately one zillion) and suddenly the electricity goes out (oops!) and (unfortunately) you had forgotten to save your work (press Ctrl+S) for several hours. Thank you for your endurance!

Andreas Sjögren who, while head of the department of medicine at Nacka Hospital, inspired me to become a cardiologist rather than an orthopedic surgeon (my inclination when I graduated from medical school) or a brain surgeon (my inclination when I began my medical studies). The ease with which you reached a correct diagnosis and gave your instructions about treatment at the rounds at the Nacka Hospital intensive care unit impressed me immensely. In the work with this thesis you have helped me with my English. Thank you for your constructive advice.

Viveka Frykman for your kind encouragement. It has always been nice to meet you at arrhythmia or pacing event, or at the Auricula register in Uppsala. Someday we'll work on a common research project together, I hope!

Ann Lundén Fernström, research nurse for helping us with the medical records when I and Mattias Ringh already had been through them twice and neither of us had any mental power left for another match with a few thousand medical records (never, never ever again!). Ann helped us to go through the records a third time and later also had the capacity to complement the information about patients who had been DC-cardioverted. Thank you for your meticulous and thorough work that was absolutely crucial for this thesis. Sine quo non, as hardcore academics put it.

SCAF = Southern California Anarchist Federation and SCAF=Svenska Chinchilla avelsföreningen for letting me use your acronym for the Stockholm Cohort of Atrial Fibrillation. (Alright, I admit that you did not explicitly say that I could have it, but I knew that you wouldn't let me down!)

Anna Nergårdh, my former colleague at the cardiology department at South Hospital of which you now are the head. Thank you for stimulating discussions about atrial fibrillation and life in general.

All of my former colleagues at the cardiology department of South Hospital. In particular I think of Inger Meier Carlsson and Inger Axelsson who both have set a high standard for how a good doctor should be.

Fariborz Tabrizi, former colleague at South Hospital where we began working at the same time. Your knowledge about cardiac arrhythmias is second to none. I miss working with you.

Lars Alveryd, for being a nice person to talk about bicycles with.

Christina Örnfeldt, my former colleague at Nacka heart clinic who knows a lot about poodles and is a good person in general.

ACKNOWLEDGEMENTS

Mats Norman, Amon Gabriel, Christer Höglund, my present colleagues at GlobenHeart for your kind encouragement and belief in my research activities. Thank you for allowing me to take leave of absence every once in a while for the purpose of my research activities. Thank you for the champagne, it helpt! Thank you, Amon, for helping me with my English. I really enjoy our daily discussions about Fender vs. Gibson , up-strokes, down-strokes, dot-necks and related important topics.

Hanna, (fellow bicycle afficinado), *Ulrika, Anna, Canan, Carina, Neda, Carro and Charlotte* of GlobenHeart for encouragement and for beeing real nice people to work with.

The late Stephen Potter and Frank Zappa for mental coaching and spiritual guidance.

Ingvar, Lasse, Kajan, Sus, Åse, Johannes, Gunnar and Carina of Märta & the Cadillacs You have contributed to this thesis by letting me forget my scientific mumblejumbo for a few hours every week when we meet to play music, and later have a beer while discussing Wittgenstein, the impending US election, the achievements of the famed Isombard Kingdom Brunel or the books of Enid Blyton. Doing this for over 23 years in a row does leave marks.

Gunnar Wall, the Odoreida of Uppsala, a Lifeman for our times. He knows all pre-69 Zappa lyrics by heart, he has met Ken Weaver of the Fugs, writes books about spies and knows me since the age of seven.

Inger, My, Agnes, Klara and Tore, my wonderful and supportive family who, strange as it may seem, somehow always have managed to act as if they believed that I knew what I was doing, which, incidentally, I was not. Thank you for acceptance and tolerance with me. I love you.