Atrial fibrillation
Treatment, associated conditions and quantification of symptoms

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“I have tremor cordis on me: My heart dances; But not for joy; not joy”

William Shakespeare
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Abstract

Background: Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia. There is a need for new pharmacological treatment strategies since the current antiarrhythmic drugs have a modest efficacy and may have severe side effects. Cardioversion (CV) of AF offers an opportunity to study related conditions in sinus rhythm (SR) and during AF. Since catheter ablation of AF is a symptomatic treatment, it is important to have tools for measurement of arrhythmia-related symptoms.

Aims: To evaluate the effect of atorvastatin on maintaining SR after CV of persistent AF. To assess if high-sensitivity C-reactive protein (hsCRP) predicts the recurrence of AF after CV in a population randomized to treatment with either atorvastatin or placebo. To quantify the symptomatic effect of left atrial catheter ablation of AF. To assess if the restoration of SR by CV, in a population with persistent AF, affects sleep apnea.

Methods: Paper I: A total of 234 patients were randomized to treatment with either high dose atorvastatin or placebo prior to CV. Paper II: In a pre-specified substudy which included 128 of the patients in study I, hsCRP was analyzed before and after CV. Paper III: Umea 22 Arrhythmia Questions (U22) is a questionnaire that quantifies paroxysmal tachycardia symptoms. A total of 105 patients underwent first-time pulmonary vein isolation and answered U22 forms at baseline and follow-up 304 (SD 121) days after ablation. Paper IV: Polysomnography was performed before and after CV in 23 patients with persistent AF scheduled for elective CV.

Results: Paper I: An intention-to-treat analysis with the available data, by randomization group, showed that 57 (51%) in the atorvastatin group and 47 (42%) in the placebo group were in SR 30 days after CV (OR 1.44, 95%CI 0.85–2.44, P=0.18). Paper II: HsCRP did not significantly predict recurrence of AF at 30 days. However, after adjusting for treatment with atorvastatin, hsCRP predicted the recurrence of AF (OR 1.14, 95% CI 1.01–1.27). Six months after CV, hsCRP at randomization predicted recurrence of AF in both univariate analysis (OR 1.30, 95% CI 1.06–1.60) and in multivariate logistic regression analysis (OR 1.33, 95% CI 1.06–1.67). Paper III: The U22 scores for well-being, arrhythmia as cause for impaired well-being, derived time-aspect score for arrhythmia, and discomfort during attack detected relevant improvements of symptoms after the ablation. U22 showed larger improvement in patients undergoing only one procedure than in patients who later underwent repeated interventions. Paper IV: Obstructive sleep apnea occurred in 17/23 patients (74%), and central sleep apnea in 6/23 patients (26%). Five patients had both obstructive and central sleep apnea.
apnea. SR at follow-up was achieved in 16 patients. The obstructive apnea-hypopnea index, central apnea-hypopnea index, and the number of patients with obstructive or central sleep apnea did not differ before and after restoration of SR.

**Conclusions:** Atorvastatin is not a treatment option with regards to maintaining SR after CV in patients with persistent AF. HsCRP was associated with AF recurrence 1 and 6 months after successful CV of persistent AF. U22 quantifies the symptomatic improvement after AF ablation with adequate internal consistency and construct validity. Both obstructive and central sleep apneas are highly prevalent in patients with persistent AF. Obstructive sleep apneas are unaffected by the CV of AF to SR.

**Keywords:** Atrial fibrillation, cardioversion, atorvastatin, high-sensitivity C-reactive protein, symptoms, sleep apnea.
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACE</td>
<td>angiotensin-converting enzyme</td>
</tr>
<tr>
<td>AF</td>
<td>atrial fibrillation</td>
</tr>
<tr>
<td>AHI</td>
<td>apnea-hypopnea index</td>
</tr>
<tr>
<td>ARB</td>
<td>angiotensin II receptor blocker</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>calcium</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CPAP</td>
<td>continuous positive airway pressure</td>
</tr>
<tr>
<td>CSA</td>
<td>central sleep apnea</td>
</tr>
<tr>
<td>CV</td>
<td>cardioversion</td>
</tr>
<tr>
<td>ECG</td>
<td>electrocardiogram</td>
</tr>
<tr>
<td>ESC</td>
<td>European Society of Cardiology</td>
</tr>
<tr>
<td>ESS</td>
<td>Epworth Sleepiness Scale</td>
</tr>
<tr>
<td>hsCRP</td>
<td>high sensitivity C-reactive protein</td>
</tr>
<tr>
<td>INR</td>
<td>international normalized ratio</td>
</tr>
<tr>
<td>IQR</td>
<td>interquartile range</td>
</tr>
<tr>
<td>LA</td>
<td>left atrium</td>
</tr>
<tr>
<td>LVESD</td>
<td>left endsystolic diameter</td>
</tr>
<tr>
<td>LVEDD</td>
<td>left ventricular end-diastolic diameter</td>
</tr>
<tr>
<td>MCS</td>
<td>mental component summary</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>NOAC</td>
<td>novel oral anticoagulant</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>OSA</td>
<td>obstructive sleep apnea</td>
</tr>
<tr>
<td>PaCO2</td>
<td>partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PCS</td>
<td>physical component summary</td>
</tr>
<tr>
<td>PVI</td>
<td>pulmonary vein isolation</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>SF-36</td>
<td>short form health survey which contains 36 questions</td>
</tr>
<tr>
<td>SR</td>
<td>sinus rhythm</td>
</tr>
<tr>
<td>TEE</td>
<td>transesophageal echocardiography</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>U22</td>
<td>Umea 22 Arrhythmia Questions</td>
</tr>
</tbody>
</table>
Populärvetenskaplig sammanfattning

Bakgrund


Vid behandling av förmaksflimmer inriktar man sig dels på att reducera risken för stroke och dels på att minska symptomen av arytmia. Risken för stroke kan reduceras med blodförtunnade läkemedel. För att minska återfall av förmaksflimmer kan man endera behandla med rytmreglerande läkemedel eller kateterablation. Om patienten har ett kroniskt förmaksflimmer brukar man inriktas sig på att reglera hjärtfrekvensen med bromsande läkemedel.


Vid kateterablation av förmaksflimmer är målet i huvudsak elektrisk isolering av lungvenerna (därav termen lungvensisolering) i vänster förmak då man har noterat att förmaksflimmer ofta startar med extra elektriska impulser från lungvensmynningarna. Behandlingen är relativt ny och den huvudsakliga effekten är symptomreduktion. I många studier har enkäter som är konstruerade för att värdera livskvalité använts för att värdera effekten av behandlingen. U22 är en enkät med arytmispecifika frågor som har visats detektera symptomatisk förbättring efter ablation av supraventrikulära takykardier.
Elkonvertering innebär att man momentant bryter förmaksflimret och återställer sinusrytm (normal hjärtrytm) med hjälp av en elektrisk stöt genom hjärtat. Detta är en rutinbehandling som också erbjuder en möjlighet att studera patienter med förmaksflimmer under såväl pågående aryti som under sinusrytm. Man kan värdera effekten av behandling men man kan också studera relaterade tillstånd. Denna möjlighet har vi utnyttjat i tre av fyra arbeten i denna avhandling.

Andningsuppehåll under sömn, sömnapné, har visat sig vara vanligt hos patienter med förmaksflimmer. Sömnapné kan indelas i obstruktiv eller central sömnapné. Obstruktiv sömnapné orsakas av en blockering av de övre luftvägarna. Vanliga orsaker till obstruktiv sömnapné är trånga övre luftvägar, övervikt och alkoholkonsumtion. Central sömnapné beror på uteblivna signaler från andningscentrum i hjärnstammen till andningsmuskulaturen och kan orsakas av bland annat skidor i centrala nervsystemet eller hjärtsvikt. Man har visat att om man behandlar obstruktiv sömnapné så minskar tendensen till återfall i förmaksflimmer, såväl efter elkonvertering som efter kateterablation. Däremot vet vi mindre om vad som händer med sömnapné om man gör det motsatta dvs. behandlar förmaksflimmer hos patienter som också har sömnapné.

**Metoder**

I arbete ett var syftet att värdera huruvida behandling med atorvastatin före och efter elkonvertering kunde påverka bibehållandet av sinusrytm 30 dagar efter elkonvertering. Vid tio centra i Sverige, inkluderades 234 patienter med persisteraende förmaksflimmer som planerades genomgå elkonvertering. Studien var dubbelblindad och patienterna randomiserades till endera behandling med atorvastatin eller placebo, 14 dagar före och 30 dagar efter elkonverteringen. Primär endpoint var hjärtrytm vid uppföljningen, 30 dagar efter elkonverteringen.

I arbete två, som en substudie till arbete ett, var syftet att värdera om en inflammationsmarkör, högsensitivt CRP (hsCRP), predikterade återfall efter elkonvertering av persisteraende förmaksflimmer. Vid sex centra togs blodprov för analys av hsCRP vid randomiseringsdagen, vid elkonvertering, två dagar efter elkonvertering och vid uppföljningen, trettio dagar efter elkonverteringen. 128 patienter inkluderades. I arbete tre var syftet att utvärdera en enkät med arytmispecifika frågor, U22, i en population av patienter som genomgick kateterablation av förmaksflimmer. Man inkluderade 105 patienter som genomgick kateterablation av förmaksflimmer vid Hjärtcentrum, Norrlands universitetssjukhus. Patienterna fyllde i enkäten före ablationen och i medeltal 304 dagar efter behandlingen. I arbete fyra var syftet att utvärdera om återställandet sinusrytm hos patienter med förmaksflimmer påverkar sömnapné. Patienter med persisteraende förmaksflimmer som planerades för elkonvertering
Tjugotre patienter genomgick polysomnografi (sömnnapnéutreding) före och efter elkonverteringen.

**Resultat**


**Slutsatser**

Behandling med atorvastatin var inte bättre än placebo när det gäller att bibehålla sinusrytm 30 dagar efter elkonvertering av förmaksflimmer. Resultatet i studien stöder inte användandet av atorvastatin som alternativ till etablerade rytmreglerande läkemedel. HsCRP var associerat till återfall av förmaksflimmer efter elkonvertering. U22 formuläret kvantifierar en symptomatisk förbättring efter kateterablation av förmaksflimmer på ett adekvat sätt. Både obstruktiv och central sömnapné var vanligt hos patienter med persistierande förmaksflimmer. Obstruktiv sömnapné påverkades inte av att man återställde sinusrytm.
List of papers

This thesis is based on the following papers which are referred to in the text using the Roman numerals I-IV:


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Introduction

Epidemiology
Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia affecting approximately 3% of the adult population in Sweden and other Western societies [1, 2]. AF is more common amongst men and the prevalence increases with age being very low under the age of 60 and increasing to approximately 15% in men and 12% women aged 85 years or more [2]. The rate of AF is different amongst different ethnic populations. In the United Kingdom, AF rates are lower amongst South Asians, despite a higher cardiovascular risk profile, than in the native British population [3]. In the United States, a lower AF risk has been reported amongst Afro-Americans compared to individuals of white European descent and amongst Chinese and Hispanics compared to non-Hispanic whites [4, 5]. In a recently published study that included the whole Swedish population aged 45 and older, the authors found an increased incidence of AF amongst certain immigrant groups, especially amongst immigrants from war-torn regions such as Bosnia and Iraq, and a lower incidence amongst immigrant groups from countries with a traditionally healthy diets like Southern Europe and Asia compared to their Swedish-born counterparts [6]. One in four middle-aged citizens in the US and EU will develop AF [7-9]. The estimated costs of AF are greater than 1% of health care expenditure, with hospitalizations being the largest contributor [10]. Future projections predict at least a doubling of AF cases by 2060 [11]. The increase in AF prevalence may be due to better detection of silent AF as well as increasing life expectancy and prevalence of predisposing factors [12, 13].

Definitions and classification

Sinus rhythm
Normal heart rhythm, sinus rhythm (SR), is determined by a pacemaker site in the upper part of the right atrium at the junction to superior vena cava, the sinus node. The sinus node consists of specialized myocardial cells which by variable ion channel activity generate action potentials. The action potentials are propagated through the cardiac conduction system to the atria and ventricles where they depolarize the myocardium and elicit myocardial contraction. The sinus node is strongly influenced by the autonomous nervous system and circulating catecholamines. The normal range for SR in adults at rest is 60-100 beats per minute.
Atrial fibrillation
In the 2010 European Society of Cardiology (ESC) guidelines for the management of AF, AF is defined as an arrhythmia with the following characteristics[14]:

1. The surface electrocardiogram (ECG) shows ‘absolutely’ irregular RR intervals (AF is therefore sometimes known as arrhythmia absoluta), i.e. RR intervals that do not follow a repetitive pattern.
2. There are no distinct P waves on the surface ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.
3. The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 milliseconds (>300 beats per minute).

By accepted convention, an episode lasting at least 30 seconds is diagnostic.

**Sinus rhythm**

![Sinus rhythm ECG](image)

**Atrial fibrillation**

![Atrial fibrillation ECG](image)

Figure 1. Typical ECG recordings of SR and AF.

**Classification**
AF is a progressive disease that usually starts as paroxysms of rare, short runs of arrhythmia. Over time the episodes become longer and more frequent. Paroxysmal AF is defined as AF with self-terminating episodes of arrhythmia that usually terminate within 48 hours but may last for up to 7 days. If the episodes are longer than 7 days or require termination by cardioversion (CV), it is considered to be a persistent AF. If the AF has persisted for more than a year when it is decided to adopt to a rhythm control strategy it is called a longstanding persistent AF. A patient has permanent AF if the AF persists and is accepted by the patient and rhythm control strategies are no longer pursued. Silent AF is asymptomatic, undetected AF.
Figure 2. Natural course of AF. The condition progresses from short sporadic runs of arrhythmia to permanent AF. The timeframe varies between individuals.

**Historical perspectives**

AF was probably first described by the emperor physician Huang Ti in China between 1696 and 2598 BC; “When the pulse is irregular and tremulous and the beats occur at intervals, then the impulse of life fades” [15]. Around 1900 James Mackenzie in Scotland and Karel Wenckebach in Holland, studied cardiac arrhythmias with the use of arterial and venous pulse tracings. Mackenzie noted the absence of the presystolic ‘a’ wave seen in the jugular phlebogram during “pulsus irregularis perpetua” [15]. A diagnosis of AF became possible with the development of the electrocardiograph by Willem Einthoven in 1902. The instrument was a complex combination of a string galvanometer, a light source, projecting microscope lenses, a timer, a glass plate photographic recording apparatus, and wires leading to saline-filled buckets [16].

In 1906 Einthoven published a review article with the title “Le Télécardiogramme” which was a 32-page article which included 26 single lead ECG strips. One strip was termed “pulsus inaequalis et irregularis” and was the first ECG tracing of AF [17].
In 1909, Thomas Lewis installed the electrocardiograph in London, convinced that it would provide useful and unique information about cardiac function and heart disease. In the same year, he published a report of studies in patients whose pulse were “continuously and extremely irregular”. He concluded that auricular fibrillation was “a common clinical condition” [18]. The term AF is used for the first time in a publication by Rothberger and Winterberg in 1909; previously, it had been referred to as “pulsus irregularis” or “arrhythmia perpetua” [19]. Willem Einthoven received the Nobel Prize in Medicine in 1924.
Electrophysiological mechanisms

In the late 1990s Haissaguerre et al. made the observation that ectopic beats from pulmonary veins may trigger AF [20]. This discovery made pulmonary vein isolation the cornerstone in AF ablation. However, mechanisms that sustain AF, once triggered, are not fully understood. There are two prevailing hypotheses. The multiple wavelet hypothesis which proposes that reentrant wavefronts sustain AF [21-23] and the localized source hypothesis that proposes that focal impulses and re-entrant circuits sustain AF [24-26]. In the CONFIRM trial, Narayan et al. demonstrated that AF may be sustained by localized sources in the form of electrical rotors and focal impulses [27]. They also showed that ablation of patient specific sources could terminate AF and improve the long-term results of AF ablation.

Atrial remodelling

Structural changes in the atria, i.e. atrial remodelling, seems to play an important role in the development of AF. Atrial remodelling alters the electrical and structural properties of the atria and promotes the development of AF. It is a slow, progressive and complex array of pathophysiological changes that are induced by conditions such as obesity, heart failure, hypertension, cardiovascular disease, and ageing (Figure 5). AF in itself, once initiated, causes a Ca^{2+} overload in the myocytes, which leads to decreased refractoriness and a propensity to sustain AF, hence the term “AF begets AF” [28]. This phenomenon
probably contributes to the progressive nature of the arrhythmia. A key part of atrial remodelling is the development of atrial fibrosis which leads to increasing distances between the myocytes and conduction heterogeneities which facilitates reentry. This is induced by atrial-stretch caused by conditions such as heart failure and hypertension [29]. Fatty infiltration also seems to contribute to the development of the AF substrate [30]. Inflammation has been associated with AF, however it is not fully understood to what extent inflammation is caused by external factors such as obesity induces AF or if inflammation in the atrial tissue is consequence of cell death due to oxidative stress and Ca\(^{2+}\) overload during the arrhythmia [31]. Furthermore, changes in intracellular Ca\(^{2+}\) handling promote triggered activity and shortening of the action potential which contributes to the development of AF [32].

![Diagram of mechanisms causing AF](image)

Figure 5. Mechanisms causing AF. Various aetiological factors cause a complex array of changes in the atria. Reprinted form the 2016 ESC Guidelines for the management of AF with permission from Oxford University Press.
Genetic predisposition may also play a role in the development of AF, especially in early onset AF [33].

**Inflammation and AF**

It has been suggested that inflammation has a potential role in the development of AF. This theory was initially based on the observation that inflammatory states like myocarditis, pericarditis and cardiac surgery were frequently associated with AF [34-36]. Inflammation may be a systemic phenomenon or a local process in the atria or both, however, most studies have not been designed to differentiate between these processes. Furthermore, underlying inflammatory pathophysiology may be different in different clinical scenarios such as paroxysmal or chronic AF.

Inflammation has been reported in atrial biopsies from patients with paroxysmal AF [37]. Goette et al. found no evidence of tissue cytokine activation in atrial tissue samples from patients with chronic AF [38]. Liuba et al. found elevated levels of IL-8, an inflammatory cytokine, in the peripheral blood, in the right atrium and in the coronary sinus, however not in the pulmonary veins of patients with permanent AF [39]. Inflammation has also been described in the pericardial adipose tissue in subjects with AF. Mazurek et al. measured epicardial inflammatory activity by $^{18}$F-fluorodeoxyglucose PET and found a 35% higher activity in patients with AF than in matched controls without AF [40]. It has also been proposed that there is a link between inflammation and the prothrombotic state associated with AF [31].

Several inflammatory markers such as C-reactive protein, tumor necrosis factor-α, and interleukins have been associated with AF [41]. C-reactive protein (CRP) is an inflammatory marker that is easily measured and reflects low-grade systemic inflammation. In several prospective studies, CRP has been shown to be a predictive marker of cardiovascular disease [42, 43]. CRP is also associated with several other risk factors for cardiovascular disease such as obesity and metabolic syndrome [44-46]. Highly sensitive methods, that are capable of measuring concentrations within the healthy reference interval (<3mg/L) must be used to assess cardiovascular risk, hence the term high-sensitivity CRP (hsCRP). A meta-analysis suggested that increased CRP levels were associated with a greater risk of AF recurrence [47]. HsCRP has also been associated with an increased AF duration and burden [48, 49].

Inflammation in patients with AF may arise from different sources. For instance, conditions like obesity, hypertension and coronary artery disease are associated with the development of AF as well as with low-grade inflammation [50-52]. An inflammatory state may initiate AF, however, there is also some evidence that AF
itself may generate an inflammatory response which enhances atrial remodelling and perpetuation of the arrhythmia[31].

Some anti-inflammatory therapies appear to reduce the incidence and recurrence of AF. Anti-inflammatory treatment with low-dose glucocorticoid, methylprednisolone, reduced recurrence of persistent AF and development of permanent AF in a study by Dernellis et al [53]. A Cochrane meta-analysis showed no beneficial effect of corticosteroid use on mortality, cardiac and pulmonary complications but a 40% risk reduction of postoperative AF in cardiac surgery patients [54].

**Clinical consequences**

Typical symptoms of AF are palpitations, dyspnea, impaired physical exercise capacity and fatigue. However, 20–40% of AF patients are asymptomatic [55, 56]. Symptoms may be explained by the hemodynamic consequences of AF, i.e. loss of coordinated atrial contraction, high ventricular rate and ventricular irregularity. The loss of coordinated atrial contraction means a reduction of cardiac output by 5-15%. This effect may be more pronounced in subjects with reduced ventricular compliance, for example patients with hypertrophic cardiomyopathy. High ventricular rates reduce cardiac output by the shortening diastolic filling time. Persistent high ventricular rate above 120-130 beats per minute may cause tachycardia induced ventricular cardiomyopathy [57]. Irregular ventricular rhythm may also cause deterioration of the left ventricular ejection fraction [58].

AF is independently associated with a doubled mortality for females and a 1.5-fold increased mortality for males [59]. It is also associated with increased morbidity such as heart failure and stroke. Heart failure and AF are intimately related. The conditions exacerbate and contribute to each other's development through mechanism like structural remodelling, activation of neurohormonal mechanisms and rate related impairment of left ventricular function. AF increases the risk of hospitalizations and mortality in patients with heart failure [60]. More than 50% of patients with permanent AF have a concurrent diagnosis of heart failure [61]. A person with AF has a fivefold increased risk of stroke compared to a person without AF [62]. Around 30 percent of all strokes are caused by AF[63]. Strokes caused by AF are associated with greater disability and mortality[64]. The prevailing paradigm has been that here is no difference in stroke risk between paroxysmal and persistent AF [65, 66]. However, a recent meta-analysis of NOAC trials shows that patients with non-paroxysmal AF has an increased risk of thromboembolism, adjusted hazard ratio 1.384 (95% CI: 1.191–1.608, p < 0.001), and death, adjusted hazard ratio 1.217 (95% CI: 1.085–1.365, p < 0.001) compared to patients with paroxysmal AF [67]. AF has also been
associated with silent white matter lesions, cognitive decline and dementia [68, 69].

**Clinical management of AF**

The clinical management of AF comprises therapies that have a prognostic impact and therapies that mainly have a symptomatic benefit. Anticoagulation therapy is a cornerstone in the management of AF and falls in to the former category. Symptomatic relief is accomplished by rhythm or rate control management strategies. Rhythm control strategies include cardioversion, antiarrhythmic drug therapy and catheter ablation. In addition, the importance of treatment of concomitant co-morbidities such as sleep apnea, obesity, hypertension, diabetes and cardiovascular disease has been recognized. Treatment of co-morbidities might have a prognostic impact as well as a symptomatic benefit [70][71, 72].
Anticoagulation

Oral anticoagulation therapy reduces the risk of stroke by two thirds and mortality by 25% compared to no treatment or aspirin in patients with AF[73]. Vitamin-K antagonists like warfarin have been widely used for stroke prevention for many years. Warfarin therapy require individual dose adjustment and regular monitoring of international normalized ratio (INR). Recently, novel oral anticoagulants (NOACs) have emerged as an alternative. NOACs include dabigatran, a thrombin-inhibitor and factor Xa inhibitors such as apixaban, rivaroxaban and endoxaban. In recent meta-analysis including the pivotal studies of warfarin versus NOACs the authors showed a 19% (RR 0.81; 95% CI 0.73–0.91; P < 0.0001) risk reduction of risk of stroke or systemic embolism with NOACs compared to warfarin [74]. Mortality was 10% lower in patients randomized to NOAC therapy (RR 0.90; 95% CI 0.85 – 0.95; P < 0.0003) and intracranial haemorrhage was halved (RR 0.48; 95% CI 0.39 – 0.59; P < 0.0001), while gastrointestinal bleeding events were more frequent (RR 1.25; 95% CI 1.01 – 1.55; P = 0.049) [74]. In addition, treatment with NOACs does not require individual dose adjustment or monitoring of INR. Antiplatelet therapy has also been widely used in past but is no longer recommended for stroke prevention since the benefits are limited compared to treatment with anticoagulants, however bleeding rates are similar [75-77].

The risk of stroke in AF patients depends on underlying conditions such as hypertension, diabetes, heart failure, vascular disease, previous stroke or transient ischemic attack (TIA) and age. Risk stratification schemes like the CHA2DS2-VASc score have been developed and validated to simplify the decision to initialize treatment with anticoagulants in AF patients (Table 1). CHA2DS2-VASc score was first included in the 2010 ESC AF guidelines but is also recommended in the current ESC guidelines [14, 78]. The annual risk of stroke increases with the number of points (Table 2). Generally, AF patients with a very low risk for thromboembolic events (CHA2DS2-VASc score =0) do not need anticoagulation therapy, however in patients with a CHA2DS2-VASc score of 1 or more, treatment should be considered.
Table 1. CHA2DS2-VASc score

<table>
<thead>
<tr>
<th>CHA2DS2-VASc risk factor</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>+1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>+1</td>
</tr>
<tr>
<td>Age ≥75 years</td>
<td>+2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>+1</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>+2</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>+1</td>
</tr>
<tr>
<td>Age 65-75 years</td>
<td>+1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>+1</td>
</tr>
</tbody>
</table>

Table 2. CHA2DS2-VASc score and annual risk of stroke/TIA/peripheral emboli according to Friberg et al. [79].

<table>
<thead>
<tr>
<th>CHA2DS2-VASc score</th>
<th>Annual risk of stroke/TIA/peripheral emboli (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>3</td>
<td>5.3</td>
</tr>
<tr>
<td>4</td>
<td>7.8</td>
</tr>
<tr>
<td>5</td>
<td>11.7</td>
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<tr>
<td>6</td>
<td>15.9</td>
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<tr>
<td>7</td>
<td>18.4</td>
</tr>
<tr>
<td>8</td>
<td>17.9</td>
</tr>
<tr>
<td>9</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Recently, percutaneous left atrial appendage occlusion has emerged as an alternative to anticoagulation especially in AF patients with a contraindication to anticoagulation therapy [80, 81].
**Antiarhythmic drug therapy**

Maintaining SR is the main goal in a rhythm control strategy and the commonly used strategy to accomplish this is treatment with antiarrhythmic drugs. Alternatively, catheter ablation might be considered (discussed in a later chapter). The mechanism of action of the antiarrhythmic drugs is blocking different ion channels and they were first categorized by Vaughan Williams in the 1980s by how they interfere with the action potentials in the myocytes [82, 83]. The efficacy of the currently available antiarhythmics is however modest. Antiarrhythmic drugs double SR maintenance compared to no therapy [84]. Successful therapy reduces recurrences rather than abolishes AF. If one drug fails another agent may be successful.

Table 2. Currently available antiarrhythmic drugs for preventing AF

<table>
<thead>
<tr>
<th>Generic substance</th>
<th>Vaughan Williams Class</th>
<th>Clinically important action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disopyramide</td>
<td>IA</td>
<td>Na channel blockade</td>
</tr>
<tr>
<td>Propafenone</td>
<td>IC</td>
<td>Na channel blockade</td>
</tr>
<tr>
<td>Flecainide</td>
<td>IC</td>
<td>Na channel blockade</td>
</tr>
<tr>
<td>Sotalol</td>
<td>III</td>
<td>$I_v$ and $\beta$ blockade</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>III</td>
<td>Blocks multiple ion channels, $\beta$ blockade</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>III</td>
<td>Blocks multiple ion channels, $\beta$ blockade</td>
</tr>
</tbody>
</table>

A drawback with antiarrhythmic drug treatment is that there are potentially dangerous side effects such as proarrrhythmia or extra cardiac toxic side effects. Side effects are frequent and have a negative impact on quality of life which often leads to discontinuation of the treatment. The conclusion in the current AF guidelines is therefore that safety rather than efficacy should be the primary consideration when choosing antiarrhythmic drug [78]. The choice of antiarrhythmic drug needs to be carefully evaluated, taking into account the presence of comorbidities, cardiovascular risk and potential for serious proarrrhythmia and extra cardiac toxic effects. This is illustrated in figure 6. In the current AF guidelines, dronedarone, flecainide, propafenone, or sotalol are recommended for prevention of recurrent symptomatic AF in patients without structural heart disease[78]. However, in a recent Cochrane analysis, sotalol was associated with increased mortality [85]. Dronendarone may be considered in patients with stable coronary heart disease. Amiodarone is the most effective drug in preventing recurrent AF but extra cardiac toxic side effects are common and the risk for extra cardiac side effects increases over time. However, in patients with heart failure, amiodarone is the only safe option.
Figure 6. Considerations when initiating antiarrhythmic drug therapy. All available antiarrhythmic drugs may be considered if the patient does not have any structural heart disease. Class I antiarrhythmics are contraindicated if the patient has structural heart disease and, in heart failure patients, the only option is amiodarone.

There are several clinical trials that have evaluated rhythm control strategy with antiarrhythmic drugs versus rate control in AF patients, however none of them have managed to prove any benefit regarding all-cause mortality or quality of life [86-92]. Most of the antiarrhythmic drugs on the market today are the same as decades ago, which indicates that it is difficult to develop both safe and efficient antiarrhythmic drugs.

**Statins and AF**

Statins have in large clinical trials been shown to reduce cardiovascular morbidity and mortality [93-96]. In addition to cholesterol reduction, statins appear to have favorable pleiotropic effects on vascular endothelial function, atherosclerotic plaque stability, thrombosis and inflammation [97-100]. Several studies have suggested that statins apart from their lipid-lowering properties may also have an antiarrhythmic effect both on ventricular arrhythmias [101-106] and on AF [107, 108]. Kumagai et al. showed that atorvastatin prevented maintenance of AF
in a canine model with sterile pericarditis by inhibiting inflammation [109]. This indicates that a possible mechanism behind an antiarrhythmic effect of statins might be anti-inflammatory properties.

**Rate control**

A rate control strategy in AF patients does not aim at restoring SR but at alleviating symptoms by controlling heart rate by slowing down the AV node conduction. A lenient heart rate control with a resting heart rate of < 110 beats per minute seems acceptable most cases [110, 111] [112]. Beta blockers are often the first line therapy but calcium channel blockers, digoxin or a combination may also be considered. Calcium channel blockers should be avoided in patients with heart failure due to their negative inotropic effects. Implantation of a pacemaker and AV node ablation may be an alternative if drug therapy fails to control heart rate and symptoms.

**Cardioversion**

Electrical cardioversion (CV) is one of the cornerstones in the treatment armamentarium of AF. CV means immediate restoration of SR by applying a direct current (DC) shock through the chest and the heart. The DC shock depolarizes the cardiac myocytes simultaneously, terminating the arrhythmia thus allowing the sinus node to restore its pacemaker function. Since the procedure is painful, it is performed with the patient sedated. Alternatively, pharmacological cardioversion, which does not require sedation or fasting can be performed [113]. The acute success rate is, however, lower (89.7% versus 69.1%) [114]. Drugs that could be considered for pharmacological cardioversion are flecainide, propafenone, ibutilide, amiodarone or vernakalant.

Cardioversion carries a risk of thromboembolic events. Analysis of data from a randomized controlled trial showed a thromboembolic event rate of 0.9% in patients undergoing cardioversion according to current anticoagulation guidelines [115]. By convention, the current AF guidelines recommend that if AF duration is < 48 hours, CV could be performed immediately [78]. Otherwise the patient has to be anticoagulated for at least 3 weeks before and 4 weeks after the cardioversion. The incidence of thromboembolic events related to cardioversion within 48 hours was reported to be 0.2-9.8% within 30 days if no anticoagulation is given after the CV in the FinCV study [116]. The risk of stroke seemed to correlate to the CHA$_2$DS$_2$-VASc score [117]. Patients with diabetes and heart failure had the highest risk while subjects with no risk factors had a very low risk. The risk of thromboembolic events is significantly reduced if the patient is properly anticoagulated [117, 118]. An alternative to three weeks of anticoagulation prior to CV is to exclude left atrial appendage thrombus via a
transesophageal echocardiography (TEE) before CV. The TEE guided approach has been compared to three weeks of anticoagulation prior to CV in a randomized controlled trial (RCT) and there was no difference in thromboembolic event rates[119]. Anticoagulation during and after CV is also recommended in a TEE guided approach [78]. CV offers both an opportunity to study factors related to relapse of AF and associated conditions in patients before CV in AF and after CV in SR. In 3 of the 4 studies in this thesis we have used this opportunity.

**Catheter ablation**

In 1998, Haïssaguerre et al. showed that ectopic activity from the pulmonary veins initiate AF. Since then pulmonary vein isolation (PVI) by catheter ablation has become a well-established treatment option for AF [20]. The aim of PVI is to electrically isolate the pulmonary veins and thereby preventing the ectopic activity from entering the atrium. PVI might be achieved either by point by point radiofrequency ablation, linear lesion encircling the pulmonary veins or cryoballoon ablation. Outcomes appear to be similar [120-122]. Complete isolation of the pulmonary veins has better outcomes than incomplete [123].

In several AF ablation studies, the endpoint has been freedom of symptomatic AF at 12-months follow-up and has been reported to be around 70% in patients with paroxysmal AF [120, 124, 125]. In a meta-analysis including studies describing outcomes ≥ 3 years after the index ablation, Ganesan et al found that single-procedure freedom from atrial arrhythmia at long-term follow-up was 53.1% (95% CI 46.2% to 60.0%) overall, 54.1% (95% CI 44.4% to 63.4%) in paroxysmal AF, and 41.8% (95% CI 25.2% to 60.5%) in non-paroxysmal AF [126]. With multiple procedures, the long-term success rate was 79.8% (95% CI 75.0% to 83.8%) overall. The average number of procedures per patient was estimated to be 1.51 (95% CI 1.36 to 1.67) in this meta-analysis [126]. According to the Swedish national registry for catheter ablation, around one fourth of the AF ablations in 2015 were “redo” procedures [127].
Figure 7. Pulmonary vein isolation. Posterior view of the left atrium derived from an electroanatomical mapping system (CARTO) used during PVI. A) A voltage map of the left atrium before PVI. B) A voltage map of the left atrium after point by point isolation of the pulmonary veins with the added dots indicating ablation points. The red colour indicates that these areas are electrically silent, i.e. the pulmonary veins are isolated.

A more extensive ablation strategy with additional lines or ablation of complex fractionated electrograms in patients with persistent AF has been suggested, however when this strategy was tested in a randomized trial (STAR AF II), it did not reduce the recurrence rate of AF [128]. Lately, alternative targets for ablation such as rotors and areas with spatiotemporal dispersion have been suggested and studied in this patient population, with promising results [27, 129].
Catheter ablation of paroxysmal AF as a first line treatment has been shown to have a modest advantage over treatment with antiarrhythmic drugs [130-132]. As a second line treatment in patients with frequent recurrences of AF despite treatment with antiarrhythmic drugs, catheter ablation has been shown to be better than antiarrhythmic drugs at maintaining SR than antiarrhythmic drugs according to several trials [125, 133, 134].

In the 2010 worldwide survey, Cappato et al reported that major complications occurred in 4.5% of patients being ablated. The most common complications were tamponade (1.33%) and vascular problems (0.93%) [135]. Other severe complications that may occur are pulmonary stenosis (<0.1%), phrenic nerve palsy (1-2%), TIA/stroke (<0.1%) and oesophageal injury (<0.5%) [78]. Deaths related to the procedure have been reported but are fortunately rare (0.06%) [136]. Asymptomatic white matter lesions in the brain have been described in 10% of patients undergoing catheter ablation of AF, but the clinical significance of these lesions is unclear [137].

Currently, the indication for catheter ablation of AF is merely relief of symptoms. There is no indication for catheter ablation to prevent stroke or other cardiovascular outcomes. Nor is a patient's desire to withdraw anticoagulation an accepted indication. The CABANA and EAST trials that will be published in the near future will shed some light on whether AF ablation affects mortality or stroke risk [138, 139].

**How to measure symptoms of AF**

Since most AF treatments such as catheter ablation are symptomatic, it is important to have tools for measurement of arrhythmia-related symptoms for evaluation and comparison between different groups. SF-36 is a 36-question protocol for the measurement of quality of life (QoL). It has been extensively validated in normal subjects, and in populations from multiple countries affected by distinct disease entities [140, 141]. From the answers, eight subscales ranging from 0 to 100 are derived, covering the physical (Physical functioning, Role physical, Bodily pain, and General health scales) and mental (Vitality, Social functioning, Role-emotional and Mental health scales) dimensions of well-being, normalized as Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

SF-36 appears to detect a relevant improvement in QoL after AF ablation and has been used in several studies [142]. However, SF-36 measures general health, rather than symptoms of AF and the scores are influenced by patient comorbidities, which are prevalent. Thus, there is a need for a validated AF-specific questionnaire.
Several questionnaires which quantify symptoms associated with tachyarrhythmias have been published. The Symptom Checklist-Frequency and Severity Scale exists in multiple versions that are not well-described in the literature [143-146]. The ASTA-questionnaire is a Swedish three-part protocol that measures arrhythmia-specific symptoms and health-related QoL in connection with arrhythmias[147]. In recent years, several AF specific QoL instruments have been validated. AF6 is a Swedish 6 item questionnaire [148]. The AFs Effect on QualiTy-of Life (AFEQT) appears to detect clinically relevant changes in QoL an English-speaking population [149]. AF-QoL is an 18-item questionnaire that is validated in a Spanish population [150]. QLAF is a protocol with 22 questions which is validated in a Brazilian population [151]. However, none of the mentioned protocols have been cross-validated which means that their generalizability is uncertain.

**Sleep apnea**

Sleep apnea or sleep disordered breathing refers to a common medical condition which includes breathing pauses (apneas - cessation of airflow) and episodes of shallow breathing (hypopneas - reduction in airflow) during sleep. The episodes may last from seconds to several minutes. There are 2 major forms of sleep apnea: obstructive sleep apnea (OSA) and central sleep apnea(CSA). The severity of sleep apnea is measured by the apnea-hypopnea index (AHI), the frequency of apneas and hypopneas per hour of sleep. An AHI ≥ 5 represents mild sleep apnea, while AHI ≥ 15 represents moderate to severe sleep apnea.

OSA is a result of partial or complete upper airway collapse. Risk factors for OSA are obesity, age, male gender, menopausal status, craniofacial anatomy, smoking and alcohol consumption[152-158]. OSA is associated with excessive daytime sleepiness and a known risk factor for cardiovascular disease, including stroke and hypertension [159-163].

CSA is caused by decreased and absent respiratory center output due to instability in the feedback mechanism that controls respiration. A strong link between heart failure and CSA is suggested in the literature[164]. Patients with heart failure and CSA hyperventilate chronically due to pulmonary congestion and hence stimulation of vagal irritant receptors in the lungs. This phenomenon is augmented when the patient is in the supine position. A further acute increase in ventilation causes reduction in arterial carbon dioxide pressure (PaCO2). When PaCO2 falls below the threshold level required to stimulate breathing, the central drive to respiratory muscles and airflow ceases and central apnea ensues. The prevalence of OSA defined as AHI ≥5 were found to be a mean of 22% (range, 9-37%) in males and 17% (range, 4-50%) in females in a recently published
review[165]. OSA syndrome defined as AHI ≥5 and excessive daytime sleepiness occurred in 6% (range, 3-18%) of males and in 4% (range, 1-17%) of females[165]. CSA affects less than 1% of otherwise healthy subjects, however the prevalence amongst patients with heart failure is reported to be 33-40% [153, 164].
Aims of the thesis

The general aim of this thesis was to study AF by comparing measures during arrhythmia to those after restoration of SR by CV or catheter ablation.

Paper I
To evaluate the effect of atorvastatin on maintaining SR after CV of persistent AF.

Paper II
To assess if hsCRP predicts the recurrence of AF after CV in a population randomized to treatment with either atorvastatin or placebo.

Paper III
To quantify the symptomatic effect of left atrial catheter ablation of AF with the Umea 22 Arrhythmia Questions (U22) protocol and relate the results to the incidence of reablation based on the clinical evaluation that serves as reference.

Paper IV
To assess if the restoration of SR by CV in a population with persistent AF affects sleep apnea.
Study designs and methods

Study designs
Paper I was a double-blinded, placebo-controlled, randomized, prospective multicentre study. Paper II-IV were prospective, observational studies.

**Paper I-Atorvastatin and persistent AF**
The aim in the first study was to evaluate effect of atorvastatin on SR maintenance after CV of persistent AF. It was an investigator-initiated, double-blinded, placebo-controlled, randomized, prospective multicentre study performed at 10 clinical centres in Sweden. Between August 2004 and January 2007, out of 783 screened patients a total of 234 patients with persistent AF and an indication for CV were included and randomized to either treatment with atorvastatin (n=118) or placebo (n=116). Inclusion criteria were persistent AF with duration > 7 days and age between 18 and 80 years. Patients with paroxysmal AF, atrial flutter, contraindications against atorvastatin, ongoing treatment with lipid-lowering drugs, ongoing treatment with class I or class III antiarrhythmic treatment, oral amiodarone 6 months before inclusion, or known liver disease or a myopathy, as well as patients with a previous electrical CV within less than 1 year were excluded. Before randomization, a detailed medical history was obtained and transthoracic echocardiographic exams, 12-lead ECG, and basic laboratory analysis were performed. Warfarin was given to all patients according to national guidelines, i.e. INR of 2–3. Treatment with either atorvastatin (40mg, two tablets once daily) or placebo was initiated 14 days before and continued for 30 days after elective CV. The production unit of the hospital pharmacy, which also packed and labelled the medical preparations and provided coding material for the study, made a computer-generated randomization list using blocks of six. Participating centres received medical preparations distributed from the hospital pharmacy in Huddinge that not was involved in the randomization and packing procedure. Compliance was monitored at CV and at day 30 after CV (end of treatment) by pill counting. Follow up was performed 2 days, 1 month and 6 months after CV. The primary endpoint was rhythm obtained by 12-lead ECG at 30 days after CV. Secondary endpoints were rhythm at 6 months after CV, safety and tolerability.
**Paper II-Inflammation and recurrence of AF**
The aim of the second study was to investigate whether an inflammatory marker, hsCRP, predicts recurrence of AF after CV in a population of patients randomized to either treatment with atorvastatin or placebo. This was a pre-specified substudy within study I. A total of 128 patients out of the 234 patients in study I were included in this substudy. Blood samples for hsCRP analysis were drawn at randomization, on the day of CV, and 2 and 30 days after CV. Patients were followed-up 2 days, 1 month, and, finally, 6 months after CV.

**Paper III-The U22 protocol**
The main objective of the third study was to quantify the symptomatic effect of left atrial catheter ablation of AF, i.e. pulmonary vein isolation, with the Umea 22 Arrhythmia Questions (U22) protocol. The study group consisted of patients who underwent pulmonary vein isolation for paroxysmal and persistent AF at the Heart Centre, University Hospital, Umeå, Sweden, between 2006 and 2011. On admission, the patients were invited to answer the baseline U22 and SF-36 forms. Pulmonary vein isolation was subsequently performed and a questionnaire follow-up with U22 and SF-36 was performed 6–9 months after the ablation. The answers were prospectively entered into a database, blinded with respect to the clinical picture. Independently from the U22 protocol, the patients underwent a clinical follow-up and a 7-day Holter-monitor recording. All decisions regarding medication and possible repeated ablation were taken without knowledge of the symptom scores. The protocol data were subsequently retrieved for the analysis. At review time the clinical data and the catheterization reports were analyzed and coded according to a pre-specified scheme by co-authors blinded with respect to the U22 results. Answers to U22 and SF-36 were compared between baseline and follow-up, group-wise and in individual patients.

**Paper IV-Sleep apnea and AF**
The main objective of this fourth study was to evaluate the prevalence of sleep apnea and the effect of restoration of SR by CV on obstructive and central sleep apnea in a population with persistent AF. The study comprised 28 patients scheduled for the elective CV of persistent AF at the Department of Cardiology, Umeå University Hospital, without previously diagnosed sleep apnea. Five patients were excluded after inclusion, because of severe heart failure, unstable angina pectoris or because they declined further participation. Inclusion took place two to four weeks before CV. A detailed medical history was obtained, a 12-lead ECG was performed and echocardiographic data were collected. Overnight polysomnography was performed within one week before CV and follow-up polysomnography and an ECG was performed within one week after CV. The Epworth Sleepiness Scale (ESS) was used to assess the degree of daytime sleepiness.
Methods

**Cardioversion**
Cardioversion was performed according to local standard clinical practice on an elective outpatient basis. CV was performed with the patients fasting. Sedation was induced by propofol administered under the supervision of an anaesthesiologist. R-wave-synchronized mono or biphasic shocks were given using a step-up protocol (usually 200, 300, and 360 J) to achieve SR.

**High-sensitivity CRP**
Plasma CRP was determined with an automated high-sensitivity CRP method (IMMULITE, Diagnostic Products Corporation, USA). The inter-assay coefficient of variation was 6%.

**Pulmonary vein isolation**
In study III, catheter ablation of AF was performed as segmental pulmonary vein isolation, wide antral circumferential isolation with an irrigated tip catheter and the CARTO mapping system (Biosense Webster, Inc., Diamond Bar, CA, USA) or isolation with a multi-polar circular ablation catheter (PVAC, Medtronic, Inc., Minneapolis, MN, USA).

**Umea 22 Arrhythmia Questions**
Umea 22 Arrhythmia Questions (U22) is a published protocol that quantifies paroxysmal tachycardia symptoms through scales with 11 answer alternatives, translated into discrete numerical scales 0–10. It has been shown to reflect the clinical improvement after ablation of supraventricular tachycardia[166, 167]. The original language of the questionnaire is Swedish. An English version is included in the Appendix. The Swedish version was used in study III.

The baseline U22 questionnaire (Figures 13 and 14, Appendix) consists of 19 questions (q) probing into multiple aspects of severity and frequency of symptoms associated with arrhythmic episodes: (1) general well-being and influence of arrhythmia on well-being (q01, q11, and q12), (2) intensity of discomfort during episode of symptomatic arrhythmia, and (3) symptom severity. The symptoms during arrhythmia are listed as fast heart rate, pounding, irregularity, dizziness, pain, fatigue, shortness of breath, the subject's sense of fear, and a relative's fear (q13–q18, q20–q22). The 11 horizontally aligned answer alternatives have verbal descriptions of the endpoints (anchors). Two questions use a bipolar (q03, q09), and 15 use unipolar verbal scales (q01, q04, q05, q11–q22). At evaluation, the answers are converted to a discrete numerical scale from 0 to 10, emulating the common VAS scale[168]. Measures are derived from the
answers, which describe the dominant symptom(s), that is, the sensation(s) perceived as most unpleasant during arrhythmia. The incidence and duration of episodes are estimated by q08 and q10, with six nonlinear answer choices scored from 0 to 5. The incidence is classified as “never”, “on single occasions”, “a few times a month”, “a few times a week”, “daily” or “all the time.” The duration is classified into “seconds”, “minutes”, “a quarter of an hour or more”, “one hour or more”, “longer than four hours,” or “all the time.” A temporal score from 0 to 10 is calculated by adding these two scores. The effects of drug therapy are measured by q03-q05. Q19 is used to test the subject’s comprehension and relevancy of the answers by including itching, a symptom irrelevant to arrhythmias. In the follow-up questionnaire q02, q06 and q07 are added to specifically evaluate the effect of a given arrhythmia treatment (Figure 15, Appendix).

In paper III, the following questions were included in the analysis:

**Question 01:** ‘On the whole, how have you felt over the past month?’ (miserable–very well), (0–10)

**Question 02 (follow-up only):** ‘Compared to the time before the treatment, do you now feel:’ (Very much worse–very much better), (0–10)

**Question 03:** ‘Do you take any prescribed medications for your heart rhythm problems?’ (No, Yes)

**Question 06 (follow-up only):** ‘Have you experienced any problems with the heart rhythm after the treatment? – please disregard the first 3 months after the treatment –’ (No; Yes, of the same type as before the treatment; Yes, of different type)

**Question 08:** ‘How often do you experience problems with heart rhythm? (despite taking any medication)’ (Never, Rarely, A few times a month, A few times a week, Daily, All the time)

**Question 10:** ‘How long does a spell usually last?’ (Seconds, More than a minute but less than 15 min, 15 min to 1 hour, 1 to 4 hours, More than 4 hours, All the time)

**Question 11:** ‘How much do the spells affect your wellbeing?’ (Not at all–very much), (0–10)

**Question 12:** ‘How bothered are you while you are experiencing a spell?’ (Not at all–very much), (0–10).
A time-aspect with range 0–10 was computed by summarizing the scores from question 08 and question 10.

**SF-36**

In paper III, SF-36 was used as generic measure of QoL. SF-36 is a 36-question protocol for the measurement of QoL which has been extensively validated. It quantifies the mental and physical wellbeing in eight scales ranging from 0 to 100, covering the physical (Physical functioning, Role physical, Bodily pain, and General health scales) and mental (Vitality, Social functioning, Role-emotional and Mental health scales) dimensions of well-being, normalized as Physical Component Summary (PCS) and Mental Component Summary (MCS) scores [140].

**Polysomnography**

The gold standard method for the diagnosis of sleep apnea is a polysomnographic study that records sleep and breathing in a sleep laboratory overnight[169]. In study IV, overnight polysomnography included continuous recordings of electroencephalograms (C3-A2, C4-A1), electro-oculograms, submental electromyograms, airflow with a three-port oro-nasal thermistor, respiratory effort from continuous esophageal pressure (PES Sensor, Gaeltec CTO-1) and piezo-electric belts (Resp-EZ, EPM Systems, Midlothian, VA, USA), finger pulsoximetry (Embla A10 flex Sensor), electrocardiograms (V5) and a body position sensor.

All the recordings were scored manually. An obstructive apnea was defined as the cessation of airflow for at least 10 seconds with continuing abdominal and thoracic movements, according to the American Academy of Sleep Medicine [170]. An obstructive hypopnea was defined as a 50% reduction in airflow for at least 10 seconds, compared with baseline, accompanied by abdominal, thoracic, esophageal pressure movements in combination with an arousal or an oxygen desaturation of 3% or more [170]. Central apneas were defined as a cessation of airflow for 10 seconds without esophageal pressure fluctuations and respiratory movements. Sleep was scored manually in 30-second epochs according to Rechtschaffen and Kales [171].
The obstructive apnea-hypopnea index was defined as the mean number of obstructive apneas and hypopneas per hour of sleep, while the central apnea index was defined as the mean number of central apneas per hour of sleep. Obstructive sleep apnea was defined when the obstructive apnea-hypopnea index was 5 or more, while central sleep apnea was defined when the central and mixed apnea-hypopnea index was 5 or more. Continuous esophageal pressure recordings in order to evaluate the respiratory effort is optional and may be added when it is of interest to optimize the discrimination between obstructive and central apneas.

**Epworth Sleepiness Scale**
The ESS was used to assess daytime sleepiness. It is a self-administered, validated questionnaire with eight questions relating to the risk of falling asleep in different
situation, with answers scoring from 0-3. Possible scores ranged from 0 to 24 and excessive daytime sleepiness was defined as an ESS score of ≥ 11 [172].
Statistics

- Continuous variables were expressed as means ± standard deviations (SD) or as medians and interquartile ranges (IQR). Proportions were expressed as percentages.

- Student’s t test was used to compare normally distributed continuous variables. Non-normally distributed variables were compared with Wilcoxon signed rank (paired variables) or Mann-Whitney (independent variables).

- Pearson’s chi-square test or Fisher’s exact test was used to compare proportions in paper I and II. McNemars test was used to compare paired proportions in paper IV.

- In paper II, a multivariate logistic regression model was used to determine predictors of AF recurrence. The variables that were considered clinically relevant such as age, gender, body mass index (BMI), smoking, cholesterol, or those that were statistically significant (p<0.05) such as treatment with atorvastatin were included in the multivariate model.

- In paper III differences between groups in continuous variables were examined by paired and unpaired two-tailed t test and global F test. Pearson’s r was used for correlation between continuous variables. Cronbach’s alpha was used for estimating internal consistency of the scores. For analysis of freedom from subsequent reablation, Kaplan–Meier curves were constructed, and differences between dichotomized groups were evaluated by log-rank test.
Ethics

All studies comply with the Declaration of Helsinki. The Regional Ethical Review Board in Stockholm at Karolinska Institute approved studies I and II (Dnr 03-207;2003-05-05). Studies III (Dnr 07-079M) and IV (Dnr 05-027M;2005-05-02) were approved by the Regional Ethical Review Board in Umeå. Signed and informed consent was obtained from all participants in all studies.
Results

Paper I-Atorvastatin and persistent AF

Of the 783 patients screened, a total of 234 patients were included and randomized to either treatment with atorvastatin (80 mg/day) or placebo. The two groups were well balanced with regards to baseline demographics. Twelve patients (atorvastatin n=7, placebo n=5) discontinued the study mainly due to logistical reasons. It was not possible to convert eight patients to SR (7%) in the atorvastatin group and 13 (12%) in the placebo group (p = 0.25).

![Figure 9](image)

Figure 9. Relative proportion of patients in SR at 2 h, 2 days, 30 days, and 6 months after CV, analyzed by intention-to-treat analysis with the available data.

Primary outcome data (rhythm by 12 lead ECG 30 days after CV) were available and included in the intention to treat analysis for 222 patients (atorvastatin n=111 and placebo n=111). The analysis showed that 57 patients (51%) in the atorvastatin group and 47 (42%) in the placebo group maintained SR 30 days after CV. At 6 months 41 (38 %) and 43 (39%) patients were in SR in respective groups (Figure 9). A summary of study endpoints is presented in Table 3. Compliance in both groups was > 90 % and no serious adverse events occurred.
Table 3. Summary of results in paper I, analyzed by intention-to-treat with available data

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Atorvastatin group (n=111)</th>
<th>Placebo group (n=111)</th>
<th>Odds ratio (95%CI)</th>
<th>P-value</th>
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<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Number of patients in SR day 30 (%)</td>
<td>57 (51.4)</td>
<td>47 (42.3)</td>
<td>1.44 (0.85-2.44)</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin group (n=109)</td>
<td>Placebo group (n=110)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients in SR at 6 months (%)</td>
<td>41 (37.6)</td>
<td>43 (39.1)</td>
<td>0.94 (0.54-1.62)</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin group (n=116)</td>
<td>Placebo group (n=115)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolerability, n (%)</td>
<td>115 (99.1)</td>
<td>115 (100)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Adverse events, n (%)</td>
<td>3 (2.6)</td>
<td>4 (3.5)</td>
<td>0.74 (0.16-3.37)</td>
<td>0.72</td>
</tr>
</tbody>
</table>
**Paper II-Inflammation and recurrence of AF**

A total of 128 patients were included in the study. Seven patients were excluded due to SR on CV day and 96 of 121 patients were successfully cardioverted and remained in SR 2 hours after CV. These 96 patients were included in the final analysis. There were no significant differences in baseline characteristics between this subgroup and the overall population. Forty-eight patients were in the atorvastatin group and 48 in the placebo group.

In the placebo group, 19 of 48 patients (40%) were in SR at day 30 compared with 30 of 48 patients (62%) in the atorvastatin group (OR 2.5, 95% CI 1.1–5.8), whereas after 6 months there was no significant difference (43% vs. 48%, respectively; OR 1.2, 95% CI 0.5–2.8). At 30 days after CV the hsCRP levels were significantly lower in the atorvastatin group compared with the placebo group (median 1.2 mg/L [IQR 0.65–3.0] vs. median 2.2 mg/L [IQR 1.3–5.0], p=0.017) (Figure 10).

![Figure 10. There was a significant decrease in hsCRP levels in the atorvastatin group both over time and compared to the placebo group.](image-url)
In univariate analysis hsCRP did not significantly (OR 1.11, 95% CI 0.99–1.25) predict recurrence of AF at 30 days. In a multivariate logistic regression analysis with gender, age, body mass index (BMI), smoking, cholesterol, and treatment with atorvastatin as covariates, the association was still significant (OR 1.14, 95% CI 1.01–1.29) (Table 4).

Table 4. Univariate and multivariate logistic regression analysis of AF recurrence 30 days after CV

<table>
<thead>
<tr>
<th>Clinical variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95%CI)</td>
<td>OR(95%CI)</td>
</tr>
<tr>
<td>Age (Years)</td>
<td>1.00(0.96-1.04)</td>
<td>0.99(0.95-1.04)</td>
</tr>
<tr>
<td>Male Gender</td>
<td>1.19(0.45-3.14)</td>
<td>0.98(0.31-3.09)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>1.03(0.96-1.10)</td>
<td>0.99(0.91-1.08)</td>
</tr>
<tr>
<td>Atorvastatin treatment</td>
<td>0.39(0.17-0.90)</td>
<td>0.3(0.12-0.73)</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>0.96(0.64-1.44)</td>
<td>0.92(0.56-1.44)</td>
</tr>
<tr>
<td>HsCRP at randomization (mg/L)</td>
<td>1.11(0.99-1.25)</td>
<td>1.14(1.01-1.29)</td>
</tr>
<tr>
<td>Smoker (yes/no)</td>
<td>2.19(0.38-12.54)</td>
<td>2.75(0.40-18.91)</td>
</tr>
</tbody>
</table>

BMI: Body mass index; Hs CRP: high-sensitivity C-reactive protein

Six months after CV, hsCRP at randomization predicted recurrence of AF in both univariate analysis (OR 1.30, 95% CI 1.06–1.60) and in multivariate logistic regression analysis (OR 1.33, 95% CI 1.06–1.67).
Paper III-The U22 protocol

A total of 105 patients, 78 men and 27 women, undergoing a first-time catheter ablation of AF on clinical indication answered all four required forms U22 and SF-36 at baseline and follow-up. They were 58±9 years old and the AF was paroxysmal in 50%, persistent in 48%, and long-standing persistent in 2% of the patients.

At the clinical follow-up 136±58 days after the ablation, 62% of the patients had no AF in the 7-day Holter-monitor recording. In 61% of the patients, the symptomatic result was considered satisfactory, and antiarrhythmic drugs were discontinued. In 20% the result was considered as satisfactory, but the antiarrhythmic therapy was continued. In 14% the result was not satisfactory, and a second catheter ablation was intended. In 5% the result was not satisfactory, but no catheter intervention was planned at the clinical follow-up. At the questionnaire follow-up 304±121 days after the ablation, 29 patients (28%) reported freedom from arrhythmia symptoms, 48 (46%) had the same type of symptoms as before the ablation, and 27 (26%) had symptoms of different type.

The main results are presented in Table 5. Compared to the state before ablation, significant improvements were recorded at follow-up in the U22 scores for well-being (q01), arrhythmia as cause for impaired well-being (q11), the time-aspect score for arrhythmia derived from q08 and q10, discomfort during an attack (q12), and the SF-36 summary scores PCS and MCS. The patients with freedom from AF in the 7-day Holter-monitor recording at clinical follow-up had significantly better mean U22 scores for well-being (q01), arrhythmia as cause for impaired well-being (q11), the time-aspect score for arrhythmia, and discomfort during an attack (q12) compared to those with some episode of AF (6.9 versus 4.4; 3.9 versus 6.7; 3.3 versus 5.7; and 4.1 versus 6.8, respectively, p < 0.0005 for all comparisons)

Of the 105 patients 69 underwent only one procedure. They were compared to the 36 patients who later underwent repeated procedures. At follow-up, U22 detected a significantly larger symptomatic improvement in the scores for well-being (q01), arrhythmia as cause for impaired well-being (q11), discomfort during an attack (q12), and derived time-aspect score for arrhythmia in the patients who underwent a singular ablation than in the group with the first of multiple ablations (Figure 11).
Cronbach’s alpha for the set of U22 scores at baseline, follow-up, and individual patients’ score differences were 0.79, 0.94, and 0.91, indicating a satisfactory to excellent internal consistency. The score for patients’ retrospective estimation of improvement in well-being measured at follow-up (q02) was 7.1 (SD 2.5). This retrospective estimate of improvement correlated moderately to the improvement computed as difference between the score for well-being at follow-up and before ablation (q01follow-up – q01baseline) ($r = 0.55, p < 0.0001$).
Figure 11. Differences in U22 scores in singular ablations compared to the first of multiple ablations. The differences for q01, q11, q12, and time-aspect in individual patients were computed as (score\textsubscript{follow-up} – score\textsubscript{baseline}). Singular ablations are represented by white boxes, the first of multiple ablations by grey boxes. The boxes are delimited by mean ± 1 SD. The central line depicts the mean, and the whiskers are placed at the extreme values. For all scores the singular ablations resulted in significantly larger improvements than the first of multiple ablations.

At baseline, U22 score for well-being (q01) correlated moderately to the SF-36 summary variables PCS and MCS (r = 0.65 and 0.49). The correlations between q11, q12, and time-aspect on one side and PCS and MCS on the other side were weak (r ≤ 0.4) or non-significant. At follow-up, q01 correlated strongly to PCS and moderately to MCS (r = 0.75 and 0.54); and q11, q12, and time-aspect correlated moderately to PCS (r = 0.59, 0.57, and 0.61) and weakly to MCS (r ≤ 0.4). The strong and moderate correlations were significant (p ≤ 0.0004, corrected for multiple comparisons by Holm’s method).
Paper IV-Sleep apnea and AF

Twenty-three patients, 14 men and 9 women, were investigated with a polysomnography before and after CV of persistent AF. They were 62 ± 7 years old, with a mean BMI of 27 ± 4 kg/m², and 19 patients (83%) had sleep apnea (AHI ≥ 5 events/h). At baseline, obstructive sleep apnea (obstructive AHI ≥ 5 events/h) occurred in 17/23 patients (74%), and central sleep apnea (central AHI ≥ 5 events/h) in 6/23 patients (26%). Twenty-two patients had a normal or slightly impaired left ventricular function, with a left ventricular ejection fraction above 45%.

Table 6. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All n=23</th>
<th>Sinus rhythm at follow up n=16</th>
<th>Atrial fibrillation at follow-up n=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>14 (61)</td>
<td>10 (62)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 ± 7</td>
<td>62 ± 8</td>
<td>61 ± 4</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27 ± 4</td>
<td>28 ± 4</td>
<td>30 ± 5</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>12 (52)</td>
<td>8 (50)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>5 (21)</td>
<td>3 (19)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Ischemic heart disease, n (%)</td>
<td>2 (9)</td>
<td>1 (6)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>1 (14)</td>
</tr>
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</table>

Echocardiography

<table>
<thead>
<tr>
<th></th>
<th>Normal or slightly impaired (LVEF &gt; 45%), n (%)</th>
<th>Moderately impaired (LVEF 30-44%), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22 (96)</td>
<td>1 (4)</td>
</tr>
<tr>
<td></td>
<td>16 (100)</td>
<td>0 (0)</td>
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<tr>
<td></td>
<td>6 (86)</td>
<td>1 (14)</td>
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</table>

Medication (baseline)

<table>
<thead>
<tr>
<th></th>
<th>All n=23</th>
<th>Sinus rhythm at follow up n=16</th>
<th>Atrial fibrillation at follow-up n=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers, n (%)</td>
<td>17 (83)</td>
<td>13 (81)</td>
<td>14 (86)</td>
</tr>
<tr>
<td>Calcium antagonists, n (%)</td>
<td>6 (26)</td>
<td>4 (25)</td>
<td>2 (29)</td>
</tr>
<tr>
<td>Digoxin, n (%)</td>
<td>5 (18)</td>
<td>4 (25)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>ACE inhibitors or ARB, n (%)</td>
<td>11 (48)</td>
<td>7 (44)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>7 (30)</td>
<td>4 (25)</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Warfarin, n (%)</td>
<td>23 (100)</td>
<td>16 (100)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>7 (39)</td>
<td>3 (19)</td>
<td>4 (57)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>All n=23</th>
<th>Sinus rhythm at follow up n=16</th>
<th>Atrial fibrillation at follow-up n=7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea-hypopnea index (AHI), events/h</td>
<td>24 ± 16</td>
<td>23 ± 16</td>
<td>28 ± 17</td>
</tr>
<tr>
<td>Obstructive AHI, events/h</td>
<td>18 ± 14</td>
<td>18 ± 15</td>
<td>18 ± 17</td>
</tr>
<tr>
<td>Central AHI, events/h</td>
<td>6.3 ± 14</td>
<td>4.8 ± 12</td>
<td>10 ± 17</td>
</tr>
</tbody>
</table>

The data are presented as the means ± standard deviation for continuous variables, or numbers and percentages for dichotomous variables; LVEF: left ventricular ejection fraction; ACE: angiotensin-converting enzyme; ARB: angiotensin II receptor blocker
Twenty-one patients were converted to SR, and 16 of the 23 patients (70%) were in SR at follow-up. Among the 16 patients who were in SR at follow-up the first polysomnography was performed median 5.5 days (IQR 2-11.2) before CV and the second polysomnography median 4 days (IQR 2-9.2) after CV and sleep apnea occurred in 13 (81%) before CV and in 14 (88%) after CV (p=1.0). Obstructive sleep apnea occurred in 11/16 (69%) patients before CV, and in 13/16 (81%) who were in SR at follow-up (p=0.5). Central sleep apnea occurred in 2/16 (12%) patients before CV, and in 3/16 (19%) who were in SR at follow-up (p=1.0). Neither the obstructive apnea-hypopnea index (mean AHI 18 ± 15 vs 18 ± 14 events/h, p=0.6) nor the central apnea-hypopnea index (mean AHI 4.8 ± 12 vs 3.4 ± 6.9 events/h, p=0.6) did change when SR was restored among patients who were in SR at follow-up (Figure 12). The proportion of patients with central sleep apnea at baseline was higher amongst those who had a recurrence of AF at follow-up (57% vs 12%, p =0.045).

![Figure 12](image-url)

Figure 12. Mean obstructive and central apnea-hypopnea index among the 16 of 23 patients who were in AF at baseline and in SR at follow-up.

Total sleep time, sleep in different sleep stages, sleep efficiency, sleep in a supine position and daytime sleepiness according to the Epworth Sleepiness Scale did not change when SR was restored.
Discussion

Statins and inflammation

Since current antiarrhythmic drugs offer limited efficacy and may have serious side effects, new pharmacological treatment options for AF are needed. Inflammation seems to be involved in the development of AF, hence treatment with drugs that have anti-inflammatory properties appears to be an appealing treatment strategy. The hypothesis in paper I was that atorvastatin would reduce AF recurrence after CV in a patient with persistent AF. Atorvastatin was chosen as a study drug since it has been proposed to have antiarrhythmic properties in other populations [101, 102] and has been shown to have an anti-inflammatory effect [173, 174]. The safety profile of atorvastatin is also well-documented. However, the main finding in paper I was that atorvastatin was not superior to placebo with regards to maintaining SR after CV of persistent AF.

Our findings were in line with the findings of Negi et al. who demonstrated in the STOP AF trial that despite a significant reduction of inflammatory markers there was no reduction in recurrence of AF after CV in patients randomized to atorvastatin treatment [175]. Similar results were also shown in a study carried out by Demir et al [176]. On the other hand, Oyazadin et al. reported reduction of AF recurrence in a randomized trial that was not placebo-controlled [108]. However, a recent meta-analysis of all the studies concluded that atorvastatin does not affect the recurrence of AF after CV [177]. Pravastatin has been evaluated in a similar population but showed no benefit [178]. Neither does atorvastatin seem to affect recurrence of AF after PVI [179]. Rosuvastatin appeared to reduce AF recurrence after CV in a small randomized trial in which the study subjects also received treatment with amiodarone [180].

In contrast to our findings, atorvastatin may have an effect in other populations. Atorvastatin has been associated with a decreased risk of postoperative AF after coronary surgery in several RCTs and meta-analyses [181-184]. The postoperative population is different since surgery induces an inflammatory response and subjects with coronary artery disease were largely excluded in our study, since these patients had a preexisting indication for statin use. However, the results of the trials concerning postoperative AF and statins are conflicting. In the recently published STICS trial, a randomized placebo controlled study which included 1922 patients scheduled for CABG, the authors could not show any benefit of perioperative rosuvastatin treatment [185]. One might argue that the lack of benefit could be due to the specific drug tested or the ethnicity of the study population (the study was conducted in China) but this is to our date the largest RCT addressing this issue. Hence, at the moment, there is not enough
evidence to support the use of statins as primary or secondary AF prevention in any population.

**HsCRP**

HsCRP is a biomarker that reflects systemic inflammation. In the second paper, which was a prespecified substudy within study I, we found that hsCRP predicted recurrence of AF 1 month and 6 months after CV. HsCRP predicted AF recurrence 30 days after CV only after adjustment for atorvastatin treatment. Our findings are partly consistent with those of Korantzopolous et al., Watanabe et al., and Loricchio et al. who showed that hsCRP levels seemed to have an independent prognostic value in predicting long-term risk of AF recurrence after CV [186-188]. On the other hand, Psychari et al. found that hsCRP level did not predict AF recurrence 30 days after CV [189]. This does not exclude that there may be an association with hsCRP, as indicated in our results, on long-term risk of AF recurrence after successful CV. In our study, there was no difference in hsCRP levels at randomization between patients in SR or those with AF at day 30. This is consistent with the findings of Cosgrave et al. who showed that there was no difference in baseline hsCRP levels between patients in SR and those with AF 8 weeks after CV [190]. Our findings are also in line with a meta-analysis in which Yo et al. concluded that hsCRP assays are moderately accurate in predicting AF recurrence after successful cardioversion [191]. CRP also appears to be a predictor of AF recurrence after cardiac surgery and catheter ablation [192]. Marott et al followed 10,276 subjects from the Copenhagen City Heart Study for 12 to 15 years for incident AF and found that hsCRP levels in the upper versus lower quintiles were associated with a 2.19-fold increased risk of AF[193].

We also found that treatment with atorvastatin reduced hsCRP levels compared to placebo and over time. Although high-dose statins may have systemic anti-inflammatory activity, this may not necessarily translate into reduced AF recurrence. Recently, Gu et al. found that pioglitazone, a peroxisome proliferator-activated receptor-gamma (PPARγ) agonists with anti-inflammatory properties, did not reduce AF recurrence after electrical CV in spite of a reduction of inflammatory markers [194]. Certain AF populations may respond differently to anti-inflammatory treatment. A meta-analysis showed no beneficial effect of corticosteroid use on mortality, cardiac and pulmonary complications but a 40% risk reduction of postoperative AF in cardiac surgery patients [54]. Higher levels of HsCRP was associated with an increased risk of incident AF in a cohort within the JUPITER trial. Randomization to treatment with rosvuastatin significantly reduced that risk [195]. However, AF was not a pre-specified endpoint in this trial.
It has been proposed that AF itself may cause inflammation and that a reduction of hsCRP after restoring SR would support this hypothesis[31]. Rotter et al found that HsCRP decreased significantly at a 3-month follow-up after catheter ablation of longstanding in the patients who were in SR (n=33) [196]. Kallergis et al found a reduction of hsCRP at 1-month follow-up after CV of persistent AF (n=40)[197]. However, in our study, there was no reduction of hsCRP between CV and day 30 amongst the 16 patients who maintained SR at day 30 in the placebo group (median 2.75 mg/L [IQR 1.7-3.8] versus median 2.15 mg/L [IQR 1.2-6.6 mg/L], p=0.92). Different sample sizes may explain the different findings.

Even though HsCRP appears to be predictor of AF recurrence and a marker of low grade systemic inflammation related to AF, elevated systemic hsCRP levels may not necessarily correspond to inflammatory changes in atrial tissue. Furthermore, AF-associated inflammation might be a local process in the atria rather than a systemic phenomenon, and biomarkers of systemic circulation might not detect early-stage atrial inflammation. In the Copenhagen City Heart Study, increased in hsCRP levels owing to genetic polymorphisms did not increase the incidence of AF, suggesting that CRP indicates inflammatory state, but does not have a pathophysiological role[193].

In study II, we found significantly more patients in SR at day 30 in the atorvastatin group (62%) compared to placebo (40%) (OR 2.5, 95% CI 1.1–5.8). This finding has to be interpreted with caution considering the results of study I, but it raises the question; were there differences in baseline characteristics between the populations in study I and study II? However, we found no discrepancies that could explain the different findings. There were also methodological differences between the two studies. In study I, the whole cohort was analyzed by intention to treat analysis, but in study II, only the subjects who were successfully cardioverted were analyzed. However, when carrying out a similar selection in the main population, we found no difference in proportions of patients being in SR at 30 days between atorvastatin or placebo arms.

The U22 protocol

The main finding in the third paper was that catheter ablation of AF resulted in a symptomatic improvement that was detected by the U22 scores. In the group undergoing repeated procedures, the clinical indication for the reablation is clearly reflected in the diminutive improvement in U22 scores after the first ablation. We also found that the patients' retrospective estimate of improvement at follow-up correlated modestly to the improvement expressed by the difference in the individual scores for well-being between the follow-up form and the baseline form. A retrospective estimation of improvement is therefore at best a rough measure for the change in well-being after ablation of AF.
The main reason for developing an arrhythmia and AF specific protocol is that it enables the assessment of domains that are relevant to AF. In our study, the correlation between U22 scores and SF-36 scores was weak to moderate. U22 is directed towards measurement of arrhythmia symptoms and their effect on well-being. SF-36, on the other hand, is a generic measurement of quality of life and mirrors aspects of AF other than U22. Likewise, Berkowitsch et al. noted that the arrhythmia specific Symptom Severity Check List was more specific for measurement of AF symptoms after PVI than SF-36[198].

Cronbach’s alpha indicated an excellent internal consistency for the set of U22 scores at follow-up and for the individual patients' score differences between baseline and follow-up. Also, the consistency of the U22 scores in the baseline measurement was satisfactory. The construct validity of U22 for measurement of symptoms in AF is supported by the relation of the U22 scores to the symptomatic effect of the initial intervention: Improvement in the scores after a clinically inefficient first ablation was significantly smaller than after a singular ablation.

In conclusion, U22 measures the symptomatic effect of pulmonary vein isolation for AF and has several practical advantages. It consists of a limited number of questions. The scales have a high resolution (scored 0–10), while many of the other symptom protocols only use four levels. The U22 scores are well suited for a statistical comparison between groups of arrhythmia patients and easily clinically interpreted in individual patients.

**Sleep apnea and AF**

**Association between AF and sleep apnea**

The prevalence of sleep apnea in AF patients is reportedly high according to several studies. Albuquerque et al. reported a prevalence of sleep apnea in patients with AF of 81.4% (OSA in 52.3%, CSA in 13.9% and 10.6% had a mixed pattern) [199]. Bitter et al. found a sleep apnea in 74% (OSA 42.7% and CSA 31.3%) of patients with persistent AF and Braga et al. reported a prevalence of OSA of 82% in AF patients [200, 201]. We found sleep apnea in 83% of the included patients, although none of them had been diagnosed with sleep apnea previously. OSA occurred in 74% and CSA in 26% of our patients. Thus, our findings are in line with previous studies.

Conversely, OSA also increases the risk of AF and the risk seems to increase in proportion with OSA severity [202, 203]. The prevalence of nocturnal AF in patients with OSA has been estimated to be 3–5% [202]. In the Sleep Heart
Health Study, Mehra et al. demonstrated a fourfold increased risk of AF in patients with sleep apnea (OR, 4.02; 95% CI, 1.03-15.74) [204].

The hazard ratio for AF in patients with versus without OSA has been estimated at 2.2 [203]. OSA seems to contribute to the development of AF in patients with cardiovascular comorbidities. This has been highlighted by data showing that the prevalence of AF was higher in patients with coronary artery disease and OSA versus coronary artery disease without OSA (32% vs. 18%, respectively) [205], in heart failure patients with versus without OSA (22% vs. 5%, respectively) [206].

In the absence of congestive heart failure, Leung et al. observed a high prevalence of AF among patients with idiopathic CSA that was significantly higher than among patients with OSA or no sleep apnea (27%, 1.7%, and 3.3%, respectively, p <0.001) [207].

**Pathophysiological mechanisms**

There are several pathophysiological mechanisms, which may contribute to the development of AF in patients with OSA. OSA causes episodes of substantial negative intrathoracic pressure, hypoxia, hypercapnia and bursts of sympathetic activation. The negative pressure in the chest caused by repetitive forced inspiration against a closed upper airway causes an increases in venous return and causes and increase in left ventricular afterload and right ventricular preload [208]. This may, over time, contribute to the development of diastolic dysfunction, left atrial dilatation and AF [209]. Several studies have associated diastolic dysfunction with OSA [210-212]. The negative intrathoracic pressure also contributes to sympathetic activation through carotid chemoreflex stimulation [213]. In addition, arousal from sleep stimulates cortical centers causing a further burst of sympathetic outflow [214]. Both hypoxia and hypercapnia have direct adverse effects on cardiac electrical stability [215]. Li et al. found that, hypoxia followed by reoxygenation did induce pulmonary vein burst firings in rabbit pulmonary vein preparations [216]. Hypercapnia causes acidosis which is believed to affect the atrial effective refractory period and probably increases the risk of AF [217].

CSA does not, on the other hand, generate a negative intrathoracic pressure but may cause AF through hypoxia, inflammation and autonomic imbalances. However, there is also some evidence that suggests that CSA may be consequence of AF. Fox et al. recently showed that CV of AF reduces CSA[218]. A possible mechanism could be that a lower cardiac output during AF results in increased pulmonary vascular pressures which might trigger hyperventilation and hypercapnia which results in central apneas.
**OSA, cardioversion and catheter ablation**

OSA seems to affect the long-term efficacy of AF therapies. Kanagala et al. showed that the recurrence rate after successful cardioversion was higher amongst patients with OSA than amongst those without [219]. The relapse rate was lower amongst OSA patients treated with CPAP than amongst those without CPAP treatment [219]. Mazza et al. reported that AHI $\geq$ 15 was a strong predictor of AF recurrence after successful cardioversion [220]. Several studies have reported a relationship between OSA and the efficacy of catheter ablation [221-223]. In a meta-analysis, Li et al. concluded that patients with OSA have a 31% greater risk of AF recurrence after catheter ablation than patients without OSA, and this risk is increased by 57% in patients with OSA not undergoing CPAP therapy. Interestingly, CPAP users have a risk of AF recurrence similar to that of patients without OSA [224].

**Cardioversion of AF and sleep apnea**

In paper IV, restoration of SR by CV did not affect the prevalence or the degree of sleep apnea. At baseline, CSA was more common among patients with recurrence of AF at follow-up. Sleep quality was normal at baseline and remained unaffected after the CV. Fox et al. recently reported that sleep apnea was reduced after restoration of SR in 116 patients with AF [218]. This reduction was due to a significant decrease in patients with CSA. We hypothesized that central apneas would be reduced when concomitant AF was converted into SR. However, we had only few patients with central apnea, and we cannot conclude about any effect on central sleep apnea. We investigated fewer patients than Fox et al. Instead we used polysomnography including esophageal pressure monitoring, which is more specific than polygraphy, the method used by Fox et al.. The differences in methodology and sample size can explain the different results.

Other studies have addressed the question of whether restoring SR reduces sleep apnea or not. Naruse et al. reported a decrease in the obstructive apnea-hypopnea index among 25 patients after radiofrequency catheter ablation of AF [225]. They, however, only investigated patients with sleep apnea at baseline and not the whole cohort, which introduces a risk for regression towards the mean because of selection bias. This is illustrated by the fact that in our material there was one patient without sleep apnea during the first polysomnography who had sleep apnea during the second polysomnography. Lissel et al. investigated only six patients with AF and observed no effect on the apnea-hypopnea index after CV [226]. Hoyer et al. reported that 74% of 23 patients with AF had sleep-disordered breathing before pulmonary vein isolation, with no change after the treatment of AF [227]. They used simplified recordings and were unable to differentiate central from obstructive apneas. A notable strength of our study was the use of
polysomnography including esophageal pressure monitoring and EEG, the gold standard to distinguish central from obstructive apneas and hypopneas.

In summary, there are indications that OSA may contribute to the development of AF and that treatment of OSA seems to improve the results of AF treatment. We found that restoring SR did not affect OSA, thus, our findings support the hypothesis that OSA contributes to the development of AF rather than the opposite. Sleep apnea is a common phenomenon in subjects with persistent AF. The results of this study underscore the importance of screening for sleep apnea in patients with AF.
Limitations

Paper I and II
A limitation of paper I was that it might have been underpowered for the detection of an effect of atorvastatin. Although there was a trend to a lower relapse rate in patients randomized to atorvastatin treatment, the study ended-up with a statistically non-significant result. Asymptomatic AF, which is known to be common, was not detected if it did not coincide with follow-up after CV. There was no data on other inflammatory indexes. The findings are relevant only to patients with persistent AF without an obvious need for statin treatment.

Paper III
In paper III, we used the incidence of reablation at review time as a clinically relevant hard end-point. Relapses occur even after successful ablations. It is therefore not entirely correct to interpret reablation as a sign of an unsuccessful first time procedure. Added co-morbidity and progress of the arrhythmia might shift a decision towards conservative treatment, in spite of significant symptomatology. Some patients may have developed an asymptomatic permanent AF after the initial ablation. They would not be reablatted, and their first-time ablation will thus be considered as successful. Formally this may be correct, since ablation of AF is performed on symptomatic indication. Most cardiologists would nevertheless hesitate to consider such an ablation as successful. These factors may decrease the specificity of reablation as a marker for continued symptoms but should, however, not affect the conclusion that the symptom quantification by U22 is related to the independent decision regarding a reablation.

Our study population was a typical AF ablation population which mainly consisted of Swedish-speaking male Caucasians in their sixties. The generalizability to other populations with a different mean age, language, gender profile or ethnicity is uncertain.

Paper IV
A significant limitation in paper IV was the low number of patients included and the even lower number of patients with central sleep apnea. This means that we could not draw any conclusions about an effect of restoring SR on central apneas.
Conclusions

- Atorvastatin was not statistically superior to placebo with regards to maintaining SR 30 days after CV of AF. The result does not support the use of atorvastatin as an alternative to antiarrhythmic drug treatment.

- HsCRP was associated with AF recurrence 1 month and 6 months after successful CV although the association at one month was only significant after adjustment for treatment with atorvastatin in this population.

- The U22 protocol measured the symptomatic effect of left atrial ablation for AF. It seems to have adequate internal consistency and construct validity.

- Obstructive and central sleep apneas were common in patients with persistent AF. Obstructive apneas or sleep were not affected by restoration of SR. It was not possible to draw any conclusions about the effect on central apneas due to the low number of patients included in the study.
**Future perspectives**

The number of patients with AF will increase in the coming years. As a consequence, there will be a growing demand for effective care, and new treatment strategies are warranted. PVI has become an established treatment but we need to know more about how to predict who benefits from catheter ablation and who does not in order to be able to offer AF patients optimal treatment. More pharmacological options and better ablation strategies are certainly needed. However, whereas many studies have focused on the treatment of AF, relatively few have been directed at prevention of AF. We have developed preventive strategies for common conditions like coronary heart disease and stroke, but the optimal preventive strategies for AF remain unproven. Thus, there must be a greater focus on prevention. We need to know more about the impact of early treatment of known AF risk factors. Systematic longitudinal studies are needed to evaluate the value of aggressively treating AF risk factors including obesity, diabetes, hypertension, and sleep apnea, for the prevention of incident AF. Early identification and treatment of these conditions may limit atrial remodelling and the tendency to develop AF. Furthermore, regarding questionnaires, we have to develop standardized and cross-validated AF-specific questionnaires to be able to evaluate and compare the symptomatic effect of different treatment strategies in different AF populations.
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clinicaltrials.gov.


Appendix

U22 AryQ, pre

<table>
<thead>
<tr>
<th>Nr</th>
<th>Name</th>
<th>Date of today</th>
</tr>
</thead>
</table>

You have **problems with the heart rhythm**. We would kindly ask you to answer this short questionnaire regarding these problems. Select **only one answer** for each question. Your answers will **anonymously** be included in a statistical evaluation.

1. **On the whole, how have you felt during the last month?**
   Select a position on the scale below by putting a cross in one of the circles.
   - Miserably
   - Very well

(2 - not applicable)

3. **Do you take any prescribed medicine for the problems with heart rhythm?**
   Select a choice:
   - No
   - Yes

4. **How effective is the medication against these problems?**
   Not at all
   - Very much

5. **How much are you troubled by side-effects from the medication?**
   Not at all
   - Very much

(2 - not applicable)

6. **How often do you have problems with the heart rhythm?**
   (in spite of any medication)
   Select a choice:
   - Never
   - On rare occasions
   - A few times a month
   - A few times a week
   - Daily
   - All the time

7. **Do the spells have a sudden start?**
   Select a choice:
   - No
   - Yes

8. **How long is usually a spell?**
   Select a choice:
   - Seconds
   - Minutes, less than a quarter of an hour
   - A quarter of an hour to one hour
   - One to four hours
   - Longer
   - All the time

...please turn...

Figure 13. Baseline U22 questionnaire, page 1. General well-being, the effect and side effects of the current medication is probed by questions with 11 choices of answers, converted to 0–10 scale. The incidence and duration of episodes are estimated by q08 and q10 with six nonlinear answer choices.
Figure 14. Page 2 of the baseline and follow-up U22 questionnaires. The questions are the same. Symptom intensity is probed by questions with 11 choices of answers, converted to 0–10 scale.
You have been treated for problems with the heart rhythm. We ask you to please answer this short questionnaire regarding your heart rhythm problems. Select only one answer for each question. Your answers will be anonymous, and will be used in a statistical evaluation.

1 On the whole, how have you felt over the past month?
Select your answer by placing an X in the circle that best reflects how you feel.

2 Compared to the time before the treatment do you now feel:

3 Do you take any prescribed medication(s) for your heart rhythm problems?

4 How effective is the medication(s) in treating your heart rhythm problems?

5 How much are you bothered by side-effects of the medication?

6 Have you experienced any problems with the heart rhythm after the treatment?
- please disregard the first three months after the treatment -

Please answer questions 7-22 only if you still have any problems with heart rhythm

7 How bothersome are the spells in comparison with those before the treatment?

8 How often do you experience problems with heart rhythm?

9 Do the spells start suddenly?

10 How long does a spell usually last?

...please go to the next page...