Atrial Fibrillation
To Tuva Eleonora Elisabeth and Meja Hanna Maria
HENRIK ALMROTH

Atrial Fibrillation
Inflammatory and pharmacological studies
Abstract


Background: Atrial fibrillation (AF) is the most common rhythm disorder. Many patients are symptomatic. Anti-arrhythmic pharmacological strategies have poor efficacy and side effects are common. Little information about the safety of anti-arrhythmic treatment, especially flecainide, is available. Thus, new pharmacological drugs with a well-documented safety profile are warranted.

Aims: To evaluate the extent and possible source of inflammation in AF. To evaluate the effect of atorvastatin on sinus rhythm (SR) maintenance following cardioversion (CV). To evaluate the safety and mortality of flecainide in patients with AF in a local cohort and nationwide in Sweden.

Materials and methods: I - Inflammatory markers in the vessels and different locations in the heart of patients with AF were compared to controls. II - A total of 234 patients with persistent AF were randomised to atorvastatin or placebo prior to CV. III - A local cohort of AF patients treated with flecainide (n=112) were studied, focusing on sudden cardiac death and pro-arrhythmia. IV - We evaluated whether current flecainide practice in Sweden is associated with increased mortality compared to a reference AF population receiving beta-blockers only.

Results: No association was found between local inflammation in the heart and AF except for elevated levels of IL-8 in persistent AF. Atorvastatin was not superior to placebo with regard to maintaining SR 30 days after CV. We found a relatively high incidence of cardiovascular death, including sudden cardiac death and pro-arrhythmia in the cohort of flecainide-treated AF patients in Örebro. However, in the nation-wide registry study, flecainide was not associated with increased mortality in patients with AF compared to patients on beta-blockers only.

Conclusions: No association was observed between local inflammation in the heart and AF. Atorvastatin does not have the potential to be a novel treatment strategy for maintaining sinus rhythm after CV. On a population basis, flecainide is not associated with increased mortality. However, the risk/benefit ratio for the individual may be in question and contraindications for the drug should be respected.

Keywords: atrial fibrillation, inflammation, randomised, sudden cardiac death, pro-arrhythmia, anti-arrhythmic, statin, atorvastatin.

Henrik Almroth, School of Health and Medical Sciences
Örebro University, SE-701 82 Örebro, Sweden, henrik.almroth@orebroll.se
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## Abbreviations

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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACM</td>
<td>all-cause mortality</td>
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<td>AF</td>
<td>atrial fibrillation</td>
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<td>CAST</td>
<td>Cardiac Arrhythmia Suppression Trial</td>
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<td>CEM</td>
<td>coarsened exact matching</td>
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<td>CV</td>
<td>cardioversion</td>
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<td>CRP</td>
<td>C-reactive protein</td>
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<tr>
<td>EAD</td>
<td>early afterdepolarisation</td>
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<td>ECG</td>
<td>electrocardiography</td>
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<td>DAD</td>
<td>delayed afterdepolarisations</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>ITT</td>
<td>Intention to treat</td>
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<tr>
<td>PV</td>
<td>pulmonary veins</td>
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<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>Px</td>
<td>paroxysmal</td>
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<tr>
<td>PxAF</td>
<td>paroxysmal atrial fibrillation</td>
</tr>
<tr>
<td>QoL</td>
<td>quality of life</td>
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<tr>
<td>RF</td>
<td>radio frequency</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SMR</td>
<td>standardised mortality ratio</td>
</tr>
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<td>SR</td>
<td>sinus rhythm</td>
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## Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Electrical remodelling</td>
<td>Changes of electrical properties in the atrial tissue (refractoriness and conduction velocities) that increase the risk of new and sustaining AF episodes over time.</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>Self-terminating</td>
</tr>
<tr>
<td>Re-entry</td>
<td>The most common mechanism of arrhythmia. Refers to the possibility of an electrical impulse to be able to propagate through more than one electrical route with different conduction and refractory properties. Given certain conditions, the electrical impulse can travel down one route, and up the other in a circular fashion and become self-sustaining.</td>
</tr>
<tr>
<td>Refractory period</td>
<td>The time it takes for myocytes to be receptive and respond to a new electrical stimulus.</td>
</tr>
<tr>
<td>Remodelling</td>
<td>Structural, anatomical and electrical changes of the atrial tissue as a result from AF, and of comorbidity. Remodelling increase the risk of new AF episodes and maintenance of AF over time.</td>
</tr>
<tr>
<td>Substrate</td>
<td>Atrial tissue in which AF can occur.</td>
</tr>
<tr>
<td>Trigger</td>
<td>A focus with ability to fire rapidly and induce AF. Triggers are often found around the pulmonary veins.</td>
</tr>
</tbody>
</table>
List of original papers

Source of inflammatory markers in patients with atrial fibrillation. 
Europace 2008; 10:848-853

Atorvastatin and persistent atrial fibrillation following cardioversion: A randomized placebo-controlled multicentre study. 
European Heart Journal 2009; 30:827-833

The safety of flecainide treatment of atrial fibrillation: long-term incidence of sudden cardiac death and proarrhythmic events. 
J Intern Med. 2011 Sep; 270(3): 281-90

IV. Almroth H, Friberg L, Bodin L, Rosenqvist M, Englund A. 
Safety of Flecainide for atrial Fibrillation – The Swedish Atrial Fibrillation Cohort Study. 
In manuscript

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Normal rhythm and impulse formation

In the normal heart, specialised cardiac cells in the conduction system (Figure 1) have the ability to create electrical impulses through variable ion channel activity. The sinus node (10-20 mm long, 2-3 mm wide) is located in the high right atrium at the junction of the superior vena cava. This region normally depolarises with the highest frequency and is the denominator of normal sinus rhythm influenced by the autonomic nervous system and circulating catecholamines. From the sinus node, the electrical impulses are discharged synchronously and propagate through three internodal pathways (the anterior “Bachmann” and middle and posterior bundle) towards the atrioventricular node (anterior to the coronary sinus ostium, above the septal leaflet of the tricuspid valve). In this region, propagation slows down to allow atrial contraction and optimise ventricular filling before the impulse is conducted to the left (left anterosuperior and posterior fascicle) and right ventricles (right bundle branch). The fascicles finally connect to Purkinje fibres, which transmit the impulses to the ventricles almost simultaneously, resulting in mechanical contraction against the outflow tracts.

Figure 1. The cardiac conduction system: 1, Sinus node; 2, The internodal pathways; 3, Atrioventricular node; 4, Bundle of His; 5, Left and right bundle branch; 6, Purkinje fibres. Reprinted with permission from Ulrika Westerberg.
Mechanism of cardiac arrhythmia

The general mechanisms underlying arrhythmogenesis can be divided into automatic or triggered impulse formation and re-entry. Automaticity can be described as the ability to initiate an electrical impulse spontaneously, without prior stimulation. In contrast, triggered activity requires a “trigger” to initiate a response. Thus, triggered activity is a consequence of a preceding electrical impulse and can be described as early or late depending on when they arise during cardiac depolarisation (Figure 2). If any of these depolarisations reach the threshold potential, they may trigger another depolarisation and become self-sustained.

Re-entry is associated with impulse propagation rather than formation, and it occurs when an impulse is able to propagate through different routes with different electrical properties. Propagation normally follows a distinct pattern, leaving the myocytes refractory to further stimulus, and cannot be excited again until they electrically recover. However, if a trigger occurs at the right time and electrically results in a depolarisation, the normal route may still be refractory. This context can allow the electrical wave to propagate through an alternative route and possibly re-excite the normal route backwards. Under the right circumstances, the areas with different electrical properties (i.e., conduction velocity and refractory period) may re-excite each other and cause sustained re-entry tachycardia.

Re-entry can be facilitated through anatomical borders (Figure 3A) as in classical isthmus-dependent atrial flutter or through different electrophys-
iological properties (e.g., heterogeneity) in neighbouring myocardial tissue. The latter is called functional re-entry, which seems to be crucial in atrial fibrillation (AF) conceptualised by “leading circle” and “spiral-wave re-entry” \(^1\). Both models depend on a proper balance between the refractory period and conduction velocities. Factors that promote this phenomenon are short refractoriness and slow conduction. In the leading circle theory (Figure 3B), re-entry may terminate if the conduction is accelerated, and the wavefront meets refractory myocardial tissue, or if refractoriness is prolonged by changes in the action potential duration (i.e. prolongation). In the spiral wave model \(^2, 3\), the wave front is spread from a rotor that rapidly rotates around a core. High excitability and short refractoriness promote stability and maintenance in this model (Figure 3C).

\[ A \quad B \quad C \]

**Figure 3**: Conceptual models for anatomical re-entry and re-entry in AF. A) In anatomical re-entry, the circuit is determined by fixed anatomical structures. B) The “Leading circle” depends on a proper balance between conduction velocity and refractory period. The circuit time must exceed the refractory period. C) Spiral-wave activity depends on tissue excitability and refractoriness, and may be suppressed by increasing the action potential duration.
Introduction to Atrial Fibrillation

Epidemiology
Atrial fibrillation (AF) challenges both patients and the clinicians trying to cope with the clinical reality of their condition. Despite being the most common rhythm disturbance in Sweden, as well as worldwide, many secrets about AF remain unsolved.

Prevalence is closely correlated with age, and approximately 25% of men and women who live past 40 will experience AF during their lifetime. AF is a rare condition before the age of 60, when it rapidly becomes more prevalent, occurring in approximately 10% of men and women aged 75 years or more.

With a prevalence of 1-2%, at least 5-10 million people are affected in Europe, a number that is estimated to increase rapidly in the coming decades. The corresponding prevalence in Sweden is estimated to about 180,000. According to data from the inpatient Hospital Discharge Register, the incidence corresponds to 40,000 new patients per year (2005-2009, unpublished data). This number has increased over the years, probably as a consequence of the aging population, general knowledge, and better detection tools.

AF initiation and maintenance
The aetiology of AF is known to be complex and is not fully understood, even though much knowledge has been gained over the last 20 years. The principal theories “explaining” AF could be described as two main mechanisms, the “multiple wavelet hypothesis” and triggering through focal ectopic activity. In 1962, Moe and colleagues were the first to hypothesise the mechanism behind AF. The initiation of AF was described to be a consequence of external stimuli at a pace equal to the minimal refractory period of myocytes. Thus, myocytes with refractory properties above the given stimuli did not have the time to recover and respond. As a result, fragmentation and formation of multiple wavelets arises. Moe showed that this activity could be more persistent and self-sustaining when larger areas of tissue were affected and more wavelets occurred.
# Electrical remodelling

The term electrical remodelling refers to Wijffels findings from 1995 in a goat model; AF episodes of short duration (minutes) promoted the perpetuation of AF \(^{10}\). This phenomenon results from a decrease in atrial refractoriness and changed conduction velocities\(^{10, 11}\). The main problem is that these changes are spread non-uniformly throughout the atrial tissue, creating regions with different electrophysiological properties, a context called heterogeneity. Importantly, the periods of AF were observed to become longer and longer as they continued to induce AF. Finally, after 2 weeks of artificial stimulation, the AF became persistent, "AF begets AF"\(^{10}\).

Daoud and co-workers validated the hypothesis about electrical remodelling in 1996. AF was induced by pacemaker stimulations in patients with prior supraventricular tachycardia, and AF rapidly (within minutes) shortened the effective refractory period in the right atrium and, if re-induced, the AF periods lasted longer \(^{12}\).

Ectopic firing rarely occurs in normal atrial tissue, and the electrical properties of atrial tissue are not suitable for AF. However, atrial electrical remodelling may create atrial tissue with altered ion-channel properties or induce fibrosis.

On a cellular level, remodelling may change Ca\(^{2+}\) handling and result in triggered activity through early or delayed afterdepolarisation (EAD or DAD). When summarised, this provides explanatory models for why paroxysmal atrial fibrillation (PxAF) tend to become more sustaining \(^{10}\), why a recurrent AF episode most often occurs in proximity to cardioversion because the process of reverse electrical remodelling can take up to a month,\(^ {13, 14}\) and why therapeutic resistance and a permanent condition occur \(^{15}\).

In 1998 Haissaguerre and colleagues took the step from goat to man. They elegantly presented evidence that the muscular sleeve of the pulmonary veins could be a source for paroxysmal atrial beats that can initiate PxAF \(^{16}\). Focal activity seems to be observed to arise most frequently in the pulmonary veins. Other atrial regions were evidently also sources for focal activity (e.g., superior vena cava and coronary sinus), which was perhaps promoted by special electrical heterogeneity in these regions. That revelation led to the development of ablation strategies for the treatment of AF, and isolation of the trigger was later shown to eliminate AF \(^{17}\).

# Structural remodelling

Alterations in atrial function and architecture have been associated with AF and are often found in patients with hypertension, cardiac heart failure and cardiovascular disease. Macroscopically, these three comorbidities come with left atrial enlargement, a clinically important variable for pre-
dicting the outcome after cardioversion\textsuperscript{18, 19}, and the success rate of ablation procedures\textsuperscript{20, 21}. Microscopically, the changes observed in animal studies are liable to be due to alterations in the interstitial tissue, as well as the cardiomyocytes \textsuperscript{22, 23}. The development of atrial fibrosis that causes electrophysiological heterogeneity as a cause or consequence of AF has been debated, especially as aging is associated with a risk of AF (age-related structural changes). In a recent post-mortem study, fibrosis and fatty infiltration were two to three times as common in patients with a history of AF compared to patients without a history of AF. In addition, no correlation was found between fibrosis and age, which might indicate causation between AF and the development of fibrosis \textsuperscript{24}. Figure 4 illustrates key mechanisms in AF.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Key mechanisms in atrial fibrillation (AF). Atrial remodelling creates a substrate (atrial tissue) with changed electrical properties that may be suitable for initiation and maintenance of AF. Remodelling may promote ectopic activity due to changes in cellular Ca\textsuperscript{2+} handling, i.e. ectopic (triggered) activity by EADs or DADs. Ectopic activity can alone result in AF, or initiate re-entrant AF in vulnerable atrial tissue. EADs, early afterdepolarisations; DADs, delayed afterdepolarisations.}
\end{figure}

**Autonomic nervous system**

The autonomic nervous system is also indicated to be involved in initiation, as well as the sustained condition \textsuperscript{25-27}. A factor that may lead to suspecting
parasympathetic involvement is vagal innervation, which may shorten the
duration of the atrial action potential and the refractory period because
they occur hand-in-hand \(^{28,29}\). Balance is achieved by sympathetic activa-
tion, which also make repolarisation inhomogeneous. Parasympathetic and
sympathetic distributions coalesce at locations as ganglionic plexi and these
may be key regions for initiating and perhaps sustaining AF \(^{30,31}\).

**Inflammation and AF**
The correlation between AF and inflammation was initially reported in
atrial biopsies from patients with PxAF \(^{32}\) and from the expression of inter-
leukin-8 (IL-8) mRNA in atrial specimens from patients with permanent
AF \(^{33}\). In case-control studies, elevated levels of C-reactive protein (CRP)
may be able to predict the outcome of cardioversion \(^{34}\) and the relapse rate
following cardioversion \(^{35}\). A correlation between AF burden (longer peri-
dods) and higher CRP levels has also been observed \(^{36}\). Moreover, a favour-
able outcome with regards to maintaining sinus rhythm has been reported
for methyl prednisolone in persistent AF \(^{37}\). Taken together, these findings
may suggest an association between AF and inflammation, cause or conse-
quence, however unclear. To further evaluate the possibility of inflam-
mation participating in the casual pathway of AF, tools for analysing inflam-
mation levels have been proposed.

CRP was first described around 1930. It is an acute-phase reactant that
acts as a non-specific systemic marker and reflects inflammation, acute
injury, or infection. CRP is produced primarily by hepatocytes \(^{38}\) in re-
sponse to IL-6 (modified by IL-1 and TNF-α) and has a half-life of roughly
19 hours.

Another marker that has been suggested as a suitable tool of inflam-
mation is IL-6. The cytokine is produced by endothelial cells, monocytes,
macrophages, and T-lymphocytes and plays an active role in inflammation,
neoplasia, and aging. IL-6 has the ability to induce an acute phase response
as a consequence of infection or trauma and promotes CRP synthesis and
fever. The half-life is approximately 2 hours. In clinical studies, IL-6 has
been used to indicate inflammation \(^{39,40}\), in addition to predicting cardio-
vascular disease \(^{41}\).

IL-8 is also a cytokine produced by macrophages, epithelial cells, and
endothelial cells. In endothelial cells, IL-8 is stored in Weibel-Palade bodies
and attracts neutrophil granulocytes when released. The secretion may
increase as a result of oxidative stress, and it has been proposed as a key
parameter in localised inflammation \(^{42}\). The half-life of IL-8 is likely less
than 1 hour \(^{43}\).
Clinical presentation and natural cause

In most cases AF is associated with symptoms, including palpitations, dyspnoea, and fatigue, but it may also occur without any subjective symptoms at all. At least one-third of all AF episodes seem to be asymptomatic,\textsuperscript{44,45} and PxAF episodes may be much more prevalent than estimated. Interestingly, patients with symptomatic PxAF have many asymptomatic episodes \textsuperscript{46-49}. This paradigm is also highlighted by the difficulty for patients to decide on sinus rhythm or AF following cardioversion \textsuperscript{50}.

In most patients AF is a progressive disease in which episodes initially come and go and slowly progress toward a permanent condition. In clinical praxis, AF is characterised by duration and usually progresses from paroxysmal (self-terminating, > 2 episodes) to persistent (non-self-terminating), and finally a permanent condition in the absence of rhythm-maintaining strategies, i.e. anti-arrhythmic therapy or ablation procedures \textsuperscript{51,52} (Figure 5). The rate of progression varies from paroxysmal to persistent or permanent AF, with 8% to 25% being reported during 1-5 years of follow-up \textsuperscript{53-55}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{afi01.png}
\caption{Types and natural time cause of AF}
\end{figure}
Definition and detection

AF is defined as a cardiac arrhythmia in which the ventricular contractions visualised through RR intervals on 12-lead electrocardiography (ECG) vary without a repetitive pattern. In general, the atrial activity is ≤200 ms (≥300 bpm) or faster 51.

The different patterns of atrial heterogeneity in regards to electrophysiological properties may be reflected in the ECG-morphology seen in AF. Single potentials can be indicative of more uniform conduction (A), whereas fragmented potentials are more indicative of slow conduction (B)56, 57.

Consequences of AF

Subjective symptoms could ideally be explained by the hemodynamic changes that occur during AF. In some patients, a rapid and irregular rhythm may have a cardiomyopathic effect that weakens the left ventricular function via impaired diastolic filling and loss of atrial contribution to ventricular filling. Observational findings have also suggested that irregular rhythm may result in worsened ejection fraction 58, 59. This is supported by an improvement in the left ventricular ejection fraction and function class after AV nodal ablation followed by regular ventricular pacing 60. The relative importance of atrial systole has typically been described in conditions in which the atrial contribution may be of greater importance. Hypertrophic cardiomyopathy 61 or mitral stenosis are such conditions in which AF can rapidly lead to hemodynamic deterioration 62. In addition, AF may also increase neurohumoral activation, which in turn may influence systemic hemodynamics63, 64. After the restoration of sinus rhythm, many patients experience better physical capability,65-67 and a significant increase in left ventricular function is often evident 68-70. However, subjective symptoms differ widely between individuals and is not always correlated with objective findings from functional tests, some of which are more capable of coping with the condition than others. The subjective symptoms often af-
fect quality of life. Patients with AF experiences are described as having significantly lower quality of life compared to healthy individuals and patients with ischemic heart disease 71.

The association of AF with comorbidities such as stroke and heart failure is well known, but little evidence is available to support AF as the reason for the doubled mortality observed in this population. Even though younger AF populations without significant heart disease have had favourable outcomes 72, 73, most studies have associated AF with a significantly increased risk of death, which is often more pronounced in women and primarily explained by excess mortality in stroke and heart failure 73-77. Non-randomised studies have failed to prove that AF itself explains the excess mortality, instead suggesting that it is a marker or confounding factor with an impact on long-term survival.
Clinical management

The management of AF has traditionally been based on two strategies, rhythm or rate control that also aims at improving subjective symptoms if present. In addition, the importance of preventing systemic embolisation has grown, regardless of AF type.

Rhythm control and rate control

The key issue in rhythm control management is the maintenance of sinus rhythm. Traditionally, this problem has been addressed with anti-arrhythmic medication, and this is still the primary rhythm-maintaining strategy. Alternative methods, such as ablation, are mainly restricted by a lack of resources.

The main problems with anti-arrhythmic medication are the low capability of these drugs to maintain sinus rhythm over time as patients continue to have AF episodes, which are often asymptomatic, and the risk of potentially dangerous side effects, such as pro-arrhythmia. The side effects may have a negative impact on quality of life and frequently lead to discontinuation.

In summary, the benefit vs. risk is sometimes in question while a patient is undergoing anti-arrhythmic treatment. “Benefit vs. risk” certainly becomes important when “choosing” the right path for each patient. This issue has become more pertinent since anti-arrhythmic drugs have failed to result in favourable mortality outcomes vs. rate control. At least seven clinical trials have tried to evaluate rhythm against rate control, all failing to prove that the rhythm strategy is superior in clinical practice regarding all-cause mortality and quality of life. These findings have been intellectually frustrating for clinicians and a drawback for the medical industry providing anti-arrhythmic drugs, but evident nonetheless.

In comparison, a rate control strategy strictly aims to control ventricular rhythm, allowing it to adapt to normal physical activities and relieving symptoms. In this concept, restoring sinus rhythm is not a goal, and it usually involves drugs that slow conduction through the AV-node (beta-blockers, non-dihydropyridine calcium antagonists), or sometimes digoxin.

The tendency of AF to recur without anti-arrhythmic therapy is high, approximately 50% relapse into AF one month after cardioversion. After one year, the relapse rate is about 70%. The relapse rate for anti-arrhythmic in paroxysmal or persistent AF is 30-60% with intermittent monitoring. These numbers may be underestimated given the nature of AF and the lack of valid tools for detection. Israel and co-workers addressed this issue using a pacemaker for continuous monitoring possible. They reported asymptomatic episodes in almost 90% of the patients during 18 months of follow-up; in 17% of these patients, the episodes exceeded...
>48 h duration. In addition, 40% of the patients reported subjective symptoms in the absence of AF.

Vaughan Williams categorised AA drugs in the 1980s, and later in the 1990s, based on their mechanism of action, i.e., which ion channels they block (Figure 6).

![Figure 6](image)

**Figure 6.** A) Presents the five phases (0 to 4) of the action potential in a ventricular myocyte and the main ionic currents involved. B) Presents where anti-arrhythmic drugs interfere with the action potential according to the Vaughan Williams classification.

This classification was developed at a time when few anti-arrhythmic drugs were available and knowledge of their action mechanisms was limited. Today we know that most of the classical anti-arrhythmic drugs are not entirely devoted to one strict class, but may convey other class effects as well, making this categorisation somewhat out of date. The anti-arrhythmic drugs available today (Table 1) are almost the same as 20 years ago because of difficulties developing efficient and safe alternatives, in addition to much harder regulatory demands preceding new drug applications and indications for use.
Table 1. Available anti-arrhythmic drugs in Sweden, by Vaughan-Williams classification.

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic substance</th>
<th>Trade name (Sweden)</th>
<th>Approval (Sweden)</th>
<th>General action</th>
</tr>
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<tbody>
<tr>
<td>I A</td>
<td>disopyramide</td>
<td>Durbis®</td>
<td>1978</td>
<td>Na⁺ channel blockade</td>
</tr>
<tr>
<td>I B</td>
<td>lidocaine</td>
<td>Xylocard®</td>
<td>2006</td>
<td>Na⁺ channel blockade</td>
</tr>
<tr>
<td></td>
<td>vernakalant</td>
<td>Brinaress®</td>
<td>2010</td>
<td>Na⁺ channel blockade</td>
</tr>
<tr>
<td>I C</td>
<td>flecainide</td>
<td>Tambocor®</td>
<td>1986</td>
<td>Na⁺ channel blockade</td>
</tr>
<tr>
<td></td>
<td>propafenone</td>
<td>Rytmonorm®</td>
<td>1991</td>
<td>Na⁺ channel blockade</td>
</tr>
<tr>
<td>II</td>
<td>beta-blockers</td>
<td></td>
<td></td>
<td>Sympathicus blocker</td>
</tr>
<tr>
<td>III</td>
<td>amiodarone</td>
<td>Cordarone®</td>
<td>1987</td>
<td>K⁺ channel blockade</td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td>Sotalol®</td>
<td>1993</td>
<td>K⁺ channel blockade</td>
</tr>
<tr>
<td></td>
<td>ibutilide</td>
<td>Corvert®</td>
<td>1996</td>
<td>K⁺ channel blockade</td>
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<tr>
<td></td>
<td>dronedarone</td>
<td>Multaq®</td>
<td>2009</td>
<td>K⁺ channel blockade</td>
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<tr>
<td>IV</td>
<td>diltiazem</td>
<td>Cardizem®</td>
<td>1985</td>
<td>L-type Ca²⁺ channel blockade</td>
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<tr>
<td></td>
<td>verapamil</td>
<td>Isoptin®</td>
<td>1971</td>
<td>L-type Ca²⁺ channel blockade</td>
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</tbody>
</table>

One of the most frequently used anti-arrhythmic drugs for maintaining sinus rhythm and controlling subjective symptoms is flecainide (Tambocor®). Flecainide has been registered in Europe since 1982, initially with the indication to suppress premature ventricular contractions (PVCs). In June 1987 the Cardiac Arrhythmia Suppression Trial (CAST) was initiated. The trial was designed to evaluate whether suppression of PVCs by anti-arrhythmic therapy (flecainide, encainide, or moricizine) reduces arrhythmic death in patients with prior myocardial infarction compared to placebo. The study was terminated early in 1989 when an interim analysis found a 2.5-fold increased risk of all cause mortality in patients treated with flecainide/encainide (mainly death by arrhythmia or cardiac arrest)\textsuperscript{91, 92}. The main indication of flecainide since CAST is “patients with symptomatic AF in the absence of structural heart disease” (cardiac heart failure, ischemic heart disease, valvular disease) according to the national and international guidelines \textsuperscript{51, 52}. However, no safety studies with the power to detect mortality differences have been published since CAST, especially not in the population that uses it most frequently, the AF population.

The development of new anti-arrhythmic drugs has demonstrated serious problems with adverse events, especially when targeting ion channels and the “electrical approach”. The result has been that remarkably few new drugs of this type have reached the market in the last 20 years: vernakalant in the setting of pharmacological cardioversion\textsuperscript{93} (AF duration < 7
days) and a derivate of amiodarone that recently experienced a drawback when given to a less healthy AF population, resulting in increased mortality and stroke\textsuperscript{84, 95}. Both of the drugs are now suitable for a small proportion of patients.

**Importance of anticoagulation**

Stroke prevention via oral K vitamin antagonists has come to be the one essential factor in mortality outcome in AF patients\textsuperscript{96, 97}. In a meta-analysis by Hart et al, warfarin and aspirin reduced the stroke incidence by 62\% and 22\%, respectively. To address the issue of who to treat, Gage proposed the CHADS\textsubscript{2} score as a tool for estimating yearly stroke incidence in AF patients\textsuperscript{98}. This scoring system used age > 75 years and comorbidities (e.g., cardiac heart failure, hypertension, diabetes, stroke or transient ischemic attack), resulting in a widely adopted tool in which annual adjusted stroke rates between 1.9\% and 18.2\% could be estimated using a straightforward scheme (Table 2). This scheme was recently refined by including vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque), sex category (female), and by dividing age into two strata, (age 65-74 years, and age ≥75 years) in the CHA\textsubscript{2}DS\textsubscript{2}-VASc score\textsuperscript{99}.

*Table 2. Annual stroke rate / 100 patient years adapted from Gage and colleagues\textsuperscript{88}*

<table>
<thead>
<tr>
<th>CHADS\textsubscript{2}-score</th>
<th>Patients (n=1733)</th>
<th>Adjusted stroke rate (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>1.9 (1.2-3.0)</td>
</tr>
<tr>
<td>1</td>
<td>463</td>
<td>2.8 (2.0-3.8)</td>
</tr>
<tr>
<td>2</td>
<td>523</td>
<td>4.0 (3.1-5.1)</td>
</tr>
<tr>
<td>3</td>
<td>337</td>
<td>5.9 (4.6-7.3)</td>
</tr>
<tr>
<td>4</td>
<td>220</td>
<td>8.5 (6.3-11.1)</td>
</tr>
<tr>
<td>5</td>
<td>65</td>
<td>12.5 (8.2-17.5)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>18.2 (10.5-27.4)</td>
</tr>
</tbody>
</table>

The importance of anticoagulation was addressed when it became evident that embolic events occurred regardless of rhythm or rate strategy in the AFFIRM and RACE studies\textsuperscript{83, 84}. However, a major proportion of the embolic events (AFFIRM 113/157 ischemic strokes, RACE 29/35 embolic events) followed warfarin discontinuation or a subtherapeutic International Normalised Ratio (INR < 2). This finding highlighted that rhythm strategy does not automatically rule out the need for oral anticoagulation and that
indications should be governed by factors other than subjective freedom of AF episodes and rhythm strategy using anti-arrhythmic.

The impact of asymptomatic and short AF episodes is debated but can be exemplified by Bottos findings from 2009. In this study, asymptomatic AF episodes of >5 min were associated with a six-fold risk of thromboembolic events compared to patients with similar CHADS2 scores and no AF. A mechanism that may be involved is the impaired atrial contractile state called “atrial stunning”, which is associated with AF and impacts blood flow. Even AF with duration as short as one hour may result in atrial stunning, often most intensely in the left atrial appendage. Consequently, flow velocity may decrease, leading to stasis that can be visualised by spontaneous contrast (aggregation of erythrocytes at low shear stress).

Cardioversion seems to be associated with an increased risk of thromboembolic events, partly due to dislodgment of a pre-existing embolus, and partly due to de novo formation of thrombi as a consequence of impaired left atrial function. Moreover, the duration of mechanical stunning following cardioversion seems to be related to the duration of AF prior to the restoration of sinus rhythm. In most cases atrial contractility returns gradually, and it is usually normalised within a month. The gradual recovery may explain why most embolic events occur within the first 10 days following cardioversion.

**Statins and AF**

Observational findings have focused interest towards targets other than ion channels, mainly medications with possible effects on atrial remodelling. Among these, statins have been developed as a possible treatment option. Initially, less frequent episodes of ventricular arrhythmia were observed in ICD-patients (Implantable Cardioverter Defibrillator), and results were consistent with findings from AVID. When MIRACL presented an association between favourable stroke incidence and statin treatment, the hypothesis was that at least part of this response could be due to less AF burden and a potential anti-arrhythmic effect. One mechanism that could explain these beneficial effects was indicated by anti-inflammatory properties observed in an animal model. Twenty dogs were randomly assigned to treatment with or without 2 mg/kg/day atorvastatin, followed by the introduction of sterile pericarditis. In addition to shorter inducible AF episodes in the atorvastatin group, lower CRP levels were measured, and the authors proposed that atorvastatin might be “a novel therapeutic agent for AF.”
Rationale for this thesis

In summary, the AF population is growing rapidly and is already an immense challenge for both patients and health care. Because many AF patients are symptomatic, a large proportion of them are subject to treatment aiming for normal sinus rhythm in order to control symptoms pharmacologically. The pharmacological treatment of AF patients is problematic due to limited efficacy and potential side effects, raising questions with regards to risk vs. benefit. Thus, information about safety of available anti-arrhythmic medication in clinical practice is warranted, as well as new, alternative pharmacological approaches to target AF and these patients. Hopefully, this thesis will add some information about these issues and increase the available knowledge on AF.
Aims of the thesis

Paper I
To investigate the extent and possible source of inflammation in patients with AF.

Paper II
To evaluate the effect of atorvastatin on sinus rhythm following electrical cardioversion in patients with persistent AF.

Paper III
To assess the safety of long-term treatment with flecainide in patients with atrial fibrillation (AF), particularly with regard to sudden cardiac death and pro-arrhythmic events, locally in Örebro, Sweden.

Paper IV
To evaluate the safety of long-term treatment with flecainide in Sweden nationwide, with particular regard to mortality compared to a control group on beta-blocking agents.
Patients and methods

Ethics
All studies were performed in keeping with the Helsinki Declaration of human rights. The Regional Ethical Board in Linköping approved study I (D.nr 03-242; 2003-06-12) and the Regional Ethical Review Board in Stockholm at Karolinska Institute approved studies II (D.nr 03-207; 2003-05-05) and IV (D.nr 2009/1378-31/1; 2009-09-23). Approval from the Swedish Medical Product Agency was also obtained for study II. Study III was conducted as a quality assurance study in line with the Swedish Health and Medical Services Act (HSL, 1982:763). Signed and informed consent was obtained for participants in studies I and II. Study IV was conducted through registry linkage and subject information was anonymised before analyses were performed.
Paper I - Source of inflammatory markers

In study one, which was designed as a pilot study, we aimed to assess inflammatory markers at different locations. We hypothesised that an inflammatory mechanism in the vicinity of the heart (atrium, pulmonary veins) might be involved in AF development. Twenty-eight patients were enrolled during 2004 and 2005 (Linköping n=18, Örebro n=10). Eligible patients were referred for ablation of symptomatic arrhythmias and free of comorbidities, including structural heart disease, diabetes mellitus, and neoplasia. Other exclusion criteria were previous ablation, cardiac heart surgery or infection <90 days before the ablation procedure, and/or the use of lipid-lowering drugs. Patients with AF were categorised according to PxAF (≥1 subjective episode of AF per month, n=10) or permanent AF (AF continuously ≥ 2 months, n=8). The control group consisted of 10 patients with a left-sided accessory pathway and no evidence of AF. Blood samples were obtained from the femoral vein, right atrium, and coronary sinus using a 7-French sheath or an Amplatz catheter (coronary sinus). Samples from the left and right pulmonary veins were drawn after transseptal puncture using the transseptal sheath after a bolus of heparin. Prior to blood sampling, 5-10 ml of blood was aspirated and discarded. Blood samples for IL-6 and IL-8 measurements were drawn from all sample sites, whereas CRP samples were obtained only from the femoral vein, though it is mainly synthesised in the liver. All samples were centrifuged and separated at room temperature, and then stored at -80°C until analysis. The lower limits of detection were 0.1 mg/L, 0.39 pg/ml, and 0.1 pg/ml for CRP, IL-6, and IL-8, respectively.
**Paper II - Atorvastatin and persistent AF**

In study two, the aim was to evaluate the effect of atorvastatin on sinus rhythm maintenance after cardioversion. This was an investigator-initiated, double-blinded, placebo-controlled, randomised study. Almost 800 patients were assessed for eligibility at 10 different participating centres in Sweden between August 2004 and January 2007. We hypothesised a 30% lower relative relapse rate in patients randomised to atorvastatin (40 mg, twice daily) compared to placebo 30 days after cardioversion.

A total of 234 patients were randomised and allocated to atorvastatin (n=118) or placebo (n=116). The production unit of the hospital pharmacy created computer-generated randomisation lists (blocks of 6) and managed packaging and labelling. Treatment was initiated 14 days before, and continued 30 days after, cardioversion. All patients received warfarin according to standard procedures (international ratio ≥2 checked weekly for 3 weeks or more) prior to cardioversion. Patients were followed up at 2 days, 1 month, and 6 months after cardioversion. Blood lipids were determined at baseline and 30 days after cardioversion.

The primary endpoint was rhythm obtained by 12-lead ECG 30 days (sinus rhythm or not) after cardioversion. Secondary endpoints were rhythm 6 months after cardioversion, safety, and tolerability. Inclusion and exclusion criteria are presented below.

**Inclusion criteria:**
- Clinical indication for cardioversion
- AF duration > 7 days
- Age >18 and ≤80

**Exclusion criteria:**
- Paroxysmal AF of atrial flutter
- On-going treatment with lipid-lowering drugs
- Contraindications against atorvastatin
- Class I or III antiarrhythmic treatment
- Oral amiodarone < 6 months prior to inclusion
- Known liver disease or cardiomyopathy
- Previous electrical cardioversion (within 1 year)
In study three, the main objective was to assess the safety of long-term treatment with flecainide in AF patients. The rationale for the study was the limited data available on flecainide treatment of AF patients, keeping the unexpected results of the CAST study in mind. Accordingly, we performed a retrospective safety study in a clinical cohort of AF patients who were managed at the University Hospital of Örebro during flecainide treatment.

All patients who started flecainide treatment at the department of Cardiology in Örebro between 1998 and 2006 were identified (n=112). This was possible because flecainide treatment was initiated while the patient was admitted to the cardiology ward for 2 to 3 days for ECG surveillance. These patients could be identified from the computerised epicrisis. Standard routine was applied prior to flecainide initiation. All patients were evaluated by transthoracic echo. Ischemia was evaluated by history in addition to an exercise test. In the case of disability or pacemaker, myocardial scintigraphy or coronary angiography was performed. Demographic data, together with data from the transthoracic echo, exercise test, and information about medications, were entered into a database. Typically, follow-up was performed once yearly. In between visits, patients were instructed to make contact if symptoms of ischemic heart disease, cardiac heart failure, dizziness, or syncope occurred. Treatment was discontinued if it was considered to be ineffective at maintaining sinus rhythm, at the occurrence of intolerable side-effects, the detection or suspicion of structural heart disease, a new bundle-branch block, or QRS duration >50% compared to pre-treatment.

The main outcome measure was death with special regard to sudden cardiac death and pro-arrhythmia. Pro-arrhythmia was defined as cardiac syncope or life-threatening arrhythmia. We used standard criteria for sudden cardiac death, i.e., death that occurred suddenly and unexpectedly in a patient with an otherwise stable condition. Witnessed deaths with or without documentation of arrhythmia were included. Un-witnessed deaths were also included if the patient had been observed within 24 h before death in the absence of premonitory heart failure, myocardial infarction, or another clear cause of death. To determine the observed mortality, comparisons were made to mortality rates from the general Swedish population using standardised mortality ratios (SMRs) adjusted for age (5-year groups) and gender. SMRs were estimated for all-cause mortality (ACM) and cardiovascular disease; the latter defined as ischemic heart disease (ICD-10 I20-I25), cardiac arrhythmia (ICD-10 I46-I49), heart failure (ICD-10 I50), and stroke (ICD-10 I61, 63-64). In addition, annualised incidence rates for
events (SCD or pro-arrhythmia, 1:1 atrial flutter, wide QRS tachycardia, or syncope during exercise) were presented.

**Paper IV - The safety of flecainide treatment in Sweden**

All patients in the Swedish National Hospital Discharge Register, with a diagnosis of AF between 1 July 2005 and 31 December 2008, were identified by their unique personal identification number. This registry covers complete information about all hospital admissions, and visits to outpatient clinics for subjects with a Swedish civic registration number since 1987. Patients with AF were ascertained by the ICD code I48.9, including subcodes A-F (International Classification of Diseases, 10th revision). Time at risk was counted from the date of first occurrence of an AF diagnosis during the study period (index date). The accuracy of diagnoses obtained from this registry is high. The register misses information about principal diagnoses in 0.5-0.9% of hospitalizations in somatic care. Recently, the diagnosis of AF or atrial flutter was found to have a positive predictive value of 97%.

The Hospital Discharge Register was also used to ascertain information about comorbidities. This register holds information of all hospital admissions, and visits to outpatient clinics with principal, and up to nine ancillary diagnoses, and up to 13 codes for surgical and interventions. Diagnosis prior to the index date and two weeks after reflected baseline comorbidity. The blanking period of 2 weeks was used since transfers between hospitals and clinics were common, and early re-appearances of a diagnosis were often intimately related to a preceding hospital period.

Information about medication was obtained from the Swedish Prescribed Drug Register. This register automatically stores detailed information about every prescription that is handled in every pharmacy in the country since July 1, 2005, and is therefore to be regarded as almost 100% complete. Dates of deaths that occurred during follow-up was obtained from the Swedish Total Population Register. To ensure anonymization before the data was analysed, the personal identification number was exchanged to a unique serial number by the statistical unit of the Swedish National Board of Health and Welfare.

The exposure group was defined as all patients who had used flecainide as the only anti-arrhythmic treatment in addition to beta-blocker during follow up. The combination with beta-blocker was motivated by the conduction slowing properties of flecainide (rate dependent block) that may result in slow AF or atrial flutter with rapid conduction to the ventricles. Patients who had used other anti-arrhythmic drugs than flecainide were
excluded. The reference population was defined as all patients who only had claimed beta-blockers.

Prescriptions that had been collected within 3 months of the index date were defined as medication at baseline.

The primary outcome measure was all cause mortality. Follow up ended at the time for death or at the end of the study period, 1 Feb 2010.

**Data sources used**

The Swedish personal identification number was introduced in 1947 and makes linkage between registries possible as it is used in all health care and population registries in Sweden. Approximately 100% of all Swedish residents are assigned this ten-digit number at birth \(^{120}\).

The **Swedish National Hospital Discharge Registry** contains nationwide information about inpatient care from 1964 onward. From 1987 onward, this registry is complete and provides information about all hospital admissions, including main and bi-diagnoses and surgical interventions using the International Classification of Disorders (ICD). The reliability of diagnoses from this registry is well validated and well suited for epidemiological studies \(^{116,121,122}\).

The **Swedish Prescribed Drug Registry** is a nationwide registry initiated 1 July 2005. It covers the entire Swedish population and is the most extensive of the Nordic prescription databases. This registry contains information about patient-specific data (age, gender, location), the prescriber, and prescribed and dispensed drugs. Prescribed drugs are identified by the international ATC classification. Information about the strength and amount of the drug dispensed is also available. In addition to the Danish counterpart, the Swedish Prescribed Drug Registry also includes information about the prescribed dose.

The **Total Population Register** contains information on the basic demographic population statistics, including gender, age, and civil status, and information about emigration and death for all Swedish citizens. Statistics Sweden is responsible for this registry, which is often used as a source in medical and behavioural sciences.
Statistics

The distribution of a normally distributed variable (continuous) is expressed as mean ± standard deviation (SD). For non-normally distributed variables, median and interquartile range or median and range are used.

The point-estimates of the odds ratio (OR) (papers II and IV), the standardised mortality ratio (SMR), and the annualised incidence rate (paper III) are shown with 95% confidence intervals. In general, p<0.05 was considered significant.

**Pearson’s chi-square test** was used to evaluate differences in proportions between groups in papers I to IV.

**Fisher’s exact test** was used instead of the chi-square test in the case of small numbers in papers I to IV.

**The Students t-test** was used to evaluate continuous variables between groups in paper II.

**Wilcoxon’s rank sum test** was used instead of the Student’s t-test to evaluate differences between independent groups in the case of skewed distributions. This test was used in papers II, III, and IV.

**Mann-Whitney U test** was used in paper I. This is analogous to Wilcoxon’s rank sum test.

**One-way analysis of variance** was used in paper I to compare continuous variables between patients with paroxysmal or permanent AF and controls (WPW-syndrome).

**Spearman rank correlation** was used to estimate the possible association between the levels of inflammatory markers at different sample sites in paper I.

**Pearson’s correlation**: We also re-analysed the inflammatory markers in paper I after a logarithmic transformation because the values indicated a skewed distribution.

**Logistic regression**: This model-based analysis, with the OR as an effect parameter, was used in paper IV before and after pre-analysis matching by coarsened exact matching. With this model, different background variables that possibly impact the outcome and have a non-ignorable correlation with exposure were screened. If any of the different variables changed the point estimate for the exposure by more than 10%, these variables were
characterised as possible confounders. In the final analysis, the possible confounding effects of all these variables were considered when the adjusted OR was calculated.

Cox proportional hazard regression was used in paper IV to validate the results obtained with the logistic regression model. It has the hazard ratio (HR) as an effect parameter.

Some additional information about statistics and terms used

Annualised incidence ratio describes the number of new cases during a specified period. This is used in paper III to estimate the number of events during flecainide exposure; sudden cardiac death and pro-arrhythmia on a yearly basis / 100 person-years.

Matching is a method to create exposure groups with similar baseline characteristics in all regards other than the variable being studied. This method reduces the risk of non-random bias, which may result in spurious associations when conclusions are to be drawn. We used coarsened exact matching (CEM) in paper IV to adjust for differences in baseline characteristics between patients on flecainide and a beta-blocker versus beta-blocker alone. This is an advanced algorithm that excludes patients in one group who have no matching counterpart in the other group with regard to the variables that are chosen for matching. In addition, CEM defines a new variable from the baseline characteristics that weighs the remaining observations in the post-matching analysis.

Odds Ratio (OR): A point estimate to approximate the magnitude of an outcome; that is, the ratio between the odds of two groups towards an outcome. In this thesis, OR is used for two outcomes: in paper II regarding sinus rhythm 30 days after cardioversion (atorvastatin vs. placebo), and in paper IV to estimate mortality from flecainide exposure versus a control group using beta-blockers only. An OR equal to 1.0 indicates no differences between the groups under examination.

Person-years: The sum of all years in a cohort to describe the time at risk or exposure. This is used in paper III to summarise years of flecainide exposure in the cohort studied.

Standardised mortality ratio (SMR) is the ratio of the observed number of deaths in one cohort compared to the expected number of deaths using mortality rates from the general Swedish population adjusted for age and gender. This ratio can be used to compare the health status in a cohort of
interest to the general population. This was used in papers III and IV to compare the patients who had been exposed to flecainide and beta-blockers or beta-blockers alone to the general population with regards to all cause mortality (papers III and IV) and cardiovascular death (paper III).

Analyses were performed using JMP 5.1.1 and Statview 5.0 (SAS Institute Inc., Cary, NC) in paper I; JMP® 7 in papers II and III (SAS Institute., Cary, NC, USA), and Statistical Package for the Social Sciences (SPSS®) version 20 (IBM, SPSS, Armonk, NY, USA) and STATA® software version 12 (StataCorp, College Station TX, USA) in paper IV.
Results

Paper I - Source of inflammatory markers

In general, the study cohort was free from comorbidities and considered to be a healthy population. The three groups were well balanced with respect to baseline characteristics with the exception of hypertension, which was more common in patients with permanent or paroxysmal AF (n=4, 22% compared to controls, n=0). Five patients with PxAF (50%) and eight patients with permanent AF (100%) were in AF during blood sampling. The remaining 15 patients were in sinus rhythm (PxAF n=5, controls n=10). In the analysis, comparisons were made between PxAF and controls and between permanent AF and controls.

Patients with permanent AF had higher levels of IL-8 in the femoral vein right atrium, and coronary sinus compared to the controls, but this difference was not found in the samples from the left and right superior pulmonary veins (p=0.023). Further analysis suggested a relationship (similar levels) between IL-8 levels in the femoral vein and right atrium, as well as the femoral vein and coronary sinus ostium (Figure 7). IL-6 trended towards higher values at all sample sites in patients with persistent AF compared to controls, especially the pulmonary veins.

![Figure 7. Regression plots presenting close correlation between IL-8 levels in the femoral vein, right atrium (RA) and coronary sinus (CS).](image)

No differences were found between PxAF and controls regarding the inflammatory markers, regardless of sampling site. Rhythm at the time of sampling and AF duration based on history did not impact these observations. CRP was similar between the groups.
A total of 234 patients were randomised and allocated to intervention with atorvastatin (80 mg/d, n=118) or placebo (n=116). Baseline characteristics were similar between the groups. In 9% of patients, cardioversion failed (atorvastatin n=8, placebo n=13) and did not result in sinus rhythm. Twelve patients (5%) discontinued intervention during follow-up (atorvastatin n=7, placebo n=5), mostly because of logistical reasons. Between randomisation and day 30 after cardioversion, six patients (3%) repeated cardioversion (atorvastatin n=2, placebo n=4).

At the primary endpoint (day 30 after cardioversion), a total of 222 patients with outcome data (rhythm by 12-lead ECG) were available and included in the primary outcome analysis, intention to treat by randomisation group. This analysis showed that 57 patients (51%) in the atorvastatin group and 47 (42%) in the placebo group maintained sinus rhythm 30 days after cardioversion. At 6 months, the corresponding numbers were 41 (38%) and 43 (39%), respectively.

Regarding concomitant medication, the groups were well balanced during follow-up, with the exception of calcium antagonist being used more often in the placebo group (22% vs. 11%, p=0.029). A summary of the primary and secondary outcomes is presented in Table 3. Study design and reasons for discontinuation is presented in Figure 8. Compliance in both groups was >90%. No serious adverse events occurred during the study.

Table 3. Summary of results, analysed 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>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No 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>Atorvastatin group (n=109)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group (n=110)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No 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>Atorvastatin group (n=116)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo group (n=115)</td>
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<td></td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolerability</td>
<td>115 (99.1)</td>
<td>115 (100)</td>
<td>-</td>
<td>1.00</td>
</tr>
<tr>
<td>Adverse events</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>
Atorvastatin 80 mg/day (n=118)
Received allocated intervention (n=118)

Placebo (n=116)
Received allocated intervention (n=116)

Discontinued intervention
adverse event (n=1)
withdrawn consent (n=1)
Logistic reasons
screening failure (n=1)
missing data (n=2)
running out of study drug prior to CV (n=2)

Discontinued intervention
withdrawn consent (n=1)
Logistic reasons
missing data (n=2)
running out of study drug prior to CV (n=2)

Cardioversion (CV)

Analysed (n=111)

Cardioversion (CV)

Analysed (n=111)

Figure 8 Design of Study II
Paper III - The safety of flecainide treatment in Örebro

Between 1998 and 2006, with follow-up until 1 December 2008, we identified 112 patients who initiated flecainide treatment. The mean age of the cohort was 60 years, and 65% were men. Ischemic and valvular heart disease was evident in 4% of the patients, and 97 (87%) had a CHADS<sub>2</sub> score of ≤1 at baseline. The mean daily dose of flecainide was 200 ± 43 mg. A total of 100 (89%) patients combined flecainide with a beta-blocker or non-dihydropyridine calcium antagonist.

During a mean follow-up of 3.4 years, more than half of the population discontinued flecainide treatment (Figure 9), mainly due to breakthrough AF and lack of efficacy, but cardiac side effects were also common.

![Figure 9. Reasons for discontinuation of flecainide](image)

On flecainide

- Discontinued flecainide
  - Ineffacy (n=36)
  - Non-cardiac side effect (n=7)
  - Successful RF ablation (n=6)
  - Cardiac side effect (n=18)

Discontinued flecainide

40 % (n=45)

60 % (n=67)

Six were classified as having pro-arrhythmia; three documented by 12-lead ECG or telemetry (monomorphic wide QRS tachycardia, n=2; 1:1 atrial flutter with broad QRS and syncope, n=1)(Figure 10). Two patients had syncope during exercise associated with palpitations and one patient had episodes of 1:1 atrial flutter during a hospital stay and symptoms (no ECG or rhythm strip available).
A) Wide QRS-tachycardia (330 ms.) in a 75 year old male with persistent AF and prior stroke after two months on flecainide.

B) Fifty-five year old woman with a dual chamber pacemaker due to bradycardia. After increasing flecainide from 200 mg to 300 mg per day, she developed a wide QRS tachycardia, RR 360 ms.

C) Seventy year old man, free from comorbidity. After almost three years on flecainide, he was admitted because of syncope and palpitations. Telemetry revealed 1:1 atrial flutter, RR 285 ms.
During follow-up, 8 patients (7%) died after flecainide exposure, which is higher than expected when compared to the age- and gender-adjusted population annual mortality rate (2.1% vs. 1.3%). Five of the observed deaths were classified as non-sudden (cancer, n=1; stroke, n=2; ST elevation myocardial infarction, n=1) and three deaths classified as sudden cardiac death. The SMRs were 1.57 (95% CI 0.68-3.09) for all-cause mortality and 4.16 (95% CI 1.53-9.06) for death from cardiovascular death during flecainide exposure.
Paper IV – The safety of flecainide treatment in Sweden

Over a period of 3.5 years, 182,678 unique patients with a diagnosis of AF were identified in the Hospital Discharge Register. Of these patients, 64,918 (45.7%) had used beta-blockers in the absence of anti-arrhythmic drugs, digoxin, and non-dihydropyridine calcium antagonists, and 5,381 (2.9%) had used flecainide. The majority of the patients had used alternative anti-arrhythmic drugs. Only 264 patients received flecainide alone. The patients who had been prescribed flecainide at any time were 15 years younger, more often male, had lower prevalence of comorbidity, and less concomitant medication (warfarin excluded) compared to the reference population. A total of 672 (12.5%) patients had structural heart disease (defined as ischemic heart disease, cardiac heart failure, or valvular disease). In the matched study group receiving flecainide and beta-blocker (n=2,178), 9.4% had structural heart disease. Figure 11 illustrates the study group distribution.

Mortality within the Cohort
The unadjusted mortality during follow-up was 2.8% among the patients exposed to flecainide compared to 30.8% among patients on beta-blockers. The median follow-up time was 2.2 years (0-4.6) in patients exposed to flecainide and 2.5 years (0-4.6) in patients on beta-blockers, respectively. After CEM, 2,178 patients who received flecainide and beta-blockers had similar baseline characteristics to 27,313 patients who received beta-blockers. The corresponding CEM-adjusted mortality was 2.6% in patients on flecainide and beta-blockers versus 8.5% in patients on beta-blockers only, (odds ratio (OR) 0.27, 95% confidence interval (CI) 0.21-0.36, P<0.001). The primary analysis was verified in a multivariable Cox regression model. The result was almost identical to the primary analysis based on logistic regression.

Mortality Compared to the General Population
Compared to age- and sex-adjusted population statistics (5-year classes), the SMR was approximately one-third in patients on flecainide (male: 0.66, 95% CI 0.46-0.91; female: 0.76, 95% CI, 0.47-1.18), indicating a healthy population compared to the reference population on beta-blockers only (male: 2.31, 95% CI 2.27-2.35; female: 2.21, 95% CI 2.16-2.25).

Characteristics of Deceased Patients on Flecainide
A total of 56 patients (2.6%) from the matched population on flecainide died during follow-up. In general, these patients were 10 years older and had more severe comorbidity at baseline than those who were still alive.
The mean daily doses of flecainide were similar (199.1 mg, SD 35.2 versus 194.0 mg, SD 42.2, \( P=0.459 \)) between the two groups. Ischemic heart disease (19.6% versus 5.3%, \( P<0.001 \)), cardiac heart failure (19.6% versus 2.7%, \( P<0.001 \)), and pacemaker use (12.7% versus 2.7%, \( P<0.001 \)) were more common among the patients who died. Sixteen (28.6%) of the flecainide-exposed patients who died had structural heart disease.

The 264 patients who were prescribed only flecainide during follow-up had a higher mortality rate than patients who received flecainide and beta-blockers (6.8% versus 2.6%, \( P<0.001 \)). At death, only 41 patients were on flecainide, 20 of which had no concomitant beta-blocker therapy.
The Swedish Atrial Fibrillation Cohort

In hospital diagnosis between 1 July 2005 and 31 December 2008

n=182,678

Any use of anti-arrhythmic medication
n=28,090

Any use of flecainide
n=5,381

Any use of beta-blocker
n=141,941

Any use of only beta-blocker
n=64,918

Only flecainide and beta-blocker during follow-up
n=2,178

Only beta-blocker during follow-up
n=27,313

Coarsened exact matching

Figure 11. Flow-chart of the study group distribution
General discussion

Study populations
The first study targeted a smaller group of patients, whereas the last study obtained information from a less select population using epidemiological data. The prevalence of AF in the last study group was estimated to be 1.9% during an inclusion period of 3.5 years. This prevalence is similar to what was found in other studies, but the true prevalence is likely higher, as many AF episodes are asymptomatic and do not result in hospital care.

The typical AF patient is roughly 75 years old with comorbidities, such as hypertension, ischemic heart disease, cardiac heart failure, or diabetes. In comparison, the patients in paper I were far healthier due to the issue addressed and the importance of not introducing factors that could introduce bias and confuse the possible association between AF and inflammation. The population in study two was more typical, but they could be considered a healthy AF population according to the inclusion and exclusion criteria used. Patients on statins were excluded. Consequently, few patients with ischemic heart disease were enrolled. The patients exposed to flecainide in studies three and four were also healthy AF patients because that treatment is contraindicated in the presence of structural heart disease. In comparison, the reference population on beta-blockers in study four was more typical, reflecting nationwide data with no restriction on age and comorbidity.

Inflammation, AF, and statins
Low-grade inflammation has been associated with cardiovascular disease, such as myocardial infarction or stroke, but it seems to not be that closely related to AF. Some 30 years ago, the coexistence of AF in patients with myocarditis and pericarditis suggested a link to inflammation. In 1997 Bruins et al observed that the peak incidence of CRP coincided with postoperative AF and proposed a casual relationship between inflammation and AF. The same year, Frustachi presented histological evidence for inflammatory changes in the atrial tissue of patients with PxAF compared to patients with WPW syndrome. Since that time, different approaches have been used to evaluate the possible casual relationship between inflammation and AF.

In paper I, we hypothesised that local inflammation in the heart is involved in the pathogenesis of AF. We used similar inflammatory parame-
ners as previous studies in a prospective setting; the main difference was that we analysed blood from different locations in the heart and vessels. The hypothesis was that concentration gradients exist with the highest levels in important trigger regions. We found no association between elevated inflammatory markers and AF to support our hypothesis.

The causal relationship between inflammation and incident AF remains unclear. Previous studies have suggested that inflammation may be correlated with the initiation, perpetuation, and burden of AF, the success rate following CV, and post-operative AF. Most studies thus far have been relatively small and observational.

Different measures have been used to study the association between inflammation and AF. C-reactive protein is the inflammatory marker that has been evaluated most extensively. However, the causal relationship between CRP and AF is unknown. During the last few years, independent associations between inflammation and AF have been reported in different cohorts. Recently a Mendelian randomisation study reported a robust association between elevated CRP levels and the risk of AF. However, this relationship was not evident in patients with genetically elevated levels of CRP and the authors suggested that, “elevated CRP levels don’t increase AF risk per se”. On the other hand, an association between the scores for different acute phase proteins and long-term incidence of AF was recently reported in prospective population-based data. These findings imply that elevated inflammatory markers precede AF, even when concomitant cardiac disease has been accounted for, which is important because increased inflammatory marker levels may be a result of cardiac comorbidity and not AF itself.

New and safe pharmacological approaches targeting AF are needed, especially in regards to rhythm control, for which treatment is problematic due to limited efficacy and potential side effects that may question the risks and benefits. If a causal association between inflammation and the initiation or perpetuation of AF exists, it would be clinically important. As several cardiovascular drugs may impact inflammatory processes in the heart, they could provide the means or new ideas for AF treatment strategies. In study two we hypothesised that atorvastatin would reduce the rate of AF recurrence following cardioversion in patients with persistent AF.

We chose atorvastatin in a proof-of-concept study supported by observational findings that proposed anti-arrhythmic properties in other populations. These effects were independent of changes in lipid levels. In addition, reduced CRP levels were observed, which was most pronounced with atorvastatin treatment. Together with a well-documented safety profile, this information made atorvastatin attractive. However, we did not
find atorvastatin to be superior to placebo with regards to maintaining sinus rhythm following cardioversion.

In contrast to our negative findings, favourable outcomes have been reported in patients with low AF burden \(^{148,149}\) and in the prevention of post-operative AF \(^{150}\). The latter involves the inflammatory response following surgery, and the study had a large proportion of patients with ischemic heart disease compared to our study. Findings consistent with ours have also been reported \(^{151}\).

A factor that seems to be important is the duration of AF preceding cardioversion or other interventions, which is explained by electrical and structural changes as a consequence of AF duration and remodelling. If we exclude patients with AF duration > 1 year based on history and documentation (duration ≤ 1 year, n=101), atorvastatin also results in a beneficial outcome at 1 month, but not at 6 months, with regards to maintaining sinus rhythm. Reached this far? Go public and claim the Old Pulteney. This observation suggests that a subpopulation with less AF burden may be beneficial, as in patients with PxAF. However, conflicting results were observed in this subset of AF patients \(^{152,153}\).

The results could suggest a possible role for statins in primary prevention. Such results were published recently in a randomised primary prevention setting, the JUPITER trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rsouavastatin). A major limitation of this study was that AF was not pre-specified as a primary endpoint. However, rsouavastatin significantly reduced the incidence of AF when reported as an adverse event compared to placebo \(^{154}\).

In summary, diverging results have been presented for statin treatment in the prevention of AF. A number of meta-analyses have addressed this issue \(^{155-158}\). To date, not enough evidence is available to support the use of statins as primary or secondary AF prevention in situations other than to prevent post-operative AF \(^{51}\).

**AF and flecainide**

Around 1970, 3M bought a small pharmaceutical company, Rieker Laboratories. One of the investigational drugs had the capabilities of suppressing irregular heartbeats (R818), which later became flecainide (Tambocor®). As premature ventricular complexes (PVCs) are markers of sudden cardiac death in patients with ischemic heart disease \(^{159,160}\), a drug like flecainide could have a beneficial impact on mortality. This hypothesis was accepted among leading cardiologists but remained unproven until the CAST study \(^{91,92}\). As mentioned earlier, this study revealed increased mortality in patients randomised to flecainide or encainide treatment. Today, flecainide is used to maintain sinus rhythm in AF patients and recommended as a first
line treatment in patients free from structural heart disease according to AF guidelines 51, 52.

In study three we evaluated flecainide exposure in AF patients in Örebro, Sweden. The rationale was the limited information regarding the safety of flecainide in the context of AF. We observed pro-arrhythmia and three cases of sudden cardiac death in a healthy AF population.

The observations of pro-arrhythmia and sudden cardiac death originate from animal studies and have been described in both the presence and absence of acute myocardial ischemia. Flecainide has the ability to affect different ion channels (mainly fast inward Na\(^+\) channel, I\(_{\text{Na}}\)) and may lengthen the duration of the action potential in both atrial and ventricular tissue 161, 162. In addition, flecainide has slow diastolic unbinding properties (use-dependent properties). Consequently, flecainide is prone to causing re-entry tachycardia by slowing conduction 163-165. The effect on propagation is especially prominent in acute ischemia (conduction slowing with little effect on refractoriness), with ventricular fibrillation as the observed pro-arrhythmia 166-168.

In light of these findings, the excess mortality seen in CAST could be explained by acute ischemia acting as a trigger of pro-arrhythmia with fatal outcomes. This possibility was hypothesised by Greenberg, 169 who observed that the three-fold higher proportion of cardiac deaths in the flecainide/encainide group was equalised by a greater number of non-fatal ischemic events in the placebo group. Acute ischemia acting as a trigger of pro-arrhythmia is supported in animal studies 167.

Less information is available in the absence of acute myocardial ischemia or post-myocardial infarction, but animal and theoretical experiments indicate that proarrhythmia may occur 167, 170-172.

Compared to previous findings, our observational deaths were equal to the few deaths reported in the adult AF population 119, 173-177. The main difference between ours and previous studies was that three of four cardiac deaths in our study had no obvious structural heart disease. These observational findings warranted further safety information. Thus, we evaluated whether flecainide exposure is associated with increased mortality compared to a population receiving beta-blockers only using epidemiological data. In this large nationwide study, we found no association with flecainide and increased mortality. Findings suggesting the opposite were difficult to understand when the mechanisms for the pro-arrhythmic potential of flecainide seem coherent and biologically plausible. An analogy is quinidine syncope 178. Experimental designs have introduced clues to causation, with exposure preceding effect (temporality), as well as an association between dose and response 167, 179. Specificity has been addressed in the setting of ischemic heart disease, in both experimental and randomised settings with consistent results in populations other than the AF population.
When analysed, a possible explanation for the beneficial effect of flecainide, could be that our study groups differed in regards of risk factors other than the variable being studied (flecainide), that we had no opportunity to adjust for.

On a population basis, we found no support for increased mortality after flecainide exposure. However, we observed that many patients with structural heart disease received flecainide. We also observed a higher death rate among patients who did not receive a beta-blocker, which may emphasise the importance of adhering to guidelines and may also suggest the importance of beta-blockers while on flecainide. This may be essential for the individual patient. Thus, continuous evaluation when comorbidity is likely to worsen or occur, not only at initiation, but also during follow-up, is important. In the end, it all comes down to improving the care of AF patients, regardless of whether the aim is treating symptoms or preventing morbidity and mortality.

**Methodological considerations**

**Generalisability**

All of the patients in studies three and four were in-hospital patients. Örebro County had a population of approximately 270,000 citizens in 2006, 40% of which the University Hospital covered. In 2006, 208 unique patients claimed flecainide prescriptions in Örebro County. We likely identified the vast majority, but not all, patients on flecainide. In comparison, 4208 unique patients were prescribed flecainide in 2006 and 5117 patients in 2008 in Sweden. From these numbers, we can conclude that the majority of patients on flecainide were identified in study four using nationwide epidemiological data, and that the findings are generalisable to populations with similar demographic and socioeconomic profiles as the Swedish.

**Validity of the registries**

The validity of the Swedish registries we used is high. Ludvigsson et al recently validated the Swedish Hospital Discharge Register. In most cases the accuracy of diagnosis obtained from this registry, including AF, myocardial infarction, and cardiac heart failure, varied between 85% and 95%. However, for many diagnoses less is known. A problem may be under-reporting or over-reporting of diagnoses. As a result, the patients in our study may have had other risk factors or comorbidities than we were aware of and could adjust for. This limitation is inherent in all registries.
The prescribed drug registry is a high quality registry that automatically stores detailed information about every prescription that has been handled since July 1, 2005. Based on its construction, this registry may be regarded as complete. One limitation of the registry is that it does not cover medicines given during a hospital stay or in nursery homes, or medicines that can be purchased without a medical prescription. When information is used from this registry, it is also assumed that the patients for whom the medication was prescribed uses it according to the instructions from the prescribing physician.

Information about deaths was obtained from the Total Population Register. This registry is administered by Statistics Sweden and is often used in different reports. The registry covers 93% of all deaths (yes/no) of persons with a Swedish personal identification number within 10 days, and is complete within a month.

Selection bias
Selection bias may be a problem when study groups are not comparable with regards to variables other than the one being studied. In most cases this bias is a consequence of an inappropriate selection of controls. In study three, we compared the patients on flecainide to population statistics; thus, the comparison group consisted of some healthier individuals, but also some sicker individuals. This comparison group likely also included patients on flecainide and other anti-arrhythmics. However, the proportion is probably very small. To summarise, we compared the flecainide cohort to an average Swedish population.

In study four, we used the Hospital Discharge Resister to identify patients with a diagnosis of AF. This approach may be a problem if the patients in our study groups are part of the registries for different reasons. Because flecainide is initiated in the hospital under cardiac monitoring, this may explain how patients who received the drug became index patients. In contrast, the reference population receiving beta-blockers were probably index patients for reasons other than AF, such as ischemic heart disease and congestive heart failure, which are all associated with a worse prognosis.

Furthermore, we could not differentiate patients into paroxysmal, persistent, or permanent AF. This is a problem as persistent AF has been shown to have a more favourable mortality outcome compared to population statistics and paroxysmal or permanent AF. The inability to differentiate the types of AF probably resulted in selection bias because flecainide is a rhythm-maintaining treatment and only used in paroxysmal or persistent AF.

We also selected patients on the basis that they either used flecainide in combination with a beta-blocker and no other anti-arrhythmic during fol-
low up or beta-blockers only. We did this to obtain the cleanest exposure groups possible, but this may introduce a risk of confounding by indication; i.e. underlying comorbidities that may have been undocumented in registries decide which patients will have which treatment. Thus, if patients with low mortality risk are selected for flecainide treatment, flecainide will come out favourably unless all reasons for patient selection are documented. As a result, the reference population may have a worse prognosis.

**Confounding**

When evaluating whether different exposures are associated with an outcome, the comparison groups must be similar with regards to baselines characteristics. If not, there is a possibility of comparing apples and oranges, which may result in biased associations.

In study two we dealt optimally with confounding given the randomised, double-blind, placebo-controlled design. Thus, variables other than those that were studied can be assumed to have been randomly and evenly distributed between the comparison groups to minimise bias. In study three, we had no natural comparison group on beta-blockers or other anti-arrhythmic treatment. Instead, we compared the observed mortality ratios in patients on flecainide to population statistics, which enabled adjustments for age (5-year classes) and gender but nothing else. In study four, we used a pre-matching algorithm, coarsened exact matching, to make the study groups as similar as possible. However, matching could only be performed using the variables provided by the registries we used. The need for a matching procedure can be exemplified by the SMRs and the crude unadjusted mortality rate obtained in study four. The unadjusted death rate was more than 10-fold in the reference population (beta-blockers only) compared to patients on flecainide. After matching, this figure decreased to 3-fold.

At least part of the favourable outcome of flecainide can be attributed to factors that we were unable to adjust for. This is exemplified by the inability of the registry data to provide information about the severity of diagnosis when most variables are given as dichotomous outcomes (yes/no). In addition, we had no information about lifestyle factors, such as smoking, physical and socioeconomic status, and obesity, which may impact both exposure and outcome and introduce differential bias.
Conclusions

We found no association between local inflammation in the heart and paroxysmal or persistent AF when measuring CRP, IL-6, or IL-8.

Elevated levels of IL-8 were detected in the systemic circulation of patients with more AF burden (persistent AF). This finding suggests a low-grade inflammation originating from sources other than the cardiac and pulmonary circulation.

The effect of atorvastatin was less than expected with regards to maintaining sinus rhythm following cardioversion. Thus, atorvastatin does not have the potential to be a pharmacological alternative in patients with persistent AF.

Compared to the general population, treatment of AF with flecainide in Örebro was associated with increased cardiovascular mortality. Sudden cardiac death and pro-arrhythmia was observed.

When flecainide exposure was evaluated in a larger cohort, no association was found with increased mortality compared to a reference population on beta-blockers or population statistics.

However, the risk/benefit ratio for the individual may be in question and contraindications for the drug should be respected.
**Swedish summary**


I den första studien (I) utvärderade vi om lokal inflammation i hjärtats förmak eller i närheten av lungvenerna är associerat med FF. Inflammatoriska markörer analyserades från systemcirklulationen och från olika delar av hjärtat. Patienter med paroxysmal FF och persistent FF jämfördes med en kontrollgrupp. Vi fann ingen koppling mellan lokal inflammation i hjärtat och FF, undantaget förhöjda nivåer av Interleukin-8 hos patienter med permanent FF.


I studie tre identifierade vi 112 patienter som behandlats med flekainid p.g.a. FF på den kardiologiska kliniken i Örebro. Vi observerade ökad kardiovaskulär mortalitet, plötslig hjärtXdöd och proarytm (definierat som kardiell svimmning eller livsfarlig arytmi). För att studera detta fyllde vi en större population utförde vi studie fyra. Data från slutenvårdsregistret användes tillsammans med data från läkemedelsregistret användes för att studera om flekainid var associerat till överdödlighet hos patienter med FF. Vi fann inte någon överdödlighet associerat till flekainid jämfört med en referenspopulation som bara behandlats med betablokkad.

Sammanfattningsvis fann vi inget samband mellan lokal inflammation i hjärtat och FF. Inte heller fann vi stöd för att använda atorvastatin i syfte att minska risken för återfall i FF efter elkonvertering. Vi observerade ingen överdödlighet hos patienter behandlade med flekainid i Sverige. Däremot kan vinsterna i förhållande till nytta med denna behandling ibland ifrågasättas hos den enskilda patienten, och dess kontraindikationer bör respekteras.
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Errata

Paper I – Source of inflammatory markers
p. 848, Abstract, Methods and results: "The study group consisted of 29 patients ...” should be "...28 patients...".

Paper II – Atorvastatin and persistent AF
p. 832, Table 3, secondary endpoints: Please go to page 39, Table 3, in the thesis for a correct table.
p. 832 Table 4, Almroth et al, Results: "Atorvastatin therapy not statistically superior to placebo OR 1.44 (0.85-2.44)” should be "... OR 0.70 (0.41-1.18)".

Paper III – The safety of flecainide treatment in Örebro
p.281 Introduction: "The CAST trial reported a 2.5 fold increased risk of sudden cardiac death...” should be ”...reported a 2.5 fold increased risk of all cause mortality”.
p.286, Discussion, mortality and AF in general, The findings of the CAST study unexpectedly revealed a 2.5-fold...” should be “...3.6-fold...”.
p.288, Mortality and pro-arrhythmia, “By comparison, one patient in our cohort with proarrhythmic events was not adequately blocked (patient no. 3, Table 2)...” should be “...(patient no. 7, Table 3)...”.
p.288, Mortality and pro-arrhythmia, “...and none of the other patients with SCD or proarrhythmia reached more than 80% of their estimated maximum pulse...” should be “One of the patients with SCD or proarrhythmia reached more than 80%...exercise test (patient no.3, Table 3)".
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