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Atrial remodeling in atrial fibrillation

Epidemiological, clinical and magnetocardiographic aspects

Mika Lehto

ACADEMIC DISSERTATION

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“A heart is what a heart can do.”

James Mackenzie (1853 – 1925)

“At this also my heart trembleth, and is moved out of its place.”

Job 37:1

To my family

Abstract

The work of this Thesis was initiated with an observational study in real-life clinical practice. We conducted a population-based evaluation of AF patients referred for their first elective CV. A total of 183 consecutive patients were included during the study period of one year. In 153 (84%) of the patients sinus rhythm (SR) was restored. Only 39 (25%) of those 153 maintained SR for one year. Shorter duration of AF and the use of sotalol were the only characteristics associated with better restoration and maintenance of SR. During the one-year follow-up period 40% of the patients ended up in permanent AF, with the mean number of 1.6 cardioversions before this decision. Female gender and older age were associated with the acceptance of permanent AF. Longer duration of AF was associated with poorer outcome of the CV, and it also tended to increase the probability to be engaged in permanent AF, probably reflecting the negative atrial remodeling during the prolonged AF burden.

The LIFE-trial was a prospective, randomised, double-blinded study that evaluated losartan and atenolol-based antihypertensive therapies on cardiovascular morbidity and mortality in patients with hypertension and left ventricular hypertrophy (LVH). 8,851 patients with SR at baseline and without a history of AF were included in the analysis where the risk of new-onset AF was assessed. A total of 371 patients developed new-onset AF during the study period (4.8 ± 1.0 years). Patients with new-onset AF had an increased risk of cardiac events, fatal or nonfatal stroke, and increased rate of hospitalisation for heart failure. Younger age, female gender, lower systolic blood pressure, lesser LVH in ECG and randomisation to losartan therapy were independently associated with lower frequency of new-onset AF. The mechanism behind the hindering effect of suppression of the renin-angiotensin-aldosterone system (RAAS) on AF was supposed to arise from regression of LVH and atrial remodeling.

The impact of AF on morbidity and mortality was evaluated in a post-hoc analysis based on the data from the OPTIMAAL trial that compared losartan with captopril in patients with acute myocardial infarction (AMI) and evidence of left ventricular (LV) dysfunction. Of 5,477 randomised patients 655 had AF at baseline, and 345 patients developed new AF during the follow-up period, median 3.0 years. Older patients and patients with signs of more serious heart disease had and developed AF more often. Patients with AF at baseline had an increased risk of mortality (hazard ratio (HR) of 1.32) and stroke (HR 1.77). New-onset AF was associated with increased mortality (HR 1.82) and stroke (HR of 2.29).

Atrial remodeling in AF patients as well as in experimental AF models is a well-documented phenomenon, while the reverse remodeling after electrical CV has been much less investigated, and reverse remodeling has not been documented with MCG. The basis to estimate atrial reverse remodeling with magnetocardiography (MCG) was set with the assessment of the reproducibility of our MCG method. In 10 healthy volunteers and 9 patients with paroxysmal lone AF both MCG and signal-averaged ECG (SAECG) were

recorded in SR and the recordings were repeated at least 1 week apart (from 1 week to 6 months). Reproducibility was best at 40-Hz filter (coefficient of variation of P-wave duration 3.3% and difference between the measurements 3.5 milliseconds on average) with no difference between patients and healthy subjects.

Twenty-six patients with persistent AF and 24 age- and disease-matched controls were studied with the MCG method. Along with MCG, SAECG and echocardiography were registered. Immediately after the CV AF patients had longer P-wave duration and higher energy of the last portion of atrial signal (RMS40) in MCG, increased P-wave dispersion in SAECG and decreased pump function of the atria as well as enlarged atrial diameter in echocardiography compared to the controls. After one month in SR, P-wave duration in MCG still remained longer and left atrial (LA) diameter greater compared to the controls, while the other measurements had returned to the same level as in the control group. These results indicate that even though there is recovery in AF patients when SR is restored, this reversal is incomplete, and electrical and structural remodeling alterations predisposing to AF are seen.

In conclusion, AF is not a rare condition in either general population or patients with hypertension or AMI, and it is also associated with increased risk of morbidity and mortality. The result of CV in clinical practice was poor and the proportion of patients assigned to permanent AF was high. Therefore, atrial remodeling that increases the likelihood of AF and also seems to be relatively stable has to be identified and prevented. MCG was found to be an encouraging new method to study electrical atrial remodeling and reverse remodeling. RAAS-suppressing medications appear to be the most promising method to prevent atrial remodeling and AF.

Contents

List of original publications

This Thesis is based on the following publications:

I Lehto Mika, Kala Risto. Chronic atrial fibrillation: a population based study of patients with their first cardioversion. International Journal of Cardiology 2003;92:145-150.

II Wachtell Kristian, Lehto Mika, Gerdts Eva, Olsen Michael H, Hornestam Björn, Dahlöf Björn, Ibsen Hans, Julius Stevo, Kjeldsen Sverre E, Lindholm Lars H., Nieminen Markku S, Devereux Richard B. Angiotensin II Receptor Blockade Reduces New-onset Atrial Fibrillation and Subsequent Stroke Compared to Atenolol (The LIFE Study). Journal of the American College of Cardiology 2005;45:712-719.

III Lehto Mika, Snapinn Steven, Dickstein Kenneth, Swedberg Karl, Nieminen Markku S on behalf of the OPTIMAAL investigators. Prognostic risk of atrial fibrillation in acute myocardial infarction complicated by left ventricular dysfunction. The OPTIMAAL-experience. European Heart Journal 2005;26:350-356.

IV Koskinen Raija, Lehto Mika, Väänänen Heikki, Rantonen Juha, Voipio-Pulkki Liisa-Maria, Mäkijärvi Markku, Lehtonen Lasse, Montonen Juha, Toivonen Lauri. Measurement and reproducibility of magnetocardiographic filtered atrial signal in patients with lone atrial fibrillation and in healthy subjects. Journal of Electrocardiology 2005;38:330-336.

V Lehto Mika, Jurkko Raija, Parikka Hannu, Mäntynen Ville, Väänänen Heikki, Montonen Juha, Voipio-Pulkki Liisa-Maria, Toivonen Lauri, Laine Mika. Reversal of atrial remodeling after cardioversion of persistent atrial fibrillation measured with magnetocardiography. Pacing and Clinical Electrophysiology (PACE) 2009**;**32,217-223**.**

The publications are referred to in the text by their Roman numerals.

Abbreviations

AC	= alternating current
ACE(i)	= angiotensin-converting enzyme (inhibitor)
AF	= atrial fibrillation
AFCL	= atrial fibrillation cycle length
(A)MI	= (acute) myocardial infarction
AngII	= angiotensin II
APB	= atrial premature beats
AP(D)	= action potential (duration)
ARB	= angiotensin receptor blocker
AT1(2)	= angiotensin II type 1 (2) receptor
AV	= atrio-ventricular
BMI	= body mass index
bpm	= beats per minute
CHF	= congestive heart failure
CHS	= Cardiovascular Health Study
CRP	= C-reactive protein
CV	= cardioversion
DC	= direct current
EF	= ejection fraction
ECG	= electrocardiography
ERP	= effective refractory period
FHS	= Framingham Heart Study
HR	= hazard ratio
LA	= left atrium
LV	= left ventricle/ventricular
LVH	= left ventricular hypertrophy
MCG	= magnetocardiography
NCX	= Na^{+}-Ca^{2+}-exchanger
NYHA	= New York Heart Association functional class
OR	= odds ratio
Pd	= P-wave duration
RAAS	= renin-angiotensin-aldosterone system
RAP	= rapid atrial pacing
SAECG	= signal-averaged ECG
SQUID	= superconducting quantum interference device
SR	= sinus rhythm
STEMI	= ST-elevation acute myocardial infarction

1 Introduction

Atrial fibrillation (AF) is a cardiac arrhythmia characterised by rapid, irregular, unorganised electrical and mechanical activity of the atria. It is the most common sustained arrhythmia in man, with prevalence and incidence in general population of about 1 - 2% and 0.2%, respectively, and it is associated with an increased mortality and risk of stroke (Feinberg et al. 1995, Benjamin et al. 1998, Fuster et al. 2006). The amount of AF increases strongly with age: while the prevalence in a population 50 years old is about 1%, it increases to about 10% in octogenarians (Feinberg et al. 1995, Benjamin et al. 1998, Fuster et al. 2006). More than 85% of AF patients have symptoms such as palpitations, shortness of breath and fatigue, AF patients having also significantly lower quality of life (Reynolds et al. 2006). Control of ventricular rate during AF, anticoagulation therapy to reduce the risk of stroke and restoration and maintenance of sinus rhythm (SR) are the three treatment lines considered in every AF patient, and also employed in most of them (Fuster et al. 2006).

Because of the symptoms, restoration and maintenance of SR has in most cases been a goal in the treatment of AF. However, it has been shown during the last decade that the rhythm control strategy aiming for SR does not improve the survival of AF patients compared to the rate control strategy where SR is not aimed at. The rhythm control strategy can even be associated with higher mortality, especially if antiarrhythmic medications are used (Van Gelder et al. 2002, Wyse et al. 2002, Corley et al. 2004, Testa et al. 2005). Paradoxically, the presence of SR has, however, been associated with better survival, better exercise capacity and quality of life (Deedwania et al. 1998, Corley et al. 2004, Opolski et al. 2004, Chung et al. 2005, Thrall et al. 2006). Therefore it seems that the treatment modalities – at least pharmacological ones – that are so far available on the market to restore and maintain SR are not safe enough. It has been asserted that transvenous AF ablation could be a safe and effective management for symptomatic AF, and it has also been associated with better survival of AF patients when compared in an unblinded, non-randomised setting to a patient group treated with antiarrhythmic agents (Pappone et al. 2003, Lubitz et al. 2008). In a recently published trial a new antiarrhythmic drug, dronedarone, increased the likelihood of SR and also decreased the number of cardiovascular deaths (Hohnloser et al. 2009). Those results might encourage attempts at restoration and maintenance of SR with newer and safer methods.

The long-term results of the restoration and maintenance of SR are generally poor, perhaps reflecting the natural trend of AF to turn out to be more stable in an individual with AF (Kopecky et al. 1987). In prospective studies SR is maintained for a one-year period after electrical cardioversion (CV) in only about 20% of patients if antiarrhythmic agents are not used, while the percentage is about 40 - 50% with common antiarrhythmics, and about 70% with amiodarone (Fuster et al. 2006, Lafuente-Lafuente et al. 2007). The proportion of patients free from AF after one year of transvenous AF ablation has been about 70% in experienced centers when a substantial proportion of patients have had more than one procedure (Cappato et al. 2005, Lubitz et al. 2008). It is also very apparent that

regardless of the treatment given – for example CV, transvenous AF ablation or surgical AF ablation – some critical features seem to have a great influence on the number of patients who continue in AF or have an AF relapse. The most often repeated factors decreasing the likelihood of SR have been the age of the patient, the duration of AF and the size of the (left) atrium (Viko et al. 1923, Parkinson and Campbell 1929, Dittrich et al. 1989, Van Gelder et al. 1996, Vasamreddy et al. 2004, Berruezo et al. 2007, Beukema et al. 2008). All these factors reflect or are surrogates of degeneration of atrial tissue; increased fibrosis during aging, atrium getting accustomed to AF during the arrhythmia ("AF begets AF") and atrial distension because of AF itself or because of other cardiovascular diseases (Morillo et al. 1995, Wijffels et al. 1995, Allessie et al. 2002, Nattel 2002). This phenomenon is called atrial remodeling that is – at least to some extent – fundamental for AF to be initiated and especially to be maintained.

AF tends to increase in frequency and duration. Therefore, and particularly because our traditional pharmacological approaches have only a limited safety-to-efficacy profile, so-called "up-stream therapies" are warranted and investigated in order to prevent primary events of AF and to decrease the frequency and duration of AF episodes. We do not have any treatment against aging, but suppression of the renin-angiotensin-aldosterone system (RAAS) seems to decrease the development of atrial fibrosis and also to prevent AF at least in patients with hypertension and heart failure (Li et al. 2001, Healey et al. 2005, Boldt et al. 2006, Burstein and Nattel 2008). When a patient gets symptomatic AF it is crucial that the treatments are started as soon as possible and SR is restored without any additional delay to prevent irreversible atrial remodeling from taking place (Van Gelder and Hemels 2006).

The present series of studies is focused on atrial remodeling and atrial fibrillation, a common and fascinating arrhythmia that can be investigated from numerous perspectives. This work was started with a clinical evaluation of patients with persistent AF referred for elective CV. Thereafter the center of attention was to study the atrial remodeling and reverse remodeling after CV with MCG. Two post-hoc analyses studying AF of two prospective randomised trials evaluating RAAS suppressing medication are included to this Thesis, because they have extended understanding of nature and importance of AF.

2 Review of the literature

2.1 Short history of atrial fibrillation and its treatment

The first documented observations of pulse have been found in ancient Chinese and Egyptian manuscripts. It was noticed very early that fast and irregular pulse was associated with poor prognosis (Lip and Beevers 1995, Lüderitz 2002a, Lüderitz 2002b). Perhaps the first description of AF is in The Yellow Emperor's Classic of Internal Medicine ("Huang Ti Nei Ching Su Wen"). He was also a physician and is believed to have ruled China between 2697 and 2598 BC. (Lip and Beevers 1995).

William Harvey (1578-1657) performed experimental work with animals, and the most valued of his work was the description of blood circulation. However, he is also probably the first to describe AF - "fibrillation of the auricles" – in animals, at least in recorded history (McMichael 1982, Flegel 1995).

The first instrument to observe heartbeat was the stethoscope, invented by René Laennec (1781-1826), and soon after Laennec's invention the association of irregular pulse and mitral stenosis was documented by Robert Adams (1791-1875) (Lip and Beevers 1995). Documentation of AF became possible with ECG. The first human ECG was recorded by Augustus Waller (1856-1922) in 1887, and in 1906 Willem Einthoven (1860-1927) described the first ECG of AF as "pulsus inaequalis and irregularis" (Lüderitz 2002b, Fye 2006). Soon thereafter it was noticed that AF was "a common clinical condition" in patients with heart diseases (Lewis 1909).

Explanation of the nature and concept of AF was advanced in the late 1800s and the early 1900s. Even though fibrillation or undulation of the atria was established in animal experiments, the similarity with the irregular pulse of a patient was not documented until 1907 (Flegel 1995). In the first ECG recordings of AF atrial activity during AF was considered an artefact, but in 1909 it was noticed that there was irregular atrial electrical activity in AF. Furthermore, Thomas Lewis (1881-1945) noticed that atrial and ventricular rhythms were disordered and that the venous pulse was of ventricular type, lacking normal atrial contraction (Lewis 1909).

In documented Western medical history, treatment of AF was first described by William Withering (1741-1799), who gave digitalis leaf to patients with heart failure. He discovered that irregular pulse became more regular and symptoms were relieved when digitalis was administered (Lip and Beevers 1995). With ECG a precise diagnosis of AF was possible and the treatment of patients became more accurate. As early as 1749 it was noticed that cinchona bark had a beneficial effect on irregular pulse, and in the late 1910s cardioversion of AF was performed with quinidine and documented with ECG (Lüderitz 2002b). During the 20th century an overwhelming expansion of medical knowledge has

given us all the other antiarrhythmic drugs to restore and maintain SR and beta blocking agents to control the ventricular rate of AF.

In the 1950s experimental work with defibrillators revealed that cardiac arrhythmias could be stopped with alternating current (AC) countershock (Zoll et al. 1956, Gibson et al. 1956, Lown et al. 1962, Gall and Murgatroyd 2007). This technique was, however, very robust, and the response was unpredictable. Bernard Lown made extensive experiments with defibrillation, and he observed that AC countershocks were associated in ECG with changes of acute myocardial infarction and caused mortality. Furthermore, he noticed that there was a vulnerable period in late systole, and a countershock given during this period caused ventricular arrhythmia. These inconveniences were solved with the implementation of QRS-complex synchronized direct current (DC) cardiac countershock and defibrillator (Lown et al. 1962). The procedure documented by Lown differs very little from that performed today, and the greatest progress since the 1960s has been the invention of the biphasic cardiac defibrillator (Gall and Murgatroyd 2007).

2.2 Epidemiology of atrial fibrillation

2.2.1 Definitions

The nomenclature and classification of AF has previously varied, causing large discrepancy between the studies published. At present, AF has been classified with good clinical relevance and simplicity, and the nomenclature has obtained international consensus (Lévy et al. 2003, Fuster et al. 2006). The currently accepted definition of AF as 1) paroxysmal AF – episodes that last less than or equal to 7 days and are self-terminating, 2) persistent AF – episodes lasting usually more than 7 days and 3) permanent AF – long-lasting episodes where cardioversion has failed or is no longer attempted – was launched in 2001 in the ACC/AHA/ESC guidelines, which were updated in 2006 (Fuster et al. 2006). Most of the earlier studies did not make any distinction between the types of AF, or the type of AF was not documented. Therefore, if the type of AF is not established and published, the prevalence and incidence figures mentioned have to be considered as including all AF. So-called "lone atrial fibrillation" is defined as a status where an AF patient does not have any concomitant cardiovascular disease or diagnosis predisposing to AF (Fuster et al. 2006).

2.2.2 Epidemiology of atrial fibrillation in general population

2.2.2.1 Prevalence of AF in general population

The first publication about the prevalence of AF in general population was written by Ostrander et al. They performed epidemiological investigation in the town of Tecumseh, Michigan, USA, where almost 90% of the total population had a complete medical examination with 12-lead ECG (Ostrander et al. 1965). More than 5,000 adult citizens were evaluated, 22 of whom (0.4%) had AF. They also found that AF was more prevalent among older citizens, and four of the six who had AF and were less than 60 years old had rheumatic heart disease.

The ATRIA study was a large-scale evaluation performed within Kaiser Permanente in Northern California. This health care organisation takes care of nearly 3 million members. The prevalence of AF in population ≥ 20 years old was 0.95%, comprising almost 18,000 AF patients. Among patients older than 55 years, AF appeared to be more common in white (2.2%) than in black (1.5%) patients (Go et al. 2001). Although the population served by the organisation was vast, there were some limitations in this study. First, the health care organisation in question did not cover all the care given in the area, having

some skewness for example in household income compared to Northern California population as a whole. Furthermore, they excluded patients with transient AF and hyperthyroidism. Based on the determined prevalence in the studied population Go et al. estimated that during the cohort assembly period in the late 1990s there were nearly 2.3 million US adults with non-transient AF. Furthermore, they estimated that this number would increase 2.5-fold to more than 5.6 million by the year 2050 because of the increase in the number of elderly persons (Go et al. 2001).

One study in England and Wales and another in Scotland have estimated the prevalence of AF in general practice settings in Great Britain (Majeed et al. 2001, Murphy et al. 2007). These studies also had a very remarkable size of registered populations served by the National Health Service; 1.4 million and 360,000, respectively. The prevalence of AF in England and Wales was 12.1/1,000 in men and 12.7/1,000 in women, the corresponding figures in Scotland being 9.4/1,000 and 7.9/1,000 (Majeed et al. 2001, Murphy et al. 2007).

The main limitation in studies with patients of health care registers is that patients with asymptomatic AF are not included. The question of asymptomatic AF was recently enlightened by Fitzmaurice et al. who documented that screening in order to find all the AF patients could increase the prevalence of AF in general practice environment about 1.6-fold (Fitzmaurice et al. 2007).

The Framingham Heart Study (FHS) is a large-scale follow-up study based on cohorts in Framingham, Massachusetts, USA. The study started in the late 1940s with more than 5,000 adult subjects, and AF has been one of the main topics evaluated over the decades, giving us numerous publications describing the epidemiology of AF (complete biography: www.framinghamheartstudy.org). The main findings of FHS regarding the prevalence of AF have been that AF is seen in 0.5% at age 50-59 years and in up to almost 9% in octogenarians, the prevalence of AF is increasing, and men have an about 1.5-fold greater age-adjusted risk of AF than women (Kannel et al. 1998). Figure 1 shows the prevalence of AF in several epidemiologic studies in general population; the studies are listed in Table 4 in the Appendix.

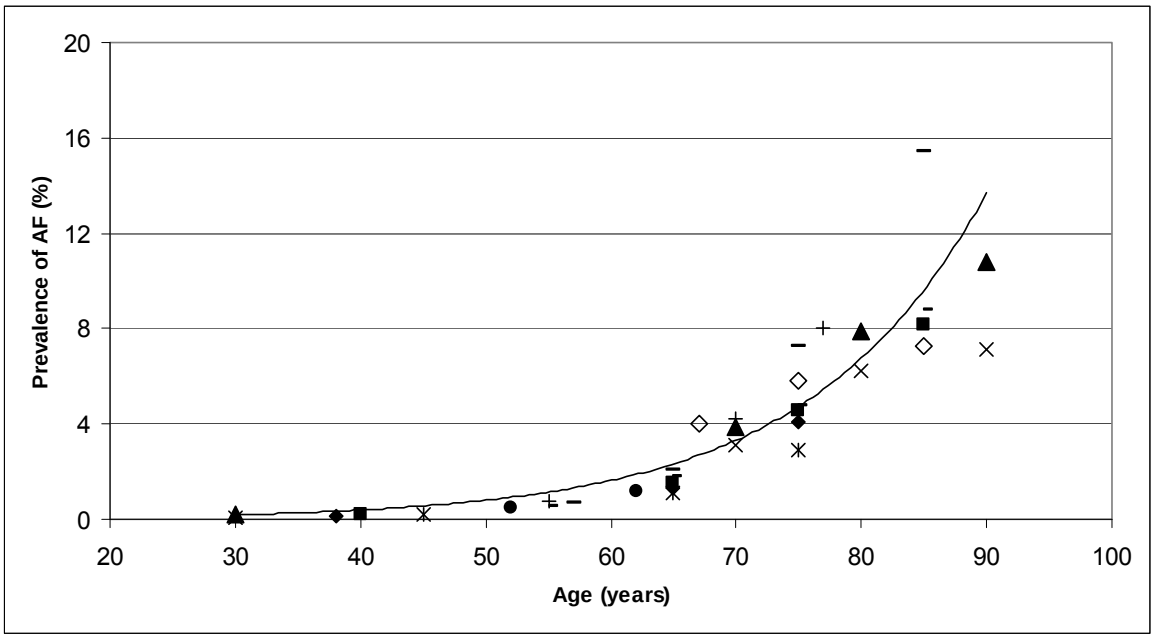

Figure 1. *The prevalence of AF in ten epidemiologic studies in general population. The data of those studies are given in Table 4 in the Appendix. Each study is presented with its own symbol, and the mean trend line is depicted.*

2.2.2.2 Incidence of AF in general population

Many of the studies mentioned in the previous chapter have also had databases to explore the incidence of AF. However, since the incidence of a disease is a time-dependent subject, cross-sectional study design is not valid, and a follow-up of the population studied is needed. Another method to evaluate the incidence of AF is to screen for a "new AF", which is defined as AF not diagnosed earlier in a particular patient.

Cardiovascular Health Study (CHS) studied a population ≥ 65 years old and also had a follow-up aspect. During their average follow-up of 3.3 years the incidence of AF was 19.2 per 1,000 person-years (Psaty et al. 1997). The Mayo Clinic in Rochester, Minnesota serves almost completely the surrounding Olmsted County, and the incidence of AF in that population has risen from 3.0 per 1,000 person-years to 3.7 per 1,000 person-years from 1980 to 2000 (Miyasaka et al. 2006). Based on these results Miyasaka et al. estimated the number of AF patients in the US to be 12 million by 2050, which is more than 2-fold assumed by the ATRIA study investigators, even if the age-adjusted incidence of AF remains stable (Go et al. 2001, Miyasaka et al. 2006).

The European perspective on AF incidence in general health care setting is based on British health care databases. In a Scottish study the incidence of AF was 0.9 per 1,000 person-years in patients older than 45 years (Murphy et al. 2007). Ruigómez et al. had a very large General Practice population of approximately 3 million residents (Ruigómez et al. 2002). They reported the incidence rate of chronic AF to be 1.7 per 1,000 person-years

in residents aged 40-89 years (Ruigómez et al. 2002). However, those studies were cross-sectional, without any follow-up, and therefore they most probably underestimate the real incidence of AF in those populations. For that reason they are not included in Figure 2 but the data are given in Table 5.

The Framingham Heart Study (FHS) has the first and longest history of monitoring a cohort at risk of AF. In 1994 it was published that of the population of about 4,700 citizens older than 55 years, 264 men and 298 women had developed new AF during up to 38 years of follow-up. Hence the incidence of AF during this very long period was 12% (Benjamin et al. 1994). In 2004 they published two reports revealing the increase of AF incidence based on the FHS database. In a paper by Wang et al. AF incidence was 10% during a 13.7-year follow-up time, and another article by Lloyd-Jones et al. demonstrated the lifetime risk of development of AF being 1 in 4 in the Framingham population (Wang et al. 2004, Lloyd-Jones et al. 2004). Figure 2 depicts the incidence of AF in several epidemiologic studies in general population. The studies are listed in Table 5 in the Appendix.

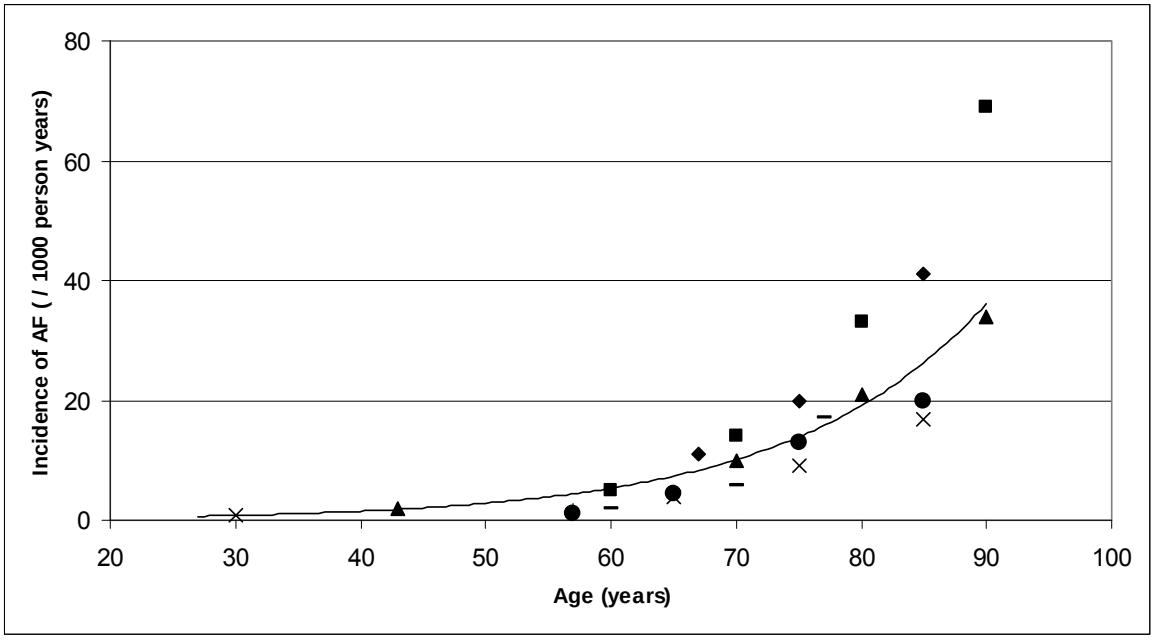

Figure 2. *The incidence of AF in seven epidemiologic studies in general population. The data of those studies are given in Table 5 in the Appendix. Each study is presented with its own symbol, and the mean trend line is depicted.*

2.2.2.3 Epidemiology of paroxysmal, persistent and permanent AF

Based on the Framingham database the prevalence and incidence of chronic and transient AF has been assumed to be of the same order (Kannel et al. 1983). There also seems to be a common pattern of short episodes of AF to lengthen and a tendency of recurrent or paroxysmal AF to become persistent and chronic AF (Kopecky et al. 1987, Lévy et al. 1999, Humphries et al. 2001, Kerr et al. 2005).

The number or percentage of AF patients arriving for elective electrical cardioversion in a population-based study setting has not been documented before. In addition, the rate of progression from paroxysmal to persistent AF has been estimated to be 8.0% at 1 year (Lévy et al. 1999), but there are no published data regarding the progression rate from persistent AF treated with cardioversion to permanent AF.

2.2.2.4 Conditions predisposing to AF in general population

Ostrander et al. already documented higher prevalence of AF in citizens with increasing age and rheumatic heart disease (Ostrander et al. 1965). Practically all of the studies considering the prevalence and incidence of AF have also evaluated the predisposing factors or associated conditions to AF. The spectrum and quantity of predisposing conditions have very large variability in relation to the study period and the population studied. The most striking change in AF patients' profile has been the proportion of patients with rheumatic valvular disease that has nearly disappeared in developed countries (Ostrander et al. 1965, Lévy et al. 1999, Fuster et al. 2006).

At population level, age is the strongest independent risk factor for AF (Greenlee and Vidaillet 2005, Fuster et al. 2006). Quite constantly about 75% of AF patients are reported to be ≥ 65 years old and the mean age of AF patients is approximately 70 years (Go et al. 2001, Majeed et al. 2001, Ruigómez et al. 2002, Fuster et al. 2006, Miyasaka et al. 2006). The odds ratio of the increased risk of AF for age has been estimated to be 1.05-1.11 per year or 2.1-2.2 per decade (Benjamin et al. 1994, Psaty et al. 1997, Stewart et al. 2001, Wilhelmsen et al. 2001, Frost et al. 2005). Increasing atrial fibrosis during aging is maybe the most important reason for the association between aging and AF (Allessie et al. 2002).

Male sex predisposes to AF with an age-adjusted odds ratio of about 1.4-1.8 (Kannel et al. 1998, Stewart et al. 2001, Ruigómez et al. 2002, Miyasaka et al. 2006). However, because of the longer life expectancy in the female population, the number of male and female AF patients is about the same. The reason for the higher propensity to AF in males might be the greater stature and therefore larger atria of men and also their higher alcohol consumption (Greenlee and Vidaillet 2005).

Great stature and especially obesity (BMI ≥ 30) is very strongly associated with increased risk of AF (Ruigómez et al. 2002, Wang et al. 2004, Frost et al. 2005, Dublin et

al. 2006). This is of great importance, bearing in mind the increasing proportion of obese people in Western countries. Miyasaka et al. estimated in their paper that a 60% increase in age- and sex-adjusted risk of AF could be attributed to obesity. If this trend continues the number of AF patients in the United States could be as high as 15.9 million by 2050, accounting for about 3% of the population (Miyasaka et al. 2006). Although a favorable effect of weight loss on P-wave duration and P-wave dispersion has been shown there are no data documenting suppression of AF with weight loss (Duru et al. 2006).

Hypertension is the background diagnosis that is most often associated with AF. With modern, strict criteria the prevalence of hypertension is 44% in European adults and 28% in North American adults (Wolf-Maier et al. 2003). The proportion of AF patients having diagnosed hypertension varies from 25% to 80% and the odds ratio for AF with a diagnosis of hypertension is 1.5 - 1.8 (Benjamin et al. 1998, Lévy et al. 1999, Humphries et al. 2001, Ruigómez et al. 2002, Go et al. 2001, Frost et al. 2005, Miyasaka et al. 2006, Murphy et al. 2007). Atrial remodeling caused by hypertension was determined as a prolongation of P-wave in signal-averaged ECG (SAECG) by Madu et al. and by Aytemir et al. showing that P-wave prolongation – a well-known indicator of the risk of AF – is strongly associated with hypertension. The P-wave duration was also associated with the severity of hypertension (Madu et al. 2001, Aytemir et al. 2005). Since those studies did not include echocardiographic data, it is not known whether the longer P-wave duration in hypertensive patients is a result of the established association between hypertension and left atrial enlargement (Vaziri et al. 1995). Indeed, it has been shown that treatment of hypertension – at least with ACE (angiotensin-converting enzyme) inhibitors – is associated with shortening of P-wave (Zaman et al. 2004).

LVH measured by either echocardiography or ECG is a well-known risk factor of AF (Kannel et al. 1998, Stewart et al. 2001). LVH is both an indicator of stressed left ventricle, most often because of hypertension, and of LV diastolic dysfunction affecting atrial emptying and pressure. In the FHS, LVH in ECG was associated with a 3.0 - 3.8-fold increased risk of AF (Kannel et al. 1998).

Heart failure is both a cause and a consequence of AF, and it is diagnosed in 20-35% of AF patients (Kannel et al. 1998, Go et al. 2001, Ruigómez et al. 2002, Miyasaka et al. 2006, Dagres et al. 2007). There is, however, some disagreement with echocardiographic findings, where AF patients seem to have well-preserved left ventricular (LV) systolic function. For example, in the FHS patients with and without AF had fractional shortenings of 37.1% and 38.6%, respectively (Kannel et al. 1998). In clinical practice it is likely that AF patients – because of older age – have more often diastolic dysfunction, which with high ventricular rate during AF might predispose to symptomatic heart failure without diminished LV systolic function. In the FHS, diagnosed heart failure was associated with a 4.5- and 5.9-fold risk of AF in men and women, respectively (Kannel et al. 1998). Patients with severe heart failure have the highest reported incidence of AF. In a patient group referred for evaluation of heart transplantation new AF was diagnosed in 8.1% of patients during a mean 19 months of follow-up (Pozzoli et al. 1998).

There is no reliable estimation of the proportion of valvular heart disease in AF patients. In the FHS 24.7% of AF patients had mitral annular calcification compared to 11.9% of patients without AF, but in the CHS valvular disease was diagnosed in only 3.8 – 8.0% of AF patients (Psaty et al. 1997, Kannel et al. 1998). At present, valvular heart disease is seldom found as a causative factor for AF in clinical practice in the developed countries (Wilhelmsen et al. 2001, Fuster et al. 2006).

2.2.2.5 Impact of AF in general population

Heart failure has a dual association with AF, being both a cause and a consequence of AF. As mentioned earlier, heart failure is diagnosed in about 20% of AF patients, and in the presence of heart failure, development of AF is highly increased. In the Framingham material the dual roles of AF and heart failure were very convincingly documented, as it was found that in AF subjects the subsequent development of CHF was associated with increased mortality with a hazard ratio of 2.7 in men and 3.1 in women. Correspondingly, in patients with heart failure, development of AF was associated with a hazard ratio of mortality of 1.6 in men and 2.7 in women (Wang 2003). A good rate control has been the key means to avoid heart failure, since the published data have previously not proven any benefit on mortality from interventions to restore and maintain SR in either patients with normal or with depressed LV systolic function (Tuinenburg et al. 1999, Van Gelder et al. 2002, Wyse et al. 2002, Roy et al. 2008). In the recently published ATHENA trial AF patients were treated with a new antiarrhythmic drug, dronedarone, and those randomised to the active drug benefited, with an increased likelihood of SR as well as a decreased number of cardiovascular deaths (Hohnloser et al. 2009). Those results might encourage intentions aimed at restoration and maintenance of SR with newer and safer methods.

The increased risk of stroke in AF patients was first documented in the FHS, being 5.6 times as frequent compared to the cohort without AF, while the risk of stroke in patients with rheumatic heart disease was 17.6-fold (Wolf et al. 1978). In the Mayo Clinic material 1.3% of patients with lone AF had a stroke during a 15-year follow-up, which is similar to expected rates (Kopecky et al. 1987). A recent analysis of the same database revealed that this risk of stroke in lone AF patients continues to be the same as expected up to 25 years, but becomes significantly higher when the follow-up is extended to more than 30 years (Jahangir et al. 2007). On average, the rate of stroke among patients with non-valvular AF and without anticoagulation therapy is 5% per year, which is 2 to 7 times that of a comparable population without AF. The risk of stroke tends to be equal in patients with sustained and paroxysmal AF (Fuster et al. 2006, Hohnloser et al. 2007).

Most studies assessing mortality in an AF population comparable to a population without AF have found an increased risk of all-cause death in AF patients. Mortality is approximately 1.5- to 2-fold with AF, and this excess mortality is seen among cardiovascular causes of death. The impact of AF on the risk of death seems to be stronger

in new AF compared to an old diagnosis of the arrhythmia (Benjamin et al. 1998, Kannel et al. 1998, Lévy et al. 1999, Vidaillet et al. 2002, Fuster et al. 2006).

2.2.3 Epidemiology of atrial fibrillation in acute myocardial infarction

2.2.3.1 Prevalence of AF in AMI patients

The mean age of AMI patients is around 70 years – with risk of AF, in addition to AMI – so the prevalence and incidence of AF is very high (Goldberg et al. 2004). The largest database on acute myocardial infarction (AMI), assessing the frequency and outcome of AF patients is from the Worcester Heart Attack Study. Since 1975, the group has collected a population-based database in Worcester, Massachusetts, USA, of residents who have been hospitalised and discharged with a diagnosis of AMI (Goldberg et al. 1990, Goldberg et al. 2004). In the 1970s and ’80s the proportion of AF patients during hospitalisations due to AMI was 16%, and AF was documented to be present on the first day of hospitalisation in 48% (Goldberg et al. 1990).

The Cooperative Cardiovascular Project (CCP) is a nationwide register in the US including patients with a primary discharge diagnosis of AMI (Rathore et al. 2000). Focusing their analysis on patients ≥ 65 years of age, they found an AF prevalence of 22% in more than 100,000 AMI hospitalisations in the middle of the 1990s (Rathore et al. 2000). Half of the patients were recorded as having AF on their admission ECG performed within 6 hours of arrival. The GRACE register collected data of acute coronary syndromes (ACS) from 14 countries in 1999-2003. From that database it was found that AF was seen during the index hospitalisation in 9% of all ACS cases and in 10% of AMI cases (Budaj et al. 2005). European and Scandinavian viewpoints are provided by the RIKS-HIA register, which includes coronary care units of a large number of Swedish hospitals (Stenestrand et al. 2005). Of the 82,000 AMI patients with first-time admission who were discharged alive between 1995 and 2002 8% had AF on the discharge ECG (Stenestrand et al. 2005).

Another perspective is given by prospective, randomised drug trials. Three large-scale trials evaluating different therapies among patients with ST-elevation AMI (STEMI) have also published the prevalence of AF. The GUSTO-I, GUSTO-III and GISSI-3 trials had AF prevalences at entry of 2.5%, 0.8% and 1.1%, respectively (Crenshaw et al. 1997, Wong et al. 2000, Pizzetti et al. 2001). The TRACE study investigated an ACEi, trandolapril, and the VALIANT study an angiotensin receptor blocker (ARB), valsartan, in treatment of patients with AMI and signs of LV dysfunction (Pedersen et al. 1999a, Køber et al. 2006). In the TRACE database 3.9% and in the VALIANT-trial 2.3% of the patients had had documented and diagnosed pre-existent AF before entry to the study (Pedersen et al. 1999a, Køber et al. 2006). However, in the VALIANT study patients with AF during entry were classified as “current AF” and were not included in this group, underestimating

the prevalence of previous AF (Køber et al. 2006). On the other hand, the total proportion of AF patients (14.7%) was of about the same order as in the TRACE database (21%) (Pedersen et al. 1999a, Køber et al. 2006). DIAMOND-MI is the only trial studying an antiarrhythmic drug in AMI patients with LV dysfunction, and 7.6% had AF at entry (Køber et al. 2000).

Prospective, randomised drug trials studies can be criticised because of selection, and comparisons between the studies are difficult to perform because of different inclusion and exclusion criteria. On the other hand, the data provided by drug studies are in principle more exact compared to register studies, and when the AF data are documented, the numbers of previous AF as well as newly developed AF are mainly presented.

2.2.3.2 Incidence of AF in AMI patients

Most AMI studies only have information about the proportion of AF patients during the study period. There are, however, some studies that differentiate between AF as a pre-existing property or a condition that has developed during or after AMI. In the Worcester Heart Attack Study and CCP registry the amount of new AF could be estimated from the proportion of patients, who had not had AF at the first hospital recording. From 1975 to 1986 in Worcester, 8.3% of patients with AMI developed new AF during the hospitalisation, about 40% developed AF within three days after admission, and 60% developed AF thereafter (Goldberg et al. 1990). In the CCP registry in patients ≥ 65 years old 11.3% of patients developed AF during AMI hospitalisation (Rathore et al. 2000).

Clinical drug trials have perhaps the most precise analysis of cardiovascular events occurring in the populations studied. In the GUSTO-I and GISSI-3 trials of patients with STEMI, 7.9% and 7.8% developed AF during hospitalisation, respectively (Crenshaw et al. 1997, Pizzetti et al. 2001). Pizzetti et al. also reported a significant 24% reduction in the incidence of AF in patients randomised to lisinopril + nitrates compared to the placebo-allocated group (Pizzetti et al. 2001). In the GUSTO-III trial a new AF during hospitalisation or within 30 days of enrolment was documented in 6.5% of patients (Wong et al. 2000).

AMI-trials evaluating patients with signs of LV dysfunction have the highest proportion of patients with new AF. In the TRACE database the percentage of a new AF was 17.1% during hospitalisation (Pedersen et al. 1999a). In the main TRACE trial, of those who had SR at baseline 2.8% allocated to trandolapril and 5.3% allocated to placebo developed AF during the up to 4-year follow-up; p-value < 0.01. This was the first study to demonstrate that blocking the renin-angiotensin-aldosterone system (RAAS) reduces significantly the incidence of AF (Pedersen et al. 1999b). In the DIAMOND-MI study long-term treatment with dofetilide was determined on mortality and morbidity in survivors of AMI and LV dysfunction (Køber et al. 2000). Among patients with SR at baseline who were assigned to dofetilide the incidence of AF by 12 months was 0.7%,

compared to 2.0% in the placebo group, but this difference was non-significant (Køber et al. 2000).

2.2.3.3 Conditions predisposing to AF in AMI

As in the general population, age is the strongest predictor for AF in AMI patients as well. In the Worcester Heart Attack Study the mean age of AMI patients with AF was 73.0 years, compared to 65.5 years in patients without AF (Goldberg et al. 1990). Based on the same material, the mean age of patients hospitalised with AMI is continuously increasing, emphasising the role of AF in this population (Goldberg et al. 2002, Goldberg et al. 2004). The finding of AF patients being older among AMI populations has been repeated in all analyses of this kind; OR for having AF for a one-year increase of age is about 1.06 and OR for age more than 70 years is about 2.8 (Pizzetti et al. 2001, Kinjo et al. 2003). Although female gender seems to be associated with higher frequency of AF during AMI, this is most probably the result of female AMI patients being also significantly older than men (Goldberg et al. 1990, Wong et al. 2000, Goldberg et al. 2002).

More severe clinical status during AMI reflects hemodynamic load and is associated with higher occurrence of AF. Both higher systolic and diastolic blood pressure at baseline as well as higher heart rate have increased the risk of AF (Crenshaw et al. 1997, Wong et al. 2000, Pizzetti et al. 2001, Køber et al. 2006). Severity of the clinical status and association with AF have been observed in the presence of congestive heart failure, higher Killip class, cardiogenic shock, anterior MI location and Q-wave AMI and ventricular arrhythmias (Goldberg et al. 1990, Behar et al. 1992, Crenshaw et al. 1997, Eldar et al. 1998, Rathore et al. 2000, Pizzetti et al. 2001, Goldberg et al. 2002, Kinjo et al. 2003, Køber et al. 2006). The amount of myocardial necrosis assessed as higher a amount of myocardial enzymes or lower LV ejection fraction have also been associated with increased the risk of AF (Behar et al. 1992, Crenshaw et al. 1997, Pedersen et al. 1999a, Køber et al. 2006). As a sign of atrial electrical remodeling or electrical predisposition to AF, P-wave duration measured with SAECG in a very early period of AMI was a useful tool in predicting the development of AF (Rosiak et al. 2003).

2.2.3.4 Impact of AF on morbidity and mortality in AMI

Since AF is associated with various baseline diagnoses and signs of more severe cardiovascular state, the independent prognostic significance of AF is not straightforward. In addition, in most analyses the impact of AF has been dissimilar when patients with a pre-existing AF and patients with a newly developed AF have been compared. Therefore, this kind of analysis has to be performed separately in patient groups comparing patients with “old AF”, “new AF” and “no-AF”, regardless of the determination of these different groups in a single study.

In the Worcester Heart Attack Study "early AF" had a non-adjusted hazard ratio (HR) of 1.66 for total mortality, but in multivariate analysis only a non-significant trend with risk of 1.04 HR was reported (Goldberg et al. 1990). On the other hand, in the CCP and in the TRACE, GUSTO-III and VALIANT trials previous AF was associated with higher mortality rate (Pedersen et al. 1999a, Rathore et al. 2000, Wong et al. 2002, Køber et al. 2006). An interesting finding is that pre-existent AF seems to increase long-term mortality with no association with in-hospital mortality (Pedersen et al. 1999a, Rathore et al. 2000, Wong et al. 2002). A history of chronic AF decreased the survival rate, while patients with paroxysmal AF had the same survival rate as patients without AF (Wong et al. 2002).

Compared to pre-existent AF, the impact of newly developed AF on the risk of death is much more widely recognised, and the HRs with new AF have been higher. The adjusted hazard ratios for death in AMI patients who develop AF has been estimated to be from 1.3 to 3.0, including both in-hospital and long-term mortality (Sakata et al. 1997, Rathore et al. 2000, Pizzetti et al. 2001). Sakata et al. also analysed separately patients who developed AF within 24 hours of onset of AMI and patients who developed AF later during the hospitalisation. Compared to the patients without AF, adjusted OR for death for early AF was 2.5 and that for later AF 3.7 (Sakata et al. 1997).

Besides the prognosis, AF is associated with a more unfortunate course of AMI, stroke being the most worrying complication. In general AMI populations, the CCP, Worcester Heart Attack Study and the GRACE registry have recorded a higher rate of stroke in AF patients. For example, in the GRACE registry AF had an adjusted OR of 2.5 for in-hospital stroke (Rathore et al. 2000, Spencer et al. 2003, Budaj et al. 2005). In the Worcester Heart Attack Study 32% of the patients with AMI and stroke had AF, compared to 15% of AF in the patients without stroke (Spencer et al. 2003). The risk of stroke in clinical trials has been estimated to be about two-fold compared to the patients without AF (Crenshaw et al. 1997, Wong et al. 2000, Køber et al. 2006).

AF is a very common arrhythmia seen during AMI. The clear relationship between AF and poorer outcome can be explained by diminished cardiac output and higher rate of congestive heart failure, and the risk of stroke by the absence of atrial systole during the arrhythmia. AF is not only a risk for complications but also a strong marker of more advanced cardiovascular disease, and the relations between AF and different endpoints have been extensively examined. However, there have been no analyses where AF has been included as a time-dependent co-variate to allow a logical demonstration of a temporal relationship between AF and the clinical outcome.

2.3 Atrial remodeling

2.3.1 Concept of atrial remodeling

It is important to understand the term "wavelength" in AF. During systole electrical activity passes over the cardiac myocardium as an electrical wavelet, but in AF there are many of those wavelets causing rapid irregular electrical activity in the atria. To put it simply, wavelength (λ) is the distance between repeating units of propagating waves of a given frequency, and can be interpreted as the result of the conduction velocity divided by the frequency (λ = CV / F); or the velocity multiplied with the effective refractory period (ERP) (λ = CV x ERP). In practice, three components of atrial properties are involved in and contribute to the stability of AF: conduction velocity, effective refractory period and atrial size (Allessie et al. 2002, Nattel 2002). When the wavelength is short, it allows more re-entering wavelets to exist in the available surface of the atria, and vice versa: if the available surface area of the atria is large, there is room for more wavelets. Slowed conduction velocity and shortened ERP – and hence decreased wavelength – allows wavelets to propagate with shorter distance from each other (Allessie et al. 2002, Nattel 2002). Therefore, in order to stabilise AF at least one of these is needed: atrial enlargement, shortening of ERP or a decrease of conduction velocity. This theory has been proven in both computer models and animal, in addition to human experiments (Moe and Abildskov 1959, Moe et al. 1964, Cox et al. 1991).

AF is very uncommon during the first decades after birth but extremely common in the elderly. If AF is diagnosed in an adolescent, most often some kind of hereditary syndrome – such as Brugada syndrome or hereditary cardiomyopathy – is diagnosed (Junttila et al. 2004, Pethig et al. 2005), and when AF develops in advanced age, the heart and the atria have for decades been exposed to hypertension, for example. When a cohort of new AF patients is examined there is always a high probability of previous asymptomatic AF episodes and therefore atrial remodeling caused by AF itself (Frykman et al. 2001, Israel et al. 2004). There is nevertheless evidence that AF patients might have some dissimilarity, especially in atrial electrical properties predisposing to AF. A Belgian cohort of subjects (2,200 patients, age > 40 years) in SR at baseline was re-evaluated after more than 10 years. The 10-year incidence of AF was 4.38 per 1,000 person years, and longer and notched or deflected P-waves at baseline were independent risk markers for development of AF (De Bacquer et al. 2007). However, AF patients also had significantly more often hypertension and "ischemic ECG changes", possibly reflecting LV strain, and thus the development of AF as well as the P-wave differences might have been the product of hypertension – a widely accepted risk for AF.

In this concept atrial remodeling is considered as any change – temporary or persistent – in appearance, layout, or properties of the atria occurring because of a heart disease (cardiovascular remodeling), or because of atrial tachycardia or AF (AF remodeling). The third "mechanism" that alters the atrial myocardium and causes atrial remodeling by increasing atrial fibrosis – aging – is not considered in this context. Atrial remodeling is a multifactorial phenomenon, and its mechanisms and elements are overlapping. Atrial remodeling is discussed separately as electrical, functional (contractile) and structural remodeling (Allessie et al. 2002).

2.3.2 Where does remodeling come from?

The principal mechanisms for atrial remodeling are atrial tachycardia and atrial stretch (Savelieva and Camm 2004). Experimental atrial tachypacing and congestive heart failure (CHF) are the two principal investigational models; recently also hypertension models have been introduced to evaluate the associations between an extra-atrial disease and AF (Allessie et al. 2002, Choisy et al. 2007, Nattel et al. 2008).

It has for a long time been observed that patients with paroxysmal AF have a tendency to develop persistent AF, and that restoration and maintenance of SR depends on the duration of AF (Viko et al. 1923, Parkinson and Campbell 1929, Bjerkelund and Orning 1968, Kopecky et al. 1987). These findings suggest that AF is a self-perpetuating phenomenon. In 1995 two separate groups established the association between atrial tachycardia and changes – remodeling – in the atria predisposing to AF. In a canine model with continuous rapid atrial pacing (RAP) (6 weeks, 400 bpm), shortening of ERP and atrial fibrillation cycle length (AFCL) plus increased inducibility of AF was observed (Morillo et al. 1995). These results were confirmed by Wijffels et al. in an ovine model with artificially maintained AF (Wijffels et al. 1995). In addition to these electrophysiological changes, Morillo et al. also found a marked increase in atrial volume as well as an increase in the number and size of the mitochondria documented by electron microscopy (Morillo et al. 1995). Wijffels et al. also found that the normal physiological rate adaptation of the refractory period (longer ERP at slower heart rate) was either attenuated or even reversed (Wijffels et al. 1995). It has to be noted that ventricular rate was not controlled in either of these studies, and there might also have been CHF-induced atrial remodeling due to long-lasting high ventricular rate. Soon after these animal experiments atrial electrical remodeling with induced AF and also in AF patients after electrical CV was documented in man (Daoud et al. 1996, Pandozi et al. 1998).

The clinical evidence of an association between CHF, hypertension and AF is vast (Benjamin et al. 1994, Kannel et al. 1998, Healey and Connolly 2003, Savelieva and Camm 2004, Fuster et al. 2006). Despite this clear clinical implication, the mechanisms of these associations have just recently been enlightened. The first CHF model experiment was performed by Professor Nattel's group in Canada. They had three groups of dogs: one as a sham group, one group with dogs with ventricular tachypacing and CHF, and a third

group with RAP with AV-node ablation (Li et al. 1999). Both tachypaced groups developed a significantly longer duration of induced AF, but CHF dogs also had markedly increased LV mass and atrial fibrosis compared to the RAP group. In electrophysiological measurements RAP dogs had decreased ERP, wavelength and AF current length, while all these variables were unchanged in CHF dogs. As a result of fibrotic atria, CHF dogs had higher heterogeneity of conduction and areas of slow conduction in atrial tissue (Li et al. 1999). In a study on human subjects, Sanders et al. had a group of patients with documented CHF during electrophysiological procedure. They established not an unchanged, but even a lengthened ERP, and like Li et al., impaired atrial conduction and increased inducibility of AF – even in the absence of prior AF (Sanders et al. 2003a). The same remodeling changes (slowed conduction, increase in the electrical heterogeneity and atrial collagen content plus tendency to AF) were noted by Kistler et al. in an ovine hypertension model (Kistler et al. 2006). The main mechanism for atrial remodeling in all of these studies is assumed to be atrial stretch (Li et al. 1999, Sanders et al. 2003a, Kistler et al. 2006, Kirchhof and Schotten 2006).

2.3.3 Electrical atrial remodeling

In AF atrial cells are very rapidly overloaded with Ca^{2+}-ions that are cytotoxic (Nattel et al. 2008). This deleterious phenomenon is attenuated by reduced Ca^{2+} influx via functional inactivation of L-type Ca-channels (I_{CaL}) during phase 2 of action potential, but this also causes a marked decrease in atrial action potential duration (APD). When tachycardia is prolonged Ca-channel protein formation is downregulated, and also protein dephosphorylation and breakdown take place, proceeding with the process of Ca^{2+} influx reduction (Nattel et al. 2008). Of the outward potassium channels I_{to} is also downregulated during the first hours of tachycardia. Downregulation of I_{to} is seen especially in patients with chronic AF, but the functional importance of this is unclear (Van Wagoner 2003, Nattel et al. 2007). The results regarding other outward potassium channels are conflicting, but it seems that atrial-specific I_{Kur} is reduced in human chronic AF (Van Wagoner 2003, Nattel et al. 2007).

AF patients without structural heart disease have atypical P-waves in standard 12-lead ECG (Robitaille and Phillips 1967). Lengthening of the P-wave has thereafter been measured and confirmed from body surface with standard 12-lead ECG, SAECG and MCG in numerous studies (Fukunami et al. 1991, Guidera and Steinberg 1993, Dilaveris et al. 1998, Winklmaier et al. 1998, Darbar et al. 2002). However, APD shortening does not cause the prolongation of the P-wave, and there have to be some other mechanisms. There is controversy about the modulation of I_{Na}, the major contributor of phase 0 of action potential, but it seems that the activation of I_{Na} is reduced, at least in man, in chronic AF, thus slowing atrial conduction (Van Wagoner 2004, Nattel et al. 2007). Redistribution or functional or quantitative changes of connexins – proteins that promote activation from cell to cell – could be the other tachycardia-related alteration explaining abnormal and deteriorated conduction, but further studies are needed for clarification of

the role of connexins in electrical remodeling (Nattel et al. 2007, Duffy and Wit 2008). Longer RAP was needed to develop reduced conduction velocity and increased heterogeneity than ERP shortening. However, ventricular rate was not controlled in this canine model either, and the impact of the development of CHF cannot be excluded (Gaspo et al. 1997). The slowed as well as distorted intra- and interatrial conduction has also been observed in AF patients (Xia et al. 2004).

CHF and hypertension have a very different effect on atrial electrophysiology compared to RAP or AF (Li et al. 1999). The reduced activity of reporalisating outward potassium channels is the main alteration in ion-channel function that is associated with prolonged repolarisation and increased APD (Nattel et al. 2007). Contrary to RAP or AF, CHF therefore induces prolonged ERP that is recognized in both animal experiments and in man (Shinagawa et al. 2002a, Sanders et al. 2003a). Shinagawa et al. also presented that shortening of lengthened ERP could be induced in CHF dogs with RAP (Shinagawa et al. 2002a). Other arrhythmia-predisposing electrophysiological changes in CHF are increased Na^{+}-Ca^{2+}-exchanger (NCX) activity increasing spontaneous activity and changes in connexin function contributing to slowed conduction (Nattel et al. 2007). Prolongation of P-wave in CHF has been documented both in animal experiments and in patients with CHF (Sanders et al. 2003a, Sakabe et al. 2004).

In hypertension models, atrial electrical remodeling has been similar to the CHF models. In a hypertensive rat model and in the already mentioned hypertensive ovine model atrial ERP was not changed, but atrial tachycardia was more susceptible (Kistler et al. 2006, Choisy et al. 2007). Hypertensive sheep also had significantly reduced conduction velocity in the atria compared to the control animals (Kistler et al. 2006).

2.3.4 Functional atrial remodeling

Heart muscle cell contraction is started via Ca^{2+} influx and promoted by Ca^{2+} release from the intracellular sarcoplasmic reticulum. Calcium overload and downregulation of I_{CaL} is the major ion channel alteration and origin of electrical remodeling that also causes tachycardia-induced contractile dysfunction (Allessie et al. 2002). Therefore it can be said that not only does “AF beget AF” but also “remodeling begets remodeling”. In experimental models, even five minutes of AF decreased atrial contractility by 55%, and five days of AF abolished atrial contractility nearly completely (Schotten et al. 2003). The vital role of Ca^{2+} and I_{CaL} was also shown when selective blocking of I_{CaL} almost completely preserved atrial contractility (Schotten et al. 2003). CHF had a more marked contribution to atrial function compared to RAP in a dog AF model (Shi et al. 2001). The diminished atrial function in AF patients has been known for decades; more recently it has also been documented with echocardiography (Logan et al. 1965, Manning et al. 1989).

Reduced atrial pump function increases blood volume in the atria, causes atrial pressure elevation and leads to atrial dilatation (White et al. 1982). Not only is atrial

contraction disturbed, but also atrial relaxation is distorted in AF (White et al. 1982, Abhayaratna et al. 2006). An important finding linking atrial functional depression (and raised atrial pressure) with atrial electrophysiology has been that both CHF and increased intra-atrial pressure increase spontaneous electrical activity from pulmonary veins (Fenelon et al. 2003, Kalifa et al. 2003).

2.3.5 Structural atrial remodeling

AF decreases atrial pump function, but AF also acutely decreases atrial distensibility, with only a small increase (about 10%) in atrial diameter (White et al. 1982). This leads to a rapid increase of atrial pressure and distension, and because of the thin muscular layer of the atria, the atria become enlarged after a while (White et al. 1982, Morillo et al. 1995). Indeed, it has been documented that left atrial dimensions increase over time in AF patients without any heart diseases; and both RAP and CHF increase atrial dimensions, but in the CHF model atrial enlargement has been more outstanding compared to the atrial tachypacing model (Sanfilippo et al. 1990, Shi et al. 2001).

Microscopic structural remodeling because of tachycardia is detected as swollen myocardial cells, accumulation of glycogen, myolysis, mitochondrial enlargement and changes in the shape and fragmentation of the sarcoplasmic reticulum (Morillo et al. 1995, Ausma et al. 1997, Schotten et al. 2001, Allessie et al. 2002). In lone AF patients increased collagen deposition has been documented in atrial tissue specimens, and AF patients with mitral valve disease had more marked collagen expression compared to AF patients without this valve disease (Frustaci et al. 1997, Boldt et al. 2004). However, it seems that the causal association between tachycardia and atrial fibrosis is not very clear, and in animal models increased fibrosis has not been documented with even up to 20 weeks of tachycardia (Ausma et al. 1997, Li et al. 1999, Ausma et al. 2001, Burstein and Nattel 2008). These animal models may have been too short in duration, because there is nevertheless an association between tachycardia and upregulation of fibroblast function (Burstein et al. 2007). The mechanisms of irreversible changes leading to atrial cell death and cellular apoptosis also seem to be dependent on stretch, because the tachycardia models have not induced apoptosis, which is seen in the atria of older patients and/or patients with associated heart diseases (Dispersyn et al. 1999, Allessie et al. 2002).

Atrial tissue specimens of AF patients have constantly revealed atrial fibrosis that is more pronounced with structural heart diseases (Frustaci et al. 1997, Boldt et al. 2004). Compared to the animal models, AF has often been long-standing before a biopsy in AF patients, predisposing the atria to both long-standing tachycardia and increased atrial pressure. An unequivocal difference exists when animal CHF models and tachycardia models are compared regarding fibrous formation. Li et al. clearly demonstrated “atrial remodeling of a different sort” having both CHF and tachycardia models in an experiment where CHF strongly promoted fibrosis that was not seen in atrial tachycardia model dogs (Li et al. 1999). The main mediators behind atrial fibrosis are increased activation of

angiotensin-II (Ang-II) and transforming growth factor-β_1 (TGF-β_1) that are activated within hours; increased atrial fibrosis is already detectable 24 hours after the onset of ventricular tachypacing (Cardin et al. 2003, Hanna et al. 2004, Burstein and Nattel 2008, Nattel et al. 2008). Atrial fibrosis is prominent in CHF models, and substantially more fibrosis as well as higher Ang-II concentrations are seen in the atria than in the ventricles during ventricular tachypacing (Li et al. 1999, Cardin et al. 2003, Hanna et al. 2004).

In hypertension animal models increased atrial fibrosis is the most striking finding, corresponding to structural remodeling seen in the CHF models, and it is observed in hypertensive rats already at 3 months of age (Kistler et al. 2006, Choisy et al. 2007). Left atrial dimension has also been increased in hypertensive animals (Kistler et al. 2006).

Fibrosis causes conduction block areas in the atria that are a source of spatial heterogeneity in atrial conduction, making re-entrant circuits possible (Allessie et al. 2002, Nattel 2002, Burstein and Nattel 2008). By decreasing atrial conduction velocity fibrosis shortens the wavelength and increases the perpetuation of AF. Diminishment of atrial pump function is enhanced by myolysis and fibrous formation, and thus it could again be said that "remodeling is causing remodeling" (Allessie et al. 2002, Burstein and Nattel 2008). The associations between different forms of atrial remodeling and AF are proposed in Figure 3.

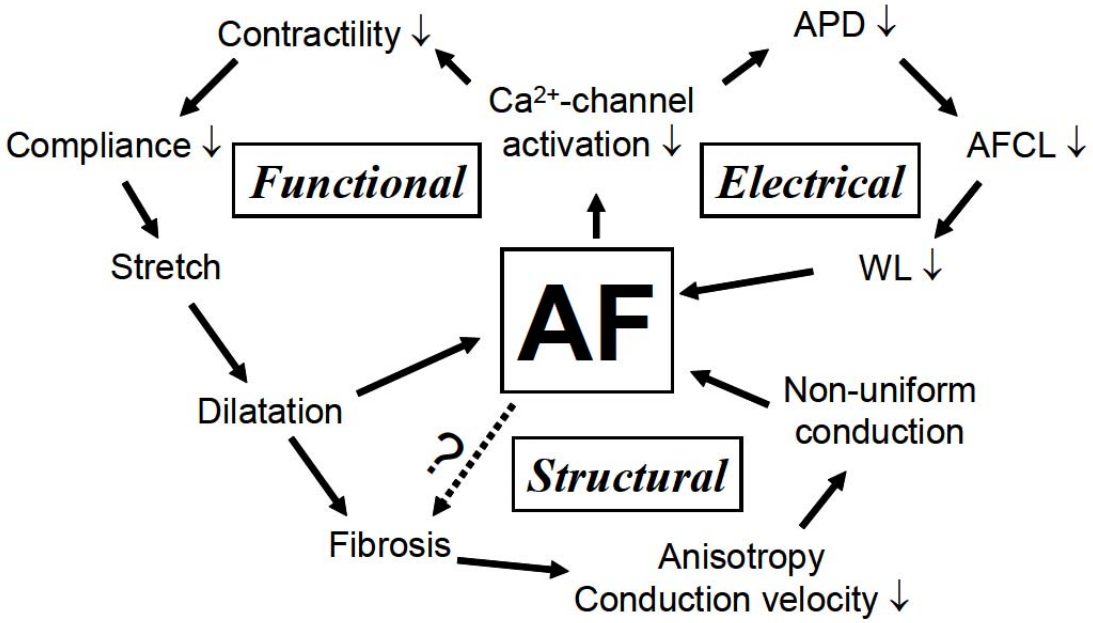

Figure 3. *Vicious circles of atrial electrical, functional and structural remodeling and their relations to atrial fibrillation.*
APD, action potential duration; AFCL, atrial fibrillation cycle length; WL, wavelength.

2.3.6 Reverse atrial remodeling

Atrial remodeling is a self-perpetuating event making AF more susceptible and more persistent; "AF begets AF". Fortunately the atria have a spontaneous tendency to cease the fibrillating arrhythmia, at least when arrhythmia is of short duration, and most often AF can be stopped and SR restored with electrical or pharmacological cardioversion. Reverse remodeling during SR is essential for the atria to avoid new episodes of AF.

Logan et al. not only documented functional remodeling, but they also recognised reversal of atrial function (Logan et al. 1965). They showed that a patient who had had AF for 8 weeks had no evidence of atrial contraction immediately after electrical cardioversion, but developed a detectable atrial a-wave twenty minutes later in cardiac catheterisation (Logan et al. 1965). Manning et al. documented with echocardiography that recovery of left atrial mechanical function may take up to three months, and in their extended study they found that the time course of recovery is related to the duration of AF before cardioversion (Manning et al. 1989, Manning et al. 1994). In fact, atrial mechanical function is even diminished immediately after cardioversion of persistent AF compared to the time before cardioversion, and thrombus formation in appendices may be enhanced during the first days after cardioversion (Grimm et al. 1993, Khan 2003, Sanders et al. 2003b).

Reversal of atrial electrical remodeling was already documented by Wijffels et al. in their classical work (Wijffels et al. 1995). In goats that had maintained AF 2 to 4 weeks, they noticed that ERP shortening, AF interval and length of induced AF episodes started to normalise after 6 hours of SR, and were improved at 24 hours, but complete reversal was not seen until one week after SR had been restored (Wijffels et al. 1995). In man, Daoud et al. found a significant shortening of atrial ERP during a mean of 7 minutes of pacing-induced AF (Daoud et al. 1996). ERP started to recover immediately when SR was restored and was entirely recovered in 8 minutes. They also found – implicating reverse atrial electrical remodeling – that the subsequent episodes of AF shortened as the elapsed time after conversion of AF was increased (Daoud et al. 1996). After cardioversion AF patients had significantly shorter ERP and prolonged atrial conduction time. After the four days of follow-up ERP was increased to similar level as in the control group, but atrial conduction times remained longer (Yu et al. 1999). Manios et al. had an electrophysiological study with similar findings as Yu et al., but they had a longer (one month vs. four days) follow-up time (Manios et al. 2000). They showed that prolongation of P-wave exhibited slower resolution, being normal not until one month after conversion to SR, implicating the same slower improvement in conduction times as documented by Yu et al. (Manios et al. 2000). The shortening of P-wave during SR after cardioversion is well established both with 12-lead ECG and SAECG, and patients with longer duration of AF before cardioversion had significantly smaller shortening of P-wave (Nishino et al. 2000, Sato et al. 2001, Chalfoun et al. 2007). Nishino et al. documented P-wave shortening in up to 6 months of follow-up (Nishino et al. 2000).

After conversion to sinus rhythm the atria have a propensity to get smaller, and this is well established in both man and animal experiments (Manning et al. 1994, Mattioli et al. 2000, Shinagawa et al. 2002b, Cha et al. 2004). There are no human data regarding microscopically assessed reverse atrial structural remodeling. Ausma et al. documented structural remodeling (myolysis) 4 months after restored SR in goats that had maintained AF for 4 months before a CV (Ausma et al. 2003). In a dog CHF model one month after cessation of tachypacing structural remodeling – assessed as atrial fibrosis – did not show a return toward control values (Cha et al. 2004). This is most probably the reason for the higher susceptibility of AF that is seen after a reasonable duration after CV of long-lasting AF, despite full hemodynamic and electrophysiological recovery (Allessie et al. 2002, Cha et al. 2004).

2.3.7 Atrial remodeling in acute myocardial infarction

In acute myocardial infarction the atria are confronted with increased sympathetic activity, atrial stretch and pressure, and possibly direct ischemia as well. Increased sympathetic activity predisposes to both atrial and ventricular arrhythmias, hence depressing normal cardiac function and increasing chamber pressures (Chen et al. 2004, Nattel et al. 2007). Furthermore, increased stretch and pressure cause atrial electrical, functional and structural remodeling, as observed (Chen et al. 2004, Nattel et al. 2007).

Direct myocardial ischemia decreases delayed-rectifier potassium currents (I_{Kr} and I_{Ks}), I_{CaL} as well as I_{Na} and resting potential (Nattel and Carlsson 2006, Nattel et al. 2007). As a consequence of these alterations, the myocardium is predisposed to increased spontaneous activation and slowed conduction (Nattel and Carlsson 2006, Nattel et al. 2007). These results are, however, from models where ventricular heart tissue was examined, and thus might not be completely applicable in atrial tissue. Direct ischemia of the sinus node may cause bradycardia, enhancing the possibility of spontaneous arrhythmias as well as AF (Sakata et al. 1997). Later on, during the course of AMI, both atrial scarring because of atrial infarction and especially left ventricular dysfunction that develops may cause atrial remodeling resembling the stretch-induced, CHF-associated remodeling predisposing to AF (Nattel et al. 2007).

2.3.8 What happens in the atria during AF? Remodeling in real life

At the beginning of tachycardia atrial cells are overloaded with Ca^{2+}-ions. This is associated with a short-lasting increase in atrial contractility measured after 20 seconds of atrial tachypacing (Schotten et al. 2003). However, after five minutes of tachypacing atrial contractility is markedly decreased, and after five days of AF atrial contractility has nearly disappeared, atrial functional remodeling being complete (Schotten et al. 2003). In man, 10 - 15 minutes of AF was not enough to decrease left atrial appendage emptying velocity, but was associated with spontaneous echo contrast formation in 58% of patients (Sparks et

al. 1999). In addition, 14% of patients with AF symptoms for less than three days had a left atrial appendage thrombus, indicating that atrial function is early disturbed during AF (Stoddard et al. 1995). Decreased contractility causes increased atrial pressure and dilatation seen already three days after initiation of AF (White et al. 1982, Schotten et al. 2004).

Atrial electrical remodeling also starts very rapidly, but it seems that 30 seconds is not enough for electrical remodeling in man (Vardas et al. 2001). However, shortening of APD and ERP is measurable within less than 10 minutes when subjected to AF (Daoud et al. 1996, Yu et al. 1998). Shortening and loss of rate dependence of APD is complete during the first days of AF, but it takes an additional 1 - 2 weeks until AF becomes persistent, and secondary remodeling mechanisms are needed for this evolution (Wijffels et al. 1997, Goette et al. 1996, Allessie et al. 2002, Kumagai et al. 2003).

When AF lasts for a week atrial changes resembling embryonic development (re-expression of fetal proteins) are initiated (Ausma et al. 2001, Allessie et al. 2002). Cell swelling and myolysis are also noted, and these are complete in about 8 weeks (Ausma et al. 2001, Allessie et al. 2002). Despite the clearly evident myolysis and cell death increased atrial fibrosis is not detectable even after four months in AF models, yet practically all human studies have revealed increased atrial fibrosis in AF patients (Frustaci et al. 1997, Ausma et al. 2001, Allessie et al. 2002, Boldt et al. 2004, Burstein and Nattel 2008). As noted, atrial tachycardia promotes increased fibroblast function in a cell experiment, but it is not known whether a longer duration of AF might also amplify fibrous formation in man (Burstein et al. 2007). However, in clinical practice approximately 70% of individuals with AF are between 65 and 85 years of age, and about 90% of AF patients have a cardiovascular background diagnosis, most often hypertension (Furberg et al. 1994, Feinberg et al. 1995). Therefore, in real life most AF patients have a substrate for AF equal to that seen in CHF or hypertension models, predisposing to AF, and AF-promoted remodeling seen thereafter (Anyukhovsky et al. 2005, Kistler et al. 2004, Kistler et al. 2006).

2.4 The renin-angiotensin-aldosterone system and AF

2.4.1 RAA system and atria

The renin-angiotensin-aldosterone system (RAAS) has a pivotal role in the regulation of cardiovascular function (Felmeden and Lip 2000, Colucci and Braunwald 2005, Schmieder et al. 2007). Figure 4 shows a simplified overview of the RAAS cascade. The main effect of RAAS is mediated by the active endproduct angiotensin II (AngII) via specific cell surface proteins, angiotensin II-receptors, and by direct stimulation of AngII for aldosterone excretion from the adrenal cortex (Colucci and Braunwald 2005, Schmieder et al. 2007). Activation of AngII type 1 receptors (AT1) by AngII causes vasoconstriction, endorses cell proliferation of fibroblasts, causes myocardial hypertrophy, increases sympathetic nerve activity and promotes inflammation (Felmeden and Lip 2000, Boos and Lip 2005, Colucci and Braunwald 2005, Schmieder et al. 2007). Activation of AngII type 2 receptors (AT2) has antagonism on the effects of AT1, causing for example vasodilatation and having antiproliferative effects on fibroblasts (Felmeden and Lip 2000, Schmieder et al. 2007). With a particular emphasis on atria, AngII via AT1 shortens atrial action potential, induces after-depolarisations in pulmonary vein tissue, promotes apoptosis and cell death and causes marked atrial dilation with increased focal fibrosis (Boos and Lip 2005, Chen et al. 2006, Zankov et al. 2006, Burstein and Nattel 2008). RAAS is activated in congestive heart failure and by increased sympathetic activity (Colucci et al. 2005). RAAS is also activated by AF itself; AF increases ACE and AngII in atrial tissue, and thereby RAAS and AF act like a self-perpetuating vicious circle (Willems et al. 2001, Boldt et al. 2003, Goette et al. 2004, Hanna et al. 2004).

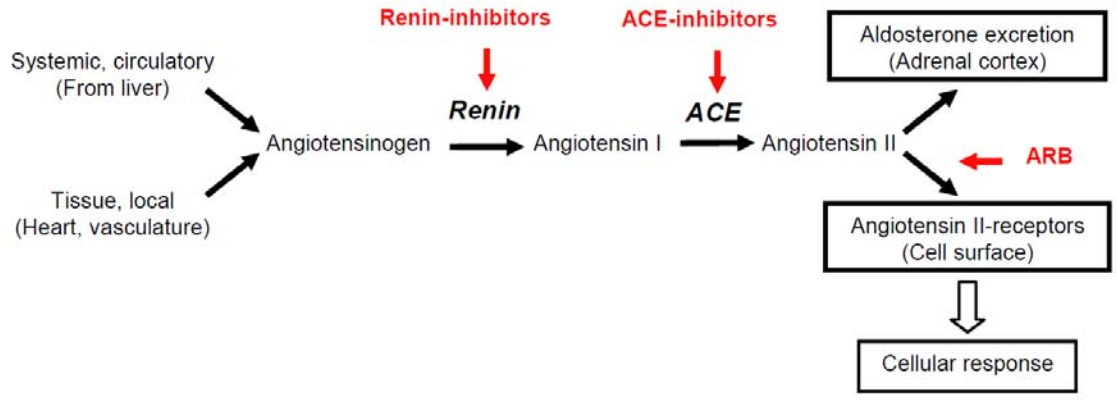

Figure 4. *Renin-angiotensin-aldosterone system. The main regulators of the system are shown in **black**, and the medications that suppress the system are shown in **red**.*
ACE – angiotensin converting enzyme, AT1 – Angiotensin II type 1-receptor, ARB – angiotensin receptor blocker.

2.4.2 Suppression of the RAA system and AF – experimental data

2.4.2.1 Animal studies

In a canine model Nakashima et al. observed a significant shortening of atrial ERP 30 minutes after commencing of atrial tachypacing maintained for 180 minutes. After cessation of pacing the changes were corrected in 10 minutes (Nakashima et al. 2000). Infusion of AngII significantly accentuated the ERP shortening. When the animals got an infusion of either an angiotensin receptor blocker (ARB), candesartan, or an angiotensin-converting enzyme inhibitor (ACEi), captopril, started before tachypacing, shortening of ERP was completely inhibited (Nakashima et al. 2000). In a comparable experimental arrangement a positive effect was not attained with the ACE inhibitor enalapril either on shortening of ERP or inducibility of AF when rapid atrial pacing was continued for 7 days and ventricular rate was controlled by AV ablation (Shinagawa et al. 2002c).

AngII increases the influx of Ca^{2+}-ions into myocardial cells, modulates ion channels of cell surface and causes shortening of ERP in both atrial and pulmonary vein tissue. This shortening of ERP is attenuated with RAAS-inhibiting drugs (Goette et al. 2004, Zankov et al. 2006, Chen et al. 2006). Besides the actions via RAAS, those drugs have direct, angiotensin-independent properties on ion channels with a small antiarrhythmic effect (Ehrlich et al. 2006). However, as noted, those direct antiarrhythmic effects are modest and may have a role in intact atria with normal action potential duration, but are not seen when atria are exposed to a rapid rhythm even for some days (Shinagawa et al. 2002c).

In their model Kumagai et al. investigated the effect of rapid atrial pacing continued for five weeks without AV ablation and hence without controlled ventricular rate (Kumagai et al. 2003). Shortening of ERP was again noted with no effect of candesartan on ERP, but candesartan attenuated significantly the lengthening of conduction time and also shortened the duration of induced AF compared to a sham group (Kumagai et al. 2003). As the ventricular rate was not controlled this result might be explained by ventricular myopathy, similar to that observed in models with ventricular tachypacing, causing markedly increased tissue concentrations of AngII as well as atrial functional and structural remodeling (Li et al. 1999, Cardin et al. 2003, Hanna et al. 2004).

In CHF or hypertension models of AF changes in atria resemble those observed in AF patients, with fibrosis, scarring, slowed conduction, increase in electrical heterogeneity and tendency to AF (Frustaci et al. 1997, Li et al. 1999, Allessie et al. 2002, Sanders et al. 2003a, Boldt et al. 2004, Kistler et al. 2006, Kirchhof et al. 2006). LV dysfunction, especially congestive heart failure, hypertension and AF by itself via atrial stasis cause atrial stretch that is a strong stimulator of RAAS (White et al. 1982, Allessie et al. 2002, Ehrlich et al. 2006). In a canine CHF model caused with rapid ventricular pacing Hanna et al. demonstrated that structural changes and increase of AngII concentration was remarkably faster and larger in atrial than in ventricular tissue (Hanna et al. 2004). When

animals in CHF models are treated with RAAS-suppressing medication before ventricular tachypacing, increase in AngII concentration is prevented, apoptosis is suppressed and an increase in fibrous tissue content is diminished. However, leukocyte infiltration and cell death rate are not affected (Li et al. 2001, Cardin et al. 2003). In CHF models RAAS suppression has also attenuated the reduction of atrial contraction and diminished the increase of dilatation, and as a consequence, shortened markedly the duration of AF (Li et al. 2001, Shi et al. 2002, Kumagai et al. 2003, Li et al. 2007).

In a rapid atrial paced canine model – without AV ablation – the above-mentioned signs of CHF-caused alterations were seen, but Sakabe et al. also measured P-wave duration, expression of connexin43 and sinus node recovery time (Sakabe et al. 2004, Sakabe et al. 2005). Enalapril-treated dogs had significantly lower P-wave duration lengthening and less over-expression of connexin43, and the prolongation of sinus node recovery time was significantly shorter in comparison with the placebo group (Sakabe et al. 2004, Sakabe et al. 2005). By these mechanisms RAAS suppression favors SR by improving the pacemaker activity of sinus node as well as by inhibiting electrical disparity in atrial tissue.

2.4.2.2 Human studies

The above-mentioned experimental data are lacking in man. It is not a surprise that genetic differences are also associated with AF, and a different angiotensinogen haplotype profile has been found in AF patients and controls (Tsai et al. 2004). Patients with pre-operative AF in open-heart surgery have had significantly higher expression of ACE and a certain mitogen activated protein kinase (Erk1/Erk2) in right atrial appendage specimens compared to surgical patients in SR (Goette et al. 2000a). The behaviour of angiotensin receptors (AT1 and AT2) seems unsolved so far, because the results have been controversial. AT1 receptors were downregulated and AT2 receptors upregulated in right atrial samples of AF patients in one study (Goette et al. 2000b), while in another AT1 receptors were found to be upregulated in the left atrium and unchanged in the right (Boldt et al. 2003). ACE is definitely activated and AngII concentration increased in AF, but the status of AT receptors might be dependent on the stages of heart disease and atrial failure. Patients treated preoperatively with ACE inhibitors had lower levels of activated Erk1/Erk2 and less expression of collagen I in atrial specimens (Goette et al. 2000a, Boldt et al. 2006).

Both ACE inhibitors and ARBs have reduced myocardial fibrosis in myocardial biopsies of hypertensive patients (Brilla et al. 2000, Díez et al. 2002, Ciulla et al. 2004). This antifibrotic effect of RAAS suppression was superior to both hydrochlorothiazide and atenolol in a randomized study setting, and those drugs were also associated with reduction of left ventricular stiffness and diastolic dysfunction (Brilla et al. 2000, Díez et al. 2002). Antifibrotic effects of these drugs can also be identified as modified

concentrations of collagen synthesis or degradation markers in venous blood samples (Ciulla et al. 2004, Nomura et al. 2008).

In a non-randomized study, patients with an ACE inhibitor before an invasive electrophysiological examination had a lower incidence of abnormal, fractionated atrial electrograms (Shibata et al. 2006). Electrophysiological advantage from RAAS suppression has non-invasively been detected as shortened P-wave duration both with SAECG and with 12-lead ECG. Shorter P-wave duration was also associated with lower recurrence risk of AF (Zaman et al. 2004, Fogari et al. 2008, Nomura et al. 2008).

With antihypertensive therapy, an enlarged left atrium (LA) reduces in size, which has also been noted with ACE inhibitors (Gottdiener et al. 1998, Tsang et al. 2006). Besides having a systemic antihypertensive effect, RAAS suppression also decreases left atrial filling pressure (Mitrovic et al. 2003). These findings – a reduction of atrial size and pressure – are crucial at the initiation of AF. Parallel with improvement in atrial electrical and structural remodeling, RAAS suppression also improves atrial functional remodeling by improving atrial emptying (Tsang et al. 2006).

2.4.3 Suppression of the RAA system and AF – clinical data

The first hints of the beneficial effect of suppression of RAAS on AF were achieved in the middle of the 1990s from two small, but placebo-controlled prospective studies in patients with congestive heart failure (Gürlek et al. 1994, van den Berg et al. 1995). A positive but statistically insignificant effect with ACE inhibitor was found as a diminished amount of AF after electrical CV. The studies were based on the assumptions that ACE inhibition induces a positive potassium balance, improves hemodynamics and attenuates adrenergic drive.

In a post-hoc analysis of the TRACE trial of those 1,577 patients who had SR on the randomisation ECG, 2.8% allocated to trandolapril and 5.3% allocated to placebo developed ECG-documented AF during the 2- to 4-year follow-up ($p < 0.01$) (Pedersen et al. 1999b). In the GISSI-3 trial a 24% reduction in the incidence of in-hospital AF in patients randomised to lisinopril + nitrates compared to the placebo group was documented, while the effect of lisinopril alone was only 8% and non-significant (Pizzetti et al. 2001, Healey et al. 2005).

The first hypertension studies that evaluated the incidence of AF were the CAPPP and STOP-H-2 trials (Hansson et al. 1999a, Hansson et al. 1999b). In both trials "new antihypertensive drugs" (ACE inhibitors or dihydropyridine Ca-channel blockers) were compared to "conventional antihypertensive drugs" (diuretics or β-blockers) with no significant differences in preventing cardiovascular morbidity and mortality. Either the frequency of new AF did not differ between the allocated groups in those trials when AF was recorded as a cardiovascular endpoint (Hansson et al. 1999a, Hansson et al. 1999b). A

large-scale registry study was performed by L'Allier et al., who investigated the use of ACE inhibitors and the risk of AF in hypertensive patients (L'Allier et al. 2004). Patients with ACE inhibitors (12 600 patients) had a hazard ratio of (HR) 0.85 for the incidence of new-onset AF, and 0.74 for AF-related hospitalisations; both results were statistically significant (L'Allier et al. 2004). The most recent analysis of AF in a hypertension trial is from the VALUE trial (Schmieder et al. 2008). Based on the centrally analysed ECGs, treatment with valsartan reduced new AF (HR 0.83) and new persistent AF (HR 0.68) compared to the amlodipine arm. A lower amount of AF was recorded despite greater reduction of blood pressure and higher regression in LVH in the amlodipine arm (Schmieder et al. 2008).

In randomized prospective controlled trials in patients with heart failure three post-hoc analyses of the incidence of AF and the association of RAA system suppressing drugs have been completed (Vermes et al. 2003, Maggioni et al. 2005, Ducharme et al. 2006). In the SOLVD, CHARM and Val-HeFT trials patients with stable, chronic heart failure were randomized to enalapril, candesartan, valsartan or placebo, and cardiovascular mortality and morbidity was analyzed. In a post-hoc analysis at a single SOLVD study centre the risk of development of ECG-documented AF was reduced with enalapril with a HR of 0.22 ($p < 0.001$) (Vermes et al. 2003). In the Val-HeFT trial AF was defined as an adverse event, but in the CHARM trial new AF was a prespecified as a secondary outcome. The use of valsartan and candesartan were associated with a reduced amount of AF with HRs of 0.80 and 0.67, respectively, both those differences being statistically significant (Maggioni et al. 2005, Ducharme et al. 2006).

The patient profiles were different in the HOPE, ONTARGET and TRANSCEND trials, which had more patients with signs or risk factors of atherosclerosis. In those trials an ACE inhibitor, ramipril, or an ARB, telmisartan, did not decrease the incidences of new AF between the groups (Yusuf et al. 2000, ONTARGET Investigators 2008, TRANSCEND Investigators 2008).

The efficacy of ACE inhibitors or ARBs preventing AF relapse after electrical CV has been evaluated in four randomized studies. In their first study, Madrid et al. treated AF patients with amiodarone or amiodarone plus irbesartan (150 mg/d or up to 300 mg/d in hypertensive patients) for a mean of 28 days before an electrical CV. No difference was observed in success rate in either pharmacological restoration of SR before the CV or electrical CV, but at the end of the follow-up (median 254 days) 80% patients in the irbesartan plus amiodarone group had remained in SR, compared to 56% in the amiodarone alone group, $p = 0.007$ (Madrid et al. 2002). In their second and smaller study Madrid et al. compared two different doses of irbesartan (150–300 mg) combined with amiodarone or amiodarone alone for restoration and maintenance of SR in lone AF patients (Madrid et al. 2004). At the end of the follow-up (median 220 days) 77% of patients with amiodarone plus irbesartan 300 mg/d, 65% of patients with amiodarone plus irbesartan 150 mg/d and 52% of patients with amiodarone alone were free of AF relapse.

The difference between the first and third group was statistically significant ($p = 0.01$); the other comparisons were statistically non-significant (Madrid et al. 2004).

Enalapril was used by Ueng et al. in their study to assess whether cardioversion outcome could be improved by an ACE inhibitor (Ueng et al. 2003). The immediate result of CV did not differ between the groups. However, both at four weeks after the CV and at the end of the follow-up period (median 270 days) patients with enalapril had maintained SR significantly more often; 84% vs. 61% and 74% vs. 57%, respectively. An interesting finding in this study was that patients receiving enalapril had significantly fewer atrial premature beats (APB) both after 2 minutes as well as four weeks after the CV, APBs associating strongly with immediate AF relapses (Ueng et al. 2003). Tveit et al. completed a randomised, double-blind, placebo-controlled study to examine the ARB candesartan in preventing recurrences of AF after electrical CV without any antiarrhythmic medication (Tveit et al. 2007). No difference in the quantity of AF was detected between the randomisation groups. All in all, electrical CV was successful in 86% of the patients, and during the six-month follow-up 68% of those successfully cardioverted had an AF relapse (Tveit et al. 2007).

In patients with paroxysmal AF or without a recent CV RAAS stimulation caused by long-standing AF is not present. The mechanism of RAAS inhibition in those cases is not directed against atrial remodeling caused by AF itself, but RAAS inhibition acts nevertheless against the primary mechanisms of AF. Fogari et al. have completed two studies in patients with hypertension and paroxysmal AF. In the first one at the end of the median follow-up of 299 days 88% of the patients with losartan and amiodarone were without AF, compared to 65% in the group with amlodipine and amiodarone ($p = 0.008$) (Fogari et al. 2006). In the second study they randomised patients to three different medications: valsartan, ramipril or amlodipine, and no antiarrhythmic medications were allowed. The reduction in blood pressure was similar, but valsartan and ramipril were more effective than amlodipine in preventing new episodes of AF (recurrence of AF 16%, 28% and 47%, respectively). In this study the reduction of P-wave dispersion measured from specifically instrumented 12-lead ECG seemed to be the greatest in the valsartan group (Fogari et al. 2008).

In patients with lone paroxysmal AF amiodarone alone was compared to amiodarone plus losartan or amiodarone plus perindopril in a Chinese study (Yin et al. 2006). This study was prospective and randomised, but the drugs were given in an open-label fashion. A significant reduction of AF recurrence was demonstrated in the groups with RAAS inhibition plus amiodarone when compared to the amiodarone only group, while no difference was found between the losartan and perindopril groups in the recurrence of AF: 19% with losartan, 24% with perindopril and 41% with placebo (Yin et al. 2006).

2.4.4 The RAA system and AF – synopsis

The active endproduct of RAAS – AngII – causes vasoconstriction, increases fibroblast proliferation and cardiac hypertrophy and arouses arrhythmias by activating AT1 receptors. Renin inhibitors, ACE inhibitors and ARBs suppress the RAA system, and all these drug groups have antiarrhythmic effects both in experimental animal models and in humans. A reduction in the incidence of AF with RAAS suppression has been studied in patients with AMI and LV dysfunction, in AMI patients and in patients with heart failure. Variation in hazard ratios (0.22 – 0.92) as well as the numbers of patients and incidence of AF is large, and AF suppression has not been statistically significant in all of the studies. In post-hoc analyses of hypertension trials and in trials studying patients with atherosclerosis but without marked hypertension or heart failure RAAS suppression has not been associated with a diminished risk of AF (Hansson et al. 1999a, Hansson et al. 1999b, Salehian et al. 2007, ONTARGET Investigators 2008, TRANSCEND Investigators 2008). In the VALUE trial the incidence of new AF was analysed in a prespecified manner with ECG data, and ARB treatment had a 0.83 hazard ratio for new AF compared to the control group (Schmieder et al. 2008). In addition, a positive effect of RAAS suppression has been documented in some small but randomised studies focusing especially on AF (Fogari et al. 2006, Yin et al. 2006, Fogari et al. 2008). In prospective randomised cardioversion studies there have been differences in patient profiles as well as in the duration of AF. The only one that failed to prove any benefit from RAAS suppression was performed without amiodarone, and it has been argued that amiodarone might have had a "bridging effect" preventing early recurrences of AF and providing time for reverse remodeling enhanced with RAAS suppression (Madrid et al. 2002, Ueng et al. 2003, Madrid et al. 2004, Tveit et al. 2007).

It seems that in populations with advanced hemodynamic abnormalities and therefore also a more activated RAA system, the suppression of this system has the highest benefits in preventing AF. The incidence of AF has also been the highest in those patient groups. This more pronounced effect of RAAS suppression in patients with more serious heart disease is also documented in a single trial (Ducharme et al. 2006). RAAS stimulates atrial electrical, structural and functional remodeling begetting AF, the antifibrotic effects of RAAS suppression drugs being probably the main mechanism behind the reduction in the propensity to AF in patients with heart diseases.

2.5 Cardioversion

2.5.1 History of cardioversion

"It is relatively easy to perform a successful cardioversion, but although the rhythm may be altered, the natural history of the disease is not changed"

Turner and Towers 1965

Antiarrhythmic properties of cinchona bark were already recognised in the 18th century, and during the 1920's the use of quinidine for termination of AF was established (Viko et al. 1923, Parkinson and Campbell 1929, Lüderitz 2002b). Many of the patients who achieved SR felt better and some of them could return to their normal activities, while patients who retained AF had a much poorer clinical course. The importance of a short history of AF in achieving a favorable result in restoration and maintenance of SR with quinidine was also noticed very early (Viko et al. 1923, Parkinson and Campbell 1929).

During the 1930s the induction and termination of ventricular as well as atrial fibrillation with electrical shock in animals was established (Wiggers and Wégria 1940). The termination or defibrillation of ventricular fibrillation in man was documented by Zoll et al., who studied intensively the external electrical stimulation of the heart with alternating current (AC) (Zoll et al. 1956, Gibson et al. 1956). However, it was already found in the 1930s that alternating electrical current was more dangerous in stimulating ventricular arrhythmias than direct current (DC) (Wiggers and Wégria 1940). Clinical application of electrical countershock became possible with the thorough work of Bernard Lown, who also launched the term "cardioversion" (Lown et al. 1962, Lüderitz 2002b). His group established that DC was more effective and safer in terminating arrhythmias than AC, and that ventricular arrhythmias could be avoided with stimulus synchronised within the terminal part of the QRS complex (Lown et al. 1962). Since then, implementation of defibrillators using impedance compensated biphasic waveforms in the 1990s is the most noticeable evolution in the field of external cardioversion (Cooper et al. 1997, Mittal et al. 2000, Adgey and Walsh 2004, Gall and Murgatroyd 2007).

2.5.2 Results of cardioversion of atrial fibrillation

2.5.2.1 Immediate results of cardioversion

In his historical paper Lown et al. reported results of "synchronised cardiac depolarisation" on 13 occasions in 12 patients with AF duration from 1 month to 5 years.

In eleven cases out of thirteen (85%) SR was restored with monophasic waveform given by the developed capacitor – "results seeming encouraging" (Lown et al. 1962). In 1967 the same group published their results of 456 episodes of atrial defibrillation in 350 patients, documenting restoration of SR in 94% of the occasions (Lown 1967). 70% of patients had rheumatic valve disease and energy requirement, and the success rate was directly related to the duration of AF before the CV (Lown 1967).

The other pioneers of electrical cardioversion during the 1960s got very similar results, reaching 77-90% success rates in the immediate result of CV with monophasic stimulus (Oram and Davies 1964, Turner and Towers 1965, Bjerkelund and Orning 1968, Radford and Evans 1968, Szekely et al. 1970). Shorter duration of AF, thyrotoxicosis, absence of P-terminal force and coarse fibrillating waves in ECG, and absence of or corrected mitral valve disease were factors documented in association with higher proportion of restoration of SR. This better instantaneous result was also observed in patients with lone AF (Oram and Davies 1964, Turner and Towers 1965, Lown 1967, Bjerkelund and Orning 1968, Radford and Evans 1968, Scott et al. 1968, Szekely et al. 1970). With defibrillators providing biphasic waveform introduced in the 1990s electrical CV has achieved success rates of 90 - 95% (Adgey and Walsh 2004, Cooper et al. 1997, Mittal et al. 2000, Gall and Murgatroyd 2007). To minimise the number of shocks given as well as the amount of total energy it is recommended that at least 200 J is applied when using monophasic waveform and at least 150 J when using biphasic waveform. Anterior-posterior electrode configuration has given some benefit over anterior-apical positioning in some studies, and it might increase the probability of successful CV (Adgey and Walsh 2004, Kirchhof et al. 2005, Fuster et al. 2006, Gall and Murgatroyd 2007).

Even though only approximately 4% of the current given traverses the heart during external defibrillation in humans, a good immediate success rate of electrical CV is achieved with monophasic shocks as well (Lerman and Deale 1990, Adgey and Walsh 2004, Gall and Murgatroyd 2007). In the 1960s it was very soon noted that "though atrial fibrillation can now be readily terminated, maintenance of SR continues as the central problem", and the focus has turned away from assessing features that only predict the initial CV result (Lown 1967).

2.5.2.2 Long-term results of cardioversion

In the 1960s most of the patients referred for electrical CV had (rheumatic) valve disease and the duration of AF was very long, even up to many years. In such circumstances the atria have been exposed to a long-lasting stretch causing atrial remodeling, and the overall result – patients restored and SR maintained for one year – was less than 30% (Oram and Davies 1964, Bjerkelund and Orning 1968, Radford and Evans 1968, Scott et al. 1968, Szekely et al. 1970). Duration of AF has been the major characteristic predicting the maintenance of SR, and it has repeatedly been reported to have this central role in recent studies as well. During the early days of electrical CV it was found that AF duration of

many years decreased the likelihood of SR, but thereafter the cut-off point of the duration of AF for a better CV result has been shortened to less than two months (Lown 1967, Bjerkelund and Orning 1968, Szekely et al. 1970, Dittrich et al. 1989, Alt et al. 1997, Verhorst et al. 1997, Antonielli et al. 2002, Biffi et al. 2002, Guo et al. 2003). With transesophageal echocardiography-guided cardioversion the delay before CV can be noticeably shortened, but improved long-term results have not so far been established (Roijer et al. 2000, Weigner et al. 2001, Klein et al. 2001).

In practice, all the documented risk factors for poorer restoration and maintenance of SR with CV illustrate atrial remodeling or are surrogates of remodeling. As basic clinical characteristics, advanced age, heart failure and valvular disease have been associated with poorer outcome and vice versa, lone AF has been associated with better outcome of CV (Oram and Davies 1964, Bjerkelund and Orning 1968, Radford and Evans 1968, Van Gelder et al. 1996, Alt et al. 1997, Berry et al. 2001, Raitt et al. 2006). Patients with coronary artery disease and thyrotoxicosis have had a somewhat better rate of restoration and maintenance of SR (Radford and Evans 1968, Scott et al. 1968, Szekely et al. 1970, Alt et al. 1997, Raitt et al. 2006). The reasons for this might be that coronary artery disease patients have more often had beta blocking agents, and thyrotoxicosis patients having more often a healthy, intact heart.

Atrial electrical remodeling as shortened APD and ERP reduces the outcome of CV (Olsson et al. 1971, Biffi et al. 2002, Okumura et al. 2005). In the frequency analysis the frequency of atrial electrical activity during AF depends on the electrical properties of the atria and is highly correlated with atrial ERP (Capucci et al. 1995). The frequency of fibrillatory signals can be measured as AF current length (AFCL) or as frequency, and both these methods have confirmed their prognostic accuracy to predict maintenance of SR (Langberg et al. 1998, Fynn et al. 2001, Holmqvist et al. 2006a). Besides the frequency of fibrillation signal, also the organisation of those frequencies as less organised rhythms or less harmonisation is associated with higher propensity to AF relapse (Holmqvist et al. 2006b). More organised atrial electrical activity prior to CV was already documented by Oram and Davies, who found that higher amplitude of F-waves favored the maintenance of SR (Oram and Davies 1964). Macroscopic atrial electrical remodeling is observed as lengthened and more dispersed P-wave, and both 12-lead ECG as well as SAECG techniques have demonstrated their capacity to find patients with an increased risk of AF relapse (Opolski et al. 1997, Aytemir et al. 1999, Raitt et al. 2000, Guo et al. 2003, Perzanowski et al. 2005, Raitt et al. 2006). Along with lengthened P-wave duration, diminished amplitude of the end of the P-wave is associated with poorer CV result (Opolski et al. 1997, Aytemir et al. 1999, Guo et al. 2003). An interesting finding in some studies has been that while duration of AF and electrophysiological measurements have predicted the result of CV in univariate analyses, only electrophysiological results as markers of atrial remodeling have remained statistically significant in multivariate analyses (Dixen et al. 2004, Dogan et al. 2004, Okumura et al. 2005). This indicates that electrical remodeling is the factor behind poorer probability of SR, and AF duration is a surrogate for the development of electrical remodeling (Goette et al. 1996).

The size of the atria has an essential role in propagation of AF, enlarged atria allowing more electrical wavelets to wander over atrial tissue. Lown already noted that patients with a markedly enlarged left atrium had a high risk of AF relapse, and when the size of atria became measurable with echocardiography, the size of the (left) atrium could be used as a predictor of the maintenance of SR (Lown 1967, Ewy et al. 1980, Höglund and Rosenhamer 1985). Thereafter, atrial size has been one of the most often reported factors associating with restoration and maintenance of SR (Dittrich et al. 1989, Alt et al. 1997, Verhorst et al. 1997, Antonielli et al. 2002, Dogan et al. 2004, Fuster et al. 2006).

More advanced functional remodeling measured as markedly decreased flow velocities in atrial appendages as well as decreased atrial emptying (mitral A-wave) have been documented in patients prone to AF relapse (Verhorst et al. 1997, Antonielli et al. 2002, Kinay et al. 2002, Dogan et al. 2004). Kinay et al. also measured the time interval from initiation of P-wave to the starting point of left atrial appendage ejection wave, illustrating nicely the association between atrial electrical and functional action. They found that the lengthening of this interval was an independent predictor of AF relapse – most probably as a sign of altered interatrial conduction because of conducting tissue fibrosis. The mean atrial size was not different in the patients with or without an AF relapse in this study (Kinay et al. 2002).

After cardioversion reverse remodeling takes place, and the probability of sustained SR increases over time. It makes sense to suppose that better reverse remodeling improves the maintenance of SR. The energy of atrial P-wave signal measured by SAECG seems to decrease more in those patients who remain in SR compared to patients with an AF relapse (Stafford et al. 1998, Guo et al. et al. 2003). However, the clinical applications of these methods are lacking.

2.5.3 How to improve the result of cardioversion in clinical practice

The duration of AF before CV has a central role in terms of the result of CV, and it is also the least demanding way to improve the CV result. In clinical practice, problems with anticoagulation therapy – subtherapeutic INR values – are the main factor in lengthening the delay before elective CV, and effort should be put into improving anticoagulation therapy as well as logistics between general practitioners and CV centers (Kim et al. 2001). Another approach aimed at shortening the duration of AF before CV is to employ transesophageal echocardiography-guided cardioversion (Roijer et al. 2000, Weigner et al. 2001, Klein et al. 2001).

Modern biphasic external defibrillators stop AF in about 95% of the cases; this can only be exceeded with the use of internal CV (Gall and Murgatroyd 2007). The probability of immediate recurrence of AF can be decreased with pre-treatment with class Ia and Ic along with class III antiarrhythmic drugs, which all seem to have some usefulness,

amiodarone having the best efficacy (Van Noord et al. 2002, Fuster et al. 2006). RAAS-suppressing medications decrease the amount of atrial premature beats and improve sinus node function, both of which might also improve the immediate result of CV (Gürlek et al. 1994, Sakabe et al. 2005).

Overload of Ca^{2+}-ions in atrial cells during AF can be reduced with the use of intracellular calcium-lowering medications (β-blocking agents, diltiazem and verapamil), which also reduce the number of early AF recurrences (Tieleman et al. 1998, De Simone et al. 1999, Villani et al. 2000). However, non-dihydropyridine Ca-channel blockers seem to have only modest, if any, effect on preventing late AF recurrences (Villani et al. 2000, Hemels et al. 2006). In adjunction with Class I or III antiarrhythmic medication, verapamil has increased the maintenance of SR (De Simone et al. 2003).

All class Ia, Ic and class III antiarrhythmic drugs improve the maintenance of SR. However, these drugs have adverse effects and in older studies class Ia drugs were also associated with increased mortality. Of the class II drugs – β-blocking agents – metoprolol and bisoprolol have proven efficacy in preventing AF relapse after CV (Kühlkamp et al. 2000, Plewan et al. 2001). Of the drugs currently on the market, amiodarone has the best efficacy with a low pro-arrhythmia risk, but it has a very challenging adverse event profile in long-term use (Fuster et al. 2006, Lafuente-Lafuente et al. 2007). RAAS-suppressing medication and also statin therapy as non-antiarrhythmic treatments seem to improve modestly the restoration and maintenance of SR after electrical CV, their benefit coming mainly from acting against atrial fibrosis and inflammation (Madrid et al. 2002, Ueng et al. 2003, Madrid et al. 2004, Fuster et al. 2006, Ozaydin et al. 2006)

When the rhythm strategy – restoration and maintenance of SR – is set as a goal in an AF patient, repeated cardioversions and application of antiarrhythmic medications are usually needed. Repeated CVs combined with antiarrhythmic drug treatment increased markedly the proportion of patients in SR (Roussane et al. 1984, Crijns et al. 1991, Bertaglia et al. 2002). This kind of policy seems to be especially successful as an aggressive strategy aiming at immediate CV after an AF relapse (Bertaglia et al. 2002, Nergårdh et al. 2007). These results also warrant the finding that reverse remodeling occurring after CV and demonstrable during SR vanishes over time after an AF relapse (Fynn et al. 2001).

2.6 Magnetocardiography

2.6.1 Theory of magnetocardiography

Activation and contraction of the heart is generated by changing concentrations of extra- and intracellular ions. Moving ions create changing electrical currents that are extracorporeally measurable by electrocardiography – ECG. Like every electrical current, also the current created by the heart generates a magnetic field (the Biot-Savart law), and as the nature of this source changes, this magnetic field also changes and is extracorporeally measurable by magnetocardiography – MCG (Malmivuo and Plonsey 1995).

An ECG lead always measures the sum of electrical activities, and a lead can even be silent if the activities have opposite directions (Baule and McFee 1963). However, the electric currents set up a detectable magnetic field. Modern multichannel MCG devices have good spatial resolution accuracy, and measured in close proximity, cardiac electromagnetic sources unattainable with ECG can be detected (Fenici et al. 1992, Koch 2004). The flux of currents in the human torso is also affected by the differences in conductivity and boundaries of the torso, while MCG is less dependent of these sources (Hosaka et al. 1976, Siltanen 1989, Fenici et al. 1992). MCG is furthermore less sensitive to electrical resistance due to pulmonary emphysema and pericardial effusion, and as a contactless modality, the MCG signal is not troubled by the noise of electrode-skin connection, as is the case with conventional ECG technique (Siltanen 1989, Fenici et al. 1992, Koch 2004).

In theory, maybe the greatest advantage of MCG over ECG is that it is more sensitive to the electrical sources that are tangential to the chest (Nousiainen et al. 1986, Siltanen 1989, Fenici et al. 1992). In a healthy, intact heart, most of the ventricular activation proceeds transmurally from the endocardium to the epicardium, directed radially towards the ECG leads. Atrial activation is mostly tangential to the heart and chest wall, as is the activation of the His-Purkinje system as well as ventricular activation interfered by myocardial scars, the sources – in theory – more achievable with MCG (Siltanen 1989, Fenici et al. 1992). The source of both ECG and MCG is the electrical activity of the heart; therefore, P-, QRS-, T- and U-waves are also recognised in the MCG, and the same nomenclature of those deflections is applied (Figure 5).

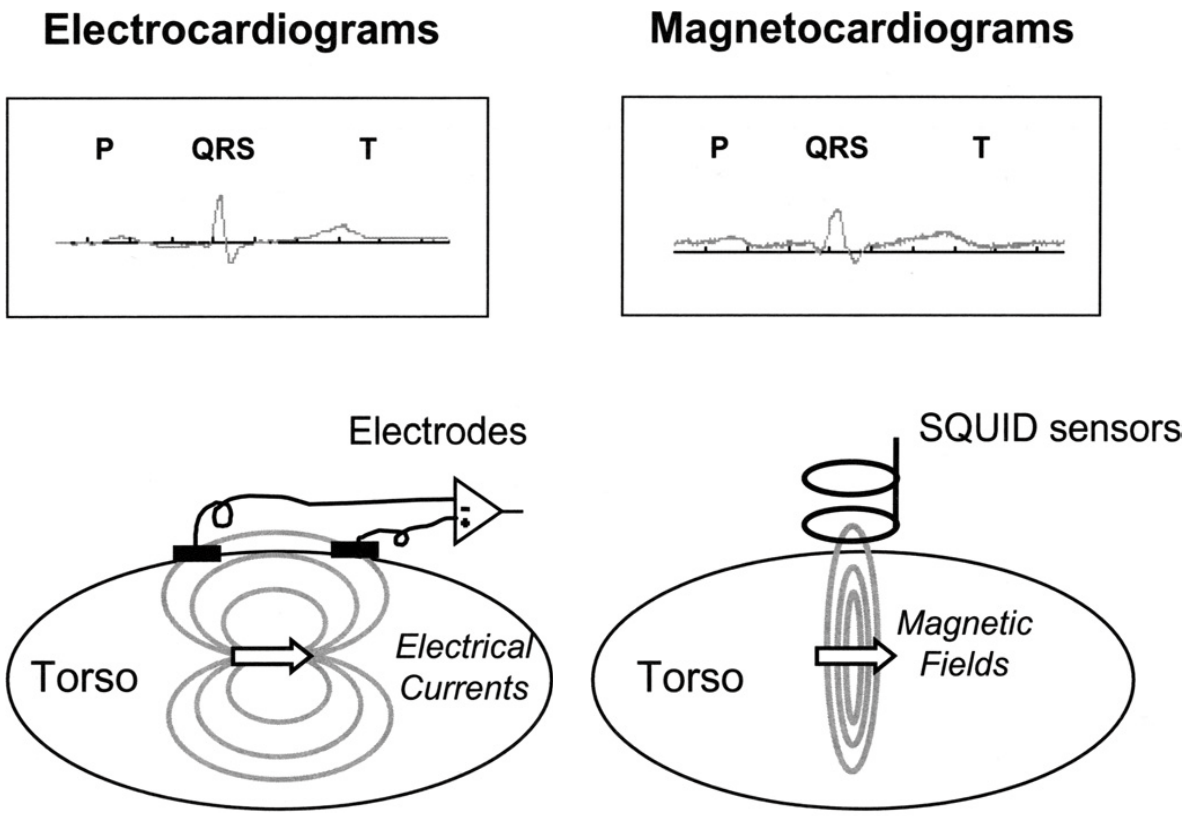

Figure 5. *Relationships between detected signals of single ECG and MCG channels, and schematic illustration of instrumentation of ECG and MCG (axial gradiometer with two magnetometer coils). SQUID: Superconducting Quantum Interference Device Used with permission from Yamada S. (Yamada and Yamaguchi 2005).*

2.6.2 Instrumentation of magnetocardiography

The human cardiac magnetic field was first detected by Baule et al. with two specially designed magnetometer coils (Baule and McFee 1963). The recorded signal was extremely small and noisy, and was measurable only "several dozen yards from the nearest source of interference", but had the recognisable feature of a cardiac signal (Baule and McFee 1963). Magnetic field of the heart is approximately 0.1 - 100x10^{-12} Tesla (pT), that is 10^{-6} of the earth's magnetic field and 10^{-3} of the background magnetic field of urban environment, and special instrumentation is needed to achieve an acceptable signal-to-noise ratio.

A major improvement in MCG was achieved in the late 1960s when David Cohen employed a magnetically shielded room using a Superconducting Quantum Interference

Device (SQUID) (Cohen et al. 1970). The SQUID technique applies a supraconducting state at a very low temperature reached with a vacuum flask ("dewar") with liquid helium at 4.2 K (-269°C) where the MCG coil(s) and SQUID amplifier(s) are immersed, which allows very low intrinsic instrumental noise (Cohen et al. 1970). With a supraconducting state, large coils with up to millions of turns were not needed and MCG was even measurable with just one copper coil. When a magnetometer coil measures cardiac magnetic field it always detects the background environmental magnetic field as well. To improve the signal-to-noise ratio magnetometers have reference coil(s), and when the common signal of the magnetometer coil and this compensation coil is subtracted, the external noise is reduced. Gradiometers have two or more axial or planar magnetometer coils that further reduce residual noise (Figure 5). With modern, sophisticated signal averaging techniques and software-based interference suppression methods the signal-to-noise ratio can be additionally improved (Koch 2004). During the 1960s and 1970s multisite MCG mapping was completed when the signal was recorded by moving the dewar point by point over the thorax in a placement grid. Currently multichannel devices are most often utilized and multichannel MCG mapping can be achieved with a single registration (Koch 2004).

There are two main routines to express MCG data: expressing the signal as scalar time-series like traditional ECG having P-, QRS-, T- and U-waves (Figure 5), or constructing a MCG map (Figure 6). Traditional MCG mapping shows the magnetic isofield strengths drawn over the mapped area at a selected time point where the direction and strength of the integral of those magnetic forces can be calculated and depicted. Pseudocurrent maps can be constructed from magnetic fields giving an intuitive representation of the electrical source (Figure 6).

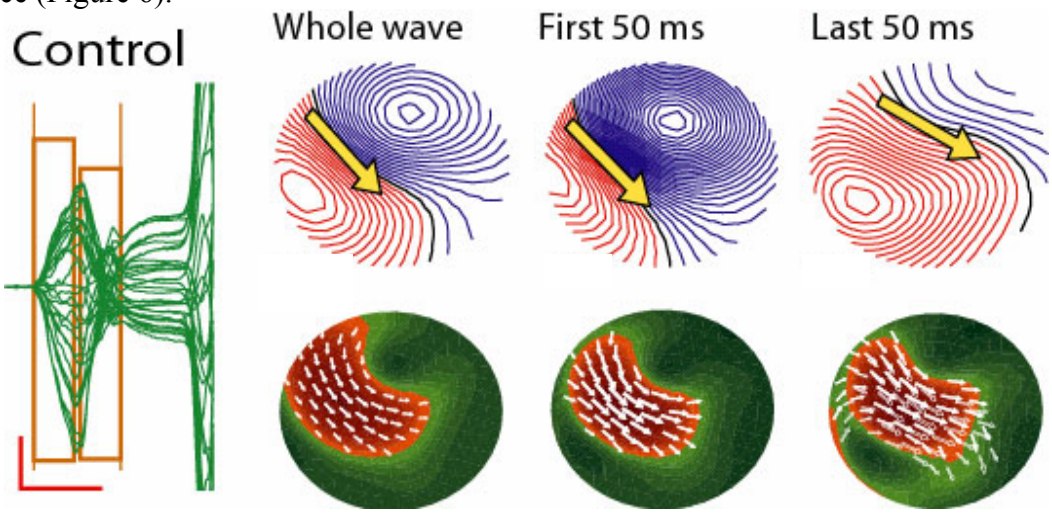

Figure 6. *An example of magnetic fields during atrial depolarization from a healthy control represented as isofield maps (upper row) and as pseudocurrent maps (lower row).) At left averaged P-wave of all included MCG-channels. The images at right illustrate integrals over the whole atrial depolarisation signal and during the first and last 50 ms of atrial depolarisation signal*
Used with permission from Raija Jurkko.

2.6.3 Magnetocardiography and the atria

2.6.3.1 Findings of atrial signal with magnetocardiography

Atrial depolarisation spreads over the atria mostly along the atrial wall and tangentially to the chest, and this atrial P-wave in MCG has been attainable since the SQUID technique was introduced (Cohen and McCaughan 1972, Siltanen 1989). In healthy subjects the P/R amplitude ratio in MCG has proven to be at least as high as in ECG, and a biphasic pattern of P-wave has been more often evident in MCG (Cohen and McCaughan 1972, Saarinen et al. 1974).

Furthermore, in atrial pathology MCG seems to have even better accuracy for diagnosis than ECG. In atrial overload the P/R ratio was more marked and sensitivity and specificity better for a diagnosis in MCG than in ECG (Saarinen et al. 1974, Sumi et al. 1986, Takeuchi et al. 1988). Siltanen et al. also noticed that a shift of the PR segment from the baseline was very pronounced in MCG both in atrial overload and in hypertrophic cardiomyopathy patients, and that phenomenon was suggested to represent atrial repolarisation not visible in the corresponding ECG tracings (Siltanen 1989). Even though the atrial MCG signal was already recorded more than 30 years ago, reproducibility of the atrial MCG signal has not been established.

2.6.3.2 Magnetocardiography and AF

The data regarding AF and MCG are few. However, Siltanen et al. were able to document coarse fibrillatory waves in AF patients when a noiseless baseline was achieved (Siltanen 1989). Nakai et al. had a 64-channel MCG device enabling visualisation of the cardiac activity integrated with cardiac anatomical silhouette during AF. They demonstrated a random micro-re-entry signal around the atrium in AF patients, while the activity in patients with atrial flutter had a macro-re-entry character (Nakai et al. 2005). After restoration of SR MCG demonstrated an organised activity pattern. They also have shown in a frequency analysis that patients who failed to maintain SR after surgical ablation had higher atrial fibrillatory frequency in MCG than patients who reached SR (Nakai et al. 2008). This confirms the findings documented with ECG that AF cycle length is shorter in patients prone to AF (Langberg et al. 1998, Fynn et al. 2001, Holmqvist et al. 2006a). Preoperative MCG mapping in a patient with mitral valve stenosis and AF made it possible to simplify the surgical AF procedure to achieve sustained SR (Kim et al. 2007).

Mäkijärvi et al. focused on patients with pre-excitation syndrome (WPW), some of whom had a history of AF attacks. AF patients had more dispersed atrial depolarisation distributions compared to WPW patients without AF. Out of the patients with AF problems, 11/20 (55%) had more than two extremas in the atrial depolarisation maps,

while 4/6 (67%) of the patients without AF had bipolar MCG maps (Mäkijärvi et al. 1993).

The atrial magnetic field had changed from organised during SR to completely disorganised during AF; moreover, when the rhythm turned to atrial flutter, the magnetic field had a circular pattern. In order to confirm their MCG data, this group had electrophysiological data of this same experience (Yamada et al. 2003). A clear difference was seen between patients with focal automatic tachycardia and AF patients, the former showing a significantly less disorganised pattern in time-frequency analysis of MCG. Therefore, this kind of analysis might be useful in differentiating between AF with multiple wavelets and focal AF with triggered activity, and it might also be valuable for evaluating degrees of electrical remodeling in AF patients (Yamada and Yamaguchi 2005).

Winklmaier et al. performed a MCG study in AF patients during SR after spontaneous conversion or electrical CV (Winklmaier et al. 1998). They recorded a multichannel MCG and 12-lead ECG, created sum channels from all the MCG channels, and separately from anterior and posterior channels as well as from ECG channels. The major focus of this study was the duration of the P-wave that was manually measured in each sum channel. AF patients had a significantly longer duration of P-wave in all the MCG sum channels compared to the controls, whereas the difference was non-significant in the ECG sum channel. The mean duration of P-wave in anterior MCG sum channels was 133 ms in AF patients compared to 100 ms in the controls. Fragmentation index measuring differences between amplitude peaks over the P-wave was also significantly higher in the AF patients. This group also constructed MCG field maps from which a particular index (“p score”) to estimate homogeneity of the atrial signal was calculated, AF patients having significantly lower homogeneity. This study can be criticised in that the control group consisted of healthy young men not comparable with the AF patient group (Winklmaier et al. 1998). There are no publications comparing patients with persistent AF with a comparable control group, or documentation of atrial reverse remodeling with MCG.

3 Aims of the study

This study was accomplished to evaluate atrial remodeling behind AF and its epidemiology, in addition the results of treatment of AF. The prevention of AF, as well as reverse atrial remodeling were elucidated.

The specific aims of the study were:

1. To study the restoration and maintenance of sinus rhythm after their first electrical cardioversion in patients with persistent AF. The relations of the clinical outcome to patient characteristics, duration of AF, and medication with anti-arrhythmic properties, as well as progression to permanent AF were evaluated.

2. To study cardiovascular morbidity and mortality in hypertensive patients with ECG-documented LVH and a new-onset AF, as well as to determine whether selective angiotensin II type 1 receptor blockade with losartan is more effective than β-blockade with atenolol in reducing the incidence of new-onset AF.

3. To establish the frequency of AF in an AMI population with left ventricular dysfunction, and to study the association of AF with the outcome of the patients.

4. To validate recording and processing of atrial depolarisation signals by multichannel MCG, and to assess reproducibility of measurement of atrial signal variables.

5. To asses if MCG-based atrial signal analysis technique is able to detect atrial remodeling and its reversal after electrical cardioversion.

4 Subjects and methods

4.1 Study I

The subjects were one hundred and eighty-three AF patients of the population of 440,000 served by the Helsinki City Hospital who underwent their first elective cardioversion in Helsinki City Hospital during 1997. None of the 183 patients had AF associated with recovery phase of open cardiac surgery, which was the only exclusion criterion in this population-based evaluation.

The patients were found from the patient registers kept at the Helsinki City Hospital sites that performed elective electrical CVs in 1997. Clinical data, including diagnoses made by the physicians in charge, were obtained retrospectively from the hospital records. Follow-up data for a one-year period after the CV was aimed at, and if needed, these data were completed through direct contacts with the patients' doctors. The purpose of the study was to evaluate the result of the CV in terms of SR. The delay between ECG-verified diagnosis of AF and cardioversion was chosen to represent the duration of arrhythmia because of the difficulty of establishing the actual duration of AF. Relapse into AF was ECG verified, but timed according to patient's subjective symptoms, if present. Patients in whom cardioversion was not successful were considered early relapses of AF in order to include these patients in the analysis.

4.2 Study II

The LIFE trial was a prospective, randomised, double-blinded study that compared the long-term effects of antihypertensive therapies based on an ARB, losartan, with those based on a β-blocker, atenolol, in 9,193 patients with hypertension and LV hypertrophy. The present study evaluated the 8,851 patients with ECG-documented SR at baseline and no history of AF who were thus at risk of developing new AF.

New-onset AF was identified from annual in-study ECGs that underwent Minnesota coding for AF at a single ECG core center. The care of the patients with new-onset AF was left to the discretion of local investigators and the patients' own doctors. This study analysed the number of patients faced by the primary composite endpoint, which was the first occurrence of cardiovascular death, fatal or nonfatal stroke, and fatal or nonfatal myocardial infarction. Additional endpoints included all-cause mortality and the first occurrence of each component of the composite endpoint. All the reported endpoints were verified by independent monitors, and adjudicated by an independent committee.

4.3 Study III

The OPTIMAAL trial compared losartan with an angiotensin-converting enzyme inhibitor, captopril, on mortality and morbidity in patients with evidence of heart failure or left ventricular dysfunction and/or anterior Q-waves after AMI. The trial included 5,477 patients. In the present study were included those 655 patients who had AF at baseline plus those 345 patients who developed new AF during the follow-up period. The total number of patients with AF in this OPTIMAAL trial subanalysis was therefore 1,000.

AF was recorded on the case report form (CRF) as a pre-existing medical condition at the time of randomisation, or as an adverse experience based on ECGs taken at baseline or at follow-up visits during the study. AF at baseline was defined as either AF recorded on the medical history CRF or seen on ECG at randomisation. New-onset AF was defined as AF detected on an ECG after the randomisation in a patient without baseline AF.

4.4 Studies IV and V

In Study IV, the methodological basis of our MCG process was set up, and we examined recording and processing of atrial depolarization signals by multichannel MCG and assessed the reproducibility of the method. The study population consisted of ten healthy volunteers with no history of arrhythmia and nine patients with paroxysmal lone AF. To assess the reproducibility, recordings were repeated at least 1 week apart (from 1 week to 6 months).

Study V was completed to evaluate differences between AF patients weighed against a comparable control group. Twenty-six patients with persistent AF who underwent elective electrical CV after appropriate anticoagulation with no hemodynamically significant valvular disease, history of MI, other structural heart disease or use of class I or III antiarrhythmic medications were included. 24 age- and disease-matched men and women without history of AF served as controls. MCG, signal-averaged ECG (SAECG) and Doppler echocardiography were performed 1 to 3 hours after CV, and in those who stayed in SR, 1 month later as well. Control subjects had the tests performed once.

The same MCG method was used in both Studies IV and V and was as follows: The MCG recordings were performed in a magnetically shielded room (ETS-Lindgren Euroshield Oy, Eura, Finland) in the BioMag Laboratory of Helsinki University Central Hospital (Figure 7). A multi-channel cardiomagnetometer (Neuromag Ltd, Helsinki, Finland) was used. It was equipped with 33 triple-sensor direct current SQUID units, in each of which a magnetometer was overlaying 2 perpendicular planar gradiometers. Sensor units were arranged on a cylindrical, slightly curved surface with a diameter of 30 cm. The magnetic field component perpendicular to the sensor array surface (Bz) was measured. In these studies, signals recorded with magnetometers were used because of their superior signal-to-noise ratio in comparison with planar gradiometers. The subjects

were in supine position and the cardiomagnetometer sensor array was placed over anterior chest, the center positioned at 15 cm below the jugular notch and 5 cm to the left of the midsternal line (Figure 7) Simultaneously with MCG, a 3-lead orthogonal SAECG with bipolar lead placement was registered using disposable Ag/AgCl electrodes. Signals were recorded in SR over 5 minutes.

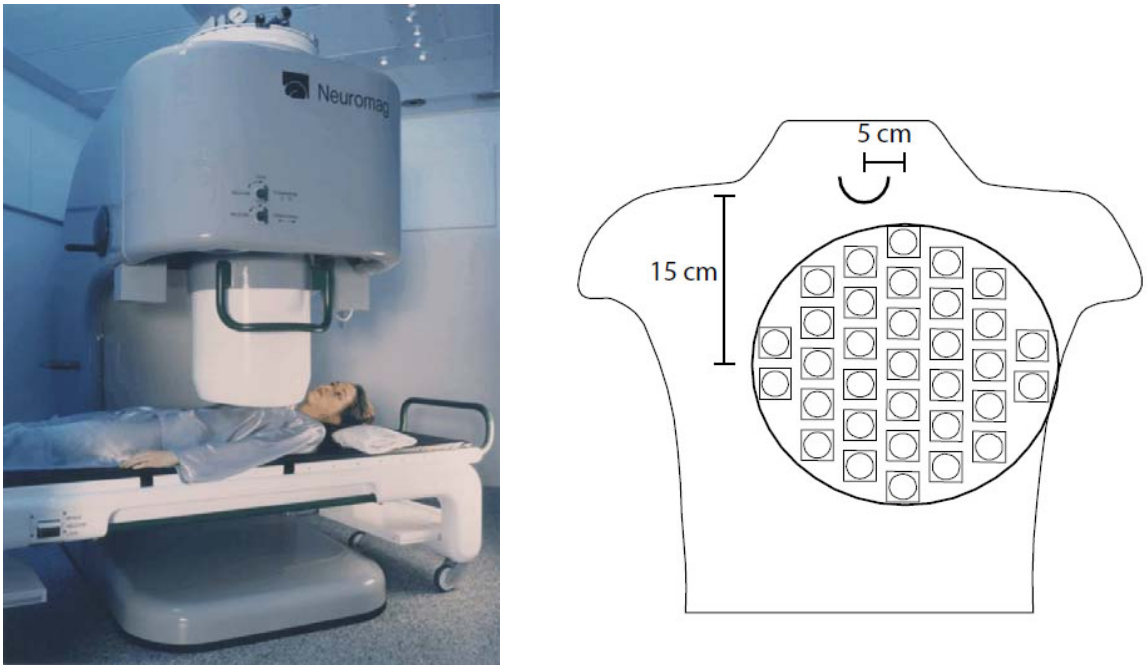

Figure 7. *MCG measurement with the cardiomagnetometer and positioning of the sensor array with 30 cm diameter containing 33 sensor units in regard to the subject's torso. The center of the array is located 15 cm below the jugulum and 5 cm to the left of the center of the chest.*

Analogue band-pass filtering of 0.03 to 300 Hz was applied and an analogy-to-digital conversion was made at sampling frequency of 1 kHz. P-wave averaging was based on QRS-triggering with the predominant P-wave morphology chosen for a template. P-wave complexes were accepted if they matched the template with cross-correlation of at least 95% for ECG-leads and 90% for MCG-channels. The goal was to have at least 100 atrial complexes averaged. In Study IV the averaged signals were highpass-filtered using bidirectional Butterworth-type, fourth-order filter having corner frequency at 25, 40, and 60 Hz to test different filterings, while in Study V only 40 Hz filter was applied. Noise was determined as the mean signal amplitude over a 40-millisecond time window in the TP segment. MCG-channels with a mean noise level greater than 20 fT were rejected. The onset and offset of atrial complex were automatically determined. The onset was defined as the midpoint of a 5-millisecond interval where the average amplitude first exceeds the mean noise level by 10 fT when approaching the atrial complex. The offset of the atrial signal was determined as follows: First, the lowest mean amplitude of a 5-millisecond

window between the atrial and QRS complexes was determined and set as reference noise level. Then, beginning from inside the atrial complex, the offset was defined as the midpoint of a 5-millisecond interval where the mean atrial signal amplitude declines to less than 10 fT above the reference noise level. The definitions for atrial signal onset and offset for SAECG were determined using a 1.0 μV limit in analogy to 10 fT in MCG. More detailed signal analyses and variables used in Studies IV and V are described in the original publications.

4.5 Statistical methods

Study I

In all the studies, data were expressed as mean ± SD, or as median when a variable with skewed distribution was considered, or number and percentage (%) of patients. The outcome in Study I was defined as the combined result of both restoration and maintenance of SR, and Kaplan-Meier survival plots were prepared, SR being considered survival. Covariates with a p-value of less than 0.20 in the log rank test were entered in the Cox proportional hazards regression analysis for multivariate modeling. To compare characteristics between the subgroups χ^2-test, Fisher exact test or two-sample t-test (two-tailed), when appropriate, was performed. A p-value of less than 0.05 was considered statistically significant.

Study II

Potential risk factors were assessed for association with new-onset AF. Cox proportional hazards models were used to compare hazard ratios (HRs) between study treatment allocation groups (losartan or atenolol) and to evaluate contributions of differences in the degree of LV hypertrophy, the Framingham risk score and other covariates. The risk of an endpoint associated with new-onset AF as well as the predictors of new AF were assessed with univariate proportional hazards regression model, and variables with significant effects were moved to multivariate analyses applying the Cox regression model. Two-tailed $p < 0.05$ was considered significant.

Study III

Differences between the groups at baseline were analysed with Student's *t*-test for continuous variables and Pearson's χ^2-test for categorical variables. The risk of developing AF associated with various baseline variables was evaluated using age-adjusted Cox regression models. The risk of total mortality, cardiovascular death, stroke, and all-cause hospitalisation associated with AF was analysed in two models. Firstly, patients with or without AF at baseline were compared in unadjusted and adjusted Cox regression models. Secondly, in patients without AF at baseline, new AF was included as a time-dependent co-variate in order to estimate the impact of new-onset AF after AMI. The impact of new-onset AF on endpoint risk was illustrated using modified Kaplan-Meier curves where the cohorts are continually updated with the existence or the extinction of AF (Simon and Makuch 1984). This modification makes the method

correspond to the Cox regression model with AF as a time-dependent co-variate. All reported p-values are two-tailed, and while no specific level of statistical significance was defined, a p-value of 0.001 should be considered to indicate strong evidence in support of a true effect.

Study IV

Correlation between variables was studied by Pearson correlation test. Coefficient of variation in repeated measurements was determined by analysis of variance, calculated as square root of mean square of within-subject variability divided by the mean of each variable (Chinn 1990, Bland and Altman 1996). Coefficient of variation was transformed to percentage value by multiplying by 100. Comparison of reproducibility between different filtering frequencies and between groups was performed using proportional difference, which was calculated as |m1 - m2| / [(m1 + m2)/2] for each subject. Differences in measured values and in reproducibility between the groups were examined with Student's *t* test. A 2-tailed p-value of < 0.05 was considered statistically significant.

Study V

The differences between patients and controls were calculated using two-sample Student's *t*-test (two-tailed) or χ^2-test, when appropriate. Analysis of covariance (ANCOVA) was performed when controls and patients were compared both at baseline and at repeated measurements including potentially confounding variables. Paired Student's *t*-test (two-tailed) was used for repeated measurements within the patient group.

5 Results

5.1 Frequency of atrial fibrillation

Frequency of AF in Study I can be estimated in perspective of the catchment areas of this part of Helsinki City covering 440,000 inhabitants. All the elective CVs of the AF patients that are the focus of the present study were performed and registered in the City Hospital during the time of the study. Based on the methods used, it was not possible to evaluate the prevalence of AF in Helsinki; neither could we estimate predictors of the incidence of AF. In Study I 183 patients were studied, and the incidence of patients with persistent AF referred for their first elective CV was thus 0.4 /1,000 person years. Our finding that 40% of patients with their first cardioversion will progress to permanent AF within one year has not been documented before (Figure 8). An interesting finding was that older age was associated with acceptance of permanent AF, and also that a longer duration of AF before the CV tended to associate with it.

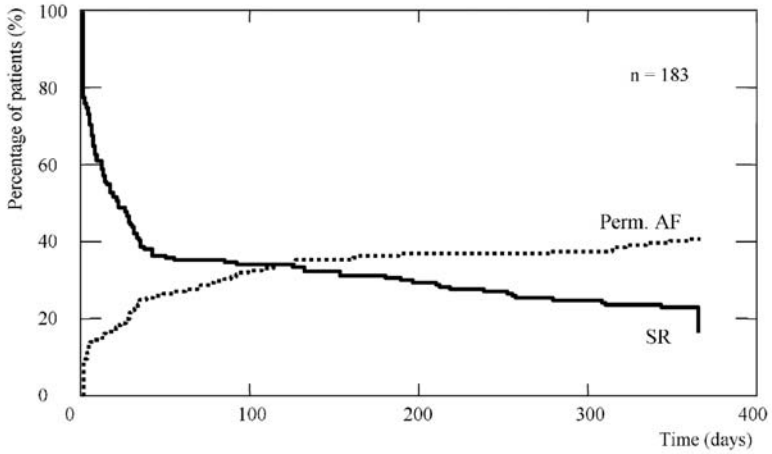

Figure 8. *The continuous line depicts restoration and maintenance of sinus rhythm after first cardioversion. The dotted line depicts cumulative proportion of patients with the decision to accept permanent atrial fibrillation (Perm. AF).*

The LIFE trial that was the source for Study II had 9,193 patients with hypertension and ECG verified LVH. At baseline, 3.7% of this population with the mean age of 66.9 years had AF. The characteristics of this cohort with baseline AF is documented in an other paper not included in this Thesis, AF patients being for example significantly older, less often women, having higher diastolic blood pressure and expression of LVH in ECG and especially having more often other cardiovascular co-morbidities (Wachtell et al. 2005). During the mean follow up of 4.8 years the incidence of new AF was 8.1 per 1,000 person years. Of the baseline characteristics higher age (HR for every year of age 1.09 $p < 0.001$), male gender (HR 1.56 $p < 0.001$), higher systolic blood pressure (HR for 10 mm

Hg 1.09, p = 0.023) and Cornell voltage duration (HR for 100 mV·ms 1.01, p = 0.030) were significantly associated with the incidence of new AF in the multivariate model.

The prevalence of AF at baseline in the OPTIMAAL trial was 12% (655 patients) of the total number of 5,477 patients randomised in this trial. As in Study II, patients with AF in Study III were significantly older and had significantly more often hypertension, ischemic heart disease, congestive heart failure, and cerebrovascular disease compared to those who did not have AF at baseline. Patients with AF had also significantly higher blood pressure and heart rate at baseline and exhibited more severe Killip class. Of the 4,822 patients without AF at baseline, 96 (2.0%) developed new-onset AF during the first 3 months after randomisation, and a total of 345 patients (7.2%) developed new AF during the follow-up period. Age-adjusted risks of development of new-onset AF in Study III were older age (HR per 10 years 1.66, p < 0.001), male sex (HR 1.65, p < 0.001), history of angina (HR 1.56, p < 0.001), more severe Killip class (relative to Class 1, p = 0.002), higher heart rate (HR 0.92 per 10 min, p = 0.041) and higher diastolic blood pressure at randomisation (HR 1.10 per 10 mmHg, p = 0.043). The results of frequencies of AF in the studies of this Thesis are collected in Table 1.

Table 1. *Frequency of AF in the studies of this Thesis.*
CV = cardioversion, HA = hypertension, LV(H) = left ventricular (hypertrophy), MI = myocardial infarction,

	Population	**Prevalence of AF**	**Incidence of AF**
Study I	General population of the catchment area of Helsinki; n = 440,000	na.	0.4 /1,000 referred for CV in one year due to persistent AF
Study II	LIFE-trial patients, Age 66.9 y, HA + LVH n = 9,193	3.7% at baseline had AF	8.1 / 1,000 person years
Study III	OPTIMAAL-trial patients, Age 67.4 y, MI + LV dysfunction; n = 5,477	12% at baseline had AF	7.2% in median 3 years

5.2 Impact of atrial fibrillation on mortality and morbidity

In Study II, cardiovascular morbidity and mortality were significantly more frequent in patients with new-onset AF than in those with persistent SR. Patients with new AF had in the adjusted model more often the primary composite endpoint (HR 1.88, $p < 0.001$), cardiovascular mortality (HR 1.57, $p = 0.021$), stroke (HR 2.82, $p < 0.001$) and heart failure (HR 4.96, $p < 0.001$). In the new-onset AF patients, those who were losartan-treated had a 40% lower rate of subsequent composite events compared to atenolol-treated patients ($p = 0.03$). There were fewer strokes (HR 0.49, $p = 0.01$), a trend toward fewer myocardial infarctions (HR 0.60, $p = 0.16$) and no difference in cardiovascular mortality between losartan- and atenolol-treated patients with new-onset AF. On the other hand, atenolol-treated patients with new-onset AF had fewer hospitalizations for HF (HR = 0.43, $p = 0.004$) and a trend toward fewer sudden cardiac deaths (HR = 0.22, $p = 0.07$).

Both baseline AF and new-onset AF were independent predictors of increased risk of total mortality, cardiovascular death and stroke in Study III. New-onset AF was associated with increased risk for 30-day mortality and stroke (HR 3.83, $p < 0.001$ and 14.6, $p < 0.001$), respectively; the absolute risk of death being almost 20% and the risk of stroke about 12% during the first month after AMI in patients with new-onset AF (Figure 9).

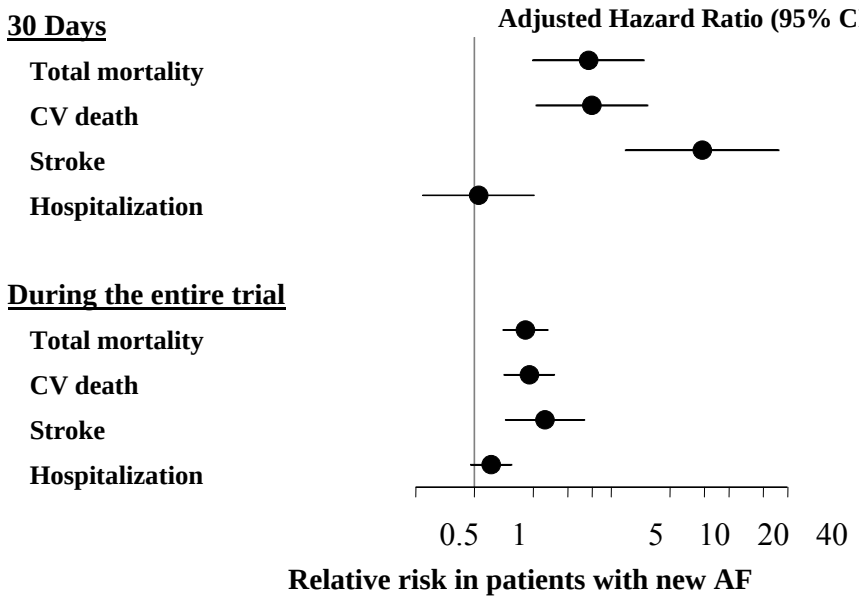

Figure 9. *Adjusted risk associated with new-onset AF in the OPTIMAAL-trial (Study III) CV = cardiovascular, CI = confidence interval*

5.3 Restoration and maintenance of sinus rhythm in patients with their first CV

One hundred and eighty-three patients underwent their first elective CV in Helsinki City Hospital during the one-year study period. CV was successful in 153 cases (84%). One-year maintenance rate of SR was 22% in all patients and 25% in those patients who had a successful CV. Age, hypertension, coronary artery disease, heart failure, valvular disease, weight, height and body mass index were not found to be associated with either restoration or maintenance of SR after the CV. Furthermore, in the subgroup of patients in whom echocardiography was performed, none of the echocardiographic parameters were associated with the outcome. The outcome in patients with lone AF was not better compared to the other patients. To study whether there was any association between the restoration and maintenance and the delay from the diagnosis of AF to cardioversion, patients were divided into two groups on the basis of the median delay of 78 days. After one year, 29% of the patients with a shorter delay maintained the restored SR, compared to 16% of the patients with a longer delay (HR 0.65, 95% CI 0.45 - 0.94, p = 0.047 in log rank, p = 0.022 in multivariate modeling) (Figure 10).

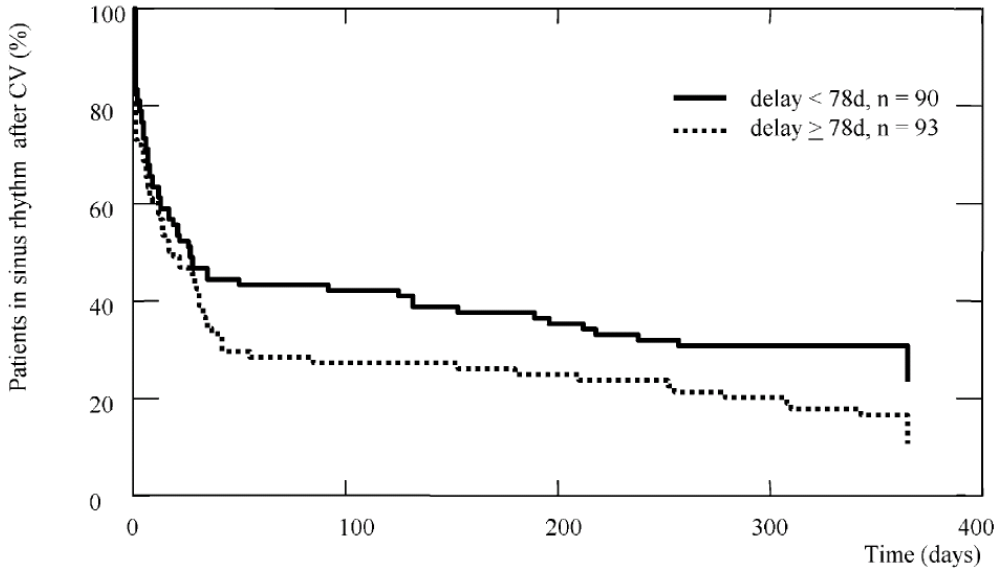

Figure 10. *Restoration and maintenance of sinus rhythm after first cardioversion. The patients have been divided into two groups by median delay (78 days) from diagnosis of atrial fibrillation to the cardioversion. p = 0.022 in Cox proportional hazards modeling.*

Three groups were large enough to allow comparisons to estimate the association of anti-arrhythmic medication on maintenance of SR. Patients treated with sotalol maintained SR significantly more often than patients who were treated with other β-blockers ($p < 0.001$ both in log rank and multivariate modelling), or patients who had no anti-arrhythmic medication ($p = 0.0017$ in log rank and $P= 0.0014$ in multivariate modelling) (Figure 11).

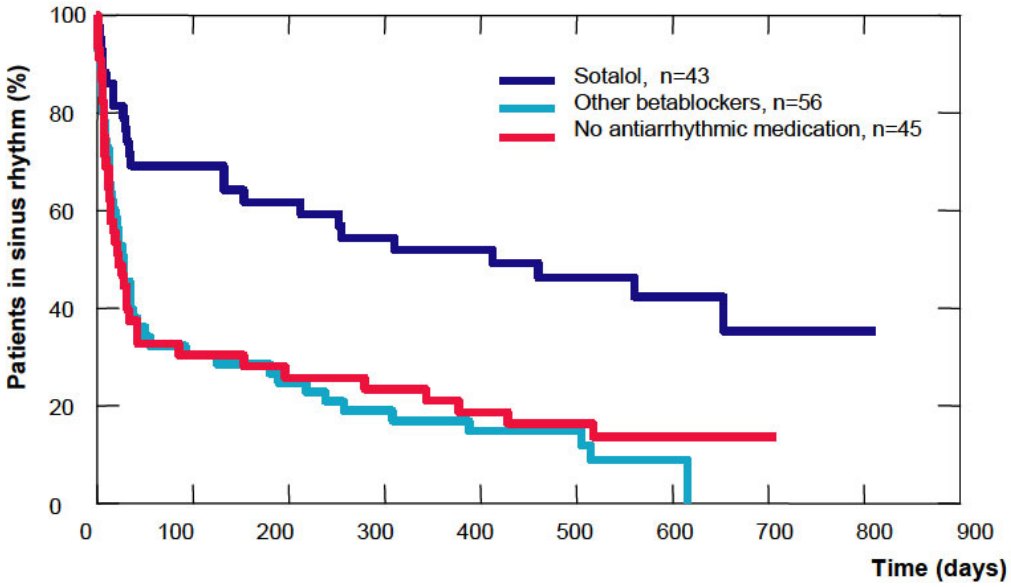

Figure 11. *Maintenance of sinus rhythm. Patients divided into three groups according to medication. P < 0.01 between sotalol and both the other groups.*

5.4 Incidence of new-onset AF and losartan

In Study II, the association of the randomisation group and the incidence of new AF was evaluated. New-onset AF occurred in 150 losartan- (6.8 per 1,000 person-years) and 221 atenolol-treated patients (10.1 per 1,000 person-years). Though the analysis of AF was not specified in the primary LIFE study analysis plan, evaluation of treatment effects in the subgroup of patients with new-onset AF was a planned secondary analysis before study termination. Randomisation to losartan remained significantly associated with lower incidence of new AF also after adjustment for other considerable variables (age, male gender, systolic blood pressure and Cornell voltage-duration product) (HR 0.67 p < 0.001). Figure 12 shows the incidence of new AF during the LIFE trial by randomisation groups.

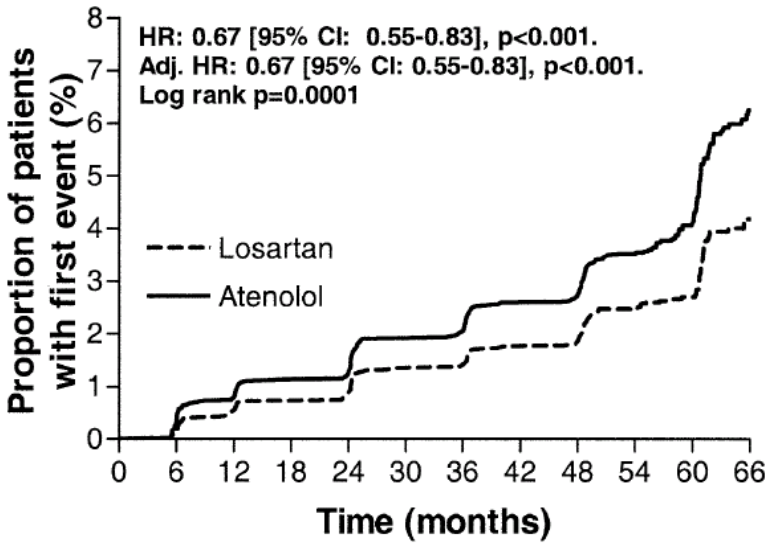

Figure 12. *Kaplan-Meier curves illustrating ECG-verified new-onset atrial fibrillation during follow-up in Study II.*
CI = confidence interval; HR = hazard ratio.

5.5 Atrial remodeling and reverse remodeling assessed with magnetocardiography

Reproducibility of the recording and analysis protocol of MCG was found to be equal in patients with paroxysmal AF and healthy controls in Study IV, 40 Hz overpass filtering giving the best reproducibility compared to 25 Hz and 60 Hz filterings. Coefficient of variation of MCG-measured atrial P-wave duration was 3.3% and difference between the measurements was on average 3.5 milliseconds, while the corresponding figures for simultaneously recoded SAECG were 6.1% and 6.9 milliseconds. These results of an agreeable reproducibility of MCG were crucial for Study V, where atrial remodeling and reverse remodeling were studied in cardioverted AF patients.

Of the 26 patients with persistent AF 15 remained in SR after CV over the one-month period and were re-examined by the protocol with MCG, SAECG and echocardiography. Immediately after CV the AF patients had in MCG significantly longer P-wave duration (Pd) and larger root mean square amplitudes of the last 40 ms portion of the P-wave (P RMS40) in comparison to controls. Pd dispersion (standard deviation of Pds of the included MCG channels and ECG-leads) in SAECG was larger in AF patients. In echocardiography AF patients had significantly lower left and right ventricle filling A-wave velocities immediately after CV. Likewise, LA and right atrial (RA) contractions were decreased, and LA diameter as well as LA and RA areas were larger when compared to controls (Tables 2 and 3). Examples of MCG recordings in a patient immediately after CV and one month after CV and in a representative control are shown in Figure 13.

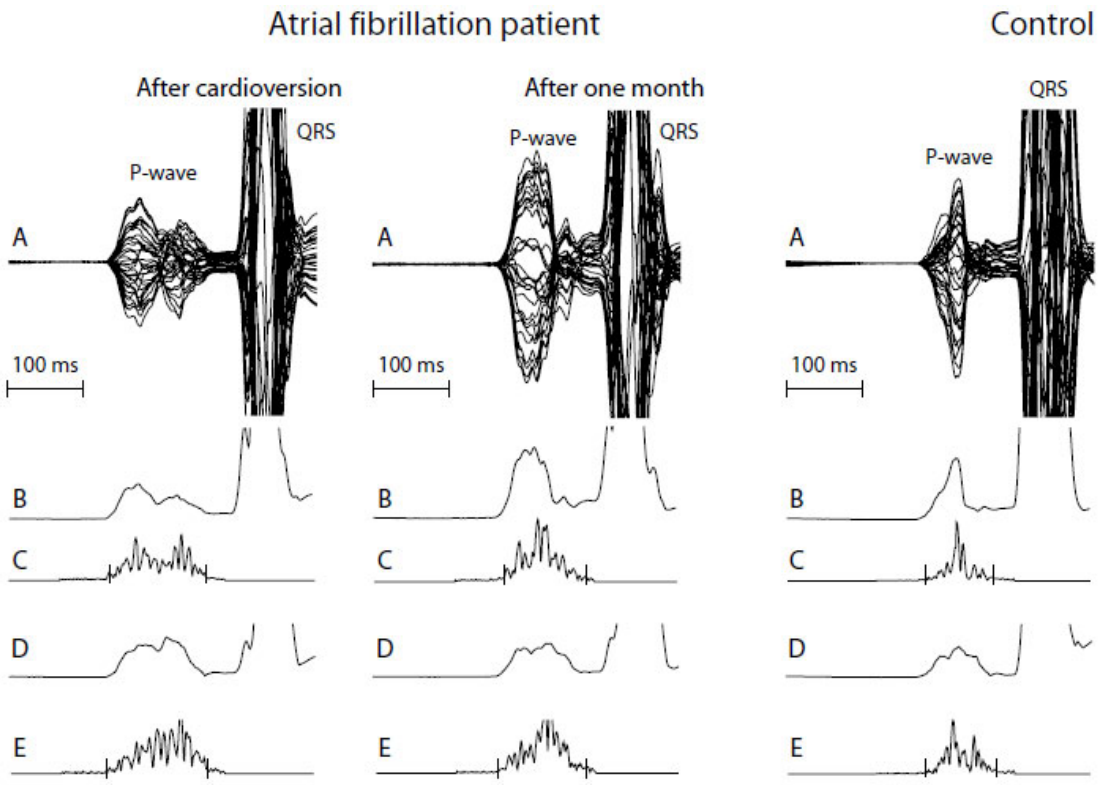

Figure 13. *Examples of MCG and SAECG recordings in a patient immediately after and one month after the CV and in a representative control.*
(A) Superimposed averaged P-wave of all included MCG-channels. (B) Spatial magnitude of MCG channels. (C) 40 Hz high-pass filtering of MCG spatial magnitude with automatically determined P-wave onset and offset (vertical bars). (D) Vector magnitude of SAECG. (E) 40 Hz high-pass filtering of SAECG vector magnitude with automatically determined P-wave onset and end.

After CV in patients who restored SR an improvement or reverse remodeling towards the values of the control group was detected in MCG, SAECG and echocardiography. LV and RV filling A-waves increased and the RA area and Pd dispersion in SAECG decreased significantly in AF patients. A trend of MCG-measured P-wave shortening and LA-diameter decrease in echocardiography was noticed. Pd in MCG, LA diameter and atrial areas in AF patients were still different from controls at re-examination after one month, emphasising that although reverse remodeling was documented, patients with a history of persistent AF still had significant abnormalities (Tables 2 and 3). In clinical practice as well as in Study I it has been noticed that the risk of AF relapse is highest during the first month after CV. The increased risk of AF relapse soon after CV is thought to arise from electrical remodeling, and rapid reduction of this risk is supposed to arise from reversal of electrical remodeling (Stafford et al. 1998, Hobbs et al. 2000, Chalfoun et al. 2007). If a patient remains in SR for one month, the risk of AF decreases and it is approximately 10-20%/year, which still is much higher compared to a population without documented AF before.

Table 2. *Atrial signal measurements of the patients at baseline and one month after cardioversion in comparison with age-matched control subjects.*
The values are means (SD). P-values refer to comparison with controls. All the p-values are from covariate analyses, where age and left atrial diameter were included as covariates. Pd, P-wave duration; MCG, magnetocardiography; SAECG, signal-averaged ECG; RMS40, root mean square of the last 40 ms of the high-pass filtered P-wave; fT, 10^{-15} tesla.

	Patients with atrial fibrillation				Controls
	After conversion to SR		After 1 month in SR		
	N=26	p	N=15	p	N=24
Pd in MCG; ms	122.8 (18.2)	0.0017	117.4 (18.2)	0.027	101.5 (14.6)
Pd in SAECG; ms	127.1 (12.7)	0.15	123.9 (13.3)	0.33	117.9 (12.6)
Pd dispersion in MCG; ms	20.4 (6.6)	0.16	17.5 (8.1)	0.44	18.9 (6.4)
Pd dispersion in SAECG; ms	18.1 (10.8)	0.040	11.0 (6.6)	0.92	12.3 (8.1)
P RMS40 in MCG; fT	60.4 (28.2)	0.021	50.1(23.0)	0.78	46.9 (19.1)

Table 3. *Doppler echocardiographic measurements of the patients at baseline and one month after cardioversion in comparison with age-matched control subjects.*
The values are means (SD). P-values refer to comparison with controls. LA, left atrium; RA, right atrium; contraction, systolic area minus diastolic area.

	Patients with atrial fibrillation				Controls
	After conversion to SR		After 1 month in SR		
	N = 26	p	N = 15	p	N = 24
Left atrial diameter; mm	42.8 (5.1)	0.0011	41.7 (4.3)	0.043	37.6 (4.9)
Ejection fraction; %	56.8 (5.4)	0.036	59.3 (5.1)	0.61	61.3 (6.2)
Mitral A-wave velocity; m/s	0.27 (0.12)	<0.001	0.52 (0.14)	0.58	0.58 (0.17)
Tricuspid A-wave velocity; m/s	0.28 (0.07)	<0.001	0.39 (0.09)	0.79	0.38 (0.08)
LA area; cm^2	24.8 (4.2)	<0.001	23.1 (4.3)	0.050	19.3 (3.8)
LA contraction; cm^2	4.2 (1.9)	0.0034	5.3 (1.7)	0.46	5.4 (1.5)
RA area; cm^2	22.4 (4.9)	<0.001	21.3 (4.1)	0.011	17.0 (2.9)
RA contraction; cm^2	3.8 (1.6)	0.022	5.1 (2.4)	0.96	4.6 (1.4)

6 Discussion

6.1 Atrial remodeling and epidemiology of atrial fibrillation

The prevalence and incidence of AF varies greatly among the populations studied. In general population the prevalence of AF is between 1.0 - 2.0% and the incidence of AF is about 2.0 per 1,000 person years (Krahn et al. 1995, Go et al. 2001, Majeed et al. 2001, Stewart et al. 2001, Ohsawa et al. 2005, Frost et al. 2005, Miyasaka et al. 2006). In older populations and patients with cardiovascular diseases the values are significantly higher. The prevalence of AF in Study I can be estimated in perspective of the catchment areas of this part of Helsinki City covering 440,000 inhabitants, of whom 183 were referred for their first elective electrical CV because of persistent AF. It can be supposed that half of the patients with new AF have persistent AF, and that most of the patients with a recent onset AF will have CV (Kannel 1983, Levy 1999, Murphy et al. 2007). Therefore our figure – 0.4/1,000 person years – can well be accepted as representing an estimation of the incidence of persistent AF in the general population in Helsinki. Remembering that in an individual, cardiovascular remodeling is a factor predisposing to AF, the concept of remodeling can be widened to populations, and one could say that epidemiology of AF reflects the degree of remodeling in the population and the subjects concerned.

The acceptance of chronic AF is a doctor-driven decision, but obviously it also reflects the remodeling phenomenon, or at least is based on more advanced atrial remodeling. In Study I we found that female gender and older age were associated with this decision, and with longer duration of AF there was a trend predisposing to chronic AF. This is well in accordance with the findings from the AFFIRM trial and the CARAF study where increasing age, longer duration of AF, atrial enlargement and diagnosis of cardiomyopathy were associated with progression to chronic AF (Curtis et al. 2005, Kerr et al. 2005).

Without structural heart disease AF is rare in populations younger than 50 years, and extremely rare in adolescents. The fact that AF virtually does not exist in young healthy hearts suggests that changes predisposing to AF occur in the atrial myocardium during aging. The majority of AF patients have a cardiovascular background diagnosis, most commonly hypertension, which is diagnosed in 50-60% of AF patients (Krahn et al. 1995, Kannel et al. 1998, Healey and Connolly 2003). Years or decades of elevated left ventricular pressure enhances left ventricular stiffness, impairs left ventricular diastolic function and causes LVH; as a consequence, left atrial pressure is increased, predisposing to atrial enlargement and spontaneous electrical activity (Healey and Connolly 2003). The importance of LVH was underlined in a substudy of the LIFE trial where it was found that regression of LVH on ECG was a predictor of lower incidence of new-onset AF regardless of the intensity of blood pressure lowering or treatment modality (Okin et al. 2006).

The other cardiovascular diseases significant at population level, such as coronary artery disease, valvular disease and heart failure, have a smaller prevalence among AF

patients and are diagnosed in 5-25%. All those conditions have some similarities when regarded as risk factors for AF. Firstly, hypertension as an independent cause of AF is also most often diagnosed along with coronary artery disease, valvular disease and heart failure. Secondly, all those diagnoses take a considerable time, most often years to develop as symptomatic diseases, with remodeling occurring in the atria at the same time because of increased atrial pressure and stretch. Additionally, because of improved survival of patients with cardiovascular diseases, aging is associated with a vast number of patients with hypertension, coronary artery disease, valvular disease and heart failure. Figure 14 illustrates relations between cardiovascular diseases, aging, atrial remodeling and AF.

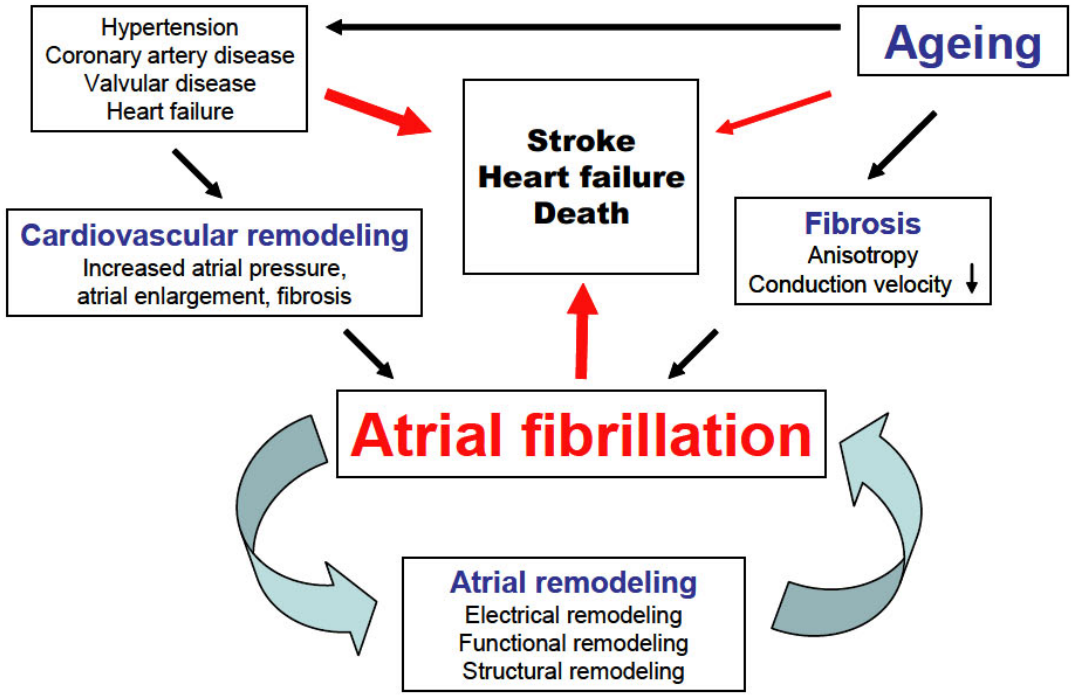

Figure 14. *Relations between atrial remodeling, cardiovascular diseases, ageing and AF.*

Aging is the most important factor that increases the frequency of AF. In the 21st century, the higher life expectancy will increase markedly the number of people older than 65 years, and very markedly the number of people older than 80 years. Remembering that the mean age of AF patients is about 70 years and that approximately 80% of AF patients are older than 65 years, there will be "a growing epidemic of AF". Because of population aging, the number of AF patients will be more than doubled during the next decades, at least in the USA (Feinberg et al. 1995, Chugh et al. 2001, Miyasaka et al. 2006). Accumulation of fibrous tissue on the atria and predisposition to cardiovascular diseases are the main mechanisms behind the increased propensity for AF with increasing ages (Allessie et al. 2002).

In patients with AMI, the elevated prevalence and incidence of AF also reflects the severity of cardiovascular remodeling. The frequency of AF is higher in older patients and in patients with more serious heart failure (Rathore et al. 2000). In epidemiological studies AF has affected 10-16% of AMI patients during the index hospitalisation, and in the TRACE trial where, as in Study III, patients with AMI and LV dysfunction were studied, 21% of the patients had AF before discharge (Goldberg et al. 1990, Sakata et al. 1997, Pedersen et al. 1999a). As a post-hoc analysis of a prospective randomised study – where AMI patients with the poorest prognosis could even have been excluded – we found a baseline frequency of AF 12%, and 18% of the patients had AF during the entire study period, mean 2.7 years.

6.2 Atrial remodeling and impact of atrial fibrillation on mortality and morbidity

Study I, even though unpowered to study mortality, did not suggest increased mortality in the patients referred for elective electrical CV. The mortality of 3 patients in 183 patient years is approximately the same as the probability of death in Finnish general population of the same age group; 15.7/1,000 person years (www.tilastokeskus.fi). In Study II where hypertensive patients with LVH were studied, new-onset AF was associated with an increased risk of cardiovascular mortality and morbidity, stroke and hospitalisation because of heart failure. In Study III where patients with AMI and LV dysfunction were studied both baseline AF and new-onset AF were associated with an increased risk of cardiovascular adverse events. Among those, the risk of stroke was most markedly increased in AF patients, and during the 30-day period after AMI the HR for risk of stroke was 14.6 in patients with new AF.

These findings are in line with published literature. In Study I, 81% of patients had a cardiovascular diagnosis, but they had stable, persistent AF and stable cardiac status during the period of the CV. Thus this cohort of AF patients in Study I was a somewhat selected AF population and presented a relatively healthy group of AF patients. Jahangir et al. evaluated a population-based cohort with lone AF for over 25 years and found no difference in the events compared to an age- and sex-matched population until the follow-up was expanded to over 25 years (Jahangir et al. 2007). Vidaillet et al. also studied a population-based cohort of patients with their first AF episode. In about half of that cohort AF diagnosis was made in the hospital setting, and AF had the HR of 1.7 for overall mortality, the risk associated with AF being highest during the immediate period after the diagnosis of AF (Vidaillet et al. 2002). The VALUE trial included patients with hypertension and a predefined cardiovascular risk. In an analysis based on this trial patients with new-onset AF had HR of the study primary endpoint of 2.2 and HR of the risk of stroke of 2.2 compared to the patients without AF (Schmieder et al. 2008). The risk of cardiovascular events related to AF, especially to new AF, is accentuated in patients with AMI (Goldberg et al. 1990, Rathore et al. 2000). Therefore it seems that the risk of a cardiovascular event associated with AF has a continuum, from a very low risk in patients

with stable lone AF to the highest risk in patients with AMI and LV dysfunction when this acute episode is complicated by a new-onset AF.

It has not, however, been solved whether AF is a cause of cardiovascular events and mortality, or a marker of more advanced status of cardiovascular diseases. The risk of stroke has a clear cause-and-consequence relationship with AF, the arrhythmia being a key source of stroke, at least in the elderly (Wolf et al. 1991). A clear temporal relationship between new AF and stroke was also found in Study III. Conversely, AF is associated with episodes – for example sudden cardiac death and coronary events – and also with overall mortality, which are not satisfactorily explained by AF (Køber et al. 2006, Marte et al. 2009). Furthermore, AF patients have had more complications even before the onset of AF, emphasising that a status predisposing to an event also predisposes to AF (Wong et al. 2000). Therefore, it is obvious that a severe heart disease with "atrio-ventricular remodeling" is a risk for an event, e.g. exacerbation of heart failure, ventricular arrhythmias and sudden cardiac death and furthermore mortality, and is also a risk for AF.

Atrial remodeling and propensity for AF as signaling ventricular disease has been documented by experiments where rapid ventricular pacing caused LV dysfunction and congestive heart failure, but compared to ventricles, atrial tissue was affected faster and to higher degree by injurious changes such as inflammation and fibrosis (Hanna et al. 2004). Additionally, in hypertensive patients left atrium enlargement has developed even before LVH (Miller et al. 1988). While the risk of developing AF and the risk of a cardiovascular episode vary a lot depending on the status of the population studied, the documented frequencies of AF can be regarded as markers of the extent of cardiac remodeling of a population.

Since advancing cardiovascular diseases cause cardiac as well as atrial remodeling predisposing to AF, AF can be understood as an indicator of more serious cardiovascular status and should be taken into consideration in treatment decisions. Associations between cardiovascular status, the risk of new-onset AF and the risk of cardiovascular events were also documented in Studies II and III. The associations between incidences of new AF and incidences of stroke and mortality in different clinical studies are illustrated in Figures 15 and 16. The source of the data of these figures is a group of prospective randomised studies where the frequencies were given acceptably; these data are shown in the Appendix in Table 6.

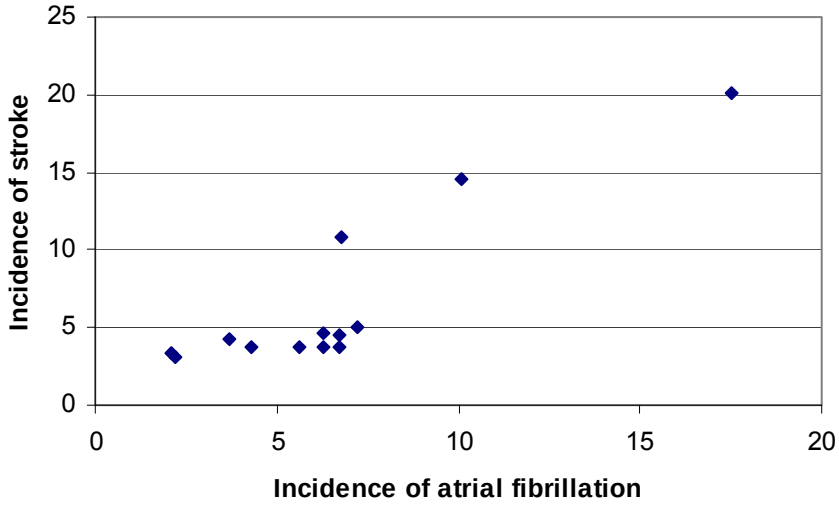

Figure 15. *Incidences of new AF and stroke in ten clinical trials with renin-angiotensin-aldosterone system-suppressing agents. Pearson's correlation matrix 0.89, $p < 0.001$.*

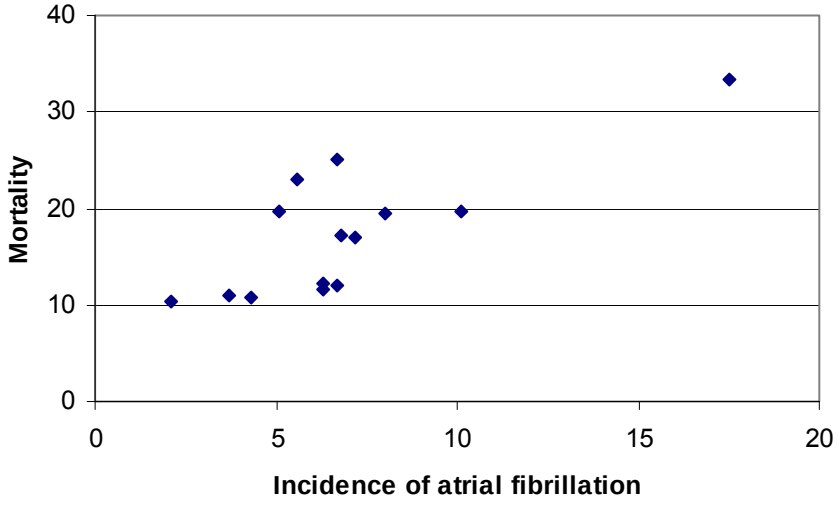

Figure 16. *Incidences of new AF and mortality in ten clinical trials with renin-angiotensin-aldosterone system-suppressing agents. Pearson's correlation matrix 0.78, $p = 0.001$.*

6.3 Atrial remodeling and the result of cardioversion

Besides the fact that markers of atrial remodeling are associated with increased frequency of AF in patients with cardiovascular diseases, atrial remodeling also hampers the efforts to restore and maintain SR in AF patients (Olsson et al. 1971, Ewy et al. 1980, Verhorst et al. 1997, Alt et al. 1997, Raitt et al. 2006). In Study I, patients with longer duration of AF and consequently longer period of exposure to atrial remodeling because of AF, had poorer restoration and maintenance of SR. The other clinical endpoint, acceptance of chronic AF, was observed more often in women and in older patients, while a longer duration of AF before the CV had a trend of being associated with this clinical decision. In Study V, the evaluation of predictors of restoration and maintenance of SR was not possible due to a limited number of patients.

6.4 Atrial remodeling and the renin-angiotensin-aldosterone system

The RAA-system is activated in hypertension and heart failure. The endproduct of RAAS, AngII, causes vasoconstriction, cardiac hypertrophy and fibrosis as well as endorses inflammation and causes electrophysiological changes (Felmeden and Lip 2000, Boos and Lip 2005, Schmieder et al. 2007). All these phenomena cause alterations predisposing to AF. Numerous studies have revealed that suppression of RAAS has an antifibrillatory effect on the atria and decreases the incidence of AF as well as increases the likelihood of SR in AF patients (Healey et al. 2005, Anand et al. 2006, Nattel et al. 2008). Formation of fibrosis in the atrial tissue of patients with cardiovascular diseases is enhanced, and antifibrotic properties are probably the main effect of those drugs preventing AF (Frustaci et al. 1997, Everett and Olgin 2007, Burstein and Nattel 2008). The finding from Study II where the incidence of new AF was decreased with an ARB, losartan, is well in line with these results. This is the first published result of an antihypertensive drug to decrease the likelihood of AF weighed against an active drug when losartan was compared to a β-blocker, atenolol. Losartan has been superior to atenolol in reducing left atrial diameter, and markers of atrial fibrosis have been significantly decreased with losartan, but not with atenolol (Ciulla et al. 2004, Gerdts et al. 2007).

6.5 Atrial remodeling and reverse remodeling

If atrial remodeling causes AF and also enhances the risk of AF relapse after restoration of SR, avoidance of remodeling and facilitating reverse remodeling would have a central role in prevention of AF. Avoidance of atrial remodeling due to cardiovascular diseases should include good primary prevention and prompt interventions to diagnose and treat those diseases in the best way achievable. Because of the great importance of hypertension in the development of cardiovascular diseases and also AF, the main emphasis should be on

prevention of high blood pressures and urgent management of hypertension. Like the treatment of hypertension, also the treatment of heart failure with RAAS suppressing agents has the best evidence to suppress cardiovascular or atrio-ventricular remodeling and also to reduce the frequency of AF. If AF is diagnosed and the rhythm strategy – restoration and maintenance of SR – is followed, SR should be restored as soon as possible to avoid atrial remodeling caused by AF itself (Van Gelder and Hemels 2006).

Atrial remodeling and reverse remodeling in all of their aspects – electrical, structural and functional remodeling – were documented in Study V. As an indicator of electrical reverse remodeling, MCG-measured P-wave was shortened in AF patients, while structurally, atrial dimensions were reduced, and functionally, atrial pump function was increased after CV. The finding of a significantly remodeled atrial P-wave recorded with MCG in AF patients when compared to a comparable control group was new. This finding proves MCG to be a valuable tool in assessing atrial electrical remodeling non-invasively. Shortening of P-wave in MCG, albeit not significantly, was documented after CV toward the values seen in the control group, but this reverse remodeling was incomplete and not enough to achieve a normal duration of P-wave. In the study of Manios et al. shortening of P-wave was also recorded during a one-month period after CV, and they found that the duration of the P-wave achieved the level of their control group. However, this study was performed with 12-lead paper ECG (Manios et al. 2000). With signal-averaging techniques – either SAECG or MCG – reverse electrical remodeling has not been documented in a study including a control group. Atrial dimensions also remained larger in AF patients. These findings suggest that patients who have had persistent AF, have long-lasting atrial electrical and structural properties predisposing to AF.

6.6 Clinical implications

AF is not a rare arrhythmia in general population, and it is very frequently diagnosed in patients with cardiovascular diseases, such as hypertension and AMI. If the status of those diseases is more severe, AF and especially new-onset AF is associated with an increased risk of stroke and mortality. Cardiovascular diseases such as hypertension, coronary artery disease and heart failure cause cardiovascular or atrio-ventricular remodeling that is more evident in the atria. The strong associations between more serious cardiovascular status, AF and cardiovascular events implicate a common factor behind those phenomena, the atrio-ventricular remodeling most probably being that factor. RAAS-suppressing medication has the best evidence of primary prevention of AF and it has also improved the restoration and maintenance of SR. Due to the nature of AF being atrial remodeling, rhythm control approaches aimed at restoring and maintaining SR are always too late when the arrhythmia is apparent, and a substantial number of patients remain in AF. To improve the outcome, SR should be restored with no delay, since patients with long-lasting AF tend to have enduring atrial electrical and structural remodeling changes predisposing to AF.

7 Conclusions

1. SR was restored in the majority of the patients (84%) referred for their first elective electrical CV due to new-onset AF. Of those who had successful CV only 25% maintained SR for one year. Duration of AF and sotalol therapy were the only predictive factors of a better outcome. During the one-year follow-up period chronic AF was accepted in 40% of the patients.

2. Hypertensive patients with LVH and new-onset AF had a significantly higher rate of cardiovascular events, stroke and cardiovascular mortality, and a trend of increased total mortality. Treatment with losartan reduced the rate of new-onset AF by 33% as compared to atenolol therapy with similar blood pressure reductions.

3. Twelve percent of patients in AMI population with LV dysfunction had AF and 7.2% developed new-onset AF during the mean follow-up of 2.7 ± 0.9 years. Older patients and patients with more severe cardiovascular disease had and developed AF more often. Patients with new-onset AF had a significantly higher risk of stroke and total mortality.

4. Atrial P-wave was reproducibly recorded and analysed with multichannel MCG both in AF patients and healthy controls. Reproducibility of an automated analysing method of MCG was not inferior in comparison with SAECG.

5. Atrial electrophysiological remodeling can be detected non-invasively with multichannel MCG in patients with persistent AF after electrical CV. When SR was maintained for one month reverse remodeling was observed, but there were still significant differences as compared to recordings from an age-matched control group with no history of AF.

Based on our results and the literature, AF is not a rare condition in either general population or patients with hypertension or AMI, and it is associated with increased risk of morbidity and mortality. Therefore, atrial remodeling that increases the likelihood of AF and also seems to be relatively stable has to be identified and prevented. RAAS-suppressing medications appear to be the most promising method to prevent atrial remodeling and AF.

Maintaining AF atrial remodeling is crucial – and reverse atrial remodeling is vital for maintaining SR in an AF patient.

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Table 4. *Summary of core studies evaluating the prevalence of atrial fibrillation*

Reference / Study	Town/Region, Country	Population	Symbol in Figure 1.	Prevalence of AF (%)				
				< 60 y	60-70 y	70-80 y	> 80 y	overall
Ostrander 1965	Tecumseh, MI, USA	5,129, RC, ≥ 16 y	♦	0.13	1.3	4.1	2.9	0.43
Go 2001 / ATRIA	California, USA	1.89 million, Kaiser Permanente (health maintenance organisation), ≥ 20 y	■	0.19	1.5	4.6	8.2	0.95
Majeed 2001	England and Wales, GB	1.5 million, GP practices, > 0 y	▲	0.18[1],1.4[2]	3.9[3]	7.9[4]	10.8[5]	1.2
Murphy 2007	Scotland, GB	0.36 million, GP practices, > 0 y	x	0.086[1], 1.1[2]	3.1[3]	6.2[4]	7.1[5]	0.87
Ohsawa 2005	300 districts in Japan	23,713, RC, ≥ 30 y	ж	0.2*	1.1	na.	2.9[6]	0.8*
Stewart 2001	Renfrew/Paisley, Scotland, GB	15,406, RC, 45 - 64 y	•	0.5**[7]	1.2**[8]	na.	na.	0.65
Wilhelmsen 2001	Göteborg, Sweden	7,495, random cohort of men, 47 - 59 y	+	0.74[9]	4.2[3]	8.0[10]	na.	0.74[9]
Wolf 1991 / FHS	Framingham, MA, USA	5,070, RC, 50 - 89 y	−	0.53[9]	1.8	4.8	8.8[11]	2.1
Heeringa 2006	Rotterdam, Netherlands	7,983, RC, ≥ 55 y	━	0.7[12]	2.1	7.3	15.4	5.5
Furberg 1994 / CHS	Four USA communities	5,201, Medicare lists, ≥ 65 y	◊	na.	4.0[13]	5.8	7.3	5.4

* Estimation from the table, ** estimation from the figure.

[1] 0 - 54 years, [2] 55 - 64 years, [3] 65 - 74 years, [4] 75 - 84 years, [5] ≥ 85 years, [6] ≥ 70 years, [7] 45 - 59 years, [8] 60 - 64 years, [9] 50 - 59 years, [10] 75 – 79, [11] 80 - 89 years, [12] 55 - 59 years, [13] 65 - 69 years.

RC = regional cohort, db. = database, GP = General Practitioner, FHS = Framingham Heart Study, CHS = Cardiovascular Health Study, y = years, na. = not available

Table 5. *Summary of core studies evaluating the incidence of AF*

Reference / Study	Town/Region, Country	Population	Symbol in Figure 2.	Incidence of AF (per 1,000 person years)				
				< 60y	60-70 y	70-80 y	> 80 y	overall
Miyasaka 2006	Rochester, MN, USA	124,000, RC (Olmsted County, Mayo Clinic), ≥ 18 y	▲	1.8*[1]	9.9 [2]	21[3]	34[4]	3.4
Benjamin 1994 / FHS	Framingham, MA, USA	4,731, RC, 55 – 94 y	■	5.0 ***[5]	14*** [2]	33*** [3]	69***[6]	na.
Wilhelmsen 2001	Göteborg, Sweden	7,495 cohort of men, 47 - 59 y	▬	2.0 [5]	5.8[2]	17[11]	na.	na.
Frost 2005	Copenhagen and Aarhus, Denmark	47,589 cohort of The Danish National Registry of Patients, 50 – 64 y	+	na.	na.	na.	na.	2.0
Heeringa 2006	Rotterdam, Netherlands	7,983, RC, ≥ 55y	●	1.1[12]	4.5	13	20	9.9
Krahn 1995 / MFUS	Manitoba, Canada	3,983 men, 18 – 62 y, mean 31 y	x	0.8***	4***	9***	16.9[13]	2.0
Psaty 1997 / CHS	Four USA communities	5,201, Medicare lists, ≥ 65 y	♦	na.	11[14]	20	41	19
Murphy 2007	Scotland, Great Britain	0.36 million, GP db., > 0 y		0.1[7], 1.1[5]	3.2[2]	6.2[3]	7.7[4]	0.9
Ruigómez 2002**	Great Britain	0.70 million, GP db., 40 – 89 y		0.2	1.5***	4.0***	8.6[8]	1.7

* Estimation from the table, ** only chronic AF included, *** estimation from the figure. [1] < 65 years, [2] 65 - 74 years, [3] 75 - 84 years, [4] >85 years, [5] 55 - 64 years, [6] 85 - 94 years, [7] < 54 years, [8] 80 - 89 years, [9] 45 - 59 years, [10] 60 - 64 years, [11] 75 - 79 years, [12] 55 - 59 years, [13] by 85 years, [14] 65 - 69 years. RC = regional cohort, FHS = Framingham Heart Study, db. = database, GP = General Practitioner, CHS = Cardiovascular Health Study, MFUS = Manitoba Follow Up Study, HA = hypertension, na. = not available.

Table 6. *Main data of the studies for Figures 15 and 16.*

Study	Incidence of AF	Risk of CV endpoint	Risk of stroke	Mortality
LIFE (Study II)	6.8 / 1,000 py. on Losartan 10.1 / 1,000 py. on Atenolol	23.8 / 1,000 py. on Losartan 27.9 / 1,000 py. on Atenolol	10.8 / 1,000 py. on Losartan 14.5 / 1,000 py. on Atenolol	17.3 / 1,000 py. on Losartan 19.6 / 1,000 py. on Atenolol
OPTIMAAL (Study III)	*7.2% / 3.0 years	na.	5.0% / 3.0 years	17% / 3.0 years
VALUE (Julius 2004, Schmieder 2008)	3.7% / 4.2 years on Valsartan 4.3% / 4.2 years on Amlodipine	10.5% / 4.2 years	4.2% / 4.2 years on Valsartan 3.7% / 4.2 years on Amlodipine	11.0% / 4.2 years on Valsartan 10.8% / 4.2 years on Amlodipine
CHARM (Pfeffer 2003, Ducharme 2006)	5.6% / 38 months on Candesartan 6.7% / 38 months on Pla.	30% / 38 months on Candesartan 35% / 38 months on Pla.	3.7% / 38 months on Candesartan 3.8% / 38 months on Pla.	23% / 38 months on Candesartan 25% / 38 months on Pla.
CAPPP (Hansson 1999a)	*2.2% / 6.1 years	na.	3.1% / 6.1 years	na.
STOP-H-2 (Hansson 1999b)	*17.5 / 1,000 py.	19.8 / 1,000 py	20.1 / 1,000 py.	33.4 / 1,000 py
Val-HeFT (Cohn 2001, Maggioni 2005)	5.1% / 23 months on Valsartan 8.0% / 23 months on Pla.	28.8% / 23 months on Valsartan 32.1% / 23 months on Pla.	na.	19.7% / 23 months on Valsartan 19.4% / 23 months on Pla.
HOPE (Yusuf 2000, Salehian 2007)	*2.1% / 4.5 years	14.0% / 4.5 years on Ramipril 17.8% / 4.5 years on Pla.	3.4% / 4.5 years on Ramipril 4.9% / 4.5 years on Pla.	10.4% / 4.5 years on Ramipril 12.2% / 4.5 years on Pla.
ONTARGET (ONTARGET Investigators 2008)	*6.7% / 56 months	16.6% / 56 months	4.5% / 56 months	12% / 56 months
TRANSCEND (TRANCEND Investigators 2008)	*6.3% / 56 months	15.7% / 56 months on Telmisartan 17.0% / 56 months on Pla.	3.8% / 56 months on Telmisartan 4.6% / 56 months on Pla.	12.3% / 56 months on Telmisartan 11.7% / 56 months on Pla.

* No difference between the arms. py. = patient years. Pla. = placebo. na. = not available.

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