Rhythm control strategies for symptomatic atrial fibrillation
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CHAPTER 1
GENERAL INTRODUCTION


Van Gelder IC, Hemels ME. The progressive nature of atrial fibrillation: a rationale for early restoration and maintenance of sinus rhythm. Europace 2006; 8:943-9. Review. (Published in part)
Atrial fibrillation is a major health problem. It is the most common sustained cardiac arrhythmia and the prevalence of atrial fibrillation continues to rise in Western nations. Recent research suggests that in the United States, for example, an estimated 2.3 million persons have atrial fibrillation. The overall lifetime prevalence of the arrhythmia is approximately 1 in 6 individuals for the general population, and roughly 1 in 4 for persons >40 years old.\(^1,2\) In the Netherlands lifetime risk of atrial fibrillation is similar, and the currently estimated prevalence of atrial fibrillation approximately 300,000 persons.\(^2\)

Atrial fibrillation causes symptoms such as palpitations, angina, dyspnea, impaired exercise tolerance and fatigue. Symptoms differ from patient to patient, ranging from mild discomfort to severe complications with a negative impact on quality of life.\(^3-6\) Patients are often substantially limited in their normal daily life because of the arrhythmia.\(^7,8\) The clinical basis of atrial fibrillation-related symptoms is not completely established. On one hand, it may be a combination of the severity of underlying heart disease and adverse hemodynamic effects due to loss of the atrial contraction and a rapid and irregular ventricular rate, especially in elderly with an impaired left ventricular systolic or diastolic function.\(^9\) In daily clinical practice it often remains difficult to differentiate between symptoms related to atrial fibrillation itself and symptoms resulting from underlying disease. On the other hand, young patients with paroxysmal atrial fibrillation without any underlying heart disease may be severely symptomatic possibly due to the sudden onset of the arrhythmia accompanied by rapid ventricular rates.\(^10,11\) In addition, anxiety and depression may play a role in the symptomatology of atrial fibrillation, which may be related to the fact that patients realize that they have a cardiac illness and the rapid heart rate suggesting a life threatening arrhythmia.\(^12-14\)

Besides reduction of symptoms and enhancing quality of life, there are two other major reasons for rhythm control (restoration and maintenance of sinus rhythm): prevention of heart failure and stroke. Atrial fibrillation may cause heart failure by reduction of cardiac output due to loss of the atrial contraction, high ventricular rate and ventricular rhythm irregularity, but also from the potential induction of tachycardia-induced cardiomyopathy.\(^15-24\) An important feature of the latter is its possible reversibility once sinus rhythm is restored.\(^17,25,26\) Atrial fibrillation also occurs frequently in the setting of heart failure and it may worsen heart failure and thereby increasing heart failure related symptoms and deteriorate prognosis.\(^27\)

Atrial fibrillation is the major cardiac cause of stroke, with an estimated annual risk of ischemic stroke of approximately 5-7%.\(^32-37\) This risk varies greatly depending on age, sex, and concomitant disease.\(^34,38\) Indeed, atrial fibrillation accounts for nearly 15% of all cerebral
thromboembolic events.\textsuperscript{39, 40} Besides embolism of thrombus due to stasis of blood in the left atrium, intrinsic cerebrovascular disease, other cardiac sources of embolism, or atheromatous plaques in the proximal aorta may also play a role in the pathogenesis of thromboembolism in patients with atrial fibrillation.\textsuperscript{41-43}

The arrhythmia is also associated with a 1.5–1.9 relative risk of mortality, at least in part related to the severity of underlying disease.\textsuperscript{35, 44-47} During the past 20 years, the age-standardized death rate (per 100,000) for atrial fibrillation patients in the United States jumped from 27.6 to 69.8 between 1980 and 1998, the latter rate being nearly 2 times as high as for those individuals in sinus rhythm.\textsuperscript{35, 48} Figure 1 shows the distribution of ‘causes of death’ in the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial and RACE (Rate Control versus Electrical Conversion) trial, both large randomized trials comparing different treatment strategies (rate and rhythm control) for patients with atrial fibrillation (patients with severe symptoms and heart failure were excluded).\textsuperscript{49, 50} In the AFFIRM trial during a mean follow-up of 3.5 years mortality rate was 16.4\% (666 patients out of 4060 patients with a mean age of 70 years at inclusion) and in the RACE trial mortality rate 7.7\% (40 out of 522 patients with a mean age of 68 years at inclusion) during mean follow-up of 2.3 years.\textsuperscript{51, 52} In both trials there were no differences in causes of death between rate and rhythm control treatment (except for non-cardiovascular death in the AFFIRM trial).

The impact of the development of atrial fibrillation on mortality in patients with chronic heart failure remains a subject of debate. Some studies showed no prognostic significance of atrial fibrillation development in these patients,\textsuperscript{53-56} while others showed a significant association of new-onset atrial fibrillation with increased mortality.\textsuperscript{45, 57, 58} More recent data suggest that atrial fibrillation predicts a high risk of cardiovascular morbidity and mortality regardless of baseline left ventricular ejection fraction, and, conversely, that atrial fibrillation is associated with greater relative increased risk of the major outcomes in patients with a preserved left ventricular systolic function than in patients with a low left ventricular ejection fraction.\textsuperscript{45, 59}
Chapter 1

Figure 1. Mortality in the AFFIRM and RACE trial according to cause.49, 50

AFFIRM (n=666)

- SCD: 24%
- Cardiac non-SCD: 14%
- Vascular: 11%
- Non-cardiovascular: 43%
- Unclassified: 8%

RACE (n=40)

- SCD: 39%
- Cardiac non-SCD: 13%
- Vascular: 38%
- Non-cardiovascular: 10%
- Unclassified: 0%

\[ N= \text{total number of deaths;} \quad \text{SCD= sudden cardiac death;} \quad \text{Vascular= non-cardiac thromboembolic and bleeding complications;} \quad \text{Unclassified= cause of death unknown.} \]

Finally, atrial fibrillation places a significant socioeconomic burden on society.60-64 The increasing number of patients with atrial fibrillation, due to the aging of the population, a rising prevalence of chronic heart disease, more frequent diagnosis through use of ambulatory monitoring devices, and other factors, has already become an extremely expensive public health problem.64 Hospitalization admissions for atrial fibrillation, being the main cost driver in the treatment of atrial fibrillation,65 have increased by 66% in the past 20 years.66 In England this resulted in almost 1% of all National Health Service expenditures (£655 million) on direct cost of atrial fibrillation in 2000. Currently, the total cost burden approaches 13.5 billion Euro
(approximately 15.7 billion U.S. dollar) in the European Union, which is approximately 3000 Euro annually per patient.63-65 This significant public health burden can be expected to grow as the prevalence of atrial fibrillation continous to rise as the population continues to age. In the RACE costs-study the cost-effectiveness of rate and rhythm control for the treatment of atrial fibrillation were compared.63 After 2.3 years of follow-up, mean costs per patient under rate control were 7,386 Euro and 8,284 Euro under rhythm control. Despite higher expenses (due to electrical cardioversions, hospital admissions and antiarrhythmic medicaton), rhythm control did not prevent morbidity and mortality, indicating that rate control is more cost-effective than rhythm control. Of note, most patients were retired so economic losses, due to time of work were neglected. However, in younger patients with symptomatic atrial fibrillation who are disabled or less productive at work, this may have significant economic consequences. In conclusion, besides factors as morbidity, mortality and quality of life, costs will increasingly aff ect the decision whether to adopt a specific treatment strategy (rate or rhythm control) for atrial fibrillation.

NATURAL HISTORY AND PATHOPHYSIOLOGY

Atrial fibrillation is primarily associated with underlying heart disease. Frequently observed underlying conditions are hypertension (most common), coronary artery disease, heart failure, and (mitral) valve disease.40,67,68 Figure 2 shows the distribution of underlying heart disease(s) of the patient group studied in the Euro Heart Survey on Atrial Fibrillation, a prospective survey on 5333 patients with atrial fibrillation (among 182 hospitals in 35 countries).68

Figure 2. Distribution of underlying heart disease(s) of the patient group (n=5333) studied in the Euro Heart Survey on Atrial Fibrillation subdivided in first detected, paroxysmal, persistent and permanent atrial fibrillation.68
Th ere is also increasing evidence that atrial fibrillation may be part of a spectrum of hypertension and diastolic dysfunction, atherosclerotic vascular disease, inflammation, and the metabolic syndromes.\textsuperscript{69-72} These acute or chronic hemodynamic, metabolic, or inflammatory stressors may lead to remodeling of the atrial tissue, thereby promoting initiation and perpetuation of atrial fibrillation.\textsuperscript{69} The association of these stressors with atrial fibrillation is a very important finding, allowing means for earlier identification of the arrhythmogenic substrate and triggers, and in developing therapies that are “upstream” to the arrhythmia and prevent their initial expression (upstream therapy).\textsuperscript{73}

Atrial fibrillation is part of a family closely interrelated supraventricular tachyarrhythmias (atrial tachycardia, atrial flutter and atrial fibrillation), and these different individual tachyarrhythmias may coexist in the same patient.\textsuperscript{74} By the use of a time-based clinical classification atrial fibrillation is divided into four groups: new-onset, paroxysmal, persistent and permanent atrial fibrillation, Table 1.\textsuperscript{75}

<table>
<thead>
<tr>
<th>Type of atrial fibrillation</th>
<th>Clinical characteristics</th>
</tr>
</thead>
</table>
| New-onset (first detected) | - Symptomatic or asymptomatic  
- Not seldom onset unknown |
| Paroxysmal                 | - Episodes of atrial fibrillation < 7 days, most often < 48 hours  
- Spontaneous conversion |
| Persistent                 | - Continuous atrial fibrillation, no spontaneous conversion  
- Can be converted to sinus rhythm (electrically) |
| Permanent                  | - Continuous atrial fibrillation  
- Cardioversion is unsuccessful or deemed unnecessary |

The recognition of these different types of atrial fibrillation is important in clinical practice, as each type of atrial fibrillation implicates a different treatment approach. In the present thesis patients with either paroxysmal or (new-onset) persistent atrial fibrillation were studied.

Ever since the first recognition of atrial fibrillation by Robert Adams in 1827, the underlying pathophysiological mechanism for initiation and perpetuation has been a subject of interest and extensive research. Different theories of atrial fibrillation mechanisms have been developed. It may either be (a) multiple functional reentrant circuits, (b) one or more rapidly discharging, spontaneously active, atrial ectopic foci, or (c) a single reentry circuit (“mother wave” or single rotor), see also Figure 3. Until recently, the multiple wavelet hypothesis, as has been formulated by Moe and experimentally confirmed by Allessie, was the generally accepted hypothesis to explain atrial fibrillation.\textsuperscript{76-78} The wavelength, being the product of the refractory period and conduction velocity, is the distance traveled by an impulse in one
refractory period. The number of wavelets being present simultaneously determines stability of atrial fibrillation. Thus, the shorter the wavelength and the larger the atria, the more waves fit into the atria and the more stable atrial fibrillation will be. Consequently, changes in refractory period and conduction velocity will affect the wavelength, and thus stability of atrial fibrillation.

Recent observations, however, have challenged the multiple wavelet hypothesis. Haissaguerre and colleagues observed in human subjects, by the use of multielectrode catheters designed to record the earliest electrical activity preceding the onset of atrial fibrillation, the spontaneous initiation of atrial fibrillation by atrial ectopic beats originating mainly from the pulmonary veins. The accuracy of the mapping was confirmed by the abrupt disappearance of triggering atrial ectopic beats after ablation with local radio-frequency energy.

Figure 3. Different theories on the mechanisms of atrial fibrillation initiation and perpetuation. (Adapted from Shiroshita-Takeshita et al. J of Int Cardiac Electrophysiol 2005, with permission)
In addition, optical mapping studies of atrial fibrillation in sheep hearts point to a primary local generator being either an ectopic focus or a small reentry circuit (rotor).\textsuperscript{33-35} These rotors, localized in the left atrial posterior wall and near the pulmonary veins, activate the atria at exceedingly high frequencies and result in fibrillatory conduction. The maintenance of atrial fibrillation may depend on the periodic activity of (a small number of) rotors. Results of recent clinical studies using radiofrequency ablation of the pulmonary veins support these findings.\textsuperscript{31, 86} These observations open new doors for both better understanding of atrial fibrillation pathophysiological mechanisms as the development of innovative treatment options to prevent or even cure atrial fibrillation.\textsuperscript{80, 86-88}

Figure 4 schematically shows the mutual relations of the four basic elements in the arrhythmogenesis of atrial fibrillation: triggers, substrate, modulating factors, and remodeling.

\textbf{Figure 4.} The four mutually related basic elements in the arrhythmogenesis of atrial fibrillation: triggers, substrate, modulating factors, and remodeling.\textsuperscript{70}
This figure illustrates the different, often strong interrelated, elements underlying atrial fibrillation. For atrial fibrillation to start, triggers are necessary. Triggers include atrial ectopic foci predominantly occurring from the sleeves of atrial tissue within the pulmonary veins and the vena caval junction, but also bradycardia, and other (supra)ventricular tachycardias. These triggers may initiate reentry if the wavelet is sufficiently short. Anatomical and functional obstacles, causing (regions of) delayed conduction or enabling reentry, may also be considered initiators (and substrate) of atrial fibrillation. A recent study performed by Hoffmann and colleagues using novel diagnostic dual-chamber pacemakers provided new insights into the initiation of paroxysmal atrial fibrillation. In 98 patients (31 of 98 patients with a conventional pacemaker indication) with recurrent, symptomatic, atrial fibrillation during a 2-month period 612 atrial fibrillation episodes were evaluated. The most common onset scenario was premature atrial complexes (PACs) before atrial fibrillation (48% onsets per patient), see also Figure 5. Furthermore, 33% of onsets per patient occurred within 5 minutes of a previous atrial fibrillation episode.

Figure 5. Frequency of onset triggers in 612 atrial fibrillation episodes of 98 patients with a novel diagnostic pacemaker (31 of 98 patients with a conventional pacemaker indication).

Onset of AF episodes (n=612)

The substrate ensures the perpetuation of atrial fibrillation for longer periods. Atrial fibrillation induction may occur in the presence of modulating factors like atrial stretch due to haemodynamic overload as is the case with hypertension or heart failure, thyroid function disturbances, influences of the autonomic nervous system, coronary artery disease. On the other hand, atrial fibrillation may beget atrial fibrillation itself. In 1995, two independent and almost simultaneously published papers were the first to demonstrate the phenomenon of atrial
tachycardia-induced electrophysiological remodeling. In healthy chronically instrumented goats, Wijffels et al. repetitively induced atrial fibrillation. The repetitive induction of atrial fibrillation increased the duration of successive episodes of atrial fibrillation, until it eventually did not convert spontaneously anymore, i.e. it became persistent. The atrial effective refractory period (AERP) significantly shortened and the physiological rate adaptation of atrial refractoriness became attenuated. As a result, the atrial wavelength decreased dramatically which, by allowing more simultaneously wandering wavelets, can explain the development of sustained atrial fibrillation. These electrophysiologic changes were termed ‘atrial electrical remodeling’. Morillo and colleagues showed besides the induction of persistent atrial fibrillation and a shortening of the AERP, a marked increase of intra-atrial conduction time (50%) and left and right atrial dilatation (45% and 67%, respectively) as explanation for the increased vulnerability for atrial fibrillation. This type of remodeling occurs rapidly (within several days) and plays a role in the increased stability of atrial fibrillation. Atrial stretch also remodels the atria. First, focal atrial premature beats or tachycardias that trigger atrial fibrillation may be induced. Second, stretch may induce shortening of the AERP, slowing of conduction, and heterogeneity in electrophysiological parameters all contributing to the occurrence and persistence of atrial fibrillation. Eventually, (ultra)structural remodeling may occur. Mary-Rabine et al. reported that patients with chronic atrial fibrillation showed the most abnormal ultrastructure consisting of abnormalities such as loss of myofibrils, intracellular accumulation of glycogen, focal accumulations of sarcoplasmic reticulum and aggregates of mitochondria while similar changes were also found by others. Atrial myocardium obtained from patients do show evidence of degeneration and/or apoptosis. However, this may also be related to underlying heart disease and not be the consequence of atrial fibrillation itself. A very interesting and important question is related to the mechanism underlying the atrial fibrillation-induced ultrastructural abnormalities. The morphological changes strikingly resemble changes seen in hibernating ventricular myocardium due to chronic low flow ischemia. Although this might be an indication that the structural changes in fibrillating atria are the result of repeated episodes of atrial ischemia, an alternative explanation would be that, next to electrophysiological and contractile remodeling also structural remodeling is caused by intracellular Ca\textsuperscript{2+}-overload (which also occurs during myocardial ischemia). Most modulating factors are potentially correctable, except for those which eventually cause irreversible, structural atrial damage. The presence of genetic disorders affecting refractory period and/or conduction velocity heterogeneously and senescence (the process of aging) are examples of mainly non-correctable modulating factors.
Atrial contractile remodeling follows a similar time course and causes a loss of contractility that may set the stage for thrombus formation. This type of remodeling may also lead to dilatation of the atria compounding the persistence of atrial fibrillation, since a dilated atrium permits the coexistence of more wavelets than a smaller atrium and may also alter electrophysiological properties (as mentioned before). In this respect, no uniform changes have been reported in various experimental studies, which have included different species, different models, and different degrees of severity and duration of atrial dilatation. Nevertheless, all studies demonstrated changes that supported the persistence of induced atrial fibrillation. Structural remodeling occurs after a period of weeks to months and includes dilatation of the atria, changes in cellular structure characterized by a loss of myofibrils, accumulation of glycogen, reduction in connexin 40, changes in mitochondrial shape and size, fragmentation of the sarcoplasmic reticulum, and dispersion of nuclear chromatin, as seen with rapid atrial pacing in a healthy goat model. These structural changes, which are indicative of a substantial deterioration of normal tissue architecture, likely promote atrial fibrillation. Moreover, they may be irreversible. Notably, these changes closely resemble those occurring in the setting of ischaemia-induced myocardial hibernation and have also been observed in patients, but only after a protracted period of persistent atrial fibrillation.

**GENETIC ASPECTS OF ATRIAL FIBRILLATION**

As mentioned before the majority of patients have atrial fibrillation in association with underlying (cardiac) diseases. In 15 to 30% of the patients, however, an etiology is absent. This condition is called idiopathic or lone atrial fibrillation. The incidence of lone atrial fibrillation depends on the type of atrial fibrillation (paroxysmal versus persistent) and how rigorously the patient has been evaluated. Some of these patients have a positive family history for atrial fibrillation and may have a genetic cause or predisposition. Darbar and colleagues observed that familial atrial fibrillation is more common than previously recognized. Of the 914 patients with atrial fibrillation they studied, 36% had lone atrial fibrillation and, of that population, a family history for atrial fibrillation was present in 15% of the patients (5% of all atrial fibrillation patients). After the first observation of Chen and colleagues, more recently Gollob and colleagues identified mutations in GJA5, the gene encoding for connexin 40, in the DNA of 4 out of 15 patients with lone atrial fibrillation, which supports the idea that atrial fibrillation may have a genetic basis.

Possible genes responsible for triggering and maintaining atrial fibrillation may
include genes that affect automaticity, atrial refractory period duration and conduction. Also observations in ageing patients with non-familial atrial fibrillation in the presence of underlying heart diseases suggest some form of genetic control in the pathogenesis of the more common form of atrial fibrillation. Table 2 gives a brief overview of current knowledge of both genotype and phenotype associated with the development of atrial fibrillation.

Obviously, these data are promising and may help to clarify why some people develop atrial fibrillation while others will never do, also in atrial fibrillation in the setting of heart failure. Furthermore, data of Tsai and colleagues might explain why drugs that affect the renin angiotensin system may have beneficial effects on the prevention of atrial fibrillation. In sum, familial atrial fibrillation is clinically and genetically heterogeneous and seems more common than previously suspected. Different phenotypes may point to distinct mechanisms and genes underlying familial atrial fibrillation. Identifying patients with genetic defects predisposing to atrial fibrillation may have important implications. Identification of the genes that play a role in the initiation of the arrhythmia may give us new insights into the development of the disease and improve our understanding and therapeutic options. Also, recognition of patients at risk may, eventually, decrease the prevalence of atrial fibrillation in turn reducing morbidity and mortality. Genetic heterogeneity and a relatively low genetic yield until now hampers extensive genetic evaluation in clinical practice.
Table 2. Genotype and phenotype associated with atrial fibrillation (AF): A. Monogenetic forms of lone AF, and B. Polymorphisms associated with AF in patients with concomitant underlying heart disease. (Adapted from Wiesfeld et al. Cardiovasc Res 2005, with permission).

### 2A. Monogenic forms of lone AF

<table>
<thead>
<tr>
<th>Gene/Chromosome</th>
<th>MOI</th>
<th>Fam</th>
<th>Type AF</th>
<th>Age</th>
<th>Race</th>
<th>HR</th>
<th>(A)symp</th>
<th>TCM</th>
<th>QTc (ms)</th>
<th>Mechanism</th>
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</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FAF 1-3</td>
<td>AD</td>
<td>3</td>
<td>PAF</td>
<td>38-51</td>
<td>?</td>
<td>high</td>
<td>symp</td>
<td>n=2</td>
<td>normal</td>
<td>?</td>
</tr>
<tr>
<td>FAF 4</td>
<td>AD</td>
<td>1</td>
<td>PAF</td>
<td>37</td>
<td>?</td>
<td>slow</td>
<td>asymp</td>
<td>no</td>
<td>too long in 2</td>
<td>?</td>
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<tr>
<td>II. Locus identified</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>10q22-q24</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAF 1</td>
<td>AD</td>
<td>1</td>
<td>CAF, (PAF)</td>
<td>18</td>
<td>Cauc</td>
<td>na</td>
<td>asymp</td>
<td>no</td>
<td>na</td>
<td>?</td>
</tr>
<tr>
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<td>2</td>
<td>CAF</td>
<td>2-46</td>
<td>Cauc</td>
<td>na</td>
<td>asymp</td>
<td>no</td>
<td>na</td>
<td>?</td>
</tr>
<tr>
<td>6q14-q16</td>
<td>AD</td>
<td>1</td>
<td>PAF, CAF</td>
<td>21-72</td>
<td>Cauc</td>
<td>na</td>
<td>na</td>
<td>no*</td>
<td>na</td>
<td>?</td>
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<tr>
<td>5p13</td>
<td>AR</td>
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<td>CAF</td>
<td>young</td>
<td>Chin</td>
<td>high</td>
<td>symp</td>
<td>some</td>
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<tr>
<td>III. Gene identified</td>
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<td>1</td>
<td>CAF</td>
<td>&gt;5</td>
<td>Chin</td>
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<td>na</td>
<td>50% long</td>
<td>*IKs↑</td>
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<td>PAF</td>
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<td>Chin</td>
<td>118-138</td>
<td>symp</td>
<td>no</td>
<td>normal</td>
<td>*IKs↑</td>
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<td>AD</td>
<td>1</td>
<td>PAF, CAF</td>
<td>50-58</td>
<td>Chin</td>
<td>63-118</td>
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<td>normal</td>
<td>*IK1↑</td>
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<td>PAF</td>
<td>30-40</td>
<td>?</td>
<td>na</td>
<td>symp</td>
<td>no</td>
<td>na</td>
<td>*IKr↓</td>
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<td>AD</td>
<td>1</td>
<td>PAF/AFL</td>
<td>12-20</td>
<td>Cauc</td>
<td>na</td>
<td>symp</td>
<td>no</td>
<td>normal</td>
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<tr>
<td>GJAS</td>
<td>?</td>
<td>1#</td>
<td>PAF</td>
<td>41</td>
<td>?</td>
<td>na</td>
<td>symp</td>
<td>na</td>
<td>na</td>
<td>dispersed conduction</td>
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### 2B. Polymorphisms associated with AF in patients with concomitant underlying heart disease

<table>
<thead>
<tr>
<th>Gene/chromosome</th>
<th>No. of Subjects</th>
<th>Type AF</th>
<th>Age</th>
<th>Race</th>
<th>HR</th>
<th>(A)symp</th>
<th>UHD</th>
<th>Mechanism</th>
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<tbody>
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<td>38G KCNE1^20</td>
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<td>CAF</td>
<td>63</td>
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<td>na</td>
<td>na</td>
<td>yes</td>
<td>I Ks ↓</td>
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<tr>
<td>38G KCNE1 ± -786T&gt;C eNOS^30</td>
<td>331</td>
<td>CAF</td>
<td>73</td>
<td>Cauc</td>
<td>na</td>
<td>na</td>
<td>yes</td>
<td>I Ks ↓</td>
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<tr>
<td>-44AA Connexin40^31</td>
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<td>PAF</td>
<td>33</td>
<td>Cauc</td>
<td>na</td>
<td>symp</td>
<td>WPW</td>
<td>possible</td>
</tr>
<tr>
<td>M235T, G-217A</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>G-6A Angiotensinogen^20</td>
<td>250</td>
<td>CAF</td>
<td>68</td>
<td>Chin</td>
<td>na</td>
<td>symp</td>
<td>yes</td>
<td>possible</td>
</tr>
<tr>
<td>C825T GNB3 G-Protein β3^32</td>
<td>227</td>
<td>PAF,CAF</td>
<td>58</td>
<td>?</td>
<td>na</td>
<td>na</td>
<td>59% hypertension</td>
<td>possible (I K,AH)</td>
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<tr>
<td>97T KCNE5^33</td>
<td>158</td>
<td>CAF,PAF</td>
<td>66</td>
<td>Cauc</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>possible (I K)</td>
</tr>
<tr>
<td>-174G/C Interleukin-6^34</td>
<td>110</td>
<td>Post op AF</td>
<td>61</td>
<td>?</td>
<td>na</td>
<td>na</td>
<td>yes</td>
<td>inflammation?</td>
</tr>
</tbody>
</table>

AF= atrial fibrillation; AFL= atrial flutter; (A)symp= (a)symptomatic; CAF= chronic/permanent AF; Cauc= Caucasian; Chin= Chinese; FAF= familial AF; Fam= Number of families; HR= heart rate; MOI= mode of inheritance; na= not available; PAF= paroxysmal AF; TCM= tachycardia induced cardiomyopathy; #: unknown; Post op AF= post operative AF; UHD= underlying heart disease; WPW= Wolf Parkinson White syndrome.

* 1 patient had a reversible tachycardia induced cardiomyopathy but no AF; **: multiple sudden deaths occurred at very young age; ***: 3 carriers suffered from stroke; #: no families but subjects.
TREATMENT OF ATRIAL FIBRILLATION

Mainstay in the treatment of atrial fibrillation is treatment of underlying diseases in patients with atrial fibrillation. Adequate treatment of the underlying (heart) disease is essential for successful treatment of atrial fibrillation, abolishing potential triggers, substrate and modulating factors. If an underlying disease is ongoing, electrical cardioversion, antiarrhythmic drug treatment and non-pharmacological interventions may have limited efficacy. Underlying disease, in particular hypertension, is often both underdiagnosed and undertreated. Besides, the type of underlying cause is an important determinant in the choice for antiarrhythmic drug treatment for atrial fibrillation (both efficacy and safety).

Rate or rhythm control
There are 2 basic strategies for the treatment of atrial fibrillation, rate and rhythm control, and each has its own benefits and drawbacks. Rate control involves acceptance of the arrhythmia and institution of ventricular rate controlling drugs and anticoagulation or (seldomly) permanent pacing after atrioventricular node ablation, aiming to regulate the ventricular rate during atrial fibrillation, and minimize potentially negative consequences such as symptoms, the development heart failure and thromboembolic complications. Rhythm control aims to restore and maintain sinus rhythm, initially by using electrical cardioversion and antiarrhythmic drugs, ultimately by non-pharmacological strategies.

The rhythm control approach was the treatment of choice for patients with atrial fibrillation, until a number of recent clinical trials — AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management), RACE (Rate Control versus Electrical Conversion), PIAF (Pharmacological Intervention in Atrial Fibrillation), STAF (Strategies of Treatment of Atrial Fibrillation), and HOT CAFÉ (How To Treat Chronic Atrial Fibrillation) — failed to demonstrate the anticipated benefits of pharmacological rhythm control strategies. In part however, this outcome may be due to a failure of pharmacological rhythm control.

Overall, only 40–73% of the rhythm control patients were in sinus rhythm at the end of follow-up, whereas the remainders were in atrial fibrillation. In line with this observation, a post-hoc analysis of AFFIRM demonstrated that maintained sinus rhythm is associated with an increased survival but antiarrhythmic drugs as presently available are deleterious. However, a post-hoc analysis of the RACE study showed that maintained sinus rhythm, under optimal conditions of continuous anticoagulation, does not ameliorate cardiovascular prognosis in patients with previous persistent atrial fibrillation. Thus, one of the reasons for choosing rate control is that rhythm control is often difficult to achieve in many patients.
and patients do not have complaints related to atrial fibrillation but to the underlying heart
disease, especially those with longer existing paroxysmal or persistent atrial fibrillation91, 112, 117,
146, 147 and those with more severe underlying heart disease.30, 67, 148-150 Furthermore, drawbacks
of the current pharmacological rhythm control options are the risk of adverse effects including
life threatening proarrhythmia. 64, 139-143, 151 In addition, many patients are not severely
symptomatic. Noteworthy, patients who were severely symptomatic from atrial fibrillation
were never included in these trials. The general consensus regarding the findings of the rate
versus rhythm control trials has been that the two strategies are essentially equivalent with
respect to the risk-benefit ratio for most patients with persistent atrial fibrillation, and that
rate control may be preferable in many patients, in particular (almost) asymptomatic patients
with persistent atrial fibrillation. However, especially in ‘younger’ symptomatic patients with
treatable underlying conditions, rhythm control remains the therapy of choice.152, 153 The
most common symptom in patients with persistent atrial fibrillation is dyspnoea and almost
half of the patients have complaints such as palpitations, angina, impaired exercise tolerance
or fatigue.67 There are many patients with paroxysmal atrial fibrillation who are (severely)
symptomatic during their episodes of atrial fibrillation because of their fast ventricular rate
and because of the sudden onset of tachycardia and irregularity induced by atrial fibrillation.
Therefore, of pivotal importance, new pharmacological and non-pharmacological therapies
are currently investigated in order to improve success of rhythm control, especially in those
who may benefit from from continuous sinus rhythm. 8, 153 The present thesis deals with
improvement of rhythm control in patients with symptomatic atrial fibrillation.

PHARMACOLOGICAL RHYTHM CONTROL

Many patients convert to sinus rhythm spontaneously after an episode of recent-onset atrial
fibrillation.154 If not, pharmacologic cardioversion with class Ic (and III) antiarrhythmic
drugs is very effective if atrial fibrillation lasts < 24 hours.155-163 If atrial fibrillation lasts >
24 hours electrical cardioversion is the therapy of choice.163, 164 Restoration of sinus rhythm
by cardioversion is highly effective, with success rates in over 90% of the procedures.163, 164
Unfortunately, in daily clinical practice recurrences of atrial fibrillation are seen frequently.147,
165 After successful cardioversion, only around 40% will remain free of atrial fibrillation after
1 year.147 With longer follow-up, this percentage is declining further.
**Efficacy and safety of currently available antiarrhythmic drugs**

To enhance maintenance of sinus rhythm a variety of drugs to prevent recurrence of atrial fibrillation have been widely tested. The choice of drug is based on the degree of structural heart disease and the underlying risk of pro-arrhythmia. Table 3 gives an overview of prospective (randomized) studies performed in the past 25 years on the efficacy of the available antiarrhythmic drugs in maintaining sinus rhythm after a episode of persistent atrial fibrillation, subdivided according to the Vaughn Williams classification.\(^{166}\) Class I, II, and III drugs, except for amiodarone, proved to be about equally effective (Table 3). Amiodarone was found to be most effective in maintaining sinus rhythm.\(^{8, 167-169}\) However, even with amiodarone recurrences still occur. Besides limited efficacy, significant adverse effects on antiarrhythmic drugs such as the risk of life threatening proarrhythmia (class I and III) and negative inotropic effects or other intolerable side effects necessitating withdrawal of the drug, are not uncommon. Table 3 shows the occurrence of significant side effects during treatment of the studied drugs.

A recent meta-analysis of Lafuente-Lafuente and colleagues showed that the use of class IA, IC and III anti-arrhythmic drugs significantly reduces recurrence of atrial fibrillation (number needed to treat, 2-9) in comparison with placebo, but all these drugs caused increased withdrawals due to adverse effects (number needed to harm, 9-27) and that in particular class IA drugs may even increase mortality.\(^{141, 170, 171}\) Other studies provided evidence about risk on life threatening proarrrhythmia by the use of class Ic and III antiarrhythmic drugs, which is especially problematic for those patients with underlying cardiovascular diseases.\(^{64, 139-143, 151}\) The major drawback of amiodarone is the frequent occurrence of non-cardiac side effects, whereas proarrrhythmia occurs seldom.\(^{172}\)

An other important recent issue concerning pharmacological management, especially in patients with paroxysmal atrial fibrillation, is the “Pill-in-the-pocket” strategy.\(^{173}\) This strategy consists of the out-hospital self-administration of a single dose of an oral antiarrhythmic drug in case of a recurrence of atrial fibrillation. In a selected, risk-stratified population of patients with atrial fibrillation, this strategy has proved to be an attractive, cost saving, and safe treatment option,\(^{172}\) after proven efficacy and safety in hospital.

In sum, despite prophylactic antiarrhythmic drugs, maintenance of sinus rhythm is cumbersome, either due to inefficacy or adverse effects necessitating withdrawal of the drug. The suboptimal risk-benefit profile of current antiarrhythmic drugs raises problems for clinicians, complicating the selection of treatments for long-term maintenance of sinus rhythm.
<table>
<thead>
<tr>
<th>Authors (acronym)</th>
<th>Journal (year)</th>
<th>Study design</th>
<th>n</th>
<th>Intervention</th>
<th>Pre-loading</th>
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<tr>
<td><strong>Class IA</strong></td>
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<tr>
<td>Boissel et al174</td>
<td>EHJ 1981</td>
<td>Randomized, open-label (n=207)</td>
<td>Quinidine 660 mg/d for 1 y (A), 3 m (B) or placebo (C) after ECV for pers AF</td>
<td>-</td>
<td>12</td>
<td>SR maintenance and side effects on quinidine treatment compared to placebo.</td>
<td>60% (A), 30% (B) and 20% (C) still in SR after 1 y*</td>
<td>20% (mostly gastrointestinal); 1 death due to pro-arrhythmia (1%)</td>
<td></td>
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<tr>
<td>Juul-Moller et al175</td>
<td>Circ 1990</td>
<td>Randomized, open-label (n=183)</td>
<td>Quinidine (A) 600 mg/d vs Sotalol (B) 160-320 mg/d after ECV for pers AF</td>
<td>-</td>
<td>6</td>
<td>SR maintenance and side effects on quinidine treatment compared to sotalol.</td>
<td>48% (A) and 52% (B) still in SR after 6 m. (NS)</td>
<td>26% (A), mostly gastrointestinal and skin, and 11% (B) (mostly CNS), no death.</td>
<td></td>
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<tr>
<td>Hohnloser et al176</td>
<td>JACC 1995</td>
<td>Randomized, open-label (n=50)</td>
<td>Quinidine (A) 0.5-1.0 g/d vs Sotalol (B) 160-320 mg before ECV for pers AF</td>
<td>+</td>
<td>6</td>
<td>Chemical CV outcome, SR maintenance and drug-induced adverse events</td>
<td>60% (A) versus 20% (B); chemical CV, 86% (A) versus 77% (B) in SR at 6 m (NS)</td>
<td>A: 28% gastrointestinal, 12% proarrhythmia; B: 4% Mobitz I block, 40% bradycardia. No death.</td>
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<tr>
<td>Karlson et al177</td>
<td>EHJ 1988</td>
<td>Randomized, double blinded (n=90)</td>
<td>Disopyramide (A) 250 mg/d vs placebo (B) after ECV for pers AF</td>
<td>-</td>
<td>12</td>
<td>SR maintenance and side effects on disopyramide treatment compared to placebo.</td>
<td>54% (A) and 30% (B) still in SR after one y*</td>
<td>11%; no drug related death</td>
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</table>

<p>| Class IC         |                |              |   |              |             |              |          |          |                |
| Van Gelder et al178 | AJC 1989 | Randomized, open-label (n=81) | Flecainide (A) 200-300 mg/d vs placebo (B) after ECV for pers AF or AFL | - | 12 | SR maintenance and side effects on flecainide treatment compared to placebo. | 49% (A) and 36% (B) still in SR after 1 y* | 9% (mostly negative dromotropic effects, 1 pro-arrhythmia); no death |
| Crijns et al179 | AJC 1991 | Prospective, non-randomized (n=127) | Serial ECV + AAD; fleca (stage I), sotalol or quinidine (stage II) or amio (stage III) after successful ECV for pers AF or AFL | + | 24 | AF free survival and side effects in each stage after 24 months | 31% after stage I, 42% after stage II, 63% after stage III. | Cardiac 4% on fleca, 13% on sotalol Non-cardiac 2% on fleca, 29% on quinidine 6% on amio, 1.6% death (1 fleca and 1 sotalol) |</p>
<table>
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<tr>
<td>Van Gelder et al</td>
<td>Arch Int Med 1996</td>
<td>Prospective, non-randomized (n=236)</td>
<td>Serial ECV for pers AF; no AAD after first ECV</td>
<td>-</td>
<td>48</td>
<td>The actuarial % of pts in SR after 1 and 4 years</td>
<td>Pts in SR after 1 y 42% and 27% after 4 y, in 51% additional AAD class I/III</td>
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<tr>
<td>Reimold et al</td>
<td>AJC 1993</td>
<td>Randomized, open-label (n=100)</td>
<td>Propafenone (A) 450-900 mg/d vs Sotalol 160-480 mg (B) after ECV for (P)AF</td>
<td>-</td>
<td>12</td>
<td>SR maintenance and side effects on propafenone treatment compared to sotalol</td>
<td>30% (A) and 37% (B) still in SR after 12 m, (NS)</td>
</tr>
<tr>
<td>Bianconi et al</td>
<td>IACC 1996</td>
<td>Randomized, double blinded (n=100)</td>
<td>Propafenone (A) 750 mg/d vs Placebo (B) started 48h before ECV of pers AF</td>
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<td>74% (A) versus 53% (B) still in SR after 48h after ECV*</td>
<td>7% withdrawal of propafenone due to adverse effects; No proarrhythmia or death</td>
</tr>
<tr>
<td>Crijns et al</td>
<td>PRODIS 1996</td>
<td>Randomized, double blinded (n=56)</td>
<td>Propafenone (A) 600-900 mg/d vs Disopyramide (B) 500-750 mg/d after ECV for pers AF</td>
<td>-</td>
<td>6</td>
<td>SR maintenance and side effects on treatment</td>
<td>55% (A) versus 67% (B) still in SR at 6 m, (NS)</td>
</tr>
<tr>
<td>Stroobandt et al</td>
<td>AJC 1997</td>
<td>Randomized, double blinded (n=136)</td>
<td>Propafenone (A) 450 mg/d vs Placebo (B) after chemical/ECV for pers AF</td>
<td>-</td>
<td>6</td>
<td>SR maintenance and side effects on treatment</td>
<td>67% (A) versus 35% (B) still in SR after 6 m.*</td>
</tr>
<tr>
<td>De Simone et al</td>
<td>IACC 1999</td>
<td>Randomized, open-label (n=107)</td>
<td>Propafenone 900 mg/d alone (A), + verap (240 mg/d until 3 d after ECV (B), or + verap continued (C), started before ECV for pers AF</td>
<td>+ 3</td>
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<td>62% (A) vs 87% (B) and 86% (C) maintenance of SR after 3 m.*</td>
<td>7.4% side effects with the combination propafenone and verapamil</td>
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<td>Bellandi et al</td>
<td>AJC 2001</td>
<td>Randomized, double blinded (n=300)</td>
<td>Propafenone (A) 450-900 mg/d, Sotalol 120-240 mg (B) or placebo (C) after (ECV for (P)AF</td>
<td>-</td>
<td>12</td>
<td>Maintenance of SR and side effects on treatment</td>
<td>56% (A), 65% (B) and 33% (C) in SR after 1 y.*</td>
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<td>Pritchett et al</td>
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<td>Propafenone 450 mg(A), 650 mg (B), 850 mg (C) vs placebo (D) for AF prevention</td>
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<td>3</td>
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<td>112 d (A), 291 d (B), &gt;300 d (C), 41 d (D)*</td>
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<td>Dogan et al</td>
<td>Acta Card 2004</td>
<td>Randomized, double blinded (n=110)</td>
<td>Propafenone (A) or placebo (B) after ECV for pers AF</td>
<td>-</td>
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<td>Maintenance of SR and side effects on treatment</td>
<td>61% (A) vs 35% (B) still in SR at 15 m.*</td>
</tr>
<tr>
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<td>Okishige et al</td>
<td>AHJ 2000</td>
<td>Randomized, double blinded (n=114)</td>
<td>Pilsicainide 150 mg/d (A) versus placebo (B) started before ECV for pers AF</td>
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<td>21% (A) versus 0% (B) chemical CV, 34% (A) versus 0% (B) still SR after 2 y*</td>
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<td>Kuhlman et al</td>
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<td>Metoprolol CR XL (A) 100-200 mg/d vs Placebo (B) after ECV for pers AF</td>
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<td>6</td>
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<tr>
<td>Plesan et al</td>
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<td>Randomized, open-label (n=128)</td>
<td>Bisoprolol (A) 5 mg/d vs Sotalol (B) 160 mg/d after ECV for pers AF</td>
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<td>Differences in arrhythmia recurrence and occurrence of proarrhythmia</td>
<td>After 1 y: 42% (A) vs 41% (B) recurrence of AF; NS</td>
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<tr>
<td>Benditt et al</td>
<td>AJC 1999</td>
<td>Randomized, double blinded (n=253)</td>
<td>Sotalol 160 mg (A), 240 mg (B), 320 mg (C) or placebo (D) for (P)AF(L)</td>
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<td>SR maintenance and side effects on treatment.</td>
<td>30% (A), 40% (B), 45% (C) and 28% (D) still in SR at 1 y; A vs B/C.*</td>
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<td>De Paola et al</td>
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<td>Sotalol (A) 160-320 mg vs Quinidine (B) 0.6-0.8 g/d after ECV for pers AF</td>
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<td>74% (A) versus 68% (B), NS, maintenance of SR after 6 m.</td>
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<td>Sotalol (A), quinidine verap (B) or placebo (C) after ECV for pers AF</td>
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<td>12</td>
<td>AF recurrence or death.</td>
<td>67% (A), 65% (B), 83% AF/death at 1 y; A vs B NS.</td>
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<td>Kochiadakis et</td>
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<td>Randomized, single blinded (n=254)</td>
<td>Sotalol (A), Propafenone (B) vs placebo (C) after ECV for (P)AF</td>
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<td>Maintenance of SR and free of side effects.</td>
<td>19% (A) and 52% (B) no AF or side effect after 18 m.*</td>
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<td>Gosselink et al</td>
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<td>Prospective, non-randomized (n=96)</td>
<td>Amiodarone (600 mg/d) before and low dose (204±66 mg/d) after ECV for pers AF</td>
<td>+</td>
<td>20.7 (mean)</td>
<td>BCV outcome, SR maintenance and intolerable adverse events on amio</td>
<td>16% chemical CV; 90% SR after ECV; 53% SR after 3 y.</td>
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<tr>
<td>Author</td>
<td>Journal</td>
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<td>Roy et al168</td>
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<td>Randomized, open-label (n=403)</td>
<td>Amiodarone (A) or sotalol/propafenone (B) before ECV for pers AF</td>
<td>+</td>
<td>16</td>
<td>SR maintenance and side effects on treatment.</td>
<td>65% (A) vs 37% (B) still in SR after 16 m. *</td>
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<td>Galperin et al195</td>
<td>JCPT 2001</td>
<td>Randomized, double blinded (n=95)</td>
<td>ECV for pers AF after amiodarone (A) or placebo (B) pre-treatment</td>
<td>+</td>
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<td>Chemical CV to SR and SR maintenance.</td>
<td>34% (A) versus 0% (B); chemical CV*, 60% (A) versus 20% (B) maintained SR*</td>
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<td>Kochiadakis et al169</td>
<td>Chest 2004</td>
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<td>Maintenance of SR and free of side effects.</td>
<td>72% (A) versus 56% (B) after 1 y, 42% (A) versus 51% (B) at 2 y.</td>
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<tr>
<td>Singh et al SAFE T</td>
<td>NEJM 2005</td>
<td>Randomized, double blinded (n=665)</td>
<td>ECV for pers AF after amiodarone (A), sotalol (B) or placebo (C) pre-treatment</td>
<td>+</td>
<td>36 (12-54)</td>
<td>Differences in maintenance of SR, chemical conversions (A,B,C) and side effects</td>
<td>SR maintenance was superior with A*, except for ischemic heart disease. No diff in CV to SR</td>
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<tr>
<td>Vijayalakshmi et al196</td>
<td>AHJ 2006</td>
<td>Randomized, open-label (n=94)</td>
<td>Amiodarone (A), sotalol (B) or no AAD (C) before ECV for pers AF</td>
<td>+</td>
<td>6</td>
<td>ECV outcome, arrhythmia recurrence between groups (A,B,C)</td>
<td>chemical CV, A,B,C: 7%, 7%/0% SR at 6 months, A,B,C: 63%, 59%, 16% (A vs B*, A or B vs C*)</td>
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<tr>
<td>Channer et al197</td>
<td>EHJ 2004</td>
<td>Randomized, double blinded (n=161)</td>
<td>Amiodarone 2 month (A), 12 month (B) or placebo (C) start before ECV for pers AF</td>
<td>+</td>
<td>12</td>
<td>Chemical CV to SR, SR maintenance and side effects.</td>
<td>21% (A+B) vs 0% (C); chemical CV, 32% (A), 49% (B) and 5% (C) SR at 1 y.</td>
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<tr>
<td>Singh et al SAEFRE D</td>
<td>Circ 2000</td>
<td>Randomized, double blinded (n=325)</td>
<td>Dofetilide 250 mcg (A), 500 mcg (B), 1000 mcg (C) or placebo (D) before ECV for pers AF</td>
<td>+</td>
<td>12</td>
<td>SR maintenance and side effects on treatment.</td>
<td>6% (A), 10% (B), 30% (C) vs 1% (D) chem CV* and 40%, 37%, 58% (A,B,C) vs 25% SR at 1 y.*</td>
</tr>
<tr>
<td>Page et al ASAP</td>
<td>Circ 2003</td>
<td>Randomized, double blinded (n=1380)</td>
<td>Azimilide (A) 35-25 mg/d versus placebo (B) for AF prevention</td>
<td></td>
<td>6</td>
<td>Occurrence of asymptomatic AF</td>
<td>13% (A) versus 18% (B) asymptomatic AF, NS.</td>
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<td>EHJ 2006</td>
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<td>+</td>
<td>6</td>
<td>SR maintenance and side effects on treatment.</td>
<td>19% (A), 33% (B) and 15% (C) SR at 6 m (A vs B* and A vs C*).</td>
</tr>
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<tr>
<td>Touboul et al²⁰¹</td>
<td>EHJ 2003</td>
<td>Randomized, double blinded (n=270)</td>
<td>Dronedarone 800 mg(A), 1200 mg (B), 1600 mg (C) vs placebo (D) started before ECV of pers AF</td>
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<td>6</td>
<td>Chemical CV to SR and SR maintenance.</td>
<td>6% (A), 8% (B) and 15% (C), 3% (D) chemical CV*, 35% (A) vs 10% (D) still in SR after 6 m.*</td>
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<td>Villani et al²⁰²</td>
<td>AHJ 2000</td>
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<td>Diltiazem (A), amiodarone (B) or digoxin (C) before ECV for pers AF</td>
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<td>1</td>
<td>Difference in outcome and arrhythmia recurrence between groups (A,B,C)</td>
<td>Spontaneous CV; A,B,C 6%, 25%, 3%<em>; 1 month recurrence; A,B,C: 56%, 28%, 78% resp.</em></td>
</tr>
<tr>
<td>Van Noord et al²⁰³</td>
<td>JCE 2001</td>
<td>Randomized, open label (n=97)</td>
<td>ECV for pers AF after verapamil (A) vs digoxin (B) pre-treatment</td>
<td>+</td>
<td>1</td>
<td>Difference in outcome and arrhythmia recurrence</td>
<td>75% (A) vs 83% (B); ECV successful and 47% (A) vs 53% (B) recur AF at 1 m (NS)</td>
</tr>
</tbody>
</table>

Class IV

# Adverse effects leading to discontinuation of drug; * p<0.05; Preloading: +=yes, -=no, SR=SR at start study; AAD=antiarrhythmic drug; AF=atrial fibrillation; ECV=electrical cardioversion; HF=heart failure; PAF=paroxysmal atrial fibrillation; Pers AF=persistent atrial fibrillation; SR=sinus rhythm.
Prohibiting electrical remodelling

One strategy to enhance rhythm control may involve prevention of remodeling. Tieleman and colleagues showed in a rapid pacing model in healthy goats that electrical remodeling was reversible over a period of slightly more than 24 hours and this process could be modulated by administrating various drugs. The finding that verapamil (a L-type calcium channel blocker, reducing intracellular calcium) reduced atrial electrical remodeling and digoxin (a Na/K-ATPase pump inhibitor, indirectly increasing intracellular calcium) delayed recovery from electrical remodeling in the goat, suggested that tachycardia-induced calcium overload might trigger the shortening of the AERP. Calcium transients underlying the excitation-contraction coupling in cardiac cells result mainly from calcium release from the sarcoplasmatic reticulum. This calcium release during each action potential, is under normal circumstances primarily triggered by calcium entering the cell through L-type calcium channels (calcium-induced calcium release). Additional fractions can enter the cell via the sodium-calcium exchanger and T-type calcium channels. All three pathways are capable of triggering sarcoplasmatic reticulum calcium release and contraction, but the relative contribution and efficacy is largest for the L-type Calcium channels (thesis dr. B.J.J.M. Brundel). When the atria go from sinus rhythm to atrial fibrillation, there is a ten-fold increase in atrial rate. As a result intracellular calcium loading is substantially enhanced. Atrial myocytes protect themselves against this process in different ways, including inactivation of functional calcium influx via L-type calcium channels (short term) and downregulation of L-type calcium channels (long-term). These changes reduce the atrial action potential duration, and as a consequence the AERP shortens. These changes increase the probability of multiple co-existing atrial wavelets, which in turn set the stage for persistence of atrial fibrillation (AF begets AF), and may promote the mostly irreversible process of structural remodeling. Several other studies supported the concept that atrial calcium overload and reduction of L-type calcium channels are the primary cause of electrical (and contractile) remodeling.

Experimentally, prevention of calcium overload by calcium antagonists may decrease intractability of atrial fibrillation by preventing remodeling processes and thus outcome of a rhythm control strategy. Table 4 shows the outcome of randomized studies in human on the efficacy of calcium-lowering therapy on the maintenance of sinus rhythm in patients with persistent atrial fibrillation. Although effective if prescribed in combination with antiarrhythmic drugs, verapamil monotherapy seems ineffective to prevent subacute recurrences. The discrepancy with experimental data may relate to the fact that in patients almost always calcium lowering treatment is started after start of atrial fibrillation. Furthermore, consecutive episodes of atrial fibrillation cumulatively increase the degree of remodeling prohibiting
prevention of remodeling by calcium lowering therapy.\textsuperscript{217}

Experimental atrial fibrillation-induced electrical remodeling takes 24-48 hours, and it is considered reversible within 1-5 days.\textsuperscript{91, 204, 205, 218} A few human studies suggest that in patients undergoing cardioversion for persistent atrial fibrillation, maintaining sinus rhythm for at least a few days is needed to develop reversed remodeling.\textsuperscript{163, 219-223} In addition, an eventual relapse of atrial fibrillation must be stopped within hours to avoid recurrence of electrical remodeling.\textsuperscript{163, 224} Stable sinus rhythm is best accomplished when atrial fibrillation is diagnosed and treated early, preventing the eventually irreversible remodeling processes.\textsuperscript{147} Following recurrences of atrial fibrillation, remodeling may happen again and again, and the efficacy of verapamil in this setting (a serial cardioversion strategy) has not been tested before. This is investigated in chapter 2 of this thesis.

\textit{Prevention of structural remodeling – substrate development}

Fibrosis increases with aging and atrial fibrillation itself also leads to fibrosis, which increases with longer duration of the arrhythmia. One of the strongest triggers for fibrosis is dilation of the atria or stretch as is most often seen in chronic heart failure, hypertension, and coronary artery disease. Fibrosis causes heterogeneity of atrial conduction and increased regional disparity of refractoriness, thereby promoting the induction and maintenance of atrial fibrillation. Several studies showed that reducing the angiotensin II levels with an angiotensin-converting enzyme inhibitor (ACE-inhibitor) resulted in attenuation of interstitial fibrosis, improvement of conduction, and shortening of atrial fibrillation duration.\textsuperscript{227, 228} The effects of Angiotensin II inhibition on fibrosis were independent of blood pressure changes. Angiotensin II may contribute to atrial fibrillation by 1) activation of intracellular pathways leading to hypertrophy and atrial dilation, 2) aldosterone production enhancing fibrosis, and 3) increase of electrical remodeling. Angiotensin II may mediate its effect on tissue structure by a GTP-coupled receptor that stimulates three mitogen-activated protein kinases (extracellular signal–regulated kinases 1 and 2 (ERK 1 and 2), c-Jun NH2-terminal kinase, and p38), leading to hypertrophy and fibrosis. Goette and colleagues found that enalapril only inhibited the ERK pathway, without affecting the others.\textsuperscript{229} This suggests that ACE inhibition is not sufficient to reduce the full spectrum of fibrosis pathways. By contrast, angiotensin receptor blockers may block all pathways by inhibiting the Angiotensin type I receptor. Surprisingly, statins downregulate the angiotensin I receptor, thereby attenuating the effects of angiotensin II on blood pressure and angiotensin II–induced hypertrophy. In animal models of infarct-related chronic heart failure, treatment with statins reduces myocyte hypertrophy and interstitial fibrosis of the noninfarcted myocardium. In these models cardiac remodeling was attenuated and cardiac function was improved.
### Table 4. Randomized trials on the efficacy of treatment with nondihydropyridine calcium-antagonists in preventing recurrences of atrial fibrillation after electrical cardioversion for persistent atrial fibrillation.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Journal (year)</th>
<th>Included patients (n); AF duration (m)</th>
<th>Intervention</th>
<th>Pre-loading</th>
<th>Follow-up (m)</th>
<th>Outcomes</th>
<th>Efficacy</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verapamil/diltiazem alone</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Villani et al225</td>
<td>AHJ 2000</td>
<td>120; 4±1</td>
<td>Diltiazem 360 mg/d (A), amiodarone (B) or digoxin (C)</td>
<td>+</td>
<td>1</td>
<td>Difference in outcome and arrhythmia recurrence between groups (A,B,C)</td>
<td>Spontaneous CV; A,B,C: 6%, 25%, 3%; 1 month recurrence; A,B,C: 56%, 28%, 78% resp*</td>
<td>None</td>
</tr>
<tr>
<td>Van Noord et al203</td>
<td>JCE 2001</td>
<td>97; 1 (0-12)</td>
<td>Verapamil 120-360 mg/d (A) vs digoxin (B)</td>
<td>+</td>
<td>1</td>
<td>Difference in outcome and arrhythmia recurrence</td>
<td>75% (A) vs 83% (B) ECV successful and 47%(A) vs 53% (B) recur AF at 1 m (NS)</td>
<td>8.3% on verapamil</td>
</tr>
<tr>
<td>Lindholm et al215</td>
<td>Heart 2004</td>
<td>100; 9±7</td>
<td>Verapamil 240 mg/d (A) vs digoxin (B)</td>
<td>+</td>
<td>3</td>
<td>Difference in outcome and arrhythmia recurrence</td>
<td>12% (A) vs 0% (B) spont CV*; 91% (A) vs 72% (B)*</td>
<td>6.1 % side effects on verapamil, 2% digoxin</td>
</tr>
<tr>
<td><strong>Verapamil combined with class I/III AAD</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>De Simone et al204</td>
<td>JACC 1999</td>
<td>107; 17±21</td>
<td>Propafenone 900 mg/d alone (A), + verap (240 mg/d) until 3 d after ECV (B), or + verap continued (C) after ECV</td>
<td>+</td>
<td>3</td>
<td>SR maintenance and side effects on treatment</td>
<td>62% (A) vs 87% (B) and 86% (C) maintenance of SR after 3 m*</td>
<td>7.4% side effects with the combination propafenone and verapamil.</td>
</tr>
<tr>
<td>Bertaglia et al216</td>
<td>Heart 2001</td>
<td>100; 8±24</td>
<td>Verapamil 240 mg/d + amiodarone (A) versus amiodarone alone (B)</td>
<td>+</td>
<td>1</td>
<td>Difference in arrhythmia recurrence between groups (A vs B)</td>
<td>no significant difference A vs B; 54% vs 43% resp.</td>
<td>2% in group A</td>
</tr>
<tr>
<td>De Simone et al216</td>
<td>EHJ 2003</td>
<td>363; 2±2</td>
<td>Amiodarone (A), flecainide (B), Amiodarone+verapamil 240 mg/d (C), flecainide + verapamil 240 mg/d (D)</td>
<td>+</td>
<td>3</td>
<td>Difference in arrhythmia recurrence between groups (A, B, C,D)</td>
<td>Recurrence A, B, C, D: 32%, 38%, 20%, 21%. A B vs D sign. reduction*, A vs C p=0.08</td>
<td>3.6% pharmacological side effects, no difference (A-D)</td>
</tr>
</tbody>
</table>

# Adverse effects leading to discontinuation of drug; * p<0.05; Preloading (before ECV): +=yes, -=no, AAD=antiarrhythmic drug; AF=atrial fibrillation; ECV=electrical cardioversion; SR=sinus rhythm.
A statin in combination with an ACE-inhibitor given to patients with hypertension resulted in a larger decline in heart size than treatment with an ACE-inhibitor alone.\textsuperscript{230} This effect was independent of the blood pressure. Indeed, ACE inhibition\textsuperscript{231, 232} and blockade of the angiotensin II type 1 receptor\textsuperscript{233} were able to prevent structural remodeling and atrial fibrillation promotion in dog models of ventricular tachycardiomyopathy. Kumagai and colleagues hypothesize that the mechanism of maintenance of atrial fibrillation involves stretch and inflammation increasing the levels of angiotensin II, which increases the level of calcium and promoting abnormal automaticity from the pulmonary veins, thereby initiating atrial fibrillation.\textsuperscript{233, 234} Angiotensin II activates the Erk cascade, promoting fibrosis and inducing slow conduction.\textsuperscript{235} AERP shortening plus slow conduction allow easy formation of reentry circuits and maintain atrial fibrillation. ACE-inhibitors or angiotensin receptor blockers thus target stretch, angiotensin II, calcium overload, Erk formation, and fibrosis. ACE-inhibitors and angiotensin receptor blockers may thus be \textit{upstream antiarrhythmic therapy} for preventing structural remodeling thereby improving rhythm control therapy. The clinical relevance has recently been illustrated.\textsuperscript{121, 233, 236-240} Table 5 gives an overview of the results of several clinical studies on the impact of ACE-inhibitor and angiotensin receptor blocker use on the primary and secondary prevention of atrial fibrillation in patients with and without systolic heart failure. Although the majority of studies were post-hoc analyses, prone to multiple-testing error and bias, the data demonstrate that a clinically significant reduction in atrial fibrillation can be expected in human subjects treated with ACE-inhibitors or angiotensin receptor blockers.

As alluded to earlier another mechanism by which angiotensin II may lead to fibrosis is via the production of aldosterone. Experimentally, mineralocorticoid-induced cardiac fibrosis and inflammation cannot only be prevented but also reversed by eplerenone.\textsuperscript{241} In the randomized aldactone evaluation study (RALES) it was shown that aldosterone antagonist spironolactone reduces left ventricular mass in patients with nonischemic chronic heart failure.\textsuperscript{242} In addition, hospital admission and survival were favorably affected. In that study, 2 serum markers of fibrosis significantly decreased with spironolactone. These results suggest that the specific blockade of aldosterone receptors in patients with atrial fibrillation might have antiarrhythmic effects. However, this remains to be proven.

As described earlier, metabolic processes like inflammation and oxidative stress, also play a role in the pathogenesis of atrial fibrillation. There is evidence to suggest that levels of C-reactive protein (CRP), a marker of systemic inflammation, are elevated in patients with atrial fibrillation.\textsuperscript{243} A recent study showed that the addition of low-dose glucocorticoid therapy to ongoing propafenone therapy decreased plasma CRP levels, producing a dramatic
reduction in atrial fibrillation recurrence in patients with persistent atrial fibrillation and normal left ventricular function. Conversely, other data suggest a higher risk of atrial fibrillation during high dose glucocorticosteroid treatment. However, while there may be a link between inflammation and atrial fibrillation, the clinically relevant protective effect of (low dose) glucocorticoids remains uncertain, also given the potential adverse effects. Also N-3 polyunsaturated fatty acids (PUFAs), of which oily fish are an important source, are believed to possess both anti-inflammatory properties and antiarrhythmic effects and to have potential in the prevention and treatment of atrial fibrillation. Although, only a few prospective (randomized) studies have been published on the therapeutic use of fish oils in atrial fibrillation. Lipid lowering drugs, especially 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), possess anti-inflammatory and antioxidative properties and are therefore considered to have potential antiarrhythmic properties. Currently, there have been several animal and human studies demonstrating reduction in serologic and tissue markers of inflammation, and decreased electrical remodeling as a result of statins. Table 6 gives an overview of recently performed clinical studies on the effect of statin treatment in the prevention of atrial fibrillation. Given the fact that most of the currently performed studies of the effect of statins on atrial fibrillation in humans have the same study limitations (i.e. post hoc analyses and in part related to initial lipid lowering effects) as studies with ACE-inhibitor and angiotensin receptor blockers, more randomized studies on the potential antiarrhythmic role of statin treatment in the prevention and treatment of human atrial fibrillation are needed. Finally, in this context, the influence of life style should never be forgotten.

Early repeated cardioversion
As mentioned before, sinus rhythm is best accomplished when atrial fibrillation is diagnosed and treated early, preventing the eventually irreversible remodeling processes. Atrial fibrillation itself causes electrical remodeling which experimentally takes 24-48 hours, and this is considered reversible within 1-5 days. These data suggest that in humans maintenance of sinus rhythm for at least a few days after cardioversion for persistent atrial fibrillation seems essential to develop reversed remodeling. In line with this, recent research of Tieleman and colleagues showed in patients with persistent atrial fibrillation treated with an electrical cardioversion, that flecainide regains its antiarrhythmic activity only in patients with recurrences of no longer than 10 hours atrial fibrillation after a preexistent period of continuous sinus rhythm for more than four days, see also Figure 6. So, an eventual relapse of atrial fibrillation must be stopped
within several hours to avoid recurrence of electrical remodeling. Moreover, after a relapse gap of 25 hours (Thesis dr. T. Van Noord) the recurrence rate of atrial fibrillation is highest during the first 2 weeks after cardioversion. Moreover, recently Todd et al showed that repetitive atrial fibrillation episodes in goats suggests the presence of a "second factor", besides electrical remodeling, in the self-perpetuation of atrial fibrillation. Early repeated cardioversions, aimed to restore normal sinus rhythm as soon as possible in case of atrial fibrillation recurrences and the eventual use of antiarrhythmic drugs to prevent (early) recurrences, might avoid electrical, contractile, and eventual (ultra)structural remodeling.

Figure 6. Results of the MEDCAR study; On the X-axis the duration of sinus rhythm (SR) until recurrence of atrial fibrillation (AF). On the Y-axis the time to flecainide infusion to treat an AF recurrence. All dots represent individual patients (n=51). Flecainide was only effective in a subset of patients (open dots, 7 out of 51 patients [14%]) with a duration of SR > 4 days and a duration of AF < 10 hours as indicated by the open circles. (Adapted from Tieleman et al. Heart Rhythm 2005, with permission)

Up to now, several (small) clinical studies have been performed to investigate whether an early repeated cardioversion could improve maintenance of sinus rhythm. External (transesophageal echocardiography facilitated) cardioversion, internal cardioversion and the implantation of an atrial defibrillator have been tested, showing diverging results. Although a policy of early repeated cardioversion may be clinically valuable in some patients who have episodes of highly symptomatic persistent atrial fibrillation, this strategy poses potential practical problems in both early detection and eventual cardioversion. In addition, data on
the effect of an early repeated cardioversion strategy on quality of life are scarce. Therefore, we investigated (in a randomized setting) whether during a serial electrical cardioversion strategy, acute cardioversion of subacute recurrences will decrease intractability of persistent atrial fibrillation (chapter 2).

**Atrial fibrillation, heart failure and rhythm control**

Outcome of a serial cardioversion approach is impaired in patients with heart failure, but the exact cause is unknown. It may be due to more severe atrial structural remodeling and a lower efficacy and safety of antiarrhythmic drugs. Both disorders profoundly increase cardiovascular morbidity and limit quality of life, and are often present in the same patient. In patients with chronic heart failure, there is an increased risk of atrial fibrillation development. With restoration and maintenance of sinus rhythm, left ventricular function, exercise capacity and maximal oxygen consumption may improve. There is no consensus whether atrial fibrillation is an independent risk factor for morbidity and mortality in chronic heart failure, or just a marker of more advanced disease. Since the issue of rate versus rhythm control in heart failure is still unsettled and currently investigate in the Atrial Fibrillation and Congestive Heart Failure (AF-CHF) trial, we investigated differences in outcome of rhythm control for new-onset persistent atrial fibrillation in patients with and without systolic heart failure (Chapter 3).

**NON-PHARMACOLOGICAL RHYTHM CONTROL**

If pharmacological rhythm control appears to be ineffective, or antiarrhythmic drugs are contraindicated or discontinued because of adverse effects, and patients remain highly symptomatic with the arrhythmia, a non-pharmacological rhythm control approach may be considered. Non-pharmacological rhythm control approaches may include surgical procedures including Cox maze III procedure, preventive atrial pacing and atrial catheter ablation including pulmonary vein isolation.

**Maze surgery**

Maze surgery as developed by Cox in 1987 was the most frequently tested treatment option a decade ago, and many patients with intractable atrial fibrillation were offered the maze procedure. The maze procedure is a open-heart operation that creates a careful maze of incisions in the atrial myocardium (thereby preventing reentry) and bilateral appendage
removal (thereby reducing critical mass). This maze can act as an electrical conduit to channel atrial impulses from the sinoatrial node to the atrioventricular node, see also Figure 7. Initially, maze surgery was associated with sinus node dysfunction (maze I), and therefore modified two times (maze II and III) to overcome this side effect. The maze procedure has been performed in combination with valve surgery, congenital anomalies or coronary artery bypass grafting, and in patients without structural heart disease. Success percentages between 73% and 97% have been reported. Table 7 summarizes a selection of studies on maze III surgery for atrial fibrillation, including the occurrence of complications.

Cox maze III surgery for patients with intractable, lone atrial fibrillation has been performed for many years in our institution including a comprehensive, prospective data collection. Since long-term follow up data of patients with lone atrial fibrillation are scarce, we investigated efficacy of Cox maze III surgery, and collected functional data including echocardiographic studies, exercise capacity and ambulatory ECG recordings, sinus node function, quality of life, and complications of the procedure (Chapter 6).

Figure 7. Schematical representation of the incisions during the the Maze III procedure (posterior view of the heart).
Table 5. Clinical studies on the effect of Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) on the occurrence of atrial fibrillation (AF) in heart failure and non-heart failure patients.

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal (year)</th>
<th>Study design and inclusion</th>
<th>Intervention and inclusion</th>
<th>Pre-loading</th>
<th>Follow-up (m)</th>
<th>Outcomes Results</th>
<th>(Relative risk reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart failure</strong></td>
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<tr>
<td>Van den Berg et al</td>
<td>J Card Fail 1995</td>
<td>Randomized double blinded (n=30)</td>
<td>Lisinopril (A) 10 mg/d vs placebo (B) started before ECV in NYHA II-III HF pts with pers AF</td>
<td>+</td>
<td>1.5</td>
<td>Only increase in peak VO2 in A, 14.7±3.4 to 15.9±2.9, p=0.03, and 71% (A) vs 40% (B) SR, p=NS. (52% AF reduction compared to B)</td>
<td></td>
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<tr>
<td>Pedersen et al TRACE#</td>
<td>Circ 1999</td>
<td>Randomized double blinded (1577)</td>
<td>Trandolapril (A) 4 mg/d vs placebo (B) in post MI pts with LVEF ≤36%</td>
<td>SR</td>
<td>24-48</td>
<td>Incidence of AF in A vs B 2.8% (A) vs 5.3% (B) incidence of AF, p&lt;0.05. (47% AF reduction compared to B)</td>
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<tr>
<td><strong>Non heart failure</strong></td>
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<tr>
<td>Madrid et al</td>
<td>Circ 2002</td>
<td>Randomized double blinded (154)</td>
<td>Irbesatan (A) 150-300 mg/d and amio vs placebo and amio (B) in pts with pers AF</td>
<td>+</td>
<td>2</td>
<td>Recurrence of AF after ECV in A vs B 9% (A) vs 24% (B), p&lt;0.01 (63% AF reduction compared to B)</td>
<td></td>
</tr>
<tr>
<td>Ueng et al</td>
<td>EHJ 2003</td>
<td>Randomized open label (145)</td>
<td>Enalapril (A) 20 mg/d and amio vs placebo alone (B) in pts with &gt; 3 m pers AF</td>
<td>+</td>
<td>12</td>
<td>Recurrence of AF after ECV in A vs B 26% (A) vs 43% (B) recurrence AF, p=0.02 (40% AF reduction compared to B)</td>
<td></td>
</tr>
<tr>
<td>Yin et al</td>
<td>EHJ 2006</td>
<td>Randomized open label (177)</td>
<td>Amio and Losartan (A) 100 mg/d, perindopril (B) 4 mg/d or placebo (C) in PAF pts</td>
<td>SR</td>
<td>24</td>
<td>Recurrence of AF in A, B, C 19% (A) vs 24% (B) vs 41% (C), p=0.05 in A vs C and B vs C. (54% AF reduc. A compared to C 41% AF reduce. B compared to C)</td>
<td></td>
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</tbody>
</table>
### Primary prevention

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Design</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Patients</th>
<th>Follow-up</th>
<th>Outcome</th>
<th>Incidence of AF in A vs B</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart failure</strong></td>
<td></td>
<td></td>
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<tr>
<td>Vermes et al. 2003</td>
<td>Circ 2003</td>
<td>Retrospective</td>
<td>Enalapril (A) 5-20 mg/d vs placebo (B) pts with LVEF ≤36%</td>
<td>SR</td>
<td>12-36</td>
<td>Incidence of AF in A vs B</td>
<td>5.4% (A) vs 24% (B) incidence of AF, p&lt;0.001. (77% AF reduction compared to B)</td>
<td></td>
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</tr>
<tr>
<td>Maggioni et al. 2005</td>
<td>AHJ 2005</td>
<td>Retrospective</td>
<td>Valsartan (A) 160-320 mg/d vs placebo (B) in NYHA II-III IV HF pts</td>
<td>SR</td>
<td>23</td>
<td>Incidence of AF in A vs B</td>
<td>5.1% (A) vs 7.9% (B) incidence of AF, p=0.2. (36% AF reduction compared to B)</td>
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<tr>
<td><strong>Non heart failure</strong></td>
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<tr>
<td>Tallier et al. 2004</td>
<td>JACC 2004</td>
<td>Retrospective</td>
<td>ACE-Inhibitor (A) vs calcium-channel blocker (B) in pts with HT</td>
<td>SR</td>
<td>72</td>
<td>Incidence of AF in A vs B</td>
<td>10.6% (A) vs 13% (B) incidence of AF, p=0.2. (38% AF reduction compared to B)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wachtell et al. 2005</td>
<td>JACC 2005</td>
<td>Randomized double blinded</td>
<td>Valsartan (A) 50 mg/d vs Atenolol 50 mg/d (B) in pts with HT and LVH</td>
<td>SR</td>
<td>48-72</td>
<td>Incidence of AF in A vs B</td>
<td>3.5% (A) vs 5.3% (B) incidence of AF, p&lt;0.001. (34% AF reduction compared to B)</td>
<td></td>
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</tr>
</tbody>
</table>

# substudy. AAD=antiarrhythmic drug; PAF=paroxysmal atrial fibrillation; ECV=electrical cardioversion; LVEF=left ventricular ejection fraction; SR=sinus rhythm.
Table 6. Clinical studies on the effect of statin treatment on the occurrence of atrial fibrillation (AF).

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Study design</th>
<th>Intervention and inclusion</th>
<th>Pre-loading</th>
<th>Follow-up (m)</th>
<th>Outcomes</th>
<th>Results (Relative risk reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siu et al&lt;sup&gt;276&lt;/sup&gt;</td>
<td>AJC</td>
<td>Retro-spective (62)</td>
<td>Atorvastatin/simvastatin (A) vs no statin (B) in pts with lone pers AF</td>
<td>+</td>
<td>48</td>
<td>Recurrence of AF after ECV in A vs B</td>
<td>40% (A) vs 84% (B) recurrence of AF p&lt;0.001 (52% AF reduction compared to B)</td>
</tr>
<tr>
<td>Tveit et al&lt;sup&gt;277&lt;/sup&gt;</td>
<td>AJC</td>
<td>Randomized open label (114)</td>
<td>Pravastatin 40 mg (A) vs no statin (B) in pts with pers AF</td>
<td>+</td>
<td>1.5</td>
<td>Recurrence of AF after ECV in A vs B</td>
<td>35% (A) vs 33% (B) recurrence of AF p=NS (-6% AF reduction compared to B)</td>
</tr>
<tr>
<td>Ozaydin et al&lt;sup&gt;278&lt;/sup&gt;</td>
<td>AJC</td>
<td>Randomized open label (99)</td>
<td>Atorvastatin 10 mg (A) vs no statin (B) in pts with pers AF</td>
<td>+</td>
<td>3</td>
<td>Recurrence of AF after ECV in A vs B</td>
<td>12.5% (A) vs 45.8% (B) recurrence of AF p&lt;0.01 (73% AF reduction compared to B)</td>
</tr>
<tr>
<td>Young-Xu et al&lt;sup&gt;279&lt;/sup&gt;</td>
<td>AJC</td>
<td>Observa-tional (449)</td>
<td>Statin (A) vs no statin (B) in pts with chronic CAD</td>
<td>SR</td>
<td>60 (1-9)</td>
<td>Incidence of AF in A vs B</td>
<td>9% (A) vs 15% (B) incidence of AF, p&lt;0.05 (40% AF reduction compared to B)</td>
</tr>
<tr>
<td>Hanna et al&lt;sup&gt;280&lt;/sup&gt;</td>
<td>Heart Rhythm</td>
<td>Observa-tional (25268)</td>
<td>Statin (A) vs no statin (B) in pts with LVEF&lt;40%</td>
<td>SR</td>
<td>?</td>
<td>Incidence of AF in A vs B</td>
<td>25.3% (A) vs 33.1% (B) incidence of AF, p&lt;0.001 (24% AF reduction compared to B)</td>
</tr>
</tbody>
</table>

# substudy. AAD=antiarrhythmic drug; PAF=paroxysmal atrial fibrillation; ECV=electrical cardioversion; LVEF=left ventricular ejection fraction; SR=sinus rhythm.
**Atrial catheter ablation**

Since the observation that the pulmonary veins play an important role in the initiation and maintenance of atrial fibrillation,\(^79,295\) there has been a rapid development of catheter ablation techniques targeting the pulmonary veins (Figure 8). The most widely used methods are segmental and circumferential radiofrequency (RF) ablation to isolate the pulmonary veins, as developed by Haissaguerre and Pappone, respectively.\(^81,296,297\) Many studies have been performed investigating the efficacy of transvenous catheter ablation to cure patients from atrial fibrillation. Complete success percentages (i.e. without antiarrhythmic drugs) range from 50-80%, but in up to one third of the patients a repeat procedure is necessary (Table 8). Complications may occur, in up to 6% of the patients,\(^298\) being predominantly pericardial effusion, pulmonary vein stenosis and stroke. Esophageal perforation occurs only rarely but is life threatening.\(^299\) Long term success data are up till now lacking, in contrast to the surgical data. New strategies include new ablation techniques including other energy sources, more left (and right) atrial lines, other approaches, e.g. epicardial ablation, and the development of better electrophysiological imaging properties (Figure 9).\(^300-302\) These issues are further discussed in chapter 8 (‘Discussion and future perspectives’).

**Figure 8.** Schematical representation of common lesion sets employed in radiofrequency atrial fibrillation ablation, which are created in a circumferential fashion around the left and right pulmonary veins (A); (B) Common sites of linear ablation lesions; (C) Additional lines between the pulmonary veins; (D) Common sites of ablation lesions for targeting complex fractionated electrograms. View on the posterior side of the left and right atrium. (Adapted from Calkins et al. Heart Rhythm 2007, with permission)\(^303\)
### Table 7. Results of Maze surgery for atrial fibrillation (AF).

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal (year)</th>
<th>Design, surgical procedure</th>
<th>PAF (n, %) or Pers AF (n, %)</th>
<th>Follow-up (y)</th>
<th>Outcome</th>
<th>Complication rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Maze surgery combined#</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kosakai et al²⁸³</td>
<td>J Thorac Card Surg (1994)</td>
<td>Prospective non randomized Maze II/ III</td>
<td>pers AF (62;100%); all valve surgery</td>
<td>0.5-2</td>
<td>84% SR at end of study without AAD</td>
<td>No death, 3% PM because of SND</td>
</tr>
<tr>
<td>Kosakai et al²⁸⁴</td>
<td>Circ (1995)</td>
<td>Prospective non randomized Maze II/ III</td>
<td>pers AF (71;100%); 87% valve surgery</td>
<td>1-3.1</td>
<td>82% SR at end of study without AAD</td>
<td>2 death (2%) early postoperative, 4% PM because of SND none</td>
</tr>
<tr>
<td>Gregori et al²⁸⁵</td>
<td>Ann Thorac Surg (1995)</td>
<td>Prospective non randomized Maze III</td>
<td>pers AF (20;100%); 100% valve surgery</td>
<td>0.5-1.3</td>
<td>90% SR at end of study without AAD</td>
<td></td>
</tr>
<tr>
<td>Kamata et al²⁸⁶</td>
<td>Heart (1997)</td>
<td>Prospective non randomized Maze III</td>
<td>pers AF (71;100%); 87% valve surgery</td>
<td>1</td>
<td>73% SR at end of study +/- AAD</td>
<td>4 death (6%) at end of study, 6% PM because of SND ?</td>
</tr>
<tr>
<td>Cox et al²⁸⁷</td>
<td>Am Heart J (1998)</td>
<td>Prospective non randomized Maze II/ III</td>
<td>pers AF (153;100%); mostly valve surgery</td>
<td>0.3-5</td>
<td>96% SR at end of study without AAD</td>
<td></td>
</tr>
<tr>
<td>Chiappini et al²⁹¹</td>
<td>Ann of Thorac Surg (2004)</td>
<td>Retro-spective, Maze III vs RF ablation</td>
<td>Pers AF (70;100%); all valve surgery</td>
<td>0.5-7.6</td>
<td>Maze 89% SR vs 69% RF; 33% vs 23% AAD use.</td>
<td>6.6% vs 7.5% perioperative death, 6% vs 7% PM because of SND</td>
</tr>
<tr>
<td><strong>Maze surgery for lone AF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jessurun et al²⁸⁸</td>
<td>Circulation (2000)</td>
<td>Prospective non randomized all Maze III</td>
<td>Lone PAF (41; 100%)</td>
<td>2.6±1.3</td>
<td>85% long term SR, 95% SR at end of study, 80% SR without AAD</td>
<td>No perioperative deaths or surgery related major complications, 2% PM because of SND</td>
</tr>
<tr>
<td>Gaynor et al²⁹²</td>
<td>J of Thorac Cardiovasc Surg (2005)</td>
<td>Prospective non randomized comparison Maze I, II, and III</td>
<td>Lone AF (179; 65%); Paroxysmal AF (159; 58%)</td>
<td>5.8±3.6</td>
<td>92% freedom of late AE, 76% SR without AAD, no diff in lone vs concomit.</td>
<td>1.4% perioperative deaths, 13% surgery related major complications, 4% PM because of SND</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Journal</td>
<td>Prospective vs Concomit.</td>
<td>Maze Type</td>
<td>AF Type</td>
<td>Duration</td>
<td>SR Rate at End of Study</td>
</tr>
<tr>
<td>---------------</td>
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<td>------------------------</td>
</tr>
<tr>
<td>McCarthy et al.</td>
<td>Sem Thor Cardiovasc Surg (2000)</td>
<td>Prospective non randomized</td>
<td>Maze I/III</td>
<td>pers AF (78.78%); PAF (22.22%)</td>
<td>3</td>
<td>90% SR at end of study +/- AAD</td>
</tr>
<tr>
<td>Prasad et al.</td>
<td>J of Thorac Cardiovasc Surg (2003)</td>
<td>Prospective non randomized lone vs concomit. all Maze III</td>
<td>Lone PAF (72; 64%) Lone pers AF (40; 36%); concomit. (86.52% PAF); 52% valve surg</td>
<td></td>
<td>5.4±3.0</td>
<td>lone AF 95.9% SR at end of study, 79.6% SR without AAD vs concomit. 97% SR +/- AAD</td>
</tr>
<tr>
<td>Ballaux et al.</td>
<td>J of Thorac Cardiovasc Surg (2006)</td>
<td>Prospective non randomized lone vs concomit. all Maze III</td>
<td>Lone AF (139): PAF (78%); pers AF (22%); concomit. (64.53% PAF); 89% valve surg</td>
<td></td>
<td>4.0±2.6</td>
<td>lone AF 80% SR at end of study, 64.5% SR without class I/III AAD</td>
</tr>
</tbody>
</table>

* = Maze combined with other surgery. AAD=antiarrhythmic drug; AF=atrial fibrillation; PAF=paroxysmal atrial fibrillation; Pers AF=persistent atrial fibrillation; SR=sinus rhythm; SND=sinus node dysfunction; Concomit.=concomitant; * p<0.05.
### Table 8. Results of different prospective (randomized) studies using (left atrial) catheter ablation for rhythm control treatment of atrial fibrillation.

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>Study design, Ablation technique</th>
<th>PAF (n, %) or Pers AF (n, %), lone AF (%)</th>
<th>Left atrial AP size (mm)</th>
<th>Follow-up (m)</th>
<th>Outcome</th>
<th>Median (range) number of procedures</th>
<th>Complication rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly lone AF</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Haissaguerre et al[^6]</td>
<td>NEJM 1998</td>
<td>Prospective, non randomized, segmental RF ablation</td>
<td>PAF (45; 100%), 86% lone AF</td>
<td>39±7 8±6</td>
<td>62% AF-free without AAD use</td>
<td>2 (1-3)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Haissaguerre et al[^304]</td>
<td>Circ 2000</td>
<td>Prospective, non randomized, segmental RF ablation</td>
<td>PAF (70; 100%), % lone AF: ?</td>
<td>4±5</td>
<td>54% AF-free without AAD use, 73% AF-free after one or two ablations and without AAD use</td>
<td>2 (1-2)</td>
<td>3% pericardial effusion, 3% femoral aneurysm</td>
<td></td>
</tr>
<tr>
<td>Haissaguerre et al[^9]</td>
<td>Circ 2000</td>
<td>Prospective, non randomized, segmental RF ablation</td>
<td>PAF (90; 100%), 63% lone AF</td>
<td>39±7 8±5</td>
<td>84% AF-free at end of study, 71% AF-free without AAD use, median of 2 (1-4) ablations</td>
<td>2 (1-4)</td>
<td>1% pericardial effusion, 1% blurred vision, 1% TIA (all reversible), 6% PV stenosis (2% sympt)</td>
<td>4% hemopericardium</td>
</tr>
<tr>
<td>Pappone et al[^86]</td>
<td>Circ 2001</td>
<td>Prospective, non randomized, circumferential RF ablation</td>
<td>PAF (14; 54%), Pers AF (12; 46%), 69% lone AF</td>
<td>38±4 9±3</td>
<td>85% AF-free, 62% AF-free without AAD use</td>
<td>?</td>
<td></td>
<td>1% cardiac tamponade</td>
</tr>
<tr>
<td>Pappone et al[^305]</td>
<td>Circ 2001</td>
<td>Prospective, non randomized, circumferential RF ablation</td>
<td>PAF (179; 71%), Pers AF (72; 39%), 85% lone AF</td>
<td>40±5 10±5</td>
<td>80% AF-free, (58% previous PAF and 68% previous pers AF), 75% AF-free without AAD use</td>
<td>?</td>
<td></td>
<td>1% stroke, 3% asymptomatic PV stenosis</td>
</tr>
<tr>
<td>Oral et al[^306]</td>
<td>Circ 2002</td>
<td>Prospective, non randomized, segmental RF ablation</td>
<td>PAF (58; 83%), Pers AF (12; 17%), 93% lone AF</td>
<td>40±4 5</td>
<td>70% and 22% AF-free without AAD use of previous PAF and pers AF patients, respectively</td>
<td>1 (1-2) (2 in 9%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral et al[^307]</td>
<td>Circ 2003</td>
<td>Randomized, Segmental versus circumferential RF ablation</td>
<td>PAF(40; 100%), 95% lone AF</td>
<td>40±6 6</td>
<td>67% and 88% AF-free without AAD use in resp. the segmental versus circumferential ablation</td>
<td>1 (1-2) (2 in 18%)</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Author</td>
<td>Journal (y)</td>
<td>Study design, Ablation technique</td>
<td>PAF (n; %) or Pers AF (n; %), Lone AF (%)</td>
<td>Left atrial AP size (mm)</td>
<td>Follow-up (m)</td>
<td>Outcome</td>
<td>Number of procedures</td>
<td>Complication rate</td>
</tr>
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</tr>
<tr>
<td>Pappone et al²⁰⁷</td>
<td>JACC 2003</td>
<td>Prospective, non randomized, circumferential RF ablation versus AAD</td>
<td>Ablation group (n=589), 69% PAF, 31% pers AF, 34% lone AF</td>
<td>46±9</td>
<td>30 (5-50)</td>
<td>80% AF-free at the end of study without AAD, (42% AF-free in the AAD treated group)</td>
<td>1 (1-2) (2 in 20%)</td>
<td>1% tamponade; 8% adverse effects (heart failure or any stroke) during follow-up None</td>
</tr>
<tr>
<td>Lemola et al³⁰⁸</td>
<td>Heart Rhythm 2004</td>
<td>Prospective, non randomized, circumferential RF ablation</td>
<td>PAF (25; 61%), Pers AF (16; 39%), Lone AF (59%)</td>
<td>46±7</td>
<td>6</td>
<td>88% AF-free without AAD use including 7% of patients with an additional Aflutter ablation</td>
<td>1 (7% additional ablation of AFL)</td>
<td>None</td>
</tr>
<tr>
<td>Cappato et al²⁰⁶</td>
<td>Circ 2005</td>
<td>Worldwide survey, Different catheter ablation techniques</td>
<td>Large and heterogeneous population (n=8745, 90 different centers)</td>
<td>?</td>
<td>12±8</td>
<td>76% of patients AF-free at the end of study, 52% AF-free without AAD use</td>
<td>1 (1-3) (2 in 24%, 3 in 3%)</td>
<td>6% major complications</td>
</tr>
<tr>
<td>Bourke et al³⁰⁹</td>
<td>Heart 2005</td>
<td>Prospective, non randomized, segmental RF ablation</td>
<td>PAF (36; 36%), Pers AF (64; 64%), 100% lone AF</td>
<td>?</td>
<td>6</td>
<td>55% AF-free, 17% AF-free without AAD use and 38% with AAD use</td>
<td>1 (1-2)</td>
<td>12% complication rate of which 50% cardiac tamponade</td>
</tr>
<tr>
<td>Wazni et al³¹⁰</td>
<td>JAMA 2005</td>
<td>Randomized, controlled trial, circumferential RF ablation vs AAD (flecainide/prepaf/sotalol) Prospective, non randomized, circumferential RF ablation</td>
<td>PAF (67; 96%), Pers AF (3; 4%), 74% lone AF</td>
<td>42±7</td>
<td>12</td>
<td>87% ablated and 37% AAD pts without AF recurrence at 1 y. Qol sign. better after ablation</td>
<td>1 (1-2) (2 in 12%)</td>
<td>6% asymptomatic moderate pulmonary vein stenosis</td>
</tr>
<tr>
<td>Oral et al³¹¹</td>
<td>NEJM 2006</td>
<td>Randomized, controlled trial, circumferential RF ablation vs amio +/- ECV</td>
<td>All pers AF (146), 92% lone AF</td>
<td>45±5</td>
<td>12</td>
<td>74% ablated versus 58% of only amio pts free of AF and or AFL at 1 y.</td>
<td>1 (1-2) (2 in 32%)</td>
<td>None</td>
</tr>
<tr>
<td>Oral et al³¹²</td>
<td>Circ 2006</td>
<td>Prospective, non randomized, segmental RF ablation</td>
<td>All PAF (153); 60% lone AF</td>
<td>41±6</td>
<td>11±4</td>
<td>77% freedom of AF and or AFL without AAD at follow-up.</td>
<td>1 (1-2) (2 in 18%)</td>
<td>2% pericardial tamponade or transient neurological events.</td>
</tr>
</tbody>
</table>
### Predominantly AF with underlying heart disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Type of Ablation</th>
<th>Control Group</th>
<th>LVEF</th>
<th>Follow-up</th>
<th>AF-Free</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen et al (2004)</td>
<td>JACC</td>
<td>Prospective, non randomized, circumferential RF ablation in heart failure patients versus controls</td>
<td>43% PAF, 56% pers AF, all HF (n=94) with LVEF &lt;40%, vs non-HF (283, lone AF 52%)</td>
<td>HF: 47±8, non-HF: 45±3</td>
<td>14±6</td>
<td>73% and 87% AF-free without AAD use in the heart failure and non heart failure group, resp.</td>
<td>1 (1-2) of HF (2 in 22% of HF)</td>
</tr>
<tr>
<td>Hsu et al (2004)</td>
<td>NEJM</td>
<td>Prospective, non randomized, segmental RF ablation in heart failure patients versus controls</td>
<td>9% PAF, 91% pers AF, all HF pts (n=58) with LVEF &lt;45% versus 58 non HF pts, lone AF 52%</td>
<td>HF: 50±7, non-HF: 45±3</td>
<td>12±7</td>
<td>69% and 71% AF-free without AAD use in the heart failure and non heart failure group, resp.</td>
<td>1 (1-2) of HF (2 in 50% of HF, 2 in 47% of non-HF)</td>
</tr>
<tr>
<td>Gaita et al (2005)</td>
<td>Circ</td>
<td>Randomized, all AF and valve disease, isolation of PVs by cryoisolation versus “U” or “7” left atrial lesions</td>
<td>All pers AF (105), Undergoing valvular surgery</td>
<td>52±6</td>
<td>24</td>
<td>In pts with “7” lesion 86% were AF-free without AAD use versus 25% of pts with PVI without AAD use.</td>
<td>1</td>
</tr>
</tbody>
</table>

AAD=antiarrhythmic drug; AF=atrial fibrillation; AP=anterior-posterior; HF=heart failure; PAF=paroxysmal atrial fibrillation; Pers AF=persistent atrial fibrillation; PV=pulmonary veins; RF=radiofrequency; SR=sinus rhythm; SND=sinus node dysfunction; TIA=transient ischemic attack.
Atrial pacing

Atrial pacing to prevent atrial fibrillation is a relatively new concept in the treatment of atrial fibrillation. Studies have demonstrated that the incidence of atrial fibrillation during pacing is significantly lower in case of atrial pacing in stead of VVIR\textsuperscript{315,316} or DDDR pacing,\textsuperscript{317} especially in patients with a sick sinus syndrome and normal atrioventricular conduction.\textsuperscript{318} This, however, seems predominantly related to atrial fibrillation triggered by impairment of left ventricular function.\textsuperscript{319,320} Atrial pacing to prevent atrial fibrillation may be effective by the combination of the prevention of triggers (atrial premature complexes, sinus pauses), and reducing the substrate (prevention of differences in conduction velocity and prevention of dispersion of the atrial effective refractory periods). As previously mentioned, a recent study performed by Hoffmann and colleagues, using a new diagnostic pacemaker, showed the most common onset scenario was premature atrial complexes (PAC) before atrial fibrillation, followed by bradycardia, sudden onset, and tachycardia, see also Figure 5.\textsuperscript{90} Novel pacemakers have several special algorithms implemented in order to prevent atrial fibrillation and are capable of measuring the atrial fibrillation burden (AF burden; defined as the percentage of time in atrial fibrillation detected by the device).\textsuperscript{321} These algorithms include: an atrial overdrive algorithm for maintenance of a pacing rate just above the intrinsic rate (atrial overdrive or preference pacing; preventing bradycardia and PACs), an atrial overdrive mode designed to avoid short-long intervals following a premature atrial complex (atrial rate stabilization; avoiding compensatory pauses), and algorithms temporary elevating the atrial rate in case of a premature atrial complex or after exercise (atrial preference pacing and post-exercise overdrive pacing). An additional aspect provided by a new generation of pacemakers
is termination of the arrhythmia by anti-tachycardia pacing of a regular atrial tachycardia or flutter that may deteriorate into atrial fibrillation. Figure 10 shows schematical examples of respectively; A) Atrial overdrive or preference pacing, B) Atrial rate stabilization after a premature atrial complex, C) The capability and programmability of a pacemaker to detect and distinguish an atrial tachycardia and/or atrial fibrillation, and D) (successful) Antitachycardia pacing (ATP).

Especially in patients with bradyarrhythmias, atrial based pacing turned out to be effective in the prevention of atrial fibrillation. Table 9 gives an overview of large randomized trials on prevention of atrial fibrillation by atrial based pacing in patients with a bradyarrhythmia related indication for a pacemaker. Beneficial effects of pacing for prevention of atrial arrhythmias in patients without bradyarrhythmias have yet not been demonstrated, see also Table 10. Other locations than conventional atrial lead placing (right atrial appendage or right atrial lateral wall, interatrial septum) may be advantageous in this respect, see also Figure 11. In chapter 4 and 5 we evaluated the efficacy of preventive pacing and antitachycardia pacing in patients with symptomatic paroxysmal or persistent atrial fibrillation with or without additional antiarrhythmic drugs and with or without septal lead placement.

If patients remain symptomatic or if they suffer from intolerable side effects, the alternative approach of atrial fibrillation is to accept the arrhythmia and to perform an atrioventricular node ablation in combination with a pacemaker implantation (ablate-and-pace) to control the ventricular rate in order to reduce symptoms and prevent a tachycardia-induced cardiomyopathy. The latter, however, may impair cardiac function.

Figure 10. Schematic examples of; A) Atrial overdrive or preference pacing, B) Atrial rate stabilization after a premature atrial complex, C) The capability and programmability of a pacemaker to detect and distinguish an atrial tachycardia and atrial fibrillation, and D) (successful) antitachycardia pacing (ATP).
### B. Atrial rate stabilization.

### C. Atrial tachycardia (AT) and atrial fibrillation (AF) detection programmability.

### D. (Successful) Antitachycardia pacing (ATP).
Table 9. Prevention of atrial fibrillation by atrial based pacing in patients with a bradyarrhythmia related indication for pacing in large randomized trials.

<table>
<thead>
<tr>
<th>Study (N)</th>
<th>Journal (year)</th>
<th>Eligibility criteria</th>
<th>Mean age (y); UHD</th>
<th>Type of pacing</th>
<th>ATP use</th>
<th>AAD use</th>
<th>Mean Follow-up (y)</th>
<th>Endpoint</th>
<th>P-value</th>
<th>POS/NEG</th>
<th>Exacerbation of Heart failure</th>
<th>Occurrence of stroke/death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danish114, 115 (225)</td>
<td>Lancet (1994/1997)</td>
<td>100% class I</td>
<td>76; N/A</td>
<td>AAI vs VVI</td>
<td>No</td>
<td>N/A</td>
<td>5.5</td>
<td>Incidence of AF; mortality</td>
<td>0.012; 0.045</td>
<td>POS; POS</td>
<td>23% AAI vs 42% VVI</td>
<td>NYHA II-IV</td>
</tr>
<tr>
<td>PASE54 (407)</td>
<td>NEJM (1998)</td>
<td>43% class I; 49% class II</td>
<td>76; 33% CAD; 27%; HF; 43% HT</td>
<td>DDD vs VVI</td>
<td>No</td>
<td>16%</td>
<td>2.5</td>
<td>Incidence of AF; QoL</td>
<td>0.00; &lt;0.001</td>
<td>NEG; POS</td>
<td>17% vs 19% stroke death</td>
<td></td>
</tr>
<tr>
<td>Mattioli et al10 (210)</td>
<td>BHJ (1998)</td>
<td>52% class I; 48% class II</td>
<td>77; 47% CAD; 48% HT</td>
<td>AAI/ DDD vs VVI</td>
<td>No</td>
<td>No</td>
<td>5</td>
<td>Incidence of chronic AF</td>
<td>0.02</td>
<td>POS</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CTOPPP9 (2568)</td>
<td>NEJM (2000)</td>
<td>34% class I; 52% class II</td>
<td>73; 36% CAD; 35% HT; 21% PAF</td>
<td>AAI/ DDD vs VVI</td>
<td>No</td>
<td>No</td>
<td>6</td>
<td>Incidence of chronic AF; risk on stroke or death</td>
<td>0.016; 0.33</td>
<td>POS; NEG</td>
<td>4.9% vs 5.8% stroke death</td>
<td></td>
</tr>
<tr>
<td>MOST9 (2010)</td>
<td>NEJM (2002)</td>
<td>100% class I; 21% also class II</td>
<td>74; 26% CAD; 20% HF; 62% HT; 45% AF</td>
<td>DDD vs VVI</td>
<td>No</td>
<td>No</td>
<td>4.5</td>
<td>Incidence of chronic AF; risk on stroke or death; new onset AF; HF; stroke</td>
<td>0.48; &lt;0.01; 0.13</td>
<td>NEG; POS; NEG</td>
<td>10.3% vs 12.3% hospitalization</td>
<td>21.5% vs 23% death/stroke</td>
</tr>
<tr>
<td>ATTEST9 (368)</td>
<td>JACC (2003)</td>
<td>72% class I; 11% class II; 100% PAF</td>
<td>70; 33% CAD; 26% HF; 61% HT</td>
<td>DDDR LR60 +/- PA</td>
<td>Yes</td>
<td>No</td>
<td>0.25</td>
<td>AT/AF burden and number</td>
<td>0.20</td>
<td>NEG</td>
<td>0.3% HF related death</td>
<td>N/A</td>
</tr>
<tr>
<td>Nielsen et al9 (177)</td>
<td>JACC (2003)</td>
<td>100% class I</td>
<td>74; 23% CAD</td>
<td>AAI vs DDD</td>
<td>No</td>
<td>9%</td>
<td>2.9</td>
<td>Incidence of AF; stroke</td>
<td>0.03; 0.32</td>
<td>POS; NEG</td>
<td>No difference</td>
<td>5.6% vs 8.9% stroke</td>
</tr>
<tr>
<td>ADOPT9 (418)</td>
<td>JACC (2003)</td>
<td>100% class I and symp AF</td>
<td>71; 36% NYHA II-IV HF</td>
<td>DDDR LR60 +/- PA</td>
<td>No</td>
<td>Yes; 67% stable</td>
<td>0.5</td>
<td>Incidence of AF; stroke</td>
<td>0.005</td>
<td>POS</td>
<td>0.7% HF related death</td>
<td>N/A</td>
</tr>
<tr>
<td>ASPECT9 (277)</td>
<td>ICE (2003)</td>
<td>70% class I; 12% class II; 100% PAF</td>
<td>70; 29% CAD; 10% HF; 61% HT</td>
<td>DDDR LR70 +/- PA</td>
<td>Yes</td>
<td>Yes; 37% stable</td>
<td>0.5 (cross-over)</td>
<td>AT/AF burden and episode of symp AF (non)septal</td>
<td>NS; 0.01</td>
<td>NEG; POS</td>
<td>1.4% HF related death</td>
<td>1.7%</td>
</tr>
<tr>
<td>UKPACE9 (2021)</td>
<td>NEJM (2005)</td>
<td>100% class II</td>
<td>80; 15% CAD; 16% HF; 33% HT; 4% PAF</td>
<td>DDD vs VVI</td>
<td>No</td>
<td>No</td>
<td>4.6</td>
<td>Mortality; chronic AF; stroke</td>
<td>0.56; 0.74; 0.20</td>
<td>NEG; NEG; NEG</td>
<td>3.3%/y vs 3.2%/y</td>
<td>1.7%/y vs 21%/y</td>
</tr>
</tbody>
</table>

CAD=coronary artery disease; Class I: sick sinus syndrome; Class II atioventricular block; HF= heart failure; HT=hypertension; PA= AF prevention algorithms; PAF=paroxysmal atrial fibrillation; UHD=underlying heart disease.
<table>
<thead>
<tr>
<th>Authors (Acronym)</th>
<th>Journal (year)</th>
<th>Eligibility criteria</th>
<th>Patients (n; UHD)</th>
<th>Type AF</th>
<th>Type of pacing</th>
<th>ATP use</th>
<th>AAD use</th>
<th>Follow-up (m)</th>
<th>Endpoint(s) Outcome</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gillis et al359</td>
<td>Circ (1999)</td>
<td>AAD intolerant or refractory PAF</td>
<td>97; 47% lone AF; 27% HT; 22% CAD</td>
<td>100% PAF</td>
<td>DDD 30 vs DDIR 70</td>
<td>no</td>
<td>yes</td>
<td>3</td>
<td>Time to first recurrence; frequency and duration of AF</td>
<td>POS</td>
</tr>
<tr>
<td>Levy et al340</td>
<td>AJC (1999)</td>
<td>AAD refractory AF</td>
<td>19; 74% lone AF; 26% cardiomyopathy</td>
<td>63% PAF; 37% pers AF</td>
<td>DDD: RA 40 vs RA 70 vs BIA 70</td>
<td>no</td>
<td>Yes</td>
<td>9</td>
<td>Time to first recurrence; frequency and duration of AF</td>
<td>POS</td>
</tr>
<tr>
<td>Lau et al360</td>
<td>AIC (2001)</td>
<td>AAD refractory PAF</td>
<td>22; 82% lone AF</td>
<td>100% PAF</td>
<td>DDD: RA 30 vs RA dual-site overdrive</td>
<td>no</td>
<td>Yes</td>
<td>9</td>
<td>Time to first AF recurrence; total AF burden; symptom scores and QoL</td>
<td>POS</td>
</tr>
<tr>
<td>Mirza et al345</td>
<td>JACC (2002)</td>
<td>AAD intolerant or refractory PAF</td>
<td>19; 37% lone AF; 37% HT; 5% CAD</td>
<td>100% PAF</td>
<td>DDD: RA 70 vs coronary sinus 70 vs BIA 70</td>
<td>no</td>
<td>Yes</td>
<td>12</td>
<td>Number of AF episodes per month</td>
<td>POS</td>
</tr>
<tr>
<td>Wiberg et al361</td>
<td>PACE (2003)</td>
<td>AAD intolerant or refractory PAF</td>
<td>35; 63% lone AF; 20% HT; 6% CAD</td>
<td>100% PAF</td>
<td>No pacing vs overdrive</td>
<td>no</td>
<td>Yes</td>
<td>6</td>
<td>Number of symptomatic AF episodes</td>
<td>POS</td>
</tr>
<tr>
<td>Kale et al350</td>
<td>Euro-pace (2003)</td>
<td>AAD refractory PAF</td>
<td>17; 100% lone AF</td>
<td>100% PAF</td>
<td>DDR 70 septal pacing +/- prevention algorithms</td>
<td>no</td>
<td>Yes</td>
<td>6</td>
<td>Reduction in AF burden +/- prevention algorithms</td>
<td>POS; NEG</td>
</tr>
</tbody>
</table>

AAD= antiarrhythmic drug; BiA=biatrial; PAF= paroxysmal atrial fibrillation; CAD=coronary artery disease; HF= heart failure; HT=hypertension; RA= right atrial UHD=underlying heart disease. * p<0.05.
In conclusion, there are several promising new concepts regarding the non-pharmacological treatment of atrial fibrillation. The choice which treatment to apply, timing of the institution of treatment, specific non-pharmacological rhythm control treatment in case of intractable recurrent symptomatic atrial fibrillation (despite pharmacological treatment) are important current issues.

**AIM OF THIS THESIS**

The aim of the present thesis is to investigate treatments in order to enhance outcome of rhythm control in patients suffering from symptomatic, paroxysmal or persistent, atrial fibrillation. For this purpose both new pharmacological and non-pharmacological treatment strategies were studied.

In part I in chapter 2 we investigated whether an acute serial cardioversion strategy, by enhancing and consolidating reversed remodeling, could improve arrhythmia outcome in persistent atrial fibrillation. In addition, we reasoned that in this setting, verapamil, by preventing repeated intracellular calcium overload, might enhance reversed remodeling and help to slow recurrent remodeling with each recurrence. The feasibility of the acute strategy and the influence on quality of life was investigated as well. In order to gain more data on outcome of rhythm control in patients with heart failure, a group of patients who certainly may benefit from sinus rhythm, we compared outcome of the serial cardioversion strategy in...
patients with new-onset persistent atrial fibrillation with and without systolic heart failure in chapter 3.

Part II consists of studies on non-pharmacological rhythm control of atrial fibrillation. In chapter 4 the effect of atrial pacing in combination with antiarrhythmic drugs to prevent recurrent atrial fibrillation in difficult-to-treat symptomatic paroxysmal or persistent atrial fibrillation was studied (non randomized). In chapter 5 we show the results of a randomized, multi-center study (performed in The Netherlands) on the effect of septal pacing and the use of additional atrial fibrillation prevention algorithms in patients with drug refractory symptomatic paroxysmal atrial fibrillation. Long-term outcome of Cox maze III surgery was investigated in patients with antiarrhythmic drug refractory symptomatic lone atrial fibrillation in chapter 6. Finally, we sought to investigate which factors determine why atrial fibrillation has such a crucial influence on patients’ complaints and quality of life that an individual patient prefers restoration of sinus rhythm even by non-pharmacological treatment strategies in chapter 7.

In part III, chapter 8, we give our view on the present status of rhythm control and discuss future developments.

REFERENCE LIST


General Introduction


Chapter 1


(101) Ravelli F, Allessie M. Effects of atrial dilatation on refractory period and vulnerability to atrial fibrillation in the isolated Langendorff-perfused rabbit heart. *Circulation* 1997 September 2;96(5):1686-95.


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(164) Van Gelder IC, Tiaurenburg AE, Schoonderwoerd BS, Tieleman RG, Crijns HJ. Pharmacologic versus direct-current electrical cardioversion of atrial flutter and fibrillation. Am J Cardiol 1999 November 4;84(9A):147R-51R.


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General Introduction


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