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ATRIAL FIBRILLATION

Clinical Presentation and Prevention of Recurrences

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Clincal Presentation and Prevention of Recurrences
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"We should first endeavour to better understand the working of the heart in all its details, and the cause of a large variety of abnormalities. This will enable us, in a possibly still-distant future and based upon a clear insight and improved knowledge, to give relief to the suffering of our patients."

Willem Einthoven (1860-1927)
Het tele-cardiogram (The tele-cardiogram) 1906

To Luis, Olivia and Martina

Abstract

Atrial fibrillation (AF) is the most common sustained arrhythmia of clinical importance. AF is known to decrease quality of life and it is related to an increased morbidity and a risk of tromboembolic events. AF may also be asymptomatic, and to what extent patients actually are able to distinguish between sinus rhythm (SR) and AF is unknown. In some patients, due to symptoms, restoration of SR is an important therapeutic goal. Electrical cardioversion mostly restores SR, but recurrence of AF is frequent even with the use of antiarrhythmic treatment. The latter, furthermore, carry proarrhythmic properties and alternative treatment regimens are therefore required.

The main purpose of the present studies was to investigate: the rate of conversion and recurrence after oral sotalol treatment in patients with direct current (DC) refractory AF, the predictive value and occurrence of episodes of AF after cardioversion, the perceived heart rhythm in relation to ECG findings after cardioversion and the ability of metoprolol CR in combination with early repetition of cardioversion to maintain SR.

The rate of conversion and recurrence after oral sotalol treatment was investigated in 53 patients with persistent AF refractory at a first DC cardioversion. Oral sotalol treatment was started after the unsuccessful cardioversion. A comparative group of patients with AF not refractory at cardioversion was also studied. A total of 43 patients (81%) in the sotalol group regained SR, of whom 10 (19%) converted pharmacologically and 33 (62%) of a second cardioversion. After four weeks SR was present in 29 patients (67%). The comparative group included 132 patients. This group differed significantly from the refractory patients only concerning weight. After four weeks SR was maintained by 50 patients (37%) in this group.

To evaluate the possibility to predict recurrence of AF and the incidence of self-limited episodes of AF 74 patients were followed with ambulatory ECG Holter monitoring (24 hours) one, three and six weeks after successful cardioversion. Six weeks after cardioversion 40 patients (54%) had SR and 34 patients (46%) had relapsed into persistent AF. Eight out of these 34 patients (24%) had episodes of AF at their first Holter recording compared with 12 patients out of 40 (30%) in SR at six weeks ($p>0.05$). On the first, second and third Holter recording 21 patients out of 51 (41%), 21 patients out of 43 (49%) and 15 out of 40 patients (38%) had self-limited bursts of AF, respectively. The incidence and duration of episodes did not vary over time during six weeks of follow-up.

The relation between perceived heart rhythm and ECG-findings after cardioversion of persistent AF was studied in 356 patients. The patients were interviewed concerning perceived heart rhythm and symptoms. An ECG was obtained after the interview. Chance-corrected measure of agreement was calculated using Cohen´s kappa-test. One week after cardioversion 160 patients (45%) thought that they had SR, and the ECG showed SR in 222 patients (62%). In 130 patients who perceived SR the ECG showed SR, $\kappa=0.34$, fair agreement. Thirty-eight patients perceived AF in agreement with AF found on their ECG, $\kappa=0.13$, poor agreement. There was a strong association between perceived SR and improvement of symptoms.

To evaluate the combination of metoprolol CR and early repeated cardioversion in patients with persistent AF cardioverted for the first time, a randomized double-blind placebo-controlled study was conducted. A careful medical history, clinical investigation, echocardiographic assay and 24-hour ECG was performed in all patients. Study treatment was started at least one week before cardioversion. Patients were followed once a week during the first six weeks after cardioversion, and in the case of relapse during this period a second cardioversion was performed within seven days. Total treatment and follow-up time was six months. In an intention to treat analysis 38 patients (46%) in the metoprolol group compared with 22 patients (26%) in the placebo group were in SR after six months ($p=0.007$).

Accordingly, in patients with DC refractory AF oral pre-treatment with sotalol prior to repeated cardioversion results in a high rate of SR restoration. After successful cardioversion self-limited bursts of AF do not predict recurrence of persistent AF although such episodes are common and constant in incidence and duration six weeks after cardioversion. Agreement between perceived heart rhythm and ECG as well as between improvement of symptom and SR on ECG is no more than poor to fair after successful cardioversion of persistent AF. The association between perceived SR and improvement of symptoms is strong. In patients with first time persistent AF, a treatment strategy with metoprolol initiated before cardioversion and promptly repeated cardioversion in case of early relapse significantly increases the number of patients in SR during six months of follow-up. The described studies increase the understanding of symptoms of AF and maintenance of SR, and may hopefully contribute to improve the care of this large group of patients.

Key words: atrial fibrillation, arrhythmias, beta-blocker, cardioversion, symptoms

ABBREVIATIONS

AF	atrial fibrillation
AV	atrio-ventricular
Ca	calcium
CR	control release
DC	direct current
ECG	electrocardiogram
EF	ejection fraction
ERAF	early reinitiation of atrial fibrillation
INR	international normalized ratios
J	joule
K	potassium
LA	left atrium
LVED	left ventricle end diastolic
NYHA	New York Heart Association
SD	standard deviation
SR	sinus rhythm
XL	extended release

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LIST OF ORIGINAL PAPERS

The present thesis is based on the following original papers, which will be referred to by their Roman numerals.

I. Nergårdh A, Nordlander R, Frick M. Rate of conversion and recurrence after sotalol treatment in patients with direct current-refractory atrial fibrillation. *Clinical Cardiology; 29: 56-60*

II. Nergårdh A, Rosenqvist M, Frick M. Self-limited bursts of atrial fibrillation following successful cardioversion. *Submitted for publication.*

III. Nergårdh A, Frick M. Perceived heart rhythm in relation to ECG-findings after DC cardioversion of atrial fibrillation. Heart *2006 Mar 17* [Epub ahead of print]

IV. Nergårdh A, Rosenqvist M, Nordlander R, Frick M. A randomized double-blind placebo-controlled study of Metoprolol CR initiated before direct current cardioversion and repeated cardioversion of atrial fibrillation - a new strategy to maintain sinus rhythm. *Submitted for publication.*

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INTRODUCTION

Historical perspective

The earliest historical description of what may have been atrial fibrillation (AF) is found in *The Yellow Emperors Classic of Internal Medicine*, by Huang Ti Nei Ching Su Wen almost 4000 years ago (1). In 1628 William Harvey made a description that is generally accepted to be the first of actual AF, reporting of ineffective contractions of the atrium in a dying animal (2). He also suggested that these heartbeats originated from the atria, a view that contradicted the earlier accepted doctrine that the arteries generated the pulse by their own movements. Adams was the first to report the association of mitral stenosis and irregular pulses, utilising Laennec´s recently invented stethoscope (3). In 1850 Hoffa and Ludwig, using electrical shocks, induced weak irregular ventricular contractions in rabbits and named this phenomenon "Flimmern" (4). The term fibrillation ("fremissement fibrillaire") was coined by Vulpian in 1874 (5).

Using a newly developed graphic method to measure venous and arterial pulses a Scottish General Practitioner, James Mackenzie (1853-1925), described the jugular venous waves during the cardiac cycle. In 1897, he discovered that the presystolic jugular A wave that was thought to represent the auricular contraction, was lost in a woman with mitral stenosis who had developed an irregular ventricular rhythm (6).

The first experimental proof for a relationship between AF and irregular ventricular rhythm was provided in 1904 by Fredericq, who showed that regular rhythm could be re-established by cutting the bundle of His (7). In 1906 Cushny and Edmunds reported that the pulse curve of a woman with irregular pulse was identical to that from a dog with fibrillatory contractions (8). The same year, 1906, Einthoven published the first AF recording performed with his electrocardiograph (9). A milestone in the history of AF was the presentation of the atrial re-entry theory by Garrey in 1914. He suggested that AF was due to "a series of ring like circuits of shifting location and multiple complexity" (10). This mechanism was further confirmed by Lewis in a dog model, and he also suggested the importance for re-entry to occur over short wave-lengths to allow multiple re-entry circuits to coexist, thereby sustaining AF (11).

In 1962, Moe formally presented the computer-driven "multiple wavelet" hypothesis (12). This demonstrated that AF may be maintained by the existence of a critical number of circulation electrical wavelets. This theory was later supported by Allessie and co-workers, who mapped isolated blood-perfused canine atria, demonstrating that re-entry may be explained by multiple wandering wavelets (13). In 1994 Wijfells finally demonstrated that AF caused a

shortening of the atrial effective refractory period, with an increase in rate, inducibility and stability of the arrhythmia, i.e. electrical remodelling (14). This mechanism is the underlying explanation to how the arrhythmia predisposes to its own perpetuation; how "AF begets AF".

Definition and Classification

AF is an arrhythmia of supraventricular origin, characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function. The electrocardiogram in AF is described by the replacement of consistent P waves by rapid oscillations or fibrillatory waves that vary in size, shape and timing, associated, in the absence of total atrio-ventricular (AV) block, with an irregular ventricular response (15), *figure 1*. Factors influencing the ventricular response to AF include the electrophysiological properties of the AV node, the level of vagal and sympathetic tone, and current drug therapy.

Figure 1. The first published Electrocardiogram of "Pulsus Inaequalis et Irregularis". From Einthoven W. Le telecardiogramme. Arch Int Physiol 1906; 4:132-163

According to the heterogeneous clinical presentation, the variety of symptoms and the presence of co-existing heart disorder various classifications of AF have been suggested. In the year of 2001 a guideline committee representing the European Society of Cardiology, the American Heart Association and the American College of Cardiology recommended a classification scheme representing a consensus driven by a desire for simplicity and clinical relevance (16). This scheme classifies the arrhythmia at a given moment, although it shall be noticed that the pattern of the arrhythmia often changes with time. According to the classification, the clinician should distinguish a first-detected episode of AF, symptomatic or asymptomatic, self-limited or sustained, recognizing that there may be uncertainty about the duration of the ongoing episode and about previous undetected episodes, *figure 2.* When a patient has experienced two or more episodes of arrhythmia, AF is considered *recurrent*. Recurrent AF is designated *paroxysmal* if spontaneously terminated and *persistent* if sustained. If

persistent AF is terminated with pharmacological therapy or electrical cardioversion does not change the designation. Persistent AF may be either the first presentations of the arrhythmia or the culmination of recurrent episodes of paroxysmal AF. Persistent AF also includes cases of longstanding AF (more than one year), in which cardioversion has not been indicated or attempted. If all attempts to restore sinus rhythm (SR) are abandoned, AF is designated permanent. The term "lone AF" has been variously defined but generally applies to young individuals (under 60 year of age) without clinical or echocardiographic evidence of cardiopulmonary disease, thereby having a favourable prognosis with respect to tromboembolism and mortality.

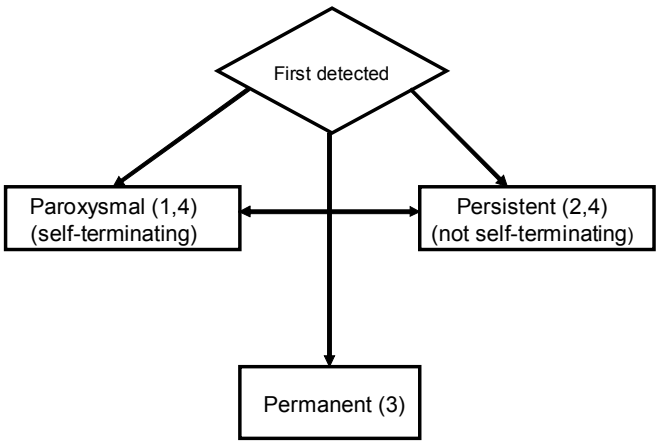

Figure 2. Patterns of AF. (1) Episodes that generally last less than or equal to seven days (most less than 24 h); (2) usually more than seven days; (3) cardioversion failed or not attempted; and (4) either paroxysmal or persistent AF may be recurrent. Modified from ACC/AHA/ESC Guidelines for the management of patients with AF (16)

Epidemiology

AF is the most common arrhythmia of clinical importance (17). The prevalence in the general population aged more than 65 years is estimated to 5.5%, and rises to more than 8% in people over 80 years of age (18, 19). For unknown reasons the prevalence of AF has increased over time, despite adjusting for age and concomitant heart disease, and in a report from the Framingham material the lifetime risk for development of AF is one in four for men and women 40 years of age or older (20). In Sweden there are approximately 100 000 people with permanent AF; the number of patients with paroxysmal AF is unknown, but estimated to be at least 50 000 (21).

Prognosis

Associated conditions

The most common medical conditions associated with AF are cardiac failure, hypertensive cardiovascular disease and rheumatic heart disease, in particular mitral stenosis (17). The risk of developing AF is generally increased in the case of heart failure both in men and women (19), however AF is also known to be the cause of symptoms of heart failure. Congenital heart disease, perimyocarditis and hypertrophic cardiomyopathy are all known to be associated with AF, as well as non-cardiac factors as hyperthyroidism, alcohol abuse, diabetes mellitus, disturbance in electrolyte balance and chronic obstructive pulmonary disease (22).

Mortality

According to the Framingham Study and other investigations the mortality rate of patients with AF is about double that of patients in SR, mainly due to cardiovascular causes and linked with the severity of underlying heart disease (23-25). In patients with known AF, recent prospective studies have failed to show any difference between patients treated with rate or rhythm control concerning prevention of death and morbidity from cardiovascular causes during a mean follow-up time of 2.3 and 3.5 years respectively (26-28). This might reflect the fact that merely the existence of AF is a marker of increased risk of several cardiac conditions, despite the strategy chosen for treating it. However, in these trials only a moderate part of the patients in the rhythm control group actually maintained SR. It is therefore still unclear to what extent the prognosis for patients with AF is superior with a strategy of rhythm control, particularly since a strategy aiming at rhythm control usually involves antiarrhythmic pharmacological treatment bearing an increased risk of ventricular arrhythmias.

Thromboembolism

Thromboembolic complications are the main cause of mortality in AF. Thromboembolic stroke occurs in about 5% of patients with AF between 60 and 70 years of age and in more than 8% of patients aged 80 to 89 years (18). Among patients with non-rheumatic AF the rate of ischemic stroke averages 5%, which is between two and seven times that of people without AF (18, 23, 29). Factors known to increase the risk of stroke in patients with AF are found in Table 1, showing pooled data from five randomized trials (30). Moreover, non-rheumatic AF is present in about 15% of cerebrovascular incidents of ischemic origin, and even if the clinical appearance of stroke is absent, patients with permanent AF are known to have a high incidence of silent cerebral infarction

(17, 31). The reason for the increased thrombogenesis in AF is not fully understood, and many factors should be taken into account, such as the influence on plasma markers of coagulation, endothelial function, platelet activation (32-34) and the prevalence of other underlying conditions such as sclerosis of the aorta and carotid arteries. In patients with AF there is also an increased risk of thrombus formation in the left atrium, particularly in the appendage (35).

Table 1. *Risk factors for ischemic stroke and systemic embolism in patients with non-valvular AF*

Risk factors (control groups)	Relative risk
Previous stroke or transient ischemic attack	2.5
History of hypertension	1.6
Congestive heart failure	1.4
Advanced age (continuous, per decade)	1.4
Diabetes mellitus	1.7
Coronary artery disease	1.5

Pooled data from five randomized, primary prevention studies (16, 30). As a group, patients with non-valvular AF carry about a six-fold increased risk of thromboembolism compared with patients in SR. Relative risk compared to patients with AF but without these risk factors.

Impaired ventricular function

In patients with AF, there are three factors known to affect hemodynamic function: loss of synchronous atrial mechanical activity, irregularity of ventricular response and inappropriate rapid ventricular rates. The irregularity of ventricular response is due to the loss of normal AV synchrony, and results in a decrease in cardiac output. Loss of atrial contractions results in a 20-30% decrease in left ventricular filling affecting cardiac output. This is especially marked in patients with impaired diastolic ventricular filling; hypertension, mitral stenosis, hypertrophic and restrictive cardiomyopathy (36). A persistently elevated ventricular rate during AF may produce dilated ventricular cardiomyopathy – tachycardia induced cardiomyopathy. In these patients, heart failure may be a consequence of, rather than the cause of AF, and control of the ventricular response or restoration of SR may lead to partial or even complete reversal of the myopathic process (37).

Pathophysiology

The patient population with AF is heterogeneous with aspect to concomitant diseases, and it is in most cases difficult to identify the explicit underlying anatomical changes responsible for the arrhythmia in the individual patient. The

pathophysiology of AF is complex, and can be divided in electrical and structural remodelling. The process known as *electrical remodelling* ("AF begets AF") reflects that AF leads to functional changes within the atria that perpetuate the arrhythmia (14). The key features of electrical remodelling are shortening of the atrial refractory period and prolongation of atrial conductivity (38, 39). There is also evidence of accumulation of calcium within atrial myocytes, leading to a reduction of the inward L-type Ca^{2+} current, which contributes to the shortening of the atrial effective refractory periods and the promotion and maintenance of multiple wavelet re-entry circuits (40).

Structural remodelling includes structural changes such as fibrosis, necrosis, fatty tissue and inflammation which are often present in the atrium of patients with AF (41, 42). Even in patients with "lone AF" abnormal atrial histology is found in biopsy specimens; however the cause of the pathological changes found in atrial septal biopsies in most patients are unknown (43). In recent years, there is emerging data supporting the association between inflammation and AF (44, 45). Although structural atrial changes may be due to underlying heart disease, AF also produces secondary abnormalities of the atrial structure, including left atrial dilation and increasing atrial fibrosis (41). The mechanism of increased fibrosis includes the deposition of increased amounts of connective tissue between individual cells, and deposition of large amounts of collagen and fibronectin (46). This further leads to separation of myocytes and subsequent impairment of atrial conduction at the microscopic level (47, 48, 49). This process culminates with alterations in the biophysical properties of atrial tissue, allowing the initiation and perpetuation of AF.

Clinical presentation

Symptoms of AF

AF may be symptomatic or asymptomatic, even in the same patient. Approximately 30% of the patients with persistent AF have earlier been reported to be asymptomatic (50). The arrhythmia may even sometimes be diagnosed when the patient presents with a thromboembolic event (51). However, many patients with AF complain of palpitations, chest pain, dyspnoea, fatigue or syncope. Different factors are thought to cause symptoms of AF, including loss of normal AV synchronisation reducing cardiac output by about 20%, marked irregular RR-intervals, uncontrolled ventricular rates, concomitant heart disease, pharmacological treatment as well as individual patient perception. For clinical purposes, it does remain difficult to recognize symptoms caused by AF in individual patients. In one recent study asymptomatic episodes of AF were seen to increase after radiofrequency catheter ablation treatment and analysis of

patient characteristics and arrhythmia patterns failed to identify a specific subset of patients that developed asymptomatic AF (52). Difficulties in defining individual symptoms caused by AF reduce the possibility to tell whether a patient will symptomatically benefit from treatment aiming at rhythm control as further discussed in study III in this thesis.

Quality of life

Although symptoms of arrhythmia may cause impairment of physical functions the rhythm disturbance per se also seems to decrease quality of life in patients with AF. In one study more than two thirds of the patients with paroxysmal AF considered that the arrhythmia influenced their lives negatively, regardless of frequency or duration of symptoms (53). In a study by Savelieva and co-workers even patients described as "asymptomatic" in their arrhythmia reported a reduced quality of life, especially concerning general health and global life satisfaction compared with healthy controls (54). The impact of rate or rhythm control on quality of life has recently been addressed in several investigations; the AFFIRM Trial (Atrial fibrillation Follow-up Investigation of Rhythm Management), the RACE Trial (Rate Control vs. Electrical Cardioversion for Persistent Atrial Fibrillation), and the PIAF Study (Pharmacological Intervention in Atrial Fibrillation) (55-57). In these studies, quality of life was similar in patients treated with either rate or rhythm control strategies. According to these findings it seems plausible to believe that the described reduction in quality of life is partly due to the perception of cardiac disease and of concomitant disease more than to symptoms of AF itself.

Management

In patients with persistent AF the goal of treatment is either restoration of SR or accepting permanent AF, the latter strategy aiming at properly controlled ventricular rates at rest as well as during exercise. In both cases adequate prevention of thromboembolic complications must be considered.

Rhythm control vs. heart rate control

Until recently conceivable reasons for restoration and maintenance of SR included relief of symptoms, prevention of thromboembolism and effect on mortality. For long, evidence documenting the achievement of these goals was sparse. However, in recent years several prospective studies have addressed these topics. In the AFFIRM Trial a total of 4060 patients were included, and randomized to a rate control regimen using beta-blockers, digoxin or calcium antagonists or a rhythm control strategy involving amiodarone, sotalol and propafenone (26). In this trial the management of AF with the rhythm control

strategy offered no survival advantage over the rate control strategy. In fact, none of the presumed benefits of rhythm control noted above were confirmed. The data from the AFFIRM trial also suggest that continuous anticoagulation is warranted in all patients with AF and risk factors for stroke. In both treatment groups the majority of strokes occurred after warfarin had been withdrawn, even in patients where SR appeared to be restored and maintained. These results are consistent with the results of the RACE trial (27), which included 522 patients with persistent AF after a previous electrical cardioversion. Patients in the rate control group received rate slowing medications, while patients in the rhythm control group underwent serial cardioversions and received antiarrhythmic drugs. Rate control was found not inferior to rhythm control for the prevention of death and morbidity from cardiovascular causes, and the authors conclude that rate control may be an appropriate therapy in patients with a recurrence of persistent AF after electric cardioversion.

Prevention of thromboembolic complications

Risk factors for stroke in non-valvular AF include advanced age (>65 years), diabetes, hypertension, heart failure, previous stroke or transient ischaemic attack as well as echocardiographic atrial enlargement or ventricular systolic dysfunction (18, 30, 58, 59). In a prospective study, however, impaired left ventricular function but not left atrial size was a risk factor (60). In patients with risk factors, several clinical trials have demonstrated the benefit of anticoagulation therapy (61-64). Pooled data from five randomized, primary prevention studies showed a risk reduction with warfarin treatment of 68% (30). The efficacy of warfarin was consistent across all studies and subgroups of patients. Current recommendation suggests that oral anticoagulation is most beneficial for AF patients at higher intrinsic tromboembolic risk, offering only modest reductions over aspirin in risk for stroke in AF patients at low risk (16). Selection of antithrombotic therapy should be made from the same criteria irrespectively of the pattern of AF, i.e. for patient with paroxysmal, persistent or permanent AF. All patients scheduled for pharmacological or electrical cardioversion of AF with a duration of more than 48 hours should receive full anticoagulation. The optimal INR in clinical practice for stroke prevention is considered to be 2.0-3.0 (65).

Electrical cardioversion

Many patients with new-onset AF experience spontaneous cardioversion within 24 to 48 hours (66-68). However, spontaneous conversion is less frequent in patients with AF of longer duration. The most effective method for restoration of SR is direct current (DC) cardioversion, with a success rate ranging from previously 65% to 95% nowadays with biphasic waveform (69-72). A number of factors are known to predict the success rate. Short duration of AF and body weight have been found to be independent predictors of successful cardioversion (73, 74). Several other factors such as age, underlying heart disease, functional New York Heart Association (NYHA) class, mitral valve disease and left ventricular enlargement have yielded inconsistent results (75-77). Although most patients do regain SR at DC cardioversion a number of patients do not, i.e. refractory AF. If a strategy of rhythm control still is the therapeutic goal, one alternative is internal low-energy cardioversion, showing a conversion rate between 75% and 90% in this group of patients (78). An alternate strategy is pre-treatment with antiarrhythmic agents of class I or III (Vaughan Williams classification), preceding a repeated external cardioversion, a strategy found to be effective with intravenous ibutilide and amiodarone (79, 80). In clinical routine oral sotalol treatment has been used preceding a renewed cardioversion. Sotalol, having class II and III antiarrhythmic properties, has been found to decrease defibrillation energy requirements in ventricular tachycardia in animal models, and also lowers defibrillation energy requirements in patients treated with implanted cardioverter defibrillators (81, 82). However, the strategy of pre-treatment with sotalol in patients with DC refractory AF has not been evaluated regarding its efficacy to increase success at DC cardioversion and prevention of recurrence.

Pharmacological cardioversion

The possibility to achieve pharmacological cardioversion is reduced dramatically with increased duration of AF. Most trials evaluating pharmacological cardioversion include patients with new-onset AF and one factor that must be taken into account is the high rate of spontaneous conversion, about 50%, during the first 48 hours (66-68). Antiarrhythmic agents of class I and III, which prolong atrial refractoriness and action potential duration have been found to terminate AF. Although pharmacological cardioversion may appear as a simpler alternative to DC cardioversion without need for general anesthesia, it is less effective than electrocardioversion. There is also a concern about the proarrhythmic effects with pharmacological options. A variety of drugs, including ibutilide, dofetilide, propafenone, flecainide and amiodarone have been proven effective in terminating new-onset AF (16). For intravenous treatment with sotalol, there are no data showing a converting effect on new or

recent-onset AF. However, some investigators have reported a conversion rate of about 20% in patients with longer duration of AF treated with oral sotalol (83, 84).

Prevention of recurrences

Although success rates at electrical cardioversion are high, the rate of relapse into AF also remains high. Without antiarrhythmic prophylactic therapy approximately 75% of the patients relapse into AF within 12 months after cardioversion (85, 86). Several studies have investigated factors that predict maintenance of SR after cardioversion. Increased duration of AF has consistently been found to correlate with the recurrence of AF, as with an impaired success rate at cardioversion (73, 76). Other factors as age, the presence of underlying structural heart disease, functional NYHA class, left and right atrial diameters as well as left ventricular diameters have been investigated and found to show inconsistent results (87-91). There might be several explanations for these inconsistent findings such as choice of antiarrhythmic treatment, inclusion of patients with different numbers of previous cardioversions, inclusion of patients with atrial flutter, definition of successful cardioversion and various echocardiographic measurements. For unknown reasons relapse into AF is most frequent during the first weeks after DC cardioversion (92). This emphasizes the need to introduce antiarrhythmic drugs for prophylactic purposes prior to cardioversion in order to secure effective therapy immediately after the restoration of SR. To what extent signs of electrical vulnerability early after cardioversion, such as episodes of paroxysmal AF, predict recurrence of persistent AF has not been evaluated.

Antiarrhythmic drugs of class I and III are known to reduce the risk of relapse into persistent AF. This effect has been shown with amiodarone (93-95), disopyramide (96, 97), flecainide (98), propafenone (99, 100), sotalol (99, 101, 102) and quinidine (84, 85). However, even with the use of these drugs the recurrence rate of AF is about 50% six months after cardioversion. Moreover, these drugs bear a risk of potential life-threatening proarrhythmic side effects. Since AF is not regarded a life-threatening arrhythmia it is mandatory with high demands on antiarrhythmic drugs used to treat it concerning safety and tolerability. This restricts the use of amiodarone, a class III antiarrhythmic drug proven to be the most effective among drugs that prevent relapse into AF. Especially in patients scheduled for their first cardioversion the use of antiarrhythmic prophylactic treatment is limited since approximately 25% of the patients remains in SR without antiarrhythmic treatment. In summary, there is a need for alternative strategies with the ability to reduce the recurrence rate of AF without intolerable side effects.

Beta-blocking agents in AF

The main purpose with beta-blocking treatment in AF has been ventricular rate control. Beta-blockers are, together with calcium channel blockers and digoxin, well documented as first line therapy for heart rate control in AF (16). In contrast to digoxin, which increases vagal influences particularly on the AV node thereby offering rate-slowing effects at rest but not during exercise, beta-blockers and calcium channel blockers effectively control ventricular response even during exercise. Beta-blockers prolong AV nodal refractoriness by their anti-adrenergic effect. An even more pronounced effect on ventricular rate is seen with a combination treatment of beta-blockers or calcium channel antagonists with digoxin (103, 104). Earlier trials have shown improved exercise capacity in patients with AF after use of calcium antagonists in comparison to digoxin (103, 105), but this effect has never been demonstrated with beta-blockers (104, 106). This is probably due to the negative inotropic properties of beta-blocking agents.

The ability of beta-blockers to prevent new-onset AF has also been investigated. Psaty and co-workers showed that in older adults followed for a mean duration of 3.3 years, beta-blocker treatment was associated with a 39% risk reduction of new-onset AF (107). This was confirmed in the Metoprolol CR/XL Randomised Intervention Trial in congestive Heart Failure (MERIT HF) comparing Metoprolol controlled release/extended release (CR/XL) and placebo in patients with heart failure (108).

Beta-blockers are less effective or incompletely studied concerning pharmacologic cardioversion (16). The short-acting beta-blocker esmolol when given intravenously has a modest efficacy in cardioversion of recent-onset AF, but this effect has not been confirmed in comparison with placebo. Esmolol, however, rapidly controls the rate of ventricular response to AF (109).

The ability of beta-blocking agents to reduce relapse into AF has been the target for previous trials. In one study atenolol 50 mg once daily was proven to be as effective as 80 mg sotalol twice daily and better than placebo in preventing ECG -documented episodes of paroxysmal AF (110). In a trial comparing bisoprolol with sotalol, equality was found concerning prevention of relapse into persistent AF after cardioversion. However, in this investigation the dose of sotalol was relatively low (160 mg/day), and since the class III anti-arrhythmic effect is less pronounced at low doses the study may be interpreted as a comparisons between two beta-blockers (111). In a placebo-controlled trial by Kühlkamp and co-workers metoprolol was found to be moderately effective in preventing post shock recurrences of AF (112). However, treatment with a beta-blocker was started only after DC cardioversion, and as most relapses are known to occur

during the first weeks after restoration of SR a strategy where treatment starts before cardioversion might be more effective. The preventive effects of beta-blocker treatment initiated before cardioversion, and in higher doses in order to achieve an optimal antiarrhythmic effect is further discussed in study IV in these thesis.

The mechanisms behind the effect of beta-blockers in preventing AF are not fully understood. One explanation is the ability to suppress atrial premature beats provoked by catecholamines (113). Beta-adrenergic stimulation is known to shorten the action potential duration by increasing the magnitude of the delayed rectifier currents, I_K (114). In pacing induced AF shortening of atrial refractoriness is thought to be an important mechanism by which AF perpetuates itself (115). Also, in human atrial repolarization the ultra rapid delayed rectifier K^+ current (I_{Kur}) has been shown to play an important role (116). Furthermore, this current is increased by isoproterenol and this effect is reversed by the addition of propranolol, a beta-blocker (117). An increase in I_{Kur} decreases the action potential duration. This evidence from clinical studies and experimental observations indicates that stimulation of adrenoceptors might facilitate the induction and perpetuation of AF, suggesting that agents with beta-blocking properties might prevent the arrhythmia.

AIMS OF THE THESIS

1. To prospectively study the effect of oral pre-treatment with sotalol on success rate and recurrence in patients with AF refractory to earlier DC cardioversion.

2. To prospectively evaluate if episodes of AF after DC cardioversion predict recurrence of persistent AF. To observe the incidence and duration of episodes of AF and their change over time.

3. To investigate the agreement between perceived heart rhythm and the ECG registered heart rhythm and the agreement between symptoms and the ECG after DC cardioversion.

4. To assess the efficacy of metoprolol CR compared with placebo in combination with prompt repetition of cardioversion in case of early relapse, with respect to the number of patients in SR six months following first time DC cardioversion.

MATERIAL AND METHODS

An Arrhythmia Section for patients with AF was established at Stockholm South Hospital which received all patients with a diagnosis of AF referred to the Department of Cardiology. During the years of the present studies, 2000-2004, this section was managed by two of the investigators. This unit also took care of patients on anticoagulation treatment scheduled for electric cardioversion. All patients in study I, II and III were recruited and investigated at the South Hospital. In study IV the majority of the patients was also recruited at South Hospital, but three patients were recruited and investigated at St Göran Hospital, Stockholm, all of them by the same investigator. Some patients participated in more than one study as is illustrated in *figure 3*.

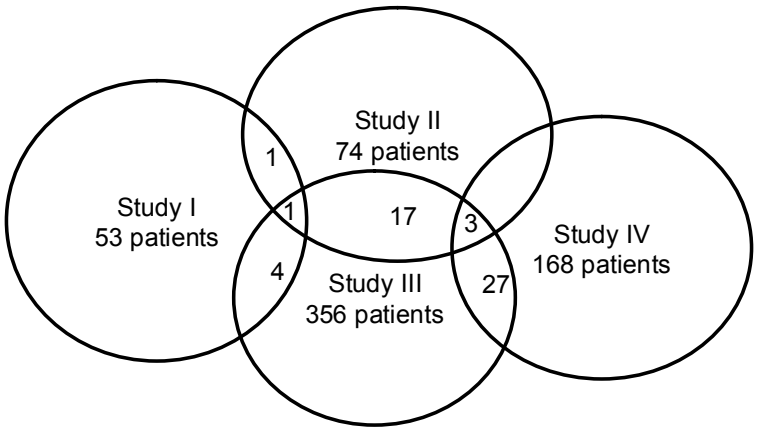

Figure 3. Distribution of patients participating in study I-IV.

Subjects

Study I

In this study 53 patients with persistent AF for at least one month who had undergone one unsuccessful DC cardioversion, and who were scheduled for a second cardioversion were included. DC refractory AF was defined as less than three heart beats in SR after the attempt of monophasic cardioversion. A careful medical history and a review of available ECG recordings were performed in all patients in an attempt to determine the duration of AF. All patients underwent transthoracic echocardiography prior to the first cardioversion. A comparative group of 132 patients with AF not refractory to cardioversion was studied concerning conditions that might influence conversion success rate. These

patients were consecutive patients referred to our Arrhythmia Section, and cared for by the same cardiologists. The patients in the comparative group had no current class I or III antiarrhythmic treatment.

Study II

To evaluate if self-limited episodes of AF after DC cardioversion predict recurrence of persistent AF and to study the incidence and duration of such episodes, 84 consecutive patients scheduled for cardioversion were prospectively investigated. All patients had symptomatic AF with a duration of more than one and less than 12 months. A complete medical history, physical examination, ECG and an examination of the patient records including a review of available ECG registrations were performed in all patients in an attempt to determine the duration of arrhythmia. All patients underwent transthoracic echocardiography prior to inclusion.

Study III

To what extent does patient awareness of their heart rhythm influence the perception of symptoms and quality of life? To investigate the agreement between perceived heart rhythm and the ECG registered heart rhythm as well as between symptoms and the ECG after DC cardioversion we conducted a prospective investigation of 356 patients with persistent symptomatic AF who had undergone successful cardioversion. A complete medical history, physical examination, ECG and a review of patient records including available ECG registrations were performed in all patients. All patients underwent transthoracic echocardiography prior to cardioversion. No change in pharmacologic treatment was allowed between cardioversion and the follow-up visit one week after cardioversion, however, in case of bradycardia a dose reduction was allowed.

Study IV

Between November 2000 and December 2004 consecutive patients with a diagnosis of symptomatic, persistent AF referred for elective cardioversion were recruited to this trial. A total of 168 patients fulfilled the criteria for inclusion. Persistent AF was confirmed using a 24-hour Holter recording. Major exclusion criteria were contraindications to treatment with beta-blocking agents, untreated thyroid dysfunction, cardiac surgery within the previous two months and absolute indication for beta-blocker treatment such as known coronary artery disease. Ongoing treatment with antiarrhythmic agents of class I or III and treatment with calcium channel blockers was also considered as an exclusion criterion. A complete medical history, physical examination, ECG and an examination of the medical notes including a review of available ECG

recordings were obtained from all patients in an attempt to determine the duration of AF. All patients underwent transthoracic echocardiography prior to inclusion. All patients were treated with warfarin, INR at levels between 2.1 and 3.0, for at least three weeks before and six weeks after cardioversion.

Methods

Study I

Treatment with oral sotalol was initiated immediately after the unsuccessful electrocardioversion and continued for at least seven days before a new attempt of cardioversion was made. The initial dose of sotalol was 80 mg twice a day, with a target dose of 160 mg twice a day. No other antiarrhythmic drug treatment was allowed. Pre-treatment with sotalol was continued at least seven days before a renewed attempt of cardioversion in order to establish the highest tolerable dose with regard to heart rate, QT-interval and blood pressure. DC cardioversion was performed on an elective basis according to standard clinical practice. Delivery of shocks started with 200 J, and if unsuccessful increased to at least two attempts at 360 J. Successful outcome was defined as SR after cardioversion that was maintained when recording a 12-lead resting ECG two hours later. All patients had a clinical examination and 12-lead ECG four weeks after cardioversion.

Study II

After successful DC cardioversion an ambulatory ECG Holter monitoring (24 hours) was performed at three occasions; one week (days 5-7), three weeks (days 18-21) and six weeks (days 42-45) after restoration of SR. Loss of p-wave and irregular ventricular rhythm for five seconds or more was regarded as an episode of AF. The patients were asked to report daily physical activity and symptoms in free text. No change in antiarrhythmic therapy was allowed during the six week follow-up. Patients who relapsed into symptomatic persistent AF during the six weeks of follow-up were withdrawn from further Holter recordings.

Study III

One week after cardioversion the patients were scheduled for an outpatient visit. All patients were asked two questions. The first question was “Do you believe that your heart rhythm is regular or in atrial fibrillation”. Elegible alternatives were “Regular”, “Atrial fibrillation” or “I don’t know”. The second question was “Do you feel better, worse or not different today, compared with before the cardioversion”. Eligible alternatives were “Better”, “Worse” or “Not different”.

After the interview a 12-lead resting ECG was obtained. A subgroup of patients was scheduled for a later visit to their physician after cardioversion. In these patients the same procedure was repeated four weeks after cardioversion. To measure the agreement between perceived and ECG recorded heart rhythm as well as between symptoms and recorded heart rhythm Cohen's kappa test was used, with a maximum of 1 when agreement is perfect and a value of zero indicating no agreement better than chance.

Study IV

The design of study IV is illustrated in *figure 4*. At time of inclusion at least seven days prior to cardioversion patients were randomized to either metoprolol CR or placebo in a double-blind fashion. Initial dose of treatment was 50 mg given once daily, with 50 mg stepwise increases to a target dose of 200 mg once daily. DC cardioversion was performed on an elective basis according to standard clinical practice. A pre-discharge 12-lead ECG was obtained two hours after cardioversion. Patients were followed on an outpatient basis once a week during the first six weeks following DC cardioversion. At each visit a 12-lead ECG was obtained. If relapse into AF during the first six weeks after DC cardioversion the patient was scheduled for a repeated cardioversion within seven days, without any change in study treatment. After the first six weeks the patients were seen three and six months after DC cardioversion. At each visit, a resting ECG was obtained. In case of relapse into AF more than six weeks after the initial cardioversion the study treatment was withdrawn, and the patient ended the study.

Ethics

The Ethics Committee at the Karolinska Institutet approved the protocols for studies I, II and IV following regular applications. The protocol and details of study III was discussed with the chairman of this committee. He did not see any need for a formal application since this study did not include any intervention and the patients were interviewed as a part of a regular visit to our outpatient clinic.

Inclusion:
Clinical investigation, 24 hours Holter, echocardiography, blood samples
↓
Initiation of warfarin treatment (if not present)
INR once a week.
↓
Initiation of study treatment
↓
One day before cardioversion: ECG, blood samples
↓
Cardioversion:
ECG before and after two hours
AF remains: withdrawal of study treatment
SR: withdrawal of digitalis (if present)
↓
One - six weeks after cardioversion:
Clinical investigation, ECG, registration of side effects
SR: continue with weekly controls
AF: scheduled for a second cardioversion within seven days
↓
Three months after cardioversion:
Clinical investigation, ECG,
registration of side effects
↓
Six months after cardioversion:
Clinical investigation, ECG, registration of side effects, tablet count

Figure 4. Study schedule for study IV

Statistics

Continuous variables are given as mean values ±SD. The unpaired t-test was used for analysis of statistical differences in variables between the groups. In comparisons of two proportions Pearson's Chi square test was used, and in the case of small numbers Fisher's exact test analysis was performed. Multivariate analysis (logistic regression) was used in study I. In comparisons over time analyses of variance were performed in study II. Cohen´s kappa test was used in study III. In study IV cumulative incidence was compared using the log-rank test. A p-value <0.05 was considered statistically significant. Calculations were performed with the statistical computer package STATISTICA 7.0 (StatSoft Inc.,Tulsa, Oklahoma).

RESULTS

Study I: Sotalol treatment in patients with DC-refractory atrial fibrillation

A total of 53 patients with AF refractory at time for DC cardioversion were enrolled in the study and 132 patients were included in the comparative group. Mean age in the treatment group was 63 (±10) years and mean duration of AF was 6 (±3) months. Mean weight was 88.4 (±15.0) kg. AF duration was unknown in 30% of the patients. The most commonly associated condition was hypertension (28%). Left atrial (LA) dimension was 44.6 ±5.5 mm, and ejection fraction (EF) 45 ±9.5%. The dose of sotalol at the time of cardioversion was 255 (±53) mg daily. In a univariate analysis, the comparative group differed significantly from the DC refractory group concerning age, weight, duration of AF, LA dimension and left ventricular end diastolic (LVED) diameter. However, after stepwise multiple regression analysis only the difference in mean (±SD) body weight remained statistically significant.

Forty-three patients (81%) in the sotalol group converted to SR. Of these, 10 (19%) converted before scheduled DC cardioversion, i.e. pharmacological cardioversion. An additional 33 patients (62%) reverted to SR with DC cardioversion, and all maintained SR until discharge from the hospital two hours later. The mean (±SD) cumulative energy delivered was significantly lower when compared to the cumulative energy delivered at the first unsuccessful cardioversion, 788 (±549) J vs. 1344 (±527) J, $p< 0.001$ as illustrated in *Figure 5*. The patients (n=8) who were refractory at the second DC cardioversion received a significantly lower dose of sotalol when compared with the patients who restored SR at the second cardioversion, 206 (±63) mg vs. 268 (±71) mg ($p= 0.04$).

In patients (n=43) who obtained SR after pre-treatment with sotalol, 29 patients (67%) were still in SR after four weeks. In an intention to treat analyses of the total study population of 53 patients, maintenance of SR at four weeks was 55%. In patients who had converted pharmacologically maintenance of SR at four weeks was more common when compared to patients who restored SR after DC cardioversion (90% vs. 60%, $p=0.03$). No signs of proarrhythmic activity such as torsade de pointes were observed.

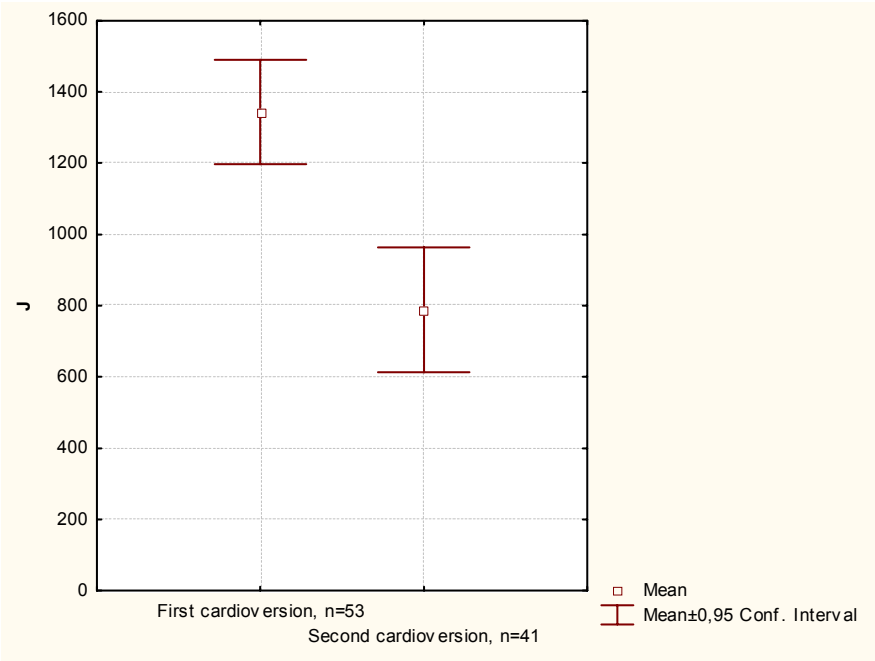

Figure 5. Cumulative Joule at first and second DC cardioversion

Study II: Self-limited bursts of atrial fibrillation following successful cardioversion

Patients (n=84) with persistent symptomatic AF and scheduled for elective DC cardioversion were enrolled in the study. Baseline clinical characteristics are presented in Table 2. During the time from inclusion to the date of cardioversion three patients were found to have paroxysmal AF and were therefore excluded from the study. Four patients who did not respond to cardioversion and three patients who converted to SR but relapsed into AF within the first two minutes were excluded from analyses. In the remaining 74 patients (88%) SR was restored at cardioversion and maintained at discharge from hospital two hours later. A total of 192 Holter recordings were performed during the study period. Of these 134 (70%) showed predominant SR and 58 (30%) revealed AF during the whole recording. Of the 134 recordings showing predominant SR there were self-limited episodes of AF in 57 registrations (43%). Of the 74 patients included in the study 65 patients (88%) had either episodes of AF or persistent AF during one or more recordings. The first, second and third Holter recordings were performed in 74, 63 and 55 patients, respectively. Patients with relapse into symptomatic persistent AF were withdrawn from further Holter recordings according to the study protocol. These patients were in most cases given other antiarrhythmic drugs, and scheduled for repeated cardioversion. However, in 12 patients further Holter recordings were made despite AF during an entire registration, reflecting that these patients were asymptomatic.

Table 2. *Clinical Characteristics of the Patients*

Characteristic	Number of patients (n = 74)
Male	56 (75%)
Age (years)	69.3 (±9.1)
Weight (kg)	83.0 (±16.7)
AF duration (months)	4,9 (±2.7)
AF, unknown duration	18 (24%)
First DC cardioversion	42 (57%)
Hypertension	32 (43%)
Ischemic heart disease	15 (20%)
Corrected thyroid disease	2
Lone AF†	25 (34%)
LA dimension (mm)	45.1 (±6.3)
LVED dimension (mm)	50.2 (±5.6)
EF (%)	50 (±8.4)
Valvular heart disease*	7 (9%)

Values are expressed as mean ±SD or number (%) of patients.
† Defined as the absence of any of the diseases mentioned above.
*Two patients with significant mitral incompetence and five patients with significant tricuspid incompetence

At six weeks of follow-up 34 patients out of 74 (46%) had relapsed into persistent AF. To investigate if the episodes of self-limited AF one week after DC cardioversion could predict relapse into persistent arrhythmia we analysed the occurrence of episodes at the first Holter recording. In patients with persistent AF at six weeks after cardioversion eight out of 34 patients (24%) had had self-limited episodes of AF at the first Holter recording, compared to 12 out of 40 patients (30%) with self-limited episodes at the first registration and SR at six weeks of follow-up ($p>0.05$).

The occurrence of self-limited episodes of AF in patients with SR was 21 out of 51 (41%), 21 out of 43 (49%) and 15 of 40 (38%) at first, second, and third registration, respectively. In patients with predominantly SR the mean (±SD) number of episodes seen in first, second and third recording were 2.2 ± 1.6, 1.6 ±0.7 and 1.9 ± 1.5 respectively ($p>0.05$), as illustrated in *Figure 6*. The mean (±SD) duration of episodes were 9.5 ±7.3 s, 8.5 ±3.1 s and 9.3 ±7.0 s for the first, second and third recordings ($p>0.05$). Numbers of SVES (mean ±SD) during the three registrations were 559 ±394, 409 ±324 and 572 ±294 respectively ($p>0.05$).

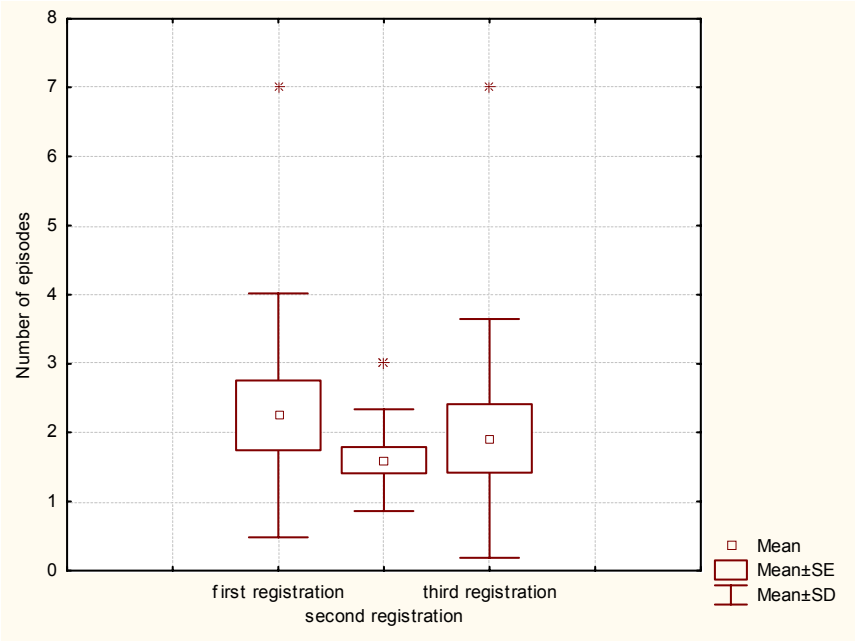

Figure 6. Number of episodes at first, second and third Holter registration

Only nine patients (12%) went through all three Holter recordings with no episodes of AF. These patients did not differ significantly concerning baseline characteristics or pharmacological treatment from patients with episodes of AF. Thirty-eight patients performed three recordings in predominant SR, i.e. did not relapse into persistent AF during the study period. In these 38 patients there were no significant differences over time in occurrence of self-limited episodes of AF. The numbers of episodes (mean ±SD) were 2.3 ±1.8, 1.6 ±0.7 and 1.9 ±1.7. ($p>0.05$) Moreover, there was no significant change concerning the mean duration of episodes; 8.8 ±3.9 seconds, 9.2 ±3.4 seconds and 10.8 ±9.6 seconds. ($p>0.05$)

Study III: Perceived heart rhythm in relation to ECG-findings

Patients (n=356) with persistent symptomatic AF who underwent successful elective DC cardioversion were prospectively enrolled for this investigation. One week after restoration of SR all patients were seen at the out-patients department. The results in answering the first question, "Do you believe that your heart rhythm is regular or in atrial fibrillation", is presented in Table 3. A total of 160 patients (45%) thought that they had SR, 59 patients (17%) believed that they had AF, and 137 patients (38%) did not know. The ECG showed SR in 222 patients (62%), and AF in 134 patients (38%). In 130 patients who perceived SR, the ECG registration also showed SR, $\kappa=0.34$ (0.24-0.44), indicating fair agreement.

Table 3. *Agreement between perceived heart rhythm and the ECG (a) and symptoms and the ECG (b) one week after DC cardioversion, n=356*

		a. Perceived heart rhythm			b. Symptoms		
		SR *n=160*	**AF** *N=59*	**Unsure** *N=137*	**Better** *n=190*	**Worse** *N=23*	**Not different** *N=143*
ECG	**SR** *n=222*	130*	21	71	141†	11	70
	AF *n=134*	30	38**	66	49	12††	73††

* κ=0.34 (0.24-0.44), fair agreement.
** κ=0.13 (0.02-0.25), poor agreement
† κ=0.26 (0.15-0.36), fair agreement.
†† κ=0.25 (0.14-0.34), fair agreement

In answering the second question, "Do you feel better, worse or not different today, compared to before the cardioversion", 190 patients (53%) stated that they felt better, 23 (6%) worse and 143 (40%) felt no difference, Table 3. Of patients who felt better 141 showed SR on their ECG, κ=0.26 (0.15-0.36), indicating fair agreement. Of those who felt worse or not different, 85 had ECG recordings showing AF, κ=0.25 (0.14-0.34), again indicating fair agreement.

To evaluate to what extent perception of heart rhythm influenced symptoms, we evaluated the association between these two parameters. There was a strong association between perceived SR and improvement in symptoms (n=129, $p<0.001$) as well as between perceived AF and worsened or no difference in the symptoms (n=37, p=0.04).

Four weeks after cardioversion, a subgroup of patients (n=93) was again presented the same questions. In this subgroup, agreement between perceived heart rhythm and the ECG as well as symptoms and the ECG at one week after cardioversion did not differ from the total study population. At this second occasion, 52 patients (56%) were in SR, and 41 (44%) had AF on the ECG. SR was perceived by 39 patients, who also showed SR on their ECG registration, κ=0.48 (0.30-0.67), indicating moderate agreement. Forty-three patients who felt better also had SR at ECG registration, κ=0.42 (0.23-0.61), indicating moderate agreement. Again, there was a strong association between perceived SR and improvement of symptoms (n=39), $p<0.001$.

Study IV: Metoprolol CR initiated before DC cardioversion and repeated cardioversion of atrial fibrillation

A total of 168 patients were enrolled in the study, 83 patients were randomized to treatment with metoprolol and 85 patients to treatment with placebo (*Figure 7*). The two treatment groups were similar with respect to all pre-treatment characteristics. Seventy nine patients in the metoprolol group and 81 patients in the placebo group underwent DC cardioversion. Mean dose of study treatment (±SD) at time of cardioversion was 169 ± 47 mg in the metoprolol group compared with 180 ± 40 mg in the placebo group (p=0.12). No patient in the metoprolol group showed early reinitiation of atrial fibrillation (ERAF), defined as relapse into AF prior to the discharge ECG two hours after cardioversion. In contrast, seven patients in the placebo group developed ERAF (p=0.008).

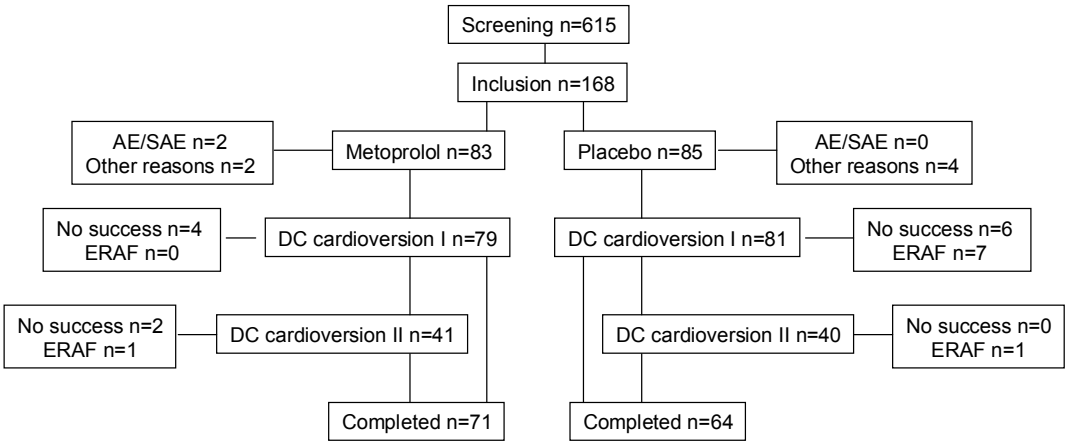

Figure 7. Flow diagram of the study. AE: Non-serious adverse event; SAE: Serious adverse event; ERAF: Early reinitiation of atrial fibrillation; DC: Direct current

Forty patients (47%) in the placebo group and 41 patients (49%) in the metoprolol group had a second DC cardioversion i.e. relapsed during the first six weeks after their initial DC cardioversion (p=0.8) The average duration from detected relapse in AF until the second cardioversion was 1.8 (±2.0) days and 2.4 (±2.4) days in the metoprolol and in the placebo groups, respectively (p=0.3).

In an intention-to-treat analysis 22 patients (26%) in the placebo group and 38 patients (46%) in the metoprolol group were in SR six months after initial DC cardioversion (p=0.0007). The difference in proportion of patients in SR between the two study groups was significant already one week after initial cardioversion, and remained highly significant thorough the follow-up period. In patients who converted to SR at the initial DC cardioversion a log-rank test of

equality over treatment groups regarding time to second relapse during first six weeks after initial cardioversion or first relapse more than six weeks after initial DC cardioversion yielded a p-value = 0.02, *figure 8*.

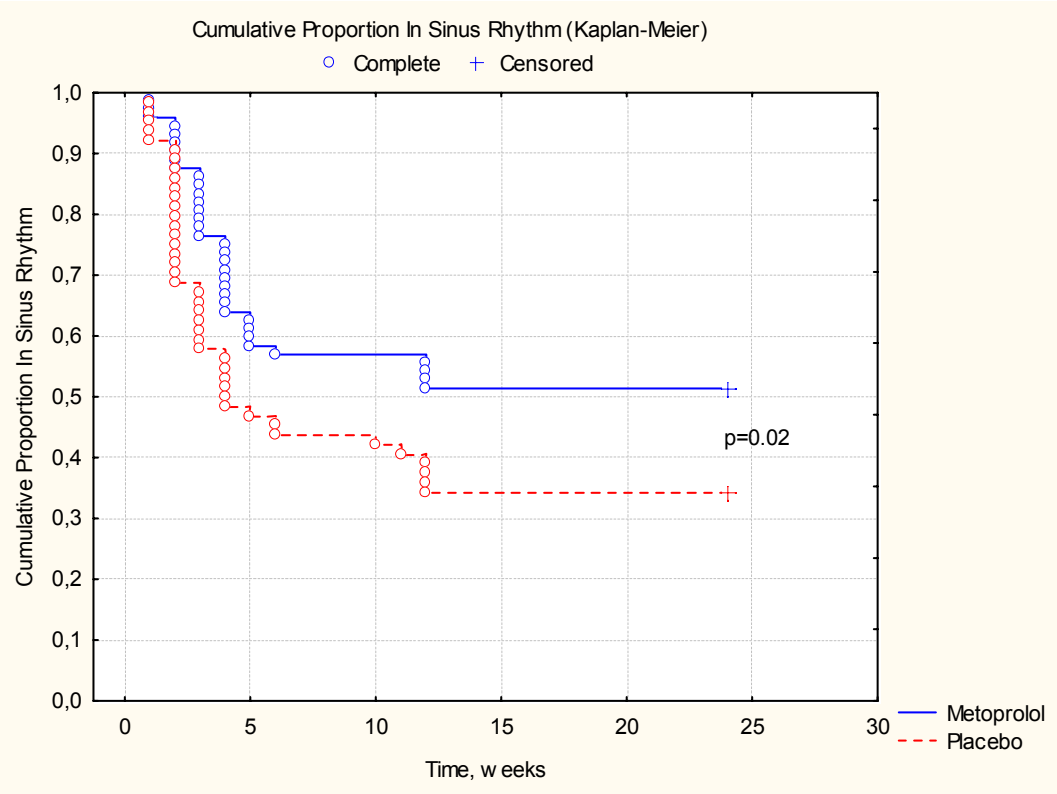

Figure 8. Cumulative number of patients in SR, subdivided by treatment group. The log-rank test of equality over treatment groups included a total number of patients=143, metoprolol=75 and placebo=68; i.e. all patients with successful initial DC cardioversion.

In patients who had a second DC cardioversion 10 out of 41 patients (24%) in the metoprolol group and three out of 40 patients (8%) in the placebo group showed SR six months after their initial cardioversion (p=0.03), Table 4.

Table 4. *Outcome after second DC cardioversion*

	Metoprolol	Placebo	p-value
Second cardioversion	41	40	Ns
SR at 3 months	12 (29%)	3 (8%)	0.01
SR at 6 months	10 (24%)	3 (8%)	0.03

Number of patients (%)

Withdrawals from the study were seen in two patients in the metoprolol group because of one serious adverse event and one adverse event (one patient with hemorrhagic stroke two days after initiation of anticoagulation treatment and one patient with AV-block II). A side effect was registered if observed on at

least at one occasion and occurring in two or more patients. Side effects were registered at each follow-up visit one week, six weeks, three months and six months after initial DC cardioversion. Overall, treatment with metoprolol was well tolerated, and a significant difference between metoprolol and placebo concerning side effects was reported only for "cold hand and feet" as illustrated in Table 5.

Table 5. *Most common adverse effects (occurring in two or more patients)*

	Metoprolol (n = 83)	Placebo (n = 85)	p-value
Bradycardia <40 bpm	2	0	0.15
Fatigue	27 (33)	19 (22)	0.14
Headache	10 (12)	10 (12)	0.95
Cold hands and feet	20 (24)	10 (12)	**0.04**
Nausea	7 (8)	3 (4)	0.18
Sleep disturbance	11 (13)	15 (18)	0.43
Dyspnea (aggravated)	19 (23)	11 (13)	0.09
Nightmares	6 (7)	8 (9)	0.61
Vertigo/dizziness	8 (10)	8 (9)	0.96
Abdominal pain, diarrhoea	5 (6)	4 (5)	0.70
Chest pain (aggravated)	4 (5)	2 (2)	0.39
Reduced physical fitness	5 (6)	1 (1)	0.09

Number (%) of patients by the most common adverse effects (occurring in two or more patients).The number of patients included in the safety analysis is not the same as that included in the efficacy analyses. The safety population includes 166 patients, and is defined as all patients who received at least one dose of study drug. Numbers in parentheses refer to %.

GENERAL DISCUSSION

AF is the most common cardiac arrhythmia of clinical importance. In different ways it may relate to almost any other condition handled in the daily work of cardiology. Although AF per se seldom is a life threatening disease, it is associated with an impaired longterm prognosis concerning mortality and morbidity, including an increased risk of stroke and heart failure. The symptomatology of AF is widely dispersed, ranging from disabling symptoms to no symptoms at all. However, even in patients with AF thought to be asymptomatic the occurrence of this arrhythmia in most patients affects daily living as it decreases their quality of life. The purpose of this thesis is to further study the clinical presentation of the arrhythmia and our ability to prevent recurrences into AF. Hopefully, this thesis may contribute to the expanding knowledge of mechanisms behind this arrhythmia, thereby increasing the ability to individualize the management of AF in this large and heterogeneous group of patients.

The effect of sotalol pre-treatment in patients with DC refractory AF

In our study we demonstrate that patients with AF refractory at DC cardioversion may be successfully converted following oral sotalol pre-treatment. In addition, a group of patients will convert pharmacologically after initiation of oral sotalol. Patients converted after oral sotalol pre-treatment remained in SR to no less extent than patient with non-refractory AF.

Several factors are known to predict the success rate at DC cardioversion. Apart from a short duration of AF, body weight has been shown to be an independent predictor of successful cardioversion (73, 74). Earlier findings support the fact that successful cardioversion depends on the amount of energy delivered to the heart, consistent with the known higher efficacy of internal cardioversion (78). In our study, refractory patients had a higher mean weight than the patients in the comparative group. However, the mechanism for AF being refractory at DC cardioversion might not include only the amount of energy delivered to the heart, but also factors influencing structural remodelling of the atrium, thereby influencing the threshold value for successful cardioversion. This is illustrated in our study by differences between the refractory group and the comparative group apart from weight, also in duration of AF, age, LA dimension and LVED diameter. In our study we chose a simple but clinical relevant approach, defining refractory AF as less than three heart beats in SR without making a difference between no conversion to SR or ERAF. The mechanism behind these two conditions most likely differs. However, from a clinician's point of view these patients are likely to be equally managed and the strategy of pre- treatment with antiarrhythmic agents is usually applied to both groups of patients. Also, the

theory behind class III antiarrhythmic treatment preceding a repeated cardioversion in these patients involves the possibility of reducing defibrillation threshold, a mechanism that applies to all patients with DC refractory AF irrespective of underlying mechanism. In our study those who restored SR after renewed cardioversion received a significantly higher dose of sotalol than the patients who did not, which might reflect a dose-dependent effect of sotalol on the success rate at cardioversion.

We also found a group of patients who converted pharmacologically after induction of sotalol treatment. Sotalol has previously been found to be lacking converting properties of new- and recent-onset AF in studies using intravenous administration, even when rapid loading doses are given (118). Although our study population is not comparable to these patients, one explanation for these seemingly contradictory results might be that trials aiming at restoration of SR in recent-onset AF are powered to reveal a significant effect compared to spontaneous conversion of approximately 50% or DC cardioversion (60-95% conversion rate) and might therefore fail to recognise a conversion rate of about 20% as found in our material. Neverless, our findings emphasize the importance of adequate anticoagulation treatment preceding the initiation of class III antiarrhythmic agents.

We investigated the recurrence rate in our patient population, since the positive effect on success could have been clinically irrelevant if a majority of the patients relapsed into AF soon after discharge from hospital. This is a reasonable concern, although factors known to affect success rate at DC cardioversion also are factors known to increase the risk of relapse. However, in our study population the maintenance of SR was high (67%) during a follow-up period of four weeks.

This study was not placebo controlled, which is a limitation. This choice was made for ethical reasons. In patients with DC refractory AF there is a very limited chance to restore SR at a second attempt of cardioversion without any change in clinical conditions (79). The method of pre-treatment with antiarrhythmic agents has also been used in clinical routine, making it difficult to withhold such treatment for investigational purposes.

Bursts of AF following successful cardioversion

We found that self-limited episodes of AF do not predict a recurrence of persistent AF during six weeks of follow up after DC cardioversion. Brief self-limited bursts of AF are common, and continue over time without change in incidence or duration.

A number of factors have been shown to predict recurrences of AF after successful cardioversion (73, 76, 87-91). Efforts have been made to find clinical feasible methods to predict relapse into AF, thereby finding patients who will benefit most from antiarrhythmic treatment or, in the opposite scenario, should not receive a treatment aiming at rhythm control at all. Relapse into AF is known to be most frequent during the first months after cardioversion, indicating an electrical vulnerability of the preconditioned atrium to AF. In one investigation by Maounis and co-workers the prognostic significance of atrial arrhythmias recorded immediately after cardioversion was evaluated using a Holter recording (119). In this study an increase incidence of atrial premature complexes early after cardioversion was found to be a risk factor for recurrence of the arrhythmia. Signal average P-waves has also been analysed in an attempt to predict early recurrences of AF, but has failed to show any prognostic value (120). In a recent publication from the AFFIRM group clinical, electrocardiographic and echocardiographic risk factors associated with AF recurrence within two months of cardioversion and more or equal to two cardioversions during the first year were identified (121). However, the clinical predictive value of these factors was low. Our data showing that brief episodes of AF after successful cardioversion do not predict the recurrence of persistent AF is in agreement with these investigations.

We also found that brief episodes of AF are common after successful cardioversion. These episodes were short, the number of episodes was low and they seem to be completely asymptomatic. These bursts of AF were unchanged in duration and incidence during six weeks of follow up. This underlines the fact that AF should be seen as a chronic disease with different manifestations changing over time. As revealed by the AFFIRM and RACE trials an increased risk of stroke remains despite restoration of SR. Whether brief episodes of AF are one of the carriers of an increased risk of stroke per se or only a marker of chronic disease needs to be clarified.

A small number of patients went through the study with no signs of arrhythmia. It is possible that these patients actually were free from episodes of heart rhythm disturbance, but another possibility is that more frequent ECG registrations might have revealed similar episodes even in those patients.

Perceived heart rhythm in relation to ECG findings

Our results shows that in patients with persistent symptomatic AF who have been successfully treated by DC cardioversion there was no more than fair agreement between the perceived and the ECG-recorded heart rhythm one week after restoration of SR. Furthermore, there was no more than fair agreement between improvement of symptoms and SR in the resting ECG. However, the

association between perceived SR and improvement of symptoms was strong. Four weeks after cardioversion, in a subgroup of patients, there was a moderate agreement between perceived heart rhythm and the ECG, and between improvement of symptoms and the ECG. Again, there was a strong association between perceived SR and improvement of symptoms.

These findings support the possibility that patients' reports and perception of symptoms are influenced by their perception of their heart rhythm. The knowledge of "abnormal heart rhythm" might decrease the overall perception of well-being, as earlier found in studies addressing quality of life in patient with AF who report significantly lower values compared with healthy controls (57, 122).

In our study we performed analyses in six subgroups of patients (lone AF, known duration of AF, valvular heart disease, EF>40%, EF<40%, history of hypertension) in an attempt to identify groups of patients with a better agreement between perceived heart rhythm and the ECG, and who therefore might benefit more from a strategy aiming at rhythm control. Patients with lone AF showed moderate agreement between perceived heart rhythm and the ECG, while all other groups showed no more than fair agreement. This indicates that patients with fewer symptoms due to concomitant diseases to a higher extent are able to perceive their actual heart rhythm.

In patients with AF symptoms show a wide variety, and several factors are thought to cause the symptoms; loss of normal AV synchronisation, markedly irregular RR-intervals, uncontrolled ventricular rates and individual patient perception (50, 123-125). Despite efforts to recognize symptoms in individual patients it has been shown that individual perception and adjustment of life style may be major determinants for the development of symptoms in AF (50). Since the decision between rhythm and rate control strategy mostly is made on patient symptoms our results support the need for objective methods to assess which patients will benefit most from a rhythm control strategy.

A subgroup of patients was asked again four weeks after cardioversion about perceived heart rhythm and symptoms. Although this group of patients were not prospectively selected the finding of slightly improved agreement between perceived heart rhythm, symptoms and ECG is worth mentioning. This might be related to normalized mechanical and hormonal functions of the atrium. This is of clinical interest as symptom improvement during the first days after cardioversion in many cases is a determining factor when deciding if a patient should undergo repeated cardioversion in the case of early relapse. Our results indicate that only a few days in SR may be too short a period to evaluate improvement of symptoms related to heart rhythm.

Metoprolol CR in combination with promptly repeated cardioversion of persistent AF

In this investigation we found that metoprolol CR in combination with promptly repeated cardioversion in the case of early relapse significantly increases the proportion of patients in SR six months after the initial DC cardioversion of persistent symptomatic AF. The reduction in recurrence rate was seen immediately after DC cardioversion, as no patients in the metoprolol group had ERAF. Although the recurrence rate during the period one to six weeks after cardioversion did not differ between the treatment groups there were fewer relapses into AF after repeated cardioversion in the metoprolol group during the follow-up period of six months.

The mechanism by which beta-blockers might prevent relapse into AF remains unexplained. It has, however, been suggested to be partly due to restoration of abnormal intracellular calcium handling (126). One previous beta-blocker trial has shown a reduction of early relapses into AF but only in patients with hypertension (127). Two studies have investigated the efficacy of beta-blockers in preventing subacute relapse after cardioversion (111, 112). One study compared a beta-blocker with sotalol and reported equality concerning prevention of relapse into AF. However, the dose of sotalol in this study may have been suboptimal regarding the class III antiarrhythmic effect, and this study may also be interpreted as a comparison between two beta-blockers (111). Kühlkamp et al in a placebo-controlled multi-centre trial with metoprolol CR/XL showed a significant decrease in relapse of AF after DC cardioversion according to a log-rank test (112). However, the proportion of patients in SR at six months differed only modestly between the treatment groups. Metoprolol treatment was started after DC cardioversion. Since relapse into AF is most frequent during the first weeks after DC cardioversion it may be beneficial to start treatment prior to DC cardioversion in order to inhibit ERAF. Moreover, it is possible that the use of a higher dose of beta-blocker in our study compared to the doses used by Kühlkamp and co-workers might have produced a more pronounced antiarrhythmic effect.

The rationale for repeated cardioversion in the case of relapse is that the duration of AF previously has been found to be an independent predictor for maintenance of SR. Persistent AF is known to cause electrophysiological changes in the atrial myocardium which are thought to explain the progressive nature of the arrhythmia. The risk of relapse into AF is known to be high the first days to weeks after restoration of SR (73, 92), due to atrial remodelling and remaining perturbations in atrial electrophysiological and mechanical properties. A regimen of repeated cardioversion in the case of relapse has previously been

addressed, and found useful in achieving SR in patients treated with class I or III anti-arrhythmic agents (128). In our study we found that patients in the placebo group who had relapsed into AF during the first six weeks and received prompt repeated cardioversion showed significantly higher rates of relapse into persistent AF during follow-up compared with patients who received metoprolol treatment. This is consistent with an earlier trial which demonstrated that early repeated internal cardioversion (within 35 h) in the case of recurrence of AF was of very limited value in patients without antiarrhythmic treatment (129).

In the present investigation, 46% of the patients in the metoprolol group compared with 26% in the placebo group were in SR six months after DC cardioversion using a strategy including both pre-treatment with a beta-blocker and promptly repeated cardioversion in the case of early relapse. The beneficial effect of beta-blockers seems to be related to inhibition of ERAF and the inhibition of relapse into AF after repeated cardioversion. There were no differences between the metoprolol group and the placebo group as regards first time relapses into AF during the first six weeks following discharge. Concerning the finding of a significantly lower incidence of relapse after a second cardioversion it might be speculated that on-going treatment with beta-blockers at the time for relapse might postpone electrical remodelling and thereby decrease the risk of early relapse after the subsequent cardioversion.

The number of patients in SR six months after cardioversion in our investigation is comparable with earlier studies in which class I and III antiarrhythmic drugs were given as prophylactic treatment (99, 102). These drugs, however, bear a substantial risk of proarrhythmic side effects. In our study metoprolol was well tolerated and safe for the patients even in relatively high doses. Withdrawal of treatment was seen only in a few patients, making this treatment strategy an attractive alternative with proven efficacy and a low risk of adverse events. The beneficial effect might be even greater in patient subgroups known to benefit most from beta-blocking treatment, such as patients with congestive heart failure or ischemic heart disease. It is also possible that this strategy may select patients suitable for rhythm control treatment, and that recurrence of AF despite this strategy indicates that the possibility to maintain SR is limited and a strategy of rate control should be preferred.

CONCLUSIONS

I. In patients with persistent AF refractory to DC cardioversion oral pre-treatment with sotalol before repeated cardioversion results in a high rate of SR restoration. The favourable maintenance rate of SR at 4 weeks is of sufficient clinical relevance to consider this treatment option in patients with AF refractory to DC cardioversion.

II. In patients successfully converted to SR self-limited bursts of AF do not predict recurrence of persistent AF during six weeks of follow up. Brief self-limited episodes of AF are common, and the incidence and duration of such episodes are constant during a six weeks period after DC cardioversion.

III. Agreement between perceived heart rhythm and that registrated on ECG as well as between improvement of symptoms and SR recorded by the ECG is no more than poor-to-fair after successful cardioversion of patients with persistent AF. The association between perceived SR and improvement of symptoms is strong.

IV. A treatment strategy of metoprolol CR in combination with prompt repetition of cardioversion in case of early relapse (one to six weeks) significantly increases the number of patients in SR six months after initial cardioversion.

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