SUMMARY

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. In The Netherlands lifetime risk of atrial fibrillation is roughly 1 in 4 for persons >40 years old, and the currently estimated prevalence of atrial fibrillation 300,000 persons. When the atria go from sinus rhythm to atrial fibrillation, there is a ten-fold increase in atrial rate (400-600 bpm), causing unorganised atrial muscle cell contractions (fibrillation). Moreover, the fast atrial rate results in an irregular and often fast ventricular rate (up to 160-170 bpm). The majority of patients have atrial fibrillation in association with underlying cardiovascular disease. Frequently observed underlying conditions are longstanding hypertension, heart failure, coronary artery disease, (mitral) valve disease, diabetes, or thyreotoxicosis. In a minority of patients an etiology is absent, which is called ‘lone’ atrial fibrillation. Atrial fibrillation causes symptoms such as palpitations, angina, dyspnea, impaired exercise tolerance, anxiety and fatigue, ranging from mild discomfort to severe complications with a negative impact on quality of life. Atrial fibrillation is the major cardiac cause of stroke, resulting from embolism of thrombus due to stasis of blood in the left atrium. In the presence of concomitant risk factors for stroke (such as prior stroke, hypertension, congestive heart failure, (mitral) valve disease, diabetes and older age), oral anticoagulation to reduce the risk of stroke is indicated, irrespective of the rhythm. Furthermore, 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. Moreover, atrial fibrillation occurs frequently in the setting of heart failure and it may worsen heart failure.

In the introduction of this thesis, chapter 1, the electrophysiological and pathophysiological aspects of atrial fibrillation, (socioeconomic) consequences and the different treatment options are described. The two mainstay therapeutic approaches are rate control, involving acceptance of the arrhythmia and the institution of ventricular rate control, and rhythm control, aiming at the restoration and maintenance of sinus rhythm. The general consensus is that the two strategies are essentially equivalent with respect to the risk-benefit ratio for the majority of patients with persistent atrial fibrillation. In severely symptomatic patients, however, still rhythm control is first choice therapy, more than ever since non-pharmacological rhythm control approaches are rapidly evolving. Another group of patients that may benefit from permanent sinus rhythm are those who have atrial fibrillation in the setting of heart failure. In this thesis we evaluated both pharmacological and
non-pharmacological rhythm control strategies aiming to contribute to the development of an optimal rhythm control strategy.

In part I, chapter 2, patients with persistent atrial fibrillation were randomized to verapamil or digoxin and acute versus routine serial cardioversion in the 'VERDICT-NHS' study (supported by the Netherlands Heart Foundation). Atrial calcium overload and reduction of L-type calcium channels are the primary cause of electrical, contractile and (ultra)structural remodeling. Prevention of intracellular calcium overload by calcium antagonists like verapamil may decrease intractability of atrial fibrillation by preventing these remodeling processes. In a serial cardioversion strategy remodeling may happen again and again, and in this setting verapamil has not been tested before. We investigated whether during a serial electrical cardioversion strategy, (a) prevention of intracellular calcium overload by verapamil, and (b) acute cardioversion of subacute recurrences in case relapses occur, will decrease intractability of persistent atrial fibrillation. Unfortunately, this study did neither show a beneficial effect of verapamil in a serial cardioversion strategy nor of an acute serial cardioversion strategy on long term sinus rhythm maintenance. However, compared to patients who were treated with verapamil or digoxin in combination with a beta-blocker, patients with digoxin as monotherapy more frequently relapsed into permanent atrial fibrillation. So we concluded that digoxin monotherapy should not be instituted in patients in whom rhythm control is indicated.

In chapter 3 we investigated outcome of a serial cardioversion strategy for new-onset persistent atrial fibrillation in patients with chronic heart failure compared to a (control) group of patients with a normal left ventricular systolic function. Especially patients with chronic heart failure may benefit from stable sinus rhythm and an adequate atrial contraction ('atrial kick'). In this study outcome of a serial cardioversion strategy in patients with heart failure was inferior compared to patients without heart failure. Interestingly however, the recurrence pattern of atrial fibrillation after electrical cardioversion and outcome of the subgroup of patients undergoing a strict serial cardioversion and antiarrhythmic drug strategy was comparable between heart failure and non heart failure patients. Future trials should define which treatment strategy is best in patients with heart failure. In this context, the development of new, safer antiarrhythmic drugs, and probably also atrial catheter ablation, may have a major impact on rhythm control in (subgroups of) heart failure patients.

In part II we studied the efficacy of pacemaker therapy and the original Cox maze III surgery in patients highly symptomatic atrial fibrillation despite pharmacological rhythm control treatment, and without structural heart disease. Furthermore, we sought to investigate which factors play a role in the choice for a non-pharmacological intervention. Pacemaker
therapy was studied in chapter 4 and 5, including the randomized 'FACET' study. Atrial based physiological pacing has proven its effectiveness in patients with bradyarrhythmias, especially in those with sinus node dysfunction. It is unknown, however, whether certain patients with symptomatic atrial fibrillation, but without symptomatic bradyarrhythmias may also benefit from pacemaker treatment. Moreover, novel pacemakers have several special algorithms implemented in order to prevent atrial fibrillation, including antitachycardia pacing (ATP), and are capable of measuring the 'AF burden' (defined as the percentage of time in atrial fibrillation detected by the device). These algorithms 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). In particular the 'FACET' study showed in patients with paroxysmal atrial fibrillation that a hybrid therapy of preventive and ATP pacing, and antiarrhythmic drugs may significantly reduce atrial fibrillation, especially if septal pacing is realized. Unfortunately, the patients' quality of life and symptoms did not improve, probably at least in part related to the fact that 'AF burden' was reduced but was clearly not completely abolished which was obviously (partially) noticed by the patients. According to the present data and the proved benefits of catheter ablation for atrial fibrillation, given the higher chance of cure, we concluded that pacing is not considered as first choice therapy in patients with symptomatic atrial fibrillation without bradyarrhythmias.

In chapter 6 we demonstrated an excellent long-term outcome of Cox maze III surgery for the treatment of intractable lone atrial fibrillation. After a mean follow-up of 4.8 years 86% of patients were free of atrial fibrillation, with only 7% on antiarrhythmic drugs. Moreover, most patients affirmed, in retrospect, their initial choice for this (extensive) surgical intervention of atrial fibrillation and would recommend maze surgery to patients with equal complaints. This is, in our view, a very important finding.

In chapter 7 we studied a group of patients with drug refractory atrial fibrillation who underwent a non-pharmacological intervention. We reasoned that psychological factors might also be implicated in the choice for non-pharmacological treatment, with a particular focus on neuroticism. Neuroticism is a steady personality trait, which gives an indication of the emotional stability of a person. Our study demonstrated that neuroticism does not appear to play an important role in this decision. Although psychological factors (i.e. somatization) always has to be taken into account, our results suggest that younger age (<55 years), frequency, drug therapy refactoriness and symptomatology of atrial fibrillation are the main determinants of the decision for a non-pharmacological intervention.

The discussion (chapter 8) includes a critical appraisal of our results and the other
currently available rhythm control approaches. Furthermore, future developments are discussed. Since each patient has a unique underlying clinical history and symptomatology, treatment of atrial fibrillation should be individualized. In most patients rate control is recommended. However, rhythm control must be improved for those patients who benefit from sinus rhythm. In this context, results of new antiarrhythmic agents and strategies, for example ‘upstream therapy’ and early atrial fibrillation treatment, and the further development of more favorable non-pharmacological rhythm control strategies are eagerly awaited. The ultimate goal is prevention by identification and early treatment of markers that predict future or recurrent atrial fibrillation.