Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in the general population as well as in patients with heart failure.\(^1,2\) It is estimated that AF is to affect more than 3% (over 500,000 patients) of the Dutch population by the year 2060.\(^3\) After the age of 40 years one out of four people will develop AF during their remaining lifetime.\(^4\) Almost all patients have some form of underlying heart disease when AF is present.\(^5,6\)

At the turn of the millennium it was depicted that AF and heart failure will become the two epidemics in cardiovascular disease of the 21st century.\(^7\) The incidence and prevalence of AF is increasing due to aging of the population, longer survival with cardiovascular diseases and lifestyle changes but also due to the increasing willingness and technical capability to diagnose AF (especially silent undiagnosed AF) with systematic screening and longer-term monitoring devices.\(^8-10\) In addition, there is a reciprocal relationship between AF and heart failure.\(^1,11\) Also genetic defects predisposing the heart to both AF and heart failure are more frequently described.

Hypertension is the most frequent associated condition to AF and may cause diastolic heart failure. This is one of the reasons that especially the incidence of heart failure with a preserved ejection fraction (HF-pEF) is increasing. Due to increased stretch and pressure in the left atrium this condition may induce AF. Also other diseases and conditions, like obesity and diabetes may cause HF-pEF and induce AF. In addition systolic heart failure, i.e. heart failure with a reduced ejection fraction (HF-rEF), may underlie AF. This may occur in ischemic and non-ischemic cardiomyopathy and in valvular diseases. An emerging differentiation is “heart failure with a genetic component” and “heart failure without a genetic component” (the latter mapping more often onto heart failure due to myocardial infarction). While these “splits” are accepted in the published community, the rationale of differentiating them remains to be established.

Both HF-pEF and HF-rEF may induce neurohormonal changes, myocardial cellular and extracellular remodeling, and electrophysiological changes that combine to create a setting that predisposes the heart to both AF and heart failure (Figure 1).\(^12-16\) Although HF-pEF and HF-rEF share the same phenotype there are distinct patterns of structural remodeling and different response to therapy indicating two different entities with different pathophysiology.\(^17\)
CHAPTER 1

Assessment of the severity of clinical situation and underlying diseases.

The severity of AF-related symptoms should indicate whether acute restoration of sinus rhythm is necessary or whether acute management of the ventricular rate is sufficient.

Thereafter, optimal treatment of the associated diseases is the first goal. The third step includes stroke risk assessment followed by institution of rate controlling drugs.

Only thereafter, one should decide whether or not a rhythm control approach should be adopted. Importantly, at present the only indication to abolish AF is to relieve patients from symptoms.

Rhythm control strategies involve anti-arrhythmic drugs and/or invasive procedures like pulmonary vein isolation or arrhythmic surgery which all include risks on potentially life-threatening adverse events. However, if successful they relieve the patients from symptoms and improve quality of life. On the other hand rate control is often a simpler strategy not only for the physician but even more for the patient. Therefore, the guidelines state that rate control can be first choice therapy in a patient with minor symptoms associated with AF.

Optimal therapy may differ depending on underlying disease and the severity of left ventricular dysfunction, i.e. whether AF occurs in patients with HF-pEF or HF-rEF.

Treatment of Atrial Fibrillation

Treatment of AF in the general population focuses on control of AF related symptoms and prevention of stroke and heart failure.

As described by Kirchhof et al. (Figure 2) the initial assessment includes assessment of the severity of clinical situation and underlying diseases and conditions. The severity of AF-related symptoms should indicate whether acute restoration of sinus rhythm is necessary or whether acute management of the ventricular rate is sufficient. Thereafter, optimal treatment of the associated diseases is the first goal. The third step includes stroke risk assessment followed by institution of rate controlling drugs. Only thereafter, one should decide whether or not a rhythm control approach should be adopted. Importantly, at present the only indication to abolish AF is to relieve patients from symptoms.

Rhythm control strategies involve anti-arrhythmic drugs and/or invasive procedures like pulmonary vein isolation or arrhythmic surgery which all include risks on potentially life-threatening adverse events. However, if successful they relieve the patients from symptoms and improve quality of life. On the other hand rate control is often a simpler strategy not only for the physician but even more for the patient. Therefore, the guidelines state that rate control can be first choice therapy in a patient with minor symptoms associated with AF. Notably, this has been demonstrated in the majority of studies for patients having AF in the setting of HF-pEF. Only one study confirmed these findings in patients with HF-rEF.

**Figure 2.** Current approach to stepwise decision making in patient with atrial fibrillation. Adapted with permission from Kirchhof et al. (34)
rate in rest of below 110 b.p.m.) was not inferior to strict rate control (heart rate in rest of below 80 b.p.m.) in patients with permanent AF. (36,46) Recent guidelines now recommend that it is reasonable to a lenient rate control aimed at a resting heart rate <110 b.p.m. in patients without heart failure. (35) The data available about which strategy to use are derived from the RACE II study, which predominantly included patients having AF in the setting of HF-pEF. Studies assessing the optimal rate control strategy in patients with AF and HF-rEF have not been performed.

Studies with HF-rEF and sinus rhythm have shown that a lower heart rate is more beneficial but for patients with AF these observations have not been made. (47-49) Chapter 2 will assess whether a more lenient heart rate strategy is as good as a more strict strategy in those patients included in the Rate Control Efficacy in Permanent Atrial Fibrillation: a comparison between Lenient and Strict Rate Control II RACE II trial having more severe heart failure.

Most frequent used drugs for rate control are beta-blockers, non-dihydropyridine calcium antagonists and digoxin. (35) Digoxin has been associated with increased mortality in patients with AF although results have been conflicting. (50-56) The fact that digoxin may have deleterious effects has been acknowledged by the Digoxin Investigation Group in patients with HF-rEF and sinus rhythm were a high serum digoxin concentration was associated with worsening outcome. (57) In Chapter 3 the safety of digoxin in patients with permanent AF included in RACE II will be assessed.

Beta-blockers are besides rate control drugs also recommended as standard treatment in stable chronic HF-rEF in order to improve survival and reduce hospital admissions for heart failure. (58-62) Although it is generally assumed that the effects of beta-blockade in AF are similar to those in sinus rhythm, no clear advantageous effects of beta-blockade in patients with AF and HF-rEF or in those with HF-pEF have been demonstrated so far. (63-65) Chapter 5 and 6 will study whether beta-blockers are associated with an improved prognosis in patients with AF as well.

The role of AF in HF-rEF patients treated with cardiac resynchronization therapy
In more severe heart failure cardiac resynchronization therapy (CRT) offers beneficial outcome with regard to heart failure hospitalization as well as survival. (66-69) A prerequisite for optimal benefit of CRT is continuous biventricular pacing. AF may lead to a high and irregular ventricular rate, and as a consequence the percentage of biventricular pacing may decrease. (26,70-75) This has been the main reason for excluding patients with AF in large randomized controlled trials. (66-69) There have been several retrospective cohort studies and substudies of large trials that demonstrate beneficial effects of CRT in patients with either a history of AF or permanent AF, but often atrioventricular node ablation was required to ensure continuous biventricular pacing. (35,71,73,76-81) Development of new-onset or recurrences of AF in HF-rEF patients treated with CRT is also common and is associated with impaired response and cardiovascular outcomes. (27,82-84) This once again underlines the need of additional data on treatment optimization for AF in patients with HF-rEF treated with a CRT. This will be studied in Chapter 7.

Prognosis
Prognosis of AF has been associated with the severity of underlying cardiovascular diseases and recently also with patients of AF (i.e. paroxysmal versus permanent AF). (85-91) However, some patients never experience adverse events.

To improve personalized therapy risk assessment is essential. At present only limited data are available. Recent studies have shown that biomarkers may help to identify which AF patients are at the highest risk for impaired outcome. High-sensitive troponin I or T and N-terminal prohormone of brain natriuretic peptide were associated with cardiovascular morbidity and mortality in a mixed group of AF patients. (92-94) The relation between clinical parameters, biomarkers and cardiovascular morbidity and mortality in patients with recent onset permanent AF is sparse and will be assessed in chapter 4.

Aim of this thesis
This thesis focuses on optimization of treatment and outcome in patients with AF in the setting of both HF-pEF and HF-rEF. In chapter 2 we assess rate control management in patients included in Rate Control Efficacy in Permanent Atrial Fibrillation: a comparison between Lenient and Strict Rate Control II (RACE II) study with more severe heart failure. In chapter 3 we will evaluate an important rate control drug which is often used in patients with HF-rEF and AF, digoxin. We will test the hypothesis whether digoxin has influence on cardiovascular
outcomes in patients with permanent AF and primarily HF-pEF and whether it is effective as a rate control drug. Chapter 4 focuses on prognosis in patients with recent onset permanent AF and explores determinants of cardiovascular morbidity and mortality.

Beta-blockers improve survival and reduce hospital admissions for HF-rEF in patients with sinus rhythm. Chapter 5 will discuss patients whether in patients with AF and HF-pEF or HF-rEF the effect of nebivolol is comparable to patients with sinus rhythm. In Chapter 6 we will assess the role beta-blockers in patients with HF-rEF and AF in post-hoc analyses of the beta-blocker landmark trials. In chapter 7 we investigate the role of CRT in patients with AF. CRT improves survival and reduce hospital admissions for HF-rEF, however, patients with AF are often excluded from CRT trials and little is known about the significance of AF on clinical outcomes. Finally, in chapter 8 the results of this thesis will be summarized and put in perspective.

References

1. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91:2D-8D.


