Optimizing therapy in patients with atrial fibrillation and heart failure

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The general aim of the present thesis was to explore the optimisation of treatment for patients with atrial fibrillation (AF) and heart failure with either a preserved (HF-pEF) or reduced ejection fraction (HF-rEF). Although HF-pEF and HF-rEF may have the same symptoms there are distinct patterns of structural remodeling and therefore these patients may have different response to therapy. (1)

We studied a variety of patients with AF and HF-pEF or HF-rEF. In chapter 2 we showed that a more lenient rate control strategy is as good as strict rate control in patients with permanent AF and predominantly HF-pEF. In chapter 3 digoxin, a drug often used for rate control in patients with HF-rEF did, in contrast to other post-hoc analyses, not deteriorate outcome in our RACE II patients with permanent AF. In chapter 4 we demonstrated that parameters associated with cardiovascular morbidity and mortality in patients whom recently progressed to permanent AF are a longer pre-existing history of AF next to higher levels of blood biomarkers high-sensitive troponin T (Hs-Trop T) and N-terminal prohormone of brain natriuretic peptide (NT-proBNP). In chapter 5 we found that in patients with AF and HF-pEF or HF-rEF the effect of nebivolol was attenuated as compared to those with sinus rhythm. When combining several AF subanalyses with beta blockers (nebivolol, bisoprolol, carvedilol, and metoprolol) this effect on mortality was even more marked. Beta-blockers were predominantly effective in patients with sinus rhythm and HF-rEF with respect to mortality (chapter 6). Finally, in patients with HF-rEF eligible for cardiac resynchronisation therapy (CRT) response and cardiovascular outcome in patients with AF as compared to sinus rhythm was comparable (chapter 7).

Mechanisms of atrial fibrillation in heart failure
At the turn of the millennium it was portrayed that AF and heart failure will become the two major epidemics in cardiovascular disease of the 21st century. (2-4) This is not only related to ageing of the population, but also to changes in lifestyle and increased survival of patients with heart diseases. In addition, there is a reciprocal relationship between AF and heart failure. (3,5) Hypertension is the most frequently associated condition related to AF. Hypertension may cause diastolic heart failure. In turn, due to increased stretch and pressure in the left atrium HF-pEF may set the stage for AF. Also other diseases and
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conditions, like obesity and diabetes may cause HF-pEF and induce AF. In addition for the patient with HF-rEF, ischemic heart disease more often is the cause of AF.(6) 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.(1,7-9) It is therefore essential to early identify the patient with AF in the setting of heart failure and to establish treatment for 1. symptom reduction and 2. optimization of prognosis.(10-12) Treatment should therefore be patient tailored therapy and focused on finding the underlying disease and symptoms of the patient.

(13)

Rate or rhythm control for AF in heart failure

Treatment of AF in the general population focuses on control of AF related symptoms and prevention of stroke and heart failure.(14) When initiating treatment for AF, the initial assessment includes assessment of the severity of clinical situation and underlying diseases and conditions.(13) 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.(15) Thereafter, optimal treatment of the associated diseases is the first goal. The third step includes stroke risk assessment followed by institution of anticoagulants if indicated and of rate controlling drugs.(16) 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.(17-19).

As mentioned in the introduction of the thesis the nomenclature rate versus rhythm should be considered misnomer. Many patients need rate control during rhythm control therapy. Therefore, rate control should be key therapy, also in patients who are treated with a rhythm control approach, just to control the ventricular rate at the very moment of recurrent AF.

Rhythm control was long regarded as the preferred therapy for AF as patients could benefit from sinus rhythm by relief of symptoms. The downside to rhythm control was that anti-arrhythmic drugs are necessary, electrical cardioversion, and in recent years pulmonary vein isolation to maintain long-term sinus rhythm. Rate control on the other hand has the advantage that anti-arrhythmic drug therapy is not necessary and therefore potential side-effects are avoided. The disadvantage was that the rhythm disturbance was than accepted. Therefore every effort was previously made in the treatment of AF to maintain sinus rhythm but long term success was poor.(20-22) In recent years several trials have shown that rate control is not inferior to pharmacological rhythm control with regard to cardiovascular morbidity and mortality.(17,18,23-25) Comparable findings have been observed for patients with chronic heart failure.(26,27)

The Rhythm Control versus Rate Control for AF and Heart Failure (AF-CHF) trial showed in 1376 patients with AF and HF-rEF (mean left ventricular ejection fraction was 27%) that a rhythm strategy did not reduce the rate of death from cardiovascular causes, symptoms, quality of life, and left ventricular ejection fraction when compared to a rate control strategy. (12,27,28) Therefore, rate control is now adopted as first choice treatment in patients with and without heart failure and without severe symptoms, although early and aggressive rhythm control could potentially show attenuated results. (15,19,29)

It is generally believed that a low heart rate is beneficial, both in patients with heart failure (11,30) and coronary artery disease.(31) However this may primarily be applicable to patients who are in sinus rhythm and not for those with AF. A major concern of a higher heart rate in patients with AF...
has always been the development or deterioration of heart failure.\(^\text{32,33}\) However, in chapter 5 we showed that a lower heart rate by means of beta-blockade in patients with AF and HF-pEF or HF-rEF did not improve prognosis, although the overall results in the main trials with patients in sinus rhythm were undoubtedly positive in favor of beta-blockade therapy.\(^\text{34-37}\) This effect was also observed in a meta-analysis (chapter 6), which showed that the cumulative effect of all beta-blockers currently indicated for HF-rEF was only beneficial for patients who were in sinus rhythm.\(^\text{38}\) There was no beneficial effect in patients with AF, despite the fact that beta-blockade significantly reduced the heart rate. It is therefore suggested that titrating the heart rate during AF as low as during sinus rhythm with a beta-blocker is not necessary. Recently, it has been demonstrated that beta-blocker therapy may reduce exercise capacity more than calcium channel blockers in patients with permanent AF.\(^\text{39}\) Nevertheless, the aforementioned beta-blocker studies were not performed to assess heart rate control strategies but did assess cardiovascular outcomes.

Only one trial randomized patients with two different rate control strategies has been performed thus far: the Rate Control Efficacy in Permanent AF: a Comparison between Lenient versus Strict Rate Control II (RACE II) study.\(^\text{16,40}\) RACE II study was a Dutch randomized multicenter study comparing long-term effects of lenient versus strict rate control on morbidity and mortality in 614 patients with permanent AF. Patients randomized to lenient rate control had a resting heart rate target < 110 beats per minute. Patients randomized to strict rate control had two heart rate targets: a resting heart rate target < 110 beats per minute and a heart rate target during moderate exercise < 110 beats per minute. After a median of 3 years of follow up no differences were observed between lenient and strict rate control in terms of cardiovascular morbidity and mortality.\(^\text{16}\) Post-hoc analyses of RACE II also showed no differences in atrial remodeling, quality of life or symptoms.\(^\text{41-43}\) Despite absence of a difference in heart failure hospitalization in RACE II one cannot exclude that excessive rate control (e.g. heart rates above 110 b.p.m.) could be harmful.\(^\text{33,44}\) In the Permanent AF Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS), the immediate rise in both co-primary composite endpoint of stroke, myocardial infarction, systemic embolism and death from cardiovascular causes after the start of the trial in the dronedarone group compared to placebo could have been related to redundant rate control. This conception is supported by the fact that the heart rate at one month in the dronedarone arm had decreased by 7.6±14.5 beats per minute whereas no change occurred in the placebo arm.\(^\text{45}\) Recently, indeed, a strong effect of concurrent digoxin use on the adverse effect of dronedarone on cardiovascular death, but not on occurrence of heart failure was demonstrated.\(^\text{46}\)

In this thesis (chapter 2) we showed in patients with permanent AF and predominantly HF-pEF that a lenient rate control strategy had no harmful effect on cardiovascular morbidity and mortality, symptoms, and quality of life.\(^\text{47}\) An important advantage of lenient rate control strategy was that it was easier to accomplish: significantly fewer additional hospital visits and lower number and dosages of rate control drugs were necessary to achieve the heart rate target. A major concern of a high heart rate has always been the development or deterioration of heart failure.\(^\text{32,33}\) This was not observed in this analysis, and also not in a prior post-hoc analysis in patients with AF and moderate heart failure treated with a more lenient approach (heart rate in rest below 100 b.p.m.).\(^\text{18,26}\) Also in more advanced heart failure patients, a high heart rate was not associated with an increase in morbidity and mortality.\(^\text{48}\) In agreement with these results was a subanalysis of the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and morbidity) Program which observed that resting heart rate was not an important predictor of outcome in patients with AF and heart failure, regardless of left ventricular ejection fraction.\(^\text{49}\) Apparently a more lenient rate control strategy could allow the physician to accomplish a heart rate low enough to prevent excess heart failure hospitalizations and other cardiovascular morbidity and mortality in patients with primarily HF-pEF.\(^\text{47}\)

**Drugs to achieve ventricular rate control**

Ventricular rate control can be achieved by several drugs; beta-blockers, nondihydropyridine calcium channel antagonists, digoxin, and amiodarone alone or in combination. Beta-blockers are effective rate-control agents in both HF-rEF and HF-pEF but only reduce morbidity and mortality in HF-rEF patients.\(^\text{37,51}\) Recent data suggest that nondihydropyridine calcium channel antagonists may be a better choice for those with HF-pEF.\(^\text{39,52}\) These studies
showed that rate-reducing treatment with diltiazem or verapamil preserved exercise capacity and reduced levels of NT-proBNP, whereas treatment with metoprolol or carvedilol reduced the exercise capacity and increased levels of NT-proBNP.\(^{(39)}\) Digoxin can particularly be used for ventricular rate control in patients with AF and HF-rEF. Especially in the patients where digoxin only is given to slow the ventricular rate at rest, but not during exercise.\(^{(53)}\) Amiodarone is also effective in patients with AF and both HF-rEF and HF-pEF.\(^{(27)}\) However, because of its potential noncardiac toxicity, amiodarone is considered a second-line drug for rate control after a beta-blocker and digoxin are proven ineffective.\(^{(15)}\) Dronedarone, effective as a rate control drug, was not considered safe as it increased rates cardiovascular outcomes in patients with permanent AF.\(^{(45)}\)

**Beta-blockers**

Beta-blockers are the cornerstone treatment in patients with HF-rEF. Beta-blockers reduce heart rate by reducing sympatholytic activity. In addition it has been shown effective in improving outcome in patients with sinus rhythm.\(^{(34-36,54-57)}\) In the present thesis (chapter 5 and 6) we showed that beta-blockers however, did not improve prognosis in patients with AF and HF-rEF or HF-pEF.\(^{(37,38)}\) Although the mean heart rate was reduced with 10 b.p.m. in patients with AF this did not lead to an improved outcome. Apparently reducing heart rate in patients with AF should merely be done to improve symptoms rather than to improve outcome.\(^{(34-37)}\)

There could be several explanations why beta-blockers are less effective in patients with AF. First, the mode of action of beta-blockers is different during AF and sinus rhythm. During sinus rhythm, beta-blockers exert their heart rate-lowering effect by targeting the sinus node, whereas during AF their main site of action is the atrioventricular node. Secondly, it could be that patients with AF and heart failure benefit from a slightly higher heart rate as compared with patients in sinus rhythm.\(^{(51,57)}\) In the before-mentioned studies, comparable heart rate reductions (mean of 10 b.p.m.) in AF patients with bisoprolol, carvedilol, and metoprolol, respectively, were achieved.\(^{(34-36)}\) Thus, achieving low heart rates, i.e. strict rate control, may not be necessary in patients with AF, which is in agreement with the previously mentioned RACE II and the post-hoc analysis in patients with predominantly a preserved ejection fraction (chapter 2).\(^{(16,40,42,47,58,59)}\) Potentially this is explained by a loss of the atrial kick and the irregularity during AF, implying that patients may need higher heart rates to compensate for similar cardiac output, maybe even more so during heart failure.\(^{(48)}\) Finally, patients with AF less often have underlying ischaemic heart disease. Beta-blockers could act differently in ischaemic versus non-ischaemic heart failure. Also, beta-blockers may work by different mechanism, making a homogenous recommendation difficult.

Of interest, although the drug is not recommended by the current guidelines, bucindolol another beta-blocker, was associated with improved cardiovascular outcome in patients with AF and HF-rEF but the numbers were too small to draw any definitive conclusion.\(^{(15,50,60)}\)

**Nondihydropyridine calcium channel antagonists**

The nondihydropyridine calcium channel antagonists verapamil and diltiazem could be used in patients with HF-pEF, but should be avoided in those with a HF-rEF due to negative inotropic effects.\(^{(15)}\)

There might be several benefits by using the nondihydropyridine calcium channel antagonists in the patient with AF and HF-pEF. In several studies by Ulimoen et al. this is highlighted in a group of 60 patients with permanent AF and relatively short follow-up.\(^{(39,52,61)}\) The RATe control in Atrial Fibrillation (RATAF) study was a prospective, randomized, investigator-blinded, crossover study design to compare four drug regimens: metoprolol slow-release tablets 100 mg/day, diltiazem sustained-release capsules 360 mg/day, verapamil modified-release tablets 240 mg/day, and carvedilol immediate-release tablets 25 mg/day. Each drug was given for a period of three weeks in every patient. It appeared that diltiazem was the most effective drug regimen for reducing the heart rate in patients with permanent AF.\(^{(52)}\) Arrhythmia-related symptoms were reduced by treatment with the calcium channel blockers diltiazem and verapamil, but not by the beta blockers.\(^{(52)}\) Also several other parameters were assessed. Diltiazem or verapamil preserved exercise capacity and reduced levels of NT-proBNP, whereas treatment with metoprolol or carvedilol reduced the exercise capacity and increased levels of NT-proBNP.\(^{(39)}\) Furthermore reduction of heart rate by the study drugs was associated with a significant reduction in levels of hs-trop T, which applied to all drugs.\(^{(61)}\)
Digoxin

Digoxin is one of the oldest drugs in cardiovascular medicine.\(^{(62)}\) Discovered more than 200 years ago and already in those days frequently used to relieve patients with dyspnea and palpitations.\(^{(62)}\) According to current AF and heart failure guidelines digoxin is only indicated for long-term rate control in patients with AF and HF-rEF or patients who have an inactive lifestyle (e.g. elderly).\(^{(15,63)}\) There are several reasons why the use of digoxin has declined, most importantly there is no evidence that digoxin is an effective rate control drug during exercise, but only during rest.\(^{(53,64-77)}\) The effect of digoxin seems to be most pronounced when combined with a beta-blocker. The latter combination has been observed to improve symptoms and left ventricular ejection fraction.\(^{(64,67,72,77)}\) However, with beta-blocker mono-therapy it may also possible to achieve an adequate heart rate in many patients (see table 1).\(^{(15,63)}\) This suggests that in general no recommendations can be given. Rate control should be instituted individually depending on symptoms. Digoxin is an old drug. Nevertheless, in patients with AF no large randomized trials have been performed thus far. The only randomized trial with digoxin, which only included patients with sinus rhythm, was the Digitalis Investigation group (DIG) trial which investigated the effect of digoxin as compared to placebo on mortality in patients with HF-rEF and sinus rhythm.\(^{(78)}\) Digoxin was not able to demonstrate mortality benefit but did reduce heart failure hospitalizations.\(^{(78)}\) Even more important, several post-hoc analyses of the DIG trial reported on side-effects of digoxin.\(^{(79-81)}\) Especially patients who had high serum concentrations of digoxin were at risk for mortality.\(^{(82)}\)

Data on cardiovascular outcomes from patients with AF who used digoxin are predominantly derived from post-hoc analyses from the AF Follow-up Investigation of Rhythm Management (AFFIRM) trial.\(^{(17)}\) A study reporting on predictors for mortality in the AFFIRM trial reported that digoxin was independently associated with increased mortality in patients with AF.\(^{(83)}\) More recently two additional post-hoc analyses of AFFIRM on the effect of digoxin were conducted and reported conflicting results of its effect on prognosis.\(^{(84,85)}\) In this thesis (chapter 3) we performed an analyses which showed that in patients with permanent AF digoxin use was not associated with an impaired outcome. Also we did not observe an increase in arrhythmic events in those using digoxin.

Why did we not observe a detrimental effect of digoxin in patients with permanent AF in RACE II? First, in RACE II the heart rate target was not achieved at all costs.\(^{(43)}\) We did not encourage pursuing high serum concentrations of digoxin as compared to AFFIRM, also not in the strict rate control group.\(^{(16,17,43,84)}\) In AFFIRM higher serum concentrations may have led to digoxin toxicity with the induction of brady- or tachyarrhythmias which may have contributed to the observed increased mortality.\(^{(86,87)}\) Due to the narrow therapeutic index, which warrants cautious institution to avoid adverse effects including life threatening brady- and tachyarrhythmias.\(^{(15,16,18,81,82,88)}\) Second, digoxin might be the drug of choice in patients who were hospitalized or had worsening heart failure. This would imply that other factors may have influenced outcome instead of the use of digoxin.\(^{(89)}\) In agreement with the latter is the observation that in the Permanent AF Outcome Study Using Dronedarone on Top of Standard Therapy (PALLAS) it was suggested that in patients with a severely impaired left ventricular systolic function digoxin was more pro-aritmic (e.g. induction of atrioventricular block with an accelerated junctional rhythm).\(^{(45)}\) Which was later confirmed in a subanalysis showing that patients who were on dronedarone and digoxin had significant higher risk on cardiovascular death.\(^{(46)}\) There is one other limitation for the use of digoxin: there are interactions with many other medications, e.g. amiodarone and verapamil, which can lead brady- or tachyarrhythmias.\(^{(90,91)}\) This is pivotal to remember as the use of digoxin has an indication in patients with an inactive lifestyle, the elderly who often use concomitant medications.\(^{(15,50,90)}\) Other important factors that can increase the risk for digoxin toxicity are older age, female sex, low lean body mass, and renal insufficiency.\(^{(90)}\) Recently, more data came available that digoxin may be associated with impaired outcome in patients with AF.\(^{(92,93)}\) In our view, the use of digoxin is predominantly indicated for patients with HF-rEF for long term rate control, and those who have an inactive lifestyle, as recommended by guidelines. Most importantly, however, institution should always be performed carefully to avoid toxicity.\(^{(15,45,50,87,90,91)}\)

Other rate control drugs

Amiodarone is also an effective rate control drug, and it could be instituted for long-term treatment, but it may cause severe extracardiac events including thyroid dysfunction and bradycardias.\(^{(15)}\) The role for amiodaron in patients
with heart failure is primarily reserved for those unable to tolerate a beta-blocker or digoxin.\(^{(50)}\)

**Non-pharmacological treatment for patients with atrial fibrillation and heart failure**

**Cardiac resynchronization therapy**

CRT is an important non-pharmacological therapeutic strategy in patients with heart failure.\(^{(50,94)}\) Although AF is common in patients with heart failure large CRT trials have always excluded patients with prevalent AF, with the exception of one.\(^{(95-98)}\) Data from patients with AF is therefore mainly derived from retrospective analyses. These studies show that outcome is worse for AF patients.\(^{(99-104)}\) The reason for that is that AF limits biventricular pacing due to its fast intrinsic ventricular response. Retrospective analyses have shown that outcome is more beneficial when biventricular pacing is more than 98%.\(^{(103)}\) Several options are available to increase this percentage of biventricular pacing in patients with AF. The most effective one and also recommended by the guidelines is atrioventricular node ablation.\(^{(101,102,104-107)}\) It remains uncertain whether this procedure, which has a substantial chance of complications and which makes patients completely pacemaker dependent, is absolutely necessary. No randomized clinical trials confirming the beneficial effect of atrioventricular junctional ablation versus optimal strict rate control have been performed.\(^{(101,102,104-109)}\) In chapter 7 we showed the results of CRT in consecutive patients with HF-rEF and AF compared to those with sinus rhythm treated in the University Medical Center Groningen in the Netherlands. Our data suggest that response can equally be obtained in those with AF as compared to those with sinus rhythm when rate control is carefully instituted and carefully monitored including an exercise test to document biventricular pacing during exercise.

Our data also show that new-onset AF itself was not associated with lower response or long-term heart failure hospitalizations or cardiovascular mortality, in contrast to earlier reports.\(^{(99,110)}\) Interestingly, the development of new-onset AF occurring shortly after CRT implantation was, however, associated with unfavorable outcome, as has been demonstrated before.\(^{(99,110)}\) Therefore, it seems reasonable to monitor AF carefully after implantation to ensure adequate therapy for AF and biventricular pacing.\(^{(15,111)}\) Home monitoring may become a way to ensure early detection and appropriate treatment of AF. Currently, this is investigated in the Clinical effect of heart failure management via home monitoring with a focus on AF (EffecT, NCT00811382).

**What to ablate?**

Atrial ablation including pulmonary vein isolation is a rhythm control option in patients with AF with HF-pEF or HF-rEF.\(^{(112,113)}\) Early rhythm control could limit structural remodeling and therefore also progression of AF into a more permanent state, also in patients with heart failure.\(^{(19,114)}\) A recent meta-analysis underlines this view. When pulmonary vein isolation is performed early after start of AF and heart failure it may improve left ventricular systolic function.\(^{(115)}\) Furthermore, this may potentially reduce AF related complications.\(^{(19,114)}\) The percutaneous technique includes pulmonary vein isolation. Most likely, due to extensive disease (this depends upon the type of AF and also degree of left atrial disease) additional ablation lines, such as linear ablation and/or focal ablations of areas with evidence of scar, fractionation, or rotor-perpetuation, may be necessary.\(^{(116-119)}\) Pulmonary vein isolation has been shown effective especially in patients with paroxysmal AF. This procedure, however, is less successful in patients with persistent AF and in AF patients with heart failure concomitantly.\(^{(120-122,122-126)}\)

![Figure 2. Left ventricular ejection fraction during follow-up in PABA-CHF, reprinted with permission from (120).](image-url)
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Failure (PABA-CHF) trial 41 AF and HF patients underwent pulmonary-vein isolation, and 40 underwent atroventricular-node ablation with biventricular pacing. These were followed for 6 months. The composite primary end point favored the group that underwent pulmonary-vein isolation, with an improved questionnaire score at 6 months, a longer 6-minute-walk distance and a higher ejection fraction. This indicates that pulmonary-vein isolation (non-pharmacological rhythm control) was superior to atroventricular-node ablation with biventricular pacing (non-pharmacological rate control) in patients with heart failure who had drug-refractory AF (figure 2). (120) However, as indicated before, success of pulmonary vein isolation is lower in patients with heart failure.

As ablation of the atroventricular node is a definitive procedure making patients pacemaker dependent the rest of their life, and complications can occur, it may be therefore be reasonable, although definitive success is low, to perform pulmonary vein isolation first in these patients depending on parameters associated with success, e.g. left atrial size. (120,123,124,126)

Prognosis, cardiovascular outcomes, AF progression and biomarkers

Whether or not AF actually influences prognosis in patients with heart failure remains a matter of debate. (4,11,100,127-135) This applies for both patients with HF-rEF and HF-pEF. (130,136,137) Recent data suggest that one of the factors associated with an impaired prognosis of AF is progression from selfterminating AF to more permanent nonselfterminating forms of AF. (138-145) Progression of AF to a more permanent state occurs in 4-15% of the patients during the first year. Parameters associated with AF progression include clinical parameters like age, congestive heart failure, history of hypertension or diabetes mellitus, (139,146) next to modifiable risk factors like sleep apnea syndrome and obesity. Adjustment of these factors may prevent AF progression. (147-150) Data on risk factors for cardiovascular morbidity and mortality in patients who recently progressed to permanent AF is sparse. In chapter 4 we showed that duration of AF prior to study enrollment is one of the key determinants for prognosis in patients who who recently progressed to non-selfterminating permanent AF. Hypothetically, the total history duration of AF (figure 3) seems more indicative for prognosis than classification of AF itself. This may relate to prolonged time in AF suggesting more progression of the associated diseases. (151,152) Other important determinants for prognosis in the RACE II study were biomarkers for heart failure and cardiac damage, namely NT-proBNP and hs-Trop T. (153-159)

In RACE II we observed two important things associated with NT-proBNP. First, in this population with permanent AF without severe heart failure NT-proBNP was elevated (figure 4). Second, in agreement with other studies, it was associated with cardiovascular outcome. The increased plasmalevel of NT-proBNP may be related to concealed heart failure, being
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To assess the actual risk, potentially, blood biomarkers assessing different cardiac and vascular remodeling processes involved in AF (Figure 6) may contribute to assess the actual risk in the individual patients.

In this respect, also biomarkers associated with a prothrombotic state (e.g. d-dimer) may help to assess the risk on and etiology of stroke in the individual patient as was recently demonstrated. Whether or not these biomarkers will be able to assess prognosis or are helpful in risk classification likewise to NT-proBNP and hs-trop T has yet to be investigated.

Future perspectives

As part of the conclusions of this thesis are based on subanalyses and non-randomized comparisons this should serve hypothesis generating for future trials. The discussion whether sinus rhythm could improve outcome as compared with rate control is once more being challenged as atrial ablation is becoming more effective, also in patients with more severe underlying disease. Whether or not pulmonary vein isolation will be superior to anti-arrhythmic drug therapy or adequate background rate control therapy is now being investigated in several large randomized trials; Catheter ablation versus anti-arrhythmic drugs therapy for AF trial (CABANA, Clinical Trials.gov Identifier NCT00911508), in the Early treatment of AF for stroke prevention trial (EAST, ClinicalTrials.gov Identifier NCT01288352), and also in heart failure patients in the Catheter Ablation With or Without Anti-arrhythmic Drug Control of Maintaining Sinus Rhythm Versus Rate Control With Medical Therapy and/or Atrio-ventricular Junction Ablation and Pacemaker Treatment for AF (RAFT-AF, Clinical Trials.gov Identifier NCT01420393), and Catheter Ablation vs. Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and AF (CASTLE-AF, Clinical Trials.gov Identifier NCT00643188). Also early identification of patients with AF and heart failure could lead to an improved outcome as early identification and therapy of high-risk patients may improve outcome. Better risk identification may in addition help to develop novel therapies for specific patients. We could, for example, start early and aggressively with ‘upstream’ therapy in high-risk patients to reverse the remodeling process at an early stage, in combination with lifestyle changes (exercise and nutrients). Results of the upstream therapy...
in patients with early AF: The relevance of the Routine versus Aggressive upstream rhythm Control for prevention of Early AF in heart failure (RACE 3) study are therefore eagerly awaited.(29,181)

Present heart failure risk scores can serve as a benchmark to study novel biomarkers and risk factors for heart failure in AF patients.(182-184) The addition of novel covariates may improve risk prediction and reclassification for heart failure in AF patients.(5,185,186) Finally, new drugs and the direct oral anticoagulants have to be tested in well-powered randomized heart failure trials of which some started recruiting patients; A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction or Stroke in Participants With Heart Failure and Coronary Artery Disease Following Hospitalization for Heart Failure (COMMANDER HF, Clinical Trials.gov Identifier NCT01877915 ). In conclusion, the treatment of AF in patients with either HF-pEF or HF-rEF is still far from perfect, and early identification, most likely more aggressive early treatment of AF, and development of new drugs for this specific patient group could eventually lead to further improvement of cardiovascular outcomes.

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