Clinical and therapeutic implications of remodeling in atrial fibrillation

Smit, Marcelle Diane

CLINICAL AND THERAPEUTIC IMPLICATIONS OF RENAL MODELING IN ATRIAL FIBRILLATION

Marcelle D. Smit

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STELLINGEN

behorende bij het proefschrift *Clinical and therapeutic implications of remodeling in atrial fibrillation* door Marcelle D. Smit

1 Ontsteking lijkt een belangrijke rol te spelen bij het vroeg recidiveren van boezemfibrilleren na een rhythm control behandeling, terwijl progressie van persisterend naar permanent boezemfibrilleren vooral geassocieerd lijkt te zijn met fibrose. *(Dit proefschrift)*

2 Een milde behandeling van boezemfibrilleren die de hartslag terugbrengt naar onder de 110 slagen per minuut leidt niet tot meer vergroting van boezems en kamers dan een intensieve behandeling die de hartslag terugbrengt naar onder de 80 slagen per minuut. *(Dit proefschrift)*

3 Bij vrouwen zit er meer rek in dan bij mannen. *(Dit proefschrift)*

4 Boezemfibrilleren hoeft de effectiviteit van cardiale resynchronizatietherapie niet nadelig te beïnvloeden. *(Dit proefschrift)*

5 Patiënten met boezemfibrilleren die daarna hartfalen ontwikkelen zijn beter af dan patiënten met hartfalen die daarna boezemfibrilleren ontwikkelen. *(Dit proefschrift)*

6 Upstream therapy heeft een goede kans van slagen ten aanzien van de verbetering van rhythm control bij patiënten met een korte voorgeschiedenis van boezemfibrilleren omdat bij hen de remodelingsprocessen minder vergevorderd zijn. *(Dit proefschrift)*

7 Het goed in kaart brengen van de mate van atriale remodeling zal de behandeling van boezemfibrilleren kunnen helpen optimaliseren.

8 Promoveren lijkt veel op een huis verbouwen, waarbij doorzettingsvermogen, creativiteit en het op het juiste moment durven inschakelen van de juiste expertise belangrijke ingrediënten zijn voor het bereiken van een mooi resultaat.

9 If you do something wrong, don't make it perfect, because then it becomes perfectly wrong. *(Michael Braungart)*

10 Vliegen valt niet mee. (...) Als je bent geland, moet je altijd even wachten tot je ziel je weer heeft ingehaald. *(Tracey Emin)*

11 A good wanderer leaves no footprints. *(Lao Tse)*

12 Happiness is only real when shared. *(Christopher McCandless)*

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CONTENTS

INTRODUCTION 1

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Currently more than 6 million people in Europe are affected and this number is expected to increase twofold during the next 30-50 years partly due to the ageing population.[1-3] AF is not a benign disease as it is responsible for an increased risk on death, stroke, and heart failure, reduced exercise capacity and left ventricular dysfunction, and an impaired quality of life.[4-6] An important associated disease of AF is heart failure. AF and heart failure often co-exist in a reciprocal relationship, the incidence of AF increasing with the severity of heart failure.[7] Both in heart failure with reduced ejection fraction and in heart failure with preserved ejection fraction, AF is also associated with increased morbidity and mortality.[8-11] As a result of improved management of patients with AF, a trend towards reduction of AF-related events is observed,[12,13] though morbidity and mortality still remain substantial. It is therefore important to develop safe treatment strategies for AF in order to improve outcome and to promote healthy ageing.

To facilitate the development of treatment strategies for AF, the pathophysiological processes leading to AF and to AF-related events should be elucidated. AF has a multifactorial etiology, the pathophysiology of AF being complex and incompletely understood. Over the past years the role of structural remodeling in the initiation and perpetuation of AF has increasingly become apparent. Structural remodeling can be caused by well-known risk factors of AF development such as age, hypertension, heart failure, valve disease, and diabetes,[14-16] less well-known risk factors such as endurance training, obesity, sleep apnea syndrome, and chronic obstructive pulmonary disease,[1,17] and other factors such as altered metabolism, autonomic changes, and genetic and environmental influences. These factors induce atrial structural changes through various pathways including the renin-angiotensin-aldosterone system and inflammation, leading to enlarged atria, hypertrophy, fibrosis, dedifferentiation, apoptosis, and myolysis.[18] Structural remodeling eventually creates a substrate for AF due to electrical dissociation between muscle bundles and local conduction heterogeneities facilitating the initiation and perpetuation of AF.[19] Of interest, the first manifestation of AF usually occurs after years of atrial remodeling.[20] In remodeled atria, triggers such as premature atrial complexes can initiate AF. Once AF develops, atrial electrophysiology is modified ("electrical remodeling") and the structural remodeling process further deteriorates, constituting a vicious cycle: "AF begets AF".[21] Hence, atrial structural remodeling in patients with AF is caused by both the associated diseases and by AF itself.

Structural remodeling may be reversible during early phases of AF, but permanent damage is induced during later stages of AF and in severe associated diseases. This is reflected by increasing electrical dissociation during AF when AF duration increases and when associated diseases become more severe.[22,23] Therefore, in the majority of cases the natural history of AF is characterized by a gradual worsening in time due to progressive adverse structural remodeling, making it challenging to restore and maintain sinus rhythm (Figure 1)[24] and perhaps contributing to the occurrence of AF-related events. One AF patient

category of interest regarding clinical and therapeutic implications of remodeling consists of patients with a short history of AF. Short-lasting AF patients have not been studied before. In patients with short-lasting AF, remodeling processes are assumingly less advanced and the induced damage may not be permanent.[20] In such patients, successful elimination of AF may freeze the remodeling process, providing opportunities to prevent AF progression and, hypothetically, to lower the risk on AF-related events.

Assessment of the degree of structural remodeling in patients with AF could be useful for identifying patients who will respond to rhythm control or other therapies aimed at halting AF progression and improving outcome, ultimately to tailor AF therapy in the individual patient.[25] As of today, it is difficult to directly measure the degree of structural remodeling in patients presenting with AF. Instead, physicians and researchers have to contend with surrogate markers that reflect the substrate complexity. Such markers consist of clinical parameters including age, associated disease, and duration of AF,[17,20,25] echocardiographic parameters such as atrial size,[26] and circulating biomarkers involved in structural remodeling processes.[27-29] Some of these markers have been shown to be of prognostic value regarding AF progression and clinical outcome. Examples of clinical markers associated with AF recurrence and progression include age, hypertension, heart failure, diabetes, chronic obstructive pulmonary disease, renal function, and previous AF burden,[30-34] which are also markers of impaired outcome in AF.[1] Echocardiographic parameters associated with AF recurrence and progression and with prognosis include left atrial size, atrial strain rate, and ventricular systolic and diastolic function.[32,35-38] Examples of biomarkers associated with AF progression and outcome include

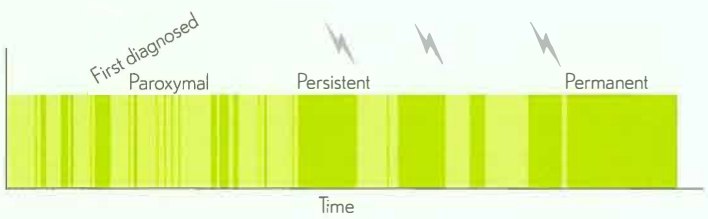

Figure 1. Natural time course of AF. Shown is a typical chaotic pattern of time in AF (dark green) and time in sinus rhythm (light green) over time. AF progresses from undiagnosed to first diagnosed, paroxysmal, persistent, to permanent. Flashes indicate cardioversions as examples for therapeutic interventions that influence the "natural" time course of the arrhythmia. Adapted with permission from Kirchhof et al.[24]

inflammatory biomarkers, e.g. high-sensitivity C-reactive protein,[32] fibrotic biomarkers, e.g. transforming growth factor-β1, matrix metalloproteinase-2, and tissue inhibitor of matrix metalloproteinase-1,[27,39,40] and markers of atrial endocrine function, e.g. N-terminal pro-B-type natriuretic peptide.[41,42] As of today, however, an atrium-specific biomarker has not yet been identified.[43] This emphasizes the limitations of markers of atrial structural remodeling, as they may vary in discriminative, diagnostic and prognostic value amongst different AF patient categories with various degrees of structural remodeling. For instance, remodeling may be less extensive in patients with a short history of AF and mild associated disease than in patients with a long history of AF and severe associated disease such as heart failure,[18,20,22,23] which in itself is associated with increased markers of remodeling.[18] It is therefore uncertain whether these markers measure atrial remodeling, ventricular remodeling, or both. Studies using surrogate markers of atrial remodeling should therefore be interpreted with this limitation kept in mind.

Structural remodeling may be halted by upstream targeting of the substrate to prevent AF progression and impaired outcome. These upstream therapies may support conventional rhythm control therapy, beside having a more favorable side-effect profile.[44] Upstream therapies target components of the remodeling process including fibrosis, inflammation, and oxidative stress, and include renin-angiotensin-aldosterone-system inhibitors, statins, fish oils, glucocorticoids, and possibly even moderate exercise.[44,45] If started early in the remodeling process, e.g. in patients with a short history of AF, upstream therapy may prevent or postpone the need for ion-channel antiarrhythmic drugs and/ or ablation, and rhythm control may be more effective while side-effects and adverse events are limited.[20,46] The effectiveness of upstream therapy, however, may vary depending on the degree of structural remodeling.[46,47] Yet again this emphasizes the need to assess the extent of remodeling in individual patients in order to tailor AF therapy to prevent AF progression and adverse outcome.

Aim of this thesis

The aim of this thesis is to investigate the clinical and therapeutic implications of remodeling in AF. We study a variety of patient categories in order of increasing stage of AF severity. In **chapter 2** we start off with patients with a short history of persistent AF in whom sinus rhythm is still pursued, and assess the mechanisms involved in early AF recurrence. In **chapter 3** we discuss various remodeling markers as potential predictors of outcome of rhythm control. In **chapter 4** we move on to patients in whom AF has become permanent and investigate the influence of stringency of rate control on echocardiographic remodeling and assess other factors possibly associated with adverse and reverse remodeling. The following two chapters embrace patients with heart failure, an important associated disease in AF. **Chapter 5** involves patients with stable severe heart failure receiving cardiac resynchronization therapy, in whom we investigate the prognostic value of circulating biomarkers and AF on

response to cardiac resynchronization therapy and on mortality. In **chapter 6** we assess whether the time course in which AF and heart failure develop sheds light on the prognosis of AF patients hospitalized for heart failure. The last two chapters focus on AF treatment strategies targeting structural remodeling. **Chapter** 7 provides an overview of upstream therapy in various AF patient categories. In **chapter** 8 we first discuss why upstream therapy is not effective in all AF patients. We then provide the rationale and design of the Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) study, performed in patients with a short history of AF in whom we expect that upstream therapy will be effective in halting AF progression.

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2 ROLE OF INFLAMMATION IN EARLY ATRIAL FIBRILLATION RECURRENCE

Marcelle D Smit, Alexander H Maass, Anne Margreet De Jong, Anneke C Muller Kobold, Dirk J Van Veldhuisen, Isabelle C Van Gelder.

Submitted

ABSTRACT

Introduction

Outcome of rhythm control in atrial fibrillation (AF) is still poor due to various mechanisms involved in the initiation and perpetuation of AF. Differences in timing of AF recurrence may depend on different types of mechanisms. The aim of this study was to assess the mechanisms involved in early AF recurrence in patients with short-lasting AF.

Methods & results

Patients with short-lasting persistent AF undergoing rhythm control (n=100) were included. Markers of mechanisms involved in the initiation and perpetuation of AF were assessed, including clinical factors, echocardiographic parameters, and biomarkers. Primary endpoint was early AF recurrence (recurrence <1 month). Secondary endpoint was progression to permanent AF. Mean age was 65±9 years, 74 patients (74%) were male, and median total AF history was short: 4.2 months. Early AF recurrences occurred in 30 patients (30%) after a median of 6 (inter-quartile range 2-14) days. Baseline $\log_2$ interleukin-6 (adjusted hazard ratio [HR] 1.3, 95% confidence interval [CI] 1.0-1.7, p=0.02) and present or previous smoking (adjusted HR 3.6, 95% CI 1.2-10.9, p=0.03) were independently associated with early AF recurrence, suggesting that inflammation played an important role in early recurrences. AF became permanent in 29 patients (29%). Baseline transforming growth factor-β1, left ventricular ejection fraction, and early AF recurrence were independently associated with progression to permanent AF.

Conclusion

In patients with short-lasting AF, early AF recurrence seemed to be associated with inflammation as represented by interleukin-6. Treatment aimed against inflammation may therefore prevent early AF recurrences, which can improve rhythm control outcome.

INTRODUCTION

Outcome of rhythm control in patients with persistent atrial fibrillation (AF) is still poor, despite the attempts that have been made to improve rhythm control therapy.[1-4] We previously failed to show that early cardioversions in case of early recurrences increased maintenance of sinus rhythm.[5] In addition, short-term peri-cardioversion amiodarone therapy could not reduce AF recurrences.[6] AF, however, is a complex condition with multiple interacting mechanisms involved in the initiation and perpetuation of the arrhythmia, including acute triggers, changes in electrical properties, and structural remodeling.[7,8] The mechanisms leading to the initiation and perpetuation of AF may contribute differently to the onset and persistence of AF in different patients, which could imply that there are distinct types of AF requiring specific types of treatment.[9] Furthermore, these mechanisms may vary according to the timing of AF recurrence and progression. Most AF recurrences occur within one month after cardioversion (early AF recurrences).[10-12] To our knowledge, mechanisms involved in early AF recurrences have not been studied before in persistent AF. Furthermore, most studies investigating rhythm control in persistent AF have included patients in whom the extent of remodeling was severe due to a long history of AF or underlying disease. In patients with a short history of AF, i.e. short-lasting AF, remodeling processes are assumed to be less advanced, providing opportunities for rhythm control to be more effective.[13] This patient category has not been studied before. The aim of this study was therefore to investigate the mechanisms involved in early AF recurrences in a patient population with short-lasting AF.

METHODS

Study population and study protocol

This was a prospectively designed observational study performed in the University Medical Center Groningen. The study was approved by the institutional review board of the University Medical Center Groningen and patients were included after obtaining written informed consent. Recruitment started in January 2008 and ended in July 2010. Patients were included if they had short-lasting persistent AF, defined as a total AF history of less than 2 years, a total persistent AF history of less than 6 months, and ≤ 1 previous electrical cardioversion.

At enrolment, a detailed medical history was obtained in all patients, transthoracic echocardiography was performed, and blood samples for biomarker analyses were obtained. Patients were treated according to our standardized rhythm control strategy which involved causal treatment of the underlying disease, anticoagulation as indicated, adequate rate control with negative dromotropic drugs, and rhythm control in accordance with the guidelines.[1,2,4,14,15] Initial rhythm control consisted of electrical cardioversion, chemical cardioversion with amiodarone, or pulmonary vein ablation. Pre-treatment with ion-channel antiarrhythmic drugs was started only in patients in whom rhythm

control was expected to be less successful, i.e. due to underlying disease.[14,15] Time to AF recurrence was carefully monitored by frequent outpatient visits and 24-hour Holter monitoring (one, three six, nine and twelve months after start of rhythm control therapy). In case of recurrence of AF after initial rhythm control therapy, ion-channel antiarrhythmic drugs were instituted as soon as possible after documentation of the recurrence, in combination with electrical cardioversion if required.[1,2,4,14,15] Amiodarone loading was started four weeks before the next planned electrical cardioversion, sotalol was started on the day of the next planned cardioversion. AF was accepted in case of failure of at least one ion-channel antiarrhythmic drug and/ or if patient declined to pursue normal sinus rhythm in the absence of severe symptoms of AF.[1,2,4,14,15]

Definitions of AF recurrence

The primary endpoint consisted of early AF recurrence, defined as any (a)symptomatic recurrence of AF within the first month after cardioversion lasting ≥ 30 seconds.[10,11,16] Secondary endpoint was progression to permanent AF within one year. Patients were defined to have permanent AF when rhythm control interventions were no longer pursued.[14,15] Shock failure was defined as no single sinus beat seen after cardioversion, immediate reinitiation of AF (IRAF) was defined as AF recurrence within 2 minutes after electrical cardioversion.[11,17]

Echocardiography

Echocardiographic evaluation was conducted at baseline and included atrial dimensions and volumes, atrial ejection fractions, septal and posterior wall thicknesses, ventricular dimensions, and left ventricular ejection fraction. Left atrial volume was measured using the biplane Simpson's method and right atrial volume was measured using the single plane area-length method.[18] Left and right atrial volumes were additionally indexed to body surface area. Left and right atrial ejection fractions were calculated using end-systolic and end-diastolic left and right atrial volumes, respectively. Echocardiograms were performed in accordance with standard recommendations.

Biomarker analyses

Pre-specified biomarkers analyzed for this study were biomarkers of hemodynamic stress, i.e. atrial natriuretic peptide (ANP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and apelin; and biomarkers of fibrosis and inflammation, i.e. growth differentiation factor (GDF)-15, matrix metalloproteinase (MMP)-1, MMP-2, MMP-9, tissue inhibitor of metalloproteinase (TIMP)-1, TIMP-2, transforming growth factor (TGF)-β1, and interleukin

(IL)-6. ANP and NT-proBNP are natriuretic hormones released from ventricular and atrial cells in response to volume expansion and increased wall stress.[8,19] Apelin is a component of the apelin-angiotensin receptor-like 1 pathway that plays an important counter-regulatory role in the effects of angiotensin.[20] GDF-15 is a member of the TGF-β cytokine family and is secreted during periods of ischemia and reperfusion and is also an anti-hypertrophic regulating factor in the heart.[21] MMPs are associated with degradation of collagen, while TIMPs inhibit the activity of MMPs.[8,22] TGF-β1 is an inflammation-associated cytokine that is central to signaling cascades stimulating cardiac fibrosis, and may be a key mediator of fibrosis.[8] IL-6 is an inflammatory cytokine that is also a potent regulator of extracellular protein metabolism through MMPs and collagen.[8,22,23] Venous blood samples for biomarker analyses were obtained at enrolment. Ethylenediaminetetraacetic (EDTA)-plasma, lithium-heparin-plasma, and serum samples were stored at -80°C until further analysis. Biomarker analyses were conducted using commercially available kits. All biomarkers except apelin were analyzed using enzyme-linked immunosorbent assays according to the manufacturer's instructions (GE Healthcare UK Ltd, Buckinghamshire, UK, for MMP-1, MMP-2, MMP-9, TIMP-1, TIMP-2; R&D systems, Minneapolis, MN, USA, for ANP, NT-proBNP, GDF-15, TGF-β1, and IL-6). Apelin-12 was analyzed using enzyme immunoassay according to the manufacturer's instructions (Phoenix Pharmaceuticals, Inc., Burlingame, CA, USA).

Statistical analysis | METHODS

Baseline descriptive statistics are presented as mean ± standard deviation or median (inter-quartile range) for continuous variables and numbers with percentages for categorical variables, as required. We evaluated differences between groups using Chi-square test and Fisher's exact test for categorical data, and Student's *t* test and Mann Whitney-U test for continuous data, dependent on whether data were normally distributed. Cumulative event proportions were calculated using Kaplan-Meier analyses. Cox proportional hazards regression analyses were conducted to evaluate predictors of early AF recurrence and permanent AF. Univariate Cox proportional hazards regression analysis was performed on all baseline variables shown in Tables 1-3. For permanent AF, early AF recurrence was added as baseline variable. Stepwise multivariable hazards regression analysis was conducted using all baseline variables with $p \leq 0.1$ in univariate analysis. The final multivariate model included all variables with $p < 0.05$. Analyses were performed with STATA 11.0 for Windows. In all statistical analyses $p < 0.05$ was considered statistically significant.

Table 1. Baseline characteristics

	Study population (n=100)	Early AF recurrence (n=30)	No early AF recurrence (n=70)
Age - mean±SD - years	65±9	63±8	65±10
Male gender - no. (%)	74 (74.0)	22 (73.3)	52 (74.3)
AF characteristics:			
Total AF history - median (IQR) - months	4.2 (1.9-9.0)	5.6 (3.0-11.1)*	3.9 (1.5-7.5)
Current AF duration - median (IQR) - months	3.0 (1.3-4.7)	3.2 (1.8-5.4)	2.9 (1.1-4.5)
Previous electrical cardioversion - no. (%)	26 (26.0)	12 (40.0)*	14 (20.0)
Previous chemical cardioversion - no. (%)	4 (4.0)	-	4 (5.7)
$CHADS_2$ score† - mean±SD	1.5±1.0	1.4±0.9	1.6±1.0
Hypertension - no. (%)	67 (67.0)	19 (63.3)	48 (68.6)
Previous admission for heart failure - no. (%)	20 (20.0)	8 (27.7)	12 (17.1)
Coronary artery disease: - no. (%)	18 (18.0)	6 (20.0)	12 (17.1)
Previous myocardial infarction	8 (8.0)	3 (10.0)	5 (7.1)
History of valve dysfunction - no. (%)	22 (22.0)	6 (20.0)	16 (22.9)
History of valve surgery - no. (%)	4 (4.0)	1 (3.3)	3 (4.3)
Other medical history:			
Diabetes mellitus: - no. (%)			
Type I	1 (1.0)	-	1 (1.4)
Type II	13 (13.0)	2 (6.7)	11 (15.7)
Hypercholesterolemia - no. (%)	30 (30.0)	8 (26.7)	22 (31.4)
Smoking: - no. (%)			
Previous smoking	49 (49.0)	19 (63.3)*	30 (42.9)
Present smoking	13 (13.0)	6 (20.0)*	7 (10.0)
Chronic obstructive pulmonary disease - no. (%)	10 (10.0)	1 (3.3)	9 (12.9)
History of transient ischemic attack/ stroke - no. (%)	7 (7.0)	1 (3.3)	6 (8.6)
History of thyroid disease: - no. (%)			
Hypothyroidism	1 (1.0)	-	1 (1.4)
Hyperthyroidism	5 (5.0)	-	5 (7.1)
Sleep apnea - no. (%)	1 (1.0)	-	1 (1.4)
AF EHRA class: - no. (%)			
I	18 (18.0)	7 (23.3)	11 (15.7)
II	49 (49.0)	15 (50.0)	34 (48.6)
III	30 (30.0)	7 (23.3)	23 (32.9)
IV	3 (3.0)	1 (3.3)	2 (2.9)
Physical examination:			
Body mass index - mean±SD - kg/m^2	28±4	28±4	27±5
Systolic blood pressure - mean±SD - mmHg	130±16	130±17	130±16
Diastolic blood pressure - mean±SD - mmHg	81±12	81±10	80±13
Electrocardiogram:			
Heart rate - mean±SD - bpm	101±28	93±20*	104±30
QRS duration - mean±SD - ms	97±15	96±10	98±17
QTc duration - mean±SD - ms	440±44	442±37	439±47
Medication at cardioversion: - no. (%)			
Beta-blocker	89 (89.0)	27 (90.0)	62 (88.6)
ACE-inhibitor/ angiotensin receptor blocker	74 (74.0)	17 (56.7)*	57 (81.4)
Aldosterone receptor antagonist	15 (15.0)	3 (10.0)	12 (17.1)

Baseline characteristics and rhythm control therapy | RESULTS

One hundred patients were included. Mean age was 65±9 years, 74 patients (74%) were male, and median total AF history was short: 4.2 months (inter-quartile range 1.9-9.0 months) (Table 1). Sixty-seven patients (67%) had their first episode of persistent AF. Baseline laboratory values are shown in Table 2. Mean left atrial size was 45±6 mm, mean left atrial volume indexed to body surface area was 45±16 mL/m^2, and mean left ventricular ejection fraction was 48±13% (Table 3).

Eighty-six patients (86%) underwent electrical cardioversion, which was successful in 76 patients (88%) and unsuccessful in 10 patients (12%) due to shock failure (n=4, 5%) and IRAF (n=6, 7%). Four patients (4%) underwent chemical conversion, 3 patients (3%) pulmonary vein ablation, and in 7 patients (7%) spontaneous conversion to sinus rhythm under antiarrhythmic drugs occurred.

AF recurrence during follow-up | RESULTS

Within one year follow-up, AF recurred in 59 patients (59%), being an early recurrence of AF in 30 patients (30%) (Figure 1). Twelve of these 30 patients (40%) had a history of a previous electrical cardioversion (Table 1). Most early AF recurrences occurred within one week after rhythm control (Figure 2); median time to early AF recurrence was 6 days (inter-quartile range 2-14 days).

Table 1. Baseline characteristics (continued)

	Study population (n=100)	Early AF recurrence (n=30)	No early AF recurrence (n=70)
Diuretic	43 (43.0)	11 (36.7)	32 (45.7)
Verapamil/ diltiazem	12 (12.0)	4 (13.3)	8 (11.4)
Dihydropyridine calcium channel blocker	9 (9.0)	1 (3.3)	8 (11.4)
Digitalis	13 (13.0)	4 (13.3)	9 (12.9)
Amiodarone	12 (12.0)	2 (6.7)	10 (14.3)
Vitamin K antagonist	99 (99.0)	30 (100.0)	69 (98.6)
Platelet aggregation inhibitor	10 (10.0)	3 (10.0)	7 (10.0)
Statin	38 (38.0)	10 (33.3)	28 (40.0)
Nitrate	1 (1.0)	1 (3.3)	-

ACE = angiotensin converting enzyme; AF = atrial fibrillation; EHRA = European Heart Rhythm Association; IQR = inter-quartile range; LA = left atrial; LV = left ventricular; NYHA = New York Heart Association; RA = right atrial; SD = standard deviation.

* $p < 0.05$.

† The $CHADS_2$ score is a measure of the risk of stroke in patients with AF, with scores ranging from 0 to 6 and higher scores indicating a greater risk.[15] Congestive heart failure, hypertension, an age of 75 years or older, and diabetes are each assigned 1 point, and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient.

Patients underwent a median of 1 (inter-quartile range 1-2) electrical cardioversions during follow-up. Seventeen of 59 patients with a first recurrence (29%) had a second AF recurrence after a median follow-up of 7 days (inter-quartile range 1-14 days). In 55 patients electrical cardioversion was the only rhythm control therapy. Anti-arrhythmic drugs were instituted in a total of 37 patients (37%); 12 were already using amiodarone at baseline (Table 1), while an additional 25 patients received sotalol (n=16) or amiodarone (n=9) because of recurrent AF. Twenty-three patients (23%) were using ion-channel antiarrhythmic drugs at one year-follow-up. AF became permanent in 29 patients (29%), of whom 16 patients (55%) had had an early AF recurrence.

Independent predictors of early AF recurrences were baseline IL-6 and present or previous smoking (Table 4). Independent predictors of permanent AF within one year were baseline TGF-β1, left ventricular ejection fraction, and early AF recurrence (Table 4). None of the other biomarkers were predictive of early AF recurrence or progression to permanent AF.

Table 2. Baseline laboratory values

	Study population (n=100)	Early AF recurrence (n=30)	No early AF recurrence (n=70)
White blood cell count - mean±SD - 10^9/L	7.7±.9	7.7±1.5	7.6±2.0
eGFR - mean±SD - mL/min/1.73 m^2	77±19	80±18	76±19
ANP - median (IQR) - pg/100uL	144 (76-232)	125 (71-213)	151 (81-232)
NT-proBNP - median (IQR) - pg/mL	1022 (552-1933)	735 (535-1775)	1110 (650-2139)
GDF-15 - median (IQR)- pg/mL	1049 (796-1604)	1010 (767-1479)	1050 (840-1608)
Apelin - median (IQR) - pg/mL	258 (145-308)	260 (102-355)	242 (160-308)
MMP-1 - median (IQR) - ng/mL	1.7 (1.7-8.3)	1.7 (1.7-8.3)	1.7 (1.7-6.1)
MMP-2 - mean±SD - ng/mL	2198±650	2194±620	2201±672
MMP-9 - mean±SD - ng/mL	28.6±15.3	28.4±17.2	28.7±14.5
TIMP-1 - median (IQR) - ng/mL	154 (130-182)	155 (138-188)	149 (130-172)
TIMP-2 - median (IQR) - ng/mL	97 (90-108)	95 (88-100)	102 (93-114)
TGF-ß1 - mean±SD - ng/mL	24.1±10.4	25.1±13.2	23.6±8.8
IL-6 - median (IQR) - pg/mL	2.5 (1.6-4.8)	2.9 (1.8-5.8)	2.3 (1.6-3.9)

ANP = atrial natriuretic peptide; eGFR = estimated glomerular filtration rate; GDF = growth differentiation factor; IL = interleukin; IQR = inter-quartile range; MMP = matrix metalloproteinase; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SD = standard deviation; TGF = transforming growth factor; TIMP = tissue inhibitor of metalloproteinase.

* $p < 0.05$.

We investigated mechanisms involved in early AF recurrences in patients with short-lasting persistent AF. We found that early AF recurrence was associated with elevated IL-6 levels, possibly representing inflammation.

Mechanisms involved in AF recurrence and progression

DISCUSSION

We found that IL-6 independently predicted early AF recurrences in short-lasting AF patients, suggesting that inflammation may play an important role in the mechanisms triggering early AF recurrence. Inflammation has been associated with a variety of cardiovascular conditions including AF.[8,24] The exact mechanism linking inflammation with (nonoperative-related) AF is unknown, and it is unclear whether inflammation is an initiator or consequence of AF though it is not unlikely that both mechanisms are interrelated. Inflammation may cause AF, as one study demonstrated that short-term hypertension led to increased inflammatory cell infiltrates in the atria and increased inducibility of

Table 3. Baseline echocardiography

	Study population (n=100)	Early AF recurrence (n=30)	No early AF recurrence (n=70)
LA size, parasternal axis - mean±SD - mm	45±6	45±6	45±7
LA volume - mean±SD - mL	91±33	96±40	89±30
LA volume index - mean±SD - mL/m²	45±16	46±18	44±15
LA ejection fraction - mean±SD - %	19±13	17±12	20±14
RA size, length - mean±SD - mm	62±6	62±7	63±6
RA volume - mean±SD - mL	73±28	74±27	73±28
RA volume index - mean±SD - mL/m²	36±14	36±13	36±14
RA ejection fraction - mean±SD - %	18±19	15±20	19±19
Septum - mean±SD - mm	10±2	10±2	10±2
Posterior wall - mean±SD - mm	9±1	9±1	9±2
LV end-diastolic diameter - mean±SD - mm	51±7	50±7	51±7
LV end-systolic diameter - mean±SD - mm	37±9	37±8	38±10
LV ejection fraction - mean±SD - %	48±13	48±12	47±13
Valve dysfunction - no. (%)	16 (16.0)	4 (13.3)	12 (17.1)

LA = left atrial; LV = left ventricular; RA = right atrial; SD = standard deviation.

* $p < 0.05$.

AF,[25] and inflammation has been shown to be associated with incident AF.[26-29] On the other hand, a recent study demonstrated that intra- and extra-cardiac markers of inflammation were increased during AF itself, instead of being higher in patients with versus without previous AF, suggesting that AF causes inflammation.[23] Markers of inflammation including IL-6, IL-8, C-reactive protein, and tumor necrosis factor-α, have been shown to be increased in patients with AF and with AF recurrence.[23,24,24,30-32] IL-6 is a pro-inflammatory cytokine that stimulates the synthesis of acute phase proteins and is a potent regulator of extracellular protein metabolism through MMPs and collagen which could induce fibrosis.[8,22] IL-6 has been correlated with the presence and duration of AF and increased left atrial diameter.[33] The association between IL-6 and AF recurrence after cardioversion has not been robust in other studies,[34] but a study population consisting of short-lasting persistent AF patients has not been studied before.

Present or previous smoking was also independently associated with early AF recurrence. Smoking is not an established risk factor for incident AF,[35] though recently a study did observe an increased risk of AF in current and former smokers.[36] Another study found that women had a greater risk on arrhythmia recurrence after cardioversion for atrial flutter if they were current smokers.[37] Smoking could have deleterious effects regarding AF through several mechanisms including direct toxicity of nicotine and carbon monoxide, sympathetic neural stimulation, regional myocardial hypoperfusion, and perhaps induction of an inflammatory state and/ or fibrosis.

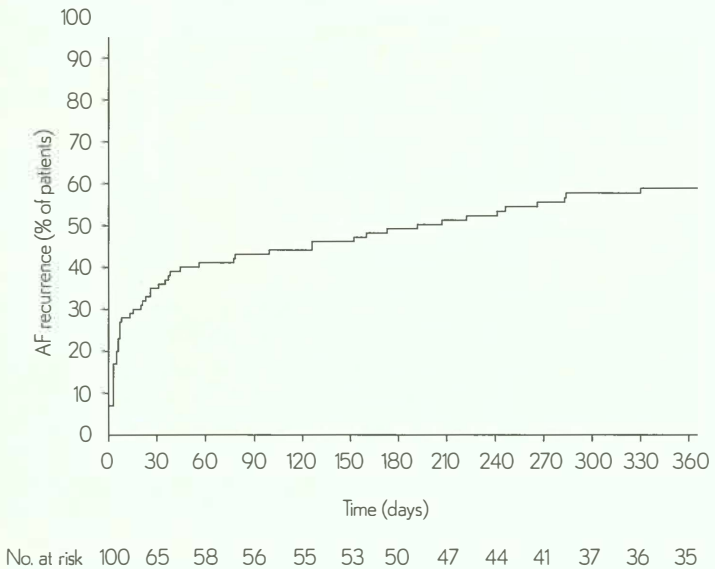

Figure 1. Time to AF recurrence

Early AF recurrence predicted progression to permanent AF, which is logical because AF recurrence is required in order for AF to be progressive, and most AF recurrences occur within one month after rhythm control.[10,11] Independent of early AF recurrence, we found that TGF-β1 was a predictor of development of permanent AF within one year. TGF-β1 is a central determinant in the signaling cascade of cardiac (atrial) fibrosis leading to structural remodeling, though it is also involved in inflammatory processes.[8] Markers of fibrosis including TGF-β1 have been associated with AF recurrence and failure of electrical cardioversion.[38-40] Fibrosis may therefore be an important contributor to progression to permanent AF. Higher left ventricular ejection fraction was also independently associated with progression to permanent AF which seems to be a counterintuitive observation, as heart failure is a well-known predictor of AF progression.[41] Progression of AF, however, is not just a passive diagnosis as it also requires decision making by patient and physician. It would seem plausible that, in case of no or mild symptoms of AF, a physician is less reluctant to accept AF when ventricular function is preserved rather than decreased. Furthermore, it is unknown whether known risk factors for AF progression also pertain for patients with short-lasting AF, whom have not been studied before.

Atrial size has been shown to be a predictor of AF recurrences and progression,[42] but this was not observed in our study. However, the degree of atrial structural remodeling may not be extensive in patients with a short history of AF, so the predictive value of atrial size regarding outcome of rhythm control may perhaps be absent in these patients.

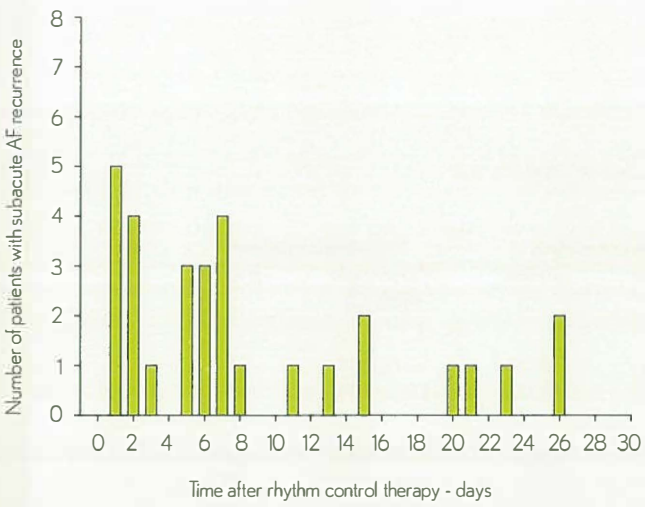

Figure 2. Daily incidence of AF recurrence during the first month after rhythm control (early AF recurrence).

Most of the recurrences occurred during the first week after rhythm control.
Day 0 = day of conversion to sinus rhythm (i.e. day of electrical cardioversion, chemical conversion, pulmonary vein ablation, or spontaneous conversion to sinus rhythm under antiarrhythmic drugs).

DISCUSSION

Rhythm control and AF recurrence in short-lasting AF

To our knowledge, this is the first study investigating rhythm control in patients with short-lasting persistent AF, in whom we may expect that remodeling processes are less widespread and in whom restoration of sinus rhythm may halt disease progression.[13] The median duration of AF history was only 4 months in the present population. Early AF recurrence, chosen as one of the primary endpoints for this study because most AF recurrences occur within one month after cardioversion,[10-12] occurred in 30% of these patients with short-lasting AF. At first glance 30% seems to be a high recurrence rate, but in other studies in which patients had a much longer AF history, early recurrences (without amiodarone treatment) were observed in 56%-68% of patients.[5,12] Early AF recurrence rates are lower with amiodarone, however, approximating 20%.[43] Despite a low early AF recurrence rate, persistent AF progressed to permanent AF in 29% of these short-lasting AF patients, which is comparable with other studies in which 25%-30% of persistent AF patients had permanent AF after one year.[5,44] However, the number of electrical cardioversions during follow-up in our study was quite low with a median of one cardioversion as compared with a median of two to three cardioversions in other studies.[3-5] This implies that relatively less of an effort was made in order to keep short-lasting AF patients in sinus rhythm during one year follow-up due to the data of the rate versus rhythm control trials, especially if symptoms were mild in case of AF recurrence.[3,4] Perhaps AF should be accepted less easily and more attempts should be done to restore and maintain sinus rhythm in patients with short-lasting AF, whom have never been studied before. Success rates may be higher, though it still remains to be established whether permanent sinus rhythm will improve prognosis in these patients.

Table 4. Predictors of early AF recurrence and of permanent AF within one year

	Univariate analysis		Multivariable analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Early AF recurrence				
Log_2 IL-6	1.3 (1.0-1.6)	0.07	1.3 (1.0-1.7)	0.02
Present or previous smoker	3.8 (1.4-9.9)	0.007	3.6 (1.2-10.9)	0.03
Permanent AF within one year				
TGF-ß1 per 5 ng/mL	1.2 (1.0-1.5)	0.09	1.3 (1.0-1.6)	0.03
LV ejection fraction	1.0 (1.0-1.1)	0.09	1.1 (1.0-1.1)	0.04
Early AF recurrence	5.2 (2.4-11.5)	<0.0001	5.7 (2.0-16.5)	0.001

CI = confidence interval; IL = interleukin; LV = left ventricular; TGF = transforming growth factor.

Clinical implications

The most important finding of our study is that inflammation, as represented by IL-6, may be involved in early AF recurrences. Anti-inflammatory therapies such as statins[24,45,46] and corticosteroids,[24,47,48] provided e.g. short before and during the first month after electrical cardioversion, may therefore prevent early AF recurrences through direct antiarrhythmic effects. Prevention of early AF recurrences may subsequently prevent progression to permanent AF.

Strengths and limitations

The novel study population taken from clinical practice, the thorough assessment of parameters reflecting various mechanisms involved in the initiation and perpetuation of AF, and the clinically valuable new results constitute the most important strengths of this study. Because some patients had a prior history of AF while others presented with their first episode, it is uncertain whether the variables we measured were associated with early AF recurrence or with the progression to persistent AF in new-onset AF patients who might have had paroxysmal AF. However, early AF recurrences occurred in a substantial proportion of patients with a previous electrical cardioversion, i.e. in patients with established persistent AF, implying that the variables studied were for an important part associated with AF recurrences in persistent AF. Furthermore, not all possible biomarkers that have been associated with AF were analyzed in this study, which means that results could have differed if a different subset of biomarkers had been used. Though set-up prospectively, a power analysis was not conducted because there were no prior data concerning patients with short-lasting AF. Our study is therefore limited by the small study population. This could have led to false positive results. On the other hand, the primary endpoint still occurred in a substantial amount of patients. Because of the small patient numbers, the results and especially the prediction models should be interpreted with caution. Larger studies are required to validate our results.

Conclusions

In patients with short-lasting AF, early AF recurrence seemed to be associated with inflammation as represented by interleukin-6. Treatment aimed against inflammation may therefore prevent early AF recurrences, which can improve rhythm control outcome.

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CONFLICTS OF INTEREST

None declared.

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3 IS INFLAMMATION A RISK FACTOR FOR RECURRENT ATRIAL FIBRILLATION?

Marcelle D Smit, Isabelle C Van Gelder.

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Atrial fibrillation (AF) poses an important problem in clinical practice. Restoration and maintenance of sinus rhythm (i.e. secondary prevention of AF) is difficult to achieve.[1] This has led to the fact that acceptance of AF in combination with adequate rate control has become a satisfactory alternative in the management of AF. However, the economic burden due to AF remains high, and morbidity and mortality in patients with AF are still substantial. It would thus seem logical to find methods to prevent AF to ever develop (i.e. primary prevention of AF), and consequently, patients at risk of developing AF must be identified to be able to implement preventative strategies.

Well-known predictors of AF include age, hypertension, valvular disease, myocardial infarction, diabetes mellitus, and congestive heart failure.[2] There are, however, patients with AF with no known underlying disease, classified as 'lone AF'. The question remains whether lone AF in fact is truly lone, and whether there are other risk factors involved in AF. Less well-known risk factors for AF have increasingly been coming to attention, including sleep apnea, alcohol or other intoxication abuse, excessive physical activity, latent hypertension (i.e. diastolic dysfunction), genetic factors, obesity or body mass index (BMI), and inflammation.[3]

Inflammation has been linked to a variety of cardiovascular conditions, including coronary artery disease, diabetes mellitus, and hypertension, and the association between inflammation and AF is increasingly being substantiated.[4,5] The exact mechanism relating inflammation with AF is still unknown, and it is also unclear whether inflammation is an initiator or rather a consequence of AF. The existence of post-operative AF would suggest that inflammation precedes AF, as surgery causes a strong inflammatory process which involves complement activation and release of pro-inflammatory cytokines. Indeed, it has been reported that markers of inflammation post-operatively are associated with the development of AF. In non-operative AF, there is also increasing evidence that inflammation plays a prominent role in the etiology and maintenance of AF. Histological studies have shown inflammatory infiltrates and fibrosis in the atria which were not found in controls, even in patients with lone AF in whom inflammation cannot be attributed to other cardiovascular conditions. One of the possible mechanisms causing inflammation and fibrosis in the atria involves the renin–angiotensin–aldosterone (RAAS) system, through angiotensin-II.[6] Increased expression of angiotensin-II, which has been observed in AF, causes increased production of pro-inflammatory cytokines, adhesion molecules, and selectins. On the other hand, inflammation itself stimulates angiotensin-II production.

Markers of inflammation include interleukin (IL)-6, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-ß, and IL-8.[4,5] Interleukin-6 is a primary cytokine that stimulates the synthesis of acute phase proteins such as C-reactive protein and fibrinogen. Various studies have demonstrated increased levels of IL-6 in both patients with persistent and paroxysmal AF when compared with controls. Increased levels of TNF-α and TGF-ß have also been observed in AF, but evidence has not been as strong. The acute phase protein C-reactive protein has more frequently been investigated using the vas-

cular marker high-sensitivity (hs)-C-reactive protein. Levels of hs-C-reactive protein have been demonstrated to be higher in patients with AF compared with patients in sinus rhythm, and also to be higher in those with persistent AF compared with paroxysmal AF, both having higher levels than controls. Furthermore, hs-C-reactive protein has been shown to be correlated with a success rate of electrical cardioversions. Fibrinogen is less well established as a marker of inflammation in AF. There is also growing evidence that white blood cell (WBC) count, not difficult to assess, is elevated in patients with AF.

Although it seems exciting that these markers of inflammation are shown to be increased in AF, it is still unknown whether these relations are mere associations or whether they say something about the pathophysiology of AF, implying that they could be used to identify patients at risk for AF or to identify patients in whom therapy for AF will be successful. The paper by Letsas et al.[7] provides a valuable contribution. In this study, clinical parameters and markers of inflammation, including hs-C-reactive protein, WBC count, and fibrinogen, were determined in 72 consecutive patients with paroxysmal or persistent AF prior to pulmonary vein isolation (PVI). The authors aimed to investigate whether these clinical parameters and markers of inflammation could be related to success of PVI. After a period of 12.5 ± 5.7 months, 28 patients (39%) had a recurrence of AF. Patients with recurrence of AF more often had the classical risk factors of hypertension, increased left atrial diameter (LAD) and reduced left ventricular ejection fraction, the less well known risk factor of increased BMI, and furthermore, they had an increased left ventricular end-diastolic diameter. In addition, patients with recurrence of AF less often used statins, and WBC count and hs-C-reactive protein levels (not fibrinogen) were elevated when compared with patients who remained in sinus rhythm. In univariate Cox proportional hazard regression analysis, all these variables except for statin use were significantly associated with recurrence of AF. After multivariate analysis, only hypertension, LAD, and WBC count remained independent predictors of recurrence of AF after PVI.

The present study had a retrospective design with a small number of patients, but it teaches us some interesting lessons and also raises new questions. First, hypertension remains to be the most important risk factor for AF and may also be an important predictor of failure of PVI, as demonstrated in the present analysis. However, no data were provided concerning the actual baseline blood pressures in these patients, and perhaps these patients could have been treated more adequately for their hypertension which may consequently have reduced the recurrence of AF after PVI. Second, the study shows that a simple diagnostic tool, i.e. WBC count, may be a possible predictor of success rate of PVI. WBC count, therefore, may potentially be a factor to be used for better selection of eligible candidates in order to improve the success of PVI and other rhythm control strategies. The other two markers of inflammation that were studied did not predict the success rate of PVI: fibrinogen was not associated with recurrence of AF, but until now fibrinogen has not been well established in association with AF. In addition, hs-C-reactive protein was not an independent predictor of recurrence of AF, in contrary to

most previous studies. However, patients with AF recurrence actually did have significantly higher baseline hs-C-reactive protein levels in the present analysis. The fact that hs-C-reactive protein lost its predictive value in multivariate analysis may be a consequence of the small patient numbers. The third interesting observation was that patients with a recurrence of AF had a significantly higher BMI, although this was not confirmed by multivariate analysis, possibly again due to small patient numbers. Obesity has previously been described as a risk factor for AF.[3] Several mechanisms have been postulated to explain why obesity may lead to AF, including left atrial enlargement and chronic low-grade inflammation. In fact, Letsas et al. mention that in their study cohort, BMI was significantly correlated with increased LAD and increased inflammation, as expressed by elevated WBC count and hs-C-reactive protein levels.

One question that arises is that if indeed inflammation predisposes to AF, will patients with increased inflammatory markers benefit from therapeutic interventions targeted against processes of inflammation? Statins have been shown to have anti-inflammatory and anti-fibrotic effects and have been associated with a decrease in (recurrence of) AF, either post-operatively, after electrical cardioversion, and in paroxysmal AF, as demonstrated by various retrospective or small observational studies.[6,8] Other promising drugs in the prevention of AF are RAAS blockers, i.e. angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone receptor antagonists.[9] Furthermore, anti-inflammatory agents such as glucocorticoids, polyunsaturated fatty acids, and vitamin C could also prevent AF. In the present study, patients with sinus rhythm at follow-up more frequently used statins, but statin use did not predict the recurrence of AF in multivariate analysis. The use of RAAS blockers was not different in patients with and without a recurrence of AF. Perhaps the number of patients was too small to detect differences, but it is also conceivable that RAAS blockade and statin use is predominantly effective in patients with an increased inflammatory status. A totally different therapeutic option that seems to have been underestimated so far in the prevention of AF is exercise: moderate physical activity has been shown to decrease the incidence of AF, which may be explained by inducing and maintaining weight loss, improving glucose control, improving mental well-being, and lowering systemic inflammation, amongst other possible mechanisms.[10]

Due to the small number of patients and the retrospective nature of the present study, the results should be interpreted with caution. However, the study is of additional value with regard to our current knowledge of risk factors for AF and predictors of success of therapy for AF. Obviously, future research is desired to further elucidate which patients are at risk for AF, which patients benefit most from therapies against AF, and which therapies are most effective in the prevention of (recurrence of) AF.

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WILL WE BE ABLE TO PREDICT IN WHICH ATRIAL FIBRILLATION PATIENTS A RHYTHM CONTROL STRATEGY WILL BE SUCCESSFUL?

3B

Marcelle D Smit, Isabelle C Van Gelder.

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Several randomized clinical trials have demonstrated that with regard to prognosis, rate control is not inferior to rhythm control in atrial fibrillation (AF).[1] This has led to the development that restoration of sinus rhythm is no longer the treatment objective for every patient presenting with AF. Rhythm control remains therapy of choice, however, for symptomatic patients.[2] Yet, when we interpret the results of the rate vs. rhythm control trials, we should keep in mind that rhythm control was never fully successful, meaning that these trials compared strategies instead of actual achieved rhythms. Restoration and maintenance of sinus rhythm indeed is challenging, even despite strong anti-arrhythmic drugs.[3] We still do not know whether true restoration of sinus rhythm, preferably without the need for anti-arrhythmic drugs, improves survival in comparison to acceptance of AF. One way to overcome this conundrum is to investigate the results of new treatment options. On the other hand, we could try to improve the outcome of rhythm control therapy by aiming to differentiate those patients in whom rhythm control will be successful from those in whom it will not be effective.

Outcome of rhythm control depends on the severity of AF, in terms of electrical and structural remodeling. The extent of remodeling is influenced by the duration of AF in addition to clinical factors like age and underlying disease including hypertension, congestive heart failure, coronary artery disease, valvular disease, diabetes mellitus, and thyroid disease. Furthermore, less well-known risk factors for AF such as obesity, alcohol abuse, excessive sports practice, genetic factors, sleep apnea, and inflammation may affect the severity of AF.[4] The severity of atrial remodeling is probably reflected through different parameters, such as atrial size and function, and circulating biomarkers of fibrosis or inflammation. Perhaps these different clinical parameters are useful in identifying those patients with AF who are more or less likely to respond to rhythm control therapy.

In the paper in the current issue by Mazza et al.,[5] the authors aimed to create a useful model that predicts recurrence of AF after successful electrical cardioversion, focusing on parameters reflecting sleep apnea (i.e. apnea/ hypopnea index) and inflammation (i.e. hs-C-reactive protein). For this study, polysomnography was performed the night before electrical cardioversion to assess the presence of apnea and/ or hypopnea. Sleep apnea syndrome was defined as moderate to severe in the case of ≥ 15 apnea and/ or hypopnea events per hour. Furthermore, hs-C-reactive protein was assessed from a blood sample taken on the day before electrical cardioversion. These parameters, together with other clinical parameters such as gender, age, left atrial diameter, AF duration, and ongoing anti-arrhythmic drug therapy, were related to recurrence of AF within 1 year after successful cardioversion. In total, 158 patients had successful cardioversion and were included in the analysis. The authors found that apnea/ hypopnea index of ≥ 15, hs-C-reactive protein of > 0.30 mg/dL, and ongoing anti-arrhythmic drug therapy were the only independent predictors of AF recurrence. They used these three factors along with the factor age to build a predictive risk model for recurrence of AF within 1 year after cardioversion. This model would, for example, calculate a risk for AF recur-

rence of 85% in a 60-year-old patient with apnea/ hypopnea index of ≥ 15, hs-C-reactive protein of > 0.30 mg/dL, and ongoing antiarrhythmic drug therapy when compared with a risk of 27% in a 60-year-old patient without these three risk factors.

In the risk model, fairly novel parameters were explored. Sleep apnea has previously been recognized to be associated with AF, perhaps due to elevated intrathoracic pressures leading to increased atrial stretch or due to intermittent hypoxaemia.[4,6] In this study,, the presence of sleep apnea was thoroughly evaluated through overnight polysomnography. We should have our reservations regarding the practicality of overnight polysomnography as part of a prediction tool, however. Certainly, it is much more arduous than assessment of other clinical parameters like echocardiographic measurements or blood analyses. Furthermore, it is remarkable that such a large proportion, namely 31% of the patients, had an apnea/ hypopnea index of ≥ 15, indicating moderate to severe sleep apnea. Does this mean that one-third of patients with persistent AF at our outpatient clinic have sleep apnea? Should we systematically assess sleep apnea, incorporating it in the standard clinical evaluation of patients presenting with AF, just like echocardiography and measurement of thyroid function? Indeed other studies report on incidences between 10 and 50% depending on definitions and diagnostic methods used and on patients selected, keeping in mind that these studies concerned relatively small patient numbers.[7] Yet, more studies are needed to evaluate the prevalence of sleep apnea in AF and whether treatment may improve the outcome of a rhythm control strategy in these patients.

The other parameter studied was hs-C-reactive protein. This is an inflammatory marker that has been observed to be elevated in AF, implying that inflammation plays an important role in AF, either as an initiator or as a consequence of AF.[8,9] Accordingly, other markers of inflammation are also increased in AF, such as white blood cell count, interleukin-6 and -8, tumor necrosis factor-α, transforming growth factor-β, and fibrinogen. When comparing it with overnight polysomnography, hs-C-reactive protein is a fairly simple marker to assess. The drawback of this marker, however, is that hs-C-reactive protein levels can vary widely between patients and even overlap between patients with and without AF recurrences, which the authors recognize. Further studies investigating the role of hs-C-reactive protein in AF are desired.

The third marker that was an independent predictor of AF recurrence was ongoing anti-arrhythmic drug therapy. This would seem illogical, because class I and III anti-arrhythmic drugs are generally more effective in preventing recurrence of AF than beta-blockers or non-dihydropyridine calcium channel blockers. On the other hand, we could explain this discrepancy because anti-arrhythmic drug use probably reflects a longer history of AF. Specifically, a longer history of AF implies that the extent of atrial structural remodeling is more advanced, making it more difficult to not only restore but especially to maintain sinus rhythm.[10] Unfortunately, the authors only provide data concerning the length of the current episode of AF, not of the length of the total history of AF.

The results of the study should be interpreted in the context of its limitations. For instance, it is intriguing that the authors decided to do the analyses only on the patients in whom cardioversion was successful, providing a selection bias. Shock failure was observed in 5% of the patients. These patients probably also had undergone polysomnography and hs-C-reactive protein analysis the day before cardioversion. In finding a prediction model that helps us choose between rate and rhythm control in AF patients, shock failure is just as important as AF recurrences. It would thus have been interesting if the authors had provided the results of the polysomnography and hs-C-reactive protein analysis in relation to shock failure.

The prediction model built by the authors is probably far from complete; not all possible parameters reflecting the severity of atrial remodeling were investigated, such as biomarkers of fibrosis or echocardiographic parameters other than left atrial size. Nonetheless, the small patient population would not have allowed to explore all these parameters. And even if it would have been complete, how should we interpret the calculated risk percentages of a prediction model? An 80% risk of recurrence of AF indeed is high, but does that mean that we should not apply a rhythm control strategy in such a patient? It also means that this patient has a 20% chance of maintaining sinus rhythm at 1 year, which is not negligible.

All in all, the present paper by Mazza et al. is much appreciated. Though the study population was too small to adequately build a predictive model for recurrent AF, this study should rather be perceived as an explorative step towards finding new risk factors that may help us predict which patients will have recurrences of AF after cardioversion. In due course such risk factors may help us to improve the outcome of rhythm control therapy and may ultimately help us predict which patients will ever develop AF.

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4 EFFECT OF LENIENT AND STRICT RATE CONTROL ON CARDIAC REMODELING IN PATIENTS WITH ATRIAL FIBRILLATION - DATA OF THE RATE CONTROL EFFICACY IN PERMANENT ATRIAL FIBRILLATION II (RACE II) STUDY

Marcelle D Smit, Harry JGM Crijns, Jan GP Tijssen, Hans L Hillege, Marco Alings, Ype S Tuininga, Hessel F Groenveld, Maarten P Van den Berg, Dirk J Van Veldhuisen, Isabelle C Van Gelder.

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ABSTRACT

Objectives

The aim of this study was to evaluate echocardiographic remodeling in permanent atrial fibrillation (AF) patients treated with either lenient or strict rate control.

Background

It is unknown whether in permanent AF, lenient rate control is associated with more adverse cardiac remodeling than strict rate control.

Methods

Echocardiography was conducted at baseline and at follow-up in 517 patients included in the RAte Control Efficacy in permanent atrial fibrillation II (RACE II) trial. Echocardiographic parameters were compared between patients randomized to lenient (n=261) or strict rate control (n=256).

Results

Baseline echocardiographic parameters were comparable between patients randomized to lenient and strict rate control. Between baseline and follow-up, significant adverse atrial or ventricular remodeling was not observed in either group. There were also no significant differences in atrial and ventricular remodeling between patients who continuously had heart rates between 80 and 110 beats per minute and patients who continuously had heart rates < 80 beats per minute during follow-up. Lenient rate control was not independently associated with changes in echocardiographic parameters: mean adjusted effect on left atrial size was 1.6 mm (p=0.09) and on left ventricular end-diastolic diameter 1.1 mm (p=0.23). Instead, female sex was independently associated with adverse remodeling: mean adjusted effect on left atrial size 2.4 mm (p=0.02) and on left ventricular end-diastolic diameter 6.5 mm (p<0.0001).

Conclusions

Female sex, not lenient rate control, seemed to be associated with significant adverse cardiac remodeling in patients with permanent AF such as those enrolled in the RACE II study.

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia, its incidence and prevalence increasing with age and life expectancy.[1] Nowadays, rate control therapy should be the initial approach in elderly patients with mild symptoms of AF.[2-5] The Rate Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II (RACE II) study has recently demonstrated that lenient rate control is not inferior to strict rate control in preventing cardiovascular events in patients with permanent AF.[6] However, long-standing AF may result in adverse cardiac remodeling including atrial enlargement and ventricular dysfunction,[7,8] which could lead to stroke, heart failure, and other cardiovascular events.[9,10] It is unknown whether lenient rate control is associated with more adverse cardiac remodeling than strict rate control. The aim of this predefined sub-analysis of the RACE II study was therefore to evaluate echocardiographic remodeling in patients with permanent AF treated with lenient or strict rate control.

METHODS

Patient characteristics and results of the RACE II study have been published previously.[2,11] The RACE II study was a randomized multi-center 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 (which allowed for a higher heart rate target than strict control) had a resting heart rate target < 110 beats per minute. Patients randomized to strict rate control had a resting heart rate target < 80 beats per minute and a heart rate target during moderate exercise < 110 beats per minute. Patients were administered one or more negative dromotropic drugs (i.e. beta-blockers, non-dihydropyridine calcium-channel blockers, digoxin) until the heart rate target or targets were achieved. Follow-up outpatient visits occurred every two weeks until the heart rate target or targets were achieved (dose-adjustment phase) and in all patients after 1, 2, and 3 years. Follow-up was terminated after a maximum period of 3 years or on June 30, 2009, whichever came first. The study was approved by the institutional review boards of all participating centers. The present pre-defined study included only patients in whom echocardiography was conducted at baseline and at end of study; patients who died before end of study (n=35) and patients with missing baseline and/ or end of study echocardiograms (n=62) were therefore excluded. There were neither statistical differences in baseline echocardiographic parameters between the included and excluded patients, nor specifically between the included patients and those who died before end of study.

Echocardiography

Primary endpoints in this study consisted of measures of structural atrial and ventricular echocardiographic remodeling, i.e. changes in left atrial size, left atrial volume, and left ventricular end-diastolic diameter. Left ventricular ejection fraction was not included as measure of remodeling because it cannot be measured accurately during AF, especially when heart rates are high. Two-dimensional transthoracic echocardiography was performed at the local hospitals at study entry and at end of follow-up, after a median of 3.0 years (inter-quartile range 2.8 to 3.1 years). For left atrial size, the anteroposterior dimension was measured from the parasternal long-axis view, taken at end-systole. Left atrial volume was calculated with the ellipsoid model using left atrial diameters in parasternal long-axis, left atrial long-axis, and left atrial short-axis in the apical four-chamber view, 12 and was available in 317 patients. Left ventricular end-diastolic diameter was measured in the parasternal long-axis view. The echocardiograms were performed in accordance with standard recommendations.[12]

Statistical analysis

Baseline descriptive statistics are presented as mean ± standard deviation or median with inter-quartile range for continuous variables and numbers with percentages for categorical variables, as required. We evaluated differences between patients treated with lenient versus strict rate control using Chi-square test and Fisher's exact test for categorical data, and Student's *t* test and Mann Whitney-U test for continuous data, dependent on whether data were normally distributed. To compare echocardiographic parameters within patient groups, paired Student's *t* test was used for the normally distributed data. Changes in echocardiographic parameters were also compared based on a per-protocol analysis, i.e. between patients who continuously had resting heart rates between 80 and 110 beats per minute and patients who continuously had resting heart rates < 80 beats per minute during follow-up, after the dose-adjustment phase. Patients who converted to sinus rhythm were excluded from the per-protocol analysis. Linear regression was conducted to determine clinical characteristics related to increase in echocardiographic parameters. Univariate linear regression was performed on all patient characteristics, i.e. randomization strategy, age, gender, duration of any AF, duration of permanent AF, hypertension, coronary artery disease, valvular heart disease, chronic obstructive pulmonary disease, diabetes, previous heart failure hospitalization, body mass index, systolic and diastolic blood pressure, heart rate at end of dose-adjustment phase, QRS duration, creatinine, all medications at end of dose-adjustment phase, and change in heart rate between baseline and end of follow-up. Stepwise multivariable linear regression analysis was conducted using all variables with $p<0.2$ in univariate analysis, randomization strategy, and duration of any AF. Additional bootstrap analyses were performed to

assess sensitivity of the multivariable models. For bootstrap analysis, automated stepwise variable selection was conducted on 100 bootstrap samples using all variables with $p<0.2$ in univariate analysis. The multivariable models included all variables with $p<0.05$. Analyses were performed with STATA 11.0 for Windows. In all analyses $p<0.05$ was considered statistically significant.

RESULTS

A total of 517 patients were included in the study: 261 patients (50.5%) had been randomized to lenient rate control, 256 patients (49.5%) to strict rate control (Table 1). Clinical characteristics were comparable between the two groups, except that patients randomized to lenient rate control more often had a history of coronary artery disease resulting in more frequent statin use. After the dose-adjustment phase, patients randomized to lenient rate control less often used beta-blockers, non-dihydropyridine calcium-channel blockers, and digoxin (Table 1). During the course of the study, heart rates were significantly higher in patients randomized to lenient rate control. The mean resting heart rate at the end of the dose-adjustment phase was 93±10 beats per minute in the lenient rate control group versus 76±12 beats per minute in the strict rate control group ($p<0.001$). After 1 and 2 years and at the end of follow-up, the resting heart rates were 83±18, 77±25, and 77±28 beats per minute, respectively, in the lenient rate control group as compared with 72±21, 68±25, and 68±26 beats per minute, respectively, in the strict rate control group ($p<0.001$ for all comparisons between the two groups). Baseline diastolic blood pressure was significantly higher in lenient rate control patients and remained higher during the course of the study; at end of study diastolic blood pressure was 82±11 mmHg in lenient rate control patients versus 80±11 mmHg in strict rate control patients ($p=0.009$). Systolic blood pressures were generally similar between the two groups. Body mass index remained stable throughout the study: mean body mass index at end of study was 28.4±4.5 kg/m2 in lenient rate control patients and 28.6±5.0 kg/m2 in strict rate control patients. Thirty-eight patients (7.4%) converted to sinus rhythm during follow-up: 20 lenient rate control patients (7.7%) versus 18 strict rate control patients (6.8%) ($p=0.08$).

Changes in echocardiographic parameters

RESULTS

Baseline echocardiographic parameters were comparable between patients randomized to lenient and strict rate control; left atria were slightly dilated, while left ventricular end-diastolic diameters fell within normal ranges (Table 2A). At end of follow-up, significant progression of adverse atrial or ventricular remodeling was not observed in either group. Furthermore, there

Table 1. Patient characteristics

	Lenient rate control (n=261)	Strict rate control (n=256)	p-value
Age - mean±SD - years	68±8	68±9	0.45
Male sex - no. (%)	174 (66.7)	166 (64.8)	0.66
Duration of any AF - months			0.27
Median	15	20	
Inter-quartile range	6-55	5-63	
Duration of permanent AF - months			0.63
Median	3	2	
Inter-quartile range	1-6	1-5	
Hypertension - no. (%)	172 (65.9)	153 (59.8)	0.15
Coronary artery disease - no. (%)	57 (21.8)	37 (14.5)	0.03
Valvular heart disease - no. (%)	53 (20.3)	55 (21.5)	0.74
Chronic obstructive pulmonary disease - no. (%)	32 (12.5)	37 (12.3)	0.29
Diabetes mellitus - no. (%)	32 (12.3)	26 (10.2)	0.45
Lone AF* - no. (%)	5 (1.9)	5 (2.0)	0.55
Previous hospitalization for heart failure - no. (%)	22 (8.4)	27 (10.6)	0.41
$CHADS_2$ score - mean±SD	1.4±1.0	1.4±1.2	0.81
Symptoms - no. (%)	149 (57.1)	150 (58.6)	0.12
Palpitations	56 (21.5)	68 (26.6)	0.17
Dyspnea	91 (34.9)	92 (35.9)	0.80
Fatigue	74 (28.4)	86 (33.6)	0.20
New York Heart Association functional class - no. (%)			0.74
I	170 (65.1)	164 (64.1)	
II	77 (29.5)	79 (30.9)	
III	14 (5.4)	13 (5.1)	
Body mass index - mean±SD - kg/m^2	28.6±4.7	28.6±4.5	0.95
Blood pressure - mean±SD - mmHg			
Systolic	138±19	135±16	0.08
Diastolic	85±12	82±11	0.005
Heart rate - mean±SD - beats per minute			
Heart rate at inclusion	97±13	95±12	0.28
Heart rate at end of dose-adjustment phase	93±10	76±12	<0.001
Rate control target achieved - no. (%)	254 (97.3)	168 (65.6)	<0.001
QRS duration - mean±SD - ms	95±18	94±18	0.61
Creatinine - mean±SD - umol/L	96±23	95±23	0.60
Medication at end of dose-adjustment phase - no. (%)			
Beta-blocker	177 (67.8)	201 (78.5)	0.006
Verapamil/ diltiazem	42 (16.1)	97 (37.9)	<0.001
Digoxin	94 (36.0)	152 (59.4)	<0.001
RAAS inhibitor	142 (54.4)	128 (50.0)	0.32
Diuretic	109 (41.8)	105 (41.0)	0.86
Statin	85 (32.6)	61 (23.8)	0.03
Vitamin K antagonist	259 (99.2)	253 (98.8)	0.64
Aspirin	3 (1.2)	3 (1.2)	0.98

AF = atrial fibrillation; RAAS = renin-angiotensin-aldosterone system; SD = standard deviation.

* Lone AF was defined as AF in the absence of cardiovascular disease and extracardiac precipitating causes of AF.

were no significant differences in changes in echocardiographic parameters between patients randomized to lenient and strict rate control, though there was a tendency that lenient rate control was associated with a relative left atrial size increase (mean difference in change in atrial size 1.6 mm, p=0.09). There were also no differences in echocardiographic remodeling according to per-protocol analysis, i.e. when comparing patients who continuously had resting heart rates between 80 and 110 beats per minute with patients who continuously had resting heart rates < 80 beats per minute after the dose-adjustment phase (Table 2B). In the remaining small number of patients with heart rates > 110 beats per minute during at least one follow-up visit, significant adverse remodeling was also not observed (Table 2C).

Changes in echocardiographic parameters

Lenient rate control was not independently associated with changes in left atrial size (Table 3), though the p-value neared significance, implying that there was a slight tendency for an association between lenient rate control and atrial size increase (mean adjusted effect 1.6 mm, p=0.09). Female sex was independently associated with an increase in left atrial size (mean adjusted effect 2.4 mm), while valvular heart disease, body mass index, and renin-angiotensin-aldosterone-system (RAAS) inhibitor use were associated with left atrial size decrease. Bootstrap analysis demonstrated similar results (data not shown). Conversion to sinus rhythm was not associated with changes in atrial size but the number of patients converting to sinus rhythm was very small.

Clinical factors associated with changes in ventricular end-diastolic diameter

Lenient rate control did not independently influence changes in left ventricular end-diastolic diameter (Table 3). Again, female sex was associated with adverse left ventricular remodeling (mean adjusted effect 5.9 mm). Valvular heart disease, previous hospitalization for heart failure, body mass index, and RAAS inhibitor use were independently associated with a decrease in left ventricular end-diastolic diameter (Table 3). Bootstrap analysis demonstrated similar results (data not shown). Conversion to sinus rhythm was not associated with changes in ventricular end-diastolic diameter taking into account the small number of patients converting to sinus rhythm.

Table 2A. Echocardiographic parameters according to randomization strategy

Echocardiographic parameter – mean±SD	Lenient rate control			Strict rate control			Lenient vs. strict rate control	
	Baseline	End of study	Δ (95% CI)	Baseline	End of study	Δ (95% CI)	Difference in Δ (95% CI)	p-value
LA size - mm	46.4±6.6	47.1±6.6	0.8 (-0.5-2.0)	46.1±7.2	45.3±6.8	-0.8 (-2.1-0.5)	1.6 (-0.3-3.4)	0.09
LA volume - mL (n=317)	71.7±26.6	76.7±24.9	5.0 (-0.7-10.6)	72.6±27.5	74.3±25.5	1.7 (-4.4-7.7)	3.2 (-5.0 11.5)	0.88
LV end-diastolic diameter - mm	51.1±7.4	50.8±6.9	-0.3 (-1.6-1.0)	51.5±7.4	50.1±6.7	-1.4 (-2.7- -0.1)	1.1 (-0.8-3.0)	0.24

CI = confidence interval; LA = left atrial; LV = left ventricular; SD = standard deviation; Δ = change between baseline and end of study.

Table 2B. Echocardiographic parameters according to resting heart rate during all follow-up visits after the dose-adjustment phase

Echocardiographic parameter – mean±SD	Heart rate 80 - 110 bpm (n=329)			Heart rate < 80 bpm (n=120)			80 - 110 bpm vs. < 80 bpm	
	Baseline	End of study	Δ (95% CI)	Baseline	End of study	Δ (95% CI)	Difference in Δ (95% CI)	p-value
LA size - mm	46.2±6.8	46.8±6.7	0.6 (-0.5-1.7)	45.8±7.7	44.9±7.3	-0.9 (-3.0-1.1)	1.5 (-0.8-3.8)	0.19
LA volume - mL	72.4±26.1	76.2±24.5	3.7 (-1.3-8.8)	69.3±30.3	74.6±27.6	5.2 (-4.2-14.6)	1.5 (-11.5-8.6)	0.77
LV end-diastolic diameter - mm	51.2±7.5	50.5±7.0	-0.7 (-1.9-0.5)	51.6±7.3	49.9±6.8	-1.7 (-3.7-0.2)	1.1 (-1.3-3.4)	0.37

CI = confidence interval; LA = left atrial; LV = left ventricular; SD = standard deviation; Δ = change between baseline and end of study.

Table 2C. Echocardiographic parameters in patients with heart rate > 110 bpm during at least one follow-up visit

Echocardiographic parameter – mean±SD	Heart rate > 110 bpm (n=32)		
	Baseline	End of study	Δ (95% CI)
LA size - mm	48.1±7.6	45.2±5.0	-2.9 (-6.8-0.9)
LA volume - mL	82.0±28.8	76.5±22.4	-5.5 (-24.2-13.1)
LV end-diastolic diameter - mm	50.4±6.5	50.7±5.0	0.3 (-2.7-3.3)

CI = confidence interval; LA = left atrial; LV = left ventricular; SD = standard deviation; Δ = change between baseline and end of study.

Left atrial volume

In 317 patients left atrial volume was available at baseline and follow-up. Baseline characteristics were comparable with the 517 patients of the present study (data not shown). There were no significant differences in left atrial volumes between patients randomized to lenient and strict rate control (Table 2A). During follow-up, left atrial volume had increased by 5.0 mL in the lenient rate control group and 1.7 mL in the strict rate control group (p=ns). There were no significant differences in changes in left atrial volume between both groups. Similar results were observed with per-protocol analysis (Table 2B). Lenient rate control was not independently associated with left atrial volume increase (Table 3). Instead, female sex was independently associated with an increase in left atrial volume, while body mass index was associated with left atrial volume decrease. Bootstrap analysis demonstrated similar results (data not shown).

DISCUSSION

The present analysis of the RACE II study suggests that stringency of rate control is not associated with significant adverse cardiac remodeling in patients with permanent AF. Instead, female sex seems to be related to adverse cardiac remodeling, whereas treatment with RAAS inhibition and increased baseline body mass index are associated with reverse atrial and ventricular remodeling.

Influence of rate control strategy on atrial and ventricular remodeling

Overall, we did not observe significant adverse atrial or ventricular remodeling during three year follow-up in these patients with permanent AF. More importantly, lenient rate control did not cause significant adverse atrial and ventricular remodeling as compared with strict rate control. There was a non-significant tendency that lenient rate control was associated with a slight left atrial size increase. This tendency was not observed regarding left atrial volume, generally considered a more accurate measure ofleft atrial size because of asymmetric remodeling of the left atrial chamber.[12] The most essential finding was that lenient rate control did not lead to adverse ventricular remodeling in these permanent AF patients. Per-protocol analysis supported the finding that lenient rate control does not seem to be associated with adverse remodeling, as there were no significant differences in atrial and ventricular remodeling between patients with continuous resting heart rates between 80 and 110 beats per minute and patients with continuous resting heart rates < 80 beats per minute after the dose-adjustment phase. Heart rate > 110 beats per minute during at least one follow-up visit was also not associated with significant

Table 3. Clinical factors associated with changes in echocardiographic parameters

	Unadjusted		Multivariable analysis	
	B (95% CI)	p-value	B (95% CI)	p-value
Change in LA size - mm				
Lenient rate control	1.6 (-0.3-3.4)	0.09	1.6 (-0.2-3.4)	0.09
Female sex	1.8 (-0.1-3.8)	0.06	2.4 (0.5-4.3)	0.02
Duration of any AF	0 (0-0)	0.98		
Duration of permanent AF	-0.1 (-0.3-0)	0.13		
Valvular heart disease	-2.2 (-4.4-0.1)	0.06	-3.2 (-5.5- -1.0)	0.005
Previous heart failure hospitalization	-2.1 (-5.2-1.0)	0.18		
Body mass index / kg/m^2	-0.4 (-0.6- -0.2)	<0.0001	-0.4 (-0.6- -0.2)	<0.0001
Systolic blood pressure	0 (-0.1-0)	0.11		
Diastolic blood pressure	-0.1 (-0.2-0.1)	0.08		
RAAS inhibitor	-2.8 (-4.7- -1.0)	0.002	-2.1 (-3.8- -0.2)	0.03
Statin	-1.9 (-3.9-0.1)	0.06		
Change in heart rate	0 (0-0.1)	0.09		
Change in LA volume - % (n=317)				
Lenient rate control	3.3 (-5.0-11.5)	0.43	2.8 (-5.4-10.9)	0.50
Female sex	13.1 (4.4-21.8)	0.003	11.9 (3.2-20.6)	0.008
Duration of any AF	0 (-0.1-0.1)	0.86		
Body mass index / kg/m^2	-1.9 (-2.8- -1.0)	<0.0001	-1.9 (-2.8- -0.9)	<0.0001
Creatinine / 10 umol/L	-1.7 (-3.7-0.2)	0.08		
RAAS inhibitor	-9.6 (-17.8- -1.5)	0.02		
Change in heart rate	0 (-0.1-0.2)	0.70		
Change in LV end-diastolic diameter - mm				
Lenient rate control	1.1 (-0.8-3.0)	0.24	1.0 (-0.8-2.8)	0.27
Age	0.1 (0-0.2)	0.03		
Female sex	5.8 (3.9-7.6)	<0.0001	6.5 (4.6-8.4)	<0.0001
Duration of any AF	0 (-0.1-0)	0.82		
Valvular heart disease	-1.9 (-4.2-0.4)	0.10	-3.8 (-6.0- -1.5)	0.001
Previous heart failure hospitalization	-4.7 (-7.8- -1.6)	0.003	-3.9 (-6.9- -0.8)	0.01
Body mass index / kg/m^2	-0.3 (-0.5- -0.1)	0.007	-0.3 (-0.5- -0.1)	0.004
QRS duration / 5 ms	-0.4 (-0.7- -0.2)	0.001		
Creatinine / 10 umol/L	-0.3 (-0.8-0.1)	0.10		
Verapamil/ diltiazem	1.6 (-0.5-3.8)	0.13		
Digoxin	-1.6 (-3.4-0.3)	0.10		
RAAS inhibitor	-3.3 (-5.2- -1.5)	<0.0001	-2.8 (-4.6- -0.9)	0.003
Change in heart rate	0 (0-0)	0.80		

AF = atrial fibrillation; CI = confidence interval; LA = left atrial; LV = left ventricular; RAAS = renin-angiotensin-aldosterone system.

adverse remodeling, though this observation should be interpreted with caution due to the small patient number.

During follow-up, heart rates differed significantly between patients randomized to strict and lenient rate control. Indeed a trial evaluating high and low heart rates in AF would ideally bring all patients to the relevant rate targets. However, in the RACE II study and in this sub-analysis the actual average difference in heart rates between the two groups during total follow-up was approximately 10 beats per minute.[6] Most patients were already using rate controlling drugs at inclusion which implied that many lenient rate control patients started off with heart rates < 110 beats per minute. In the strict group the target was only achieved in 67% of the patients, whereas in the lenient group it was virtually always achieved without much change in therapy. We cannot exclude differences between strategies if we would have had more effective means of strict rate control, and if we had kept heart rates just below 110 in the lenient group.

Previously we have demonstrated that heart rates > 100 beats per minute are associated with poor clinical outcome in AF patients.[13] Also in our main paper we showed that event rates were similar except for those with heart rates > 100 beats per minute in the strict group only. This group, however, consisted of only a few patients.[6] It may therefore still seem to be uncertain whether heart rates between 100 and 110 beats per minute are associated with worse outcome. The current analysis at least demonstrates that with regard to adverse atrial and ventricular remodeling, there are no differences between a rate control strategy aiming at heart rates < 80 beats per minute and a rate control strategy aiming at heart rates < 110 beats per minute.

Previous studies have demonstrated atrial enlargement as a consequence of AF in contrast to our study.[8,14,15] On the other hand, regarding the ventricles, other studies have demonstrated unchanged left ventricular end-diastolic diameters in the presence of adequate rate control.[14,15] The absence of significant adverse remodeling in the present study may be caused by improved therapies of associated diseases, such as a more frequent use of RAAS inhibitors. Indeed, we found that RAAS inhibitors were independently associated with a decrease in left atrial size and in left ventricular end-diastolic diameter. RAAS inhibitors are known to induce reverse ventricular remodeling in heart failure.[16,17] Regarding atrial remodeling, RAAS inhibitors have been associated with left atrial size decrease in patients with diastolic dysfunction[18] and in hypertensive patients.[19] Lack of angiotensin-converting-enzyme inhibitor use was independently associated with atrial size increase in a post-hoc analysis of the RAte Control versus Electrical cardioversion for persistent AF (RACE) study.[14] Reversal of the process of atrial enlargement has been seen after restoration of sinus rhythm,[20,21] though we did not find an association between conversion to sinus rhythm and changes in atrial diameters. To our knowledge, the present study is the first to observe that RAAS inhibition is associated with reverse echocardiographic remodeling in permanent AF patients.

Role of female sex and BMI regarding cardiac remodeling

Not stringency of rate control, but female sex seemed to be associated with adverse cardiac remodeling. There is increasing evidence that there are gender differences regarding presentation, management and outcome of cardiovascular disease, being disadvantageous for females. Women with AF treated with a rhythm control strategy tend to have an adverse outcome compared with men.[22] Furthermore, women carry an increased stroke risk.[23] Though women are generally five years older than men when they first present with AF,[24] differences in outcome of cardiovascular disease may be caused by differences in inherent biological factors, especially in post-menopausal women in whom potential protective effects of estrogens are absent. For example, gene expression profiles of patients with new-onset heart failure differ between males and females.[25] In addition, male and female human hearts have significant differences in the composition of ion-channel subunits, making females more susceptible for arrhythmias associated with repolarization abnormalities.[26] Possible differences in biological factors may explain why females are more prone to adverse cardiac remodeling than men.

In the present study, reverse atrial and ventricular remodeling was associated with increased baseline body mass index, which at first glance seems to be an odd observation. Increased body mass index has been associated with slightly larger left ventricular end-diastolic diameters.[27] Another study observed in a general population that obesity resulted in left atrial volume increase after ten years follow-up.[28] In the present study, body mass index remained stable during the course of follow-up, implying that reverse remodeling could not have been caused by a reduction in body mass index. A possible explanation for the decrease in atrial and ventricular diameters could be that, instead of eccentric remodeling, concentric remodeling took place in patients with an increased body mass index.[29]

Limitations

Both baseline and end of study echocardiograms were necessary for the present analysis. This means that patients who died before end of study and patients with missing baseline and/ or end of study echocardiograms were excluded. The extent of adverse cardiac remodeling in those patients is therefore unknown. However, we believe that this does not create a bias because in the main study mortality was comparable between lenient and strict rate control, and baseline characteristics including baseline echocardiographic parameters in the present analysis were comparable with those of the main study.

In patients with permanent AF such as those enrolled in the RACE II study, female sex, not lenient rate control, seemed to be associated with significant adverse cardiac remodeling.

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5 PROGNOSTIC IMPORTANCE OF NATRIURETIC PEPTIDES AND ATRIAL FIBRILLATION IN PATIENTS RECEIVING CARDIAC RESYNCHRONIZATION THERAPY

Marcelle D Smit, Alexander H Maass, Hans L Hillege, Ans CP Wiesfeld, Dirk J Van Veldhuisen, Isabelle C Van Gelder.

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ABSTRACT

Aim

The aim of this study was to investigate the prognostic value of natriuretic peptides and atrial fibrillation (AF) on response to CRT and mortality.

Methods and results

This study included 338 consecutive CRT patients. Response to CRT was defined as a reduction in left ventricular end-systolic volume of ≥ 15% in the absence of death at 6 months follow-up. During follow-up (27±19 months), 139 patients (41%) had AF, being new-onset in 40 patients (21%). Forty-two patients (12%) had permanent AF. Response to CRT was observed in 168 of 302 patients (56%): 60 of 123 patients (43%) with versus 108 of 179 patients (60%) without AF (p=0.047). Low baseline atrial natriuretic peptide (ANP) (odds ratio for $\log_2$ ANP 0.49, 95% confidence interval (CI) 0.35-0.68, p<0.001) and large left ventricular end-systolic volume (odds ratio for every 50 mL 1.40, 95% CI 1.09-1.79, p=0.009) were independent predictors of response. Neither presence of AF nor increasing AF burden independently predicted response. Ninety patients (27%) died; 50 patients (36%) with versus 40 patients (20%) without AF (log rank p=0.029). Important predictors of all-cause mortality were new-onset AF (hazard ratio 8.11, 95% CI 3.31-19.85, p<0.001), permanent AF (hazard ratio 3.19, 95% CI 1.61-6.30, p=0.001), and baseline N-terminal pro-B-type natriuretic peptide (NT-proBNP) (hazard ratio for $\log_2$ NT-proBNP 0.77, 95% CI 0.66-0.90, p=0.001).

Conclusion

In patients treated with CRT, lower ANP and larger left ventricular end-systolic volume were independent predictors of response. New-onset AF, permanent AF and NT-proBNP were independently associated with increased all-cause mortality.

INTRODUCTION

Atrial fibrillation (AF) is often present in patients with heart failure, its incidence increasing with the severity of heart failure.[1] Cardiac resynchronization therapy (CRT) is an accepted non-pharmacological therapy for patients with severe heart failure.[2-4] Many patients receiving CRT therefore have or develop AF.[5] AF may interfere with CRT because it can decrease effective biventricular pacing due to a too fast intrinsic ventricular response.[6] It is still uncertain whether AF patients benefit from CRT to the same extent as patients with sinus rhythm.[7-12] Natriuretic peptides such as atrial and N-terminal pro-B-type natriuretic peptides (ANP and NT-proBNP) are increased in heart failure and are strong predictors of mortality.[13,14] Plasma levels of natriuretic peptides are correlated with the extent of left ventricular dysfunction and may be affected by AF.[15] The influence of ANP and NT-proBNP in addition to AF on response to CRT has not been studied before. Therefore, it was our aim to investigate the prognostic value of ANP and NT-proBNP in addition to AF on response to CRT and on mortality.

METHODS

Patient population and study protocol

Consecutive patients who received a CRT device in the University Medical Center Groningen from January 2001 to July 2009 were included in this single-center prospective observational study. Eligibility criteria for CRT were based on the standard guidelines and included New York Heart Association functional class III or IV despite optimal pharmacological treatment, left ventricular ejection fraction ≤ 35%, left ventricular end-diastolic diameter ≥ 55 mm, and QRS duration ≥ 130 ms. Significant dyssynchronywas not a prerequisite for CRT implantation, nor was presence of sinus rhythm. Our CRT protocol has been described before.[11,16] Coronary angiography was performed prior to implantation. At baseline and 6 months follow-up patient history, physical examination, treadmill cardiopulmonary exercise testing, 12-lead electrocardiogram, transthoracic echocardiography, and radionuclide ejection fraction were examined and blood samples were collected. Baseline data were collected at hospital admission prior to CRT implantation. ANP and NT-proBNP were analyzed with enzyme-linked immunosorbent assays using commercially available kits (R&D systems, Minneapolis, MN, USA). Patients gave written informed consent for the biomarker analyses. All patients were seen at the outpatient department and for CRT interrogation at baseline and 6-monthly thereafter. At each CRT interrogation, data were stored both on computer disc and in a computerized medical record database of the University Medical Center Groningen. To increase response rates, patients underwent atrioventricular delay optimization at two weeks post implantation. Effective biventricular pacing was assessed by performing treadmill cardiopulmonary exercise tests in addition to monitoring device counters. Imperfect biventricular stimulation during exercise testing was defined as heart rates exceeding

the upper rate of the device at moderate exercise levels, defined as 25% of the maximal achieved exercise duration.[16] AF was carefully monitored during follow-up and was treated aggressively with rhythm control including institution of amiodarone and electrical cardioversion if required. In case of unsuccessful rhythm control, AF was accepted and rate control therapy was instituted aiming at effective biventricular pacing. Atrioventricular node ablation for permanent AF was performed only if pharmacological rate control therapy failed.

METHODS

Echocardiographic evaluation

Transthoracic echocardiography was conducted using a commercially available echocardiographic system (VIVID 7, General Electric Vingmed Ultrasound, Milwaukee, WI, USA). Images were obtained from the parasternal (long- and short-axis) and apical (two- and four-chamber) views and were digitally stored for offline analysis (Echopac 6.1, General Electric Vingmed Ultrasound). Left ventricular end-diastolic and end-systolic volumes were measured with the modified biplane Simpson method using the apical two- and four-chamber views. Ventricular dyssynchrony was assessed by interventricular mechanical delay (IVMD), i.e. right ventricular pre-ejection time subtracted from left ventricular pre-ejection time, and septal to lateral delay using tissue Doppler imaging. An IVMD > 40 ms was considered indicative of interventricular dyssynchrony, a septal to lateral delay > 60 ms of intraventricular dyssynchrony. PA-TDI interval, the time between initiation of the electrocardiographic P-wave in lead II to the A' wave on the lateral left atrial tissue Doppler tracing, was analyzed in sinus rhythm.[17]

METHODS

Definitions of AF and response

AF was defined as any AF episode lasting at least 30 seconds as verified by electrocardiogram, Holter recording, or device interrogation. History of AF was defined as a history of documented AF before implantation. AF during follow-up was defined as any documented AF episode occurring during follow-up. New-onset AF was defined as AF during follow-up occurring in patients who did not have a history of AF. Paroxysmal AF was defined as AF terminating spontaneously, persistent AF as AF lasting more than seven days or requiring termination by cardioversion, and permanent AF as long-standing AF in which cardioversion has failed or has been foregone, i.e. if AF was accepted.[18] AF burden was determined by the device and was defined as the proportion of time in AF. Average AF burden during overall follow-up was categorized into four groups: less than 0.35% AF burden, i.e. minor paroxysmal AF; 0.35%-50% AF burden, i.e. moderate paroxysmal AF; 50%-99% AF burden, i.e. long-lasting AF; and, additionally, 100% AF burden, i.e. permanent AF during total follow-up (sinus rhythm was never observed).[19] This categorization of AF burden was predefined.

Response to CRT was the primary endpoint of the study. Response was defined as a reduction in left ventricular end-systolic volume of 15% or more in the absence of death at 6 months in accordance with current literature[20,21] and was determined by an independent examiner who was blinded to the clinical response of the patient. All-cause mortality during total follow-up was the secondary endpoint of the study and was carefully documented during follow-up. Duration of follow-up was computed from the time of CRT implantation until all-cause mortality or until the date when the last follow-up data were obtained, as appropriate.

Statistical analysis

Baseline descriptive statistics are presented as mean ± standard deviation or median (inter-quartile range) for continuous variables and numbers with percentages for categorical variables, as required. We evaluated differences between groups using Chi-square test and Fisher's exact test for categorical data, and Student's *t* test and Mann Whitney-U test for continuous data, dependent on whether data were normally distributed. To compare data within patient groups, paired Student's *t* test was used for normally distributed data and Wilcoxon signed rank test for not normally distributed data. Box plots were used to represent biomarker levels: boxes symbolize medians and inter-quartile ranges, whiskers correspond to 5th/95th percentiles. Spearman's correlations were used for correlations between biomarkers and clinical variables. Cumulative event proportions were calculated using Kaplan-Meier analysis. The log-rank test was used to compare groups. Logistic regression analysis was conducted to evaluate predictors of response. Cox proportional hazards regression analysis was conducted to evaluate predictors of all-cause mortality. All baseline variables were included in the regression analyses including echocardiographic parameters and biomarkers. Multivariate analyses were performed using all variables with $p < 0.1$ in univariate analysis. A stepwise approach was used. The final multivariate models included all variables with $p < 0.05$. Interactions were investigated. The predictive value of the natriuretic peptides regarding response and all-cause mortality was additionally evaluated using the *c*-statistic, a generalization of the area under the Receiver Operator Characteristic (ROC) curve. In all statistical analyses $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

A total of 338 CRT patients were included. Mean age was 65±11 years and 145 patients (43%) had a previous history of AF (Table 1).

Table 1. Baseline characteristics at implant

	AF during follow-up (n=139)	Sinus rhythm during follow-up (n=199)	Total population (n=338)	p-value
Age - years	65±11	65±11	65±11	0.88
Male sex - n (%)	109 (78)	141 (71)	250 (74)	0.12
History of AF - n (%)	99 (71)	46 (23)	145 (43)	<0.001
Type of AF: - n (%)				
Paroxysmal AF	13 (9)	28 (14)	41 (12)	0.19
Persistent AF	45 (32)	17 (9)	62 (18)	<0.001
Permanent AF	41 (30)	1 (1)	42 (12)	<0.001
Total AF duration - months	48 (13-114)	39 (11-120)	48 (13-115)	0.81
AF at implantation - n (%)	66 (48)	8 (4)	74 (22)	<0.001
Current AF duration - months	13 (5-52)	9 (1-10)	12 (4-39)	0.02
Non-ischaemic cardiomyopathy - n (%)	71 (51)	98 (49)	169 (50)	0.83
Ischaemic cardiomyopathy - n (%)	68 (49)	102 (51)	170 (50)	0.67
Previous myocardial infarction	53 (38)	83 (42)	136 (40)	0.51
Previous cardiac surgery - n (%)	54 (39)	69 (35)	123 (36)	0.43
Hypertension - n (%)	56 (40)	85 (43)	141 (42)	0.70
Diabetes - n (%)	32 (23)	44 (22)	76 (23)	0.82
NYHA class for heart failure: - n (%)				0.73
II	15 (11)	17 (9)	32 (10)	
III	114 (82)	165 (83)	279 (83)	
IV	10 (7)	17 (9)	27 (8)	
Systolic blood pressure - mmHg	117±19	118±20	118±20	0.61
Diastolic blood pressure - mmHg	72±11	71±11	71±11	0.38
Body mass index - kg/m^2	27±4	27±5	27±5	0.63
Peak VO2 - mL/min/kg	15.0±9.5	15.2±4.5	15.1±17.1	0.82
Electrocardiogram:				
AF/AFL - n (%)	63 (45)	8 (4)	71 (21)	<0.001
Heart rate - bpm	76±14	74±15	75±15	0.45
QRS duration - ms	163±31	164±28	164±30	0.76
Medication: - n (%)				
Beta-blocker	103 (74)	166 (83)	269 (80)	0.04
ACEi / ARB	130 (94)	180 (91)	310 (92)	0.31
Diuretic	128 (92)	182 (92)	310 (92)	0.84
Digoxin	36 (26)	25 (13)	61 (18)	0.002
Amiodarone	32 (23)	40 (20)	72 (21)	0.52
Statin	80 (58)	106 (53)	186 (55)	0.44
Nitrate	20 (14)	38 (19)	58 (17)	0.26
Oral anticoagulation	125 (90)	143 (72)	268 (79)	<0.001
Aspirin	27 (19)	52 (26)	79 (23)	0.15
Echocardiographic parameters:				
LA size, parasternal - mm	52±9	47±7	49±8	<0.001
LA size, length - mm	72±10	64±9	67±10	<0.001
LA size, width - mm	53±9	49±8	51±8	<0.001
LA volume index - mL/m^2	52±20	41±14	45±17	<0.001
RA size, length - mm	63±10	57±9	59±10	<0.001
RA size, width - mm	49±8	45±8	47±8	<0.001

AF was present in 139 patients (41%) during a mean follow-up of 27±19 months (inter-quartile range 13-37 months) (Table 1). New-onset AF developed in 40 of 193 patients (21%), which was persistent in 20 patients and paroxysmal in 20 patients (of whom 19 patients had an AF burden < 0.35%). Electrical cardioversion was conducted in 15 new-onset AF patients, and amiodarone was instituted in 12 patients. At end of follow-up, 30 of the 40 new-onset AF patients (75%) were in sinus rhythm: 13 of the 20 persistent AF patients (65%) and 17 of the 20 paroxysmal AF patients (85%).

AF patients more often had heart rates exceeding the upper rate of the device at moderate exercise than sinus rhythm patients (12% of AF patients versus 4% of sinus rhythm patients, p=0.02). In these patients beta-blockers were first increased to allow optimal biventricular pacing. In 10 patients (3%) it was necessary to perform atrioventricular node ablation. Distribution of AF burden during total follow-up is shown in Figure 1.

Response to CRT

Of the 302 patients in whom left ventricular end-systolic volumes could be assessed, 168 patients (56%) were responders to CRT at 6 months follow-up: 60 of 123 patients (43%) with AF during follow-up versus 108 of 179

Table 1. Baseline characteristics at implant (continued)

	AF during follow-up (n=139)	Sinus rhythm during follow-up (n=199)	Total population (n=338)	p-value
Septum - mm	10±2	9±2	9±2	0.49
Posterior wall - mm	9±2	9±2	9±2	0.03*
LV end-diastolic volume - mL	248±102	266±93	259±97	0.14
LV end-systolic volume - mL	192±85	209±78	202±81	0.09
LV ejection fraction - %	24±9	24±14	24±12	0.91
Mitral valve regurgitation - n (%)	43 (31)	48 (24)	91 (27)	0.17
Tricuspid valve regurgitation - n (%)	12 (9)	15 (8)	27 (8)	1.00
IVMD > 40 ms	39 (28)	75 (38)	114 (34)	0.10
Septal to lateral delay > 60 ms	38 (27)	84 (42)	122 (36)	0.054
PA-TDI interval - ms	159 (126-186)	139 (120-161)	140 (120-167)	0.007
Laboratory values:				
eGFR - mL/min/1.73 m²	59±22	62±21	61±22	0.17
ANP - pg/100 uL	100 (59-165)	83 (43-120)	88 (51-144)	0.03
NT-proBNP - ng/L	1855 (882-3245)	1145 (494-2642)	1399 (649-3014)	0.004

Data expressed as mean ± standard deviation or median (inter-quartile range), as required.

ACEi = angiotensin converting enzyme inhibitor; AF = atrial fibrillation; AFL = atrial flutter; ANP = atrial natriuretic peptide; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; IVMD = interventricular mechanical delay; LA = left atrial; LV = left ventricular; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association functional class; RA = right atrial; VO2 = aerobic capacity.

* 9.36±1.78 mm for AF during follow-up versus 8.95±1.57 mm for sinus rhythm during follow-up.

sinus rhythm patients (60%) (p=0.047). Nine of the ten patients (90%) who had undergone atrioventricular node ablation were responders. Independent predictors of response to CRT were lower baseline ANP levels and larger left ventricular end-systolic volume (Table 2). The *c*-statistic for ANP was 0.68. Neither presence of AF nor increasing AF burden were independent predictors of response.

A significant decrease in left atrial volume was observed at 6 months only in responders with sinus rhythm (40±13 mL/m² at baseline versus 34±11 mL/m² at 6 months, p=0.003) but not in responders with AF (51±18 mL/m² at baseline versus 48± 15 mL/m² at 6 months, p=0.08). Patients with AF during follow-up had higher baseline ANP levels than sinus rhythm patients (Table 1). Non-responders had higher baseline ANP levels than responders only in sinus rhythm patients, and ANP decreased at 6 months only in non-responders with AF during follow-up (Figure 2A). Baseline ANP was correlated with increased left atrial volume index ($r = 0.402$, $p<0.001$) and increased left ventricular end-systolic volume ($r = 0.219$, p=0.044) only in sinus rhythm patients. In patients with AF during follow-up, baseline ANP was correlated with increasing AF burden ($r = 0.409$, p=0.038), but not with left atrial or ventricular volumes. Baseline NT-proBNP levels overall were higher in patients with AF (Table 1). A decrease in NT-proBNP levels was only observed in responders with sinus rhythm (Figure 2B). Both in patients with and without AF, non-responders had higher follow-up NT-proBNP levels.

Of all patients who were in sinus rhythm during the first 6 months of follow-up, 21 of 82 non-responders (26%) developed AF during further follow-up as compared with 23 of 141 responders (16%) (p=0.09).

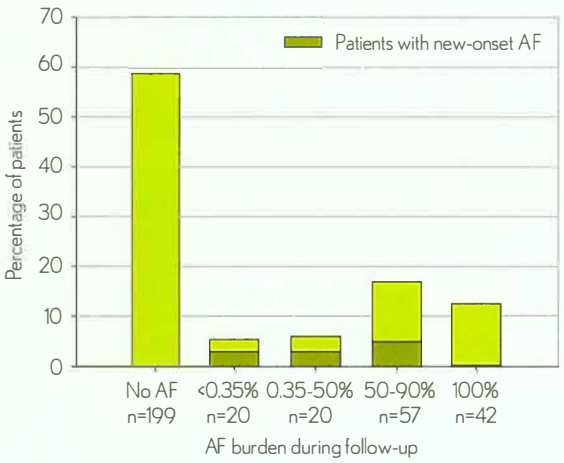

Figure 1. AF burden during total follow-up. The distribution of AF burden in new-onset AF patients is shown in dark green.

All-cause mortality

During follow-up, 90 patients (27%) died: 50 of 139 patients (36%) with versus 40 of 199 patients (20%) without AF during follow-up (log rank p=0.029). Two of the 10 patients (20%) who had undergone atrioventricular node ablation died during follow-up. Independent predictors of mortality were new-onset AF during the first 6 months, permanent AF (100% AF burden) during total follow-up, higher baseline NT-proBNP levels, ischaemic cardiomyopathy, and lower systolic blood pressure (Table 3). The *c*-statistic for NT-proBNP was 0.66.

DISCUSSION

We found that lower baseline ANP, but not the presence of AF or increasing AF burden, was an independent predictor of response to CRT. New-onset AF, permanent AF, and high baseline NT-proBNP were associated with increased all-cause mortality.

Table 2. Predictors of response to CRT

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Permanent AF in history	0.43 (0.22-0.85)	0.015		
Systolic blood pressure / 10 mmHg	1.21 (1.06-1.37)	0.003		
Diastolic blood pressure / 10 mmHg	1.24 (1.01-1.52)	0.038		
Beta-blocker	2.57 (1.42-4.67)	0.002		
LA size, length / 10 mm	0.77 (0.61-0.99)	0.038		
LA volume index / 10 mL/m^2	0.85 (0.72-0.997)	0.046		
LV end-diastolic volume / 50 mL	1.22 (1.06-1.40)	0.005		
LV end-systolic volume / 50 mL	1.34 (1.13-1.58)	0.001	1.40 (1.09-1.79)	0.009
Septal to lateral delay > 60 ms	1.71 (1.03-2.82)	0.037		
Log_2 ANP - pg/100 uL*	0.56 (0.41-0.76)	<0.001	0.49 (0.35-0.68)	<0.001
Log_2 NT-proBNP - ng/L*	0.96 (0.82-1.12)	0.96		

AF = atrial fibrillation; ANP = atrial natriuretic peptide; CI = confidence interval; LA = left atrial; LV = left ventricular.

* Biomarkers are log_2 transformed. E.g. an odds ratio of 0.49 of log_2 ANP implies that a doubling of any ANP value corresponds to an odds ratio of 0.49.

Prognostic value of ANP regarding response to CRT

The response rate to CRT of 56% in our study was similar to response rates seen in other CRT studies using the same definition.[21] Low baseline ANP predicted response. ANP is predominantly produced in the atria, but especially in heart failure the ventricles also contribute to ANP secretion. AF instead of sinus rhythm may further increase ANP levels in heart failure patients.[15] Low ANP may reflect a haemodynamic status still sensitive for reverse remodelling and thus for response to CRT. The role of ANP regarding response in CRT patients has barely been studied before. In two small studies response to CRT was associated with a decrease in ANP.[22,23] In one study, low baseline ANP was also a predictor of response.[23] It is unknown, however, whether these studies had included patients with AF, which is a relevant issue. We observed that baseline ANP was correlated with increasing left atrial volume and left

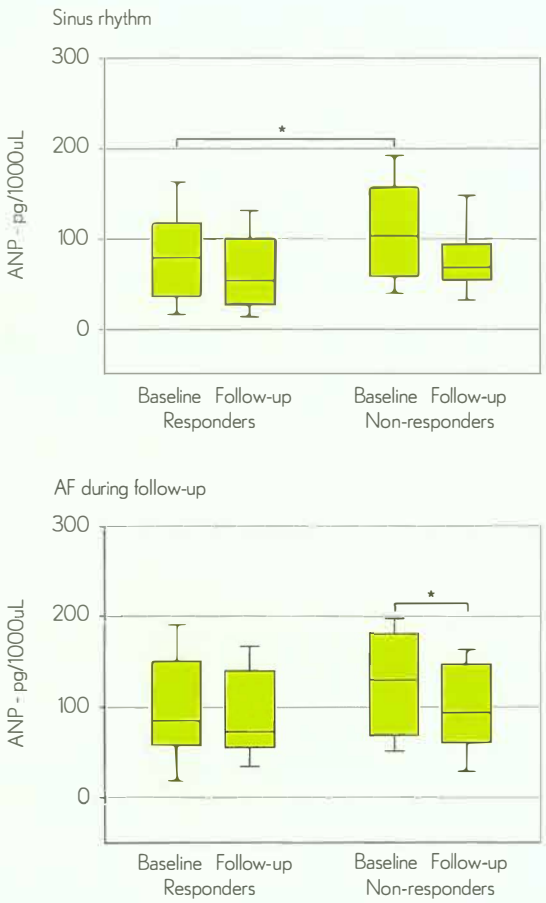

Figure 2A. ANP levels in responders and non-responders in patients with sinus rhythm and patients with AF during follow-up.

Follow-up = 6 months after implantation.

* $p < 0.05$.

ventricular end-systolic volume in sinus rhythm patients, while in patients with AF, ANP only correlated with increasing AF burden. Unlike the two previous studies, ANP did not decrease in responders, but it decreased in non-responders with AF during follow-up. This ANP decrease in AF patients may be explained by depleting ANP levels during longstanding AF which is seen after an acute surge of ANP levels at the start of AF.[24]

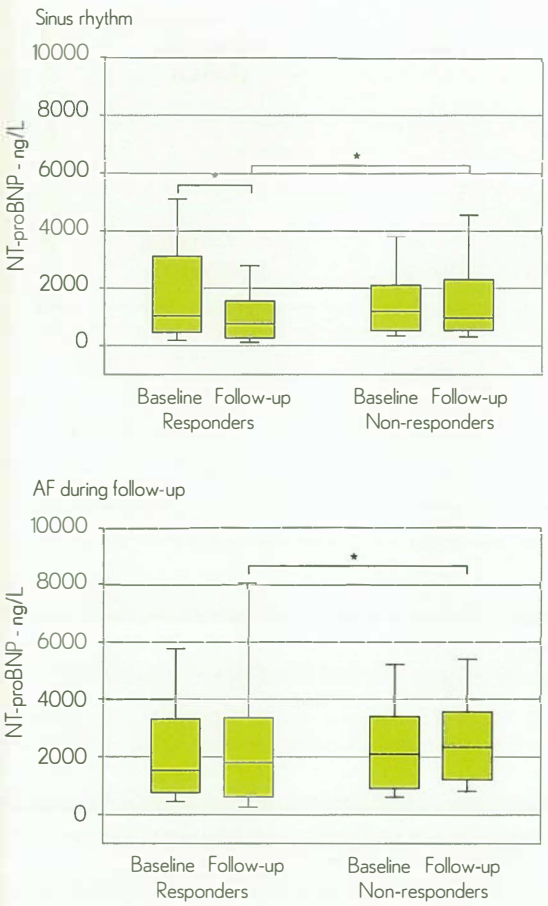

Figure 2B. NT-proBNP levels in responders and non-responders in patients with sinus rhythm and patients with AF during follow-up.

Follow-up = 6 months after implantation.

* $p < 0.05$.

Influence of AF on response to CRT

Previous results concerning the influence of AF on response are conflicting. Several studies have demonstrated comparable clinical response to CRT in sinus rhythm and permanent AF patients, in whom 100% and 15% of patients had undergone atrioventricular node ablation.[7,12] In other studies only permanent AF patients with atrioventricular node ablation showed similar clinical response to CRT as compared with sinus rhythm patients.[25,26] In contrast, more non-response has been observed among AF patients despite the fact that atrioventricular node ablation was present in 57% of patients.[9] In our study AF during the first 6 months was not an independent predictor of response even though a small number of patients underwent atrioventricular

Table 3. Predictors of all-cause mortality

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age / 10 years	1.24 (1.01-1.51)	0.038		
Male gender	1.74 (1.02-3.00)	0.044		
AF during follow-up	1.59 (1.05-2.41)	0.030		
New-onset AF	4.43 (2.12-9.27)	<0.001	8.11 (3.31-19.85)	<0.001
Permanent AF (100% AF burden)	2.34 (1.32-4.16)	0.004	3.19 (1.61-6.30)	0.001
Non-ischaemic cardiomyopathy	0.59 (0.38-0.89)	0.013	0.46 (0.26-0.81)	0.007
Systolic blood pressure / 10 mmHg	0.70 (0.61-0.79)	<0.001	0.77 (0.66-0.90)	0.001
Peak VO2 - mL/min/kg	0.91 (0.85-0.97)	0.002		
Beta-blocker	0.57 (0.36-0.90)	0.016		
Oral anticoagulation	2.13 (1.13-4.00)	0.019		
LA size, parasternal / 10 mm	1.40 (1.08-1.08)	0.011		
LA size, length / 10 mm	1.54 (1.25-1.89)	<0.001		
LA volume index / 10 mL/m^2	1.24 (1.11-1.39)	<0.001		
RA size, length / 10 mm	1.41 (1.15-1.74)	0.001		
Septum / 10 mm	0.31 (0.10-0.98)	0.047		
eGFR / 10 mL/min/1.73 m^2	0.85 (0.76-0.94)	0.003		
Log_2 ANP - pg/100 uL*	1.42 (1.11-1.81)	0.005		
Log_2 NT-proBNP - ng/L*	1.45 (1.24-1.70)	<0.001	1.27 (1.07-1.51)	0.006

AF = atrial fibrillation; ANP = atrial natriuretic peptide; CI = confidence interval; LA = left atrial; LV = left ventricular; eGFR = estimated glomerular filtration rate; LA = left atrial; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RA = right atrial.

* Biomarkers are log_2 transformed. E.g. a hazard ratio of 1.27 of log_2 NT-proBNP implies that a doubling of any NT-proBNP value corresponds to a hazard ratio of 1.27.

node ablation. This may in part be explained by the aggressive treatment of AF in our center,[27-29] as demonstrated by the large proportion of new-onset AF patients that were in sinus rhythm during follow-up. On the other hand, successful CRT may prevent or reduce AF, as we also observed a trend that responders less often developed AF during follow-up.

AF and mortality in CRT patients

Both new-onset AF and permanent AF predicted mortality in our study. It is still uncertain whether AF influences mortality in CRT patients. AF may increase mortality by further deterioration of heart failure and induction of ventricular arrhythmias.[30-32] In AF patients without heart failure, mortality is high in new-onset AF and in permanent AF.[33] In CRT studies AF during follow-up and permanent AF have been associated with adverse prognosis.[9,12,34] Other studies have demonstrated comparable survival between permanent AF and sinus rhythm patients,[10,35,36] though survival was better in case of atrioventricular node ablation.[10,36] Survival may have increased in our permanent AF patients if atrioventricular node ablation had been performed more often. On the other hand, the acceptance of AF may reflect the patients' overall condition, making permanent AF a marker of more advanced underlying disease instead of a direct cause of increased mortality.[37]

Although AF independently predicted mortality, it was not an independent predictor of response. This apparently discrepant finding might be explained by the difference in follow-up duration between response, defined at 6 months, and all-cause mortality, analyzed at [27] months. Six months may be too short for AF to influence response to CRT, which is supported by the observation that AF patients did not have a reduction in left atrial volume and ANP levels at 6 months despite the presence of response.

Limitations

This is an observational study which means that no randomization took place, it was not powered on mortality, and causality could not be determined. The compilation of the multivariate models of response and all-cause mortality may have been different with a larger sample size. Response to CRT may have differed if atrioventricular node ablation had been performed in more AF patients. Some patients may have been diagnosed with new-onset AF due to the monitoring capacities of the device while they could have had unrecognized AF before implantation. AF during follow-up was defined as AF being present anytime during the total follow-up period, which means that some patients did not have AF during the first six months. Natriuretic peptide levels may fluctuate according to the presence of AF. This means that the value of

natriuretic peptide levels determined at 6 months and changes in these levels between baseline and 6-months in the context of "AF during follow-up" should be interpreted with caution as there may have been an interaction with the presence or absence of AF. The study population is relatively large and the follow-up duration is substantial, and we deliberately chose all-cause mortality as one of the outcome parameters because it is a hard endpoint. Our study bears an important message, but the non-randomized observational design precludes definite conclusions. Our study generates new hypotheses, namely that ANP may be used in the selection of candidates for CRT and that early detection and treatment of new-onset AF may improve outcome in CRT, which should be investigated in future studies.

Conclusion

In patients treated with CRT, lower ANP and larger left ventricular end-systolic volume, but not the presence of AF or increasing AF burden, were independent predictors of response. However, new-onset AF, permanent AF, and higher baseline NT-proBNP were associated with increased all-cause mortality.

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CONFLICT OF INTEREST

Dr. Van Veldhuisen reports receiving consulting fees from Medtronic and Biotronik, and lecture fees from Medtronic. Dr. Van Gelder reports receiving grant support from Medtronic, Biotronik, and St. Jude Medical, and lecture fees from Medtronic. No other potential conflict of interest relevant to this article was reported.

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6 THE IMPORTANCE OF WHETHER ATRIAL FIBRILLATION OR HEART FAILURE DEVELOPS FIRST REGARDING OUTCOME

Marcelle D Smit, Alexander H Maass, Marjolein L Moes, Ismaël D Achekar, Dirk J Van Veldhuisen, Isabelle C Van Gelder.

Submitted

ABSTRACT

Objectives

We assessed the prognosis of atrial fibrillation (AF) patients hospitalized for heart failure based on the time course of AF and heart failure development.

Background

AF and heart failure often co-exist. It is unknown whether the sequence in which AF and heart failure develop is of significance regarding prognosis.

Methods

Consecutive AF patients hospitalized for heart failure were included. Patients who had developed AF before or at the same time as heart failure ("AF first") were compared with patients who had developed heart failure before AF ("heart failure first"). Primary endpoint was a composite of cardiovascular hospitalization or all-cause mortality.

Results

More patients with AF first than with heart failure first were hospitalized for AF and heart failure (137 of 182 patients, 75%, versus 45 of 182 patients, 25%). The two groups were similar regarding age and gender, but patients with AF first less often had coronary artery disease and had higher ejection fractions than patients with heart failure first (39±14% versus 32±13%, p=0.004). During 16±11 months follow-up, the primary composite endpoint occurred less often in patients with AF first than in patients with heart failure first (49.6% versus 77.7% of patients, p=0.001). Development of AF first remained beneficial regarding the primary endpoint on multivariable analysis (adjusted hazard ratio 0.49, 95% confidence interval 0.29-0.82, p=0.007).

Conclusions

The majority of patients hospitalized for AF and heart failure consisted of patients who had developed AF first. Prognosis in these patients was relatively benign as compared to those who had developed heart failure first.

INTRODUCTION

Atrial fibrillation (AF) and heart failure often coexist in a reciprocal relationship, the incidence of AF increasing with the severity of heart failure.[1] AF has been associated with increased mortality in heart failure, though the impact of AF on outcome seems to be less important in severe heart failure than in mild to moderate heart failure.[2-6] Furthermore, it is still uncertain whether AF is an independent contributor to an impaired outcome in heart failure or whether it is merely a marker of severe disease. Patients hospitalized for heart failure constitute a distinct patient category as hospitalization occurs frequently in more advanced stages of the disease and may precede adverse outcome in terms of readmission and death.[7] AF is present in up to one third of patients hospitalized for heart failure, and especially new-onset AF seems to indicate increased mortality risk in these patients.[8-10] However, the time course in which AF and heart failure develop may be a more important marker regarding clinical presentation and prognosis than merely new onset-AF itself. The temporal relation between AF and heart failure development has been shown to be of prognostic value in a general heart failure population,[11] but it is unknown whether this also pertains for patients hospitalized for heart failure. We therefore assessed the prognosis of AF patients hospitalized for heart failure based on the time course of AF and heart failure development.

METHODS

Study population and definitions

This was a prospective observational study performed in the University Medical Center Groningen between September 2007 and September 2010. Consecutive patients with persistent or permanent AF hospitalized for heart failure were included. Heart failure hospitalization was defined as heart failure necessitating hospitalization and the start of or increase in dose of diuretics.[12] Persistent AF was defined as an AF episode lasting longer than seven days or requiring termination by cardioversion.[13,14] Permanent AF was defined as accepted persistent AF, i.e. rhythm control interventions were no longer pursued.[13,14]

Patients who had developed AF first were compared with patients who had developed heart failure first. "AF first" was defined as persistent AF developing before or at the same time as heart failure. "Heart failure first" was defined as persistent AF developing (at least two weeks) after heart failure. The chronological sequence of development of persistent AF and heart failure was based on the difference between the date of onset of persistent AF (total persistent AF history) and the date of onset of heart failure (total heart failure history). The onset date of persistent AF was assigned to the date when persistent AF was first documented by electrocardiogram, taking signs and symptoms of AF into consideration. If there were no (new or worsening of) signs and symptoms attributable to AF, then the middle of the date of the last electrocardiographic registration of sinus rhythm and first electrocardiographic registration of per-

sistent AF was used as date of onset of AF. If there was no previous registration of sinus rhythm in the absence of signs and symptoms of AF, then January 1 of the calendar year of the first electrocardiographic registration of persistent AF was used as date of onset of persistent AF. The onset date of heart failure was assigned to the date when heart failure was first documented, i.e. a heart failure hospitalization or left ventricular ejection fraction < 40%, taking signs and symptoms of heart failure into consideration. In case of left ventricular ejection fraction < 40% and no (new or worsening of) signs and symptoms attributable to heart failure, then the middle of the date of the last documentation of normal left ventricular function and first documentation of left ventricular ejection fraction < 40% was used as date of onset of heart failure. If there was no previous documentation of left ventricular function in the absence of signs and symptoms, then January 1 of the calendar year of first detection of left ventricular ejection fraction < 40% was used as date of onset of heart failure. If hospitalization was the first presentation of heart failure, then the date of the first heart failure hospitalization was used as onset date of heart failure.

Study protocol

At enrolment, a detailed clinical history was obtained in all patients including AF, heart failure, hypertension, coronary artery disease, valvular disease, congenital heart disease, and co-morbid conditions such as diabetes and chronic obstructive pulmonary disease. Symptoms, physical examination, electrocardiogram, and laboratory values (renal function and N-terminal pro-B-type natriuretic peptide (NT-proBNP)) were determined at admission. During admission, the acute precipitating factor leading to the heart failure hospitalization was assessed. Cardiac precipitating factors included acute coronary syndrome, acute progression of valve dysfunction, and endocarditis. Non-cardiac precipitating factors included exacerbations of chronic obstructive pulmonary disease, pneumonia, and other acute infections. If no acute precipitating factor could be found or if the hospitalization was likely a consequence of heart failure progression, then the precipitating factor was classified as unknown/ progression of heart failure. AF was not defined as a precipitating factor because of uncertainty of AF as cause or consequence of acute decompensation. Transthoracic echocardiography was conducted in a stable phase, before or early after discharge. Medication at admission and at discharge was recorded. The medical management of heart failure during and after discharge was left at the discretion of the attending cardiologist.[7] Regarding AF treatment, oral anticoagulation was prescribed as indicated,[13] and rate control therapy was instituted aiming at a resting heart rate below 100 beats per minute.[15] Rhythm control was performed in case of complaints and/ or in case of deterioration of left ventricular function due to AF.

Endpoints and follow-up | METHODS

Primary endpoint of this study was a composite of cardiovascular hospitalization or all-cause mortality. Secondary endpoints were (1) a composite of heart failure hospitalization or all-cause mortality, and (2) all-cause mortality. Cardiovascular hospitalizations and mortality were prospectively documented during follow-up. Cardiovascular hospitalizations were defined as unplanned hospitalizations for cardiac reasons including heart failure, acute coronary syndrome, syncope, sustained ventricular arrhythmias, (in)appropriate implantable cardioverter-defibrillator shocks, AF, stroke, systemic embolisms, and bleeding due to vitamin K antagonist use. Duration of follow-up was computed from the time of the heart failure hospitalization at which patients were included until death or until the date when the last follow-up data were obtained, accordingly.

Statistical analysis | METHODS

Baseline descriptive statistics are presented as mean ± standard deviation or median (inter-quartile range) for continuous variables and numbers with percentages for categorical variables, as required. We evaluated differences between the two groups using Chi-square test and Fisher's exact test for categorical data, and Student's *t* test and Mann Whitney-U test for continuous data, dependent on whether data were normally distributed. Cumulative event proportions were calculated using Kaplan-Meier analysis. The log-rank test was used to compare groups. Cox proportional hazards regression analysis was conducted to evaluate predictors of the primary endpoint. Univariate Cox proportional hazards regression analysis was performed on all baseline variables shown in Table 1 and on medication at discharge. Stepwise multivariable hazards regression analysis was conducted using all variables with $p<0.1$ in univariate analysis. The final multivariate model included all variables with $p<0.05$. Analyses were performed with STATA 11.0 for Windows. In all statistical analyses $p<0.05$ was considered statistically significant.

Baseline characteristics | RESULTS

A total of 182 consecutive patients were included: 137 patients (75.3%) with AF first, and 45 patients (24.7%) with heart failure first (Table 1). The two groups were similar regarding age and gender. In contrast, patients with AF first had a borderline significantly longer history of persistent AF (median 21.0 versus 5.9 months, $p=0.05$) and a shorter history of heart failure (median 0.5 versus 79.6 months, $p<0.001$). Furthermore, they almost half as often had a previous admission for heart failure, more often had heart failure with preserved ejection fraction, less often had coronary artery disease, a shorter QRS duration, and a better renal function than patients with heart failure first

Table 1. Baseline characteristics

	AF first (n=137)	Heart failure first (n=45)	p-value
Age - mean±SD - years	74±11	72±9	0.30
Male sex - no. (%)	73 (53.3)	27 (60.0)	0.43
AF characteristics:			
Total AF history - median (IQR) - months	38.3 (2.0-108.9)	15.7 (1.2-69.0)	0.12
Total persistent AF history - median (IQR) - months	21.0 (1.7-84.3)	5.9 (0.4-58.3)	0.05
First detected AF - no. (%)	51 (37.2)	13 (28.9)	0.31
Current type AF: - no. (%)			0.67
Persistent AF	84 (61.3)	26 (57.8)	
Permanent AF	53 (38.7)	19 (42.2)	
Heart failure characteristics:			
Total heart failure history - median (IQR) - months	0.5 (0-21.0)	79.6 (22.7-121.6)	<0.001
Previous admission for heart failure - no. (%)	48 (35.0)	31 (68.9)	<0.001
Heart failure with preserved ejection fraction - no. (%)	55 (40.2)	5 (11.1)	<0.001
Precipitating factor of heart failure hospitalization: - no. (%)			
Unknown/ progression of heart failure	92 (67.2)	37 (82.2)	0.05
Acute precipitating factor:	45 (32.9)	8 (17.8)	
Cardiac precipitating factor	21 (15.3)	3 (6.7)	0.14
Non-cardiac precipitating factor	24 (17.5)	5 (11.1)	
$CHADS_2$ score - mean±SD	3±1	3±1	0.39
Hypertension - no. (%)	115 (83.9)	41 (91.1)	0.23
Coronary artery disease: - no. (%)	53 (43.1)	29 (64.4)	0.01
Previous myocardial infarction	26 (19.0)	23 (51.1)	<0.001
Valve dysfunction - no. (%)	76 (58.9)	31 (68.9)	0.24
Valve surgery - no. (%)	20 (14.6)	6 (13.3)	0.83
Other medical history:			
Diabetes mellitus - no. (%)	37 (27.0)	16 (35.6)	0.27
Hypercholesterolemia - no. (%)	50 (36.5)	17 (37.8)	0.88
Smoking: - no. (%)			0.02
Previous smoking	43 (34.7)	21 (51.2)	
Present smoking	14 (11.3)	8 (19.5)	
Chronic obstructive pulmonary disease - no. (%)	32 (23.4)	9 (20.0)	0.64
History of transient ischemic attack/ stroke - no. (%)	25 (18.3)	5 (11.1)	0.26
History of thyroid disease: - no. (%)			0.69
Hypothyroidism	15 (11.0)	3 (6.7)	
Hyperthyroidism	10 (7.3)	3 (6.7)	
Previous bleeding due to anti-coagulants - no. (%)	5 (3.7)	1 (2.2)	0.64
Symptoms at presentation:			
NYHA class: - no. (%)			0.88
I	4 (3.0)	2 (4.8)	
II	37 (28.0)	11 (26.2)	
III	56 (42.4)	16 (38.1)	
IV	35 (26.5)	13 (31.0)	
AF EHRA class: - no. (%)			0.73
I	31 (36.9)	11 (45.8)	
II	35 (41.7)	8 (33.3)	
III	16 (19.1)	5 (20.8)	
IV	2 (2.4)	-	

(Table 1). Patients with AF first borderline significantly more often had an acute precipitating factor leading to the hospitalization. At discharge, patients with AF first less frequently received angiotensin converting enzyme-inhibitors or angiotensin receptor blockers, diuretics, and statins (Table 2). There were no significant differences regarding AF therapy: rhythm control was attempted in 26 patients (19.0%) with AF first and in 7 patients (15.6%) with heart failure first (p=0.61). Four patients of the AF first and one of the heart failure first patients converted to sinus rhythm during hospitalization after start of heart failure treatment.

Follow-up

During a mean follow-up of 16±11 months, the primary composite endpoint of cardiovascular hospitalization or all-cause mortality occurred in 103 patients (56.6%); less frequent in patients with AF first (68 patients, 49.6%) than in patients with heart failure first (35 patients, 77.7%, p=0.001) (Figure 1). The secondary endpoints also occurred less often in patients with AF first (Figures 2 and 3). Cardiovascular hospitalizations in patients with AF first included heart failure (n=29, 21.2%), acute coronary syndrome (n=2, 1.5%), collapse or bradycardia (n=3, 2.2%), ventricular arrhythmias (n=1, 0.7%),

Table 1. Baseline characteristics (continued)

	AF first (n=137)	Heart failure first (n=45)	p-value
Physical examination:			
Body mass index - mean±SD - kg/m²	29±6	29±5	0.97
Systolic blood pressure - mean±SD - mmHg	134±26	126±29	0.13
Diastolic blood pressure - mean±SD - mmHg	78±17	73±19	0.08
Electrocardiogram at presentation:			
Heart rate - mean±SD - bpm	109±31	102±29	0.23
QRS duration - mean±SD - ms	112±30	127±29	0.004
QTc duration - mean±SD - ms	483±42	490±50	0.37
Laboratory values:			
eGFR - mean±SD - mL/min/1.73 m²	66±27	57±26	0.05
NT-proBNP - median (IQR) - ng/L	4221 (2222-6327)	6982 (3226-10981)	0.04
Echocardiogram:			
LA size, parasternal - mean±SD - mm	48±8	50±9	0.19
Indexed - mean±SD - mm/m²	25±4	26±6	0.16
LV end diastolic diameter - mean±SD - mm	52±9	57±10	0.002
Indexed - mean±SD - mm/m²	27±4	30±4	0.001
LV end systolic diameter - mean±SD - mm	41±11	46±11	0.002
Indexed - mean±SD - mm/m²	21±5	24±5	0.003
LV ejection fraction - mean±SD - %	39±14	32±13	0.004

AF = atrial fibrillation; AFL = atrial flutter; eGFR = estimated glomerular filtration rate; EHRA = European Heart Rhythm Association; IQR = inter-quartile range; LA = left atrial; LV = left ventricular; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; SD = standard deviation.

inappropriate implantable cardioverter-defibrillator shocks (n=1, 0.7%), AF (n=3, 2.2%), systemic embolism (n=2, 1.5%), bleeding (n=2, 1.5%), and dehydration with electrolyte disturbances (n=2, 1.5%). Cardiovascular hospitalizations in heart failure first patients consisted of heart failure (n=20, 44.4%), acute coronary syndrome (n=3, 6.7%), ventricular arrhythmias (n=2, 4.4%), and inappropriate implantable cardioverter-defibrillator shocks (n=2, 4.4%). At end of follow-up, 104 AF first patients (75.9%) and 35 heart failure first patients (77.8%) were in AF (p=0.80).

Predictors of cardiovascular hospitalization or all-cause mortality

Development of AF first was independently associated with a lower risk on the primary endpoint of cardiovascular hospitalization or all-cause mortality (adjusted hazard ratio 0.49, 95% confidence interval 0.29-0.82, p=0.007) (Table 3). Other independent predictors of the primary endpoint were previous admission for heart failure and higher baseline NT-proBNP value. Angiotensin converting enzyme-inhibitor or angiotensin receptor blocker use at discharge was independently associated with a decreased risk on the primary endpoint (Table 3). Bootstrap analysis demonstrated comparable results (data not shown). First-detected AF was only univariately associated with a decreased risk on the primary endpoint. Rhythm control as primary treatment approach for AF was not associated with the primary endpoint (unadjusted hazard ratio 1.02, 95% confidence interval 0.60-1.73, p=0.93).

DISCUSSION

The majority of patients hospitalized for AF and heart failure consisted of patients who had developed AF first. Prognosis in these patients was relatively benign as compared to those who had developed heart failure first.

Diagnostic and prognostic value of the chronological sequence of AF and heart failure development

In our study, 75% of consecutive AF patients hospitalized with heart failure consisted of patients who had developed AF before or at the same time as heart failure. Similarly, population studies observed that between 59% and 76% of AF and heart failure patients develop AF before or simultaneously with heart failure.[11,16] Patients with AF first had a more advantageous clinical profile and less deleterious outcome than patients with heart failure first. The pathophysiological processes leading to heart failure may have been different between both groups, being less advanced in AF first patients, which may have contributed to their more favorable outcome. In AF first patients,

Table 2. Medication at presentation and at discharge

Medication – no. (%)	At presentation			At discharge		
	AF first (n=137)	Heart failure first (n=45)	p-value	AF first (n=137)	Heart failure first (n=45)	p-value
Beta-blocker	86 (62.8)	35 (778)	0.06	108 (78.8)	38 (84.4)	0.41
ACE-inhibitor/ ARB	74 (54.0)	38 (84.4)	<0.001	92 (67.2)	38 (84.4)	0.03
Aldosterone receptor antagonist	22 (16.1)	14 (31.1)	0.03	54 (39.4)	22 (48.9)	0.26
Diuretic	89 (65.0)	34 (75.6)	0.19	110 (80.3)	42 (93.3)	0.04
Verapamil/ diltiazem	15 (11.0)	3 (6.7)	0.40	12 (8.8)	2 (4.4)	0.35
Dihydropyridine calcium channel blocker	13 (9.5)	1 (2.2)	0.11	4 (2.9)	1 (2.2)	0.80
Digitalis	11 (8.0)	4 (8.9)	0.86	33 (24.1)	9 (20.0)	0.57
Class III antiarrhythmic drug	11 (8.0)	10 (22.2)	0.01	17 (12.4)	9 (20.0)	0.21
Vitamin K antagonist	96 (70.1)	36 (80.0)	0.20	129 (94.2)	43 (95.6)	0.72
Platelet aggregation inhibitor	30 (21.9)	14 (31.1)	0.21	42 (30.7)	16 (35.6)	0.54
Statin	46 (33.6)	26 (57.8)	0.004	49 (35.8)	28 (62.2)	0.002
Nitrate	18 (13.1)	6 (13.3)	0.97	15 (11.0)	4 (8.9)	0.70

ACE = angiotensin converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker.

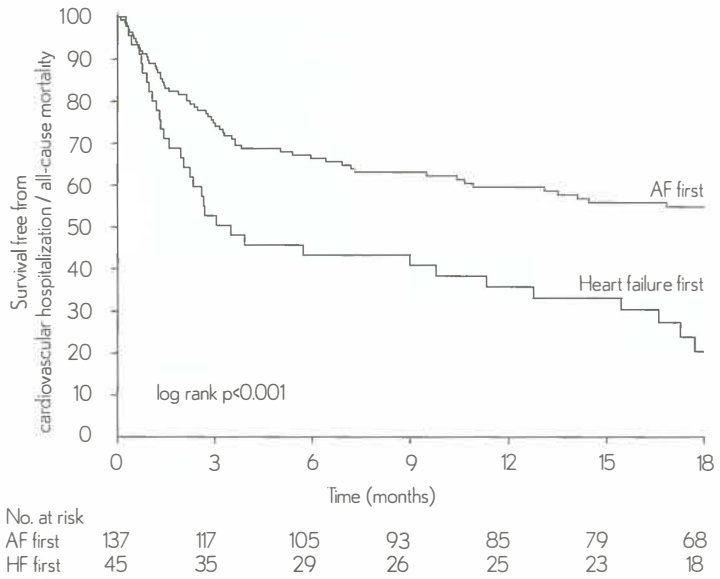

Figure 1. Kaplan-Meier estimates of cardiovascular hospitalization / all-cause mortality.
AF = atrial fibrillation; HF = heart failure.

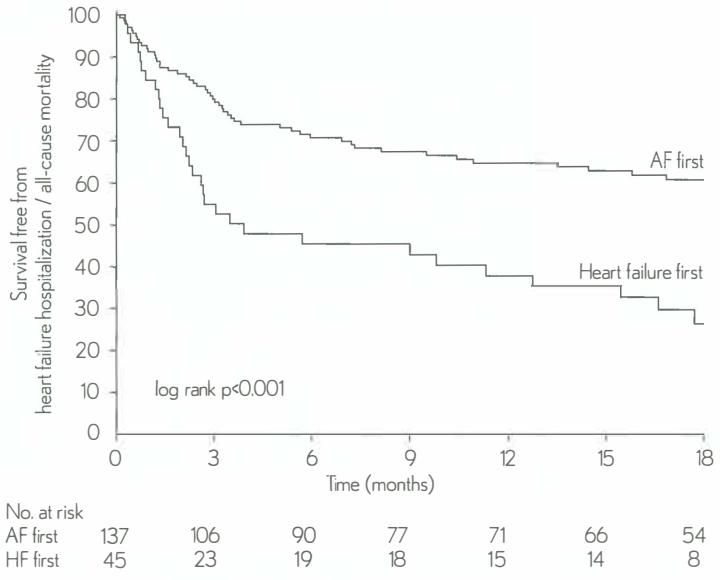

Figure 2. Kaplan-Meier estimates of heart failure hospitalization / all-cause mortality.
AF = atrial fibrillation; HF = heart failure.

AF itself may cause or aggravate heart failure through functional changes, i.e. an irregular and rapid rhythm, loss of atrioventricular synchrony, and loss of atrial transport; and structural changes, i.e. gradual cellular and extracellular matrix remodeling in atria and ventricles.[17-20] In case of functional changes dominating this process, ventricular dysfunction may be reversible. Indeed, heart failure developing at the same time as AF may be even more benign than heart failure developing after AF, for instance in case of a reversible tachycardia-induced cardiomyopathy.[21] Furthermore, the higher ejection fractions and more frequent presence of heart failure with preserved ejection fraction insinuate that AF first patients predominantly had diastolic heart failure.[7] The onset of AF and the consequent loss of atrial transport may be an important trigger to functionally decompensate in case of impaired diastolic filling. However, though diastolic heart failure is a pathophysiological different entity from systolic heart failure, outcome has been shown to be similar in AF patients.[6]

In heart failure first patients, severe structural remodeling may predominate above functional changes. These patients were the "sickest", having a longer heart failure history. Interestingly, they more often had coronary artery disease as associated disease and more often had previous myocardial infarctions. Intriguingly, in these heart failure first patients AF occurred late during the course of the disease.

In line with the above, an acute non-cardiac precipitating cause of the heart failure hospitalization was (borderline significantly) more often present in AF first patients. This could imply that heart failure was, at least in part, revers-

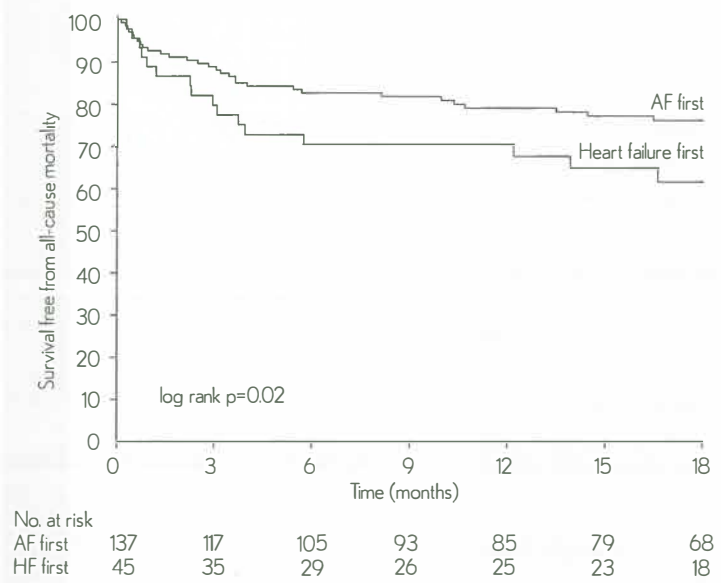

Figure 3. Kaplan-Meier estimates of all-cause mortality.
AF = atrial fibrillation; HF = heart failure.

ible after treatment of the precipitating cause. In contrast, the absence of an acute precipitating factor could imply that hospitalizations were often a consequence of progression of the disease in heart failure first patients. Accordingly, the development of AF in patients with a long heart failure history could predominantly be a marker of progression of the underlying disease.[11,22-24]

On the whole, our results demonstrate that two distinct clinical conditions can be recognized when the chronological sequence of AF and heart failure development is used to describe AF patients hospitalized for heart failure. These conditions could basically be described as "AF patients" who develop heart failure versus "heart failure patients" who develop AF. "AF patients" with heart failure seem to have less extensive underlying disease and, consequently, a relatively benign outcome, while "heart failure patients" who develop AF constitute a patient population with more severe underlying disease and increased baseline risk on deleterious outcome. The classification of AF and heart failure patients into these two conditions seems to reveal that AF is a marker of deleterious outcome particularly in patients with a known history

Table 3. Predictors of the primary endpoint of cardiovascular hospitalization or all-cause mortality

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
AF first	0.46 (0.31-0.70)	<0.0001	0.49 (0.29-0.82)	0.007
Log_2 total AF history	1.06 (1.01-1.11)	0.01		
First detected AF	0.56 (0.36-0.87)	0.01		
Log_2 heart failure history	1.04 (1.01-1.08)	0.009		
Previous admission for heart failure	2.01 (1.35-2.97)	0.001	1.99 (1.23-3.23)	0.005
Age	1.02 (1.00-1.04)	0.03		
Systolic blood pressure	0.99 (0.98-0.998)	0.02		
Diastolic blood pressure	0.99 (0.97-0.997)	0.02		
eGFR	0.99 (0.98-0.997)	0.006		
Log_2 NT-proBNP	1.32 (1.11-1.56)	0.001	1.28 (1.07-1.53)	0.006
Beta-blocker at discharge	0.66 (0.42-1.06)	0.08		
ACE-inhibitor/ ARB at discharge	0.62 (0.41-0.93)	0.02	0.45 (0.27-0.74)	0.002
Diuretic at discharge	1.88 (1.02-3.46)	0.04		
Class III antiarrhythmic drug at discharge	1.67 (1.02-2.73)	0.04		
Nitrate at discharge	1.96 (1.17-3.41)	0.01		

AF = atrial fibrillation; CI = confidence interval; eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

of heart failure. Furthermore, this classification may have therapeutic implications. For example, rhythm control may be more beneficial in AF first patients than in heart failure first patients.[25]

Previous studies concerning implications of AF in heart failure

The influence of AF in heart failure patients on prognosis has often been investigated with varying results depending on the patient categories studied.[2,4,5,22-24,26,27] It is still uncertain whether AF is an independent contributor to an impaired outcome in heart failure or whether it is merely a marker of severe disease. The sequence in which AF and heart failure develop at least seems to reveal two different clinical conditions regarding prognosis. To our knowledge, only Wang et al. have studied the influence of the sequence of AF and heart failure development on prognosis, which they had investigated in the Framingham population.[11] They found that preexisting heart failure adversely affected survival in patients with AF, i.e. development of new AF in patients with heart failure was associated with increased mortality, which is comparable with our study. On the other hand, preexisting AF was not associated with adverse survival in heart failure patients.[11] In contrast, in our study AF first patients certainly did not have an event-free outcome. These discrepancies may be caused by the different patient populations and by the heart failure definitions used. In the Framingham study, the definition of heart failure was based on signs and symptoms which perhaps could have been attributable to AF itself.[11] Our study population consisted of patients in whom heart failure had required hospitalization, which implies that our patients already had an increased baseline risk on re-hospitalization or mortality.[7]

Strengths and limitations

An important strength of this study consists of the rather innovative classification of AF patients hospitalized for heart failure, which, as we demonstrated, sheds light on the prognosis of these patients. Furthermore, the study population was taken from clinical practice and consecutive patients were included. Though this was an observational study, it was not powered on the primary endpoint of cardiovascular hospitalization and all-cause mortality. Follow-up was quite short, but the primary endpoint occurred in a substantial number of patients. Determination of the chronological sequence of AF and heart failure development was in part determined retrospectively. Conclusions concerning causality should therefore be interpreted with caution. Furthermore, we did not include patients in sinus rhythm, implying that our conclusions are only relevant for AF patients hospitalized with heart failure.

Conclusion

In AF patients hospitalized for heart failure, two distinct clinical conditions can be recognized based on the chronological sequence of AF and heart failure development: patients who develop AF first have a relatively benign prognosis as compared to those who develop heart failure first.

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7 UPSTREAM THERAPY OF ATRIAL FIBRILLATION

Marcelle D Smit, Isabelle C Van Gelder.

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SUMMARY

Failure of current pharmacological therapy for atrial fibrillation in maintaining sinus rhythm may be due to structural atrial remodeling caused by inflammation and fibrosis. Upstream therapy that interferes in the structural remodeling process may be effective in maintaining sinus rhythm. This study reviews upstream therapy in atrial fibrillation. Various prospective and retrospective studies demonstrate that upstream therapy consisting of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins, fish oils, glucocorticoids, or moderate physical activity, is associated with a reduced incidence of new-onset atrial fibrillation (i.e. primary prevention) and with a reduced recurrence of atrial fibrillation (i.e. secondary prevention). Larger clinical trials are required to further elucidate the position of upstream therapy in the primary and secondary prevention of atrial fibrillation.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia. It is a growing epidemic, being responsible for substantial economic costs, morbidity, and mortality. Restoration and long-term maintenance of sinus rhythm, i.e. rhythm control, is challenging,[1] even with amiodarone.[2] Moreover, no survival benefit over acceptance of AF in combination with rate control has been shown.[3-5] For patients with symptomatic AF, however, rhythm control remains therapy of choice. In addition, though underlying heart disease may be a more important determinant of prognosis than rhythm control,[6] results of the rate versus rhythm control trials may have been influenced by failure of current pharmacological means to maintain sinus rhythm.

One reason why pharmacological therapy has failed to maintain sinus rhythm may be that currently available ion-channel antiarrhythmic drugs mainly affect electrical remodeling, and do not influence the substrate for AF in terms of structural remodeling. Important substrates for structural remodeling are inflammation and fibrosis, which already commence before the onset of AF due to underlying disease states such as hypertension, heart failure, or coronary artery disease (Figure 1).[7-10]

Once AF is present, the remodeling processes in the atria progress further to constitute a vicious circle.[11,12] This causes a gradual worsening of AF in time, which makes it challenging to maintain patients in sinus rhythm in the long term. Current pharmacological therapy is initiated too late during the course of the disease, i.e. after development of AF when structural remodeling is already present, which may be another explanation why rhythm control often fails.[13] Moreover, many physicians are reluctant to prescribe ion-channel antiarrhythmic drugs due to their many, sometimes hazardous, side-effects,[2] which delays the institution of these drugs even further.

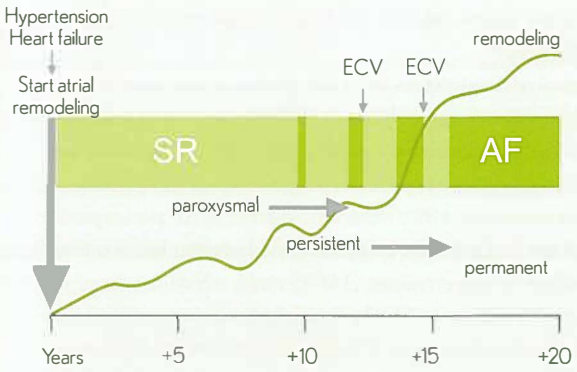

Figure 1. Time course of atrial substrate remodeling (adapted with permission from ref.[13]): hypothetical representation of how underlying disease such as hypertension or heart failure induces atrial remodeling long before the onset of AF and of how atrial remodeling progresses in relation to the clinical appearance of AF.

AF = atrial fibrillation; ECV = electrical cardioversion; SR = sinus rhythm.

Therapies that interfere early in the structural remodeling process, i.e. "upstream therapy" or non-channel antiarrhythmic drugs, are upcoming in the treatment of AF.[14] These therapies may be more effective in maintaining sinus rhythm beside having a more favorable side-effect profile. This article aims to review the current knowledge concerning upstream therapy of AF, including renin-angiotensin-aldosterone system modulators, statins, fish oils, glucocorticoids, and lifestyle changes including moderate physical activity.

RAAS BLOCKERS

One of the mechanisms involved in AF is the renin-angiotensin-aldosterone system (RAAS). The activity of RAAS is pronounced in AF,[15] which causes increased levels of angiotensin II and/or aldosterone, which have been shown to promote fibrosis and to induce cardiac hypertrophy.[16-18] Blockade of RAAS through angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone receptor antagonists (ARAs) may therefore potentially reverse atrial remodeling which consequently may reduce the initiation and perpetuation of AF.

ACE inhibitors and ARBs

There is growing experimental evidence that RAAS blockade with ACE inhibitors and ARBs may reduce AF. In a dog model of congestive heart failure caused by tachypacing,[19] atrial angiotensin II concentrations increased, and more atrial fibrous tissue was found which was paralleled by increased heterogeneity of atrial conduction. Concomitant institution of the ACE inhibitor enalapril significantly reduced atrial angiotensin II concentrations and attenuated the heart failure induced effects on atrial fibrosis and atrial conduction. In another study, rats infused with angiotensin II had higher levels of collagen synthesis and increased atrial fibrosis, which was reduced by the simultaneous institution of the ARB losartan.[17] These effects may consequently reduce AF: in a canine heart failure model induced by rapid ventricular pacing, enalapril not only attenuated heart failure induced atrial fibrosis and remodeling, as it also decreased AF duration.[20]

The potential role of ACE inhibitors and ARBs in the prevention of AF has also been investigated in clinical studies (Table 1).[21] In the primary prevention of AF various patient categories have been studied, especially in hypertension and in heart failure. In a large retrospective study of hypertensive patients, ACE inhibitor use was associated with a reduced incidence of AF as compared with calcium blocker use.[22] A post-hoc analysis of the Losartan Intervention for End Point Reduction in Hypertension (LIFE) study, which consisted of hypertensive patients and patients with electrocardiogram-documented left ventricular hypertrophy, the authors found that treatment with the ARB losartan reduced the incidence of new-onset AF as compared with atenolol (3.5%

of losartan- versus 5.3% of atenolol-treated patients, p<0.001), and time to onset of AF tended to be longer in patients treated with losartan. These observations were present despite similar blood pressure reduction in losartan- and atenolol-treated patients.[23] Preventive effects of valsartan therapy on new-onset AF in hypertensive patients were seen in a post-hoc analysis of the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) study.[24] Decreased development of AF has also been demonstrated in post-hoc analyses concerning patients with heart failure. A retrospective analysis of 374 patients from the Studies of Left Ventricular Dysfunction (SOLVD) trial showed that, 5.4% of patients in the enalapril group developed new-onset AF, compared with 24% of patients in the placebo group (p<0.0001).[25] The ARB candesartan was studied in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program concerning patients with symptomatic chronic heart failure. A prespecified secondary analysis demonstrated that new-onset AF developed in 5.55% of the candesartan group versus 6.74% of the placebo group, which was statistically significant, bearing in mind that this reduction was small.[26] Valsartan was associated with reduced AF in another retrospective analysis of the Valsartan Heart Failure Trial (Val-HeFT) concerning heart failure patients.[27] In post-myocardial infarction patients, ACE inhibitor use has been associated with decreased development of new AF. A post-hoc analysis of the TRAndolapril Cardiac Evaluation (TRACE) study of patients with reduced left ventricular function secondary to acute myocardial infarction demonstrated that significantly more patients developed new-onset AF in the placebo group than in the trandolapril group (5.3% versus 2.8%, p<0.05).[28] In contrast, preventive effects of ramipril on new-onset AF could not be reproduced in a retrospective analysis of the Heart Outcomes Prevention Evaluation (HOPE) trial of patients with high risk of cardiovascular disease.[29]

Evidence for the use of RAAS blockers in the secondary prevention of AF, on the other hand, has not only been established by post-hoc analyses but has been investigated in randomized prospective trials in several subgroups of patients with AF. In a randomized clinical trial concerning patients with lone paroxysmal AF comparing amiodarone versus amiodarone plus losartan versus amiodarone plus perindopril, the primary endpoint of incidence of AF after 14 days and within 24 months after randomization occurred in 19% of patients treated with losartan, 24% of patients treated with perindopril, and 41% of patients treated with amiodarone only (p=0.02).[30] There was no significant difference in AF recurrence between the losartan and perindopril groups. Beside a decrease in recurrent AF, losartan and perindopril use was associated with a significant smaller left atrial diameter after 24 months follow-up. ACE inhibitors or ARBs on top of amiodarone have also been studied on recurrence of AF after electrical cardioversion by Madrid et al.[31] Of the 154 patients analyzed, 63% of patients treated with amiodarone and 85% of patients treated with amiodarone plus irbesartan were free of recurrent AF (p=0.008) after 2 months. This lower rate of AF recurrence in the irbesartan group persisted during the median follow-up period of 254 days. In another study by Ueng et al. of patients with persistent AF and mean left ventricular ejection fraction

Table 1. Clinical studies of ACE inhibitors and ARBs for primary or secondary prevention of AF

Study	Design	Primary/secondary AF prevention	No. of pts	Patient characteristics
L'Allier et al., 2004[22]	Retrospective cohort study of ACE inhibitor use vs. calcium blocker use	Primary prevention	11054	Hypertension
LIFE, 2005[23]	Post-hoc analysis of RCT comparing losartan vs. atenolol	Primary prevention	8851	Hypertension or ECG-documented LV hypertrophy
VALUE[24]	Post-hoc analysis of RCT comparing valsartan vs. amlodipine	Primary prevention	13760	Hypertension and at least one other cardiovascular risk/ disease factor
SOLVD, 2003[25]	Retrospective analysis of RCT comparing enalapril vs. placebo	Primary prevention	374	LVEF ≤ 35%
.CHARM, 2006[26]	Prespecified secondary analysis of RCT comparing candesartan vs. placebo	Primary prevention	6378	Symptomatic chronic heart failure + reduced or preserved LVEF
Val-HeFT[27]	Post-hoc analysis of RCT comparing valsartan vs. placebo	Predominantly primary prevention	5000	LVEF < 40%; 12% AF on baseline ECG
TRACE, 1999[28]	Post-hoc analysis of RCT comparing trandolapril vs. placebo	Primary prevention	1577	Reduced LV function secondary to acute myocardial infarction
HOPE[29]	Post-hoc analysis of RCT comparing ramipril vs. placebo and vitamin E vs. placebo	"Primary" prevention (sinus rhythm on baseline ECG)	8335	Evidence of vascular disease or diabetes plus at least one additional cardiovascular risk factor; LVEF ≥ 40%
Yin et al., 2006[30]	RCT comparing amiodarone vs. amiodarone + losartan vs. amiodarone + perindopril for prevention of AF recurrence	Secondary prevention	177	Lone paroxysmal AF; Total history of AF 2.0-2.7 y
Madrid et al., 2002[31]	RCT comparing amiodarone vs. amiodarone + irbesartan started 3 weeks before scheduled ECV	Secondary prevention	154	Persistent AF; Total history of AF 18-20 mo; Mean LVEF 63%
Ueng et al., 2003[32]	RCT comparing amiodarone vs. amiodarone + enalapril started 4 weeks before scheduled ECV	Secondary prevention	144	Persistent AF; Total history of AF 37-41 mo; Mean LVEF 51%
CTAF, 2008[33]	Retrospective analysis of RAAS blocker use in RCT comparing amiodarone vs. sotalol or propafenone started within 21 days before ECV	Secondary prevention	403	Paroxysmal AF: 43-49%; Persistent AF: 51-57%; LVEF < 50%: 12%; 12% RAAS blocker at baseline
Van Noord et al., 2005[34]	Retrospective analysis of ACE inhibitor use in pts undergoing ECV	Secondary prevention	107	Persistent AF; Total history of AF 144 (95-232) days; 21% LV dysfunction; 26% ACE inhibitor at baseline

Follow-up	Results	Conclusion
4.2-4.6 y	New-onset AF in 17.9% of ACE inhibitor pts vs. 18.9% of calcium blocker pts per 1000 person-years (HR 0.85, 95% CI 0.74-0.97).	ACE inhibition reduced AF
4.8±1.0 y	New-onset AF in 150 (3.5%) losartan pts vs. 221 (5.3%) atenolol pts (p<0.001). Time to onset of AF longer in losartan pts vs. atenolol pts (1809 vs. 1709 days, p=0.057).	Losartan reduced AF
5 y	New-onset AF in 252 (3.67%) valsartan pts vs. 299 (4.34%) amlodipine pts (HR 0.843, 95% CI 0.713-0.997, p=0.0455).	Valsartan reduced AF
2.9±1.0 y	New-onset AF in 10 (5.4%) enalapril pts vs. 45 (24%) placebo pts (p<0.0001). Enalapril most powerful predictor for risk reduction of AF (HR 0.22, 95% CI 0.11-0.44, p<0.0001).	Enalapril reduced AF
Median 37.7 mo	New-onset AF in 177 (5.55%) candesartan pts vs. 215 (6.74%) placebo pts (OR 0.812, 95% CI 0.662-0.998, p=0.048).	Candesartan reduced AF
23 mo	AF occurrence during follow-up in patients with sinus rhythm at baseline in 113 (5.12%) of valsartan pts vs. 174 (7.95%) of placebo pts (p=0.001) (HR 0.63, 95% CI 0.49-0.81, p=0.0003).	Valsartan reduced AF
2-4 y	New-onset AF in 22 (2.8%) trandolapril pts vs. 42 (5.3%) placebo pts (p<0.05). Trandolapril independent predictor of reduced risk of developing AF (RR 0.45, 95% CI 0.26-0.76, p<0.01).	Trandolapril reduced AF
Median 4.5 y	AF in 86 (2.0%) pts vs. 91 (2.2%) pts (OR 0.92, 95% CI 0.68-1.24, p=ns).	No sign. AF reduction
24 mo	Incidence of AF in 24 (41%) amiodarone vs. 11 (19%) amiodarone + losartan pts vs. 14 (24%) amiodarone + perindopril pts (p=0.02). KM analysis demonstrated sign. reduction in AF recurrence in amiodarone + losartan pts (p=0.006) and amiodarone + perindopril pts (p=0.04) vs. amiodarone pts. No difference between amiodarone + losartan and amiodarone + perindopril pts.	Losartan and perindopril reduced AF
Median 254 days (range 60-610)	After 2 months 19 (85%) amiodarone + irbesartan pts vs. 7 (63% amiodarone) pts (p=0.008) were free of recurrent AF. Time to first recurrence of AF during total FU longer in amiodarone + irbesartan pts (78%) vs. amiodarone pts (56%, p=0.007).	Irbesartan reduced AF
Median 270 days (range 61-575)	After 4 weeks 59 (84.3%) amiodarone + enalapril pts pts vs. 46 (61.3%) amiodarone pts still in sinus rhythm (p=0.002). After total FU 52 (74.3%) amiodarone + enalapril pts vs. 43 (57.3%) amiodarone pts (p=0.021) still in sinus rhythm.	Enalapril reduced AF
468±150 days	Recurrent AF in 59 (38.3%) amiodarone pts, 14 (29.8%) amiodarone + RAAS blocker pts, 93 (61.6%) sotalol/propafenone pts, 32 (62.8%) sotalol/propafenone + RAAS blocker pts: Use of RAAS blockers not associated with reduced risk of recurrent AF.	No sign. AF reduction
1 mo	ECV successful in 96% of ACE inhibitor pts vs. 80% of no ACE inhibitor pts (p=0.04). At 1 month, 49% of ACE inhibitor pts vs. 50% of no ACE inhibitor pts still in sinus rhythm (p=ns).	No sign. AF reduction

Table 1. Clinical studies of ACE inhibitors and ARBs for primary or secondary prevention of AF (continued)

Study	Design	Primary/secondary AF prevention	No. of pts	Patient characteristics
Tveit et al., 2007[35]	RCT comparing candesartan vs. placebo 3-6 weeks before scheduled ECV until 6 months after ECV	Secondary prevention	171	Persistent AF; Mean fractional shortening 30%
Van den Berg et al., 1995[36]	RCT comparing lisinopril vs. placebo	Secondary prevention	30	Persistent AF + congestive heart failure
Belluzzi et al., 2009[37]	RCT comparing ramipril vs. placebo started after cardioversion with propafenone	Secondary prevention	62	First episode of lone AF
GISSI-AF[38]	RCT comparing valsartan vs. placebo	Secondary prevention	1442	Paroxysmal or persistent AF; Total history of AF unknown

ACE = angiotensin converting enzyme; AF = atrial fibrillation; CI = confidence interval; ECG = electrocardiogram; ECV = electrical cardioversion; FU = follow-up; HR = hazard ratio; KM = Kaplan-Meier; LV = left ventricular; LVEF = left ventricular ejection fraction; OR = odds ratio; RAAS = renin angiotensin aldosterone system; RCT = randomized clinical trial; RR = relative risk.

of 51%, patients were randomized to amiodarone or amiodarone plus enalapril 4 weeks before electrical cardioversion.[32] Patients treated with the ACE inhibitor enalapril on top of amiodarone had a higher probability of remaining in sinus rhythm after 4 weeks (84.3% versus 61.3%, p=0.002) and after median follow-up of 270 days (74.3% versus 57.3%, p=0.021) than patients treated with amiodarone only. These positive results of RAAS blockers with concurrent use of antiarrhythmic drugs in the secondary prevention of AF has not been confirmed in a recent retrospective analysis of the Canadian Trial of Atrial Fibrillation (CTAF), which investigated the superiority of amiodarone over sotalol or propafenone in maintaining sinus rhythm in patients with AF.[33] Multivariate analysis revealed that the use of RAAS blockers on top of antiarrhythmic drugs was not associated with reduced recurrence of AF, keeping in mind that only 12% of patients were using RAAS blockers at baseline.

Few and predominantly small studies have investigated the effects of ACE inhibitors or ARBs without concurrent use of antiarrhythmic drugs in the secondary prevention of AF. One retrospective study demonstrated improved acute outcome of electrical cardioversion when pretreated with ACE inhibitors, but this did not lead to better maintenance of sinus rhythm at one month of follow-up.[34] Tveit et al. conducted a trial in patients with persistent AF who were randomized to the ARB candesartan or placebo for 3-6 weeks before electrical cardioversion until 6 months after cardioversion.[35] There was no difference in recurrence of AF between patients treated with candesartan (71%)

Follow-up	Results	Conclusion
6 mo	Recurrent AF in 48 (71%) candesartan pts vs. 46 (65%) placebo pts (p=ns). Median time to recurrent AF 8 days in candesartan pts vs. 9 days in placebo pts (p=ns).	No sign. AF reduction
6 wks	Maintenance of sinus rhythm 6 weeks after ECV: 71% of lisinopril pts vs. 36% placebo pts (p=ns).	No sign. AF reduction
3 y	Recurrent AF in 3 (10%) ramipril pts vs.10 (32%) placebo pts (p<0.03).	Ramipril reduced AF
1 y	Recurrent AF in 371 (51.4%) valsartan pts vs. 375 (52.1%) placebo pts (HR 0.97, 96% CI 0.83-1.14, p=ns).	No sign. AF reduction

and placebo (65%), as there was also no difference in time to recurrence between both groups. A small randomized clinical trial of patients with heart failure demonstrated that the ACE inhibitor lisinopril reduced AF recurrences 6 weeks after electrical cardioversion (29% versus 64%), though this difference was statistically not significant.[36] Recently more promising results concerning the role of RAAS blockers without concurrent use of antiarrhythmic drugs came from a randomized study by Belluzzi et al.[37] A total of 62 patients with a first detected episode of lone AF were randomized to the ACE inhibitor ramipril or placebo after successful pharmacological cardioversion. AF relapses were seen in 3 ramipril-treated and 10 placebo-treated patients ($p<0.03$). The most recent, by far largest trial of RAAS blockade in secondary prevention of AF with or without concomitant antiarrhythmic drug therapy, however, failed to demonstrate that valsartan can reduce recurrence of AF.[38]

The results from these studies suggest that ACE inhibitors and ARBs appear to be more effective in the primary prevention of AF, i.e. early during the course of the (underlying) disease when atrial structural remodeling can still be reversed and when we can really speak of "upstream" therapy. In the secondary prevention of AF the effects of ACE inhibitors and ARBs are most promising on top of ion-channel antiarrhythmic drugs. In most secondary prevention studies, however, patients had a long history of AF, which means that atrial structural remodeling may have deteriorated too much and intervention with upstream therapy came too late. Furthermore, many of these studies are limited by small

patient numbers, and studies differ in when upstream therapy is started, ranging from various weeks before ECV until immediately after cardioversion. It would seem logical that upstream therapy requires at least several weeks to intervene in the structural remodeling processes. This means that it should be started before sinus rhythm is restored. In addition, a meta-analysis concluded that ACE inhibitors and ARBs seem to be most effective in patients with LV dysfunction or clinical heart failure.[21] It should be noted however that there is quite some heterogeneity in the definition and documentation of AF recurrences between all studies, demanding better-defined outcome parameters.[39] Currently, larger randomized studies investigating the role of ACE inhibitors and ARBs in the secondary prevention of AF are much awaited.

ARAs

ARAs such as spironolactone and eplerenone are other RAAS blockers that also have a potential role in the prevention of AF, mainly by attenuating electrical and structural remodeling. In experimental data it has been shown that aldosterone increases the sensitivity of cardiac tissue to arrhythmias, and, consequently, antagonism of aldosterone reduces the incidence of arrhythmias. With regard to ventricular arrhythmias, this has been investigated in a cardiomyopathic hamster model, where the ARA eplerenone reduced the incidence of ventricular arrhythmias concomitantly with a decrease in the extent of left ventricular fibrosis as compared with controls.[60] With regard to atrial arrhythmias, Milliez et al. compared the effects of treatment with spironolactone, lisinopril, atenolol alone or in combination on atrial fibrosis and ectopic electrical activity in a rat model of congestive heart failure following myocardial infarction.[61] Only rats treated with spironolactone, alone or in combination with the other drugs, showed decreased fibrosis in the atria and reduced P-wave duration. In a canine model of heart failure induced by rapid ventricular pacing, concurrent treatment with eplerenone significantly prolonged atrial effective refractory periods and suppressed sustained atrial tachyarrhythmia inducibility.[62] These experimental data suggest that ARAs may be beneficial in the prevention of AF.

So far no human studies have been published investigating the role of ARAs in the prevention of AF except for one study where a reduction of AF was observed in patients with congestive heart failure treated with spironolactone.[63] There is some human evidence that ARAs interfere in the structural remodeling processes in the atria, which may consequently prevent AF: in a study in hypertensive patients with diastolic heart failure, spironolactone tended to decrease left atrial area.[64] The potential role of ARAs as upstream therapy in persistent AF is currently under investigation in the Eplerenone in the Prevention of Atrial Fibrillation Recurrences after Cardioversion (EPLERAF) study.

STATINS

Beside their lipid-lowering abilities, statins are well-known for their pleiotropic effects including reduction of inflammation and oxidative stress, though the exact mechanisms underlying these effects are not yet well understood.[8,65,66] Through these pleiotropic properties, statins may also play an important role in the prevention of AF.

Experimental models have demonstrated various mechanisms by which statins may prevent AF, one mechanism involving electrical remodeling. In a model of atrial tachypacing in dogs, simvastatin reversed the decrease in atrial effective refractory period and also reduced the duration of induced AF.[67] Furthermore, simvastatin attenuated tachypacing induced downregulation of L-type calcium channel alpha-subunit expression. Comparable effects were also seen in a study of sterile pericarditis created in dogs: atorvastatin lengthened atrial effective refractory period and shortened intra-atrial conduction time and duration of AF. In addition, it showed anti-inflammatory effects by lowering C-reactive protein levels.[68] Statins have also been demonstrated to decrease atrial structural remodeling in a rat study where atrial fibrosis caused by infusion with angiotensin II was attenuated by simvastatin.[17]

In patients, statins have been associated with a decreased incidence or recurrence of AF (Table 2), independent of the reduction in serum cholesterol levels, and these effects have not been observed with other lipid lowering drugs.[65,69] Many clinical studies have focused on postoperative AF, as cardiac surgery is associated with an increased inflammatory status which may be one of the causes of the development of AF postoperatively. Three prospective observational studies in patients undergoing thoracic surgery demonstrated that statin use was associated with a decrease in the incidence of postoperative AF.[40-42] In a randomized placebo-controlled clinical trial by Patti et al. of patients undergoing elective cardiac surgery, 40 mg atorvastatin daily started 7 days before surgery significantly reduced the incidence of AF as compared with placebo (35% versus 57%, p=0.003).[43] Another randomized trial also found that in patients undergoing coronary artery bypass graft (CABG) surgery, patients treated with atorvastatin 20 mg daily had significantly less AF (13%) than the control group (27%, p=0.04) postoperatively.[44] A large meta-analysis also demonstrated a significant reduction of postoperative AF by statin use.[70] The positive results of these studies were not replicated in a retrospective analysis of 4044 patients undergoing cardiac surgery, where preoperative statin use was not associated with a decreased incidence of postoperative AF.[45] In this study, however, postoperative AF was only assessed by continuous telemetry monitoring during the hospitalization for cardiac surgery.

Another large patient population that has been studied with regard to statin use consists of patients with coronary artery disease. Results concerning the preventive efficacy of statins in AF have been varying, and no well-conducted randomized clinical trial has been published yet of this patient category. One of the first studies was an observational study by Young-Xu et al. of patients with chronic stable coronary artery disease.[46] During follow-up 12%

of patients developed AF, and statin use was associated with a significantly reduced risk of developing AF. Recently a post-hoc analysis of the Heart and Estrogen-Progestin Replacement Study (HERS) of post-menopausal women with coronary artery disease demonstrated that baseline statin use was associated with a lower odds of having AF at baseline but also with a lower odds of developing new-onset AF during follow-up.[47] In a large observational study of 13783 patients with coronary artery disease, however, there was no difference in the incidence of AF during follow-up between patients treated with or without statins.[48] Interestingly, the authors did find that in a subgroup consisting of patients with congestive heart failure, statin treatment was associated with a reduction of AF. Indeed, in a post-hoc analysis of the National Registry to Advance Heart Health (ADVANCENT) of patients with left ventricular ejection fraction ≤ 40%, these patients with left ventricular dysfunction had a significantly reduced prevalence of AF if they used lipid-lowering drugs.[50] This effect on the reduction of AF was larger than that of ACE inhibitors or ARBs (Table 2). Intriguingly, the intensity of statin use may not be that important for the prevention of AF, as demonstrated by a post-hoc analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) and Aggrastat to Zocor (A to Z) trials. Higher-intensity statin therapy was compared with lower-intensity statin therapy, and no differences in the incidence of AF after acute coronary syndromes were found between the two intensity groups (Table 2).[49]

In the secondary prevention of AF, a number of studies have investigated the role of statins in the prevention of AF recurrences after electrical cardioversion. Siu et al. conducted a retrospective study in patients with lone persistent AF and found that AF recurrences occurred in 40% of patients using statins versus 84% of patients not using statins ($p=0.007$).[51] In a small, not placebo controlled, randomized trial of patients who received 10 mg atorvastatin daily or no atorvastatin from 48 hours before electrical cardioversion to 3 months post cardioversion, recurrence of AF at 3 months was significantly lower in the group receiving atorvastatin (12.5%) than in the control group (45.8%, $p=0.02$).[52] In a post-hoc analysis of two Canadian Registries of Atrial Fibrillation (CARAF) by Humphries et al. only a trend was seen that patients on statins had less AF recurrences 1 year after electrical cardioversion than patients not on statins.[53] In multivariate analysis statin use was associated with significantly reduced AF recurrences only in patients who were also using beta-blockers. Possible preventive effects of statins on AF recurrences after electrical cardioversion, however, were not confirmed in a randomized open trial of patients who received 40 mg pravastatin daily or no pravastatin between 3 weeks before until 6 weeks after cardioversion (recurrence rate of AF 35% versus 33%, respectively, p=ns).[54] Again in a more recent randomized placebo-controlled trial, 80 mg atorvastatin daily did not increase the number of patients in sinus rhythm at 30 days after cardioversion as compared with placebo (51% versus 42%, respectively, p=ns).[55] In the secondary prevention of paroxysmal AF the preventive efficacy of statins was confirmed in a randomized study: patients who received atorvastatin had a significant reduction in

paroxysmal AF during follow-up.[56] Furthermore, the authors concluded that paroxysmal AF was completely resolved in more patients in the atorvastatin group (65%) than in the placebo group (10%), as assessed by ambulatory 48-hour monitoring at the end of the study.

With the improving technologies in pacemakers and implantable-cardioverter defibrillators enabling continuous registration of atrial high rate episodes, it has become easier and more reliable to detect AF episodes. These patient categories have also been studied with regard to statin use. In an observational cohort study by Gillis et al. patients with known paroxysmal AF were followed after dual-chamber pacemaker implantation to detect recurrence of atrial tachycardia (AT) or AF.[57] After 1 year, patients on statin therapy more often had no recurrence of AT/AF than patients without statin therapy (37% versus 14%, p=0.0009). Moreover, the authors found that statin use was associated with a significantly lower AT/AF burden. Less clear but overall positive results were seen in a small open-label randomized study of patients with an atrial-based or dual-chamber pacemaker receiving 20 mg atorvastatin daily or no atorvastatin.[58] Atrial high rate episodes detected by the device were chosen as surrogate for AF. This study demonstrated that there was no difference in atrial high rate episodes lasting more than 1 minute between the statin and no statin groups. Indeed with regard to atrial high rate episodes lasting more than 10 minutes, which may be more clinically relevant,[71,72] there was a significant difference between both groups. The authors provided no information regarding the history of AF in these patients. Another observational study investigated the role of statins in the primary and secondary prevention of AF in 1445 patients with an implantable cardioverter-defibrillator.[59] During follow-up, statin use was associated with a significantly decreased risk on the development of AF in combination with (inappropriate) shocks, and also on the development of AF that was not accompanied by shocks.

Indeed, most of the studies investigating statins show beneficial effects regarding primary and secondary prevention of AF. The positive results in patients undergoing surgery suggest that anti-inflammatory effects of statins may play a role. However, just like the studies concerning ACE inhibitors and ARBs, the statin studies have a number of limitations including small patient numbers, differences in length of history of AF, differences in underlying diseases, differences in when statin therapy is started, significant differences in dosages and that many of these studies are retrospective or post-hoc analyses. Larger, randomized clinical trials are needed to further elucidate the effectiveness of statins in the prevention of AF.

Table 2. Clinical studies of statins for primary or secondary prevention of AF

Study	Design	Primary/secondary AF prevention	No. of pts	Patient characteristics
Postoperative AF				
Amar et al., 2005[40]	Prospective observational analysis of statin use in pts undergoing surgery	Predominantly primary prevention	131	Age ≥ 60 years undergoing major lung or esophageal resection; In SR prior to surgery; 24% statins at baseline
Marin et al., 2006[41]	Prospective observational analysis of statin use in pts undergoing surgery	Predominantly primary prevention	234	Undergoing CABG; No history of persistent/permanent AF; 4% paroxysmal AF; 62% statins at baseline
Ozaydin et al., 2007[42]	Retrospective observational analysis of statin use in pts undergoing surgery	Primary prevention	362	Undergoing first elective CABG; 74% statins at baseline
ARMYDA-3, 2006[43]	RCT comparing atorvastatin vs. placebo started 7 days before surgery	Primary prevention	200	Undergoing elective cardiac surgery with cardiopulmonary bypass; No prior statin use
Song et al., 2008[44]	RCT comparing atorvastatin vs. no atorvastatin started 3 days before surgery	Primary prevention	124	Undergoing elective off-pump CABG; No prior statin use
Virani et al. 2008[45]	Retrospective analysis of statin use in pts undergoing surgery	Primary prevention	4044	Undergoing cardiac surgery (CABG/valve/both); 52% statins at baseline
Coronary artery disease				
Young-Xu et al., 2003[46]	Observational analysis of statin use in pts with coronary artery disease	Primary prevention	449	Chronic stable coronary artery disease; Mean LVEF 59-60%
HERS, 2009[47]	Post-hoc analysis of RCT comparing estrogens vs. placebo in postmenopausal women with known coronary artery disease	Primary and secondary prevention	2673	Postmenopausal women < 80 yrs old with known coronary artery disease; 37% statins at baseline; 29 pts with history of AF
Adabag et al., 2007[48]	Observational analysis of statin use in pts with coronary artery disease	Primary prevention	13783	Coronary artery disease; 39% statins at baseline
PROVE IT-TIMI 22/A to Z, 2008[49]	Post-hoc analysis of 2 RCTs comparing high-intensity statin therapy vs. low-intensity statin therapy	?	8659	Stable after acute coronary syndrome; No data regarding history of AF
LV dysfunction				
ADVANCENT, 2006[50]	Post-hoc analysis of cross-sectional registry of pts with LVEF ≤ 40%	Primary and secondary prevention	25268	Mean LVEF 31%; 28% history of AF; 72% coronary artery disease; 67% lipid-lowering drugs at baseline

Follow-up	Results	Conclusion
Median 3 days	Statin use independently associated with decreased risk of postoperative AF (OR 0.26, 95% CI 0.08-0.82, p=0.022). No difference in C-reactive protein and Interleukin-6 levels between pts with and without AF.	Statins reduced AF
1 mo	Statin use independently associated with decreased risk of postoperative AF (OR 0.52, 95% CI 0.28-0.96, p=0.038). Higher TIMP-1/MMP-1 ratio at 24 h after surgery present in those pts who did not develop AF.	Statins reduced AF
1 wk	Postoperative AF in 22 (8.2%) statin pts vs. 16 (16.8%) no statin pts (p=0.03) Duration of postoperative AF shorter in pts on statins (180±60 min vs. 338±153 min, p=0.0001).	Statins reduced AF
30 days	Postoperative AF in 35 (35%) atorvastatin pts vs. 56 (57%) placebo pts (p=0.003). Atorvastatin use independently associated with reduced risk of AF (OR 0.39, 95% CI 0.18-0.85, p=0.017).	Atorvastatin reduced AF
1 mo	Postoperative AF in 8 (13%) atorvastatin pts vs. 17 (27%) no atorvastatin pts (p=0.04). Atorvastatin independently associated with reduced risk of postoperative AF (OR 0.34, 95% CI 0.12-0.93, p=0.04).	Atorvastatin reduced AF
Duration of post-surgery hospitalization	Preoperative statin use not associated with decreased incidence of postoperative AF (OR 1.13, 95% CI 0.98-1.31, p=0.08).	No sign. AF reduction
5 y (range 1-9 y)	New-onset AF in 24 (9%) of statin pts vs. 28 (15%) of no statin pts (crude OR 0.48, 95% CI 0.28-0.83).	Statins reduced AF
4.1 y	Statin use in 19 (22%) of pts with baseline AF vs. 957 (37%) of pts without AF at baseline. (p=0.003). Statin use independently associated with lower odds of having AF at baseline (OR 0.35, 95% CI 0.13-0.93, p=0.04). Statin use independently associated with lower odds of developing new-onset AF during FU (HR 0.45, 95% CI 0.26-0.78, p=0.004).	Statins reduced AF
4.8 y	Statin use not associated with AF (HR 1.00, 95% CI 0.88-1.14, p=0.99). In pts with congestive heart failure, statin independently associated with reduced incidence of AF (HR 0.57, 95% CI 0.33-1.00, p=0.04).	No sign. AF reduction except in heart failure
2 y	Onset of AF in 2.9% of high-intensity statin pts vs. 3.3% of low-intensity statin pts (p=ns, PROVE IT-TIMI 22) and in 1.6% of high-intensity statin pts vs. 0.99% of low-intensity statin pts (p=ns, A to Z).	No sign. difference in high- vs. low-intensity statin use
N/A	AF prevalence 25.1% in pts taking lipid-lowering drugs vs. 32.6% in untreated hyperlipidemic pts and 32.8% in pts without hyperlipidemia and not taking lipid-lowering drugs (p<0.001). Lipid-lowering drugs independently associated with reduced odds of AF (OR 0.69, 95% CI 0.64-0.74); larger than effects of RAAS blockers (OR 0.85, 95% CI 0.79-0.92) or beta-blockers (OR 0.95, 95% CI 0.88-1.02). Effects of lipid-lowering drugs independent of their effects on lipid profile.	Lipid-lowering drugs reduced AF

Table 2. Clinical studies of statins for primary or secondary prevention of AF (continued)

Study	Design	Primary/secondary AF prevention	No. of pts	Patient characteristics
Post cardioversion				
Siu et al., 2003[51]	Retrospective analysis of statin use in pts undergoing ECV	Secondary prevention	62	Lone persistent AF ≥ 3 months; Total history of AF 21-28 mo; 16% statins at baseline; LVEF 65-68%
Ozaydin et al., 2006[52]	RCT comparing atorvastatin vs. no atorvastatin from 48 h before ECV until 3 months after ECV	Secondary prevention	48	Persistent AF > 48 h; Total history of AF 616-710 days; LVEF 62-63%
CARAF, 2007[53]	Post-hoc analysis of 2 registries of pts with new-onset AF	Secondary prevention	625	New-onset AF and successful pharmacological/ electrical cardioversion; 12.3% statins at baseline; LV dysfunction in 22-29% of pts
Tveit et al., 2004[54]	RCT comparing pravastatin vs. no pravastatin from 3 weeks before until 6 weeks after ECV	Secondary prevention	114	AF > 48 h; Current AF episode median 8 weeks (range 0.6-156)
Almroth et al., 2009[55]	RCT comparing atorvastatin vs. placebo from 2 weeks before until 30 days after ECV	Secondary prevention	234	Persistent AF > 7 days; Duration of last AF episode 3.7-3.9 mo; Total history of AF not provided; 90% of pts LVEF > 45%
Paroxysmal AF				
Dernellis et al., 2005[56]	RCT comparing atorvastatin vs. placebo	Secondary prevention	80	Paroxysmal AF; 15-20% previous cardioversion
Pacemaker/ICD				
Gillis et al., 2008[57]	Observational prospective cohort study investigating statin use in pts with paroxysmal AF and dual-chamber pacemaker	Secondary prevention	185	Paroxysmal AF; Dual-chamber pacemaker implanted; 31% statins at baseline; Median LVEF 66%
Tsai et al., 2008[58]	RCT comparing atorvastatin vs. no atorvastatin	?	103	Dual- or single-chamber pacemaker for sick sinus syndrome or AV conduction block; No data regarding history of AF; Mean LVEF 60-63%
Bhavnani et al., 2008[59]	Observational analysis of statin use in pts receiving an ICD	Primary and secondary prevention	1445	Pts with ICD; Prior AF 29%; 52% statins at baseline; Mean LVEF 29%

AF = atrial fibrillation; AFL = atrial flutter; AT = atrial tachycardia; CABG = coronary artery bypass grafting; CI = confidence interval; ECG = electrocardiogram; ECV = electrical cardioversion; FU = follow-up; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MMP-1 = matrix metalloproteinase-1; OR = odds ratio; RR = relative risk; TIMP-1 = tissue inhibitor matrix metalloproteinase-1.

Follow-up	Results	Conclusion
44±1 mo	Statin pts less recurrent AF than controls (40% vs. 84%, p=0.007). Statin use independently associated with decreased risk of AF recurrence (RR 0.31, 95% CI 0.103-0.905, p=0.032).	Statins reduced AF
3 mo	AF recurrence in 3 (12.5%) statin pts vs. 11 (45.8%) control pts (p=0.02). Atorvastatin independently associated with reduced risk of AF recurrence (RR 0.19, 95% CI 0.052-0.72, p=0.01).	Atorvastatin reduced AF
1 y	AF recurrence in 23.4% statin pts vs. 33.8% no statin pts (p=0.07). Statin use only independently associated with decreased risk of AF recurrence in pts on beta-blockers (OR 0.26, 95% CI 0.10-0.66, p<0.01).	Statins only reduced AF in combination with beta-blockers
6 wks	AF recurrence in 18 (35%) pravastatin pts vs. 17 (33%) control pts (p=ns).	No sign. AF reduction
30 days	Sinus rhythm on ECG at 30 days in 57 (51%) atorvastatin pts vs. 47 (42%) placebo pts (p=ns).	No sign. AF reduction
6 mo	Number of paroxysmal AF episodes/48 h 0 (range 0-9) in atorvastatin pts vs. 12 (range 0-23) in placebo pts (p=0.001). Duration of AF episodes/48 h 222 (range 0-910) min in atorvastatin pts vs 0 (range 0-167) min in placebo pts (p=0.001). Paroxysmal AF completely resolved in 26 (65%) of atorvastatin pts vs. 4 (10%) of placebo pts.	Atorvastatin reduced AF
1 y	No AT/AF recurrence in 21 (37%) statin pts vs. 18 (14%) no statin pts (p=0.0009). Statin use only sign. predictor of AT/AF recurrence (OR 0.33, 95% CI 0.14-0.74, p=0.007). Median AT/AF burden 0.10 h/day in statin pts vs. 0.39 h/day in no statin pts (p=0.0059).	Statins reduced AT/AF
1 y	Atrial high rate episodes ≥ 10 min in 3 (6%) of atorvastatin pts vs. 10 (19%) control pts (p=0.041). Atrial high rate episodes ≥ 1 min in 28 (55%) atorvastatin vs. 31 (60%) control pts (p=ns).	Atorvastatin reduced atrial high rate episodes
874±805 days	Statin use independently associated with decreased risk of AF/AFL development accompanied with shocks (HR 0.472, 95% CI 0.349-0.638, p<0.001). Statin use independently associated with decreased risk of AF/AFL development without shocks (HR 0.613, 95% CI 0.496-0.758, p<0.001).	Statins reduced AF

FISH OILS

Fish consumption has been associated with reduced cardiovascular death which has mainly been attributed to the active element in fish oils, namely omega-3 polyunsaturated fatty acids (PUFAs).[73] PUFAs have also been investigated in the prevention of AF.[74] Experimental studies have investigated different mechanisms through which PUFAs may prevent AF. One mechanism may be through reduction of electrical remodeling. In a recent study by Li et al. using a whole-cell patch voltage clamp technique with human atrial myocytes obtained from patients undergoing CABG, the authors found that PUFAs inhibit atrial transient outward and ultra-rapid delayed rectifier potassium currents and the voltage-gated sodium current in a concentration-dependent manner.[75] Another study, however, did not find that PUFAs affected atrial electrical remodeling caused by atrial tachypacing, as measured by atrial effective refractory period.[76] Another mechanism involves inflammation. In a rat study of pressure overload-induced cardiac dysfunction, dietary supplementation of PUFAs derived from fish caused a dose-dependent increase in the anti-inflammatory adipokine adiponectin and a decrease in urinary thromboxane B2 and serum tumor necrosis factor alpha, beside preventing an increase in left ventricular end-diastolic and end-systolic volumes.[77] Furthermore, in a canine pacing model, supplementation with PUFAs led to a smaller increase in atrial matrix metalloproteinase-9 activity and in collagen type I and III messenger RNA expression, denoting attenuation of structural remodeling. In addition, reduced AF inducibility and persistence were observed.[78] Comparable results were seen in a study by Sarrazin et al. where oral treatment with fish oils reduced vulnerability to induction of AF in a dog model of vagally induced AF.[79] In this study markers of structural remodeling were also lower in fish oil treated dogs.

The results of these experimental studies seem promising but conflicting results have come from clinical studies. One clinical trial of 160 patients randomized to PUFA supplementation or control at least 5 days before elective CABG surgery until the day of hospital discharge demonstrated that PUFAs significantly reduced incidence of postoperative AF (33.3% in the control group and 15.2% in the PUFA group, p=0.013).[80] Other, observational population-based studies of predominantly healthy subjects have focused on fish consumption instead of PUFA supplementation. One large study of 4815 subjects with mean age 73 years investigated the relationship between fish intake and incidence of AF during 12 years of follow-up.[81] Higher consumption of tuna or other broiled or baked fish was associated with a reduction of incidence of AF, as assessed by annual electrocardiograms and hospital discharge records. This was not confirmed in a larger observational study of 5184 subjects aged 67.4±7.7 years, where fish intake was not associated with the risk of AF during a mean follow-up of 6.4 years, as determined using electrocardiograms conducted during two follow-up visits, hospital discharge diagnoses, and records from general practitioners.[82] The largest observational study of 47949 subjects with mean age 56 years and follow-up of 5.7 years also did not find an asso-

ciation between fish consumption and reduction of risk of AF as assessed by hospital discharge diagnoses only.[83] When evaluating these population-based studies, one should not forget that increasing age is one of the most important predictors of AF development and may therefore influence results. Another large limitation of these studies is that fish consumption in general was investigated, whereas there were no precise data of actual PUFA intake. Clearly, more evidence is needed before PUFAs or fish can be recommended as evidence based therapy for the prevention of AF.

GLUCOCORTICOIDS

The inflammatory status associated with AF makes it plausible to assume that inflammatory agents such as glucocorticoids may suppress AF. In an experiment where dogs were subjected to atrial tachypacing in combination with prednisone, ibuprofen, cyclosporine or no treatment, only prednisone suppressed electrical remodeling (i.e. effective refractory period shortening and AF promotion), decreased C-reactive protein concentrations, and attenuated the increase in endothelial nitric oxide synthase expression.[84]

In humans, most studies investigating glucocorticoids have focused on postoperative AF, and these have not been unequivocal. In an older randomized double-blind placebo-controlled study by Chaney et al. examining the pulmonary effects of methylprednisolone in patients undergoing CABG, there was no difference in the occurrence of postoperative AF, a secondary endpoint.[85] A post-hoc analysis of a study that investigated the effects of dexamethasone on postoperative shivering, demonstrated that patients treated with dexamethasone had less new-onset AF during the first 3 days post-operatively than patients treated with placebo (18.9% versus 32.3%, p=0.027).[86] The same author conducted a randomized double-blind placebo-controlled trial a few years later to test the effects of dexamethasone on AF after cardiac surgery in 78 patients, but the positive results found earlier could not be replicated.[87] After cardiac surgery, 41% of patients in the placebo group and 30% of patients in the dexamethasone group developed AF, which was not significantly different (p=0.31). Another double-blind randomized trial with more patients (n=241), however, did find that the incidence of postoperative AF was significantly lower in patients receiving hydrocortisone (30%) than in patients receiving placebo (48%, p=0.004).[88]

Only one double-blind randomized trial focused on the interaction between methylprednisolone and C-reactive protein in recurrent AF after cardioversion.[89] In this study 104 patients were randomized to methylprednisolone and placebo and underwent a rhythm control strategy involving electrical cardioversion after which they received propafenone. During follow-up recurrent AF occurred less frequently in patients treated with methylprednisolone (9.6%) as compared with patients treated with placebo (50%). Furthermore,

methylprednisolone significantly lowered C-reactive protein levels, where C-reactive protein was a significant predictor of recurrent AF. All in all, there is too little evidence that glucocorticoids are effective in the prevention of AF and, considering the side-effect profile, they are not a realistic option in the treatment of such a relatively benign arrhythmia as AF.

OTHER UPSTREAM THERAPY

Other potential upstream therapies that target different underlying mechanisms of AF have been investigated in a small number of studies. One of these agents is Vitamin C, a potent anti-oxidant, which has been associated with reduced incidence of post-operative AF and fewer early AF recurrences after electrical cardioversion.[90-92] Still in an experimental phase are agents such as pirfenidone and pioglitazone, which may prevent AF through anti-fibrotic, anti-inflammatory and anti-oxidant properties.[93,94]

An entirely different kind of upstream therapy may potentially consist of moderate exercise. Interesting results came from the Cardiovascular Health Study, a registry of 5446 men and women ≥ 65 years of age enrolled between 1989 and 1990 with a follow-up of 10 years.[95] In these subjects leisure-time activity was assessed at baseline and at the third and seventh annual visit and electrocardiogram was registered annually. During follow-up, 1061 subjects developed new AF. Leisure-time activity, i.e. exercise, was associated with lower incidence of AF, but this depended on the intensity of exercise: AF incidence was lowest in moderate-intensity exercise (i.e. leisure-time activity and walking), whereas high-intensity exercise did not decrease risk of AF. In another study heavy physical activity was associated with increased risk of AF.[96] High-intensity exercise seems to be a risk factor of AF, perhaps through chronic atrial and ventricular volume and pressure overload due to increased RAAS activation, but perhaps increased inflammatory status may also play a role. However, moderate exercise may prevent AF. It may be beneficial through physiological mechanisms (e.g. inducing and maintaining weight loss, lowering blood pressure, and reducing RAAS activation), psychological mechanisms (i.e. improving mental well-being), and by decreasing inflammation, in contrast to heavy exercise.

CONCLUSION

Upstream therapy for AF has increasingly been coming to attention, and the numbers of studies demonstrating that ACE inhibitors, ARBs, ARAs, statins, fish oils, glucocorticoids, and/or moderate physical activity are able to prevent the development or recurrence of AF are growing. Upstream therapy seems to reduce AF, probably in part by improving the underlying cardiovascular disease but possibly also by attenuating structural remodeling processes caused by inflammation, fibrosis, and other not yet identified mechanisms.

Larger randomized clinical trials in well-defined patient groups with well-defined and well-documented outcome parameters are much anticipated for[97] to further elucidate the potential beneficial effects of upstream therapy and to find out in which patients upstream therapy should be indicated.

EXPERT COMMENTARY & FIVE-YEAR VIEW

Current pharmacological rhythm control therapy in AF insufficiently maintains sinus rhythm in most patients because it does not affect the underlying substrate, i.e. structural remodeling. Upstream therapy, which interferes in this remodeling process, seems to be promising and may be more effective in preventing AF recurrences. One condition for upstream therapy to be successful is that it is started early during the course of the disease, when structural remodeling can still be attenuated or reversed, at least long before sinus rhythm is restored, but preferably even at first presentation of AF. In the future, upstream therapy may become a new approach to rhythm control that may support or even in part replace conventional rhythm control, while having a more favorable side-effect profile. Additionally, it possibly may facilitate success of ablation for AF. In all probability, one type of upstream therapy will not suffice, and this new rhythm control approach will include a combination of upstream therapies (e.g. RAAS blockers, statins, ánd lifestyle changes such as moderate exercise) beside conventional rhythm control therapies. In five years upstream therapy will probably be part of the standard treatment of AF. Ultimately, upstream therapy may be used for the primary prevention of AF in selected patients at high risk of developing AF, e.g. patients with hypertension, but results of future studies concerning primary prevention by upstream therapy are to be awaited.

KEY ISSUES

- Structural atrial remodeling caused by inflammation and fibrosis is one of the underlying substrates of AF.
- Upstream therapy that interferes in the structural remodeling process may be more effective in maintaining sinus rhythm.
- Various prospective and retrospective studies demonstrate that upstream therapy consisting of ACE inhibitors, ARBs, statins, fish oils, glucocorti coids, or moderate physical activity, is associated with a reduced incidence of new-onset AF (i.e. primary prevention) and with a reduced recurrence of AF (i.e. secondary prevention).
- Larger randomized clinical trials in well-defined patient groups and with well-defined outcome parameters are required to further elucidate the position of upstream therapy in the primary and secondary prevention of AF.

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VALSARTAN AND RECURRENT ATRIAL FIBRILLATION

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TO THE EDITOR

Disertori et al. (April 16 issue)[1] describe the effects of valsartan on the recurrence of atrial fibrillation. The disappointing results of the trial may be explained by two important limitations. First, no data were provided concerning how long patients were known to have had either atrial fibrillation or underlying heart disease. We would expect that the extent of remodeling would become more severe and even irreversible in patients with a longer history of atrial fibrillation or underlying heart disease. In patients with a shorter history, however, remodeling processes are less advanced, providing more opportunities for blockade of the renin–angiotensin–aldosterone system (RAAS) to be effective.[2] Second, RAAS blockade was probably started too late in the trial – namely, when sinus rhythm was already obtained. Upstream therapy requires more time to influence remodeling processes, and it would have been better if valsartan had been started several weeks before instead of at least 2 days after obtaining sinus rhythm.[3] Thus, the question still remains whether RAAS blockade is effective in maintaining sinus rhythm if it is started as soon as possible after presentation with atrial fibrillation.

Marcelle D Smit, Isabelle C Van Gelder

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THE AUTHORS REPLY

Smit and Van Gelder raise the question of the timing of the administration of valsartan in the evaluation of its effects. We reported the results of two additional analyses involving patients who were in sinus rhythm at 15 days (as prespecified in the protocol)[1] and at 8 weeks (a post hoc analysis) after randomization. No trend in favor of valsartan was apparent. In the 8-week analysis, atrial fibrillation recurred at 1 year in 42.7% of patients in the valsartan group, as compared with 44.0% of those in the placebo group (hazard ratio, 0.96; 96% confidence interval, 0.80 to 1.14; P = 0.62).

With respect to the duration of the history of atrial fibrillation, we do not have this information for the patients in our study. However, we performed a

subgroup analysis as to whether the duration of the last episode of atrial fibrillation had an effect on the results. We did not observe any difference in the effect of valsartan between patients with episodes lasting more than 48 hours and those with shorter episodes.

As Tomoda correctly points out, the efficacy of RAAS blockade in the primary prevention of atrial fibrillation is still an open issue, with current evidence coming from post hoc analyses of large trials, databases, and overviews. Thus, a large, randomized clinical trial of such therapy in the primary prevention of atrial fibrillation may be appropriate. However, such a trial is likely to be difficult to carry out because of the broadening range of use of RAAS inhibitors in a variety of cardiovascular conditions.

Marcello Disertori, Roberto Latini, Aldo P Maggioni

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8B UPSTREAM THERAPY IN PATIENTS WITH EARLY ATRIAL FIBRILLATION - THE RELEVANCE OF THE ROUTINE VERSUS AGGRESSIVE UPSTREAM RHYTHM CONTROL FOR PREVENTION OF EARLY ATRIAL FIBRILLATION IN HEART FAILURE (RACE 3) STUDY

Isabelle C Van Gelder, Marcelle D Smit, Marco Alings, Harry JGM Crijns.

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Atrial fibrillation (AF) is not a benign disease. It is associated with an increased risk of death, stroke, heart failure and hospitalization, an impaired quality of life, and reduced exercise capacity and left ventricular dysfunction. Development of AF is a result of continuous remodeling of the atria, altered metabolism and autonomic changes secondary to ageing, progression of the underlying heart disease, and genetic and environmental factors. Hypertension, congestive heart failure, ischemic heart disease, and diabetes are all well-known risk factors for the development of AF.[1] The first manifestation of AF usually occurs after years of atrial and ventricular remodeling, caused by hypertension or heart failure (Figure 1).[2] Important substrates for AF are fibrosis and inflammation, which form the basis of atrial and ventricular remodeling. One mechanism involved in these processes is activation of the renin-angiotensin-aldosterone system (RAAS), causing increased levels of angiotensin-II and aldosterone, which stimulate fibrosis, hypertrophy and inflammation.[3,4]

Upstream therapy refers to the use of non-antiarrhythmic drugs that modify the atrial substrate to prevent the occurrence of new onset AF (primary prevention) or recurrence of the arrhythmia (secondary prevention). It includes treatment with RAAS blockers (angiotensin-converting enzyme inhibitors [ACEIs], angiotensin receptor blockers [ARBs], and aldosterone antagonists [ARAs]), statins, and omega-3 polyunsaturated fatty acids. ACEIs, ARBs, and ARAs may prevent or reduce atrial structural remodeling especially by decreasing fibrosis. In addition, these drugs improve hemodynamics by lowering of blood pressure and reduction of left ventricular and atrial wall stress.[5] Statins, known for their lipid-lowering capacities, have a variety of pleiotropic properties including attenuation of inflammation through antiatherogenic and antioxidant actions. There is evidence that, through these properties, statins may play a protective role against the development of AF.[6] Rehabilitation programs

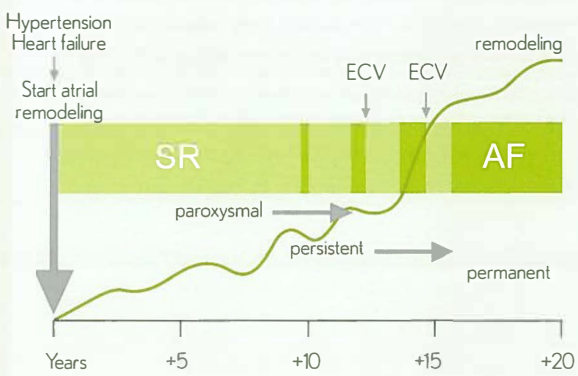

Figure 1. Time course of atrial substrate remodeling starting long before the first episode of AF. Substrates for AF include fibrosis and inflammation induced by activation of the renin-angiotensin-aldosterone system, which may be prevented or reduced by upstream therapy. Adapted with permission from Cosio et al.[2]

AF = atrial fibrillation; ECV = electrical cardioversion; SR = sinus rhythm.

have been introduced as a safe and cost-effective method to increase patients' well-being and exercise tolerance. Besides an increase of 20% in peak oxygen consumption,[7] rehabilitation therapy in patients with heart failure is associated with reversed left ventricular remodelling.[8] Interestingly, rehabilitation therapy is associated with significantly lower AF incidence in older adults.[9]

Rhythm control is the treatment of choice in patients who are symptomatic due to AF. Outcome of a pharmacological rhythm control strategy, however, is still cumbersome. Upstream therapy may improve outcome of pharmacological therapy and, in the long term, may even prevent the need for complex pulmonary vein isolation, which is still a complex procedure with possibly severe complications.[1] Results of upstream therapy for the prevention of AF in animal experiments, hypothesis-generating small clinical studies and retrospective analyses in selected patient categories have been encouraging. Larger prospective randomized trials, however, did fail to show AF prevention with upstream therapy.[10] This disappointing outcome may have been caused by inclusion of patients in whom the extent of remodeling was more severe and even irreversible due to a longer history of AF and underlying heart disease. In patients with a shorter history of AF, remodeling processes are assumingly less advanced, providing more opportunities for RAAS blockade to be effective. This patient category with a short history of both AF and underlying heart disease has not been studied before. In the RACE 3 study we aim to investigate these patients. It is our hypothesis that in patients with early AF and mild to moderate early systolic or diastolic heart failure, aggressive upstream rhythm control, consisting of non-ion-channel antiarrhythmic drugs (ACEIs and/or ARBs, ARAs, and statins), cardiac rehabilitation therapy, counseling and dietary restrictions besides conventional heart failure drugs, increases persistence of sinus rhythm. The institution of a combination of different classes of upstream therapies may have synergistic effects on the atrial substrate by decreasing AF directly through reduction of atrial remodeling and indirectly through reduction of ventricular remodeling. It is our belief that this may ultimately enhance persistence of sinus rhythm and possibly also improve prognosis.

In RACE 3 patients are included with early symptomatic persistent AF (total AF history <2 years, total persistent AF duration <6 months, and ≤1 previous electrical cardioversion), and mild to moderate early heart failure (total heart failure history <1 year, and left ventricular function ≥ 45% and NYHA II to III, and signs of heart failure, or left ventricular ejection fraction 25 to 45% and NYHA class I to III). The primary endpoint of the study is sinus rhythm after one year of follow-up, defined as sinus rhythm during ≥6/7th of assessable time of continuous seven-day Holter monitoring during the last week of the study.

Once more, a study on how to improve therapy and outcome in patients with AF is being performed in the Netherlands with financial support of the Netherlands Heart Foundation (NHS), the Interuniversity Cardiology Institute the Netherlands (ICIN) and the Working Group on Cardiovascular Research the Netherlands (WCN). If we succeed in including all 250 patients within the next 18 months, this combined effort of cardiologists throughout the Netherlands may add to our knowledge on optimal therapy of AF and, once again, may alter forthcoming guidelines for AF.

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9 DISCUSSION AND FUTURE PERSPECTIVES

In this thesis we investigated the clinical and therapeutic implications of remodeling in AF. We studied a variety of patient categories in order of increasing stage of AF severity. We found that in patients with a short history of persistent AF, inflammation seemed to be associated with early AF recurrences (**chapter 2**). Inflammation and sleep apnea as risk factors for AF recurrence were then discussed (**chapter 3**). In permanent AF patients, stringency of rate control did not seem to influence atrial and ventricular remodeling. Instead, progressive adverse remodeling was observed in females (**chapter 4**). In stable severe heart failure patients receiving cardiac resynchronization therapy, low atrial natriuretic peptide (ANP) seemed to reflect a hemodynamic status sensitive for reverse ventricular remodeling, i.e. response to cardiac synchronization therapy, while new-onset AF, permanent AF, and high N-terminal pro-B-type natriuretic peptide (NT-proBNP) were associated with increased mortality (**chapter 5**). In AF patients hospitalized for heart failure, the time course of AF and heart failure development revealed two distinct clinical conditions: patients who developed AF first had a relatively benign prognosis as compared with patients who developed heart failure first (**chapter 6**). We then assessed the potential of influencing the remodeling process in AF by upstream therapy including angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, and statins (**chapter 7**). Upstream therapy may be more effective in patients with a short history of AF due to less extensive remodeling (**chapter 8**).

CAUSES OF ATRIAL REMODELING

Atrial structural remodeling is an important contributor to the initiation and perpetuation of AF and may play a role in AF-related complications. Atrial remodeling starts long before the first manifestation of AF due to underlying disease and other conditions (Figure 1).[1] For years, a number of conditions have been thought to be associated with an increased risk on AF development. Established risk factors include advancing age, hypertension, heart failure, valve disease, diabetes, hyperthyroidism, and coronary artery disease (Table 1).[2] Ageing itself can lead to increased vulnerability to development of AF through various mechanisms including increasing atrial conduction delay, arterial stiffening, and fibrosis, even in the absence of cardiovascular disease.[3,4] Hypertension, heart failure, and valve disease have in common that they lead to atrial hemodynamic overload and stretch, activating a range of processes that cause structural remodeling.[5] Hypertension is one of the most common associated diseases in AF, its prevalence being as high as 80% in the AF patient population while this percentage continues to increase, being responsible for an increasing AF burden.[6,7] Heart failure and valve disease are present in 25-30% of patients with AF.[6] AF and heart failure often co-exist in a reciprocal relationship,[8] as heart failure may cause AF due to hemodynamic and neurohumoral changes and (extra-) cellular remodeling,[9-11] while AF may cause or aggravate heart failure through functional changes (i.e. rapid ventricular

response rates, loss of atrioventricular synchrony, loss of atrial transport) and/ or structural changes (i.e. cellular and extracellular matrix remodeling in atria and ventricles) leading to ventricular dysfunction.[5,9-11] The causal link between diabetes, present in one fifth of AF patients,[6] and AF is complex and not completely understood but may include direct damage to the atrial tissue, atherosclerosis and microvascular disease, autonomic dysregulation, and electrical instability.[2,12] Hyperthyroidism is present in 1% of AF patients.[6] The causal link between increased thyroid hormone as found in hyperthyroidism or, as more recently established, in subclinical hyperthyroidism, may in part be explained by an increased sympathetic tone and by direct myocardial damage and changes in electrophysiological properties induced by thyroid hormone.[2,13-15] Coronary artery disease is present in over 20% of patients with AF and has therefore been classified as a risk factor for AF.[16-18] However, because merely an association between coronary artery disease and AF has been demonstrated, it is uncertain whether uncomplicated coronary artery disease itself causes AF. Furthermore, these associations are based on population studies conducted two decennia ago. Indeed, in a more recent AF population referred for myocardial perfusion imaging because of possible ischemia as suggested by patients' signs and symptoms or by exercise testing, only 3.9% of patients actually had significant angiographic coronary artery disease.[19]

Less well-known, less established, or sometimes perhaps even disregarded risk factors for AF include a range of clinical conditions, physical characteristics, predisposing factors, lifestyle components, and psychological determinants (Table 1). It is uncertain whether all of these conditions are risk factors for AF as some may instead be markers representing cardiovascular risk or AF severity. Chronic obstructive pulmonary disease is one such condition,[2] though reduced lung function has been shown to be associated with increased risk on new-onset AF so there may be a causal link.[20] Diastolic dysfunction

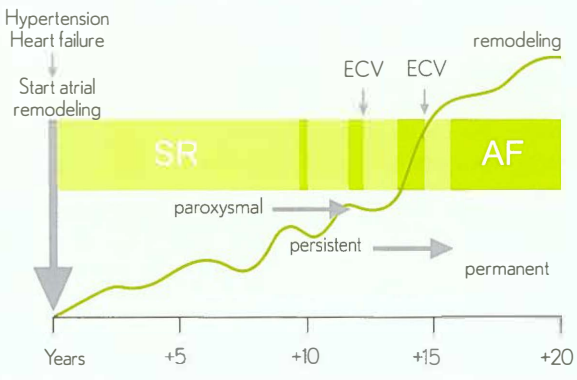


Figure 1. Time course of atrial substrate remodeling starting long before the first episode of AF: Hypothetical representation of how underlying disease such as hypertension or heart failure induces atrial remodeling long before the onset of AF and of how atrial remodeling progresses in relation to the clinical appearance of AF. Adapted with permission from Cosio et al.[1]

AF = atrial fibrillation; ECV = electrical cardioversion; SR = sinus rhythm.

is another clinical condition associated with AF.[21] This would seem logical because of the strong association between hypertension and AF, but the relation between increasing severity of diastolic dysfunction and incident AF has been demonstrated even after adjustment for hypertension history.

Diastolic dysfunction probably causes increased atrial pressures resulting in atrial stretch, again leading to atrial structural remodeling. Sleep apnea is also seen in AF patients and may cause atrial remodeling due to rising atrial pressure or through autonomic changes, though it is uncertain whether the association between sleep apnea and AF is independent of body mass index.[22,23] Another less established risk factor or risk marker in AF is renal dysfunction. Chronic kidney disease, microalbuminuria, and decreasing glomerular filtration rate

Table 1. Conditions associated with AF

Established risk factors

Age[2,16,18,36,51]

Male gender[16,36,51]

Hypertension[2,16,51,52]

Heart failure[2,16,18,36]

Valve disease[2,16,18]

Diabetes[2,16,18,51,52]

Hyperthyroidism[2,53]

Coronary artery disease[2,16,17,51]

Other and less validated associated conditions

Pulmonary disease[2,20]

Diastolic dysfunction[21]

Sleep apnea[2,22]

Renal dysfunction/ proteinuria[2,24-26]

Subclinical thyroid disease[13,14,54]

Subclinical atherosclerosis[27]

Metabolic syndrome[28]

Blood pressure/ pulse pressure[18,30,36,37]

Length[18,31,32,51]

Overweight and obesity[2,33,36,51]

Birth weight[39]

Genetic factors/ familial predisposition[40]

Smoking[24,43]

Alcohol[44,45]

Coffee(?)[34,46]

Endurance training/ excessive exercise[31,47-49,55,56]

Psychological determinants[34,50]

have all been associated with incident AF,[24-26] and may increase risk on AF-related complications.[2] As mentioned previously, not only hyperthyroidism, but high-normal thyroid dysfunction in the presence of normal thyroid stimulating hormone also seems to increase AF risk.[13,27] Subclinical atherosclerosis is associated with increased AF risk as well.[27] The metabolic syndrome, and especially certain components of this clinical condition such as elevated blood pressure, low high-density lipoprotein cholesterol levels, high body mass index, and impaired fasting glucose have been associated with AF.[28,29] Indeed, individual physical characteristics including blood pressure or pulse pressure, length, and body weight or obesity, have also been demonstrated to be correlated with AF risk, not merely in the presence of the metabolic syndrome.[18,23,30-32,32 36] For example, even below the threshold for the diagnosis of hypertension, increasing blood pressures are associated with incident AF,[37,38] though on the other hand low blood pressures also increase AF risk.[38] An early life determinant associated with risk on AF is birth weight, as has been demonstrated in women.[39] Another important predisposing, non-modifiable factor associated with increased AF risk encompasses genetic factors, ranging from familial predisposition to monogenic mutations.[23,40-42] These factors are difficult to influence, in contrast to lifestyle components such as smoking, alcohol, coffee, excessive exercise, and body weight as mentioned previously, which all have more or less been shown to have an incremental association with development of AF.[23,24,34,43-49] Last, psychological factors including anger and acute psychological stress may also increase AF risk.[34,50]

It is evident that the number of conditions possibly associated with AF is substantial. Awareness of the presence of less well-established conditions should increase because many of these conditions, and especially factors attributable to lifestyle, should be relatively easy to influence. Furthermore, there is an important conclusion that can be drawn when discussing conditions such as subclinical hyperthyroidism and blood pressure: the association between certain parameters and risk on AF is probably continuous, even when parameters are below threshold levels conventionally used to determine clinical disease.

The established and less well established risk factors and conditions mentioned above may stimulate atrial remodeling long before the onset of AF. Structural remodeling induces a substrate for the initiation and perpetuation of AF through electrical dissociation.[57] In remodeled atria, triggers such as premature atrial complexes can initiate AF. Once AF is present, atrial electrophysiology is modified ("electrical remodeling"), and structural and electrical remodeling in the atria further deteriorate, constituting a vicious cycle: "AF begets AF".[58] This means that atrial structural remodeling in patients with AF is caused by both the associated diseases and by AF itself. Structural remodeling is a progressive condition, as reflected by increasing electrical dissociation during AF when AF duration increases and as associated diseases progress.[57,59,60] Remodeling may be reversible during early phases of the underlying disease and/ or AF, but in severe associated diseases and during later stages of AF, permanent damage may be induced. Therefore, in the majority of cases the

natural history of AF is characterized by a gradual worsening in time due to progressive adverse structural remodeling.[1] Progressive remodeling makes it challenging to restore and maintain sinus rhythm and may contribute to the occurrence of AF-related complications.

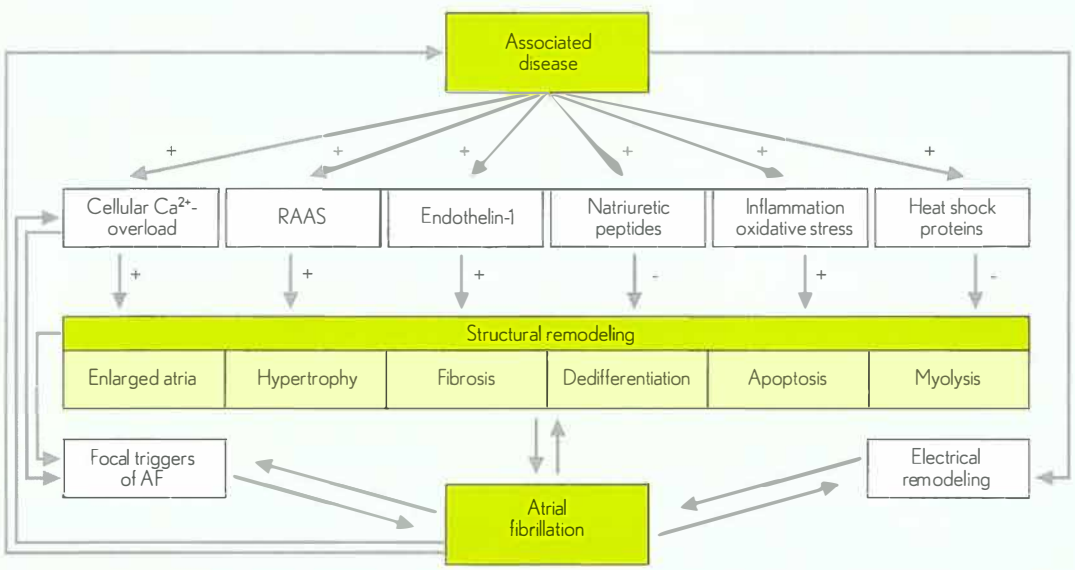
MECHANISMS INVOLVED IN ATRIAL STRUCTURAL REMODELING

Atrial structural remodeling encompasses enlarged atria, hypertrophy, fibrosis, dedifferentiation, apoptosis, and myolysis.[5] In particular, fibrosis constitutes the formation of excessive extracellular matrix consisting of mainly fibroblasts and elastic and collagen fibers through actions of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs).[11,61] The precise mechanisms involved in atrial structural remodeling in AF patients still remain to be elucidated, though a number of pathways have been identified. These pathways are interrelated and include cellular calcium overload, the renin-angiotensin-aldosterone system, transforming growth factor (TGF)-β1, endothelin-1, natriuretic peptides, inflammation, and oxidative stress (Figure 2).[5]

Cellular calcium overload is a result of increased atrial rates during AF enhancing cardiomyocyte calcium influx, and can be cytotoxic, leading to activation of adaptive mechanisms to reduce intracellular calcium. These mechanisms incorporate calcium channel remodeling, altered calcium handling, and structural changes such as atrial hypertrophy and fibrosis which all contribute to calcium overload reduction.[5,62] Activity of the renin-angiotensin-aldosterone system is pronounced in AF due to associated diseases and atrial stretch, which causes increased levels of angiotensin II and aldosterone.[61,63] Angiotensin II and/ or aldosterone stimulate cellular hypertrophy, apoptosis, interstitial fibrosis through extracellular matrix accumulation, and may also have pro-inflammatory properties.[61,64] Angiotensin-II upregulates TGF-β1, an inflammation-associated cytokine that is an important determinant in the signaling cascades stimulating fibrosis.[11,63] Atria seem to be particularly prone to fibrosis due to TGF-β1, as atrial fibroblasts proliferate more upon TGF-β1 stimulation than ventricular fibroblasts, even in the absence of ventricular dysfunction.[11] Endothelin-1 is a potent vasoconstrictor produced by vascular endothelial cells, smooth muscle cells, fibroblasts, and cardiomyocytes. It is promoted by a variety of stimuli including hypoxia, ischemia, and stretch, and may stimulate atrial dilatation, hypertrophy, and fibrosis.[5,65] Natriuretic peptides such as ANP and NT-proBNP are endogenous hormones released from atrial and ventricular cells in response to volume expansion and increased wall stress. They cause natriuresis, vasorelaxation, inhibit aldosterone and renin, and have antihypertrophic, anti-apoptotic, anti-inflammatory, and antifibrotic effects.[5,61] Natriuretic peptides therefore seem to be part of an adaptive response of the atria and ventricles to correct hemodynamic imbalances and prevent further remodeling. Inflammation is another mechanism involved in remodeling, and can be caused by associated diseases such as hypertension.[66]

Inflammatory cytokines including tumor necrosis factor (TNF)-α and interleukin (IL)-6 are potent regulators of extracellular matrix accumulation. Last, calcium accumulation and other mechanisms can lead to oxidative stress.[63] Reactive oxygen species activate MMPs and TIMPs and lead to altered extracellular matrix metabolism.[61,63] Reactive oxygen species are also influenced by the renin-angiotensin-aldosterone system through angiotensin-II, which again underscores the interrelatedness of the mechanisms involved in atrial structural remodeling.[63]

Figure 2. Flow chart showing the series of events caused by stretch. Hypothetical scheme of stretch induced by hypertension, heart failure and possibly extreme endurance exercise leading to calcium overload, activation of the renin-angiotensin-aldosterone system (RAAS) and release of different factors, resulting in structural remodeling and finally in AF. Adapted with permission from De Jong et al.[5]



ASSESSMENT OF ATRIAL REMODELING IN THE AF PATIENT

Components of atrial structural remodeling can be found in atrial tissue biopsies of AF patients, including enlarged atria, hypertrophy, fibrosis, cell death, myolysis, and inflammation.[5] It is neither possible nor desirable to obtain atrial tissue biopsies from the AF patient in clinical practice, which means that physicians and researchers will have to contend with less or non-invasive surrogate markers to assess the degree of atrial remodeling in AF patients. These markers include clinical parameters such as age, associated disease, and AF duration, parameters obtained through imaging or other non-invasive techniques, and circulating biomarkers involved in the structural remodeling process.

There is probably quite some overlap between clinical parameters that can suggest severity of remodeling and clinical conditions associated with increased risk on AF as mentioned in Table 1. It is unknown whether there is a straightforward correlation between these clinical parameters and the extent of remodeling, nor has the influence on structural remodeling been investigated for all of these clinical parameters. Clinical conditions in which atrial remodeling has been substantiated include increasing age, hypertension, heart failure, valve disease, and increasing AF duration.[5,11,57,66-68] Gender may be another clinical parameter, as females may be more at risk of adverse remodeling than males (**chapter 4**).[69] In general, clinical parameters seem to be non-specific measurements, representing an overall risk on atrial remodeling in AF patients.

Imaging and other non-invasive techniques can be used to measure degree of atrial remodeling in more specific terms and are increasingly being developed. One of the most simple and easily applicable tools consists of transthoracic echocardiography. Atrial dilatation is one of the changes seen in atrial remodeling, and increased echocardiographic left atrial size has been shown to be correlated with degree of atrial fibrosis.[70] Atrial size can be assessed by measuring linear dimensions of left and right atria, though they inaccurately represent true atrial size because of asymmetric remodeling of the atrial chambers.[71] Atrial volume measurements provide more accurate assessments. Left atrial volume can be quantified using various methods, of which the biplane Simpson's method is considered to be the most accurate.[71] There are less data available on quantification of right atrial size, and because biplane measurements are not standard, we have to contend with less accurate single plane methods for assessment of right atrial volume.[71] When assessing atrial size it is important to realize that these dimensions are influenced by body size. Atrial measurements should therefore be indexed to body size in order to be able to compare atrial sizes between patients,[71] especially between males and females. Since atrial volumes are assessable, it is possible to determine atrial ejection fractions, which could possibly reflect atrial function. An upcoming method to assess atrial function consists of Doppler-derived atrial strain rate imaging, which reflects atrial myocardial deformation and may be a potential marker of atrial remodeling,[72,73] though this method is technically limited due to the thin

atrial wall. Other accurate tools to quantify atrial size consist of magnetic resonance imaging, multi-slice computed tomography, and real-time three-dimensional echocardiography,[74] though as of today, these methods are not easily applied in clinical practice. Magnetic resonance imaging is more recently also being used to detect atrial fibrosis using delayed enhancement techniques.[75] Beside atrial size and fibrosis, electrophysiological parameters can represent remodeling. Using tissue velocity imaging assessed with transthoracic echocardiography, it is possible to measure total atrial conduction time during sinus rhythm and cycle length of the atrial fibrillatory wall motion and atrial fibrillatory wall velocities during AF.[76,77] Mapping studies reveal electrical activity observed in AF, showing conduction disturbances caused by atrial remodeling and thereby representing the complexity of the atrial substrate.[78,79] However, mapping constitutes an invasive technique that is performed during cardiac surgery or electrophysiological studies. Noninvasive electrocardiographic mapping tools are now being developed, using between 56 and 256 electrodes applied to the patients' torso surface,[80-82] and seem to be promising techniques to assess severity of atrial remodeling in the AF patient in clinical practice.

Circulating biomarkers measured in serum or plasma that may be involved in atrial remodeling may indeed also reflect severity of atrial remodeling. One limitation of these biomarkers is that they are also affected by other factors such as underlying disease and ventricular remodeling, and as of today no atrium-specific biomarker has been identified.[83] A broad range of biomarkers have been studied in relation to atrial remodeling, incident AF, and AF progression. These biomarkers include direct components of the renin-angiotensin-aldosterone system, i.e. renin, angiotensin II, and aldosterone; TGF-β1; natriuretic peptides and other markers of hemodynamic stress such as apelin; inflammatory markers including (high sensitivity) C-reactive protein (CRP), TNF-α, IL-6, soluble intercellular adhesion molecule-1, fibrinogen, and myeloperoxidase; markers of oxidative stress such as homocysteine; the vasoconstrictor endothelin-1; and downstream profibrotic markers including MMPs and TIMPs.[65,84-90] Regarding incident AF in the general population, natriuretic peptides and inflammatory markers seem to have the best predictive value,[84,88,89,91] though such results should be interpreted with the limitation kept in mind that not all potential biomarkers involved in atrial remodeling have been studied. Regarding AF progression, the balance between MMPs and TIMPs seems to differ between paroxysmal and persistent AF, suggesting that the intensity of collagen turnover is related to AF burden.[92] The inflammatory biomarkers IL-6 and CRP have been shown to be positively related to increased left atrial diameter and AF duration even in nonoperative-related AF.[93] In heart failure patients, ANP is positively correlated with increasing AF burden in AF patients, though a correlation between ANP and increasing left atrial volume only exists in patients without AF (**chapter 5**). Low ANP also seems to reflect a hemodynamic status sensitive for reverse ventricular remodeling, i.e. response to cardiac synchronization therapy, in heart failure patients (**chapter 5**). A number of biomarkers seem to be predictive of AF recurrence, perhaps reflecting more extensive remodeling, though studies have shown

varying results. Increased TGF-β1 levels have been associated with failure of electrical cardioversion,[85] and increased ANP and NT-proBNP seem to predict AF recurrence in patients with paroxysmal and/ or persistent AF.[87,94] Several studies have demonstrated a relation between CRP and recurrence of AF,[95,96] though in general the association between inflammatory biomarkers and AF recurrence is not robust.[97] The varying associations found between circulating biomarkers and AF recurrence and progression can probably be explained by the heterogeneous study populations with varying underlying disease, AF history, and type of AF, by diverse selections of biomarkers investigated, by differences in time points at which the biomarkers were assessed, e.g. during AF directly before cardioversion or later during sinus rhythm, and by different endpoints and definitions of AF recurrence used. Levels of biomarkers can be influenced by severity of underlying disease and by the presence and duration of AF.[98,99] Furthermore, specific mechanisms may influence type of AF recurrence, e.g. inflammation and thus inflammatory biomarkers may be associated with early AF recurrences, while fibrosis and thus fibrotic biomarkers may be associated with progression to permanent AF (**chapter 2**).

CONSEQUENCES OF ATRIAL REMODELING

Atrial remodeling is a progressive condition, making it challenging to restore and maintain sinus rhythm in patients with AF and perhaps contributing to the occurrence of AF-related complications. Indeed, paroxysmal AF progresses to persistent or permanent AF in a substantial number of patients (Table 2). In patients with persistent AF, recurrence rates within one month after electrical cardioversion are high, ranging between 37% and 68%.[100-102] Despite rhythm control treatment, within a year persistent AF progresses to permanent AF in one third of persistent AF patients.[102,103] As shown in Table 2, and as can be appreciated from a pathophysiological point of view, progression rates seem to vary depending on the varying prevalence of underlying disease. Recently a scoring system was developed to help identify patients who are likely to progress to persistent AF within one year: in the HATCH (heart failure, age, previous transient ischemic attack or stroke, chronic obstructive pulmonary disease, hypertension) score, one point is scored for every component.[7] In the Euro Heart Survey study, almost half of patients with a HATCH score > 5 progressed to persistent AF while AF progression was observed in only 6% of patients with a HATCH score of 0.7

AF progression is probably of clinical and prognostic relevance, since increased major adverse events including hospital admissions and stroke are observed in patients in whom AF progresses to more sustained forms.[7] Interestingly, the $CHADS_2$ (cardiac failure, hypertension, age, diabetes, stroke [doubled]) risk score, used to assess stroke risk in AF patients,[2] contains almost the same components as the HATCH score. Markers of AF progression therefore also seem to be markers of AF-related complications. At first glance it would therefore seem logical that AF progression is associated with

Table 2. Progression of AF

Study	Patients	Follow-up	AF progression
Kerr et al., Canadian registry of AF[104]	Median age 64 years 38% female 100% paroxysmal AF 37% hypertension 15% heart failure 30% coronary artery disease 15% respiratory disease	1 year	8.6% progressed to chronic AF
De Vos et al., Euro Heart Survey[7]	Mean age 64 years 43% female 14% first detected AF 86% paroxysmal AF 62% hypertension 21% heart failure 19% valve disease 32% coronary artery disease 11% respiratory disease	1 year	15% progressed to persistent AF
Smit et al. (chapter 2)	Mean age 65 years 26% female 100% persistent AF 67% hypertension 20% heart failure 18% coronary artery disease 10% respiratory disease	1 year	29% progressed to permanent AF
Gianfranchi et al.[105]	Mean 70 years 49% female 100% paroxysmal AF + AVJ ablation + dual-chamber PM 10% valve disease 19% coronary artery disease 41% other cardiac disease (22% after 1 year)	23 months	35% progressed to permanent AF
Ruigomez et al.[106]	Mean age males 67 years Mean age females 73 years 51% female 100% paroxysmal AF 43% coronary artery disease 7% valve disease 7% other cardiac disease	2.7 years	16.7% progressed to chronic AF
Kato et al.[107] (Japanese study)	Mean age 58 years 27% female 100% paroxysmal AF 35% hypertension 21% heart failure 21% valve disease 16% coronary artery disease	14.1 years	77.2% progressed to chronic AF (5.5% per year)
Jahangir et al., Olmsted County[108]	Mean age 44 years 22% female 45% paroxysmal AF 49% persistent AF 7% permanent AF 100% lone AF	25.2 years	31% of paroxysmal/ persistent AF patients progressed to permanent AF

AF = atrial fibrillation; AVJ = atrioventricular junctional; PM = pacemaker.

worse outcome because progression risk increases as severity of associated diseases increases, which themselves may be responsible for higher event rates. On the other hand, large baseline left atrial size and increasing left atrial size during follow-up are associated with adverse cardiovascular events in hypertensive patients and lone AF patients, respectively.[109,110] There also seems to be some evidence that, at least in patients with heart failure, development of AF in patients with a known heart failure history (**chapters 5 and 6**) and increasing AF burden (**chapter 5**) is independently associated with worse prognosis. However, it remains difficult to establish whether adverse atrial remodeling and increasing AF burden or AF progression independently lead to adverse events or whether they just reflect severity of the associated disease, as until now we have not succeeded in eliminating AF.[111,112] This problem may therefore only be solved once we can truly maintain sinus rhythm and reverse atrial remodeling in the AF patient. Current studies investigating outcome after catheter ablation in AF such as the CABANA trial (ClinicalTrials.gov Identifier NCT00911508) and the EAST trial (conducted by the German Atrial Fibrillation Competence Network and the European Heart Rhythm Association) may therefore provide more insight into the question whether true elimination of AF will actually improve prognosis.

THERAPEUTIC IMPLICATIONS OF ATRIAL REMODELING AND FUTURE PERSPECTIVES

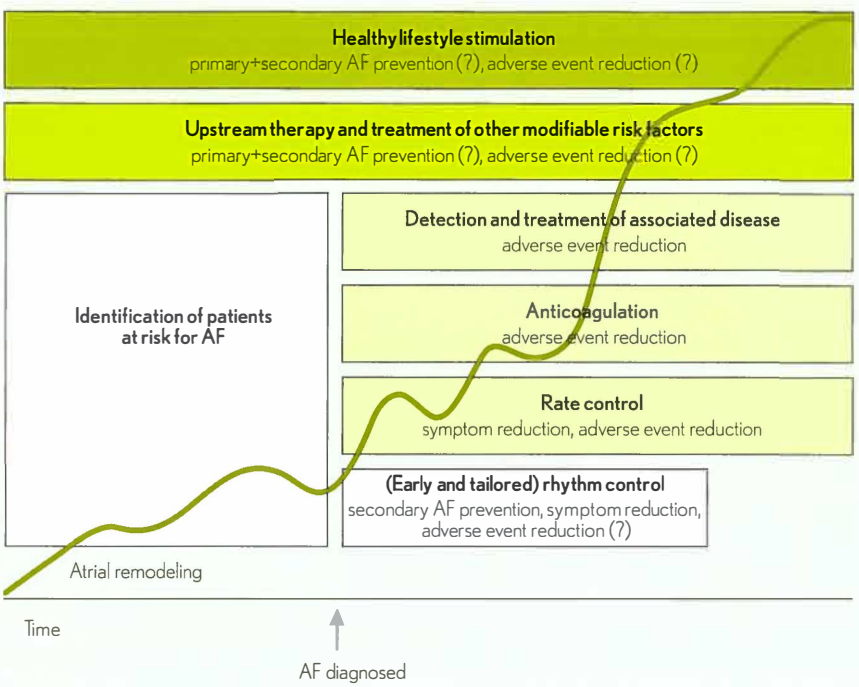
Current management of AF is aimed at preventing AF-related events and at reducing symptoms.[2] Prevention of AF-related events relies on adequate detection and treatment of associated diseases, anticoagulation, and control of ventricular rate (Figure 3). Symptom reduction is primarily pursued with rate control therapy, though additional rhythm control consisting of cardioversion, antiarrhythmic drug therapy, or ablation may be required. Regarding rate control, lenient rate control has been shown to be neither related to more adverse atrial and ventricular remodeling (**chapter 4**) nor to increased cardiovascular morbidity and mortality than strict rate control in permanent AF patients.[113] This makes it reasonable to initiate a lenient rate control strategy aimed at a resting heart rate < 110 beats per minute in patients with AF.[2]

In the future, management of AF will probably expand (Figure 3). Aggressive detection and treatment of associated conditions including conditions and risk factors that previously were not considered to be pathological, such as subclinical hyperthyroidism and high-normal blood pressures, may become increasingly important. Treatment of associated conditions and modifiable risk factors should become more stringent and will probably incorporate therapies aimed against atrial remodeling and stimulation to adopt a healthy lifestyle, though it remains to be investigated whether this will improve outcome in terms of AF progression and AF-related events. Of interest, such treatment could even prevent AF to ever develop if started long before the first manifestation of AF. Indeed, primary prevention will become an ultimate goal in AF management, but it requires adequate identification of patients at

risk for AF and adequate, tailored treatment. Improved understanding of the genetic basis of AF is expected to play an important role in the development of tailored primary prevention therapies.

Upstream therapy, including renin-angiotensin-aldosterone system inhibitors and statins, should possibly also be incorporated in the management of AF (Figure 3).[2] Various upstream therapies are already indicated in a variety of associated diseases including hypertension and heart failure, and they may halt the structural remodeling process by targeting components of atrial remodeling including fibrosis, inflammation, and oxidative stress. Indeed, reverse echocardiographic remodeling has even been observed in patients with ongoing AF (**chapter 4**). Upstream therapy may improve outcome of rhythm control therapy and could prevent or postpone the need for ion-channel antiarrhythmic drugs and/ or ablation while having less side-effects and lower risk on adverse events (**chapter 7**).[114] Beside prevention of AF progression

Figure 3. Schematic representation of current and possible future components of AF treatment with atrial remodeling in the background. Long before AF is diagnosed, identification of patients at risk for AF (white box) in order to start treatment of modifiable risk factors and other therapies targeted against atrial remodeling (medium green box) may prevent development of AF, i.e. primary AF prevention. Such therapies may also improve rhythm control in AF (secondary prevention) and reduce adverse events. A healthy lifestyle (dark green box) should be incorporated in everyday life and may also prevent AF development, AF progression, and adverse events. Once AF is present, the three light green boxes denote current established treatment recommendations in case of diagnosed AF.[2] Rhythm control is now recommended to support symptom reduction if required. In the future rhythm control should be tailored to the individual patient based on the extent of atrial remodeling and, if true sinus rhythm can be maintained, may ultimately reduce adverse events.
AF = atrial fibrillation.



by improvement of rhythm control, there is evidence that upstream therapy also lowers the risk on cardiovascular morbidity and mortality in AF patients (**chapter 6**).[115-118] Over the past years, a trend towards reduction of events can be observed (Figure 4), probably because of improved treatment of associated conditions in which upstream therapy may play a role. Due to the increasing prevalence of AF especially in the elderly and its impact on cardiovascular morbidity and mortality, upstream therapy constitutes a promising and safe intervention that can improve outcome in AF and therefore promote healthy ageing. Similarly, dronedarone could become an important constituent of AF treatment. This new antiarrhythmic drug has a beneficial safety profile both in AF patients without structural heart disease and in those with stable mild to moderate heart disease.[119,120] Dronedarone may improve outcome of rhythm control therapy and has been shown to reduce cardiovascular hospitalizations in patients with AF.[119-121]

Based on the current knowledge, assessment of the degree of atrial remodeling will be useful to identify which AF patients will respond to therapies aimed at halting AF progression and improving outcome. Such assessment will enable institution of tailored therapy for the individual AF patient. For example, in patients in whom the damage of the remodeling process has become permanent, rhythm control should not be attempted anymore. On the other hand, in patients with a short history of AF, the substrate for AF is probably less complex and may be even reversible when rhythm control, complemented by upstream therapy, is initiated early during the course of the disease.[122,123] Early catheter ablation could become part of such early rhythm control management. Other tailored therapy in AF patients could consist of specific therapies targeting specific mechanisms involved in the remodeling process.

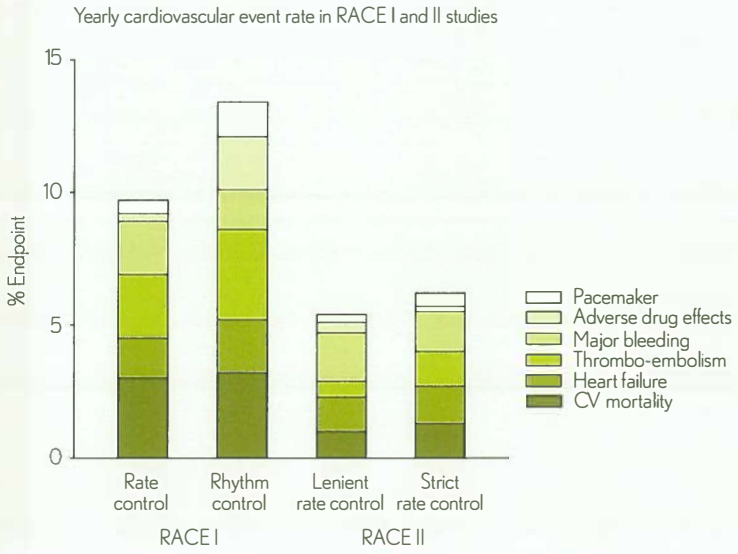


Figure 4. Yearly cardiovascular morbidity and mortality rate in the RACE I study (published in 2002) [112] and the RAte Control Efficacy in permanent atrial fibrillation (RACE) II study (published in 2010).[113]
CV = cardiovascular.

For instance, short and intensive anti-inflammatory treatment with glucocorticoids started short before and stopped one month after electrical cardioversion may prevent early AF recurrences, which consequently could decrease the risk on AF progression (**chapter 2**). Whether true maintenance of sinus rhythm and reversal or interruption of the atrial remodeling process will ultimately improve outcome in AF patients remains to be elucidated. Future studies aimed at improving detection of the extent of remodeling and at investigating new treatment strategies specifically tailored to the "severity of AF" in individual AF patients are much awaited for.

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SUMMARY

Atrial fibrillation is the most common cardiac arrhythmia. Currently more than 6 million people in Europe are affected and this number is expected to increase twofold during the next 30 to 50 years partly due to the ageing population. Atrial fibrillation is responsible for an increased risk on death, stroke, and heart failure, reduced exercise capacity, and an impaired quality of life, even though treatment has improved over the past decades. Furthermore, atrial fibrillation is a persevering arrhythmia that keeps on recurring despite continuing attempts to restore normal sinus rhythm including electrical cardioversions and strong anti-arrhythmic drugs. This means that there is still much progression to be made in the treatment of atrial fibrillation.

Over the past years the role of structural atrial remodeling in atrial fibrillation has increasingly become apparent. Structural remodeling of the atrial chambers of the heart constitutes atrial dilatation and changes in the atrial tissue including enlargement of cardiac muscle cells, fibrosis (deposition of elastic and collagen fibers between cardiac muscle cells), changes in function of cardiac cells, and programmed cell death. Remodeling starts long before the first manifestation of atrial fibrillation due to increasing age and underlying conditions such as increased blood pressure, heart failure, valve disease, and diabetes, and is probably also influenced by other factors such as genetic and environmental influences. As a consequence of structural remodeling, a substrate is created for atrial fibrillation due to electrical dissociation between muscle bundles and disarray of conduction circuits which favors the development and perseverance of atrial fibrillation. Furthermore, once atrial fibrillation develops, it activates the structural remodeling processes even more, causing a vicious cycle. Hence, structural remodeling in patients with atrial fibrillation is caused both by the associated conditions and by atrial fibrillation itself. Structural remodeling may be reversible during early phases of atrial fibrillation, but permanent damage may be induced during later stages of atrial fibrillation and in severe associated diseases. Therefore, in the majority of cases the natural history of atrial fibrillation is characterized by a gradual worsening in time due to progressive structural remodeling. This explains why atrial fibrillation is such a perseverant arrhythmia. Furthermore, the continuing remodeling processes may also contribute to the impaired prognosis in atrial fibrillation patients.

Assessment of the degree of structural remodeling in patients with atrial fibrillation could therefore be useful for identifying patients who will respond to treatment aimed at restoring and maintaining normal sinus rhythm or other therapies aimed at freezing the progression of atrial fibrillation and improving outcome. As of today, however, it is difficult to directly measure the degree of remodeling in atrial fibrillation patients. Indirectly, degree of remodeling may be reflected by clinical parameters such as age, underlying disease, and duration of atrial fibrillation, echocardiographic parameters such as atrial size, and markers ("biomarkers") obtained from blood samples that may be involved in the remodeling process.

Therapy that halts the remodeling process in atrial fibrillation is called upstream therapy. Upstream therapy targets specific mechanisms involved

in atrial remodeling and generally has a side-effect profile preferable to conventional antiarrhythmic medication. Examples of upstream therapy include angiotensin-converting-enzyme inhibitors (antihypertensive medication) and statins (lipid-lowering medication). Such therapy may be more effective in atrial fibrillation patients in whom remodeling processes are less extensive and perhaps even reversible, such as patients with a short history of atrial fibrillation ("short-lasting atrial fibrillation") and/ or underlying disease.

The aim of this thesis was to investigate the clinical and therapeutic implications of remodeling in atrial fibrillation. In **chapter 1** the general introduction and background of this thesis was discussed, as summarized above.

Then a variety of patient categories with increasing stages of severity of atrial fibrillation and underlying disease were studied. In **chapter 2** we started off with patients with short-lasting atrial fibrillation, whom have never been studied before. We assessed the mechanisms of atrial remodeling involved in early atrial fibrillation recurrence by investigating several markers of remodeling. Short-lasting atrial fibrillation patients undergoing treatment to restore normal sinus rhythm ("rhythm control") were included in this study, and various markers of remodeling were collected, including risk factors and underlying disease, echocardiographic parameters, and biomarkers obtained from blood samples. We found that recurrences within one month ("early atrial fibrillation recurrences") seemed to be predominantly associated with inflammation. This finding is clinically valuable, because this could imply that specific treatment targeting inflammation may increase restoration and persistence of normal sinus rhythm. In **chapter 3** we discussed various mechanisms and risk factors involved in atrial remodeling, including inflammation and the sleep apnea syndrome.

In **chapter 4** we moved on to permanent atrial fibrillation patients in whom restoration of normal sinus rhythm is not attempted anymore. The primary treatment in patients with permanent atrial fibrillation consists of rate control, which means that the fast heart rate in atrial fibrillation is lowered by use of rate control medication. We investigated whether remodeling was influenced by the strictness in which heart rate was controlled. Changes in echocardiographic parameters were compared between patients undergoing lenient rate control therapy (heart rate < 110 beats per minute) and patients undergoing strict rate control therapy (heart rate < 80 beats per minute). We found that lenient rate control did not seem to lead to more adverse remodeling than strict rate control. Instead, adverse remodeling was observed in females.

Patients receiving a special biventricular pacemaker to improve prognosis in severe heart failure, called cardiac resynchronization therapy, were studied in **chapter 5.** Not all patients respond to cardiac resynchronization therapy, and atrial fibrillation may be one of the factors influencing effectiveness of this treatment modality. In this study we investigated the influence of natriuretic peptides (biomarkers of hemodynamic stress released from atrial and ventricular tissue) and atrial fibrillation on two outcome parameters of cardiac resynchronization therapy. These outcome parameters consisted of response, defined as reversal of ventricular chamber dilatation, and mortality.

We found that low levels of atrial natriuretic peptide and dilated ventricular chambers were associated with response to cardiac resynchronization therapy. Furthermore, we found that development of atrial fibrillation for the first time ("new-onset atrial fibrillation"), permanent atrial fibrillation, and elevated levels of N-terminal pro-B-type natriuretic peptide were associated with increased mortality.

The most severe patient category studied in this thesis consisted of patients with atrial fibrillation hospitalized for heart failure (**chapter 6**). We assessed their prognosis based on the time course in which atrial fibrillation and heart failure developed. In other words, we compared clinical presentation and outcome between patients who developed atrial fibrillation before or consecutively with heart failure ("atrial fibrillation first") and patients who developed atrial fibrillation after heart failure ("heart failure first"). Two distinct clinical conditions were revealed: patients who developed atrial fibrillation first had a relatively benign prognosis as compared with patients who developed heart failure first.

We then assessed the potential of influencing the remodeling process and outcome of atrial fibrillation by upstream therapy. In **chapter** 7 we reviewed the current literature regarding upstream therapy for atrial fibrillation, including angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, and statins. In **chapter** 8 we discussed why upstream therapy may not be effective in all atrial fibrillation patients and provided the rationale and design of the Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) study, performed in short-lasting atrial fibrillation patients in whom we expect that upstream therapy will be effective in freezing atrial fibrillation progression.

Finally we discussed the overall clinical and therapeutic implications of remodeling in atrial fibrillation in **chapter 9** while referring to the findings of this thesis. In the future, we believe that assessment of the degree of atrial remodeling will be useful to develop therapies aimed at freezing atrial fibrillation progression that are specifically tailored to the individual patient. Ultimately such therapies will improve prognosis of atrial fibrillation.

SAMENVATTING

Boezemfibrilleren is de meest voorkomende hartritmestoornis. Op dit moment hebben meer dan 6 miljoen mensen in Europa deze ritmestoornis en de verwachting is dat dit aantal zich de komende 30 tot 50 jaar zal verdubbelen, mede door de vergrijzing. De gevolgen van boezemfibrilleren zijn ernstig: een verhoogd risico op overlijden, beroerte en hartfalen, een afgenomen inspanningstolerantie en een afgenomen kwaliteit van leven. Ondanks continue inspanningen om het normale sinusritme te herstellen met behulp van onder andere elektrische cardioversies en sterke anti-aritmische medicijnen, keert deze stoornis steeds terug. Dit betekent dat er nog veel te verbeteren valt aan de behandeling van boezemfibrilleren.

De afgelopen jaren is de rol van structurele remodeling in de boezems ("atria") ten aanzien van boezemfibrilleren steeds duidelijker aan het worden. Structurele remodeling van de boezemkamers van het hart bestaat uit dilatatie (vergroting) van de boezems en veranderingen in het boezemweefsel, zoals vergroting van hartspiercellen, fibrose (afzetting van elastische en collageenvezels tussen de hartspiercellen), veranderingen in functie van hartcellen en geprogrammeerde celdood. Remodeling begint, lang voordat boezemfibrilleren zich voor het eerst manifesteert, door toenemende leeftijd en onderliggende aandoeningen zoals verhoogde bloeddruk, hartfalen, hartklepaandoeningen en suikerziekte, en wordt waarschijnlijk ook beïnvloed door genetische en omgevingsfactoren. Als gevolg van structurele remodeling wordt een substraat voor boezemfibrilleren gecreëerd dat de ontwikkeling en instandhouding van boezemfibrilleren bevordert dankzij elektrische dissociatie tussen hartspierbundels en wanorde in geleidingsbanen. Bovendien wordt het structurele remodelingsproces nog verder geactiveerd zodra boezemfbrilleren eenmaal aanwezig is, waardoor een vicieuze cirkel ontstaat. Structurele remodeling bij patiënten met boezemfibilleren wordt dus zowel veroorzaakt door onderliggende aandoeningen als door boezemfibrilleren zelf. Structurele remodeling kan omkeerbaar zijn in vroege fasen van boezemfibrilleren, maar in latere stadia en bij ernstige onderliggende aandoeningen kan de schade permanent zijn geworden. In de meeste gevallen wordt het natuurlijke beloop van boezemfibrilleren dus gekenmerkt door een geleidelijke verslechtering door progressieve structurele remodeling. Dit verklaart waarom boezemfibrilleren zo'n hardnekkige ritmestoornis is. Bovendien zou het continuerende remodelingsproces ook een bijdrage kunnen leveren aan de verminderde prognose van patiënten met boezemfibrilleren.

Voor de identificatie van patiënten met boezemfibrilleren die zullen reageren op behandeling gericht op herstel en behoud van het normale sinusritme of op andere behandelingen gericht op het stilzetten van progressie van boezemfibrilleren en het verbeteren van de prognose, zou een inschatting van de mate van structurele remodeling bruikbaar kunnen zijn. Vandaag de dag is het echter moeilijk om de mate van remodeling rechtstreeks te meten in patiënten met boezemfibrilleren. Indirect zou de mate van remodeling vertegenwoordigd kunnen worden door klinische parameters zoals leeftijd, onderliggende ziekte en duur van boezemfibrilleren, echocardiografische parameters zoals boezemgrootte, en stofjes in het bloed ("biomarkers") die betrokken zijn bij het remodelingsproces.

Behandeling die het remodelingsproces stilzet heet upstream therapy. Upstream therapy richt zich op specifieke mechanismen die betrokken zijn bij atriale remodeling en heeft vaak een gunstiger bijwerkingenprofiel dan gebruikelijke antiaritmische medicatie. Voorbeelden van upstream therapy zijn angiotensine-converting-enzyme inhibitoren (bloeddrukverlagende medicatie) en statines (cholesterolverlagende medicatie). Dergelijke therapie zou effectiever kunnen zijn bij patiënten bij wie de remodelingsprocessen minder vergevorderd zijn en misschien zelfs omkeerbaar, zoals patiënten met een korte voorgeschiedenis van boezemfibrilleren ("kortdurend boezemfibrilleren") en/ of onderliggende hartziekte.

Het doel van dit proefschrift was om de klinische en therapeutische implicaties van remodeling in boezemfibrilleren te onderzoeken. In **hoofdstuk 1** werd de algemene introductie en achtergrond van dit proefschrift behandeld, zoals boven is samengevat.

Daarna werd een reeks patiëntencategorieën bestudeerd in volgorde van toenemende ernst van boezemfibrilleren en onderliggende aandoeningen. In **hoofdstuk 2** begonnen we met patiënten met kortdurend boezemfibrilleren. Deze categorie patiënten is nooit eerder bestudeerd. We onderzochten mechanismen van atriale remodeling die betrokken zijn bij het recidiveren van boezemfibrilleren door diverse parameters van remodeling te analyseren. Patiënten met kortdurend boezemfibrilleren die een behandeling ondergingen om het normale sinusritme te herstellen ("ritmecontrole") werden in deze studie ingesloten en er werden verscheidene remodelingsparameters verzameld, zoals risicofactoren en onderliggende aandoeningen, echocardiografische parameters en biomarkers die in het bloed zijn gemeten. We ontdekten dat het recidiveren van boezemfibrilleren binnen één maand ("vroege recidieven") vooral geassocieerd leek te zijn met inflammatie, ofwel ontsteking. Deze bevinding is klinisch relevant, want dit zou kunnen betekenen dat bepaalde therapieën, die inflammatie aanpakken, het herstel en behoud van het normale sinusritme zouden kunnen verbeteren. In **hoofdstuk 3** bespraken we diverse mechanismen en risicofactoren die betrokken zijn bij atriale remodeling, zoals inflammatie en het slaapapneusyndroom.

In **hoofdstuk 4** gingen we verder met patiënten met permanent boezemfibrilleren, bij wie er geen pogingen meer worden gedaan om het normale sinusritme te herstellen. De primaire behandeling van deze patiënten bestaat uit rate control, ofwel het verlagen van de snelle hartslag met behulp van rate control medicatie. We onderzochten of remodeling beïnvloed werd door de strengheid waarop de hartslag werd beheerst. Veranderingen in echocardiografische parameters werden vergeleken tussen patiënten die met soepele rate control behandeld werden (hartslag < 110 slagen per minuut) en patiënten die met strenge rate control behandeld werden (hartslag < 80 slagen per minuut). We ontdekten dat soepele rate control niet tot meer nadelige remodeling leek te leiden dan strenge rate control. In plaats daarvan bleek juist dat nadelige remodeling plaatsvond bij vrouwen.

Patiënten die een speciale pacemaker ontvingen die bedoeld is om de prognose te verbeteren van ernstig hartfalen, zogenaamde cardiale resynchro-

nizatietherapie, werden bestudeerd in **hoofdstuk 5**. Niet alle patiënten die cardiale resynchronizatietherapie ondergaan reageren goed op deze behandeling. Bovendien kan boezemfibrilleren de effectiviteit van deze therapie nadelig beïnvloeden. In deze studie onderzochten we de invloed van natriuretische peptiden (biomarkers van hemodynamische stress die uitgescheiden worden door boezem- en kamerweefsel) en boezemfibrilleren op twee uitkomstparameters van cardiale resynchronizatietherapie. Deze uitkomstparameters bestonden uit respons, gedefinieerd als omkering van hartkamerdilatatie, en overlijden ("mortaliteit"). We ontdekten dat lage spiegels van atriale natriuretische peptide en gedilateerde hartkamers geassocieerd waren met respons op cardiale resynchronizatietherapie. Ten tweede bleek dat er drie factoren waren geassocieerd met toegenomen mortaliteit: het ontwikkelen van boezemfibrilleren voor de eerste keer, permanent boezemfibrilleren en hoge spiegels van N-terminal pro-B-type natriuretische peptide.

De meest ernstige patiëntencategorie die in dit proefschrift werd onderzocht bestond uit patiënten met boezemfibrilleren die zijn opgenomen voor hartfalen (**hoofdstuk** 6). We onderzochten hun prognose gebaseerd op de volgorde waarin boezemfibrilleren en hartfalen zich hebben ontwikkeld. Met andere woorden: we vergeleken de klinische presentatie en uitkomst tussen patiënten die boezemfibrilleren vóór of tegelijkertijd met hartfalen ontwikkelden ("boezemfibrilleren eerst") en patiënten die boezemfibrilleren ná hartfalen ontwikkelden ("hartfalen eerst"). We ontdekten dat dit twee afzonderlijke klinische aandoeningen onthulde. Patiënten die eerst boezemfibrilleren ontwikkelden hadden een relatief gunstige klinische presentatie en prognose vergeleken met patiënten die eerst hartfalen ontwikkelden.

Daarna bespraken we de mogelijkheid om het remodelingsproces en de prognose van boezemfibrilleren te beïnvloeden met behulp van upstream therapy. In **hoofdstuk** 7 bekeken we de huidige literatuur over upstream therapy voor boezemfibrilleren, zoals angiotensine-converting-enzyme inhibitoren, angiotensinereceptorblokkers, aldosteronreceptorantagonisten en statines. In **hoofdstuk** 8 bediscussieerden we de vraag of upstream therapy effectief is in alle patiënten met boezemfibrilleren. Ook verschaften we de achtergrond en het design van de Routine versus Aggressive upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) studie. Deze studie wordt uitgevoerd in patiënten met vroeg boezemfibrilleren, bij wie we verwachten dat upstream therapy effectief zal zijn in het stilzetten van progressie van boezemfibrilleren.

Tot slot behandelden we in **hoofdstuk 9** de algehele klinische en therapeutische implicaties van remodeling in boezemfibrilleren waarbij we verwezen naar de bevindingen van dit proefschrift. In de toekomst denken we dat inschatting van de mate van atriale remodeling gebruikt kan worden om behandelingen, gericht op het stilzetten van progressie van boezemfibrilleren, te ontwikkelen die op maat gemaakt zullen worden voor de individuele patiënt. Uiteindelijk zullen dergelijke behandelingen de prognose van boezemfibrilleren mogelijk kunnen verbeteren.

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