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Atrial Fibrillation Beyond the Electrocardiogram

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Atrial Fibrillation Beyond the Electrocardiogram – Towards Understanding and Preventing Progression

Ruben R. de With

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Towards understanding and preventing progression

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Paranimfen

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Voor Boris

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1

Introduction

PROLOGUE

“The French sometimes refer to atrial fibrillation (AF) as ‘l’arythmie complete’, which literally means ‘the complete arrhythmia’. The actual sense in French is that AF results in complete irregularity of cardiac rhythm. However, AF can also be considered the ‘complete’ arrhythmia in the sense of the consummate nature of its mechanisms and determinants. There is evidence for involvement of all forms of arrhythmia mechanisms in AF, including enhanced automaticity, delayed afterdepolarizations, early afterdepolarizations and re-entry.(1) A rich and wide range of determinants have been found to be involved in the pathophysiology of AF—various forms of ionic remodelling, structural remodelling, changes in connexin function and distribution, a whole gamut of signalling systems, anatomical determinants related to the complex three-dimensional atrial structure, hemodynamic factors and the involvement of electrical activity in the great veins. ‘The complete arrhythmia’ can further reflect to the wide variety of underlying risk factors or comorbidities that usually underlie development of AF.”(2)

- Adapted from Nattel *et al.*, Cardiovascular Research 2002;54:197-203

Atrial fibrillation (AF) is an atrial arrhythmia characterized by rapid and irregular atrial electrical activity, usually resulting in fast, irregular ventricular contractions. Since its first documentation in 1906, it has emerged as a global epidemic. It is the most common sustained cardiac arrhythmia with an estimated 33.5 million patients worldwide.(3) In The Netherlands, more than 250,000 patients suffer from AF, and that number is estimated to increase rapidly over the next decades.(4,5) Apart from improved screening for AF, the rising prevalence of AF can be accounted to an ageing population, improved survival of patients with cardiovascular diseases and an increase in prevalence of risk factors and comorbidities associated with AF.(6) The latter resulting in the fact that an increasing number of patients develop AF at a relatively young age nowadays.(7)

AF is bad news, as it is associated with major adverse cardiovascular and cerebral events (MACCE), including a 5-fold increase in stroke risk and a 2-fold increase in heart failure and mortality, even in patients with short (>6 minutes) atrial high rate episodes detected on their atrial lead in patients with a pacemaker or defibrillator.(8-13) On top of that, even AF patients without a history of stroke have an increased risk of dementia.(14) The increased risk of adverse events, but also symptoms of AF itself contribute to an impaired quality of life in patients with AF.(15,16) Also, AF has a huge economic burden, consuming 1.4% of the total health care budget in The Netherlands.(4)

RISK FACTORS AND COMORBIDITIES FOR DEVELOPING AF

AF usually does not appear in absence of risk factors and comorbidities.(2) Traditional risk factors and comorbidities include ageing, coronary heart disease, heart failure, hypertension, diabetes, valvular disease, thyroid dysfunction, and obesity (Figure 1).(17,18) But also physical inactivity or even excessive exercise increases the risk of developing AF.(2,19)

Underlying risk factors and comorbidities result in progressive, electrical, mechanical and structural atrial remodelling, which are the foundation of AF development.(20-22) Thirty years ago, Philip Coumel described the triangle of an arrhythmogenic substrate, triggering factors and modulators to be essential in developing and maintaining a clinical arrhythmia, which is still a relevant concept (Figure 2).(23) Atrial remodelling refers to alterations that are made upon a higher demand, e.g. atrial stretch due to pressure and volume overload or inflammation.(24,25) These changes result in a more favourable condition for AF to recur and sustain. Atrial remodelling starts years before the first episode of AF is detected (Figure 3).(26)

Figure 1. An overview of several risk factors that can be involved in AF development.

CLASSIFICATION OF AF

AF can be classified in numerous ways, including by temporal pattern, aetiology and mode of onset. In the late '90s, Gallagher and Camm described the generally accepted temporal AF patterns paroxysmal, persistent and permanent AF, often referred to as 'the 3 Ps'.⁽²⁷⁾ This classification is still incorporated in the European Society of Cardiology AF guidelines.^(27,28) In paroxysmal AF, episodes come and go and last <7 consecutive days and are terminated spontaneously or by an intervention. Persistent AF is a more advanced stage in which episodes last ≥7 days. If sinus rhythm is no longer pursued by the treating physician or if sinus rhythm restoration is no longer possible, patients are said to have permanent AF. Improved classification that looks more closely to the temporal AF patterns, especially in selfterminating paroxysmal AF may be of additional value to personalize therapy, particularly in the early stages; however, little is known on this topic.

Figure 2. Coumel's triangle for initiation of a clinical arrhythmia.

AF PROGRESSION

Over time, AF commonly progresses from paroxysmal, self-terminating to non-self-terminating AF (i.e. persistent or permanent AF; Figure 3) – a phenomenon often referred to as AF progression.(12,29-33)

AF progression is of clinical importance because it is strongly related to MACCE, including stroke, increased cardiovascular hospitalizations, mortality due to heart failure and myocardial infarction.(30,31,34-36) AF progression may also result in impaired quality of life.(37) An important aspect is that AF frequently starts unnoticed, which allows it to progress freely and results in MACCE before it is actually detected.(38) In addition, this may result in a delay of diagnosis and treatment of underlying cardiovascular disease. The Cryptogenic Stroke and Underlying AF (CRYSTAL-AF) trial found an 8.9% incidence of AF in 6 months after a cryptogenic stroke using implantable loop recorders in patients with a cryptogenic stroke without known AF, i.e. stroke as first presentation of still silent AF.(39)

In order to identify the ones at risk for AF progression, De Vos *et al.* used data from the Euro Heart Survey, which was a large European survey program which enrolled patients in 2003 and 2004 from 35 participating countries.(30) They found that 15% progressed from paroxysmal, self-terminating AF to non-self-terminating AF within 1 year. The HATCH score was developed as an AF progression prediction score, which is an acronym for Hypertension, Age ≥ 75 years, Transient ischemic attack or stroke, Chronic obstructive pulmonary

Figure 3. Conceptual figure of AF progression. Atrial remodelling starts long before the first episode of AF due to ageing and underlying comorbidities. Driven by transient triggers, episodes of AF may eventually develop – often of paroxysmal nature in the beginning. In time, this may progress to persistent and permanent AF. Abbreviations: AF=atrial fibrillation.

disease and Heart failure. It shows that underlying disease and age are not only important in developing AF, but presumably also in progression of AF. However, applying the HATCH score in independent cohorts showed only a moderate predictive value for AF progression (C-statistic 0.6).(40) This indicates that more factors are involved in AF progression.

Apart from clinical markers, imaging markers are increasingly being associated with AF initiation, AF progression and MACCE, also in patients in sinus rhythm.(41-43) Atrial size and function are associated with AF initiation, progression and failure of rhythm control therapy. Atrial size is also an important predictor for the occurrence of MACCE.(44-47) Additionally, special techniques are available showing atrial fibrosis by late gadolinium enhancement in magnetic resonance imaging. The degree of atrial fibrosis was able to predicts success of AF ablation during 5-year follow-up.(48)

The current knowledge on AF progression is limited due to (I) imperfect rhythm monitoring, mostly only using 10-second electrograms to assess the type of AF; (II) incomplete phenotyping of patients, which only allows limited parameters to be linked to AF progression; and (III) a non-uniform definition of AF progression, usually as a direct result of inadequate rhythm monitoring. Extensive studies carefully phenotyping AF patients in addition to investigating biomarkers and atrial imaging markers are needed to understand the basic mechanisms of AF progression.

AIMS OF THE THESIS

Part I focuses on improving our understanding of AF progression. Since AF incidence is also increasing in young patients, we aim to describe the clinical profile of patients with young-onset AF, long-term AF progression rate and cardiovascular outcome in **Chapter 2**. In **Chapter 3**, we aim to identify factors associated with AF progression, including blood biomarkers in a well-phenotyped cohort of patients with a short history of paroxysmal or persistent AF. In the era of implantable loop recorders, it is now possible to have continuous rhythm monitoring in patients with AF. In **Chapter 4** we aimed to optimize characterization of paroxysmal AF, including short-term AF progression, by the use of continuous rhythm monitoring. And finally, **Chapter 5** aimed to evaluate sex differences in clinical profile, AF progression rate and cardiovascular events in young-onset AF.

Part II focuses on several aspects aiming to prevent AF progression. Risk factor management has shown to be effective in maintaining sinus rhythm in AF patients. In **Chapter 6** we evaluated sex differences in blood biomarkers to gain insight in differences in underlying pathophysiological mechanisms to AF substrate formation and personalize prevention of AF progression. In **Chapter 7** we identified factors associated with prevention of AF progression in patients with early-persistent AF. And finally, in **Chapter 8**, we aimed to investigate the effects of targeted therapy of underlying conditions to prevent AF progression on quality of life in patients with early-persistent AF.

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PART I

Progression of Atrial Fibrillation

2

Atrial Fibrillation Progression and Outcome in Patients with Young-Onset Atrial Fibrillation

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Isabelle C. Van Gelder, and Michiel Rienstra

Adapted from Europace 2018;20:1750-1757.

ABSTRACT

Aims. Clinicians increasingly encounter patients with young-onset atrial fibrillation (AF). Aim is to study clinical profile, AF progression and outcome of patients with young-onset AF.

Methods. A total of 468 patients with paroxysmal or persistent AF starting <60 years of age were included. Clinical profile, AF progression, defined as development of permanent AF, and cardiovascular events were prospectively collected.

Results. Onset of AF was at 46 ± 10 years, 354 (76%) were men, 329 (70%) had paroxysmal AF, 50 (11%) had AF without risk factors or comorbidities and 118 (25%) had familial AF. Hypertension was present in 207 (44%), heart failure in 44 (9%). During 7.2 (2.7-10.0) years, 56 (12%) had AF progression (2.0%/year). Progression rate in patients receiving antiarrhythmic drugs or pulmonary vein isolation during follow-up was not different from patients who did not. Multivariable determinants of AF progression included diastolic blood pressure (HR 1.031, 95% CI 1.007-1.055, $P=0.010$) and left atrial size (HR 1.055, 1.012-1.099, $P=0.012$). Cardiovascular events occurred in 61 patients (13%; 2.4%/year). Multivariable determinants of cardiovascular events were PR interval (HR 1.015, 1.005-1.024, $P=0.002$) and left ventricular hypertrophy (HR 3.429, 1.712-6.868, $P=0.001$). Yearly event rate was higher in patients who had developed AF progression, compared to patients without progression [4.9 (2.3-9.0)% vs. 1.9 (1.4-2.6)%, $P=0.006$].

Conclusion. Nine out of 10 patients with young-onset AF had risk factors and comorbidities, 25% had familial AF. AF progression to permanent AF and cardiovascular events occurred in 2.0% and 2.4% per year, respectively. Cardiovascular events increased after AF progression had occurred.

INTRODUCTION

Atrial fibrillation (AF) often occurs at an older age, and most commonly in the presence of concomitant cardiovascular risk factors or diseases.⁽¹⁾ Yet, AF incidence at young age is increasing.⁽²⁾ This may relate to changes in life-style, including consumption pattern, obesity and lack of physical activity, which may lead to earlier development of cardiovascular risk factors and comorbidities.^(2,3) The relative contribution of heritability may also be of greater importance in younger individuals.⁽¹⁾ Data on the exact clinical phenotype of young-onset AF, however, is sparse.⁽³⁾ The general notion often is that many young-onset AF patients have AF without comorbidities, i.e. AF occurring in the absence of AF risk factors, but also that data is sparse.⁽⁴⁾

AF frequently emerges as a progressive disease that starts off as simple, paroxysmal self-terminating AF and eventually progresses to persistent and permanent non-self-terminating AF. Underlying clinical and subclinical diseases guide the process of ongoing structural atrial remodelling and thus progression of AF. Atrial remodelling is thought to start years before the first AF episode.⁽⁵⁾ Yearly progression rates that have been reported vary between <1% to >30%, depending on the severity of underlying cardiovascular diseases, and AF progression definition.⁽⁶⁾ AF progression is of clinical importance because it has been associated with worse cardiovascular outcome.⁽⁷⁻⁹⁾ Therefore, it is of importance to predict the patients at risk for AF progression. Current risk-stratification for AF progression is limited. Even less is known on AF progression in young patients.

In the present single-centre, observational study we aim to describe the clinical profile, AF progression to permanent AF, and cardiovascular outcome of patients with young-onset paroxysmal and persistent AF.

METHODS

Study population

The Phenotyping Young-Onset Atrial Fibrillation Patients study (YOUNG AF) is a prospective, single-centre, observational study that was performed at the University Medical Centre Groningen, The Netherlands. A total of 500 patients were included between August 2012 and December 2013. The institutional review board approved the study protocol, and all patients provided written informed consent. At the outpatient clinic patients with AF onset <60 years, who were at least 18 years at time of inclusion were asked to participate. Patients with post-operative AF, myocardial infarction or acute coronary syndrome <1 month prior to onset of AF were non-eligible. Also, patients with AF due to another acute trigger (e.g. infection)

and patients with hyperthyroidism <3 months before AF onset were non-eligible. In total, 3 patients were excluded because not meeting the inclusion criteria (1 hyperthyroidism <3 months before AF onset, 2 aged >60 years at AF onset). Of the 497 patients, no follow-up data was available of 9 patients and 20 had permanent AF at baseline. All analyses were performed using the remaining 468 patients. Data regarding clinical profile was collected closest to the moment of the diagnosis of AF (index-visit). Information regarding family history, cardiovascular risk factors and diseases, life style-related risk factors for AF, physical examination, 12-lead electrocardiogram, laboratory analyses, and echocardiography was also collected prospectively. The follow-up frequency and follow-up investigations, after the index-visit, were led to the discretion of the treating physician. In the majority at least yearly follow-up visits were planned. Information regarding these visits was collected from the electronic medical records.

Definitions

AF progression was defined as development of permanent AF (i.e. sinus rhythm that cannot be restored or is no longer pursued by the treating physician). Type of AF was defined according to the 2016 European Society of Cardiology AF guidelines into paroxysmal (<7 consecutive days of AF), persistent (≥ 7 consecutive days of AF) and permanent AF.⁽¹⁾ Heart failure was defined as the presence of signs or symptoms associated with heart failure (New York Heart Association functional class II or III), previous hospitalization for heart failure or left ventricle ejection fraction (LVEF) $\leq 45\%$ as assessed by echocardiography or any other imaging modality. Left ventricular hypertrophy (LVH) was classified using echocardiographic left ventricular mass index (LVMI) $>95 \text{ g/m}^2$ in women and $>115 \text{ g/m}^2$ in men. Hypertension was defined as systolic blood pressure $>140 \text{ mmHg}$, diastolic blood pressure $>90 \text{ mmHg}$, or by use of medication prescribed for hypertension. Coronary heart disease was defined as a history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting. Peripheral artery disease was defined on the basis of a clinical diagnosis by a vascular specialist or observed with Doppler ultrasonography or other imaging modality. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease formula. Chronic kidney disease was defined as an eGFR $<60 \text{ mL/min}$. Body mass index (BMI) was calculated by dividing weight to height squared (kg/m^2). Obesity was defined as BMI $>30 \text{ kg/m}^2$. Familial AF was defined as a history of AF <60 years in ≥ 1 first-degree family member. AF without comorbidities was diagnosed in the absence of congenital heart disease, cardiomyopathies, hypertension, coronary artery disease, peripheral artery disease, pulmonary diseases, heart failure, diabetes mellitus, chronic kidney disease, obesity, LVH, diastolic dysfunction ($e' < 8 \text{ cm/sec}$ and/or lateral $e' < 10 \text{ cm/sec}$), moderate or severe valvular disease, subclinical hypertension (systolic blood pressure $>130\text{--}140 \text{ mmHg}$ or diastolic blood pressure $>80\text{--}90 \text{ mmHg}$), smoking, excessive sports practice and excessive alcohol use. The stroke risk-score $\text{CHA}_2\text{DS}_2\text{-VASc}$ was calculated by counting points for congestive heart failure, hypertension, age ≥ 75 years (2 points), diabetes mellitus, stroke or transient ischemic

attack (TIA; 2 points), vascular disease, age 65-74 years and female sex. The HATCH score, an AF progression score, was calculated by counting points for hypertension, age ≥ 75 years, stroke or TIA (2 points), chronic obstructive pulmonary disease and heart failure (2 points).

Follow-up

We used electronic medical records to obtain information on development of AF progression and cardiovascular events. Rhythm control including atrial ablation was first choice therapy in symptomatic patients.⁽¹⁾ During follow-up, data on AF therapies was collected, including use of class I and III anti-arrhythmic drugs (AAD) and atrial ablation. Cardiovascular events included cardiovascular death and heart transplantation, heart failure hospitalization, stroke, systemic embolism, major bleeding, syncope, life-threatening adverse effects of AF drugs, sustained ventricular tachycardia, cardiac arrest and implantation of a pacemaker or implantable cardiac defibrillator (ICD). Cardiovascular death was defined as death occurring due to any cardiovascular disease. Stroke was defined as the sudden onset of a focal deficit with permanent damage and categorized as either ischemic (occlusion of a major cerebral artery documented by means of imaging) or haemorrhagic. Systemic embolism was defined as an acute vascular occlusion of an extremity or organ documented by any imaging modality, operative report or autopsy report. Major bleeding was defined as a reduction in the haemoglobin level by more than 2g/dL, requiring transfusion of ≥ 2 units of blood or symptomatic bleeding in a critical area or organ necessitating hospitalization. Syncope was defined as a transient loss of consciousness potentially to be caused by a rhythm disorder. Life-threatening adverse effects of AF drugs included conduction disturbances and ventricular arrhythmias necessitating hospitalization. Sustained ventricular tachycardia was defined as ventricular tachycardia lasting >30 seconds or necessitating termination by electrical cardioversion because of hemodynamic instability. Cardiac arrest was defined as circulatory arrest necessitating resuscitation and hospitalization. Follow-up started at index-visit and was continued until February 2016 with a maximum of 10 years, or until death.

Statistical analysis

Descriptive statistics of the total population, and subgroups with and without AF progression, were presented as mean $\pm$ standard deviation or median with interquartile range (IQR) for continuous variables, depending on normality of the data. Categorical variables are presented as numbers with percentages. Yearly event rates were calculated by dividing the number of follow-up years by the number of events, with censoring post first event. Additionally, repeated events analyses were performed as well. In an individual patient differences in event rates and 95% confidence interval (CI) were calculated by the incidence rate comparison tool using MedCalc for Windows version 17.6. Differences in patient characteristics between patients with and without AF progression were evaluated using Fisher's exact test (2 categories) and Chi-square test (>2 categories) for categorical data, and the student's

T-test and Mann-Whitney-U test for continuous data, depending on the normality of the data. Univariable Cox proportional hazard regression was used to find determinants of AF progression and cardiovascular outcome. Results are given as hazard ratios (HR) with 95% CI. All covariates with a $P < 0.1$, excluding those with significant correlations with other covariates, were used to create a stepwise multivariable Cox proportional hazard regression model. Only statistically significant ($P < 0.05$) remained in the final model. As secondary analyses, we additionally adjusted the multivariable model for sex and treatment during follow-up. Variables included in the final regression model were tested for significant interactions. The proportionality hazards assumption was evaluated by testing the correlation coefficient between survival time and the scaled Schoenfeld residuals. A P -value < 0.05 was considered statistically significant. Kaplan Meier curves were created to illustrate the course of AF progression and cardiovascular events during follow-up. Statistical analyses were performed using IBM SPSS Statistics version 23.0 (Armonk, NY, USA) unless otherwise mentioned.

RESULTS

Clinical characteristics

Table 1 shows the baseline characteristics. Mean age at onset of AF was 46 ± 10 years, and 354 (76%) were men. On average, there was an approximate 3-year difference between the index-visit and AF onset. The majority had paroxysmal AF (329 [70%]). Overall, patients had a low number of comorbidities. A total of 50 (11%) patients had AF without comorbidities. Familial AF was present in 118 (25%). Patients with AF without comorbidities had a higher percentage of familial AF (40% vs. 23%, $P = 0.015$). Despite their low stroke risk, 27 (6%) had a history of stroke or TIA.

Atrial fibrillation progression

During a median follow-up of 7.2 (2.7-10.0) years, 56 (12%) out of 468 patients had AF progression to permanent AF, equivalent to 2.0%/year (Figure 1-a). There was no difference in progression rate in patients who underwent pulmonary vein isolation (PVI) or received class I or III AAD during follow-up, compared to patients who did not [26 (10.1%) vs 30 (14.3%), $P = 0.197$]. Patients with AF progression were more often men, had persistent AF at the index-visit, valvular disease and heart failure (Table 1). Both systolic and diastolic blood pressure were higher in patients with AF progression. Echocardiographic differences included a larger left atrial size and a higher LVMI. The HATCH score was significantly higher in patients with AF progression (HR 1.273, 95% CI 1.024-1.584, $P = 0.029$). Multivariable determinants of AF progression included diastolic blood pressure (HR 1.031, 95% CI 1.007-1.055, $P = 0.01$) and left atrial size (HR 1.055, 95% CI 1.012-1.099, $P = 0.012$; Table 2). After adjustment for sex and treatment during follow-up, this effect remained present.

Table 1. Patient characteristics at index-visit of total population, with and without AF progression.

	All patients (n=468)	AF progression (n=56)	No AF progression (n=412)	P-value
Age at index-visit (years)	49 ± 9	50 ± 9	49 ± 9	0.41
Age at AF-onset (years)	46 ± 10	47 ± 9	46 ± 10	0.46
Men	354 (76%)	49 (84%)	305 (74%)	0.03
Type of AF				<0.001
Paroxysmal	329 (70%)	25 (45%)	304 (74%)	
Persistent	139 (30%)	31 (55%)	108 (26%)	
Heart failure	44 (9%)	10 (18%)	34 (8%)	0.02
Hypertension	207 (44%)	30 (54%)	177 (43%)	0.21
Diabetes mellitus	21 (5%)	2 (4%)	19 (5%)	0.72
COPD	17 (4%)	1 (2%)	16 (4%)	0.57
Coronary artery disease	45 (10%)	5 (9%)	40 (10%)	0.85
Peripheral artery disease	8 (2%)	2 (4%)	6 (2%)	0.25
Stroke or TIA	27 (6%)	5 (9%)	22 (5%)	0.28
Chronic kidney disease	10 (2%)	2 (4%)	8 (2%)	0.43
Hypercholesterolemia	175 (41%)	26 (50%)	149 (40%)	0.18
History of hyperthyroidism	10 (2%)	2 (4%)	8 (2%)	0.43
AF without comorbidities	50 (11%)	6 (11%)	44 (11%)	1.00
Familial AF	118 (25%)	13 (23%)	105 (26%)	0.87
CHA ₂ DS ₂ -VASC score	1 (0-2)	1 (0-2)	1 (0-2)	0.20
HATCH score	1 (0-1)	1 (0-2)	1 (0-1)	0.04
EHRA symptom class				<0.001
I	39 (9%)	14 (26%)	25 (7%)	
II	325 (74%)	35 (65%)	290 (76%)	
III	69 (16%)	4 (7%)	65 (17%)	
IV	4 (1%)	1 (2%)	3 (1%)	
Physical examination				
Height (cm)	182 ± 10	182 ± 10	182 ± 10	0.99
Weight (kg)	91 ± 17	88 ± 15	92 ± 18	0.08
BMI (kg/m ²)	27 (24-30)	26 (24-28)	27 (24-30)	0.05
Obesity (BMI>30)	86 (26%)	6 (15%)	80 (27%)	0.17
Systolic blood pressure (mmHg)	131 ± 20	136 ± 20	130 ± 20	0.02
Diastolic blood pressure (mmHg)	82 ± 12	86 ± 12	81 ± 11	<0.001
Electrocardiography				
Heart rate (bpm; in sinus rhythm)	65 (57-72)	64 (57-70)	65 (58-73)	0.46
PR interval (ms)	160 (146-176)	165 (157-188)	160 (144-174)	0.05
Echocardiography				
Moderate or severe valve disease	35 (7%)	8 (14%)	27 (7%)	0.04
Left ventricular hypertrophy	50 (11%)	8 (14%)	42 (10%)	0.35

Table 1. Patient characteristics at index-visit of total population, with and without AF progression. (continued)

	All patients (n=468)	AF progression (n=56)	No AF progression (n=412)	P-value
Left ventricular mass index (g/m ²)	80 (69-93)	88 (81-98)	79 (69-92)	0.01
LA volume (mL)	54 (42-68)	60 (50-70)	53 (41-65)	0.02
LA volume index (mL/m ²)	25 (20-31)	28 (24-33)	24 (20-31)	0.07
LA parasternal long axis (mm)	41 ± 6	43 ± 6	40 ± 6	0.002
LVEF (%)	60 (55-60)	60 (50-60)	60 (58-60)	0.05
Laboratory results				
Creatinine (μmol/L)	85 (73-95)	91 (79-102)	84 (72-95)	0.01
eGFR (mL/min)	81 ± 17	76 ± 20	81 ± 16	0.27
Total cholesterol (mmol/L)	5.3 ± 1.1	5.0 ± 1.1	5.3 ± 1.1	0.13
HDL cholesterol (mmol/L)	1.2 (1.0-1.4)	1.1 (0.9-1.3)	1.2 (1.0-1.5)	0.23
LDL cholesterol (mmol/L)	3.3 (2.7-4.0)	3.2 (2.4-4.0)	3.3 (2.7-4.0)	0.52

Data is expressed as mean ± standard deviation ± SD, median (IQR) or numbers (%). Abbreviations: AF=atrial fibrillation; BMI=body mass index; CHA₂DS₂-VASc=acronym for congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke or transient ischemic attack, vascular disease, age 65-74 years and female sex; COPD=Chronic obstructive pulmonary disease; eGFR=estimated glomerular filtration rate; EHRA=European Heart Rhythm Association; HATCH=acronym for hypertension, age ≥75 years, stroke or transient ischemic attack, chronic obstructive pulmonary disease and heart failure; HDL=high density lipoprotein; ICD=implantable cardiac defibrillator; LA=left atrial; LDL=low density lipoprotein; LVEF=left ventricular ejection fraction; PM=pacemaker; TIA=transient ischemic attack; VF=ventricular fibrillation; VT=ventricular tachycardia.

Cardiovascular outcome

During 7.2 (2.7-10.0) years of follow-up, 61 (11%; 2.4% per follow-up year) patients had at least 1 cardiovascular event (Figure 1-b). A total of 20 patients had >1 event and the total number of events was 90 during follow-up. Including the repeated events, event rate was 3.0% per year.

Figure 1 A-B. A. Kaplan Meier curve showing the cumulative AF progression rate to permanent AF during follow-up. B. Kaplan Meier curve illustrating the cumulative incidence of cardiovascular events during follow-up.

Table 2. Univariable and multivariable determinants of AF progression.

	Univariable			Multivariable		
	HR	95% CI	P-value	HR	95% CI	P-value
Diastolic blood pressure (mmHg)	1.036	1.015-1.058	0.001	1.031	1.007-1.055	0.010
LA parasternal long axis (mm)	1.056	1.014-1.098	0.008	1.055	1.012-1.099	0.012
Creatinine ($\mu\text{mol/L}$)	1.088	1.001-1.015	0.020			
HATCH	1.273	1.024-1.584	0.029			
PR interval (ms)	1.011	1.000-1.021	0.050			
Heart failure	1.963	0.990-3.891	0.053			
Male sex	2.580	1.361-4.891	0.081			
LVEF (%)	1.273	1.024-1.584	0.082			
Total cholesterol (mmol/L)	0.794	0.605-1.043	0.097			

Cox proportional hazards regression on determinants associated with AF progression. Abbreviations: CI=confidence interval; HATCH=acronym for hypertension, age ≥ 75 years, stroke or transient ischemic attack, chronic obstructive pulmonary disease and heart failure; HR=hazard ratio; LA=left atrial; LVEF=left ventricular ejection fraction.

Patients who developed AF progression had higher yearly cardiovascular event rates (Table 3). Sixteen patients with AF progression had a total of 25 events. Ten of those events occurred before AF had progressed to permanent AF. Ten patients had 15 events after progression of AF. After AF progression, patients had a higher event rate [4.9 (2.3-9.0)% vs. 1.9 (1.4-2.6)% a year, $P=0.006$; Figure 2]. Including repeated events, this effect remained significant [6.3 (3.5-10.4)% vs. 2.0 (1.5-3.2), $P<0.001$]. AF progression had a HR of 2.222 (95% CI 1.114-4.430, $P=0.023$) for cardiovascular events. This effect remained after adjusting for differences in diastolic blood pressure, heart failure, sex and LVH (HR 2.347, 95% CI 1.109-4.968, $P=0.026$).

Pacemaker implantation, heart failure hospitalization, syncope and ICD implantation were most frequently observed. A total of 7 (2%) ischemic strokes were observed. Four patients used anticoagulation therapy at the time of stroke, 3 not because a CHA₂DS₂-VASc of 0 or 1. Heart failure hospitalizations and ICD implantations were more common in patients with AF progression. No differences in other individual components were observed.

Table 4 shows the univariable and multivariable determinants of cardiovascular outcome. Multivariable determinants included a longer PR interval (HR 1.015, 95% CI 1.005-1.024, $P=0.002$) and presence of LVH (HR 3.429, 95% CI 1.712-6.868, $P=0.001$).

Table 3. Cardiovascular events in patients after AF progression had occurred (i.e. were in permanent AF) and without AF progression.

	After AF progression (n=56)	No AF progression (n=412)	P-value
Composite endpoint	4.87%/year	1.93%/year	0.006
Endpoint components			
Death from cardiovascular I cause or heart transplantation	0.42%/year	0.04%/year	0.039
Heart failure hospitalization	1.79%/year	0.40%/year	0.005
Ischemic stroke	-	0.27%/year	0.419
Systemic embolism	-	-	
Major bleeding	-	0.08%/year	0.667
Syncope	0.86%/year	0.27%/year	0.132
Life-threatening adverse effect of rate- or rhythm-control drugs	-	0.12%/year	0.598
Sustained ventricular tachycardia	0.87%/year	0.24%/year	0.088
Cardiac arrest	0.42%/year	0.16%/year	0.353
ICD implantation	0.86%/year	0.24%/year	0.090
Pacemaker implantation	1.37%/year	0.77%/year	0.352

Data is expressed as yearly event rates. P value is given for the difference between patients after AF progression had occurred (i.e. were in permanent AF) and without AF progression. Abbreviations: AF=atrial fibrillation; ICD=implantable cardiac defibrillator.

Figure 2. Yearly event rate in patients with permanent AF versus patients without AF progression.

Table 4. Univariable and multivariable determinants of cardiovascular events.

	Univariable			Multivariable		
	HR	95% CI	P-value	HR	95% CI	P-value
PR interval (ms)	1.015	1.006-1.024	0.001	1.015	1.005-1.024	0.002
LVH	2.312	1.277-4.184	0.006	3.429	1.712-6.868	0.001
LVMI (g/m ²)	1.016	1.003-1.029	0.019			
Heart rate (bpm)	0.975	0.949-1.001	0.063			
COPD	2.365	0.857-6.520	0.096			

Cox proportional hazards regression on determinants associated with cardiovascular events during follow-up. Abbreviations: bpm=beats per minute; CI=confidence interval; COPD=Chronic obstructive pulmonary disease; HR=hazard ratio; LVH=left ventricular hypertrophy; LVMI=left ventricular mass index.

DISCUSSION

The present study shows that 9 out of 10 patients with young-onset AF had risk factors and comorbidities. AF without comorbidities occurred in a minority of patients, but familial AF was present in one out of four. AF progression to permanent AF and cardiovascular events occurred at a low yearly rate. Of importance, the cardiovascular event rate increased after AF progression to permanent AF.

Clinical profile

The clinical profile in the young-onset AF patients was comparable to patients in whom AF started at an older age.(7,9) In the present cohort, patients with young onset AF, however, were more often men compared to older AF cohorts.(7,10) This may be partly explained by electrophysiological differences between pre- and post-menopausal women. Among other factors, protective effects of oestrogens on cardiovascular diseases may have accounted for the lower percentage of women with young-onset AF.(11)

Most patients had comorbidities despite their age. Hypertension was most often prevalent. Obesity, considered a more novel risk-factor, was present in one out of four.(2) More and more data become available that identifying and treating risk factors and comorbidities is key in AF treatment, preventing progression of atrial remodelling. This includes subclinical vascular diseases and subclinical hypertension.(1,12) Identifying and implementing these factors in risk-stratification models may improve prognosis in AF patients.

Familial AF was present in 25%, which is consistent with earlier findings that familial AF is a risk factor for developing AF. Its incidence varies widely, ranging from 5 to 46%.(13,14) Weng *et al.* described the long-term probability of developing AF considering genetic predisposition.(15) In those within the lowest tertile of genetic predisposition for developing AF, the

incidence was 22.3%, compared to 48.2% in patients within the highest tertile. Thus, genetics can play a substantial role in AF development, which may play a role in daily practice in the future. For now, the role of genetics in daily AF management is limited and was therefore not included in the analyses.

It is generally believed that many young patients have AF without comorbidities. The prevalence of AF without comorbidities varies between <1% to 68%, depending on type of AF, age of AF onset and lone AF definition. Wyse *et al.* advocate limiting the use of the term 'lone AF', since comorbidities are often underdiagnosed and its definition is used inconsistently. (4) Our data shows that only 11% had young-onset AF without a risk-factor or comorbidity, which may still be an overestimation since this definition did not include subclinical vascular diseases. Thorough work-up is needed to identify cardiovascular diseases or risk-factors and treat them accordingly.(1)

Atrial fibrillation progression

During follow-up, our young-onset AF patients showed a progression rate to permanent AF of 2.0% per year. In patients with self-terminating AF the progression rate varies with the population studied and the means and duration of rhythm monitoring and follow-up, ranging from <1% to >30% per year. Potpara *et al.* examined 242 patients (age 43 ± 10) with newly diagnosed AF without known comorbidities.(16) A 26.9% progression rate was observed during 12.1 years of follow-up, equivalent to yearly AF progression rate of 2.2%, thus comparable to our data.

Treatment during follow-up could potentially influence AF progression. We did not observe any difference in AF progression rate in patients receiving AAD and/or PVI during follow-up, compared to patients who did not.

Multiple clinical factors have been associated with AF progression. De Vos *et al.* developed the previously mentioned AF progression risk score HATCH.(7) They showed a yearly progression rate of 15% in older patients (mean age 64 ± 13 years). We also could show that the HATCH score was associated with AF progression. Independent factors associated with AF progression in our cohort were diastolic blood pressure and left atrial size. High diastolic blood pressure might indicate inadequate treatment of underlying hypertension, enhancing the atrial remodelling processes and thus enabling the arrhythmia to become permanent. Larger left atrial dimensions are also considered as marker of more advanced atrial remodelling, further contributing to AF progression.(17)

Cardiovascular outcome

We observed a cardiovascular event rate of 2.4%/year. De Vos *et al.* reported data from the Euro Heart Survey on several major adverse cardiovascular events during 1 year follow-up, including a combined event rate of stroke and death of 3%.(7) Our data shows that after progression to permanent AF, the event rate is higher compared to patients without AF progression. We observed a very low yearly stroke and death rate. Camm *et al.* showed that, in a cohort of over 5000 patients with recent-onset AF (mean age 66 ± 12 years) 18% had a clinical outcome event in 1 year of follow-up – including stroke (2%), and death (3%).(10) Vannasche *et al.* observed a worse cardiovascular outcome in patients with persistent or permanent AF compared to paroxysmal AF.(9) Our current data shows that this is also the case in young-onset AF patients. After patients had progressed to permanent AF, the event rate was much higher. This could partly be explained by expression of more advanced atrial remodelling due to more severe underlying risk factors and cardiovascular diseases, and the higher burden of AF itself. After adjusting for differences in some characteristics, AF progression itself remained significantly associated with cardiovascular events. However, whether AF progression is just a marker of more severe underlying cardiovascular disease, or also a cause cannot be concluded from our data. PR interval and LVH assessed by echocardiography were associated with cardiovascular events, both being markers of severity of associated diseases and cardiac remodelling. The relation of AF and PR interval is well known and a longer PR interval has been associated with adverse events, i.e. pacemaker implantations, thromboembolism and mortality(18) LVH can be considered a result of increased workload of the left ventricle due to several underlying conditions, and has been associated with cardiovascular morbidity and mortality.(19) One could hypothesize that the association of LVH and cardiovascular events may be due to diastolic dysfunction that is highly prevalent in these patients, resulting in heart failure with a preserved ejection fraction.(20)

Study strengths and limitations

Strengths of present study include the well characterized cohort and the unique large young onset AF population. Associations that have been found do not necessarily reflect a cause-effect relationship, which may be considered a limitation. Treatment of AF was led to the discretion of the treating physician, which may have influenced our final results. We did not implement dynamic risk profiling in our analyses. Sleep apnoea syndrome was not routinely screened for and was therefore not included in our analyses.

CONCLUSION

The present study demonstrates that the large majority of patients with young-onset AF had AF in the setting of risk factors. One in four had familial AF. Yearly event rates for AF

progression and cardiovascular events in these patients were low. Patients with AF progression had a higher yearly event rate compared to patients without AF progression in our study population.

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3

Atrial Fibrillation Progression Risk Factors and Associated Cardiovascular Outcome in Well-Phenotyped Patients – Data from the AF-RISK Study

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ABSTRACT

Aims. Atrial fibrillation (AF) is a progressive disease, but identifying patients at risk for AF progression is challenging. We aimed to identify factors associated with AF progression.

Methods. AF progression was assessed in 392 patients with recent-onset paroxysmal or persistent AF included in the prospective, observational, multicentre identification of a risk profile to guide atrial fibrillation (AF-RISK) study. Progression of AF was assessed by Holter-monitoring and 2-week event recorder at baseline and 1-year follow-up. AF progression was defined as: 1) doubling in AF burden at 1-year compared to baseline with a minimum AF burden of 10% in paroxysmal AF; or 2) transition from paroxysmal to persistent or permanent AF; or 3) persistent to permanent AF.

Results. Age was 60 ± 11 years, 62% were men, 83% had paroxysmal AF. At 1 year, 52 (13%) had AF progression (11% in paroxysmal; 26% in persistent AF). Multivariable logistic regression showed that left atrial volume [odds ratio (OR) per 10mL 1.251, 95% confidence interval (CI) 1.078-1.450, $P < 0.001$], NT-proBNP (OR per standard deviation increase 1.583, 95% CI 1.099-2.281, $P = 0.014$) and plasminogen activator inhibitor-1 (PAI-1; OR per standard deviation increase 0.660, 95% CI 0.472-0.921, $P = 0.015$) were associated with AF progression. In an additional follow-up of 1.9 (0.9-3.3) years patients with AF progression developed more cardiovascular events and all-cause mortality (12.4%/year versus 2.3%/year, $P < 0.001$).

Conclusion. AF progression occurred in 13% of patients with recent-onset AF during 1-year follow-up. Left atrial volume, NT-proBNP and PAI-1 were associated with AF progression. Patients with AF progression had a higher cardiovascular event rate.

INTRODUCTION

Atrial fibrillation (AF) is a dynamic disease.(1) Atrial remodelling due to cardiovascular risk factors and comorbidities are associated with progression of AF to more advanced forms, e.g. paroxysmal AF transcending into persistent AF.(2) Adequately treating risk factors and comorbidities can, however, prevent AF progression.(3) Depending on the exact definition and characteristics of the population studied, AF progression rates range from <1% to 30% per year.(4) Identifying patients at risk for AF progression is of importance, because its association with worse cardiovascular outcome.(5-8)

Our current knowledge on AF progression is based on registries with limited rhythm monitoring (4-6,8) and AF progression is often defined by transition from self-terminating to non-self-terminating AF on the basis of repeated ECGs and clinical evaluation. This misclassifies patients who progress from low-burden paroxysmal AF to high-burden paroxysmal AF as having no progression. The American Heart Association recently released a statement which advocates more research on AF beyond a binary entity (either present or absent).(9) This also includes a more refined definition of AF progression, its determinants, pathophysiological mechanisms and outcome.

In the present multicentre, prospective study, we aimed to assess AF progression rate, clinical, echocardiographic factors and blood biomarkers associated with AF progression in patients with a short history of AF, and the association of AF progression with cardiovascular morbidity and mortality.

METHODS

Study design

The identification of a risk profile to guide atrial fibrillation therapy (AF-RISK) study was a prospective, observational, multicentre study. Primary aim was to assess AF progression. The study was performed in The Netherlands (University Medical Centre Groningen and the Maastricht University Medical Centre +). The study was performed in concordance with the Declaration of Helsinki, was approved by the institutional review boards, and was registered on ClinicalTrials.gov (identifier NCT01510197). All patients gave written informed consent.

Patient population

Between May 2011 and March 2016, 499 patients were included. Patients aged ≥ 18 years who presented at either the inpatient or outpatient cardiology clinic with recent-onset paroxysmal AF (total AF history <2 years, or total AF history <3 years in case of ≤ 2 AF episodes

of ≤ 48 hours per month terminating spontaneously) or with a short history of persistent AF (total AF history < 2 years, and total persistent AF duration > 7 days and < 1 year) in whom a rhythm control strategy was preferred, were eligible. Patients with history of heart failure > 3 years; severe valvular disease; contra-indication for oral anticoagulation; acute coronary syndrome < 1 month; or post-operative AF were not eligible. Heart failure was defined as one of the following: 1) history of heart failure admission, regardless of the left ventricular ejection fraction (LVEF); 2) LVEF $< 45\%$; 3) LVEF $> 45\%$, a history of elevated N-terminal pro B-type natriuretic peptide (NT-proBNP) with either structural heart disease and/or diastolic dysfunction.(3)

Study procedures

All patients were treated according to the European Society of Cardiology AF management guidelines.(1) At inclusion, patients' demographic and clinical characteristics concerning underlying disease, cardiovascular risk factors, lifestyle, AF triggers, symptomatology and medication use were carefully collected. All patients underwent physical examination, electrocardiogram, echocardiography, and exercise test. Patients were seen at the outpatient clinic at 1, 3, 6 and 9 months and at 1-year. Detailed study related activities are shown in the *Supplementary file 1*. All patients with persistent AF were in sinus rhythm at baseline, either by scheduled cardioversion or spontaneous conversion.

Rhythm monitoring was done by a 24-hour Holter at baseline and 6 months, a 48-hour Holter at 1-year follow-up, and 2-week event monitor (Vitaphone 100IR, Vitagroup, Mannheim, Germany) at baseline and 1-year. In a subset of 76 patients, only baseline information was collected, including blood sampling, and were therefore not included in the current analysis (Figure 1).

Echocardiography

A two-dimensional transthoracic echocardiogram was performed according to the recommendations of the European Society of Cardiology.(10) For speckle tracking analysis of atrial strain, the endocardial surface was manually traced. A point-and-click approach was used and the additional tracing was automatically generated (GE, EchoPac BT12), and manually checked for accuracy. Values of reservoir, conduit and contraction strain for the left atrium were measured in all patients who were in sinus rhythm during the echo.

Blood biomarkers

At baseline, blood samples were collected. Multiplex immunoassay by proximity extension assay technology (Olink Bioscience, Uppsala, Sweden) was used to assess 92 cardiovascular biomarkers from the Cardiovascular III panel in EDTA plasma. Values of 4 biomarkers had $> 10\%$ of the values below the limit of detection and were therefore excluded from the

Figure 1. Flowchart of all patients included in the AF-RISK study. Primary analysis included 392 patients.

analysis. Data are presented as arbitrary units on a Log2-scale. The total list of available biomarkers is shown in *Supplementary file 2*.

AF Progression

Type of AF was defined as paroxysmal (≤ 7 days of continuous AF), persistent (> 7 days of continuous AF), and permanent AF (inability to restore sinus rhythm or sinus rhythm is no longer pursued by the treating physician). (1) AF progression was defined as one of the following: 1) a doubling in AF burden at 1-year follow-up compared to baseline with a minimum AF burden of 10%, in patients with paroxysmal AF; 2) progression from paroxysmal to either persistent or permanent AF; 3) progression from persistent to permanent AF. The AF burden was calculated by the amount of time of AF divided by the total monitoring time.

Cardiovascular morbidity and mortality

Cardiovascular events and all-cause mortality were prospectively collected after AF progression was assessed through electronic patient records. All-cause mortality, heart failure hospitalization, stroke, systemic embolism, major bleeding, syncope, life-threatening adverse effects of AF drugs, sustained ventricular tachycardia, myocardial infarction, and implantation of a pacemaker or implantable cardiac defibrillator were events of interest.

Statistical analysis

Descriptive data of continuous variables are presented as mean $\pm$ standard deviation in normally distributed data or median (interquartile range) in non-normally distributed data. Categorical variables are presented as numbers with percentages. Differences between groups were evaluated by Student's T-test or Mann-Whitney U test for continuous variables, and Fisher's exact test (2 categories) or χ^2 (>2 categories) for categorical variables. Univariable logistic regression analysis was performed to identify factors associated with AF progression. A multivariable model of AF progression was made by stepwise logistic regression. Odds ratios (OR) were presented with a 95% confidence interval (CI). The final model was tested for significant interactions and collinearity. The multivariable regression model found for AF progression was additionally adjusted for type of AF at baseline (either paroxysmal or persistent AF; model 1) and type of AF at baseline, pulmonary vein isolation during study period and anti-arrhythmic drug use (model 2).

After assessment of AF progression at 1-year, cardiovascular events were collected. Yearly event rates were calculated by dividing the number of follow-up years after assessing AF progression by the number of events, with censoring after the first event. Differences in event rates and 95% CI were calculated using MedCalc (version 18.2, MedCalc Software, Belgium). Differences in event rates in patients with and without AF progression was illustrated by a Kaplan-Meier made using GraphPad Prism version 7.02 (GraphPad Software, La Jolla, USA), and was tested by log-rank test. Cox proportional hazards regression was performed and hazard ratio (HR) and 95% CI was given and additionally adjusted for age, sex, CHA₂DS₂-VASc score and left atrial volume. All other analyses were performed using SPSS (IBM, Armonk, NY) statistical software, version 23. A *P*-value <0.05 was considered statistically significant.

RESULTS

Figure 1 shows the study profile. Baseline characteristics are shown in Table 1 (not different from the total AF-RISK population, data not shown). Patients with persistent AF were older (63 $\pm$ 10 versus 59 $\pm$ 12 years, *P* =0.016), more often men (77% versus 58%, *P* =0.004)

Table 1. Baseline characteristics.

Characteristic	Total population (N=392)	AF progression in 1 year (N=52)	No AF progression in 1 year (N=340)	P-value
Age (years)	60±11	64±10	60±12	0.015
History of AF (months)	5(2-15)	6(3-17)	5(2-15)	0.139
Male sex	241(62%)	29(55%)	212(62%)	0.364
Type of AF				0.001
Paroxysmal AF	323(82%)	34(65%)	289(85%)	
Persistent AF	69(18%)	18(35%)	51(15%)	
Heart failure	205(52%)	24(46%)	181(53%)	0.373
Hypertension	201(51%)	30(58%)	161(47%)	0.182
Diabetes mellitus	39(10%)	6(12%)	33(10%)	0.624
Coronary artery disease	33(8%)	4(8%)	29(9%)	1.000
Peripheral artery disease	10(3%)	5(10%)	5(2%)	0.005
Stroke or TIA	26(7%)	4(8%)	21(6%)	0.759
COPD	27(7%)	5(10%)	22(7%)	0.381
CHA ₂ DS ₂ -VASc score*	1.7±1.4	2.2±1.5	1.6±1.4	0.007
Number of comorbidities†	1.9±1.3	2.3±1.4	1.8±1.3	0.013
EHRA class				0.294
I	109(28%)	11(21%)	98(29%)	
II	217(55%)	34(65%)	183(54%)	
III	66(17%)	7(14%)	59(17%)	
Height (cm)	178±10	177±9	178±10	0.544
Weight (kg)	89±17	91±20	88±17	0.368
BMI (kg/m ²)	28±5	29±5	28±5	0.236
Obesity (BMI>30)	108(28%)	15(29%)	93(27%)	0.868
Blood pressure (mmHg)				
Systolic	131±17	132±18	130±17	0.529
Diastolic	78±10	79±10	78±9	0.845
Medications				
β-Blocker	243(62%)	31(60%)	212(62%)	0.760
Verapamil/Diltiazem	39(10%)	9(17%)	20(9%)	0.078
Digoxin	16(4%)	1(2%)	15(4%)	0.706
ACE-inhibitor	115(29%)	17(33%)	98(29%)	0.624
Angiotensin Receptor Blocker	53(14%)	9(17%)	44(13%)	0.386
Anticoagulant	265(68%)	41(79%)	224(66%)	0.050
Class Ic AAD	34(9%)	2(4%)	32(9%)	0.287
Class III AAD	23(6%)	3(6%)	20(6%)	1.000
PQ time (ms)	168±27	176±30	167±27	0.054

Table 1. Baseline characteristics. (continued)

Characteristic	Total population (N=392)	AF progression in 1 year (N=52)	No AF progression in 1 year (N=340)	P-value
Echocardiographic variables				
Left atrial volume (mL)	71±23	85±27	69±22	<0.001
Left atrial volume index (mL/m ²)	34±11	41±12	33±10	<0.001
LV ejection fraction (%)	57±5	55±6	57±5	0.096
LV mass (g)	170±46	178±56	169±44	0.191
LV mass index (g/m ²)	83±19	85±22	82±18	0.334
LV hypertrophy	35(9%)	5(10%)	30(9%)	0.792
Left atrial strain (%)				
Reservoir	33.5±12.6	31.0±13.1	33.7±12.5	0.325
Conduit	17.9±9.1	16.8±8.2	18.0±9.2	0.553
Contraction	15.6±7.2	14.2±6.4	15.7±7.3	0.334

Data are mean (standard deviation), number of patients (%), or median (interquartile range). AAD=anti-arrhythmic drug; ACE=angiotensin-converting enzyme; AF=atrial fibrillation; BMI=body mass index; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; EHRA= European Heart Rhythm Association class for symptoms; HF=heart failure. LV=left ventricular; NOAC= novel oral anticoagulant drugs; TIA=transient ischemic attack. *The CHA₂DS₂-VASc score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A₂=age ≥75 years; D=diabetes mellitus; S₂=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc (sex category (female sex); †The number of comorbidities was calculated by awarding a point for hypertension, age >65 years, diabetes, coronary artery disease, body mass index >25, kidney dysfunction and moderate or severe mitral valve regurgitation.

and had more comorbidities (2.6±1.4 versus 1.7±1.3, $P < 0.001$), as well as larger left atrial volume (89±25 versus 67±21, $P < 0.001$) and lower left atrial reservoir (34±13 versus 26±13, $P < 0.001$) and contraction strain (16±7 versus 10±7, $P < 0.001$) compared to paroxysmal AF (*Supplementary file 3*). During 1-year follow-up, 177 (45%) patients had no documented AF recurrence. Patient with paroxysmal AF on baseline had a higher proportion of patients without recurrence (48% versus 32%, $P < 0.001$).

AF progression

AF progression occurred in 52 of 392 patients (13%), 34 of 323 (11%) with paroxysmal AF (Figure 2), and in 18 of 69 (26%) persistent AF patients. Twenty-three (7%) patients with paroxysmal AF had a significant increase in AF burden during follow-up, and 11 patients (3%) progressed from paroxysmal to persistent or permanent AF. A total of 18 (26%) patients with persistent AF on baseline developed permanent AF. We observed no sex differences in progression rate (OR for women versus men 1.314, 95% CI 0.728-2.369; $P = 0.365$). A total of 3 clinical variables were univariably associated with AF progression, including age (OR 1.037 per year, 95% CI 1.007-1.069, $P = 0.016$), type of AF (OR 3.000 for persistent AF versus paroxysmal AF, 95% CI 1.575-5.713, $P < 0.001$) and left atrial volume (OR 1.328 per 10 mL, 95%

CI 1.168-1.511, $P < 0.001$). Additionally, two risk scores were also univariably associated with AF progression: CHA₂DS₂-VASc (OR 1.293 per point, 95% CI 1.070-1.562, $P = 0.008$) and the HATCH score (OR 1.300 per point, 95% CI 1.002-1.685, $P = 0.048$). We observed no differences in progression rate on individual components of the HATCH score, except for age, including heart failure (OR 0.753, 95% CI 0.419-1.352; $P = 0.342$), COPD (OR 1.538, 95% CI 0.555-4.257; $P = 0.407$) or prior stroke or transient ischemic attack (OR 1.266, 95% CI 0.419-1.352; $P = 0.678$). A total of 17 biomarkers were univariably associated with AF progression (*Supplementary file 4*). Multivariable analysis revealed that left atrial volume (OR per 10mL 1.251, 95% CI 1.078-1.450, $P < 0.001$), NT-proBNP (OR per standard deviation 1.583, 95% CI 1.099-2.281, $P = 0.014$) and plasminogen activator inhibitor-1 (PAI-1; OR per standard deviation 0.660, 95% CI 0.472-0.921, $P = 0.015$) were associated with AF progression (Table 2). Changes in therapy during follow-up included pulmonary vein isolation in 59 (15%); 51 (16%) in paroxysmal AF and 8 (12%) in persistent AF. In 40 (10%) patients, anti-arrhythmic drugs were initiated or dosage was increased; 31 (10%) in paroxysmal AF and 9 (13%) in persistent AF (*Supplementary file 5*).

Figure 2. Change in type of AF from baseline to 1 year. Red arrows and numbers represent patients with AF progression and grey arrows and numbers represent patients without AF progression. *Increase in AF burden was defined according to the AF progression definition: a doubling in AF burden at one year with at least an AF burden of 10%. † All patients with persistent AF underwent a cardioversion at baseline. Abbreviations: AF, atrial fibrillation; LA, left atrium; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAI-1, plasminogen activator inhibitor.

In patients with AF progression, 2 (4%) had an ablation during follow-up, compared to 57 (17%) of patients without AF progression ($P = 0.012$). Factors included in the multivariable regression model remained significant after adjusting for type of AF (model 1); and type of AF, pulmonary vein isolation during study period and anti-arrhythmic drug use (model 2). During follow-up, patients with AF progression had an average weight gain of 1 ± 4 kg, which was comparable to patients without AF progression (1 ± 4 kg, $P = 0.971$). There was also no difference in the proportion of patients who had significant ($\geq 5\%$) weight loss [5 (10%)

Table 2. Multivariable factors associated with AF progression. Model 1 was adjusted for type of AF at baseline (paroxysmal or persistent). Model 2 was adjusted for type of AF at baseline, pulmonary vein isolation during study period and the use of anti-arrhythmic drugs.

	Unadjusted model		Adjusted model 1		Adjusted model 2	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
LA volume (per 10mL)	1.251 (1.078-1.450)	0.003	1.248 (1.070-1.456)	0.005	1.242 (1.062-1.452)	0.007
NT-proBNP (per SD)	1.583 (1.099-2.281)	0.014	1.575 (1.071-2.315)	0.021	1.588 (1.075-2.345)	0.020
PAI-1 (per SD)	0.660 (0.472-0.921)	0.015	0.660 (0.472-0.921)	0.015	0.680 (0.487-0.950)	0.024

Abbreviations: CI=confidence interval; LA=left atrium; NT-proBNP= N-terminal pro-B-type natriuretic peptide; OR=odds ratio; PAI-1= plasminogen activator inhibitor; SD=standard deviation.

patients with AF progression and 29 (9%) without AF progression, $P = 0.815$].

Cardiovascular morbidity and mortality

Additional follow-up to assess events was 1.9 (0.9-3.3) years. A total of 32 events occurred in 27 (8%) patients (Table 3). The yearly event rate in patients with AF progression was 12.4%/year (95% CI 6.4%-21.6%) versus 2.3%/year (95% CI 1.3%-3.8%) in patients without AF progression (HR 5.764, 95% CI 1.820-18.258, $P < 0.0001$; Figure 3). Excluding patients with pulmonary vein isolation during follow-up or initiation or dose-change of anti-arrhythmic drugs did not affect results (HR 5.966, 95% CI 2.612-13.627, $P < 0.0001$), nor did adjustment for differences in age, sex, CHA₂DS₂-VASc and left atrial volume (HR 3.591, 95% CI 1.401-9.206, $P = 0.008$). Also, in patients with paroxysmal AF on baseline only the event rate was higher in those with AF progression (HR 5.880, 95% CI 2.235-15.467, $P = 0.0003$; *Supplementary file 3*).

DISCUSSION

In patients with recent-onset of AF we observed an AF progression rate of 13% in 1-year follow-up, with higher AF progression rates in persistent (26%), compared to paroxysmal AF (11%). Larger left atrial volume, higher levels of NT-proBNP and lower levels of PAI-1 were associated with AF progression. Patients with AF progression had a higher all-cause mortality and cardiovascular event rate.

Table 3. Cardiovascular event and all-cause mortality after 1-year, including yearly event rates during additional follow-up.

	Total (N=350)	AF progression (N=49)	No AF progression (N=301)	P-value*
Patients with an event	27 (8%)	12 (24%)	15 (5%)	<0.001
Total number of events	32	15	17	
Cardiovascular event rate	3.6%/year	12.4%/year	2.3%/year	<0.001
All-cause mortality	7 (0.9%/year)	2 (1.8%/year)	5 (0.8%/year)	0.287
HF hospitalization	4 (0.5%/year)	2 (1.9%/year)	2 (0.3%/year)	0.040
Stroke	3 (0.4%/year)	1 (0.9%/year)	2 (0.3%/year)	0.347
Systemic embolism	-	-	-	
Major bleeding	4 (0.5%/year)	2 (1.9%/year)	2 (0.3%/year)	0.038
Syncope	4 (0.5%/year)	3 (2.8%/year)	1 (0.2%/year)	<0.001
Life-threatening AE of AF drugs	-	-	-	
Sustained Ventricular Tachycardia	1 (0.1%/year)	-	1 (0.2%/year)	0.681
Myocardial infarction	3 (0.4%/year)	3 (2.8%/year)	-	<0.001
PM implant	5 (0.7%/year)	2 (1.9%/year)	3 (0.5%/year)	0.095
ICD implant	1 (0.1%/year)	-	1 (0.2%/year)	0.679

Abbreviations: AE=adverse events; AF=atrial fibrillation; HF=heart failure; ICD=implantable cardiac defibrillator; PM=pacemaker.

*P-value is given for differences in yearly event rate between patients with and without AF progression.

Figure 3. Kaplan Meier estimates showing the composite of cardiovascular events and all-cause mortality for patients with and without AF progression during additional follow-up.

* Follow-up duration began after AF progression assessment at 1-year.

Abbreviations: AF=atrial fibrillation; CI=confidence interval.

AF progression

Assessment of AF progression is limited by the amount of rhythm monitoring. A uniformly accepted definition is lacking, but most often the transition from self-terminating to non-self-terminating AF is used.(4,5) Our definition also included increase in AF burden, to avoid misclassifying patients who progress from low to high burden paroxysmal AF.(9) By using a threshold of 10% burden, we tried to prevent misclassifying patients as having progression with minimal absolute increase in burden (e.g. 1% at baseline and 2.5% at 1-year). Using the traditional definition, a yearly progression rate of 15% was found in the Euro Heart Survey (5). However, using the same definition, Padfield *et al.* only found 8.6% progression in 1-year in patients who were slightly younger and had less underlying cardiovascular conditions. (11) And in patients with young-onset AF (<60 years) with few comorbidities, a yearly AF progression rate to permanent AF as low as 2% was observed.(6) In AF-RISK, 3% had progression to persistent or permanent AF in 1 year follow-up. This relatively lower number can be explained by the low-risk profile of our patients. Using our definition, including progression from low to higher AF burden of paroxysmal AF, we found a progression rate of 13%, with higher AF progression rates in persistent (26%), compared to paroxysmal AF (11%). Different AF progression rates for paroxysmal and persistent AF were also found in a recent meta-analysis, with AF progression rates of 7.1% (paroxysmal to non-paroxysmal) and 18.6% (persistent to permanent AF), which is comparable to our progression rates.(4) Higher progression rates in patients with persistent AF could be explained by more structural remodelling, due to more comorbidities and a higher age. This is supported by lower left atrial reservoir and contract strain and larger left atrial size, that we found in persistent AF, compared to paroxysmal AF.

Factors associated with AF progression

Left atrial volume, NT-proBNP and PAI-1 were associated with AF progression. Treatment differences during follow-up that interfere with assessing the true AF progression rate remain an important limitation in studies on AF progression. Yet, the same factors remained associated with progression after correction for type of AF and treatment during follow-up. Increased left atrial volume has often been associated with AF incidence, recurrence and cardiovascular events.(12) An enlarged left atrium is a sign of an atrial myopathy due to progressive atrial remodeling caused by risk factors and comorbidities including ageing, stretch from pressure and volume overload, inflammation, and oxidative stress.(2) This results in atrial fibrosis, loss of atrial contractile function, and formation of both an arrhythmogenic and thrombogenic substrate.(13)

Multiple blood biomarkers, including interleukin-6, C-reactive protein and troponin have previously been associated with incident and recurrent AF. Yet, limited data is available on blood biomarkers in AF progression. Progression from persistent to permanent AF has been

associated with higher levels of fibrotic and inflammatory markers, such as transforming growth factor β 1.(14) In a small study, Akutsu *et al.* linked baseline elevated levels of BNP with AF progression to persistent AF.(15) In our cohort, NT-proBNP was also associated with AF progression. NT-proBNP, a cardiac specific marker, has been associated with incident AF and increased risk of mortality.(16) Secretion of NT-proBNP is promoted by cardiac myocyte stretch. Since atrial stretch also causes release of NT-proBNP, it reflects a degree of atrial dysfunction.

PAI-1 serves as marker of fibrinolysis with its main function being inhibition of tissue plasminogen activator and urokinase, thereby attenuating fibrinolysis. The role of PAI-1 in AF is less known. In a large community-based study no clear association of PAI-1 with incident AF was found.(17) Despite being a marker of increased fibrinolysis, low PAI-1 levels do not necessarily reflect hypocoagulability or a reduced atherothrombotic risk, as thrombin and/or fibrin formation might be normal, or even increased. Hypercoagulability has previously been linked to atrial remodeling, promoting AF.(13) Promotion of fibrosis has been demonstrated in PAI-1 deficient mice.(18) One explanation for this latter observation could be increased inflammation and chemotaxis induced by fibrin degradation products. Indeed, fibrin degradation products, including D-dimer, have been shown to cause an inflammatory response.(19) This can in turn enhance atrial substrate formation and explain our observed association between lower PAI-1 levels and AF progression.

In the recent meta-analysis, Blum *et al.* found history of hypertension, frequency of paroxysmal AF at baseline, age, history of heart failure and duration of follow-up to be predictors of AF progression.(4) This is partly in agreement with earlier findings of De Vos *et al.*, who developed the HATCH AF-progression risk-score, which is an acronym for Hypertension, Age ≥ 75 years, previous Transient ischemic attack or stroke, Chronic obstructive pulmonary disease or Heart failure.(5) Both indicate that underlying (cardiovascular) disease and number of comorbidities underlie AF progression and should be treated accordingly in order to prevent AF progression.(3)

Cardiovascular events and mortality

Patients with AF progression showed a higher rate of cardiovascular events and all-cause mortality as has been demonstrated before.(5-8) This effect was observed in both paroxysmal AF and persistent AF, and remained after adjusting for several factors, including left atrial size and CHA₂DS₂-VASc score. However, most definitions did not include progression from low to high burden paroxysmal AF. Increased morbidity and mortality associated with AF progression has been shown in patients with progression of subclinical AF episode duration.(7) AF progression defined as prolongation to atrial high-rate episodes >24 hours was associated with a higher rate of heart failure hospitalizations. In ECG-detected AF this has

been demonstrated as well. Vanassche *et al.* found type of AF being one of the strongest predictors of stroke.(8) Go *et al.* found a 3-fold increase in stroke risk in patients within the highest tertile of AF burden.(20) These results signify that the amount of AF itself may have prognostic value. Yet, whether this is due to a causal relation of AF burden with events or that these patients have more severe underlying diseases, being therefore more challenging to treat, cannot be concluded from our data.

Future perspectives

More data is needed to clarify the relation of cardiovascular events and the amount of AF and whether preventing AF progression also leads to a more favorable prognosis. The Reappraisal of Atrial Fibrillation: Interaction Between HyperCoagulability, Electrical Remodeling, and Vascular Destabilisation in the Progression of Atrial Fibrillation (RACE V; Clinicaltrials.gov identifier NCT02726698) registry is currently enrolling patients with paroxysmal AF and aims to elucidate the factors associated with AF progression, with special emphasis on the role of hypercoagulability. This is done by deep phenotyping patients with paroxysmal self-terminating AF and the use of continuous rhythm monitoring through an implantable loop recorder or a pacemaker, and will be able to validate the present findings and provide in the process of AF progression in a population with continuous rhythm monitoring.

Strengths and limitations

Strengths of the present analysis include the prospective study design with AF progression as primary aim, the well-phenotyped population with frequent study-related outpatient clinic visits on top of rhythm monitoring by Holter and event recording at several time points during 1 year. Continuous rhythm monitoring was not used, which may be considered an important limitation. Yet, the combination of Holter monitoring and event recording as rhythm monitoring strategy during follow-up may have provided more accurate data on AF progression compared to other studies.

Although the study population consisted of both paroxysmal and persistent AF, adding the type of AF to the regression model did not affect results, as well as differences in treatment during follow-up between patients. And indeed, higher progression rates were found in more advanced forms of AF (e.g. persistent AF compared to paroxysmal AF). The AF-RISK population was a relatively low risk AF population, limiting the number of AF progression events and cardiovascular events during follow-up. Therefore, our data cannot be translated to higher risk AF patients. And finally, the associations that have been found do not necessarily reflect causal relation.

CONCLUSION

AF is a progressive disease. We found a 13% progression rate during 1-year follow-up with higher progression rates in persistent (26%) compared to paroxysmal AF (11%). A larger left atrial volume, higher NT-proBNP plasma levels and a lower PAI-1 plasma level were associated with AF progression, also after adjusting for type of AF at baseline. Patients with AF progression had a higher morbidity and mortality rate.

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SUPPLEMENTARY FILES

Supplementary file 1. Study procedures

	Inclusion	1 month FU	3 month FU	6 month FU	9 month FU	1 year
Informed consent	X					
Clinical history	X	X	X	X	X	X
Clinical factors	X					X
Current medication	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X
ECG	X	X	X	X	X	X
Body surface ECG*	X					X
24-hr blood pressure measurement	X					X
Biomarkers (+DNA*)	X					X
Echocardiography	X					X
Exercise test	X					
2-week event recorder	X					X
24-hr Holter	X		X	X	X	
48-hr Holter	X					X

* Only in patients providing additional informed consent. Abbreviations: ECG= electrocardiogram; FU= follow-up.

Supplementary file 2. Biomarkers Olink CARDIOVASCULAR III (v.6111) panel. The 4 biomarkers marked by * were excluded because of >10% of the values below the limit of detection.

Assay	Uniprot ID	Olink ID
TNFRSF14	Q92956	OID00563
LDL receptor	P01130	OID00564
ITGB2	P05107	OID00565
IL-17RA	Q96F46	OID00566
TNF-R2	P20333	OID00567
MMP-9	P14780	OID00568
EPHB4	P54760	OID00569
IL2-RA	P01589	OID00570
OPG	O00300	OID00571
ALCAM	Q13740	OID00572
TFF3	Q07654	OID00573
SELP	P16109	OID00574
CSTB	P04080	OID00575
MCP-1	P13500	OID00576
CD163	Q86VB7	OID00577
Gal-3	P17931	OID00578
GRN	P28799	OID00579
NT-proBNP	N/A	OID00131
*BLM hydrolase	Q13867	OID00581
PLC	P98160	OID00582
LTBR	P36941	OID00583
Notch 3	Q9UM47	OID00584
TIMP4	Q99727	OID00585
CNTN1	Q12860	OID00586
CDH5	P33151	OID00587
TLT-2	Q5T2D2	OID00588
FABP4	P15090	OID00589
TFPI	P10646	OID00590
PAI-1	P05121	OID00591
CCL24	O00175	OID00592
TR	P02786	OID00593
TNFRSF10C	O14798	OID00594
GDF-15	Q99988	OID00595
SELE	P16581	OID00596
AZU1	P20160	OID00597
DLK-1	P80370	OID00598
*SPON1	Q9HCB6	OID00599
MPO	P05164	OID00600

Supplementary file 2. Biomarkers Olink CARDIOVASCULAR III (v.6111) panel. The 4 biomarkers marked by * were excluded because of >10% of the values below the limit of detection. (continued)

Assay	Uniprot ID	Olink ID
CXCL16	Q9H2A7	OID00601
IL-6RA	P08887	OID00602
RETN	Q9HD89	OID00603
IGFBP-1	P08833	OID00604
CHIT1	Q13231	OID00605
TR-AP	P13686	OID00606
GP6	Q9HCN6	OID05026
PSP-D	P35247	OID00608
*PI3	P19957	OID00609
Ep-CAM	P16422	OID00610
AP-N	P15144	OID00611
AXL	P30530	OID00612
IL-1RT1	P14778	OID00613
MMP-2	P08253	OID00614
FAS	P25445	OID00615
MB	P02144	OID00616
TNFSF13B	Q9Y275	OID00617
PRTN3	P24158	OID00618
PCSK9	Q8NBP7	OID00619
U-PAR	Q03405	OID00620
OPN	P10451	OID00621
*CTSD	P07339	OID00622
PGLYRP1	O75594	OID00623
CPA1	P15085	OID00624
JAM-A	Q9Y624	OID00625
Gal-4	P56470	OID00626
IL-1RT2	P27930	OID00627
SHPS-1	P78324	OID00628
CCL15	Q16663	OID00629
CASP-3	P42574	OID00630
uPA	P00749	OID00631
CPB1	P15086	OID00632
CHI3L1	P36222	OID00633
ST2	Q01638	OID00634
t-PA	P00750	OID00635
SCGB3A2	Q96PL1	OID00636
EGFR	P00533	OID00637
IGFBP-7	Q16270	OID00638

Supplementary file 2. Biomarkers Olink CARDIOVASCULAR III (v.6111) panel. The 4 biomarkers marked by * were excluded because of >10% of the values below the limit of detection. (continued)

Assay	Uniprot ID	Olink ID
CD93	Q9NPY3	OID00639
IL-18BP	O95998	OID00640
COL1A1	P02452	OID00641
PON3	Q15166	OID00642
CTS2	Q9UBR2	OID00643
MMP-3	P08254	OID00644
RARRES2	Q99969	OID00645
ICAM-2	P13598	OID00646
KLK6	Q92876	OID00647
PDGF subunit A	P04085	OID00648
TNF-R1	P19438	OID00649
IGFBP-2	P18065	OID00650
vWF	P04275	OID00651
PECAM-1	P16284	OID00652
MEPE	Q9NQ76	OID00132
CCL16	O15467	OID00654

Supplementary file 3.

Table 1. Baseline characteristics for patients with either paroxysmal or persistent AF on baseline. P-value indicates differences between patients with paroxysmal and persistent AF on baseline.

Characteristic	Total population (N=392)	Paroxysmal AF at baseline (N=323)	Persistent AF at baseline (N=69)	P-value
Age (years)	60±11	59±12	63±10	0.016
History of AF (months)	5(2-15)	5(2-15)	5(2-13)	0.871
Male sex	241(62%)	188(58%)	53(77%)	0.004
Heart failure	205(52%)	159(49%)	46(67%)	0.011
Hypertension	201(51%)	148(46%)	43(62%)	0.017
Diabetes mellitus	39(10%)	30(9%)	9(13%)	0.375
Coronary artery disease	33(8%)	19(6%)	14(20%)	<0.001
Peripheral artery disease	10(3%)	7(2%)	3(4%)	0.390
Stroke or TIA	26(7%)	19(6%)	6(9%)	0.414
COPD	27(7%)	21(7%)	6(9%)	0.599
CHA ₂ DS ₂ -VASC score*	1.7±1.4	1.6±1.4	2.2±1.5	0.004
Number of comorbidities†	1.9±1.3	1.7±1.3	2.6±1.4	<0.001
EHRA class				0.001
I	109(28%)	94(29%)	15(22%)	
II	217(55%)	185(57%)	32(46%)	
III	66(17%)	44(14%)	22(32%)	
Height (cm)	178±10	178±10	180±9	0.083
Weight (kg)	89±17	87±17	95±18	0.002
BMI (kg/m ²)	28±5	28±5	29±5	0.018
Obesity (BMI>30)	108(28%)	85(26%)	23(33%)	0.238
Blood pressure (mmHg)				
Systolic	131±17	131±17	129±17	0.441
Diastolic	78±10	78±9	81±11	0.038
Medications				
β-Blocker	243(62%)	193(60%)	50(73%)	0.056
Verapamil/Diltiazem	39(10%)	32(10%)	7(10%)	1.000
Digoxin	16(4%)	7(2%)	9(13%)	<0.001
ACE-inhibitor	115(29%)	83(26%)	32(46%)	0.001
Angiotensin Receptor Blocker	53(14%)	45(14%)	8(12%)	0.701
Anticoagulant	265(68%)	198(61%)	67(97%)	<0.001
Class Ic AAD	34(9%)	33(10%)	1(1%)	0.017
Class III AAD	23(6%)	18(6%)	5(7%)	0.575
PQ time (ms)	168±27	165±25	187±32	<0.001
Echocardiographic variables				
Left atrial volume (mL)	71±23	67±21	89±25	<0.001

Table 1. Baseline characteristics for patients with either paroxysmal or persistent AF on baseline. P-value indicates differences between patients with paroxysmal and persistent AF on baseline. (continued)

Characteristic	Total population (N=392)	Paroxysmal AF at baseline (N=323)	Persistent AF at baseline (N=69)	P-value
Left atrial volume index (mL/m ²)	34±11	33±10	42±11	<0.001
LV ejection fraction (%)	57±5	57±4	53±8	<0.001
LV mass (g)	170±46	166±44	193±46	<0.001
LV mass index (g/m ²)	83±19	81±18	90±20	<0.001
LV hypertrophy	35(9%)	26(8%)	9(13%)	0.247
Left atrial strain (%)				
Reservoir	33.5±12.6	34±13	26±13	0.042
Conduit	17.9±9.1	18±9	15±7	0.333
Contraction	15.6±7.2	16±7	10±7	0.020

Data are mean (standard deviation), number of patients (%), or median (interquartile range). AAD=anti-arrhythmic drug; ACE=angiotensin-converting enzyme; AF=atrial fibrillation; BMI=body mass index; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; EHRA= European Heart Rhythm Association class for symptoms; HF=heart failure. LV=left ventricular; NOAC=novel oral anticoagulant drugs; TIA=transient ischemic attack. *The CHA₂DS₂-VASc score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A₂=age ≥75 years; D=diabetes mellitus; S₂=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc (sex category (female sex); †The number of comorbidities was calculated by awarding a point for hypertension, age >65 years, diabetes, coronary artery disease, body mass index >25, kidney dysfunction and moderate or severe mitral valve regurgitation.

Supplementary file 4.

Results of the univariate analysis on the Olink Biomarker panel on AF progression. Full list of biomarkers is shown in Supplementary file 2. All biomarkers with a *P*-value <0.05 have been displayed.

Biomarker	P-value	Odds ratio (95% confidence interval)
NT-proBNP	<0.001	1.493 (1.215-1.833)
TLT-2	0.003	0.420 (0.236-0.747)
IL1RT2	0.009	0.382 (0.186-0.785)
TFPI	0.010	0.389 (0.189-0.799)
GP-6	0.013	0.668 (0.486-0.919)
PECAM1	0.019	0.596 (0.388-0.917)
JAMA	0.020	0.734 (0.566-0.952)
EGFR	0.021	0.295 (0.105-0.830)
SELP	0.026	0.690 (0.497-0.957)
MEPE	0.035	0.552 (0.318-0.958)
PAI-1	0.037	0.769 (0.601-0.984)
AXL	0.039	0.505 (0.264-0.966)
TRAP	0.040	0.511 (0.269-0.970)
TNFRSF14	0.042	0.517 (0.274-0.976)
EpCAM	0.042	0.753 (0.573-0.989)
PON3	0.046	0.651 (0.427-0.992)
CASP3	0.048	0.827 (0.686-0.999)

Supplementary file 5.

The tables below show the use and changes of antiarrhythmic drugs (AAD) and performance of pulmonary vein isolation (PVI) in the total population (Table 1) and for paroxysmal atrial fibrillation (AF) only (Table 2).

Table 1. Total population

		Antiarrhythmic drug therapy*				Total N
		No	Started	Stopped	Continuous	
PVI	No	267	38	4	24	333
	Yes	28	2	19	10	59
Total N		295	40	23	34	392

Table 2. Paroxysmal AF patients

		Antiarrhythmic drug therapy*				Total N
		No	Started	Stopped	Continuous	
PVI	No	220	29	2	21	272
	Yes	21	2	19	9	51
Total N		241	31	21	30	323

*Patients were divided into receiving no AAD throughout the first year (no), patients who started AAD during the first study year (started), patients who stopped AAD (stopped) and patients using AAD throughout the first study year (yes).

Supplementary figure 1. Kaplan Meier estimates showing the composite of cardiovascular events and all-cause mortality for all paroxysmal AF patients with and without AF progression during additional follow-up.

4

Temporal Patterns and Short-Term Progression of Paroxysmal Atrial Fibrillation: Data from RACE V

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ABSTRACT

Aims. Atrial fibrillation (AF) often starts as a paroxysmal selfterminating arrhythmia. Limited information is available on AF patterns and episode duration of paroxysmal AF. In paroxysmal AF patients we longitudinally studied the temporal AF patterns, the association with clinical characteristics, and prevalence of AF progression.

Methods and Results. In the Reappraisal of AF: Interaction Between HyperCoagulability, Electrical Remodelling, and Vascular Destabilisation in the Progression of AF (RACE V) registry 202 patients with paroxysmal AF were followed with continuous rhythm monitoring (implantable loop recorder or pacemaker) for 6 months. Mean age was 64 ± 9 years, 42% were women. AF history was $2.1(0.5-4.4)$ years, CHA₂DS₂-VASc 1.9 ± 1.3 , 101(50%) had hypertension, 69(34%) heart failure. One third did not show any AF during follow-up. Patients with long episodes (>12 hours) were often men with more comorbidities (heart failure, coronary artery disease, higher left ventricular mass). Patients with higher AF burden (>2.5%) were older with more comorbidities (worse renal function, higher calcium score, thicker intima media thickness). In 179(89%) patients 1-year rhythm follow-up was available. On a quarterly basis, average daily AF burden increased from 3.2% to 3.8, 5.2 and 6.1%. Compared to the first 6 months, 111(62%) patients remained stable during the second 6 months, 39(22%) showed progression to longer AF episodes, 8(3%) developed persistent AF, 29(16%) patients showed AF regression.

Conclusions. In paroxysmal AF, temporal patterns differ suggesting that paroxysmal AF is not one entity. AF burden is low and determined by number of comorbidities. AF progression occurred in 1 out of 5.

INTRODUCTION

Traditionally, atrial fibrillation (AF) is clinically categorized into paroxysmal, persistent, long-standing persistent and permanent AF.(1) Often starting as short-lasting, paroxysmal episodes, AF commonly progresses over time to persistent and permanent, non-selfterminating AF.(2) Progression of AF is associated with a higher incidence of major adverse cardiovascular and cerebrovascular events.(3,4) However, most data on AF and AF progression is obtained with intermittent rhythm monitoring, providing limited information on the total burden and the temporal pattern of AF.(5-7) In the era of implantable loop recorders, it is now possible to assess progression of AF more precisely.(8) These devices also provide information on the exact temporal AF pattern and number and duration of AF episodes, which may help explaining differences in underlying pathophysiological AF mechanisms and related clinical outcomes. Ultimately this could aid to personalize AF therapy and may have clinical utility for the assessment of AF treatment response.

Recently, the first initiatives for an improved classification for paroxysmal AF have been proposed, based on single-lead electrocardiogram (ECG) monitoring.(9) The Reappraisal of Atrial Fibrillation: Interaction Between HyperCoagulability, Electrical Remodelling, and Vascular Destabilisation in the Progression of Atrial Fibrillation (RACE V) registry aims to elucidate the factors associated with AF progression. At baseline, deep phenotyping of patients with paroxysmal selfterminating AF is performed. Exact longitudinal assessment of episode number and duration and AF burden is provided by continuous rhythm monitoring through an implantable loop recorder or pacemaker with the same AF detection algorithm. In the present interim analysis, we aim to longitudinally study AF temporal patterns, burden and short-term progression of AF and their association with clinical characteristics, in patients with paroxysmal selfterminating AF using continuous rhythm monitoring.

METHODS

Patient population

The RACE V is an investigator-initiated, prospective, multicentre registry aiming to include 750 patients in multiple centres in The Netherlands. A total of 202 patients were included in 5 centres for the current interim analysis between June 2016 and December 2017. Inclusion criteria included patients aged >18 years with paroxysmal AF; a maximum history of 10 years since diagnosis at the moment of inclusion; a maximum CHA₂DS₂-VASc score of 5; and no other indication for anticoagulation drugs (e.g. mechanical valve prosthesis). Patients had to have at least two documented episodes of paroxysmal AF in the past year or one documented episode combined with at least two symptomatic episodes in the past

year suspected to be AF. In patients with a Medtronic Advisa® pacemaker, atrial high-rate episodes (AHRE) >190 beats per minute lasting >6 minutes were qualified as AF episodes. Patients with other types of pacemakers, defibrillators or cardiac resynchronization therapy could not participate due to differences in AHRE algorithm or incompatibility with the type of home-monitoring. Patients with a history of persistent AF, currently treated with amiodarone, current pregnancy or a life expectancy <2.5 years were not eligible to participate. Patients with AF caused exclusively by transient triggers (e.g. postoperative, due to infection) could also not participate, as well as patients with a previous pulmonary vein isolation (PVI), or intention to undergo PVI. The study was performed in concordance with the Declaration of Helsinki. The Institutional Review Board approved the protocol and the study was registered at Clinicaltrials.gov (identifier NCT02726698). All centres approved the protocol and all patients gave written informed consent. Intended total follow-up duration is 2.5 years.

Study procedures

All patients received causal therapy for AF, as well as rate and rhythm control according to the European Society of Cardiology AF guidelines.⁽¹⁾ At baseline, information on clinical characteristics, medical history, AF characteristics, symptomatology and current medication were collected. Additionally, all patients underwent physical examination, a 12-lead ECG, echocardiography, cardiac computed tomography (CT), vascular assessment and blood sampling. Quality of life, AF related symptoms, and physical activity were assessed through questionnaires. After baseline, additional follow-up visits were planned at 1 and 2.5 years.

The cardiac CT was performed as a non-contrast ECG-gated scan with slice collimation of 0.6 mm and a tube voltage of 120 kV. Beta-blockers were administered in case of high heart rates to improve image quality. Cranial demarcation was placed at the aortic arch or higher and caudal demarcation was placed to include the whole heart. Automated coronary calcium scores (Agatston) were collected.

Vascular assessment included pulse wave velocity (PWV) and intima media thickness (IMT) measurements. PWV velocity was measured by SphygmoCor (Atcor Medical Blood Pressure Analysis System, Australia) or Complior (Alam Medical, France) at the carotid and femoral arteries. To determine aortic PWV, ≥ 20 consecutive pressure waveforms were collected at the carotid artery and the femoral artery. The system software calculated the wave transit time, using the R wave of the simultaneously recorded ECG. Distance between both measure points was determined and corrected by multiplying the distance by 0.8. The PWV was calculated by dividing the corrected distance by the wave transit time. IMT measurements were performed by ultrasound (Siemens Acuson S2000) with the Syncho US Workplace 3.5,

Arterial Health Package for automated IMT measurement. IMT was bilaterally assessed in the common carotid artery, the carotid bifurcation and internal carotid artery.

Rhythm follow-up

All patients had continuous rhythm monitoring to detect the exact AF burden (time spent in AF) and temporal AF pattern (the number and duration of AF episodes). Patients either received a Medtronic Reveal LINQ® implantable loop recorder subcutaneously or had a Medtronic Advia® pacemaker implanted prior to inclusion. All patients received a home monitoring device (Medtronic Carelink®) in order to receive all data regarding cardiac arrhythmias on the Carelink Network®. Patients were instructed to perform at least weekly manual data transmissions to prevent potential data loss. AT/AF detection setting was set to AF detection only. Additional settings included a tachy-pause-brady data storage priority and balanced sensitivity for AF detection with nominal ectopy rejection for all patients. All episodes of AF ≥ 2 minutes were automatically detected. Episodes ≥ 182 beats per minute with a duration of ≥ 24 beats were automatically classified as tachycardia and if applicable, corrected to AF episodes. First, a dedicated service (Fysiologic, Amsterdam, The Netherlands) adjudicated all episodes. As a second assessment all episodes were independently adjudicated by 2 physicians (R.R.D.W.; Ö.E.) and corrected if needed. Information on changes in anti-arrhythmic drug (AAD) therapy, electrical cardioversions (ECV) and PVI were collected during follow-up.

Atrial fibrillation patterns

AF patterns during 6 months (183 days) were visualized by custom-made software using Microsoft Visual Basic. First day of monitoring started at midnight the day after loop recorder implantation or at midnight the day after inclusion in patients with a pacemaker. AF patterns were independently adjudicated by 4 physicians (R.R.D.W.; Ö.E.; H.J.G.M.C.; I.C.V.G.). At first, all patients were divided into having no recurrence of AF or ≥ 1 episode of AF during follow-up. Secondly, patients with AF episodes were divided by into short AF episodes duration (< 6 hours), intermediate (6-12 hours), and long AF episodes (> 12 hours) by their longest AF episode during the first 6 months. Third, AF burden was calculated by the cumulative time in AF divided by the total follow-up time, expressed as a percentage. In addition, patients were divided according to degree of AF burden: low AF burden ($> 0-0.5\%$), intermediate ($> 0.5-2.5\%$), and high AF burden ($> 2.5\%$). The aforementioned cut-offs for AF burden were used to create equally-sized groups.

AF progression was assessed in 179 patients in whom 1 year (366 days) of rhythm follow-up was available. These patients were also divided into no AF, short, intermediate and long episodes according to the second 6 months of rhythm follow-up. Progression of AF was defined as deterioration of episode duration category (e.g. short to intermediate episodes)

in the second 6 months, compared to the first 6 months. Regression was defined as episode category improvement (e.g. intermediate to short episodes). Daily averaged AF burden was calculated by the sum of the daily AF burden from all patients and divided by the number of patients. Patients with episodes >7 days were considered to have persistent AF.

Covariate definition

Covariate definitions that were used are shown in the *Supplementary files*.

Statistical analysis

Data was presented as means $\pm$ standard deviation or median with interquartile range, depending on normality of the data. Categorical data was presented as numbers with percentages. Differences between patients with and without AF recurrence were tested by Student's T-test, Man-Whitney U test or Fisher's exact (2 categories) or χ^2 (>2 categories). Differences between different AF patterns were analysed by one-way ANOVA in normally distributed data, Kruskal-Wallis test in non-normally distributed data or χ^2 in categorical data. Additional sensitivity analyses were performed excluding the following groups: (1) patients that underwent PVI or ECV during follow-up; (2) patients that underwent PVI, ECV or had changes in AAD therapy during follow-up; and (3) patients that underwent PVI, ECV or any AAD therapy during follow-up. Spearman's correlation coefficient, including 95% confidence interval (CI), was calculated to assess the relation of AF burden and the duration of the longest AF episode. Changes in the duration of longest AF episode category in the first 6 months and second 6 months were visualised using a Sankey diagram. All analyses were performed by IBM SPSS Statistics for Windows version 23.0 (Armonk, New York, USA) and GraphPad Prism version 7.02 (GraphPad Software, La Jolla, USA). A P-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Baseline characteristics are shown in Table 1. Mean age was 64 ± 9 years, 85 (42%) were women and median history of AF at baseline was 2.1 (0.5-4.4) years. The majority had an implantable loop recorder (185 [92%]); 17 (8%) had a pacemaker. Patients with a pacemaker were older (72 ± 9 versus 64 ± 9 years, $P < 0.001$) and had more comorbidities (2.9 ± 1.5 versus 2.3 ± 1.3 , $P = 0.049$).

AF episodes

A total of 13,657 episodes of AF in 202 patients were automatically detected by the implanted device during follow-up of 183 days, of which 2,231 (16%) episodes were adjudicated

Table 1. Baseline characteristics of the total population, and split on recurrence of AF during 6-month follow-up. A P-value is given for the difference between recurrence versus no recurrence of AF.

Characteristic	Total (N=202)	No Recurrence of AF (N=63)	Recurrence of AF (N=139)	P-value (no recurrence vs recurrence)
Age (years)	64±9	64±10	64±9	0.900
Male sex	117 (58%)	36 (57%)	81 (58%)	0.880
Total history AF (years)	2.1 (0.5-4.4)	1.9 (0.5-5.3)	2.2 (0.6-4.5)	0.574
Heart failure	69 (34%)	21 (33%)	48 (35%)	0.868
Hypertension	101 (50%)	40 (64%)	61 (44%)	0.010
Diabetes mellitus	19 (9%)	8 (13%)	11 (8%)	0.304
Coronary artery disease	23 (11%)	5 (8%)	18 (13%)	0.299
Thromboembolic events	22 (11%)	9 (14%)	13 (9%)	0.297
Chronic obstructive pulmonary disease	11 (5%)	3 (5%)	8 (6%)	0.773
Number of Comorbidities*	2.3±1.3	2.5±1.3	2.3±1.3	0.199
CHA ₂ DS ₂ -VASc score**	1.9±1.3	2.2±1.3	1.8±1.3	0.030
0	25 (12%)	4 (6%)	21 (15%)	0.143
1	56 (28%)	14 (22%)	42 (30%)	
2	60 (30%)	25 (39%)	35 (25%)	
3	35 (17%)	8 (12%)	27 (19%)	
4	18 (9%)	7 (11%)	11 (8%)	
5	8 (4%)	5 (8%)	3 (2%)	
EHRA class				
I	22 (11%)	9 (14%)	13 (9%)	0.873
Ila	84 (42%)	24 (38%)	60 (43%)	
Ilb	78 (39%)	28 (44%)	50 (36%)	
II	18 (9%)	2 (3%)	16 (12%)	
Height (cm)	176±10	176±10	176±11	0.873
Weight (kg)	86±17	85±15	86±18	0.747
BMI (kg/m ²)	28±5	28±5	28±5	0.956
Obesity (BMI>30)	50 (25%)	17 (27%)	33 (24%)	0.621
Waist circumference (cm)	102±13	103±14	102±13	0.692
Blood pressure (mmHg)				
Systolic	136±18	135±17	137±19	0.458
Diastolic	81±10	80±11	81±9	0.649
NT-proBNP (pg/ml)	50 (22-144)	54 (27-123)	48 (19-159)	0.540
Creatinine (μmol/L)	82 (70-92)	82 (70-92)	82 (71-92)	0.476
eGFR (mL/min)	80 (68-88)	82 (68-91)	79 (68-88)	0.491
Medications				
β-blocker	104 (52%)	33 (52%)	71 (51%)	0.864
Verapamil/Diltiazem	31 (15%)	9 (14%)	22 (16%)	0.778

Table 1. Baseline characteristics of the total population, and split on recurrence of AF during 6-month follow-up. A P-value is given for the difference between recurrence versus no recurrence of AF. (continued)

Characteristic	Total (N=202)	No Recurrence of AF (N=63)	Recurrence of AF (N=139)	P-value (no recurrence vs recurrence)
Class I antiarrhythmic drugs	41 (20%)	6 (10%)	35 (25%)	0.013
Class III antiarrhythmic drugs	11 (5%)	3 (5%)	8 (6%)	1.000
Digoxin	2 (1%)	-	2 (1.4%)	0.339
ACE-inhibitor	43 (21%)	18 (29%)	25 (18%)	0.089
Angiotensin Receptor Blocker	44 (22%)	22 (35%)	22 (16%)	0.002
Mineralocorticoid Receptor Antagonist	3 (2%)	-	3 (2%)	0.240
Statin	80 (40%)	27 (43%)	53 (38%)	0.524
Diuretic	33 (16%)	17 (26%)	16 (12%)	0.006
Anticoagulant				0.079
Vitamin K antagonist	33 (16%)	11 (17%)	22 (16%)	
NOAC	114 (56%)	40 (63%)	74 (53%)	
Echocardiographic variables				
Left atrial volume (mL)	69±23	62±20	72±24	0.013
Left atrial volume index (mL/m ²)	35±12	31±10	37±12	0.002
Left ventricular ejection fraction (%)	58 (55-60)	58 (55-60)	58 (55-60)	0.661
Left ventricular ejection fraction <45%	4 (2%)	2 (3%)	2 (1%)	0.412
Left ventricular mass (g)	162±47	156±45	164±47	0.417
Left ventricular mass index (g/m ²)	79±18	77±17	80±19	0.468
Left ventricular hypertrophy	8 (4%)	2 (3%)	6 (4%)	0.700
CT				
Calcium score (Agatston)	31 (0-227)	41 (0-262)	26 (0-216)	0.733
Vascular assessment				
IMT-CCA (mm)	0.72 (0.63-0.87)	0.71 (0.62-0.88)	0.73 (0.64-0.87)	0.418
IMT-all segments (mm)	0.73 (0.62-0.90)	0.70 (0.60-0.94)	0.74 (0.63-0.87)	0.835
Pulse wave velocity (m/s)	8.3 (7.3-9.7)	8.6 (7.2-9.7)	8.1 (7.3-9.7)	0.382

Data are presented as mean±standard deviation, number of patients (%), or median (interquartile range). Abbreviations: ACE=angiotensin-converting enzyme; AF=atrial fibrillation; BMI=body mass index; CT=computed tomography; eGFR=estimated glomerular filtration rate; EHRA= European Heart Rhythm Association class for symptoms; IMT=intima media thickness; NOAC= novel oral anticoagulation; NT-pro BNP=N-terminal pro-brain natriuretic peptide; *The number of comorbidities was calculated by awarding points for hypertension, heart failure, age >65 years, diabetes mellitus; coronary artery disease, BMI>25kg/m², moderate or severe mitral valve regurgitation and kidney dysfunction (eGFR<60); **The CHA₂DS₂-VASc score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A₂=age ≥75 years; D=diabetes mellitus; S₂=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc=sex category (female sex).

as false positive for AF, for example due to premature atrial beats, ventricular extra beats or artefacts. Most (93%) false positive episodes lasted ≤ 10 minutes. Forty episodes of AF were originally classified as tachycardia. After applying all corrections, 11,466 episodes of AF remained, with a median AF burden of 0.3% (0-2.1%, maximal burden 61.1%) during 6-months follow-up (total of 36,966 days of continuous day-to-day heart rhythm data for analysis). Of these 11,466 episodes, 11,456 (>99.9%) episodes were selfterminating. Ten episodes in 8 patients were non-selfterminating AF. These patients underwent an ECV. Of these 8 patients, 2 had short, 3 had intermediate and 3 had long selfterminating AF episodes. Changes in AAD therapy were made in 6 patients (4 patients started with flecainide; 1 patient started sotalol; and in 1 patient flecainide was stopped). Three patients underwent a PVI within 6 months (at day 64, 162 and 171 of follow-up, respectively), of which 1 patient had episodes of intermediate duration; and 2 had long episodes.

AF patterns

During follow-up 63 patients (31%) had no recurrence of AF (Table 1). Patients without AF recurrence had more often hypertension, a higher CHA₂DS₂-VASc score, smaller left atria, and were more often treated with ACE/ARB and diuretics. The estimated number of AF episodes the year before inclusion was not different from the ones with AF recurrence [9 (2-50) versus 10 (4-50) episodes, $P=0.357$].

Forty-five (22%) patients had short, 38 (19%) had intermediate, and had 56 (28%) long episodes. Figure 1 shows examples of patients with short, intermediate and long episodes. Patients with long episodes were more often men, had more often heart failure, coronary artery disease, a higher number of comorbidities, a larger waist circumference and higher left ventricular mass (Table 2). Several sensitivity analyses were performed, excluding patients with AAD therapy, ECV or PVI during follow-up (*Supplementary files*). Although not all differences remained significant, similar trends were observed.

Fifty (25%) patients had low; 44 (22%) had intermediate; and 45 (22%) had high AF burden (Table 3). Patients with high AF burden were older, had a higher number of comorbidities, a higher CHA₂DS₂-VASc score, a lower eGFR, higher coronary calcium score and a larger IMT. Figure 2 shows the correlation between AF burden and the duration of the longest AF episode [Spearman's ρ 0.917 (95% CI 0.891-0.937), $P<0.001$]. Only 4 patients had long episodes accompanied by a low AF burden and 2 had short episodes with a high AF burden (*Supplementary Figure 1*). Examples of different AF burdens are shown in *Supplementary Figure 2*.

Figure 1. Examples of patients with short (A), intermediate (B) and long (C) episodes during 6-month follow-up. Each day is represented by a bar. White means no AF is present, and blue represents ongoing episodes of AF. AF initiations are shown in red and AF terminations are shown in green. Shaded areas indicate nightly hours. The Y-axis is the time of day and the X-axis represents 6 months of follow-up.

Figure 2. Scatterplot showing a high rate of agreeability between the AF burden (X-axis) and the duration of the longest AF episode (Y-axis), both on logarithmic scales. Data shown for 139 patients with AF recurrence during 6-month follow-up. In red 4 patients are identified with long AF episodes, with low AF burden. In yellow, 2 patients are identified with short episodes, and high AF burden. Abbreviations: AF=Atrial fibrillation; CI=confidence interval.

AF progression

In 179 (89%) patients 1-year rhythm follow-up was available. Figure 3 shows the categorisation of patients based on the longest AF episode duration during the first 6 months as compared to the second 6 months. During follow-up, 111 (62%) patients remained in the same category, 39 (22%) had progression, and 29 (16%) had regression. Twenty-nine (74%) out of 39 patients with progression only progressed to the next category (e.g. short to intermediate or intermediate to long episodes). Eight patients developed persistent AF. A total of 5 patients started antiarrhythmic drugs, 3 showed AF regression and 2 remained in the same category. Six patients underwent pulmonary vein isolation, 3 showed regression and 3 remained in the same category. On a quarterly basis, average daily AF burden increased from 3.2% to 3.8, 5.2 and 6.1%. When only selecting episodes >1 hour (instead of all episodes ≥2 minutes) the numbers remained similar: 3.1% to 3.6%, 5.0% and 5.9%.

Table 2. Patients' characteristics and longest AF episode duration during 6-month follow-up.

Characteristic	Short episodes (N=45)	Intermediate episodes (N=38)	Long episodes (N=56)	P-value (between groups)
Age (years)	63±10	63±10	67±7	0.068
Male sex	17 (38%)	23 (61%)	41 (73%)	0.002
Total history AF (years)	2.1 (0.7-4.5)	1.8 (0.4-3.9)	2.5 (0.6-4.8)	0.384
Heart failure	9 (20%)	16 (42%)	23 (41%)	0.044
Hypertension	20 (44%)	13 (34%)	28 (50%)	0.317
Diabetes	3 (7%)	1 (3%)	7 (13%)	0.205
Coronary artery disease	3 (7%)	3 (8%)	12 (21%)	0.049
Thromboembolic events	6 (13%)	3 (8%)	4 (7%)	0.533
Chronic obstructive pulmonary disease	2 (4%)	2 (5%)	4 (7%)	0.836
Number of Comorbidities*	1.9±1.2	2.0±1.2	2.7±1.4	0.007
CHA ₂ DS ₂ -VASC score**	1.9±1.1	1.6±1.4	1.9±1.2	0.407
0	4 (9%)	11 (29%)	6 (11%)	
1	14 (31%)	10 (26%)	18 (32%)	
2	14 (31%)	7 (18%)	14 (25%)	
3	10 (22%)	5 (13%)	12 (21%)	
4	2 (4%)	4 (11%)	5 (9%)	
5	1 (2%)	1 (3%)	1 (2%)	
EHRA class				0.965
I	4 (9%)	3 (8%)	6 (11%)	
IIa	17 (38%)	17 (45%)	26 (46%)	
IIb	22 (49%)	15 (40%)	13 (23%)	
III	2 (4%)	3 (8%)	11 (20%)	
Height (cm)	173±10	176±11	178±11	0.057
Weight (kg)	82±18	86±16	90±18	0.084
BMI (kg/m ²)	27±5	28±4	28±5	0.353
Obesity (BMI>30)	9 (20%)	8 (21%)	16 (29%)	0.543
Waist circumference (cm)	97±13	101±11	105±13	0.010
Blood pressure (mmHg)				
Systolic	135±18	139±20	136±18	0.675
Diastolic	80±10	82±10	81±8	0.616
NT-proBNP (pg/ml)	33 (14-130)	62 (23-165)	48 (22-197)	0.312
Creatinine (μmol/L)	76 (67-85)	80 (71-92)	86 (77-95)	0.009
eGFR (mL/min)	83 (69-90)	79 (66-86)	76 (65-87)	0.297
Medications				
β-blocker	21 (47%)	18 (47%)	32 (57%)	0.501
Verapamil/Diltiazem	6 (13%)	9 (24%)	7 (13%)	0.296
Class I antiarrhythmic drugs	17 (38%)	11 (29%)	7 (13%)	0.012

Table 2. Patients' characteristics and longest AF episode duration during 6-month follow-up. (continued)

Characteristic	Short episodes (N=45)	Intermediate episodes (N=38)	Long episodes (N=56)	P-value (between groups)
Class III antiarrhythmic drugs	2 (4%)	1 (3%)	5 (9%)	0.393
Digoxin	1 (2%)	-	1 (2%)	0.671
ACE-inhibitor	7 (16%)	5 (13%)	13 (23%)	0.403
Angiotensin Receptor Blocker	5 (11%)	5 (13%)	12 (21%)	0.321
Mineralocorticoid Receptor Antagonist	-	1 (3%)	2 (4%)	0.458
Statin	14 (31%)	8 (21%)	31 (55%)	0.002
Diuretic	4 (9%)	4 (11%)	8 (15%)	0.683
Anticoagulant				0.128
Vitamin K antagonist	5 (9%)	5 (13%)	12 (21%)	
NOAC	24 (53%)	18 (47%)	32 (57%)	
Echocardiographic variables				
Left atrial volume (mL)	71±25	71±23	72±24	0.973
Left atrial volume index (mL/m ²)	37±13	37±11	36±11	0.850
Left ventricular ejection fraction (%)	58 (55-60)	58 (55-62)	58 (55-61)	0.573
Left ventricular ejection fraction <45%	1 (2%)	1 (3%)	-	0.498
Left ventricular mass (g)	141±36	166±36	178±55	0.009
Left ventricular mass index (g/m ²)	74±14	78±18	85±21	0.046
Left ventricular hypertrophy	1 (2%)	1 (3%)	4 (7%)	0.402
CT				
Calcium score (Agatston)	20 (0-149)	6 (0-143)	58 (1-299)	0.090
Vascular assessment				
IMT-CCA (mm)	0.71 (0.62-0.82)	0.72 (0.63-0.89)	0.76 (0.69-0.89)	0.192
IMT-all segments (mm)	0.71 (0.62-0.79)	0.72 (0.62-0.87)	0.77 (0.64-0.94)	0.101
Pulse wave velocity (m/s)	7.9 (7.2-9.8)	7.9 (7.4-10.0)	8.3 (7.4-9.4)	0.976

Data are presented as mean±standard deviation, number of patients (%), or median (interquartile range). Abbreviations: ACE=angiotensin-converting enzyme; AF=atrial fibrillation; BMI=body mass index; CT=computed tomography; eGFR=estimated glomerular filtration rate; EHRA= European Heart Rhythm Association class for symptoms; IMT=intima media thickness; NOAC= novel oral anticoagulation; NT-pro BNP=N-terminal pro-brain natriuretic peptide; *The number of comorbidities was calculated by awarding points for hypertension, heart failure, age >65 years, diabetes mellitus; coronary artery disease, BMI>25kg/m², moderate or severe mitral valve regurgitation and kidney dysfunction (eGFR<60); **The CHA₂DS₂-VASc score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A₂=age ≥75 years; D=diabetes mellitus; S₂=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc=sex category (female sex).

Table 3. Patients' characteristics and AF burden during 6 months.

Characteristic	Low AF burden (N=50)	Intermediate AF burden (N=44)	High AF burden (N=45)	P-value (between groups)
Age (years)	62±10	64±8	68±8.8	0.005
Male sex	24 (48%)	29 (66%)	28 (62%)	0.173
Total history AF (years)	1.8 (0.6-4.8)	2.9 (0.9-4.6)	1.9 (0.3-4.0)	0.530
Heart failure	13 (26%)	17 (39%)	18 (40%)	0.282
Hypertension	21 (42%)	21 (48%)	19 (42%)	0.824
Diabetes	3 (6%)	1 (2%)	7 (16%)	0.056
Coronary artery disease	3 (6%)	5 (11%)	10 (22%)	0.059
Thromboembolic events	5 (10%)	3 (7%)	5 (11%)	0.770
Chronic obstructive pulmonary disease	2 (4%)	3 (7%)	3 (7%)	0.801
Number of Comorbidities*	1.9±1.2	2.3±1.1	2.2±1.3	0.032
CHA ₂ DS ₂ -VASC score**	1.6±1.1	1.6±1.3	2.2±1.3	0.019
0	9 (18%)	8 (18%)	4 (9%)	
1	14 (28%)	18 (41%)	10 (22%)	
2	16 (32%)	8 (18%)	11 (24%)	
3	9 (18%)	6 (14%)	12 (27%)	
4	2 (4%)	2 (5%)	7 (16%)	
5	-	2 (5%)	1 (2%)	
EHRA class				0.017
I	3 (6%)	3 (7%)	7 (16%)	
IIa	21 (42%)	15 (34%)	24 (53%)	
IIb	24 (48%)	18 (41%)	8 (18%)	
III	2 (4%)	8 (18%)	6 (13%)	
Height (cm)	176±10	177±11	177±11	0.785
Weight (kg)	85±18	90±18	84±17	0.280
BMI (kg/m ²)	28±5	29±5	27±5	0.253
Obesity (BMI>30)	13 (26%)	11 (25%)	9 (20%)	0.768
Waist circumference (cm)	100±14	103±12	102±13	0.486
Blood pressure (mmHg)				
Systolic	137±18	139±19	135±19	0.631
Diastolic	82±9	84±10	78±8	0.012
NT-proBNP (pg/ml)	32 (12-127)	46 (22-125)	53 (24-214)	0.101
Creatinine (μmol/L)	79 (68-89)	83 (74-87)	83 (73-100)	0.056
eGFR (mL/min)	85 (71-90)	79 (73-87)	73 (62-86)	0.020
Medications				
β-blocker	25 (50%)	21 (48%)	21 (56%)	0.748
Verapamil/Diltiazem	6 (12%)	10 (23%)	6 (13%)	0.312
Class I antiarrhythmic drugs	19 (38%)	11 (25%)	5 (11%)	0.011

Table 3. Patients' characteristics and AF burden during 6 months. (continued)

Characteristic	Low AF burden (N=50)	Intermediate AF burden (N=44)	High AF burden (N=45)	P-value (between groups)
Class III antiarrhythmic drugs	1 (2%)	3 (7%)	4 (9%)	0.332
Digoxin	-	1 (2%)	1 (2%)	0.565
ACE-inhibitor	8 (16%)	6 (14%)	11 (24%)	0.373
Angiotensin Receptor Blocker	6 (12%)	7 (16%)	9 (20%)	0.566
Mineralocorticoid Receptor Antagonist	-	1 (2%)	2 (4%)	0.330
Statin	13 (26%)	19 (43%)	21 (47%)	0.083
Diuretic	4 (8%)	7 (16%)	5 (11%)	0.485
Anticoagulant				0.025
Vitamin K antagonist	5 (10%)	7 (16%)	10 (22%)	
NOAC	26 (52%)	20 (45%)	28 (62%)	
Echocardiographic variables				
Left atrial volume (mL)	73±26	71±24	71±22	0.927
Left atrial volume index (mL/m ²)	37±12	37±13	37±10	0.989
Left ventricular ejection fraction (%)	58 (55-60)	58 (55-61)	58 (58-61)	0.333
Left ventricular ejection fraction <45%	1 (2%)	1 (2%)	-	0.611
Left ventricular mass (g)	152±38	177±52	165±50	0.151
Left ventricular mass index (g/m ²)	73±17	84±19	83±20	0.054
Left ventricular hypertrophy	1 (2%)	2 (5%)	3 (7%)	0.533
CT				
Calcium score (Agatston)	21 (0-161)	6 (0-96)	94 (16-360)	0.012
Vascular assessment				
IMT-CCA (mm)	0.71 (0.61-0.80)	0.74 (0.67-0.91)	0.78 (0.68-0.91)	0.029
IMT-all segments (mm)	0.72 (0.61-0.81)	0.72 (0.62-0.86)	0.78 (0.64-0.95)	0.104
Pulse wave velocity (m/s)	8.0 (7.2-9.9)	8.3 (7.5-9.7)	8.1 (7.3-9.4)	0.903

Data are presented as mean±standard deviation, number of patients (%), or median (interquartile range). Abbreviations: ACE=angiotensin-converting enzyme; AF=atrial fibrillation; BMI=body mass index; CT=computed tomography; eGFR=estimated glomerular filtration rate; EHRA= European Heart Rhythm Association class for symptoms; NOAC= novel oral anticoagulation; NT-pro BNP=N-terminal pro-brain natriuretic peptide; *The number of comorbidities was calculated by awarding points for hypertension, heart failure, age >65 years, diabetes mellitus; coronary artery disease, BMI>25kg/m², moderate or severe mitral valve regurgitation and kidney dysfunction (eGFR<60); **The CHA₂DS₂-VASC score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A₂=age ≥75 years; D=diabetes mellitus; S₂=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc=sex category (female sex).

Figure 3. Sankey diagram illustrating the categorisation based on the longest AF episode during the first 6 months on the left, and the second 6 months on the right.

DISCUSSION

In patients with paroxysmal selfterminating AF we longitudinally investigated the temporal pattern, burden and progression of AF and the association with clinical characteristics using continuous rhythm monitoring. We found that: 1) paroxysmal selfterminating AF has very heterogeneous temporal arrhythmia patterns. One third of the patients with previous documented AF did not show any recurrence during 6 months of follow-up. In those with recurrences, AF patterns varied both with respect to duration of AF episodes as well as AF burden but patients with longer episodes had a higher AF burden; 2) patients with longer AF episodes and higher AF burden had more severe underlying comorbidities; and 3) modest AF progression within 1-year occurred in a substantial number of patients.

Quantifying paroxysmal AF

The currently used clinical AF classification poorly reflects the temporal pattern and burden of AF.(8-10) Patients classified in the same clinical AF category may be inherently

heterogeneous in terms of temporal AF persistence and AF burden. In patients known with clinical paroxysmal selfterminating AF we now observed that one third of our patients did not show any recurrence during follow-up. In those with recurrent AF our data disclose that paroxysmal AF is a heterogeneous arrhythmia consisting of different patterns, both when classified according to duration of AF episode and according to AF burden. Patients either had short episodes of AF, or only longer AF episodes. There was, however, a strong correlation between duration of the selfterminating AF episodes and AF burden. In general, in our population AF burden was low. Only 10 episodes were electrically cardioverted, all other episodes remained selfterminating during follow-up.

Recently, it was acknowledged that an important knowledge gap includes understanding the best parameter for AF quantification, including specific thresholds, e.g. for starting oral anticoagulation, as well as the relation of the amount of AF and stroke and other major adverse cardiovascular events.⁽¹¹⁾ The first initiatives for an improved classification for paroxysmal AF have been proposed, based on single-lead electrocardiogram (ECG) monitoring for a mean of 11 days in 13,000 patients.⁽⁹⁾ Patients were categorized into either the 'staccato' AF subtype with frequent and short episodes of paroxysmal AF, or the 'legato' AF subtype with infrequent and long episodes of paroxysmal AF. Unfortunately, no exact cut-off values for this classification were provided nor were AF patterns correlated to clinical characteristics. In general, intermittent short-term monitoring precludes optimal classification of the type of AF. Both continuous ECG monitoring and data from intracardiac monitoring provide now new evidence for the heterogeneity of AF.⁽¹²⁾ Our study extends these findings by proposing three patterns of paroxysmal selfterminating AF based on the duration of the longest episode.

Comorbidities and AF

The duration of AF episodes may reflect the severity of the atrial cardiomyopathy which itself relates to the presence of risk factors and comorbidities next to AF burden.⁽¹³⁾ Our data support this concept by showing differences in clinical and echocardiographic characteristics within the three groups of AF episode duration and of AF burden, e.g. more male patients with coronary artery disease, a higher left ventricular mass as well as more comorbidities in patients with longer AF episodes. Comparably, patients with a higher AF burden were older, had more comorbidities and a higher CHA₂DS₂-VASc score, more chronic kidney disease, a higher coronary calcium score and a denser IMT. Episode duration might reflect the degree of the substrate, while the number of shorter AF episodes may be mainly driven by the number of triggers. The latter may explain the lack of association between very short episodes and cardiovascular outcome.⁽¹⁴⁾ Both AF episode duration and AF burden may be correlated to symptoms, thereby influencing quality of life. Proietti *et al.* showed that daily

activity level correlated with the daily AF burden, with decrease in daily activity in patients with a higher AF burden.(15)

No recurrence of AF

Despite selecting patients with at least 2 episodes of AF in the past year, approximately one third of our patients did not show any recurrent AF episode during the first 6 months of follow-up. The lower left atrial volume in these patients might indicate less severe structural remodelling. On the other hand, the number of comorbidities in patients in this group was similar to that in patients with recurrences. The higher proportion of hypertension and higher CHA₂DS₂-VASc score in these patients at baseline together with higher rates of antihypertensive drugs (ARBs and diuretics) may indicate that comorbidities were more frequently diagnosed and potentially treated more appropriately. As has been shown by The Routine versus Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) trial and The AggReSSive Risk factor rEduction STudy for Atrial Fibrillation (ARREST-AF) trials by Sanders *et al.*, risk factor management improves sinus rhythm maintenance in patients with AF.(16,17) Alternatively, patients without recurrences during 6 months of follow-up may belong to a group of patients who only very infrequently suffer from AF, which is also an interesting and important observation.

AF progression

To assess AF progression, the transition from selfterminating to non-selfterminating persistent or permanent AF, or from persistent to permanent AF is frequently used, since this can be determined fairly well even with intermittent rhythm monitoring. Using this definition, a recent meta-analysis showed a pooled incidence of AF progression of 8.1 per 100 patient-years of follow-up.(18) This meta-analysis, however, was hampered by differences in follow-up duration and patient characteristics between the respective studies, and the use of intermitted rhythm monitoring. Continuous rhythm monitoring may better define AF progression.(12) The relevance of AF progression is that it is associated with worse clinical outcome. In clinical AF, De Vos *et al.* showed that progression from selfterminating to non-selfterminating AF had prognostic clinical value, which was supported by other studies. (5,14) Also in subclinical AF (SCAF) prolongation of duration of SCAF episodes from ≤24 to >24 hours was associated with more strokes as well as more heart failure hospitalizations. (4,19) In a recent high risk elderly population (mean age 76 years, median CHA₂DS₂-VASc score 3.9) without known AF, the median AF burden was 0.13% during 40 months of follow-up. Progression to 24-hour episodes occurred in 33 of 590 patients (5.6%) indicating that in these high-risk patients AF burden was low, and progression was limited.(12) In our cohort with lower risk paroxysmal AF patients (mean age 64 years, median CHA₂DS₂-VASc score 1.9), we observed a small increase in averaged AF burden throughout follow-up. The averaged daily AF burden increased from 3.2% during the first 3 months to 6.1% during the

last 3 months. Using our definition of AF progression, 22% of patients showed AF episode prolongation during 1 year. This indicates that AF progression is a slow and subtle process. Interestingly, we also found a significant number of patients with AF regression, which has also been shown previously.⁽²⁰⁾ Factors such as changes in antiarrhythmic therapy, which only occurred in a few patients, or more intense risk factor control may partially explain this interesting observation.^(16,20)

Clinical implications

Continuous rhythm monitoring enables an improved characterization of patients with AF. Diverse patterns may reflect differences in underlying diseases and mechanisms, warranting personalized therapeutic interventions and patient tailored therapies. More details on AF patterns may aid in selecting patients for specific AAD, PVI or other therapies. For example, episodes that occur frequently and are of short duration may reflect presence of triggers combined with the absence of a strong substrate for AF. Such patients may well respond to PVI while in those with longer episodes, AF could be sustained by a substrate present outside of the PVs. Additionally, since AF classification is dynamic, observed longitudinal changes in AF patterns may have clinical utility for assessing the progression of the underlying substrate as well as monitoring response to therapeutic interventions.

Strengths and Limitations

Strengths of the current study include the well-phenotyped cohort and availability of continuous rhythm monitoring, for the vast majority in patients without implanted cardiac devices prior to study enrolment. In contrast, most other studies with continuous rhythm monitoring were performed in patients with a pacemaker or defibrillator.^(5,8,12,19)

Limitations of the current analyses include the modest sample size, the limited follow-up time and the observational nature. At this point it is not yet possible to show any prognostic value of the different paroxysmal AF entities. Another limitation is the changes made in antiarrhythmic therapies or modification of risk factors which is inherent to the nature of the arrhythmia. To correct for this, sensitivity analyses were performed that showed similar results, although not all differences remained significant. This is most likely due to a lack of power.

CONCLUSION

Our main findings include that paroxysmal selfterminating AF is a very heterogeneous arrhythmia: one third of the patients did not show any recurrence during 6 months of follow-up. In those with recurrences, AF patterns varied considerably both with respect to

duration of AF episodes as well as AF burden. Patients with longer episodes and higher AF burden had more severe underlying comorbidities. Finally, AF progression occurred in 1 out of 5. Therefore, longitudinally assessment of the temporal patterns and progression of AF burden by continuous rhythm monitoring may help to personalize AF therapies and monitor treatment effects in paroxysmal AF patients.

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SUPPLEMENTARY FILES.

Inclusion and exclusion criteria for RACE V

Inclusion criteria

- Age > 18 years;
- Total history <10 years of paroxysmal, self-terminating AF;
- At least one documented episode of AF and 2 symptomatic episodes in the past year or two documented episodes, documented as:
 - o AF on ECG, Holter-recording, loop recorder, event recorder or MyDiagnostic; or
 - o Subclinical AF (SCAF) detected in a Medtronic pacemaker (atrial read > 190 bpm lasting > 6 minutes).
- Able and willing to sign informed consent for the registry;
- Able and willing to undergo implantation of ILR (in patients without a CIED);
- CHA2DS2-VASc score ≤ 5 ;
- No other indication for oral anticoagulation (e.g. mechanical valve prosthesis).

Exclusion criteria

A potential study candidate who meets any of the following criteria will be excluded from participation in this study:

- Non-self-terminating, persistent AF;
- Only AF due to a trigger (i.e. postoperative, due to infection);
- Congenital heart disease;
- Refusing to temporarily stop (N)OAC for coagulation phenotyping (in patients already on (N)OAC before inclusion in this study), with the exception for patients with a history of ischemic stroke/ transient ischemic attack;
- Prior pulmonary vein isolation (PVI) or on waiting list for PVI or expected to be placed on waiting list within one year;
- Expected to start with, or currently using amiodarone;
- Pregnancy;
- ICD, CRT or pacemaker that is not a Medtronic pacemaker;
- Life expectancy of less than 2.5 years;
- Ventricular pacing >50% In patients with a Medtronic pacemaker.

Covariate definitions

Total history of AF was calculated by the difference in years between the date of AF diagnosis and date of study inclusion. Heart failure was defined as one of the following: 1) history of heart failure admission; 2) left ventricular ejection fraction <45%; 3) left ventricular ejection fraction >45%, a history of elevated N-terminal pro b-type natriuretic peptide (>400 ng/l) with either signs of structural heart disease (left ventricular hypertrophy [left ventricular

mass index $>95 \text{ g/m}^2$ in women and $>115 \text{ g/m}^2$ in men], posterior wall thickness $\geq 11 \text{ mm}$ or septal wall thickness $\geq 11 \text{ mm}$) and/or signs of diastolic dysfunction (mean E velocity $<8 \text{ cm/s}$, deceleration time $>220 \text{ ms}$ and $E/e' >8$). Hypertension was defined as systolic blood pressure $>140 \text{ mmHg}$, diastolic blood pressure $>90 \text{ mmHg}$, or by use of medication prescribed for hypertension. Diabetes was defined as either type I or II diabetes, requiring the use of anti-diabetic drugs. Coronary artery disease was defined as either angina, a previous percutaneous intervention, myocardial infarction and/or coronary artery bypass grafting. Thromboembolic complications were defined as a history of either a stroke, transient ischemic attack or pulmonary embolism. The number of comorbidities and well-known AF risk-factors was calculated by awarding points for hypertension; heart failure (as defined above); age >65 years; diabetes mellitus; coronary artery disease; body mass index (BMI) $>25 \text{ kg/m}^2$; kidney dysfunction (estimated glomerular filtration rate [eGFR] $<60 \text{ ml/min/1.73m}^2$). eGFR was calculated using modification of diet in renal disease formula; and moderate to severe mitral valve insufficiency (grade $\geq \text{II}$). The $\text{CHA}_2\text{DS}_2\text{-VASc}$ risk score for stroke was calculated by counting points for congestive heart failure (1 point), hypertension (1 point), age >75 years (2 points), diabetes mellitus (1 point), stroke or transient ischaemic attack (2 points), vascular disease (1 point), age 65–74 years (1 point), and female sex (1 point). Sotalol was considered a class III AAD in case of daily dosages $\geq 160 \text{ mg}$, and was classified as β -blocker in case of daily dosages $<160 \text{ mg}$.

Sensitivity analyses

All patients

No recurrence	Short episodes	Intermediate episodes	Long episodes	Total
63	45	38	56	202

1. Patients:
 - o No PVI during follow-up;
 - o No ECV during follow-up.

No recurrence	Short episodes	Intermediate episodes	Long episodes	Total
63	43	35	51	192

2. Patients:
 - o No PVI during follow-up;
 - o No ECV during follow-up;
 - o No change in AAD therapy.

No recurrence	Short episodes	Intermediate episodes	Long episodes	Total
63	40	34	50	187

3. Patients:

- o No PVI during follow-up;
- o No ECV during follow-up;
- o No AAD therapy.

No recurrence	Short episodes	Intermediate episodes	Long episodes	Total
51	20	20	35	126

Supplementary table 1. Sensitivity analysis 1.

Characteristic	Short episodes (N=43)	Intermediate episodes (N=35)	Long episodes (N=51)	P-value (between groups)
Age (years)	63±10	65±9	67±7	0.085
Male sex	16 (37%)	21 (60%)	37 (73%)	0.002
Total history AF (years)	2.1 (0.6-4.3)	1.7 (0.5-3.8)	2.3 (0.5-4.8)	0.506
Heart failure	9 (21%)	14 (40%)	22 (43%)	0.060
Hypertension	20 (47%)	12 (34%)	26 (51%)	0.301
Diabetes	3 (7%)	1 (3%)	7 (14%)	0.188
Coronary artery disease	3 (7%)	3 (9%)	10 (20%)	0.130
Thromboembolic events	6 (14%)	3 (9%)	3 (6%)	0.400
Chronic obstructive pulmonary disease	2 (5%)	2 (6%)	4 (8%)	0.807
Number of Comorbidities*	2.0±1.2	2.0±1.3	2.7±1.4	0.009
CHA ₂ DS ₂ -VASc score**	1.9±1.1	1.7±1.5	1.9±1.2	0.542
0	3 (7%)	10 (29%)	5 (10%)	0.209
1	14 (33%)	8 (23%)	17 (33%)	
2	13 (30%)	7 (20%)	12 (24%)	
3	10 (23%)	5 (14%)	11 (22%)	
4	2 (5%)	4 (11%)	5 (10%)	
5	2 (5%)	1 (3%)	1 (2%)	
EHRA class				0.209
I	4 (9%)	3 (9%)	6 (12%)	
IIa	17 (40%)	14 (40%)	24 (47%)	
IIb	20 (47%)	15 (43%)	12 (24%)	
III	2 (5%)	3 (9%)	9 (18%)	
Height (cm)	173±10	177±11	178±11	0.044
Weight (kg)	81±17	85±15	89±17	0.078
BMI (kg/m ²)	27±5	27±4	28±5	0.640
Obesity (BMI>30)	8 (19%)	6 (17%)	13 (26%)	0.581
Waist circumference (cm)	97±12	100±11	105±13	0.007

Supplementary table 1. Sensitivity analysis 1. (continued)

Characteristic	Short episodes (N=43)	Intermediate episodes (N=35)	Long episodes (N=51)	P-value (between groups)
Blood pressure (mmHg)				
Systolic	135±19	140±21	137±18	0.510
Diastolic	80±10	82±11	81±8	0.606
NT-proBNP (pg/ml)	37 (14-132)	62 (23-165)	49 (22-205)	0.331
Creatinine (μmol/L)	76 (68-85)	80 (70-92)	85 (74-96)	0.023
eGFR (mL/min)	82 (69-89)	79 (66-86)	76 (63-88)	0.415
Medications				
β-blocker	20 (47%)	17 (49%)	29 (57%)	0.569
Verapamil/Diltiazem	6 (14%)	9 (26%)	6 (12%)	0.200
Class I antiarrhythmic drugs	16 (37%)	10 (29%)	6 (12%)	0.015
Class III antiarrhythmic drugs	2 (5%)	1 (3%)	6 (12%)	0.215
Digoxin	1 (2%)	-	1 (2%)	0.678
ACE-inhibitor	7 (16%)	5 (14%)	12 (24%)	0.496
Angiotensin Receptor Blocker	5 (12%)	5 (14%)	11 (22%)	0.400
Mineralocorticoid Receptor Antagonist	-	1 (3%)	1 (2%)	0.570
Statin	14 (33%)	8 (23%)	27 (53%)	0.012
Diuretic	4 (9%)	4 (11%)	8 (16%)	0.632
Anticoagulant				0.218
Vitamin K antagonist	5 (12%)	5 (14%)	10 (20%)	
NOAC	23 (53%)	17 (49%)	30 (59%)	
Echocardiographic variables				
Left atrial volume (mL)	72±26	73±23	72±24	0.976
Left atrial volume index (mL/m ²)	38±13	38±11	36±11	0.648
Left ventricular ejection fraction (%)	58 (55-60)	58 (55-62)	58 (58-61)	0.569
Left ventricular ejection fraction <45%	1 (2%)	1 (3%)	-	0.506
Left ventricular mass (g)	143±35	165±34	176±57	0.024
Left ventricular mass index (g/m ²)	75±13	78±17	85±22	0.079
Left ventricular hypertrophy	1 (2%)	1 (2%)	4 (8%)	0.377
CT				
Calcium score (Agatston)	20 (0-140)	8 (0-191)	58 (1-299)	0.138
Vascular assessment				
IMT-CCA (mm)	0.71 (0.62-0.82)	0.75 (0.65-0.90)	0.77 (0.71-0.91)	0.187
IMT-all segments (mm)	0.71 (0.60-0.78)	0.73 (0.618-0.90)	0.77 (0.67-0.95)	0.056
Pulse wave velocity (m/s)	7.9 (7.2-9.7)	7.9 (7.5-10.1)	8.4 (7.4-9.7)	0.869

Supplementary table 2. Sensitivity analysis 2.

Characteristic	Short episodes (N=40)	Intermediate episodes (N=34)	Long episodes (N=50)	P-value (between groups)
Age (years)	63±10	64±9	67±7	0.106
Male sex	15 (38%)	21 (62%)	37 (%)	0.002
Total history AF (years)	2.0 (0.6-4.3)	1.8 (0.5-3.9)	2.3 (0.5-4.8)	0.597
Heart failure	9 (23%)	14 (41%)	22 (44%)	0.085
Hypertension	19 (48%)	11 (32%)	25 (50%)	0.248
Diabetes	3 (8%)	1 (3%)	6 (12%)	0.322
Coronary artery disease	3 (8%)	3 (9%)	10 (20%)	0.151
Thromboembolic events	6 (15%)	3 (9%)	3 (6%)	0.350
Chronic obstructive pulmonary disease	2 (5%)	1 (3%)	4 (8%)	0.601
Number of Comorbidities*	2.0±1.2	2.0±1.3	2.7±1.4	0.019
CHA ₂ DS ₂ -VASc score**	2.0±1.2	1.6±1.4	1.9±1.2	0.417
0	3 (8%)	10 (29%)	5 (10%)	0.272
1	13 (33%)	8 (24%)	17 (34%)	
2	11 (28%)	7 (21%)	12 (24%)	
3	10 (25%)	5 (15%)	11 (22%)	
4	2 (5%)	3 (9%)	4 (8%)	
5	1 (3%)	1 (3%)	1 (2%)	
EHRA class				
I	4 (10%)	3 (9%)	6 (12%)	0.272
IIa	16 (40%)	14 (41%)	24 (48%)	
IIb	18 (45%)	15 (44%)	12 (24%)	
III	2 (5%)	2 (6%)	8 (16%)	
Height (cm)	173±10	177±11	179±11	0.032
Weight (kg)	82±17	85±15	89±18	0.135
BMI (kg/m ²)	27±5	27±4	28±5	0.821
Obesity (BMI>30)	8 (20%)	6 (18%)	12 (24%)	0.769
Waist circumference (cm)	97±12	100±11	105±13	0.020
Blood pressure (mmHg)				
Systolic	136±18	138±18	136±18	0.813
Diastolic	80±10	81±8	81±8	0.841
NT-proBNP (pg/ml)	39 (15-137)	71 (23-171)	49 (22-207)	0.476
Creatinine (μmol/L)	76 (67-85)	80 (70-92)	84 (74-97)	0.033
eGFR (mL/min)	83 (68-89)	79 (66-86)	76 (64-88)	0.511
Medications				
β-blocker	19 (48%)	17 (50%)	28 (56%)	0.708
Verapamil/Diltiazem	5 (13%)	8 (24%)	6 (12%)	0.296
Class I antiarrhythmic drugs	15 (38%)	10 (29%)	6 (12%)	0.017

Supplementary table 2. Sensitivity analysis 2. (continued)

Characteristic	Short episodes (N=40)	Intermediate episodes (N=34)	Long episodes (N=50)	P-value (between groups)
Class III antiarrhythmic drugs	2 (5%)	1 (3%)	6 (12%)	0.233
Digoxin	-	-	1 (2%)	0.474
ACE-inhibitor	7 (18%)	5 (15%)	12 (24%)	0.535
Angiotensin Receptor Blocker	4 (10%)	5 (15%)	11 (22%)	0.296
Mineralocorticoid Receptor Antagonist	-	1 (3%)	1 (2%)	0.582
Statin	14 (35%)	8 (24%)	27 (54%)	0.015
Diuretic	4 (10%)	4 (12%)	8 (16%)	0.682
Anticoagulant				0.219
Vitamin K antagonist	5 (13%)	5 (15%)	10 (20%)	
NOAC	21 (53%)	16 (50%)	29 (58%)	
Echocardiographic variables				
Left atrial volume (mL)	74±26	73±24	72±24	0.938
Left atrial volume index (mL/m ²)	38±13	39±11	36±11	0.563
Left ventricular ejection fraction (%)	58 (55-60)	58 (55-61)	58 (55-61)	0.584
Left ventricular ejection fraction <45%	1 (3%)	1 (3%)	-	0.498
Left ventricular mass (g)	146±35	168±32	178±57	0.044
Left ventricular mass index (g/m ²)	76±13	78±17	86±22	0.090
Left ventricular hypertrophy	1 (3%)	1 (3%)	4 (8%)	0.401
CT				
Calcium score (Agatston)	21 (0-153)	5 (0-143)	58 (1-274)	0.162
Vascular assessment				
IMT-CCA (mm)	0.71 (0.62-0.82)	0.75 (0.65-0.89)	0.76 (0.70-0.91)	0.260
IMT-all segments (mm)	0.71 (0.64-0.79)	0.74 (0.62-0.91)	0.77 (0.66-0.95)	0.114
Pulse wave velocity (m/s)	7.9 (7.2-9.7)	7.9 (7.4-10.0)	8.4 (7.4-9.7)	0.920

Supplementary table 3. Sensitivity analysis 3. Recurrence versus no recurrence.

Characteristic	No Recurrence (N=51)	Recurrence (N=75)	P-value (between groups)
Age (years)	64±10	67±8	0.105
Male sex	22 (43%)	29 (39%)	0.712
Total history AF (years)	1.6 (0.4-4.0)	1.5 (0.3-3.8)	0.401
Heart failure	17 (33%)	32 (43%)	0.353
Hypertension	28 (55%)	33 (44%)	0.277
Diabetes	6 (12%)	6 (8%)	0.544
Coronary artery disease	5 (10%)	12 (16%)	0.428
Thromboembolic events	9 (18%)	6 (8%)	0.158
Chronic obstructive pulmonary disease	3 (6%)	4 (5%)	1.000
Number of Comorbidities*	2.5±1.3	2.4±1.3	0.785
CHA ₂ DS ₂ -VASc score**	2.2±1.4	1.9±1.2	0.194
0	4 (8%)	9 (12%)	0.206
1	12 (24%)	23 (31%)	
2	19 (37%)	18 (24%)	
3	6 (12%)	18 (24%)	
4	5 (10%)	5 (7%)	
5	5 (10%)	2 (3%)	
EHRA class			0.206
I	9 (18%)	12 (16%)	
IIa	18 (35%)	34 (45%)	
IIb	22 (43%)	21 (28%)	
III	2 (4%)	8 (11%)	0.704
Height (cm)	176±10	177±11	
Weight (kg)	86±16	85±15	
BMI (kg/m ²)	28±5	27±4	
Obesity (BMI>30)	14 (28%)	17 (23%)	0.674
Waist circumference (cm)	103±15	102±11	0.722
Blood pressure (mmHg)			0.500
Systolic	133±17	136±18	
Diastolic	81±10	79±9	0.473
NT-proBNP (pg/ml)	53 (26-117)	75 (23-178)	0.302
Creatinine (μmol/L)	83 (70-93)	82 (71-92)	0.950
eGFR (mL/min)	81 (67-90)	78 (69-87)	0.638
Medications			1.000
β-blocker	32 (63%)	47 (63%)	
Verapamil/Diltiazem	4 (8%)	12 (16%)	
Class I antiarrhythmic drugs	-	-	
Class III antiarrhythmic drugs	-	-	-

Supplementary table 3. Sensitivity analysis 3. Recurrence versus no recurrence. (continued)

Characteristic	No Recurrence (N=51)	Recurrence (N=75)	P-value (between groups)
Digoxin	-	1 (1%)	1.000
ACE-inhibitor	13 (26%)	15 (20%)	0.516
Angiotensin Receptor Blocker	17 (33%)	12 (16%)	0.031
Mineralocorticoid Receptor Antagonist	-	2 (3%)	0.514
Statin	23 (45%)	26 (35%)	0.267
Diuretic	15 (29%)	9 (12%)	0.020
Anticoagulant			0.302
Vitamin K antagonist	7 (14%)	13 (17%)	
NOAC	34 (68%)	41 (55%)	
Echocardiographic variables			
Left atrial volume (mL)	64±31	72±24	0.080
Left atrial volume index (mL/m ²)	32±11	37±12	0.022
Left ventricular ejection fraction (%)	58 (55-60)	58 (55-60)	0.140
Left ventricular ejection fraction <45%	2 (4%)	2 (3%)	1.000
Left ventricular mass (g)	154±41	168±51	0.180
Left ventricular mass index (g/m ²)	77±16	83±20	0.120
Left ventricular hypertrophy	1 (2%)	5 (7%)	0.400
CT			
Calcium score (Agatston)	39 (0-255)	37 (0-257)	0.925
Vascular assessment			
IMT-CCA (mm)	0.71 (0.63-0.88)	0.78 (0.69-0.92)	0.275
IMT-all segments (mm)	0.69 (0.58-0.95)	0.75 (0.65-0.93)	0.045
Pulse wave velocity (m/s)	8.6 (7.1-9.6)	8.3 (7.3-9.7)	0.798

Supplementary table 4. Sensitivity analysis 3.

Characteristic	Short episodes (N=20)	Intermediate episodes (N=20)	Long episodes (N=35)	P-value (between groups)
Age (years)	64±7	67±10	68±8	0.234
Male sex	9 (45%)	12 (60%)	25 (71%)	0.152
Total history AF (years)	1.2 (0.1-3.7)	0.9 (0.2-4.4)	1.6 (0.3-3.3)	0.799
Heart failure	6 (30%)	10 (50%)	16 (46%)	0.390
Hypertension	8 (40%)	6 (30%)	19 (54%)	0.200
Diabetes	2 (10%)	1 (5%)	3 (9%)	0.832
Coronary artery disease	2 (10%)	3 (15%)	7 (20%)	0.617
Thromboembolic events	2 (10%)	2 (10%)	2 (6%)	0.792
Chronic obstructive pulmonary disease	-	-	4 (11%)	0.089
Number of Comorbidities*	1.9±1.2	2.3±1.4	2.7±1.3	0.064
CHA ₂ DS ₂ -VASc score**	1.7±1.0	2.0±1.5	2.0±1.2	0.551
0	2 (10%)	4 (20%)	3 (9%)	
1	8 (40%)	4 (20%)	11 (31%)	
2	5 (25%)	5 (25%)	8 (23%)	
3	5 (25%)	4 (20%)	9 (26%)	
4	-	2 (10%)	3 (9%)	
5	-	1 (5%)	1 (3%)	
EHRA class				0.917
I	3 (15%)	3 (15%)	6 (17%)	
IIa	10 (50%)	8 (40%)	16 (46%)	
IIb	6 (30%)	7 (35%)	8 (23%)	
III	1 (5%)	2 (10%)	5 (14%)	
Height (cm)	173±10	178±12	178±10	0.312
Weight (kg)	82±14	85±14	86±16	0.566
BMI (kg/m ²)	27±4	27±4	27±4	0.978
Obesity (BMI>30)	5 (25%)	5 (25%)	7 (20%)	0.875
Waist circumference (cm)	99±12	101±11	104±11	0.350
Blood pressure (mmHg)				
Systolic	133±18	133±15	138±21	0.512
Diastolic	78±8	78±8	81±9	0.361
NT-proBNP (pg/ml)	39 (20-120)	135 (49-193)	74 (22-281)	0.143
Creatinine (μmol/L)	75 (68-85)	80 (72-92)	86 (76-99)	0.036
eGFR (mL/min)	83 (75-89)	79 (65-86)	74 (63-87)	0.154
Medications				
β-blocker	11 (55%)	12 (60%)	24 (69%)	0.581
Verapamil/Diltiazem	3 (15%)	5 (25%)	4 (11%)	0.414

Supplementary table 4. Sensitivity analysis 3. (continued)

Characteristic	Short episodes (N=20)	Intermediate episodes (N=20)	Long episodes (N=35)	P-value (between groups)
Class I antiarrhythmic drugs	-	-	-	-
Class III antiarrhythmic drugs	-	-	-	-
Digoxin	-	-	1 (1%)	0.560
ACE-inhibitor	3 (15%)	3 (15%)	9 (26%)	0.512
Angiotensin Receptor Blocker	2 (10%)	2 (10%)	8 (23%)	0.317
Mineralocorticoid Receptor Antagonist	-	1 (5%)	1 (3%)	0.615
Statin	5 (25%)	5 (25%)	16 (46%)	0.171
Diuretic	2 (10%)	2 (10%)	5 (14%)	0.850
Anticoagulant				0.031
Vitamin K antagonist	2 (10%)	5 (25%)	6 (17%)	
NOAC	8 (40%)	10 (50%)	23 (66%)	
Echocardiographic variables				
Left atrial volume (mL)	72±25	73±22	71±24	0.988
Left atrial volume index (mL/m ²)	38±13	37±10	36±12	0.934
Left ventricular ejection fraction (%)	59 (56-60)	59 (57-60)	58 (55-61)	0.983
Left ventricular ejection fraction <45%	1 (5%)	1 (5%)	-	0.407
Left ventricular mass (g)	147±38	172±34	176±62	0.319
Left ventricular mass index (g/m ²)	75±15	83±14	87±24	0.285
Left ventricular hypertrophy	-	1 (5%)	4 (11%)	0.247
CT				
Calcium score (Agatston)	3 (0-173)	8 (0-354)	96 (1-299)	0.166
Vascular assessment				
IMT-CCA (mm)	0.72 (0.62-0.85)	0.80 (0.70-0.93)	0.78 (0.71-0.94)	0.213
IMT-all segments (mm)	0.71 (0.65-0.79)	0.75 (0.61-0.96)	0.77 (0.70-0.97)	0.251
Pulse wave velocity (m/s)	7.7 (6.6-9.5)	8.1 (7.3-10.5)	8.4 (7.4-9.7)	0.534

Supplementary figure 1. Four patients had long episodes accompanied by a low burden (orange= episode terminated by cardioversion).

Supplementary figure 2. An example of a patient with (A) low, (B) intermediate, and (C) high AF burden during 6 months of rhythm follow-up.

5a

Young-Onset Atrial Fibrillation: Sex Differences in Clinical Profile, Progression Rate and Cardiovascular Outcome

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ABSTRACT

Background. Women are underrepresented in major atrial fibrillation (AF) trials. In addition, data clinical profile and outcome in young AF patients is limited. Therefore, we aimed to investigate the clinical profile, AF progression rate and cardiovascular outcome between sexes in patients with young-onset AF.

Methods. A total of 497 patients with AF-onset <60 years of age were included. Data on clinical profile and cardiovascular outcome were prospectively collected.

Results. Of 497 patients, 125 (25%) patients were women. Women had more often familial AF (34% versus 22%, $P=0.012$) and obesity (26% versus 18%, $P=0.03$). Men had more often coronary artery disease (11% versus 5%, $P=0.04$), a longer PR interval [163 (148-180) versus 150 (138-167) ms, $P<0.001$] and higher left ventricular mass index [82 (71-96) versus 72 (61-83) g/m², $P<0.001$]. During a median follow-up of 7.0 (2.7-10.0) years AF progression rate was comparable (HR 2.03 for men versus women, 95%CI 0.92-4.48; $P=0.08$), and no difference in cardiovascular events was observed between women and men (Log rank P -value =0.07).

Conclusions. In young patients with AF, clinical patient profile is different between the sexes but did not result in differences in cardiovascular outcome.

INTRODUCTION

Atrial fibrillation (AF) is strongly associated with morbidity and mortality.⁽¹⁾ Most data on AF is obtained from clinical trials, yet women are often underrepresented.⁽²⁻⁴⁾ Limited data suggest that women are generally older and have different comorbidities, i.e. more often hypertension and less often coronary artery disease.⁽²⁻⁴⁾ Additionally, sex is an independent stroke risk modifier that increases the risk of AF associated stroke in women. On top of higher stroke risk, stroke in women with AF have worse long-term outcome.⁽⁵⁻⁷⁾

Data regarding underlying diseases in young patients with AF is rare, and may be different compared to older patients.⁽⁸⁾ One would ideally like to identify underlying comorbidities early on in order to potentially prevent disease progression.⁽⁹⁾ It has been shown that familial history of AF is often present in young-onset AF.⁽⁸⁾ Whether there are risk factors that specifically affect women or men in young-onset AF has not yet been reported. Therefore, we aimed to investigate sex-differences in clinical profile, AF progression rate and cardiovascular outcome in young-onset AF patients.

METHODS

Study population

The protocol of the Phenotyping Young-Onset Atrial Fibrillation Patients study (YOUNG-AF) has been published previously.⁽¹⁰⁾ In brief, YOUNG-AF was a partly prospective, partly retrospective, observational study performed at the University Medical Centre Groningen, The Netherlands. Between August 2012 and December 2013, 500 patients were included. The study was performed in compliance to the Declaration of Helsinki and the institutional review board approved the study protocol. All patients provided written informed consent. At the outpatient clinic patients with AF onset <60 years, ≥ 18 years at time of inclusion were asked to participate. Patients with an overt triggered AF were excluded (i.e. post-operative). A total of 120 patients had first-detected AF, the remaining 377 patients had recurrent AF. In those patients, data regarding clinical profile was collected closest to the moment of the diagnosis of AF (index-visit). Follow-up frequency after the index-visit was led to the discretion of the treating physician and all patients received treatment according to the guidelines.⁽¹¹⁾ Three patients were excluded because of violation of the inclusion and exclusion criteria.

Definitions

The majority of definitions have been previously published.⁽¹⁰⁾ Familial history of AF, sudden cardiac death, coronary artery disease or heart failure was defined as ≥ 1 first-degree family member affected <60 years of age. Atrial fibrillation progression was defined as

development of permanent AF (i.e. sinus rhythm that cannot be restored or is no longer pursued). The number of comorbidities was calculated by awarding a point for hypertension; heart failure; diabetes mellitus; coronary artery disease; body mass index $>25 \text{ kg/m}^2$; kidney dysfunction (estimated glomerular filtration rate $<60 \text{ ml/min/1.73m}^2$); and moderate to severe mitral valve regurgitation.

Follow-up

Data from electronic medical records were used to obtain information on AF progression and cardiovascular events, including cardiovascular death, heart failure hospitalization, stroke, systemic embolism, major bleeding, syncope, life-threatening adverse effects of AF drugs, sustained ventricular tachycardia, cardiac arrest and implantation of a pacemaker or implantable cardiac defibrillator. All cardiovascular events were adjudicated by physicians. Follow-up started at index-visit and was continued until February 2016 with a maximum of 10 years, or until death. Follow-up data was available in 488 out of 497 patients (98%). Data on AF progression was available in 468 (94%) patients with paroxysmal or persistent AF at the index visit.

Statistical analysis

Descriptive statistics of the total population and between sexes were presented as mean and standard deviation or median (interquartile range) for continuous variables, depending on normality. Categorical variables are presented as numbers with percentages. AF progression rate differences between sexes were calculated using univariable Cox proportional hazards regression, indicated as hazard ratios (HR) with 95% confidence interval (CI). Yearly event rates were calculated by dividing the number of follow-up years by the number of events, with censoring post first event. Differences in event rates and 95% CI were calculated by the MedCalc incidence rate comparison tool. Differences in patient characteristics between sexes were evaluated using χ^2 for categorical data, and Student's T-test and Mann-Whitney-U for continuous data, depending on the normality. A P-value <0.05 was considered significant. Kaplan Meier analysis was performed to illustrate cardiovascular events during follow-up. Statistical analyses were performed using IBM SPSS Statistics version 23.0 (Armonk, NY, USA) unless otherwise mentioned.

RESULTS

Clinical patient profile

Out of 497 patients, 125 (25%) were women. Most conventional risk factors, including age, hypertension, heart failure and diabetes mellitus, were not different between sexes (Table 1). Women had more often familial AF and obesity. Men had more often coronary artery

Table 1. Patient characteristics at index-visit of total population, and per sex category.

	All patients (n=497)	Women (n=125)	Men (n=372)	P-value
Age at index-visit (years)	49 ± 9	51 ± 8	49 ± 9	0.057
Age at AF-onset (years)	46 ± 9	47 ± 9	46 ± 10	0.128
Type of AF				0.249
Paroxysmal	337 (68%)	89 (71%)	248 (67%)	
Persistent	140 (28%)	29 (23%)	111 (30%)	
Permanent	20 (4%)	7 (6%)	13 (4%)	
Heart failure	53 (11%)	10 (8%)	43 (12%)	0.317
Cardiomyopathy	30 (6%)	5 (4%)	25 (7%)	0.269
Hypertension	218 (44%)	52 (42%)	166 (45%)	0.603
Diabetes mellitus	25 (5%)	7 (6%)	18 (5%)	0.813
Coronary artery disease	47 (10%)	6 (5%)	41 (11%)	0.040
Peripheral artery disease	9 (2%)	2 (2%)	7 (2%)	0.838
Stroke or transient ischemic attack	30 (6%)	8 (6%)	22 (6%)	0.844
COPD	19 (4%)	7 (6%)	12 (3%)	0.279
Family history				
Familial AF	124 (25%)	42 (34%)	82 (22%)	0.012
Familial sudden cardiac death	48 (10%)	14 (11%)	34 (9%)	0.520
Familial coronary artery disease	109 (22%)	31 (25%)	78 (21%)	0.369
Familial heart failure	25 (5%)	7 (5%)	18 (5%)	1.000
CHA ₂ DS ₂ VASc score	1 (0-2)	2 (1-2)	1 (0-1)	<0.001
Number of comorbidities	1.3 ± 1.1	1.3 ± 1.1	1.4 ± 1.1	0.328
EHRA symptom class (n=460)				0.508
I	46 (10%)	12 (10%)	34 (10%)	
II	337 (73%)	82 (69%)	255 (75%)	
III	73 (16%)	22 (18%)	51 (15%)	
IV	4 (<1%)	2 (2%)	2 (<1%)	
Height (cm)	182 ± 10	171 ± 7	185 ± 8	<0.001
Weight (kg)	92 ± 17	83 ± 20	94 ± 15	<0.001
BMI (kg/m ²)	27 (24-30)	28 (23-32)	27 (25-30)	0.446
Obesity (BMI>30)	98 (20%)	33 (26%)	65 (18%)	0.030
PR interval (ms)	160 (144-176)	150 (138-167)	163 (148-180)	<0.001
Class I antiarrhythmic drug use	68 (14%)	22 (18%)	46 (13%)	0.131
Class III antiarrhythmic drug use	88 (18%)	20 (17%)	68 (18%)	0.684
Echocardiography				
Moderate or severe valve disease	39 (8%)	8 (6%)	31 (8%)	0.568
Left ventricular mass index (g/m ²)	80 (69-93)	72 (61-83)	82 (71-96)	<0.001
LA volume index (mL/m ²)	31 (25-31)	19 (23-32)	26 (21-32)	0.261
LVEF (%)	60 (55-60)	60 (55-60)	60 (55-60)	0.673

Data is expressed as mean and standard deviation, median (IQR) or numbers (%).

Abbreviations: AF=atrial fibrillation; BMI=body mass index; EHRA=European Heart Rhythm Association; LA=left atrial; LVEF=left ventricular ejection fraction. The number of comorbidities was calculated by awarding points for a history of hypertension, heart failure, diabetes, coronary artery disease, body mass index >25 kg/m², kidney dysfunction and moderate or severe mitral valve disease.

disease, a longer PR interval and higher left ventricular mass index. As expected, men were taller and heavier. There were no sex differences in familial history of sudden cardiac death, early-onset coronary artery disease or heart failure. Thirty patients were diagnosed with a cardiomyopathy, which was not different between sexes [12 (2%) hypertrophic; 17 (3%) dilated; and 1 (<1%) arrhythmogenic].

AF progression

AF progression to permanent AF was assessed in 468 patients with paroxysmal or persistent AF at the index visit [114 (24%) women]. Fifty-six patients (12%) had AF progression. Without correcting for underlying diseases, there was a trend towards more AF progression in men compared to women (14% in men, 7% in women; HR 2.02, 95%CI 0.92-4.48, *P*=0.08). There were no differences in class I or III antiarrhythmic drug use during follow-up between sexes [114 (31%) in men versus 42 (35%) in women, *P*=0.500], nor in pulmonary vein isolations performed during follow-up [150 (41%) in men versus 51 (42%) in women, *P*=0.832]. Corrected for antiarrhythmic drug use and pulmonary vein isolation performed during follow-up, progression rate remained similar between sexes (HR 1.93, 95% CI 0.88-4.28, *P*=0.10).

Figure 1. Kaplan Meier curve illustrating the cumulative incidence of cardiovascular events during follow-up.

Cardiovascular outcome

During follow-up of 7.0 [2.7-10.0; in men 7.6 (2.9-10.0) versus 6.4 (2.5-10.0) in women, $P=0.160$] years, 66 cardiovascular events occurred (yearly event rate 2.24%, 95%CI 1.73-2.85%). No difference between sexes in the composite of cardiovascular events was observed (yearly event rate 2.76%, 95%CI 1.71-4.22 in women; 2.01%, 95% CI 1.46-2.70 in men, $P=0.07$; Figure 1). Corrected for treatment during follow-up, including the use of antiarrhythmic drugs and pulmonary vein isolation, the results remained (HR 1.91, 95% 0.86-4.24, $P=0.11$). Sex specific cardiovascular event rates are shown in *Supplementary table 1*. Occurrence of ventricular tachycardia was more frequent in women [yearly event rate 0.57% (95%CI 0.18-1.32%) versus 0.12% (95% CI 0.03-0.37%), $P=0.02$]. Two out of 5 women used antiarrhythmic drugs at the time of VT. Also, a trend towards more pacemaker implantations in women was observed [1.34% (95%CI 0.67-2.39) versus 0.65% (95%CI 0.36-1.07); $P=0.06$]. Sick sinus syndrome (50%), atrioventricular node conduction disorders (19%) and therapy resistant AF (31%) were causes for pacemaker implantation.

DISCUSSION

We studied sex differences in clinical profile and cardiovascular outcome in young-onset AF patients. Women with young-onset AF had more often familial AF and obesity, whereas men had more coronary artery disease, a longer PR interval and higher left ventricular mass. We observed no difference in AF progression rate nor in cardiovascular outcome between sexes during 7-year follow-up.

In our prospective cohort, one out of four patients were women. AF is a rare disease in the young, and the probable misnomer 'lone AF' remains a diagnosis of exclusion.(8-10) Careful evaluation for cardiovascular risk factors should therefore be performed. Women had more often a family history of AF. Familial AF has been reported in 5-30% of patients.(8) Besides the genetic risk of AF itself, genetic susceptibility to other cardiovascular diseases may also play a role in the high rate of familial AF in young-onset AF.(12) Yet, many risk factors may remain subclinical and therefore untreated for years. In fact, AF might be the first clinical presentation of an underlying cardiomyopathy. The number of cardiomyopathies was, however, still low in our population. Of interest is the relatively high number of reported familial sudden cardiac death, which may be due to underlying cardiomyopathies or other untreated cardiovascular (genetic) diseases.

Identification and treating risk factors and comorbidities is important in AF treatment, and preventing progression of atrial remodelling.(9,13) We observed no difference in AF progression rate between sexes. AF progression is a complex process mainly driven by

comorbidity and ageing related atrial remodelling.(14) The equal number of comorbidities and similar age between men and women in our cohort may have contributed in finding similar progression rate.

Obesity, a modifiable risk factor for AF, was observed more often in women.(15,16) Obesity has been associated with a prothrombotic state.(17,18) On top of that, obesity-related cardiac remodelling, including epicardial adipose tissue infiltration, inflammation and fibrosis, enhances AF substrate formation, also causing AF to progress and sustain.(18) The higher incidence of coronary artery disease in men is well known. It should therefore always be considered causal factor associated with AF – especially in men. Even in patients diagnosed with idiopathic AF, half showed coronary artery disease as assessed by non-invasive imaging.(19) PR interval and left ventricular mass were both higher in men compared to women. Both have previously been associated with cardiovascular outcome in patients with AF.(10)

Women with AF may have worse cardiovascular outcome, yet women tend to be older and have more comorbidities.(3) We found no sex difference in cardiovascular outcome in our young-onset AF cohort, which can be partially accounted to the relatively low number of events in general due to the young age. Yet, a trend was observed towards a higher event rate in women, especially after 3 years of follow-up, which could be related to differences in underlying disease in men and women.

Limitations

Strengths of present study include a well-characterized cohort and unique dataset of young-onset AF patients. Whether the associations that were found reflect cause-effect relationships cannot be concluded from our data, which may be considered a limitation, as well as the limited number of cardiovascular events. A time-to-event analysis was performed for AF progression to permanent AF without structured rhythm monitoring during follow-up, limiting its accuracy. Because of this, we were also unable to determine progression from paroxysmal to persistent AF. Furthermore, we did not have follow-up data on blood pressure and weight, limiting our knowledge on risk factor management in our population.

CONCLUSION

The clinical profile between men and women with young-onset AF is different. We observed no differences in AF progression rate between men and women, nor differences in cardiovascular outcome.

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SUPPLEMENTARY FILES

Supplementary table 1. Yearly cardiovascular events rates in women and men.

	Women (N=121)	Men (N=367)	
	Yearly event rate (95% CI)	Yearly event rate (95% CI)	P-value
Composite of all events	2.76% (1.71-4.22)	2.01% (1.46-2.70)	0.23
Individual event components			
Cardiovascular death or heart transplantation	0.11% (0-0.60)	0.04% (0-0.23)	0.48
Heart failure hospitalization	0.45% (0.12-1.15)	0.64% (0.36-1.05)	0.53
Ischemic stroke	0.44% (0.12-1.14)	0.17 (0.05-0.43)	0.15
Systemic embolism	-	-	-
Major bleeding	0.11% (0-0.60)	0.04% (0-0.23)	0.48
Syncope	0.33% (0.07-0.95)	0.29% (0.12-0.60)	0.87
Life-threatening adverse effect of rate- or rhythm-control drugs	0.22% (0.03-0.79)	0.04% (0-0.23)	0.13
Sustained ventricular tachycardia	0.57% (0.18-1.32)	0.12% (0.03-0.37)	0.02
Cardiac arrest	0.11% (0-0.60)	-	0.10
ICD implantation	0.11% (0-0.61)	0.42% (0.20-0.78)	0.16
Pacemaker implantation	1.34% (0.67-2.39)	0.65% (0.36-1.07)	0.06

Data is expressed as yearly event rates (95% confidence interval). P-value is given for differences in yearly event rates between sexes. Abbreviations: AF=atrial fibrillation; ICD=implantable cardiac defibrillator.

5b

Gender differences and daily variation in atrial fibrillation risk factor profiles: Considerations for risk factor management

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Editorial comment on "Young-Onset Atrial Fibrillation: Sex Differences in Clinical Profile, Progression Rate and Cardiovascular Outcome".

Adapted from International Journal of Cardiology Heart & Vasculature
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Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with significant morbidity, increased risk of stroke, reduced quality of life, and increased mortality (1–4). Several studies suggest, that there are significant gender differences in clinical presentation of AF, utilization of AF therapy and clinical management of AF and outcomes (5). On top of a higher AF-associated stroke risk, women have higher rates of dementia over time than men (6). Additionally, in women, AF is associated with more severe or non-traditional symptoms and worse prognosis which negatively affects health-related quality of life measures (7). Despite these gender-differences in AF symptoms and stroke risk, the AF progression rate, its mechanisms and impact on outcomes in AF in women versus men is unclear. Progression from paroxysmal to persistent or permanent AF may occur in 1–15% of the general AF population annually depending on definition of progression. Additionally, the rate of AF progression is dependent on the presence of specific risk factors (8), the number of concomitant risk factors (9) or certain combinations of risk factors, where individual risk factors may act as disease modifiers. Young-onset AF may represent a scenario, where AF is mainly maintained by concomitant or underlying risk factors rather than by increased ageing. Women are underrepresented in major AF trials, and therefore it remains unclear whether there are risk factors that specifically affect AF progression in women with young-onset AF.

In this Issue of the IJC Heart & Vasculture, Marcos *et al.* (10) investigated gender-differences in clinical AF risk factor profiles, AF progression rates and cardiovascular outcomes between sexes in a prospective cohort study including 497 patients with young-onset AF <60 years of age, a quarter of whom were women. Most conventional risk factors, including age, hypertension, heart failure and diabetes mellitus, were not different between sexes at base-line. However, there were a few gender-specific differences in risk factor profile: men were taller, more often presented with coronary artery disease, had a longer PR interval and higher left ventricular mass index, while women reported more often familial AF and were more likely obese. During a median follow-up of 7 years, AF progression was seen in 12% and there was no significant difference in AF progression in men compared to women. Despite these gender-specific differences in the AF risk factor profile, the absolute number of comorbidities and the mean age was comparable in men and women. This suggests, that not one individual risk factor, but more likely the absolute number of concomitant risk factors is more relevant for AF progression in young-onset AF patients and may explain the similar AF progression in this cohort of young-onset AF patients. It is also of interest that in this cohort women presented more often with familial AF, suggesting that genetics may make a larger contribution to AF-risk in women than in men (Figure 1).

Interestingly, the Kaplan-Meier curve suggests a trend towards a higher AF progression rate in women over time. Although the number of women was low at this time point, factors

Figure 1. Longitudinal risk factor assessment to capture the dynamic nature of atrial fibrillation (AF) risk factors and prevent progression. Risk factors may be in a subclinical state and should be considered as precursors which often progress to clinical risk factors. The management of risk factors within a multidisciplinary and integrated care model may reverse progression of AF. Future studies are required to answer the questions whether there are gender differences in risk factors profiles and in response to risk factor modification programs.

such as gender-differences in the development of new AF risk factors over time, in the treatment strategy of risk factors or in the responses to antiarrhythmic treatment may contribute to this late divergence at 3 years follow-up. An alternative explanation is that risk factors determine AF progression in young-onset AF, while intrinsic gender-specific risk factor independent mechanisms become more relevant when AF patients get older. A study of over 8.3 million participants reported higher prevalence and incidence of AF with increasing age, with disproportionate rates between men and women, peaking beyond 80 years of age (11). Possibly, a follow-up study reporting on gender-differences in AF progression beyond the 7 years reported in the study by Marcos *et al.* may still unmask gender-specific AF progression differences in this or larger populations with increasing age.

There is no question that risk factor management represents an important pillar of AF management. Different groups, including the authors themselves, have demonstrated that comprehensive management of concomitant risk factors helps to maintain sinus rhythm (12–16). Although a lot of effort has been invested to develop comprehensive programs for

aggressive and combined risk factor management, it remains questionable, whether our current approaches for the assessment of modifiable risk factors are sufficient to detect all potential targets for risk factor management in our patients.

According to current clinical practice, Marcos *et al.* assessed established risk factors in a structured way at the timepoint, when AF patients present the first time in the AF clinic (10). However, in addition to the established risk factors, emerging risk factors such as sleep apnoea (17), chronic obstructive pulmonary disease or gastrointestinal reflux (18) were not assessed in this study. Sleep apnoea with a treatment indication is present in 30–60% of all patients with AF (19). Importantly, patients with AF and sleep apnoea do not report typical sleep apnoea symptoms such as daytime sleepiness (19). Therefore, sleep apnoea remains to be undiagnosed and untreated in the majority of cases, if questionnaires to assess daytime sleepiness are used as pre-screening tools. Additionally, risk factors may be in a subclinical state, which will be missed by standard non-longitudinal approaches. Subclinical risk factors including prehypertension (20) or exercise-induced hypertension should be considered as precursors which often progress to a clinical manifestation. As several AF risk factors may show a high day- to day variability (e.g. sleep apnoea; 21,22) or may just occur during specific conditions (e.g. exercise induced hypertension) clinically relevant risk factors will be missed, if just one assessment is performed or the evaluation is just undertaken under resting conditions. This day-to-day variability in risk factors may be more pronounced in younger women than in older women after menopause or in men, because of the hormonal changes during the menstrual cycles. Even in AF-patients without overt risk factors, the inter-visit variability of metabolic parameters showed a close association with the risk of AF (23). All of these factors justify a more structured and importantly longitudinal risk factor assessment to capture the dynamic nature of AF risk factors (24). Repeated longitudinal assessment of established and emerging risk factors may be important in young-onset AF patients, particularly if no risk factor can be identified to explain the presence of AF. AF is a rare disease in the young and should be always considered as a manifestation of clinical or subclinical risk factors or as the presentation of an underlying (atrial) cardiomyopathy (25). Excluding conventional AF risk factors at one timepoint should not result in the diagnosis of 'lone AF', which remains a diagnosis of repeated exclusions of risk factors.

It is important to note that, as with many AF studies, the current study also had an underrepresentation of women with only 25% of the cohort being female. A further limitation of the study by Marcos *et al.* (10) is that a time-to-event analysis was performed for AF progression to permanent AF only. Without structured rhythm monitoring during follow-up, the authors were unable to report on progression from paroxysmal to persistent AF. Further, the progression to permanent AF may not be an exact time-point given that the decision to not pursue rhythm control, and therefore gaining the 'permanent AF' label, is one that can

be dynamic and differs from one patient to another, and from one healthcare provider to another. Additionally, the authors did not report on any reverse progression, i.e. reversal from permanent to less persistent or paroxysmal AF. Recent studies showed that with weight-loss and risk factor management, it is possible to halt or even reverse the progression of AF (26). Focusing on AF progression and ignoring the possibility of AF regression in a dynamic arrhythmia such as AF may have introduced some bias.

Marcos *et al.* are to be congratulated on their effort to perform a unique analysis of gender-specific differences in AF-progression. They illustrate that the number of concomitant risk factors, rather than one individual risk factor, determines AF progression in patients with young-onset AF and that a few gender-specific differences in risk factor profile exist. New emerging (often non-cardio-vascular) AF risk factors increase the number of potential targets for combined AF risk factor management within a multidisciplinary and integrated care model. In addition to documentation of AF progression by continuous rhythm monitoring, also longitudinal assessment of concomitant conditions might be useful to monitor risk factor progression or daily risk factor variations in AF patients. Finally, further studies are required to identify how to assess risk factors longitudinally and whether gender differences in risk factor profiles require consideration in clinical practice when it comes to personalized AF risk factor management.

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Part II

Towards Prevention of Atrial Fibrillation Progression

6

Different Circulating Biomarkers in Women and Men with Paroxysmal Atrial Fibrillation: results from the AF-RISK and RACE V studies.

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ABSTRACT

Aims. The clinical risk profile of AF patients is different in men and women. Our aim was to identify sex differences in blood biomarkers in patients with paroxysmal AF.

Methods. Sex differences in 92 blood biomarkers were measured in 364 patients included in our discovery cohort, the identification of a risk profile to guide atrial fibrillation therapy (AF-RISK) study, assessed by multivariable logistic regression and enrichment pathway analysis. Findings were subsequently confirmed in 213 patients included in our validation cohort, the Reappraisal of Atrial Fibrillation: Interaction between HyperCoagulability, Electrical remodelling, and Vascular Destabilisation in the Progression of AF (RACE V) study.

Results. In the discovery cohort, mean age was 59 ± 12 years, 41% were women. CHA₂DS₂-VASc-score was 1.6 ± 1.4 . A total of 46% had hypertension, 10% diabetes and 50% had heart failure, predominantly with preserved ejection fraction (47%). In women, activated leukocyte cell adhesion molecule (ALCAM) and fatty acid binding protein-4 (FABP-4) were higher. In men, matrix metalloproteinase-3 (MMP-3), C-C motif chemokine-16 (CCL-16) and myoglobin were higher in men. In the validation cohort, four out of five biomarkers could be confirmed: levels of ALCAM ($P=1.73 \times 10^{-4}$) and FABP-4 ($P=2.46 \times 10^{-7}$) and adhesion biological pathways ($FDR=1.23 \times 10^{-8}$) were higher in women. In men, levels of MMP-3 ($P=4.31 \times 10^{-8}$) and myoglobin ($P=2.10 \times 10^{-4}$) and markers for extracellular matrix degradation biological pathways ($FDR=3.59 \times 10^{-9}$) were higher.

Conclusion. In women with paroxysmal AF, inflammatory biomarkers were more often higher, while in men with paroxysmal AF, biomarkers for vascular remodelling were higher.

Our data support the clinical notion that pathophysiological mechanisms in women and men with AF may differ.

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia around the world and the number will increase due to aging populations and active search for early diagnosing.(1,2) The development of AF is driven by risk factors including, but not limited to, aging, obesity and underlying cardiovascular risk factors and diseases.(2) The cumulative prevalence of AF over the years is high and comparable in both sexes. However, women and men with AF differ regarding age and presence of comorbidities; women with AF are older, have more hypertension, valvular heart disease and heart failure with preserved ejection fraction, and men with AF present more often coronary artery disease. (2) Whether the age difference or clustering of comorbidities are causative of the difference in clinical risk profile of AF between women and men is yet to be determined. Other factors such as sex hormones or differentially expressed blood biomarkers representing distinct biological pathways may also play a role.(1-3)

Blood biomarkers can be seen as representation of distinct biological pathways and may differ between men and women with AF. C-reactive protein (CRP), an inflammatory biomarker, and B-type natriuretic peptide (NT-proBNP), a biomarker indicating cardiac stretch, have been shown to differ in women and men. CRP has been associated with AF incidence in men, whereas NT-proBNP has been associated with incident AF in women.(1) NT-proBNP and fibroblast growth factor 23, a hormone regulating biomarker associated with AF, have been suggested to help to identify those at risk for AF(4); NT-proBNP and Cancer Antigen 125 (CA-125) have been associated with AF in patients without any concomitant disease. (5) Therefore biomarkers may help to find guidance for a personalized approach to patients with AF.(2-5)

Our aim was to identify sex differences in blood biomarkers in patients with paroxysmal AF, to provide an insight into potential sex-specific pathophysiological mechanisms in a well-phenotyped AF population.

METHODS

Study Population

Patients included in the identification of a risk profile to guide atrial fibrillation therapy (AF-RISK) study were used as discovery cohort. The methods of the AF-RISK study have previously been described.(6) In short, AF-RISK was a prospective, multicentre, observational study including patients with a short history of AF, performed in The Netherlands between May 2011 and March 2016. Inclusion criteria were patients aged ≥ 18 years who presented

at either the inpatient or outpatient cardiology clinic with short-lasting paroxysmal AF (total AF history <2 years, or total AF history <3 years in case of ≤ 2 AF episodes of ≤ 48 hours per month terminating spontaneously) or with short-lasting persistent AF (total AF history <2 years, and total persistent AF duration >7 days and <1 year) in whom a rhythm control strategy was preferred. Exclusion criteria were patients with history of heart failure >3 years, severe valvular disease, contra-indication for oral anticoagulation, acute coronary syndrome <1 month, or post-operative AF. In total 472 patients had available blood samples; from this amount, 108 (23%) were in AF at the time of sampling and were therefore excluded, to ensure a homogeneous sample of AF patients with blood draw in sinus rhythm. Samples from the remaining 364 patients were used in the current analyses.

Patients included in the Reappraisal of Atrial Fibrillation: Interaction between HyperCoagulability, Electrical remodelling, and Vascular Destabilisation in the Progression of AF (RACE V) study were used as validation cohort.⁽⁷⁾ In short, RACE V is an ongoing investigator-initiated, prospective, multicentre registry aiming to include 750 patients in multiple centres in The Netherlands. Inclusion criteria were patients aged >18 years with paroxysmal AF, a maximum AF history of 10 years since diagnosis at the moment of inclusion, a maximum CHA₂DS₂-VASc score of 5, and no other indication for anticoagulation drugs (e.g. mechanical valve prosthesis). Patients had to have at least two documented episodes of paroxysmal AF in the past year or one documented episode with at least two symptomatic episodes in the past year suspected to be AF without documentation. In patients with a Medtronic pacemaker, atrial high-rate episodes (AHRE) >190 beats per minute lasting >6 minutes were qualified as AF episodes. Patients with other types of pacemakers, defibrillators or cardiac resynchronization therapy could not participate due to differences in AHRE algorithm and/or incompatibility with the type of home-monitoring. Further exclusion criteria were patients with a history of persistent AF, currently on amiodarone, current pregnancy or a life expectancy <2.5 years, patients with AF caused exclusively due to transient triggers (e.g. postoperative, due to infection), patients with a previous pulmonary vein isolation (PVI), or intention to undergo PVI, or diagnosed congenital heart disease. In total, 247 patients had available blood samples; from this amount, a total of 34 (14%) were excluded because of AF at the moment of sampling. Samples from the remaining 213 patients were used for the current analyses.

Both AF-RISK and RACE V were performed in concordance with the Declaration of Helsinki. The Institutional Review Board approved both protocols. AF-RISK was registered at Clinicaltrials.gov (Clinicaltrials.gov identifier NCT01510210), as well as RACE V (Clinicaltrials.gov identifier NCT02726698) and all patients gave written informed consent.

Blood biomarkers

An electrocardiogram was performed to assess the heart rhythm prior to blood sampling. Blood sampling was performed in a similar fashion at baseline in both cohorts. EDTA anticoagulated plasma was obtained from ethylenediaminetetraacetic acid tubes and was stored at -80°C. Multiplex immunoassay by proximity extension assay technology (Olink Bioscience, Uppsala, Sweden) was used to measure 92 biomarkers from the Olink cardiovascular panel III (full list shown in *Supplementary table 1*). Data are given as arbitrary units on a Log₂-scale. Four biomarkers (bleomycin hydrolase, spondin-1, elafin and cathepsin D) had $\geq 10\%$ of the values below the limit of detection and were therefore excluded. The remaining 88 biomarkers were used for the analyses.

Comorbidities

Heart failure was defined as one of the following: (i) history of heart failure admission, regardless of the left ventricular ejection fraction (LVEF); (ii) LVEF <45%; (iii) LVEF >45%, an elevated NT-proBNP (> 400 ng/l) with either structural heart disease (average annular e' < 8 cm/s, and deceleration time > 220 ms, and average E/e' > 8) or diastolic dysfunction (history of left ventricular hypertrophy or wall diameter ≥ 11 mm or septum diameter ≥ 11 mm) on echocardiography.(8) Hypertension was defined by a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication. Diabetes mellitus was defined by use of antidiabetic drugs. Coronary artery disease was defined as history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting.

Statistical analysis

Sex differences in blood biomarkers were tested by univariable and multivariable logistic regression. In the multivariable logistic regression model additional adjustment for obesity, age, heart failure and coronary artery disease was performed based on differences found between women and men at baseline and knowledge from previous literature.(2) The final model was tested for significant interactions. Odds ratios (OR) per standard deviation with 95% confidence intervals (CI) were given. Biomarkers with higher values in men were expressed as OR versus women, biomarkers higher in women were presented as OR versus men. Biomarkers found in the discovery cohort were subsequently tested by univariable and multivariable logistic regression in the validation cohort.

Enrichment pathway analyses were performed for blood biomarkers with higher values in women in comparison to men. The median value of each biomarker in women was divided by the median value of the same biomarker in men to produce a sex difference ratio per biomarker. This ratio was then transformed into percentage (*Supplementary table 2*). Biomarkers found in the discovery cohort were subsequently tested in the validation cohort.

Confirmed biomarkers in the validation cohort were additionally enriched in a network analysis using STRING to identify relevant biological pathways in which the biomarkers are involved.⁽⁹⁾ STRING is a database that provides assessment of physical and functional protein interactions which contribute to common biological processes. This knowledge derives from databases and text-mining highly calibrated, such as Gene Ontology (GO) Resource using high level groupings established by the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway maps. Biomarkers that entered the pathway analysis were two layer enriched.

In both multivariate logistic regression and pathway analyses, a multiple testing correction was performed using a Bonferroni correction for the 88 biomarkers that were tested. A P-value $<5.68 \times 10^{-4}$ ($\frac{0.05}{88}$) was considered statistically significant. Additionally, pathway enrichment underwent false discovery rate (FDR) correction for multiple testing. Pathways with higher FDR were selected as main representative processes.

RESULTS

Patient characteristics

Clinical characteristics of patients from the discovery cohort are shown in Table 1. Patient characteristics were comparable to the entire AF-RISK cohort (data not shown).⁽⁶⁾ In short, mean age was 59 ± 12 years, 150 (41%) were women. CHA₂DS₂-VASc-score was 1.6 ± 1.4 . A total of 182 (50%) had heart failure [171 (47%) with preserved and 11 (3%) with reduced ejection fraction] and 167 (46%) hypertension. Women compared to men were slightly older (60 ± 12 vs 58 ± 12 years, $P=0.03$) and had slightly higher LVEF (58 ± 3 versus 57 ± 5 , $P=0.01$).

Baseline characteristics from the validation cohort are shown in Table 2. Compared to the discovery cohort, the proportion of women was comparable in the validation cohort (41%). CHA₂DS₂-VASc-score was 1.9 ± 1.3 . A total of 62 (29%) had heart failure [60 (28%) with preserved and 2 (1%) with reduced ejection fraction] and 101 (47%) hypertension. Within the validation cohort, women compared to men were older (66 ± 9 versus 63 ± 10 years, $P=0.01$), had less often heart failure (22 versus 38%, $P=0.01$) and had more often obesity (39 vs 21%, $P=0.008$). Patients in the validation were older in comparison to the discovery cohort (64 ± 9 versus 59 ± 12 years, $P<0.01$) and had longer history of AF (29 versus 6 months, $P<0.01$).

Biomarker analysis

The multivariable logistic regression in the discovery cohort showed that levels of activated leukocyte cell adhesion molecule (ALCAM, $P=4.03 \times 10^{-4}$) and fatty acid binding protein-4 (FABP-4, $P=4.48 \times 10^{-12}$) were higher in women. While levels of matrix metalloproteinase-3

Table 1. Baseline characteristics AF-RISK discovery cohort.

Characteristic	Total population (N=364)	Women (N=150)	Men (N=214)	P-value
Age (years)	59±12	60±12	58±12	0.030
History of AF (months)	6 (2-18)	5 (2-17)	6 (2-20)	0.329
Heart failure	182 (50%)	66 (44%)	116 (54%)	0.070
HFpEF	171 (47%)	65 (43%)	106 (50%)	0.289
HFrEF	11 (3%)	1 (1%)	10 (5%)	0.059
Hypertension	167 (46%)	76 (51%)	91 (43%)	0.164
Diabetes mellitus	35 (10%)	12 (8%)	23 (11%)	0.471
Coronary artery disease	21 (6%)	6 (4%)	15 (7%)	0.260
Peripheral artery disease	9 (3%)	3 (2%)	6 (3%)	0.741
Stroke or TIA	23 (6%)	10 (7%)	13 (6%)	0.830
COPD	23 (6%)	7 (5%)	16 (8%)	0.382
CHA ₂ DS ₂ -VASc score *	1.6±1.4	2.3±1.3	1.1±1.2	<0.001
EHRA class**				0.296
I	110 (30%)	34 (23%)	76 (36%)	
II	204 (56%)	94 (63%)	110 (51%)	
III	49 (14%)	22 (15%)	27 (13%)	
Height (cm)	178±10	170±7	184±7	<0.001
Weight (kg)	88±18	81±17	92±17	<0.001
BMI (kg/m ²)	28±5	28±6	27±5	0.129
Obesity (BMI>30)	99 (27%)	43 (29%)	56 (26%)	0.633
Blood pressure (mmHg)				
Systolic	131±18	134±20	128±15	0.004
Diastolic	78±9	78±11	78±8	0.693
PQ time (ms)	165±25	161±24	168±25	0.007
Left atrial volume (mL)	67±21	62±19	69±21	0.002
Left atrial volume index (mL/m ²)	33±10	33±10	32±10	0.696
LV ejection fraction (%)	57±4	58±3	57±5	0.016

Data are mean (standard deviation), number of patients (%), or median (interquartile range). AF=atrial fibrillation; BMI=body mass index; COPD=chronic obstructive pulmonary disease; EHRA= European Heart Rhythm Association class for symptoms; LV=left ventricular; TIA=transient ischemic attack; HF= heart failure; pEF=preserved ejection fraction; rEF=reserved ejection fraction. *The CHA₂DS₂-VASc score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A₂=age ≥75 years; D=diabetes mellitus; S₂=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc (sex category (female sex)). **In 363 patients, EHRA class data was available.

(MMP-3 $P=6.46 \times 10^{-13}$), C-C motif chemokine-16 (CCL-16 $P=4.17 \times 10^{-5}$) and myoglobin ($P=2.34 \times 10^{-4}$) were higher in men (Figure 1).

Table 2. Baseline characteristics RACE V validation cohort.

Characteristic	Total population (N=213)	Women (N=88)	Men (N=125)	P-value
Age (years)	64±9	66±9	63±10	0.011
History of AF (months)	29 (8-56)	32 (7-57)	27 (8-56)	0.973
Heart failure	62 (29%)	19 (22%)	48 (38%)	0.014
HFpEF	60 (28%)	17 (19%)	43 (34%)	0.024
HFrEF	2 (1%)	0 (0%)	2 (2%)	0.638
Hypertension	101 (47%)	40 (46%)	61 (49%)	0.732
Diabetes mellitus	21 (10%)	12 (14%)	9 (7%)	0.187
Coronary artery disease	26 (12%)	6 (7%)	20 (16%)	0.071
Peripheral artery disease	2 (1%)	-	2 (2%)	0.638
Stroke or TIA	18 (9%)	6 (7%)	12 (10%)	0.639
COPD	16 (8%)	8 (9%)	8 (6%)	0.639
CHA2DS2-VASc score *	1.9±1.3	2.6±1.2	1.4±1.2	<0.001
EHRA class				0.023
I	24 (11%)	6 (7%)	18 (14%)	
IIa	89 (42%)	30 (34%)	59 (48%)	
IIb	78 (37%)	40 (46%)	38 (31%)	
III	22 (10%)	12 (14%)	10 (8%)	
Height (cm)	176±10	167±7	183±7	<0.001
Weight (kg)	87±18	80±17	92±17	<0.001
BMI (kg/m2)	28±5	28±5	28±5	0.159
Obesity (BMI>30)	60 (28%)	34 (39%)	26 (21%)	0.008
Blood pressure (mmHg)				
Systolic	136±18	137±19	136±17	0.559
Diastolic	81±10	80±11	81±9	0.614
PQ time (ms)	172±35	169±38	174±34	0.349
Left atrial volume (mL)	69±23	69±25	69±22	0.923
Left atrial volume index (mL/m2)	35±11	36±12	34±11	0.094
LV ejection fraction (%)	59±5	60±5	58±5	0.031

Data are mean (standard deviation), number of patients (%), or median (interquartile range). AF=atrial fibrillation; BMI=body mass index; COPD=chronic obstructive pulmonary disease; EHRA= European Heart Rhythm Association class for symptoms; HF=heart failure; pEF=preserved ejection fraction; rEF=reserved ejection fraction. LV=left ventricular; TIA=transient ischemic attack. *The CHA2DS2-VASc score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A2=age ≥75 years; D=diabetes mellitus; S2=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc (sex category (female sex)).

The five biomarkers found in the discovery cohort were univariably tested in the validation cohort and all but CCL-16 (univariably OR 1.090, 95% CI 0.829-1.432, $P=0.537$) were confirmed to be differently expressed between sexes (Table 3). Based on differences on baseline

Figure 1. Blood biomarker sex differences in discovery cohort.

CI=confidence interval; SD=standard deviation; MMP-3=matrix metalloproteinase-3; CCL-16=C-C motif chemokine-16; ALCAM=activated leukocyte cell adhesion molecule; FABP-4=fatty acid binding protein-4; OR=odds ratio.

Table 3. Multivariate logistic regression results of biomarkers in validation cohort

	OR	95%CI	P-value
MMP-3	6.289*	3.257-12.195	4.31×10^{-8}
CCL-16			NS
Myoglobin	3.135*	1.712-5.747	2.10×10^{-4}
ALCAM	3.165	1.735-5.774	1.73×10^{-4}
FABP-4	5.975	3.030-11.78	2.46×10^{-7}

*Odds ratios are expressed versus women.

Abbreviations: CI=confidence interval; SD=standard deviation; MMP-3=matrix metalloproteinase-3; CCL-16=C-C motif chemokine-16; ALCAM=activated leukocyte cell adhesion molecule; FABP-4=fatty acid binding protein-4; OR=odds ratio; NS= not significant

characteristics and knowledge from previous literature (2), it was adjusted for obesity, age and heart failure; after this adjustment, only FABP-4 remained higher in women (OR 7.442, 95% CI 3.680-15.051, $P=2.32 \times 10^{-8}$). MMP-3 (OR 8.403, 95% CI 4.329-16.393, $P=3.12 \times 10^{-10}$) remained higher in men.

In the pathway analysis, six biomarkers in women and eight in men were statistically significant (*Supplementary table 3*), which included the biomarkers from the multivariate logistic regression analysis in the discovery cohort. These biomarkers were subsequently tested in the validation cohort; six remained statistically significant in women [FABP-4, ALCAM, NT-proBNP, contactin-1 (CNTN1), metalloproteinase inhibitor 4 (TIMP4), and integrin beta-2 (ITGB2)]; and three remained statistically significant in men [matrix extracellular phosphoglycoprotein (MEPE), myoglobin and MMP3]. (*Supplementary table 4 and 5*).

Figure 2 A-D. Pathway enrichment analysis. A. Pathway enrichment analysis with layers of proteins on validated biomarkers in women in comparison to men from both cohorts. B. Pathway enrichment analysis with layers of proteins on validated biomarkers in men in comparison to women from both cohorts. C. Biological processes with higher FDR in women in comparison to men. Colours represent biological processes in which the proteins (nodes) are involved as depicted in A. D. Biological processes with higher FDR in women in comparison to men. Colours represent biological processes in which the proteins (nodes) are involved as depicted in B. GO=Gene Ontology; KEGG= Kyoto Encyclopedia of Genes and Genomes; FDR=false discovery rate; ACAN=aggrecan; ALCAM=activated leukocyte cell adhesion molecule; CD6= T-cell differentiation antigen CD6; CNTN1=contactin-1; DCN=decorin; DMP1=dentin matrix acidic phosphoprotein 1; FDR= false discovery rate; ICAM1=intercellular adhesion molecule 1; ITGA4=integrin subunit alpha 4; ITGAD=integrin subunit alpha D; ITGAL=integrin subunit alpha L; ITGAM=integrin subunit alpha M; ITGAX=integrin subunit alpha X; ITGB2=integrin subunit beta 2; MMP10=integrin subunit beta 2; MMP3=matrix metalloproteinase-3; PLG=plasminogen; SPP1=secreted phosphoprotein 1; TIMP1=metalloproteinase inhibitor 1.

After a two-layer protein enrichment, in women compared to men, pathways with higher FDR under GO analysis showed cell-cell adhesion ($FDR=1.23 \times 10^{-8}$), integrin-mediated signalling pathway ($FDR=3.83 \times 10^{-8}$) and cell adhesion (6.13×10^{-8}); moreover, cell adhesion molecules ($FDR=5.19 \times 10^{-12}$) pathways resulted under KEGG analysis. In men, extracellular matrix organization ($FDR 3.59 \times 10^{-9}$) pathway resulted from GO analysis without any results under KEGG analysis (Figure 2).

Figure 3. Sex differences in blood biomarkers in patients with paroxysmal AF
Abbreviations: MMP-3=matrix metalloproteinase-3; CCL-16=C-C motif chemokine-16; ALCAM=activated leukocyte cell adhesion molecule; FABP-4=fatty acid binding protein-4.

DISCUSSION

The aim of this study was to identify sex differences in blood biomarkers in patients with AF. We identified five biomarkers that were differently expressed between sexes with paroxysmal AF. In a validation cohort, four out of five markers were confirmed to be differently expressed between sexes.

Blood biomarkers in women

In women, ALCAM and FABP-4 were higher. Cell adhesion molecules, like ALCAM, are involved in leukocyte recruitment in case of tissue damage. In patients with stroke, ALCAM has been associated with long-term mortality.(10) Also, Lim *et al.* previously showed that higher levels of ALCAM were associated with early recurrence after AF ablation.(11) Moreover, cell adhesion mechanisms increase the adhesiveness of platelets and leucocytes incrementing the risk of thrombogenesis even when in sinus rhythm (12); in the presence of other stroke risk factor, the risk of stroke is higher in women compared to than men.(13) FABP-4 is mainly expressed in adipose tissue and has been associated with metabolic syndrome, including a systemic pro-inflammatory state.(14) Higher FABP-4 levels have also been linked to post-operative AF.(16) In contrast to what we found, Magnussen *et al.* previously found that CRP was associated with incident AF in men but not in women, but with very low hazards ratio; this may be explained by the lack of specificity of C-reactive protein, or use of a relatively healthy population; the latter is supported by the low values that were found.(1) Despite the fact that our biomarker panel consists of 32 inflammatory markers, only two were found to be higher in women. This can be explained by the fact that most inflammatory markers are derived from similar biological pathways and are therefore not all included in the final multivariable model. Therefore, these data suggest that the contribution of inflammation seems to be more critical in AF substrate formation in women (Figure 3).

Blood biomarkers in men

In men, levels of MMP-3 and myoglobin were higher. MMP-3 is part of the family of matrix metalloproteinases that are involved in extracellular matrix degradation and deposition. MMP-3 has been associated with vascular remodelling, including atrial stiffening and coronary artery disease (17), and has also been suggested as potential therapeutic target in atherosclerosis.(18) Moreover, Yue *et al.* concluded that the excess of proteins involved in extracellular matrix biological pathways may lead to tissue fibrosis, contributing to vascular remodelling; this affects mechanical and electrical function, and therefore can promote AF.(19) Myoglobin can be detected in case of muscle degradation. Recurrent episodes of silent ischemia, also in patients with subclinical coronary artery disease may be the underlying substrate for myocardial myoglobin release.(20) In addition, higher muscle mass in men could contribute to the observed outcome. The combination of MMP-3 and myoglobin may indicate that in men, vascular remodelling plays an important role in AF substrate formation. Prevalence of clinical coronary artery disease was, however, not different between sexes in our discovery nor validation cohorts. When corrected for differences in underlying disease, MMP-3 remained associated with higher values in men. This could indicate that subclinical vascular disease is more prominent in men (Figure 3). This in accordance with findings from the Rotterdam study which described subclinical atherosclerosis as an independent risk factor for new onset AF but not only in men.(21) Subclinical atherosclerosis, which may

be present in many patients with AF, was, however, not routinely assessed in our discovery cohort. Since the biomarker panel used in this analysis did not include CA-125, our results cannot be compared to previous findings of this biomarker.(5)

Strengths and limitations

Limitations of the current analysis include the use of a biomarker panel with relative values, which impairs comparison with absolute values of other cohorts. Also, this was a cross-sectional study which precludes definite conclusions regarding cause-effect relations. In addition, the AF duration of the validation cohort is longer than in the discovery cohort, implying greater atrial remodelling substrate and differentiated expression of blood biomarkers. Lastly, residual confounding may have affected results, despite adjustment-analysis. Strengths of the current analysis are the well-phenotyped cohorts and the availability of a large number of biomarkers representative of multiple biological pathways. Furthermore, the use of 2 analytical approaches and 2 independent cohorts yielded synergic results.

CONCLUSION

In conclusion, in this exploratory analysis, we identified biomarkers differentially expressed in women and men with paroxysmal AF. In a validation cohort, four out of five biomarkers were confirmed. In women with paroxysmal AF, inflammatory biomarkers were higher, while in men with paroxysmal AF biomarkers for vascular remodelling were higher. Our data suggest that pathophysiological mechanisms in women and men with AF may differ. This advocates more research on sex differences in AF and endorses a personalized medicine approach, taking sex differences into account.

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Determinants of Sinus Rhythm Maintenance in Patients with Early-Persistent Atrial Fibrillation and Heart Failure

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INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) often coexist. Rate versus rhythm control trials showed no differences in outcome, which can in part be accounted to the inability to maintain sinus rhythm, and lack of direct interference of antiarrhythmic drugs with cardiovascular risk factors underlying AF progression.(1) It has been shown that the more advanced types of AF have worse outcome, suggesting that sinus rhythm maintenance may be of importance.(2) Recently, the Routine versus Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) trial showed that targeted therapy of underlying conditions was superior in sinus rhythm maintenance during 1-year follow-up in patients with early-persistent AF and HF.(3) In the current manuscript, we aimed to identify factors associated with sinus rhythm maintenance in patients with a short history of persistent AF and HF included in the RACE 3.

METHODS

The RACE 3 design was described previously.(3) In short, patients with early symptomatic persistent AF and early HF were included. Total AF history up to 5 years was allowed, total persistent AF duration >7 days but <6 months, ≤ 1 electrical cardioversion). Patients with both HF with a preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) were eligible. HFpEF was defined as left ventricular ejection fraction (LVEF) $\geq 45\%$, New York Heart Association (NYHA) functional Class II–III, and additional criteria consisting of echo parameters and/or elevated N-terminal pro-brain natriuretic peptide. HFrEF was defined as LVEF $< 45\%$ and NYHA class I–III. Exclusion criteria included LVEF $< 25\%$, NYHA IV, left atrial size $> 50\text{mm}$, MRA use, and AF associated with surgery or acute illness. Patients were randomized to targeted therapy of underlying conditions or conventional therapy and subsequently received a cardioversion. On top of conventional therapy, targeted therapy received 4 additional therapies: mineralocorticoid receptor antagonists, statins, angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, and cardiac rehabilitation including physical therapy, dietary restrictions and counseling. Primary outcome was sinus rhythm maintenance at 1-year follow-up, assessed by 7-day Holter. Sinus rhythm maintenance was defined as sinus rhythm $\geq 6/7^{\text{th}}$ of the time during the 7-day Holter. The study was approved by the institutional review board and was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent.

The association of sinus rhythm maintenance with baseline clinical and echocardiographic parameters were tested by univariable logistic regression. All factors with an univariable P-value < 0.1 were used to create a stepwise multivariable logistic regression model for sinus

rhythm maintenance. The final model was tested for significant interactions and collinearity. Odds ratios (OR) and 95% confidence intervals (CI) were given. The model was adjusted for randomization strategy, as targeted therapy showed to be superior in sinus rhythm maintenance.⁽³⁾ As sensitivity analysis, 100% sinus rhythm at the 7-day Holter was additionally used as outcome parameter, instead of $\geq 6/7^{\text{th}}$ of the time. A *P*-value <0.05 was considered statistically significant. Thromboembolic complications were defined as stroke, transient ischemic attack of pulmonary embolism.

RESULTS

All 245 RACE 3 patients were included in the present analysis. Table 1 shows the baseline characteristics of the trial population.

Table 1. Baseline characteristics for the study population and split based on the rhythm on the 7-day Holter at 1-year.

Characteristic	Total (n = 245)	SR at 1 year (n = 168)	AF at 1 year (n = 77)	P-value (between groups)
Age (years)	65 ± 9	65 ± 9	65 ± 9	0.527
Male sex	193 (79%)	134 (80%)	59 (77%)	0.615
Hypertension	144 (59%)	98 (58%)	46 (60%)	0.889
Diabetes	26 (11%)	12 (7%)	14 (18%)	0.009
Coronary artery disease	33 (14%)	23 (14%)	10 (13%)	0.881
Ischemic thromboembolic complication	10 (4%)	4 (2%)	6 (8%)	0.076
Chronic obstructive pulmonary disease	20 (8%)	12 (7%)	8 (10%)	0.452
CHA ₂ DS ₂ -VASc score*	2 (1-3)	2 (1-3)	2 (1-3)	0.302
Body mass index (kg/m ²)	28 (26-31)	29 (26-32)	28 (26-31)	0.628
Blood pressure (mmHg)				
Systolic	129 ± 15	129 ± 15	130 ± 16	0.669
Diastolic	83 ± 10	83 ± 10	82 ± 10	0.800
Left atrial size, long axis (mm)	43 (40-47)	44 (39-47)	43 (40-47)	0.811
Left atrial volume (mL)	80 (65-97)	82 (66-100)	73 (56-95)	0.051
LVEF (%)	50 (43-59)	50 (50-58)	54 (45-60)	0.363

Data are mean (standard deviation), number of patients (%), or median (interquartile range). *The CHA₂DS₂-VASc score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A₂=age ≥ 75 years; D=diabetes mellitus; S₂=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc=sex category (female sex).

Sinus rhythm maintenance at 1-year was observed in 168 (69%). A total of 3 variables had an univariable P -value <0.1 , including prior ischemic thromboembolic events (OR 0.289, 95% CI 0.079-1.054, $P=0.060$), diabetes (OR 0.346, 95% CI 0.152-0.790, $P=0.012$) and left atrial volume (OR 1.014, 95% CI 1.001-1.027, $P=0.033$). In multivariable logistic regression analysis, prior ischemic thromboembolic complications and diabetes were both negatively associated with sinus rhythm maintenance (Figure 1). In a sensitivity analysis, both thromboembolic complications (OR 0.160, 95% CI 0.033-0.782, $P=0.024$) and diabetes (OR 0.412, 95% CI 0.170-0.995, $P=0.049$) remained negatively associated with 100% sinus rhythm maintenance. No factors were associated with sinus rhythm maintenance in either randomization group separately.

Figure 1. Multivariable associated with sinus rhythm maintenance, adjusted for randomization strategy. Abbreviations: CI=confidence interval.

Baseline levels of HbA1c were similar in patients who were in sinus rhythm at 1 year and who were in AF [40 (37-43) versus 41 (38-46), $P=0.126$]. But at 1-year, HbA1c was significantly lower in patients who were in sinus rhythm, compared to patients who were in AF [38.5 (36-42) versus 42 (37.5-46), $P=0.002$].

DISCUSSION

We showed that in patients with early-persistent AF and HF, both prior thromboembolic complications and diabetes were negatively associated with sinus rhythm maintenance.

Preventing thromboembolic complications, including stroke, is one of the pillars for AF treatment.(4) Risk of stroke is generally increased by the number of underlying risk factors and age, indicating that patients with more underlying (heart)disease and advanced age are at higher risk of stroke. More underlying conditions result in more advanced cardiac remodelling, explaining the inverse relation to sinus rhythm maintenance in patients with prior thromboembolic complications. Also, asymptomatic AF may be detected years after onset, allowing atrial remodelling to continue. This can result in stroke being the first symptom of underlying AF. Secondly, stroke can be a result of undiagnosed vascular disease (e.g. carotid artery plaques). As previously, Weijs *et al.* showed that vascular disease is often present, even in patients originally diagnosed as having 'lone AF'.(5) Lastly, thromboembolic complications can be a result of a hypercoagulable state that is often found in AF.(6) A hypercoagulable state can result both in stroke and atrial fibrosis through protease activated receptor stimulation.(7)

Diabetes is a notorious risk-factor for AF and affects multiple organs, as well as endothelial function. This can in turn enhance vascular and atrial remodelling, which promotes progression of AF and thus the inability to maintain sinus rhythm. An analysis from Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) found diabetes to be associated with higher risk of mortality in AF.(8) Question remains whether diabetes increases AF risk independent of other risk factors. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) showed no differences in AF incidence in patients with intensified glucose control, compared to conventional control.(9) This implicates that diabetes-related complications are hard to prevent by adequate treatment. We showed that Hb1Ac was lower in patients receiving targeted therapy of underlying conditions at 1-year follow-up. Whether this indicates that targeted therapy improves glucose tolerance – and could thereby lower the risk on diabetes – is not to be concluded from this data and clearly warrants further research.(10)

Limitations of the current manuscript include the moderate sample size, which limits the power to perform subgroup analyses. Additionally, all associations found do not necessarily reflect causal relations, which may also be considered a limitation.

CONCLUSION

In conclusion, both diabetes and a history of thromboembolic complications were negatively associated with sinus rhythm maintenance in patients with early-persistent AF and HF.

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8a

Targeted therapy of underlying conditions improves quality of life in patients with persistent atrial fibrillation: results of the RACE 3 study

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ABSTRACT

Aim. Atrial fibrillation (AF) reduces quality of life (QoL). We aim to evaluate effects of targeted therapy of underlying conditions on QoL in patients with AF and heart failure (HF).

Methods. The Routine versus Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) study randomized patients with early-persistent AF and HF to targeted or conventional therapy. Both groups received guideline-driven treatment. The targeted group received 4 additional therapies: mineralocorticoid receptor antagonists; statins; angiotensin converting enzyme inhibitors and/or receptor blockers; and cardiac rehabilitation including physical activity, dietary restrictions, and counselling. QoL was analysed in 230 patients at baseline and 1-year with available Medical Outcomes Study Short-Form Health Survey (SF-36), University of Toronto AF Severity Scale (AFSS) questionnaires and European Heart Rhythm Association (EHRA) class.

Results. Improvements in SF-36 subscales were larger in the targeted group for physical functioning ($\Delta 12 \pm 19$ versus $\Delta 6 \pm 22$, $p=0.007$), physical role limitations ($\Delta 32 \pm 41$ versus $\Delta 17 \pm 45$, $P=0.018$), and general health ($\Delta 8 \pm 16$ versus $\Delta 0 \pm 17$, $P<0.001$). Dyspnoea at rest improved more ($\Delta -0.8 \pm 1.3$ versus $\Delta -0.4 \pm 1.2$, $P=0.018$) and EHRA class was lower at 1-year follow-up in the targeted group. Patients with AF at 1-year, improvement in physical functioning ($\Delta 9 \pm 9$ versus $\Delta -3 \pm 16$, $P=0.001$), general health ($\Delta 7 \pm 16$ versus $\Delta -7 \pm 19$, $P=0.004$) and social functioning ($\Delta 6 \pm 23$ versus $\Delta -4 \pm 16$, $P=0.041$) were larger in the targeted group.

Conclusions. A strategy aiming to treat underlying conditions improved QoL more compared to conventional therapy in patients with early-persistent AF and HF. Its benefit was even observed in patients in AF at 1-year.

INTRODUCTION

Apart from being a major cause of cardiovascular morbidity and mortality, atrial fibrillation (AF) is associated with reduced quality of life (QoL).(1,2) Patients with AF have lower QoL compared to healthy controls, and similar to or worse than QoL seen in patients after myocardial infarction.(1,2) Restoration and maintenance of sinus rhythm has been associated with improvement of QoL, but in contrast, rate versus rhythm control studies showed a similar QoL in both groups.(3,4) This can probably be explained by a low success rate of sinus rhythm maintenance.

Recently, the Routine versus Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) study showed that targeted therapy of underlying conditions in patients with early persistent AF and mild to moderate heart failure (HF) was associated with a reduction of blood pressure, body mass index, lipid levels, and lowering of NT-proBNP, indicating improvement of HF. On top of those beneficial effects on underlying conditions, this strategy improved maintenance of sinus rhythm at 1-year follow-up.(5) Targeted therapy of underlying conditions aims to improve risk factors associated with AF and, in relation to that, to slow down the atrial remodelling processes, which underlies the progression of AF. In the RACE 3 trial targeted therapy included four additional therapies on top of conventional care: mineralocorticoid receptor antagonists (MRAs), statins, angiotensin-converting enzyme inhibitors (ACE-Is) and/or angiotensin receptor blockers (ARBs), and cardiac rehabilitation including physical therapy, dietary restrictions and counselling.(5,6)

We hypothesized that targeted therapy could increase QoL through the improved maintenance of sinus rhythm, in combination with a better treatment of underlying conditions. Secondly, we hypothesized that because of the latter, it might also improve QoL by other mechanisms than sinus rhythm maintenance, since it focuses on optimal blood pressure regulation, treatment of HF and physical activity to improve fitness. Meanwhile, side effects of the additional drugs could impact QoL in a negative way. Therefore, in this predefined secondary endpoint analysis of the RACE 3 study we aimed to evaluate the effects of targeted therapy of AF on QoL.

METHODS

Study design and population

This study was performed in patients with early persistent AF and mild to moderate HF included in the RACE 3 study. The institutional review board of each participating hospital

approved the study, and all patients provided written informed consent. The RACE 3 study has been described previously (5,6). In brief, the RACE 3 study was a multicentre, prospective, randomized, open-label trial in patients with early persistent AF and mild to moderate HF (ClinicalTrials.gov identifier NCT00877643). All patients received causal treatment of AF and HF and were subsequently randomized to receive either targeted therapy of underlying conditions or conventional therapy. Patients in the targeted therapy group received four therapies on top of conventional therapy: MRAs, statins, ACE-Is and/or ARBs, and cardiac rehabilitation including counselling on drug adherence, sodium restriction, dietary restriction, alcohol use, caffeine use, fluid restriction and physical activity. Psychological counselling was not part of the intervention. Full details on the counselling program in RACE 3 are given in the *Supplementary files*. Three weeks after inclusion, patients in both groups underwent electrical cardioversion. Both groups received rhythm control and treatment of HF according to the guidelines.(7,8) Follow-up duration was 1 year. The primary endpoint was sinus rhythm during more than 6/7th of the time on 7-day Holter monitoring at 1 year. QoL-related questionnaires were administered at baseline immediately after inclusion and at 1 year. A total of 230 out of 245 patients had available questionnaire data and were included in the present analysis.

QoL-related questionnaires

QoL-related questionnaires used included the Medical Outcomes Study Short-Form Health Survey (SF-36) questionnaire, the University of Toronto AF Severity Scale (AFSS) Part C, the Multidimensional Fatigue Index (MFI-20), and the Minnesota Living with Heart Failure Questionnaire (MLHFQ). Additionally, the European Heart Rhythm Association (EHRA) class and New York Heart Association (NYHA) function class was assessed.

The SF-36 is a well-validated questionnaire that is often used to assess health-related QoL in AF.(9) It consists of 36 questions, which are used to calculate eight subscales, with three physical scales (physical functioning, physical role limitations, and bodily pain), three mental scales (social functioning, emotional role limitations, and mental health), two mixed scales (general health and vitality), and one question regarding health change. Each scale consists of varying numbers of questions, which in turn have response levels varying from two to six. Each scale was translated to a score from 0 to 100, with scores of 100 indicating the best possible QoL. Scores were calculated using the SF-36 scoring method as originally described by Ware *et al.*(9)

The AFSS Part C was used to assess AF-related symptoms. It contains seven questions on seven AF-related symptoms during the past week (palpitations, dyspnoea at rest, dyspnoea during exercise, reduced exercise capacity, fatigue at rest and chest pain), from which a total score of 0-35 is calculated, with higher scores indicating more AF-related symptoms.(1) The

EHRA class was also used to classify the severity of AF-related symptoms, dividing patients into four classes: asymptomatic (class I), mild symptoms (class II), severe symptoms (III) and disabling symptoms (class IV). The EHRA class was determined by physicians at study visits.

The MFI-20 was used in order to assess fatigue. It is composed of twenty questions, divided across five subscales (general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue), with higher scores indicating higher levels of fatigue.⁽¹⁰⁾

The MLHFQ consists of 21 questions related to HF. Three scores are calculated: a physical score ranging from 0 to 40, a mental score ranging from 0 to 25, and a total score ranging from 0 to 105, with higher scores indicating more HF-related constraints.⁽¹¹⁾ The NYHA class is an international standard for heart failure related complaints, divided in class I (no symptoms), II (mild symptoms), III (marked limitation in activity) and IV (severe limitations).

Statistical analysis

Baseline characteristics are presented as mean $\pm$ standard deviation (SD) for normally distributed data, as median and interquartile range for non-normally distributed continuous data, and as number and percentage for categorical data. The results of the QoL-related questionnaires and EHRA class are presented as mean $\pm$ SD.

Scores of questionnaire data at baseline and 1 year were compared between the targeted and conventional therapy group using a Mann Whitney U test. A within-group comparison of scores at baseline and 1 year was performed using the Wilcoxon signed-rank test. For each patient, the changes in scores between baseline and 1 year were calculated (overall change). The overall changes between groups were compared using a Mann Whitney U test.

Additionally, the number of patients with a relevant improvement or worsening was determined for each SF-36 subscale, as well as for the scores of the AFSS, MFI-20, and MLHFQ. Relevant changes per questionnaire were pre-specified.⁽³⁾ For the SF-36, a relevant change was defined as an improvement or worsening of a predetermined number of steps on a subscale score (i.e. before conversion to a 0-100 score). For physical functioning, general health, vitality and mental health, an increase or decrease of three steps was considered a relevant change. For bodily pain and social functioning, the required number was two, for physical and emotional role limitations one step was required. Corresponding with the relevant changes of SF-36 subscales, an effect size of 0.58 SD was used in determining relevant changes for the AFSS, MFI-20, and MLHFQ. The proportions of relevant improvement and worsening were compared between the two randomization groups using a Fischer's exact test.

In order to identify differences in QoL based on heart rhythm at 1-year follow-up, the study population was subdivided according to heart rhythm at 1 year (as defined for the primary endpoint of the RACE 3 study). For both subgroups, scores at baseline and 1 year, as well as within-group and between-group changes were compared between the targeted and conventional therapy group, in the same manner as described above.

All analyses were performed on an intention-to-treat basis. For all analyses, a *P*-value <0.05 was considered statistically significant.

RESULTS

Patients and baseline characteristics

Of the 230 patients included in this analysis, 114 were randomized to targeted therapy and 116 to conventional therapy. Baseline characteristics were comparable between the targeted and conventional therapy group (Table 1) and not different from the total RACE 3 population (data not shown). Mean age was 65 ± 9 years and 180 (78%) were men. The median duration of AF and HF was short, 3 (2-6) and 2 (1-4) months, respectively. Left ventricular ejection fraction was below 45% in 63 patients (27%).

Table 1. Baseline characteristics.

Characteristic	Total (n = 230)	Targeted therapy (n = 114)	Conventional therapy (n = 116)	P-value (between groups)
Age (years)	65 ± 9	64 ± 9	65 ± 8	0.332
Male sex	180 (78%)	89 (78%)	91 (78%)	1.000
Total duration AF (months)	3 (2-6)	4 (2-7)	3 (2-5)	0.084
Total persistent AF (months)	2 (1-4)	2 (1-4)	2 (1-4)	0.357
Duration HF (months)	2 (1-4)	2 (1-4)	2 (1-3)	0.677
Hospital admission for HF	29 (13%)	14 (12%)	15 (13%)	1.000
LVEF <45%	63 (27%)	33 (29%)	30 (26%)	0.658
Hypertension	139 (60%)	65 (57%)	74 (64%)	0.345
Diabetes	22 (10%)	9 (8%)	12 (11%)	0.502
Coronary artery disease	30 (13%)	18 (16%)	12 (10%)	0.245
Ischemic thromboembolic complication	10 (4%)	6 (5%)	4 (3%)	0.537
Chronic obstructive pulmonary disease	18 (8%)	9 (8%)	9 (8%)	1.000
History of moderate or severe valvular heart disease	21 (9%)	11 (10%)	10 (9%)	0.822
CHA ₂ DS ₂ -VASC score*	2 (1-3)	2 (1-3)	2 (1-3)	
Body mass index (kg/m ²)	28 (26-31)	29 (26-31)	28 (25-31)	0.525

Table 1. Baseline characteristics. (continued)

Characteristic	Total (n = 230)	Targeted therapy (n = 114)	Conventional therapy (n = 116)	P-value (between groups)
Blood pressure (mmHg)				
Systolic	129 ± 15	131 ± 16	128 ± 15	0.299
Diastolic	83 ± 10	84 ± 11	82 ± 10	0.311
Heart rate at rest in AF (bpm)	88 (78-97)	87 (77-95)	88 (78-99)	0.435
NYHA classification				0.670
I	51 (22%)	28 (25%)	23 (20%)	
II	155 (67%)	75 (66%)	80 (69%)	
III	24 (10%)	11 (10%)	13 (11%)	
EHRA classification				0.813
I	26 (11%)	14 (12%)	12 (10%)	
II	171 (74%)	85 (75%)	86 (74%)	
III	33 (14%)	15 (13%)	18 (16%)	
NT-pro BNP (pg/mL)	1045 (698-1628)	1055 (691-1635)	1008 (711-1567)	0.926
Medications				
Beta-blocker	201 (88%)	99 (87%)	102 (88%)	0.692
Verapamil/Diltiazem	11 (5%)	1 (1%)	10 (9%)	0.010
Digoxin	59 (26%)	32 (28%)	27 (23%)	0.453
ACE-inhibitor	80 (35%)	37 (32%)	43 (37%)	0.489
Angiotensin receptor blocker	50 (22%)	23 (20%)	27 (23%)	0.632
Mineralocorticoid Receptor Antagonist	3 (1%)	1 (1%)	2 (2%)	1.000
Statin	77 (34%)	38 (33%)	39 (34%)	1.000
Diuretic	93 (41%)	50 (44%)	43 (37%)	0.348
Anticoagulant	226 (98%)	112 (98%)	114 (98%)	0.622
Echocardiographic variables				
Left atrial size, long axis (mm)	43 (40-47)	43 (40-47)	44 (39-47)	0.674
Left atrial volume (mL/m ²)	38 (31-48)	38 (30-48)	38 (32-48)	0.685
LVEF (%)	52 (43-60)	50 (43-58)	53 (44-60)	0.449

Data are presented as mean±SD, number of patients (%), or median (IQR). Abbreviations: ACE=angiotensin-converting enzyme; AF=atrial fibrillation; bpm= beats per minute; EHRA= European Heart Rhythm Association class for symptoms; HF=heart failure; LVEF=left ventricular ejection fraction; NT-pro BNP=N-terminal pro-brain natriuretic peptide; NYHA=New York Heart Association. *The CHA₂DS₂-VASC score assesses thromboembolic risk. C=congestive heart failure/LV dysfunction, H=hypertension; A₂=age ≥75 years; D=diabetes mellitus; S₂=stroke/transient ischemic attack/systemic embolism; V=vascular disease; A=age 65-74 years; Sc=sex category (female sex).

SF-36

At baseline, there were no differences in SF-36 scores between the targeted and conventional group (Table 2). Between baseline and 1 year of follow-up, all eight SF-36 subscales improved in the targeted group, compared to six out of eight subscales in the conventional group. Figure 1 shows the overall change between baseline and 1 year for each SF-36 subscale in the targeted and conventional therapy group. The targeted therapy group improved more in physical functioning ($\Delta 12 \pm 19$ versus $\Delta 6 \pm 22$, $P = 0.007$), physical role limitations ($\Delta 32 \pm 41$ versus $\Delta 17 \pm 45$, $P = 0.018$) and general health ($\Delta 8 \pm 16$ versus $\Delta 0 \pm 17$, $P < 0.001$). The targeted group showed a larger proportion of patients with a relevant improvement between baseline and 1 year in physical functioning (43% versus 28%, $P = 0.035$) and general health (37% versus 20%, $P = 0.010$) when compared to the conventional group (Figure 2). On top of that, relevant worsening was less often seen in the targeted group for physical role limitations (5% versus 16%, $P = 0.018$) and general health (7% versus 20%, $P = 0.019$).

Table 2. SF-36 scores at baseline and 1 year.

SF-36 subscale	Treatment strategy	Baseline	1 year	P-value within-group change	P-value between-group change
Physical functioning	Targeted	67 ± 23	79 ± 21	<0.001	0.007
	Conventional	69 ± 25	75 ± 23	0.024	
Physical role limitations	Targeted	43 ± 43	75 ± 37	<0.001	0.018
	Conventional	51 ± 45	68 ± 41	0.001	
Bodily pain	Targeted	80 ± 22	85 ± 21	0.018	0.830
	Conventional	77 ± 25	81 ± 22	0.047	
General health	Targeted	59 ± 19	68 ± 19	<0.001	<0.001
	Conventional	59 ± 19	59 ± 21	0.866	
Vitality	Targeted	58 ± 22	66 ± 20	<0.001	0.361
	Conventional	60 ± 21	66 ± 19	0.001	
Social functioning	Targeted	77 ± 24	86 ± 19	0.001	0.277
	Conventional	81 ± 20	86 ± 17	0.026	
Emotional role limitations	Targeted	74 ± 41	86 ± 30	0.009	0.414
	Conventional	77 ± 38	84 ± 34	0.136	
Mental health	Targeted	79 ± 16	83 ± 14	0.001	0.405
	Conventional	77 ± 15	80 ± 15	0.027	

Data are presented as mean ± SD. Abbreviations: SF-36 = Medical Outcomes Study 36-item Short-Form Health Survey.

Figure 1. Changes in mean SF-36 subscale scores from baseline to 1-year follow-up

* $P < 0.05$ for difference between targeted and conventional therapy group.

** $P < 0.001$ for difference between targeted and conventional therapy group.

Figure 2. Proportions of relevant improvement and worsening for individual SF-36 scales

* $P < 0.05$ for difference between targeted and conventional therapy group.

At 1 year, 85 patients (75%) in the targeted group and 73 (63%) in the conventional group were in sinus rhythm during more than 6/7th of the time during a 7-day Holter recording. There was no difference in the number of atrial ablations or cardioversions performed, nor was there any difference in antiarrhythmic drugs instituted between groups during follow-up. Clinical characteristics for both sinus rhythm and AF groups were not different for both randomization strategies. In all patients who were in sinus rhythm at 1 year follow-up, overall change in general health was larger in the targeted group ($\Delta 9 \pm 16$ versus $\Delta 4 \pm 14$, $P = 0.043$; Figure 3-a). Improvement in SF-36 subscales were smaller in patients in AF at 1-year, compared to patients in sinus rhythm. Differences between both randomization groups were, however, more prominent in patients who were in AF. The targeted group improved more in physical functioning ($\Delta 9 \pm 9$ versus $\Delta -3 \pm 16$, $P = 0.001$), general health ($\Delta 7 \pm 16$ versus $\Delta -7 \pm 19$, $P = 0.004$), and social functioning ($\Delta 6 \pm 23$ versus $\Delta -4 \pm 16$, $P = 0.041$; Figure 3-b).

Figure 3 A-B. Changes in mean SF-36 subscale scores, subdivided according to rhythm at 1 year. These figures show the overall changes in SF-36 subscales between baseline and 1 year for the subgroups of patients in sinus rhythm at 1-year follow-up (A) and patients in AF at 1-year follow-up (B).
* $P < 0.05$ for difference between targeted and conventional therapy group.

AFSS and EHRA class

Table 3 shows the AFSS scores at baseline and 1 year for both groups. All scores improved during follow-up, except for dizziness in the targeted group. Dyspnoea at rest improved more in the targeted group between baseline and 1-year ($\Delta-0.8\pm1.3$ versus $\Delta-0.4\pm1.2$, $P=0.018$). Patients who received targeted therapy were also more likely to have a relevant improvement of dyspnoea at rest (52% versus 37%, $P=0.041$) and exercise capacity (59% versus 44%, $P=0.044$). The proportions of relevant worsening did not differ between groups.

Patients of the conventional group who were in sinus rhythm at the 7-day Holter showed more reduction in dizziness compared to the targeted group (conventional $\Delta-0.3\pm1.3$ versus targeted group $\Delta 0\pm1.4$, $P=0.015$). Patients of the targeted group who were in AF at 1-year had more improvement in exercise capacity, as shown by a larger reduction in the reduced exercise capacity score (targeted $\Delta-0.9\pm1.2$ versus conventional $\Delta-0.2\pm1.2$, $P=0.024$). This was also true for the total AFSS score (targeted $\Delta-3.6\pm4.6$ versus conventional $\Delta-0.8\pm4.9$, $P=0.045$).

Baseline EHRA class was not different between both groups (2.0 ± 0.5 versus 2.1 ± 0.5 , $P=0.520$). At 1-year both groups had a lower EHRA class compared to baseline. At that time the targeted group showed a lower EHRA class (1.3 ± 0.5 versus 1.5 ± 0.6 , $P=0.003$).

MFI-20

Baseline scores on all MFI-20 subscales were comparable in both groups (Table 3). In the targeted group, all five MFI-20 subscales improved during the study. In the conventional group, all except the mental fatigue scale improved. Targeted therapy showed larger improvements of physical fatigue ($\Delta-4\pm5$ versus $\Delta-2\pm6$, $P=0.001$) and reduced activity scales ($\Delta-3\pm4$ versus $\Delta-1\pm6$, $P=0.030$) between baseline and 1-year. Patients in the targeted group were also more likely to have a relevant improvement on fatigue (61% versus 44%, $P=0.021$) and reduced activity (54% versus 39%, $P=0.040$) compared to conventional therapy. There were no differences in the proportions of relevant worsening.

MLHFQ and NYHA class

Total scores of MLHFQ were low in both groups at baseline (Table 3) and were not different, indicating that HF related symptoms were mild. In both groups, physical, emotional and total scores improved between baseline and 1 year. At 1-year, there were no differences between the two groups, nor were there any differences in the overall changes of MLHFQ scores or the proportions of relevant improvement or worsening.

Table 3. AFSS, MFI-20 and MLHFQ scores at baseline and 1 year.

AFSS scores	Treatment strategy	Baseline	1 year	P-value within-group change	P-value between-group change
Palpitations	Targeted	1.5 ± 1.5	0.5 ± 0.8	<0.001	0.383
	Conventional	1.5 ± 1.5	0.7 ± 1.1	<0.001	
Dyspnoea at rest	Targeted	1.3 ± 1.3	0.5 ± 0.8	<0.001	0.018
	Conventional	1.2 ± 1.2	0.8 ± 1.2	0.004	
Dyspnoea during exercise	Targeted	2.5 ± 1.4	1.4 ± 1.4	<0.001	0.215
	Conventional	2.4 ± 1.4	1.6 ± 1.4	<0.001	
Reduced exercise capacity	Targeted	2.1 ± 1.5	1.1 ± 1.2	<0.001	0.052
	Conventional	1.9 ± 1.5	1.3 ± 1.3	<0.001	
Fatigue at rest	Targeted	1.4 ± 1.5	0.7 ± 1.0	<0.001	0.138
	Conventional	1.2 ± 1.2	0.9 ± 1.1	0.019	
Dizziness	Targeted	0.9 ± 1.2	0.8 ± 1.1	0.512	0.157
	Conventional	1.2 ± 1.3	0.9 ± 1.2	0.023	
Chest pain	Targeted	0.6 ± 1.0	0.3 ± 0.5	0.001	0.517
	Conventional	0.8 ± 1.3	0.5 ± 0.8	0.004	
Total	Targeted	10.5 ± 6.8	5.5 ± 5.0	<0.001	0.081
	Conventional	10.2 ± 6.9	6.7 ± 5.8	<0.001	
MFI-20 subscales	Treatment strategy	Baseline	1 year	P-value within-group change	P-value between-group change
General fatigue	Targeted	15 ± 6	12 ± 6	<0.001	0.163
	Conventional	15 ± 6	13 ± 6	<0.001	
Physical fatigue	Targeted	15 ± 6	11 ± 5	<0.001	0.001
	Conventional	14 ± 6	13 ± 6	0.002	
Reduced activity	Targeted	15 ± 6	12 ± 5	<0.001	0.030
	Conventional	13 ± 5	12 ± 5	0.012	
Reduced motivation	Targeted	12 ± 6	10 ± 5	0.001	0.415
	Conventional	11 ± 5	10 ± 5	0.021	
Mental fatigue	Targeted	10 ± 5	9 ± 5	0.029	0.141
	Conventional	9 ± 5	9 ± 5	0.945	
MLHFQ scores	Treatment strategy	Baseline	1 year	P-value within-group change	P-value between-group change
Physical	Targeted	14 ± 11	7 ± 7	<0.001	0.164
	Conventional	13 ± 10	8 ± 8	<0.001	
Emotional	Targeted	4 ± 5	3 ± 5	0.002	0.837
	Conventional	4 ± 4	3 ± 4	0.021	
Total	Targeted	26 ± 21	15 ± 15	<0.001	0.064
	Conventional	23 ± 18	18 ± 16	0.005	

Data are presented as mean±SD. Abbreviations: AFSS = University of Toronto Atrial Fibrillation Severity Scale Part C; MFI-20 = Multidimensional Fatigue Index; MLHFQ = Minnesota Living with Heart Failure Questionnaire.

NYHA class was not different between both groups at baseline (1.9 ± 0.6 versus 1.9 ± 0.6 , $P = 0.387$), nor at 1-year (1.2 ± 0.5 for targeted therapy versus 1.3 ± 0.6 for conventional therapy, $P = 0.711$).

DISCUSSION

The present study demonstrates that targeted therapy of underlying conditions improved QoL more compared to conventional therapy in patients with early persistent AF and HF. Interestingly, we found that beneficial effects of targeted therapy were also observed in patients who were in AF at 1-year follow-up.

Improvement of QoL was observed in both randomization groups, which can partly be explained by the fact that a high proportion of both groups was in sinus rhythm at 1-year follow-up. Improvement of QoL through sinus rhythm maintenance has been demonstrated before, albeit not in all studies.(2,12,13) In a post-hoc analysis from the RACE study, no differences in QoL between permanent AF and long-term sinus rhythm were found – nor did long-term sinus rhythm improve prognosis.(14) This might have been caused by non-optimal risk factor management at that time, including, for example, a more lenient blood pressure target compared to current standards.(7)

The finding that targeted therapy improves several aspects of QoL more than conventional therapy is relevant, especially considering that rhythm control is mainly instituted to relieve symptoms and thereby improve QoL.(7) The four interventions were specifically chosen to optimize blood pressure, improve the treatment of HF and improve the overall cardiovascular risk profile. It is thought that a combined intervention would have a synergistic effect. The RACE 3 study, as well as several studies by the group of Sanders *et al.* showed beneficial effects of treating underlying risk factors of AF more aggressively, including life-style interventions.(5,15,16) Abed *et al.* randomized patients with symptomatic AF and overweight to either weight management or general lifestyle advice.(16) The weight management group showed a reduction in symptom burden and severity as well as reduced cardiac remodeling. The use of ACE-Is and/or ARBs aimed to optimize blood pressure. Lee *et al.* included 899 patients with uncontrolled hypertension and divided these patients as having either controlled or non-controlled hypertension at 6 months follow-up.(17) The main finding included that blood pressure control was correlated with health-related QoL. MRAs were added to improve HF treatment. In patients with HF with a preserved ejection fraction, the use of spironolactone has shown to improve QoL.(18) Of interest, in that same population several modifiable cardiovascular risk factors were associated with QoL deterioration, e.g. obesity. The last intervention, the use of statins, was mainly instituted to prevent coronary

and other vascular events. On top of that, the anti-inflammatory effect might contribute to limiting atrial remodelling. Clear positive effects on QoL have thus far not been described. Carlsson *et al.* found no change in QoL in elderly patients taking pravastatin during 1 year. (19)

The beneficial effects of targeted therapy on QoL could be caused by higher proportion of sinus rhythm, as well as optimal treatment of comorbidities and improvement of lifestyle. These beneficial effects of targeted therapies of comorbidities on QoL based on other mechanisms than sinus rhythm maintenance are supported by the results from our subgroup analysis based on the actual rhythm at 1-year. Patients in whom sinus rhythm was not maintained seem to have also benefited from targeted therapy in terms of QoL. Several SF-36 subscales did not show any differences between groups, which can partly be explained by the already high scores, with limiting power to detect any differences.

Analyses of AFSS scores showed that in both groups all AF-related complaints improved, except for dizziness in the targeted therapy group, which remained stable. This may be explained by the more aggressive blood pressure control as a result of adding MRAs, ACE-Is and ARBs as part of the intervention, possibly causing orthostatic hypotension. The SPRINT trial, which randomized patients to either intensive or standard blood pressure control, showed that intensive blood pressure control caused less fatal and non-fatal cardiovascular events and mortality compared to standard blood pressure control.(20) Despite intensive blood pressure control, the number of serious adverse events due to hypotension (2.4%) and syncope (2.3%) was relatively low.

Apart from the scores for dizziness, the other questionnaire data showed better scores in the targeted group fairly consistently, although not all differences between the groups were significant. A lack of power for detecting differences in QoL may have played a role in this respect. Alternatively, questionnaires such as the AFSS Part C may not have shown any differences between treatment groups since patients had low scores (indicating relatively few complaints) on these questionnaires at baseline. This is supported by the finding of relatively low EHRA class, especially at 1-year follow-up. Similar to the SF-36 scores, AFSS scores between groups of patients in AF at 1-year also showed a difference in favour of the targeted group.

Scores of MLHFQ at baseline and 1-year follow-up were fairly low, indicating that HF related symptoms were mild. This is supported by the relatively low NYHA class at 1 year follow-up. This might have to do with the fact that the questionnaire was originally designed for patients with more advanced stages of HF.(11)

Symptoms of AF and HF often overlap. We aim to contribute to a better collaboration between heart failure cardiologists and electrophysiologists in order to improve outcome in AF-HF patients, as they often intertwine.

Limitations

Limitations of the present study include the fact that it was not primarily designed to detect differences in QoL, and the fact that the institution of four targeted therapies at once makes it difficult to analyse individual contributions of each therapy on QoL. Furthermore, the open-label design of the study for both patient and physician with lack of placebo, might have accounted to additional positive effects on QoL in the targeted therapy group. This could have contributed to a potential bias that influenced the self-assessment in the targeted group. Study-related follow-up visits were very frequent for both randomization groups, which may have had an additional positive effect on QoL in both groups compared to real-life health care. Finally, as with any subgroup analysis, the results of the post-hoc subgroup analysis based on heart rhythm should be interpreted with caution because of the modest sample size, even though baseline characteristics were comparable within the subgroups.

CONCLUSION

In conclusion, the present study demonstrates that targeted therapy of underlying conditions results in larger improvements in QoL compared to conventional therapy in patients with early persistent AF and mild to moderate HF. These effects seem to be at least partially related to mechanisms other than sinus rhythm maintenance. The results further underline the importance of risk factor management in AF and may thus contribute to improving current treatment strategies and improvement of QoL in patients with AF.

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SUPPLEMENTARY FILES.

Supplementary file 1

Counselling guidelines RACE 3 upstream group for research nurses

The following guidelines can be used at the counselling visits:

Sodium restriction

On average a western diet contains 9 grams of salt (= 3600 mg sodium) per day.

It is advisable to use no more than 3000 mg of sodium (7.5 grams of salt) per day.

Basic rules for restriction of sodium intake:

- Do not use salt when cooking
- At the table, do not add salt to the food ("don't sprinkle").
- Avoid using salt-containing products as much as possible, such as ready-cooked meals, take-away meals, canned vegetables, conserved meats and cheese. More comprehensive information about salt restriction can be obtained from brochures and dieticians in the own hospital.

Caloric restriction

In severely overweight people (BMI more than 30 or abdominal circumference more than 88 cm in women or more than 102 cm in men) counselling by a dietician is necessary for following a low-caloric diet. Mildly overweight people (BMI between 25 and 30 or abdominal circumference between 80 and 88 cm in women and between 94 and 102 cm in men) can be advised on healthy, low caloric food. Use brochures from the own hospital or guidelines from the National Health Service or Foods Standards Agency. Alcohol use Atrial fibrillation may be triggered by alcohol use. In general, it is advised not to use more than 2 alcoholic consumptions per day.

Caffeine intake

Also, the use of caffeine may trigger AF. The sensitivity for caffeine highly differs between different people. In people sensitive to caffeine it is generally advised to use at most 400 mg of caffeine per day. This corresponds to 5 cups of coffee or 3 cups of coffee and 4 cups of tea per day.

Fluid restriction advice

The extent of fluid restriction advised to the patient is dependent of the severity of symptoms and has to be determined by the treating physician.

Physical activity

Sports or walking and cycling, preferably 5x per week during one half hour on the same intensity as during the cardiac rehabilitation programme. It is important that people continue to be physically active, also when the cardiac rehabilitation programme has ended!

Supplementary file 2

Training protocol for home trainer/bicycle ergometer during the RACE 3 study

Warming-up: 3 minutes of calm cycling

- 1 minute, e.g. 10 Watt
- 2 minutes, e.g. 20 Watt

Exercise: approximately 25 minutes of training

Gradually increase the workload, taking into account the intensity of the exercise as experienced by the patient (see underneath). The objective is to maintain this intensity, or to reduce it if needed. If necessary heavier and lighter levels of intensity can be altered in intervals of 1-2 minutes.

Cooling-down: 3 minutes of calm cycling

- 2 minutes, e.g. half the intensity during exercise
- 1 minute on lower level of intensity

Experienced intensity of the exercise

During exercise the patient should be cycling at a level of intensity that still enables her/him to speak in whole sentences. This corresponds to moderately fatiguing (not too light, not too heavy).

8b

Risk factor modification: another win for our fight against atrial fibrillation

Lin Y. Chen and Mina K. Chung

Editorial comment on 'Targeted therapy of underlying conditions improves quality of life in patients with persistent atrial fibrillation: results of the RACE 3 study'

Adapted from Europace. 2019 Apr 1;21:527-528.

Atrial fibrillation (AF) is a growing public health problem because of its increasing prevalence (1,2)– fed by the obesity epidemic and ageing of the population – and the associated risks of ischaemic stroke,(3) heart failure (HF), (4) cognitive decline or dementia, (5) and death. (6-8) For several decades, the management of AF has been focused on the ‘holy trinity’ of stroke prevention, rate control, and rhythm control strategy. However, since Sanders *et al.* (9,10) reported their findings that a strategy targeting weight loss and other cardiovascular risk factors can be effective in reducing AF burden, the electrophysiology community has gradually embraced a fourth pillar of AF management, namely lifestyle and risk factor modification.(11,12) Professional societies are also endorsing lifestyle and risk factor modification as a critical component in our armamentarium in combating AF.(13)

RACE 3 (Routine vs. Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure) investigators sought to evaluate the effects of targeted therapy of underlying cardiovascular risk factors in patients with early persistent AF and HF.(14) Two hundred and forty-five patients were randomized to two groups: 119 were randomized to targeted therapy and 126 to conventional therapy. Both groups received rhythm control and treatment of HF according to current guidelines. Patients in the targeted therapy group additionally received four treatments on top of conventional therapy: mineralocorticoid receptor antagonists, statins, angiotensin converting enzyme inhibitors and/or receptor blockers, and cardiac rehabilitation, including counselling on drug adherence, sodium restriction, dietary restriction, alcohol use, caffeine use, fluid restriction, and physical activity. The primary endpoint of the main study was sinus rhythm at 1 year during 7 days of Holter monitoring; sinus rhythm was found in 75% of patients in the targeted therapy group and 63% in the conventional group (odds ratio 1.765, 95% confidence interval 1.021–3.051; $P=0.042$).

In the substudy reported in this issue of EP-Europace,(15) RACE 3 investigators studied the impact of the interventions on quality of life (QoL). Two hundred and thirty patients were included in this analysis: 114 were randomized to targeted therapy and 116 to conventional therapy. QoL-related questionnaires [Medical Outcomes Study Short-Form Health Survey (SF-36), the University of Toronto AF Severity Scale (AFSS) Part C, the Multidimensional Fatigue Index (MFI-20), and the Minnesota Living with Heart Failure Questionnaire (MLHFQ)] were administered at baseline and at 1 year follow-up. Between baseline and 1 year of follow-up, all eight SF-36 subscales improved in the targeted group, compared with six out of eight subscales in the conventional group. The targeted therapy group improved more than the conventional group in physical functioning ($\Delta 12 \pm 19$ vs. $\Delta 6 \pm 22$, $P=0.007$), physical role limitations ($\Delta 32 \pm 41$ vs. $\Delta 17 \pm 45$, $P=0.018$), and general health ($\Delta 8 \pm 16$ vs. $\Delta 0 \pm 17$, $P<0.001$). Based on the AFSS, dyspnoea at rest improved more in the targeted group than the conventional group between baseline and 1 year ($\Delta 0.8 \pm 1.3$ vs. $\Delta 0.4 \pm 1.2$, $P = 0.018$). Based on the MFI-

20 subscales, targeted therapy showed larger improvements of physical fatigue ($\Delta 4 \pm 5$ vs. $\Delta 2 \pm 6$, $P=0.001$) and reduced activity scales ($\Delta 3 \pm 4$ vs. $\Delta 1 \pm 6$, $P=0.030$) than the conventional group between baseline and 1 year. Collectively, this sub-analysis in RACE 3 has advanced the field by showing that a multipronged strategy targeting different cardiometabolic risk factors can result in better QoL in patients with early persistent AF and HF.

Although instructive, several knowledge gaps remain. First, although the multipronged approach in targeted therapy makes sense, the multitude of interventions makes it challenging to pinpoint the specific intervention that has the greatest impact. It is particularly important to distinguish whether it is pharmacologic or nonpharmacologic intervention (in this case, cardiac rehabilitation) that explains the observed benefit. It is also notable that the four interventions in targeted therapy were chosen to optimize blood pressure, and weight management was not included as part of targeted therapy. Second, the mechanisms underlying the salutary effect of targeted therapy on QoL are not definitively elucidated in this study. One would naturally assume that the multipronged approach in targeted therapy is more effective in improving QoL through better maintenance of sinus rhythm. However, in this study, patients in whom sinus rhythm was not maintained seemed to have also benefited from targeted therapy, prompting the need to define the exact pathways leading to improved QoL. Third, QoL measures were reassessed at 1-year follow-up. For targeted therapy to be promulgated as an effective public health intervention, its durability will need confirmation in studies with longer follow-up. Fourth, the reduction in AF burden was modest in the primary study; whether greater reduction in AF burden could further improve QoL would be of interest to study. Fifth and importantly, whether or not targeted therapy would improve other AF-related outcomes such as reducing the risk of ischaemic stroke or dementia is unknown.

Despite the knowledge gaps, the findings in this study constitute another win for our ongoing fight against AF, and RACE 3 investigators should be congratulated. Without doubt, the landscape for management of AF is evolving rapidly, and perhaps in the future, lifestyle and risk factor modification may emerge to be the central strategy in tackling the burgeoning public health problem of AF.

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9

Discussion and future perspectives

Atrial fibrillation (AF) is a complex arrhythmia that serves as a red flag for both patients and physicians. It should trigger physicians to also look beyond the ECG, because of a large variety of potential underlying cardiovascular risk factors often are present. We described the progressive nature of AF and its impact on clinical outcome in part I. Part II focused on several aspects to potentially prevent progression of AF.

Part I: Progression of AF

AF is a dynamic disease in which several temporal patterns are distinguished.(1) Paroxysmal AF is characterized by AF episodes that come and go and are, usually spontaneously, terminated within 7 days, either spontaneously or with intervention. Persistent AF that is continuously sustained beyond 7 days, including episodes terminated by cardioversion (drugs or electrical cardioversion) after ≥ 7 days.(2) In patients with permanent AF, sinus rhythm maintenance is no longer possible or no longer pursued. Progression of AF refers to an increase in the amount of AF over time. However, a heterogeneous definition of AF progression with limited rhythm monitoring is being used in the current literature, limiting our exact knowledge on prevalence and predictors of AF progression.(3) AF progression is of clinical relevance because of the strong relation with cardiovascular events that has been shown.(4-6)

Despite AF being primarily a disease in the elderly, an increasing number of patients have young-onset AF.(7) Because little is known on AF progression in these young patients, we examined 468 patients with AF onset before the age of 60 in Chapter 2. All were enrolled in The Phenotyping Young-Onset Atrial Fibrillation Patients study (YOUNG-AF).(8) Despite their young age (mean age 46 years), nine out of ten had at least one risk factor for AF, which provides further evidence that AF without risk factors is rare – even in the young.(9) Additionally, we studied the long-term progression rate to permanent AF with a median follow-up of 7.2 years, during which 56 (12%) developed permanent AF (equivalent to 2.0% per year). The progression rate is lower compared to most other studies, presumably due to the younger study population with less comorbidities (Table 1).(3,4,8,10-16) Both diastolic blood pressure and left atrial size were associated with AF progression. Sixty-one patients (13%) had at least 1 cardiovascular event during follow-up, which was 2.4% per year. And finally, we observed a higher cardiovascular event rate after AF progression had occurred. Whether the event rate was higher due to AF itself or that this was merely due to more complex underlying comorbidities, cannot be concluded from our data.(17) Yet, it further emphasizes that AF progression is associated with adverse cardiovascular outcome.

Comparable to Chapter 2, we aimed to quantify and find factors associated with AF progression in Chapter 3 in an older population with a short history of AF.(16) Despite being older than the YOUNG AF population, the mean age was still relatively low compared to other

AF cohorts (60 ± 11 years). In 392 patients who completed 1-year rhythm monitoring by Holter and event recorder, 13% had progression to a more sustained form of AF (paroxysmal to persistent or permanent, or persistent to permanent AF), or a significant increase in AF burden. Higher left atrial volume, higher levels of N-terminal pro B-type natriuretic peptide (NT-proBNP) and lower levels of plasminogen activator inhibitor-1 (PAI-1) were associated with AF progression. Left atrial volume is likely an easily accessible parameter that reflects the degree of atrial cardiomyopathy.(18) Like left atrial volume, NT-proBNP probably also reflects a degree of atrial dysfunction, thus an atrial cardiomyopathy, or could be an expression of heart failure which is often present in AF and has previously been associated with AF progression.(4) PAI-1 is a marker of fibrinolysis. Lower levels of PAI-1 indicate increased

Table 1. Overview of several important papers on AF progression.

Study	Number of patients	Age (years)	Type of AF	Follow-up (years)	AF progression rate (%)	Progression predictors
Al-Khatib et al. 2000	231	60 ± 13	Paroxysmal, 41% lone AF	4	18% (8% at 1 year)	Age, AF at presentation
Kerr et al. 2005 CARAF	757	Median 64	First detected AF	8	8.6% at 1 year; 24.7% at 5 years	Age, cardiomyopathy, aortic stenosis, mitral regurgitation, left atrial enlargement
Jahangir et al. 2007, Omstead County	1	44 ± 11	First diagnosed AF without comorbidities (48% paroxysmal)	25	31%	Age, QRS abnormalities
De Vos et al. 2010 Euro Heart Survey	1219	64 ± 13	Paroxysmal AF, 17% lone AF	1	15%	HATCH: age ≥ 75 ; heart failure; hypertension; stroke/TIA; COPD
De Vos et al. 2012 RECORD-AF	2137	65 ± 12	Paroxysmal AF, 20% lone AF	1	15% (rhythm 11%, rate control 26%)	Heart failure; hypertension; rate control (vs rhythm control)
Smit et al. 2012	100	65 ± 9	Short-lasting persistent AF	1	29% (to permanent AF)	TGF- $\beta 1$; left ventricular ejection fraction; early AF recurrence
Potpara et al. 2012	890	53 ± 12	Lone, paroxysmal AF	12 ± 7	27% (to permanent AF)	Age; development of heart failure
Meta-analysis Blum et al. 2019	27,266	-	-	4.0 (1.6-6.7)	8.1%	Age; hypertension
De With et al. 2018 YOUNG-AF	468	46 ± 10	70% paroxysmal AF	7.2 (2.7-10.0)	11% (2%/year)	Diastolic blood pressure; left atrial size
De With et al. 2020 AF-RISK	392	60 ± 11	83% paroxysmal AF	1	13%	Left atrial volume, NT-proBNP, PAI-1

fibrinolysis. This in turn could increase inflammation and chemotaxis induced by fibrin degradation products, like D-dimer, and enhance atrial remodelling, thereby explaining the relation to AF progression and lower levels of PAI-1. The exact role of hypercoagulation and AF and progression warrants further research, and is currently investigated by the RACE V consortium including a clinical registry (Clinicaltrials.gov identifier NCT02726698).(19,20)

After assessing AF progression at 1-year follow-up, additional follow-up was available in 350 patients with a mean of 1.9 years. Patients with AF progression had a more than 5-fold increase in cardiovascular event rate, compared to patients without progression. This effect remained after correcting for several factors, including age, sex, CHA₂DS₂-VASc score left atrial volume and treatment differences during follow-up.

A meta-analysis by Blum *et al.* evaluated 47 studies on AF progression, with a total of 27,266 patients included.(3) The pooled incidence of AF progression was 8.1% per year, yet this was hampered by differences in clinical characteristics, AF progression definition and follow-up duration. Higher age and hypertension were found most importantly associated with AF progression. Age was not significantly associated with AF progression in neither Chapter 2 or 3 and may be explained by the relatively young age in those populations. At present, the only clinical risk score for AF progression is the HATCH score, which is an acronym for the risk factors Heart failure, Age (≥ 75 years), Transient ischemic attack or stroke, Chronic obstructive pulmonary disease and Hypertension.(4) In YOUNG AF, as well as in AF RISK, the HATCH score was univariably associated with AF progression. Individual components of the HATCH score, however, were not. Compared to YOUNG AF and AF RISK, de Vos *et al.* report a much higher cardiovascular event rate and progression rate and, paradoxically, also a higher proportion of 'lone AF' (Table 2). Yet, in most of the major AF risk factors only modest differences can be detected. Apart from differences in clinical characteristics, including a higher age, one of the major differences may be that patients of De Vos *et al.* were included in 2003 and 2004, with less attention for strict risk factor identification and management of cardiovascular comorbidities. This could have resulted in not recognizing risk factors and comorbidities.(21) Those risk factors and comorbidities could therefore have been inadequately treated, which resulted in both cardiovascular events and progression of AF. Adversely, if comorbidities like hypertension are recognized and treated, its effect on AF progression may be more limited compared to untreated subclinical hypertension.(22) And finally, at that time oral anticoagulation was often stopped 4 weeks after sinus rhythm restoration – increasing stroke risk. Important differences can also be detected in the amount of heart failure, most likely due to different definitions of heart failure. The diagnosis of heart failure can be challenging in patients with AF, especially with a preserved ejection fraction: symptoms overlap, echocardiographic parameters are less reliable and NT-proBNP could be elevated in both entities.(23)

Table 2. Direct comparison of baseline characteristics, AF progression and cardiovascular events in the YOUNG AF, AF RISK and the Euro Heart Survey (by De Vos *et al.*)

	YOUNG AF (8)	AF RISK (16)	De Vos <i>et al.</i> 2010 (4)
Number of patients	468	392	1,219
Age at inclusion (years)	49 ± 9	60±11	64±13
Age ≥75 years (%)	0%	8%	Not provided
Women (%)	24%	38%	43%
Paroxysmal AF (%)	70%	82%	100%
Hypertension (%)	44%	51%	62%
Heart failure (%)	9%	52%	21%
Diabetes mellitus (%)	5%	10%	15%
Coronary disease (%)	10%	8%	32%
COPD (%)	4%	7%	11%
Stroke or TIA (%)	6%	8%	9%
Lone AF (%)	11%	4%	17%
AF progression (% per year)*			
Total	2.0%	13%	15%
Paroxysmal only	1.2%	3.4%	15%
Progression predictors	Diastolic blood pressure; left atrial size	Left atrial volume; NT-proBNP; PAI-1	Hypertension, heart failure, age≥75, COPD, stroke/TIA
Event rate (% per year)	2.4%	3.6%	Not provided
Mortality or stroke (% per year)	0.32%	1.3%	5.0%

Abbreviations: AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; NT-proBNP: n-terminal pro-brain natriuretic peptide; PAI-1: plasminogen activator inhibitor-1; TIA: transient ischemic attack.

*Definition of AF progression: YOUNG AF: progression to permanent AF; AF RISK: persistent to permanent AF, paroxysmal to persistent AF or in paroxysmal AF a doubling of AF burden with a minimum >10% AF burden at 1 year; De Vos *et al.*: paroxysmal to persistent AF.

The recently published Atrial Fibrillation Detected by Continuous ECG Monitoring Using Implantable Loop Recorder to Prevent Stroke in High-risk Individuals (LOOP study), included patients at high risk for AF, but without clinical AF.(24) All patients received an implantable loop recorder for long-term rhythm monitoring. In the LOOP study, levels of NT-proBNP were found to be an important factor associated with both incident AF as well as the cumulative amount of AF in the next 3 years. Whether this is due to early signs of (unrecognized) heart failure or merely an expression of a developing atrial cardiomyopathy cannot be fully concluded from their data.

The LOOP study was one of the first studies with the use of implantable loop recorders to detect AF in a population with risk factors for AF, but without known AF. Little is known on exact patterns of AF, except in patients with continuous monitoring with an implanted device like a pacemaker or defibrillator.(25) However, these data cannot be directly translated

to a general AF population without atrial lead. Chapter 4 discussed the first results of the previously mentioned Reappraisal of Atrial Fibrillation: Interaction between hyperCoagulability, Electrical remodelling, and Vascular Destabilisation in the Progression of AF (RACE V) registry.(26) The aim of Chapter 4 was to study AF patterns, their association with clinical characteristics and prevalence of short-term AF progression in 202 patients. Paroxysmal selfterminating AF was found to be a very heterogeneous arrhythmia: one third of the patients did not show any recurrence during 6 months of follow-up. In those with recurrences, AF patterns varied enormously both with respect to duration of AF episodes as well as AF burden. Patients with longer AF episodes and higher AF burden had more and more severe underlying comorbidities. During follow-up, both AF progression and regression were observed. Overall, the average AF burden increased over time. Figure 1 A and B show two the AF patterns of two patients included in RACE V. Both have an identical AF burden of 2.0%, yet the patterns seem entirely different: one with 8 relatively long episodes with long periods without AF. Patient B has 108 episodes of short duration, which may be more trigger dependant. Additionally, Figure 2 shows a patient A with merely nightly AF episodes which may be vagally triggered, as opposed to patient B who seems to have AF almost exclusively during the day. The complexity of AF patterns indicates that the 3P division is a simplification, and more information may be hidden in those AF patterns. Continuous rhythm monitoring may help to characterize the patterns of AF. With the increased popularity and technological improvements, many wearables would make continuous monitoring easier and feasible, which in turn may have a role to personalize and improve AF therapies and monitor treatment effects in the future. This obviously warrants further research.

Sex differences in clinical profile of AF patients are well known, yet not in patients with young-onset AF. Therefore, Chapter 5 focused on sex differences in terms of clinical profile, progression rate and cardiovascular outcome in patients with young-onset AF.(27) In nearly 500 patients, we showed that women had more often familial AF and were more often obese. Men had more frequently coronary heart disease, higher left ventricle mass and a longer PR interval. Despite differences in clinical profile, no difference in AF progression rate or cardiovascular events was observed during follow-up. Yet, a trend towards more events after 3 years of follow-up was observed in women, which might be explained by differences in clinical profile or development of additional risk factors later on. Larger groups with prolonged follow-up may provide additional information whether the observed trend towards more events in women is present. The 2020 European Society of Cardiology AF guidelines are addressing sex differences in AF for the first time.(2) Apart from acknowledging differences in clinical profile, they mainly advocate for more research on sex differences in AF. Therefore, including more women in clinical trials is encouraged to ultimately aim to personalize AF therapy based on sex.

Figure 1. Examples of AF patterns of two patients included in RACE V during 6 months of follow-up. Each day is represented by a bar. White means no AF is present, and blue represents ongoing episodes of AF. AF initiations are shown in red and AF terminations are shown in green. Shaded areas indicate nightly hours. The Y-axis is the time of day and the X-axis represents 6 months of follow-up. Both have an identical AF burden of 2.0%. Patient A shows 8 relatively long episodes, compared to patient B who has 108 episodes with a short duration.

Figure 2 A-B. Examples of AF patterns of two patients included in RACE V during 6 months of follow-up. Each day is represented by a bar. White means no AF is present, and blue represents ongoing episodes of AF. AF initiations are shown in red and AF terminations are shown in green. Shaded areas indicate nightly hours. The Y-axis is the time of day and the X-axis represents 6 months of follow-up. Patient A primarily has AF during nighttime hours, in contrast to patient B who only has AF during the day.

Concluding from the abovementioned Chapters, AF progression, and AF patterns are heterogeneous. Common denominator seems to be the total load of comorbidities, that cause atrial remodelling through several pathways, including fibrosis and inflammation. But the variety of AF progression may also depend on individual susceptibility – as suggested by variability in AF progression rate in a well-controlled animal model.(28) This may be one explanation why preventing progression, or maintaining sinus rhythm as the opposite, can be hard.

Part II – Towards prevention of Atrial Fibrillation Progression

One size fits all strategies rarely are the best. It is therefore important to identify specific groups that may benefit more or less from specific treatment approaches. An obvious step to obtain this is to evaluating sex differences. As a first step, Chapter 6 reports on blood biomarker sex differences to gain insight into different pathophysiological mechanisms in men and women with AF. In the discovery cohort of 384 patients included in AF RISK, 92 cardiovascular biomarkers were measured in blood samples that were drawn in sinus rhythm. Of 92 biomarkers, 3 were higher expressed in man, 2 were higher expressed in women. In the validation cohort consisting of patients included in the RACE V registry, four out of five biomarkers were found to be differently expressed in men and women. In women, levels of both activated leukocyte cell adhesion molecule (ALCAM) and fatty acid binding protein-4 (FABP-4) were significantly higher. In men, matrix metalloproteinase-3 (MMP-3) and myoglobin were found to be significantly higher expressed. These differences in biomarker levels between sexes provide further evidence that the pathophysiological mechanisms differ between sexes, with more prominent vascular remodelling processes being present in men, and more inflammatory responses in women. In addition to clinical parameters, a biomarker approach in several subgroups may aid to identify groups that would benefit more from a specific intervention (e.g. pulmonary vein isolation), as has been done in heart failure previously.(29)

With the aim to improve prognosis and prevent AF progression, the Routine versus Aggressive risk factor driven upstream rhythm Control for prevention of Early atrial fibrillation in heart failure (RACE 3) randomized patients with early persistent AF and early mild to moderate heart failure to targeted or conventional therapy, and showed the superiority of targeted therapy in maintenance of sinus rhythm at 1 year follow-up.(30) In Chapter 7, we investigated factors associated with sinus rhythm maintenance – corrected for randomization strategy at 1 year. Diabetes and prior thromboembolic complications were both negatively associated with sinus rhythm maintenance, i.e. associated with AF progression.(31) Thromboembolic complications may be seen as a consequence of AF, a cause or simply an expression of vascular disease. Diabetes is a well-known risk factor for a wide variety of cardiovascular disease including AF. Intensified glucose control focusing on lowering HbA1c has not shown to be

able to improve outcome. However, the relatively novel Sodium-glucose co-transporter-2 inhibitors have shown only a modest effect on HbA1c levels, but a relevant decrease in cardiovascular risk, including preventing AF, which seems to lower cardiovascular events by different pathways than merely glucose control.(32)

Other than cardiovascular complications, including stroke and heart failure, AF impairs quality of life. Dudink *et al.* has shown AF progression also negatively impacts quality of life.(33) In Chapter 8, we aimed to evaluate the effects of multilevel targeted therapy on quality of life in patients with persistent AF.(20) Main findings included an improved quality of life in patients randomized to targeted therapy of underlying risk factors and comorbidities. Even in patients in receiving targeted therapy in whom sinus rhythm could not be maintained, quality of life improved significantly, compared to conventional therapy. Similar to RACE 3, several Australian trials also showed benefit of upstream therapies and lifestyle changes, albeit especially in obese patients.(34-36) Abed *et al.* showed that obese patients (mean BMI 33 kg/m²) randomized to an aggressive weight loss program (compared to conventional care) showed improvement terms of AF symptoms, AF burden and reducing interventricular septal thickness.(34) Similarly, the REVERSE AF showed that 88% of patients with >10% weight loss were able to regress from persistent AF to paroxysmal or no AF.(36) Main difference with RACE 3 is the fact that patients in RACE 3 were less aggressively motivated to lose weight and increase physical activity, and in turn were unsuccessful in losing weight. On the other hand, three targeted therapies were instituted and maintained in the RACE 3 patients. This indicates that several comorbidities and risk factors can be and probably should be influenced to lower the rate of AF progression (i.e. maintenance of sinus rhythm). In fact, many trials with only one intervention failed to show superior results in preventing AF progression. In order to successfully prevent AF progression, the common denominators seem to be comorbidity control and life-style interventions.

Future perspectives

What combination of interventions results in the best long-term outcome in the individual patients is unclear at this point, as is the recent re-activation of the benefit of rhythm control therapy debate. Since AF progression is associated with more cardiovascular events, using rhythm control to prevent AF could hypothetically improve cardiovascular outcome. However, the Rate Control Versus Electrical Cardioversion (RACE) trial showed no benefit of rhythm over rate control in terms of cardiovascular events.(37) In this study, like AFFIRM, PIAF and AF-CHF, the success of sinus rhythm maintenance was low with only 39% of rhythm control patients in sinus rhythm at the end of the study.(38-40) Almost two decades down the line, in the era where pulmonary vein isolation is an easily accessible and effective treatment option, several trials are ongoing or have just been completed to evaluate whether

rhythm control is able to prevent AF recurrence, or cardiovascular events by preventing progression of the atrial substrate – thereby also preventing AF progression.

STOP-AF showed that cryoballoon ablation as initial therapy was superior to drug therapy for the prevention of atrial arrhythmia recurrence in patients with paroxysmal atrial fibrillation with low adverse event-rates.(41) EARLY-AF showed similar results.(42) The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) randomized 2204 patients to catheter ablation or conventional treatment.(43) Among patients with AF, the strategy of catheter ablation, compared with medical therapy, did not significantly reduce the primary composite end point of death, disabling stroke, serious bleeding, or cardiac arrest. Yet, the study was burdened by a high cross-over rate. Adversely, catheter ablation of AF in a heart failure population was found associated with a lower rate of all-cause mortality and heart failure hospitalization.(44) However, this study included a limited number of patients and was performed in a highly selective population, which limits the generalizability of these results.

The recently published Early treatment of atrial fibrillation for stroke prevention (EAST) trial tested whether an early, comprehensive, rhythm control therapy can improve cardiovascular outcome compared to usual care.(45,46) Primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome. Early rhythm-control therapy was associated with a lower risk of the primary endpoint (hazard ratio, 0.79; 96% confidence interval, 0.66 to 0.94). The positive result of the EAST trial may be explained by the early intervention that limits the recurrence rate of AF and thereby the AF related remodelling and accompanying atrial cardiomyopathy. On top of that, patients included in the EAST study may have had better background therapy regarding risk factor management, which has gained attention over the past decades. EAST started including patients in 2011, compared to RACE which included patients starting in 1998. The EAST trial may be a first step towards rhythm control in patients with a short history of AF, in addition to adequate risk factor management.(30) The initiation of early rhythm control furthermore underlines the need for adequate AF screening.(47) The use of current technology, including smart watches may be able to better detect and monitor AF.(48) As shown by RACE V, patterns differ in paroxysmal AF.(20) This information on AF patterns could be easily accessible by the use of smart watches or other monitoring techniques that allow continuous monitoring, and may help to personalize therapies, maintain sinus rhythm and potentially prevent cardiovascular events.

Both CABANA and EAST aimed for sinus rhythm maintenance (i.e. prevention of AF progression), yet neither specifically act on risk factor management. The Reversal of Atrial Substrate to Prevent Atrial (RASTA AF) trial is currently underway (Clinicaltrials.gov identifier

NCT03682991), which randomizes patients undergoing an ablation procedure for AF to an aggressive risk factor management program versus care as usual. Primary endpoint is recurrence of AF after ablation. This approach could theoretically target the substrate formation by aggressive risk factor management, as well as trigger elimination and substrate modification by pulmonary vein isolation. Ultimately, this could help in preventing progression of AF. (Figure 3)

The 2020 AF guidelines introduced the ABC-approach for each patient with AF.(2) A standing for adequate Anticoagulation therapy for stroke prevention. B referring to Better symptom control (e.g. rate or rhythm control strategy) and finally C standing for Cardiovascular risk factors and concomitant disease, which has been classified as a Class I recommendation for the first time. The importance of the latter is also emphasized in the current thesis. It includes an adequate diagnostic work-up to identify and treat underlying conditions to potentially limit atrial remodelling, thereby aiming to prevent AF progression and potentially improve prognosis. Despite risk factor management already being present in previous guidelines, there is still room for improvement regarding care management. It calls for a structured approach with a coordinated collaboration between general practitioners, physician assistants, cardiologists and other health care professionals. The RACE 4 (Rate Control vs. Electrical Cardioversion Trial 4 – Nurse-led Care vs. Usual-care) showed no difference in cardiovascular outcome in patients treated by a specialized AF clinic compared to usual care by a cardiologist alone.(49) Yet, a secondary analysis showed that experienced AF clinics were indeed able to improve cardiovascular outcome. On top of that, adherence to the guidelines was better in the specialised AF clinics, compared to a cardiologist. Future studies should be focusing on evaluating cardiovascular outcome in different AF management methods, including collaboration with general practitioners (Figure 3). Furthermore, future studies should focus more on personalizing targeted therapies, as one size fits all approaches will benefit some, and harm others. Personalized therapy for AF could be based on the underlying conditions, known sex differences, differences in blood biomarkers or even temporal AF patterns as assessed by continuous rhythm monitoring. In risk factor management in AF, the saying should be 'more is less' as opposed to 'less is more'.

Figure 3 A-B. Hypothetical figure showing the course of AF in patients receiving care as usual (A) and a potential future approach (B), with more focus on health care collaboration, aggressive risk factor management and a personalized medicine approach.

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I. Nederlandse samenvatting

II. Dankwoord

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Nederlandse samenvatting

Atriumfibrilleren (AF) is een veelvoorkomende hartritmestoornis en telt meer dan 250.000 patiënten in Nederland. De verwachting is dat het aantal patiënten met AF gaat toenemen door betere screening, maar ook door vergrijzing, toename van risicofactoren voor AF en verbeterde overleving van patiënten met hart- en vaatziekten. AF is geassocieerd met vele complicaties, waaronder het optreden van een beroerte, hartfalen en dementie.

AF een progressieve ziekte, die veelal aanvalsgewijs (paroxysmaal) begint en geleidelijk hardnekkiger wordt. Aanvallen worden frequenter en langer en kunnen uiteindelijk niet meer gestopt worden met medicatie of een elektrische cardioversie (permanent AF). De overgang van paroxysmaal AF naar aanvallen die meer dan zeven dagen achtereen aanwezig zijn (persisterend AF), wordt AF progressie genoemd. Patiënten die AF progressie vertonen hebben vaker cardiovasculaire complicaties, en dus een slechtere prognose. Onderzoek naar AF progressie wordt vaak beperkt doordat er te weinig gegevens van patiënten beschikbaar zijn. Zo wordt de controle van het hartritme vaak beperkt tot enkele elektrocardiogrammen (ECG's).

Deel I – Atriumfibrilleren progressie

In deel 1 van dit proefschrift wordt gepoogd om het proces van AF progressie beter te begrijpen, met name door te kijken welke factoren hiermee geassocieerd zijn.

In hoofdstuk 2 is gebruikt gemaakt van de database van YOUNG AF: een groep van 468 patiënten die AF ontwikkelden voor hun 60^e levensjaar. Vaak wordt gedacht dat deze patiënten weinig onderliggende risicofactoren hebben voor AF, en daarom een goede prognose hebben. Er is echter weinig onderzoek gedaan naar AF op jongere leeftijd. Het doel van hoofdstuk 2 is om het klinische profiel van deze populatie te beschrijven en daarnaast het optreden van AF progressie en cardiovasculaire complicaties te onderzoeken. De belangrijkste bevindingen van dit hoofdstuk zijn dat negen van de tien patiënten onderliggende risicofactoren hebben voor het krijgen van AF. Gedurende een mediane follow-up van ruim zeven jaar toonde 12% van de patiënten AF progressie (2% per jaar) en 11% een cardiovasculaire complicatie (2% per jaar). Patiënten met AF progressie hadden significant vaker cardiovasculaire complicaties (4.9% vergeleken met 1.9%). AF progressie was geassocieerd met een hogere diastolische bloeddruk en een verdikte linkerhartkamer (linkerventrikelpertrofie).

In hoofdstuk 3 is gekeken naar een preciezere definitie van AF progressie, waarbij toename in het percentage van AF (AF burden) gedurende één jaar ook gerekend is tot AF progressie. Na dit jaar werd tevens gekeken of deze patiënten ook vaker cardiovasculaire complicaties kregen, vergeleken met patiënten zonder AF progressie. Doelen van dit hoofdstuk zijn het vinden van factoren die geassocieerd kunnen worden met AF progressie, waarbij ook ge-

keken is naar een groot panel bloed biomarkers. Daarnaast is ook onderzocht of er bij deze definitie van AF progressie een associatie is met het optreden van cardiovasculaire complicaties. Hiervoor werden in totaal 392 patiënten met een gemiddelde leeftijd van 60 jaar van het AF RISK onderzoek gevolgd. Na één jaar toonde 13% AF progressie. Een hoger linker atrium volume en hogere waarden van de biomarker N-terminaal pro-breinnatriuretisch peptide (NT-proBNP) en lagere waarden van biomarker plasminogeenactivatorremmer type 1 (PAI-1) waren geassocieerd met AF progressie. NT-proBNP is een biomarker die vrijkomt bij rek op het hart en PAI-1 is geassocieerd met afbraak van stolsels. Lagere waarden zijn geassocieerd met een hogere afbraak van bloedstolsels die ook tot ontsteking en fibrose kunnen leiden. In een aanvullende mediane follow-up van 22 maanden hadden patiënten met AF progressie vijfmaal vaker cardiovasculaire complicaties vergeleken met patiënten zonder AF progressie.

In hoofdstuk 4 werd gebruik gemaakt van continue hartritmemonitoring door loop-recorders die geplaatst werden bij patiënten uit het RACE V onderzoek. Het doel van deze interim-analyse van 202 patiënten was om de patronen van boezemfibrilleren te kunnen onderzoeken, met het bijbehorende klinisch profiel van de eerder geconstateerde verschillende patronen. Tevens werd gekeken naar AF progressie op korte termijn. De belangrijkste bevindingen zijn dat paroxysmaal AF zeer heterogene aanvalspatronen laat zien. Een derde van de patiënten had geen AF gedurende de eerste zes maanden. Patiënten met langere AF aanvallen en een hogere AF burden hadden meer en ernstigere onderliggende comorbiditeiten. Tijdens de follow-up werd zowel AF progressie als regressie gezien. De gemiddelde AF burden nam voor de gehele populatie toe tijdens de een jaar durende follow-up.

In hoofdstuk 5a is specifiek gekeken naar de verschillen tussen mannen en vrouwen bij patiënten met AF op jonge leeftijd. Vrouwen hadden vaker familieleden met AF en vaker obesitas. Mannen hadden vaker coronairlijden, meer spiermassa van de linkerhartkamer en PR-interval op het ECG. Ondanks deze verschillen was er geen verschil in het optreden van AF progressie of het aantal cardiovasculaire complicaties tussen mannen en vrouwen. In hoofdstuk 5b worden deze bevindingen besproken door Pluymaekers *et al.*, waarbij zij met name aandacht vragen voor risicofactorbehandeling bij AF, waarbij ook nieuwe risicofactoren aandacht vereisen.

Deel II – Naar het voorkomen van atriumfibrilleren progressie

In deel 2 werd de nadruk gelegd op enkele aspecten die in de toekomst de kans op AF progressie mogelijk kunnen verkleinen. Daarvoor werd in hoofdstuk 6 eerst gekeken naar man-vrouwverschillen in onderliggende processen die ten grondslag liggen aan atriale hermodellering, en daarmee aan AF progressie. Dit werd gedaan door 92 bloed biomarkers te vergelijken in 384 patiënten uit de AF RISK. Waarden van drie biomarkers waren signi-

ficant hoger bij mannen, en twee biomarkers waren hoger bij vrouwen. De bevindingen werden vervolgens gevalideerd in patiënten van het RACE V cohort. Hierbij werden vier van de vijf biomarkers gevalideerd. Bij vrouwen waren waarden van geactiveerd leukocyt celadhesiemolecuul (ALCAM) en vetzuurbindingproteïnase-4 (FABP-4) hoger. Bij mannen waren waarden van matrixmetalloprotease-3 en myoglobine hoger. Deze bevindingen ondersteunen de gedachte dat vasculaire hermodellering vaker een rol speelt bij mannen en inflammatie bij vrouwen.

De RACE 3 studie werd gestart met de hypothese dat agressieve behandeling van onderliggende risicofactoren en leefstijlverbetering uiteindelijk progressie van AF zou kunnen voorkomen en daarmee zou kunnen zorgen voor minder cardiovasculaire complicaties. Hiervoor werden 250 patiënten gerandomiseerd naar de interventiegroep of de controlegroep. Gekeken werd naar behoud van sinusritme na één jaar, wat significant vaker het geval was in de interventiegroep. In hoofdstuk 7 werd gekeken naar factoren die gelinkt zijn aan het behoud van sinusritme in de gehele RACE 3 groep. Eerdere trombo-embolische complicaties en diabetes mellitus waren allebei negatief geassocieerd met het behoud van sinusritme.

Hoofdstuk 8a beschrijft de effecten van agressieve risicofactormanagement en leefstijlinterventies op kwaliteit van leven in 230 patiënten uit de RACE 3 studie. Vergeleken met de controlegroep toonde de interventiegroep een significante verbetering in fysiek functioneren, algehele gezondheidswelbevinden en fysieke rolbeperkingen. Vergelijkbare effecten werden ook gezien in een subgroepanalyse van alle patiënten die in AF waren na één jaar follow-up. In hoofdstuk 8b worden deze resultaten becommentarieerd door Chen *et al.* Hierbij wordt besproken dat het combineren van de verschillende interventies het lastig maakt om de rol van elke individuele therapie te evalueren, maar dat het netto-effect positief is. De vraag of de strategie ook cardiovasculaire complicaties kan voorkomen op de lange termijn.

Toekomstig perspectief

Dit proefschrift probeert inzicht te geven van de onderliggende factoren die geassocieerd zijn met progressie van AF en hoe dit mogelijk in de toekomst voorkomen kan worden. De titel "Atrial fibrillation beyond the electrocardiogram" ("atriumfibrilleren voorbij het electrocardiogram") heeft hierbij een tweeledige betekenis. Enerzijds dat AF niet enkel als één entiteit gezien moet worden, en anderzijds dat bij AF verder gekeken moet worden naar de vele potentiële onderliggende risicofactoren die adequate therapie vereisen.

De vraag is welke strategie het beste is om AF progressie te voorkomen. RACE 3 toonde een positief resultaat bij een mix van medicatie en lifestyle-interventies, waarbij patiënten

bijvoorbeeld niet slaagden een significante gewichtsreductie te bewerkstelligen. Dit is in tegenstelling tot vele Australische onderzoeken, waarbij agressieve gewichtsreductie in korte tijd effectief bleek.

Daarnaast is de discussie omtrent ritme versus hartfrequentie strategie opnieuw actueel als het gaat om het voorkomen van cardiovasculaire complicaties en AF progressie. Uit eerder onderzoek bleek ritmecontrole geen voordeel te hebben in het voorkomen van cardiovasculaire complicaties, bovendien was ritmecontrole vaak niet succesvol op lange termijn. Huidige onderzoeken lijken hier weer positieve resultaten van te laten zien – mogelijk door de algehele verbetering in risicofactormanagement en de toegenomen mogelijkheden om succesvol ritmecontrole te bewerkstelligen. Daarnaast is de mogelijkheid om AF patronen beter te bestuderen door verbetering van de hartritmemonitoring, o.a. door het gebruik van smartwatches en andere wearables, een mogelijkheid om de behandeling van AF beter af te stemmen op individueel niveau.

Naast het onderzoeken van succesvolle behandelingen voor het voorkomen van AF progressie, is het ook van belang dat de zorg op de juiste wijze geleverd wordt. De RACE 4 studie toonde aan dat ervaren atriumfibrilerenpoli's betere naleving van de behandelrichtlijnen kunnen bewerkstelligen, vergeleken met behandeling door enkel een cardioloog. Door continue verandering van de organisatie van de zorg, waarbij steeds meer zorg verplaatst naar de eerste lijn, is het tevens van belang te onderzoeken hoe cardiologen en huisartsen uit de eerste lijn beter kunnen samenwerken om samen AF progressie te kunnen voorkomen.

Toekomstige studies zullen de rol van ritmecontrole, risicofactormanagement (inclusief leefstijlinterventies) en de algehele organisatie van de zorg met bijvoorbeeld atriumfibrilerenpoli's en samenwerkingen met huisartsen verder moeten onderzoeken. Samen met informatie over specifieke AF patronen zou uiteindelijk de beste combinatie van therapieën gevonden moeten worden, gepersonaliseerd per patiënt, om hiermee uiteindelijk de prognose van patiënten met AF te kunnen verbeteren.

Dankwoord

Hoewel het proefschrift klaar is, moeten de belangrijkste pagina's nog geschreven worden: het dankwoord. Niet alleen omdat dit de meest gelezen pagina's zijn, maar ook omdat het cliché waar is dat je promoveren nooit alleen doet.

Allereerst wil ik mijn eerste promotor prof. dr. I.C. van Gelder bedanken. Beste Isabelle, in 2015 stuurde ik een mailtje om meer informatie te krijgen over het RACE V project. Het gesprek dat volgde was meteen een sollicitatiegesprek, waarbij ik al snel instemde met een promotietraject. Tijdens mijn promotie was het opzetten van de RACE V een belangrijke taak. Nu ik dit van dichtbij heb meegemaakt, is de bewondering des te groter als ik zie welke studies jullie allemaal succesvol verricht hebben. Tijdens mijn promotie heb ik ook de kans gehad om aan meerdere studies mee te werken die uiteindelijk in de *New England Journal of Medicine* gepubliceerd zijn, zoals de ACWAS en de EAST. Dit bewijst dat wetenschap bij jullie op het hoogste niveau beoefend wordt. Je gedrevenheid en vermogen om het maximale uit anderen te halen is groot, en ik hoop in de toekomst nog vaker samen te werken.

Mijn tweede promotor prof. dr. M. Rienstra. Beste Michiel, via jou ben ik uiteindelijk het ritmeonderzoek ingerold nadat je mijn zaalsupervisor was tijdens mijn semi-arts stage. Oorspronkelijk ben je begonnen als mijn co-promotor en eerste aanspreekpunt. Maar met de jaren is je agenda behoorlijk drukker geworden en ben je nu geen co-promotor meer, maar mijn tweede promotor. Jouw doelgerichtheid en hoge mate van efficiëntie zijn aanstekelijk, en ik hoop er de komende jaren nog veel van te kunnen leren. En wie weet zullen we ooit nog burens worden op Curaçao.

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Prof. G. Dwivedi. Dear Girish, you came from India to England, and from England to Canada where our roads crossed. Your drive is contagious and I wish you all the best with your professorship in Australia. And as promised, I'll meet you there again some time.

dr. Chadi Ayoub and dr. Manuja Premaratne. Dear Chadi and Manuja, you made my stay in Canada a lot more fun, and you helped me a lot, both in and outside the hospital. All the best in the States and Australia.

Mijn paranimfen. Beste Wouter, je schreef al eerder dat wij het bewijs zijn dat hartfalen en ritme goed samengaan – dat hebben we recent nog bewezen met een potje 30 seconds. Ruim 2 jaar geleden was ik jouw paranimf, en vandaag zijn de rollen omgedraaid. Op nog vele gezellige avonden en veel geluk met Elles! Beste Dirk, we kennen elkaar al ruim 17 jaar en ik vind het fijn dat je vandaag mijn paranimf wil zijn. Ik ben geen voorstander van uithuwelijken, maar dat je dochter Veerle precies op de verjaardag van Boris geboren is, lijkt me toch wel voorbestemd. Veel geluk samen met Linda!

Alma, Audrey, Daniëlle & Minke. Zichtbaar en onzichtbaar zorgen jullie ervoor dat alles binnen de afdeling soepel loopt, zo ook bij de ondersteuning tijdens mijn promotietraject, dank hiervoor. Net als de afdeling cardio research, die veel geholpen heeft tijdens het opstarten en lopend houden van alle studies.

De steering committee, sponsors, includerende ziekenhuizen, patiënten en andere betrokkenen bij de RACE V studie wil ik bedanken voor hun inzet. Hoewel het soms een gevulde dagtaak was om alles op te starten en lopende te houden, heb ik het met veel plezier gedaan.

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IV

Biography

Ruben René de With was born on June 9th 1989 in Leeuwarden. He grew up in Hoogeveen where he attended the Roelof van Echten College, which he finished in 2007. Immediately after, he started medical school at the University of Groningen. After finishing clinical rotations at the University Medical Center Groningen and Medical Center of Leeuwarden, he performed his scientific internship at the University of Ottawa Heart Institute (Canada) under supervision of prof. B.J. Chow. Ruben obtained his MD in 2015 and subsequently started his PhD at the group of prof. dr. I.C. van Gelder and prof. dr. M. Rienstra, with focus on progression of atrial fibrillation. He coordinated several studies, including the RACE V, AF-RISK and EAST. His research was presented at several international congresses, including European Heart Rhythm Association congress 2018 in Barcelona and American Heart Association congress 2018 in New Orleans. The results of his PhD are presented in the current thesis entitled "Atrial Fibrillation Beyond the Electrocardiogram – towards understanding and preventing progression", which he aims to defend September 22nd 2021.

From 2019 to 2021, he performed his residency in internal medicine at the Medical Center of Leeuwarden (dr. M. Hoogendoorn) and he is currently working as a cardiology resident at the University Medical Center Groningen (dr. A.H. Maass). He lives in Groningen with his wife Carlijn and son Boris.