Structured Management, Symptoms, Health- related Quality of Life and Alcohol in Patients with Atrial Fibrillation

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Till Alena, Tíbelio, Leonora och Ilona

We know accurately only when we know little,
with knowledge doubt increases.
(Johann Wolfgang von Goethe, 1749-1832)

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ABSTRACT

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting at least 2.9 % of the Swedish population. Although AF is associated with increased risk of ischaemic stroke, there have been many reports on the underuse of oral anticoagulants (OAC) and non-adherence to guidelines in other areas as well. AF is also associated with disabling symptoms and decreased health-related quality of life (HRQoL), but some patients are asymptomatic. The reasons for the great variation of symptoms remain unclear. Furthermore, although research on AF has increased, studies have mainly focused on treatment, while studies on risk factors, such as alcohol consumption, have only recently gained attention.

The aim of this thesis was to investigate whether structured care of patients with AF could improve guideline adherence and HRQoL compared to standard care, and to determine which factors affect symptoms and HRQoL prior to treatment with radiofrequency catheter ablation (RFA), as well as improvement after RFA. Furthermore, we aimed to examine the associations of alcohol consumption with cardiac biomarkers, the size of the left atrium (LA), and re-ablation.

This thesis is based on two studies. In the 'Structured Management and Coaching – Patients with Atrial Fibrillation' (SMaC-PAF) study, 176 patients were recruited to the intervention group, receiving a structured follow-up programme, and 146 patients were recruited to the control group, receiving standard care. The two groups were compared in regard to adherence to guidelines and patient-reported outcome measures (PROMs) assessing symptoms and HRQoL.

In the 'Symptom burden, Metabolic profile, Ultrasound findings, Rhythm, neurohormonal activation, haemodynamics and health-related quality of life in patients with atrial Fibrillation' (SMURF) study, 192 patients referred for their first RFA of AF were included. PROMs questionnaires were filled out, echocardiography was performed, and cardiac biomarkers were analysed. Alcohol consumption was assessed through interview and through analysis of ethyl glucuronide in hair (hEtG). AF recurrence and re-ablation within 12 months were examined.

In the first study, after one year, 94% (n=112) and 74% (n=87) of patients with indication for OAC in the intervention and the control groups, respectively, actually received treatment with OAC ($p < 0.01$). Both groups improved in anxiety and HRQoL scores over the year, but in the interven-

tion group, arrhythmia-specific symptoms were less frequently experienced and the SF-36 scores were more similar to the norm population.

In the second study, the most important predictors of arrhythmia-related symptoms and HRQoL prior to RFA were anxiety, depression and low-grade inflammation, while frequent AF attacks prior to RFA, freedom from AF recurrence after RFA, female gender, no enlarged LA, absence of diabetes, and the presence of heart failure were significant predictors of improvement in symptoms and HRQoL after RFA. Men with hEtG ≥ 7 pg/mg had higher levels of cardiac biomarkers, larger LA volumes and a higher re-ablation rate than men with hEtG < 7 pg/mg, while no such findings were present in women.

In conclusion, structured management was superior to standard care in patients with AF, emphasising the importance of structured care, adjusted to local requirements, in order to improve the care and well-being of patients with AF. Although the reasons for the great variety of symptoms in patients with AF still are not yet fully understood, it seems that psychological factors and inflammation play a role, and that improvement in symptoms and HRQoL after RFA is influenced by gender, diabetes, heart failure, LA size and the frequency of attacks before, as well as freedom from AF after, RFA. Finally, alcohol consumption corresponding to hEtG ≥ 7 pg/mg was associated with higher levels of cardiac biomarkers, larger LA size and a higher rate of re-ablation in men, implying that men with an hEtG-value ≥ 7 pg/mg have a higher risk for LA remodelling that could potentially lead to a deterioration of the AF situation.

SVENSK POPULÄRVETENSKAPLIG SAMMANFATTNING

Ca 300 000 svenskar beräknas lida av förmaksflimmer, en sjukdom som leder till att hjärtat slår oregelbundet och oftast för snabbt. Förmaksflimmer ökar risken för stroke, dvs. blodpropp i hjärnan, vilket kan förebyggas med proppförebyggande läkemedel, men som använts i alldeles för liten utsträckning. Utöver förebyggande av stroke, består behandlingen också av att hålla förmaksflimmerattacker borta, och på så sätt förbättra symtom. Det kan åstadkommas med hjälp av ablation, som innebär att en isoleringslinje mellan förmaken och lungvenerna åstadkommes med hjälp av värmeenergi. De senaste åren har forskning kring förmaksflimmer ökat markant, men orsaken till varför vissa har uttalade symtom medan andra inte känner något, kvarstår dock som något av ett mysterium. Forskningen har dessutom framförallt fokuserat på behandling snarare än på förebyggande åtgärder och riskfaktorer, så som alkoholkonsumtion.

Syftet med denna avhandling var att undersöka huruvida ett strukturerat omhändertagande av patienter med förmaksflimmer kan förbättra behandling samt livskvalitet, samt att undersöka vilka faktorer som påverkar symtom och livskvalitet vid behandling med ablation. Vidare var syftet att undersöka eventuella samband mellan alkoholintag och hjärt-specifika blodprover, vänster förmaksstorlek samt upprepad ablation. Alkoholintaget värderades genom analys av koncentrationen av det alkohol-specifika ämnet ethyl glucuronide i hår.

Sammanfattningsvis ledde det strukturerade omhändertagandet, jämfört med gängse rutin, till en klart förbättrad behandling enligt riktlinjer, färre sjukdomsspecifika symtom samt livskvalitet som i högre utsträckning nådde normalbefolkningens. Även om gåtan gällande den stora symtomvariationen ännu till fullo inte är löst, visar denna studie att psykologiska faktorer som ångest och depression, samt inflammation, verkar spela roll. Störst förbättring av symtom och livskvalitet efter ablation ses hos de med många förmaksflimmerattacker före ablation, frihet från flimmerattacker efter ablation, kvinnor, de utan förstorat vänster förmak, de utan diabetes, samt de med hjärtsvikt. Slutligen var ethyl glucuronide mer än 7 picogram per milligram hos män, en nivå tydandes på måttlig konsumtion av alkohol, associerat med högre nivåer av hjärt-specifika blodprover, större förmak och större andel upprepade ablationer, tyndes på att män med denna grad av alkoholkonsumtion har en större risk för förändringar i vänster förmak vilket kan förvärra sjukdomen.

LIST OF PAPERS

The thesis is based on the papers listed below, which will be referred to in the text by their Roman numbers.

- I. Barmano N, Walfridsson U, Walfridsson H, Karlsson J-E. Structured Care of Patients with Atrial Fibrillation Improves Guideline Adherence.
Journal of Atrial Fibrillation. 2016 Dec;**9**(4):1498.
doi:10.11529/jafib.1498.
- II. Charitakis E, Barmano N, Walfridsson U, Walfridsson H. Factors Predicting Arrhythmia-Related Symptoms and Health-Related Quality of Life in Patients Referred for Radiofrequency Ablation of Atrial Fibrillation
JACC: Clinical Electrophysiology. 2017 May;**3**(5):494-502
doi: 10.1016/j.jacep.2016.12.004
- III. Barmano N, Charitakis E, Kronstrand R, Walfridsson U, Karlsson JE, Walfridsson H, Nystrom FH.
The Association between Alcohol Consumption, Cardiac Biomarkers, Left Atrial Size and Re-ablation in Patients with Atrial Fibrillation Referred for Catheter Ablation.
PLoS ONE, 2019 Apr;**14**(4): e0215121.
<https://doi.org/10.1371/journal.pone.0215121>
- IV. Barmano N, Charitakis E, Karlsson JE, Nystrom FH, Walfridsson H, Walfridsson U.
Predictors of Improvement in Arrhythmia-specific Symptoms and Health-related Quality of Life after Catheter Ablation of Atrial Fibrillation.
Clinical Cardiology. 2019 Feb;**42**(2) :247-255.
doi: 10.1002/clc.23134

ABBREVIATIONS

1Y	One year
4M	Four months
5-HIAA	5-hydroxyindole-3-acetic acid
5-HTOL	5-hydroxytryptophol
β-HEX	β-hexosaminidase
AAD	Anti-arrhythmic drugs
ACEi	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blocker
ARREST-AF	Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation study
AST	Aspartate aminotransferase
ASTA	The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia
B	Baseline
BMI	Body Mass Index
BP	Bodily pain
CABANA	Catheter Ablation versus Anti-arrhythmic Drug Therapy in Atrial Fibrillation study
CASTLE-AF	Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation
CDT	Carbohydrate-deficient transferrin
CHA ₂ DS ₂ -VASc	Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65-74, Sex category (i.e. female gender)
CHADS ₂	Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke (doubled)
CI	Confidence interval
CKD	Chronic kidney disease
CT	Computed tomography

CV	Coefficient of variation
DC-cardioversion	Direct Current - cardioversion
ECG	Electrocardiogram
EF	Ejection fraction
EHRA	European Heart Rhythm Association
EQ-5D	EuroQol Health Questionnaire, five dimensions
EQ-VAS	EuroQol Health Questionnaire, Visual Analogue Scale
ER	Emergency room
ES	Effect size
EtG	Ethyl glucuronide
EtS	Ethyl sulphate
FAEEs	Fatty acid ethyl esters
FU	Follow-up
GFR	Glomerular filtration rate
GH	General health
GT	Glutamyl transferase
HADS	Hospital Anxiety and Depression Scale
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age>65), Drugs/alcohol
HDL	High density lipoprotein
hEtG	Ethyl glucuronide in hair
HRQoL	Health-related Quality of Life
hsCRP	High-sensitive C-reactive protein
LA	Left atrium
LAV	Left atrial volume
LAVI	Left atrial volume index
LDL	Low density lipoprotein
LV	Left ventricle
MANTRA-PAF	Medical Anti-arrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation
MCS	Mental component summary
MCV	Mean corpuscular volume
MH	Mental health
MR-proADM	Mid-regional portion of pro-adrenomedullin

MR-proANP	Mid-regional fragment of pro atrial natriuretic peptide
NA	Not applicable
Ns	Non-significant
NT-proBNP	N-terminal pro B-type natriuretic peptide
NYHA	New York Heart Association
OAC	Oral anticoagulants
PCS	Physical component summary
PEths	Phosphatidylethanol species
PF	Physical functioning
PROMs	Patient-reported outcome measures
QoL	Quality of life
RA	Right atrium
RACE	Rate Control Efficacy in Permanent AF study
RE	Role-emotional
RFA	Radiofrequency catheter ablation
RP	Role-physical
RV	Right ventricle
RVDP	Right ventricular diastolic pressure
RVSP	Right ventricular systolic pressure
SD	Standard deviation
SF	Social functioning
SF-12	The 12-Item Short Form Health Survey
SF-36	The Medical Outcomes Study 36-Item Short-Form Health Survey
SMaC-PAF	Structured Management and Coaching – Patients with Atrial Fibrillation study
SMURF	Symptom burden, Metabolic profile, Ultrasound findings, Rhythm, neurohormonal activation, haemodynamics and health-related quality of life in patients with atrial Fibrillation study
SoHT	Society of Hair Testing
SR	Sinus rhythm
TEE	Transoesophageal echocardiography
TG	Triglycerides
TIA	Transient ischaemic attack
TSA	Total serum sialic acid

TTE	Transthoracic echocardiography
UK	United Kingdom
US	United States
VT	Vitality
WHO	World Health Organization

INTRODUCTION

Atrial Fibrillation

History

The oldest description of atrial fibrillation (AF) might be the Assyrians' description of symptoms that probably included AF¹, or perhaps the one found in "The Yellow Emperor's Classic of Medicine"². Although it is said to have been written by the Chinese emperor Huangdi around 2600 BC, it is more likely to be a compilation of writings of several authors dating from about 300 BC³. In the recorded history, William Harvey was probably the first to describe "fibrillation of the auricles" in animals in 1628². Other notable physicians who described an irregular pulse that most likely was AF were Stokes and Wenckebach in the 19th century⁴.

After the invention of the electrocardiograph in 1900, Lewis was the first to record an electrocardiogram (ECG) in a patient with AF². The mechanisms remained controversial until 1970, when it was recognised that the irregular ventricular beating was a response to "randomly spaced atrial impulses of random strength reaching the atrioventricular node from random directions"². Since then, there has been an exponential increase in publications concerning AF, especially in the last two decades, which has led to remarkable improvements not only in understanding the mechanisms behind AF, but also the treatment of it⁵ (Figure 1).

Figure 1. Annual number of search hits in PubMed using the term "atrial fibrillation", from 1945-2018.

File obtained from PubMed (<https://www.ncbi.nlm.nih.gov/pubmed/>) on 18th February 2019.

Epidemiology

AF is the most common cardiac arrhythmia in the world, affecting at least 2.9% of the Swedish population, not counting “silent AF”⁶. It has a significant impact on healthcare costs, accounting for 1% of the total healthcare costs in the United Kingdom (UK), and between 6-26 billion dollars in the US for 2008, mainly due to hospitalisations and stroke^{7,8}.

The prevalence increases with age and reaches 9-14% in the population above 80 years (Figure 2)^{6,9}. Accordingly, the prevalence differs in different regions depending on the mean age in that region. The prevalence is higher in men, and more common in developed countries than in developing countries (Figure 3)⁷. Besides ethnic background, better surveillance could be a reason for the global variation⁷.

Figure 2. Prevalence of diagnosed atrial fibrillation in relation to age on 31 December 2010

Reprinted from Friberg et al. *JIM*, 2013; 274(5): 461-468, with permission.

Figure 3. World map showing the age-adjusted prevalence rates (per 100 000 population) of atrial fibrillation in the 21 Global Burden of Disease regions.

Reprinted from Chugh et al. *Circulation*, 2014;**129**:837-47, with permission.

Definitions

AF is characterised by disorganised atrial depolarisations leading to a rapid chaotic rhythm without effective atrial contraction¹⁰. The diagnosis of AF, according to European and American guidelines, requires rhythm documentation through ECG, fulfilling the following typical characteristics of irregular RR intervals (when atrioventricular conduction is present) and absence of discernible distinct p-waves (and additionally irregular atrial activity in the American guidelines)^{8,11}. An episode of at least 30 seconds is diagnostic by accepted convention⁸.

Pathophysiology

AF is a complex arrhythmia, requiring in general both a trigger to initiate the arrhythmia and a substrate/driver to maintain it^{10,12}. As shown by Haisaguerre et al., cardiomyocytes with enhanced electrical activity located in the pulmonary vein sleeves are the most important source for ectopic beats initiating paroxysms of AF^{10,13}. The more AF persists, the more non-pulmonary vein sources become important¹⁰.

AF can be maintained by a driver mechanism which may be rapid focal ectopic firing or by re-entry circuits (single or multiple)^{10,12}. Re-entry requires a substrate (modified atrium) and a trigger (usually an ectopic beat)¹⁰. The excitation advances through the susceptible substrate with a circular or a spiral wave front (rotor)¹⁰. Should the arrhythmia sustain, it will lead to remodelling (electric, structural and neural/autonomic) of the atrium, which in turn further promotes the arrhythmia¹². However, upon termination of the arrhythmia, the process is reversible (reverse remodelling)¹².

Whereas electric remodelling can occur within hours, days or weeks, structural remodelling occurs on a longer time scale over months or years, and is associated with age and other underlying conditions¹⁰. Furthermore, the autonomic nervous system is also an important part of the remodelling process¹².

Although much has been learned and understood concerning the mechanisms behind AF in the last few decades, much has still to be learned in order to improve preventive and therapeutic measures. For example, several genetic variants are known to predispose to AF, and genetic information may be an important tool in the future in order to customise treatment to a single individual⁸.

Clinical Presentation and Screening for Atrial Fibrillation

AF can present itself in different ways. For example, a patient can suffer from palpitations, chest pain, shortness of breath or dizziness. In some, an embolic complication may be the first symptom. In others, AF can be detected en passant.

Silent AF is common^{8,14}, raising the issue of screening for AF in order to prevent stroke. Sequential stratified ECG monitoring in stroke survivors has been able to detect AF as an embolic cause in 24%¹⁵. The European guidelines recommend screening in patients that have suffered from a transient ischaemic attack (TIA) or stroke, in patients with cardiac devices (interrogation for atrial high rate episodes), and opportunistic screening in patients above 65 years of age⁸. Concerning systematic screening in the general population, AF meets the World Health Organization (WHO) criteria for screening of a disease. In the large STROKESTOP study, in which a general Swedish population aged 75-76 years were screened for AF through intermittent ECG recording using a hand-held ECG trans-telephonic recorder for two weeks, 5.1% of the screened population were found to have untreated AF¹⁶. A five-year follow-up (FU) showed that the incidence of stroke declined to a greater extent compared to a control area in which screening was not performed¹⁷ and the screening method was found to be cost-effective¹⁸. Currently, according to the European guidelines, screening of patients >75 years or those at high stroke risk may be considered (Class IIb recommendation with a B level of evidence)⁸.

Classification

In most patients, AF progresses from short infrequent episodes to longer and more frequent episodes and finally to a permanent condition⁸. In a few patients, AF will remain paroxysmal over several decades⁸. Based on the presentation and duration of AF episodes, AF can be classified into five types⁸:

1. First diagnosed AF: AF that is diagnosed for the first time
2. Paroxysmal AF: AF that terminates spontaneously within seven days (most often within 48 hours) or is cardioverted within seven days
3. Persistent AF: AF that lasts longer than seven days
4. Long-standing persistent AF: Continuous AF lasting for more than one year when a decision is made to adopt rhythm control therapy
5. Permanent AF: AF that is accepted by the patient and the physician, without further attempts to restore sinus rhythm (SR)

Consequences

AF is independently associated with a doubled risk of all-cause mortality, increased risk of stroke and heart failure¹⁹. Cognitive impairment with white matter lesions and decreased health-related quality of life (HRQoL) are also common in patients with AF⁸. Furthermore, 10-40% of AF patients are hospitalised every year⁸.

Management

The management of AF aims to improve symptom burden and HRQoL, and to prevent adverse events. This is accomplished through four main treatment measures: risk factor modification, stroke prevention, rate control, and rhythm control²⁰.

Risk Factor Modification

Established risk factors for the development of AF, of which some are modifiable and some are not, include age, gender, heart failure, previous myocardial infarction, hyperthyroidism, chronic obstructive pulmonary disease, chronic kidney disease, valvular heart disease, myocardial infarction, hypertension, diabetes mellitus, obesity, smoking, alcohol consumption and habitual vigorous exercise^{8,21}. Although AF prevention in the form of assessment of modifiable risk factors is a cornerstone in the management of AF, research in this field has been scant. However, the field is an emerging research area, and studies have demonstrated improvement in AF burden and outcomes following radiofrequency catheter ablation

(RFA) via weight management and cardiorespiratory fitness, which might also improve HRQoL²². In the ‘Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation’ (AR-REST-AF) study, treatment of several risk factors was included as elements of an aggressive cardiovascular risk factor management programme, leading to improved AF-related outcomes²³.

Stroke Prevention

The Framingham study showed that 15% of all strokes, and 25% of all strokes after the age of 80, were due to AF²⁴. When stroke occurs in association with AF, mortality is higher and disability greater²⁵. The risk of stroke in patients with paroxysmal or persistent AF is as great as for those with permanent AF, and absence of symptoms does not reduce the risk of thromboembolism²⁶⁻²⁸. So far, anticoagulation is the only intervention that has proven to have an impact on mortality in patients with AF⁸. Although AF per se increases the risk of stroke, the risk is largely dependent on concomitant risk factors. Previous guidelines recommended the use of the CHADS₂-score, while current guidelines recommend the use of the CHA₂DS₂-VASc-score for the decision-making on whether a patient should be treated with OAC or not (Table 1 and Table 2)^{8,11,29}.

Table 1. The CHA₂DS₂-VASc-score

Risk factor	Score
C - Congestive heart failure/LV dysfunction	1
H - Hypertension	1
A₂ - Age ≥75	2
D - Diabetes mellitus	1
S₂ - Stroke/TIA/thrombo-embolism	2
V - Vascular disease	1
A - Age 65–74	1
Sc - Sex category (i.e. female gender)	1

Note 1: The CHA₂DS₂-VASc-score is a stroke risk classification scheme, using a points system ranging from zero to nine. Congestive heart failure, hypertension, diabetes, vascular disease, age 65-75 years, and female gender give one point each, while age above 75 and previous stroke/TIA or other arterial embolism give two points. In the previous CHADS₂-score, vascular disease, age-65-74, and female gender were not included as risk factors, and only previous stroke/TIA gave two points, yielding a score ranging from zero to six.

LV, left ventricle; TIA, transient ischaemic attack

Table 2. Stroke risk according to CHA₂DS₂-VASc-score

Total score	Adjusted stroke rate (%/year) according to CHA ₂ DS ₂ -VASc-score
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

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In patients with a CHA₂DS₂-VASc-score of 0, or female gender as a sole risk factor, it is reasonable to omit OAC, while OAC is recommended in men with a score ≥ 2 and in women with a score ≥ 3 ^{8,11}. A score of 1 in men and 2 in women indicates that OAC should be considered, considering individual characteristics and patient preferences⁸. Simultaneously, the bleeding risk has to be taken into consideration, in which the HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly (age >65), Drugs/alcohol) score can be used⁸. However, the risk factors overlap, and the HAS-BLED should not be used to withhold OAC, but rather to identify and correct treatable factors⁸.

Rate Control

Untreated AF often results in a high ventricular rate. Most AF patients therefore require medical treatment that reduces the ventricular rate, which improves symptoms and HRQoL, and reduces morbidity and the likelihood of developing tachycardia-induced cardiomyopathy¹¹. An optimal target heart rate that applies to every patient with AF cannot be given, but should rather be individualised. In the 'Rate Control Efficacy in Permanent AF' (RACE) study, there was no difference in a composite of clinical events with a lenient heart rate target <100 b.p.m. compared to a strict heart rate target <80 b.p.m.³⁰. However, some patients will remain symptomatic although the heart rate is controlled, requiring additional measures.

Pharmacological rate control can be achieved with beta-blockers, digoxin and calcium-channel blockers⁸. Should pharmacological treatment have no effect in the setting of an emergent unstable patient, urgent cardioversion should be considered⁸. If pharmacological treatment is insufficient to control rate and symptoms in the long term, and if rhythm control

therapy is excluded as a treatment option, atrioventricular node ablation with implantation of a pacemaker can be an alternative^{8,11}.

Rhythm Control

Rhythm control means that the aim is to restore and maintain SR. Restoration of SR can be achieved either through pharmacological cardioversion, or through electrical direct current (DC) cardioversion, which can be applied both in the acute setting and electively. Repetition of DC-cardioversions as a means to control the rhythm is rarely effective in the long term and should only be an alternative for those with infrequent AF episodes. Instead, consideration of different options to maintain SR should be carried out early in the management of a patient with paroxysmal or persistent AF.

Maintaining SR can be achieved through medication with anti-arrhythmic drugs (AAD), or via catheter ablation with isolation of the pulmonary veins, most commonly achieved with radiofrequency energy^{8,11,31}. Treatment with AAD is a non-invasive rhythm control method, but the disadvantages with AADs are the safety issues, and their relatively low capacity to maintain SR^{32,33}. RFA of AF is more effective than AAD in maintaining SR and in improving HRQoL³⁴⁻³⁹, and is in general recommended when AAD has failed, but can be recommended as a first-line therapy in selected patients⁸.

No study has so far shown advantages of rhythm control over rate control concerning mortality, bleeding or thromboembolic events in a general AF population⁴⁰⁻⁴⁴. Although the 'Catheter Ablation versus Standard Conventional Therapy in Patients with Left Ventricular Dysfunction and Atrial Fibrillation' (CASTLE-AF) study showed beneficial results with RFA over AAD, this was a specific AF population⁴⁵. The recently published 'Catheter Ablation versus Anti-arrhythmic Drug Therapy in Atrial Fibrillation' (CABANA) trial did not show superiority of RFA over AAD in the intention-to-treat analysis of the primary end point (a composite of death, disabling stroke, serious bleeding, or cardiac arrest)⁴⁶. However, in a secondary end point analysis concerning death or cardiovascular hospitalisation, and in the treatment received and per protocol analysis of the primary endpoint, RFA was superior to AAD⁴⁶. The results are thus exploratory, demanding further studies in order to be clarified. One must therefore keep in mind that rhythm control therapy is still mainly aimed at improving symptoms and HRQoL.

Adherence to Guidelines

In the first decade of this century, there were several studies showing a discrepancy between guideline recommendations and actual management of patients with AF in an everyday clinic, especially concerning stroke prevention⁴⁷⁻⁵⁰. Reasons for non-adherence were underestimation of stroke risk, exaggeration of bleeding risk, lack of knowledge of guidelines and trials, reluctance to change current antithrombotic therapy, high age, and patients unwilling to medicate with OAC^{27,49-52}.

Structured Care of Atrial Fibrillation

In order to improve the care of patients with AF, different approaches in dedicated structured care models have been tested in recent years⁵³⁻⁵⁷. At the time of planning of the studies that constitute this thesis, no such study had been conducted. The studies have shown positive results, with the greatest impact in a study by Hendriks et al., leading to a recommendation for an integrated approach with structured organization of care and FU in all patients with AF in the current European guidelines (Figure 4)⁸.

Figure 4. Fundamentals of structured care of atrial fibrillation patients.

Patient involvement	Multidisciplinary teams	Technology tools	Access to all treatment options for AF
<ul style="list-style-type: none"> - Central role in care process - Patient education - Encouragement and empowerment for self-management - Advice and education on lifestyle and risk factor management - Shared decision-Making 	<ul style="list-style-type: none"> - Physicians (general physicians, cardiology and stroke AF specialists, surgeons) and allied health professionals work in a collaborative practice model - Efficient mix of communication skills, education, and experience 	<ul style="list-style-type: none"> - Information on AF - Clinical decision support - Checklist and communication tools - Used by healthcare professionals and patients - Monitoring of therapy adherence and effectiveness 	<ul style="list-style-type: none"> - Structured support for lifestyle changes - Anticoagulation - Rate control - Anti-arrhythmic drugs - Catheter and surgical interventions (ablation, LA appendage occluder, AF surgery etc.)
<i>Informed, involved, empowered patient</i>	<i>Working together in a multidisciplinary chronic AF care team</i>	<i>Navigation system to support decision-making in treatment team</i>	<i>Complex management decisions underpinned by an AF Heart Team</i>

Note: Fundamentals of structured care of patients with atrial fibrillation according to the European guidelines.

AF: Atrial fibrillation; LA: Left atrium

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Symptoms and Health-related Quality of Life

Symptoms

A symptom is defined as “the subjective evidence of disease or physical disturbance observed by a patient”⁵⁸. In contrast to signs of a disease, which can be objectively assessed (such as heart murmurs, or fever), symptoms can only be known through the patient’s communication⁵⁸. Symptoms can be produced by the disease itself, by the treatments against the disease, or by comorbid medical conditions⁵⁸. The primary objective of many treatments is to relieve symptoms, rather than cure the disease.

Health-related Quality of Life

The concept of quality of life (QoL) emerged in the late 1940s, when the WHO defined health as being not only the absence of disease, but also the presence of physical, mental and social well-being⁵⁹⁻⁶¹. Although QoL does not have a universally accepted clear definition⁶², the WHO defines it as “an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept that is affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment”⁶³.

An individual’s QoL can be influenced by many factors and it can mean different things to different people. For example, socio-economic status is one factor that can influence QoL⁶⁴, and QoL is one thing for a town planner and another for a patient. However, there is rarely an interest in QoL in such broad terms in medical trials, but rather in those aspects that are affected by a disease or a treatment⁶². To distinguish between the broader sense of the term QoL and QoL that is affected by health status or medical interventions, the term HRQoL is used⁶².

It is generally recognised that HRQoL has several dimensions, and that it can be measured subjectively, by asking the individual^{59,62}. Patient-reported outcome measures (PROMs) is another term to describe instruments that measure different aspects of HRQoL by asking the patient. Questionnaires can consist of a different number of questions (or items), that may focus on a single dimension, or several dimensions. Thus, some questionnaires are multi-dimensional, while some focus on one or few dimensions, such as anxiety and depression for example. Furthermore, some questionnaires are intended for general use, irrespective of the illness or condition, or even apply to healthy people^{59,62}. These generic in-

struments can be used to compare the HRQoL of patients from different conditions, and in the general population. Their disadvantage is that they often lack the ability to illustrate aspects of HRQoL that are specific to a certain condition, which has led to the development of disease-specific instruments.

There are several reasons to measure HRQoL in medical studies. To name a few, HRQoL can be the most important endpoint in studies on treatments that do not affect survival, in health-economic evaluations, or when comparing study treatments that have the same efficacy and safety, but possibly a substantial different effect on HRQoL⁶².

Symptoms and Health-related Quality of Life in Atrial Fibrillation

Assessing symptoms and measuring HRQoL is especially useful in chronic conditions such as AF, which is not immediately life-threatening but can have a great impact on HRQoL⁶⁰. Except for stroke prevention, different treatment modalities in AF, such as rate and rhythm control, mainly aim at improving symptoms and HRQoL. Thus, assessing symptoms and measuring HRQoL is an important part of AF treatment.

Data show that patients with AF have significantly poorer HRQoL than the general population and worse or similar HRQoL than patients with structural heart disease and coronary artery disease⁶⁰. Women with AF often report significantly worse HRQoL and a greater symptom burden than men^{59,65-67}. HRQoL does not seem to be correlated to traditional objective measures of illness severity, such as frequency and duration of the arrhythmia, cardiac dysfunction or New York Heart Association (NYHA) class⁶⁸.

Anxiety and depression are common in patients with AF⁶⁹. Thrall et al. showed that approximately one third of patients with AF have elevated levels of anxiety and depression⁶⁹. Anxiety and depression are also known predictors of HRQoL⁶⁹, and are associated with AF recurrence after RFA⁷⁰. Although several possible mechanisms behind this relationship have been suggested, such as correlation with systemic inflammation and elevated sympathetic tone⁷⁰, the actual mechanism remains unclear. Both anxiety and depression have been shown to be improved after RFA^{70,71}.

The European guidelines recommend health care professionals to use the European Heart Rhythm Association (EHRA) symptom scale in order to assess symptom severity (Figure 5), to guide symptom-oriented treatment decisions, and for longitudinal patient profiling⁸.

Figure 5. The European Heart Rhythm Association symptom scale.

Modified EHRA score	Symptoms	Description
1	None	AF does not cause any symptoms
2a	Mild	Normal daily activity not affected by symptoms related to AF
2b	Moderate	Normal daily activity not affected by symptoms related to AF, but patient troubled by symptoms
3	Severe	Normal daily activity affected by symptoms related to AF
4	Disabling	Normal daily activity discontinued

AF: atrial fibrillation; EHRA: European Heart Rhythm Association
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At least 34 HRQoL instruments have been used in AF studies⁵⁹. The most commonly used and validated instruments in AF studies are The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), the 12-Item Short Form Health Survey (SF-12) and The EuroQol Health Questionnaire, five dimensions (EQ-5D)⁵⁹. However, these are generic instruments reflecting general health, which is influenced by comorbidities commonly present in patients with AF. Recommendations urge the use of disease-specific instruments, which allow the detection of disease-specific changes between patients and over time, especially when measuring changes in symptom burden³¹. Several arrhythmia- and AF-specific instruments have been developed^{31,59}, although they are constrained by a lack of cross-validation⁸.

Alcohol

Since the beginning of recorded history, alcohol has been a part of human culture⁷². Alcohol contributes substantially to the global burden of disease, accounting for approximately 4% of total mortality, mainly caused by injury, liver cirrhosis, cancer and cardiovascular disease⁷². However, the association between cardiovascular disease and alcohol is a matter of debate.

Alcohol and the Heart

Although there is no doubt that heavy drinking has a negative effect on the cardiovascular system, there are data supporting a beneficial effect of light to moderate drinking on cardiovascular disease, especially ischaemic heart disease⁷²⁻⁷⁴. Explanatory mechanisms that have been suggested are activation of the fibrinolytic system, the effect on platelet aggregation, an antioxidant effect, an improved lipid profile, an improved endothelial function, and an improvement of diabetes and hypertension^{74,75}. The cardio protective effect of alcohol consumption seems to be J-shaped, with a sharp initial decline and a slow turn upwards, indicating cardio protection already at very low doses⁷⁶. However, the shape of the curve differs depending on which population is examined. Furthermore, the nadir of the curve, in which a maximum cardio protective effect is seen, is at a dose that from a clinical and public health perspective is associated with many other disease outcomes⁷⁶.

The effect of excessive alcohol intake on the myocardium is a process that progresses gradually, ultimately leading to a state known as alcohol cardiomyopathy, characterised by a non-ischaemic dilated cardiomyopathy with, in latter stages, heart failure⁷⁷. Alcohol consumption is also linked to arrhythmias. In 1978 the term “holiday heart syndrome” was described, indicating an acute cardiac rhythm disturbance, most frequently AF, after binge drinking, in healthy people⁷⁵. The exact mechanisms are not clear, but some mechanisms have been suggested, such as cardiac conduction interference facilitating re-entry, shortening of the atrial refractory period, increased sympathetic, but also parasympathetic, activity, a rise in plasma free fatty acids and acetaldehyde arrhythmogenic effects through an increase in systemic and intramyocardial catecholamines⁷⁵. Also chronic alcohol intake has been associated with increased risk of AF. Data from the Framingham study showed that heavy alcohol consumption, i.e. >36g /day, significantly increased the risk of AF⁷⁸. More contemporary data show an increased risk even at moderate intake (1-2 standard drinks a day, each standard drink containing 10-12 g alcohol), at least in men⁷⁹. Some studies suggest a dose-dependent relationship, in which each increase of one standard drink per day, increases the risk of AF by

8%^{80,81}. However, in a more recent meta-analysis, low levels of alcohol intake (less than 6-7 standard drinks per week) were not associated with increased risk of AF⁷⁹.

Alcohol Intake Recommendations

Due to the heterogeneity concerning the J-shaped alcohol curve depending on the population being examined, a potential cardio protective association cannot be generally assumed, even at low levels of intake, making it hard to advocate alcohol consumption for health reasons⁷⁶. Governments, though far from all, instead have recommendations that define a threshold of alcohol intake, above which risk consumption is defined. While the WHO defines risky drinking as more than two standard drinks (in some countries called units) a day, each standard drink containing 10 g of pure ethanol, in both men and women⁸², the definitions of a standard drink and the definitions of risk consumption differ greatly among those countries that have adopted drinking recommendations. The definitions of standard drinks range from 8-20 g, and the definitions of risky drinking range from 10-42 g/day for women and 10-56 g/day for men⁸². For example, in the UK, the recommendations are not to exceed 14 units (1 unit equal to 8 g of alcohol) per week for both genders. In Sweden, a standard drink equals 12 g of alcohol, and the recommendations are below 14 and 9 drinks/week for men and women, respectively⁸³.

Assessing Alcohol Consumption

One method of assessing alcohol consumption is to ask the patient. Although self-report is considered to be the gold-standard, it can be unreliable and prone to underreporting, especially in legal contexts^{84,85}. Therefore, an objective tool that retrospectively gives reliable information about the long-term alcohol consumption would be desirable. However, a perfect such tool does not exist. Still, alcohol biomarkers are currently used and can have important applications in medicine and public safety⁸⁴.

Although acute alcohol consumption can easily be detected through the measurement of the blood or breath levels of ethanol itself, it does not give any information about long-term alcohol consumption, which is often of interest⁸⁴. There are several biomarkers of long-term alcohol consumption, none being perfect in the sense of sensitivity and specificity, and with variable results in different populations (Table 3)^{84,86}. In contrast to elevated concentrations of the widely and traditionally used biomarkers (mean corpuscular volume, alanine aminotransferase, aspartate aminotransferase, γ -glutamyl transferase, carbohydrate-deficient transferrin), which can be due to many different conditions, elevated concentrations of ethyl glucuronide (EtG) are apparent only in the presence of

alcohol, since the formation of EtG (as well as ethyl sulphate (EtS), phosphatidylethanol species (PEths) and fatty acid ethyl esters (FAEEs)) is dependent on the presence of ethanol^{84,87}.

Table 3. Biomarkers of alcohol consumption

Alcohol bi- omarker	Source	Sensitivity (%)	Specificity (%)	Time frame	Confounders
MCV	Blood	30–75	60–90	2–4 months	Liver diseases, vitamin B12 or folic acid deficiency, haematological diseases, reticulocytosis or hypothyroidism
EtG	Blood Urine Hair Nails	70–90 (hair)	80–95 (hair)	8 h (blood) 80 h (urine)	None
TSA	Blood	48–82	18–96	NA	Cancer, cardiovascular disease
5-HTOL/5-HIAA	Urine	100	NA	5–15 h	
PEths	Blood	94.5–100	100	4 days	None
CDT	Blood	60–70	80–95	1.5–2 weeks	Anorexia nervosa, pregnancy, iron deficiency, chronic illnesses and menopausal status
GGT	Blood	40–60	80–90	14–26 days	Liver damage, cardiovascular disease, diabetes
ALT/AST	Blood	18–58 (ALT) 15–69 (AST)	50–95 (AST)	NA	Liver damage
β-HEX	Blood Urine	69–94 (blood) 81–85 (urine)	91–98 (blood) 84–96 (urine)	6.5 days (blood)	Hypertension, diabetes, cirrhosis, myocardial infarction, in pregnancy and after oral contraceptive use
Acetaldehyde adducts	Blood	65–73	88–94	Up to 3 weeks	NA
Sialylation of Apo J	Blood	90–92	~100	Up to 8 weeks	NA
Fatty acid ethyl esters	Blood Hair	NA	NA	100 h (blood) 2 months (hair)	NA
Cytokines	Blood	NA	NA	NA	NA
CDT + GT	Blood	60–90	80–95	NA	See CDT and GGT
CDT + MCV	Blood	60–95	80–95	NA	See CDT and MCV

Note: Bio fluid sources, sensitivity and specificity values are listed for established alcohol biomarkers. Confounding factors for each biomarker are listed, as well as their diagnostic time frames (time period during which the marker is indicative of alcohol intake).

5-HIAA: 5-hydroxyindole-3-acetic acid; 5-HTOL: 5-hydroxytryptophol; β-HEX: β-hexosaminidase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CDT: Carbohydrate-deficient transferrin; EtG: Ethyl glucuronide; GT: Glutaryl transferase; MCV: Mean corpuscular volume; NA: Not applicable; PEths: Phosphatidylethanol species; TSA: Total serum sialic acid.

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Ethyl Glucuronide in Hair

Hair testing is especially useful when aiming for a retrospective assessment of consumption of drugs after they have been eliminated from the body, and is possible because compounds are incorporated into hair⁸⁷. Hair testing is a well-established technique with applications in both clinical and forensic toxicology, and the Society of Hair Testing (SoHT) provides practice guidelines that include recommended sample collection and storage procedures, sample preparation, pre-treatment, analysis and the use of cut-offs⁸⁸.

Ingested ethanol is mainly eliminated from the body through oxidative metabolism but a small proportion (<0.1%) is eliminated through non-oxidative metabolism, i.e. conjugation reactions, resulting in EtG, EtS, PEths and FAEs⁸⁷. These metabolites can be detected in the blood or urine, but with a relatively narrow diagnostic time frame⁸⁹. In contrast, hair analysis has a wide diagnostic time frame, yielding information about the consumption over months to years, depending on the hair length being analysed⁸⁹. While detection of ethanol itself is not possible in hair, due to its volatile nature⁸⁷, EtG is a stable marker that can be detected in hair and analysed. The average hair growth is 1 cm/month, and the SoHT recommends analysis of 0-3 up to 0-6 cm proximal scalp hair, preferably from the vertex posterior part of the scalp⁸⁸. Consequently, the EtG concentration in a 3 cm length of hair corresponds to the alcohol consumption during the previous three months.

Although studies have shown a relationship between the administered dose of ethanol and the hEtG concentration, there is a high degree of biological variability in the dose-concentration relationship^{90,91}. For this reason, cut-off values are used as signs of excessive/chronic alcohol consumption and repeated alcohol consumption. Although different values have been suggested, the SoHT consensus states that hEtG concentrations ≥ 30 pg EtG/mg strongly suggest excessive/chronic alcohol consumption, defined as consumption of more than 60 g of pure ethanol per day, while hEtG concentrations ≥ 7 pg/mg (but below 30 pg/mg) strongly suggest repeated alcohol consumption (contradicting self-reported abstinence)⁹². The cut-off value of 30 pg/mg has been proven to have a high sensitivity and specificity⁹¹.

Aims

The aims of this thesis were:

- to investigate whether structured care compared to standard care of a general AF-population could improve guideline adherence and HRQoL as well as decrease symptoms, anxiety and depression (Paper I).
- to explore predictors of arrhythmia-specific symptoms and HRQoL prior to RFA (Paper II), as well as the predictors of their improvement after RFA (Paper IV), and to evaluate the effect of RFA on symptoms, HRQoL, anxiety and depression, in patients with AF (Paper IV).
- to examine the associations of objectively measured and self-reported alcohol consumption with cardiac biomarkers, the size of the left atrium (LA), and re-ablation, and to describe long-term alcohol consumption, evaluated with an objective marker, in a population with AF referred for RFA (Paper III). Furthermore, the association of alcohol consumption with symptoms and HRQoL was not included in any of the papers, but was one of the initial aims of this thesis and is thus presented in this thesis.

METHODS

The thesis is based on data from the two studies ‘Structured Management and Coaching – Patients with Atrial Fibrillation’ (SMaC-PAF) which forms the basis for Paper I, and ‘Symptom burden, Metabolic profile, Ultrasound findings, Rhythm, neurohormonal activation, haemodynamics and health-related quality of life in patients with atrial Fibrillation’ (SMURF), which forms the basis for Papers II-IV.

Ethical Considerations and Informed Consent

Concerning the SMaC-PAF study, one might argue that it is unethical to provide more structured care to only half of the study population. However, all patients received at least standard care, and before the study was undertaken it was not known whether the structured care would be better than standard care.

Concerning the SMURF study, the RFA procedure in the study was more time-consuming than a normal RFA. Furthermore, additional blood tests were taken and the amount of hair taken was a tuft of the same size as a pen’s thickness. Overall, the benefits of carrying out the study and thus answering the study questions were judged to exceed any discomfort that study patients might feel.

In both studies participation was completely voluntary and the patients had the right to discontinue the study at any time, without the need for any explanation. The Regional Ethical Review Board in Linköping, Sweden, approved both studies (Dnr M145-09 and Dnr 2011/40-31). All patients gave their written consent and the studies complied with the Declaration of Helsinki⁹³.

The SMaC-PAF Study – Paper I

Design

The study had a non-randomised prospective design. The intervention took place at the Ryhov county hospital in Jönköping, Sweden, while patients in the control group were enrolled at three county hospitals in the same area (Kalmar, Eksjö and Norrköping, Sweden). All patients were asked to fill out questionnaires at inclusion and after one year, and their medical records were examined one year after inclusion. There was no study-related contact with patients in the control group, while patients in the intervention group were followed at the AF clinic as described below.

The first patient was included in December 2009 and the last FU was made in April 2014.

Inclusion and Exclusion Criteria

Inclusion criteria were:

- Patient visiting the emergency room (ER) due to AF
- Age ≥ 18 years

Exclusion criteria were:

- unwillingness to participate
- unstable coronary artery disease
- sepsis or other severe infection
- AF early after thoracic surgery
- acute pulmonary embolism
- hyperthyroidism
- malignant disease with expected survival less than one year
- dementia or insufficient knowledge of the Swedish language making it difficult to independently fill out the questionnaires.

Eligible patients were informed about the study at the ER or at the cardiac ward. Written informed consent was obtained prior to enrolment. Enrolled patients at the intervention centre were then scheduled for an outpatient visit at the AF outpatient clinic (see below) within two weeks. Patients enrolled at the hospitals serving as control centres were only asked to fill out the questionnaires and then received “standard care”.

Structured Care of Patients with Atrial Fibrillation

Education and Preparations

Prior to the study onset, physicians at the emergency care unit in the intervention centre were educated concerning current guidelines. A pocket sized laminated algorithm was presented, containing recommendations for treatment with OAC and with suggestions for outpatient management.

Atrial Fibrillation Outpatient Clinic

The AF outpatient clinic was active one day weekly and manned by two cardiologists and two nurses. All patients included in the study were followed at the AF outpatient clinic one or two weeks after discharge and then at three and additionally at 12 months FU. Data were entered in the Swedish National quality AF registry (Auricula) at the first and last visits.

The nurses' perspective was to increase the patients' knowledge about AF through information and education. They also provided lifestyle advice focusing on overweight/obesity, alcohol, coffee, stress and psychological distress. An information booklet from the Swedish Heart and Lung Foundation was handed out containing general information about AF including basic anatomy, physiology, symptoms and treatment.

The physicians used a checklist to ensure that treatment was given according to guidelines. If OAC was not prescribed when indicated, an explanation was mandatory.

Increased availability was also ensured in the structured AF outpatient clinic. Patients could reach a nurse every weekday morning. The AF outpatient clinic was also equipped with a trans-telephonic thumb ECG, which was handed out to some patients, for example when investigating whether the patients' symptoms were due to AF or not.

Patient-reported Outcome Measure Questionnaires

The Medical Outcomes Study 36-Item Short Form Health Survey

SF-36 is a generic questionnaire designed to measure an individual's physical and mental health. It comprises 35 items grouped into eight scales and one question concerning changes in health outside the scales. The eight scales are physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH)⁹⁴. For each of the eight scales, scores were coded, summed, and transformed to a scale from 0 (worst possible health) to 100 (best possible health)⁹⁴. The eight scales are summarised in physical and mental component summaries (PCS and MCS, respectively), standardised to a norm with a mean of 50 and a standard deviation (SD) of 10⁹⁵. SF-36 has been widely used in research, including studies of patients with arrhythmias^{59,60}.

The EuroQol Health Questionnaire, Five Dimensions and EuroQol Health Questionnaire, Visual Analogue Scale

The EQ-5D/EuroQol Health Questionnaire-Visual Analogue Scale (EQ-VAS) questionnaire was used to characterise health state. The EQ-5D questionnaire assesses five dimensions: mobility, self-care, activity, pain/discomfort, and mood, each with three levels of severity. The UK EQ-5D index tariff was used to obtain a weighted index, with a range from -0.59 to 1.0, where 1.0 represents full health⁹⁶. The EQ-VAS records the respondents' self-rated health status on a vertically graduated (0–100) visual analogue scale with 100 (best imaginable health state) at the top

and o (worst imaginable health state) at the bottom. EQ-5D/EQ-VAS has been extensively validated and has often been used in AF studies⁵⁹.

The Hospital Anxiety and Depression Scale

The domain-specific questionnaire Hospital Anxiety and Depression Scale (HADS) consists of 14 items constituting two subscales, where seven items assess anxiety and seven assess depression. Responses are scored from 0 to 3 with higher scores denoting more psychological distress. The score for each subscale ranges from 0 to 21. The scores are categorised as normal (0-7), possible (8-10), and probable (≥ 11) anxiety and depression, respectively^{97,98}. HADS has previously been used in patients with AF⁹⁹.

The Arrhythmia-Specific Questionnaire in Tachycardia and Arrhythmia

The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia (ASTA) is a disease-specific, validated, questionnaire divided into three separate parts: Part I evaluates the patient's latest episode of arrhythmia and current medication^{100,101}. Part II assesses symptom burden, and includes a nine-item symptom scale with a four-point response scale (ASTA symptom scale)¹⁰¹. Outside of the symptom scale there are questions concerning the frequency and duration of arrhythmia episodes and experience of near syncope, syncope and palpitations in connection with arrhythmia. Part III assesses HRQoL with a 13-item scale, with the same four-point response scale (ASTA HRQoL scale) as for the symptom scale¹⁰⁰. Values range from 0 to 100 and higher scores reflect higher symptom burden and a worse effect on HRQoL, due to the arrhythmia^{100,101}. In an earlier version of ASTA, which was used in the SMaC-PAF study, there were no scale score calculations, and Part II consisted of 10 items, but has since then been reduced to nine items during the validation process¹⁰⁰.

Norm Population

In 2006, a survey of the population in south-eastern Sweden was conducted, including assessment of HRQoL measured with, among others, SF-36¹⁰². In total, 7 238 individuals responded to the survey, and the individuals aged 65-74 years were used for comparison.

Outcomes/Endpoints – Paper I

The primary outcomes were the effect of structured care on:

- 1) adherence to guidelines, evaluated by five criteria:

- a) appropriate prescription of OAC according to the CHADS₂ and CHA₂DS₂-VASc criteria (Table 1 and Table 2)
 - b) echocardiogram performed
 - c) thyroid laboratory tests performed
 - d) no AAD prescribed to patients with permanent AF
 - e) no class 1c-AAD prescribed in the presence of structural heart disease
- 2) symptoms, anxiety, depression and HRQoL, as assessed by the PROMs questionnaires described above.

At study onset, the recommendations in the guidelines were based on the CHADS₂ classification scheme and suggested the use of OAC when CHADS₂ ≥ 2 in patients without contraindications. During the study, new guidelines were published recommending the use of the CHA₂DS₂-VASc classification scheme and treatment with OAC for scores ≥ 1 .

Statistics

In order to detect a five-point difference in the scales in SF-36 between the groups, using an alpha of 0.05 and a power of 0.80, 200 patients in each group were required.

Normally distributed variables are presented as means $\pm$ SD, whereas categorical variables are presented as percentages and numbers. Differences between the two groups for normally distributed variables were tested with the independent t-test, and the paired t-test for differences over time within the groups. For non-normally distributed variables the Mann-Whitney U test was used for testing differences between the two groups, and Wilcoxon's signed rank test, or McNemar's test for dichotomous variables, within groups over time. For categorical variables the Chi-square test or Fischer's exact test were used between groups, and for proportions the z-test with continuity correction was used. All calculations were made with SPSS statistical software version 20.0 (Armonk, NY: IBM Corp). P-values < 0.05 were considered as statistically significant.

The SMURF Study, Papers II-IV

Design

The SMURF study was conducted between January 2012 and April 2014. Patients referred to the University Hospital in Linköping, Sweden, for RFA due to AF, were considered for participation. The SMURF study consisted of an observational and an interventional part. In this thesis, only the observational part of the study was used, which was a single centre cohort study (Figure 6). The study was registered at www.clinicaltrials.gov (NCT01553045).

After screening, potentially eligible patients received written information about the study and the PROMs questionnaires. Prior to the RFA, oral information was given and informed consent was signed. The questionnaires were collected. A full baseline evaluation including medical history, physical examination and 12-lead ECG was performed. Transoesophageal and transthoracic echocardiography (TEE and TTE), and a CT scan of the heart were performed according to clinical routine. Patients were then catheterised according to clinical routine and blood samples for the analysis of high-sensitive C-reactive protein (hsCRP), N-terminal pro B-type natriuretic peptide (NT-proBNP), the mid-regional fragment of pro atrial natriuretic peptide (MR-proANP) and the mid-regional portion of pro-adrenomedullin (MR-proADM) were taken from the femoral vein. Intracardiac pressures were recorded in the right atrium (RA), LA and right ventricle (RV). Blood samples were repeated the day after the RFA and FU was made after four and 12 months (Figure 6).

Inclusion and Exclusion Criteria

Consecutive patients were asked about study participation if they met the inclusion criteria and did not have any of the exclusion criteria.

The inclusion criteria were:

- Age ≥ 18 years with paroxysmal or persistent AF
- Patients referred for first time RFA
- Patients with sufficient knowledge of the Swedish language to fill out the study questionnaires independently.

Exclusion criteria were:

- Patients who had previously undergone catheter or surgical AF ablation
- Patients with previous or planned heart surgery
- Patients with left ventricular ejection fraction (EF) $< 35\%$

- Patients with acute coronary syndrome during the past three months.

Figure 6. Enrolment and follow-up chart of the SMURF-study.

Note: The right column with grey background depicts the flow for patients included in the interventional part of the study, and was not included in this thesis.

AF: atrial fibrillation; CT: Computed tomography; ECG: Electrocardiogram; PROMs: Patient-reported outcome measures; RFA: radiofrequency catheter ablation

Patient-reported Outcome Measures

PROMs were assessed with SF-36, HADS and ASTA at baseline, at the four-month FU and 12-month FU.

Echocardiography

All patients underwent TEE and TTE prior to RFA. GE Vivid 7 or GE Vivid E9 system (GE Healthcare, Horten, Norway) were utilised with a 3.5-MHz transducer for TTE and a 7-MHz transducer for TEE. The measurements and evaluation were performed according to the guidelines of the European Society of Echocardiography.

Left ventricular EF was calculated using the biplane Simpson's method. Left atrial volume (LAV) was measured using the biplane area-length method and was corrected for body surface area to obtain the LAV index (LAVI).

Radiofrequency Catheter Ablation Procedure

All procedures were performed under conscious sedation using propofol and remifentanyl. Two trans-septal sheaths were inserted through the right femoral vein into the LA and perfused using heparinised saline with irrigation rate 2ml/h. Heparin was administered to maintain an activated clotting time of >350 s throughout the procedure. RFA was performed under the guidance of a computer-based mapping system, CARTO (Biosense Webster, Diamond Bar, California, USA). Mapping and ablation were performed using an open-irrigated catheter (ThermoCool, Biosense Webster, Diamond Bar, California, USA). A 7-F, 20-pole circumferential diagnostic catheter was used for the assessment of pulmonary vein activation and isolation (Lasso, Biosense Webster, Diamond Bar, California, USA). Radiofrequency energy was delivered in a power-controlled mode with a maximum energy setting of 35 W at an irrigation rate of 17–30 mL/min, and the maximum energy setting in the posterior wall was 25 W. The endpoint of the procedure was electrical disconnection of all pulmonary veins by antral ablation verified during SR by entry and exit block of all pulmonary veins. In patients with persistent AF, additional ablation in order to create LA lines was at the discretion of the operator and verified by pacing manoeuvres. Patients with AF were routinely converted to SR on completion of the RFA procedure.

Cardiac Biomarkers and Other Blood Tests

Blood samples were collected in plastic vials containing ethylenediaminetetraacetic acid and analyses were performed at the Department of

Clinical Chemistry at Linköping University hospital. The vials were centrifuged at 3100g for 20 min and then frozen at -70°C . No sample was thawed more than twice.

The concentrations of NT-proBNP were measured on the Elecsys 2010 platform (Roche Diagnostics, Mannheim, Germany). The total coefficient of variation (CV) for NT-proBNP was 4.6% at 426.5 pg/mL ($n=487$) and 3.2% at 2308 pg/mL ($n=485$). Plasma concentrations of MR-proANP were measured on a kryptor platform (Brahms AG, Hennigsdorf, Germany). The intra assay CV for MR-proANP according to the manufacturer was $\leq 5\%$ for concentrations between 10 and 20 pmol/L, $<3.5\%$ for concentrations between 20 and 1000 pmol/L, and $<3.5\%$ for concentrations over 1000 pmol/L.

The hsCRP analysis was performed using the wide range C-Reactive Protein immunoturbidimetric assay on the ADVIA 1650 system (Siemens Healthcare GmbH, Erlangen, Germany). The total CV was 5.35% at 0.9 mg/l and 1.17% at 12.3 mg/l.

Liver enzymes, lipid profile and serum creatinine were measured and analysed according to clinical routine. The glomerular filtration rate (GFR) was estimated through the Cockcroft-Gault formula: $\text{GFR} = ((140 - \text{Age}) * \text{weight} * k) / \text{serum creatinine}$, where k is 1.23 for men and 1.04 for women (weight measured in kilograms and the unit for serum creatinine $\mu\text{mol/l}$).

Pressure Measurements

The sagittal thoracic diameter was measured in the fourth intercostal space and the reference pressure (zero level) was placed in the middle of this diameter. The mean pressures were measured in the RA and LA, and the systolic and end-diastolic pressures in the right ventricle after trans-septal puncture by using the multipurpose high flow 5 French catheter (MR A1, Cordis®, Miami, Fl., USA) during quiet breathing. The pressures were recorded for at least 15 s and stored for offline analysis (EP-WorkMate; St. Jude Medical, Saint Paul, MN, USA).

Assessment of Alcohol Consumption

Self-reported Alcohol Consumption

Patients were interviewed about their weekly alcohol consumption, and the reported amount of alcohol was translated into units. In this study, one unit corresponded to eight grams of alcohol, ingested in the form of beer, wine or spirits. High consumption was defined as more than 14 and nine units/week in men and women, respectively, and low consumption as consumption below this level.

Ethyl Glucuronide in Hair

Hair samples were collected as close as possible to the scalp and the proximal 3 cm were used for estimation of hEtG. The hair was placed in marked envelopes and sent to the National Board of Forensic Medicine, where it was cut into smaller segments and prepared, handled and analysed according to routine⁹⁰. The total CV for hEtG was 16% at 7 pg/mg, 8.3% at 33 pg/mg, and 6.2% at 267 pg/mg hair.

Recurrence of Atrial Fibrillation and Re-ablation

AF recurrence after RFA and re-ablation was analysed up to 12 months after the initial RFA, through examination of medical records, the Swedish national registry for catheter ablation, and the 24 h ECG monitoring at the four-month FU. AF recurrence was defined as a documented episode of AF or atrial flutter lasting more than 30 seconds, and/or the need for re-ablation.

Outcomes/Endpoints

The primary endpoints of the studies were:

Paper II

- to examine possible predictors of arrhythmia-specific symptoms and HRQoL, as well as general HRQoL, prior to RFA of AF.

Paper III and the Association of Alcohol Consumption with Symptoms and Health-related Quality of Life

- 1) to examine associations of both objectively measured and self-reported alcohol consumption with cardiac biomarkers, LA size, re-ablation, symptoms and HRQoL

- 2) to describe long-term alcohol consumption, measured objectively, in a population with AF referred for RFA

Paper IV

- 1) to explore possible predictors of improvement in arrhythmia-specific symptoms and HRQoL after RFA of AF
- 2) to analyse the effect of RFA on symptoms, HRQoL, anxiety and depression in a population undergoing RFA for their first time

Statistics

When calculating the sample size for the SMURF study, the main objective was to determine the effect of restoration of SR and initiation of AF on NT-proBNP and MR-proANP (the interventional part of the SMURF study and thus not part of this thesis). The patients included in the study by Wozakowska-Kaplon et al.¹⁰³ and possible dropouts were taken into account, after which the conclusion was drawn that 200 patients would be sufficient to meet all the aims of the SMURF study.

Normally distributed continuous variables are generally expressed as means $\pm$ SD and non-normally distributed variables as medians with 25th to 75th percentiles within brackets. Categorical data are presented as counts with percentages within brackets. The analyses were performed using the SPSS 24.0 (IBM, Armonk, New York). All reported p-values were two-sided and a p-value <0.05 was considered statistically significant.

Paper II

Multiple linear regression analysis was performed to determine possible predictors of arrhythmia-related symptoms and HRQoL. The baseline ASTA symptom scale score was used as a dependent variable to assess arrhythmia-related symptoms, while baseline ASTA HRQoL scale score, PCS and MCS were used as dependent variables to assess the patients' HRQoL. The independent predictors used in the analyses were NT-proBNP, MR-proADM, low-grade inflammation (hsCRP >3 mg/L vs. $\leq$ 3 mg/L), the RV systolic and diastolic pressures, LA dilatation (body surface area indexed LAV >35 ml/m² vs. $\leq$ 35 ml/m²), heart failure (EF <45% vs. $\geq$ 45%), obesity (body mass index (BMI) >30 kg/m² vs. $\leq$ 30 kg/m²), anxiety and depression (assessed by the HADS questionnaire), CHA₂DS₂-VASc score ($\geq$ 2 points vs. <2 points), age, frequency of AF episodes (>10 episodes vs. $\leq$ 10 episodes of AF in the last month before RFA) and AF episode duration (longest AF episode duration of $\geq$ 1 hour vs. <1 hour). The models were fit by an enter method, in which all variables were entered

into the original model and then variables with p-values over 0.05 were removed.

Paper III and the Association of Alcohol Consumption with Symptoms and Health-related Quality of Life

Independent two-group analysis was performed with the independent t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Wilcoxon's signed rank test was used for dependent two-group analyses. The Chi-square test was used for categorical variables. Spearman's correlation coefficient was used to assess the correlation between self-reported alcohol consumption and hEtG.

Multiple linear regression analysis was performed in order to correct for gender when evaluating the relationship between analysable hEtG and high density lipoprotein (HDL), and CHA₂DS₂VASc score. The dependent variable was HDL and CHA₂DS₂VASc score, respectively, with analysable hEtG (yes/no) as an independent variable and gender (male/female) as a covariate. Multiple linear regression analysis was also performed in order to evaluate the predictive role of gender and sagittal abdominal diameter on HDL. The dependent variable was HDL and the independent variables were sagittal abdominal diameter, gender and the use of statins.

Possible differences in cardiac biomarkers, echocardiographic measurements and number of re-ablations between the two groups based on the hEtG cut-off level of 7 pg/mg, and also based on self-report, i.e. high vs. low consumption, were evaluated. Analyses were also stratified according to gender, due to the fact that cosmetic hair treatment can affect the hEtG analysis, and adjusted for age, systolic blood pressure, BMI, heart failure (yes/no) and actual heart rhythm (SR/AF), through multiple linear regression analysis. In this analysis, logarithmic transformation was used for NT-proBNP and MR-proANP in order to achieve normal distribution.

Binary logistic regression analysis was performed, with adjustment for the above mentioned co-variables, except for heart rhythm being replaced by AF type (paroxysmal/persistent), in order to analyse the association between alcohol consumption and re-ablation.

Paper IV

In order to analyse possible predictors of improvement in arrhythmia-specific symptoms and HRQoL, the difference between the scores at the one-year FU and baseline were calculated for the ASTA symptom scale and the ASTA HRQoL scale, and used as the dependent variable in a simple linear regression analysis. The independent predictors used were: age, gender, BMI, hypertension (yes/no), heart failure (yes/no), diabetes

(yes/no), AF type (paroxysmal or persistent), CHA₂DS₂-VASc score, AF episode duration (longest AF episode duration of ≥ 1 hour vs. < 1 hour in the last three months before RFA), frequency of AF episodes (> 10 episodes vs. ≤ 10 episodes of AF in the last month before RFA), hsCRP, EF, LAV, AF recurrence (yes/no), and finally, possible and probable anxiety and depression as assessed with HADS. All variables that turned out to be significant were used in a multiple linear regression analysis, conducted in a stepwise backward elimination fashion.

Analysis of the changes in all of the questionnaires summary scores, and in each item in ASTA, throughout the three measure points was performed using Friedman's test. In order to analyse between which time points there was a significant change, Wilcoxon's signed rank test was used between two measurement points. The magnitude of the change between baseline and one-year FU was assessed with effect size (ES), which was calculated and interpreted according to standard criteria where < 0.20 denotes trivial, $0.20-0.49$ small, $0.50-0.79$ moderate and ≥ 0.80 large ES¹⁰⁴.

RESULTS

The SMaC-PAF Study – Paper I

Baseline Characteristics

The intervention group consisted of 199 patients and the control group of 162 patients, while 176 (88%) and 146 (90%) patients, respectively, were available for analysis (Figure 7). The two groups differed at baseline concerning educational degree, number of patients with CHADS₂ 0 p, and the number of patients having their first episode of AF (Table 4).

Figure 7. Study inclusion flow chart.

Table 4. Baseline characteristics in the SMaC-PAF study.

Characteristics	Intervention group (n = 176)	Control group (n = 146)	p-value
Age years, mean $\pm$ SD	66 $\pm$ 10	68 $\pm$ 11	0.06
Male gender, no. (%)	112 (64)	84 (58)	0.26
Type of AF, no. (%)			0.12
First episode	42 (24)	50 (35)	<0.05
Paroxysmal	62 (35)	49 (34)	ns.
Persistent	57 (32)	38 (26)	ns.
Permanent	15 (9)	7 (5)	ns.
Comorbidity, no. (%)			
Hypertension	81 (46)	79 (54)	0.13
Diabetes	13 (7)	20 (14)	0.06
Ischaemic heart disease	21 (12)	24 (17)	0.34
Congestive heart failure	23 (13)	14 (10)	0.28
Chronic pulmonary disease	10 (6)	5 (3)	0.42
Previous Stroke/TIA	11 (6)	15 (10)	0.15
CHADS ₂ -score no. (%)	n = 176	n = 143	0.09
0	70 (40)	40 (28)	<0.05
1	57 (32)	57 (40)	ns.
≥ 2	49 (28)	46 (32)	ns.
CHA ₂ DS ₂ -VASc-score no. (%)			0.16
0	30 (17)	15 (11)	ns.
1	40 (23)	29 (20)	ns.
≥ 2	106 (60)	99 (69)	ns.
OAC when indicated, no. (%)			
CHADS ₂ ≥ 2	24 (65)	17 (63)	ns.
CHA ₂ DS ₂ -VASc ≥ 2	44 (60)	34 (60)	ns.
CHADS ₂ ≥ 1	42 (58)	35 (55)	ns.
CHA ₂ DS ₂ -VASc ≥ 1	51 (61)	42 (55)	ns.
Cohabitation, no. (%)	n = 176	n = 123	0.90
Living alone	39 (22)	28 (23)	ns.
Living with partner and/or child	137 (78)	95 (77)	ns.
Educational level no. (%)	n = 171	n = 124	0.02
Primary school	66 (39)	68 (55)	<0.05
High school	56 (33)	31 (25)	ns.
University	49 (29)	25 (20)	ns.
Occupation no. (%)	n = 176	n = 120	0.32
Employed	58 (33)	33 (28)	ns.
Unemployed/retirement	118 (67)	87 (73)	ns.

Cursive letters in the last column indicate significant ($p < 0.05$) or non-significant (ns.) p-values for that specific category within the variable, by calculating the z score with continuity correction, while normal letters indicate the p-value for the complete variable, analysed with Chi2-test

AF: atrial fibrillation; OAC: Oral anticoagulants; SD: standard deviation; CHADS₂: congestive heart failure, hypertension, age ≥ 75 , diabetes, stroke/TIA; CHA₂DS₂-VASc: congestive heart failure, hypertension, age ≥ 75 , diabetes, stroke/TIA, vascular disease, age 65-74 years, sex category (i.e. female gender); TIA: transient ischaemic attack

Guideline Adherence

At baseline, there was no difference in treatment with OAC according to guidelines between the intervention group and the control group, 24 (65 %) vs. 17 (63 %, $p = 0.88$) using CHADS₂, and 51 (61 %) vs. 42 (55%, $p = 0.43$) using CHA₂DS₂-VASc.

After one year, the number of patients treated according to guidelines in terms of adherence to all five criteria investigated, was significantly better in the intervention group, 152 (93%) vs. 105 (74%, $p < 0.01$). The difference in adherence to guidelines was greater using the CHA₂DS₂-VASc-score, in favour of the intervention group, 148 (91%) vs. 89 (63%, $p < 0.01$). This was mainly due to an improvement in OAC treatment (Figure 8).

Figure 8. The proportion of patients treated with oral anticoagulation when indicated, at baseline and at the one-year follow-up.

CHADS₂: congestive heart failure, hypertension, age ≥ 75 , diabetes, stroke/TIA; CHA₂DS₂-VASc: congestive heart failure, hypertension, age ≥ 75 , diabetes, stroke/TIA, vascular disease, age 65-74 years, sex category (i.e. female gender)

There was also a significant difference in whether thyroid function was tested or not, 175 (99%) vs. 126 (86%, $p < 0.01$). However, there were no differences in investigations with echocardiogram, 164 (93%) vs. 133 (92%, $p = 0.62$), in whether patients were treated with AAD despite permanent AF (none in both groups), or in whether a class Ic-AAD drug was

used despite the presence of structural heart disease (two patients in each group).

During the FU, stroke, TIA or peripheral embolus occurred in five patients (3%) in the intervention group and three patients (2%) in the control group. Two patients in the intervention group suffered from intracerebral bleeding, while one patient in the intervention group and one patient in the control group suffered from gastrointestinal bleeding.

The number of patients with CHA₂DS₂-VASc 0 p after one year was 21 (12 %) in the intervention group and 11 (8 %) in the control group. However, seven (33 %) and five (46 %) of those patients were treated with OAC (n.s.) and the reasons were recent or planned ablation or DC-cardioversion, patients' own desire to continue, being close to 65 years of age and in one patient a second echocardiography was planned since the left ventricular function was hard to evaluate due to arrhythmia in the first echocardiography.

Patient-reported Outcome Measures

The number of enrolled patients that did not return the questionnaires at FU was seven (4%) in the intervention group and 48 (33%) in the control group. There were also a number of missing answers within the returned questionnaires. Hence, the number of patients excluded from some of the PROMs analyses was larger than 4% in the intervention group and 33% in the control group.

Symptoms, Anxiety and Depression

Compared to the intervention group, patients in the control group reported more dizziness, cold sweats, weakness/fatigue, and tiredness at baseline, and after one year more weakness/fatigue, as assessed with ASTA (Figure 9). Over the year, significantly fewer patients were feeling pressure in the chest in the intervention group while no significant change was seen in the control group (Figure 9).

Figure 9. Percentage of patients with any symptoms, assessed with ASTA, at baseline and the one-year follow-up, in the control and intervention groups.

Note 1: The nine symptom items in the ASTA symptom scale, part II, are shown. The four-point response scale has been dichotomised to no symptoms/any symptoms.
Note 2: The Mann-Whitney U test was used to analyse possible differences in the four-point response scale between the intervention and control groups, at baseline and at follow-up. McNemar's test was used to analyse possible differences in the dichotomised variable within the groups between baseline and follow-up. p-values <0.05 were considered as statistically significant.
* There were significant differences between the intervention and control groups at baseline in the following items: dizziness, p = 0.01; cold sweats, p = 0.03; weakness p = 0.02 and tiredness, p = 0.04.
† There was a significant difference between the intervention and control groups at follow-up in the following item: weakness, p = 0.04.
There was a significant difference within the intervention group between baseline and follow-up in the following item: pressure/discomfort in the chest, p = 0.02.
ASTA: The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia

The degree of anxiety as assessed with HADS was normal at baseline, i.e. ≤ 7 , in 120 (75 %) patients in the intervention group and in 96 (79 %) patients in the control group. The degree of depression was normal in 128 (81%) and 106 (86 %) patients, in the intervention group and control group, respectively. There were no significant differences between the groups.

The degree of anxiety was reduced over the year in both groups, while depression did not change significantly (Table 5). The scoring did not differ between the groups at the one-year FU (Table 5).

Health-related Quality of Life

At baseline, patients in the control group reported a higher degree of inability to work, study or carry out daily activities ($p=0.01$), avoiding spending time with acquaintances ($p=0.03$) and family/relatives ($p=0.03$), compared to the intervention group, as assessed with ASTA. There were baseline differences between the groups also in SF-36, in which patients in the intervention group scored higher in four scales (PF, RP, SF and RE, Table 5). Over the year, there was a significant improvement in both groups in RP, VT, SF, MH, EQ-VAS and additionally RE in the control group (Table 5). There were no significant differences between the groups at the one-year FU in either subscale of SF-36 or EQ-5D/EQ-VAS (Table 5). However, in ASTA, more patients in the control group reported inability to work, study or carry out daily activities at the one-year FU, as compared to the intervention group ($p = 0.01$).

Comparisons with the Norm Population

When comparing the two patient groups at baseline with a norm population, the patients in the intervention group scored significantly worse ($p<0.05$) in six out of eight scales (RP, GH, VT, SF, RE, MH) while the patients in the control group scored worse in seven of the scales (PF, RP, GH, VT, SF, RE, MH, Figure 10).

After one year, the patients in the intervention group improved in two scales (SF and MH) and scored similarly to the norm population and even better than the norm population in the BP scale. The patients in the control group still scored worse in seven out of eight scales, i.e. in all except BP, equal to the situation at baseline.

Table 5. Health-related quality of life, anxiety, and depression scores at baseline and after one year, assessed with SF-36, EQ-5D/EQ-VAS, and HADS.

Questionnaire	Group	Baseline	One-year FU	Changes over the year	Difference between groups at baseline (p-value)	Difference between groups at the one-year FU (p-value)	Difference between groups over time (p-value)	Difference within groups over time (p-value)
SF-36	PF	Intervention 73±23 Control 63±27	71±25 60±24	-1±17 2±17	<0.01	0.54	0.12	0.48 0.17
	RP	Intervention 45±44 Control 35±42	42±44 52±44	17±48 15±43	0.04	0.07	0.75	<0.01 <0.01
	BP	Intervention 68±28 Control 65±27	71±26 66±28	2±26 0±29	0.29	0.21	0.63	0.29 0.87
	GH	Intervention 58±20 Control 55±20	60±21 56±22	3±17 0±17	0.19	0.14	0.21	0.05 0.91
	VT	Intervention 53±23 Control 52±24	58±23 68±24	5±20 6±20	0.62	0.92	0.78	<0.01 <0.01
	SF	Intervention 77±23 Control 71±26	83±20 77±25	6±21 6±20	0.03	0.06	0.92	<0.01 <0.01
	RE	Intervention 69±41 Control 55±43	73±39 67±41	5±45 11±43	<0.01	0.15	0.34	0.15 0.02
	MH	Intervention 74±18 Control 71±19	78±18 76±19	3±16 4±17	0.24	0.39	0.77	<0.01 0.03
	EQ-5D index	Intervention 0.75±0.20 Control 0.73±0.21	0.78±0.20 0.75±0.21	0.03±0.23 0.00±0.23	0.49	0.72	0.33	0.12 0.98
	EQ-VAS	Intervention 66±23 Control 62±23	73±18 73±20	7±22 11±24	0.13	0.91	0.30	<0.01 <0.01
	HADS-A	Intervention 4.9±4.0 Control 5.0±3.8	4.2±3.7 4.4±3.9	-0.7±3.3 -1.0±2.4	0.83	0.67	0.51	<0.01 <0.01
	HADS-D	Intervention 3.8±3.4 Control 4.1±3.5	3.5±3.2 4.0±3.6	-0.1±0.5 -0.1±0.5	0.51	0.25	0.70	0.31 0.14

Notes: Scores are presented as means±SD. Differences between groups at baseline, at FU and over time were tested with the independent t-test, and differences within groups over time with the paired t-test. p-values <0.05 were considered as statistically significant.
BP: bodily pain; EQ-5D/EQ-VAS: EuroQol 5 dimensions/EuroQol visual analogue scale; FU: Follow-up; GH: general health; HADS: Hospital anxiety and depression scale; HADS-A: Hospital anxiety and depression scale – anxiety score; HADS-D: Hospital anxiety and depression scale – depression score; MH: mental health; PF: physical functioning; RE: role-emotional; RP: role-physical; SD: standard deviation; SF: social functioning; SF-36: Short form 36; VT: vitality

Figure 10. SF-36 scores in the control and intervention groups at baseline and after one year compared to a Swedish norm population, aged 65 to 74 years.

Note 1: The mean scores of the eight scales in SF-36 are shown for the intervention group and control group at baseline, and follow-up in red and blue bars. The mean scores of the aged-matched Swedish norm population are shown in the black line.

Note 2: The t-test was used to check for significant differences between the different study population groups and the norm population. p-values < 0.05 were considered as statistically significant

BP: bodily pain; GH: general health; MH: mental health; PF: physical functioning; RE: role-emotional; RP: role-physical; SF: social functioning; VT: vitality

The SMURF Study – Papers II-IV

Baseline Characteristics

In total, 338 patients with AF were referred to the Department of Cardiology, Linköping University Hospital, Sweden and were eligible for participation in the study. Of those, 192 patients were included in the study. Any exclusions from the study were primarily due to logistical reasons, since we were only able to include four patients per week (Figure 11). Baseline characteristics are shown in Table 6.

Figure 11. Study inclusion flow chart in the SMURF study

Note: Exclusion for logistical reasons was due to the fact that a maximum of four patients per week could be included.
AF: atrial fibrillation; EF: ejection fraction; RFA: radiofrequency catheter ablation

Table 6. Baseline characteristics in the SMURF study

Variables	
Characteristics and concomitant diseases	
Age	60.5±10.2
Female gender	56 (29%)
Sagittal abdominal diameter (cm)	24.6±4.4
BMI (kg/m ²)	28.0±4.2
Paroxysmal AF	71 (37%)
Longest AF episode ≥1h	148 (77%)
>10 AF episodes last month	78 (41%)
Current smokers	5 (3%)
Previous smokers	93 (48%)
Hypertension	82 (43%)
Diabetes mellitus	16 (8%)
Vascular disease	13 (7%)
Heart failure	18 (9%)
CKD (GFR<60mL/min/1.73 m ²)	40 (21%)
Stroke/TIA	19 (10%)
CHA ₂ DS ₂ VASc	2 (0-3)
Self-reported alcohol consumption (units/week)	4 (1-9)
Anxiety	
possible anxiety	35 (18%)
probable anxiety	20 (10%)
Depression	
possible depression	18 (9%)
probable depression	15 (8%)
Medication	
Beta-blockers	139 (72%)
ACEi/ARB	77 (40%)
Statins	56 (29%)
AAD	105 (55%)
Amiodarone	42 (22%)
Flecainide	35 (18%)
Dronedarone	23 (12%)
Physical status and laboratory test results	
Systolic blood pressure (mmHg)	146±20
Diastolic blood pressure (mmHg)	90±11
AST (μkat/L)	0.46 (0.39-0.52)
ALT (μkat/L)	0.46 (0.36-0.59)
GT (μkat/L)	0.46 (0.34-0.74)
Total cholesterol (mmol/L)	5.0±1.2
LDL (mmol/L)	3.2±1.0
HDL (mmol/L)	1.2±0.34
hsCRP>3 mg/l	44 (23%)
TG (mmol/L)	1.2±0.60

Hair ethyl glucuronide concentration (pg/mg)	0 (0-8)
NT-proBNP (pg/ml)	170 (72-500)
MR-proANP (pmol/l)	135 (92-195)
MR-proADM	0.68±0.18

Procedural variables

AF at the ablation lab	51 (27%)
Procedural time (min)	188±50
Fluoroscopy time (min)	21 (16-28)
Number of patients requiring additional ablation lines in the LA	17 (9%)
Number of patients with an RA isthmus line	11 (6%)
Primary successful procedure	172 (90%)
Complications*	7 (4%)
AF recurrence within 12 months†	119 (62%)
Re-ablation within 12 months	58 (30%)

Echocardiographic measurements and cardiac pressures

EF (%)	56.7±8.9
Max LAV (ml)	56 (46-70)
Max LAVI (ml/m ²)	26.6 (22.3-32.5)
Min LAV (ml)	30 (23-42)
Min LAVI (ml/m ²)	15.0 (10.7-20.3)
RVSP (mmHg)	30 (26-34)
RVDP (mmHg)	11 (9-15)

Note: Continuous normally distributed data are presented as means±SD and non-normally distributed data as medians with 25th to 75th percentiles within brackets. Categorical data are presented as counts with percent values within brackets.

AAD: anti-arrhythmic drugs; ACEi: angiotensin converting enzyme inhibitor; AF: atrial fibrillation; ARB: angiotensin receptor blocker; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index CHA₂DS₂ VASc: congestive heart failure, hypertension, age ≥75, diabetes, stroke/TIA, vascular disease, age 65-74 years, sex category (i.e. female gender); CKD: chronic kidney disease; EF: ejection fraction; GT: glutamyl transferase; h: hour; HDL: high density lipoprotein; hsCRP: high-sensitive C-reactive protein; GFR: glomerular filtration rate; LA: left atrium; LAV: left atrial volume; LAVI: left atrial volume index; LDL: low density lipoprotein; MR-proADM: mid-regional portion of pro-adrenomedullin; MR-proANP: mid-regional fragment of the N-terminal precursor of atrial natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; RA: Right atrium; RVDP: right ventricular diastolic pressure; RVSP: right ventricular systolic pressure; SD: standard deviation; TG: triglycerides; TIA: transient ischaemic attack.

*Reported complications were: two cardiac tamponade requiring pericardiocentesis, one pericardial effusion without the need of pericardial drainage, three pseudo aneurysms, one larger than normal hematoma of the groin

†AF recurrence was defined as occurrence of AF or atrial flutter documented with ECG, or re-ablation, within one year from ablation.

Papers II and IV

Missing PROMs summary scores varied between 1-19% for SF-36, 2-20% for ASTA and 4-18% for HADS, and were due to not returning the questionnaire or due to missing answers removing the possibility of calculating a summary score.

The Predictors of Arrhythmia-related Symptoms and Health-related Quality of Life

Arrhythmia-related Symptoms

Anxiety, low-grade inflammation and LA dilatation significantly predicted arrhythmia-related symptoms at baseline (Table 7).

Female gender and >10 AF episodes in the last month before RFA were significant positive predictors, while diabetes and AF recurrence were significant negative predictors of improvement in ASTA symptom scale score between baseline and one-year FU (Table 8 and Figure 12).

Health-related Quality of Life

Anxiety, depression, low-grade inflammation, age, heart failure, MR-proADM and AF episode duration significantly predicted arrhythmia-related HRQoL at baseline, as assessed with the ASTA questionnaire (Table 7). Significant factors predicting PCS at baseline were obesity, RV diastolic pressure, >10 AF episodes in the last month before treatment, CHA₂DS₂-VASc score ≥ 2 , low-grade inflammation and depression (Table 7), while the factors that significantly predicted MCS at baseline were anxiety, depression and longest AF episode duration ≥ 1 h (Table 7).

More than 10 AF episodes in the last month before treatment and heart failure were significant positive predictors, while diabetes, LAV and AF recurrence were significant negative predictors of improvement in ASTA HRQoL scale score between baseline and 12 months FU (Table 8 and Figure 12).

Table 7. Predictors of arrhythmia-related symptoms and health-related quality of life, assessed with ASTA and SF-36, prior to radiofrequency catheter ablation of atrial fibrillation.

Scales	Predictors	Standardised beta	Predictor's p-value	Model's R ²	Model's p-value
ASTA symptom scale score				0.313	<0.001
	Anxiety				
	probable anxiety	0.5	<0.001		
	possible anxiety	0.233	0.001		
	low-grade inflammation*	0.211	0.002		
ASTA HRQoL scale score	LA dilatation†	0.141	0.033	0.513	<0.001
	Depression				
	probable depression	0.406	<0.001		
	possible depression	0.127	0.076		
	Anxiety				
	probable anxiety	0.343	<0.001		
	possible anxiety	0.288	<0.001		
	Age	0.227	0.001		
	MR-proADM	-0.218	0.004		
	Heart failure‡	0.156	0.011		
	Low-grade inflammation*	0.15	0.012		
	AF episode duration ≥1h	0.131	0.026		
				0.359	<0.001
	Obesity§	-0.301	<0.001		
	RVDP	0.244	0.001		
	>10 AF episodes/month	-0.233	0.001		
	CHA₂DS₂-VASc ≥2	-0.223	0.001		
	Low-grade inflammation*	-0.204	0.002		
MCS	Depression			0.568	<0.001
	probable depression	-0.135	0.039		
	possible depression	-0.04	0.558		
	Anxiety				
	probable anxiety	-0.437	<0.001		
	possible anxiety	-0.23	<0.001		
	Depression				
	probable depression	-0.256	<0.001		
	possible depression	-0.232	<0.001		
	AF episode duration ≥1h	-0.158	0.003		

Note 1: Multiple linear regression analysis was performed in order to determine possible predictors of variation in patients' symptoms and HRQoL. The models were fit by an enter method where all variables were entered into the original model and then variables with p-values over 0.05 were removed.

Note 2: Anxiety and depression were assessed with the HADS questionnaire

Note 3: The ASTA symptom scale score was used as a dependent variable in order to express symptom variation. The disease-specific ASTA HRQoL and the generic SF-36 component summaries (PCS and MCS) were used in order to express the variation in HRQoL.

Note 4: All reported p-values are two-sided and a p-value <0.05 was considered statistically significant.

AF: atrial fibrillation; ASTA: Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; CHA₂DS₂-VASc: congestive heart failure, hypertension, age ≥75, diabetes, stroke/TIA, vascular disease, sex category (i.e. female gender); EF: ejection fraction; HADS: Hospital Anxiety and Depression Scale; h: hour; LA: left atrium; LAV: left atrial volume; MCS: mental component summary; MR-proADM: mid-regional portion of pro-adrenomedullin; PCS: physical component summary; RVDP: right ventricular diastolic pressure; SF-36: 36-Item Short Form Health Survey.

* Low-grade inflammation was defined as high sensitive C-reactive protein >3mg/l

†LA dilatation was defined as LAV >35ml/m²

‡HF was defined as ejection fraction <45%

§obesity was defined as Body Mass Index >30 kg/m²

Table 8. Predictors of improvement in arrhythmia-related symptoms and health-related quality of life in ASTA after radiofrequency catheter ablation of atrial fibrillation.

Scale	Variable	Univariate		Multivariate		
		Standardised beta	p-value	Standardised beta	p-value	Models R ² Models p-value
ASTA symptoms scale score	Female gender	-0.179	0.020	-0.181	0.015	0.183 <0.001
	>10 AF episodes last month	-0.169	0.031	-0.158	0.031	
	Diabetes	0.210	0.006	0.227	0.002	
	AF recurrence within 12 months	0.291	<0.001	0.271	<0.001	
ASTA HRQoL scale score	>10 AF episodes last month	-0.203	0.009	-0.172	0.030	0.198 <0.001
	Diabetes	0.197	0.010	0.180	0.018	
	Heart failure	-0.201	0.009	-0.180	0.022	
	LAV max	0.188	0.018	0.193	0.013	
	AF recurrence within 12 months	0.259	0.001	0.244	0.002	
	Probable anxiety	-0.182	0.019		ns.	ns.
	Probable depression	-0.157	0.043		ns.	

Note 1: Univariate linear regression was performed in order to determine possible predictors of improvement in arrhythmia-related symptoms and health-related quality of life. Only significant variables in the univariate analysis are shown in this table. The dependent variable was the scale score at the one-year follow-up with the score at baseline subtracted. The independent predictors analysed were: age, gender, BMI, hypertension (yes/no), heart failure (yes/no), diabetes (yes/no), AF type (paroxysmal or persistent), CHA₂DS₂-VASC score, AF episode duration (longest AF episode duration of ≥1 hour vs. <1 hour in the last three months before RFA), frequency of AF episodes (>10 episodes vs. ≤10 episodes of AF in the last month before RFA), hsCRP, EF, LAV, AF recurrence (yes/no), and finally possible and probable anxiety and depression as assessed with HADS. Variables that were significant in the univariate analysis were inputted in the multivariate analysis, which was conducted in a stepwise backward elimination fashion.

Note 2: Higher scores reflect a higher symptom burden and a worse HRQoL. The larger the improvement, the larger the decrease in ASTA-score.

Note 3: All reported p-values were two-sided, and a p-value < 0.05 was considered statistically significant.

AF: atrial fibrillation; ASTA: The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; CHA₂DS₂-VASC: congestive heart failure, hypertension, age ≥75, diabetes, stroke/TIA, vascular disease, age 65-74 years, sex category (i.e. female gender); EF: ejection fraction; HADS: The Hospital Anxiety and Depression Scale; HRQoL: health-related quality of life; hsCRP: high-sensitive C-reactive protein; LAV: left atrial volume; RFA: radiofrequency catheter ablation

Figure 12. Mean improvement in ASTA symptom scale score (A) and HRQoL scale score (B) depending on AF episodes in the month before radiofrequency catheter ablation, and on atrial fibrillation recurrence within one year after radiofrequency catheter ablation.

Note 1: Improvement in absolute values. AF: atrial fibrillation; ASTA: The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; HRQoL: health-related quality of life

The Effect of Radiofrequency Catheter Ablation on Patient-reported Outcome Measures

Arrhythmia-related Symptoms

At baseline, in those patients with ASTA questionnaires available, 135 (71%) had experienced their latest AF episode within the last month prior to RFA. During an AF episode, 126 (66%) patients reported the heart beating fast, 151 (79%) reported irregular heartbeat, 90 (47%) reported harder heart beats than usual and 105 (55%) had felt one or more missed heart beats. The most commonly reported symptoms were breathlessness during activity and tiredness, while the least frequently reported symptom was chest pain (Figure 13).

After one year, in those patients that completed the ASTA questionnaire, 83 (47%) were asymptomatic and the number that had experienced their latest AF episode within the last month had decreased significantly to 74 (42%, $p < 0.001$). Each item in the ASTA symptom scale improved significantly over time (Figure 13), and there was a significant improvement in the ASTA scale score with large ES (Table 9).

Health-related Quality of Life

The most commonly reported affected arrhythmia-specific HRQoL domains, as assessed with ASTA, were impaired physical activity, deteriorated life situation, avoiding planning things one would have liked to do, and feeling unable to work, study or carry out daily activities (Figure 14). All individual items in the ASTA HRQoL part, as well as the ASTA HRQoL scale score, improved significantly over time, the latter with large ES (Table 9, Figure 15).

The subscales in general HRQoL with the lowest scores at baseline, as assessed with SF-36, were RP and VT (Table 9). Each subscale in SF-36 improved significantly over time, as did the MCS and PCS, with small ES (Table 9, Figure 15).

Anxiety and Depression

The baseline HADS scores indicated normal levels of anxiety and depression (Table 9). Still, 55 (29%) and 33 (17%) patients had possible or probable anxiety and depression, respectively (Table 6). Both anxiety and depression scores improved significantly over time with trivial or small ES (Table 9).

Figure 13. Symptoms reported in ASTA prior to radiofrequency catheter ablation and at one-year follow-up.

Note: The nine items in the ASTA symptom scale are shown on the X-axis, with the percentage of the four-point response scale ("No", "Mild", "Moderate", "Severe") on the Y-axis (Response "No" not shown). 1Y: One year; ASTA: The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; B: Baseline; FU: Follow-up

Table 9. ASTA, SF-36, and HADS questionnaire summary scores at baseline, four-month and one-year follow-up.

	B	4M FU	1Y FU	ES from B to 1Y FU	Fried- man's test p-value	Pairwise comparisons Time	p-value
ASTA							
Symptom scale score	37 (26-50)	11 (0-33)	4 (0-30)	-1.20	<0.001	B-4M B-1Y 4M-1Y	<0.001 <0.001 0.528
HRQoL scale score	36 (21-49)	10 (0-31)	0 (0-28)	-1.00	<0.001	B-4M B-1Y 4M-1Y	<0.001 <0.001 0.117
SF-36							
PF	75 (55-90)	85 (65-95)	85 (70-95)	0.43	<0.001	B-4M B-1Y 4M-1Y	<0.001 <0.001 0.103
RP	50 (0-100)	75 (25-100)	100 (25-100)	0.43	<0.001	B-4M B-1Y 4M-1Y	0.013 <0.001 0.069
BP	74 (41-100)	74 (51-100)	80 (52-100)	0.16	0.018	B-4M B-1Y 4M-1Y	0.248 0.040 0.204
GH	60 (45-77)	67 (47-82)	67 (47-82)	0.22	0.020	B-4M B-1Y 4M-1Y	0.108 0.001 0.119
VT	50 (30-70)	65 (45-80)	60 (40-85)	0.40	<0.001	B-4M B-1Y 4M-1Y	<0.001 <0.001 0.574
SF	75 (63-100)	100 (75-100)	100 (63-100)	0.20	0.021	B-4M B-1Y 4M-1Y	0.005 0.008 0.273
RE	100 (33-100)	100 (67-100)	100 (67-100)	0.31	0.028	B-4M B-1Y 4M-1Y	0.005 0.001 0.636
MH	76 (60-88)	84 (76-92)	84 (68-92)	0.25	<0.001	B-4M B-1Y 4M-1Y	<0.001 <0.001 0.332
PCS	41 (34-50)	47 (37-52)	48 (39-54)	0.39	<0.001	B-4M B-1Y 4M-1Y	0.006 <0.001 0.006
MCS	48 (37-55)	53 (44-57)	53 (43-56)	0.28	0.006	B-4M B-1Y 4M-1Y	0.001 0.002 0.640
HADS							
Anxiety scale	5 (2-8)	3 (1-6)	3 (1-7)	0.24	<0.001	B-4M B-1Y 4M-1Y	0.001 <0.001 0.743
Depres- sion scale	3 (1-6)	2 (1-5)	2 (1-6)	0.18	<0.001	B-4M B-1Y 4M-1Y	0.002 0.001 0.819

Note 1: Summary scores are presented as medians (25th – 75th percentiles).

Note 2: ASTA and SF-36 scores range from 0 to 100 and HADS from 0-21. In SF-36, a higher score reflects better health status while the opposite is the case in ASTA and HADS.

Note 3: Analysis of the change throughout the three measurement points was performed with Friedman's test. In order to analyse between which time points there was a significant change, Wilcoxon's signed rank test was used. A p-value <0.05 was considered statistically significant.

Note 4: ES was calculated by dividing the mean difference between baseline and one-year follow-up by the SD at baseline. A result <0.20 denotes trivial, 0.20-0.49 small, 0.50-0.79 moderate and ≥0.80 large ES.

1Y: One year; 4M: Four months; ASTA: The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; B: Baseline; BP: bodily pain; ES: Effect size; FU: Follow-up; GH: general health; HADS: Hospital anxiety and depression scale; HRQoL: Health-related quality of life; MCS: Mental component summary; MH: mental health; PCS: Physical component summary; PF: physical functioning; RE: role-emotional; RP: role-physical; SF: social functioning; SF-36: Short form 36; VT: vitality

Figure 15. Symptom and health-related quality of life scores in ASTA and SF-36 at baseline and follow-up.

Note 1: A) ASTA symptom scale score (symptoms) and ASTA HRQoL scale score (HRQoL). Values range from 0 to 100 and higher scores reflect a higher symptom burden and a worse effect on HRQoL.
Note 2: B) The eight subscale scores of SF-36 and the mental and physical component summary scores are shown. Values range from 0 to 100 and lower scores reflect worse HRQoL.
1Y: One year; 4M: four months; B: Baseline; ASTA: The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; BP: bodily pain; FU: follow-up; GH: general health; HRQoL: Health-related quality of life; mcs: mental component summary; MH: mental health; pcs: physical component summary; PF: physical functioning; RE: role-emotional; RP: role-physical; SF: social functioning; SF-36: Short Form 36; VT: vitality;

Paper III and the Association of Alcohol Consumption with Symptoms and Health-related Quality of Life

Alcohol Consumption

Information on self-reported alcohol consumption was available for 181 (94%) patients and hEtG was analysable in 156 (81%) patients. Of those with non-analysable hEtG, one was a woman whose sample analysis failed for technical reasons, while the other 35 patients were men whose hair was too short to take a sample (Table 10). The group with non-analysable hEtG had lower HDL and CHA₂DS₂-VASc scores (Table 10), which was probably gender-related since adjustment for gender showed that analysable hEtG was not correlated to HDL ($p = 0.438$, model: $R^2 = 0.208$, $F = 24.759$, $p < 0.001$), nor to CHA₂DS₂-VASc score ($p = 0.749$, model: $R^2 = 0.179$, $F = 20.658$, $p < 0.001$), but gender was ($p < 0.001$ for both HDL and CHA₂DS₂-VASc scores). Men were younger, had a larger sagittal abdominal diameter, higher alanine aminotransferase (ALT), aspartate aminotransferase (AST), glutamyl transferase (GT), and triglycerides (TG), as well as lower HDL, and CHA₂DS₂-VASc scores than women (Table 10). Analyses regarding the predictive role of gender and sagittal abdominal diameter on HDL showed that sagittal abdominal diameter (inversely related, $p < 0.001$) and gender ($p < 0.001$), but not the use of statins ($p = 0.349$), were related to HDL (model $R^2 = 0.266$, $F = 22.243$, $p < 0.001$). There was a statistically significant correlation between self-reported alcohol consumption and hEtG ($r = 0.63$, $p < 0.001$).

Associations between Alcohol Consumption, Cardiac Biomarkers, Left Atrial Size, Re-ablation, Symptoms and Health-related Quality of Life

Ethyl Glucuronide in Hair

Of those patients with analysable hEtG, 88 (56%) had a value of 0 pg/mg, and nine (6%) patients had a value strongly indicating chronic excessive alcohol consumption, i.e. ≥ 30 pg/mg. Forty-three (28%) patients had values indicative of repeated alcohol consumption, providing evidence to refute a claim of abstinence, i.e. ≥ 7 pg/mg, while the remaining 113 (72%) had values below this level.

Patients with hEtG ≥ 7 pg/mg were more likely to be previous smokers, and had larger sagittal abdominal diameter and higher GT levels compared to the group with hEtG < 7 pg/mg (Table 10). NT-proBNP, ad-

justed MRpro-ANP, maximum and minimum LAVI were significantly higher in men with hEtG ≥ 7 pg/mg as compared to men with hEtG < 7 pg/mg, while there were no such findings for women (Table 11 and Figure 16).

Re-ablation was performed in 58 (30%) patients. The frequency of re-ablation in patients with hEtG ≥ 7 pg/mg vs. < 7 pg /mg was 14 (42%) vs. 16 (24%, $p = 0.051$) in men, and 3 (30%) vs. 13 (29%, $p = 0.944$) in women. Adjusted analysis showed a significant correlation between hEtG and re-ablation in men (OR 3.5; 95% confidence interval (CI) 1.3-9.6; $p = 0.017$) but not in women (OR 0.60; 95% CI 0.1-3.1; $p = 0.541$).

There were no significant differences in ASTA symptom and HRQoL scale scores between men with hEtG ≥ 7 pg/mg vs. < 7 pg /mg, either at baseline, or at the one-year FU (Table 12). In men, both groups improved significantly between baseline and FU in both scale scores (Table 12).

While there were no significant differences at baseline in ASTA symptom scale score between women with hEtG ≥ 7 pg/mg vs. < 7 pg /mg, AS-TA HRQoL scale score was significantly better in women with hEtG ≥ 7 pg/mg vs. < 7 pg /mg (Table 12). Women with hEtG < 7 pg /mg improved significantly between baseline and the one-year FU in both scores while women with hEtG ≥ 7 pg/mg improved in ASTA symptom scale score but not ASTA HRQoL scale score (Table 12). Neither score differed significantly between women with hEtG ≥ 7 pg/mg vs. < 7 pg /mg, at FU.

Self-reported Alcohol Consumption

Median self-reported alcohol consumption was four (1-9) units/week, with 22 (12%) patients reporting a high consumption. Men reported a higher intake than women (Table 10).

Patients with self-reported high alcohol consumption were more likely to be previous smokers but no other significant differences were observed in baseline characteristics, cardiac biomarkers, echocardiographic measurements (Table 10 and Table 13) or in the frequency of re-ablation (crude analysis, high vs. low consumption, men: 7 (47%) vs. 32 (29%), $p = 0.161$; women: 2 (29%) vs. 14 (29%), $p = 0.974$; adjusted analysis, men: OR 2.7; 95% CI 0.8-8.9, $p = 0.09$; women: OR 1.3; 95% CI 0.2-10.0, $p = 0.77$).

There were no significant differences at baseline in either ASTA score in either gender (Table 14). Although all groups improved significantly between baseline and FU, the improvement was less pronounced in men with high consumption, who scored significantly worse in both scores at FU compared to men with low consumption (Table 14).

Table 10. Baseline characteristics according to analysable hEtG, gender, and different levels of alcohol consumption.

Variables	hEtG analysable (n = 156)	hEtG not analysable (n = 36)	p-value	Men (n = 136)	Women (n = 56)	p-value	hEtG <7 pg/mg (n = 113)	hEtG ≥7 pg/mg (n = 43)	p-value	Low consumption (n = 159)	High consumption (n = 22)	p-value
Characteristics and concomitant diseases												
Age	61.1±10.1	57.7±10.2	0.075	58.7±10.4	64.8±8.5	<0.001	61±11	60±9	0.615	60±11	61±8	0.651
Female gender	55 (35%)	1 (3%)	<0.001	-	-	-	45 (40%)	10 (23%)	0.053	48 (30%)	7 (32%)	0.876
Sagittal abdominal diameter (cm)	24.4±4.2	25.5±5.0	0.158	25.1±4.4	23.4±4.2	0.014	23.8±4.3	25.8±3.8	0.008	24.5±4.4	24.9±3.9	0.725
BMI (kg/m²)	27.9±4.2	28.3±4.4	0.573	28.2±4.3	27.3±4.1	0.171	27.7±3.4	28.9±3.7	0.064	27.8±4.3	28.6±4.0	0.414
Current smokers	5 (3%)	0	§	3 (2%)	2 (4%)	§	4 (4%)	1 (2%)	§	4 (3%)	1 (5%)	§
Previous smokers	79 (51%)	14 (39%)	0.203	64 (47%)	29 (52%)	0.551	49 (43%)	30 (70%)	0.003	72 (45%)	16 (73%)	0.016
Hypertension	69 (44%)	13 (36%)	0.375	57 (42%)	25 (45%)	0.728	50 (44%)	19 (44%)	0.994	67 (42%)	11 (50%)	0.485
Diabetes mellitus	12 (8%)	4 (11%)	§	10 (7%)	6 (11%)	0.444	9 (8%)	3 (7%)	0.836	16 (10%)	0 (0%)	§
Vascular disease	10 (6%)	3 (8%)	§	9 (7%)	4 (7%)	§	6 (5%)	4 (9%)	0.363	8 (5%)	2 (9%)	§
Heart failure	16 (10%)	2 (6%)	§	15 (11%)	3 (5%)	0.220	12 (11%)	4 (9%)	0.809	15 (9%)	2 (9%)	§

Structured Management, Symptoms, Health-related Quality of Life and Alcohol in Patients with Atrial Fibrillation

CKD (GFR<60mL/min/1.7 3 m ²)	31 (20%)	9 (25%)	0.495	29 (21%)	11 (20%)	0.794	20 (18%)	11 (26%)	0.270	32 (20%)	3 (14%)	§
Stroke/TIA	14 (9%)	5 (14%)	0.373	12 (9%)	7 (13%)	0.438	10 (9%)	4 (9%)	0.930	13 (8%)	4 (18%)	0.132
CHA ₂ DS ₂ -VAsc	2 (1-3)	1 (0-2)	0.048	1 (0-2)	3 (2-3)	<0.001	2 (1-3)	1 (1-3)	0.542	2 (0-3)	2 (1-3)	0.297
Systolic blood pres- sure (mmHg)	146±20	147±21	0.662	146±20	145±22	0.662	146±20	146±20	0.988	126±18	121±20	0.168
Diastolic blood pres- sure (mmHg)	90±11	90±11	0.864	91±11	89±11	0.414	90±12	91±9	0.457	74±12	75±11	0.741
AST (µkat/L)	0.45 (0.38-0.52)	0.47 (0.40-0.57)	0.378	0.47 (0.40-0.54)	0.43 (0.34-0.49)	0.012	0.44 (0.37-0.52)	0.46 (0.41-0.51)	0.382	0.46 (0.35-0.59)	0.44 (0.39-0.55)	0.681
ALT (µkat/L)	0.46 (0.35-0.60)	0.43 (0.38-0.59)	0.985	0.47 (0.38-0.61)	0.37 (0.30-0.51)	<0.001	0.46 (0.34-0.60)	0.47 (0.37-0.62)	0.276	0.46 (0.35-0.59)	0.41 (0.34-0.62)	0.670
GT (µkat/L)	0.45 (0.32-0.75)	0.47 (0.38-0.74)	0.432	0.50 (0.38-0.78)	0.37 (0.29-0.57)	0.002	0.42 (0.30-0.62)	0.60 (0.42-1.40)	<0.001	0.45 (0.34-0.74)	0.52 (0.34-1.15)	0.261
Total cholesterol (mmol/L)	5.0±1.2	4.8±1.2	0.397	4.9±1.1	5.1±1.3	0.288	5.0±1.2	4.9±1.1	0.735	4.9±1.2	5.2±1.0	0.313
LDL (mmol/L)	3.2±1.0	3.1±1.1	0.649	3.2±1.0	3.2±1.1	0.938	3.2±1.1	3.1±1.0	0.443	3.2±1.1	3.3±0.9	0.458
HDL (mmol/L)	1.3±0.4	1.1±0.3	0.016	1.1±0.27	1.5±0.4	<0.001	1.3±0.3	1.2±0.4	0.550	1.2±0.4	1.3±0.3	0.486
TG (mmol/L)	1.2±0.6	1.3±0.6	0.401	1.3±0.6	1.0±0.5	0.006	1.1±0.5	1.3±0.8	0.111	1.2±0.6	1.3±0.6	0.594
Alcohol consump- tion												

Self-reported consumption (units/week)	4 (1-9)	3 (0-8)	0.488	5 (1-9)	3 (0-6)	0.041	2.5 (0-6)	9 (6-15)	<0.001	3 (0-6)	18 (13-24)	<0.001
Ethyl glucuronide concentration (pg/mg)	-	-	-	0 (0-8.2)	0 (0-5.6)	0.213	0 (0-0)	15 (10-26)	<0.001	0 (0-7.7)	3.8 (0-8.3)	0.421

Note 1: Baseline data are presented for groups according to whether hEiG was analysable or not, gender, hEiG <7 vs. ≥7 pg/mg and low vs. high self-reported alcohol consumption.

Note 2: Continuous data are presented as means with standard deviation for normally distributed variables or as median values with 25th to 75th percentile within brackets for non-normally distributed variables. Categorical data are presented as counts with percent values within brackets.

Note 3: p-values for the differences between groups were calculated with the t-test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed continuous variables and with the Chi-square test for categorical variables.

AF: atrial fibrillation; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: Body Mass Index; CHA₂DS₂-VASc: congestive heart failure, hypertension, age ≥75, diabetes, stroke/TIA, vascular disease, age 65-74, sex category (i.e. female gender); CKD: chronic kidney disease; GT: glutamyl transferase; GFR: glomerular filtration rate; hEiG: hair ethyl glucuronide; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglycerides; TIA: transient ischaemic attack.

\$p\$-values not reported due to no fulfilment of assumptions for Chi-square test

Table 11. Cardiac biomarkers and echocardiographic measurements according to different levels of ethyl glucuronide in hair.

	Total study population				Men			Women				
	hEtG <7 pg/mg (n = 113)	hEtG ≥7 pg/mg (n = 43)	Crude p- value	Adjusted p-value	hEtG <7 pg/mg (n = 68)	hEtG ≥7 pg/mg (n = 33)	Crude p- value	Adjusted p-value	hEtG <7 pg/mg (n = 45)	hEtG ≥7 pg/mg (n = 10)	Crude p- value	Adjusted p-value
Cardiac biomarkers												
NT-proBNP (pg/ml)	170 (66-489)	250 (110-660)	0.109	0.031	130 (49-346)	250 (96-695)	0.010	0.002	230 (125-910)	230 (125-480)	0.810	0.909
MR-proANP (pmol/l)	133 (88-194)	140 (101-221)	0.229	0.055	117 (83-179)	142 (100-224)	0.120	0.047	153 (93-249)	139 (112-206)	0.965	0.587
Echocardiographic measurements												
EF (%)	57±9	55±8	0.238	0.454	56±10	53±8	0.113	0.409	58±9	62±4	0.086	0.743
Max LAVI (ml/m ²)	25.8 (21.6-32.7)	29.1 (23.7-32.2)	0.103	0.317	25.8 (21.4-32.0)	30.1 (26.7-33.9)	0.017	0.024	25.7 (21.7-34.6)	25.0 (18.9-29.6)	0.438	0.079
Min LAVI (ml/m ²)	14.9 (11.1-19.4)	16.2 (11.1-21.4)	0.190	0.368	14.6 (10.5-19.3)	17.5 (12.0-22.7)	0.029	0.038	15.0 (11.9-19.9)	12.1 (9.4-19.1)	0.228	0.097

Note 1: Normally distributed continuous data are presented as means with standard deviation and non-normally distributed continuous data as median values with 25th to 75th percentiles within brackets.
Note 2: Crude p-values for differences between groups were calculated with the t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. Adjustment for age, systolic blood pressure, BMI, heart failure and actual heart rhythm, was made using multiple linear regression analysis, and using the logarithmic transformation for NT-proBNP and MR-proANP in order to achieve normal distribution.
BMI: body mass index; EF: ejection fraction; hEtG: hair ethyl glucuronide; LAVI: left atrial volume index; MR-proANP: mid-regional fragment of the N-terminal precursor of atrial natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide

Figure 16. Cardiac biomarkers in different hair ethyl glucuronide groups in men and women.

Note 1: The p-values were obtained through multiple linear regression analysis, using age, systolic blood pressure, BMI, heart failure (yes/no) and actual heart rhythm (SR/AF) as co-variables.
AF: Atrial fibrillation; BMI: body mass index; hEtG: Ethyl glucuronide in hair; MR-proANP: mid-regional fragment of the N-terminal precursor of atrial natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide; SR: Sinus rhythm

Table 12. Arrhythmia-specific symptoms and health-related quality of life scores in ASTA according to different levels of ethyl glucuronide in hair.

	Men		Women	
	hEtG <7 pg/mg (n = 68)	hEtG ≥7 pg/mg (n = 33)	hEtG <7 pg/mg (n = 45)	hEtG ≥7 pg/mg (n = 10)
ASTA symptom scale score				
Baseline	37 (26-52)	41 (22-52)	41 (30-52)	30 (21-49)
One-year follow-up	6 (0-32)	0 (0-44)	0 (0-26)	0 (0-24)
p-value†	<0.001	<0.001	<0.001	0.027
ASTA HRQoL scale score				
Baseline	35 (23-56)	31 (21-53)	38 (27-51)	23 (7-46)
One-year follow-up	4(0-31)	0 (0-33)	0 (0-24)	0 (0-26)
p-value†	<0.001	<0.001	<0.001	0.183

Note: Data are presented as medians with 25th to 75th percentiles within brackets.
ASTA: The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; hEtG: hair ethyl glucuronide; HRQoL: Health-related quality of life
* p-value for differences between groups at baseline or one-year follow-up, analysed using the Mann-Whitney U test.
† p-value for differences within groups between baseline and one-year follow-up, analysed using Wilcoxon's signed rank test.

Table 13. Cardiac biomarkers and echocardiographic measurements according to different levels of self-reported alcohol consumption.

	Total study population				Men				Women			
	Low con- sumption (n = 159)	High con- sumption (n = 22)	Crude p- value	Adjust- ed p- value	Low con- sumption (n =111)	High con- sumption (n =15)	Crude p- value	Adjust- ed p- value	Low con- sumption (n =48)	High con- sumption (n =7)	Crude p- value	Adjust- ed p- value
Cardiac biomarkers												
NT-proBNP (pg/ml)	170 (67-529)	223 (133-465)	0.344	0.477	150 (58-455)	220 (100-450)	0.390	0.257	240 (130-868)	320 (150-1628)	0.605	0.531
MR-proANP (pmol/l)	129 (89-188)	140 (101-217)	0.460	0.713	121 (83-179)	140 (107-200)	0.386	0.254	163 (98-203)	139 (78-309)	0.791	0.411
Echocardiograph- ic measurements												
EF (%)	56.9±8.7	55.5±9.5	0.502	0.347	55.7±8.9	56.1±8.8	0.883	0.840	59.6±7.6	54.4±11.5	0.119	0.163
Max LAVI (ml/m ²)	26.4 (22.4-32.7)	29.4 (23.4-33.0)	0.506	0.754	27.2 (22.8-32.3)	29.1 (23.3-33.4)	0.417	0.359	25.9 (21.7-33.8)	30.0 (22.1-34.2)	0.905	0.730
Min LAVI (ml/m ²)	14.9 (11.0-19.7)	15.0 (10.7-20.3)	0.931	0.633	14.9 (10.9-19.3)	15.0 (10.5-20.7)	0.887	0.942	14.7 (11.3-20.2)	15.6 (11.8-23.5)	0.933	0.640

Note 1: Normally distributed continuous data are presented as means with standard deviation and non-normally distributed continuous data as median values with 25th to 75th percentiles within brackets.

Note 2: Crude p-values for differences between groups were calculated with the t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. Adjustment for age, systolic blood pressure, BMI, heart failure and actual heart rhythm, was made using multiple linear regression analysis, and using the logarithmic transformation for NT-proBNP and MR-proANP in order to achieve normal distribution.

Note 3: High consumption was defined as more than 14 or 9 units/week (1 unit = 8 grams alcohol) in men and women, respectively, and low consumption as consumption below this level, including teetotalers.

BMI: body mass index; EF: ejection fraction; LAVI: left atrial volume index; MR-proANP: mid-regional fragment of the N-terminal precursor of atrial natriuretic peptide; NT-proBNP: N-terminal pro B-type natriuretic peptide

Table 14. Arrhythmia-specific symptoms and health-related quality of life scores in ASTA according to different levels of self-reported alcohol consumption.

	Men		Women	
	Low consumption (n =111)	High consumption (n =15) p-value*	Low consumption (n =48)	High consumption (n =7) p-value*
ASTA symptom scale score				
Baseline	37 (25-52)	37 (26-48) 0.758	39 (30-52)	30 (26-44) 0.184
One-year follow-up	4 (0-31)	22 (3-57) 0.043	0 (0-26)	0 (0-22) 0.551
p-value†	<0.001	0.044	<0.001	<0.001
ASTA HRQoL scale score				
Baseline	33 (21-49)	33 (21-67) 0.695	36 (23-49)	41 (26-59) 0.356
One-year follow-up	0 (0-26)	23 (8-36) 0.033	0 (0-28)	0 (0-9) 0.397
p-value†	<0.001	0.012	0.042	0.028

Note 1: Data are presented as medians with 25th to 75th percentiles within brackets.
Note 2: High consumption was defined as more than 14 or 9 units/week (1 unit = 8 grams alcohol) in men and women, respectively, and low consumption as consumption below this level, including teetotalers.
ASTA: The Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia; HRQoL: Health-related quality of life
* p-value for differences between groups at baseline or one-year follow-up, analysed using the Mann-Whitney U test.
† p-value for differences within groups between baseline and one-year follow-up, analysed using Wilcoxon's signed rank test.

DISCUSSION

The main findings of this thesis were that 1) structured care given through an AF outpatient clinic was superior to usual care in improving guideline adherence, arrhythmia-specific symptoms, and HRQoL, 2) anxiety and depression, as well as low-grade inflammation had a central role in both arrhythmia-related symptoms and HRQoL in patients with AF prior to RFA, 3) the most important predictors of improvement in both arrhythmia-specific symptoms and HRQoL one year after RFA were frequent AF attacks in the month before RFA, freedom from AF recurrence after RFA, and the absence of diabetes, while female gender was an additional predictor for symptom improvement and the presence of heart failure and the absence of an enlarged LA were additional predictors for HRQoL improvement, 4) men with an alcohol consumption corresponding to hEtG ≥ 7 pg/mg had elevated cardiac biomarkers, larger LAV, and a higher rate of re-ablations than men with hEtG < 7 pg/mg, while no such findings were present in women.

The SMaC-PAF Study – Paper I

The Effect of Structured Management of Patients with Atrial Fibrillation on Guideline Adherence

Appropriate treatment with OAC was better in the control group at FU than the results from older studies⁴⁷ and consistent with new and promising reports¹⁰⁵. However, the structured care resulted in a greater improvement in adequate use of OAC as well as in overall adherence to guidelines. The results are consistent with the study conducted by Hendriks et al., who showed not only a significant improvement in guideline adherence, but also a significant reduction in cardiovascular mortality and hospitalisation with structured care of AF patients⁵³. Guideline adherence concerning AF management and especially antithrombotic treatment, is improving worldwide¹⁰⁵, but these studies show the importance of structured care in order to improve guideline adherence to the fullest.

The Effect of Structured Management of Patients with Atrial Fibrillation on Patient-reported Outcome Measures

Another similarity between the SMaC-PAF study and the study by Hendriks et al., is the results concerning PROMs. In both studies, the control group scored lower at baseline in symptom burden and HRQoL compared to the intervention group, the scores of the generic SF-36 questionnaire improved and anxiety reduced in both groups, with no significant difference between the groups at FU⁹⁹. However, in the SMaC-PAF study, the SF-36 scores in the intervention group reached the scores of the age-matched norm population to a greater extent than the control group. Moreover, in the SMaC-PAF study, a disease-specific questionnaire was used, demonstrating differences in arrhythmia-specific symptoms and HRQoL after one year, in favour of the intervention group, emphasising the importance of disease-specific questionnaires in addition to generic questionnaires, as discussed further below.

The SMURF study – Papers II-IV

Papers II and IV

The Predictors of Symptoms and Health-related Quality of Life

Anxiety was an important predictor of arrhythmia-specific symptoms and HRQoL at baseline, but did not influence improvement of symptoms and HRQoL after RFA. Previous studies have shown that anxiety is strongly correlated with AF symptoms^{69,106}, and that a depressed mood and worry can increase perceptions of AF symptom burden and cause disengagement from daily activities¹⁰⁷. Still, their relationship can be regarded as a “the egg or the chicken” situation, i.e. are symptoms causing anxiety or is anxiety exaggerating symptoms? Nevertheless, treating the arrhythmia has a positive effect on both symptoms and anxiety, as discussed further below.

Low-grade inflammation was also a significant predictor of arrhythmia-specific symptoms and HRQoL at baseline, consistent with previous studies^{108,109}. It is unclear whether low-grade inflammation is the cause or the result of AF. Low-grade inflammation could be a marker of more long-standing and severe AF, or a marker of co-existing comorbidities, both affecting symptoms and HRQoL negatively.

Another possible indicator of more severe and long-standing AF, is enlargement of the LA. LAV was a negative predictor of arrhythmia-specific symptoms at baseline and of arrhythmia-specific HRQoL improvement. Large LAV is a known predictor of AF recurrence post RFA¹¹⁰, and AF recurrence reduces the likelihood of improvement in HRQoL, especially when using a disease-specific instrument¹⁰⁴. However, although an arrhythmia-specific instrument was used in this study, both LAV and AF recurrence remained significant negative predictors of HRQoL improvement, indicating that larger LAV per se is negatively associated with HRQoL improvement, and could thus be a sign of more severe and long-standing AF, affecting HRQoL negatively, even after a successful RFA.

The occurrence of frequent attacks of AF before RFA was a predictor of baseline PCS, consistent with the study by van den Berg et al., in which the frequency of AF paroxysms was an important predictor of physical functioning¹¹¹. The occurrence of frequent AF attacks was also a significant predictor of improvement in arrhythmia-specific symptom and HRQoL. In a study by Gaita et al. a higher reduction of arrhythmic burden and a higher freedom from AF recurrence after RFA correlated with a significant improvement in HRQoL¹¹². A low arrhythmic burden prior to RFA is likely to be reduced to a lesser extent compared to a high arrhythmic burden, explaining why the occurrence of frequent attacks of AF was a significant predictor of improvement in symptom burden and HRQoL.

There was an inverse relationship between recurrence of AF and improvement in symptoms and in HRQoL, which might be regarded as a quite self-evident fact. However, the two factors do not have to be mutually exclusive. In a previous study by Wokhlu et al., substantial improvement in general HRQoL was also noted in patients with AF recurrence after RFA¹¹³. However, only a minor improvement in arrhythmia-specific symptoms occurred, highlighting the difference between generic and disease-specific instruments. While the former reflects general health, influenced by comorbidities commonly present in patients with AF, the latter reflects health specific to a certain disease. In a study by Björkenheim et al., an arrhythmia-specific questionnaire was more sensitive to changes related to AF burden than a generic questionnaire, and more accurately reflected the effect of RFA¹⁰⁴. This indicates the importance of using a disease-specific instrument when evaluating the effects of RFA, and can explain why AF recurrence was one of the strongest inverse predictors of symptom and HRQoL improvement in this study.

The most important predictor of PCS at baseline was obesity. Obesity has been linked to AF development and progression, as well as to low HRQoL, with impaired diastolic function, inflammation and pericardial fat as possible mechanisms^{114,115}. However, it is a modifiable risk factor, and AF-related outcomes have been shown to be improved post RFA with

weight management as a part of an overall aggressive cardiovascular risk factor management programme²³. Although BMI was not a significant negative predictor of improvement in symptoms and HRQoL, the presence of diabetes was. In contrast to our study, Mohanty et al. reported a higher post ablation improvement in generic HRQoL in patients with the metabolic syndrome⁴. However, only a generic instrument was used in that study, and there was no significant change in patients with AF recurrence⁴. In this study, both diabetes and AF recurrence remained significant predictors in the multivariate regression analysis, indicating that diabetes per se, regardless of whether AF recurred or not, was a negative predictor of improvement in symptoms and HRQoL.

The presence of heart failure was a negative predictor of ASTA HRQoL at baseline, but a positive predictor of its improvement after RFA. In the CASTLE-AF study, in which RFA was compared to medical therapy in AF patients with heart failure, RFA was associated with a significantly lower rate of the composite end point of death or hospitalisation, improved EF and improved six-minute walk test⁴⁵. Although the CASTLE-AF study only included patients with an EF<35%, which was an exclusion criterion in this study, the diagnosis of heart failure in our study was also associated with improvement after RFA.

Chronic conditions, such as diabetes and heart failure, can affect HRQoL negatively. In this study, they had an opposite effect on HRQoL improvement post RFA. While affection of several organs may be the reason for reduced HRQoL in diabetic patients, cardiac dysfunction is most likely to be the cause of reduced HRQoL in patients with heart failure. Improving cardiac function through restoration of atrial function consequently has a greater effect on HRQoL in heart failure patients than in patients with diabetes.

Finally, female gender was a significant predictor of symptom improvement. A previous study by Forleo et al. pointed in the same direction¹¹⁶. Previous studies show that women tend to have higher symptom burden and are referred for RFA later and less often than men, despite equal results after RFA concerning clinical outcomes, such as AF recurrence, treatment success rate, hospitalisation and complications^{116,117}. These gender-related inequalities have no obvious explanations.

The Effect of Radiofrequency Catheter Ablation on Patient-reported Outcome Measures

Breathlessness during activity and tiredness were the most commonly reported symptoms, consistent with the 'Medical Anti-arrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation' (MANTRA-PAF) trial¹¹⁸. Each symptom item, as well as the ASTA symp-

tom scale score, improved after RFA. The large ES implies a large effect of RFA on symptom improvement, which is in line with other studies¹¹⁸⁻¹²⁰.

There was also a large improvement in the disease-specific ASTA HRQoL score, which is in line with previous studies¹²¹. General HRQoL improved also, but to a lesser extent, probably due to the above mentioned differences between generic and disease-specific instruments.

Both anxiety and depression improved after RFA, which is in line with previous studies^{70,71}. Thrall et al. showed that anxiety and depression, which are known predictors of HRQoL⁶⁹ and associated with AF recurrence after RFA⁷¹, affect approximately one third of patients with AF⁶⁹, as was the case in this study. Several possible mechanisms have been suggested, such as elevated sympathetic tone and correlation with systemic inflammation⁷⁰, but the mechanisms behind this relationship remain unclear.

Paper III and the Association of Alcohol Consumption with Symptoms and Health-related Quality of Life

Associations between Alcohol Consumption, Cardiac Biomarkers, Left Atrial Size, Re-ablation, Symptoms and Health-related Quality of Life

hEtG ≥ 7 pg/mg was associated with higher NT-proBNP and MR-proANP concentrations in men, consistent with previous studies which have shown a dose-response related positive correlation between reported alcohol consumption and ANP, and a relationship between excessive alcohol consumption and elevated levels of B-type natriuretic peptide¹²²⁻¹²⁴. This study showed that even moderate consumption, as indicated by an hEtG-value ≥ 7 pg/mg, was associated with increased levels.

Men with hEtG ≥ 7 pg/mg had larger LAV than men with hEtG < 7 pg/mg. This is consistent with the study by McManus et al., who showed a 0.16 mm larger LA dimension with every additional 10 g of alcohol per day¹²⁵. Similarly, Hung et al. showed that light to moderate intake of alcohol in a dose-dependent manner was related to larger LAV as well as impaired LA strain¹²⁶.

There were three-fold increased odds of having a re-ablation in men with hEtG ≥ 7 pg/mg than men with hEtG < 7 pg/mg, consistent with the study by Takigawa et al. and Qiao et al., who showed a strong association between alcohol consumption and unfavourable ablation outcomes^{127,128}. Contrary to those studies, this study also used an objective marker of alcohol consumption in addition to self-reported alcohol intake.

Baseline HRQoL scores were better in women with hEtG ≥ 7 pg/mg compared to women with hEtG < 7 pg/mg. This might be explained by the fact that the relationship between alcohol consumption and HRQoL has been described as a J- or U-curve, in which light to moderate drinkers tend to have the best HRQoL, while both abstinence and heavy consumption is associated with poor HRQoL¹²⁹⁻¹³¹. The reason there was no significant difference in men, might be due to the fact that men have a higher alcohol consumption than women¹³⁰, possibly diminishing the effect of light to moderate drinkers' HRQoL on the result.

After RFA, HRQoL improved in both genders and irrespective of alcohol consumption, except for women with hEtG ≥ 7 pg/mg, probably due to the low number in that group, rendering the analysis underpowered. In men with self-reported high alcohol consumption, improvement was clearly not as great as in the low consumption group, leading to a statistically significant difference between the high and low alcohol consumption groups in men at the one-year FU. Men with high alcohol consumption might thus benefit from RFA, but probably not as much as those with low consumption, in terms of symptom and HRQoL improvement.

The pathophysiology behind the negative effects of alcohol on the heart is complex and several possible mechanisms for the increased risk of AF have been suggested^{127,132}. Before a left ventricular systolic dysfunction is evident, subclinical alterations in myocardial contractility may occur¹²⁶. Studies have shown a possibly dose-response relationship between alcohol consumption and atrial remodelling¹²⁷, and that even moderate intake of alcohol is associated with the risk of AF⁸⁰. In that context, it is interesting that the relatively low cut-off level of 7 pg/mg used in this study was sufficient to observe a difference in cardiac biomarkers, LA size and in the rate of re-ablations. Studies have also shown that impaired systolic LA mechanics can predict success in maintaining SR after cardioversion and RFA^{133,134}, potentially explaining the more frequent re-ablations in men with hEtG ≥ 7 pg/mg that we found.

Methodological Considerations and Limitations

The SMaC-PAF Study

The most important limitation of the SMaC-PAF study is its non-randomised design with different centres recruiting patients to either the intervention group, or the control group, but not both. This is probably an important reason for the observed differences between the groups at baseline. Due to the nature of the intervention, in which many care-givers and patient flows were involved, it was considered that the risk of unplanned crossovers would have been significant if both patient groups had been enrolled at the same site. To avoid this, recruitment at different sites was preferred, increasing the risk of selection bias. An alternative could have been a cluster randomised study.

Interestingly, despite its randomised design baseline differences in favour for the intervention group were also observed in the study by Hendriks et al., which is the largest study in this area⁹⁹. Both studies also suffered from a considerable number of non-responders. The design of the study with the intention to do as little as possible to the control group in order to resemble usual care as much as possible, probably also led to lower motivation for filling in and returning the questionnaires.

Furthermore, in the intervention group, the questionnaires were handed out and brought back to the first visit at the outpatient AF clinic. The knowledge that one was being taken care of in a structured way could thus have influenced HRQoL, and may not have reflected the original HRQoL prior to inclusion. The patients in the control group on the other hand, often filled out the questionnaires while still at the hospital. These factors might also have been a reason for baseline differences.

The initial intention of the SMaC-PAF study was to include patients only at two centres. However, due to a slow inclusion rate at the control centre, two more centres were added and the time for enrolment was extended. Still, the intended recruitment goal of 200 patients in each group was not met, rendering the study underpowered to a certain extent.

The SMURF Study

Some of the limitations of the SMURF study were that it was a single centre observational cohort study of moderate size without any control group, and that it was constituted of a heterogenic group of patients including people with both paroxysmal and persistent AF, SR or AF upon admission, normal or reduced EF etc.

The major reason for not being included in the study despite eligibility was a logistical reason. It was only possible to include four patients per

week, due to the fact that an included patient was expected to be considerably more time-consuming. Blood samples and pressure measurements were handled by extra personnel, who were not available throughout the week. However, a separate analysis, which has previously been published¹³⁵, showed that there were no baseline differences between the participants included in our study and those not included due to logistical difficulties or because they declined participation. This makes selection bias less likely.

There was a numeral gender imbalance in the study, which has been observed in other studies¹³⁶, and as discussed above, might be due to the fact that women seem to be referred more seldom and later than men^{116,117}. The low number of women could have rendered the analyses concerning alcohol underpowered in the female group.

Assessing AF recurrence post RFA with an implantable loop recorder could have been an alternative to examination of medical records, the local RFA register and 24-hour Holter monitoring. However, this would mean a greater cost, and especially a greater inconvenience for the patient, and thus was considered ethically not motivated. Thus, the number of patients with AF recurrence was probably underestimated.

In line with previous studies, in which social drinkers often have unmeasurable hEtG results^{137,138}, some patients in this study who reported that they drank, had 0 pg/mg in hEtG. There might be different reasons for this. Although hEtG has been proved to perform excellently in the cut-off level of 30 pg/mg, the performance in the lower ranges is less accurate⁹⁰. hEtG can also be influenced by cosmetic hair treatments and thermal hair straightening tools, leading to false negative results⁹². This may not be known by the researcher and is only rarely reported¹³⁷, which was also the case in this study. Furthermore, hEtG cannot be analysed in men without hair, or with hair that is very short, which is the explanation for the gender differences between the groups with analysable and non-analysable hEtG. Moreover, drinking pattern (such as seldom binge drinking vs. continuous moderate intake) can influence hEtG⁹⁰. In this study, self-reported alcohol consumption was assessed with only a single question concerning weekly alcohol intake. A more thorough alcohol questionnaire and other blood tests in addition to hEtG, could have added valuable information.

CONCLUSIONS

The SMaC-PAF study showed that structured care of AF led to an improvement in guideline adherence, mainly driven by an improvement in OAC prescription. Although the degree of anxiety and the scoring concerning HRQoL were improved in both patient groups at FU, the arrhythmia-specific symptoms were less frequently experienced, and the SF-36 scores were more similar to the norm population, in the intervention group compared to the control group.

The SMURF study showed that the most important predictors of arrhythmia-related symptoms and HRQoL at baseline in patients with AF eligible for RFA were anxiety, depression and low-grade inflammation, and that the most significant predictor of general physical status was obesity. The most important predictors of improvement in arrhythmia-specific symptoms and HRQoL at the one-year FU were frequent AF attacks before RFA, freedom from AF recurrence after RFA, absence of diabetes, and additionally, female gender for symptom improvement and the presence of heart failure and the absence of an enlarged LA for HRQoL improvement.

In contrast to previous studies relying on self-reported alcohol consumption, the SMURF study is, to the best of my knowledge, the first study using an objective marker of long-term alcohol consumption in patients undergoing RFA. hEtG ≥ 7 pg/mg was associated with higher cardiac biomarker concentrations, larger LAV and a higher rate of re-ablations in men, while no such differences were found in women. This implies that men with an alcohol consumption corresponding to an hEtG-value ≥ 7 pg/mg, have a higher risk for LA remodelling, which could potentially worsen the AF situation.

FUTURE PERSPECTIVES

All the previous studies on structured care of patients with AF have either been conducted in, or recruited patients from, tertiary care centres. However, most patients are treated and followed up at primary health care centres. Future studies should investigate the outcomes of implementation of a structured management programme for patients with AF in primary care.

Although this thesis has increased our knowledge about the predictors of symptoms and HRQoL before and after RFA, the results have to be confirmed in future studies. Furthermore, the wide variety of symptoms in patients with AF is still a puzzle that is far from being solved. Further studies, investigating the associations of symptoms and HRQoL with more sensitive markers of AF impairment and remodelling, such as magnetic resonance findings and atrial strain, are needed to gain further insights into the reasons for the great variety of symptoms in patients with AF.

The indication for RFA is symptom-driven. Still, trials have most often used AF recurrence as the primary endpoint instead of symptom and HRQoL improvement. Although this thesis has shown that AF recurrence is an important issue when it comes to symptom and HRQoL improvement post RFA, future studies on RFA should to a greater extent use symptoms and HRQoL as endpoints, preferably using a combination of general and disease-specific PROMs. Clinicians following up the patients after RFA should also to a greater extent use PROMs as tools to assess symptoms and HRQoL in order to improve patient-centred care.

The role of light to moderate alcohol consumption in AF is an interesting subject that needs further clarification. To my knowledge, the SMURF study is the first study using an objective marker of long-term alcohol consumption in patients conducting RFA. The findings of the study have to be confirmed in further studies, suggestively using a more comprehensive alcohol questionnaire such as the AUDIT questionnaire, combined with more than one objective measure of alcohol consumption, such as hEtG and PETHs.

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