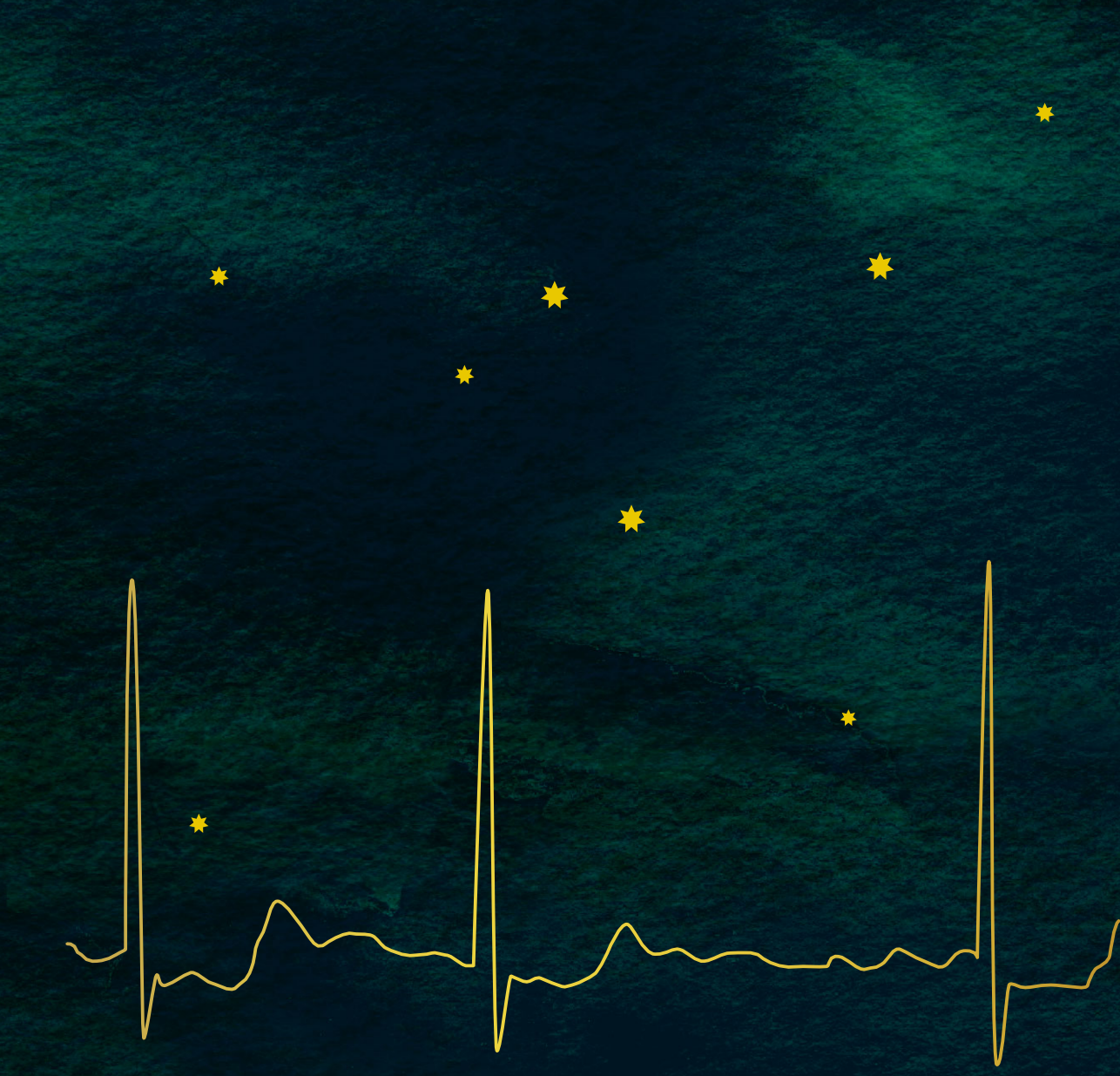
Integrating novel care approaches for atrial fibrillation patients undergoing ablation



INTEGRATING NOVEL CARE APPROACHES FOR ATRIAL FIBRILLATION PATIENTS UNDERGOING ABLATION

Dominique V.M. Verhaert

Integrating novel care approaches for atrial fibrillation patients undergoing ablation

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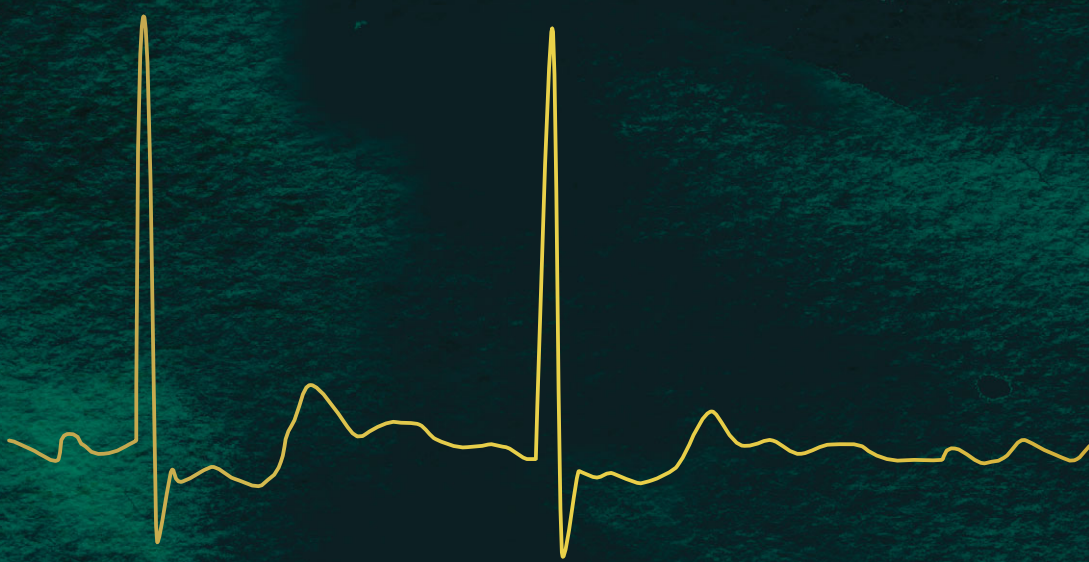


CHAPTER 1

General introduction and outline of the thesis

INTRODUCTION

Over the past decades, atrial fibrillation (AF) has grown into a true cardiovascular disease epidemic as a result of the improving global life expectancy, increasing prevalence of predisposing risk factors, and improved detection methods. As the most common sustained cardiac arrhythmia, AF affects over 350,000 patients in the Netherlands and over 43.5 million patients worldwide. [1, 2] In Western countries its lifetime risk is estimated between 30-40%. [3, 4] The arrhythmia is often accompanied by symptoms as palpitations, dyspnea, fatigue, and chest complaints, although about one third of AF patients is asymptomatic. [5] Regardless of symptoms, AF patients are at increased risk of developing major adverse events including ischemic stroke, heart failure, cognitive decline, and even mortality. [6]

Pathophysiology and comorbidities

The complex pathophysiology of AF can be summarized by an interplay of electrical triggers against a background of an arrhythmogenic substrate. Electrical triggers are induced by enhanced automaticity and occurrence of early and delayed afterdepolarizations, whereas the arrhythmogenic substrate (e.g., structural or electrical changes) facilitates perpetuation of AF through areas of slow conduction, heterogeneity in conduction velocity and re-entry. [7]

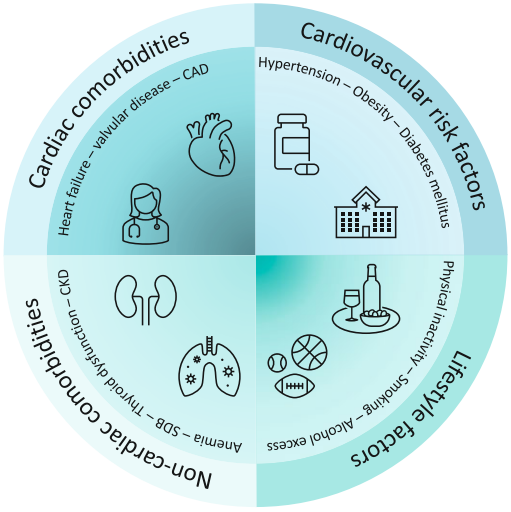

Figure 1. Factors contributing to the development and progression of an atrial arrhythmogenic substrate.

Abbreviations: CAD: coronary artery disease, CKD: chronic kidney disease, SDB: sleep disordered breathing.

Various comorbidities and risk factors have been described to contribute to the development of an arrhythmogenic substrate, either through atrial scarring or fibrosis, mechanical atrial wall stretch, myocyte ischemia, or inflammatory mediators. These comorbidities and risk factors include coronary artery disease, heart failure with preserved or reduced ejection fraction, valvular disease, hypertension, obesity, sleep disordered breathing, diabetes mellitus, anemia, thyroid dysfunction, and chronic kidney disease (*Figure 1*). Moreover, lifestyle factors such as smoking, alcohol excess, habitual vigorous exercise, and excessive physical inactivity are related to the extent of atrial substrate. [3, 8]

Once, up to one-third of patients was thought to suffer from 'lone AF', which was characterized as AF in young patients in absence of underlying comorbidities or structural changes. However, as understanding of AF pathophysiology advanced and screening methods for comorbidities improved, the identification of underlying comorbidities has become more common and the term 'lone AF' falls into disuse. [9] Data from a Scottish primary care cohort demonstrated that over 90% of AF patients had at least one comorbidity, and almost two-thirds had three or more other chronic conditions. [10] In young patients without any comorbidities, AF is often an expression of channelopathies or incipient cardiomyopathies. [11] Therefore, AF is no longer seen as just an isolated arrhythmia, but as a composite of different mechanisms and potentially an expression of concomitant morbidities. Consequently, although the direct management of the arrhythmia itself remains the cornerstone of treating AF patients, underlying sustaining factors should not be neglected and their recognition and treatment are an important pillar of AF care. [12]

Catheter ablation for AF

The two strategies to treat AF itself are heart *rate* control (allowing AF to persist on the atrial level while controlling the frequency of ventricular contractions) and heart *rhythm* control (attempting to restore and maintain sinus rhythm). Options in both groups include pharmaceutical choices as well as invasive procedures. The most used invasive heart *rhythm* control option is catheter ablation, a transvenous procedure during which scar tissue is created in the myocardium, usually around the ostia of the pulmonary veins. This scar tissue electrically isolates the pulmonary veins, blocking the conduction of AF triggers originating from the myocardial sleeves in the pulmonary veins to the rest of the atria (*Figure 2*). Depending on specific patient characteristics, additional lesions may be created to decrease the chance of recurrences of AF. [13] Different energy sources are currently used to create scar tissue, including application of

heat (radiofrequency ablation), cold (cryoablation), or electroporation (pulsed field ablation). The procedure is successful in 55-90% of cases, depending on patient characteristics, definitions of ablation success and postprocedural screening methods. [13]

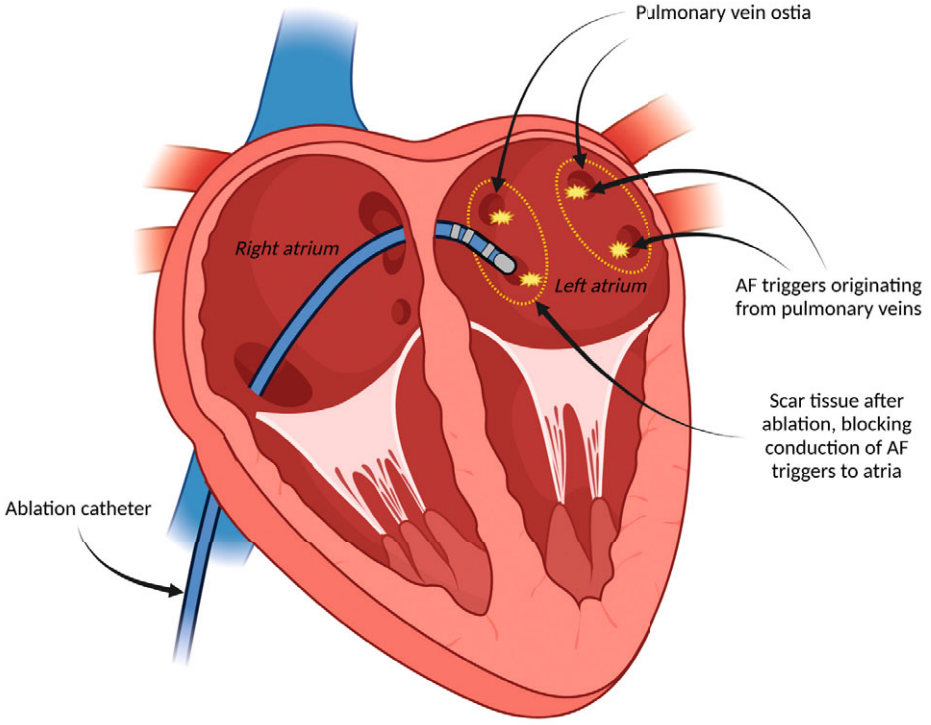

Figure 2. The principle of pulmonary vein isolation: blocking the conduction of AF triggers to the atria.

Abbreviations: AF: atrial fibrillation.

Although invasive therapies such as catheter ablation used to be reserved for highly symptomatic patients in whom antiarrhythmic drug therapy had failed, recent insights and technological advances have led to it being applied in broader patient populations and earlier into the disease process. A recent trial found that patients in whom AF was treated from an early stage with strict rhythm control, including AF ablation in almost one fifth of cases, were less likely to experience major cardiovascular events than those in whom a more lenient strategy was adopted. [14] These results fueled the call for stricter rhythm control and earlier application of catheter ablation in AF patients. It has even been suggested to use catheter ablation as a first-line therapy in AF patients,

as it is consistently found to be more potent in preserving sinus rhythm than antiarrhythmic drugs. [15, 16]

The population of potential AF ablation candidates broadens not only to healthier, recent onset AF patients, but also in the opposite direction to patients with more advanced underlying heart disease. In heart failure patients, catheter ablation of concomitant AF has been shown to not only reduce AF symptoms, but also to prevent deterioration of heart failure. Hereby, the treatment goal moves from symptom-directed therapy towards improvement of patients' prognosis. [17, 18] These findings broaden the population in whom catheter ablation may be considered over the entire spectrum.

INTEGRATED MANAGEMENT AND OUTLINE OF THESIS

The increasing prevalence of AF and the expanding population for whom catheter ablation is indicated is expected to lead to rising numbers of procedures in the coming years. This creates a challenge for the organization of patient selection, preparation, planning, and follow-up after AF ablation. In addition, the risk exists that with the focus shifting to AF ablation, other pillars of AF care such as management of risk factors and comorbidities will receive less attention. To achieve high-quality and efficient care for patients undergoing AF ablation, integrated care is key. In the context of AF care, integrated care is defined as 'a coordinated, patient-centered approach by interdisciplinary specialists to improve AF outcomes', a broad description covering diverse facets of AF care. [19]

This thesis aims to contribute to improving different components of integrated care for patients undergoing AF ablation. Herein, the focus was placed on the following elements: integrating mobile health (mHealth), integrating (translational) research, integrating risk factor management, and integrating heart failure care into peri-AF ablation care (*Figure 3*). The thesis is divided into three parts. Part I will focus on integrated mHealth and research, part II on integrated risk factor management, and part III on integrated heart failure and AF care.

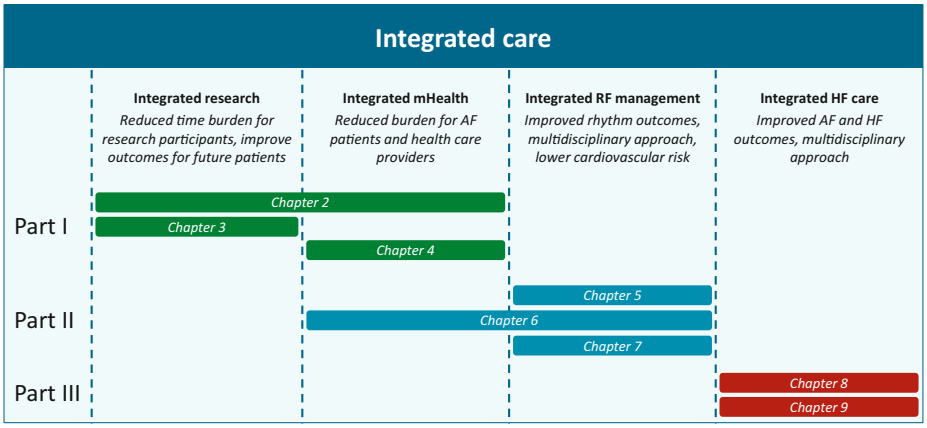

Figure 3. Different facets of integrated AF care as described in this thesis.
Abbreviations: AF: atrial fibrillation, HF: heart failure, mHealth: mobile health, RF: risk factor.

PART I: Integrating (translational) research and mHealth into AF care

Research integration

The first part of this thesis focuses on the integration of research studies and mHealth into standard AF care. Despite the amount of research that has been conducted on the topic of AF ablation, gaps of evidence still remain plentiful and AF recurrences after ablation remain relatively common.[20, 21] Large prospective studies may help to improve patient selection and outcomes. The ongoing two-center "IntenSive mOlecular and eLectropathological chAracterization of patienTs undergoIng atrial fibrillatiOn ablation" (ISOLATION) cohort study addresses this topic. The rationale and design of the ISOLATION study are described in **chapter 2** of this thesis. This study aims to systematically examine predictors of successful AF ablation in the following domains: 1) clinical factors, 2) AF patterns detected using (mHealth) rhythm monitoring devices, 3) anatomical characteristics, 4) electrophysiological characteristics, 5) circulating biomarkers, and 6) individual genetic background. Factors from these domains will be combined in a multimodality model for the prediction of ablation success, which may help to improve future patient selection for invasive AF management.

Structural enrollment of patients into clinical studies is often challenging. Study populations are therefore usually a poor reflection of real-world patients, typically omitting older and frailer patients. Integrating research with standard AF ablation care may help to solve this problem. Keeping additional study visits to a minimum, hereby reducing the required time investment by patients,

and incorporating strategies to structurally identify potential study participants enable inclusion across a diverse range of patient types. [22] As described in **chapter 2**, all ISOLATION study procedures are integrated in a standardized pre- and post-AF ablation pathway, thus facilitating data collection to broaden understanding of AF mechanisms without the need for additional visits by study participants.

Chapter 3 describes the course and impact of a health care optimization project that was conducted to restructure the preparatory AF ablation pathway using the Lean Six Sigma methodology. [23] Lean Six Sigma is a strategy that can be used to facilitate the redesign of an existing care process into a structured care pathway. The aims of this project were to improve the evaluation and preparation of patients considered for AF ablation, to reduce the required resources, and to facilitate integration of the ISOLATION study procedures into the clinical process.

mHealth integration

In the digital era, outpatient contacts for management of chronic diseases are replaced by remote consultations (e.g., teleconsultations or video consultations) in increasing frequency. [24] For AF patients, remote managing is often challenging: while symptoms can be assessed by detailed history taking, the standard 12-lead electrocardiogram (ECG) that is usually recorded preceding face-to-face consultations requires physical presence at an outpatient clinic. Consequently, during a remote consultation no objective information on the heart rhythm and rate is available. As symptom-rhythm correlation is relatively poor in many AF patients, they often cannot indicate whether they are currently in AF or in sinus rhythm, nor can their ventricular rate be estimated in case of AF. [25] This complicates treatment decisions and titration of medication dosages during remote consultations.

Combining remote consultations with remote heart rate and rhythm recordings using mHealth applications can solve this obstacle. Many different mHealth options for heart rhythm monitoring are available, including different device types (e.g., handheld devices or wearables), temporal types of monitoring (intermittent or continuous), and technologies (e.g., ECG or photoplethysmography [PPG]). [26, 27] PPG is a technology which determines blood volume pulse variation in the arterioles of the fingertip by measuring the amount of reflected light in the built-in camera of a smartphone, which after conversion can be used to determine individual pulse waves. [28] This technique

is easily available for most AF patients thanks to the ubiquity of smartphones and the easy installation of smartphone apps, and therefore is an attractive option for supporting remote consultations. However, many physicians feel unfamiliar with the technology, leading to a lack of confidence and making physicians less likely to use it in clinical practice. [29]

To overcome this obstacle, in **chapter 4** a structured stepwise practical guide is provided on how to analyze and interpret PPG signals. This PPG dictionary is supported by several representative PPG recording serving as examples. Additionally, different clinical scenarios are introduced where the use of on-demand app-based PPG monitoring can be of clinical benefit.

Over the past years, PPG monitoring and other types of mHealth have gained a place in standard practice in many AF outpatient clinics. As described in **chapter 2**, PPG has become a standard part of the clinical follow-up after AF ablation in the two ISOLATION centers. In addition, the ISOLATION study also incorporates ECG-based handheld mHealth devices, which are used to characterize AF patterns preceding AF ablation. However, mHealth may not only be used to monitor heart rhythm and rate, but it may also be applied for risk factor screening and management. [30] In **part II** of this thesis, the application of mHealth in screening for sleep-disordered breathing is discussed in more detail.

PART II: Integrating cardiovascular risk factor management into AF care

The second part of this thesis focuses on integrating screening for and management of relevant risk factors into peri-AF ablation care. Although current guidelines define risk factor management as an integral part of AF treatment, structural implementation into standard AF care continues to pose a challenge. [13, 31] It is complicated by many factors, such as the multiplicity of potentially relevant risk factors, unclear treatment targets, organizational hurdles in multidisciplinary collaboration, and lack of uniform integrated care models. [32] This lack of structural integration forms a challenge for AF care, particularly in patients in whom a rhythm control strategy is pursued. Several studies have demonstrated that integrated risk factor management programs on top of standard care are associated with better rhythm outcomes than standard care alone, regardless of whether standard care consisted of (antiarrhythmic) drug therapy, electrical cardioversion, or AF ablation. [33-37] Especially when an invasive procedure such as AF ablation is considered, strict

risk factor management should therefore be advocated to improve rhythm outcomes.

In **chapter 5**, the prevalence of modifiable risk factors and compliance to risk factor treatment targets were studied in a cohort of 1143 patients scheduled for AF ablation included in the ISOLATION study. Most patients included in this cohort were originally under treatment in external hospitals and were only referred to a tertiary center for consideration of AF ablation, thus providing an interesting insight in the degree of AF risk factor management in a diverse range of hospitals in the Netherlands.

As many risk factors for AF also increase susceptibility to (atherosclerotic) cardiovascular diseases including myocardial infarction, stroke, and cardiovascular death, combined risk factor modification programs may likewise reduce major adverse cardiovascular events (MACE). [38] The risk of developing atherosclerotic cardiovascular disease was estimated for each AF patient in **chapter 5**.

Sleep-disordered breathing

One frequently underdiagnosed AF risk factor is sleep-disordered breathing (SDB). Its most common subtype, obstructive sleep apnea (OSA), often coexists with AF due to shared upstream risk factors and direct synergistic effects. Its prevalence ranges from 21%-74% in AF patients, the wide range resulting from differing diagnostic techniques and criteria. [39] Nonetheless, in clinical practice its prevalence is often underestimated due to the lack of conventional symptoms in AF patients: most AF patients report low daytime sleepiness levels, which often precludes them from being investigated for SDB. [40] Undiagnosed and thus untreated SDB, however, reduces success rates of heart rhythm control strategies and contributes to progression of AF. [41] Structured testing is therefore indicated, but only occurs in a minority of AF patients due to limited access to polysomnography (PSG) caused by long waiting lists, high labor intensity and high costs. [42]

Several mHealth solutions in the form of home sleep tests have shown to be inexpensive, reliable and sensitive alternative technologies to PSG in a sleep laboratory. In **chapter 6** of this thesis, the VIRTUAL-SAFARI study (A VIRTUAL Sleep Apnea management pathway For the workup of Atrial fibrillation patients in a digital Remote Infrastructure) is described. This chapter outlines the structure and implementation of a fully remote SDB screening

and management pathway, using simple and validated peripheral arterial tone based home sleep tests, into the existing pre-AF ablation preparation. Subsequently, the utility, feasibility and patient satisfaction of this new approach in detecting sleep-disordered breathing are described. The new SDB screening and management approach was initiated in October 2020 and has since been offered to all patients undergoing AF ablation in the Maastricht UMC+ and the Radboudumc without recent sleep screening.

Although this SDB screening approach was received well, implementing structural screening approaches leads to increased use of healthcare resources. Pre-selecting patients unlikely to have SDB, not warranting referral to the screening pathway, might limit this burden. Therefore, **chapter 7** investigated whether preselection could be further optimized to better use the available resources. Firstly, the accuracy of the STOP-Bang questionnaire, a widely accepted preselection tool for SDB screening, and its potential impact on referral rates to the SDB screening pathway were assessed in a cohort of AF ablation patients.[43, 44] Secondly, an AF-specific adjustment of the STOP-Bang was proposed, considering that some of the STOP-Bang items had limited predictive value due to overlapping SDB and AF symptoms and risk factor profiles.[45, 46] Several items were replaced or refined, resulting in the new BOSS-GAP score.

PART III: Integrating heart failure care and AF care

The final part of this thesis focuses on the interrelation between AF and heart failure, one of its most important comorbidities. These two conditions often go hand in hand as each can provoke, sustain and aggravate the other. Moreover, AF and heart failure share a risk profile with several coinciding cardiovascular risk factors, increasing the odds of developing both separately from each other. In **chapter 8**, the pathophysiological coherence of AF and heart failure is reviewed in more detail. Current knowledge on the management of the concomitant diseases is discussed and future developments in this field are outlined.

Considering the deteriorating effect that AF can have on heart failure, adopting a rhythm control strategy to maintain sinus rhythm would be expected to be beneficial for heart failure outcomes. Nevertheless, medication-based rhythm control has no clinical benefit over rate control in terms of major clinical endpoints in this population.[47] This lack of improvement may be a result from the limited efficacy of drugs in maintaining sinus rhythm, in addition

to potential harmful side-effects. The more potent invasive treatment with catheter ablation, however, improves important surrogate outcomes such as left ventricular function, quality of life, and exercise capability when compared to medication-based strategies. [18, 48-50] Whether this translates to improved clinical outcomes such as improved survival and decreased hospitalization rates remains a topic of debate. Until now, only two randomized trials have been conducted that directly studied this question, but the trials had conflicting results and there are serious questions regarding their generalizability to the entire heart failure population. [17, 51, 52]

The ongoing multicenter RACE-8-HF trial was initiated to address this uncertainty. In **chapter 9** the study design of this prospective, randomized, open-label trial with blinded endpoint evaluation is described. The trial compares early rhythm control through cryoballoon ablation with conventional therapy in patients with heart failure and AF with regards to mortality, unplanned cardiovascular hospitalizations, and stroke. This trial holds several distinctive aspects from previous trials, such as the targeted population (patients with left ventricular ejection fraction 35-50% in addition to those with ejection fraction <35%), the ablation technique (the fast, uniform cryoballoon ablation method), and incorporation of a prespecified cost-effectiveness analysis on patient-level data. The results of this trial will be used to confirm whether early invasive rhythm control is truly superior to medication-based treatment options in this large population.

The main findings and conclusions presented in the three parts of this thesis are summarized and discussed in **chapter 10** and **chapter 11**. **Chapter 10** contains a general discussion, including clinical implications and future research priorities. **Chapter 11** summarizes the main results of this thesis.

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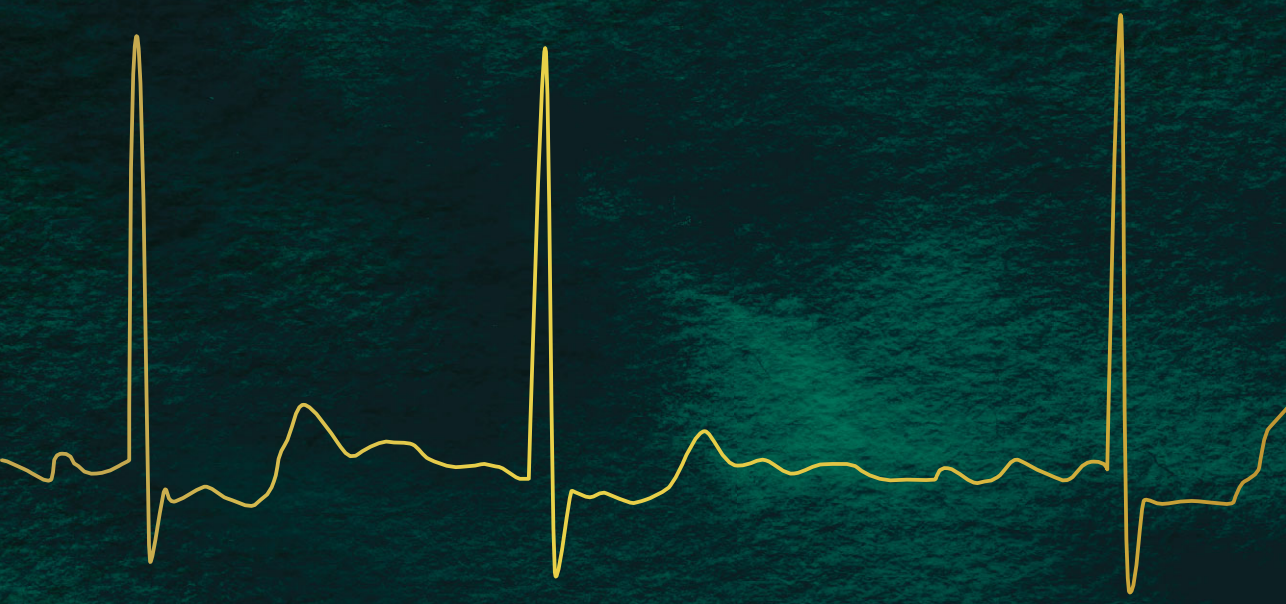
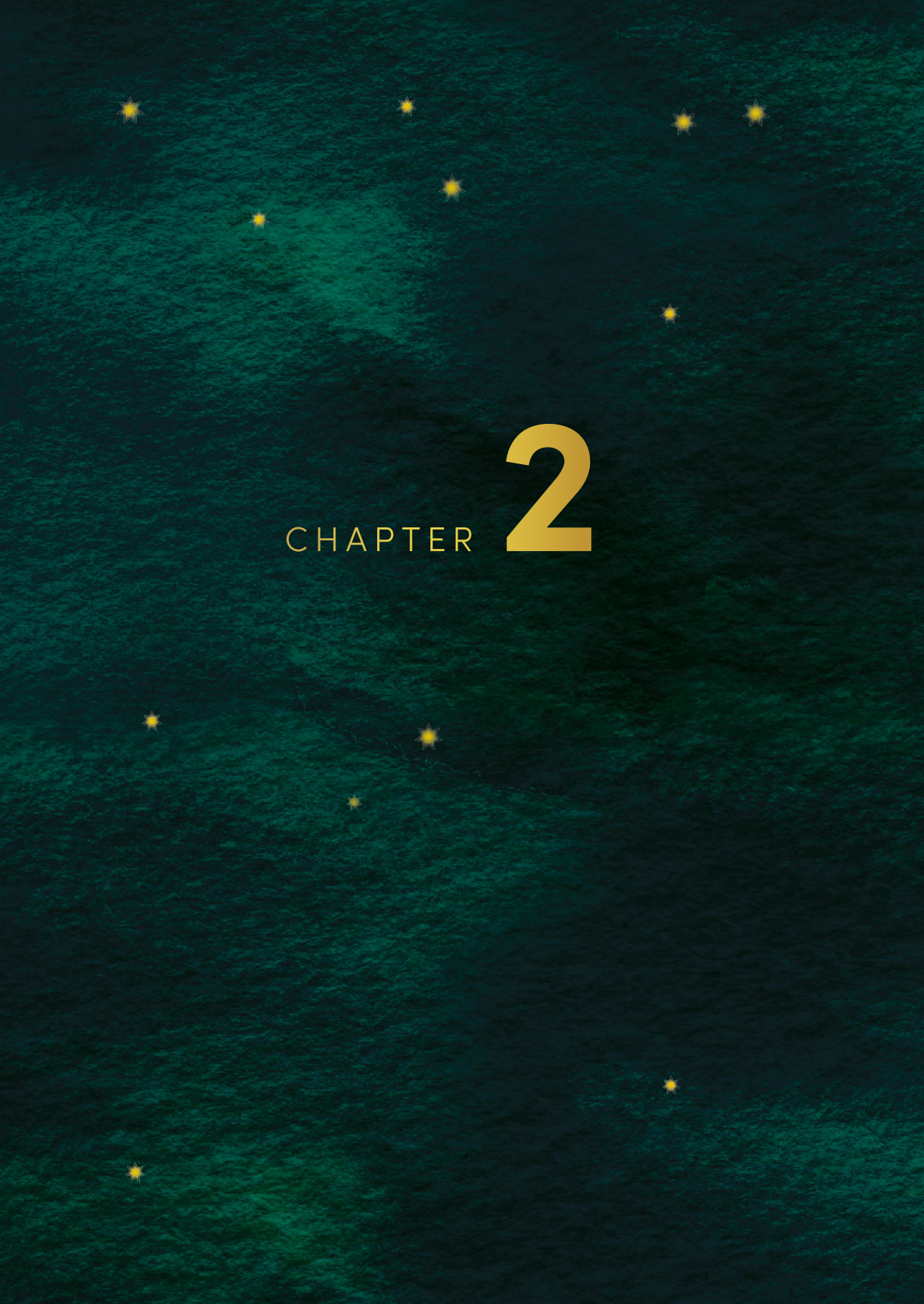
PART I

Integrating (translational) research & mobile health into AF care




CHAPTER 2

Rationale and design of the ISOLATION study: a multicenter prospective cohort study identifying predictors for successful atrial fibrillation ablation in an integrated clinical care and research pathway

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ABSTRACT

Introduction

Continuous progress in atrial fibrillation (AF) ablation techniques has led to an increasing number of procedures with improved outcome. However, about 30-50% of patients still experience recurrences within one year after their ablation. Comprehensive translational research approaches integrated in clinical care pathways may improve our understanding of the complex pathophysiology of AF and improve patient selection for AF ablation.

Objectives

Within the "**I**nten**S**ive m**O**lecular and e**L**ectropathological ch**A**racterization of patien**T**s undergo**I**ng atrial fibrillati**O**n ablatio**N**" (ISOLATION) study, we aim to identify predictors of successful AF ablation in the following domains: 1) clinical factors, 2) AF patterns, 3) anatomical characteristics, 4) electrophysiological characteristics, 5) circulating biomarkers, and 6) genetic background. Herein, the design of the ISOLATION study and the integration of all study procedures into a standardized pathway for patients undergoing AF ablation are described.

Methods

ISOLATION is a two-center prospective cohort study including 650 patients undergoing AF ablation. Clinical characteristics and routine clinical test results will be collected, as well as results from the following additional diagnostics: determination of body composition, pre-procedural rhythm monitoring, extended surface electrocardiogram, biomarker testing, genetic analysis, and questionnaires. A multimodality model including a combination of established predictors and novel techniques will be developed to predict ablation success.

Discussion

In this study, several domains will be examined to identify predictors of successful AF ablation. The results may be used to improve patient selection for invasive AF management and to tailor treatment decisions to individual patients.

Clinicaltrials.gov identifier: NCT04342312

INTRODUCTION

The prevalence of atrial fibrillation (AF) has risen substantially over the past decade, and it continues to rise due to the aging population and the increasing rate of concomitant risk factors and underlying structural heart diseases.[1] AF is associated with an increased risk of ischemic stroke, developing and worsening of heart failure, and a significant symptom and financial burden.[2] To maintain sinus rhythm and to decrease symptoms related to AF, catheter ablation is recommended in symptomatic patients.[3] However, despite advanced ablation techniques and improved ablation outcomes over the last decade, about 30-50% of patients still experience recurrences of atrial arrhythmias within 1 year after the procedure.[4, 5]

Although several readily available characteristics (including demographic information, established clinical AF risk factors, and left atrial volume) have previously been identified as predictors for AF ablation success, it remains challenging to estimate the success rate for an individual case.[6] For this purpose, a range of novel techniques estimating the extent of the atrial AF substrate has been proposed: biomarkers, such as inflammatory mediators and markers for fibrosis, common gene variants associated with AF, and non-invasive electrophysiological characteristics recorded on surface electrocardiograms (ECG).[7-10] Additionally, a more detailed characterization of different AF patterns based on frequency, duration, and manner of conversion of AF episodes might further help to characterize the AF phenotype, although its predictive value for ablation success has not yet been described.[11]

It is the aim of the multicenter prospective "**I**nten**S**ive m**O**lecular and e**L**ectropathological ch**A**racterization of patien**T**s undergo**I**ng atrial fibrillati**O**n ablatio**N** (ISOLATION)" cohort study to systematically examine predictors of successful AF ablation in the following domains: 1) clinical factors, 2) AF patterns detected using rhythm monitoring devices, 3) anatomical characteristics, 4) electrophysiological characteristics, 5) circulating biomarkers, and 6) individual genetic background. Factors from these domains will be combined in a multimodality model for the prediction of ablation success, which may help to improve patient selection for invasive AF management. Herein, we outline the design of the ISOLATION study and describe how all study procedures are implemented into a standardized, integrated clinical care and research AF ablation pathway.

METHODS

Study design

The ISOLATION is a multicenter prospective cohort study designed to identify predictors of successful AF ablation in six different domains (*Figure 1*). The study was initiated in July 2020 and aims to include 650 patients scheduled for AF ablation in two Dutch university hospitals, the Maastricht University Medical Center (MUMC) and the Radboud University Medical Center (Radboudumc). Clinical characteristics, results of routine clinical tests (e.g., laboratory results, cardiovascular imaging) and several additional study procedures are collected before, during, and after the ablation. The study protocol was reviewed and approved by the ethics committee of the MUMC (METC azM/UM, NL70787.068.19) and is registered at clinicaltrials.gov (NCT04342312) and the Netherlands Trial Register (NL7894).

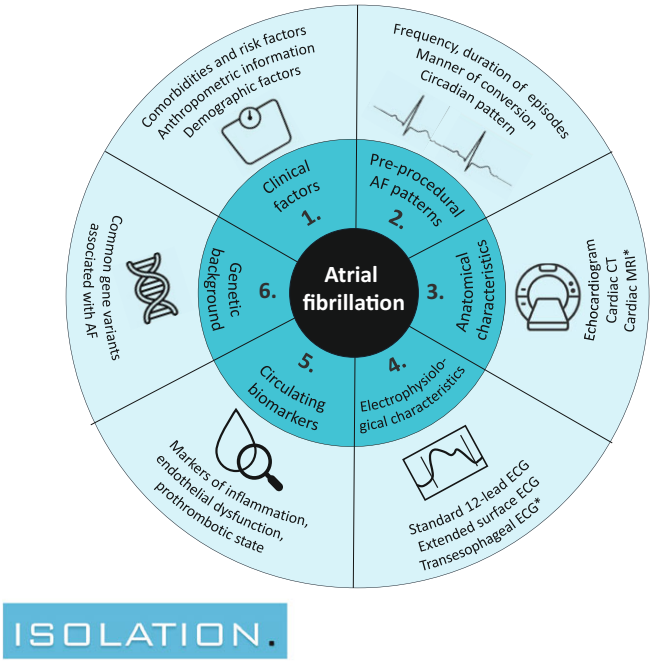

Figure 1. The different domains in which predictors for successful atrial fibrillation ablation are sought.

The 6 domains of interest for predictors of AF ablation success in the ISOLATION study: (1) clinical risk factors, (2) pre-procedural AF patterns, (3) anatomical characteristics, (4) electrophysiological characteristics, (5) circulating biomarkers, and (6) genetic background.

** Study procedures with an asterisk are conducted for a subset of patients.*

Abbreviations: AF: atrial fibrillation, CT: computed tomography, ECG: electrocardiogram, MRI: magnetic resonance imaging.

Study population

Patients are eligible for participation in this study if they are 18 years of age or older, have documented AF, are scheduled for an AF ablation (first procedure or redo) in either participating center, and are able and willing to provide written informed consent. There are no restrictions for AF ablation modality nor for potential previous ablation procedures. Possible ablation modalities include percutaneous techniques (cryoballoon ablation or radiofrequency ablation), surgical ablations (epicardial ablation, concomitant ablation) or a combined procedure (hybrid ablation). Patients are excluded if they are deemed unfit to participate due to a serious medical condition or if they undergo an emergency procedure. In- and exclusion criteria are listed in *Table 1.*

Table 1. In- and exclusion criteria of the ISOLATION study.

Inclusion criteria	
1	18 years of age or older;
2	Documented atrial fibrillation;
3	Scheduled for atrial fibrillation ablation or redo atrial fibrillation ablation;
4	Able and willing to provide written informed consent.
Exclusion criteria	
1	Patients deemed unfit to participate due to a serious medical condition before ablation, as deemed by their treating physician;
2	Patients undergoing an emergency ablation procedure.

Endpoints

The primary outcome measure is ablation success, defined as freedom from documented recurrence of atrial arrhythmia 12 months after the index procedure. Recurrences in the first 3 months are exempted (blanking period). Atrial arrhythmias are defined as AF, atrial tachycardia, or non-isthmus dependent atrial flutter. Episodes of atrial arrhythmia must be documented on an ECG, Holter monitoring (minimum duration of 30 seconds), or an implanted device (atrial high-rate episode during at least 5 minutes or mode switch, confirmed as being AF or another atrial arrhythmia by a trained physician). To detect symptomatic and asymptomatic recurrences of atrial arrhythmias, 48-hour Holter monitoring is performed at 6 and 12 months after the ablation procedure. Holter recordings may be extended or additional Holter recordings may be added when clinically indicated. 12-lead ECGs are obtained at 3 and 12 months, and patients are encouraged to have additional ECGs recorded if they experience symptoms between visits.

Key secondary outcomes include time to first recurrence of atrial arrhythmia or AF after the blanking period, freedom from documented recurrence of atrial arrhythmia at 24 months, redo procedures, disease progression to persistent or permanent AF, changes in circulating biomarkers, and changes in non-invasive electrophysiological markers for substrate quantification (*Table 2*).

Table 2. Primary and secondary endpoints in the ISOLATION study.

Primary endpoint
• Ablation success, defined as freedom from documented recurrence of atrial arrhythmia after 12 months. Recurrences in the first 3 months after the index procedure (blanking period) are exempted.
Secondary endpoints
• Time to recurrence of atrial arrhythmia after the blanking period; • Time to recurrence of AF after the blanking period; • Freedom from documented recurrence of atrial arrhythmia after 24 months. Recurrences in the blanking period are exempted; • Early AF recurrences, defined as any episode of AF during the blanking period; • Early recurrences of atrial arrhythmia, defined as any episode of AF, atrial tachycardia or non-isthmus dependent atrial flutter during the blanking period; • Disease progression to persistent or permanent AF; • Changes in circulating biomarkers and non-invasive electrophysiological markers for substrate quantification; • Use of antiarrhythmic drugs one year after ablation; • Redo procedures, defined as repeated ablation procedure with the goal to prevent recurrence of AF or reduce the AF burden after one or more previous attempts to achieve the same goal; • Number of veins with pulmonary vein reconnection at redo procedure; • Major adverse cardiovascular events.

Abbreviations: AF: atrial fibrillation.

Study enrollment

Patients accepted for AF ablation receive verbal and written information about the ISOLATION study and are scheduled to visit a standardized AF ablation work-up pathway. Patients willing to participate provide written informed consent for ISOLATION prior to their visit at the work-up pathway, or during this pathway but prior to all study procedures. Patients that decline participation in the ISOLATION study are asked to participate in the 'light' version of the study, the "Clinical electrophysiology registry MUMC+ and Radboudumc" (ethical committee number 2019-1022). Participants in this ISOLATION 'light' registry undergo the same standardized pre- and post AF ablation pathway, with the exception that most of the study procedures are omitted. Patients that do not wish to participate in either study complete the standardized pathway without any additional study procedures (*Figure 2*).

Pre-ablation work-up

The standard work-up for ablation in the participating centers consists of a systematic collection of clinical information, vital signs, 12-lead ECG, blood tests, imaging to assess pulmonary vein anatomy (either computed tomography or cardiac magnetic resonance imaging), and screening by an anesthesiologist. Echocardiography is performed in patients without recent imaging or when recent imaging is of insufficient quality. During the work-up, patients are systematically screened for common comorbidities and triggers for AF such as hypertension, obesity, hyperlipidemia, diabetes mellitus, and chronic obstructive pulmonary disease (COPD) according to current AF guidelines.[3] In addition, all patients without known obstructive sleep apnea (OSA) are referred for remote testing for sleep disordered breathing, as described previously in more detail.[12] If any of the risk factors is present, applicable treatment is initiated parallel to the AF treatment.

The pre-ablation preparation is structured in a care pathway at the outpatient clinic that allows the entire work-up to be completed in a single visit (*Figure 3, panel A*, standard work-up procedures in white). All patients scheduled for AF ablation complete this pre-AF ablation work-up, regardless of study participation.

Study procedures during pre-ablation work-up

For ISOLATION study participants, the standard pre-AF ablation work-up is combined with the following baseline study procedures: determination of body composition, extended surface ECG (extECG), analysis of biomarkers and common gene variants, questionnaires, and characterization of AF patterns (*Figure 3, panel A*, study procedures in black). For ISOLATION 'light' registry participants the study procedures are limited to analysis of biomarkers, common gene variants and questionnaires.

Both the clinical facets and research aspects of the pre-ablation work-up are overseen by a case manager. The case manager educates patients on the AF ablation procedure and study participation, coordinates study procedures, notifies abnormalities in results of diagnostic tests, and provides patients with information on logistics and planning.

AF ablation

AF ablation comprises pulmonary vein isolation (PVI) with or without additional lesions. The type of ablation that is performed is determined in a multidisciplinary team meeting and depends on the patient's preference and characteristics. The choice of ablation strategy is not influenced by study participation. In the participating centers, first ablations for paroxysmal AF and for persistent AF with normal to modestly dilated atria or in elderly patients are usually performed by cryoablation (*Figure 2*). First ablations for persistent AF with advanced atrial dilation or with concomitant atrial flutter or atrial tachycardia are mostly performed by wide atrial circumferential ablation (WACA) using radiofrequency applications, if needed complemented with cavo-tricuspid isthmus ablation (in case of typical atrial flutters). Patients with longstanding persistent AF (>1 year) are usually treated with thoracoscopic or hybrid AF ablation. Patients with recurrent AF undergoing a second (redo) procedure are mainly treated with radiofrequency ablation or thoracoscopic/ hybrid AF ablation, whereas for third or further procedures hybrid procedures are recommended, if patients are suitable candidates and no earlier hybrid treatment was performed. Patients with an indication for cardiac surgery and known AF are discussed in an arrhythmia team and considered for concomitant epicardial AF ablation. Treating physicians may choose to deviate from these recommendations depending on specific patient characteristics and patient preference. All patients planned to undergo an endocardial procedure are treated with oral anticoagulants around the ablation. [3] In addition, a transesophageal echocardiogram is performed prior to all endocardial procedures to exclude intracardiac thrombi.

Study procedures during AF ablation

Whether additional, optional study procedures are performed during the procedure depends on the type of ablation selected (*Figure 3, panel B*). If endocardial electroanatomical mapping is performed during the ablation procedure, these data may be used for additional offline analyses. In the case of hybrid or concomitant epicardial ablation, additional epicardial mapping and left atrial appendage (LAA) biopsies may be performed (*Supplement 1*).

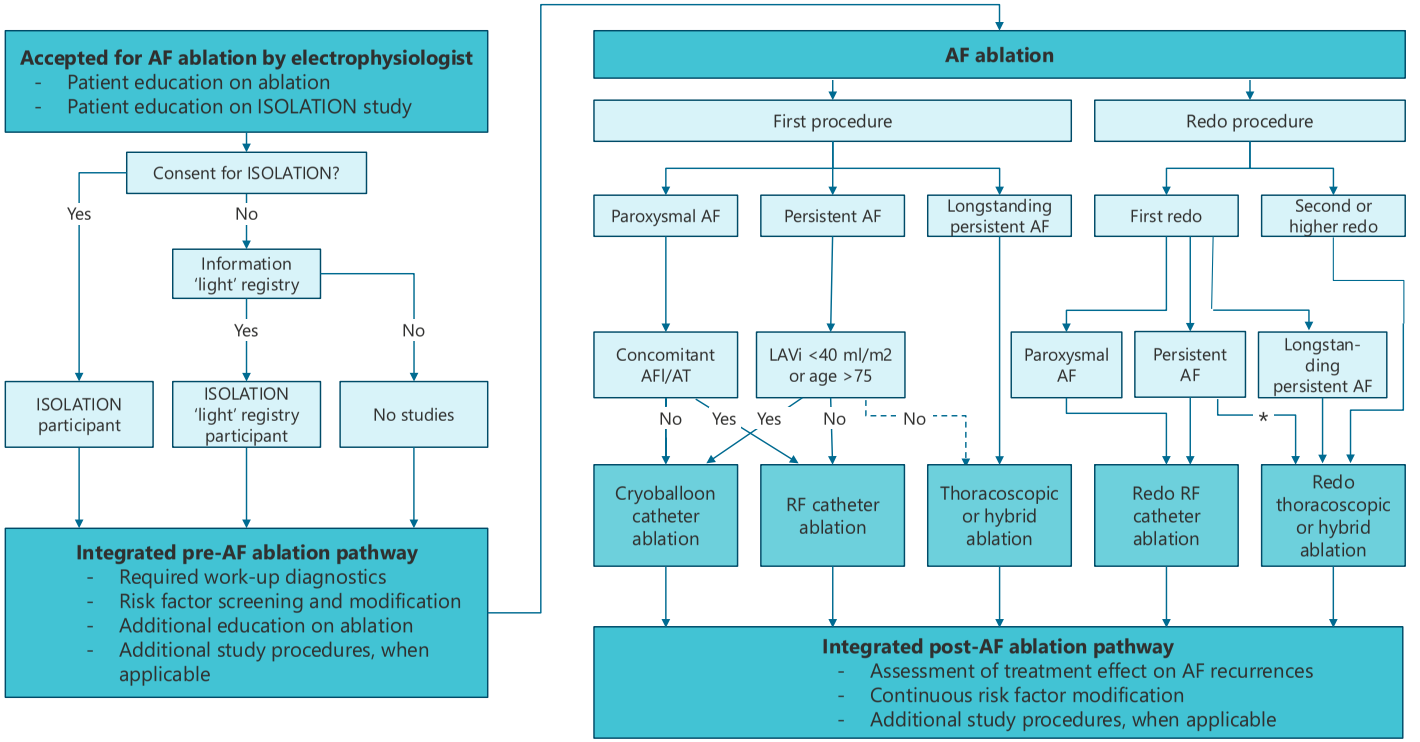

Figure 2. Flowchart of the standardized, integrated clinical care and research pre- and post AF ablation pathway.

Structure of the pre- and post AF ablation pathway and general recommendations for the type of AF ablation. Physicians may choose to deviate from these recommendations depending on patient characteristics of patient preference.

** = strongly consider thoracoscopic/hybrid ablation if LAVi >50 ml/m2 or in case of patient preference.*

Abbreviations: AF: atrial fibrillation, LAVi: left atrial volume index, RF: radiofrequency.

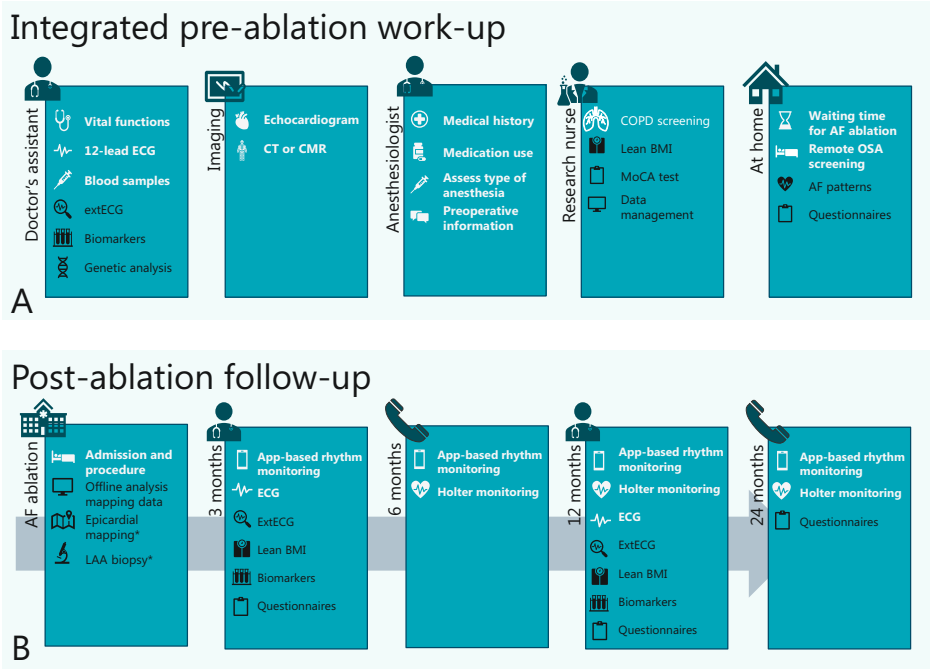

Figure 3. Integration of clinical diagnostics and study procedures at baseline and after AF ablation.

Integration of clinical diagnostics and study procedures in the work-up before (panel A) and the follow-up after (panel B) AF ablation. Procedures in white are standard clinical procedures, procedures in black are added for research purposes.

** = when applicable (in case of epicardial or hybrid ablation).*

Abbreviations: AF: atrial fibrillation, BMI: body mass index, CMR: cardiac magnetic resonance imaging, CT: computed tomography, ECG: electrocardiogram, extECG: extended surface electrocardiogram, LAA: left atrial appendage, MoCa: Montreal Cognitive Assessment.

Post-ablation follow-up

After the ablation procedure, patients return to the outpatient clinic at 3 and 12 months and have scheduled teleconsultations after 6 and 24 months. Prior to the contacts at 6, 12, and 24 months, a 48-hour Holter recording is performed. 12-lead ECGs are obtained during every on-site follow-up visit. In addition, patients receive an on-demand 7-day prescription for the use of the smartphone application FibriCheck (Qompium, Hasselt, Belgium) prior to all scheduled consultations. FibriCheck is an app that uses photoplethysmography (PPG) signals to assess heart rate regularity and symptom-rhythm correlation.[13] Patients are instructed to measure 3 times per day and in the case of symptoms, in accordance with the TeleCheck-AF approach described previously.[14] If irregularity of the heartbeat is detected and AF is suspected, additional or longer Holter recordings may be performed to confirm AF

recurrence by ECG documentation (*Figure 3, panel B,* standard follow-up procedures in white).

Study procedures during post-ablation follow-up

For ISOLATION participants, on-site follow-up visits are complemented with the following study procedures: determination of body composition, extECG, and analysis of biomarkers. Questionnaires are repeated at 3, 12 and 24 months after the ablation (*Figure 3, panel B*, study procedures in black). For ISOLATION 'light' registry participants, study procedures are limited to the questionnaires.

Short description of study procedures

The rationale for the different study procedures is described in *Supplement 1*, along with detailed descriptions of the procedures. A condensed version is provided here.

Determination of body composition

To explore the correlation between different anthropometric measures and ablation success, weight, fat percentage and lean body mass indices are estimated using bioelectrical impedance measurements obtained with body composition monitors. The results of these measurements are part of domain 1: clinical factors (*Figure 1*).

Pre-procedural rhythm monitoring

To gain more insight into pre-ablation AF patterns, patients awaiting the AF ablation procedure receive a handheld patient-operated device which records single-lead ECGs. Patients are asked to record their heart rhythm three times a day during a maximum of four weeks. Additional registrations are recorded at each onset or relief of arrhythmia symptoms. Symptoms and their correlation to ECG recordings are documented in a patient diary. The obtained AF patterns are studied in domain 2 (*Figure 1*).

Extended surface electrocardiogram

Detailed analysis of P-wave and fibrillation wave (F-wave) features from surface ECGs are increasingly used to characterize the degree of electrophysiological changes in the atria. In this study, unfiltered extECGs using a total of 21 leads will be recorded for up to five minutes to allow for signal-averaged analyzation of P-waves (for patients in sinus rhythm) and for examination of F-wave frequency and complexity (for patients in AF). The results are a component of domain 4: electrophysiological characteristics (*Figure 1*).

Blood samples

Blood for biomarker analyses is drawn at three separate time points during the study. Genetic analysis is performed on the blood drawn at baseline. Biomarkers of interest include inflammatory mediators, markers of myocardial wall stress, markers of fibrosis, markers of endothelial dysfunction and pro-thrombotic state, and markers for expression of genes regulating electrophysiological characteristics. The results are studied in domain 5: circulating biomarkers and domain 6: genetic background (*Figure 1*).

Questionnaires

The following questionnaires are completed: Montreal Cognitive Assessment (MoCA), Toronto AF Severity Scale (AFSS), Atrial Fibrillation Effect on QualiTy-of-life (AFEQT), STOP-Bang, and a combined COPD questionnaire. Additional information on the questionnaires is provided in *Supplement 1*.

Additional procedures for substudies

Specific subsets of patients may be eligible to participate in a substudy of the ISOLATION study and/or ISOLATION 'light' registry. Current areas of interest include cardiovascular imaging, noninvasive and invasive electrophysiological characterization, and concomitant comorbidities. Substudies that are currently actively enrolling patients and their primary objectives are listed in *Supplement 2*. Patients eligible for participation in a substudy are asked for additional consent.

Data management

Patient identifiers are removed from study data, biological samples and recordings and replaced with a unique study number. Coded data are entered in a password-protected, secure electronic case report file (Castor EDC [15]). Raw data of procedures (e.g., extECGs) are stored under the respective patient identifier and will be available for further offline analysis. All information generated in this study will be considered confidential and is handled in according to the General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation. Monitoring is performed by the Clinical Trial Center Maastricht (CTCM) in accordance with the predefined monitoring plan and prevailing guidelines.

Statistical considerations and sample size calculation

Data analyses will be performed with SPSS Statistics, version 25.0 or higher (IBM SPSS Inc. Chicago IL). Baseline data will be presented by count

(percentage) for categorical variables and compared using the Chi-square test. Continuous data will be presented as means (± standard deviation) or medians (interquartile range) and compared using the independent samples t-test or Mann-Whitney U test. Missing data will be estimated using multiple imputation by chained equations. Uni- and multivariable regression analyses will be performed to analyze the relation of dependent variables with the primary and applicable secondary endpoints. The secondary endpoints time to recurrence of atrial arrhythmia and AF will be assessed using Cox proportional hazard regression. All endpoints will be assessed using a level of significance of $\alpha = 0.05$.

Prediction model and sample size calculation

An exploratory multimodality model will be created to predict the primary endpoint (ablation success) in patients undergoing a first catheter ablation. Ideally, to develop a reliable prediction model all variables of interest that will be studied in the model should be defined prior to the data collection. However, this study includes several relatively new techniques, which each provide a multitude of possible variables of interest for which the predictive value has not been established yet. Defining variables to be included in the model up-front could limit its eventual predictive value, as the predefined variables might not prove to be the most discriminative variables. Therefore, an exploratory multivariable regression analysis of variables in the following categories will be performed first (*Figure 1*): (1) clinical risk factors, (2) pre-procedural AF patterns, (3) anatomical characteristics, (4) electrophysiological characteristics, (5) circulating biomarkers, and (6) genetic background. For subcategory 1-5 the three variables with the strongest relation with ablation success are selected and are used to construct the final prediction model. For subcategory 6 the two strongest predictors are used. The ablation technique that is chosen (cryoballoon ablation or radiofrequency catheter ablation) is used as a separate predictor. This approach leads to a total of 18 variables that will be used to develop the exploratory multimodality model. To ensure sufficient power to explore these 18 variables, a total of 180 events is required to conform to the rule-of-thumb to aim for 10 events per variable. When assuming an event rate of 32% (68% successful AF ablations), inclusion of 563 patients is required to achieve sufficient events.[4, 5] Accounting for a lost-to-follow-up rate of 15%, the aim is to include 650 patients scheduled for first catheter ablation.

Variables with possible interrelation (e.g., left atrial volume index or AF type with chosen ablation technique) will be tested for interaction and, if present,

interaction terms will be included in the model. The model will be developed using logistic regression by forward selection with the use of the Akaike Information Criterion (AIC) as stopping rule. The discriminative performance of the model is evaluated by calculating the area under the receiver operator characteristic (AUROC) curve (C-statistic) and by comparisons of observed groups of different predictive frequencies. To assess the potential confounding effect of the ablation strategy that was chosen, performance analyses will be done for the entire cohort and separately for patients treated with different ablation strategies for sensitivity purposes.

Current study status

The first ISOLATION patient was enrolled on 8 July 2020. On 1 January 2022, 405 patients have been included in the ISOLATION study (267 in the MUMC and 147 in the Radboudumc). In the same time period, 206 patients have been included in the ISOLATION 'light' registry, and only 79 patients undergoing AF ablation did not consent to study participation (*Supplement 3*). The intended number of 650 participants is expected to be reached in October 2022, with complete follow-up data in October 2024.

DISCUSSION

Despite the advances in ablation techniques and the increasing knowledge of AF mechanisms, ablation outcomes remain relatively poor.[4] Improved patient selection for invasive management and a graded choice for the type of ablation could help to enhance success rates and avoid unnecessary procedures and associated risks. In the multicenter, prospective ISOLATION cohort study, a range of possible predictors for ablation success is investigated. As AF is a multifactorial disease with numerous possible underlying mechanisms, predictors for successful treatment can be identified in several different domains. Combining recognized predictors with newer techniques that take different disease mechanisms into account may improve patient selection strategy. For this purpose, several established predictors within the clinical domain (e.g., age and comorbidities) are collected and complemented with possible predictors from investigational methods such as anthropometric information.[16] Preprocedural AF patterns, while traditionally only described as paroxysmal, persistent, or longstanding persistent, are further specified towards a more detailed pattern description concerning the duration and frequency of the episodes. Echocardiography-derived information on cardiac anatomy will be supplemented with findings from cardiac CT or CMR. Non-

invasive electrophysiological information will incorporate predictors derived from extECGs, in addition to those from the standard 12-lead ECGs. Biomarkers reflecting inflammation, prothrombotic state and endothelial dysfunction are measured and related to AF ablation success and common gene variants are scrutinized to determine the predictive value of an individual's genetic background.

Keeping in mind the daily clinical practice, it would be desirable to implement a limited number of additional modalities to improve patient selection. Therefore, results from different examinations will be grouped and compared to determine the most suitable variable(s) and modalities for outcome prediction. Identifying these variables which hold the largest predictive value may help to tailor treatment strategy and timing to the individual patient.

To achieve a clinically relevant and heterogeneous study population, the aim is to include a representative cohort of consecutive patients undergoing AF ablation in the two participating centers. Therefore, the in- and exclusion criteria are broad, and the study is embedded in the pre-ablation work-up to ensure maximum efficiency for patients, clinicians, nurses and researchers. The seamless integration of the informed consent procedure and research procedures in the clinical pathway reduces 'missed inclusions' due to logistical reasons or lack of identification of eligible patients, and it decreases the additional time burden placed on participating patients. Patients who are still apprehensive of participation in ISOLATION are offered participation in the 'light' version of the study, which omits almost all additional study procedures and primarily facilitates collection of data which are collected as part of clinical care. With this approach, almost 90% of consecutive AF ablation patients have been included in either of the studies in the first year of enrollment, providing a nearly complete representation of patients undergoing AF ablation in the two ablation centers.

Besides the benefits of an integrated clinical care and research pathway for research purposes, this pathway also provides opportunities to integrate important components of AF management as recommended in the European Society of Cardiology (ESC) AF guidelines.[3] All patients undergo structured risk factor assessment as part of the pre-AF ablation work-up, and in this context, they are screened for hypertension, hyperlipidemia, diabetes mellitus, obesity, OSA, and structural heart disease. This approach makes it, to our knowledge, one of the first large cohorts with systematically assessed data

on all classical comorbidities in AF patients, which are often underreported in other studies. Furthermore, it enables timely initiation of treatment of these risk factors. Patient engagement is encouraged by extensive education upon AF, risk factors, research participation, and the ablation procedure itself. The entire process, from patient education to management of comorbidities and research participation, is organized in an integrated, multidisciplinary care approach, overseen by a case manager, thus implementing all guideline-recommended pillars of AF care.

The described AF ablation pathway provides a research platform which addresses not only the primary aim, but which also offers opportunities to study numerous secondary objectives. Interventional or other observational substudies can easily be incorporated, either for the entire cohort or subgroups of patients. In addition, it is possible to include a randomization module into this observational study to realize a registry-based randomized clinical trial. This type of study is gaining popularity, as it combines the advantages of a prospective randomized trial (high level of evidence, strict control of confounding factors) with those of a large-scale all-comers' clinical registry (less selection bias, fewer logistical challenges).[17] Questions regarding process or treatment variations may be easily addressed with such a randomization module built into the existing registry, without the disadvantage of constructing an entirely new trial with accompanying logistical pathways and high associated costs. During the course of the study, several collaborations with (sub)specialties within our institutions have been established, such as cardiac imaging (e.g., evaluation of extent of fibrosis on cardiac magnetic resonance imaging before and after AF ablation, examination of flow patterns), translational cardiac electrophysiology (e.g., ECG-imaging, analysis of endocardial mapping signals), cardio-thoracic surgery (LA biopsies, epicardial mapping), pulmonology, and anesthesiology. This illustrates the role of ISOLATION as a crucial step towards the structural integration of high-profile electrophysiological research in top referral clinical care pathways.[18]

Limitations

The ISOLATION study and ISOLATION 'light' registry have several limitations. First, the type of AF ablation that is performed is not standardized but is decided upon by a patients' treating physician. Success rates of different strategies vary, and this may impact the rate in which the primary endpoint occurs. Second, monitoring for recurrences of atrial arrhythmia is performed intermittently using ECGs, Holter recordings and PPG-based monitoring, but

lack of continuous rhythm monitoring may lead to an underestimation of the number of endpoints.[19] Third, only AF patients scheduled for AF ablation are included. Results found in this cohort may not be generalizable to the entire AF population. Fourth, not all patients undergoing AF ablation will agree to study participation. Although the integration with the ISOLATION 'light' registry helps to include nearly all patients undergoing AF ablation, the specific study procedures are only conducted for participants in the main ISOLATION study. Fifth, the study reflects a large, real-world cohort of AF ablation patients. Due to the world-wide COVID-19 pandemic and to incident logistical reasons, protocol deviations may occur (e.g., a longer than desirable waiting time for ablation or out-of-window follow-up visits).

Conclusion

This cohort study explores 6 different domains for predictors of successful AF ablation: 1) clinical factors, 2) AF patterns, 3) anatomical characteristics, 4) electrophysiological characteristics, 5) circulating biomarkers, and 6) genetic background. All study procedures are incorporated into a standardized, integrated clinical care and research pathway allowing an almost complete consecutive recruitment of patients undergoing AF ablation in two Dutch AF centers. The findings from different domains will be combined to determine the optimal combination of established predictors and novel techniques. This combination of predictors could then be used to tailor treatment decisions specifically to individual patients and to improve patient selection for invasive management.

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SUPPLEMENTS

Supplement 1. Description and discussion of study procedures

The following procedures are performed as additional study measurements for all participants in the ISOLATION study: determination of body composition, pre-procedural rhythm monitoring, extended surface electrocardiogram (extECG), biomarker testing, genetic analysis, and questionnaires.

Determination of body composition

Although obesity is a well-known risk factor for atrial fibrillation (AF) development and AF burden, recent studies have indicated that obesity-related anthropometric measures such as fat percentage and total body mass index are not associated with AF development after adjusting for lean body mass.[1] To explore whether the same association is present with the development of recurrences after AF ablation, this study will examine the correlation between different anthropometric measures (*Table S1*) and ablation success. Weight, fat percentage, and lean body mass indices will be estimated using previously developed and validated[2] sex-specific equations on bio-electrical impedance, measured with body composition monitors (Omron BF511 Body Composition monitor, Omron Healthcare). The results of these measurements are part of domain 1: clinical factors.

Pre-procedural rhythm monitoring

The predictive value of different AF patterns for successful AF ablation has not been previously studied. However, this domain may yield interesting information. Frequent, short AF episodes may identify patients with frequent triggers initiating AF, while longer sustained AF episodes may identify those with pronounced atrial structural remodeling maintaining AF. As pulmonary vein isolation (PVI) targets AF triggers originating from the pulmonary veins (PVs), it is thus expected to be more successful in patients who predominantly suffer from frequent, short paroxysms. Indeed, ablation success rates of PVI only are higher for patients with paroxysmal AF than for those with persistent AF, who often have more extensive LA fibrosis potentially harboring extra-PV triggers for AF.[3] However, many more AF phenotypes exist within the groups of paroxysmal and persistent AF. A more detailed classification of AF patterns taking frequency and duration of separate paroxysms into account is therefore desirable.[4] To gain more insight in these patterns, ISOLATION patients awaiting the AF ablation procedure receive a handheld patient-operated device (MyDiagnostick 1001R, Applied Biomedical Systems, Maastricht, the

Netherlands), which records and stores one-lead ECGs. Patients are asked to record their heart rhythm three times a day during a maximum of four weeks. Additional registrations are recorded at each onset or relief of arrhythmia symptoms. Symptoms and their correlation to measurements are recorded in a patient diary. The AF patterns are studied in domain 2 (*Table S1*).

Extended surface electrocardiogram

Detailed analysis of P-wave and fibrillation wave (F-wave) features from surface electrocardiograms (ECGs) are increasingly used to characterize the degree of electrophysiological changes in the atria. Several P-wave characteristics (e.g., P-wave duration, amplitude, area, and force [5-7]) and fibrillation wave (F-wave) characteristics (e.g., dominant frequency, amplitude, and organization index [8-12]) have been demonstrated to predict response to rhythm control strategies. ECG recordings using additional leads that specifically focus on the atria may provide even more information. [13-15] In the ISOLATION study, extECGs are recorded at three separate time points. Eleven additional electrodes are placed on the front and the back of the patient (*Figure S1*), besides the ten electrodes used to acquire the standard 12-lead ECG. Eight of the additional electrodes are placed to construct a cuboid box from which 3D vectorcardiograms can be calculated. Three electrodes are placed in positions focusing on signals from the left and right atrium. The extECG will be recorded unfiltered for up to five minutes to acquire about 300 P-waves (in the case of sinus rhythm) or 1500 to 2000 fibrillation waves (in the case of AF). The longer recordings allow for signal-averaged analyzation of P-waves and for QRST cancelation to examine F-wave frequency and complexity dynamics with minimum artifacts. ExtECGs are recorded using the YRS100 cardiac amplifier (YourRhythmics BV, Maastricht, The Netherlands). Variables of interest include those listed in *Table S1* and are studied in domain 4: electrophysiological characteristics.

Table S1. Variables of interest in the ISOLATION study in domain 1-5.

Parameters of interest per domain		
Domain 1: Clinical factors		
Age	Congestive heart failure	Body mass index
Sex	Previous thromboembolic events	Fat percentage
Comorbidities	Sleep apnea	Fat mass
Hypertension	Smoking status	Visceral fat level
Diabetes mellitus	Alcohol consumption	Muscle percentage
Dyslipidemia	**Anthropometric information**	Muscle mass
Coronary artery disease	Height	Fat-free mass (lean mass)
Vascular disease	Weight	Basal metabolic rate
Domain 2: Pre-procedural AF patterns		
AF type	N° of non-AF episodes	Maximum heart rate in AF
N° of AF episodes	Median duration non-AF episodes	Median heart rate in SR
Median duration of AF episodes	Percentage of time in AF	AF pattern classification
Duration of longest AF episode	Predominant onset of AF in morning/ afternoon/evening/night	
Duration of shortest AF episode	Median heart rate in AF	
Domain 3: Anatomical characteristics		
Left ventricular ejection fraction	Left atrial diameter	N° of right-sided pulmonary veins
Left ventricular end-diastolic dimension	Left atrial volume	N° of left-sided pulmonary veins
Left ventricular mass	Left atrial volume index	Agatson calcium score
Left ventricular mass index	Right atrial area	Presence of coronary plaques
Mean E/e'	Right atrial volume	
Right ventricular systolic pressure	N° of pulmonary veins	

Table S1. Variables of interest in the ISOLATION study in domain 1-5. (continued)

Parameters of interest per domain		
Domain 4: Electrophysiological characteristics		
Rhythm	Terminal force	f-wave amplitude
Heart rate	Shannon entropy	Organization index
QRS duration	Sample entropy	Regularity index
QT duration	P-wave complexity	Spectral entropy
QTc interval	Euclidean distance	Sample entropy
P-wave characteristics	Similarity index	f-wave power
P-wave duration	Spatial similarity	Harmonic decay
P-wave area	**F-wave characteristics**	N° of principal components
P-wave amplitude	Dominant frequency	Spatiotemporal organization
Domain 5: Circulating biomarkers		
Hemoglobin	Endothelial cell-specific molecule 1	Dickkopf-related protein 3
Creatinine	Pro-brain natriuretic peptide 2	Insulin-like growth factor-binding protein 7
Interleukin 6	N-terminal pro-BNP	Bone morphogenetic protein 10
Angiopoietin 2	Fibroblast growth factor 23	

Variables of interest collected in the ISOLATION study and ISOLATION 'light' registry. In case of newly gained insights during the study, the list may be supplemented with additional parameters.

Abbreviations: AF: atrial fibrillation, BNP: brain natriuretic peptide, ECG: electrocardiogram, f-wave: fibrillation wave, QTc: corrected QT-interval, SR: sinus rhythm.

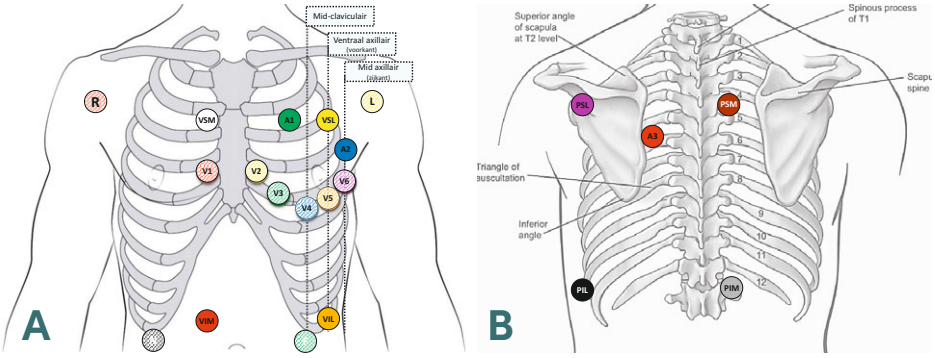


Figure S1. Placement leads extended surface electrocardiogram.

Placement of the electrodes of the extended surface electrocardiogram at the front (A) and the back (B) of the patient. Eight electrodes are placed to construct a cuboid box (VSM, VSL, VIL, VIM, PSM, PSL, PIL, PIM). Three electrodes are placed in positions focusing on signals from the left and right atrium (A1, A2, A3). The remaining 10 electrodes (R, L, F, N, V1, V2, V3, V4, V5, V6) are placed in the usual positions for standard 12-lead electrocardiograms.

Blood samples

Several biomarkers and common gene variants have been identified that predict AF development, AF-related complications, and recurrences of AF after ablation.[16-20] The biomarkers of interest that are studied in the ISOLATION and ISOLATION 'light' studies are listed in *Table S2* and include inflammatory mediators,[17] markers of myocardial wall stress,[17] markers of fibrosis,[21, 22] markers of endothelial dysfunction and pro-thrombotic state,[23-25] and markers for expression of genes regulating electrophysiological characteristics.[16] In addition, the results of several ongoing trials collecting a broad set of biomarkers and genetic data in large cohorts will be taken into account in this study's analysis.[26, 27] Blood for biomarker analyses is drawn at three separate time points. Genetic analysis is performed on the blood drawn at baseline. The procedures for the collection, processing and storage of blood samples are described in a standardized operating procedure to assure maximum quality and comparability of the samples. Frozen samples will be shipped periodically to external laboratories for biomarker analyses (Roche – Roche Diagnostics Rotkreuz, Switzerland) and genetic analysis (University Hospital Münster, Germany, Department of human genetics and genetic epidemiology). The results are studied in domain 5: circulating biomarkers and 6: genetic background.

Table S2. Biomarkers of interest.

Biomarker/genetic background	Abbreviation	Category
Interleukin 6	IL-6	Inflammatory mediator
Angiopoietin 2	ANG-2	Inflammatory mediator, marker of endothelial disfunction
Endothelial cell-specific molecule 1	ESM-1	Marker of endothelial disfunction
Pro-brain natriuretic peptide 2	pro-BNP2	Marker of myocardial wall stress
N-terminal pro-brain natriuretic peptide	NT-proBNP	Marker of myocardial wall stress
Fibroblast growth factor 23	FGF-23	Marker of fibrosis
Dickkopf-related protein 3	DKK-3	Marker of fibrosis
Insulin-like growth factor-binding protein 7	IGFBP-7	Marker of pro-thrombotic state
Bone morphogenetic protein 10	BMP-10	Marker for expression of genes regulating electrophysiological characteristics
Transcription factor PITX2	PITX2	Transcription factor involved in the development of the left and right atria and pulmonary veins

Several biomarkers of interest in the ISOLATION study and ISOLATION 'light' registry. In the case of new insights during the course of the studies, the list may be supplemented with additional biomarkers of interest.

Questionnaires

The following questionnaires are completed at baseline: Montreal Cognitive Assessment (MoCA), Toronto AF Severity Scale (AFSS), Atrial Fibrillation Effect on QualiTy-of-life (AFEQT), STOP-Bang, and a combined COPD questionnaire consisting of a modified Respiratory Health Screening Questionnaire (RHSQ), COPD assessment test (CAT), and modified Medical Research Council (mMRC) Dyspnea scale. The MoCA test is completed on site with the help of trained study personnel. The AFSS, AFEQT, STOP-Bang, and combined COPD questionnaire are completed using either paper versions or electronic versions, depending on patient preference. Additional information on the questionnaires is provided in *Table S3*.

Study procedures for subsets of patients

The following procedures are performed as additional study measurements in a subset of ISOLATION participants: trans-esophageal electrocardiogram (TE-ECG), additional analysis of endo- or epicardial mapping, and left atrial appendage (LAA) biopsies.

Transesophageal electrocardiogram

Participants are asked for separate permission to record a transesophageal ECG. The TE-ECG is recorded using a catheter containing multiple unipolar leads. This catheter is either swallowed or inserted through the nostril, depending on the researchers and patient's preference, to reach the esophagus. It is held in place to record for 2 minutes, or as long as tolerated, and is then removed.

Table S3. Questionnaires.

	Prior to ablation (baseline)	3 months after ablation	12 months after ablation	24 months after ablation
Toronto AF Severity Scale (AFSS) *Questionnaire on type and intensity of AF-related symptoms* 19 questions				
Timing	X	X	X	X
Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) *Assessment of quality of life specifically for AF patients* 22 questions				
Timing	X	X	X	X
Montreal Cognitive Assessment (MoCA) *Assessment of cognitive impairment in multiple cognitive domains* 30 questions				
Timing	X	X	X	
Stop-BANG *Risk estimation for obstructive sleep apnea* 8 questions				
Timing	X			
Combined COPD questionnaire* *Assessment of symptoms of COPD and its impact on the patient's health* 15 questions				
Timing	X			

Timing and purpose of questionnaires in the ISOLATION study.

** The combined COPD questionnaire includes a modified Respiratory Health Screening Questionnaire (RHSQ), COPD assessment test (CAT), and modified Medical Research Council (mMRC) Dyspnea scale.*

Abbreviations: COPD: chronic obstructive pulmonary disease.

Endo- or epicardial mapping

Depending on the selected ablation technique, endocardial or epicardial electroanatomical mapping may be performed. Epicardial mapping is performed as additional study procedure, endocardial mapping is standard practice in some transcatheter endocardial procedures. When performed, results of epi- and endocardial mapping are saved to use for additional analysis in a later stadium. Custom-made algorithms will be used to identify activation times based on electrograms and to reconstruct waves that inform on the predominant activation pattern and conduction velocity during sinus rhythm, AF and routine atrial pacing. These activation patterns will be correlated to the electrogram properties that have been used for individualized and targeted ablation (e.g., low voltage areas, high degree of electrogram fractionation). This investigation will deepen our understanding on the mechanism of AF termination by ablation of such areas. Besides, a newly developed algorithm to detect repetitive conduction patterns and reconstruction of macro-reentry circuits based on these patterns will be used and further refined. This algorithm will allow to determine critical paths for re-entry that independently from electrogram morphology may constitute a target for AF ablation.

Biopsy of left atrial appendage (LAA)

During hybrid ablations or concomitant surgical ablations, the LAA is usually clipped to reduce the risk of thromboembolisms. After the structure is clipped, a biopsy can be taken easily and safely. Studying this tissue will provide additional information about structural changes and differences in electrical conduction in the atria.

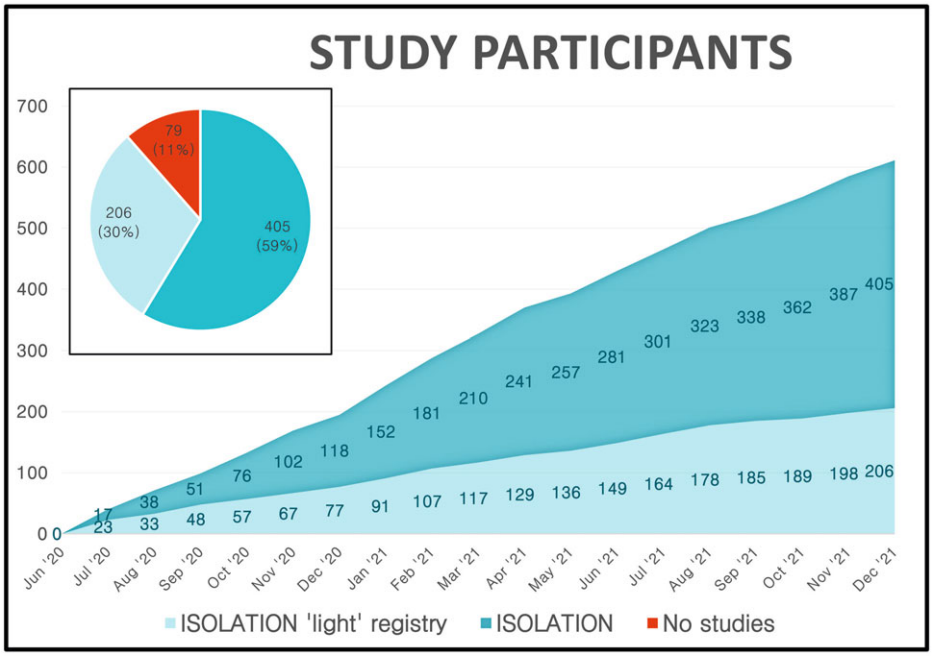
Supplement 2. Substudies of the ISOLATION and ISOLATION 'light' registry.

Subject	Subset of patients	Primary aims
Transesophageal ECG	RF ablation (incl. electroanatomic mapping)	• To investigate the correlation between atrial depolarization waves measured with transesophageal ECG and the real activation patterns obtained from invasive electroanatomic mapping. • To explore the association between f-wave characteristics and P-wave characteristics derived from transesophageal ECG with arrhythmia recurrence.
ECG-imaging	RF ablation (incl. electroanatomic mapping)	• To investigate whether atrial depolarization waves measured with ECGi accurately reflect the real activation patterns obtained from invasive electroanatomic mapping. • To investigate the relation between activation patterns obtained from ECGi with clinical parameters (e.g., paroxysmal vs persistent, left atrial size, recurrences).
CMR C-SUBSTRATE	RF ablation (incl. electroanatomic mapping)	• To investigate left atrial substrate for AF with innovative cardiac CMR techniques. • To investigate the effect of AF ablation on left atrial substrate by evaluating anatomical, hemodynamic and functional changes by CMR. • To explore the association between left atrial substrate (in 3 domains) and arrhythmia recurrence
LAA biopsy Epicardial electroanatomic mapping	Surgical ablation or hybrid ablation	• To study structural changes and differences in electrical conduction in the atria by determining overall connective tissue content, endomysial fibrosis, capillary density and fibroblast abundance. • To unravel molecular pathways associated with AF or recurrences of AF by mRNA sequencing • To study AF mechanisms measured by epicardial mapping and to relate the AF conduction patterns to the underlying atrial tissue characteristics
Concomitant hybrid AF ablation COMBAT-AF	CABG + concomitant AF	• To evaluate the feasibility, safety and effectivity of a staged hybrid concomitant treatment in patients with persistent AF that undergo a CABG and did not have prior AF ablations. • To evaluate the potential of non-invasive parameters to predict the completeness of surgical ablation lines • To study the underlying AF mechanism based on the epicardial and endocardial mapping and to relate the AF conduction patterns to the underlying atrial tissue characteristics.

Supplement 2. Substudies of the ISOLATION and ISOLATION 'light' registry. (continued)

Subject	Subset of patients	Primary aims
OSA screening VIRTUAL-SAFARI [28]	All patients	• To evaluate the feasibility of structural, remote OSA screening in patients awaiting AF ablation • To assess the prevalence of previously undiagnosed OSA in patients awaiting AF ablation • To explore the impact of structural OSA screening and treatment on AF ablation outcomes and symptoms
COPD screening	MUMC+ patients	• To evaluate the feasibility of structural COPD screening using handheld spirometry in patients awaiting AF ablation • To assess the prevalence of previously undiagnosed COPD in patients awaiting AF ablation • To explore the impact of structural COPD screening and treatment on AF ablation outcomes and symptoms

Abbreviations: AF: atrial fibrillation, CABG: coronary artery bypass grafting, CMR: cardiac magnetic resonance imaging, COPD: chronic obstructive pulmonary disease, ECG: electrocardiogram, ECGi: electrocardiographic imaging, LAA: left atrial appendage, mRNA: messenger ribonucleic acid, MUMC+: Maastricht University Medical Center, OSA: obstructive sleep apnea syndrome, RF: radiofrequency energy.



Supplement 3. Inclusion in ISOLATION study and ISOLATION 'light' registry.

Inclusion rates in the ISOLATION study and the ISOLATION 'light' registry over time from June 2020 until December 2021. The pie chart in the upper left corner displays the percentages of all patients undergoing atrial fibrillation ablation in the two participating centers that was included in the ISOLATION study (59%), in the ISOLATION 'light' registry (30%) and patients that declined participation in either study (only 11%).

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CHAPTER 3

A new efficient and integrated pathway for patient evaluation prior to atrial fibrillation ablation

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ABSTRACT

Aim

In this quality improvement project, a care pathway for patients considered for atrial fibrillation (AF) ablation was optimized with the goal to improve the patient journey and simultaneously integrate prospective data collection into the clinical process.

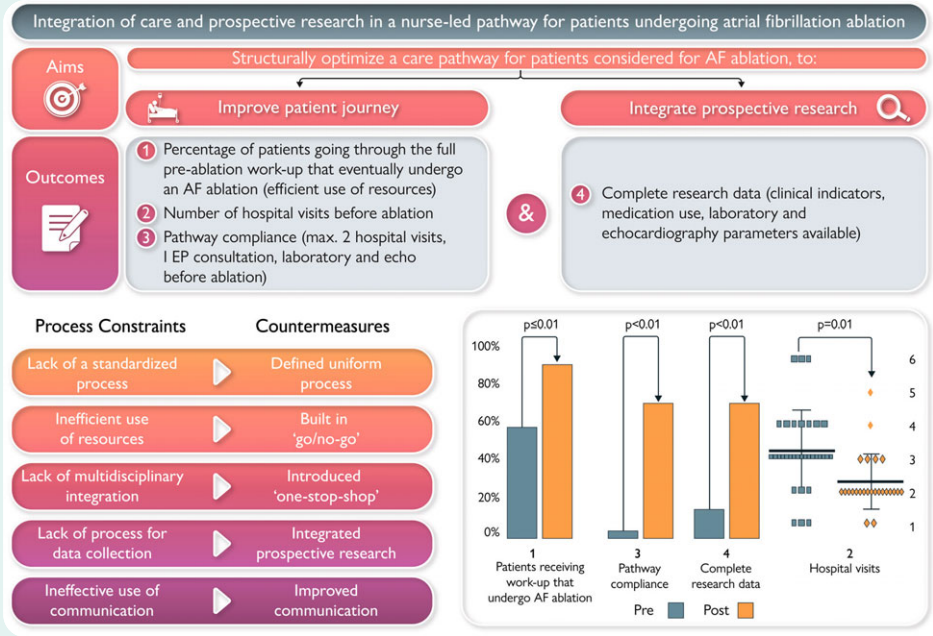
Methods and results

The Lean Six Sigma approach was used to map the pre-existing process, identify constraints and formulate countermeasures. The percentage of patients going through the full pre-ablation preparation that eventually underwent AF ablation, number of hospital visits and consultations, pathway compliance, and completeness of scientific data were measured before and after pathway optimization. Constraints in the process were (1) lack of standardized processes, (2) inefficient use of resources, (3) lack of multidisciplinary integration, (4) lack of research integration, and (5) suboptimal communication. The impact of the corresponding countermeasures (defining a uniform process, incorporating 'go/no-go' moment, introducing a 'one-stop-shop', integrating prospective data collection, and improving communication) was studied for 33 patients before and 26 patients after pathway optimization. After optimization, the percentage of patients receiving a full pre-ablation preparation that eventually underwent AF ablation increased from 59% to 94% ($p < 0.01$). Fewer hospital visits (3.2 ± 1.2 versus 2.3 ± 0.8, $p = 0.01$) and electrophysiologist consultations (1.8 ± 0.7 versus 1.0 ± 0.3, $p < 0.01$) were required after pathway optimization. Pathway compliance and complete collection of scientific data increased significantly (3% versus 73%, $p < 0.01$ and 15% versus 73%, $p < 0.01$, respectively).

Conclusion

The optimization project resulted in a more efficient evaluation of patients considered for AF ablation. The new, more efficient process includes prospective data collection and facilitates easy conduct of research studies focused on improvement of patient outcomes.

GRAPHICAL ABSTRACT



INTRODUCTION

The number of ablation procedures to treat atrial fibrillation (AF) has increased in the past decade as a result of the increasing prevalence of AF and the high success rate of ablation to maintain sinus rhythm.[1] However, as the number of AF ablations increases, so do the health care expenses.[2] To keep health care accessible and affordable, it is important for health care providers to efficiently and effectively use the medical resources at their disposal.

Prior to AF ablation, all patients need to undergo a comprehensive diagnostic evaluation. The planning and organization of this preparation is complex and expensive. Introduction of a structured care pathway may help to create a more effective and homogeneous (i.e., less complex) patient journey and could result in reduced costs.[3, 4] Because of its multidisciplinary involvement (electrophysiologist, AF nurse, radiologist and anesthesiologist), the diagnostic evaluation process for patients considered for AF ablation is very suitable for care pathway creation or optimization.

Optimizing a care pathway also provides an excellent opportunity to update clinical processes to comply with recent guidelines and insights. In an AF pre-ablation trajectory, organizing care in an integrated manner with a specialized AF nurse in a central role is desirable.[4-6] This specialized nurse may coordinate clinical, organizational and communicational facets, while simultaneously contributing to patient education and improved patient outcomes through guideline-adherent care.[4, 5, 7-9] Moreover, renewal of a care pathway provides the possibility to integrate prospective (translational) studies into the flow of routine clinical care, making research easier to conduct. Results of such studies focusing on pathophysiological mechanisms of AF may contribute to improved selection of patients benefitting from invasive AF management and improved care for future patients.[10, 11]

In the Maastricht University Medical Center+ (MUMC+), Maastricht, The Netherlands, a quality improvement project was conducted which aimed to improve the evaluation and preparation of patients considered for AF ablation, to reduce the required resources, and to facilitate prospective data collection into the clinical process. Herein, the development, implementation and evaluation of this new care pathway are described.

METHODS

This study describes a single-center experience with a clinical care pathway optimization project for patients considered for AF ablation using the Lean Six Sigma approach. [12] In short, the pre-existing care process was mapped in detail and constraints in the process were identified. Countermeasures addressing these constraints were formulated and implemented in a stepwise method, which resulted in a new and refined care pathway. Finally, the optimized situation was compared to the pre-existing situation to determine whether the project goals had been met (*Figure 1*).

The quality improvement project was conducted in the Department of Cardiology of the MUMC+ and supported by Lean Six Sigma specialists (Medtronic Integrated Health Solutions). It was part of the preparation of the infrastructure for the ISOLATION study (NCT04342312), a prospective multicenter cohort study aimed at identifying predictors for successful AF ablation on several investigational domains. [13] The collection of data for the current project was approved by the Medical Ethics Review Committee of the MUMC+ (registration number 2020-1488). Given the observational design, written informed consent was not necessary to obtain according to the Dutch Act on Medical Research involving Human Subjects.

The Lean Six Sigma approach

Lean Six Sigma is a strategy that can be used to facilitate the redesign of an existing care process into a structured care pathway. Lean Six Sigma is a combination of Lean Thinking (systematically eliminating waste) and Six Sigma (removing errors and minimalizing variation in a process). [12] Although originally developed to improve production processes in the car and electronics industry, Lean and Six Sigma have since been used to improve processes in several other fields including the health care sector. In the latter, the approach has been deployed successfully to enhance capacity, improve patient satisfaction, reduce medical errors, shorten lead times, and reduce costs. [14-18] The Lean Six Sigma approach provides guidance to solve problems using the five DMAIC steps (*Figure 1*). The acronym DMAIC denotes the actions to *define* the problem (D), to *measure* the current situation (M), to *analyze* the underlying (root) causes of structural problems (A), to *improve* the situation (I), and to *control* and sustain the new situation (C). In each DMAIC step, several strategies originating from the Lean and the Six Sigma methodologies are employed to visualize, quantify, and formulate potential constraints (factors that limit the capability of

the process to achieve its purpose) and countermeasures (solutions for the root causes of these constraints). During this project, the DMAIC steps were applied in a continuous, iterative approach, while continuously monitoring the impact of separate countermeasures and re-evaluating which constraints remained and should be addressed.

Pre-existing work-up

Most patients considered for AF ablation in the MUMC+ are referred by other hospitals. In the pre-existing situation, most patients, upon referral to the MUMC+, visited an AF ablation preparation care pathway. This care pathway was a series of consecutive appointments consisting of an intake by a nurse (listing concomitant comorbidities, cardiovascular risk factors, medication, and vital functions), followed by an electrocardiogram, laboratory tests, echocardiography, and exercise test. The last stop was a consultation with an electrophysiologist, during which the patient was informed on AF treatment options including AF ablation and the decision whether to proceed with the procedure was made. If they were accepted for AF ablation, additional written information was provided and separate appointments were made for the remaining part of the preparation (computed tomography scan, consultation with anesthesiologist).

For most patients this care pathway was their first entry after referral to the MUMC+, and they first underwent the diagnostic preparation procedures before the decision to proceed with the ablation was made. However, due to the limited availability of the care pathway some patients underwent the individual components of the pre-AF ablation preparation in separate visits, or visited the care pathway after the initial consultation with an electrophysiologist had taken place and the decision to proceed with an AF ablation had been made. Different possible patient journeys in the pre-existing evaluation for AF ablation upon referral to the MUMC+ are outlined in *Figure 1, upper panel*.

Outcome measures and definitions

The primary aims of this optimization project were to improve the evaluation process of patients considered for AF ablation, to reduce the required resources, and to integrate prospective research conduct into the clinical process. To be able to evaluate the impact of the interventions, the following outcome measures were formulated: (1) the percentage of patients going through the full pre-ablation preparation that eventually underwent an AF ablation, (2) the number of hospital visits and electrophysiologist consultations for patients preceding AF ablation, (3) pathway compliance, and (4) systematic and complete collection of scientific data.

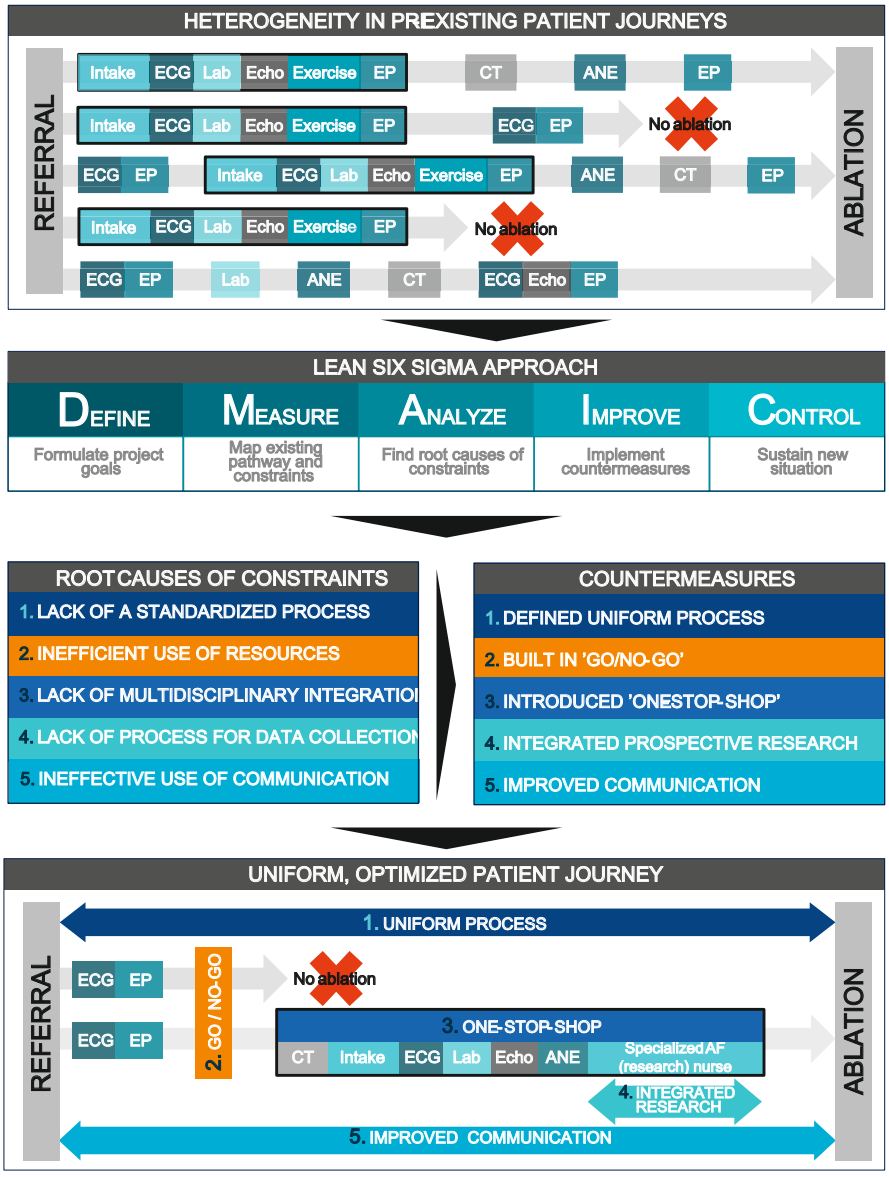


Figure 1. Care pathway optimization for patients considered for atrial fibrillation ablation.

The upper panel reflects the heterogeneity of patient journeys in the pre-existing evaluation process. The process was optimized using the Lean Six Sigma approach, following the 5 DMAIC steps (Define, Measure, Analyze, Improve, Control, second panel). These steps were used to identify the root causes of constraints in the pre-existing process (left panel) and formulate corresponding countermeasures (right panel). Implementation of these countermeasures resulted in an optimized and uniform patient journey from referral to ablation (lower panel).

Abbreviations: ANE: anesthesiologist, ECG: electrocardiogram, Echo: echocardiography, EP: electrophysiologist, CT: computed tomography scan.

The percentage of patients going through the full pre-ablation preparation that eventually underwent an AF ablation represents the efficient use of medical resources. The aim was to reserve the costly and time-consuming preparatory resources for patients who were truly accepted for ablation, instead of for those who eventually chose not to undergo an ablation. The number of hospital visits was defined as the number of days on which the patient visited the hospital in the period between referral and ablation. If multiple appointments (e.g., electrophysiologist consultation and echocardiography) were scheduled on the same day, this counted as a single visit. Only visits related to the preparation for AF ablation were included. Pathway compliance was defined as the percentage of patients that underwent AF ablation and completed the care pathway according to the following goals: a maximum of two outpatient hospital visits, a maximum of one electrophysiologist consultation, available laboratory results (defined as at least estimated glomerular filtration rate assessed during preparation), and a complete echocardiogram performed in the MUMC+ (to ensure sufficient recency, completeness and quality of images). These factors were deemed representative indicators for an efficient, yet realistic and complete preparation in a multidisciplinary team meeting with different health care professionals involved in the pre-AF ablation process. Last, complete collection of scientific data was defined as the availability of a predefined set of relevant variables consisting of clinical indicators (date of AF diagnosis, AF type and CHA_2DS_2-VASc score), cardiovascular medication, laboratory results (hemoglobin, thyroid stimulating hormone, estimated glomerular filtration rate and N-terminal pro-B-type natriuretic peptide) and echocardiography derived data (left atrial volume index and left ventricular ejection fraction).

Data collection

Data were collected from the hospitals electronic patient management system (SAP Healthcare Solutions, SAP SE, Walldorf, Germany) and stored anonymously in a research database. The percentage of patients going through the full pre-ablation preparation that eventually underwent an AF ablation was assessed by comparing patients completing the pre-AF ablation evaluation process in the 3 months before versus the 3 months after the project was completed. The other outcome measures were assessed for consecutive patients who were accepted for AF ablation during the last 3 months prior to the start of the project versus the first 3 months after the project. Patients who were considered for AF ablation were identified from a list of referrals based on the presence of a registered *atrial fibrillation* diagnosis treatment combination

(DBC) code. DBCs are codes used in the Netherlands for the registration and reimbursement of hospital and medical specialist care.[19] Health care activities related to the AF DBC (e.g., consultations with medical specialists, visits to the hospital and diagnostics tests) were collected, as well as the presence and completeness of the variables that were deemed relevant to the pathway.

Statistical analysis

Continuous data were reported as means ± standard deviation and compared using the student's t-test. Categorical variables were reported as percentages (numbers/total) and compared using the Fisher's exact test. A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics software (version 25.0, IBM Corp., Amonk, NY, USA).

RESULTS

Systematic analysis and optimization of the pre-existing care pathway

The systematic analysis of the pre-existing care pathway using the Lean Six Sigma strategies revealed 38 constraints that limited the capability of the process (*Supplement 1*). For these constraints, five critical root causes were identified. These root causes were the targets for the main countermeasures (*Figure 1*).

Lack of a standardized process

Before the optimization of the pre-AF ablation pathway, the patient journey was heterogeneous and fragmented. Almost a third of patients required 4 or more hospital visits to complete the evaluation. In addition, the required diagnostics before AF ablation were not clearly defined. As countermeasure, the process that a patient goes through in preparation for AF ablation was redesigned based on current guidelines, consensus documents and other literature.[4, 6, 20] The exercise test was identified as an unnecessary test, as all patients underwent a cardiac computed tomography scan to assess left atrial anatomy and the presence of coronary plaques. The newly established 'uniform process' functioned as the foundation on which all other countermeasures could be built.

Inefficient use of health care resources

More than 40% of patients that visited the pre-AF ablation preparation care pathway eventually did not undergo an ablation due to lack of indication, unsuitability, or patient preference. This led to unneeded diagnostic tests and avoidable strain on the capacity of the preparatory care pathway. As

countermeasure, a 'go/no-go' moment was built in at the start of the process, in which the electrophysiologist checks the indication and the patient is informed about the procedure. Only if the patient and physician decide to 'go' for AF ablation, the pre-ablation preparation is performed.

Lack of multidisciplinary integration

The non-central planning of appointments at the departments of cardiology, anesthesiology, radiology, and research resulted in a fragmented patient journey throughout the preparation. As countermeasure, a 'one-stop-shop' combining all appointments into one hospital visit was introduced. Once the decision to 'go' for ablation has been made, the patient is invited to an adapted version of the preparatory care pathway including a computed tomography scan, electrocardiogram, laboratory tests, echocardiography, and a consultation with an anesthesiologist. The one-stop-shop is wrapped up by a newly appointed specialized AF nurse. This nurse acts as a case manager as well as a research nurse and in these capacities provides the patient with additional information on the ablation procedure and its planning, answers questions, monitors results of investigations, coordinates risk factor screening and guideline adherence, takes care of research activities (such as performing additional study investigations and data collection), and manages the entire evaluation process.

Lack of process for prospective data collection

In the pre-existing situation scientific data were predominantly collected retrospectively which caused missing data, limited the value of data sets, and caused double work. Moreover, patients that were eligible for a study were not routinely recognized and inclusions into clinical studies and registries were missed. As a countermeasure, research procedures were embedded in the 'one-stop-shop'. This way, there is no need for additional hospital visits or retrospective searches to achieve complete data sets. In addition, this approach facilitates easy implementation of non-clinical study procedures, when applicable, executed by the specialized AF (research) nurse.

Suboptimal use of communication

Non-structured communication between healthcare professionals and insufficient patient education often led to unnecessary delay in the planning of the procedure and to uncertainties for the patients. As a countermeasure, clearer agreements were made about the moment and manner of planning and contact, and existing communication materials for patients were updated to comply with the new process. Additionally, a consultation with the specialized

AF nurse was added to the 'one-stop-shop'. During this consultation patients are educated upon the procedure further and remaining uncertainties are clarified. The goals of these countermeasures are to provide the patient with sufficient information about the ablation as well as to provide them and their healthcare professionals with on-time information about the journey to come.

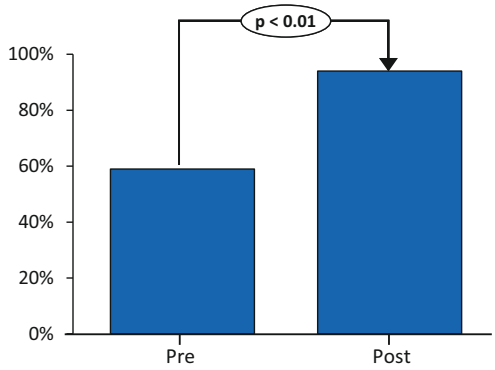


Figure 2. Impact of pathway optimization on efficient use of medical resources (i.e., the percentage of patients going through the full pre-ablation preparation that eventually underwent an AF ablation)

Impact on the percentage of patients going through the full pre-ablation preparation that eventually underwent an AF ablation

The pre-AF ablation evaluation pathway was visited by 34 patients in the 3 months before and 68 patients in the 3 months after this optimization project. After implementation of all countermeasures, the percentage of patients that completed the pre-AF ablation preparation and eventually underwent an ablation increased from 59% (20/34) to 94% (64/68, $p < 0.01$, *Figure 2*). All patients visiting the pre-AF ablation preparation pathway after optimization had been accepted by an electrophysiologist prior to their visit to the pathway, whereas a definite decision to proceed with the ablation had only been made in 47% (16/34) of patients in the group prior to the optimization project.

Impact on hospital visits and pathway compliance

To assess the impact of the implemented countermeasures on the number of hospital visits, electrophysiologist consultations, pathway compliance, and complete collection of research data, 33 consecutive patients accepted for AF ablation prior to the start of the project and 26 patients accepted after the project was completed were studied.

The implementation of the countermeasures resulted in a significant reduction in hospital visits from 3.2 ± 1.2 visits before optimization to 2.3 ± 0.8 visits after optimization (p = 0.01). In addition, the number of consultations with an electrophysiologist decreased significantly from 1.8 ± 0.7 consultations before to 1.0 ± 0.3 consultations after optimization (p < 0.01, *Figure 3*). In the optimized situation, a single consultation with an electrophysiologist was sufficient in 96% of patients, whereas in the pre-existing situation 64% of patients who underwent an ablation needed two or more consultations.

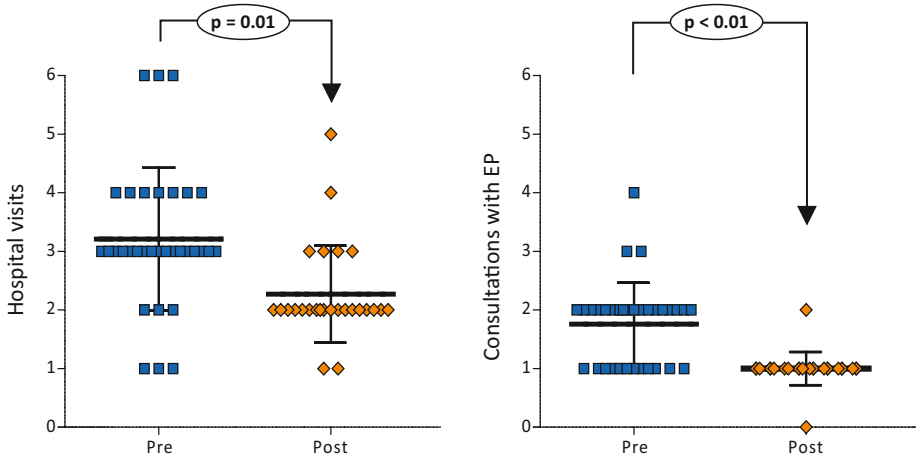


Figure 3. Impact of pathway optimization on mean number of hospital visits (left) and consultations with an electrophysiologist (right) before AF ablation.
Abbreviations: EP: electrophysiologist.

Before the optimization project, 3% (1/33) of patients complied to the criteria for pathway compliance (maximum of 2 hospital visits, maximum 1 consultation with an electrophysiologist, laboratory tests available and a complete echocardiogram available). After the pathway optimization, the pathway compliance increased to 73% (19/26, p < 0.01). This increase was reflected in all separate components of overall pathway compliance (*Figure 4*).

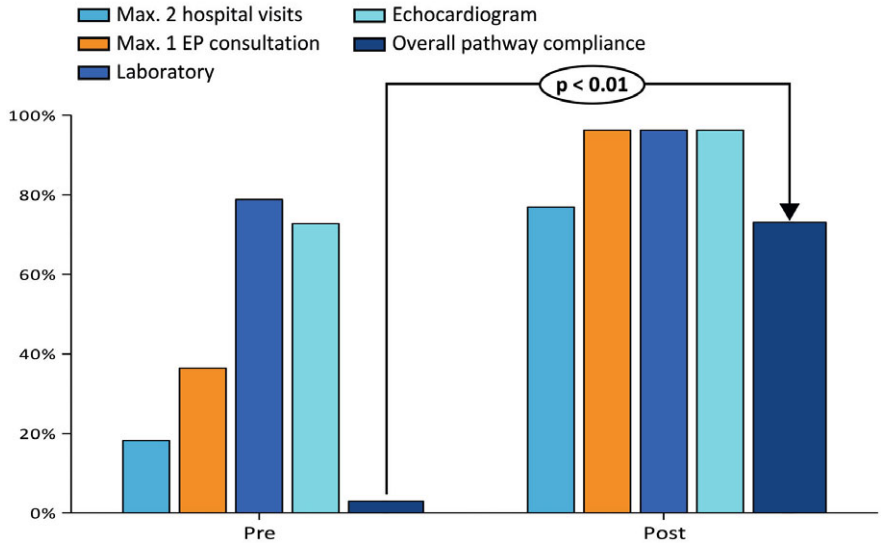


Figure 4. Impact of pathway optimization on pathway compliance.

Overall pathway compliance is defined as the percentage of patients that underwent ablation and completed the care pathway according to the following goals: a maximum of 2 outpatient hospital visits, a maximum of 1 electrophysiologist consultation, laboratory results available (defined as at least estimated glomerular filtration rate assessed during preparation), and a complete echocardiogram performed in the MUMC+.

Abbreviations: EP: electrophysiologist.

Impact on complete collection of scientific data

With the implementation of the new care pathway, the collection of complete scientific data improved significantly as well. Overall, the percentage of completed variables increased from 80% to 94% ($p < 0.01$). This resulted in a complete dataset in 73% (19/26) of patients, compared to a complete dataset in only 15% (5/33) of patients prior to the optimization project ($p < 0.01$). The improvement in availability of scientific data was most pronounced in the biochemical and clinical data (*Figure 5*).

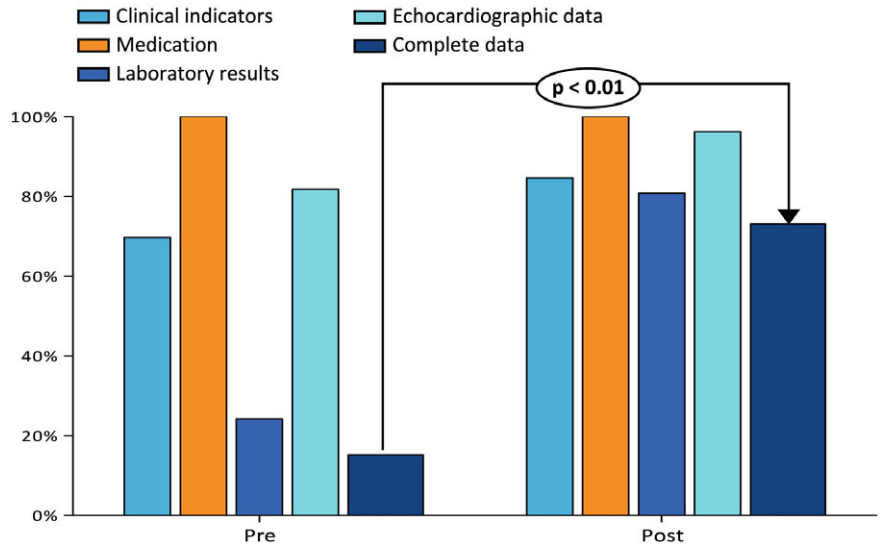


Figure 5. Impact of pathway optimization on completeness of data for scientific research.

Clinical indicators comprise the date of AF diagnosis, the AF type and the CHA_2DS_2-VASc score. Laboratory results comprise hemoglobin, thyroid stimulating hormone, estimated glomerular filtration rate and N-terminal pro-B-type natriuretic peptide. Echocardiographic data are left atrial volume index and left ventricular ejection fraction. Complete data is defined as the availability of all relevant clinical indicators, cardiovascular medication, laboratory results, and echocardiographic data.

Abbreviations: AF: atrial fibrillation.

DISCUSSION

Herein, a single-center experience is described to optimize a care pathway for patients considered for AF ablation using the Lean Six Sigma approach. The most important findings are that this structured approach resulted in more efficient use of medical resources, a reduction in hospital visits, an increase in pathway compliance and an improvement in systematic and complete collection of research data. For patients considered for AF ablation, this means less hospital visits and a seamless integration of the complete preparation for the procedure. From a clinical point of view, the reduced use of resources means that the unlocked resources (i.e., improved capacity) can be used elsewhere. From a scientific point of view, the systematic collection of data will advance the understanding of AF and help to improve the outcome of catheter ablation for AF.

This optimization project is an example of value-based health care. Value-based health care is a framework that supports management and decision

making in health care, in which professionals strive to provide their patients with optimal value. Patient value is defined as the ratio between patient relevant outcomes and the costs per patient to achieve these outcomes. [21] Therefore, patient value can be increased by improving outcomes or by optimizing the efficient use of medical resources with potential impact on the health care costs per patient. Although in the current project no direct data on patient relevant outcomes and costs were collected, the improved quality of care, decreased number of hospital visits, and improved communication towards patients may have improved patient experience and quality of life. [22] Therefore, the patient value is expected to have increased, which is consistent with previously described care pathway optimization projects [3, 23] and Lean Six Sigma-based projects. [15, 16]

Despite the amount of research that has been conducted on the topic of AF ablation, gaps of evidence in this field remain plentiful, as underlined by a recent European Heart Rhythm Association (EHRA) white paper on knowledge gaps in arrhythmia management. [24] Large prospective studies may help to address these uncertainties. However, structural enrollment of patients into clinical studies often remains a challenge. Study populations are therefore usually a poor reflection of real-world patients, typically omitting older and frailer patients. Establishing a clear 'system' for identification of potential study participants and decreasing the need for additional visits and patients' time investment, as realized in the current project, are crucial to support inclusion across the range of patient types. [25, 26] Moreover, prospective instead of retrospective research data collection allows for obtaining additional information and for adding specific research investigations. With the integration of prospective studies into clinical processes, as realized in this project, valuable research data were produced for a heterogeneous range of patients. These data can be used to further improve treatment strategies in the future.

Of note, apart from the outcome measures described in this study, improvement of the overall peri-ablation care was another important goal in this optimization project. The new process was, in accordance with recent guidelines and literature, designed to become an integrated, multidisciplinary, patient-centered pathway led by a specialized AF nurse. [4-8] The realized pathway allows for active patient involvement, improved patient education and shared decision making. In addition, special emphasis was placed on screening for and treatment of concomitant risk factors for AF, such as hypertension, hyperlipidemia, diabetes mellitus, obesity, sleep disordered breathing, and

structural heart disease, as previous studies demonstrate that strict risk factor management improves AF outcomes.[6, 27, 28] Although the results of these interventions could not yet be assessed in this short-term evaluation project, their impact on AF ablation outcomes may be investigated in future studies.

Limitations

This study had several limitations. First, patients were divided into an intervention and a control group based on the timing of their hospital visits and not by randomization. Possible influence of confounding factors could therefore not be ruled out. Second, data on patient experiences were not available. The optimization project is hypothesized to have a positive effect on patient experience as a result of the decreased hospital visits and improved communication, but this could not be supported by objective data. Third, no data on health care costs and exact time savings were available. Although the avoided use of resources and decreased number of visits are expected to result in lower costs and saved time for health care professionals, a formal cost-effectiveness analysis could not be performed. Last, no long-term data were collected. Whether the results are sustainable over a longer time period should be evaluated in future studies.

Conclusion

The current optimization project using the Lean Six Sigma approach resulted in an efficient, nurse-led, patient-centered care pathway for patients considered for AF ablation. With this new pathway, the patient journey was improved and health care resources are used more efficiently. In addition, the structural integration of prospective data collection into the care pathway will make enrollment of patients and data collection for (translational) research studies easier to conduct. Such studies may lay the foundations for further improvements of AF care in the future. The optimization approach used in this project may be useful for improvement of other care pathways.

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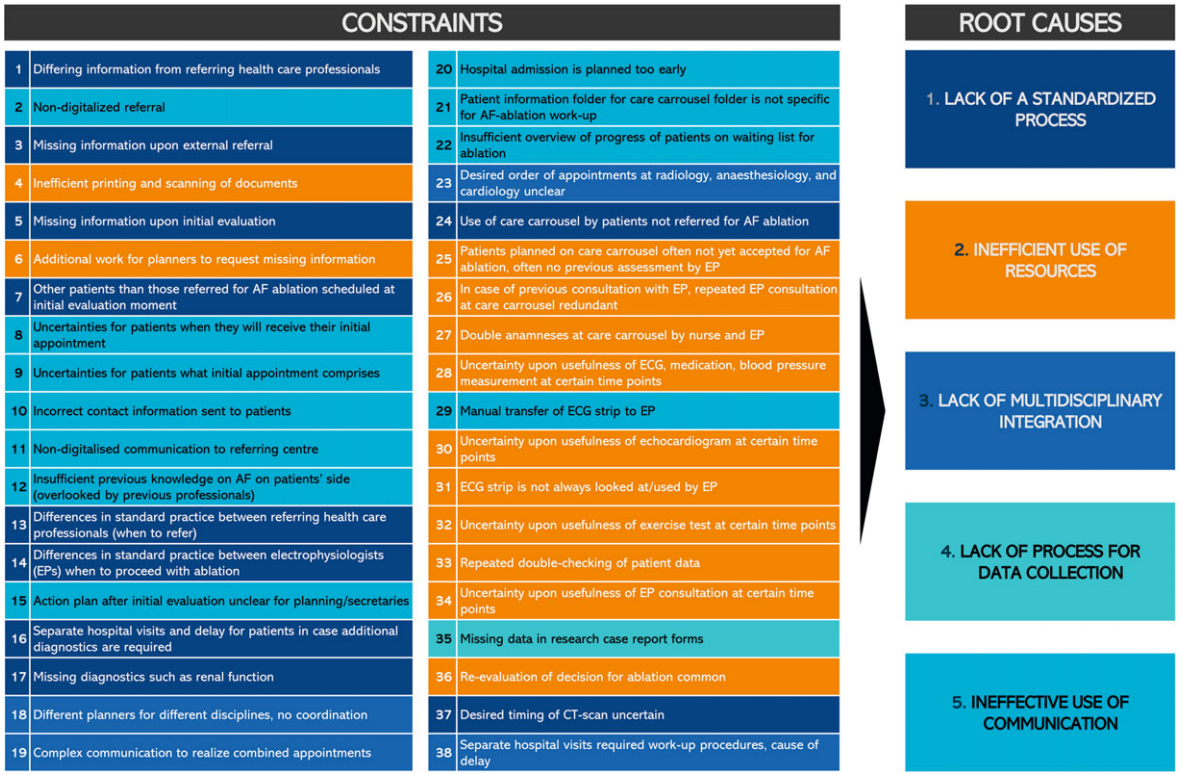
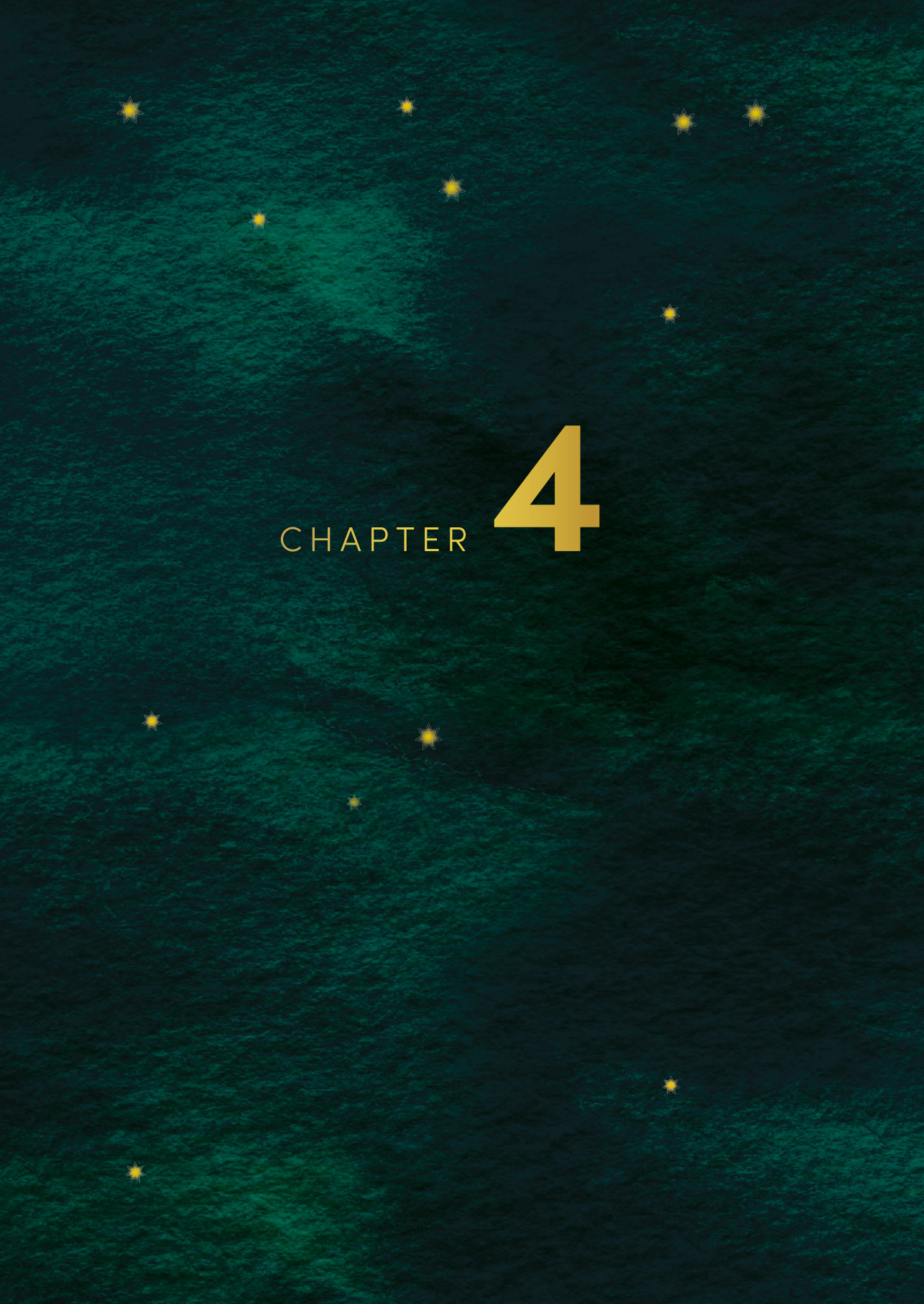
SUPPLEMENTS



Supplement 1. Constraints in the process and corresponding root causes.

Colors of constraints correspond with colors of root causes. In case of several root causes for one constraint, the most applicable constraint is used.

Abbreviations: AF: atrial fibrillation, CT: computed tomography, ECG: electrocardiogram, EP: electrophysiologist.


CHAPTER 4

The photoplethysmography dictionary: Practical guidance on signal interpretation and clinical scenarios from TeleCheck-AF

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ABSTRACT

Aim

Within the TeleCheck-AF project, numerous centers in Europe used on-demand photoplethysmography (PPG) technology to remotely assess heart rate and rhythm in conjunction with teleconsultations. Based on the TeleCheck-AF investigator experiences, we aimed to develop an educational structured stepwise practical guide on how to interpret PPG signals and to introduce typical clinical scenarios how on-demand PPG was used.

Methods

During an online conference, the structured stepwise practical guide on how to interpret PPG signals was discussed and further refined during an internal review process. We provide the number of respective PPG recordings (FibriCheck®) and number of patients managed within a clinical scenario during the TeleCheck-AF project.

Results

To interpret PPG recordings, we introduce a structured stepwise practical guide and provide representative PPG recordings. In the TeleCheck-AF project, 2522 subjects collected in total 90616 recordings. The majority of these recordings was classified by the PPG algorithm as sinus rhythm (57.6%), followed by AF (23.6%). In 9.7% of recordings the quality was too low to interpret. The most frequent clinical scenarios where PPG technology was used in the TeleCheck-AF project were follow-up after AF ablation (1110 patients), followed by heart rate and rhythm assessment around (tele)consultation (966 patients).

Conclusion

We introduce a newly developed structured stepwise practical guide on PPG signal interpretation developed based on presented experiences from TeleCheck-AF. The present clinical scenarios for the use of on-demand PPG technology derived from the TeleCheck-AF project will help to implement PPG technology in the management of AF patients.

INTRODUCTION

Heart rhythm disorders are frequently encountered and treated in cardiology outpatient clinics. Traditionally, an electrocardiogram (ECG) is recommended to assess heart rate and rhythm and to diagnose potential cardiac arrhythmias. In addition to ECG, novel mobile health (mHealth) technologies have been introduced to assist in the detection of arrhythmias as well as to support remote management of patients with arrhythmias. [1] Some of these mHealth devices use (single/poly-lead) ECGs, whereas others base their assessment on photoplethysmography (PPG).

The differences in technologies have important implications. Current AF guidelines state that ECG documentation, either on standard 12-lead ECG or on a single-lead ECG tracing, is required to establish the diagnosis of AF. [2] Although PPG technology thus cannot be used to diagnose AF, it displays an excellent accuracy to detect AF in patients with diagnosed AF. [3] Therefore, PPG technology can be of value in heart rate and rhythm assessment to support the management of patients with a diagnosis of a typical arrhythmia such as AF.

During the coronavirus disease 2019 (COVID-19) pandemic, we initiated the TeleCheck-AF project. TeleCheck-AF is an international, multicenter project to provide an infrastructure to maintain AF management through the combination of teleconsultation with on-demand heart rate and rhythm monitoring using a CE-marked mobile phone app incorporating PPG-technology (FibriCheck®, Qompium, Hasselt, Belgium). [4, 5]

Despite the rapid uptake and wide use of PPG-based technology in current clinical practice, physicians and allied health care professionals are not introduced to this new technology in a structured way. In contrast to ECG courses, PPG analysis and interpretation is not yet part of the medical curricula. The 2020 ESC core curriculum for the cardiologist states that a physician should be able to ''use modalities of heart rhythm monitoring'', but also stresses the limitations of consumer devices, particularly in patients with palpitations. [6] In addition, surveys distributed within the TeleCheck-AF project and the result of the recent wEHRAbles survey showed that physicians are less likely to take clinical actions based on a PPG recording alone, as compared to a single-lead ECG alone. [7,8] Unfamiliarity with the technology might lead to a lack of confidence, therewith making physicians less likely to use it in clinical practice.

This PPG dictionary aims to provide an overview on PPG technology and describe an educational structured stepwise practical guide on how to analyze and interpret PPG signals recorded within the TeleCheck-AF project. By introducing clinical scenarios where the use of on-demand app-based PPG heart rate and rhythm monitoring can be of clinical benefit and presenting several representative PPG recordings, the task of this manuscript also covers the creation of an educational tool and support to implement PPG technology in clinical practice.

METHODS

The TeleCheck-AF project

The TeleCheck-AF approach and the onboarding of centers as well as the center- and patient- experiences are described elsewhere. [4,7]

PPG technology and accuracy to detect AF

In the TeleCheck-AF project, a CE-marked mobile phone app incorporating PPG-technology (FibriCheck®, Qompium, Hasselt, Belgium) was used. [4, 5] PPG is a technology which determines blood volume pulse variation in the local arterioles of the fingertip by measuring the amount of reflected light in the built-in camera of smart devices. [9, 10] The application then converts the 60 Hertz video data to raw signals. [11] In this way, each individual pulse wave can be detected. The time intervals between consecutive pulse signals can be used to determine the heart rhythm and differentiate normal sinus rhythm from AF. [9] *Figure 1* depicts an overview of the PPG mechanism.

Several studies have been performed to determine the accuracy of PPG-based devices to detect ECG-confirmed AF. [3, 12, 13] A meta-analysis by O'Sullivan et al. including four PPG-based mHealth devices presented an overall sensitivity and specificity of 94.2 and 95.8%, respectively. [3] The FibriCheck® algorithm involving artificial intelligence shows an overall sensitivity and specificity for AF detection of 95.6% and 96.6%, respectively, when compared to a standard 12-lead ECG. [9] A study comparing the beat-to-beat detection by the FibriCheck® algorithm with wearable ECG recorders showed a high correlation of 0.993. [11] This correlation was strong, both for patients with regular rhythms as well as for patients with AF. Importantly, within the TeleCheck-AF project, the treating healthcare providers have access to the raw data of the PPG signals together with the RR-tachogram and Poincaré/Lorenz plot. Additionally, certified technicians review all irregular PPG recordings and the results are integrated

in the cloud dashboard. This may even further increase the accuracy to detect AF episodes.

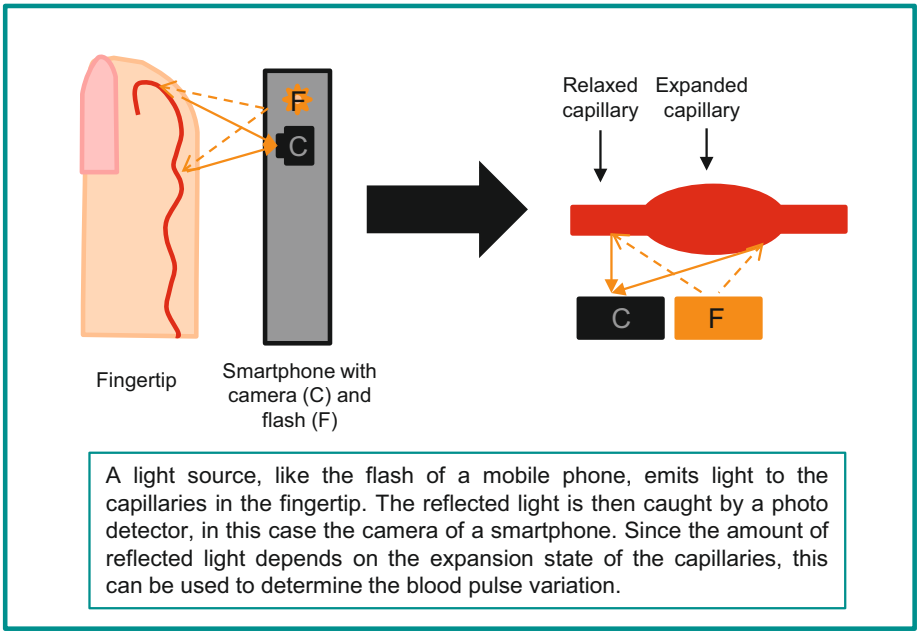


Figure 1. Overview of photoplethysmography mechanism.

Visual presentation of the raw PPG traces

Figure 2a shows the result of a representative 60-seconds PPG recording of a regular rhythm (sinus rhythm) (FibriCheck® application). In this graph, each peak indicates one pulse wave. The number of peaks in this trace represents the pulse rate in beats per minute. The cycle length is determined by measuring the time difference between two consecutive peaks. *Figure 2b* illustrates a tachogram representing the time intervals (y-axis) of consecutive pulse signals (x-axis). Thus, the tachogram can visualize signal-to-signal time interval variability. In this figure, limits for bradycardia and tachycardia are indicated in amber. *Figure 2c* shows a Lorenz or Poincaré plot representing the pulse signal interval as a function of the preceding interval. The structured evaluation of a tachogram pattern or Poincaré/Lorenz plot cluster pattern can support in detecting and identifying certain arrhythmias. Additional examples are presented in *Supplement 1*.

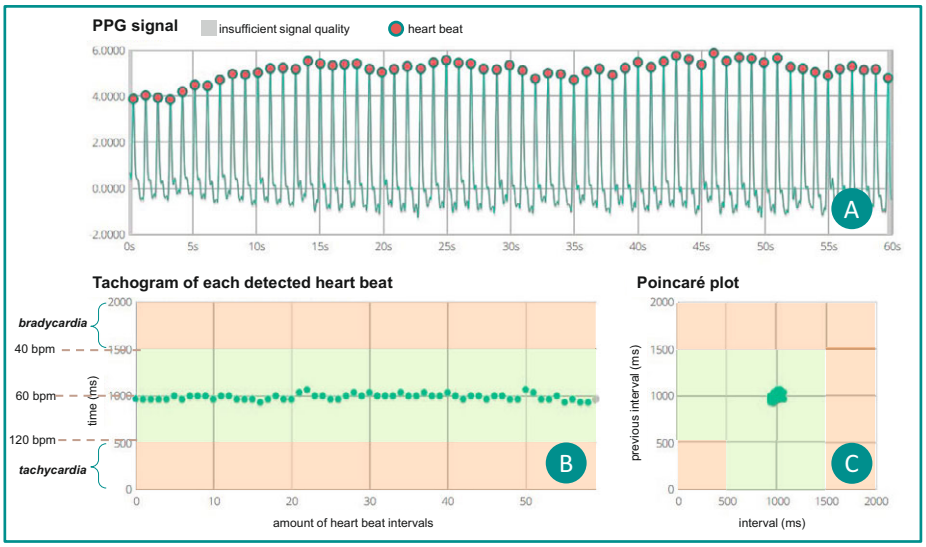


Figure 2. Overview of a regular (sinus rhythm) recording.

(A) Raw PPG signals of a 60-seconds recording. The equal distance between consecutive peaks indicates a regular rhythm.

(B) The tachogram showing all consecutive pulse signal intervals. In this case the interval is regular around 1000 milliseconds, indicating a heart rate of 60 beats per minute.

(C) The Poincaré or Lorenz plot shows a condensed cluster of points, which corresponds to a regular rhythm. Small variations in all graphs are caused by respiratory variation, suggestive of sinus rhythm.

Abbreviations: PPG: photoplethysmography, bpm: beats per minute.

Development of the structured stepwise practical guide on how to evaluate and interpret PPG signals

On 22 December 2020, an online conference on Zoom was organized to discuss a structured stepwise practical guide to evaluate and interpret PPG signals. The TeleCheck-AF investigators of the best including centers of the TeleCheck-AF project and three experiences experts in the fields of PPG monitoring were invited. The result of this meeting was used to design a first draft of this stepwise practical guide. The practical guide was further refined during an internal review process. After appropriate revisions the practical guide was approved by all the TeleCheck-AF investigators involved. All TeleCheck-AF investigators were invited to describe typical clinical scenarios which they practice in their center. Of note, the current practical guide was designed as an educational tool to satisfy a need for structural education on PPG technology and its interpretation. The impact of this practical guide on clinical practice has not yet been assessed and validation of this tool is beyond the scope of the current manuscript.

Data collection

The total number of heart rate and rhythm measurements, the number of AF, sinus rhythm and low-quality recordings identified by the FibriCheck® algorithm and the representative PPG recordings were obtained anonymously from the FibriCheck® cloud. Data are presented as numbers or percentages.

RESULTS

Structured stepwise practical guide on how to evaluate and interpret PPG signals

Figure 3 provides a flowchart for the systematic interpretation of PPG tracings. Within the TeleCheck-AF project, 2522 subjects collected a total of 90616 recordings. *Supplement 2* displays the incidence of respective recordings in the TeleCheck-AF project.

Step 1: Check for quality of the PPG tracings

The quality of a signal can be rated as good when there are clear distinguishable peaks. If the signal is noisy with erratic peaks, the quality of the signal might be too low to interpret. If more than 50% of the recording time (>30 seconds) is of insufficient quality, the measurement cannot be interpreted correctly. In general, the FibriCheck® PPG algorithm already identifies sections with low-quality PPG signals and marks them in grey. If the quality of the measurement is too low, this recording is labeled in blue. Whenever this happens, the app will automatically notify the user and ask for a new recording. Within the TeleCheck-AF project, 9.7% (8814) recordings were rated as low quality. Some examples of recordings with low quality are presented in *Supplement 3*.

Step 2: Check the output of the PPG FibriCheck® algorithm.

The FibriCheck® algorithm has been validated to detect AF with high sensitivity and specificity [9]. Within the TeleCheck-AF project, 21,404 recordings were classified as AF (23.6%). However, visual confirmation is recommended. AF typically presents with irregularly varying intervals between the peaks in the PPG tracing, randomly distributed points on the tachogram and the absence of a distinct cluster of points in the Poincaré/Lorenz plot. If there is substantial doubt about the diagnosis or if the FibriCheck® algorithm does not classify a recording as AF, proceed to step 3.

Step 3: Check for regularity

Equal intervals between the peaks in the raw PPG signal, a single line without deviations in the tachogram and one dense clustered cloud of points in the Poincaré/Lorenz plot are indicative of a regular rhythm. Anything deviating from this pattern, can be labeled as ''irregular'', in which the most likely diagnosis is dependent on the specific pattern.

Step 3a: Evaluate the regular rhythm by checking the heart rate in consecutive recordings

As RR-intervals in heart rhythm disorders like atrial flutter, atrial tachycardia, AVRT, AVNRT or hemodynamically tolerated VT are usually regular, it is easy to confuse these rhythm disorders with normal sinus rhythm when measured by PPG. [9] This can be especially challenging in case of a heart rate within normal ranges, as could be the case in atrial flutters with low ventricular rates. In the TeleCheck-AF project, 57.6% of all recordings were classified as sinus rhythm with a heart rate between 40 and 110 bpm, whereas 1.4% were classified as tachycardia with a heart rate above 110 bpm. For these recordings, interpretation and confirmation by a health care professional is of importance. In case of sinus rhythm, consecutive measurements typically do not show exactly the same heart rate. If the heart rate in consecutive recordings is identical (strictly regular), an underlying regular arrhythmia should be suspected. Typical heart rates for atrial flutter are 120-160/min (2:1 conduction), 100/min (3:1 conduction) or 75/min (4:1 conduction). However, the availability of consecutive recordings is dependent on the initial instruction of the patient. Additionally, respiratory sinus arrhythmias are typically present during sinus rhythm, but are often absent during regular tachycardias. Attention should be given to the occurrence of blocked beats during variable conduction with similar coupling intervals. In this case, proceed to step 3b. Furthermore, the presence of symptoms during the recording period, particularly newly developed palpitations or dyspnea, may increase suspicion for the presence of a regular rhythm disorder. Indeed, in TeleCheck-AF, in 21.6% of recordings classified as sinus rhythm the patient indicated symptoms. Sometimes, a definitive diagnosis cannot be made based on the PPG signals only. If suspicion for the presence of a regular arrhythmia is high, an ECG should be performed to further characterize the arrhythmia.

Step 3b: Evaluate the irregular rhythm by checking the pattern of the recordings

The first consideration in case of an irregular rhythm is to check whether the irregularity is solely caused by increased heart rate variability (HRV). In

a small number of recordings, the FibriCheck® algorithm might also indicate this. However, in other instances visual confirmation is necessary. Increased HRV presents as a wave pattern on the tachogram in combination with an ellipse-shaped figure in the Poincaré/Lorenz plot. If the irregularity is based on occasional beats with fixed coupling intervals, it is important to differentiate between a sporadic irregularity and a repeated pattern. Sporadic irregularity is usually caused by ectopic atrial or ventricular beats and could present as shorter intervals (premature beats) followed by longer intervals (pauses) with fixed coupling intervals in the raw PPG signal or the tachogram. In the Poincaré/Lorenz plot, beats with similar coupling intervals will result in additional dense clusters. In case of a repeated pattern, multiple options are possible. If a low heart rate is present, bradyarrhythmia based on a blocked beats due variable conduction of an underlying supraventricular tachycardia should be considered. In contrast, when the heart rate is normal, a bigeminy or trigeminy episode could be present. This can be seen by identifying a series of peaks that follow the previous one too quickly in the raw PPG signal, two or three distinct lines in the tachogram due to green points alternately deviating up and down or high-middle-low, respectively, and different dense clusters of green points in the Poincaré/Lorenz plot. *Figure 4* shows examples of ectopic beats and associated patterns. Of all recordings in the TeleCheck-AF project, the FibriCheck® algorithm classified 4.7% as extrasystoles, 1.8% as bigeminy (episodes) and 0.6% as trigeminy (episodes). Especially in recordings with these classifications and in case of the presence of fixed coupling intervals, attention should be paid to the possibility of atrial flutter with variable conduction as underlying cause of the pattern seen on the PPG recordings. The FibriCheck® algorithm itself classifies just 0.2% of all recordings as atrial flutter, mainly because of the difficult distinction. If none of the above patterns are present and the PPG waveform shows a completely irregular pattern, the possibility of AF should be re-evaluated.

Step 4: Check for known, previously documented arrhythmias and underlying cardiovascular conditions

As discussed in steps 3a and 3b, some arrhythmias may cause similar patterns on the PPG recordings making a differentiation difficult. The clinical history of a patient may increase the likeliness of a certain arrhythmia and can be used to increase the pre-test probability. In *Case Box 1,* an example for this assessment is provided.

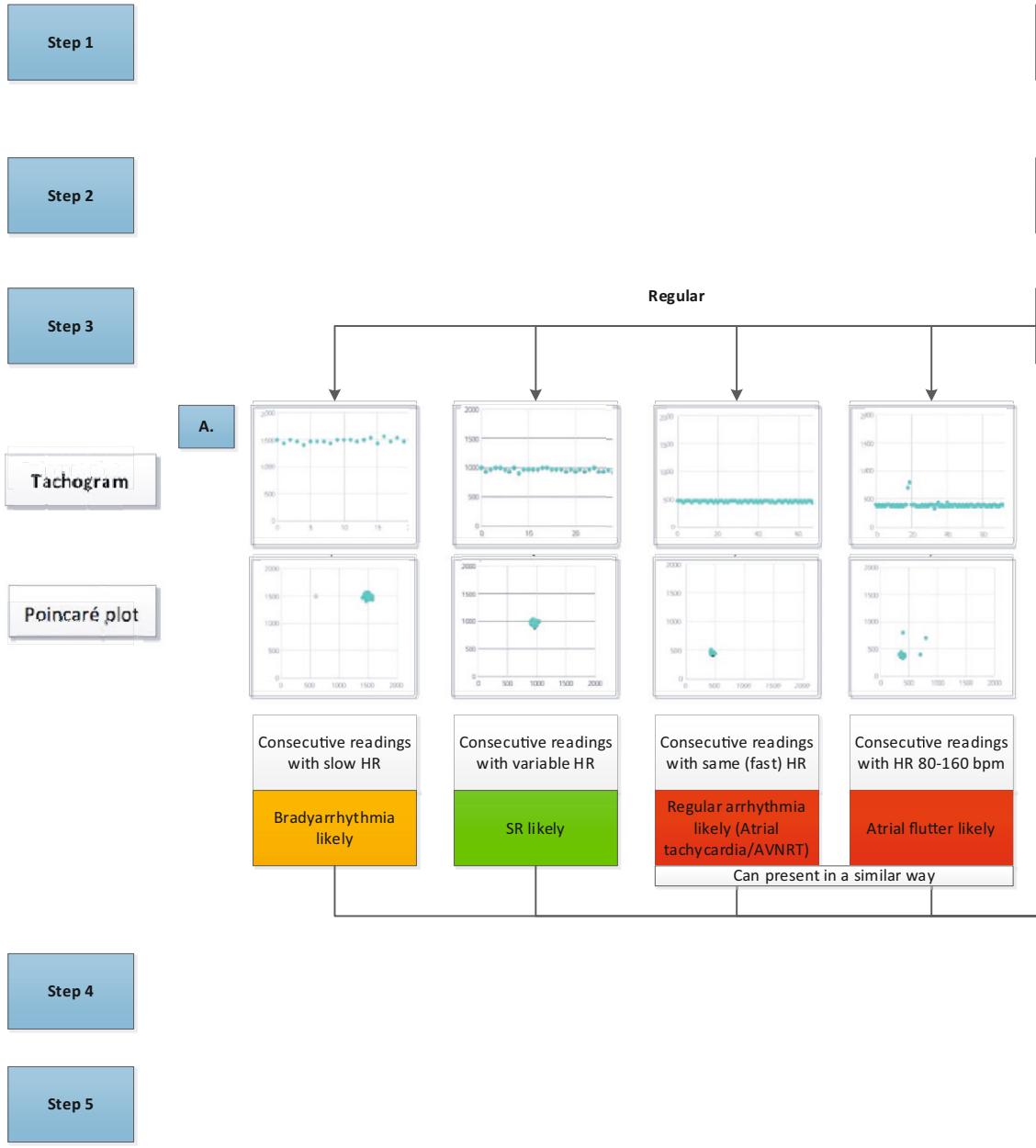
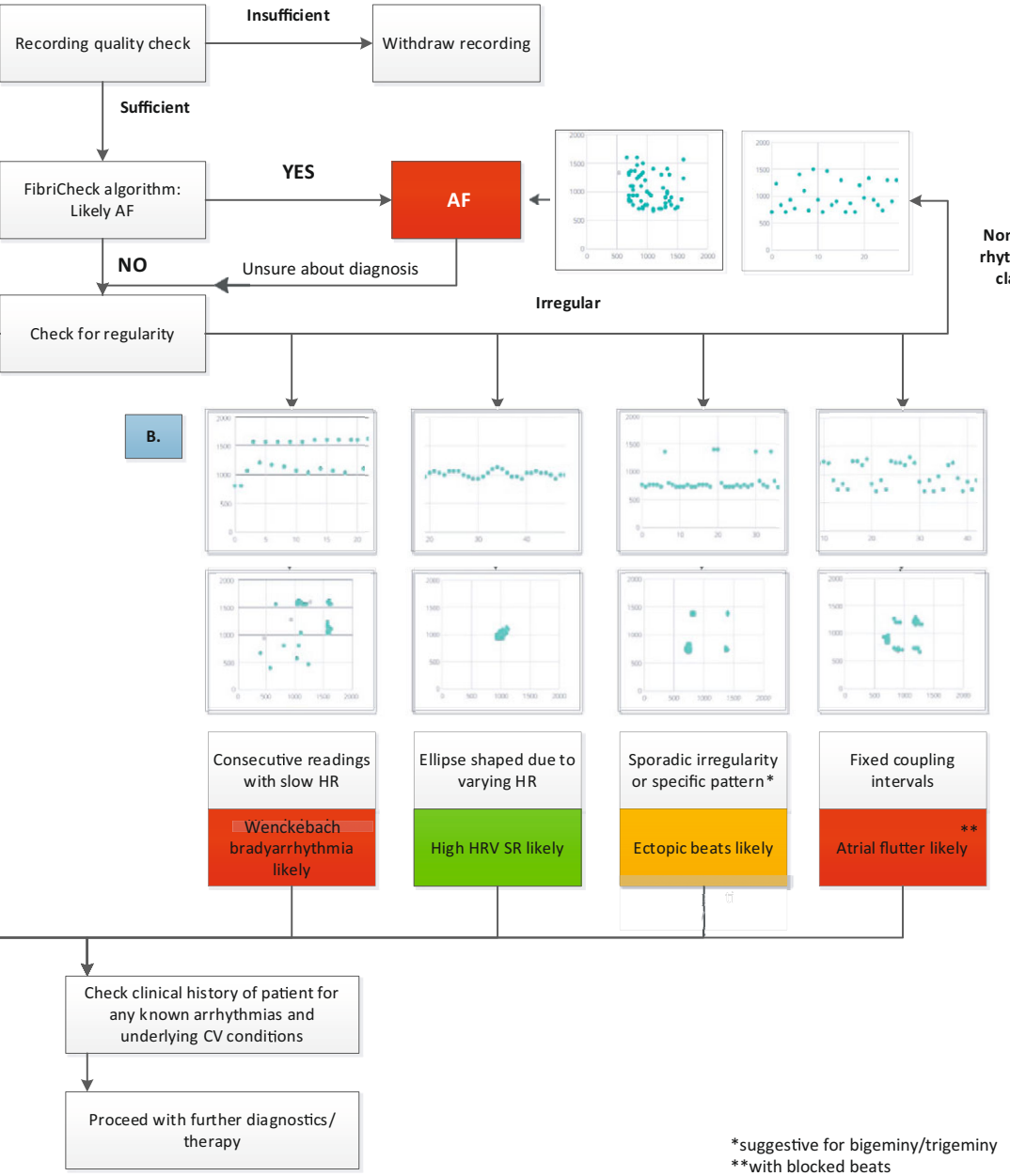


Figure 3. Structured stepwise practical guide on PPG signal interpretation.

Abbreviations: AF: atrial fibrillation, HR: heart rate, SR: sinus rhythm, AVNRT: atrioventricular nodal re-entrant tachycardia, HRV: heart rate variability, CV: cardiovascular.


Recording quality check
Insufficient
Withdraw recording
Sufficient
FibriCheck algorithm: Likely AF
YES
AF
NO
Unsure about diagnosis
Check for regularity
Irregular
None of the other rhythms, physician classifies as AF
B.
Consecutive readings with slow HR
Wenckebach bradyarrhythmia likely
Ellipse shaped due to varying HR
High HRV SR likely
Sporadic irregularity or specific pattern*
Ectopic beats likely
Fixed coupling intervals
Atrial flutter likely
**
Check clinical history of patient for any known arrhythmias and underlying CV conditions
Proceed with further diagnostics/ therapy
*suggestive for bigeminy/trigeminy
**with blocked beats

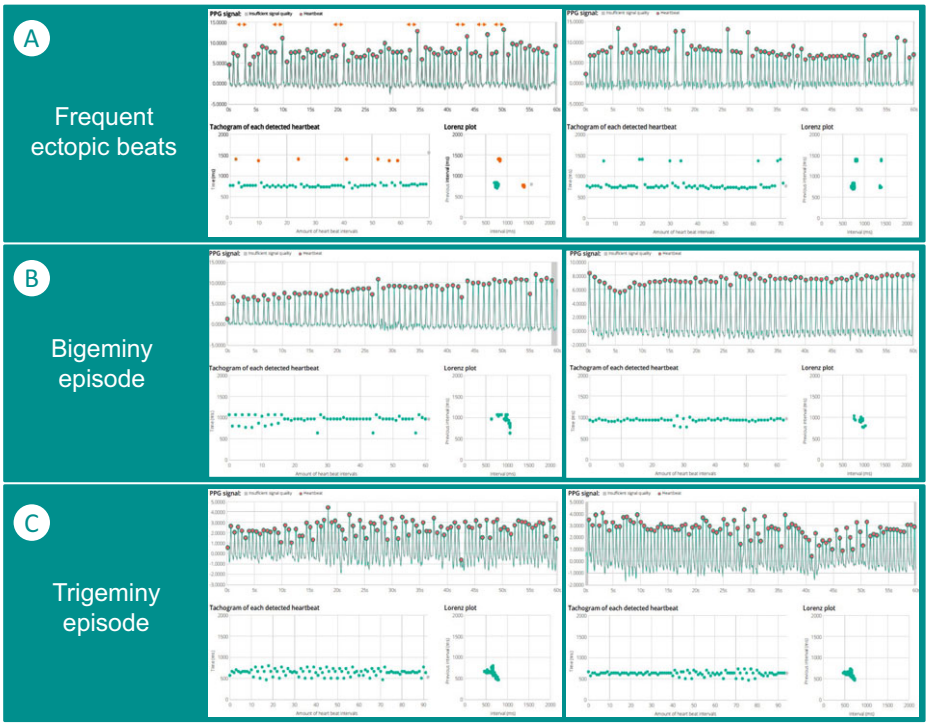


Figure 4. Ectopic beats.

(A) Two recordings with frequent ectopic beats. This can be seen by the bigger pauses between two consecutive beats, indicated in amber in the graphs. In the PPG-signal, the distance between consecutive peaks is larger, which leads to a longer RR-interval in the tachogram and multiple clusters in the Poincaré/Lorenz plot.

(B) Two examples of bigeminy episodes, in which the tachogram shows fixed coupled intervals.

(C) Two examples of trigeminy episodes, in which the tachogram shows three alternating lines during the episode.

Step 5: Proceed with further diagnostics or therapy as indicated.

Depending on the clinical scenario for which PPG monitoring was implemented, further steps can be taken. In case of diagnostic uncertainties, PPG recordings should prompt further diagnostic ECG recordings via a 12-lead resting ECG in the case of ongoing arrhythmias, extended Holter monitoring in the case of regularly (daily) occurring paroxysmal arrhythmias or ECG-based wearable devices in the case of rarely occurring paroxysmal arrhythmias.

CASE BOX 1: ASSESSMENT OF PPG RECORDINGS IN A PATIENT WITH REGULAR RHYTHM DISORDERS

Medical history

A 65-year-old woman is treated at the rhythm outpatient clinic for different atrial arrhythmias. She has a history of AF, cavo-tricuspid isthmus (CTI)-dependent atrial flutter, atypical atrial flutter, and atrial tachycardia. In 2018 she underwent a combined mitral valve repair and Maze procedure. Due to frequent symptomatic episodes of atrial flutter and atrial tachycardia she underwent an endocardial CTI ablation procedure in April 2019. In January 2020, she underwent another procedure in an attempt to treat an atypical superior vena cava dependent atrial flutter, which was unsuccessful. After repeated electrical cardioversion she developed another regular atrial tachyarrhythmia, suspect for macro reentrant atrial tachycardia (MRAT), upon which a rate control strategy was adopted. PPG-monitoring was used to evaluate the rate control strategy.

Recordings and MRAT with variable conduction

The patient recorded 28 registrations within 7 days. The recordings demonstrated various heart rhythms. Two examples are provided in *Figure 5*. *Figure 5a* presumably depicts MRAT (focal atrial tachycardia and MRAT including typical and atypical atrial flutter are differential diagnoses) with 4:3 conduction to the ventricles, given the repetitive pattern of 2 subsequent increasing intervals before a shorter interval occurs. *Figure 5b* illustrates a pattern which most frequently appears in sinus rhythm with premature atrial complexions in bigeminy. However, as sinus rhythm is very unlikely in this patient with persistent atrial arrhythmias, the probable explanation for this pattern is similar to the left figure: macro reentrant atrial tachycardia or atrial flutter with variable conduction, although now occurring in a 3:2 ratio.

Typical clinical scenarios for PPG monitoring practiced within the TeleCheck-AF project

PPG monitoring is predominantly useful in patients with a diagnosis of AF but may also be used for patients in whom other arrhythmias are suspected or necessitate monitoring. In addition, it might also be a valuable screening tool to guide further (ambulatory) ECG monitoring in high-risk patients. Several clinical scenarios for PPG monitoring are summarized in *Table 1* and in *Case Boxes 2-5*. In addition, we provide the number of AF patients managed in the respective clinical scenario

within the TeleCheck-AF project. Of note, patients could use the app more than once or for various indications and thereby can be included in more than one groups.

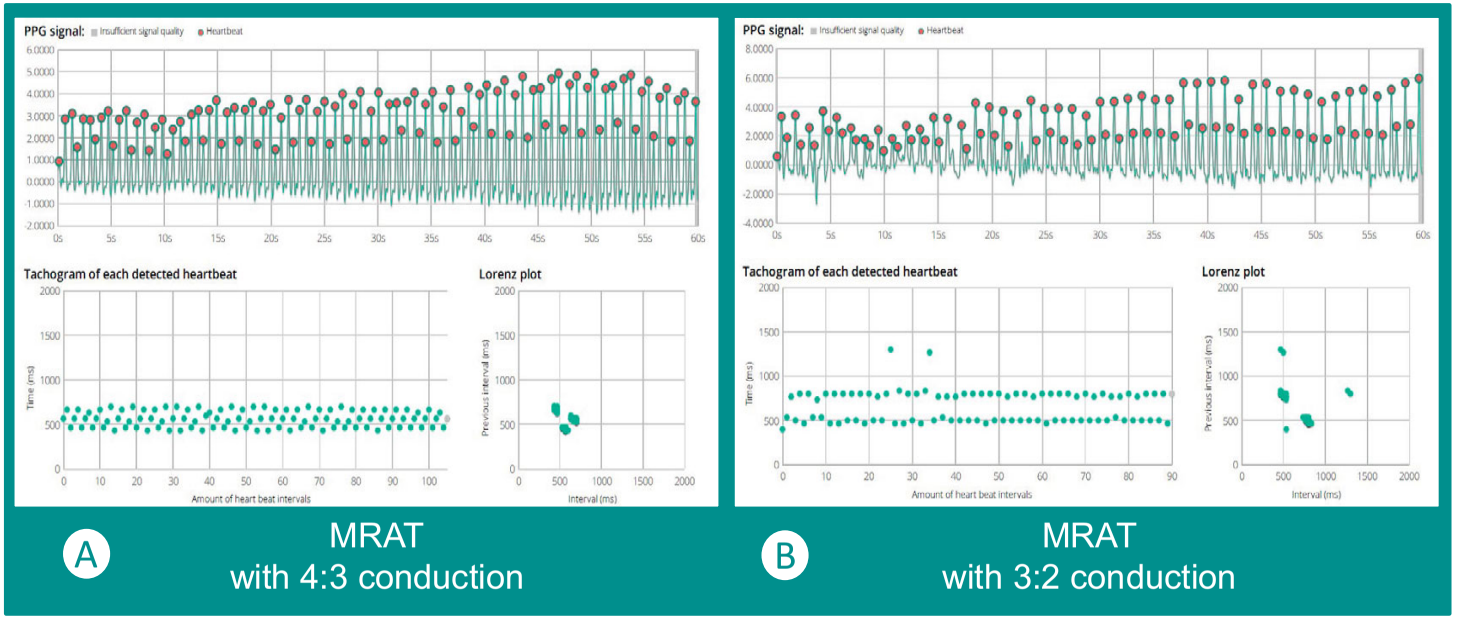


Figure 5. Macro reentrant atrial tachycardia (MRAT) with variable conduction.
(A) Presumably MRAT with 4:3 conduction.
(B) Presumably MRAT with 3:2 conduction.

Table 1. Possible clinical scenarios for photoplethysmography monitoring.

Atrial fibrillation	Other arrhythmias/palpitations
• Remote heart rate and rhythm assessment prior to scheduled (tele) consultation • Follow-up after initiation of rhythm control therapy (antiarrhythmic drugs, scheduled cardioversion, ablation) • Remote adaption of heart rate control medication • Monitoring for spontaneous conversion • Evaluating the presence of other arrhythmias besides atrial fibrillation	• Remote heart rate assessment • Remote adaption of heart rate control • Symptom-rhythm correlation • Step up for Holter (type of ECG based) monitoring in symptomatic undiagnosed patients

Abbreviations: ECG: electrocardiogram.

On-demand remote heart rate and rhythm assessment

Within the TeleCheck-AF project, PPG monitoring was primarily used to acquire heart rate and rhythm information prior to a scheduled teleconsultation and to guide follow-up management of AF patients.[4, 5] Remote monitoring can also be used prior to an outpatient face-to-face consultation. In total, 966 patients with diagnosed AF were managed this way, with recruitment both during lockdown restrictions and after easing the lockdown restrictions.[7]

Post-ablation follow-up

Similar to the use of Holter monitoring post-ablation, PPG technology can be used in patients who have undergone AF catheter ablation, to monitor the heart rhythm in order to check for recurrences during the post-ablation period. Within the TeleCheck-AF project, 1110 patients were followed up by PPG technology after ablation. A survey conducted in the participating centers suggested that physicians see an additional value of using PPG technology particularly in these patients.[7]

PPG-guided remote adaptation of heart rate and rhythm control medication

PPG technology can also be used to guide the remote adaption of heart rate and rhythm control medication. Case examples in a patient with persistent AF (*Case Box 2*) and a patient with atrial flutter (*Case Box 3*) are described below. In 78 patients rate or rhythm control was adopted during the teleconsultation.

CASE BOX 2: RATE CONTROL IN A PATIENT WITH ATRIAL FIBRILLATION

A 75-year-old man who has been diagnosed with paroxysmal AF in 2008, without recurrences since 2010, presented to the cardiology outpatient clinic in autumn 2019 because of a recurrent AF episode. A follow-up appointment combined with echocardiography was scheduled. Because of the COVID-19 pandemic, this consultation was converted into a teleconsultation. During echocardiography and the patient's remote heart rhythm monitoring using PPG prior to teleconsultation, paroxysms of AF with high ventricular rate (130-140) were observed. Digoxin was added to the rate control medication. Thereafter, he was again remotely monitored using PPG to evaluate the effect of the medication. His resting heart rate during AF was now 80-90 bpm, which was accepted, considered that PPG recordings might underestimate the heart rate in AF by approximately 10 bpm due to a pulse deficit. Therefore, it is advised to aim for stricter rate control compared to the ECG-based cut-off of a heart rate of 110 bpm. Precise cut-off values for PPG-based rate control are currently determined in ongoing studies.

CASE BOX 3: RATE CONTROL IN A PATIENT WITH ATRIAL FLUTTER

A 59-year-old man presented to the emergency department (ED) because of palpitations and tachycardia which had started that morning. He experienced palpitations once before, a few weeks ago. He had no other complaints. ECG showed a typical atrial flutter with a heart rate of 165 bpm. He was given a beta blocker and digoxin at the ED. In addition, he was scheduled for a catheter ablation in four weeks. To optimize rate control in the meantime, the patient was discharged with a prescription for the FibriCheck app. After discharge from the ED, his heart rate showed the same pattern every day: adequately controlled after daily ingestion of beta blockers, but suboptimal in the mornings. Therefore, his heart rate control medication was first distributed over the day by subscribing beta blocker in the morning and digoxin in the evening. However, this did not result in the desired effect, so digoxin was reverted to mornings, and an extra dose of beta blocker was added in the evenings. Because therapy was still suboptimal in the morning, the dose of digoxin was increased, after which therapy regime stayed optimal until catheter ablation. A timeline for remote heart rate control adaption, together with PPG examples, is provided in *Figure 6*.

PPG monitoring for spontaneous conversion

Recently, a study comparing early cardioversion to delayed cardioversion within 48 hours after symptom-onset showed that delayed cardioversion is a safe and efficient treatment for patients with acute episodes of paroxysmal AF. [14] Up to 70% of the patients in the delayed cardioversion group spontaneously converted to sinus rhythm within 48 hours. PPG monitoring can be applied to monitor rate control and spontaneous conversion in these patients in whom a delayed conversion approach is implemented (*Case Box 4*). [15]

CASE BOX 4: DELAYED CARDIOVERSION IN A PATIENT WITH ATRIAL FIBRILLATION AND ATRIAL TACHYCARDIA

A 51-year-old man with a history of paroxysmal AF and atrial tachycardia presented to the ED due to tachycardia and dyspnea. ECG showed AF with a heart rate of 120 bpm. Before arrival at the ED, the patient had already taken flecainide (pill in the pocket), which had not led to conversion to sinus rhythm. At the ED, verapamil was given to optimize rate control and alleviate symptoms. Afterwards, the patient was discharged to await spontaneous conversion at home. The FibriCheck app was prescribed to the patient to monitor whether spontaneous conversion occurred, or whether the patient should return the next day for delayed cardioversion. The next day, FibriCheck showed conversion to sinus rhythm. A teleconsultation with the patient took place, in which he was informed of the findings. No cardioversion was necessary.

Other scenarios

On-demand PPG monitoring could potentially be used to support decision making whether patients with specific palpitations would require Holter monitoring. Moreover, PPG may support the assessment of symptom-rhythm correlation. If no heart rhythm disorders are captured by PPG, a symptom-rhythm correlation can likely be excluded. If some signs of heart rhythm disorders are present without a diagnosis yet, this could prompt additional Holter monitoring. Furthermore, ectopic beats as underlying cause for palpitations can be captured by PPG monitoring. However, Holter monitoring will still be required to determine whether ectopic beats are predominantly supraventricular or ventricular and to locate its origin (*Case Box 5*). In addition, PPG can also be used for symptom-rhythm assessment around rhythm interventions in patients with known rhythm disorders (i.e., planned electrical cardioversion).

Figure 6. Timeline remote rate control adaption in a patient with atrial flutter.

Upper panel: Timeline presenting the different adaptions to rate control. Lower panel: two examples of PPG recordings. Left: PPG recording taken in the morning, before administration of rate control medication. Right: PPG recording taken in the afternoon, after administration of rate control medication.

Abbreviations: ED: emergency department, PPG: photoplethysmography.

Establishing the presence of a symptom-rhythm correlation is of importance to guide treatment decisions, since poor symptom-rhythm correlation might negatively affect outcomes of rhythm interventions. During the TeleCheck-AF project, 275 were followed around cardioversion using PPG technology. Similar to heart rate assessment in patients with AF or other sustained arrhythmias, PPG monitoring can also be used for heart rate monitoring during up-titration of negatively chronotropic medication in patients heart failure.

Screening

PPG screening for AF in high risk patients has the benefit of being easily available and convenient for the patient.[16] PPG can easily be used for a longer period of time without the necessity of an implantable device. Suspect AF on PPG recordings may then prompt further intensive ECG monitoring. However, AF screening was not the goal of the TeleCheck-AF project.

Supplement 4 presents an overview of PPG and ECG recordings for the arrhythmias described in *Case boxes 2-5*. Of note, these recordings are not taken simultaneously, but could have some time in between.

DISCUSSION

Over the last years, novel mHealth applications using PPG technology have been developed for the screening and management of AF. Studies suggest that mHealth devices have some advantages for users compared to standard 12-lead ECG or Holter monitoring in terms of convenience, portability and flexibility.[10] In addition, they enable longer monitoring which makes capturing of rhythm disorders more likely, without the need for implantable devices.[13] Interestingly, a recent mHealth study found that with long-term (4 weeks) intermittent heart rhythm monitoring after ablation, significantly more recurrences were captured compared to short-term Holter monitoring.[17] Additionally, data show that PPG technology is nearly as accurate as ECG to detect AF.[18, 19]

Despite good accuracy of PPG-based devices for the detection of AF, the PPG algorithms are not validated to detect arrhythmias other than AF, such as atrial flutter, atrial tachycardia, AVNRT, AVRT or others.[9, 18, 20] Regular rhythms can be easily mistaken for normal sinus rhythm, leading to false negative results. In this manuscript, we developed a structured stepwise guide on how to analyze and interpret PPG signals. Combining the PPG raw data with the tachogram and Poincaré/Lorenz plot as shown in this dictionary may improve the readability of

CASE BOX 5: PPG-MONITORING AS STEP UP FOR HOLTER RECORDING

A 58-year-old woman with a history of AF was seen at the outpatient clinic because of persistent palpitations despite pharmacological heart rate and rhythm control attempts. Therefore, she was now scheduled for pulmonary vein isolation (PVI). Awaiting the procedure, she used the FibriCheck app to examine her heart rate and rhythm control. The first three days she mainly had sinus bradycardia, alternated with short episodes of AF with normal ventricular frequencies. However, the fourth day she had an episode of a very fast (190 bpm), regular rhythm, later turning into AF. Upon contact, she explained that she had been experiencing these fast palpitations alternating with the slower, irregular palpitations in the previous months, not realizing these might be due to another arrhythmia than AF. To determine the cause of these regular tachyarrhythmias, Holter monitoring was scheduled within one week. However, one day after the teleconsultation she experienced the fast palpitations again, this time accompanied by chest pain. She contacted the emergency medical services and upon arrival of the ambulance, an ECG suggestive of AVNRT was acquired. After coughing, the rhythm first converted to AF, and several minutes later she spontaneously converted to sinus rhythm. She had not been previously diagnosed with any other arrhythmias than AF, nor had her history been very suggestive of it.

Since the episodes of AVNRT were associated with more severe symptoms than the AF episodes, and episodes of AVNRT seemed to provoke AF, the intended PVI was converted to a supraventricular tachycardia ablation first. The PVI was postponed and, depending on the results of the planned procedure, might even be dispensable.

PPG recordings. The representative PPG recordings may provide a dictionary for PPG documentations of typical cardiac arrhythmias. Although it may seem that the knowledge of PPG analysis is superfluous, PPG-based devices can, like any algorithm, provide a misdiagnosis. Therefore, in our opinion a physician's own interpretation of the record together with the knowledge of the patient's medical history can improve the diagnosis and even extend it to arrhythmias other than AF. Of note, the interpretation of PPG tracings in the TeleCheck-AF project was only based on the FibriCheck app. Other PPG apps might present the data in slightly different ways, but PPG waveforms, tachograms and the Poincaré/Lorenz plot should constitute the basis for interpretation of PPG.

Additionally, we introduced clinical scenarios encountered during the TeleCheck-AF project to demonstrate how on-demand PPG technology within this approach may be implemented in clinical practice. [21] Results from the TeleCheck-AF project showed that on-demand mHealth combined with teleconsultation is feasible and was received positively by both physicians and patients. [7] This is in line with other studies reporting good adherence to mHealth, also when used long term (>1 year). [22] Reduced risk of rehospitalization and clinical adverse events was previously demonstrated for an integrated AF care approach supported by mHealth. [22, 23] However, clinical outcomes have not been evaluated in the TeleCheck-AF project, yet.

Accelerated through the COVID-19 pandemic and the initiation of the TeleCheck-AF project, more and more centers in Europe have been using PPG technology on-demand around teleconsultations to allow remote heart rate and rhythm assessment of consulted patients. However, the implementation in existing hospital infrastructures remains a challenge. One important step is that adaption of existing care coordination and the set-up of clinical pathways is necessary. Due to lack of PPG technology validation, many patients and health care professionals are not convinced about introducing PPG-based devices in daily routine. Initiatives such as the TeleCheck-AF project will help step-by-step to implement this technology in clinical care pathways by providing information on the effectiveness of this technology and education on PPG analysis to expand the level of patient arrhythmia diagnostics and management.

Up until now, implementation of PPG-based devices into clinical practice mostly occurred through patient-initiated paying-models, probably due to several concerns with mHealth devices such as fear of data overload and a call for practical guidance. [21] Although this educational manuscript may help to familiarize cardiologists and allied health specialists with the PPG technology, various other research questions still need to be answered. To this end, the data from the TeleCheck-AF project are currently retrospectively collected. Several mHealth trials, such as RACE 9 OBSERVE-AF (NCT04612335), are currently conducted and will help to implement PPG technology into clinical practice and to determine whether on-demand mHealth use increases health care efficiency. In addition, further research focusing on the application of PPG technology for the assessment of hemodynamic changes is warranted.

Limitations

An important limitation that should be mentioned is that the validation of this structured guide and its subsequent clinical impact is beyond the scope of this manuscript. In addition, several limitations of the use of PPG-based mHealth devices should be mentioned. PPG cannot differentiate between regular tachycardias such as fast sinus rhythm, atrial tachycardia, AVNRT, AVRT, VT and fast atrial flutter. A final diagnosis still requires an ECG documentation or an electrophysiological study. However, PPG recordings can be indicative for the presence of these arrhythmias and can therefore be used as a step-up for Holter monitoring. Caution should also be taken when implementing PPG technology for rate control in patients with very fast irregular rhythms, because of the possible occurrence of a pulse deficit. However, an often-mentioned limitation of smartphone applications for remote monitoring not being eligible for older patients has proven not to be a large concern within the TeleCheck-AF project.

Conclusions and future perspectives

Herein, we provide a structured stepwise practical guide on how to analyze and interpret PPG signals. Additionally, we introduce clinical scenarios, where the use of PPG-based heart rate and rhythm monitoring will be of clinical benefit. Further research and validation studies, including educational approaches for both health care professionals and patients on its use and possible indications, is warranted.

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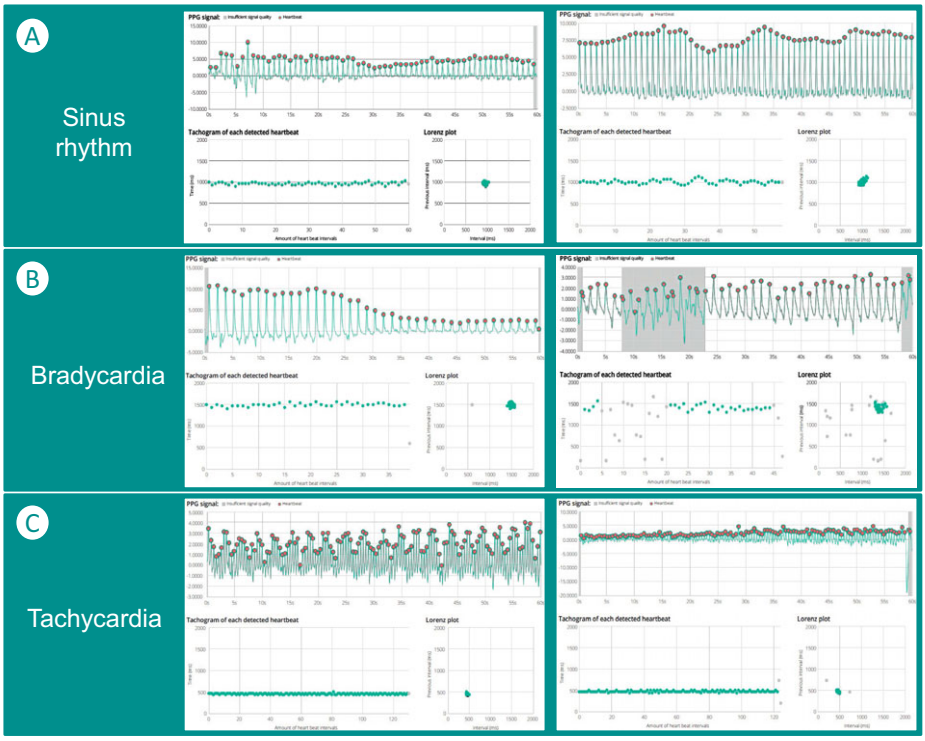
SUPPLEMENTS

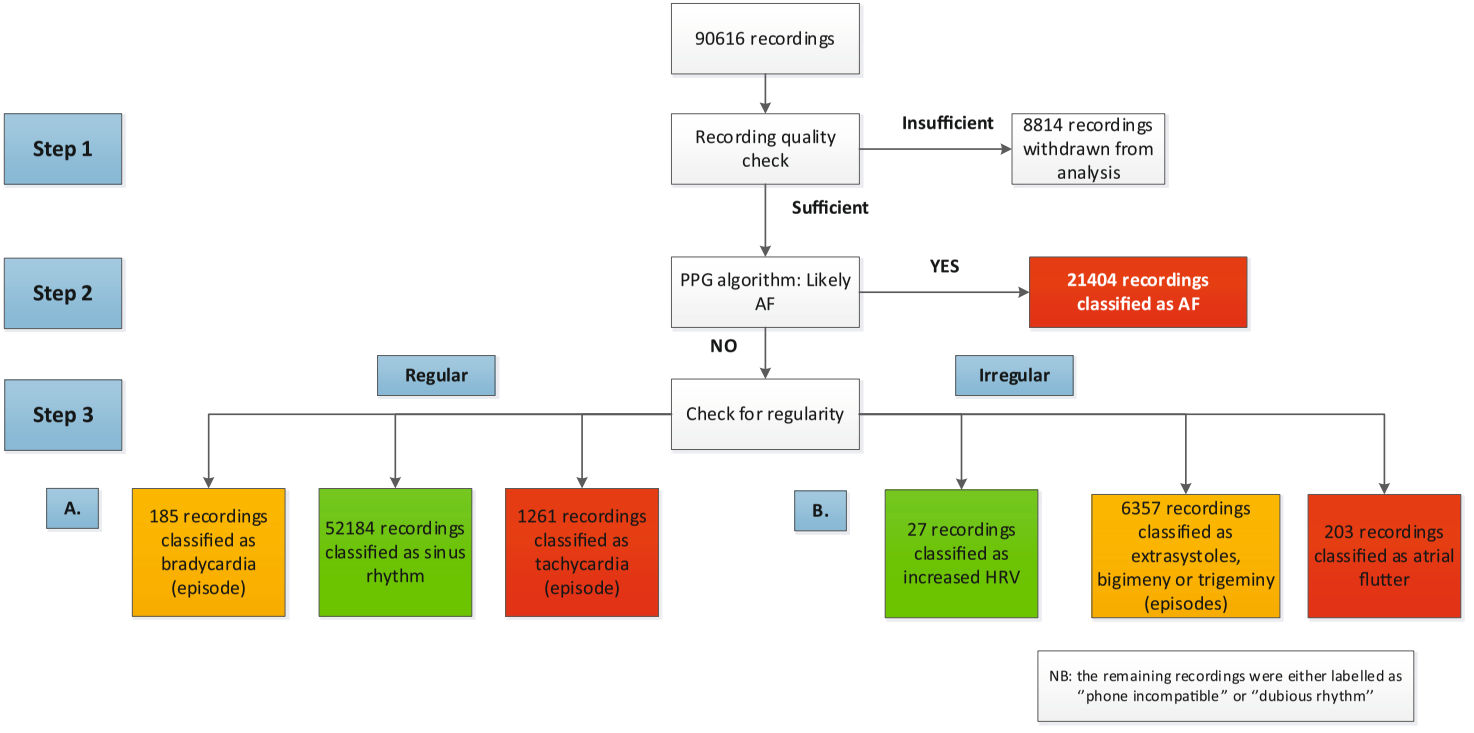


Supplement 1. Examples of sinus rhythm, bradycardia and tachycardia photoplethysmography (PPG) recordings.

(A) Normal sinus rhythm PPG recording, as can be seen from the regularity of the measurement in combination with a heart rate of 60 beats per minute and respiratory variation.

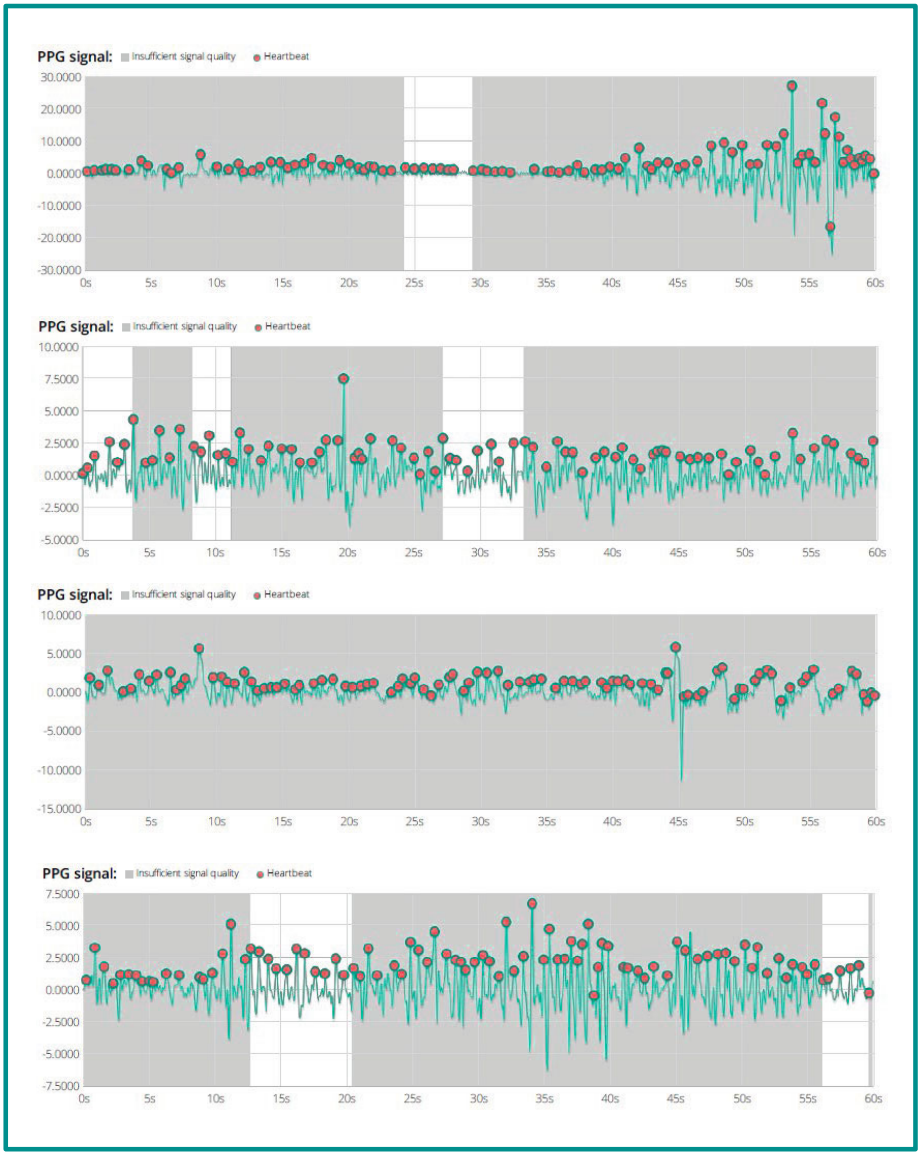
(B) PPG recordings showing bradycardia, as can be seen from the tachogram demonstrating an RR interval of 1500 milliseconds, corresponding to a heart rate of 40 beats per minute.

(C) PPG recordings showing tachycardia with an RR interval of 500 milliseconds, corresponding to a heart rate of 120 beats per minute.



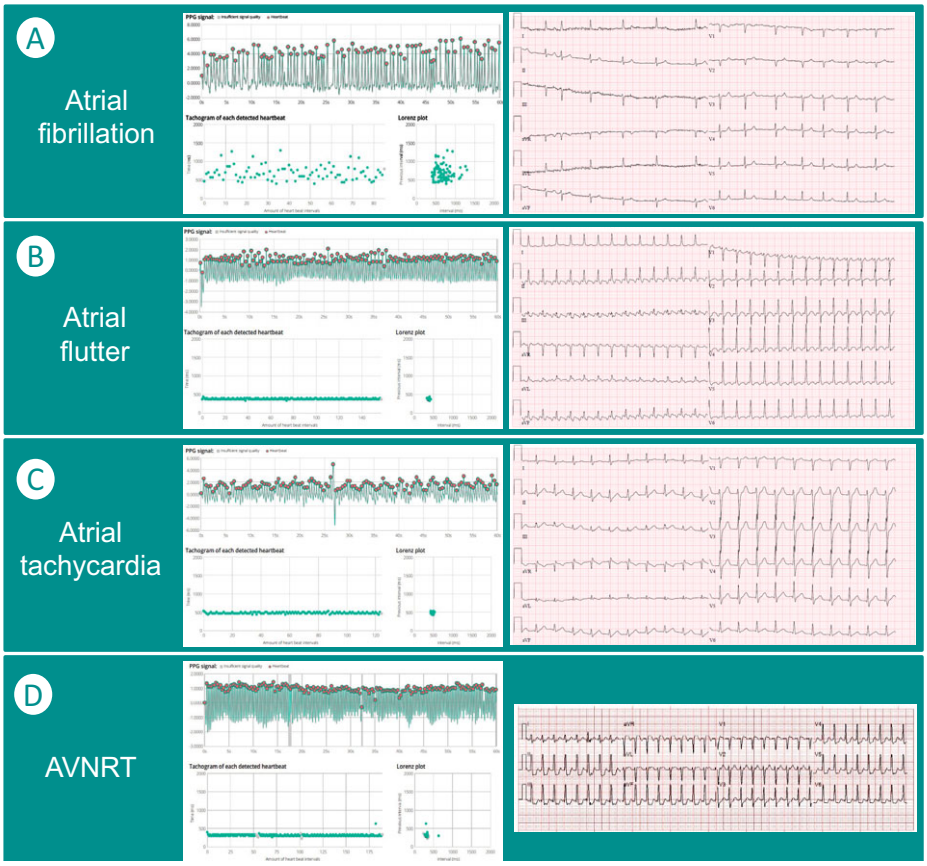
Supplement 2. Results from the TeleCheck-AF project: Number of respective photoplethysmography (PPG) recordings for step 1-3 of the step-wise approach.

Abbreviations: AF: atrial fibrillation, HRV: heart rate variability.



Supplement 3. Examples of low quality photoplethysmography (PPG) recordings.

This figure shows four examples of recordings which cannot be adequately interpreted because of low quality. This can be seen from the large gray colored parts of the recordings. If more than 30 seconds of a recording contains noise or erratic peaks, the algorithm will classify the recording as "quality too low".



Supplement 4. PPG examples for different arrhythmias and the corresponding ECG-recordings.

(A) PPG recording and corresponding ECG of a patient with atrial fibrillation. Both the PPG signal and the ECG show complete irregularity.

(B) PPG recording and ECG recording of the patient described in Case Box 3. Shown is a fast, regular tachycardia without respiratory changes.

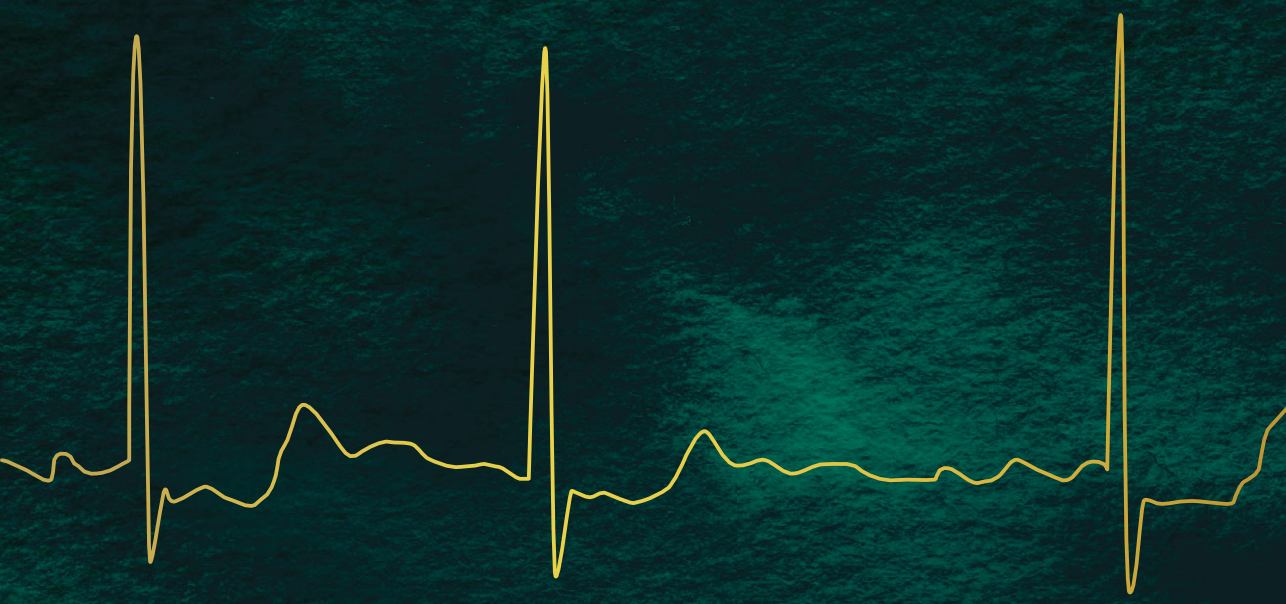
(C) PPG recording and ECG recording of the patient described in Case Box 4.

(D) PPG recording and ECG recording of the patient described in Case Box 5. Of note, these recordings are not taken simultaneously, but could have some time in between.

Abbreviations: AVNRT: AV-nodal reentry tachycardia, ECG: electrocardiogram, PPG: photoplethysmography.

PART II

Integrating cardiovascular risk factor management into AF care



CHAPTER 5

Integration of risk factor screening and cardiovascular risk assessment in the preparation of atrial fibrillation patients undergoing catheter ablation

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** Authors contributed equally*

In preparation for submission.

ABSTRACT

Background and aims

In patients with atrial fibrillation (AF), comprehensive risk factor management prevents AF progression and improves success rates of rhythm control interventions. The preparation for AF ablation offers an opportunity for identification of existing risk factors, estimation of atherosclerotic cardiovascular disease (CVD) risk, reappraisal of appropriate risk factor treatment targets, and intensification of risk factor management.

Methods

In consecutive AF patients referred for catheter ablation, 10-year risks of developing atherosclerotic CVD were assessed based on comorbidities, risk factors and pre-ablation computed tomography (CT) scans. Treatment targets for seven modifiable risk factors (hypertension, dyslipidemia, overweight, smoking, alcohol use, hyperglycemia, and obstructive sleep apnea [OSA]) were reappraised, taking these CVD risks into account, and adherence to these targets was assessed.

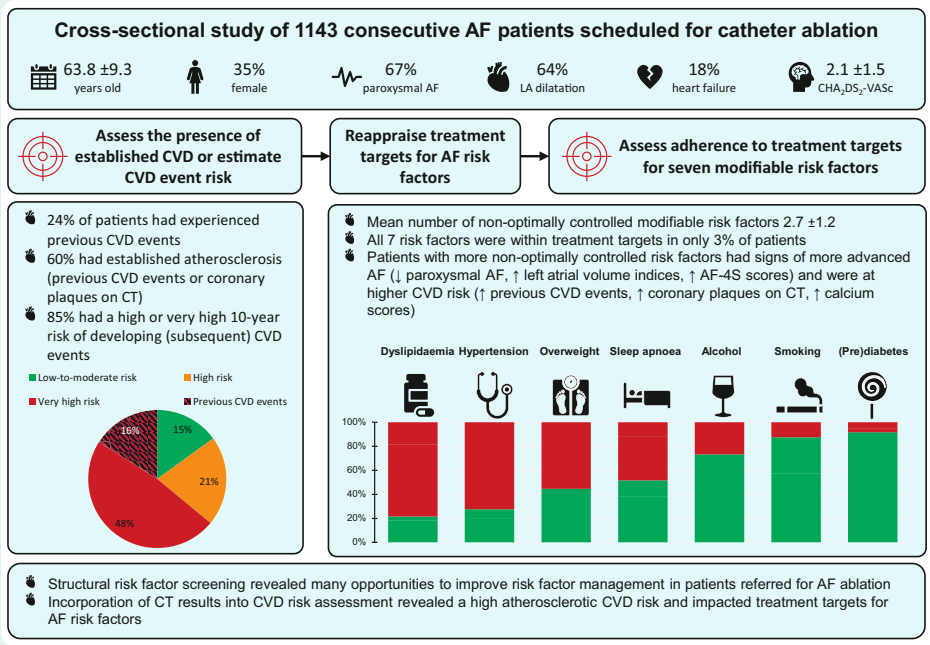
Results

In 1143 included patients (age 63.8 ± 9.3, 35% female, 67% paroxysmal AF), overall atherosclerotic CVD risk was high. 64% of patients classified as 'very high' risk (often based on atherosclerotic plaques identified with CT), which impacted risk factor treatment targets. Treatment targets for all seven risk factors were reached in 3% of patients, and patients had a mean of 2.7 ± 1.2 non-optimally controlled risk factors. Lipids were most often above target values (78%, n=738/941), followed by blood pressure (72%, n=804/1111), weight (55%, n=631/1138) and OSA (49%, n=194/397). Patients with more risk factors above treatment targets had signs of more advanced AF.

Conclusions

In patients scheduled for AF ablation, structured screening revealed a high atherosclerotic CVD risk and several opportunities for optimization of treatment for modifiable risk factors. Combined risk factor management should be intensified in this population.

GRAPHICAL ABSTRACT



Abbreviations: AF: atrial fibrillation, CT: computed tomography, CVD: cardiovascular disease, LA: left atrium

INTRODUCTION

In patients with atrial fibrillation (AF), several modifiable risk factors are associated with development or progression of the arrhythmia and higher recurrence rates after rhythm control interventions. [1-3] Combined risk factor modification programs have been demonstrated to reverse the progression of AF and improve the success rates of rhythm control strategies. [4] A systematic assessment and management of eight concomitant risk factors is therefore recommended by the 2020 European Society of Cardiology (ESC) guidelines for the diagnosis and management of AF. [5] However, a recent study examining comorbidities in AF across Europe identified several barriers to referring specialist services for AF comorbidities, including lack of integrated care models, organizational or institutional issues, and issues with patient adherence. [6] These barriers may impact risk factor control in patients, including those scheduled for invasive rhythm control interventions.

Cardiovascular risk factors also increase susceptibility to atherosclerotic cardiovascular diseases (CVD) including myocardial infarction, stroke, and cardiovascular death, and therefore AF and atherosclerotic CVD often coexist. Simultaneous existence of the two conditions may impact guideline-directed treatment targets, e.g., targets for cholesterol levels are stricter when patients also show signs of atherosclerotic CVD. [5,7] Since the preparation for AF ablation includes a cardiac computed tomography (CT) scan, coincidental identification of coronary plaques on this scan may therefore impact risk factor treatment targets in AF patients.

In order to structurally identify concomitant risk factors in AF patients scheduled for catheter ablation, we previously incorporated a screening checkpoint in the preparation for ablation in two University Hospitals in the Netherlands. [8,9] Herein, we describe the prevalence of previously identified risk factors, estimated atherosclerotic CVD risks (incorporating results of pre-ablation CT scans), and patients' adherence with the reappraised treatment targets in a cohort of AF patients scheduled for catheter ablation.

METHODS

Study population

This study was a subanalysis of the ISOLATION cohort study (NCT04342312), the design of which was described in detail elsewhere. [8] In brief, consecutive,

adult patients with symptomatic AF in the preparatory process for catheter ablation in the Maastricht University Medical Centre (MUMC+), Maastricht, the Netherlands, and the Radboud University Medical Centre (Radboudumc), Nijmegen, the Netherlands, were prospectively enrolled. Patients underwent a standardized pre-ablation preparation consisting of collection of clinical information, risk factor screening, vital signs, electrocardiogram (ECG), blood tests, and screening by an anesthesiologist. In addition, the majority of patients underwent a CT scan to assess pulmonary vein anatomy and the presence of coronary artery plaques. Follow-up to evaluate ablation success (absence of atrial arrhythmia) for up to two years after the ablation procedure is ongoing. The ISOLATION study was approved by the ethical review board MUMC+/ Maastricht University (METC number 19-052) and complies with the Declaration of Helsinki. All participants provided written informed consent.

Estimation of (atherosclerotic) cardiovascular disease risk

CVD risk was assessed according to the 2021 ESC guidelines on cardiovascular disease prevention (*Figure 1*).[7] In short, patients were classified as being either at low-to-moderate, high, or very high CVD risk according to their estimated 10-year risk of developing first or subsequent fatal or non-fatal CVD. Very high risk was defined as a 10-year risk of ≥7.5% for those under 50 years of age, ≥10% for patients 50-69 years old, and ≥15% for patients ≥70 years old. Similarly, high CVD risk was defined as a 10-year risk of 2.5 to <7.5% for those under 50 years of age, 5 to <10% for patients 50-69 years old, and 7.5 to <15% for patients ≥70 years old. In case of lower estimated risk percentages, patients were classified as being at low-to-moderate CVD risk (*Figure 1*).

Patients were classified as being at very high CVD risk if they had established atherosclerotic CVD, had diabetes mellitus combined with chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) <45 ml/min/1.73 m^2, or had severe CKD (eGFR <30 ml/min/1.73 m^2). In accordance with current guidelines, established atherosclerotic CVD included previous clinical events such as acute coronary syndromes, coronary revascularization, and stroke or TIA, as well as unequivocally documented atherosclerosis on imaging such as coronary or peripheral plaques on CT or angiography. [7] In the majority of patients CT scans were performed as part of the preparation for AF ablation to assess pulmonary vein anatomy and left atrial anatomy. Coincidental findings of atherosclerotic plaques on these standard CT scans were incorporated in patients' CVD risk estimation, and may therefore have impacted CVD risk assessment and treatment targets.

Risk category	Criteria	Estimated 10-year CVD risk	Target LDL
Very high CVD risk	Established atherosclerotic CVD*	≥7.5% for patients <50 years old ≥10% for patients 50-69 years old ≥15% for patients ≥70 years old	LDL <1.4 mmol/l
	At least one of: - Diabetes mellitus and CKD (eGFR <45 ml/min/1.73 m²) - Severe CKD (eGFR <30 ml/min/1.73 m²) - Very high risk based on the SCORE2 or SCORE2-OP classification		
High CVD risk	One of: - Diabetes mellitus without CKD - Moderate CKD (eGFR <45 ml/min/1.73 m²) - High risk based on the SCORE2 or SCORE2-OP classification AND - No *very high risk* criteria	2.5-7.5% for patients <50 years old 5-10% for patients 50-69 years old 7.5-15% for patients ≥70 years old	LDL <1.8 mmol/l
Low-to-moderate CVD risk	No *very high risk* or *high risk* criteria	<2.5% for patients < 50 years old <5% for patients 50-69 years old <7.5% for patients ≥70 years old	None

Figure 1. Criteria for different categories of (atherosclerotic) cardiovascular disease risk and corresponding treatment targets.

**Established atherosclerotic CVD includes previous clinical events such as acute coronary syndromes, coronary revascularization, and stroke or transient ischemic attack, as well as unequivocally documented atherosclerosis on imaging such as coronary or peripheral plaques on computed tomography or angiography*

Abbreviations: CKD: chronic kidney disease, CVD: cardiovascular disease, eGFR: estimated glomerular filtration rate, LDL: low-density lipoprotein, SCORE2: Systematic Coronary Risk Estimation 2, SCORE2-OP: Systematic Coronary Risk Estimation 2-Older Persons.

Patients were classified as being at high risk if they had diabetes mellitus without CKD or if they had moderate CKD (eGFR <45 ml/min/1.73 m^2). In case of absence of previous atherosclerotic CVD, CKD and diabetes mellitus, cardiovascular risk was estimated using the Systematic Coronary Risk Estimation 2 (SCORE2) or SCORE2-Older Persons (SCORE2-OP). [7,10,11]

Structured risk factor assessment and management

In accordance with the 2020 ESC guidelines for the diagnosis and management of AF, the following seven modifiable risk factors were evaluated as outcome measures for this study: overweight, smoking, regular alcohol use, dyslipidemia, hypertension, hyperglycemia or (pre)diabetes, and obstructive sleep apnea (OSA). [5] Although the guidelines mention physical activity as a factor of interest as well, it was excluded as an outcome measure here because objective data on this topic were lacking. For most risk factors, treatment targets were provided in the AF guidelines. [5] In cases where no specific treatment targets were provided, targets were derived from the 2021 ESC guidelines on cardiovascular disease prevention. [7]

As such, overweight was defined as body mass index (BMI) ≥27 kg/m^2 in accordance with the AF guidelines (using body weight that was measured on-site indexed by patient-reported height). [5] Smoking was defined as any current self-reported smoking. [5,7] Regular alcohol use was defined as self-reported consumption of >5 standardized units/week (equivalent to 50 g alcohol/week). This cut-off value differed from the target provided in the prevention guidelines (<100 g/week) due to class-wise reporting of the data in this study. [7] Hypertension was defined as an in-office systolic blood pressure during the AF work-up >130 mmHg and/or a diastolic blood pressure >80 mmHg. [5] Dyslipidemia was defined as a low-density lipoprotein (LDL) value above a patient's individual target based on their estimated atherosclerotic CVD risk (*Figure 1*). [5,7] For patients at very high CVD risk, the primary lipid target was LDL <1.4 mmol/l (equivalent to <50 mg/dL), for patients at high CVD risk, LDL was targeted at <1.8 mmol/l (equivalent to <70 mg/dL) and for patients at low to moderate CVD risk, any LDL was accepted. [7] Hyperglycemia or (pre) diabetes was based on hemoglobin A1c (HbA1c) measured in blood collected at baseline (non-fasting) and was defined as HbA1c ≥6.5% (equivalent to ≥48 mmol/mol). [5,7]

OSA was defined as a home sleep test-derived apnea-hypopnea index (AHI) of ≥15. Results of OSA screening were available for a subset of patients, as structural remote sleep apnea screening using home sleep tests was initiated during the course of the study. [12] From October 2020 onwards, all patients without recent prior sleep testing were referred for OSA screening.

Results of risk factor assessment were collected by a case manager. [9] If any risk factor appeared not to be adequately controlled (e.g., due to the risk factor not being previously identified, suboptimal treatment doses or insufficient patient compliance), patients were educated about the impact of the respective risk factor on AF ablation outcomes and the risk of atherosclerotic CVD. Subsequently, either targeted treatment was directly initiated or intensified (e.g., lifestyle recommendations, initiation of statins or other cholesterol-modifying drugs, or initiation of continuous positive airway pressure) or patients were referred for more intensive screening and/or treatment approaches (e.g., 24-hour ambulatory blood pressure monitoring, repeated home blood pressure monitoring, stricter glycemic control in patients with diabetes mellitus, or combined lifestyle intervention programs).

AF characterization

AF was characterized according to the 4S-AF scheme, which distinguishes 4 domains (stroke, symptoms, severity of AF burden, and substrate) in which a set number of points may be accumulated. [5,13] In the first category (*'stroke'*), 0 points were appointed for patients at low stroke risk (defined as CHA_2DS_2-VASc 0 for males, 1 for females), in case of a higher stroke risk 1 point was appointed. In the *'symptoms'* category, potential points ranged from 0 points (none or mild symptoms, EHRA class 1) via 1 point (moderate symptoms, EHRA class 2) to 2 points (severe or disabling symptoms, EHRA class 3-4). In '*severity of AF burden*', 3 points may be scored based on 2 categories: spontaneously terminating AF (0 points for yes, 1 point for no) and duration and density of AF episodes (0 points for short and infrequent episodes, 1 point for intermediate and/or frequent episodes, and 2 points for long or very frequent episodes). The last 'substrate' category yields a maximum of 5 points based on comorbidities (0 points for none, 1 for a single and 2 for multiple comorbidities), LA enlargement (0 points for none, 1 for mild to moderate enlargement and 2 for severe enlargement) and age (1 point if over 75 years of age).

Statistical analyses

Continuous variables with normal distribution were expressed as mean ± standard deviation (SD) and compared using the unpaired t-test (in case of two subgroups). For comparisons between three subgroups, homogeneity of the variance was established using Levene's test and variables were subsequently compared using ANOVA (post hoc comparisons were conducted using Tukey test) or ANOVA with Welch's statistic (post hoc comparisons were conducted using Games-Howell). Nonparametric continuous variables were expressed as median [interquartile range (IQR)] and compared using the Mann-Whitney U test (in case of two subgroups) or the Kruskall-Wallis test (in case of three subgroups, in case of post hoc comparisons Bonferroni correction was applied). Categorical variables were presented as counts (n) with percentages (%) and compared using the Chi-square test. Bonferroni correction was applied in case of post hoc comparisons for variables with significant differences between three subgroups.

The number of non-optimally controlled risk factors was defined as the sum of each of the seven risk factors for which the values were out of the target range. Analyses were performed on patients with a complete set of variables over the seven risk factors, with the exemption of OSA as this variable was available in a subset of patients. When no details on OSA status were available, OSA

was assumed to be absent. Additional analyses were performed for patients with a complete set of variables (including OSA details), and for the complete cohort after estimation of missing values using multiple imputation by chained equations using 5 iterations. A two-sided P value of 0.05 was considered statistically significant for all analyses. Statistical analyses were performed using IBM SPSS Statistics software (version 25.0, IBM Corp., Amonk, NY, USA).

RESULTS

From July 2020 - September 2022, 1143 patients scheduled for catheter ablation were included in the ISOLATION study. Their mean age was 63.8 ± 9.3 years old and 35% (n=399) was female. The majority (67%) of patients had paroxysmal AF, and 64% of patients had left atrial dilatation (left atrial volume index ≥35 ml/m^2). More than half of patients had a previously established diagnosis of at least one cardiovascular comorbidity (46% hypertension, 16% previous acute coronary syndromes or coronary interventions, 11% OSA, 11% previous thromboembolic events, 8% diabetes mellitus, and 4% CKD, *Table 1* and *Table 2*).

The mean AF-4S score was 5.7 ± 1.9 out of a maximum of 11 points. Seventy-eight percent (n=894) scored the maximum of 1 point in the 'stroke' category, 29% (n=332) the maximum of 2 points in the 'symptoms' category, 7% (n=74) scored the maximum of 3 points in the combined 'severity of AF burden' category, and 2% (n=18) scored the maximum of 5 points in the 'substrate' category. Twelve percent of patients (n=106) scored no points in the 'substrate' category, indicating the combination of a non-dilated left atrium, absence of comorbidities, and an age below 75 years old.

Table 1. Patient characteristics

	Overall (n=1143)	Patients with low-to-moderate CVD risk *(n=171, 15%)*	Patients with high CVD risk *(n=245, 21%)*	Patients with very high CVD risk *(n=727, 64%)*	P-value
Demographics and AF characteristics					
Age	63.8 ± 9.3	53.4 ± 10.3	63.7 ± 7.4	66.3 ± 7.8	<0.001[a]
Female	399 (35%)	89 (52%)	82 (33%)	228 (31%)	<0.001[b]
AF type *(n=1129)*		n=170	n=239	n=720	
Paroxysmal	759 (67%)	126 (74%)	159 (67%)	474 (66%)	0.298
Persistent	356 (32%)	44 (26%)	77 (32%)	235 (33%)	
Longstanding persistent	14 (1%)	0 (0%)	3 (1%)	11 (2%)	
			n=243	n=724	
Time since AF diagnosis (years, *n=1138)*	2.5 [1.0-6.7]	1.9 [0.8-5.5]	3.0 [1.1-7.3]	2.6 [1.0-7.0]	0.025[c]
		n=131	n=189	n=582	
LAVi (ml/m^2, *n=902)*	41.0 ± 13.4	37.2 ± 11.8	40.4 ± 12.7	42.1 ± 13.8	0.001[c]
		n=168	n=244	n=716	
CHA_2DS_2-VASc score (*n=1128*)	2.1 ± 1.5	1.0 ± 0.9	1.6 ± 1.1	2.5 ± 1.6	<0.001[a]
4S-AF classification					
Stroke (*n=1140*)		n=169	n=245	n=726	
Low thrombo-embolic risk (0 pt)	246 (22%)	106 (63%)	54 (22%)	86 (12%)	<0.001[a]
At thrombo-embolic risk (1 pt)	894 (78%)	63 (37%)	191 (78%)	640 (88%)	
Symptoms (*n=1130*)		n=169	n=243	n=718	
None or mild (EHRA I, 0 pt)	36 (3%)	2 (1%)	6 (2%)	28 (4%)	0.226
Moderate (EHRA II, 1 pt)	762 (67%)	123 (73%)	167 (69%)	472 (66%)	
Severe or disabling (EHRA III-IV, 2 pt)	332 (29%)	44 (26%)	70 (29%)	218 (30%)	

Table 1. Patient characteristics (continued)

	Overall (n=1143)	Patients with low-to-moderate CVD risk *(n=171, 15%)*	Patients with high CVD risk *(n=245, 21%)*	Patients with very high CVD risk *(n=727, 64%)*	P-value
Severity of AF burden					
Spontaneously terminating AF *(n=1134)*		n=170	n=243	n=1134	
Always or often (0 pt)	762 (67%)	126 (74%)	161 (66%)	475 (66%)	0.113
Never or rarely (1 pt)	372 (33%)	44 (26%)	82 (34%)	246 (34%)	
Density and duration of AF episodes *(n=1135)*			n=243	n=721	
Short and infrequent (0 pt)	247 (22%)	40 (23%)	53 (22%)	154 (22%)	
Intermediate and/or frequent (1 pt)	392 (35%)	55 (32%)	77 (32%)	260 (36%)	0.687
Long or very frequent (2 pt)	496 (43%)	76 (44%)	113 (47%)	307 (43%)	
Substrate					
Age					
≤75 years old (0 pt)	1050 (92%)	171 (100%)	235 (96%)	644 (89%)	<0.001[a]
>75 years old (1 pt)	93 (8%)	0 (0%)	10 (4%)	83 (11%)	
Comorbidities *(n=1126)*		n=168	n=244	n=714	
None (0 pt)	311 (28%)	95 (57%)	77 (32%)	139 (19%)	
Single (1 pt)	321 (29%)	56 (33%)	86 (35%)	179 (25%)	<0.001[a]
Multiple (2 pt)	494 (44%)	17 (10%)	33 (33%)	396 (55%)	
Left atrial enlargement *(n=902)*		n=131	n=189	n=582	
LAVi <35 ml/m^2 (0 pt)	325 (36%)	66 (50%)	68 (36%)	191 (33%)	
LAVi 35-48 ml/m^2 (1 pt)	347 (38%)	41 (31%)	78 (41%)	347 (39%)	0.003[c]
LAVi >48 ml/m^2 (2 pt)	230 (25%)	24 (18%)	43 (23%)	163 (28%)	

Table 1. Patient characteristics (continued)

	Overall (n=1143)	Patients with low-to-moderate CVD risk *(n=171, 15%)*	Patients with high CVD risk *(n=245, 21%)*	Patients with very high CVD risk *(n=727, 64%)*	P-value
		n=128	n=186	n=559	
AF-4S score *(n=873)*	5.7 ± 1.9	4.2 ± 2.0	5.5 ± 1.9	6.1 ± 1.8	<0.001[a]
Non-modifiable comorbidities					
		n=170			
Previous coronary artery event *(n=1142)* *	181 (16%)	0 (0%)	0 (0%)	181 (25%)	<0.001[d]
		n=90	n=117	n=509	
Coronary artery calcium score *(n=716)*	73 [0-296]	0 [0-0]	0 [0-8]	161 [40-473]	<0.001[d]
		n=90	n=117	n=509	
Coronary artery calcium score ≥100 *(n=716)*	316 (63%)	2 (2%)	10 (9%)	304 (60%)	<0.001[d]
		n=118	n=141	n=649	
Coronary plaques on baseline CT *(n=908)*	606 (67%)	0 (0%)	0 (0%)	606 (93%)	<0.001[d]
		n=169	n=244	n=716	
Congestive heart failure *(n=1129)*	207 (18%)	23 (14%)	45 (18%)	139 (19%)	0.215
HF type (n=184)		n=380	n=380	n=380	
HFpEF (LVEF >49%)	43 (23%)	4 (19%)	5 (13%)	34 (27%)	
HFmrEF (LVEF 40-49%)	68 (37%)	8 (38%)	16 (41%)	44 (35%)	0.430
HFrEF (LVEF <40%)	73 (40%)	9 (43%)	18 (46%)	46 (37%)	
		n=169			
Thromboembolic events *(n=1141)*	122 (11%)	2 (1%)	2 (1%)	118 (16%)	<0.001[d]

Table 1. Patient characteristics (continued)

	Overall (n=1143)	Patients with low-to-moderate CVD risk *(n=171, 15%)*	Patients with high CVD risk *(n=245, 21%)*	Patients with very high CVD risk *(n=727, 64%)*	P-value
		n=169			
Peripheral arterial disease *(n=1141)*	19 (2%)	0 (0%)	0 (0%)	19 (3%)	0.004[e]
Renal dysfunction					
GFR (ml/min/1.73m^2)	77 [65-89]	85 [76-90]	77 [68-90]	75 [63-87]	<0.001[a]
GFR <30 ml/min/1.73m^2	5 (0.4%)	0 (0%)	0 (0%)	5 (1%)	0.283
GFR <45 ml/min/1.73m^2	51 (4%)	0 (0%)	9 (4%)	42 (6%)	0.004[b]

**Coronary artery events include acute coronary syndromes, percutaneous coronary interventions, and coronary artery bypass grafts.*

[a] *significant difference between all subgroups (low-to-moderate vs high risk, low-to-moderate vs very high risk, high vs very high risk).*

[b] *significant difference between low-to-moderate vs high risk and between low-to-moderate vs very high-risk subgroups.*

[c] *significant difference between low-to-moderate vs very high-risk subgroups.*

[d] *significant difference between low-to-moderate vs very high risk and between high vs very high-risk subgroups.*

[e] *significant difference between high vs very high-risk subgroups.*

Abbreviations: AF: atrial fibrillation, BMI: body mass index, CT: computed tomography, CVD: cardiovascular disease, EHRA: European Heart Rhythm Association, GFR: glomerular filtration rate, HFmrEF: heart failure with mildly reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, LAVi: left atrial volume index, LVEF: left ventricular ejection fraction.

Estimation of (atherosclerotic) cardiovascular disease risk

Structural assessment of CVD risk revealed that as much as 64% of patients (n=727) had a very high risk of developing first or subsequent CVD events in the following 10 years. The high percentage could in part be explained by previous occurrence of atherosclerotic events (24%, n=269, composite of coronary artery events, peripheral arterial disease, and thromboembolic events). However, half of patients at very high CVD risk was classified as such based on previously undetected atherosclerosis discovered on the pre-ablation CT scan (*Supplement 1*). Of 908 pre-ablation CT scans that were of sufficient quality to assess the coronary arteries, coronary plaques were observed in 67% (n=606). Taking both previous evidence of atherosclerosis and the results of the pre-ablation CT scans into account, a total of 60% (n=688) of the overall cohort had established atherosclerotic disease. Three percent of patients (n=39) were at very high risk of developing a first atherosclerotic event without irrefutable evidence of atherosclerotic processes already present. Twenty-one percent (n=245) had a high 10-year risk of developing CVD events, and 15% (n=171) had a low-to-intermediate 10-year risk. The shift from low-to-intermediate or high to the very high-risk category based on coronary plaques on CT impacted treatment targets for LDL in 364 patients (32%).

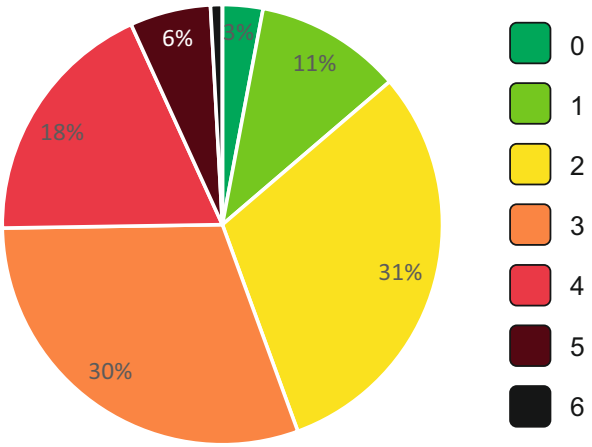


Figure 2. Number of risk factors for which treatment targets were not reached per patient (n=808).

Structured risk factor assessment

This structural risk factor screening approach revealed that the mean number of risk factors for which the reappraised treatment targets were not reached was 2.7 ± 1.2 per patient in the cohort of patients with complete data on all risk factors with the exception of OSA details (n=808). Inherently, this number was slightly higher when assessed in the subset of patients with a complete dataset including OSA details (3.0 ± 1.3, n=327), as underdiagnosis of OSA was now excluded. After imputation of missing variables, the mean number of risk factors for which treatment targets were not reached in the total cohort was 3.1 ± 1.3 (n=1143).

Only 3% (n=24) of patients with complete data on all risk factors with the exception of OSA details complied to the treatment targets of all seven risk factors (*Figure 2*). Patients' lipid levels were most often above treatment targets (78%, n=738/941), followed by blood pressure (72%, n=804/1111) and weight (55%, n= 631/1138, *Table 2 and Figure 3*). AHI was ≥15 in 49% of patients (n=194/397) in whom OSA screening was performed. A weekly alcohol consumption of ≥5 units was reported by 27% (n=296/1105) of patients, 13% (n=141/1124) smoked actively, and HbA1c was found to be above target ranges in 8% (75/900) of patients.

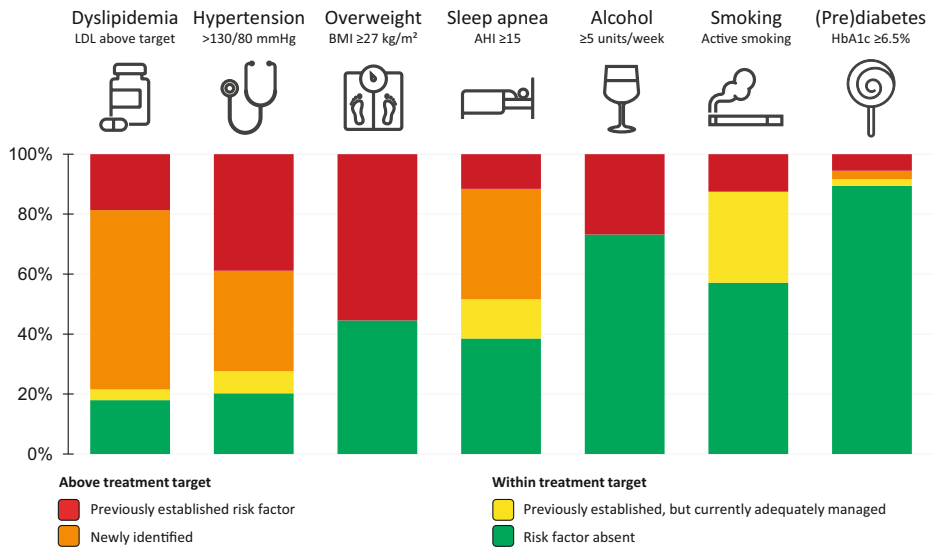


Figure 3. Compliance to treatment targets for each modifiable risk factor.

Abbreviations: AHI: apnea-hypopnea index, BMI: body mass index, HbA1c: hemoglobin A1c, LDL: low-density lipoprotein.

Table 2. Modifiable comorbidities and compliance to treatment targets.

	Overall *(n=1143)*	**Patients with previously diagnosed comorbidity**	**Patients without previously diagnosed comorbidity**
Dyslipidemia		**n=263 (23%)**	**n=879 (77%)**
		n=210	n=732
LDL (mmol/l, *n=942*)	2.7 ± 0.9	2.3 ± 0.9	2.9 ± 0.9
LDL ≥1.4 mmol/l (≥50 mg/dl)	81 (95%)	187 (89%)	704 (96%)
LDL ≥1.8 mmol/l ≥70 mg/dl)	793 (84%)	144 (69%)	649 (89%)
LDL ≥2.6 mmol/l (≥100 mg/dl)	524 (56%)	64 (30%)	460 (63%)
		n=210	n=732
LDL above individual primary target *(n=941)*	738 (78%)	176 (84%)	562 (77%)
		n=210	n=732
LDL above more lenient 'first step' individual target *(n=941)* *	604 (64%)	121 (58%)	483 (66%)
Use of lipid lowering drugs *(n=1142)*	378 (33%)	200 (76%)	178 (20%)
Hypertension		**n=528 (46%)**	**n=614 (54%)**
		n=514	n=598
Systolic BP (mmHg, *n=1112*)	139 ± 19	145 ± 20	133 ± 16
Systolic BP >130 mmHg	696 (63%)	377 (73%)	319 (53%)
Systolic BP ≥140 mmHg	484 (44%)	293 (57%)	191 (32%)
		n=514	n= 597
Diastolic BP (mmHg, *n=1111*)	82 ± 11	86 ± 12	79 ± 10
Diastolic BP >80 mmHg	572 (51%)	326 (63%)	246 (41%)
Diastolic BP ≥90 mmHg	262 (24%)	173 (34%)	89 (15%)

Table 2. Modifiable comorbidities and compliance to treatment targets. (continued)

	Overall *(n=1143)*	**Patients with previously diagnosed comorbidity**	**Patients without previously diagnosed comorbidity**
		n=514	n= 597
BP >130/80 mmHg *(n=1111)*	804 (72%)	432 (84%)	372 (62%)
		n=514	n= 597
BP >140/90 mmHg (*n=1111*)	552 (50%)	330 (64%)	222 (37%)
Diabetes mellitus		**n=88 (8%)**	**n=1054 (92%)**
		n=70	n=830
HbA1c (%, *n=900*)	5.7 ± 0.6	6.9 ± 1.0	5.6 ± 0.4
HbA1c ≥7.0% (≥53 mmol/mol)	35 (4%)	28 (40%)	7 (1%)
		n=70	n=830
Hyperglycemia: HbA1c ≥6.5% (≥48 mmol/mol, *n=900)*	75 (8%)	50 (71%)	25 (3%)
Obstructive sleep apnea *(n=1138)*		**n=130 (11%)**	**n=1008 (89%)**
			n=397
Apnea-hypopnea index		-	15 [8-24]
AHI ≥30			61 (15%)
			n=397
Newly diagnosed OSA (AHI ≥15)			194 (49%)
		n=130	-
Treatment with PAP		69 (53%)	

Table 2. Modifiable comorbidities and compliance to treatment targets. (continued)

	Overall *(n=1143)*	Patients with previously diagnosed comorbidity	Patients without previously diagnosed comorbidity
Overweight			
Weight (kg, *n=1140*)	87.9 ± 16.1		
Body mass index (kg/m^2, *n=1138*)	28.0 ± 4.2		
BMI ≥25 kg/m^2	859 (75%)		
BMI ≥30 kg/m^2	317 (28%)		
Above target BMI (≥27 kg/m^2, *n=1138*)	631 (55%)		
Alcohol consumption *(n=1105)*			
None	329 (30%)		
<5 units/week (<50 g/week)	480 (43%)		
5-15 units/week (50-150 g/week)	256 (23%)		
≥15 units/week (≥150 g/week)	40 (4%)		
Regular alcohol use (>5 units or >50 g/week)	296 (27%)		
Smoking status *(n=1124)*			
Never	642 (57%)		
Former (quit >1 year ago)	309 (27%)		
Former (quit <1 year ago)	32 (3%)		
Current smoker	141 (13%)		
Quantity (cigarettes/day)	10 [5-19]		
n=97 (for current smokers)			

** According to the 2021 ESC guidelines on cardiovascular disease prevention.*

Abbreviations: AHI: apnea-hypopnea index, BP: blood pressure, HbA1c: hemoglobin A1c, LDL: low-density lipoprotein, PAP: positive airway pressure.

Dyslipidemia

Mean LDL-cholesterol was 2.7 ± 0.9 mmol/l and was higher in patients without (2.9 ± 0.9) than with (2.3 ± 0.9) previously diagnosed dyslipidemia (*Table 2*). In more than three quarters of patients with an LDL above the target value this was the first acknowledgement of higher than desired cholesterol levels (76%, n=562/738). This high percentage presumably results from the shift in LDL treatment targets following recognition of atherosclerotic plaques on the pre-ablation CT scan (*Supplement 1*).

One-third (33%, n=378/1142) of the total cohort was treated with statins or other lipid lowering drugs. For treated patients in whom lipid levels were measured, compliance with individual targets occurred in only 19% (n=58/310), in the other 81% of patients (n=252) LDL was still above the target value despite treatment. However, targets may have become stricter after the CT scan.

Blood pressure

Mean systolic and diastolic blood pressure were 139 ± 19 and 82 ± 11 mmHg, respectively. Blood pressure was above 130/80 mmHg in 72% of patients, of whom 54% had previously been diagnosed with hypertension (46% of total cohort). Hypertension was newly identified in 33% of patients. High blood pressure was mostly driven by a higher than targeted systolic blood pressure (63%) rather than diastolic blood pressure (51%).

Obstructive sleep apnea

OSA had previously been diagnosed in 11% (n=130/1138) of patients. During the course of the study structural OSA screening was implemented, and results of this screening were available for 397 patients without a previous OSA diagnosis. Median AHI in these patients was 15 [8-24], corresponding with moderate OSA (AHI 15-30) in 34% of patients (n=133) and severe OSA (AHI ≥30) in 15% (n=61). After imputation of missing AHI values for patients who had not undergone screening, moderate-to-severe OSA (AHI ≥15) was estimated to be present in 55% of patients without the previously identified comorbidity (67% of the study cohort).

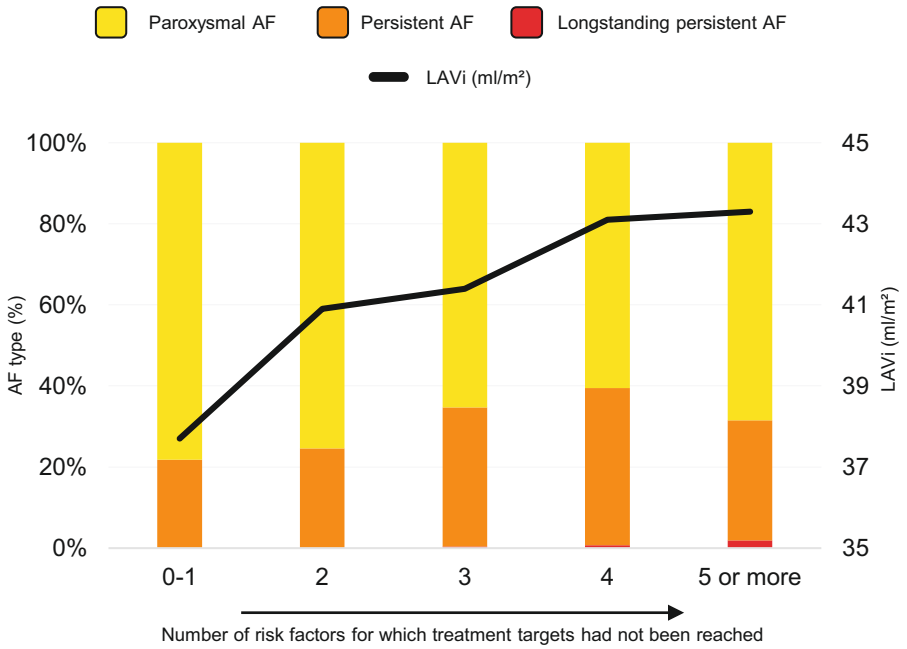


Figure 4. Compliance to risk factor treatment targets in relation to AF characteristics.
Abbreviations: AF: atrial fibrillation, LAVi: left atrial volume index.

Compliance to treatment targets and AF characteristics

Patients in whom ≥3 treatment targets for risk factors had not been reached displayed signs of more advanced AF than those with more adequately controlled risk factors. They less often had paroxysmal AF (64% vs 76%, $p < 0.001$), had higher left atrial volume indices (42.2 ± 14.1 vs 39.9 ± 12.3, $p = 0.026$), and higher AF-4S scores (6.1 ± 1.8 vs 5.3 ± 2.0, $p < 0.001$, *Supplement 2 and Figure 4*). Symptom severity did not differ between the groups with more or less non-adequately controlled risk factors.

DISCUSSION

This multicenter cross-sectional study of AF patients scheduled for catheter ablation described the prevalence of seven common modifiable risk factors for AF, estimated atherosclerotic CVD risks, and assessed adherence with risk factor treatment targets. The main findings were that treatment targets for all seven risk factors were reached in only 3% of patients, with a mean number of 2.7 risk factors above targets per patient. In addition, structural assessment of atherosclerotic CVD risk revealed that as much as 85% of patients was at

high or very high risk of developing new or subsequent CVD in the following 10 years. Improving management of cardiovascular risk factors is therefore not only indicated to improve rhythm outcomes, but also to modify overall risk of CVD in AF patients undergoing catheter ablation.

Previous studies demonstrated that clinical or subclinical coronary artery disease is present in a significant percentage of patients undergoing AF ablation. [14] We could confirm this finding in the current study and showed that coronary plaques were present in more than two-thirds of patients in whom a CT was performed, which is clearly over the estimated prevalence of coronary plaques in the general population. [15,16] Whether this is due to a direct pathophysiological relation or to the shared risk profile is uncertain, but the high percentage of patients with established atherosclerosis found in this study underlines the importance of structural CVD risk assessment and, when applicable, risk factor modification in this population.

In this cohort of AF patients undergoing catheter ablation, cholesterol levels and blood pressure were most often insufficiently controlled, both in almost three quarters of cases. The high percentage of cholesterol levels above targets was for an important part the result of a shift in LDL targets caused by incidental findings of coronary atherosclerosis on the pre-ablation CT scan. As many patients did not have previous indications for (non-)invasive coronary imaging, this atherosclerosis had often not yet been detected and LDL treatment targets had previously not been this strict. Presence of coronary plaques is correlated with CVD events, even when found incidentally on scans performed for other indications, although it is unsure if this correlation is as strong as in symptomatic patients. [17] Still, the LDL treatment targets provided in the guidelines do not make a distinction between these forms, and this study therefore highlights the importance of structural integration of standard pre-ablation imaging results into CVD risk assessment to ensure correct establishment of treatment targets for AF risk factors. [7]

Although the target value for blood pressure of ≤130/80 mmHg that was used in this study may seem strict, it was chosen in accordance with the current AF guidelines. [5] Nevertheless, it must be noted that blood pressure values used in this study were based on a single, in-office measurement and that data on ambulatory 24-hour blood pressure monitoring were not available. As blood pressure is particularly sensitive for variability, poor management of this hypertension may be overestimated due to white coat hypertension or

to suboptimal measurement technique. [7] Conversely, patients with masked hypertension may have been missed. Sustained uncontrolled hypertension and masked hypertension have been demonstrated to affect AF- and CVD-related outcomes in similar extents, whereas white coat hypertension seems to less strongly affect prognosis. [7,18] Therefore, future studies may benefit from more structural ambulatory blood pressure monitoring to perform a more thorough risk assessment and improve classification into the different types of hypertension.

In the current study, the effect of risk factor interventions on AF recurrence was not evaluated. However, the positive impact of risk factor management on AF recurrences after rhythm interventions has well been established, especially when provided in an integrated manner addressing multiple risk factors simultaneously and, where possible, with the use of remote (e-health) approaches. [2,3,19-22] In a study in obese patients, the number of risk factors for which treatment goals were achieved was associated with rhythm outcomes, i.e., more adequately treated risk factors may lead to less AF recurrences. [23] It seems plausible, therefore, that particularly patients with several non-optimally managed factors or patients at high risk of AF recurrences could benefit most from extensive risk factor modification.

The optimal timepoint when such a program should be initiated remains under debate. Waiting until a patient with AF is referred for catheter ablation may be later than desirable, since as long as risk factors remain present, both atrial arrhythmogenic substrate formation and atherosclerotic processes progress. [4] However, it never seems to be too late: aggressive risk factor management prevents late recurrences of AF even when initiated after catheter ablation. [24] Regardless of the desired timepoint, structural implementation of comprehensive risk factor programs remains challenging. A recent Europe-wide survey revealed that for more than half of respondents integrated care models were lacking, and over one third reported organizational or institutional issues and issues with patient adherence. [6] The ongoing EHRA-PATHS project aims to address hurdles on this road and develop a generic, multidisciplinary, evidenced-based, lean care pathway, using clearly defined target outcomes. [25] This may contribute to more structurally implemented and uniform care for AF comorbidities in an earlier stage. The current study again underlines the importance of such initiatives, not just for the improvement of rhythm outcomes, but also to reduce CVD risk.

Limitations

This study evaluated compliance to cardiovascular risk factor treatment targets and CVD risk in a large, unselected cohort of patients undergoing catheter ablation for AF. However, there were several limitations that should be addressed. First, although this cohort seems a representative Western AF ablation cohort (based on similar characteristics as in a large European all-comer cohort of AF ablation patients), findings from this study cannot be generalized to the general AF population. [26] Second, due to the retrospective nature of this analysis, baseline data were missing for several patients. Data on physical activity, which represents another important risk factor for AF and CVD, were not collected, and structured OSA screening was only initiated during the course of the study. Third, as discussed above the practical, real-world use of only in-office blood pressure measurements and not ambulatory monitoring is likely to have impacted the prevalence of above-target blood pressure values. Fourth, the presence of coronary plaques could not be assessed for all patients since baseline CT was only performed when clinically indicated and was primarily aimed to assess left atrial anatomy. Last, data on treatment initiated in response to this structured risk factor assessment were not collected. As the ISOLATION cohort study is still ongoing, follow-up data on risk factor status and outcome data after ablation are not yet available.

Conclusion and implications

Structural assessment revealed a high percentage of modifiable risk factors for which treatment targets were not yet reached in patients scheduled for AF ablation. This population represents a population at high risk of developing first or subsequent atherosclerotic CVD. Future studies should focus on a broad and effective implementation of comprehensive risk factor modification programs.

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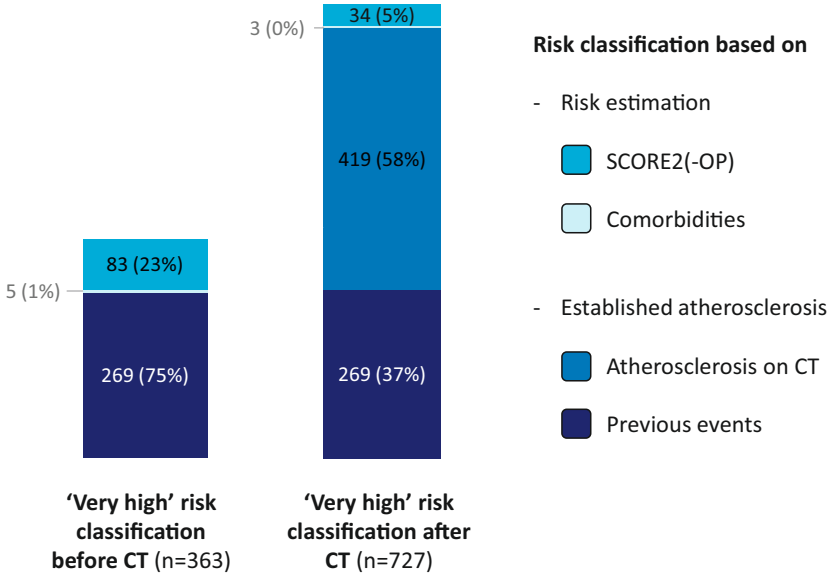
SUPPLEMENTS



Supplement 1. Atherosclerotic cardiovascular disease risk classification before and after CT

Abbreviations: CT: computed tomography, SCORE2(-OP): Systematic Coronary Risk Estimation 2 (-Older Persons)

Supplement 2. Patient characteristics.

	Overall (n=1143)	Patients with ≤2 risk factors *(n=359, 44%)*	Patients with ≥3 risk factors *(n=449, 56%)*	P-value
Demographics and AF characteristics				
Age	63.8 ± 9.3	62.0 ± 10.1	65.2 ± 8.1	<0.001
Female	399 (35%)	146 (41%)	140 (31%)	0.005
AF type *(n=1129)*		n=355	n=443	
Paroxysmal	759 (67%)	270 (76%)	284 (64%)	0.001
Persistent	356 (32%)	85 (24%)	156 (35%)	
Longstanding persistent	14 (1%)	0 (0%)	3 (1%)	
Time since AF diagnosis (years, *n=1138)*	2.5 [1.0-6.7]	2.3 [0.9-6.7]	n=448 2.7 [1.0-7.1]	0.271
LAVi (ml/m^2, *n=902)*	41.0 ± 13.4	n=301 39.9 ± 12.3	n=382 42.2 ± 14.1	0.026
CHA_2DS_2-VASc score (*n=1128*)	2.1 ± 1.5	n=356 1.7 ± 1.3	n=447 2.3 ± 1.6	<0.001
4S-AF parameters				
Stroke (*n=1140*)				
Low thrombo-embolic risk (0 pt)	246 (22%)	114 (32%)	70 (16%)	<0.001
At thrombo-embolic risk (1 pt)	894 (78%)	245 (68%)	379 (84%)	
Symptoms (*n=1130*)		n=355	n=444	
None or mild (EHRA I, 0 pt)	36 (3%)	8 (2%)	15 (3%)	0.591
Moderate (EHRA II, 1 pt)	762 (67%)	244 (69%)	296 (67%)	
Severe or disabling (EHRA III-IV, 2 pt)	332 (29%)	103 (29%)	133 (30%)	

Supplement 2. Patient characteristics. (continued)

	Overall (n=1143)	Patients with ≤2 risk factors *(n=359, 44%)*	Patients with ≥3 risk factors *(n=449, 56%)*	P-value
Severity of AF burden				
Spontaneously terminating AF *(n=1134)*		n=357	n=446	
Always or often (0 pt)	762 (67%)	272 (76%)	285 (64%)	<0.001
Never or rarely (1 pt)	372 (33%)	85 (24%)	161 (36%)	
Density and duration of AF episodes *(n=1135)*		n=358	n=447	
Short and infrequent (0 pt)	247 (22%)	83 (23%)	89 (20%)	
Intermediate and/or frequent (1 pt)	392 (35%)	109 (30%)	175 (39%)	0.037
Long or very frequent (2 pt)	496 (43%)	166 (46%)	183 (41%)	
Substrate				
Age				
Under 75 years old (0 pt)	1050 (92%)	346 (96%)	398 (89%)	<0.001
Over 75 years old (1 pt)	93 (8%)	13 (4%)	51 (11%)	
Comorbidities *(n=1126)*		n=356	n=446	
None (0 pt)	311 (28%)	139 (39%)	94 (21%)	
Single (1 pt)	321 (29%)	107 (30%)	113 (25%)	<0.001
Multiple (2 pt)	494 (44%)	110 (31%)	239 (54%)	
Left atrial enlargement *(n=902)*		n=301	n=382	
LAVi <35 ml/m^2 (0 pt)	325 (36%)	114 (38%)	120 (31%)	
LAVi 35-48 ml/m^2 (1 pt)	347 (38%)	117 (39%)	156 (41%)	0.171
LAVi >48 ml/m^2 (2 pt)	230 (25%)	70 (23%)	106 (28%)	
		n=292	n=372	
AF-4S score *(n=873)*	5.7 ± 1.9	5.3 ± 2.0	6.1 ± 1.8	<0.001

Supplement 2. Patient characteristics. (continued)

	Overall (n=1143)	Patients with ≤2 risk factors *(n=359, 44%)*	Patients with ≥3 risk factors *(n=449, 56%)*	P-value
Non-modifiable comorbidities				
Previous coronary artery event *(n=1142)* *	181 (16%)	40 (11%)	82 (18%)	0.005
		n=224	n=294	
Coronary artery calcium score *(n=716)*	73 [0-296]	29 [0-174]	117 [6-383]	<0.001
		n=303	n=354	
Coronary plaques on baseline CT *(n=908)*	606 (67%)	171 (56%)	266 (75%)	<0.001
		n=356	n=447	
Congestive heart failure *(n=1129)*	207 (18%)	53 (15%)	95 (21%)	0.021
HF type (n=184)		n=48	n=85	
HFpEF (LVEF >49%)	43 (23%)	12 (25%)	18 (21%)	
HFmrEF (LVEF 40-49%)	68 (37%)	15 (31%)	30 (35%)	0.841
HFrEF (LVEF <40%)	73 (40%)	21 (44%)	37 (44%)	
Thromboembolic events *(n=1141)*	122 (11%)	26 (7%)	61 (14%)	0.004
Peripheral arterial disease *(n=1141)*	19 (2%)	3 (1%)	7 (2%)	0.355
Renal dysfunction				
GFR (ml/min/1.73m^2)	77 [65-89]	81 [67-90]	76 [64-88]	0.001
GFR <30 ml/min/1.73m^2	5 (0.4%)	2 (0.6%)	2 (0.4%)	0.822
GFR <45 ml/min/1.73m^2	51 (4%)	12 (3%)	28 (6%)	0.060
Cardiovascular risk assessment				
High or very high cardiovascular disease risk	972 (85%)	255 (71%)	433 (96%)	<0.001
Very high cardiovascular disease risk	727 (64%)	190 (53%)	328 (73%)	<0.001

**Coronary artery events include acute coronary syndromes, percutaneous coronary interventions, and coronary artery bypass grafts.*

Abbreviations: AF: atrial fibrillation, BMI: body mass index, CT: computed tomography, EHRA: European Heart Rhythm Association, GFR: glomerular filtration rate, HFmrEF: heart failure with mildly reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, LAVi: left atrial volume index, LVEF: left ventricular ejection fraction.

CHAPTER 6

A VIRTUAL Sleep Apnea management pathway For the workup of Atrial fibrillation patients in a digital Remote Infrastructure: VIRTUAL-SAFARI

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ABSTRACT

Background

In atrial fibrillation (AF) patients, untreated sleep-disordered breathing (SDB) is associated with lower success rates of rhythm control strategies and as such structured SDB testing is recommended. Herein, we describe the implementation of a virtual SDB management pathway in an AF outpatient clinic and examine the utility and feasibility of this new approach.

Methods

Prospectively, consecutive AF patients accepted for AF catheter ablation procedures without previous diagnosis of SDB were digitally referred to a virtual SDB management pathway and instructed to use WatchPAT-ONE (ITAMAR) for one night. Results were automatically transferred to a virtual sleep laboratory, upon which a teleconsultation with a sleep physician was planned. Patient experience was measured using surveys.

Results

SDB testing was performed in 119 consecutive patients scheduled for AF catheter ablation procedures. The median time from digital referral to finalization of the sleep study report was 18 (11-24) days. In total, 65 patients (55%) were diagnosed with moderate-to-severe SDB. Patients with SDB were prescribed more cardiovascular drugs and had higher body mass indices (BMI, 29 ± 3.3 vs 27 ± 4.34, $p < 0.01$). Patients agreed that WatchPAT-ONE was easy to use (91%) and recommended future use of this virtual pathway in AF outpatient clinics (86%). Based on this remote SDB testing, SDB treatment was initiated in the majority of patients.

Conclusion

This novel virtual AF management pathway allowed remote SDB testing in AF outpatient clinics with a short time to diagnosis and high patient satisfaction. Structured SDB testing results in a high detection of previously unknown SDB in AF patients scheduled for AF ablation.

INTRODUCTION

Remote monitoring by means of novel mobile health technologies provides an opportunity to bring the evidence-based standard of care and expertise to the patient rather than the patient having to visit a hospital. [1] Previously, we introduced the TeleCheck-AF approach, which is an on-demand mHealth infrastructure incorporating mobile app-based heart rate and rhythm monitoring to allow remote atrial fibrillation (AF) management through teleconsultation. [2,3] Although the TeleCheck-AF solution can mitigate some of the limitations of remote AF consultations, the remote assessment and overall management of risk factors in AF patients remains challenging. [1]

An important component of comprehensive risk factor management in AF patients is sleep-disordered breathing (SDB) testing and appropriate management. [4] Undiagnosed and thus untreated SDB reduces success rates of heart rhythm control strategies and contributes to progression of AF. [4] SDB has been reported to be present in up to 70% of patients in systematically screened AF populations. However, clinically, SDB is largely underestimated, as most AF patients report low daytime sleepiness levels, which often precludes them from being investigated for the potential presence of concomitant SDB. [5] Moreover, as shown by a recent survey by the European Heart Rhythm Association (EHRA) and the Association of Cardiovascular Nurses and Allied Professions (ACNAP), structured testing for SDB only occurs in the minority of AF patients due to the fact that access to polysomnography (PSG) in a sleep laboratory as well as the reference method for SDB diagnosis is limited due to long waiting lists, high labor intensity and high costs. [6] Several home SDB testing solutions have shown to be an inexpensive, reliable and sensitive alternative technologies to PSG in a sleep laboratory, but implementation of SDB testing and management in a remote AF sleep clinic pathway has not been achieved, yet.

The goal of this VIRTUAL-SAFARI (A VIRTUAL Sleep Apnea management pathway For the workup of Atrial fibrillation patients in a digital Remote Infrastructure) study was (1) to describe the implementation of a digital SDB management pathway via a virtual sleep laboratory into existing pre-ablation workup in two AF outpatient clinic infrastructures in the Netherlands and (2) to examine the utility, feasibility and patient satisfaction of this new approach to detect and manage SDB in AF patients scheduled for AF ablation.

METHODS

The new virtual SDB management pathway was introduced in the Maastricht University Medical Center+ (MUMC+; Maastricht, the Netherlands) and in the Radboud University Medical Center (Radboudumc, Nijmegen, the Netherlands) in collaboration with The Netherlands Sleep Institute (in Dutch: Het Nederlands Slaap Instituut, Amersfoort, the Netherlands) in October 2020. SDB testing was prospectively performed in all patients who visited the AF ablation workup care pathway in the two participating centers, unless they had known SDB which was effectively treated.

Study design and population

All consecutive patients with symptomatic paroxysmal or persistent AF accepted for AF ablation in the participating centers were prospectively enrolled. Patients were referred for SDB screening, unless they had a) previously diagnosed with and/or treated for SDB, b) completed a negative SDB test, c) underwent SDB testing elsewhere with pending results or d) refused to undergo SDB. Importantly, no screening questionnaires or patient characteristics were used to increase pre-test probability for patient selection. This VIRTUAL-SAFARI study is part of the prospective ISOLATION (ClinicalTrials.gov identifier: NCT04342312) and 'clinical electrophysiology registry of MUMC+ and Radboudumc' studies. The studies were approved by the ethical review board MUMC+/Maastricht University (UM) (NL number: 70787.068.19 / METC number: 19-052) and complied with the Declaration of Helsinki. All participants provided written informed consent.

Virtual SDB management pathway

In the participating centers, all patients awaiting AF ablation are educated on the impact of concomitant SDB, amongst other cardiovascular comorbidities and risk factors, on heart rhythm and symptom control. In addition, the potential benefits of SDB treatment on AF ablation success rates are discussed. Subsequently, patients are informed about the virtual SDB pathway, which consists of the following steps: patient education, digital referral to virtual sleep laboratory, home sleep test, results and data submission, virtual consultation, and treatment. The virtual SDB pathway is overseen by a case manager, who keeps track of the progress of the referral process and ensures implementation of the results and treatment decision in the electronic patient systems.

The pathway is summarized in *Figure 1*. A (tele-)consultation between patient and electrophysiologist is performed to discuss SDB (step 1). After this, a digital referral to the collaborating sleep physicians from The Netherlands Sleep Institute is initiated (step 2). Three to five days later, a portable home sleep test is sent to patients (step 3). Patients who have a smartphone available receive the disposable WatchPAT-ONE, whereas patients without smartphone use the non-disposable WatchPAT 300. The WatchPAT devices includes a wrist device that is utilizing a plethysmography-based finger-mounted probe that measures the peripheral arterial tone (PAT) signal (which reflects indirectly the level of sympathetic activation) and oxygen saturation (*Supplement 1*). That information is used as a proxy for respiratory disturbances and overnight sleep. A chest sensor records snoring, body position and the chest movement signals. The WatchPAT-ONE incorporates the same algorithm and technology as the WatchPAT model 300, which exerted a sensitivity and specificity of 85-89.1% and 63-76.9% respectively, versus PSG for diagnosing sleep apnea according to the new American Academy of Sleep Medicine (AASM) scoring criteria using a threshold of apnea-hypopnea index (AHI) ≥ 15. [7-10] WatchPAT was specifically validated in AF patients. [9] Patients that receive the WatchPAT-ONE are instructed to download the WatchPAT application on their mobile phone, which contains SDB educational materials and video instructions for the use of the device. The device is activated after Bluetooth pairing with the mobile phone. Patients use this device for one night (step 3). For WatchPAT-ONE users, the sleep recording is automatically transferred to a secured cloud (CloudPAT) and is directly accessible for the sleep physician (step 4).

Patients that use the WatchPAT 300 return the device to The Netherlands Sleep Institute via post mail. The recordings are automatically downloaded from the Web Server and analyzed in an offline procedure using the "zzzPAT" software that utilizes automatic algorithms to detect respiratory and sleep stages and awakenings. Once the results of the home sleep testing device are available, a virtual consultation (tele- or video consultation) between the sleep physician and the patient is organized to discuss results and management (step 5). The sleep report and the patient records are shared via a secured cloud between a sleep physician and the treating cardiologist. Complex cases can be further discussed in a video conference or via mail in a digital multidisciplinary team meeting. When applicable, treatment recommendations for positive airway pressure devices, sleep position trainer or mandibular repositioning appliance are digitally referred to a home care provider (step 6). In general, mandibular repositioning appliance and sleep position trainer (in case of

positional obstructive sleep) is preferred in mild or moderate SDB, while PAP is preferred in severe SDB. The home care provider visits the patients at home and initiates the fitting and adjustment of the treatment provides adequate training according to the digital prescription by the sleep physician.

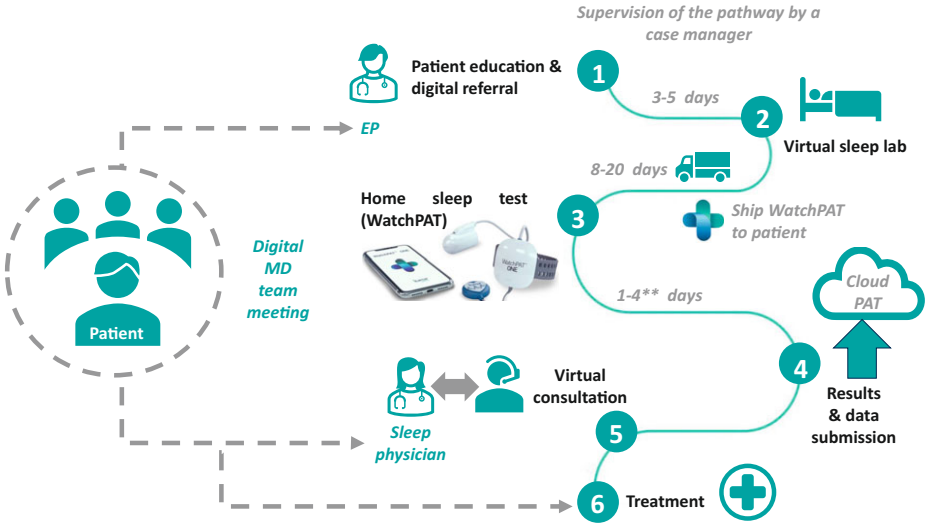

Figure 1. Structure of the virtual sleep apnea management pathway.

A teleconsultation between patient and electrophysiologist (EP) (1) to inform and discuss sleep-disordered breathing (SDB). After this, a digital referral (2) to a virtual sleep lab is initiated. 3-5 days later, the patient receives a disposable WatchPAT device, including instructions and video material on the correct use (3). After activation and use of the device, the recording is submitted to a secured cloud (4). The data can be viewed and discussed by EP and sleep physician within a multidisciplinary team meeting (5). If SDB is diagnosed, a digital prescription is sent by the sleep physician to a home care provider to initiate SDB treatment (6). The pathway is supervised by a case manager.

Analysis of sleep recordings

A minimum of four hours valid recording time was required. WatchPAT data were analyzed by a validated algorithm and reviewed by a certified sleep physician according to methods described in the American Academy of Sleep Medicine manual for the scoring of sleep and associated events.[11] The WatchPAT device detects respiratory events by the detection of sympathetic activations and concomitant oxygen desaturations.[7-10] The number of obstructive and central apneas was recorded.[7] If the proportion of central apneas over the total number of apneas equaled or exceeded 50%, these patients were considered to have predominant central sleep apnea. The number of hypopneas was determined, but not further differentiated. The WatchPAT derived AHI (pAHI) was calculated as the total number of apneas

plus hypopneas divided by the total sleep time. SDB-severity was determined according to the following pAHI categories: pAHI 5 to <15, mild SDB; pAHI 15 to <30, moderate SDB; pAHI≥30, severe SDB; pAHI≥15, moderate-to-severe SDB.

Patient characteristics

AF was confirmed by at least one 12-lead electrocardiogram (ECG) documentation. Type of AF was defined according to the AF guideline of the European Society of Cardiology. [12] Demographic and anthropometric data were collected at the time of referring the patients to the virtual sleep lab for all patients and included age, sex, and body mass index (BMI). AF type, symptom severity as well as associated treatment (anticoagulation, antiplatelet therapy, antiarrhythmic therapy and cardiovascular drugs) were retrieved from medical records. Clinical risk factors were actively screened and included the presence of congestive heart failure (defined in accordance with the ESC heart failure guidelines [13]) hypertension, type 2 diabetes mellitus (or impaired glucose tolerance), thromboembolic events (stroke or transient ischemic attack or peripheral thromboembolism), vascular disease (coronary and/or peripheral artery disease and/or aortic plaque), hypercholesterolemia, dementia assessed based on Montreal Cognitive Assessment (MoCA) questionnaire and the CHA_2DS_2-VASc score was calculated accordingly.

Patient experience and knowledge survey

We conducted a patient experience and knowledge survey which encompassed a 5-scale Likert questionnaire with five questions (in Dutch) regarding sleep apnea knowledge (English translation: "It has been known to me for some time that SDB is relevant for the treatment of AF."), satisfaction on remote management ("I liked being able to complete the SDB test at home, instead of in a sleep center."), installation of the app ("The instruction, consisting of the manual and the video, was helpful."), ease of use ("Using the WatchPAT-ONE was easy."), and willingness to use the app in the future ("I would recommend using the WatchPAT-ONE for SDB testing in the AF clinic in the future.").

Statistical analysis

All continuous variables were tested for normality with the Kolmogorov-Smirnov test. Variables with normal distribution were expressed as mean ± standard deviation (SD). Nonparametric variables were expressed as median and interquartile range (IQR), and categorical variables as counts (n) with percentages (%). Fisher's exact test (two group comparison) or Chi-square test (three or more group comparison) were used to compare categorical

variables. Differences in continuous parameters were compared using Mann-Whitney U test (two group comparison) or Kruskal-Wallis test (three groups comparison) in case of nonparametric variables and unpaired t-test (two group comparison) or ANOVA (three groups comparison) in case of parametric variables. A two-sided p value of 0.05 was considered statistically significant. For database management and statistical analysis, we used SAS Institute Inc. 2015. SAS/IML® 14.1 User's Guide. Cary, NC: SAS Institute Inc.

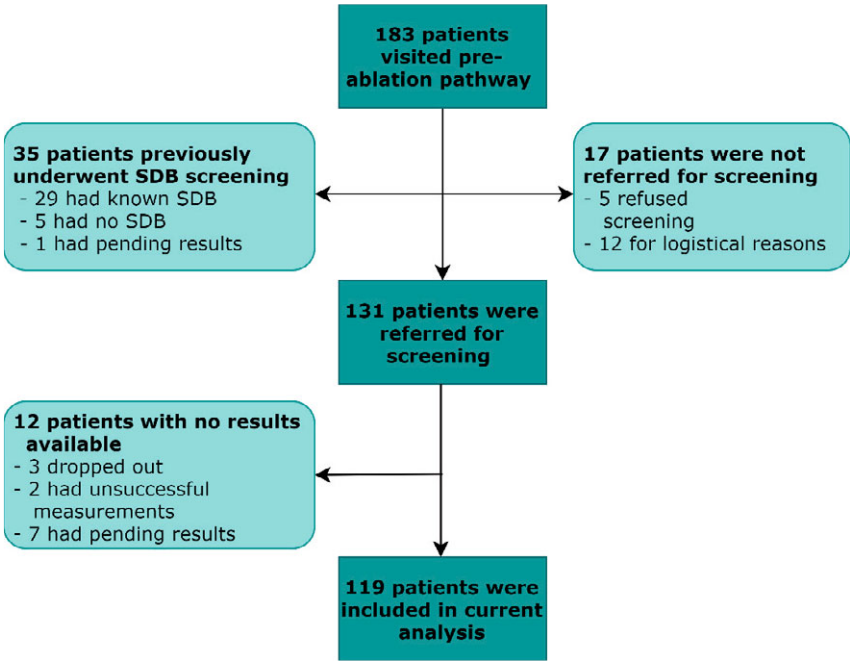

Figure 2. Study flow-chart.
Abbreviations: SDB: sleep disordered breathing.

RESULTS

Study population

From October 2020 until February 2021, a total of 183 patients visited the pre-ablation workup pathway in the participating centers and were included in the ISOLATION study or EFO registry (125 from MUMC and 58 from Radboudumc). 131 patients were referred to the virtual sleep lab. Twenty-nine patients had previously diagnosed and/or treated SDB, 5 patients had recently completed a negative SDB test and 1 patient underwent SDB testing elsewhere with pending results. Seventeen patients were not referred for screening (5 patients refused

SDB testing, 12 patients for logistical reasons). In May 2021, 7 of the 131 referred patients had not completed the pathway, yet. Five patients dropped out or had unsuccessful measurements. The results of the remaining 119 patients who completed the pathway were included in the current analysis. A study flow-chart is provided in *Figure 2*.

Results of sleep assessment

Of the 119 patients recruited (55% males; mean age 65 ± 9.5 years), 65 (55%) were diagnosed with moderate-to-severe SDB (*Figure 3*). Conversely, moderate-to-severe SDB was reported in only 9% (12 of 131) of patients who completed the pre-ablation work-up during the 5 months before the initiation of the virtual SDB pathway, while characteristics of the two groups were comparable (*Supplements 2 and 3*).

Patients' characteristics of the screened cohort and comparisons between patients with vs without diagnosed moderate-to-severe SDB are presented in *Table 1*. Patients with moderate-to-severe SDB diagnosis were more obese (BMI 29 ± 3.3 vs 27 ± 4.4, $p < 0.01$), had higher thromboembolic risk assessed via CHA_2DS_2-VASc score (median 2 (1-3) vs 1 (1-2), $p = 0.02$) and were prescribed with higher number of cardiovascular drugs, primarily renin-angiotensin inhibitors as compared to those without SDB diagnosis.

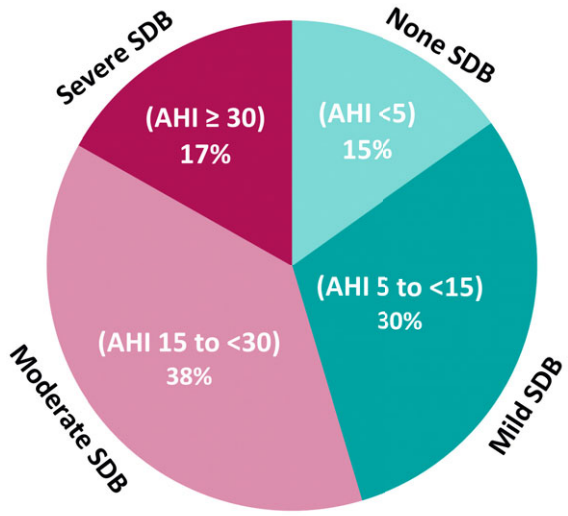

Figure 3. Distribution of patients with diagnosed sleep disordered breathing via WatchPAT.
Abbreviations: AHI: apnea-hypopnea index, SDB: sleep disordered breathing.

Table 1. Baseline characteristics of study population (n=119).

Variable	Overall (n=119)	None and mild SDB (n=54)		Moderate-to-severe SDB (n=65)		p value
		None (AHI <5) (n=18)	Mild (AHI 5 to <15) (n=36)	Moderate (AHI 15 to <30) (n=45)	Severe (AHI ≥30) (n=20)	
Demographics						
Age	65±9.5	63±11		66±7.6		0.09
		63±11	62±11	66±7.8	67±7.3	
Males	65 (55%)	6 (33%)	22 (61%)	26 (58%)	11 (55%)	0.71
BMI (kg/m^2)	28±4.0	27±4.4		29±3.3		<0.01
		25±2.7 [1]	27±4.8 [1]	28±3.2 [1]	30±3.2 [1]	
BMI≥25 kg/m^2	88 (74%)	9 (50%)	23 (64%)	38 (84%)	18 (90%)	<0.01
BMI≥30 kg/m^2	30 (25%)	0 (0%) [1]	8 (22%) [1]	13 (29%)	9 (45%)	0.02
Atrial fibrillation						
Paroxysmal	85 (72%) n=118	16 (89%)	26 (74%)	34 (76%) [1]	9 (47%) [1] n=19	0.22
Persistent	33 (28%) n=118	2 (11%)	10 (28%)	11 (24%) [1]	10 (53%) [1] n=19	
Symptom intensity						0.50
EHRA I	4 (3.4%)	1 (5.6%)	0 (0%)	2 (4.8%)	1 (5.0%)	
EHRA II	69 (58%)	8 (44%)	26 (72%)	23 (55%)	11 (55%)	
EHRA III	46 (39%)	9 (50%)	10 (28%)	17 (40%)	8 (40%)	
Medical history						
CHA_2DS_2-VASc score	2 [1-3]	1.0 [1.0-2.0]		2.0 [1.0-3.0]		0.02
		1.5 [1.0-3.0]	2.0 [1.0-2.0]	2.0 [1.0-3.0]	3.0 [1.5-3.5]	

Table 1. Baseline characteristics of study population (n=119). (continued)

Variable	Overall (n=119)	None and mild SDB (n=54)		Moderate-to-severe SDB (n=65)		p value
		None (AHI <5) (n=18)	Mild (AHI 5 to <15) (n=36)	Moderate (AHI 15 to <30) (n=45)	Severe (AHI ≥30) (n=20)	
CHA_2DS_2-VASc ≥3 (female), ≥2 (male)	56 (47%)	7 (39%)	13 (36%)	21 (50%)	13 (65%)	0.06
Congestive heart failure	17 (14%)	0 (0%)	2 (5.7%)	8 (18%)	7 (35%)	<0.01
Hypertension	47 (40%)	5 (28%)	10 (28%)	21 (47%)	11 (55%)	0.02
Diabetes	9 (7.6%)	2 (11%)	3 (8.3%)	1 (2.2%)	3 (15%)	0.73
Thromboembolic events	13 (11%)	0 (0%)	3 (8.3%)	7 (16%)	3 (15%)	0.14
Vascular disease	10 (8.4%)	1 (5.6%)	3 (8.3%)	3 (6.7%)	3 (15%)	1.00
Hypercholesterolemia	20 (17%)	0 (0%)	6 (17%)	10 (22%)	4 (20%)	0.15
Dementia (MoCA <26)	46 (42%) n=109	7 (41%) n=17	12 (40%) n=30	17 (39%) n=44	10 (56%) *n=18*	0.85
MoCA score	26±2.5 n=109	26±2.9 n=47		26±2.1 n=62		0.12
		26±3.6 n=17	27±2.3 n=30	26±2.0 n=44	25±2.2 n=18	
Cardiovascular drugs						
0-1	13 (11%)	5 (28%)	5 (14%)	3 (6.7%)	0 (0%)	0.02
2-3	63 (53%)	8 (44%)	25 (69%)	23 (51%)	7 (35%)	0.14
≥4	43 (36%)	5 (28%)	6 (17%)	19 (42%)	13 (65%)	<0.01
Beta-blockers	56 (47%)	4 (22%)	14 (39%)	27 (60%)	11 (55%)	<0.01
Digitalis	7 (5.9%)	1 (5.6%)	2 (5.6%)	1 (2.2%)	3 (15%)	1.00
Antiarrhythmic drugs	76 (64%)	13 (72%)	21 (61%)	28 (62%)	13 (65%)	1.00

Table 1. Baseline characteristics of study population (n=119). (continued)

Variable	Overall (n=119)	None and mild SDB (n=54)		Moderate-to-severe SDB (n=65)		p value
		None (AHI <5) (n=18)	Mild (AHI 5 to <15) (n=36)	Moderate (AHI 15 to <30) (n=45)	Severe (AHI ≥30) (n=20)	
RAS inhibitors	49 (41%)	4 (22%)	10 (28%)	23 (51%)	12 (60%)	<0.01
MRA	1 (0.8%)	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	1.00
Diuretics	15 (13%)	1 (5.6%)	4 (11%)	4 (8.9%)	6 (30%)	0.41
CCB	9 (7.6%)	1 (5.6%)	1 (2.8%)	3 (6.7%)	4 (20%)	0.18
Statins	41 (34%)	5 (28%)	9 (25%)	20 (44%)	7 (35%)	0.08
Vasodilators	5 (4.2%)	1 (5.6%)	1 (2.8%)	2 (4.4%)	1 (5.0%)	1.00
VKA	4 (3.4%)	0 (0%)	0 (0%)	3 (6.7%)	1 (5.0%)	0.13
NOAC	107 (90%)	17 (94%)	30 (83%)	41 (91%)	19 (95%)	0.37
APT drugs	1 (0.8%)	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	1.00
Other	1 (0.8%)	0 (0%)	0 (0%)	0 (0%)	1 (5.0%)	1.00

Number provided in italic indicates the total number of patients available for that variable.

P-value is given for comparison between patients with none/mild SDB vs moderate-to-severe SDB.

[1] denotes a statistically significant difference ($p < 0.05$) between subgroups of patients within none and mild SDB (AHI<5 vs AHI 5 to <15) and moderate-to-severe SDB (AHI 15 to <30 vs AHI ≥30).

Abbreviations: AHI: apnea-hypopnea index, APT: antiplatelet, BMI: body mass index, CCB: calcium channel blocker, MoCA: Montreal Cognitive Assessment, MRA: mineralocorticoid receptor antagonist, NOAC: non-vitamin K antagonist oral anticoagulant, RAS: renin-angiotensin system, SDB: sleep disordered breathing, TIA: transient ischemic attack.

Most patients diagnosed with moderate-to-severe SDB showed predominant obstructive sleep apnea, with a very low median central apnea index of 1.6 (0.7-3.3). Number of central apneas are low ranging from 0 [0-0.2] in none SDB, 0.3 [0-0.6] in mild SDB, 1.3 [0.5-2.7] in moderate SDB to 3.0 [1.1-7.2] per hour during overall sleep time in severe SDB.

Mean study time and sleep time were 490 ± 59 and 414 ± 66 minutes, respectively, with a median of 22 (19-32) minutes of sleep latency and from 6 to 12 awakenings during the overall sleep duration (*Table 2*). Not surprisingly, the pAHI, the respiratory disturbance index and the oxygen desaturation indices were higher in patients with compared to patients without moderate-to-severe SDB. Statistically significant differences were observed in mean desaturation nadir and time spent with oxygen saturation below 90% that increased with SDB severity. Pulse rate was comparable between patients with and without SDB.

One hundred thirteen (95%) patients were managed completely remotely by the WatchPAT-ONE device. The remaining patients were managed by the WatchPAT 300. For sensitivity analysis purposes, the results of sleep assessment excluding WatchPAT 300 are provided in *Supplement 4* and showed no statistically significant difference between those subgroups.

Time to sleep study results

The median time from digital referral from the AF clinic to finalization of the sleep study report was 18 (11-24) days. The time to the sleep study results was mainly determined by the time of device delivery which took a median of 14 (8-20) days. Once the device arrived at the patient´s home, it was used within a median time of 2 (1-4) days. No statistically significant difference concerning the time to sleep study results was observed between patients with and without SDB recognition (*Table 2*). By comparing patients according to sex (female vs male), thromboembolic risk (low vs high), number of prescribed cardiovascular drugs (0-1 vs 2-3 vs 4-7) groups, no statistically significant differences were observed regarding particular times (to delivery/analysis and sleep study results). However, older patients needed more time to performed sleep analysis. Interestingly, sexagenarians needed less time to perform sleep analysis than younger patients. Importantly, irrespective on cognitive status assessed by MoCA) questionnaire, there was not statistically significant difference in time to sleep study results between patients with cognitive impairment (MoCA <26) and with normal cognitive function (MoCA≥26) (*Table 3*).

Table 2. Sleep statistics according to diagnosed sleep disordered breathing (n=119).

Variable	Overall (n=119)	None and mild SDB (n=54)		Moderate-to-severe SDB (n=65)		p value
		None (AHI <5) (n=18)	Mild (AHI 5 to <15) (n=36)	Moderate (AHI 15 to <30) (n=45)	Severe (AHI ≥30) (n=20)	
WatchPAT model 300	6 (5.0%)	0 (0%)	2 (5.6%)	3 (6.7%)	1 (5.0%)	0.69
Time to diagnosis[3] (days)		18 [11-23] *(n=46)*		18 [11-24] *(n=52)*		0.99
	18 [11-24] n=98	12 [10-23] n=15	18 [13-27] n=31	18 [11-23] n=35	20 [15-27] n=17	
Time to delivery[4] (days)		13 [9.0-21] *(n=46)*		16 [7.5-20] *(n=52)*		0.91
	14 [8.0-20] n=98	10 [7.0-20] n=15	14 [9.0-21] *n=31*	16 [6.0-19] n=35	15 [9.0-24] n=17	
Time to analysis[5] (days)		3.0 [1.0-5.0] *(n=50)*		2.0 [1.0-4.0] *(n=56)*		0.67
	2.0 [1.0-4.0] n=106	2.5 [1.0-4.5] n=16	3.0 [1.0-5.0] n=34	2.0 [1.0-4.0] n=37	3.0 [2.0-4.0] n=19	
Sleep architecture						
Recording time (min)		485±52 *(n=50)*		495±64 *(n=56)*		0.34
	490±59 n=106	500±46 n=16	478±54 n=34	481±62 n=37	522±60 n=19	
Sleep time (min)		410±60		417±71 *(n=61)*		0.82
	414±66 n=115	428±64	401±57	406±63 n=41	443±83 n=19	
Sleep latency (min)		22 [19-33] *(n=50)*		20 [16-31] *(n=56)*		0.14
	22 [19-32] n=106	21 [19-28] n=16	22 [19-36] n=34	22 [18-31] n=37	19 [16-22] n=19	
Awakenings		7.5 [5.0-10] *(n=50)*		9.0 [7.0-14] *(n=56)*		0.01
	9 [6-12] n=106	7.0 [5.0-10] n=16	8.0 [5.0-10] n=34	8.0 [6.0-11][2] n=37	12 [9.0-17][2] n=19	

Table 2. Sleep statistics according to diagnosed sleep disordered breathing (n=119). (continued)

Variable	Overall (n=119)	None and mild SDB (n=54)		Moderate-to-severe SDB (n=65)		p value
		None (AHI <5) (n=18)	Mild (AHI 5 to <15) (n=36)	Moderate (AHI 15 to <30) (n=45)	Severe (AHI ≥30) (n=20)	
Sleep study results[6]						
pRDI[7]	20 [13-29] n=106	13 [7.6-16] *(n=50)* 7.2 [3.9-9.7] [2] n=16	14 [11-17] [2] n=34	28 [23-39] *(n=56)* 25 [20-28] [2] n=37	44 [38-51] [2] n=19	<0.01
pAHI[7]	17 [8.1-25] n=115	7.5 [3.8-11] 3.1 [1.5-3.8] [2]	9.3 [7.5-12] [2]	24 [19-34] 21 [18-24] [2]	43 [37-50] [2]	<0.01
pAHI central	0.6 [0.1-2.1] n=106	0.2 [0-0.5] *(n=50)* 0 [0-0.2] [1] n=16	0.3 [0-0.6] [1] n=34	1.6 [0.7-3.3] *(n=56)* 1.3 [0.5-2.7] [1] n=37	3.0 [1.1-7.2] [1] n=19	<0.01
ODI	6.4 [1.7-11] n=118	1.7 [0.8-2.9] 0.6 [0.3-1.0] [2]	2.6 [1.6-3.8] [2]	10 [7.6-17] *(n=64)* 8.7 [6.6-11] [2] n=44	22 [16-26] [2]	<0.01
Mean of desaturation nadirs (%)	92 [91-93] n=115	92 [92-93] 92 [92-93]	92 [92-93]	91 [91-92] *(n=61)* 91 [91-92] n=41	91 [90-92]	<0.01
Oxygen saturation<90% of sleep time (min)	0.2 [0-1.5] n=108	0 [0-0.2] *(n=51)* 0 [2] n=17	0 [0-0.3] [2] n=34	0.9 [0.2-4.8] *(n=57)* 0.3 [0.1-1.4] [2] n=38	7.0 [0.9-16] [2] n=19	<0.01
Oxygen saturation<90% of sleep time (%)	0 [0-0.5] n=116	0 0 [1]	0 [0-0.1] [1]	0.2 [0-1.2] *(n=62)* 0.1 [0-0.5] [2] n=42	1.2 [0.2-2.8] [2]	<0.01

Table 2. Sleep statistics according to diagnosed sleep disordered breathing (n=119). (continued)

Variable	Overall (n=119)	None and mild SDB (n=54)		Moderate-to-severe SDB (n=65)		p value
		None (AHI <5) (n=18)	Mild (AHI 5 to <15) (n=36)	Moderate (AHI 15 to <30) (n=45)	Severe (AHI ≥30) (n=20)	
Pulse rate statistics						
Mean (bpm)		59 [54-69] *(n=50)*		59 [53-72] *(n=56)*		0.65
	59 [53-70] n=106	67 [60-76] [2] n=16	57 [53-61] [2] n=34	56 [52-63] n=37	67 [54-75] n=19	
Maximal (bpm)		96 [87-110] *(n=50)*		92 [83-110] *(n=56)*		0.32
	93 [84-110] n=106	99 [89-118] n=16	93 [85-109] n=34	88 [83-104] n=37	98 [85-111] n=19	

Number provided in italic indicates the total number of patients available for that variable.

P value is given for comparison between patients with none/mild SDB vs moderate-to-severe SDB.

[1] denotes a statistically significant difference (p < 0.05) between subgroups of patients within none and mild SDB (AHI<5 vs AHI 5 to <15) and moderate-to-severe SDB (AHI 15 to <30 vs AHI ≥30).

[2] denotes a statistically significant difference (p < 0.01) between subgroups of patients within none and mild SDB (AHI<5 vs AHI 5 to <15) and moderate-to-severe SDB (AHI 15 to <30 vs AHI ≥30).

[3] from patient registration to SDB diagnosis.

[4] from patient registration to first time device usage.

[5] from first time device usage to SDB diagnosis.

[6] calculated using valid sleep time.

[7] calculated using oxygen desaturations ≥3%.

Abbreviations: AHI, apnea-hypopnea index; bpm, beat per minute; ODI, oxygen desaturation index; RDI, respiratory disturbance index; SDB, sleep disordered breathing

Although the digital SDB testing approach does not include a real-time attended supervision, the results showed that only a small number of patients had problems with receiving proper recordings (6 of 125 patients), most of the times due to an incorrect connection of the device (3 of 6 patients) or due to disconnection of sensors (3 of 6 patients). In four cases, WatchPAT recordings were successfully repeated. Until May 2021, only two patients with invalid WatchPAT recordings were sent to in-laboratory PSG.

Table 3. Time to delivery, analysis and diagnosis according to selected factors.

Variable	Time to diagnosis (days)[2] n=98	Time to delivery (days)[3] n=98	Time to analysis (days)[4] n=106
Age (years)			
<60	18 [11-25]; *n=28*	16 [8.0-21]; *n=28*	2.0 [1.0-4.0][1]; *n=31*
60-69	18 [12-23]; *n=34*	15 [9.0-23]; *n=34*	1.0 [1.0-3.0][1]; *n=37*
≥70	16 [11-23]; *n=36*	10 [7.0-19]; *n=36*	4.0 [2.0-7.0][1]; *n=38*
Male	18 [11-23]; *n=51*	14 [9.0-20]; *n=51*	2.0 [1.0-4.0]; *n=56*
Female	18 [11-24]; *n=47*	14 [8.0-21]; *n=47*	3.0 [1.0-5.0]; *n=50*
CHA_2DS_2-VASc			
low risk[5]	18 [11-23]; *n=53*	14 [7.0-21]; *n=53*	2.0 [1.0-4.0]; *n=56*
high risk[6]	18 [11-24]; *n=45*	14 [9.0-20]; *n=45*	3.0 [1.0-5.0]; *n=50*
MoCA score			
<26	14 [11-20][1]; *n=40*	9.0 [6.0-17][1]; *n=40*	3.0 [1.0-6.0]; *n=42*
≥26	18 [13-25][1]; *n=52*	16 [9.5-21][1]; *n=52*	2.5 [1.0-4.0]; *n=57*
Cardiovascular drugs			
0-1	17 [11-23]; *n=10*	12 [9.0-18]; *n=10*	2.0 [2.0-7.0]; *n=11*
2-3	18 [11-22]; *n=50*	13 [8.0-20]; *n=50*	2.0 [1.0-4.0]; *n=55*
4-7	19 [13-27]; *n=38*	15 [9.0-24]; *n=38*	3.0 [1.0-6.0]; *n=40*

Number provided in italic indicates the total number of patients available for that variable.

[1] denotes a statistically significant difference ($p < 0.05$) within each group (age<60 vs 60-69 vs >70; male vs female, low vs high thromboembolic risk assessed by CHA2DS2-VASc score; MoCA <26 vs >26; cardiovascular drugs 0-1 vs 2-3 vs 4-7).

[2] from patient registration to SDB diagnosis.

[3] from patient registration to first time device usage.

[4] from first time device usage to SDB diagnosis.

[5] low risk means CHA2DS2-VASc <3 (if female), <2 (if male).

[6] high risk means CHA2DS2-VASc >3 (if female), >2 (if male).

Abbreviations: MoCA: Montreal Cognitive Assessment.

Treatment recommendations

Based on the result of the WatchPAT recordings, PAP treatment was recommended in 25%, sleep position trainer was recommended in in 5% and a mandibular repositioning appliance was recommended in 15% of patients (*Figure 4*). In 14% of patients, multiple therapy options were advised, whereas in 23% of patients the type of treatment recommendation was not decided on, yet. One in six patients (16%), majority in AHI<5 group, no further treatment was recommended.

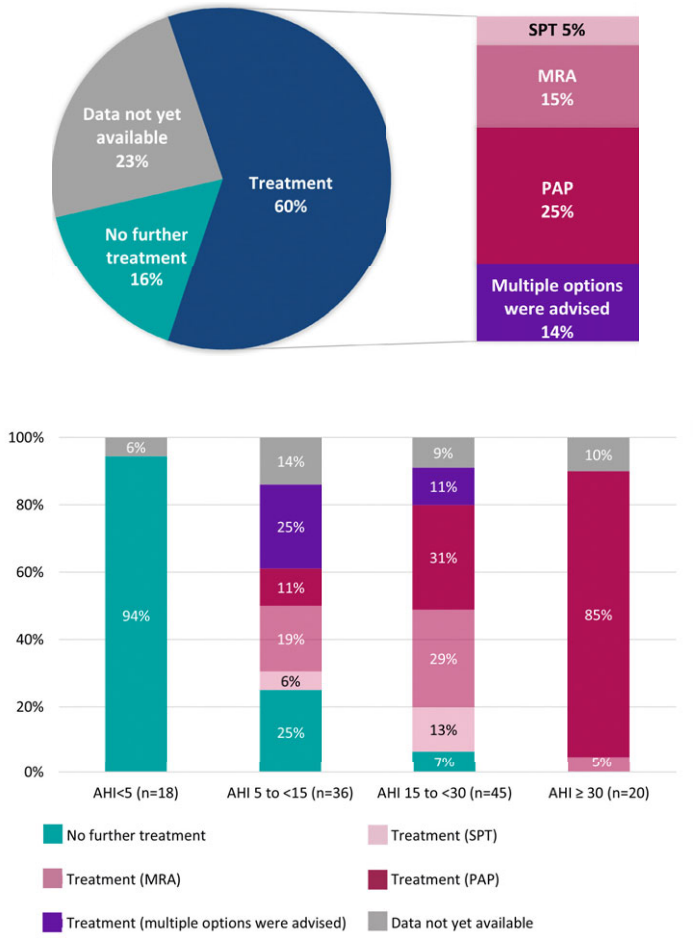

Figure 4. Sleep apnea treatment (n=111).

Abbreviations: AHI: apnea-hypopnea index, PAP: positive airway pressure, MRA: mandibular repositioning appliances, SPT: sleep position trainer.

Patients experience and knowledge

Sixty-two percent of patients disagreed or strongly disagreed with the statement, that it has been known to them that SDB is relevant for the treatment of AF. The majority of patients liked being able to complete the sleeping test at home, instead of in a sleep center (95%). Patients agreed that the instruction, consisting of the manual and the video, was helpful (95%) and that WatchPAT-ONE was easy to use (91%). Eighty-six percent of the patients agreed or strongly agreed that they would recommend using the WatchPAT-ONE for SDB testing in the AF clinic in the future. The results of the patient experience survey are presented in *Figure 5*.

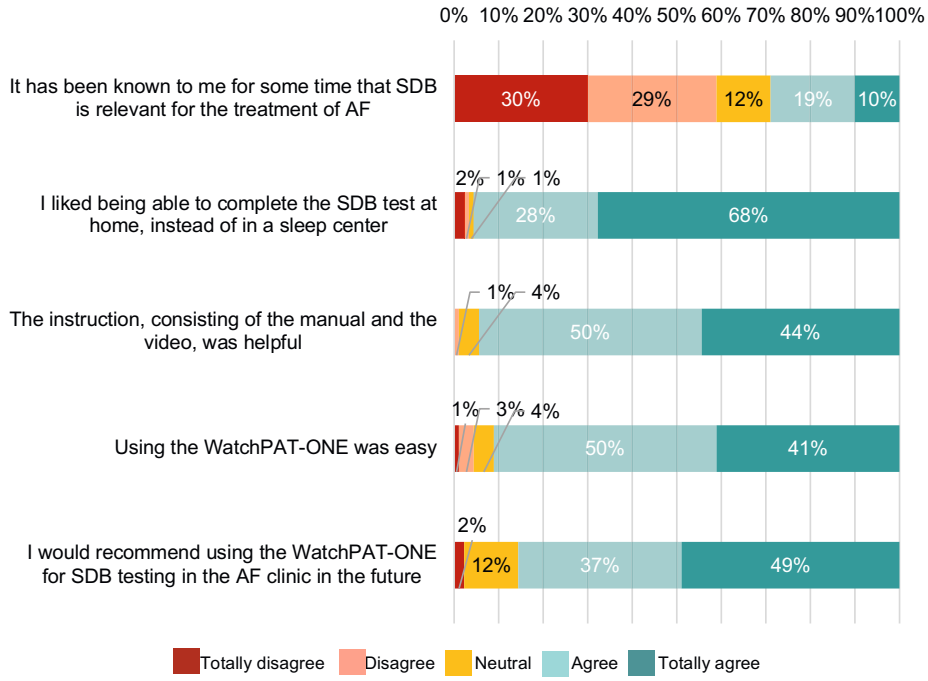

Figure 5. Survey: Patients experience and knowledge (n=88).
Abbreviations: AF: atrial fibrillation, SDB: sleep-disordered breathing.

DISCUSSION

Herein we describe a novel, innovative and completely remote digital SDB management pathway, which could be implemented in existing AF clinic infrastructures in two University hospitals in the Netherlands.

The reliability of the WatchPAT device, which was used for the digital remote SDB testing, has been previously validated against in-laboratory sleep testing. [7-10] The accuracy of the detection of SDB and the effective differentiation between central and obstructive SDB was comparable to PSG studies in a sleep laboratory. [7] According to the new SDB management guideline, the WatchPAT derived PAT information in combination with oximetry and actigraphy is "technically adequate" to diagnose SDB in patients likely to have the condition. [14] Previous studies comparing WatchPAT to PSG demonstrated a shorter time to diagnosis (21 days versus 79.8 days, $p < 0.001$). [15] In our remote approach of digital SDB testing via a virtual sleep lab, time to diagnosis was even shorter with a median of 18 days, maybe because of direct integration of the pathway in the existing pre-ablation outpatient clinic which prevents fragmentation and standardizes the management process.

Although the digital SDB testing and management approach does not include real-time attended supervision, the results showed that only a small number of recordings were invalid, most of the time due to an incorrect connection of the device. Importantly, elderly patients and those with cognitive decline (assessed by the MoCA questionnaire) were able to successfully use this infrastructure.

The use of a disposable home sleep testing device (e.g., WatchPAT-ONE) requires active involvement of patients in their treatment process, and it is crucial to instruct and empower patients to monitor their risk factors and to self-manage their condition. The herein discussed virtual sleep clinic setting aims to increase the patients' self-care by instructing them to monitor their sleep at home and provides vital data which contribute to determine the best possible treatment. As such, the patient could be considered an important member of the multidisciplinary team.

Interestingly, as shown by our patient experience and knowledge survey, the majority of patients were initially not aware that SDB may contribute to AF. Patient engagement and education prior to an AF ablation procedure during the teleconsultations initiated by the AF clinic or virtual sleep lab and by the manuals and videos provided by the WatchPAT app, allow to clarify the role of SDB management as part of a comprehensive AF management approach. This also leads to an informed decision towards the management of SDB and the planned AF ablation procedure and supports agreement of the patient to undergo SDB testing and adherence to SDB treatment afterwards. [16]

The treatment of concomitant risk factors, including SDB, is recommended in current AF ESC guidelines.[12] The herein discussed digital pathway includes a digital multidisciplinary team meeting via a shared cloud, where cardiologists and sleep physicians have access to the sleep reports and the patients' records to decide which patient should be treated and how. Importantly, patients showed predominant obstructive sleep apnea with very low central apnea indices and could be managed completely remotely based on the results of the WatchPAT-ONE device. An informed recommendation and initiation of SDB treatment was possible just based on the WatchPAT-ONE result without the need of more in-depth polysomnography characterization of SDB. During the follow-up appointments after the AF ablation procedure, adherence to SDB treatment and the occurrence of possible side-effects can be interrogated. In case of occurring problems, the patients can be digitally referred back to the virtual sleep lab.

An important advantage of ambulatory and remote pathways for SDB testing is the improved patient comfort compared to an overnight stay in a sleep laboratory.[17] In our patient experience survey, patients reported that WatchPAT-ONE was easy to use and that they would recommend use of this virtual SDB management pathway in the future. Additionally, remote AF management, including SDB testing within our virtual sleep management pathway, may provide AF patients the opportunity to receive an SDB diagnostic in a given time period and may thereby contribute to equity in AF care;[18] not just during the COVID-19 pandemic but also beyond.

This study is the first allowing the estimation of the impact of a structured SDB testing approach of consecutive patients, as conducted in our study, compared to standard of care, as conducted before the implementation of the virtual SDB pathway, on the increased detection of previously unknown SDB. Whether structured testing of SDB, early detection of SDB and earlier initiation of treatment is cost-effective needs to be investigated in further studies. Furthermore, whether the improved treatment of concomitant SDB will improve AF outcomes in patients undergoing catheter ablation remains unclear. Most of the available studies on this topic are either non-randomized or potentially underpowered to detect the true effect of CPAP treatment on AF recurrences.[19,20] To confirm the relationship between SDB and AF and the benefits of treatment of SDB, prospective randomized controlled trials on this topic are required and are on their way (SLEEP-AF: ACTRN12616000088448, A3: NCT02727192).

Limitations

This is the first completely remote SDB management pathway. However, this study may also have some limitations. First, although current SDB management guidelines[14] state that WatchPAT is an accepted alternative for polysomnography and can distinguish between obstructive and central apneas, just one validation study was performed specifically in AF patients.[7-10] Second, WatchPAT-ONE uses the same algorithm and sensor technology as WatchPAT 300, but studies using the WatchPAT-ONE device are limited. Third, patients who refused to undergo SDB testing were excluded. As there were only 5 patients who refused screening, the impact of this selection bias on the reported high positive patient experience should be limited. Fourth, this digital SDB management pathway was tested in AF patients scheduled for ablation only. Whether the pathway is of benefit in elderly AF patients or those with newly diagnosed AF without a scheduled elective ablation procedure warrants further study. Fifth, we implemented the digital pathway in only two centers. Whether the herein introduced virtual sleep lab approach can be upscaled even further needs to be tested in the future.[18] Sixth, to determine the definite effect of structured sleep apnea management within the herein presented virtual pathway on outcomes of AF ablation procedures requires future randomized clinical trials.

Conclusion

In the VIRTUAL-SAFARI study, a novel and innovative virtual SDB management pathway allowed completely remote SDB testing and management in AF outpatient clinics with a short time to diagnosis with a median of 16 days. In two AF outpatient clinics, the structured virtual SDB pathway detected previously unknown moderate-to-severe SDB in more than half of the consecutive patients. SDB treatment was initiated in the majority of AF patients with newly diagnosed SDB, and participating patients reported a high patient satisfaction level. Whether this virtual SDB management pathway also results in better rhythm control outcomes needs to be investigated in future randomized studies.

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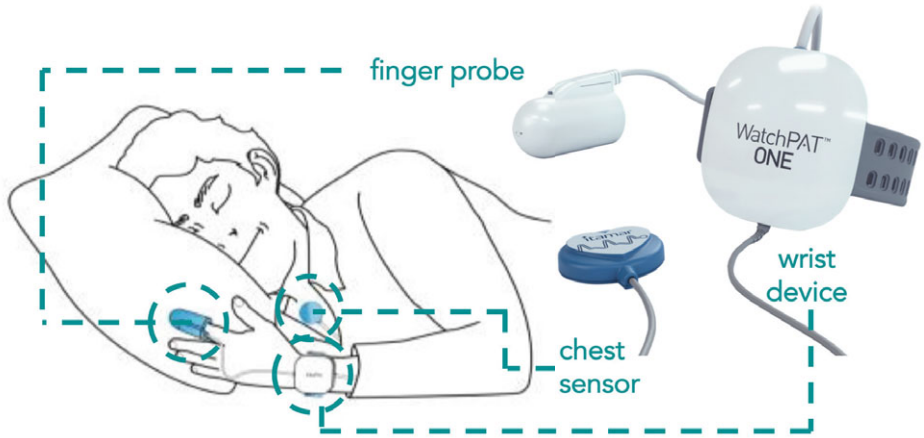
SUPPLEMENTS



Supplement 1. WatchPAT-ONE device

Supplement 2. Comparison between baseline characteristics of all consecutive patients managed through the pre-ablation pathway after vs. before the implementation of the virtual SDB pathway.

	Patients recruited between Oct '20 and Feb '21 (VIRTUAL-SAFARI) (n=183)	Patients recruited between May '20 and Sep '20 (Before VIRTUAL-SAFARI) (n=131)	P-value
Demographics			
Age	65±8.9	63±10	0.33
Males	112 (61%)	82 (63%)	0.81
BMI (kg/m^2)	28±4.1	28±4.7	0.80
BMI ≥25 kg/m^2	140 (77%)	98 (75%)	0.89
BMI ≥30 kg/m^2	48 (26%)	40 (31%)	0.44
Atrial fibrillation			
Paroxysmal	125 (69%)	88 (69%)	1.00
Persistent	57 (31%) n=182	39 (31%) n=127	
Symptom intensity			0.42
EHRA I	9 (5.0%)	2 (2.3%)	
EHRA II	100 (55%)	73 (56%)	
EHRA III	73 (23%)	54 (41%)	
EHRA IV	0 (0%)	1 (0.8%)	
Medical history			
CHA_2DS_2-VASc score	2.0 [1.0-3.0] n=182	2.0 [1.0-3.0]	0.44
CHA_2DS_2-VASc ≥3 (female), ≥2 (male)	96 (52%) n=182	63 (48%)	0.49
Congestive heart failure	37 (20%) n=182	17 (13%)	0.10
Hypertension	78 (43%)	57 (44%)	0.91
Diabetes	14 (7.7%)	10 (7.8%)	1.00
Thromboembolic events	22 (12%)	13 (9.9%)	0.59
Vascular disease	20 (11%)	22 (17%)	0.18
Hypercholesterolemia	38 (21%)	23 (18%)	0.56
Dementia (MoCA <26)	72 (43%) n=166	54 (51%) n=106	0.26
Cardiovascular drugs			
0-1	16 (8.7%)	13 (9.9%)	0.84
2-3	93 (51%)	70 (53%)	0.73
≥4	74 (40%)	48 (37%)	0.56

Supplement 2. Comparison between baseline characteristics of all consecutive patients managed through the pre-ablation pathway after vs. before the implementation of the virtual SDB pathway. (continued)

	Patients recruited between Oct '20 and Feb '21 (VIRTUAL-SAFARI) (n=183)	Patients recruited between May '20 and Sep '20 (Before VIRTUAL-SAFARI) (n=131)	P-value
Beta-blockers	89 (49%)	56 (43%) n=130	0.36
Digitalis	14 (7.7%)	11 (8.5%) n=130	0.83
Antiarrhythmic drugs	120 (66%)	93 (72%) n=130	0.27
RAS inhibitors	82 (45%)	47 (36%)	0.13
MRA	4 (2.2%)	2 (1.5%)	1.00
Diuretics	25 (14%)	16 (12%)	0.74
CCB	15 (8.2%)	7 (5.3%)	0.38
Statins	69 (38%)	41 (31%)	0.28
Vasodilators	6 (3.3%)	5 (3.8%)	1.00
VKA	8 (4.4%)	11 (8.5%) n=130	0.15
NOAC	165 (90%)	109 (84%) n=130	0.12
APT drugs	2 (1.1%)	3 (2.3%)	0.65
Other	4 (2.2%)	7 (5.3%)	0.21

Comparison between baseline characteristics of all consecutive patients managed through the pre-ablation pathway after (October 2020 - February 2021, n=183) and before the implementation of the virtual SDB pathway (May 2020 and September 2020, n=131).

Numbers provided in italic indicate the total number of patients available for that variable.

P value is given for comparison between patients visited pre-ablatio pathway and those recruited before the course of the study.

Abbreviations: AHI: apnea-hypopnea index, APT: antiplatelet, BMI: body mass index, CCB: calcium channel blocker, MoCA: Montreal Cognitive Assessment, MRA: mineralocorticoid receptor antagonist, NOAC: non-vitamin K antagonist oral anticoagulant, RAS: renin-angiotensin system, SDB: sleep disordered breathing, TIA: transient ischemic attack.

Supplement 3. Baseline characteristics of patients managed before the implementation of the VIRTUAL-SAFARI pathway.

Variable	Overall (n=131)	No moderate-to-severe SDB or never tested (n=119)	Moderate-to-severe SDB diagnosed (n=12)	P value
Age	63.2±10.0	63.2±9.9	63.2±12.0	0.99
Males	82 (63%)	73 (61%)	9 (75%)	0.53
BMI (kg/m^2)	28.1±4.7	28.0±4.6	30.1±5.6	0.23
CHA_2DS_2-VASc score	2	2	1	
Congestive heart failure	14 (11%)	13 (11%)	1 (8%)	1.00
Hypertension	56 (43%)	51 (43%)	5 (42%)	1.00
Diabetes mellitus	10 (8%)	9 (8%)	1 (8%)	1.00
Vascular disease	22 (17%)	20 (17%)	2 (17%)	1.00
Thromboembolic events	13 (10%)	12 (10%)	1 (8%)	1.00
Use of CPAP	6 (5%) n=130	N/A	6 (55%) n=11	
Smoking (current/ former)	71 (55%) n=128	65 (56%) n=116	6 (50%) n=12	
Hypercholesterolemia	23 (18%)	21 (18%)	2 (17%)	1.00
VKA	11 (9%) n=130	9 (8%) n=118	2 (17%) n=12	0.27
NOAC	109 (84%) n=130	101 (86%) n=118	8 (67%) n=12	0.10
APT drugs	3 (3%)	3 (0%)	0 (2%)	1.00
Beta-blockers	56 (43%) n=130	51 (43%) n=118	5 (42%) n=12	1.00
Digitalis	11 (9%) n=130	10 (9%) n=118	1 (8%) n=12	1.00
Antiarrhythmic drugs	93 (72%) n=130	86 (73%) n=118	7 (58%) n=12	0.32

Baseline characteristics of patients managed before the implementation of the VIRTUAL-SAFARI SDB management pathway (1 May – 30 September 2020, n=131). No moderate-to-severe SDB or never tested compared to moderate-to-severe SDB diagnosed based on available sleep study reports or the diagnosis list in the letter of the referring physician.

Abbreviations: APT: antiplatelet, BMI: body mass index, CPAP: continuous positive airway pressure, NOAC: non-vitamin K antagonist oral anticoagulant, SDB: sleep disordered breathing.

Supplement 4. Sleep statistics according to diagnosed sleep disordered breathing only by WatchPAT-ONE (n=113).

Variable	Overall (n=113)	None and mild SDB (n=52)		Moderate-to-severe SDB (n=61)		p value
		None (AHI <5) (n=18)	Mild (AHI 5 to <15) (n=34)	Moderate (AHI 15 to <30) (n=39)	Severe (AHI ≥30) (n=19)	
Time to diagnosis[3] (days)		18 [11-23] *(n=44)*		18 [11-23] *(n=48)*		0.87
	18 [11-23] n=92	12 [10-23] n=15	18 [13-23] n=29	18 [11-22] n=32	19 [13-26] n=16	
Time to delivery[4] (days)		13 [9.0-21] *(n=44)*		16 [7.5-19] *(n=48)*		0.90
	14 [8.5-20] n=92	10 [7.0-20] n=15	14 [9.0-21] *n=29*	16 [6.5-19] n=32	15 [9.0-22] n=16	
Time to analysis[5] (days)		3.0 [1.0-4.0] *(n=48)*		2.0 [1.0-4.0] *(n=52)*		0.54
	2.0 [1.0-4.0] n=100	2.5 [1.0-4.5] n=16	3.0 [1.0-4.0] n=32	1.0 [1.0-3.0][1] n=34	3.0 [2.0-4.0][1] n=18	
Sleep architecture						
Recording time (min)		489±48 *(n=48)*		495±63 *(n=52)*		0.48
	492±56 n=100	500±46 n=16	484±49 n=32	483±64 n=34	517±58 n=18	
Sleep time (min)		413±60 *(n=52)*		417±70 *(n=60)*		0.97
	415±65 n=109	428±64	405±56	407±64 n=38	437±81 n=18	
Sleep latency (min)		22 [19-34] *(n=48)*		20 [16-31] *(n=52)*		0.07
	20 [19-31] n=100	21 [19-28] n=16	23 [19-38] n=32	21 [17-31] n=34	19 [16-22] n=18	
Awakenings		8.0 [5.0-10] *(n=48)*		10 [7.0-14] *(n=52)*		0.01
	9.0 [6.0-11] n=100	7.0 [5.0-10] n=16	8.5 [5.5-10] n=32	8.0 [6.0-11][2] n=34	13 [10-17][2] n=18	

Supplement 4. Sleep statistics according to diagnosed sleep disordered breathing only by WatchPAT-ONE (n=113). (continued)

Variable	Overall (n=113)	None and mild SDB (n=52)		Moderate-to-severe SDB (n=61)		p value
		None (AHI <5) (n=18)	Mild (AHI 5 to <15) (n=34)	Moderate (AHI 15 to <30) (n=39)	Severe (AHI ≥30) (n=19)	
Sleep study results[6]						
pRDI[7]		13 [7.5-17] *(n=48)*		29 [24-39] *(n=52)*		<0.01
	20 [13-29] n=103	7.2 [3.9-9.7] [2] n=16	15 [12-17] [2] n=32	25 [20-28] [2] n=34	43 [38-51] [2] n=18	
pAHI[7]	17 [8.1-24] n=109	7.5 [3.7-11]		24 [19-34]		<0.01
		3.1 [1.5-3.8] [2]	9.3 [7.9-12] [2]	21 [18-24] [2]	42 [36-49] [2]	
pAHI central	0.6	0.2 [0-0.5] *(n=48)*		1.6 [0.7-3.3] *(n=52)*		<0.01
	[0.1-2.1] n=100	0 [0-0.2] [1] n=16	0.3 [0-0.7] [1] n=32	1.4 [0.5-2.7] [1] n=34	2.7 [1.1-6.7] [1] n=18	
ODI	6.4	1.7 [0.8-2.8]		10 [7.7-17]		<0.01
	[1.7-11] n=112	0.6 [0.3-1.0] [2]	2.6 [1.6-3.6] [2]	8.7 [6.9-11] [2]	22 [15-25] [2]	
Mean of desaturation nadirs (%)		92 [92-93]		91 [91-92] *(n=56)*		<0.01
	92 [91-93] n=109	92 [92-93]	93 [91-93]	91 [91-92] n=37	91 [90-92]	
Oxygen saturation<90% of sleep time (min)		0 [0-0.1] *(n=49)*		0.9 [0.2-4.8] *(n=53)*		<0.01
	0.2 [0-1.6] n=102	0 [2] n=17	0 [0-0.4] [2] n=32	0.3 [0.1-1.6] [2] n=35	5.2 [0.9-9.4] [2] n=18	
Oxygen saturation<90% of sleep time (%)		0		0.3 [0-1.2] *(n=57)*		<0.01
	0 [0-0.5] n=110	0 [1]	0 [0-0.1] [1]	0.1 [0-0.5] [2] n=38	0.9 [0.2-2.3] [2]	

Supplement 4. Sleep statistics according to diagnosed sleep disordered breathing only by WatchPAT-ONE (n=113). (continued)

Variable	Overall (n=113)	None and mild SDB (n=52)		Moderate-to-severe SDB (n=61)		p value
		None (AHI <5) (n=18)	Mild (AHI 5 to <15) (n=34)	Moderate (AHI 15 to <30) (n=39)	Severe (AHI ≥30) (n=19)	
Pulse rate statistics						
Mean (bpm)		59 [55-70] *(n=48)*		59 [53-71] *(n=52)*		0.44
	59 [53-70] n=100	67 [60-76] [2] n=16	57 [54-62] [2] n=32	56 [52-63] n=34	64 [54-74] n=18	
Maximal (bpm)		97 [88-111] *(n=48)*		92 [83-110] *(n=52)*		0.22
	93 [85-111] n=100	99 [89-118] n=16	94 [88-109] n=32	89 [82-104] n=34	97 [85-111] n=18	

Numbers provided in italic indicate the total number of patients available for that variable.

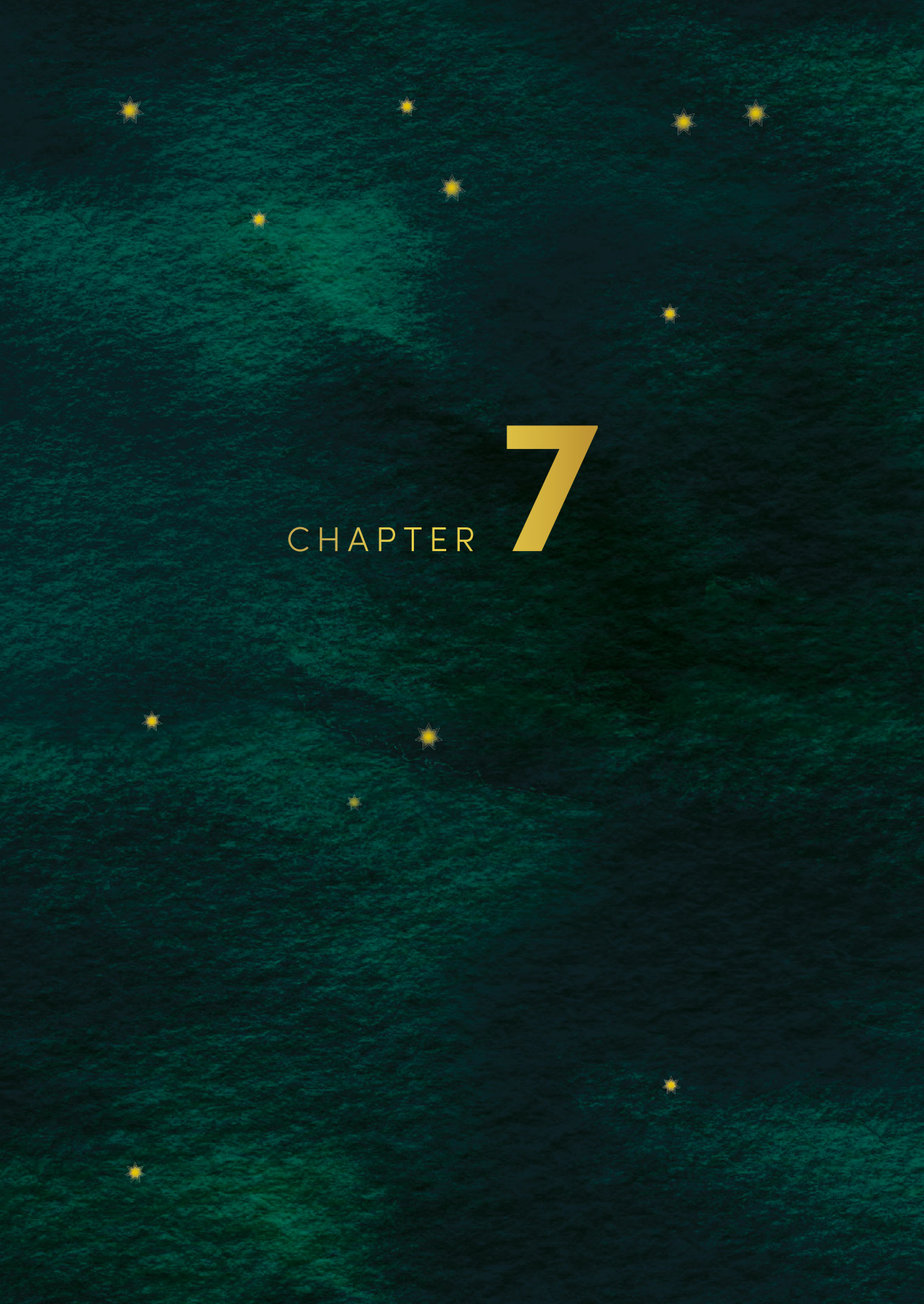
P value is given for comparison between patients with none/mild SDB vs moderate-to-severe SDB.

[1] indicates statistically significant difference (p < 0.05) between subgroups of patients within none and mild SDB (AHI<5 vs AHI 5 to <15) and moderate-to-severe SDB (AHI 15 to <30 vs AHI >30).

[2] indicates statistically significant difference (p < 0.01) between subgroups of patients within none and mild SDB (AHI<5 vs AHI 5 to <15) and moderate-to-severe SDB (AHI 15 to <30 vs AHI >30).

[3] from patient registration to SDB diagnosis.

[4] from patient registration to first time device usage. 5 from first time device usage to SDB diagnosis.


CHAPTER 7

Atrial fibrillation-specific refinement of the STOP-BANG sleep apnea screening questionnaire: Insights from the Virtual-SAFARI study

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ABSTRACT

Background

Sleep-disordered breathing (SDB) is prevalent in up to 50% of patients referred for atrial fibrillation (AF) catheter ablation (CA). Currently, it remains unclear how to improve preselection for SDB screening in patients with AF. We aimed to (1) assess the accuracy of the STOP-Bang screening questionnaire for detection of SDB within an AF population referred for CA; (2) derive a refined, AF-specific SDB score to improve preselection.

Methods

Consecutive AF patients referred for CA without a history of SDB and/or SDB screening were included. Patients were digitally referred to the previously implemented Virtual-SAFARI SDB screening and management pathway including a home sleep test. An apnea–hypopnea index (AHI) of ≥15 was interpreted as moderate-to-severe SDB. Logistic regression analysis was used to assess characteristics associated with moderate-to-severe SDB to refine preselection for SDB screening.

Results

Of 206 included patients, 51% were diagnosed with moderate-to-severe SDB. The STOP-Bang questionnaire performed poorly in detecting SDB, with an area under the receiver operating characteristic curve (AUROC) of 0.647 (95% Confidence-Interval (CI) 0.573–0.721). AF-specific refinement resulted in the BOSS-GAP score. Therein, body mass index with cut-off point ≥27 kg/m2 and previous stroke or transient ischemic attack were added, while tiredness and neck circumference were removed. The BOSS-GAP score performed better with an AUROC of 0.738 (95% CI 0.672–0.805) in the overall population.

Conclusion

AF-specific refinement of the STOP-Bang questionnaire moderately improved detection of SDB in AF patients referred for CA. Whether questionnaires bring benefits for preselection of SDB compared to structural screening in patients with AF requires further studies.

GRAPHICAL ABSTRACT

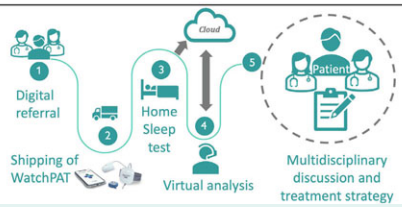
Atrial fibrillation specific refinement of the STOP-Bang sleep apnoea screening questionnaire: Insights from the Virtual-SAFARI study.

Aim

- Assess accuracy of the STOP-Bang questionnaire for sleep-disordered breathing (SDB) screening in patients scheduled for atrial fibrillation (AF) ablation
- Derive a refined, AF-specific SDB score to improve pre-selection of patients requiring SDB screening

Methods

- Patients were digitally referred to the Virtual-SAFARI SDB screening and management pathway (below)
- Logistic regression analysis was performed to assess patient characteristics associated with moderate-to-severe SDB



Results

- 206 patients included, 51% had moderate-to-severe SDB (AHI ≥ 15)
- STOP-BANG performed poorly in detecting SDB (AUROC of 0.647)
- BOSS-GAP performed better (AUROC 0.738)

AF- specific BOSS-GAP Score:
Green = same variables (as STOP-Bang questionnaire)
Yellow = added variable or additional points
removed variables: neck circumference + tiredness

B	3	BMI ≥27 KG/M²
O	2	OBSERVED APNOEA
S	1	SNORING
S	2	STROKE OR TIA
G	1	MALE GENDER
A	3	AGE >50
P	1	HYPERTENSION

Conclusions

1. STOP-Bang questionnaire performed poorly in detecting SDB in AF patients referred to catheter ablation
2. Refined questionnaire performed better, but not ideally
3. Questionnaire-based pre-selection for SDB screening remains challenging in this population

INTRODUCTION

Comprehensive risk factor control is one of the main pillars of atrial fibrillation (AF) management. [1] One established risk factor for AF is sleep-disordered breathing (SDB), which is present in up to 50% of all AF patients and is associated with AF progression and increased recurrence rates after AF catheter ablation (CA), when undiagnosed and thus untreated. [2,3]

The limited access to SDB testing complicates the implementation of SDB management in AF patients, as demonstrated in a joint survey by the European Heart Rhythm Association (EHRA) and the European Society of Cardiology's Association of Cardiovascular Nurses and Allied Professions (ACNAP). [4] Previously, we introduced the Virtual-SAFARI approach, a remote SDB screening and management pathway using a simple and validated peripheral arterial tone (PAT) based home sleep test in a cohort of consecutive AF patients scheduled for CA. This structural screening approach was feasible, fast, and accompanied by high patient satisfaction. [5] Nevertheless, implementing such a structural screening approach in the workup of patients with AF may lead to an increased burden of healthcare resources and costs. Identifying patients most likely to have SDB might limit this burden. Therefore, the question remains whether the preselection process of patients requiring SDB testing can be further optimized to better use the available resources for SDB screening.

Herein, we assessed the accuracy and performance of the STOP-Bang questionnaire, a widely accepted preselection tool for SDB screening, for detection of SDB in a cohort of patients with AF scheduled for CA who underwent a home sleep test. [2,6,7] We further aimed to improve preselection of patients requiring SDB screening by an AF-specific adjustment of the STOP-Bang questionnaire.

METHODS

In the Maastricht University Medical Center (MUMC+) and Radboud University Medical Center (Radboudumc), consecutive patients referred for CA undergo systematic screening for common comorbidities and triggers for AF, including SDB. In this context, patients complete the STOP-Bang questionnaire and are subsequently referred to a virtual SDB screening and management pathway, irrespective of results of the questionnaire, unless they have been previously diagnosed with SDB, have recently completed a sleep test that indicated

absence of SDB, or refuse SDB screening. A detailed description of this approach is provided elsewhere.[5] In brief, patients are educated about the interaction between AF and SDB and are digitally referred to a virtual sleep lab. Within 1–3 weeks, they receive a WatchPAT-ONE or WatchPAT 300 device at home. After a one-time overnight use of the device, the recordings are submitted to a sleep physician via a secured cloud. The sleep physician reviews the results and discusses the diagnosis with the patient and referring physician.

Study population

This is a sub-study of the ongoing ISOLATION cohort study (NCT04342312) and ISOLATION 'light' registry.[8] These studies prospectively enroll consecutive patients with symptomatic paroxysmal or persistent AF referred for CA in the MUMC+ or Radboudumc. The ISOLATION cohort study and ISOLATION 'light' registry were approved by the ethical review boards MUMC + /Maastricht University (METC numbers 19-052, 2019-1022) and Radboudumc (METC number 2019-5629) and comply with the Declaration of Helsinki. All participants provided written informed consent.

Patients were eligible for this study if they were included between October 2020 and January 2022. Patients were excluded if they did not undergo the remote sleep test, if they failed to complete the STOP-Bang questionnaire, or if the time between completing the STOP-Bang questionnaire and the sleep test was more than 6 months.

Sleep apnea diagnosis

SDB was diagnosed using the WatchPAT-ONE or WatchPAT 300 device. These devices include a wrist device that uses a plethysmography-based finger-mounted probe that measures the PAT signal and oxygen saturation, which is used as a proxy for respiratory disturbances and overnight sleep. A chest sensor records snoring, body position, and chest movement signals. The WatchPAT-ONE incorporates the same algorithm and technology as the WatchPAT 300, which exerted high sensitivity (85–89%) and fair specificity (63–77%) when compared to polysomnography for diagnosing sleep apnea.[9-11] WatchPAT was specifically validated in AF patients.[10]

A minimum of 4 hours of valid recording time with the WatchPAT device was required. WatchPAT data were analyzed by a validated algorithm and reviewed by a certified sleep physician according to methods described in the American Academy of Sleep Medicine manual for the scoring of sleep and

associated events. [12] The WatchPAT device detects respiratory events by the detection of sympathetic activations and concomitant oxygen desaturations. The WatchPAT-derived apnea–hypopnea index (pAHI) was calculated as the total number of apneas plus hypopneas divided by the total sleep time in hours. The apnea-severity was determined according to the following pAHI categories: pAHI 5–15: mild SDB; pAHI 15–30: moderate SDB; pAHI ≥30: severe SDB; pAHI ≥15: moderate-to-severe SDB. In the current study, moderate-to-severe SDB was considered to be clinically relevant SDB.

STOP-Bang questionnaire

The STOP-Bang questionnaire is a validated and widely used screening tool for SDB. [2,7] The questionnaire consists of eight dichotomous questions (S, Snoring; T, tiredness; O, observed apneas; P, high blood pressure; B, body mass index (BMI) ≥35 kg/m2; A, age >50 years; N, neck circumference >40 cm; and G, male gender). [13] Each positive answer is assigned one point. The sum of these points determines the risk of moderate-to-severe SDB: patients with a score of 0–2 are classified as having a low risk of SDB, patients with a score of 3–4 as having an intermediate-to-high risk, and patients with a score of 5–8 as having a high risk of SDB. For the current study, a score of ≥3 (intermediate-to-high risk of SDB) was considered as a positive test. Study participants completed the questionnaire digitally upon entry in the study.

Improving pre-selection with the BOSS-GAP score

Even though the STOP-Bang questionnaire is one of the most frequently used SDB screening tools, previous studies indicate a limited validity to detect SDB in patients with AF. [6,7] Next to assessing the accuracy of STOP-Bang questionnaire in detecting moderate-to-severe SDB in our cohort, we aimed to develop a refined, AF-specific SDB screening tool based on the existing STOP-Bang questionnaire combined with additional patient characteristics. To develop this score, consecutive groups of patients were divided into a training (n = 106) and a validation cohort (n = 100). Within the training cohort, STOP-Bang items were included in multivariable logistic regression. Those STOP-Bang items with beta-coefficients of <0.05 or negative correlation in multivariable logistic regression were considered of limited additional value to the endpoint and were removed from the AF-specific score, while STOP-Bang items associated with moderate-to-severe SDB remained. Moreover, clinical variables associated with the presence of moderate-to-severe SDB in univariable analyses were included in a multivariable regression analysis. Variables with a significant association ($\alpha = 0.1$) in this multivariable analysis

were added to the remaining STOP-Bang items to create an AF-specific score. Optimal cut-off points for continuous variables (age and BMI) were determined as the point maximizing the Youden's index. The calibrated beta-coefficients from the multivariable model were used to derive a clinical point-based scoring system, with the lowest coefficient as a denominator. The performance of the resulting score was assessed in the validation cohort.

Statistical analyses

Continuous variables were tested for normality with the Kolmogorov–Smirnov test and by visual interpretation. Variables with normal distribution were expressed as mean ± standard deviation (SD) and compared using the unpaired t-test, nonparametric variables were expressed as median with interquartile range (IQR) and compared using the Mann–Whitney U test. Categorical variables were presented as counts (n) with percentages (%) and compared using the $\chi 2$ test or Fisher's Exact test, whichever appropriate. Spearman correlations were performed to assess correlation between components of the STOP-Bang questionnaire. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and Cohen's kappa were calculated for different cut-off points of screening tools to assess their capability to detect moderate-to-severe SDB (pAHI ≥15). The predictive performance of screening tools was evaluated by calculating the area under the receiver operating characteristic (ROC) curves (AUROC). For the new AF-specific score, separate ROC curves were constructed for the training (n=106), validation (n=100) and total (n=206) cohort. Screening tools were considered to perform well if the AUROC exceeded 0.7. In addition, calibration was evaluated (Spiegelhalter's Z-test), net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated. Reclassification was further assessed in a reclassification table. Decision curve analysis was performed to compare net benefit of using the STOP-Bang and the new AF-specific score as preselection tools. A two-sided P value of 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics software (version 25.0, IBM Corp., Amonk, NY, USA) and SAS®.

RESULTS

A total of 268 patients completed SDB screening via the Virtual-SAFARI management pathway at the time of the current analysis. Of those, 62 were excluded due to failure to complete the STOP-Bang questionnaire (n=36) or failure to complete it within six months of SDB screening (n=26). The remaining 206 patients (77%) were included in the current study.

Table 1. Baseline characteristics of the entire cohort (n=206) and comparison between different groups of severity of sleep disordered breathing.

Variable	Overall (n=206)	None and mild SDB (n=100)		Moderate-to-severe SDB (n=106)		P -value[1]
		None (pAHI <5) (n=30)	Mild (pAHI 5 to <15) (n=70)	Moderate (pAHI 15 to <30) (n=71)	Severe (pAHI >30) (n=35)	
Demographics						
Age	65 [58-70]	65 [55-70]		65 [61-71]		0.101
		60 [50-69]	66 [59-70]	65 [60-70]	64 [61-73]	
Male	120 (58%)	9 (30%)	43 (61%)	47 (66%)	21 (60%)	0.077
BMI (kg/m^2)	27 [25-30]	26 [24-29]		28 [26-31]		<0.001
		25 [23-27][2]	27 [24-30][2]	27 [25-30][3]	31 [28-33][3]	
BMI ≥27 kg/m^2	108 (52%)	6 (20%)[2]	36 (51%)[2]	37 (52%)[3]	29 (83%)[3]	0.004
AF characteristics						
Paroxysmal AF	139 (68%)	25 (83%)	44 (63%)	49 (70%)	21 (60%)	0.721
EHRA class						
EHRA I	3 (2%)	1 (3%)	0 (0%)	2 (3%)	0 (0%)	0.650
EHRA II	130 (63%)	18 (60%)	48 (69%)	43 (61%)	21 (60%)	
EHRA III	73 (35%)	11 (37%)	22 (31%)	26 (37%)	14 (40%)	
CHA_2DS_2-VASc score	2 [1-3]	2 [1-3]		2 [1-3]		0.022
		1 [1-2]	2 [1-3]	2 [1-3]	2 [1-3]	
Comorbidities and risk factors						
Dyslipidemia	36 (18%)	1 (3%)	10 (14%)	17 (24%)	8 (23%)	0.017
Diabetes mellitus	19 (9%)	3 (10%)	5 (7%)	7 (10%)	4 (11%)	0.556
Congestive heart failure	32 (16%)	2 (7%)	9 (13%)	14 (20%)	7 (20%)	0.081
Vascular disease	31 (15%)	0 (0%)[2]	10 (14%)[2]	14 (20%)	7 (20%)	0.049

Table 1. Baseline characteristics of the entire cohort (n=206) and comparison between different groups of severity of sleep disordered breathing. (continued)

Variable	Overall (n=206)	None and mild SDB (n=100)		Moderate-to-severe SDB (n=106)		P -value[1]
		None (pAHI <5) (n=30)	Mild (pAHI 5 to <15) (n=70)	Moderate (pAHI 15 to <30) (n=71)	Severe (pAHI >30) (n=35)	
Previous stroke or TIA	20 (10%	0 (0%)	3 (4%)	11 (15%)	6 (17%)	0.002
Smoking	n=203		n=69	n=69	n=35	
Actively	21 (10%)	0 (0%)	7 (10%)	8 (12%)	6 (17%)	0.525
Previously	59 (29%)	7 (23%)	23 (33%)	22 (32%)	7 (20%)	
Never	123 (61%);	23 (77%)	39 (57%)	39 (57%)	22 (63%)	
Alcohol consumption	n=201		n=69	n=68	n=34	
None	50 (25%)	9 (30%)	17 (25%)	14 (21%)	10 (29%)	
<5 units/week	99 (49%)	13 (43%)	38 (55%)	29 (43%)	19 (59%)	0.551
5-15 units/week	47 (23%)	8 (27%)	12 (17%)	24 (35%)	3 (8.8%)	
>15 units/week	5 (2.5%)	0 (0%)	2 (2.9%)	1 (1.5%)	2 (5.9%)	
STOP-Bang components (reported by patients)						
Snoring	51 (25%)	0 (0%)[2]	17 (24%)[2]	20 (28%)	14 (40%)	0.012
Tiredness	118 (57%)	17 (57%)	43 (61%)	32 (45%)[3]	26 (74%)[3]	0.444
Observed apneas	50 (24%)	3 (10%)	12 (17%)	23 (32%)	12 (34%)	0.003
High blood pressure	103 (50%)	9 (30%)	36 (51%)	36 (51%)	22 (63%)	0.163
BMI >35 kg/m^2	26 (13%)	3 (10%)	5 (7%)	8 (11%)	10 (29%)	0.052
Age >50 years	186 (90%)	22 (73%)	61 (87%)	71 (100%)[3]	32 (91%)[3]	0.001
Neck circumference >40 cm	52 (25%)	1 (3.3%)[2]	22 (31%)[2]	16 (23%)	13 (37%)	0.472
Male	122 (59%)	10 (33%)[2]	43 (61%)[2]	48 (68%)	21 (35%)	0.077

Table 1. Baseline characteristics of the entire cohort (n=206) and comparison between different groups of severity of sleep disordered breathing. (continued)

Variable	Overall (n=206)	None and mild SDB (n=100)		Moderate-to-severe SDB (n=106)		P -value[1]
		None (pAHI <5) (n=30)	Mild (pAHI 5 to <15) (n=70)	Moderate (pAHI 15 to <30) (n=71)	Severe (pAHI >30) (n=35)	
Available STOP-Bang components (based on electronic health records)						
Hypertension	95 (46%)	7 (23%)[2]	32 (46%)[2]	36 (51%)	20 (57%)	0.047
BMI >35 kg/m^2	9 (4%)	0 (0%)	4 (6%)	3 (4%)	2 (6%)	0.801
Age >50 years	188 (91%)	22 (73%)2	61 (87%)2	71 (100%)	34 (97%)	<0.001
Male	120 (58%)	9 (30%)[2]	43 (61%)[2]	47 (66%)	21 (60%)	0.077
Cardiovascular drugs						
Beta-blockers	93 (45%)	12 (40%)	29 (41%)	35 (49%)	17 (49%)	0.246
Digitalis	15 (7%)	4 (13%)	4 (6%)	4 (6%)	3 (9%)	0.700
Antiarrhythmic drugs	127 (62%)	19 (63%)	39 (56%)	47 (66%)	22 (63%)	0.295
VKA	4 (2%)	0 (0%)	0 (0%)	4 (6%)	0 (0%)	0.050
NOAC	n=205 192 (93%)	28 (93%)	n=69 63 (90%)	66 (93%)	35 (100%)	0.361

[1] P-values are given for comparison between none-to-mild vs. moderate-to-severe SDB

[2] represents statistically significant differences between none vs mild SBD (BMI: p = 0.013, BMI ≥27 kg/m^2: p = 0.004, hypertension: p = 0.035, vascular disease p = 0.030; age >50 years: p = 0.044)

[3] represents statistically significant differences between moderate vs severe SDB (BMI: p = 0.001, BMI ≥27 kg/m^2: p = 0.002)

Abbreviations: AF: atrial fibrillation, AHI: apnea hypopnea index, BMI: body mass index, EHRA: European Heart Rhythm Association, NOAC: non-vitamin K antagonist oral anticoagulant, SDB: sleep disordered breathing, TIA: Transient Ischemic Attack VKA: vitamin K antagonist.

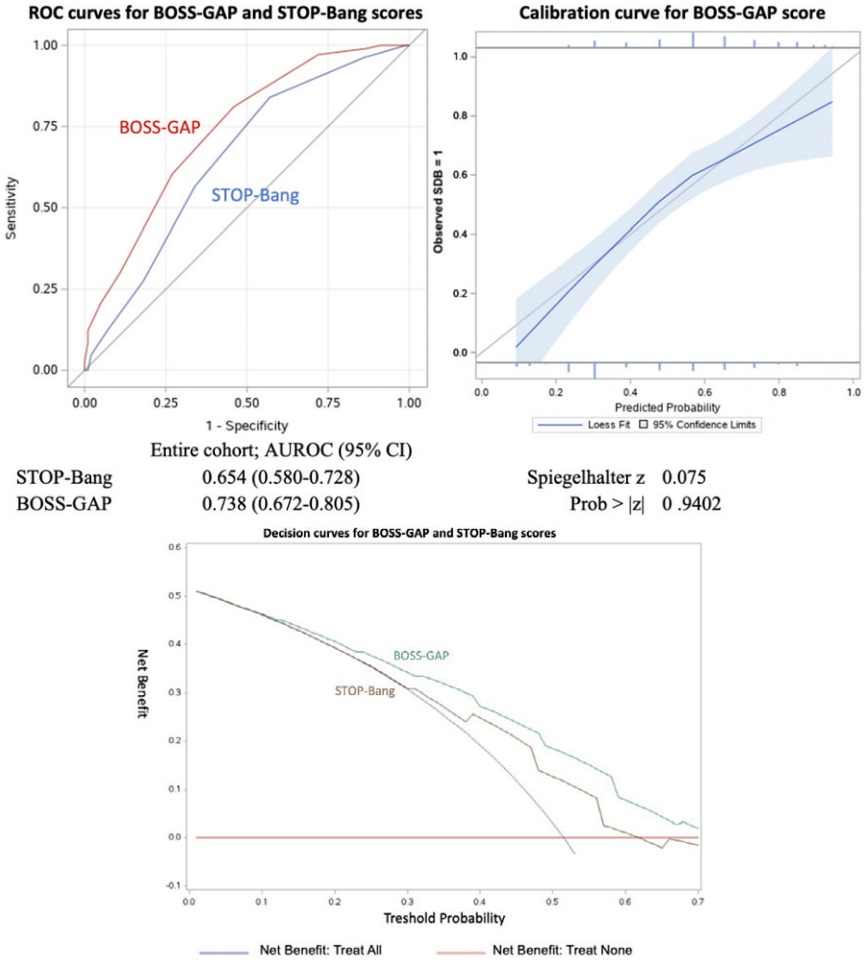


Figure 1. Receiver operating characteristic curve, calibration curve and decision curve analyses of models to predict moderate-to-severe sleep disordered breathing (n=206).

Abbreviations: AUROC: area under the receiver operator characteristic curve, CI: coincidence interval.

Study population

In this cohort of AF patients awaiting CA (58% male, median age 65 [58–70] years), the prevalence of moderate-to-severe SDB was 51% (n=106). Mild, moderate and severe SDB were newly diagnosed in 70 (34%), 71 (34%), and 35 (17%) patients, respectively. Patients' characteristics are presented in *Table 1.* Patients with moderate-to-severe SDB had a higher BMI (28 [26–31] vs 26 [24–29] kg/m^2, p < 0.001), higher thromboembolic risk (CHA_2DS_2-VASc score 2 [1–3] vs 2 [1–3], p = 0.022), more often had hypertension (53% vs 39%, p = 0.047), dyslipidemia (24% vs 11%, p = 0.017), previous thromboembolic events (17% vs 3%,

p = 0.002), or vascular disease (10% vs 20%, p = 0.049), and were more often prescribed vitamin K antagonists (0% vs 4%, p = 0.050) compared to those with none or mild SDB.

Performance of the STOP-Bang questionnaire

The median STOP-Bang score in the overall study population was 3 [2–4]. The STOP-Bang questionnaire performed poorly as a screening tool for moderate-to-severe SDB (AUROC 0.654, 95% CI 0.580–0.728, *Figure 1*). The sensitivity, specificity, PPV and NPV for different STOP-Bang scores are provided in *Table 2*. The most frequently used cut-off point for the STOP-Bang questionnaire, ≥3 points, demonstrated a sensitivity of 84% and an NPV of 72%.

When comparing patient-reported STOP-Bang items and items derived from electronic health records (hypertension, BMI, age, and sex were available), some misclassifications were found (n=62, 7.4%). Substituting patient-reported variables with results derived from electronic health records did not impact the STOP-Bang performance (sensitivity for cut-off point ≥3 81%, NPV 70%, AUROC 0.647, 95% CI 0.573–0.721), as described in *Table 2*.

Table 2. Sensitivity, specificity, positive predictive value, negative predictive value and kappa for different cut-off points of the STOP-Bang questionnaire and the BOSS-GAP score to predict moderate-to-severe sleep disordered breathing.

Cut-off point	Sensitivity	Specificity	PPV	NPV
STOP-Bang (patient reported)				
≥2	96% (102/106)	14% (14/100)	54% (102/188)	78% (14/18)
≥3 (moderate-to-high risk)	84% (89/106)	43% (43/100)	61% (89/146)	72% (43/60)
≥5 (high risk)	27% (29/106)	82% (82/100)	62% (29/47)	52% (82/159)
STOP-Bang (based on electronic health records)				
≥2	98% (104/106)	15% (15/100)	55% (104/189)	88% (13/17)
≥3 (moderate-to-high risk)	81% (86/106)	46% (46/100)	61% (86/140)	70% (46/66)
≥5 (high risk)	25% (26/106)	84% (84/100)	62% (26/42)	51% (84/164)
BOSS-GAP				
≥4 (moderate-to-high risk)	97% (103/106)	24% (24/100)	58% (103/179)	89% (24/27)
≥6 (high risk)	81% (86/106)	55% (55/100)	66% (86/131)	73% (55/75)

Abbreviations: NPV: negative predictive value, PPV: positive predictive value.

Several correlations between individual STOP-Bang components were observed. Components positively correlated were snoring and observed apneas or neck circumference >40 cm, high blood pressure or hypertension

and neck circumference >40 cm, and male gender and neck circumference >40 cm. Components negatively correlated were age >50 years and BMI >35 kg/m^2, tiredness and male gender (*Figure 2*).

	Snoring	Tiredness	Observed apnoeas	Hyper-tension	BMI>35 kg/m2	Age >50 years	Neck circumference >40cm	Male gender
Snoring	1,000	0,132	0,305*	0,079	-0,013	0,058	0,288*	0,052
Tiredness	0,132	1,000	0,123	-0,107	-0,055	-0,059	-0,086	-0,154*
Observed apnoeas	0,305*	0,123	1,000	0,090	-0,010	0,135	0,114	0,135
Hypertension	0,079	-0,107	0,090	1,000	0,136	0,148*	0,225*	-0,046
BMI>35 kg/m^2	-0,013	-0,055	-0,010	0,136	1,000	-0,186*	0,094	-0,108
Age>50 years	0,058	-0,059	0,135	0,148*	-0,186	1,000	0,061	0,017
Neck circumference >40cm	0,288*	-0,086	0,114	0,225*	0,094	0,061	1,000	0,333*
Male gender	0,052	-0,154*	0,135	-0,046	-0,108	0,017	0,333*	1,000

Figure 2. Spearman correlation between STOP-Bang components.

*The colors correspond with the strength of correlation. Green and yellow signify positive correlations, orange and red colors signify negative correlations. * denotes a significant correlation.*

Abbreviations: BMI: body mass index.

AF-specific refinement of the STOP-Bang questionnaire: the BOSS-GAP score

The training cohort used to derive the AF-specific SDB score consisted of 106 patients. There were no significant differences in baseline characteristics between the training- and validation cohort (*Supplement 1*). In the training cohort, uni- and multivariable regression analyses revealed that neck circumference and tiredness were not positively correlated with moderate-to-severe SDB (*Supplements 2 and 3*). These variables were removed from the refined AF-specific score. Several baseline characteristics were associated with moderate-to-severe SDB (*Supplement 2*). After multivariable regression analysis, the following variables remained important: BMI (optimal cut-off point ≥27 kg/m^2), age (optimal cut-off point >50 years old, corresponding with the existing STOP-Bang item), snoring, observed apneas, previous stroke or transient ischemic attack (TIA), hypertension and male gender. BMI with cut-off point ≥27 kg/m^2 and previous stroke or TIA were added to the new AF-

specific SDB screening score. Based on the beta coefficients in the multivariable regression model, the highest points (3) were assigned for age >50 years and BMI ≥27 kg/m2, and two points were assigned for observed apnea and previous stroke or TIA (*Supplement 4*). The remaining items received one point. This approach resulted in the BOSS-GAP score (*Figure 3*).

In the training cohort of 106 patients, the BOSS-GAP score demonstrated a good predictive power in estimating the risk of moderate-to-severe SDB, with an AUROC of 0.803 (95% CI 0.721–0.885) (*Supplement 5*). Calibration plots graphically showed good agreement (p = 0.961 for the Spiegelhalter's Z-test) on the presence of moderate-to-severe SDB between the risk estimation by the BOSS-GAP and WatchPAT confirmation.

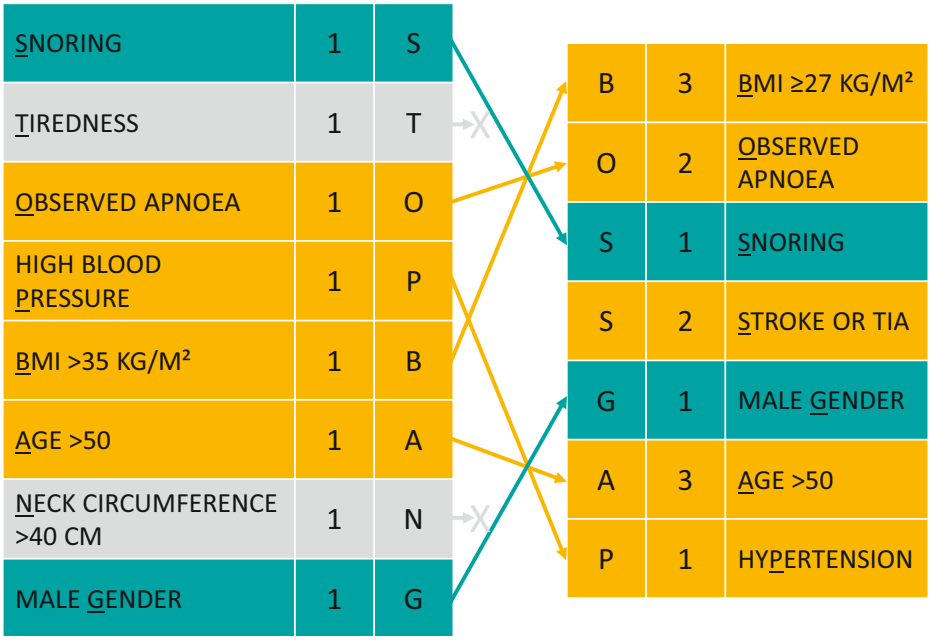


Figure 3. STOP-Bang and BOSS-GAP scores.

The original STOP-Bang score and the new, AF-specific BOSS-GAP score. STOP-Bang variables that were removed from the AF-specific score (not included in BOSS-GAP) are shown in grey. Green variables were included in the BOSS-GAP score without any modifications. Yellow variables were either newly added to the BOSS-GAP score, or additional points were assigned based on multivariable regression coefficients.

Abbreviations: BMI: body mass index, TIA: transient ischemic attack.

In the validation cohort, the BOSS-GAP displayed an AUROC of 0.673 (95% CI 0.568–0.778) for the estimation of moderate-to-severe SDB risk. The observed frequencies and the estimated probability of moderate-to-severe SDB presence showed a good calibration curve (p = 0.955 for the Spiegelhalter's Z-test) for risk estimation (*Supplement 5*). In the overall study population, the score displayed an AUROC of 0.738 (95% CI 0.672–0.805, *Figure 1*). The category free NRI for the new BOSS-GAP Score compared to STOP-Bang results for moderate-to-severe SDB was 0.201 (0.085–0.917, $p < 0.05$) and the integrated discrimination improvement was 1.35 (0.885–1.815, $p < 0.001$) in the overall cohort.

Clinical value of the STOP-Bang and BOSS-GAP score in pre-selection for SDB screening

The STOP-Bang questionnaire was able to correctly identify 89 (84%) of confirmed SDB patients as at risk for SDB (cut-off value ≥3). If STOP-Bang would have been used as a preselection tool to determine which patients should be referred for SDB screening in our cohort of AF patients, a total of 60 (29%) of patients would not have been referred for screening. However, this would have led to missed diagnoses of SDB cases in 17 (8%) of patients.

The refined AF specific BOSS-GAP score (cut-off value ≥4) correctly marked 103 (97%) of SDB patients as being at risk. A total of 25 (12%) of patients had a negative BOSS-GAP score, hence, this proportion of WatchPAT referrals could have been prevented. Since only three of these patients (1.5%) had SDB, omitting SDB screening for patients with a BOSS-GAP score below 4 may be considered with low risk of missing SDB cases (*Supplement 6*).

The decision curves analysis (*Figure 1*) suggests that using the STOP-Bang or BOSS-GAP scores as preselection tools might be useful for threshold probabilities above 30% for STOP-Bang and 12% for BOSS-GAP. The BOSS-GAP score had higher net benefit than STOP-Bang across the range of threshold probabilities. However, as WatchPAT is not an invasive test, for most patients lower threshold probabilities may be acceptable (i.e., the number of patients needed to screen with WatchPAT to detect one case of SDB may be higher than 8, corresponding with a threshold probability of 12.5%). In the lower range of threshold probabilities (<12%), both the BOSS-GAP and the STOP-Bang curves overlap with the 'treat all' line. Therefore, for lower threshold probabilities both questionnaires provide no net benefit over structural WatchPAT screening.

DISCUSSION

In the current study, we demonstrated that the STOP-Bang questionnaire performed poorly to pre-select AF patients at risk of SDB. If it would have been used as a preselection tool, a high proportion of patients with SDB would have been classified as false negative for risk of SDB. However, we demonstrated that a refined version of the STOP-Bang score, the BOSS-GAP score, performed better in our cohort of AF patients scheduled for CA. In the overall cohort, using this score as a preselection tool to determine which patients should be referred for SDB screening had the potential to save one in six home sleep tests, with a low probability to miss SDB cases.

This study is not the first to demonstrate the limited value of the STOP-Bang questionnaire as an SDB-screening tool in AF patients. Several studies reported its moderate to poor performance in detecting moderate-to-severe SDB in AF patients in different clinical settings. [6,7,14-16] The relatively high false negative rate and low sensitivity have been mentioned as factors limiting the usefulness of the STOP-Bang questionnaire. [17] However, causes for this limited usability in AF patients may be unrelated to the questionnaire items themselves. [6] Originally, the questionnaire was not developed specifically for AF patients. Due to interrelations between SDB and AF, the shared risk factor profile, and the fact that symptoms of SDB and AF are often overlapping, the STOP-Bang items might have limited predictive value. [6,7,14-19] Indeed, in our cohort, some overlapping characteristics could be revealed with correlation analysis of the STOP-Bang items, for example, between the item neck circumference and observed apnea and snoring, high blood pressure or male gender. However, when further analyzing the different STOP-Bang items, the item neck circumference did not appear to be a predictive characteristic for SDB presence in our cohort.

Another explanation of the poor performance of the STOP-Bang questionnaire is the subjective nature of some of its items. [6] For example, SDB patients with AF report lower daytime sleepiness than those without AF [20] and other STOP-Bang items (snoring, observed apnea) are self-reported, while we noticed an inaccuracy in several STOP-Bang characteristics when comparing self-reported items to those derived from electronic health records. This is in line with a previous study reporting on large differences in patient-reported risk factors, patient characteristics and CHA_2DS_2-VASc score compared to these factors assessed by healthcare professionals. [21] However, substituting patient-reported STOP-Bang items with data from electronic health records did not

change the overall performance of the STOP-Bang questionnaire in our cohort. After refinement of the STOP-Bang questionnaire in our cohort, the STOP-Bang items neck circumference and tiredness were not associated with an elevated chance of moderate-to-severe SDB but having had a previous stroke or TIA (which is also included in the CHA_2DS_2-VASc score) was. The refined STOP-Bang-based BOSS-GAP score showed a stronger discriminatory performance to identify patients with increased risk of moderate-to-severe SDB than the STOP-Bang questionnaire. However, even after refinement of the screening questionnaire, a good performance (AUROC >0.7) could not be achieved in the validation cohort. Further studies are required to determine the clinical relevance of the refined score. The value of preselection for SDB screening in patients with AF based on questionnaires might therefore still be limited.

Implementation of AF-specific pre-selection tools for SDB screening

SDB remains a highly prevalent comorbidity in AF and SDB screening and management is mentioned as an important component of a combined risk factor management program. However, official recommendations and practical guides for implementation of systematic SDB screening in AF patients scheduled for CA are missing. [2,7,22] An integrated AF care approach with a multidisciplinary, patient-focused collaboration between sleep physicians and AF teams has been proposed [2,22,23] and implemented within the Virtual-SAFARI project. [5] However, several barriers might appear in the implementation of systematic SDB testing, such as a lack of skills and knowledge, financial and workforce-related resources, and missing collaboration between cardiology and sleep medicine, as described by the previously mentioned EHRA and ACNAP survey. [4] Incorporating questionnaires or scoring systems, such as the BOSS-GAP score, into electronic health records, so that risk scores are automatically calculated, may simplify preselection of patients who should be referred to SDB management pathways. [6] However, our findings indicate that adequate preselection for SDB screening in patients with AF, especially by using questionnaires, remains challenging. Available safe and easy options such as ambulatory, systematic screening approaches might therefore still be the best solution. In the future, incorporation of data from wearable devices, smartphone apps and cardiac implantable devices in the preselection process may help to refine identification of those patients requiring SDB assessment further, which may lead to easier identification of patients at risk of SDB.

Implications for future research and clinical practice

When compared to systematic SDB screening in patients with AF, preselection of patients at higher risk for SDB could reduce the number of patients who are

referred for SDB screening. However, the current results should first be validated to assess whether the newly developed BOSS-GAP performs consistently in other AF populations. Furthermore, future research is needed regarding cost efficacy of preselection methods such as proposed in our study. Additionally, further research is needed towards the optimal method for dissemination and broad implementation of the score. This could be achieved by implementing a BOSS-GAP score-based preselection as part of an integrated AF and SDB management pathway in patients scheduled for CA, as previously proposed and implemented. [2,5,23]

Limitations

Our study has several limitations. Firstly, SDB diagnosis was based on an overnight home sleep test with the WatchPAT device, and not on polysomnography. This together with the fact that the screening is based on a single measurement, which does not consider possible night-to-night variations of SDB, may influence the SDB diagnosis. Secondly, although WatchPAT-ONE uses the same algorithm and sensor technology as WatchPAT 300 which has been validated in AF patients, studies using the WatchPAT-ONE device are limited. Thirdly, patients with known SDB or previous SDB screening were excluded from our study, which might influence pre-test probability in our study cohort. However, previous studies assessing SDB prevalence in AF patients in different clinical settings report equally high percentages. Fourthly, the digital SDB management pathway was tested in AF patients scheduled for CA only and we implemented the digital pathway in only two centers in the Netherlands, where inclusion of patients with a BMI >35 kg/m2 was limited. Finally, the BOSS-GAP was based on a relatively small training group and validated in a small group as well. Therefore, it requires validation in a larger, preferably external cohort.

Conclusions

In our cohort of consecutive patients scheduled for AF CA, the STOP-Bang questionnaire showed limited value when used as a preselection tool for SDB screening. The AF-specific refinement of the STOP-Bang questionnaire resulted in the novel BOSS-GAP questionnaire which demonstrated slightly improved, but still limited accuracy in identifying AF patients with moderate-to-severe SDB. Whether questionnaires bring an advantage regarding preselection for SDB screening compared to systematic screening in all patients with AF, requires further larger studies.

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SUPPLEMENTS

Supplement 1. Comparison of baseline characteristics between training (n=106) and validation (n=100) cohorts.

Variable	Training cohort (n=106)	Validation cohort (n=100)	*P*-value
Demographics (based on electronic health records)			
Age	66 [59-73]	64 [58-69]	0.139
Age >50 years	97 (92%)	91 (91%)	0.897
Male	58 (55%)	62 (62%)	0.289
BMI, kg/m^2	27 [25-31]	27 [25-30]	0.444
BMI ≥27 kg/m^2	56 (53%)	52 (52%)	0.508
BMI >35 kg/m^2	6 (6%)	3 (3%)	0.350
AF characteristics (based on electronic health records)			
Paroxysmal AF	74 (70%)	65 (66%)	0.525
EHRA I	3 (2.8%)	0 (0%)	
EHRA II	60 (57%)	70 (70%)	0.052
EHRA III	43 (41%)	30 (30%)	
CHA_2DS_2-VASc score	2 [1-3]	2 [1-3]	0.312
Comorbidities and risk factors (based on electronic health records)			
Hypertension	50 (47%)	45 (45%)	0.755
Dyslipidemia	17 (16%)	19 (19%)	0.576
Diabetes mellitus	9 (8%)	10 (10%)	0.708
Congestive heart failure	17 (16%)	15 (15%)	0.837
Vascular disease	13 (12%)	18 (18%)	0.250
Previous stroke/TIA	1 (10%)	9 (9%)	0.739
Smoking	n=105	n=98	
Actively	12 (11%)	9 (9.2%)	0.885
Previously	32 (31%)	27 (28%)	
Never	61 (58%)	62 (63%)	
Alcohol consumption	n=103	n=98	
None	25 (24%)	25 (26%)	
<5 units/week	50 (49%)	49 (50%)	0.435
5-15 units/week	27 (26%)	20 (20%)	
>15 units/week	1 (1.0%)	4 (4.1%)	
STOP-Bang components (patient reported)			
Snoring	28 (26%)	23 (23%)	0.570
Tiredness	59 (56%)	59 (59%)	0.628
Observed apneas	22 (21%)	28 (28%)	0.225

Supplement 1. Comparison of baseline characteristics between training (n=106) and validation (n=100) cohorts. (continued)

Variable	Training cohort (n=106)	Validation cohort (n=100)	*P*-value
High blood pressure	52 (49%)	51 (51%)	0.780
BMI >35 kg/m^2	15 (14%)	11 (11%)	0.496
Age >50 years	97 (92%)	89 (89%)	0.543
Neck circumference >40 cm	30 (28%)	22 (22%)	0.298
Male	58 (55%)	64 (64%)	0.175
Cardiovascular drugs (based on electronic health records)			
Beta-blockers	49 (46%)	44 (44%)	0.781
Digitalis	9 (8.5%)	6 (6.0%)	0.596
Antiarrhythmic drugs	65 (61%)	62 (62%)	1.000
VKA	3 (2.8%)	1 (1.0%)	0.622
NOAC	97 (92%)	n=99 95 (96%)	0.255

Abbreviations: AF: atrial fibrillation, BMI: body mass index, EHRA: European Heart Rhythm Association, NOAC: non-vitamin K antagonist oral anticoagulant, TIA: transient ischemic attack, VKA: vitamin K antagonist.

Supplement 2. Comparison of baseline characteristics and STOP-Bang components within the training cohort (n=106).

Variable	None and mild SDB (n= 50)	Moderate-to-severe SDB (n=56)	*P* value
Demographics (based on electronic health records)			
Age, years	65 [56-70]	66 [61-74]	0.053
Age >50 years	41 (82%)	56 (100%)	0.001
Male	24 (48%)	34 (61%)	0.189
BMI, kg/m^2	26 [24-29]	29 [26-32]	0.001
BMI ≥ 27 kg/m^2	18 (36%)	38 (68%)	0.001
BMI > 35 kg/m^2	4 (8%)	2 (4%)	0.325
AF characteristics (based on electronic health records)			
Paroxysmal AF	35 (70%)	39 (70%)	0.968
EHRA I	1 (2%)	2 (4%)	
EHRA II	31 (62%)	29 (52%)	0.548
EHRA III	18 (35%)	25 (45%)	
CHA_2DS_2-VASc score	2 [1-3]	2 [1-3]	0.034
Comorbidities and risk factors (based on electronic health records)			
Hypertension	19 (38%)	31 (55%)	0.074
Dyslipidemia	5 (10%)	12 (21%)	0.109

Supplement 2. Comparison of baseline characteristics and STOP-Bang components within the training cohort (n=106). (continued)

Variable	None and mild SDB (n= 50)	Moderate-to-severe SDB (n=56)	*P* value
Diabetes mellitus	4 (8%)	5 (9%)	0.864
Congestive heart failure	4 (8%)	13 (23%)	0.033
Vascular disease	4 (8%)	9 (16%)	0.206
Previous stroke/TIA	1 (2%)	10 (18%)	0.008
Smoking		N=55	
Actively	3 (6.0%)	9 (16%)	0.141
Previously	15 (26%)	17 (31%)	
Never	32 (64%)	29 (53%)	
Alcohol consumption		N=53	
None	13 (26%)	12 (23%)	
<5 units/week	26 (52%)	24 (45%)	0.581
5-15 units/week	11 (22%)	16 (30%)	
>15 units/week	0 (0%)	1 (1.9%)	
STOP-Bang components (patient reported)			
Snoring	10 (20%)	18 (32%)	0.157
Tiredness	28 (56%)	31 (55%)	0.947
Observed apneas	5 (10%)	17 (30%)	0.010
High blood pressure	22 (44%)	30 (54%)	0.325
BMI >35 kg/m^2	4 (8%)	11 (20%)	0.086
Age >50 years	41 (82%)	56 (100%)	0.001
Neck circumference >40 cm	11 (22%)	19 (34%)	0.174
Male	24 (48%)	34 (61%)	0.189
Cardiovascular drugs (based on electronic health records)			
Beta-blockers	18 (36%)	31 (55%)	0.053
Digitalis	4 (8.0%)	5 (8.9%)	1.000
Antiarrhythmic drugs	30 (60%)	35 (63%)	0.843
VKA	0 (0%)	3 (5.4%)	0.245
NOAC	45 (90%)	52 (93%)	0.732

Abbreviations: AF: atrial fibrillation, BMI: body mass index, EHRA: European Heart Rhythm Association, NOAC: non-vitamin K antagonist oral anticoagulant, TIA: transient ischemic attack, VKA: vitamin K antagonist.

Supplement 3. Multivariable regression beta coefficients of the original STOP-Bang items (training cohort).

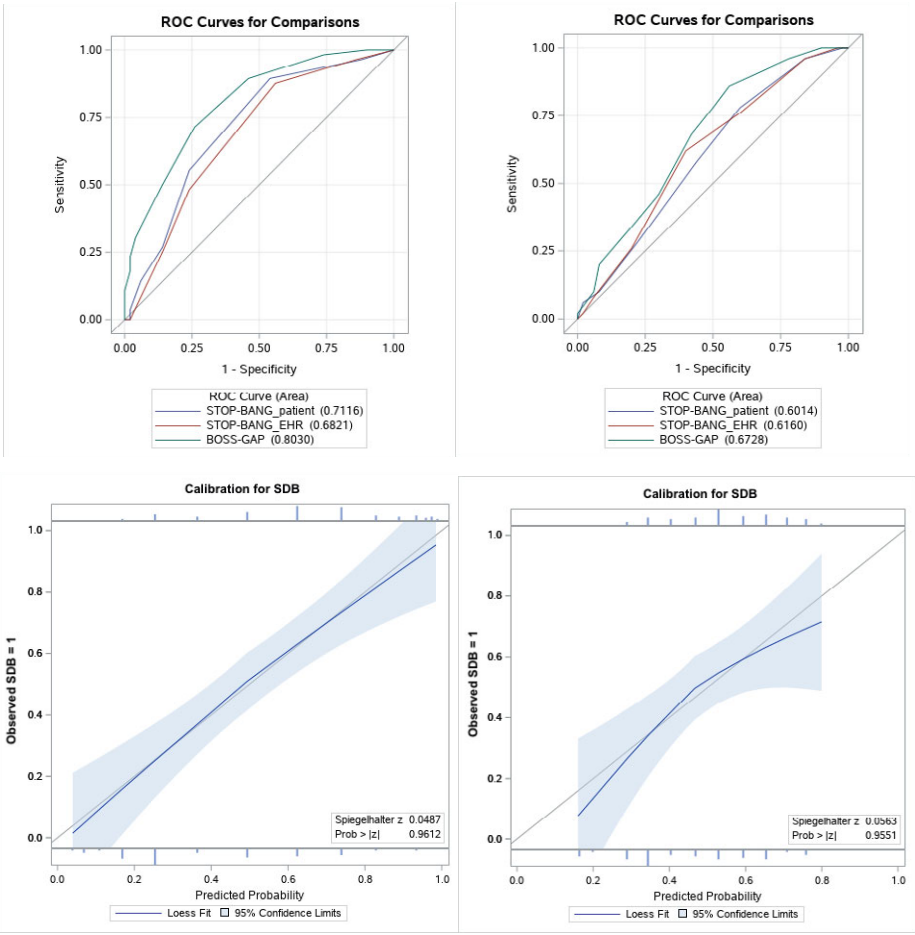
Variable	Beta coefficient
Snoring	0.073
Tiredness	0.031
History of observed apnea	0.183
Hypertension	0.184
BMI >35 kg/m2	-0.026
Age >50 years old	0.315
Neck circumference >40cm	0.011
Male	0.120

Abbreviations: BMI: body mass index.

Supplement 4. Multivariable regression beta coefficients of AF-specific predictors for moderate-to-severe sleep disordered breathing and corresponding points assigned in the BOSS-GAP score.

Variable	Beta coefficient	Points
Snoring	0.048	1
History of observed apnea	0.170	2
Hypertension	0.066	1
BMI ≥27 kg/m2	0.252	3
Age >50 years old	0.287	3
Stroke/TIA	0.180	2
Male	0.104	1

Abbreviations: BMI: body mass index, TIA: transient ischemic attack.



	Training cohort; AUROC (95% CI)	Validation cohort; AUROC (95% CI)
STOP-Bang (patient-reported items)	0.712 (0.614-0.810)	0.601 (0.492-0.711)
STOP-Bang (items derived from electronic health records, where possible)	0.682 (0.582-0.783)	0.616 (0.507-0.725)
BOSS-GAP	0.803 (0.721-0.885)	0.673 (0.568-0.778)

Supplement 5. Receiver operating characteristic curve and calibration curves for the performance of the STOP-Bang and the BOSS-GAP scores to predict moderate-to-severe SDB in training (left side) and validation (right side) cohorts.

Abbreviations: AUROC: area under the receiver operator characteristic curve, ROC: receiver operator characteristic, SDB: sleep disordered breathing.

Supplement 6. Reclassification table.

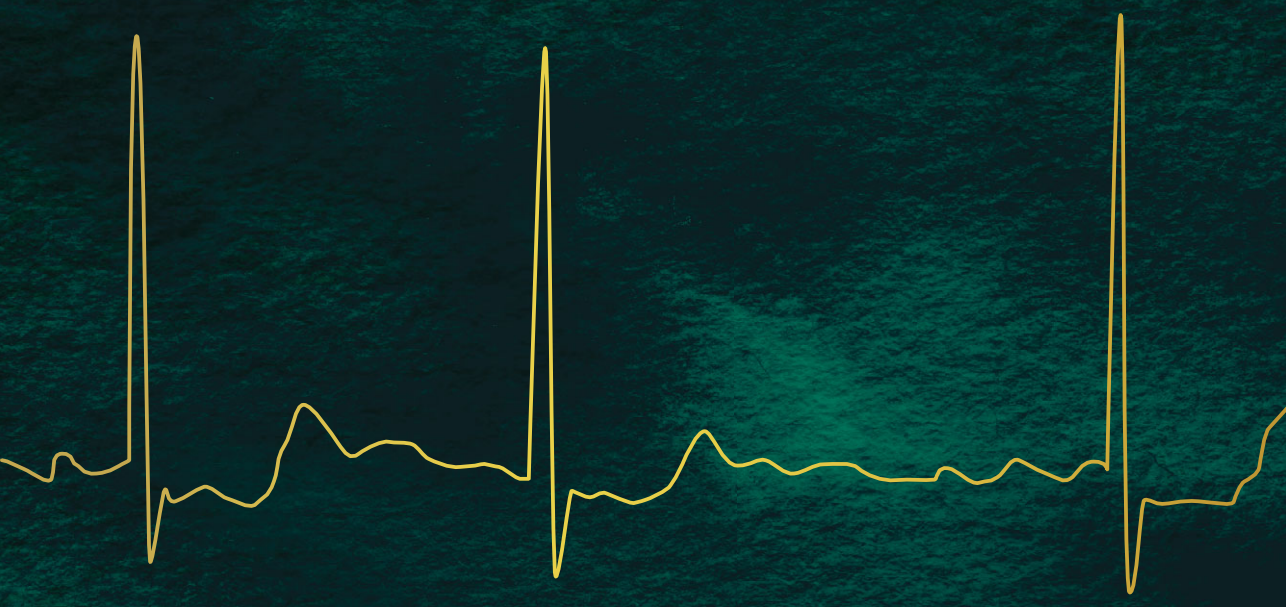
Moderate-to-high SDB risk		**BOSSGAP ≥4**		**Total**
		No	Yes	
STOP-Bang ≥3	No	2 (1.9%)	15 (14.2%)	17 (16.0%)
	Yes	1 (0.9%)	88 (83.0%)	89 (84.0%)
Total		3 (2.8%)	103 (97.2%)	106 (100%)

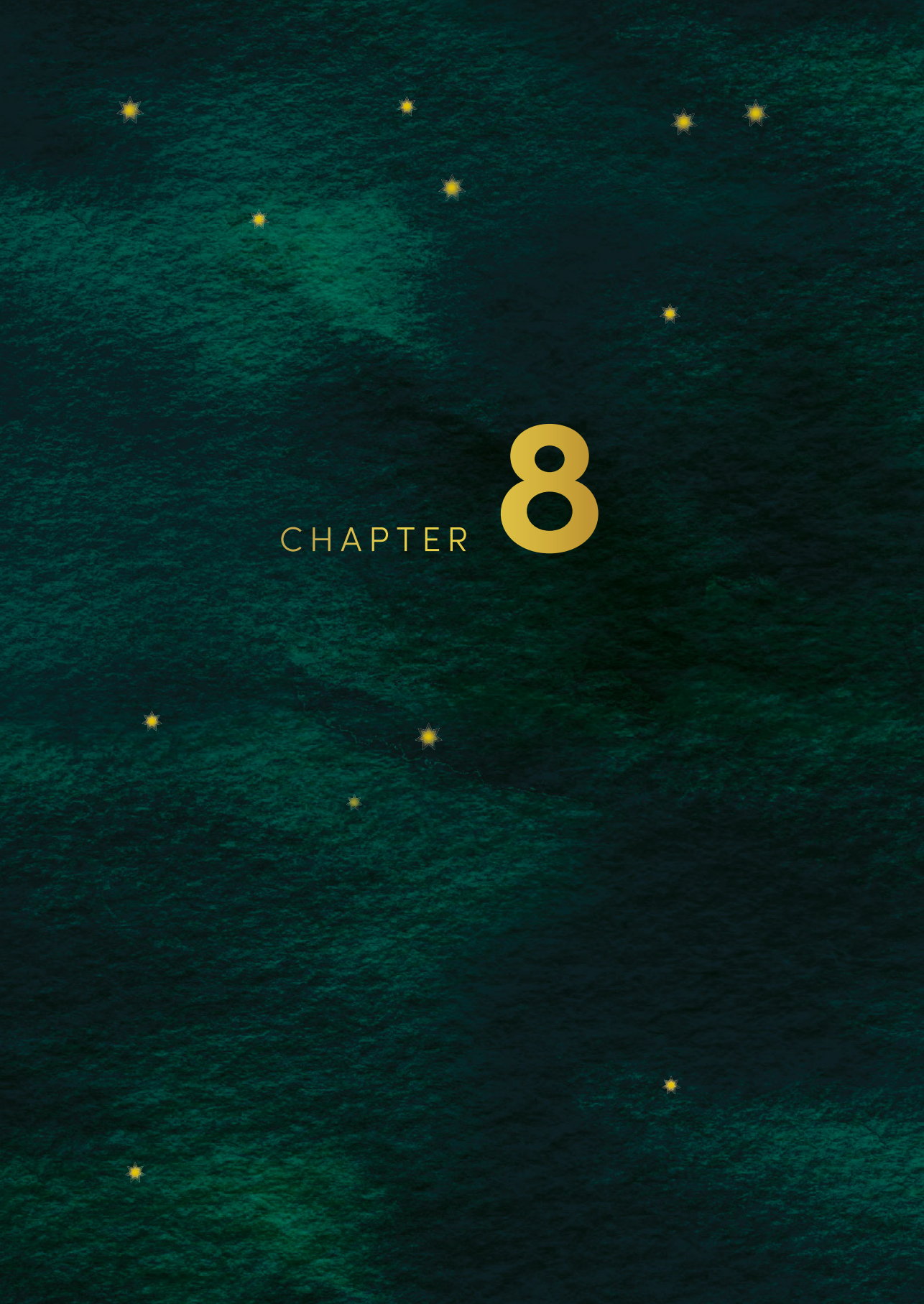
No-to-mild SDB risk		**BOSSGAP ≥4**		**Total**
		No	Yes	
STOP-Bang ≥3	No	21 (21.0%)	22 (22.0%)	43 (43.0%)
	Yes	1 (1.0%)	56 (56.0%)	57 (57.0%)
Total		22 (22.0%)	78 (78.0%)	100 (100%)

Abbreviations: SDB: sleep disordered breathing.

PART III

Integrating heart failure and atrial fibrillation care




CHAPTER 8

The bidirectional interaction between atrial fibrillation and heart failure: consequences for the management of both diseases

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ABSTRACT

Atrial fibrillation (AF) and heart failure (HF) are both highly prevalent diseases and are accompanied by a significant disease burden and an increased mortality. Although the conditions may exist independently, they often go hand in hand as each is able to provoke, sustain and aggravate the other. In addition, the diseases share a risk profile with several coinciding cardiovascular risk factors, promoting the odds of developing both AF and HF separately from each other. When the diseases coexist, this provides additional challenges but also opportunities for the optimal treatment. The recommended management of the comorbidities has been much debated in the past decades. In this review, we describe the pathophysiological coherence of AF and HF, illustrate the current knowledge on the management of them as comorbidities of each other and look forward to future developments in this field.

INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) are both highly prevalent diseases, with an estimated number of 33 million individuals that are affected by AF and 26 million by HF worldwide. [1,2] The prevalence of both diseases is expected to rise even further in the years to come as a result of increased life expectancy and the increasing prevalence of cardiovascular risk factors and underlying diseases; an alarming trend given that both AF and HF are accompanied by significant morbidity and mortality. Although the conditions may exist independently, they often coexist as each is able to provoke, sustain and aggravate the other. They strongly affect each other's outcome, with higher hospitalization rates and a two to three times increase in mortality risk when compared to the separate diseases. [3]

Numerous studies have been conducted that aimed to elucidate the complex pathophysiological mechanisms between AF and HF, both with reduced (HFrEF) and preserved ejection fraction (HFpEF), and to discover the optimal treatment strategy for the combination of both diseases. In this review, we describe the pathophysiological coherence of AF and HF, illustrate the current knowledge on the management of them as comorbidities and look to future developments in this field.

PATHOPHYSIOLOGY

The increased risk of patients with AF to develop HF and vice versa, is attributable to two factors. First, the diseases are interrelated pathophysiologically and as such can provoke and sustain each other. Secondly, both diseases share a risk profile with several coinciding cardiovascular risk factors, increasing the odds of developing both conditions separately from each other.

Atrial fibrillation-induced heart failure

AF can provoke the development of HF via different mechanisms. The arrhythmia causes several immediate hemodynamic changes, which may contribute to decreased cardiac output and acute HF. In addition, continuous AF or frequent AF paroxysms may lead to persistent or irreversible structural changes causing impaired systolic and diastolic function not only of the atria but also the ventricles. Mechanisms responsible for the acute and chronic development of HF in AF patients include loss of atrial contraction, irregular

heart rate, (persistent) tachycardia, neurohumoral activation, and structural myocardial changes (*Figure 1*).

Loss of atrial contraction

In normal sinus rhythm, the atrial contraction contributes about 20-25% of the total left ventricular (LV) stroke volume, with maximum effect at heart rates between 50-80 beats per minute. When diastolic dysfunction is present, the contribution of the atrial contraction becomes more important due to the decreased passive filling. [4] As such, the (sudden) loss of atrial contraction during AF episodes accompanied by the corresponding decrease in stroke volume can contribute to the development of HF, especially in patients with diastolic dysfunction.

Irregularity

The irregularity of ventricular contractions during AF may negatively impact systolic and diastolic function, even when ventricular rates are sufficiently treated with rate controlling drugs. This is partially caused by the beat-to-beat variability in duration of the diastolic interval, resulting in variable LV filling and end-diastolic volume. In addition, shorter cycle lengths affect the filling and release of calcium from the sarcoplasmic reticulum to a larger extent than longer cycle lengths, decreasing myocardial contractibility and reducing total cardiac output during irregular rhythms compared to regular rhythms with the same average frequency. [5]

Tachycardia

In the absence of rhythm or rate modulating drugs, AF is often accompanied by high ventricular rates. Continuous high heart rates may, independent of the cause of the tachycardia, lead to abnormal calcium signaling between the cardiomyocyte surface membrane and the sarcoplasmic reticulum, as well as decreased calcium levels in the sarcoplasmic reticulum. The resulting altered excitation-contraction coupling of the cardiomyocyte causes decreased myocardial contractility, smaller stroke volume, and LV dilatation, also referred to as tachycardia-mediated cardiomyopathy. Several animal studies demonstrated a correlation between a higher rate and longer duration of rapid ventricular pacing and the severity of LV systolic dysfunction. [6] Thus, both relatively short episodes of tachycardia with high frequency and longer episodes with moderate frequencies may cause tachycardia-mediated cardiomyopathy.

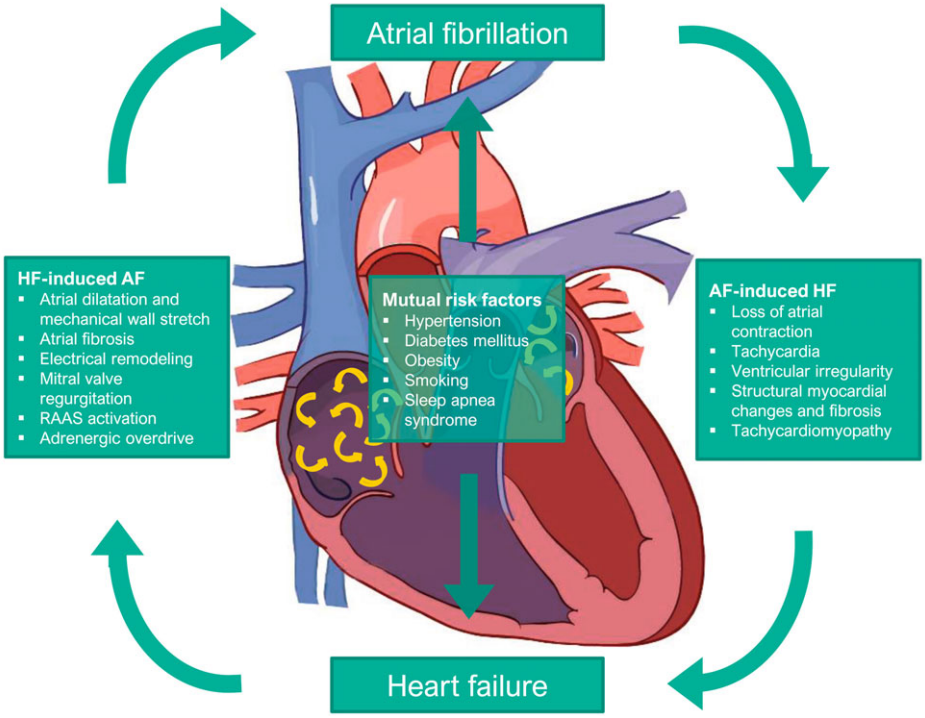

Figure 1. Pathophysiological relationship between atrial fibrillation and heart failure.
Abbreviations: AF: atrial fibrillation, HF: heart failure, RAAS: renin-angiotensin-aldosterone system.

Neurohumoral activation

The reduced cardiac output resulting from the loss of atrial contraction, irregularity and tachycardia accompanying AF may cause activation of several neurohumoral pathways, including the renin-angiotensin-aldosterone system (RAAS) and adrenergic system. Increased levels of angiotensin and aldosterone cause vasoconstriction, fluid retention and increased blood pressure. When elevated during longer periods of time, however, RAAS hormones also lead to structural changes including cardiomyocyte hypertrophy, apoptosis, and adverse structural remodeling in the atrial and ventricular wall, promoting the development of systolic and diastolic LV dysfunction. [7] Additionally, the increased sympathetic stimulation during AF results in increased contractility and heart rate in an attempt to maintain sufficient cardiac output. Although this may be beneficial in the short term, it may cause HF development and deterioration in the long term.

Structural myocardial changes

The combined effects of hemodynamic alterations and overactivated regulatory mechanisms may cause permanent effects on the structural integrity of the atrial and ventricular myocardium. Although the systolic function of tachycardia-mediated cardiomyopathy patients usually recovers when the arrhythmia is discontinued, prolonged AF may cause permanent damage. The extracellular matrix is particularly susceptible to long-term changes such as interstitial fibrosis, i.e., increased fibroblast activity and deposition of collagen and elastin fibers. Notably, these interstitial adjustments predominantly develop in the recovery phases between episodes of tachycardia, not during the higher ventricular rates itself. [8] Even in patients with normal LV systolic ventricular function, cardiac magnetic resonance (CMR) imaging in AF patients reveals increased levels of diffuse interstitial ventricular fibrosis, associated with the AF burden but independent of other risk factors such as ischemic heart disease and systolic dysfunction. [9] These remnants of the arrhythmia episodes may cause increased LV stiffness and diastolic dysfunction.

Heart failure-induced atrial fibrillation

The increased risk of HF patients developing AF can primarily be explained by structural atrial remodeling, mitral valve regurgitation, and altered neurohumoral balances (*Figure 1*).

Structural remodeling of atria in HF

Both HFrEF and HFpEF are often associated with increased atrial filling pressures, although the mechanisms responsible may be different. HFrEF is characterized by reduced LV ejection fraction and increased end-diastolic LV volume. In diastolic HF, the end-diastolic volume is usually not increased, but LV relaxation is disturbed. The elevated LV pressure in both types of HF causes increased atrial filling pressure, which in turn lead to a cascade of structural changes in the atrial wall, strongly associated with AF.

The first step in this cascade is atrial dilatation and mechanical atrial wall stretch due to the elevated atrial filling pressures. Wall stretch may be present in strongly varying extents through different parts of the atria, with peaks around the pulmonary vein ostia, LA appendage ridge, the high posterior wall, anterior wall regions, and the septal regions. [10] Atrial stretch provokes atrial scarring and fibrosis, predominantly in the areas where it is most severe. Atrial dilatation and atrial fibrosis are considered important factors for the occurrence and maintenance of AF. In dilated atria, multiple circuits coexist. Fibrosis leads to

inhomogeneities in conduction and refractoriness and the arrhythmia itself causes persistent shortening of refractoriness. All of these changes favor re-entry. [11]

Mitral regurgitation

Mitral regurgitation is common in HF, with different underlying etiologies for HFrEF and HFpEF. In HFrEF, structural ventricular remodeling and LV dilatation may lead to secondary mitral regurgitation, whereas HFpEF may induce atrial functional mitral regurgitation predominantly due to annular dilatation and anterior leaflet flattening. [12] Moderate or severe mitral regurgitation causes left atrial volume and pressure overload, resulting in increased local atrial wall stress, thus promoting the development of AF. The severity of regurgitation is correlated with the development of AF. Notably, AF itself may cause atrial functional mitral regurgitation similar to the manner in which HFpEF does, thereby indirectly sustaining itself.

Neurohumoral changes in HF

The decreased cardiac output during acute and chronic HF, similarly to that during AF, often causes RAAS and sympathetic activation. Besides their impact on HF development, these neurohumoral changes promote atrial remodeling and increase susceptibility for AF as well. The structural myocardial changes in the atria following increased RAAS hormone levels lead to increased development and sustenance of AF. Furthermore, sympathetic stimulation causes increased early and delayed afterdepolarizations, increased focal firing and favorable conditions for re-entry, thus increasing the susceptibility for AF. [13] Importantly, as these neurohumoral changes are both a cause of and a result of AF as well as HF, a continuous process is created in which the presence of (one of) the diseases may provoke or deteriorate both itself and the other.

Mutual risk factors

Additionally, AF and HF share a common risk profile, increasing the possibility of developing both conditions separately from each other. Both HF and AF are more commonly seen in older patients with cardiovascular risk factors such as hypertension, diabetes mellitus, obesity, smoking, and sleep apnea syndrome.

Hypertension and sleep apnea may cause structural myocardial changes such as LV hypertrophy and interstitial fibrosis, leading to increased filling pressures and provoking the development of HF and AF. Obesity, diabetes mellitus and smoking cause a pro-inflammatory state, creating an environment in which

a patient is more susceptible to both diseases. [14] In addition, besides their direct effects these risk factors contribute to the development of ischemic heart disease, which is one of the most prevalent causes of HF and is associated with an increased risk of developing AF. [15]

TREATMENT CONSIDERATIONS

Heart failure management

Standard treatment for HFrEF patients, independently of the presence or absence of AF, involves at least treatment with a RAAS inhibitors and beta-blockers (*Figure 2*). [16] Given the close involvement of the RAAS and the sympathetic nervous system in developing and maintaining AF, treatment with inhibitors of these pathways is thought to not just inhibit HF progression, but to also reduce structural atrial remodeling and prevent AF in at-risk patients. Indeed, these pharmacological interventions seem to have the potential to reduce the rate of new-onset AF in this population. However, a meta-analysis based on individual patient data comparing beta-blockers with placebo in 1677 patients with concomitant HF and AF did not demonstrate a beneficial effect, in contrast to HF patients in sinus rhythm. [17] This may be caused by the questionable positive effect of strict rate control in AF patients and the increased risk of longer pauses in excessive rate control. [18,19] However, these findings did not lead to changed treatment recommendations for AF patients in the most recent guidelines.

For HFpEF, the optimal treatment strategy remains unclear. As no single drug has yet demonstrated a survival benefit in this complex and heterogeneous population, the cornerstone of the treatment of these patients remains treatment of underlying comorbidities. [16] Notably, up to 80% of HFpEF patients are still prescribed RAAS inhibitors or beta-blockers, presumably mainly for the treatment of common cardiovascular comorbidities such as hypertension and coronary artery disease.

Risk factor management

There has been extensive research studying the effect of strict risk factor management on AF burden. Positive effects from weight loss, blood pressure management, lipid management, and treatment of obstructive sleep apnea syndrome have been demonstrated in patients with (lone) AF. [14] In a population with both AF and HF, strict risk factor management reduced AF burden as well. [20] Less is known about the effect of risk factor management on HF in this

population. In addition, the optimal target weight for patients with concomitant AF and HF remains unclear. Although associated with a higher arrhythmia burden in AF patients, obesity actually improves prognosis in the HF population. [21] This phenomenon has become known as the obesity paradox, and its effect on prognosis of combined HF and AF remains to be determined.

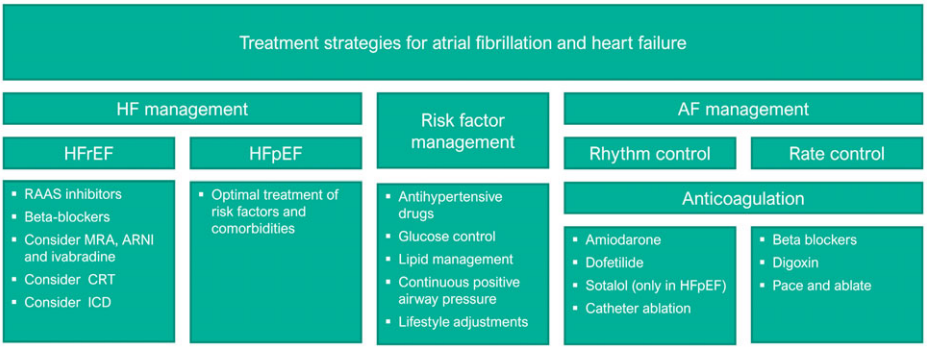

Figure 2. Treatment strategies for atrial fibrillation and heart failure.

Abbreviations: AF: atrial fibrillation, ARNI: angiotensin receptor-neprilysin inhibitor, CRT: cardiac resynchronization therapy, HF: heart failure, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction, ICD: implantable cardioverter defibrillator, MRA: mineralocorticoid receptor antagonist, RAAS: renin-angiotensin-aldosterone system.

Atrial fibrillation management

AF can be treated with either rhythm control, i.e., attempting to maintain sinus rhythm, or rate control, i.e., allowing AF to persist but controlling the frequency of ventricular contractions (*Figure 2*). [22] In light of the negative effect AF can have on HF, adopting a rhythm control strategy would be expected to be beneficial in terms of survival and disease progression. This theory is supported by the recently published EAST trial, which confirmed the positive effects of rhythm control in patients with early AF. [23] However, most antiarrhythmic drugs are contraindicated in HF patients, providing a challenge to the pursuit of rhythm control in this patient category. The only available options are amiodarone and dofetilide in HFrEF patients and amiodarone, dronedarone and dofetilide in HFpEF patients, while dofetilide is not widely available in Europe. [14] Amiodarone, although a potent antiarrhythmic drug, is known for its extracardiac side-effects and high discontinuation rate, limiting its low-threshold prescription.

Studies comparing rhythm and rate control in patients with AF and HF did not demonstrate benefit of medication-based rhythm control over rate control in terms of major clinical endpoints. [24] A recent meta-analysis comparing rhythm and rate control in a total of 2486 patients demonstrated comparable rates of mortality, stroke and thromboembolic events between the two groups. [25] The hospitalization rate was higher in the rhythm control group, mainly driven by the need for repeated cardioversion, adjustment of antiarrhythmic therapy and adverse drug reactions. However, the lack of improvement may be the limited efficacy of drugs in maintaining sinus rhythm, in addition to the harmful side-effects of currently available antiarrhythmic therapies.

Catheter ablation in HF patients with paroxysmal or persistent AF

Considering these limitations of medical therapy, more potent options to maintain sinus rhythm, such as invasive treatment with catheter ablation, might be effective to improve outcome. In the past years, considerable advancements in this technique have been made and it has proven to be an effective treatment to reduce AF burden and complaints. Several observational studies investigated if these results can be extrapolated to the HF population. Indeed, positive effects of catheter ablation were demonstrated in HFrEF patients on important surrogate outcomes such as LV ejection fraction, quality of life, and exercise capability. Observational data of HFpEF patients suggest, similar to those in HFrEF patients, that catheter ablation is associated with decreased HF symptoms, as well as with regression of echocardiographic diastolic dysfunction parameters. [26] However, randomized trials confirming these promising results are not yet available in the HFpEF population.

In the HFrEF population, the first randomized trial comparing catheter ablation and pharmacological treatment was published in 2011. [27] This small study in 38 patients did not demonstrate an improvement on the primary endpoint of LV ejection fraction following catheter ablation compared to pharmacological rate control. However, this lack of effect might be attributable to the modest success percentage of maintaining sinus rhythm of only 50%. In subsequent randomized studies, which all achieved higher success rates from catheter ablation, positive results on LV ejection fraction, improved functional capacity, and quality of life were demonstrated. [28-30]

In 2016, the AATAC trial demonstrated a trend toward lower mortality and hospitalizations following catheter ablation when compared to amiodarone, although the study was not powered to demonstrate significant effects. [31] After

these promising results, the outcomes of the CASTLE-AF were eagerly awaited, as this was the first sufficiently powered study to demonstrate possible effects on clinical endpoints. Indeed, the CASTLE-AF described an important reduction in the composite endpoint of death and HF hospitalizations, from 44.6% in the standard medical therapy group to 28.5% in the AF ablation group (hazard ratio 0.62 [0.43-0.87]). [32] In contrast, the most recent study comparing catheter ablation and pharmacological treatment, the CABANA trial, did not demonstrate a significant difference in the primary composite endpoint of mortality, disabling stroke, serious bleeding, or cardiac arrest between the two groups. [33]

A meta-analysis combining efficacy data of all seven aforementioned randomized trials found that catheter ablation was associated with significantly lower mortality (relative risk reduction of 49%), hospitalization (relative risk reduction of 56%), improved LV ejection fraction, and improved quality of life. [25] Still, it is important to note that the positive reported effects of catheter ablation are strongly dependent on several factors, such as patient characteristics, HF etiology, follow-up duration and ablation strategy (*Figure 3*). Hence, although catheter ablation has demonstrated favorable effects on important clinical endpoints, as well as functional status and quality of life, careful patient selection and selection of ablation technique remains a point of attention.

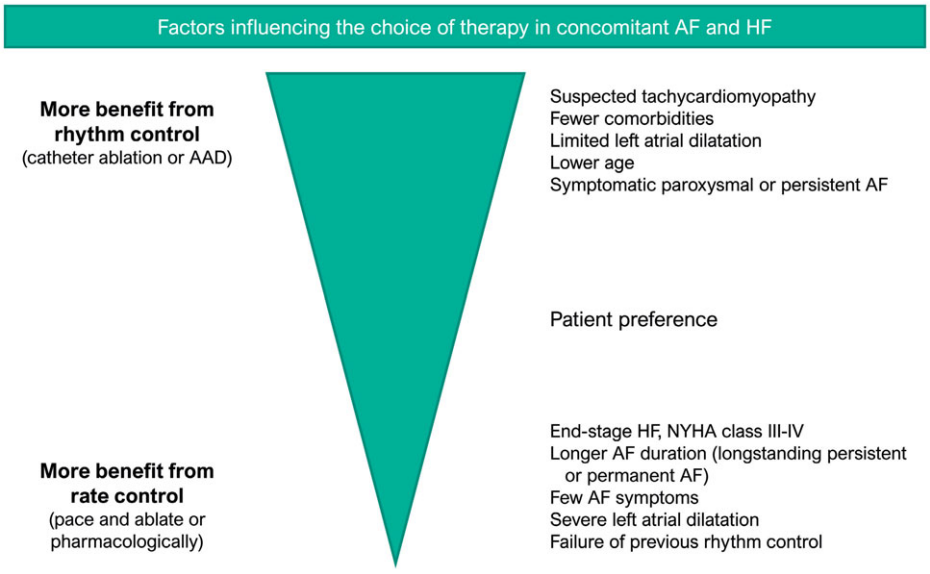

Figure 3. Therapy choice for atrial fibrillation and concomitant heart failure.
Abbreviations: AAD: antiarrhythmic drugs, AF: atrial fibrillation, HF: heart failure, NYHA: New York Heart Association.

Pace and ablate (rate control) in HF patients with permanent AF

For patients with permanent AF, a pace and ablate strategy (atrioventricular junction ablation combined with cardiac resynchronization therapy (CRT)) may be considered. In this strategy the persistence of AF and the associated loss of atrial contractions is accepted, while biventricular pacing assures strict rate control and regular ventricular contractions. Several studies have demonstrated markedly improved HF outcomes of a pace and ablate strategy compared to pharmacological rate control in patients with and without a previous CRT indication. [34] However, when pace and ablate is compared with catheter ablation aimed to achieve rhythm control, rhythm control demonstrated superior results. Therefore, it seems reasonable to reserve a pace and ablate strategy for those patients in whom catheter ablation is expected to be ineffective (e.g., due to comorbidities, severely dilated atria or permanent AF) or in whom previous catheter ablation has failed (*Figure 3*).

CONCLUSION

The optimal therapy for coexisting AF an HF remains a topic of debate. In light of the harmful effect AF can have on HF, adopting a rhythm control strategy could be expected to be beneficial in terms of survival and disease progression. However, pharmacological rhythm control does not lead to significant health gain when compared to rate control in this patient population. Catheter ablation is an effective option to achieve rhythm control without the unfavorable effects of antiarrhythmic drugs, and seems to improve the HF prognosis as well. However, several unaddressed questions remain despite the current evidence, in particular with regards to the optimal patient selection for this invasive therapy. Further studies with long-term follow-up may clarify the remaining uncertainties.

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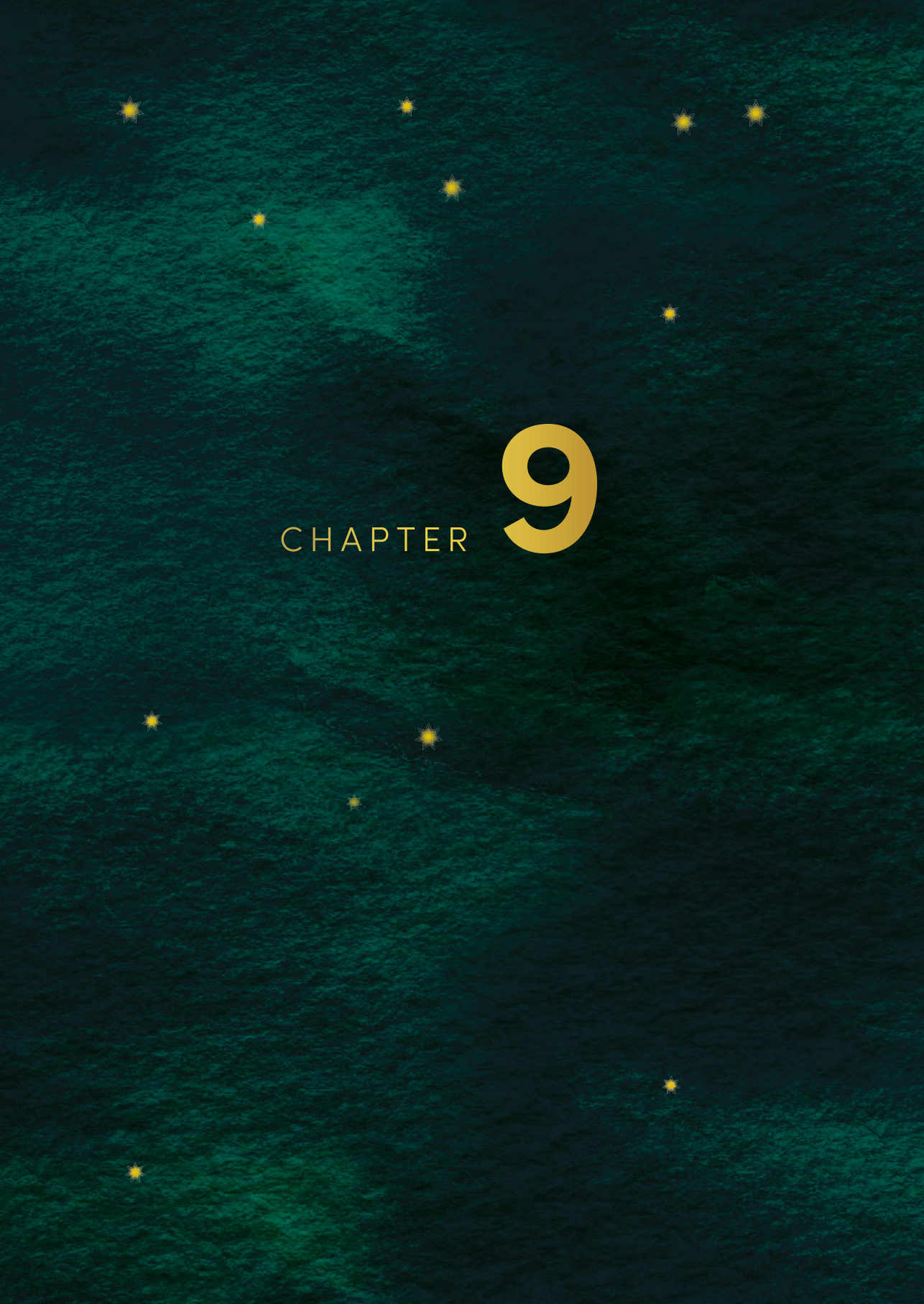
CHAPTER 9

Cryoballoon ablation versus medical therapy in patients with heart failure and atrial fibrillation: rationale and design of the RACE-8-HF trial

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In preparation for submission.

ABSTRACT

Background

Atrial fibrillation (AF) and heart failure often coexist and negatively impact each other's prognosis. Previous studies demonstrated that catheter ablation for AF improved heart-failure related outcomes such as left ventricular function and quality of life in heart failure patients. Catheter ablation has also been reported to reduce clinical events in patients with tachycardia-mediated cardiomyopathy, but it remains unclear whether this effect is sustained in the general heart failure population.

Methods

The c**R**yoballoon **A**blation versus medi**C**al th**E**rapy in patients with **H**eart **F**ailure and atrial fibrillation (RACE-8-HF) trial is a prospective, randomized, controlled, open-label, blinded endpoint (PROBE), multicenter clinical trial. Patients with symptomatic AF and heart failure (left ventricular ejection fraction <50%) are randomized to early invasive therapy (cryoballoon ablation) or conventional treatment. The primary endpoint is a composite of all-cause mortality, unplanned cardiovascular hospitalizations, and stroke. Key secondary endpoints include cost-effectiveness and a hierarchal endpoint of all-cause mortality, stroke, unplanned cardiovascular hospitalizations, and change in heart failure complaints. A total of 600 patients will be included in 10 centers in The Netherlands.

Discussion

The RACE-8-HF trial aims to strengthen evidence on the effects of catheter ablation in patients with heart failure with (mildly) reduced ejection fraction and AF. Additionally, it will enable the first trial-based economical evaluation studying catheter ablation in this population.

Clinicaltrials.gov identifier: NCT04342832

INTRODUCTION

Atrial fibrillation (AF) and heart failure are two highly prevalent cardiovascular conditions that often go hand in hand, both due to direct bidirectional interrelations and to a shared risk factor profile. [1, 2] The elevated left ventricular pressures associated with heart failure result in increased atrial wall stress and atrial dilation, which in turn leads to formation of atrial fibrosis and an increased tendency to develop AF. [3] Conversely, AF causes immediate, reversible hemodynamic changes, as well as persistent structural changes in the myocardial wall of the atria and the ventricles which may lead to heart failure. The immediate and persistent effects of AF are often more pronounced in heart failure patients than in those with normal cardiac function. Therefore, the combination of heart failure and AF is associated with a higher symptom burden and a poorer prognosis than when the morbidities occur independently, regardless of the temporal sequence in which the comorbidities developed. [4]

In light of the causal connection between AF and heart failure, adopting a rhythm control strategy to maintain sinus rhythm would be expected to be beneficial for heart failure outcomes. Nevertheless, medication-based rhythm control has no clinical benefit over rate control in terms of major clinical endpoints in this population. [5] This lack of improvement may be a result of the limited efficacy of antiarrhythmic drugs in maintaining sinus rhythm in heart failure patients, in addition to potential harmful side effects. In contrast, catheter ablation, being a more potent rhythm control strategy than medication-based options, has been demonstrated to improve important surrogate outcomes such as left ventricular function, quality of life, and exercise capability in patients with heart failure with reduced ejection fraction (HFrEF). [6-9] In early AF patients strict rhythm control strategies including catheter ablation also reduce major adverse clinical events (i.e., mortality, heart failure hospitalizations, and stroke), but whether this translates to patients with previous heart failure remains a topic of debate. [10] Until now, only a few randomized trials have been conducted that directly studied this question, but there are important questions regarding their generalizability to the entire heart failure population and one of the trials was considerably underpowered, leading to discordant results. [11-13] In addition, these trials only included patients with HFrEF. Whether the results found in these trials also apply to patients with heart failure with mildly reduced ejection fraction (HFmrEF), a heart failure subtype that closely resembles HFrEF, cannot be determined based on these studies.

The ongoing RACE-8-HF trial was initiated to compare the effect of early invasive rhythm control through cryoballoon ablation with conventional therapy in a representative subset of patients with AF and HFrEF or HFmrEF. Herein, the rationale and design of this trial are described.

METHODS

The c**R**yoballoon **A**blation versus medi**C**al th**E**rapy in patients with **H**eart **F**ailure and atrial fibrillation (RACE-8-HF) trial is a prospective, randomized, controlled, open-label, blinded endpoint (PROBE), multicenter clinical trial including patients with symptomatic AF and heart failure. The effectiveness of early invasive rhythm control for AF consisting of cryoballoon ablation is compared to conventional treatment, with a composite primary endpoint of all-cause mortality, unplanned cardiovascular hospitalizations, and stroke. Participants undergo a baseline visit, are concurrently randomized and thereafter complete several follow-up visits (*Figure 1*). The study is endpoint driven and the duration of the follow-up thus varies per patient, with a minimum follow-up duration of one year for each patient.

The trial was investigator-initiated and is funded by ZonMw (852002030) and the Netherlands Heart Institute (CRYO-PVI project). It was designed following the SPIRIT recommendations for reporting outcomes in trial protocols and is registered at clinicaltrials.gov (NCT04342832). [14] Enrollment started in July 2020 and is currently ongoing in ten Dutch hospitals (*Supplement 1*). The inclusion period is estimated to last five years, median follow-up duration two years, and total study duration ± six years.

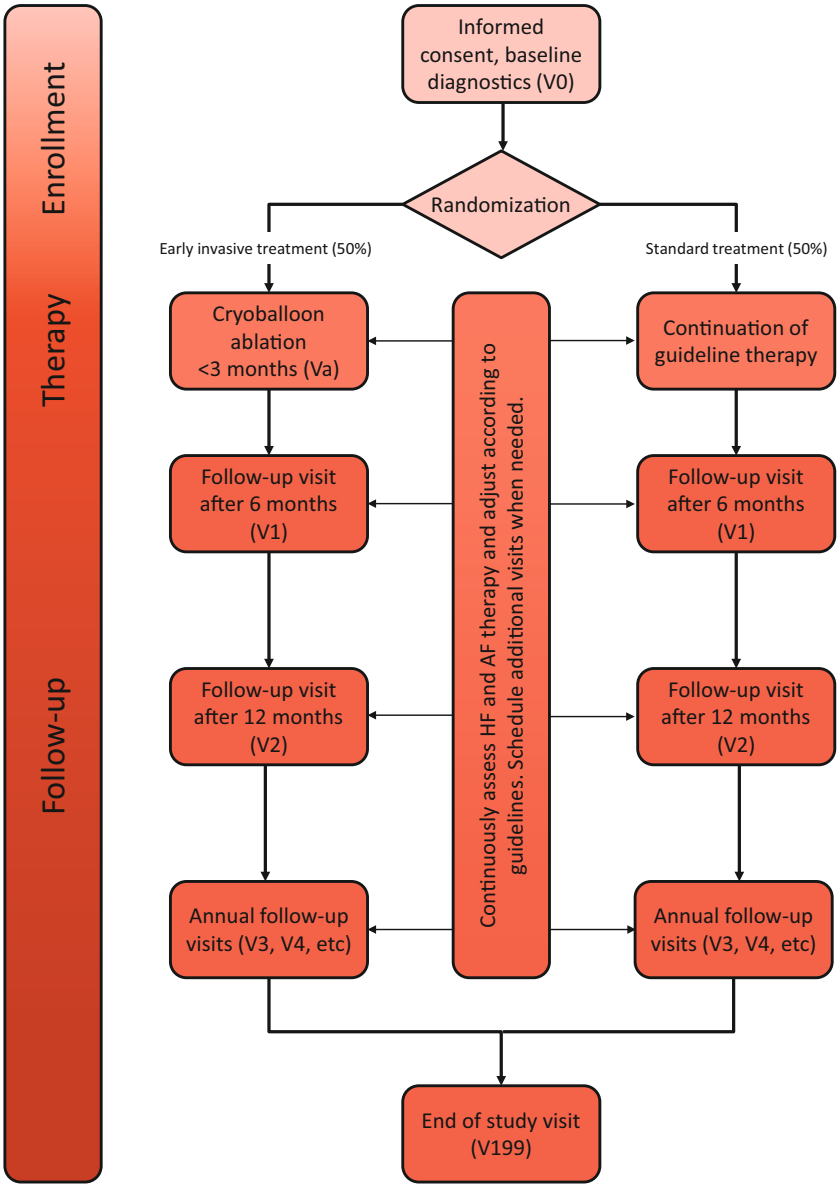

Figure 1. Study flowchart.
Abbreviations: AF: atrial fibrillation, HF: heart failure, V: visit.

Participants and enrollment

The trial aims to include 600 symptomatic patients with HF(m)rEF (left ventricular ejection fraction [LVEF] <50%) and paroxysmal or persistent AF. The in- and exclusion criteria are provided in *Table 1*. Eligible patients receive verbal and written information about the study. After obtaining written consent, baseline data are collected including medical history, New York Heart Association (NYHA) class, questionnaires, results of physical examination, electrocardiogram (ECG), device interrogation (when applicable), and blood sampling (*Table 2*). Subsequently, patients are randomized between the two treatment options.

Table 1. In- and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Patients aged 18-80; • Heart failure with ejection fraction <50%, as assessed by recent (<6 months) echocardiography, cardiovascular magnetic resonance imaging or other cardiac imaging;[1] • Documented AF; • Eligible for both treatment arms; • Signed and dated informed consent prior to admission to the trial.	• End-stage heart failure: NYHA class IV, patients on waiting list for cardiac transplant and/or left ventricular assist device; • Long-standing persistent AF (> 1 year *uninterrupted* AF) or permanent AF; • Asymptomatic patients; • Previous pulmonary vein isolation or surgical ablation; • Impaired renal function, defined as estimated glomerular filtration rate ≤25 ml/min/1.73m$^{2;}$ • Recent (<90 days) acute coronary syndrome, cardiac intervention[2], or stroke/transient ischemic attack; • Planned or expected cardiac surgery in the following year • Active infectious disease or malignancy; • Women who are pregnant or planning to become pregnant during the trial; • Contraindication for cryoballoon ablation or other condition that may prevent patients from adhering to the trial protocol, in the opinion of the investigator.

[1] When changes in the left ventricular function are unlikely (i.e., in stable patients without cardiovascular events such as acute coronary syndrome, severe incessant arrhythmias, or cardiac resynchronization therapy (CRT) implantation since last imaging), imaging from 6-12 months ago is accepted.

[2] Cardiac interventions include percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), and heart valve repair or replacement (endovascular or surgical).

Abbreviations: AF: atrial fibrillation, NYHA: New York Heart Association.

Randomization and interventions

Patients are randomized to the treatment arms in a 1:1 ratio via an interactive response technology system (Castor EDC [15]) by block randomization using random block sizes. Stratified randomization blocks are used for men or women

and LVEF <30% or ≥30% to ensure an even distribution of these characteristics between the treatment groups. Given the nature of the treatment arms, patients and the investigators team are unblinded for treatment allocation.

Background therapy for all patients

Investigators are encouraged to treat all patients with optimal background therapy for AF and heart failure consistent with current guidelines, including thorough risk factor assessment and management, independent of treatment allocation.[16, 17] Background treatment (including medication, blood pressure, ventricular heart rate, and physical activity) is assessed during each study visit. If a patient's background therapy is considered suboptimal, a message appears in the electronic case report form (CRF) requiring an explanation, and the treating physician is encouraged to adjust or intensify treatment when indicated and possible.

Early invasive rhythm control

In addition to this background therapy, patients allocated to the intervention arm undergo a cryoballoon ablation. The procedure is planned as soon as possible, but no later than three months after randomization. The ablation is performed by an experienced cardiac electrophysiologist using CE-certified equipment. Via the femoral vein a guiding catheter is advanced through the inferior vena cava to the right atrium and into the left atrium via transseptal puncture. The cryoballoon is advanced, inflated, and placed against one of the four pulmonary veins (PVs). PV occlusion is assessed by selective contrast injection. When adequate PV antral seal is confirmed, ablation of the tissue in contact with the balloon is performed using pressurized liquid nitrous oxide, creating circular lesions around the PV. The balloon and tissue interface are then allowed to reach normal temperatures. Depending on local practice, the freeze-thaw cycle may be repeated twice. Electrical isolation is assessed and when it is confirmed, the next PV is treated in the same way. The procedure ends when all PVs are isolated.

After the ablation procedure, a blanking period of 3 months is maintained. Anticoagulants are preferably not interrupted prior to or during the procedure. The continuation or discontinuation of other medication (including antiarrhythmic drugs) during the procedure and after the blanking period is decided upon by local practices of the center that performs the ablation.

Table 2. Study procedures.

Trial phase	**Enrollment**	**Therapy**	**Follow-up**			
Visit	**V0 (baseline)**	**Va (if applicable)**	**V1**	**V2**	**V3, V4, V5, etc.**	**V199**
Trial month	**0**	**0–3**	**6 (+/- 1 month)**	**12 (+/- 1 month)**	**24, 36, 48, etc. (+/- 1 month)**	**End of study**
Medical history	√					
NYHA class	√		√	√	√	√
Cardiovascular medications	√		√	√	√	√
Assess therapy for HF, AF, and comorbidities and adjust if necessary	√		√	√	√	√
Physical examination	√			√	√	√
12-lead ECG	√			√	√	√
Device interrogation[1]	√	√	√	√	√	√
48-h Holter monitoring[2]	√		√	√		
Blood samples (local laboratory)	√[3]			√[4]		√[4]
Questionnaires: EQ-5D-5L, MLHFQ, iMCQ, iPCQ	√		√	√	√	√
Cryoballoon ablation		√				
Collection of serious adverse events, endpoints, study deviations			As they occur			

[1] *Only for patients with implanted device or implantable loop recorder.*

[2] *Only for patients without implanted device or implantable loop recorder.*

[3] *Hemoglobin, sodium, potassium, creatinine, N-terminal pro-brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP), thyroid stimulating hormone (TSH), cholesterol spectrum, and ferritin.*

[4] *Hemoglobin, sodium, potassium, creatinine, and N-terminal pro-brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP)*

Abbreviations: AF: atrial fibrillation, ECG: electrocardiogram, HF: heart failure, iMCQ: iMTA Medical Consumption Questionnaire, iPCQ: iMTA Productivity Cost Questionnaire, MLHFQ: Minnesota Living with Heart Failure Questionnaire, NYHA: New York Heart Association, V: visit.

Redo ablation procedures

Redo ablation is indicated in patients who, after the blanking period of the initial ablation, still experience symptomatic and documented recurrences of atrial arrhythmia, and who demonstrate insufficient improvement or worsening of AF symptoms. In the case of a redo ablation, the operator is encouraged to assess PV reconnection and, when present, to treat potential gaps with radiofrequency ablation. In the case of ostial scars, additional antral lesions may be created. Cavo-tricuspid isthmus lesions may be created as well, when applicable. Additional substrate modification or box lesions are not encouraged.

Standard treatment

The control group will receive conventional (non-invasive) therapy for heart failure and AF. Both heart rhythm and heart rate control are allowed, whichever is deemed applicable to the patient and treating physician. There are no restrictions in types of prescribed medication.

Follow-up

Follow-up visits are scheduled at six and twelve months after enrollment, and thereafter on a yearly basis (*Figure 1*). During follow-up visits, results of the following procedures are collected: NYHA class, questionnaires, physical examination, ECG, device interrogation (when applicable), and blood sampling. Patients without an implanted cardiac device undergo Holter monitoring at 6 and 12 months after enrollment. Further specification of examinations is provided in *Table 2*.

Outcome measures and definitions

The primary endpoint is time to a composite of all-cause mortality, unplanned cardiovascular hospitalizations, and stroke (time-to-event analysis). The three key secondary endpoints are (1) a combined endpoint of all-cause mortality, number of unplanned cardiovascular hospitalizations and stroke (recurrent-event analysis), (2) a hierarchal endpoint of all-cause mortality, stroke, unplanned cardiovascular hospitalizations, and change in heart failure complaints (Finkelstein-Schoenfeld analysis), and (3) cost-effectiveness and budget impact. Additional exploratory endpoints are provided in *Table 3*.

Hospitalization is defined as an admittance in the hospital or emergency department for 24 hours or more, and is deemed unplanned when the decision to admit the patient is made less than 3 days in advance. The hospital admission

for the initial cryoballoon ablation or redo-ablations are not considered unplanned cardiovascular hospitalizations as they are planned procedures. Change in heart failure complaints is defined as change between the first and last score on the Minnesota Living with Heart Failure Questionnaire (MLHFQ), a 21-point questionnaire designed to evaluate symptoms, physical and social limitations, and quality of life in patients with heart failure. Recurrence of AF is defined as AF on an entire standard 12-lead ECG recording, AF with a duration of ≥30 seconds on alternative ECG tracing (e.g., on single-lead ECG or Holter monitoring), or as an atrial high-rate episode on an implanted device that lasts at least five minutes or triggers a mode switch, and is confirmed as being AF by a trained physician. [16]

Table 3. Secondary and exploratory endpoints.

Secondary endpoints	Exploratory endpoints
• Combined endpoint of all-cause mortality, total number of unplanned cardiovascular hospitalizations and stroke (recurrent-event analysis); • Hierarchical endpoint of all-cause mortality, stroke, unplanned cardiovascular hospitalizations, and change in heart failure complaints determined by the Minnesota Living with Heart Failure Questionnaire; • Cost-effectiveness and budget impact.	• All-cause mortality; • Cardiovascular mortality; • Unplanned cardiovascular hospitalizations; • Hospitalizations for heart failure; • Hospitalizations related to AF or other atrial arrhythmia; • Days alive out of the hospital; • Recurrence of atrial arrhythmia; • Electrical or chemical cardioversions; • Change in heart failure complaints; • Improvement in LVEF after 12 months; • Stroke or TIA; • Quality of life; • Changes in non-invasive electrophysiological markers for substrate quantification; • Recurrence of AF and AF burden;[1] • Incidence of appropriate ICD therapy;[1] • Incidence of inappropriate ICD therapy.[1]

[1] *to be determined in patients with an implanted cardiac device or implantable loop recorder (ILR).*

Abbreviations: AF: atrial fibrillation, ICD: implantable cardiac defibrillator, LVEF: left ventricular ejection fraction, TIA: transient ischemic attack.

Detailed definitions for other endpoints are provided in a separate endpoint charter. Potential endpoints are reviewed by an independent Endpoint Adjudication Committee that is blinded for treatment allocation. All events that occur after randomization are included in the analyses, including those occurring before a patient undergoes the allocated treatment.

Study organization

The trial is overseen by a Steering Committee, Data Safety Monitoring Board (DSMB) and Event Adjudication Committee. Detailed descriptions of the responsibilities of the different trial committees are provided in separate charters. The composition of the committees is specified in *Supplement 2*. In short, the Steering Committee consists of two Principal Investigators (KV, MR) and 14 general members including cardiologists specialized in heart failure and electrophysiology, an epidemiologist, and a translational research expert. The Steering Committee is responsible for the overall organization and management of the trial and for scientific integrity, scientific validity, and study quality.

An independent DSMB monitors the safety of participants during the trial and advises and assists the steering committee to protect the validity and credibility of the trial. The DSMB independently reviews the accumulating safety data and monitors overall trial conduct. Conclusions reached by the DSMB are shared as advice with the Steering Committee, who will then prepare the final decision.

The Event Adjudication Committee evaluates source documentation of potential endpoint events to independently confirm whether they meet the predefined endpoint definitions. The Committee is blinded for patients' treatment allocation.

Data management

A unique study code is assigned to each patient and patient identifiers are removed. Coded data are entered in a password-protected, secure electronic CRF (Castor EDC).[15] All data are handled in accordance with the EU General Data Protection Regulation (GDPR; in Dutch AVG) and the Dutch Act on Implementation of the General Data Protection Regulation (UAVG). Monitoring is performed by Clinical Trial Center Maastricht (CTCM, Maastricht, Netherlands) according to a predefined monitoring plan in accordance with prevailing regulations and guidelines.

Statistical considerations

Analyses of the primary and secondary endpoints will primarily be executed on an intention-to-treat population. Missing data will be estimated using multiple imputation, assuming missing at random. For all statistical tests, a level of significance of $\alpha = 0,05$ will be used. Given the many occurrences of cross-over in previous AF ablation studies, exploratory per-protocol analyses

will be performed. [11, 18] In addition, several exploratory subgroup analyses are planned (*Supplement 3*). No scheduled interim analyses will be executed. Data analyses will be performed with SPSS Statistics, version 25.0 or higher (IBM SPSS Inc. Chicago IL).

Primary endpoint analysis

The primary endpoint will be examined with the use of time-to-first-event analysis. Event-free survival curves will be estimated by the Kaplan-Meier method and compared using the log-rank test. Event or censoring times will be measured from the time of randomization (V0) onwards. Follow-up of patients who did not experience events will be censored at the end-of-study visit (V199). Patients who are lost to follow-up will be censored after the date of the last clinical contact. Hazards with associated 95% confidence intervals will be calculated using Cox's proportional hazards model.

Secondary endpoint analyses

The first secondary endpoint of all-cause mortality, number of unplanned cardiovascular hospitalizations and stroke will be analyzed using the Andersen-Gill model for recurrent-event analysis. [19]

The hierarchical secondary endpoint of all-cause mortality, stroke, unplanned cardiovascular hospitalizations, and change in heart failure complaints will be calculated using the Finkelstein-Schoenfeld method. [20] Patients in the early invasive rhythm control group will be consecutively matched to all patients in the medical therapy group. For each matched pair, the first patient who reached the endpoint of all-cause death will be determined. If neither of the two patients in the pair meets this endpoint, the first patient who experiences a stroke will be determined. If neither of the two experienced a stroke, the patient with the most unplanned cardiovascular hospitalization will be determined. In case of a tie, the first cardiovascular hospitalization will be determined. If none of these events happen, increase in heart failure symptoms will be compared (*Figure 2*). The 'win ratio' in the two treatment groups will be calculated and presented with 95% confidence interval.

The final secondary endpoints are cost-effectiveness and budget impact. A trial-based economical evaluation will be performed from a societal perspective. As the costs from early invasive therapy are expected to be higher than those of standard treatment on a short term, but lower on a long term, additional Markov modelling will be performed to estimate lifetime incremental

cost-effectiveness ratio (ICER). Resource use is based on hospital records and questionnaires on medical consumption and productivity loss. Unit prices will be derived from the standardized Dutch cost manual or based on calculations that follow the recommendations of this manual.[21] A discount rate of 4% will be applied, following standard practice in the Netherlands.[22] Patient outcome is based on survival data and quality of life (EQ-5D-5L questionnaire). Quality adjusted life years (QALYs) will be calculated from the area under the curve. A discount rate of 1,5% will be applied, following standardized practice in The Netherlands. The ICER will be calculated by dividing the difference in costs by the difference in effectiveness between the treatment groups. As most resource use volumes follow a skewed distribution, differences between the two groups will be analyzed with bias-corrected bootstrap analysis. Bootstrap analysis will also be used to quantify the uncertainty surrounding the ICER. Results of this analysis will be presented in cost-effectiveness planes and acceptability curves.

Sample size calculation and interim analyses

Regarding the primary endpoint of all-cause mortality, unplanned cardiovascular hospitalization and stroke, a risk reduction of 10-15% is considered clinically relevant given the seriousness of the conditions that are included in the endpoints. However, considering the results of the AATAC, CASTLE-AF, and RAFT-AF trials, a much higher risk reduction of ± 30% is expected in the intervention arm.[9, 11, 12] The event rate in the control arm is estimated to be 40% per two years.[9, 11, 23] The expected event rates of 40% in the control group and 28% in the intervention group (30% reduction) correspond with a hazard ratio of 0.643. The sample size for this study was calculated using the Cox's proportional hazards model. To achieve 80% power at a significance level of 0.050 to detect an expected hazard ratio of 0.643, the number of required events is 162. To achieve this number of events, a sample size of 474 patients with a median follow-up duration of 2 years is required. Anticipating a loss to follow-up percentage of 5% and cross-over of 15%, the estimated number of patients that need to be included is 600 to ensure sufficient evaluable patient data.

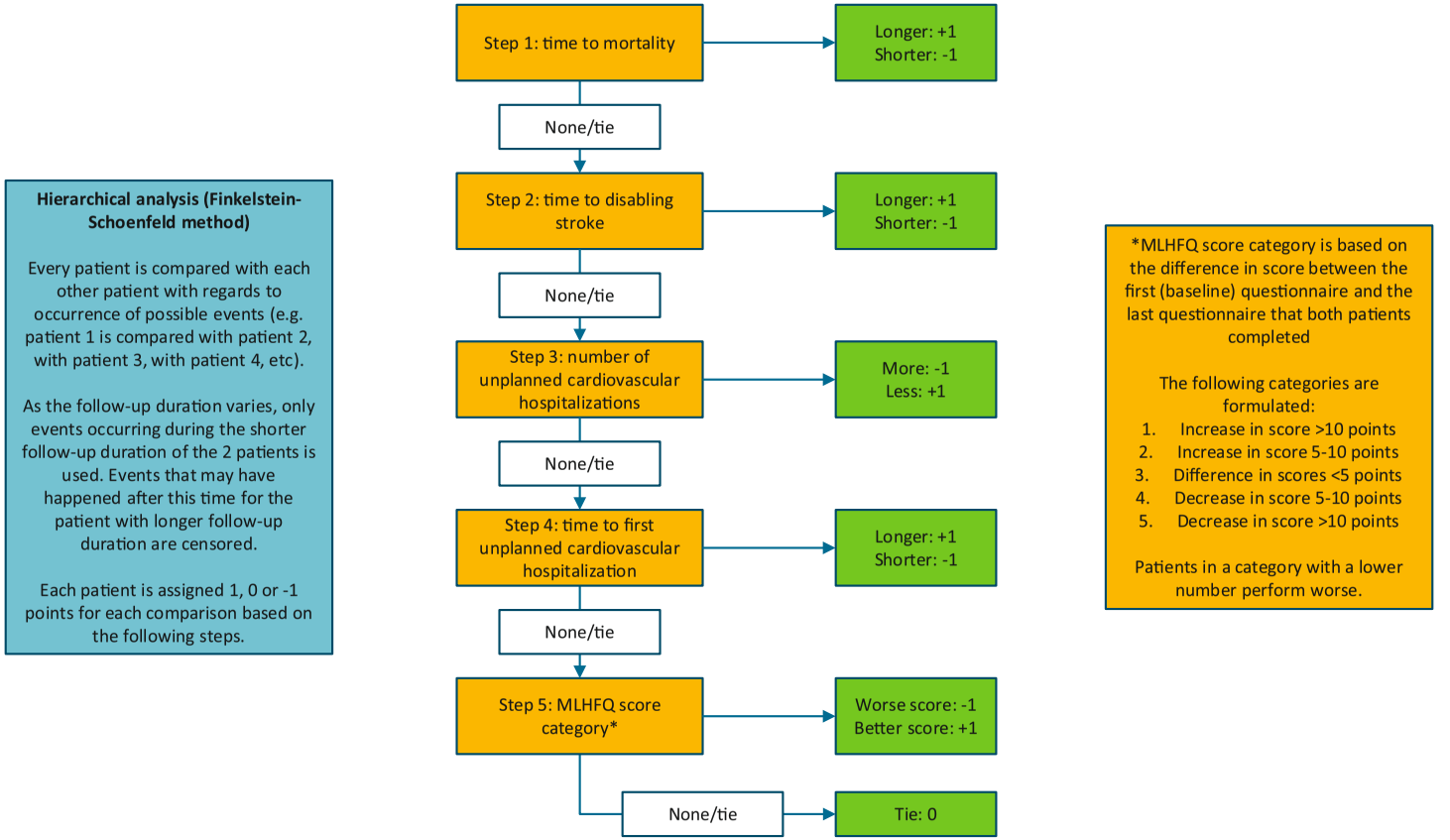

Figure 2. Hierarchical Finkelstein-Schoenfeld analysis.

Abbreviations: MLHFQ: Minnesota living with heart failure questionnaire.

Ethical considerations

The trial is conducted in accordance with the Declaration of Helsinki, guidelines for Good Clinical Practice (GCP), the Medical Research Involving Human Subjects Act (WMO) and other relevant Dutch and international laws, regulations and codes of conduct. The research ethics committee of the Maastricht University Medical Center has reviewed the study protocol and passed a positive judgment (19-084/NL71710.068.19). All patients provide written informed consent before enrollment in the trial.

DISCUSSION

In the RACE-8-HF trial, early invasive rhythm control through cryoballoon ablation is compared with conventional therapy in symptomatic patients with AF and HFrEF or HFmrEF. Despite the widespread interest for the position of catheter ablation in the treatment of HF(m)rEF, only four randomized trials have focused on its effect on important clinical outcomes such as mortality, cardiovascular hospitalizations or heart failure hospitalizations. Three trials (CASTLE-AF, AATAC, and a subanalysis from CABANA) demonstrated a significant difference favoring catheter ablation, whereas one (the RAFT-AF trial) did not find a significant improvement. [9, 11, 12, 24] However, this negative result must be interpreted with caution, as the trial was stopped early due to apparent futility at the time of interim analysis. Nevertheless, of these four trials, only the CASTLE-AF was adequately powered to demonstrate significant differences in a HF(m)rEF population, with a total of 363 included patients with LVEF ≤35%. [11] The AATAC trial primarily focused on recurrence of atrial arrhythmia (203 patients included with LVEF <40%), whereas the RAFT-AF was underpowered due to premature discontinuation (411 patients included, of whom 240 had LVEF ≤45%). [9, 12] The CABANA was a subanalysis of a larger trial that included 2204 patients with and without heart failure. Of those, 778 patients were classified as having heart failure (defined as NYHA class II or higher), and only 120 had a baseline ejection fraction <50%. [24] Therefore, the RACE-8-HF trial is only the second trial powered to study the effect of catheter ablation on major clinical endpoints in HF(m)rEF patients. Additionally, the RACE-8-HF trial has some characteristics that are importantly different from previous trials, such as the composition of the study population, uniform ablation technique, and incorporation of cost-effectiveness as secondary endpoint.

Rationale for study population

The RACE-8-HF trial not only includes patients with reduced, but also with mildly reduced ejection fraction (LVEF 40-50%). Although HFmrEF represents roughly a quarter of all heart failure cases, catheter ablation trials studying this heart failure subtype are scarce. [2] Only the previously mentioned RAFT-AF trial and CABANA subanalysis included these patients, and in the latter HFmrEF and HFrEF together represented less than a quarter of the total study population. [12, 24] We expect that catheter ablation will have a similar, potentially even larger benefit in HFmrEF than in HFrEF patients. This expectation is based on comparable reaction patterns in HFrEF and HFmrEF to other heart failure therapies, as well as on subgroup analyses of the CASTLE-AF trial, where the positive effect of catheter ablation was more pronounced in patients with relatively better ejection fraction (25-35% versus <25%). [11, 25-27]

As in most previous trials, asymptomatic patients are excluded from participation in the RACE-8-HF. However, in this trial symptoms are not solely determined by NYHA classification at enrollment, as it is often difficult to differentiate symptoms caused by AF from those caused by heart failure. [28] For instance, a patient may be in NYHA class I when in sinus rhythm, but may experience recurrent episodes of AF with secondary symptoms of congestion. By excluding asymptomatic patients but not patients in NYHA class I, this important subset of patients is still eligible for enrollment.

Patients with long-standing persistent AF (> one year uninterrupted AF) are excluded from participation. In these patients, the success rates of catheter ablation are significantly lower than in other AF subtypes. [29] Combined with the already reduced success rates of ablation in heart failure patients, the benefits of the procedure are expected not to outweigh potential risks in these patients. [30] The same holds true for patients in end-stage heart failure (NYHA IV or patients on the waiting list for cardiac transplant and/or left ventricular assist device). Furthermore, patients with planned or expected cardiac surgery are excluded as they may qualify for concomitant epicardial or hybrid ablation instead of cryoballoon ablation, which although more invasive yields higher success rates. [31]

Rationale for the treatment groups

Opposed to previous trials, this study will use a standardized ablation protocol to minimize differences in treatment strategy. Cryoballoon ablation was selected over radiofrequency ablation because it is a relatively fast,

straightforward, 'single-shot' method to realize electrical pulmonary vein isolation. The reproducibility of the cryoballoon procedure is high and the procedure will therefore be less susceptible to inter-performer variability.

In the control group, both pharmaceutical rhythm and rate control strategies are permitted, if required complemented with electrical or chemical cardioversions. The choice of therapy is left to the discretion of the patients' physician. This freedom in treatment strategy is based on the results from the AF-CHF trial, which demonstrated comparable rates of major adverse cardiovascular events in HFrEF patients treated with pharmaceutical rhythm or rate control. [32]

Rationale for endpoints

The primary endpoint is a composite of mortality, cardiovascular hospitalization, and stroke. This endpoint is comparable to that of previous trials, although there are variations in the definition of heart failure events (admission or non-admission), the inclusion of non-heart failure cardiovascular hospital admissions, and the inclusion of stroke in the primary composite. [11, 12, 24] An important feature of this trial is the blinded evaluation of endpoints by an independent endpoint adjudication committee. Due to the nature of the intervention, patients and investigators are unblinded for treatment allocation, but the classification of potential endpoints will be performed by a team that remains blinded for treatment allocation.

Two important secondary endpoints are the hierarchical and cost-effectiveness endpoint. The strength of a hierarchical (Finkelstein-Schoenfeld) endpoint is that nearly all patients will experience an endpoint: if not a fatal event or hospitalization, then an increase or decrease in heart failure symptoms. In contrast to classic composite endpoints, where the majority of the study population often does not experience any events and their participation therefore contributes minimally to the study conclusions, in this type of analysis data from all patients contribute to the overall result. Although this type of endpoint analysis is not the standard yet, cardiovascular studies using it are growing in numbers. [33, 34] In the future, this type of analyses may ease the conduct of forthcoming trials and bring them to completion faster, making results available to the public faster and exposing less patients to study examinations.

Cost-effectiveness is another secondary endpoint studied in the RACE-8-HF trial. The need to keep healthcare costs manageable and weigh the benefits of treatment to the money spent on it grows. As catheter ablation is an invasive procedure, this treatment arm will be associated with higher initial costs (approximately €4,700 in the Netherlands). However, the resulting reduced AF burden is anticipated to result in improved clinical outcome, and thus less healthcare utilization. Hereby the procedure is expected to be cost-effective and possibly even cost-saving. This is in line with results from a propensity-matched study and a Markov model based on meta-analyses studying cost-effectiveness of catheter ablation in heart failure populations. [35, 36] However, to our knowledge, cost-effectiveness has not yet been studied on patient-level data from randomized controlled trials on this topic.

Limitations and pitfalls

One important limitation that may occur in every randomized trial is selection bias of study participants. Especially the inclusion criterion 'eligible for both treatment arms', although necessary to ensure ethical study conduct, may introduce bias as some investigators will define eligibility differently than others. Screening logs will be kept in a subset of the centers to record reasons for non-inclusion, and in case of perceived non-eligibility, a specification of its reason will be provided.

Another pitfall is a slow inclusion rate. Previous trials in this population demonstrated insufficient enrollment speed, resulting in long inclusion periods of 6.5 years (CABANA, 778 patients), 7 years (RAFT-AF, 411 patients) and 8 years (CASTLE-AF, 363 patients). [11, 12, 24] All three described the enrollment to be more difficult than expected, resulting in a change of the primary endpoint in the CABANA trial and premature termination in the RAFT-AF trial and CASTLE-AF trial. In this light, in the RACE-8-HF trial we included the option in advance to substitute the primary endpoint with the hierarchical ('Finkelstein-Schoenfeld') secondary endpoint, if deemed appropriate and necessary. By this substitution, the sample size may markedly be brought down if enrollment rates are deemed insurmountably low.

Conclusion

The multicenter randomized controlled RACE-8-HF trial studies whether early invasive rhythm control is truly superior to medication-based treatment options in patients with heart failure with (mildly) reduced ejection fraction. The trial aims to strengthen previously published evidence on the positive effect of

catheter ablation for AF in patients with concomitant HFrEF, and is among the first to also include patients with HFmrEF. In addition, it is the first trial studying whether the procedure is cost-effective based on randomized, patient-level healthcare data.

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SUPPLEMENTS

Supplement 1. Participating centers.

Supplement 2. Composition of study committees.

Steering committee	**Participating Center Principal Investigators**
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Dr. C.P. (Cor) Allaart	Dr. V.P.M. (Vanessa) van Empel (HF)
Dr. Y. (Yuri) Blaauw	
Dr. A. (Arif) Elvan	Radboudumc
Dr. V.P.M. (Vanessa) van Empel	Drs. S.W. (Sjoerd) Westra (EP)
Prof. dr. I.C. (Isabelle) van Gelder	Drs. L. (Louise) Bellersen (HF)
Prof. dr. J.R. (Joris) de Groot	
Dr. M. (Mieke) van den Heuvel	UMC Groningen
Dr. J.S.S.G. (Jonas) de Jong	Dr. Y. (Yuri) Blaauw (EP)
Dr. J.G.L.M. (Justin) Luermans	Prof. dr. P. (Peter) van der Meer (HF)
Prof. dr. P. (Peter) van der Meer	
Prof. dr. U. (Ulrich) Schotten	Medisch Spectrum Twente
Prof. dr. J.G.P. (Jan) Tijssen	Dr. J.M. (Jurren) van Opstal (EP)
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Dr. B.A.B. (Brigitte) Essers	Erasmus MC
Data Safety Monitoring Board	Dr. T. (Tamas) Szili-Török (EP)
Prof. dr. H. (Hugo) ten Cate	Dr. S.C. (Sing-Chien) Yap (EP)
Prof. dr. A. (Adriaan) A. Voors	Dr. J.J. (Jasper) Brugts (HF)
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Clinical Endpoint Committee	Isala
Dr. A.M.W. (Twan) van Stipdonk	Dr. A. (Arif) Elvan (EP)
Dr. G.V.A. (Vincent) van Ommen	Dr. A. (Abdul) Ghani (HF)
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	Dr. C.P. (Cor) Allaart (EP)
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	UMC Utrecht
	Drs. N. (Nick) Clappers (EP)
	Dr. M.G. (Manon) van der Meer (HF)
	OLVG-locatie Oost
	Dr. J.S.S.G. (Jonas) de Jong (EP)
	Dr. L. (Loek) van Heerebeek (HF)

Abbreviations: EP: electrophysiology, HF: heart failure

Supplement 3. Subgroup analyses.

Planned subgroups for stratified exploratory analyses
• Male and female patients; • Patients aged 18-60, aged 61-70 and aged >70 years old; • Patients with ischemic cardiomyopathy or cardiomyopathy with other etiologies; • Patients with LVEF <30%, LVEF 30-40%, and >40%; • Patients with a heart failure duration of <1 year and ≥1 year; • Patients with paroxysmal and persistent AF; • Patients with low and high AF burden (only for patients with CIED); • Patients with AF duration of <1 year and ≥1 year; • Patients undergoing a single ablation procedure and patients undergoing multiple procedures.

Abbreviations: AF: atrial fibrillation, CIED: cardiac implantable electronic device, LVEF: left ventricular ejection fraction.


CHAPTER 10

General discussion and future perspectives

INTRODUCTION

In this thesis, several components of integrated atrial fibrillation (AF) management and challenging aspects in peri-AF ablation care have been addressed. These included integrated risk factor screening and management, efficient AF management (organizational aspects, remote management and integrated research), and studies aiming to optimize future patient selection for invasive management (*Figure 1*). Here, these topics are discussed in more detail.

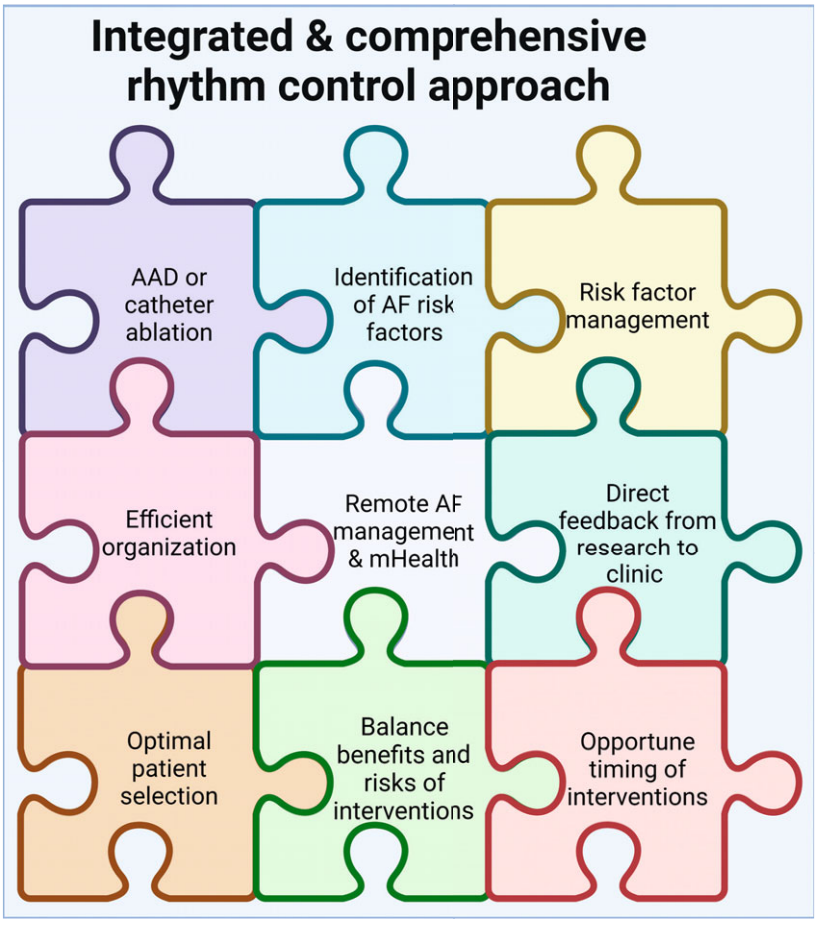

Figure 1. A selection of pieces that make up the puzzle of integrated AF management.
Abbreviations: AAD: antiarrhythmic drugs, AF: atrial fibrillation, mHealth: mobile health.

COMPREHENSIVE AF MANAGEMENT

Comprehensive management of AF begins with (A) appropriate anticoagulation therapy to avoid stroke, (B) better symptom control consisting of a careful consideration between heart rhythm and heart rate control, and (C) treatment of relevant comorbidities and risk factors.[1,2] In the consideration whether to opt for rhythm or rate control the expected benefits, potential disadvantages, and estimated success rates of rhythm control approaches should be taken into account. For a long time, the only indication for choosing rhythm control over rate control was reducing AF symptoms and improving AF-related quality of life in symptomatic patients.[3,4] However, novel evidence in patients with recent-onset AF suggests that early initiation of strict rhythm control is not only associated with symptom reduction, but also with reduced rates of major adverse cardiovascular events.[5] These findings may cause a shift in the indications for rhythm control: from aiming to reduce symptoms towards improving prognosis.

Rhythm control strategies are most effective when initiated early in the AF disease process, presumably as a result of less extensive arrhythmogenic substrate present in the atria.[6] In addition, when successful, rhythm control itself is associated with less remodeling of the atria resulting in less arrhythmogenic substrate.[7,8] Therefore, early initiation of rhythm control therapy interrupts the vicious circle of AF leading to more incessant AF. A rhythm control approach should therefore at least be considered early on in every patient presenting with new-onset AF.

Comprehensive rhythm control consists not only of directly targeting AF itself (e.g., with antiarrhythmic drugs [AAD], cardioversions or catheter ablation), but should also include an attempt to slow substrate progression. Uncontrolled AF risk factors such as obesity, hypertension, and obstructive sleep apnea (OSA) lead to gradual progression of atrial remodeling and thus contribute to eventual recurrences of AF.[9] Although the sense of urgency for extensive and chronic treatment of AF risk factors may be lower in patients with few or absent AF paroxysms, it remains an important pillar of a rhythm control strategy, even when AF paroxysms are adequately suppressed by AAD or rhythm interventions.[10,11]

Integrated risk factor identification and management

Successful risk factor management begins with identification of potential risk factors. After all, comorbidities that have not been identified will never be treated. Therefore, when restructuring the preparatory process for AF ablation as described in **chapter 3**, a structured risk factor screening checkpoint was incorporated. The first results of this integrated screening checkpoint are presented in **chapter 5**. We found a high prevalence of previously diagnosed modifiable risk factors (46% hypertension, 23% dyslipidemia, 8% diabetes mellitus, 13% current smokers, and 11% OSA). These numbers were largely in line with those found in a Europe-wide registry of 3593 AF patients undergoing catheter ablation across 27 countries, which described concomitant hypertension in 55%, dyslipidemia in 33%, diabetes mellitus in 10%, and current smoking in 10% of patients. [12] However, although all-comer registries like this one often describe the prevalence of AF risk factors, they rarely incorporate a structured risk factor screening method. This may lead to underestimation of comorbidities. In **chapter 5,** we found that on top of the high prevalence of previously diagnosed risk factors, structural screening often identified additional risk factors, as demonstrated for example by the high percentage of newly diagnosed OSA. In addition, we found that absence of any risk factor for which treatment could be initiated or intensified was scarce. Given these findings and the fact that strict management of AF risk factors improves short- and long-term outcomes of rhythm control interventions, it seems reasonable to advocate implementation of structured risk factor screening checkpoint in other preparatory pathways for rhythm interventions. [11,13,14]

The ideal composition of such a screening checkpoint remains to be determined and is the topic of current study. [15] Ideally, a multidisciplinary care approach would be designed for each separate risk factor, which would incorporate a uniform screening method with a short time to diagnosis and direct therapeutic consequences in case of abnormal results. However, standards for such pathways are lacking. [16] We proposed a new structured OSA screening and management pathway, the Virtual-SAFARI approach, which was described in detail in **chapter 6**. Since October 2020 all patients undergoing catheter ablation for AF in the Maastricht University Medical Center (Maastricht UMC+), Maastricht, The Netherlands, and the Radboud University Medical Center (Radboudumc), Nijmegen, The Netherlands, without recent OSA testing have been offered this fully remote screening program. As described in **chapter 6**, the pathway had a high yield: 55% of patients who underwent screening were diagnosed with moderate-to-severe OSA, and treatment was initiated in the

majority of them. This prevalence fell in the middle range of previous studies in AF patients, which describe OSA to be present in the wide range of 21-74%. [17,18] The Virtual-SAFARI approach allowed for a fast diagnosis and was associated with high patient satisfaction. The screening and management pathway has therefore become a standard part of the preparation for AF ablation.

Indisputably, structural risk factor screening and management pathways such as the Virtual-SAFARI approach require additional organization and investments in terms of time and finances. Therefore, reserving such pathways for patients who are at particular risk for that specific risk factor may save costs. For instance, a very limited prevalence (3%) of newly identified hyperglycemia or potential diabetes mellitus was found in **chapter 5**. Given this modest yield, structural screening for this risk factor may not be required in all patients. History taking or use of validated questionnaires may support preselection of patient in whom more rigorous screening should be initiated, although this may depend on the risk factor and on the preselection tool chosen.

In **chapter 7**, we aimed to find a preselection tool which could identify low-risk patients in whom structural OSA screening via the Virtual-SAFARI pathway could be omitted. The frequently used validated STOP-Bang questionnaire was proposed for this goal, as this questionnaire previously demonstrated the most favorable performance in AF patients. [19,20] Unfortunately, although there was a clear correlation between STOP-Bang score and OSA, the questionnaire demonstrated a poor specificity in this AF ablation cohort and thus had limited value in identifying AF patients not requiring screening. The poor specificity may be due to the high prevalence of other comorbidities in AF patients, which differs from the general population for whom the STOP-Bang was developed. [21] This resulted in very few scores indicative of low OSA risk, and therefore the questionnaire was of little added value as a preselection tool. Hence, before an established questionnaire is used to determine whether structural screening may be withheld, it is important to first assess its impact in the specific population in which it will be used. In our centers, we will therefore disregard preselection tools for now and continue to offer the Virtual-SAFARI approach to all patients until additional guidance becomes available.

Future directions

Concerning other AF risk factors, a Europe-wide survey recently revealed that for most AF risk factors integrated care models are lacking and organizational hurdles to address them remain plentiful, not to mention that for several risk

factors optimal treatment targets have not been established.[16] Future studies should address which populations should be screened for which risk factors, how screening should be approached, and which targets should be pursued. Proposed risk factor management approaches, such as the Virtual-SAFARI pathway, warrant external validation before they can be widely implemented. Development of generic, evidenced-based, lean care pathways may contribute to uniform and optimal care for AF patients and allow for pooling data from different centers for quality registries and research purposes.[15] Additionally, increasing physicians' awareness for the importance of risk factor assessment and management is important to further improve AF care.

EFFICIENT AF MANAGEMENT

Future-proof AF management is not only comprehensive in nature, but also requires efficient organization. The strong increase in the number of catheter ablation procedures per year[22] calls for approaches to keep the intervention accessible and affordable.[23] Efficiently organizing the procedure, including its preparatory and follow-up trajectory, will contribute to this goal. A detailed reappraisal of customs and procedures that are habitually performed during this trajectory may identify potentially redundant use of resources. For instance, several studies have demonstrated that same-day discharge after ablation procedures is a safe alternative for an overnight stay, and applying these findings in practice can reduce overcrowding of clinical wards.[24]

An effective approach to realize structural improvements in processes is the Lean Six Sigma methodology.[25,26] In **chapter 3** of this thesis, a single-center project was described in which the preparatory pathway before AF ablation was critically reappraised and redesigned with the use of this methodology. This redesign resulted in less fragmented care and in an important reduction of hospital visits and resources that could now be deployed elsewhere. Applying the Lean Sig Sigma method periodically could help in identifying and subsequently removing unnecessary customs in any type of process.[27,28] It may therefore not only be useful to improve the efficiency of preparatory care pathways for interventions, as in this project, but also reduce redundancies in ablation procedures themselves[29] and in other AF clinics or other fields of cardiology.[30,31]

Remote management and mHealth

Another approach to manage AF more efficiently is a partial replacement of face-to-face care by remote care, where possible supplemented with mobile health (mHealth) technology. Shifts towards remote mHealth-based approaches are generally associated with higher access to care, lower costs, and improved clinical outcomes. [32,33]

In AF care, the most recognized use of mHealth is remote heart rhythm monitoring via electrocardiogram (ECG) or photoplethysmography (PPG) registrations using portable devices such as smartphones, smartwatches, or specific devices. Remote heart rhythm monitoring may be applied in a multitude of scenarios, including AF screening, remote AF management, and assessment of symptom-rhythm correlation. [34] Additionally, mHealth applications and platforms may be used to improve patient education and involvement, with previous studies demonstrating that integrated mobile AF applications improved drug adherence, increased quality of life, and even reduced AF-related hospitalizations. [35,36]

mHealth is often used to screen or prescreen for disease in high-risk populations. Its advantage is that apps and devices are often more easily available and waiting times are shorter than for the diagnostic approaches that are conventionally used. In the context of AF, they are therefore attractive options for AF screening (partially replacing Holter monitoring), but also for screening for underlying conditions in known AF patients. [37] In **chapter 6**, we established that remote OSA screening using an mHealth approach was feasible within short times from referral to diagnosis (median 18 days), whereas waiting times for conventional polysomnography in sleep laboratories are usually much longer. In addition, this approach in which the standard polysomnography is (partly) circumnavigated by an mHealth option may also result in a decreased demand for the conventional diagnostic approach, hereby potentially reducing waiting lists and improving accessibility, although studies on this topic are not yet available.

Another clinical scenario in which mHealth is frequently used is to support remote care for patients with established (chronic) conditions. This use of mHealth was accelerated by the world-wide coronavirus 2019 (COVID-19) pandemic, during which in many countries face-to-face consultations were replaced by teleconsultations to prevent the spreading of the virus. The TeleCheck-AF project, which was initiated during the pandemic, is an example

of such an mHealth-based remote care approach.[38] This infrastructure incorporates on-demand, short-term prescription of PPG-based heart rate and rhythm monitoring to facilitate remote AF management via teleconsultations. A structured, uniform mHealth approach as is TeleCheck-AF proved to be in high demand: in the first 11 weeks 36 centers across Europe joined in on the program.[39] This interest was certainly instigated by the pandemic, but after the pandemic many of the TeleCheck-AF centers remained active users of the original infrastructure. Since then, utilization of TeleCheck-AF has expanded towards several clinical scenarios that are portrayed in **chapter 4**, including patient monitoring around rhythm interventions, establishing symptom-rhythm correlation, detecting arrhythmias in patients with palpitations, and guiding remote titration of heart rhythm and rate control medication. As described in **chapter 2**, in the Maastricht UMC+ and Radboudumc outpatient clinics PPG-based rhythm monitoring is currently being used as part of the standardized follow-up after AF ablation. As of now it complements standard Holter recordings, though it may gradually substitute those as first-line monitoring thanks to its higher accessibility and lower labor intensity.

Although a project such as TeleCheck-AF can expedite the uptake of mHealth for heart rhythm monitoring across centers, its integration into standard care remains challenging. One of these challenges is the unfamiliarity of health care professionals with when and how to use mHealth and how to interpret results.[40] This problem may be partially overcome by step-by-step guides for systematic interpretation of recordings, as proposed in **chapter 4**. However, health care providers remain faced with a multitude of different mHealth apps, devices, and platforms, all with their own methods of data visualization and varying levels of approval by authorized bodies.[41] Many mHealth applications are freely available to the public, and this often leads to unsolicited sharing of recordings by patients originating from different platforms. Hereby, mHealth may lead to increased instead of decreased workloads and to resistance among health care professionals.[42] Clear infrastructures using on-prescription, physician-initiated mHealth approaches[38] with predetermined apps and devices may help to overcome these phenomena.

Future directions

For mHealth to truly become a part of standard care both patients and health care providers must feel comfortable using it, and it must contribute to either improved outcomes, savings in time and/or resources, or both. For health care providers, this requires improved education on mHealth, better alignment

between different mHealth options, and combination of results from different devices in user-friendly platforms or direct integration into electronic health records. [42-44] Additionally, installment of high-quality automated algorithms that triage recordings that should be verified or acted upon by a physician may prevent data overload. For patients, this requires improved digital literacy and uptake of an active role in the management of their own disease. The latter may not be desirable for each patient, as in some patients increased awareness of their disease by mHealth is associated with anxiety or an unsafe feeling. [39] Ultimately, the majority of patients may be managed in a combined remote and on-site AF and AF risk factor management pathway incorporating different mHealth approaches (e.g., PPG, smart scales, blood pressure monitors, and home sleep tests), while other patients with lower digital literacy or insight in their care process may benefit from standard, on-site management. Shared decision making will be required in determining in which approach is appropriate.

Integrating research and clinical care

At first sight, integrating research and clinical care primarily appears advantageous for more efficient research conduct through preventing double work, simplifying identification of potential study participants, and combining mechanistic data and information on clinical phenotypes. [45] Although this may well be true, integrated research is also able to directly impact the way in which care is delivered. As described in **chapter 2**, the ISOLATION study is interwoven with the standardized clinical peri-ablation pathway in our clinics. Even though the study is still ongoing and the primary results are not yet available, it has already contributed to advances of standard care.

Firstly, the existing ethical committee approval and ongoing infrastructure for data collection enabled fast analysis of the impact of our Virtual-SAFARI pathway (**chapter 6**). As such, a comparison between OSA prevalence before and after implementation of this pathway could easily be made, which demonstrated an increase from 9% to 55%. These high detection rates of previously undiagnosed OSA motivated the decision to continue structural screening in this population. Subsequently, the analysis in **chapter 7**, which demonstrated that the STOP-Bang questionnaire added little added value in preselecting which patients require OSA screening, motivated us to abate this questionnaire in current patients.

The findings from **chapter 5** have raised internal awareness for the fact that patients undergoing catheter ablation are predominantly either at high risk for developing coronary artery disease or already show signs of established coronary atherosclerosis. Consequently, the attention for conscious cardiovascular risk assessment and, when appropriate, initiation of statins or other targeted treatment has grown. This heightened attention will hopefully result in improved guideline-directed therapy (data not yet available).

Ongoing ISOLATION substudies are currently assessing which patients in our cohort may profit from screening for other common comorbidities for AF, such as chronic obstructive pulmonary disease or asthma. In addition, parameters are being collected to determine whether other types of ablation techniques can shorten procedural times without compromising efficacy and safety. In conclusion, this integration of research and clinical care facilitates continuous data collection in a diverse cohort of catheter ablation patients, which has directly enabled adaptations in several aspects of peri-ablation care.

PATIENT SELECTION FOR INVASIVE MANAGEMENT

Over time, the indications for catheter ablation for AF have expanded.[2,46,47] This is the result of emerging evidence on which patients will benefit from catheter ablation most, improvement in procedure techniques and safety, as well as increased understanding in the progressive nature of AF and its associated complications.[5,48-51] However, patient selection for invasive management still remains challenging. This thesis includes the rationale and design of two ongoing projects that aim to contribute to improved selection of patients who will benefit from invasive rhythm control procedures the most: the ISOLATION cohort study and the RACE-8-HF trial.

The ISOLATION study (**chapter 2**) aims to further improve risk stratification on which patients will have low perceived success rates of catheter ablation. Complications of catheter ablation still occur with moderate frequency, and new predictors for ablation failure may help to determine in which patients the potential risks of the procedure outweigh the anticipated benefits.[52] Potential predictors are sought in several domains including non-invasive electrophysiological, biochemical, anatomical, and AF pattern-related parameters based on previous studies.[53-56] The integration of the study into clinical care allows for a nearly unselected study cohort of patients undergoing AF ablation, contributing to representative results.

The RACE-8-HF trial (**chapter 9**) aims to study whether the indications for catheter ablation should be further broadened towards patients with heart failure with (mildly) reduced ejection fraction, regardless of AF symptoms. Based on previous studies, catheter ablation is currently recommended in asymptomatic AF patients with presumed tachycardia-mediated cardiomyopathy. [2, 48, 57] However, in patients with other causes of reduced ejection fraction the indication is less established. The hypothesis is that reduction of the AF burden will prevent deterioration of the left ventricular function (as further portrayed in **chapter 8**), and therefore in improved heart failure outcomes in addition to improved AF symptoms. The results of this trial will contribute to answering the question which heart failure patients should be referred for invasive management, a matter becoming more important as the prevalence of both diseases grows.

CONCLUSIONS

The work in this thesis focused on integrating novel care approaches in the standard management of AF patients undergoing catheter ablation. The increasing prevalence of AF and the expanding indications for rhythm control warrant more efficient approaches for undertaking pre-, peri- and post-ablation care. Smart organization may decrease costs and free up resources, as may use of mHealth to facilitate a partial shift towards remote management, provided that several challenges currently associated with mHealth will be addressed. However, only making care processes simpler and more unidirectionally focused on catheter ablation does not do justice to the complex substrate underlying AF. Rhythm interventions should be complemented with treatment of AF risk factors to impede progressive atrial remodeling, even when AF recurrences are scarce. AF risk factors remain highly prevalent, and their treatment should be further improved, but the optimal approach to screen for and manage comorbidities may vary per risk factor. We proposed a structured pathway for OSA screening incorporating an mHealth application, which resulted in high revenues of newly diagnosed OSA and patient satisfaction. Integrated pathways for other risk factors are warranted. In addition, additional evidence is warranted to improve patient selection for invasive therapy and balance risks and benefits of the procedure. The ongoing ISOLATION cohort study and RACE-8-HF trial aim to contribute to this improved selection.

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CHAPTER 11


Impact

SCIENTIFIC AND SOCIETAL IMPACT

Affecting over 43.5 million patients worldwide and over 350,000 individuals in The Netherlands, atrial fibrillation (AF) is the most commonly encountered sustained arrhythmia.[1, 2] Its prevalence continues to grow due to increasing predisposing risk factors, improved detection methods and improving life expectancy, and so does its associated burden on health care systems.[3, 4] Over the past decades, catheter ablation has been emerging as an effective therapy to prevent AF recurrences and AF-related complications and to improve quality of life.[5, 6] These facts together with improving techniques and higher accessibility have led to a doubling of the number of catheter ablations in the Netherlands in only eight years: from 2,627 procedures in 2013 to 5,350 in 2021.[7] This expansive growth highlights the need for a critical reappraisal of the structure of peri-AF ablation care. The work reported in this thesis focused on the integration of several novel care approaches in standard care for patients undergoing catheter ablation.

Several results presented in this thesis have already directly impacted clinical AF care as practiced in the Maastricht UMC+ and the Radboudumc. As previously described in more detail (**chapter 10**), the integration of the ISOLATION study into standard care (**chapter 2**) has led to increased awareness for risk factor management (**chapter 5**) before and after AF ablation and has led to implementation of a structured, fully remote screening and management pathway for sleep disordered breathing (**chapter 6** and **chapter 7**). In addition, restructuring the pre-AF ablation care pathway (**chapter 3**) has led to a decreased use of resources and a lower time burden placed on patients undergoing catheter ablation.

Scientifically, large-scale registries with real-world data, such as the ISOLATION study (**chapter 2**), play an important role in advancing the understanding of AF mechanisms and therapies.[8] They provide data from a diverse range of AF patients that may be used for clinical and translational research. The integrated approach of the ISOLATION cohort study allowed the study to grow into an umbrella under which a range of study topics have been added. The first results of some of these topics are presented in **chapters 5-7**. However, the majority of these studies is still ongoing and new ones are continuously being added in a fruitful multidisciplinary collaboration of researchers from the Departments of Cardiology, Cardiothoracic surgery, Radiology, Anesthesiology, Pulmonology, Physiology, and Biomedical engineering (*Figure 1*). Furthermore, the preparations for the subsequent, long-term 'ISOLATION 2.0' study are

currently in progress. The main ISOLATION results, as well as most results from different substudies, are expected in the coming years. Therefore, the largest scientific impact of the ISOLATION study is presumably still to come.

Uniform integration of mobile health (mHealth) approaches into standard AF care, although highly promising, is being hampered by the multitude of different apps, devices, platforms, and methods that are being used, and structured mHealth pathways are still lacking. The photoplethysmography (PPG) dictionary (**chapter 4**) and Virtual-SAFARI pathway (**chapter 6**) incorporated in this thesis aim to provide blueprints for more uniform use of two different mHealth options. The PPG dictionary was composed as part of the TeleCheck-AF project, an mHealth infrastructure for remote management of AF. [9] This infrastructure was developed in the Maastricht UMC+ and has now spread to over 40 centers across Europe. [10] In many of these, this mHealth approach has impacted daily AF care. To our knowledge, the Virtual-SAFARI approach, providing an mHealth approach for remote screening and management of sleep disordered breathing, is currently only applied in the two initiating centers (Maastricht UMC+ and Radboudumc). However, the interest of the scientific community in such integrated remote pathways is highlighted by the fact that this research was nominated for and awarded with several prizes by local, national and international societies.

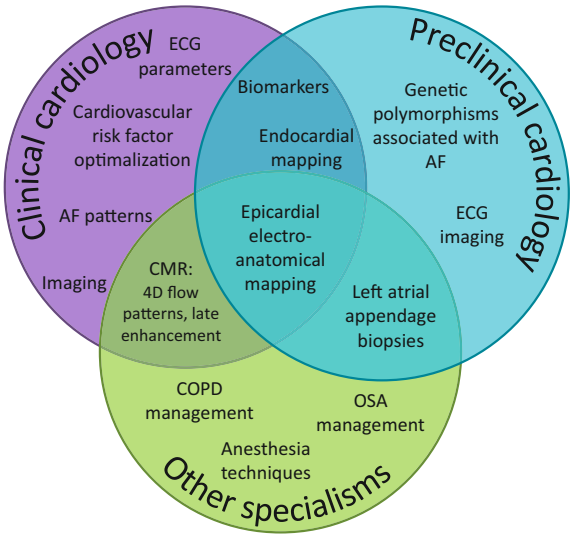

Figure 1. Multidisciplinary involvement and research topics studied under the umbrella of the ISOLATION study.

Abbreviations: AF: atrial fibrillation, CMR: cardiac magnetic resonance imaging, COPD: chronic pulmonary obstructive disease, ECG: electrocardiography, OSA: obstructive sleep apnea.

The ongoing RACE-8-HF study (**chapter 9**) aims to further elucidate the impact of catheter ablation in patients with concomitant AF and heart failure. The results of this study are not yet available, but are aspired to strengthen knowledge on the optimal treatment for the expanding group of patients suffering from both diseases.

In conclusion, the work described in this thesis has directly impacted clinical care for AF patients undergoing catheter ablation in the Maastricht UMC+ and the Radboudumc, and potentially in other centers beyond these two. The ongoing studies presented in **chapter 2 and 9** are expected to lead to new insights into optimal patient selection for invasive care, ablation techniques, and AF mechanisms, and will influence care for future AF patients.

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CHAPTER 12a

Summary

SUMMARY

The central theme in this thesis is the integration of different novel care approaches into standard care for atrial fibrillation (AF) patients undergoing catheter ablation procedures. Within this theme the integration of scientific research and mobile health (mHealth) applications in clinical AF care pathways, treatment of cardiovascular risk factors, and integrated heart failure care are emphasized.

Part I of the thesis mainly focuses on the integration of research and mHealth in peri-AF ablation care. Despite continuously improving AF ablation techniques, 30-50% of patients still experience recurrences of arrhythmias within one year after their ablation procedure. Comprehensive translational research approaches integrated in clinical care pathways, such as the ISOLATION cohort study, may lead to a better understanding of the complex pathophysiology of AF and improve future patient selection for invasive approaches. In **chapter 2** the rationale and design of the currently ongoing ISOLATION study are described. Data from 650 AF patients undergoing catheter ablation are used to develop a multimodality model that predicts the probability of a successful outcome of ablation, incorporating a combination of established predictors and newer techniques. All study procedures are seamlessly integrated into a standardized care pathway for patients undergoing AF ablation. In preparation for the ISOLATION study, this care pathway was redesigned using the Lean Six Sigma methodology to improve its efficiency and integrate prospective data collection into the clinical process (**chapter 3**). A detailed analysis of the existing care pathway revealed several constraints, for which countermeasures were formulated and implemented. This optimization project resulted in a more efficient process indeed, requiring fewer hospital visits and electrophysiologist consultations per patient with a concomitant more efficient deployment of diagnostic resources. In addition, scientific data are collected more easily and more completely.

In recent years, mHealth has increasingly been used in AF management. Smartphone apps using photoplethysmography (PPG) to remotely measure heart rhythm and heart rate are ubiquitous. However, many care providers acknowledge a lack in familiarity with the interpretation of these PPG signals. Therefore, in **chapter 4** an educational, stepwise practical guide on how to interpret PPG signals was described. This guide is supported by representative PPG recordings and several typical clinical scenarios in which PPG may be useful.

Part II of this thesis focuses on the integration of risk factor management in standard AF care. Comprehensive risk factor management prevents AF progression and improves success rates of rhythm control interventions, but often risk factors remain undiagnosed and thus untreated. The pre-AF ablation work-up offers an excellent opportunity for identification of existing risk factors, reappraisal of appropriate treatment targets, as well as intensification of management in referred patients. **Chapter 5** presents the results of a cross-sectional study in which the presence of seven modifiable risk factors (hypertension, dyslipidemia, obesity, smoking, alcohol use, hyperglycemia, and obstructive sleep apnea [OSA]) was assessed in 1143 patients on the waiting list for AF ablation. In a structured atherosclerotic cardiovascular disease (CVD) risk assessment, two-thirds of patients were classified as 'very high CVD risk', predominantly driven by newly detected coronary plaques on the routine pre-ablation computed tomography (CT) scan. This assessment impacted risk factor treatment targets, and consequently the treatment targets for all seven risk factors were reached in only 3% of patients. Lipids were most often above target values, followed by blood pressure, weight and OSA. These results highlight the need for stringent combined risk factor management in this population.

Chapter 6 and 7 zoom in on OSA screening and management. If left untreated, this risk factor is associated with lower success rates of rhythm control strategies. Structured testing is therefore recommended, but is often accompanied by logistical hurdles. **Chapter 6** describes a novel virtual OSA screening and management pathway and evaluates the utility and feasibility of this new approach. As part of the preparation for catheter ablation, AF patients are digitally referred to a virtual OSA pathway using the WatchPAT-ONE, which is an easy to use, PPG-based wearable mHealth device designed as a home sleep apnea test. This remote approach was found to be fast, had a high yield, and was associated with a high patient satisfaction. The novel structured screening approach has resulted in treatment of previously undiagnosed OSA in the majority of patients awaiting AF ablation. **Chapter 7** evaluates whether the use of a preselection tool can reduce the number of patients requiring OSA screening. However, the frequently used STOP-Bang questionnaire was found to perform poorly in detecting moderate-to-severe OSA in this population. Tailoring the STOP-Bang specific to AF populations (by removing characteristics having limited association with OSA and adding or assigning additional points to items with a strong association) resulted in the BOSS-GAP score. This score moderately improved OSA detection in this

population, but whether the use of any questionnaire as preselection tool for OSA can partially replace structural screening in AF populations requires further study.

Part III of this thesis focuses on the management of patients with concomitant AF and heart failure. These two diseases often go hand in hand as each can provoke, maintain, and exacerbate the other. In **chapter 8**, the interrelations between the two comorbidities are described in more detail. When the two coexist, this provides additional challenges but also opportunities for optimal treatment. Previous studies have shown that AF ablation can improve heart failure-related outcomes and even reduce clinical events (mortality, hospitalizations) in patients with tachycardia-mediated cardiomyopathy, but it remains unclear whether this effect persists in the general heart failure population. The ongoing RACE-8-HF trial aims to answer this question. In **chapter 9**, the rationale and design of this prospective, randomized, controlled, multicenter clinical trial are described. 600 patients with both symptomatic AF and heart failure are randomized to early invasive therapy (cryoballoon ablation) or standard therapy and are subsequently monitored for the occurrence of all-cause mortality, unplanned cardiovascular hospitalizations, and stroke. This trial aims to provide more insight into the effect of catheter ablation in patients with heart failure with reduced ejection fraction and AF.

Finally, **chapter 10** provides an overview of the research presented in this thesis, discusses its place in current literature and in clinical settings, and looks ahead to future developments in the field. This thesis exemplifies that cardiology is a field in which new insights follow each other in rapid succession, but optimal care for our AF patients undergoing catheter ablation can only be achieved if these new insights and approaches are consciously and continuously integrated into clinical practice.

CHAPTER 12b

Nederlandse samenvatting

SAMENVATTING

Het centrale thema in dit proefschrift is de integratie van verschillende nieuwe benaderingen in de zorg voor patiënten met atriumfibrilleren (AF) die een katheterablatie ondergaan. Binnen dit thema ligt de focus op de integratie van wetenschappelijk onderzoek en mobile health (mHealth) applicaties in de AF zorg, behandeling van cardiovasculaire risicofactoren en geïntegreerde zorg voor hartfalen. Het proefschrift bestaat uit drie delen.

Deel I richt zich op met name op de integratie van onderzoek en mHealth in de zorg voor patiënten die een ablatie voor AF ondergaan. Ondanks voortdurend verbeterende ablatietechnieken ervaart 30-50% van de patiënten binnen een jaar na hun ablatie nog steeds recidieven van hartritmestoornissen. Translationele onderzoeken geïntegreerd in klinische zorgpaden, zoals de ISOLATION-cohortstudie, kunnen leiden tot een beter begrip van de complexe pathofysiologie van AF en de toekomstige selectie van patiënten voor invasieve benaderingen verbeteren. In **hoofdstuk 2** wordt de achtergrond en onderzoekopzet van de lopende ISOLATION-studie beschreven. Hierin worden de gegevens van 650 patiënten met AF die een katheterablatie ondergaan gebruikt om een predictiemodel te ontwikkelen dat de kans op een succesvolle ablatie berekent, en waarin een combinatie van bekendere voorspellers en nieuwere technieken meegenomen wordt. Alle studieprocedures zijn geïntegreerd in een gestandaardiseerd zorgpad voor patiënten die een ablatie ondergaan. Ter voorbereiding op de ISOLATION-studie werd dit zorgpad met behulp van de Lean Six Sigma methodologie heringericht om het zo efficiënt mogelijk te maken en tegelijkertijd prospectieve dataverzameling binnen het klinische proces mogelijk te maken (**hoofdstuk 3**). Bij een nauwkeurige analyse van het bestaande zorgpad werden verschillende knelpunten geïdentificeerd, waarvoor oplossingen geformuleerd en vervolgens geïmplementeerd werden. Deze herinrichting zorgde voor een efficiënter proces, waarin per patiënt minder ziekenhuisbezoeken en consulten met een elektrofysioloog nodig waren en waarin diagnostische onderzoeken effectiever ingezet werden. Daarnaast werden wetenschappelijke data eenvoudiger en completer verzameld.

In de afgelopen jaren wordt binnen de behandeling van AF steeds vaker gebruik gemaakt van mHealth. Smartphone-apps die met behulp van photoplethysmografie (PPG) het hartritme en de hartfrequentie kunnen meten zijn alomtegenwoordig. Veel zorgverleners geven echter aan onvoldoende bekend te zijn met de interpretatie van deze PPG-signalen. Daarom wordt

in **hoofdstuk 4** een educatieve, stapsgewijze, praktische gids voor het interpreteren van PPG-signalen geïntroduceerd. Deze handleiding wordt ondersteund door representatieve PPG-registraties en verschillende typische klinische scenario's waarin PPG van toegevoegde waarde kan zijn.

Deel II van dit proefschrift richt zich op de integratie van risicofactormanagement in standaard AF-zorg. Adequate behandeling van risicofactoren vertraagt de progressie van AF en verhoogt de slagingskans van ritme-interventies. Risicofactoren worden vaak echter niet gediagnosticeerd, waardoor ze onbehandeld blijven. De periode waarin een verwezen patiënt wordt opgewerkt voor een AF ablatie biedt een uitstekende gelegenheid voor gelijktijdige identificatie van bestaande risicofactoren, herbeoordeling van streefwaarden en intensivering van de behandeling. **Hoofdstuk 5** beschrijft de resultaten van een cross-sectionele studie waarin de aanwezigheid van zeven behandelbare risicofactoren (hypertensie, hypercholesterolemie, obesitas, roken, alcoholgebruik, hyperglycemie en obstructieve slaapapneu [OSA]) werd beoordeeld bij 1143 patiënten op de wachtlijst voor een AF-ablatie. Na een gestructureerde risicobeoordeling op atherosclerotische hart- en vaatziekten (HVZ) werd tweederde van de patiënten geclassificeerd als 'zeer hoog HVZ-risico', voornamelijk als gevolg van nieuw ontdekte kransslagaderplaques op de pre-ablatie computertomografie (CT)-scan. Dit had gevolgen voor de streefwaarden voor risicofactoren, en slechts 3% van de patiënten voldeed dan ook aan de behandeldoelen voor alle zeven risicofactoren. De cholesterolwaarden lagen het vaakst boven de streefwaarden, gevolgd door de bloeddruk, het gewicht en OSA. Deze resultaten benadrukken de behoefte aan een intensievere, gecombineerde behandeling van risicofactoren in deze populatie.

Hoofdstuk 6 en 7 zoomen in op de screening naar en de behandeling van OSA. Onbehandeld OSA is geassocieerd met een lagere slagingskans van ritme-interventies. Richtlijnen bevelen daarom gestructureerde screening aan, maar hiervoor bestaan vaak veel logistieke hindernissen. In **hoofdstuk 6** wordt een nieuw, virtueel OSA screenings- en behandelzorgpad beschreven en wordt de haalbaarheid van deze nieuwe aanpak geëvalueerd. Als onderdeel van de voorbereiding op katheterablatie worden AF-patiënten digitaal doorverwezen naar dit virtuele zorgpad waarin gebruikt gemaakt wordt van de WatchPAT-ONE, een gebruiksvriendelijke, draagbare mHealth-slaaptest die patiënten thuis kunnen gebruiken. Deze aanpak leidde tot een snelle diagnose, had een hoge opbrengst en ging gepaard met een hoge patiënttevredenheid. De gestructureerde screening resulteerde bij de meerderheid van de patiënten die

wachten op AF-ablatie tot behandeling van voorheen niet gediagnosticeerd OSA. In **hoofdstuk 7** wordt vervolgens geëvalueerd of het gebruik van een preselectietool het aantal patiënten bij wie OSA-screening verricht moet worden kan verlagen. De veelgebruikte STOP-Bang-vragenlijst bleek in deze populatie slecht te presteren voor het opsporen van matig tot ernstig OSA. De STOP-Bang werd specifiek voor AF-populaties aangepast door items met een beperkte associatie met OSA te verwijderen en door extra punten toe te voegen of toe te kennen aan items met een sterke associatie. Dit resulteerde in de BOSS-GAP-score. Deze score verbeterde de OSA-detectie in deze populatie, maar of de inzet van vragenlijsten als preselectietools voor OSA de structurele screening gedeeltelijk kan vervangen vereist nader onderzoek.

Deel III van dit proefschrift richt zich op de behandeling van patiënten met zowel AF als hartfalen. Deze twee ziektes gaan vaak hand in hand, omdat elk de ander kan uitlokken, in stand houden en verergeren. In **hoofdstuk 8** worden de onderlinge relaties tussen de twee comorbiditeiten in meer detail beschreven. Wanneer de twee naast elkaar bestaan levert dit uitdagingen op, maar ook kansen voor een optimale behandeling. Eerdere studies toonden aan dat een AF ablatie hartfalenuitkomsten kan verbeteren en bij patiënten met tachycardiomyopathie zelfs de kans op harde klinische eindpunten (mortaliteit, ziekenhuisopnames) kan verlagen, maar het is nog onduidelijk of dit effect aanhoudt in de algemene hartfalenpopulatie. De lopende RACE-8-HF-studie heeft tot doel antwoord te geven op deze vraag. In **hoofdstuk 9** worden de achtergrond en opzet van deze prospectieve, gerandomiseerde, gecontroleerde, multicenter klinische studie beschreven. 600 patiënten uit tien centra met symptomatisch AF en hartfalen worden gerandomiseerd naar vroege invasieve therapie (cryoballonablatie) of standaard (medicamenteuze) therapie en gevolgd met betrekking tot het optreden van mortaliteit, ongeplande cardiovasculaire ziekenhuisopnames en beroertes. Deze studie heeft als doel om meer inzicht te bieden in het effect van katheterablatie bij patiënten met zowel hartfalen met verminderde ejectiefractie als AF.

Tot slot geeft **hoofdstuk 10** een overzicht van het onderzoek dat opgenomen is in dit proefschrift, bespreekt de plaats ervan in de huidige literatuur en kijkt vooruit naar toekomstige ontwikkelingen in het veld. De cardiologie is een vakgebied waarin nieuwe inzichten elkaar snel opvolgen, maar optimale zorg voor onze AF-patiënten die een katheterablatie ondergaan kan alleen worden gerealiseerd als deze inzichten ook daadwerkelijk bewust en continu worden geïntegreerd in de klinische praktijk.

APPENDICES &

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Curriculum vitae
List of publications

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"Tell me and I forget, teach me and I may remember, involve me and I learn"
– Benjamin Franklin

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**"Don't adventures always have an end? I suppose not.
Someone else always has to carry on the story"**

– Bilbo Baggins, Lord of the Rings

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"Whatever you do in this life, it's not legendary unless your friends are there to see it"

– Barney Stinson, how I met your mother

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"To know your direction, you must know both your roots and your reach"

– The woman in the white kimono

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– Een schitterend gebrek

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CURRICULUM VITAE

Dominique Verhaert werd op 8 februari 1993 geboren in Pasadena (Verenigde Staten), waarna ze opgroeide in Breda. In 2010 behaalde ze haar gymnasiumdiploma aan het Stedelijk Gymnasium te Breda. Ze verhuisde naar Nijmegen voor de studie geneeskunde aan de Radboud Universiteit, en in 2017 rondde ze deze *cum laude* af. Tijdens haar bachelor en wetenschapsstage deed ze onderzoek naar reanimaties buiten het ziekenhuis, waarmee haar interesse voor wetenschappelijk onderzoek en de cardiologie als vak gewekt werd.

Na haar studie startte ze als ANIOS in het Rijnstate ziekenhuis, Arnhem, waar ze meer ervaring binnen de cardiologie opdeed. Na een leerzame tijd in de kliniek maakte ze de overstap naar onderzoek en was ze werkzaam als trialarts in het Radboudumc. In 2019 startte ze onder leiding van prof. dr. K. Vernooy, prof. dr. U. Schotten, dr. D. Linz en dr. R. Beukema haar promotietraject op het gebied van ablaties voor atriumfibrilleren. Dit project was een samenwerking tussen het Radboudumc en het Maastricht UMC+, en tijdens haar promotie werkte ze dan ook in beide centra. In het eerste jaar van haar promotie schreef ze een beursaanvraag die resulteerde in een ZonMw doelmatigheidsgrant voor de RACE-8-HF trial, een gerandomiseerde studie die momenteel in tien Nederlandse ziekenhuizen loopt. Ook zette ze de ISOLATION studie op, een prospectieve registratiestudie waaraan inmiddels meer dan 1300 patiënten deelnemen. Met hulp van een steeds verder groeiende groep gedreven onderzoekers werd dit onderzoek al snel uitgebreid tot een translationeel onderzoeksplatform.

Het werk in deze thesis is gepresenteerd op verschillende (inter)nationale congressen en werd beloond met verschillende prijzen, waaronder beste voordracht (NVVC, 2022), beste *digital medicine* publicatie (DGDM, 2022) en runner-up voor beste e-cardiology presentatie (EHRA, 2022). Naast haar onderzoek gaf Dominique onderwijs aan (gespecialiseerd) verpleegkundigen en coassistenten, begeleidde ze studenten en hielp ze bij de organisatie van een internationale Summer School.

Buiten haar werk besteedt ze graag tijd met haar vrienden en familie, het liefst op het terras, in een goed restaurant of op een festival, en aan haar hobby's koken, lezen en bootcamp. Daarnaast vormden de reizen naar Zuid-Amerika, Japan, New York, Namibië en Lapland, de skivakanties met vrienden en collega's en de internationale congressen hoogtepunten van haar promotietraject.

In maart 2023 startte ze met de opleiding tot cardioloog vanuit het Radboudumc, waarvoor ze nu werkzaam is op de afdeling interne geneeskunde in het Rijnstate ziekenhuis.

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