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DOCTORAL DISSERTATION

Towards more integrated care for patients with atrial fibrillation

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"Every accomplishment starts with the decision to try."

— John F. Kennedy

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LIST OF ABBREVIATIONS

€	Euro
AAD	Antiarrhythmic drug
ACC	American College of Cardiology
AF	Atrial fibrillation
AFEQT	Atrial Fibrillation Effect on QualiTy-of-Life
AHA	American Heart Association
AHI	Apnea-hypopnea index
ANOVA	Analysis of variance
APT	Antiplatelet therapy
BID	Bis in die or twice a day
BMI	Body mass index
bpm	Beats per minute
CI	Confidence interval
CPAP	Continuous positive airway pressure
CRT-D	Cardiac resynchronisation therapy defibrillator
CRT-P	Cardiac resynchronisation therapy pacemaker
CSA	Central sleep apnea
DCC	Direct current cardioversion
ECG	Electrocardiogram
EEG	Electroencephalography
EHRA	European Heart Rhythm Association
EMG	Electromyography
EOG	Electrooculography
ESC	European Society of Cardiology
ESS	Epworth sleepiness scale
GP	General practitioner
HF	Heart failure
HR	Hazard ratio
ICD	Implantable cardioverter defibrillator
ICER	Incremental cost-effectiveness ratio
INR	International normalized ratio
IQR	Interquartile range
JAKQ	Jessa Atrial fibrillation Knowledge Questionnaire
LAA	Left atrial appendage

LARQ	Leuven ARrhythmia Questionnaire
LV	Left ventricle
MCS	Mental component summary
mEHRA	Modified European Heart Rhythm Association score
MEMS	Medication Event Monitoring System
min	Minute(s)
MMAS-8	8-item Morisky Medication Adherence Scale
NOAC	Non-vitamin K antagonist oral anticoagulant
NPV	Negative predictive value
OAC	Oral anticoagulation
Obs	Observation
OD	Omne in die or once a day
OR	Odds ratio
OSA	Obstructive sleep apnea
PC	Personal computer
PCS	Physical component summary
PDC	Period of days covered
PG	Polygraphy
PM	Pacemaker
PPV	Positive predictive value
PROM	Patient Reported Outcome Measure
PSG	Polysomnography
PVI	Pulmonary vein isolation
QOL	Quality of life
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
s	Second(s)
SD	Standard deviation
SF-12	12-Item Short Form Survey
SPSS	Statistical Package for the Social Sciences
Tm	Telemonitoring
Tm + F	Telemonitoring with additional feedback
UEQ	User Experience Questionnaire
VKA	Vitamin K antagonist
vs.	Versus

GENERAL INTRODUCTION

Definition of atrial fibrillation

Atrial fibrillation (AF) is a sustained cardiac arrhythmia that arises in the upper chambers of the heart (i.e. the atria). It is characterized by an uncoordinated high-frequency excitation of the atria causing dyssynchronous atrial contractions.[1-3] This in turn results in an often too fast and irregular ventricular heart rate.

The diagnosis of AF requires the documentation of the arrhythmia using an electrocardiogram (ECG).[4] In a patient with AF, the ECG shows an irregular ventricular rhythm (i.e. irregular RR interval) without discernible, distinct P waves **(Figure 1)**.[3,4]

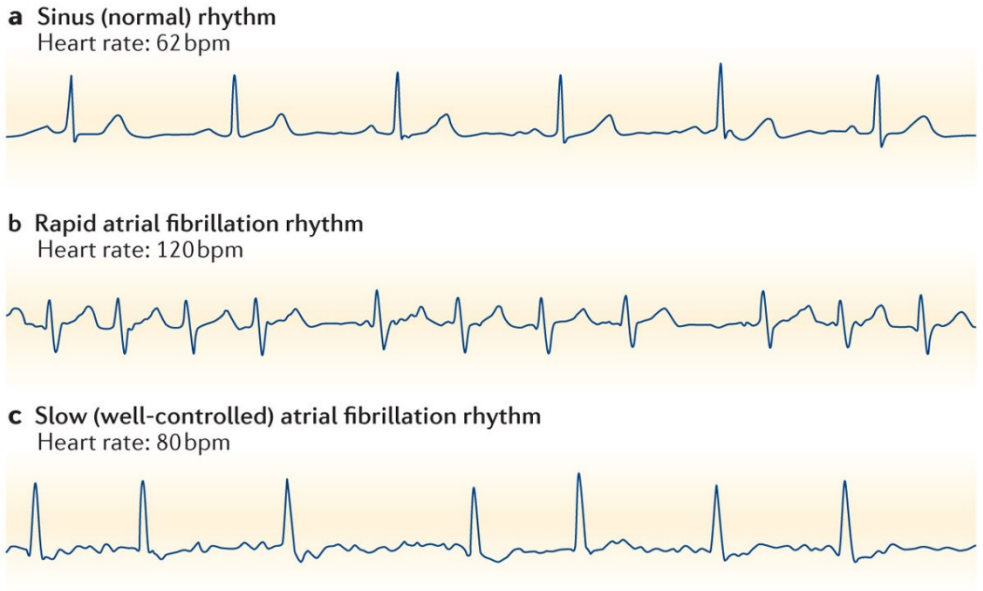

Figure 1: Typical electrocardiogram of a patient with (a) normal sinus rhythm, (b) rapid atrial fibrillation, and (c) slow (well-controlled) atrial fibrillation. Adapted by permission from Springer Customer Service Centre GmbH [Springer Nature; Nature Reviews Disease Primers. Atrial fibrillation. Lip GY, Fauchier L, Freedman SB, Van Gelder I, Natale A, Gianni C, Nattel S, Potpara T, Rienstra M, Tse HF, Lane DA. (2016; 2:16016)].[2] bpm: beats per minute.

Initially, many AF episodes resolve spontaneously. However, AF is a progressive disorder and over time a lot of patients will develop more sustained forms of the arrhythmia.[3,4] In most patients, AF therefore progresses from infrequent, short attacks to more frequent and longer episodes.

Atrial fibrillation can appear in several forms based on the presentation, duration and spontaneous termination of the episodes[4]: (i) First diagnosed AF; (ii) Paroxysmal AF which is self-terminating, usually with a spontaneous conversion to normal sinus rhythm within 48 hours. In some cases, it can however continue for up to 7 days; (iii) In persistent AF, the episode lasts more than 7 days and is not self-terminating, requiring a cardioversion (pharmacological or electrical) to stop the arrhythmia; (iv) Long-standing persistent AF denotes continuous AF which lasts for more than 1 year but there is still the intent to restore sinus rhythm; (v) In permanent AF, the presence of the arrhythmia is accepted by the physician and the patient without further attempts to restore sinus rhythm.

Atrial fibrillation is associated with a variety of cardiovascular, but also non-cardiovascular conditions that may predispose patients to the development, recurrence and progression of the arrhythmia. Most prevalent cardiovascular underlying diseases include: hypertension, heart failure, valvular heart disease, myocardial infarction,….[3,4] Moreover, AF commonly presents in association with different non-cardiovascular conditions, including thyroid dysfunction, obesity, obstructive sleep apnea,….[3,4]

Epidemiology

The current overall AF prevalence is about 2% in the general population.[5-7] The prevalence in persons over 55 years is however 7.7% and in those over 80 years 15.7%.[8] Middle-aged adults (i.e. above the age of 40) have a one in four lifetime risk to develop AF.[9-11] The prevalence of AF not only varies with age, but also with gender as a higher age-adjusted incidence of AF is observed in men compared to women.[5,8,9,12-15]

The incidence and prevalence of AF will steadily increase as the population ages and predisposing factors become more prevalent in our society.[8,15-17] It is expected that the worldwide prevalence will at least double over the next 50 years.[11,14,17]

Impact for the patient

Although AF is usually not life-threatening by itself, it has important effects on patient health as it causes or is associated with stroke and other thromboembolic events, heart failure, death, a reduced quality of life (QOL) and a decreased exercise capacity.[3] Taking into account these severe complications and its high prevalence, AF leads to an increased morbidity and mortality in the general population.[3]

It was shown that AF is independently associated with a 2-fold increased risk of all-cause mortality in women and a 1.5-fold increased risk in men, mostly due to stroke, heart failure and sudden death.[18,19]

Although thrombogenesis in AF is not fully elucidated, a combination of different factors, including blood stasis due to the loss of atrial contractile function, endothelial dysfunction, and a prothrombotic state will lead to an increased thromboembolic risk.[1,4] Different studies showed that about 20–30% of the patients presenting with an ischemic stroke, have received the diagnosis of AF before, during, or after the initial event.[20-22] Patients with AF have a 5-fold increased risk to develop stroke, which can largely be mitigated by proper anticoagulation therapy.[23] Moreover, strokes in AF patients are more severe, will more often result in permanent disability and will recur more often compared to strokes of another origin.[22,24,25]

It is known that heart failure and AF often coexist, since each condition facilitates the other and since they share common risk factors.[1,18,26] In 20-30% of the AF patients, left ventricular dysfunction is present often exacerbated by the fast and irregular ventricular rate.[3]

The most common symptoms associated with AF are palpitations, chest pain, dizziness, weakness, and dyspnea.[27] Nevertheless, AF can still present asymptomatically in almost one in three patients and many symptomatic patients have additional asymptomatic episodes.[28,29] Symptoms and AF in general will impact the QOL of these patients independently of other cardiovascular conditions.[30,31] Additionally, AF is also associated with cognitive impairment and dementia.[32-35]

Impact on the healthcare system

Atrial fibrillation is an important public health challenge with major social and economic implications.[17] The high AF prevalence together with the morbidity and mortality associated with AF result in many emergency department visits, increased hospital admissions, prolonged hospital stays, increased disability and the need for long-term care, all of which put a significant strain on the health care budget.[4,36]

The estimated annual proportions of overall health care expenditures attributed to AF range from 0.81% to 2.49% depending on the country, with hospitalizations as the largest contributor.[17,37-42] The Euro Heart Survey showed that the mean costs of an inpatient admission of an AF patient in 2003-2004 in 5 European countries were estimated between €1363 and €6445, depending on the country.[40] Mean annual costs for AF patients were between €1010 and €3225.[40] Unfortunately, these values are not available for Belgium. Nevertheless, it is known that a hospitalization for stroke has a mean cost of €8943 in Belgium, without even taking into account any costs related to rehabilitation and follow-up visits.[43]

Depending on demographical factors, about 10–40% of the AF patients are hospitalized each year with the highest risk for hospitalization during the first year after diagnosis.[4,36,44-55] Recent Australian data showed that between 1993 and 2013, there was a relative increase in AF hospitalizations of 295%, compared to only 73% for myocardial infarction and 39% for heart failure related hospitalizations.[56] Although the use of AF ablation (2.8% of all hospitalizations for AF in 2013) increased significantly during this period, it is unlikely that this accounted for the observed rise in AF hospitalizations.[56]

Overall management of AF

In 2001, a working group of experts from the American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology (ESC) wrote the first guidelines concerning the management of patients with AF.[57] These guidelines were updated in 2006.[58] In 2010, the ESC published its first own AF guidelines[59], with a focused update in 2012[60] and a fully new version in 2016[4]. The most recent 2016 guidelines consist of more than

90 pages with more than 1000 references, summarizing and evaluating the available evidence at that time point, with the aim to assist healthcare professionals in selecting the best management strategies and to help them to make thoughtful decisions in the daily care of AF patients.[4] This enormous amount of evidence already indicates that the management of AF patients is a complex task due to the availability of different medical interventions and because it needs to address multiple goals.

In the acute setting, one should first strive for hemodynamic stability in an AF patient through restoration of sinus rhythm (i.e. rhythm control) and/or by controlling the ventricular rate (i.e. rate control).[4] In a hemodynamically stable AF patient, appropriate thromboprophylaxis, adequate rate control, and successful rhythm control in symptomatic patients are essential to obtain the best possible outcomes **(Figure 2)**.[3,4]

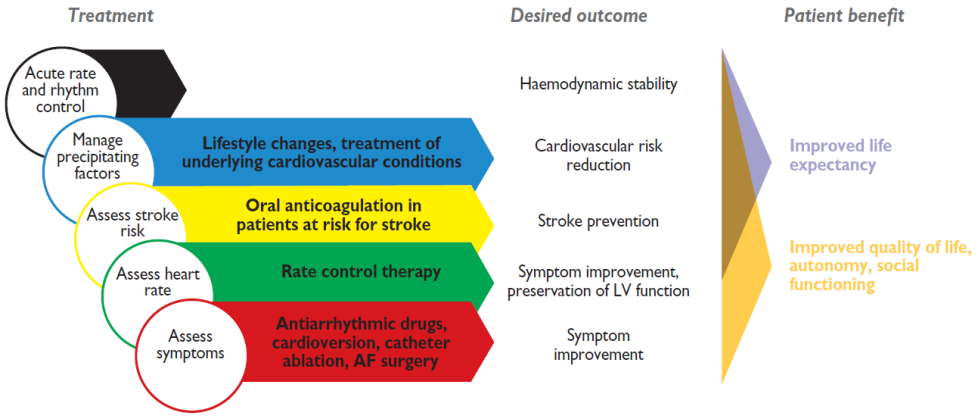

Figure 2: Schematic overview of the acute and chronic management of patients with AF. Reproduced from Kirchhof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal 2016; 37 (38): 2893-2962, doi:10.1093/eurheartj/ehw21. Reproduced by permission of Oxford University Press on behalf of the European Society of Cardiology. Please visit: www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Atrial-Fibrillation-Management.[4] AF: atrial fibrillation, LV: left ventricle.

The most important pillar in AF management is adequate antithrombotic therapy to prevent stroke and other thromboembolism. Therefore the individual stroke risk should be calculated for each patient based on the CHA_2DS_2-VASc score and anticoagulation should be started when indicated.[4] Currently, non-vitamin K antagonist oral anticoagulants (NOACs) are recommended in preference to a

vitamin K antagonist (VKA) when there are no contraindications. A strict adherence to the prescribed oral anticoagulation (OAC) therapy is of pivotal importance to provide optimal thromboembolic prevention and to minimize bleeding complications.[4,61,62]

Additional rhythm control therapy - by means of antiarrhythmic drugs, direct current cardioversion or ablation - is indicated for symptom relief in patients with AF.[4]

Addressing the different underlying diseases and comorbidities of AF further complicate the management of AF patients.[3,4,17] Recent studies showed however the potential beneficial effects of lifestyle and risk factor management for AF as an upstream noninvasive therapy to reverse pathological processes underlying AF and to reduce AF burden.[63-71] Therefore, the detection and management of (modifiable) cardiovascular risk factors was included as the fourth pillar in the management of AF patients.[4,71-73]

As already indicated, AF is an arrhythmogenic expression of complex processes occurring in the atria due to many etiological factors such as age, genetic predisposition, hypertension, heart failure, coronary artery disease, diabetes, obesity, endurance exercise, etc.[3,4] All these factors together lead to many pathophysiological changes in the atria: e.g. fibrosis, inflammation, contractile dysfunction, fatty infiltration, ischemia.[4,74] These processes not only increase hypercoagulability, they also result in cellular and structural remodeling leading to the development of multiple ectopic foci (triggering premature atrial contractions and short runs) and to the presence of AF rotors and multiple reentry activity.[1,3,74] The actual treatment targets in AF (i.e. rate control, rhythm control via antiarrhythmic medication or even an ablation procedure, and anticoagulation) do not focus directly on these cellular mechanisms. Nevertheless, the recent ESC Guidelines for the management of AF recognize the importance of the different etiological and often modifiable factors in order to create a prognostic impact.[4] This not only includes medication prescribed by the physician, but also a good education and adherence by the patient to the different therapeutic advices (e.g. blood pressure control, weight management,…) to invert pathophysiological alterations.[1,4]

Adherence to atrial fibrillation guidelines

Although there are established evidence-based guidelines for the management of AF, adherence to these guidelines is suboptimal in daily practice.[75-77] Non-adherence to these guidelines leads to inadequate symptom control, less benefits from proven treatments with worse outcomes and suboptimal resource use such as consultations, emergency room visits and hospitalizations.

The Euro Heart Survey, already performed in 2003-2004, provided the first but important evidence for the discordance between the AF guidelines and daily clinical practice.[75] Based on data from 5333 AF patients from 182 hospitals in 35 countries, they showed that there was an important disagreement concerning (i) the use of rhythm control therapy: 46% of the patients who had no previous symptoms were on a rhythm control strategy; (ii) the performance of different diagnostic procedures such as an echocardiography and assessment of the thyroid function; (iii) appropriate prescription and use of OAC.[75,78,79]

Numerous other and more recent studies showed the misuse of antithrombotic therapy (i.e. overtreatment or undertreatment) both with VKA and with NOACs.[80-96] Solutions are needed to bridge this gap between 'evidence and guideline based' care and 'real-life' daily care.[77]

Integrated atrial fibrillation care

The increasing number of patients, the complexity of the disease, the opportunity to optimize guideline-adherence, and the limited healthcare resources strengthen the need for new initiatives to optimize the management of AF. Only a better structured and efficient care system, from detection to guideline-based treatment, may help stem the tide.[97]

A proposed approach to handle this complex management is the establishment of an "interdisciplinary nurse-led AF clinic".[97] Such an integrated care management approach can coordinate and follow-up on many different aspects of AF care including: improved AF detection activities in high-risk patient groups, proper anticoagulation, rate control and rhythm control, addressing and management of comorbidities, etc. All this should be combined with adequate patient education, empowerment and stimulation of self-care, also allowing shared decision-making.[97,98] In such a care model, trained AF nurses are invaluable to support

this interdisciplinary care together with and under the supervision of the cardiologist. Further, a good communication with other care providers (general practitioners, specialists,…), but also with the patient himself, is of great importance.

Three large studies **(Table 1)** have shown the benefit of systematic care delivery in AF patients, as it could lead to less cardiovascular hospitalizations and a lower mortality, also being less costly.[47,99-102]

In 2012, Hendriks et al. were the first to show that nurse-led outpatient care steered by guideline-based decision support software and supervised by a cardiologist led to less cardiovascular hospitalizations and cardiovascular death.[47] This approach not only improved survival, it also saved costs and improved the QOL of AF patients.[99,103]

The Standard versus Atrial Fibrillation-specific strategy (SAFETY) trial performed by Stewart et al. was a multicenter Australian study focusing on participants who had a hospital admission primarily due to AF.[100] The intervention was diverse, but mainly home-based. Although this led to proportionately more event-free days (i.e. days alive and out of hospital) in the intervention group, it had no significant impact on a composite outcome of all-cause mortality and hospitalizations.[100]

Finally, the most recent study by Carter et al. was a "before and after study" from Canada that included patients who visited the emergency department and were newly diagnosed with AF.[101] The intervention consisted of a brief post-discharge educational telephone call by a cardiac nurse, a group education session and one visit in a nurse-led, cardiologist supervised clinic. In propensity matched groups, this approach led to a significant reduction in the primary composite endpoint of all-cause death, cardiovascular hospitalizations and AF-related emergency visits.[101]

Table 1: Overview of the three important trials concerning integrated care for AF patients.

	Hendriks et al. (2012)[47,99]	Stewart et al. (2015)[100]	Carter et al. (2016)[101]
Design	Single center RCT	Multicenter RCT	Before and after study
Number of patients	712 (93.7% of the recruited patients were included)	335 (13.7% of the recruited patients were included)	336
Patient population	AF patients referred to outpatient clinic (without any unsatisfactory treated comorbidities)	Hospitalized AF patients (no valvular disease, no HF, no new AF,…)	New AF patients presented at the emergency department
Mean age	66.5 ± 13 years	72 ± 11 years	62.8 ± 15.4 years
Intervention	Nurse-led outpatient care, supervised by cardiologist • Protocoled diagnostic testing (blood test, holter, cardiovascular risk factors, echocardiography,…) • Patient education • Psychosocial support • Decision support software to facilitate guideline adherence and to guide treatment recommendations • Telephone support when needed	Nurse-led home-based intervention • Home visit by specialist cardiac nurse 1-2 weeks post discharge (was repeated if necessary) + holter • Patient education • Telephone support • Referral to other healthcare professionals • Recommendation to the medical team concerning optimal AF care	Nurse-run, physician-supervised outpatient care • Brief educational telephone call by cardiac nurse shortly after discharge • Group education session • Patient was discussed by AF team + additional examinations were planned • 1 visit in the nurse-led outpatient clinic: checklist was used by nurse • Management plan was prepared by a nurse → sent to electrophysiologist for verification → sent to GP
Follow-up	• Total: 1.83 year • Minimum follow-up: 12 months • Visits: 3, 6, 12, 18, 24 months	• Total: 2.48 year • Minimum follow-up: 24 months • Clinical review at 12 and 24 months	• Total: 2.06 year • Minimum follow-up: 12 months
Primary outcome	• Cardiovascular hospitalizations and death: 14.3% AF clinic vs. 20.8% standard care. HR 0.65 (95% CI: 0.45-0.93) • Cost-effective strategy	• Cardiovascular complications: all-cause mortality and/or unplanned readmission: 76% intervention group vs. 82% standard care group HR 0.97 (95% CI: 0.76-1.23) • Proportionally more event-free days in the intervention group HR 0.22 (95% CI: 0.21-0.23)	• Death, cardiovascular hospitalizations, emergency department visits for AF: 17.3% AF clinic vs. 26.2% standard care OR 0.59 (95% CI: 0.35-1.00)

AF: atrial fibrillation, CI: confidence interval, GP: general practitioner, HF: heart failure, HR: hazard ratio, OR: odds ratio, RCT: randomized controlled trial.

A meta-analysis, published in 2017 by Gallagher and colleagues, combined the results of these three trials and concluded that the use of an integrated care approach for AF was associated with a reduction in all-cause mortality (OR 0.51, 95% CI: 0.32 - 0.80, P = 0.003) and cardiovascular hospitalizations (OR 0.58, 95% CI: 0.44 - 0.77, P = 0.0002).[102] It had however no significant impact on AF-related hospitalizations (OR 0.82, 95% CI: 0.56 - 1.19, P = 0.29) or cerebrovascular events (OR 1.00, 95% CI: 0.48 - 2.09, P = 1.00).[102]

Although every study used an integrated AF care approach, the interventions that were tested, the care that was provided, and the patient populations that were targeted in these studies were very different from each other. Therefore, at this moment it cannot be determined which components of the integrated care program contributed to the overall beneficial results and which components might have been redundant.

Nevertheless, since 2016, the ESC guidelines for the management of AF were the first to recommend that the use of an 'integrated care' approach should be considered to optimize the care and outcomes of AF patients (class IIa, level of evidence B).[4] A schematic overview of the different fundamentals was provided in the guidelines **(Figure 3)**. Moreover, placing patients in a central role in decision-making should be considered (class IIa, level of evidence C). This will allow to tailor the management to the patient preferences and to improve their adherence to long-term therapy.[4]

Integrated AF management			
Patient involvement	**Multidisciplinary teams**	**Technology tools**	**Access to all treatment options for AF**
• Central role in care process • Patient education • Encouragement and empowerment for self-management • Advice and education on lifestyle and risk factor management • Shared decision making	• Phycisians (general physicians, cardiology and stroke AF specialists, surgeons) and allied health professionals work in a collaborative practice model • Efficient mix of communication skills, education, and experience	• Information on AF • Clinical decision support • Checklist and communication tools • Used by healthcare professionals and patients • Monitoring of therapy adherence and effectiveness	• Structured support for lifestyle changes • Anticoagulation • Rate control • Antiarrhythmic drugs • Catheter and surgical interventions (ablation, LAA occluder, AF surgery, etc.)
• ***Informed, involved, empowered patient***	• ***Working together in a multidisciplinary chronic AF care team***	• ***Navigation system to support decision making in treatment team***	• ***Complex management decisions underpinned by an AF Heart Team***

Figure 3: Schematic overview of the fundamentals of integrated care for AF patients as suggested by the 2016 European Society of Cardiology guidelines for the management of AF. Reproduced from Kirchhof P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal 2016; 37 (38): 2893-2962, doi:10.1093/eurheartj/ehw21. Reproduced by permission of Oxford University Press on behalf of the European Society of Cardiology. Please visit: www.escardio.org/Guidelines/Clinical-Practice-Guidelines/Atrial-Fibrillation-Management.[4] AF: atrial fibrillation, LAA: left atrial appendage.

However, the use of this approach is still a new concept in the field of AF. Hospitals and cardiology practices do not have any predefined and structured guidance how this nurse-led patient-centered integrated care can be implemented in daily practice, and therefore patients cannot benefit from proven positive results associated with this care model. Moreover, the payers of healthcare need information on which investments in transmural care have the best intermediate patient outcomes and economic outcomes.

Objectives and project outline

Setting up and implementing an interdisciplinary AF expert center is a complex task and an important challenge. Questions remain as there are no exact blueprints available on how this 'integrated care' should be implemented and delivered. Different intermediate steps are needed to test the feasibility and effectiveness of various elements of an integrated care model for AF. Preparatory studies and extra scientific evidence are therefore highly needed.

The aim of this thesis is to contribute to different aspects of integrated care for AF patients, to provide answers to open questions, and to evaluate new tools, strategies and ideas in this extensive but fast evolving research area. We try to provide important building blocks based on unique and innovative projects that fit along the line of our way to an interdisciplinary (nurse-coordinated) AF clinic. While doing this, we try to give patients a central role by actively involving them in their care process and by focusing on their needs. Patients with AF require long-term and structured care.[4,104] The projects described in this dissertation therefore often include interventions provided in a systematic and tailored way with the support of a multidisciplinary team and with the ultimate goal to optimize different outcome parameters and the overall care of these patients.

We focus on four main areas to improve the management of AF patients **(Figure 4)**:

i) Screening for AF: with a focus on the usability and effectiveness of handheld ECG devices to detect AF in a hospital setting.

ii) Educating patients with AF: providing insights concerning AF-related knowledge gaps of patients and the most efficient way to provide education to these patients.

iii) Adherence to OAC: research into ways to improve the adherence to NOACs in AF patients.

iv) Risk factor management: providing guidance on how to tackle modifiable risk factors in AF patients.

Along the different studies described in this dissertation, attention was paid to various other parameters than only the primary and secondary clinical outcome measures, i.e. practical implementation of study interventions (e.g. time investments of study personnel, feasibility), cost-effectiveness of the evaluated tools or interventions, and/or the opinion and feedback of the patients themselves. All these aspects can provide important guidance on the need and feasibility of integrated care for AF patients. These data are key to know before implementation in daily practice.

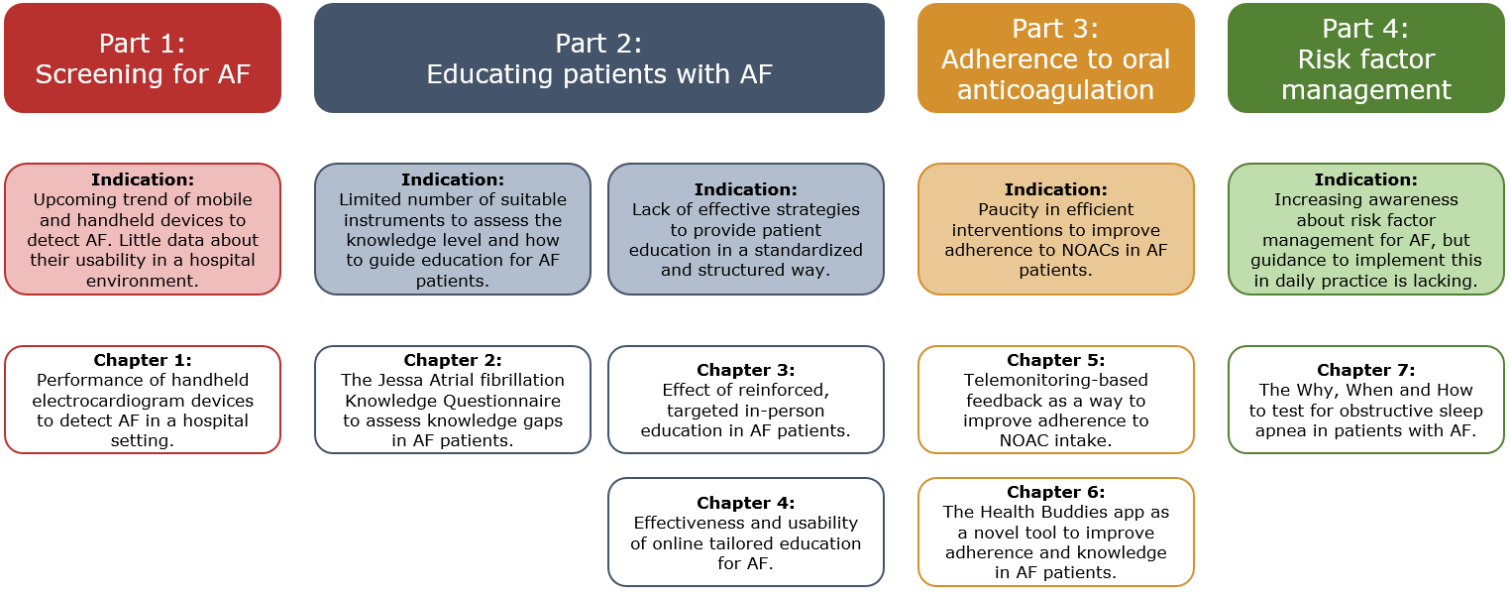

Figure 4: Schematic overview of the different studies that were performed in the context of this thesis. AF: atrial fibrillation, NOAC: non-vitamin K antagonist oral anticoagulant.

PART 1

Screening for atrial fibrillation

Chapter 1

Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting

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ABSTRACT

Aims

To determine the usability, accuracy, and cost-effectiveness of two handheld single-lead electrocardiogram (ECG) devices for atrial fibrillation (AF) screening in a hospital population with an increased risk for AF.

Methods and results

Hospitalized patients (n = 445) at cardiological or geriatric wards were screened for AF by two handheld ECG devices (MyDiagnostick and AliveCor). The performance of the automated algorithm of each device was evaluated against a full 12-lead or 6-lead ECG recording. All ECGs and monitor tracings were also independently reviewed in a blinded fashion by two electrophysiologists. Time investments by nurses and physicians were tracked and used to estimate cost-effectiveness of different screening strategies. Handheld recordings were not possible in 7 and 21.4% of cardiology and geriatric patients, respectively, because they were not able to hold the devices properly. Even after the exclusion of patients with an implanted device, sensitivity and specificity of the automated algorithms were suboptimal (Cardiology: 81.8 and 94.2%, respectively, for MyDiagnostick; 54.5 and 97.5%, respectively, for AliveCor; Geriatrics: 89.5 and 95.7%, respectively, for MyDiagnostick; 78.9 and 97.9%, respectively, for AliveCor). A scenario based on automated AliveCor evaluation in patients without AF history and without an implanted device proved to be the most cost-effective method, with a provider cost to identify one new AF patient of €193 and €82 at cardiology and geriatrics, respectively. The cost to detect one preventable stroke per year would be €7535 and €1916, respectively (based on average CHA_2DS_2-VASc of 3.9 ± 2.0 and 5.0 ± 1.5, respectively). Manual interpretation increases sensitivity, but decreases specificity, doubling the cost per detected patient, but remains cheaper than sole 12-lead ECG screening.

Conclusion

Using AliveCor or MyDiagnostick handheld recorders requires a structured screening strategy to be effective and cost-effective in a hospital setting. It must exclude patients with implanted devices and known AF, and requires targeted additional 12-lead ECGs to optimize specificity. Under these circumstances, the expenses per diagnosed new AF patient and preventable stroke are reasonable.

INTRODUCTION

Early detection of atrial fibrillation (AF) is gaining interest as the arrhythmia is becoming more prevalent in our society.[11] Atrial fibrillation is associated with increased morbidity and mortality, mainly related to thromboembolism and heart failure.[59,60] These complications may be preventable in case of an early identification of AF and appropriate evidence-based management.[59,60] One out of three AF patients is asymptomatic but nevertheless carries the same risks.[59,60] Therefore, screening for silent AF is becoming increasingly important. The latest guidelines recommend opportunistic screening above the age of 65 using pulse palpation, followed by a 12-lead electrocardiogram (ECG) in case of an irregular pulse.[60] Pulse checks may be sensitive but they are not specific, while only using 12-lead ECGs definitely is no cost-effective screening strategy.[105,106] To overcome these problems, new technologies are emerging that could optimize the early identification of AF patients in a variety of settings: e.g. long-term ECG recorders, implantable loop recorders, blood pressure monitors, smartphone applications and devices, handheld single-lead ECG recorders, and ECG patches. Handheld ECG recording devices receive most interest for opportunistic screening, as they are easy to use, portable, low-cost, allow fast rhythm strip recordings, do not require experienced personnel and often have built-in algorithms that provide an immediate interpretation of the ECG. In out-of-hospital settings, such devices have shown high sensitivity (94.0–100%) and good specificity (90.0-99.1%), both when interpreted by an automated algorithm or after manual supervision by someone with sufficient expertise.[107-113] Moreover, handheld devices have even shown to be cost-effective when used in a community screening programme[109,114,115] and they can be used for the follow-up assessment of the effectiveness of AF treatment.[108]

In contrast, little is known about their usability in a hospital environment although there may be a much higher prevalence of patients at risk for AF and its complications. Even in this setting, early detection and management of AF patients can be improved since not every patient on every ward will undergo regular 12-lead ECGs and the effectiveness of pulse checks by nurses to detect silent AF may be suboptimal.[96] For that reason, easy, reliable and widespread early AF screening could be valuable in a hospital setting.

The aim of this study was to determine the usability and accuracy of two handheld single-lead ECG devices (AliveCor and MyDiagnostick) for AF screening in a hospital population with an increased risk for AF. On the basis of our findings, we did cost-effectiveness simulations for different screening approaches.

METHODS

Study population and setting

This non-randomized blinded observational study was performed at two departments of a large Belgian tertiary care hospital. First, a cardiac ward setting was chosen to perform an initial validation of the handheld ECG devices. Afterwards, a similar screening study was performed at the geriatric ward because of the higher expected prevalence of AF patients but absence of systematic ECG recording. Patients needed to be able to give oral informed consent. Exclusion criteria were age <18 years, patients in isolation, and those who were unable to hold both devices properly. The study complied with the Declaration of Helsinki and the research protocol was approved by the local ethics committee.

Electrocardiogram recordings

Each patient was asked by a single researcher to consecutively hold two handheld ECG devices, more specifically the MyDiagnostick (Applied Biomedical Systems BV, The Netherlands) and the AliveCor (AliveCor Inc., USA) **(Figure 1.1)**. At the cardiology department, a full 10-s 12-lead ECG recording was performed by a trained nurse immediately before recording with the two handheld devices. At the department of geriatrics, a 6-lead limb ECG was taken, but of 30 s duration.

To record a single-lead ECG with the MyDiagnostick, the patient has to hold the rod-like device with both hands for 1 min. For this study, the device was programmed in screening mode, meaning that all ECG recordings are stored together with a recording time, date, and automated algorithm diagnosis. During the screening, the recording time and the patient's identification data were noted by the operator. After a screening session, the ECG recordings were uploaded to a computer and linked to the patients' identification by means of the accompanying software. The algorithm of the MyDiagnostick will indicate AF based

on an irregular RR interval which is present during at least 75% of the 1-min recording.[112]

The AliveCor is coupled with an iPhone and allows a noise-filtered lead I ECG recording by means of the corresponding AliveECG app. After each 30 s recording, identification data are directly entered and stored in the app. Together with the automated rhythm diagnosis, these data are wirelessly transferred to a web-based software platform. The automated algorithm of the AliveCor is based on the criteria of P-wave absence and RR interval irregularity to diagnose AF.[110]

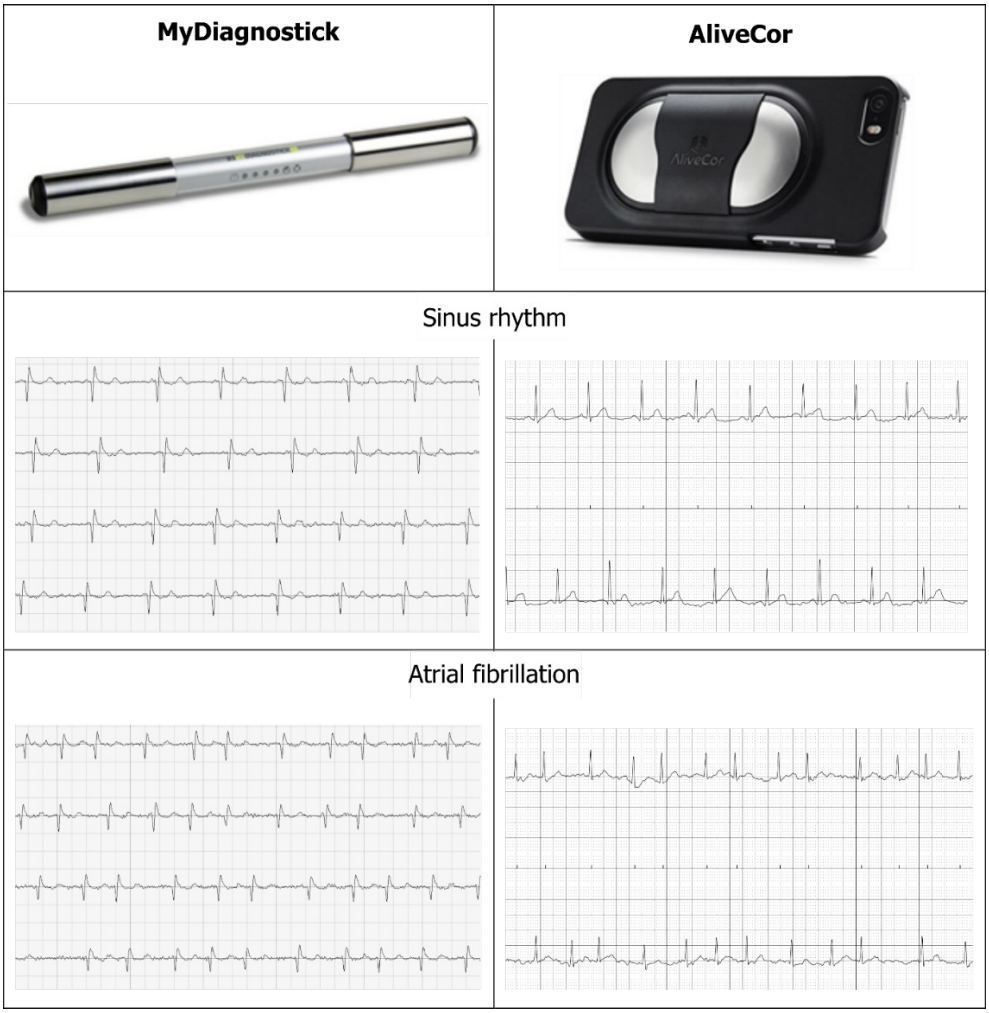


Figure 1.1: MyDiagnostick (left) and AliveCor (right) with representative recordings in a patient with sinus rhythm and a patient with atrial fibrillation.

Data collection and management

For each patient, three ECG tracings were collected: reference 6-lead or 12-lead ECG, MyDiagnostick, and AliveCor, each with their automated rhythm interpretation. Moreover, every recording was later reviewed randomly and independently by two electrophysiologists (H.H. and P.V.), who were blinded for the automated analysis of the devices. Electrocardiogram tracings had to be classified as sinus rhythm, AF, atrial flutter, or 'not interpretable due to insufficient quality'. Atrial flutter and AF were seen as one diseased state since consequences and management are similar, and were classified as AF for further analysis. A chart review was done for every patient to evaluate the known presence of AF and to record clinical and demographic data. Throughout the study, all time investments of nurses and physicians were tracked.

Electrode solution spray substudy

To investigate whether electrode solution spray may optimize the quality of the handheld ECG recordings, a substudy was performed in 53 patients hospitalized at the cardiology ward. The patients were asked to successively hold the MyDiagnostick and the AliveCor. Thereafter, patients' hands were moisturized with an electrode solution spray (SignaSpray, Parker Laboratories, USA) and they were asked to hold both devices for a second time. All paired recordings were randomly presented to two blinded electrophysiologists to indicate which of the two had the best quality.

Cost-effectiveness simulation

On the basis of the screening results and time-investment measurements, a cost-effectiveness simulation was performed for different screening strategies. Taking into account the Belgian staff costs, these values were translated into a hospital cost together with the costs of the three screening tools. A calculation was made as cost per newly identified AF patient. Moreover, to calculate the costs per preventable stroke, the yearly expected stroke risk of patients admitted to both wards was calculated, based on their mean CHA_2DS_2-VASc score.[59] Given that about two out of three strokes (64%) can be prevented using proper oral anticoagulation therapy, this allowed us to give an estimate of the screening costs needed to prevent one stroke every year (excluding the cost of the anticoagulation therapy itself).[116] All costs were expressed in Euro (€).

Statistical analysis

Statistical analysis was performed using SPSS 22.0. The interpretation of the 12-lead and 6-lead ECG by the two electrophysiologists (obtained as a consensus in the case of different independent analyses) was considered as the 'gold standard' to calculate sensitivity and specificity of the automated device algorithms to detect AF. Additionally, the same analyses were performed for the manual interpretation of the handheld ECG recordings by each electrophysiologist. The kappa coefficient was determined to assess the agreement between the reference ECG, the automated analysis of the devices and the interpretation by the electrophysiologists, and the agreement between the two electrophysiologists. A kappa statistic of >0.8 was considered as 'excellent agreement'.[117] A two-sample t-test was used to compare kappa values of both devices at each ward. Logistic regression analysis, including age as a variable into the model, was used to evaluate the effect of different variables on the readability of the handheld ECG recordings. A logistic mixed model was used to check whether both electrophysiologists had a preference for handheld ECG recordings with electrode solution spray, for each device. A P-value of <0.05 was considered statistically significant.

RESULTS

Cardiology ward

None of the 344 patients who were asked to participate in the study refused. Nevertheless, 24 patients (7%) had to be excluded because they were not able to hold the devices properly. In total, 320 patients with a mean age of 67.9 ± 14.6 years were analysable (Supplementary material, Figure S1.1 and Table S1.1). Patients with an implanted device comprised 17.2% of the cardiology population: 60% was actively paced, 7.3% was intermittently paced, and 32.7% was not being paced during the recordings. Based on chart review, 35.6% of the screened study population was known with AF. At the moment of the study, 11.9% showed AF on their 12-lead ECG. Of the entire AF population, the majority had paroxysmal AF (54.4%) while those in AF at the time of screening were mostly permanently in AF (Supplementary material, Table S1.2). One patient was newly detected with asymptomatic AF on the 12-lead ECG. He was also recognized both on automated and manual analysis for each of both devices.

Including device patients (pacemaker or implantable cardioverter defibrillator) in the analysis, MyDiagnostick had 60.5% sensitivity and 93.3% specificity to detect AF **(Table 1.1)**. AliveCor had a lower sensitivity (36.8%) but higher specificity (96.1%). After the manual review by the electrophysiologists, the sensitivity for MyDiagnostick and AliveCor mostly improved without major impact on the specificity.

Both ECG devices yielded ~3.9% non-interpretable recordings as judged by the electrophysiologists **(Table 1.1)**. Factors associated with non-readability were age (76.2 ± 8.2 vs. 67.4 ± 14.8; P = 0.004), presence of an implanted device (42.9 vs. 15.4%; P = 0.028), and presence of AF itself (33.3 vs. 10.7%; P = 0.029).

After the exclusion of device patients, the sensitivity and specificity of both devices improved, both for automated analysis and for manual interpretation. The automated analysis of the MyDiagnostick had a higher sensitivity (81.8%) compared with the interpretation of Electrophysiologist 1 (77.3%) and Electrophysiologist 2 (72.7%). The opposite was true for the AliveCor device: both electrophysiologists identified a sensitivity of 90.9% of the AF patients on the handheld recordings, compared with a sensitivity of only 54.5% by the AliveCor algorithm itself.

There was no difference in agreement (based on kappa values) between both devices when including all patients (P = 0.677) and after the exclusion of patients with an implanted device (P = 0.411).

The agreement between the two electrophysiologists for the interpretation of the ECG traces was substantial with a kappa statistic value of 0.80 for the MyDiagnostick and 0.69 for the AliveCor for the full cohort. After exclusion of the patients with an implanted device, this further increased to 0.86 and 0.84, respectively **(Table 1.2)**.

Table 1.1: Performance of both devices for atrial fibrillation screening at the cardiology ward, based on automated analysis and manual interpretation by both electrophysiologists.

MyDiagnostick	True Positive (n)	False Negative (n)	False Positive (n)	True Negative (n)	Illegible (n)	Sensitivity* (%)	Specificity* (%)	PPV (%)	NPV (%)	Kappa (κ)
PM/ICD patients included (n=320)										
Automated Algorithm vs. 12-lead ECG	23	15	19	263	-	60.5	93.3	54.8	94.6	0.51
Electrophysiologist 1 vs. 12-lead ECG	26	8	16	257	13	**68.4**	91.1	61.9	97.0	**0.55**
Electrophysiologist 2 vs. 12-lead ECG	21	14	7	266	12	55.3	**94.3**	75.0	95.0	0.53
PM/ICD patients excluded (n=265)										
Automated Algorithm vs. 12-lead ECG	18	4	14	229	-	**81.8**	94.2	56.3	98.3	0.63
Electrophysiologist 1 vs. 12-lead ECG	17	3	11	226	8	77.3	93.0	60.7	98.7	0.58
Electrophysiologist 2 vs. 12-lead ECG	16	4	4	233	8	72.7	**95.9**	80.0	98.3	**0.65**

AliveCor	True Positive (n)	False Negative (n)	False Positive (n)	True Negative (n)	Illegible (n)	Sensitivity* (%)	Specificity* (%)	PPV (%)	NPV (%)	Kappa (κ)
PM/ICD patients included (n=320)										
Automated Algorithm vs. 12-lead ECG	14	24	11	271	-	36.8	**96.1**	56.0	91.9	0.39
Electrophysiologist 1 vs. 12-lead ECG	26	8	8	261	17	**68.4**	92.6	76.5	97.0	0.58
Electrophysiologist 2 vs. 12-lead ECG	24	14	4	270	8	63.2	95.7	85.7	95.1	**0.61**
PM/ICD patients excluded (n=265)										
Automated Algorithm vs. 12-lead ECG	12	10	6	237	-	54.5	**97.5**	66.7	96.0	0.57
Electrophysiologist 1 vs. 12-lead ECG	20	0	5	230	10	**90.9**	94.7	80.0	100.0	0.71
Electrophysiologist 2 vs. 12-lead ECG	20	2	3	234	6	**90.9**	96.3	87.0	99.2	**0.76**

Best values for sensitivity, specificity and kappa values are displayed in bold.
ECG: electrocardiogram, ICD: implantable cardioverter defibrillator, NPV: negative predictive value, PM: pacemaker, PPV: positive predictive value
*Unreadable recordings are taken into account when calculating the sensitivity and specificity.

Table 1.2: Degree of inter-observer variation between the two electrophysiologists.

	Kappa (95% CI)	
	Cardiology ward	Geriatric ward
MyDiagnostick with PM/ICD patients	0.80 (0.71; 0.89)	0.78 (0.66; 0.90)
MyDiagnostick without PM/ICD patients	0.86 (0.77; 0.96)	0.84 (0.73; 0.96)
AliveCor with PM/ICD patients	0.69 (0.58; 0.81)	0.72 (0.59; 0.86)
AliveCor without PM/ICD patients	0.84 (0.75; 0.94)	0.76 (0.62; 0.89)

CI: confidence interval, ICD: implantable cardioverter defibrillator, PM: pacemaker

Geriatric ward

The usability of both devices at the geriatric ward was lower: in 21.4% of the patients, no handheld recording could be performed **(Figure 1.2)**. Eventually, ECG recordings were performed in 125 patients (mean age 83.3 ± 5.8 years; 37.6% male). Twelve patients (9.6%) had an implanted device of which six were actively paced, one was intermittently paced, and five patients were not being paced during the recordings. Total AF prevalence was also very high (36.0%) with a point prevalence of 17.6%. Two patients (1.6%; no device patients) were discovered with new AF on the 6-lead ECG recording. The automated algorithm of both MyDiagnostick and AliveCor detected only one of these two patients, while the other patient was only identified after manual interpretation of the handheld ECG recording by Electrophysiologist 1.

Table 1.3 lists the screening performance of both devices, used automatically or after manual review of the tracings. Most findings parallel those for the cardiology patients. Again, no difference was observed in agreement (based on kappa values) between both devices when including all patients (P = 0.911) and after exclusion of patients with an implanted device (P = 0.822). However, noticeable differences were as follows: (i) the sensitivities of both the automated algorithm and the physicians were higher; (ii) both physicians classified more ECG tracings as false-positives, resulting in lower specificities and a lower kappa agreement compared with the 6-lead ECG recordings.

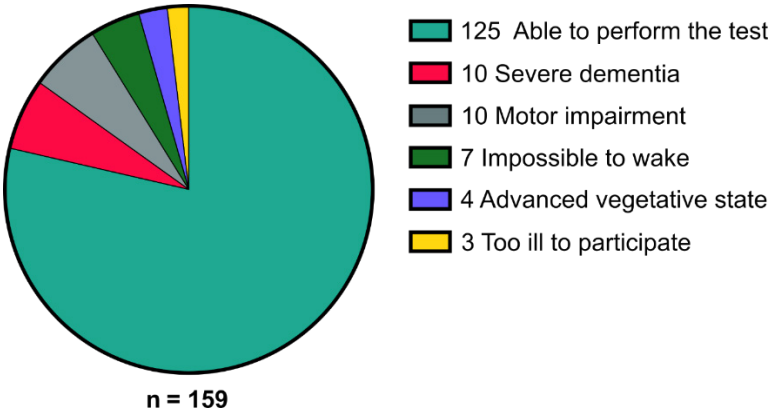


Figure 1.2: Patient inclusion and exclusion at the geriatric ward.

Electrode solution spray substudy

We found that electrode spray did not improve the quality of the ECG recordings by MyDiagnostick, as both electrophysiologists had no preference ($P = 0.617$) for the ECG recordings with the electrode spray, i.e. 50.9% and 54.7% for Electrophysiologists 1 and 2, respectively. In contrast, the quality of the AliveCor tracings clearly benefited from the electrode spray, with a significant preference for both electrophysiologists ($P < 0.001$). More specifically, Electrophysiologists 1 and 2 classified 64.2% and 77.4%, respectively, of the ECG recordings with the electrode spray as the ones with the better quality.

Table 1.3: Performance of both devices for atrial fibrillation screening at the geriatric ward, based on automated analysis and manual interpretation by both electrophysiologists.

MyDiagnostick	True Positive (n)	False Negative (n)	False Positive (n)	True Negative (n)	Illegible (n)	Sensitivity* (%)	Specificity* (%)	PPV (%)	NPV (%)	Kappa (κ)
PM/ICD patients included (n=125)										
Automated Algorithm vs. 6-lead ECG	18	4	4	99	-	81.8	**96.1**	81.8	96.1	**0.78**
Electrophysiologist 1 vs. 6-lead ECG	20	2	19	84	-	**90.9**	81.6	51.3	97.7	0.56
Electrophysiologist 2 vs. 6-lead ECG	20	2	10	93	-	**90.9**	90.3	66.7	97.9	0.71
PM/ICD patients excluded (n=113)										
Automated Algorithm vs. 6-lead ECG	17	2	4	90	-	89.5	**95.7**	81.0	97.8	**0.82**
Electrophysiologist 1 vs. 6-lead ECG	19	0	15	79	-	**100.0**	84.0	55.9	100.0	0.64
Electrophysiologist 2 vs. 6-lead ECG	18	1	9	85	-	94.7	90.4	66.7	98.8	0.73

AliveCor	True Positive (n)	False Negative (n)	False Positive (n)	True Negative (n)	Illegible (n)	Sensitivity* (%)	Specificity* (%)	PPV (%)	NPV (%)	Kappa (κ)
PM/ICD patients included (n=125)										
Automated Algorithm vs. 6-lead ECG	16	6	2	101	-	72.7	**98.1**	88.9	94.4	**0.76**
Electrophysiologist 1 vs. 6-lead ECG	20	0	12	89	4	**90.9**	86.4	62.5	100.0	0.65
Electrophysiologist 2 vs. 6-lead ECG	19	2	11	92	1	86.4	89.3	63.3	97.9	0.67
PM/ICD patients excluded (n=113)										
Automated Algorithm vs. 6-lead ECG	15	4	2	92	-	78.9	**97.9**	88.2	95.8	**0.80**
Electrophysiologist 1 vs. 6-lead ECG	18	0	10	82	3	**94.7**	87.2	64.3	100.0	0.68
Electrophysiologist 2 vs. 6-lead ECG	18	1	11	83	-	**94.7**	88.3	62.1	98.8	0.69

Best values for sensitivity, specificity and kappa values are displayed in bold.
ECG: electrocardiogram, ICD: implantable cardioverter defibrillator, NPV: negative predictive value, PM: pacemaker, PPV: positive predictive value
*Unreadable recordings are taken into account when calculating the sensitivity and specificity.

Overview of screening scenarios

We translated our results to virtual wards of 100 patients, after exclusion of patients with an implanted device **(Figure 1.3)**.

Automated MyDiagnostick analysis misses one of the eight patients who are actually in AF at a cardiology ward. After manual review of its tracings, even two AF patients would be missed, due to poor quality tracings classified as illegible by the electrophysiologists. Moreover, two to three additional 12-lead ECGs will be needed to rule out a false-positive AF detection in patients who were not known with AF before (**Figure 1.3**, red symbols for dark green patients). We consider the three false-positive detections in patients known with AF (light green) as less relevant. The lower sensitivity of the automated AliveCor algorithm leads to a detection of only four of the eight AF patients. There were also two false-positive results requiring an additional ECG. Manual review here improves sensitivity (leading to only one missed AF patient) without more need for standard ECGs.

At a geriatric ward, automated screening detects one of two unknown AF, while manual supervision may lead to detection of the second, although this was only true for one of our reviewers (**Figure 1.3**, bottom). One (with AliveCor) to four (with MyDiagnostick) of the 100 patients would require an extra 12-lead ECG to rule out false-positive AF detection, a number which increases to five or even eight after manual review.

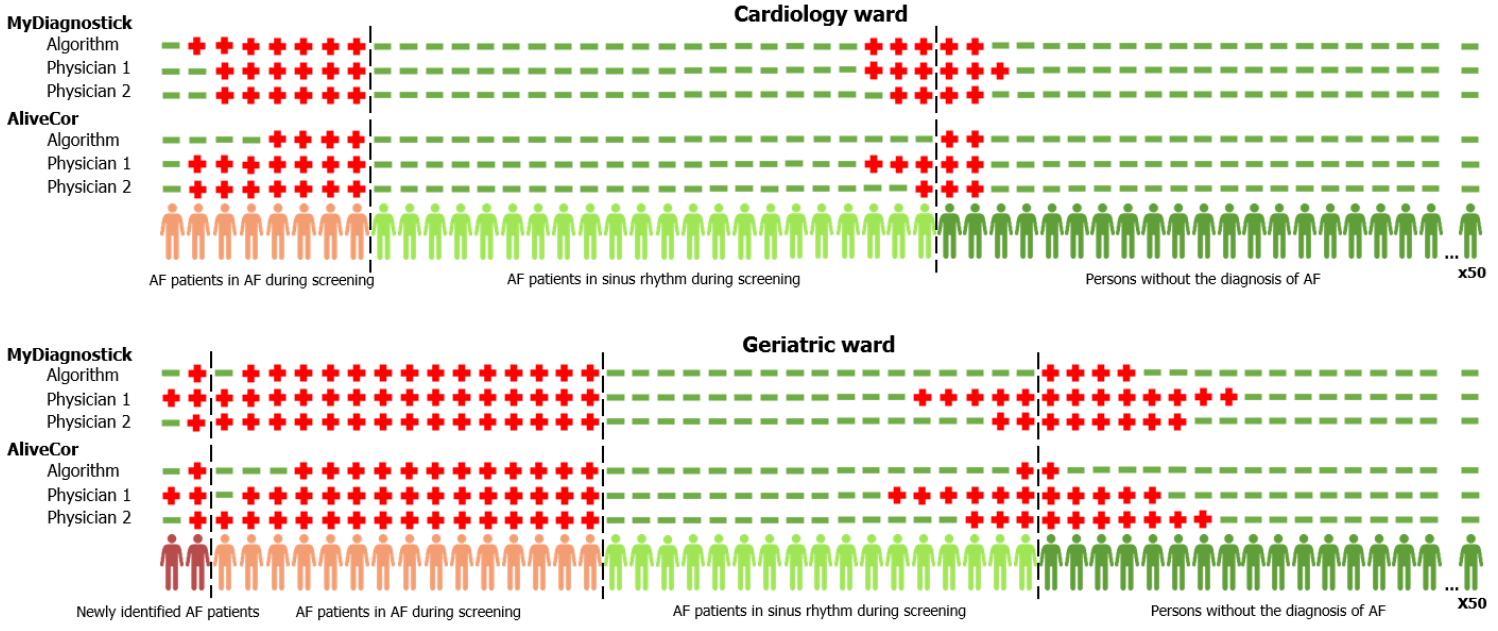


Figure 1.3: Summary of atrial fibrillation (AF) screening approaches in a cardiology or geriatric ward, based on our findings. Representation is based on a population of 100 patients excluding patients with an implanted device. Red individuals represent patients with undetected AF. Orange individuals are patients who are in AF at the moment of screening. Light green individuals represent AF patients who are in sinus rhythm at the moment of screening, and dark green individuals are persons without the diagnosis of AF. The red plus symbol indicates AF as diagnosed by the automated algorithm of the handheld device or by the interpretation by the electrophysiologist. The green minus represents the absence of AF (automated algorithm or manual).

Cost-effectiveness simulation

On the basis of the prior findings, a cost-effectiveness simulation was performed for the different screening strategies, extrapolating numbers to settings of 1000 patients without implantable devices, in scenarios with or without known AF **(Table 1.4)**. When only patients without AF history were screened, the AliveCor algorithm seemed to be the most cost-effective method to identify new AF patients, with a direct hospital cost of €193 at the cardiology ward and €82 at the geriatric ward. Review of all handheld ECG recordings by a physician almost doubled the cost per detected patient (but for screening with improved sensitivity), with sole 12-lead screening as the least cost-effective screening strategy. Translating these costs into hospital screening costs to prevent one stroke per year in patients who are not known with AF, €1916–€5253 would be needed at the geriatric ward (average CHA_2DS_2-VASc score = 5.0 ± 1.5) depending on the used screening method **(Figure 1.4)**. For the cardiology ward (average CHA_2DS_2-VASc score = 3.9 ± 2.0), costs varied between €7535 and €40756.

DISCUSSION

The purpose of our study was to investigate the accuracy and applicability of two handheld ECG recorders to detect AF in a hospital setting. We have shown that the sensitivity and specificity of these devices are still not optimal, even after manual interpretation by experienced electrophysiologists. Moreover, it seems challenging to adequately use these devices in patients with an implanted device and in a population with the highest risk for AF, namely the very elderly. Nevertheless, when addressing these limitations, the devices can be used for a screening strategy that is reasonable from a cost-effectiveness perspective.

Table 1.4: Time investment, hospital costs, and yield of atrial fibrillation screening in a cardiology or geriatric ward (excluding patients with an implanted device) using different strategies in 1000 patients.

Cardiology	Cumulative time (min)		Cumulative costs (Euro)					Total cost (Euro)	Yield (n)			Cost per new AF diagnosis (Euro)
	Nurse	Physician	Nurse	Physician	12-lead	MyDiagn.	AliveCor		Newly identified AF	False negative	False positive	
All patients (n=1000)												
12-lead screening	6000	750	3183	2188	592	-	-	5963	4	0	0	1491
MyDiagn. algorithm	2750	91	1459	265	72	124	-	1920	4	15	53	480
MyDiagn. algorithm + physician review*	2750	835	1459	2435	67	124	-	4085	4	21	51	1021
AliveCor algorithm	1750	51	928	149	40	-	84	**1201**	4	38	23	**300**
AliveCor algorithm + physician review*	1750	838	928	2443	69	-	84	3524	4	8	42	881
Patients without AF history (n=700)												
12-lead screening	4200	525	2228	1531	414	-	-	4173	4	0	0	1043
MyDiagn. algorithm	1925	17	1021	50	14	87	-	1172	4	0	19	293
MyDiagn. algorithm + physician review*	1925	548	1021	1598	18	87	-	2724	4	0	27	681
AliveCor algorithm	1225	17	650	50	14	-	59	**773**	4	0	19	**193**
AliveCor algorithm + physician review*	1225	544	650	1585	15	-	59	2309	4	0	21	577

Geriatrics	Cumulative time (min)		Cumulative costs (Euro)					Total cost (Euro)	Yield (n)			Cost per new AF diagnosis (Euro)
	Nurse	Physician	Nurse	Physician	12-lead	MyDiagn.	AliveCor		Newly identified AF	False negative	False positive	
All patients (n=1000)												
12-lead screening	6000	750	3183	2188	592	-	-	5963	18	0	0	331
MyDiagn. algorithm	2750	140	1459	408	110	124	-	2101	9	9	36	233
MyDiagn. algorithm + physician review*	2750	953	1459	2778	160	124	-	4521	14	4	107	323
AliveCor algorithm	1750	113	928	330	89	-	84	**1431**	9	9	18	**159**
AliveCor algorithm + physician review*	1750	946	928	2759	154	-	84	3925	14	4	102	280
Patients without AF history (n=680)												
12-lead screening	4080	510	2164	1488	402	-	-	4054	18	0	0	225
MyDiagn. algorithm	1870	34	992	99	27	84	-	1202	9	9	36	134
MyDiagn. algorithm + physician review*	1870	573	992	1671	50	84	-	2797	14	4	71	200
AliveCor algorithm	1190	14	631	41	11	-	57	**740**	9	9	9	**82**
AliveCor algorithm + physician review*	1190	566	631	1651	44	-	57	2383	14	4	62	170

Best values are displayed in bold.

*mean of conclusions from Electrophysiologist 1 and 2

AF: atrial fibrillation, MyDiagn.: MyDiagnostick

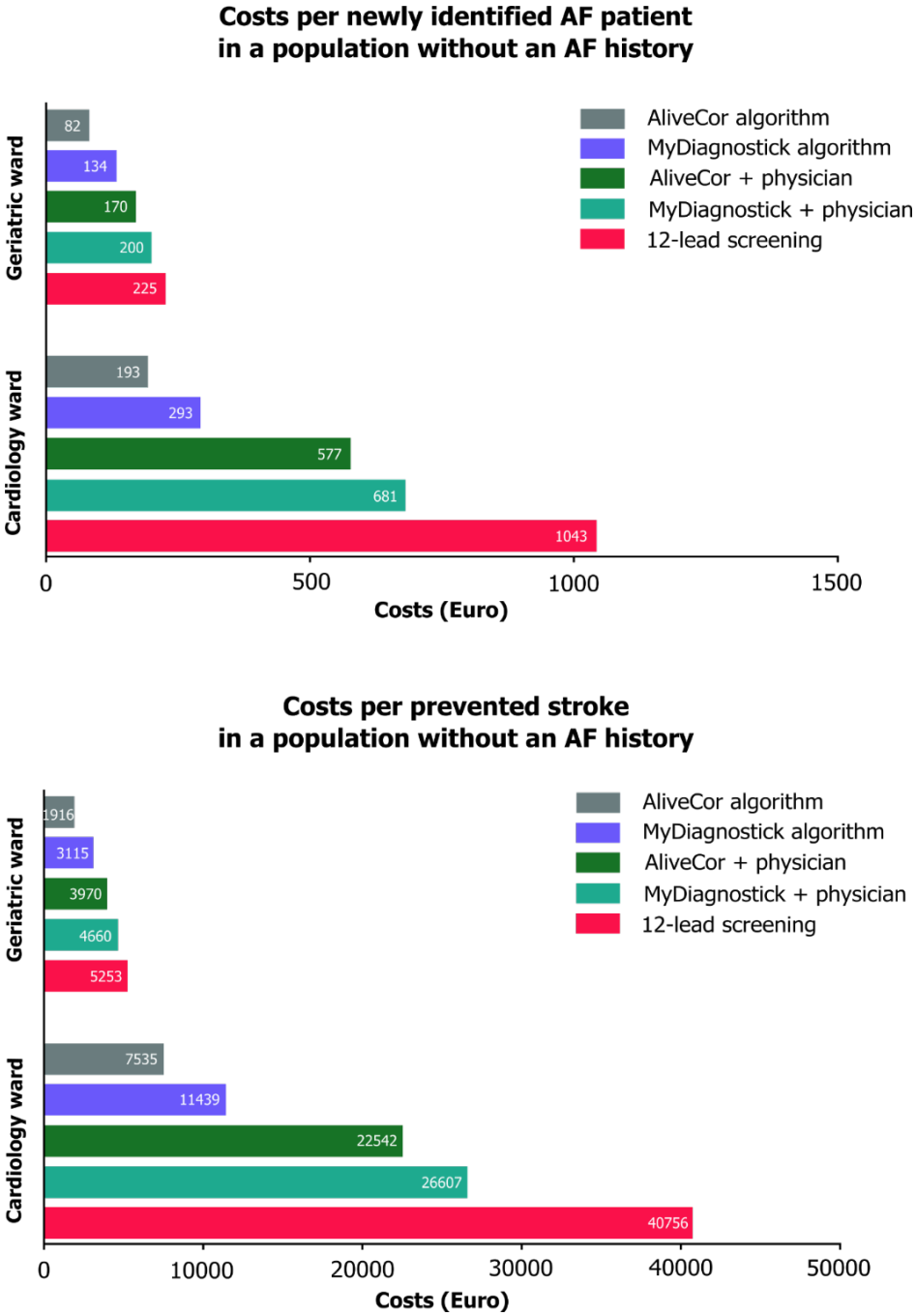


Figure 1.4: Costs per newly identified atrial fibrillation (AF) patient and costs per prevented stroke, using different screening strategies in a cardiology and geriatric ward, based on our findings. Cost-effectiveness simulation is based on our results in a population of 1000 patients excluding patients with an implanted device and patients with a known history of AF.

Performance of handheld screening devices compared with that of other studies

The usability and accuracy of both handheld devices have already been tested in ambulatory settings[107-112,118] but never in a setting with hospitalized patients. Results of those prior studies with outpatient use of both devices, often showing a higher accuracy compared with our results, are summarized in Supplementary material, Table S1.3.

The performance of the algorithm of the AliveCor was much lower in our study compared with the study of Lau et al. who found a sensitivity and specificity of, respectively, 98 – 100% and 96 – 97%.[110,118] Apart from our study, this was the only study prospectively validating the algorithm against a simultaneous 12-lead ECG recording. On the other hand, the automated algorithm of the MyDiagnostick showed very high sensitivities (94 – 100%) and specificities (93 – 95.9%) in other trials when compared with that of a simultaneous 12-lead ECG recording.[111,112]

Most other studies screened less patients, probably in more controlled populations and conditions, e.g. (partly) recruiting patients with a known history of AF[110-112], excluding patients with an implanted device[109,111], screening a relatively younger population[107,108], using a combination of three recordings to make a diagnosis[111] and classifying patients with atrial flutter as not having AF[112]. Moreover, the interpretation of the handheld ECG recording by only one cardiologist may have influenced the results given the inter-rater variability between physicians, as we have shown.

Quality issues

We found that the most common reason for discordance between manual interpretation of the handheld tracings and 12-lead ECG was the presence of repetitive atrial or ventricular premature beats, misguiding the device or physician to classify these handheld ECGs incorrectly as AF. Moreover, the tracings often have an unstable baseline and noise, further complicating the assessment of P-waves that are often not recognizable even in high-quality recordings. A similar observation was made by Mant et al. who proved that there were large differences not only when the interpretation was based on different ECGs (12-lead, limb lead, and single lead) but also when the diagnosis was made by special software or different operators.[119] Interpretation of the single-lead ECG recordings can

therefore depend on the experience of the operator in general and on the device recordings in particular. An optimal ECG recording, in the context of AF, not only allows assessment of the irregularity of RR intervals. The quality of the tracing should also allow to assess P-waves, to discern different QRS morphologies (e.g. from premature beats) and to notice the presence of pacemaker spikes.

The quality of the handheld ECG recordings was not optimal with one or more unreadable tracings in 6.6 and 3.2% of the patients admitted to, respectively, the department of cardiology and geriatrics. At the geriatric ward, illegible ECG recordings were less common and accuracy of both devices was better, possibly due to the higher rate of excluded patients compared with cardiology patients. Our numbers are higher compared with those of other studies using the AliveCor (0.84 – 2.5%).[108,109] Possible reasons for uninterpretable recordings are that patients performed arm movements despite being informed not to do so, suffered from tremor, or were too weak to hold the devices firmly enough. We showed that ECG recording quality can be improved by using an electrode contact spray leading to a more stable baseline and less noise, however, only with the AliveCor device. In any case, illegible tracings should trigger an extra 12-lead verification since our data indicated that unreadable tracings were significantly more often recorded in patients who were in AF at the moment of screening.

Patient acceptance

No patient objected against a handheld recording. Although we did not formally evaluate user-friendliness, there are some differences between both devices. AliveCor offers the advantage that the ECG recordings are immediately available for review, which allows the investigator to judge bedside whether the ECG recording is of sufficient quality and whether a second attempt is needed. Although the MyDiagnostick attaches a date and time to each ECG, the operator needs to carefully pay attention to the order of the measurements or use a screening logbook to not mix up different patient's recordings when used in a high-turnover screening setting. The MyDiagnostick has the advantage of a simpler design that is easier to use in an older population.

Atrial fibrillation screening in a hospital setting

The AF prevalence numbers at our hospital (35.6% and 36.0% at the cardiology and geriatric ward, respectively) were in line with the findings of Berti et al., who showed an AF prevalence of 30.4% at the cardiovascular medicine ward and 42.6% at the department of geriatrics.[96]

In an ambulatory setting, prior research has shown that AF screening using handheld devices could save lives in a cost-effective way. This was shown in settings of patients with a recent ischaemic stroke,[114] a 75/76-year-old general study population[115] and in a community screening through pharmacies.[109] Lowres et al. showed that pharmacy screening above the age of 65 using the automated algorithm of the AliveCor was able to newly identify AF in 1.5% of the customers, which proved to be cost-effective.[109] They calculated a cost of €15993 per avoided stroke in case of 55% treatment adherence to oral anticoagulation therapy with warfarin.

We have shown that the use of handheld devices in a hospital screening setting requires a structured strategy to optimize results, minimizing unreadable tracing and omitting known AF patients and those with implanted devices. Different considerations come into play: we found that the automated algorithm of the MyDiagnostick was the more sensitive of both devices, but that sensitivity was even better for AliveCor after review by an electrophysiologist. On the other hand, while specificity was slightly higher for automated AliveCor screening, this benefit was lost after manual review. These findings make it complex to understand the impact of either strategy in a real-life setting. Nonetheless, we have shown that a very reasonably cost-effective strategy can be devised, with a direct hospital cost per newly identified AF patient of €193 and €82 at the department of cardiology and geriatrics, respectively. To prevent one stroke, €1916 would be needed when screening at the geriatric ward and €7535 at the cardiology ward.

While the relative cost findings are important to gauge the cost-effectiveness of different strategies, the absolute numbers need to be interpreted with caution: (i) these are based on Belgian healthcare cost data, which may not be representative for other countries; (ii) costs for training and deployment were not included; (iii) inefficiencies in the screening system were not taken into account, like higher or lower education level (and related accuracy) of those performing the screening

and interpreting the results; (iv) costs of oral anticoagulation are not included (i.e. the figures represent the screening part of the costs); and (v) costs were calculated as direct provider costs, not from the societal perspective of healthcare costs, which needs to include indirect costs for reimbursement.

The cost-effectiveness will also depend on other factors: (i) the prevalence of newly detected AF patients and the proportion of patients requiring thromboprophylaxis. In the wards studied, AF was highly prevalent, with all patients having at least a moderate risk for stroke (CHA_2DS_2-VASc ≥ 2). (ii) We evaluated only a single screening scenario in our study: repetitive measurements in the same patients during hospitalization might increase the yield of newly identified paroxysmal AF patients but will also impact costs. Other studies reported that intermittent ECG screening could be a more efficient and cost-effective strategy.[113,114,120,121]

It is clear that more sophisticated algorithms offering a more accurate diagnosis of AF without the input of a clinician could make screening more affordable. Besides the two devices that we have studied here, many wireless technologies to detect AF are rapidly emerging. Each device will need study of its merits as a screening tool in a structured approach to validate its use in several populations.

Limitations

This was not a large population scale screening study as the main aim was to determine the feasibility and accuracy of these devices in a hospital setting. Still, with a total of 445 patients, it is larger than many prior validation studies. Moreover, with the evaluation of two different devices in the same setting, our results give a first indication about comparative performance. This single-centre study was focused on two specific hospital wards because of the expected high prevalence of AF. Extrapolation of these results to other wards or hospitals should be made with caution. At the department of geriatrics, only four out of five patients could be included. This may have influenced the results: e.g. the observed higher sensitivity of the two devices at geriatrics compared with that of cardiology could be related to inclusion bias. Although the time between the three consecutive recordings was kept to a minimum, different rhythm presence between the different recordings in paroxysmal AF patients cannot be fully

excluded. Its statistical chance is small, however, and is highly unlikely to have affected the results of this study.

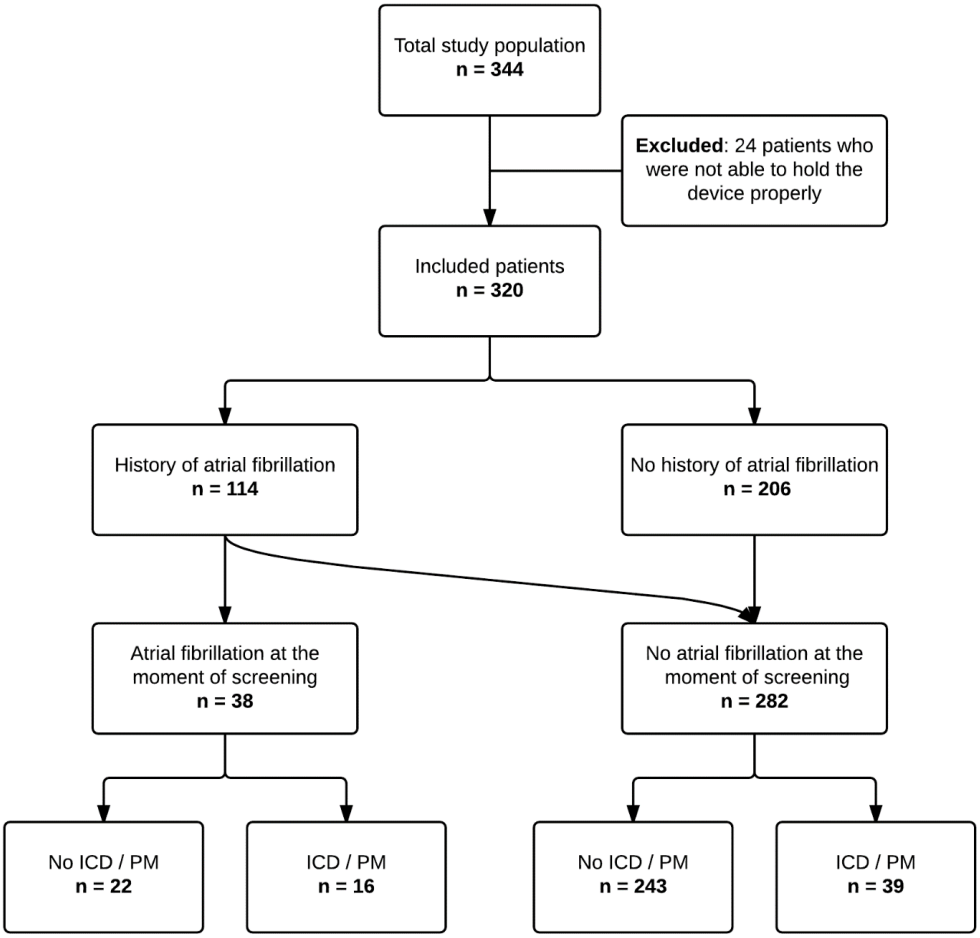
CONCLUSION

We have shown that in a hospital setting, AliveCor or MyDiagnostick handheld recorders integrated within a well-planned screening strategy, i.e. excluding patients with implanted devices and known AF, with measures to optimize specificity (like using electrode spray with AliveCor), and with targeted additional 12-lead ECGs in those with a handheld suspicion of AF, may provide an effective and cost-effective screening approach.

ACKNOWLEDGMENT

Applied Biomedical Systems BV and AliveCor, Inc., provided the devices for this study for free but were not involved in any aspect of the trial.

SUPPLEMENTARY MATERIAL



Supplementary Figure S1.1: Flow chart of study patients at the cardiology ward. ICD: implantable cardioverter defibrillator, PM: Pacemaker.

Supplementary Table S1.1: Patient characteristics at the department of cardiology.

	All subjects	AF	No AF	P-value
Patients, n	320	114	206	-
Female gender, n (%)	138 (43.1%)	59 (51.8%)	79 (38.3%)	0.02
Age, mean ± SD	67.9 ± 14.6	73.1 ± 12.2	65.1 ± 15.0	< 0.001
Main reason for hospital admission, n (%)				-
Coronary angiography/ elective revascularisation	100 (31.2%)	8 (7.0%)	92 (44.7%)	
Electrophysiological examination/ ablation	64 (20.0%)	35 (30.7%)	29 (14.1%)	
Heart failure	37 (11.6%)	26 (22.8%)	11 (5.3%)	
Acute Coronary Syndrome	36 (11.3%)	9 (7.9%)	27 (13.1%)	
Device implantation or replacement	32 (10.0%)	12 (10.5%)	20 (9.7%)	
Symptomatic AF	11 (3.4%)	11 (9.6%)	-	
Other	40 (12.5%)	13 (11.4%)	27 (13.1%)	

AF: atrial fibrillation, SD: standard deviation

Supplementary Table S1.2: Characteristics of AF patients at the cardiology ward.

	All AF patients	AF at the moment of screening
Kind of AF, n (%)	114	38
First diagnosed AF during hospital admission	4 (3.5%)	1 (2.6%)
Paroxysmal AF	62 (54.4%)	11 (28.9%)
Persistent AF	16 (14.0%)	7 (18.4%)
Permanent AF	17 (14.9%)	17 (44.7%)
Atrial flutter	15 (13.2%)	2 (5.3%)
CHA_2DS_2-VASc score, mean ±SD	3.90 ± 1.99	4.84 ± 1.69
HAS-BLED score, mean ±SD	1.78 ± 1.10	1.92 ± 0.97
Anticoagulation/antithrombotic therapy, n (%)		
VKA	23 (20.2%)	10 (26.3%)
NOAC	62 (54.4%)	24 (63.2%)
Only antiplatelet therapy	16 (14.0%)	4 (10.5%)
None	13 (11.4%)	0 (0.0%)

AF: atrial fibrillation, NOAC: non-vitamin K antagonist oral anticoagulants, SD: standard deviation, VKA: vitamin K antagonist

Supplementary Table S1.3: Literature overview and results of studies using AliveCor and MyDiagnostick for the detection of atrial fibrillation in ambulatory settings.

	Device and interpretation	Setting	Sensitivity	Specificity	Reference standard	Remarks and attention points
Lau et al., Circulation, 2012.	AliveCor algorithm (version 1 and 2) and interpretation by 2 cardiologists	109 patients (39 in AF)	Algorithm 1: 87% Algorithm 2: 100% Cardiologist 1: 100% Cardiologist 2: 95%	Algorithm 1: 97% Algorithm 2: 96% Cardiologist 1: 90% Cardiologist 2: 94%	12-lead ECG	• Algorithm was optimised to version 2 after unblinding of the tracings
Lau et al., Int. J. Cardiol., 2013.	AliveCor algorithm	207 patients (48 in AF)	98%	97%	12-lead ECG	• Optimised AliveCor algorithm was used
Lowres et al., Thromb Haemost, 2014.	AliveCor tracings interpreted by a pharmacist and retrospectively use of the automated algorithm	Pharmacy screening in 1000 participants above the age of 65 (67 in AF)	Algorithm: 98.5% Pharmacist: 77%	Algorithm: 91.4% Pharmacist: 87%	AliveCor recordings interpreted by a cardiologist	• No 12-lead as reference standard • 2.5% of the ECG's were only interpretable when a noise-reduced ECG was used • 1.5% newly detected AF patients • PM patients were excluded
Haberman et al., J. Cardiovasc. Electrophysiol., 2015.	AliveCor interpretation by an electrophysiologist	130 outpatients at the department of cardiology (18 in AF)	94.4%	99.1%	12-lead ECG	• Younger patients (59±15 years) were included
Tarakji et al., Heart Rhythm, 2015.	AliveCor interpretation by an electrophysiologist	60 post-AF ablation patients	100%	97%	Transtelephonic monitor ECG recordings interpreted by an electrophysiologist	• No 12-lead as reference standard • 0.84% (7/831) of the AliveCor readings were noninterpretable • Younger patients (60±12 years) familiar with an iPhone were included
Chan et al., J. Am. Coll. Cardiol., 2015.	AliveCor	Population screening in 2001 people (36 in AF)	No validation			• 1.2% newly detected AF patients

	Device and interpretation	Setting	Sensitivity	Specificity	Reference standard	Remarks and attention points
Willems et al., British Journal of Cardiology, 2015.	AliveCor ECG recording interpreted by a cardiologist and a GP	99 patients attending an AF outpatient clinic (29 in AF)	cardiologist: 90% GP: 93%	cardiologist: 86% GP: 76%	12-lead ECG	• 4% (4/99) of the AliveCor tracings were illegible
Tieleman et al., Europace, 2014. (part 1)	MyDiagnostick algorithm	192 patients attending an outpatient clinic (53 in AF)	100%	95.9%	12-lead ECG	• Atrial flutter patients were classified as not having AF
Tieleman et al., Europace, 2014. (part 2)	MyDiagnostick algorithm	Population screening in 676 patients attending their GP (55 in AF)	100%	99%	MyDiagnostick recordings interpreted by a cardiologist	• No 12-lead as reference standard • 1.6% newly identified AF patients
Vaes et al., BMC Fam Pract, 2014.	MyDiagnostick algorithm	191 patients visiting a GP (103 in AF)	94%	93%	12-lead ECG	• 161 AF patients and 30 healthy controls • Combination of 3 consecutive measurements was taken • No consensus in the diagnosis of the three measurements in 8.3% of the cases • Exclusion of patients with an active PM

AF: atrial fibrillation, ECG: electrocardiogram, GP: general practitioner, PM: pacemaker

PART 2

Educating patients with atrial fibrillation

Chapter 2

Knowledge gaps in patients with atrial fibrillation revealed by a new validated knowledge questionnaire: JAKQ

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ABSTRACT

Objective

The aim of this study was to develop and validate a new questionnaire, the Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ), to test the knowledge of patients with atrial fibrillation (AF) about the arrhythmia, its treatment and their ability for self-management.

Methods

The JAKQ was developed based on other questionnaires, two educational checklists and patient information support websites. The JAKQ was validated based on content validity, face validity, response process, discriminatory potential and sensitivity of the questionnaire, construct validity and reliability. It was presented to both outpatients and hospitalised patients.

Results

A total of 466 AF patients completed the JAKQ. The final 16-item JAKQ consists of 8 questions about AF in general, 5 questions about oral anticoagulation (OAC) therapy and either 3 questions about vitamin K antagonists (VKA) or non-vitamin K antagonist oral anticoagulants (NOAC). The questionnaire is completed in 6.5 ± 2.4 min. The mean score on the JAKQ is 55.8 ± 18.6% with a wide discriminatory span of scores. The JAKQ reveals important knowledge gaps, like 28.8% of the patients not being aware of their medical condition named 'atrial fibrillation', 33.7% being unaware that AF can cause thromboembolism and stroke, and 78.6% of the patients taking VKA and 57.0% of the patients on NOACs not knowing what to do when missing an OAC dose.

Conclusions

The JAKQ is a brief, complete and valid AF-specific knowledge questionnaire that can be used in daily practice to assess patients' insight into their condition. It could be used as a tool for individually tailored patient education.

INTRODUCTION

Large international surveys[122-124] and a recent position paper of the European Heart Rhythm Association (EHRA) indicate that patient education is an important aspect of atrial fibrillation (AF) care which should receive more attention.[125] The EHRA position paper stated that education should be provided in a standardised, structured way, with specific educational goals. Moreover, it points out that validated instruments that assess AF patients' knowledge and self-management abilities are needed to allow individualised targeted education. Patients themselves indicated that more education in daily practice is warranted, which is currently not always possible due to time constraints of physicians and the paucity of appropriate educational material.[122,125]

Atrial fibrillation is becoming an important public health problem due to an ageing population.[59,60] It is associated with a high morbidity and mortality and it is an important driver of hospitalisations and emergency room visits.[36,59,60] A good knowledge by the patient about the arrhythmia, the risk factors, the consequences, the treatment and self-management attitudes is a key factor in the management of these patients.

Various studies investigated the knowledge of AF patients by means of questionnaires, all demonstrating important knowledge gaps about the arrhythmia and the oral anticoagulation (OAC) therapy.[123,124,126-136] Most of these studies were directed to a specific group of AF patients, e.g. patients new on OAC therapy[130,133], newly diagnosed AF patients[134], AF patients during a hospitalisation[136] or an emergency room visit[135], outpatients often attending anticoagulation clinics[126-128,132] and patients undergoing radiofrequency catheter ablation[129]. Some questionnaires focused on OAC therapy only.[123,124,127,128,131,136] Most studies used own instruments, not always validated and often not practical in daily routine. A standardised, validated, complete and fast questionnaire is lacking.

Treatment with OAC therapy to prevent stroke and thromboembolism is a cornerstone in the management of AF patients.[59] As more than 82% of the AF patients receive OAC therapy, education concerning this topic is of great importance.[137] Some validated questionnaires assess specifically the knowledge about vitamin K antagonists (VKA).[131,138,139] Due to the introduction of the non-

vitamin K antagonist oral anticoagulants (NOACs) which are currently increasingly prescribed by physicians, there is also a need for knowledge testing and education concerning these medications.[124,125,140,141] Up until now, there is no validated instrument to assess the knowledge concerning NOAC management.

Given the interest in and the current need for AF education with a limited number of suitable instruments to guide and target this patient education, the aim of this study was to develop and validate a new questionnaire to test patients' knowledge about the arrhythmia itself and its treatment, and the patients' self-management capabilities. After validation, a cross-sectional study with the new AF knowledge questionnaire examined knowledge gaps of AF patients.

METHODS

Development of the questionnaire

The Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ) was developed based on 1) other questionnaires[126,129,132] 2) an educational checklist for healthcare professionals to use with patients starting on NOAC therapy[140] 3) a list with educational topics for AF patients on OAC therapy[142] and 4) patient information on support websites concerning AF such as http://www.afibmatters.org/, http://www.atrialfibrillation.org.uk/, or http://www.anticoagulationeurope.org/.

We opted for a format with multiple choice questions having one correct answer and two distracters. An 'I do not know' option was added in order not to force patients to guess. Before completing the JAKQ, patients had to fill in their name, age, gender, diploma and a question stating if they have ever been diagnosed with AF. The questionnaire was implemented electronically and could be accessed via a tablet or Internet browser. Patients completed the JAKQ individually without any help from family members or healthcare professionals. Assistance was only provided when patients were not able to indicate the chosen answer using the application. Responses to the JAKQ were dichotomised, in which correct answers were scored as 1 point and incorrect and 'I do not know' answers as 0 points. The total score on the JAKQ was divided by the number of completed questions, resulting in a percentage. The JAKQ was developed in Dutch and a forward- and back-translation procedure was completed to translate the JAKQ into English.

Population and procedure

The JAKQ in its different forms (i.e. 24-item and 16-item version) was presented to 466 patients known with AF, both outpatients at the cardiology clinic as patients on the cardiology wards. Patients younger than 18 years were excluded. A chart review was performed for every patient to evaluate the medical history and pattern of AF. The study complied with the Declaration of Helsinki. Ethical approval for the study was obtained from the local ethical committee and all patients provided informed consent.

The mean age of the population was 71.1 ± 10.0 years; 47.4% of them were outpatients; 61.2% were men **(Table 2.1)**. Mean CHA_2DS_2-VASc score was 3.2 ± 1.6. One third of the patients had paroxysmal AF (36.9%), followed by persistent (29.2%) and permanent AF (12.0%). There were also 69 patients (14.8%) who only experienced a first AF episode and 33 patients (7.1%) were diagnosed with predominant atrial flutter (and short episodes of AF during Holter or ECG).

Of the 466 patients who completed the JAKQ, 277 patients completed the 24-item version and 189 patients completed the 16-item final version. For the purpose of knowledge assessment, results were calculated for the 16 final questions, and they were pooled from both the short version and the long version of the JAKQ. Through the different validation process steps, we considered that no fundamental changes were made to these questions that would preclude pooling of the answer results.

Table 2.1: Characteristics of AF patients who completed the JAKQ questionnaire.

	All AF patients (n=466)	Outpatients (n=221)	Hospitalised patients (n=245)	P-value*
Age, mean ± SD	71.1 ± 10.0	71.1 ± 9.7	71.1 ± 10.3	0.817
Male, n (%)	285 (61.2)	132 (59.7)	153 (62.4)	0.547
Highest level of education completed, n (%)				0.896
Primary school	144 (30.9)	65 (29.4)	79 (32.2)	
Secondary school	210 (45.1)	100 (45.2)	110 (44.9)	
College	86 (18.4)	43 (19.5)	43 (17.6)	
University	26 (5.6)	13 (5.9)	13 (5.3)	
Kind of AF, n (%)				**0.008**
First AF episode	69 (14.8)	23 (10.4)	46 (18.8)	
Ended spontaneously	*34 (49.3)*	*9 (39.1)*	*25 (54.3)*	
Persistent	*35 (50.7)*	*14 (60.9)*	*21 (45.7)*	
Paroxysmal AF	172 (36.9)	84 (38.0)	88 (35.9)	
Persistent AF	136 (29.2)	68 (30.8)	68 (27.7)	
Permanent AF	56 (12.0)	35 (15.8)	21 (8.6)	
Predominant atrial flutter	33 (7.1)	11 (5.0)	22 (9.0)	
CHA_2DS_2-VASc score, mean ± SD	3.2 ± 1.6	3.2 ± 1.5	3.3 ± 1.7	0.467
HAS-BLED score, mean ± SD	1.4 ± 1.0	1.2 ± 0.8	1.5 ± 1.1	**0.019**
Time since AF diagnosis (months), mean ± SD	58.7 ± 69.3	64.2 ± 69.4	53.8 ± 68.9	**0.006**
< 1 month, n (%)	39 (8.4)	7 (3.2)	32 (13.0)	
1 month – 1 year, n (%)	104 (22.3)	45 (20.3)	59 (24.1)	
1 year – 5 years, n (%)	161 (34.5)	91 (41.2)	70 (28.6)	
> 5 years, n (%)	162 (34.8)	78 (35.3)	84 (34.3)	
Implanted device, n (%)				**0.028**
ICD	16 (3.4)	4 (1.8)	12 (4.9)	
PM	79 (17.0)	46 (20.8)	33 (13.5)	
CRT-D or CRT-P	16 (3.4)	6 (2.7)	10 (4.1)	
Anticoagulation/antithrombotic therapy, n (%)				**<0.001**
NOAC only	265 (56.9)	148 (67.0)	117 (47.8)	
VKA only	67 (14.4)	31 (14.0)	36 (14.7)	
NOAC + APT	35 (7.5)	13 (5.9)	22 (9.0)	
VKA + APT	17 (3.6)	3 (1.4)	14 (5.7)	
APT only	37 (7.9)	10 (4.5)	27 (11.0)	
None	45 (9.7)	16 (7.2)	29 (11.8)	

AF: atrial fibrillation, APT: antiplatelet therapy, CRT-D: cardiac resynchronisation therapy defibrillator, CRT-P: cardiac resynchronisation therapy pacemakers, ICD: implantable cardioverter-defibrillator, JAKQ: Jessa Atrial fibrillation Knowledge Questionnaire, NOAC: non-vitamin K antagonist oral anticoagulant, PM: pacemaker, VKA: vitamin K antagonist, SD: standard deviation.
Significant values ($P < 0.05$) are indicated in bold.
* Comparison between outpatients and hospitalised patients.

JAKQ validation

The full validation process of JAKQ has been summarised in **Figure 2.1**.

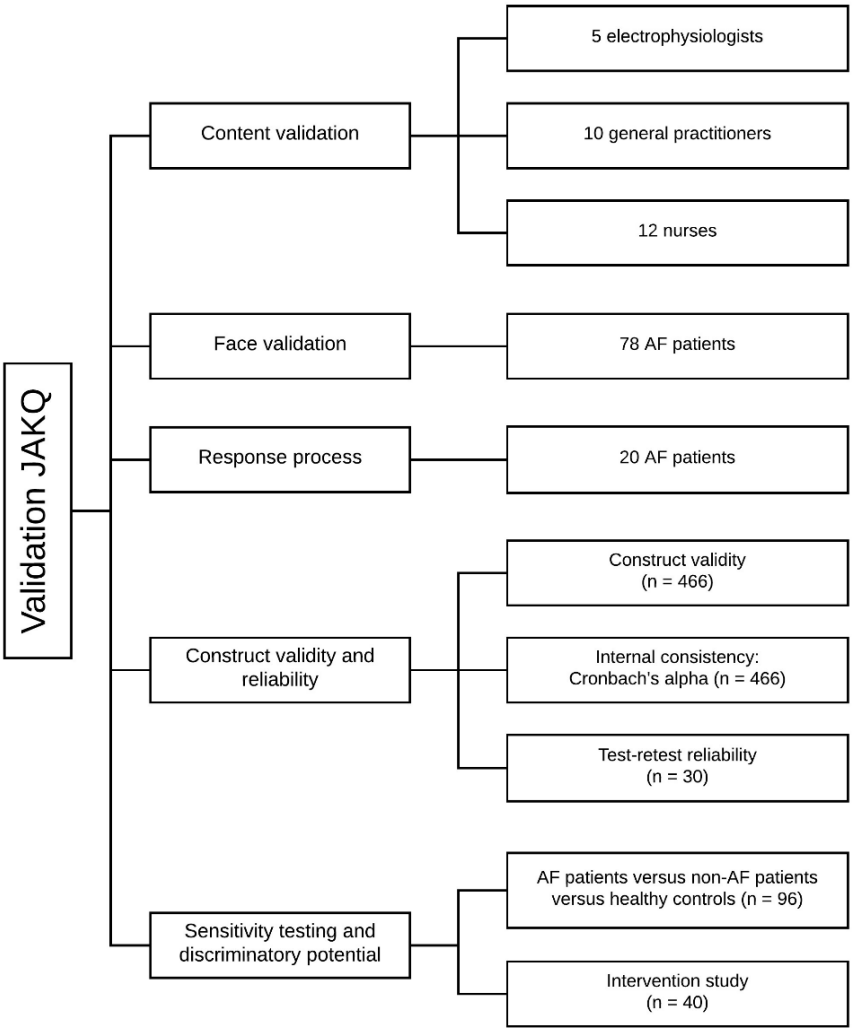

Figure 2.1: Overview of the different steps in the validation process of the Jessa Atrial fibrillation Knowledge Questionnaire.
AF: atrial fibrillation, JAKQ: Jessa Atrial fibrillation Knowledge Questionnaire.

Content validity, face validity and response process

Three expert panels were consulted to ensure content validity of the JAKQ: i.e. 5 electrophysiologists, 12 nurses with experience in the management of AF patients (hospital ward and intensive care unit) and 10 general practitioners (GPs). The

three expert panels received the initial 24-item draft questionnaire in paper format and could make suggestions where needed. They received three general questions to evaluate the content of the JAKQ: 1) What is your opinion on this questionnaire and the individual questions? 2) Is it relevant that AF patients know the answer to every question, or are there certain questions which are redundant? 3) Are there any gaps in our questionnaire or any other problems?

Face validation was ascertained by presenting the questionnaire to 78 randomly selected AF patients, more specifically 40 AF patients who completed the long version (24 items) of the JAKQ and 38 patients who completed the final 16 item questionnaire. They were asked to validate the JAKQ for question clarity, readability and time required for completion.

An additional response process validation was performed in 20 patients. These patients had to read all questions aloud and were recommended to think out loud in order to evaluate and to ensure that all questions were correctly interpreted.

Construct validation, internal consistency and reliability

An exploratory factor analysis was performed to determine the construct validity of the different components of the JAKQ based on the pre-final 16-item version. With this analysis, underlying variables in a questionnaire, called factors, were measured. Factor analysis was conducted using the principal component method with varimax rotation. Kaiser's criterion of extracting factors with eigenvalues greater than 1.0 was used. Taken into account the large sample size, factor loadings above 0.4 were acceptable. The Kaiser-Meyer-Olkin measure of sampling adequacy was calculated with values above 0.5 being acceptable and values above 0.7 being good.

The internal consistency of the JAKQ was determined by calculating Cronbach's alpha to assess the degree to which all of the items of the JAKQ measure the same construct. A Cronbach's α above 0.7 is considered as an adequate internal consistency of a questionnaire.[143]

The reliability of the JAKQ was investigated by means of a test–retest sub-study to assess if the results on the JAKQ are consistent over time. A subset of 30 AF patients completed the JAKQ at baseline with a retest after one month without receiving any educational intervention.

Sensitivity testing and discriminatory potential

The final version of the JAKQ was tested for sensitivity and discriminatory potential by means of three sub-studies.

As a first sub-study, the JAKQ was presented to three different groups to investigate its discriminatory potential: i.e. 1) 32 hospitalised AF patients; 2) 32 hospitalised patients not known with AF but admitted for another cardiac condition; 3) 32 healthy controls recruited out of hospital, not taking antiplatelet or OAC therapy, who had no close relatives who had been recently admitted for a cardiac reason. All three groups were matched for age and educational degree and the first 8 questions concerning AF in general were taken into account for this analysis.

As a second sub-study, 20 other hospitalised AF patients were tested with the JAKQ for the first time. Subsequently, targeted education was provided to these patients by indicating which answers were wrong and by giving them the correct answer with some additional information. About two days later and without them knowing beforehand, these patients were again asked to complete the questionnaire.

In a similar experiment, another group of 20 AF patients was recruited to test their knowledge using the JAKQ. Afterwards they received education concerning the questions incorrectly answered and after one month their knowledge was retested.

Statistics

Statistical analyses were performed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were reported as means ± standard deviation and categorical variables as numbers and percentages. Spearman's rho and a Wilcoxon test were used to assess the test–retest reliability of the JAKQ. A Kruskal Wallis test was performed to evaluate the difference in scores on the JAKQ between hospitalised AF patients, hospitalised non-AF patients and healthy controls. A One-Way ANOVA analysis and a X^2 test were used to investigate if these three groups were age- and diploma-matched. A Wilcoxon test was applied to evaluate the effect of targeted education on the short term and on the longer term. Correlations between demographic variables and the score on the JAKQ

were calculated using Spearman's rho. Continuous variables between two groups were compared using an independent t-test or a Mann–Whitney U test, as appropriate. Categorical variables were compared using the X^2 test. There were no missing data and a p-value < 0.05 was considered statistically significant.

RESULTS

Development of the questionnaire and time needed for its completion

The originally constructed questionnaire contained 24 questions: 12 about AF in general, 8 about OAC therapy in general and either 4 about VKA or about NOACs. Based on the input of the validation process, the JAKQ was reduced to 16 questions. The final JAKQ first presents patients 8 questions about AF in general, e.g. its definition, the possible consequences and its management. Afterwards, patients need to indicate if they are taking VKA, NOAC or no OAC. When patients indicate 'no OAC', the questionnaire is finished. Otherwise, they receive 5 questions about OAC therapy in general (e.g. the possible side-effects and related self-care), and either 3 questions about VKA or NOAC therapy.

In total, 9 questions (i.e. 4 about AF in general, 3 about OAC therapy, 1 about VKA and 1 about NOAC) have been deleted from the original questionnaire because of different reasons: 1) time constraints to complete the JAKQ; 2) difficulties understanding the questions as revealed during the face validation and the response process validation aspects; 3) questions considered less relevant by the expert groups or patients and 4) questions partially addressed in other questions or which could be linked to other questions.

The original 24 question JAKQ took 7.0 ± 4.5 min (n = 18) to complete only the first 12 questions about AF in general and 11.6 ± 3.7 min (n = 102) to complete the entire questionnaire, which was considered too long for routine use in clinical practice. The final 16-item version of the JAKQ could be completed in 3.6 ± 1.2 min (n = 34) for the first 8 questions about AF and 6.5±2.4 min (n = 131) for the entire questionnaire, which was significantly shorter than the 24-item JAKQ (p < 0.001).

JAKQ validation

Content validity, face validity and response process

Content validation of the 24-item JAKQ was good as the three expert panels indicated that all facets concerning AF management were present in the questionnaire. They had only minor comments concerning phrasing and clarification of certain questions, which were adjusted. Although most GPs indicated that the questionnaire was complete, four GPs suggested that a shorter questionnaire would be more useful in a daily setting. This later contributed to a shortening and simplification of the JAKQ.

For the initial face validation, 40 AF patients completed the 24-item version of the JAKQ and were asked for their opinion. Overall reactions were positive and the patients indicated that the questionnaire is relevant. They had no major complaints about the JAKQ and only minor word changes were necessary according to them (e.g. 'oral anticoagulation therapy' was changed to 'blood thinners'). Some questions were indicated as less applicable or redundant by some patients and therefore deleted from the JAKQ.

The response process validation by 20 patients revealed a long reflection time for a question concerning pulse measurements. This question seemed difficult to interpret and was therefore deleted.

As a final face validation, 38 patients were asked to complete the shortened 16-item questionnaire and no more remarks were indicated.

Construct validaty, internal consistency and reliability

The Kaiser-Meyer-Olkin measure showed an acceptable to good sampling adequacy. Values were respectively 0.774 for the 8 questions about AF, 0.668 for the 8 questions about OAC therapy plus VKA, and 0.670 for the 8 questions about OAC therapy plus NOAC. Two factors were identified for the 8 questions about AF and the 8 OAC items including the NOAC questions **(Table 2.2)**. For the 8 questions about OAC therapy including the VKA items, three factors were identified. The first and second factors concerning the AF questions could be attributed to a definition of AF together with its consequences, and self-management, respectively. The questions about OAC therapy in patients taking VKA could be classified into adherence-related items (factor 1), self-care

interventions (factor 2) and theory driven questions (factor 3). The OAC questions for patients on NOAC therapy loaded in two factors concerning adherence to the medication regimen (component 1) and self-management capabilities (component 2).

The JAKQ has an acceptable internal consistency. Cronbach's α for the 8 general questions about AF was 0.674 (n = 466). This value can be increased up to 0.689 if the question concerning the effect of overweight is deleted from the questionnaire. However, taking into account the fact that this item is an important question to motivate AF patients to maintain a healthy life style and that Cronbach's α can only be improved slightly, this question was kept in the final version of the JAKQ. For the 8 questions about OAC therapy, Cronbach's α was 0.604 and 0.522 for patients on VKA (n = 84) or NOAC therapy (n = 300), respectively. The latest values could not be improved by deleting one of the questions.

The test–retest sub-analysis, showed an acceptable reliability (r_s = 0.528). There was no significant difference between the score on the JAKQ at baseline and after one month if no additional education was provided in between (60.4 ± 18.6% vs. 62.3 ± 18.5%; p = 0.551).

Table 2.2: Topics of the JAKQ classified in their factors with the representative factor loadings.*

8 questions about AF in general	Factor 1	Factor 2
Blood thinners are often prescribed for patients with AF in order to prevent the development of blood clots in the heart, which can lead to stroke	0.765	
AF can cause blood clots which can lead to stroke (cerebral infarction)	0.733	
AF is a condition where the heart beats irregularly and often faster than normal	0.687	
AF is not always accompanied by symptoms	0.505	
An AF patient should not go to the general practitioner or emergency room each time he/she feels AF		0.731
Being overweight exacerbates AF		0.652
Medication cannot prevent AF permanently, as the arrhythmia will increasingly occur with ageing, even when taking medication		0.549
Patients can detect AF by taking their pulse regularly		0.495

8 questions about OAC therapy including VKA questions	Factor 1	Factor 2	Factor 3
If an AF patient needs an operation, he/she should consult a doctor to discuss possible options	0.774		
Patients with AF should always take their blood thinners, even if they do not feel AF	0.731		
When AF patients taking VKA have forgotten to take their blood thinner, they should still take their forgotten pill (immediately or at the next dose)	0.595		
AF patients taking VKA should have their blood thinning checked at least once a month		0.826	
When AF patients regularly have minor nose bleeds (that spontaneously cease), they should contact the general practitioner or specialist, while continuing to take their blood thinners		0.712	
Possible side effects of blood thinners are the occurrence of bleedings and longer bleeding times in case of injuries			0.765
INR is a measure to check how thick or how thin the blood is			0.667
AF patients may only take painkillers based on paracetamol			0.596

8 questions about OAC therapy including NOAC questions	Factor 1	Factor 2
Patients with AF should always take their blood thinners, even if they do not feel AF	0.789	
For patients taking NOAC, it is important to take their blood thinner at the same time every day	0.647	
AF patients may only take painkillers based on paracetamol	0.531	
When AF patients taking NOAC have forgotten to take their blood thinner, they can still take that dose, unless the time till the next dose is less than the time after the missed dose	0.479	
Possible side effects of blood thinners are the occurrence of bleedings and longer bleeding times in case of injuries		0.688
NOAC blood thinners come with a card, which AF patients have to show to their general practitioner and specialist		0.548
When AF patients regularly have minor nose bleeds (that spontaneously cease), they should contact the general practitioner or specialist, while continuing to take their blood thinners		0.532
If an AF patient needs an operation, he/she should consult a doctor to discuss possible options		0.478

AF: atrial fibrillation, INR: international normalised ratio, JAKQ: Jessa Atrial fibrillation Knowledge Questionnaire, NOAC: non-vitamin K antagonist oral anticoagulants, VKA: vitamin K antagonist.

* The JAKQ with questions and full answers can be obtained from the authors as the JAKQ is not in the public domain.

Sensitivity testing and discriminatory potential

To test the discriminatory potential of the JAKQ, 32 hospitalised AF patients were matched for age ($p = 0.989$) and educational degree ($p = 0.456$) to similarly sized groups of hospitalised patients not known with AF and healthy controls **(Table 2.3)**. The hospitalised AF patients had a mean JAKQ score of 64.8 ± 17.5%. The non-AF hospitalised patients scored significantly less (43.8 ± 21.5%; $p = 0.002$) and the healthy control group scored even lower (28.5 ± 21.1%; $p < 0.001$ compared to the AF patients and $p = 0.047$ compared to the non-AF patients) **(Figure 2.2)**.

To test the sensitivity of the questionnaire, the effect of targeted education was assessed in two populations. Compared to the initial score on the JAKQ, 20 hospitalised AF patients scored significantly better about two days after they had received individualised education (60.9 ± 16.6% vs. 78.8 ± 14.8%, $p < 0.001$) **(Figure 2.3A)**. Also with a longer time span of one month after the initial completion of the JAKQ followed by targeted education, the learning effect was still significant in a different population of 20 AF patients (61.6 ± 14.5% vs. 76.9 ± 13.8%, $p < 0.001$) **(Figure 2.3B)**.

Knowledge about AF and its treatment

Eighty-two of the 466 patients (17.6%) completed only the first 8 questions about AF in general since they had no indication for long-term OAC therapy. The entire 16-item JAKQ was completed by 384 patients (82.4%). Of these patients, 21.9% and 78.1% completed the OAC section concerning VKA and NOAC therapy respectively. The mean score on the questionnaire was 55.8 ± 18.6%, with a minimum score of 0 and a maximum score of 15 on 16. The questionnaire showed a good discriminatory potential **(Figure 2.4)**. There were no questions to which all patients gave the correct answer or to which none of the patients gave the correct answer. For each question of the JAKQ, answers were distributed over all three options.

Although the demographics of the hospitalised and outpatients were different in many aspects **(Table 2.1)**, there was no significant difference in overall scoring on the JAKQ between outpatients and hospitalised patients (57.4 ± 17.7% vs. 54.3 ± 19.2%; $p = 0.07$), nor between men and women (56.3 ± 18.2% vs. 54.9 ± 19.1%; $p = 0.597$).

Table 2.3: Characteristics of hospitalised AF patients, hospitalised non-AF patients and healthy controls, all matched for age and diploma.

	Hospitalised AF patients (n=32)	Hospitalised non-AF patients (n=32)	Healthy controls (n=32)
Age, mean ± SD	65.3 ± 9.8	64.9 ± 10.0	65.1 ± 7.6
Male, n (%)	26 (81.3)	25 (78.1)	22 (68.8)
Highest level of education completed, n (%)			
Primary school	10 (31.3)	10 (31.3)	3 (9.4)
Secondary school	14 (43.7)	14 (43.7)	19 (59.3)
College	6 (18.7)	6 (18.7)	7 (21.9)
University	2 (6.3)	2 (6.3)	3 (9.4)
Kind of AF, n (%)			
First diagnosed AF	5 (15.6)	-	-
Paroxysmal AF	13 (40.6)	-	-
Persistent AF	11 (34.4)	-	-
Permanent AF	-	-	-
Predominant atrial flutter	3 (9.4)	-	-
CHA_2DS_2-VASc score, mean ± SD	2.6 ± 1.8	-	-
HAS-BLED score, mean ± SD	1.0 ± 0.9	-	-
Implanted device, n (%)			
ICD	2 (6.3)	1 (3.1)	-
PM	3 (9.4)	-	-
CRT-D of CRT-P	1 (3.1)	2 (6.3)	-
Anticoagulation/antithrombotic therapy, n (%)			
NOAC only	16 (50.0)	-	-
VKA only	4 (12.5)	-	-
NOAC + APT	2 (6.3)	-	-
VKA + APT	1 (3.1)	-	-
APT only	1 (3.1)	22 (68.8)	-
None	8 (25.0)	10 (31.2)	31 (100)
Main reason for hospital admission, n (%)			
Coronary angiography/elective revascularisation	5 (15.6)	21 (65.6)	-
Electrophysiological examination/ablation	13 (40.6)	1 (3.1)	-
Heart failure	1 (3.1)	-	-
Acute Coronary Syndrome	-	5 (15.6)	-
Device implantation or replacement	2 (6.3)	1 (3.1)	-
Symptomatic AF	7 (21.9)	-	-
Other	4 (12.5)	4 (12.5)	-

AF: atrial fibrillation, APT: antiplatelet therapy, CRT-D: cardiac resynchronisation therapy defibrillator, CRT-P: cardiac resynchronisation therapy pacemaker, ICD: implantable cardioverter-defibrillator, NOAC: non-vitamin K antagonist oral anticoagulant, PM: pacemaker, SD: standard deviation, VKA: vitamin K antagonist.

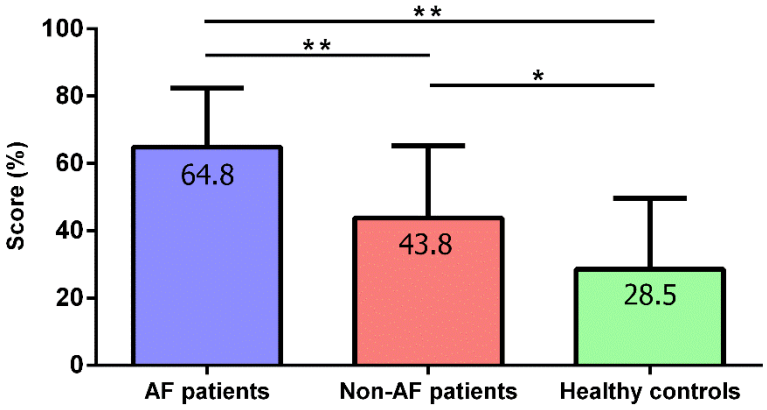

Figure 2.2: Score on the Jessa Atrial fibrillation Knowledge Questionnaire of 32 hospitalised AF patients, 32 hospitalised non-AF patients and 32 healthy controls in which all groups were matched for age and diploma. *p < 0.05, and **p < 0.01.

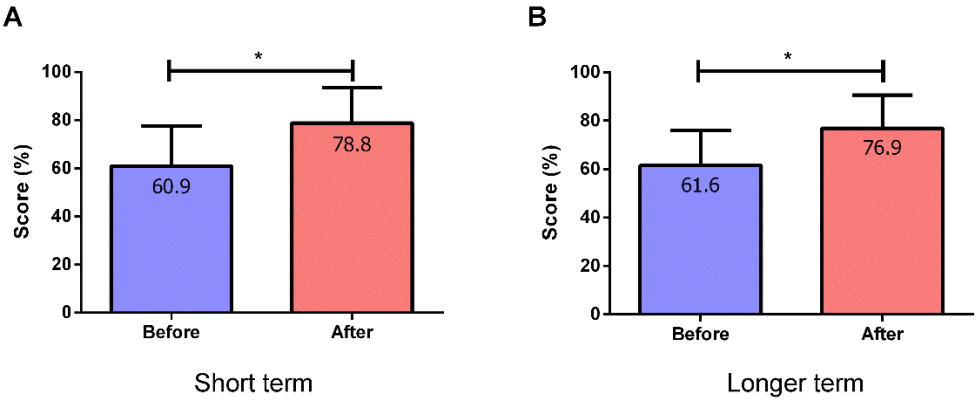

Figure 2.3: Effect of targeted education on the score of the Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ). A. Score on the JAKQ of 20 hospitalised AF patients before and after they received education based on the questions incorrectly answered on a short time span (1–3 days). **B.** Score on the JAKQ of 20 AF patients before and after they received education concerning the AF questions incorrectly answered on a longer time span of one month. *p < 0.001.

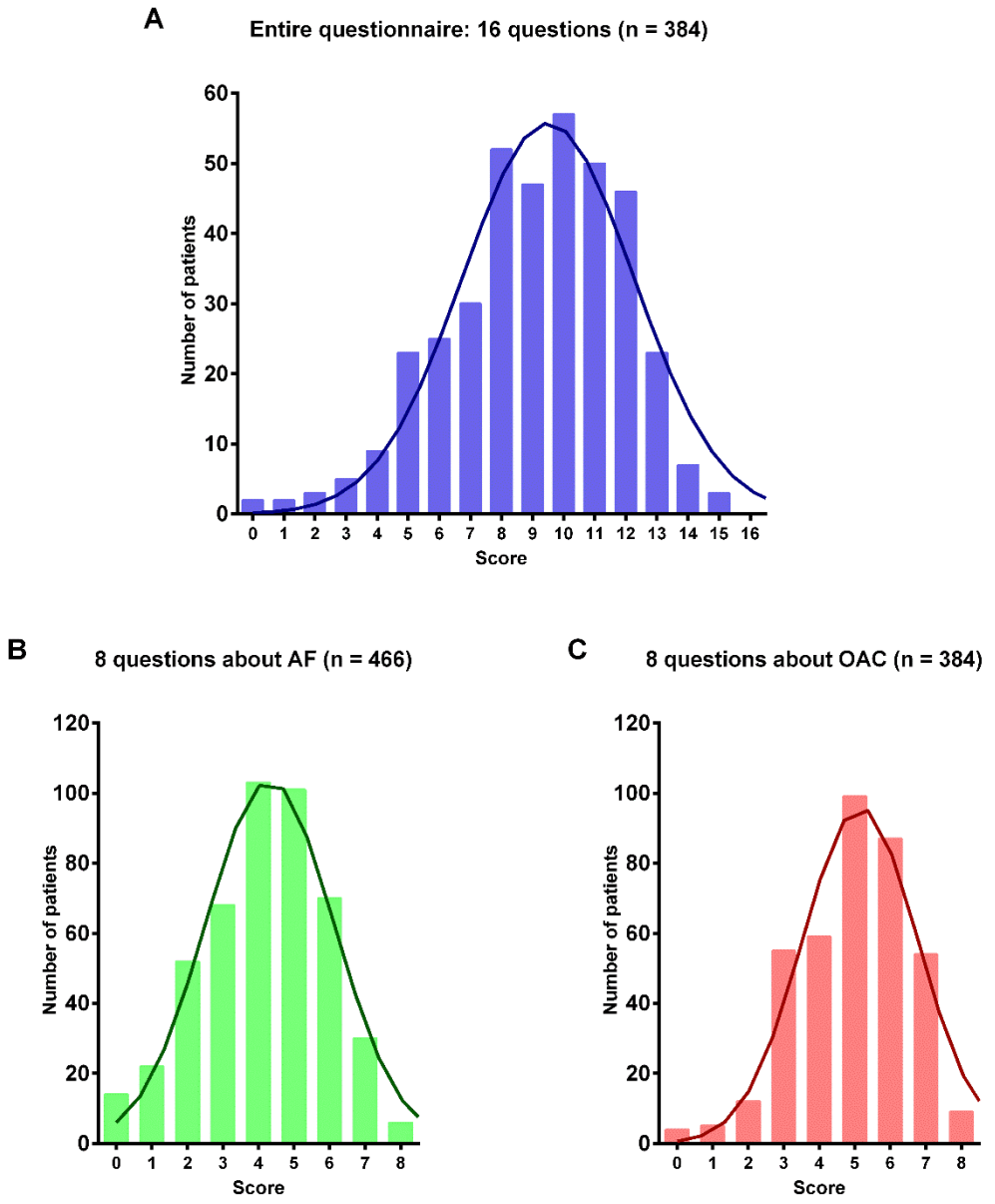

Figure 2.4: Frequency distribution of the scores on the Jessa Atrial fibrillation Knowledge Questionnaire. A. Scores of patients who completed the entire questionnaire of 16 questions (n = 384). **B.** Scores on the first 8 questions dealing with AF in general (n = 466). **C.** Scores on the 8 questions about OAC therapy including the 5 general questions as well as the 3 questions about VKA or NOACs (n = 384). AF: atrial fibrillation, OAC: oral anticoagulation.

Knowledge gaps of AF patients

Remarkably, more than one out of four patients (28.8%) was not aware of a personal medical condition named 'atrial fibrillation', as 14.2% and 14.6% of the patients answered respectively 'no' and 'I do not know' on the preliminary question asking if they had ever been diagnosed with AF. Moreover, 27.1% was not able to define the arrhythmia. Knowledge deficits on all the other questions are evident from the overall low correct response rates, as shown in **Table 2.4**. Interestingly, one in three patients (33.7%) did not know that AF can cause thromboembolism and stroke. Only 43.6% of all AF patients indicated that you can detect AF by regularly taking your pulse. Less than half of the patients (47.2%) knew that live style factors, such as being overweight, can facilitate AF. Furthermore, only 64.8% of the patients on OAC medication was aware of the possible bleeding complications associated with the therapy. Another knowledge gap was the use of painkillers which can be used safely in combination with OAC therapy. In case of an operation, 28.4% will probably not consult their physician concerning possible adjustment of OAC therapy. More than half of the patients on VKA (58.3%) did not know the meaning of the international normalised ratio (INR). Only 18.7% of patients on NOACs knew about the existence of an OAC card. Intriguingly, 78.6% of the patients taking VKA and 57.0% of the patients on NOACs did not know what to do when missing an OAC dose.

Patients recently diagnosed with AF (<1 month, n = 39) knew less about AF and its management than those with longer-standing AF (>1 year after diagnosis of AF, n = 321) with a score of 48.4 ± 20.7% and 57.3 ± 18.4%, respectively ($p = 0.005$). Patients with AF who indicated 'no' or 'I do not know' on the introductory question asking if they had ever been diagnosed with AF, scored significantly less compared to the other patients (45.0 ± 19.5% vs. 60.1 ± 16.3%, $p < 0.001$). Patients with heart failure, diabetes and those taking antiplatelet therapy also scored significantly less ($p = 0.001$, $p = 0.006$ and $p = 0.008$ respectively).

The score on the JAKQ was significantly correlated with the educational degree of the patients ($r_s = 0.364$, $p < 0.001$). An inverse relation was also found between the age and the JAKQ score ($r_s = -0.237$, $p < 0.001$).

Table 2.4: Specific topics addressed in the JAKQ with the percentage of correct responses.*

8 questions about AF in general (n = 466)	**%**
AF is a condition where the heart beats irregularly and often faster than normal	73.0 %
AF is not always accompanied by symptoms	30.9 %
Patients can detect AF by taking their pulse regularly	43.6 %
AF can cause blood clots which can lead to stroke (cerebral infarction)	66.3 %
Medication cannot prevent AF permanently, as the arrhythmia will increasingly occur with ageing, even when taking medication	32.6 %
An AF patient should not go to the general practitioner or emergency room each time he/she feels AF	43.3 %
Being overweight exacerbates AF	47.2 %
Blood thinners are often prescribed for patients with AF in order to prevent the development of blood clots in the heart, which can lead to stroke	76.2 %
5 questions about OAC therapy (n = 384)	**%**
Patients with AF should always take their blood thinners, even if they do not feel AF	88.8 %
Possible side effects of blood thinners are the occurrence of bleedings and longer bleeding times in case of injuries	64.8 %
AF patients may only take painkillers based on paracetamol	55.7 %
When AF patients regularly have minor nose bleeds (that spontaneously cease), they should contact the general practitioner or specialist, while continuing to take their blood thinners	64.1 %
If an AF patient needs an operation, he/she should consult a doctor to discuss possible options	71.6 %
3 questions about VKA (n = 84)	**%**
AF patients taking VKA should have their blood thinning checked at least once a month	81.0 %
When AF patients taking VKA have forgotten to take their blood thinner, they should still take their forgotten pill (immediately or at the next dose)	21.4 %
INR is a measure to check how thick or how thin the blood is	41.7 %
3 questions about NOAC (n = 300)	**%**
For patients taking NOAC, it is important to take their blood thinner at the same time every day	88.7 %
When AF patients taking NOAC have forgotten to take their blood thinner, they can still take that dose, unless the time till the next dose is less than the time after the missed dose	43.0 %
NOAC blood thinners come with a card, which AF patients have to show to their general practitioner and specialist	18.7 %

AF: atrial fibrillation, INR: international normalised ratio, JAKQ: Jessa Atrial fibrillation Knowledge Questionnaire, NOAC: non-vitamin K antagonist oral anticoagulant, OAC: oral anticoagulant, VKA: vitamin K antagonist.

* The JAKQ with questions and full answers can be obtained from the authors as the JAKQ is not in the public domain.

DISCUSSION

Although education of AF patients is increasingly recommended as an important aspect to optimise the management of these patients, it is a demanding task in the limited time frame of each consultation visit.[122,125,144] Good instruments to guide education in daily practice are lacking.[125]

The Jessa Atrial fibrillation Knowledge Questionnaire

The JAKQ was developed to be a fast, complete and valid tool to assess the existing knowledge of AF patients. It shows a good content and face validity. Construct validity demonstrates good sampling adequacy and the different parts of the JAKQ could be subdivided into two or three factors in which the questions loaded adequately depending on the subject. Internal consistency is also acceptable with Cronbach's α values between 0.522 and 0.674 for small subsets of 8 questions each. The test–retest sub-study revealed good reliability. The JAKQ is able to discriminate between knowledge levels and it is sensitive enough to evaluate the effect of education.

The JAKQ addresses most important aspects of AF management and OAC therapy as indicated in a recent EHRA position paper.[125] This not only includes theoretical questions, but also questions that relate to self-management behaviour concerning pulse measurements, healthy lifestyle and what should be done in certain situations. Since the main management focus of AF concerns the prevention of thromboembolic stroke, half of the JAKQ is attributed to OAC therapy, its possible side-effects, the use of co-medications, self-care and the importance of good adherence. As indicated in our study, in which already 78.1% of the patients on OAC therapy take NOACs, there is an urgent need for education about these drugs.[140] However, in some patients VKAs will stay the preferred OAC therapy. The JAKQ combines the key aspects of both OAC therapies in one questionnaire.

With a mean time of about 6 min to fill out the JAKQ, it is practical enough to be used on a daily basis to provide tailored education in a structured and uniform way to all AF patients without overloading them with too much or too difficult information. Our online implementation of the JAKQ improves the educational efficiency since patients can complete it at home or in the waiting room before

their consultation visit. During the follow-up visit, the healthcare practitioner can then provide individualised education. The same questionnaire and educational strategy can be applied in hospitalised patients during their stay or at discharge. Such educational interventions can be part of integrated care as provided by specialised multidisciplinary AF clinics.[47,97,100,101] Since education requires continuous reinforcement, the JAKQ can be used during each encounter with a healthcare provider.

Patients' knowledge and the effect of education

Atrial fibrillation is a chronic condition in which shared decision making with active patient involvement is desired. However, shared decision making requires that AF patients have an acceptable knowledge level about their condition and its treatment.[125,142,145] Together with our survey, many other studies have shown that the opposite is true in daily care. Lane et al. and Lip et al. reported that only 49% respectively 63% of patients were aware that their cardiac condition was called AF.[127,132] McCabe and colleagues reported that only 46% of patients recently diagnosed with AF knew that AF leads to an increased risk of stroke.[134] A study performed by Koponen et al. at the emergency room showed that only 29% of the 200 AF patients knew AF can recur during therapy with inhibiting medication.[135] This was consistent with the results on the JAKQ as only 32.6% correctly stated that medication cannot prevent AF permanently. Poor patient knowledge was also confirmed by the studies of Nadar et al.[128], Hendriks et al.[126] and Xu et al.[129] who demonstrated an average score of 5.5, 7 and 11.8 on a standardised 9-item, 11-item and 25-item knowledge questionnaire, respectively. A large international survey by the AF Aware group in 825 patients and 810 cardiologists demonstrated that physicians tend to overestimate the knowledge of AF patients about treatment complications.[122] A recent EHRA survey assessed the knowledge of 1147 AF patients about OAC therapy.[123] It revealed that 76% of the patients on VKA medication were aware of the mandatory monthly INR monitoring, which was confirmed in our study with a percentage of 81%. Although these large European surveys provide insights in the awareness about AF, they did not use standardised validated questionnaires which can be used in daily practice.[122-124]

Currently, the best educational strategy is not known. Different methods have been investigated in AF patients: booklets[130,132,134], educational videos[130,133,134], group education sessions[133], and in-person education[47]. Some of these interventions showed beneficial results, but in other studies there was almost no effect of the educational intervention. A systematic review did not find any effect of educational and behavioural interventions on time in therapeutic range in AF patients taking OAC therapy.[146] Also in a study performed by Lane et al., an educational intervention with informational booklets had no impact on the awareness about AF and about the potential side effects and benefits of OAC therapy.[132] Finally, McCabe and colleagues tested the effect of education by a nurse by means of an AF brochure, a video and information about OAC therapy in hospitalised patients with recently detected AF.[134] Two weeks after the hospitalisation their knowledge was hardly improved.[134] On the other hand, Hendriks et al. showed that a chronic care program for AF patients in which education is reinforced after each scheduled follow-up visit, can lead to a significant increase in knowledge at one year follow-up.[103]

The results on the JAKQ revealed that the elderly and those with comorbidities scored lower. This finding is alarming as these patients have the highest risk of stroke. Extra educational efforts should also be performed in patients recently diagnosed with AF and those with a lower formal education, which was also shown in other studies.[124,129,134,135]

Study limitations

The data for this study were collected in one large tertiary care centre. Knowledge levels of AF patients can possibly differ between hospitals, regions and countries. Therefore, generalisability of these results to other settings should be made with caution. The score on the JAKQ will also depend on the level of educational efforts implemented in the hospital. In our hospital, brochures are available and handed out to AF patients on top of the education provided by nurses and physicians, but no standard educational program was incorporated yet. This study did not take dementia or other cognitive problems into account which may have influenced the score on the JAKQ. However, also in these patients, who may have more difficulties to complete the questions due to cognitive impairment, additional education should be provided.

Future perspectives

This was a first study with the JAKQ, which needs to be further tested in other patient cohorts. Still, these results should be a trigger for physicians that patients' knowledge is far from optimal and that educational efforts in daily practice are needed. Large randomised controlled multicentre trials should be performed to evaluate the impact of targeted education on the quality of life, adherence to the prescribed medication and hard outcome measures such as complications, hospitalisations, emergency room visits and unplanned consultation visits. Additionally, the cost-effectiveness of such interventions and long-term benefits should be taken into account.

CONCLUSION

The JAKQ is a validated, brief but still complete questionnaire to assess the knowledge of AF patients about their arrhythmia, the associated OAC therapy and their self-management skills. A first survey showed important knowledge gaps among AF patients and especially in those with an increased stroke risk, highlighting the need for educational interventions. The JAKQ is an ideal tool to efficiently guide and target personalised education in AF patients. Further research is needed to evaluate if such educational efforts can improve the overall outcomes of AF patients.

ACKNOWLEDGMENT

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Chapter 3

Effect of reinforced, targeted in-person education using the Jessa Atrial fibrillation Knowledge Questionnaire in patients with atrial fibrillation

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Revision submitted

ABSTRACT

Background

The knowledge level of atrial fibrillation (AF) patients about their arrhythmia, its consequences and treatment is poor. The best strategy to provide education is unknown.

Aim

To investigate the effect of reinforced targeted in-person education using the Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ).

Methods

Sixty-seven AF patients were randomized to standard care (including brochures) or targeted education. Follow-up visits were scheduled after 1, 3, 6 and 12 months. Targeted education during each visit focused on the knowledge gaps revealed by the JAKQ. Patients completed two questionnaires to assess their quality of life (QOL) and symptom profile. Adherence to non-vitamin K antagonist oral anticoagulants was measured using electronic monitoring.

Results

Sixty-two patients (31 education; 31 standard care) completed follow-up. Median baseline score on the JAKQ was similar in education (62.5%) and standard care group (56.3%; P = 0.815). The intervention group scored significantly better over time (1 month: 75.0%, 12 months: 87.5%; P < 0.001) whereas there was no significant improvement in the control group (1 month: 62.5%, 12 months: 62.5%; P = 0.085). Providing targeted education after completion of the JAKQ required on average 6.9 ± 4.6 min. Some improvements on QOL, symptom burden and adherence were shown, without significant differences between both groups (P-values between 0.282 and 0.677).

Conclusion

The JAKQ is an effective tool for providing individualized education. A first targeted educational session significantly improved patients' knowledge level. Additional educational sessions maintained and strengthened this effect. A larger scale study is warranted to evaluate the impact on adherence and outcome measures.

INTRODUCTION

Atrial fibrillation (AF) is putting a large burden on the healthcare system and its prevalence is further increasing.[15] Optimal care of AF patients includes a proper understanding by the patient about the arrhythmia, its treatment and its management.[4,125] The 2016 European Guidelines on the management of AF indicate that a more integrated patient education is warranted.[4] Better patient knowledge can contribute to enhanced self-management and shared decision making.[4] Nevertheless, education is not systematically provided during the current care of AF patients and is likely suboptimal to achieve proper patient knowledge.[122,142] Different studies showed that the knowledge and insight of AF patients about their arrhythmia and its management are poor even after receiving verbal and/or written information.[122,126,127,132-135,147-149] Various educational interventions that were previously tested only led to mixed results and a feasible and effective manner of providing education is difficult to establish.[103,132-134,150-152] A consensus paper of the European Heart Rhythm Association stated that education should be provided in a standardized, structured and tailored way.[125] Validated questionnaires can be helpful in this respect as a way to map knowledge deficits and to target education specifically to the needs of every patient but such strategy has never been evaluated in daily practice.[125] Therefore, the main aim of this study was to investigate the effect of reinforced, targeted, in-person education of AF patients on their knowledge level. Enhancing disease-related knowledge is an important part of an integrated approach to optimize overall care and to improve other clinical outcome parameters in patients with chronic conditions, such as AF.[103,104,150,153,154] This has previously been demonstrated in for example heart failure patients.[155,156] Therefore, a possible influence on quality of life (QOL), symptom burden, and medication adherence was additionally explored in this study.

METHODS

Design and study population

A prospective randomized controlled study was performed at a large Belgian tertiary care hospital between January 2016 and April 2017. Patients with AF hospitalized at the cardiology ward or seen at the out-patient clinic were recruited for this study. Patients were excluded if they were younger than 18 years, not capable to sign the informed consent, unable to speak Dutch or when they were cognitive-impaired. A chart review was performed to evaluate demographic variables and the medical history of every patient. The study complied with the Declaration of Helsinki. Ethical approval was obtained from the local ethical committee and all patients provided written informed consent.

Study procedure and targeted education

After inclusion at baseline, all AF patients were requested to come to the hospital for a study visit (i.e. data collection for the control group and additional education for the intervention group) during fixed time points: after 1, 3, 6 and 12 months **(Figure 3.1)**. In the event that a patient was too ill or not able to come to the hospital for a follow-up visit, this in-person visit was replaced by a telephone follow-up. Patients had to complete three questionnaires during each visit to assess their QOL, symptom burden, and knowledge level about AF and oral anticoagulation (OAC) therapy. From the first till the third month, patients' adherence to their non-vitamin K antagonist oral anticoagulant (NOAC) was measured, if possible (i.e. only adherence to apixaban and rivaroxaban could be monitored). Details about the questionnaires and adherence measurements are described below.

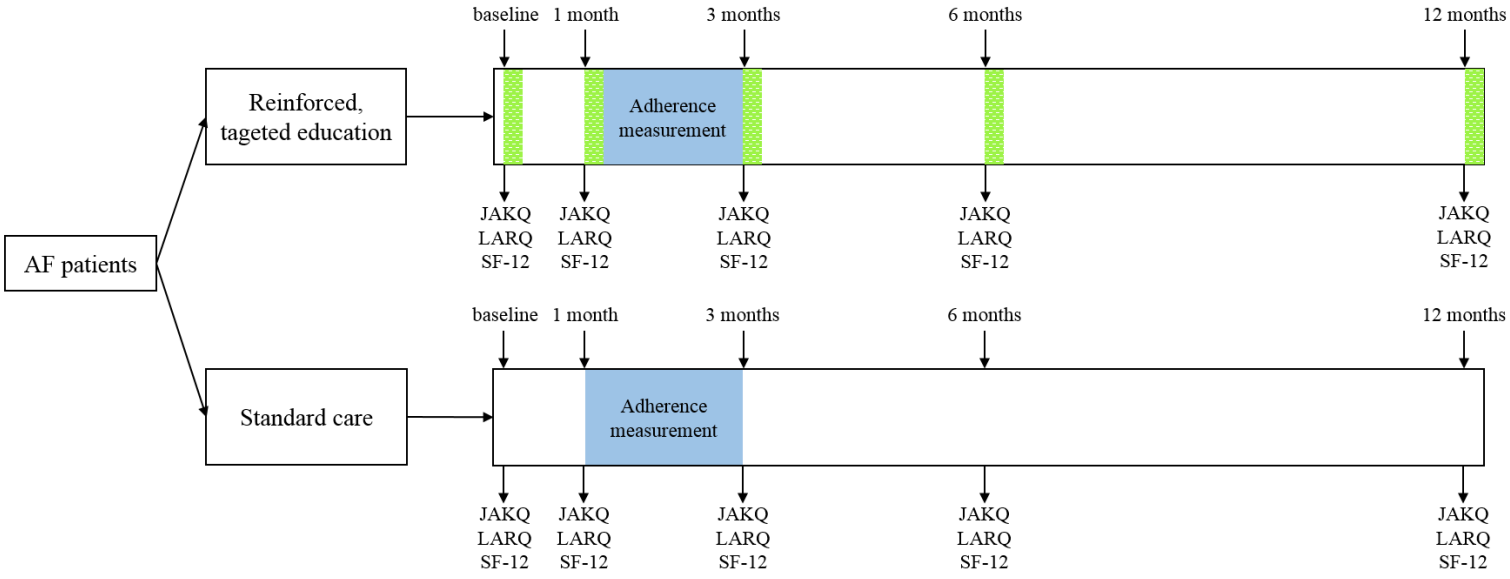


Figure 3.1: Study design. The green striped vertical bars indicate the moments when each AF patient received targeted education based on specific knowledge gaps of that patient. The blue period represents the two months of adherence measurement (only adherence to apixaban and rivaroxaban could be monitored). JAKQ: Jessa Atrial fibrillation Knowledge Questionnaire, LARQ: Leuven ARrhythmia Questionnaire.

Patients were randomly assigned in a 1:1 allocation to an education group (intervention group) or a standard care group (control group). Patients were allocated based on a computer-generated number randomization list with block sizes of four, six and eight prepared by a researcher who was not clinically involved. Stratification occurred based on age, highest educational degree and time since the diagnosis of AF. In the intervention group, on top of standard care, the study team consisting of two allied health professionals (L.D., L.E.), reinforced education based on the incorrectly answered questions of the Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ; Supplementary material, Table S3.1).[147] More specifically, after completion of the JAKQ, the study team went through the questionnaire together with the patient and indicated for each question if the answer was correct or not. If the answer was correct, the study team immediately moved on to the next question. If the answer was wrong, the correct answer was indicated and shortly motivated. No additional educational materials were used. To assure consistency between the two allied health professionals in delivering the intervention, the following training was provided by the electrophysiology team before the start of the trial: i) literature study, ii) attending out-patient visits (on a regular basis for 4 weeks) at which an experienced electrophysiologist provided general AF education, iii) during the following 4 weeks the study members regularly provided patient education themselves (by means of the JAKQ) under supervision of an electrophysiologist. In the control group, patients received standard care with no extra focused reinforcements and knowledge evolution was only monitored. Standard care in our hospital includes information from the cardiologist during outpatient visits or hospitalizations, and an information booklet about AF and OAC therapy (Supplementary material, appendix S3.1) which was provided at the first visit.

Measured parameters

Together with the AF knowledge assessment (using the JAKQ), other parameters such as symptom burden (using the Leuven ARrhythmia Questionnaire (LARQ)), QOL (using the SF-12 questionnaire) and adherence to NOACs were evaluated. Time to complete the JAKQ and to provide targeted in-person education were measured. The JAKQ and the LARQ were implemented electronically and patients could complete these questionnaires using a tablet. The SF-12 was in paper format. Patients had to complete the questionnaires individually without any help from family members or healthcare professionals. Assistance by the study team was only provided to mark their answers on the tablet if needed.

Knowledge level about atrial fibrillation

The 16-item JAKQ underwent a thorough validation process which was previously published[147], i.e. content validation, face validation, response process, construct validity, internal consistency (Cronbach's α 0.674-0.792[147,157]), test-retest reliability, sensitivity testing and discriminatory potential. The JAKQ consists of 16 questions: 8 about AF in general, 5 about OAC therapy and 3 about vitamin K antagonists (VKA) or NOACs depending on the medication use of the patient.[147] Patients without OAC indication only had to complete the first 8 questions of the JAKQ. In patients who completed both 8 and 16 questions during the trial - because they had to start or stop OAC - only the first 8 questions were taken into account for data analyses. The JAKQ contains only multiple choice questions with one correct answer, two distracters and one 'I do not know' option. A correct answer was scored as 1 point; incorrect and 'I do not know' answers as 0 points. The total score on the JAKQ was divided by the number of completed questions, resulting in a percentage.

Quality of life

The SF-12v2 consists of 12 questions to evaluate eight health and well-being concepts including physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems and mental health.[158,159] Additionally, the physical component summary (PCS) and mental component summary (MCS) score were calculated. For each item, the weighted sum of the questions was calculated and transformed in a 0-100 scale. The higher the score, the better the QOL. The recall

period was four weeks. The SF-12v2 was previously evaluated in the US National Health and Wellness Survey in AF patients[160], and the questionnaire was able to show an impact of AF-related interventions such as a pulmonary vein isolation[161] and a percutaneous closure of the left atrial appendage[162].

Symptom burden

The LARQ is based on the six most important AF-related symptoms: palpitations, shortness of breath, chest pain, syncope, dizziness and fatigue.[163] The LARQ was previously validated based on content, face, construct (known-groups and convergent) validity, and internal consistency reliability (Cronbach's α 0.909-0.952).[163] For each of these symptoms (except syncope), symptom prevalence, occurrence (frequency, duration, severity), distress, circumstances triggering the symptom, and effect on daily activities were requested. Questions were based on a recall period of four weeks. By means of specific algorithms, subscale scores on five domains (symptom frequency, duration, effect on daily activities, severity and distress) were calculated by summing the raw scores and transforming them to a 0-100 scale. Higher scores represent a more pronounced symptom burden.

Adherence

Adherence to NOACs was measured in AF patients taking apixaban (twice daily NOAC) and rivaroxaban (once daily NOAC) by means of electronic monitoring. Adherence to apixaban was measured with the "Helping Hand" device (WestRock, Switzerland). This device in the form of a blister sleeve measures the exact date and time whenever a patient removes the blister from the device to take his/her medication. Adherence to rivaroxaban was measured with the medication event monitoring system (WestRock, Switzerland), which is a special cap that fits on a medication bottle recording the exact date and time of bottle openings. Devices without a display were used. Dabigatran adherence could not be measured with the monitoring devices, as this drug should be stored in the original package to protect it from moisture and the blister does not fit into the Helping Hand. Edoxaban was not yet approved for use at the time of study initiation. Taking adherence (proportion of prescribed doses taken), regimen adherence (proportion of days with the correct number of doses taken) and number of unprotected days (≥3 or ≥1 consecutively missed doses for apixaban or rivaroxaban, respectively, or excess doses during the prior 24 hours) were calculated based on the retrieved

data assuming that every bottle opening or blister removal represents a medication intake.[164] Pill counts were performed during the three month follow-up visit.

Statistical analysis

According to the power calculation (power of 80%; alpha of 5%), at least 56 AF patients (28 in each study group) had to be included to achieve a 25% increase in the primary outcome of knowledge level after one year compared to baseline.[147] This estimated effect size was based on previous pilot data showing a 29.4% increase after a few days and a 24.9% increase after 1 month.[147] An additional drop-out margin of 15% was taken into account, resulting in a minimal inclusion rate of 66 patients. The study was not powered for the secondary outcome measures. Statistical analyses were performed using SPSS 25.0 (IBM, Armonk, USA). Continuous variables were reported as means ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical variables were reported as numbers and percentages. Normal distribution was assessed using the Shapiro-Wilk test and Q-Q plots. Independent t-tests and Chi-squared tests were used to evaluate possible demographic differences between the two study groups. To investigate the effect of targeted education or standard care over time on the knowledge level, QOL and symptom burden, Friedman tests or repeated measures analyses of variance (ANOVAs) were used, when appropriate. Bonferroni correction was used to counteract the problem of multiple testing. Comparisons between groups were performed with Mann-Whitney U tests, independent t-tests, Chi-squared tests, mixed model or mixed ANOVAs, as appropriate. A P-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Of the 129 AF patients asked to participate, 62 patients (36 hospitalized and 26 outpatients) were excluded as they did not want to participate (37%) or were too ill (29%) **(Figure 3.2)**. Of the 67 included patients (26 hospitalized and 41 outpatients), 33 were randomized to the intervention group and 34 to the control group. There was a dropout rate of 7.5% and 31 patients in each group completed all follow-up visits. Eventually, 94.4% of the follow-up visits occurred in-person and 5.6% (4.0% in the control and 1.6% in the intervention group) by telephone follow-up. The included AF population was 72.1 ± 8.6 years old and most patients (73.1%) received the AF diagnosis more than 1 year before study initiation. Patients randomized to the control group and the education group were well matched on different demographic characteristics **(Table 3.1)**.

Effect on knowledge level

Patients needed 6.9 ± 3.0 min to complete the JAKQ. Eight patients completed the 8-item JAKQ and 54 patients the 16-item JAKQ with OAC questions. Providing targeted in-person education required an extra 8.5 ± 4.9 min at baseline, 8.5 ± 6.0 min at 1 month, 6.2 ± 3.0 min at 3 months, 6.7 ± 4.1 min at 6 months and 4.5 ± 3.1 min at 12 months. The score on the JAKQ at baseline was similar for the education [median (IQR): 62.5% (50.0-68.8); mean ± SD: 58.5 ± 15.9%] and the control group (median (IQR): 56.3% (50.0-75.0); mean ± SD: 58.5 ± 18.6%; P = 0.815) **(Figure 3.3)**. It was significantly higher in the education group after 1 [75.0% (68.8-87.5) vs. 62.5% (43.8-75.0); P = 0.002], 3 [81.3% (75.0-93.8) vs. 62.5% (50.0-81.3); P < 0.001], 6 [87.5% (68.8-100.0) vs. 62.5% (43.8-75.0); P < 0.001] and 12 months [87.5% (75.0-100.0) vs. 62.5% (43.8-75.0); P < 0.001] compared to the standard care group. The intervention group scored significantly better over time (P < 0.001) whereas there was no significant improvement in the control group (P = 0.085). One targeted education session significantly improved the knowledge level (P = 0.001 between baseline and 1 month). Additional education sessions further increased and maintained this knowledge level (P = 0.080 between 1 and 12 months). The knowledge score over time was significantly different between both groups (P = 0.0006).

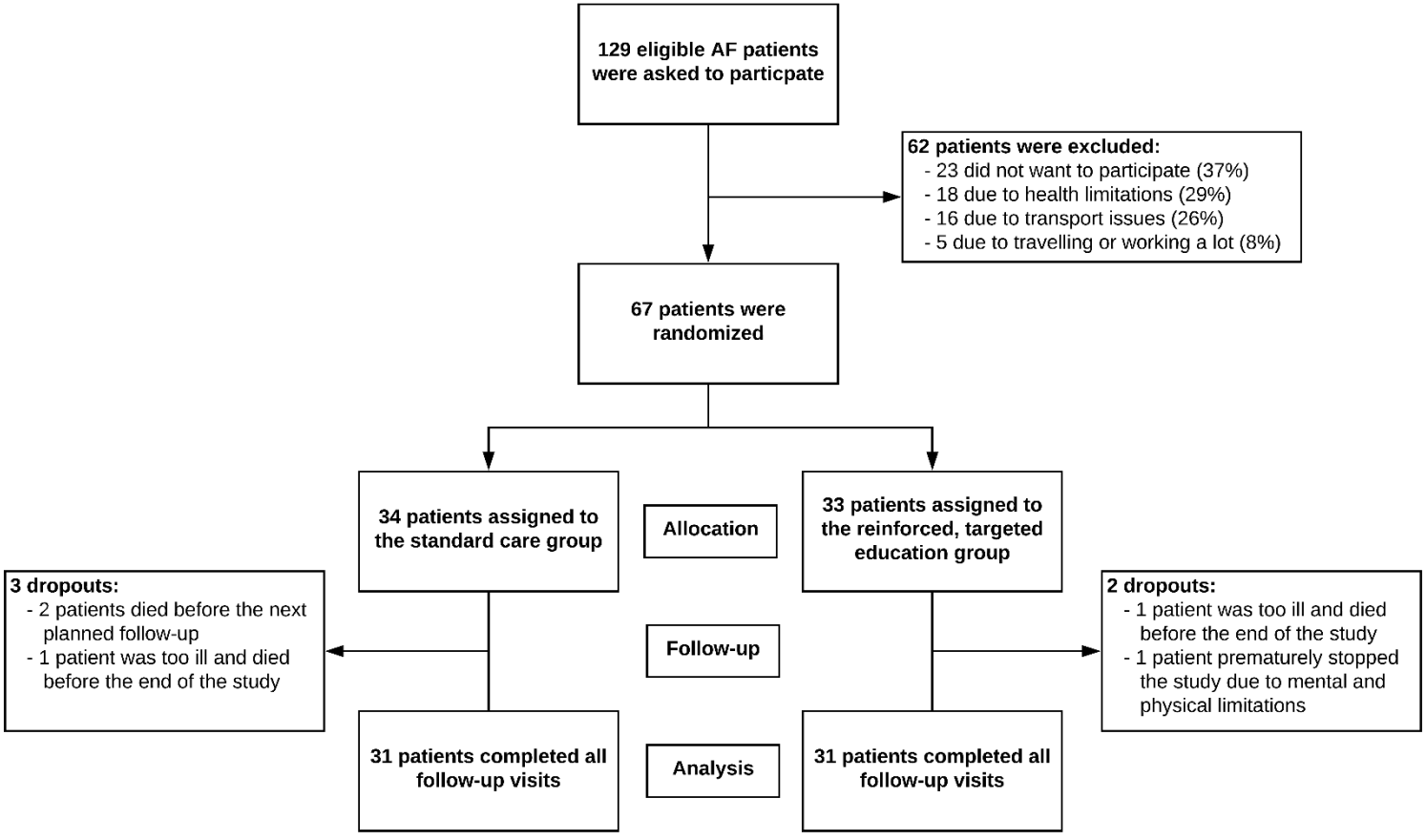


Figure 3.2: Patient inclusion flow chart. AF: atrial fibrillation

Table 3.1: Baseline characteristics of AF patients included in this study.

	Total study population (n=67)	Control group (n=34)	Education group (n=33)	P-value*
Age, mean ± SD	72.1 ± 8.6	72.7 ± 8.1	71.5 ± 9.3	0.558
Male, n (%)	42 (62.7)	22 (64.7)	20 (60.6)	0.729
Highest level of education completed, n (%)				0.809
Primary school	16 (23.9)	9 (26.5)	7 (21.2)	
Secondary school	30 (44.8)	16 (47.1)	14 (42.4)	
College	15 (22.4)	6 (17.6)	9 (27.3)	
University	6 (9.0)	3 (8.8)	3 (9.1)	
Type of AF, n (%)				0.886
First AF episode	8 (11.9)	4 (11.8)	4 (12.1)	
Paroxysmal AF	24 (35.8)	11 (32.3)	13 (39.4)	
Persistent / long-standing persistent AF	18 (26.9)	11 (32.3)	7 (21.2)	
Permanent AF	8 (11.9)	4 (11.8)	4 (12.1)	
Predominant atrial flutter	9 (13.4)	4 (11.8)	5 (15.2)	
CHA_2DS_2-VASc score, mean ± SD	3.3 ± 1.5	3.3 ± 1.4	3.4 ± 1.6	0.669
HAS-BLED score, mean ± SD	1.4 ± 0.9	1.5 ± 0.9	1.3 ± 0.9	0.382
Time since AF diagnosis, n (%)				0.618
< 1 month	4 (6.0)	3 (8.8)	1 (3.0)	
1 month – 1 year	14 (20.9)	6 (17.6)	8 (24.2)	
1 year – 5 years	27 (40.3)	15 (44.1)	12 (36.4)	
> 5 years	22 (32.8)	10 (29.4)	12 (36.4)	
Anticoagulation/antithrombotic therapy, n (%)				0.739
NOAC only	41 (61.2)	20 (58.8)	21 (63.6)	
VKA only	12 (17.9)	5 (14.7)	7 (21.2)	
NOAC + APT	5 (7.5)	3 (8.8)	2 (6.1)	
VKA + APT	2 (3.0)	2 (5.9)	0 (0.0)	
APT only	5 (7.5)	3 (8.8)	2 (6.1)	
None	2 (3.0)	1 (2.9)	1 (3.0)	

AF: atrial fibrillation, APT: antiplatelet therapy, NOAC: non-vitamin K antagonist oral anticoagulant, VKA: vitamin K antagonist, SD: standard deviation.
* Comparison between patients randomized to the control group and the education group.

Targeted education improved the knowledge level for all different AF aspects. At the end of the study, significantly more patients in the education group knew that AF can be asymptomatic compared to baseline (74.2% vs. 25.8%; P < 0.001). At the start, only 41.9% of all patients indicated that one can detect AF by regularly taking his pulse; this was 74.2% after reinforced education (P = 0.010). At the start, only one in four patients (25.8%) knew that AF will increasingly recur with ageing, despite medication; this was 64.5% after 12 months (P = 0.002). Furthermore, at 12 months 96.3% of the patients on OAC vs. only 63.0% at baseline were aware of the possible bleeding complications associated with the therapy (P = 0.002). Finally, 77.8% of the patients taking VKA or NOAC knew what to do when missing a dose; this was only 25.9% at the start of the study (P < 0.001).

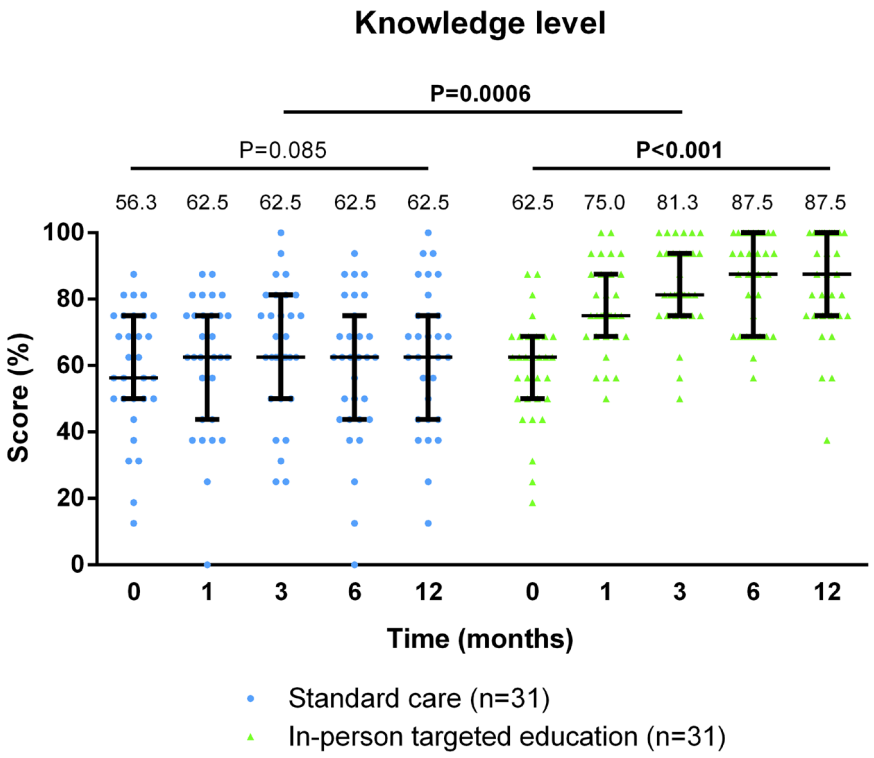


Figure 3.3: Score on the Jessa Atrial fibrillation Knowledge Questionnaire over time in the standard care group (blue dots) and the group receiving targeted in-person education (green triangles). Data are represented as scatter dot plots with indicated median and interquartile range. Statistical analysis: Friedman tests for differences over time within each group and mixed model for comparison between groups.

Impact on quality of life

At baseline, none of the eight items of the SF-12 questionnaire were significantly different between both study groups (P-values between 0.276 and 0.908), with both the PCS and MCS showing comparable results (control vs. education: 45.3 ± 7.4 vs. 45.0 ± 9.6, P = 0.909 respectively 47.5 ± 8.0 vs. 47.7 ± 11.0, P = 0.927) (Supplementary material, Figure S3.1). The PCS did not change significantly over time in either group (control: P = 0.873; education: P = 0.077). The MCS did not change significantly over time in the control group (P = 0.094), but there was a significant increase in the MCS score between baseline and three months (P = 0.008) and one month and three months (P = 0.026) in the in-person education group. The PCS and MCS score over time were however not significantly different between both groups (P = 0.462 and P = 0.677 respectively).

Effect on symptom burden

The overall symptom burden on the LARQ was the highest at baseline and decreased over time (standard care: P = 0.007, education: P = 0.239; Supplementary material, Figure S3.2). However, the overall symptom burden score over time was not significantly different between both groups (P = 0.669). A detailed representation of the symptom experience per symptom and per burden domain during the different follow-up visits is shown in Supplementary material, Figure S3.3.

Impact on adherence

Adherence to NOACs was measured in 29 patients, 14 in the control group (10 rivaroxaban, 4 apixaban) and 15 in the education group (10 rivaroxaban, 5 apixaban). Taking adherence (P = 0.464), regimen adherence (P = 0.619) and pill count (P = 0.282) were numerically higher in the education group, but not significantly so due to the small groups and large variability in adherence measures (Supplementary material, Figure S3.4). The number of unprotected days was also not statistically lower in the intervention group (P = 0.417).

DISCUSSION

Patients' knowledge about AF and OAC therapy is of pivotal importance for their overall management. However, this aspect is often overlooked and not systematically addressed due to time constraints of physicians and the lack of proven efficient educational interventions.[122,125]

Patient knowledge regarding atrial fibrillation

The score on the JAKQ (58.5%) at baseline in both study groups was comparable with two previous large population surveys with the JAKQ (55.8%-61.6%).[147,149] This indicates that a representative subset of patients was included in this study, despite the fact that almost half of the patients was not willing or not able to participate. Although standard care consisted of an information brochure on top of information from the cardiologist, very important knowledge gaps were still present. The standard care in our study was probably better than the average daily care in most centers since a European survey showed that only 22.7% of cardiology centers make use of a patient information brochure.[144] Notwithstanding, 43.4% of the centers indicated they had a structured program for patient education.[144] The lack of knowledge by patients concerned various aspects of AF care and OAC therapy, as previously also shown by other studies making use of (validated) questionnaires.[122,126,127,132-135,147-149]

Educational strategies for atrial fibrillation

Our study shows that the JAKQ is a good instrument to guide education in a more individualized and targeted manner. After one targeted in-person education session, the knowledge level had significantly improved. Additional education sessions at 1 and 3 months further increased the knowledge level and this improved level was maintained during the following visits due to repeated reinforced education, stressing the importance of the repetitive character of such intervention. It was somewhat surprising to note that providing the JAKQ to the control group during each visit did not improve their scoring over time. Although we have not systematically evaluated this aspect, it seems that JAKQ taking by itself hardly triggered those patients to look up deficient knowledge in the brochures that were provided to them, by asking health care workers, or by active searching on online resources.

Various other educational methods, frequently focusing on OAC therapy, have been evaluated in AF patients, with mixed results: brochures[132-134,150], educational videos[133,134], group education sessions[133], general face-to-face education[103,150], a complex general practice driven program[151] and a mobile application[152]. An intervention in which an information booklet was given to and discussed with the patient had no significant impact on the awareness about AF and the potential side effects and benefits of OAC therapy.[132] McCabe et al. evaluated the effect of education by nurses in hospitalized patients with recently detected AF using AF and OAC brochures together with a video about OAC therapy: two weeks after the hospitalization, knowledge was not retained.[134] Hendriks et al. showed that a nurse-led AF chronic care program including reinforced in-person education at regular time points, can lead to a significant increase (with 14.1%) in AF-related knowledge after one year.[103] This education was more comprehensive including general information about AF, treatment options, and lifestyle interventions combined with psychosocial support.[103,126] The educational visits in that study took 30 minutes of time, which of course impacts personnel costs. In Hendriks' study, the knowledge level of the control group also significantly improved with 10.8%, which was not the case in our study.

Feasibility of reinforced targeted education based on the JAKQ

The JAKQ has proven to be a fast and valid tool to assess existing knowledge of AF patients in about 6-7 minutes. Moreover, by targeting the education to only the knowledge deficits of the patient, limited time of an allied health professional (i.e. up to 8.5 min) was needed during each visit. Only a short training period of the health care providers is required to implement this way of education as the JAKQ provides guidance. Targeted education based on the JAKQ is therefore feasible to be used in daily care both from the perspective of the hospital and the patient. All patients will receive education in a uniform way without overwhelming them with too much or superfluous information and by only focusing on the important key aspects in their management. By implementing the JAKQ in a tablet application, as performed in this study, patients are able to complete it at home or in the waiting room before their visit. During the visit, a healthcare practitioner can then provide immediate targeted education. This way, providing targeted education was implemented as an integral piece of the entire care framework of a specialized AF clinic.[97,165]

Impact of education in atrial fibrillation patients

Only a few studies have investigated so far the effect of an educational strategy on clinical outcome parameters. Although our study was not powered for these secondary outcome parameters, some statistically significant differences were found in QOL and symptom burden. Emotional health was lowest and symptom burden highest at baseline in both groups. It is difficult, however, to draw definitive conclusions about the effect size of the education intervention itself on improvements in QOL and symptom burden. E.g., 38.8% of the participants were included during an (un)planned hospitalization, which is a state of high symptom burden, which tends to regress towards a more stable out-patient setting. The contribution of education to improved patient coping with AF-related symptoms remains to be determined. In any case, education seems to be an important driver of improved QOL. The nurse-led integrated chronic care program by Hendriks et al. that included patient education as an important pillar, also showed that the QOL (measured with the SF-36 questionnaire) significantly improved over time in both the intervention group and the standard care group.[103] This also led to a decrease in anxiety over time in both study groups.[103]

Optimal adherence to OAC medication, especially with NOACs, is of great importance to achieve the prognostic benefit of anticoagulation. Therefore, half of the JAKQ questions are attributed to OAC. A systematic review from 2017, however, did not find any effect of educational and behavioral interventions on time in therapeutic range in AF patients taking VKA.[166] Three large trials investigated the effect of an educational intervention on NOAC adherence.[154,167,168] Although the AEGEAN trial did not show any impact of a structured educational program (i.e. booklet, reminder tools and follow-up telephone calls) on adherence to apixaban[167], the IMPACT-AF trial (majority of patients still on VKA) showed that an educational intervention for both patients and healthcare providers improved OAC use in AF patients.[154] The FACILITA study showed that a mixed intervention, consisting of patient education and a simple calendar reminder, led to a dabigatran regimen adherence of 89.2% compared to 63.2% in a control group after one year.[168] In our study the effect of targeted education was evaluated on NOAC adherence measured with electronic monitoring, showing lower values in the standard care group but not significantly different from the education group, possibly due to the small sample size and the

short monitoring period. Electronic adherence monitoring can also be used as a tool to promote a good adherence by discussing the measured data together with the patient or even by providing direct feedback based on telemonitoring, as part of an educational program.[169]

Study limitations

This is a single center study with a small sample size, although it was correctly sized for the primary outcome. Almost half of the eligible patients did not participate. Beyond a study setting this probably would have been lower, i.e. the possibility to be randomized to a control group could have had an impact and in daily practice education sessions can be coupled to planned hospital visits. Generalizability of these results to other settings should be made with caution as the impact of this intervention can depend on the experience and enthusiasm of the healthcare workers providing education. In our hospital no standardized educational program for AF patients is implemented yet beyond regular physician contacts and provision of information brochures. Although electronic monitoring is assumed as one of the most accurate ways to measure adherence, it is always possible that patients do not use the device correctly for a certain period or do not take their medication although a device registration occurred.[170] Moreover, using such devices can already lead to an increased patient awareness to take their medications better than usual.[169]

Future perspectives

A large randomized controlled multicenter trial could be set up to evaluate the impact of targeted in-person education as part of daily care on different clinical outcome data (e.g. complications, hospitalizations, emergency room visits) and on other secondary outcome measures for which this trial was not powered. Fuenzalida et al. recently showed in a study with 240 patients that specific nurse-led education at discharge of the emergency department significantly decreased AF-related complications, treatment-related complications, and death (31.9% compared to 48.4% in the control group after one year; P = 0.005).[150] The educational intervention consisted of i) personalized education about the arrhythmia, its treatment, precautions and warning signs; ii) training to take the pulse; iii) an individualized information leaflet with an overview of the prescribed medication; iv) a recommendation to have a follow-up visit with the general

practitioner.[150] Further, the cost-effectiveness of such interventions should be evaluated. We have currently started such a large-scale prospective trial, including integral targeted patient education, funded through the Flemish government. It demonstrates the interest of health authorities in finding ways to optimize implementation of guideline-based care through enhanced patient involvement.

CONCLUSION

The JAKQ is a suitable tool to provide individualized education for AF patients. A first targeted in-person educational session based on the JAKQ significantly improved patients' knowledge level. Additional educational sessions maintained and strengthened this effect. This study showed some improvements on QOL, symptom burden and likely medication adherence, although not significantly different between both groups. Integrated targeted education opens the perspective for improving clinical outcomes and prognosis of AF patients.

ACKNOWLEDGMENT

The JAKQ with questions and full answers is not in the public domain, but can be obtained from Hasselt University through a user agreement. If interested, please send an e-mail to jakq.uhasselt@gmail.com.

WestRock Switzerland Ltd. supported this study with devices, but they were not involved in study planning, conduct, analysis or reporting.

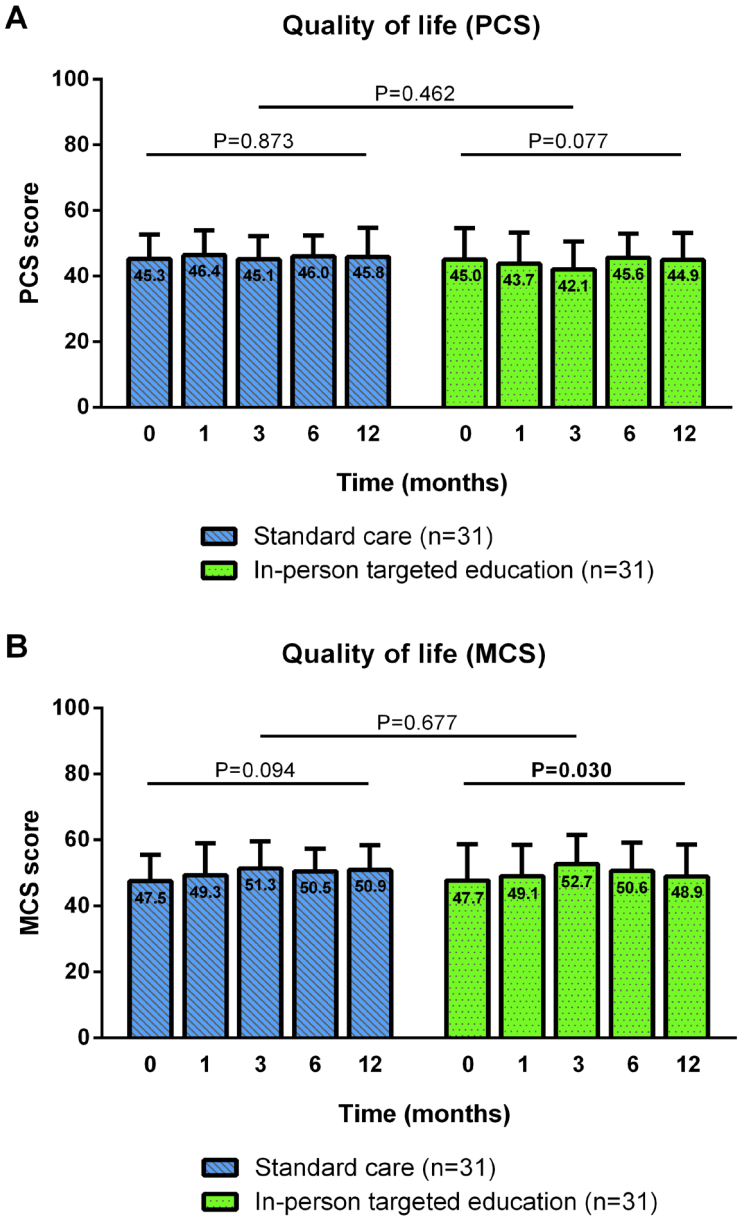
SUPPLEMENTARY MATERIAL

Supplementary Table S3.1: Specific topics addressed in the Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ).*

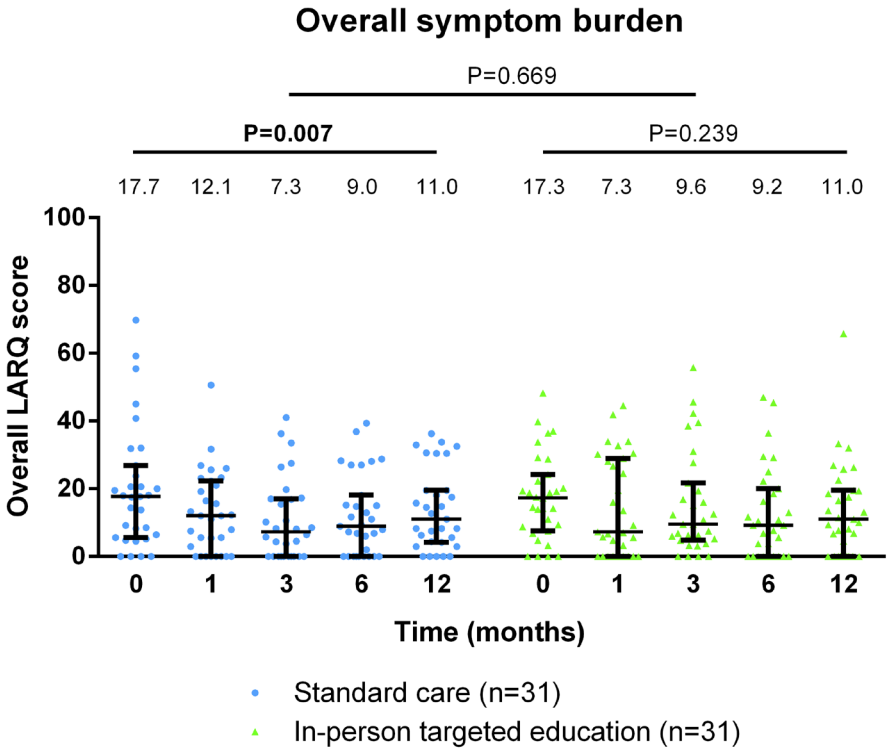
8 questions about AF in general
AF is a condition where the heart beats irregularly and often faster than normal
AF is not always accompanied by symptoms
Patients can detect AF by taking their pulse regularly
AF can cause blood clots which can lead to stroke (cerebral infarction)
Medication cannot prevent AF permanently, as the arrhythmia will increasingly occur with ageing, even when taking medication
An AF patient should not go to the general practitioner or emergency room each time he/she feels AF
Being overweight exacerbates AF
Blood thinners are often prescribed to patients with AF in order to prevent the development of blood clots in the heart, which can lead to stroke
5 questions about OAC therapy
Patients with AF should always take their blood thinners, even if they do not feel AF
Possible side effects of blood thinners are the occurrence of bleedings and longer bleeding times in case of injuries
AF patients may only take painkillers based on paracetamol
When AF patients regularly have minor nose bleeds (that spontaneously cease), they should contact the general practitioner or specialist, while continuing to take their blood thinners
If an AF patient needs an operation, he/she should consult a doctor to discuss possible options
3 questions about VKA
AF patients taking VKA should have their blood thinning checked at least once a month
When AF patients taking VKA have forgotten to take their blood thinner, they should still take their forgotten pill (immediately or at the next dose)
INR is a measure to check how thick or how thin the blood is
3 questions about NOAC
For patients taking NOAC, it is important to take their blood thinner at the same time every day
When AF patients taking NOAC have forgotten to take their blood thinner, they can still take that dose, unless the time till the next dose is less than the time after the missed dose
NOAC blood thinners come with a card, which AF patients have to show to their general practitioner and specialist

AF: atrial fibrillation, INR: international normalised ratio, JAKQ: Jessa Atrial fibrillation Knowledge Questionnaire, NOAC: non-vitamin K antagonist oral anticoagulants, VKA: vitamin K antagonist.

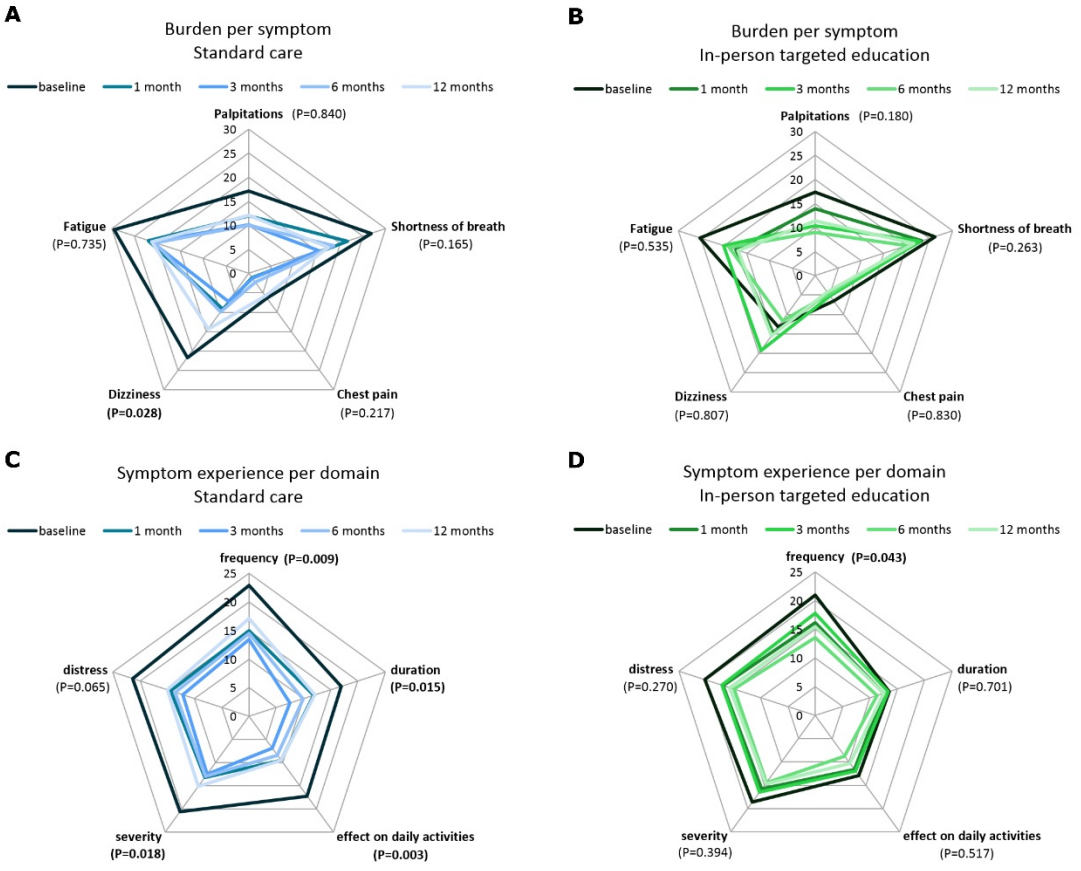
* The JAKQ with questions and full answers can be obtained from the authors through a user agreement as the JAKQ is not in the public domain.



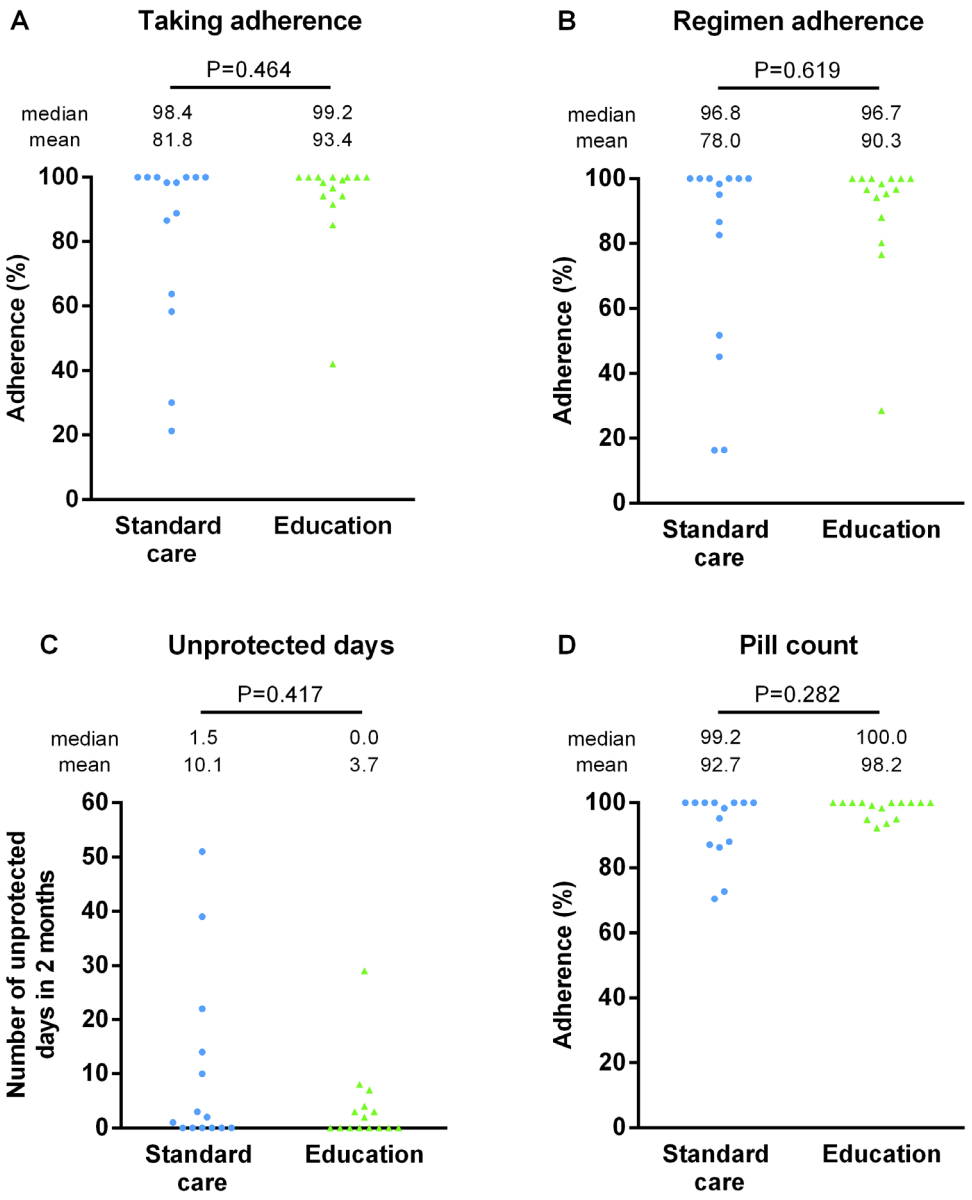
Supplementary Figure S3.1: Physical component summary (PCS; A) and mental component summary (MCS; B) score measured with the SF-12 during the different follow-up visits in the standard care group (blue striped columns) and the targeted in-person education group (green dotted columns). Data are represented as means ± standard deviation. Statistical analysis: repeated measures analyses of variance (ANOVAs) for differences over time within one group and mixed ANOVAs for comparison between groups.



Supplementary Figure S3.2: Overall symptom burden measured with the Leuven ARrhythmia Questionnaire during the different study visits in the standard care group (blue dots) and the group that received targeted in-person education (green triangles). Data are represented as scatter dot plots with indicated median and interquartile range. Statistical analysis: Friedman tests for differences over time within each group and mixed model for comparison between groups.



Supplementary Figure S3.3: Radar diagrams showing an overview of the AF symptom experience represented as a burden per symptom (A: standard care group; B: education group) and as a burden per domain classification (C: standard care group; D: education group) measured with the Leuven ARrhythmia Questionnaire. Statistical analysis: Friedman tests.



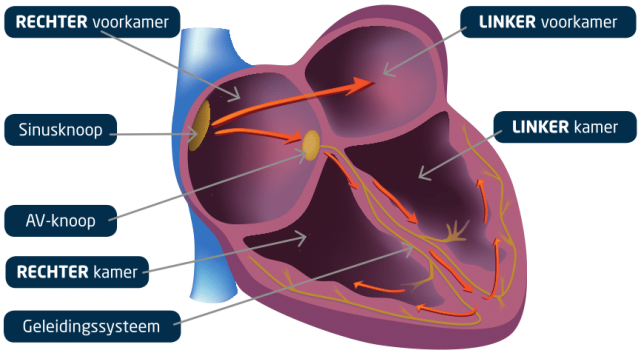
Supplementary Figure S3.4: Adherence measures between the 1 month and 3 month follow-up visit in the standard care group (blue dots) and the education group (green triangles). Adherence measures are analyzed as A) Taking adherence B) Regimen adherence C) Unprotected days and D) Pill count. Data are represented as scatter dot plots. Statistical analysis: Mann-Whitney U tests.

Supplementary appendix 1: Patient information booklet that is handed over to AF patients as part of standard care (Dutch version). Every patient in both the standard care group and the in-person targeted education group received this brochure providing basic information about atrial fibrillation, accompanying symptoms, risk factors, possible consequences and key treatment aspects.

Inhoudstafel

1. Een **normale hartfunctie**

Het hart is de pomp van uw lichaam. Het moet ervoor zorgen dat het hele lichaam van zuurstof en voedingsstoffen wordt voorzien.
Het hart bestaat uit 4 delen: **twee voorkamers**, de linker en rechter voorkamer (atria) en **twee kamers**, de linker en rechter kamer (ventrikels).

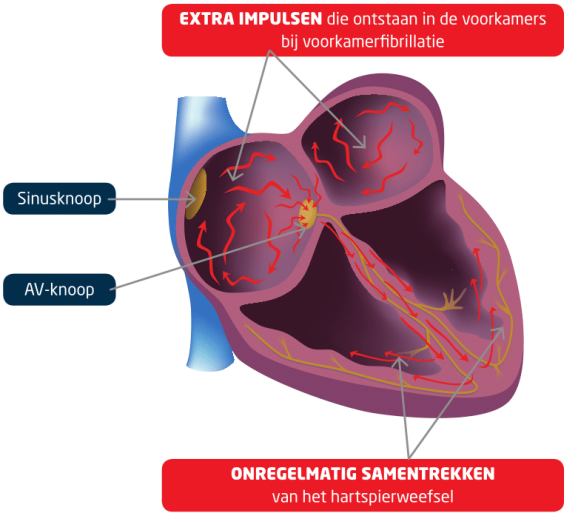


De pompfunctie van het hart wordt gecoördineerd door een **elektrisch systeem dat prikkels vormt en voortgeleidt**. Iedere hartslag start door een elektrisch signaal dat ontstaat in de sinusknoop. Van hieruit verspreidt deze elektrische prikkel zich door de voorkamers waardoor ze samentrekken. Onderaan in de voorkamers ligt de AV-knoop, via dewelke de prikkel verder geleid wordt naar de beide kamers. Via snelle elektrische geleidingsbanen trekken de kamers gelijktijdig en op het juiste moment samen.

Een normaal hartritme varieert **tussen de 50 en 100 slagen per minuut in rust** en is vrij regelmatig.

2. Wat is voorkamerfibrillatie?

Voorkamerfibrillatie (VKF) is een veel voorkomende ritmestoornis die vooral optreedt in de tweede helft van het leven. Vanaf de leeftijd van 40 jaar heeft men één kans op vier om met VKF geconfronteerd te worden.
Bij VKF is het **elektrisch systeem ter hoogte van de voorkamers verstoord**. De normale prikkel heeft plaats gemaakt voor chaotische elektrische activiteit in de voorkamers. Om die reden gaan de voorkamers fibrilleren (trillen) = voorkamerfibrillatie. Die chaotische prikkels vinden willekeurig een weg naar de kamers. Die gaan daardoor **onregelmatig en vaak veel te snel samentrekken**.



3. Wat zijn de symptomen van voorkamerfibrillatie?

Voorkamerfibrillatie kan aanleiding geven tot volgende **klachten**:

- Hartkloppingen: meestal voelen patiënten een snel en onregelmatig hartritme alsof het hart op hol slaat. Het wordt ook vaak beschreven als een gevoel waarbij het hart in de borst of in de keel klopt.
- Kortademigheid bij lichte inspanningen
- Moeheid, zwakte
- Pijn op de borstkas
- Zelden: duizeligheid, flauwvallen

Nochtans komt VKF ook vaak symptoomloos voor. In feite zal de behandeling er ook vooral op gericht zijn VKF episodes zonder symptomen te laten verlopen.

Bij 1 op 3 nieuwe patiënten met VKF veroorzaakt de ritmestoornis **geen symptomen!**

4. Welke gevolgen heeft voorkamerfibrillatie?

Doordat de voorkamers zeer snel trillen, valt hun pompfunctie weg (die van de kamers blijft wel behouden!). Hierdoor stroomt het bloed minder goed in de voorkamers waardoor de kans bestaat dat zich daar **bloedklonters** vormen. Deze kunnen loskomen en meestromen met de bloedcirculatie. Deze bloedklonters kunnen in het lichaam voor problemen zorgen doordat ze bloedvaten plots opstoppen. Men spreekt dan van **embolie**.

Als een bloedklonter in de longen terecht komt, betreft het een longembolie. Daarnaast kan de embolie ook de bloedtoevoer naar andere organen beperken of afsluiten (vb.: nieren, darmen). Wanneer de bloedklonter in de hersenen terecht komt, kan deze een **beroerte** of een herseninfarct veroorzaken, met een eventuele verlamming en/of uitval van de spraak tot gevolg. Dat is de ergste vorm van embolie.

Wees niet ongerust: mits goede detectie en een correcte behandeling van VKF is een normale levensactiviteit perfect mogelijk en kunnen embolieën worden voorkomen!

Door **behandeling** hebben patiënten met VKF **vijf keer minder kans op een beroerte** en kunnen ze een nagenoeg **normaal leven** leiden!

5. Risicofactoren

Het is niet zo dat iedere onregelmatige pols verwijst naar VKF. Soms kunnen er ook goedaardige onregelmatige ritmes voorkomen.

Toch zijn er bepaalde factoren die het risico op het ontwikkelen van VKF verhogen:

- Toenemende leeftijd
- Verhoogde bloeddruk
- Zwaarlijvigheid
- Hartziekten (vb. hartkleplijden, hartfalen, een vroeger hartinfarct)
- Schildlkierproblemen
- Chronische ziekten (vb. diabetes)
- Alcoholmisbruik
- Doorgedreven duursport (> 3 u intensief per week)

Uw arts zal samen met u ook bekijken hoe deze risicofactoren opgespoord en behandeld kunnen worden. Hun behandeling kan bijdragen om minder aanvallen van voorkamerfibrillatie te ontwikkelen, maar kan ook belangrijk zijn om andere gevolgen van die aandoeningen te voorkomen. VKF is dus een soort van 'knipperlicht' dat waarschuwt dat één en ander aanpak vereist.

6. **Behandeling** van voorkamerfibrillatie?

Voorkamerfibrillatie is dus vooral een ouderdomskwaaltje dat bij sommige mensen al op relatief jonge leeftijd voor het eerst kan optreden door andere risicofactoren. Het aantal aanvallen en de duur ervan zal doorgaans toenemen met het ouder worden.

De juiste behandeling kan in de meeste gevallen het aantal aanvallen duidelijk verminderen, verkorten en vooral draaglijk maken. Ondanks de beste behandeling is herval altijd mogelijk, maar kunnen de symptomen toch gecontroleerd worden.

De behandeling van VKF hangt af van verschillende factoren zoals het hartritme, de symptomen en andere medische aandoeningen.

De behandeling van VKF bestaat uit 3 aspecten:

1. Het proberen te stoppen van de ritmestoornis
   en te voorkomen dat ze opnieuw optreedt (= ritmecontrole).
2. Het zo goed mogelijk controleren van het levenscomfort
   wanneer de ritmestoornis toch doorkomt (= frequentiecontrole).
3. Optimale preventie van beroertes door correcte bloedverdunning.

1. Ritmecontrole

Het doel van ritmecontrole is het proberen te **herstellen en behouden van het normale regelmatige hartritme**.

Het herstellen van dit hartritme wordt cardioversie genoemd. Dit kan onder meer gebeuren door het toedienen van een geneesmiddel. Daarnaast kan dit ook gebeuren door middel van het toedienen van een elektrische stroomstoot. De patiënt wordt dan kortdurend in slaap gebracht.

Opdat het normale hartritme ook behouden blijft, krijgen deze patiënten vaak "anti-aritmica" voorgeschreven. Dat is medicatie die de ritmestoornis tracht te voorkomen.

2. Frequentiecontrole

Bij frequentiecontrole richt men zich op het **vertragen van een te snel hartritme** waardoor de pompfunctie van het hart efficiënter wordt en de **symptomen van de patiënt zullen verminderen of verdwijnen**.

Dit kan gebeuren aan de hand van geneesmiddelen zoals bètablokkers, calciumantagonisten of digitalis. Deze medicatie kan zonder problemen langdurig genomen worden en zal geen aanleiding geven tot bijzondere complicaties. De dosis en combinatie is bij elke patiënt anders.

3. Ontstollingstherapie

Om het risico op het **ontwikkelen van beroertes en embolieën tot een minimum te herleiden**, is het belangrijk dat het bloed preventief verdund wordt. Welk soort **bloedverdunner** voor u in aanmerking komt, wordt besproken met de arts.

In het verleden was er maar één behandelingskeuze, meer bepaald vitamine K-antagonisten (Marcoumar®, Marevan® en Sintrom®). Het effect van deze medicatie is soms moeilijk voorspelbaar waardoor regelmatige bloedcontroles noodzakelijk waren.

Tegenwoordig beschikken we ook over nieuwere medicatie waarbij dergelijke controles minder nodig zijn. Deze medicijnen worden niet-vitamine K-antagonist bloedverdunners (of NOACs) genoemd, zoals Pradaxa®, Eliquis® en Xarelto®.

Een ontstollingsbehandeling kan wel de kans op bloedingen vergroten, maar uw arts heeft dit nadeel afgewogen ten opzichte van de voordelen en schrijft u geen ontstollingstherapie voor als het niet wenselijk zou zijn.

Sommige pijnstillers zoals aspirine mag je **niet combineren met ontstollingstherapie!**
Vraag altijd aan je (huis)arts of je iets mag combineren!

7. Vragen?

Als u of uw arts **bijkomende vragen** heeft, kan u altijd terecht bij:

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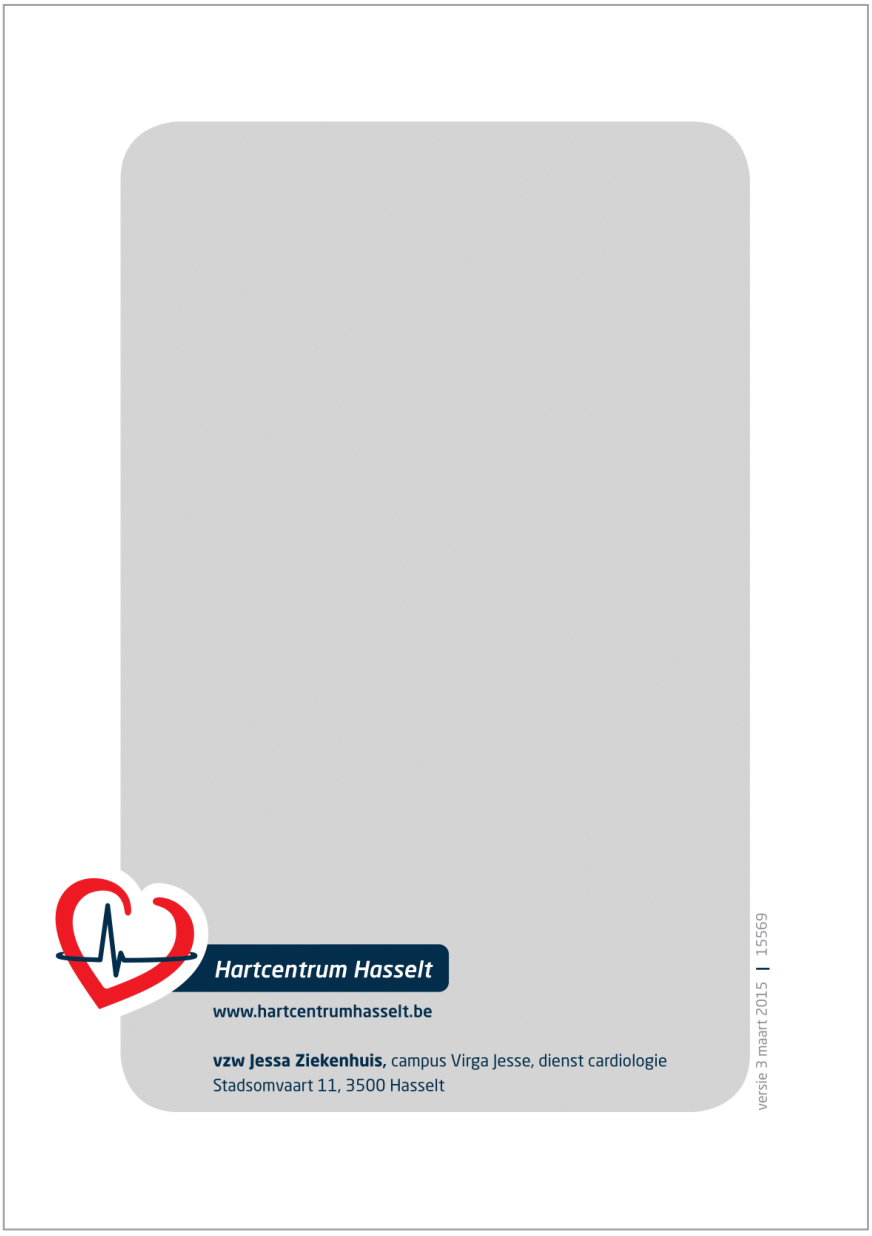
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Chapter 4

Effectiveness and usability of an online tailored education platform for atrial fibrillation patients undergoing a direct current cardioversion or pulmonary vein isolation

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ABSTRACT

Aims

Atrial fibrillation (AF) care should strive for more informed, involved and empowered patients. However, few effective educational programs are available. The aim of this study was to evaluate the effectiveness of an online tailored education platform to inform AF patients undergoing a direct current cardioversion (DCC) or a pulmonary vein isolation (PVI).

Methods

120 AF patients requiring DCC or PVI were allocated to an online education group (n = 35), a standard care group despite having online access (n = 36; randomized with group 1), and a group without a computer/tablet/smartphone receiving standard care (n = 49). The Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ), supplemented with procedure-specific questions, had to be completed 1-3 weeks before hospitalization, at hospitalization, and 6 and/or 12 weeks post-procedurally.

Results

Major AF-related and procedure-related knowledge gaps were shown. The online tailored education group scored significantly better at hospitalization compared to baseline ($P = 0.001$). This knowledge increase was retained after 6 ($P = 0.010$) and 12 ($P < 0.001$) weeks. In the online standard care group there was no change in knowledge from planning till hospitalization ($P = 1.000$), although knowledge was improved 6 weeks post-procedurally ($P = 0.010$). Knowledge did not improve in the group without computer/tablet/smartphone at any time ($P = 0.248$). Most patients indicated that the platform was easy to use (87.9%), understandable (97.0%), and 72.7% indicated that an online platform was their preferred way to receive future AF-related information.

Conclusion

Tailored online education is an effective strategy to improve AF- and procedure-related knowledge with lasting effects up to 12 weeks post-procedurally. The platform was positively evaluated by patients.

INTRODUCTION

One of the pillars of integrated atrial fibrillation (AF) care is optimal patient education to strive for more informed, involved and empowered patients.[63,125,142] Nevertheless, various studies showed there is room for improvement.[122-124,126,127,129,132,134-136,147-149] Ideally, a more structured and tailored approach to provide education is desired.[63,125,142] In our current society, the Internet is a major source of health information. Even though an AF population often consists of elderly, many patients tend to seek for information themselves. Online resources are highly accessible but the quality and nature of this information is sometimes questionable. Moreover, online information for AF patients can be limited, restricted to certain languages, imbalanced, and not specifically tailored to their specific situation.[171] It is therefore the responsibility of healthcare professionals to make use of or to refer patients to appropriate educational resources. There is few data available neither on the knowledge level of AF patients about rhythm restoring procedures including risks and benefits, nor on patients' expectations about the outcome of such procedures. The aim of this study was to evaluate the effectiveness and usability of an online tailored education platform to inform AF patients undergoing a direct current cardioversion (DCC) or a pulmonary vein isolation (PVI). The impact of education was measured on knowledge level and AF related quality of life (QOL).

METHODS

Online education platform

An e-learning tool allowing personalized and tailored education was developed. It consisted of different educational topics (Supplementary material, Figure S4.1). General AF-related information was available for all patients. Education about oral anticoagulation (OAC; depending on the indication and type of medication) and procedure-related information (DCC, PVI, and type of PVI procedure) was exclusive content and was only activated for the patient when applicable. The content of the platform, developed and approved by three experienced cardiologists/electrophysiologists, was based on hospital brochures and on information from patient support websites (e.g. Atrial Fibrillation Association, European Heart Rhythm Association, American Heart Association, Alliance for

Aging Research). Education was provided via text, images, and movies. Fact boxes highlighted key educational messages. Every patient had a unique log-in and patients were able to visit the platform as often as they wanted, except for the moments when various questionnaires had to be completed. The AF e-learning tool (developed with Meplis Campus software, Meplis, Lubbeek, Belgium) was available via a web browser or via an iOS and Android application. The Meplis Care Monitor software was used to automatically send questionnaires to patients having a computer/tablet/smartphone at predefined time points.

Study population

A prospective randomized controlled study was performed at a Belgian tertiary care hospital. Consecutive AF patients planned to undergo a PVI or DCC procedure were recruited. Exclusion criteria were: age below 18 years, too mentally (e.g. severe dementia) or physically (e.g. hearing loss) impaired, inability to read or understand Dutch and not capable to sign the informed consent. Patients were contacted by telephone 1-3 weeks before their procedure to evaluate eligibility and willingness to participate. At baseline, sociodemographic data were gathered on top of clinical data and AF-history that was collected from the patients' medical record. The study complied with the Declaration of Helsinki, ethical approval was obtained from the local ethical committee and patients provided written informed consent.

Study procedure

At baseline, patients were asked about the possession of a computer, tablet and/or smartphone with Internet access and the ability to work with it. Recruited patients willing to participate were assigned to three different groups: 1) patients with a computer/tablet/smartphone and Internet receiving online tailored education; 2) patients with a computer/tablet/smartphone and Internet receiving standard care (randomized with group 1), and 3) patients without a computer/tablet/smartphone receiving standard care **(Figure 4.1)**. Stratification (for group 1 and 2) was based on age and highest educational degree.[147] Standard care included information from the cardiologist and provision of procedure specific information booklets and a general AF brochure.

The Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ) and a QOL questionnaire had to be completed at different time points: two in the group without a compatible device (i.e. during hospitalization and at follow-up) and four in the patient groups having a computer/tablet/smartphone (i.e. 1-3 weeks before hospitalization, immediately pre-procedurally at hospitalization, and 6- and 12-weeks post-procedurally) **(Figure 4.1)**. Only the online tailored education group was given access to the platform after completion of the first questionnaires. Follow-up in patients without a computer/tablet/smartphone occurred during their control consultation visit (6 weeks for DCC; 12 weeks for PVI). If this was not possible, the JAKQ was conducted by telephone. The QOL questionnaire was sent to the patients by regular mail with a request to complete and send back to the study center (performed by all patients; two had withdrawn consent).

Measured parameters

Knowledge about atrial fibrillation

The 16-item JAKQ contains 8 questions about AF in general, 5 questions about OAC therapy and 3 questions about either vitamin K antagonists (VKA) or non-vitamin K antagonist oral anticoagulants (NOAC).[147] AF patients not or temporally taking OAC medication (i.e. only peri-procedurally), only completed the first 8 questions of the JAKQ. The JAKQ is composed of multiple choice questions with one correct answer, two distracters and one 'I do not know' option. For the purpose of this study, the JAKQ was supplemented with four specific PVI- or DCC-related questions depending on the planned procedure. Every correct answer was scored as 1 point. The final score was divided by the number of answered questions, resulting in a percentage. The 16-item JAKQ underwent a thorough validation process which was previously published, i.e. content validation, face validation, response process, construct validity, internal consistency, test-retest reliability, sensitivity testing and discriminatory potential.[147] An additional internal consistency testing of the 20-item JAKQ and the 8 questions about AF in general occurred in this study sample. This was performed by calculating Cronbach's alpha to assess the degree to which all of the items of the JAKQ measure the same construct. A Cronbach's α above 0.7 is considered as an adequate internal consistency.[143]

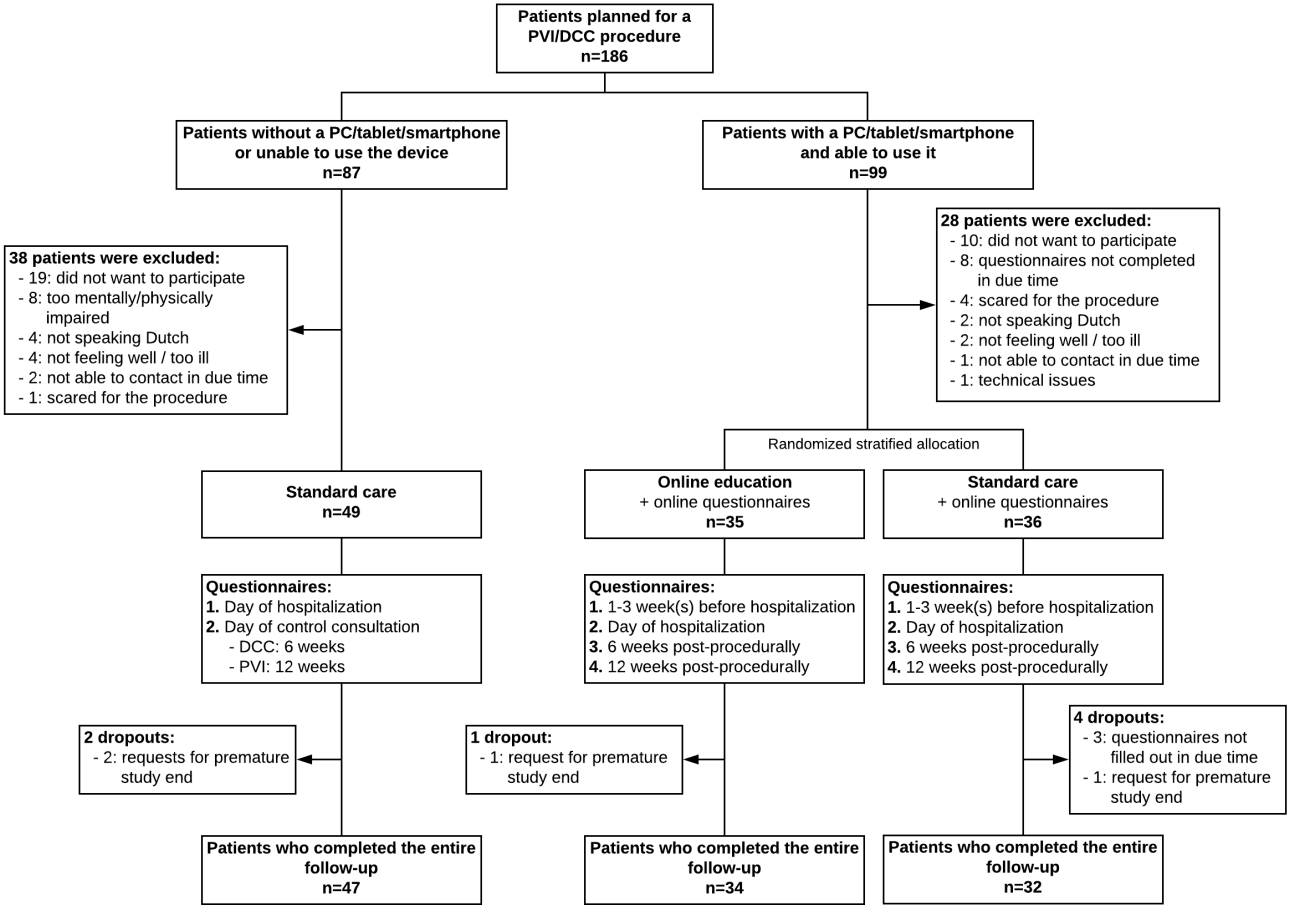

Figure 4.1: Flow chart representing the screening, patient inclusion and follow-up. AF: atrial fibrillation, DCC: direct current cardioversion, PC: portable computer, PVI: pulmonary vein isolation.

Quality of life

The AF Effect on QualiTy of life (AFEQT) questionnaire evaluates health-related QOL based on 18 questions in the domain of symptoms, daily activities and treatment concerns.[172] A treatment satisfaction score was calculated based on 2 additional questions. All questions had to be rated on a seven point Likert scale, with a recall period of 4 weeks. A scoring key was used to determine an overall AFEQT score and a treatment satisfaction score ranging from 0 to 100. A lower score indicated worse health-related QOL or lower treatment satisfaction. The AFEQT questionnaire was previously validated based on factor analyses, internal consistency (>0.88 for all domains), test-retest reliability, convergent and divergent validity, known group validity, and responsiveness.[172]

Feasibility of online education and patient feedback

The online platform kept track on how many times every patient visited the platform, for how long they studied the content and which educational topics they studied. Patients' experience and opinions regarding the online education platform were evaluated by means of the validated User Experience Questionnaire (UEQ)[173] and a study-specific patient reported outcome measures (PROM) questionnaire that had to be completed on the day of hospitalization and 12 weeks post-procedurally, respectively. The 26-item UEQ assesses the patients' overall impression of the platform and its usefulness, by scoring opposite characteristics on a scale of -3 to +3.[173] The UEQ addresses 6 topics: attractiveness, perspicuity (clarity and ease at becoming familiar with the platform), efficiency, dependability (reliability), stimulation, and novelty. Based on an analysis tool, a score per topic was calculated. A score <-0.8 represents a negative evaluation; scores between -0.8 and 0.8 a neutral evaluation and values >0.8 a positive evaluation. The PROM was used to gather feedback regarding the satisfaction, usability, understandability, preferred way of receiving education and effects of the study.

Statistics

According to the power calculation (power of 80%; alpha of 5%; drop-out of 15%), at least 70 AF patients (35 in each online group) had to be included to achieve a 20% increase in the primary outcome of knowledge level.[147] Data were analyzed using SPSS 25.0 (IBM, Armonk, USA). Variables were described as numbers and percentages, median and interquartile range (IQR) or as mean ±

standard deviation, as appropriate. Normal distribution was assessed using the Shapiro-Wilk test. Continuous (demographic) variables were tested using Kruskal Wallis tests when comparing all study groups and Mann-Whitney U tests when comparing the two online groups. Categorical demographic variables were tested by means of Chi-squared tests. To evaluate the effect of education or standard care over time on the knowledge level and QOL in both online groups, Friedman tests were used. Comparisons in knowledge level and QOL between hospitalization and follow-up within the group that did not have a computer/tablet/smartphone, were performed with Wilcoxon signed-rank tests. A Spearman correlation was applied to evaluate a possible relation between the time spent on the platform and the knowledge increase. P-values <0.05 were considered statistically significant.

RESULTS

Patient characteristics

In total, 186 patients were recruited (61.3% DCC; 38.7% PVI). Of these, 66 patients were excluded or refused participation **(Figure 4.1)**. Mean age of the 120 study patients was 68.0 ± 10.2 years. Thirty-five patients were allocated to online tailored education, 36 to online standard care, and 49 had no computer/tablet/smartphone and received standard care. There was a drop-out of 7 patients during the trial (5.8%). The two online groups were well matched on different demographic characteristics **(Table 4.1)**. As expected, the group without a compatible device was significantly older, had a lower educational degree and had a higher bleeding and stroke risk. About half of the included patients (53.3%) received a procedure-specific brochure before their hospitalization. Of the patients with a computer/tablet/smartphone, 63.4% searched for additional disease and procedure-related information via the Internet. In both online groups 97.2% had a personal computer, 64.8% a tablet, and 60.6% a smartphone.

Table 4.1: Baseline characteristics of the study population.

	Total study population (n=120)	Online tailored education (n=35)	Online standard care (n=36)	Standard care without PC/tablet/ smartphone (n=49)	P-value all AF groups	P-value two online groups
Age, mean ± SD	68.0 ± 10.2	61.9 ± 10.1	65.4 ± 8.9	74.4 ± 7.6	<0.001	0.137
Male, n (%)	78 (65.0)	27 (77.1)	25 (69.4)	26 (53.1)	0.059	0.464
Highest level of education completed, n (%)					<0.001	0.810
Primary school	32 (26.7)	4 (11.4)	3 (8.3)	25 (51.0)		
Secondary school	47 (39.2)	15 (42.9)	14 (38.9)	18 (36.7)		
College/University	41 (34.2)	16 (45.7)	19 (52.8)	6 (12.2)		
Kind of AF, n (%)					0.016	0.734
Paroxysmal AF	37 (30.8)	15 (42.9)	14 (38.9)	8 (16.3)		
Persistent AF	83 (69.2)	20 (57.1)	22 (61.1)	41 (83.7)		
mEHRA score, n (%)					0.681	0.850
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
2a	43 (35.8)	11 (31.4)	10 (27.8)	22 (44.9)		
2b	25 (20.8)	9 (25.7)	8 (22.2)	8 (16.3)		
3	42 (35.0)	13 (37.1)	14 (38.9)	15 (30.6)		
4	10 (8.3)	2 (5.7)	4 (11.1)	4 (8.2)		
Time since AF diagnosis, n (%)					0.028	0.908
< 1 month	15 (12.5)	2 (5.7)	3 (8.3)	10 (20.4)		
1 month – 1 year	42 (35.0)	10 (28.6)	12 (33.3)	20 (40.8)		
1 year – 5 years	38 (31.7)	11 (31.4)	11 (30.6)	16 (32.7)		
> 5 years	25 (20.8)	12 (34.3)	10 (27.8)	3 (6.1)		
CHA_2DS_2-VASc score, mean ± SD	2.6 ± 1.6	2.0 ± 1.2	2.1 ± 1.5	3.4 ± 1.5	<0.001	0.972
HAS-BLED score, mean ± SD	1.2 ± 0.9	0.7 ± 0.9	1.1 ± 0.9	1.5 ± 0.7	<0.001	0.089
Anticoagulation therapy, n (%)					0.129	0.367
NOAC	95 (79.2)	27 (77.1)	26 (72.2)	42 (85.7)		
VKA	11 (9.2)	4 (11.4)	2 (5.6)	5 (10.2)		
None	14 (11.7)	4 (11.4)	8 (22.2)	2 (4.1)		
Rhythm restoring procedure, n (%)					0.002	0.697
PVI	57 (47.5)	22 (62.9)	21 (58.3)	14 (28.6)		
DCC	63 (52.5)	13 (37.1)	15 (41.7)	35 (71.4)		

AF: atrial fibrillation, DCC: direct current cardioversion, mEHRA: modified European Heart Rhythm Association score, NOAC: non-vitamin K antagonist oral anticoagulant, PC: portable computer, PVI: pulmonary vein isolation, VKA: vitamin K antagonist, SD: standard deviation.

Procedure and atrial fibrillation-related knowledge

The 20-item JAKQ including the procedure-specific questions has a good internal consistency, i.e. Cronbach's α of 0.803 (n = 106). Cronbach's α for the 8 general questions about AF was 0.792 (n = 120). Major AF-related and procedure-related knowledge gaps were found at the start of the study **(Table 4.2)**. Moreover, 29.2% of the patients was unaware that their condition was named 'atrial fibrillation'. The median (IQR) knowledge score on the JAKQ supplemented with the procedure-specific questions was not significantly different at baseline between both online groups [standard care: 60.0% (55.0-75.0), education: 68.3% (59.6-75.0), P = 0.233] (**Figure 4.2**, Supplementary material Table S4.1). The group without a computer/tablet/smartphone scored significantly worse [45.0% (35.0-60.0), P < 0.001]. The online tailored education group had improved its knowledge significantly by the time of hospitalization (75.0% IQR 66.7-85.0, P = 0.001) and this knowledge persisted at 6 (77.5% IQR 65.0-85.0, P = 0.010) and 12 (80.0% IQR 70.0-90.0, P < 0.001) weeks after the procedure. By contrast, no improvement in overall knowledge level was observed in the online standard care group by the time of hospitalization (65.0% IQR 50.0-73.8; P = 1.000). There was only a significant difference between baseline and 6 weeks post-procedurally (P = 0.010) and between hospitalization and 6 weeks post-procedurally (P = 0.016). At hospitalization, AF-related and procedure-related knowledge was significantly better in the online tailored education group (P = 0.001 and P = 0.009, respectively). There was no knowledge improvement in the standard care group without a compatible device over the course of the study period (P = 0.248).

Table 4.2: Specific topics addressed in the JAKQ, supplemented with four specific PVI- or DCC-related questions, with the percentage of correct responses.*

8 questions about AF in general (n = 120)	**%**
AF is a condition where the heart beats irregularly and often faster than normal	80.0 %
AF is not always accompanied by symptoms	27.5 %
Patients can detect AF by taking their pulse regularly	41.7 %
AF can cause blood clots which can lead to stroke (cerebral infarction)	66.7 %
Medication cannot prevent AF permanently, as the arrhythmia will increasingly occur with ageing, even when taking medication	40.8 %
An AF patient should not go to the general practitioner or emergency room each time he/she feels AF	65.8 %
Being overweight exacerbates AF	40.0 %
Blood thinners are often prescribed for patients with AF in order to prevent the development of blood clots in the heart, which can lead to stroke	84.2 %
5 questions about OAC therapy (n = 106)	**%**
Patients with AF should always take their blood thinners, even if they do not feel AF	86.8 %
Possible side effects of blood thinners are the occurrence of bleedings and longer bleeding times in case of injuries	67.9 %
AF patients may only take painkillers based on paracetamol	66.0 %
When AF patients regularly have minor nose bleeds (that spontaneously cease), they should contact the general practitioner or specialist, while continuing to take their blood thinners	71.7 %
If an AF patient needs an operation, he/she should consult a doctor to discuss possible options	72.6 %
3 questions about VKA (n = 11)	**%**
AF patients taking VKA should have their blood thinning checked at least once a month	100.0 %
When AF patients taking VKA have forgotten to take their blood thinner, they should still take their forgotten pill (immediately or at the next dose)	45.5 %
INR is a measure to check how thick or how thin the blood is	54.5 %
3 questions about NOAC (n = 95)	**%**
For patients taking NOAC, it is important to take their blood thinner at the same time every day	90.5 %
When AF patients taking NOAC have forgotten to take their blood thinner, they can still take that dose, unless the time till the next dose is less than the time after the missed dose	40.0 %
NOAC blood thinners come with a card, which AF patients have to show to their general practitioner and specialist	27.4 %

4 questions about DCC (n = 63)	%
AF can reoccur after a DCC (as AF will increasingly recur with ageing despite the DCC)	36.5 %
It is allowed to perform a DCC multiple times	22.2 %
A DCC can only be performed if there is no thrombus present in the heart and a transoesophageal echocardiography might be performed to rule this out	71.4 %
In some AF patients the arrhythmia is accepted making them no longer eligible for a DCC	28.6 %

4 questions about PVI (n = 57)	%
The success rate of a PVI procedure is about 70%-80%	52.6 %
In approximately 20% of the cases a second PVI procedure is necessary to stop AF permanently	43.9 %
A PVI procedure carries a risk for major complications of ≥1%	28.1 %
The possibility to stop OAC medication after PVI depends on risk factors to develop a stroke and not on the outcome of the PVI itself	56.1 %

AF: atrial fibrillation, DCC: direct current cardioversion, INR: international normalised ratio, JAKQ: Jessa Atrial fibrillation Knowledge Questionnaire, NOAC: non-vitamin K antagonist oral anticoagulant, OAC: oral anticoagulant, PVI: pulmonary vein isolation, VKA: vitamin K antagonist. * The JAKQ with questions and full answers can be obtained from the authors as the JAKQ is not in the public domain.

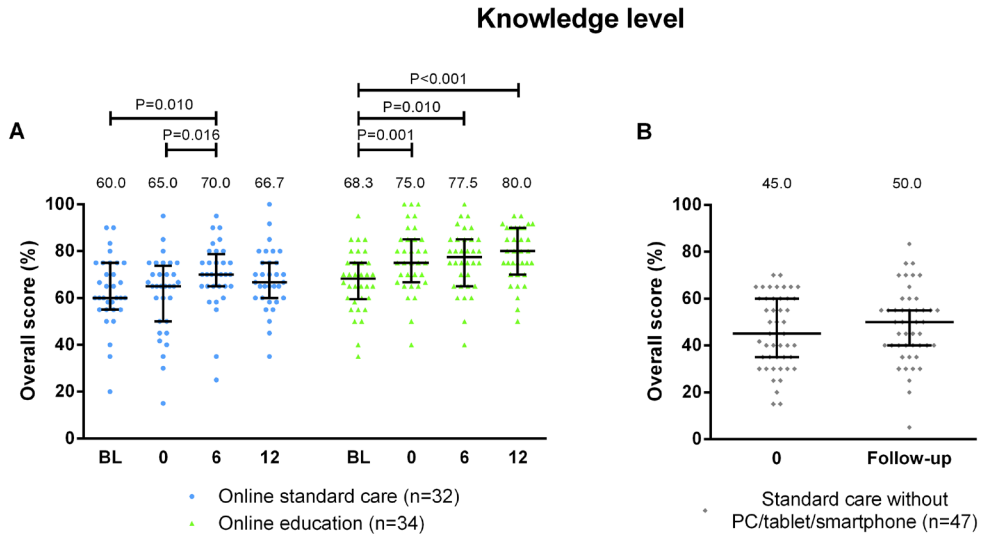

Figure 4.2: Overall knowledge level in the two online groups (A) and the standard care group without a computer/tablet/smartphone (B) over the course of the study. Patients in the online groups completed the questions at planning 1-3 weeks before hospitalization (baseline, BL); during their hospitalization (0); and 6 and 12 weeks post-procedurally. The standard care group without a computer/tablet/smartphone only completed the knowledge questions during hospitalization (0) and the follow-up visit. Significant P-values within each group are shown on the figures. Data are represented as scatter dot plots with indicated median and interquartile range. PC: portable computer.

Quality of life

Median (IQR) overall AFEQT score and treatment satisfaction score were similar in both online groups at baseline [standard care: 56.0 (46.3-78.2) and 54.2 (50.0-72.9), education: 61.6 (49.5-70.1) and 58.3 (47.9-75.0), P = 0.985 and P = 0.932, respectively] (Supplementary material, Figure S4.2). No significant changes were observed in both scores in the online standard care and online education group by the time of hospitalization (all P = 1.000). The overall AFEQT score and the treatment satisfaction score significantly increased in both online groups 6 and 12 weeks post-procedurally compared to baseline and at hospitalization (Supplementary material, Figure S4.2). In the group without an Internet supported device, there was no significant difference in overall AFEQT and treatment satisfaction score over time (P = 0.082 respectively P = 0.850). This group had however a significantly higher treatment satisfaction score at hospitalization compared to both online group (P = 0.014).

Feasibility and usability of the education platform

Of all patients approached to participate, 59.1% had a computer, tablet or smartphone, but 10% of them was not able to use the device themselves. Patients from the education group indicated that they used most frequently a personal computer (65.7%) to search for online information (Supplementary material, Figure S4.3). Based on user data, 60% of the patients visited the education platform only once but most patients (85.7%) studied the entire content of the course. One person (2.9%) did not visit the platform at all. On average, patients spent 27.7 ± 22.0 min on the platform. The time spent on the platform was not correlated with the increase in AF knowledge level (r_s = 0.278, P = 0.111).

User experience and patient reported outcome measures

Based on the user experience questionnaire, the online platform was positively rated by the patients for all aspects: attractiveness (1.56), perspicuity (1.68), efficiency (1.51), dependability (1.21), stimulation (1.65) and novelty (1.00) (Supplementary material, Figure S4.4).

Most patients (90.9%) would participate again in the study. The majority indicated that the platform was easy to use (87.9%), understandable (97.0%) and contained a good amount of information (87.9%). The majority found the education platform instructive (75.8%) although 24.2% indicated that they knew most information. Three out of four patients (72.7%) stated that an online platform was the preferred way to receive AF information, while 12.1% preferred brochures, 12.1% preferred information via their specialist only, and one patient (3.0%) had no need for extra information. Most patients (78.8%) confirmed the added value of an education platform that can be consulted repeatedly, while 18.2% considered a single visit to the platform sufficient, and one patient (3.0%) did not find the platform useful at all. Most patients (69.7%) stated that the study and the online platform motivated them to take better care of their own health. Finally, 81.8% indicated that it would be an added value if they would receive extra remote follow-up by means of questionnaires (e.g. about their symptoms) at regular time points.

DISCUSSION

This was a first study evaluating the usability and effectiveness of tailored education and remote follow-up via an online platform in AF patients.

Patient knowledge regarding atrial fibrillation and rhythm restoring procedures

In our hospital, no standardized AF educational program is implemented yet, but brochures about the interventions and AF in general are available on top of information by the cardiologist. Nevertheless, only in 53.3% of the cases, a brochure was handed out to the patients. A European survey in 2015 showed that only 22.7% of the cardiology centers have an information brochure about AF despite the fact that 43.4% stated that they had a structured educational program.[144]

In an average AF population, the mean knowledge score on the JAKQ is 55.8-61.6%.[147,149] Both online groups already scored better at baseline (mean score of 68.6% and 70.8%), while the group without an Internet compatible device scored worse (48.9%) compared to the general population. These deviations could be attributed to demographic differences: patients without a computer/tablet/smartphone were older and had a lower educational degree. Notwithstanding, education is at least as important in these elderly AF patients with an increased risk profile. A more tailored in-person approach, ideally making use of standardized questionnaires, can be used to provide these patients with the necessary information.[103,174]

In order to get an overview of the knowledge level of the entire AF population, patients without a compatible device and Internet access were not excluded from this study. Major knowledge gaps concerning AF in general and AF-related procedures in particular, were present in all study groups. Time constraints of physicians and the lack of appropriate and efficient educational interventions are likely the most important reasons.[122,125] Knowledge gaps concerning AF and OAC therapy were reported previously.[122-124,126-129,131-136,147-149,151] Knowledge deficits concerning AF-related procedures are less well investigated. Only Xu et al. evaluated the knowledge of 113 AF patients undergoing a catheter ablation.[129] In this study, 57% of the patients thought that a PVI procedure has a treatment efficacy of 100% and only 28% knew the complications of this procedure. Also in our study, the success rates of these procedures were overestimated and the possible risks underestimated. The present study was unique in revealing DCC-specific knowledge gaps. Also in a large survey of the AF AWARE group, patients indicated that they were less familiar with more specific issues like the role for DCC, AF ablation, and new medications, indicating the need for online platforms as evaluated in our study.[122]

E-learning and other tools for atrial fibrillation

Online or mobile education - especially when provided in a tailored way - could have a substantial added value on top of in-person education. It could bridge the gap between the cardiology clinic and the patients' home as patients are able to read through the information at their own pace and can consult the platform as frequently as they want.

There is an urgent need for more reliable sources giving patients balanced and unbiased information.[63,142] In the survey from the AF AWARE group, 51% of the physicians indicated that more patient information is warranted and 60% pinpointed that available information was poor and difficult to find for patients.[122] The Internet is increasingly consulted as a source of health-related information. Also in our study, 63.4% of the patients in the online groups had already searched for additional disease and procedure-related information via the Internet. Pandya et al. evaluated the available web-based English resources covering thromboprophylaxis in AF patients.[171] They concluded that websites often give imbalanced information of suboptimal quality: e.g. only 21.2% of the resources clearly mentioned that OAC therapy is often long term; hardly 21% discussed both stroke and bleeding risk factors; and only 18.2% cautioned patients regarding OAC use during surgery and/or dental procedures. Moreover, the benefit of stroke prevention with OAC was often overshadowed by focusing on information concerning bleeding risk.[171] This might confuse patients and impact their therapy belief and adherence.

The fact that the platform was available as a website as well as a mobile application together with the premise that patients only had access to personally relevant aspects, were major strengths of our study. Reliable and validated education apps for AF are scarce. In 2017, the CATCH ME Consortium developed the MyAF patient app.[175] The MyAF app aims to improve patient education, enhance communication between patients and healthcare providers, and encourage active patient involvement. Although this application is freely available, the impact on knowledge level and other parameters has never been evaluated. The mAF app (available in a version for patients and one for physicians) developed by Guo et al. integrates decision support, educational materials and patient involvement strategies with self-care protocols and structured follow-up.[152]

Possible impact of (tailored) online education in atrial fibrillation patients

This study showed that an online tailored platform led to a significant increase in knowledge level even before patients were hospitalized and with lasting effects up to 12 weeks post-procedurally. Patients had a better idea about the expected results of their rhythm restoring procedure and about the overall care before and after the intervention. Such improved knowledge contributes to shared decision making concerning treatment strategies. In the online standard care group,

knowledge was only improved for a short period (i.e. 6 weeks) after the procedure, likely due to aspects of the hospitalization. The previously mentioned mAF app pilot study showed improved AF-related knowledge in patients who completed the 1 and 3 month follow-up visits.[152] This application was also positively rated by the patients. Self-care, drug adherence and the prescription of medication for secondary prevention was improved in the mAF app group versus a usual care group.[152]

At hospitalization no impact of education or standard care was shown on the overall AFEQT and treatment satisfaction score in the online groups. These scores improved only post-procedurally representing the effect of the rhythm restoring procedure. The group without a computer/tablet/smartphone had already a significantly higher treatment satisfaction score at hospitalization which did not improve at follow-up. Similarly, the overall AFEQT score hardly improved during follow-up. The deviating results in this last group are possibly due to imbalances in baseline characteristics: patients underwent significantly more DCC procedures which are no permanent treatment solution; patients were older and maybe more inclined to accept the arrhythmia; patients suffered from more comorbidities that could overshadow the treatment effects.

The platform applied in this study could be used as a way to remotely follow-up AF patients (e.g. QOL, symptoms), which was indicated as an added value by 81.8% of the patients. E-health and m-health have a large potential to improve future healthcare and reduce the burden on the healthcare system in chronic patient populations such as AF, but these tools need to be validated in clinical practice before implementation.

Study limitations

The four procedure-related questions were not as extensively validated as the rest of the JAKQ, although the concept of questioning was the same. Nevertheless, the 20-item JAKQ showed a good internal consistency. Patients without a computer/tablet/smartphone were only able to complete the questionnaires when they were at the hospital, i.e. immediately pre-procedurally and during their control consultation. This impedes an exact comparison with the online groups that had an extra remote assessment moment 1-3 weeks before the procedure and an extra follow-up moment post-procedurally. When patients in the education group had to complete the questionnaires, their access to the platform was

temporarily blocked to make sure they did not look up the answers on the platform. However, patients were still able to search for correct answers on the Internet or get help from family members. This was also true for the online standard care group. Unfortunately, of all selected patients, about one in three were excluded or declined participation, which could have biased inclusion towards more motivated and knowledgeable patients. Moreover, in this study sample, it is difficult to make concrete conclusions about the contribution of tailored online education on QOL.

Future perspectives

Education in this study was tailored towards OAC therapy and rhythm restoring procedures. It could be expanded with many more educational aspects that can be activated in a patient-specific fashion: aspects concerning cardiovascular diseases (e.g. heart failure), topics concerning self-care and risk factor management (e.g. overweight, smoking). A communication tool to ask questions to the study center can also be implemented. As the online platform is available in a mobile application format, it can be extended with adherence reminders, AF detection with wearables, etc. Patients can be involved in the further development of this platform. A large randomized controlled trial will be needed to evaluate the impact of online tailored education and follow-up on long term outcome parameters, and study cost-effectiveness.

CONCLUSION

Our study shows that AF patients underestimate the risks associated with rhythm restoring procedures and overestimate the success rates of these treatments. Online tailored education significantly improved patients' AF-related and procedure-related knowledge with lasting effect after three months. The online platform was positively rated by the patients and the majority would like to receive future information via such a platform.

SUPPLEMENTARY MATERIAL

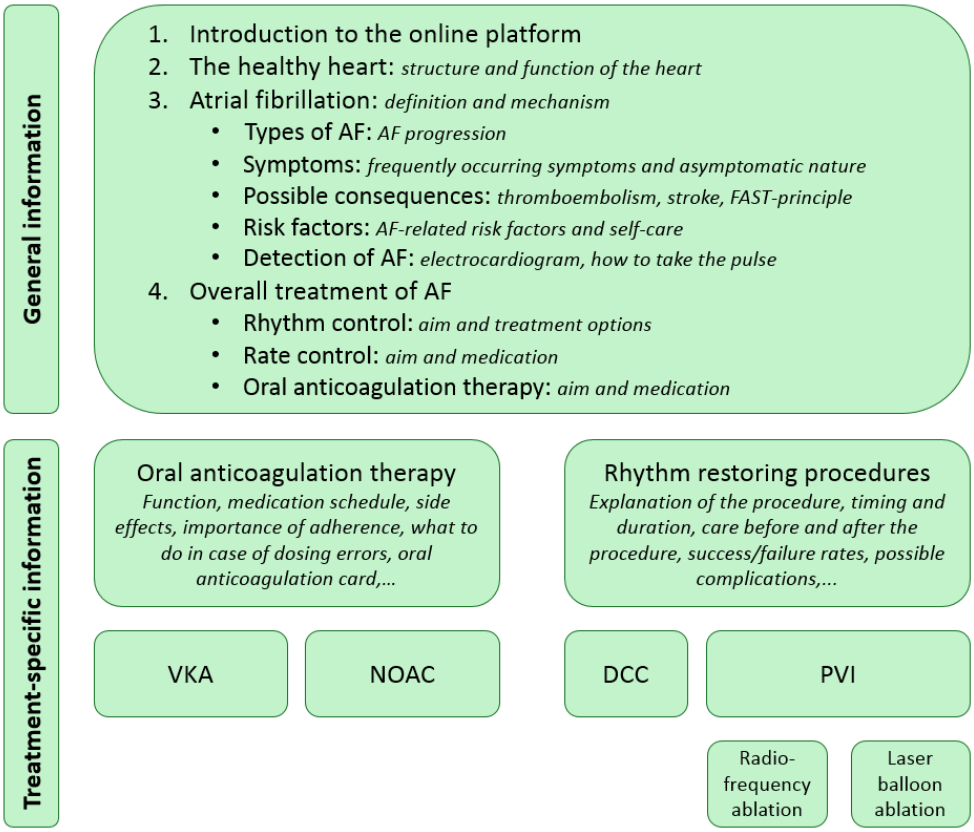

Figure S4.1: Different educational topics covered on the online platform. AF: atrial fibrillation, DCC: direct current cardioversion, NOAC: non-vitamin K antagonist oral anticoagulant, OAC: oral anticoagulation, VKA: vitamin K antagonist, PVI: pulmonary vein isolation (Cryoballoon ablation is not performed in our center).

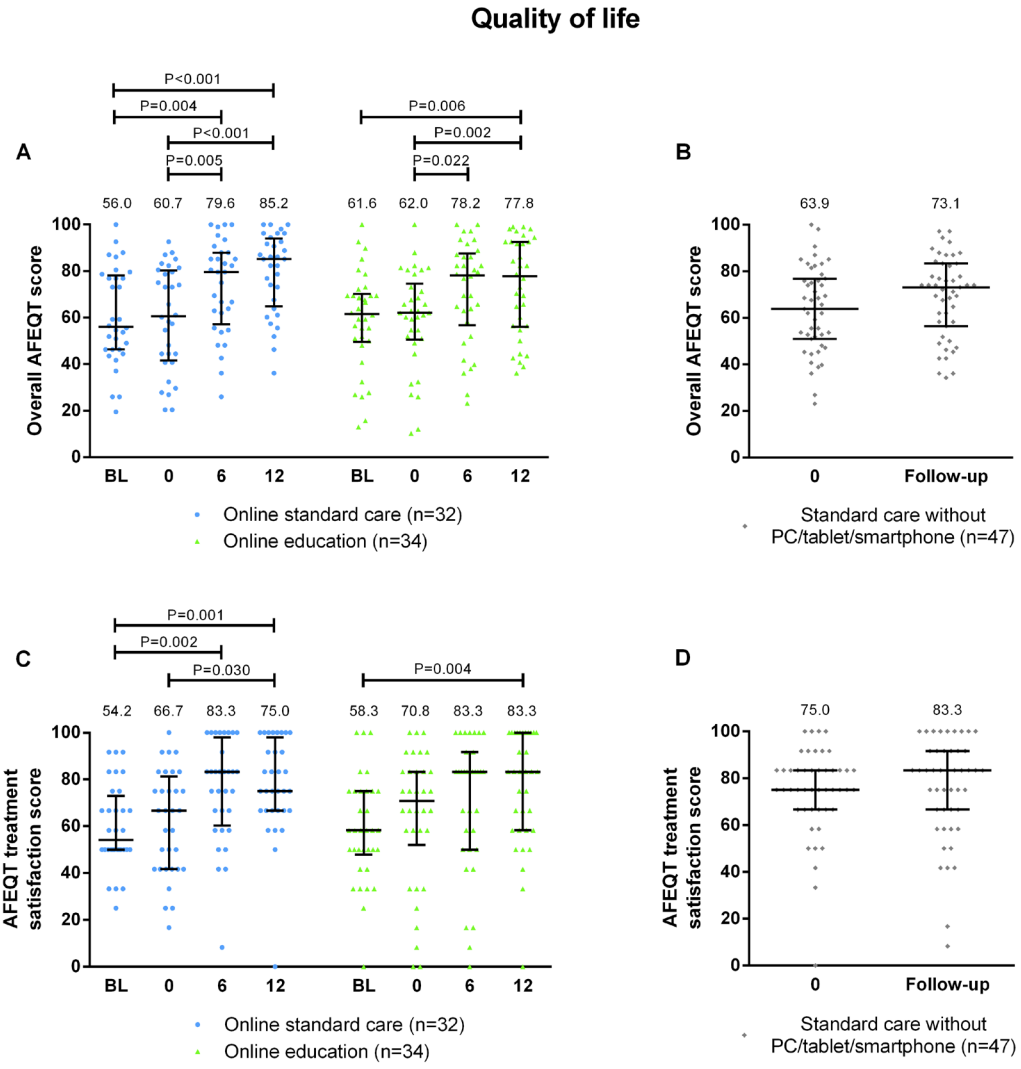

Figure S4.2: Overall AFEQT score and AFEQT treatment satisfaction score in the two online groups (A and C, respectively) and the standard care group without a computer/tablet/smartphone (B and D, respectively) during the different follow-up moments. Patients in the online groups completed the questions at planning 1-3 weeks before hospitalization (baseline, BL); during their hospitalization (0); and 6 and 12 weeks post-procedurally. The standard care group without a computer/tablet/smartphone only completed the questionnaire during hospitalization (0) and the follow-up visit. Significant P-values within each group are displayed on the figures. Data are represented as scatter dot plots with indicated median and interquartile range. PC: portable computer.

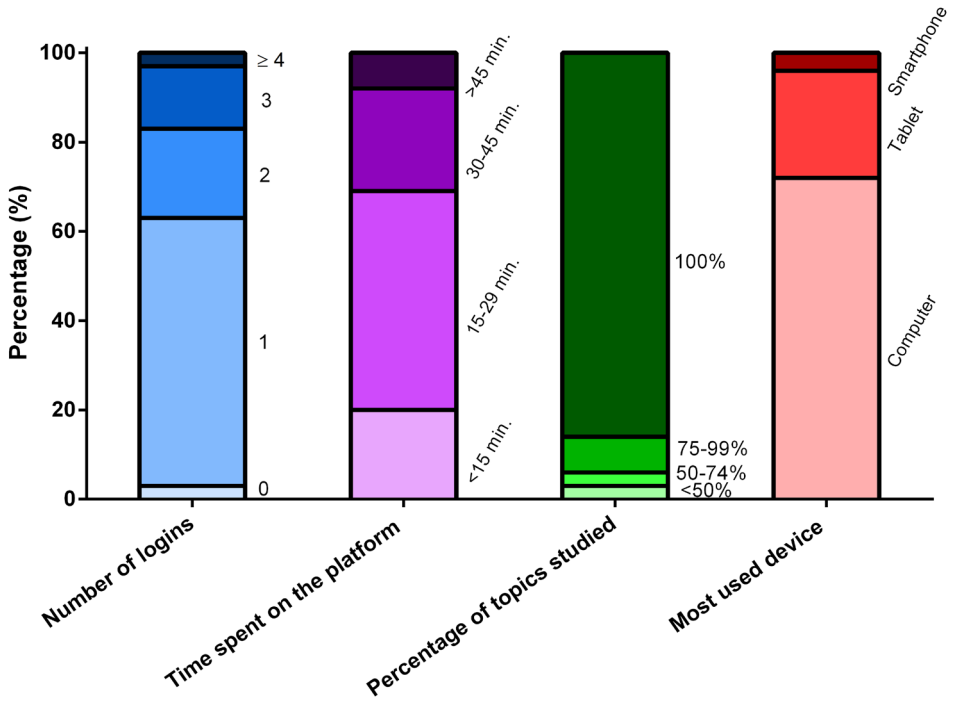

Figure S4.3: Overview of the user data of the patients who had access to the online education platform.

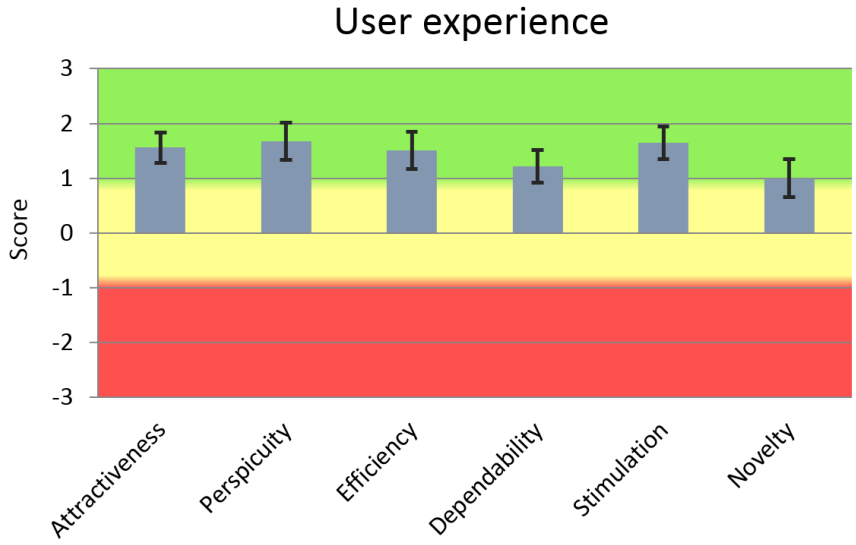

Figure S4.4: Scores on the user experience questionnaire completed by the intervention group to evaluate the online education platform. Green = positive (>0.8), yellow = neutral (between -0.8 and 0.8), red = negative (<-0.8). Perspicuity: i.e. clarity and ease at becoming familiar with the platform.

Table S4.1: Overview of the knowledge level in the two online groups and the standard care group without a computer/tablet/smartphone over the course of the study. Overall knowledge score, Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ) subscore and procedure-related subscore are shown. Patients in the online groups completed the questions at planning 1-3 weeks before hospitalization (baseline, BL); during their hospitalization (0); and 6 and 12 weeks post-procedurally. The standard care group without a computer/tablet/smartphone only completed the knowledge questions during hospitalization (0) and the follow-up visit. Significant P-values within each group are shown. Data are represented as mean with standard deviation (SD) and median with interquartile range (IQR).

	Online standard care (n=32)			**Online education (n=34)**			**Standard care without computer/tablet/smartphone (n=47)**		
	Mean ± SD	**Median (IQR)**	**P-value**	**Mean ± SD**	**Median (IQR)**	**P-value**	**Mean ± SD**	**Median (IQR)**	**P-value**
Overall knowledge score (%)									
Baseline (BL)	62.9 ± 14.9	60.0 (55.0 - 75.0)	BL-0: 1.000	67.1 ± 13.0	68.3 (59.6 - 75.0)	**BL-0: 0.001**	-	-	
Hospitalization (0)	61.6 ± 16.9	65.0 (50.0 - 73.8)	**BL-6: 0.010** BL-12: 0.199	76.6 ± 13.9	75.0 (66.7 - 85.0)	**BL-6: 0.010** **BL-12: <0.001**	45.9 ± 15.5	45.0 (35.0 - 60.0)	0-follow-up: 0.248
6 weeks post-procedurally (6)	69.7 ± 14.2	70.0 (65.0 - 78.8)	**0-6: 0.016** 0-12: 0.283	76.1 ± 13.2	77.5 (65.0 - 85.0)	0-6: 1.000 0-12: 1.000	48.5 ± 15.7	50.0 (40.0 - 55.0)	
12 weeks post-procedurally (12)	67.7 ± 13.1	66.7 (60.0 - 75.0)	6-12: 1.000	78.5 ± 11.6	80.0 (70.0 - 90.0)	6-12: 1.000			
JAKQ subscore (%)									
Baseline (BL)	68.6 ± 15.3	75.0 (62.5 - 81.3)	BL-0: 1.000	70.8 ± 12.0	71.9 (62.5 - 81.3)	**BL-0: 0.045**	-	-	
Hospitalization (0)	63.7 ± 16.9	65.6 (56.3 - 75.0)	BL-6: 0.252 BL-12: 1.000	77.6 ± 12.5	75.0 (68.8 - 87.5)	BL-6: 0.145 **BL-12: 0.010**	48.9 ± 15.5	50.0 (37.5 – 62.5)	0-follow-up: 0.279
6 weeks post-procedurally (6)	73.2 ± 13.7	75.0 (68.8 - 85.9)	**0-6: 0.026** 0-12: 0.728	77.8 ± 11.2	81.3 (68.8 - 87.5)	0-6: 1.000 0-12: 1.000	51.3 ± 16.5	50.0 (43.8 - 56.3)	
12 weeks post-procedurally (12)	70.7 ± 12.0	75.0 (62.5 - 75.0)	6-12: 1.000	79.6 ± 10.7	81.3 (68.8 - 87.5)	6-12: 1.000			
Procedure-related subscore (%)									
Baseline (BL)	43.8 ± 28.4	50.0 (25.0 - 50.0)	BL-0: 0.800	52.9 ± 25.2	50.0 (50.0 - 75.0)	**BL-0: 0.004**	-	-	
Hospitalization (0)	53.1 ± 31.6	50.0 (25.0 - 75.0)	BL-6: 0.354 BL-12: 0.156	73.5 ± 28.8	75.0 (50.0 - 100.0)	BL-6: 0.059 **BL-12: 0.007**	34.0 ± 25.8	25.0 (25.0 - 50.0)	0-follow-up: 0.323
6 weeks post-procedurally (6)	57.8 ± 28.7	50.0 (50.0 - 75.0)	0-6: 1.000 0-12: 1.000	70.6 ± 27.2	75.0 (50.0 - 100.0)	0-6: 1.000 0-12: 1.000	37.2 ± 23.2	50.0 (25.0 - 50.0)	
12 weeks post-procedurally (12)	57.0 ± 27.1	50.0 (31.3 - 75.0)	6-12: 1.000	73.5 ± 27.5	75.0 (68.8 - 100.0)	6-12: 1.000			

PART 3

Adherence to oral anticoagulation medication

Chapter 5

Telemonitoring-based feedback improves adherence to non-vitamin K antagonist oral anticoagulants intake in patients with atrial fibrillation

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ABSTRACT

Aims

To evaluate the effect of telemonitoring on adherence to non-vitamin K antagonist oral anticoagulants (NOACs) in atrial fibrillation (AF) patients.

Methods and results

A randomized, single-blind, crossover, controlled trial in 48 AF patients on once or twice daily (OD or BID) NOAC. The Medication Event Monitoring System tracked NOAC intake during three phases of 3 months each: daily telemonitoring, telemonitoring with immediate telephone feedback in case of intake errors, and an observation phase without daily transmissions. Unprotected days were defined as ≥3 or ≥1 consecutively missed doses for a BID or OD NOAC, respectively, or excess dose intake. Cost-effectiveness was calculated based on anticipated stroke reduction derived from patients' risk profile and measured intake. Persistence over the entire study was 98%. Telemonitoring-only already led to very high taking and regimen adherence (97.4% respectively 93.8%). Nevertheless, direct feedback further improved both to 99.0% and 96.8%, respectively ($P < 0.001$ respectively $P = 0.002$). Observation without daily monitoring resulted in a significant waning of taking adherence (94.3%; $P = 0.049$). Taking adherence was significantly higher for OD compared to BID NOAC, although unprotected days were similar. Feedback intervention had an incremental cost of €344289 to prevent one stroke, but this could be as low as €15488 in high-risk patients with low adherence and optimized technology.

Conclusion

Telemonitoring resulted in high NOAC adherence due to the notion of being watched, as evidenced by the rapid decline during the observation period. Feedback further optimized adherence. Telemonitoring with or without feedback may be a cost-effective approach in high-risk patients deemed poorly adherent.

INTRODUCTION

Treatment with oral anticoagulation (OAC) therapy is of pivotal importance to prevent stroke and thromboembolism in atrial fibrillation (AF) patients.[63] More than 82% of AF patients receive OAC therapy in daily practice.[137] Since NOACs have shown an improved net clinical outcome compared to vitamin K antagonists (VKA), these drugs are now recommended as first choice therapy for thromboembolic prevention in patients with non-valvular AF.[63,141]

Given the short half-lives of NOACs, correct adherence to the prescribed medication regimen is a critical factor for their safety and effectiveness.[141,176,177] Non-adherence or failed persistence can result in poor clinical outcomes and associated increased health care costs.[170,178] Since systematic monitoring of anticoagulation or medication intake is not performed in NOAC patients (unlike international normalized ratio follow-up in VKA patients), non-adherence may remain undetected and uncorrected.

To date, interventions to improve adherence to NOACs in AF patients are almost absent and/or have shown to be not effective.[179] As a result, there is a need for new initiatives to measure and optimize NOAC therapy adherence.

The aim of this study was to investigate the effect of in-person feedback, based on daily telemonitoring of medication intake, on adherence to NOACs in AF patients. Such a strategy of direct feedback has never been evaluated for NOAC therapy. We assessed its feasibility, effectiveness, and potential health-economic impact.

METHODS

Study design and participants

Consecutive AF patients already taking or initiating the once daily (OD) NOAC rivaroxaban or the twice daily (BID) NOAC apixaban were recruited for this single-blind, crossover, randomized controlled trial (RCT). Dabigatran could not be used with the telemonitoring system (as it should be stored in the original package in order to protect it from moisture); edoxaban was not yet approved for use. Patients had to complete three phases of 3 months each **(Figure 5.1)**. All patients

initially received telemonitoring with daily automatic transmissions about their NOAC intake but were randomized to personalized feedback in case of suboptimal adherence or not. Stratification occurred by gender and time since start of NOAC therapy. Patients were crossed over after 3 months. Thereafter, all patients went through a purely observational phase in which medication intake was recorded but not transmitted daily (only read-out after 3 months). The study was conducted in compliance with the Declaration of Helsinki. Ethics approval for the study was obtained from the local ethics committee, and all patients provided written informed consent.

Procedure and measurements

Adherence to NOACs was measured using the electronic Medication Event Monitoring System (MEMS, WestRock, Switzerland). This is a special cap that fits on a medication bottle recording the exact date and time of bottle openings. For the first two telemonitoring phases, patients had to place the medication bottle with the MEMS cap on a wireless reader after each medication intake. Subsequently, the information from the cap was wirelessly and automatically transmitted to an Internet server. A MEMS cap without a display and without showing the medication intake was used in this study. Using the medAmigo software, the medical study team reviewed the adherence data daily on weekdays. This online evaluation allowed to directly give feedback to the patient during the 'feedback phase'. For the last observation phase, patients had to hand in the wireless reader and only used their MEMS medication bottle which still registered daily intake but without the notable telemonitoring transmissions.

During the feedback phase, patients received a phone call in case of an 'unprotected day' (≥3 or ≥1 consecutively missed doses for a BID or OD NOAC, respectively, or excess doses during the prior 24 h).[164] Corrective actions were discussed with the patient, conform to the guidelines.[141] Taking adherence (i.e. proportion of prescribed doses taken), regimen adherence (i.e. proportion of days with the correct number of doses taken), and number of unprotected days were calculated based on the MEMS data assuming that every bottle opening represents a medication intake.[180] Pill counts and a refill of the medication bottle were performed after each phase. Morisky scale (MMAS-8), a self-report adherence

measure, was completed by the patients at the beginning of each visit.[181-183] After 9 months, patients completed a questionnaire about their study experience.

Cost-effectiveness analysis

Time investment measurements for MEMS refill visits, daily evaluations of the transferred data, annotating adherence irregularities in the software and direct telephone feedback were converted into total personnel costs (including a 56.6% general overhead cost, as proposed by the national health technology assessment agency).[184] Together with the devices and calling cost, total provider costs were calculated for both observation and feedback phases. These costs were converted into an estimated incremental cost per yearly preventable stroke, given that 70.84% of the strokes can be prevented using proper OAC therapy with NOACs (i.e. 19% reduction in strokes using NOAC[185] in addition to 64% stroke reduction with VKA[116]). Adherence to NOAC therapy in the large RCTs was considered as an estimated regimen adherence of 88.51%.[179] This value was adopted from the control group of the AEGEAN trial, as no other reliable prospective data or adherence data from the four NOAC RCTs are present.[179] Estimated incremental cost per yearly preventable stroke was calculated based on the adherence percentage revealed by this study. The yearly expected stroke risk of included patients was estimated by their average CHA_2DS_2-VASc score.[186] Stroke is associated with a financial burden of €8943 per hospital episode per patient, based on reimbursement payments made to Belgian hospitals.[43] Base case calculations were modified using different study parameters and cost simulation scenarios as well as variable baseline adherence measurements.

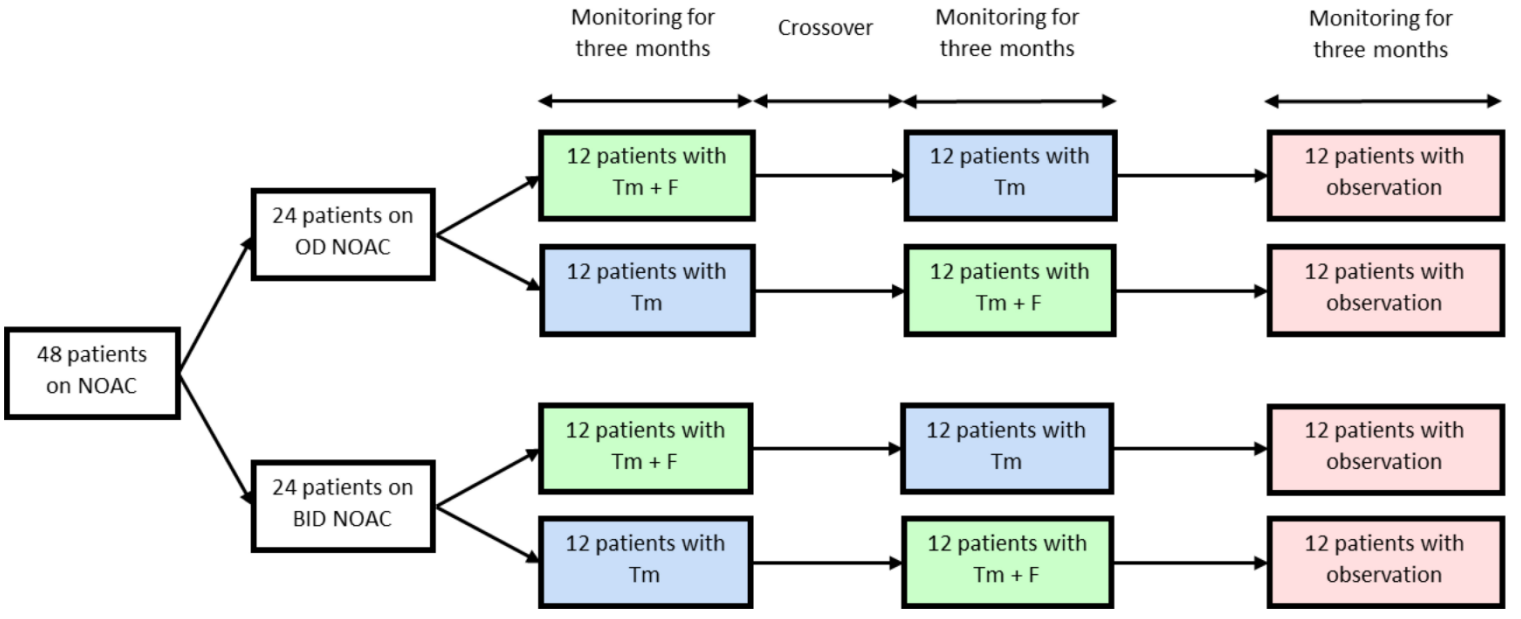


Figure 5.1: The study design consisted of three periods of 3 months each, with a crossover between the first two study periods. BID: 'bis in die' or twice a day, NOAC: non-vitamin K antagonist oral anticoagulant, OD: 'omne in die' or once a day, Tm: telemonitoring phase, Tm+F: telemonitoring with additional feedback phase.

Statistics

Statistical analyses were performed using SPSS 24.0 (SPSS Inc, Chicago, IL, USA). Normality of distribution was assessed using the Shapiro–Wilk test. To investigate the effect between telemonitoring and telemonitoring-based feedback on adherence, appropriate Mann–Whitney U tests were used in accordance to the crossover design. The effect of the observation phase was analysed using the Friedman tests. Differences in adherence and number of telephone calls between OD and BID NOAC patients were analysed with the Mann–Whitney U tests. Correlations between adherence measures and MMAS-8 score were calculated using the Spearman's rho. A result characterized by P-value <0.05 was considered statistically significant. Additional and detailed analyses are described in the Supplementary material.

RESULTS

Patient population

Fifty-seven AF patients on apixaban or rivaroxaban were invited to participate, of whom 48 (mean age 72 ± 9 years) were included **(Table 5.1; Figure 5.2)**. No patient stopped OAC treatment during the 9 months study period. Only one patient was switched from apixaban to VKA after 3 months due to thrombosis of the subclavian vein secondary to a pacemaker lead (i.e. persistence of 98%) despite a high taking (97.9%) and regimen (93.8%) adherence.

Table 5.1: Characteristics of atrial fibrillation patients.

	All AF patients (n = 48)	Patients on a BID NOAC (n = 24)	Patients on a OD NOAC (n = 24)
Age, mean ±SD	71.6 ± 8.6	73.1 ± 8.5	70.2 ± 8.5
Male, n (%)	24 (50.0)	12 (50.0)	12 (50.0)
Highest level of education completed, n (%)			
Primary school	18 (37.5)	11 (45.8)	7 (29.2)
Secondary school	20 (41.7)	8 (33.3)	12 (50.0)
College or University	10 (20.8)	5 (20.8)	5 (20.8)
Kind of AF, n (%)			
First AF episode	7 (14.6)	4 (16.7)	3 (12.5)
Paroxysmal AF	24 (50.0)	11 (45.8)	13 (54.2)
Persistent AF	7 (14.6)	2 (8.3)	5 (20.8)
Permanent AF	7 (14.6)	5 (20.8)	2 (8.3)
Predominant atrial flutter	3 (6.3)	2 (8.3)	1 (4.2)
CHA_2DS_2-VASc score, mean ±SD	3.3 ± 1.2	3.6 ± 1.2	3.0 ± 1.2
HAS-BLED score, mean ±SD	1.0 ± 0.5	1.2 ± 0.6	0.9 ± 0.5
Time since AF diagnosis, n (%)			
< 1 month	9 (18.8)	4 (16.7)	5 (20.8)
1 month – 1 year	8 (16.7)	3 (12.5)	5 (20.8)
1 year – 5 years	13 (27.1)	7 (29.2)	6 (25.0)
> 5 years	18 (37.5)	10 (41.7)	8 (33.3)
Employment status, n (%)			
Working	5 (10.4)	2 (8.3)	3 (12.5)
Not working	2 (4.2)	0 (0.0)	2 (8.3)
Retired	41 (85.4)	22 (91.7)	19 (79.2)
Smoking status, n (%)			
Current smoker	5 (10.4)	1 (4.2)	4 (16.7)
Ex-smoker	24 (50.0)	12 (50.0)	12 (50.0)
Never-smoked	19 (39.6)	11 (45.8)	8 (33.3)
Married/cohabiting, n (%)			
Yes	43 (89.6)	20 (83.3)	23 (95.8)
No	5 (10.4)	4 (16.7)	1 (4.2)
Time since start NOAC, n (%)			
< 6 weeks	24 (50.0)	12 (50.0)	12 (50.0)
6 months – 1 year	10 (20.8)	5 (20.8)	5 (20.8)
> 1 year	14 (29.2)	7 (29.2)	7 (29.2)
Previous VKA, n (%)			
Yes	15 (31.2)	8 (33.3)	7 (29.2)
No	33 (68.8)	16 (66.7)	17 (70.8)
Using a pill organiser, n (%)			
Day box	6 (12.5)	3 (12.5)	3 (12.5)
Week box	21 (43.8)	13 (54.2)	8 (33.3)
No	21 (43.8)	8 (33.3)	13 (54.2)
Number of medications each day, mean ±SD	5.4 ± 2.0	5.7 ± 1.9	5.2 ± 2.1
Number of pills each day, mean ±SD	6.5 ± 2.6	7.1 ± 2.3	6.0 ± 2.7

AF: atrial fibrillation, BID: bis in die or twice daily, NOAC: non-vitamin K antagonist oral anticoagulant, OD: omne in die or once daily, SD: standard deviation, VKA: vitamin K antagonist.

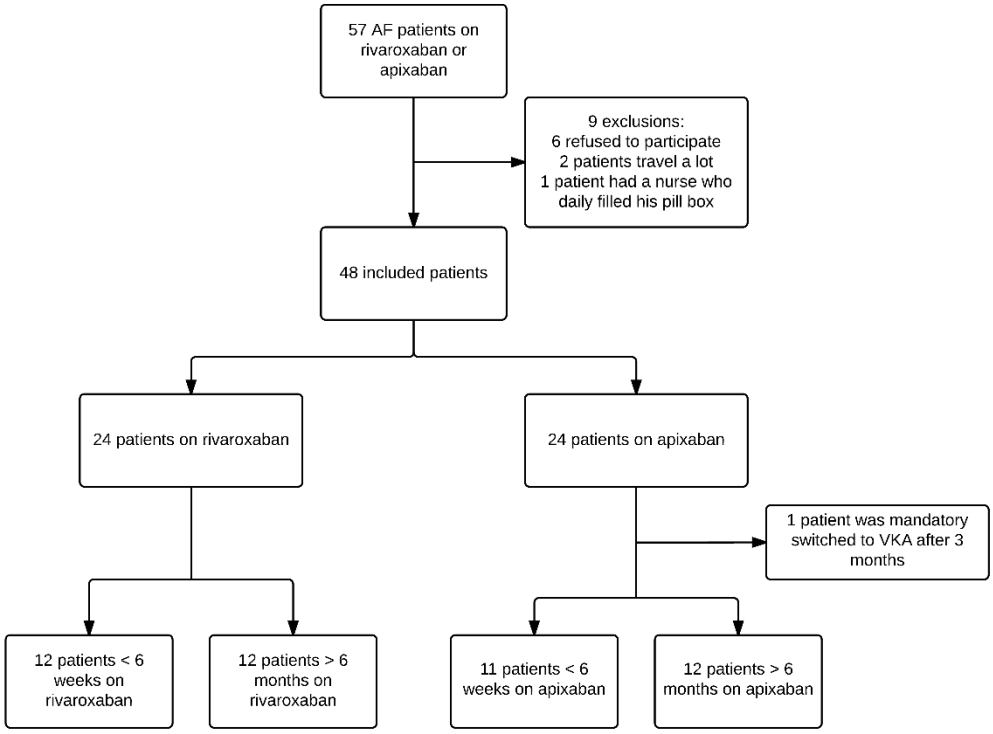


Figure 5.2: Flow chart of the inclusion of study patients. AF: atrial fibrillation, VKA: vitamin K antagonist.

Effect of telemonitoring-based feedback compared to active telemonitoring

Active telemonitoring already led to a very high taking and regimen adherence (97.4% vs. 93.8%, respectively) (Supplementary material, Figure S5.1). There were only 2.6 unprotected days during 3 months. Pill count-based adherence was 97.9%. Adherence further improved through direct feedback: taking adherence increased to 99.0% ($P < 0.001$), regimen adherence to 96.8% ($P = 0.002$), and pill count to 99.0% ($P = 0.002$). The number of unprotected days decreased to 1.5 ($P = 0.153$). During the active telemonitoring and feedback phases, taking adherence was higher with the OD NOAC ($P = 0.002$ respectively $P = 0.014$) although unprotected days were similar ($P = 0.272$ respectively $P = 0.251$) (Supplementary material, Figure S5.2). Direct feedback significantly improved taking adherence ($P = 0.002$), regimen adherence ($P = 0.002$), and pill count (P

= 0.001) in the BID NOAC patients where there were no significant effects in the OD NOAC patients (Supplementary material, Figure S5.2). No period effects (observed differences between the first two periods irrespective of the intervention) were found in patients on a BID NOAC, while evidence for period effects was present concerning the regimen adherence (P = 0.016) and unprotected days (P = 0.019) in OD NOAC patients.

Effect of the observation phase

Adherence data of seven patients were excluded for the analyses of the observation phase. These patients did not stop NOAC treatment but used the MEMS bottle incorrectly (they used the medication in the MEMS bottle to refill their own pill organizer). Adherence values in the remaining 40 AF patients declined during the observation phase **(Figure 5.3)**. There was a significant decrease in taking adherence from 99.1% to 94.3% (P = 0.049) and pill count from 99.1% to 96.7% (P = 0.013) compared to the feedback phase.

The observation phase was characterized by a significantly higher number of unprotected days due to missed doses (105 of the 3499 monitored days) compared to the telemonitoring phase (45/3631) and the telemonitoring-based feedback phase (19/3647; P < 0.001). There was however no significant difference in the number of unprotected days due to excess doses between the three phases (59 for the observation phase, 58 for the telemonitoring phase and 44 for the feedback phase; P = 0.203).

Mean MMAS-8 score was 7.4 ± 0.9 during telemonitoring, 7.8 ± 0.4 during telemonitoring-based feedback, and 7.6 ± 0.5 during the observation phase. The score was an indicator for the adherence during the observation phase, as it was significantly correlated with taking adherence (r_s = 0.453; P = 0.003), regimen adherence (r_s = 0.498; P = 0.001), unprotected days (r_s = -0.474; P = 0.002), and pill count (r_s= 0.630; P < 0.001).

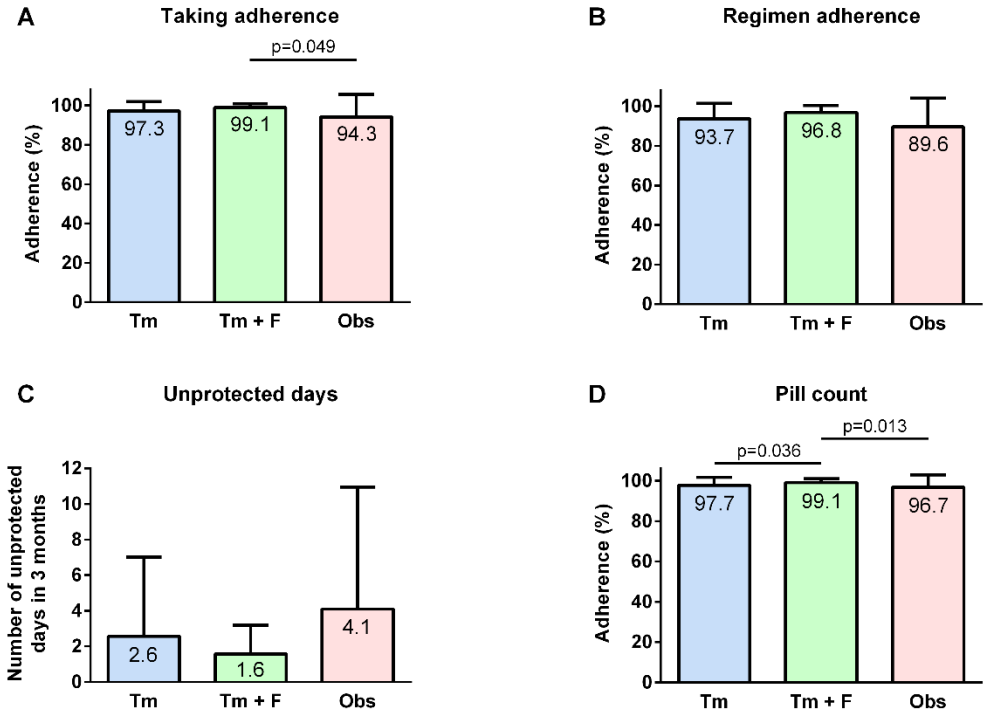


Figure 5.3: Mean adherence measures during the telemonitoring (Tm), telemonitoring with additional feedback (Tm + F) and observation (Obs) phase in 40 AF patients who correctly used the MEMS device during all three phases (i.e. three patients on apixaban and four patients on rivaroxaban used the medication in the MEMS bottle to refill their own pill organizer during the observation phase and were therefore not included in this analysis). Adherence measures are analysed as **(A)** taking adherence, **(B)** regimen adherence, **(C)** unprotected days, and **(D)** pill count.

Time investments and provided feedback

Daily telemonitoring for 3 months took an average time for the nursing staff of 31 min per patient. To annotate all adherence irregularities in the medAmigo software another 17 min were needed. Direct feedback required 115 phone calls during 3 months, 47.8% triggered by an overdosing and 52.2% by an underdosing. This often revealed patient explanations for the observed irregularity like: (i) data was not sent in due time, while a bottle opening was registered (21.7%), (ii) the patient had no concrete explanation (18.3%), and (iii) the patient took more pills at once out of the MEMS bottle as provision for the following days (12.2%) (Supplementary material, Table S5.1). Only in 11.3% of the phone calls, the

adherence irregularity was admitted by the patient and corrected when possible. Patients on rivaroxaban were called significantly more often compared to patients taking apixaban (P = 0.006). Another 203 phone calls were performed for other reasons than an unprotected day (Supplementary material, Table S5.2), like follow-up on study visits (72.4%), patients asking advice about the dose, intake schedule or temporary pausing of the NOAC (8.4%), and patients asking if telemonitoring data could check whether he/she took his/her NOAC (3.0%).

Cost-effectiveness analysis

To provide observation for 1 year and 100 patients, a total cost of €16374 would be needed (Supplementary material, Table S5.3). For active telemonitoring with direct feedback, the costs increase to €75419. Included patients had an anticipated yearly stroke risk of 3.7% (mean CHA_2DS_2-VASc score of 3.3). Non-vitamin K antagonist oral anticoagulant therapy at a base case regimen adherence level of 89.6% could reduce this incidence to 1.04%. Assuming a linear gain in efficacy with increasing regimen adherence, feedback-induced improved adherence could reduce the yearly stroke risk further to 0.83%. Therefore, the incremental cost to prevent one stroke in this population would be €344289/year (€75419 cost for feedback-based monitoring minus €1909 for reduced stroke cost, for 0.21 prevented strokes).

Our study showed that telemonitoring-based feedback led to a relative increase in regimen adherence of 69.5% of the maximal possible adherence gain (89.6% to 96.8%). If real-world patients would start with a lower adherence, feedback could lead to a higher absolute gain in regimen adherence. Although total costs would increase (due to more frequent feedback interventions), the cost per percentage increase in regimen adherence would decrease (Supplementary material, Table S5.4; **Figure 5.4A**). The cost per prevented stroke decreases when baseline adherence in the population is lower **(Figure 5.4B)**. Combined with a smarter software system and reduced telemonitoring device cost, the incremental cost to prevent one stroke would be only €15488/year in patients with a mean CHA_2DS_2-VASc of 5 having a baseline adherence of 70%. The cost-effectiveness of different scenarios is summarized in **Table 5.2** and **Figure 5.5**.

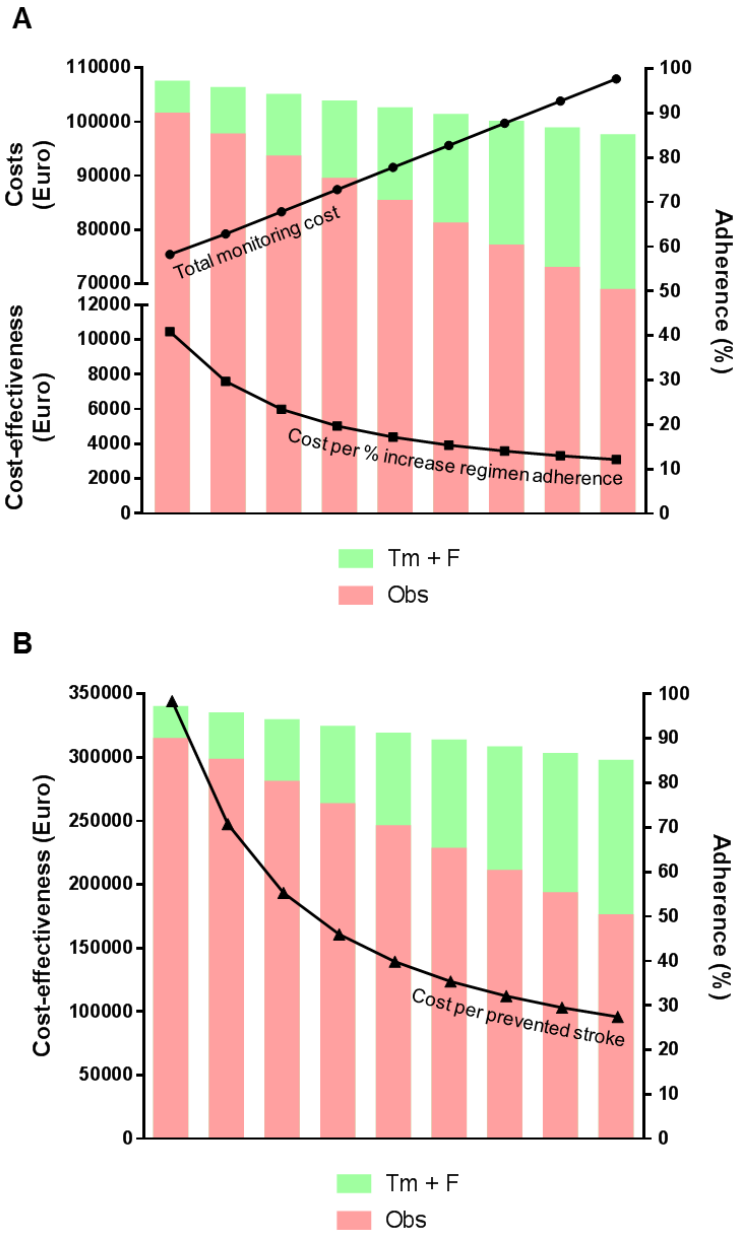


Figure 5.4: Simulations of cost scenarios associated with the provision of telemonitoring with direct feedback to 100 AF patients with different baseline adherence levels for 1 year. Baseline taking adherence levels (i.e. adherence during the observation phase) are depicted in red. Additional gain in adherence due to telemonitoring-based feedback is represented in green. **(A)** Total monitoring costs and costs per percentage gain in regimen adherence are plotted against the different adherence percentages. **(B)** Incremental costs per prevented stroke are shown for each adherence scenario. Obs: observation, Tm + F: telemonitoring with additional feedback.

Table 5.2: Costs per prevented stroke for different simulations in 100 patients receiving telemonitoring with direct personalized feedback for 1 year.

	Mean regimen adherence (%)		Variable study parameters			Costs (Euro)			Number of strokes per year (n)			Cost per prevented stroke
	Baseline	With Tm+F	CHA_2DS_2-VASc	% device cost	Number of nursing visits	Total Tm+F cost	Reduced stroke cost	Net cost	With baseline adherence	Remaining with Tm+F	Prevented with Tm+F	
Base case	89.6	96.8	3.3	100	5	75419	1909	73510	1.04	0.83	0.21	344289
Different simulations												
1. Reduced device costs	89.6	96.8	3.3	*25*	5	39419	1909	37510	1.04	0.83	0.21	175681
2. Reduced nursing visits	89.6	96.8	3.3	100	*3*	72494	1909	70584	1.04	0.83	0.21	330586
3. Decreased baseline adherence of 70%	*70.0*	*90.9*	3.3	100	5	91533	5524	86009	1.63	1.01	0.62	139245
4. Decreased baseline adherence of 50%	*50.0*	*84.8*	3.3	100	5	107950	9206	98744	2.22	1.19	1.03	95917
5. Mean CHA_2DS_2-VASc=4	89.6	96.8	*4.0*	100	5	75419	2838	72581	1.56	1.24	0.32	228686
6. Mean CHA_2DS_2-VASc=5	89.6	96.8	*5.0*	100	5	75419	4335	71084	2.37	1.89	0.48	146647
7. BID patients	*87.7*	*95.8*	3.3	100	5	74557	2153	72404	1.04	0.80	0.24	300734
8. OD patients	*91.6*	*97.9*	3.3	100	5	76282	1688	74614	1.04	0.86	0.18	399936
9. Smarter software system reducing the telemonitoring time needed with 70%*	89.6	96.8	3.3	100	5	64410	1909	62501	1.04	0.83	0.21	292727
10. Combination of 1, 2 and 9	89.6	96.8	3.3	*25*	*3*	25484	1909	23575	1.04	0.83	0.21	110415
11. Combination of 1, 2, 3 and 9	*70.0*	*90.9*	3.3	*25*	*3*	34260	5524	28736	1.63	1.01	0.62	46523
12. Combination of 1, 2, 3, 5 and 9	*70.0*	*90.9*	*4.0*	*25*	*3*	34260	8211	26049	2.42	1.50	0.92	28370
13. Combination of 1, 2, 3, 6 and 9	*70.0*	*90.9*	*5.0*	*25*	*3*	34260	12541	21719	3.69	2.29	1.40	15488
14. Base case but no initiation or persistence for one year	*0.0*	96.8	3.3	100	5	75419	25666	49753	3.7	0.83	2.87	17336

Varying regimen adherence and study parameters for each of the 14 different scenarios are indicated in italics.

BID: bis in die or twice daily, OD: omne in die or once daily, Tm + F: telemonitoring with direct personalized feedback.

*During this study, adherence data of every patient was viewed in detail on a daily basis. The software can be made smarter, e.g. by giving automatic alerts for patients with an unprotected day, reducing the telemonitoring time with 70%. More complex automatic decision algorithms can further reduce the need for nurse interventions.

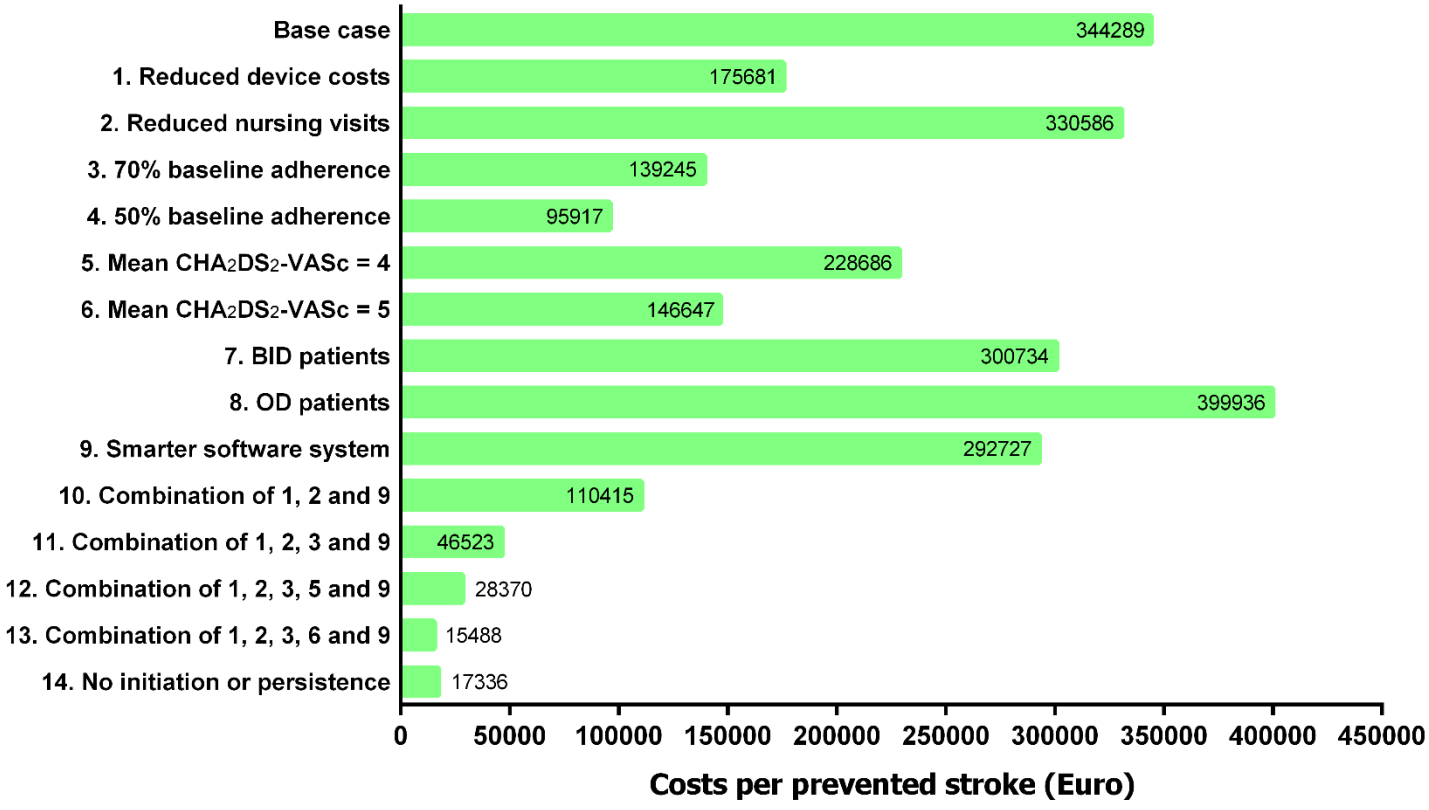


Figure 5.5: Different scenarios showing the incremental costs per prevented stroke when study parameters or associated costs would change. Figures are based on 100 patients receiving telemonitoring with personalized direct feedback for 1 year. BID: 'bis in die' or twice a day, OD: 'omne in die' or once daily.

Patient reported experience

Most patients (87.2%) found the MEMS practical to use and 97.6% of those who received a phone call indicated telephone feedback as useful (Supplementary material, Figure S5.3). Moreover, 63.8% mentioned that the study increased their awareness about a strict medication adherence, largely attributed to the telemonitoring aspect. Two in three patients indicated that the study motivated them to take their medication more correctly in the future.

DISCUSSION

This is the first report on using automatic telemonitoring and closed-loop patient feedback (in analogy with telemonitoring of cardiac implanted devices) as a tool to document and enhance adherence to correct NOAC intake.

Adherence and persistence to NOACs

One of the most accurate ways to measure medication adherence is via electronic monitoring devices, such as the MEMS.[170] Adherence values for NOACs are mostly based on administrative claims and often retrospectively collected.[187,188] Yao et al. found that only 47.5% of 26471 AF patients initiating on NOAC had a period of days covered (PDC) ≥80% after 1 year.[177] Prescription data from Germany showed that 61.4% of AF patients initiated on rivaroxaban, and 49.5% of dabigatran users had a PDC ≥80% after 180 days.[189] It is doubtful if a PDC value ≥80% is an acceptable adherence value in NOACs as the effect of missed doses may be more severe due to the short half-life of these drugs. Besides our study, the AEGEAN study is the only prospective trial evaluating the implementation of NOACs in daily care using electronic monitoring. Although reported in 2015, it has not been published so far. AEGEAN showed an adherence to apixaban of 88.51% and a persistence of 90.5% in AF patients receiving standard care after 24 weeks of electronic monitoring.[179] This adherence value is similar compared to the 89.6% taking adherence obtained during the observation phase of our trial. It is still not known how representative these data are for real-world adherence to NOACs. Intriguingly, the four large NOAC RCTs did not report (pill count-based) adherence rates. They only reported discontinuation rates, which varied between 18 and 34% after 2–3 years follow-

up.[187,188] In general, discontinuation rates remain very high, and it is important to resolve this problem.[187-191] Telemonitoring-based feedback can contribute to this as we showed a high persistence of 98% after 9 months.

It is known that an OD dosing regimen is associated with higher adherence.[170,192,193] Our study confirmed this in NOAC patients as a higher taking and regimen adherence was found in patients on rivaroxaban during both telemonitoring phases. However, this was not accompanied by a significant difference in unprotected days between both NOAC regimen. In contrast, patients taking rivaroxaban required significantly more telephone calls for an unprotected day. This affirms theoretical considerations that although an OD regimen is the best from an adherence perspective, it may not necessarily be superior to prevent thromboembolic complications as a BID NOAC regimen could be more forgiving for missed or extra doses.[164] However, the effect of different NOAC dosing regimens on clinical outcomes and safety still remains to be investigated. More research is also needed concerning the effect of adherence rates and unprotected periods on thromboembolic events in NOAC patients. Short-term interruption of NOACs for invasive procedures may not place the patient at a substantially increased risk for cardiovascular or bleeding event,[194] although this does not exclude a potential clinical relevance of repetitive such periods.

Interventions to increase adherence

The very high adherence values obtained in this study, already in the absence of feedback, are possibly due to the patients' knowing that their adherence was monitored on a daily basis ('radar effect'). Additional phone calls strengthened this feeling, even though in only 11.3% of the phone calls the adherence irregularity was admitted by the patient. A review by Demonceau et al. concluded that an intervention with patient feedback based on electronically monitored adherence data (without direct feedback) could increase medication adherence with 8.8%.[195] Although there was not much room for improvement, our study showed that regimen adherence increased with 4.1% during active telemonitoring and with 7.2% using additional direct feedback.

Adherence is a problem worsening over time.[196] One could wonder if telemonitoring should be continued long-term to maintain those very high adherence rates. This requires further study. Another option could be to use this

intervention during initiation in order to ensure a correct implementation of the regimen. An alternative is to screen for poorly adherent patients by providing them with a MEMS for a short period without telemonitoring and/or via the Morisky scale. Patients showing poor adherence would qualify for telemonitoring-based feedback.

Two other trials already tried to improve the adherence rate for NOACs. The AEGEAN study did not show any impact of an educational program on the adherence for apixaban.[179] The educational program consisted of an educational booklet, reminder tools, and follow-up telephone calls by a virtual clinic. Besides the increased awareness due to the used electronic monitoring device, there were also many planned study visits creating an extra follow-up effect in both the usual care and education group. A possible missed opportunity of AEGEAN was to use the adherence data captured by the electronic devices to provide patient feedback as part of the educational intervention. In a recent study by Labovitz et al., 19 NOAC patients were randomized to an intervention group receiving an artificial intelligence application that visually identified the patient, the medication and the confirmed ingestion or to a control group.[197] Visual confirmation of NOAC administration using the app showed a 90.1% adherence after 12weeks. Pill count-based adherence revealed a value of 90.9% in the control group and 96.4% in the intervention group. Plasma samples taken four times throughout the study showed that 33% of the patients in the control and 100% of those in the intervention group had a drug concentration level above the minimum required therapeutic range.[197]

Although not prospectively evaluated, Shore et al. found that pharmacist-based activities (i.e. follow-up and monitoring of adverse events and adherence) led to improved dabigatran adherence.[198] Some studies tried to improve the adherence for VKA; however, results were disappointing.[187,199] It is still not clear which interventions are the best to optimize adherence to OAC therapy. The European Heart Rhythm Association proposed the development of structured systems to improve AF care, including medication adherence.[141] A possible way is via nurse-coordinated AF clinics.[97] Dedicated nurses can not only discuss adherence issues and advise aids to ensure medication persistence but can also follow-up on renal function, NOAC dosing and adverse events, provide education, etc.[140,141]

Cost-effectiveness

If non-adherence to NOACs translates into worse outcomes, it also affects health care costs.[177] We have estimated the cost to prevent one stroke using telemonitoring-based feedback assuming a direct relationship between adherence and stroke. Using simulation, we have highlighted the different elements that have an impact on this figure. We did not include saved costs for reduced bleeding events, since there is no data relating bleeding to the degree of NOAC adherence. Our data show that telemonitoring will only be cost-effective when higher risk, lower adherent patient groups are targeted, and when technology would become cheaper. Apart from the initial hospitalization costs, we did not include costs for stroke rehabilitation or medical follow-up visits, due to the paucity of reliable data. Moreover, a MEMS device is capable to monitor adherence for 3 years, making this intervention more cost-effective when used long-term.

Study limitations

Although this study was limited by its sample size, it was correctly sized to give a good indication about the effects on adherence and time investments of direct telemonitoring-based feedback. There was almost no patient selection bias, as only 15.8% of the patients had to be excluded or was not willing to participate. One can argue that our study design should have included also an observation phase as the first phase, whereas it was only used now as the last phase. The design was decided out of concern that patients would not use the MEMS bottle correctly without the daily monitoring phases first. In retrospect, it would have been more opportune to schedule this phase also as the first, or in random order, since it is conceivable that the adherence values during the observation phase at the end were higher than in real practice. This was most likely due to the 6 months of study experience of the patients which helped them to develop adherence improving habits, outweighing the fact that adherence tends to decrease over time.

Future perspectives

This is the first study proposing a validated approach that can be used to maximize adherence to NOACs, but its impact should be confirmed in a larger RCT. However, one intervention may not fit all patients. New interventions and technologies to enhance adherence need to be developed and tested, ideally in large prospective RCTs taking into account clinical outcomes as a primary endpoint.

CONCLUSION

Electronic monitoring revealed an unexpectedly high adherence to NOAC therapy in an elderly unselected population. This may be due to highly motivated patients but certainly also to the sense of being watched by technology. Nevertheless, telemonitoring-based rapid and personalized feedback further optimized adherence. Such intervention seems cost-effective when higher risk, poorly adherent patient groups are targeted and when the used technology would become cheaper.

ACKNOWLEDGMENT

WestRock Switzerland Ltd supported this study with devices and free access to the Medigo software platform, but they were not involved in study planning, conduct, analysis or reporting.

SUPPLEMENTARY MATERIAL

Supplementary Methods

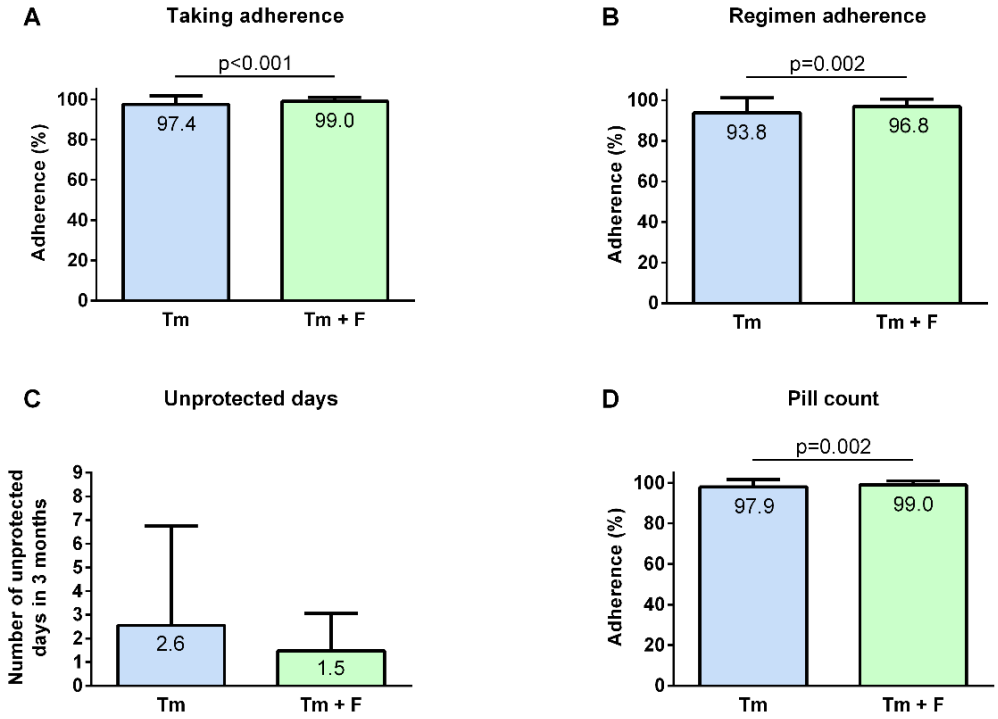
Statistical and cost-effectiveness analyses

Continuous variables were reported as mean ± standard deviation and categorical variables as numbers and percentages. In case calculated adherence percentages were >100% for pill count and taking adherence, adherence was traced to 100%. Appropriate Mann-Whitney U tests were applied to the within-subject differences, to evaluate the effect of telemonitoring and telemonitoring-based feedback on adherence. This way, possible period effects, due to the crossover design of the study, were taken into account. See for example: "Putt M.E. and Chinchilli V.M. Non-parametric Approaches to the Analysis of Crossover Studies. Statistical Science. 2004;19(4):713-719". Moreover, under the assumption that potential carry-over effects go in the same direction as the underlying true feedback effects, it can be shown that only the power of the tests may be affected, see: "Senn S. Crossover Designs. Encyclopedia of Biostatistics. 2005;2:127-144". Possible period effects in patients receiving a once or a twice daily NOAC were analysed by means of a Mann-Whitney U test on the crossover differences. To evaluate the effect of the third observation phase, Friedman tests were used taking the repeated measures design into account. The results are discussed assuming that: a) The intervention effect will be the same for the patients on a once daily NOAC and patients on a twice daily NOAC; b) Potential period effects will be equal for both patients on a once daily NOAC and patients on a twice daily NOAC. Unfortunately, because of the design of the study, the effect of the observation phase is still confounded with the third period effect. It is therefore impossible to attribute the observed results of the observation phase solely to the telemonitoring-based feedback intervention.

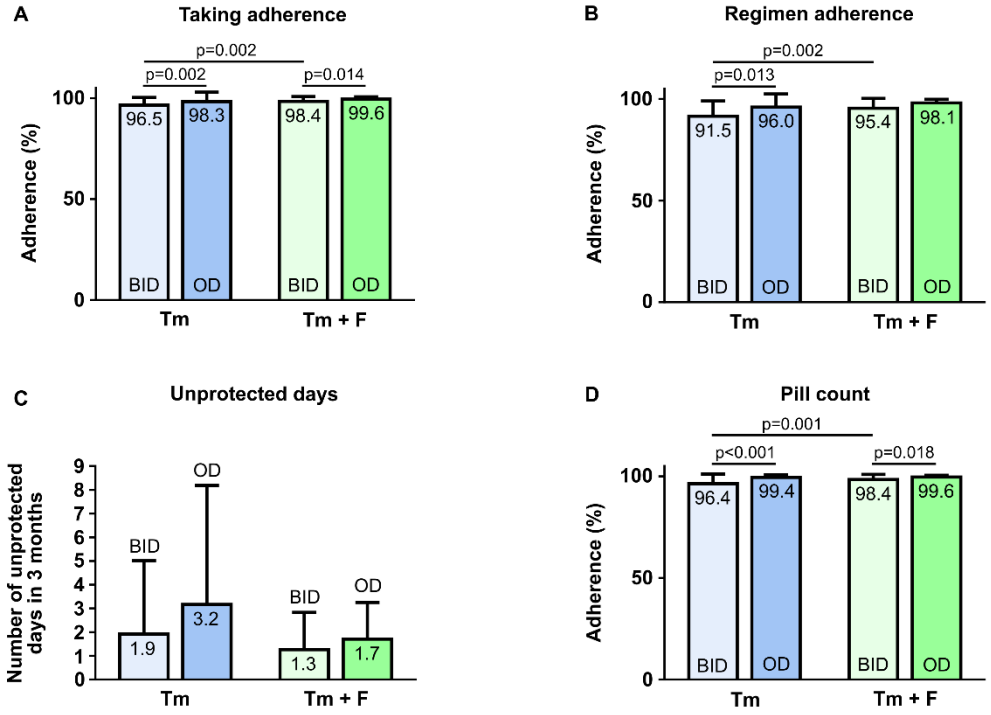
Various data were used to perform the cost-effectiveness analyses based on Belgian health care data: a) total provider cost for the observation and feedback phase (the cost for an intervention of 3 months) was extrapolated to a time period of 1 year and 100 patients; b) yearly expected stroke rate was based on the CHA_2DS_2-VASc score (event-rates per 100 patient-years); c) saved costs per prevented hospital episode for one stroke per patient were based on official Belgian cost data; d) regimen adherence data as measured in our study. Given that, based on literature, 70.84% of the strokes can be prevented with a regimen adherence rate of 88.51%, estimated incremental cost per yearly preventable stroke was calculated for the regimen adherence rate measured during the feedback phase of this study (as the base case scenario).

$$\text{Incremental cost per yearly preventable stroke} = \frac{\text{Cost for telemonitoring based feedback} - \text{Reduced stroke cost}}{\text{Number of prevented strokes per year}}$$

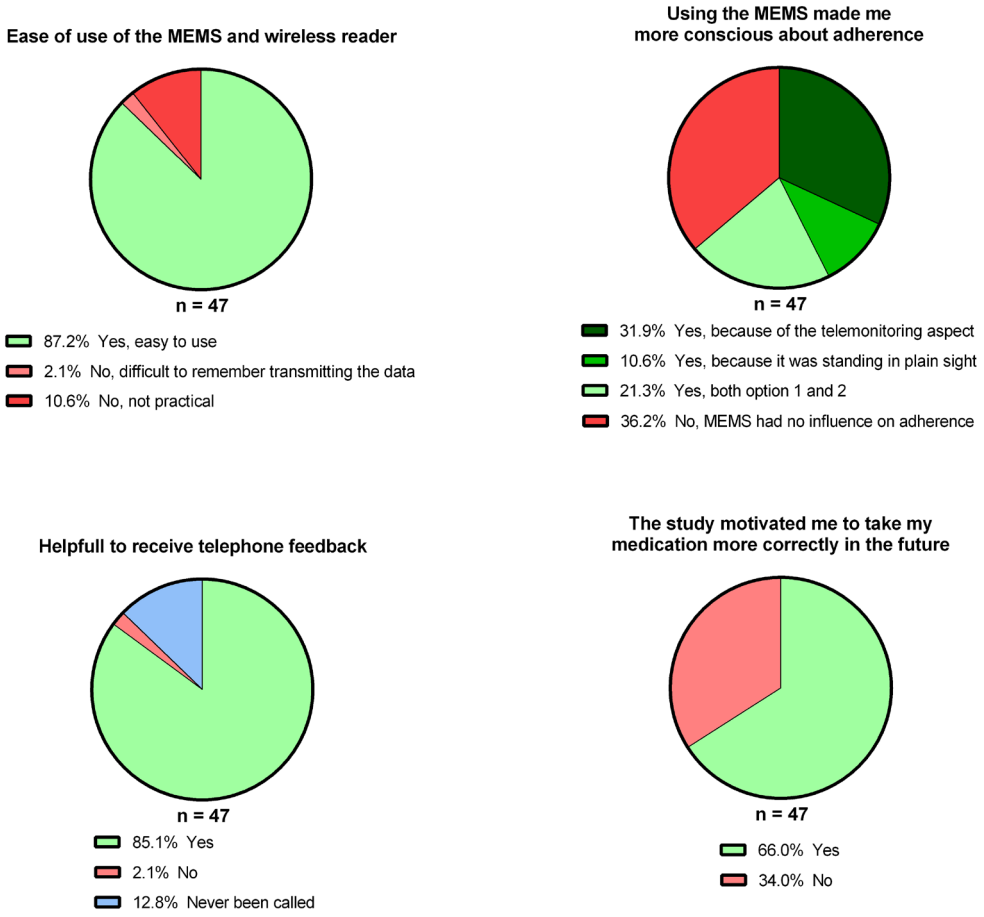
Different sensitivity simulations for this base case calculation were made for various study parameters or a combination of those: a) device cost (the used telemonitoring devices are early development units. Since the manufacturer estimates that the price of the devices could become as low as 25% of the current values, a cost-effectiveness simulation scenario was calculated for a quarter of the current device cost); b) reduced nursing visits (three visits instead of five per year); c) different baseline adherence values (assuming a linear gain/loss in efficacy of the NOAC for stroke prevention with increasing/decreasing regimen adherence); d) patient populations with other average CHA_2DS_2-VASc scores; e) once or twice daily dosing regimens; f) 70% reduced telemonitoring time with smarter software system.



Supplementary Figure S5.1: Adherence measures during the telemonitoring (Tm) and telemonitoring with additional feedback (Tm + F) phase in 47 AF patients. Adherence measures are analysed as **(A)** Taking adherence, **(B)** Regimen adherence, **(C)** Unprotected days, and **(D)** Pill count.



Supplementary Figure S5.2: Difference in adherence between patients on a twice daily NOAC (n=23) and patients on a once daily NOAC (n=24) during the telemonitoring (Tm) and telemonitoring-based feedback phase (Tm + F). Adherence data are represented as **(A)** Taking adherence, **(B)** Regimen adherence, **(C)** Unprotected days, and **(D)** Pill count.



Supplementary Figure S5.3: Pie charts representing the patient's reported experience. The represented data was extracted from the questionnaires that had to be completed at the end of the study. MEMS: Medication Event Monitoring System.

Supplementary Table S5.1: Overview of time investments for providing feedback for an unprotected day, listing the explanations provided by patients.

Telephone calls		Call for overdosing or underdosing (%)	Explanation of the patient for the 'unprotected day'
n (%) of the calls (total calls=115)	n (%) of the time (total time=413 min)		
25 calls **(21.7%)**	107 min **(25.9%)**	Underdosing: 100% Overdosing: 0%	Data was not sent in due time, but after the resending of the data a bottle opening was registered.
21 calls **(18.3%)**	61 min **(14.8%)**	Underdosing: 14.3% Overdosing: 85.7%	Patient had no concrete explanation.
14 calls **(12.2%)**	68 min **(16.5%)**	Underdosing: 57.1% Overdosing: 42.9%	The patient took more pills at once out of the MEMS bottle for the next days.
13 calls **(11.3%)**	37 min **(9.0%)**	Underdosing: 0% Overdosing: 100%	The medication bottle was opened by another person or the patient showed the system to someone else.
13 calls **(11.3%)**	33 min **(8.0%)**	Underdosing: 76.9% Overdosing: 23.1%	**The unprotected period was admitted by the patient and was corrected when possible (according to the EHRA Practical Guide on the use of NOAC for AF)**
10 calls **(8.7%)**	44 min **(10.6%)**	Underdosing: 100% Overdosing: 0%	The patient was not taking his medication from the MEMS bottle but from his own blisters pack (mostly due to holiday).
7 calls **(6.1%)**	26 min **(6.3%)**	Underdosing: 0% Overdosing: 100%	The patient himself was counting the pills in the bottle.
7 calls **(6.1%)**	17 min **(4.1%)**	Underdosing: 0% Overdosing: 100%	The patient was testing the medication bottle and MEMS cap.
3 calls **(2.6%)**	15 min **(3.6%)**	Underdosing: 100% Overdosing: 0%	The NOAC was stopped temporarily and correctly due to surgery or a another intervention.
2 calls **(1.7%)**	5 min **(1.2%)**	Underdosing: 50% Overdosing: 50%	Other reasons

AF: atrial fibrillation, EHRA: European Heart Rhythm Association, NOAC: non-vitamin K antagonist oral anticoagulant.

Supplementary Table S5.2: Overview of the time investments and reasons for telephone calls other than feedback for unprotected periods.

Telephone calls		Reason of the telephone call
n (%) of the calls (total calls=203)	**n (%) of the time (total time=539 min)**	
147 calls **(72.4%)**	347 min **(64.4%)**	Planning, changing or reminding patients to their follow-up appointment.
17 calls **(8.4%)**	62 min **(11.5%)**	**Patient asked advice about the dose, intake schedule or temporary pausing the NOAC.**
15 calls **(7.4%)**	57 min **(10.6%)**	Technical difficulties or advice using the MEMS bottle or wireless reader.
7 calls **(3.4%)**	18 min **(3.3%)**	Patient notified the study team of an intervention or surgery in the near future which requires a temporarily stop of the NOAC.
6 calls **(3.0%)**	12 min **(2.2%)**	**Patient asked for the telemonitoring data to confirm if he/she took his/her NOAC.**
11 calls **(5.4%)**	43 min **(8.0%)**	Other reasons

NOAC: non-vitamin K antagonist oral anticoagulant.

Supplementary Table S5.3: Time investments and hospital costs in 100 patients who receive observation or telemonitoring-based feedback for 1 year.

	Cumulative time nurse (min)			Cumulative costs (Euro)				Total cost (Euro)	Mean adherence % (increase in adherence/decrease in unprotected days compared to the observation phase)*			Cost per % increase in adherence or per decrease in one unprotected day (Euro)
	Visit	Telemonitoring + medAmigo	Telephone feedback	Nurse + overhead	MEMS + software	Wireless reader	Calling costs		Taking adherence	Regimen adherence	Unprotected days	
Observation												
All patients	7500	-	1160	7194	9140	-	40	**16374**	94.3%	**89.6%**	4.1	-
Patients on a BID NOAC	7500	-	1160	7194	9140	-	40	16374	95.4%	87.7%	4.0	-
Patients on an OD NOAC	7500	-	1160	7194	9140	-	40	16374	93.2%	91.6%	4.3	-
Telemonitoring based feedback												
All patients	7500	18932	5000	26111	9140	40000	168	**75419**	99.1% (+4.8%)	**96.8%** (+7.2%)	1.6 (-2.5)	Taking adh.: 15811 Regimen adh.: 10460 Unpr. days: 29928
Patients on a BID NOAC	7500	18932	4000	25281	9140	40000	136	74557	98.6% (+3.2%)	95.8% (+8.1%)	1.3 (-2.7)	Taking adh.: 23154 Regimen adh.: 9171 Unpr. days: 28135
Patients on an OD NOAC	7500	18932	6000	26942	9140	40000	200	76282	99.5% (+6.3%)	97.9% (+6.3%)	1.9 (-2.4)	Taking adh.: 12089 Regimen adh.: 12108 Unpr. days: 31784

Data is based on time investments made during the observation phase in 40 patients and the telemonitoring-based feedback phase in 48 patients. Time and hospital costs for an intervention of 3 months were extrapolated to a time period of 1 year. The calculations are based on Belgian healthcare data and exclude the cost of the anticoagulation therapy itself.

A total of five visits with a nurse were taken into account in this cost simulation including a baseline visit and follow-up visits every 3 months.

*Mean increase in adherence or decrease in unprotected periods due to telemonitoring-based feedback is based on data of 40 patients who perfectly completed all three phases.

BID: bis in die or twice daily, MEMS: medication event monitoring system, NOAC: non-vitamin K antagonist oral anticoagulant, OD: omne in die or once daily.

Supplementary Table S5.4: Simulations of scenarios of different baseline adherences and the associated time investments and provider costs in 100 patients who receive additional telemonitoring-based feedback for 1 year.

	Cumulative time nurse (min)				Cumulative costs (Euro)				Total cost (Euro)	Mean regimen adherence % and increase in regimen adherence compared to the observation phase*			Cost per % increase in regimen adherence (Euro)
	Visit	Telemoni-toring	MedAmigo	Telephone feedback	Nurse + overhead	MEMS + software	Wireless reader	Calling costs		Obs	Tm + F	Increase in adherence	
Baseline adherence of **89.63%**	*7500*	*12266*	6666	5000	26111	*9140*	*40000*	168	**75419**	89.63	96.84	**7.21**	**10460**
Baseline adherence of **85%**	*7500*	*12266*	9642	6537	29860	*9140*	*40000*	220	**79220**	85.00	95.43	**10.43**	**7596**
Baseline adherence of **80%**	*7500*	*12266*	12856	8196	33909	*9140*	*40000*	275	**83324**	80.00	93.91	**13.91**	**5992**
Baseline adherence of **75%**	*7500*	*12266*	16070	9856	37958	*9140*	*40000*	331	**87429**	75.00	92.38	**17.38**	**5030**
Baseline adherence of **70%**	*7500*	*12266*	19284	11515	42006	*9140*	*40000*	387	**91533**	70.00	90.86	**20.86**	**4388**
Baseline adherence of **65%**	*7500*	*12266*	22499	13174	46055	*9140*	*40000*	443	**95637**	65.00	89.33	**24.33**	**3930**
Baseline adherence of **60%**	*7500*	*12266*	25713	14834	50103	*9140*	*40000*	498	**99742**	60.00	87.81	**27.81**	**3586**
Baseline adherence of **55%**	*7500*	*12266*	28927	16493	54152	*9140*	*40000*	554	**103846**	55.00	86.29	**31.29**	**3319**
Baseline adherence of **50%**	*7500*	*12266*	32141	18153	58200	*9140*	*40000*	610	**107950**	50.00	84.76	**34.76**	**3105**

Data is based on time investments made during the observation phase in 40 patients and the telemonitoring-based feedback phase in 48 patients.

A total of five visits with a nurse were taken into account in this cost simulation including a baseline visit and follow-up visits every 3 months.

* Mean increase in taking adherence due to telemonitoring-based feedback assuming that adherence can be increased with 69.5% compared to the maximal possible adherence gain. Analysis is based on the data of 40 patients who perfectly completed all three phases.

Important numbers are indicated in bold and fixed costs are in italics.

MEMS: Medication Event Monitoring System, Obs: observation, Tm + F: telemonitoring with additional feedback.

Chapter 6

The Health Buddies app as a novel tool to improve adherence and knowledge in atrial fibrillation patients: a pilot study

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JMIR Mhealth and Uhealth

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ABSTRACT

Background

Atrial fibrillation (AF) constitutes an important risk for stroke, especially in an ageing population. A new app (Health Buddies) was developed as a tool to improve adherence to non-vitamin K antagonist oral anticoagulants (NOACs) in an elderly AF population by providing a virtual contract with their grandchildren, spelling out daily challenges for both.

Objective

The aim of this pilot study was to assess the feasibility and usability of the Health Buddies app in AF patients.

Methods

Two workshops were conducted to steer app development and to test a first prototype. The feasibility of the finalized app was investigated by assessing the number of eligible AF patients (based on current prescription of NOACs, the presence of grandchildren between 5 and 15 years old, availability of a mobile phone, computer, or tablet), and the proportion of those who were willing to participate. Participants had to use the app for 3 months. The motivation of the patients to use the app was assessed based on the number of logins to the app. Their perception of its usefulness was examined by specific questionnaires. Additionally, the effects on knowledge level about AF and its treatment, and adherence to NOAC intake were investigated.

Results

Out of 830 screened AF patients, 410 were taking NOACs and 114 were eligible for inclusion. However, only 3.7% (15/410) of the total NOAC population or 13.2% of the eligible patients (15/114) were willing to participate. The main reasons for not participating were no interest to participate in general or in the concept in particular (29/99, 29.3%), not feeling comfortable using technology (22/99, 22.2%), no interest by the grandchildren or their parents (20/99, 20.2%), or a too busy lifestyle (12/99, 12.1%). App use significantly decreased towards the end of the study period in both patients ($P = 0.009$) and grandchildren ($P < 0.001$). NOAC adherence showed a taking adherence and regimen adherence of

88.6 ± 15.4% and 81.8 ± 18.7%, respectively. Knowledge level increased from 64.6 ± 14.7% to 70.4 ± 10.4% after 3 months P = 0.09. The app scored positively on clarity, novelty, stimulation, and attractiveness as measured with the user experience questionnaire. Patients evaluated the educational aspect of this app as a capital gain.

Conclusions

Only a small proportion of the current AF population seems eligible for the innovative Health Buddies app in its current form. Although the app was positively rated by its users, a large subset of patients was not willing to participate in this study or to use the app. Efforts have to be made to expand the target group in the future.

INTRODUCTION

Medication nonadherence in general is an important aspect requiring attention as it increases complications, hospitalizations, and hence is associated with avoidable health care costs.[170] However, interventions to improve adherence have shown mixed results and the most effective strategy in different populations remains unclear.[200] mHealth and eHealth solutions to assist medication management and to enhance adherence are gaining interest, with some promising results in different chronic diseases, including some cardiovascular diseases.[201-205]

Specific data about adherence-improving interventions in atrial fibrillation (AF) patients are very scarce and interventions are often ineffective.[187] AF, the most common cardiac arrhythmia affecting about 3% of the adult population, is associated with an increased risk for stroke.[63,206] Therefore, the majority of AF patients have to take oral anticoagulation (OAC) medication. Due to their better risk-benefit profile, non-vitamin K antagonist oral anticoagulants (NOAC) are now preferred over vitamin K antagonists.[63,137,141] However, a strict adherence to the prescribed NOAC medication regimen is of pivotal importance for optimal stroke prevention since their anticoagulant effect lasts for only 12-24 hours after each intake.[141] Coagulation monitoring for NOACs is not routinely required nor feasible for detection of nonadherence due to the short half-life of the drugs in contrast to the longer-lasting impact of vitamin K antagonists on the international normalized

ratio. It is known that chronic use of cardiovascular medication has a nonadherence rate of up to 50% after 1 year.[193,196] A similar low adherence rate would be a threat for the effectiveness of NOAC therapy.

New initiatives are needed to enhance medication adherence in the elderly population of AF patients taking NOACs. The Health Buddies app was developed to target this population. The app is based on an innovative concept of a virtual contract between AF patients and their grandchildren, both receiving daily challenges (i.e., NOAC adherence for AF patients and a self-chosen "healthy" challenge for the grandchild). Additionally, the app also includes other adherence-stimulating aspects such as patient education, reminders, communication, and motivation.

The aim of this pilot study was to assess the feasibility and usability of the Health Buddies app in a target group of AF patients. Additionally, the effects of the app on adherence, knowledge level about the arrhythmia and the OAC therapy, and other patient-reported outcomes were investigated.

METHODS

Development of the Health Buddies app

The general concept of this app to improve the adherence for NOACs stemmed from pooled ideas gathered from experts in the field and social entrepreneurs. The Health Buddies application was developed by DAE Studios (Kortrijk, Belgium), in association with the i-propeller consultancy group (Brussels, Belgium) and the Jessa Hospital (Hasselt, Belgium), funded by a grant of Bayer SA-NV (Diegem, Belgium). Two workshops (in April and September 2015) with a focus group of AF patients and their grandchildren were organized to steer app development and to test a first prototype. The first workshop was organized to obtain input about the different elements and the concept of the Health Buddies app. Various activities were organized to gain input from a focus group on all aspects of the game, including the game initiation with drafting an agreement, different content ideas (mini-games, educational content, etc), reminders for taking their medication, and ideas for an end reward. The aim of the second workshop was to get input from a second focus group about the clarity and fun of the selected content (quizzes, "did

you know questions", mini-games) and the usability and layout of the prototype of the app. The patients and their grandchildren tested all aspects of the app, starting with registering and setting up the contract and testing the mini-games and educational content.

Concept of the Health Buddies app

The Health Buddies app focuses on the relationship between a grandparent, diagnosed with AF, and their grandchild or grandchildren (aged 5-15 years old) — the patient's "health buddy." The patient and grandchild have to sign a contract at the start of the app in which they both declare to conduct a "healthy" challenge every day **(Figure 6.1)**. The challenge of the patient is to take their NOAC medication every day. The patient is also able to include other challenges (e.g., taking their pulse, taking other medication). The grandchild has to choose their own healthy challenge, such as eating one piece of fruit every day or not forgetting to brush their teeth twice a day. The duration of the contract was set at 90 days for this pilot study, and patients and their health buddies were supposed to use the app daily and equally during this period.

Both patients and grandchildren had to check a box to indicate on a daily basis if they completed their challenge or not **(Figure 6.2)**. If they did, patients received educational quizzes with an explanation of the correct answer or facts about AF and OAC therapy. The grandchildren instead were able to play educational games (four mini-games with an increasing difficulty over time), take and edit photos that were shared with their grandparent, or fill in a quiz.

The goal of the game was to meet each other in the success zone **(Figure 6.3)**, by completing as many challenges as possible in 3 months. If patient and grandchild were able to complete the contract, they could share a reward that they chose together at the start of the contract, for example, planning an amusing activity or going on a little trip together.

Other features of the app include managing the patient's NOAC medication stock with a reminder when a refill is necessary and the possibility to communicate with the health care professionals involved in this study and ask questions about their health.

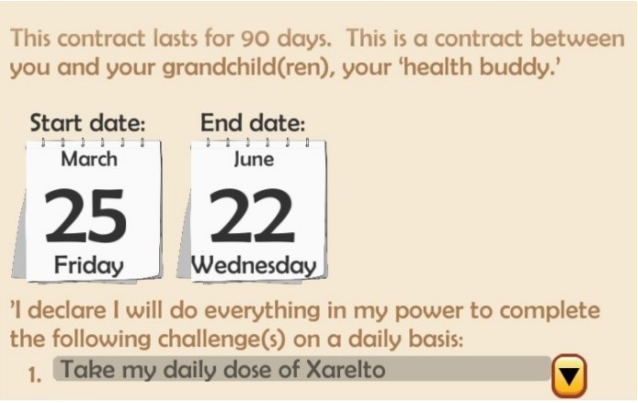

Figure 6.1: Screenshot of the Health Buddies app representing the contract after filling out the daily challenge.

Figure 6.2: Screenshot of the Health Buddies app showing the check box that patients receive daily to indicate if they have completed their challenge.

Figure 6.3: Screenshot of the Health Buddies app showing the home screen with the success zone in the middle where patient and grandchild meet at the end of the 90-day period.

Study participants

A prospective feasibility pilot study was performed with AF patients taking NOACs. Patients were recruited from the department of cardiology at the Jessa Hospital when they came for a consultation visit or when they were hospitalized at the cardiology ward for various reasons. Patients were considered eligible for inclusion if they met the following criteria: (1) having a documented diagnosis of AF, (2) eligibility and current prescription of NOAC therapy (i.e., dabigatran, rivaroxaban, and apixaban, as edoxaban was not yet approved for use), (3) having a grandchild between 5 and 15 years old (age limits were based on the feedback and experiences from the workshops), and (4) having a tablet, mobile phone, or computer with Internet connection. Patients enrolled in other studies and non-Dutch speaking patients were excluded. The study was approved by the local ethical committee of Hasselt University and the Jessa Hospital. All participants provided written informed consent, together with the legal representative of the grandchildren who participated. Clinical and demographic variables were obtained from patients' medical records. Screening, inclusion, and follow-up of the patients occurred between October 2015 and August 2016.

Feasibility, data collection, and outcome measures

The feasibility of the Health Buddies app was investigated by assessing the number of AF patients that met the inclusion criteria and the proportion of eligible patients that were willing to participate. The motivation of patients and their grandchildren to use the Health Buddies app on a daily basis was investigated by following up the frequency of app use (i.e., number of days with logins to the app).

At the end of the 3-month study period, patients had to complete the User Experience Questionnaire (UEQ) to assess their overall impression of the app and their perception of its usefulness [16].[207] The UEQ consists of pairs of opposite characteristics that the patient had to score on a scale from -3 to +3, with 0 as a neutral answer. The 26-item UEQ is divided into six scales: (1) attractiveness, (2) perspicuity (clarity and ease at becoming familiar with the app), (3) efficiency, (4) dependability (reliability of the app), (5) stimulation, and (6) novelty. An average score between -0.8 and 0.8 represents a neutral evaluation, a score >0.8 is a positive evaluation, and a score <-0.8 is a negative evaluation. A second

questionnaire, designed by the study team for the purpose of this study, was used to gather feedback of patients about the app. It contained questions regarding the satisfaction, usability, content, and effects of the Health Buddies app.

The medication adherence level of patients was assessed in different ways throughout the study period. First, the self-reported 8-item Morisky medication adherence scale (MMAS-8) was used to get an idea about the adherence level from the viewpoint of the patient.[181-183] Patients had to complete the MMAS-8 questionnaire at baseline and at the end of the study period. Second, patients could indicate via the app if they had completed their challenge, which corresponds to taking their NOAC medication that day (once or twice daily depending on the therapy). Data of completed or uncompleted challenges of the patients were collected throughout the study period. Finally, the electronic Medication Event Monitoring System (MEMS) and Helping Hand devices (WestRock, Switzerland) were used during the total study period to monitor the medication use of the patients taking rivaroxaban and apixaban, respectively. The electronic monitoring devices were not suitable to measure dabigatran adherence. The MEMS is a special cap that fits on a medication bottle, recording the exact date and time of bottle opening for the administration of medication. The Helping Hand is a monitoring system with a blister sleeve, registering the time and date of removing and reinserting the blister into the device. A read-out of the dosing history data was performed at the end of the study period. These data were used to calculate taking adherence (i.e., the percentage of prescribed doses taken) and regimen adherence (i.e., the proportion of days with the correct number of doses taken). In these patients, an additional pill count was performed after 3 months. Calculated taking adherence or pill count values >100% were traced to 100%.

As a final element of this study, the effect of this app on the knowledge level of AF patients about their arrhythmia and the NOAC therapy was investigated. Patients had to complete the validated Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ) at baseline and at the end of the study.[147] The JAKQ consists of 16 multiple choice questions (8 about AF in general, 5 about OAC therapy, and 3 questions about NOAC therapy). A percentage of correctly answered questions was calculated.

Statistics

Statistical analyses were performed using SPSS 24.0 (SPSS Inc). Continuous variables were reported as means and standard deviation (SD), and categorical variables as numbers and percentages. Categorical variables were compared using the chi-square test. The Shapiro-Wilk test was used to assess normal distribution, and a Mann-Whitney U test was used to ascertain differences in days logged in to the app between patients and grandchildren. A Pearson correlation analysis was used to evaluate the relation between app use by the patients and their grandchildren. To evaluate the frequency of logins to the app over time, Friedman tests were performed. A paired student t-test and the Wilcoxon test were used respectively to evaluate differences in the average score on the JAKQ and MMAS-8 between baseline and follow-up. Correlations between different adherence measures and the percentage of logins to the app were calculated using Spearman rho. A P value <0.05 was considered statistically significant.

RESULTS

Results of the workshops

During the first workshop, the focus group consisted of 6 AF patients, 10 grandchildren of different ages (ages 6, 6, 7, 8, 8, 10, 11, 12, 13, and 15 years old), 1 partner of a patient, and 2 mothers of grandchildren. The grandchildren came up with ideas for their challenge. Besides the healthy challenges, they also suggested that a challenge could be a reduction in something, for example, eating less unhealthy food. This was made possible in the app as grandchildren were free to indicate their own challenge. For the agreement made between patient and grandchild, most participants thought that "giving their word" would be good enough to make it binding, which was implemented in the game as signing a virtual contract. The workshop also revealed that the content preference differed between the younger (<10 years old) and older (≥10 years old) grandchildren. The facts and quizzes were less interesting for the younger grandchildren, while these were more popular with the older grandchildren. Both age groups liked the content creation (making and editing photos) and mini-games the most. It was decided to differentiate content of the app at a later development phase, after this

pilot study. The patients were mostly interested in receiving content from the grandchildren and in quizzes. Interestingly, some patients indicated that they did not need reminders for taking their medication. Those who did like a reminder preferred reminders at various moments, that is, after 3-4 days, after a week, or at the end of a 30-day period. Patients preferred to receive the reminders by text message, which was integrated into the game as push notifications when the app was used on a tablet or mobile phone. Various rewards for the end of the game were proposed by the participants, which led to the incorporation of several rewards into a pool from which the families could pick one, together with the option to indicate their own reward. Of the 6 participating patients, 4 owned a tablet, 3 patients had a mobile phone, and 5 patients had a personal computer. This indicated that the incorporation of a multiplatform app that could be used on both mobile phone/tablet and computer was the best option. In general, the patients experienced the Health Buddies app as an interesting concept and they liked to be connected with their grandchildren by using this app.

The second workshop consisted of 4 families, with 4 AF patients being present together with 8 grandchildren (ages 4, 7, 8, 9, 11, 11, 13, and 15 years old) and 2 parents. Feedback from this workshop especially led to an optimization of the layout and usability of the app. All different topics of the Health Buddies app were clear to the patients. Only small adjustments were needed to simplify two aspects (i.e., the creation of the account and taking/editing photos) before the start of the pilot trial. The Health Buddies app became an innovative tool that educates, reminds, motivates, and supports AF patients to be adherent for their NOAC medication.

Eligibility and patient inclusion

Out of the 830 screened AF patients, only 114 (13.7%) were eligible for inclusion **(Figure 6.4)**. A total of 224 patients (27.0%) were not on OAC therapy and 196 (23.6%) were on vitamin K antagonist therapy and were therefore excluded. The remaining 410 AF patients on NOAC therapy were approached for participation in the study. However, 228 of these patients (55.6%) had no grandchildren between 5 and 15 years old; 43 patients (10.5%) had grandchildren in the right age category, but did not have a tablet, mobile phone or computer; and another 25 patients (6.1%) were excluded for other reasons.

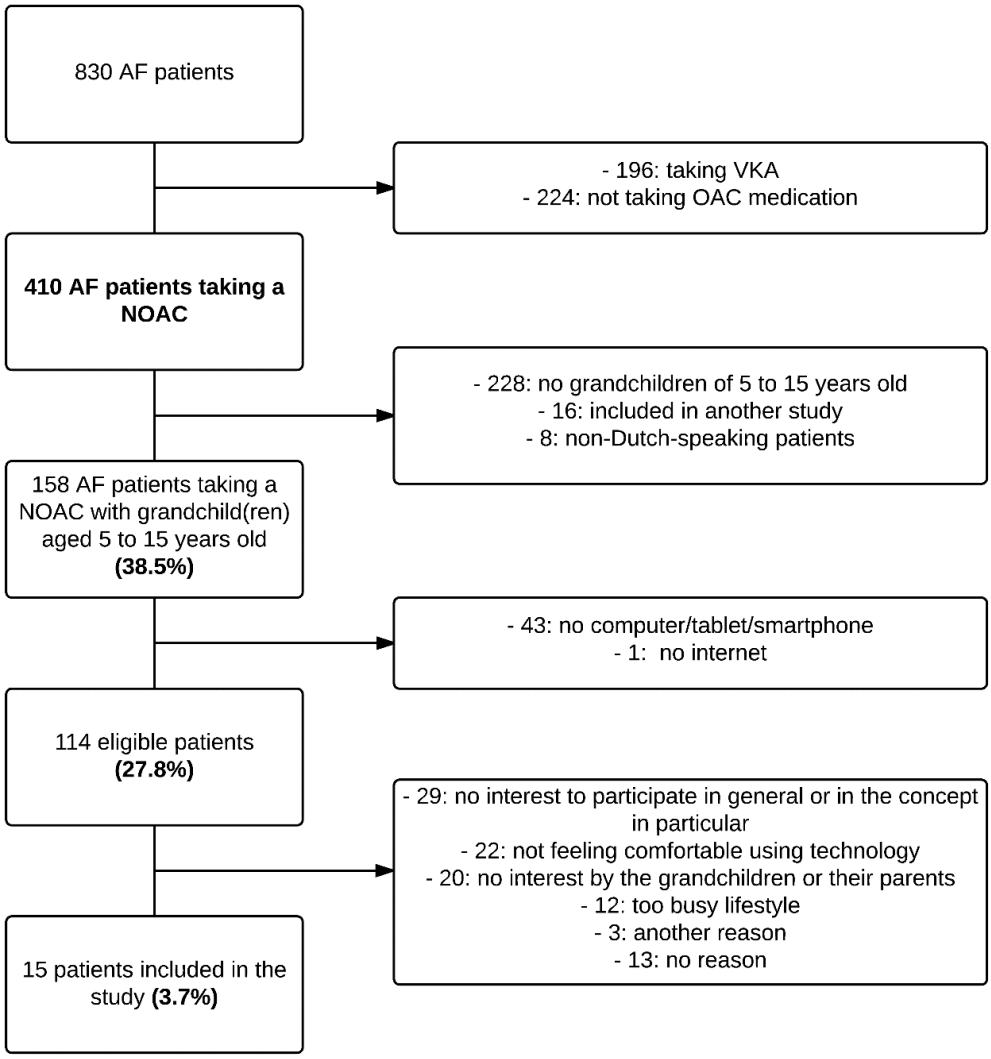

Figure 6.4: Flowchart of the different inclusion and exclusion criteria that resulted in 15 patients included (numbers between brackets refer to percentages of the 410 AF patients taking NOACs). AF: atrial fibrillation, NOAC: non-vitamin K antagonist oral anticoagulant, OAC: oral anticoagulation, VKA: vitamin K antagonist.

Of the remaining 114 eligible AF patients, only 15 (13.2%) were willing to participate in the study. Main reasons cited by the 99 patients (mean age 70.0 ± 6.2 years) for not participating were no interest to participate in general or in the concept in particular (29/99, 29.3%), not feeling comfortable using technology (22/99, 22.2%), no interest by the grandchildren or their parents (20/99, 20.2%), or too busy a lifestyle (12/99, 12.1%).

The study population of 15 AF patients had a mean age of 69.2 ± 3.7 years **(Table 6.1)**. A portable computer (9/21, 42.9%) and a tablet (9/21, 42.9%) were mostly used to play with the Health Buddies app. All patients together had 46 eligible grandchildren between 5 and 15 years old, of whom 20 participated in this project (mean age 9.5 ± 3.0 years old). One patient initiated a contract with 3 grandchildren and 3 patients used the app together with 2 grandchildren. Nine patients were taking a twice daily NOAC (4 on apixaban and 5 on dabigatran). Six patients were taking rivaroxaban, a once daily NOAC. Almost half of the patients (7/15, 46.7%) used no pill organizer for their medication.

Motivation to use the app

Of the 15 patients who started the study and set up the agreement, 13 (86.7%) completed the contract of 90 days. One patient had technical difficulties using the app, and the other patient was eventually not willing to use the app because the grandchild did not use it.

The frequency of app use after signing the contract differed widely among patients and grandchildren, with the proportion of days logged in to the app ranging from 0% - 99% **(Figure 6.5)**. Mean percentage of days logged in was significantly higher in patients compared to grandchildren (57.7 ± 30.0% and 24.3 ± 23.8%, respectively; $P = 0.002$). A weak correlation was found between app use by the patients and their grandchildren ($r = 0.37$, $P = 0.11$). Main reasons given not to log in on a daily basis were forgetfulness, holidays, technical problems with the app, hospital admission, not using an electronic device daily, health issues, and the grandchild not using the app. App use significantly decreased towards the end of the study period in both patients ($P = 0.009$) and grandchildren ($P < 0.001$) **(Figure 6.6)**.

Table 6.1: Characteristics of AF patients.

	All AF patients (n=15)
Age, mean ± SD	69.2 ± 3.7
Male, n (%)	10 (66.7)
Highest level of education completed, n (%)	
Primary school	1 (6.7)
Secondary school	8 (53.3)
College or University	6 (40.0)
Kind of AF, n (%)	
Paroxysmal AF	4 (26.7)
Persistent AF	9 (60.0)
Permanent AF	2 (13.3)
CHA_2DS_2-VASc score[a], mean ± SD	2.9 ± 1.5
HAS-BLED score[b], mean ± SD	1.3 ± 0.8
Time since AF diagnosis, n (%)	
< 1 year	1 (6.7)
1 year – 5 years	8 (53.3)
> 5 years	6 (40.0)
Married/cohabiting, n (%)	
Yes	15 (100.0)
No	0 (0.0)
Used electronic device[c], n (%)	
Portable computer	9 (42.9)
Tablet	9 (42.9)
Smartphone	3 (14.2)
Total number of eligible grandchildren per patient, mean ± SD	3.1 ± 1.9
Total number of included grandchildren per patient[d], mean ± SD	1.3 ± 0.6
Age included grandchildren, n (%)	
< 10 years	9 (45.0)
≥ 10 years	11 (55.0)
Dosing regimen NOAC, n (%)	
Once daily	6 (40.0)
Twice daily	9 (60.0)
Time since start NOAC, n (%)	
< 6 months	2 (13.3)
6 months – 2 years	7 (46.7)
> 2 years	6 (40.0)
Using a pill organiser, n (%)	
Day box	1 (6.7)
Week box	7 (46.7)
No	7 (46.7)
Number of medications each day, mean ± SD	5.9 ± 3.0
Number of pills each day, mean ± SD	7.0 ± 3.8

[a] The CHA_2DS_2-VASc score calculates the stroke risk for patients with atrial fibrillation.
[b] The HAS-BLED score estimates the risk of major bleeding for AF patients on anticoagulation therapy.
[c] Some patients used more than one electronic device to use this app (n=21).
[d] Some patients played the game with more than 1 grandchild; 20 grandchildren used the app.
AF: atrial fibrillation, NOAC: non-vitamin K antagonist oral anticoagulant, SD: standard deviation.

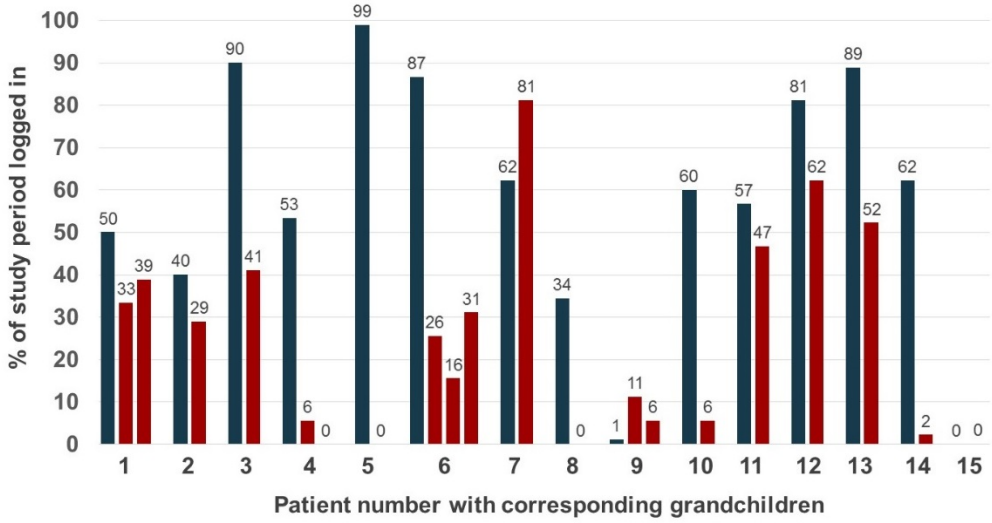

Figure 6.5: Average percentage of the days logged in to the app by the patients (blue) and grandchildren (red) over the study period of 90 days.

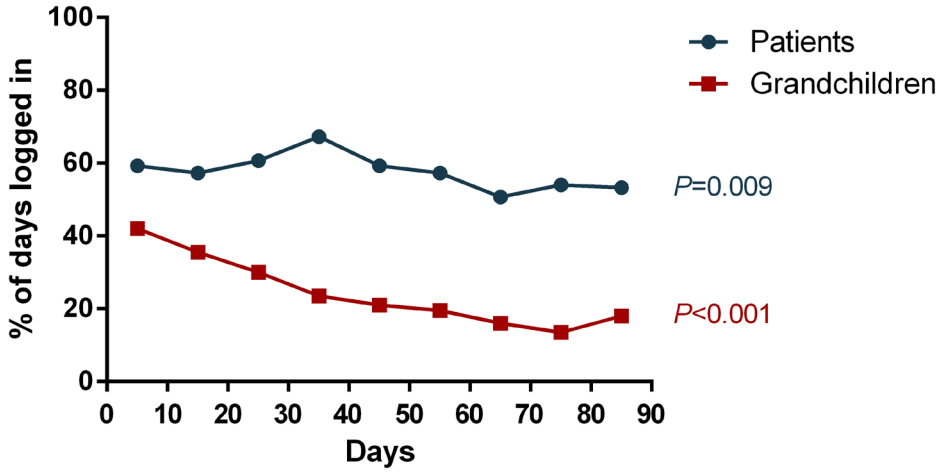

Figure 6.6: Percentage of the total study period logged in to the app by the patients (blue, n=15) and the corresponding grandchildren (red, n=20).

Effects of the app

Patients who completed the contract indicated that they correctly completed their challenge (i.e., took their NOAC medication) 99.0 ± 1.8% of the time. However, electronic monitoring of the medication adherence in 10 patients showed a lower taking adherence and regimen adherence of 88.6 ± 15.4% and 81.8 ± 18.7%, respectively. Pill count revealed an adherence percentage of 94.5 ± 9.2%. Patients had an average MMAS-8 score of 7.7 ± 0.6 at baseline and 7.4 ± 0.9 at the end of the study period (P = 0.44). The percentage of logins to the app over a 3-month period was not significantly correlated with any of the adherence measurements.

At the start of the study, a fifth of patients (3/15, 20.0%) indicated that they did not know they were diagnosed with AF. After using the app, all patients were aware of their personal medical condition named atrial fibrillation (P = 0.07). The overall score on the JAKQ improved from 64.6 ± 14.7% at baseline to 70.4 ± 10.4% after 3 months (P = 0.09).

After signing the contract, 2 patients used the app alone (i.e., without their grandchildren), as the grandchild (15 years old) of one patient felt too old to use the app and the grandchild of the other patient was not able to use the app on their device. Of the 13 patients who started to use the app together with their grandchildren, 5 patients (38.5%) indicated that the use of the app improved their relationship with their grandchildren.

Patient experience with the app

Based on the UEQ, patients who played the game and completed the contract (n=13) rated the Health Buddies app positively on clarity (1.500), novelty (0.942), stimulation (0.923), and attractiveness (0.859). Efficiency (0.577) and dependability (0.481) got a neutral evaluation.

Four patients (4/15, 26.7%) indicated that they would like to use the app together with their grandchild for another period of 3 months. Of these patients whose contract was restarted, only one completed a second 90-day period. Five patients (5/15, 33.3%) indicated that they would use the app for a second time, but their grandchild would not. The remaining six patients (6/15, 40.0%) did not want to use the app again. Ten out of 15 patients (66.7%) found the app easy to use,

whereas the remaining 33.3% (5/15) often encountered technical difficulties or problems. Most patients (11/15, 73.3%) indicated that the educational aspect of the app was one of its most positive facets. Seven of the 13 patients (53.8%) using the app together with their grandchildren indicated that their grandchildren liked to play the app.

Although only 1 patient (1/15, 6.7%) indicated that the app helped to improve his NOAC adherence, 6 patients (6/15, 40.0%) stated that the project made them more conscious about strict medication adherence and motivated them to be more correct in taking their medication in the future. However, the majority of the patients (8/15, 53.3%) indicated that they already had very good adherence to their NOAC therapy.

Almost two-thirds of the patients (9/15, 60.0%) found it useful to receive reminders when they did not play the app, 26.7% of the patients (4/15) indicated that they never received a reminder, and the minority (2/15, 13.3%) indicated that they did not like the reminders. Patients suggested broadening the educational aspect as this was a positive feature of the app. They also indicated that their grandchildren would be happy with a larger variety of mini-games and with an adjustment of the difficulty of the mini-games to the age of the grandchild. Some patients suggested adding an alarm function to the app that automatically reminds them to take their medication. However, this is possible only when they use the app on their tablet or mobile phone, which was the case in about half of the patients.

DISCUSSION

With the increasing number of patients having access to mobile phones, tablets, personal computers, etc., novel methods using these technologies can be used to improve medication adherence and overall management of patients with chronic diseases. In AF patients receiving NOACs, strict medication adherence should be stimulated and ensured to provide an optimal thromboembolic prevention.[141,208]

Usability of the Health Buddies app

The Health Buddies app tries to make therapy adherence fun and stimulating for the patients. However, only 13.7% of the screened AF patients were eligible for inclusion and only 13.2% of those eligible patients were interested in participating. Overall, only 3.7% of the NOAC-taking AF population was included in this project.

More than half of the patients were not eligible as they did not have grandchildren in the right age category. At the end of the study, 60% of the patients were willing to use the app again, but 56% of those indicated that their grandchild would not use the app for a second time. These figures indicate that the target group of patients able to use this app needs to be expanded. However, the concept of a social contract, with completion of challenges between the AF patient and their health buddy, seems valid. With some adjustments (i.e., matching the content of the app to the specific health buddy or adding more informative content and reducing the mini-game aspect), it could be possible to involve other health buddies in this app, for example, the patient's spouse, other family members, friends, or even other AF patients.

Modifications are also necessary to make the app more varied, stimulating, and challenging as app use was lower than expected and decreased over time in patients but especially in grandchildren. The app was developed to target (newly diagnosed) AF patients initiating NOAC therapy to provide them with extra education, to make them conscious about the importance of good adherence, and to create a habit of taking their medication strictly as prescribed. Therefore, the app in its current form was not intended to be used long term, explaining some of the decreased app use over time together with the fact that patients aged >65 years do not typically use their mobile devices and computers as often as younger generations. The majority of the included patients were prescribed NOAC therapy for many months before inclusion, which meant that most of those patients already developed suitable adherence strategies and habits. Furthermore, about half of those patients had a pill organizer to help them adhere. The pilot trial also revealed that it is important to keep the grandchildren motivated to use the app more often, for example, by adjusting the content and difficulty of the app to the age of the grandchildren.

Not all patients seemed to be ready for the innovative concept of this app, mostly because they were not interested and not familiar with the technology. Nevertheless, after playing, patients rated the app positively based on the user experience questionnaire and indicated that the educational aspect was a capital gain.

The effect of the Health Buddies app on adherence to NOACs

Only one patient indicated that the app improved his adherence, although 40% of the patients became more conscious about strict medication adherence. Interestingly, the majority of the patients indicated that they already had very good adherence to their NOAC therapy, also reflected in the self-reported Morisky scale with a mean patient score of 7.7 (out of 8) at the start of the study. It is known that the MMAS-8 often overestimates actual adherence.[170] Electronic monitoring is a more accurate manner to assess medication adherence to NOACs, and it showed a taking adherence of only 88.6% and a regimen adherence of 81.8% in our study. Intriguingly, in the app, patients indicated that they took their NOAC medication 99.0% of the time. Therefore, self-reported adherence through the app is clearly an unreliable way to follow patient adherence. In general, a possible pitfall of the Health Buddies app as well as other adherence promoting apps is that they may only encourage participants to use the app. Equally, they need to motivate them to be adherent to their medication.

Interventions to improve adherence to NOACs are scarce, although it has been shown that nonadherence to NOACs affects health care costs, morbidity, and mortality in the aging AF population.[177] Up until now, there have been only three interventions tested. First, the AEGEAN study investigated the effect of education (i.e., booklets and the availability of reminder tools) together with telephone follow-up by a virtual clinic on adherence to apixaban. However, AEGEAN did not find any difference in electronically measured adherence between the usual care group and the intervention group with an adherence value of respectively 88.5% and 88.3% after 24 weeks.[179] Another study by Shore et al, although not prospective, showed that enhanced pharmacist involvement with a longer monitoring and follow-up of patients was associated with an improved adherence to dabigatran.[198] Third, a prior study by our group showed that daily telemonitoring of medication intake with direct personalized telephone feedback

led to very high NOAC adherence values with a taking adherence and regimen adherence of 99.0% and 96.8%, respectively.[209]

Educational and Other Effects

The Health Buddies app is also an educational game as patients receive facts and quizzes about AF and the associated therapy. This new way of providing education is needed as different studies showed that the knowledge of AF patients about their arrhythmia and its treatment is low.[123,126,129,132,134,135,147] Included patients had a mean score on the JAKQ of 64.6% at the start of the study, which is already higher than the score of the average AF patient (i.e., 55.8%).[147] Use of the app led to a small further increase in knowledge level with 5.8%. Moreover, after 3 months, all patients were aware of their heart rhythm disorder, which was not the case for 3 patients at the start of the study.

Increasing patient knowledge seems to be a logical pathway to contribute to better medication adherence and improved overall management.[133,140] However, finding a successful intervention to optimize the knowledge of AF patients is not easy as different interventions were tested with mixed results.[126,132,134,146,147] Most studies used information booklets or educational videos and did not show any significant effect of the intervention.[132,134,146] Only two studies using personalized education found a significant increase in knowledge level.[126,147]

Another aim of the app was to strengthen the relationship between patients and their grandchildren. At the end of the study, this was also positively evaluated for about 1 in 3 AF patients.

Finally, the app allowed AF patients to stay in contact with their health care provider by sending emails. We noted, however, that during the 3-month study period, this feature was used only by patients to discuss possible technical difficulties concerning the app.

mHealth to improve adherence

Medication adherence can be addressed in many ways, including automatic reminders, reminder packaging, medication boxes, device aids, counselling, telephone support, patient education, etc., or a combination of those.[195,200,210,211] It remains unclear which interventions are most effective in improving medication adherence in chronic conditions, and it is especially difficult to prove their effect on clinical outcomes.[195,200,212] Ongoing technological advancements have led to the use of telehealth, eHealth, and mHealth in different domains of health care including medication adherence. Especially mHealth with different mobile apps is being increasingly explored due to its popularity, its portability, and the reachability of a large proportion of the population.

The Health Buddies app was the first mHealth intervention being tested in AF patients to improve adherence to NOACs. In other chronic diseases and also in some cardiovascular illnesses (e.g., hypertension and ischemic heart disease), the use of mHealth showed early but promising results in improving medication adherence.[201,202,204] A review by Anglada-Martinez showed that 65% of the mHealth interventions using text messages to send reminders or motivational content found a positive impact on adherence.[204] Another systematic review found that 83% of trials using mHealth technologies in cardiovascular diseases were able to improve adherence and 54% could improve clinical outcomes.[202] The results of most mHealth studies should be interpreted with caution as many interventions used only self-reported adherence to investigate possible improvements in adherence.

However, challenges with mHealth remain as it is not clear which interventions are the most promising, suitable, user-friendly, secure, cost-effective, and how they should best be integrated in daily care.[213] Only by extensive testing of apps and incorporating patients in this process of development and elaboration of the app, as we did with Health Buddies, can these challenges be addressed.

Study limitations

An important limitation of this study was the small number of motivated study participants, already having good adherence and acceptable patient knowledge. Moreover, no control group was considered as it was still a pilot study. Nevertheless, the findings from this pilot project provide new insights in the development, usability, and feasibility of the Health Buddies app and mHealth in general for AF patients taking OAC therapy. Other possible limitations are that there were no baseline adherence data gathered with electronic monitoring before patients started using the app and that the study was performed in only one large tertiary care hospital.

Possibilities for future improvements

Even though the Health Buddies app was promising before the start of the pilot study receiving positive reactions during the workshop, it turned out that the usability was low and effects on adherence and knowledge improvement were only limited. Therefore, already suggested adjustments can lead to an upgraded, more accessible, and more effective version of the app. Although patients were already able to include more than one challenge, the app can be made more user-friendly allowing patients to include their entire medication schedule with the possibility of activating appropriate daily reminder alarms. This aspect was not yet incorporated in the app as most patients in the workshops indicated that only occasional and no daily reminders were needed. Other features that can be integrated are the ability of the app to capture overdoses and to allow patients to check for other drug interactions. Another option to broaden the target group is to make a version of the app that can be used individually, although then the Health Buddy concept has to be abandoned and the app should be targeted more on reminders, education, and communication with health care providers. An updated version of the app can be tested in a new pilot study or in a larger prospective randomized controlled trial with the ultimate goal to improve health outcomes in AF patients. Studies could also investigate if the Health Buddies concept can be applied to other chronic diseases.

Still, other new interventions, strategies, and technologies to enhance long-term adherence to NOACs need to be developed and investigated as AF patients are a large and diverse patient population and not all have access to newer mHealth tools. Nonadherence behavior is often multifactorial indicating the necessity of providing patients with tailored, personalized tools.

CONCLUSIONS

The innovative Health Buddies app, based on a social contract concept between AF patients and their grandchildren, was perceived as clear, novel, attractive, stimulating, and educational by its users. However, only a small proportion of the current AF population treated with NOACs seems eligible or is willing to use the app in its current form. Modifications to the app can expand the target group and make it even more motivational and attractive, so that it can be used by more patients and for a longer period of time. That will allow an evaluation of its impact beyond education, that is, on adherence and clinical outcomes.

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PART 4

Risk factor management

Chapter 7

The Why, When and How to test for obstructive sleep apnea in patients with atrial fibrillation.

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ABSTRACT

Sleep apnea is associated with increased cardiovascular risk and may be important in atrial fibrillation (AF) management. It is present in up to 62% of the AF population and is highly under-recognized and underdiagnosed. Obstructive sleep apnea (OSA) is strongly associated with AF and non-randomized trials have shown that its treatment can help to reduce AF recurrences and maintain sinus rhythm. The 2016 European Society of Cardiology guidelines for the management of AF recommend that AF patients should be questioned regarding the symptoms of OSA and that OSA-treatment should be optimized to improve AF treatment results. However, strategies on how to implement OSA testing in the standard work-up of AF patients are not provided in the guidelines. Additionally, overnight OSA monitoring rather than interrogation for OSA-related clinical signs alone may be necessary to reliably identify OSA in the majority of AF patients.

This review summarizes the available clinical data on OSA in AF patients, and discusses the following key questions: Why and When is testing for OSA needed in AF patients? How and Where should it be performed and coordinated? and Who should test for OSA? To implement OSA testing in a cardiology or electrophysiology clinic, we propose a multidisciplinary integrated care approach based on a chronic care model. We describe the tools, infrastructure and coordination needed to test for OSA in the standard work-up of patients with symptomatic AF prior to the initiation of directed invasive or pharmacological rhythm control management.

INTRODUCTION

Modifiable cardiovascular risk factors are gaining interest in the care of atrial fibrillation (AF) patients.[63-71] In addition to anticoagulation, rate control and rhythm control, the identification, management and treatment of concomitant risk factors has been introduced as the fourth pillar in the management of AF patients to optimize outcomes.[71] Sleep apnea is considered to be an emerging risk factor that is strongly associated with the development and occurrence of AF.[214-216] Moderate or severe sleep apnea is a highly prevalent, although often underdiagnosed, condition in AF patients affecting up to 62% of the AF population.[217-223] Non-randomized studies suggest that the treatment of obstructive sleep apnea (OSA) in AF patients can help to reduce AF recurrences and maintain sinus rhythm.[223-233]

The 2016 European Society of Cardiology (ESC) guidelines for the management of AF recommend to consider questioning AF patients regarding symptoms of OSA and to treat OSA, when present, to achieve optimal antiarrhythmic management.[63] However, the ESC AF guidelines provide no guidance on how medical centers should implement these recommendations. Several strategies and methods are available to identify and characterize sleep disordered breathing like OSA, but there is uncertainty regarding the optimal care pathway in AF patients. This makes that testing for OSA is at best performed haphazardly in this population. Theoretically, an integrated approach would be more likely to establish dedicated multidisciplinary care pathways for OSA in the growing AF population in current cardiology and electrophysiology clinics.[63,234]

The aim of this review is to evaluate the role of OSA testing in AF patients. Based on available evidence, it will provide guidance on why, when, where and how to test for OSA in AF patients and who is best equipped to perform, manage and coordinate this testing **(Figure 7.1)**.

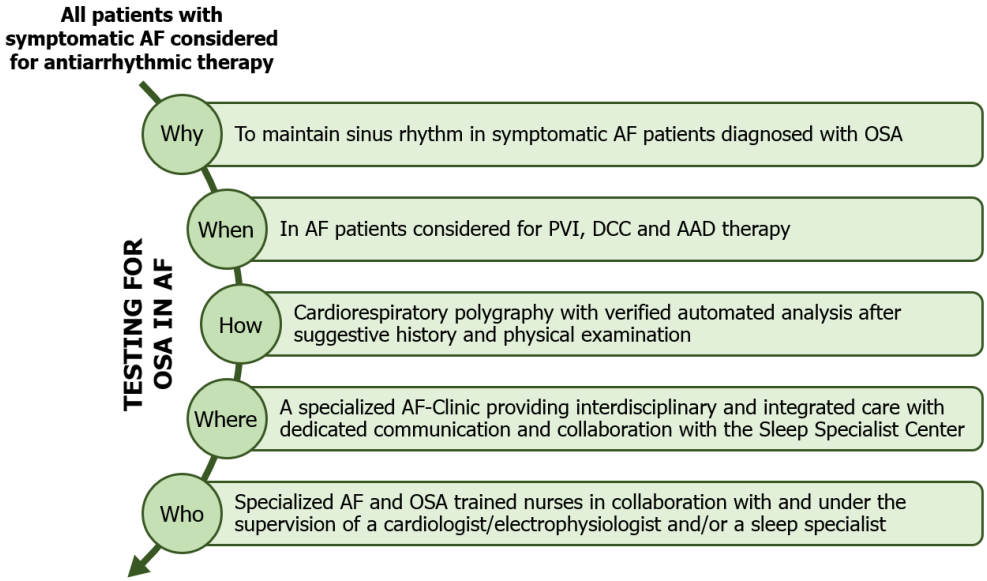

Figure 7.1: Summary of the rationale why, when, how, where and by whom to test for obstructive sleep apnea in atrial fibrillation patients. AAD: antiarrhythmic drug, AF: atrial fibrillation, CPAP: continuous positive airway pressure, DCC: direct current cardioversion, OSA: obstructive sleep apnea, PVI: pulmonary vein isolation.

ROLE OF SLEEP APNEA IN ATRIAL FIBRILLATION PATIENTS

The gold standard for the diagnosis and characterization of sleep apnea is an overnight polysomnography (PSG) in a dedicated sleep clinic.[235,236] The severity of sleep apnea is usually assessed using the apnea-hypopnea index (AHI) which represents the total number of apnea and hypopnea events per hour of sleep[237] and is classified as mild (AHI between 5 and 15 events/hour), moderate (AHI between 15 and 30 events/hour) and severe (AHI ≥30 events/hour).[238,239] The prevalence of sleep apnea in AF patients differs widely depending on the applied AHI severity threshold used to define the condition (AHI thresholds of 5/hour and 15/hour), changes in and increased sensitivity of sleep-study recording techniques and the type of AF.[217-223,228,229,240-245] Notwithstanding these methodological limitations, the estimated prevalence of sleep apnea in patients with AF has been found to be much higher (18%-74%) than in controls without AF (3-49%).[217-223,228,246]

OSA is the most common form of sleep disordered breathing and is characterized by episodic partial or complete obstruction of the upper airways during sleep. In

contrast, central sleep apnea (CSA) is characterized by periods of a diminished or absent respiratory effort and/or periodic episodes of hyper- and hypoventilation (Cheynes-Stokes respiration) during sleep. In OSA, hypopneas (partial obstructive events) typically occur far more frequently than apneas (complete obstructive events), and both obstructive as well as central respiratory events may occur during the same night in a patient; however, individual patients generally show either predominant OSA or predominant CSA.

A possible pathophysiological link between OSA and AF is becoming increasingly clear and has already been summarized in different reviews and in a meta-analysis of observational studies.[214,215,247-257] OSA is associated with intermittent hypoxia, hypercapnia, large swings in intrathoracic pressure, autonomic dysfunction, oxidative stress and inflammation which may contribute to the development, recurrence and progression of AF in OSA patients.[214,215,249-251] Chronic OSA may not only lead to acute apnea-associated electrophysiological changes but may also contribute to structural remodeling of the heart including atrial enlargement and increased atrial fibrosis which provides a substrate for AF.[214,249-253,258,259]

Predominant CSA is less prevalent in AF patients and is more often present in patients with heart failure.[214,260-262] One recent clinical observation in AF patients admitted to hospital with persistent AF and preserved left ventricular function for electrical cardioversion showed, that predominant CSA may be almost as prevalent as predominant OSA in this subset of AF patients.[218] This high and unexpected prevalence of CSA in patients with persistent AF needs to be confirmed in future studies. Interestingly, the same group reported, that rhythm control by electrical cardioversion reduced nocturnal central respiratory events and unmasked OSA suggesting, that a high proportion of central respiratory events may be a consequence of AF, rather than representing a causal factor for AF.[263] Particularly in patients with concomitant heart failure with reduced or preserved left ventricular function, AF may result in acute hemodynamic impairments and factors such as prolonged circulation time and rostral fluid shift which may contribute to the occurrence of central apneas and hypopneas.[259] In heart failure patients with reduced and preserved left ventricular function, AF substrates are mainly characterized by structural alterations and subsequent local conduction disturbances.[264] Whether CSA contributes further to the AF substrate and progression of AF is unclear and needs to be investigated in future studies.[214,259]

WHY TO TEST FOR OBSTRUCTIVE SLEEP APNEA IN ATRIAL FIBRILLATION PATIENTS

Under-recognition of obstructive sleep apnea in atrial fibrillation populations

In different cardiovascular diseases, including AF, OSA remains largely undetected.[265,266] Underdiagnosis of OSA in AF can be attributed to several factors including a low awareness amongst physicians about OSA and about the positive effects of its treatment in AF patients. The extra coordination and cost needed to conduct an ambulatory and/or an in-patient overnight sleep study in a dedicated clinic may dissuade physicians from implementing OSA testing in their routine work-up of AF patients. Additionally, many AF patients do not report symptoms of daytime sleepiness, which can mask the presence of OSA and steer physicians away from ordering sleep-related investigations.[219,239,244,248,265,266] Therefore, active OSA testing may be required to identify OSA, particularly in patients with symptomatic and complicated AF without concomitant typical OSA related symptoms.

Impact of obstructive sleep apnea on atrial fibrillation and its therapy

Screening and diagnosing OSA may help to identify patients with an increased risk of failure to respond to antiarrhythmic drugs[267], higher recurrence of AF after cardioversion[228,268] or catheter ablation[229,242,243,248,269-276] and an increased risk for stroke[277,278].

Monahan and colleagues showed that 23 AF patients with severe OSA responded less to antiarrhythmic drugs than 38 patients with mild OSA (39% vs. 70%).[267]

An observational study with 118 patients (27 with untreated OSA, 12 with treated OSA and 79 controls with an unknown OSA status) undergoing direct current cardioversion found that the presence of untreated OSA was associated with significantly higher rates of AF recurrence (82% versus 53% in the control group).[228] In the treated OSA group, the recurrence rate was only 42%.[228]

A meta-analysis involving approximately 4000 patients by Ng et al. found that OSA patients had a 25% increased risk of AF recurrence after catheter ablation compared to non-OSA patients.[248] A recent prospective study with 251 AF patients showed that those patients with OSA had significantly more unsuccessful AF ablations (65.2%) compared to non-OSA patients (45.6%). They also concluded that more severe OSA was associated with higher AF recurrence rates.[273]

It has been shown that patients with OSA have higher CHA_2DS_2-VASc scores (i.e. estimation of the stroke risk) compared to non-OSA AF patients.[245] Nevertheless, OSA is independently associated with an increased thromboembolic risk in AF patients. Yaranov et al. reported that ischemic stroke was about three times more common in AF patients diagnosed with OSA compared to those without OSA, after controlling for confounders.[277] Finally, OSA is a risk factor for several other cardiovascular diseases (e.g. hypertension, heart failure), which in turn can enhance the risk of AF development, progression, and morbidity.[261,279-281]

Some of the above-mentioned studies are limited by the method used to diagnose OSA and by the often retrospective study design which could have led to an under- or overestimation of OSA in AF patients or lack of systematic exclusion of OSA in the control group.

Beneficial effects of obstructive sleep apnea treatment on atrial fibrillation

Continuous positive airway pressure (CPAP) is the therapy of choice to treat OSA patients.[282] The positive pressure prevents collapse of the pharyngeal area and thereby helps alleviate the airway obstruction.

The ORBIT-AF registry showed that AF patients with OSA receiving CPAP treatment were less likely to progress to more permanent forms of the arrhythmia compared to OSA patients without CPAP.[223] Another observational study concluded that CPAP therapy may significantly decrease the occurrence of paroxysmal AF.[283]

Different non-randomized observational studies have shown that appropriate treatment of OSA with CPAP may improve rhythm control management in AF patients.[224-233] In a prospective non-randomized study by Fein et al. which included 62 AF patients with OSA undergoing a pulmonary vein isolation (PVI), arrhythmia-free survival after one year in CPAP users (71.9%) was higher compared to non-CPAP users (36.7%) and similar to a group of patients who did not have OSA (66.7%).[224] In another study with 720 AF patients undergoing PVI, AF recurrence after 42 months was 30% in patients without sleep apnea, 68% in those with inadequately treated (<4 hours CPAP/night) sleep apnea, and 35% in those patients on adequate CPAP treatment (>4 hours/night).[226] All of these results are further supported by three meta-analyses.[227,230,232] Li et al. showed that patients with OSA not using CPAP had a 57% higher risk of arrhythmia recurrence than patients without OSA.[230] Shukla et al. and Qureshi et al. concluded in two independent meta-analyses that the use of CPAP was associated with a significant overall relative risk reduction on AF recurrence of 42%.[227,232]

Importantly, all available data are derived from non-randomized observational studies. Currently, patients are being recruited in multicenter prospective randomized controlled trials to investigate the impact of CPAP on AF burden in patients with OSA (Trial-ID: ACTRN12616000262404, ACTRN12616000903482 and ACTRN12616000088448). The outcomes of these prospective randomized controlled trials are required before definite therapeutic implications can be recommended.

Effects of obstructive sleep apnea treatment on cardiovascular outcome, hypertension and symptom-burden

In contrast to the encouraging impact of CPAP therapy on AF, there have been the outcomes of randomized controlled trials of CPAP use in cardiovascular patients. CPAP treatment failed to reduce cardiovascular events and death in patients with high cardiovascular risk and OSA in a large randomized controlled trial (SAVE study)[284], a finding which is confirmed by a recent meta-analysis[285]. In SAVE, new-onset AF was not different in the CPAP-treated OSA patients compared to CPAP non-users. Of note, AF was not a predetermined endpoint, rhythm-monitoring was not sufficient to systematically detect incident AF and the effects on rhythm control in patients with established AF was not reported. CPAP

has been shown to improve blood pressure in OSA patients with and without hypertension and is one of the most effective non-pharmacological therapies for hypertension.[286-299] Evidence from randomized controlled trials of CPAP in patients with OSA and hypertension shows, that CPAP reduces arterial blood pressure most effective in patients with severe OSA with daytime sleepiness.[290,292,293] Reduction in symptom burden, particularly daytime sleepiness, is to date the most common and important reason for treatment initiation.[284,285,300]

WHEN TO TEST FOR OBSTRUCTIVE SLEEP APNEA IN ATRIAL FIBRILLATION PATIENTS

The previous two sections underline the potential importance of OSA treatment to improve AF management. OSA is a prevalent modifiable cardiovascular risk factor in patients with AF. It seems reasonable to test for OSA prior to the initiation of invasive or pharmacological rhythm control management in patients having symptomatic AF with the aim of maintaining sinus rhythm and reducing symptomatic AF recurrence and the risk of failure of expensive interventions. In the ARREST-AF cohort study and LEGACY study, an aggressive risk factor reduction program focusing on weight management, hyperlipidemia, OSA, hypertension, diabetes, smoking cessation and alcohol reduction[66,70] reduced the duration, frequency and symptom severity of AF, and thus resulted in a longer arrhythmia-free survival after PVI ablation.[66,70] A multimodal integrated care pathway for aggressive risk factor management of potential modifiable AF risk factors should include testing for OSA.[63,66,70] However, it remains unclear how and when to test for OSA and implement management of OSA in the standard work-up of patients with AF.

HOW TO TEST FOR OBSTRUCTIVE SLEEP APNEA IN ATRIAL FIBRILLATION PATIENTS

History taking and physical examination

Every AF patient should be asked for typical OSA related symptoms such as disrupted sleep, snoring, nocturnal choking or gasping, witnessed apneas, nocturia, tiredness, morning headaches and especially excessive daytime sleepiness.[239,260,301,302] The Epworth Sleepiness Scale (ESS) is a self-administered, short questionnaire used to assess the presence of subjective daytime sleepiness.[303] In a population with persistent AF, Albuquerque et al. found a low prevalence of excessive daytime sleepiness without any significant association between the ESS score and sleep apnea severity determined by the AHI.[244] Therefore, the ESS has a low sensitivity of 32.2% and a specificity of 54.5% to detect sleep apnea in patients with AF.[244]

As different studies have shown that these typical OSA related symptoms are often minimally present in AF patients[219,239,244,248,265], healthcare professionals (both nurses and physicians) should also specifically ask for sleep related cardiac symptoms such as nocturnal angina pectoris, nocturnal dyspnea, nocturnal palpitations and nocturnal paroxysmal AF episodes.[304]

As part of the history taking and physical examination, different parameters such as obesity, middle age or older, male gender, alcohol use, smoking and increased neck circumference should be taken into account as important risk factors for OSA.[239,260,301,305,306]

Clinicians should also be aware of a high likelihood of OSA in patients with drug resistant AF or resistant hypertension.[239,260,267,301,307] Furthermore, they should be aware that specific findings on long-term ambulatory blood pressure or electrocardiogram (ECG) recordings such as non-dipping of nocturnal blood pressure measurements, nocturnal AV-block, cyclic variation of heart rate during the night, nocturnal premature atrial contractions, and nocturnal AF on Holter monitoring are typically associated with sleep disordered breathing.[308-310]

Screening for obstructive sleep apnea by the quantification of sleep apnea related symptoms

Different questionnaires and scales have been used to identify patients at risk for sleep apnea based on their symptoms, medical history and anthropomorphic characteristics **(Table 7.1)**.

The Berlin Questionnaire consists of 3 categories related to the risk of having sleep apnea (i.e. snoring, daytime sleepiness and a high blood pressure or obesity).[311] When this questionnaire was used in an AF population it showed an acceptable sensitivity (86%-100%) but a variable specificity (30%-89%).[216,312]

The STOP-Bang questionnaire is a simple 8-item questionnaire that was developed and validated to screen for OSA in surgical patients.[313] Although it is not validated in an AF population, Farrehi et al. showed that among patients who underwent an AF ablation, 79% were at high risk for OSA using this questionnaire and these patients were significantly less likely to maintain sinus rhythm after their ablation.[243]

Several other questionnaires and screening tools exist to identify patients with OSA such as the Wisconsin sleep questionnaire[314], the 4-Variable screening tool[315], the OSA50 screening questionnaire[316] and the recent NoSAS scoring system[317]. However, these have not been used nor validated in an AF population to screen for OSA.

In summary, questionnaires help to quantify the typical OSA related demographic features and symptoms such as daytime sleepiness or snoring, which may lead to the initiation of OSA treatment for OSA-related symptom control. However, none of the available questionnaires have been properly validated for their accuracy in an AF population and the few studies to date suggest they lack specificity as most AF patients do not report daytime sleepiness. Patients with cardiovascular disease and concomitant OSA are less obese and less sleepy than patients with the same degree of OSA without known cardiovascular disease.[318,319] Therefore, questionnaires most likely have a lower sensitivity in these patient populations and many AF patients at risk for sleep apnea may be missed.

Table 7.1: Questionnaires to screen for obstructive sleep apnea and sleep disordered breathing.

	Explanation	Diagnosis based on	Accuracy	Advantages	Disadvantages
Berlin Questionnaire[311]	10 questions in 3 domains (snoring, fatigue or waketime sleepiness, and a history of obesity or hypertension)	Patients are at high risk for sleep apnea if there are 2 or more categories with a positive score	• Sensitivity of 86% and specificity of 77% in primary care[311] • 100% sensitivity and 30% specificity in 30 AF patients undergoing PVI[312] • Sensitivity of 86% and specificity of 89% in 44 AF patients undergoing electrocardioversion[216]	• Completed in <5 minutes • Quite high sensitivity	• Subjective, self-reportable • Somewhat difficult to score • Often low specificity
STOP-Bang questionnaire[313]	8-item questionnaire (related to snoring, daytime tiredness, observed apnea, hypertension, BMI, age, neck circumference, gender)	Risk for OSA: • Low: score 0-2 • Intermediate: score 3-4 • High: score 5-8	• Sensitivity: 90-96%[320] • Specificity: 25-49%[320] • No accuracy values in an AF population	• Completed in <5 minutes • Simple questionnaire • High sensitivity	• Partly subjective, self-reportable • Low specificity • Not validated in a study with AF patients

AF: atrial fibrillation, BMI: body mass index, OSA: obstructive sleep apnea, PVI: pulmonary vein isolation

Testing for obstructive sleep apnea by the determination of the apnea-hypopnea index

Since interrogation for clinical signs of OSA and screening questionnaires are of limited value as a stand-alone diagnostic tool for OSA in AF patients, additional approaches for OSA testing are required.

OSA severity is clinically determined based on the number of recurrent episodes of partial or complete upper airway collapse per hour of sleep (i.e. AHI) or recording time during night.[301] Devices for OSA monitoring and diagnosis can be classified into four different levels based on the number of recording channels used and whether the study is conducted in a sleep laboratory with a technologist in attendance **(Table 7.2)**.[321,322]

Table 7.2: Evaluation approaches for sleep apnea.

	Characteristics
Level 1	In-laboratory, technologist attended, standard polysomnography (Gold standard)
Level 2	Comprehensive portable polysomnography This monitor includes a minimum of seven channels: i.e. EEG, EOG, EMG, ECG or heart rate, airflow, respiratory effort and oxygen saturation.
Level 3	Modified portable sleep apnea testing This monitor incorporates a minimum of four monitored channels: i.e. ventilation and/or airflow (at least two channels of respiratory movement, or respiratory movement and airflow), heart rate or ECG, and oxygen saturation.
Level 4	Continuous single- or dual-bioparameter recordings These portable monitors measure a single parameter or two parameters: e.g. oxygen saturation and/or airflow.

ECG: Electrocardiography EEG: electroencephalography, EMG: electromyography, EOG: Electrooculography.

The gold standard for the diagnosis and characterization of OSA is an attended, in-patient, formal overnight PSG in a dedicated sleep laboratory (i.e. level 1 study).[235,236] It monitors respiration and sleep stages by electroencephalography (EEG) in addition to a range of other variables. Despite the intensive pool of data and information provided by an overnight PSG study, this procedure is expensive, labour-intensive and time-consuming. Additionally, most sleep centers have long waiting lists. Due to these limitations, laboratory PSG studies are not a feasible screening tool for OSA in large numbers of AF patients.

Level 3 cardiorespiratory polygraphy (PG) is a valuable, suitable and accepted alternative for the monitoring of sleep apnea. PG devices use the same respiratory channels (nasal airflow cannula, thoracic and abdominal respiratory effort belts and oximetry monitoring) as PSG.[323] Therefore, the detection of apneas and hypopneas to determine the AHI, as well as the discrimination in obstructive and central apneas by PG and PSG is identical. In contrast to PSG, PG does not include EEG measurements. Consequently, assessment of sleep stages, total sleep time and the detailed discrimination between central and obstructive hypopneas are possible by PSG but not by PG. Cardiorespiratory PG gives an indication about the AHI score over the entire recording time, which is often longer than the total sleep time, potentially resulting in an underestimation of OSA severity and an increase in the rate of false negative results.[324] PG can be assembled at home by the patients themselves using simple instructions. This may result in a slightly higher failure rate of about 3-18% compared to in-hospital PSG[325] but increases the acceptability by patients.[239] Current PG devices can be paired with software programs that enable automated analysis of the recordings and accurate determination of the AHI.[326,327] However, manual review of the raw data to assess the quality of recordings and exclude artefacts is recommended[328] and manual review and rescoring might be necessary in some cases. The semi-automated read-out of the measurements could potentially be interpreted by trained nurses or other healthcare professionals. A number of randomized controlled trials have demonstrated comparable outcomes for patients when managed using models of care that involved home PG testing with good diagnostic accuracy.[329-334] It must be acknowledged that these studies were generally performed in patients with predominant OSA and few comorbidities. The exact sensitivity and specificity of home sleep testing devices compared to PSG specifically in AF patients is unclear. A negative PG result may not always rule out OSA and a PSG should be considered when clinical suspicion remains high.[335,336]

Overnight oximetry via a finger probe may be useful for identifying patients with severe OSA and high nocturnal hypoxemic burden. Previous studies performed in the general population or in smaller cohorts of patients with specific concomitant conditions such as a high cardiovascular risk or stroke suggested a good performance of overnight oximetry to diagnose sleep apnea.[337,338] However, other studies have questioned the diagnostic utility of oximetry-derived

parameters in these populations.[339-343] Validation studies of the diagnostic accuracy of overnight oximetry specifically in patients with paroxysmal and persistent AF are not available.

Algorithms implemented in implantable electronic devices, such as pacemakers, have been developed to remotely monitor OSA severity by quantifying apneic events based on changes in breathing-synchronous transthoracic impedance and minute ventilation sensors.[344] Different studies have shown a sensitivity of 75-89% and specificity of 67-94% for the diagnosis of OSA.[345-348] Recently, Mazza et al. showed that pacemaker-diagnosed severe sleep apnea was predictive for new-onset AF and that it was independently associated with a higher AF burden.[349] However, it is not clear whether these algorithms and provided parameters can be used in a broad screening approach in AF patients. Additionally, different mobile applications have been developed to track sleep time and sleep stages. Breathing movements and breathing abnormalities can be detected by analysis of breathing synchronous changes in reflected frequency-modulated sound signals emitted by a smartphone located next to the bed. These apps are not yet validated in an AF population.[350,351] Continuous monitoring of OSA burden in patients with diagnosed sleep disordered breathing and who are using CPAP treatment could provide insight into therapeutic efficacy and compliance with CPAP. More research about these features is needed.

Cardiorespiratory PG may be a suitable method to optimize patient access and to implement OSA testing in the standard work-up of AF patients considered for rhythm control strategies, although specific validation studies in AF populations are needed. PSG is useful to further characterize treatment resistant causes of OSA or obesity hypoventilation syndrome. In patients with AF and concomitant heart failure, confirmation of the diagnosis of predominant CSA and Cheyne-Stokes respiration by PSG is advised, because it may influence the type of positive airway pressure therapy applied.[322] However, neither clinical relevance of a further characterization of sleep apnea nor treatment recommendations for AF patients with sleep disordered breathing other than predominant OSA are mentioned or discussed in the current AF-guidelines.[63]

WHERE TO TEST AND WHO SHOULD TEST FOR OBSTRUCTIVE SLEEP APNEA IN ATRIAL FIBRILLATION PATIENTS

Given the high prevalence of undiagnosed OSA without OSA specific symptoms in AF patients, most patients will present for the management of AF and AF related problems in a cardiology or electrophysiology clinic without prior consultation with a sleep physician.[219,244,248,265] From a practical point of view, it would be desirable to incorporate home cardiorespiratory PG testing and analyses in cardiology or electrophysiology clinics, where most AF patients first present. This service can be offered to patients in the same way as ambulatory ECG Holter or blood pressure monitoring without putting a high burden on the patients. Nurses in AF-Clinics, who are generally experienced in the management and analysis of long-term remote monitoring such as ECG Holter, can be trained by sleep specialists to perform specific history taking and to manage and interpret the results of the PG sleep study.[352] Initiation of CPAP or other OSA therapies, when indicated, should be arranged through a sleep specialist center. However, long term follow-up to evaluate patient progress and monitor CPAP adherence could be conducted by the dedicated AF-Clinic in collaboration with a sleep specialist center in an interdisciplinary manner, with referrals to the sleep clinic when required.

Providing a comprehensive care approach underlines the importance of risk factor management as the fourth pillar in the treatment of AF patients.[71] Consequently, the proposed OSA testing strategy could be implemented following an interdisciplinary risk factor management approach within a specialized AF-Clinic.[66,67,70,353,354] Such clinics focus on the assessment of important cardiovascular risk factors, provide continuous support and patient education and assure guideline-adherent AF management.[97,98,102] Different trials have shown that a structured and integrated care approach within a nurse-led AF-Clinic is effective as it improves outcomes (i.e. reduced cardiovascular hospitalizations and mortality) in a dominant and cost-effective way.[47,99-101,355,356] In the ARREST-AF cohort study and LEGACY study, a physician-led aggressive risk factor reduction program in overweight AF patients reduced the duration, frequency and symptom severity of AF, and thus resulted in a longer arrhythmia-free survival after PVI ablation,[66,70] which also resulted in a reduction in the number of specialist visits, hospitalizations, emergency presentations and ablation procedure-related costs.[354]

Similar to AF, OSA is considered a chronic condition and hence it should be included in the long-term management of AF patients. To achieve this, a more integrated approach to care with interdisciplinary collaboration is needed to coordinate care between the cardiology clinic and the sleep clinic and optimize management in patients with AF. Whether the implementation of OSA testing and management in AF patients can further help to reduce symptoms and maintain sinus rhythm needs to be investigated in prospective randomized trials.

A PROPOSAL FOR AN INTEGRATED CARE PATHWAY TO TEST FOR AND TO COORDINATE THE MANAGEMENT OF OBSTRUCTIVE SLEEP APNEA IN ATRIAL FIBRILLATION PATIENTS

Here, we present a proposal for an integrated care pathway to test for and to coordinate the management of OSA in patients with symptomatic AF considered for antiarrhythmic therapy to optimize treatment outcomes **(Figure 7.2)**. This proposal serves as a practice example. However, application in practice may need to be adapted to suit cultural and country-specific differences in health policy and available resources.

An integrated care approach, as recommended by the ESC guidelines, should incorporate four major elements: i) patient involvement, ii) interdisciplinary care teams, iii) use of technology and devices and iv) a comprehensive approach to care.[63] A nurse could take the lead in this process and act as the care coordinator.[47,100-102,355-359]

Ideally all patients with newly detected AF will be seen at least once in the cardiology or AF-Clinic for diagnostic work-up and guideline based treatment accordingly. As recommended by the ESC guidelines, a comprehensive treatment approach incorporating management of AF, stroke prevention as well as detection and management of risk factors such as OSA should be applied. When a patient is considered for antiarrhythmic therapy or reports excessive daytime sleepiness, testing for OSA should commence with history taking along with an assessment of relevant clinical parameters. The patient should be questioned about typical OSA related symptoms, as well as general sleep behaviors and nocturnal symptoms suggestive of AF episodes. Therefore, it is important to involve spouses in these conversations, since they may have witnessed apneas or snoring during

sleep and this information is particularly valuable in patients without other OSA related symptoms. In addition to older age and male gender, body mass index and drug resistant hypertension or non-dipping blood pressure patterns at night can be factors that should raise suspicion for OSA. Screening questionnaires alone are likely to be of limited value to diagnose OSA in AF patients but can be important to evaluate the severity of OSA symptoms like daytime sleepiness.

PG home monitoring is likely the way forward to test for OSA in patients with symptomatic AF considered for antiarrhythmic therapy. These devices provide reliable results for an initial assessment of OSA while reducing costs and the burden on the patient. PG could be implemented within the cardiology or AF-Clinic. Level 3 PG sleep testing devices **(Table 7.2)** that include additional ECG channels might be helpful to detect a temporal relationship between apneas and nocturnal bradycardia or AF episodes. PG recording can be digitally exported and sent to a sleep specialist center for analysis and interpretation. Alternatively, the PG data can be analyzed using a semi-automated algorithm provided with several PG systems followed by a manual review of the raw data to exclude artefacts and interpretation by OSA-trained technicians or nurses in the AF-Clinic.

Currently, there is no consensus concerning which AHI threshold determined by PG should trigger referral of AF patients to a sleep specialist center for CPAP initiation. Based on the inclusion criteria from most of the available non-randomized studies on the effect of CPAP in AF patients[227,230,232], the authors propose that an evidenced based OSA treatment (e.g. CPAP, mandibular advancement devices, a position modification device to prevent supine sleep, and surgery for severe tonsillar hypertrophy) should be initiated in all patients having symptomatic AF with an AHI of greater than 15/h and predominant OSA. Initiation of CPAP, the first line treatment for moderate-severe OSA, and follow-up of CPAP adherence should be conducted by an interdisciplinary team consisting of the dedicated AF-Clinic and sleep specialist center. This allows nurses and physicians to provide patient-centered care including education, motivational interviewing and encourage patients to actively perform self-management (e.g. consistent and efficient use of CPAP in the home situation) aiming to incorporate such therapies into the patient's lifestyle.

For the initiation of CPAP or further characterization of sleep disordered breathing, if needed, the patient can be referred from the AF-Clinic directly to the sleep specialist center. CPAP should always be initiated in conjunction with additional lifestyle interventions including risk factor modification, weight reduction, exercise and alcohol avoidance. These interventions have been shown to reduce OSA severity as well as AF burden, independent of an OSA diagnosis.[66,70]

Efficacy of CPAP depends on adherence levels. CPAP adherence can be checked and evaluated during standard follow-up visits in the AF-Clinic. Data downloads from CPAP devices can provide useful information, including CPAP usage time, residual AHI and air leakage of the CPAP mask. Additionally, CPAP side effects such as dry nose and eyes, mask leaks and irritation of the skin should be evaluated. Standard annual PG during CPAP treatment is not recommended[336] although reassessment of sleep apnea severity off CPAP therapy is advised if and when a patient is successful in losing substantial body weight. Recurrence of AF during CPAP treatment in patients with severe OSA may trigger a further examination and possibly a new referral to the sleep specialist center.

A care coordinator should monitor and document the patient's care process and inform all involved specialists and the patient about test results and overall progress. In fact, the care coordinator forms the intermediary between specialists and can act as the spokesperson for the patient in the interdisciplinary communication. OSA and AF trained nurses can evaluate demographic features, history taking and AF and OSA symptom burden following standardized OSA related questionnaires or checklists. In addition to the dedicated tasks of physicians and nurses in this care pathway, AF patients should also be well-informed and actively engaged in their own self-management to ensure good compliance with CPAP therapy and other aspects of their care. Dedicated communication and close collaboration between the AF-Clinic with the cardiologists and well-trained AF nurses or care coordinators, and the sleep clinic with the sleep physician, is paramount in this respect and underlies the integrated approach.

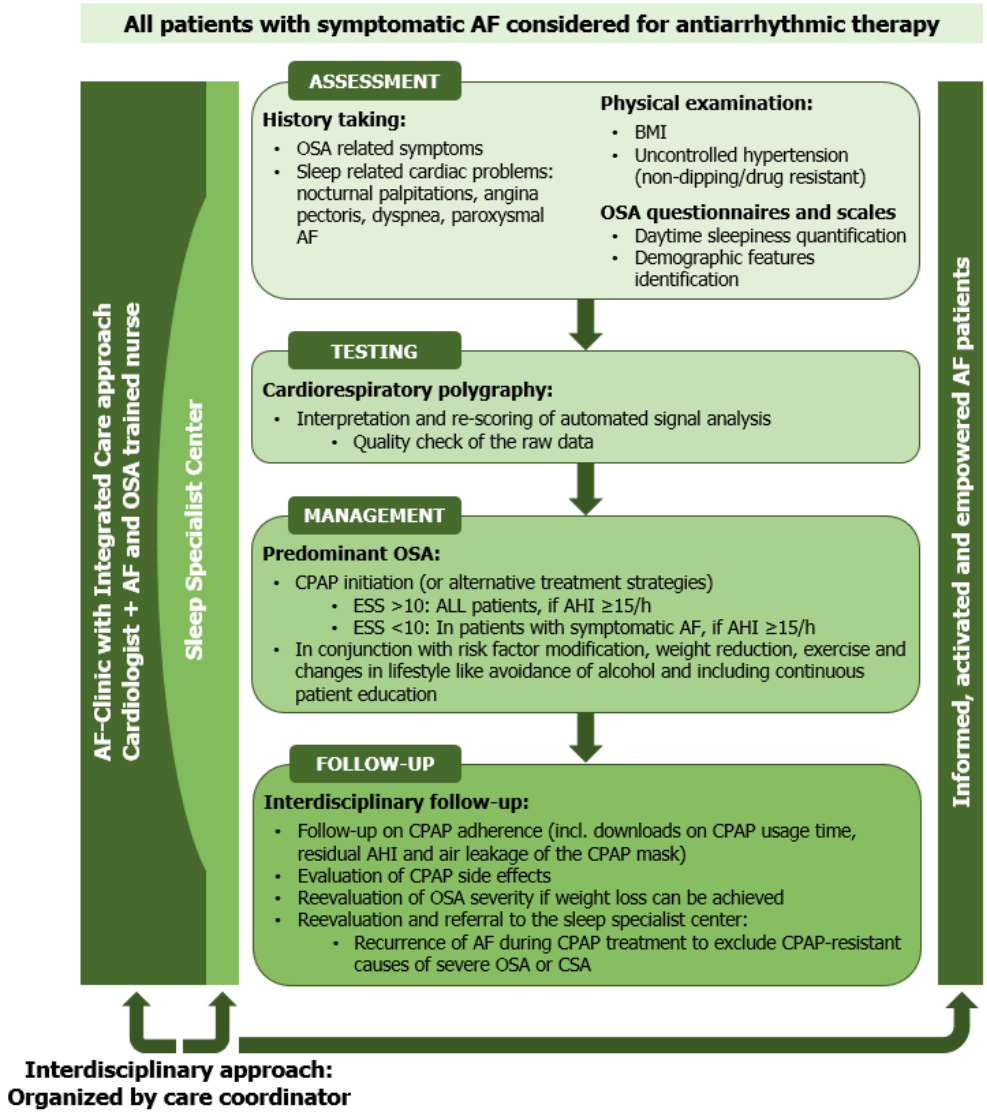

Figure 7.2: Proposal of an integrated care pathway on testing for obstructive sleep apnea in atrial fibrillation patients. AF: atrial fibrillation, AHI: apnea–hypopnea index, BMI: body mass index, CPAP: continuous positive airway pressure, CSA: central sleep apnea, ESS: Epworth Sleepiness Scale, OSA: obstructive sleep apnea.

FUTURE PERSPECTIVES AND OPEN QUESTIONS

Besides the fact that current evidence advocates a more integrated role for OSA testing and treatment in AF management, there is still a need for large-scale prospective trials testing proposed identification strategies like the one recommended in this paper. From a theoretical point of view, not just testing for OSA and follow-up during CPAP treatment, but even CPAP initiation could be performed and organized by a more integrated sleep specialist center as part of the AF-Clinic, bearing in mind cultural differences and healthcare organization. More information is needed concerning the feasibility, accuracy, impact and especially the cost-effectiveness of the implementation of universal testing and treatment strategies for OSA in daily AF care. Additional randomized controlled studies are required to confirm the success of OSA treatment on different outcomes in AF (e.g. arrhythmia burden, stroke, quality of life). Moreover, it is known that 11.5-46% of the patients with OSA are not able to tolerate or to be compliant with their CPAP therapy, or even do not initiate it.[360-364] CPAP compliance in AF patients treated for AF symptom burden without excessive daytime sleepiness or in patients with low AF symptom burden and without excessive daytime sleepiness is unknown. The effects of alternative treatment options such as a mandibular advancement device, weight reduction, a position modification device to prevent supine sleep or surgical treatment of sleep related upper airway obstructions on AF burden and symptoms have not been studied so far. It is also not known whether commencing antiarrhythmic therapy, including pharmacological or interventional strategies, should be postponed until OSA and other cardiovascular risk factors have been evaluated and addressed. More research is also needed to evaluate which AHI thresholds and indications are required for OSA treatment in AF patients.

In summary, further research should reveal whether the recommendation in the ESC 2016 AF guidelines[63] to interrogate AF patients for clinical signs of OSA and the proposed integrated care pathway is an effective and cost-effective part of AF management.

CONCLUSIONS

OSA represents a well-established, but possibly under-recognized and underdiagnosed risk factor for AF patients in current care settings. This review makes a case for structured OSA testing and appropriate CPAP treatment in patients with symptomatic AF being considered for rhythm control strategies and antiarrhythmic therapy to optimize treatment outcomes. Questionnaires alone cannot rule out OSA in AF patients as most AF patients with concomitant OSA do not report daytime sleepiness. An integrated care approach within a cardiology or specialized AF-Clinic, using cardiorespiratory PG home sleep testing is likely the way forward to systematically characterize OSA in AF patients. Interdisciplinary follow-up on CPAP adherence should be organized by the dedicated AF-Clinic in collaboration with the sleep specialist center which could facilitate early referrals to a sleep specialist clinic if needed.

GENERAL DISCUSSION

The main aim of this thesis was to set up and evaluate different unique and innovative projects within the framework of an integrated care approach for patients with AF. In this way, we wanted to contribute to important steps that can be instrumental to help tertiary care centers to establish an AF clinic.

Main findings

Different steps were taken in this PhD dissertation to evaluate the feasibility, effectiveness and cost-effectiveness of key interventions for patients with AF.

In **chapter 1** the usability, accuracy and cost-effectiveness of two handheld ECG devices were evaluated as not much was known about their performance in an in-hospital setting. In wards of patients with a high prevalence of AF, a more systematic screening for AF than pulse taking by the nurses may be able to detect unknown AF. Although we showed that the accuracy of these devices was much lower than previously reported in out-of-hospital settings, a well-planned screening strategy can be applied to effectively and cost-effectively screen for AF in hospital wards using these devices.[365,366]

The newly developed and validated Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ) is a brief but complete questionnaire that can be used to assess patients' insight into their condition **(Chapter 2)**.[147] In this study, major knowledge gaps were revealed. Afterwards, two strategies were used to improve the knowledge level of AF patients about their arrhythmia and its treatment. First, in **chapter 3**, a targeted educational approach was used. During regular time points, AF patients received short in-person education sessions in which education was specifically targeted to the aspects incorrectly answered on the JAKQ. Next, in **chapter 4**, a more tailored approach was used. Patients undergoing a direct current cardioversion (DCC) or pulmonary vein isolation (PVI), received access to an online education platform that allowed tailored education, i.e. patients only had access to the aspects that were personally relevant. Both strategies based on a more personalized approach to provide education showed to be effective in an AF population.

Given (i) the fact that non-vitamin K antagonist oral anticoagulants (NOACs) are now the first choice therapy for thromboembolic prevention in AF patients (unless contraindications); (ii) the short half-lives of these NOACs; (iii) that routine coagulation monitoring is not required anymore with NOACs, initiatives are needed to improve adherence to these medications as a critical factor for their safety and effectiveness. In **chapter 5**, we showed that daily telemonitoring and telemonitoring with immediate telephone feedback in case of intake errors are effective and possibly also cost-effective approaches in selected patients to achieve a strict therapy adherence to NOACs.[169] In **chapter 6**, we described the development process, feasibility and effectiveness of the Health Buddies application, which was an innovative concept based on a social contract between AF patients and their grandchildren.[367] Although the app was perceived as clear, novel, attractive, stimulating, and educational by its users, only a small proportion of the current AF population was eligible or was willing to use the app in its current form.

Finally, **chapter 7** summarizes the available literature concerning the need for obstructive sleep apnea (OSA) testing and management in patients with AF.[368] With the recent attention for the management and treatment of concomitant (modifiable) cardiovascular risk factors in AF patients, a team of experts in the field of both sleep medicine and AF, came forward with a proposal for an integrated care pathway to test for OSA in AF patients.

The studies described in this thesis do not primarily target themselves cellular or pathophysiological processes involved in AF development and progression, but can nevertheless indirectly contribute to a more causal treatment of AF.

Atrial fibrillation burden will further increase

Atrial fibrillation is a highly prevalent heart rhythm disorder and it is associated with many other comorbidities.[3,4] It requires long-lasting treatment and follow-up and it puts a large burden on the healthcare system and the society.[4,17,36] Moreover, its prevalence will dramatically increase during the following years further putting a significant strain on healthcare resources and probably resulting in capacity problems for hospitals and increased waiting lists at outpatient clinics.[10,11,13,15] Given the complex and multifactorial management of patients with AF, there is an urgent need for a more structured care for these patients. A

more sustainable approach should not only benefit the patient, but also the healthcare providers and the policy makers.

Fundamentals of an integrated AF care

At the start of this PhD project, little was known about "AF clinics" or integrated care for patients with AF and how this should be implemented. The only study that was published at that point in time was the single center randomized controlled trial (RCT) by Hendriks et al. performed in the Netherlands (see Table 1 in the introduction for more details).[47] Throughout the time course of this PhD, more and more evidence became available to support an AF management that is based on integrated nurse-led care.[98,100-102,356,369,370] However, despite this evidence, it is still hard to figure out which components of the integrated care program led to the beneficial results. It is even more important to know how these components and/or interventions should be implemented. Only few hospitals worldwide have succeeded to set up some sort of an AF clinic providing a more structured daily care to these patients.

Nevertheless, the 2016 European Society of Cardiology (ESC) Guidelines on the management of AF came up with a framework to structure AF management based on an integrated approach (see Figure 3 in the introduction) taken into account four different aspects.[4] Also the 2015 and 2018 Updates of the European Heart Rhythm Association (EHRA) Practical Guide on the use of NOACs in patients with AF make a strong point for a more structured care, education and follow-up of these patients.[61,62,141,371]

Towards informed, involved and empowered patients

First, patient involvement is very important and AF patients should have a central role in the entire care process. Every patient should be correctly informed and trained and is in the end responsible to be adherent to his therapy, to adhere to follow-up appointments with different healthcare providers and to adopt a healthy lifestyle. However, a proper self-care or shared decision-making is not possible without the necessary education provided by physicians and other healthcare professionals and by making use of different tools. Nevertheless, during the previous years, a bunch of studies showed that the knowledge level and insight of AF patients about their arrhythmia and its management are poor even after they

received verbal and/or written information.[122-124,126-129,131-136,147-149] Also the results from our own center, gathered by means of the validated JAKQ, showed important knowledge gaps in our AF population. Patients had a mean score of 55.8% on the JAKQ **(Chapter 2)**.[147] In less than two years, more than 20 physicians, nurses and researchers from around the world requested to use the JAKQ in daily care or for their research. Data from Poland in which the JAKQ was completed by almost 500 AF patients revealed similar results with a mean knowledge score of 60.7% in patients on NOACs and 61.6% in those taking a VKA.[149] The JAKQ showed again a good discriminatory potential indicating the validity and usability of this questionnaire. This study provided additional evidence that there is room for improvement and a need for a structured educational program for AF patients.

During the previous years, different educational interventions were tested in AF patients: brochures[130,132,134,150], educational videos[130,133,134,372], group education sessions[133], general face-to-face education[47,150], a complex general practice driven program[151] and a mobile application[152]. However, the results of most of these interventions were disappointing: e.g. patients were not able to retain much knowledge after even a short period of time; the educational intervention had no or limited impact on the adherence to oral anticoagulation (OAC) therapy. Recently, the results of the IMPACT-AF trial were published.[154] Vinereanu and colleagues were able to show that an educational intervention for healthcare providers and patients together with regular monitoring and feedback (i.e. identifying study participants not on OAC treatment or at risk for not staying on medications and trying to intervene to (re)start OAC or to prevent discontinuation and improve adherence) resulted in an increased proportion of patients treated with OACs.[154] The majority of the 2281 patients included in this trial was however still on VKA therapy. Notwithstanding the positive results of this trial, it is not clear if the impact was mostly due to the training of the healthcare providers or due to a possibly improved knowledge and self-care of the AF patients. The FACILITA study, published in 2018, showed that an intervention consisting of patient education and a simple calendar reminder, led to an improved adherence to dabigatran.[168] These results were in stark contrast with the large international AEGEAN trial.[167] This trial in more than 1100 patients did not show any impact of an elaborate and structured educational program (i.e. booklet,

reminder tools, follow-up telephone calls and access to a virtual clinic) on adherence to NOAC apixaban.[167] Although the education studies described in this thesis included a small number of patients, we proved that reinforced targeted in-person education **(chapter 3)** and tailored online education **(chapter 4)** are both structured and effective methods to provide patient education. Moreover these methods are feasible to implement in daily care and do not require much time or efforts from healthcare providers. The impact of online tailored education on the long-term needs further investigation.

An increased patient involvement also includes a better self-management of (modifiable) cardiovascular risk factors. The ARREST-AF and LEGACY study, provided key evidence that an aggressive risk factor reduction program focusing on weight management, hyperlipidemia, OSA, hypertension, diabetes, smoking cessation and alcohol reduction decreased the duration, frequency and symptom severity of AF after a PVI ablation.[66,70] The CARDIO-FIT study provided further evidence that this risk factor management together with a tailored exercise program can improve cardiorespiratory fitness and weight loss, resulting in a reduction in AF burden and maintenance of sinus rhythm in obese individuals with symptomatic AF.[353] Such an approach is not only clinically effective, it also proved to be cost saving.[354] Integrated care pathways as described in **chapter 7** can be of added value to implement this risk factor management in daily practice.

A multidisciplinary AF care team

Second, working together in a multidisciplinary chronic AF care team is the way to move forward.[4,97,98,373] Managing the entire care of AF patients by the cardiologist/electrophysiologist only is no longer at issue. Specific tasks could and should be delegated from the specialist to nurses, allied health professionals and general practitioners (GPs). Thorough training and education of the different healthcare providers is however required. Specialized allied health professionals or AF-nurses can play an important role in educating patients and in coordinating their overall care, while the cardiologist will remain responsible for the medical aspects. This care management can occur in both a nurse-coordinated or a more nurse-assisted care approach as nicely elaborated in a current opinion paper by experts in the field of AF care.[97] The exact implementation will depend on the

structure and requirements of each institution. The different interventions described in this thesis **(Chapter 1-6)** were all performed by allied health professionals. Also in the proposed integrated care pathway to manage OSA **(Chapter 7)**, there was a central role for a specialist nurse as a care coordinator.

Technology tools, mHealth and eHealth

Third, technology tools cannot be ignored anymore in the care of AF patients. A dedicated navigation system or decision support software would be of added value to support the implementation of guideline-based AF care.[4,97] This should work as an expert tool for the management of AF, that includes checklists and a systematic overview of the patient and his medical history, to guide cardiologists as well as allied health professionals and AF-nurses through the care of every AF patient in a more individualized manner. It is however difficult to make a uniform system that can be used in every country and care system. Care centers are therefore often self-reliant to develop and to implement such systems. In 2017, the CATCH ME Consortium proposed the MyAF patient app as well as the AF Manager app.[175] The MyAF app aims to improve patient education, enhance communication between patients and healthcare providers, and encourage active patient involvement. The patient app also provides a personal health record and symptom diary. The AF Manager app was developed as a guideline-based decision support and patient management tool for healthcare providers.[175] The functionality and impact of both applications remains to be investigated.

Timely detection of AF is an important aspect that fits within a holistic approach of an AF clinic. **Chapter 1** of this thesis addressed this topic as it is a first step towards the prevention of AF-related complications in high risk, often asymptomatic patients. Different new technologies and tools exist to screen for AF, e.g. automated blood pressure monitors, patches, smartwatches, small holters, sticks, handheld devices, smartphone cases, applications based on photoplethysmography, etc.[374,375] In our own study we chose to evaluate AliveCor and MyDiagnostick as both devices were already validated in an outpatient setting and were commercially available. One should bear in mind that all these devices should be thoroughly validated before they should be implemented in daily practice. Accuracy and usability can be different between certain populations and settings as we showed in **chapter 1**. Moreover,

confirmation of AF on an electrocardiogram (ECG), as these devices do, is still needed before OAC therapy can be initiated according to the Guidelines.[374]

Telemedicine (i.e. providing health care from a distance) becomes important in different subspecialties of cardiology and can also be used to remotely follow-up on AF patients.[376] It can be used to (i) monitor the frequency and burden of AF by the different tools stated above, (ii) follow-up on symptoms, quality of life (QOL), etc. (iii) support AF patients in their rehabilitation programs, and (iv) provide patient education. In **chapter 4**, in which we evaluated the usability and effectiveness of an online education platform for AF patients, more than 80% of the patients indicated the perceived added value from receiving extra remote follow-up by means of questionnaires at regular time points. Also in **chapter 5**, 63.8% of the patients indicated that telemonitoring of NOAC intake, increased their awareness about a strict medication adherence. Moreover, almost all patients (97.6%) acknowledged that receiving direct telephone feedback based on telemonitoring was useful.

The upcoming trend of mHealth and eHealth is unavoidable. It opens a way of different opportunities but also includes many challenges. mHealth and eHealth tools are often scalable which allows us to reach and support a lot of patients with often less efforts from healthcare providers. It provides us with much more data that can be used to map the arrhythmia burden and overall healthcare status of the patient and can provide information to set up a management plan and evaluate the effectiveness of the chosen treatment strategy. However, from the different trials performed in the context of this thesis, it is shown that the average age of the AF population is about 71-73 years.[147,366] Although the use of technology and mobile devices is increasing in this population, it cannot be used for all AF patients because they have no device or are not yet familiar to use it. In **chapter 4**, 53% of the patients planned to undergo a DCC or a PVI ablation, had a portable computer, tablet or smartphone and was able to use it by themselves. In **chapter 6**, about 30% of the patients recruited for the study with the Health Buddies application had no compatible device. When making use of mobile applications, it is an added value to develop these tools together with the patients by organizing focus groups and workshops, as was performed with the Health Buddies application, to better take into account their suggestions and wishes.

Complex AF treatment and management guided by an AF Heart Team

Fourth, optimal AF management includes that all patients have access to the entire spectrum of treatment options. Not only the AF-specific therapy (OAC, rate control and rhythm control), but also a structured support to improve their general lifestyle.[4] The cardiologist remains responsible for the correct treatment initiation and follow-up but can be assisted by an AF-nurse, allied health professionals, GPs, and other specialists. Together, an AF Heart Team can be set up to individualize and guide the complex management of AF patients especially for those complex cases requiring specialist multidisciplinary input.[373]

Structured clinics should also enable a more systematic feedback between management actions and their effects, which currently is largely lacking in classical care: if we educate patients, how well does this improve their understanding and ability for self-care?; if we prescribe medications, how well are they taken?; if we plan follow-up visits (with the GP, cardiologist, other specialists), do patients really present for those visits; etc.?

A good collaboration and communication between the cardiology department or AF clinic and other specialists (neurologists, surgeons, endocrinologists,…) is of paramount importance and can also be supported by technology tools or supportive management software. An AF-center should be able to provide a hospital-wide support. It should be able to provide support (e.g. patient education) or advice (e.g. concerning stroke prevention, management of comorbidities, perioperative management of OAC) to other non-cardiology wards, when needed. In **chapter 1**, we showed that the total prevalence of AF patients hospitalized at the geriatric ward was 36%, indicating the high burden of AF patients in this ward.[366]

Also a good communication between the different healthcare providers and the patient himself about the treatment plan is a very important aspect that is sometimes overlooked.

Towards a more individualized atrial fibrillation care

A structural change in the entire approach of care delivery is needed to be able to provide every AF patient with a Guideline-based individualized care.[4,98,125,145,377] In this way, patient outcomes can be improved and also patient's satisfaction can be optimized.[4,47,100-103,356] In different studies described in this thesis **(Chapter 4, 5 and 6)** we used general or very study-specific patient reported outcome measure (PROM) questionnaires not only to evaluate the impact of the intervention on secondary outcome measures but also to take into account the opinion and feedback of the patient, an aspect that is often lacking in a lot of trials.

According to a consensus document from ERHA published in 2015, it was indicated that education should be provided in a more structured and individualized manner.[125] Both targeted in-person education **(Chapter 3)** and tailored online education **(Chapter 4)** were personalized methods to provide education and both were proved to be effective. Likewise, in the telemonitoring project of adherence to NOACs **(Chapter 5)**, feedback to optimize therapy compliance was provided in an individualized way.

As every AF patient is different, clinical decision support systems or software will be key to guide this individualized care as described above. It should allow to set up a completely individualized management plan for every patient. This individualized AF care should be available for both hospitalized patients as well as patients visiting the outpatient clinic.

Health economic impact

The effectiveness of a tested intervention is of course very important, but the health economic impact should not be overlooked. In the longer term, cost-effectiveness data about integrated care for AF patients is instrumental in defining correct reimbursement schemes to set-up and implement AF centers.

In **chapter 1** we evaluated the costs per newly identified AF patient and the costs per prevented stroke, using different screening strategies with the MyDiagnostick and the AliveCor screening device.[366] In **chapter 5** we performed different simulations of cost scenarios associated with the provision of telemonitoring of NOAC adherence with direct feedback to AF patients and we also calculated the

incremental costs per prevented stroke for the different adherence scenarios.[169] In **chapter 3**, the time to provide targeted in-person education based on the JAKQ was measured during each visit. These data can be used to gain insight into the burden for the allied health professionals providing education and the associated personnel costs.

However, due to the short study duration and the low number of patients included in the trials described in this thesis, we did not make use of other health economic evaluations, such as the calculation of the incremental cost-effectiveness ratio (ICER) with possible effects on life-years gained (i.e. cost-effectiveness analyses) or on quality-adjusted life years (QALY) (i.e. cost-utility analyses).[378]

Of the three important integrated care studies for AF (summarized in Table 1 in the introduction), only one included a health economic analysis. The study of Hendriks et al. showed that a nurse-led integrated care approach was able to save costs (from a hospital perspective) together with an improved survival and QOL.[99] The CENT study by Pathak et al. showed that concentrating on the prevention and management of cardiovascular risk factors in AF patients can also be cost saving. Physician-directed risk factor management led to an ICER of $62,653 saved per QALY gained, based on a 10-year model.[354]

Other data are not available at this moment and the cost-effectiveness of integrated care for AF patients therefore requires further investigation. Yet, it can of course be expected that costly adjustments are needed to restructure care in the start-up phase of an AF-clinic, but this can certainly pay off on the long term.

Future perspectives and upcoming trials

Despite the available evidence and the studies performed and described in the scope of this PhD project, many questions remain and more research is needed. The studies described in this thesis were often promising but were still single center studies and generalizability of the results to other hospitals should be made with caution. Larger multicenter RCTs are therefore desired to evaluate the impact of the various interventions that were tested on different clinical outcome data (e.g. complications, hospitalizations, emergency room visits) and on other secondary outcome measures for which most trials were not powered.

Data about cost-effectiveness and implementation strategies are largely lacking at this very moment. Future studies should clearly indicate the methodology applied, personnel required, and the tools that were used. Only in this way, replication or implementation of the study results in other centers is possible. Nevertheless, cultural and regional differences should always be kept in mind and can complicate this implementation process.

Additional evidence is on its way. The integrated care for atrial fibrillation RACE-4 study (NCT01740037) is built upon the results of the study of Hendriks et al.[47,99,103,379] This multicenter RCT from the Netherlands will further evaluate if an integrated care treatment at a specialized AF clinic is superior to usual care in terms of cardiovascular mortality and cardiovascular hospitalizations, cost-effectiveness, QOL and guideline adherence. The study targets 1716 patients newly diagnosed with AF or AF patients without a regular control at a cardiologist for AF in the last 2 years who are referred to the outpatient clinic. Results are probably expected in 2019.

The multicenter Australian iCare-AF RCT (ACTRN12616001109493) was recently set up to investigate the effectiveness of integrated specialized clinics for AF focusing on structured AF management by a multidisciplinary team and aggressive risk factor management on all-cause hospitalization and mortality. The study population will consist of 1376 AF patients presenting to the emergency department or cardiology outpatient clinic. Final results are expected in 2021-2022.

Finally, recruitment recently started in the CardioCare MV (NCT03317951) study. This German RCT evaluates a novel integrated care concept for patients suffering from a chronic cardiovascular disease and more specifically heart failure, AF or therapy resistant hypertension. The intervention combines telemedicine with intensive support by a call center, together with an integrated care network including in- and outpatient care providers and guideline therapy. With 2930 patients and a patient follow-up of one year, the researchers expect an impact on: (i) a composite endpoint of mortality, stroke and myocardial infarction; (ii) the number of hospitalizations; (iii) a composite endpoint of death and broader cardiovascular events (including cardiac decompensation).

The results from these three upcoming trials will provide important evidence about whether integrated AF care effectively works in a multicenter setting. However, it also needs to be stressed that performing a RCT is not always the gold standard for complex interventions such as integrated care provided by an AF clinic. Although RCTs are considered to provide the highest level of evidence to test the validity of a certain intervention, they have their limitations.[380] If the results of these RCTs cannot be implemented in clinical practice, these trials lose part of their validity. Therefore, preparatory studies as performed in this thesis are also important to make a first evaluation of the feasibility and effectiveness of the intervention.

Likewise, our own research group will start with two new multicenter projects within the scope of an integrated care for AF patients further focusing on the factors that could have contributed to the success of a nurse-led integrated AF care program. These projects are funded through the Flemish government, which demonstrates the interest of health authorities in finding ways to optimize the implementation of guideline-based care through enhanced patient involvement. In these studies (registration at ClinicalTrials.gov is pending) an implementation aspect will be coupled to a research aspect together with a health economic aspect. The first study is a large-scale prospective trial, focusing on integral targeted and structured educational programs for AF patients. The educational programs are largely based on the interventions tested and insights acquired from the studies described in **chapter 2-5.** The pillar that will be focused on in the second multicenter trial is the improvement of the communication aspect between different healthcare providers as well as the patient himself. We will evaluate the implementation, feasibility and impact on the delivery of AF care via a new concept, namely the 'AF passport' as a communication tool. Further, as we are convinced that AF care delivery has to span the whole spectrum of AF patients, both trials will not focus on specific AF populations: they will include nearly every AF patient, ambulatory or hospitalized with almost no restriction on inclusion criteria.

General conclusion

This PhD thesis provides important knowledge about the feasibility, effectiveness, cost-effectiveness and practical implications of different interventions that fit within the framework on our way to the development of an interdisciplinary nurse-coordinated AF clinic. Projects were built around 4 different cornerstones of an integrated AF care: screening for AF, education for patients with AF, adherence to NOACs and risk factor management.

For most projects described in this thesis, further multicenter research is necessary to determine the generalizability of the approaches and their effectiveness on different clinical outcomes as well as overall cost-effectiveness, before widespread implementation can occur. We are not there yet, but the insights gathered from this thesis could be an important step forward on our road towards the implementation of a patient-centered nurse-led AF clinic and a better overall care for patients with AF.

SUMMARY

Atrial fibrillation (AF) is the most common heart arrhythmia and is associated with increased morbidity and mortality. It places an enormous burden on the current society and healthcare system and it is expected that the worldwide prevalence will at least double over the next 50 years. Optimization of AF management will need to be a prime public health focus over the next decades. There is a high need for more efficient care models and a structured approach for the treatment and follow-up of AF patients. A proposed approach to better structure this complex AF management is the establishment of an "interdisciplinary nurse-led AF clinic". Recent studies have shown that nurse-led integrated care is an efficient and cost-effective manner to improve the care of AF patients. However, hospitals and cardiology practices do not have any predefined and structured guidance how this nurse-led integrated care can be implemented in daily practice. Moreover, from the studies that have shown a positive outcome, it is unclear which aspects of the integrated care had most impact on the improved outcomes.

The aim of this thesis was to study the contribution of specific interventions to the effectiveness of an interdisciplinary AF expert program with a focus on four different aspects: **(i)** screening for AF; **(ii)** education for patients with AF; **(iii)** adherence to non-vitamin K antagonist oral anticoagulants (NOACs); **(iv)** risk factor management.

We have shown that the usability and accuracy of handheld electrocardiogram devices to detect AF are not optimal when they are applied in a hospital setting. Nevertheless, making use of a well-planned screening strategy, these devices may provide an effective and cost-effective screening approach **(Chapter 1)**.

The Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ) was developed and validated within the scope of this PhD thesis. It is a brief but complete questionnaire that can be used to assess patients' insight into their condition **(Chapter 2)**. The JAKQ revealed major knowledge gaps in the general AF population. Notwithstanding, it is an ideal tool to efficiently guide and target personalized education. A first targeted educational session based on the JAKQ will significantly improve patients' knowledge level. Additional educational sessions will maintain and even strengthen this effect **(Chapter 3)**. Furthermore,

we showed that tailored education via an online platform is also an effective strategy to improve the knowledge level of AF patients about their arrhythmia and the associated treatment **(Chapter 4)**.

Although electronic monitoring already revealed an unexpectedly high adherence to NOAC therapy, it was shown that telemonitoring-based rapid and personalized feedback could further optimize adherence. This intervention could be cost-effective when higher risk, poorly adherent patients are targeted and when the used technology would become cheaper **(Chapter 5)**. The Health Buddies app was developed as a tool to improve adherence to NOACs in an elderly AF population by providing a virtual contract with their grandchildren. In a pilot study, it was however shown that only a small proportion of the current AF population was eligible for this innovative app in its current form. Still the app was positively rated by its users on most aspects **(Chapter 6)**.

Together with a team of experts in the field we summarized the literature about obstructive sleep apnea testing and management in patients with AF and we came up with a proposal for an integrated care pathway to tackle this cardiovascular risk factor in daily care **(Chapter 7)**. Similar pathways can be developed to provide guidance on how to deal with different modifiable risk factors in AF patients.

These results provide further insights and guidance into the practical aspects, workload, feasibility and impact of different aspects of a patient-centered integrated AF care approach. This can be instrumental for future studies with the aim to improve the overall care of AF patients.

SAMENVATTING

Voorkamerfibrillatie (VKF) is de meest voorkomende hartritmestoornis en het is geassocieerd met een hoge morbiditeit en mortaliteit. Daarenboven zorgt het voor een enorme impact op zowel de maatschappij als het gezondheidssysteem. Er wordt tevens verwacht dat de wereldwijde prevalentie de volgende 50 jaar nog minstens zal verdubbelen. Het is dus van cruciaal belang te werken aan een nieuwe aanpak om de zorg voor VKF patiënten te optimaliseren. Er is nood aan een meer efficiënt zorgsysteem en aan een gestructureerde aanpak voor de behandeling en opvolging van VKF patiënten. Een "interdisciplinair, verpleegkundig-gecoördineerde VKF kliniek" wordt aanzien als een veelbelovende aanpak om deze complexe VKF zorg beter te structureren. Recente studies hebben ook aangetoond dat dit soort geïntegreerde zorgprogramma's een efficiënte en kostenefficiënte manier zijn om de zorg van VKF patiënten te verbeteren. Desondanks is het voor ziekenhuizen en cardiologen zeer moeilijk om deze verpleegkundig-gecoördineerde zorg effectief te implementeren in de dagdagelijkse praktijk omdat er eigenlijk geen duidelijke richtlijnen zijn hoe dit zou moeten gebeuren. Tevens kan er uit de voorgaande studies niet opgemaakt worden welke aspecten van een geïntegreerde zorg nu net bijgedragen hebben tot de positieve effecten.

Het doel van dit proefschrift was om de toegevoegde waarde van specifieke interventies na te gaan die kunnen bijdragen aan de doeltreffendheid van een interdisciplinair VKF zorgprogramma. Hierbij werd er gefocust op vier verschillende aspecten: **(i)** screenen voor VKF; **(ii)** educatie voor patiënten met VKF; **(iii)** therapietrouw voor niet-vitamine K antagonist orale anticoagulantia (NOACs); **(iv)** aanpakken van risicofactoren.

We hebben aangetoond dat de bruikbaarheid en accuraatheid van mobiele elektrocardiogram toestelletjes voor de detectie van VKF niet optimaal zijn wanneer ze gebruikt worden binnen het ziekenhuis. Desondanks kunnen deze toestellen op een effectieve en kosteneffectieve manier ingezet worden om te screenen voor VKF als er een goed georganiseerde aanpak is **(Hoofdstuk 1)**.

In het kader van deze thesis werd de "Jessa Atrial fibrillation Knowledge Questionnaire" (JAKQ) ontwikkeld en gevalideerd. Het is een korte maar volledige vragenlijst die gebruikt kan worden om de inzichten die VKF patiënten hebben in

hun ritmestoornis in kaart te brengen **(Hoofdstuk 2)**. Met behulp van de JAKQ konden er grote lacunes in de kennis van de VKF populatie aangetoond worden. Daarom is de vragenlijst een belangrijk instrument om op een efficiënte manier gerichte educatie te geven. Een eerste gerichte educatiesessie op basis van de JAKQ zal het kennisniveau van de patiënt significant verbeteren. Extra educatiesessies zullen dit effect behouden en zelfs versterken **(Hoofdstuk 3)**. Verder konden we ook aantonen dat gepersonaliseerde educatie via een online platform eveneens een doeltreffende manier is om het kennisniveau van VKF patiënten over hun ritmestoornis en behandeling te verbeteren **(Hoofdstuk 4)**.

Het van op afstand opvolgen van de therapietrouw voor NOACs zorgde reeds voor zeer hoge adherentiewaarden. We konden echter aantonen dat telemonitoring met snelle en gepersonaliseerde feedback deze adherentie verder kon optimaliseren. Deze interventie kan tevens een kosteneffectieve oplossing zijn voor hoog risicopatiënten met een slechte therapietrouw en op voorwaarde dat de technologie goedkoper wordt **(Hoofdstuk 5)**. De nieuw ontwikkelde "Health Buddies" applicatie had als doel de therapietrouw voor NOACs te verhogen bij VKF patiënten en dit door gebruik te maken van een virtueel contract tussen hen en hun kleinkinderen. In een pilootproject bleek echter dat slechts een kleine groep van de huidige VKF populatie in aanmerking kwam om deze innovatieve app in zijn huidige vorm te gebruiken. Nochtans werd de app op verschillende vlakken positief beoordeeld door diegenen die ze gebruikt hebben **(Hoofdstuk 6)**.

Samen met een groep experten, hebben we een overzicht gegeven van de reeds beschikbare literatuur over obstructieve slaapapneu en het testen en opvolgen hiervan bij VKF patiënten. Op basis hiervan kwamen we met een voorstel voor een geïntegreerd zorgtraject om deze cardiovasculaire risicofactor aan te pakken in de dagelijkse zorg **(Hoofdstuk 7)**. Gelijkaardige zorgtrajecten kunnen ontwikkeld worden om op die manier verschillende risicofactoren bij VKF patiënten aan te pakken.

De resultaten van dit proefschrift zullen bijdragen aan betere inzichten omtrent de praktische aanpak, de werklast, de haalbaarheid en de impact van verschillende aspecten van een geïntegreerde VKF zorg waarbij de patiënt centraal staat. Dit kan een hulpmiddel zijn voor toekomstige studies met als uiteindelijk doel de globale zorg voor VKF patiënten te verbeteren.

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CURRICULUM VITAE

"Experience Is One Thing You Can't Get For Nothing."

— Oscar Wilde

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EDUCATION

2012 – 2014	Master Biomedical Sciences: clinical molecular sciences Hasselt University Graduated with: summa cum laude
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RESEARCH EXPERIENCE

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CERTIFICATES

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Experiment Leader in Laboratory Animal Sciences (FELASA C)
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Radiation protection
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SCIENTIFIC AWARDS

June 2017	Best poster prize, LCRP Symposium 2017 - mHealth Visions on the Future, Hasselt, Belgium
October 2016	Best poster prize, Third European Congress on eCardiology and eHealth, Berlin, Germany

SCIENTIFIC GRANTS

January 2018	EHRA 2018 Congress - Educational Grant
June 2017	EHRA EUROPACE-CARDIOSTIM 2017 - NAP Grant
January 2017	Research Foundation Flanders (FWO) Traval Grant K200617N, research internship at the Centre for Heart Rhythm Disorders, University of Adelaide, Royal Adelaide Hospital, Adelaide, Australia, Prof. Dr. Prash Sanders
March 2016	ESC Congress Educational Grant

PAPERS PUBLISHED IN INTERNATIONAL PEER-REVIEWED JOURNALS

1. **Desteghe L**, Germeys J, Vijgen J, Koopman P, Dilling-Boer D, Schurmans J, Delesie M, Dendale P, Heidbuchel H. Effectiveness and usability of an online tailored education platform for atrial fibrillation patients undergoing a direct current cardioversion or pulmonary vein isolation. International journal of cardiology. Epub ahead of print. *(IF: 6.189)*

2. **Desteghe L***, Hendriks ML J*, Chai-Coetzer CL, Dendale P, Sanders P, Heidbuchel H^{+}, Linz D^{+}. The Why, When and How to test for obstructive sleep apnea in patients with atrial fibrillation. Clinical Research in Cardiology. 2018;107(8):617-31. *Shared first authorship, $^{+}$Shared last authorship. *(IF: 4.760)*

3. Konieczyńska M, Sobieraj E, Bryk AH, Dębski M, Polak M, Podolec P, Małecka B, Pająk A, **Desteghe L**, Heidbuchel H, Undas A. Differences in knowledge among patients with atrial fibrillation receiving non-vitamin K antagonist oral anticoagulants and vitamin K antagonists. Kardiologia Polska. 2018;76(7):1089-96. *(IF: 1.341)*

4. Steffel J, Verhamme P, Potpara T, Albaladejo P, Antz M, **Desteghe L**, Häusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbuchel H. 2018 Update of the European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation: Executive summary. Europace. 2018;20(8):1231-42. *(IF: 4.521)*

5. Steffel J, Verhamme P, Potpara T, Albaladejo P, Antz M, **Desteghe L**, Häusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, Sinnaeve P, Collins R, Camm AJ, Heidbuchel H. 2018 Update of the European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. European Heart Journal. 2018;39(16):1330-93 *(IF: 20.212)*

6. **Desteghe L**, Vijgen J, Koopman P, Dilling-Boer D, Schurmans J, Dendale P, Heidbuchel H. Telemonitoring based feedback improves adherence to non-vitamin K antagonist oral anticoagulants intake in patients with atrial fibrillation. European Heart Journal. 2018;39(16):1394-403. *(IF: 20.212)*

7. **Desteghe L**, Kluts K, Vijgen J, Koopman P, Dilling-Boer D, Schurmans J, Dendale P, Heidbuchel H. The Health Buddies App as a Novel Tool to Improve Adherence and Knowledge in Atrial Fibrillation Patients: A Pilot Study. JMIR mHealth and uHealth. 2017;5(7):e98. *(IF: 4.636)*

8. **Desteghe L**, Engelhard L, Raymaekers Z, Kluts K, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. Knowledge gaps in patients with atrial fibrillation revealed by a new validated knowledge questionnaire. International journal of cardiology. 2016;223:906-14. *(IF: 4.638)*

9. **Desteghe L** and Heidbuchel H. 'Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting: authors' response'. Europace. 2017;19(8):1408-1409. *(IF: 4.021)*

10. **Desteghe L**, Raymaekers Z, Lutin M, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Vanduynhoven P, Dendale P, Heidbuchel H. Performance of handheld electrocardiogram devices to detect atrial fibrillation in a cardiology and geriatric ward setting. Europace. 2017;19(1):29-39. *(IF: 4.021)*

11. Heidbuchel H, Berti D, Campos M, **Desteghe L**, Freixo AP, Nunes AR, Roldán V, Toschi V, Lassila R. Implementation of non-vitamin K antagonist oral anticoagulants in daily practice: the need for comprehensive education for professionals and patients. Thrombosis Journal. 2015;13(1):22. *(IF: 3.900)*

PAPERS SUBMITTED TO INTERNATIONAL PEER-REVIEWED JOURNALS

1. **Desteghe L**, Engelhard L, Vijgen J, Koopman P, Dilling-Boer D, Schurmans J, Delesie M, Dendale P, Heidbuchel H. Effect of reinforced, targeted in-person education using the Jessa Atrial fibrillation Knowledge Questionnaire in patients with atrial fibrillation: a randomized controlled trial. *Revision submitted.*

2. Konieczynska M, Bijak P, **Desteghe L**, Heidbuchel, H, Undas A. Knowledge gaps in patients with venous thromboembolism: usefulness of a new questionnaire.

PUBLISHED ABSTRACTS IN INTERNATIONAL PEER-REVIEWED JOURNALS

1. **Desteghe L**, Germeys J, Vijgen J, Koopman P, Dilling-Boer D, Schurmans J, Dendale P, Heidbuchel H. The impact of an online directed education platform on the knowledge level of atrial fibrillation patients undergoing cardioversion or pulmonary vein isolation. 2018, 20 (suppl_1), i24, 210.
    - *Moderated poster presentation at EHRA 2018, March 18-20, 2018, Barcelona, Spain.*

2. Hendriks JML, **Desteghe L**, McEvoy D, Chai-Coetzer CL, Gallagher C, Dendale P, Sanders P, Linz D, Heidbuchel H. An integrated interdisciplinary approach for screening of obstructive sleep apnoea in patients with atrial fibrillation. 2018, 20 (suppl_1), i160, P857.
    - *Poster presentation at EHRA 2018, March 18-20, 2018, Barcelona, Spain.*

3. Germeys J, **Desteghe L**, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. The effect of online targeted education on procedure-specific knowledge of atrial fibrillation patients undergoing cardioversion or ablation. Acta Cardiologica. 2017, 72:5, p. 573.
    - *Oral presentation at 11th Belgian Heart Rhythm Meeting, October 5-6, 2017, Zaventem, Belgium.*

4. **Desteghe L**, Engelhard L, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. Effect of individualised education sessions on the knowledge level of patients with atrial fibrillation. Europace. 2017, 19 (suppl_3), iii147, P817.
    - *Poster presentation at the EHRA EUROPACE – CARDIOSTIM 2017 Conference, June 18-21, 2017, Vienna, Austria.*

5. **Desteghe L**, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. Telemonitoring based feedback improves adherence to non-vitamin K antagonist oral anticoagulant intake in patients with atrial fibrillation. European Journal of Preventive Cardiology. 2016, 23 (2S), p. 51-52.
    - *Poster presentation at the Third European Congress on eCardiology and eHealth, October 26-28, 2016, Berlin, Germany.*
      (Winner of the Price for the Best Poster)

6. **Desteghe L**, Engelhard L, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. Effect of individualised education on knowledge, symptom profile and quality of life of patients with atrial fibrillation. Acta Cardiologica. 2016, 71 (6), p. 750-751.
    - *Poster presentation at 10th Belgian Heart Rhythm Meeting, October 6-7, 2016, Zaventem, Belgium.*

7. **Desteghe L**, Kluts K, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. The 'Health Buddies' application: a novel way to improve the medication adherence and knowledge of atrial fibrillation patients. Acta Cardiologica. 2016, 71 (6), p. 751.
    - *Poster presentation at 10th Belgian Heart Rhythm Meeting, October 6-7, 2016, Zaventem, Belgium.*

8. **Desteghe L**, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. Telemonitoring based feedback improves adherence for non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Acta Cardiologica. 2016, 71 (6), p. 750.
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9. **Desteghe L**, Raymaekers Z, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Vanduynhoven P, Dendale P, Heidbuchel H. Accuracy and cost-effectiveness of two handheld electrocardiogram recorders to screen for atrial fibrillation in a hospital setting. European Heart Journal. 2016, 37 (suppl 1), 1265, P6172.
    - *Poster presentation at the ESC CONGRESS 2016, August 27-31, 2016, Rome, Italy.*

10. **Desteghe L**, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. Telemonitoring based feedback improves adherence for non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. European Heart Journal. 2016, 37 (suppl 1), 1044-1045, P5209.
    - *Poster presentation at the ESC CONGRESS 2016, August 27-31, 2016, Rome, Italy.*

11. Engelhard L, **Desteghe L,** Kluts K, Raymaerkers Z, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Vanduynhoven P, Dendale P, Heidbuchel H. Development and validation of an atrial fibrillation knowledge questionnaire. Europace. 2016, 18 (suppl 1), i52, 56-78.
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    - *Oral presentation at 9th Belgian Heart Rhythm Meeting, October 8-9, 2015, Zaventem, Belgium.*

OTHER ABSTRACT PRESENTATIONS

1. Wei-Ru C, **Desteghe L**, Heidbuchel H, Lee Y, Lin P, Chen Y. Knowledge Gaps Affect Technology Acceptance Model of Atrial Fibrillation Alert System - An Example of the Chinese Edition of the Jessa Atrial Fibrillation Knowledge Questionnaire.
    - *Poster presentation at the 11th Asia Pacific Heart Rhythm Society Scientific Session, October 17-20, 2018, Taipei, Taiwan.*

2. **Desteghe L**, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. Telemonitoring based feedback improves adherence to non-vitamin K antagonist oral anticoagulant intake in patients with atrial fibrillation.
    - *Poster presentation at the LCRP Symposium 2017 - mHealth Visions on the Future, June 1, 2017, Hasselt, Belgium.*
      (Winner of the Price for the Best Poster)

3. Vandenberk T, D' Onofrio V, **Desteghe L**, Heidbuchel H, Vanherendael H, Rivero M, Grieten L, Vandervoort P, Nuyens D. Smartphone application for instantly detection of recurrent atrial fibrillation.
    - *Poster presentation at the Third European Congress on eCardiology and eHealth, October 26-28, 2016, Berlin, Germany.*

4. **Desteghe L**, Kluts K, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. A novel way to improve medication adherence – the 'Health Buddies' application.
    - *Poster presentation at the Third European Congress on eCardiology and eHealth, October 26-28, 2016, Berlin, Germany.*

5. Engelhard L, **Desteghe L**, Kluts K, Raymaerkers Z, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. Effect of reinforced education on knowledge, symptom profile and quality of life of patients with atrial fibrillation.
    - *Poster presentation at Biomedica, The European Life Sciences Summit, May 30-31, 2016, Aachen, Germany.*

6. Kluts K, **Desteghe L**, Engelhard L, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Dendale P, Heidbuchel H. An innovative way to improve medication adherence – the buddy project.
    - *Poster presentation at Biomedica, The European Life Sciences Summit, May 30-31, 2016, Aachen, Germany.*

7. **Desteghe L**, Raymaekers Z, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Vanduynhoven P, Dendale P, Heidbuchel H. Patient knowledge as a critical factor in adherence to oral anticoagulants: use of an atrial fibrillation and anticoagulation questionnaire to tailor patient education.
    - *Oral presentation at the 19th ESPACOMP conference, November 13-14, 2015, Prague, Czech Republic.*

8. Raymaekers Z, **Desteghe L**, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Vanduynhoven P, Dendale P, Heidbuchel H. Usability of Handheld Electrocardiogram Devices to detect Atrial Fibrillation in a Cardiology Ward Setting.
    - *Poster presentation at Biomedica, The European Life Sciences Summit, June 2-3, 2015, Genk, Belgium.*

9. **Desteghe L**, Raymaekers Z, Vijgen J, Dilling-Boer D, Koopman P, Schurmans J, Vanduynhoven P, Dendale P, Heidbuchel H. Patient Knowledge about Atrial Fibrillation: Construction of a New Questionnaire and First Results.
    - *Poster presentation at Biomedica, The European Life Sciences Summit, June 2-3, 2015, Genk, Belgium.*

OTHER ORAL PRESENTATIONS

1. ESC Congress 2018
    - *Does increased patient knowledge improve outcomes in atrial fibrillation?*
    - Munich, Germany
    - 27 August 2018

2. ESC Congress 2018
    - *"Health Buddy" apps as a tool to improve adherence in atrial fibrillation.*
    - Munich, Germany
    - 27 August 2018

3. Centre for Heart Rhythm Disorders
    - *More and better feedback to improve the management of patients with atrial fibrillation.*
    - South Australian Health and Medical Research Institute, Adelaide, Australia
    - 10 March 2017

4. Symposium "Snapshots uit de Hasseltse ritmologie".
    - *I'll take care of you: Towards a better care for patients with atrial fibrillation.*
    - Kinepolis, Hasselt, Belgium
    - 10 September 2016

5. LCRP lunch session Cardiology Jessa Hospital Hasselt.
    - *Towards a better care for patients with atrial fibrillation.*
    - Jessa Ziekenhuis, Hasselt, Belgium
    - 13 May 2016

6. PhD-Symposium - Medisch-wetenschappelijk onderzoek in de Limburgse ziekenhuizen: de weg naar een betere zorginnovatie.
    - *Atrial fibrillation: towards a better care for and by the patient.*
    - Ziekenhuis Oost-Limburg, Genk, Belgium
    - 19 March 2016

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"Strive not to be a success, but rather to be of value."

— Albert Einstein

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"A pessimist sees the difficulty in every opportunity; an optimist sees the opportunity in every difficulty."

— Winston Churchill

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