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# Effect of targeted education for atrial fibrillation patients: Design of the EduCare-AF Study

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## 1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide with an already high prevalence (7.7% in a Dutch reference population >55 years), and this will further increase over the next decades.[1, 2]

AF is associated with a reduced quality of life and an increased morbidity and mortality which leads to high health-related expenditures.[3] The overall management of AF is complex and needs to be tailored to the individual patient.[1] However, adherence to evidence-based management guidelines is suboptimal in daily practice throughout Europe.[4]

The 2016 ESC Guidelines for the management of AF (applicable at the time this study protocol was being composed) strive to optimize the care for AF patients based on the concept of 'Integrated AF management' which is based on four pillars, i.e. (I) patient involvement, (II) multidisciplinary team approach, (III) support by technology tools both for AF patients and for healthcare providers, and (IV) access to all treatment options for these patients.[1]

Only a few studies have investigated the delivery of this integrated AF care in which a recent meta-analysis demonstrated a significant reduction in all-cause mortality and cardiovascular hospitalisations.[5] Although, a more recent multicentre study could not show that nurse-led integrated AF care was superior to usual-care.[6] Important limitations in these studies were (i) the included subset of AF patients (e.g. only patients with chronic AF or newly diagnosed AF), which precluded interpretation of the effectiveness of the interventions for the entire AF population and (ii) the different approaches to deliver integrated care. Therefore, at this point, it remains unknown which components of such integrated care programs contribute to the overall beneficial results and which components may be redundant.

One of the four main pillars of integrated care, as mentioned above, is patient involvement and empowerment to allow shared decision making. This is only possible when AF patients are adequately educated about their disease and its management. Our research group has shown that targeted education, i.e. education that is focused on knowledge gaps of the patient (as assessed by the validated Jessa Atrial fibrillation Knowledge Questionnaire, JAKQ) significantly improved the

knowledge of AF patients about their arrhythmia.[7-9] This was true for education delivered in-person or online.

An essential component of the fourth pillar of integrated AF care is treatment with oral anticoagulation (OAC) for prevention of thrombo-embolic events. Non-vitamin K antagonist oral anticoagulants (NOACs) are nowadays recommended as first choice anticoagulant therapy in AF patients with an elevated $CHA_2DS_2$-VASc score.[1] Strict adherence to the prescribed NOAC regimen is of utmost importance but is often suboptimal in clinical practice.[10] Our research group has investigated the use of electronic monitor devices and the positive impact on adherence by using telemonitoring-based feedback.[11]

A recent review emphasized the importance of lifestyle and cardiovascular risk factor management (hypertension, obstructive sleep apnea, diabetes,…) which has shown to reduce AF burden and symptoms but also to improve success rates of rhythm restoring procedures and the quality of life in AF patients. [12] This is also incorporated in the integrated AF care model.

The premises described above formed the fundamentals of the EduCare-AF study, of which we will describe the protocol below. This study, including all types of AF patients, focusses on 4 aspects of integrated AF care: (i) targeted education about AF and OAC; (ii) emphasize the importance of a high adherence to OAC using electronic tools, (iii) making patients more aware of their AF risk factors and how to tackle them according to the current guidelines and (iv) being available for AF related questions (Figure 1).

## 2. Materials and Methods

### 2.1. Design

The EduCare-AF study is an open, prospective, multicentre, randomized clinical trial (parallel-group), currently ongoing in three large tertiary Belgian centres, namely the University Hospital of Antwerp, the University Hospital Leuven and Jessa Hospital Hasselt. The research protocol and amendments have been approved by the Ethics committees of the three participating centres (Belgian study number: B300201836720). The study is being conducted in compliance with the Declaration of Helsinki and all patients will provide written informed consent. EduCare-AF is

supported by a grant from the Scientific Fund for Research, Flanders (T002917N) and has been registered on ClinicalTrials.gov (NCT03707873). Reporting of this design paper conforms to broad EQUATOR guidelines.[13]

### 2.2. Study population and randomisation

AF patients hospitalized at the department of cardiology or AF patients who come for an outpatient visit at one of the three participating Belgian hospitals and who meet the eligibility criteria (listed in supplementary annex 1) are being enrolled in this study.

The included AF patients are then randomly assigned to one of the three study groups: in-person education, online education or standard care (Figure 2). After patient inclusion, a minimum follow-up period of 18 months is foreseen, i.e. the first included patient will be in follow-up until the last included patient has completed his/her minimum study follow-up of 18 months. Details about the randomization process can be found in supplementary annex 2.

### 2.3. Interventions

Patients randomized to the in-person and online education groups, will have to complete the JAKQ (and other questionnaires) at predefined time points (Figure 2). All questionnaires will be completed by means of a tablet/web application with direct input of the answers into the patient's electronic Case Report Form (eCRF).

The in-person education group will receive targeted education, directed at the specific knowledge gaps of the patient (i.e. questions incorrectly answered on the JAKQ). After the study patient has completed the JAKQ, the study personnel can electronically reconsult his/her wrong answers. Individualized education is given by trained study personnel (consisting out of study nurses, doctoral students and AF specialist nurses) and is repeated during each follow-up visit. The same workflow and education procedure is maintained at each participating centre. The time needed for answering the questionnaires will automatically be logged, as well as of the educational moments.

The online education group will fill out the JAKQ at the same predefined time points through a self-developed educational website (FileMaker software). This will be followed by automatic educational provision related to the questions incorrectly answered on the JAKQ. The patients from this group will also have unrestricted access to the online educational platform (except for the periods when the JAKQ has to be completed to avoid 'cheating') which contains information about different aspects of AF in an easily accessible and attractive way (supplementary Figure 1).

Education in both groups will also be directed to improve patients' self-care capabilities. This is assessed by a self-developed validated questionnaire, the self-care questionnaire (SCQ), and is directed to AF risk factors such as weight-/blood pressure control, physical fitness, alcohol consumption, tobacco use, signs or symptoms of sleep apnea and specific blood work parameters (supplementary Figure 2). Based on the answers of patients, the trained study personnel will discuss with the patient how they think that specific shortcomings can be addressed and will help find the best approach for the individual patient, based on the inherent motivation of the patient.

During the entire follow-up, patients of both intervention groups are able to contact the study personnel (and thus easier accessible assistance) at the three centres during normal working hours if they have questions about AF or its management. The study personnel can escalate specific questions to the treating cardiologist and later implement appropriate action.

EduCare-AF will also assess adherence of AF patients to their OAC, i.e. vitamin K antagonist (VKA) or NOAC, if taken. In both intervention groups, adherence (= 'ADH' in Figure 2) will be monitored using an electronic Medication Event Monitoring System (MEMS). Every time point the patient needs to take his/her OAC, he or she has to open the medication bottle. This action will be registered by the MEMS cap and stored as data. An LCD screen on the cap also displays the number of openings of the medication bottle over a period of 24 hours, providing feedback about the correct intake. Due to practical issues regarding VKA (dosing variation) and dabigatran (storage) intake, a proxy-medication will be chosen to monitor adherence for these drugs.

Monitoring phases will take place during the first three months of the study and again after 12 months (for a period of three months). The medication bottle will be read out at the 3- and 15-

months follow-up visit. Bottle openings for refilling, or medical approved interruption of the medication, are logged to allow correction of adherence calculations.

If the patients have a regimen adherence rate (i.e. proportion of days with the correct number of doses taken) <80%, they are categorised as "low adherence". Since the MEMS allows immediate wireless transmissions of bottle openings to an Internet server (through an NFC compatible smartphone), the 'low adherence' subgroup will be set up for telemonitoring on a daily basis. This permits during the following three months to provide telephone feedback in case of intake irregularities (= 'ADH+FB' in Figure 2). We have shown in a prior study that such daily telemonitoring with personal feedback was feasible and effective.[11]

In order to minimally intervene in the standard care groups and in order to avoid triggering these patients by giving them the JAKQ questionnaire at baseline, this group will only complete the JAKQ at 18 months and at the end of the trial. It can be assumed that the baseline knowledge level is the same in all groups since all patients are provided with a general AF brochure at inclusion. Three-month electronic adherence will be monitored in a limited subsample of this group at the beginning and after 12 months, to compare it with the intervention groups. The subsample size is kept as small as possible in order to not trigger too many patients in this control group to focus on their actual medication intake habits. Also for this latter reason, the MEMS cap is not equipped with an LCD screen and these standard care patients will also not receive any feedback after the monitoring phases.

### 2.4. Outcome parameters

#### 2.4.1. Primary outcome parameter

The primary outcome parameter of EduCare-AF is the cumulative occurrence of cardiovascular events including cardiovascular death, total cardiovascular hospitalizations (first and recurrent), unplanned cardiovascular or neurological consultations (first and recurrent) and emergency department (ED) visits for cardiovascular reasons (first and recurrent) over a mean estimated follow-up of about 27 months (analyzed when the last included subject completes the minimum of 18 months of follow-up).

In addition, during the first year of patient recruitment, the primary outcome parameter was changed from only the first occurrence of cardiovascular events to the first and recurrent-occurrence of cardiovascular events. Details can be found in the supplementary annex 3.

#### 2.4.2. Secondary outcome parameters

The effect of targeted individualized, in-person or online, education on each clinical component of the primary endpoint and on other events of interest will be investigated during the follow-up period.

Specification of these endpoints are summarized in detail in supplementary table 1.

#### 2.4.3. Tertiary outcome parameters

Other non-clinical parameters will be evaluated such as evolution of patients' AF knowledge, quality of life, AF symptom burden, self-care capabilities, satisfaction of their intervention and adherence to their (N)OAC. Measurement of these endpoints are outlined in table 1.

#### 2.4.4. Other outcome parameters

Logistic and economic expenditures to provide the education will be evaluated, mainly based on total time spent by the health care practitioners to provide patient education, advise and conducting telemonitoring. All these time allocations are systematically logged. The financial investments will also be tracked (personnel costs, software and hardware costs). These data will allow us to perform a cost-effectiveness and a cost-utility analysis.

### 2.5. Sample size

A sample size of 346 patients for each study group was calculated, resulting in a total of 1038 AF patients that will be included.

Specific details regarding the sample size calculation can be found in supplementary annex 4.

### 2.6. Statistical considerations

The main analysis for the primary endpoint, i.e. recurrent events in the in-person education group versus the standard care group, will be the modified Wei-Lin-Weissfeld method (Li and Lagakos modification) (In collaboration with I-BioStat).[14]

Details about additional analysis of the primary endpoint and the analysis of the other outcome parameters can be found in the supplementary annex 5.

## 3. Discussion

AF is a very prevalent condition with a high personal, societal and economic burden. The goals of AF management are to improve the quality of life, autonomy, social functioning and life expectancy of patients. Better structured and integrated care will also be important to reduce the strain on the health care system and on society at large.

EduCare-AF is based on all elements of the integrated model and is the first in its kind to investigate this in a fully representative AF population. Another strength of the study is the participation of three major Belgian hospitals so that clinical and socio-economical findings in this population can be projected to other Western countries with comparable healthcare settings.

The use of a novel and more relevant primary outcome will provide a better assessment of the true disease burden of AF and the impact of integrated AF care on the total clinical and economic burden of the arrhythmia.

In summary, the EduCare-AF study will provide evidence whether systematic patient education, targeted to knowledge gaps, and aimed at improving self-care capabilities, contributes to improved outcomes for all types of AF patients, and whether this is a cost-effective intervention. It will also evaluate whether online education can substitute for in-person education.

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**Potential conflicts of interest**

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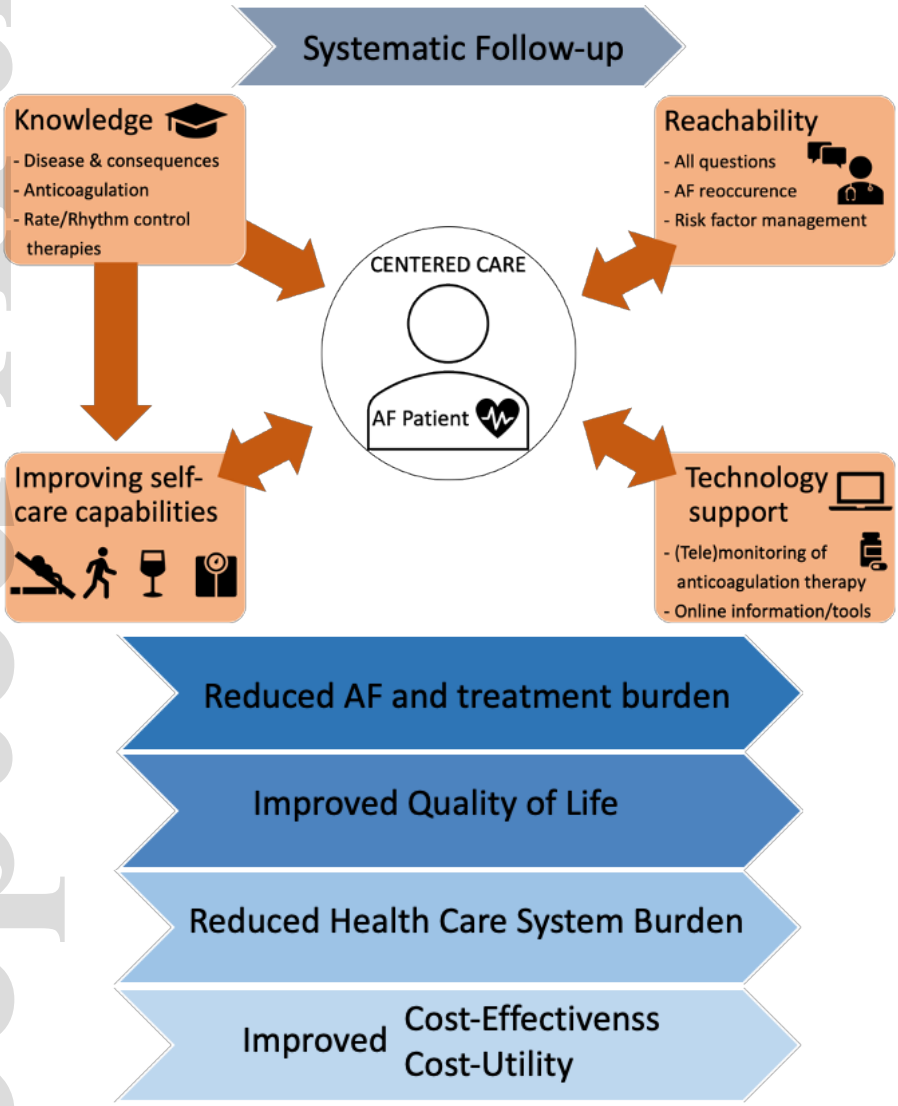
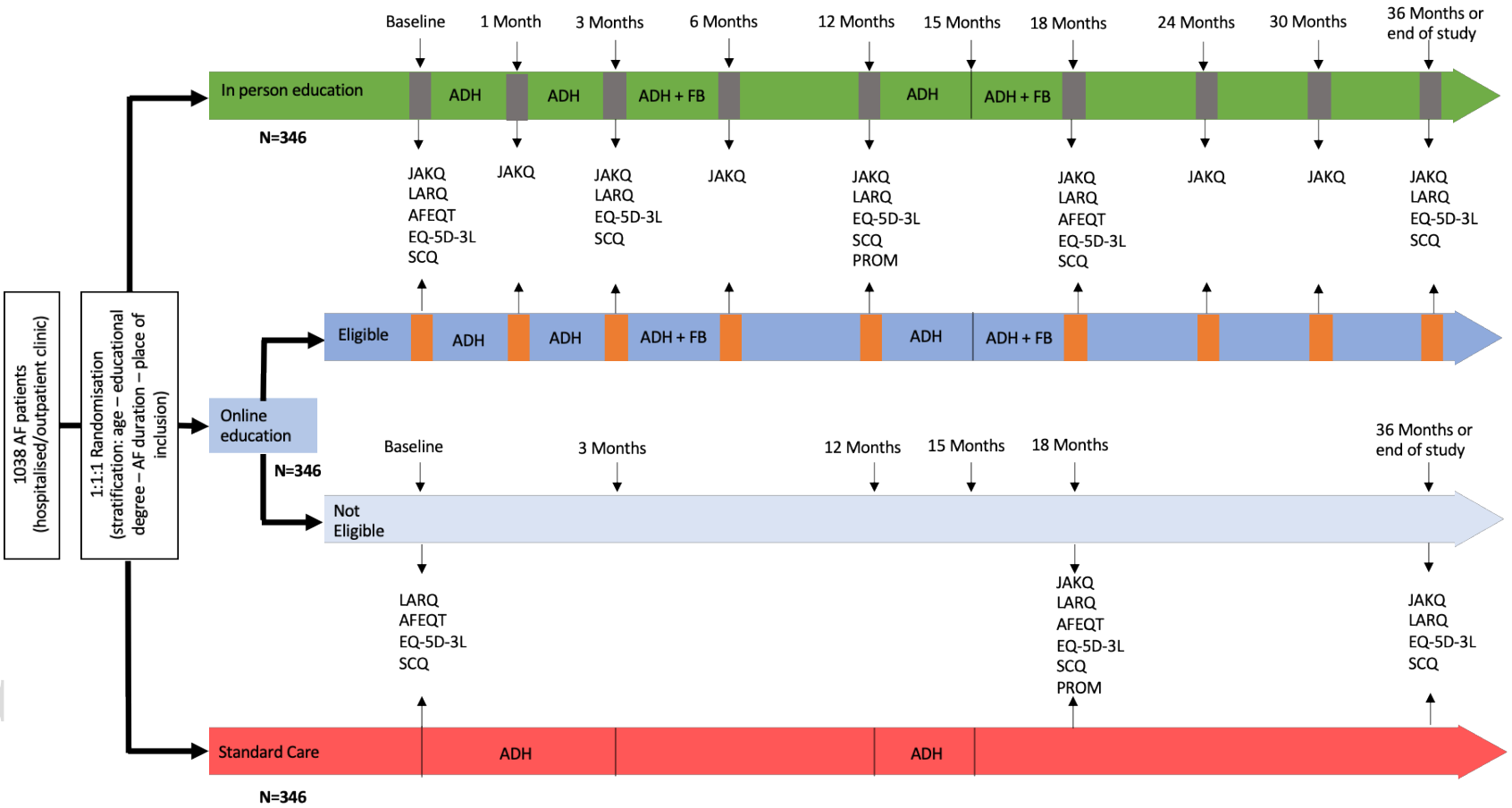
**Figure 1: EduCare-AF study interventions and aims**




AF= Atrial Fibrillation

**Figure 2: EduCare-AF Design**



AF= Atrial Fibrillation; JAKQ= Jessa Atrial fibrillation Knowledge Questionnaire; SCQ= Self-Care Questionnaire; AFEQT= Atrial Fibrillation Effect on Quality-of-life questionnaire; LARQ = Leuven Arrhythmia Questionnaire; EQ-5D-3L= EuroQol-5 dimensions-3 level questionnaire; PROM= Patient Reported Outcome Measures; Grey beam= reinforced in-person education; Orange beam= reinforced online education; ADH= adherence monitoring ; ADH + FB= adherence monitoring with feedback in case of a bad adherence (<80%)

Table 1: Tertiary study endpoints

| Tertiary outcome parameters | | | |
|---|---|---|---|
| Parameter | Questionnaire or tool | Time point | Score |
| Evolution of patients' knowledge about AF and its treatment | Jessa Atrial fibrillation Knowledge Questionnaire (JAKQ) | Intervention groups: at baseline, 1-, 3-, 6-, 12-,18 month(s) and at 24-, 30- and 36 months or at the end of the study (if applicable)<br><br>Standard care group: at 18 months and at the end of the study (if applicable) | 0 - 100% |
| Evolution of patients' general quality of life | EuroQol-5 dimensions-3 Level Questionnaire (EQ-5D-3L) | Intervention groups: at baseline, 3-, 12- and 18 months and at the end of the study (if applicable)<br><br>Standard care group: at baseline and 18 months and at the end of the study (if applicable). | -0.5 - 1;<br><br>Visual analogue scale: 0 - 100 |
| Evolution of patients'AF-related quality of life | Atrial Fibrillation Effect on QualiTy-of-life questionnaire (AFEQT) | Intervention- and standard care groups: at baseline and 18 months. | 0 - 100 |
| Evolution of patients' AF related symptom burden | Leuven Arrhythmia Questionnaire (LARQ) | Intervention groups: at baseline, 3- ,12- and 18 months and at the end of the study (if applicable)<br><br>Standard care group: at baseline, 18 months and at the end of the study (if applicable) | 0 - 100 |

| | | | |
|---|---|---|---|
| Evolution of patients' self-care questionnaire | self-care questionnaire (SCQ) | Intervention groups: at baseline, 3-,12- and 18 months and at the end of the study (if applicable).<br><br>Standard care group: at baseline, 18 months and at the end of the study (if applicable) | / |
| Patients' satisfaction of each educational effort | Patient reported outcome measures (PROM) | Intervention groups: at 12 months<br>Standard care group: at 18 months. | / |
| Patients' adherence to their oral anticoagulation | MEMS cap | Intervention groups: using the smart Cap; between 0-3 months and 12-15 months<br><br>Sample of standard care group: using the track cap; between 0-3 months and 12-15 months | taking adherence, regimen adherence and unprotected days* |

* taking adherence = proportion of prescribed doses taken; regimen adherence = proportion of days with the correct number of doses taken; unprotected days = once daily regimen: miss 1 dose or take ≥1 excess dose on a single day; twice daily regimen: miss 3 consecutive doses or take ≥1 excess dose on a single day.