Integrated management of atrial fibrillation including tailoring of anticoagulation in primary care: study design of the ALL-IN cluster randomised trial

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ABSTRACT

Introduction In our ageing society, we are at the merge of an expected epidemic of atrial fibrillation (AF). AF management requires an integrated approach, including rate or rhythm control, stroke prevention with anticoagulation and treatment of comorbidities such as heart failure or type 2 diabetes. As such, primary care seems to be the logical healthcare setting for the chronic management of patients with AF. However, primary care has not yet played a dominant role in AF management, which has been in fact more fragmented between different healthcare providers. This fragmentation might have contributed to high healthcare costs. To demonstrate the feasibility of managing AF in primary care, studies are needed that evaluate the safety and (cost-)effectiveness of integrated AF management in primary care.

Methods and analysis The ALL-IN trial is a multicentre, pragmatic, cluster randomised, non-inferiority trial performed in primary care practices in a suburban region in the Netherlands. We aim to include a minimum of 1000 patients with AF aged 65 years or more from around 18 to 30 practices. Duration of the study is 2 years. Practices will be randomised to either the intervention arm (providing integrated AF management, involving a trained practice nurse and collaboration with secondary care) or the control arm (care as usual). The primary endpoint is all-cause mortality. Secondary endpoints are cardiovascular risk disease management programmes that improve the cardiovascular risk profile of community dwelling adults.

Strengths and limitations of this study

► This is the first randomised clinical trial to evaluate integrated care for patients with atrial fibrillation (AF) in primary care.
► Patient relevant outcomes, such as all-cause mortality, hospitalisation and quality of life, will be evaluated.
► A possible limitation is the lack of contrast between intervention and care as usual due to cardiovascular risk disease management programmes that improve the cardiovascular risk profile of community dwelling adults.
► The multifaceted concept makes it difficult to assess the contribution of each individual component of the intervention on the outcome

INTRODUCTION

With the ageing population and the increasing disease burden of atrial fibrillation (AF), both clinically and economically, a change in the organisation of care for patients with AF seems imperative.1 From 2010 to 2060, the number of patients with AF is expected to more than double, to amount to the alarming number of almost 18 million people in Europe.2 Most of these patients are old, or even very old.3

Currently, in many healthcare settings, care for these elderly patients with AF is fragmented between cardiologists, general practitioners (GPs) as well as specialised anticoagulation clinics. However, most patients with AF have multiple comorbidities, with each disease requiring adequate attention in relation to their possible impact on health-related quality of life (hrQoL), mortality, and also treatment goals for AF.4-6 For instance, common comorbidities in elderly patients
with AF, such as hypertension, type 2 diabetes, heart failure and ischaemic cardiovascular diseases, are all more or less ‘thrombogenic’ and increase the risk of stroke and premature death by thromboembolic events. This influences the need to prescribe anticoagulation, and perhaps even the intensity of the required dosage, for example, if impaired renal function concurrently exists or in the case of an intercurrent infection. Also, there is a mutually reinforcing relationship between AF and many other conditions, leading to (prolonged) hospitalisation if not recognised or treated in time. Importantly, the relative and absolute risks of many of these conditions or their associated hospitalisation, especially heart failure, are much larger than the risk of stroke. In addition, AF may worsen heart failure or chronic obstructive pulmonary disease (COPD), and vice versa. Hence, AF is not merely a cardiac arrhythmia, yet rather an exponent of multiple cardiac and non-cardiac illnesses all more or less leading to accelerated ageing of the heart. This calls for an integrated approach to AF management.

Such integrated AF care clearly requires good communication and cooperation between patients, GPs, cardiologists and the anticoagulation clinics. The best way to deliver this type of care for patients with chronic AF is however less clear. For instance, the latest guideline from the European Society of Cardiology on AF calls for integrated management of AF, and states that ‘more research is needed into the best way of delivering integrated AF care’. A systematic review and meta-analysis of integrated care in AF by Gallagher et al showed reduced all-cause mortality (OR 0.51, 95% CI 0.32 to 0.80) and reduced cardiovascular hospitalisation (OR 0.58, 95% CI 0.44 to 0.77). The three studies included in this meta-analysis all involved cardiac nurses from AF clinics at tertiary care hospitals. Currently, an increasing number of patients are treated at these specialised AF clinics. However, in the era of rapidly evolving knowledge in understanding AF, the focus of AF treatment is evolving as well: rhythm control (including ablation) in symptomatic AF, to integrative management for the large group of older, frail patients with AF, with treatment being focused on rate control and treatment of concurring comorbidity. If integrated AF care could be performed equally effective and safe in primary care, this could have important clinical benefits for older patients with AF with multimorbidity, but could also help to reduce healthcare costs, especially in view of the increasing prevalence of AF.

For more than a decade, ‘small-team based integrated disease management’ exists in primary care, with GPs and dedicated practice nurses specialised in the disease management of diabetes, COPD and cardiovascular risk management. As an example, a large nurse-coordinated cardiovascular disease prevention programme has been shown to improve blood pressure control and lifestyle. Such a structured integrated care does not yet exist for patients with AF in primary care. Hence, we want to evaluate a newly developed integrated management programme for the elderly patients with chronic AF in primary care, with cooperative care of the GP and practice nurse in a cluster-randomised non-inferiority trial: the ALL-IN study. We will compare case management of AF in primary care with usual care that mainly involves cardiologists and anticoagulation clinics.

OBJECTIVES
To evaluate whether integrated AF management in primary care is non-inferior to usual care in terms of all-cause mortality (primary outcome), and also in terms of cardiovascular mortality, cardiovascular and non-cardiovascular hospitalisations, major adverse cardiac events (MACE), stroke, major bleeding, clinically relevant non-major bleeding (CRNMB), quality of life and cost-effectiveness (all secondary outcomes).

METHODS AND ANALYSIS

Study design
This is a multicentre, prospective, open-label, cluster randomised pragmatic trial in patients with AF aged 65 years or more, managed in primary care in the Netherlands. The participating primary care practices are affiliated to three centres (hospitals): the Isala hospital in Zwolle, the Röpcke Zweers Hospital in Hardenberg and the Deventer Hospital in Deventer. The duration of follow-up will be 24 months.

Randomisation
Randomisation of primary care practices will be stratified according to cluster size, defined as the total number of patients in the primary care practice aged 65 years and older. Primary care practices are randomised to the intervention or the control (care as usual) arm, following a computerised block randomisation with a 1:1 allocation ratio. If, during the subsequent randomisation of practices within approximately 1 year, an unequal distribution of patients across the intervention and control arm appears (eg, due to cluster effects or the modified informed consent procedure, in which only patients in the intervention arm need to provide informed consent, see below), an adaptive design with a 2:1 allocation ratio will be applied allowing the randomisation module to allocate more practices to the intervention arm, if applicable. As this is a pragmatic trial, there is no blinding for index or control treatment.

Study population
Inclusion criteria
Participating primary care practices need to be willing and able to provide integrated management to their patients with AF. Patients aged 65 years or more with documented AF in the primary care practice (by an ECG or specialist’s letter to the GP) are eligible for participation if they do not meet any of the following exclusion criteria.
Exclusion criteria
1. An internal cardioverter defibrillator or a cardiac resynchronisation therapy device
2. Cardiac resynchronisation treatment, cardiac ablation or cardiac surgery <3 months prior to inclusion or one of these procedures planned
3. Heart valve surgery in the past or a rheumatic mitral valve stenosis
4. Pulmonary vein isolation in the past or being planned
5. Being legally incapable of providing informed consent
6. Life expectancy shorter than 3 months
7. Participation in another randomised trial on AF

Sample size calculation
To our knowledge, the currently only available randomised controlled trial on the effectiveness of nurse-led care versus care as usual (in the cardiology outpatient clinic setting) in patients with AF is from Hendriks et al.19 Based on their results (cardiovascular mortality 1.1% intervention vs 3.9% care as usual; all-cause mortality is not specifically reported by Hendriks et al), we anticipate that all-cause mortality, our primary endpoint, will occur in 8% of the patients receiving usual care versus 4% in those receiving the intervention with integrated AF management. Our study uses a non-inferiority design, as its first purpose is to demonstrate that integrated AF management can be performed safely in a primary care setting. Based on non-inferiority with a margin of 1%, chosen on clinical grounds, using an \( \alpha \) of 0.05 (one sided, as any improvement on all-cause mortality is desirable) and a power of 80% we need approximately 300 patients with AF in each study arm. However, as this study follows a cluster randomised design, adjustment for clustering is needed. The amount of clustering is unknown, but as the outcomes of this study are likely driven by individual-level characteristics rather than cluster-level characteristics, we expect little clustering. Nevertheless, using an intracluster coefficient (ICC) of 0.005, the inflation factor (or design effect, \( DE \)) can be calculated as follows: \( DE = 1 + ((m-1) \times ICC) \), where \( m \) is the total number of participants in each cluster. Given the known AF prevalence of 1%–2% in the general population, and a total number of about 2350 patients registered within each practice (ie, the defining cluster), we would expect about 30 patients with AF in each practice. If we define \( m=30 \) patients with AF per cluster, the DE=1.145. This thus would inflate the total sample size to 343 patients in each treatment arm, leading to about 23 clusters. However, if the number of patients with AF in each cluster (ie, \( m \)) is lower or higher in each practice, which could be the case indeed, the DE would change accordingly, and thereby also the number of clusters needed. For instance, if \( m=20 \), DE would change to 1.095, inflating our sample size to 329 patients thereby requiring 33 clusters. Similarly, if \( m=50 \), DE would change to 1.245, with a sample size of 374 patients per cluster, and requiring only 15 clusters for the whole study. Yet, given these uncertainties on the exact number of patients with AF who are eligible in each practice, the number of patients who will provide informed consent for the intervention, the uncertainty around the amount of clustering, as well as considering 10% loss to follow-up, we (conservatively) aim to include between 18 and 30 primary care practices in each study arm with a minimum of 500 patients with AF per arm.

This sample size would also be sufficient to demonstrate superiority for the secondary outcome cardiovascular hospitalisation, considering the same effect size as reported by Hendriks et al (HR 0.60). In that case, based on an \( \alpha \) of 0.05 (two sided), a power of 80% and an ICC of 0.005, we would need at least 357 patients in each arm, estimating that cardiovascular hospitalisation will occur in 25% vs 16.5% of patients in the control arm and intervention arm, respectively.

Study procedures
The study design is shown in figure 1. First, primary care practices willing to participate will be randomised. After randomisation, the researchers will identify eligible patients with AF by searching the GPs’ electronic patient files of all patients aged 65 years or more, labelled with the Internal Classification of Primary Care code K78 (AF/flutter). Next, baseline data of these patients will be collected. Subsequently, patients will receive either integrated AF management (intervention arm) or care as usual (control arm), based on the randomisation allocation of their primary care practice.

Intervention under study
After providing informed consent for participating in the intervention, patients who used to receive care by a cardiologist will get a ‘closing visit’. With this closing visit, the cardiologist is notified that the patient will receive integrated AF care in primary care without routine cardiology outpatient visits for AF, if appropriate. Also, the cardiologist can give final instructions on AF treatment. These patients will still receive cardiologist’s care if needed for other cardiac diseases, that is, pacemaker or valvular dysfunction.

Integrated AF management will be performed by the practice nurse under supervision of the GP. This integrated AF management encompasses (1) case management of anticoagulation in primary care, (2) quarterly check-ups for AF and its related comorbidities and (3) easy-access consultation with cardiologists and thrombosis experts.

Case management of anticoagulation in primary care
Patients treated with a vitamin K antagonist (VKA) are offered tailored anticoagulation monitoring with International Normalised Ratio (INR) measurements using point-of-care INR measurement, performed by a trained practice nurse or GPs assistant at the practice, or if necessary at the patient’s home. They will communicate the INR value and relevant medical information (eg, fever, diarrhoea, medication changes) to the Anticoagulation
Expert Centre of the Dutch Thrombosis Service through an online portal. The same day, the practice nurse will receive the recommended dosage calendar for the subsequent time period from the Anticoagulation Expert Centre. Importantly, primary care practices are the first to know when a change in clinical condition occurs that might influence the anticoagulation status, and are instructed to then perform an extra INR measurement, for instance when fever or (progression of) heart failure occurs. Patient education about when to contact the practice is also part of the intervention. Patients will only have one or two easy-access practice nurses to address their anticoagulation issues with, in contrast to the situation at the anticoagulation clinics where they often see many different faces.

For patients treated with a non-VKA oral anticoagulant (NOAC), adherence and other aspects of the NOAC therapy will be part of the quarterly routine primary care visits, as detailed in Quarterly check-ups for AF and its related comorbidities section. Each participating primary care practice will receive financial reimbursement in order to facilitate the aforementioned individualised anticoagulant case management.

**Quarterly check-ups for AF and its related comorbidities**

Patients will visit the primary care practice every 3 months (three times the practice nurse and once a year the GP). With a standardised protocol (based on guidelines from the Dutch College of General Practitioners, including the guideline for AF30), patients will be checked for their health condition and the management of AF, including evaluation of all cardiac and non-cardiac comorbidities. Blood pressure, heart rate and body weight are measured, and when in doubt of adequate rate control because of
a possible pulse deficit, an ECG is made to know the actual heart rate. Special attention will be paid to lifestyle, drug compliance (notably for the NOACs), monitoring of kidney function (at least once a year) and the early detection of heart failure. Hereo, practice nurses are instructed to ask about dyspnoea, orthopnoea and check for peripheral oedema. If necessary, treatment will be adjusted. In case of an intercurrent illness, the GP can easily signal (and intervene on) the interaction of the illness with AF and the patient’s anticoagulant status. The practice nurses will be trained in the management of AF, including education about the causes, signs and symptoms, and treatment of AF.

**Easy access consultation with Cardiology and Anticoagulation Expert Centres**

The GP and the practice nurse will have easy access to consultation of the Cardiology Expert Centre and Anticoagulation Expert Centre of the hospital in their region. Consultation is possible through a separate email address and/or telephone number. Physicians and nurses from the expert centres are involved in the training of the practice nurses, also to get acquainted with each other and hopefully lower the threshold for the GP or practice nurse to contact the expert centres. Also, evaluation meetings between the practices and the expert centres will be organised twice a year, with educational purposes and to make further agreements. Patients may also be referred promptly to secondary care if necessary. In that case, patients will not drop out of the study, but continue to participate in the intervention, as the need for the main aspects of the integrated management remains, that is, close follow-up and care for both cardiac and in particular also non-cardiac comorbidity, as well as close anticoagulation monitoring.

**Control group**

In the control arm, patients will receive care as usual. Essentially, this implies partly fragmented care with at least the absence of an integrated approach looking at all AF and anticoagulation management-related aspects in a holistic manner with a coordinating role in primary care. It generally consists of a routine visit to the cardiologist once a year. In stable elderly patients with AF, the cardiologist may or may not have already ended routine follow-up though, depending on patient and physician preference. Usually, these patients only visit the GP on demand, without routine visits or regular check-ups on the disease burden associated with AF. Some of these patients are seen by the practice nurse in case of type 2 diabetes, COPD or hypertension, yet again without paying specific attention to AF. INR checks and adjustment of the dosage are organised by the anticoagulation clinics, on average once every 3 weeks. To define usual care, the following characteristics will be collected: (1) the proportion of patients (still) seen regularly by a cardiologist for routine care visits in the outpatient department; (2) the proportion of patients seen by a practice nurse in primary care of routine follow-up for type 2 diabetes, COPD or hypertension; and finally (3) the average number of INR measurements performed for each patient managed with a VKA.

**Data collection**

**Baseline data collection**

All data will be collected from the GP’s electronic patient files. We will collect (1) the individual’s CHA2DS2-VASc score (history of congestive heart failure, hypertension, age≥75 (doubled), diabetes, stroke or Transient Ischaemic Attack (TIA) (doubled)—vascular disease, age 65–74 and female sex), (2) the individual’s HAS-BLED score (history of hypertension, abnormal renal or liver function, previous stroke, bleeding history, labile INR values, elderly, and concomitant drugs and/or alcohol excess), (3) medication use, (4) the most recent laboratory results and (5) type of AF at baseline (paroxysmal or non-paroxysmal).

**Outcome assessment**

After 24 months of follow-up, we will collect data on the primary endpoint all-cause mortality and the secondary endpoints cardiovascular mortality, cardiovascular and non-cardiovascular hospitalisation, MACE, stroke, major bleeding, CRNMB, hrQoL and cost-effectiveness. HrQoL will be measured with the 12-Item Short Form Health Survey (SF12) and the 5-level EuroQol 5D questionnaire (EQ-5D-5L, at baseline, after 1 year and after 24 months.

The EQ-5D-5L is used to calculate quality-adjusted life-years (QALYs) in both arms. Actual healthcare expenses will be calculated from data in the GPs’ electronic patient files (eg, hospitalisation). An independent committee adjudicates the causes of death based on all available patient’s data, blinded for the allocation of the study arm of the patients.

**Data analysis**

The aim of the main analysis is to compare the cumulative incidence of the primary endpoint (all-cause mortality) in 2 years in both study arms, that is, the study patients in the control group receiving usual care and the study patients in the index group that provided informed consent to undergo the intervention. As is recommended in non-inferiority trials, we will perform an intention-to-treat analysis and a per-protocol analysis. As is common in cluster randomised trials, those patients undergoing the intervention in the index clusters may differ from eligible study patients in the control clusters, as it is likely that providing informed consent for the intervention is selective. As this could introduce bias, we will collect information on the outcomes of patients who were eligible in the intervention arm, but preferred not to undergo the intervention. This will allow us to compare this group with both the intervention and control group patients on essential determinants such as age, sex and comorbidities, and to judge whether we had selective
study participation for those providing informed consent to receive integrated AF management. It also allows us to adjust for any selection bias introduced by such selective study participation.

Kaplan Meier and survival analysis will be used to analyse the primary and secondary outcomes. To account for the clustered design, a frailty model will be used, with the cluster being the random effect. For the dichotomous outcomes, risk differences and ratios (with 95% CIs) between the two groups will be calculated, using a multilevel generalised linear model including the random cluster effect. For the continuous outcome hrQoL, the differences in means (95% CI), after 12 and 24 months of follow-up, will be calculated using a linear mixed effects model, again including the random cluster effect. Cost-effectiveness will be assessed in terms of the incremental cost-effectiveness ratio (ICER), which is the difference in average cost between the intervention arm and control arm, divided by the difference in QALYs between the two arms. The ICER thus represents the incremental cost per QALY gained by following the intervention instead of care as usual.

ETHICS AND DISSEMINATION

Informed consent

For this cluster randomised trial, we will follow a modified informed consent procedure. In the intervention arm, all eligible patients are personally invited by their GP to participate and they need to provide full written informed consent before participating in the intervention. In the control arm, informed consent is only required for filling out the hrQoL questionnaires, without directly revealing the true purpose of our study to control group patients.

As to be expected, not all eligible patients will provide informed consent, probably the very old and frail patients with AF in particular. This may induce selection bias. To address this issue and to adjust for it, we will gather information on determinants relevant for the baseline thromboembolic risk plus outcome assessment on all eligible patients in an encrypted manner for both the intervention arm and the control arm. For this specific reason, we obtained a waiver for informed consent from the Medical Ethics Committee. Patients’ privacy will be cared for throughout the study and during data handling.

Safety monitoring

An independent Data and Safety Monitoring Board (DSMB) will be installed to assess the progress of the study and in particular the occurrence of the three most relevant serious adverse events: death, stroke and major bleeding (‘major’ according to the International Society on Thrombosis and Haemostasis’ definition35).

Dissemination policy

Results of the trial are expected in 2019 and will be disseminated through peer-reviewed publications and presentations at (inter)national conferences.

DISCUSSION

With the ALL-IN cluster randomised trial, we will evaluate structured, integrated management of patients with AF in primary care. This is characterised by (1) a key role for the practice nurse, (2) special attention for comorbidities and (anticoagulant) drug adherence and (3) easy access to the Cardiology and Anticoagulation Expert Centres. We hypothesise that such an integrated primary care approach will be at least non-inferior (in terms of all-cause mortality) to usual care by cardiologists, anticoagulation clinics and GPs. Transition of care from the hospital to the community is deemed necessary, for example, by insurance companies and policymakers, because of the ageing of the population and the growing healthcare cost, but a formal evaluation of the safety and efficacy prior to such transitions is often lacking.27 This study deliberately therefore uses a non-inferiority design, as it is pivotal that such transition of integral care for patients with AF to primary care is safe in terms of all-cause mortality. However, we hypothesise that by regularly monitoring these patients with regard to early signs of heart failure, for example, cardiovascular hospitalisation could be prevented. As stated earlier, the sample size would allow us to potentially demonstrate superiority for this endpoint.

We chose our exclusion criteria in a way that our study population includes the somewhat more ‘stable’ patients with AF, who are probably older and have more often permanent AF than those generally treated in secondary or tertiary care. However, we want to emphasise that this is not a low-risk population, as cardiac and non-cardiac comorbidity are frequent and the risk of mortality and hospitalisation is very high in elderly patients with AF.12 13 A possible limitation of this study is that the rise in prescription of NOACs in patients with AF might somewhat impact the generalisability of this study over time. In 2014, around 9% of all patients treated with oral anticoagulants in the Netherlands were receiving an NOAC.34 This percentage is expected to increase in the coming years. However, prescription of NOACs is allowed for in this study, and we expect that the uptake of NOACs in fact may be enhanced due to study participation, predominantly thus for patients with AF receiving integrated AF care in the intervention arm. Second, evaluating a multifaceted intervention means that it will be difficult to examine which elements of the intervention are responsible for a certain observed effect. Finally, many primary care practices have disease management programme for cardiovascular risk and type 2 diabetes, and also those in the control arm. Therefore, usual care could already be of high quality regarding the management of cardiovascular risk factors. This can diminish contrast between the intervention and care as usual. Nevertheless, in this pragmatic trial, care as usual is the best comparator to evaluate the safety and (cost-)effectiveness of the intervention. Moreover, the existing primary care disease management programme do not involve special attention for AF or management of anticoagulant therapy.
To conclude, this will be the first study to structurally and prospectively evaluate integrated care for patients with AF in primary care. If proven safe and effective, widespread implementation of this strategy should be aimed for.

Contributors
RO, GJJG, KGM, FHR, CJD and AWH designed the study. RO, CJD, SJCML and AE contributed to the implementation of the intervention and AE and SJCML established the Cardiology and Anticoagulation Expert Centres of the Isala hospital, respectively. CJD drafted the first version of the manuscript. All authors critically reviewed and revised the manuscript before providing final approval.

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Competing interests
None declared.

Patient consent
Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval
The Medical Research Ethics Committee of the Isala hospital Zwolle, the Netherlands, provided approval of the study on 1 August 2015.

Provenance and peer review
Not commissioned; externally peer reviewed.

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