**Mobile Health to improve optimization of integrated care in patients with atrial fibrillation: mAFA-II trial**

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MAFA II Investigators: See Online Appendix.

**ABSTRACT**

**BACKGROUND:**Current management of patients with atrial fibrillation (AF) is limited by low detection of AF, non-adherence to guidelines and lack of consideration of patient's preferences, thus highlighting the need for a more holistic and integrated approach to AF management.

**OBJECTIVE:**To determine whether a mobile Health (mHealth) technology-supported AF integrated management strategy would reduce AF-related adverse events, compared to usual care.

**METHODS:** A cluster randomised trial of AF patients aged over 18 years were enrolled in 40 cities in China. Recruitment began on June 1, 2018 and follow-up ended on August 16, 2019. AF patients were randomized to receive usual care, or integrated care based on a mobile AF Application (mAFA) incorporating the ABC (Atrial Fibrillation Better Care) Pathway: ‘A’ Avoid stroke; ‘B’ Better symptom management; ‘C’ Cardiovascular and other comorbidity risk reduction. The primary composite outcome was a composite of stroke/thromboembolism, all-cause death, and rehospitalization. Rehospitalization alone was a secondary outcome. Cardiovascular events were assessed using Cox proportional hazard modelling after adjusting for baseline risk.

**RESULTS:** There were 1646 patients allocated to mAFA intervention (mean age 67.0 years, 38.0% female) with mean follow-up of 262 days, while 1678 patients were allocated to usual care (mean age 70.0 years, 38.0% female) with mean follow-up of 291 days. Rates of the composite outcome of ‘ischaemic stroke/systemic thromboembolism, death, and rehospitalization’ were lower with the mAFA intervention compared to usual care (1.9% vs. 6.0%, hazard ratio, HR 0.39, 95% confidential interval, CI: 0.22-0.67, P < 0.001). Rates of rehospitalization were lower with the mAFA intervention (1.2% vs 4.5%, HR 0.32, 95% CI: 0.17-0.60, P < 0.001).

Subgroup analyses by gender, age, AF type, risk score and comorbidities, demonstrated consistently lower HRs for the composite outcome for patients receiving the mAFA intervention compared to usual care (all p<0.05).

**CONCLUSIONS:**An integrated care approach to holistic AF care, supported by mobile health technology, reduces the risks of rehospitalization and clinical adverse events.

**CONDENSED ABSTRACT**: This study aims to investigate whether a mHealth technology-supported AF integrated management strategy would reduce AF-related adverse events, compared to usual care. In this cluster randomized clinical trial, patients allocated to integrated care management based on a mobile AF Application(mAFA) using the ABC Pathway (Avoid stroke with Anticoagulation; Better symptom management; Cardiovascular and comorbidity risk optimisation), significantly reduced the rate of composite outcome of ‘ischaemic stroke/systemic thromboembolism, death, and rehospitalization’ and rehospitalisation, compared to usual care. An integrated care approach to holistic AF care, supported by mobile health technology, reduces the risks of clinical adverse events in patients with AF.

**KEY WORDS：**atrial fibrillation, integrated care, mobile health, adverse events

**ABBREVIATIONS**:

AF = atrial fibrillation

ECG = electrocardiogram

PPG = photoplethysmography

mAF App = mobile atrial fibrillation application

SD = standard deviation

IQR = interquartile range

CI = confidential interval

CHA2DS2-VASc = congestive heart failure, hypertension, age ≥75, diabetes, stroke, vascular disease, age 65–74, and sex category (female)

HAS-BLED = hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalised ratio, elderly, drugs/alcohol concomitantly

**INTRODUCTION**

Atrial fibrillation (AF), being the commonest sustained arrhythmia, remains one of the major global causes of stroke, heart failure, dementia, sudden death, and cardiovascular morbidity (1). Although there has been substantial progress on the management of AF, doctor's non-adherence to AF management guidelines and lack of incorporation of patient's preferences in treatment decisions remain major problems (2,3). New approaches to AF management, including the use of novel technologies and a more structured integrated or holistic approach to AF care, are proposed to optimize treatment options for AF(4)

The emergence and rapid growth of digital health technology may enable doctors and patients to improve AF management(5). The digital health refers to the use of mobile computing and communication technologies (eg, mobile phones, wearable sensors) for health services and information(6). Indeed, mHealth tools have been studied as an aid to support shared decision making for anticoagulation, to achieve telemonitoring-based feedback, and to improve medication adherence(7,8). In our pilot study, a mHealth technology-supported AF management model (mobile Atrial Fibrillation Application, mAFA I) was designed, including clinical decision support tools(9). We demonstrated that the mHealth tool could be used for AF management to improve knowledge and drug adherence (9). However, strategies to incorporate such technology effectively into the AF management pathways that can be applicable from primary care to secondary care management, as well as allowing patient engagement in an integrated care approach, remain untested.

AF clinical integrated care aims to support a multidisciplinary approach to optimize stroke prevention, patient-centred or symptom directed decisions on rate or rhythm control, and management of cardiovascular risks and comorbidities, including lifestyle interventions. Such a holistic approach to AF care is simplified into a practical, simple ABC pathway (Atrial Fibrillation Better Care pathway, i.e. Avoid stroke; Better symptom management with patient-centred, symptom directed decisions on rate or rhythm control; Cardiovascular and other comorbidity risk reduction)(10,11). The simple ABC pathway has been retrospectively validated in independent retrospective or prospective cohort studies, demonstrating a lower risk of adverse outcomes for AF patients who were managed according to the ABC pathway (12-14).

We hypothesized that implementation of a mHealth technology-supported integrated management strategy would reduce AF-related adverse events (stroke/thromboembolism, all-cause death, and rehospitalization) compared to usual care. We tested this hypothesis in a prospective cluster randomized trial, as part of the mobile health technology for improved screening, patient involvement and optimizing integrated care in Atrial Fibrillation (mAFA II) study programme(15).

**METHODS**

The design and rationale of the mAFA II trial has been described previously(15). In brief, we conducted a two-arm, prospective, cluster-randomised controlled trial that prospectively enrolled patients with AF (Supplementary online Figure 1). The study registered on WHO International Clinical Trials Registry Platform (ICTRP) chictr.org.cn, and registration number was ChiCTR-OOC-17014138 (http://www.chictr.org.cn/showprojen.aspx?proj=24191).

Clusters (sites) were identified by each coordinating centre based on hospital size, patient volume, the time the doctors could spend on patients after discharge, patient's smart phone usage and general education level of the patient population (Online Table 1). All clusters demonstrated access to adequate numbers of eligible patients by pre-trial feasibility questionnaires. The sites were matched based on hospital size and the proportion of enrolled patients. The hospital sizes were classified as “big” hospitals with enrollment of over 20 patients per month, and “small” hospitals with enrollment of under 20 patients per month, respectively. The ratio of big: small hospitals was 1:2 based on feasibility checks, thus 142 patients from individual big hospitals and 71 for small hospitals would be needed.

Inclusion criteria were: i) patients aged ≥18 years old, diagnosed with new-onset, paroxysmal, persistent or permanent AF confirmed with electrocardiogram (ECG) or 24-hour Holter monitors; and ii) Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke, Vascular disease, age 65–74, and Sex category (female), CHA2DS2VASc score ≥2. Patients were excluded if they met any of the following criteria: age <18 years old, those with mechanical prosthetic valve or moderate/severe mitral stenosis, unable to provide informed consent, or unable to be followed up for one year for any reason.

Suitable patients were enrolled into the mAFA II trial from two sources: (i) the initial AF screening programme (‘pre-mAFA’ )(16); and (ii) out-patient and in-patient departments of participating centres. Trial patients were consecutively recruited at each site in China between June 1, 2018 and August 16, 2019. The study was approved by the Central Medical Ethic Committee of Chinese PLA General Hospital (Approval number: S2017-105-02), and by local institutional review boards. The study was compliant with the Declaration of Helsinki.

*Randomization and Intervention*

In the cluster randomized parallel intervention trial design, 40 participating cluster hospitals were randomized in a 1:1 ratio to the mAFA intervention or usual care. Randomisation was done using a computer-generated randomization list. Investigators and site personnel were not masked to the intervention. Patients into usual care group received treatment and management by local doctors according to local clinical practice.

A user-friendly mAFApp was developed for smart phones based on the Android Operating System (Google Inc., MountainView, Calif) and Apple iOS (Cupertino, Calif) for doctors (DmAFA) and patients (PmAFA). In the mAFA intervention group, the doctors used the mAFA platform (Supplementary online Figure 2, 3, 4) to manage AF patients. The mAFA platform provided clinical decision support tools (CHA2DS2-VASc, HAS-BLED, SAMeTT2R2 scores) to facilitate guideline-based treatment recommendations, educational materials and patient involvement strategies with self-care protocols and structured follow-up, to support implementation of the ABC pathway for integrated or holistic AF management, compliant with guidelines on AF management (1), as follows:

***A****void stroke*

Oral anticoagulants (OACs) were chosen based on clinical decision support tools and patients’ preferences at baseline. The App provided guidance on appropriate dosing, based on the particular drug label or guideline recommendations. Given the dynamic nature of stroke and bleeding risk factors(17), regular clinical risk (re)assessment was incorporated into the App, after the initial baseline assessment. For example, dynamic bleeding risks were automatically monitored with the Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalised ratio, Elderly, Drugs/alcohol concomitantly, HAS-BLED score by the mAFA platform, once the patient’s data (comorbidities, laboratory tests, etc.) were updated. The trends of bleeding risks over time are shown in line charts and personalized modifiable bleeding risk factors were flagged up for both doctors and patients, to help to achieve safe anticoagulant use. The time in therapeutic range (TTR) in patients taking warfarin was automatically calculated for the patients on warfarin; liver function was assessed with Child-Tucotte-Pugh score; and dynamic evaluation of renal function was calculated the creatinine clearance (Cockroft–Gault). Optimized dose adjustments of warfarin or non-vitamin K antagonist oral anticoagulants (NOACs) were proposed based on changes on TTR, liver, or renal function, being consistent with practice guidelines (Supplementary online Figure 2) (18). A mean TTR of >65% was defined as ‘good anticoagulation control’. Patient-reported thromboembolism or bleeding events were captured using the structured questionnaire developed by the mAFA platform. Patient-reported thromboembolism or bleeding events were captured using structured questionnaires developed for the mAFA platform. Once patients reported thromboembolism or bleeding events, they were required to upload the supporting files, e.g. pictures of the bleeding, medical material. Doctors could also communicate with patients to confirm the reported events and decide if it needed to be further diagnosed and treated in the hospital or could be managed remotely through the mAFA app.

***B****etter symptom management*

Cardiac rhythm monitoring was available in mAFA platform, using photoplethysmography (PPG)-smart devices, as previously reported(16). AF symptoms were evaluated using the European Heart Rhythm Association (EHRA) classification and assessment, once ‘AF episodes’ were detected using photoplethysmography (PPG). Other reported symptoms, such as headache, dizziness, shortness of breath and chest pain, etc. could be monitored and recorded. Once such data were updated, the instant message function could be used to communicate information to doctors. Doctors could also communicate with the patients on the mAFA in a timely manner and regulate use of antiarrhythmic drugs or rate control therapies according to guidelines on AF management (1) (Supplementary online Figure 3).

***C****ardiovascular and other comorbidities risk management*

Associated comorbidities could be proactively managed, for example, blood pressure could be monitored, and treatment optimized, aiming for BP<140/85mmHg (and ideally, 130/80); statins used in association with vascular disease, etc. Lifestyle factors were recorded, such as alcohol intake (with education and recommendations for reduction, as appropriate).

The App also encouraged patient engagement, by encouraging their participation in educational programs, provision of informative articles, videos, game playing, etc. Educational materials were about AF, hypertension, acute coronary syndrome (ACS), heart failure, valvular disease, self-care, etc. (Supplementary online Figure 4).

Supplementary online Figure 2D and 3C show how the doctors with DmAFA and patients with PmAFA achieved integrated care management.

*Outcomes*

All patients were followed up in the outpatient clinics at 6 and 12 months for clinical events. The *primary endpoint* was the composite of stroke/thromboembolism, all-cause death, and rehospitalization. The thromboembolism endpoint included ischaemic stroke, pulmonary embolism, deep vein thromboembolism (DVT), and other thromboembolism (peripheral embolism, atrial thrombus and left atrial appendage thrombus, etc.). All-cause death included cardiac death, vascular death, and non-cardiovascular death. Cardiac death included death caused by ST-segment elevation myocardial infarction /non-ST-segment elevation myocardial infarction (STEMI/NSTEMI), heart failure (HF), arrhythmia, cardiac perforation / tamponade, and other deaths of cardiac origin. Vascular death included death ascribed to ischemic stroke, haemorrhagic stroke, systemic haemorrhage, peripheral embolism, and pulmonary embolism. We also recorded rehospitalization for any cause for AF, thromboembolism, major bleeding, HF, ACS, and admission for other cardiovascular disease. Other cardiovascular outcomes included recurrent AF, which was defined as recurrent onset of AF for patients with paroxysmal AF or with AF ablation.

A *secondary outcome* included event rates for the components of the primary endpoint, and the change in the proportion of patients able to continue anticoagulation.

*Statistical analysis*

Sample size and power for the primary outcome was calculated according to Eldridge's method(19). Study feasibility was investigated among 52 researchers from 42 hospitals between September 1, 2017-March 31, 2018, in relation to hospital size, the ability of enrollment per month, age distribution of patients, the possible time doctors would like to spend on patient after discharge, mobile phone usage, educational levels, etc. (**Figure 1**).

Assuming the coefficient of variation of the cluster sizes of 2.60 based on the hospital size and enrollment ability, with an intra-cluster correlation of 0.02, 20 clusters per group with an average cluster size of 71-142 patients, and a two-sided type 1 error of 0·05, the study was powered >90% to detect a 5% absolute difference in the composite of stroke/thromboembolism, all-cause death, and rehospitalization at 1 year, and to achieve 80% power to detect 3% absolute difference of such an improvement between mAFA intervention and usual care. Therefore, a total of 3294 patients needed to be enrolled in this study.

All analyses followed the intention-to-treat principle. Baseline characteristics for continuous variables are summarised as means (standard deviation, SDs) and medians (interquartile, IQRs). Frequencies and percentages per group as well as hazard ratios with 95% confidence interval (CI) are reported for binary outcomes. Cox proportional hazards models, *with shared frailties to account for the effect of clustering*, adjusted for baseline risk factors, were used to analyse the primary composite outcome of stroke/thromboembolism, all-cause death, and rehospitalization. Additionally, the impact of the mAFA intervention on clinical outcomes was investigated with the frailty Cox model, including the time to first occurrence of ischaemic stroke, systemic thromboembolism, ACS, HF, rehospitalization, or all-cause death, also adjusting for baseline risk factors. Adjusted model included age, gender, AF type, prior AF treatment (cardioversion, AF ablation, rhythm control), and comorbidities (hypertension, diabetes, coronary artery disease (CAD), obstructive sleep apnea syndrome (OSAS), HF, hyperthyroidism, prior ischaemic stroke, dilated cardiomyopathy, hypertrophic cardiomyopathy) .

Subgroup analyses for the primary composite outcome and secondary outcomes (rehospitalizations), were conducted by age strata, gender, CHA2DS2-VASc score, HAS-BLED score, hypertension, CAD, paroxysmal AF and persistent/permanent AF, after adjusting for baseline risk factors. The change in proportion of patients on anticoagulation was evaluated with Mantel-Haenszel statistics and *adjusted for the effect of clustering*. All statistical tests were done at the nominal 0·05 (two-sided) significance level. All statistical analyses were conducted using IBM SPSS Statistics, version 22.0 (SPSS Inc), MedCalc version 19. 0.4 (MedCalc Software), and SAS software, version 9·4 (SAS Institute, Cary, NC, USA) for frailty Cox model.

**RESULTS**

We enrolled 3324 patients in 40 centers between June 1, 2018 and August 16, 2019 (**Figure 1**). Most of patients both mAFA intervention and usual care were enrolled from Inpatient Department (Online Table 2). 1646 patients were allocated to mAFA intervention (mean age 67.0 years, 38.0% female) with mean follow-up of 262 days, while 1678 patients were allocated to usual care (mean age 70.0 years, 38.0% female), with mean follow-up of 291 days. The baseline characteristics of the mAFA intervention group and usual care are shown in **Table 1**.

The treatments, with respected to the ABC pathway, with mAFA intervention and usual care respectively, are summarized in Online Table 3. For the patients with mAFA, there were 1260 patients using PPG-based smart devices to monitor pulse rhythm, and then achieved adequate symptom control using mAFA (B criterion of ABC pathway, ie. Better symptom control; Case shown in Online Figure 3).

*Cardiovascular outcomes*

The rates of the composite outcome of ischaemic stroke/systemic thromboembolism, death, and rehospitalization were significantly lower in those allocated to the mAFA intervention group compared to usual care (1.9%, vs. 6.0%, respectively, HR 0.39, 95% CI: 0.22-0.67, P <0.001). The rate of rehospitalization was significantly lower in the mAFA group compared to usual care (1.2% and 4.5%, respectively, HR 0.32, 95% CI: 0.17-0.60, P < 0.001) (**Table 2**). Detailed reasons of rehospitalization are summarised in Online Table 4.

The cumulative risk of cardiovascular events over time, adjusting for age, AF type, prior AF treatment and comorbidities, are shown in **Figures 2, 3**, respectively.

*Changes of OACs in mAFA and usual care groups*

The baseline proportions of OAC use in the usual care and mAFA arms was 48.4% (812/1678) and 66.1% (1088/1646), respectively (p<0.001). Patients with mAFA more commonly received NOACs than usual care (Online Table 3). The change in the use of OAC among high risk patients (with CHA2DS2-VASc≥2 in males, ≥ 3 in females) between baseline and 12 months are shown in Supplementary online Figure 5.

*Subgroup Analyses*

Subgroup analyses by age, sex, AF type, risk scores (CHA2DS2-VASc and HAS-BLED scores), and comorbidities, demonstrated consistently lower HRs for the primary composite outcome and rehospitalization for patients allocated to mAFA intervention when compared to patients receiving usual care (all p< 0.05 vs usual care, **Figure 4**).

**Discussion**

In the present prospective, multi-centre, cluster randomized trial of subjects with AF, an integrated care pathway approach based on the ABC pathway, supported by mobile health technology, significantly reduced the composite outcome of ischaemic stroke/systemic thromboembolism, death and rehospitalization. Second, lower rehospitalization rates in the mAFA intervention group were observed, even after adjusting baseline age, AF type, treatment and comorbidities, compared to usual care. Third, the impact of mAFA intervention on the composite outcome was consistent irrespective of age, sex, AF type, risk scores (CHA2DS2-VASc and HAS-BLED scores), and comorbidities.

The integrated care approach to disease management originates in the chronic care model, which aimed to redesign daily practice to facilitate treatment optimization and enhance patient outcomes(20). An integrated care approach to AF management was proposed in the 2016 European Society of Cardiology (ESC) guidelines on AF management (1), but how best to operationalize an integrated, structured approach to AF care remained unclear. A nurse-led integrated outpatient AF care approach demonstrated improved adherence to guidelines, with psychosocial support and educational interventions during follow-up (21). Another post-discharge integrated care plan, consisting of home visits and 7-14 day Holter monitoring by a cardiac nurse and multidisciplinary support showed improvements in survival compared to usual care(22).

Other studies have aimed to explore improvements in (anticoagulant) drug adherence in primary care (23,24). Educational interventions such as IMPACT-AF have led to improved rates of OAC use, which would translate to stroke reduction in the developing countries(24). Although some progress on integrated care approaches are implied, prior studies on integrated care have not covered all main treatment targets for AF and avoidance of AF-related complications.

In the present trial, we tested implementation of the ABC pathway for the holistic, integrated management of AF patients: (i) “A” Avoid stroke with anticoagulation with dynamic monitoring of stroke/bleeding risks, clinical decision support with dosage-adjustments of warfarin based on changes on TTR, or label-adherent use of non-vitamin K antagonist oral anticoagulants (NOACs); (ii) “B” Better symptom management with patient-centered, symptom directed decisions on rate or rhythm control; and (iii) “C” cardiovascular and comorbidity risk reduction, with the timely monitoring (and treatment) of blood pressure, optimization of cardiovascular prevention strategies (e.g. statins for vascular disease, ACE inhibitors or angiotensin receptor blockers for heart failure, etc.). The ABC pathway simplifies and streamlines the patient journey (‘Easy as ABC…’), is uniformly applicable across the whole AF patient pathway, starting with primary care and linking with secondary care (including cardiologist and non-cardiologists), and understandable for the AF patients *per se* to enable them to engage with their care. Indeed, the ABC pathway covers all main treatment options for patients with AF, relevant to primary care physicians, secondary care (whether cardiology or non-cardiology clinics) and patient-centred approaches. Patients could monitor their pulse rhythm with smart devices, assess their symptom, and communicate to their doctors in a timely manner, using mAFA, and with better symptom management delivered and tailored to the patient’s needs and values (Supplementary online Figure 3). Moreover, AF patients could take part in educational programs via different methods, for example, articles, videos and games, as well as mAFA providing encouragement for self-care and lifestyle changes, through the Questions and Answer sections (Supplementary online Figure 4).

Our results are consistent with prior studies testing the impact of ABC pathway adherence on clinical outcomes (12-14). For example, Proietti et al conducted a post-hoc ancillary analysis of the AFFIRM trial, which showed AF patients managed with the ABC pathway had a lower risk of mortality, stroke/major bleeding/cardiovascular death, and hospitalization (12). In the ATHERO-AF study, Pastori et al reported that ABC pathway adherent management resulted in a significantly lower rate of cardiovascular events (13) as well as lower healthcare costs (25). Indeed, adherence with the ABC pathway also had an impact on a nationwide scale, leading to reduced clinically relevant outcomes in a nationwide cohort of 204,842 nonvalvular AF patients (14).

We found a significant reduction in hospitalisations in those allocated to the mAFA intervention. Comorbid chronic diseases are increased in association with increased hospitalization rates for AF (26). Indeed, hospitalizations for AF itself and related complications are the main driver for healthcare costs (26), and may be preventable with appropriate guideline adherent care delivery to enhance outcomes in this population.

High risk patients with CHA2DS2-VASc score ≥3 in females, ≥2 in males using mAFA had a high rate of OAC use (>80%) which generally persisted over time (Supplementary online Figure 5). In various registries from China, OAC use was substantially lower, being 25%-31% (27-29). In the IMPACT-AF trial including China, OAC use was increased from 68% at baseline to 80% at 1 year, following intervention an educational program (24). The high rate of OAC use in the present study could have been facilitated by the mAFA App providing clinical decision support, dynamic risk monitoring and timely communication between doctors and patients, as well as educational and interactive programs. Bleeding risk was low, approximately 2% in both intervention and usual care groups perhaps related to the App assessing bleeding risk based on dynamic calculation of HAS-BLED score in a timely manner, thus facilitating optimal management guided by the doctors (even remotely) using the mAFA App. This could also be one reason for the lower rate of OAC discontinuations among these patients. Finally, mHealth technology in the present study provided a clinical decision support tool, which improved guideline adherence for anticoagulant therapy (30), as well as a clinical managemental pathway with mHealth technology to streamline and simplify clinical practice.

*Strengths and Limitations*

As far as we are aware, mAFA is the first integrated programme that links AF screening (‘pre-mAFA’)(16), with eligible patients entered into a structured care pathway. Another integrated care trial of chronic cardiovascular diseases (AF, HF, hypertension) using a mobile tool (phone, tablet) is ongoing, providing vital-sign measurements and on-remote communications between patients and physicians, but not proactive management options (24). Nevertheless, there were some limitations. Although the present study was cluster randomized control trial, the patients in mAFA arm were younger than the usual care arm and compared to the general AF population. Some differences in baseline comorbidities were also evident given the *cluster randomized trial design*, rather than individual randomization. Nevertheless, the outcomes were fully adjusted for age and other comorbidities, using statistical methodology appropriate for analyses of cluster randomized trials. There was also no statistical interaction in relation to the beneficial impact of mAFA intervention on the composite outcome, even amongst the elderly (age≥75) which constituted approx. 32% of the study cohort. The low mean age overall may also reflect that mobile health devices are more likely to be used in the younger population in a real-world setting.

Third, we are testing a ‘package of care’ with the mAFA intervention in a holistic approach to AF management, and it was never the intention to investigate the individual components of the ABC pathway, nor the factors *within* the A, B or C components, e.g. warfarin or NOAC, blood pressure control or not, etc. Indeed, adherence with therapy (for example, oral anticoagulation) may reduce over time – but our ‘holistic’ package of care includes more than only the ‘A’ (anticoagulation) component per se. Fourth, we did not observe a significant difference in the individual endpoints of stroke/thromboembolism and major bleeding, which may perhaps be related to the low rate of events during the mean follow-up of 286 days, and the some loss to follow up. Further analyses of adherence and long-term outcomes in the mAFA II trial are planned.

Fifth, most research centers in present study are Grade 3 level in China (Online Table 1), presenting the ‘top medical level’ hospitals. The finding of the present study may not necessarily generalize to Grade 2 level hospitals or Community Service Centers, which will be explored in future studies. Finally, this trial was conducted in China, and further studies in non-Asian cohorts from different healthcare systems are in progress or planned.

**CONCLUSION**

An integrated care approach to holistic AF care, supported by mobile health technology, significantly reduced clinical adverse outcomes in AF patients. Implementation of the ABC pathway using an App-based mHealth approach may improve clinical outcomes in AF patients.

**PERSPECTIVES**

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS**: We demonstrate that a holistic approach to AF care, simplified into a practical, simple ABC pathway, reduces the risks of rehospitalization and clinical adverse events. Such mHealth technology assists implementation of AF integrated care, combining clinical decision support, dynamic risk monitoring, educational program, and patient-involving self-management (**Central Illustration**).

**TRANSLATIONAL OUTLOOK**: Implementation of an integrated care ABC pathway, Avoid stroke; Better symptom management with patient-centred, symptom directed decisions on rate or rhythm control; Cardiovascular and other comorbidity risk reduction, using an App-based mHealth approach, may streamline the clinical care and improve clinical outcomes in AF patients.

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**Figure Legends**

**Figure 1: Flow chart of patients included into mAFA-II trial.** AF: atrial fibrillation. mAFA: mobile atrial fibrillation application.
**Figure 2: Cumulative risk of composite outcome of ischaemic stroke/TE, death, and rehospitalization**. mAFA: mobile atrial fibrillation application. TE: other systemic thromboembolism. HR: hazard ratio. CI: confidential interval.

**Figure 3: Cumulative risk of rehospitalization.** mAFA: mobile atrial fibrillation application. HR: hazard ratio. CI: confidential intervention. Rehospitalization included any cause for AF, heart failure, thromboembolism, major bleeding, artery coronary disease, and other cardiovascular disease.

**Figure 4: Hazard Ratios of primary composite outcome of ischaemic stroke/TE, death, and rehospitalization, and secondary endpoint (rehospitalization), by gender, age, AF type, risk score, and comorbidities, adjusting for cluster effect，baseline risk factors.** A. Composite outcome of ischaemic stroke/TE, death and rehospitalization. B. Rehospitalization. \* mAFA: mobile atrial fibrillation application. HRs: hazard ratios. TE: thromboembolism

**Central Illustration.** mAFA: mobile atrial fibrillation application. TTR: time in therapeutic range. AF: atrial fibrillation. CAD: coronary artery disease. HF: heart failure. NOAC: non-vitamin K antagonist oral anticoagulants.

**Table 1: Baseline characteristics of the mAFA intervention and usual care.**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **mAFA Intervention****(n=1646)** | **Usual care****(n=1678)** |
| Age, mean (SD) | 67.0 | (15.0) | 70.0 | (12.0) |
| Female, n (%) |  | 625 | 38.0% | 637 | 38.0% |
| Current smoking, n (%) | 159 | 9.5% | 168 | 10.2% |
| Medical history |  |  |  |  |
| Hypertension, n (%) | 908 | 55.2% | 962 | 57.3% |
| CAD, n (%) | 635 | 38.6% | 724 | 43.1% |
| Diabetes mellitus, n (%) | 381 | 23.1% | 366 | 21.8% |
| Heart failure, n (%) | 360 | 21.9% | 354 | 21.1% |
| Prior ischaemic stroke, n (%) | 191 | 11.6% | 232 | 13.8% |
| PAD, n (%) | 172 | 10.4% | 172 | 10.3% |
| Renal dysfunction, n (%) | 138 | 8.4% | 172 | 10.3% |
| Pulmonary hypertension, n (%) | 87 | 5.3% | 83 | 4.9% |
| Liver dysfunction, n (%) | 55 | 3.3% | 48 | 2.9% |
| Prior TE, n (%) | 54 | 3.3% | 59 | 3.5% |
| Prior other bleeding, n (%) | 54 | 3.3% | 67 | 4.0% |
| Dilated cardiomyopathy, n (%) | 44 | 2.7% | 61 | 3.6% |
| Hyperthyroidism, n (%) | 37 | 2.2% | 51 | 3.0% |
| Hypertrophic cardiomyopathy, n (%) | 25 | 1.5% | 29 | 1.7% |
| Prior brain bleeding, n (%) | 24 | 1.5% | 38 | 2.3% |
| AF type |  |  |  |  |
| New onset AF, n (%) | 195 | 11.9% | 232 | 13.8% |
| Paroxysmal AF, n (%) | 673 | 40.9% | 660 | 39.3% |
| Persistent AF, n (%) | 380 | 23.1% | 448 | 26.7% |
| Longstanding AF, n (%) | 56 | 3.4% | 101 | 6.0% |
| Permanent AF, n (%) | 48 | 2.9% | 123 | 7.3% |
| Unknown AF type, n (%) | 281 | 17.1% | 113 | 6.7% |
| Prior AF treatment |  |  |  |  |
| Pharmacy cardioversion, n (%) | 213 | 12.9% | 155 | 9.2% |
| Electrical cardioversion, n (%) | 30 | 1.8% | 35 | 2.1% |
| AF ablation, n (%) | 183 | 11.1% | 173 | 10.3% |
| Dual chamber pacemaker, n (%) | 76 | 4.6% | 85 | 5.1% |
| LAAO, n (%) | 33 | 2.0% | 30 | 1.8% |
| CHA2DS2-VASc, median (IQR) | 3 | 2-4 | 3 | 2-4 |
| HAS-BLED, median (IQR) | 1 | 1-2 | 1 | 1-2 |
| SAMe-TT2R2, median (IQR) | 4 | 3-4 | 4 | 3-4 |

\* mAFA: mobile Atrial Fibrillation Application. SD: standard deviation. CAD：coronary artery disease. PAD: peripheral arterial disease. AF: atrial fibrillation. LAAO: left atrial appendage occlusion. IQR: interquartile. CHA2DS2-VASc: chronic heart failure, hypertension, age>75 years, diabetes, stroke, vascular disease, age 65-74 years, sex. HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly. SAMe-TT2R2: sex, age, medical history, treatment, tobacco use, race.

**Table 2: Clinical outcomes in the mAFA and usual care groups**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **mAFA****(n=1646)** | **Usual care****(n=1678)** | **Hazard ratio \***(mAFA vs. Usual care) | **95%CI** | **P** |
| **Thromboembolism** |  |  |  |  |  |
| Ischaemic stroke | 3 (0.2%) | 3 (0.2%) | 1.31 | 0.18-9.31 | 0.78 |
| Other systemic thromboembolism | 4 (0.2%) | 3 (0.2%) | 1.02 | 0.18-5.93 | 0.97 |
|  |  |  |  |  |  |
| **Bleeding events** |  |  |  |  |  |
| Intracranial bleeding | 0 (0) | 2 (0.1%) | - | - | - |
| Extracranial bleeding | 31 (1.9%) | 36 (2.1%) | 0.95 | 0.54-1.66 | 0.85 |
|  |  |  |  |  |  |
| **Cardiovascular outcomes** |  |  |  |  |  |
| Recurrent atrial fibrillation | 23 (1.4%) | 56 (3.3%) | 0.48 | 0.29-0.79 | **0.004** |
| Heart failure | 24 (1.5%) | 33 (2.0%) | 0.99 | 0.51-1.92 | 0.97 |
| Acute coronary syndrome | 2 (0.1%) | 9 (0.5%) | 0.21 | 0.04-1.21 | 0.08 |
|  |  |  |  |  |  |
| **All-cause death** | 12 (0.7%) | 25 (1.5%) | 0.71 | 0.26-1.91 | 0.49 |
|  |  |  |  |  |  |
| **Rehospitalization** | 20 (1.2%) | 75 (4.5%) | 0.32 | 0.17-0.60 | **<0.001** |
|  |  |  |  |  |  |
| **Composite outcome of IS/TE, death, and rehospitalization** | 32 (1.9%) | 101 (6.0%) | 0.39 | 0.22-0.67 | **<0.001** |

Data are n (%). \* The frailty Cox model, adjusted for cluster effect, age, comorbidities, AF type, and prior AF treatment, was used to assess the effect of mAFA intervention on the clinical events. IS: ischaemic stroke. TE: thromboembolism. Extracranial bleeding included gastrointestinal, urogenital, skin, eye bleeding, and other non-major bleeding. Recurrent atrial fibrillation: recurrent onset of AF for patients with paroxysmal AF or with AF ablation. Reasons for rehospitalization included any cause for AF, heart failure, thromboembolism, major bleeding, artery coronary disease, and other cardiovascular disease (Online Table 4). The causes of death are shown in Online Table 5.