Mobile Health (mHealth) technology for improved screening, patient involvement and optimizing integrated care in atrial fibrillation: The mAFA (mAF-App) II randomized trial

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Abbreviations

AF: Atrial fibrillation; OAC: oral anticoagulation; NOAC: non-vitamin K antagonist oral anticoagulants; mAFA：mobile atrial fibrillation application; QoL: quality of life; PPG：photoplethysmography; ECG: electrocardiogram; CHA2DS2-VASc: a history of congestive heart failure, hypertension, diabetes, vascular disease (myocardial infarction and peripheral artery disease), and female sex (sex category) ; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs, elderly, drugs or alcohol; SAMe-TT2R2: sex, age, medical history, treatment, tobacco, race; TTR：time in therapeutic range；EHRA：European Heart Rhythm Association；NYHA：New York Heart Assessment；SpO2：Pulse Oxygen Saturation；TIA: transient ischemic attack; DVT: deep vein thromboembolism; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; HF: heart failure; HCRU: HealthCare Resource Utilization; QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio; CHEERS: Consolidated Health Economic Evaluation Reporting Standards; ICC: intracluster correlation coefficient; HR: hazard ratio.

Abstract

Background   Current management of patients with atrial fibrillation (AF) is limited by low detection of AF, nonadherence to guidelines and lack of consideration of patient's preferences, thus highlighting the need for a holistic and integrated approach to AF management. The present study aims to determine whether a mHealth technology-supported AF integrated management strategy will reduce AF-related adverse events.

Methods/design The mAFA II trial is a prospective, cluster randomized controlled trial. The 40 sites will be randomized to mAFA-integrated care intervention or usual care arms. Prior to randomization, study sites will be paired to be matched in size and the proportion of study eligible patients.   All AF patients aged over 18 years old with CHA_2DS_2-VASc score ≥ 2 will be enrolled.

Assuming a composite adverse event rate of 10% pre-intervention, reduced to 5% after intervention, we aim to recruit 3660 patients assuming a 10% loss to follow-up. The primary study endpoint is a composite of stroke/thromboembolism, all-cause death, and rehospitalization. Ancillary analyses would determine patient-related outcome measures, health economics and cost effectiveness, as well as an embedded qualitative study.

Discussion The mAFA II trial will provide evidence for an integrated care approach to holistic AF care, supported by mobile health technology to improve screening, patient involvement and optimization of management.

Trial registration WHO   Chinese Clinical Trial Registry, chictr.org.cn (ChiCTR-OOC-17014138).

Key words Atrial fibrillation, integrated management, stroke, all-cause death, rehospitalization, anticoagulant

What is already known about this topic?

- Current management of patients with atrial fibrillation (AF) is limited by low detection of AF, nonadherence to guidelines and lack of consideration of patient's preferences.
- The need for a holistic and integrated approach to AF management, that includes stroke prevention, rate or rhythm control for symptom management, and associated comorbidity or lifestyle changes.

What does this article add?

- This article highlights the design of a prospective clinical trial (mAFA II) testing a holistic approach to AF management may be simplified into a practical, simple ABC pathway (Avoid stroke; Better symptom management; Cardiovascular and other comorbidity risk reduction).
- The mAFA II trial will provide evidence for an integrated care approach to holistic AF care, supported by mobile health technology to improve screening, patient involvement and optimization of management.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia globally, with an increased risk of mortality and morbidity from stroke and heart failure [1]. Given the increasing prevalence and incidence of AF with an ageing population, this arrhythmia represents an increasing public health burden. There will be 12.1 to 15.9 million patients suffering from AF in the United States by 2050, and 17.9 million people in Europe by 2060 [2,3].

Given the largest population in developing countries and the increasingly ageing population, the burden of AF is greatly increasing in China. Indeed, there has been a 20-fold increase in AF prevalence and 13-fold rise in AF-related stroke during the last 11 years in China [4]. We have previously modelled projections for the risks related with AF in East Asia, and the burden of ischaemic stroke and death remains large, despite the introduction of new guidelines and therapies [5].

An integrated, structured approach to AF care has been proposed in the 2016 European Society of Cardiology (ESC) guidelines on AF management [6], which is consistent with the Innovative Care for Chronic Conditions Framework proposal put forward by the World Health Organization [7]. Integrated AF care combines patient involvement, multidisciplinary teams, and technology tools to achieve all treatment options for AF, for example, a structured support for lifestyle changes, anticoagulation, rate control, antiarrhythmic drugs, and catheter and surgical interventions [6]. In small sized studies, the use of an integrated care approach in AF has been associated with reduced cardiovascular hospitalisations and all-cause mortality, but not AF-related hospitalisations or cerebrovascular events [8].

Various comprehensive and complex proposals for integrated care AF management have been proposed [9]. This holistic approach to AF management may be simplified into a practical, simple ABC pathway (Avoid stroke; Better symptom management; Cardiovascular and other comorbidity risk reduction) [10]. A major challenge is how

to operationalize the concept of integrated AF care in busy "real-world" clinical practice, especially in low-middle income countries.

The individual components of the ABC pathway are facets of a holistic approach to AF patient management [10]. For example, stroke prevention with oral anticoagulation (OAC) is the cornerstone of AF management [11]. Nonetheless, suboptimal thromboprophylaxis in AF patients is highly prevalent in Asian countries [12-15], despite the various guidelines on AF management [6,16-18]. Even moving into the new era of the non-vitamin K antagonist oral anticoagulants (NOACs), many patients remain undertreated in Asia [19].

Nonadherence to AF management guidelines is also common, ranging from 33% to 68% in the Middle East/Africa and Asia, respectively [20]. Nevertheless, patient's preferences are another important reason for non-adherence of therapy [21]. Indeed, optimal stroke prevention relies on patients taking medications properly and continuously. A patient with good knowledge of AF is more likely to be concerned about a stroke and would want to be involved in joint decision-making for anticoagulant treatment [22], thus increasing treatment adherence and persistence. Lifestyle changes are also part of this comprehensive approach, whereby healthy lifestyle and addressing cardiovascular risk factors may improve uptake of treatments and ultimately, patient outcomes [23].

Besides, a simple and cost-effective approach to AF care, streamlining management pathways from the hospital to the home is needed [24]. Furthermore, up to two-thirds of AF patients are asymptomatic and have the same risks as symptomatic AF. Detection of these AF episodes and initiation of appropriate management could reduce the risks of AF-related stroke and other complications [25].

Novel strategies that incorporate eHealth or mobile Health (mHealth) encompasses the use of information and communication technologies in the management of disease,

providing innovative solutions to the problem of long-term management after discharge [26-27]. Mobile communication and internet service are well established in China, and the high penetration rate of mobile devices and communication networks provides an excellent foundation and great opportunities for mHealth development, which may facilitate the management of AF in China [28].

In a pilot study, we designed a mHealth technology-supported AF application model (mAF App), integrating clinical decision support tools as part of patient clinical decision support tools (CHA$_2$DS$_2$-VASc, HAS-BLED, SAMe-TT$_2$R$_2$ scores), guideline-based treatment, educational materials and patient involvement strategies with self-care protocols and structured follow-up.[28] In this first prospective randomized trial of mHealth technology in patients with AF, the mAFA (mAF-App I) trial, use of the mAF App significantly improved knowledge, drug adherence, quality of life (QoL) and anticoagulation satisfaction [28].

The pilot mAFA I trial focused efforts on improving stroke prevention and assessed surrogate outcomes. Apart from stroke prevention, symptom management and lifestyle changes, as well as management of cardiovascular and other comorbidities are required in the content of AF care. Hence, we updated the mAFA platform (mAFA II) with integrated care for AF using the ABC pathway, thus providing an opportunity for implementing holistic AF integrated management. More recently, emerging evidence suggested that photoplethysmography (PPG) could be used for AF screening in large population [29,30].

In the mAFA II trial, we would investigate whether implementation of a mHealth technology-supported AF screening with PPG[29] and integrated ABC strategy could reduce AF-related adverse events (stroke/thromboembolism, all-cause death, and rehospitalization). Ancillary analyses would determine patient-related outcome measures, health economics and cost effectiveness, as well as an embedded qualitative study.

Methods and Design

The mAFA II trial is a prospective, cluster randomized controlled trial, conducted in 40 hospitals and patients will be followed up for one year.

Study population

Inclusion criteria would include i) patients aged $\geq$ 18 years old, diagnosed with new-onset, paroxysmal, persistent or permanent AF confirmed with electrocardiogram (ECG) or 24-hour Holter monitors; and ii) CHA_2DS_2-VASc score $\geq$ 2. We excluded individuals aged <18 years old, those with mechanical prosthetic valve or moderate/severe mitral stenosis, unable to provide informed consent, or unable to have one year of follow-up for any reason. The patients are enrolled into the mAFA II trial from AF screening approach in the general population, as well as Out-patient and In-patient Departments in participating hospitals.

Patients will be consecutively recruited at each site to ensure representative inclusion of the overall population in each practice setting in China. Enrollment occurs between June 1, 2018 and December 31, 2019. The flowchart of AF screening and MAFA II project is shown in Fig. 1.

AF screening plan

AF screening with smart devices of PPG technology (Huawei Technologies Co., Ltd., Shenzhen, China) will be available for the population aged over 18 years across China.

At least 14-day monitoring with wristband (HUAWEI HONOR BAND 4), wristwatch (HUAWEI WATCH GT, HONOR WATCH) (PPG algorithm developed by Huawei), will be proposed for the high-risk population for AF (CHA_2DS_2-VASc $\geq$2). The patients with identified "AF" episodes by PPG algorithm will be further confirmed by the health providers with ECG, 24-h Holter among MAFA hospitals.

Randomization

The 40 participating cluster hospitals will be randomized in a 1:1 ratio to receive either the mAFA intervention or usual care. A pilot feasibility investigation was carried out for possible study sites, with respect to hospitals (size, the volume of patients for the study per month), doctors (willingness to be involve in mAFA II, their concerns and obstacles to AF management, the possible time doctors would like to spend on patients out of discharge, study fees, etc), patient catchment (smart phone use, education level, etc.). The sites will be 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. Our pilot investigation demonstrated that the ratio of big:small hospitals was 1:2, thus 142 patients from individual big hospitals and 71 for small hospitals will be needed assuming 10% loss of follow-up.

Intervention

Hospitals randomised to the intervention arm will use the mAFA platform to manage AF patients. The mAFA platform provides clinical decision support tools (CHA_2DS_2-VASc, HAS-BLED, $SAMe-TT_2R_2$ scores), 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 [Figure 2].

<u>A</u>void stroke

The dynamic bleeding risk will be monitoring using HAS-BLED score by MAFA platform automatically with updated blood pressure, hemoglobin, renal/liver function, etc. (Fig.3A). Modifiable bleeding risk factors would be flagged up (for example, systolic blood pressure over 160 mmHg), addressed for the patients and doctors.

A personalized OACs management would be tailored to the patients. For example, the time in therapeutic range (TTR) will be automatically calculated for the patients on warfarin (Fig.3B). If the patients were taking dabigatran or rivaroxaban (the only two NOACs that are currently approved in China), the relative dose optimisation of taking those drugs and the checklist of requirements will be provided by the mAFA app. Drug adherence will be recorded, as patients can use the mAFA platform to record their dose and drug use. Liver and renal function monitoring plans will be recommended to the patients matched the patient's age, comorbidities, co-medications and the use of OACs.

Patient-reported thromboembolism or bleeding events would be captured using the structured questionnaire developed by the mAFA platform. Doctors can also communicate with patients on these events through instant messages on the mAFA platform.

Better symptom management
The European Heart Rhythm Association (EHRA) AF symptom assessment scale will be used for assessing the severity of AF symptom. The smart device with PPG will be undertaken for monitoring AF occurrence (Fig. 4). Take the patients with AF ablation for example, the reminder would be sent to the patients and doctors for further confirmation and management when doubtful "AF" episode were monitored (Fig. 4).

Cardiovascular and other comorbidities risk management
Blood pressures will be recorded, and suboptimal readings would be 'flagged up' for optimization of treatment (Fig.5). Heart failure and angina management would be optimized, as needed. Primary and secondary prevention drugs (eg. statins, ACE inhibitors or angiotensin receptor antagonists) would be optimized for patients with comorbidities such as vascular disease.

Follow up and study outcomes

All patients will be followed in the outpatient clinics at 6 and 12 months for clinical events. The clinical events will be adjudicated by a clinical events committee.

The *primary endpoint* is the composite of stroke/thromboembolism, all-cause death, and rehospitalization. The thromboembolism endpoint includes ischaemic stroke, transient ischemic attack (TIA), pulmonary embolism, deep vein thromboembolism (DVT), other thromboembolism (peripheral embolism, atrial thrombus and left atrial appendage thrombus, etc.). All-cause death will include cardiac death, vascular death, and non-cardiovascular death. Cardiac death includes 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 will include death ascribed to ischemic stroke, haemorrhagic stroke, systemic haemorrhage, peripheral embolism, and pulmonary embolism. Rehospitalization for AF and AF-related complications, will include stroke, systemic thromboembolism, angina, STEMI/NSTEMI, HF, etc.

Secondary outcomes will include the following: i) incidence of AF identified in 2 weeks, among high-risk population; ii) the change in proportion of patients able to continue anticoagulation; iii) the mAFA intervention costs, individual-level HealthCare Resource Utilization (HCRU) as well as associated costs, and quality adjusted life year (QALY) gained with mAFA use compared to usual care; and iiii) event rates: event rate for composite of ischaemic stroke/TIA and systemic thromboembolism, HF, cardiovascular death, or rehospitalization for any cause for AF.

mAFA training, data management, monitoring and quality control

The mAFA trial program will deliver the training on mAF App use for the researchers before the study. Self-reported healthcare utilisation including medicine usage, visits for AF-related adverse outcomes, hospitalisations, etc. will be assessed by AF cost

questionnaires at 6 and 12 months. Patients will also be asked to fill in a patient-specific cost diary every month during study period to avoid missing information.

An independent third party (CheckTruth, Ltd, Beijing, China) will monitor the project onsite, ensuring health, safety and the relevant rights of subjects are protected. Monitoring will also ensure the sites carry out the study according to protocol, the data collected are true and accurate, and the site staff and facility meet the protocol requirements.

All sites that enroll at least one patient will undergo a data control audit by completing a site visit. The visits will spread over the entire study period, with first visit of approximately 30% being done around the time of enrollment. In addition, all sites would undergo further data monitoring as necessary, based on performance, queries initiated or missing data. For the sites undergoing monitoring, the case report forms for patients enrolled at site will be monitored for source documentation and accuracy.

Statistical analysis

Analyses will be conducted according to the intention-to-treat principle [31]. The primary analyses of primary, secondary and exploratory outcomes will be based on the intention-to-treat population adjusted for the effect of clustering. All primary tests of significance will be two-sided with alpha=5%. Frequencies and percentages per group as well as hazard ratios with 95% confidence interval (CI) will be reported for binary outcomes. Continuous variables and rate variables will be summarized using mean, standard deviation as appropriate, and minimum and maximum values. All statistical analyses will be completed with IBM SPSS Statistics, version 22.0 (SPSS Inc)

Cox proportional hazard model analysis will be used to assess the effect of mAFA intervention on the primary composite outcome of stroke/thromboembolism, all-cause death, and rehospitalization. Additionally, the impact of the mAFA intervention on clinical outcomes will be explored, including the time to first occurrence of ischaemic

stroke/TIA and systemic thromboembolism, rehospitalization, and cardiovascular death will be analyzed. Change in proportion of patients on anticoagulation will be evaluated with Mantel-Haenszel statistics and adjusted for the effect of clustering.

Subgroup and sensitivity analyses

The subgroup analyses for the primary and secondary outcomes will be conducted by age strata, gender, and educational level. Sensitivity analyses of the primary and secondary outcomes will be repeated among all randomized patients without major protocol violations and classified according to the intervention to which they were randomized.

Health economic evaluation

The healthcare resource utilization (hospitalizations, physician office visits, etc.) and healthcare costs (hospitalizations, primary care, medications, etc) of mAFA and usual care will be examined by descriptive statistics.

For mAFA intervention costs, the included costs are those that are likely to differ across the mAFA intervention and usual care, specifically the costs of:

(i)   Costs of the mAF app design (for patients and doctors) and also associated Apps including AF decision support tool, and other apps to provide stroke and bleeding risk calculations.   These costs can be derived from financial statement or unit costs multiplied by total personnel-time.

(ii) Costs resulting from additional time spent by patients in learning the App, uploading their laboratory tests, learning educational programs, and their involvement with self-care, etc.

(iii) Costs of the app-integrated Patient's Educational Program development.

(iv) Personnel costs spent in double check the structured data and the source documentation of mAF App.

(v)   Costs resulting from additional time spent by doctors compared to control group.

Protocol-driven costs for research purposes shall not be included, which may also be balanced between arms.

mAFA intervention differences in the mean number of health care resources utilized and in the average rate per unit of time will be estimated. Further, the longitudinal models will be utilized for the analysis of health care resource use data [32].

The Kaplan–Meier method will be used for the analysis of cost data, considering the presence of censoring in the clinical trial data [33]. The cost-effectiveness (improvements in life years, quality of life, QALYs, the cost per QALY gained, and the incremental cost-effectiveness ratio (ICER) of mAFA compared to usual care will be calculated. The economic assessments will be reported in alignment with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [34]. The bootstrap method will be used to construct the confidence interval for the ICER [35].

Power calculation
The mAFA II trial power calculation is shown in Fig. 3. An intracluster correlation coefficient (ICC) is assumed to be 0.02, and a reduction in stroke risk would be 52% after intervention (Hazard ratio, HR 0.48, 95% CI 0.23-0.99) according to a prior study, IMPACT-AF [36]. There would be 10% difference of anticoagulant uptake after mAFA intervention and after usual care [28], so we will assume baseline anticoagulant use of 40%, with a post-mAFA intervention use of 60% and a post-control arm rate of 50%, respectively. The composite adverse events (stroke/thromboembolism, all-cause death, and rehospitalization) is estimated as 10% during first one year with baseline anticoagulant use of 40%. Thus, the sample size will be 3294 patients with type I error under 5% and power of over 90%. Trends of sample size from cluster randomization are seen in Fig. 6. Considering 10% loss to follow-up, a total of 3660 patients will be needed, randomized into the mAFA arm and usual care arms [37].

Current trial status

The first patient was enrolled in June 2018, and 1136 AF patients have been enrolled into MAFA II trial as of January 31, 2019. Those patients were mostly recruited from Out-patient, In-patient Department of hospitals, with some from the AF screening approach in the general population, who were confirmed with their AF diagnosis by doctors in the mAFA trial hospitals. Enrollment will continue to December 31, 2019, and the last follow-up will be completed until December 31, 2020.

There were 32259 subjects participating in the AF screening approach using smart devices with PPG until January 15, 2019, and 83 "AF episodes" have been identified with the PPG algorithm. Eight subjects (10%) were lost the follow up, while 66 (91%) have been confirmed with AF diagnosis with a 12 lead ECG or 24-Holter among those with follow-up, and entered into MAFA II trial.

Discussion

The increasing global burden of AF leads to a high incidence of stroke, systemic embolism, dementia, heart failure, and death. In recent years, new anticoagulant drugs (eg. the NOACs) and technologies (cryoballoon ablation, percutaneous left atrial appendage occlusion, etc) have been introduced for the treatment of patients with AF. Despite this, suboptimal management of AF is still common, and all-cause or cardiovascular death remains high amongst the AF population.[37] Indeed, death is the most frequent adverse event in AF, with CHF, MI, stroke and major bleeding contributing to AF mortality [39,40].

The comorbidities associated with the worse outcomes in AF patients are often sub-optimally treated with guideline-recommended drugs. Thus, AF integrated care has been proposed to provide a holistic approach to AF management and improve outcome. Integrated AF care requires patient involvement and empowerment, lifestyle changes, educational guidance and shared decision-making. Use of new technologies may facilitate this, especially in healthcare systems with a high penetration rate of mobile devices and communication networks.

This was tested in the pilot mAFA I trial, which was a small study which showed that mHealth technology-supported AF management strategy was feasible, effective and safe.[28] The clinical decision support provided by the mAF App streamlined guideline-based decision-making for the stroke prevention in patients with AF, and was easily handled by doctors and understood by patients. The clinical decision support tools in the mAF App automatically assesses stroke and bleeding risk, stratified the patients at high-risk of stroke/TE to anticoagulant treatment, while balancing bleeding risks. Bleeding risk factors were also labeled and could be reviewed by doctors and patients for proactive correction of modifiable risk factors. Personalized choices of OAC could also be advised, and if warfarin was being considered (a common option in China, as NOACs are not reimbursed), the SAMe-TT_2R_2 score would help 'flag up' those patients

are less likely (if score >2) to achieve good anticoagulation control (as reflected by TTR) for more regular INR checks, education/counselling, etc – or alternatively, to consider a NOAC. Thus, the mAFA app helps in rational decision-making on anticoagulant management options, with patient engagement.

The mAF App then automatically makes a follow-up plan, permitting patient's self-monitoring and timely feedback. Indeed, the pilot mAFA study (mAFA I trial) also showed that the mAF App-based self-monitoring and feedback enhanced compliance and adherence of drug therapy and anti-coagulant satisfaction.[28] While the mAFA I study focused on stroke/TE prevention, it is well-recognised that interventions beyond anticoagulation are needed to further reduce mortality in AF. Thus, the objective of the present study (mAFA II) is to develop and implement a holistic approach to integrated AF management, covering AF screening, prevention strategies (oral anticoagulation, symptom management with rate or rhythm control), and risk factor management with the aim of reducing recurrent stroke, HF, rehospitalization, and death, etc.

Screening strategies can improve the detection of AF in high-risk population,[29] and could modify morbidity and mortality by early institution of preventive therapies, such as OAC. Thus, a cost-effective, screening strategy using PPG technology has been integrated into the mAFA II study to help improve AF care, using a simple detection tool.

Given the limitations of the cluster-randomised study design, some imbalances between the intervention and control site populations may occur. However, the fully randomized clusters and similar enrolment procedures at intervention and control sites would limit this. In addition, AF screening with HUAWEI smart devices will be performed in general population across China, then the "doubtful" AF event will be further confirmed by doctors in participating mAFA hospitals with an ECG or 24 h-Holter. The AF screening application can be freely available on appstore.huawei.com. While we cannot

randomize the general population to AF screening or not, the feasibility of AF screening with PPG technology among a large population will be tested.

Conclusion

The mAFA II trial will provide evidence for an integrated care approach to holistic AF care, supported by mobile health technology to improve screening, patient involvement and optimization of management. This trial tests an innovative solution to reduce AF-related stroke/systemic thromboembolism, all-cause death and hospitalisations, with associated patient involvement and empowerment, educational guidance and shared decision-making.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Data sharing statement

Not applicable.

Authors' contributions

YG, and GYHL had the main idea of the study. DAL, LW, and YC contributed to the design of the study. YG and GYHL drafted the manuscript. Y DAL, LW, and YC were involved in the editing of the manuscript. All of the authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study is approved by the Central Medical Ethic Committee of Chinese PLA General Hospital (Approval number: S2017-105-02), and also, by local institutional review boards. The study will comply with the Declaration of Helsinki, and all patients will give written informed consent. The study is also registered at www.chictr.org.cn (ChiCTR-OOC-17014138) on Dec 26, 2017.

Competing interests

GYHL is a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife, and Daiichi-Sankyo; and a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche, and Daiichi-Sankyo. No fees are received personally. Other authors: None declared.

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FIGURE LEGENDS

Fig.1 Flowchart of AF screening and mAFA II project. *PPG: Photoplethysmography.

Fig.2 mAFA II study design

Fig.3 mAFA II: AF integrated care pathway A. 3A. Dynamic bleeding monitoring 3B. Anticoagulant quality control of TTR. TTR: Time in therapeutic range.

Fig.4 mAFA II: AF integrated care pathway B. 4A. AF risk monitoring with smart device with PPG. Green: normal rhythm, Yellow: irregular cardiac rhythm, Red: doubted AF episodes. The alert would be sent to the users for further confirmation and management when "doubted" AF were monitored. 4B. ECG monitoring.

Fig.5 mAFA II: AF integrated care pathway C. 5A. Systolic blood pressure monitoring on PmAFA, while suboptimal readings would be flagged up'for optimization of treatment. 5B. Reminders for optimization of blood control on DmAFA. * PmAFA: mAFA for patients, DmAFA: mAFA for doctors.

Fig. 6 Sample size calculations for cluster randomization.

Appendix

Executive Steering Committee:

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