**Regular bleeding risk assessment associated with reduction in bleeding outcomes: report from the mAFA II trial**

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Running head: Dynamic bleeding assessment reduced the bleeds.

**Highlights**

* In this prospective clinical trial cohort, dynamic risk monitoring and reassessment using the HAS-BLED score, together with holistic App-based management significantly reduced major bleeding events, addressed modifiable bleeding risks and increased uptake of anticoagulants.
* In the ‘usual care’ arm of mAFA II trial, the use of anticoagulants overall decreased by 25% in atrial fibrillation patients with usual care, when comparing baseline to 12 months.

**ABSTRACT**

**BACKGROUND:** The mobile Atrial fibrillation application (mAFA-II) randomised trial reported that a holistic management strategy supported by mobile Health reduced atrial fibrillation-related adverse outcomes. The present study aimed to assess whether regular reassessment of bleeding risk using the HAS-BLED score would improve bleeding outcomes and anticoagulant (OAC) uptake.

**METHODS**: Bleeding risk (HAS-BLED score) was monitored prospectively using mAFA, and calculated as 30 days, Days 31-60, Days 61-180, and Days 181-365. Clinical events and OAC changes in relation to the dynamic monitoring were analysed.

**RESULTS:** We studied 1793 patients with atrial fibrillation (mean, standard deviation, age 64, 24 years, 32.5% female).

Comparing baseline and 12 months, the proportion of atrial fibrillation patients with HAS-BLED ≥3 decreased (11.8% vs. 8.5%, p=0.008), with changes in use of concomitant NSAIDs/antiplatelets, renal dysfunction, and labile international normalized ratio contributing to the decreased proportions of patients with HAS-BLED ≥3 (p<0.05).

Among 1077 (60%) patients who had four bleeding risk assessments, incident bleeding events decreased significantly from Days 1-30, to Days 181-365 (1.2% to 0.2%, respectively, p<0.001). Total OAC usage increased from 63.4% to 70.2% (ptrend<0.001). Compared to atrial fibrillation patients receiving usual care (n=1136), bleeding events were significantly lower in atrial fibrillaiton patients with dynamic monitoring of their bleeding risk (mAFA vs usual care, 2.1%, 4.3%, p=0.004). OAC use decreased significantly by 25% among atrial fibrillation patients receiving usual care from baseline to 12 months (p<0.001).

**CONCLUSION** Dynamic risk monitoring using the HAS-BLED score, together with holistic App-based management using mAFA II reduced bleeding events, addressed modifiable bleeding risks and increased uptake of OACs.

**KEY WORDS** atrial fibrillation, anticoagulants, mobile health, dynamic risk assessment, bleeding, HAS-BLED

**INTRODUCTION**

Oral anticoagulants (OAC) are highly effective for the prevention of stroke in patients with atrial fibrillation.1,2 However, bleeding events are a detrimental side effect of OAC use, even despite the reduced risk of intracranial haemorrahge with the use of non–vitamin K antagonist oral anticoagulants (NOACs) with major bleeding rates at 2% to 4% and any bleeding of 11%-18% per year.3 Some of these bleeding events are non-clinically relevant bleeding, and overall there is a positive net clinical benefit for using OACs for stroke prevention for the majority of atrial fibrillation patients.4 Nevertheless, the perceived fear of bleeding, among physicians and patients, results in lower OAC prescription and uptake and poor adherence with guidelines and dosing recommendations in patients with atrial fibrillation, especially in Asian populations.

At the practical level, the assessment of modifiable bleeding risk factors, anticoagulant adherence, checks for thromboembolic- and bleeding events have been proposed during follow-up of atrial fibrillation patients that are taking OAC.5 There are several risks factors for bleeding, and the more common and validated factors have been used to derive risk stratification scores to aid clinical decision-making.6,7 In various systematic reviews and evidence appraisals, the Hypertension, Abnormal renal and/or liver function, history of Stroke or thromboembolism, history of Bleeding or bleeding diathesis (e.g., severe anemia), Labile international normalized ratio (INR), Elderly (age >65 years), use of aspirin or nonsteroidal anti-inflammatory Drugs, and alcohol abuse, the HAS-BLED score has been found to have the best evidence for predicting bleeding risk, compared to other clinical risk scores for bleeding.8 Indeed, these reviews and evidence-appraisals are complemented by various other studies, including those from Asian cohorts9,10, that have shown that formal bleeding risk assessment tools are superior to a strategy that only uses modifiable bleeding risk factors for assessment of bleeding risk.9,11-13 The HAS-BLED score was introduced to draw attention to modifiable bleeding risk factors and to identify patients with atrial fibrillation at high-risk of bleeding on OAC for early review and closer follow-up.14

With greater awareness of bleeding (and stroke) risk over time, management of OAC therapy can be tailored, modifiable bleeding risks managed, and follow-up visits individually scheduled and as part of an integrated care management patient pathway. This integrated approach would require consideration of the patients' preferences,15 physicians' decision-making support,16 and good physician-patient communication. Given the increasing use of mobile Health (mHealth) technology, which can provide as an easy-to-use tool, thereby streamlining decision support, improved patient knowledge and drug adherence, as well as facilitating the implementation of educational programs for both patients and physicians/healthcare professionals.17-19

In the Mobile Health to improve optimization of integrated care in patients with atrial fibrillation (mobile Atrial Fibrillation Application, mAFA-II) prospective randomised trial, we reported that a holistic management strategy using App-based mobile Health technology support reduced atrial fibrillation-related adverse outcomes, compared to usual care.20 The objective of this ancillary analysis from the mAFA-II clinical trial was to assess whether regular reassessment of bleeding risk using the HAS-BLED score, over a 12-month period, would improve bleeding outcomes and OAC uptake, with the support of mHealth technology.

**METHODS**

The design and rationale of the mAFA II trial has been previously described19. In brief, the mAFA II trial was a two-arm, prospective, cluster-randomised controlled clinical trial that enrolled patients with atrial fibrillation, within randomized participating centres to either the mAFA intervention with integrated care, or to usual care. The study was registered on WHO International Clinical Trials Registry Platform (ICTRP) chictr.org.cn, with registration number ChiCTR-OOC-17014138 (<http://www.chictr.org.cn/showprojen.aspx?proj=24191>).

We included atrial fibrillation patients aged ≥18 years old who were enrolled from 40 centeres across China, which were randomly divided into mAFA intervention arm and usual care arm. Exclusion criteria included age <18 years old, those with mechanical prosthetic valve or moderate/severe mitral stenosis, those unable to provide informed consent, or those unable to be followed up for up to one year for any reason.

A user-friendly mAFApp was developed for smart phones based on the Android Operating System (Google Inc., MountainView, Calif) and Apple iOS (Cupertino, Calif) platforms for doctors (DmAFA) and patients (PmAFA). The mAFA platform provided clinical decision support tools (chronic heart failure, hypertension, age>75 years, diabetes, stroke, vascular disease, age 65-74 years, sex; CHA2DS2-VASc; hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly, drugs/alcohol concomitantly, HAS-BLED; and sex, age, medical history, treatment, tobacco use, race. SAMeTT2R2 scores) to facilitate guideline-based treatment recommendations, plus educational materials and patient involvement strategies with self-care protocols and structured follow-up, to support implementation of an atrial fibrillation integrated care approach based on the ABC pathway: **A, A**void stroke with **A**nticoagulation; **B, B**etter symptom management with patient-centred, symptom directed decisions on rate or rhythm control; **C, C**ardiovascular and other **C**omorbidity risk reduction, including lifestyle changes.19,21 The present ancillary study focused on the ‘**A**void stroke with **A**nticoagulants’ part, where there was dynamic stroke and bleeding risk monitoring, modification of modifiable bleeding risk factors and associated changes in antithrombotic drugs. The flow chart for the risk assessments is shown in **Figure 1**.

The ‘**A**void stroke with **A**nticoagulants’ part of the mAFA allowed for regular clinical bleeding and stroke risk (re)assessments which were automatically performed using the HAS-BLED score and CHA2DS2-VASc score, respectively. The time in therapeutic range (TTR) in patients taking warfarin was automatically calculated using the Rosendaal method.22 Labile international normalised ratio (INR) was defined as: 2 INR values that were higher than 5 or one INR value higher than 8 within the past six months; 2 INR values were less than 1.5 within the past 6 months; or if TTR was less than 65%.

Trends in bleeding risk profile over time and individual modifiable bleeding risk factors were flagged up for both doctors and patients. In warfarin users, adjustment of dosages based on TTR, liver and renal function was proposed for the doctors and patients by mAFA, complying with clinical guidelines. In NOAC users, guidance on optimizing label-adherent dosing was provided.

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, for example, pictures of the bleeding, medical materials or documentation. Doctors communicated in a timely manner with patients using mAFA platform (using the Chat function) to confirm the reported events and decide if it needed further diagnosis and/or treatment in hospital or whether it could be managed remotely through the mAFA. An educational and interactive program on atrial fibrillation, discussing atrial fibrillation-related comorbidities, OACs etc. were provided for patients on mAFA platform.18,19

*Dynamic risk monitoring*

Bleeding risk (HAS-BLED score) and stroke risk (CHA2DS2-VASc score) were monitored prospectively using the mAFA platform, and automatically calculated once the patient’s medical record (comorbidities, blood test, liver/renal function, and other lab test), or patient's reported event details were updated. The risk profiles were calculated during 4 periods: 30 days, Days 31-60, Days 61-180, and Days 181-365. Clinical events (including thromboembolism and bleeding events and OAC changes in relation to the dynamic monitoring and reassessments were analysed.

Data for this analysis were drawn from the mAFA intervention arm, from patients participating in the pilot mAFA trial (February 2018 to June 2019) and the mAFA-II trial (June 2019 to January,2020). 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.

*Statistical analysis*

Baseline characteristics for continuous variables are summarised as means (standard deviation, SD). Data with a non-normal distribution are presented as median (interquartile range, IQR) and analyzed by the Mann–Whitney U test. The comparison of discrete variables was done via the chi-square test. Clinical events (thromboembolic, bleeding events) and OAC changes in relation to the dynamic monitoring and reassessments (30 days, Days 31-60, Days 61-180, and Days 181-365) were analysed. Changes in OAC use over time were also recorded.

The changes in stroke and bleeding risk, and their-related clinical risk factors, were analysed among atrial fibrillation patients using the ‘**A**void stroke with **A**nticoagulants’ part of the mAFA.

To reflect dynamic bleeding risk monitoring on OAC management and bleeding events, we reviewed the patients with all four-periods of assessment (Days 1-30, 31-60, 61-180, and 181-365) for bleeding risk, rates of bleeding events and changes on OAC use. We also reviewed communications between doctors and patients as the average sum of patient’s reported events, instant messages from patients, and the doctor’s response messages, which were also stratified by the four-periods of assessment (30 days, Days 31-60, Days 61-180, and Days 181-365).

Further, OAC use at baseline and 12 months, together with bleeding events, defined as intracranial bleeding, major bleeding, and other extracranial bleeding, were compared between atrial fibrillation patients receiving either the mAFA or usual care for one year.

All statistical tests were done using the nominal 0·05 (two-sided) significance level. All statistical analyses were conducted using IBM SPSS Statistics, version 22.0 (SPSS Inc).

**RESULTS**

There were 1793 patients with atrial fibrillation (mean (SD) age 64 (24) years, female 583 (32.5%); 919 (51.3%) with paroxysmal atrial fibrillation), who used the ‘**A**void stroke with **A**nticoagulants’ part of the mAFA. Common comorbidities in these patients were hypertension, coronary artery disease, and obstructive sleep apnea syndrome (OSAS) (**Table 1**).

Comparing baseline and 12 months HAS-BLED scores, the proportion of atrial fibrillation patients with HAS-BLED ≥3 decreased significantly (11.8%, 8.5%, p=0.008, **Table 2**), associated with changes in the use of concomitant nonsteroidal anti-inflammatory drugs (NSAIDs)/antiplatelets, changes in renal dysfunction, and optimising the management of the labile international normalized ratio (INR), as some of modifiable bleeding risk factors, which contributed to the decreased proportions with HAS-BLED score ≥3 over time (p<0.05, **Table 2**). There were no significant changes in the mean CHA2DS2-VASc score over time (**Table 3**).

There was 15 thromboembolic events and 38 bleeding events (34 extracranial) for the 1793 patients with atrial fibrillation during a mean (SD) followup of 252 days (SD 181; range 16-695 days) (Online Table 1). Timely communication between patients and doctors on mAFA is summarised in online Table 2. The use of NOAC, warfarin, and any antiplatelet drug was 47.1%, 13.8%, and 15.5 % at baseline.

Among 1077 (60%) patients who had four bleeding risk assessments, incident bleeding events decreased significantly from 1.2% during the initial Day Days 1-30, to 0.2% at Day 181-365 (p<0.001). Total OAC usage increased from 63.4% to 70.2%, respectively, ie. especially in the early months: specifically, warfarin uses significantly increased from 17.0% during Days 1-30 to 18.4% at Days 181-365, while the use of NOACs also increased significantly from 46.4% to 51.8% over the same period (all p<0.001, **Table 4**).

Incident bleeding events decreased significantly from Days 1-30, to Days 181-365 among the 1077 patients with all four bleeding assessments (1.2% to 0.2%, respectively, p<0.001; **Table 4**, **Figure 2**).

Compared to atrial fibrillation patients receiving usual care (n=1136, online Table 3), bleeding events were significantly lower in atrial fibrillation patients with dynamic monitoring of their bleeding risk (mAFA vs usual care, 2.1%, 4.3%, p=0.004, **Figure 2**). OAC use decreased significantly by 25% among atrial fibrillation patients receiving usual care, when comparing baseline to 12 months (p<0.001, **Figure 2**).

**DISCUSSION**

The main findings of the present ancillary study to the mAFA trial programme were: i) the bleeding risks of atrial fibrillation patients are dynamic, and with regular re-assessments using the mAFA intervention and proactive management of modifiable bleeding risk factors, the proportion of patients with high-risk HAS-BLED scores decreased significantly over time, especially after 6 months; ii) concomitant drugs (NSAIDs/antiplatelets), renal dysfunction, and labile INR were the common modifiable factors influencing the bleeding risk profile; and iii) holistic App-based management using the mAFA II intervention were associated with a reduction in bleeding events, and increased uptake of OACs over time.

Atrial fibrillation -related risk varies with changes in the patient's clinical risk profile, especially with increasing age, incident risk factors and proactive medical management.23 In a nationwide cohort study, follow-up quantification of the HAS-BLED score demonstrated much better predictive ability for major bleeding compared to using the HAS-BLED score determined at baseline.11 Therefore, dynamic monitoring of risk, rather than ‘static’ one-off assessment at baseline, would be helpful to optimise atrial fibrillation management over time. Although the follow-up of patients was initially proposed at 1 month after inclusion, subsequent follow-up intervals would be based on individual characteristics and needs5. Indeed, the HAS-BLED score was introduced to draw attention to modifiable bleeding risk factors and to identify ‘high bleeding risk’ patients for their early review and closer follow-up after initial assessment/diagnosis, for example, initially at 4 weeks rather than 4 -6 months later. In this analysis, we found that the bleeding risk assessed by HAS-BLED reduced significantly after 6 months, with intervention on mitigating the modifiable risk factors for bleeding. Hence, it would be reasonable with the reassessment of bleeding risk every 6 months, after an initial 6-month of more intensive monitoring in those at high bleeding risk.

In our anticoagulated atrial fibrillation patients, the concomitant use of NSAIDs/antiplatelets, renal dysfunction, and labile INR were the common modifiable factors which impacted on bleeding risk, consistent with prior studies.24 Adjustment of OACs dosage based on TTR (if on warfarin) and renal function (if on NOAC) by mAFA, with adherence to the prescribing label and dosing guidelines, was associated with a reduction in the bleeding risk in our study. Indeed, the ability to correct modifiable bleeding risk factors, followed by regular reassessment of risk profiles of atrial fibrillation patients, facilitated good management of OAC therapy.

In this study, extracranial bleeds accounted for 89% of the recorded bleeds, most minor bleeding, commonly gum bleeds, bloody stool, skin ecchymoses/subcutaneous hematoma, nose bleeds, etc (Online Table 1). In real-world clinical practice, these nuisance bleeds or minor bleeding events are a frequent cause of discontinuation of OACs. With more patients being treated with OACs, some OAC-related bleeding events are inevitable. In our study, the structured questions and supporting files developed for the mAFA platform helped doctors to understand the individual clinical situation(s) of reported bleeding events. Further timely communication between doctors and patients on mAFA (ie. patient’s reported events, instant messages, and the doctor’s response messages, see online Table 2), permitted doctors to become familiar with the detailed clinical information, helping decision-making on dosage adjustment, correction of the modifiable bleeding risk factors, etc. and alleviating patient concerns about bleeding and coming to an agreed decision about continuation/discontinuation of OAC.

Indeed, we found that bleeding events reduced from 1.2% at Days 1-30, to 0.2% at Days 181-365, while the uptake of OACs increased by 6.8%. A high HAS-BLED score is not an excuse to withhold OAC, and more contemporary studies have shown that physicians are heeding this recommendation.25 In the present analysis, OAC use actually increased over time, with the use of HAS-BLED score to aid risk assessments and decision-making. Good adherence with OAC has been associated with better clinical outcomes without increasing bleeding risk,26,27 while poor adherence at 12-month follow-up has been associated with a significantly higher risk of thromboembolic events.28

Nonetheless, it is challenging to maintain good treatment adherence with OAC in routine clinical practice. Indeed, OACs use decreased by 25% in the first year among atrial fibrillation patients receiving usual care in the present study. In a UK primary care study involving in 36 652 individuals with incident AF, the adherence was 55.2% for OAC, being 51.2% for warfarin, and 64.8% for NOAC, while one-year persistence was 65.9% for OAC, 63.4% for warfarin, and 70.8% for NOAC.29 Multiple-level factors, patient preferences, OAC-related factors, and systematic support are the practical issues which influence adherence and persistence to OAC. Furthermore, the educational program provided for patients on mAFA19,20 may have helped to improve knowledge on AF and anticoagulation, which may have improved OAC adherence.18,30

*Limitations*

Data from the mAFA intervention arm of mAFA II trial were utilized to investigate dynamic risk reassessment, OACs usage and clinical events. The dynamic bleeding reassessment, together with its impact on OACs use, bleeding events, were analysed in patients with mAFA, given that the patterns of dynamic risk changes could only be properly documented from patients using the mAFA.. The improved OAC use might reflect that many users got used to using the mAFA. Also, the mAFA functions were gradually improved with software updates, and the added educational programs provided by mAFA over time might have altered preferences of OACs being prescribed by physicians and chosen by patients.

**CONCLUSIONS**

In this prospective clinical trial cohort, dynamic risk monitoring and reassessment of bleeding risk using the HAS-BLED score, together with holistic App-based management using mAFA II was associated with a reduction in bleeding events, addressing modifiable bleeding risks and increased uptake of OACs.

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**Figure legends**

**Figure 1. Flow chart of included patients**

The bleeding and stroke risk monitored dynamically by mAFA. mAFA: mobile Atrial Fibrillation Application. The CHA2DS2-VASc and HAS-BLED scores were automatically calculated once the patient’s medical record (comorbidities, lab test, etc), or patient's reported event were updated. To represent the dynamic risk monitoring, the scores were broken down into 4 periods: 1- 30 days, Days 31-60, Days 61-180, and Days 181-365. In every time-window period, the value most closely associated to the cut-off timepoint (e.g. 30 days, 60 days, 180 days, and 365 days) was collected.

**Figure 2 Changes in OAC use and the number of bleeding events over a 12-month period among in patients receiving the mAFA intervention or usual care.**

The bleeding events included intracranial bleeding, major bleeding, and other extracranial bleeding. mAFA: mobile Atrial Fibrillation Application. OACs: anticoagulants. NOAC: non-vitamin K antagonist oral anticoagulants.