European Journal of Internal Medicine 107 (2023) 46–51

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

# Mobile health-technology integrated care in atrial fibrillation patients with heart failure: A report from the mAFA-II randomized clinical trial

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ARTICLE INFO

*Keywords:*
Atrial fibrillation
Integrated care
Heart failure
Outcomes

ABSTRACT

*Background:* To assess the effect of mobile health (mHealth) technology-implemented 'Atrial fibrillation Better Care' (ABC) pathway-approach (mAFA intervention) in AF patients with Heart Failure (HF).
*Methods:* From the Mobile Health Technology for Improved Screening and Optimized Integrated Care in AF (mAFA-II) cluster randomized trial, we evaluated the effect of mAFA intervention on the risk of major outcomes in patients with HF using Inverse Probability of Treatment Weighting. Primary outcome was the composite outcome of stroke/thromboembolism, all-cause death, and rehospitalization. The effect of mAFA and the interaction with HF at baseline was assessed through Cox-regressions.
*Results:* Among the 3,324 patients originally enrolled in the trial, 714 (21.5%; mean age: 72.7±13.1 years; 39.9% females) had HF. The effect of mAFA intervention on the primary outcome was consistent in patients with and without HF (Hazard Ratio, (HR): 0.59, 95% Confidence Interval (CI): 0.29-1.22 vs. HR: 0.40, 95%CI: 0.21-0.76, p for interaction=0.438); similar findings were found for rehospitalisations and bleeding events. A trend towards lower efficacy of mAFA in HF patients was observed for all-cause death, while the risk of the composite outcome of 'recurrent AF, HF and acute coronary syndrome' was higher among AF-HF patients allocated to mAFA (p for interaction: <0.001).
*Conclusion:* A mHealth-technology implemented ABC pathway provides consistent effects on the risks of primary outcome, rehospitalisation and bleeding, in AF patients both with and without HF. However, AF-HF patients may need tailored approaches to improve their overall prognosis, specifically to reduce the risk of recurrent AF, HF and acute coronary syndrome.

## 1. Introduction

Heart Failure (HF) and Atrial Fibrillation (AF) are two of the most common cardiovascular diseases worldwide, both entailing an increased morbidity and mortality [1,2] Sharing common risk factors and a robust pathophysiological relationship, these two conditions commonly occur together [3], imposing a significant challenge to treating physicians, particularly in the management of antithrombotic treatment and rhythm and rate control strategy [4].

Recent guidelines on HF [5] and AF [6,7] has advocated for the implementation of integrated and holistic care programmes, recognizing the increased clinical complexity that AF and HF patients often

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https://doi.org/10.1016/j.ejim.2022.11.002
Received 19 July 2022; Received in revised form 28 October 2022; Accepted 1 November 2022
Available online 5 November 2022

experience, and reflecting a paradigm shift towards a more patient-centered approach to the management of these diseases [8,9].

The 'Atrial fibrillation Better Care' (ABC) pathway has been proposed to streamline the implementation of holistic or integrated care management in AF patients [10]. The ABC pathway consists of three pillars: A, anticoagulation/avoiding stroke; B, better symptom control, through patient-centred symptom directed decisions on rate or rhythm control; and C, cardiovascular and comorbidity optimization.

The Mobile Health Technology for Improved Screening and Optimized Integrated Care in AF (mAFA-II) prospective cluster randomized trial investigated whether a mobile health (mHealth) implemented ABC pathway (mAFA intervention) was effective in reducing risk of adverse outcome among AF patients. In the primary analysis, ABC pathway significantly reduced rates of composite outcome of ischaemic stroke/systemic thromboembolism, death, and hospitalization, compared to usual care [11]. However, whether these results can be applied to AF patients with HF is still unclear.

In this post-hoc ancillary analysis of the mAFA-II trial, we aim at evaluating the effect of mAFA intervention in patients with versus without HF.

## 2. Methods

Complete details on the design and results of the mAFA-II trial can be found elsewhere [11–13]. Briefly, adult patients with AF ($\geq$ 18 years) were enrolled and randomized in a 1:1 ratio to the mAFA intervention or usual care clusters, across 40 participating centres in China, between June 1$^{st}$, 2018 and August 16$^{th}$, 2019. Patients with mechanical prosthetic valve, those with moderate to severe mitral stenosis, and those unable to be followed up for 1 year for any reason or to provide informed consent were excluded. Ultimately, 1646 AF patients received the mAFA intervention, and 1678 were allocated to usual care. The study was conducted in accordance with the Declaration of Helsinki and the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline, and was approved by the Central Medical Ethic Committee of Chinese PLA General Hospital and by local institutional review boards; all patients gave written informed consent.

Consistent with the trial's primary analysis, the ABC pathway implemented in the mAFA intervention was defined as follows. 'A' criterion: administration of anticoagulant according to regular and dynamic assessment of thromboembolic and bleeding risk, with adjustment of doses according to renal and liver function reassessment. 'B' criterion: regular assessment of patient-reported symptoms (evaluated according to the European Heart Rhythm Association classification), and symptoms-directed management (including antiarrhythmics and rhythm control therapies). 'C' criterion: optimization and management of concurrent comorbidities (e.g. blood pressure monitoring and consequent hypertension management). Patients allocated to "usual care" were managed according to local practices.

In this post-hoc analysis, we analyzed the effect of the mAFA intervention according to the presence of HF at baseline. HF at baseline was defined as recent decompensated HF (irrespective of LVEF, thus including HF with reduced or preserved LVEF), a prior history of HF, or the presence of moderate-severe left ventricular systolic impairment on cardiac imaging.

### 2.1. Outcomes and follow-up

Follow-up for the occurrence of clinical events at 6 and 12 months after the inclusion was performed for all patients. The primary endpoint was the composite outcome of ischaemic stroke or systemic thromboembolism, all-cause death and rehospitalization. We also evaluated the interaction between HF at baseline and effect of mAFA on secondary exploratory endpoints, including thromboembolism (including ischemic stroke and other systemic thromboembolism), bleeding events (intracranial and extracranial), the composite of cardiovascular outcomes (recurrent AF, heart failure, acute coronary syndrome), all-cause death and rehospitalization.

### 2.2. Statistical analysis

Continuous variables were reported as mean and standard deviation (SD) or median and interquartile range [IQR] for normally and non-normally variables, respectively; frequencies and percentages were reported for categorical variables.

To achieve balance of baseline characteristics among patients allocated to mAFA or usual care in patients with and without HF at baseline, we first calculated a subgroup balancing propensity score (PS) [14] of being allocated to mAFA arm using a multivariable logistic regression model that included 26 variables (age, sex, smoking status, hypertension, coronary artery disease (CAD), prior thromboembolic events, diabetes, peripheral artery disease (PAD), renal dysfunction, pulmonary hypertension, liver dysfunction, prior intracerebral haemorrhage and other bleeding, anaemia, hyperthyroidism, dilated and hypertrophic cardiomyopathy, smoking status, type of AF, previous AF treatment, $CHA_2DS_2$-VASc and HAS-BLED scores). We therefore performed an inverse probability of treatment weighting (IPTW) according to the calculated PS. We assessed balance of baseline characteristics after IPTW using standardized mean differences (SMD) for continuous variables and raw differences in proportion for binary variables; differences <0.10 indicated adequate balance. Cox regression with IPTW and robust estimation of SE were performed to evaluate the interaction between HF at baseline and effect of mAFA intervention on outcomes.

A 2-sided p-value <0.05 was considered statistically significant. All statistical analyses were conducted using R 4.2.0 (R Foundation for Statistical Computing 2020, Vienna, Austria).

## 3. Results

3,324 patients were originally enrolled in the trial between June 1, 2018, and August 16, 2019. Of these, 714 patients had HF (mean age: 72.7 $\pm$ 13.1 years, 39.9% females) (Fig. 1), with 360 (50.4%) patients allocated to the mAFA intervention, with a median [IQR] follow-up of 281 [160-395] days, and 354 (49.6%) allocated to the usual care group, with a median [IQR] follow-up of 284 [160-395] days. Baseline characteristics among patients with and without HF at baseline are reported in Table S1 in Supplementary Materials, while characteristics according to mAFA allocation and HF at baseline are reported in Table 1.

Patients with HF at baseline were older and with high prevalence of all the comorbidities investigated; they were also more likely to have received a pacemaker implant, while less likely to have underwent AF ablation. Both $CHA_2DS_2$-VASc and HAS-BLED scores were higher in HF patients (4.0 $\pm$ 1.5 vs. 2.4 $\pm$ 1.4, p<0.001 and 1.8 $\pm$1.2 vs. 1.4 $\pm$ 1.0, p<0.001 respectively).

Among patients with HF at baseline, those allocated to mAFA intervention were more likely females and with an overall higher burden of comorbidities. Hypertension (p=0.001), CAD (p=0.015), diabetes (p<0.001) and history of ischemic stroke (p<0.001) were significantly more prevalent among those allocated to mAFA; consistently, $CHA_2DS_2$-VASc and HAS-BLED scores were also higher in these patients (Table 1). Patients with HF allocated to mAFA were also more likely to be prescribed NOACs (p<0.001), beta-blockers (p<0.001), ACEi/ARB (p=0.003), calcium channel blockers (p=0.006), statins (p<0.001) and digoxin (p=0.023), while being less likely treated with aspirin (p=0.034) and ticagrelor (p=0.021) (Table S2 in Supplementary Materials).

Among patients without HF, those allocated to mAFA were younger (65.2 $\pm$ 14.8 vs. 69.5 $\pm$ 12.6 years, p<0.001) and with statistically significant lower prevalence of hypertension, CAD, diabetes, history of ischemic stroke, intracerebral hemorrhage and renal dysfunction. Consistently, those allocated to mAFA were more treated with NOACs, and less likely receiving aspirin and clopidogrel, as well as most of the

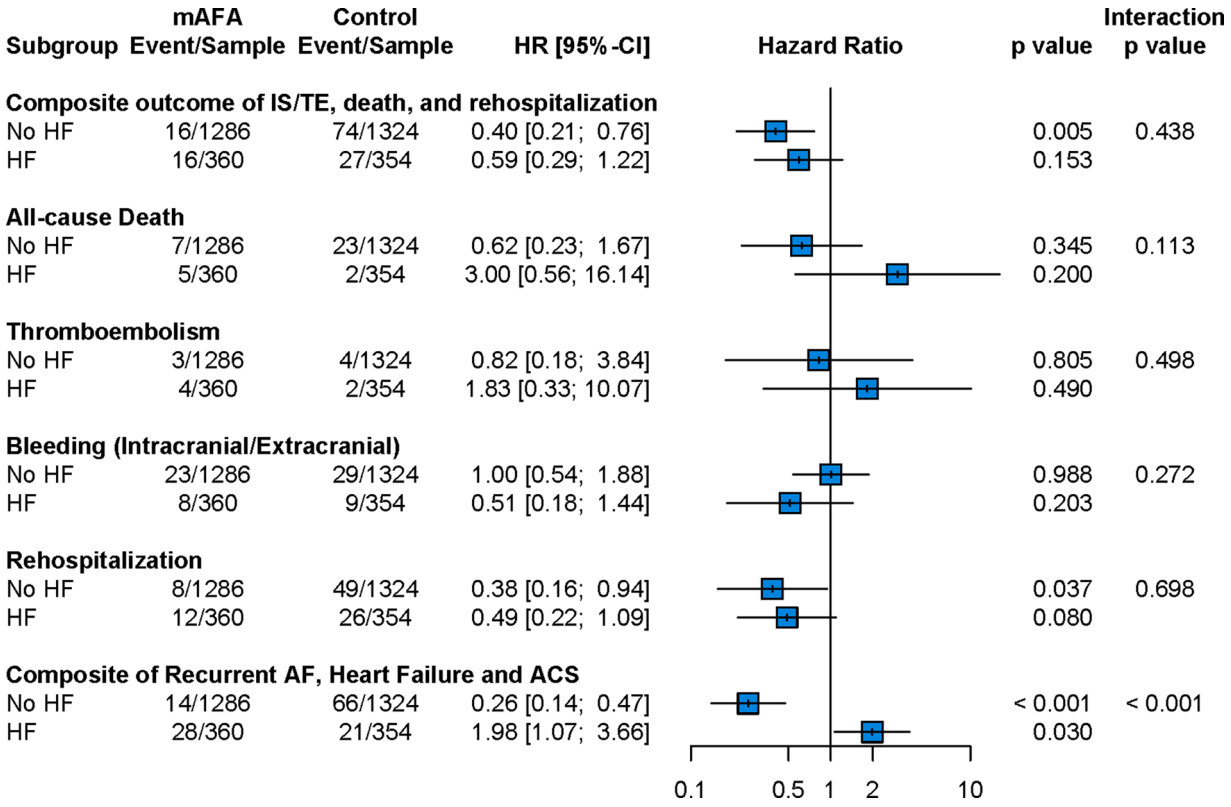


**Fig. 1.** Risk of major outcomes according to mAFA intervention in patients with vs. without history of HF. Legend: CI= Confidence Interval; HR= Hazard Ratio; HF= Heart Failure.

other drugs recorded (Table S2 in Supplementary Materials).

### *3.1. Major outcomes according to mAFA intervention*

We performed IPTW based on subgroup balancing PS, to achieve balance of baseline characteristics and risk factors. The evaluation of balance in the baseline characteristics before and after IPTW is shown in Tables S3 and S4 in Supplementary Materials for patients with and without HF at baseline, respectively. Globally, IPTW provided good balance of all baseline characteristics between mAFA intervention and usual care group in both patients with and without HF at baseline.

Results of the IPTW-Cox regression analyses on the risk of primary and secondary outcomes according to mAFA allocation and HF at baseline are reported in Fig. 1 and Table 2. In patients without HF at baseline, mAFA intervention was associated with beneficial risk reduction of the primary outcome of ischemic stroke/thromboembolism, all-cause death and rehospitalizations (HR: 0.40, 95%CI: 0.21-0.76); a similar, non-statistically significant trend was observed in patients with HF (HR: 0.59, 95%CI: 0.29-1.22), but no significant statistical interaction was observed between the two groups ($p_{int}$=0.438).

Among the exploratory secondary outcomes, no statistically significant interaction for the effect of mAFA intervention was observed in patients with and without HF for the risk of thromboembolism ($p_{int}$=0.498), bleeding events ($p_{int}$=0.272) and rehospitalizations ($p_{int}$=0.698). The effect of mAFA intervention on the risk of all-cause death was also not statistically significant in patients with HF (HR: 3.00, 95%CI: 0.56-16.14), althout without statistically significant interaction ($p_{int}$=0.113). Finally, mAFA intervention was associated with a significant reduction of the risk of composite outcome of 'recurrent AF, HF and ACS' in patients *without* HF at baseline (HR: 0.26, 95% CI: 0.14-0.48), but a higher risk was found in HF-patients (HR: 1.99, 95%CI: 1.08-3.69), with a significant interaction between groups ($p<0.001$) (Fig. 1, Table 2).

## 4. Discussion

In this post-hoc analysis of the mAFA-II trial, our principal results are as follows: (i) patients with AF-HF had a higher burden of comorbidities and risk factors than AF patients without HF, and are at increased risk of major outcomes; (ii) patients with AF and HF allocated to the mAFA intervention were more likely to receive optimized medical treatment, with higher prescription of NOACs, ACEi/ARBs, CCBs and statins; (iii) the effect of mHealth technology-implemented ABC pathway on the primary outcome of ischemic stroke/thromboembolism, all-cause death and rehospitalisations was consistent in AF patients with vs. without HF; similar findings were observed for the risk of rehospitalization alone, and other exploratory secondary outcomes; and (iv) the risk of the composite outcome of non-fatal cardiovascular events ('recurrent AF, HF and acute coronary syndrome') was increased among HF patients allocated to mAFA intervention.

In recent years, much interest on the relationship between AF and HF has emerged, due to their "dual epidemic" that has led to increasing prevalence of both diseases, [15] with a synergistic and bidirectional detrimental effect on prognosis [16,17]. Although most studies aimed at investigating the efficacy of rate or rhythm control strategies in these patients [18,19], the greater clinical complexity of these subjects (many of whom also suffer from other comorbidities) requires an integrated and multidisciplinary approach to improve their outcomes [27].

In this context, the ABC pathway has been proposed to streamline a holistic and integrated model of care in a simple and effective manner, focused not only on anticoagulation, but also on symptom control and comorbidities management optimization [10]. These aspects are particularly important among HF patients, that often require multifaceted treatment schemes due to their underlying condition, which are frequently suboptimally implemented [20,21]; however, the effect of ABC pathway in patients with both AF and HF has not been previously investigated as yet.

**Table 1**
Demographic Characteristics.

| | No HF at baseline | | | HF at baseline | | |
|---|---|---|---|---|---|---|
| Variables, n (%) | mAFA (n= 1286) | Control (n= 1324) | p | mAFA (n= 360) | Control (n= 354) | p |
| Age, mean ± SD | 65.2 ± 14.8 | 69.5 ± 12.6 | <0.001 | 72.8 ± 12.5 | 72.6 ± 13.8 | 0.878 |
| Female gender (%) | 463 (36.0) | 514 (38.8) | 0.148 | 162 (45.0) | 123 (34.7) | 0.007 |
| Medical History | | | | | | |
| Smokers | 125 (9.7) | 133 (10.0) | 0.832 | 34 (9.4) | 35 (9.9) | 0.941 |
| Hypertension | 661 (51.4) | 764 (57.7) | 0.001 | 247 (68.6) | 198 (55.9) | 0.001 |
| CAD | 389 (30.2) | 514 (38.8) | <0.001 | 246 (68.3) | 210 (59.3) | 0.015 |
| Diabetes | 229 (17.8) | 283 (21.4) | 0.025 | 152 (42.2) | 83 (23.4) | <0.001 |
| Prior Ischemic Stroke | 75 (5.8) | 191 (14.4) | <0.001 | 116 (32.2) | 41 (11.6) | <0.001 |
| PAD | 115 (8.9) | 118 (8.9) | 1.000 | 57 (15.8) | 54 (15.3) | 0.912 |
| Renal dysfunction | 61 (4.7) | 96 (7.3) | 0.009 | 77 (21.4) | 76 (21.5) | 1.000 |
| Pulmonary Hypertension | 31 (2.4) | 34 (2.6) | 0.895 | 56 (15.6) | 49 (13.8) | 0.589 |
| Liver Dysfunction | 24 (1.9) | 26 (2.0) | 0.969 | 31 (8.6) | 22 (6.2) | 0.281 |
| Prior Brain Bleeding | 8 (0.6) | 22 (1.7) | 0.021 | 16 (4.4) | 16 (4.5) | 1.000 |
| Prior Other Bleeding | 31 (2.4) | 44 (3.3) | 0.201 | 23 (6.4) | 23 (6.5) | 1.000 |
| Hyperthyroidism | 21 (1.6) | 31 (2.3) | 0.248 | 16 (4.4) | 20 (5.6) | 0.572 |
| Dilated Cardiomyopathy | 13 (1.0) | 24 (1.8) | 0.117 | 31 (8.6) | 37 (10.5) | 0.477 |
| Hypertrophic Cardiomyopathy | 16 (1.2) | 13 (1.0) | 0.651 | 9 (2.5) | 16 (4.5) | 0.206 |
| Type of AF | | | <0.001 | | | 0.023 |
| Unknown | 252 (19.8) | 98 (7.4) | | 29 (8.1) | 15 (4.2) | |
| New-Onset AF | 155 (12.2) | 201 (15.2) | | 40 (11.2) | 31 (8.8) | |
| Paroxysmal AF | 562 (44.1) | 554 (41.9) | | 111 (31.0) | 106 (29.9) | |
| Persistent AF | 253 (19.8) | 326 (24.6) | | 127 (35.5) | 122 (34.5) | |
| Long-Standing AF | 36 (2.8) | 63 (4.8) | | 20 (5.6) | 38 (10.7) | |
| Permanent AF | 17 (1.3) | 81 (6.1) | | 31 (8.7) | 42 (11.9) | |
| Prior AF Treatment | | | | | | |
| Pharmacological Cardioversion | 173 (13.5) | 117 (8.8) | <0.001 | 40 (11.1) | 38 (10.7) | 0.967 |
| Electrical Cardioversion | 24 (1.9) | 22 (1.7) | 0.804 | 6 (1.7) | 13 (3.7) | 0.152 |
| AF Ablation | 162 (12.6) | 144 (10.9) | 0.192 | 21 (5.8) | 29 (8.2) | 0.277 |
| Pacemaker | 45 (3.5) | 54 (4.1) | 0.502 | 31 (8.6) | 31 (8.8) | 1.000 |
| LAAO | 26 (2.0) | 22 (1.7) | 0.590 | 7 (1.9) | 8 (2.3) | 0.974 |
| Scores | | | | | | |
| CHA2DS2-VASc, mean ± SD | 2.4 ± 1.4 | 2.5 ± 1.5 | 0.008 | 4.4 ± 1.5 | 3.6 ± 1.4 | <0.001 |
| HAS-BLED, mean ± SD | 1.2 ± 1.0 | 1.5 ± 1.0 | <0.001 | 2.0 ± 1.3 | 1.6 ± 1.1 | <0.001 |

Legend: AF= Atrial Fibrillation CAD= Coronary Artery Disease; CHF= Congestive Heart Failure; CKD= Chronic Kidney Disease; IQR= Interquartile Range; LAAO= Left Atrial Appendage Occlusion; PAD= Peripheral Artery Disease; SD= Standard Deviation; TE= Thromboembolic Events.

**Table 2**
Clinical outcomes in mAFA and Control groups according to HF at baseline.

| | Number of Events | | IR [95%CI] per 100 persons-year | | | | |
|---|---|---|---|---|---|---|---|
| Outcome | mAFA | Control | mAFA | Control | HR (95%CI)* | p | Interaction p |
| Composite Outcome of IS/TE, Death and Rehospitalization | | | | | | | |
| No HF at Baseline | 16/1286 | 74/1324 | 1.8 [1.0-2.9] | 7.2 [5.6-9.0] | 0.40 [0.21-0.76] | 0.005 | 0.438 |
| HF at Baseline | 16/360 | 27/354 | 6.3 [3.6-10.2] | 11.0 [7.2-16.0] | 0.59 [0.29-1.22] | 0.153 | |
| All-cause Death | | | | | | | |
| No HF at Baseline | 7/1286 | 23/1324 | 0.8 [0.3-1.6] | 2.2 [1.4-3.2] | 0.62 [0.23-1.67] | 0.345 | 0.113 |
| HF at Baseline | 5/360 | 2/354 | 1.9 [0.6-4.5] | 0.8 [0.1-2.8] | 3.00 [0.56-16.14] | 0.201 | |
| Thromboembolism (IS or Systemic Embolism) | | | | | | | |
| No HF at Baseline | 3/1286 | 4/1324 | 0.3 [0.1-1.0] | 0.4 [0.1-1.0] | 0.82 [0.18-3.84] | 0.805 | 0.498 |
| HF at Baseline | 4/360 | 2/354 | 1.5 [0.4-4.0] | 0.8 [0.1-2.8] | 1.83 [0.33-10.07] | 0.490 | |
| Bleeding | | | | | | | |
| No HF at Baseline | 23/1286 | 29/1324 | 2.5 [1.6-3.8] | 2.7 [1.8-3.9] | 1.00 [0.54-1.88] | 0.988 | 0.272 |
| HF at Baseline | 8/360 | 9/354 | 3.1 [1.3-6.1] | 3.1 [1.3-6.2] | 0.51 [0.18-1.44] | 0.203 | |
| Rehospitalisation | | | | | | | |
| No HF at Baseline | 8/1286 | 49/1324 | 0.9 [0.4-1.7] | 4.7 [3.5-6.2] | 0.38 [0.16-0.94] | 0.037 | 0.698 |
| HF at Baseline | 12/360 | 26/354 | 4.7 [2.4-8.2] | 10.6 [6.9-15.5] | 0.49 [0.22-1.09] | 0.080 | |
| Composite of Recurrent AF, HF and Acute Coronary Syndrome | | | | | | | |
| No HF at Baseline | 14/1286 | 66/1324 | 1.5 [0.8-2.6] | 6.3 [4.9-8.0] | 0.26 [0.14-0.47] | <0.001 | <0.001 |
| HF at Baseline | 28/360 | 21/354 | 11.2 [7.5-16.2] | 8.4 [5.2-12.8] | 1.98 [1.07-3.66] | 0.030 | |

Legend: *HR [95%CI] after IPTW-Cox regression analysis. AF= Atrial Fibrillation; HF= Heart Failure; HR= Hazard Ratio; IR= Incidence Rate.

Our study provides the first analysis on the effect of a mHealth-technology implemented ABC pathway in patients with AF and HF. Our results confirms that AF-HF patients had a significant higher risk of major adverse outcomes, and suggests that patients with AF and HF allocated to the mAFA intervention were more likely to receive an optimized treatment bundle, as reflected by the higher prescription of NOACs, ACEi/ARBs, CCBs and statins, and lower administration of aspirin/ticagrelor. Although we do not have information on the type of CAD and the timing of potential coronary interventions, the lower rate of antiplatelet prescription in the mAFA group (despite the higher prevalence of CAD and the overall cardiovascular risk) appears in line with current guidance, which recommends OAC monotherapy for the long-term treatment of AF patients with history of CAD (providing no recent coronary intervention or ischemic event has occurred) [6]. These findings show how the systematic implementation of an integrated care approach can improve the quality of care and adherence to treatment recommendations. As our study was conducted in 40 centres in China, some geographical differences in the management of HF may have

influenced our findings, as differences in healthcare systems and reimbursement methods in China compared to data from Wester countries. Our results on the prescription of HF-related drugs are consistent with a previous report that showed similar uptake of these drugs. [22] This is also consistent with the high rate of digoxin prescription observed among HF patients allocated to mAFA, perhaps different from European/North-American based recommendations for the treatment of HF patients [23,5]. Overall, these issues can explain the lower than expected prescription of several HF-specific drugs in our patients.

Our analysis also shows that mAFA intervention has a consistent effect in both HF and non-HF patients on the risk of the primary composite outcome of stroke or thromboembolism, death and rehospitalization, as well as rehospitalizations only and other secondary outcomes. These findings are particularly important, also considering the overall clinical complexity of HF patients, and the higher risk of major adverse events that these patients have, irrespective of the concurrent presence of AF. The results of this analysis are consistent with those observed in the primary trial [11], as well as in a post-hoc analysis focused on multimorbidity patients [24] and in a sensitivity analysis of a recent meta-analysis which showed how the effect of ABC pathway is also conserved in patients at high-risk of major events (as reflected by a high $CHA_2DS_2$-VASc score). [25] Given the increased risk of adverse outcomes imposed by HF among AF patients [26,27], our findings show the ABC pathway as a suitable approach to tackle the detrimental effects in these AF subjects with HF.

On the other side, the observation of an increased risk of the secondary composite outcome (non-fatal 'recurrent AF, HF and acute coronary syndrome'), as well as the observation of no effect on the risk of all-cause death in patients with HF allocated to mAFA deserves further attention. These results may suggest that the clinical complexity and overall burden of risk factors (which were higher in patients allocated to mAFA compared to usual care) cannot be completely reverted in AF-HF patients, and that a higher risk of major events still remains in these patients. Furthermore, the management of HF requires a complex bundle of care [5], and that the ABC pathway was not specifically designed for the treatment of HF patients. Indeed, optimal management of HF is only one part of the much broader, holistic and integrated approach streamlined by the ABC pathway, which has been specifically designed for AF patients, and is not focused on HF alone. It is therefore expected that these patients require further efforts to improve their overall prognosis, especially to tackle their overall cardiovascular risk and reduce the risk of recurrent AF, HF and ACS. This is also in accordance with the higher complexity observed in HF patients allocated to mAFA, which may predispose to an increase in the risk of cardiovascular outcomes.

Our findings have several clinical implications. The observation of an increased risk of adverse events in AF-HF patients confirms that these patients require specific attention and awareness, and that adequate policies should be implemented to tackle their risk of major outcomes. Most importantly, we show how the implementation of a structured and integrated bundle of care (as encompassed by the mHealth technology implemented ABC pathway) can improve treatment patterns and is also effective in mitigating the risk of major outcomes, although some exploratory secondary outcomes pointed towards reduced or no effect in HF patients. Taken together, these findings still support the use of ABC pathway in patients with AF and HF, although a more specific and integrated approach for the treatment of HF patients may be required to further improve outcomes and to provide a more dramatic reduction of the associated risks of AF and concomitant HF.

### 4.1. Strengths and limitations

This is the first report on the effect of a mHealth-implemented ABC pathway in AF patients with HF; also, the results on the primary composite outcome were consistent with the main analysis of the trial. Nevertheless, our study has several limitations. First, we lack information on detailed phenotyping of HF at baseline, including left ventricular ejection fraction, and we were also not able to analyse data according to NYHA class and time from HF diagnosis. We are therefore not able to stratify results according to the type of HF (e.g. reduced vs. preserved ejection fraction), and further studies, adequately powered and specifically designed, will be required to explore potential differences. Moreover, proportion of patients prescribed with ACEi/ARB and diuretics was lower than expected in our study. This may be due to local and regional differences in the management of HF patients from the 40 centres nationwide in China, which may have influenced these results. Hence, caution should be used when interpreting these results to other geographical contexts. Furthermore, given the design of the study, we collected data only on the most commonly prescribed drugs in AF patients; therefore, we did not have detailed data on the use of mineralcorticoid receptor antagonist, or the sequence of initiation of HF-related drugs, and we were unable to evaluate these in our analysis. Second, given the post-hoc design of this analysis, this study lacks statistical power for some of the analyses, and particularly for the secondary outcomes. These results should be therefore interpreted with caution and be regarded as hypothesis generating. Third, given the cluster randomized design, there would be a significant imbalance in the distribution of some baseline characteristics among those allocated to the mAFA intervention and the usual care when stratifying patients according to the diagnosis of HF at baseline. Although we have aimed at balancing difference in baseline characteristics through subgroup-balancing PS and IPTW, we cannot exclude the contribution of unaccounted confounder in the results observed. Finally, as the mAFA-II trial was conducted in 40 centres in China, further studies are required to evaluate whether these findings can be confirmed and applicable in other geographical locations, including Europe and North America; therefore, these results should be interpreted and applied to other geographical contexts with caution.

## 5. Conclusions

In this post-hoc analysis of the mAFA-II trial, a mHealth-technology implemented ABC pathway provides consistent effects on the risks of the primary outcome, as well as rehospitalisation and bleeding, in AF patients both with and without HF. However, AF-HF patients may need specific and tailored approaches to improve their overall prognosis, specifically to reduce the risk of recurrent AF, HF and acute coronary syndrome.

## Declaration of Competing Interest

GYHL has been consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are directly received personally. All the disclosures happened outside the submitted work. All other authors have nothing to declare.

*Funding*

This research was funded by the National Natural Science Foundation of China (82170309). This study was an investigator-initiated project, with limited funding by independent research and educational grants.

*Acknowledgements*

We are grateful of all participants into the mAFA programme for their contribution.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.11.002.

## References


[1] Savarese G, Lund LH. Global Public Health Burden of Heart Failure. Card Fail Rev 2017;03:7. https://doi.org/10.15420/cfr.2016:25:2.

[2] Dai H, Zhang Q, Much AA, Maor E, Segev A, Beinart R, et al. Global, regional, and national prevalence, incidence, mortality, and risk factors for atrial fibrillation, 1990-2017: results from the Global Burden of Disease Study 2017. Eur Heart J Qual Care Clin Outcomes 2021;7:574–82. https://doi.org/10.1093/ehjqcco/qcaa061.

[3] Santhanakrishnan R, Wang N, Larson MG, Magnani JW, McManus DD, Lubitz SA, et al. Atrial fibrillation begets heart failure and vice versa: temporal associations and differences in preserved versus reduced ejection fraction. Circulation 2016; 133:484–92. https://doi.org/10.1161/CIRCULATIONAHA.115.018614.

[4] Mulder BA, Rienstra M, van Gelder IC, Blaauw Y. Update on management of atrial fibrillation in heart failure: a focus on ablation. Heart 2022;108:422–8. https://doi.org/10.1136/heartjnl-2020-318081.

[5] McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42:3599–726. https://doi.org/10.1093/eurheartj/ehab368.

[6] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373–498. https://doi.org/10.1093/eurheartj/ehaa612.

[7] Chao TF, Joung B, Takahashi Y, Lim TW, Choi EK, Chan YH, et al. 2021 Focused update consensus guidelines of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation: executive summary. Thromb Haemost 2022;122. https://doi.org/10.1055/s-0041-1739411.

[8] Forsyth F, Blakeman T, Burt J, Chew-Graham CA, Hossain M, Mant J, et al. Cumulative complexity: a qualitative analysis of patients' experiences of living with heart failure with preserved ejection fraction. Eur J Cardiovascular Nurs 2022;00:1–8. https://doi.org/10.1093/EURJCN/ZVAC081.

[9] Romiti GF, Proietti M, Bonini N, Ding WY, Boriani G, Huisman M v, et al. Clinical complexity domains, anticoagulation, and outcomes in patients with atrial fibrillation: a report from the GLORIA-AF registry phase II and III. Thromb Haemost 2022. https://doi.org/10.1055/S-0042-1756355.

[10] Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol 2017;14:627–8. https://doi.org/10.1038/nrcardio.2017.153.

[11] Guo Y, Lane DA, Wang L, Zhang H, Wang H, Zhang W, et al. Mobile health technology to improve care for patients with atrial fibrillation. J Am Coll Cardiol 2020;75:1523–34. https://doi.org/10.1016/j.jacc.2020.01.052.

[12] Guo Y, Lane DA, Wang L, Chen Y, Lip GYH, Eckstein J, et al. Mobile Health (mHealth) technology for improved screening, patient involvement and optimising integrated care in atrial fibrillation: the mAFA (mAF-App) II randomised trial. Int J Clin Pract 2019;73. https://doi.org/10.1111/ijcp.13352.

[13] Guo Y, Guo J, Shi X, Yao Y, Sun Y, Xia Y, et al. Mobile health technology-supported atrial fibrillation screening and integrated care: a report from the mAFA-II trial Long-term Extension Cohort. Eur J Intern Med 2020;82:105–11. https://doi.org/10.1016/J.EJIM.2020.09.024.

[14] Dong J, Zhang JL, Zeng S, Li F. Subgroup balancing propensity score. Stat Methods Med Res 2020;29:659–76. https://doi.org/10.1177/0962280219870836.

[15] Anter E, Jessup M, Callans DJ. Atrial fibrillation and heart failure: treatment considerations for a dual epidemic. Circulation 2009;119:2516–25. https://doi.org/10.1161/CIRCULATIONAHA.108.821306.

[16] Chamberlain AM, Redfield MM, Alonso A, Weston SA, Roger VL. Atrial fibrillation and mortality in heart failure. Circ Heart Fail 2011;4:740–6. https://doi.org/10.1161/CIRCHEARTFAILURE.111.962688.

[17] Carlisle MA, Fudim M, DeVore AD, Piccini JP. Heart failure and atrial fibrillation, like fire and fury. JACC Heart Fail 2019;7:447–56. https://doi.org/10.1016/j.jchf.2019.03.005.

[18] Roy D, Talajic M, Nattel S, Wyse DG, Dorian P, Lee KL, et al. Rhythm control versus rate control for atrial fibrillation and heart failure. N Engl J Med 2008;358: 2667–77. https://doi.org/10.1056/NEJMoa0708789.

[19] Marrouche NF, Brachmann J, Andresen D, Siebels J, Boersma L, Jordaens L, et al. Catheter ablation for atrial fibrillation with heart failure. N Engl J Med 2018;378: 417–27. https://doi.org/10.1056/NEJMoa1707855.

[20] Hayhoe B, Kim D, Aylin PP, Azeem-Majeed F, Cowie MR, Bottle A. Adherence to guidelines in management of symptoms suggestive of heart failure in primary care. Heart 2019;105:678–85. https://doi.org/10.1136/heartjnl-2018-313971.

[21] Jarjour M, Henri C, de Denus S, Fortier A, Bouabdallaoui N, Nigam A, et al. Care gaps in adherence to heart failure guidelines: clinical inertia or physiological limitations? JACC Heart Fail 2020;8:725–38. https://doi.org/10.1016/j.jchf.2020.04.019.

[22] Zhang Y, Zhang J, Butler J, Yang X, Xie P, Guo D, et al. Contemporary epidemiology, management, and outcomes of patients hospitalized for heart failure in China: results from the China heart failure (China-HF) registry. J Card Fail 2017; 23:868–75. https://doi.org/10.1016/J.CARDFAIL.2017.09.014.

[23] Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:E895–1032. https://doi.org/10.1161/CIR.0000000000001063.

[24] Yao Y, Guo Y, Lip GYH. The effects of implementing a mobile health-technology supported pathway on atrial fibrillation-related adverse events among patients with multimorbidity: the mAFA-II randomized clinical trial. JAMA Netw Open 2021;4:2140071. https://doi.org/10.1001/jamanetworkopen.2021.40071.

[25] Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D, et al. Adherence to the "Atrial Fibrillation Better Care" pathway in patients with atrial fibrillation: impact on clinical outcomes-a systematic review and meta-analysis of 285,000 patients. Thromb Haemost 2022;122:406–14. https://doi.org/10.1055/a-1515-9630.

[26] Ambrosio G, Camm AJ, Bassand JP, Corbalan R, Kayani G, Carluccio E, et al. Characteristics, treatment, and outcomes of newly diagnosed atrial fibrillation patients with heart failure: GARFIELD-AF. ESC Heart Fail 2021;8:1139–49. https://doi.org/10.1002/ehf2.13156.

[27] GF Romiti, M Proietti, M Vitolo, N Bonini, AM Fawzy, WY Ding et al., Clinical complexity and impact of the ABC (Atrial fibrillation Better Care) pathway in patients with atrial fibrillation: a report from the ESC-EHRA EURObservational Research Programme in AF General Long-Term Registry, BMC Med 20, 326, https://doi.org/10.1186/s12916-022-02526-7.