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Mobile health technology integrated care in atrial fibrillation patients with diabetes mellitus in China: A subgroup analysis of the mAFA-II cluster randomized clinical trial

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Abstract

Background: The Mobile Health Technology for Improved Screening and Optimized Integrated Care in AF (mAFA-II) prospective randomized trial showed the efficacy of a mobile health (mHealth) implemented 'Atrial fibrillation Better Care' (ABC) pathway for the integrated care management of patients with atrial fibrillation (AF). In this ancillary analysis, we evaluated the effect of mAFA intervention according to the history of diabetes mellitus (DM).

Methods: The mAFA-II trial enrolled 3324 AF patients across 40 centres in China, between June 2018 and August 2019. In this analysis, we assessed the interaction between history of DM and the effect of mAFA intervention on the risk of the primary composite outcome of stroke, thromboembolism, all-cause death and rehospitalizations. Results were expressed as adjusted hazard ratio (aHR) and 95% confidence intervals (95%CI). The effect of mAFA intervention on exploratory secondary outcomes was also assessed.

Results: Overall, 747 (22.5%) patients had DM (mean age: 72.7 ± 12.3, 39.6% females; 381 allocated to mAFA intervention). mAFA intervention was associated with a significant risk reduction for the primary composite outcome both in patients with and without DM (aHR [95%CI]: .36 [.18–.73] and .37 [.23–.61], respectively, p for interaction = .941). A significant interaction was found only for the composite of recurrent AF, heart failure and acute coronary syndromes (p_{int} = .025), with lower effect of mAFA intervention in patients with DM.

Conclusions: A mHealth-technology implemented ABC pathway showed a consistent effect in reducing the risk of the primary composite outcome in AF patients with and without DM.

Yutao Guo and Bernadette Corica are joint first authors.

Trial Registration: WHO International Clinical Trials Registry Platform (ICTRP) Registration number: ChiCTR-OOC-17014138.

KEYWORDS

atrial fibrillation, diabetes mellitus, integrated care, outcomes

1 | INTRODUCTION

Atrial Fibrillation (AF) is the most frequent cardiac arrhythmia and is a leading cause of mortality and morbidity worldwide.[1] AF can be considered a growing epidemic because of the increasing incidence and prevalence worldwide[2] and for its high burden of hospitalization costs.[3] This arrhythmia is also commonly associated with other comorbidities, which contribute to increasing the risk of stroke and adverse events.

Diabetes mellitus (DM) represents one of the most frequent concurrent diseases in people with AF and, at the same time, increases the risk of thromboembolism and overall worse prognosis.[4] Indeed, DM is currently one of the most common diseases worldwide, with increasing incidence and prevalence.[5]

The relationship between AF and DM is well known when for the first time in 1994, the Framingham study demonstrated the increased risk of AF in patients with DM.[6] This observation was further confirmed in subsequent studies, which demonstrated how DM increases by at least one-third the risk of incident AF.[7] On the other side, DM is commonly found in patients with AF, with a prevalence of 1 of 7 patients with AF,[8] thus underlining the bidirectional relationship of these two diseases. Recent epidemiological studies have found a higher prevalence of DM in patients newly diagnosed with AF,[9] and it is expected that with the ageing general population, these numbers are likely to increase further in the next decades, leading to a syndemic of these two diseases.

The pathophysiological relationship between DM and AF is complex. Fluctuating glycaemic levels, inflammation and oxidative stress caused by DM can in turn promote electrical and structural changes of the atria, making them more susceptible to the onset of arrhythmias.[10] Notwithstanding, these effects can explain the higher risk of cardiovascular events such as stroke,[11] myocardial infarction, heart failure and cardiovascular mortality[12,13] which are usually found in patients with AF and DM. Unsurprisingly, DM is considered among one of the risk factors used to stratify thromboembolic risk in AF patients.[14]

Given the complex interplay between AF and DM, a more comprehensive and holistic approach is needed to manage these patients. This holistic or integrated care approach has been formulated as the "Atrial fibrillation Better Care" (ABC) Pathway[15] and consists of three pillars: Avoid stroke with appropriate anticoagulation (A); Better symptom management, through patient-centred decisions on rate and rhythm control (B); and Cardiovascular and comorbidities management optimization, including lifestyle changes (C). Adherence to the ABC pathway is associated with a reduction in mortality, stroke and bleeding, hence an improved prognosis in AF patients.[16–19] This has led the ABC pathway to be recommended in AF management guidelines.[20,21] Evidence in diabetic people with AF is more limited, although one post hoc analysis based on the Gulf SAFE Registry confirmed a substantial mortality risk reduction in ABC pathway compliant patients with DM, but also suggesting that most patients with DM and AF were not optimally treated despite their high risk of stroke.[22]

The Mobile Health Technology for Improved Screening and Optimized Integrated Care in AF (mAFA-II) randomized cluster trial showed the efficacy of a mobile health (mHealth) implemented ABC pathway approach (mAFA intervention)[23,24] in reducing the primary composite outcomes of ischemic stroke (IS)/systemic thromboembolism (TE), all-cause death and rehospitalization among AF patients.[24] Whether these benefits apply also to patients with DM is still not completely understood.

In this post hoc, ancillary analysis from the mAFA-II trial, we aim to assess the efficacy of the mAFA intervention in AF patients according to their history of DM at baseline.

2 | METHODS

2.1 | Study design

Full details on the design, sample size calculation and primary results of the mAFA-II trial have been previously reported elsewhere.[23,24] Briefly, this was a prospective, cluster-randomized multicentre trial that enrolled patients with AF (≥18 years old) across 40 centres in China, that were randomized in a 1:1 ratio to the mAFA intervention or usual care. Exclusion criteria were as follows: (i) patients with mechanical prosthetic valves, (ii) patients with moderate to severe mitral stenosis and (iii) patients unable to complete

1-year of follow-up for any reason. Between 1 June 2018 and 16 August 2019, 1646 subjects with AF were allocated to mAFA intervention, while 1678 AF patients were allocated to usual care. 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 and was conducted in accordance with the Declaration of Helsinki and the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline; all the patients gave their written informed consent.

A user-friendly mAFA platform for smartphones was used for doctors and patients. In the mAFA intervention group, the doctors used the mAFA platform in order to manage patients with AF. The platform provided clinical decision support tools (CHA_2DS_2-VASc, HAS-BLED, sex, age, medical history, comorbidities and treatment) to help in treatment decision based on guidelines recommendations, educational materials and patient involvement plan with self-care protocols, and planned follow-up, to support the implementation of the ABC pathway for integrated AF management, following guidelines on AF management. Patients in the mAFA group were encouraged, through the mAFA platform, in the participation in educational programs, and they were provided with informative articles, videos, games, etc. Educational materials were about AF, comorbidities, self-care, etc. Patients allocated to the mAFA intervention clusters implemented the ABC pathway according to the following criteria: 'A' criterion: anticoagulation prescription according to regular assessment of thromboembolic and bleeding risk, with dose adjustment based on renal and liver function reassessment; 'B' criterion: regular monitoring of patient-reported symptoms (which were evaluated according to the European Heart Rhythm Association classification), along with symptoms-directed management that included antiarrhythmics and rhythm control therapies; 'C' criterion: active management and treatment optimization of concurrent comorbidities (e.g. hypertension management according to blood pressure monitoring). Patients allocated to "usual care" were treated by local healthcare providers, according to local clinical practices.

In this ancillary analysis, we evaluate the effect of mAFA intervention according to the presence of DM at baseline. Diagnosis of DM was recorded by investigators at baseline and reported in the case report form accordingly. Reporting of the study conforms to broad EQUATOR guidelines.[25]

2.2 | Outcomes and follow-up

All the patients enrolled were followed up for the occurrence of clinical adverse events at 6 and 12 months after the inclusion. In this analysis, consistently with the primary analysis of the trial, our primary endpoint was the composite outcome of ischemic stroke (IS) or systemic thromboembolism (TE), all-cause death, and rehospitalization. Other secondary exploratory outcomes investigated were thromboembolism (defined as IS or other systemic TE), bleeding events (intracranial and/or extracranial), cardiovascular outcomes [recurrent AF, heart failure (HF), acute coronary syndrome], all-cause death and rehospitalization. For each outcome, we evaluated the effect of mAFA intervention according to the presence of DM at baseline.

2.3 | Statistical analysis

Baseline characteristics for the primary analysis population were reported as mean and standard deviation (SD) for normally distributed continuous variables, or median and interquartile range [IQR] for non-normally distributed continuous variables. Frequency and percentage were reported for binary or categorical variables. Cox-proportional hazard regression models were performed to evaluate the interaction between the diagnosis of DM at baseline and the effect of mAFA intervention on the outcomes of interest. All the models were adjusted for age, sex, type of AF, comorbidities [hypertension, coronary artery diseases (CAD), history of heart failure (HF), peripheral artery disease (PAD), history of IS], previous AF treatment and cluster effect. Survival curves were also reported for the primary composite outcome, and survival distribution were compared with log-rank test. A 2-sided p-value $< .05$ was considered statistically significant. All statistical analyses were conducted using R 4.2.0 (R Foundation for Statistical Computing 2020, Vienna, Austria).

3 | RESULTS

A total of 3324 patients were originally enrolled in the trial (Figure 1), and 747 (22.5%) had DM at baseline. Of these, 381 (51.0%) were allocated to mAFA intervention (mean age ± SD: 73.0 ± 12.2; 42.3% females), while 366 (49.0%) were allocated to usual care (mean age ± SD: 72.4 ± 12.4; 36.9% females). Baseline characteristics according to the allocation to mAFA intervention or usual care, and according to the diagnosis of DM at baseline, are reported in Table 1. Among patients with DM, those allocated to mAFA intervention had a higher prevalence of hypertension, CAD, HF and a lower prevalence of prior ischemic stroke; on the other side, patients without DM allocated to mAFA intervention had a lower prevalence of hypertension, CAD, HF and prior cerebral bleeding.

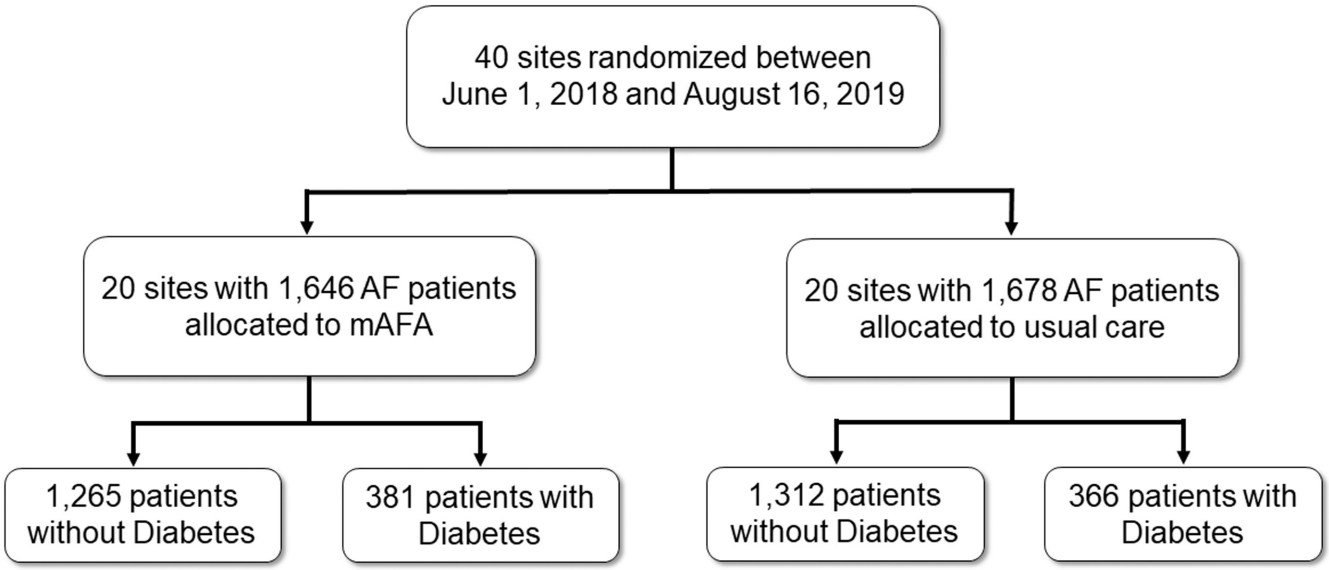

FIGURE 1 Flowchart of the subgroup analysis on patients with DM in the mAFA-II trial. AF, atrial fibrillation.

Table S1 summarizes the different treatments prescribed at the baseline in patients with and without DM according to the group of assignment. Unsurprisingly, patients allocated to mAFA intervention were more treated with Non-Vitamin K oral anticoagulants (NOACs, $p < .001$) and with beta-blockers ($p < .001$) both in patients with and without DM. Patients with DM allocated to the mAFA group were more likely treated with hypoglycaemic agents, statins and calcium-channel blockers, while less likely treated with insulin.

3.1 | Risk of major outcomes

The results of the Cox-regression model on the interaction between DM at baseline and the effect of mAFA intervention on major outcomes are reported in Figure 2, while survival curves for the primary composite outcome according to mAFA allocation and DM at baseline are reported in Figure 3. mAFA intervention was associated with a statistically significant reduction in the risk of the primary composite outcome in both patients with DM (aHR: .36, 95%CI: .18–.73) and without DM (aHR: .37, 95%CI: .23–.61), without statistically significant interaction (p for interaction [p_{int}] = .941). Kaplan–Meier survival analysis (Figure 3) showed a similar beneficial effect on mAFA intervention in both patients with and without DM.

Regarding the exploratory secondary outcomes, similar results were observed for rehospitalizations only ($p_{int} = .618$), with no statistically significant interaction also observed for thromboembolism ($p_{int} = .841$), all-cause death ($p_{int} = .325$) and bleeding events ($p_{int} = .477$). A statistically significant interaction was observed for the risk of the composite of non-fatal cardiovascular outcomes (recurrent AF, HF and ACS), with mAFA intervention associated with reduced risk in patients without DM at baseline (aHR: .38, 95%CI .23–.63) but not in patients with DM (aHR: .95, 95%CI: .51–1.76, $p_{int} = .025$).

4 | DISCUSSION

In this analysis on the effects of mAFA intervention in patients with and without DM, our principal findings are as follows: (i) the mAFA intervention showed similar effectiveness in in reducing the risk of the primary composite outcome of IS/TE, death and rehospitalization in AF patients with and without DM; (ii) no significant interaction was observed for the effect of mAFA intervention according to the presence of DM for most of the exploratory secondary outcomes, including thromboembolism, all-cause death, rehospitalization and bleeding events; and (iii) a statistically significant DM-based interaction was observed for the exploratory composite outcome of cardiovascular events (including recurrent AF, HF and ACS), with the effect of mAFA intervention being higher in non-diabetic patients.

The synergistic role of DM and AF in determining unfavourable outcomes is already known;[26] however, as mechanisms underlying this effect are not completely understood, there is still a significant uncertainty on how to tackle the risk due to the co-existence of DM and AF. Different studies show that DM increases the risk of cardiovascular events in AF patients,[27] and DM is regarded as one of the key thromboembolic risk factors in AF patients.[14] The effect of DM on outcomes can be

TABLE 1 Baseline characteristics.

Variables, *n* (%)	No diabetes mellitus			Diabetes mellitus		
	mAFA (*n* = 1265)	Usual Care (*n* = 1312)	*p*	mAFA (*n* = 381)	Usual Care (*n* = 366)	*p*
Age, mean (SD)	65.0 (14.8)	69.5 (13.0)	**<.001**	73.0 (12.2)	72.4 (12.4)	.473
Females	464 (36.7)	502 (38.3)	.430	161 (42.3)	135 (36.9)	.154
Comorbidities, n (%)						
Smoking	122 (9.6)	131 (10.0)	.823	37 (9.7)	37 (10.1)	.953
Hypertension	612 (48.4)	715 (54.5)	**.002**	296 (77.7)	247 (67.5)	**.002**
CAD	396 (31.3)	530 (40.4)	**<.001**	239 (62.7)	194 (53.0)	**.009**
Heart failure	208 (16.4)	271 (20.7)	**.007**	152 (39.9)	83 (22.7)	**<.001**
Prior ischemic stroke	130 (10.3)	141 (10.7)	.745	61 (16.0)	91 (24.9)	**.004**
PAD	110 (8.7)	123 (9.4)	.594	62 (16.3)	49 (13.4)	.315
Renal dysfunction	84 (6.6)	107 (8.2)	.164	54 (14.2)	65 (17.8)	.215
Pulmonary hypertension	59 (4.7)	58 (4.4)	.840	28 (7.3)	25 (6.8)	.894
Liver dysfunction	40 (3.2)	31 (2.4)	.263	15 (3.9)	17 (4.6)	.767
Prior brain bleeding	10 (0.8)	26 (2.0)	**.016**	14 (3.7)	12 (3.3)	.924
Prior thromboembolism	31 (2.5)	42 (3.2)	.303	23 (6.0)	17 (4.6)	.495
Prior other bleeding	31 (2.5)	47 (3.6)	.118	23 (6.0)	20 (5.5)	.858
Dilated cardiomyopathy	32 (2.5)	41 (3.1)	.428	12 (3.1)	20 (5.5)	.167
Hyperthyroidism	25 (2.0)	37 (2.8)	.204	12 (3.1)	14 (3.8)	.761
Hypertrophic cardiomyopathy	14 (1.1)	17 (1.3)	.795	11 (2.9)	12 (3.3)	.922
Type of AF, n (%)			**<.001**			**<.001**
Unknown	238 (18.9)	99 (7.6)		43 (11.4)	14 (3.8)	
New-onset AF	149 (11.9)	182 (13.9)		46 (12.2)	50 (13.7)	
Paroxysmal AF	514 (40.9)	500 (38.1)		159 (42.2)	160 (43.7)	
Persistent AF	276 (22.0)	363 (27.7)		104 (27.6)	85 (23.2)	
Long-standing AF	43 (3.4)	78 (5.9)		13 (3.4)	23 (6.3)	
Permanent AF	36 (2.9)	89 (6.8)		12 (3.2)	34 (9.3)	
Prior AF treatment, n (%)						
Pharmacological cardioversion	165 (13.0)	115 (8.8)	**.001**	48 (12.6)	40 (10.9)	.552
Electrical cardioversion	25 (2.0)	26 (2.0)	1.000	5 (1.3)	9 (2.5)	.376
AF ablation	149 (11.8)	140 (10.7)	.407	34 (8.9)	33 (9.0)	1.000
Pacemaker	45 (3.6)	61 (4.6)	.195	31 (8.1)	24 (6.6)	.493
LAAO	24 (1.9)	16 (1.2)	.218	9 (2.4)	14 (3.8)	.345
Scores						
CHA_2DS_2-VASc, median [IQR]	2 [1–3]	2 [1–3]	.839	4 [3–5]	4 [3–5]	.084
CHA_2DS_2-VASc, mean (SD)	2.42 (1.46)	2.41 (1.36)	.902	4.08 (1.49)	3.89 (1.48)	.083
HAS-BLED, median [IQR]	1 [0–2]	1 [1–2]	**<.001**	2 [1–2]	2 [1–2]	.144
HAS-BLED, mean (SD)	1.27 (1.03)	1.42 (.95)	**<.001**	1.75 (1.11)	1.85 (1.11)	.214

Note: Significant *p*-values are in bold.

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; IQR, interquartile range; LAAO, left atrial appendage occlusion; PAD, peripheral artery disease; SD, standard deviation.

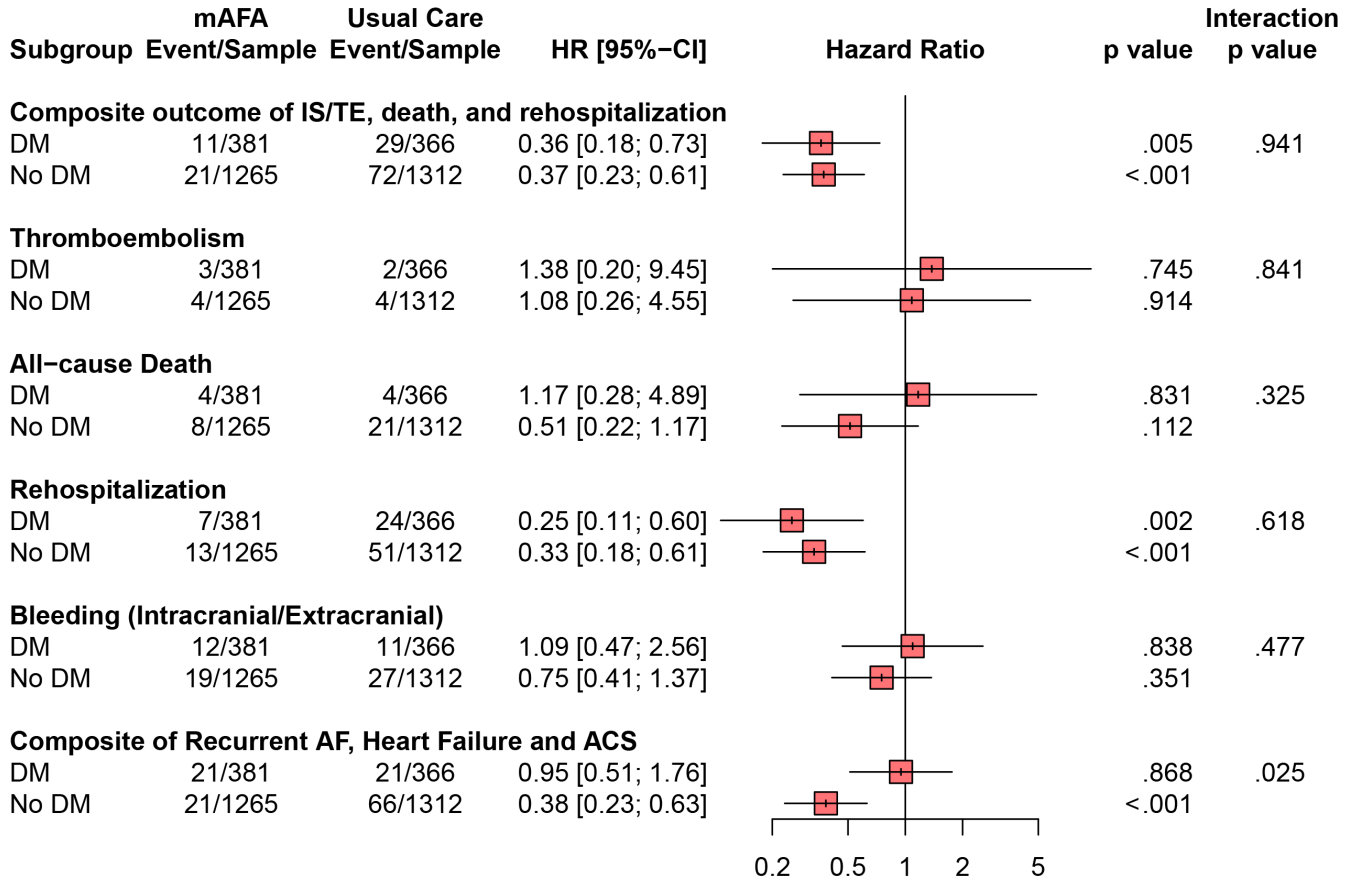

FIGURE 2 Cox-regression models for the interaction between DM and effect of mAFA intervention. AF, atrial fibrillation; DM, Diabetes Mellitus; adjusted for age, sex, type of AF, comorbidities (hypertension, coronary artery diseases (CAD), history of heart failure (HF), Peripheral Artery Disease (PAD), history of IS), previous AF treatment and cluster effect. HR, hazard ratio; IS, Ischemic Stroke; TE, Thromboembolism.

partially explained, among others, by the microvascular and macrovascular effects of poor glycaemic control thus being higher in those with long duration of DM, thus resulting in myocardial and electrical structural changes which in turn can lead to the onset of additional comorbidities and AF progression/recurrence.[11] Finally, the presence of DM can also reflect an increased "complexity" of AF patients, as encompassed by older age, and a higher number of concomitant comorbidities (such as HF, hypertension, CAD and chronic kidney disease).[28,29]

In recent years, the need for a holistic and integrated approach for the treatment of AF patients has been emphasized, given their ageing and progressively higher multimorbidity. The ABC pathway has been proposed to streamline such a holistic approach, introducing a structured management and optimization of cardiovascular risk factors and comorbidities. Recent international guidelines have recommended its implementation as the cornerstone of the treatment of AF patients,[20] while previous evidence showed the effectiveness of adherence to the approach in improving outcomes of these subjects.[15,18,19]

Nevertheless, the optimal treatment of DM clearly represents a key area of intervention for those AF patients who also have DM, and while retrospective studies have demonstrated the efficacy of the ABC pathway in reducing mortality and other adverse events in diabetic patients,[22] there is still uncertainty on whether a mHealth implemented-ABC pathway can improve prognosis of AF-DM patients.[30]

The results of our analysis, which focused specifically on the interaction between DM and the effect of the mAFA intervention, show how the implementation of a patient-centred approach to the treatment of AF patients (as encompassed by the mAFA intervention) prescribed at the baseline, lead to a significant increase in the uptake of both anticoagulants (and specifically, NOACs) as well as DM-specific drugs, such as hypoglycaemic agents, and other agents used to treat associated conditions (including statins for dyslipidaemia and calcium-channel blockers for hypertension). This can certainly explain—at least partly—the results observed for the risk of major outcomes, hence the mAFA intervention being associated with a similar reduction in the risk of the primary composite

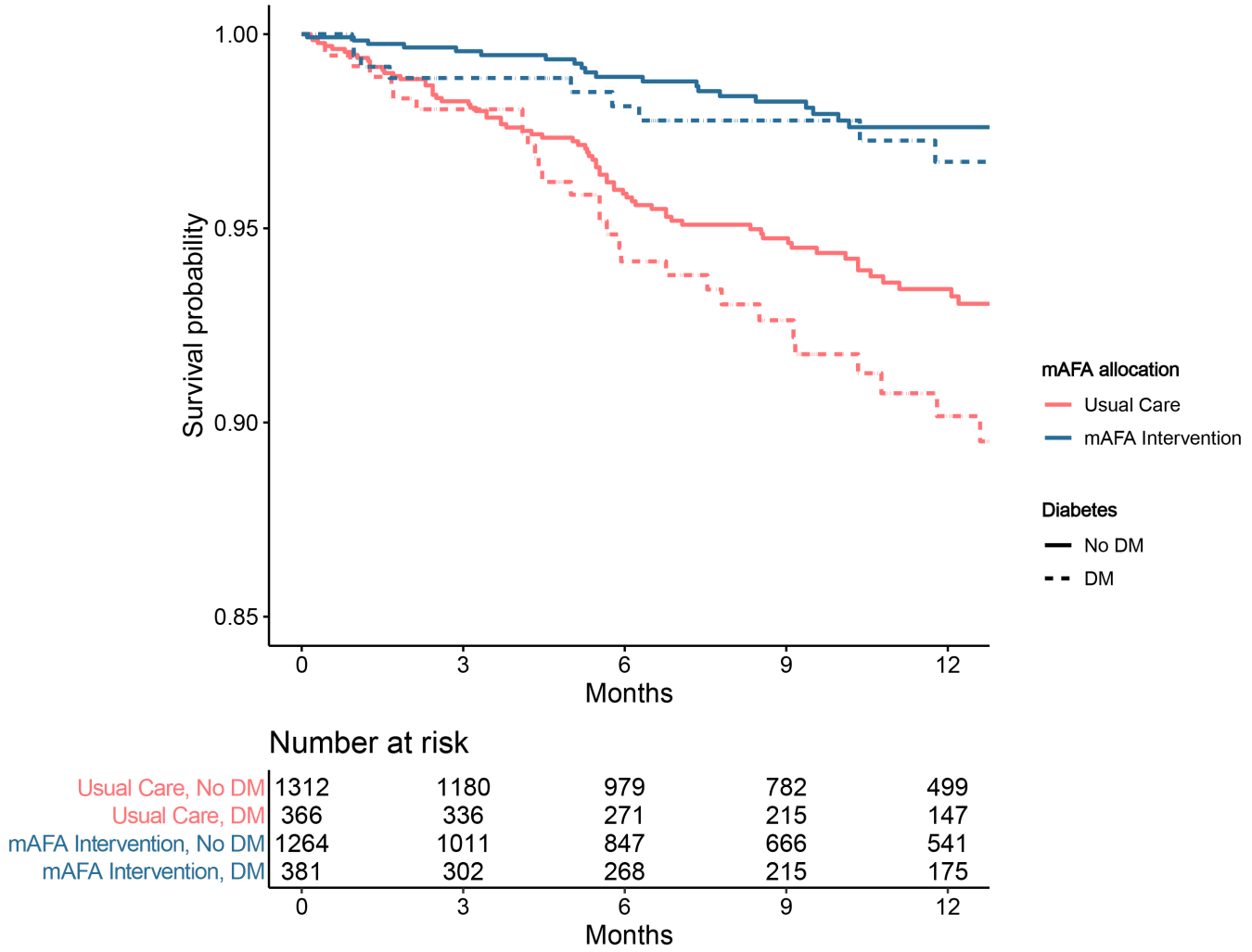

FIGURE 3 Survival curves for the primary composite outcome of IS/TE, death and rehospitalization during the 12 months of the mAFA-II trial follow-up, stratified by treatment allocation and presence of DM at baseline. *p*-value = .005 for DM patients; *p*-value < .001 for No DM patients. mAFA intervention group = blue line; usual care group = red line; No DM = solid line; DM = dash line.

outcome of IS/TE, all-cause death and rehospitalization in both patients with and without DM. While no statistically significant DM-based interaction was observed for most of the other exploratory secondary outcomes, the beneficial effect of mAFA intervention was lower on the risk of the composite outcome of cardiovascular events (including recurrent AF, HF and ACS) in DM patients, and a non-statistically significant trend was observed for all-cause death. These results should be interpreted in view of the exploratory nature of our secondary outcomes, which this analysis is not sufficiently powered, and the differences in the baseline burden of comorbidities and risk factors in patients with DM allocated to mAFA intervention or usual care. Indeed, a higher prevalence of hypertension, CAD and HF was observed among patients with DM allocated to mAFA intervention, with also a lower proportion of the history of IS. These differences (which are expected given the cluster-randomized design of the trial), and the resulting higher baseline cardiovascular risk of these patients, may be responsible for the lower effect observed for mAFA intervention in DM patients. So, the multimorbid DM patients allocated to mAFA intervention had greater opportunity for 'contact' with healthcare providers, possibly leading to more detection of AF recurrences, or diagnosis of HF or ACS. As the ABC pathway implemented in the mAFA intervention was developed for the optimal management of AF, these patients with such a high cardiovascular risk may need other specific strategies (such as for the management of CAD and HF) to further improve their overall prognosis. Moreover, the digital technology, for example wearable technology and transdermal biosensors, may be employed to support non-invasive blood glucose monitoring to empower patients with the more intensive, individualized glucose control care, thus reducing the risk of AF occurrence.[31]

Taken together, our results have several clinical implications. First, as patients with AF and DM are disproportionately affected by the risk of major outcomes, these

subjects require specific interventions, in order to manage the complexity associated with their clinical conditions, and ultimately to improve their prognosis. In this scenario, the ABC pathway represents a pragmatic—yet comprehensive—approach to streamline a holistic bundle of care, able to improve the treatment patterns in AF-DM patients, and to ameliorate their prognosis, as shown in our analysis. Our results are consistent with other previous analyses on the mAFA-II trial, which showed how the mAFA intervention was effective in reducing the risk of adverse events in other high-risk subgroups of patients, such as the elderly and those with history of heart failure.[32,33]

4.1 | Strengths and limitations

Our study is the first to provide a stratified analysis of the efficacy of a mHealth-implemented ABC pathway according to the presence of DM in AF patients. Furthermore, our results were largely consistent with the primary analysis of the trial, thus contributing to the overall reliability of our estimates.

Nonetheless, our study has some limitations. First, this was a post hoc subgroup analysis of a cluster randomized trial, and there were some imbalances in the baseline characteristics among patients with and without DM and according to the treatment allocation. While this is expected, given the design of the trial and the nature of this analysis, these imbalances may have influenced the results observed, especially for the secondary exploratory outcomes. Furthermore, this analysis may lack statistical power for some of the comparisons performed and secondary outcomes investigated. Second, there were some imbalances on the baseline characteristics in diabetic or non-diabetic patients allocated to mAFA intervention vs. usual care. We were unable to explore the influence of the duration of DM history or glycaemic control (such as glycated haemoglobin level); also, we were not able to explore the impact of a new-onset DM occurring during the follow-up period. While these factors are important and should be explored by further studies, we believe they are unlikely to have critically influenced our results, considering the duration of follow-up and the characteristics of our cohort, as well as the primary trial objective to test the impact of holistic or integrated care AF management. Additionally, the interpretation of the exploratory secondary outcomes merits caution, considering the much reduced sample size in the subgroup of patients with DM and the lower rates of events, as well as the exploratory nature of such outcomes. Further studies are required to clarify whether these aspects may have a role in determining the efficacy of the ABC pathway on the risk of major outcomes. Moreover, further studies (with a larger sample size and longer follow-up) are needed to confirm and expand these findings. As the mAFA-II trial was conducted in China, the results observed and reported in this study should be interpreted and applied with caution to other geographical contexts, in view of the potential regional-based differences in the epidemiology of AF and treatments. The ongoing AFFIRMO programme,[34] which will include a multinational cluster randomized trial to evaluate the efficacy of the ABC pathway, will provide further evidence on the effect of such approach in improving outcomes in European AF patients. Finally, although we have performed Cox-regression models after the adjustment for several potential confounders, we cannot exclude the contribution of other unaccounted moderators or residual confounding on the results observed.

5 | CONCLUSIONS

In this post hoc analysis of the mAFA-II trial, a mHealth-technology implemented ABC pathway was associated with a similar reduction in the risk of the primary composite outcome of IS/TE, all-cause death and rehospitalization in AF patients with and without DM. Given their high cardiovascular risk, AF patients with DM may require further specific strategies to reduce non-AF related cardiovascular risk and to further improve their prognosis.

AUTHOR CONTRIBUTIONS

YG, BC and GYHL conceived and design the analysis; BC and GFR analysed, interpreted the data and drafted the manuscript; YG, MP, HZ and GYHL revised the manuscript and gave relevant intellectual contribution. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

GFR reports consultancy for Boehringer Ingelheim and an educational grant from Anthos, outside the submitted work. No fees are directly received personally. MP is investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under

grant agreement No. 899871. GYHL has been consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Anthos and Daiichi-Sankyo. No fees are directly received personally. All the disclosures happened outside the submitted work. GYHL is co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 899871. All other authors have nothing to declare.

DATA AVAILABILITY STATEMENT

Data supporting the current study are available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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