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Mobile Health-Technology-Integrated Care for Atrial Fibrillation: A Win Ratio Analysis from the mAFA-II Randomized Clinical Trial

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Abstract

Background The Mobile Health (mHealth) Technology for Improved Screening and Optimized Integrated Care in atrial fibrillation (AF) (mAFA-II) cluster randomized trial assessed the efficacy of an integrated care approach in improving the prognosis of AF patients. In this study, we provide a reanalysis of the trial outcomes using the win ratio (WR) approach.

Methods The mAFA-II trial allocated patients to receive a mHealth-technology implemented Atrial Fibrillation Better Care (ABC) pathway (mAFA intervention) or usual care. The primary outcome was the composite of all-cause death, ischemic stroke or systemic thromboembolism, and rehospitalization. The efficacy of the mAFA intervention was analyzed according to the WR method using the unmatched pairs approach, with the components of the primary outcome analyzed hierarchically as follows: (1) all-cause death; (2) ischemic stroke or thromboembolism; (3) rehospitalization. Results were reported as WR and 95% confidence intervals (CIs). In addition, we calculated win odds (WO) and 95% CI.

Results A total of 3,324 patients were enrolled in the mAFA-II trial and included in this analysis (1,646 allocated to mAFA intervention and 1,678 to usual care). Among 2,761,988 unmatched pairs comparisons, the number of wins was higher in the mAFA intervention group, with a WR: 2.78 (95% CI: 1.85–4.17). WO confirmed the effect of mAFA intervention, although with a lower magnitude (WO: 1.06; 95% CI: 1.04–1.08).

Conclusion In this posthoc WR analysis of the mAFA-II trial, a mHealth-technology-implemented integrated care approach was effective in reducing the risk of the primary composite outcome of all-cause death, ischemic stroke or thromboembolism, and rehospitalization, even when prioritizing fatal events.

Keywords
- atrial fibrillation
- integrated care
- composite outcomes
- win ratio

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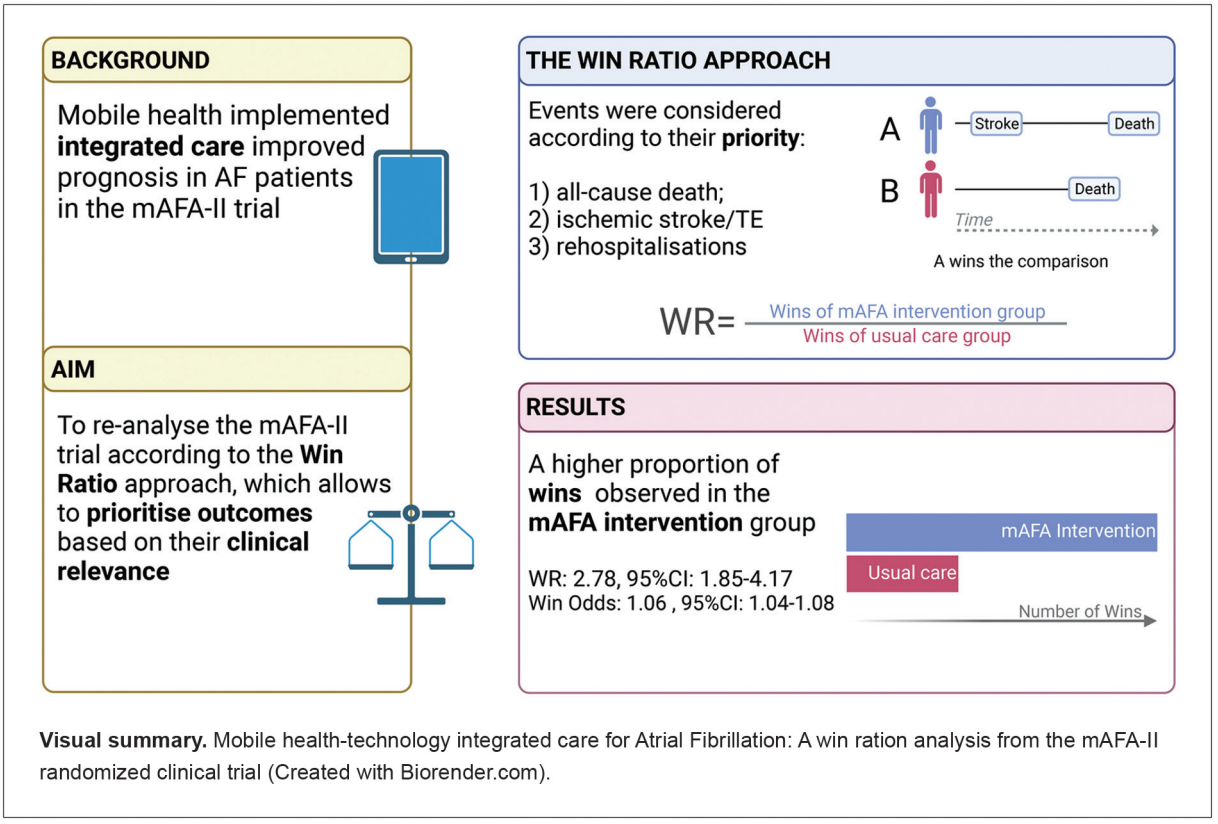

Visual summary. Mobile health-technology integrated care for Atrial Fibrillation: A win ration analysis from the mAFA-II randomized clinical trial (Created with Biorender.com).

Introduction

The use of composite endpoints, with the inclusion of multiple types of events (often encompassing both fatal and nonfatal outcomes, such as cause-specific rehospitalizations) has increased over the last decades and is currently widespread among cardiovascular trials.[1] The popularity of composite endpoints is mainly due to the ability of reducing sample sizes while preserving statistical power. Indeed, since the incidence of the composite endpoint is predictably higher than those of the single components, this ultimately allows for the recruitment of smaller cohorts of patients, as well as shorter follow-up times.[2]

Nonetheless, several criticisms have been made on the use of such composite endpoints to evaluate the efficacy of interventions in clinical trials, according to the heterogeneity of the components, and the issues related to the interpretation of the results.[1] Moreover, such an approach assigns equal weights to fatal and nonfatal events, despite their highly different clinical significance, and can lead us to ignore relevant events that occur after other less significant ones.[1]

To overcome these issues and to provide a more clinically relevant analysis of such composite endpoints, several approaches have been developed. Among these, the win ratio (WR) has been proposed to prioritize the events based on their importance, by considering them according to their clinical priority (e.g., fatal events first and then nonfatal events), thus accounting for their clinical relevance and the different weight that such events have on the management and natural history of patients.[3] The analysis can be performed either considering matched pairs of patients according to their risk profile or using an unmatched pair approach, in which each patient in one arm is compared with each patient in the other treatment group.[3]

Thus far, previous studies have provided analyses of randomized clinical trials using the WR approach,[4–6] showing the feasibility of this methodology, and the clinical implications related to the prioritization of specific clinical outcomes (such as death) which are perhaps more relevant to both clinicians and patients. Indeed, the WR approach may provide more clinically relevant information than time-to-first event analysis, by first considering all the fatal events, including the ones occurring after nonfatal ones.[4] Of note, while similar estimates are frequently observed in Cox and WR analyses, the latter approach also allows for the inclusion of nonevent outcomes (e.g., quality of life, patient-reported outcomes), while still recognizing clinical priorities.[4,6]

Nonetheless, the WR approach could be particularly useful in the context of atrial fibrillation (AF), given that several outcomes are of clinical interest, and should considered in the overall prognosis of AF patients.

The Mobile Health (mHealth) Technology to Improve Care for Patients with Atrial Fibrillation (mAFA-II) cluster randomized trial evaluated the efficacy of an mHealth technology-implemented integrated care approach to AF care (mAFA intervention).[7] The primary results showed that the mAFA intervention was associated with a reduced risk of the primary composite outcome of all-cause death, ischemic stroke or

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systemic thromboembolism, and rehospitalization (hazard ratio [HR]: 0.39, 95% confidence intervals [CIs]: 0.22–0.67), compared with usual care.[7] Nonetheless, the analysis was based on a time to first event analysis using the Cox-regression model, thus not taking into account the clinical relevance of the different outcomes included in the composite endpoint.

In this post-hoc analysis, we aimed to reanalyze the effectiveness of the mAFA intervention using a WR approach. The latter has not been previously applied to an AF population, where severe clinical outcomes have major implications for prognosis.

Methods

Details on the design and primary results of the mAFA-II have been reported elsewhere.[7,8] Briefly, the mAFA-II was a cluster randomized trial which enrolled adult patients with AF (≥18 years), between June 1st, 2018 and August 16th, 2019. Clusters were randomized in a 1:1 ratio to the mAFA intervention or usual care, across 40 participating centers in China. The main exclusion criteria were as follows: patients with mechanical prosthetic valve, patients with moderate-to-severe mitral stenosis, and subjects unable to be followed up for 1 year for any reason, or to provide informed consent. The study was approved by the Central Medical Ethic Committee of the Chinese People's Liberation Army General Hospital and by local institutional review boards. All patients gave a written informed consent at enrolment. The study was conducted in accordance with the Declaration of Helsinki and the Consolidated Standards of Reporting Trials reporting guidelines.

The mAFA intervention consisted of a mHealth-technology-implemented "Atrial Fibrillation Better Care" (ABC) pathway, which is an integrated approach proposed to improve AF management.[9] Consistently with the original definition, the ABC pathway, implemented in the mAFA intervention, was defined as follows: "A" criterion: administration of anticoagulant according to the regular and dynamic assessment of thromboembolic and bleeding risks, with dose adjustments according to the regular reassessment of renal and liver function; "B" criterion: periodical assessment of patient-reported symptoms (evaluated according to the European Heart Rhythm Association classification), as well as symptoms-directed management (which included patient-centered and symptom-directed rate or rhythm control treatments); "C" criterion: management optimization of the concurrent conditions and comorbidities (e.g., monitoring of blood pressure monitoring, and consequent management of hypertension), including lifestyle factors.

Subjects allocated to "usual care" were managed according to local practices.

Outcomes and Follow-up

All patients were followed up for the occurrence of clinical events at 6 months and 1 year after the inclusion. The *primary endpoint* was the composite outcome of all-cause death, ischemic stroke or systemic thromboembolism, and rehospitalization. Information regarding other *secondary outcomes* (which included bleeding events [intracranial and extracranial] and cardiovascular outcomes [recurrent AF, heart failure, acute coronary syndrome]) were also collected during follow-up.

The primary analysis of the trial was conducted according to a time to first event approach, using adjusted Cox-regression models.[7] Here, we analyzed the effect of the mAFA intervention on the primary composite outcome according to the WR method, using the unmatched pairs approach. The events composing the primary composite outcome were considered as follows, according to their priority (high to low): (1) all-cause death, (2) ischemic stroke or systemic thromboembolism, and (3) rehospitalization.

Statistical Analysis

For this analysis, we used the unmatched pairs approach described by Finkelstein and Schoenfeld.[10] Full details on the calculation of WR[3,6] and calculation of 95% CI[11] used in this analysis are reported elsewhere. Briefly, each patient in the mAFA intervention was compared with each patient in the usual care group, for the occurrence of the highest-priority event (i.e., all-cause death); for each comparison, the "winner" was determined as the patient who did not have the event or who experienced the event later. If no winner could be declared (e.g., because no event occurred in both patients, etc.), the comparison was then performed for the subsequent outcome in order of priority (i.e., ischemic stroke or thromboembolism), and so on. The number of comparisons "won" by patients in each group was noted, as well as the number of comparisons with "no winner" (ties). The WR was then expressed as the ratio of wins of patients assigned to mAFA intervention on wins of patients assigned to usual care. A WR >1, therefore, indicated a beneficial effect of the mAFA intervention (i.e., the number of comparisons won by the patients allocated in the mAFA intervention outnumbered those won by patients allocated to usual care). We reported WR along with 95% CI; we additionally reported for comparison the 1/HR (95% CI) derived from the adjusted Cox-regression models, as reported in the primary analysis of the mAFA-II trial.[7]

Given the potential issues in interpreting WR in the presence of a large amount of ties,[12] we additionally calculated the win odds (WO), which has been proposed to account for ties, and in which ties are counted as half win and half losses.[13,14]

All the statistical analyses were conducted using R 4.2.1 (R Foundation for Statistical Computing 2020, Vienna, Austria), using "survival"[15], "WinRatio," and "WINS" packages.

Results

Between June 1, 2018 and August 16, 2019, 3,324 patients were enrolled in the trial; 1,646 were allocated to mAFA intervention and 1,678 to usual care. Baseline characteristics and treatments of the cohort and primary results of the trial were reported elsewhere.[7] Briefly, over a mean follow-up of 291 days, 133 primary outcomes occurred (32 in mAFA intervention group and 101 in the usual care group), with a total number of 12 deaths, 7 ischemic stroke/systemic thromboembolism, and 20 rehospitalizations among

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patients allocated to mAFA intervention, and 25 deaths, 6 ischemic stroke/systemic thromboembolism, and 75 rehospitalizations among patients allocated to usual care.

Results of the WR analysis are summarized in ►**Fig. 1** and ►**Table 1**. There was a total of 2,761,988 unmatched patient pairs in this analysis, with a total of 119,601 (4.3% of the total comparisons) wins for mAFA intervention and 43,032 (1.6%) wins for the usual care group, while the number of comparisons with no winner (ties) was 2,599,355.

The WR analysis showed that patients allocated to mAFA intervention had a lower risk of the primary composite outcome of all-cause death, ischemic stroke or systemic thromboembolism, and rehospitalization (WR: 2.78, 95% CI: 1.85–4.17, $p < 0.001$), consistent with the original analysis according to the adjusted Cox-regression model[7] (1/HR: 2.56, 95% CI: 1.49–4.55).

A beneficial effect of the mAFA intervention was observed also according to WO analysis, although the inclusion of ties substantially mitigated the difference between mAFA intervention and the usual care group (WO: 1.06, 95% CI: 1.04–1.08, $p < 0.001$).

Discussion

In this post-hoc analysis from the mAFA-II trial using the WR approach, we found that mAFA intervention was associated with a significant reduction of the risk of the primary outcome, with a higher proportion of wins in the mAFA intervention group, compared with subjects allocated to usual care.

To our knowledge, this is the first analysis to have applied the WR methodology to an AF trial, which showed a significant reduction in the risk of the primary composite outcome of ischemic stroke/thromboembolism, all-cause death, and rehospitalizations, in patients managed according to an integrated care approach. This finding was consistent with the primary analysis of the trial[7]; nonetheless, given the relatively low incidence of events in the trial, a considerable amount of "ties" were observed, and the difference between the groups was mitigated in the WO analysis. This post-hoc analysis reinforces the efficacy of the mAFA intervention based on the ABC pathway on the risk of the primary composite outcome, acknowledging the highest priority of the different components of the outcomes (i.e., attributing the highest relevance to all-cause death, followed by ischemic stroke/systemic thromboembolism, and finally rehospitalization).

With the widespread use of composite endpoints in cardiovascular trials, the approach of collating hard and soft endpoints (and even more frequently, fatal and nonfatal outcomes) has become standard practice in cardiovascular research, leading to several criticisms related to the clinical interpretation of the results of such investigations using composite outcomes, giving equal weights attributed to events that have highly different clinical significance.[1] The availability of new techniques to analyze such composite

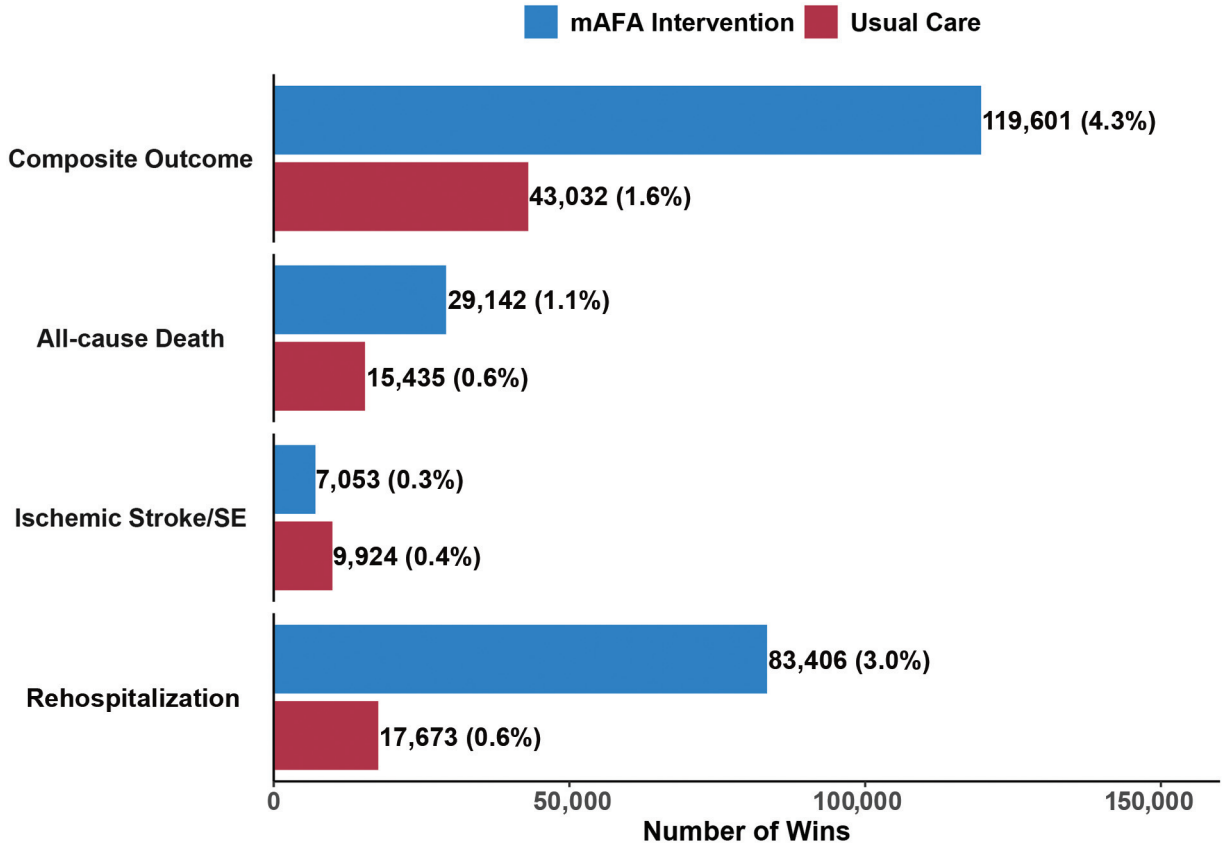

Fig. 1 Number of wins in the mAFA Intervention and usual care group, for the primary composite outcome and the individual component. Figures are per number of comparisons won in each group, percentages are on the total of 2,761,988 unmatched pair comparisons. IS, ischemic stroke; SE, systemic embolism.

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Table 1 Win ratio analysis of the mAFA-II randomized cluster trial

	Number of Events and IR (95% CI) per 100 persons-year				
Outcome	mAFA ($n = 1646$)	Usual Care ($n = 1678$)	1/HR (95%CI)[a]	WR (95%CI)	WO (95%CI)
Composite outcome of death, IS/TE, and rehospitalization	32 (IR: 2.8 [1.9–3.9])	101 (IR: 7.9 [6.4–9.6])	2.56 [1.49–4.55]	2.78 [1.85–4.17]	1.06 [1.04–1.08]
All-cause death[†]	12 (IR: 1.0 [0.5–1.8])	25 (IR: 1.9 [1.2–2.8])			
IS/TE[†]	7 (IR: 0.6 [0.2–1.2])	6 (IR: 0.5 [0.2–1.0])			
Rehospitalization[b]	20 (IR: 1.7 [1.0–2.7])	75 (IR: 5.9 [4.6–7.3])			

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; IS, ischemic stroke; TE, thromboembolism; WO, win odds; WR, win ratio.
[a]As reported in Guo et al, 2020.[7]
[b]Numbers and IR (95%CI) for total number of events occurred during follow-up.

endpoints in a more clinically meaningful way, taking into account their relevance and weight, offers an opportunity to provide more insights on the efficacy of such interventions, thus contributing to better inform physicians' decision-making processes. Among these, the WR method accounts for clinical priorities, is easy to use, and provides meaningful estimates of treatment effects.[3,6]

The findings of our analysis have clinical relevance. Indeed, while the Cox-regression (which was used in the primary analysis of the trial) considers only the first occurring event of the composite outcome, the WR approach presented in our paper prioritizes the most clinically meaningful outcomes, without ignoring those relevant events (such as death and thromboembolism) which may occur after rehospitalization. Importantly, we obtained consistent results with the primary analysis, thus emphasizing how a mHealth-technology-implemented ABC pathway is effective in improving the prognosis of AF patients, even when considering fatal and hard endpoints as the ones with the highest priority (as physicians would do in real-world practice). We also show, similarly to other previous analyses,[5,6,16] that WR is a feasible approach for the hierarchical evaluation of composite outcomes and may be useful to overcome some of the limitations associated with the use of composite endpoints in clinical trials,[1] including the ones related to AF. Indeed, our prioritization of the events (i.e., first all-cause death, then thromboembolic events, and lastly rehospitalization) appears solid and broadly in line with the approach that would be followed in clinical practice. The results of our analysis also show the importance of considering ties, which may contribute to determine the magnitude of WR and may lead to difference between WR and WO[14]; indeed, the incidence of adverse events in the mAFA-II trial was relatively low, thus resulting in a considerable number of ties. Notwithstanding the mitigated effect, a significant beneficial effect of mAFA intervention was found also according to WO.

Our findings add to the current body of evidence that shows how the ABC pathway is effective in reducing the risk of major outcomes, including all-cause death, thus improving the prognosis of AF patients.[17,18] These results are particularly important also considering the current epidemiology of AF patients, and the trends regarding mortality and hospitalization,[19–22] that remain major clinical issues in AF patients. The impact in reducing the risk of hospitalizations using the ABC pathway is particularly interesting given the health care costs related to AF, which are expected to rise significantly in the near future,[22] and add to previous analysis showing the efficacy of mHealth-integrated ABC pathway in improving outcomes in elderly patients,[23] who are at higher risk of adverse outcomes. Hence, the results of our analysis help to contextualize the role of an integrated care approach according to the ABC pathway in the clinical scenario, acknowledging the higher clinical relevance of death and thromboembolism but also considering the potential impact of other, soft endpoints such as rehospitalization in the comprehensive evaluation of the benefit of such integrated care model. The ongoing "Atrial fibrillation integrated approach in frail, multimorbid and polymedicated older people" AFFIRMO program will provide further evidence on the efficacy of the ABC pathway in the context of integrated care, with a specific focus on elderly patients with multimorbidity, also including a comprehensive geriatric assessment.[24]

Strengths and Limitations

This analysis, using a WR approach, provides consistent results compared with the primary analysis[7] and is based on a rational prioritization of the components of the primary endpoint.

Nonetheless, there are several limitations. First, this is a post-hoc analysis, and the results should be interpreted as exploratory and hypothesis generating. Second, we used the unmatched pairs approach to perform this WR analysis; while this approach have been used previously,[5,16] it may lead to the comparisons of patients with different baseline risk profiles, and may be somewhat influenced by "unfair" comparisons.[3] Nonetheless, matching patients according to their risk score can be likewise challenging, especially considering that the risk factors for mortality, thromboembolic events, and rehospitalization in AF patients may be different, and with different influence on these events; in this scenario, the use of the unmatched pairs comparison approach

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appears reasonable. Finally, a significant proportion of comparisons resulted in "ties," as no winner could be declared between mAFA intervention and usual care; this reflects the overall low rates of event (especially regarding deaths and thromboembolic events). Caution has been recommended in the use of WR when the amount of ties is considerable[12]; nonetheless, we calculated and reported also WO, which has been proposed to account for ties.[13,14] As expected, given the number of ties, the WO showed mitigated differences between mAFA intervention and usual care group, although statistically significant. Therefore, further studies are required to analyze whether these results can be confirmed in other cohorts, with different—and specifically higher—risk of clinical outcomes.

Conclusion

A mHealth-technology-implemented-integrated care approach according to the ABC pathway is effective in reducing the risk of the composite outcome of all-cause death, thromboembolism, and rehospitalization, even when prioritizing fatal events. These results support the implementation of the ABC pathway in clinical practice for the management of patients with AF.

What is known about this topic?

- The WR approach has been proposed for the analysis of composite endpoints, to prioritize adverse outcomes according to their clinical relevance.
- In the mAFA-II trial, a mHealth-technology implemented ABC pathway (mAFA intervention) reduced the risk of the composite outcome of all-cause death, ischemic stroke or thromboembolism, and rehospitalization.

What does this paper add?

- In this post-hoc analysis, mAFA intervention was effective in reducing the risk of the primary outcome even when using the WR approach, thus prioritizing mortality over other outcomes.
- Ensuring implementation of the ABC pathway in clinical practice is pivotal to reduce the risk of adverse events, including fatal events, in patients with AF.

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Conflict of Interest
G.F.R. reports consultancy for Boehringer Ingelheim and an educational grant from Anthos, outside the submitted work. No fees are directly received personally. G.Y.H.L. 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. All other authors have nothing to declare. G.Y.H.L. is coprincipal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 899871.

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