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REVIEW

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Integrated care and outcomes in patients with atrial fibrillation and comorbidities

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Abstract

Background: Integrated care for management of atrial fibrillation (AF) patients has been associated with a reduction in adverse events. The 'Atrial fibrillation Better Care (ABC) pathway' has been proposed to streamline such integrated management. In this paper, we analysed the impact of ABC pathway adherent clinical management on outcomes in AF patients with high-risk 'metabolic' comorbidities (i.e. diabetes mellitus [DM], chronic kidney disease [CKD], metabolic syndrome [MetS].

Methods: Patients from the SPORTIF III and V trials and with available data to evaluate ABC criteria were analysed. DM, CKD and MetS were evaluated according to baseline data. A composite of major adverse cardiovascular events and all-cause death was the study outcome.

Results: A total of 3637 patients (median age 72 [IQR 66-77], 30.3% female) were analysed. DM was evident in 23.4%, CKD in 25.8% and MetS in 31.5% among the overall cohort. Respectively, 23.2% were ABC pathway adherent in the DM subgroup, 21.2% in CKD and 23.7% in MetS subgroups. Composite outcome occurred less frequently in patients managed adherent to ABC pathway than those nonadherents, in all three groups. In the final multivariate model, ABC adherent care was inversely associated with a lower risk of composite outcome in the DM (HR 0.45, 95% CI 0.23-0.88), CKD (HR 0.60, 95% CI 0.36-0.98) and MetS (HR 0.37, 95% CI 0.19-0.71) subgroups.

Conclusions: In high-risk AF patients with DM, CKD and MetS, ABC pathway adherent management was associated with a lowered risk of the composite outcome of cardiovascular events, cardiovascular and all-cause death.

KEYWORDS

ABC pathway, atrial fibrillation, integrated care, outcomes

1 | INTRODUCTION

Comprehensive evaluation and management of patients with atrial fibrillation (AF) has been proposed to improve clinical outcomes and is now recommended in guidelines.[1,2] The use of a more integrated model of care is needed to mitigate the risk of adverse outcomes, particularly those of cardiovascular and noncardiovascular death, which remains significant despite the increasing use of oral anticoagulant (OAC) therapy for reducing stroke and thromboembolism.[3,4]

As a simple approach to integrated care, the 'Atrial fibrillation Better Care (ABC) pathway' has been proposed to streamline the implementation of holistic care for AF patients.[5] This pathway refers to three main pillars: **'A' A**void stroke (with **A**nticoagulants); **'B' B**etter symptom management, with patient-centred decisions on rate or rhythm control; **'C' C**ardiovascular and **C**omorbidity risk optimization.[5] The ABC pathway is now recommended in several clinical guidelines.[1,6,7]

Several post hoc analyses in various studies showed that the use of clinical care compliant to the ABC pathway criteria was associated with a reduction in risk of adverse outcomes.[8-12] In a recent cluster randomized trial, a mobile health-based ABC pathway management strategy significantly reduced the risk of the composite outcome of major clinical events.[13] Considering that AF patients with specific 'metabolic' comorbidities (i.e. diabetes mellitus, chronic kidney disease and metabolic syndrome) have a particularly higher risk of major adverse outcomes,[14-16] we explored if an ABC pathway compliant clinical approach would be associated with a lower risk of clinical outcomes in these three high-risk patient subgroups.

2 | METHODS

For the present analysis, we used the pooled study populations of the 'Stroke Prevention using an Oral Thrombin Inhibitor in patients with atrial Fibrillation' (SPORTIF) III and V trials, which tested a direct thrombin inhibitor, ximelagatran, compared to warfarin in nonvalvular AF. The original protocol and principal results have been previously described.[17-19] SPORTIF III was an open-label study, while SPORTIF V was a double-blind trial, and both trial protocols have been previously published.[17] Signed, informed consent was required from each participant of the trial in accordance with protocol regulations approved by the local review boards governing research involving human subjects, and the Declaration of Helsinki. In order of ensuring a good representation of the cohort considered, we included in the analysis only those patients assigned to the warfarin arms of the two studies. Reporting of the study conforms to broad EQUATOR guidelines.

2.1 | Definition of comorbidities

We focused on 3 major 'metabolic' comorbidities: (a) diabetes mellitus; (b) chronic kidney disease (CKD); (c) metabolic syndrome (MetS). History of diabetes mellitus was collected at baseline during the clinical interview performed by any investigator at each site and inserted into the case report form (CRF) of the study. The presence of CKD was established according to the estimated glomerular filtration rate (eGFR), calculated from the serum creatinine as measured at baseline blood sample with the Cockroft-Gault equation. An eGFR < 60 mL/min qualified for the presence of CKD.

MetS was defined according to the presence of three out of five of the following criteria[20]: (a) presence of obesity; (b) baseline serum triglycerides $\geq$1.7 mmol/L; (c) baseline serum high-density cholesterol $<$1 mmol/L for males and $<$1.3 mmol/L for females; (d) baseline sitting blood pressure $\geq$130/85 mm Hg or history of hypertension as recorded at baseline in the CRF; (e) baseline fasting plasma glucose $\geq$6.1 mmol/L.

2.2 | ABC-compliance evaluation

The ABC pathway has been described elsewhere in detail.[5] In the current database, the three main pillars of ABC pathway have been defined as follows: (a) A Criterion: adherence to this criterion was considered as optimal anticoagulation control, with a time in therapeutic range $\geq$70%; (b) B Criterion: since we did not have available a systematic evaluation of symptomatic status, we used the baseline evaluation of the modified Rankin Scale (mRS) to evaluate the adherence to an optimal symptoms control. In this study, the mRS was used to quantify the baseline level of disability due to significant symptoms related to AF. We defined 'optimal symptom control' for all those patients with mRS equal to 0 ('No symptoms at all') at the baseline evaluation; (c) C Criterion: To evaluate the adherence to the 'C' criterion, we considered the most frequent comorbidities associated with AF: hypertension; coronary artery disease; peripheral artery disease; heart failure; stroke/transient ischaemic attack. A patient qualified for the 'C' criterion when affected with $\geq$1 of these conditions and prescribed/treated according to the best medical treatment. For hypertension, we considered controlled blood pressure if $\leq$140/90 mm Hg was recorded at baseline; for coronary artery disease, treatment with angiotensin converting enzyme

(ACE) inhibitors, beta-blockers and statins; for peripheral artery disease, treatment with statins; for previous stroke/transient ischaemic attack, treatment with statins; for heart failure, we considered treatment with ACE inhibitors/angiotensin receptor blockers, beta-blockers and diuretics. In the case of clinical history for ≥1 condition considered; the patient needed to be properly treated for all the conditions to qualify for the 'C' criterion.

2.3 | Study outcomes

The primary outcome of the study was the composite of adjudicated major adverse cardiovascular events (MACE) (i.e. stroke, systemic thromboembolism, acute coronary syndrome and cardiovascular death) and all-cause death. Deaths were categorized as cardiovascular (stroke, systemic embolism, myocardial infarction, or bleeding related) or noncardiovascular of specified cause and unknown reason. All-cause death was related to the death incident as reported by any investigator. All components of the composite outcome were centrally adjudicated and underpinned by the original study protocol.[17]

2.4 | Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR) and compared according to Mann-Whitney *U* test. Categorical variables were expressed as counts and percentages and analysed by chi-square test. Differences in cumulative risk for outcomes between patients treated as adherent and nonadherent to the ABC pathway management were evaluated with log-rank test and plotted with Kaplan-Meier curves.

A Cox regression model, both as univariate and multivariable, was drafted to establish the relationship between compliance to the ABC pathway and risk of outcomes. Two different multivariable models were compiled. Model 1 was adjusted for CHA_2DS_2-VASc score and concomitant use of aspirin, while Model 2 was adjusted for the total number of concomitant comorbidities and the total number of concomitant drugs taken by the patient. CHA_2DS_2-VASc score was computed according to the original model as described by Lip et al,[21] while use of aspirin was evaluated at baseline visit, during the assessment of patient's pharmacological therapy as part of the original studies case report form (CRF).[17] Similarly, number of concomitant comorbidities and total number of concomitant drugs was derived from the information originally collected by study investigators during baseline visit and reported in the studies CRF.[17] Concomitant conditions were evaluated according to the International Classification of Disease 9th Revision–Clinical Modification (ICD-9-CM), while concomitant medications were evaluated according to Anatomical Therapeutic Chemical (ATC) classification. All the main analysis Cox models were tested for proportionality of hazards assumption on the basis of the Schoenfeld residuals test. To better substantiate the results, we performed two additional sensitivity analyses. In the first sensitivity analysis, we examined the association between the number of ABC criteria fulfilled and the risk of the composite outcome. In the second sensitivity analysis, we elaborated a propensity score on the basis of the variables reported at baseline (Table 1). In order not to report a significant loss in sample size and number of events, we have not performed a 1:1 match, but we adjusted the main Cox models for the propensity score obtained.

A two-sided P value <.05 was considered to be statistically significant. All analyses were performed using SPSS v. 25.0 (IBM, NY, USA).

3 | RESULTS

Among the original 3665 patients included in the warfarin arms of SPORTIF III and V trials, 3637 (99.2%) had available data to evaluate ABC pathway compliance and data about comorbidities. Among these, 853 (23.4%) had a history of diabetes mellitus, 940 (25.8%) had CKD, and 1145 (31.5%) had criteria for the presence of MetS. Baseline characteristics are reported in Table 1. Patients with CKD were older than those in the other subgroups, with a higher prevalence of female patients. Conversely, patients with diabetes mellitus had more comorbidities and were treated with a higher number of concomitant drugs. Both CHA_2DS_2-VASc and HAS-BLED scores were higher in the CKD cohort. In the overall cohort, 961 (26.4%) were managed as compliant with the ABC pathway. At baseline (Table S1), patients managed compliant to ABC were younger, less likely female, more affected with coronary artery disease and congestive heart failure, but less affected with most of the other clinical conditions reported (Table S1) than those noncompliant to ABC. Notwithstanding, the overall number of comorbidities was similar among the two groups, with more concomitant drugs in ABC noncompliant, which also showed slightly higher CHA_2DS_2-VASc and HAS-BLED scores (Table S1).

Furthermore, 198 patients (23.2%) in the diabetes mellitus cohort were compliant with the ABC pathway, with 199 (21.2%) in the CKD cohort and 271 (23.7%) in the MetS cohort (Table 1).

During follow-up, patients managed according to the ABC pathway had a lower rate of the composite outcome (5.5% vs 9.3%; $P < .001$) overall, compared to those nonABC compliant. Those managed adherent to the ABC pathway reported a lower rate of the composite outcome in the diabetes mellitus (5.1% vs 11.1%; $P = .011$), CKD (9.0% vs 14.8%; $P = .034$) and MetS (3.7% vs 9.3%; $P = .003$) subgroups.

TABLE 1 Baseline characteristics

	Overall N = 3637	Diabetes Mellitus N = 853	CKD N = 940	MetS N = 1145
Age, *years* median [IQR]	72 [66-77]	71 [65-76]	78 [74-82]	70 [63-75]
Female Sex, n (%)	1102 (30.3)	242 (28.4)	447 (47.6)	373 (32.6)
Hypertension, n (%)	2788 (76.7)	712 (83.5)	706 (75.1)	975 (85.2)
Coronary Artery Disease, n (%)	1610 (44.3)	446 (52.3)	445 (47.3)	501 (43.8)
Peripheral Artery Disease, n (%)	107 (2.9)	43 (5.0)	33 (3.5)	43 (3.8)
Previous Stroke/ TIA, n (%)	749 (20.6)	179 (21.0)	261 (27.8)	205 (17.9)
Congestive Heart Failure, n (%)	1362 (37.4)	368 (43.1)	375 (39.9)	456 (39.8)
Previous Bleeding, n (%)	206 (5.7)	53 (6.2)	54 (5.7)	58 (5.1)
Aspirin Use, n (%)	721 (19.8)	188 (22.0)	202 (21.5)	215 (18.8)
Comorbidities, N median [IQR]	5 [3-7]	6 [4-9]	5 [3-8]	5 [3-8]
Drugs, N median [IQR]	10 [7-15]	13 [9-18]	11 [7-16]	11 [8-16]
CHA_2DS_2-VASc, median [IQR]	3 [2-4]	3 [2-4]	4 [3-5]	3 [2-4]
HAS-BLED, median [IQR]	3 [2-4]	3 [2-4]	4 [4-5]	3 [2-4]
ABC Compliant, n (%)	961 (26.4)	198 (23.2)	199 (21.2)	271 (23.7)

Abbreviations: ABC, Atrial Fibrillation Better Care; CKD, Chronic Kidney Disease; IQR, Interquartile Range; MetS, Metabolic Syndrome; TIA, Transient Ischaemic Attack.

Kaplan-Meier curves demonstrate that the cumulative incidence of the composite outcome was significantly lower for patients managed compliant with the ABC pathway compared to those noncompliant for the overall cohort as well as for the three high-risk subgroups (Figure 1).

In the Cox regression analysis (Table 2), univariate analysis demonstrated that ABC pathway compliance was associated with lower risk of the composite clinical outcome in both the overall cohort and all the three subgroups. In both multivariable Model 1 and Model 2 Cox regression analyses, compliance with the ABC pathway was independently associated with a lower risk of composite clinical outcome in all the four groups, with patients with MetS showing the larger risk reduction with both models.

All Cox models were tested for proportionality of hazards assumption, which was always met, except in the case of the overall cohort for Model 2, which showed the assumption not met in the original analysis (chi-square: 8.36, $P = .0392$). In that case, we converted the number of concomitant comorbidities and drugs with multimorbidity (concomitant comorbidities ≥ 2) and polypharmacy (concomitant drugs ≥ 5) in the model. This new model showed similar results (Table 2), compared to the previous one, repristinating the assumption of proportionality of hazards (chi-square: 4.11, $P = .2499$).

3.1 | Sensitivity analyses

In the first sensitivity analysis, a progressive stronger inverse association with risk of composite outcome was found according to the increasing number of ABC pathway criteria fulfilled, in the overall cohort with both multivariable Model 1 and Model 2 (Figure 2, Upper and Lower Panel).

Similarly, a progressively stronger risk reduction according to the increasing number of ABC pathway criteria fulfilled was found in the CKD subgroup, while in the diabetes mellitus and MetS subgroups, only full ABC pathway compliance was significantly associated with a lowered risk of the composite outcome.

In the second sensitivity analysis, performing the Cox multivariable models by adjusting for the propensity score obtained, we did not find any substantial changes to the main results, except for a slight mitigation of the association

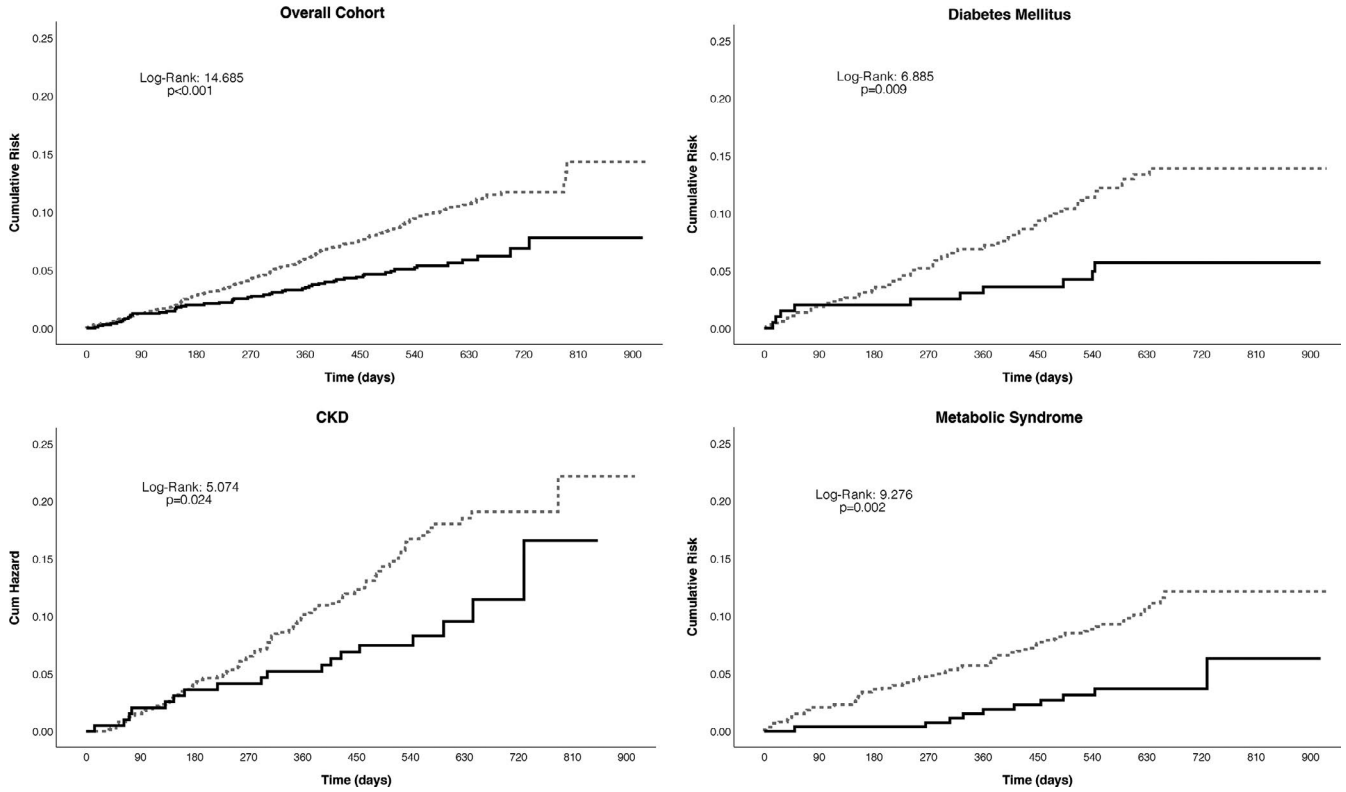

FIGURE 1 Kaplan-Meier curves for composite outcome. Black Solid Line = ABC Compliant; Grey Dotted Line = ABC Noncompliant; ABC = Atrial Fibrillation Better Care; CKD = Chronic Kidney Disease

between ABC compliant care and the occurrence of the composite outcome in the CKD subgroup (Table S2).

4 | DISCUSSION

In this post hoc analysis derived from a large randomized clinical trial cohort of anticoagulated AF patients, ABC pathway compliant clinical management was associated with a reduced risk of the composite outcome of MACE and all-cause death in the overall cohort, with a similar or even larger effect found in high-risk patients with diabetes mellitus, CKD and MetS. Second, increasing the number of ABC pathway criteria fulfilled was progressively associated with greater reduction of the composite outcome both in the overall cohort and diabetes mellitus subgroups. The overall good validity of the models performed, and the sensitivity analysis adjusted for the propensity score, further corroborated our main results.

AF patients presenting with concomitant diabetes mellitus, CKD and MetS have an increased risk of adverse outcomes compared to those without those conditions.[14-16,22,23] Diabetes mellitus and CKD are well-recognized to be associated with an increased risk for both thromboembolic and nonthromboembolic events (cardiovascular events, cardiovascular death and all-cause death).[14,15,22,23] Also, MetS has a major impact on cardiovascular events and death, increasing these around 2-fold compared to patients

TABLE 2 Cox regression analysis for outcomes

	ABC Compliant vs ABC Noncompliant	
	Composite Outcome	
	HR [95% CI]	*P*
Univariate		
Overall	0.56 [0.42-0.76]	<.001
Diabetes Mellitus	0.42 [0.22-0.82]	.011
CKD	0.57 [0.35-0.94]	.026
MetS	0.37 [0.19-0.72]	.003
Multivariable Mod. 1[a]		
Overall	0.61 [0.45-0.83]	.001
Diabetes Mellitus	0.46 [0.24-0.90]	.024
CKD	0.56 [0.34-0.93]	.025
MetS	0.40 [0.20-0.77]	.006
Multivariable Mod. 2[b]		
Overall	0.57 [0.42-0.77][c]	<.001
Diabetes Mellitus	0.45 [0.23-0.88]	.019
CKD	0.60 [0.36-0.98]	.043
MetS	0.37 [0.19-0.71]	.003

Abbreviations: ABC, Atrial Fibrillation Better Care; CI, Confidence Interval; CKD, Chronic Kidney Disease; HR, Hazard Ratio; MetS, Metabolic Syndrome.

[a]Adjusted for CHA_2DS_2-VASc and concomitant aspirin use;

[b]Adjusted for number of concomitant comorbidities and number of concomitant drugs;

[c]Adjusted for presence of multimorbidity and polypharmacy.

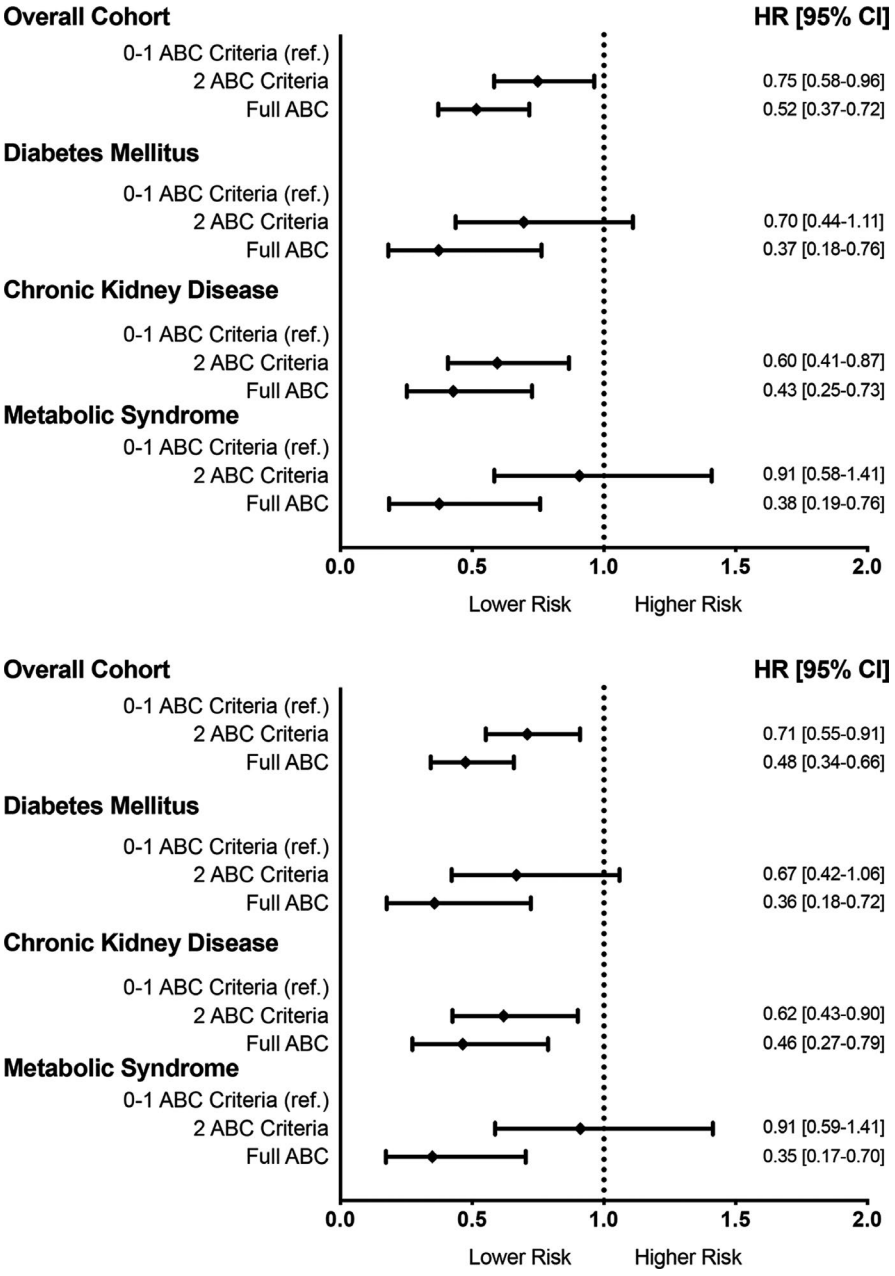

FIGURE 2 Sensitivity Analysis on ABC criteria for composite outcome. ABC = Atrial Fibrillation Better Care; CI = Confidence Interval; HR = Hazard Ratio

without this condition.[16] Moreover, patients with diabetes mellitus and CKD also have an increased risk for major bleeding events.[6] This underlines how such high-risk patients should be managed in a integrated and comprehensive manner, beyond OAC prescription and rate/rhythm control management.

While the management of thromboembolic risk by using OAC reduces the risk of thromboembolic events in AF patients,[4] there remains a major risk of cardiovascular events, cardiovascular death and all-cause death.[3,24,25] Despite the progressive worldwide uptake of OAC, the age-standardized incidence of death in AF patients has remained steady over the last 30 years.[26] Hence, the need for a more integrated holistic approach to optimize the clinical management of AF patients has been strongly advocated.[2,27]

The 'Atrial fibrillation Better Care' (ABC) pathway has been proposed to streamline the integrated management of AF patients, as follows: **'A' A**void stroke; **'B' B**etter symptom management; **'C' C**ardiovascular and **C**omorbidity risk optimization.[5] Since its proposal, the ABC pathway has been evaluated in observational retrospective studies[8-10,28,29] and one randomized controlled trial.[13] Also, ABC pathway adherent care was associated with a reduced risk of adverse events even in clinically complex AF patients (those with multimorbidity, polypharmacy and hospitalized ones),[11] as well as in those AF patients found to be frail.[30] All the observational studies consistently reported an association with a significant reduction in the risk of cardiovascular events and all-cause death, ranging from 10% to 60% per cent reduction in risk according to the various cohorts studied, together with a reduction in the

risk of hospitalization.[8-11,28-30] In a contemporary European-wide AF cohort, clinical management adherent to the ABC pathway was associated with a 40% to 50% reduction in the major clinical outcomes.[28] In the recent mAFA randomized clinical trial, ABC pathway use resulted in a 60% reduction in the composite outcome of thromboembolic events/rehospitalization/all-cause death over a 1 year follow-up.[13]

Our paper provides more evidence for the integrated management of AF patients as streamlined by the ABC pathway, in patients with high risk for adverse clinical outcomes, that is those with diabetes mellitus, CKD and MetS, ranging from 40% in the CKD cohort up to 60% in the MetS group. These results underline how the implementation of an integrated holistic approach is needed, especially in those with a higher risk of adverse events such as those examined in our paper. These represent a large proportion of AF patients, since all these conditions were highly prevalent, as reported in our paper. Also, we confirm and extend previous observations regarding the association of ABC pathway adherent care and a reduced risk of adverse events in patients with diabetes from a Middle East cohort of AF patients.[31] Of note, our results are derived from a large global well-conducted randomized controlled trial, with protocol-defined centrally adjudicated outcomes. We show that in the overall trial population, ABC pathway adherent care was associated with a 40% reduction in risk, over and above the high standard of usual care generally seen in randomized trial settings.

4.1 | Limitations

There are some limitations to this study. As this study was a post hoc ancillary analysis of a controlled clinical trial, the population might not reflect a contemporary real-world AF population. Since this analysis was not prespecified, it may be a limited statistical power to detect differences in the subgroups identified. Due to the fact that the trial was conducted between 2000 and 2002, the treatment regimens and clinical practice have changed over the time, which might have influenced the general results. Nonetheless, we analysed a large cohort of AF patients with a high level of data quality and with centrally adjudicated events. This work should be considered as a 'proof of concept', to be confirmed in more contemporary cohorts, and with properly designed and powered studies to investigate these high-risk subgroups.

5 | CONCLUSIONS

In high-risk AF patients with DM, CKD and MetS, ABC pathway adherent management was associated with a lowered risk of the composite outcome of cardiovascular events, cardiovascular and all-cause death.

CONFLICT OF INTEREST

MP has served as consultant for Boehringer Ingelheim. **GYHL** has served as consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Microlife and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Microlife, Roche and Daiichi-Sankyo. No fees are received personally. Other authors have no disclosures to declare.

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REFERENCES

1. Hindricks G, Potpara T, Dagres N, 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*. 2020. https://doi.org/10.1093/eurheartj/ehaa612
2. Kotecha D, Breithardt G, Camm AJ, et al. Integrating new approaches to atrial fibrillation management: the 6th AFNET/EHRA Consensus Conference. *Europace*. 2018;20(3):395-407. https://doi.org/10.1093/europace/eux318
3. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ*. 2016;354:i4482. https://doi.org/10.1136/bmj.i4482
4. Cowan JC, Wu J, Hall M, Orlowski A, West RM, Gale CP. A 10 year study of hospitalized atrial fibrillation-related stroke in England and its association with uptake of oral anticoagulation. *Eur Heart J*. 2018;39(32):2975-2983. https://doi.org/10.1093/eurheartj/ehy411
5. Lip GYH. The ABC pathway: an integrated approach to improve AF management. *Nat Rev Cardiol*. 2017;14(11):627-628. https://doi.org/10.1038/nrcardio.2017.153
6. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST guideline and expert panel report. *Chest*. 2018;154(5):1121-1201. https://doi.org/10.1016/j.chest.2018.07.040
7. Joung B, Lee JM, Lee KH, et al. 2018 Korean guideline of atrial fibrillation management. *Korean Circ J*. 2018;48(12):1033-1080. https://doi.org/10.4070/kcj.2018.0339
8. Proietti M, Romiti GF, Olshansky B, Lane DA, Lip GYH. Improved outcomes by integrated care of anticoagulated patients with atrial fibrillation using the simple ABC (Atrial Fibrillation Better Care) pathway. *Am J Med*. 2018;131(11):1359-1366.e6. https://doi.org/10.1016/j.amjmed.2018.06.012
9. Pastori D, Pignatelli P, Menichelli D, Violi F, Lip GYH. Integrated Care management of patients with atrial fibrillation and risk of cardiovascular events. *Mayo Clin Proc*. 2019;94(7):1261-1267. https://doi.org/10.1016/j.mayocp.2018.10.022
10. Yoon M, Yang P-S, Jang E, et al. Improved population-based clinical outcomes of patients with atrial fibrillation by compliance with the simple ABC (Atrial Fibrillation Better Care) pathway for integrated care management: a nationwide cohort study. *Thromb Haemost*. 2019;119(10):1695-1703. https://doi.org/10.1055/s-0039-1693516
11. Proietti M, Romiti GF, Olshansky B, Lane DA, Lip GYH. Comprehensive management with the ABC (Atrial Fibrillation Better Care) pathway in clinically complex patients with atrial

fibrillation: a post hoc ancillary analysis from the AFFIRM trial. *J Am Heart Assoc*. 2020;9(10):e014932. https://doi.org/10.1161/JAHA.119.014932
12. Yang P-S, Sung J-H, Jang E, et al. The effect of integrated care management on dementia in atrial fibrillation. *J Clin Med*. 2020;9(6):1696. https://doi.org/10.3390/jcm9061696
13. Guo Y, Lane DA, Wang L, et al. Mobile health technology to improve care for patients with atrial fibrillation. *J Am Coll Cardiol*. 2020;75(13):1523-1534. https://doi.org/10.1016/j.jacc.2020.01.052
14. Echouffo-Tcheugui JB, Shrader P, Thomas L, et al. Care patterns and outcomes in atrial fibrillation patients with and without diabetes: ORBIT-AF registry. *J Am Coll Cardiol*. 2017;70(11):1325-1335. https://doi.org/10.1016/j.jacc.2017.07.755
15. Proietti M, Lane DA, Lip GY. Chronic kidney disease, time in therapeutic range and adverse clinical outcomes in anticoagulated patients with non-valvular atrial fibrillation: observations from the SPORTIF trials. *EBioMedicine*. 2016;8:309-316. https://doi.org/10.1016/j.ebiom.2016.04.013
16. Polovina M, Hindricks G, Maggioni A, et al. Association of metabolic syndrome with non-thromboembolic adverse cardiac outcomes in patients with atrial fibrillation. *Eur Heart J*. 2018;39(45):4030-4039. https://doi.org/10.1093/eurheartj/ehy446
17. Halperin JL. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: Rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). *Am Heart J*. 2003;146(3):431-438. https://doi.org/10.1016/S0002-8703(03)00325-9
18. Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with nonvalvular atrial fibrillation (SPORTIF III): randomised controlled trial. *Lancet*. 2003;362(9397):1691-1698. http://www.ncbi.nlm.nih.gov/pubmed/14643116. Accessed April 20, 2015
19. Albers GW, Diener H-C, Frison L, et al. Ximelagatran vs warfarin for stroke prevention in patients with nonvalvular atrial fibrillation: a randomized trial. *JAMA*. 2005;293(6):690-698. https://doi.org/10.1001/jama.293.6.690
20. Cleeman JI. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *J Am Med Assoc*. 2001;285(19):2486-2497. https://doi.org/10.1001/jama.285.19.2486
21. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-272. https://doi.org/10.1378/chest.09-1584
22. Wang A, Green JB, Halperin JL, Piccini JP. Atrial fibrillation and diabetes mellitus: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74(8):1107-1115. https://doi.org/10.1016/j.jacc.2019.07.020
23. Lau YC, Proietti M, Guiducci E, Blann AD, Lip GYH. Atrial fibrillation and thromboembolism in patients with chronic kidney disease. *J Am Coll Cardiol*. 2016;68(13):1452-1464. https://doi.org/10.1016/j.jacc.2016.06.057
24. Proietti M, Laroche C, Nieuwlaat R, et al. Increased burden of comorbidities and risk of cardiovascular death in atrial fibrillation patients in Europe over ten years: a comparison between EORP-AF pilot and EHS-AF registries. *Eur J Intern Med*. 2018;55:28-34. https://doi.org/10.1016/j.ejim.2018.05.016
25. Fauchier L, Villejoubert O, Clementy N, et al. Causes of death and influencing factors in patients with atrial fibrillation. *Am J Med*. 2016;129(12):1278-1287. https://doi.org/10.1016/j.amjmed.2016.06.045
26. Dai H, Zhang Q, Much AA, 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*. Epub ahead of print. 2020. https://doi.org/10.1093/ehjqcco/qcaa061
27. Kirchhof P. The future of atrial fibrillation management: integrated care and stratified therapy. *Lancet*. 2017;390(10105):1873-1887. https://doi.org/10.1016/S0140-6736(17)31072-3
28. Proietti M, Lip GYH, Laroche C, et al. Relation of outcomes to ABC (Atrial Fibrillation Better Care) pathway adherent care in European patients with atrial fibrillation: an analysis from the ESC-EHRA EORP Atrial Fibrillation General Long-Term (AFGen LT) Registry. *Europace*. Epub ahead of print. 2020. https://doi.org/10.1093/europace/euaa274
29. Gumprecht J, Domek M, Proietti M, et al. Compliance of atrial fibrillation treatment with the atrial fibrillation better care (ABC) pathway improves the clinical outcomes in the middle east population: a report from the gulf survey of atrial fibrillation events (SAFE) registry. *J Clin Med*. 2020;9(5):1286. https://doi.org/10.3390/jcm9051286
30. Yang PS, Sung JH, Jang E, et al. Application of the simple atrial fibrillation better care pathway for integrated care management in frail patients with atrial fibrillation: a nationwide cohort study. *J Arrhythmia*. 2020;36(4):668-677. https://doi.org/10.1002/joa3.12364
31. Domek M, Gumprecht J, Li Y-G, et al. Compliance of atrial fibrillation treatment with the ABC pathway in patients with concomitant diabetes mellitus in the Middle East based on the Gulf SAFE registry. *Eur J Clin Invest*. Epub ahead of print. 2020:e13385. https://doi.org/10.1111/eci.13385

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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