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Impact of ABC (Atrial Fibrillation Better Care) Pathway Adherence in High-Risk Subgroups with Atrial Fibrillation: A report from the ESC-EHRA EORP-AF Long-Term General Registry

--Manuscript Draft--

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Abstract:	Background:Effects of Atrial Fibrillation Better Care(ABC) adherence among high-risk atrial fibrillation(AF) subgroups remains unknown. We aimed to evaluate the impact of ABC adherence on clinical outcomes in these high-risk patients. Methods:EORP-AF General Long-Term Registry is a prospective, observational registry from 250 centres across 27 European countries. High-risk patients were defined as those with either CKD(eGFR <60 mL/min/1.73m2), elderly patients(≥75 years) or prior thromboembolism. Primary outcome was a composite event of all-cause death, thromboembolism and acute coronary syndrome. Results:6646 patients with AF were screened (median age was 70[IQR 61-77] years; 40.2% females). There were 3304(54.2%) patients with either CKD(n=1750), older age(n=2236) or prior thromboembolism(n=728). Among these, 924(28.0%) were managed as adherent to ABC. At 2-year follow-up, 966(14.5%) patients reported the primary outcome. The incidence of the primary outcome was significantly lower in high-risk patients managed as adherent to ABC pathway(IRR 0.53[95%CI,0.43-0.64]). Consistent results were obtained in the individual subgroups. Using multivariable Cox proportional hazards analysis, ABC adherence in the high-risk cohort was independently associated with a lower risk of the primary outcome(aHR 0.64[95%CI,0.51-0.80]), as well as in the CKD(aHR 0.51[95%CI,0.37-0.70]) and elderly subgroups(aHR 0.69[95%CI,0.53-0.90]). Overall, there was greater reduction in the risk of primary outcome as more ABC criteria were fulfilled, both in the overall high-risk patients(aHR 0.39[95%CI,0.25-0.61]), as well as in the individual subgroups. Conclusion:In a large, contemporary cohort of patients with AF, we demonstrate that adherence to the ABC pathway was associated with a significant benefit among high-risk patients with either CKD, advanced age(≥75 years old) or prior thromboembolism

6 West Derby Street
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31st October 2022

Dear Professor G. Agnelli (Editor-in-Chief),

Re: Impact of ABC (Atrial Fibrillation Better Care) Pathway Adherence in High-Risk Subgroups with Atrial Fibrillation: A report from the ESC-EHRA EORP-AF Long-Term General Registry

We would be grateful if you would consider the enclosed revised manuscript for publication in *European Journal of Internal Medicine.* We thank the editors and reviewer for the helpful comments which we have used to improve our article. Please also see attached a PBP response to each of these comments.

We confirm that: 1) the paper is not under consideration elsewhere; 2) none of the paper's contents have been previously published; 3) all authors have read and approved the manuscript; 4) the full disclosure of any relationship with industry or that no such relationship exists, is stated; and 5) the study received the proper ethical oversight.

Yours faithfully,

Professor Gregory YH Lip
Corresponding author

RESPONSE TO EDITORAND REVIEWERS (EJINME-D-22-01358R2)

Thank you very much for your careful evaluation of our article. Please find point-by-point responses to your comments below:

Editor

1. **Please check carefully the correctness of the affiliation of the authors with particular reference to Dr. Proietti.**

Response: Thank you. We have reviewed and updated the affiliations.

Changes:

Wern Yew Ding[1*]; Marco Proietti[1,2,3*]; Giulio Francesco Romiti[1,4]; Marco Vitolo[1,5,6]; Ameenathul Mazaya Fawzy[1]; Giuseppe Boriani[5]; Francisco Marin[7]; Carina Blomström-Lundqvist[8,9]; Tatjana S. Potpara[10,11]; Laurent Fauchier[12]; Gregory Y. H. Lip[1,13];
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Impact of ABC (Atrial Fibrillation Better Care) Pathway Adherence in High-Risk Subgroups with Atrial Fibrillation: A report from the ESC-EHRA EORP-AF Long-Term General Registry

Short title: ABC pathway in high-risk subgroups with AF

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Disclosures
GB: small speaker's fees from Medtronic, Boston, Biotronik, Boehringer, and Bayer, outside of the submitted work. FM: receiving grants from Ferrer, and personal fees from Bayer,

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Pfizer/BMS. Boehringer-Ingelheim and Astra-Zeneca outside the submitted work. CBL: receiving grants from Medtronic, Cardiome, and personal fees from Bayer, Sanofi, Boston Scientific, and Merck Sharp & Dohme outside the submitted work. TSP: Consultant for Bayer and Pfizer, no fees. LF: consultant or speaker fees of small amounts for Bayer, BMS/Pfizer, Boehringer Ingelheim, Medtronic and Novartis outside of this work. GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. Other authors declare no conflict of interest.

Data availability statement: The data underlying this article will be shared on reasonable request to the corresponding author.

Abstract

Background:Effects of Atrial Fibrillation Better Care(ABC) adherence among high-risk atrial fibrillation(AF) subgroups remains unknown. We aimed to evaluate the impact of ABC adherence on clinical outcomes in these high-risk patients.

Methods:EORP-AF General Long-Term Registry is a prospective, observational registry from 250 centres across 27 European countries. High-risk patients were defined as those with either CKD(eGFR <60 mL/min/1.73m^2), elderly patients(≥75 years) or prior thromboembolism. Primary outcome was a composite event of all-cause death, thromboembolism and acute coronary syndrome.

Results:6646 patients with AF were screened (median age was 70[IQR 61-77] years; 40.2% females). There were 3304(54.2%) patients with either CKD(n=1750), older age(n=2236) or prior thromboembolism(n=728). Among these, 924(28.0%) were managed as adherent to ABC.

At 2-year follow-up, 966(14.5%) patients reported the primary outcome. The incidence of the primary outcome was significantly lower in high-risk patients managed as adherent to ABC pathway(IRR 0.53[95%CI,0.43-0.64]). Consistent results were obtained in the individual subgroups. Using multivariable Cox proportional hazards analysis, ABC adherence in the high-risk cohort was independently associated with a lower risk of the primary outcome(aHR 0.64[95%CI,0.51-0.80]), as well as in the CKD(aHR 0.51[95%CI,0.37-0.70]) and elderly subgroups(aHR 0.69[95%CI,0.53-0.90]). Overall, there was greater reduction in the risk of primary outcome as more ABC criteria were fulfilled, both in the overall high-risk patients(aHR 0.39[95%CI,0.25-0.61]), as well as in the individual subgroups.

Conclusion:In a large, contemporary cohort of patients with AF, we demonstrate that adherence to the ABC pathway was associated with a significant benefit among high-risk patients with either CKD, advanced age(≥75 years old) or prior thromboembolism.

Keywords: chronic kidney disease; elderly; thromboembolism; registry; holistic; integrated.

Introduction

Atrial fibrillation (AF) is a significant public health issue with a global prevalence of 33.5 million patients affected by the condition and approximately 5 million new cases identified each year (1). The number of patients with AF are increasing, with projections of a surge in incidence and prevalence by 63% and 66%, respectively, over the next 30 years (2). The significance of AF is characterised by major contribution to excess morbidity and mortality (3–5), as well as increasing healthcare cost (6).

Because of the increasing number of AF patients with co-existing conditions, there has been a move towards better characterisation and evaluation (7), and a more holistic or integrated care approach to AF patient care (8). Such an approach has been associated with improved clinical outcomes (9–11), and recommended in clinical guidelines (12,13). A previous study using the EURObservational Research Programme Atrial Fibrillation (EORP-AF) Long-Term General Registry demonstrated that patients managed adherent to the ABC pathway had lower rates of composite events of thromboembolism, acute coronary syndrome or cardiovascular death, cardiovascular death and all-cause death (14).

However, most studies have evaluated the ABC pathway in the general AF population. Hence, the effects of ABC adherence among specific high-risk subgroups with AF in whom it may be argued that an integrated care approach is crucial remain unknown. In this study, we aimed to evaluate the impact of ABC adherence on high-risk subgroups of patients with AF from the ESC-EHRA EORP-AF General Long-Term Registry.

Methods

Study design and population

The ESC-EHRA EORP-AF General Long-Term Registry is a prospective, observational, large multicentre registry from 250 centres in 27 participating European countries. The study design has previously been described (15). Briefly, adults with recently diagnosed AF (within 12 months) who presented to cardiology services at participating centres between October 2013 and September 2016 were enrolled. For the purposes of this analysis, patients with available data to evaluate the ABC pathway and a minimum of 1 year follow-up were included. High-risk patients were defined as patients with either chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2), elderly patients (≥75 years) or those with prior thromboembolism. Also, the single subgroups were considered separately. Event exposure was determined based on adherence to the ABC pathway. Institutional review board approval of the study protocol was obtained for every institution, and the study was performed in accordance with the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and Declaration of Helsinki.

Data collection and definitions

Data on demographics, comorbidities and medication use were collected at baseline with prospectively designed data collection tools. eGFR was assessed using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation (16). AF classification was determined according to the European Society of Cardiology recommendations (17). Severity of AF-related symptoms was ascertained with the European Heart Rhythm Association (EHRA) classification (18). CHA_2DS_2-VASc score was calculated as described (19).

Adherence to the ABC pathway was defined as per our previously published study (14) and was evaluated at baseline. The ABC pathway has been proposed to streamline integrated care in AF patients based on the following pillars: i) Avoid stroke with Anticoagulation; ii) Better symptom management, with patient-centred symptom-directed decisions on rate or rhythm control; iii) Cardiovascular comorbidities and risk factors optimisation (including changes in lifestyle). A patient was considered as ABC pathway compliant if all the 3 criteria were fulfilled, otherwise the patient was considered as being managed with an ABC non-compliant care.

Study outcomes

Study outcomes were considered at 2-year follow-up. The primary outcome of interest was a composite event of all-cause death, thromboembolism and acute coronary syndrome. Secondary outcomes of interest were all-cause death, major adverse cardiovascular events (MACEs) and major bleeding as single outcomes. MACEs were defined as any thromboembolism, acute coronary syndrome or cardiovascular death. Thromboembolism was defined as stroke, transient ischaemic attack, and any peripheral embolism. During follow-up, all incident MACEs were recorded on a centralised electronic case report form.

Statistical analysis

Continuous variables were described with median and interquartile range (IQR), and tested for differences with Mann-Whitney U test. Categorical variables were described as count (percentage) and tested for differences with Chi-squared test. Incidence rate ratio (IRR) of the study outcomes were calculated using previously described methods (20–22). Plots of Kaplan-Meier curves were performed, and survival distributions compared using log-rank test. Cox proportional hazards analyses were performed to investigate the effects of full and

partial ABC adherence on the primary outcome of interest. A multivariable model with forward selection of covariates was used to account for possible confounders including age, sex, coronary artery disease, diabetes mellitus, heart failure, hypertension, peripheral artery disease and prior thromboembolism. A two-sided p value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 27 (IBM Corp, Armonk, NY) and RStudio (Version 1.3.1093).

Results

Baseline characteristics

For this analysis, we screened 6646 patients with AF (**Supplementary Figure 1**). The median age of this cohort was 70 (IQR 61 - 77) years with 2669 (40.2%) females. A total of 3304 patients were classified as high-risk ones, out of which there were 924 (28.0%) treated as adherent to ABC pathway. In terms of the individual subgroups, there were 1750 (26.3%) patients with CKD, of whom 452 (25.8%) were ABC pathway adherent; 2236 (33.6%) elderly patients, of whom 646 (28.9%) were ABC pathway adherent; and 728 (10.9%) patients with prior thromboembolism, of whom 152 (20.9%) were ABC pathway adherent. Baseline characteristics in high-risk patients and among the single subgroups are reported in **Table 1**.

Occurrence of Outcomes during Follow-Up

At 2-year follow-up, there were a total of 966 (14.5%) patients with the primary composite event of all-cause death, thromboembolism and acute coronary syndrome; 598 (9.0%) all-cause deaths; 634 (9.5%) MACEs; and 144 (2.2%) major bleeding. Among high-risk patients, the incidence of the primary composite outcome was significantly lower among those who were ABC pathway adherent (IRR 0.53 [95% CI, 0.43 - 0.64]) (**Table 2**). Furthermore, ABC adherence was linked to a reduction in the incidence of all-cause death (IRR 0.55 [95% CI, 0.43 - 0.79]) and MACEs (IRR 0.47 [95% CI, 0.36 - 0.61]), but no difference in major bleeding (IRR 0.87 [95% CI, 0.53 - 1.39]). Similar results were evident in the various single subgroups of high-risk conditions, except for the occurrence of all-cause death in patients with prior thromboembolism, which showed only a nonsignificant trend in reduction for the patients adherent to ABC pathway (**Table 2**).

Kaplan-Meier survival curves with log-rank p values are shown in **Figure 1**. Using multivariable Cox proportional hazards analysis, ABC adherence in high-risk patients was associated with a significantly lower risk of primary composite outcome (aHR 0.64 [95% CI, 0.51 - 0.80]) (**Table 3**). Overall, there was a graded reduction in the risk of primary outcome as patients fulfilled a higher number of ABC criteria. Adherence to the ABC pathway also provided reduction in primary composite outcome in all the subgroups considered, with the greater magnitude obtained in patients with CKD. The greater number of ABC criteria attained provided the greater reduction in the risk of composite outcome, being the highest in patients that fulfilled all 3 criteria (**Table 3**).

Discussion

In this large, contemporary cohort study of European AF patients, we found that 'high-risk' patients, with either CKD, advanced age or prior thromboembolism: 1) accounted for a significant proportion of this cohort, 2) infrequently received holistic care as assessed by adherence to the ABC pathway, 3) who were ABC pathway adherent had a significant reduction in the composite risk of all-cause death, thromboembolism and acute coronary syndrome, and 4) who fulfilled an increasing number of ABC criteria had a progressive improvement in long-term prognosis. Furthermore, the benefits of ABC pathway adherence were also demonstrated in individual subgroups of those with CKD, advanced age, and prior thromboembolism.

The effects of ABC pathway adherence in the general AF population have previously been described in several studies. A nationwide cohort study demonstrated that adherence to the ABC pathway was associated with a reduction in the rates of all-cause death (aHR 0.82 [95% CI, 0.78 - 0.86]) and composite outcome of all-cause death, ischaemic stroke, major bleeding and myocardial infarction (aHR 0.86 [95% CI, 0.83 - 0.89]) (23). More recently, data from the Chinese Atrial Fibrillation registry showed that ABC adherence was related to a decrease in all-cause death (aHR 0.82 [95% CI, 0.70 - 0.95]) and composite outcome of all-cause death, ischaemic stroke and intracranial haemorrhage (aHR 0.86 [95% CI, 0.76 - 0.96]) (24). Furthermore, there was a graded improvement in outcomes with fulfilment of greater number of components in the ABC pathway. The aforementioned findings were confirmed in a meta-analysis of 8 studies comprising 285253 patients showing that adherence to the ABC pathway in patients with AF was associated with a significant reduction in all-cause death, ischaemic stroke and major bleeding (11).

Though the benefits of the ABC pathway are established, few studies have evaluated whether its effects extend to specific high-risk patients such as those with CKD, advanced

age and/or prior thromboembolism. The importance of evaluating the ABC pathway among these patients should not be underestimated as they are inherently more complex, have a higher risk of adverse events and may respond poorly to medications that are introduced as part of this approach. In this study, we found that among this large contemporary AF cohort, these characteristics are largely prevalent. Furthermore, only a small proportion of these high-risk patients were deemed to have received holistic care based on the ABC pathway which may reflect the difficulties faced by clinicians in the management of such patients. Nonetheless, adherence to the ABC pathway was demonstrated to be independently associated with a 36% reduction in the risk of composite outcome in these patients. Moreover, there was a graded reduction in the risk of adverse outcomes with the fulfilment of a greater number of ABC criteria. Similar findings were demonstrated in the CKD, elderly, and prior thromboembolism subgroups.

Of note, the ABC pathway has been studied in a number of other subgroups. In a retrospective study of 2043 patients with AF and diabetes from the Gulf Survey of Atrial Fibrillation Events (Gulf SAFE) registry, ABC adherence was shown to significantly lower all-cause death (adjusted odds ratio [OR] of 0.29 [95% CI, 0.11 - 0.76]) and a composite outcome of stroke or systemic embolism, all-cause death and cardiovascular hospitalisation (adjusted OR of 0.57 [95% CI, 0.33 - 0.97]) at 1 year (25). A cohort study of patients with AF from the Korean National Health Insurance Service database found that ABC adherence in those with high frailty risk, based on the Hospital Frailty Risk Score, was associated with lower all-cause death (aHR 0.74 [95% CI, 0.56 - 0.97]) and major bleeding (aHR 0.72 [95% CI, 0.54 - 0.96]) but not ischemic stroke, heart failure admission or acute myocardial infarction(26). Post-hoc analysis of patients with AF from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial found that ABC adherence in subgroups of ‘clinically complex’ patients was related to improved prognosis though this was

observed mainly among patients with multiple comorbidities and prior hospitalisations while the effects were attenuated in patients with polypharmacy (27). In a secondary analysis derived by the SPORTIF III and V trials, a clinical management adherent to the ABC pathway was associated with a reduction in risk for clinical outcomes in patients with diabetes, CKD and metabolic syndrome, also with a progressively lower risk with an increasing number of criteria fulfilled (28). Taken together, the results from these prior studies and our current findings highlight the possible shortcomings of the simple ABC pathway in some complex high-risk patient subgroups with AF and the need for better management strategies among such patients.

Limitations

The main limitations of this study relate to potential misclassification bias due to the observational nature and limited power to detect differences in subgroups not prespecified in the study design. Moreover, despite adjustment for potential confounders, we could not exclude the possibility of residual confounders which restricts our ability to prove a cause-effect relationship. As the EORP-AF General Long-Term Registry was based exclusively on cardiology practices in Europe, generalisation of our findings to other general AF cohorts needs to be done with caution.

Conclusions

In a large, contemporary cohort of European AF patients, we demonstrate that adherence to the ABC pathway was associated with a reduction in major clinical outcomes among high-risk patients with either CKD, advanced age (≥75 years old) or prior thromboembolism. Furthermore, there was a graded benefit with the fulfilment of a greater

number of ABC criteria. Overall, our findings support the implementation of a holistic care approach in complex patients with AF.

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References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014 Feb;129(8):837–47.

2. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. Int J stroke. 2021 Feb;16(2):217–21.

3. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation. 1998 Sep;98(10):946–52.

4. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med. 2002 Oct;113(5):359–64.

5. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, et al. Incidence of Atrial Fibrillation and Relationship With Cardiovascular Events, Heart Failure, and Mortality A Community-Based Study From the Netherlands. J Am Coll Cardiol. 2015 Sep;66(9):1000–7.

6. Burdett P, Lip GYH. Atrial Fibrillation in the United Kingdom: Predicting Costs of an Emerging Epidemic Recognising and Forecasting the Cost Drivers of Atrial Fibrillation-related costs. Eur Hear J - Qual Care Clin Outcomes. 2022 Dec;8(2):187–94.

7. Potpara TS, Lip GYH, Blomstrom-Lundqvist C, Boriani G, Van Gelder IC, Heidbuchel H, et al. The 4S-AF Scheme (Stroke Risk; Symptoms; Severity of Burden;

Substrate): A Novel Approach to In-Depth Characterization (Rather than Classification) of Atrial Fibrillation. Thromb Haemost. 2021 Aug;121(3):270–8.

8. Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol. 2017 Nov;14(11):627–8.

9. Pastori D, Pignatelli P, Menichelli D, Violi F, Lip GYH. Integrated Care Management of Patients With Atrial Fibrillation and Risk of Cardiovascular Events: The ABC (Atrial fibrillation Better Care) Pathway in the ATHERO-AF Study Cohort. Mayo Clin Proc. 2019 Jul;94(7):1261–7.

10. Gumprecht J, Domek M, Proietti M, Li Y-G, Asaad N, Rashed W, 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 Apr;9(5):1286.

11. 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 May;122(3):406–14.

12. 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 of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021 Aug;42(5):373–498.

13. Chao T-F, Joung B, Takahashi Y, Lim TW, Choi E-K, Chan Y-H, 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 Nov;122(1):20–47.

14. Proietti M, Lip GYH, Laroche C, Fauchier L, Marin F, Nabauer M, 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. 2021 Oct;23(2):174–83.

15. Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, et al. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. Europace. 2018 May;20(5):747–57.

16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May;150(9):604–12.

17. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016 Oct;37(38):2893–962.

18. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener H-C, et al. Outcome parameters for trials in atrial fibrillation: recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association. Europace. 2007 Nov;9(11):1006–23.

19. 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 Feb;137(2):263–72.

20. Woodward M. Epidemiology : study design and data analysis. Boca Raton: Chapman & Hall/CRC; 2005. 381–426 p.

21. Kelsey JL, Thompson WD, Evans AS. Methods in observational epidemiology [Internet]. New York; Oxford: Oxford University Press; 1986. 254–284 p. Available from: http://www.tandfonline.com/toc/rwhi20/

22. Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol. 1990 Feb;131(2):373–5.

23. Yoon M, Yang P-S, Jang E, Yu HT, Kim T-H, Uhm J-S, 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 Oct;119(10):1695–703.

24. Wang Y-F, Jiang C, He L, Du X, Sang C-H, Long D-Y, et al. Integrated Care of Atrial Fibrillation Using the ABC (Atrial fibrillation Better Care) Pathway Improves Clinical Outcomes in Chinese Population: An Analysis From the Chinese Atrial Fibrillation Registry. Front Cardiovasc Med. 2021;8:762245.

25. Domek M, Gumprecht J, Li Y-G, Proietti M, Rashed W, Al Qudaimi A, 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. 2021 Aug;51(3):e13385.

26. Yang P-S, Sung J-H, Jang E, Yu HT, Kim T-H, Lip GYH, 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 Aug;36(4):668–77.

27. 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 May;9(10):e014932.

28. Proietti M, Vitolo M, Lip GYH. Integrated care and outcomes in patients with atrial fibrillation and comorbidities. Eur J Clin Invest. 2021 Jan;e13498.

Figure Legends

Figure 1: Kaplan-Meier Survival Curves for Composite Outcome in High-Risk Groups

Legend: ABC, **Atrial Fibrillation Better Care**; CKD, chronic kidney disease; TE, thromboembolism.

Tables

Table 1. Baseline Characteristics of High-Risk Patients with Atrial Fibrillation

Parameters*	**High-risk (n=3304)**	**CKD (n = 1750)**	**Elderly (n = 2236)**	**Prior TE (n = 728)**
Age (years)	77 (72-81)	76 (70-81)	80 (77-83)	73 (66-79)
Female sex	1581 (47.9%)	896 (51.2%)	1118 (50.0%)	336 (46.2%)
Heart rate (bpm)	78 (67-93)	79 (68-95)	77 (67 - 92)	76 (66-90)
sBP (mmHg)	130 (120-145)	130 (120-144)	132 (120-149)	130 (120-144)
dBP (mmHg)	80 (70-86)	80 (70-86)	80 (70-85)	80 (70-85)
BMI (kg/m^2)	27.3 (24.6-30.5)	27.7 (24.8-31.2)	26.8 (24.3-30.0)	27.3 (24.8-30.6)
eGFR ($mL/min/1.73m^2$)	56.5 (45.6-71.2)	48.1 (38.8-54.6)	59.1(46.6-73.2)	65.3 (50.5-80.3)
LVEF (%)	55 (45-62)	55 (43-60)	55 (48-64)	56 (47-62)
LVH	883 (32.2%)	498 (34.3%)	609 (33.0%)	187 (30.9%)
AF classification				
First-detected	625 (19.3%)	336 (19.5%)	432 (19.7%)	119 (16.6%)
Paroxysmal	805 (24.8%)	436 (25.3%)	505 (23.1%)	196 (27.3%)
Persistent	576 (17.8%)	324 (18.8%)	336 (15.4%)	119 (16.6%)
Long-standing persistent	130 (4.0%)	63 (3.7%)	78 (3.6%)	36 (5.0%)
Permanent	1106 (34.1%)	562 (32.7%)	837 (38.3%)	248 (34.5%)
EHRA classification				
I	1541 (46.6%)	751 (42.9%)	1097 (49.1%)	363 (49.9%)
II	1095 (33.1%)	592 (33.8%)	719 (32.2%)	220 (30.2%)
III	574 (17.4%)	344 (19.7%)	350 (15.7%)	132 (18.1%)
IV	94 (2.8%)	63 (3.6%)	70 (3.1%)	13 (1.8%)
Comorbidities				
COPD	329 (10.0%)	197 (11.3%)	231 (10.4%)	57 (7.9%)
Coronary artery disease	1033 (33.1%)	591 (36.1%)	717 (34.2%)	211 (31.0%)
Heart failure	1463 (44.7%)	932 (53.8%)	977 (44.1%)	305 (42.4%)
Hypercholesterolaemia	1395 (44.0%)	773 (35.7%)	889 (41.7%)	343 (49.4%)

Hypertension	2233 (68.2%)	1206 (69.5%)	1549 (69.9%)	480 (66.8%)
Peripheral artery disease	337 (10.4%)	201 (11.8%)	225 (10.3%)	106 (15.1%)
Previous haemorrhagic event	253 (7.8%)	155 (9.0%)	178 (8.1%)	68 (9.5%)
Previous TE	728 (22.3%)	255 (14.7%)	322 (14.6%)	728 (100%)
Previous ischaemic stroke	373 (11.4%)	142 (8.2%)	153 (6.9%)	373 (51.2%)
Sleep apnoea	139 (4.3%)	82 (4.8%)	69 (3.1%)	38 (5.3%)
CHA_2DS_2-VASc	4 (3-5)	4 (3-5)	4 (3-5)	5 (4-6)

* Expressed as median (IQR) or n (%).

AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; dBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; IQR, interquartile range; LA, left atrium; LVEF, left ventricle ejection fraction; LVH, left ventricular hypertrophy; sBP, systolic blood pressure; TE, thromboembolism.

Table 2. Incidence of Adverse Events in High-Risk Patients with Atrial Fibrillation

	ABC (+) n (%)	**ABC (-)** n (%)	**IRR (95% CI)**
High-Risk patients			
Composite Outcome	130 (14.5%)	570 (25.0%)	0.53 (0.43 - 0.64)
All-cause death	91 (9.9%)	394 (16.7%)	0.55 (0.43 - 0.70)
MACEs	74 (8.2%)	364 (16.0%)	0.47 (0.36 - 0.61)
Major bleeding	25 (2.7%)	69 (2.9%)	0.87 (0.53 - 1.39)
CKD subgroup			
Composite Outcome	66 (14.9%)	368 (29.6%)	0.45 (0.34 - 0.58)
All-cause death	46 (10.3%)	268 (20.8%)	0.45 (0.32 - 0.61)
MACEs	43 (9.7%)	235 (18.9%)	0.46 (0.32 - 0.64)
Major bleeding	18 (4.0%)	42 (3.3%)	1.12 (0.61 - 1.99)
Elderly subgroup			
Composite Outcome	95 (15.2%)	410 (26.7%)	0.51 (0.40 - 0.64)
All-cause death	72 (11.2%)	303 (19.2%)	0.54 (0.41 - 0.70)
MACEs	47 (7.5%)	240 (15.7%)	0.43 (0.31 - 0.59)
Major bleeding	19 (3.0%)	50 (3.2%)	0.86 (0.48 - 1.49)
Prior TE subgroup			
Composite Outcome	24 (16.1%)	139 (25.1%)	0.58 (0.36 - 0.90)
All-cause death	14 (9.2%)	84 (14.7%)	0.58 (0.30 - 1.03)
MACEs	17 (11.4%)	100 (18.1%)	0.57 (0.32 - 0.96)
Major bleeding	6 (3.9%)	23 (4.0%)	0.90 (0.30 - 2.28)

Legend: CI, confidence interval; CKD, chronic kidney disease; IRR, incidence rate ratio; MACE, major adverse cardiovascular event; TE, thromboembolism.

Table 3. Effects of ABC Adherence on Adverse Outcomes in High-Risk Patients with Atrial Fibrillation

	Composite of all-cause death, TE and ACS aHR (95% CI) *
High-risk patients	
ABC non- adherence	Ref.
ABC adherence	0.64 (0.51 - 0.80)
No ABC criteria	Ref.
1 ABC criteria	0.80 (0.52 - 1.24)
2 ABC criteria	0.52 (0.34 - 0.80)
3 ABC criteria	0.39 (0.25 - 0.61)
CKD subgroup	
ABC non- adherence	Ref.
ABC adherence	0.51 (0.37 - 0.70)
No ABC criteria	Ref.
1 ABC criteria	0.93 (0.55 - 1.55)
2 ABC criteria	0.54 (0.32 - 0.89)
3 ABC criteria	0.33 (0.19 - 0.59)
Elderly subgroup	
ABC non- adherence	Ref.
ABC adherence	0.69 (0.53 - 0.90)
No ABC criteria	Ref.
1 ABC criteria	0.82 (0.46 - 1.47)
2 ABC criteria	0.63 (0.36 - 1.11)
3 ABC criteria	0.47 (0.26 - 0.86)
Prior TE subgroup	
ABC non- adherence	Ref.
ABC adherence	0.58 (0.34 - 1.01)
No ABC criteria	Ref.
1 ABC criteria	0.53 (0.24 - 1.17)
2 ABC criteria	0.28 (0.13 - 0.61)
3 ABC criteria	0.21 (0.09 - 0.52)

* Adjusted for age, sex, coronary artery disease, diabetes mellitus, heart failure, hypertension, peripheral artery disease and prior thromboembolism. ACS, acute coronary syndrome; AF, atrial fibrillation; aHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; TE, thromboembolism.

Figure(s)

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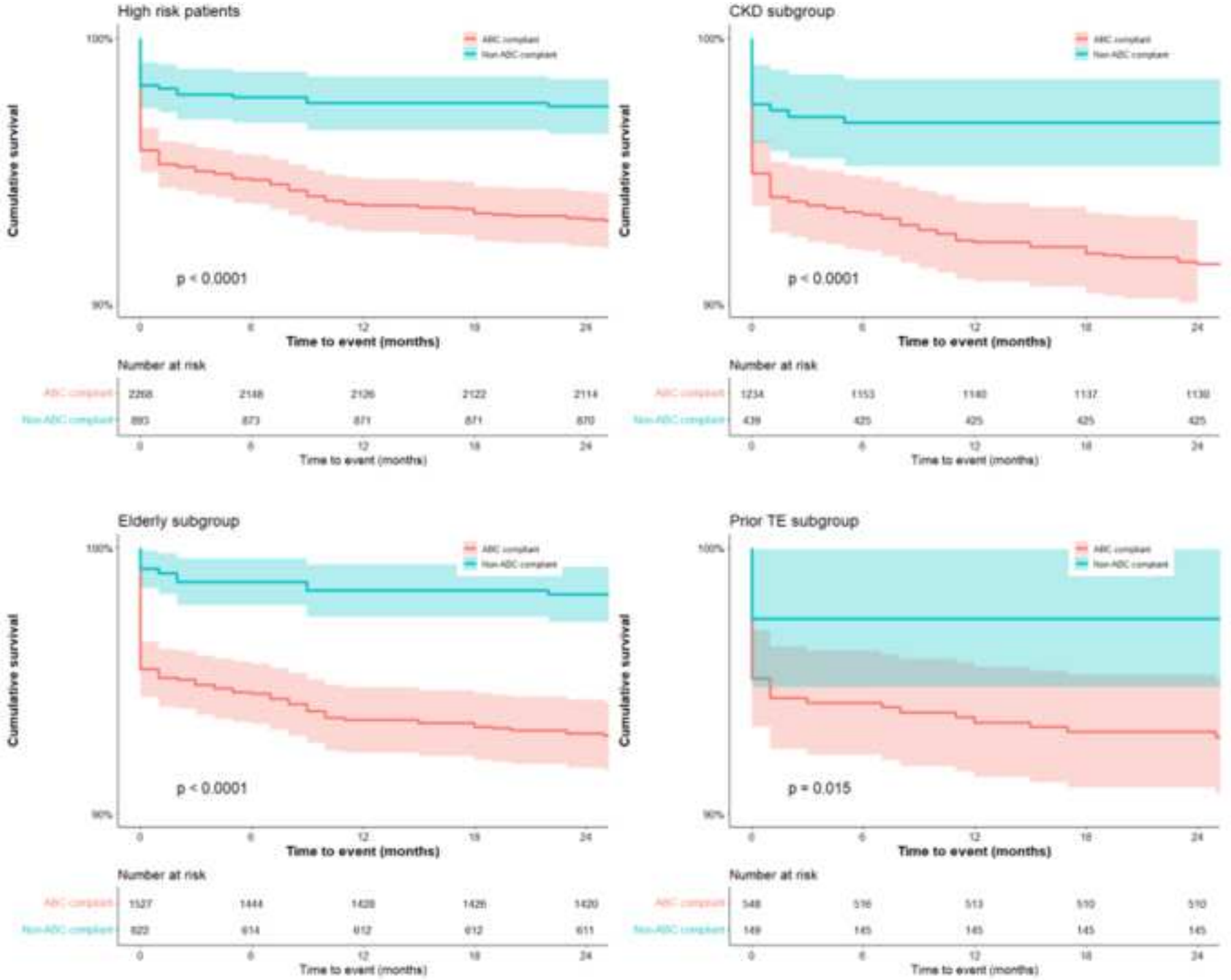

Supplementary File

Impact of ABC (Atrial Fibrillation Better Care) Pathway Adherence in High-Risk Subgroups with Atrial Fibrillation: A report from the ESC-EHRA EORP-AF Long-Term General Registry

Short title: ABC pathway in high-risk subgroups with AF

Wern Yew Ding[1*]; Marco Proietti[1,2,3*]; Giulio Francesco Romiti[1,4]; Marco Vitolo[1,5,6]; Ameenathul Mazaya Fawzy[1]; Giuseppe Boriani[5]; Francisco Marin[7]; Carina Blomström-Lundqvist[8,9]; Tatjana S. Potpara[10,11]; Laurent Fauchier[12]; Gregory Y. H. Lip[1,13]; on behalf of the ESC-EHRA EORP-AF Long-Term General Registry Investigators[14]

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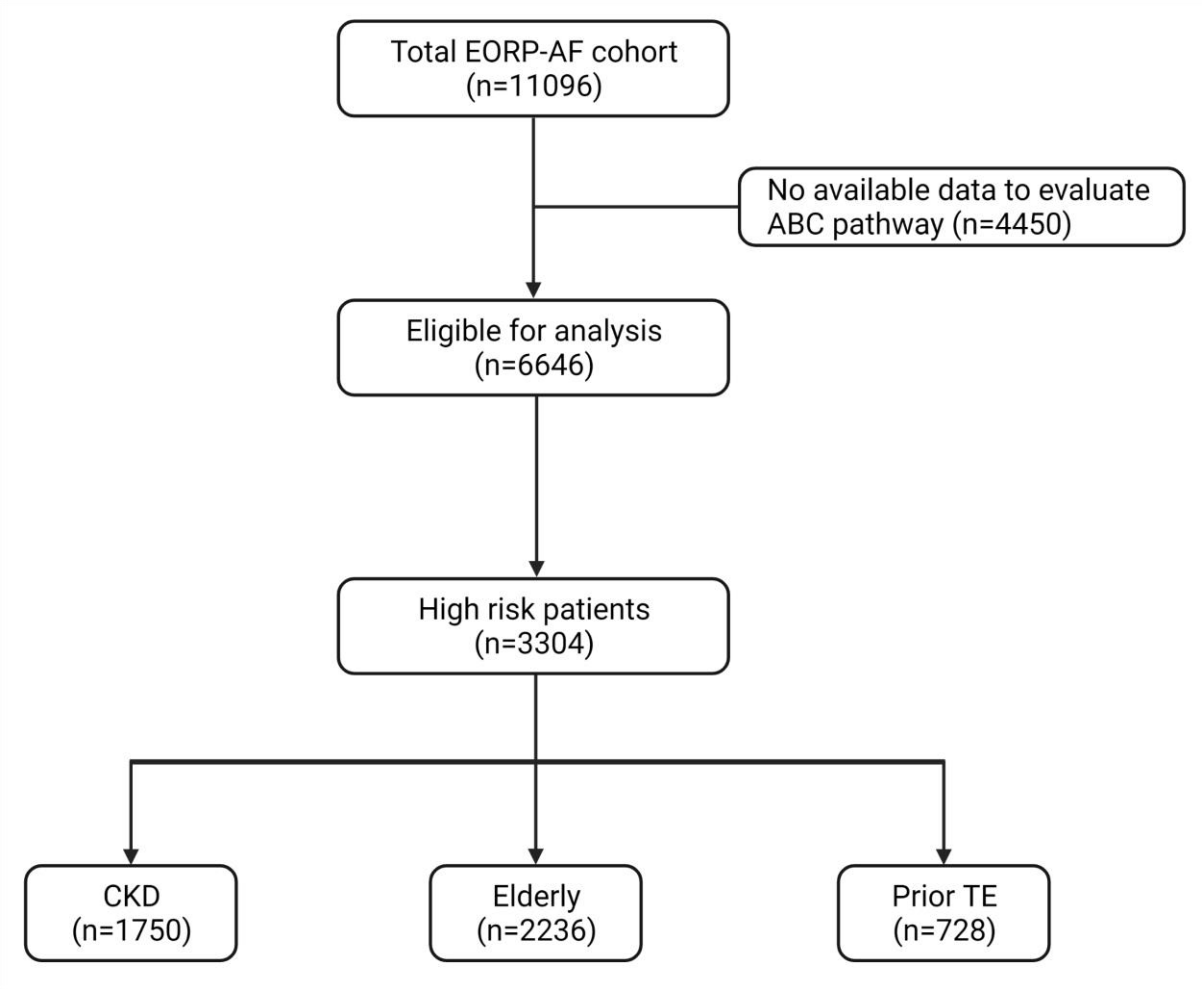
Supplementary Figure 1: Study Flowchart



ABC, Atrial Fibrillation Better Care; CKD, chronic kidney disease; TE, thromboembolism.

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Abstract

Background:Effects of Atrial Fibrillation Better Care(ABC) adherence among high-risk atrial fibrillation(AF) subgroups remains unknown. We aimed to evaluate the impact of ABC adherence on clinical outcomes in these high-risk patients.

Methods:EORP-AF General Long-Term Registry is a prospective, observational registry from 250 centres across 27 European countries. High-risk patients were defined as those with either CKD(eGFR <60 mL/min/1.73m^2), elderly patients(≥75 years) or prior thromboembolism. Primary outcome was a composite event of all-cause death, thromboembolism and acute coronary syndrome.

Results:6646 patients with AF were screened (median age was 70[IQR 61-77] years; 40.2% females). There were 3304(54.2%) patients with either CKD(n=1750), older age(n=2236) or prior thromboembolism(n=728). Among these, 924(28.0%) were managed as adherent to ABC.

At 2-year follow-up, 966(14.5%) patients reported the primary outcome. The incidence of the primary outcome was significantly lower in high-risk patients managed as adherent to ABC pathway(IRR 0.53[95%CI,0.43-0.64]). Consistent results were obtained in the individual subgroups. Using multivariable Cox proportional hazards analysis, ABC adherence in the high-risk cohort was independently associated with a lower risk of the primary outcome(aHR 0.64[95%CI,0.51-0.80]), as well as in the CKD(aHR 0.51[95%CI,0.37-0.70]) and elderly subgroups(aHR 0.69[95%CI,0.53-0.90]). Overall, there was greater reduction in the risk of primary outcome as more ABC criteria were fulfilled, both in the overall high-risk patients(aHR 0.39[95%CI,0.25-0.61]), as well as in the individual subgroups.

Conclusion:In a large, contemporary cohort of patients with AF, we demonstrate that adherence to the ABC pathway was associated with a significant benefit among high-risk patients with either CKD, advanced age(≥75 years old) or prior thromboembolism.

Keywords: chronic kidney disease; elderly; thromboembolism; registry; holistic; integrated.

Introduction

Atrial fibrillation (AF) is a significant public health issue with a global prevalence of 33.5 million patients affected by the condition and approximately 5 million new cases identified each year (1). The number of patients with AF are increasing, with projections of a surge in incidence and prevalence by 63% and 66%, respectively, over the next 30 years (2). The significance of AF is characterised by major contribution to excess morbidity and mortality (3–5), as well as increasing healthcare cost (6).

Because of the increasing number of AF patients with co-existing conditions, there has been a move towards better characterisation and evaluation (7), and a more holistic or integrated care approach to AF patient care (8). Such an approach has been associated with improved clinical outcomes (9–11), and recommended in clinical guidelines (12,13). A previous study using the EURObservational Research Programme Atrial Fibrillation (EORP-AF) Long-Term General Registry demonstrated that patients managed adherent to the ABC pathway had lower rates of composite events of thromboembolism, acute coronary syndrome or cardiovascular death, cardiovascular death and all-cause death (14).

However, most studies have evaluated the ABC pathway in the general AF population. Hence, the effects of ABC adherence among specific high-risk subgroups with AF in whom it may be argued that an integrated care approach is crucial remain unknown. In this study, we aimed to evaluate the impact of ABC adherence on high-risk subgroups of patients with AF from the ESC-EHRA EORP-AF General Long-Term Registry.

Methods

Study design and population

The ESC-EHRA EORP-AF General Long-Term Registry is a prospective, observational, large multicentre registry from 250 centres in 27 participating European countries. The study design has previously been described (15). Briefly, adults with recently diagnosed AF (within 12 months) who presented to cardiology services at participating centres between October 2013 and September 2016 were enrolled. For the purposes of this analysis, patients with available data to evaluate the ABC pathway and a minimum of 1 year follow-up were included. High-risk patients were defined as patients with either chronic kidney disease (CKD; estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2), elderly patients (≥75 years) or those with prior thromboembolism. Also, the single subgroups were considered separately. Event exposure was determined based on adherence to the ABC pathway. Institutional review board approval of the study protocol was obtained for every institution, and the study was performed in accordance with the European Union Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and Declaration of Helsinki.

Data collection and definitions

Data on demographics, comorbidities and medication use were collected at baseline with prospectively designed data collection tools. eGFR was assessed using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation (16). AF classification was determined according to the European Society of Cardiology recommendations (17). Severity of AF-related symptoms was ascertained with the European Heart Rhythm Association (EHRA) classification (18). CHA_2DS_2-VASc score was calculated as described (19).

Adherence to the ABC pathway was defined as per our previously published study (14) and was evaluated at baseline. The ABC pathway has been proposed to streamline integrated care in AF patients based on the following pillars: i) Avoid stroke with Anticoagulation; ii) Better symptom management, with patient-centred symptom-directed decisions on rate or rhythm control; iii) Cardiovascular comorbidities and risk factors optimisation (including changes in lifestyle). A patient was considered as ABC pathway compliant if all the 3 criteria were fulfilled, otherwise the patient was considered as being managed with an ABC non-compliant care.

Study outcomes

Study outcomes were considered at 2-year follow-up. The primary outcome of interest was a composite event of all-cause death, thromboembolism and acute coronary syndrome. Secondary outcomes of interest were all-cause death, major adverse cardiovascular events (MACEs) and major bleeding as single outcomes. MACEs were defined as any thromboembolism, acute coronary syndrome or cardiovascular death. Thromboembolism was defined as stroke, transient ischaemic attack, and any peripheral embolism. During follow-up, all incident MACEs were recorded on a centralised electronic case report form.

Statistical analysis

Continuous variables were described with median and interquartile range (IQR), and tested for differences with Mann-Whitney U test. Categorical variables were described as count (percentage) and tested for differences with Chi-squared test. Incidence rate ratio (IRR) of the study outcomes were calculated using previously described methods (20–22). Plots of Kaplan-Meier curves were performed, and survival distributions compared using log-rank test. Cox proportional hazards analyses were performed to investigate the effects of full and

partial ABC adherence on the primary outcome of interest. A multivariable model with forward selection of covariates was used to account for possible confounders including age, sex, coronary artery disease, diabetes mellitus, heart failure, hypertension, peripheral artery disease and prior thromboembolism. A two-sided p value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 27 (IBM Corp, Armonk, NY) and RStudio (Version 1.3.1093).

Results

Baseline characteristics

For this analysis, we screened 6646 patients with AF (**Supplementary Figure 1**). The median age of this cohort was 70 (IQR 61 - 77) years with 2669 (40.2%) females. A total of 3304 patients were classified as high-risk ones, out of which there were 924 (28.0%) treated as adherent to ABC pathway. In terms of the individual subgroups, there were 1750 (26.3%) patients with CKD, of whom 452 (25.8%) were ABC pathway adherent; 2236 (33.6%) elderly patients, of whom 646 (28.9%) were ABC pathway adherent; and 728 (10.9%) patients with prior thromboembolism, of whom 152 (20.9%) were ABC pathway adherent. Baseline characteristics in high-risk patients and among the single subgroups are reported in **Table 1**.

Occurrence of Outcomes during Follow-Up

At 2-year follow-up, there were a total of 966 (14.5%) patients with the primary composite event of all-cause death, thromboembolism and acute coronary syndrome; 598 (9.0%) all-cause deaths; 634 (9.5%) MACEs; and 144 (2.2%) major bleeding. Among high-risk patients, the incidence of the primary composite outcome was significantly lower among those who were ABC pathway adherent (IRR 0.53 [95% CI, 0.43 - 0.64]) (**Table 2**). Furthermore, ABC adherence was linked to a reduction in the incidence of all-cause death (IRR 0.55 [95% CI, 0.43 - 0.79]) and MACEs (IRR 0.47 [95% CI, 0.36 - 0.61]), but no difference in major bleeding (IRR 0.87 [95% CI, 0.53 - 1.39]). Similar results were evident in the various single subgroups of high-risk conditions, except for the occurrence of all-cause death in patients with prior thromboembolism, which showed only a nonsignificant trend in reduction for the patients adherent to ABC pathway (**Table 2**).

Kaplan-Meier survival curves with log-rank p values are shown in **Figure 1**. Using multivariable Cox proportional hazards analysis, ABC adherence in high-risk patients was associated with a significantly lower risk of primary composite outcome (aHR 0.64 [95% CI, 0.51 - 0.80]) (**Table 3**). Overall, there was a graded reduction in the risk of primary outcome as patients fulfilled a higher number of ABC criteria. Adherence to the ABC pathway also provided reduction in primary composite outcome in all the subgroups considered, with the greater magnitude obtained in patients with CKD. The greater number of ABC criteria attained provided the greater reduction in the risk of composite outcome, being the highest in patients that fulfilled all 3 criteria (**Table 3**).

Discussion

In this large, contemporary cohort study of European AF patients, we found that 'high-risk' patients, with either CKD, advanced age or prior thromboembolism: 1) accounted for a significant proportion of this cohort, 2) infrequently received holistic care as assessed by adherence to the ABC pathway, 3) who were ABC pathway adherent had a significant reduction in the composite risk of all-cause death, thromboembolism and acute coronary syndrome, and 4) who fulfilled an increasing number of ABC criteria had a progressive improvement in long-term prognosis. Furthermore, the benefits of ABC pathway adherence were also demonstrated in individual subgroups of those with CKD, advanced age, and prior thromboembolism.

The effects of ABC pathway adherence in the general AF population have previously been described in several studies. A nationwide cohort study demonstrated that adherence to the ABC pathway was associated with a reduction in the rates of all-cause death (aHR 0.82 [95% CI, 0.78 - 0.86]) and composite outcome of all-cause death, ischaemic stroke, major bleeding and myocardial infarction (aHR 0.86 [95% CI, 0.83 - 0.89]) (23). More recently, data from the Chinese Atrial Fibrillation registry showed that ABC adherence was related to a decrease in all-cause death (aHR 0.82 [95% CI, 0.70 - 0.95]) and composite outcome of all-cause death, ischaemic stroke and intracranial haemorrhage (aHR 0.86 [95% CI, 0.76 - 0.96]) (24). Furthermore, there was a graded improvement in outcomes with fulfilment of greater number of components in the ABC pathway. The aforementioned findings were confirmed in a meta-analysis of 8 studies comprising 285253 patients showing that adherence to the ABC pathway in patients with AF was associated with a significant reduction in all-cause death, ischaemic stroke and major bleeding (11).

Though the benefits of the ABC pathway are established, few studies have evaluated whether its effects extend to specific high-risk patients such as those with CKD, advanced

age and/or prior thromboembolism. The importance of evaluating the ABC pathway among these patients should not be underestimated as they are inherently more complex, have a higher risk of adverse events and may respond poorly to medications that are introduced as part of this approach. In this study, we found that among this large contemporary AF cohort, these characteristics are largely prevalent. Furthermore, only a small proportion of these high-risk patients were deemed to have received holistic care based on the ABC pathway which may reflect the difficulties faced by clinicians in the management of such patients. Nonetheless, adherence to the ABC pathway was demonstrated to be independently associated with a 36% reduction in the risk of composite outcome in these patients. Moreover, there was a graded reduction in the risk of adverse outcomes with the fulfilment of a greater number of ABC criteria. Similar findings were demonstrated in the CKD, elderly, and prior thromboembolism subgroups.

Of note, the ABC pathway has been studied in a number of other subgroups. In a retrospective study of 2043 patients with AF and diabetes from the Gulf Survey of Atrial Fibrillation Events (Gulf SAFE) registry, ABC adherence was shown to significantly lower all-cause death (adjusted odds ratio [OR] of 0.29 [95% CI, 0.11 - 0.76]) and a composite outcome of stroke or systemic embolism, all-cause death and cardiovascular hospitalisation (adjusted OR of 0.57 [95% CI, 0.33 - 0.97]) at 1 year (25). A cohort study of patients with AF from the Korean National Health Insurance Service database found that ABC adherence in those with high frailty risk, based on the Hospital Frailty Risk Score, was associated with lower all-cause death (aHR 0.74 [95% CI, 0.56 - 0.97]) and major bleeding (aHR 0.72 [95% CI, 0.54 - 0.96]) but not ischemic stroke, heart failure admission or acute myocardial infarction(26). Post-hoc analysis of patients with AF from the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial found that ABC adherence in subgroups of ‘clinically complex’ patients was related to improved prognosis though this was

observed mainly among patients with multiple comorbidities and prior hospitalisations while the effects were attenuated in patients with polypharmacy (27). In a secondary analysis derived by the SPORTIF III and V trials, a clinical management adherent to the ABC pathway was associated with a reduction in risk for clinical outcomes in patients with diabetes, CKD and metabolic syndrome, also with a progressively lower risk with an increasing number of criteria fulfilled (28). Taken together, the results from these prior studies and our current findings highlight the possible shortcomings of the simple ABC pathway in some complex high-risk patient subgroups with AF and the need for better management strategies among such patients.

Limitations

The main limitations of this study relate to potential misclassification bias due to the observational nature and limited power to detect differences in subgroups not prespecified in the study design. Moreover, despite adjustment for potential confounders, we could not exclude the possibility of residual confounders which restricts our ability to prove a cause-effect relationship. As the EORP-AF General Long-Term Registry was based exclusively on cardiology practices in Europe, generalisation of our findings to other general AF cohorts needs to be done with caution.

Conclusions

In a large, contemporary cohort of European AF patients, we demonstrate that adherence to the ABC pathway was associated with a reduction in major clinical outcomes among high-risk patients with either CKD, advanced age (≥75 years old) or prior thromboembolism. Furthermore, there was a graded benefit with the fulfilment of a greater

number of ABC criteria. Overall, our findings support the implementation of a holistic care approach in complex patients with AF.

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References

1. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation. 2014 Feb;129(8):837–47.

2. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. Int J stroke. 2021 Feb;16(2):217–21.

3. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: The Framingham Heart Study. Circulation. 1998 Sep;98(10):946–52.

4. Stewart S, Hart CL, Hole DJ, McMurray JJ. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med. 2002 Oct;113(5):359–64.

5. Vermond RA, Geelhoed B, Verweij N, Tieleman RG, Van der Harst P, Hillege HL, et al. Incidence of Atrial Fibrillation and Relationship With Cardiovascular Events, Heart Failure, and Mortality A Community-Based Study From the Netherlands. J Am Coll Cardiol. 2015 Sep;66(9):1000–7.

6. Burdett P, Lip GYH. Atrial Fibrillation in the United Kingdom: Predicting Costs of an Emerging Epidemic Recognising and Forecasting the Cost Drivers of Atrial Fibrillation-related costs. Eur Hear J - Qual Care Clin Outcomes. 2022 Dec;8(2):187–94.

7. Potpara TS, Lip GYH, Blomstrom-Lundqvist C, Boriani G, Van Gelder IC, Heidbuchel H, et al. The 4S-AF Scheme (Stroke Risk; Symptoms; Severity of Burden;

Substrate): A Novel Approach to In-Depth Characterization (Rather than Classification) of Atrial Fibrillation. Thromb Haemost. 2021 Aug;121(3):270–8.

8. Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol. 2017 Nov;14(11):627–8.

9. Pastori D, Pignatelli P, Menichelli D, Violi F, Lip GYH. Integrated Care Management of Patients With Atrial Fibrillation and Risk of Cardiovascular Events: The ABC (Atrial fibrillation Better Care) Pathway in the ATHERO-AF Study Cohort. Mayo Clin Proc. 2019 Jul;94(7):1261–7.

10. Gumprecht J, Domek M, Proietti M, Li Y-G, Asaad N, Rashed W, 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 Apr;9(5):1286.

11. 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 May;122(3):406–14.

12. 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 of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021 Aug;42(5):373–498.

13. Chao T-F, Joung B, Takahashi Y, Lim TW, Choi E-K, Chan Y-H, 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 Nov;122(1):20–47.

14. Proietti M, Lip GYH, Laroche C, Fauchier L, Marin F, Nabauer M, 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. 2021 Oct;23(2):174–83.

15. Boriani G, Proietti M, Laroche C, Fauchier L, Marin F, Nabauer M, et al. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. Europace. 2018 May;20(5):747–57.

16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May;150(9):604–12.

17. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016 Oct;37(38):2893–962.

18. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener H-C, et al. Outcome parameters for trials in atrial fibrillation: recommendations from a consensus conference organized by the German Atrial Fibrillation Competence NETwork and the European Heart Rhythm Association. Europace. 2007 Nov;9(11):1006–23.

19. 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 Feb;137(2):263–72.

20. Woodward M. Epidemiology : study design and data analysis. Boca Raton: Chapman & Hall/CRC; 2005. 381–426 p.

21. Kelsey JL, Thompson WD, Evans AS. Methods in observational epidemiology [Internet]. New York; Oxford: Oxford University Press; 1986. 254–284 p. Available from: http://www.tandfonline.com/toc/rwhi20/

22. Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). Am J Epidemiol. 1990 Feb;131(2):373–5.

23. Yoon M, Yang P-S, Jang E, Yu HT, Kim T-H, Uhm J-S, 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 Oct;119(10):1695–703.

24. Wang Y-F, Jiang C, He L, Du X, Sang C-H, Long D-Y, et al. Integrated Care of Atrial Fibrillation Using the ABC (Atrial fibrillation Better Care) Pathway Improves Clinical Outcomes in Chinese Population: An Analysis From the Chinese Atrial Fibrillation Registry. Front Cardiovasc Med. 2021;8:762245.

25. Domek M, Gumprecht J, Li Y-G, Proietti M, Rashed W, Al Qudaimi A, 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. 2021 Aug;51(3):e13385.

26. Yang P-S, Sung J-H, Jang E, Yu HT, Kim T-H, Lip GYH, 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 Aug;36(4):668–77.

27. 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 May;9(10):e014932.

28. Proietti M, Vitolo M, Lip GYH. Integrated care and outcomes in patients with atrial fibrillation and comorbidities. Eur J Clin Invest. 2021 Jan;e13498.

Figure Legends

Figure 1: Kaplan-Meier Survival Curves for Composite Outcome in High-Risk Groups

Legend: ABC, **Atrial Fibrillation Better Care**; CKD, chronic kidney disease; TE, thromboembolism.

Tables

Table 1. Baseline Characteristics of High-Risk Patients with Atrial Fibrillation

Parameters*	**High-risk (n=3304)**	**CKD (n = 1750)**	**Elderly (n = 2236)**	**Prior TE (n = 728)**
Age (years)	77 (72-81)	76 (70-81)	80 (77-83)	73 (66-79)
Female sex	1581 (47.9%)	896 (51.2%)	1118 (50.0%)	336 (46.2%)
Heart rate (bpm)	78 (67-93)	79 (68-95)	77 (67 - 92)	76 (66-90)
sBP (mmHg)	130 (120-145)	130 (120-144)	132 (120-149)	130 (120-144)
dBP (mmHg)	80 (70-86)	80 (70-86)	80 (70-85)	80 (70-85)
BMI (kg/m^2)	27.3 (24.6-30.5)	27.7 (24.8-31.2)	26.8 (24.3-30.0)	27.3 (24.8-30.6)
eGFR ($mL/min/1.73m^2$)	56.5 (45.6-71.2)	48.1 (38.8-54.6)	59.1(46.6-73.2)	65.3 (50.5-80.3)
LVEF (%)	55 (45-62)	55 (43-60)	55 (48-64)	56 (47-62)
LVH	883 (32.2%)	498 (34.3%)	609 (33.0%)	187 (30.9%)
AF classification				
First-detected	625 (19.3%)	336 (19.5%)	432 (19.7%)	119 (16.6%)
Paroxysmal	805 (24.8%)	436 (25.3%)	505 (23.1%)	196 (27.3%)
Persistent	576 (17.8%)	324 (18.8%)	336 (15.4%)	119 (16.6%)
Long-standing persistent	130 (4.0%)	63 (3.7%)	78 (3.6%)	36 (5.0%)
Permanent	1106 (34.1%)	562 (32.7%)	837 (38.3%)	248 (34.5%)
EHRA classification				
I	1541 (46.6%)	751 (42.9%)	1097 (49.1%)	363 (49.9%)
II	1095 (33.1%)	592 (33.8%)	719 (32.2%)	220 (30.2%)
III	574 (17.4%)	344 (19.7%)	350 (15.7%)	132 (18.1%)
IV	94 (2.8%)	63 (3.6%)	70 (3.1%)	13 (1.8%)
Comorbidities				
COPD	329 (10.0%)	197 (11.3%)	231 (10.4%)	57 (7.9%)
Coronary artery disease	1033 (33.1%)	591 (36.1%)	717 (34.2%)	211 (31.0%)
Heart failure	1463 (44.7%)	932 (53.8%)	977 (44.1%)	305 (42.4%)
Hypercholesterolaemia	1395 (44.0%)	773 (35.7%)	889 (41.7%)	343 (49.4%)

Hypertension	2233 (68.2%)	1206 (69.5%)	1549 (69.9%)	480 (66.8%)
Peripheral artery disease	337 (10.4%)	201 (11.8%)	225 (10.3%)	106 (15.1%)
Previous haemorrhagic event	253 (7.8%)	155 (9.0%)	178 (8.1%)	68 (9.5%)
Previous TE	728 (22.3%)	255 (14.7%)	322 (14.6%)	728 (100%)
Previous ischaemic stroke	373 (11.4%)	142 (8.2%)	153 (6.9%)	373 (51.2%)
Sleep apnoea	139 (4.3%)	82 (4.8%)	69 (3.1%)	38 (5.3%)
CHA_2DS_2-VASc	4 (3-5)	4 (3-5)	4 (3-5)	5 (4-6)

* Expressed as median (IQR) or n (%).

AF, atrial fibrillation; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; dBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EHRA, European Heart Rhythm Association; IQR, interquartile range; LA, left atrium; LVEF, left ventricle ejection fraction; LVH, left ventricular hypertrophy; sBP, systolic blood pressure; TE, thromboembolism.

Table 2. Incidence of Adverse Events in High-Risk Patients with Atrial Fibrillation

	ABC (+) n (%)	**ABC (-)** n (%)	**IRR (95% CI)**
High-Risk patients			
Composite Outcome	130 (14.5%)	570 (25.0%)	0.53 (0.43 - 0.64)
All-cause death	91 (9.9%)	394 (16.7%)	0.55 (0.43 - 0.70)
MACEs	74 (8.2%)	364 (16.0%)	0.47 (0.36 - 0.61)
Major bleeding	25 (2.7%)	69 (2.9%)	0.87 (0.53 - 1.39)
CKD subgroup			
Composite Outcome	66 (14.9%)	368 (29.6%)	0.45 (0.34 - 0.58)
All-cause death	46 (10.3%)	268 (20.8%)	0.45 (0.32 - 0.61)
MACEs	43 (9.7%)	235 (18.9%)	0.46 (0.32 - 0.64)
Major bleeding	18 (4.0%)	42 (3.3%)	1.12 (0.61 - 1.99)
Elderly subgroup			
Composite Outcome	95 (15.2%)	410 (26.7%)	0.51 (0.40 - 0.64)
All-cause death	72 (11.2%)	303 (19.2%)	0.54 (0.41 - 0.70)
MACEs	47 (7.5%)	240 (15.7%)	0.43 (0.31 - 0.59)
Major bleeding	19 (3.0%)	50 (3.2%)	0.86 (0.48 - 1.49)
Prior TE subgroup			
Composite Outcome	24 (16.1%)	139 (25.1%)	0.58 (0.36 - 0.90)
All-cause death	14 (9.2%)	84 (14.7%)	0.58 (0.30 - 1.03)
MACEs	17 (11.4%)	100 (18.1%)	0.57 (0.32 - 0.96)
Major bleeding	6 (3.9%)	23 (4.0%)	0.90 (0.30 - 2.28)

Legend: CI, confidence interval; CKD, chronic kidney disease; IRR, incidence rate ratio; MACE, major adverse cardiovascular event; TE, thromboembolism.

Table 3. Effects of ABC Adherence on Adverse Outcomes in High-Risk Patients with Atrial Fibrillation

	Composite of all-cause death, TE and ACS aHR (95% CI) *
High-risk patients	
ABC non- adherence	Ref.
ABC adherence	0.64 (0.51 - 0.80)
No ABC criteria	Ref.
1 ABC criteria	0.80 (0.52 - 1.24)
2 ABC criteria	0.52 (0.34 - 0.80)
3 ABC criteria	0.39 (0.25 - 0.61)
CKD subgroup	
ABC non- adherence	Ref.
ABC adherence	0.51 (0.37 - 0.70)
No ABC criteria	Ref.
1 ABC criteria	0.93 (0.55 - 1.55)
2 ABC criteria	0.54 (0.32 - 0.89)
3 ABC criteria	0.33 (0.19 - 0.59)
Elderly subgroup	
ABC non- adherence	Ref.
ABC adherence	0.69 (0.53 - 0.90)
No ABC criteria	Ref.
1 ABC criteria	0.82 (0.46 - 1.47)
2 ABC criteria	0.63 (0.36 - 1.11)
3 ABC criteria	0.47 (0.26 - 0.86)
Prior TE subgroup	
ABC non- adherence	Ref.
ABC adherence	0.58 (0.34 - 1.01)
No ABC criteria	Ref.
1 ABC criteria	0.53 (0.24 - 1.17)
2 ABC criteria	0.28 (0.13 - 0.61)
3 ABC criteria	0.21 (0.09 - 0.52)

* Adjusted for age, sex, coronary artery disease, diabetes mellitus, heart failure, hypertension, peripheral artery disease and prior thromboembolism. ACS, acute coronary syndrome; AF, atrial fibrillation; aHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; TE, thromboembolism.

Highlights

- Patients with atrial fibrillation often suffer from other comorbidities such as chronic kidney disease, advanced age or prior thromboembolism
- These patients were treated infrequently with a holistic care approached as assessed by adherence to the ABC pathway
- ABC pathway adherence was associated with a significant reduction in the composite risk of all-cause death, thromboembolism and acute coronary syndrome
- Patients who fulfilled an increasing number of ABC criteria had a progressive improvement in long-term prognosis