**Adherence and Outcomes with Adherence to the ‘Atrial Fibrillation Better Care’ (ABC) Pathway in Patients with Atrial Fibrillation:**

**A Systematic Review and Meta-Analysis of 285,000 Patients**

**Running Title:** ABC Pathway in AF

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**Conflict of Interests**

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**ABSTRACT**

**Aims:** The ‘Atrial Fibrillation Better Care’ (ABC) pathway has been recently proposed as a holistic approach for the comprehensive management of patients with Atrial Fibrillation (AF). We performed a systematic review of current evidence for the use of the ABC pathway on clinical outcomes.

**Methods and Results:** We performed a systematic review and meta-analysis according to PRISMA Guidelines. Pubmed and EMBASE were searched for studies reporting the prevalence of ABC pathway adherent management in AF patients, and its impact on clinical outcomes (all-cause death, cardiovascular death, stroke, and major bleeding). Metanalysis of odds ratio (OR) was performed with random-effect models; subgroup analysis and meta-regression were performed to account for heterogeneity. Among the 8 studies included, we found a pooled prevalence of ABC adherent management of 21% (95% confidence intervals (CI), 13-34%), with a high grade of heterogeneity, explained by the increasing adherence to each ABC criterion. Patients treated according to the ABC pathway showed a lower risk of all-cause death (OR:0.42, 95%CI 0.31-0.56), cardiovascular death (OR:0.37, 95%CI 0.23-0.58), stroke (OR:0.55, 95%CI 0.37-0.82) and major bleeding (OR:0.69, 95%CI 0.51-0.94), with moderate heterogeneity. Prevalence of comorbidities were moderators of heterogeneity for all-cause and cardiovascular death, while longer follow-up was associated with increased effectiveness for all outcomes.

**Conclusion:** Adherence to the ABC pathway was suboptimal, being adopted in 1 in every 5 patients. Adherence to the ABC pathway was associated with a reduction in the risk of major adverse outcomes.

**KEY WORDS:** atrial fibrillation; integrated care; ABC pathway; outcomes.

**INTRODUCTION**

In the last ten years, great advancements have been done in the treatment of patients with atrial fibrillation (AF), in particular regarding stroke prevention by an increasing use of oral anticoagulant (OAC) drugs1. As a consequence, rates of stroke and thromboembolic events have decreased markedly, being very low in more contemporary cohorts2.

Despite the improvements in reducing thromboembolic events, epidemiological data suggest that there were no significant temporal changes to the overall age-adjusted risk of death associated to the presence of AF3, being particularly related to an increase in the risks of hospitalisation and non-cardiovascular (CV) death4, also re-emphasising the close relationship between comorbidity, multimorbidity and AF5,6.

In order to address the burden of adverse clinical outcomes beyond thromboembolism, implementation of more comprehensive and integrated approach to AF management has been advociated7–9. To streamline the implementation of such a holistic care approach for AF patients, the ‘Atrial Fibrillation Better Care’ (ABC) pathway has been proposed. The ABC pathway stands on three main pillars: **‘A’** **A**void stroke (with **A**nticoagulants); **‘B’ B**etter symptom management; **‘C’ C**ardiovascular and **C**omorbidity management9. The ABC pathway is now recommended in several clinical guidelines, including the recent European Society of Cardiology (ESC) AF management guidelines10–12.

The objective of this paper is to present a systematic review of the current evidence for use of the ABC pathway on clinical outcomes. We aimed to establish the overall prevalence of adherence to the ABC criteria in the retrospective analyses available, and second, to perform a meta-analysis of ABC pathway compliance on clinical outcomes.

**MATERIALS AND METHODS**

 This systematic review has been performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and recommendations (<http://www.prisma-statement.org/>). The protocol was registered into the international register of systematic reviews PROSPERO, N. CRD42020218088. The data underlying this article are available in the article and in its online supplementary material.

*Search Strategy*

A systematic and comprehensive literature search was performed on Pubmed and EMBASE databases, from inception to 8th December 2020. The search strategy included a combination of key relevant terms related to the research question, including ‘ABC Pathway’ and ‘Atrial Fibrillation Better Care’. The full search strategy is reported in Supplementary Materials (Table S1).

 All details regarding studies selection, inclusion and exclusion criteria, data extraction, quality assessment and outcomes have been reported in the Supplementary Methods.

*Statistical Analysis*

Prevalence of ABC pathway adherent management was pooled from each of the studies included using a random intercept logistic regression model14 with the ‘metaprop’ function in R.

The number of events and the total number of patients of each group of interest were pooled and compared using a random-effects model. Pooled estimates were reported as odds ratios (OR) with 95% confidence intervals (CI). The inconsistency index (I2) was calculated to measure heterogeneity. According to pre-specified cut-offs, low heterogeneity was defined as an I2 of <25%, moderate heterogeneity when I2 falls between 25 and 75%, and high heterogeneity when I2 was >75%.

For each outcome, a sensitivity analysis was performed with a “leave-one-out” approach, in which all studies are removed one at a time to analyse their influence on pooled estimate and heterogeneity. We also performed several subgroup analyses: (i) for the prevalence of ABC adherent management, according to the geographical location of the original studies; (ii) for outcomes (All Cause Death, Cardiovascular Death and Ischemic Stroke), according to pre-specified CHA2DS2-VASc score groups (i.e., 0-2, 3-5, 6-9).

To further investigate potential sources of heterogeneity, we performed a meta-regression. Regarding the prevalence of the ABC pathway adherent management, we performed a multivariate meta-regression with the Knapp-Hartung method15 using the adherence to each of the ABC pathway criteria as covariates. For the outcomes, we performed univariate meta-regression according to the duration of follow-up and thromboembolic risk factors (i.e., age, sex, hypertension, diabetes mellitus, coronary artery disease (CAD), history of stroke, CHF).

Publication bias was assessed for studies reporting outcomes according to the adherence to the ABC pathway, with the use of funnel plots, which were visually inspected for asymmetricity. Egger’s test was also performed. All the statistical analyses were performed using R (version 4.0.3, The R Foundation, 2020), with the use of ‘meta’, ‘metafor’ and ‘dmetar’16 packages.

**RESULTS**

 A total of 2,862 results were retrieved from the literature search (761 from Pubmed and 2,101 from EMBASE). After the titles and abstracts screening, 14 full texts were evaluated, and eight studies were included in the final systematic review and meta-analysis17–24 (Table 1) [Figure S1], with a total of 285,253 AF patients included24. Four studies were based in Europe18,19,21,25, two in Asia23,24, one in North America20 and one was multinational22.

Among the eight included studies, two were post-hoc subgroup analyses of previously performed RCTs20,22, four were based on observational registries17–19,21 while the last one was derived from a nationwide claims registry23. One study did not include a follow-up phase18. The only RCT, the ‘mobile Atrial Fibrillation Application II’ (mAFA-II), a cluster-randomized study conducted in China, implemented the ABC pathway through a mobile phone application. Six out of eight studies18–22,24enrolled both out- and inpatients, while the remaining two only considered hospitalised patients17,23.

*Prevalence of ABC Pathway Adherent Care*

Among the seven observational studies included in the systematic review, we found a pooled prevalence of a clinical management adherent to the ABC pathway criteria equal to 21% (95% CI: 13-34%), with a high heterogeneity (I2 = 100%) [Figure 1]. In order to evaluate the factors accounting for such a high degree of heterogeneity, we performed a multivariate meta-regression analysis (Table S2). Among the factors included in the multivariate analysis, adherence to the ‘A’, ‘B’ and ‘C’ components of the ABC pathway were found to be directly associated with the prevalence of ABC pathway adherent clinical management (Table S2). The final model was able to explain most of the heterogeneity reported (R2= 98.9%, p=0.004).

*Impact of ABC Adherent Care on Outcomes*

We performed a meta-analysis on the impact of the ABC pathway on major clinical outcomes [Figure 2]. Overall, the use of ABC pathway adherent care was associated with a significant reduction of all-cause death compared non-adherence (OR: 0.42, 95% CI: 0.31-0.56), with high between-studies heterogeneity (I2 = 88%) [Figure 2, Panel A]. The risk of CV death was significantly lower in patients treated adherent to the ABC pathway (OR: 0.37, 95% CI: 0.23-0.58) with a high degree of heterogeneity (I2 = 89%) [Figure 2 – Panel B]

The risk of stroke (OR: 0.55, 95% CI: 0.37-0.82) [Figure 2, Panel C] and major bleeding (OR: 0.69, 95% CI: 0.51-0.94) [Figure 2, Panel D] were significantly lower in those patients that were treated adherent to the ABC pathway management, with an overall moderate degree of heterogeneity.

*Subgroup Analyses*

In order to evaluate the high degree of heterogeneity for the all-cause death outcome, we performed a subgroup analysis in relation to the geographic location of the patients in each study [Figure 3] (for one study, which was multinational, we analysed the results according to the regions included). While we did not find a significant difference between European, Asian and North American patients, this analysis found that the geographic location accounted for most of the heterogeneity in the main model, with a 40% residual heterogeneity.

*Meta-Regression Analysis*

We performed a univariable meta-regression analysis to examine the relationship between the clinical variables and the association of adherence to ABC pathway with the risk of all-cause death and CV death. In these analyses (Table S3 and S4), we found a direct association between the length of follow-up and an increase in effectiveness, while conversely an increasing prevalence of diabetes mellitus, CAD, CHF and stroke were associated with a reduction in effectiveness of the ABC pathway for both all-cause death and CV death occurrence, all accounting for most of the heterogeneity for the two outcomes (Table S3 and S4). Furthermore, the meta-regression analysis for stroke (Table S5) and major bleeding (Table S6) found a direct association between length of follow-up and an increase in effectiveness for both these outcomes, accounting for a significant proportion of heterogeneity (Table S5 and Table S6).

*Sensitivity Analysis*

The sensitivity analysis for the four outcomes according to the “leave-one-out” approach did not show any significant differences for each study included and any outcome [Figure S2-S5]. In the CHA2DS2-VASc stratified analysis [Figure 4], we found that for all-cause death, increasing CHA2DS2-VASc strata was associated with a progressively greater reduction of risk amongst patients adherent to the ABC pathway, being greatest at the highest CHA2DS2-VASc strata (OR: 0.30, 95% CI: 0.17-0.54 for CHA2DS2-VASc 6-9) [Figure 4, Panel A]. No difference in ABC pathway effectiveness was found across CHA2DS2-VASc strata for CV death and stroke occurrence [Figure 4, Panel B and Panel C].

*Bias Assessment*

The risk of bias assessment (Table S7-S8) showed an overall high quality of studies, with the exception of Yang et al23 which was found at high risk of bias for both prevalence and outcomes analysis.

Significant publication bias was found for all-cause death (Egger’s test p=0.021) and stroke (Egger’s test p=0.008, Table S9). Visual inspection of the funnel plots [Figure S6, Panel A and C] revealed that, in both cases, asymmetricity was caused by a void in the left side of the funnel plot, in which one would expect to find studies with positive results. The addition of these potential studies may lead to lower pooled ORs for both all-cause death and stroke.

**DISCUSSION**

In this systematic review and meta-analysis, clinical management adherent to the ABC pathway was suboptimal, being adopted in 1 of every 5 AF patients. Second, meta-analysis regarding clinical events showed that adherence to the ABC pathway was associated with a significant reduction in the risk of major adverse outcomes. Third, adherence to the ABC pathway was largely driven by the implementation of adequate antithrombotic therapy, adequate symptom control and by optimal control of cardiovascular risk factors and comorbidities. Lastly, the meta-regression analyses regarding outcomes showed that the increasing clinical complexity directly affects the effectiveness of an integrated management strategy, while a longer follow-up was associated to a greater reduction in risk.

Epidemiologically, the worldwide impact of AF has increased in the last 40 years. Despite a significant reduction in age-standardized prevalence and incidence, the absolute number of AF patients has almost doubled, being significantly increased in countries with middle and low socio-demographic levels3. Additionally, observational studies have shown that the clinical risk profile of AF patients has worsened over time, due to an increase in the prevalence of comorbidities28. This public health burden of AF has a major impact on mortality, where the total number of attributable deaths has more than doubled, almost reaching 300,000 in 2017, especially in middle and low socio-demographic countries3. Furthermore, an increasing effect on healthcare associated costs has been found29,30.

Given these concerns, a more holistic approach to AF management was needed. In 2018, the 6th AFNET/EHRA Consensus Conference defined integrated care as “a coordinated patient-centred approach by interdisciplinary specialists to improve AF outcomes”, by improving all the specific domains related to AF management7,31. A model of care was proposed in which any AF patient should ideally be managed by the AF Heart Team (specifically addressing the specific electrophysiology/cardiology issues) and the Integrated Care AF Clinic, where several specialists could provide the specific expertise to handle any aspect of the patient’s care7,8,27.

In 2017, the ‘Atrial fibrillation Better Care’ (ABC) pathway was proposed to streamline and simplify the implementation of integrated management in AF patients9. This simple model focuses on three main components, which are all essential to reduce the risk of major adverse outcomes in AF. The **‘A’** criterion (**A**void stroke) refers to the management of thromboembolic and bleeding risks by appropriate prescription and use of OAC drugs; The **‘B’** criterion **(B**etter symptom management) aims to reduce and control symptom burden patient-centred, symptom directed decsions on rate or rhythm control therapy; The **‘C’** criterion(**C**ardiovascular and **C**omorbidity risk optimisation) refers to the optimised management of any concomitant comorbidity or cardiovascular risk factor.

Our systematic review demonstrates that a significant amount of evidence has already been produced regarding the potential role of the ABC pathway in mitigating the risk of major adverse outcomes. The retrospective analyses showed that the level of adherence to the ABC pathway was low, with just one fifth of the patients being managed optimally. In particular, our meta-regression results suggest that more efforts are needed to obtain more optimal adherence to all the ABC pathway components: for example, implementation of adequate antithrombotic therapy and by more optimal control of cardiovascular risk factors and comorbidities. However, we cannot exclude that some factors not considered in this analysis may affect the integrated care of AF patients, such as education level, health perception, household income, availability of a public healthcare system, distance from healthcare services/hospitals, presence of caregiver for patients with disability26,27. Furthermore, while is important to underline that a clear heterogeneity exist in the various definition of “ABC pathway adherent care” across the retrospective studies (as further reported below), the importance of our results stands in the fact that irrespective of how the studies defined components of the ABC pathway, good control of anticoagulation quality, improved control of symptoms burden and the proper management of the most relevant comorbidities requires an effort from the treating physician which is “integrated or holistic care”. This paper shows how few patients are clinically managed in this way.

The pivotal role of a holistic approach to AF care is underlined by the results of this meta-analysis, showing that all the major adverse outcomes are significantly and consistently reduced in the ABC pathway adherent group of patients. Indeed, ABC pathway adherent care was associated with a 40% to 60% risk reduction for all the outcomes considered. Moreover, the positive results of the only RCT about the ABC pathway produced strengthen the view that more effort should be put into translating this evidence-based approach into daily clinical practice. Our evidence that a longer observation is associated with a greater reduction in risk for all the outcomes corroborates the evidence for the effectiveness of the intervention, where there is a ‘dose-response’ effect, extending the evidence from the mAFA-II rial secondary analyses32. The negative impact of a higher prevalence of several comorbidities on the effectiveness of ABC pathway adherent care emphasises the role of comorbidities and increased clinical complexity in influencing the clinical course. Indeed, an increasing prevalence of diabetes mellitus, CAD, CHF and stroke were associated to a reduction of effectiveness. Such evidence is reinforced by several studies illustrating how an increasing levels of multimorbidity are independently associated with an increased risk of outcomes, also determining a differential approach in OAC prescription5,6. In our study, the results of the CHA2DS2-VASc stratified analysis showed a greater risk reduction for all-cause death in patients with the highest thromboembolic risk; looking at this evidence and given prior evidence regarding the specific impact of ABC pathway adherent care in reducing the risk of outcomes in ‘clinically complex’ AF patients, for example those with multimorbidity33, we would suggest that such a holistic approach is even more needed in those with the highest risk profiles.

 This evidence, together with other data generated by secondary analyses of the studies included in this systematic review, which showed a significant impact of the ABC pathway adherent care in reducing the risk of dementia34 and a significant reduction in healthcare associated costs35, strongly support the recent changes introduced in the 2020 ESC AF clinical guidelines12. In these guidelines, there is a paradigm shift in approach, placing the patient at the centre of the physicians’ action, not the disease itself. With the aim of managing the patient holistically, the application of the ABC pathway is central to the guideline recommendations.

*Limitations*

Our paper has some limitations. First, the observational and retrospective nature of most of the included studies inherently limits the generalizability of the results. Even though we performed several meta-regression analyses, unmeasured residual confounders may have influenced our results given that the data were mostly from observational studies. Furthermore, since two of the studies included were originally performed >10 years ago, the different clinical practices then could have impacted the overall rate of adverse outcomes. Another major limitation which we can recognize is related to an inevitable heterogeneity in the ABC pathway criteria definition, particularly in relation to the ‘B’ criterion, which varied significantly between the studies. Notwithstanding this, it should be taken in mind that in the spirit of the original ABC pathway proposal, the point is related to the best control of the particular criterion in the individual studies, irrespective of the methods used to obtain the control or compliance with uniform targets, and to evaluate the effect on outcomes. Even though there was heterogeneity of assessments used in each study, the evaluation of the ABC criteria aimed to identify patients who were best managed to obtain the best control possible for each criterion. Lastly, for the evaluation of the ‘C’ criterion, most of the studies limited the evaluation to the main cardiovascular risk factors and comorbidities.

**CONCLUSIONS**

In this systematic review and meta-analysis, clinical management adherent to the ABC pathway was suboptimally applied, being adopted in 1 in every 5 AF patients. Adherence to the ABC pathway was associated with a significant reduction in the risk of major adverse outcomes, with a significantly reduced risk of all-cause death, cardiovascular death, stroke and major bleeding.

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**Figure 1 – Pooled Prevalence of ABC Adherent Management**

Legend: ABC= Atrial Fibrillation Better Care; CI= Confidence Interval; GLMM= Generalised Linear Mixed Model.

**Figure 2 – Impact of ABC Adherent Management on Outcomes**

Legend: Panel A) All-Cause Death; Panel B) Cardiovascular Death; Part C) Stroke; Part D) Major Bleeding; MH= Mantel-Haenszel; for other acronyms see Figure 1.

**Figure 3 – Impact of ABC Adherent Management on All-Cause Death according to Regions**

Legend: for acronyms see other figures legend.

**Figure 4 – Impact of ABC according to CHA2DS2-VASc Strata on Outcome**

Legend: Legend: Panel A) All-Cause Death; Panel B) Cardiovascular Death; Part C) Stroke; for acronyms see other figures legend.

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**Table 1 – Characteristics of the studies included in the systematic review**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **STUDY** | **REGION** | **DESIGN** | **N** | **ABC** **(N)** | **A Criterion****(%)** | **B Criterion****(%)** | **C Criterion****(%)** | **AGE****(Y)** | **CHA2DS2-VASC** | **HAS-BLED** | **OAC****(%)** | **FU****(Y)** |
| ***i) Retrospective Studies*** |
| **Gumprecht 2020**17 | Europe | MulticentreObservational | 2021 | 168 | 55.3 | 75.1 | 19.2 | 56.7 | 2.3 | 1.1 | 56.4 | 1 |
| **Koziel 2020**18 | Europe | MulticentreObservational | 2312 | 1013 | 74.5 | 90.2 | 72.2 | 69.3 | 3.4 | 2.0 | 68.6 | NA |
| **Proietti 2018**20 | North America | RCT Post-Hoc | 3169 | 222 | 46.3 | 37.5 | 32.4 | 70† | 2.9 | NA | 100 | 3.7 |
| **Proietti 2020**21 | Europe | MulticentreObservational | 6646 | 1996 | 75.1 | 80.2 | 50.8 | 68.3 | 2.9 | 1.5 | 89.6 | 1 |
| **Proietti 2021**22 | Multinational | RCT Post-Hoc | 3637 | 961 | 46.7 | 75.9 | 72.8 | 72 | 3.0 | 3.2 | 100 | 1.6 |
| **Yang 2020**23 | Asia | Nationwide Claim Registry | 262987 | 49533 | 31.4 | 82.6 | 54.3 | 62.2 | 2.0 | 1.4 | 3.2 | 5.9 |
| ***ii) Prospective Studies*** |
| **Guo 2020**24 | Asia | RCT | 3324 | 1646 | NA | NA | NA | 68.5 | 3† | 1† | 29.2 | 1 |
| **Pastori 2020**19 | Europe | Single CentreObservational | 1157 | 428 | 61.8 | 81.9 | 70.5 | 75.2 | 3.5 | 1.5 | 100 | 1.9† |

**Legend:** †median value; ABC= Atrial fibrillation Better Care; DM= Diabetes Mellitus; FU= Follow Up; HTN= Hypertension; NA= Not Available; OAC= Oral Anticoagulants; RCT= Randomized Controlled Trial.