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Main cause or reflection of multimorbidity?

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Polypharmacy and adverse events in atrial fibrillation: Main cause or reflection of multimorbidity?

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ABSTRACT

Background: Previous evidence indicated that atrial fibrillation (AF) patients with polypharmacy presented increased probability of adverse events. We investigated the prevalence of polypharmacy, risk factors for polypharmacy, and the impact of polypharmacy in clinical outcomes in a 'real-world' cohort of AF patients starting vitamin K antagonists (VKAs).

Methods: Prospective study including AF outpatients starting VKA therapy from July, 2016 to June, 2018. At inclusion, all concomitant drugs were carefully collected and recorded. Polypharmacy was defined as the intake of ≥ 5 concomitant drugs. During 2-years of follow-up, ischemic strokes/transient ischemic attacks (TIAs), fatal/nonfatal myocardial infarctions (MIs), bleeding events, venous thromboembolisms, and all-cause deaths were recorded.

Results: 1050 patients (51.5 % females, median age 77 [69–83] years) were included, and the prevalence of polypharmacy was 32.9 % (345). Female sex (OR 1.5; 95 % CI 1.11–2.03), hypertension (OR 2.53; 95 % CI 1.51–4.22), diabetes (OR 3.11; 95 % CI 2.31–4.17), vascular disease (OR 3.08; 95 % CI 2.19–4.33), heart failure (OR 1.86; 95 % CI 1.35–2.58) and dyslipidemia (OR 2.61; 95 % CI 1.9–3.58) were independently associated to the polypharmacy. Patients with polypharmacy showed significantly higher incidence of major bleeding, net clinical outcomes (composite of major bleeding, ischemic stroke/TIA, and mortality), MACE (composite of ischemic stroke/TIA, MI, and cardiovascular death), and composite thrombotic/thromboembolic events; being an independent risk factor for major bleeding (HR 1.77, 95 % CI 1.07–2.92), and composite thrombotic/thromboembolic events (HR 1.55, 95 % CI 1.05–2.31).

Conclusion: In this "real world" AF cohort, polypharmacy was highly prevalent and conditioned worse prognosis due to its association with bleeding and thromboembolic events.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia. Its prevalence is about ~2 % in the overall population, and up to 15 % in the elderly aged ≥ 80 years old [1]. However, the increasing life expectancy of the population worldwide is contributing to the increase in the prevalence of chronic diseases, including several cardiovascular conditions such as AF [2]. Classically, AF associates high morbidity and mortality mainly due to its increased risk of stroke and thromboembolism, but also secondary to the high prevalence of hypertension, heart

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failure, coronary artery disease, valvular heart disease, obesity, diabetes mellitus or chronic kidney disease, and the risk of incident comorbidities over time is higher compared to the general population [3]. Thus, to manage their comorbidities, patients with AF would need the prescription of several drugs according to different treatment guidelines, leading to polypharmacy.

Although there are different definitions of polypharmacy, the most commonly accepted is the intake of 5 or more drugs [4]. As expected, the polypharmacy is more frequent in patients aged ≥ 65 years, and therefore it has been reported a prevalence from 40 % to 95 % in AF patients [5,6]. A recent meta-analysis showed that polypharmacy is highly prevalent in AF patients and associates numerous adverse outcomes, *i.e* all-cause (and cardiovascular) mortality, major bleeding (and clinically relevant non-major bleeding [CRNMB]), heart failure, hospitalization, reduced quality of life and poorer physical function [7,8].

Patients with AF usually received oral anticoagulation (OAC, either with vitamin K antagonists [VKAs] or non-vitamin K antagonists [NOACs]), to reduce the risk of stroke and thromboembolism [9]. Despite the increasing use of NOACs, VKAs are still the most commonly used OAC in several countries, even though the efficacy and safety of VKAs depend on the quality of anticoagulant control, as reflected by the time in therapeutic range (TTR) of international normalized ratio (INR) 2.0–3.0 [10]. As VKAs are influenced by many different factors (including race, dietary vitamin K intake, comorbidities [e.g, liver disease and acute illness], and interacting drugs) [11], polypharmacy could also impact in patient prognosis when on VKA therapy.

The aim of the present study was to investigate i) the prevalence of polypharmacy and the potential associated risk factors, and ii) the impact of polypharmacy in clinical outcomes in a 'real-world' prospective cohort of AF patients starting OAC therapy with VKAs.

2. Methods

Methods of the present study have been previously published [12]. Briefly, this is a prospective observational cohort study including all outpatients from July 1, 2016 to June 30, 2018 with a recent diagnosis of AF and naïve for OAC in an anticoagulation clinic of a tertiary hospital (Murcia, Spain). The inclusion criteria were: adults AF patients (*i.e.* ≥18 years old) with documented evidence of AF on ECG and not previously taking OAC for another reason, starting VKAs for the first time. Patients with prosthetic heart valves and severe (mainly rheumatic) valvular AF were excluded. No other exclusion criteria were established.

At baseline, a complete medical history was recorded, including socio-demographic and anthropometric data, comorbidities, concomitant therapies and results of the most recent lab test. Stroke risk (CHA_2DS_2-VASc) and bleeding risk (HAS-BLED) were estimated. All concomitant drugs were carefully collected and recorded. Polypharmacy was defined as the intake of ≥ 5 concomitant drugs, accordingly to previous definitions [4]. The quality of anticoagulation with VKA was measured by using the TTR calculated by the linear interpolation method of Rosendaal at 1-year after entry [13].

The study protocol was approved by the Ethics Committee from the University Hospital Morales Meseguer (reference: EST: 20/16) and was carried out in accordance with the ethical standards established in the 1964 Declaration of Helsinki its subsequent amendments. Informed consent was required to participation in this study.

2.1. Follow-up and clinical outcomes

Follow-up was performed according to the standard of care at each routine visit to the outpatient anticoagulation clinic or visits for the anticoagulation control. If the patient never attends to these visits, medical records and telephone calls were used to obtain the information needed and vital status, with no specific interventions and no specific visits for study purposes.

Follow-up was extended for two years. During this period, ischemic stroke/transient ischemic attack (TIA), major bleeding (defined based on 2005 International Society on Thrombosis and Haemostasis (ISTH) criteria [14]), and all-cause mortality, were recorded as the *primary endpoints*. Net clinical outcomes (as the composite of major bleeding, ischemic stroke/TIA, and all-cause mortality), major adverse cardiovascular events (MACE, as the composite of fatal/nonfatal myocardial infarction, cardiovascular death, and ischemic stroke/TIA), composite thrombotic/thromboembolic events (any of the following: myocardial infarction, ischemic stroke/TIA, venous thromboembolism [VTE, including both deep vein thrombosis and pulmonary embolism]) and the composite of major bleeding/CRNMB (according to the 2015 ISTH criteria [15]), were settled as *secondary outcomes*. The investigators identified, confirmed, and recorded all clinical outcomes.

Table 1
Baseline demographic and clinical characteristics of patients with and without polypharmacy.

	Polypharmacy N = 345	No polypharmacy N = 705	p-value
Demographic			
Female sex, n (%)	186 (53.9)	354 (50.2)	0.260
Age (years), median (IQR)	78 (71–83)	77 (69–83)	0.442
Comorbidities, n (%)			
Hypertension	324 (93.9)	555 (78.7)	< 0.001
Dyslipidemia	264 (76.5)	349 (49.5)	< 0.001
Diabetes	206 (59.7)	189 (26.8)	< 0.001
Heart failure	122 (35.4)	141 (20.0)	< 0.001
Coronary artery disease	123 (35.7)	68 (9.6)	< 0.001
Peripheral artery disease	33 (9.6)	33 (4.7)	0.002
Stroke/TIA/ thromboembolism	72 (20.9)	91 (12.9)	0.001
Renal disease	94 (27.2)	103 (14.6)	< 0.001
COPD/OSAH	82 (23.8)	149 (21.1)	0.333
Cancer	43 (12.5)	107 (15.2)	0.238
History of bleeding	64 (18.6)	110 (15.6)	0.228
Smoking habit	55 (15.9)	104 (14.8)	0.613
Anemia	76 (22.0)	97 (13.8)	0.001
Abuse of alcohol	24 (7.0)	48 (6.8)	0.929
Hepatic disease	29 (8.4)	40 (5.7)	0.093
% TTR, median (IQR)*	63.4 (50.5–75.4)	64.6 (50.2–79.2)	0.187
TTR < 65 %, n (%)*	158/296 (53.4)	318/626 (50.8)	0.464
TTR < 70 %, n (%)*	184/296 (62.2)	373/626 (59.6)	0.455
CHA_2DS_2-VASc, median (IQR)	5 (4–6)	4 (3–5)	< 0.001
HAS-BLED, median (IQR)	3 (2–4)	2 (2–3)	< 0.001

COPD/OSAH = chronic obstructive pulmonary disease/obstructive sleep apnoea/hypopnoea; IQR = interquartile range; TIA = transient ischemic attack; TTR = time in therapeutic range.
*Time in therapeutic range available in 922 patients (296 from the group with polypharmacy and 626 from the group without polypharmacy).

2.2. Statistical analysis

Quantitative variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) as appropriate, whilst categorical variables were expressed as absolute frequencies and percentages. The Pearson Chi-squared test was used to compare proportions and differences between quantitative and categorical variables were assessed using the Mann-Whitney U test or the Student *t* test, as appropriate.

Logistic regression was used to investigate baseline variables associated with polypharmacy. A univariate significance level of 0.05 was required to allow a variable into the multivariate model (SLENTRY = 0.05) and a multivariate significance level of 0.05 was required for a variable to stay in the model (SLSTAY = 0.05). Results were reported as odds ratio (OR) with 95 % confidence interval (CI). Similarly, Cox proportional hazard regression models were performed to determine the association between polypharmacy and the different endpoints. Again, univariate significance level of 0.05 was required to allow a variable into the multivariate model (SLENTRY = 0.05) and a multivariate significance level of 0.05 was required for a variable to stay in the model

Table 2
Distribution of drugs in patients with and without polypharmacy.

Drug, n (%)	Polypharmacy N = 345	No polypharmacy N = 705	p-value
Antiarrhythmics	54 (15.7)	70 (9.9)	0.007
Amiodarone	64 (18.6)	55 (7.8)	< 0.001
Flecainide	22 (6.4)	47 (6.7)	0.859
Digoxin	53 (15.4)	41 (5.8)	< 0.001
ACE inhibitors	98 (28.4)	161 (22.8)	0.049
Angiotensin II receptor blockers	194 (56.2)	262 (37.2)	< 0.001
Calcium channel blockers	152 (44.1)	168 (23.8)	< 0.001
Lipids-lowering agents	282 (81.7)	276 (39.1)	< 0.001
Beta-blockers	292 (84.6)	434 (61.6)	< 0.001
Diuretics	273 (79.1)	301 (42.7)	< 0.001
Oral antidiabetics	164 (47.5)	88 (12.5)	< 0.001
Insulin	71 (20.6)	20 (2.8)	< 0.001
Antiplatelets	161 (46.7)	97 (13.8)	< 0.001

ACE = angiotensin converting enzyme.

Table 3
Multivariate logistic regression analysis of the variables associated with polypharmacy.

	OR	95 % CI	p-value
Female sex	1.50	1.11–2.03	0.008
Hypertension	2.53	1.51–4.22	< 0.001
Diabetes	3.11	2.31–4.17	< 0.001
Dyslipidemia	2.61	1.90–3.58	< 0.001
Heart failure	1.86	1.35–2.58	< 0.001
Vascular disease*	3.08	2.19–4.33	< 0.001

*Coronary artery disease and/or peripheral artery disease.
CI = confidence interval; OR = odds ratio.

(SLSTAY = 0.05). Results were reported as hazard ratio (HR) with 95 % CI.

Annual event rates with their Poisson 95 % CI were calculated for patients with and without polypharmacy as the number of adverse clinical outcomes divided by the exposure period in patients-years (PYs), and expressed as number of events per 100 PYs. The difference between two annual event rates and the associated p-value was calculated. Finally, survival analyses by Kaplan-Meier estimates were performed to assess differences in event-free survival distributions, which were compared using the log-rank test.

A p-value < 0.05 was accepted as statistically significant. Statistical analyses were performed using SPSS v. 25.0 (SPSS, Inc., Chicago, IL, USA), and MedCalc v. 16.4.3 (MedCalc Software bvba, Ostend, Belgium) for Windows.

3. Results

A total of 1050 patients (51.5 % females with a median age of 77 [IQR 69–83] years old) were included in the study. The median CHA_2DS_2-VASc was 4 (IQR 3–5) and the median HAS-BLED was 2 (IQR 2–3).

The prevalence of polypharmacy was 32.9 % (n = 345). Patients with polypharmacy took a median of 5 drugs (IQR 5–6) whereas the median of drugs prescribed in patients without polypharmacy was 3 (IQR 2–4) (p < 0.001).

Table 1 shows demographic and clinical characteristics of patients with and without polypharmacy. The prevalence of several comorbidities was higher in patients with polypharmacy, as it did the CHA_2DS_2-VASc and HAS-BLED scores. Of note, patients with polypharmacy had a similar median TTR than patients without polypharmacy (63.4 % [IQR 50.5–75.4] *vs.* 64.6 % [IQR 50.2–79.2]; p = 0.187), with no significant difference in the proportion of patients with TTR < 65 % (53.4 % *vs.* 50.8 %; p = 0.464). Regarding drugs, all were significantly more common in patients with polypharmacy, except in the case of flecainide. The most common drug in both groups was beta-blockers, followed by lipids-lowering agents and diuretics in patients with polypharmacy; and diuretics and lipids-lowering agents in patients with no polypharmacy (Table 2).

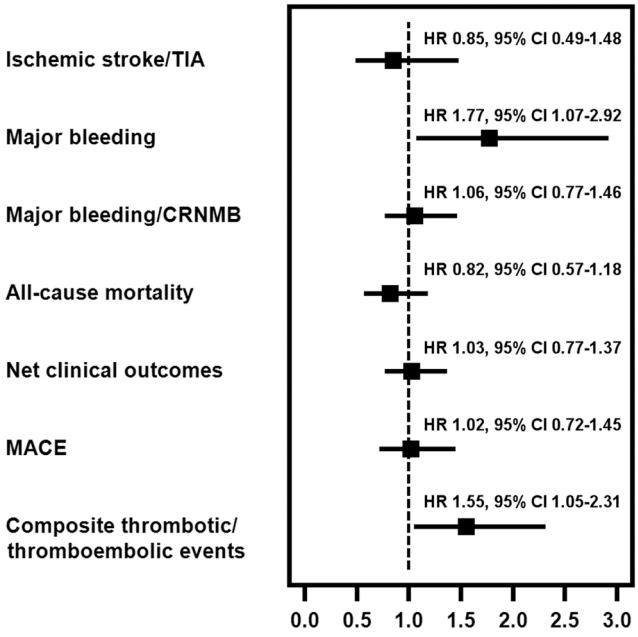

Fig. 1. Forest plot of adjusted hazard ratios for the primary and secondary outcomes according to the presence of absence of polypharmacy. TIA = transient ischemic attack; CRNMB = clinically relevant non-major bleeding; MACE = major adverse cardiovascular events. *Adjusted hazard ratios by the following variables: age, sex, hypertension, diabetes, ischemic stroke/TIA/SE, vascular disease, heart failure, chronic kidney disease, history of bleeding, alcohol abuse, hepatic disease, and cancer.

When we investigate variables associated with polypharmacy, we found that female sex (OR 1.50; p = 0.008), hypertension (OR 2.53; p < 0.001), diabetes (OR 3.11; p < 0.001), vascular disease (OR 3.08; p < 0.001), heart failure (OR 1.86; p < 0.001) and dyslipidemia (OR 2.61; p < 0.001) were independently related to the presence of polypharmacy, thus showing that polypharmacy is subordinate mainly to multimorbidity (Table 3).

3.1. Polypharmacy and adverse events

Regarding clinical events during the follow-up, the incidence of ischemic stroke/TIA was 3.62 (95 % CI 2.34–5.35) per 100 PYs in patients with polypharmacy and 2.98 (95 % CI 2.15–4.03) per 100 PYs in patients without polypharmacy (p = 0.437). Major bleeding events were more frequent in patients with polypharmacy (4.64 [95 % CI 3.17–6.55] *vs.* 2.27 [95 % CI 1.55–3.20] per 100 PYs; p = 0.003), but not the composite of major bleeding/CRNMB (11.01 [95 % CI 8.68–13.79] *vs.* 9.22 [95 % CI 7.70–10.95] per 100 PYs; p = 0.218). Similarly, there were no significant differences in terms of all-cause mortality between patients with and without polypharmacy (9.13 [95 % CI 7.02–11.68] *vs.* 7.80 [95 % CI 6.41–9.40] per 100 PYs; p = 0.319). However, patients with polypharmacy demonstrated a significantly higher incidence of net clinical outcomes (15.07 [95 % CI 12.32–18.26] *vs.* 11.21 [95 % CI 9.53–13.10] per 100 PYs; p = 0.019), MACE (10.00 [95 % CI 7.78–12.66] *vs.* 6.80 [95 % CI 5.51–8.31] per 100 PYs; p = 0.014), and composite thrombotic/thromboembolic events (7.83 [95 % CI 5.88–10.21] *vs.* 4.04 [95 % CI 3.06–5.24] per 100 PYs; p < 0.001), as compared to patients without polypharmacy.

Importantly, multivariate Cox regression analyses demonstrated that

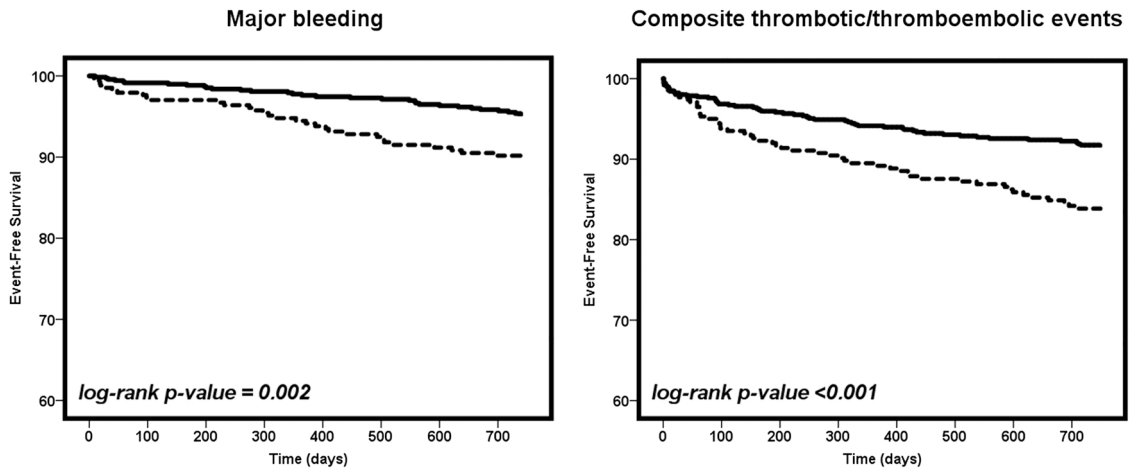

Fig. 2. Kaplan-Meier survival curves for the major bleeding and composite thrombotic/thromboembolic outcomes according to polypharmacy. Solid line = patients without polypharmacy; Dashed line = patients with polypharmacy.

polypharmacy was an independent risk factor for major bleeding (aHR 1.77, 95 % CI 1.07–2.92; p = 0.026), and composite thrombotic/thromboembolic events (aHR 1.55, 95 % CI 1.05–2.31; p = 0.030) (Fig. 1). Kaplan-Meier survival analyses confirmed these observations (log-rank p-value = 0.002 for major bleeding and <0.001 for composite thrombotic/thromboembolic events) (Fig. 2).

3.2. Subanalysis of polypharmacy and bleeding outcomes

We further investigated whether the association of polypharmacy with bleeding outcomes was particularly driven by concomitant administration of antiplatelets. Thus, patients who had not antiplatelets among one of the *at least* 5 drugs to be considered polypharmacy presented not significantly higher risk of major bleeding (aHR 1.17, 95 % CI 0.60–2.30; p = 0.642). On the contrary, patients whom polypharmacy included antiplatelets showed 252 % higher risk of major bleeding (aHR 2.52, 95 % CI 1.43–4.44; p = 0.001).

Similar results were found regarding major bleeding/CRNMB. Patients whom polypharmacy did not included antiplatelets prescribed had not significantly higher risk of major bleeding/CRNMB (aHR 0.95, 95 % CI 0.64–1.40; p = 0.796), whereas patients whom polypharmacy included antiplatelets demonstrated increased major bleeding/CRNMB risk (aHR 1.60, 95 % CI 1.14–2.26; p = 0.007).

4. Discussion

This prospective real-world study shows that polypharmacy is highly prevalent among patients with AF taking VKAs, and that polypharmacy is associated with worse clinical outcomes. This is in accordance with data derived from previous studies and clinical trials, whereby the reported prevalence of polypharmacy in patients with AF ranged from 30 % to 64 %, although it varied according to the study population and the criteria established as the definition of polypharmacy [16–18].

Previous evidence indicated that anticoagulated patients with polypharmacy have an increased probability of adverse events such as bleeding, and mortality [5,7]. A recent systematic review showed that polypharmacy is associated with 36–84 % increase in all-cause and cardiovascular mortality, 12–48 % increase in non-relevant bleeding, and 21–68 % increase of major bleeding [19]. A sub-study of the ROCKET trial also reported that patients with polypharmacy had an increased risk of non-major clinically relevant or major bleeding (aHR 1.47, 95 % CI 1.31–1.65) [20]. Accordingly, our data show that polypharmacy is associated with an increase in major bleeding events. This is could be particularly relevant if antiplatelets are one of the drugs leading to polypharmacy, as the risk of bleeding is higher when antiplatelet therapy is combined with OAC [21]. Furthermore, in our cohort, polypharmacy was associated with an increase of thrombotic events. Thus, we demonstrated that polypharmacy is associated with higher risk of both bleeding and thrombosis.

On the other hand, it is well known that VKAs interact with several drugs, which make difficult to reach and maintain a therapeutic INR, leading an unpredictable dose-response and an increased risk of bleeding or thromboembolic events [22,23]. In the ThrombEVAL study, the TTR was lower in individuals taking more of 5 drugs compared with individuals without polypharmacy. In addition, a significantly higher variability of INR measurements was found in the presence of polypharmacy, and higher risk of bleeding, hospitalization and all-cause mortality [7]. Similarly, patients with polypharmacy in our study also showed lower TTR and a higher risk of adverse clinical outcomes. The use of NOACs might mitigate the interacting effect of several drugs on anticoagulation therapy, as they present less drug-drug interactions [24]. In fact, in an analysis of pooled data from the US Centers for Medicare and Medicaid Services and US commercial claims databases, the rate of adverse events was lower in patients with AF and polypharmacy who were receiving NOACs compared to VKAs [25].

The underlying mechanisms by which polypharmacy is associated with adverse effects are multifactorial. It is important to highlight that patients with AF usually suffer from several cardiovascular risk factors and other comorbidities, which favors the administration of multiple drugs. Indeed, polypharmacy is a marker of multimorbidity and we clearly demonstrated here that polypharmacy was independently associated with some of these common comorbidities, including hypertension, diabetes vascular disease, and heart failure. Thus, polypharmacy could be a marker of health status in AF patients, characterizing patients with a higher risk profile of multiple comorbidities and helping to identify frail patients. Beyond stroke prevention, symptom management and management of cardiovascular risk factors are equally needed in AF. Indeed, multimorbidity is common amongst AF patients and contributes to worse clinical outcomes and quality of life [26]. The management of AF could be well-addressed by following the integrated and holistic Atrial fibrillation Better Care (ABC) pathway [27], which encompasses the three main pillars of AF: avoiding stroke by using OAC therapy (A); better symptom management (B); and cardiovascular risk factors and comorbidities optimization (C).

Patients with polypharmacy require special attention, based on closer and more intensive follow-up focused on their needs. It is central to carefully review the patients' prescriptions to evaluate potential drug-drug interactions, the risk-benefit ratio of each treatment and to implement a close monitoring strategy. Strategies aimed at reducing inappropriate prescriptions or the cessation of unnecessary drugs that

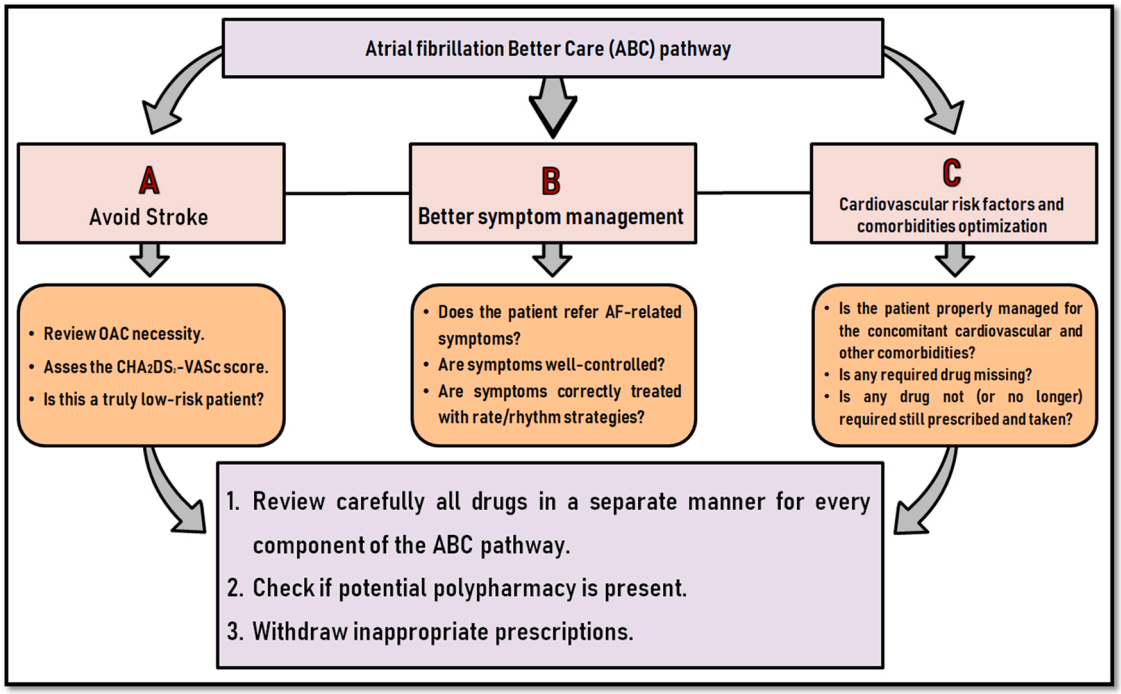

Fig. 3. Proposed algorithm for integrating the assessment of polypharmacy within the ABC pathway.

sometimes are used lifelong are necessary. The de-prescription process can be associated with a reduction in adverse events [18,28]. For example, different focused interventions may aid in the de-prescription process of not yet required antiplatelets, leading to a reduction of bleeding [29]. Moreover, the use of polypills may help in achieving therapeutic targets and reduce the number of daily pills [30].

In this sense, an algorithm is proposed in Fig. 3, integrating the process of assessing polypharmacy and therefore also deprescribing, across the ABC pathway.

4.1. Limitations

Our study has some limitations. The main is its observational nature, with a Caucasian-based population and single centre design. It was performed in a single anticoagulation clinic. In addition, it should be noted that we included patients starting OAC therapy with VKA for the first time. Previous studies have shown that the initial period of OAC is associated with higher variability in INR values and an increased risk of adverse events, particularly bleeding ones, especially during the first three months of VKA therapy [11], which may have some influence on the results. However our dataset was collected prospectively, under a careful follow-up. Thus, all events (even very early ones) were recorded. Importantly, no patient was lost to follow-up for the present analysis.

Additionally, we would like to recognize that our results could not apply to a NOAC-treated population, were the risk of several outcomes could be attenuated by the effect of NOACs, and polypharmacy may have a different degree of importance. Also, we should acknowledge the lack of data on non-cardiovascular drugs including those to treat epilepsy that may also affect TTR for drug-drug interactions and have an impact on clinical outcomes.

5. Conclusions

In this "real world" AF cohort, we demonstrated that polypharmacy is highly prevalent and conditioning a worse prognosis due to its association with bleeding and thromboembolic events. Interestingly, the association of several conditions that were independently related to the presence of polypharmacy demonstrated that polypharmacy is subordinate mainly to multimorbidity.

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CRediT authorship contribution statement

José Miguel Rivera-Caravaca, Vanessa Roldán, Lorena Martínez-Montesinos and Eva Soler contributed to data collection, performed statistical analyses and drafted the manuscript. Stefan Agewall, Gregory Y.H. Lip and Francisco Marín conceived the study and critically revised the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest statement

JMRC: Consultant for Idorsia Pharmaceuticals LTD. SA: Consultant and speaker for Bayer, Boehringer Ingelheim and Daiichi-Sankyo. GYHL: Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim and Daiichi-Sankyo. No fees are received personally. There is nothing to disclose for other authors.

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