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Original Article

Prognostic implications of adherence to oral anticoagulants among patients with atrial fibrillation: Insights from MISOAC-AF trial

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ABSTRACT

Objectives: To explore the implications of adherence to oral anticoagulants (OACs) on all-cause mortality and cardiovascular outcomes in patients with atrial fibrillation (AF).
Methods: This post-hoc analysis of the MISOAC-AF trial included recently hospitalized patients with AF. Adherence to OACs was assessed by the proportion of days covered (PDC). Good adherence was defined as PDC >80 %. Cox regression models were used to associate PDC with clinical outcomes of all-cause death, cardiovascular death (CVD), stroke, and bleeding. A sub-analysis was performed among adherent patients to compare outcomes between vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs).
Results: During a median 31-month follow-up, 778 cardiac patients with comorbid AF who had been prescribed OACs upon hospital discharge were studied. The mean PDC was 0.78; 66 % of patients had good adherence (>80 %) which was associated with lower risk of all-cause death [adjusted hazard ratio (aHR): 0.64; 95 % confidence interval (CI): 0.46 to 0.84, $p < 0.001$] and CVD (aHR: 0.70; 95 % CI: 0.50 to 0.97, $p = 0.03$). The risk of stroke and major or non-major bleeding did not differ by adherence status. Among adherent patients to OACs, VKA use was associated with higher rates of all-cause death ($p < 0.001$), CVD ($p < 0.001$), and stroke ($p = 0.01$); no differences were found regarding major or non-major bleeding risk.
Conclusions: In recently hospitalized patients with AF, good adherence to OACs was associated with a reduced risk of all-cause death and CVD. The rates of stroke or bleeding events were not significantly different. VKAs were associated with more adverse events compared to DOACs.

Introduction

Atrial fibrillation (AF) constitutes the most common sustained arrhythmia worldwide [1] and is a leading cause of mortality and morbidity [2]. Its proper management is guided by anticoagulation regimens to reduce the risk of thromboembolic events [3]. However, outside the controlled environment of hospitals, the effectiveness of anticoagulant therapy largely depends on patients' adherence.

Although direct oral anticoagulants (DOACs) have managed to circumvent safety concerns and inconvenience following vitamin K antagonist (VKA) use [4], suboptimal adherence remains at high rates [5]. There are also concerns that adherence to DOACs may be compromised by the absence of regular monitoring of the coagulation level. Several studies have previously attempted to elucidate adherence to oral anticoagulants (OACs) in patients with AF [6–8], with the results being controversial and depending on the type of anticoagulant, the characteristics of the study population, and sample size [9–11]. However, there are scarce data correlating the adherence implementation phase, which reflects whether patients actually follow their prescribed dose, with hard clinical outcomes.

This study aimed to analyze a 'real-world' contemporary cohort of hospitalized patients with coexisting AF. Our primary aim was to assess the association between adherence to OAC regimens and hard clinical outcomes. In addition, we explored the potential association of OAC type with the risk of all-cause death, CVD, stroke, and major or non-major bleeding.

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Methods and materials

Study design and study population

This is a post-hoc analysis of the MISOAC-AF (Motivational Interviewing to Support Oral AntiCoagulation Adherence in patients with non-valvular Atrial Fibrillation; NCT 2941978) trial. Briefly, the MISOAC-AF trial included 1140 consecutive adult patients (aged >18 years) who were hospitalized with any diagnosis and comorbid electrocardiographically confirmed non-valvular AF or atrial flutter (first diagnosed, paroxysmal, persistent, or permanent) from December 2016 to June 2018. The trial aimed to assess the prognostic role of encouraging compliance to OACs in patients with AF, via patient-physician interviews and improved individualized scripted guidance. The design and

Table 1
Population baseline characteristics grouped by adherence status.

Parameters	Adherent to OACs	Non-adherent to OACs	*p*-Value
	$N = 511$	$N = 267$	
Demographics			
Male sex - No (%)	259(50.7)	139(52.1)	0.65
Age (years) - Means (±SD)	73.9(±9.8)	73.1(±11.4)	0.32
BMI (kg/m^2) - Means (±SD)	28.8(±5.3)	29.0(±5.3)	0.78
Education level - No (%)			
None or primary	318(64.4)	164(63.4)	0.12
Secondary	109(21.7)	50(19.3)	
Tertiary	70(13.9)	42(16.2)	
Place of living - No (%)			0.92
Countryside with INR measurement	154(30.7)	77(33.3)	
Countryside without INR measurement	28(5.6)	16(6.2)	
City	320(62.6)	166(64.1)	
Case - No (%)			<0.01
Intervention	294 (57.5)	96(36.0)	
Control	217(42.5)	171(64.0)	
PDC - Means (±SD)	0.97(±0.05)	0.43(±0.25)	<0.01
Medical history - No (%)			
Alcohol consumption	190(37.9)	93(35.9)	0.58
History of angina during or prior to hospitalization	65(13.0)	43(16.6)	0.17
Physical exercise - No (%)	208(41.6)	95(36.7)	0.18
History of ischemic stroke, TIA, or unspecified stroke	73(14.6)	45(17.4)	0.30
History of cardiac arrest	7(1.4)	13(5.0)	<0.01
Prior major bleeding or predisposition to bleeding	55(11.0)	43(16.6)	0.02
History of smoking	219(43.7)	134(51.7)	0.03
Underlying diseases - No (%)			
AF types - No (%)			0.02
First diagnosed	50(10.1)	19(7.4)	
Paroxysmal or atrial flutter	181(36.6)	75(21.9)	
Persistent or permanent	264(53.3)	164(63.6)	
Thyroid disease	113(22.6)	58(22.4)	0.96
COPD	63(12.6)	49(18.9)	0.02
CKD	63(10.3)	55(16.2)	<0.01
GID	94(18.8)	52(20.1)	0.66
Diabetes mellitus	166(33.1)	87(33.6)	0.89
Rheumatic disease	7(1.4)	13(5.0)	<0.01
Cardiomyopathy	18(7.0)	30(7.0)	0.20
History of acute MI prior to hospitalization	88(17.6)	66(25.5)	0.01
History of coronary artery disease	188(37.5)	124(47.5)	<0.01
Parameters on admission - Means (±SD)			
SBP	142.4(±23.8)	141.3(±25.8)	0.93
DBP	82.4(±15.2)	79.7(±15.6)	0.29
Hemoglobin	12.4(±2.1)	12.5(±2.6)	0.93
INR	1.5(±0.9)	1.7(±0.9)	0.02
eGFR	65.4(±31.4)	68.2(±33.8)	0.27
CHA2DS2-VASC score - Means (±SD)	3.4(±1.8)	4.5(±2.0)	0.14
HAS-BLED score - Means (±SD)	1.7(±1.0)	2.0(±1.2)	0.01
Type OACs at discharge - No (%)			
Acenocumarol	112(21.9)	149(55.8)	<0.01
Apixaban	137(26.8)	54(20.2)	
Rivaroxaban	184(36.0)	40(15.0)	
Dabigatran	78(15.3)	24(9.0)	
Other medication at discharge - No (%)			
Rate control	473(76.7)	276(81.2)	0,38
Rhythm control	126(21.1)	57(22.6)	0.77
Antiplatelets	116(23.7)	58(22.8)	0.26
LMWH	6(1.2)	1(0.4)	0.49
ACE/ARB	246(50.4)	109(43.3)	0.07

AF, atrial fibrillation; PDC, proportion of days covered; SD, standard deviation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; TIA, transient ischemic attack; GID, Gastrointestinal Disease; MI, myocardial infraction; LMWH, Low-molecular-weight heparin; CHA2DS2-VASC score, Congestive Heart Failure, High blood pressure, Age, Diabetes, Previous stroke or clot, Vascular disease, Age, Sex (one point if female); HAS-BLED, Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage; SBP, systolic blood pressure; DBP, diastolic blood pressure; INR, international normalized ratio; eGFR, estimated glomerular filtration rate; OACs, oral anticoagulants; ACE, angiotensin-converting–enzyme; ARB, angiotensin II–receptor blocker, BMI, body mass index.

main results of the MISOAC-AF trial have been already published [12, 13]. In the present study patients with i) missing data concerning OACs adherence or ii) an intentionally short-term anticoagulation prescription under a physician's recommendation (e.g. a recent single episode of AF) or iii) ascertained death within 3 months of discharge or iv) no prescription of OACs at discharge were excluded. The study has been performed in accordance with the general principles outlined in the Declaration of Helsinki and has been approved by the Ethics Committee of the Aristotle University of Thessaloniki.

Study variables

All demographic, clinical, and medication variables were obtained from the MISOAC-AF database. Patients' adherence to OACs was determined according to the proportion of days covered (PDC) and the corresponding proportion of claimed prescriptions during the follow-up period. PDC ranges from 0 to 100 % and good adherence was defined as PDC >80 %, a threshold supported by the International Society for Pharmaceutical and Outcomes Research [14] and the Pharmacy Quality Alliance [15]. For instance, during a 365-month follow-up, a patient with 300 prescriptions of DOACs would have a PDC of 300/365 = 0.82, which indicates good adherence to OAC treatment since 0.82 > 0.80. In this study, VKA refers to acenocoumarol as it is the only VKA used in Greece, while using DOACs are: apixaban, rivaroxaban, and dabigatran. AF was determined as an electrocardiographically reported episode of atrial arrhythmia with abnormal heart rhythm, and non-detectable P waves, which lasts >30 s. Major or non-major bleeding events were defined according to International Society on Thrombosis and Haemostasis bleeding scale (ISTH) and the Subcommittee on Control of Anticoagulation (SCC) [16]. CHA_2DS_2-Vasc (Congestive Heart Failure, High blood pressure, Age, Diabetes, Previous stroke or clot, Vascular disease, Sex) and HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol) scores were calculated. The above formulas measure thrombotic and bleeding risk, respectively. Estimated glomerular filtration rate (eGFR) was estimated by inputting the respective creatinine values into the Cockcroft-Gault formula.

Follow up and study outcomes

Follow-up data concerning deaths were collected twice a year using the web-based national health insurance system while stroke and bleeding events were identified either through hospital reports or by telephone contact. The follow-up process was completed in April 2020. PDC was calculated for any OAC administered at discharge in each patient. Patients under VKA usage were asked during the interviews whether their international normalized ratio (INR) measurements that were taken throughout the first year after discharge were within therapeutic range. Labile INR for a patient on VKAs was defined as poor time in therapeutic range (<65 %).

Our main analysis included the classification of patients according to their adherence status (PDC <0.8 or PDC ≥0.8) and the comparison between adherents and non-adherents regarding all-cause death, CVD, stroke, and major or non-major bleeding. The secondary analysis included the comparison between VKAs and DOACs of the aforementioned outcomes in the group of adherent patients.

Statistical analysis

Patients were grouped by adherence status during follow up, as defined above. Baseline characteristics were compared using the chi-square test or Fisher's exact test for categorical variables and the 2-sided Student's *t*-test or Mann-Whitney's for continuous variables. Continuous variables are summarized by mean ± standard deviation (SD), or median and interquartile range (IQR), and categorical variables are represented by frequencies and percentages (%). A two-sided *p*-value of <0.05 was accepted as statistically significant, and all outcomes are reported with 95 % confidence intervals. Time-to-event analyses were conducted to compare the two adherence statuses and the different types of OACs regarding outcomes. Patients were censored at the time of the event or last contact from the study investigator. Missing data were handled using imputation method. Event rates between groups were presented with the use of Kaplan-Meier (KM) curves and compared by the long-rank and long rank-Mantel-Cox tests. For our main analyses, multivariable Cox proportional hazard models were utilized to adjust the hazard for the following clinically relevant and potentially confounding baseline covariates: age, gender, body mass index, AF subtypes, HAS-BLED score at discharge, PDC, any prior history of stroke (ischemic, transient ischemic accident, unspecified), history of major bleeding, smoking, history of rheumatic disease, history of obstructive pulmonary disease, history of coronary artery disease, history of thyroid disease, history of cardiac arrest, history of diabetes mellitus, and case type (intervention or control). All measured hazard ratios concerning adherence demonstrate the hazard for events, considering patients with PDC <0.8 as the reference group. IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) was used for data management and analysis and R version 4.1.3 by the first author (R Foundation, Vienna, Austria).

Results

Patients' characteristics

A total of 1140 patients with AF (mean age 73.6 ± 10.0 years; 53.9 % male) discharged from the cardiology ward were studied. Of them, 778 patients were eligible for the present analysis. Clinical characteristics of patients on admission and post-discharge are presented in Table 1. Generally, there was homogeneity among groups concerning demographic characteristics, medical history, and treatment. Overall, 511 (65.6 %) patients with AF were adherent to OAC treatment after discharge compared to 267 (34.4 %) non-adherents. The mean PDC of the population was 0.78 and while it did not differ

Outcomes	n	Unadjusted HR (95% CI)	p value	Adjusted HR (95% CI)	p value
All cause death	265	0.56 (0.43-0.71)	<0.001	0.64 (0.46-0.84)	<0.001
CVD	200	0.55 (0.41-0.72)	<0.001	0.70 (0.50-0.97)	0.03
Stroke	29	1.24 (0.54-2.82)	0.60	2.11 (0.82-5.30)	0.11
Major or non-major bleeding	61	0.85 (0.50-1.43)	0.55	0.62 (0.32-1.21)	0.16

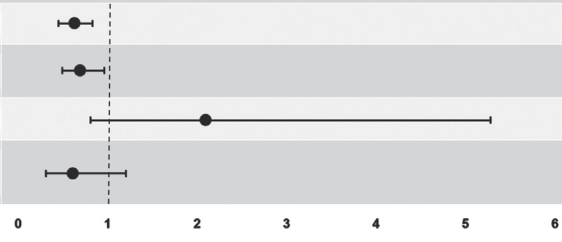
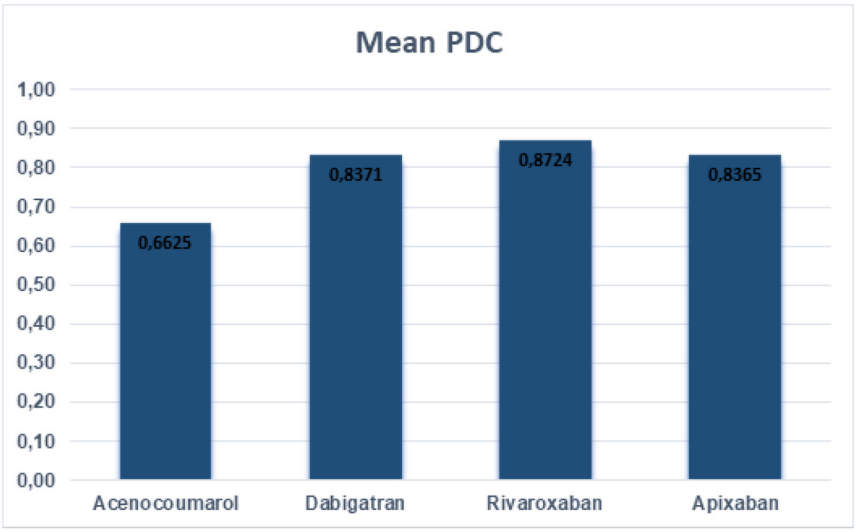
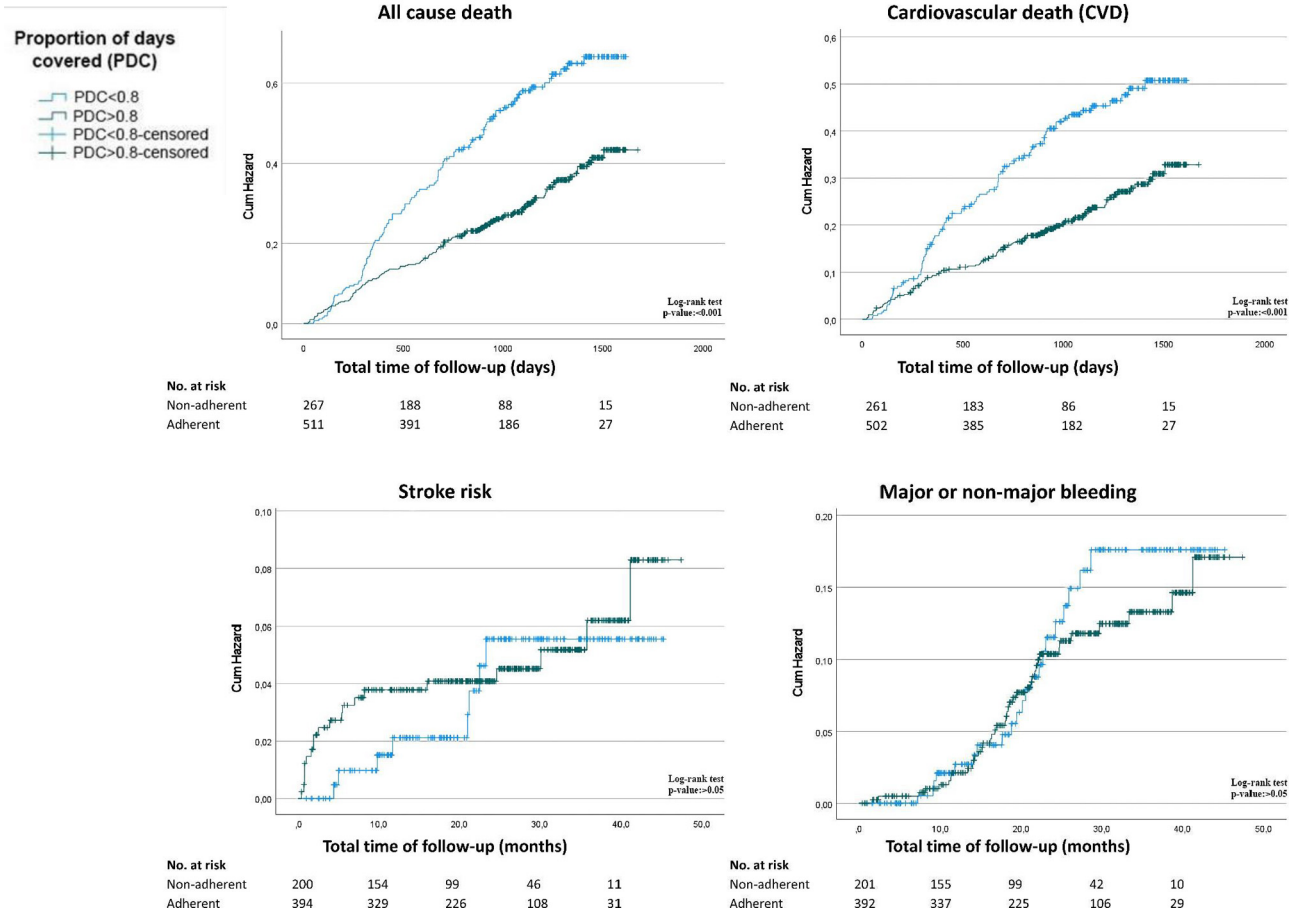


Fig. 1. Mean proportion of days covered (PDC) of oral anticoagulants (OACs) after discharge from the hospital.

between males and females a difference appeared regarding VKA compared to DOACs (Fig. 1). As compared to non-adherents, adherents had a higher mean INR level on admission, but a lower HAS-BLED score. Moreover, the presence of a history of coronary artery disease and acute myocardial infarction prior to hospitalization was more frequent in adherent patients compared to non-adherent (Table 1), while most patients with a history of cardiac arrest appeared to be non-adherent.

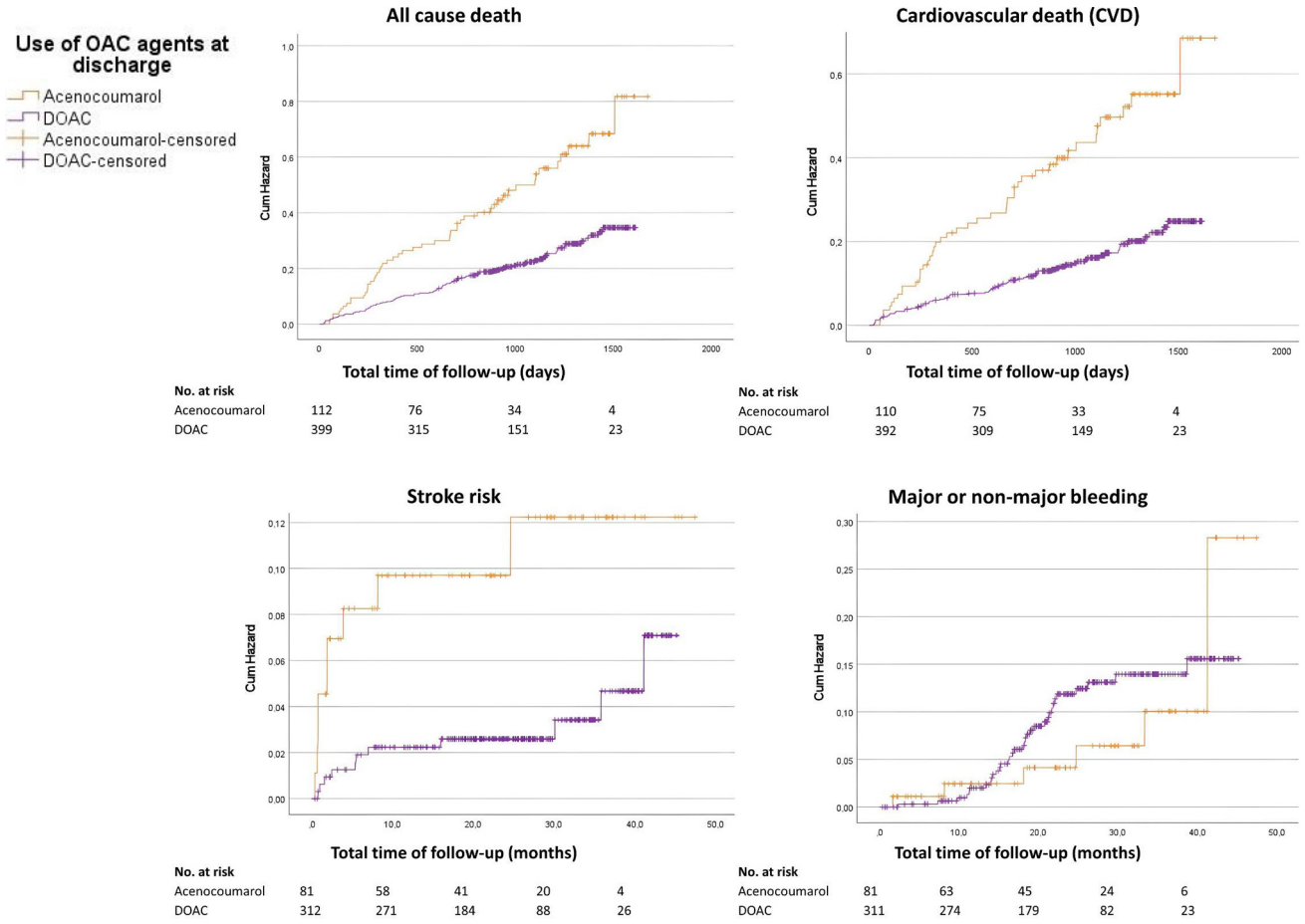


A. Mean PDC of different OACs after discharge of the hospital.



B. Kaplan-Meier curves demonstrating the cumulative hazard for all outcomes regarding the comparison of adherents and non-adherents to OACs.

Fig. 2. (A) Unadjusted and adjusted hazard ratios (HR) for all outcomes regarding adherence to oral anticoagulants. CI, confidence interval; n, number of events; CVD, cardiovascular death. (B) Kaplan-Meier curves demonstrating the cumulative hazard for all outcomes regarding the comparison of adherents (PDC > 0.8) and non-adherents (PDC < 0.8) to oral anticoagulants. (C) Kaplan-Meier curves demonstrating the cumulative hazard for all outcomes regarding the comparison of vitamin-K antagonist (acenocoumarol) and direct oral anticoagulants (DOACs). OAC, oral anticoagulant.



C. Kaplan-Meier curves demonstrating the cumulative hazard for all outcomes regarding the comparison of VKA (acenocoumarol) and DOACs.

Fig. 2 (*continued*).

Outcomes

Primary analysis

Overall, 265 patients (34.1 %) died over a median follow-up of 31 months (IQR: 10 to 52 months). Regarding adherence in those patients, 143 (28 %) were defined as adherent to the administered prescription and 122 (45.7 %) as non-adherents. The group of adherents showed a lower risk of all-cause death and CVD [(aHR): 0.64; 95 % confidence interval (CI): 0.46 to 0.84, $p < 0.001$ and 0.70; 95 % CI: 0.50 to 0.97, $p = 0.03$, respectively]. Stroke occurred in 28 (3.6 %) patients, 16 (57 %) of them being under VKA use and 12 (43 %) under DOAC use. No difference in terms of stroke risk was observed between the two groups ($p > 0.05$). Major or non-major bleeding events occurred in 61 (7.8 %) patients, 21 (34.4 %) on VKA and 40 (65.6 %) on DOACs. The risk of bleeding did not differ significantly between the adherent and non-adherent groups ($p > 0.05$). All the unadjusted and adjusted hazard ratios for all-cause death, CVD, stroke, and major bleeding or non-major bleeding are shown in Fig. 2A. The results were consistent in the sub-analysis conducted among the DOACs groups (Online Fig. 1), while in VKA group the risk of all-cause death and CVD did not differ between the two groups (Online Fig. 2). Moreover, with regards to VKA users it was found that at 1 year, labile INR was highly correlated with lower PDC (Pearson's R coefficient = −0.91). Kaplan-Meier curves for the cumulative incidence of all-cause mortality, CVD, stroke, and major or non-major bleeding by adherence status are presented in Fig. 2B.

Secondary analysis

In the group of adherent patients with AF, 112 patients (21.9 %) were on VKA (acenocoumarol) and 399 (78.1 %) on DOACs After multivariate adjustment, acenocoumarol was associated with higher rates of all-cause death (aHR: 2.46; 95 % CI: 1.67 to 3.62, $p < 0.001$), CVD (aHR: 2.91; 95 % CI: 1.90 to 4.45, $p < 0.001$), and stroke (aHR: 4.06; 95 % CI: 1.33 to 12.31, $p = 0.01$) compared to DOACs group (apixaban, rivaroxaban, and dabigatran). No statistical difference was ascertained between VKA and DOACs regarding major or non-major bleeding risk. The comparisons between all four different OACs included in the study are shown in Online Fig. 3. Time-to-event analyses using Kaplan-Meier curves for the cumulative incidence of all-cause death, CVD, stroke, and major or non-major bleeding by OAC type are presented in Fig. 2C and all the respective unadjusted and adjusted hazard ratios are shown in Fig. 3.

Discussion

In the present analysis, roughly one out of three AF patients had suboptimal adherence, with the lowest adherence rates observed among patients receiving acenocoumarol. Furthermore, good adherence to OACs was associated with a lower incidence of all-cause death and CVD, while stroke risk was not affected, and major or non-major bleeding risk was not increased. Additionally, adherent patients on acenocoumarol demonstrated worse outcomes compared to adherent

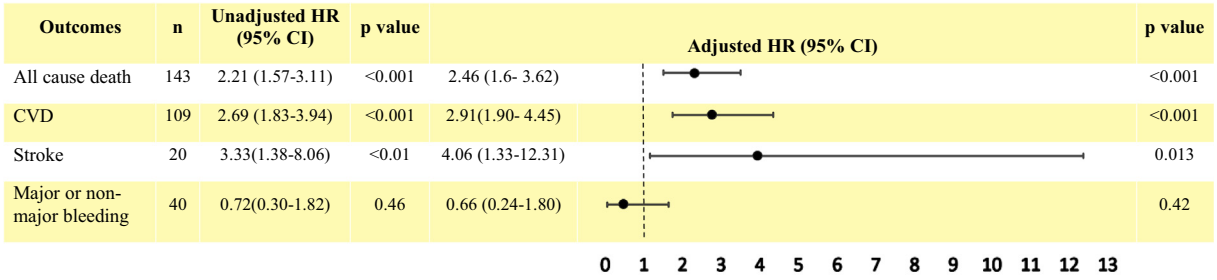


Fig. 3. All unadjusted and adjusted HRs of the secondary analysis. As a reference group in all comparisons is considered the direct oral anticoagulants (DOACs) group. HRs, hazard ratios; CI, confidence interval; n, number of events.

AF patients receiving DOACs regarding all-cause death, CVD, and stroke. To our knowledge, this is one of the few studies associating OAC adherence with hard outcomes in real-world AF patients transitioning from inpatient to outpatient care.

The main analysis of the study, in line with the previous literature [17,18], demonstrates that good adherence to OAC therapy constitutes an independent protective factor against all-cause and cardiovascular mortality. Patients' adherence was assessed through searches in electronic medical records and patient-physician interviews. Hence, the validation of prescription implementation enhanced objectivity; thus, consumption and dispensing mismatches were reduced. Other real-world studies which measured adherence to OACs mostly focused on stroke incidence rates [19,20], and the medication dispensing data relied on pharmacy databases. Additionally, a longer mean follow-up (31 months) on adherence and outcomes was reported. Regarding stroke risk, our results did not yield statistical significance, maybe due to few reported events ($n = 28$) during follow-up and the fact that above half of them that reported a stroke event were on acenocoumarol which is a drug with narrow therapeutic window and challenging regarding monitoring and optimal dose especially in "real-world" patients with comorbidities.

The secondary analysis, in accordance with the existing literature concerning hard clinical outcomes [21,22], reported a higher risk for acenocoumarol regarding all-cause death, CVD, and stroke when compared with the DOACs group. The low adherence that acenocoumarol demonstrated in the present study could explain the above outcomes combined with often unpredictable variability in response to dose [23]. The presence of other unmeasured confounders such as medication cost, especially for acenocoumarol, a low-cost drug that could be bought without a prescription, income, health literacy level, treatment anxiety, and possible concomitant medication may have led to incomplete adjustment.

Admittedly, as it has been previously described [24], medication adherence involves challenging to measurement variables that may be interconnected and interdependent. In such an observational study, the association of adherence to OACs with better outcomes could be affected by time-dependent unmeasured confounders that increase the analysis complexity. These confounders constitute a set of several behavioral and socioeconomic factors [25–27] associated with access to optimal treatment, education level, and life quality. In addition, medication treatment for AF is not a standardized intervention but a longitudinal and interactive process that may vary over time, followed by corresponding variations in adherence. In fact, optimum treatment outcomes may have an unpredictable effect on future adherence. Thus, in the present study, a partial association between adherence and hard outcomes could be established by adjusting our Cox model for baseline covariates.

Overall, good adherence (PDC >80 %) to OACs was associated with a lower risk of adverse events, while it did not increase the risk of bleeding events. However, since adherence is both a time-varying and patient-dependent covariate, it can be rather complex to demonstrate its effect on clinical outcomes. As for future studies, although supportive interviews and similar interventions showed encouraging evidence [28,29], our results suggest that there is scope for improvement. The integration of adherence and persistence counselling should be systematically encouraged during the course of treatment.

Limitations

This study has several limitations. It is a post-hoc analysis, and its design was not prespecified; thus, there were missing values, albeit in a small percentage. Moreover, the medium-sized sample resulted in smaller subgroups; therefore, caveats should be kept when interpreting those data. However, it is a single-center study and, thus, has the advantage of homogeneity of inpatient care in one cardiology ward. Another limitation is that our results may not be generalizable to the wider non-hospitalized AF population and different settings. In addition, using PDC for measuring adherence in patients on VKA carries a risk of bias due to the high variability of dosage in these regimens. Therefore, various alternative methods should be examined to assess adherence in this category, such as counting unused drugs or pills counting.

Furthermore, by nature, the study claims correlation, not causation. Finally, the vast majority of follow-up assessments were completed via telephonic contact due to the COVID-19 pandemic, which may have led to underreported stroke events. Had they been available, data concerning potential hidden confounders could have assisted in extracting more robust associations.

Conclusions

In this study of AF patients, post-discharge poor adherence to OACs was ascertained in approximately 33 % of them. Good adherence to OAC was associated with lower all-cause mortality and CVD rates. Stroke event rates in the adherent group showed no difference compared to non-adherents, while the composite of major or non-major bleeding risk was not increased. In adherent AF patients, acenocoumarol appeared to be related to a higher event risk compared to DOACs regarding all-cause death, CVD, and stroke.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jjcc.2022.09.009.

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