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RESEARCH ARTICLE

STOPP/START Anti-aggregation and Anticoagulation Alerts in Atrial Fibrillation

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Abstract: ***Background:*** Atrial Fibrillation (AF) is common in the elderly. A key component of AF management is Oral Anticoagulant Therapy (OAT), consisting of Vitamin K Antagonists (VKAs) or Direct Oral Anticoagulants (DOACs). The aim of the present study is to check, using STOPP (Screening Tool of Older Persons' Prescriptions)/START (Screening Tool to Alert to Right Treatment) Criteria, if such drugs are potentially inappropriately prescribed/omitted in an elderly population with AF, and to determine their impact on mortality.

Methods: This study included patients (n = 427) with nonvalvular AF consecutively evaluated between 2013 and 2019 at the Geriatric Outpatient Service, University Hospital of Monserrato, Cagliari, Italy, and followed up for 36 months. The OAT group included 330 patients; the other 97 patients constituted the non-OAT group. The sample was assessed for STOPP/START criteria.

Results: We found no difference ($p > 0.1$) in comorbidity burden, frailty, and cardio-cerebro-vascular disease prevalence in the two groups, which also did not present a difference in 36-month mortality ($p = 0.97$). OAT was overall appropriately taken, and 62.4% of OAT-group presented the START criterion to take antiplatelets but also the STOPP criterion not to take them, because of the simultaneous anticoagulant intake. In the non-OAT group, 69.1% presented the START criterion to take anticoagulants, and 21.6% the START criterion to take antiplatelets.

Conclusion: Patients with AF are often prone to under or over-prescription, particularly of antithrombotic drugs. The STOPP/START criteria are a valid tool to assess and correct wrong therapeutic choices. In frail and comorbid subjects, survival is not correlated with the assumption of OAT.

Keywords: Atrial fibrillation, comorbidities, comprehensive geriatric assessment (CGA), potentially inappropriate medication (PIM), potentially prescribing omission, screening tool to alert to right treatment (START), screening tool of older persons' prescriptions (STOPP), STOPP/START criteria, potential prescribing omission (PPO).

1. INTRODUCTION

Given the progressive aging of the population [1], comprehensive geriatric assessment [2], and the incidence of age-related diseases, such as immobilization syndrome, neurocognitive disorders, hypertension, and multifactorial anemia [3-6] are likewise increasing. Among them, atrial fibrillation (AF) is the most common arrhythmia in the elderly [7], and it is associated with increased frailty, morbidity, and mortality [8]. Its management may lead to control the rhythm – with electrical cardioversion, catheter ablation, or drugs (anti-arrhythmic-class Ia, Ic, III) -, the ventricular frequency, for high-frequency forms, with ablation, or drugs (*e.g.*, anti-arrhythmic-class II, *i.e.*, beta-blockers) -, and the prevention of arterial thromboembolism [9]. Oral anticoagulant therapy (OAT) is prescribed in order to prevent the risk of embolism and is represented by Vitamin K Antagonists (VKAs), including warfarin and acenocoumarol [10], and Direct Oral Anticoagulants (DOACs), earlier defined "New Oral Anticoagulants" (NOACs), including factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban), and factor IIa inhibitor (dabigatran) [11]. DOACs seem to be more manageable, present fewer drug-drug interactions, and are progressively replacing VKAs [12]. OAT uses exposed patients to an increased risk of bleeding [13-15], particularly impacting the safety of elderly people [16]; on the other hand, their non-assumption is related to increased stroke risk [13].

Anticoagulation management of AF requires particular care, especially in the elderly, due to the difficult balance of embolic and bleeding risk [17]. The Screening Tool of Older People's Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment (START) criteria [18, 19] can help physicians with appropriate prescription, and, in particular, Potentially Inappropriate Medications (PIMs) and Potentially

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Prescribing Omissions (PPOs). Their specific alerts suggest the indication to initiate and discontinue of OAT assumption, and also a potential necessity to modify posology or active principles. Nowadays, these tools are not widely used, except in specialist contexts, though, paradoxically, their administration would undoubtedly be helpful for physicians in primary care [20].

To the best of our knowledge, a few studies focused on STOPP/START alert-specific use in AF patients [21-25].

Taking the abovementioned into consideration, the primary aim of this study is to establish the necessity to initiate, modify posology, or discontinue anticoagulant therapy in a group of patients with nonvalvular AF. The secondary aim of this study is to establish if the assumption of anticoagulant drugs, or their non-assumption, is related to increased mortality.

2. METHODS

2.1. Design of the Study

This prospective study included patients consecutively evaluated at the Geriatric Outpatient Service of the University Hospital of Monserrato, Cagliari, Italy, from July 2013 to April 2019: the participants first underwent a cardio geriatric assessment and were subsequently followed up for 36 months to determine the incidence of deaths.

2.2. Inclusion Criteria

Age ≥65 years; the presence of nonvalvular AF.

2.3. Exclusion Criteria

Age <65 years; anticoagulants assumption for other reasons (*e.g.*, treatment of venous thromboembolism or pulmonary embolism); informed consent not provided.

A total of 427 patients met the inclusion criteria.

2.4. Assessment

The enrolled subjects were evaluated with:

- Charlson Comorbidity Index (CCI) [26, 27] for comorbidity burden assessment
- Fatigue. Resistance, Ambulation, Illness, and Loss of weight (FRAIL) scale [28] for the categorization of frailty
- Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65 to 74, Sex category (CHA_2DS_2-VASc) score [29,30] for estimating the risk of stroke
- Hypertension, Abnormal renal/liver function, Stroke – Bleeding history or predisposition, Labile International Normalized Ratio (INR), Elderly, Drugs/alcohol concomitantly (HAS-BLED) [13, 31] for the assessment of the 1-year risk of major bleeding in people taking anticoagulants
- STOPP/START Criteria [18,19] for the screening of PIMs and PPOs

The abovementioned tests were administered by trained geriatricians in an outpatient setting.

2.5. Statistical Analysis

Variables were expressed as means and standard deviations (SDs) or as percentages (%), as appropriate. The Kolmogorov-Smirnov test was used to check the normal distribution of the variables. Student's *t*-test test was used to compare continuous variables and the chi-squared test (χ^2) was used to compare qualitative variables. Kaplan-Meier curves were designed to estimate survival probability. Multivariate analysis was performed with a logistic regression – stepwise, excluding from the model any variables with $p > 0.1$.

The results reported indicated P-values and a 95% confidence interval (CI). MedCalc software (Version 19.5, Ostend, Belgium) was used for the statistical analysis.

3. RESULTS

The study included 427 community-dwellers with AF aged ≥ 65 years (average age: 81.5 years, SD 6.3), of whom 266 (62.3%) were women. The characteristics of the sample are shown in Table **1**.

Of the whole study population, 330 (77.3%) took oral anticoagulant drugs (OAT-group) and 97 did not (non-OAT-group), of whom 35 did not take any antiplatelet or anticoagulant drugs. The most common comorbidities were hypertension and vascular diseases (both cerebral and peripheral), followed by type 2 Diabetes Mellitus (DM), and coronary heart disease.

The two groups did not show statistically significant differences in age (p=0.175), frailty (p=0.279), comorbidity burden (p=0.868), and CHA_2DS_2-VASc scores (p=0.354), nor in the prevalence of coronary disease (p=0.382), cerebrovascular disease (p=0.300), peripheral artery disease, hypertension (p=0.975), and type 2 DM (p=0.274).

In the OAT group, 110 patients taking VKA (30 on warfarin, and 80 on acenocoumarol) were suitable for DOAC. Among 115 patients taking DOAC, 16 (13.9%) were undertreated, 11 (9.6%) presented a risk, indicating to reduce the posology, and 4 (3.5%) indicated to switch to VKA (START) due to chronic kidney failure (Fig. **1**). No STOPP alerts were found in this group.

In the non-OAT-group, as in Fig. (**2**), 67 (69.1%) patients showed the START criterion for "anticoagulation – for AF, using the CHA_2DS_2-VASc and HAS-BLED score and the need to discuss the risk and benefit with the patient. Anticoagulation was offered to those with a CHA_2DS_2-VASc score of ≥2 (≥1 or above for males), taking bleeding risk into account. Anticoagulation can be either with warfarin or a DOAC", but 28 subjects (28.9%) would show the STOPP criterion "aspirin, clopidogrel, dipyridamole, warfarin or DOACs with concurrent significant bleeding risk, *i.e.*, uncontrolled severe hypertension, bleeding diathesis, recent non-trivial spontaneous bleeding (*high risk of bleeding*)".

About platelet anti-aggregation therapy, according to the START criterion "antiplatelet therapy (aspirin, clopidogrel, prasugrel or ticagrelor) with a documented history of coronary, cerebral or peripheral artery disease", a sum of 227 patients should have taken it, of whom 206 were in the OAT-group (62.4% of the group), and 21 in the non-OAT-group (21.6% of the group).

Table 1. Characteristics of OAT and non-OAT group.

Variable	OAT (n=330)		non-OAT (n=97)		p
	Mean	*SD*	*Mean*	*SD*	*t-test*
Age	81.2	6.1	82.2	6.9	0.1748
CCI	6.69	2.1	6.7	2.2	0.8679
FRAIL	2.7	1.5	2.9	1.3	0.2786
CHA_2DS_2-VASc	4.9	1.4	5.0	1.5	0.3544
HAS-BLED	2.3	1.0	-	-	-
Co-morbidities	*%*		*%*		χ^2
Coronary Heart Disease	22.7		18.6		0.3822
Cerebrovascular Disease	38.8		32.9		0.3002
Peripheral Artery Disease	39.4		36.1		0.5564
Hypertension	83.6		83.5		0.9755
Type 2 Diabetes Mellitus	29.4		23.7		0.2743
Drugs taken	*%*		*%*		χ^2
Antiplatelet	9.7		71.1		<0.0001
Acenocoumarol	42.4		-		-
Warfarin	16.7		-		-
Apixaban	15.5		-		-
Rivaroxaban	13.9		-		-
Dabigatran	9.4		-		-
Edoxaban	2.1		-		-

Abbreviations: OAT, Oral Anticoagulant Therapy; CCI, Charlson Comorbidity Index; FRAIL, Fatigue. Resistance, Ambulation, Illness, and Loss of weight; CHA_2DS_2-VASc, Congestive heart failure, Hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65 to 74, Sex category; HAS-BLED, Hypertension, Abnormal renal/liver function, Stroke – Bleeding history or predisposition, Labile International Normalized Ratio (INR), Elderly, Drugs/alcohol concomitantly.

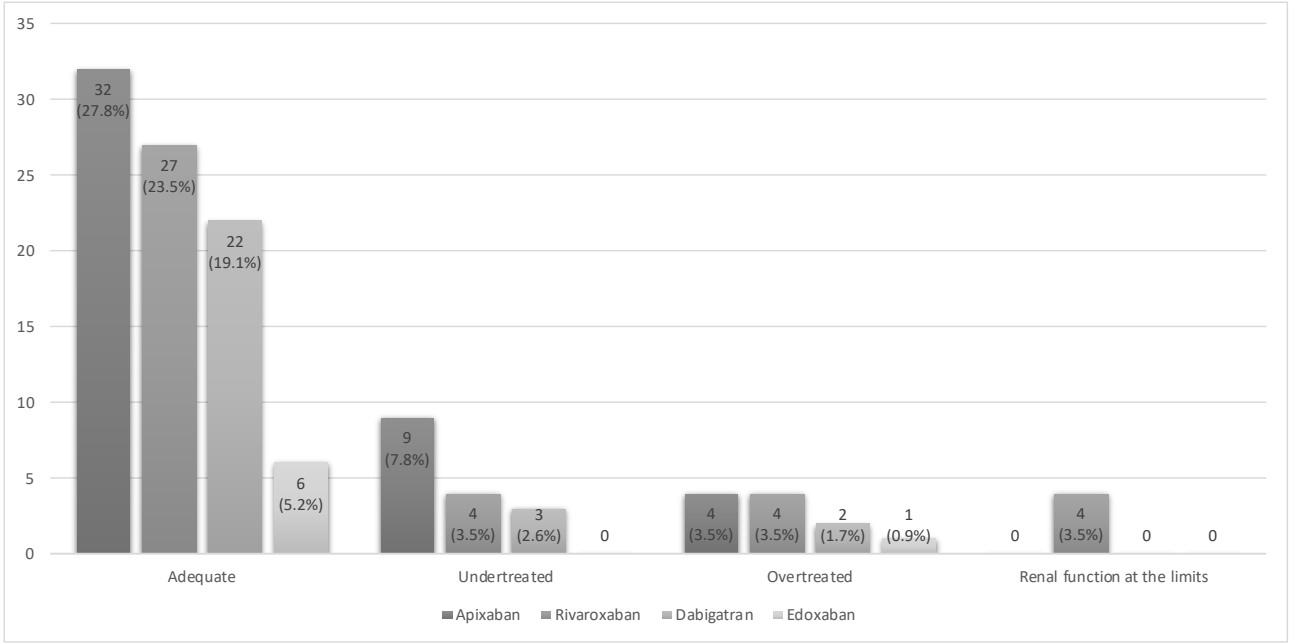

Fig. (1). OAT-group - Patients treated with DOAC. **Abbreviations:** OAT, Oral Anticoagulant Therapy; DOAC, Direct Oral Anticoagulant.

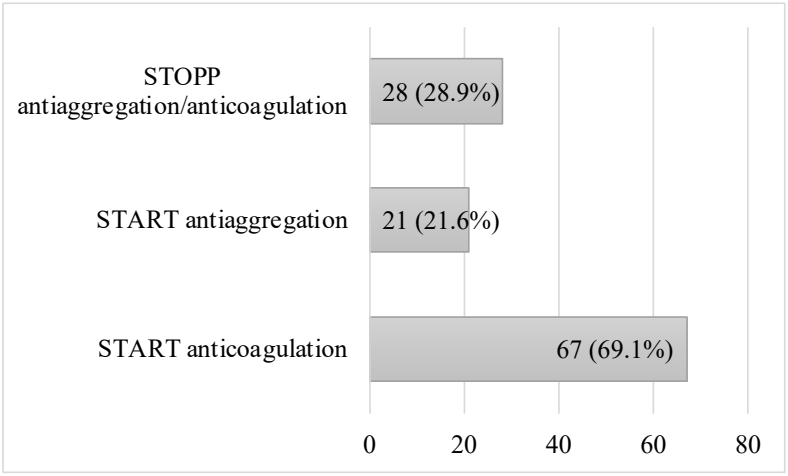

Fig. (2). Non-OAT-group – STOPP/START alerts. **Abbreviations:** OAT, Oral Anticoagulant Therapy; STOPP, Screening Tool of Older Persons' Prescriptions; START, Screening Tool to Alert to the Right Treatment.

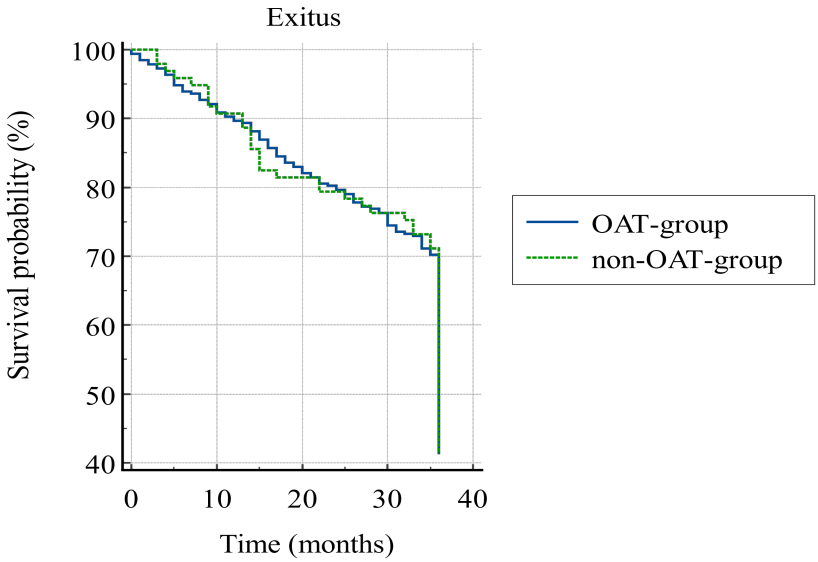

Fig. (3). Kaplan-meier curves (survival rate). **Abbreviations:** OAT, oral anticoagulant therapy. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

The Kaplan-Meier model (Fig. **3**), considering the survival endpoint (only 1 data missing in OAT-group), showed a 22.8% cumulative 3-year mortality. No difference was found between OAT- and non-OAT-group (p=0.974).

In order to extend our results, we performed a logistic regression – stepwise, considering belonging to OAT- or non-OAT-group as the dependent variable, and age, CCI, FRAIL, and the prevalence of comorbidities shown in Table **1** as independent variables. We found that none of the mentioned variables were associated with the dependent variable.

4. DISCUSSION

VKAs and DOACs are commonly used drugs in AF patients [16], as they modify the history and the incidence of complications in such a common disease [12]. STOPP/START alerts are specialist tools that can help with AF management by preventing PIMs and PPOs [18].

Since few studies considered PIMs and PPOs in AF [21-25], this study aims to establish the necessity to initiate, modify posology, or discontinue anticoagulant therapy in a group of patients with nonvalvular AF, and to establish if the assumption or non-assumption of anticoagulants is related to mortality.

Firstly, the relatively low prescription of DOACs is related to the fact that the sampling started years ago, as stated in Methods. The distribution of comorbidities is consistent with the literature [32], with hypertension extremely common and also associated with AF.

After the follow-up period, we found higher mortality than the literature [33], since our sample was made up of elderly people with moderate or severe comorbidities and frailty. We also did not find any significant difference in mortality between people taking and not taking anticoagulants. This aspect, although this could appear paradoxical,

because of the evidence of anticoagulants – and especially DOACs [34] - reducing all-cause mortality [35], is justified by our study population. This consisted of older, more medically complicated patients, with a greater frailty and comorbidity burden than the populations usually studied in clinical trials and scientific studies.

Our data showed no difference in comorbidity burden, frailty, and ischemic risk between patients assuming and non-assuming OAT; additionally, clinical history included similar cardio-cerebro-vascular disease prevalence in the two groups.

More than three-fourths of the sample appropriately assumed OAT, with only 9.6% of DOAC over-prescriptions, and 3.5% of renal function at the limits for rivaroxaban. Moreover, we found a high prevalence of patients not taking antiplatelet therapy, although this could seem appropriate, considering their clinical history. Such data can be explained by the higher risk of bleeding affecting people assuming both anticoagulant and antiaggregant drugs [36], without any supplemental advantage, according to the STOPP alert "aspirin in combination with vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors in patients with chronic AF fibrillation (no added benefit from aspirin)" [18, 19].

We, therefore, focused on the non-OAT group, representing about the remaining quarter of the sample. A large part of the group had the START criterion to take an anticoagulant, demonstrating that often AF patients do not assume appropriate blood-thinning drugs even in the presence of indications. According to START criteria, we also found that a small proportion of the group did not inappropriately assume antiplatelets.

After the follow-up period, we found higher mortality than the literature [34], since our sample was made up of elderly people with moderate or severe comorbidities and frailty. We also did not find any significant difference in mortality between people taking and not taking anticoagulants. This aspect could appear paradoxical, because of the evidence of anticoagulants – and especially DOACs [35] – reducing all-cause mortality [36]. However, it may be justified by the specific population included in our study.

CONCLUSION

Our study demonstrated that patients with AF represent a population who, regardless of frailty status or comorbidity burden, is often prone to under or over-prescription of antithrombotic drugs. In specific, patients assuming and non-assuming OAT show an opposing trend regarding antiplatelet drug use. Our data also showed that STOPP/START Criteria can represent a valid tool to help investigate PIMs and PPOs in such a specific population.

AUTHORS' CONTRIBUTION

FS, AP, and AM contributed to the study design, performed data analyses and the interpretation of the findings; FS, AP, GD, and MIS contributed to data collection; FS and AP wrote the manuscript. All authors read and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AF	=	Atrial Fibrillation
CCI	=	Charlson Comorbidity Index
DOAC	=	Direct Oral Anticoagulant
NOAC	=	Novel Oral Anticoagulants
OAT	=	Oral Anticoagulant Therapy
PIM	=	Potentially Inappropriate Medication
PPO	=	Potentially Prescribing Omissions
SD	=	Standard Deviation
START	=	Screening Tool to Alert to Right Treatment
STOPP	=	Screening Tool of Older Persons' Prescriptions
VKA	=	Vitamin K Antagonist

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board (or Ethics Committee) of the University of Cagliari (protocol code NP/2022/1382, 30 March 2022).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committees and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants in the study.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and materials used and/or analyzed during the current study are not publicly available. They are available from the corresponding author upon reasonable request.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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