Appropriateness of oral anticoagulant therapy prescription and its associated factors in hospitalized older people with atrial fibrillation

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Abstract:	Background: Oral anticoagulants (OACs) are effective in preventing stroke in older people with atrial fibrillation (AF). Despite this, they are often underused in this at particularly high risk population. Objectives: To assess the appropriateness of OAC prescription and its associated factors in hospitalized patients aged 65 years or older. Methods: Data were obtained from the retrospective phase of SIM-AF study, held in 32 Italian internal medicine and geriatric wards. Appropriateness of OAC prescription was assessed grouping patients in those prescribed or not at hospital discharge. Multivariable logistic regression was used to establish factors independently associated with appropriateness of OAC prescription. Results: 328 patients were included in the retrospective phase of the study. Of them 44% (N=143) were inappropriately prescribed with OACs, being mainly under prescribed or prescribed with an inappropriate antithrombotic drug (N=88). Among those patients prescribed with OACs (N=221), errors on the prescribed doses were the most frequent cause of inappropriate use (N=55). Factors associated with a higher degree of patient frailty were inversely associated with the appropriateness of OAC prescription. Conclusion: In hospitalized older patients with AF there is still a high prevalence of inappropriate OAC prescribing. Characteristics usually related to frailty are associated with the inappropriate prescribing. These findings point out the need for targeted interventions designed for internists and

	geriatricians aimed at improving the appropriate prescribing of OACs in this complex and at high risk population.

Appropriateness of oral anticoagulant therapy prescription and its associated factors in hospitalized older people with atrial fibrillation

Running title: OAC prescription appropriateness

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** The investigators and co-authors of the SIM-AF **(**SIMulation-based technologies to improve the appropriate use of oral anticoagulants in hospitalized elderly patients with Atrial Fibrillation**)** Study are listed in the Online Appendix.

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ABSTRACT

Background: Oral anticoagulants (OACs) are effective in preventing stroke in older people with atrial fibrillation (AF). Despite this, they are often underused in this at particularly high risk population.

Objectives: To assess the appropriateness of OAC prescription and its associated factors in hospitalized patients aged 65 years or older.

Methods: Data were obtained from the retrospective phase of SIM-AF study, held in 32 Italian internal medicine and geriatric wards. Appropriateness of OAC prescription was assessed grouping patients in those prescribed or not at hospital discharge. Multivariable logistic regression was used to establish factors independently associated with appropriateness of OAC prescription.

Results: 328 patients were included in the retrospective phase of the study. Of them 44% (N=143) were inappropriately prescribed with OACs, being mainly under prescribed or prescribed with an inappropriate antithrombotic drug (N=88). Among those patients prescribed with OACs (N=221), errors on the prescribed doses were the most frequent cause of inappropriate use (N=55). Factors associated with a higher degree of patient frailty were inversely associated with the appropriateness of OAC prescription.

Conclusion: In hospitalized older patients with AF there is still a high prevalence of inappropriate OAC prescribing. Characteristics usually related to frailty are associated with the inappropriate prescribing. These findings point out the need for targeted interventions designed for internists and geriatricians aimed at improving the appropriate prescribing of OACs in this complex and at high risk population.

KEY WORDS: oral anticoagulant, atrial fibrillation, older patients, internal medicine and geriatric wards, appropriateness of prescription

What is already known

- Oral anticoagulants represent the recommended choice to prevent stroke in the patients with AF, also in older people;
- Available data on oral anticoagulant prescriptions are mainly provided in the frame of cardiology settings.

What this study adds

- In older patients with atrial fibrillation hospitalized in internal medicine and geriatric wards there is still a high prevalence of inappropriate oral anticoagulant prescription;
- Inappropriate oral anticoagulant prescribing in older people is mainly related to their underuse or to errors on their doses prescribed;
- Characteristics usually related to frailty are associated with their inappropriate prescribing;
- Targeted interventions aimed at improving the appropriate prescribing of oral anticoagulants in this complex and at high risk population are needed.

INTRODUCTION

Atrial Fibrillation (AF) is the most common cardiac arrhythmia, whose prevalence increases with age [1]. Vitamin K antagonists (VKAs) have been for decades the only available oral anticoagulants (OACs) in patients with non valvular AF for prevention of stroke [2]. The narrow therapeutic index, drug-drug interactions, and the need for close monitoring were the main disadvantages of VKAs. With the aim to overcome these problems the non-vitamin K antagonist oral anticoagulants (NOACs) have been introduced in the market, with the advantages to allow a fixed-dose regimen and no need of a regular anticoagulation monitoring. NOACs including the direct thrombin inhibitor dabigatran, and the factor Xa inhibitors apixaban, edoxaban and rivaroxaban have been demonstrated to be effective in reducing stroke or systemic embolic events and safer then the most used VKA, warfarin [3]. Thus they represent nowadays the recommended choice to prevent stroke in the patients with AF, also in older people [4]. Notwithstanding these recommendations, different studies highlighted the frequent underuse of OACs in up to 40-60% of older people with AF [5,6], even though the benefit has been widely demonstrated also in these patients [7,8]. In older patients OAC underuse was associated to the prescription of antiplatelet drugs [6,9]. However, antiplatelets alone have a limited role in reducing the thromboembolic risk in AF, in addition to the fact that they are not safer than OAC in terms of risk of bleeding, especially in the elderly [10]. Furthermore, to date most of the available data on OAC prescriptions are provided by in the frame of cardiology settings in patients belonging to a younger population. The only data on OAC prescriptions in older people with AF hospitalized in internal medicine and geriatric wards comes from the REPOSI register, which confirmed that the majority of them were undertreated or inappropriately treated with antiplatelet drugs, both before [11] and after the introduction of NOACs into the market [12].

With this background, the objectives of this study were 1) to assess the appropriateness of OAC therapy at hospital discharge, according to criteria set up by means of a revision of the published literature, and 2) to identify the factors associated with the appropriate prescription of OACs in a cohort of older patients retrospectively included in the SIM-AF study by 32 Italian internal medicine and geriatric wards.

METHODS

Setting and data collection

This study was conducted in 32 Italian internal medicine and geriatric wards participating to the SIM-AF study (ClinicalTrials.gov #NCT03188211), a cluster randomized controlled trial aimed at assessing the effectiveness of simulation-based technologies in order to improve the appropriate use of OACs in hospitalized older patients with NVAF. The wards participating to the SIM-AF study were recruited on a voluntary basis among the Italian internal medicine and geriatric wards belonging to the REPOSI register network [13]. A detailed description of the study protocol has been published [14]. Briefly, the SIM-AF study was divided in a retrospective pre-intervention phase, that preceded the randomization of wards to intervention (educational program with simulation technologies) or control (current clinical practice), and in an in-hospital post-intervention prospective phase. In the pre-intervention observational phase, every ward retrospectively analysed the medical records of at least 10 AF patients aged 65 years or older, consecutively admitted over the previous 8 months in their hospital wards (from October 2016 up to May 2017). The principal data collected included socio-demographic characteristics, laboratory parameters (such as serum creatinine, alanine aminotransferase - ALT, aspartate aminotransferase – AST etc.), pharmacological therapies and previous diseases (such as stroke, major bleeding, coronary artery by-pass graft etc.) at hospital discharge.

For the purpose of this study, patients included in the observational retrospective phase of SIM-AF were considered for analysis. To assess the prescription of OACs we used the following Anatomical Therapeutic Chemical classification system (ATC) codes: B01AA03 (warfarin), B01AA07 (acenocoumarol), B01AF01 (rivaroxaban), B01AF02 (apixaban), B01AF03 (edoxaban), B01AE07 (dabigatran). The SIM-AF project was approved by the Ethics Committee of the Ca' Granda Maggiore Policlinico Hospital Foundation and then by the local ethical committees of the participating centres. The study was conducted according to the Good Clinical Practice and the Declaration of Helsinki.

Criteria for prescription appropriateness

By means of a revision of the published literature, we considered the European Society of Cardiology (ESC) guidelines [4], the Beers criteria [15], the European public assessment report (EPAR) - summary of products characteristics [16] in order to define whether or not the prescribed drug was appropriate. The Supplementary **Table S1** reports the criteria employed for the purpose of the study. The OAC appropriateness was first defined looking at the type and then at the dose of the drug chosen. To assess OAC therapy appropriateness, patients were grouped in those prescribed or not with OACs at the time of hospital discharge. When a patient was labeled as 'not appropriate' for one criterion, his/her assessment on prescription appropriateness was stopped and thus he/she was included in the inappropriately prescribed group.

The ESC guidelines recommend to estimate the stroke risk in AF patients through the CHA_2DS_2-VASc score [4]. In general, men with CHA_2DS_2-VASc score of 1 or more and women with 2 or more were considered at moderate or high risk and likely to benefit from OAC therapy. Thus they were considered as 'appropriate' for non-prescription only if they reported a contraindication to OAC treatment, such as previous adverse drug reaction or bleeding, risk of poor drug adherence or potential drug-drug interaction. Because we included people aged 65 years or more, no patients

with low risk (CHA_2DS_2-VASc score equal to 0) were represented in this cohort. Men with CHA_2DS_2-VASc score ≥1 and women with ≥2 not prescribed with OAC but prescribed with any other antithrombotic agent (such as antiplatelets or heparins) were considered as 'not appropriate' owing to the wrong choice of drug prescribed. A combination of OAC with antiplatelets (aspirin or clopidogrel) were considered as 'appropriate' only if prescribed within the period of 1 up to 12 months after an elective coronary stenting [4].

Concerning the dosage of OACs, the recommended doses for dabigatran are 150 mg twice daily , rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, edoxaban 60 mg once daily and warfarin depending on the values of the International Normalized Ratio (INR) and the Time in Therapeutic Range (TTR). Given that INR and TTR were assessed only at discharge, we assumed that all the warfarin and acenocoumarol prescriptions were 'appropriate'. As reported in Table S1, the recommended and thus appropriate adjustments for NOACs doses based upon the presence of chronic kidney disease (as assessed by high values of serum creatinine or creatinine clearance - CrCl), older age, specific drug-drug interactions, high risk of gastrointestinal bleeding (as assessed by means of a HAS-BLED score ≥3 [4] and/or presence of previous gastrointestinal bleeding) and severe hepatic impairment (as assessed by the presence of liver failure and/or values of ALT ≥ 41 U/L and AST ≥ 33 U/L, respectively [17]). Patients with missing values of serum creatinine, CrCl or AST plus ALT were considered 'not assessable'. Finally, contraindicated and major drug-drug interactions were assessed for NOACs according to the INTERCheck® software database, routinely updated by the IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri" and validated in the hospital setting [18].

Statistical Analysis

Continuous variables have been expressed as median and interquartile range [IQR]. Comparisons between groups were performed using the Mann-Whitney U test. Categorical variables were

expressed as counts and percentages and compared with the chi-square test. To establish factors independently associated with appropriateness of OAC prescription or non-prescription, a logistic regression analysis was performed. All variables with a $p<0.20$ at baseline for comparison between appropriate and not appropriate patients underwent univariate analysis. All variables with a $p<0.10$ at univariate analysis were entered in the multivariable models. Two multivariable models were set up in order to consider the body mass index (BMI) both as a continuous variable (first model) or as classes according to WHO definition (second model). A two-sided p value <0.05 was considered statistically significant. All analyses were been performed using SPSS v. 24.0 (IBM, NY, USA).

RESULTS

Overall, 328 older patients were included in the study by 32 internal medicine and geriatric wards at hospital discharge. Among them, 221 (67.4%) were prescribed with at least an OAC at hospital discharge. Our previous work reported the main characteristics of prescribed and non prescribed patients of this cohort [14]. Briefly, most of the patients prescribed with OAC (52%) were males, with a mean age of 83 years. The most prescribed NOAC was apixaban (46.5%) [14].

In the present analysis, out of the 328 patients, 172 (52.4%) were considered as appropriately prescribed with OAC, while 143 (43.6%) were not appropriately prescribed. Table 1 shows the profiles of OAC prescription in prescribed and non-prescribed patients. Those prescribed with OACs, 153 (69.2%) were appropriate, 55 (24.9%) were not appropriate and 13 (5.9%) not assessable. Among those not appropriate, most of them (43/55, 78.2%) presented errors in the dose prescribed (i.e. full dosage when there was indication for a reduction / reduced dose when there was no indication for a reduction), being the majority in the reduced (32/43 patients, 74.4%). Among patients with no OAC prescription, only 19 (18%) were appropriate because even though they were at high risk of thromboembolic events they had a contraindication for the OAC

treatment (Table S1). On the other hand, most of them (82%) were not prescribed with OAC but with another inappropriate antithrombotic drug (wrong choice of drug). Only 2 patients presented a risk for drug-drug interaction, being both prescribed with apixaban together with clarithromycin or ritonavir, respectively.

Table 2 reports the main characteristics of patients according to the appropriateness of OAC therapy at hospital discharge. Compared to patients not appropriate, those appropriate for OAC prescription were younger, had a higher BMI, acute coronary syndromes but less history of falls, hepatic or vascular disease (defined as the previous history of acute coronary sindrome or peripheral artery disease) and risk of bleeding. Table 3 shows the results of univariate and multivariable logistic regression analyses. In the multivariable analysis, overweight ($p=0.04$) and the presence of coronary artery by-pass graft ($p=0.01$) were independently associated with the appropriate prescription of OACs, while history of falls ($p<0.05$), vascular disease ($p=0.002$) and liver disease ($p=0.02$) were inversely associated.

DISCUSSION

This study evaluated the appropriateness of oral anticoagulant therapy in older patients with atrial fibrillation who have been hospitalized in internal medicine and geriatric wards and enrolled in the frame of SIM-AF study. Nearly the 44% of patients were inappropriately prescribed with OACs, being mainly underprescribed or prescribed with a wrong antithrombotic drug. Among patients prescribed with OACs, dosage errors were the most frequent cause of inappropriate prescription. Factors associated with a higher perceived frailty such as older ages, history of falls, liver disease and vascular disease were inversely associated with the appropriateness of OAC prescription.

Many studies have shown that OACs are underprescribed in older people with AF and the use of antiplatelets is linked to a high likelihood of OAC underuse [5,6,11,12]. Our study confirmed the underprescription of OACs in favour of other antithrombotic therapy among hospitalized older

patients with AF. The under or non prescription of OACs in the elderly with AF represents a clinical paradox: those subjects who may benefit the most from such a therapy are indeed those who are undertreated or alternatively prescribed with inappropriate antiplatelet agents. Indeed the older patients present peculiarities and clinical characteristics that make the therapeutic decision process highly challenging for clinicians: they are frailer, affected by multimorbidities, take several medications [19,20] and are *per se* at a high risk of bleeding [21]. Moreover, in non-cardiologic setting, a poor knowledge of the specific guidelines could negatively impact on OAC prescription in this at risk population. A recent study confirmed that even if the use of anticoagulant drugs increased over time in older AF patients, the non-use of anticoagulants was due to a high bleeding risk in these patients [22]. On the other hand, the overall positive assessment of the risk/benefit ratio for these drugs has been established in this population [23].

Among patients prescribed with OACs, errors on doses used were the most frequent cause of inappropriate prescription. Even if the NOACs are marketed as having simplified dosing as compared to warfarin, their appropriate dose is dependent upon several patient-specific factors such as age, weight, baseline renal and hepatic impairments and concomitant drug use [16]. As shown in a previous study, in which the majority of patients on the inappropriate dose were found to be on a lower dose than recommended [24], we also found that most errors were due to unnecessarily reduced doses. This is probably due to the fact that it has been shown that lower doses are associated with a reduction of the risk of major bleeding [25]. Moreover, given that an antidote for NOACs is available only for dabigatran, prescribing lower doses makes clinicians more confident of a safer prescribing. Given the complexity of dose adjustments and the potential adverse events that may derive from inappropriate dosing, it is recommended that clinicians take into strong account the baseline clinical patient characteristics and which drugs are taken before starting a NOAC. This means also that some liver function tests, such as ALT and AST levels, often

omitted or not routinely collected in internal medicine and geriatric wards at variance with others such as hemoglobin or serum creatinine, must be considered for NOAC prescription.

Finally, our evaluation of factors associated with OAC prescription appropriateness pointed out that frailer patients are usually inappropriately prescribed with OACs. These findings are in line with our previous results [14] and those coming from a sub-analysis from the PREFER-AF (Prevention of thromboembolic events – European Registry in Atrial Fibrillation) study [26]. History of falls was inversely associated with the appropriate use of OACs. Among the 35 patients with history of falls inappropriately prescribed, approximately one third were prescribed no antithrombotic (data not shown). This is probably due to the fear to treat old patients who already underwent a traumatic event leading to bleeding. On the other hand, another third of them not prescribed with OAC were inappropriately prescribed with an antiplatelet drug (data not shown). It is known that anticoagulation is often avoided in patients with AF who are at an increased risk of falling, but a recent study showed that even in those patients the NOAC edoxaban resulted in a greater absolute risk reduction in severe bleeding events and all-cause mortality compared with warfarin [27]. The concomitant presence of vascular disease/peripheral artery disease was associated to inappropriate prescription of OACs. This is an important issue, since recently the ESC guidelines for peripheral arterial diseases reccomended to prescribe only OACs in AF patients with those diseases [28].

LIMITATIONS AND STRENGTHS

This study have some limitations. The main limitation is the overall small number of subjects, that affects the multivariable analysis results for some variables (i.e. age). Moreover, some data on laboratory values such as AST and ALT levels were missing. Furthermore, we did not collect repeated measures of INR and TTR. Finally, we were not able to follow up these patients after hospital discharge. Despite all these limitations, our data provided a realible view on current

clinical practice and on the appropriateness of OAC prescribing in older AF patients hospitalized in a large sample of Italian internal medicine and geriatric wards.

CONCLUSIONS

This study emphasises that in hospitalized older patients with AF still exists a high prevalence of inappropriate prescribing of OACs and that characteristics linked to frailty are associated with the inappropriate prescribing of this class of drugs. These findings call the need for targeted interventions for clinicians aimed to 1) solicit a deeper knowledge of benefits and risks of OACs; and 2) improve their appropriate prescribing in the older population with AF, thus increasing their use and decreasing the mistakes in the doses prescribed. For this purpose, we hope that the SIM-AF trial will demonstrate that an educational simulation-based intervention will be effective to improve the appropriateness of OAC prescription in old patients with AF admitted to internal medicine and geriatric hospital wards and thus perhaps reduce the risk of thromboembolic complications in this at high-risk population.

AUTHOR CONTRIBUTIONS

C.F. and S.A. conceived the study idea, the study design and contributed to the acquisition and assessment of the data. C.F. wrote the manuscript. M.P. performed the statistical analysis. All authors participated in the discussion and interpretation of the results, revised the manuscript critically for important intellectual content and approved the final draft.

CONFLICT OF INTEREST

None

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Table 1. Profiles of prescription appropriateness of OACs in 328 prescribed and non-prescribed patients at hospital discharge

	Patients with OAC N(%)	Patients without OAC N(%)
Overall	***221***	***107***
APPROPRIATE	***153 (69.2)***	***19 (18)***
a) CHA2DS2-VASc≥1 (men) and ≥2 (women) but with contraindication for OAC	**-**	**19**
b) Dose	**153**	-
Dabigatran	11	-
Rivaroxaban	13	-
Apixaban	22	-
Edoxaban	8	-
Warfarin	93	-
Acenocumarol	6	-
NOT APPROPRIATE	***55 (24.9)***	***88 (82)***
a) CHA_2DS_2-VASc≥1 (men) and ≥2 (women) and no contraindication for OAC	-	-
b) CHA2DS2-VASc≥1 (men) and ≥2 (women) with other antithrombotic monotherapy (underprescription-wrong choice of drug)	-	88
c) Dual/Triple therapy without elective coronary stenting	**12**	-
d) Dose	**43**	-
Dabigatran	5	-
Rivaroxaban	14	-
Apixaban	21	-
Edoxaban	3	-
Warfarin	-	-
Acenocumarol	-	-
NOT ASSESSABLE	***13 (5.9)***	-
Dabigatran	1	-
Rivaroxaban	3	-
Apixaban	9	-
Edoxaban	-	-
Warfarin	-	-
Acenocumarol	-	-

Legend: OAC= oral anticoagulants

Table 2: Characteristics of patients at hospital discharge according to the appropriateness of OAC prescription

	Appropriateness		
	No	**Yes**	**p-value**
	N= 143	**N= 172**	
Age, *years* (median [IQR])	84 [79-88]	82 [77-87]	0.033
Age Classes, n (%)			0.108
65-74 years	18 (12.6)	29 (16.9)	
75-84 years	56 (39.2)	80 (46.5)	
≥85 years	69 (48.3)	63 (36.6)	
Female Sex, n (%)	76 (53.1)	84 (48.8)	0.446
Living Status, n (%)			0.312
Alone	9 (6.4)	9 (5.2)	
Family	106 (75.2)	119 (69.2)	
Institutionalized	26 (18.4)	44 (25.6)	
Marital Status, n (%)			0.488
Alone	14 (10.0)	12 (7.0)	
Married	65 (46.4)	89 (52.0)	
Divorced/Widowed	61 (43.6)	70 (40.9)	
Scholar Status, n (%)			0.351
None/Primary	64 (45.1)	77 (45.0)	
Secondary	68 (47.9)	88 (51.5)	
High Degree	10 (7.0)	6 (3.5)	
History of Falls, n (%)	35 (24.5)	24 (14.0)	0.017
Current Smoking, n (%)	33 (23.1)	31 (18.0)	0.267
Alcohol Use, n (%)	22 (15.4)	19 (11.0)	0.255
ALT, *UI/L* (median [IQR]) *277*	18 [13-30]	19 [14-25]	0.875
AST, *UI/L* (median [IQR]) *253*	22 [15-31]	20 [15-29]	0.422
CrCl, *mL/min* (median [IQR]) *295*	44.4 [30.1-65.1]	44.7 [31.8-62.3]	0.944
CrCl Classes, n (%) *295*			0.412
≥60 mL/min	39 (29.5)	45 (27.6)	
30-59 mL/min	61 (46.2)	87 (53.4)	
<30 mL/min	32 (24.2)	31 (19.0)	
BMI, kg/m^2 (median [IQR]) *297*	24.2 [22.2-27.3]	25.7 [22.7-28.9]	0.038
BMI Classes, n (%)			0.027
Underweight	7 (5.3)	2 (1.2)	
Normal Weight	69 (51.9)	67 (40.9)	
Overweight	42 (31.6)	69 (42.1)	
Obesity	15 (11.3)	26 (15.9)	
SBP, *mmHg* (median [IQR]) *312*	120 [110-130]	120 [110-130]	0.688
DBP, *mmHg* (median [IQR]) *312*	70 [60-80]	70 [60-80]	0.947
Type of AF, n (%)			0.083
Paroxysmal	36 (25.2)	50 (29.1)	
Persistent	77 (53.8)	97 (56.4)	
Permanent	16 (11.2)	20 (11.6)	
Unknown	14 (9.8)	5 (2.9)	

Stroke/TIA, n (%)	34 (23.8)	30 (17.4)	0.164
Hypertension, n (%)	105 (73.4)	139 (80.8)	0.118
Diabetes Mellitus, n (%)	35 (24.5)	52 (30.2)	0.255
CKD, n (%)	61 (43.0)	85 (49.7)	0.233
Neoplasm, n (%)	31 (21.7)	27 (15.7)	0.173
Pulmonary Disease, n (%)	38 (26.6)	56 (32.6)	0.248
Heart Failure, n (%)	80 (55.9)	103 (59.9)	0.480
Vascular Disease, n (%)	63 (44.1)	55 (32.0)	0.027
PTCA/CABG, n (%)	15 (10.5)	30 (17.4)	0.079
Liver Disease, n (%)	18 (12.6)	11 (6.4)	0.058
Previous Major Bleeding, n (%)	19 (13.3)	16 (9.3)	0.263
Dementia, n (%)	37 (25.9)	30 (17.4)	0.069
Depression, n (%)	21 (14.7)	24 (14.0)	0.853
Polypharmacy, n (%)	107 (74.8)	139 (80.8)	0.201
HAS-BLED (median [IQR])	3 [2-4]	2 [2-3]	0.015
CHA_2DS_2-VASc (median [IQR])	5 [4-6]	5 [4-6]	0.271

Legend: ACS= Acute Coronary Syndrome; AF= Atrial Fibrillation; ALT= Alanine aminotransferase; AST= Aspartate Aminotransferase; BMI= Body Mass Index; CABG= Coronary Artery By-Pass Graft; CKD= Chronic Kidney Disease; CrCl= Creatinine Clearance; DBP= Diastolic Blood Pressure; IQR= Interquartile Range; PTCA= Percutaneous Transluminal Coronary Angioplasty; PVD= Peripheral Vascular Disease; OAC= Oral Anticoagulant; SBP= Systolic Blood Pressure; TIA= Transient Ischemic Attack.

Table 3: Results from univariate and multivariable logistic regression analyses for appropriateness of OAC prescription

	OR	95% CI	p-value
Univariate Analysis			
Age *(per year)*	0.97	0.94-1.00	0.030
History of Falls	0.50	0.28-0.89	0.018
BMI *(per kg/m^2)*	1.07	1.01-1.12	0.020
BMI Classes			
Underweight	0.29	0.06-1.47	0.136
Normal Weight (ref.)	-	-	-
Overweight	1.69	1.02-2.82	0.043
Obesity	1.79	0.87-3.66	0.114
Type of AF			
Paroxysmal (ref.)	-	-	-
Persistent	0.91	0.54-1.53	0.714
Permanent	0.90	0.41-1.97	0.792
Unknown	0.26	0.09-0.78	0.016
Stroke/TIA	0.68	0.39-1.18	0.166
Hypertension	1.52	0.90-2.59	0.120
Neoplasm	0.67	0.38-1.19	0.174
PTCA/CABG	1.80	0.93-3.50	0.082
Vascular Disease	0.60	0.38-0.95	0.028
Liver Disease	0.47	0.22-1.04	0.063
Dementia	0.61	0.35-1.04	0.070
Multivariable Analysis Model 1			
History of Falls	0.53	0.29-0.97	0.038
BMI *(per kg/m^2)*	1.08	1.02-1.14	0.010
PTCA/CABG	2.67	1.25-5.70	0.011
Vascular Disease	0.42	0.25-0.72	0.002
Liver Disease	0.36	0.16-0.83	0.016
Multivariable Analysis Model 2			
History of Falls	0.55	0.30-1.01	0.056
BMI Classes			
Underweight	0.31	0.60-1.59	0.161
Normal Weight (ref.)	-	-	-
Overweight	1.76	1.04-3.00	0.037
Obesity	2.72	0.97-4.40	0.060
PTCA/CABG	2.72	1.27-5.85	0.010
Vascular Disease	0.42	0.25-0.72	0.002
Liver Disease	0.37	0.16-0.84	0.018

Legend: ACS= Acute Coronary Syndrome; AF= Atrial Fibrillation; BMI= Body Mass Index; CABG= Coronary Artery By-Pass Graft; CI= confidence interval; OAC= Oral Anticoagulant; OR= odd ratio; PTCA= Percutaneous Transluminal Coronary Angioplasty; PVD= Peripheral Vascular Disease; TIA= Transient Ischemic Attack.

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SUPPLEMENTARY MATERIALS

Table S1. Criteria of appropriateness of oral anticoagulant (OAC) therapy in patients with atrial fibrillation

	Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**	**Warfarin**
CHA_2DS_2-VASc	≥1 (men)	≥1 (men)	≥1 (men)	≥1 (men)	≥1 (men)
	≥2 (women)	≥2 (women)	≥2 (women)	≥2 (women)	≥2 (women)
	If ≥1 (men) and ≥2 (women) without OAC or with antiplatelet monotherapy: Not appropriate (under prescription)*	*If ≥1 (men) and ≥2 (women) without OAC or with antiplatelet monotherapy:* Not appropriate (under prescription)*	*If ≥1 (men) and ≥2 (women) without OAC or with antiplatelet monotherapy:* Not appropriate (under prescription)*	*If ≥1 (men) and ≥2 (women) without OAC or with antiplatelet monotherapy:* Not appropriate (under prescription)*	*If ≥1 (men) and ≥2 (women) without OAC or with antiplatelet monotherapy:* Not appropriate (under prescription)*
Combination of OAC with antiplatelets or with other anticoagulants (duplications)**	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate
Dose					
Recommended	150 mg twice daily	20 mg once daily	5 mg twice daily	60 mg once daily	Starting dose: 2,5 a 5 mg once daily depending on INR and TTR Maintenance dose: 2,5 a 10 mg daily depending on INR and TTR
Adjusted with:					
CKD	-	*If CrCl 15-49 mL/min* 15 mg once daily	*If serum creatinine ≥ 1.5 mg/dL + age≥80 or body weight ≤60 kg* 2.5 mg twice daily	*If CrCl 15-50 mL/min and/or body weight ≤60 kg and/or with P-gp inhibitors* 30 mg once daily	-
	If CrCl < 30 mL/min Not appropriate	*If CrCl < 15 mL/min* Not appropriate	*If CrCl < 15 mL/min* Not appropriate	*If CrCl < 15 mL/min* Not appropriate	

Age	*If ≥75 years* 110 mg twice daily	-	-		-
Drug-drug interactions	*If with verapamil* 110 mg twice daily	-	-	*If with P-glicoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole)* 30 mg once daily	-
High-risk of gastrointestinal bleeding	110 mg twice daily	15 mg once daily	5 mg twice daily	30 mg once daily	Depending on INR
Severe hepatic impairment	Not appropriate	Not appropriate	Not appropriate	Not appropriate	Not appropriate

Legend: ALT= Alanine aminotransferase; AST= Aspartate Aminotransferase; CKD= Chronic Kidney Disease; CrCl= Creatinine Clearance; International Normalized Ratio (INR); Time in Therapeutic Range (TTR). *** Under prescription has been considered 'appropriate' for the following contraindications:** past adverse drug reaction; past event of bleeding; poor drug adherence; drug-drug interactions; patient refusal. **** except in the following clinical condition:**

Clinical condition	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Warfarin
****Triple/Dual therapy after elective coronary stenting**	1)Triple therapy with aspirin + clopidogrel + OAC for 1 month (max 6 months) Dual therapy 2)OAC + aspirin/clopidogrel up to 12 months OR 1) Dual therapy OAC + clopidogrel 75 mg instead of the triple therapy	1)Triple therapy with aspirin + clopidogrel + OAC for 1 month (max 6 months) Dual therapy 2)OAC + aspirin/clopidogrel up to 12 months OR 1) Dual therapy OAC + clopidogrel 75 mg instead of the triple therapy	1)Triple therapy with aspirin + clopidogrel + OAC for 1 month (max 6 months) Dual therapy 2)OAC + aspirin/clopidogrel up to 12 months OR 1) Dual therapy OAC + clopidogrel 75 mg instead of the triple therapy	1)Triple therapy with aspirin + clopidogrel + OAC for 1 month (max 6 months) Dual therapy 2)OAC + aspirin/clopidogrel up to 12 months OR 1) Dual therapy OAC + clopidogrel 75 mg instead of the triple therapy	1)Triple therapy with aspirin + clopidogrel + OAC for 1 month (max 6 months) Dual therapy 2)OAC + aspirin/clopidogrel up to 12 months OR 1) Dual therapy OAC + clopidogrel 75 mg instead of the triple therapy

Legend: OAC: oral anticoagulant