PrevAleNce and Associated factors of inappropriaTe dosing of direct Oral anticoaguLants In pAtients with Atrial Fibrillation: The ANATOLIA-AF Study

Umut Kocabaş (umutkocabas@hotmail.com)
Başkent Üniversitesi: Baskent Universitesi https://orcid.org/0000-0001-6424-9399

Işıl Ergin
Ege University: Ege Universitesi

Veysel Yavuz
Akhisar State Hospital

Selda Murat
Osmangazi University: Eskisehir Osmangazi Universitesi

İbrahim Özdemir
Manisa State Hospital: Manisa Devlet Hastanesi

Ömer Genç
Ağrı Training and Researh Hospital

Cihan Altın
İzmir Ekonomi Üniversitesi: Izmir Ekonomi Universitesi

Haşim Tüner
Hakkari State Hospital

Bengisu Keskin Meriç
Babaeski State Hospital

Ali Çoner
Başkent Üniversitesi: Baskent Universitesi

Elif İlkay Yüce
Fethiye State Hospital: Fethiye Devlet Hastanesi

Bedrettin Boyraz
Tatvan State Hospital

Onur Aslan
Mersin District Hospital: Mersin Sehir Egitim ve Arastirma Hastanesi

Ahmet Dal
İzmir Ekonomi Üniversitesi: Izmir Ekonomi Universitesi

Taner Şen
Kutahya Saglik Bilimleri Universitesi Tip Fakultesi

Ersin İbişoğlu
Çam ve Sakura Şehir Hastanesi
Aslan Erdoğan
Çam ve Sakura Şehir Hastanesi
Mehmet Özgeyik
Eskişehir Devlet Hastanesi: Eskisehir Cifteler Devlet Hastanesi
Mevlüt Demir
Kutahya Saglik Bilimleri Universitesi Tip Fakultesi
Ziya Gökalp Bilgel
Başkent Üniversitesi: Baskent Universitesi
Büşra Güvendi Şengör
Maltepe State Hospital
Örsan Deniz Urgun
Kozan State Hospital
Mustafa Doğduş
Uşak Üniversitesi: Usak Universitesi
Deniz Dilan Naki Tekin
Çam ve Sakura Şehir Hastanesi
Sinem Çakal
Haseki Training and Research Hospital: Istanbul Haseki Egitim Ve Arastirma Hastanesi
Sercan Çayırlı
Adnan Menderes University: Adnan Menderes Universitesi
Arda Güler
Mehmet Akif Ersoy Göğüs Kalp Damar Cerrahisi Eğitim Araştırma Hastanesi: Mehmet Akif Ersoy Gogus Kalp Damar Cerrahisi Egitim Arastirma Hastanesi
Dilay Karabulut
Bakirkoy Dr Sadi Konuk Training and Research Hospital: Istanbul Bakirkoy Dr Sadi Konuk Egitim ve Arastirma Hastanesi
Onur Dalgıç
Kardiya Medical Center
Osman Uzman
Sarıkamış State Hospital
Bektaş Murat
Eskişehir Devlet Hastanesi: Eskisehir Cifteler Devlet Hastanesi
Şeyda Şahin
Turhal State Hospital
Umut Karabulut
Acıbadem Sağlık Grubu: Acibadem Saglik Grubu
Tarık Kıvrak

Fırat Üniversitesi: Firat Universitesi

Muharrem Said Coşgun

Erzincan Üniversitesi: Erzincan Binali Yildirim Universitesi

Ferhat Özyurtlu

Grandmedical Hospital

Mehmet Kaplan

Gaziantep University: Gaziantep Universitesi

Emre Özçalık

Başkent Üniversitesi: Baskent Universitesi

Research Article

Keywords: atrial fibrillation, direct oral anticoagulants, inappropriate dosing, stroke, systemic embolism.

Posted Date: July 22nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1828621/v1

Abstract

Purpose: Inappropriate dosing of direct oral anticoagulants is associated with an increased risk of stroke, systemic embolism, major bleeding, cardiovascular hospitalization, and death in patients with atrial fibrillation. The main goal of the study was to determine the prevalence and associated factors of inappropriate dosing of direct oral anticoagulants in real-life settings.

Methods: This study was a multicenter, cross-sectional, observational study that included 2,004 patients with atrial fibrillation. The study population was recruited from 41 cardiology outpatient clinics between January and May 2021. The main criteria for inappropriate direct oral anticoagulant dosing were defined according to the recommendations of the European Heart Rhythm Association.

Results: The median age of the study population was 72 years and 58% were women. Nine hundred and eighty-seven patients were prescribed rivaroxaban, 658 apixaban, 239 edoxaban, and 120 dabigatran. A total of 498 patients (24.9%) did not receive the appropriate dose of direct oral anticoagulants. In a logistic regression model, advanced age, presence of chronic kidney disease, presence of permanent atrial fibrillation, prescription of reduced doses of direct oral anticoagulants, prescription of edoxaban treatment, concomitant use of amiodarone treatment, and non-use of statin treatment were significantly associated with potentially inappropriate dosing of direct oral anticoagulants.

Conclusion: The study demonstrated that the prevalence of inappropriate direct oral anticoagulant dosing according to the European Heart Rhythm Association recommendations was 24.9% in patients with atrial fibrillation. Several demographic and clinical factors were associated with the inappropriate prescription of direct oral anticoagulants.

Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia in clinical practice and is associated with a 5-fold increased risk of stroke and systemic embolism [1]. Oral anticoagulant therapy, including vitamin K antagonists and direct oral anticoagulants, is the cornerstone of atrial fibrillation management to prevent stroke and systemic embolism [2].

Direct oral anticoagulants have been developed with the aim of overcoming several limitations of vitamin K antagonists, such as delayed onset and offset of anticoagulation, narrow therapeutic window, need for close monitoring, and several drug-food interactions [2]. In four pivotal randomized controlled trials, dabigatran, rivaroxaban, apixaban, and edoxaban demonstrated non-inferiority or superiority to warfarin in the prevention of stroke and systemic embolism with similar or better safety profiles [3–6]. Recently published European and American guidelines recommend direct oral anticoagulants as first-line therapies for stroke and systemic embolism prevention in patients with atrial fibrillation without a mechanical heart valve or moderate-to-severe mitral regurgitation [1, 7].

Direct oral anticoagulants have been widely used and preferred over vitamin K antagonists because of their efficacy and safety profile, fixed-dose regimen, and lower potential to develop drug–drug interactions. However, prescribing the appropriate direct oral anticoagulant in an appropriate dose can be challenging in real-world clinical practice [8, 9]. All direct oral anticoagulants have different standards and reduced doses, and each direct oral anticoagulant has specific dose reduction criteria that mainly depend on patient-related factors such as age, renal function, body weight, bleeding profile, and concomitant medications [8–10]. Despite the presence of specific dose reduction criteria for each direct oral anticoagulant, inappropriate dosing of direct oral anticoagulants in patients with atrial fibrillation is not uncommon in real-life settings [8, 11]. Real-world studies reported that the prevalence of inappropriate dosing of direct oral anticoagulants vary between 12.8–39% [9–16].

Inappropriate dosing of direct oral anticoagulants in patients with atrial fibrillation has serious clinical consequences, including an increased risk of stroke and systemic embolism, major bleeding, cardiovascular hospitalization, and death [8, 12, 13]. Therefore, it is important to determine the demographic and clinical factors associated with inappropriate dosing of direct oral anticoagulants in order to develop strategies to overcome this problem. The main goal of the ANATOLIA-AF study was to identify the prevalence and predictors of inappropriate dosing of direct oral anticoagulants in patients with atrial fibrillation.

Methods

The ANATOLIA-AF study is a national, multicenter, cross-sectional, observational study that included outpatients with atrial fibrillation and was conducted between January and May 2021. The baseline study population included 2,782 patients enrolled at 41 cardiology centers (11 university hospitals, 11 education and research hospitals, 15 state hospitals, and four private hospitals). We excluded 182 patients with a mechanical heart valve or moderate-to-severe mitral regurgitation, 61 patients with missing clinical data, and 535 patients who were not taking a direct oral anticoagulant at baseline. Of the enrolled patients, 2,004 were eligible for inclusion and the final analysis.

Patients with atrial fibrillation were diagnosed based on documentation on 12-lead electrocardiography and/or 24-hour Holter electrocardiography recording. Patients aged < 18 years were excluded. The patients' demographic, clinical, and laboratory data, including age, sex, body mass index, atrial fibrillation type, medical history and comorbidities, renal function (serum creatinine levels and creatinine clearance), previous bleeding history, and anticoagulant treatments, were collected at the first visit and recorded in a case report form with standardized definitions for all fields. Creatinine clearance was calculated for each patient from the serum creatinine level using the Cockcroft-Gault equation [17], a method that was used in the pivotal trials of direct oral anticoagulants [3–6]. CHA_2DS_2-VASc (congestive heart failure or left ventricular dysfunction, hypertension, age ≥ 75 or 65–74 years, diabetes, history of stroke and/or systemic embolism, vascular disease, and sex) and HAS-BLED (hypertension, renal failure and/or liver failure, history of stroke, bleeding history, labile international normalized ratio, age > 65 years,

concomitant drug use that predisposed to bleeding and/or excessive alcohol use) scores were calculated for each study patient to assess thrombotic and bleeding risk [1].

Study participants were classified as receiving a standard dose of direct oral anticoagulant (dabigatran 150 mg, rivaroxaban 20 mg, apixaban 5 mg, or edoxaban 60 mg) or a reduced dose of direct oral anticoagulant (dabigatran 110 mg, rivaroxaban 15 mg, apixaban 2.5 mg, or edoxaban 30 mg). The criteria proposed by the European Heart Rhythm Association Practical Guide on the use of direct oral anticoagulants in patients with atrial fibrillation was used to determine the appropriate dose [18]. The criteria for defining a patient as requiring a reduced dose of direct oral anticoagulant is listed in Table 1. Finally, the study participants were classified as follows: 1) appropriate dose of direct oral anticoagulant (using appropriate standard dose of direct oral anticoagulant or appropriate reduced dose of direct oral anticoagulant in compliance with the dose reduction criteria of the European Heart Rhythm Association Practical Guide); 2) inappropriate dose of direct oral anticoagulant (using reduced dose of direct oral anticoagulant without dose reduction criteria of the European Heart Rhythm Association Practical Guide [inappropriate low dose of direct oral anticoagulant] or using a standard dose of direct oral anticoagulant with dose reduction criteria of the European Heart Rhythm Association Practical Guide [inappropriate high dose of direct oral anticoagulant]).

Table 1
Criteria for defining a patient as requiring a reduced dose of direct oral anticoagulants in the ANATOLIA-AF study

For patients receiving dabigatran ● **Age ≥ 80 years** ● **Concomitant usage of verapamil** ● **≥ 2 of the following criteria: age 75–79 years, GFR 30–50 mL/min/1.73 m^2, HAS-BLED score ≥ 3, concomitant usage of antiplatelet therapy, concomitant usage of amiodarone, or body weight ≤ 60 kg**
For patients receiving rivaroxaban ● GFR 15–49 mL/min/1.73 m^2 ● ≥ 2 of the following criteria: age ≥ 75 years, HAS-BLED score ≥ 3, concomitant usage of antiplatelet therapy, concomitant usage of amiodarone, or body weight ≤ 60 kg
For patients receiving apixaban ● ≥ 2 of the following criteria: age ≥ 80 years, serum creatinine ≥ 1.5 mg/dL, or body weight ≤ 60kg ● GFR 15–29 mL/min/1.73 m^2 ● ≥ 2 of the following criteria: age ≥ 75 years, HAS-BLED score ≥ 3, concomitant usage of antiplatelet therapy, concomitant usage of amiodarone, or concomitant usage of diltiazem
For patients receiving edoxaban ● GFR 15–49 mL/min/1.73 m^2 ● Body weight ≤ 60kg ● Concomitant usage of strong P-glycoprotein inhibitor (e.g. dronedarone, ketoconazole, erythromycin) ● ≥ 2 of the following criteria: age ≥ 75 years, HAS-BLED score ≥ 3, concomitant usage of antiplatelet therapy, concomitant usage of amiodarone, or concomitant usage of verapamil
GFR = glomerular filtration rate; HAS-BLED = uncontrolled hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile international normalized ratios, elderly (age > 65 years), drugs or alcohol (1 point each) (concomitant use of antiplatelet agents or non-steroidal anti-inflammatory drugs, alcohol abuse).

In statistical analysis, for continuous variables, mean ± standard deviation or median (interquartile range) was reported according to the normality of distribution tested with one-sample Kolmogorov-Smirnov test. For categorical variables, frequencies were presented. The Pearson's $\chi 2$ test or Fisher's exact test was used for assessing difference in distribution of categorical variables between inappropriate/appropriate dose groups (Table 2a and 2b) and inappropriately high/inappropriately low/ appropriate groups (Table 3a and 3b). Student's t-test, Mann–Whitney U test and ANOVA were applied with the same purpose for continuous variables, when appropriate. Variables that were detected to present statistically significant difference were included in the logistic regression analysis. The univariate regression analysis revealed

unadjusted odds ratios. In Model 1, each group of variables (demographic features, medical history and laboratory findings, atrial fibrillation related features, and treatments) were adjusted for age. In Model 2, all variables were included in the Model. Nagelkerke R Square value provided for each Model indicated the amount of variation in the dependent variable. All statistical analyses were performed using SPSS version 23 for Windows (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered significant

Table 2

a. The comparison of the socio-demographic profile, clinical features, medical history, and laboratory studies between appropriate dose and inappropriate dose groups

Variable	Appropriate dose	Inappropriate dose	*P*-value
Socio-demographics			
● Age, median (IQR), years	71 (13)	76 (12)	< 0.001
● Age group, n (%)			
● < 65 years	353 (23.4)	44 (8.8)	< 0.001
● 65–74 years	613 (40.7)	158 (31.7)	
● ≥ 75 years	540 (35.9)	296 (59.4)	
● Female sex, n (%)	874 (58)	289 (58)	0.999
● Urban population, n (%)	938 (62.3)	303 (60.8)	.566
● Marital status (single or widowed or divorced), n (%)	417 (27.7)	190 (38.2)	< 0.001
● Individuals with higher education, n (%)	81 (5.4)	22 (4.4)	0.053
Physical examination			
● BMI, median (IQR), kg/m^2	28.1 (5.6)	27.5 (6.4)	0.013
● Systolic BP, median (IQR), mmHg	130 (20)	130 (20)	0.768
● Diastolic BP, median (IQR), mmHg	80 (15)	78 (18)	0.628
● Heart rate, median (IQR), bpm	83 (25)	83 (25)	0.142
AF-related information			
● Permanent atrial fibrillation, n (%)	726 (48.2)	299 (60.1)	< 0.001
● CHA_2DS_2-VASc score, median (IQR)	4 (3)	4 (2)	< 0.001
● CHA_2DS_2-VASc score, mean ± SD	3.58 ± 1.53	4.13 ± 1.36	
● High stroke risk, n (%)	1281 (85.1)	474 (95.2)	< 0.001
● HAS-BLED score, median (IQR)	1 (1)	2 (1)	< 0.001
● HAS-BLED score, mean ± SD	1.41 ± 0.90	1.72 ± 0.91	

Variable	Appropriate dose	Inappropriate dose	*P*-value
● High bleeding risk, n (%)	150 (9.9)	99 (19.9)	< 0.001
Medical history			
● Previous stroke and/or TIA, n (%)	212 (14.1)	84 (16.7)	0.125
● Coronary artery disease, n (%)	499 (33.1)	184 (36.9)	0.120
● Congestive heart failure, n (%)	541 (35.9)	227 (45.6)	< 0.001
● Hypertension, n (%)	1155 (76.7)	397 (79.7)	0.168
● Diabetes mellitus, n (%)	431 (28.6)	141 (28.3)	0.889
● Dyslipidemia, n (%)	436 (28.9)	132 (26.5)	0.294
● Peripheral artery disease, n (%)	49 (3.3)	27 (5.4)	0.028
● Chronic kidney disease, n (%)	415 (27.6)	203 (40.8)	< 0.001
● Anemia, n (%)	278 (18.4)	121 (24.3)	0.005
● Current smoker, n (%)	249 (16.5)	71 (14.3)	0.229
● Cardioversion, n (%)	141 (9.3)	33 (6.6)	0.060
● AF ablation, n (%)	62 (4.1)	7 (1.4)	0.004
Previous bleeding history			
● Major bleeding, n (%)	41 (2.7)	23 (4.6)	0.037
● CRNM bleeding, n (%)	66 (4.3)	34 (6.8)	0.030
● Major and/or CRNM bleeding, n (%)	102 (6.7)	55 (11)	0.002
● Minor bleeding, n (%)	339 (22.5)	130 (26.1)	0.101
● History of GI bleeding, n (%)	69 (4.6)	34 (6.8)	0.047
Laboratory data			
● Serum creatinine, median (IQR), mg/dL	0.90 (0.35)	0.97 (0.39)	0.029
● GFR, median (IQR), mL/min	72 (33)	63 (31)	< 0.001
● GFR group, n (%)			
● GFR ≥ 60 mL/min/1.73 m^2	981 (79.6)	252 (20.4)	< 0.001

Variable	Appropriate dose	Inappropriate dose	*P*-value
● GFR 30–59 mL/min/1.73 m^2	380 (66)	196 (34)	
● GFR 15–29 mL/min/1.73 m^2	35 (83.3)	7 (16.7)	
● Hemoglobin, mean ± SD, mg/dL	13.1 ± 1.9	12.5 ± 2.0	< 0.001

IQR = interquartile range; SD = standart deviation; BMI = body mass index; BP = blood pressure; AF = atrial fibrillation; CHA2DS2-VASc = congestive heart failure, hypertension, age ≥ 75 (2 points), diabetes, stroke (2 points), vascular disease, age 65–74, sex category (female); HAS-BLED = uncontrolled hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile international normalized ratios, elderly (age > 65 years), drugs or alcohol (1 point each) (concomitant use of antiplatelet agents or non-steroidal anti-inflammatory drugs, alcohol abuse); TIA = transient ischemic attack; CRNM = clinically relevant non-major bleeding; GI = gastrointestinal; GFR = glomerular filtration rate.

Table 2

b. The comparison of direct oral anticoagulant treatment patterns and cardiovascular medical therapies between appropriate dose and inappropriate dose groups

Variable	Appropriate dose	Inappropriate dose	*P*-value
DOACs, n (%)			
● Dabigatran	83 (69.2)	37 (30.8)	0.081
● Rivaroxaban	764 (77.4)	223 (22.6)	
● Apixaban	487 (74)	171 (26)	
● Edoxaban	172 (72)	67 (28)	
Standard and low doses of DOACs, n (%)			
● Dabigatran 150 mg B.I.D.	51 (83.6)	10 (16.4)	< 0.001
● Dabigatran 110 mg B.I.D.	32 (54.2)	27 (45.8)	
● Rivaroxaban 20 mg O.D.	597 (85.2)	104 (14.8)	
● Rivaroxaban 15 mg O.D.	167 (58.4)	119 (41.6)	
● Apixaban 5 mg B.I.D.	399 (80.8)	95 (19.2)	
● Apixaban 2.5 mg B.I.D.	88 (53.7)	76 (46.3)	
● Edoxaban 60 mg O.D.	141 (74.2)	49 (25.8)	
● Edoxaban 30 mg O.D.	31 (63.3)	18 (36.7)	
Other therapies, n (%)			
● Antiplatelet therapy	151 (10.1)	74 (14.9)	0.003
● Beta – blockers	1136 (75.4)	370 (74.3)	0.777
● Verapamil	21 (1.4)	6 (1.2)	0.750
● Diltiazem	164 (10.9)	69 (13.9)	0.070
● Digoxin	221 (14.7)	86 (17.3)	0.151
● Amiodarone	58 (3.9)	31 (6.2)	0.026
● Propafenone	74 (4.9)	15 (3)	0.073
● ACE-inhibitors or ARBs	911 (60.5)	295 (59.2)	0.677
● ARNI	34 (2.3)	16 (3.2)	0.236
● MRAs	278 (18.5)	98 (19.7)	0.176

Variable	Appropriate dose	Inappropriate dose	*P*-value
● Diuretics	742 (49.2)	291 (58.4)	< 0.001
● DHP-CCB	292 (19.4)	90 (18.1)	0.525
● Alpha blockers	40 (2.7)	16 (3.2)	0.507
● Statins	329 (21.8)	87 (17.5)	0.041
● PPIs	759 (50.4)	257 (51.6)	0.619
● NSAIDs	149 (9.9)	63 (12.6)	0.046
● Steroids	14 (0.9)	10 (2)	0.054

B.I.D. = twice daily; O.D. = once daily; DOACs = direct oral anticoagulants; ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; MRAs = mineralocorticoid receptor antagonists; DHP-CCB = dihydropyridine calcium-channel blockers; PPIs = proton pump inhibitors; NSAIDs = non-steroidal anti-inflammatory drugs.

Table 3

a. The comparison of the socio-demographic profile, clinical features, medical history, and laboratory studies between appropriate dose, inappropriate low lose, and inappropriate high dose groups

Variable	Appropriate dose	Inappropriate low dose	Inappropriately high dose	*P*-value
Demographics				
● Age, median (IQR), years	71 (13)	73 (12)	77 (7)	< 0.001#
● Age group, n (%)				
●< 65 years	353 (88.9)	25 (6.3)	19 (4.8)	< 0.001#
●65–74 years	613 (79.5)	115 (14.9)	43 (5.6)	
● ≥ 75 years	540 (64.6)	100 (12)	196 (23.4)	
● Female sex, n (%)	874 (58)	136 (56.7)	153 (59.3)	0.838
● Urban population, n (%)	938 (62.3)	136 (56.7)	167 (64.7)	0.153
● Marital status (single or widowed or divorced), n (%)	417 (27.7)	90 (37.5)	100 (38.8)	< 0.001§
● Individuals with higher education, n (%)	81 (5.4)	15 (6.3)	7 (2.7)	0.071
Physical examination				
● BMI, median (IQR), kg/m^2	28.1 (5.6)	28.3 (6.5)	26.6 (6)	< 0.001†
● Systolic BP, median (IQR), mmHg	130 (20)	130 (25)	130 (30)	0.210
● Diastolic BP, median (IQR), mmHg	80 (15)	77 (18)	80 (18)	0.578
● Heart rate, median (IQR), bpm	83 (25)	83 (29)	84 (23)	0.250
AF-related information				
● Permanent atrial fibrillation, n (%)	726 (48.2)	150 (62.5)	149 (57.8)	< 0.001#
● CHA_2DS_2-VASc score, median (IQR)	4 (3)	4 (2)	4 (1)	< 0.001#
● CHA_2DS_2-VASc score, mean ± SD	3.58 ± 1.53	3.83 ± 1.33	4.41 ± 1.34	
● High stroke risk, n (%)	1281 (85.1)	223 (92.9)	251 (97.3)	< 0.001#

Variable	Appropriate dose	Inappropriate low dose	Inappropriately high dose	*P*-value
● HAS-BLED score, median (IQR)	1 (1)	1 (1)	2 (2)	< 0.001†
● HAS-BLED score, mean ± SD	1.41 ± 0.90	1.45 ± 0.68	1.97 ± 1.02	
● High bleeding risk, n (%)	150 (9.9)	10 (4.2)	89 (34.5)	< 0.001#
Medical history				
● Previous stroke and/or TIA, n (%)	212 (14.1)	36 (15)	48 (18.6)	0.159
● Coronary artery disease, n (%)	499 (33.1)	78 (31.2)	106 (41.1)	0.039†
● Congestive heart failure, n (%)	541 (35.9)	114 (47.5)	113 (43.8)	< 0.001§
● Hypertension, n (%)	1155 (76.7)	184 (76.7)	213 (82.6)	0.112
● Diabetes mellitus, n (%)	431 (28.6)	65 (27.1)	76 (29.5)	0.834
● Dyslipidemia, n (%)	436 (28.9)	56 (23.3)	76 (29.5)	0.183
● Peripheral artery disease, n (%)	49 (3.3)	9 (3.8)	18 (6.9)	0.015†
● Chronic kidney disease, n (%)	415 (27.6)	66 (27.5)	137 (53.1)	< 0.001†
● Anemia, n (%)	278 (18.4)	51 (21.3)	70 (27.1)	0.005†
● Current smoker, n (%)	249 (16.5)	29 (12.1)	42 (16.3)	0.215
● Cardioversion, n (%)	141 (9.3)	17 (7.1)	16 (6.2)	0.160
● AF ablation, n (%)	62 (4.1)	4 (1.7)	3 (1.2)	0.015§
Previous bleeding history				
● Major bleeding, n (%)	41 (2.7)	13 (5.4)	10 (3.9)	0.070
● CRNM bleeding, n (%)	66 (4.3)	18 (7.5)	16 (6.2)	0.076
● Major and/or CRNM bleeding, n (%)	102 (6.7)	31 (12.9)	24 (9.3)	0.003#
● Minor bleeding, n (%)	339 (22.5)	68 (28.3)	62 (24)	0.137
● History of GI bleeding, n (%)	69 (4.6)	16 (6.7)	18 (6.9)	0.138
Laboratory data				

Variable	Appropriate dose	Inappropriate low dose	Inappropriately high dose	*P*-value
● Serum creatinine, median (IQR), mg/dL	0.90 (0.35)	0.90 (0.35)	1.03 (0.41)	< 0.001†
● GFR, median (IQR), mL/min	72 (33)	70 (26)	53 (28)	< 0.001†
● GFR group, n (%)				
● GFR ≥ 60 mL/min/1.73 m^2	981 (79.6)	155 (12.6)	97 (7.9)	< 0.001#
● GFR 30–59 mL/min/1.73 m^2	380 (66)	66 (11.5)	130 (22.6)	
● GFR 15–29 mL/min/1.73 m^2	35 (83.3)	0 (0)	7 (16.7)	
● Hemoglobin, mean ± SD, mg/dL	13.1 ± 1.9	12.7 ± 2.1	12.3 ± 2.0	< 0.001*

IQR = interquartile range; SD = standart deviation; BMI = body mass index; BP = blood pressure; AF = atrial fibrillation; CHA2DS2-VASc = congestive heart failure, hypertension, age ≥ 75 (2 points), diabetes, stroke (2 points), vascular disease, age 65–74, sex category (female); HAS-BLED = uncontrolled hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile international normalized ratios, elderly (age > 65 years), drugs or alcohol (1 point each) (concomitant use of antiplatelet agents or non-steroidal anti-inflammatory drugs, alcohol abuse); TIA = transient ischemic attack; CRNM = clinically relevant non-major bleeding; GI = gastrointestinal; GFR = glomerular filtration rate.

Significant for appropriate dose group versus inappropriately low dose group; appropriate dose group versus inappropriately high dose group; and inappropriately low dose group versus inappropriately high dose group.

§ Significant for appropriate dose group versus inappropriately low dose group and appropriate dose group versus inappropriately high dose group.

*Significant for appropriate dose group versus inappropriately high dose group.

†Significant for appropriate dose versus inappropriately high dose group and inappropriately low dose group versus inappropriately high dose group.

Table 3

b. The comparison of direct oral anticoagulant treatment patterns and cardiovascular medical therapies between appropriate dose, inappropriate low lose, and inappropriate high dose groups

Variable	Appropriate dose	Inappropriately low dose	Inappropriately high dose	*P*-value
DOACs, n (%)				
● Dabigatran	83 (69.2)	27 (22.5)	10 (8.3)	< 0.001[#]
● Rivaroxaban	764 (77.4)	119 (12.1)	104 (10.5)	
● Apixaban	487 (74)	76 (11.6)	95 (14.4)	
● Edoxaban	172 (72)	18 (7.5)	49 (20.5)	
Standard and low doses of DOACs, n (%)				
● Dabigatran 150 mg B.I.D.	51 (83.6)	–	10 (16.4)	< 0.001[#]
● Dabigatran 110 mg B.I.D.	32 (54.2)	27 (45.8)	–	
● Rivaroxaban 20 mg O.D.	597 (85.2)	–	104 (14.8)	
● Rivaroxaban 15 mg O.D.	167 (58.4)	119 (41.6)	–	
● Apixaban 5 mg B.I.D.	399 (80.8)	–	95 (19.2)	
● Apixaban 2.5 mg B.I.D.	88 (53.7)	76 (46.3)	–	
● Edoxaban 60 mg O.D.	141 (74.2)	–	49 (25.8)	
● Edoxaban 30 mg O.D.	31 (63.3)	18 (36.7)	–	
Other therapies, n (%)				
● Antiplatelet therapy	151 (10.1)	24 (10.7)	50 (22.2)	< 0.001[†]
● Beta – blockers	1136 (75.4)	185 (77.1)	185 (71.7)	0.439
● Verapamil	21 (1.4)	3 (1.3)	3 (1.2)	0.948
● Diltiazem	164 (10.9)	19 (7.9)	50 (19.4)	< 0.001[#]
● Digoxin	221 (14.7)	27 (11.2)	59 (22.9)	0.001[#]
● Amiodarone	58 (3.9)	4 (1.7)	27 (10.7)	< 0.001[#]
● Propafenone	74 (4.9)	11 (4.6)	4 (1.6)	0.053
● ACE-inhibitors or ARBs	911 (60.5)	135 (56.2)	160 (62)	0.360

Variable	Appropriate dose	Inappropriately low dose	Inappropriately high dose	P-value
● ARNI	34 (2.3)	7 (2.9)	9 (3.5)	0.453
● MRAs	278 (18.5)	41 (17.1)	57 (22.1)	0.043†
● Diuretics	742 (49.2)	131 (54.6)	160 (62)	< 0.001#
● DHP-CCB	292 (19.4)	45 (18.7)	45 (17.4)	0.773
● Alpha blockers	40 (2.7)	6 (2.5)	10 (3.9)	0.516
● Statins	329 (21.8)	35 (14.6)	52 (20.2)	0.037&
● PPIs	759 (50.4)	108 (45)	149 (57.8)	0.015#
● NSAIDs	149 (9.9)	29 (12.1)	34 (13.2)	0.031§
● Steroids	14 (0.9)	3 (1.3)	7 (2.7)	0.051

B.I.D. = twice daily; O.D. = once daily; DOACs = direct oral anticoagulants; ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; ARNI = angiotensin receptor-neprilysin inhibitor; MRAs = mineralocorticoid receptor antagonists; DHP-CCB = dihydropyridine calcium-channel blockers; PPIs = proton pump inhibitors; NSAIDs = non-steroidal anti-inflammatory drugs.

Significant for appropriate dose group versus inappropriately low dose group; appropriate dose group versus inappropriately high dose group; and inappropriately low dose group versus inappropriately high dose group.

†Significant for appropriate dose group versus inappropriately high dose group and inappropriately low dose group versus inappropriately high dose group.

& Significant for appropriate dose group versus inappropriately low dose group and inappropriately low dose group versus inappropriately high dose group.

§ Significant for appropriate dose group versus inappropriately low dose group and appropriate dose group versus inappropriately high dose group.

This study was conducted in accordance with the principles of the Declaration of Helsinki, and all patients provided written informed consent for participation. This study was approved by the Ethics Committee of Başkent University, School of Medicine (Date: 08.01.2021, Project No. KA20/463 and E-94603339-604.01.02-1547).

Results

A total of 2,004 patients with atrial fibrillation were included in the present study, with a median age of 72 years and 58% female patients. The most common comorbidities were hypertension (77.4%), congestive heart failure (38.3%), coronary artery disease (34.1%) and diabetes (28.5%). The mean CHA2DS2-VASc

and HAS-BLED scores of the study population were 3.72 ± 1.51 and 1.49 ± 0.91, respectively. The median glomerular filtration rate was 70 mL/min/1.73 m^2, and 30.8% of patients had a glomerular filtration rate < 60 mL/min/1.73 m^2.

The most commonly prescribed direct oral anticoagulant was rivaroxaban (Fig. 1). Among the study population, more than one-fourth of the patients (27.8%) received a reduced dose of direct oral anticoagulant, and the proportion of patients receiving a reduced dose of each direct oral anticoagulant was 49.6% for dabigatran, 29.1% for rivaroxaban, 25.1% for apixaban, and 21.6% for edoxaban.

According to the criteria proposed by the European Heart Rhythm Association [18], 1506 patients (75.1%) received the appropriate dose of direct oral anticoagulants and 498 patients (24.9%) received an inappropriate dose. Among patients receiving an inappropriate dose of direct oral anticoagulants, 12% (n = 240) received an inappropriately low dose, and 12.9% (n = 258) received an inappropriately high dose (Fig. 2). The proportion of appropriate prescriptions was higher for rivaroxaban (77.4%) than for apixaban (74%), edoxaban (72%), or dabigatran (69.2%) (Fig. 3). Inappropriately low doses were more frequent than inappropriately high doses for dabigatran (22.5% vs. 8.3%, respectively), and an inappropriately high dose was more frequent than an inappropriately low dose for edoxaban (20.5% vs. 7.5%, respectively) (Fig. 3). The baseline characteristics of the study groups are shown in Table 2a.

Compared with patients receiving an appropriate dose of direct oral anticoagulants, those receiving an inappropriate dose of direct oral anticoagulants were significantly older, more likely to be single, and more likely to have permanent atrial fibrillation, congestive heart failure, chronic kidney disease, peripheral artery disease, anemia, have a history of major and/or clinically relevant non-major bleeding and gastrointestinal bleeding, higher CHA2DS2-VASc and HAS-BLED scores, lower body mass index, glomerular filtration rate, and hemoglobin (Table 2a). Prescription of concomitant antiplatelet drugs (including aspirin, clopidogrel, prasugrel, or ticagrelor), amiodarone, diuretics, and non-steroidal anti-inflammatory drug therapy was higher in patients who received an inappropriate dose of direct oral anticoagulants. In contrast, the prescription of concomitant statin therapy and previous atrial fibrillation ablation procedures were lower in these patients (Table 2b).

In the univariate analysis, patients receiving an inappropriately high dose of direct oral anticoagulants were significantly older, more likely to have chronic kidney disease or coronary artery disease, had higher CHA2DS2-VASc and HAS-BLED scores, and had lower body mass index and glomerular filtration rate than those receiving an appropriate or inappropriately low dose of direct oral anticoagulants (Table 3a). In addition, prescription of edoxaban treatment and rates of concomitant antiplatelet, diltiazem, digoxin, amiodarone, diuretic, and proton-pump inhibitor therapy were significantly higher in patients receiving an inappropriately high dose of direct oral anticoagulants than in patients receiving an appropriate or inappropriately low dose of direct oral anticoagulants (Table 3b). In contrast, patients receiving an inappropriately low dose of direct oral anticoagulants were more likely to have permanent atrial fibrillation and a history of major and/or clinically relevant non-major bleeding than those receiving an appropriate or inappropriately low dose of direct oral anticoagulants (Table 3a). Prescription of

dabigatran was associated with receiving an inappropriately low dose of direct oral anticoagulant (Table 3b).

In the logistic regression model, advanced age (odds ratio [OR]: 2.32; 95% confidence interval [CI], 1.47–3.65, $P-$ value < 0.001 for patients ≥ 75 years; and OR: 1.57; 95% CI, 1.03–2.39, $P-$ value < 0.05 for patients between 65 to 74 years), presence of chronic kidney disease (OR: 4.25; 95% CI, 1.79–10.11, $P-$ value < 0.001 for patients with stage 3 chronic kidney disease; and OR: 3.73; 95% CI, 1.55–8.99, $P-$ value < 0.05 for patients with stage 4 chronic kidney disease), presence of permanent atrial fibrillation (OR: 2.16; 95% CI, 1.06–4.41, $P-$ value < 0.05), prescription of edoxaban treatment (OR: 1.60; 95% CI, 1.11–2.31, $P-$ value < 0.05), prescription of reduced dose of direct oral anticoagulants (OR: 2.54; 95% CI, 1.96–3.29, $P-$ value < 0.001), concomitant usage of amiodarone treatment (OR: 2.79; 95% CI, 1.63–4.79, $P-$ value < 0.001), and non-use of statin treatment (OR: 1.63; 95% CI, 1.19–2.21, $P-$ value < 0.05) were significantly associated with potentially inappropriate dosing of direct oral anticoagulants (Table 4).

Table 4
Unadjusted variables and age-adjusted logistic regression analysis/models of factors associated with inappropriate dose of direct anticoagulants

	Unadjusted	**Model 1†**	**Model 2‡**
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Demographic features			
Age			
● < 65 years (reference group)			
● 65–74 years	2.07 (1.44–2.96) **	2.02 (1.41–2.90) **	1.57 (1.03–2.39) *
● ≥ 75 years	4.40 (3.12–6.20) **	4.16 (2.92–5.93) **	2.32 (1.47–3.65) **
Marital status			
● Married (reference group)			
● Single or widowed or divorced	1.61 (1.30–1.99) **	1.16 (0.92–1.45)	1.05 (0.81–1.37)
		Nagelkerke R2 = 0.075	
Medical history and laboratory findings			
BMI, kg/m^2	0.97 (0.95–0.99) *	0.99 (0.97–1.01)	0.99 (0.96–1.01)
Presence of CHF	1.49 (1.21–1.83) **	1.28 (1.02–1.60) *	1.08 (0.82–1.42)
Presence of PAD	1.70 (1.05–2.76) *	1.44 (0.84–2.45)	1.46 (0.83–2.58)
Absence of AF ablation procedure history	3.01 (1.37–6.61) *	1.62 (0.71–3.68)	1.90 (0.77–4.67)
History of major and/or CRNM bleeding	1.71 (1.21–2.41) *	1.30 (0.89–1.90)	1.15 (0.77–1.71)
GFR group			
● GFR 15–29 mL/min/1.73 m^2 (reference group)			
● GFR 30–59 mL/min/1.73 m^2	2.58-1.13-5.91) *	3.23 (1.40–7.50)*	4.25 (1.79–10.11) **
● GFR ≥ 60 mL/min/1.73 m^2	1.28 (0.56–2.93)	2.39 (1.03–5.56) *	3.73 (1.55–8.99) *

	Unadjusted	Model 1†	Model 2‡
Hemoglobin, mg/dL	0.88 (0.83–0.92) **	0.96 (0.90–1.01)	0.98 (0.92–1.04)
		Nagelkerke R2 = 0.096	
AF-related features			
AF type			
● New-onset AF (reference group)			
● Paroxysmal AF	1.33 (0.68–2.62)	1.44 (0.72–2.87)	1.52 (0.73–3.16)
● Persistent or long-standing persistent AF	1.44 (0.71–2.90)	1.37 (0.67–2.81)	1.60 (0.75–3.44)
● Permanent AF	2.17 (1.12–4.20) **	1.98 (1.01—3.89) *	2.16 (1.06–4.41) *
CHA_2DS_2-VASc score	1.28 (1.19–1.37) **	1.07 (0.98–1.16)	1.07 (0.96–1.18)
HAS-BLED score	1.43 (1.27–1.59) **	1.12 (0.97–1.28)	1.022 (0.87–1.21)
		Nagelkerke R2 = 0.088	
Treatments			
DOACs			
● Rivaroxaban (reference group)			
● Edoxaban	1.34 (0.97–1.84)	1.50 (1.07–2.12) *	1.60 (1.11–2.31) *
● Dabigatran	1.53 (1.01–2.31) *	1.26 (0.81–1.97)	1.19 (0.75–1.91)
● Apixaban	1.20 (0.96–1.51)	1.23 (0.96–1.57)	1.16 (0.89–1.50)
Dosage of DOAC			
● Standard dose (reference group)			
● Reduced dose	3.48 (2.80–4.31) **	2.68 (2.12–3.40) **	2.54 (1.96–3.29) **
Usage of antiplatelet therapy	1.57 (1.16–2.12) *	1.43 (1.02-2.00) *	1.34 (0.91–1.96)
Usage of amiodarone	1.66 (1.06–2.60) *	2.02 (1.25–3.28) *	2.79 (1.63–4.79) **

	Unadjusted	Model 1†	Model 2‡
Usage of diuretics	1.46 (1.19–1.79) *	1.20 (0.96–1.49)	1.01 (0.78–1.32)
Usage of NSAIDs	1.35 (0.99–1.84)	1.18 (0.84–1.65)	1.20 (0.83–1.75)
Non-use of statins	1.31 (1.01–1.71) *	1.57 (1.18–2.10) *	1.63 (1.19–2.21) *
		Nagelkerke R2 = 0.145	**Nagelkerke R2 = 0.168**

OR = odds ration; CI = confidence interval; BMI = body mass index; CHF = congestive heart failure; PAD = peripheral artery disease; AF = atrial fibrillation; CRNM = clinically relevant non-major bleeding; GFR = glomerular filtration rate; CHA2DS2-VASc = congestive heart failure, hypertension, age ≥ 75 (2 points), diabetes, stroke (2 points), vascular disease, age 65–74, sex category (female); HAS-BLED = uncontrolled hypertension, abnormal renal and liver function (1 point each), stroke, bleeding, labile international normalized ratios, elderly (age > 65 years), drugs or alcohol (1 point each) (concomitant use of antiplatelet agents or non-steroidal anti-inflammatory drugs, alcohol abuse); DOACs = direct oral anticoagulants; NDAIDs = non-steroidal anti-inflammatory drugs.

† The variables included in each subtitle of **MODEL – 1** were: **Demographic features** (age and marital status); **Medical history and laboratory findings** (age, BMI, presence of CHF, presence of PAD, absence of AF ablation procedure history, history of major and/or CRNM bleeding, GFR group, and hemoglobin); **AF-related features** (age, AF type, CHA_2DS_2-VASc score, and HAS-BLED score); **Treatments** (age, DOACs, dosage of DOAC, usage of antiplatelet therapy, usage of amiodarone, usage of diuretics, usage of NSAIDs, and non-use of statins).

‡ All variables were included in the **MODEL – 2**.

***** P – value < 0.05 and ****** P – value < 0.001

Discussion

The nationwide ANATOLIA-AF study provides important real-world data on the prevalence and associated factors of inappropriate direct oral anticoagulant dosing in patients with atrial fibrillation. The principal findings of this study are as follows: 1) more than one-fourth of the patients with atrial fibrillation receiving direct oral anticoagulant therapy received a reduced dose of direct oral anticoagulants; 2) according to the European Heart Rhythm Association recommendations, nearly one-fourth of the patients with atrial fibrillation received inappropriate doses of direct oral anticoagulant in real-life settings; 3) in contrast to previously published registries and studies, the rate of inappropriate high-dose prescription of direct oral anticoagulants was similar to the rate of inappropriate low-dose prescription; and 4) advanced age, chronic kidney disease, presence of permanent atrial fibrillation, prescription of edoxaban, reduced dose of direct oral anticoagulants, concomitant usage of amiodarone, and non-use of statin treatment were independently associated with inappropriate direct oral anticoagulant dosing.

The efficacy and safety of reduced doses of direct oral anticoagulants, especially rivaroxaban and apixaban, have been tested in a small proportion of patients in pivotal randomized controlled trials [3–6]. In the ROCKET-AF trial [4], 21% of patients received a reduced dose of rivaroxaban, and in the ARISTOTLE trial [5], only 4.7% of study participants received a reduced dose of apixaban. However, national registries and observational studies have demonstrated that the frequency of reduced doses of direct oral anticoagulant prescription varies between 29–56% [10, 19, 20]. In the ANATOLIA-AF study, the percentage of individuals that were prescribed reduced doses of direct oral anticoagulants was 27.8%, which is higher than that in pivotal trials and similar to that in national registries and observational studies [4, 5, 10, 19, 20]. Compared with the patients enrolled in phase 3 randomized controlled trials, patients in routine clinical practice are older, more frail, more likely to have chronic kidney disease, have a history of major and/or clinically relevant non-major bleeding and/or gastrointestinal bleeding, and more likely to receive concomitant antiplatelet therapy and/or interacting drugs [8]. As a result, the prescription of low doses of direct oral anticoagulants (appropriate or inappropriate) is more common in real-life settings [9, 10, 12, 14–16]. This considerable difference in the prescription of reduced doses of direct oral anticoagulants between randomized controlled trials and real-world studies may be due to numerous reasons, including patient-related factors such as advanced age, frailty, and the presence of multiple comorbidities, or physician-related factors such as lack of awareness about the recommendations of the guidelines and/or fear of bleeding and other adverse events.

Inappropriate dosing of direct oral anticoagulants is associated with major adverse cardiovascular events [8, 12, 13, 15]. The prescription of inappropriately low doses of direct oral anticoagulants may increase the risk of stroke and/or systemic embolism and cardiovascular hospitalization [8, 13, 21], and the prescription of inappropriately high doses of direct oral anticoagulants may increase the risk of major bleeding and all-cause mortality [8, 21]. Previously published national registries and studies have reported a wide range of inappropriate direct oral anticoagulant dosing in real-life settings [9, 10, 12–16]. The FANTASIIA Registry from Spain revealed that inappropriate doses of direct oral anticoagulants were prescribed to 32% of study participants, and the SAKURA AF Registry from Japan reported that 26.2% of patients with atrial fibrillation received inappropriate doses of direct oral anticoagulants [10, 12]. The prevalence of inappropriate direct oral anticoagulant dosing reaches 39% in the Middle East region [15]. In contrast, the ORBIT-AF II Registry, showed that an inappropriate dose of a direct oral anticoagulant was prescribed to only 12.8% of the patients [13]. A recently published epidemiological meta-analysis comprising 23 real-world studies and 162,474 patients with atrial fibrillation reported that the overall prevalence of inappropriate direct oral anticoagulant dosing was 24% [11]. In our study, we found that the prevalence of inappropriate direct oral anticoagulant dosing was 24.9%. The wide range in the prevalence of inappropriate dosing of direct oral anticoagulants between real-world observational studies might be related to the differences in the criteria for establishing appropriate doses, geographic and clinical variations, patient and/or center selection, and physicians' knowledge.

Data from national registries and observational studies suggest that while the proportion of patients receiving inappropriately low doses of direct oral anticoagulants vary between 19.3% and 39% [12, 19, 15, 22, 23], the prevalence of inappropriate high-dose direct oral anticoagulant prescription varies between

1.3% and 4% [12, 13, 19, 22]. A recently published epidemiological meta-analysis reported that the estimated global prevalence of inappropriate low-dose direct oral anticoagulant prescriptions is 20%, and the estimated global prevalence of inappropriate high-dose direct oral anticoagulant prescriptions is relatively low (4–6%) [11]. In contrast, the prevalence of inappropriate high-dose prescriptions of direct oral anticoagulants was similar to the prevalence of inappropriate low-dose prescriptions in our study (12.8% versus 12%, respectively). These inconsistent results might be related to differences in the criteria for establishing an appropriate dose of direct oral anticoagulants. Most observational studies have assessed the appropriateness of direct oral anticoagulant dosing according to the summary of product characteristics written by pharmaceutical companies. In contrast, we used the criteria proposed by the European Heart Rhythm Association for the use of direct oral anticoagulants in patients with atrial fibrillation in the present study. The European Heart Rhythm Association Practical Guide recommends a systematic assessment algorithm for dose reduction for each direct oral anticoagulant. These recommendations comprise several patient-related risk factors, such as older age, impaired kidney function, lower body weight, high bleeding risk, and concomitant use of antiplatelet therapy, verapamil, diltiazem, amiodarone, or strong P-glycoprotein inhibitors. Some of these criteria are called yellow dose reduction criteria in the European Heart Rhythm Association Practical Guide. This document recommends dose reduction if two or more yellow criteria are present, which are not completely present in the summary of product characteristics [18]. For example, the summary of product characteristics of rivaroxaban reported only one dose reduction criterion, which recommends a dose reduction if the patient has a creatinine clearance below 50 mL/min. However, the European Heart Rhythm Association Practical Guide took into account the patients' age (≥ 75 years), bleeding risk (HAS-BLED score ≥ 3), low body weight (≤ 60 kg), and concomitant usage of antiplatelet therapy or amiodarone as yellow criteria for rivaroxaban dose reduction. The FANTASIIA Registry, which determined the appropriateness of direct oral anticoagulant dosing according to the European Heart Rhythm Association Practical Guide recommendations, reported results similar to those of the present study. In this registry, the prevalence of inappropriately high-dose direct oral anticoagulant prescriptions was 15%, which is higher than previously published registries, and was approximately similar to the prevalence of inappropriately low-dose direct oral anticoagulant prescriptions (17%) [10]. Another important real-life study that analyzed the appropriateness of direct oral anticoagulant dosing according to both the summary of product characteristics and European Heart Rhythm Association Practical Guide revealed that the rates of inappropriate direct oral anticoagulant dosing were 18.3% and 23.4%, respectively. According to the summary of product characteristics, the rate of inappropriately low-dose direct oral anticoagulant prescriptions (9.8%) was higher than the rate of inappropriate high-dose direct oral anticoagulant prescriptions (7.8%). In contrast to the summary of product characteristics criteria, the inappropriately high-dose direct oral anticoagulant prescription was more frequent than the inappropriately low-dose direct oral anticoagulant prescription according to the European Heart Rhythm Association Practical Guide recommendations in the same study population (15.0% versus 7.6%, respectively). The authors concluded that 'nearly 10% of dosing recommendations by the summary of product characteristics and the European Heart Rhythm Association Practical Guide were inconsistent, with the summary of product characteristics recommending the use of the standard direct oral anticoagulant dose while the European

Heart Rhythm Association Practical Guide recommending dose reduction' [9]. It is important to highlight that several risk factors were not considered by the summary of product characteristics of direct oral anticoagulants. Although advanced age is a well-known risk factor for both stroke and bleeding [9, 24, 25], neither the summary of product characteristics of rivaroxaban nor that of edoxaban consider age as a risk factor for stroke or bleeding. According to the European Heart Rhythm Association Practical Guide, age ≥ 75 years is a yellow criterion for dose reduction for all direct oral anticoagulants [18]. Low body weight is another important risk factor for adverse events, especially major and/or clinically relevant non-major bleeding, in patients with atrial fibrillation who are receiving direct oral anticoagulants [1]. However, only the summary of product characteristics of apixaban and edoxaban included body weight as a dose reduction criterion. The European Heart Rhythm Association Practical Guide includes body weight ≤ 60 kg as one of the yellow criteria for dose reduction of dabigatran and rivaroxaban [18]. Concomitant use of antiplatelet drugs, non-steroidal anti-inflammatory drugs, or amiodarone increases bleeding risk and/or affects drug plasma levels in patients receiving direct oral anticoagulant treatment [1, 7, 8, 11]. Although the summary of product characteristics of each direct oral anticoagulant does not have a specific recommendation, the European Heart Rhythm Association Practical Guide recommends direct oral anticoagulant dose reduction in those patients [18]. In the context of inconsistent direct oral anticoagulant dosing recommendations by the summary of product characteristics and the European Heart Rhythm Association Practical Guide, prescribing the appropriate direct oral anticoagulant dose can be challenging in clinical practice. Thus, there is a need for more research on the clinical importance of risk factors causing inconsistencies in dosing recommendations between the European Heart Rhythm Association Practical Guide and the summary of product characteristics of direct oral anticoagulants.

Previously published registries and meta-analyses have reported an association between older age and inappropriate direct oral anticoagulant dosing [8, 11, 16, 26, 27]. Similarly, we observed a strong association between age and inappropriate direct oral anticoagulant dosing. In our study, patients who received inappropriate low or high doses of direct oral anticoagulants were significantly older than those who received an appropriate dose of direct oral anticoagulants. Moreover, we found that older age was an independent predictor of inappropriate direct oral anticoagulant dosing according to the logistic regression analysis. Future directions and efforts targeting gaps in the elderly patient population may lead to improved adherence to the recommendations of the European Heart Rhythm Association Practical Guide.

Chronic kidney disease has been associated with inappropriate direct oral anticoagulant dosing in previous studies [10, 13, 26, 28]. In the ORBIT-AF II Registry, creatinine clearance was significantly lower in patients with inappropriate direct oral anticoagulant dosing, and mild-to-moderate renal impairment had the highest rates of inappropriate dosing [13]. An analysis of a large administrative database including 14,865 patients with atrial fibrillation showed that 43% of the patients with a renal indication for dose reduction received inappropriate high-dose direct oral anticoagulants, which was associated with a higher risk of major bleeding [29]. In our study, the estimated glomerular filtration rate, which was calculated using the Cockcroft-Gault equation, was significantly lower in patients with inappropriate direct oral anticoagulant dosing. According to the logistic regression analysis, mild-to-moderate renal impairment

(estimated glomerular filtration rate 30–50 mL/min/1.73 m^2) is associated with prescription of inappropriate direct oral anticoagulant dosing. This result suggests that many clinicians may not adjust the direct oral anticoagulant dose according to the renal function and estimated glomerular filtration rate. There may be several reasons for this, including a lack of awareness about dose reduction criteria, physicians' knowledge, and the use of different calculations to estimate renal function (e.g., Modification of Diet in Renal Disease formula). Physician awareness of renal function in appropriate direct oral anticoagulant dosing should be increased, and physicians should be encouraged to use the Cockcroft-Gault equation, a method used in pivotal trials of direct oral anticoagulants to calculate estimated glomerular filtration rate in patients with atrial fibrillation and direct oral anticoagulant treatment.

The prescription of a reduced dose of direct oral anticoagulants without dose reduction criteria is associated with an increased risk of stroke, systemic embolism, cardiovascular hospitalization, and death [8, 12, 13, 15, 16]. Jacobs et al. [30] reported that receiving a reduced dose of direct oral anticoagulants was associated with a 2.7-fold increased risk of inappropriate dosing. Similarly, we found that prescription of a reduced dose of direct oral anticoagulants was independently associated with inappropriate direct oral anticoagulant dosing. According to age-adjusted logistic regression analysis, receiving a reduced dose of direct oral anticoagulants was associated with a 2.5-fold increased risk of inappropriate direct oral anticoagulant dosing in our study population. Thus, to ensure the safety and efficacy of direct oral anticoagulants, a reduced dose of direct oral anticoagulants should be prescribed in accordance with the recommendations of the guidelines in real-life clinical practice [11].

A limited number of real-life observational studies are available on inappropriate dosing of edoxaban [8]. An epidemiological meta-analysis comprising of 1213 edoxaban-treated patients reported that the highest prevalence of inappropriate direct oral anticoagulant dosing was found in rivaroxaban and edoxaban [11]. The prevalence of inappropriate high-dose prescriptions of edoxaban was 9%, while the pooled prevalence of inappropriate high-dose prescriptions for all direct oral anticoagulants was 5% [11]. Similar to this meta-analysis, the highest prevalence of inappropriate high-dose prescriptions of direct oral anticoagulant was found in edoxaban (20.5%) in the present study. Moreover, the age-adjusted logistic regression model demonstrated that edoxaban treatment was independently associated with inappropriate direct oral anticoagulant dosing. Although both regimens of edoxaban were non-inferior to warfarin with respect to the prevention of stroke or systemic embolism in the ENGAGE AF-TIMI 48 trial, the rate of ischemic stroke was higher in the low-dose edoxaban group than in the active comparator group [6]. Thus, physicians may have concerns about the efficacy of low-dose edoxaban in the prevention of ischemic stroke. These concerns may lead to the prescription of high-dose edoxaban despite the presence of impaired renal function, low body weight, or concomitant use of strong P-gp inhibitors.

Concomitant use of amiodarone is another important risk factor affecting direct oral anticoagulant plasma levels and/or bleeding risk. Amiodarone is the most frequently used pharmacokinetic interacting drug in direct oral anticoagulant-treated patients [9, 29]. Therefore, the European Heart Rhythm Association Practical Guide recommends dose reduction in patients receiving direct oral anticoagulant and amiodarone treatment in the presence of at least one other yellow criterion, while the summary of

product characteristics does not. The FANTASIIA Registry reported that the prescription of concomitant amiodarone therapy was significantly higher in patients receiving inappropriately high doses of direct oral anticoagulants [10]. Similarly, we found that the prescription of amiodarone was significantly higher in patients who received an inappropriately low or high dose of direct oral anticoagulants compared to patients receiving an appropriate dose of direct oral anticoagulants. More importantly, age-adjusted logistic regression analysis demonstrated that the concomitant use of amiodarone was significantly associated with potentially inappropriate dosing of direct oral anticoagulants. These results suggest that physicians should consider pharmacokinetic drug-drug interactions, especially between amiodarone and direct oral anticoagulants, to determine the appropriate dose of direct oral anticoagulants in real-life settings.

The present study has some limitations. First, the most important limitation of the ANATOLIA-AF study was its observational design, which may have led to patient evaluation and/or patient selection bias. Second, the study population was enrolled from cardiology outpatient clinics, and this population did not include those presenting at family medicine and internal medicine outpatient clinics. Finally, the present study data were based on the documentation of demographics, medical history, and treatments during the first outpatient clinic visit; follow-up data were not obtained. Thus, we were unable to report the stroke, systemic embolism, bleeding, and mortality rates in the study population. We will assess the association between inappropriate direct oral anticoagulant dosing and major adverse cardiac events when our follow-up data become available. Due to these limitations, the results of this study should be interpreted carefully.

Conclusion

The present prospective, multicenter, real-world study demonstrated that the prevalence of inappropriate direct oral anticoagulant dosing according to the European Heart Rhythm Association recommendations was 24.9% in patients with atrial fibrillation. Several demographic and clinical factors, including advanced age, mild-to-moderate renal impairment, prescription of reduced doses of direct oral anticoagulants and edoxaban treatment, and concomitant use of amiodarone, were associated with inappropriate direct oral anticoagulant dosing. Further research is needed to confirm these findings and to investigate the reasons for inappropriate direct oral anticoagulant dosing. Future guidelines should consider the specific characteristics of patients with atrial fibrillation who are underrepresented in randomized controlled trials and the limitations of the summary of product characteristics.

Declarations

Funding: Not applicable.

Conflicts of interest: Not applicable.

Availability of data and material: The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Code availability: Not applicable.

Author Contributions: All authors contributed to the study conception, design, and data collection. Material preparation, and analysis were performed by Umut Kocabaş and Işıl Ergin. The first draft of the manuscript was written by Umut Kocabaş and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: This study was approved by the Ethics Committee of Başkent University, School of Medicine (Date: 08.01.2021, Project No. KA20/463 and E-94603339-604.01.02-1547).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

Consent for publication: Not applicable.

References

1. Hindricks G, Potpara T, Dagres N, et al.; ESC Scientific Document Group. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J* 2021; 42: 373–498.
2. Kocabas U, Kaya E, Avcı G. Novel oral anticoagulants in non-valvular atrial fibrillation: Pharmacological properties, clinical trials, guideline recommendations, new antidote drugs and real-world data. Int J Cardiovasc Acad. 2016;2:167–73.
3. Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:11391151.
4. Patel MR, Mahaffey KW, Garg J, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883891.
5. Granger CB, Alexander JH, McMurray JJ, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981992.
6. Giugliano RP, Ruff CT, Braunwald E, et al. ENGAGE AF-TIMI Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:20932104.
7. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice

Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019;140:e125–51.

8. Santos J, António N, Rocha M, Fortuna A. Impact of direct oral anticoagulant off-label doses on clinical outcomes of atrial fibrillation patients: A systematic review. Br J Clin Pharmacol. 2020;86:533–47.
9. Capiau A, De Backer T, Grymonprez M, et al. Appropriateness of direct oral anticoagulant dosing in patients with atrial fibrillation according to the drug labelling and the EHRA Practical Guide. Int J Cardiol. 2021;328:97–103.
10. Ruiz Ortiz M, Muñiz J, Raña Míguez P, et al. FANTASIIA study investigators. Inappropriate doses of direct oral anticoagulants in real-world clinical practice: prevalence and associated factors. A subanalysis of the FANTASIIA Registry. Europace. 2018;20:1577–83.
11. Shen NN, Zhang C, Hang Y, et al. Real-World Prevalence of Direct Oral Anticoagulant Off-Label Doses in Atrial Fibrillation: An Epidemiological Meta-Analysis. Front Pharmacol. 2021;12:581293.
12. Murata N, Okumura Y, Yokoyama K, et al, SAKURA AF Registry Investigators. Clinical Outcomes of Off-Label Dosing of Direct Oral Anticoagulant Therapy Among Japanese Patients With Atrial Fibrillation Identified From the SAKURA AF Registry. Circ J. 2019;83:727–35.
13. Steinberg BA, Shrader P, Thomas L, et al. ORBIT-AF Investigators and Patients. Off-Label Dosing of Non-Vitamin K Antagonist Oral Anticoagulants and Adverse Outcomes: The ORBIT-AF II Registry. J Am Coll Cardiol. 2016;68:2597–604.
14. Wakamatsu Y, Nagashima K, Watanabe R, et al. Clinical Outcomes of Off-Label Underdosing of Direct Oral Anticoagulants After Ablation for Atrial Fibrillation. Int Heart J. 2020;61:1165–73.
15. Arbel R, Sergienko R, Hammerman A, et al. Effectiveness and Safety of Off-Label Dose-Reduced Direct Oral Anticoagulants in Atrial Fibrillation. Am J Med. 2019;132:847–55.
16. Sanghai S, Wong C, Wang Z, et al. Rates of Potentially Inappropriate Dosing of Direct-Acting Oral Anticoagulants and Associations With Geriatric Conditions Among Older Patients With Atrial Fibrillation: The SAGE-AF Study. J Am Heart Assoc. 2020;9:e014108.
17. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serumcreatinine. Nephron. 1976;16:31–41.
18. Steffel J, Collins R, Antz M, et al. External reviewers. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021;23:1612–76.
19. Nielsen PB, Skjøth F, Søgaard M, Kjældgaard JN, Lip GY, Larsen TB. Effectiveness and safety of reduced dose non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study. BMJ. 2017;356:j510.
20. Miyazaki M, Matsuo K, Uchiyama M, et al. Inappropriate direct oral anticoagulant dosing in atrial fibrillation patients is associated with prescriptions for outpatients rather than inpatients: a single-center retrospective cohort study. J Pharm Health Care Sci. 2020;6:2.

21. Shinoda N, Mori M, Tamura S, Korosue K, Kose S, Kohmura E. Risk of Recurrent Ischemic Stroke with Unintended Low-Dose Oral Anticoagulant Therapy and Optimal Timing of Review. J Stroke Cerebrovasc Dis. 2018;27:1546–51.
22. Sato T, Aizawa Y, Fuse K, et al. The Comparison of Inappropriate-Low-Doses Use among 4 Direct Oral Anticoagulants in Patients with Atrial Fibrillation: From the Database of a Single-Center Registry. J Stroke Cerebrovasc Dis. 2018;27:3280–88.
23. Ferrat E, Fabre J, Galletout P, et al. Inappropriate direct oral anticoagulant prescriptions in patients with non-valvular atrial fibrillation: cross-sectional analysis of the French CACAO cohort study in primary care. Br J Gen Pract. 2021;71:e134–9.
24. Lip GYH, Skjøth F, Nielsen PB, Kjældgaard JN, Larsen TB. The HAS-BLED, ATRIA, and ORBIT Bleeding Scores in Atrial Fibrillation Patients Using Non-Vitamin K Antagonist Oral Anticoagulants. *Am J Med* 2018; 131: 574.e13-574.e27.
25. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955–62.
26. Sørensen R, Gislason G, Torp-Pedersen C, et al. Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. BMJ Open. 2013;3:e002758.
27. Howard M, Lipshutz A, Roess B, et al. Identification of risk factors for inappropriate and suboptimal initiation of direct oral anticoagulants. J Thromb Thrombolysis. 2017;43:149–56.
28. Carley B, Griesbach S, Larson T, Krueger K. Assessment of dabigatran utilization and prescribing patterns for atrial fibrillation in a physician group practice setting. Am J Cardiol. 2014;113:650–4.
29. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-Vitamin K. Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. J Am Coll Cardiol. 2017;69:2779–90.
30. Jacobs MS, van Hulst M, Campmans Z, Tieleman RG. Inappropriate non-vitamin K antagonist oral anticoagulants prescriptions: be cautious with dose reductions. Neth Heart J. 2019;27:371–7.

Figures

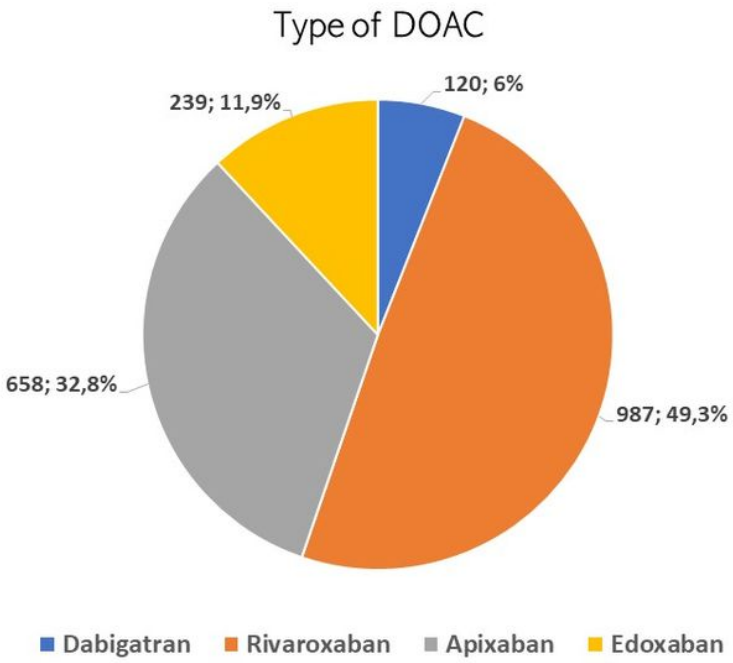

Figure 1

Frequency of direct oral anticoagulants among study population

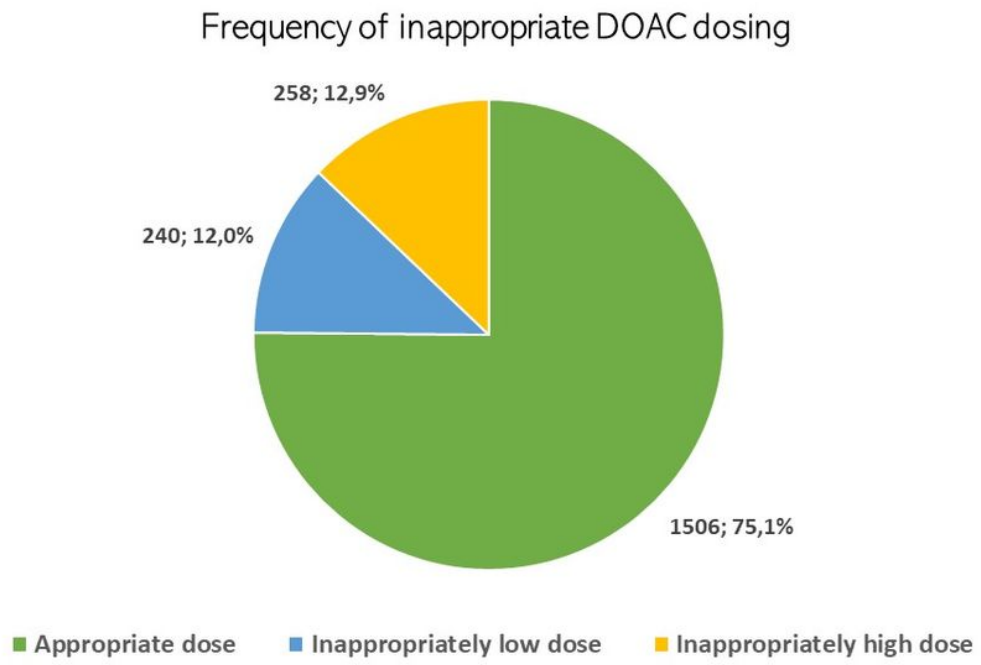

Figure 2

Frequency of appropriate dose of direct oral anticoagulant, inappropriate low dose of direct oral anticoagulant, and inappropriate low dose of direct oral anticoagulant prescription for the entire cohort

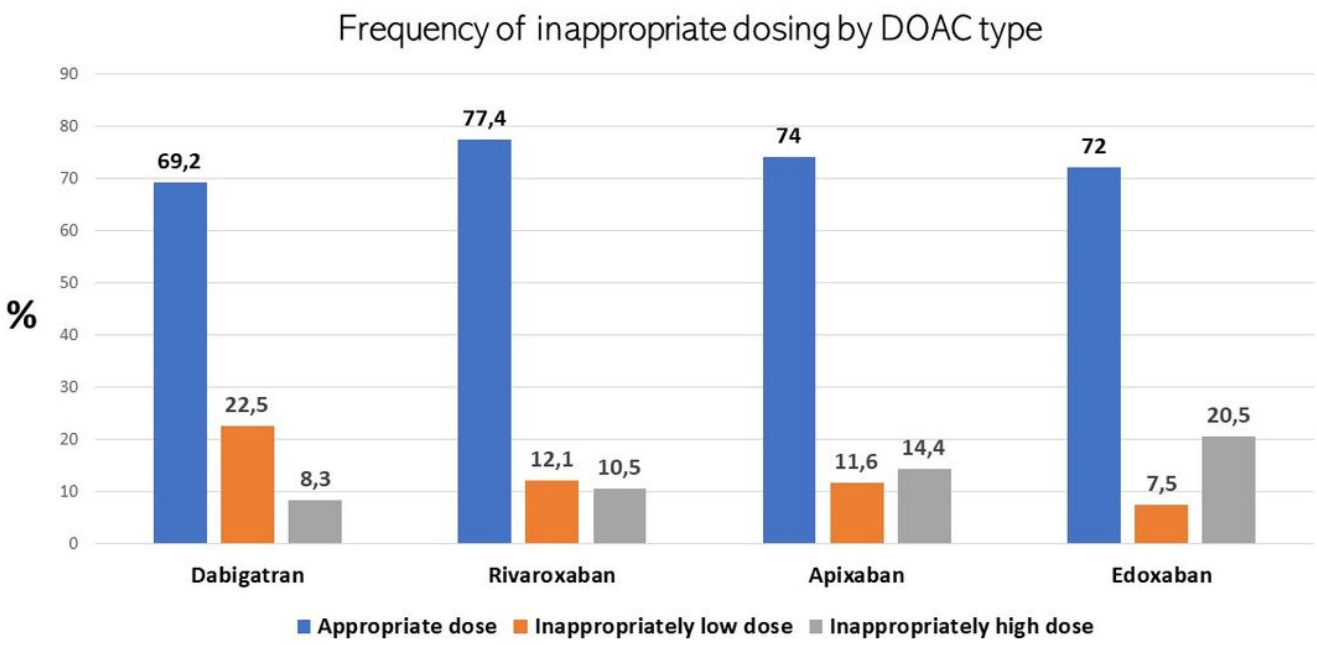

Figure 3

Frequency of inappropriate low and high dosing by each direct oral anticoagulant type