CLINICAL RESEARCH STUDY

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Effectiveness and Safety of Off-Label Dose-Reduced Direct Oral Anticoagulants in Atrial Fibrillation

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ABSTRACT

BACKGROUND: Direct oral anticoagulants (DOACs) reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation but may result in serious bleeding complications. Off-label dose-reduced use of DOACs to mitigate bleeding is common in routine clinical practice although data about its consequences on patient outcomes are limited. Therefore, our objective was to evaluate the effectiveness and safety of off-label dose-reduced vs per-label standard-dose DOAC treatment.

METHODS: The study cohort included newly diagnosed patients with nonvalvular atrial fibrillation that had initiated DOAC therapy between 2011 and 2017 in Clalit Health Services (Tel Aviv, Israel). Effectiveness was defined as the composite outcome of all-cause mortality, stroke, or myocardial infarction. The safety outcome was defined as bleeding events requiring hospitalization. Patients were followed until March 30, 2018 or until occurrence of an outcome event. Hazard ratios (HR) were adjusted for 21 variables, including comorbidities, concomitant medications, and socioeconomic factors, using multivariate regression.

RESULTS: A total of 8425 patients met the study criteria; 5140 (61%) patients were treated with DOACs at per-label dosing and 3285 (39%) patients were treated with off-label dose-reduced DOAC. Off-label dose-reduced treatment was associated with a higher rate of the composite effectiveness outcome: adjusted HR 1.57 (95% confidence interval, 1.34-1.83; $P < .001$) and a higher rate of bleeding: adjusted HR 1.63 (95% confidence interval, 1.14-2.34; $P = .008$).

CONCLUSIONS: Almost 4 of 10 patients were treated with off-label dose-reduced DOAC, which was associated with reduced effectiveness without a safety benefit. Compliance with per-label dosage may significantly improve outcomes of this population.

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KEYWORDS: Anticoagulation; Atrial fibrillation; Dose-reduced; Outcomes

INTRODUCTION

Direct oral anticoagulants (DOACs) are administered at either a higher or a lower dose, according to the drug label.[1] Recently, several population-based studies have examined the doses of DOACs administered among patients with nonvalvular atrial fibrillation in routine clinical practice. These studies show that a greater proportion of patients receive the lower vs higher doses of the DOACs than was the case in the randomized clinical trials. The use of the reduced dose was frequently not in compliance with the approved label and clinical guidelines.[2-6]

Off-label dose-reduced DOAC was found to be associated with an increased risk of stroke and systemic embolism,[2-5] but its relationship to bleeding risk and to overall

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mortality has not been well studied. Therefore, we performed this large cohort study to examine the rates of all major adverse events of stroke, myocardial infarction, bleeding requiring hospitalization, and mortality associated with off-label dose-reduced vs per-label dose of DOAC therapy among high-risk patients with nonvalvular atrial fibrillation initiating anticoagulation therapy with DOACs.

METHODS

Patient Population

We identified all newly diagnosed high-risk nonvalvular atrial fibrillation patients exposed to DOAC therapy from January 1, 2011 until December 31, 2017 in Clalit Health Services (CHS; Tel Aviv, Israel). Patients were identified based on physician-assigned diagnoses of atrial fibrillation on either hospital discharge, outpatient clinic, or during a primary care physician visit.

Patients with <60 days of exposure to a DOAC or who switched between different DOACs during the study follow-up were excluded from this analysis. Patients treated with per-label dose-reduced and patients treated with off-label higher dosing were also excluded.

Exposure and Dosage

The DOACs that were available in Israel and that were reimbursed by CHS during the study period were dabigatran, rivaroxaban, and apixaban. Patient exposure was determined based on CHS's electronic dispensing records.[7] Dose was defined as that dispensed immediately prior to an outcome event or to the end of the study period.

Outcomes

Effectiveness was defined as a composite outcome of all-cause mortality, stroke, and myocardial infarction. Safety was defined as any bleeding event that required hospitalization, determined by the primary diagnosis code recorded in the discharge summary.[7] Patients were followed until March 30, 2018, or an outcome event. Detailed definitions of the end-point events are provided in Supplementary Table 1 (available online).

Hazard Ratio Adjustments to Minimize Bias by Confounders

Hazard ratios (HR) were adjusted for 21 variables, including comorbidities, concomitant medications, and socioeconomic factors, using multivariate regression. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS; IBM, Armonk, NY) software, version 24. *P*-values < .05 determined statistical significance in all analyses.

Subgroup Analysis

HRs for myocardial infarction and stroke were determined in various patient subgroups. The subgroups included demographic factors: age >75 years, sex, socioeconomic status; comorbidities: body mass index >30, previous stroke, congestive heart failure (CHF), peripheral vascular disease (PVD), diabetes, kidney disease; and concomitant medications: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, aspirin, diuretics, and lipid-lowering agents.

Compliance to Guidelines and Ethical Approvals

The study was designed and reported according to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) statement, as detailed in Supplementary Table 2 (available online). The study was approved by CHS's data extraction committee and ethical approval was provided by the institutional review board of CHS.

CLINICAL SIGNIFICANCE

- A large fraction of patients is treated with off-label dose-reduced direct oral anticoagulants (DOAC), mainly to mitigate bleeding.
- Off-label dose-reduced DOAC is associated with reduced effectiveness without a safety benefit.
- Compliance with per-label dosage is safe and may significantly improve the effectiveness of DOACs.

RESULTS

Study Population

The CONSORT diagram of the patient cohort is presented in Figure 1. A total of 8425 patients met the study criteria; 5140 (61%) patients were treated with DOACs at per-label dosing and 3285 (39%) patients were treated with off-label dose-reduced DOAC. Their key clinical characteristics are presented in Table 1. The mean follow-up was 23 months (median 20; interquartile range 12 and 31 months).

Effectiveness Outcomes

Off-label dose-reduced DOAC administration was associated with a higher risk of the composite outcome of all-cause mortality, stroke, and myocardial infarction, as presented in Table 2 and Figure 2. The primary driver of the lower effectiveness of off-label dose-reduced DOAC was all-cause mortality, whereas stroke and myocardial infarction rates were similar between the groups.

Safety Outcomes

Off-label dose-reduced DOAC administration was also associated with a higher risk of bleeding: 101 events in the off-label dose-reduced group, vs 80 events in the per-label group. Unadjusted HR: 2.02 (95% confidence interval, 1.50-2.71; $P < .001$). Risk-adjusted HR: 1.58 (95% confidence interval, 1.16-2.16; $P = .003$). As of note, because the dose was defined as that dispensed immediately prior to an outcome event (or end of follow-up), the per-label group

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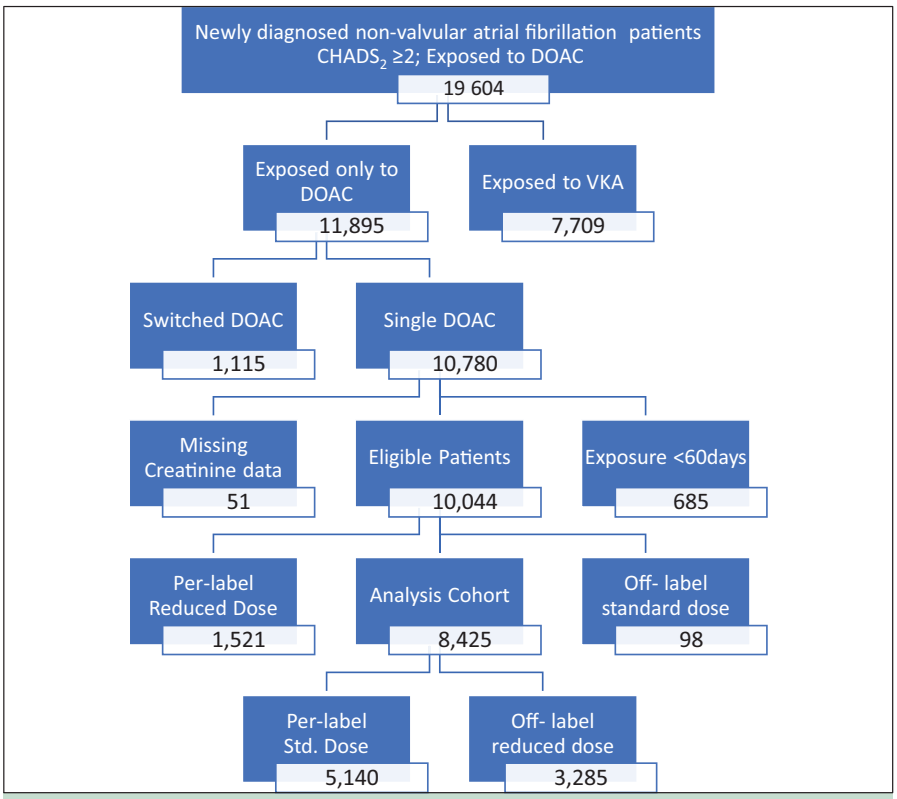

Figure 1 CONSORT diagram of the study population.

for safety analysis included 5144 patients (vs 5140 in the effectiveness analysis), and the off-label dose-reduced group included 3274 patients (vs 3285 in the effectiveness analysis).

HR Adjustments to Minimize Bias by Confounders

The linear regression model for adjustment of observed confounders for effectiveness outcomes is presented in Supplementary Table 3 (available online). Age, Charlson Comorbidity Index, previous stroke, heart failure, diabetes, chronic renal failure, estimated glomerular filtration rate, and the use of platelet aggregation inhibitors and high-ceiling diuretics were observed as confounders for higher risk for the composite end-point events. High body mass index and use of angiotensin receptor blockers and lipid-modifying agents were observed as confounders for lower risk for the composite end-point events. Sex, socioeconomic status, hypertension, peripheral vascular disease, and use of angiotensin-converting enzyme inhibitors, anti-inflammatory, antiarrhythmic, and low-ceiling diuretics did not affect the risk for the composite end-point events. The linear regression model for adjustment of observed confounders for safety outcomes is presented in Supplementary Table 4 (available online).

Subgroup Analysis

The effectiveness of off-label dose-reduced vs per-label DOAC therapy in patient subgroups is presented in Figures 3A (for socioeconomic factors and comorbidities) and 3B (for concomitant medications, detailed in Supplemental Table 5). The rate of the composite outcome was higher in the off-label dose-reduced across all sub-groups, except for a small sub-group of patients with creatinine ≥1.5 mg/dL.

The safety of off-label dose-reduced vs per-label DOAC therapy in patient subgroups is presented in Figures 4A (for socioeconomic factors and comorbidities) and 4B (for concomitant medications). The rate of bleeding was higher in the off-label dose-reduced DOAC therapy across all subgroups, except for the subgroups of patients with either peripheral vascular disease or chronic heart failure.

DISCUSSION

In this study of newly diagnosed patients with nonvalvular atrial fibrillation initiating DOAC treatment, we found that off-label dose-reduced DOAC administration that occurred in 39% of patients at the time of an event and was associated with a significant increase of a composite of death, myocardial infarction, or stroke events. Similarly, the HR for severe bleeding events was increased among patients receiving off-label reduced DOAC dosing. The observed

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Table 1 Baseline Characteristics of the Patients

Patient Characteristic	Per-Label Dosing n = 5140	Off-Label Dose-Reduced n = 3285	*P* Value
Age (years; mean, SD)	72 (9)	81 (8)	< .001
Age >75 years, n (%)	2115 (41%)	2639 (80%)	< .001
Female sex, n (%)	2558 (50%)	1816 (55%)	< .001
BMI kg/m^2 (mean)	31	29	< .001
Socioeconomic status (mean)	5.44	5.61	< .001
Creatinine clearance (mean)	0.89	1.03	< .001
Estimated glomerular filtration rate (mL/min/1.73m^2) (mean)	77	63	< .001
Concomitant illnesses, n (%)			
Congestive heart failure	1234 (24)	1034 (33)	< .001
Hypertension	4879 (95)	3160 (96)	.008
Peripheral vascular disease	752 (15)	649 (20)	< .001
Diabetes mellitus	3221 (63)	1,814 (55)	< .001
Chronic renal failure	549 (11)	966 (29)	< .001
Cerebrovascular incident	1575 (31)	1072 (33)	.055
CHA_2DS_2-VASc (mean)	4.37	5.05	< .001
$CHADS_2$ (mean)	2.91	3.34	< .001
Charlson Comorbidity Index (mean)	2.88	3.59	< .001
Concomitant medications at baseline, n (%)*			
Platelet aggregation inhibitors	2028 (40)	1551 (47)	< .001
Cardiac glycosides	224 (4)	183 (6)	.011
Antiarrhythmics	1,682 (33)	820 (25)	< .001
Low-ceiling diuretics	639 (12)	411 (12)	.914
High-ceiling diuretics	1883 (37)	1875 (57)	< .001
Angiotensin receptor blockers (ARBs)	2108 (41)	1251 (38)	.007
Lipid-modifying agents	4139 (81)	2356 (72)	< .001
Angiotensin-converting enzyme inhibitors (ACEi)	2598 (51)	1625 (50)	.338
Nonsteroidal anti-inflammatories	2382 (43)	1258 (38)	< .001

BMI = body mass index; $CHADS_2$ = Congestive heart failure; Hypertension; Age ≥75 years; Diabetes mellitus; S2 = prior Stroke or transient ischemic attack or thromboembolism; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke, transient ischemic attack, or thromboembolism, Vascular disease, Age 65-74 years, Sex category.

*Anatomical Therapeutic Chemical Classification System (ATC) coding is detailed in Supplementary Table 5 (available online).

reductions in effectiveness and increased bleeding risk were observed in most of the patient subgroups analyzed.

DOACs are currently treatment of choice for most nonvalvular atrial fibrillation patients requiring anticoagulation.[8,9] Abundant data have accrued confirming that the effectiveness and safety of these drugs relative to vitamin K antagonists in clinical practice is comparable with those observed in the pivotal randomized controlled trials (RCTs) of these agents.[10-13] However, it has become apparent that the use of lower doses of the DOACs is far more prevalent in routine clinical practice than in the RCTs.[2-6] In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial, patients were randomly assigned to receive dabigatran 150 mg or 110 mg twice daily,[14] whereas the ROCKET-AF trial assigned the standard dose of rivaroxaban 20 mg daily to all patients, but required dose reduction to 15 mg daily for patients with an estimated glomerular filtration rate of 30-49 mL/min/m.[2,15] Likewise in the AVERREOS[16] and ARISTOTLE studies,[17] apixaban 5 mg twice daily was the standard dose, with a dose reduction to 2.5 mg twice daily only for patients fulfilling 2 or more of the following 3 criteria: age ≥80 years, serum creatinine ≥1.5 mg/dL, and weight <60 kg. In RE-LY, the randomization to standard- and lower-dose dabigatran resulted in the same proportion of patients receiving each dose, while in the

Table 2 Effectiveness Outcomes

Event	Per-Label Dosage (5140 Patients) Events (n)	Off-Label Reduced Dosage (3285 Patients) Events (n)	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Death	354	686	3.60 (3.14-4.13)	< .001	1.72 (1.45-2.03)	< .001
Stroke	84	86	1.61 (1.19-2.18)	.002	1.02 (0.71-1.46)	.91
MI	48	44	0.7 (0.46-1.04)	.0078	0.92 (0.56-1.50)	.727
Composite	447	749	3.10 (2.73-3.52)	< .001	1.57 (1.34- 1.83)	< .001

CI = confidence interval; DOAC = direct oral anticoagulant; HR = hazard ratio; MI = myocardial infarction.

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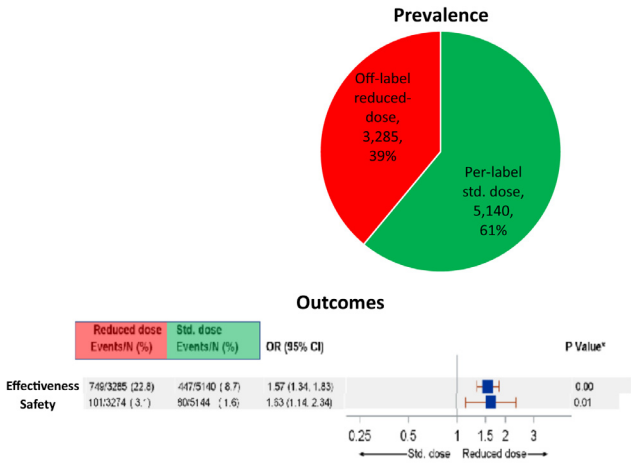


Figure 2 Off-label reduced-dose direct anticoagulants: prevalence and outcomes.

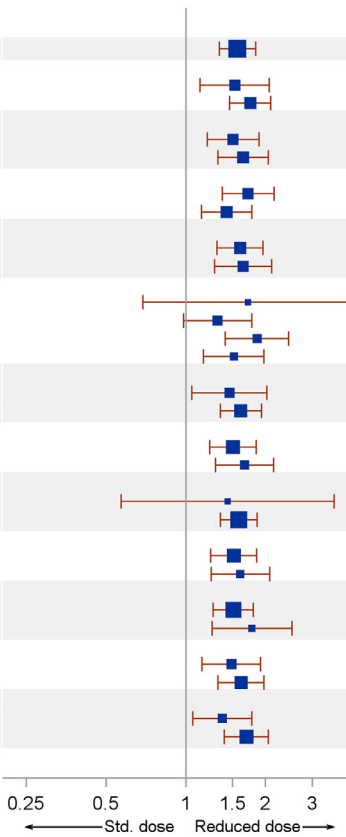
ROCKET-AF and ARISTOTLE trials, only small proportions of patients received the lower DOAC doses. The labeled recommendation for reduced-dose dabigatran is reduced renal function or an increased bleeding risk,[18] and for rivaroxaban and apixaban, the labeled recommendations for reduced dose are those used in the pivotal RCTs.[19,20]

Dose-reduced apixaban was associated with a trend toward higher rates of stroke and systemic embolism compared with warfarin in a nationwide Danish study.[21] This was not the case for rivaroxaban or dabigatran. Conversely, bleeding was less frequent compared with warfarin in the reduced-dose dabigatran group, but not for reduced-dose apixaban and rivaroxaban. This study did not report on the proportion of patients in which the low dosing was not according to the approved label, nor did it compare reduced- with standard-dose DOACs. Notably, this study also demonstrated an increased overall mortality rate among the reduced-dose DOAC patients compared with those treated with warfarin. The reason for this observation could not be determined in this study.

Fay et al[22] have reported on the dosing patterns of DOACs for nonvalvular atrial fibrillation from more than 4600 physicians' prescriptions in France, Germany, and the UK during 2015. They show that a preference for lower-dose DOACs is widespread. Of apixaban-treated patients,

A

Subgroup	Reduced dose Events/N (%)	Std. dose Events/N (%)	OR (95% CI)	P Value*
All Patients	749/3285 (22.8)	447/5140 (8.7)	1.57 (1.34, 1.83)	0.00
Age				0.68
< 75 yr	109/646 (16.9)	206/3025 (6.8)	1.53 (1.13, 2.06)	
≥ 75 yr	640/2639 (24.3)	241/2115 (11.4)	1.75 (1.46, 2.09)	
Gender				0.29
Male	350/1469 (23.8)	242/2582 (9.4)	1.51 (1.21, 1.89)	
Female	399/1816 (22.0)	205/2558 (8.0)	1.65 (1.32, 2.05)	
Socioeconomic Score				0.29
< 6	353/1508 (23.4)	217/2554 (8.5)	1.72 (1.37, 2.15)	
≥ 6	396/1777 (22.3)	230/2586 (8.9)	1.42 (1.14, 1.77)	
BMI				0.86
< 30	502/2067 (24.3)	252/2550 (9.9)	1.60 (1.31, 1.95)	
≥ 30	247/1218 (20.3)	195/2590 (7.5)	1.65 (1.29, 2.11)	
Charlson				0.26
0	23/221 (10.4)	14/502 (2.8)	1.72 (0.69, 4.29)	
1-2	180/1088 (16.5)	138/2160 (6.4)	1.32 (0.98, 1.77)	
3-4	233/995 (23.4)	138/1481 (9.3)	1.86 (1.41, 2.45)	
≥ 5	313/981 (31.9)	157/997 (15.7)	1.52 (1.17, 1.97)	
CHADS2				0.74
< 3	128/952 (13.4)	122/2312 (5.3)	1.46 (1.06, 2.02)	
≥ 3	621/2333 (26.6)	325/2828 (11.5)	1.61 (1.35, 1.93)	
Previous Stroke				0.89
No	426/2213 (19.2)	269/3565 (7.5)	1.50 (1.23, 1.84)	
Yes	323/1072 (30.1)	178/1575 (11.3)	1.67 (1.30, 2.14)	
Hypertension				0.87
No	23/125 (18.4)	16/261 (6.1)	1.44 (0.57, 3.62)	
Yes	726/3160 (23.0)	431/4879 (8.8)	1.58 (1.35, 1.86)	
Chronic Heart Failure				0.37
No	426/2211 (19.3)	275/3906 (7.0)	1.52 (1.24, 1.85)	
Yes	323/1074 (30.1)	172/1234 (13.9)	1.61 (1.25, 2.07)	
Peripheral Vascular Disease				0.92
No	572/2636 (21.7)	364/4388 (8.3)	1.51 (1.27, 1.80)	
Yes	177/649 (27.3)	83/752 (11.0)	1.78 (1.26, 2.51)	
Diabetes				0.95
No	306/1471 (20.8)	156/1919 (8.1)	1.48 (1.15, 1.92)	
Yes	443/1814 (24.4)	291/3221 (9.0)	1.62 (1.32, 1.97)	
Estimated Glomerular Filtration Rate				0.06
< 60	379/1576 (24.0)	111/895 (12.4)	1.37 (1.06, 1.77)	
≥ 60	370/1709 (21.7)	336/4245 (7.9)	1.69 (1.40, 2.05)	



* P-Value is the test of interaction between treatment and each subgroup unadjusted for multiplicity. The adjusted p-value for multiple testing is 0.94 for all subgroups.

Figure 3 (**A**) composite effectiveness outcome events socio-demographic factors and comorbidities. (**B**) Composite effectiveness outcome events concomitant medications. BMI = body mass index; $CHADS_2$ = Congestive heart failure; Hypertension; Age ≥75 years; Diabetes mellitus; S2 = prior Stroke or transient ischemic attack or thromboembolism.

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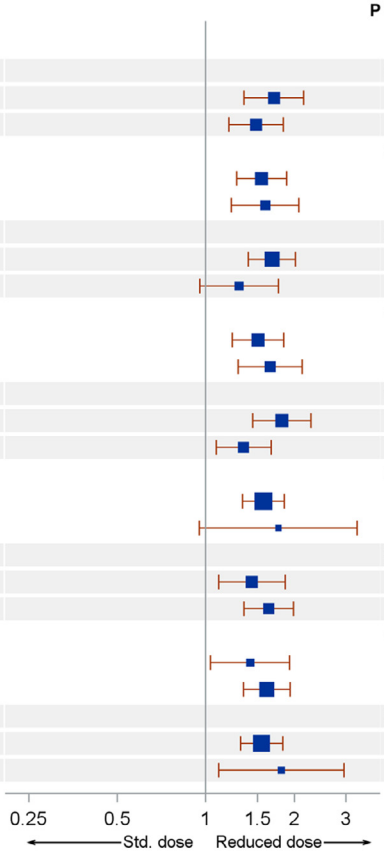
B

Subgroup	Reduced dose Events/N (%)	Std. dose Events/N (%)	OR (95% CI)	P Value*
Angiotensin converting enzyme inhibitors (ACEi)				0.18
No	381/1660 (23.0)	200/2542 (7.9)	1.70 (1.35, 2.15)	
Yes	368/1625 (22.6)	247/2598 (9.5)	1.48 (1.20, 1.83)	
Angiotensin receptor blockers (ARBs)				0.85
No	494/2034 (24.3)	287/3032 (9.5)	1.55 (1.27, 1.88)	
Yes	255/1251 (20.4)	160/2108 (7.6)	1.59 (1.22, 2.07)	
Antiarrhythmic agents				0.18
No	577/2465 (23.4)	304/3458 (8.8)	1.68 (1.40, 2.02)	
Yes	172/820 (21.0)	143/1682 (8.5)	1.30 (0.95, 1.76)	
Anti-inflammatory, non-steroids				0.32
No	488/2027 (24.1)	266/2758 (9.6)	1.51 (1.23, 1.84)	
Yes	261/1258 (20.7)	181/2382 (7.6)	1.66 (1.29, 2.13)	
Platelet Aggregation inhibitors				0.00
No	368/1734 (21.2)	203/3112 (6.5)	1.81 (1.44, 2.28)	
Yes	381/1551 (24.6)	244/2028 (12.0)	1.34 (1.08, 1.67)	
Cardiac Glycosides				0.77
No	696/3102 (22.4)	414/4916 (8.4)	1.57 (1.33, 1.85)	
Yes	53/183 (29.0)	33/224 (14.7)	1.76 (0.95, 3.27)	
High ceiling diuretics				0.40
No	207/1410 (14.7)	179/3257 (5.5)	1.43 (1.10, 1.86)	
Yes	542/1875 (28.9)	268/1883 (14.2)	1.64 (1.35, 1.99)	
Lipid-modifying agents				0.92
No	241/929 (25.9)	107/1001 (10.7)	1.41 (1.04, 1.93)	
Yes	508/2356 (21.6)	340/4139 (8.2)	1.61 (1.34, 1.93)	
Low ceiling diuretics				0.69
No	667/2874 (23.2)	402/4501 (8.9)	1.55 (1.31, 1.82)	
Yes	82/411 (20.0)	45/639 (7.0)	1.81 (1.10, 2.95)	



* P-Value is the test of interaction between treatment and each subgroup unadjusted for multiplicity. The adjusted p-value for multiple testing is 0.94 for all subgroups.

Figure 3 Continued.

44% received a reduced dose, and among rivaroxaban-treated patients, 32.4% received reduced dose. These proportions are similar to that described in the current study; however, it should be noted that in their study, Fay et al[22] did not distinguish between off-label and per-label lower dose use.

Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) II, a large prospective international registry, has provided more detailed data about DOAC dosing in nonvalvular atrial fibrillation patients.[2] In this study, 9.4% of patients received off-label dose-reduced DOACs. Among these patients, factors shown to be associated with off-label dose-reduced DOAC use included older age, female sex, treatment by a nonelectrophysiologist, and higher Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, prior Stroke, transient ischemic attack, or thromboembolism, Vascular disease, Age 65-74 years, Sex category (CHA_2DS_2)-Vasc stroke and ORBIT bleeding scores. When compared with patients receiving per-label DOAC doses, the reduced dosing was associated with a small increase in stroke and systemic embolism risk (2 vs 1.3 per 100 patient-years), myocardial infarction (1.1 vs 0.8 per 100 patient-years), and a more pronounced increase in overall mortality (6.3 vs 3 per 100 patient-years), similar to the findings in our study (Table 2). Concordant with our findings, this registry study demonstrated that off-label dose-reduced vs per-label DOAC therapy was not associated with a reduced rate of major bleeding (4.1 vs 3.6 events per 100 patient-years).

Another study reported a large proportion of patients receiving off-label dose-reduced DOAC therapy.[3] This was a small retrospective single institution study in which 224 patients received dose-reduced DOACs, and in 89.6% this was off-label. Thromboembolism occurred in 10.7%, 3.6%, and 5.1% of patients in the apixaban, rivaroxaban, and dabigatran groups, respectively, while the frequency of bleeding complications of all severities was 17.9%, 18.2%, and 23.7% in the apixaban, rivaroxaban, and dabigatran groups, respectively.

Our study of DOAC dosing among nonvalvular atrial fibrillation patients in routine clinical practice has several strengths. We had access to comprehensive patient characteristics and outcomes including demographic, clinical, laboratory, and dispensed-drug data. Additionally, our database included hospitalization and mortality data, allowing us to directly link patient variables and outcomes. This allowed us to perform extensive bias reduction between the

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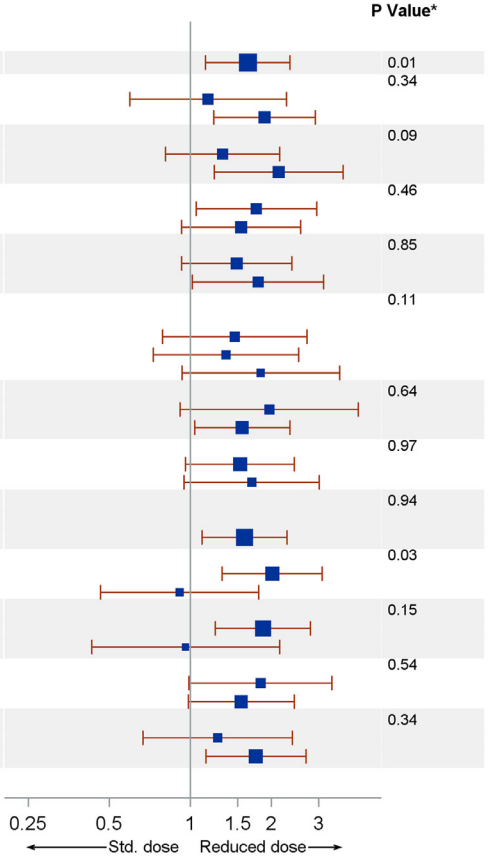
patient groups and to compare the groups despite this being a noncontrolled, population-based study. Furthermore, we studied patients initiating anticoagulation and thus avoided bias related to previous successful or unsuccessful administration of anticoagulants. Also, our study had a long follow-up period with a mean of 23 months. Finally, because dose reduction may be implemented after the initial prescription and the pharmacologic effect of DOAC is short-lived, we report on the dose that patients received proximate to an outcome event. This may account for the relatively large proportion of patients receiving off-label reduced-dose DOAC in our study.

Our study has some important limitations. Primarily, it is a retrospective analysis, and despite adjustment for numerous confounding variables, our patient groups cannot be considered to be fully comparable because of the potential for residual and unobserved confounding variables. Also, we included patients who received DOACs for a minimum of 2 months and thus may have missed patients who experienced an endpoint event within this period. However, we thought that a minimum duration of therapy was needed to provide meaningful drug-exposure time and to exclude patients with potential noncompliance and those not persisting with treatment for other unknown reasons. Finally, we could not confirm cause of death and thus cannot provide insight into the reasons for this key outcome, which is increased in a number of population-based studies in which patients received reduced-dose DOAC treatment.

The results of our study are of importance to clinicians. We demonstrate that when DOACs are prescribed in a lower-than-recommended dose, they are associated with reduced effectiveness and with an increased risk of bleeding. While the reason for loss of effectiveness is intuitive, we can only speculate as to the increased bleeding risk associated with this practice. It is plausible that physicians are able to identify patients at increased risk for bleeding for reasons not captured on the drug label recommendation for dose reduction and provide these patients with reduced doses of the DOACs based on clinical judgment. Alternatively, patients may elect to receive a reduced dose because of concerns about bleeding. In either case, this dose reduction is not associated with a lower bleeding risk compared with that of patients receiving the per-label standard dose. Whether or not the dose-reduced patients would have had

A

Subgroup	Reduced dose Events/N (%)	Std. dose Events/N (%)	OR (95% CI)	P Value*
All Patients	101/3274 (3.1)	80/5144 (1.6)	1.63 (1.14, 2.34)	0.01
Age				0.34
< 75 yr	15/641 (2.3)	46/3029 (1.5)	1.16 (0.60, 2.28)	
≥ 75 yr	86/2633 (3.3)	34/2115 (1.6)	1.89 (1.22, 2.92)	
Gender				0.09
Male	47/1465 (3.2)	52/2585 (2.0)	1.32 (0.81, 2.15)	
Female	54/1809 (3.0)	28/2559 (1.1)	2.13 (1.23, 3.69)	
Socioeconomic Score				0.46
< 6	48/1501 (3.2)	39/2555 (1.5)	1.76 (1.05, 2.94)	
≥ 6	53/1773 (3.0)	41/2589 (1.6)	1.54 (0.93, 2.57)	
BMI				0.85
< 30	68/2062 (3.3)	42/2548 (1.6)	1.49 (0.93, 2.38)	
≥ 30	33/1212 (2.7)	38/2596 (1.5)	1.78 (1.02, 3.12)	
Charlson				0.11
0	4/222 (1.8)	3/502 (0.6)	NA	
1-2	34/1085 (3.1)	27/2160 (1.3)	1.46 (0.79, 2.71)	
3-4	33/990 (3.3)	28/1482 (1.9)	1.36 (0.73, 2.53)	
≥ 5	30/977 (3.1)	22/1000 (2.2)	1.83 (0.93, 3.59)	
CHADS2				0.64
< 3	19/949 (2.0)	22/2314 (1.0)	1.96 (0.92, 4.21)	
≥ 3	82/2325 (3.5)	58/2830 (2.0)	1.56 (1.04, 2.34)	
Previous Stroke				0.97
No	57/2213 (2.6)	48/3564 (1.3)	1.53 (0.96, 2.44)	
Yes	44/1061 (4.1)	32/1580 (2.0)	1.69 (0.95, 3.01)	
Hypertension				0.94
No	3/124 (2.4)	1/262 (0.4)	NA	
Yes	98/3150 (3.1)	79/4882 (1.6)	1.59 (1.11, 2.29)	
Chronic Heart Failure				0.03
No	75/2201 (3.4)	56/3909 (1.4)	2.01 (1.31, 3.09)	
Yes	26/1073 (2.4)	24/1235 (1.9)	0.91 (0.46, 1.80)	
Peripheral Vascular Disease				0.15
No	81/2630 (3.1)	62/4389 (1.4)	1.86 (1.24, 2.79)	
Yes	20/644 (3.1)	18/755 (2.4)	0.96 (0.43, 2.15)	
Diabetes				0.54
No	44/1459 (3.0)	25/1929 (1.3)	1.82 (0.99, 3.36)	
Yes	57/1815 (3.1)	55/3215 (1.7)	1.54 (0.98, 2.43)	
Estimated Glomerular Filtration Rate				0.34
< 60	45/1571 (2.9)	17/895 (1.9)	1.26 (0.67, 2.39)	
≥ 60	56/1703 (3.3)	63/4249 (1.5)	1.75 (1.14, 2.69)	



* P-Value is the test of interaction between treatment and each subgroup unadjusted for multiplicity. The adjusted p-value for multiple testing is 0.94 for all subgroups.

Figure 4 (**A**) Safety outcome events sociodemographic factors and comorbidities. (**B**) Safety outcome events concomitant medications.

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B

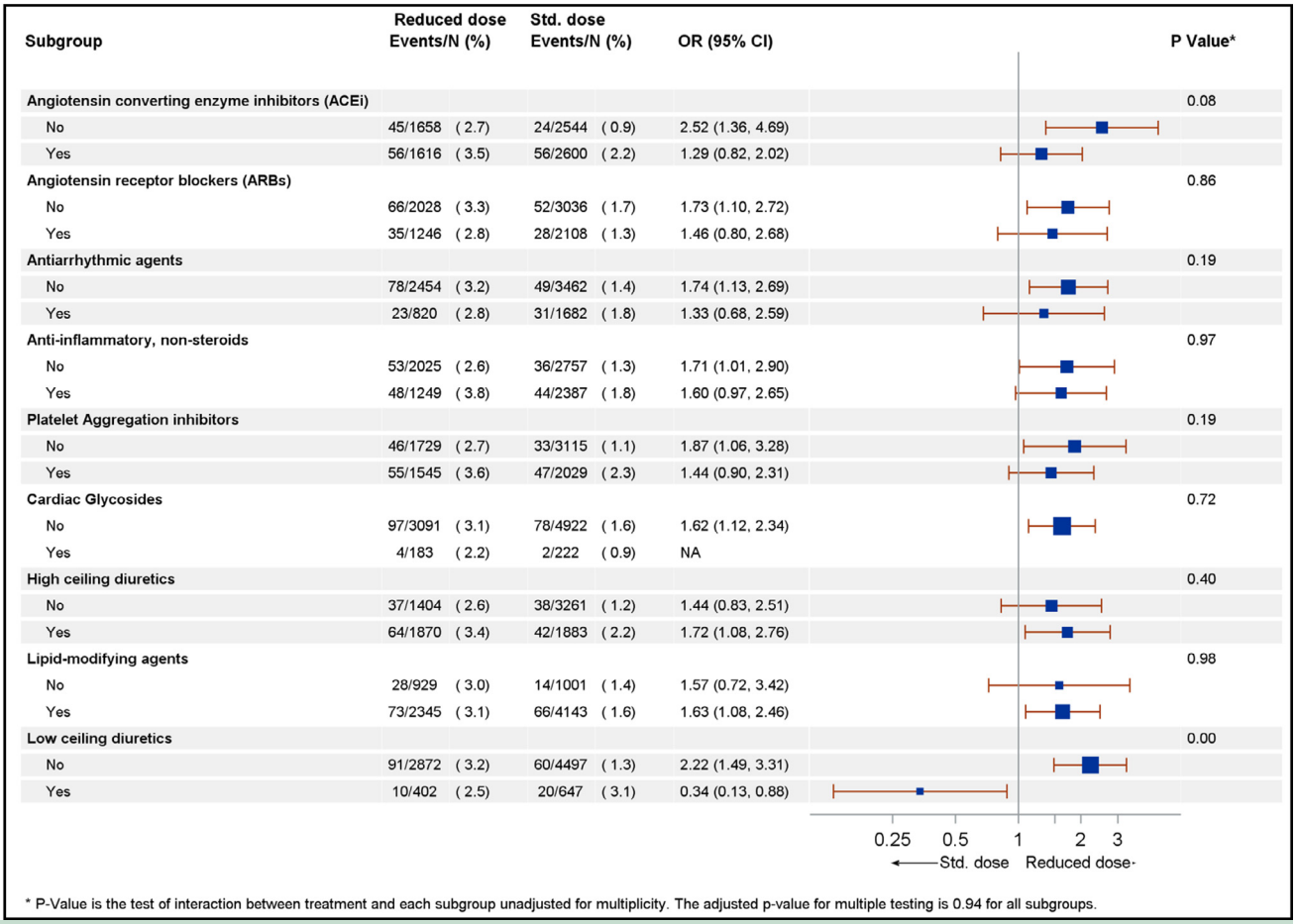

Figure 4 Continued.

an even higher bleeding rate had they received standard-dose DOAC remains speculative. Further research should be directed at the specific reasons for off-label dose-reduced DOAC.

CONCLUSIONS

Almost 4 of 10 patients in this study were treated with off-label dose-reduced DOAC at the time of an event or end of the follow-up period. Off-label dose-reduced DOAC was associated with reduced effectiveness without a safety benefit. Compliance with per-label dosage may significantly improve outcomes of this population. Further studies are required to understand the reasons for off-label dose-reduced DOAC administration.

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Supplemental Table 1: ICD 9-CM codes used to define the study cohort and clinical outcomes.

Disease	ICD9-CM Codes
Atrial fibrillation	427.3, 427.31
Ischemic stroke	433.x1, 434.x1
Myocardial infarction	410.x
Transient ischemic attack	435, 435.8, 435.9
Intracranial hemorrhage	430, 431, 432.x
Gastrointestinal bleeding	456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.x1,537.83, 537.84, 562.02, 562.03, 562.12, 562.13 568.81, 569.3, 569.85, 578.x
Other critical site bleeding	459.0, 599.7x, 626.6

Supplemental Table 2: compliance to STROBE statement checklist

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	2
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5, Suppl. T1*
Bias	9	Describe any efforts to address potential sources of bias	6 Suppl. T2,T3
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6 eTable 2,3
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	Fig. 1
		(d) If applicable, explain how loss to follow-up was addressed	N/R
		(e) Describe any sensitivity analyses	N/R
Results	Page		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Figure 1
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	eTable 3

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Supplemental Table 2: (*Continued*)

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7, Table 2
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7, Table 2
		(b) Report category boundaries when continuous variables were categorized	Table 1
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8 Figures 3,4
Discussion			
Key results	18	Summarize key results with reference to study objectives	Table 2
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-13
Generalizability	21	Discuss the generalizability (external validity) of the study results	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/R

*Give information separately for exposed and unexposed groups.

Supplemental Table 3: Cox regression model for effectiveness outcomes.

	P Value	Exp(B)	95% CI Low	High
DOSAGE_GROUP	0.000	1.566	1.340	1.831
age	0.000	1.041	1.031	1.051
gender_code	0.856	1.013	0.878	1.170
ScorePoints	0.639	1.008	0.976	1.041
BMI	0.000	0.970	0.957	0.982
Charlson_Score_BASELINE	0.000	1.097	1.064	1.131
CVA_BASELINE	0.000	1.589	1.375	1.837
Bp_BASELINE	0.081	1.387	0.960	2.003
Chf_BASELINE	0.003	1.262	1.081	1.474
PVD_BASELINE	0.460	0.935	0.784	1.117
Diabetes_BASELINE	0.016	1.206	1.035	1.405
CRF	0.000	2.028	1.703	2.414
eGFR_test_result_baseline	0.000	1.009	1.004	1.014
ACE_INHIBITORS	0.449	0.944	0.813	1.096
ANGIOTENSIN_II_ANTAGONISTS	0.003	0.791	0.677	0.924
ANTIARRHYTHMICS	0.893	0.990	0.848	1.155
ANTIINFLAMMATORY_AND_ANTIRHEUMATIC_PRODUCTS	0.259	0.922	0.801	1.062
ANTITHROMBOTIC_AGENTS	0.000	1.437	1.249	1.655
CARDIAC_GLYCOSIDES	0.154	1.217	0.929	1.595
HIGH_CEILING_DIURETICS	0.000	2.108	1.799	2.471
LIPID_MODIFYING_AGENTS	0.000	0.750	0.638	0.882
LOW_CEILING_DIURETICS	0.452	0.921	0.742	1.142

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Supplemental Table 4: Cox regression model for safety outcomes

	Sig. (P value)	Exp(B)	95% C.I.for EXP(B) Lower	Upper
DOSAGE_GROUP	0.008	1.634	1.139	2.344
age	0.110	1.018	0.996	1.040
gender_code	0.048	0.719	0.519	0.997
ScorePoints	0.149	0.949	0.884	1.019
BMI	0.403	0.987	0.959	1.017
Charlson_Score_BASELINE	0.418	1.030	0.958	1.108
CVA_BASELINE	0.021	1.471	1.060	2.040
Bp_BASELINE	0.152	2.347	0.731	7.538
Chf_BASELINE	0.128	0.747	0.512	1.088
PVD_BASELINE	0.933	0.983	0.657	1.470
Diabetes_BASELINE	0.469	1.138	0.802	1.613
CRF	0.741	0.930	0.606	1.428
eGFR_test_result_baseline	0.758	1.002	0.991	1.012
ACE_INHIBITORS	0.041	1.439	1.015	2.038
ANGIOTENSIN_II_ANTAGONISTS	0.774	0.950	0.667	1.351
ANTIARRHYTHMICS	0.622	1.089	0.775	1.531
ANTIINFLAMMATORY_AND_ANTIRHEUMATIC_PRODUCTS	0.017	1.464	1.071	2.000
ANTITHROMBOTIC_AGENTS	0.019	1.467	1.065	2.023
CARDIAC_GLYCOSIDES	0.301	0.644	0.280	1.483
HIGH_CEILING_DIURETICS	0.003	1.699	1.194	2.420
LIPID_MODIFYING_AGENTS	0.508	0.879	0.600	1.288
LOW_CEILING_DIURETICS	0.189	1.321	0.872	2.002

Supplemental Table 5: ATC coding for drugs

	Drugs	ATC code
1	Platelet Aggregation inhibitors (Aspirin, clopidogrel, etc.)	B01AC
2	Cardiac Glycosides	C01A
3	Antiarrhythmic agents	C01B
4	Low ceiling diuretics	C03A, C03B
5	High ceiling diuretics	C03C
6	Angiotensin converting enzyme inhibitors (ACEi)	C09A, C09B
7	Angiotensin receptor blockers (ARBs)	C09C, C09D
8	Lipid-modifying agents	C10

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