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Mortality in Patients With Atrial Fibrillation Receiving Nonrecommended Doses of Direct Oral Anticoagulants

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ABSTRACT

BACKGROUND The recommended doses for direct oral anticoagulants (DOACs) to prevent stroke and systemic embolism (SE) in patients with atrial fibrillation (AF) are described in specific regulatory authority approvals.

OBJECTIVES The impact of DOAC dosing, according to the recommended guidance on all-cause mortality, stroke/SE, and major bleeding, was assessed at 2-year follow-up in patients with newly diagnosed AF.

METHODS Of a total of 34,926 patients enrolled (2013 to 2016) in the prospective GARFIELD-AF (Global Anticoagulant Registry in the FIELD-AF), 10,426 patients received a DOAC.

RESULTS The majority of patients (72.9%) received recommended dosing, 23.2% were underdosed, and 3.8% were overdosed. Nonrecommended dosing (underdosage and overdosage combined) compared with recommended dosing was associated with a higher risk of all-cause mortality (hazard ratio [HR]: 1.24; 95% confidence interval [CI]: 1.04 to 1.48); HR: 1.25 (95% CI: 1.04 to 1.50) for underdosing, and HR: 1.19 (95% CI: 0.83 to 1.71) for overdosing. The excess deaths were cardiovascular including heart failure and myocardial infarction. The risks of stroke/SE and major bleeding were not significantly different irrespective of the level of dosing, although underdosed patients had a significantly lower risk of bleeding. A nonsignificant trend to higher risks of stroke/SE (HR: 1.51; 95% CI: 0.79 to 2.91) and major bleeding (HR: 1.29; 95% CI: 0.59 to 2.78) was observed in patients with overdosing.

CONCLUSIONS In GARFIELD-AF, most patients received the recommended DOAC doses according to country-specific guidelines. Prescription of nonrecommended doses was associated with an increased risk of death, mostly cardiovascular death, compared with patients on recommended doses, after adjusting for baseline factors. (Global Anticoagulant Registry in the Field-AF [GARFIELD-AF]; NCT01090362) (J Am Coll Cardiol 2020;76:1425–36) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

AP = antiplatelet

CI = confidence interval

CKD = chronic kidney disease

CrCl = creatinine clearance

DOAC = direct oral anticoagulant

HR = hazard ratio

SE = systemic embolism

VKA = vitamin K antagonist

Direct oral anticoagulants (DOACs) have been recently introduced in clinical practice for several indications including stroke prevention in AF. They were shown to be at least as effective as vitamin K antagonists (VKAs) for stroke prevention in AF with lower risk of bleeding, particularly intracranial bleeding, without the need for blood monitoring (1). The uptake of DOACs is growing all over the world, particularly but not only in Western countries. They are all approved in most countries worldwide, but with differences in regard to regulatory authority-specific guidance that takes into account baseline characteristics of the patients, particularly kidney function and/or low body weight (≤60 kg), age (≥80 years), bleeding risk, and drug-drug interactions. These country-specific guidelines vary according to the different DOACs with anti-IIa or -Xa actions (2–4). In this context, the rules for the correct prescription dose may be to some extent poorly understood, and may be the cause of inappropriate dosing (either underdosing or overdosing).

SEE PAGE 1437

The aims of this analysis were to: 1) assess the patterns of DOAC prescription as regards dosing; 2) assess the impact of regulatory and guideline recommended versus nonrecommended DOAC dosing on the rate of events at 2-year follow-up; and 3) identify the predictors of underdosing in patients in newly diagnosed AF patients from the GARFIELD-AF (Global Anticoagulant Registry in the FIELD-AF).

METHODS

The design of the GARFIELD-AF registry was reported previously (5,6) and is available in full in the Supplemental Appendix. Briefly, men and women age ≥18 years with AF diagnosed according to standard local procedures within the previous 6 weeks, with at least 1 risk factor for stroke as judged by the local investigator, and with no valvular disease were eligible for inclusion. All data was validated internally, and 20% of all data submitted electronically were monitored against source documentation (6). In total 52,080 patients were enrolled prospectively and consecutively from March 2010 to August 2016 in 35 countries, and 5 consecutive cohorts of approximately 10,000 patients with an intended 2-year follow-up. At baseline, investigators collected data on patient demographics, medical history, care setting, type of AF (also collected during follow-up), and antithrombotic treatment (VKAs, DOACs, and antiplatelet [AP] treatment). Data on components of the CHA_2DS_2-VASc and HAS-BLED risk stratification schemes were used to assess the risks of stroke and bleeding, retrospectively.

Clinical events were defined using previously reported standardized definitions (5,6). Vascular disease included peripheral artery disease or coronary artery disease with a history of acute coronary syndromes. Chronic kidney disease was classified according to National Kidney Foundation guidelines into 2 groups: moderate-to-severe (stages 3 to 5), mild (stages 1 and 2), or none (7–9). Congestive heart failure was defined as current/prior history of congestive heart failure or left ventricular ejection

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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fraction <40%. In addition to the investigator designation of an International Society on Thrombosis and Haemostasis bleed classification, an algorithm was applied to verify appropriate application. Data for this analysis were extracted from the study database on November 19, 2018.

The rules of prescription for all 4 DOACs available for stroke prevention in at-risk patients with nonvalvular atrial fibrillation (rivaroxaban, apixaban, edoxaban, dabigatran) approved by the European Medicines Agency (EMA) (2), the U.S. Food and Drug Administration (FDA) (3), or the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) (4) were reviewed to define recommended dosing, underdosing, or overdosing. These rules take into account the baseline characteristics of the patients, particularly kidney function, body weight, age, and bleeding risk. In addition, regulatory authorities also expect repeated reassessment of dose over time (2–4) (10,11). Regarding kidney function, all rules of DOAC prescription refer to creatinine clearance (CrCl) except for apixaban, whose labeling refers to the components of the CrCl equation, namely serum creatinine, body weight, and age. In GARFIELD-AF, neither CrCl nor serum creatinine were routinely assessed as it is a nonintervention study. Kidney function was reported by the investigators in the form of stages of renal function impairment as described by the National Kidney Foundation (7–9,12). We therefore reviewed the rules for prescription of every DOAC to establish a correspondence between levels of CrCl and stages of kidney dysfunction as reported by the investigators. This review also took into account the additional rules for prescription based on body weight, age, and bleeding risk as stipulated for certain DOACs (Supplemental Table 1).

ETHICS STATEMENT. Independent ethics committee and hospital-based Institutional Review Board approvals were obtained, as necessary, for the registry protocol. Additional approvals were obtained from individual study sites. The registry is being conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonisation Good Pharmacoepidemiological and Clinical Practice Guidelines. Written informed consent was obtained from all study participants. Confidentiality and anonymity of all enrolled patients are maintained.

STATISTICAL ANALYSIS. Univariable results are presented as medians with interquartile range for continuous variables and as absolute frequencies with percentages for categorical variables. The GARFIELD scores for mortality, stroke, and bleeding were calculated using a single-imputed dataset. The presented GARFIELD score for mortality refers to the reduced model version because of the high missing proportion of some variables across the groups.

Five multiple imputation datasets were generated using multivariate imputation by chained equations. Logistic least absolute shrinkage and selection operator regression was applied on a randomly selected single imputed dataset to determine predictors of nonrecommended low dosing. The linearity assumption was evaluated using restricted cubic splines, and appropriate transformations applied with linear splines as needed. The predictors were selected among the following variables collected at enrollment: sex, age, ethnicity, body weight, systolic and diastolic blood pressure, pulse, type of AF, care setting specialty and location, congestive heart failure, acute coronary syndrome, vascular disease, carotid occlusive disease, venous thromboembolism, prior stroke, transient ischemic attack, systemic embolism (SE), bleeding, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate-to-severe chronic kidney disease (CKD), hyperthyroidism, hypothyroidism, concomitant AP therapy, current smoking, and heavy alcohol consumption. This selection procedure was repeated not considering the variables directly involved in the definition of nonrecommended low dosing (namely, moderate-to-severe CKD, age, and body weight). This approach allowed the evaluation in dosing decisions of the relative significance of factors beyond those described in dosing guidelines. A 30-fold cross-validation was applied during the modeling process.

Odds ratios and corresponding 95% confidence intervals (CIs) for the variables selected by logistic least absolute shrinkage and selection operator regression were computed using multivariable logistic regression models. Combined estimates from 5 imputations are presented.

The time at risk for selected events was calculated from the time of enrollment in GARFIELD-AF to the time of the first event or 2 years, whichever occurred first. Occurrence of major clinical outcomes, namely all-cause mortality, stroke/SE, and major bleeding, is described using the number of events and the event rate (per 100 person-years) with the corresponding 95% CIs. We estimated person-year rates using a Poisson model, with the number of events as the dependent variable and the log of time as an offset (i.e., a covariate with a known coefficient of 1). Only the first occurrence of each event was included.

Unadjusted and adjusted Cox proportional hazards models were performed to test the association of off-label DOAC dose and outcomes. A categorical variable

TABLE 1 Baseline Characteristics by DOAC Dosing

	Nonrecommended Low Dosing (n = 2,423)	Recommended Dosing (n = 7,603)	Nonrecommended High Dosing (n = 400)
Sex			
Male	1,192 (49.2)	4,435 (58.3)	206 (51.5)
Female	1,231 (50.8)	3,168 (41.7)	194 (48.5)
Age, yrs	77.0 (69.0-83.0)	70.0 (63.0-77.0)	75.0 (68.0-82.0)
Age, yrs			
<65	405 (16.7)	2,195 (28.9)	70 (17.5)
65-69	249 (10.3)	1,427 (18.8)	40 (10.0)
70-74	375 (15.5)	1,471 (19.3)	71 (17.8)
≥75	1,394 (57.5)	2,510 (33.0)	219 (54.8)
Ethnicity			
Caucasian	1,114 (46.6)	5,347 (71.8)	283 (72.0)
Hispanic/Latino	117 (4.9)	252 (3.4)	17 (4.3)
Asian	1,105 (46.3)	1,694 (22.7)	83 (21.1)
Afro-Caribbean/mixed/other	51 (2.2)	154 (2.1)	10 (2.5)
Body mass index, kg/m^2	25.3 (22.8-28.8)	27.4 (24.3-31.2)	27.4 (23.9-32.0)
Weight, kg	68.0 (57.0-80.0)	78.0 (67.0-91.0)	78.0 (62.0-90.0)
Systolic blood pressure, mm Hg	130.0 (120.0-142.0)	132.0 (120.0-146.0)	132.0 (120.0-146.5)
Diastolic blood pressure, mm Hg	79.0 (70.0-85.0)	80.0 (70.0-90.0)	80.0 (70.0-88.0)
Pulse, beats/min	84.0 (72.0-103.0)	85.0 (70.0-110.0)	82.5 (70.0-105.5)
Type of atrial fibrillation			
Permanent	305 (12.6)	861 (11.3)	53 (13.3)
Persistent	392 (16.2)	1,322 (17.4)	72 (18.0)
Paroxysmal	919 (37.9)	2,378 (31.3)	113 (28.3)
New onset (unclassified)	807 (33.3)	3,042 (40.0)	162 (40.5)
Care setting specialty at diagnosis			
Internal medicine	327 (13.5)	1,191 (15.7)	92 (23.0)
Cardiology	1,866 (77.0)	5,382 (70.8)	259 (64.8)
Neurology	22 (0.9)	105 (1.4)	3 (0.8)
Geriatrics	9 (0.4)	17 (0.2)	2 (0.5)
Primary care/general practice	199 (8.2)	908 (11.9)	44 (11.0)
Care setting location at diagnosis			
Hospital	1,033 (42.6)	3,822 (50.3)	508 (52.0)
Office	1,216 (50.2)	3,016 (39.7)	156 (39.0)
Anticoagulation clinic/thrombosis center	4 (0.2)	13 (0.2)	1 (0.3)
Emergency department	170 (7.0)	752 (9.9)	35 (8.8)
Medical history			
Congestive heart failure	575 (23.7)	1,510 (19.9)	117 (29.3)
Coronary artery disease	494 (20.4)	1,386 (18.2)	88 (22.0)
Acute coronary syndromes	237 (10.9)	623 (9.1)	40 (11.4)
Coronary artery bypass graft	67 (2.8)	245 (3.2)	18 (4.5)
Stenting	186 (7.7)	499 (6.6)	35 (8.8)
Vascular disease	369 (15.3)	927 (12.2)	66 (16.5)
Carotid occlusive disease	81 (3.4)	218 (2.9)	17 (4.3)
Pulmonary embolism/deep vein thrombosis	43 (1.8)	179 (2.4)	24 (6.0)
Prior systemic embolism	15 (0.6)	39 (0.5)	2 (0.5)
Prior transient ischemic attack	95 (4.0)	332 (4.4)	18 (4.5)
Prior stroke	179 (7.4)	520 (6.8)	27 (6.8)
Prior bleeding	53 (2.2)	137 (1.8)	15 (3.8)
Hypertension	1,873 (77.4)	5,803 (76.5)	327 (81.8)
Hypercholesterolemia	947 (40.1)	3,395 (45.9)	174 (45.8)
Diabetes	529 (21.8)	1,601 (21.1)	96 (24.0)
Cirrhosis	9 (0.4)	25 (0.3)	3 (0.8)
Moderate to severe CKD	172 (7.1)	652 (8.6)	270 (67.5)
Dementia	81 (3.4)	86 (1.1)	12 (3.0)
Hyperthyroidism	44 (1.8)	131 (1.7)	4 (1.0)
Hypothyroidism	145 (6.1)	463 (6.2)	33 (8.3)
Concomitant AP therapy	418 (17.6)	1,065 (14.3)	63 (16.0)

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TABLE 1 Continued

	Nonrecommended Low Dosing (n = 2,423)	Recommended Dosing (n = 7,603)	Nonrecommended High Dosing (n = 400)
Alcohol consumption			
Abstinent	1,253 (61.6)	3,037 (47.4)	203 (59.9)
Light	588 (28.9)	2,413 (37.6)	110 (32.4)
Moderate	161 (7.9)	829 (12.9)	22 (6.5)
Heavy	31 (1.5)	131 (2.0)	4 (1.2)
Smoking status			
Nonsmoker	1,487 (68.9)	4,381 (62.8)	247 (65.5)
Ex-smoker	480 (22.3)	1,817 (26.0)	99 (26.3)
Current smoker	190 (8.8)	783 (11.2)	31 (8.2)
CHA_2DS_2-VASc score	4.0 (3.0–5.0)	3.0 (2.0–4.0)	4.0 (3.0–5.0)
HAS-BLED score*	1.0 (1.0–2.0)	1.0 (1.0–2.0)	2.0 (1.0–2.0)
GARFIELD death score†	3.3 (1.9–5.7)	2.2 (1.3–3.7)	4.7 (2.8–8.8)
GARFIELD stroke score	0.9 (0.7–1.3)	0.7 (0.6–1.0)	1.4 (1.0–2.0)
GARFIELD bleeding score	1.2 (0.8–1.5)	0.9 (0.6–1.2)	1.7 (1.1–2.3)

Values are n (%) or median (interquartile range). *The risk factor "labile INRs" is not included in the HAS-BLED score as it is not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points (not 9). †GARFIELD death score is based on the "reduced model" version.

CKD = chronic kidney disease; DOAC = direct oral anticoagulation; GARFIELD = Global Anticoagulant Registry in the FIELD-AF.

for dose category with 3 levels (recommended dosing, nonrecommended low dosing, nonrecommended high dosing) was included in the model, with patients receiving recommended dosing treated as the reference group. This analysis was also performed combining nonrecommended low and high dosing into 1 category. Hazard ratios (HRs) with 95% CIs are presented. Multivariable models were adjusted for clinically relevant patient characteristics. Both a Kolmogorov-type supremum statistical test and a graphical examination of the Schoenfeld residuals were used to assess the proportional hazards assumption.

Statistical analyses were conducted using R statistical software and SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

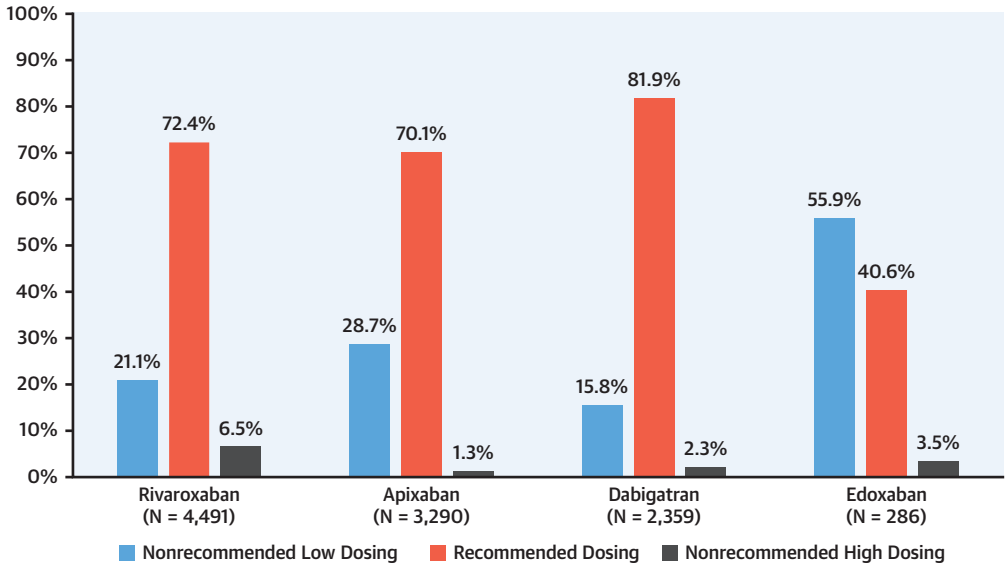
RESULTS

This analysis involved patients from cohorts 3 to 5 only (n = 34,926) as no individual drug names were collected in the first 2 cohorts. Patients on no anticoagulant treatment or not treated with a DOAC (n = 23,503); with more than 1 DOAC type simultaneously at baseline (n = 11); or with no information on starting date, no CKD stage information, or unavailable dose information (n = 986) were excluded from the analysis, leaving a total of 10,426 patients, of whom 4,491 (43.1%) received rivaroxaban, 3,290 (31.6%) apixaban, 2,359 (22.6%) dabigatran, and 286 (2.7%) edoxaban.

BASELINE CHARACTERISTICS. The majority of patients (n = 7,603; 72.9%) received the recommended dosing, 2,423 (23.2%) were underdosed, and 400 (3.8%) were overdosed. Compared with patients who received recommended doses, patients with nonrecommended doses were more likely to be women; more likely to be older; more likely to have higher CHA_2DS_2-VASc and GARFIELD-AF scores for the risks of death, stroke/SE, and bleeding; and were more prone to abstain from alcohol and to be nonsmokers. The rates of nonrecommended doses increased with increasing CHA_2DS_2-VASc score, indicating that the highest-risk patients were more prone to receive a wrong dose of DOACs (Supplemental Figure 1). Underdosed patients were more likely to be Asians, to have a lower body weight, to more often experience dementia, to have the paroxysmal form of AF, and to be taken care by a cardiologist and in an office setting than patients of the other 2 subgroups. Overdosed patients were more likely to have moderate-to-severe renal impairment (67.5%) and a higher HAS-BLED score than patients in the other 2 subgroups (Table 1).

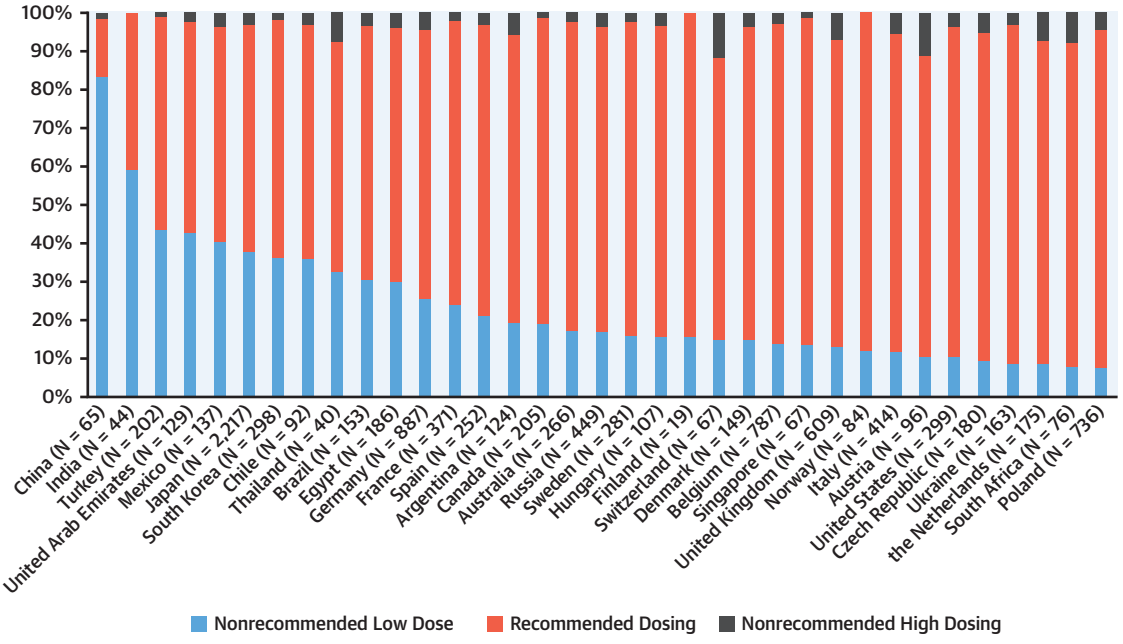
PATTERNS OF DOSING. Recommended dosing was in the range of 70.1% to 81.9% for rivaroxaban, dabigatran, and apixaban, but was much lower for edoxaban (40.6%), which was prescribed in only 286 patients (mostly in Japan). Underdosage affected 15.8% to 28.7% of patients for rivaroxaban, dabigatran, and apixaban, but at a much higher rate for edoxaban (55.9%). Last, overdosage rates were low, from 1.3% with dabigatran to 6.5% with rivaroxaban (Figure 1). Among patients with overdosage, 67.5% had moderate-to-severe CKD as opposed to 8.6% of

FIGURE 1 DOAC Dosing Prescribed at Diagnosis



Dosing proportions are calculated for each treatment and among patients with available information to define dosing appropriateness. The number of patients who received each treatment is reported under the treatment name. DOAC = direct oral anticoagulation.

FIGURE 2 DOAC Dosing Distribution by Country



Dosing proportions are calculated for each country and among patients with available information to define dosing appropriateness. The number of patients who received each treatment is reported under the country of enrollment. Results are sorted by nonrecommended low-dose proportion. DOAC = direct oral anticoagulation.

TABLE 2 Event Rates (per 100 Person-Years) and Unadjusted and Adjusted* HRs at 2 Years After Enrollment by Dosing

Outcome	Dosing	Events	Rate (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
All-cause mortality	Recommended dosing	360	2.5 (2.2–2.7)	1.00 (ref)	1.00 (ref)
	Nonrecommended low dosing	195	4.2 (3.7–4.9)	1.74 (1.46–2.07)	1.25 (1.04–1.50)
	Nonrecommended high dosing	33	4.4 (3.1–6.1)	1.79 (1.25–2.55)	1.19 (0.83–1.71)
	Nonrecommended dosing	228	4.3 (3.7–4.9)	1.74 (1.48–2.06)	1.24 (1.04–1.48)
Stroke/SE	Recommended dosing	102	0.7 (0.6–0.9)	1.00 (ref)	1.00 (ref)
	Nonrecommended low dosing	39	0.9 (0.6–1.2)	1.22 (0.84–1.77)	0.92 (0.62–1.37)
	Nonrecommended high dosing	10	1.3 (0.7–2.5)	1.91 (1.00–3.65)	1.51 (0.79–2.91)
	Nonrecommended dosing	49	0.9 (0.7–1.2)	1.32 (0.94–1.85)	1.01 (0.70–1.45)
Major bleeding	Recommended dosing	82	0.6 (0.5–0.7)	1.00 (ref)	1.00 (ref)
	Nonrecommended low dosing	15	0.3 (0.2–0.5)	0.58 (0.34–1.01)	0.50 (0.28–0.88)
	Nonrecommended high dosing	7	0.9 (0.5–2.0)	1.66 (0.77–3.59)	1.29 (0.59–2.78)
	Nonrecommended dosing	22	0.4 (0.3–0.6)	0.74 (0.46–1.18)	0.62 (0.38–1.02)

*Hazard ratios (HRs) were adjusted for age, sex, ethnicity, type of atrial fibrillation, diabetes, hypertension, history of bleeding, prior stroke/transient ischemic attack/systemic embolism (SE), congestive heart failure, vascular disease, smoking, and heavy alcohol consumption.
CI = confidence interval.

patients with recommended dosing and 7.1% of patients with underdosing (Table 1).

The nonrecommended low-dose prescription rate was highly variable worldwide. It was <20% in most European countries, United States, Canada, Argentina, Australia, and South Africa; 20% to 30% in France, Germany, Spain, and Egypt; 30% to 40% in Brazil, Chile, Thailand, South Korea, and Japan; and >40% in Mexico, the Middle East, India, and China. In 9 countries, the number of patients was too low (n = <100) to derive meaningful information (Figure 2, Supplemental Figure 2).

OUTCOMES. More events occurred in patients with nonrecommended doses compared with patients with recommended doses. All-cause death and stroke/SE rates were higher in nonrecommended doses, both underdosed and overdosed patients, than in patients receiving recommended doses. The rates of bleeding were lower in underdosed patients, and higher in overdosed patients compared with patients treated with the recommended doses (Table 2).

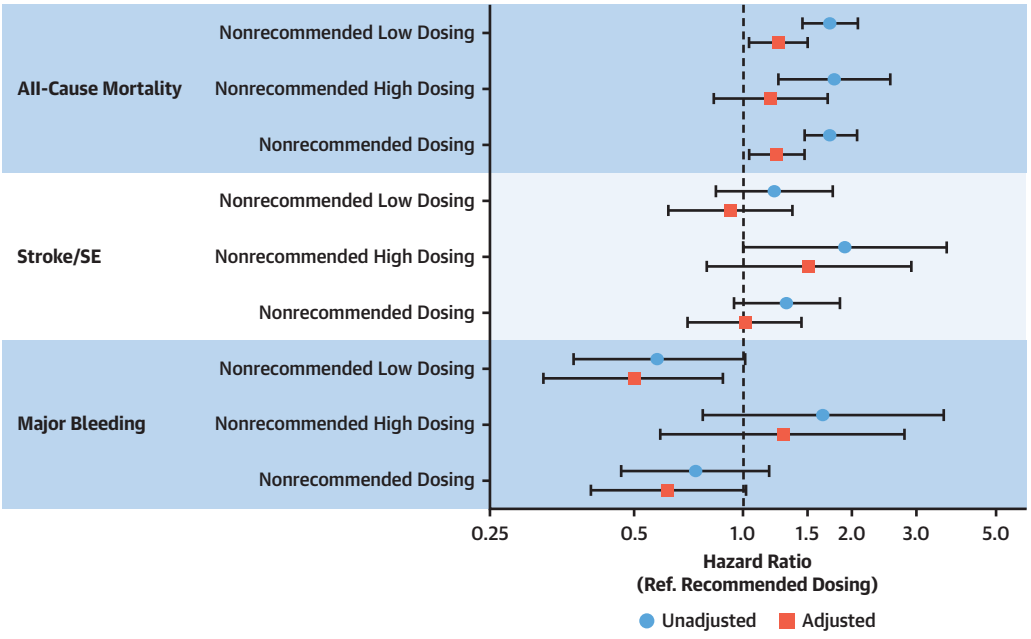
After adjustment, the risk of all-cause death was significantly higher in patients given nonrecommended doses overall and in underdosed patients compared with patients treated with the recommended doses. The risk of major bleeding in underdosed patients was lower than in appropriately dosed patients (HR: 0.50; 95% CI: 0.28 to 0.88) (Table 2, Central Illustration). The excess of all-cause death was mostly due to numerically higher rates of cardiovascular death (congestive heart failure and myocardial infarction) in underdosed patients compared with the recommended dosing subgroup (Table 3). There was no excess in the rates of stroke-related death. The limited number of events in overdosed patients prevents from deriving meaningful conclusions.

PREDICTORS OF UNDERDOSING. This analysis was carried out only in underdosed patients. Two models were used, the first including the baseline characteristics after which recommended dosing was defined. The second model excluded these baseline characteristics. The most potent predictors of underdosage were female sex, non-Caucasian ethnicity, acute coronary syndrome, vascular disease, prior stroke, diabetes, and concomitant AP therapy. The variables used to define underdosing, namely age, weight, and moderate-to-severe CKD, were found to be strong predictors. When these variables were removed from the automatic selection procedure, congestive heart failure, management in office or anticoagulant clinics, and diastolic blood pressure also emerged as significant (Table 4, Figure 3, Supplemental Table 2).

DISCUSSION

The main findings of this study are that DOACs were appropriately dosed in most patients to whom they were prescribed with wide variations between countries, but that underdosage was not uncommon in the range of 25%, and overdosage was rare. Use of nonrecommended doses of DOACs had an impact on outcomes. After adjustment, nonrecommended doses overall and underdosage were associated with a higher risk of all-cause mortality, but with no significantly higher risk of stroke/SE. As expected, a significantly lower risk of bleeding was associated with underdosing. The excess of death was mostly

CENTRAL ILLUSTRATION **Unadjusted and Adjusted Hazard Ratios at 2 Years After Enrollment by Direct Oral Anticoagulant Dosing**



Camm, A.J. et al. J Am Coll Cardiol. 2020;76(12):1425–36.

The reference category is patients prescribed with the recommended dosing at enrollment. Hazard ratios were adjusted for age, sex, ethnicity, type of AF, diabetes, hypertension, history of bleeding, prior stroke/TIA/SE, congestive heart failure, vascular disease, smoking, and heavy alcohol consumption. AF = atrial fibrillation; SE = systemic embolism; TIA = transient ischemic attack.

linked to numerically higher rates of cardiovascular death, including congestive heart failure and myocardial infarction. Overdosage was associated with a nonsignificant trend to higher risk of all-cause death, stroke/SE, and bleeding. The number of patients with overdosage was not large enough to derive meaningful conclusions.

The uptake of DOACs for the prevention of stroke in patients with AF at risk is rapidly growing worldwide but with large variations depending mostly, but not only, on the socioeconomic status of the countries under consideration (13,14). This has resulted in an increase in the rates of at-risk patients receiving guideline-recommended anticoagulant therapy (15,16). Kidney function, age, and body weight are important characteristics to take into account when deciding the dose of DOACs. This is reflected in the Summaries of Product Characteristics (SPC)/drug labels that differ for each DOAC and vary according to regulatory agencies, EMA (2), FDA (3), or PMDA (4), as each of them has issued different SPCs for the 4 different DOACs (2–4). This is a limiting factor for the prescription and a source of confusion over the rules of prescription even though there has been an attempt to clarify them in European consensus documents (17,18). Therefore, there was a need to assess the patterns of DOAC dose prescription, and to assess the impact of recommended versus nonrecommended DOAC dosing on outcomes.

Underdosing in over 30% of patients was observed in all LATAM (Latin America) countries except Argentina, and in all Asian countries except Singapore. Uptake of anticoagulants in stroke prevention is low in LATAM countries (16,19,20). Underdosing of VKAs prescribed for stroke prevention in AF is common in Asia (10,21–23) where lighter anticoagulation (lower target international normalized ratio) was shown to be associated with less risk of bleeding and no higher risk of stroke/SE than in non-Asian countries (23,24). In J-ROCKET AF (Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), low doses of rivaroxaban were shown to be noninferior to dose-adjusted VKA therapy on the efficacy composite endpoint of death and/or stroke or

SE and on the primary safety composite endpoint of major and clinically relevant nonmajor bleeding, but the trial was underpowered (25). This may explain the high rate of underdosing of DOACs in Japan (even when assessed according to Japanese regulations), but also in Korea and other Asian countries that may unofficially follow the rules of prescriptions applied in Japan, despite local SPCs instructing otherwise (22,26,27). The lowest rates (<20%) of underdosage were observed chiefly in North America and in European countries except France, Germany, and Spain, where underdosage ranged from 20% to 30%. Overdosage was observed at rates <5%. Strikingly, almost 70% of patients with excessive dosage had moderate-to-severe renal impairment. The investigators may have unintentionally disregarded the rules of prescription related to renal function or may have relied on different rules issued by national or regional organizations.

In addition, the investigators may not have accurately assessed the risk profile of patients. At baseline, both underdosed and overdosed patients tended to be at higher risk of stroke/SE, bleeding, and death than patients who were on recommended doses, and the rates of nonrecommended doses increased with increasing CHA_2DS_2-VASc scores. The highest-risk patients were more prone to receive nonrecommended doses of DOACs, perhaps because of bleeding concerns.

Last, as shown in a recent report, access to high-quality health care is highly variable between countries, including those involved in GARFIELD-AF (28). This may have had an impact on compliance to prescription rules and recommended dosage of anticoagulants.

The prescription of the recommended doses also varies with the different products. Prescription according to the labeling was more frequently seen for the DOACs initially marketed, namely dabigatran and rivaroxaban, whereas higher rates of low dosing were seen with apixaban and edoxaban (over 50% with this drug), both of which have been marketed more recently, and in the case of edoxaban, experience in GARFIELD-AF was confined mostly to the Japanese market.

Not surprisingly, age, weight, and moderate-to-severe CKD were strong predictors of underdosage, as recommendation of dosage is mainly defined according to these 3 variables. Additionally, female sex, non-Caucasian ethnicity, acute coronary syndrome, vascular disease, prior stroke, diabetes, and concomitant AP therapy had a strong effect on the risk of underdosing. When variables used in the definition of underdosing were removed from the selection procedure, congestive heart failure, management in office or anticoagulant clinics, and diastolic blood pressure emerged as strong predictors of underdosing. The effect of ethnicity is not unexpected, as it is a surrogate of the region/country of enrollment in the registry.

TABLE 3 Distribution* of Causes of Death Among Patients Deceased Within the First 2 Years After Atrial Fibrillation Diagnosis by Dosing

Cause of Death	Nonrecommended Low Dosing (n = 195 Deaths)	Recommended Dosing (n = 360 Deaths)	Nonrecommended High Dosing (n = 33 Deaths)
Cardiovascular cause	60 (30.8)	104 (28.9)	9 (27.3)
Congestive heart failure	25 (12.8)	37 (10.3)	6 (18.2)
Sudden or unwitnessed death	5 (2.6)	16 (4.4)	1 (3.0)
Myocardial infarction	8 (4.1)	11 (3.1)	0 (0.0)
Nonhemorrhagic stroke	6 (3.1)	11 (3.1)	1 (3.0)
Atherosclerotic vascular disease	3 (1.5)	3 (0.8)	0 (0.0)
Intracranial hemorrhage	1 (0.5)	5 (1.4)	0 (0.0)
Pulmonary embolism	0 (0.0)	5 (1.4)	0 (0.0)
Dysrhythmia	1 (0.5)	2 (0.6)	1 (3.0)
Directly related to revascularization	0 (0.0)	1 (0.3)	0 (0.0)
Other/unknown cardiovascular cause	11 (5.6)	13 (3.6)	0 (0.0)
Noncardiovascular cause	74 (37.9)	171 (47.5)	19 (57.6)
Malignancy	24 (12.3)	60 (16.7)	4 (12.1)
Respiratory failure	11 (5.6)	29 (8.1)	2 (6.1)
Infection	7 (3.6)	17 (4.7)	0 (0.0)
Sepsis	7 (3.6)	14 (3.9)	1 (3.0)
Renal disease	5 (2.6)	5 (1.4)	2 (6.1)
Accidental/trauma	2 (1.0)	8 (2.2)	1 (3.0)
Liver failure	3 (1.5)	2 (0.6)	0 (0.0)
Suicide	0 (0.0)	2 (0.6)	0 (0.0)
Other/unknown noncardiovascular cause	15 (7.7)	34 (9.4)	9 (27.3)
Other/unknown cause	61 (31.3)	85 (23.6)	5 (15.2)

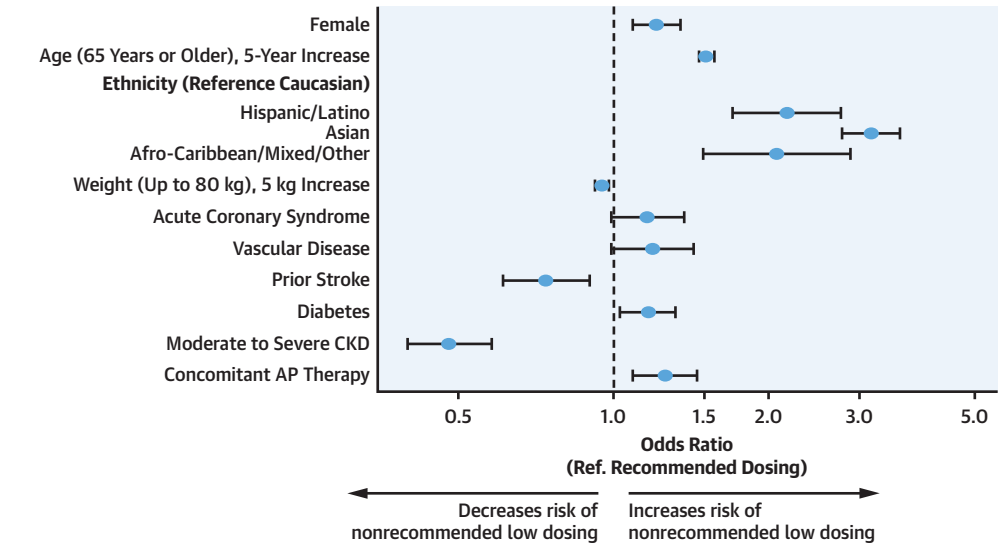
Values are n (%). *Percentages calculated among the total number of deaths within each dosing group.

TABLE 4 Odds Ratios for Selected Predictors of Nonrecommended Low Dosing

Predictor	OR (95% CI)
Female	1.21 (1.09–1.35)
Age (65 yrs or older), 5-yr increase	1.51 (1.46–1.57)
Ethnicity (reference Caucasian)	
Hispanic/Latino	2.17 (1.70–2.76)
Asian	3.16 (2.77–3.59)
Afro-Caribbean/mixed/other	2.07 (1.49–2.88)
Weight (up to 80 kg), 5-kg increase	0.95 (0.92–0.98)
Acute coronary syndrome	1.16 (0.99–1.37)
Vascular disease	1.19 (0.99–1.43)
Prior stroke	0.74 (0.61–0.90)
Diabetes	1.17 (1.03–1.32)
Moderate to severe CKD	0.48 (0.40–0.58)
Concomitant AP therapy	1.26 (1.09–1.45)

AP = antiplatelet; CI = confidence interval; CKD = chronic kidney disease; OR = odds ratio.

FIGURE 3 Odds Ratios for Selected Predictors of Nonrecommended Low Dosing



Percentages calculated among the total number of deaths within each dosing group. AP = antiplatelet; CKD = chronic kidney disease.

Underdosing has been reported in various registries or observational studies (29–31). In the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry, the rate of nonrecommended doses was quite low, in the range of 12%, and was associated with poor outcomes, significantly higher risk of all-cause death in overdosed patients, and higher rates of cardiovascular rehospitalization in underdosed patients. The population of patients receiving nonrecommended doses was at higher risk at baseline than patients receiving the recommended dose. Older age, female sex, and noncardiologist-treating physicians were the most important predictors of off-label prescription (30). In XANTUS (Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation), a prospective, international, observational study of patients receiving rivaroxaban for AF, recommendation of dosing was based on CrCl assessment. Nonrecommended (higher and lower than recommended) dosage was significantly associated with a higher risk of death and of reaching the composite endpoint of the study (major bleeding, stroke/SE, and death) than patients with recommended dosage. The excess of risks, including death, was no longer significant after adjustment, suggesting that the higher rates of events associated with nonrecommended dosage were more related to comorbidities than to the dose of the drug and the comorbidities used for determining the dose (32). In a more recent report retrospectively reviewing recommendations of dosing of rivaroxaban and adherence to dietary requirements, the rate of nonrecommended administration (dosing and/or dietary requirements) was reported as high as 40%, mostly when the drug was prescribed by noncardiologists (33). In the retrospective analysis of patients with nonvalvular AF that was conducted by OptumLabs, 13.3% of patients had received reduced doses. The reduced dose of apixaban was associated with a nearly 5-fold higher risk of stroke and a similar risk of major bleeding when compared with standard dose of apixaban (34). The data from three nationwide registries in Denmark demonstrated that the rates of ischemic stroke or SE with a reduced dose of apixaban (2.5 mg) were higher but not significantly different when compared with warfarin (35).

STUDY STRENGTHS AND LIMITATIONS. The strength of this study is that dosage recommendations of each DOAC was carefully assessed on a national/regional basis, taking into account the Summaries of Product Characteristics (SPC) of each DOAC issued by EMA (2), FDA (3), or PMDA (4) depending on the country where the drug was used. EMA SPCs were used for European countries, FDA SPCs for Northern America, and PMDA SPCs for Japan only. For all other countries, we assumed that EMA rules for prescription as summarized in an European consensus document (18) were implemented, although some countries may have their own rules for prescription that may differ from

EMA rules. This is true for South Korea, China, and India (10,22,26,27,36–41).

By design and according to the requirements of purely observational registries, renal function testing was not mandatory, but was reported by the investigators as CKD defined according to eGFR. Creatinine clearance is used in the labeling of most DOACs instead of eGFR according to the National Kidney Foundation. It is possible that, in some instances, uncertainty over renal function may have led investigators to unintended overdosing. In addition, coadministration of drugs with potential influence on the pharmacokinetics/pharmacodynamics of the various DOACs, particularly P-glycoprotein inhibitors, was not captured in the CRF. Similarly, food-drug interactions that may affect the pharmacokinetics/pharmacodynamics of certain DOACs were not captured (33). Treatment discontinuations or changes in dosage over time were also not considered because of the very complicated nature of discontinuations, interruptions, dosing changes, and switching between anticoagulants. However, discontinuation may have had an additional deleterious impact on outcomes. Outcomes may have been at least partially influenced by uncaptured information, although frequent and prospective data collection and site-audit minimized this. In addition, because of limited sample sizes, no firm conclusions can be drawn about overdosage and about edoxaban. In Austria, Chile, China, Finland, India, Norway, Switzerland, Singapore, and Thailand, the number of patients recruited was <100. The rates of DOAC prescription in these countries have to be considered with caution.

CONCLUSIONS

In the GARFIELD-AF registry, most patients prescribed DOACs for stroke prevention received the recommended doses according to country-specific guidelines. The use of nonrecommended doses was not uncommon and was associated with worse outcome, namely higher risk of all-cause death, mostly cardiovascular death, but was not associated with a significant increased risk of stroke/SE and/or major bleeding. Treatment above the recommended doses was relatively rare compared with nonrecommended low dosing. Of those who were treated over the recommended doses, 67.5% had moderate-to severe CKD, as opposed to 8.6% of patients with recommended dosing and 7.1% of patients with underdosing. The highest-risk patients were more prone to receive nonrecommended doses of DOACs.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL OUTCOMES: In a practice-based registry of patients with recently detected atrial fibrillation, prescription of nonrecommended doses of target-specific oral anticoagulant (DOACs) was associated with a higher risk of death, mostly cardiovascular death, compared with patients prescribed recommended doses.

TRANSLATIONAL OUTLOOK: More pervasive strategies are needed to promote approved dosing of DOACs.

REFERENCES

1. 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.

2. Lindo VS, Kakkar VV, Melissari E. Cleaved antithrombin (ATc): a new marker for thrombin generation and activation of the coagulation system. Br J Haematol 1995;89:157–62.

3. Krawczak M, Smith-Sorensen B, Schmidtke J, Kakkar VV, Cooper DN, Hovig E. Somatic spectrum of cancer-associated single basepair substitutions in the TP53 gene is determined mainly by endogenous mechanisms of mutation and by selection. Hum Mutat 1995;5:48–57.

4. Patel Y, Kakkar VV, Authi KS. Calpain-induced down-regulation of protein kinase C inhibits dense-granule secretion in human platelets. Inhibition of platelet aggregation or calpain activity preserves protein kinase C and restores full secretion. Biochim Biophys Acta 1994;1224:480–8.

5. Kakkar AK, Mueller I, Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS One 2013;8:e63479.

6. Kakkar AK, Mueller I, Bassand JP, et al. International longitudinal registry of patients with atrial fibrillation at risk of stroke: Global Anticoagulant Registry in the FIELD (GARFIELD). Am Heart J 2012;163:13–9.e1.

7. Stevens PE, Levin A. Evaluation and management of chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2012 clinical practice guideline. Ann Intern Med 2013;158:825–30.

8. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1–266.

9. Vassalotti JA, Centor R, Turner BJ, Greer RC, Choi M, Sequist TD. Practical approach to detection and management of chronic kidney disease for the primary care clinician. Am J Med 2016;129:153–62.e7.

10. Group. JJW. Guidelines for pharmacotherapy of atrial fibrillation (JCS 2008): digest version. Circ J 2010;74:2479–500.

11. Ogawa S, Koretsune Y, Yasaka M, et al. Antithrombotic therapy in atrial fibrillation: evaluation and positioning of new oral anticoagulant agents. Circ J 2011;75:1539–47.

12. Estrella MM, Jaar BG, Cavanaugh KL, et al. Perceptions and use of the national kidney foundation KDOQI guidelines: a survey of U.S. renal healthcare providers. BMC Nephrol 2013;14:230.

13. Lunde ED, Nielsen PB, Riahi S, et al. Associations between socioeconomic status, atrial fibrillation, and outcomes: a systematic review. Expert Rev Cardiovasc Ther 2018;16:857–73.

14. Sholzberg M, Gomes T, Juurlink DN, Yao Z, Mamdani MM, Laupacis A. The influence of socioeconomic status on selection of anticoagulation for atrial fibrillation. PLoS One 2016;11:e0149142.

15. Camm AJ, Accetta G, Ambrosio G, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. Heart 2017;103:307–14.

16. Huisman MV, Rothman KJ, Paquette M, et al. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF Registry Phase 2. J Am Coll Cardiol 2017;69:777–85.

17. Heidbuchel H, Verhamme P, Alings M, et al. EHRA practical guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. Eur Heart J 2013;34:2094–106.

18. Steffel J, Verhamme P, Potpara TS, et al. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J 2018;39:1330–93.

19. Gamra H, Murin J, Chiang CE, Naditch-Brule L, Brette S, Steg PG. Use of antithrombotics in atrial fibrillation in Africa, Europe, Asia and South America: insights from the International RealiseAF Survey. Arch Cardiovasc Dis 2014;107:77–87.

20. Singer DE, Hellkamp AS, Piccini JP, et al. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF clinical trial. J Am Heart Assoc 2013;2:e000067.

21. Haas S, Ten Cate H, Accetta G, et al. Quality of vitamin K antagonist control and 1-year outcomes in patients with atrial fibrillation: a global perspective from the GARFIELD-AF Registry. PLoS One 2016;11:e0164076.

22. Ogawa S, Aonuma K, Tse H-F, et al. The APHRS's 2013 statement on antithrombotic therapy of patients with nonvalvular atrial fibrillation. Journal of Arrhythmia 2013;29:190–200.

23. Inoue H. Thromboembolism in patients with nonvalvular atrial fibrillation: comparison between Asian and Western countries. J Cardiol 2013;61:1–7.

24. Atarashi H, Inoue H, Okumura K, Yamashita T, Kumagai N, Origasa H. Present status of anticoagulation treatment in Japanese patients with atrial fibrillation: a report from the J-RHYTHM Registry. Circ J 2011;75:1328–33.

25. Hori M, Matsumoto M, Tanahashi N, et al. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study. Circ J 2012;76:2104–11.

26. Chen CH, Chen MC, Gibbs H, et al. Antithrombotic treatment for stroke prevention in atrial fibrillation: the Asian agenda. Int J Cardiol 2015;191:244–53.

27. Tse HF, Wang YJ, Ahmed Ai-Abdullah M, et al. Stroke prevention in atrial fibrillation—an Asian stroke perspective. Heart Rhythm 2013;10:1082–8.

28. GBD 2016 Healthcare Access and Quality Collaborators. Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: a systematic analysis from the Global Burden of Disease Study 2016. Lancet 2018;391:2236–71.

29. Marzec LN, Wang J, Shah ND, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. J Am Coll Cardiol 2017;69:2475–84.

30. Steinberg BA, Shrader P, Thomas L, et al. 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.

31. Barra ME, Fanikos J, Connors JM, Sylvester KW, Piazza G, Goldhaber SZ. Evaluation of dose-reduced direct oral anticoagulant therapy. Am J Med 2016;129:1198–204.

32. Amarenco P, Haas S, Hess S, et al. Outcomes associated with non-recommended dosing of rivaroxaban: results from the XANTUS study. Eur Heart J Cardiovasc Pharmacother 2019;5:70–9.

33. Leiter MR, Packard KA, Qi Y, Krueger SK. Improved dosing and administration of rivaroxaban when prescribed by a cardiologist. Heart International 2019;13:24–7.

34. 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.

35. Nielsen PB, Skjoth F, Sogaard M, Kjaeldgaard 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.

36. Chiang C-E, Wu T-J, Ueng K-C, et al. 2016 guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation. J J Formos Med Assoc 2016;115:893–952.

37. Dalal J, Bhave A, Oomman A, et al. The Indian consensus guidance on stroke prevention in atrial fibrillation: an emphasis on practical use of non-vitamin K oral anticoagulants. Indian Heart J 2015;67 Suppl 2:S13–34.

38. Lee JM, Joung B, Cha M-J, et al., for the Stroke Outcomes Research Working Group. 2018 KHRS Guidelines for stroke prevention therapy in Korean patients with nonvalvular atrial fibrillation. Korean J Med 2018;93:87–109.

39. Guo Y, Pisters R, Apostolakis S, et al. Stroke risk and suboptimal thromboprophylaxis in Chinese patients with atrial fibrillation: would the novel oral anticoagulants have an impact? Int J Cardiol 2013;168:515–22.

40. Sabir I, Khavandi K, Brownrigg J, Camm AJ. Oral anticoagulants for Asian patients with atrial fibrillation. Nat Rev Cardiol 2014;11:290.

41. Jung BC, Kim NH, Nam GB, et al. The Korean Heart Rhythm Society's 2014 statement on antithrombotic therapy for patients with nonvalvular atrial fibrillation: Korean Heart Rhythm Society. Korean Circ J 2015;45:9–19.

KEY WORDS atrial fibrillation, direct oral anticoagulants, dosing, stroke prevention

APPENDIX For an expanded Methods section, supplemental tables and figures, and a full list of study investigators, please see the online version of this paper.