JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 8, 2019
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PUBLISHED BY ELSEVIER

Direct Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation and Low Body Weight

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ABSTRACT

BACKGROUND It is unclear whether the overall effectiveness and safety of direct oral anticoagulants (DOACs) are consistent in patients with nonvalvular atrial fibrillation (AF) and extremely low body weight (<50 kg).

OBJECTIVES This study compared DOACs with warfarin in AF patients with low body weight.

METHODS Using data from the Korean National Health Insurance Service database from January 2014 to December 2016, AF patients with body weight ≤60 kg and who were treated with oral anticoagulants (n = 14,013 taking DOACs and n = 7,576 taking warfarin) were included and examined for ischemic stroke, intracranial hemorrhage (ICH), gastrointestinal bleeding, major bleeding, all-cause death, and composite outcome. The propensity score weighting was used to balance the 2 groups.

RESULTS Baseline characteristics were well balanced between the 2 groups (mean age 73 years, mean CHA_2DS_2-VASc score 4, and 28% of patients weighed <50 kg). DOACs were associated with lower risks of ischemic stroke (hazard ratio [HR]: 0.591; 95% confidence interval [CI]: 0.510 to 0.686) and major bleeding (HR: 0.705; 95%: CI 0.601 to 0.825), which were caused by a reduction in ICH (HR: 0.554; 95% CI: 0.429 to 0.713) compared with warfarin. DOAC improved the net clinical benefit compared with warfarin (HR for composite outcome: 0.660; 95% CI: 0.606 to 0.717), and this was consistent in patients who weighed <50 kg (HR for composite outcome: 0.665; 95% CI: 0.581 to 0.762).

CONCLUSIONS In this real-world Asian AF population with low body weight, DOACs showed better effectiveness and safety than warfarin. These results were consistent in patients with extremely low body weight. Regular dosages of DOACs showed comparable results as reduced dosages of DOACs in both effectiveness and safety.
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Oral anticoagulation (OAC) therapy is the most fundamental treatment for patients with atrial fibrillation (AF) because it prevents ischemic stroke and reduces mortality (1). With the aging population, the prevalence of AF has been increasing (2,3). Patients with AF tend to be older with more comorbidities; thus, almost 85% of patients with AF are prescribed OACs (3,4). For

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Manuscript received November 2, 2018; revised manuscript received November 20, 2018, accepted November 26, 2018.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2018.11.051

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

ASD = absolute standardized difference

CI = confidence interval

Cmax = mean maximal plasma concentration

CrCl = creatinine clearance

DOAC = direct oral anticoagulant

GI = gastrointestinal

HR = hazard ratio

ICH = intracranial hemorrhage

IPW = inverse probability weighting

NHIS = National Health Insurance System

OAC = oral anticoagulant

PAD = peripheral artery disease

PS = propensity score

TTR = time in the therapeutic range

decades, warfarin was the only available OAC for these patients, but it was largely underused because of its narrow therapeutic range, the need for frequent monitoring, and concerns about bleeding complications (e.g., intracranial hemorrhage [ICH]) (5-7). Since the introduction of direct oral anticoagulants (DOACs), which are convenient, safe, and effective alternatives to warfarin, OAC use has become more widespread (3,4,8).

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With increasing OAC use, the prevalence of frailty in patients using OACs has also increased in the aging population. Patients with low body weight are more common among Asians than among non-Asians (9). The effects of DOACs are closely related to plasma concentrations, which are affected by body distribution volume; thus, extremely low body weight may influence the efficacy and safety of DOACs (10). Although DOACs have shown better net clinical benefits than warfarin, which are mainly due to a reduction in ICH, being underweight has been associated with an increased risk of major bleeding in patients taking DOACs (11). It has not been established whether DOACs have similar benefits in patients with low body weight, especially in those with extremely low body weight (<50 kg). In this nationwide cohort study, we aimed to compare the effectiveness and safety of DOACs with those of warfarin in patients with nonvalvular AF and low body weight.

METHODS

In this retrospective cohort, all patient data were acquired from the Korean National Health Insurance Service (NHIS) (a registry of the entire approximately 50 million South Korean population) and the National Health Insurance Corporation Health checkup database. Briefly, the Korean NHIS database includes subjects' demographic information, prescription dispensing records, as well as procedure and diagnosis codes for inpatient and outpatient services. Diagnoses were coded based on the International Classification of Disease, Tenth Revision, Clinical Modification codes. Detailed information regarding the Korea NHIS database was described elsewhere (12). This study was exempt from review by the Seoul National University Hospital Institutional Review Board (E-1802-091-923).

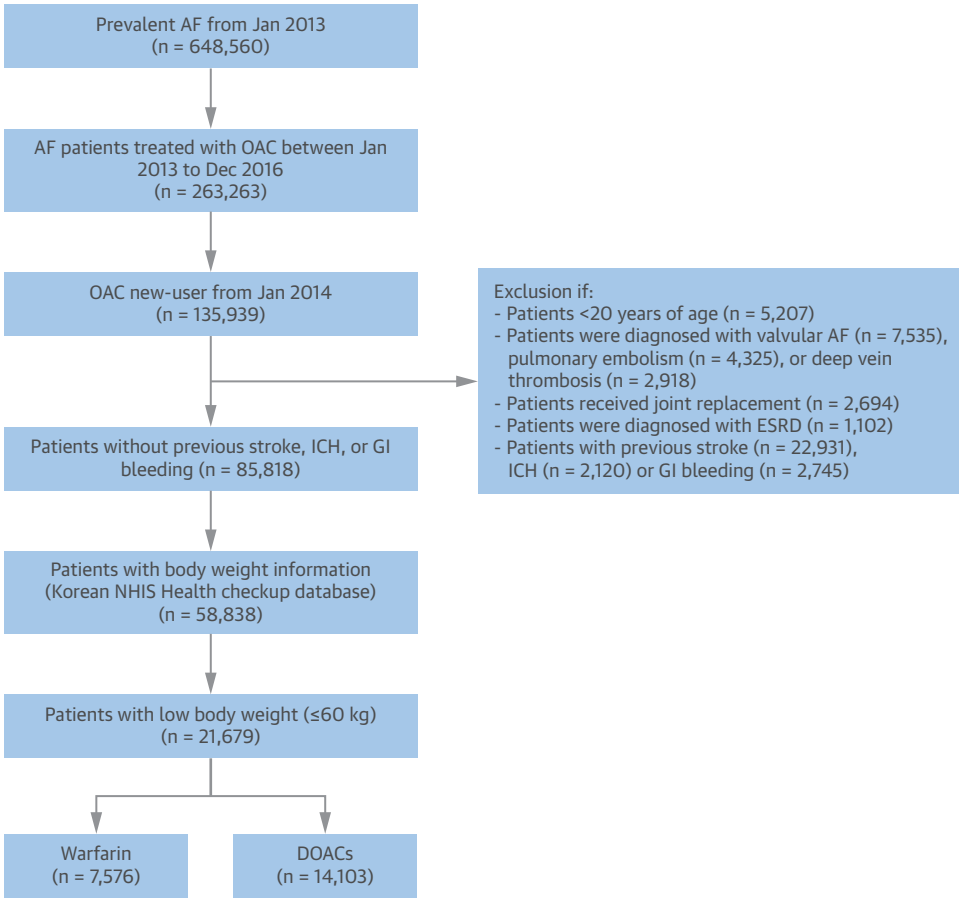
STUDY DESIGN. We studied adult patients with nonvalvular AF treated with warfarin or DOACs (rivaroxaban, dabigatran, apixaban, or edoxaban). We identified 263,263 patients who had ≥1 pharmacy claim for warfarin or DOACs during the identification period (from January 1, 2013 to December 31, 2016) and excluded the patients who were prescribed any OAC before January 1, 2014. Therefore, we only included new users of an index OAC. We excluded patients with valvular AF, end-stage renal disease, those <20 years of age, and those who had alternative indications for OAC treatment (e.g., deep vein thrombosis, pulmonary embolism, or joint replacement surgery). In the Korean NHIS database, we could not differentiate between new and recurrent episodes; thus, we excluded patients with a history of ischemic stroke, ICH, or gastrointestinal (GI) bleeding (13,14). Of the 85,818 patients, body weight data was available for 58,838 patients, and finally, 21,679 patients with a body weight ≤60 kg were included in the analysis (**Figure 1**).

COVARIATES. Baseline characteristics, including age, sex, and comorbidities (hypertension, diabetes, dyslipidemia, congestive heart failure, peripheral artery disease [PAD], chronic obstructive pulmonary disease, and previous myocardial infarction), were evaluated. Comorbidities were defined by diagnosis codes, prescription records, and inpatient and/or outpatient hospital visits within 1 year before the index date (Online Table 1). The CHA_2DS_2-VASc score was calculated by assigning 2 points each for those age 75 years or older and those with previous stroke, transient ischemic attack, and/or systemic thromboembolism, and 1 point each for age 65 to 74 years, female sex, congestive heart failure, hypertension, diabetes, and vascular disease (PAD or previous myocardial infarction) (15). We also analyzed body weight, body mass index, and renal function of the patients, which was calculated by creatinine clearance (CrCl) using the Cockcroft-Gault method.

DEFINITIONS. We included patients with a body weight of ≤60 kg because low body weight thresholds were often used to define underweight in randomized clinical trials (16-18). In addition, body weight ≤60 kg was a clinical indication for a dose reduction of apixaban (if age ≥80 years and/or serum creatinine ≥1.5 mg/dl was also present) and edoxaban (16,17). Among these populations, extremely low body weight was defined as <50 kg (10,18,19).

STUDY OUTCOMES AND FOLLOW-UP. Six clinical outcomes were used to determine the effectiveness and safety of DOACs and warfarin, including ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and the composite outcome (ischemic stroke + ICH +

FIGURE 1 Study Population Enrollment Flow



From a total of 135,939 new users of oral anticoagulants (OACs) since January 2014, 7,576 warfarin users and 14,103 direct oral anticoagulant (DOAC) users were included in this study. AF = atrial fibrillation; ESRD = end-stage renal disease; GI = gastrointestinal; ICH = intracranial hemorrhage; NHIS = National Health Insurance System.

hospitalization for GI bleeding + all-cause death) (14). Detailed definitions of study outcomes are described in Online Table 1. The index date was the first date of warfarin or DOAC use. To assess clinical outcomes, patients were censored at the outcome events or the end of the study period (December 31, 2016), whichever occurred first. We also performed a sensitivity analysis in analogy with the on-treatment analysis, whereby patients were also censored at the discontinuation of index treatment during the study period. Discontinuation was defined as a 30-day gap from the last day of supply of the last prescription.

STATISTICAL ANALYSIS. To compare the warfarin and pooled DOAC groups, propensity score (PS) methods were used (20). The PS of being in each treatment group was assessed using a logistic regression model with all baseline covariates (Online Table 2). To balance the baseline characteristics between the 2 treatment groups, inverse probability weighting (IPW) analysis was used regarding time-to-event analyses using stabilized weights calculated from PS (21). Because the sample sizes of the 2 treatments were different, IPW was used rather than PS matching so the whole study population would not be lost and to keep generalizability. IPW used the whole data set, assigned inverse probability of received treatment weighting by corresponding to 1/PS for patients in the treated cohort and [1/(1-PS)] for those in the control cohort, and generated a pseudo-population with an almost perfect covariate balance between the 2 treatment groups (22). Furthermore, we trimmed the individuals with extreme PS values to avoid extreme weights in IPW. In IPW with 5% trimming, stabilized weights were trimmed at the 5th

TABLE 1 Baseline Characteristics of Patients Using Warfarin Versus DOACs

	Propensity Score Weighting					
	Before			After (With 5% Trimming)		
	DOACs (n = 14,103)	Warfarin (n = 7,575)	ASD	DOACs (n = 12,810)	Warfarin (n = 6,692)	ASD
Age, yrs	73.4 ± 8.1	70.1 ± 10.8	0.348	72.6 ± 7.4	72.9 ± 8.5	0.043
<65	13	28		14	17	
65–74	39	33		43	36	
≥75	48	39		43	47	
Men	31	34	0.095	32	32	0.009
CHA_2DS_2-VASc score	3.91 ± 1.61	3.86 ± 1.87	0.031	3.92 ± 1.64	3.97 ± 1.83	0.032
0–1	5	11		6	9	
2–3	36	33		36	32	
≥4	59	56		58	59	
Body weight, kg	53.2 ± 5.5	53.3 ± 5.5	0.010	53.2 ± 5.5	53.2 ± 5.6	0.002
50–60	72	72		72	72	
<50	28	28		28	28	
Body mass index, kg/m^2	22.3 ± 2.5	22.1 ± 2.5	0.116	22.3 ± 2.5	22.3 ± 2.5	0.007
CrCl, ml/min	79.7 ± 35.1	80.1 ± 32.7	0.011	78.9 ± 22.7	78.6 ± 20.4	0.010
Hypertension	67	67	0.003	68	68	0.009
Diabetes mellitus	18	18	0.004	19	19	0.010
Dyslipidemia	38	36	0.048	38	39	0.013
Heart failure	32	43	0.223	36	36	0.013
Previous MI	3	5	0.088	3	4	0.025
PAD	19	17	0.045	18	18	0.007
COPD	21	24	0.065	22	23	0.012
DOAC dose						
Regular dose*	38	–	–	40	–	-
Reduced dose†	62	–	–	60	–	-

Values are mean ± SD or %, unless otherwise indicated. *Regular dose DOACs are 20 mg rivaroxaban once daily, 150 mg dabigatran twice daily, 5 mg apixaban twice daily, and 60 mg edoxaban once daily. †Reduced dose DOACs are 15 or 10 mg rivaroxaban once daily, 110 mg dabigatran once daily, 2.5 mg apixaban twice daily, and 30 mg edoxaban once daily.

ASD = absolute standardized difference; 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 (female); COPD = chronic obstructive pulmonary disease; CrCl = creatinine clearance; DOAC = direct oral anticoagulant; IQR = interquartile range; MI = myocardial infarction; PAD = peripheral artery disease.

and 95th percentile of the weights (23). After IPW with trimming, the balance of covariates between the 2 groups was evaluated using the absolute standardized difference (ASD). The ASD calculated the balance of covariates independently on the sample size of groups (24,25). An ASD ≤0.1 (10%) indicated that the 2 groups were well-balanced in a covariate, with a negligible difference (26).

Incidence rates were calculated based on weighted number of events during the follow-up period divided by 100 person-years at risk. The risk of the 6 clinical outcomes for pooled DOACs versus warfarin (reference) was obtained using survival analysis with the Kaplan-Meier method (log-rank test) and weighted Cox proportional hazards regression models with IPW. For clinical outcome analysis of the extremely low body weight group (<50 kg), a subgroup analysis was conducted, and patients were categorized by body weight (<50 kg and 50 to 60 kg). The balance of covariates between the warfarin and DOAC groups was evaluated in each subgroup using ASD.

Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SAS 9.3 (SAS Institute Inc, Cary, North Carolina).

SENSITIVITY ANALYSES. For the clinical outcome analysis, we used a weighted Cox proportional hazards regression model with 5% trimmed IPW in the main analysis. To provide complementary analyses, we also used multivariable Cox proportional hazards regression models. All variables using the PS calculation were included for multivariable adjustment: age, sex, CHA_2DS_2-VASc score, hypertension, diabetes, dyslipidemia, congestive heart failure, PAD, previous myocardial infarction, chronic obstructive pulmonary disease, body weight, and CrCl. We also performed IPW without trimming for the sensitivity analysis.

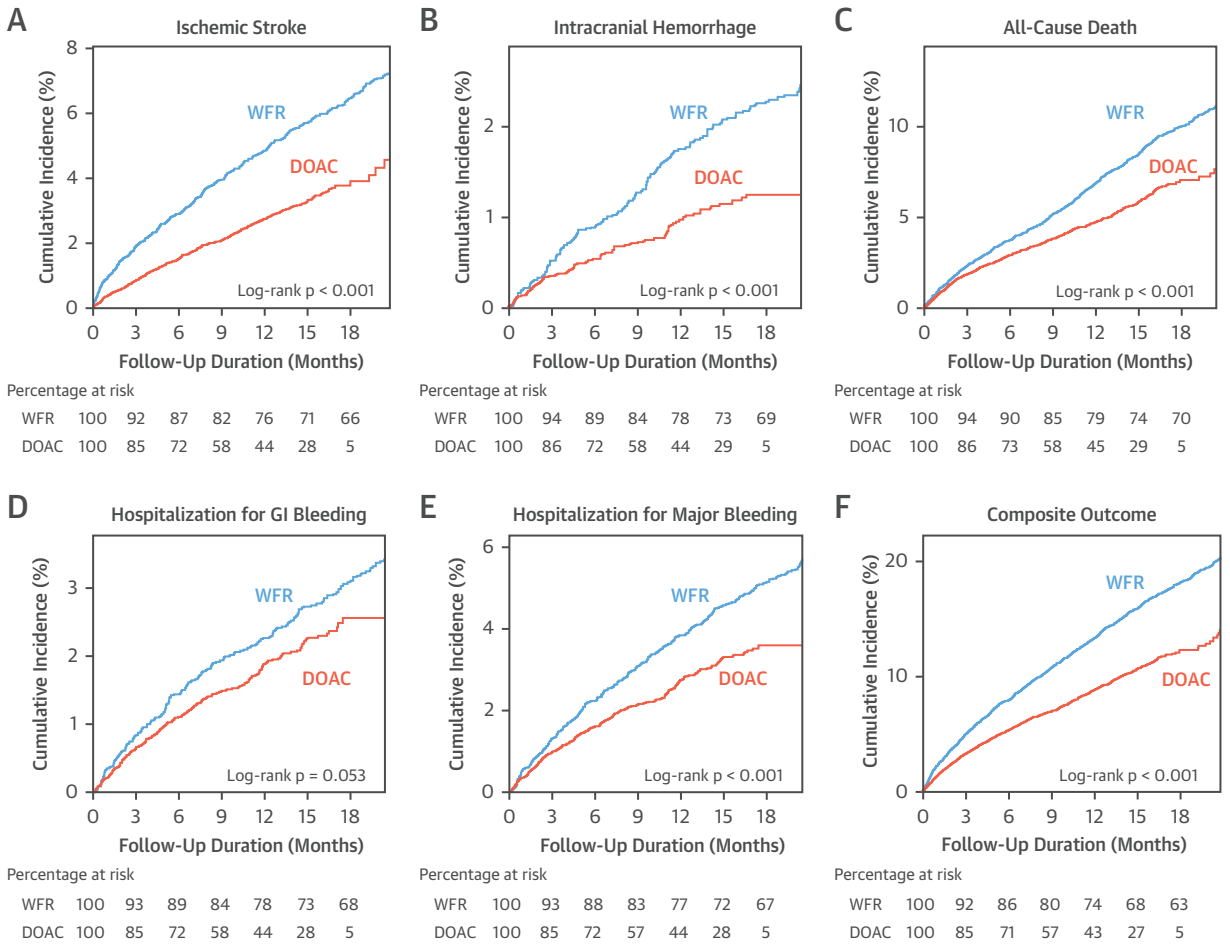
SUBGROUP ANALYSES. The analyses of comparisons between pooled DOACs and warfarin in the total study population were supplemented by stratified analyses according to the doses (regular and reduced), label adherence of DOAC dosing, and DOAC types (rivaroxaban, dabigatran, apixaban, and edoxaban).

Regular doses of DOACs were defined as rivaroxaban 20 mg once daily, dabigatran 150 mg twice daily, apixaban 5 mg twice daily, and edoxaban 60 mg once daily. For subgroup analysis by label adherence to DOAC dosing, patients were categorized as follows: dosing consistent with label (on-label), off-label underdosed, and off-label overdosed, according to the approved dose criteria. Dose reduction criteria were specific to each DOAC based on patient baseline characteristics (Online Table 3). Because there were some differences in dosing labels among different countries, we applied the criteria used in pivotal clinical trials that were generally consistent with approved drug labeling in Korea during the study period. Patients in whom a selected DOAC was contraindicated were classified as off-label overdosed. Subgroup analyses were performed using a multivariable Cox proportional hazards regression model.

RESULTS

BASELINE CHARACTERISTICS. After application of inclusion and exclusion criteria, 21,589 patients with AF, low body weight (≤60 kg), and newly prescribed warfarin (n = 7,576) or DOACs (n = 14,103) were included. In the pooled DOAC group, 43% of patients

FIGURE 2 **Cumulative Incidence Curves of 6 Clinical Outcomes in Pooled DOAC Versus Warfarin in the Total Study Population (≤60 kg)**

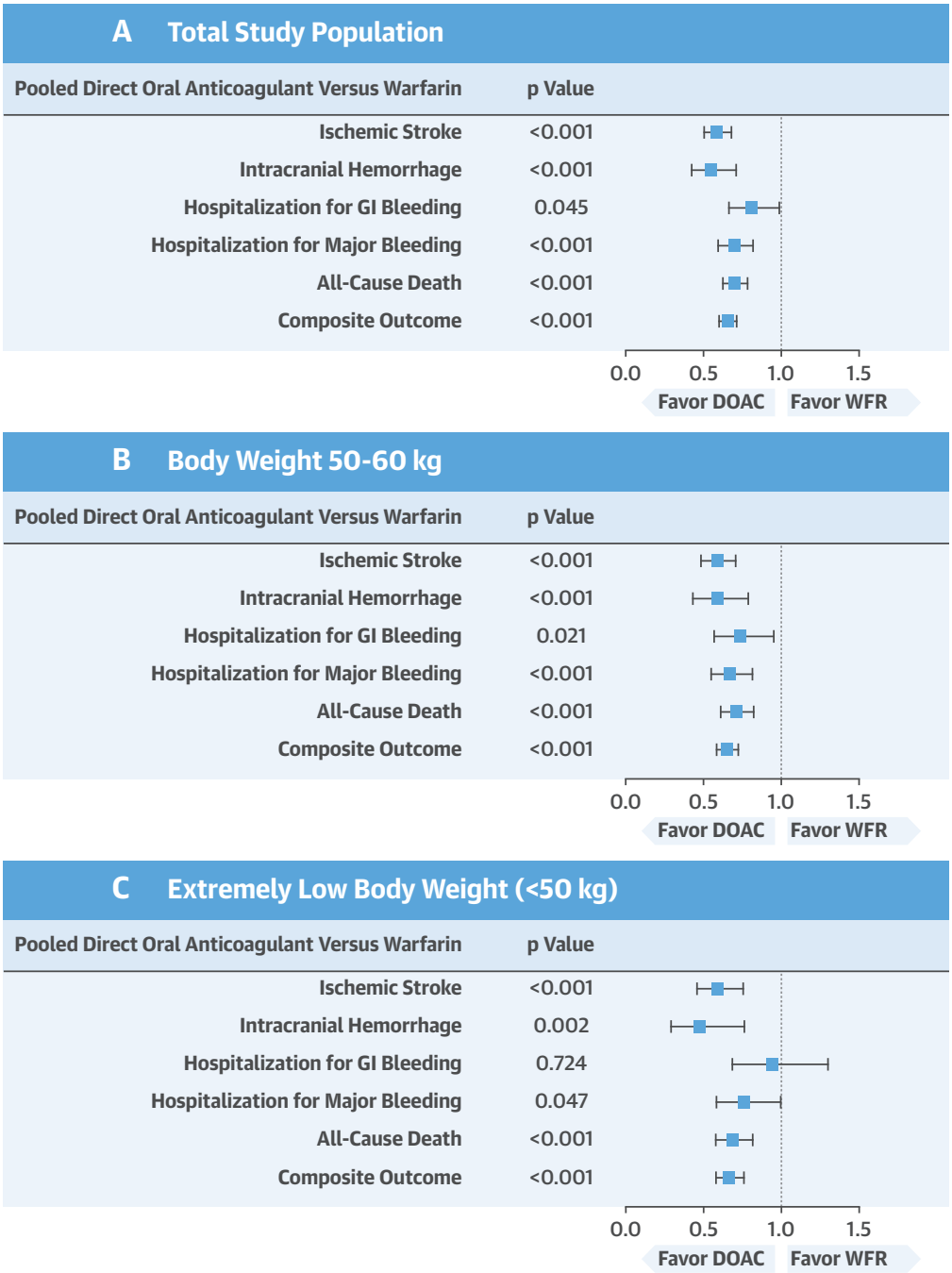


Compared with warfarin (WFR), DOACs carried significantly lower risks for ischemic stroke, major bleeding, all-cause death, and composite outcome. Cumulative incidence curves for **(A)** ischemic stroke, **(B)** intracranial hemorrhage, **(C)** all-cause death, **(D)** hospitalization for GI bleeding, **(E)** hospitalization for major bleeding, and **(F)** composite outcome. Abbreviations as in Figure 1.

received rivaroxaban, 26% received dabigatran, 24% received apixaban, and 8% received edoxaban. Before PS weighting, patients treated with DOACs were older, had a slightly higher body mass index, and showed lower prevalence of heart failure than those treated with warfarin (Table 1). After PS weighting, the warfarin and DOAC groups were well-balanced in all variables (all ASDs <0.1%) (Table 1, Online Figure 1). The mean age was 73 years, and the mean CHA_2DS_2-VASc score was 4. In both the warfarin and DOAC groups, 28% of patients weighed 50 kg. In the DOAC group, 60% of patients received a reduced dose of DOACs.

CLINICAL OUTCOMES IN PATIENTS WEIGHING ≤60 KG. The cumulative incidence curves of the 6 clinical outcomes are shown in Figure 2, and hazard ratios (HRs) of DOAC treatment with warfarin as the reference are shown in the Central Illustration and Online Table 4. The incidence rates of all outcomes during a median of 1.2 years (interquartile range: 0.6 to 1.7 years) are listed in Table 2. Compared with warfarin, DOAC was associated with a 41% lower risk of ischemic stroke (HR: 0.591; 95% confidence interval [CI]: 0.510 to 0.686; $p < 0.001$). Compared with warfarin, DOAC use was associated with a 30% reduction in the risk of major bleeding (HR: 0.705; 95% CI: 0.601 to 0.825; $p < 0.001$), which was mainly driven by a reduction in ICH (HR: 0.554; 95% CI: 0.429 to 0.713; $p < 0.001$). For hospitalization due to GI bleeding, DOAC treatment was associated with a

CENTRAL ILLUSTRATION **6 Clinical Outcomes in Direct Oral Anticoagulant Versus Warfarin (Reference) Groups in Total Study Population and in Subgroup Patients Who Weighed 50 to 60 kg and <50 kg**



Lee, S.-R. et al. J Am Coll Cardiol. 2019;73(8):919–31.

Compared with warfarin use (WFR) as the reference, direct oral anticoagulants (DOACs) were associated with lower risks of ischemic stroke (hazard ratio [HR]: 0.591; 95% confidence interval [CI]: 0.510 to 0.686), major bleeding (HR: 0.705; 95% CI 0.601 to 0.825), a greater reduction in intracranial hemorrhage (HR: 0.554; 95% CI: 0.429 to 0.713), and had a lower risk of all-cause death (HR: 0.705; 95% CI: 0.630 to 0.789). DOAC use showed improved net clinical benefit compared with warfarin (HR for composite outcome: 0.660; 95% CI: 0.606 to 0.717), and this was consistent in patients who weighed <50 kg (HR for composite outcome: 0.665; 95% CI: 0.581 to 0.762). GI = gastrointestinal.

lower risk than that of warfarin (HR: 0.816; 95% CI: 0.668 to 0.996; p = 0.045). DOAC use was associated with a 30% lower risk of all-cause death (HR: 0.705; 95% CI: 0.630 to 0.789; p < 0.001) and an improved net clinical benefit compared with warfarin (HR for composite outcome: 0.660; 95% CI: 0.606 to 0.717; p < 0.001). On-treatment analysis showed the similar trends with the main results across all 6 clinical outcomes (Online Table 5, Online Figure 2). The benefit of DOACs compared with warfarin were slightly accentuated in the on-treatment analysis.

CLINICAL OUTCOMES STRATIFIED BY BODY WEIGHT. Before comparing clinical outcomes, we evaluated the balance of all covariates between the 2 study groups in each subgroup categorized by body weight. The DOAC and warfarin groups were well-balanced in all variables (all ASDs of <0.1) in each subgroup (Online Table 6). Patients who weighed <50 kg were older, more likely to be women, and had higher CHA_2DS_2-VASc scores than patients who weighed 50 to 60 kg (Online Table 6). The proportion of those taking a reduced dose DOAC prescription was higher in patients weighing <50 kg than in patients weighing 50 to 60 kg (67% vs. 58%). In general, patients weighing <50 kg showed higher incidences of all 6 clinical outcomes than that of patients weighing 50 to 60 kg (**Table 2**). The **Central Illustration** shows the HRs of the clinical outcomes for DOACs compared with warfarin in each subgroup.

In both subgroups, DOACs showed consistently better outcomes than warfarin for ischemic stroke, ICH, hospitalization for major bleeding, all-cause death, and the composite outcome (**Central Illustration**, Online Table 4). Although DOACs showed outcomes comparable to those of warfarin for hospitalization for GI bleeding in patients who weighed <50 kg, the DOAC group had a lower risk of major bleeding and improved net clinical benefit. The cumulative incidence curves for the 6 clinical outcomes are presented in Online Figure 3 and **Figure 3**.

SENSITIVITY ANALYSIS. The consistent benefits of DOACs were shown by the sensitivity analysis. Using a multivariable Cox regression model and IPW without trimming, DOACs were associated with better outcomes than warfarin, with similar HRs for all 6 clinical outcomes as shown in the main analysis using IPW with 5% trimming (Online Figure 4).

SUBGROUP ANALYSES. DOAC doses: regular dose versus reduced dose. Among DOAC users, 8,723 (61.9%) patients used a reduced dose. Among patients who weighed <50 kg, 2,704 (68.3%) DOAC users were prescribed a reduced dose of DOACs (Online Table 7). The results for the 6 clinical outcomes were consistent across regular and reduced doses of DOACs (Online Figure 5).

TABLE 2 Incidence Rates of 6 Clinical Outcomes During Follow-Up Period

	Incidence Rate*					
	Total		50–60 kg		<50 kg	
	DOAC	Warfarin	DOAC	Warfarin	DOAC	Warfarin
Ischemic stroke	2.82	4.13	2.50	3.56	3.64	5.72
Intracranial hemorrhage	0.92	1.39	0.94	1.32	0.87	1.55
Hospitalization for GI bleeding	1.79	1.77	1.44	1.58	2.73	2.26
Hospitalization for major bleeding	2.67	3.09	2.34	2.85	3.52	3.74
All-cause death	5.09	6.66	4.00	5.44	7.91	9.92
Composite outcome	9.37	12.2	7.96	10.5	13.0	16.8

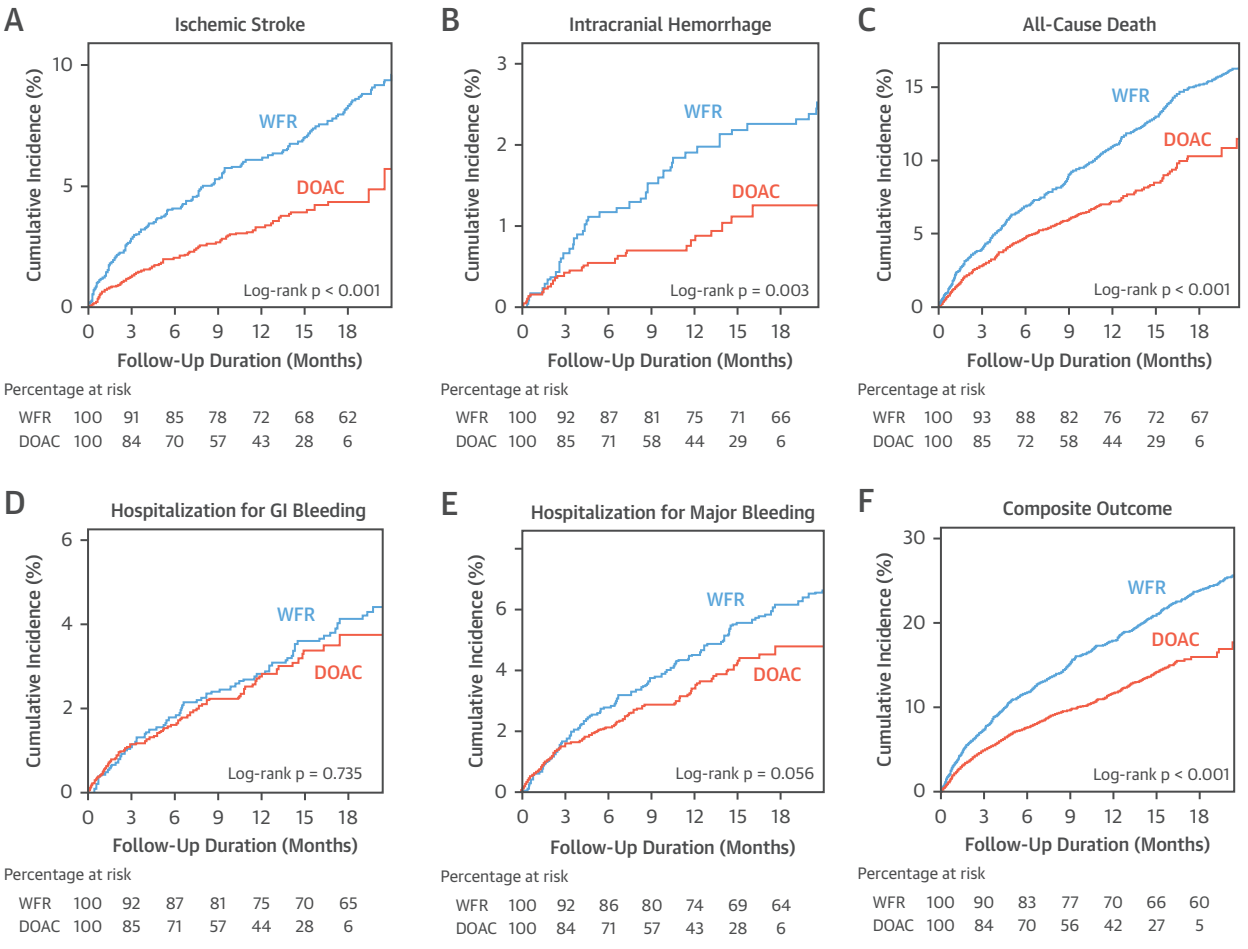
*Incidence rate was calculated based on weighted number of events in weighted cohort (per 100 person-years).
DOAC = direct oral anticoagulant; GI = gastrointestinal.

Baseline characteristics between reduced and regular doses of DOACs are listed in **Table 3**. Before PS weighting, patients treated with a reduced dose of DOACs were significantly older and had higher CHA_2DS_2-VASc scores than patients treated with regular doses of DOACs. After PS weighting using a 5% trimmed IPW method, all covariates were well-balanced. In weighted cohorts, patients who received a reduced dose of DOACs showed slightly higher incidence rates of ischemic stroke in the total population, similar to patients who weighed 50 to 60 kg and <50 kg (**Table 4**). The incidence of ICH was slightly higher in patients who received a regular dose in the total population and in patients who weighed 50 to 60 kg, but not in patients who weighed <50 kg.

Figure 4 shows the HRs of the clinical outcomes for a regular dose of DOACs compared with a reduced dose of DOACs in each subgroup. In patients who weighed 50 to 60 kg, a regular dose of DOACs showed a slightly favorable trend for ischemic stroke and an unfavorable trend for ICH, but there was no statistical significance, and the net clinical benefit was almost neutral compared with a reduced dose of DOACs. Because 73% of the patients were 50 to 60 kg, the trends in the total study population followed that of patients who weighed 50 to 60 kg. In patients who weighed <50 kg, wider CIs were observed due to the small number of patients, but all 6 clinical outcomes of a regular dose of DOACs were neutral compared with a reduced dose of DOACs.

Label adherence of DOAC dosing. Patients were categorized by label adherence of DOAC dosing (Online Table 3). Of the total study population, 65.3% were prescribed on-label doses of DOACs, 30.7% were prescribed off-label underdose DOACs, and 4% were prescribed off-label overdosed DOACs. Edoxaban

FIGURE 3 Cumulative Incidence Curves of 6 Clinical Outcomes in Pooled DOAC Versus WFR in Patients With Extremely Low Body Weight (<50 kg)



Cumulative incidence curves for **(A)** ischemic stroke, **(B)** intracranial hemorrhage, **(C)** all-cause death, **(D)** hospitalization for GI bleeding, **(E)** hospitalization for major bleeding, and **(F)** composite outcome. Abbreviations as in Figures 1 and 2.

showed higher off-label overdosing rates (27.8%) than other DOACs (rivaroxaban, dabigatran, and apixaban: 1.9%, 0.2%, and 4.4%, respectively) (Online Table 8).

Patients with on-label doses of DOACs showed consistently lower crude incidence rates than that of warfarin for the 6 clinical outcomes (Online Figures 6 and 7). Patients prescribed off-label overdosed DOACs showed a higher incidence of ischemic stroke, bleeding, all-cause death, and the composite outcome compared with those with on-label doses of DOAC and even compared with those on warfarin.

Overall, an on-label dose of DOACs showed better clinical outcomes than warfarin, as shown in the main analysis (Online Figure 8). Among the 3 groups (on-label dosing, off-label underdosing, and off-label overdosing), an on-label prescription of DOACs was associated with the largest risk reduction for the composite clinical outcomes compared with warfarin, and this result was consistent even in patients who weighed <50 kg.

DOAC types. Baseline characteristics by DOAC types are shown in Online Table 9. Overall, the net clinical benefit of DOACs compared with warfarin was consistent across all types of DOACs (Online Figures 9 and 10). The number of patients prescribed edoxaban was small, which led to wide CIs and statistical nonsignificance.

DISCUSSION

To the best of our knowledge, this was the first comparison of the effectiveness and safety of warfarin and DOACs in a large nationwide AF

cohort with data on low body weight. The main findings of this study were as follows: 1) DOAC use was associated with lower risks of ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and the composite outcome in patients with low body weight (≤60 kg); 2) a consistent trend was observed in patients with extremely low body weight (<50 kg), except for hospitalization for GI bleeding; 3) a regular dose of DOACs showed comparable results to a reduced dose of DOACs; and 4) on-label DOAC prescriptions showed the best net clinical outcomes compared with (off-label) underdosed or overdosed DOACs.

Generally, DOACs resulted in comparable or better outcomes than warfarin in patients with nonvalvular AF (8). However, the anticoagulant effects of DOACs were closely related to plasma concentration, and their distribution volume was closely related to body size; therefore, body weight could affect their anticoagulant effects (27).

The published pharmacokinetics data were slightly different for each DOAC. Apixaban showed a 27% increase in the mean maximal plasma concentration (Cmax) and a 20% increase in the area under the curve, respectively, in patients who weighed <50 kg compared with those with normal body weight (19). The effect of low body weight on apixaban exposure was estimated as modest, and low body weight alone did not suffice for dose reduction (16). Thus, apixaban 5 mg twice daily was recommended for patients with isolated body weight ≤60 kg, and a reduced dose was recommended if patients were also aged 80 years or older and/or had serum creatinine ≥1.5 mg/dl (16,28). The Cmax of edoxaban increased approximately 40% in patients <60 kg (29), and a 50% dose reduction was recommended in this population (17). Although dabigatran concentration showed a 21% increase in patients who weighed <50 kg compared with those with normal weight, pharmacokinetic analysis showed that renal function had a stronger effect on drug concentrations, and dose adjustment was only recommended in patients with renal impairment (dabigatran 75 mg is recommended in the United States for CrCl of <30 ml/min) (30,31). Routine dose reductions in patients who weighed <50 kg without renal impairment were not recommended, but these patients need close clinical surveillance (32). According to the pharmacokinetics of rivaroxaban, there were no clinically relevant changes in Cmax or the area under the curve in patients who weighed <50 kg (33).

TABLE 3 Baseline Characteristics of Patients Treated With Regular Dose and Reduced Dose DOACs

	Propensity Score Weighting					
	Before			After (With 5% Trimming)		
	Reduced Dose* (n = 8,723)	Regular Dose† (n = 5,380)	ASD	Reduced Dose* (n = 7,883)	Regular Dose† (n = 4,840)	ASD
Age, yrs	75.1 ± 7.5	70.6 ± 8.2	0.564	72.6 ± 7.4	72.9 ± 8.5	<0.001
<65	8	21		10	9	
65–74	35	46		42	46	
≥75	57	33		48	45	
Men	30	31	0.027	31	31	0.001
CHA_2DS_2-VASc score	4.09 ± 1.58	3.62 ± 1.61	0.292	3.92 ± 1.64	3.97 ± 1.83	<0.001
0–1	4	8		4	4	
2–3	33	42		37	37	
≥4	63	51		59	59	
Body weight, kg	52.8 ± 5.7	53.9 ± 5.2	0.202	53.2 ± 5.5	53.2 ± 5.6	0.006
50–60	69	77		73	73	
<50 kg	31	22		27	27	
Body mass index, kg/m^2	22.3 ± 2.6	22.4 ± 2.4	0.049	22.3 ± 2.5	22.3 ± 2.5	0.002
CrCl, ml/min	78.3 ± 38.6	81.9 ± 28.6	0.103	78.9 ± 22.7	78.6 ± 20.4	0.026
Hypertension	68	65	0.056	68	67	0.006
Diabetes mellitus	18	18	0.004	19	18	0.003
Dyslipidemia	38	39	0.013	39	39	0.003
Heart failure	33	30	0.062	32	32	<0.001
Previous MI	3	3	0.031	3	3	0.010
PAD	19	18	0.037	19	19	<0.001
COPD	22	19	0.087	21	21	0.008
DOAC type						
Rivaroxaban	39	49		39	52	
Dabigatran	30	18		31	17	
Apixaban	22	27		21	26	
Edoxaban	9	6		9	5	

Values are mean ± SD or %, unless otherwise indicated. *Reduced dose DOACs are 15 or 10 mg rivaroxaban once daily, 110 mg dabigatran once daily, 2.5 mg apixaban twice daily, and 30 mg edoxaban once daily. †Regular dose DOACs are 20 mg rivaroxaban once daily, 150 mg dabigatran twice daily, 5 mg apixaban twice daily, and 60 mg edoxaban once daily.

Abbreviation as in Table 1.

Beyond pharmacokinetic evidence, clinical experience with DOACs in patients with low body weight is lacking. Patients with low body weight (≤60 kg) and extremely low body weight (<50 kg) were

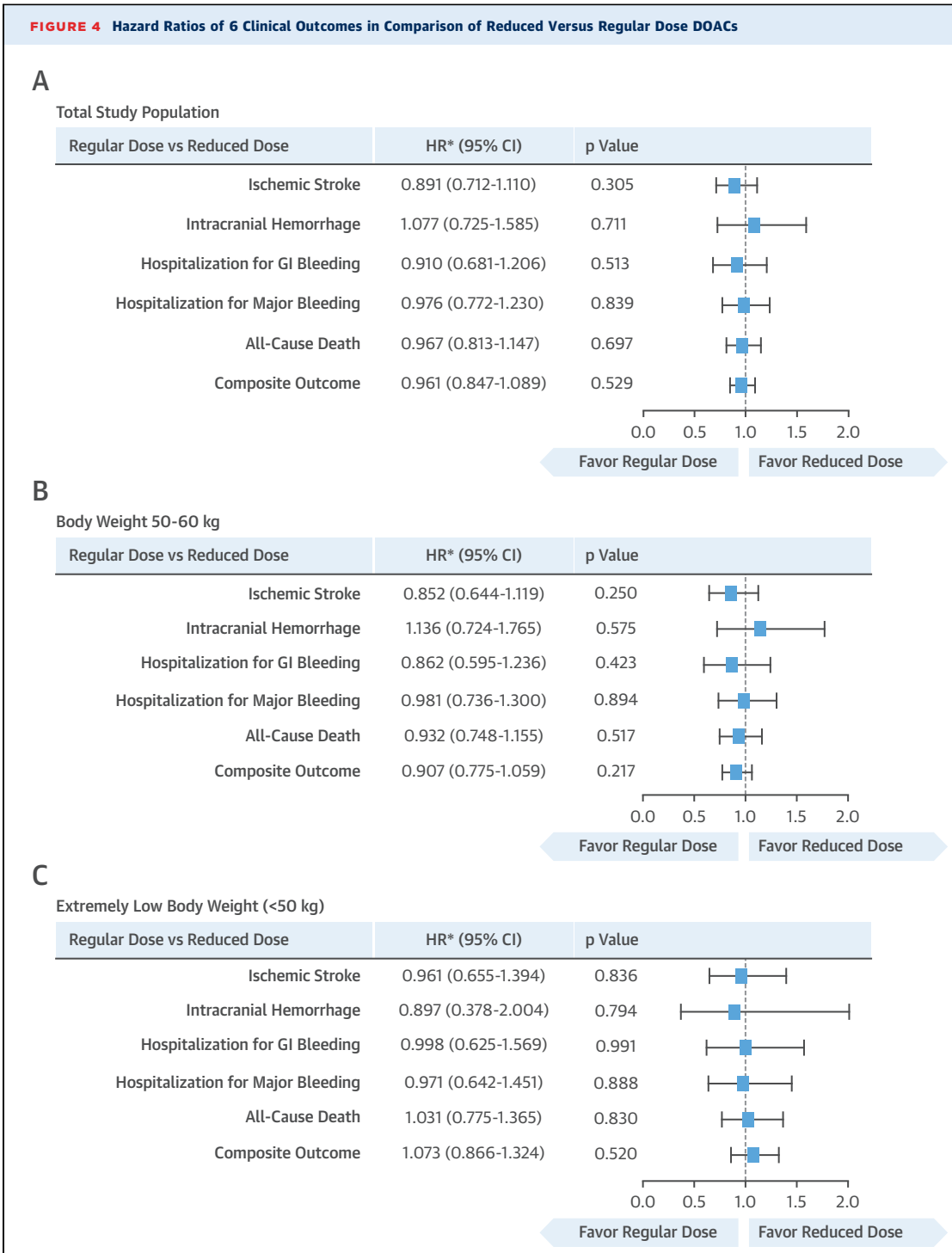
TABLE 4 Incidence Rates of 6 Clinical Outcomes During Follow-Up Period: Regular and Reduced Dose DOACs

	Incidence Rate*					
	Total		50–60 kg		<50 kg	
	Reduced	Regular	Reduced	Regular	Reduced	Regular
Ischemic stroke	3.16	2.77	2.90	2.44	3.89	3.69
Intracranial hemorrhage	0.90	0.96	0.93	1.04	0.83	0.74
Hospitalization for GI bleeding	1.88	1.69	1.63	1.39	2.54	2.50
Hospitalization for major bleeding	2.71	2.62	2.50	2.42	3.30	3.15
All-cause death	4.94	4.71	4.35	4.02	6.49	6.60
Composite outcome	9.55	9.04	8.77	7.86	11.62	12.27

*Incidence rate was calculated based on weighted number of events in weighted cohort (per 100 person-years).

Abbreviations as in Tables 1 and 2.

FIGURE 4 Hazard Ratios of 6 Clinical Outcomes in Comparison of Reduced Versus Regular Dose DOACs



The regular dose showed slightly favorable (HR directed to **Favor Regular Dose**) in ischemic stroke and unfavorable (HR directed to **Favor Reduced Dose**) in ICH, but there was no statistical significance, and net clinical benefit was almost neutral compared with the reduced dose in patients who weighed 50 to 60 kg. Because 73% of the patients were 50 to 60 kg, the trend in the total study population followed that of patients who weighed 50 to 60 kg. In patients who weighed <50 kg, wider confidence intervals (CIs) were observed due to the small number of patients, but all 6 clinical outcomes of the regular dose of DOACs were neutral compared with the reduced dose of DOACs. **(A)** Total study population. **(B)** Body weight 50 to 60 kg. **(C)** Extremely low body weight (<50 kg). *Reduced dose served as the reference.
CI = confidence interval; HR = hazard ratio; other abbreviation as in Figure 1.

under-represented in pivotal randomized clinical trials (Online Table 10) (16,17,34,35). Data were limited even for DOACs that included low body weight as a dose reduction criterion (apixaban and edoxaban) (16,17).

Low body weight is relatively common in Asian populations (≤60 kg: ~50%), and individuals frequently present with comorbidities such as old age, frailty, and renal impairment, which may increase the risk of thromboembolic and bleeding events (14). However, no data were available for patients who weighed <60 kg or <50 kg based on a large real-world AF cohort that analyzed 4 DOACs. In our study, we included 14,103 DOAC users and demonstrated that DOAC treatment was associated with better outcomes for both thromboembolic and bleeding events in patients who weighed ≤60 kg. These benefits were consistent in patients who weighed <50 kg, except for hospitalization for GI bleeding. The risk of hospitalization for GI bleeding was comparable in the DOAC and warfarin groups for patients who weighed <50 kg.

Overall, all DOACs showed similar trends in the main analysis (Online Figures 9 and 10). In patients who weighed <50 kg, rivaroxaban showed a nonsignificant trend toward an increased risk of hospitalization for GI and major bleeding compared with warfarin. Edoxaban showed neutral HRs and wide CIs in some clinical events because of the small numbers and its more recent introduction as a drug therapy. The numbers of patients treated with each DOAC were not sufficient to make definite conclusions, and edoxaban had a shorter follow-up duration than other OACs because of its recent introduction to the market. In addition, the proportion of regular or reduced doses and label adherence of DOAC dosing was not adjusted in this analysis.

When stratifying by DOAC doses, both the regular and the reduced doses of DOACs showed better outcomes than warfarin in the 6 clinical outcomes (Online Figure 5). Between the regular and reduced dose of DOACs, there was no profound differences between the 2 dose regimens in all 6 clinical outcomes (**Figure 4**). Considering label adherence by DOAC dosing, patients with off-label overdosing of DOAC showed the worst outcomes in all 6 clinical outcomes compared with those prescribed on-label dosed DOACs and even compared with those with warfarin (Online Figure 8). These findings were consistent with those of previous reports (36,37). Compared with appropriate dosing, off-label overdosing was associated with an increased risk of major bleeding or all-cause death (36,37). In addition, off-label underdosing showed an increased risk of first cardiovascular hospitalization or thromboembolic events (only in apixaban) (36,37). In our study, on-label DOAC dosing showed a larger risk reduction in all 6 clinical outcomes than off-label underdosing and overdosing compared with warfarin. Although we adopted the dosing labels from pivotal clinical trials, modified dosing labels were implemented among different countries. According to the dosing label and what the standard dose is in a particular country's approved prescribing label, it is possible the patient classification and the clinical outcomes by label adherence of DOAC dosing may be changed. The impact of off-label dosing should therefore be carefully interpreted in the context of the dosing label for each country.

STUDY LIMITATIONS. First, the quality of warfarin treatment represented as time in the therapeutic range (TTR) was not evaluated. The Korean NHIS claims database and health checkup database did not include individual data on the international normalized ratio of prothrombin time. Poor TTR control in Asian patients treated with warfarin was consistently observed in previous studies (38–40). In subanalyses of the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, although the benefit of dabigatran was consistent across wide ranges of TTR, TTR of Korean patients was significantly lower (55%) than that of total study population (64%) (41). In a recent retrospective analysis, mean TTR was reported as 50% for Korean AF patients (42). Although we could not provide TTR in our study group, the results should be carefully interpreted considering the relatively lower TTR of Asian patients. In addition, actual drug adherence could not be evaluated, which was an inherent limitation of claim data. Second, patients with a history of ischemic stroke, ICH, or GI bleeding were excluded from this study. Third, although we carefully matched the 2 study groups using the IPW method and achieved well-balanced cohorts, the possibility of residual confounding from unmeasured factors still exists. Finally, this study was designed from the claims database of the entire Korean population; therefore, the ethnic uniformity of the cohort should be considered when these results are interpreted and generalized.

CONCLUSIONS

In this real-world Asian population with nonvalvular AF and low body weight (≤60 kg), DOACs showed

better effectiveness and safety than warfarin. This result remained consistent in patients with extremely low body weight (<50 kg). Also, regular doses of DOACs showed comparable results to reduced doses of DOACs.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Compared with warfarin in patients with atrial fibrillation and low body weight, anticoagulation with target-specific oral anticoagulants was associated with net clinical benefit.

TRANSLATIONAL OUTLOOK: Studies that include a higher proportion of Asian patients are needed to confirm the generalizability of our observations.

REFERENCES

1. Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. Comparing the guidelines and practical decision-making. Thromb Haemost 2017;117:1230–9.

2. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. Lancet 2015;386:154–62.

3. Lee SR, Choi EK, Han KD, Cha MJ, Oh S. Trends in the incidence and prevalence of atrial fibrillation and estimated thromboembolic risk using the CHA_2DS_2-VASc score in the entire Korean population. Int J Cardiol 2017;236:226–31.

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

5. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? Arch Intern Med 2000;160:41–6.

6. Lip GY, Wang KL, Chiang CE. Non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in Asian patients with atrial fibrillation: time for a reappraisal. Int J Cardiol 2015;180:246–54.

7. Lee SR, Choi EK, Han KD, Cha MJ, Oh S, Lip GYH. Temporal trends of antithrombotic therapy for stroke prevention in Korean patients with nonvalvular atrial fibrillation in the era of non-vitamin K antagonist oral anticoagulants: a nationwide population-based study. PLoS One 2017;12:e0189495.

8. 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.

9. Pan WH, Flegal KM, Chang HY, Yeh WT, Yeh CJ, Lee WC. Body mass index and obesity-related metabolic disorders in Taiwanese and US whites and blacks: implications for definitions of overweight and obesity for Asians. Am J Clin Nutr 2004;79:31–9.

10. De Caterina R, Lip GYH. The non-vitamin K antagonist oral anticoagulants (NOACs) and extremes of body weight-a systematic literature review. Clin Res Cardiol 2017;106:565–72.

11. Park CS, Choi EK, Kim HM, Lee SR, Cha MJ, Oh S. Increased risk of major bleeding in underweight patients with atrial fibrillation who were prescribed non-vitamin K antagonist oral anticoagulants. Heart Rhythm 2017;14:501–7.

12. Song SO, Jung CH, Song YD, et al. Background and data configuration process of a nationwide population-based study using the Korean national health insurance system. Diabetes Metab J 2014;38:395–403.

13. Cha MJ, Choi EK, Han KD, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation. Stroke 2017;48:3040–8.

14. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH. Edoxaban in Asian patients with atrial fibrillation: effectiveness and safety. J Am Coll Cardiol 2018;72:838–53.

15. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation. Chest 2010;137:263–72.

16. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981–92.

17. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093–104.

18. Rocca B, Fox KAA, Ajjan RA, et al. Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis. Eur Heart J 2018;39:1672–86.

19. Upreti VV, Wang J, Barrett YC, et al. Effect of extremes of body weight on the pharmacokinetics, pharmacodynamics, safety and tolerability of apixaban in healthy subjects. Br J Clin Pharmacol 2013;76:908–16.

20. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med 2014;33:1242–58.

21. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661–79.

22. Heinze G, Jüni P. An overview of the objectives of and the approaches to propensity score analyses. Eur Heart J 2011;32:1704–8.

23. Elze MC, Gregson J, Baber U, et al. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. J Am Coll Cardiol 2017;69:345–57.

24. McMurry TL, Hu Y, Blackstone EH, Kozower BD. Propensity scores: methods, considerations, and applications in the Journal of Thoracic and Cardiovascular Surgery. J Thorac Cardiovasc Surg 2015;150:14–9.

25. Imai K, King G, Stuart EA. Misunderstandings between experimentalists and observationalists about causal inference. J Roy Stat Soc: Ser A 2008;171:481–502.

26. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28:3083–107.

27. Scaglione F. New oral anticoagulants: comparative pharmacology with vitamin K antagonists. Clin Pharmacokinet 2013;52:69–82.

28. Alexander JH, Andersson U, Lopes RD, et al. Apixaban 5 mg twice daily and clinical outcomes in patients with atrial fibrillation and advanced age, low body weight, or high creatinine: a secondary analysis of a randomized clinical trial. JAMA Cardiol 2016;1:673–81.

29. Yin OQ, Tetsuya K, Miller R. Edoxaban population pharmacokinetics and exposure-response analysis in patients with non-valvular atrial fibrillation. Eur J Clin Pharmacol 2017;70:1339–51.

30. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-

Term Anticoagulation Therapy). J Am Coll Cardiol 2014;63:321–8.

31. Liesenfeld KH, Lehr T, Dansirikul C, et al. Population pharmacokinetic analysis of the oral thrombin inhibitor dabigatran etexilate in patients with non-valvular atrial fibrillation from the RE-LY trial. J Thromb Haemost 2011;9:2168–75.

32. Ingelheim Boehringer. Summary of product characteristics. Pradaxa. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000829/WC500041059.pdf. Accessed August 23, 2018.

33. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Body weight has limited influence on the safety, tolerability, pharmacokinetics, or pharmacodynamics of rivaroxaban (BAY 59-7939) in healthy subjects. J Clin Pharmacol 2007;47:218–26.

34. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51.

35. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883–91.

36. 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.

37. 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.

38. Oh S, Goto S, Accetta G, et al. Vitamin K antagonist control in patients with atrial fibrillation in Asia compared with other regions of the world: real-world data from the GARFIELD-AF registry. Int J Cardiol 2016;223:543–7.

39. 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.

40. Chiang CE, Wang KL, Lip GY. Stroke prevention in atrial fibrillation: an Asian perspective. Thromb Haemost 2014;111:789–97.

41. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalized ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010;376:975–83.

42. Hong KS, Kim YK, Bae HJ, et al. Quality of anticoagulation with warfarin in Korean patients with atrial fibrillation and prior stroke: a multicenter retrospective observational study. J Clin Neurol 2017;13:273–80.

KEY WORDS atrial fibrillation, direct oral anticoagulant, low body weight, nonvitamin K antagonist oral anticoagulants, warfarin

APPENDIX For supplemental figures and tables, please see the online version of this paper.