**Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Non-Valvular Atrial Fibrillation and Low Body Weight**

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**Short title:** NOAC in AF with low body weight

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**Abstract**

**Background:** It is unclear whether theoveralleffectiveness and safety of non-vitamin K oral antagonist anticoagulants (NOACs) are consistent in patients with non-valvular atrial fibrillation (AF) and extremely low body weight (<50 kg).

**Objectives:** To compare NOACs 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 treated with OAC (n=14,013 taking NOACs and n=7,576 taking warfarin) were included and analyzed ischemic stroke, intracranial hemorrhage (ICH), gastrointestinal bleeding, major bleeding, all-cause death, and composite outcome. The propensity score weighting was used to balance the two groups.

**Results:** Baseline characteristics were well balanced between the two groups (mean age 73 years, mean CHA2DS2-VASc score 4, and 28% of patients weighed <50 kg). NOACs were associated with lower risks of ischemic stroke (hazard ratio (HR) 0.591, 95% confidence interval (CI) 0.510–0.686) and major bleeding (HR 0.705, 95% CI 0.601–0.825), induced by a reduction in ICH (HR 0.554, 95% CI 0.429–0.713) than warfarin. NOAC improved net clinical benefit compared to warfarin (HR for composite outcome 0.660, 95% CI 0.606-0.717), and this was consistent in patients weighed <50 kg (HR for composite outcome 0.665, 95% CI 0.581-0.762).

**Conclusion:** In this real-world Asian AF population with low body weight, NOACs showed better effectiveness and safety than warfarin. These results were consistent in patients with extremely low body weight. Regular dose of NOACs showed comparable results as reduced dose of NOACs in both effectiveness and safety.

**Condensed Abstract**

We compared NOACs with warfarin in AF patients with low body weight (≤60 kg) (n=14,013 taking NOACs and n=7,576 taking warfarin). In this real-world Asian AF population with low body weight, NOAC was associated with lower risks of ischemic stroke, major bleeding, and all-cause death than warfarin. These results were consistently observed in patients with extremely low body weight (<50 kg). Both regular and reduced doses of NOACs had an improved net clinical benefit compared to warfarin; regular dose of NOACs showed comparable results as reduced dose NOACs in both effectiveness and safety.

**Keywords:** Atrial fibrillation, non-vitamin K antagonist oral anticoagulants, warfarin, low body weight

**ABBREVIATIONS and ACRONYMS**

AF = atrial fibrillation

ASD = absolute standardized difference

CI = confidence interval

CrCl = creatinine clearance

GI = gastrointestinal

HR = hazard ratio

ICH = intracranial hemorrhage

NHIS = National Health Insurance System

NOAC = non-vitamin K antagonist oral anticoagulant

OAC = oral anticoagulant

**Introduction**

Oral anticoagulation (OAC) therapy is the most fundamental treatment for patients with atrial fibrillation (AF) by preventing ischemic stroke and reducing 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 decades, warfarin was the only available OAC for these patients, but it was largely underutilized owing to its narrow therapeutic range, the need for frequent monitoring, and concerns about bleeding complications, such as intracranial hemorrhage (ICH) (5-7). Since the introduction of non-vitamin K antagonist oral anticoagulants (NOACs), which are convenient, safe, and effective alternatives to warfarin, OAC use has become more widespread (3,4,8).

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 NOACs 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 NOACs (10). Although NOACs have shown better net clinical benefits than warfarin, mainly due to a reduction in ICH, being underweight was associated with an increased risk of major bleeding in patients taking NOACs (11). It has not been established whether NOACs have similar benefits in patients with low body weight, especially those with extremely low body weight (<50 kg). In this nationwide cohort study, we aimed to compare the effectiveness and safety of NOACs with those of warfarin in patients with non-valvular 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 approximately 50 million entire Korean population) and the National Health Insurance Corporation Health checkup database. Briefly, the Korean NHIS database includes subjects’ demographic information, prescription dispensing records, 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 Korea NHIS database has been 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 non-valvular AF treated with warfarin or NOACs (rivaroxaban, dabigatran, apixaban, or edoxaban). We identified 263,263 patients who had ≥1 pharmacy claim for warfarin or NOACs during identification period (from January 1, 2013 to December 31, 2016) and excluded the patients prescribed any OAC before January 1, 2014 for only including new-user of index OAC. We excluded patients with valvular AF, end-stage renal disease, those under 20 years old, and those who had alternative indications for OAC treatment, such as 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 (COPD), and prior myocardial infarction (MI)) were evaluated. Comorbidities were defined by diagnosis codes, prescription records, and inpatient/outpatient hospital visits within 1 year prior to the index date (Online Table 1). The CHA2DS2-VASc score was calculated by assigning 2 points each for ≥75 years old and prior stroke/transient ischemic attack/systemic thromboembolism and 1 point each for age 65-74 years, female sex, congestive heart failure, hypertension, diabetes, and vascular disease (PAD or prior MI) (15). We also analyzed patients’ body weight, body mass index (BMI), and renal function calculated by creatinine clearance (CrCl) using the Cockcroft-Gault method.

**Definitions**

We included patients with a body weight of ≤60 kg, as low body weight thresholds are often used to define underweight in randomized clinical trials (RCTs) (16-18). Additionally, body weight ≤60 kg was a clinical indication for dose reduction with apixaban (if age ≥80 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 NOACs and warfarin, including ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and composite outcome (ischemic stroke + ICH + 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 warfarin or NOAC use. To assess the 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 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 NOAC 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 two treatment groups, inverse probability weighting (IPW) analysis was used regarding time-to-event analyses by using stabilized weights calculated from PS (21). Because the sample sizes of two treatments were different, IPW was used rather than PS matching not to lose whole study population and keep generalizability. IPW uses the whole dataset, assigns inverse probability of received treatment weighting by applying corresponding to 1/PS for patients in the treated cohort and [1/(1-PS)] for those in the control cohort, and generates a pseudopopulation with almost perfect-covariate balance between the two 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 and 95th percentile of the weights (23). After IPW with trimming, the balance of covariates between the two 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%) indicates that the two 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 (PY) at risk. The risk of six clinical outcomes for pooled NOAC versus warfarin (reference) was obtained using a 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), subgroup analysis was conducted, and patients were categorized by body weight (<50 kg and 50-60 kg). The balance of covariates between the warfarin and NOAC 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, NC, USA).

**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 PS calculation were included for multivariable adjustment: age, sex, CHA2DS2-VASc score, hypertension, diabetes, dyslipidemia, congestive heart failure, PAD, prior MI, COPD, body weight, and CrCl. Also, we performed IPW without trimming for sensitive analysis.

**Subgroup analyses**

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

Regular dose NOACs 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 of NOAC dosing, patients were categorized as follows: dosing consistent with label (on-label), off-label underdosed, and off-label overdose, according to the approved dose criteria. Dose reduction criteria were specific to each NOAC based on patient baseline characteristics (Online Table 3). Because there were some differences in dosing label among different countries, we applied the criteria used in pivotal clinical trials which was generally consistent with approved drug labelling in Korea during study period. Patients for whom a selected NOAC 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 NOACs (n=14,103) were included. In the pooled NOAC group, 43% of patients received rivaroxaban, 26% received dabigatran, 24% received apixaban, and 8% received edoxaban. Before PS weighting, patients treated with NOACs were older, had slightly higher BMI, and showed lower prevalence of heart failure than those treated with warfarin (Table 1). After PS weighting, the warfarin and NOAC groups were well balanced in all variables (all ASDs <0.1%) (Table 1 and Online Figure 1). The mean age was 73 years, and the mean CHA2DS2-VASc score was 4. In both the warfarin and NOAC groups, 28% of patients weighed 50 kg. In the NOAC group, 60% of patients received reduced dose NOACs.

**Clinical outcomes in patients weighing ≤60 kg**

The cumulative incidence curves of six clinical outcomes are shown in Figure 2 and hazard ratios (HRs) of NOAC treatment with warfarin as the reference are summarized in Central Illustration. The incidence rates of all outcomes during a median of 1.2 years (interquartile range, 0.6-1.7 years) were summarized in Table 2. Compared to warfarin, NOAC was associated with a 41% lower risk of ischemic stroke (HR: 0.591, 95% confidence interval (CI): 0.510-0.686, p<0.001). Compared to warfarin, NOAC use was associated with a 30% reduction in the risk of major bleeding (HR: 0.705, 95% CI: 0.601–0.825, p<0.001), mainly driven by a reduction in ICH (HR: 0.554, 95% CI: 0.429–0.713, p<0.001). For hospitalization due to GI bleeding, NOAC treatment was associated with a lower risk than warfarin (HR: 0.816, 95% CI: 0.668–0.996, p=0.045). NOAC use was associated with a 30% lower risk of all-cause death (HR: 0.705, 95% CI: 0.630–0.789, p<0.001) and an improved net clinical benefit compared to warfarin (HR for composite outcome: 0.660, 95% CI: 0.606–0.717, p<0.001). On-treatment analysis showed the similar trends with main results across all six clinical outcomes (Online Table 4 and Online Figure 2). The benefit of NOAC compared to 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 two study groups in each subgroup categorized by body weight. The NOAC and warfarin groups were well balanced in all variables (all ASDs of <0.1) in each subgroup (Online Table 5). Patients weighing <50 kg were older, more likely to be women, and had higher CHA2DS2-VASc scores than patients weighing 50-60 kg (Online Table 5). The proportion of reduced dose NOAC prescription was higher in patients weighing <50 kg than in patients weighing 50-60 kg (67% vs. 58%). In general, patients weighing <50 kg showed higher incidences of all six clinical outcomes than patients weighing 50-60 kg (Table 2). Central Illustration summarizes the HRs of the clinical outcomes for NOACs compared to warfarin in each subgroup.

In both subgroups, NOACs showed consistently better outcomes than warfarin for ischemic stroke, ICH, hospitalization for major bleeding, all-cause death, and composite outcome (Central Illustration). Although NOACs showed outcomes comparable to those of warfarin for hospitalization for GI bleeding in patients weighing <50 kg, the NOAC group was associated with a lower risk of major bleeding and improved net clinical benefit. The cumulative incidence curves for the six clinical outcomes are presented in Online Figure 3 and Figure 3.

**Sensitivity analysis**

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

**Subgroup analyses**

*(a) NOAC doses: regular dose vs. reduced dose*

Among NOAC users, 8,723 (61.9%) patients used reduced dose. Among patients weighing <50 kg, 2,704 (68.3%) NOAC users were prescribed reduced dose NOACs (Online Table 6). The results for six clinical outcomes were consistent across regular and reduced doses of NOACs (Online Figure 5).

Baseline characteristics between reduced and regular doses NOACs are summarized in Table 3. Before propensity score weighting, patients treated with reduced dose NOACs were significantly older and had higher CHA2DS2-VASc score than patients treated with regular dose NOACs. After propensity score weighting using a 5% trimmed IPW method, all covariates were well balanced. In weighted cohorts, patients with reduced dose NOACs showed slightly higher incidence rates of ischemic stroke in the total population, patients weighing 50-60 kg, and <50 kg (Table 4). The incidence of ICH was slightly higher in patients with regular dose in the total population and in patients weighing 50-60 kg, but not in patients weighing <50 kg.

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

*(b) Label adherence of NOAC dosing*

Patients were categorized by label adherence of NOAC dosing (Online Table 3). Of the total study population, 65.3% were prescribed on-label dosed NOAC, 30.7% were prescribed off-label underdosed NOAC, and 4% were prescribed off-label overdosed NOAC. Edoxaban showed a higher off-label overdosing rate (27.8%) than other NOACs (rivaroxaban, dabigatran, and apixaban: 1.9%, 0.2%, and 4.4%, respectively) (Online Table 7).

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

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

*(c) NOAC types*

Baseline characteristics by NOAC types are shown in Online Table 8. Overall, the net clinical benefit of NOAC compared to warfarin was consistent across all type of NOACs (Online Figures 9 and 10). The number of patients prescribed edoxaban was small, leading to wide confidence intervals and statistical non-significance.

**Discussion**

To the best of our knowledge, this is the first comparison of the effectiveness and safety of warfarin and NOACs in a large nationwide AF cohort with data on low body weight. The main findings of this study are as follows: (1) NOAC use was associated with lower risks of ischemic stroke, ICH, hospitalization for GI bleeding, hospitalization for major bleeding, all-cause death, and 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) regular dose NOAC showed comparable results as reduced dose of NOAC; and (4) on-label NOAC prescription showed the best net clinical outcomes compared to (off-label) underdosing or overdosing NOAC.

Generally, NOACs resulted in comparable or better outcomes than warfarin in patients with non-valvular AF (8). However, the anticoagulant effect of NOACs is closely related to plasma concentration, and their distribution volume is closely related to body size; therefore, body weight could affect their anticoagulant effect (27).

The published pharmacokinetics data are slightly different for each NOAC. Apixaban shows a 27% and 20% increase of mean maximal plasma concentration (Cmax) and the area under the curve (AUC), respectively, in patients weighing <50 kg compared to those with normal body weight (19). The effect of low body weight on apixaban exposure is estimated as modest, and low body weight alone does not suffice for dose reduction (16). Thus, apixaban 5 mg twice daily is recommended for patients with isolated body weight ≤60 kg, and reduced dose if patients are also ≥80 years old and/or have serum creatinine ≥1.5 mg/dL (16,28). Edoxaban Cmax increases approximately 40% in patients <60 kg (29), and a 50% dose reduction is recommended in this population (17). Although dabigatran concentration shows a 21% increase in patients weighing <50 kg compared to those of normal weight, pharmacokinetic analysis shows that renal function has a stronger effect on drug concentrations, and dose adjustment is only recommended in patients with renal impairment (dabigatran 75 mg is recommended in the USA for creatinine clearance <30 mL/min) (31,31). Patients weighing <50 kg without renal impairment are not recommended to have routine dose reduction but need close clinical surveillance (32). According to the pharmacokinetics of rivaroxaban, there are no clinically relevant changes in Cmax or AUC in patients weighing <50 kg (33).

Beyond pharmacokinetic evidence, clinical experience with NOACs in patients with low body weight is lacking. Patients with low body weight (≤60 kg) and extremely low body weight (<50 kg) were under-represented in pivotal RCTs (Online Table 9) (16,17,34,35). Data were limited even for NOACs 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: approximately 50%)and frequently presents with comorbidities such as old age, frailty, and renal impairment, which may increase the risk of thromboembolic and bleeding events (14). However, no data are available for patients <60 kg or <50 kg based on a large real-world AF cohort including four NOACs. In our study, we included 14,103 NOAC users and demonstrated that NOAC treatment was associated with better outcomes for both thromboembolic and bleeding events in patients weighing ≤60 kg. These benefits were consistent in patients weighing <50 kg except for hospitalization for GI bleeding. The risk of hospitalization for GI bleeding was comparable for NOAC and warfarin groups in patients weighing <50 kg.

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

When stratifying by NOAC doses, both regular and reduced dose NOACs showed better outcomes than warfarin in six clinical outcomes (Online Figure 5). Comparison between regular and reduced dose NOACs, there was no profound differences between the two dose regimens in all six clinical outcomes (Figure 4). Considering label adherence by NOAC dosing, patients with off-label overdosing of NOAC showed the worst outcomes in all six clinical outcomes compared to those prescribed on-label dosed NOAC and even compared to those with warfarin (Online Figure 8). These findings were consistent with those of previous reports (36,37). Compared to appropriate dosing, off-label overdosing was associated with an increased risk of major bleeding or all-cause death (36,37). Additionally, off-label underdosing showed an increased risk of first cardiovascular hospitalization or thromboembolic events (only in apixaban) (36,37). In our study, on-label NOAC dosing showed a larger risk reduction in all six clinical outcomes than off-label underdosing and overdosing when compared to warfarin. Although we adopted dosing label from pivotal clinical trials, modified dosing label were implemented among different countries. According to 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 NOAC dosing could be changed. The impact of off-label dosing should therefore be carefully interpreted in a context of each countries’ dosing label.

**Study limitations**

There are several limitations to this study. 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 international normalized ratio of prothrombin time. Poor TTR control in Asian patients treated with warfarin was consistently observed in previous studies (38-40). In sub-analyses of RE-LY trial, even though 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. Additionally, actual drug adherence could not be evaluated, an inherent limitation of claim data. Second, patients with prior history of ischemic stroke, ICH, or GI bleeding were excluded from this study. Third, although we carefully matched two study groups using the IPW method and achieved well-balanced cohorts, the possibility of residual confounding from unmeasured factors still exists. Lastly, this study was designed from the claims database of entire Korean population, therefore, the ethnic uniformity of the cohort should be considered when this result was interpreted and generalized.

**Conclusions**

In this real-world Asian population with non-valvular AF and low body weight (≤60 kg), NOACs showed better effectiveness and safety than warfarin. This result remained consistent in patients with extremely low body weight (<50 kg). Also, regular dose NOACs showed comparable results as reduced dose NOACs.

**Clinical Perspectives**

**Competency in Medical Knowledge 1:** Thiswas the first population-based study to demonstrate the effectiveness and safety of NOACs compared with warfarin in AF patients with low body weight. NOAC improved net clinical benefit both in patients with low (≤60 kg) and extremely low (<50 kg) body weight.

**Translational Outlook:** Further study including more Asian patients will be needed to confirm the findings of this study regarding the effectiveness and safety NOAC across the subgroups.

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**Figure legends**

**Central Illustration. Hazard ratios of six clinical outcomes in NOAC versus warfarin (reference) groups in total study population and in subgroup patients with 50-60 kg and <50 kg.**

Compared to warfarin user as the reference, NOACs were associated with lower risks of ischemic stroke (HR 0.591, 95% CI 0.510–0.686), major bleeding (HR 0.705, 95% CI 0.601–0.825), driven by a reduction in ICH (HR 0.554, 95% CI 0.429–0.713) and a lower risk of all-cause death (HR 0.705, 95% CI 0.630-0.789). NOAC use showed improved net clinical benefit compared to warfarin (HR for composite outcome 0.660, 95% CI 0.606-0.717), and this was consistent in patients weighed <50 kg (HR for composite outcome 0.665, 95% CI 0.581-0.762). CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant.

**Figure 1. Study population enrollment flow**

From a total of 135,939 new users of OAC from January 2014, 7,576 warfarin users and 14,103 NOAC users were included in this study. AF = atrial fibrillation; ESRD = end-stage renal disease; GI = gastrointestinal; ICH = intracranial hemorrhage; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation.

**Figure 2. Cumulative incidence curves of six clinical outcomes in pooled NOAC versus warfarin in total study population (≤ 60kg)**

Compared with warfarin, NOACs carried significantly lower risks for ischemic stroke, major bleeding, all-cause death, and composite outcome. (A) ischemic stroke, (B) intracranial hemorrhage, (C) all-cause death, (D) hospitalization for GI bleeding, (E) hospitalization for major bleeding, and (F) composite outcome. GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; WFR, warfarin.

**Figure 3. Cumulative incidence curves of six clinical outcomes in pooled NOAC versus warfarin in patients with extremely low body weight (<50 kg)**

(A) ischemic stroke, (B) intracranial hemorrhage, (C) all-cause death, (D) hospitalization for GI bleeding, (E) hospitalization for major bleeding, and (F) composite outcome. GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant; WFR, warfarin.

**Figure 4. Hazard ratios of six clinical outcomes in comparison of reduced versus regular dose NOACs**

Regular dose slightly showed favorable in ischemic stroke and unfavorable in ICH, but there was no statistical significance and net clinical benefit was almost neutral compared with reduced dose in patients weighing 50-60 kg. As 73% of the patients were 50-60kg, the trend in total study population followed that of patients with 50-60 kg. In patients weighing <50 kg, wider CI was observed due to small number of patients, but all six clinical outcomes of regular dose NOACs were neutral compared with reduced dose NOACs. CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant.

**Table 1. Baseline characteristics of patients using warfarin versus NOACs**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Propensity Score Weighting** | | | | | | |
|  | **Before** | | |  | **After (with 5% trimming)** | | |
|  | **NOACs**  **(n=14,103)** | **Warfarin**  **(n=7,575)** | **ASD** |  | **NOACs**  **(n=12,810)** | **Warfarin**  **(n=6,692)** | **ASD** |
| **Age, years** | 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 |
| **CHA2DS2-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 kg** | 72 | 72 |  |  | 72 | 72 |  |
| **<50 kg** | 28 | 28 |  |  | 28 | 28 |  |
| **Body mass index, kg/m2** | 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 |
| **Prior 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 |
| **NOAC dose** |  |  |  |  |  |  |  |
| **Regular dose\*** | 38 | - | - |  | 40 | - | - |
| **Reduced dose†** | 62 | - | - |  | 60 | - | - |

Values are mean ± standard deviation or %.

\*Regular dose NOACs are 20 mg rivaroxaban once daily, 150 mg dabigatran twice daily, 5 mg apixaban twice daily, and 60 mg edoxaban once daily. †Reduced dose NOACs are 15/10 mg rivaroxaban once daily, 110 mg dabigatran once daily, 2.5 mg apixaban twice daily, and 30 mg edoxaban once daily.

Abbreviation: ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; IQR, interquartile range; MI, myocardial infarction; PAD, peripheral artery disease; SD, standard deviation.

**Table 2. Incidence rates of six clinical outcomes during follow-up period**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Total** | |  | **50-60 kg** | |  | **<50 kg** | |
| **Incidence rate\*** | |  | **Incidence rate\*** | |  | **Incidence rate\*** | |
| **NOAC** | **Warfarin** |  | **NOAC** | **Warfarin** |  | **NOAC** | **Warfarin** |
| **Ischemic stroke** | 2.82 | 4.13 |  | 2.82 | 3.56 |  | 2.82 | 5.72 |
| **Intracranial hemorrhage** | 0.92 | 1.39 |  | 0.92 | 1.32 |  | 0.92 | 1.55 |
| **Hospitalization for GI bleeding** | 1.79 | 1.77 |  | 1.79 | 1.58 |  | 1.79 | 2.26 |
| **Hospitalization for major bleeding** | 2.67 | 3.09 |  | 2.67 | 2.85 |  | 2.67 | 3.74 |
| **All-cause death** | 5.09 | 6.66 |  | 5.09 | 5.44 |  | 5.09 | 9.92 |
| **Composite outcome** | 9.37 | 12.2 |  | 9.37 | 10.5 |  | 9.37 | 16.8 |

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

Abbreviation: GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant

**Table 3. Baseline characteristics of patients treated with regular dose and reduced dose NOACs**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **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, years** | 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 |
| **CHA2DS2-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 kg** | 69 | 77 |  |  | 73 | 73 |  |
| **<50 kg** | 31 | 22 |  |  | 27 | 27 |  |
| **Body mass index, kg/m2** | 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 |
| **Prior 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 |
| **NOAC type** |  |  |  |  |  |  |  |
| **Rivaroxaban** | 39 | 49 |  |  | 39 | 52 |  |
| **Dabigatran** | 30 | 18 |  |  | 31 | 17 |  |
| **Apixaban** | 22 | 27 |  |  | 21 | 26 |  |
| **Edoxaban** | 9 | 6 |  |  | 9 | 5 |  |

Values are mean ± standard deviation or %.

\*Regular dose NOACs are 20 mg rivaroxaban once daily, 150 mg dabigatran twice daily, 5 mg apixaban twice daily, and 60 mg edoxaban once daily. †Reduced dose NOACs are 15/10 mg rivaroxaban once daily, 110 mg dabigatran once daily, 2.5 mg apixaban twice daily, and 30 mg edoxaban once daily.

Abbreviation: ASD, absolute standardized difference; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; IQR, interquartile range; MI, myocardial infarction; PAD, peripheral artery disease; SD, standard deviation.

**Table 4. Incidence rates of six clinical outcomes during follow-up period: regular and reduced dose NOACs**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Total** | |  | **50-60 kg** | |  | **<50 kg** | |
| **Incidence rate\*** | |  | **Incidence rate\*** | |  | **Incidence rate\*** | |
| **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).

Abbreviation: GI, gastrointestinal; NOAC, non-vitamin K antagonist oral anticoagulant