**Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation and Prior Gastrointestinal Bleeding**

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**Abstract**

**Background and Purpose**: Limited data support the benefits of non-vitamin K oral anticoagulants (NOACs) among atrial fibrillation (AF) patients with prior gastrointestinal bleeding (GIB). We aimed to evaluate the effectiveness and safety of NOACs compared to those of warfarin among AF patients with prior GIB.

**Methods**: Oral-anticoagulant-naïve individuals with AF and prior GIB between January 2010 to April 2018 were identified from the Korean claims database. NOAC users were compared with warfarin users by balancing covariates using the inverse probability of treatment weighting (IPTW) method. The primary outcomes were ischemic stroke, major bleeding, and the composite outcome (combined ischemic stroke and major bleeding). Fatal events from each outcome were evaluated as secondary outcomes.

**Results**: A total of 42,048 patients were included (24,781 in the NOAC group and 17,267 in the warfarin group). The mean time from prior GIB to the initiation of OAC was 3.1±2.6 years. After IPTW, baseline characteristics were balanced between the two groups (mean age: 72 years; male: 57%; and mean CHA2DS2-VASc score: 4). Lower risks of ischemic stroke, major bleeding, and the composite outcome were associated with NOAC use than with warfarin use [weighted hazard ratio (HR) 0.608, 95% confidence interval (CI) 0.543-0.680; HR 0.731, 95% CI 0.642-0.832; and HR 0.661, 95% CI 0.606-0.721, respectively]. For all secondary outcomes, NOACs showed greater risk reductions compared with warfarin.

**Conclusions:** NOACs were associated with lower risks of ischemic stroke and major bleeding than warfarin among AF patients with prior GIB.

**Non-standard Abbreviations and Acronyms**

AF: atrial fibrillation

ASD: absolute standardized difference

CI: confidence interval

GIB: gastrointestinal bleeding

HR: hazard ratio

ICH: intracranial hemorrhage

IPTW: inverse probability treatment weighting

NOAC: non-vitamin K antagonist oral anticoagulant

NSAID: non-steroidal anti-inflammatory drug

OAC: oral anticoagulant

PPI: proton pump inhibitor

RCT: randomized controlled trial

TTR: time in therapeutic range

**Introduction**

Oral anticoagulant (OAC) therapy is essential for the prevention of thromboembolic events in patients with atrial fibrillation (AF), and the introduction of non-vitamin K antagonist oral anticoagulants (NOACs) has facilitated uptake of thromboprophylaxis. The efficacy and safety of NOACs are well documented in several previous randomized controlled trials (RCTs) as well as real-world studies.1,2 Even in frail patients for whom OAC treatments were once thought to be risky, NOACs have demonstrated significant net clinical benefit.3-5 However, the effectiveness and safety of NOACs in AF patients at high bleeding risk have not been well documented.

Gastrointestinal bleeding (GIB) is one of the most frequent adverse events that occur during anticoagulation therapy and confers a significant health care burden.6 Previous studies have reported that NOAC use is associated with a comparable or higher risk of GIB than that noted with warfarin.7-10 Furthermore, patients with a prior history of GIB are at high risk of further bleeding events, so an optimal anticoagulation strategy is needed for this population. However, pivotal RCTs have generally excluded these patients, so there is insufficient evidence for the optimal anticoagulation therapy for AF patients with a history of GIB.11-14 The restarting of OACs may benefit the latter population, but little is known about prognoses by type of OAC. Considering that many NOACs (*i.e.*, dabigatran 150 mg bid, rivaroxaban 20 mg and edoxaban 60 mg) increase the risk of GIB by 25 to 30% compared with warfarin, the safety of NOACs is of some concern for patients with prior GIB.1,15 Despite the lack of strong evidence, current guidelines generally recommend the use of ‘optimal OAC therapy’ for patients with prior GIB.16,17 In recent International Consensus Guidelines, proton pump inhibitors (PPIs) have been recommended in patients with a previous history of ulcer bleeding requiring continued cardiovascular prophylaxis with anticoagulant therapy with or without aspirin, but with low-quality evidence.18,19

The recommended use of OACs in patients with prior GIB is of some concern especially in Asia, where AF patients appear to be at high risk of major bleeds compared to non-Asians, and many physicians tend to under-anticoagulate AF patients due to a perceived risk of bleeds.19 This reflects the relative paucity of data in Asian patients with prior GIB. Therefore, in this large nationwide Asian cohort study, we aimed to evaluate the effectiveness and safety of NOACs compared with those of warfarin in AF patients with prior GIB.

**Methods**

*Data source and study design*

Anonymized data and materials are publicly available at the Korean Health Insurance Review and Assessment (HIRA) database upon a request. This was a retrospective observational cohort study that analyzed claims data between January 2010 and April 2018 in the well-established HIRA database, which contains the medical claims of virtually the entire Korean population.20 The HIRA claims database consisted of individual demographic information and diagnoses encoded in the International Classification of Disease, Tenth Revision, Clinical Modification codes. Additionally, medical expenses, including prescriptions and procedures at both inpatient and outpatient services, were included.20

The flowchart of the study is illustrated in **Figure I**. We included AF patients with OAC prescription between January 2010 and April 2018. Among them, we excluded patients who had prescribed OACs between January 2008 and December 2009 to enroll OAC-naïve patients. Among a total of 157,833 OAC-naïve patients with AF, we selected 46,967 patients who had a history of GIB before the index treatment of OACs. GIB was defined as an event with hospitalization diagnostic codes (**Table I in the Data Supplement**). We excluded those aged less than 20 years (*n* = 13) and those with valvular AF (*n* = 2413). Those who had other indications of OACs (pulmonary thromboembolism, deep vein thrombosis, or joint replacement surgery) or those who had contraindication of NOACs (end-stage renal disease) were also excluded (*n* = 2493). Finally, a total of 42,048 patients were analyzed.

This study conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Institutional Review Board of Seoul National University Hospital (IRB No: E-1812-042-993). Informed consent was exempted since the claims database was available to the researcher in anonymized forms only.

*Covariates*

We defined the following variables as covariates: age, sex, comorbidities, and concomitant medications. Detailed definitions of comorbidities are summarized in **Table I in the Data Supplement.**2,21 The CHA2DS2-VASc score, the HAS-BLED score, and the Charlson comorbidity index were used to estimate stroke risk, bleeding risk, and the burden of comorbidities, respectively.22,23 The HAS-BLED score was calculated with all variables except for international normalized ratio and alcohol use, since they were not available from the claims database.23 The detailed method used to calculate the Charlson comorbidity index is presented in **Table II in the Data Supplement**.

*Study outcomes and follow-up*

In the patients’ follow-up period, we investigated ischemic stroke, major bleeding, and composite outcome (combined ischemic stroke and major bleeding) events to assess the comparative effectiveness and safety of warfarin versus NOACs. Major bleeding events were defined as either new occurrences of intracerebral hemorrhage (ICH) or major GIB requiring hospitalization. Detailed definitions of these outcomes are summarized in **Table I in the Data Supplement**. Secondary outcomes were defined as events resulting in death during the index hospitalization period due to primary outcomes: fatal ischemic stroke, fatal major bleeding, or death from a composite outcome. Study patients were removed at the occurrence of a clinical outcome, discontinuation of the index treatment (≥ 30-day absence of index OAC claims), or the end of the study period (April 30, 2018), whichever came first.

*Subgroup and sensitivity analyses*

Several subgroup analyses were performed to compare NOAC and warfarin users: age strata (<75 and ≥75 years), sex, selected comorbidities (hypertension, diabetes, heart failure, myocardial infarction, and renal disease), CHA2DS2-VASc scores (<3 and ≥3 points), HAS-BLED scores (<3 and ≥3 points), Charlson Comorbidity Index (<3 and ≥3 points), and concomitant medications [antiplatelet agents, PPIs, and non-steroidal anti-inflammatory drugs (NSAIDs)]. For all subgroup analyses, multivariable Cox proportional hazards models were adjusted with the same covariates as in the main analyses. A *p*-value ≤ 0.1 was considered a statistically significant indication of interaction between treatment effects and subgroup variables.

For sensitivity analyses, we compared regular dosesof NOACs (rivaroxaban 20 mg once daily, dabigatran 150 mg twice daily, apixaban 5 mg twice daily, and edoxaban 60 mg once daily) with warfarin using inverse probability of treatment weighting (IPTW). Therefore, to balance this difference in the follow-up period, we performed an additional sensitivity analysis by restricting the follow-up periods to one year or six months.24,25 Since death is in a competitive event with other clinical outcomes, we also performed competing risk analysis by setting death as a competing risk and observed how the results changed.26 To evaluate the population with longer follow-up periods, we performed additional sensitivity analysis among patients with a 6-month or longer follow-up period to evaluate whether the main results were consistent in those who had neither drug discontinuation nor any clinical outcomes during in the first 6-month.

*Statistical analyses*

The two treatment groups (pooled NOACs and warfarin) were compared after balancing the covariates with the IPTW of propensity scores.27,28 The IPTW was preferred over propensity score matching in our study because it can retain all eligible study subjects and it is more suitable to analyze between more than two treatment groups.29,30 For any covariate, the difference between the two groups was regarded as negligible if the absolute standardized difference (ASD) was ≤ 0.1.31 Weighted incidence rates in 100 person-years were compared in the two groups. For survival analysis, treatment groups and study outcomes were evaluated using the Kaplan-Meier method with the log-rank test and weighted Cox proportional hazard models. A comparison of users of the five OACs (rivaroxaban, dabigatran, apixaban, edoxaban, and warfarin) was also performed using the IPTW of propensity scores for the covariates across the five groups. Statistical significance was assumed for analyses with a two-tailed *p*-value < 0.05. All statistical analyses were performed with SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

**Results**

*Baseline characteristics*

Among a total of 42,048 OAC-treated individuals with non-valvular AF and prior GIB, 24,781 (58.9%) NOAC users and 17,267 (41.1%) warfarin users were included (**Figure I**). The mean time from prior GIB to the initiation of OAC was 3.1±2.6 years. A comparison of the baseline characteristics of the two treatment groups before IPTW is presented in **Table I**. Before IPTW, compared with warfarin users, NOAC users were significantly older (72.9±9.4 versus 69.7±11.0 years) and had higher CHA2DS2-VASc scores (3.8±1.5 versus 3.5±1.7). After IPTW, there were no significant differences in any covariates (ASDs ≤ 0.1). The weighted population had a mean age of 71.8 years, a male proportion of 56.8%, a mean CHA2DS2-VASc score of 3.7, a mean HAS-BLED score of 4.2, and a mean Charlson comorbidity index of 4.5. The IPTW distributions of the two treatment groups are presented in **Figure I in the Data Supplement**. Among NOAC users, 9629 (38.9%) patients received regular dose NOACs.

*Effectiveness and safety of NOAC versus warfarin*

During a median 0.6 years (interquartile range 0.2-1.7) of follow-up, 1426 (3.4%) ischemic strokes, 1053 (2.5%) major bleedings, and 2386 (5.7%) composite outcome events occurred. The weighted cumulative incidence curves of NOAC users showed significantly lower rates of events with NOACs compared to warfarin users for all primary outcomes (all log-rank *p*-values < 0.001) (**Figure II**). Compared with warfarin, NOAC was associated with 39%, 27%, and 34% risk reductions in ischemic stroke, major bleeding, and composite outcome, respectively [weighted hazard ratio (HR) 0.608, 95% confidence interval (CI) 0.543-0.680; HR 0.731, 95% CI 0.642-0.832; and HR 0.661, 95% CI 0.606-0.721, respectively, for all *p*-values < 0.001] (**Figure III** ).

*Fatal outcomes*

Compared with warfarin, NOACs were associated with significantly lower rates of events for all secondary outcomes (all log-rank *p*-values < 0.001, **Figure II** **in the Data Supplement** and **Table III in the Data Supplement**). Risk analysis of the fatal outcomes showed results consistent with the primary outcomes, with greater risk reductions for fatal ischemic stroke (HR 0.479, 95% CI 0.375-0.608), fatal major bleeding (HR 0.448, 95% CI 0.284-0.689), and fatal composite outcomes (HR 0.475, 95% CI 0.384-0.587) for all *p*-values < 0.001 (**Figure III**). Also, NOAC use was associated with an 18% lower risk of all-cause death compared with warfarin.

*Major bleeding: intracranial hemorrhage and recurrent gastrointestinal bleeding*

The weighted incidence rates and cumulative incidence curves for ICH, GIB, fatal ICH, and fatal GIB are illustrated in **Table III in the Data Supplement** and **Figure III in the Data Supplement**. In a weighted Kaplan-Meier survival analysis, NOAC users showed lower risk of major bleeding events compared with warfarin users except for fatal GIB (HR 0.464, 95% CI 0.346-0.618 for ICH; HR 0.827, 95% CI 0.714-0.958 for GIB; HR 0.272, 95% CI 0.144-0.479 for fatal ICH; and HR 1.152, 95% CI 0.539-2.514 for fatal GIB) (**Figure IV**).

*Details of gastrointestinal bleeding events*

We performed a detailed analysis of GIB events (**Table II**). There were no significant differences in the proportions of upper or lower GIB by OAC types. However, length of hospital stay was significantly shorter in NOAC users than in warfarin users; 6.2±5.2 versus 7.9±6.9, respectively; *p*-value <0.001. Also, the number of cases of transfusion requirements and that of endoscopic interventions were significantly lower in NOAC users than in warfarin users; 208 (60.1) versus 321 (67.0) for transfusion; 256 (74.0) versus 385 (80.4) for endoscopic intervention; *p*-value = 0.042 and 0.030 by Pearson’s chi-square test, respectively. Possibly due to the low event numbers, there was no significant difference in the number of radiologic interventions between the two treatment groups. Considering such results, the degrees of GIB presentation may have been more severe in warfarin users than in the NOAC users.

*Subgroup and sensitivity analyses*

*(a) NOAC types*

NOACs were prescribed to patients in the following proportions: 9539 (38.5%) rivaroxaban, 4358 (17.6%) dabigatran, 6404 (25.8%) apixaban, and 4480 (18.1%) edoxaban. The baseline characteristics of warfarin and the four NOACs before and after IPTW are presented in **Table IV** and **Table V in the Data Supplement**. All four NOACs had significantly lower weighted risks of all primary and secondary outcomes compared with warfarin (**Table VI, Table VII, Figure IV, and Figure V in the Data Supplement**). Among the four NOACs, edoxaban was associated with the lowest risk of ischemic stroke (HR 0.426, 95% CI 0.322-0.552) and the composite outcome (HR 0.542, 95% CI 0.446-0.652), whereas apixaban was associated with the lowest risk of major bleeding (HR 0.653, 95% CI 0.523-0.807). All NOACs had a lower risk of ICH compared with warfarin, while only dabigatran and apixaban had a lower risk of recurrent GIB compared with warfarin (HR 0.762, 95% CI 0.576-0.989 and HR 0.724, 95% CI 0.565-0.917, respectively).

*(b) Various patient subgroups*

The results of other subgroup analyses are summarized in **Tables VIII** and **Table IX in the Data Supplement**. In line with the main results, NOAC users showed a trend of lower risk of both non-fatal and fatal clinical outcomes compared with warfarin users in subgroup analyses except for the interaction between hypertension and ischemic stroke. NOACs had a lower risk of composite outcomes compared with warfarin irrespective of concomitant drug usage, including antiplatelet agents, NSAIDs, and PPI.

*(c) Sensitivity analysis*

We further evaluated patients on regular doses of NOACs that were mostly for on-label use. Baseline characteristics between users of regular doses of NOACs and warfarin are compared in **Table X in the Data Supplement**. Compared with warfarin users, regular dose NOAC users had a lower mean HAS-BLED score (4.0±1.2 versus 4.2±1.2); a lower mean Charlson comorbidity index (4.2±2.5 versus 4.6±2.7); and lower proportions of renal disease (11.4% versus 17.6%), COPD (9.4% versus 12.8%), and concomitant antiplatelet agents (19.4% versus 41.3% for aspirin, and 11.0% versus 18.6% for clopidogrel). In IPTW analysis, regular doses of NOACs were associated with lower risks of all primary and secondary outcomes except fatal GIB (**Table XI in the Data Supplement**). Regarding the duration of follow-up, both one-year and six-month follow-up durations showed results similar to the primary analysis (**Table XII** an **Table XIII in the Data Supplement**). Also, the results of competing risk analysis were in line with the primary analysis (**Table XIV in the Data Supplement**). In those with more than 6 months of follow-up, the results were consistent with the primary analysis (**Table XV in the Data Supplement**).

**Discussion**

To the best of our best knowledge, this is the first study to comprehensively compare NOACs with warfarin in patients with AF and prior GIB. Our key findings are as follows: (1) NOACs showed better results in lowering the risks for ischemic stroke, major bleeding, and the composite outcome compared with warfarin in AF patients with prior GIB; (2) NOACs were associated with lower risk of fatal clinical outcomes except for fatal GIB; and (3) several subgroup analyses, including NOAC types and dosage, showed results consistent with the main analysis.

The risk of bleeding during OAC treatment can be assessed using bleeding risk scores, such as the HAS-BLED.19,32 Physicians tend to avoid prescribing or resuming OACs after major bleeding episodes, which increases the risk of thromboembolism and all-cause mortality compared with those who subsequently restart OAC therapy.11 Therefore, current guidelines recommend resuming OAC therapy once the source of bleeding is corrected.16,17,33

GIB is the bleeding event most frequently associated with OAC therapy, and it increases both a risk of mortality and health care burden.34 Although NOACs showed favorable outcomes, especially in cases with ICH, pivotal RCTs and their meta-analyses have reported an increased risk of GIB associated with some NOACs compared with warfarin.1,8-10,35 Duration of treatment or dosage effects of NOACs could partly explain the difference in risk of GIB among different indications. Indeed, the most recent meta-analysis combining both pivotal RCTs and high-quality real-world studies reported that there was no significant difference in risk of major GIB between NOACs and conventional treatment.9 Such a discrepancy between RCTs and real-world studies may lie in the strict inclusion and exclusion criteria of RCTs, such that patients with relatively low risk of GIB likely are included in such RCTs. In line with pivotal RCTs, a recent meta-analysis based on high-quality real-world studies showed that the risk of GIB was the similar between NOACs and warfarin in patients with AF.9

Also, Asians may exhibit difference responses to NOACs in regarding the risk of GIB. Compared with warfarin, NOACs have generally better efficacy and safety in Asian patients than in non-Asians in the RCTs.36,37 Although the risk of ICH was higher for Asians on warfarin, the risk of GIB was broadly similar in Asians and non-Asians.37 Indeed, real-world data of Asians show that NOACs had a lower risk of GIB compared with warfarin.2,38 In a recent meta-analysis comparing Asians and non-Asians, NOACs reduced the risk of ischemic stroke in both populations but showed an increased risk of GIB for non-Asians only.36

Regarding individual NOACs, there are controversial results on the risk of GIB, especially for dabigatran and rivaroxaban. In meta-analyses, AF patients on dabigatran showed increased or similar risk of GIB compared with warfarin.9,10 A possible mechanism of GIB might be related to tartaric acid in dabigatran, which causes direct caustic injury and inhibits mucosal healing.39 Conversely, a standard dose (20 mg daily) of rivaroxaban was associated with an increased risk of GIB in several meta-analyses.9,10 Apixaban consistently showed a lower risk of GIB in RCTs and real-world registries.7,9 Although high-dose edoxaban showed an increased risk of GIB compared with warfarin in non-East Asian patients enrolled in the ENGAGE AF-TIMI 48 study, East Asian patients showed no significant difference in GIB between warfarin and either dose regimen of edoxaban.40 Also, a recent network analysis showed edoxaban was associated with a lower risk of GIB compared with dabigatran.8,41 In a recent real-world study, edoxaban showed a 40% lower risk of hospitalization for GIB compared with warfarin.25

Additionally, most contemporary Asian real-world data show all NOACs have a lower risk of GIB compared with warfarin, whereas apixaban, dabigatran, and edoxaban have a lower risk of GIB compared with rivaroxaban.2 In a Taiwanese nationwide population study, apixaban and edoxaban were associated with a lower risk of major GIB, whereas the risk of major bleeding was comparable.39 The high prevalence of reduced-dose prescriptions of NOACs and poor control of warfarin in Asians may justify the benefit of NOACs to GIB, especially in the Asian population. In line with previous studies, we also found that apixaban, dabigatran, and edoxaban were associated with a lower risk of clinical events than rivaroxaban in AF patients with prior GIB. However, there are no direct head-to-head clinical trial comparisons among NOACs to compare the risk of GIB, so it is difficult to draw a conclusion about which NOACs have the lowest risk of GIB. Also, most previous studies have limitations on the selection of OACs and when OAC treatment is resumed in patients with prior GIB.

*Limitations*

Several limitations of the study should be noted. First, due to the nature of retrospective observational cohort studies, our results cannot provide causal relationships, and the conclusions reflect associations that should not be overstated. Although we tried to minimize the difference between the two groups with IPTW using given 20 covariates, there might be remaining possibilities for residual confounding. Since this study was not a prospective or a controlled randomized trial, there should be some caution in interpreting the results. Second, since the HIRA claims database does not offer any laboratory data, the quality of anticoagulation control amongst those prescribed warfarin cannot be evaluated.42 Of note, the proportion of time in therapeutic range (TTR) amongst warfarin users is substantially lower in Asian countries than other regions of the world.43 Indeed, Hong et al. have reported that the mean TTR of Koreans with both AF and stroke was only 49.1% (95% CI 47.9-50.3%).44 Such a suboptimal quality of anticoagulation therapy can add to the disadvantages of warfarin compared to NOAC. Third, 60.7% of NOAC users received reduced doses, but label adherence could not be investigated due to lack of relevant information (e.g., body weight and serum creatinine levels) in the HIRA database. Such a high proportion of reduced doses of NOAC among Asians has been previously reported in various other studies.45,46 Some explanations for this trend are that Asians have a lower body mass and a higher risk of ICH than the Western population, and some physicians prefer reduced-dose prescriptions because of concerns about a higher bleeding risk in older patients. Nonetheless, according to our previous report, 95% of the prescriptions of *regular* doses of NOAC were shown to adhere to the Korean approved drug label.45 This finding suggests, compared to reduced doses, the majority of regular doses can be regarded to be label adherent. Given the above limitations of the claims database, we performed a sensitivity analysis for those with regular doses of NOAC only to focus on label-adhered data (**Table XI in the Data Supplement**), and the results were in line with the primary analysis. These results suggest that regular doses, which are considered to be mostly on-label, would be safe and effective compared to warfarin in AF patients with a previous history of GIB. However, this finding does not guarantee that off-label doses can be considered equivalent to on-label doses for AF patients with prior GIB. For example, Yu et al. have reported that off-label reduced doses may not offer safety benefits compared to on-label doses.46 Therefore, further studies are needed to investigate the association of label adherence of NOAC and clinical outcomes among AF patients with prior GIB. Fourth, the location of GIB was not identified, so it is unknown whether newly developed GIB events originated in the same or different sites. Fifth, the average time interval from GIB events to OAC treatment was about three years, so the results cannot provide evidence for patients who started OAC therapy within several weeks. Lastly, since this study mainly focused on the Asians, extrapolation of the study results to non-Asian AF patients would be cautiously managed.

**Conclusions**

In this nationwide cohort study, NOACs were associated with lower risks of ischemic stroke and major bleeding than warfarin among AF patients with prior GIB. NOACs were also associated with a lower rate of fatalities from each clinical outcome compared with warfarin. NOACs may be a better option than warfarin for stroke prevention in AF patients with prior GIB.

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**Supplemental Materials**

Online Figures I-V

Online Tables I-XV

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**Figure Legends**

**Figure I. The flowchart of the study population**

Abbreviations: AF, atrial fibrillation; DVT, deep vein thrombosis; ESRD, end stage renal disease; GIB, gastrointestinal bleeding; NOAC, non-vitamin K oral anticoagulant; OAC; oral anticoagulant; PE, pulmonary thromboembolism.

**Figure II. Weighted cumulative incidence curves of clinical outcomes in warfarin and NOAC groups**

Abbreviations: NOAC, non-vitamin K oral anticoagulant.

**Figure III. Hazard ratios of clinical outcomes in warfarin and NOAC groups**

Abbreviations: CI, confidence interval; HR, weighted hazard ratio; MB, major bleeding; NOAC, non-vitamin K oral anticoagulant; WFR, warfarin.

**Figure IV. Hazard ratios by causes of major bleeding in warfarin and NOAC groups**

Abbreviations: CI, confidence interval; GI, gastrointestinal; HR, weighted hazard ratio; ICH, intracranial hemorrhage; NOAC, non-vitamin K oral anticoagulant; WFR, warfarin.

**Table I. Baseline characteristics of warfarin and NOAC groups: before and after IPTW**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Before IPTW** |  |  |  | **After IPTW** |  |
|  | **Warfarin**  **(n=17,267)** | **Pooled NOAC**  **(n=24,781)** | **ASD** |  | **Warfarin**  **(n=17,232)** | **Pooled NOAC**  **(n=24,731)** | **ASD** |
|  |
| **Age, years** |  |  |  |  |  |  |  |
| **Mean±SD** | 69.7±11.0 | 72.9±9.4 | 0.310 |  | 71.8±10.4 | 71.8±9.9 | 0.001 |
| **Median (IQR)** | 71 (63-77) | 74 (67-79) | - |  | 73 (66-79) | 73 (66-79) | - |
| **Men** | 10,279 (59.5) | 13,659 (55.1) | 0.089 |  | 9766 (56.7) | 14,079 (56.9) | 0.005 |
| **CHA2DS2-VASc score** |  |  |  |  |  |  |  |
| **Mean±SD** | 3.5±1.7 | 3.8±1.5 | 0.195 |  | 3.7±1.6 | 3.7±1.5 | 0.003 |
| **Median (IQR)** | 4 (2-5) | 4 (3-5) | - |  | 4 (3-5) | 4 (3-5) | - |
| **0-1** | 2050 (11.9) | 1193 (4.8) | - |  | 1575 (9.1) | 1467 (5.9) | - |
| **2-3** | 6554 (38.0) | 9350 (37.7) | - |  | 6008 (34.9) | 9764 (39.5) | - |
| **≥4** | 8663 (50.2) | 14,238 (57.5) | - |  | 9684 (56.2) | 13,500 (54.6) | - |
| **HAS-BLED score\*** |  |  |  |  |  |  |  |
| **Mean±SD** | 4.2±1.2 | 4.2±1.2 | 0.007 |  | 4.2±1.2 | 4.2±1.2 | 0.004 |
| **Median (IQR)** | 4 (3-5) | 4 (3-5) | - |  | 4 (3-5) | 4 (3-5) | - |
| **≥3** | 15,822 (91.6) | 22,851 (92.2) | - |  | 15,891 (92.2) | 22,771 (92.1) | - |
| **CCI** |  |  |  |  |  |  |  |
| **Mean±SD** | 4.6±2.7 | 4.4±2.5 | 0.067 |  | 4.5±2.6 | 4.5±2.6 | 0.001 |
| **Median (IQR)** | 4 (3-6) | 4 (3-6) | - |  | 4 (3-6) | 4 (3-6) | - |
| **≥3** | 13,188 (76.4) | 18,636 (75.2) | - |  | 13,193 (76.6) | 18,874 (76.3) | - |
| **Comorbidities** |  |  |  |  |  |  |  |
| **Hypertension** | 14,998 (86.9) | 21,759 (87.8) | 0.028 |  | 15,113 (87.7) | 21,675 (87.6) | 0.002 |
| **Diabetes** | 5044 (29.2) | 7255 (29.3) | 0.001 |  | 5117 (29.7) | 7323 (29.6) | 0.002 |
| **Dyslipidemia** | 9582 (55.5) | 14,537 (58.7) | 0.064 |  | 10,026 (58.2) | 14,352 (58.0) | 0.003 |
| **Heart failure** | 7467 (43.2) | 11,660 (47.1) | 0.077 |  | 7981 (46.3) | 11,387 (46.0) | 0.005 |
| **Myocardial infarction** | 993 (5.8) | 1317 (5.3) | 0.019 |  | 967 (5.6) | 1375 (5.6) | 0.002 |
| **PAD** | 4198 (24.31) | 6578 (26.5) | 0.051 |  | 4453 (25.8) | 6394 (25.9) | <0.001 |
| **Renal disease** | 3032 (17.6) | 3781 (15.3) | 0.062 |  | 2891 (16.8) | 4118 (16.7) | 0.003 |
| **COPD** | 2201 (12.8) | 2706 (10.9) | 0.057 |  | 2054 (11.9) | 2963 (12.0) | 0.002 |
| **Cancer** | 1792 (10.4) | 2627 (10.6) | 0.007 |  | 1810 (10.5) | 2640 (10.7) | 0.006 |
| **Prior ischemic stroke** | 5039 (29.2) | 7678 (31.0) | 0.039 |  | 5336 (31.0) | 7483 (30.3) | 0.015 |
| **Prior ICH** | 414 (2.4) | 754 (3.0) | 0.040 |  | 475 (2.8) | 691 (2.8) | 0.002 |
| **Concomitant medication** |  |  |  |  |  |  |  |
| **Aspirin only** | 7130 (41.3) | 5038 (20.3) | 0.466 |  | 4922 (28.6) | 7037 (28.5) | 0.002 |
| **Clopidogrel only** | 3209 (18.6) | 3155 (12.7) | 0.162 |  | 2585 (15.0) | 3743 (15.1) | 0.004 |
| **Dual antiplatelet agent** | 2092 (12.1) | 1507 (6.1) | - |  | 1455 (8.4) | 2095 (8.5) | - |
| **NSAID** | 8781 (50.9) | 11,749 (47.4) | 0.069 |  | 8342 (48.4) | 12,000 (48.5) | 0.002 |
| **Proton pump inhibitor** | 6754 (39.1) | 10,244 (41.3) | 0.045 |  | 7022 (40.8) | 10,087 (40.8) | 0.001 |
| **NOAC dose** |  |  |  |  |  |  |  |
| **Reduced dose** | - | 15,047 (60.7) | - |  | - | 14,650 (59.2) | - |
| **Regular dose** | - | 9629 (38.9) | - |  | - | 9960 (40.3) | - |

Data are N (%), mean±SD or median (IQR). An ASD ≤0.1 indicates that the variable was well-balanced between the two treatment groups.

Abbreviations: ASD, absolute standardized difference; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; IPTW, inverse probability of treatment weighting; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; NSAID, non-steroidal anti-inflammatory drug; PAD, peripheral artery disease; SD, standard deviation.

\* Labile international normalized ratio and alcohol use could not be evaluated from claims and were excluded from scoring in this study.

**Table II. Details of recurrent gastrointestinal bleeding events according to the types of oral anticoagulants**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Total**  **(n=825)** | **Warfarin**  **(n=479)** | **NOAC**  **(n=346)** | **P-value** |
| **Upper GIB** | 732 (88.7) | 427 (89.1) | 305 (88.2) | 0.656 |
| **Lower GIB** | 93 (11.3) | 52 (10.9) | 41 (11.9) |
| **Length of hospital stay (days)** | 7.2±6.3 | 7.9±6.9 | 6.2±5.2 | <0.001 |
| **Transfusion requirement** | 529 (64.1) | 321 (67.0) | 208 (60.1) | 0.042 |
| **Endoscopic intervention** | 641 (77.7) | 385 (80.4) | 256 (74.0) | 0.030 |
| **Radiologic intervention** | 12 (1.5) | 9 (1.9) | 3 (0.9) | 0.231 |

Data are N (%) or mean±SD.

Abbreviations: GIB, gastrointestinal bleeding; NOAC, non-vitamin K antagonist oral anticoagulant.