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Predictors of Major Bleeding Among Working-Age Adults with Atrial Fibrillation: Evaluating the Effects of Potential Drug-drug Interactions and Switching from Warfarin to Non-vitamin K Oral Anticoagulants

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Abstract

Purpose—This study aims to evaluate the associations between switching from warfarin to non-vitamin K oral anticoagulants (NOACs), exposure to potential drug-drug interactions (DDIs), and major bleeding events in working-age adults with atrial fibrillation (AF).

Methods—We conducted a retrospective cohort study using the claims database of commercially insured working-age adults with AF from 2010 to 2015. Switchers were defined as patients who switched from warfarin to NOAC; non-switchers were defined as those who remained on warfarin. We developed novel methods to calculate the number and proportion of days with potential DDIs with NOAC/warfarin. Multivariate logistic regressions were utilized to evaluate the associations between switching to NOACs, exposure to potential DDIs, and major bleeding events.

Results—Among a total of 4126 patients with AF, we found a significantly lower number of potential DDIs and the average proportion of days with potential DDIs in switchers than non-switchers. The number of potential DDIs (AOR 1.14, 95% CI 1.02–1.27) and the HAS-BLED score (AOR 1.64, 95% CI 1.48–1.82) were significantly and positively associated with the

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of West Virginia University's Institutional Review Board (IRB) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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likelihood of a major bleeding event. The proportion of days with potential DDIs was also significantly and positively associated with risk for bleeding (AOR 1.42, 95% CI 1.03, 1.96). We did not find significant associations between switching to NOACs and major bleeding events.

Conclusions—The number and duration of potential DDIs and patients' comorbidity burden are important factors to consider in the management of bleeding risk in working-age AF adults who take oral anticoagulants.

Keywords

Drug-drug interactions; Atrial fibrillation; Bleeding; Switching; Non-vitamin K oral anticoagulants

Introduction

The number of atrial fibrillation (AF) diagnoses has been growing in the United States (US) and is estimated to increase to 12.1 million in 2030 [1].Adults who are 40 years of age and older have a lifetime risk of 25% to develop AF [2]. According to the most recent guidelines published by the American College of Cardiology (ACC) and the American Heart Association (AHA), AF patients with a high risk of stroke should be treated with oral anticoagulants, for example, warfarin [3], as well as non-vitamin K oral anticoagulants (NOACs) that have been approved by the US Food and Drug Administration for patients with AF since 2010 [4].

Warfarin is known to interact with numerous drugs and foods, and the list of interactions continues to expand [5]. A large number of drug-drug interactions (DDIs) with warfarin were reported to increase the international normalized ratio (INR) and risk of hemorrhage [5–8]. NOACs are also known to interact with quite a number of drugs that increase the risk of bleeding, which includes prescription medications frequently taken along with NOACs by patients with AF, such as rhythm control medications (e.g., amiodarone) [9, 10]. However, the fewer number of drug-drug and drug-food interactions are considered major advantages of NOACs, as compared with warfarin. Yet, the burden of potential DDIs with NOACs has not been well studied in patients with AF. On the other hand, current clinical guidelines thus recommend AF patients on anticoagulant therapy be evaluated for risk of bleeding using the HAS-BLED index [3, 11]. However, potential DDIs with oral anticoagulants are not included in the design of the HAS-BLED index [3]. To date, no population-based studies have investigated the burden of DDIs among patients with AF on anticoagulant therapy and the influence of DDIs on bleeding events in these patients.

In addition to a decreased risk of DDIs with NOACs, another major advantage is that NOAC users, in contrast to patients on warfarin, do not require routine blood monitoring. This may help explain why many working-age adults switch to NOACs, for example, to avoid missed time at work due to the frequent doctor visits associated with warfarin therapy. When compared to warfarin, NOACs showed the favorable or noninferior effectiveness and safety profiles in most clinical trials and recent observational studies [12–17]. A 2017 study in AF patients of all ages revealed that those who switched from warfarin to dabigatran were significantly more likely to suffer gastrointestinal (GI) bleeding, but were significantly less

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likely to experience intracranial bleeding, than persistent warfarin users [18]. However, population-based studies have not assessed safety outcomes in working-age AF patients who switch from warfarin to NOACs, known to have a lower risk of DDIs than warfarin. Therefore, the objective of this study was to evaluate the associations between switching to NOACs, exposure to potential DDIs, and major bleeding events in this population.

Methods

Conceptual Framework

To guide the study design and the selection of variables, we utilized Andersen's behavioral model for health service use [19]; this model includes (1) predisposing factors (e.g., demographics, pre-existing conditions, and other factors that may influence patient use of health care and services), (2) enabling factors (e.g., insurance and other factors related to health care access), and (3) need factors that reflect patients' disease severity and overall health condition.

Study Design

This retrospective cohort study used commercial insurance claims data between January 2010 and December 2015 to compare the incidence of major bleeding between switchers and non-switchers and to assess the influence of potential DDIs on bleeding risk. The index date was defined as the initial date of NOAC or warfarin prescription for the switcher and the non-switcher, respectively. The baseline period was defined as 183 days (6 months) prior to the index date, the assessment period was defined as 183 days after the index date, and the follow-up period was defined as 183 days following the assessment period.

Data Source

We used an adjudicated claims database of commercially insured individuals. The database includes medical, pharmacy, and enrollment data. It is similar in age and gender to the US commercially insured census population for individuals less than 65 years of age. This data is made available through a license to IQVIA's Real World Data: Adjudicated Claims - US (also known as PharMetrics Plus), 10% sample January 2006–December 2015.

Study Sample

Patients were included in our study if they (1) had the first observed oral anticoagulant date (the index date) between 2010 and 2014; (2) were diagnosed with AF; (3) were continuously enrolled in a health plan during the baseline, assessment, and the follow-up periods; and (4) were aged between 18 and 63 years at the index date (we restricted patients' age 63 to account for the 1-year follow-up period). Patients who switched to warfarin/NOACs during the assessment or follow-up period were excluded (Fig. 1).

Measures

Dependent Variable—Major bleeding events (yes/no) during the follow-up period were identified by at least one diagnosis code (the ICD-9-CM codes and ICD-10-CM codes) from the inpatient or outpatient claims provided by the data source (Appendix. Table 1).

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Key Independent Variables

Switching from Warfarin to NOACs: Switchers were defined as patients who switched from warfarin to NOAC, and we operationalized the definition as having at least one prescription of warfarin at the baseline as well as no prescription of warfarin in the assessment and the follow-up periods. Non-switchers refer to those who only took warfarin during our study period. They were identified as having no NOACs in any observed study period.

Potential Drug-Drug Interactions: Potential DDIs were defined as the concomitant use of medications that can result in clinically significant interactions with warfarin (e.g., simvastatin) or NOACs (e.g., itraconazole for dabigatran, clarithromycin for rivaroxaban, and vortioxetine for apixaban) as per IBM Micromedex® Drug Interaction Checking [20]. We calculated the potential DDI burden as the number of potential DDIs and the proportion of days with potential DDIs.

Number of Potential DDIs: The number of potential DDIs was defined as the highest observed number of potential DDIs in a single day during the assessment period (Fig. 2). In other words, we obtained the number of potential DDIs for each day of the assessment period and used the highest value as the number of potential DDIs. In our calculations, we required at least a 1-day overlap of warfarin or NOAC use and consumption of medications with the potential to interact with these anticoagulants (potential DDIs) based on prescription claim data. This measure of potential DDIs is thought to reflect the cumulative effects of concomitant medication use with oral anticoagulants.

Proportion of Days with Potential DDIs: We also calculated the proportion of days with potential DDIs by dividing the number of days of potential DDIs (i.e., concomitant use of oral anticoagulant therapy with medications that can lead to clinically relevant drug interactions) by the length of the assessment period, as presented below:

$$\text{Proportion of days with potential DDIs} = \frac{\text{the number of days with potential DDIs}}{\text{the number of days of the assessment period}}$$

When we counted the number of days with potential DDIs, we required concomitant (same day) use of oral anticoagulants in combination with medications likely to interact with these specific anticoagulants based on the prescription claim data. The proportion of days with potential DDIs thus reflects the simultaneous use of and duration of exposure to these potential DDIs.

Other Independent Variables: We included (1) predisposing factors (gender, age at index date, geographic region of residence), (2) enabling factors (type of healthcare plan), and (3) need factors. Need factors included adherence to the warfarin/NOACs, measured by the proportion of days covered (PDC) during the assessment period [21]; and medical history, including prior ischemic stroke/transient ischemic attack (TIA), prior cardioembolic complications (ischemic stroke, TIA, systemic embolism, and myocardial infarction), and scores of CHA_2DS_2-VASc [3] index and HAS-BLED index (hypertension, prior stroke, prior

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major bleeding, liver disease, renal disease, labile INR, age > 65, concomitant medication use, and alcohol abuse) [11], which measured the risk of ischemic stroke and major bleeding, respectively. We also calculated the number of chronic conditions (arthritis, asthma, cancer, COPD, dementia, depression, diabetes, hyperlipidemia, hepatitis, HIV, osteoporosis, schizophrenia, and substance abuse disorders) based on the framework used by the US Department of Health and Human Services, which were not included in the CHA_2DS_2-VASc or HAS-BLED indexes [22]. We did not include antiplatelet or nonsteroidal anti-inflammatory drug (NSAIDs) use and data of labile INR in the calculation for the HAS-BLED score. Because antiplatelet and NSAID use was captured in the exposure to DDIs and information of labile INR was not observable in the data source. All conditions were identified during the baseline and assessment periods. Additionally, we measured the potential DDIs with rhythm control medications (yes/no) because AF patients commonly use these drugs.

Statistical Analyses

In univariate analyses, we used chi-squared tests to analyze the associations between the outcome variables and the categorical independent variables. We performed the two-sample *t* tests or Wilcoxon signed-rank tests for the continuous variables. We used multivariate logistic regression to assess the association of switching to NOACs and potential DDIs to bleeding risk, controlling for the other independent variables. We also performed subgroup analyses by only focusing on hemorrhagic stroke, intracranial hemorrhage, and gastrointestinal hemorrhage for the dependent variables.

Secondary Analyses—To control selection bias, we used the inverse probability of treatment weighting (IPTW) in our secondary analyses, which balanced the switchers and non-switchers and minimized the observed selection bias because of potential confounders, including the HAS-BLED score, the CHA_2DS_2-VASc score, number of chronic conditions, sex, gender, geographical regions, and type of health insurance.

In addition, we utilized a random forest prediction model to identify the leading predictors of major bleeding in the study sample. Random forest is a machine learning method often used for predictive accuracy, which has been applied in health outcome research in recent years [23–25]. As compared with traditional statistical analyses, random forest prediction is suitable for high-dimension variable selection and can be used to target the AF patients at higher risk for major bleeding. In the random forest regression, we randomly split the original data into two parts: (1) a training dataset with 60% of the original sample and (2) a validation dataset with the remaining 40% of the original sample. Collection of classification trees was built from bootstrap samples of data and variables. The performance of the predictive model was evaluated using the area under the receiver operating characteristic curve (AUC). SAS 9.4 (SAS Institute Inc., Cary, NC, USA) and R programming language (version 3.3.3; R Foundation, Vienna, Austria) were used for the analyses.

Results

A total of 4126 AF patients met the inclusion criteria in this study. Demographic characteristics, clinical profiles, and medication-related information are presented in Table 1.

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Patients were predominantly male (70.2%), with the majority living in South (33.5%) or Mid-West (33.9%); most were identified as non-switchers (88.3%). Patient age averaged 55.6 years (SD = 7.2). The average number of potential DDIs was 1.09 days (SD = 1.01, range = 0 to 7), and the mean proportion of days with potential DDIs averaged was 0.30 (SD = 0.34, range = 0 to 1) in the assessment period.

A significantly lower number of potential DDIs in switchers than non-switchers were found (0.51 ± 0.74 vs.1.17 ± 1.02, $p < 0.0001$). The average proportion of days with potential DDIs was also lower among switchers than among non-switchers (0.22 ± 0.34 vs. 0.31 ± 0.34, $p < 0.0001$), suggesting a lower burden of potential DDIs among the switchers. The most commonly used medications that could result in a DDI were simvastatin (20.5%) among non-switchers and rhythm control medication (15.6%) among switchers (data not presented).

A total of 360 AF patients had major bleeding events in the follow-up period. The univariate analysis (Table 2) did not demonstrate a significant association between switching and major bleeding ($p = 0.50$). However, the number of potential DDIs and the proportion of days with potential DDIs were significantly and positively associated with major bleeding events ($p < 0.0001$ for both variables). Other factors significantly associated with the major bleeding included female gender, older age, types of health insurance, history of stroke/TIA, cardioembolic complications, renal disease, liver disease, hypertension, and prior bleeding events; in addition, number of chronic conditions, CHA_2DS_2-VASc score, and HAS-BLED score were also significantly and positively associated with the occurrence of major bleeding (Table 2).

Because of significant multicollinearity between the two measures of exposure to DDIs in this study, we present the results from two multivariate logistic regression models (Table 3). Switching to NOACs was not significantly related to bleeding risk in any models. In model 1, the factors significantly and positively associated with the likelihood of a major bleeding event included the number of potential DDIs (AOR 1.14, 95% CI 1.02–1.27) and HAS-BLED score (AOR 1.64, 95% CI 1.48–1.82), as well as female sex, older age, and having health insurance of preferred provider organization versus other types of insurance. In model 2, the proportion of days with potential DDIs was significantly and positively associated with risk for bleeding (AOR 1.42, 95% CI 1.03, 1.96), and the other significant associations in model 1 remained. Additionally, because of collinearity between the number of chronic conditions, the CHA_2DS_2-VASc score, and the HAS-BLED score, we added the number of chronic conditions and the CHA_2DS_2-VASc score into the models separately without the HAS-BLED score. Significant positive associations between the number of chronic conditions, the CHA_2DS_2-VASc score, and the major bleeding events were found in the adjusted models, and the other results were similar to model 1 and model 2.

In the secondary analyses, the association between switching to NOACs and major bleeding events remained insignificant after applying IPTW (data not presented). To evaluate the interactions between multiple variables and to examine the relative importance of variables as predictors of major bleeding, we performed additional analyses using the random forest prediction model. As illustrated in Fig. 3, the HAS-BLED score was the most important

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predictor for major bleeding, followed by prior major bleeding, the proportion of days with potential DDIs, prior stroke events, and the number of potential DDIs. Switching from warfarin to NOAC did not appear to be a significant predictor of major bleeding. The AUC for the model was 0.67, indicating a fair prediction.

In the subgroup analyses, the associations between key independent variables and major bleeding events (i.e., hemorrhagic stroke, intracranial hemorrhage, and gastrointestinal hemorrhage) remained significant. However, we did not find significant associations between the other independent variables (i.e., sex, age, health insurance types) and major bleeding events based on the results of multivariate logistic regression models. Similar findings were also observed in the random forest prediction model in the subgroup analysis.

Discussion

To our knowledge, this is the first population-based study to examine the influence of switching from warfarin to NOACs and potential DDI exposure on the bleeding risk in the US working-age population with AF. Both measures of exposure to potential DDI (i.e., the number of potential DDIs and the proportion of days with potential DDIs) were significantly and positively associated with risk for major bleeding events among the working-age adults with AF. On the other hand, no significant associations between switching from warfarin to NOACs and major bleeding events were observed in our analyses. In addition, the HAS-BLED score was an important predictor of major bleeding risk, showing a stronger association with risk for major bleeding events.

Interestingly, exposure to potential DDI was an independent predictor of risk for major bleeding and was identified as an important predictor in the random forest prediction model. However, switching from warfarin to NOACs was not associated with major bleeding events. Switching from warfarin to NOAC indicated a significantly lower potential DDI burden than in those patients persistently treated with warfarin, although the burden was high in both groups. Therefore, even though the patients' burden of DDIs might decrease after switching from warfarin to NOACs, the degree of bleeding risk reduction may not be substantial. Furthermore, it is also possible that the non-significant association is a result of unobserved selection bias and limited follow-up period, which requires further examinations to address these issues.

AF management includes rate control, rhythm control, and prevention of thromboembolism [3]. Both warfarin and NOACs have major interactions with rhythm control medications such as amiodarone that may lead to bleeding complications. Although we found that DDIs with rhythm control medications were very common in patients with NOACs, we did not find a significant association between concomitant use of these agents and major bleeding events. According to the 2014 AHA/ACC/HRS and the 2010 European Society of Cardiology guidelines, there is no indication to reduce the dosage of dabigatran in patients taking amiodarone; however, the cumulative effects from other drug interactions may still elevate the risk of hemorrhage [3, 10]. Given the current incomplete knowledge regarding NOAC interactions and the lack of specific reversal agents for all NOAC agents except dabigatran, large prospective studies regarding the safety of co-administration of NOACs

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and medications that may lead to DDIs are needed for risk prevention and management strategies for AF patients on oral anticoagulant therapy.

Overall, our findings suggest both comorbid conditions and potential DDIs are important predictors of major bleeding. In the secondary analyses, the HAS-BLED index, the number of potential DDIs, and the proportion of days with potential DDIs were identified among the top five predictors of major bleeding. This suggests that models of predicting major bleeding events should include information on potential DDIs for increased accuracy and precision. On the other hand, given the fair performance of prediction models, the risk for major bleeding may be affected by multiple factors, including but not limited to comorbid conditions and concomitant medications use measured in this study. The sex difference on major bleeding was probably because we included postmenopausal bleeding events, and this significant association disappeared when only hemorrhagic stroke, intracranial hemorrhage, and gastrointestinal hemorrhage were considered for the major bleeding.

Based on our findings, clinicians should consider all potential DDIs linked to the increased risk of hemorrhage in the management of patients on anticoagulation therapy. A recent single-center study utilizing a comprehensive protocol to manage significant antimicrobial DDIs with warfarin (e.g., to document significant DDIs and duration of interaction in progress notes and discharge summary notes) demonstrated a significant reduction in bleeding events [26]. Utilizing computerized drug interaction surveillance systems can be helpful in improving management of issues related to DDIs [27]. However, the current design of these electronic systems allows only for simple warnings regarding each potential DDI. Current surveillance systems do not take into account the effects of cumulative exposure to DDIs, nor important patient characteristics such as comorbidities and disease severity. Thus, limitations of current drug interaction surveillance systems may reduce their utility in clinical practice. The continued development of DDI surveillance software is needed to provide more detailed and patient-specific management options [28]. Furthermore, a recent study demonstrated that e-health-based coagulation service, which comprised electronic health records and computer-assisted patient care, was associated with fewer adverse events in patients taking oral anticoagulants [29]. Thus, we recommend optimizing the anticoagulation management services by adopting health technology that incorporates the summarized information of potential DDIs and comorbid conditions to improve collaborative care for patients with AF.

We had several limitations in this study. First, we did not include all possible DDIs (i.e., the moderate and mild DDIs) in our analyses, and we only assessed the encounter of potential DDIs in a limited length of time using conservative measures. Hence, the prevalence of potential DDIs may be underestimated. Secondly, we did not capture the labile INR and actual alcohol use in the HAS-BLED index due to the limited data availability. But, INR does not apply to NOAC users, and it may confound the comparison between warfarin and NOACs in this study. Thirdly, prescription drug claims used in the study may not reflect the actual use of medications in patients, for example, if they discontinued OAC treatment. In addition, we assessed NOACs as a group in analyses. Each NOAC may have different safety and DDI profiles, which warrants further longitudinal studies to look into the specific agents in this drug class. Given that our definitions for the switcher and non-switchers were based

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on arbitrarily classified study periods, our findings may not apply to patients who frequently changed their oral anticoagulant therapies or patients who were identified as multiple switchers in our study period. Due to our study design, we may not capture detailed information regarding time-to-major bleeding events. Additionally, our findings were limited to US working-age adults with AF. The applicability to other populations (e.g., older patients or patients from countries outside the US) needs to be explored by future research. Lastly, our study may exclude patients who died before switching from warfarin to NOACs, which might introduce immortal time bias.

This study has several strengths. First, our investigation employed a novel approach measuring DDI burden, allowing capture of two important aspects of DDIs—the number of drugs used in combination with oral anticoagulants that may result in DDIs (the number of potential DDIs) and the cumulative duration of drug exposure (the proportion of days with potential DDIs). Another major strength of this study is that we used an algorithmic model to evaluate the robustness of our statistical findings and to identify the most important predictors of bleeding risk. Also, we used an advanced statistical method, IPTW, to control observed selection bias. Moreover, this study used a population-based design and a nationally representative sample of commercially insured US working-age adults: incorporating typical prescribing patterns and clinical settings in the US. Our study findings have implications directly relevant to real-world practice and settings.

Conclusions

Concomitant use of drugs known to interact adversely with oral anticoagulant therapy was common in working-age US adults with AF. Those who switched from warfarin to NOACs had a significantly lower DDI burden than did those who remained on warfarin. The number of potential DDIs and proportion days with DDIs were significant and independent predictors of bleeding risk, as were HAS-BLED scores. However, switching from warfarin to NOACs did not predict bleeding risk. Collectively, these findings suggest that potential DDIs and patients' comorbidity burden are important factors to consider in the management of bleeding risk in working-age AF adults who take oral anticoagulants. We recommend developing DDI surveillance systems and highlighting serious DDIs in the AF guideline to better inform clinicians and patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We used an adjudicated claims database of commercially insured individuals, which is made available through a license to IQVIA's Real World Data: Adjudicated Claims - US (also known as PharMetrics Plus), 10% sample. All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IQVIA or any of its affiliated or subsidiary entities.

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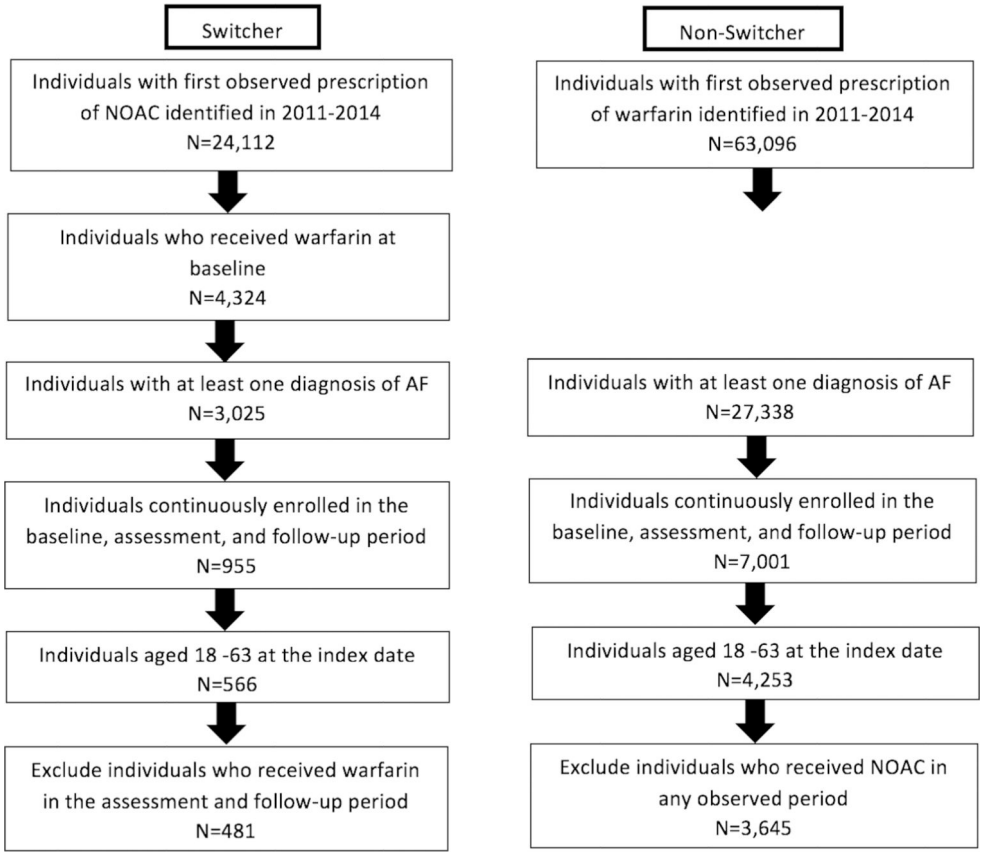

Fig. 1.
Flow chart to obtain the final study sample

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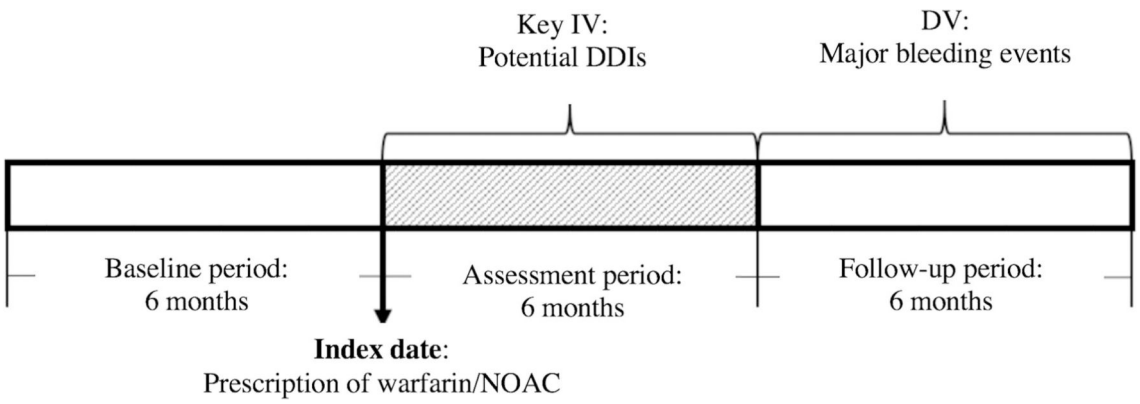

Fig. 2.

Study design and periods to identify the key independent variables and dependent variable. DDIs: drug-drug interactions; IV: independent variable; DV: dependent variable; NOAC: non–vitamin K oral anticoagulant

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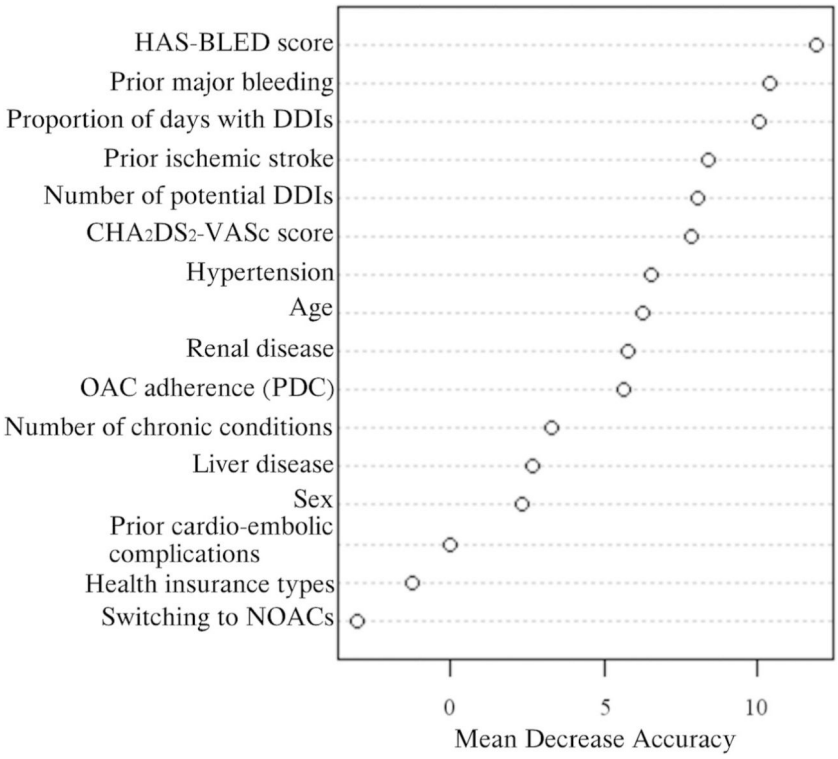

Fig. 3.

Important predictors of major bleeding events in working-age adults with atrial fibrillation who were treated with oral anticoagulants (random forest prediction model) Note: AUC = 0.67, accuracy = 91.2%. AUC, the area under the receiver operating characteristic curve; DDIs, drug-drug interactions; NOACs, non–vitamin K oral anticoagulants; OAC, oral anticoagulants; PDC, proportion days covered.

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Table 1

Descriptive statistics of working-age adults with atrial fibrillation who were treated with oral anticoagulants (*N* = 4126)

	***N* (%)/mean ± SD**
Key independent variables	
Switched from warfarin to NOACs No	
No	3645 (88.3%)
Yes	481 (11.7%)
Exposure to potential DDIs Number of potential DDIs	1.09 ± 1.01
Proportion of days with potential DDIs	0.30 ± 0.34
Other independent variables	
Predisposing factors	1228 (29.8%)
Sex	
Female	1228 (29.8%)
Male	2898 (70.2%)
Patient region	
East	1015 (24.6%)
Mid-West	1382 (33.5%)
South	1398 (33.9%)
West	331 (8.0%)
Age	55.59 ± 7.15
Enabling factors	
Insurance type	
HMO	538 (13.0%)
PPO	3073 (74.5%)
Other	515 (12.5%)
Need factors	
Medical history	
Major bleeding in the baseline or assessment period	
No	3257 (78.9%)
Yes	869 (21.1%)
Stroke/TIA in the baseline or assessment period	

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	***N* (%)/mean ± SD**
No	3735 (90.5%)
Yes	391 (9.5%)
Cardio-embolic complications event in the baseline or assessment period	
No	3467 (84.0%)
Yes	659 (16.0%)
Hypertension in the baseline or assessment period	
No	3017 (73.1%)
Yes	1109 (26.9%)
Renal disease in the baseline or assessment period	
No	3671 (89.0%)
Yes	455 (11.0%)
Liver disease in the baseline or assessment period	
No	3700 (89.7%)
Yes	426 (10.3%)
Medication profile	
Having DDI with rhythm control medications	
No	3510 (85.1%)
Yes	616 (14.9%)
OAC adherence (PDC) in the assessment period	0.74 ± 0.28
Health status	
CHA_2DS_2-VASc in the baseline or assessment period	1.90 ± 1.25
Number of chronic conditions in the baseline or assessment period	1.40 ± 1.12
HAS-BLED score in the baseline or assessment period	1.27 ± 0.96

DDI, drug*DDI*-drug interaction; *HMO*, health maintenance organization; *NOACs*, non–vitamin K oral anticoagulants; *OAC*, oral anticoagulants; *PDC*, proportion days covered; *PPO*, preferred provider organization; *SD*, standard deviation; *TIA*, transient ischemic attack

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Table 2

Factors associated with major bleeding in working-age adults with atrial fibrillation who were treated with oral anticoagulants—univariate analyses (N = 4126)

		Major bleeding in the follow-up period *N* (%)/mean (SD)		*p* value
		No	Yes	
		3766	360	
Key independent variables				
Switched to NOACs				0.50
No	3645	3323 (91.2%)	322 (8.8%)	
Yes	481	443 (92.1%)	38 (7.9%)	
Exposure to potential DDIs				
Number of potential DDIs		1.07 ± 0.99	1.37 ± 1.14	< 0.0001
Proportion of days with potential DDIs		0.29 ± 0.34	0.37 ± 0.35	< 0.0001
Other independent variables				
Predisposing factor				
Age				
		55.46± 7.21	56.91 ± 6.35	< 0.0001
Sex				
Female	1228	1088 (88.6%)	140 (11.4%)	< 0.0001
Male	2898	2678 (92.4%)	220 (7.6%)	
Regions				
East	1015	925 (24.6%)	90 (25.0%)	0.39
Mid-West	1382	1275 (33.9%)	107 (29.7%)	
South	1398	1264 (33.5%)	134 (37.2%)	
West	331	302 (8.0%)	29 (8.1%)	
Enabling factors				
Health insurance type				
HMO	538	488 (13.0%)	50 (13.9%)	0.03
PPO	3073	2823 (75.0%)	250 (69.4%)	
Other	515	455 (12.0%)	60 (16.7%)	
Need factors				

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		Major bleeding in the follow-up period *N* (%)/mean (SD)		*p* value
Medical history				
Major bleeding events in the baseline or assessment period				
No	3357	3068 (94.2%)	189 (5.8%)	< 0.0001
Yes	869	189 (80.3%)	171 (19.7%)	
Stroke in the baseline or assessment period				
No	3735	3424 (91.7%)	311 (8.3%)	0.005
Yes	391	342 (87.5%)	49 (12.5%)	
Cardioembolic complications event in the baseline or assessment period				
No	3467	3182 (91.8%)	285 (8.2%)	0.0008
Yes	659	584 (88.6%)	75 (11.4%)	
Hypertension in the baseline or assessment period				
No	1109	1031 (93.0%)	78 (7.0%)	0.02
Yes	3017	2735 (90.7%)	282 (9.3%)	
Renal disease in the baseline or assessment period				
No	3671	3385 (92.2%)	286 (7.8%)	< 0.0001
Yes	455	381 (83.7%)	74 (16.3%)	
Liver disease in the baseline or assessment period				
No	3700	3397 (91.8%)	303 (8.2%)	0.0003
Yes	426	303 (86.6%)	57 (13.4%)	
Medication profile				
DDI with rhythm control medication				
No	3510	3209 (91.4%)	301 (8.6%)	0.42
Yes	616	557 (90.4%)	59 (9.6%)	
OAC PDC		0.74 ± 0.28	0.76 ± 0.26	0.13
Health status				
Number of chronic conditions		1.37 ± 1.10	1.80 ± 1.30	< 0.0001
CHA_2DS_2-VASc score		1.87 ± 1.23	2.27 ± 1.31	< 0.0001
HAS-BLED score		1.22 ± 0.93	1.79 ± 1.11	< 0.0001

DDI, drug-drug interaction; *HMO*, health maintenance organization; NOACs, non–vitamin K oral anticoagulants; *OAC*, oral anticoagulants; *PDC*, proportion days covered; *PPO*, preferred provider organization; *SD*, standard deviation

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Table 3

Factors associated with major bleeding in working-age adults with atrial fibrillation who were treated with oral anticoagulants—multivariate logistic regressions ($N = 4126$)

	Model 1		**Model 2**	
	AOR (95%CI)	*p* value	AOR (95%CI)	*p* value
Predisposing factors				
Sex				
Female vs. male	1.74 (1.34, 2.26)	0.0004	1.74 (1.34, 2.25)	< 0.0001
Age	1.03 (1.01, 1.05)	0.0008	1.03 (1.01, 1.05)	0.003
Region				
East vs West	0.85 (0.53, 1.34)	0.47	0.84 (0.53, 1.33)	0.45
Mid-West vs West	0.75 (0.48, 1.16)	0.19	0.75 (0.48, 1.15)	0.18
South vs West	1.07 (0.70, 1.65)	0.76	1.07 (0.70, 1.65)	0.75
Enabling factors				
Type of health care				
HMO vs other	0.76 (0.51, 1.15)	0.19	0.75 (0.50, 1.12)	0.16
PPO vs other	0.63 (0.46, 0.87)	0.004	0.62 (0.45, 0.86)	0.004
Need factors				
Switcher vs non-switcher	1.01 (0.70, 1.46)	0.96	0.94 (0.66, 1.35)	0.75
Proportion of days with potential DDIs	–	–	1.42 (1.03, 1.96)	0.03
Number of potential DDIs	1.14 (1.02, 1.27)	0.02	–	–
HAS-BLED score	1.64 (1.48, 1.82)	< 0.0001	1.67 (1.51, 1.85)	< 0.0001

AOR, *AOR*, adjusted odds ratio; *DDI*, drug-drug interaction; *HMO*, health maintenance organization; *PDC*, proportion days covered; *PPO*, preferred provider organization