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The risk of acute kidney injury in Asians treated with apixaban, rivaroxaban, dabigatran, or warfarin for non-valvular atrial fibrillation: A nationwide cohort study in Taiwan☆

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ABSTRACT

Background: Whether or not non-vitamin K antagonist oral anticoagulants (NOACs) are associated with a lower risk of acute kidney injury (AKI) in patients with non-valvular atrial fibrillation (NVAF) remains unknown in real world practice.

Methods: In this nationwide retrospective cohort study, 1507, 3200, 5765 and 4227 NVAF patients with chronic kidney disease (CKD) and 4368, 16,945, 22,301, and 16,908 NVAF patients without CKD taking apixaban, dabigatran, rivaroxaban, and warfarin, respectively, from June 1, 2012 to December 31, 2016 were enrolled from the Taiwan National Health Insurance Program. Propensity-score weighted method was used to balance covariates across study groups. Patients were followed until occurrence of AKI or end date of study.

Results: Three NOACs were all associated with a significantly lower risk of AKI compared with warfarin for both CKD-free (hazard ratio, [95% confidential interval]; 0.65, [0.60–0.72] for apixaban; 0.68, [0.64–0.74] for dabigatran; 0.73, [0.68–0.79] for rivaroxaban) and CKD cohorts (0.50, [0.45–0.56] for apixaban; 0.54, [0.49–0.59] for dabigatran; 0.53, [0.49–0.58] for rivaroxaban). The annual incidence of AKI for all NOACs and warfarin increased gradually as the increment of CHA_2DS_2-VASc for both CKD-free and CKD cohorts after propensity score weighting. The reduced risk of AKI for three NOACs persisted in most subgroups in either CKD-free or CKD cohort. Multivariate analysis indicated that all three NOACs were all associated with lower risk of AKI than warfarin in either CKD-free or CKD cohort.

Conclusions: All three NOACs are associated with a lower risk of AKI than warfarin among Asians with NVAF in real-world practice.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a world-wide prevalence of 2–3%. AF significantly increases the risk of comorbidity and mortality [1,2] with a 5-fold increased risk of stroke [3–5]. Oral anti-coagulants (OAC) including vitamin K antagonists (e.g. warfarin) and non-vitamin K oral anti-coagulants (e.g. apixaban, dabigatran, and rivaroxaban), have been shown to decrease the risk of thromboembolic events and mortality in patients with non-valvular AF (NVAF). In addition to the common side effect with major bleeding risk when taking warfarin, warfarin-related nephropathy (WRN) was recently noted as an important adverse event related to anticoagulant therapy, which was defined as acute kidney injury (AKI) with

Abbreviations: AF, atrial fibrillation; AKI, acute kidney injury; CHA_2DS_2-VASc, congestive heart failure, hypertension, aged 75 years or older, diabetes mellitus, previous stroke/transient ischemic attack, vascular disease, aged 65 to 74 years, female; CKD, chronic kidney disease; HAS-BLED, hypertension, abnormal renal or liver function, stroke, bleeding history, labile international normalized ratio, aged 65 years or older, and antiplatelet drug or alcohol use; INR, international normalized ratio; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist; NHI, National Health Insurance; NVAF, non-valvular atrial fibrillation.

☆ The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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supratherapeutic international normalized ratio (INR) values with or without overt hematuria [6–8]. Non-vitamin K antagonist oral anticoagulants (NOACs), including apixaban, dabigatran, rivaroxaban, and edoxaban are all excreted through the kidney in different portions [9]. Recent meta-analysis showed that the risk of renal failure associated with NOACs (dabigatran, apixaban, and/or rivaroxaban) was similar to the traditional anticoagulants including warfarin and low molecular weight heparin (LMWH) [10]. Of note, rivaroxaban was associated with an adverse effect of serum creatinine elevation in some studies [11,12]. Our recent study indicated that dabigatran was associated with a reduced risk of AKI compared with warfarin in a large Asian cohort either with or without CKD [13]. However, whether Xa inhibitors (e.g. apixaban, edoxaban, and rivaroxaban) also have a lower risk of AKI than warfarin in NVAF patients remains unclear. The risk of AKI associated with the use of all NOACs in NVAF patients needed to be clarified in real-world practice. The objective of the study was to compare the risk of AKI associated with apixaban, dabigatran, and rivaroxaban versus warfarin among patients with NVAF in real world practice.

2. Methods

2.1. Study population

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The patient data were obtained from National Health Insurance (NHI) Database, which provides comprehensive medical care records of about >99% of patients in Taiwan. Because the original NHIRD identification number of each patient was encrypted and de-identified to protect patient's privacy by undergoing consistent encrypting procedure, informed consent was exempted.

2.2. Study design

Four study groups (apixaban, dabigatran, rivaroxaban, and warfarin) were enrolled in the dynamic cohort study. Each group was further divided into two groups according to a diagnosis indicating chronic kidney disease (CKD) (ICD-9-CM 580–589) before the index date. A flowchart of the study enrollment is shown in Fig. 1. A total of 279,776 patients diagnosed with AF (*International Classification of Diseases (the ninth revision) Clinical Modification (ICD-9-CM)* codes (427.31) from January 1, 2010 to December 31, 2015 or *ICD-10-CM codes* (I48)) from January 1, 2016 to December 31, 2016 were identified in this study. Patients who had their first prescription of a NOAC including dabigatran (approval date: June 1, 2012), rivaroxaban (approval date: February 1, 2013), or apixaban (approval date: June 1, 2014), as well as patients who started warfarin treatment (from June 1, 2012) up to December 31, 2016 were enrolled in this study. The index date was defined as the first prescription date for any NOAC or warfarin after June 1, 2012 for each group. The follow-up period was defined from the index date until the first occurrence of AKI or the end date of study period (December 31, 2016), whichever came first.

2.3. Exclusion criteria

Patients who took more than one kind of NOAC during their entire treatment course were excluded. To establish a cohort of NVAF patients who took oral anticoagulant for the primary purpose of stroke prevention, those patients with diagnoses indicating valvular AF (mitral stenosis or valvular surgery), venous thromboembolism (pulmonary embolism or deep vein thrombosis) or joint replacement therapy within 6 months before the index date were excluded.

2.4. Study outcomes

The outcomes of AKI were defined as those who received a diagnosis coded as ICD-9-CM 580.X, 584.X, or 586 (until January 1, 2016) and ICD-10-CM N17.x (from January 1, 2016 to December 31, 2016) during hospitalization or an outpatient visit at least once. A blanking period of 7 days after the drug index date was applied because the occurrence of AKI within the first few days of drug prescription is most likely related to initial presentation rather than a new event. The validation of ICD-9-CM codes for identifying AKI has been performed before [13]. The ICD-9-CM and ICD-10-CM codes used to identify the study outcomes and the baseline covariates are summarized in Supplemental Table I.

2.5. Covariates

Baseline covariates were referred to any claim record with the above diagnoses or medication codes prior to the index date. A history of prescription for medicine was confined to at least once within 3 months preceding the index date. Medical history and risk factors for AKI were referenced to any record with the previous diagnoses or medication codes prior to index date [13].

2.6. Statistical analysis

The study outcomes of AKI for three NOACs and warfarin were estimated by using the propensity score method. Inverse probability of treatment weights of propensity scores was used to balance covariates across the four groups in time-to-events analyses. We used generalized boosted models, based on 5000 regression trees, to calculate weights for optimal balance between the treatment populations. The weights were derived to obtain estimates representing average treatment effects in the treated groups [14,15]. The covariates in Supplemental Tables II and III were included in the propensity models except for the CHA_2DS_2-VASc score, because CHA_2DS_2-VASc score was a combination of other covariates. Incidence rates were estimated using the total number of study outcomes during the follow-up period divided by person–years at risk. The risk of time-dependent study outcomes for three NOACs versus warfarin (reference) was obtained using survival analysis (Kaplan–Meier method and Cox proportional hazards regression for multivariate analysis). The balance of potential confounders at baseline (index date) between each study group was assessed using the absolute standardized mean difference (ASMD) rather than statistical testing, because balance is a property of the sample and not of an underlying population. The value of ASMD ≤0.1 indicated an insignificant difference in potential confounders between the two study groups [16]. Statistical significance was defined as a P-value <0.05. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

A total of 1507, 3200, 5765, and 4227 consecutive patients with previous history of CKD, and 4368, 16,945, 22,301, and 16,908 consecutive patients without CKD taking apixaban, dabigatran, rivaroxaban, and warfarin, respectively, were enrolled from June 1, 2012 to December 31, 2016. Before propensity score weighting, three NOAC groups were older, had a higher CHA_2DS_2-VASc and a higher proportion of comorbidities than the warfarin group (Supplemental Table II). After propensity score weighting, three NOAC and warfarin groups were well-balanced in most characteristics (most ASMD <0.1) (Table 1). Similar to the CKD-free cohort, three NOAC groups with CKD were older and had higher CHA_2DS_2-VASc scores than the warfarin group with CKD before propensity score weighting (Supplemental Table III). Again, three NOAC and warfarin groups among the CKD cohort were well-balanced in most characteristics after adjustment (most ASMD <0.1) (Table 2).

For the CKD-free cohort, the incidence rate of AKI was 5.01 [95% confidential interval (CI): 4.964–5.41], 4.16 [95% CI: 3.92–4.41], 4.74 [95% CI: 4.46–5.03], and 6.02 [95% CI: 5.74–6.31] per 100 person–years for the apixaban, dabigatran, rivaroxaban, and warfarin group, respectively. For the CKD cohort, the incidence rate of AKI was 20.68 [95% CI: 18.97–22.55], 14.85 [95% CI: 13.82–15.97], 16.71 [95% CI: 15.50–18.01], and 28.68 [95% CI: 27.17–30.26] per 100 person–years for apixaban, dabigatran, rivaroxaban, and warfarin group, respectively. The cumulative risk curve showed early separation of event-free curves for AKI after propensity score weighting for either CKD-free or CKD cohorts (Fig. 2 and Supplemental Fig. I). Three NOACs were all associated with significantly lower risks of AKI compared with warfarin for both CKD-free (hazard ratio (HR), [95% CI]: 0.65, [95% CI: 0.60–0.72] for apixaban; 0.68, [95% CI: 0.64–0.74] for dabigatran; 0.73, [95% CI: 0.68–0.79] for rivaroxaban) and CKD cohorts (0.50, [95% CI: 0.45–0.56] for apixaban; 0.54, [95% CI: 0.49–0.59] for dabigatran; 0.53, [95% CI: 0.49–0.58] for rivaroxaban) after propensity score weighting. No differences in risk of AKI were found between any two-paired NOACs. All NOACs were associated with significantly lower risks of all-cause mortality compared with warfarin for both CKD-free (hazard ratio (HR), [95% CI]: 0.62, [95% CI: 0.58–0.66] for apixaban; 0.69, [95% CI: 0.66–0.73] for dabigatran; 0.67, [95% CI: 0.64–0.71] for rivaroxaban) and CKD cohorts (0.66, [95% CI: 0.60–0.72] for apixaban; 0.69, [95% CI: 0.64–0.74] for dabigatran; 0.63, [95% CI: 0.58–0.69] for rivaroxaban) after propensity score weighting.

We calculated the annual risk of AKI among those patients taking oral anticoagulants according to different CHA_2DS_2-VASc scores. The annual incidence of AKI for the three NOACs and warfarin increased gradually as the increment of CHA_2DS_2-VASc for both CKD-free and CKD cohorts after propensity score weighting. In general, warfarin had a numerically higher annual risk of AKI than three NOACs in each category of CHA_2DS_2-VASc scores either in CKD-free or CKD cohort (Supplemental Fig. II). It was noted that apixaban had a numerically higher annual