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Original Article

Rivaroxaban is associated with higher risk of acute kidney disease in patients with non-valvular atrial fibrillation

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Abstract: Introduction: We aimed to investigate the risk of acute kidney disease (AKD) in patients with non-valvular atrial fibrillation (NVAF) who were taking rivaroxaban compared with patients who were not taking rivaroxaban. Methods: A retrospective cohort study was performed using a database to screen out patients with atrial fibrillation who had taken rivaroxaban for 3 months. A total of 793 patients were enrolled in the rivaroxaban group, meanwhile 631 NVAF patients who were not given rivaroxaban with matched age and baseline data were selected as the control group. Characteristics of two groups were compared and the incidence and relative risk of AKD while taking rivaroxaban were analyzed. Results: The incidenc of AKD while taking rivaroxaban was increased compared with those not taking anticoagulation treatment [58/793 Vs. 14/631, relative risk (RR) = 3.297, X^2 = 19.001, P<0.001]. Multivariate logistic regression analysis correcting confounding factor showed that the risk factors of AKD were independently associated with taking rivaroxaban (OR = 3.441, 95% CI 1.818-6.512, P<0.001), pre-existing proteinuria (OR = 5.420, 95% CI 3.121-9.415, P<0.001) in patients with NVAF. Conclusions: We are the first group to verify that taking rivaroxaban is associated with higher risk of acute kidney disease, as well as pre-existing proteinuria compared with patients without anticoagulation treatment in patients with NVAF.

Keywords: Rivaroxaban, acute kidney disease, non-valvular atrial fibrillation

Introduction

Non-vitamin K antagonist oral anti-coagulants (NOACs), including apixaban, dabigatran, rivaroxaban, and edoxaban have been correlated with induced acute kidney injury or end stage renal disease recently [1]. Meta-analysis showed that the risk of renal failure associated with NOACs was lower than traditional anticoagulants including warfarin and low molecular weight heparin [2]. Ziv Harel. et al. reported on a population-based cohort study which included 20,683 outpatients, with older patients (age ≥66 years) and atrial fibrillation who were prescribed warfarin, dabigatran, rivaroxaban, or apixaban, and they demonstrated that each direct oral anticoagulant was associated with a significantly lower risk of acute kidney injury (AKI) compared with warfarin. Direct oral anticoagulants were associated with a lower risk of AKI compared with warfarin [3].

Yao, et al. verified that warfarin resulted in a ≥30% decline in eGFR at the end of 2 years, with a doubling of serum creatinine at 4.0%, AKI was 14.8%, and kidney failure was 1.7%. When the 3 NOACs (apixaban, dabigatran, rivaroxaban) were pooled, they were associated with reduced risk of ≥30% decline in eGFR within two years (hazard ratio [HR]: 0.77; and AKI [HR]: 0.68) compared with warfarin [4].

There hasn't been a report of acute kidney disease caused by rivaroxaban compared with cases not taking rivaroxaban. The Kidney Disease Improving Global Outcomes acute kidney injury (KDIGO AKI) workgroup in 2012 proposed a definition of acute kidney disease (AKD) that impacts kidney function, which included AKI, or estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2, a decrease in GFR >35%, an increase in serum creatinine of >50%, or any kidney damage lasting longer than 3 months

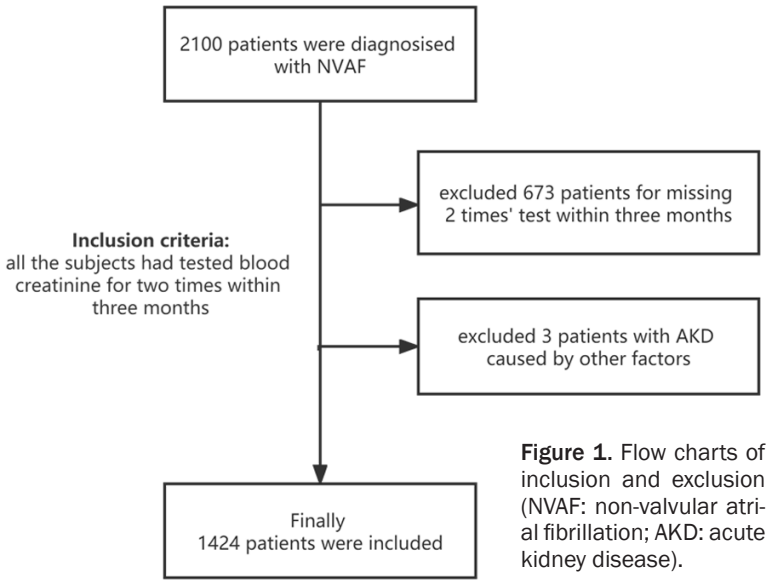

Figure 1. Flow charts of inclusion and exclusion (NVAF: non-valvular atrial fibrillation; AKD: acute kidney disease).

[5]. Because it is difficult in outpatients to test serum creatinine and repeat testing within 48 hours or even up to one week, it is possible to check serum creatinine within three months, so we can apply the criteria of AKD, not the definition of AKI, to assess the risk of kidney injury from prescriptions of rivaroxaban in our outpatients.

Our research aimed to explore the possibility of acute kidney disease caused by rivaroxaban in patients with non-valvular atrial fibrillation in this cohort study.

Methods

Study population

We conducted a retrospective cohort analysis using the database of Xuanwu Hospital Capital Medical University from October 1, 2016 to June 30, 2019. This study was approved by the Ethics Committee of Xuanwu Hospital of Capital Medical University (approval No. [2019] 014). Because this is a retrospective study, the original identification number of each patient was encrypted and de-identified to protect the patient's privacy by undergoing consistent encrypting procedures, and as such informed consent was exempt.

Study design

Two study groups (those taking rivaroxaban and those not) were enrolled in the retrospective cohort study. Inclusion criteria: Patients who were diagnosed with non-valvular atrial fibrillation; all the subjects had tested blood creatinine on two occasions within three months. Exclusion criteria: Patients in the rivaroxaban group who had taken rivaroxaban before, those who took other medications besides rivaroxaban, or those who took more doses of rivaroxaban in our hospital outside of the study period were excluded. Patients in the rivaroxaban group and control group with AKD caused by other factors (such as kidney trauma, operation, infection, obstruction) were also identified and excluded. A total of 1424 patients were finally included from October 1, 2016 to June 30, 2019. (See **Figure 1**).

Among them, 793 patients were classified into the rivaroxaban group who were administrated rivaroxaban (10 mg/tablet/per day) for the first time and the course of treatment was more than 3 months. The remaining 631 patients without anti-coagulation treatment were selected as the control group. These control patients were matched in terms of age and gender with patients in the rivaroxaban group, but they were not taking rivaroxaban, warfarin or other new oral anticoagulants.

All NVAF patients were prescribed anti-coagulation medication when scores for male ≥2 or scores for female ≥3, based on the risk of thrombosis or embolism in CHA2DS2-VASc score system assessment [6]. The definition of AKD: Acute kidney disease (AKD) and no known acute kidney disease (NKD) were used to assess the kidney health. The definition of AKD and NKD were proposed in the KDIGO Clinical Practice Guideline for Acute Kidney Injury in 2012 [5]. AKD includes acute kidney injury, or decrease in glomerular filtration rate (GFR) by ≥35% or increase in serum creatinine (Scr) by >50% for <3 months. NKD was defined as GFR ≥60 ml/min per 1.73 m^2 and stable Scr, as well as no markers of kidney injury. GFR was evaluated by estimated GFR (eGFR), which was cal-

Table 1. Baseline demographic and clinical characteristics in the rivaroxaban and control group

Items	Rivaroxaban group (n = 793)	Control group (n = 631)	t/X^2 value	P
Age (years)	71.06±12.81	71.19±8.48	0.221	0.825
Sex ratio (male/female)	404/389	295/336	2.474	0.122
HGB (g/L)	125.75±21.62	136.96±15.59	5.861	<0.001
Platelet count (*10^9/L)	206.10±74.92	206.33±58.67	0.053	0.957
Creatinine (μmol/L)	75.61±37.75	74.82±28.60	0.437	0.662
Urea (mmol/L)	7.17±4.48	6.28±2.42	4.357	<0.001
Uric acid (μmol/L)	344.27.16±117.56	345.96±92.57	0.289	0.772
Triglyceride (mmol/L)	1.60±1.72	1.71±1.34	1.423	0.155
Cholesterol (mmol/L)	4.27±1.33	4.25±1.06	0.158	0.874
Alanine aminotransferase (IU/L)	24.54±27.27	17.29±14.76	6.015	<0.001
Total protein (g/L)	66.63±7.34	70.24±5.33	9.016	<0.001
Albumin (g/L)	38.55±5.16	41.48±2.44	13.157	<0.001
Pre-existing hypertension n (%)	551 (69.48)	462 (72.87)	1.963	0.161
Pre-existing diabetes n (%)	216 (27.23)	224 (35.33)	10.820	0.001
Pre-existing proteinuria n (%)	122 (15.38)	54 (8.50)	15.284	<0.001
ACEI/ARB utilization n (%)	554 (69.86)	418 (66.24)	2.275	0.131

RBC: Red Blood Cell; HGB: Hemoglobin; ACEI: Angiotensin Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker.

culated by CKD-EPI formula recommended by KIDGO [7]. According to the diagnostic criteria above, the patients in the rivaroxaban and control group were divided into the AKD group and NKD group respectively. The differences of clinical and laboratory data, concomitant diseases and the relative risk of AKD were compared between the two groups. We defined pre-existing proteinuria as proteinuria consisting of protein (+) to (+++) by routine urine testing over three months.

Sample size calculation: According to previous publications, we assumed the proportion of AKD in those taking rivaroxaban P1 = 7.5%, the proportion of AKD in control group *P0* = 2.5%, *q0 = 1-P0*, *q1 = 1-P1,* the power = 1-β = 0.9, μβ = 1.28, α = 0.05, μα/2 = 1.96, P = (P0+P1)/2, q = (q0+q1)/2, to utilize the cohort study formula calculating the sample size.

$$n = \frac{\left(\mu_{\alpha/2}\sqrt{2pq} + \mu_{\beta}\sqrt{p_0 q_0 + p_1 q_1}\right)^2}{(p_1 - p_0)^2} = 171$$

Each group needed 171 patients, and if 1:1 match, consisted of a total of 342 patients, of which our study enrolled 1424 patients, so the sample size was large enough.

Statistical analysis

Results are expressed as proportions (percentages) for categorical variables, means ± standard deviation (S.D.) for continuous normally distributed variables, and medians (interquartile) for continuous non-normally distributed variables. The student's t-test was employed to compare differences between the two groups for normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. The counting data was expressed by percentage or composition ratio, and the comparison between groups was expressed by X^2 test. The risk factors of AKD were analyzed by Univariate logistic and Multivariate logistic regression, we selected the significant variables by the Univariate logistic regression analysis. SPSS version 23.0 was used for statistical analysis, all analyses were two-tailed, and a *P* value <0.05 was defined as the threshold of statistical significance.

Results

Baseline demographic and clinical characteristics in the rivaroxaban and control group

Finally, we enrolled 793 patients in the rivaroxaban group and 631 patients in the control group. As shown in **Table 1**, there was no significant difference in gender and age between the two groups (X^2 = 2.474, P = 0.122; t = 0.221, P = 0.825). The hemoglobin concentration, total protein and albumin levels were significantly lower in the rivaroxaban group than those in the control group (P<0.05), while urea

Table 2. Comparison of baseline demographic and clinical characteristics in AKD and those without AKD group in the rivaroxaban and control groups

Variates	AKD (n = 72)	Without AKD (n = 1352)	t/X^2	P
Age (years)	72.07±10.66	71.04±11.06	0.772	0.440
Sex ratio (male/female)	36/36	663/689	0.025	0.874
Taking rivaroxaban n (%)	58 (80.56)	735 (54.36)	19.004	<0.001
RBC count (*10^9/L)	3.82±1.27	4.23±0.94	3.120	0.002
HGB (g/L)	130.57±22.32	132.41±19.76	0.690	0.491
Platelet count (*10^9/L)	198.38±80.52	206.63±68.90	0.887	0.375
Creatinine (μmol/L)	100.90±39.62	73.91±30.23	6.697	<0.001
Urea (mmol/L)	8.59±4.30	6.67±3.67	4.245	<0.001
Uric acid (μmol/L)	386.00±159.84	343.87±103.25	3.172	0.002
Triglyceride (mmol/L)	2.08±3.72	1.62±1.34	2.800	0.005
Cholesterol (mmol/L)	4.48±1.58	4.25±1.20	1.563	0.118
Alanine aminotransferase (IU/L)	18.22±15.55	21.45±23.06	0.994	0.320
Total protein (g/L)	68.29±7.66	67.98±6.82	0.424	0.671
Albumin (g/L)	39.53±5.52	39.89±4.33	0.702	0.483
Primary disease				
Pre-existing hypertension n (%)	45 (62.50)	968 (71.60)	2.756	0.097
Pre-existing diabetes n (%)	25 (34.72)	415 (30.70)	0.519	0.471
Pre-existing proteinuria n (%)	29 (40.28)	148 (10.95)	54.030	<0.001

RBC: Red Blood Cell; HGB: Hemoglobin.

levels were higher than those in the control group (P<0.05). There were no significant differences in serum creatinine, uric acid, triglyceride, platelet count and cholesterol levels between the two groups (See **Table 1**).

Those taking rivaroxaban had increased relative risk of AKD in comparison to these in the control group with NVAF

Among the 793 patients who took rivaroxaban, 58 patients developed AKD within 3 months; while 14 patients developed AKD within 3 months in the 631 patients in the control group. Patients taking rivaroxaban had increased relative risk of AKD in comparison to the control group of NVAF patients (58/793 Vs. 14/631, relative risk (RR) = 3.297, X^2 = 19.001, P< 0.001).

Comparison of baseline characteristics between AKD and NKD in the rivaroxaban and control group

In our current study, there were 72 patients who developed AKD while 1352 patients did not develop AKD (NKD). The AKD group had significantly more patients taking rivaroxaban, significantly lower serum red blood counts, higher serum creatinine, urea, uric acid and triglyceride, as well as more pre-existing proteinuria (P<0.05) in comparison to without AKD (NKD) patients (**Table 2**).

Multivariate logistic regression analysis for risk factors of AKD

We chose some variates that had significant differences between AKD and NKD groups and performed univariate logistic regression analysis, then we selected the variates with P<0.1 and entered them into multivariate logistic regression analysis to correct for confounding factors.

Our results demonstrated that taking rivaroxaban and pre-existing proteinuria were the determinant risks of AKD in patients with non-valvular atrial fibrillation (**Table 3**).

Discussion

Abt, et al. reported the first case of acute renal injury in patients who took warfarin excessively [8]. Since then, researchers have begun to pay attention to the effect of oral anticoagulants on the kidney. Anticoagulation related nephropathy (ARN) is a renal complication caused by

Table 3. Multivariate logistic regression analysis of the risk factors of AKD in the rivaroxaban and control groups

Variates	B	*P* value	OR	95% CI of OR
Pre-existing proteinuira	1.690	<0.001	5.420	3.121-9.415
Rivaroxaban/Control	1.236	<0.001	3.441	1.818-6.512
Constant	-4.341	<0.001	0.013	

anticoagulant drugs. It is closely related to the incidence rate of kidney disease and all-cause mortality [9].

Besides warfarin, in recent years, new oral anticoagulants such as rivaroxaban, dabigatran and apixaban have been widely used around the world. Yao et al. found that the incidence of acute renal injury in patients taking new oral anticoagulants was 5.90%-9.20%, and the cumulative incidence of AKI caused by rivaroxaban in 6 months was 4.5% [4] which was lower than warfarin-induced nephropathy (19.33-20.5%). They also confirmed that new oral anticoagulants were associated with reduced 23% risks of ≥30% decline in eGFR within two years compared with warfarin [4].

Nakagawara, et al. reported real-world outcomes of rivaroxaban treatment in patients with nonvalvular atrial fibrillation and worsening renal function. They confirmed 16.2% (1299 cases) patients with worsening renal function and 83.6% (6280 cases) patients with stable renal function. In their study, patients with worsening renal function were defined as those with a creatinine clearance decrease of 20% of the enrollment measurement, at any time during the 1-year follow-up. Patients with stable renal function were defined as those without such a decrease [10].

Coleman observed 36,318 rivaroxaban and 36,281 warfarin users. CKD Stages 3 and 4 CKD were present in 5% and 1% of patients at baseline, and proteinuria was present in 2%. Rivaroxaban appears to be associated with lower hazards of undesirable renal end points (AKI, progression to stage 5 CKD or hemodialysis) versus warfarin in patients with NVAF [11]. Lee investigated 3657 patients and the mean observation time was 3.3 years, the results showed that warfarin was associated with a higher incidence of AKI compared with novel oral anticoagulants [12].

At present, the studies compared the risk of kidney injury between warfarin, new oral anticoagulants such as rivaroxaban, dabigatran and apixaban, and confirmed that renal function decline is common among patients with atrial fibrillation treated with oral anticoagulant agents NOACs, particularly dabigatran and rivaroxaban, which may be associated with lower risks of adverse renal outcomes than warfarin [4].

Our current study investigated the risk of acute kidney disease in Chinese patients while taking rivaroxaban with non-valvular atrial fibrillation compared with patients without treatment as a control group, we found that relative risk of AKD in the rivaroxaban group was 3.2 times higher in the first three months in comparison to those in the control group. In previous publications we chose inpatients to assess acute kidney injury. In our current study, we chose outpatients as the participants, because very few patients are retested for serum creatinine within 48 hours, and even at 1 week in outpatients, some patients who could be diagnosed with AKI might be missed.

The pathogenesis of anticoagulant related nephropathy is believed to have several aspects: the destruction of the glomerular filtration barrier leads to the hemorrhage in Bowman's capsule and renal tubules, and the red cells in the renal tubules eventually cause obstruction of the lumen, resulting in local ischemia, finally leading to the occlusion of the renal tubules [13]. Other pathogenic mechanisms include arterial embolism [14], interstitial inflammatory response [15], apoptosis of glomerular endothelial cells, and direct damage from anticoagulants to the glomerulus [16].

What are the risk factors of anticoagulant related nephropathy? It is reported that patients with high risk factors of glomerular hemorrhage or chronic kidney disease are more likely to have warfarin related nephropathy when using warfarin [17]. In addition, old age, hypoproteinemia, increased glutamic oxaloaminase, comorbidities of diabetes and hypertension also increase the risk of warfarin related nephropathy [8]. However, the risk factors of renal damage caused by using rivaroxaban, a new anticoagulant, have not been reported due to the

small sample size study. Our current study showed lower hemoglobin, lower total protein and albumin, higher baseline serum urea and more preexisting proteinuria which may increase the risk of AKD while taking rivaroxaban as some confounding factors, so we utilized multivariate logistic regression analysis to correct these confounding factors. As for comorbidities of diabetes and hypertension, the rivaroxaban group had less diabetes and hypertension burden that also abolished the effect of increasing AKD. We demonstrated that taking rivaroxaban and pre-existing proteinuria also were the independent determinant risk factors for developing AKD in non-valvular atrial fibrillation patients.

Previous studies focused on rivaroxaban in comparison to warfarin as induced acute kidney injury (serum increased within one week) or end stage renal disease (kidney injury occurred over three months), or a decrease in GFR20->30%, or any kidney damage lasting 1-2 years [5]; however, we are the first to investigate rivaroxaban's effect on a decrease in glomerular filtration rate (GFR) by ≥35% or increase in serum creatinine (Scr) by >50% after <3 months as defined acute kidney disease. Moreover, we compared patients taking rivaroxaban with control patients without taking medicines.

Our study had some limitations. First, this study was a retrospective cohort study and so we could not draw cause-effect conclusions; moreover, the characteristic of control groups patients did not completely match with those taking rivaroxaban, so we performed multivariate logistic regression for correcting confounding factors and verified that taking Rivaroxaban and pre-existing proteinuria were the independent determinant risks for AKD in non-valvular atrial fibrillation.

Conclusions

We are the first to demonstrate that taking rivaroxaban increases the risk of AKD in the first three months by retrospective cohort study. Moreover, patients with pre-existing proteinuria, and those taking rivaroxaban are the independent determinant risk factors of AKD in NVAF patients informed by multiple logistic regression.

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Disclosure of conflict of interest

None.

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