Editorial

Anticoagulating atrial fibrillation patients: is there a kidney-friendly choice?

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Atrial fibrillation is the most common sustained arrhythmia that will increase the risk of ischemic stroke, systemic thromboembolism as well as mortality. Reduced kidney function and albuminuria are independently associated with higher incidence of atrial fibrillation (1). Without anticoagulation, the risk of thromboembolism is greater with more severe proteinuria and lower estimated glomerular filtration rate (eGFR), according to a follow-up study of the observational ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) cohort (2). Warfarin has been the mainstay of oral anticoagulation therapy since 1954. An observational study using Danish nationwide registries reviewed discharged patients with non-valvular atrial fibrillation from 1997 to 2008, during which the prevalence of renal disease increased from 3.4% to 7.0%. Warfarin was less frequently prescribed in patients with chronic kidney disease (CKD) (17.0%) or receiving renal replacement therapy (RRT) (19.8%) than in those without renal disease (28.6%). Warfarin reduced the risk of stroke or systemic thromboembolism in patients on RRT in this study. However, warfarin was associated with a ~30% increase in the bleeding risk in general, and bleeding occurred more frequently in CKD and RRT groups (3). In another population-based cohort study enrolling patients aged ≥66 years and eGFR <45 mL/min/1.73 m^2, warfarin did not lower the risk of stroke, but a significantly higher risk of bleeding was observed (4). The net clinical benefit of anticoagulation in patients with moderate to severe CKD, including end-stage renal disease (ESRD), is still controversial and requires careful patient selection.

The concern of bleeding is a main barrier to the initiation of warfarin in patients with renal failure since the risk raises as renal function worsens (5). Limdi *et al.* studied warfarin responsiveness in the POAT (Pharmacogenetic Optimization of Anticoagulation Therapy) cohort. The dose required to achieve target international normalized ratio (INR) was lower in patients with severe CKD (eGFR <30 mL/min/1.73 m^2, including dialysis). The risk of excessive anticoagulation (INR >3) was inversely correlated with GFR after adjusting for *VKORC1*, *CYP2C9* genotype and clinical factors. Major hemorrhage doubled in patients with severe CKD compared to those with less severe or no renal failure (6). Lately, the advent of non-vitamin-K dependent oral anticoagulants (NOACs), including direct thrombin inhibitor and factor Xa inhibitors, provides more options for patients with atrial fibrillation and CKD. Dabigatran, apixaban, rivaroxaban, and edoxaban were non-inferior to warfarin regarding risk reduction of stroke, systemic thromboembolism, intracranial hemorrhage and mortality. However, patients with stage 5 CKD were excluded from these pivotal randomized trials and NOACs have not been approved so far in patients with eGFR <15 mL/min/1.73 m^2 (7).

Dabigatran, the only oral thrombin inhibitor, is largely dependent on renal elimination (80%) and can be partly removed by hemodialysis (5). The RE-LY (Randomized

Evaluation of Long-Term Anticoagulation Therapy) trial showed that dabigatran 110-mg twice daily was equivalent to warfarin in preventing stroke or systemic thromboembolism with a lower risk of major bleeding. Dabigatran 150-mg twice daily was superior to warfarin in reducing stroke, thromboembolism, and hemorrhagic stroke, but the risk of bleeding was similar (8). The therapeutic efficacy was preserved in different GFR categories (≥80, 50–80, or <50 mL/min/1.73 m^2) as shown in a subgroup analysis study (9). In a *post hoc* analysis of RE-LY study, dabigatran 110- and 150-mg group experienced slower rate of GFR decline (–2.57±0.24 and –2.46±0.23 mL/min, respectively) compared to warfarin (–3.68±0.24 mL/min) (10). Notably, a study using Nationwide Inpatient Sample in the United States reported that dialysis-requiring acute kidney injury (AKI) increased from 0.3 to 1.5 per 1,000 hospitalizations primarily due to atrial fibrillation over a decade. Dialysis-requiring AKI was associated with 4-fold higher in-hospital mortality and adverse discharge (11). Since AKI is a well-established risk factor in the development and progression of CKD, identifying modifiable risk factors for AKI in patients with atrial fibrillation may potentially improve patient outcome (12,13).

Chan *et al.* conducted a retrospective study using Taiwan National Health Insurance Registry Database to elucidate the characteristics of AKI in warfarin or dabigatran users (14). They reviewed 304,252 patients with incident non-valvular atrial fibrillation from 1996 to 2012. Baseline characteristics and pharmacotherapy were retrieved; renal diagnosis and comorbidities were represented by ICD-9 diagnostic codes, and ESRD patients were excluded. CHA_2DS_2-VASc and HAS-BLED scores (omitting INR criteria) were calculated to represent embolic and bleeding risks. The study finally enrolled 9,958 patients who started or switched to dabigatran and 9,974 patients who started warfarin after June 1, 2012 and followed until the occurrence of first AKI or 18 months. Twenty-one percent of the patients had CKD, defined by ≥2 occurrences of CKD-related codes. The median follow-up duration was 0.69 years for dabigatran users and 0.79 years for warfarin users. The presence of CKD at baseline was associated with a higher incidence of AKI. Moreover, patients treated with dabigatran had a significantly lower risk of AKI than those taking warfarin, and the difference existed in both CKD [hazard ratio (HR) =0.56] and CKD-free (HR =0.62) cohorts. Similar risk discrepancy between dabigatran and warfarin was observed in the rates of receiving RRT and mortality. As CHA_2DS_2-VASc score increased from 0/1 to ≥6, the annual incidence of AKI raised from 2.00% to 6.16% in the CKD-free group and 6.82% to 26.03% in the CKD group. The magnitude of risk escalation was more prominent in warfarin users than in dabigatran users. Multivariate Cox proportional hazard models showed that age, warfarin use, prior corticosteroid use, and heart failure were independent risk factors for incident AKI in patients with atrial fibrillation on anticoagulation.

The epidemiology of AKI in non-valvular atrial fibrillation remains largely unknown. The observation in this large-scale Asian population-based cohort study by Chan *et al.* is thus of paramount importance. First, their finding supported the notion that CKD patients are more prone to develop AKI (13). The susceptibility to AKI also increased in patients with higher CHA_2DS_2-VASc score; therefore, periodic monitoring of renal function is crucial in the management of atrial fibrillation accompanied with CKD or high thromboembolic risk. Further prospective study with extended follow-up is required to find out disease- or treatment-related risk factors unique to atrial fibrillation. Second, the risk of AKI was substantially lower in patients treated with dabigatran, compared to warfarin. The renal and patient outcomes following an episode of AKI vary with the etiology, severity and duration (13). The detailed characteristics of AKI and severity of CKD were not available in this study, because laboratory values were not included in Taiwan National Health Insurance Registry Database. Therefore, the cause of risk discrepancy in AKI between dabigatran and warfarin users was not clear. Moreover, proteinuria is also an independent risk factor for stroke and nephrotic syndrome per se leads to hypercoagulability, mainly due to urinary loss of coagulation inhibitors, such as anti-thrombin III (15). The presence of nephrotic syndrome and the extent of proteinuria should be categorized as independent variables. Interestingly, prior corticosteroid use was associated with an increased risk of AKI in this cohort. Administration of corticosteroid possibly reflects the presence of active inflammatory or autoimmune disorders, which may be hidden confounding factors to the development of AKI. Further investigations taking nephrotic syndrome, proteinuria level and more detailed comorbidities into account will lead to better risk stratification.

There is increased concern about anticoagulant-related nephropathy, including warfarin-related nephropathy (WRN), and excessive anticoagulation is the most recognized risk factor. Other putative mechanisms include

vascular calcification secondary to vitamin K antagonism and altered thrombin signaling (16). Two case series reviewed kidney biopsy specimens in 13 and 9 patients over-anticoagulated with vitamin K antagonists. The nephropathy manifested as AKI, and gross or microscopic hematuria was invariably present. Light microscopic finding was characterized by severe glomerular hemorrhage, red blood cells (RBCs) in the Bowman space and formation of compact RBC casts in the tubular lumen. Of note, coexisting glomerular or tubulointerstitial abnormalities, and positive immunofluorescence staining were present in the majority of specimens (17,18). Co-occurrence of WRN with diverse glomerular diseases, including lupus nephritis, IgA nephropathy, and thin basement membrane disease were also described in case reports. Similar pathologic findings were reported in two cases of dabigatran administration with coexisting IgA nephropathy (19,20). Two retrospective studies in the United States and Korea enrolled patients with excessive anticoagulation (INR >3), 20% of which experienced AKI, defined by the Acute Kidney Injury Network (AKIN) criteria. The presence of heart failure and CKD were associated with a higher risk of AKI. Both studies commonly showed that the risk of mortality was higher in patients who experienced WRN (21,22). In this study by Chan *et al.*, nearly 90% of dabigatran users in the study took 110-mg dose, in contrary to 50% in the RE-LY trial. However, the lack of INR and eGFR precludes comparison of anticoagulation efficacy, and whether the risk of anticoagulant-related nephropathy was modified by the type or dose of anticoagulant requires further investigation.

Warfarin is primarily metabolized in the liver by CYP2C9. Monitoring INR response and consideration of sophisticated food and drug interactions are critical to ensure safe anticoagulation. The prescription of NOACs obviates the need of routine monitoring and has a favorable benefit-to-risk ratio in general population. However, NOACs are eliminated by the kidneys; the half-lives are prolonged in the presence of renal failure, and therefore, proper dosing is required to prevent over-anticoagulation. Currently there is no need and no readily available parameter to indicate the level of anticoagulation in daily clinical practice, physicians should pay attention to renal function monitoring and dose titration, especially in patients with advanced age, impaired or rapid deterioration in renal function, or heart failure. In patients treated with warfarin or NOACs who developed unexplained rise of serum creatinine with gross or microscopic hematuria, nephropathy associated with excessive anticoagulation has to be considered and the level of anticoagulation should be corrected to avoid irreversible renal damage and adverse patient outcome.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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