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Editorial

Does renal function have incremental predictive value of stroke in atrial fibrillation?

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It is well known that both atrial fibrillation (AF) and chronic kidney disease (CKD) are respectively independent predictors of stroke and systemic thromboembolism. A number of epidemiological and observational studies have shown that there are close relationships between AF and CKD [1–3]. Indeed, the prevalence of AF increases from non-CKD to CKD stages of 1 to 2, 3 and 4 to 5 by 1.0%, 2.8%, 2.7%, and 4.2%, respectively [1], and the prevalence is 7% to 27% in patients with end-stage renal disease who are undergoing hemodialysis therapy [2]. The prevalence of CKD is 10% to 15% in patients with AF [3]. AF develops even in the presence of mild CKD and the prevalence of AF increases in relation to decrease in renal function. CKD is also associated with AF.

Several possible mechanisms by which CKD and AF cause stroke and systemic thromboembolism have been postulated. CKD and AF have common traditional cardiovascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, aging, obesity and smoking. In addition, CKD and AF per se and traditional cardiovascular risk factors induce activation of the renin-angiotensin-aldosterone system, enhancement of sympathetic nervous activity, increase in inflammation, activation of oxidative stress, increases in thrombogenic factors, leading to endothelial dysfunction abnormality of vascular structure, and hypercoagulation including platelet activation and fibrinolysis, resulting in stroke and systemic thromboembolism (Fig. 1). The coexistence of AF and CKD should additionally and synergistically increase the risk of stroke and systemic thromboembolism.

It is therefore expected that the ability to predict stroke and systemic thromboembolism would be greatly improved by using conventional stroke risk scores, $CHADS_2$ and CHA_2DS_2-VASc, with the addition of an index of renal function compared with using only $CHADS_2$ or CHA_2DS_2-VASc in patients with AF. Indeed, Piccini et al. used a new stroke risk score that was calculated similarly to the $CHADS_2$ score with the addition of 2 points for renal dysfunction (estimated glomerular filtration rate of less than 60 mL/min) as named "R_2CHADS_2" in patients with AF, and R_2CHADS_2 predicted stroke and systemic thromboembolism after adjustment of $CHADS_2$ and CHA_2DS_2-VASc in these patients using data from the Rivaroxaban Once-daily, oral, direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) and AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) [4]. Several lines of evidence have also shown that $CHADS_2$ score with the addition of renal dysfunction significantly improves the ability to predict future events of stroke and systemic thromboembolism in patients with AF [5,6]. However, in the study by O'Brien et al. (in the current issue), impaired renal function assessed by creatinine clearance of less than 60 mL/min did not improve the ability to predict the incidence of stroke and systemic thromboembolism events in both patients with AF who were treated with oral anticoagulation and were used without oral anticoagulation when $CHADS_2$ and CHA_2DS_2-VASc were used [7].

In a clinical setting, it is important to determine whether renal dysfunction is significantly associated with an increase in the incidence of stroke and systemic thromboembolism in patients with AF. However, it is controversial whether renal dysfunction is an independent predictor of stroke in patients with AF [4–9]. In addition, unfortunately, there is no reliable information from large-scale randomized controlled trials showing relationships of renal function with stroke and systemic thromboembolism and the effects of oral anticoagulation on stroke and systemic thromboembolism in elderly AF patients with non-end-stage CKD. There are a number of difficulties in performing large clinical trials for targeting cardiovascular events including stroke and systemic thromboembolism in patients with AF. The difficulties include the lack of an accurate system for monitoring the presence of AF (underdiagnosis of asymptomatic AF and definition of paroxysmal AF or persistent AF), an insufficient predictive scoring of events, different dosages and kinds of oral anticoagulation, different ages, different races, and different follow-up periods. In this comment for the current issue, I focus on the length of the study follow-up period. Since it is thought that the interdependence between AF and CKD grows greater over time, the follow-up period should be taken into consideration for determining whether renal function significantly contributes to the occurrence of stroke and systemic thromboembolism in patients with AF. Most of the previous studies in which the relationship between renal function and cardiovascular events in patients with AF was evaluated were

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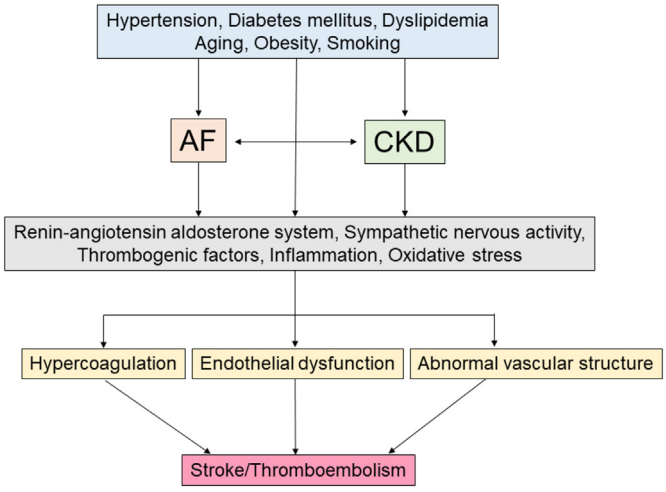

Fig. 1. Figure Putative mechanisms of atrial fibrillation (AF)-induced and chronic kidney disease (CKD)-induced stoke and systemic thromboembolism.

cross-sectional studies, not observational studies, and had follow-up periods of less than a few years. In the current issue [7], the length of the follow-up period was 2 years using data from the Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF), and it is relatively short. Observations in a much longer follow-up period would enable more specific conclusions concerning the role of renal function in stroke and systemic thromboembolism in this study population to be drawn. Such observations would indicate the optimal option for prevention of stroke and systemic thromboembolism in AF patients with CKD.

Does renal function ($CHADS_2$-R_n and CHA_2DS_2-VASc-R_n) have no incremental predictive value for stroke in patients with AF compared with conventional stroke risk scores, $CHADS_2$ and CHA_2DS_2-VASc? Or will $CHADS_2$ and CHA_2DS_2-VASc be changed to new stroke risk scores, $CHADS_2$-R_n and CHA_2DS_2-VASc-R_n, in the future?

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