Editorial

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Atrial fibrillation and chronic kidney disease: A bad combination

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Atrial fibrillation (AF) affects approximately 2% of the population worldwide, and this percentage is projected to increase over the next 50 years. AF frequently complicates chronic kidney disease (CKD) and is associated with adverse outcomes. Evolution to end-stage renal disease (ESRD) is a key complication of CKD, and the presence of AF is associated with a higher risk of developing ESRD in patients with CKD. Furthermore, CKD is often associated with hypertension and high atrial pressure, both of which may lead to AF. Therefore, the development of AF in patients with CKD may reflect mechanical stress in the atrium. CKD and AF share risk factors and putative mechanisms, suggesting that common pathophysiologic processes may drive both pathologies. One possible common link between AF and CKD is activation of the renin–angiotensin–aldosterone system (RAAS). Evidence suggesting a role for the RAAS in the pathogenesis of AF has been previously provided. Angiotensin II can increase atrial pressure, promote atrial fibrosis, and modulate ion channels, all of which are involved in structural and electrical remodeling of the atria, thus resulting in AF. In addition, polymorphisms in genes encoding components of this pathway have been linked to the development of AF. We consider that atrial remodeling caused by CKD may contribute to the higher incidence of AF recurrence in patients with CKD than in those without.

In this issue of *Journal,* Shin et al. [1] reported that chronic digoxin treatment in AF patients with pre-existing ischemic heart disease (IHD) and CKD classes III–V was significantly associated with a greater risk of fatal major adverse cardiac and cerebrovascular events (MACCEs), in the form of heart failure (HF) death, fatal myocardial infarction, sudden cardiac death and fatal stroke. Thus, close monitoring should be done in chronic digoxin-treated AF patients with pre-existing IHD and CDK III–V. According to this manuscript, pre-existing IHD associated with decreased glomerular filtration rate (GFR) (≤ 60 mL/min/1.73 m^2) was significantly related to MACCEs (hazard ratio, 1.52; 95% confidence inverval [CI], 1.26–1.83; $P < 0.001$). The Kaplan-Meier curve showed that both pre-existing IHD and GFR (≥ 60 mL/min/1.73 m^2) in AF patients were significantly associated with a negative impact on survival free from MACCEs during 10-year follow-up [1].

The development of an electrophysiological and structural substrate for AF results from an interplay of various mechanisms: atrial stretch and dilatation, interstitial fibrosis, oxidative stress, and disturbed intracellular calcium homeostasis. Moreover, the autonomic nervous system plays an important role in the genesis and sustainability of AF. Over the past decade, growing evidence has highlighted the importance of the pulmonary veins and posterior left atrium in harboring potential foci for producing AF. This area has distinctive anatomic, molecular, and electrophysiological properties that favor the progress and maintenance of AF. The autonomic nervous system (both sympathetic and parasympathetic) plays a critical role in creating a 'dynamic' substrate for atrial arrhythmia, both in a normal heart and in structural car-

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diac disease. Sympathetic stimulation predisposes to arrhythmia via Ca^{++} influx and Ca^{++} release from the sarcoplasmic reticulum, thus enhancing the automaticity and triggered activity. On the other hand, vagal activation induces non-homogenous shortening of the atrial effective refractory period, enhancing the potential for reentry [2]. Animal studies that employed direct nerve recording also demonstrated that patterns of increased sympathetic and vagal discharge were involved in paroxysmal and persistent AF [3]. Increased atrial sympathetic innervation was also revealed in the atrial tissue, as opposed in sinus rhythm, from individuals with persistent AF undergoing coronary artery bypass grafting.

Note that in a CASTLE-AF trial [4], both randomized groups at baseline had the same percentage of hypertensive patients and left ventricular ejection fraction; 72% vs. 74% and 29% vs. 30% for the ablation and pharmacological groups, respectively. Further, for New York Heart Association classes, the use of angiotensin-converting enzyme vs. angiotensin receptor blocker was found to be 94% vs. 91%, vs. β-blocker was 93% vs. 95%, and vs. diuretics including spironolactone was 93% vs. 93% for the ablation and pharmacological groups, respectively [4]. Considering this, we suggest that these subjects exhibit similar blockade degrees of the RAAS. However, the number of individuals presenting with type 2 diabetes mellitus are different between the ablation (24%) and pharmacological (36%) treatment groups ($P = 0.010$). Even if the requirement of dialysis due to terminal renal failure was an exclusion criterion, we could not measure or affirm if the percentages of CKD stages between groups were similar or significantly different.

We know that activation of the sympathetic nervous systems contributes to insulin resistance and that metabolic syndrome is associated with risk of developing diabetes mellitus. This suggests that growth in forearm noradrenaline release accompanied by reduced blood flow is linked with reduced glucose uptake, indicating an impaired ability of the cell to transport glucose across its membrane. This is associated with a neurally mediated decrease in the number of open capillaries, resulting in an augmented distance that insulin must travel to reach the cell membrane from the intravascular compartment. This condition is further amplified by how the insulin-mediated increase in muscle perfusion is reduced by approximately 30% in insulin resistant states [5]. The significance of these hemodynamic consequences of sympathetic activation is emphasized by studies demonstrating a direct association between muscle sympathetic nerve activity and insulin resistance, as well as by an inverse association between insulin resistance and the number of open capillaries. It is well stablished that sympathetic activation is a hallmark of the essential hypertensive state occurring early in the clinical course of the disease. In CKD, sympathetic overactivity appears to be manifested at the earliest clinical stage of the disease and is directly associated with the severity of renal failure. In both conditions, i.e., hypertension and renal failure, the mechanisms of the hyperadrenergic state are numerous and include reflex and neurohumoral pathways. Adrenergic activation displays adverse impacts on cardiovascular morbidity, and in the case of renal failure, on cardiovascular mortality [6,7].

In this issue, Shin et al. [1] also demonstrated some important different baseline features between subjects without pre-existing IHD and with preexisting IHD; specifically, there are larger percentages of hypertension, diabetes, and CKD III–V, and a higher CHA_2DS_2-VASC in the last group. On the other hand, the baseline clinical characteristics of patients with GFR ≤ 60 compared with GFR > 60 mL/min/1.73 m^2 had higher percentages of hypertension, diabetes, and pre-existing IHD, higher CHA_2DS_2-VASC, and an elevated serum digoxin concentration. By evaluating and comparing the baseline clinical characteristics between groups without MACCE and with MACCE, we observed that the number of hypertensive subjects was equal in both groups, and in the latter group, we found major incidence of sympathetic hyperactivity diseases such as diabetes, pre-existing IHD, and CKD III–V. As expected, the unique predictors of MACCEs were pre-existing IHD alone, CKD III–V alone, and pre-existing IHD + CKD III–V combined. We attribute these findings to the feedback loop of the RAAS and the sympathetic hyperactivity action; here, observations of the renal sympathetic afferent nerves suggest the kidneys as the origin of the central sympathetic drive.

According to "2016 ESC Guidelines for the management of AF developed in collaboration with EACTS" [8], for acute rate control, beta-blockers and diltiazem/verapamil were preferred over digoxin because of their rapid onset and effectiveness at high sympathetic tone. Regarding the long-term pharmacological rate control,

β-adrenoreceptor blocker monotherapy is often used as the first-line rate-controlling agent, largely based on observations of better acute heart rate control than digoxin. Digoxin and digitoxin have been used for over 200 years, even though prescriptions have been continually decreasing over the past 15 years. In a randomized Digitalis Investigation Group trial, digoxin had no effect on mortality compared to placebo in HF with reduced ejection fraction patients in sinus rhythm (relative risk [RR], 0.99; 95% CI, 0.91—1.07), but digoxin was associated with reduced hospital admissions (RR, 0.72; 95% CI, 0.66—0.79) [9,10]. There have been no one-on-one randomized controlled trials of digoxin in AF individuals. Observational studies have associated digoxin use with excess mortality in AF patients, but this association is likely due to selection and prescription biases rather than harm caused by digoxin, especially given that digoxin is commonly prescribed to sicker patients [8].

Even though digoxin augments cardiac oxygen consumption and contractility, it is expected that the increases in these parameters in pre-existing IHD subjects are likely due to coronary vasoconstriction. Consequently, a rise in heart rate, more frequent ischemia, and more oxygen consumption may lead to an augmented effect on the feedback loop of the RAAS and the sympathetic hyperactivity action, thus resulting in arrhythmias, myocardial infarction, and worsening of renal function. In conclusion, digoxin should be avoided in patients with pre-existing IHD associated with CKD III—V.

Conflicts of interest

All authors have no conflicts of interest to declare.

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