Internal and Emergency Medicine (2019) 14:1025–1027
https://doi.org/10.1007/s11739-019-02141-0

IM - COMMENTARY

Atrial fibrillation and kidney disease: insights on a close relationship

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Received: 31 May 2019 / Accepted: 26 June 2019 / Published online: 17 July 2019

The association between atrial fibrillation (AFib) and kidney disease is common but represents a challenge for clinicians, since patients experience significant morbidity and mortality and require a careful management [1, 2]. These two diseases have a similar distribution in the general population, with prevalence increasing with age, and share several risk factors, including hypertension, diabetes and cardiovascular disease [3, 4]. Recent observations have highlighted that they are closely related and each predisposes to the development of the other.

Population-based studies have found that the incidence of AFib is significantly higher in patients with chronic kidney disease (CKD) as compared to the general population, after adjusting for demographic features and comorbidities [5, 6]. The risk is particularly increased among patients on dialysis and kidney transplant recipients [7, 8]. AFib may be favoured by a number of disorders associated to advanced kidney impairment, including myocardial hypertrophy, fluid overload and electrolyte imbalance. However, even mild kidney dysfunction is associated with incident AFib, suggesting that additional mechanisms are likely involved.

Moreover, AFib also increases the risk of kidney disease. In a large prospective study on more than 230,000 Japanese individuals, AFib patients were nearly twofold more likely to develop glomerular filtration rate (GFR) reduction and proteinuria than those without [9]. This association remained significant among those without treated hypertension and diabetes and in multivariate models adjusted for risk factors. Incident AFib was also independently associated with progression toward end-stage renal disease (ESRD) in CKD patients [10]. Moreover, the presence of AFib is a strong predictor of acute kidney injury (AKI) in patients undergoing cardiac surgery [11].

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In this issue of *Internal and Emergency Medicine*, Hu et al. further characterise the association between atrial arrhythmia and kidney disease, comparing the risk of adverse renal outcomes between AFib and atrial flutter (AFlu) [12]. Two cohorts of 17,450 subjects diagnosed with either AFib or AFlu were 1:1 propensity-score matched for age, sex, index date and comorbidities using logistic regression model and followed starting since AFib/AFlu detection until occurrence of AKI, CKD, ESRD or death. The data were collected from the Taiwan National Health Insurance Research Database, which covers nearly the whole national population. For each patient, the diagnosis was obtained from medical claims data coded according to the International Classification of Diseases, 9th Revision, Clinical Modification. This approach has the potential disadvantage of missing some cases but anyway was used in numerous observational studies with reliable results [7, 13–15].

This study is the first to determine the rate of renal complications in two distinct types of atrial arrhythmia with similar clinical manifestations and management. Compared to AFlu patients matched for established risk factors and after adjusting for covariates and consideration of the competing risk of death, those with AFib experienced higher risks of acute and chronic kidney dysfunction (respectively 1.08, 1.18 and 1.32 times more likely to suffer from AKI, CKD and ESRD respectively). This supports the concept of a close relationship between AFib and kidney disease that is not fully accounted for by the presence of comorbidities and may imply the existence of further pathogenic links.

In the study, the cumulative incidence of AKI did not differ significantly between the cohorts, suggesting that AFib and AFlu share determinants of acute renal failure, such as haemodynamic decompensation and systemic thromboembolism. On the contrary, the cumulative incidence of CKD and ESRD was significantly superior in AFib patients compared to those with AFlu, possibly indicating that mechanisms promoting chronic kidney damage are peculiar to AFib and may account for the higher incidence of events.

Since AFib has been found to predispose to CKD and vice versa, it seems likely that common pathways underlie both

conditions. In this sense, chronic inflammation and renin-angiotensin system (RAS) have been proposed as possible mediators. C-reactive protein (CRP), a well-recognised marker of inflammation, is significantly higher in patients with paroxysmal and persistent AFib versus controls and correlates with increased risk of dysrhythmia [16–19]. CRP and other inflammatory markers, including fibrinogen and interleukin-6, have also been found elevated in patients with moderate to severe kidney dysfunction and are independently associated with further progression of renal disease [20, 21]. In addition, increased RAS activity is known to accelerate the GFR decline and seems to be involved in AFib triggering and maintaining [22–24]. The links between AFib and CKD may also include increased oxidative stress and high sympathetic nervous system activation as part of a complex dysregulated milieu [25–27]. These alterations are interrelated and may contribute to renal sclerosis and atrial fibrosis, which are the anatomical substrate of chronic kidney damage and AFib [28–30]. A deeper knowledge of these mechanisms is warranted and seems to be encouraged by the results of this study. Such pathways could also represent therapeutic targets to prevent and improve both conditions. Intriguingly, statin administration has shown positive effects on CRP levels and can reduce the risk of AFib in both general and CKD population [31–33]. Moreover, CKD patients treated with atorvastatin reported significant improvement in proteinuria and dampening of GFR decline [34]. RAS blockade with angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers has an established renoprotective effect but is also able to lower inflammatory markers and reduce the risk of incident or recurrent AFib in patients with cardiovascular disease [35–37].

It must, however, be acknowledged that an unequal distribution of residual confounders may have influenced the outcomes. The authors were not able to stratify patients according to the type of arrhythmia (paroxysmal, persistent or permanent), its resolution or persistence and the received treatment. Moreover, the database included neither subclinical relevant markers, such as left ventricular hypertrophy and albuminuria at baseline, nor possible cardiovascular events during follow-up. Although these factors could have played a causal role in renal complications, it seems unlikely that they can fully explain the difference in incidence between AFib and AFlu patients, given the large size of the cohorts and the careful matching. Thus, the existence of multiple dysregulated pathways increasing risk of AFib and kidney disease remains a reasonable hypothesis.

AFib patients require a wide screening and a tight monitoring for the frequent development of organ damage, including kidney dysfunction. However, this study also shows that the risk of kidney impairment in AFlu patients, although inferior to that of AFib patients, is non-negligible and should be taken into account during follow-up. Kidney disease associated to atrial arrhythmia needs to be further investigated, e.g., by retrospectively analysing clinical and pathological features of patients who developed adverse renal outcomes. Future studies might identify the subset at higher risk of renal complications and define the optimal treatment strategy.

Compliance with ethical standards

Conflict of interest The author declares that they have no conflict of interest.

Statement of human and animal rights I undersign and certificate that the procedures employed to draft this manuscript respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2000, as well as the national law.

Informed consent For this type of study formal consent is not required.

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