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LETTER TO THE EDITOR
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Short-term observation of direct oral anticoagulant use in an atrial fibrillation patient with high bleeding risk and kidney transplant: a case report

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Kidney transplant (KTx) is considered to be the best treatment for end-stage renal diseases compared with hemodialysis or peritoneal dialysis, because it significantly improves renal function, reduces cardiovascular events and mortality, enhances quality of life and prolongs life expectancy.[1,2] Atrial fibrillation (AF) is frequently coexistent with KTx, and a higher risk will occur in KTx recipients with AF compared with those aren't with AF.[3] Patients with AF are at risk of stroke, systemic emboli and death. It is recommended that high-risk AF patients should use oral anticoagulants for preventive treatment. Direct oral anticoagulants (DOACs), including dabigatran, rivaroxaban, apixaban and edoxaban, are widely recommended for use in the general population compared to vitamin K antagonists (VKA).[4,5] However, in the chronic kidney disease population, the evidence for the use of DOACs is limited because all these drugs are partially eliminated by the kidney and may cause subsequent accumulation and bleeding risks.[6] To date, clinical evidence regarding the use of DOACs in KTx recipients is scarce. Herein, we report a successful case of the use of DOACs for an AF patient with high bleeding risk and a history of KTx several months ago and the short-term follow-up shows that its safety is good.

A 63-year-old male complained of paroxysmal palpitations for seven years and recurrence in recent months. The electrocardiogram (ECG) showed AF and the medical history of this patient included aspirin antiplatelet therapy which was discontinued five years ago due to massive upper gastrointestinal bleeding and hemorrhagic shock caused by gastric ulcer. For the past several months, the patient felt palpitation and irregular pulses which lasted for about 1 h to 2 h each time and relieved spontaneously. This patient was admitted in Beijing Tsinghua Changgung Hospital for further evaluation, and ECG confirmed AF (Figure 1). At the same time, the patient with a history of hypertension, hyperlipidemia, coronary heart disease, and end-stage renal disease caused by IgA nephropathy and allograft renal transplantation. Currently, the drugs, including tacrolimus 3.5 mg twice daily, mycophenolate mofetil dispersible tablets 0.5 mg twice daily, prednisone acetate tablets 10 mg once daily, metoprolol tartrate sustained-release tablets 11.875 mg once daily, nifedipine controlled release tablets 30 mg once daily, eseomeprazole enteric coated tablets 40 mg once daily, calcium carbonate tablets 750 mg once daily and atorvastatin calcium tablets 10 mg once nightly, have been taken. Blood tests showed serum creatinine of 147.1 umol/L, estimated glomerular filtration rate (eGFR) of 43.5 mL/min per 1.73 m^2, mild anemia (red blood counter: 2.9 × 10^{12}/L, hemoglobin: 94 g/L, and hematocrit: 29.1%), normal range of white blood cell count and platelet count, routine urine and liver function, negative occult blood, and D-dimer of 2.2 mg/L. The 24-hour Holter monitoring revealed paroxysmal AF (Figure 2) and ultrasonic cardiogram (Figure 3) showed left and

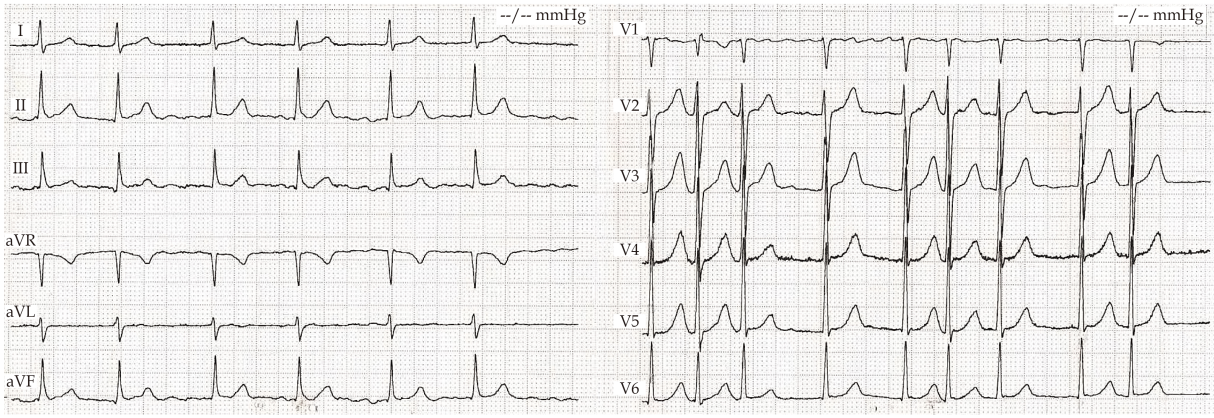

Figure 1 Continuous electrocardiogram monitoring for outpatient. Electrocardiogram shows the atrial fibrillation rhythm, with frequency of 93 beats/min.

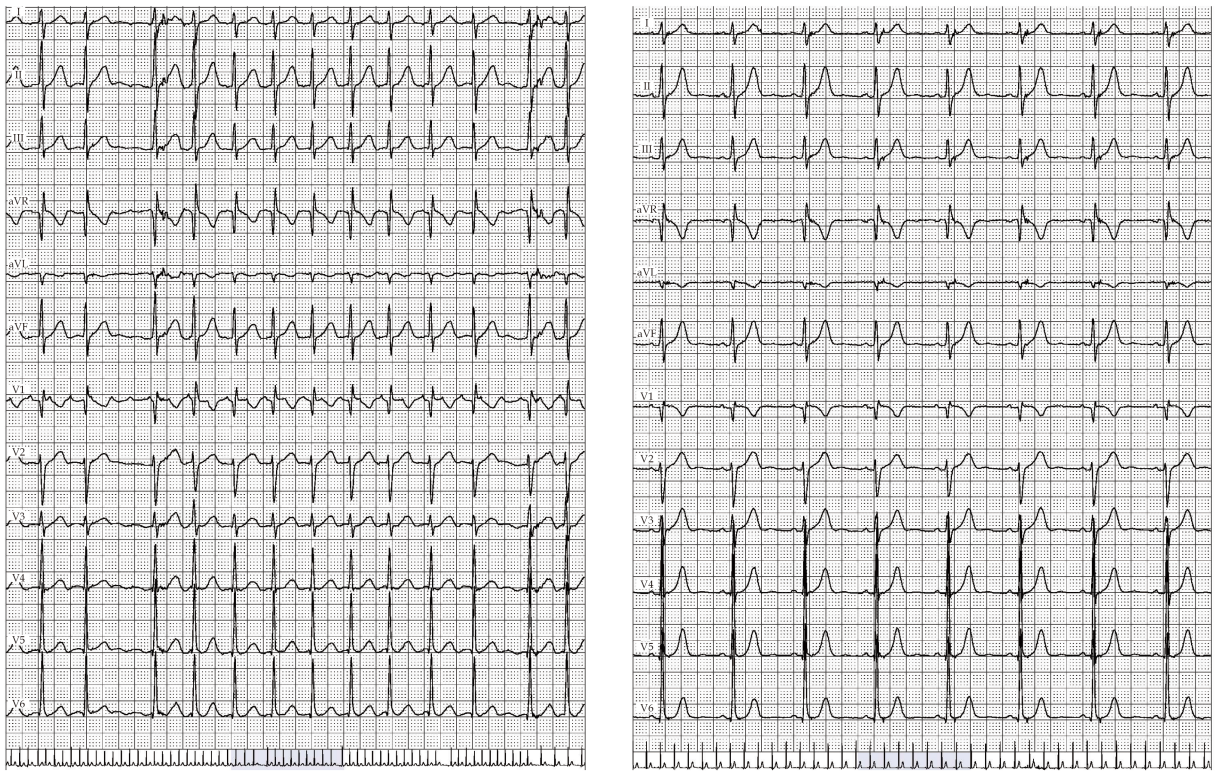

Figure 2 Continuous 24-hour Holter monitoring for outpatient. The 24-hour Holter monitoring shows the paroxysmal atrial fibrillation.

right atrium enlargement, left ventricular ejection fraction of 65%, which can exclude structural valvular heart disease. Tacrolimus blood concentration level was 8.69 ng/mL before the use of DOACs. The patient had CHA_2DS_2-VASc score of 2 (hypertension = 1, coronary heart disease = 1) and HAS-BLED score of 4 (hypertension = 1, abnormal renal function = 1, bleeding history = 1, concomitant glucocorticoid = 1). After fully communicating with doctors and the patient's family and reaching an agreement, the anticoagulation therapy was selected and radiofrequency ablation or left atrium appendage occlusion was refused to perform. Rivaroxaban 15 mg once daily was delivered. Blood serum creatinine and tacrolimus concentrations were determined after the starting of anticoagulation therapy, which ranged from 129.8 to 171.0 umol/L (eGFR: 35.9–50.2 mL/min per 1.73 m^2) (Figures 4 & 5) and from 4.75 to 10.45 ng/mL (Figure 6), respectively. After three-month follow-up, the patient reported no discom-

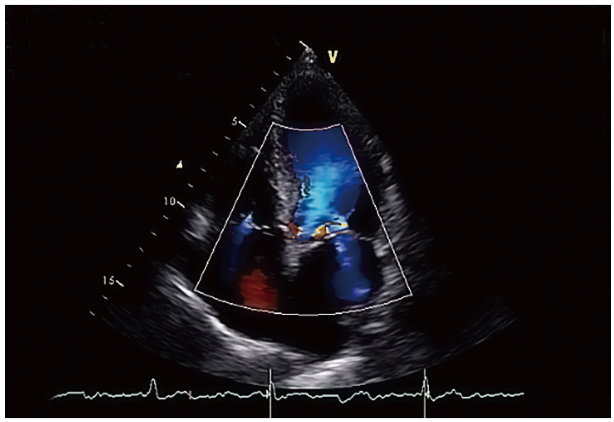

Figure 3 Outpatient ultrasonic cardiogram. Ultrasonic cardiogram shows enlarged left and right atrium under atrial fibrillation rhythm, and moderate amount mitral regurgitation, with no evidence of structural valvular heart disease.

fortable symptoms or any signs of bleeding.

The AF is the most common cardiac arrhythmia with an increasing prevalence among KTx recipients. A meta-analysis shows that the pooled estimated prevalence of pre-existing AF in patients undergoing KTx was 7.0% (95% CI: 5.6%–8.8%) and pooled estimated incidence of AF following KTx was 4.9% (95% CI: 1.7%–13.0%).[3] There is a significant association of AF with increased stroke [odds ratios (OR) = 2.54], death-censored allograft loss (OR = 1.55) and mortality (OR = 1.86), primarily from cardiovascular disease after KTx.[3] The association between AF and increased risk of graft failure may be explained by a higher risk of recurrent micro-embolism in KTx patients.[7] The American College of Cardiology/American Heart Association Task Force on the management of patients with AF and the European Society of Cardiology guidelines for the management of AF have indicated that DOACs are superior to VKA in stroke prevention for the general AF population, especially for newly initiated, because DOACs have the fixed dosing, wider therapeutic window, no need to close laboratory monitoring and lower frequency of intracranial bleedings compared with VKA.[4,5] All the DOACs are substrates of the multidrug transporter P-glycoprotein, and rivaroxaban and apixaban are also substrates of CYP_3A_4.[8] KTx patients need to receive oral immunosuppressive therapies to avoid rejection episodes, such as tacrolimus or cyclosporine, which are both substrates as well as *in vitro* inhibitors of CYP_3A_4 and P-glycoprotein,[9] but only cyclosporine appears

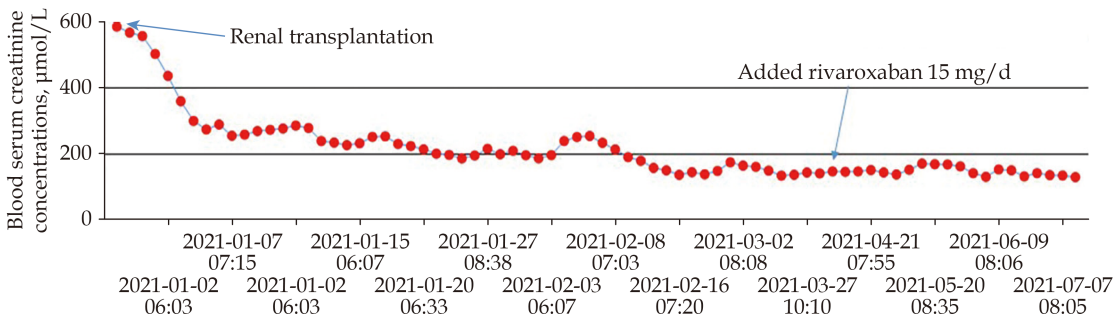

Figure 4 Blood serum creatinine concentrations. The figure shows the blood serum creatinine level kept stable after the initiation of rivaroxaban compared with using the drug before.

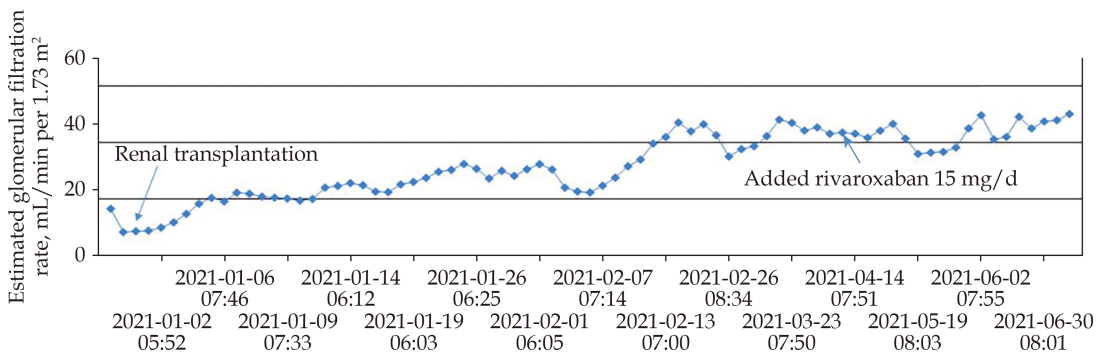

Figure 5 Estimated glomerular filtration rate. The figure shows the estimated glomerular filtration rate level kept stable after the initiation of rivaroxaban compared with using the drug before.

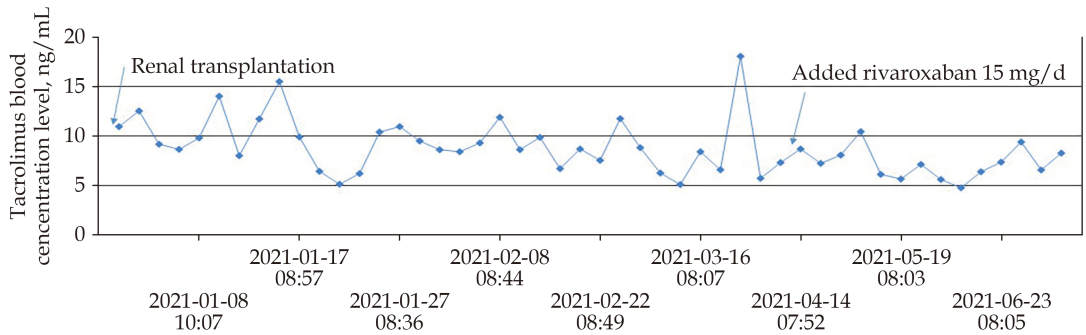

Figure 6 Blood concentration level of tacrolimus. The figure shows the tacrolimus concentrations kept stable after the initiation of rivaroxaban compared with using the drug before.

to be a powerful *in vivo* inhibitor of P-glycoprotein and a moderate inhibitor of CYP_3A_4.[10] It has been reported that all DOACs are partially eliminated via kidneys: dabigatran (80%), rivaroxaban (35%), apixaban (27%) and edoxaban (50%).[11] Therefore, the dosing regimen should be selected based on the estimated renal function[11] and the possible drug-drug interactions between DOACs and concomitant immunosuppressive agents need to be carefully considered when DOACs are used in KTx recipients.[5] However, there are no reference guidelines or randomized clinical trial literature on the use of DOACs in KTx recipients with AF.[4,5] Most likely because KTx recipients are a vulnerable population and they are excluded from the most clinical trials. A previously published literature reports that KTx improves renal function and transfer patients from Stage 5 in the KDIGO classification (eGFR < 15 mL/min per 1.73 m^2) to predominantly Stage 3, rarely to Stage 1 or 2.[7]

Although there are some small retrospective observational studies on the safety and effectiveness of DOACs use, mainly apixaban and rivaroxaban, in KTx patients with AF or deep vein thrombosis.[12–15] Steffel, *et al.*[11] found that dabigatran was not recommended for patients taking with tacrolimus and cyclosporine, and the treatment with cyclosporine raises the concentration of edoxaban by 73%, while Camporese, *et al.*[12] reported that rivaroxaban seems not to interact with tacrolimus in KTx recipients with AF or deep vein thrombosis. Previous foreign studies have found that during the 12–24 months follow-up, there were no reports of thrombotic complications and a small number of bleeding events occurred. Compared with VKA (22.9 per 100 patient-y), the bleeding rate under DOACs (11.5 per 100 patient-y) was significantly lower during the same period, with an OR of 0.39.[14] Bukhari, *et al.*[15] and Nikolina, *et al.*[13] reported that only 7.1% (3/42) and 8.7% (2/23) of bleeding complications occurred in their studies, including one patient treated with rivaroxaban and two patients received apixaban, and one patient treated with rivaroxaban and one patient treated with dabigatran, respectively. In addition, the graft function remained stable after 12–24 months of treatment with DOACs.[13,15] However, there are very few studies in China on this specific population. In this case, we chose rivaroxaban 15 mg once daily based on the estimated renal function and proton pump inhibitors were added to prevent gastrointestinal bleeding. Our case demonstrated for the first time the effectiveness and safety of short-term follow-up, and there were no thromboembolic or bleeding events. In addition, the serum creatine level and tacrolimus concentration kept stable after the initiation of rivaroxaban.

Although our case are not powered to verify the effectiveness and safety of rivaroxaban in an AF patient with high bleeding risk and KTx during long-term follow-up, vigilance should still be raised to prevent bleeding.[5] The strengths of our case is that the patient is relatively older, with a clear risk of bleeding in the past, and the safety and effectiveness of DOAC use are quite encouraging. Furthermore, the successful treatment experience provides a certain reference value for anticoagulant therapy of such patients and promotes the publication of clinical practice guidelines or expert consensus for KTx patients with AF in China as early as possible.

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