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Editorial**Changes in renal function in patients with atrial fibrillation: efficacy and safety of the non-vitamin K antagonist oral anticoagulants**

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Impaired renal function is relatively common in patients with atrial fibrillation (AF). For example, one European study reported that 47.2% of AF patients had mild renal impairment as defined by an estimated glomerular filtration rate (eGFR) <80 mL/min, and 17.6% had moderate to severe renal impairment (eGFR <50 mL/min).¹ Thus, the assessment of cardiac and renal conditions is of clinical importance for managing the risk of thromboembolism, bleeding, and mortality.^{2,3}

The relationship between AF and renal function has gained much attention, given the increasingly elderly population with more prevalent AF. A bidirectional relationship between renal dysfunction and cardiovascular disease (including AF) is evident. Indeed, renal impairment is a significant predictor of cardiovascular disease, as well as the incidence of new-onset AF, which is approximately 2- to 3-fold higher than in patients without chronic kidney disease.^{4,5} Likewise, AF is associated with an increased risk of stroke or systemic embolism, cardiovascular death, and also the progression of chronic kidney disease, even among those with relatively normal renal function.⁶

The propensity of renal dysfunction to worsen thromboembolism is supported by underlying pathophysiological mechanisms including increased hypercoagulability through reduced blood flow in left atrium⁷ and increased procoagulant/inflammatory complexes,^{8,9}. Moreover, fibrin clot structure in patients with end-stage renal disease has been reported to be less porous compared to health controls,¹⁰ which can also be visualized using scanning electron microscopy and related to the severity of renal function.¹¹ In the latter study, across worsening degrees of renal function from chronic kidney disease stage 1 to stage 4, the visualized fibrin clot structure had increased protofibril number, fibrin clot density and fiber diameter, and also decreased number of pores. More tightly laced fibrin networks are more resistant to fibrinolysis and be more prothrombotic,¹² while fibrin network permeability rises with elevation of Prothrombin Time International Normalized Ratio in AF patients on vitamin K antagonists (VKAs).¹³

More recently, the non-vitamin K antagonist oral anticoagulants (NOACs) have been introduced and offer relative favorable efficacy, safety and convenience in patients

with AF for stroke prevention.¹⁴ All the NOACs have some degree of renal excretion (with the greatest renal dependency for dabigatran), thus leading to dose adjustment when a renal impairment is present (i.e. eGFR <50 ml/min). Some cohort studies have investigated the clinical impact of renal impairment on thromboembolism and bleeding in patients with AF,¹⁵ as well as in those with venous thromboembolism.¹⁶ Although the balance of benefit and risk in patients on NOACs constantly needs to be assessed according to individual condition,¹⁷ NOACs have been reported to provide effective and safe thromboprophylaxis in patients with mild to moderate renal dysfunction. However, these studies reported on renal function at the initiation of oral anticoagulants (OACs), and changes in renal function over time were not taken into account.¹⁸

Previous studies showed that a significant proportion of AF patients, ranging from 21% to 32.4%, show a rapid worsening in renal function (WRF), as defined by a loss in eGFR >5 ml/min/1.73 m²/year during VKAs therapy.^{19, 20} Data on WRF in AF patients treated with NOACs are controversial. A sub-analysis of the RE-LY trial investigated this issue,

showing that a decrease in eGFR >25% was less frequently observed in patients on dabigatran 110 mg (hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.69-0.96, $p=0.017$) or dabigatran 150 mg (HR 0.79, 95%CI 0.68-0.93, $p=0.0056$) compared to warfarin.²¹ Similarly, there was a significantly higher decline of CrCl among patients on warfarin (-4.3 ± 14.6 mL/min) compared with patients those on rivaroxaban (-3.5 ± 15.1 mL/min; $p<0.001$).²² Conversely, a sub-analysis of the ARISTOTLE trial showed a decline in CrCl of -0.96 ($-1.18/-0.74$) in patients with warfarin, and of -1.37 ($-1.59/-1.15$) in patients with apixaban ($p=0.01$).²³ Thus, current guidelines recommend that renal function should be regularly monitored to allow the prescription of the appropriate dose of NOACs, and allow dose adaptation over time.²⁴

In this issue of the American Heart Journal, the work by Hijazi et al.²⁵ highlights the clinical impact of worsening renal function on AF-related outcomes in a subgroup analysis of the RE-LY trial including >16,000 AF patients on either warfarin or dabigatran. During the study, 24.2% of patients were observed to have WRF defined as a decrease of >20% in eGFR from the baseline, which was associated with a higher risk

of all-cause mortality and major bleeding (HR 2.17 and 1.43, 95%CI 1.81-2.59 and 1.19-1.71, respectively). Furthermore, the efficacy and safety of dabigatran, as compared to warfarin, was maintained irrespectively of renal function changes over time. In particular, dabigatran 110 mg showed a greater relative risk reduction of major bleeding in patients with a stable renal function (HR 0.75, 95%CI 0.62-0.90) compared to the group with WRF (HR 1.28, 95%CI 0.85-1.92).

The relationship between WRF and outcomes has also been analyzed in sub-group analysis of randomized clinical trials of NOACs such as ROCKET AF and ARISTOTLE.^{22, 23}

These post-hoc analyses also defined WRF as a decrease >20% in eGFR from baseline, and compared outcomes with stable renal function (SRF). When we perform a meta-analysis to assess the risk of ischemic and bleeding outcomes between patients with WRF and those with SRF on treatment with NOACs (Figure), we clearly show that when compared to SRF, the presence of WRF is significantly associated with an increased risk of stroke or systemic embolism, major bleeding, and all-cause mortality (HR 1.30, 95%CI 1.07-1.58, HR 1.35, 95%CI 1.12-1.65, HR 2.01, 95%CI 1.62-2.50,

respectively). Thus, our results confirm the findings from the study by Hijazi et al., suggesting that in addition to the baseline evaluation of renal function in AF patients starting a NOAC, change of renal function over time should be always assessed, given the clinical impact on AF-related outcomes.

Furthermore, these studies investigated the efficacy and safety of NOACs versus warfarin according to change of renal function over time. Although the results varied a little among each study, the benefit of NOACs over warfarin appeared to be sustained irrespective of change of renal function over time, suggesting the effective and safe use of NOACs as an alternative to warfarin for long-term anticoagulation therapy even in patients with deteriorating renal function over time.

In conclusion, development of renal impairment is common in AF, conferring an additional risk for ischemic and bleeding outcomes in AF patients on oral anticoagulation. Although there are limited real-world data on the efficacy and safety

of NOACs in patients with renal impairment, post-hoc analyses from phase III randomized clinical trials suggest that NOACs are safe and effective also in AF patients with WRF. Despite this, renal impairment is a dynamic and variable risk factor, which could be partially prevented by a tight control of risk factors, such as adequate blood pressure and blood glucose levels. Renal function in AF patients does not remain stable over time and WRF should be regularly assessed over time for a tailored and more appropriate holistic approach to management of oral anticoagulation²⁶.

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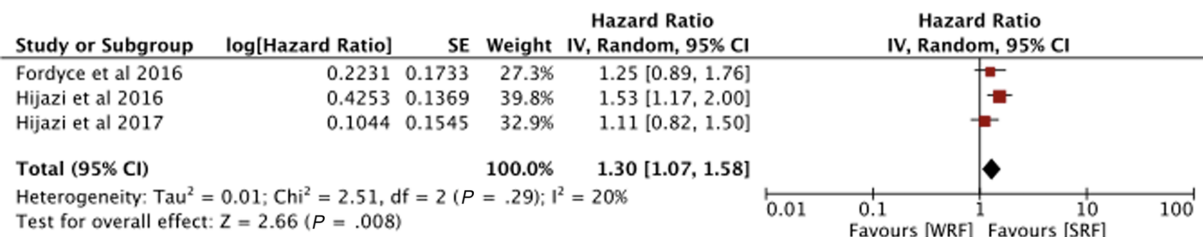
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Figure legends

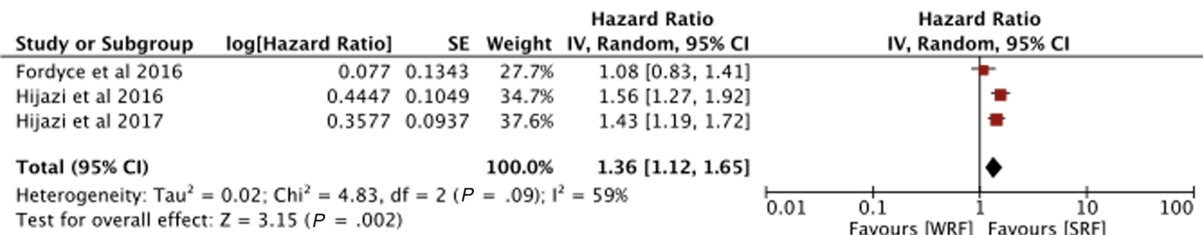
Figure. Risk of stroke or systemic embolism (A), ischemic stroke (B), and all-cause mortality (C) in the comparison of WRF and SRF. SRF; stable renal function, WRF; worsening renal function.

ACCEPTED MANUSCRIPT

A) Stroke or systemic embolism



B) Major bleeding



C) All-cause mortality

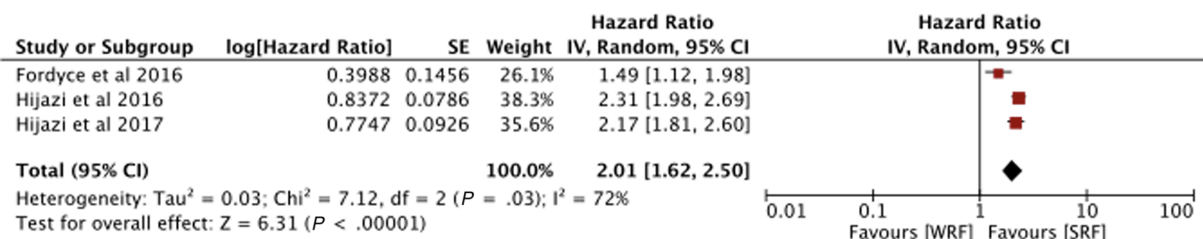


Figure 1