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Anticoagulation in Atrial Fibrillation Patients With Renal Impairment

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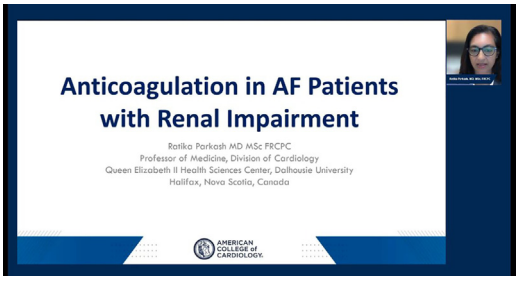
Atrial fibrillation (AF) is on the rise globally.[1] A recent study from the Danish nationwide patient register indicated that AF is more commonly diagnosed than the top 4 cancer diagnoses combined.[2] The morbidity and mortality from AF are decreased quality of life, loss of work in younger patients, heart failure, and stroke.[3] There have been many advances made in the treatment for AF in the areas of stroke prevention, understanding of risk factors to prevent progression of AF, AF in the setting of concomitant heart failure, and use of early rhythm control therapy with or without catheter ablation.[4-7] AF has been cited as one of the 7 causes of death that has been increasing worldwide.[8] It is associated with a 6-fold risk of stroke and a 2-fold increase in mortality;[9,10] the main cardiac reason for death 1 year after presenting to the emergency department with AF is heart failure.[11]

The following is the video related to this paper.



Direct oral anticoagulants (DOACs) have been recommended over warfarin for stroke prevention in patients with AF.[12,13] However, their use can be complicated in patients with varying degrees of chronic kidney disease (CKD) because renal clearance plays a significant role in the elimination of these drugs. Several randomized controlled trials have compared the efficacy and safety of DOACs against warfarin. The RELY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial demonstrated a significant reduction in the risk of stroke and systemic embolism with dabigatran compared with warfarin (HR: 0.66; $P = 0.0001$) but showed no significant difference in major bleeding (HR: 0.94; $P = 0.34$).[4] In the ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trial, rivaroxaban showed a nonsignificant reduction in stroke risk (HR: 0.88; $P = 0.12$) and no significant difference in major bleeding compared with warfarin (HR: 1.03; $P = 0.72$).[14] In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, apixaban significantly reduced the risk of stroke and systemic embolism (HR: 0.80; $P = 0.012$) and major bleeding (HR: 0.71; $P < 0.0001$) compared with warfarin.[15] Finally, in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48) trial, edoxaban showed a nonsignificant reduction in stroke risk (HR: 0.88;

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$P = 0.10$) and a significant reduction in major bleeding (HR: 0.80; $P = 0.0002$).[16]

There is significant overlap in pathophysiology underlying AF and CKD including effects on the renin angiotensin aldosterone system and upregulation of cytokines.[17,18] CKD also leads to alterations in platelet function, with reduction of platelet activation, reduced binding of platelets to the vessel wall, and reduced platelet adhesion and aggregation resulting in a prohemorrhagic state. Concurrently, CKD and AF result in a prothrombotic state due to increased atrial fibrosis, endothelial dysfunction, and elevated hypercoagulable factors.[19] In addition, both disorders are impacted by similar risk factors including prediabetes, smoking, obesity, aging, and hypertension.[20] Patients with CKD who develop AF have a higher rate of stroke and death. In a cohort of 116,184 adults with CKD and no AF, 12% developed new AF over 4 years of follow-up. The adjusted odds ratio of stroke in those with AF and CKD was 2.0, whereas the adjusted odds ratio for mortality was 1.8.[21]

Renal function significantly impacts the choice and dosing of DOACs. Apixaban is recommended for patients with mild to moderate renal impairment due to its relatively low renal clearance (27%). Dabigatran is primarily eliminated by the kidneys (80% renal clearance), making it less suitable for patients with severe renal impairment. Rivaroxaban (33% renal clearance) and edoxaban (50% renal clearance) also require dose adjustments based on renal function, with edoxaban being noted for its favorable bleeding profile in patients with impaired renal function. Data from randomized clinical trials are limited with respect to the use of these agents in CKD. Patients with estimated glomerular filtration rate <30 mL/min were excluded from the trials previously discussed. The data regarding the use of these agents in stage 4 and 5 CKD and dialysis agents are derived primarily from smaller observational studies. A network meta-analysis including patients with creatinine clearance ≥ 25 mL/min found that, compared with warfarin, DOACs (apixaban, dabigatran, rivaroxaban) were associated with lower risks of stroke (4.8% decrease in HR of stroke per 10 mL/min decrease in creatinine clearance with DOAC vs vitamin K antagonist [VKA]).[22] No significant difference in bleeding or intracranial hemorrhage with standard dose compared with lower dose DOAC was found, but lower intracranial hemorrhage with DOAC over VKA was found. Apixaban and edoxaban 30 mg daily have consistently been associated with reduction in bleeding compared with other DOACs and warfarin, particularly in patients with severe renal impairment.[23] The ETNA-AF (Edoxaban Treatment in Routine Clinical Practice for Patients With Non Valvular Atrial Fibrillation) study examined the effect of worsening renal function with edoxaban treatment and found that patients who exhibit worsening renal function (11%-23% of patients with AF) have a higher risk of mortality and major bleeding but similar risk of stroke/systemic embolism.[24] Kuno et al[25] examined the use of oral anticoagulation for patients with AF on long-term hemodialysis and found no reduction in stroke, but found a higher risk of bleeding with VKAs, dabigatran, and rivaroxaban.

These data in combination provide uncertainty for treatment of patients with stage 4 and 5 CKD in terms of risk and benefit of oral anticoagulation in AF. To date, the Food and Drug Administration has approved the use of apixaban in patients on hemodialysis. It is reasonable to consider no oral anticoagulation in these patients given the lack of evidence and efficacy. For patients with creatinine clearance of 15 to 29 mL/min, dabigatran 75 mg twice a day is also approved. Dose-adjusted dabigatran, apixaban, rivaroxaban, and edoxaban have all been approved for creatinine clearance of 30 to 50 mL/min.[12,26] Patient involvement in the decision-making process is crucial for achieving optimal outcomes with DOAC therapy. Factors (eg, treatment adherence, convenience, bleeding risk profiles) should be considered to tailor the best anticoagulant therapy for individual patients.

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