

# Use of Direct Oral Anticoagulants in Patients With Atrial Fibrillation and Kidney Failure

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**D**irect oral anticoagulants (DOACs) are recommended for stroke prevention in patients with atrial fibrillation (AF) and mild to moderate chronic kidney disease (CKD). However, data are limited regarding the use of DOACs in patients with severe kidney disease and kidney failure (patients with a creatinine clearance [CrCl] of <30 mL/min,<sup>1</sup> or patients with estimated glomerular filtration rate [eGFR] of less than 15 mL/min/1.73 m<sup>2</sup> or requiring hemodialysis [HD]).<sup>2</sup>

The 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines<sup>3</sup> recommended dose adjustments when using DOACs in moderate CKD (eGFR, 31-60 mL/min/1.73 m<sup>2</sup>) and severe CKD (eGFR ≤60 mL/min/1.73 m<sup>2</sup>) and recommended warfarin as the drug of choice in patients with kidney failure.<sup>4,5</sup> Although findings from observational studies support the use of warfarin in stage 4 CKD, many studies regarding the use of warfarin in kidney failure have shown a lack of benefits and possible risks, including an increased risk of bleeding complications.

Recent updates have stated that using apixaban or warfarin for patients with kidney failure or on HD may be reasonable. Compared with warfarin, DOACs have many benefits such as decreased need for routine monitoring, decreased frequency of dose adjustments, and fewer numbers of medication and food interactions.<sup>4</sup> The recommendations remain conflicting for this patient group regarding the use of DOACs in kidney failure.

## AF IN KIDNEY FAILURE

AF is frequently seen in patients with advanced CKD, particularly in those older than 60 years. Additionally, AF is noted to be 10 times more prevalent in patients with CKD younger than 55 years compared with non-HD patients of similar age. AF is noted to become more prevalent as kidney function declines.<sup>6</sup> In patients with CKD, the presence of AF is associated with increased risk of stroke, development of heart failure, progression of CKD, and death.<sup>7</sup> In patients with kidney failure and concomitant AF, the 2-year mortality increases to 37% from 21%.<sup>7</sup>

AF is recognized as a marker of underlying cardiovascular disease. The presence of kidney failure and AF increases thromboembolic and hemorrhagic risks as the kidney dysfunction results in changes in the hemostatic systems, leading to the presence of a prohemorrhagic state as well as a prothrombotic state.<sup>2,7</sup> Retrospective studies have found that patients with kidney failure have almost twice the risk of a thromboembolic event compared with patients with AF without kidney failure.

In addition to stroke, other possible clinical presentations of thrombosis include deep-vein thrombosis, HD vascular access thrombosis, acute coronary syndrome, central venous catheter thrombosis, and pulmonary embolus. Clinical presentations of hemorrhagic complications in patients with kidney failure include gastrointestinal tract bleed, hemoptysis, subdural hematoma, petechiae, and epistaxis.<sup>2</sup>

The most commonly used scoring system to estimate the thromboembolic risk in a patient with AF is the CHA<sub>2</sub>DS<sub>2</sub>-VASc, which takes into account the patient's age and sex along with the presence of factors such as hypertension, congestive heart failure, diabetes, transient ischemic attack, and vascular disease. The HAS-BLED score is the most commonly used scoring system to estimate a patient's bleeding risk and takes into account age, labile international normalized ratio, and alcohol and drug use, as well as the presence of abnormal liver or kidney function, hypertension, bleeding tendency, or stroke.<sup>7</sup>

Because patients with CKD and AF have higher rates of thromboembolic events compared with patients without CKD, the use of anticoagulation may have a role in decreasing this risk; however, the use of anticoagulants can increase the risk of bleeding complications in these patients who already have a

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**Table 1. Summary of DOACs, Their Renal Clearance, and Their Risks and Benefits<sup>3,10-14</sup>**

DOAC	% Renal Clearance	Risk vs Benefits
Apixaban	27%	<ul style="list-style-type: none"> <li>• Least reliant on renal clearance compared with other DOACs</li> <li>• Lower risk of major bleeding events compared with warfarin</li> <li>• Absolute rates of bleeding are still high</li> <li>• Uncertainty regarding net benefit for use in patients with kidney failure</li> </ul>
Rivaroxaban	33%	<ul style="list-style-type: none"> <li>• Minimally dialyzable compared with dabigatran</li> <li>• Increased risk of major and fatal bleeding events compared with warfarin</li> <li>• Not recommended due to lack of evidence that benefits exceed risks</li> </ul>
Dabigatran	80%-85%	<ul style="list-style-type: none"> <li>• Highly dependent on renal clearance compared with other DOACs</li> <li>• Increased risk of bleeding in patients with kidney failure</li> <li>• Increased risk of major and fatal bleeding events compared with warfarin</li> <li>• Not recommended due to lack of evidence that benefits exceed risks</li> </ul>
Edoxaban	50%	<ul style="list-style-type: none"> <li>• Clearance of edoxaban does not differ with HD</li> <li>• Not well-studied compared with other DOACs in patients with kidney failure</li> <li>• Not recommended due to lack of evidence that benefits exceed risks</li> <li>• Lack of reversal agent</li> </ul>

prohemorrhagic state in the setting of the kidney dysfunction.<sup>5</sup> Currently, the use of DOACs in patients with kidney failure is not well-studied and remains an area of discussion.

## DOACs IN KIDNEY FAILURE

DOACs—including direct factor Xa inhibitors such as apixaban, rivaroxaban, and edoxaban and direct thrombin inhibitors (DTIs) such as dabigatran—have been approved by the Food and Drug Administration (FDA) for the treatment of AF. Randomized controlled trials have shown benefit with the use of DOACs compared with warfarin in patients with mild to moderate CKD (**Table 1**). Additionally, a meta-analysis of these trials has shown increased efficacy and safety with DOACs compared with warfarin in that DOACs were associated with

fewer major bleeding events.<sup>8,9</sup> As such, DOACs are recommended over vitamin K antagonists such as warfarin for CKD stages 1 through 3. These trials excluded patients with kidney failure, and there are no adequate studies on the safety and efficacy of DOACs in this patient population.<sup>5</sup> Despite this, based on pharmacokinetic studies, rivaroxaban and apixaban have been FDA-approved for use in patients with kidney failure. Additionally, prescribing of DOACs for patients with kidney failure has been increasing.<sup>2,5</sup>

## APIXABAN

Apixaban is a factor Xa inhibitor that is least reliant on renal clearance compared with the other DOACs, since approximately 27% of the drug is eliminated by the kidneys.<sup>10,11</sup>

One retrospective observational study of more than 25,000 patients with AF on HD noted that DOACs were increasingly being used in this patient population despite a lack of data and guideline recommendations regarding their use in this population.<sup>10</sup> According to this study, apixaban accounted for 25% of new anticoagulation prescriptions in patients with kidney failure in 2015. This study also demonstrated that apixaban was associated with an approximately 30% lower risk of major bleeding events compared with warfarin, although the absolute rates of bleeding were noted to be high in both study groups.

The event rate for major bleeding was 19.7 per 100 patient-years in the apixaban group compared with 22.9 per 100 patient-years in the warfarin group (hazard ratio, 0.72 favoring apixaban; 95% CI, 0.59-0.87;  $P<.001$ ). Major events included bleeding in critical sites such as intracranial bleeds, the need for blood product transfusion during the same admission, or bleeding associated with death.<sup>10</sup>

This study also compared apixaban dosed at 5 mg twice daily with apixaban dosed at 2.5 mg twice daily; the 5-mg dosing was associated with lower risks of systemic embolism or ischemic stroke and death compared with warfarin, although this finding was not noted with the 2.5-mg dosing. Discontinuation rates were noted to be high—approximately two-thirds of patients in each group had discontinued the anticoagulant 12 months after it had been initially prescribed, possibly indicating poor tolerability of any type of anticoagulant in this population of patients, given the increased risk of bleeding events.<sup>10</sup>

Despite this study showing some benefits with apixaban use compared with warfarin use, uncertainty still exists regarding the net benefit of using anticoagulants for stroke prevention in patients with AF and kidney failure.<sup>10</sup> According to the updated 2019 AHA/ACC/HRS guidelines,<sup>3</sup> it may be reasonable to use apixaban in patients with kidney failure for anticoagulation. Andexanet alfa is available as a reversal agent for use in cases of uncontrolled or life-threatening bleed.<sup>3</sup> Further study is needed to assess the net benefit of anticoagulation use for stroke reduction in patients with kidney failure and AF.

## RIVAROXABAN

Rivaroxaban is another factor Xa inhibitor that is being used for stroke prevention in patients with kidney failure and AF despite a lack of data regarding its safety and efficacy in this population. In a period of only 4 years after these drugs had been approved, approximately 5% of patients in this group were on either rivaroxaban or dabigatran therapy.<sup>12</sup>

Rivaroxaban is renally cleared, and approximately 33% of the drug is eliminated in the proximal tubule. Rivaroxaban is minimally dialyzable, since 92% to 95% of the drug is bound to plasma proteins.<sup>11,12</sup> The results of a study by Chan and colleagues, which evaluated the use of dabigatran and rivaroxaban in patients with kidney failure using prescription patterns, indicated that the risk of a major bleeding event with rivaroxaban increased by 38%, and the risk for a fatal bleeding event increased by 58% compared with warfarin.<sup>12</sup>

According to the updated 2019 AHA/ACC/HRS guidelines for the management of patients with AF, rivaroxaban is not recommended for use in patients with AF and kidney failure or on HD, given the lack of evidence that benefit exceeds the risk.<sup>3</sup> Like apixaban, the reversal agent andexanet alfa is available in cases of uncontrolled or life-threatening bleed.<sup>3</sup>

Despite the recommendation against the use of rivaroxaban in patients with kidney failure, this medication is being started in an increasing number of these patients.<sup>12</sup> Again, further study is needed to evaluate the risk-benefit profile of this drug before it can be recommended for use in patients with kidney failure.

## DABIGATRAN

Dabigatran is a DTI that has also been increasingly used in patients with AF and kidney failure for stroke prevention. Approximately 80% to 85% of the drug is renally excreted, and compared with rivaroxaban, dabigatran is dialyzable. As such, the potential exists for an increased risk of bleeding given that this medication may accumulate in patients with significantly impaired kidney function as a result of decreased clearance.

In the study by Chan and colleagues,<sup>12</sup> dabigatran was noted to increase the risk of a major bleeding event by 48% and increase the risk of a fatal bleeding even higher by 88% compared with warfarin. Currently, the updated 2019 AHA/ACC/HRS guidelines do not recommend the use of dabigatran in patients with AF and kidney failure or on HD, given the lack of evidence that the benefit outweighs the risk.<sup>3</sup> Idarucizumab is a reversal agent recommended for use in cases of a life-threatening bleed or urgent procedure.<sup>3</sup> Dabigatran is another anticoagulant that requires further study to evaluate the risk-benefit profile before being recommended for use in patients with kidney failure.

## EDOXABAN

Edoxaban is the most recent factor Xa inhibitor to have been FDA-approved for use in patients with nonvalvular AF. Like the

**Table 2. Practice Recommendations for DOACs**

- It may be reasonable to use apixaban for oral anticoagulation in patients with AF and kidney failure (evidence level B).
- Dabigatran, a DTI, is not recommended in patients with AF and kidney failure due to lack of evidence that the benefits exceed the risks (evidence level C).
- Rivaroxaban and edoxaban, factor Xa inhibitors, are not recommended for use in patients with AF and kidney failure due to lack of evidence that the benefits exceed the risks (evidence level C).

Strength of Recommendation Taxonomy (SORT): A, based on good-quality and consistent patient-oriented evidence; B, limited-quality or inconsistent patient-oriented evidence; C, based on usual practice, consensus, opinion, case series, or disease-oriented evidence.

other DOACs, edoxaban has not been well-studied in for stroke prevention in patients with AF and kidney failure. Approximately 50% of the drug is renally excreted, and a small randomized crossover study<sup>13</sup> noted that the clearance of edoxaban did not differ with HD in patients with kidney failure.<sup>14</sup> As with rivaroxaban and dabigatran, the updated 2019 AHA/ACC/HRS guidelines do not recommend use of edoxaban in patients with AF and kidney failure or on HD, given the lack of evidence supporting that the benefits exceed the risk.<sup>3</sup> Additionally, no reversal agent for edoxaban is currently recommended for use in cases of life-threatening bleed, which may complicate management in these patients with kidney failure.

## SUMMARY

DOACs have been increasingly used for stroke prevention in patients with AF despite the lack of data evaluating their safety and efficacy in patients with kidney failure. Additionally, management is complicated in these patients given the increased risk of bleeding in the setting of renal impairment.

Limited studies have noted that apixaban was associated with a lower risk of major bleeding events compared with warfarin; however, uncertainty still exists regarding its use in these patients.<sup>10</sup> On the other hand, rivaroxaban and dabigatran were associated with an increased risk of major bleeding events in one study.<sup>12</sup> Few studies have been published regarding the use of edoxaban in this patient population. As such, the updated AHA/ACC/HRS 2019 guidelines do not recommend the use of rivaroxaban, dabigatran, and edoxaban in patients with AF and kidney failure or on HD.<sup>3</sup> **Table 2** summarizes practice recommendations for the DOACs.

Given the complexities of management in this patient population, this area remains a topic of discussion and requires further study to assess the risks and benefits of using these anticoagulants for stroke prevention in patients with kidney failure. ■

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stability is not present, the patient may need additional anti-VEGF injections. Intravitreal corticosteroid can provide benefit in patients initially, but that benefit may regress. Long-term use of corticosteroids can cause complications; however, certain cases may require continuous intravitreal corticosteroids.<sup>8</sup> HRVO is managed very similarly to CRVO.<sup>6</sup>

BRVO occlusions will also require a referral to a retinal specialist after initial evaluation. BRVO is often managed with both laser photocoagulation and anti-VEGF injections if nonperfusion is present. There is research that scatter laser photocoagulation reduces the chance of neovascularization developing in patients with a BRVO.<sup>5,8</sup>

The patients' primary care physician needs to be involved in all of these cases and help manage the systemic risk factors, including hypertension, diabetes, hypercoagulable conditions, and other risk factors. Based on their risk factors, patients will need an assessment that may include fasting blood glucose level, hemoglobin A<sub>1c</sub> level, lipid profile, erythrocyte sedimentation rate, C-reactive protein level, syphilis testing, angiotensin-converting enzyme level, a complete blood cell count with differentials and platelets, and prothrombin time/partial thromboplastin time.

In appropriate cases, a hypercoagulable panel (ie, protein C activity, protein S activity, homocysteine, antiphospholipid antibody, antithrombin III, factor V Leiden) may need to be obtained. Patients should also be educated on cessation of smoking and maintaining a healthy weight and lifestyle.<sup>5</sup>

## THE TAKE-HOME MESSAGE

Overall, it is important that a patient with sudden unilateral painless vision loss be recognized and managed appropriately. Primary care physicians need to be aware that these cases need referral to a retinal specialist in order to properly manage the ocular condition. The primary care physician is also critical in managing the systemic factors that have contributed to a vein occlusion. ■

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