Case Presentation: A 68-year-old woman with hypertension, diabetes mellitus, and congestive heart failure presented to the emergency department with palpitations. On physical examination, her heart rate was 130 bpm and irregularly irregular, her blood pressure was 120/70 mm Hg, and she weighed 60 kg. The ECG demonstrated atrial fibrillation (AF) with a rapid ventricular rate. Laboratory evaluation was remarkable for a serum creatinine of 1.3 mg/dL. Her symptoms resolved with heart rate control.

Background
AF is the most common arrhythmia in patients with chronic kidney disease (CKD) and is associated with increased risk of stroke and thromboembolism. The risk of stroke increases as renal function declines. Conversely, patients with CKD, particularly those on hemodialysis, are at an increased risk of bleeding. Oral anticoagulation is the most effective form of thromboprophylaxis in patients with AF at increased risk of stroke. Concern for bleeding has resulted in the underuse of anticoagulation in these patients.

Warfarin and novel oral anticoagulants (NOACs) have been shown to be effective in preventing stroke in the general population of patients with AF. However, most randomized trials of antithrombotic therapy have excluded patients with severe renal impairment (estimated creatinine clearance [eCrCl] <30 mL·min⁻¹·1.73 m⁻²). Thus, whether antithrombotic therapy with warfarin and NOACs is safe and reduces stroke in patients with AF and CKD is unclear.

Stroke Risk Assessment in CKD
The CHA₂DS₂-VASc score (congestive heart failure, hypertension, age ≥75 years [doubled], diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism [doubled], vascular disease, age 65–74 years, sex category), as recommended in the current guidelines, should be used to determine stroke risk and indication for anticoagulation in patients with AF, including those with CKD. Periodic re-evaluation is recommended to assess stroke and bleeding risk.

Aspirin in AF With CKD
Aspirin monotherapy is not effective in stroke prevention in AF, including in patients with CKD. The risk of bleeding with aspirin is not trivial. Thus, in patients at an increased risk of stroke, aspirin monotherapy should not replace anticoagulation. Combined treatment with aspirin and warfarin in CKD patients is associated with increased risk of bleeding; this combination should not be routinely used in patients with AF with CKD.

Warfarin in AF With CKD
No large, randomized, controlled trial has studied the role of warfarin in preventing stroke in patients with AF specifically with severe renal impairment. Some studies have reported a reduced risk of stroke, whereas others found no difference or even increased risk of stroke with warfarin in CKD. As with any observational analysis, these studies have several limitations resulting from residual confounding, and the associations found may not be causal.

One study of 132,372 patients with AF in Denmark demonstrated that warfarin compared with no antithrombotic...
therapy resulted in a lower incidence of stroke in patients with CKD, including those on dialysis. The authors found that warfarin compared with no antithrombotic therapy was associated with a higher risk of bleeding in patients with CKD. Similarly, among patients with AF, CKD, and myocardial infarction in the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDHEART) registry, treatment with warfarin compared with no anticoagulation reduced all-cause mortality, recurrent myocardial infarction, and stroke without an increased risk of bleeding.

A recent analysis of 154,259 patients from Danish national registries found warfarin to be beneficial for stroke prevention in patients with CKD. This study showed lower risks of all-cause mortality, cardiovascular death, and a composite of fatal stroke or fatal bleeding with warfarin compared with no antithrombotic therapy in patients with CKD. Additionally, the investigators found no increased risk of hemorrhagic stroke or major bleeding with warfarin.

Contrary to these findings, a retrospective analysis of 205,836 patients with CKD in Canada demonstrated a higher risk of bleeding with warfarin compared with no warfarin. However, this study showed a reduced risk of stroke with warfarin compared with no warfarin. Furthermore, a retrospective study of 1671 patients on dialysis in the United States and Canada reported an increased risk of stroke with warfarin versus no antithrombotic therapy. In this cohort, the risk of stroke was highest in patients who did not undergo routine monitoring of anticoagulation with the international normalized ratio.

Warfarin treatment in AF patients with CKD presents additional risks that are less common in the non-CKD population. Warfarin is associated with an increased risk of vascular calcification, calciphylaxis, and access site bleeding in dialysis patients. Warfarin-induced vascular calcification may possibly have a detrimental effect on renal function. A post hoc analysis of 16,490 patients in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial found a greater decline in renal function among patients treated with warfarin versus dabigatran.

**NOACs in AF With CKD**

NOACs have emerged as a promising alternative to warfarin for the prevention of stroke and systemic thromboembolism in patients with AF. Unlike warfarin, NOACs have a predictable effect without the need for frequent monitoring and have fewer diet and drug interactions. The pharmacokinetic profile of each NOAC is unique and should be taken into consideration in the selection of an antithrombotic therapy for patients with AF (Table 1). All NOACs undergo some degree of renal clearance; as a consequence, the risk of bleeding increases with deterioration of renal function. Dose modification is recommended in patients with reduced renal function (Table 2).

Contemporary trials of apixaban, dabigatran, edoxaban, and rivaroxaban showed efficacy and safety that were comparable or superior to those of warfarin in patients with AF and moderate CKD (eCrCl, 30–49 mL·min⁻¹·1.73 m⁻²; Figure). The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial demonstrated that apixaban compared with warfarin was associated with a lower risk of stroke, thromboembolism, major bleeding, and death in patients with moderate CKD. Similarly, in the RE-LY trial, dabigatran was superior to warfarin in patients with

### Table 1. Pharmacokinetic Characteristics of NOACs

<table>
<thead>
<tr>
<th>Target</th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability, %</td>
<td>66</td>
<td>6.5</td>
<td>50</td>
<td>80</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Half-life, h</td>
<td>8–13</td>
<td>12–14</td>
<td>9–11</td>
<td>7–13</td>
</tr>
<tr>
<td>Renal clearance, %</td>
<td>25</td>
<td>80</td>
<td>35</td>
<td>66; half as inactive drug</td>
</tr>
</tbody>
</table>

NOAC indicates novel oral anticoagulant.

### Table 2. Summary of the US Food and Drug Administration Dose Recommendations of NOACs for Patients With Nonvalvular AF and CKD

<table>
<thead>
<tr>
<th>eCrCl, mL·min⁻¹</th>
<th>Apixaban†</th>
<th>Dabigatran</th>
<th>Edoxaban‡</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;90</td>
<td>5 or 2.5 mg twice daily</td>
<td>150 mg twice daily</td>
<td>60 mg once daily</td>
<td>20 mg once daily with evening meal</td>
</tr>
<tr>
<td>51–90</td>
<td>5 or 2.5 mg twice daily</td>
<td>150 mg twice daily</td>
<td>60 mg once daily</td>
<td>20 mg once daily with evening meal</td>
</tr>
<tr>
<td>31–50</td>
<td>5 or 2.5 mg twice daily</td>
<td>150 mg twice daily</td>
<td>30 mg once daily</td>
<td>15 mg once daily with evening meal</td>
</tr>
<tr>
<td>15–30</td>
<td>5 or 2.5 mg twice daily</td>
<td>75 mg twice daily</td>
<td>30 mg once daily</td>
<td>15 mg once daily with evening meal</td>
</tr>
<tr>
<td>&lt;15 not on dialysis</td>
<td>5 or 2.5 mg twice daily</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
<tr>
<td>&lt;15 on dialysis</td>
<td>5 or 2.5 mg twice daily</td>
<td>Not recommended</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; CKD, chronic kidney disease; eCrCl, estimated creatinine clearance; and NOAC, novel oral anticoagulant.

*eCrCl measured with the Cockcroft-Gault method.
†Apixaban 2.5 mg twice daily if patient has any 2 of the following: serum creatinine ≥1.5 mg/dL, age ≥80 years, or body weight ≤80 kg.
‡Not recommended in patients with eCrCl >95 mL/min.
moderate CKD in preventing stroke and thromboembolism. In patients with moderate CKD in the Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE-AF TIMI 48) trial, edoxaban compared with warfarin showed similar efficacy in preventing stroke and a lower risk of bleeding and cardiovascular death. In agreement with previous studies, the Rivaroxaban Once-Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) trial demonstrated a trend toward lower risk of stroke, thromboembolism, and fatal bleeding with rivaroxaban compared with warfarin in the subgroup with moderate CKD. Overall, these findings suggest that in patients with moderate CKD, NOACs have a favorable net clinical benefit.

None of the NOACs have been well studied in patients with AF who are on dialysis or have eCrCl <30 mL·min⁻¹·1.73 m⁻². Dabigatran, edoxaban, and rivaroxaban are not approved for use in patients on dialysis. Apixaban is approved on the basis of pharmacokinetic data. In a retrospective analysis of 29977 patients with AF on hemodialysis in the United States, Chan et al found dabigatran or rivaroxaban to be associated with an increased risk of hospitalization or death resulting from bleeding compared with warfarin.

**Summary and Management of Present Case**

The efficacy and safety of NOACs are superior or comparable to those of warfarin in patients with AF and moderate CKD. If clinicians choose to use NOACs in patients with moderate CKD, frequent monitoring of renal function and dose adjustments are crucial. Large-scale, randomized, controlled trials would be desirable to examine the efficacy and safety of NOACs and warfarin in patients with severe renal impairment (eCrCl <30 mL·min⁻¹·1.73 m⁻²) and those on dialysis. Until then, in the absence of major contraindications, warfarin with careful international normalized ratio monitoring should generally be prescribed in patients with AF and severe renal impairment, including those on dialysis, although apixaban is an approved option.

Our patient represents a patient with AF with moderate CKD. Despite her modest creatinine elevation, her eCrCl calculates to 39.2 mL/min, underscoring the importance of not basing decisions on creatinine alone. Her annual stroke risk is 6.7% based on a CHA₂DS₂-VASc score of 5. We recommended anticoagulation with apixaban 5 mg twice daily for the prevention of stroke and systemic embolism, with a plan for close monitoring of her renal function. We chose apixaban because of the lower risk of bleeding compared with warfarin. Thromboprophylaxis with adjusted dosing of dabigatran, edoxaban, or rivaroxaban or with warfarin would also have been reasonable.

**Disclosures**

Dr Bhatt discloses the following relationships: Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; Board of Directors: Boston VA Research Institute and Society of Cardiovascular Patient Care; chair: American Heart Association Get With The Guidelines Steering Committee; Data Monitoring Committee: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, and Population Health Research Institute; honoraria: American College of Cardiology (senior associate editor, *Clinical Trials and News, ACC.org*), Belvoir Publications (editor in chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (editor in chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor; associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today’s Intervention*), and WebMD (CME steering committees); other: *Clinical Cardiology* (deputy editor); research funding: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Forest Laboratories, Ischemix, Medtronic, Pfizer, Roche, Sanofi Aventis, and The Medicines Company; site coinvestigator: Biotronik and St. Jude Medical; trustee: American College of Cardiology; and unfunded research: FlowCo, PLx Pharma, and Takeda. Dr Qamar reports no conflicts.

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