Clinical Pharmacology of Oral Anticoagulants in Patients with Kidney Disease

Nishank Jain¹-² and Robert F. Reilly³-⁴

Abstract
Oral anticoagulants are commonly used drugs in patients with CKD and patients with ESKD to treat atrial fibrillation to reduce stroke and systemic embolism. Some of these drugs are used to treat or prevent deep venous thrombosis and pulmonary embolism in patients with CKD who undergo knee and hip replacement surgeries. Warfarin is the only anticoagulant that is approved for use by the Food and Drug Administration in individuals with mechanical heart valves. Each oral anticoagulant affects the coagulation profile in the laboratory uniquely. Warfarin and apixaban are the only anticoagulants that are Food and Drug Administration approved for use in patients with CKD and patients with ESKD. However, other oral anticoagulants are commonly used off label in this patient population. Given the acquired risk of bleeding from uremia, these drugs are known to cause increased bleeding events, hospitalization, and overall morbidity. Each anticoagulant has unique pharmacologic properties of which nephrologists need to be aware to optimally manage patients. In addition, nephrologists are increasingly asked to aid in the management of adverse bleeding events related to oral anticoagulant use in patients with CKD and patients with ESKD. This article summarizes the clinical pharmacology of these drugs and identifies knowledge gaps in the literature related to their use.

introduction
The number of patients with CKD and patients with ESKD is increasing in the United States on the basis of the National Health and Nutrition Examination Survey data from 1999 to 2014 (1). Although heart failure, thrombotic cardiovascular events, and sudden cardiac death are common in CKD and ESKD, this population is also at a disproportionately higher risk of nonvalvular atrial fibrillation (AF) compared with the general population. Prevalence of AF increases as kidney disease worsens, and it is close to 15% by the time that patients with CKD become dialysis dependent, which is more than three times that of age-matched controls (2). Use of oral anticoagulants is common, and these agents are among the top 15 drugs prescribed to patients with CKD and patients with ESKD enrolled in Medicare Part D, Medicare Advantage, or Managed Care prescription drug programs (1). Warfarin is one of the most commonly prescribed oral anticoagulants. In the general population, newer oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) reduce risk of stroke or systemic embolism and bleeding versus warfarin in patients with AF, and they are increasingly prescribed in patients with CKD and patients with ESKD. Newer anticoagulants may be favored over warfarin in patients with ESKD and calciphylaxis (3). The reader can refer to previous review articles that have discussed extensively the clinical utility of oral anticoagulants in CKD (4). This review article will focus on the pharmacology of commonly used oral anticoagulants that are important in nephrology practice. In addition, it will identify knowledge gaps regarding use of these drugs in this patient population.

Warfarin Pharmacology
Warfarin is the oral anticoagulant with which clinicians have the most experience. It is a racemic mixture of two optically active isomers (R and S) in equal proportion (5). Its pharmacokinetic and pharmacodynamic (PK/PD) properties are shown in Tables 1 and 2. Common drug-drug interactions are shown in Table 3. Polymorphisms in vitamin K epoxide reductase gene and cytochrome P450 type 2C9 (CYP2C9) are not race specific, and they account for 25% and 10%, respectively, of the interindividual variability in warfarin dosing (6). Vitamin K epoxide reductase genotype may be the best predictor of warfarin dose, because it is responsible for the conversion of vitamin K epoxide to vitamin K (Figure 1) (6). CYP2C9 alleles (e.g., CYP2C9*2 and *3) are poor metabolizers, leading to prolonged t1/2 compared with the wild type (*1 allele) (5). The observed frequencies of CYP2C9*2 are 8%–19% in whites and <4% in blacks. The corresponding frequencies for *3 alleles are 6%–10% and <2%, respectively. The mechanism of action of warfarin is shown in Figures 1 and 2.

Laboratory Measurement of Anticoagulant Effect
Internal normalized ratio (INR) is the most common test used to monitor warfarin response. Drugs, dietary
changes, and disease processes alter warfarin effects. Therefore, its use requires frequent monitoring to maximize individual time spent in the therapeutic range on the basis of an INR between 2.0 and 3.0. Compared with individuals spending the least amount of individual time in the therapeutic range (57%), those with the highest amount of individual time spent in the therapeutic range (73%) experienced lower rates of stroke or systemic embolism (2% versus 1%), major bleeding (5% versus 3%), and all-cause mortality (7% versus 3%).

**Pharmacology in Kidney Disease**

The PK/PD of warfarin in CKD and ESKD is not well established (7). Clinical practice guidelines do not recommend dosage reduction for CKD or ESKD (5,8). Limdi et al. (9,10) found that mean (95% confidence interval [95% CI]) dose reductions of 10% (95% CI, 4% to 14%) and 19% (95% CI, 11% to 26%) were required in patients with eGFR=30-59 and <30 ml/min per 1.73 m² compared with individuals with eGFR≥60 ml/min per 1.73 m² to maintain therapeutic warfarin dosing. This cross-sectional analysis also adjusted for other confounders in the multivariable statistical model, and thus, interpretation of dose reductions solely on the basis of eGFR may be an oversimplified approach. Yet, it provides major evidence of increased exposure of drugs cleared by the liver in patients with CKD. With a single warfarin dose (0.75 mg/kg), individuals with GFR of 30-59 ml/min per 1.73 m² had a shorter t1/2 at 29.9±5.0 versus 44.8±6.0 hours in healthy controls. An increase in warfarin clearance was observed from 2.6 ml/kg per hour in healthy controls to 3.7 ml/kg per hour in CKD (7). It remains to be established whether the dialysis procedure (hemodialysis or peritoneal dialysis) results in changes in warfarin kinetics and dynamics.

**Warfarin**’s antithrombotic effects are reversed by low doses of vitamin K (Table 4). When pharmacologic doses

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**Table 1. Summary of pharmacokinetic and pharmacodynamic properties of commonly used oral anticoagulants**

<table>
<thead>
<tr>
<th>OAC</th>
<th>Type</th>
<th>Prodrug</th>
<th>Pharmacokinetics</th>
<th>Pharmacodynamics: Binding to Effector</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Metabolism</td>
<td>Renal Dose Adjustment</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Vitamin K-dependent factor inhibitor</td>
<td>No</td>
<td>Extensive metabolism by CYP2C9</td>
<td>No</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>Yes</td>
<td>Metabolized by esterases, 80% excreted by kidney</td>
<td>Yes</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Free and clot-bound Xa inhibitor</td>
<td>No</td>
<td>Metabolized in liver by CYP3A4, then excreted in feces and kidney (25%), no active metabolite</td>
<td>No</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Free and clot-bound Xa inhibitor</td>
<td>No</td>
<td>66% Excreted by kidney, 36% unchanged, minimal in feces</td>
<td>Yes</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Free Xa inhibitor</td>
<td>No</td>
<td>50% Excreted unchanged by the kidney, 10% hydrolyzed by carboxyesterase 1</td>
<td>Yes</td>
</tr>
</tbody>
</table>

OAC, oral anticoagulant; CYP2C9, cytochrome P450 type 2C9; Xa, factor Xa; CYP3A4, cytochrome P450 type 3A4.

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**Table 2. Additional pharmacokinetic properties in those with normal kidney function**

<table>
<thead>
<tr>
<th>OAC</th>
<th>Cmax, h</th>
<th>t1/2, h</th>
<th>Protein binding, %</th>
<th>Vd, L</th>
<th>Bioavailability, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>2–6</td>
<td>42</td>
<td>97–99</td>
<td>10</td>
<td>99</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>1–2</td>
<td>12–14</td>
<td>38</td>
<td>50–70</td>
<td>3–7</td>
</tr>
<tr>
<td>Apixaban</td>
<td>3–4</td>
<td>12</td>
<td>87</td>
<td>21</td>
<td>50</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>2–4</td>
<td>6–13</td>
<td>&gt;90</td>
<td>50</td>
<td>66–100</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>1–2</td>
<td>10–14</td>
<td>55</td>
<td>107</td>
<td>62</td>
</tr>
</tbody>
</table>

OAC, oral anticoagulant; Cmax, peak concentration; Vd, volume of distribution.
of vitamin K (phytonadione 2.5–5 mg) are administered, reduced vitamin K is generated by a mechanism that bypasses epoxide reductase (via vitamin K reductase) that is less sensitive to warfarin (Figure 1) (5). Large vitamin K doses (10 mg) can result in warfarin resistance for 1 week (5). The American College of Chest Physicians guidelines recommend, for INRs ≥ 9 and no bleed, a single oral 2.5- to 5-mg dose to bring the INR down in 1–2 days (5). For serious bleeding, regardless of INR value, 10 mg is administered parentally, and it is supplemented by fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa. These measures are repeated every 12 hours if the INR remains elevated (5). Because hemorrhagic effects can be prolonged in patients with CKD and patients with ESKD for a given INR value compared with in non-CKD individuals (11), clinicians should consider repeated therapy to ensure adequate reversal.

**Efficacy and Safety**

Compared with those with normal kidney function, CKD, especially GFR < 30 ml/min per 1.73 m², or ESKD complicates warfarin therapy. Specifically, lower doses are required to maintain therapeutic INR. Greater fluctuations in INR values with lower individual time in the therapeutic range and higher risks of major bleeding events for any given INR value are reported (9,10). In an observational study of 1273 long-term warfarin users, one third had a GFR of < 60 ml/min per 1.73 m² (11). Compared with individuals with GFR of > 60 ml/min per 1.73 m², those with GFR of 30–44 ml/min per 1.73 m² and those with GFR < 30 ml/min per 1.73 m² had 2.2- and 5.8-fold higher risks, respectively, of major bleeding events at an INR value ≥ 4. GFR did not modify risk of hemorrhage for INR values < 4 (11).

Because higher stroke rates were reported in patients with ESKD with versus without AF (4.57 versus 0.48 per 100 person-years, respectively) (12), previous cost utility

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**Table 3. Common drug-drug interactions of oral anticoagulants**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Increase Anticoagulant Effects</th>
<th>Decrease Anticoagulant Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Amiodarone, fluconazole, tigecycline, voriconazole, fluoroquinolones, verapamil, diltiazem,</td>
<td>Rifampin, phenobarbital, carbamazepine, cigarette smoking</td>
</tr>
<tr>
<td></td>
<td>other anticoagulants, antiplatelet drugs, NSAIDs, and SSRIs</td>
<td></td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Amiodarone, verapamil, ketoconazole, dronaderone, clopidogrel, enoxaparin, other anticoagulants,</td>
<td>Rifampin</td>
</tr>
<tr>
<td></td>
<td>antiplatelet drugs</td>
<td></td>
</tr>
<tr>
<td>Apixaban</td>
<td>Ketoconazole, other anticoagulants, antiplatelet drugs</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Other anticoagulants, antiplatelet drugs, fluconazole, ketoconazole, erythromycin, and clarithromycin</td>
<td>Rifampin, phenytoin, carbamazepine, St. John’s Wort</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Other anticoagulants, antiplatelet drugs</td>
<td>Rifampin</td>
</tr>
</tbody>
</table>

NSAID, nonsteroidal anti-inflammatory drug; SSRI, serotonin reuptake inhibitor.

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**Figure 1.** Carboxylation of vitamin K–dependent proteins requires the reduced form of vitamin K, γ-glutamyl carboxylase enzyme, molecular oxygen, and carbon dioxide. Because body stores of vitamin K are low, the oxidized (inactive) form of vitamin K is recycled to the reduced (active) form by vitamin K epoxide reductase, which is inhibited by warfarin. Inhibition results in reduced hepatic synthesis of these clotting factors and reduction in their activities by 40%–50%.

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analyses reported an increase in quality-adjusted life years with aspirin or warfarin treatment (13). However, warfarin increases bleeding risk, including intracranial hemorrhage, in patients with ESKD. In a retrospective study of patients with ESKD and AF, warfarin doubled stroke risk, presumably hemorrhagic, compared with no treatment (14). Another study evaluated patients with ESKD in the Fresenius Medical Care North America (FMCNA) database and reported 27% higher death risk with warfarin treatment (15). Observational studies are fraught with selection bias, especially because patients with ESKD and AF may be more likely to die compared with individuals with ESKD without AF. Data are limited to confirm or refute these concerns. There is concern of increased vascular calcification and calciphylaxis with warfarin given that it reduces function of vitamin K–dependent vascular calcification inhibitors, such as matrix Gla proteins (14,16). Finally, there are concerns about the possibility of AKI secondary to glomerular hemorrhage due to thrombin depletion in patients on warfarin with INR >3 in whom there is no other identifiable etiology of AKI (17). It is also believed to result in accelerated progression of CKD and worsen all-cause mortality in the short and long term (17). However, exact mechanisms and clinical presentation remain elusive to date. Despite a Food and Drug Administration (FDA) black box warning for warfarin use in patients with kidney dysfunction due to increased risk of major bleeding, it is still commonly used. Furthermore, clinical practice guidelines continue to recommend warfarin in treating AF among patients with CKD and patients with ESKD (18). The American Heart Association 2014 updated guidelines for anticoagulation management in AF recommend warfarin as the drug of choice in patients with advanced CKD (creatinine clearance <30 ml/min) and patients with ESKD (8,19). The jury is still out regarding potential benefits and risks. If this high-risk patient population is not treated, it is estimated that stroke rate, including intracranial hemorrhage, would be approximately 7% (18). However, three distinct observational studies reported that warfarin did not reduce ischemic strokes among patients with ESKD. In addition, these studies reported an alarmingly higher intracranial hemorrhage rate compared with in the general population (3% versus 1% per year, respectively) (18).

**Direct Thrombin Inhibitor—Dabigatran**

**Pharmacology**

Dabigatran etexilate, 150 mg twice daily, is FDA approved to prevent stroke or systemic embolism in patients with AF. Nonspecific, ubiquitous esterases rapidly convert this nonpeptide prodrug into a potent, direct, and selective inhibitor of free and fibrin-bound thrombin (Table 1) (20).

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**Table 4. Reversal agents for oral anticoagulants and hemodialysis as an option to reverse antithrombotic effects**

<table>
<thead>
<tr>
<th>Reversal by antidotes</th>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin complex concentrate</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Recombinant factor VIIa</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Factor VIII inhibitor bypass activity</td>
<td>Not reported</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Specific antidote</td>
<td>No</td>
<td>Idaracizumab</td>
<td>Investigational (andexanet alfa)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dialysis as a treatment option for major bleeding events**

| Hemodialysis | Yes | No | No | No | No |
PK/PD properties are shown in Tables 1 and 2. Common drug-drug interactions are shown in Table 3. Its capsule (75 or 150 mg) contains dabigatran-coated pellets with a tartaric acid core to augment bioavailability at low pH. The core increases dyspepsia risk and gastrointestinal bleeding, especially with the 150-mg dose (20). Patients should not chew, break, or open capsules, because bioavailability increases dramatically (21). Substantial inter-individual drug exposure variability exists (22). Dabigatran is approved at lower doses (75 mg twice daily), with a creatinine clearance of 15–30 ml/min (21).

### Laboratory Measurement of Anticoagulant Effect

Activated partial thromboplastin time (APTT) is better than prothrombin time (PT) to detect dabigatran presence, but it cannot reliably distinguish between therapeutic and subtherapeutic concentrations (Table 4) (20,23). A normal thrombin time has the best negative predictive value to exclude the presence of dabigatran (20,23). Ecarin, a metalloproteinate, cleaves prothrombin to meizothrombin. Dabigatran inhibits this step. Ecarin-based assays, such as the ecarin clotting time, are highly sensitive and correlate strongly with drug concentrations. Studies showed that thrombin time and ecarin clotting time are linearly correlated with drug concentration measured by liquid chromatography tandem mass spectrometry (23).

### Pharmacology in Kidney Disease

An open label, controlled study investigated PK/PD properties of a single 150-mg dabigatran dose in 23 patients with CKD and 50 mg in six patients with ESKD. The comparator group (six non-CKD controls) received two doses of 150 mg (standard dose) (24). Versus controls, areas under the plasma concentration-time curve (AUCs) were 1.5-, 3.2-, and 6.3-fold higher in patients with CKD and creatinine clearances of 50–80, 30–50, and ≤30 ml/min, respectively. Time to maximal plasma concentration (Cmax) was similar in patients with CKD and controls.

### Table 5. Comparative efficacy and safety data on dabigatran versus warfarin in patients with kidney disease and atrial fibrillation (36–41)

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Sample Size of CKD Subgroup</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran in patients with CKD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laufenburger et al. (37)</td>
<td>Patients having commercial or Medicare supplemental insurance</td>
<td>6727</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hernandez et al. (38)</td>
<td>5% Random sample of Medicare beneficiaries</td>
<td>2964</td>
</tr>
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<td></td>
<td></td>
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<tr>
<td>Majeed et al. (39)</td>
<td>Pooled analyses of five phase 3 RCTs</td>
<td>1034 with any bleeding event, no mention of percentage with CKD</td>
</tr>
<tr>
<td>Graham et al. (40)</td>
<td>Medicare beneficiaries</td>
<td>13% of 134,414 had CKD</td>
</tr>
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<tr>
<td>Romanelli et al. (36)</td>
<td>Meta-analysis</td>
<td>348,750 Patients and no CKD subgroup analysis</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dabigatran in patients on hemodialysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al. (41)</td>
<td>Fresenius Medical Care of North American database of patients on hemodialysis</td>
<td>8345</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

S/SE, stroke or systemic embolism; GI, gastrointestinal; ICH, intracranial hemorrhage; RCT, randomized, controlled trial.

*Adjusted hazard ratio.

†Adjusted odds ratio.

‡Adjusted rate ratio.
Evaluation $t_{1/2}$ doubled in patients with CKD (creatinine clearance $\leq 30 \text{ ml/min}$) compared with non-CKD controls. Although six patients with ESKD received a reduced dose (50 mg), AUC was twofold higher than in non-CKD controls. A single hemodialysis session removed 62%–68% of the 50-mg dose. APTT and ecarin clotting time increased in correlation with changes in plasma drug concentration. Another PK/PD study was conducted in 15 patients with creatinine clearance of 15–30 ml/min. Participants received 75 mg twice daily, a dose resulting in mean steady-state drug exposure without drug accumulation (25). These studies suggest that drug exposure correlates with kidney disease severity and prescribed dose, which can be measured by APTT or ecarin clotting time.

Reversal of Antithrombotic Effects

There are patient reports using fresh frozen plasma and prothrombin complex concentrate to reverse dabigatran's effects in patients with major bleeding (26). A recent randomized, controlled trial (RCT) in subjects with normal kidney function raised questions about the efficacy of prothrombin complex concentrate as an effective reversal agent (27). In another study in subjects with normal kidney function, nonspecific anti-inhibitor coagulant complex (e.g., factor VIII inhibitor bypass activity) but not recombinant factor VIIa reversed dabigatran's anticoagulant effects (28).

No studies have evaluated these agents in patients with CKD and patients with ESKD. A patient series of 11 life-threatening dabigatran-related major bleeding episodes reported use of hemodialysis and continuous venovenous hemofiltration (29). A PK/PD study of dabigatran 150 mg twice daily for 3 days in seven patients on hemodialysis reported 49% and 59% drug removal with blood flow rates of 200 and 400 ml/min, respectively, over a 4-hour treatment (30). Another study reported 62%–68% dabigatran removal with a single dialysis session (24). Although studies are limited by lack of control groups, randomization, and small sample size, available data suggest a possible role for kidney replacement therapy in reversal of dabigatran's antithrombotic effects.

Recently, the FDA approved idarucizumab to reverse the antithrombotic effects of dabigatran (31). As a humanized mAb fragment directed against dabigatran and its acylglucuronide metabolites, its binding affinity to dabigatran is higher than dabigatran to thrombin, thus neutralizing the anticoagulant effect immediately after a single 5-g intravenous dose (32). Nearly one third (32%) of idarucizumab is excreted in urine, and the remaining undergoes metabolism primarily in kidney (32). In 12 subjects with creatinine clearance $\geq 60$ to $<90 \text{ ml/min}$ and six subjects with creatinine clearance $\geq 30$ to $<60 \text{ ml/min}$, total antidote clearance was reduced, resulting in higher drug exposure by 44% and 84%, respectively (32). The package insert recommends no dose reduction for kidney dysfunction. More studies are needed to assess its efficacy in patients with CKD and patients with ESKD.

Efficacy and Safety

After FDA approval, patient reports of major bleeding were reported in frail elderly individuals, patients with CKD, and patients with ESKD (26,33). In the Randomized Evaluation of Long-Term Therapy Trial, 19% of patients had a baseline creatinine clearance $<50 \text{ ml/min}$, and individuals with baseline creatinine clearance $<30 \text{ ml/min}$ were excluded (34). A subgroup analysis reported lower rates of stroke or systemic embolism with dabigatran 150 mg twice daily versus warfarin across all creatinine clearance categories ($\geq 80, 50$ to $<80$, and $<50 \text{ ml/min}$) (35). Lower major bleeding rates were observed only in participants with creatinine clearance $\geq 80 \text{ ml/min}$. Table 5 summarizes four retrospective cohort studies and one meta-analysis reporting comparative effectiveness and safety data for dabigatran versus warfarin in CKD subgroups, and they concluded that dabigatran versus warfarin reduces risk of stroke or systemic embolism and intracranial hemorrhage, with an increased risk of gastrointestinal bleeding events (36–40). There is only one study in patients on hemodialysis using the FMCNA database; it reported a 1.5-fold higher risk of death or hospitalization from bleeding with dabigatran versus warfarin (Table 5) (41).

Factor Xa Inhibitors

Rivaroxaban

Rivaroxaban is FDA approved in patients with AF to prevent stroke or systemic embolism (42). It is also FDA approved for deep venous thrombosis (DVT) and pulmonary embolism (PE) prophylaxis after knee and hip replacement (42,43). Like dabigatran, it is not approved in patients with mechanical heart valves. Oral bioavailability varies with dosing strength: 80%–100% with a 10-mg dose and 66% with a 20-mg dose. Other PK/PD properties are shown in Tables 1 and 2 (20). It is prescribed at a fixed oral dose with the evening meal: 20 mg/d for patients with a creatinine clearance of $>50 \text{ ml/min}$ and 15 mg/d for patients with a creatinine clearance of 30–50 ml/min (42). It should be avoided in patients with AF and a creatinine clearance of $<15 \text{ ml/min}$ (42). With a creatinine clearance of 15 to 50 ml/min the package insert recommends a reduced dose of 15 mg once daily with the evening meal in patients with nonvalvular atrial fibrillation. Rivaroxaban is not recommended for other indications with a creatinine clearance $<30 \text{ ml/min}$. It does not interact with foods and interacts minimally with other drugs (Table 3). For DVT and PE prophylaxis, dosage is 10 mg/d. Rivaroxaban has a shorter $t_{1/2}$ and more rapid onset of action than warfarin (43). Timing of initiation after procedures and daily adherence are prerequisites for clinical success (43). It is typically started 6–10 hours after surgery for DVT/PE prophylaxis, and it is continued for 35 days after hip replacement and 12 days after knee replacement (42). To transition from heparin to rivaroxaban, infusion is stopped, and rivaroxaban is started simultaneously. When transitioning from low molecular weight heparin, rivaroxaban is initiated within 2 hours of the next scheduled administration (42).

Pharmacology in Kidney Disease

A subgroup analysis of 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) with impaired creatinine clearance ($<80 \text{ ml/min}$) reported no effect of kidney
disease on rivaroxaban’s effectiveness and safety (44). A PK/PD study extended this finding by reporting similar AUCs (plasma concentration-time curve) in patients with ESKD and a 10-mg dose and healthy controls with a 20-mg dose (45). However, other controlled PK/PD studies challenged these findings and reported a 56% increase in AUC in patients with ESKD after a 15-mg dose administered postdialysis (46). Predialysis administration resulted in reduced drug exposure by only 5%. Finally, a PK/PD study of a single 10-mg dose was conducted in 24 patients with CKD (creatinine clearance <30 ml/min) and eight healthy controls (creatinine clearance ≥80 ml/min) (47). Compared with controls, the AUCs were 1.4-, 1.5-, and 1.6-fold higher with creatinine clearances of 50–80, 30–50, and <30 ml/min, respectively. The AUCs (factor Xa inhibition-time curve) were 1.5-, 1.9-, and 2.0-fold, respectively. This study suggests that reduced rivaroxaban clearance with worsening creatinine clearance resulted in increased drug exposure (47). Rivaroxaban is likely to accumulate in patients with CKD and patients with ESKD even at lower doses (10 or 15 mg/d), and it is poorly cleared by hemodialysis.

Apixaban
Apixaban is FDA approved for reduction of stroke or systemic embolism in patients with AF at 5 mg twice daily (48). With serum creatinine ≥1.5 mg/dl, age ≥80 years old, or body weight ≤60 kg, a reduced dose of 2.5 mg twice daily is recommended (48). It is also approved for DVT/PE prophylaxis after hip and knee replacement at 2.5 mg twice daily (48) and treatment of DVT/PE at 10 mg twice daily for a week followed by 5 mg twice daily (48). It is not approved for use with mechanical heart valves (48). PK/PD properties are shown in Tables 1 and 2. Drug-drug interactions are minimal (Table 3) (43).

Pharmacology in Kidney Disease
No significant kinetic changes were observed in peak plasma drug concentration (Cmax) or AUC among patients with CKD (creatinine clearance of 15–29 ml/min) and patients with ESKD (48). An open label, parallel group, single 5-mg dose PK/PD study was conducted in eight patients with ESKD and eight healthy controls (49). After 2 hours of drug administration, a 4-hour hemodialysis session was performed with dialysate flow rate of 500 ml/min and blood flow rate of 350–500 ml/min. The AUC in patients with ESKD was 36% higher versus controls (49). Because of its high degree of protein binding, dialysis clearance is low (18 ml/min), resulting in a 14% decrease in drug exposure (49). In a recent retrospective analysis of patients on hemodialysis, cumulative days of apixaban use in an outpatient setting, higher total daily apixaban doses, and total hemodialysis sessions were independent risk factors for bleeding events (adjusted odds ratio, 13.07; 95% CI, 1.54 to 110.54; adjusted odds ratio, 1.72; 95% CI, 1.20 to 2.48; and adjusted odds ratio, 2.04; 95% CI, 1.06 to 3.92, respectively) (50). Another PK/PD study prescribed a single 10-mg dose to 24 patients with CKD and various categories of creatinine clearance and eight healthy controls (51). Compared with controls, geometric mean AUCs increased by 16%, 29%, and 38% in patients with CKD and creatinine clearances of 50–80, 30–50, and <30 ml/min, respectively. Overall, elimination t1/2 was slightly increased in all subjects with CKD (17 hours) versus controls (15 hours). A direct linear relationship was observed between apixaban plasma concentration and antifactor Xa activity. These studies suggest that apixaban accumulates in patients with CKD and patients with ESKD and that it is poorly dialyzable.

In another PD/PK study seven hemodialysis patients were given apixaban at 2.5 mg twice daily for eight days. The AUC, Cmax, and Cmin all increased when measured at day 8 compared to day 1 suggesting accumulation of the drug. At day 8 drug levels were still within the normal reference range. Drug levels comparing day 5 versus day 8 suggested that a steady state had been reached. Despite that it still would be of interest to examine levels with a longer duration of exposure (52).

Edoxaban
Edoxaban was FDA approved after a trial that established noninferiority compared with warfarin in patients with AF (53). It is also approved for treatment of DVT/PE only after an initial 5- to 10-day treatment with parenteral anticoagulation (19). It is recommended at 60 mg once daily for patients with creatinine clearance of 50–95 ml/min and 30 mg once daily for patients with creatinine clearance of 15–50 ml/min (54). PK/PD properties are shown in Tables 1 and 2. Common drug-drug interactions are shown in Table 3.

Pharmacology in Kidney Disease
Drug exposure increases by 32%, 74%, and 72% with creatinine clearances of 50–80, 30–50, and <30 ml/min, respectively (55). Although its molecular weight is 738 g/mol and it is only 55% protein bound, it is poorly cleared by dialysis (9% with a blood flow rate of 350 ml/min, a dialysate flow rate of 500 ml/min, and an F180NR dialyzer), possibly due to the large volume of distribution (107±20 L) (56).

Laboratory Measurement of Anticoagulant Effects
PT prolongation occurs to a greater degree than APTT prolongation with factor Xa inhibitors (Table 4) (20). A prolonged PT on warfarin does not equate to a similar anticoagulant effect on factor Xa inhibitors with the exact same PT value (23). Compared with PT and APTT assays, chromogenic anti-Xa activity assay (e.g., Rotachrom) may be more reliable and accurate (20,23). There is strong correlation between antifactor Xa activity and factor Xa inhibitor concentration (r²=0.95–1.00) (20). There are no FDA-approved kits that can be used for universal standardization of the anti-Xa activity assay.

Reversal of Antithrombotic Effects
Prothrombin concentrate complex, recombinant factor VIIa, and factor VIII inhibitor bypass activity can reverse their anticoagulant effects (Table 4) (27,28,57–60). There are no specific antidotes. Andexanet alfa, a modified recombinant human factor Xa molecule that acts as a decoy molecule, is under investigation (61).

Efficacy and Safety
The RCT (the ROCKET-AF) that led to FDA approval of rivaroxaban for AF included participants with CKD
and excluded individuals with a creatinine clearance <30 ml/min (62). On the basis of studies in the general population, newer oral anticoagulants (dabigatran, rivaroxaban, or apixaban) compared with warfarin were more effective in reducing stroke or systemic embolism without an increased risk of intracranial hemorrhage and gastrointestinal bleeding (63). As a result, off-label use is increasing in patients with a creatinine clearance of <30 ml/min and ESKD (41). A study of the FMCNA database of patients with AF on chronic hemodialysis reported a 1.7-fold higher risk of death or hospitalization from bleeding with rivaroxaban versus warfarin (adjusted rate ratio, 1.71; 95% CI, 0.94 to 3.12) (41).

With apixaban, there is one published patient report of a major bleeding event noted in a patient on hemodialysis (64). Apixaban was superior to warfarin in reducing stroke or systemic embolism rates and major bleeding among participants with kidney dysfunction in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial (65). A meta-analysis of RCTs comparing newer oral anticoagulants (dabigatran, rivaroxaban, and apixaban) with warfarin reported no difference in stroke, systemic embolism risk, or major bleeding in the CKD subgroup (relative risk, 0.64; 95% CI, 0.39 to 1.04 and relative risk, 0.89; 95% CI, 0.68 to 1.16, respectively) (66). Another meta-analysis reported reduced bleeding risk in the CKD subgroup (risk ratio, 0.80; 95% CI, 0.66 to 0.96) (67). In addition, bleeding rates were similar between individuals with creatinine clearance of 50–80 versus 30–50 ml/min on apixaban (67).

Compared with participants with creatinine clearance >50 ml/min, individuals with creatinine clearance of 30–50 ml/min in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction Study 48 reported similar stroke or systemic embolism risk on edoxaban (68). Another subgroup analysis reported similar findings and a 24% reduction in bleeding risk (adjusted hazard ratio, 0.76; 95% CI, 0.58 to 0.98) (19). Finally, no difference in bleeding was reported between 15- and 30- to 60-mg/d doses in patients with GFR 15–30 ml/min per 1.73 m² (19).

A recent Cochrane review reported reduced risk of stroke or systemic embolism and similar risk of major bleeding among patients with AF and CKD treated with factor Xa inhibitors versus warfarin (risk ratio, 0.81; 95% CI, 0.65 to 1.00 and risk ratio, 0.79; 95% CI, 0.59 to 1.04, respectively) (69). For both rivaroxaban and apixaban major clinical trials excluded patients on hemodialysis. With both drugs, at reduced dosages in hemodialysis patients, drug concentrations approximate those found in patients without kidney disease. However, the number of patients studied is very small and no conclusions can be drawn regarding their safety or efficacy, and caution should be exercised with their use in this patient population.

Gaps in the Literature

Although patients with CKD and patients with ESKD account for nearly 10% of the overall Medicare paid claims costs and although oral anticoagulant drugs are one of the top ten prescription drugs of Medicare prescription drug expenditure (70), comparative efficacy and safety data remain limited to support use of one oral anticoagulant over another in patients with CKD stages 4–5 or ESKD. Because these patients suffer from increased rates of hospitalization, adverse outcomes, and high health care–related costs (71), RCTs to investigate efficacy and safety of oral anticoagulants to improve hard clinical outcomes are critically important. Finally, there is lack of a standardized approach to assess kidney function in research, because debate continues regarding the preferred method for adjusting drug dosage. For example, the Modification of Diet in Renal Diseases eGFR calculation and the Cockcroft Gault creatinine clearance calculation were reported to over- or underestimate kidney function in various clinical settings (72,73).

Summary

Oral anticoagulants are commonly prescribed in patients with kidney disease. Understanding their clinical pharmacology and changes that occur as GFR declines is key to their effective use. Risks and benefits of oral anticoagulants are different in patients with CKD and patients with ESKD. All of these factors must be considered regardless of whether oral anticoagulants are prescribed for FDA-approved indications or used off label. Patients with GFR<30 ml/min per 1.73 m², including those on dialysis, were systematically excluded from landmark trials. Extrapolation of comparative efficacy and safety in this patient population is difficult. Warfarin remains the most widely used oral anticoagulant. In our opinion, INR should be closely monitored in patients with ESKD. In our clinical practice, we check INR once a week in patients with ESKD. In our opinion, if the individual time in therapeutic INR range is <50% or if patients experience complications, such as calciphylaxis, we consider switching them to apixaban. Finally, until more data become available, we currently do not use dabigatran, rivaroxaban, and edoxaban in patients with CKD stage 5 and ESKD. Future studies are needed to establish whether use of oral anticoagulants result in net clinical benefit for individuals with CKD stages 4–5 and individuals with ESKD.

Acknowledgments

This study was supported by American Heart Association Scientist Development grant 16SDG31000045 (to N.J.).

Disclosures

None.

References


Correction


Due to author error, a correction has been issued for the above referenced article. The text below was incorrectly worded:

“With serum creatinine $\geq 1.5$ mg/dl, age $\geq 80$ years old, or body weight $\leq 60$ kg, a reduced dose of 2.5 mg twice daily is recommended (48).”

The text should have been worded as follows:

The package insert recommends a reduced dose of 2.5 mg twice daily in patients with at least two of the following three clinical characteristics: serum creatinine $\geq 1.5$ mg/dl, age $\geq 80$ years or body weight $\leq 60$ kg.

Published online ahead of print. Publication date available at www.cjasn.org.