REVIEW TOPIC OF THE WEEK

Nonvitamin K Anticoagulant Agents in Patients With Advanced Chronic Kidney Disease or on Dialysis With AF

Kevin E. Chan, MD, MSc,a,b Robert P. Giugliano, MD, SM,c Manesh R. Patel, MD,d Stuart Abramson, MD,e Meg Jardine, MBBS, PHD,f Sophia Zhao, MD, PhD,a Vlado Perkovic, MBBS, PhD,f Franklin W. Maddux, MD,b Jonathan P. Piccini, MD, MHS,c

ABSTRACT

Nonvitamin K-dependent oral anticoagulant agents (NOACs) are currently recommended for patients with atrial fibrillation at risk for stroke. As a group, NOACs significantly reduce stroke, intracranial hemorrhage, and mortality, with lower to similar major bleeding rates compared with warfarin. All NOACs are dependent on the kidney for elimination, such that patients with creatinine clearance <25 ml/min were excluded from all the pivotal phase 3 NOAC trials. It therefore remains unclear how or if NOACs should be prescribed to patients with advanced chronic kidney disease and those on dialysis. The authors review the current pharmacokinetic, observational, and prospective data on NOACs in patients with advanced chronic kidney disease (creatinine clearance <30 ml/min) and those on dialysis. The authors frame the evidence in terms of risk versus benefit to bring greater clarity to NOAC-related major bleeding and efficacy at preventing stroke specifically in patients with creatinine clearance <30 ml/min. (J Am Coll Cardiol 2016;67:2888–99)

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Patients with atrial fibrillation (AF) are increasingly being treated with nonvitamin K-dependent oral anticoagulant agents (NOACs) because these drugs are at least as effective as warfarin, are safer, do not require routine monitoring, and are simpler to use (1–5). In 2013, NOACs accounted for 62% of new prescriptions of anticoagulant agents in the United States, and their adoption is increasing (1).

Although NOACs hold great promise, they also have drawbacks, such as limited availability of and little experience with reversal agents, as well as higher costs. Currently, all NOACs depend to some extent on renal function for clearance. Consequently, NOACs may potentially accumulate in patients with renal dysfunction, leading to an increased risk for bleeding. Additionally, patients with advanced chronic kidney disease (CKD) (creatinine clearance [CrCl] <30 ml/min) are already at increased risk for bleeding from uremia-induced platelet dysfunction (6,7). Patients on hemodialysis have added bleeding risks from repeated vascular access cannulation,
dialysis membrane interactions, higher than average blood pressures, and considerable heparin administration during treatment. Because patients with advanced CKD and end-stage renal disease (ESRD) were excluded from all of the pivotal phase 3 NOAC trials, no randomized controlled trial data guide NOAC use when the CrCl is <25 ml/min, although the U.S. Food and Drug Administration (FDA) label supports NOAC dosing for patients with CrCl =15 ml/min.

The most recent 2014 American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS) guideline for the management of patients with AF who are anticoagulated was prescribed NOACs (Central Illustration). Among the NOAC-treated patients with CKD (n = 102,504), the most commonly used drug was apixaban (10.4%), followed by rivaroxaban (9.5%), dabigatran (3.5%), and edoxaban (0.1%). Among the NOAC-treated dialysis patients (n = 140,918), the most commonly used drug was apixaban (10.5%), followed by rivaroxaban (0.8%), dabigatran (0.3%), and edoxaban (0.01%).

This review summarizes the available evidence regarding the efficacy (prevention of stroke) and safety (major bleeding) of the 4 currently available NOACs (apixaban, rivaroxaban, dabigatran, and edoxaban), with particular emphasis on the outcomes in subgroups of patients with AF with CKD. Pharmacokinetic (PK) data for patients with advanced CKD and those on dialysis will be discussed, as well as the data on reversal agents. Finally, we outline the steps required to determine if NOACs are appropriate treatment options in patients with AF with advanced CKD or on dialysis.

**RENAI PHARMACOKINETICS OF ANTICOAGULANT AGENTS**

Uremia affects every organ system in the body and influences the pharmacokinetics of many drugs. Uremia can impair plasma protein binding, which may lead to increased free drug levels in the blood, and in turn, renal failure can also impair nonrenal drug metabolism by reduction and hydrolysis reactions (10,11).

Renal elimination of drugs occurs predominantly through glomerular filtration and occasionally through tubular secretion and reabsorption. When the glomerular filtration rate and tubular function are impaired by renal disease, the clearance of drugs eliminated by these mechanisms will be decreased, and the plasma half-lives of the drugs will be prolonged. This can result in increased total drug exposure, as quantified by the area under the curve (Figure 1). Without appropriate dose adjustment, repeated dosing of a drug that is inadequately cleared could lead to bioaccumulation over time and toxicity from supratherapeutic levels of the drug (Figure 2). To counteract decreased renal drug elimination, medications can be given at a lower dose or frequency to prevent unintended drug accumulation (11).

Anticoagulant drug dosing in patients with renal impairment is based on glomerular filtration rate, which is impractical to measure directly in an office setting. Instead, the glomerular filtration rate can be estimated by measuring the 24-h urine CrCl, because almost all creatinine is eliminated through the glomerulus. Because collecting urine for 24 h is a tedious process, CrCl is typically estimated by an equation, using a single serum creatinine measurement.

For NOAC dosing, CrCl should be calculated using the Cockcroft-Gault formula, because the pivotal phase 3 NOAC trials have reported outcomes by CrCl using that formula (12). This is despite the fact that the Cockcroft-Gault formula can overestimate true CrCl by 10% to 40%, and newer estimating equations,
Prevalence of nonvitamin K-dependent oral anticoagulant agent (NOAC) use is rising among patients with advanced chronic kidney disease (CKD) and those on dialysis anticoagulated for atrial fibrillation, despite the most recent American Heart Association, American College of Cardiology, and European Heart Rhythm Society guideline, which discourages the use of NOACs when creatinine clearance (CrCl) is <30 ml/min. There are few randomized trial data on NOACs in this population. All NOACs depend on the kidney for elimination, and it is unclear if severe renal impairment leads to drug bioaccumulation to precipitate inadvertent bleeding.

**FIGURE 1** Pharmacokinetic Curves for Renally Cleared Drugs in Patients With Normal and Impaired Kidney Function

Pharmacokinetic (PK) curves illustrating the peak, trough, and total drug exposure for a renally cleared drug in a patient with normal kidney function (A) and in a patient with impaired kidney function (B). Decreased drug clearance resulted in increased peak level, trough level, and total drug exposure. Total drug exposure is quantified by the area under the PK curve, in blue.
such as the MDRD (Modification of Diet in Renal Disease) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equations, have been shown to be more accurate (13–15). The Cockcroft-Gault equation is as follows:

\[
\text{CrCl (ml/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times \text{sex}}{72 \times \text{serum creatinine (mg/dl)}}
\]

where sex = 1 in men and 0.85 in women. It is also important to note that CrCl estimations derived from these equations are valid only when a patient’s creatinine level is in a steady state. It is a mistake to extrapolate CrCl calculations using creatinine values from acutely ill patients with acute kidney injury. Drug dosing in patients with acute kidney injury should be individualized until the creatinine level stabilizes, which may take weeks or longer (11).

Drug removal through hemodialysis is determined primarily by molecular size. Small molecules (<1,500 Da) are amenable to removal through high-flux dialysis membranes. Protein-bound drugs are not cleared by dialysis, whereas unbound drugs in the intravascular space may be cleared. A drug with a high volume of distribution, arbitrarily defined at >0.7 l/kg, indicates a highly tissue-bound drug, where a significant amount of drug is distributed in the extravascular space that is not directly accessible to the extracorporeal circulation for removal by dialysis. Measured drug levels are expected to rebound after hemodialysis is completed and are the result of drug concentrations in the intra- and extravascular compartment reequilibrating after dialysis (11).

**WARFARIN**

Warfarin, originally used as a rodenticide in 1948, was later found to be effective and relatively safe for preventing thrombosis and was approved for use as an anticoagulant agent in 1954 (16). Warfarin is not dialyzable, because 99% is bound to plasma proteins, and elimination of the drug is almost entirely by hepatic metabolism into an inactive metabolite (Figure 3). Very little of the parent compound is excreted in the urine (11,17,18). Studies also suggest that patients with advanced CKD and on dialysis require reduced doses of warfarin. This may be in part due to alterations of hepatic metabolism of warfarin secondary to renal failure (19). Animal studies in CKD have shown a significant down-regulation (40% to 85%) of hepatic cytochrome P-450 metabolism, which corroborates with clinical data (17,19–21).

Warfarin is minimally dependent on the kidney for elimination, such that progression of CKD or acute changes in creatinine can minimally influence anticoagulation levels from the drug. Warfarin has the advantages of clinical familiarity, low cost, and widespread availability of reversal agents. Reversal of warfarin’s anticoagulant effect can be accomplished with vitamin K or fresh-frozen plasma for non-emergent situations, with 4-factor prothrombin complexes recommended for life-threatening bleeding (22). Warfarin significantly increases the risk for bleeding as CrCl decreases. This is likely secondary to superimposed platelet dysfunction from worsening uremia. A patient on warfarin with CrCl <30 ml/min has a 4.9-fold (95% confidence interval [CI]: 2.6 to 9.1) increased relative risk for bleeding compared

**FIGURE 2** Pharmacokinetic Curve Illustrating the Effect of Drug Multidosing in a Patient With Impaired Renal Function, Resulting in Bioaccumulation of the Drug Level

A mismatch between drug dose and drug clearance results in the carryover of excess drug level to the next dosing interval, which occurs every 24 h.

**FIGURE 3** Pharmacokinetics of Warfarin

Warfarin does not depend on the kidney for elimination.
with patients on warfarin without renal disease (Table 1) (17).

**NOACs**

Currently, there are 4 FDA-approved NOACs for stroke prevention in patients with AF: apixaban, rivaroxaban, dabigatran, and edoxaban. Table 2 summarizes the renal clearance, effect of dialysis, and reversal agents for these medications; in addition, it outlines the hazard ratios (HRs) for stroke and bleeding from the pivotal phase 3 trials among subjects with CrCl <50 ml/min (referent to warfarin).

**APIXABAN.** Apixaban is a direct factor Xa inhibitor with 27% renal elimination (Figure 4A). In the AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trial (n = 5,599 subjects with creatinine <2.5 mg/dl), subjects with AF who were unable to take warfarin were randomized to apixaban 5 mg twice per day or aspirin. A reduced dose of apixaban 2.5 mg twice per day was given to patients who met at least 2 of the following criteria: serum creatinine between 1.5 and 2.5 mg/dl, age ≥80 years, and body weight ≤60 kg. The study showed that apixaban was superior to aspirin in preventing stroke or systemic embolization (HR: 0.32; 95% CI: 0.19 to 0.56), and the trial was stopped prematurely by the Data and Safety Monitoring Board because of overwhelming efficacy (23). No significant difference in the rate of major bleeding between the groups was observed (HR: 1.06; 95% CI: 0.58 to 1.93). The superiority of apixaban over aspirin in stroke prevention and a similar incidence of major bleeding were preserved among patients with CrCl of 25 to 50 ml/min in the study.

In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial (n = 18,201 subjects with creatinine <2.5 mg/dl), patients were randomized to apixaban 5 mg twice per day or warfarin. Because they met the same criteria used in the AVERROES trial for dose reduction, 4.7% of apixaban patients received a lower dose of 2.5 mg twice per day. Overall, apixaban significantly decreased the risk for stroke and systemic embolism (HR: 0.79; 95% CI: 0.66 to 0.95) and major bleeding (HR: 0.69; 95% CI: 0.60 to 0.80) compared with warfarin (2). These trends persisted in post hoc analyses among patients with CrCl of 25 to 50 ml/min, in whom apixaban demonstrated a nonsignificantly decreased risk for stroke (HR: 0.79; 95% CI: 0.55 to 1.14) and a significantly decreased risk for bleeding (HR: 0.50; 95% CI: 0.38 to 0.66) referent to warfarin (24,25). Because of multiple criteria for dose reduction, it is uncertain how many patients with CrCl of 25 to 50 ml/min received the 2.5-mg versus the 5-mg apixaban dose and whether dose affects these HR estimates.

Apixaban was FDA approved in December 2012 for the prevention of stroke and systemic embolism in patients with nonvalvular AF at a dose of 5 mg twice per day and with a 2.5-mg twice-daily dose in patients with 2 of the following: serum creatinine between 1.5 and 2.5 mg/dl, age ≥80 years, and body weight ≤60 kg. In the original labeling, the drug was not recommended for patients with CrCl <25 ml/min.

The drug label was amended in January 2014 for patients with renal impairment, including those with ESRD maintained on hemodialysis. For these patients, no dose reduction (5 mg twice daily) was suggested unless patients were also ≥80 years of age or had body weight ≤60 kg, in which case the reduced dose of 2.5 mg twice per day could be used. Patients with creatinine >2.5 mg/dl, with CrCl <25 ml/min, or on long-term dialysis were excluded from the ARISTOTLE trial; therefore, these dosing suggestions were based partially on a single-dose (not multidose) PK study in 8 hemodialysis subjects matched to 8 subjects with normal renal function (26). In this study, the post-hemodialysis administration of 5 mg apixaban resulted in 36% higher drug exposure compared with healthy subjects with normal renal function. In another 10-mg single-dose PK study of 24 subjects with mild and moderate CKD compared with 8 subjects with normal kidney function, total apixaban exposure was estimated via regression models to be 44% greater in subjects with CrCl of 15 ml/min than in subjects with normal kidney function (27). Thus, under current dosing suggestions on the apixaban label, patients with advanced and end-stage kidney disease could be exposed to 40% more drug. Further studies are needed to establish the optimal apixaban dose in this population.

In terms of dialysis clearance, only 6.7% of apixaban is cleared by a 4-h hemodialysis session.
(Optiflux F180NR dialyzer, dialysate flow rate 500 ml/min, blood flow rate 350 to 500 ml/min, no heparin) (26); therefore, in patients who have overdosed or are having life-threatening bleeding, dialysis would not be an effective means to remove apixaban from the circulation.

**RIVAROXABAN.** Rivaroxaban is also a direct factor Xa inhibitor, and the kidneys eliminate 36% of the parent drug and the remainder is hepatically metabolized into an inactive form (Figure 4B) (28). In ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K

![Figure 4 Pharmacokinetics of Nonvitamin K-Dependent Oral Anticoagulant Agents](image)

**TABLE 2** Characteristics of Warfarin and Nonvitamin K-Dependent Oral Anticoagulant Agents

<table>
<thead>
<tr>
<th></th>
<th>Warfarin</th>
<th>Apixaban</th>
<th>Rivaroxaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal clearance of parent drug</td>
<td>&lt;1%</td>
<td>27%</td>
<td>36%</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>Removal with 4 h of hemodialysis</td>
<td>&lt;1%</td>
<td>7%</td>
<td>&lt;1%</td>
<td>50%-60%</td>
<td>9%</td>
</tr>
<tr>
<td>Volume of distribution, l</td>
<td>8</td>
<td>21</td>
<td>50</td>
<td>50-10</td>
<td>107</td>
</tr>
<tr>
<td>Reversal agent</td>
<td>Vitamin K, FFP, 4F-PCC</td>
<td>4F-PCC</td>
<td>4F-PCC</td>
<td>Idarucizumab</td>
<td>4F-PCC</td>
</tr>
<tr>
<td>Lowest CrCl drug can be prescribed per FDA label, ml/min</td>
<td>&lt;15*</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI) of stroke referent to warfarin, CrCl &lt;50 ml/min</td>
<td>Reference</td>
<td>0.79 (0.55-1.14)</td>
<td>0.88 (0.65-1.19)</td>
<td>0.56 (0.37-0.85)</td>
<td>0.87 (0.65-1.18)</td>
</tr>
<tr>
<td>HR (95% CI) of major bleeding referent to warfarin, CrCl &lt;50 ml/min</td>
<td>Reference</td>
<td>0.50 (0.38-0.66)</td>
<td>0.98 (0.84-1.14)</td>
<td>1.01 (0.79-1.30)</td>
<td>0.76 (0.58-0.98)</td>
</tr>
</tbody>
</table>

*A 5-mg twice-daily dose of apixaban is suggested for patients with CrCl <15 ml/min. This dosing suggestion was based on a small single-dose pharmacokinetic and pharmacodynamic (anti-Xa activity) study. Clinical efficacy and long-term safety studies have not been done in this population; therefore, use apixaban with caution in patients with advanced or end-stage chronic kidney disease. 150-50 ml/min for the comparison of edoxaban versus warfarin (27).

CI = confidence interval; CrCl = creatinine clearance; FDA = U.S. Food and Drug Administration; FFP = fresh-frozen plasma; 4F-PCC = 4-factor prothrombin complex concentrate; HR = hazard ratio.

(A) Apixaban, (B) rivaroxaban, (C) dabigatran, and (D) edoxaban.
Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), a randomized controlled trial of 14,264 patients with AF at moderate to high risk for stroke (mean CHADS<sub>2</sub> score 3.5 ± 0.9), all of whom had CrCl >30 ml/min, rivaroxaban was noninferior to warfarin at preventing stroke and systemic embolism (3). Additionally, the occurrence of nonmajor clinically relevant or major bleeding was not significantly different between the 2 groups. Patients with CrCl >50 ml/min received 20 mg rivaroxaban once daily, whereas subjects with CrCl of 30 to 49 ml/min received 15 mg once daily. There was no evidence of heterogeneity in outcomes in patients treated with the 15- or 20-mg dose compared with warfarin (29); furthermore, the effect estimates for stroke prevention were similar for rivaroxaban subjects with CrCl of 50 to 80 ml/min (HR: 0.85; 95% CI: 0.67 to 1.08) and 30 to 50 ml/min (HR: 0.88; 95% CI: 0.65 to 1.19) relative to warfarin. For major bleeding, there was no difference in bleeding risk in the CKD population between rivaroxaban and warfarin overall.

The FDA approved a 20-mg once-daily rivaroxaban dose in November 2011. The label included a recommended 15-mg once-daily dose for patients with CrCl between 15 and 50 ml/min. Of note, Kubitza et al. (28) reported a 52% increase in drug exposure and a 26% increase in peak concentration after a single 10-mg dose among 8 patients with a mean CrCl of 43 ml/min. These data suggest that the dose of rivaroxaban in patients with moderate CKD needed to match the exposure of patients with no renal impairment may have to be lower than 15 mg; however, these PK findings were not validated by outcomes from the ROCKET-AF subgroup analysis of patients with CKD. No increased bleeding was seen in patients with moderate CKD on 15 mg of rivaroxaban (HR: 0.98; 95% CI: 0.84 to 1.14) referent to warfarin, which was the same as the main conclusion of the full study. Rivaroxaban is not recommended for use in patients with CrCl <15 ml/min or those on dialysis. An inconsequential amount of rivaroxaban is cleared by dialysis (30). A 7-day trial of rivaroxaban 10 mg daily among 18 maintenance hemodialysis patients (FX60, 4 h, blood flow rate 400 ml/min, dialysate flow rate 500 ml/min, citrate anticoagulation) resulted in drug exposure levels similar to healthy volunteers given 20 mg; however, the coefficient of variation was twice as high, suggesting moderate interpatient variability in the clearance or metabolism of the drug.

DABIGATRAN. Dabigatran is a direct thrombin inhibitor and was the first FDA-approved NOAC, at a dose of 150 mg twice per day for CrCl >30 ml/min. The drug has a renal clearance of at least 80% and is thus highly dependent on the kidney for removal from the body (Figure 4C). In the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, dabigatran 150 mg twice daily was superior to warfarin for the prevention of stroke and systemic embolism (HR: 0.66; 95% CI: 0.53 to 0.82) in patients with AF and 1 or more additional risk factors for stroke; furthermore, no increase in major bleeding was seen with the drug (HR: 0.93; 95% CI: 0.81 to 1.07) (4). In a separate analysis in relation to renal function, cubic splines were used to model the rate of major bleeding by CrCl for warfarin and 150 mg of dabigatran. Here, there was no statistical difference in bleeding between the 2 drugs; however, the rate of major hemorrhage among dabigatran-treated patients accelerated and surpassed warfarin when the CrCl fell below 50 ml/min (31). Thus, multiple dosing guidelines advise caution with dabigatran when CrCl is between 30 and 50 ml/min (32). Accordingly, the U.S. label prohibits dabigatran coadministration with drugs that inhibit P-glycoprotein. Dabigatran is also the only dialyzable NOAC. A 4-h hemodialysis session will remove 50% to 60% of plasma dabigatran, with a 10% rebound in dabigatran levels post-dialysis (33).

The FDA approved a low dose of dabigatran (75 mg twice daily) for patients with CrCl between 15 and 30 ml/min in 2010. The approval of a 75-mg dose in patients with stage 4 CKD was on the basis of a phase I PK study of 29 subjects, 11 of whom had CrCl <30 ml/min. Model simulations showed that dabigatran 75 mg daily in patients with advanced CKD had a 32% lower steady-state peak and 42% lower trough level compared with patients with moderate CKD on 150 mg of dabigatran twice per day (34,35). This is in contrast to another study that found a 6-fold increase in dabigatran exposure in patients with CrCl <30 ml/min compared with healthy subjects (33).

EDOXABAN. Edoxaban is the most recent factor Xa inhibitor approved for use in the United States. The kidneys clear approximately 50% of the unmetabolized drug (Figure 4D). Total drug exposure was found to increase by 32%, 74%, and 72% in patients with mild, moderate, and severe renal impairment, respectively (36).

In the ENGAGE AF–TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction 48) trial of 21,105 patients with AF with CrCl >30 ml/min, subjects received 60 mg of edoxaban, or 30 mg if their CrCl was between 30 and 50 ml/min, body weight was <60 kg, or a strong P-glycoprotein inhibitor was coadministered. Edoxaban was noninferior at preventing stroke and systemic embolism...
and superior at preventing major bleeding (HR: 0.80; 95% CI: 0.71 to 0.91) compared with warfarin. In subgroup analyses among patients with CrCl between 30 and 50 ml/min, edoxaban remained noninferior for stroke prevention compared with warfarin. Bleeding was also significantly decreased (HR: 0.76; 95% CI: 0.58 to 0.98) with edoxaban (37).

A post hoc analysis of the ENGAGE AF-TIMI 48 trial for patients on edoxaban (vs. warfarin) whose CrCl fell below 30 ml/min after baseline (n = 1,202) showed that stroke (2.36 vs. 1.89 events per 100 patient-years) and major bleeding (6.83 vs. 6.49 events per 100 patient-years) rates were similar (38). Another prospective safety study of 93 patients found similar 3-month bleeding rates in patients with stage 4 CKD on 15 mg of edoxaban versus 30 or 60 mg of edoxaban with mean CrCl of 70 ml/min (39). Both of the studies mentioned in the preceding text were underpowered, and these results should be regarded as hypothesis generating, given how few events occurred in these studies.

Edoxaban is poorly cleared by dialysis: 4 h of hemodialysis decreased total drug exposure by only 9% (F180NR, blood flow rate 350 ml/min, dialysate flow rate 500 ml/min) (40).

**SHOULD WE ANTICOAGULATE PATIENTS WITH AF WITH ADVANCED OR END-STAGE KIDNEY DISEASE TO PREVENT STROKE?**

Patients with AF with advanced CKD or on dialysis are at high risk for adverse events and are complicated to manage. Most of these patients will have CHA2DS2-VASc scores >2, and studies indicate that the rates of AF, stroke, and bleeding all increase as kidney function worsens (25). There are no prospective randomized studies on the efficacy and safety of anticoagulation to prevent stroke in this population. Thus, we do not know the magnitude of stroke prevention conferred by anticoagulation in patients with advanced CKD or on dialysis, nor whether the stroke prevention benefit of warfarin or NOACs outweighs the increased risk for bleeding. The risk for anticoagulant-related bleeding remains a serious clinical concern. Dialysis patients are more likely to die of bleeding events than from embolic stroke. An unpublished analysis from the Fresenius Medical Care Research database showed that 2.7% of all deaths were secondary to hemorrhage, and 1% were from embolic stroke.

Multiple observational studies in CKD and dialysis have identified an association between warfarin use and increased risk for embolic stroke and bleeding (41–44), whereas other studies suggest that warfarin is protective against stroke in this population (45). Interpretation of these findings is challenging, as the results may be confounded by indication and the inclination to treat sicker patients.

Overall, it remains uncertain whether anticoagulation provides more benefit than harm when used to prevent stroke in patients with AF with advanced CKD or on dialysis. The 2014 AHA, ACC, and HRS guideline for the management of patients with AF states that it is reasonable to prescribe warfarin (international normalized ratio 2.0 to 3.0) to patients with nonvalvular AF with CHA2DS2-VASc scores of 2 or greater who have CrCl <15 ml/min or are on hemodialysis (8). In contrast, the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines state that routine anticoagulation of dialysis patients with AF for the primary prevention of stroke is not indicated (46).

Taken together, the aggregated data suggest that anticoagulation increases the risk for bleeding by at least 20% in patients with advanced CKD or on dialysis, but what remains unclear is the degree to which warfarin and NOACs reduce the risk for stroke in patients with advanced CKD or ESRD (41,42,45). Randomized clinical trials in the general population have suggested that warfarin reduces the risk for stroke by 64% in patients with AF compared with placebo (47). There is some evidence that anticoagulation does not lead to similar risk reduction in the advanced CKD and ESRD populations (48). Although patients with advanced CKD and ESRD are at higher risk for stroke, this risk for stroke may not be significantly modifiable by anticoagulation in patients with advanced renal disease. There are several reasons to explain why vitamin K antagonism may be associated with a lower margin of benefit in patients with advanced CKD or dialysis. First, uremia-induced platelet dysfunction may protect against thrombosis. Second, competing comorbid risks may attenuate the opportunity for benefit. More specifically, patients with CKD have numerous competing comorbidities that shorten their life expectancies and the follow-up time for stroke events. The average life expectancy of a dialysis patient is 5 years; moreover, 24% of CKD stage 4 and 45% of CKD stage 5 patients will die within 5 years (49,50). Until well-done, prospective, randomized studies are available, physicians must individually balance the risk for stroke in each patient against the perceived magnitude of stroke prevention anticoagulant agents may provide.

**NOAC USE IN PATIENTS WITH LATE-OR END-STAGE KIDNEY DISEASE**

If oral anticoagulation is indicated and the perceived benefits outweigh the risks for therapy, the 2014
AHA, ACC, and HRS guidelines endorse warfarin as the first-line therapy in patients with CKD stage 4 (CrCl 15 to 30 ml/min) or CKD stage 5 (CrCl <15 ml/min) or on dialysis, because all NOACs partially rely on the kidney for elimination (8). Similarly, the 2015 updated European Heart Rhythm Association practical guide on the use of nonvitamin K antagonist anticoagulant agents in patients with nonvalvular AF recommends refraining from NOAC use in dialysis patients and patients with CKD with CrCl <30 ml/min, given that there are few randomized trial data in this population (32). Although the U.S. label for NOACs supports their use when CrCl is as low as 15 ml/min, extreme caution should be used, as these recommendations were based mostly on PK data, and limited efficacy data support this practice. PK studies are only moderately reliable for quantifying the relationship between NOAC dose with total drug exposure and anticoagulation level (e.g., factor Xa activity), which are used as surrogates of efficacy and safety in PK studies (51). Renal disease progression, hemodynamically related fluctuations in creatinine, and acute kidney injury commonly occur in patients with poor kidney function. This can lead to unexpected decreases in CrCl and create a mismatch between NOAC dose and renal function to increase the risk for bleeding. Ultimately, randomized, prospective studies are needed to establish the efficacy and safety of NOACs in the advanced CKD and dialysis population.

Despite the paucity of evidence and guidelines that clearly recommend against the use of NOACs in ESRD, observational data have shown NOAC use among dialysis patients to be substantial and increasing; furthermore, 1 study found that many patients were prescribed higher doses of rivaroxaban and dabigatran that were not properly reduced to account for any renal impairment (9). There was evidence of higher bleeding risk associated with dabigatran (relative risk: 1.48; 95% CI: 1.21 to 1.81) and rivaroxaban (relative risk: 1.38; 95% CI: 1.03 to 1.83) compared with warfarin, yet there was inadequate power to compare stroke outcomes between the groups.

NOACs may be considered first-line therapy in patients who need anticoagulation with concurrent calcific uremic arteriolopathy, a rare but devastating calcific disease of the small vessels, where warfarin has been strongly associated with disease progression (52). Patients who are intolerant of warfarin and have histories of warfarin skin necrosis or protein C/S deficiency might benefit from off-label NOAC therapy; however, this is highly speculative. If NOACs are used in patients with advanced CKD, close monitoring of renal function is advised, perhaps every 2 to 4 months and during acute illness. In these rare instances in which NOACs are prescribed, a suggested dose of apixaban 2.5 to 5 mg twice daily can be given to patients on dialysis, but rivaroxaban or edoxaban at a reduced dose could also be effective. Dabigatran is less favorable because the risk for bleeding substantially increases when CrCl drops below 50 ml/min. In dialysis patients, drug levels would substantially fluctuate with dialysis treatment, given that dialysis clears 50% to 60% of the drug. Drug bioaccumulation would occur when patients miss their dialysis treatment, which could lead to serious bleeding. Finally, patients who are intolerant of warfarin may consider nonpharmacological therapy for stroke prevention with percutaneous left atrial appendage closure (53). Occlusion of the left atrial appendage may be particularly attractive in patients with ESRD, given the observed large reduction in bleeding (54).

Last, reducing the intradialytic heparin dose merits consideration in patients initiated on warfarin or a NOAC to potentially decrease the risk for peritreatment bleeding. There is little evidence to guide such practices, but stopping or reducing the heparin dose by at least 50% appears reasonable. Patients can be rechallenged on heparin if they experience clotting during treatment.

### MAJOR HEMORRHAGE IN THE SETTING OF NOACS: ISSUES SPECIFIC TO ADVANCED CKD AND DIALYSIS PATIENTS

Dabigatran is the only NOAC that is very dependent on the kidney for elimination and is also highly dialyzable, with 50% to 60% of plasma dabigatran removed with a 4-h hemodialysis session (55). Hemodialysis for dabigatran removal should be considered when the severity of bleeding necessitates faster drug clearance, and it would be unsafe to wait for the drug to be completely eliminated by the native kidneys. A patient with CrCl of 55 ml/min could clear 88% of total body dabigatran in 45 h (3 half-lives; Table 3) through intrinsic kidney function or with 3 serial 4-h hemodialysis sessions (1 half-life per session). It may be reasonable to wait 45 h if bleeding is controlled, but active bleeding that does not respond to conventional measures merits consideration for more aggressive measures.

In patients with life-threatening bleeding who need immediate dabigatran reversal, physicians may consider idarucizumab, which was shown to neutralize the anticoagulant effect of dabigatran within 30 min in a study of 90 patients with median
two-thirds of uremic patients (61 in vitro tests of platelet function in approximately can also partially correct the bleeding time and other bleeding patients can be given desmopressin. Dialysis prone to uremic platelet dysfunction. Actively furthermore, it is encouraging that these favorable with a bleeding risk that remains acceptable. the general population with warfarin and NOACs, prove to be similar to or greater than those shown in on dialysis who are prone to volume overload (60).

CrCl of 58 ml/min (56). Idarucizumab is partially dependent on the kidney for elimination (32% within the first 6 h) but is approved for patients with kidney disease.

The anticoagulant effects of warfarin, apixaban, rivaroxaban, and edoxaban can be reversed by 4-factor prothrombin complex concentrate (57–59), which can replete coagulation factors much faster than fresh-frozen plasma, with less volume overload, which is favorable to patients with advanced CKD and on dialysis who are prone to volume overload (60).

Last, patients with advanced CKD or on dialysis are prone to uremic platelet dysfunction. Actively bleeding patients can be given desmopressin. Dialysis can also partially correct the bleeding time and other in vitro tests of platelet function in approximately two-thirds of uremic patients (61–63).

**SUMMARY AND FUTURE DIRECTIONS**

NOAC use in patients with advanced CKD and on dialysis is substantial and increasing, despite AHA, ACC, and HRS and European Heart Rhythm Association guidelines that endorse warfarin as the anticoagulant of choice when CrCl is <30 ml/min. There are few randomized trial data on NOACs among patients with advanced CKD or on dialysis.

Phase 3 AF trials in the general population have shown that NOACs decrease both stroke and bleeding in comparison with warfarin, whereas patients with advanced CKD and ESRD have a baseline increased risk for both stroke and bleeding (64,65). Because of their high risk, patients with advanced CKD and ESRD could potentially derive great benefit from NOACs if the benefits for stroke and cardiovascular events prove to be similar to or greater than those shown in the general population with warfarin and NOACs, with a bleeding risk that remains acceptable. Furthermore, it is encouraging that these favorable effects carried over to subgroup analyses among patients with CrCl between 25 and 50 ml/min who were enrolled in the phase III AF trials and that the effects are similar in other high-risk groups, such as those with advanced age or low body weight.

All NOACs are dependent on the kidney for elimination. Thus, the most critical development issue for NOAC use in the advanced CKD and dialysis population is to determine the appropriate dose reduction that optimizes the prevention of stroke yet minimizes the risk of bleeding. Well-done multidose PK studies are necessary to estimate the appropriate NOAC dose, recognizing that PK models have limited accuracy in predicting population pharmacokinetics.

Randomized controlled trials are ultimately needed to validate PK-driven hypotheses by demonstrating clinical efficacy (stroke prevention) and safety (bleeding) of NOACs versus placebo in patients with AF with advanced CKD and on dialysis. Prevention of stroke with NOACs in patients with AF would become the standard of care if such a trial indicated superiority at stroke prevention, with acceptable bleeding risks referent to placebo. Comparative efficacy trials between NOACs and other anticoagulant agents would be less informative. This is because warfarin and aspirin have not been proved to be effective and safe for preventing stroke in patients with AF with severe renal impairment, as no phase III efficacy trials have been conducted in patients with CrCl <25 ml/min; furthermore, some observational studies suggest that warfarin may cause harm in this population.

In conclusion, the improved safety profile of NOACs compared with warfarin for the general population raises the prospect of an improved anticoagulation strategy for patients with advanced renal impairment and an indication for anticoagulation. High-quality randomized trials should be conducted in these populations, given their altered drug metabolism profile and high rates of both clotting and bleeding events.

**REFERENCES**


**TABLE 3** Dabigatran Half-Lives by Renal Function

<table>
<thead>
<tr>
<th>Creatinine Clearance, ml/min</th>
<th>Half-Life (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥80</td>
<td>13</td>
</tr>
<tr>
<td>50–80</td>
<td>15</td>
</tr>
<tr>
<td>30–49</td>
<td>18</td>
</tr>
<tr>
<td>&lt;30</td>
<td>28</td>
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KEY WORDS apixaban, dabigatran, edoxaban, renal dialysis, rivaroxaban, stroke