

## Risky Business: Judging the Use of Non-Vitamin K Antagonist Oral Anticoagulants for Non-Valvular Atrial Fibrillation in Patients with Renal Dysfunction

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### Abstract

Warfarin, for many years, was the only oral anticoagulant available on the market for the prevention of stroke in patients with atrial fibrillation. Despite being safe and effective, warfarin's medication and food interactions, along with its requirement for frequent monitoring, make it less ideal in some patient populations. More recently, non-vitamin K oral antagonists (NOACs) have emerged as an appealing option as they have fewer medication interactions, do not have food interactions and do not require frequent monitoring. However, patients with a creatinine clearance (CrCl) of less than 30 mL/min were excluded in original drug trials for these agents. Leaving providers without certainty that these agents can be used safely and effectively in patients with renal dysfunction. This review article will summarize the current available data on the use of NOACs for the prevention of stroke in atrial fibrillation patients with renal dysfunction.

### Introduction

Atrial fibrillation is a supraventricular tachyarrhythmia that affects millions of Americans.<sup>1-2</sup> Common causes of atrial fibrillation include uncontrolled hypertension, coronary heart disease, heart failure and congenital heart defects.<sup>2</sup> Patients that are female, are above 65 years of age, are of European descent or have heart disease are at greater risk for atrial fibrillation, which can result in heart failure and/or stroke.<sup>2-3</sup> The risk of stroke is increased 3 to 5-fold in patients with atrial fibrillation and anticoagulation may be required to prevent stroke and/or thromboembolism.<sup>4</sup>

Indication for anticoagulation in patients with atrial fibrillation is dependent upon the patient's specific risk factors for these complications. Although all patients with atrial fibrillation are at an increased risk of stroke, patients have different levels of risk. Validated scoring tools, such as the CHA<sub>2</sub>DS<sub>2</sub>VASc score, are available to assist in stratifying the risk of stroke in patients with atrial fibrillation. The 2014 ACC/AHA/HRS Guideline for the Management of Patients with Atrial Fibrillation: Recommendations for Non-Valvular Atrial Fibrillation, referred to from here on out as the current guidelines, recommends using the CHA<sub>2</sub>DS<sub>2</sub>VASc score to quantify a patient's risk of stroke, with a higher score signifying a higher level of stroke

risk (Table 1). Recommendations, as shown in Figure 1, are based on a patient's risk for stroke. Of note, according to these guidelines, oral anticoagulation is recommended in patients with a CHA<sub>2</sub>DS<sub>2</sub>VASc score of  $\geq 2$ , while oral anticoagulation may be considered in patients with a CHA<sub>2</sub>DS<sub>2</sub>VASc score of 1, as their risk for stroke is lower.<sup>5</sup> Oral anticoagulation options include warfarin, dabigatran, rivaroxaban and apixaban, although only warfarin is recommended for patients with end-stage chronic kidney disease (CKD) or on hemodialysis (HD). Warfarin is a vitamin K antagonist that for many years was the only oral anticoagulant available on the market for the prevention of stroke in patients with atrial fibrillation. Despite being safe and effective, warfarin's medication and food interactions, along with its requirement for frequent monitoring, make it less ideal in some patient populations. Dabigatran, rivaroxaban, and apixaban are agents that belong to a class called non-vitamin K antagonist oral anticoagulants (NOACs). These agents are an appealing option as they have fewer medication interactions and do not require frequent monitoring. An additional NOAC agent, edoxaban, was introduced to the market in 2015, however this agent is not in the current guidelines, as they have not been updated since 2014. In addition, the 2014 apixaban label change stating that apixaban 5 mg twice daily can be used in patients with creatinine clearance (CrCl)  $< 15$  mL/min and in patients with hemodialysis is not reflected in the current guidelines.<sup>5</sup>

### Key Words

NOACs, Atrial Fibrillation, Renal Impairment, Renal Dysfunction

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In addition to assessing a patient's risk of stroke when initiating anticoagulation, it is also important to assess the patient's risk of bleeding as bleeding is the major side effect of anticoagulation. Similarly to stroke risk, bleeding risk also varies between patients as it

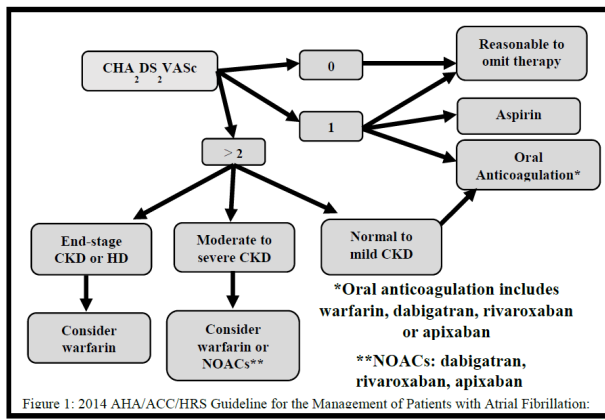


Figure 1: 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation:

**Figure 1: 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation.**

**Table 1: CHA2DS2VASc Score**

RISK FACTOR	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease (prior MI, PAD or aortic plaque)	1
Age 65-74 years	1
Sex category (i.e. female sex)	1
Maximum score	10

is based on specific risk factors and should be taken into consideration when determining use of anticoagulation for the prevention of stroke or thrombosis in patients with atrial fibrillation. The HAS-BLED score is a validated scoring tool that can be used to determine a patient’s risk for bleeding (Table 2)<sup>5,6</sup>. A score of ≥ 3 indicates the patient is at a high risk of bleeding<sup>5,6</sup>. The current guidelines do not make specific recommendations on the use of the HAS-BLED score, however, this scoring tool along with the CHA<sub>2</sub>DS<sub>2</sub>VASc score may be used to help guide clinical decisions by quantifying the risk of

**Table 2: HAS-BLED Score**

Risk Factor	Score
Age > 65	1
Hypertension Uncontrolled, > 160 mmHg systolic	1
Stroke History	1
Renal disease Dialysis, transplant, Cr > 2.26 mg/dL or > 200 μmol/L	1
Liver disease Cirrhosis or bilirubin > 2x normal with AST/ALT/AP > 3x normal	1
Alcohol use ≥ 8 drinks/week	1
Prior major bleeding or predisposition to bleeding	1
Labile INR Unstable/high INRs, time in therapeutic range <60%	1
Medication usage predisposing to bleeding Antiplatelet agents, NSAIDs	1
Interpretation	High risk ≥ 3

stroke versus the risk of bleeding<sup>5</sup>.

### Anticoagulation in Renal Impairment

The incidence of atrial fibrillation is 10 to 20-fold higher in patients with end-stage renal disease (ESRD)<sup>1-2</sup>. ESRD, independent of atrial fibrillation, is a risk factor for cardiovascular events, which may increase thromboembolic complications, such as arrhythmias, ischemic heart disease and peripheral vascular disease. Therefore, determining the need for anticoagulation in patients with ESRD and atrial fibrillation is especially necessary for the prevention of stroke and other thromboembolic complications.<sup>7-9</sup> Conversely, a complication of end-stage renal disease called uremia increases the risk for bleeding. Uremia develops from the accumulation of nitrogenous compounds and other toxic substances that are normally excreted by the kidney, resulting in defects in platelet aggregation, platelet secretion and platelet–vessel wall interaction and adhesion, all of which predisposes patients to bleeding<sup>10-12</sup>. As a result, the use of anticoagulation in this patient population may predispose patients to an even higher risk of bleeding. This risk of bleeding is especially of concern in patients with renal dysfunction as all available oral anticoagulants depend on the kidney to some extent for elimination and, consequently, accumulation of these agents can increase the risk of bleeding. Anticoagulants that rely more heavily on the kidneys for elimination, and are more likely to accumulate in renal dysfunction, include warfarin (92%), dabigatran (80%) and edoxaban (50%)<sup>13-18</sup>. Rivaroxaban (35%), apixaban (27%) and betrixaban (11%), however, rely less on the kidney for excretion, and are less likely to accumulate in renal dysfunction and they may be safer options compared to those agents that rely more heavily on the kidneys for elimination<sup>19-24</sup>. Despite their hesitation to use NOAC agents in the ESRD population due to limited data of their use in this patient population, health care providers are seeking anticoagulation alternatives to warfarin because of its interactions, frequent monitoring and high reliance on the kidney for elimination.

Current guidelines for non-valvular atrial fibrillation recommend against the use of dabigatran or rivaroxaban in patients with end-stage CKD or those receiving HD, but state that a dose reduction of dabigatran or rivaroxaban may be considered if a patient has moderate to severe CKD. The guidelines, however, do not make a recommendation regarding apixaban use in ESRD, because at the time of guideline publication the manufacturer did not comment on use of apixaban in this patient population. For patients with a CHA<sub>2</sub>DS<sub>2</sub>VASc score of ≥ 2 and a CrCl < 15 mL/min or on hemodialysis, the guidelines state it is reasonable to prescribe warfarin.<sup>5</sup>

The trials for which each NOAC was approved excluded patients with severe renal impairment. In the dabigatran, rivaroxaban and edoxaban trials, patients were excluded if their CrCl was < 30 mL/min and in the apixaban trial, patients were excluded if their CrCl was < 25 mL/min or SCr was ≥ 2.5 mg/dL.<sup>25-28</sup> Despite excluding patients with severe renal impairment from trials, NOAC manufacturers have made recommendations for their use in this patient population based on pharmacokinetic studies (Table 3 & 4). Overall, these pharmacokinetic studies have shown that there is an increase in drug concentration in patients with renal impairment. It

**Table 3: Pharmacokinetic Studies of NOACS in Renal Impairment.**

Study	Drug	Study Design	Population	Results
Stangier 2010 <sup>29</sup>	Dabigatran	<ul style="list-style-type: none"> <li>Open-label single dose study</li> <li>150 mg dose given to healthy patients and patients with mild to severe renal impairments</li> <li>50 mg dose given to patients with ESRD</li> </ul>	<ul style="list-style-type: none"> <li>CrCl &gt; 50 mL/min to ≤ 80 mL/min (mild): 6 patients</li> <li>CrCl &gt; 30 mL/min to ≤ 50 mL/min (moderate): 6 patients</li> <li>CrCl ≤ 30 mL/min (severe): 11 patients</li> <li>ESRD: 6 patients</li> </ul>	<ul style="list-style-type: none"> <li>When compared to healthy patients' dabigatran increased by: <ul style="list-style-type: none"> <li>1.5-fold in patients with mild impairment</li> <li>3.2-fold in patients with moderate impairment</li> <li>6.3-fold in patients with severe impairment</li> <li>2-fold in patients on hemodialysis</li> </ul> </li> <li>With increasing renal impairment increase the exposure to dabigatran</li> <li>Dabigatran is partly removed by HD</li> </ul>
Hariharan 2012 <sup>30</sup>	Dabigatran	<ul style="list-style-type: none"> <li>Phase 1 Pharmacokinetic/ Pharmacodynamics study.</li> <li>Evaluated 150 mg daily dose, 75 mg daily dose and 75 mg BID</li> </ul>	<ul style="list-style-type: none"> <li>CrCl &gt; 80 mL/min: 6 patients</li> <li>CrCl &gt; 50 mL/min to ≤ 80 mL/min (mild): 6 patients</li> <li>CrCl &gt; 30 mL/min to ≤ 50 mL/min (moderate): 6 patients</li> <li>CrCl ≤ 30 mL/min (severe): 11 patients</li> </ul>	When compared to healthy patients, patients with severe renal impairment (CrCl 15-30 mL/min) had matched exposure to dabigatran when taking 75 mg BID
Kubitza <sup>31</sup>	Rivaroxaban	<ul style="list-style-type: none"> <li>Pharmacokinetic/ Pharmacodynamics and safety of single 10 mg dose</li> </ul>	<ul style="list-style-type: none"> <li>CrCl ≥ 80 mL/min (healthy): 8 patients</li> <li>CrCl 50 to 79 mL/min (mild): 8 patients</li> <li>CrCl 30 to 49 mL/min (moderate): 8 patients</li> <li>CrCl &lt; 30 mL/min (severe): 8 patients</li> </ul>	Compared to healthy patients rivaroxaban exposure increased by: <ul style="list-style-type: none"> <li>44 % in patients with mild impairment</li> <li>52 % in patients with moderate impairment</li> <li>64 % in patients with severe impairment</li> </ul>
Dias 2015 <sup>32</sup>	Rivaroxaban	<ul style="list-style-type: none"> <li>Open-label single dose study</li> <li>15 mg dose</li> </ul>	<ul style="list-style-type: none"> <li>Healthy: 8 patients</li> <li>ESRD: 8 patients</li> </ul>	<ul style="list-style-type: none"> <li>35% decrease in clearance when dosed after dialysis</li> <li>30% decrease in clearance when dosed before dialysis</li> </ul>
De Vriese 2015 <sup>33</sup>	Rivaroxaban	<ul style="list-style-type: none"> <li>Cohort dose finding study</li> <li>10 mg single dose</li> </ul>	<ul style="list-style-type: none"> <li>18 patients on HD</li> <li>12 patients received single dose administration</li> <li>6 patients multiple dose administration</li> </ul>	<ul style="list-style-type: none"> <li>Dialysis has little effect on elimination</li> <li>AUC of 10 mg dose in ESRD patients similar to 20 mg dose in healthy patients</li> <li>Multiple 10 mg doses C-trough is similar to ROCKET-AF patients with residual kidney function</li> </ul>
Chang 2015 <sup>34</sup>	Apixaban	<ul style="list-style-type: none"> <li>Open-label single dose study</li> <li>10 mg dose</li> </ul>	<ul style="list-style-type: none"> <li>CrCl &gt; 80 mL/min: 8 patients</li> <li>CrCl &gt; 50 mL/min to ≤ 80 mL/min: 10 patients</li> <li>CrCl ≥ 30 mL/min to ≤ 50 mL/min: 7 patients</li> <li>CrCl &lt; 30 mL/min: 7 patients</li> </ul>	<ul style="list-style-type: none"> <li>CrCl &gt; 50 mL/min to ≤ 80 mL/min → 16% apixaban AUC increase</li> <li>CrCl ≥ 30 mL/min to ≤ 50 mL/min → 29% increase in apixaban AUC</li> <li>CrCl &lt; 30 mL/min → 38% increase in apixaban AUC</li> </ul>
Wang 2016 <sup>35</sup>	Apixaban	<ul style="list-style-type: none"> <li>Open-label parallel single dose study</li> <li>10 mg dose</li> </ul>	<ul style="list-style-type: none"> <li>Healthy: 8 patients</li> <li>ESRD: 8 patients</li> </ul>	Apixaban AUC was 36% higher when administered after HD

**Table 4: Manufacturer Dosing Recommendations**

Drug	CrCl > 50 mL/min	CrCl > 30 mL/min to < 50 mL/min	CrCl 15 to 30 mL/min	CrCl < 15 mL/min	Dialysis
Dabigatran	150 mg BID	150 mg BID	75 mg BID	Not approved	Not approved
Rivaroxaban	20 mg daily	15 mg daily	15 mg daily	Not approved	Not approved
Apixaban	2.5 or 5 mg BID	2.5 or 5 mg BID	2.5 or 5 mg BID	2.5 or 5 mg BID	2.5 or 5 mg BID
Edoxaban	60 mg daily	60 mg daily	30 mg daily	Not approved	Not approved

is important to note that the majority of these studies were based on a single dose and therefore do not give insight into the extent of accumulation of the drug over time and its effect on patients with renal impairment<sup>29-35</sup>.

Dabigatran was the first NOAC approved by the FDA in 2010. The Randomized Evaluation of Long-Term Anticoagulant Therapy,

Warfarin compared to Dabigatran (RE-LY) trial, was the trial for which dabigatran received approval. Dabigatran 150 mg twice daily was shown to be superior to warfarin in preventing stroke and systemic embolism. Dabigatran was also shown to have significantly less major and minor bleeding when compared to warfarin, which had more intracranial bleeding, but less gastrointestinal bleeding. Patients with mild to moderate renal impairment were included in this study<sup>25</sup>. A RE-LY trial analysis compared the safety and efficacy of dabigatran to warfarin in regards to renal function, with patients divided into groups of CrCl ≥ 80 mL/min, 50 to < 80 mL/min and 30 to < 50 mL/min. There was no statistically significant difference in efficacy or safety of dabigatran 150 mg twice daily with changing renal function. Based on this analysis, patients with mild to moderate renal dysfunction are able to take the full recommended dose of 150 mg twice daily. There are no studies that evaluate the clinical efficacy and safety of dabigatran in patients with a CrCl < 30 mL/min, however there is a pharmacokinetics study that was conducted in patients with renal impairment including those with a CrCl < 30 mL/min. The study showed that a dose of 75 mg twice daily in patients with a CrCl

of 15 to 30 mL/min rendered a matched exposure to dabigatran when compared to 150 mg twice daily in healthy patients.<sup>36</sup> Based on these findings, the manufacturer recommends a dose reduction to 75 mg twice daily in patients with a CrCl of 15 to 30 mL/min.<sup>16</sup>

Edoxaban was approved by the FDA in 2017 for the prevention of stroke and systemic embolism in patients with atrial fibrillation. In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48), the study for which edoxaban was approved, edoxaban 60 mg daily was shown to be superior to warfarin in preventing stroke and systemic embolism and associated with fewer bleeding events. Patients with mild to moderate renal impairment were included in the study and the dose of edoxaban was divided in half if patients had a CrCl of 30 to 50 mL/min.<sup>26</sup> A sub-analysis of the ENGAGE AF-TIMI 48 trial evaluated the impact of renal function on outcomes in patients treated with edoxaban. There was no significant difference in safety or efficacy outcomes based on renal function, which was evaluated in three groups: CrCl > 95 mL/min, > 50 to 95 mL/min and 30 to 50 mL/min. However, although not statistically significant, there was a decrease in efficacy seen in patients with a CrCl > 95 mL/min<sup>37</sup>. As a result, the manufacturer recommends a dose reduction to 30 mg daily in patients whose CrCl is 15 to 50 mL/min and avoiding edoxaban in patients with a CrCl > 95 mL/min as patients with this renal function clear the drug too quickly and are not able to maintain therapeutic drug concentrations.<sup>10,11</sup>

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) was the trial for which rivaroxaban was approved by the FDA in 2011. Rivaroxaban, 20mg daily for patients with a CrCl over 49 mL/min and 15 mg daily for patients with a CrCl of 30 to 49 mL/min, was shown to be non-inferior to warfarin in preventing stroke and systemic embolism. Although there was no statistically significant difference in overall bleeding events, warfarin had significantly more critical bleeding, fatal bleeding and intracranial bleeding.<sup>27</sup> An analysis of treatment outcomes based on baseline renal function was conducted on the ROCKET-AF trial and patients were grouped based on renal function: CrCl of  $\geq$  80 mL/min, 50 to < 80 mL/min and 30 to < 50 mL/min. There was no significant difference between rivaroxaban and warfarin in safety or efficacy outcomes based on renal function.<sup>38</sup> There are no studies that evaluate the clinical efficacy and safety of rivaroxaban in patients with a CrCl of < 30 mL/min, but the manufacturer currently recommends a dose of 15 mg daily in patients with a CrCl of 15 to 50 mL/min and 20 mg daily for patients with a CrCl of > 50 mL/min<sup>13</sup>.

In the Apixaban for the Reduction of Stroke and other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, the study for which apixaban was approved, apixaban was shown to be superior to warfarin in preventing stroke and systemic embolism and had significantly less major bleeding compared to warfarin. Patients with mild to moderate renal impairment were included in the study and in an analysis of ARISTOTLE, the efficacy of apixaban compared to warfarin was evaluated based on renal function.<sup>28</sup> In this analysis, patients were grouped based on renal function: CrCl > 80 mL/min, > 50 to 80 mL/min and  $\leq$  50 mL/min. There was no statistically significant difference in efficacy and safety between

warfarin and apixaban regardless of renal impairment<sup>39</sup>. Originally, in 2012, when apixaban was approved by the FDA, the manufacturer did not have a recommendation on the use of apixaban in patients with a CrCl of < 15 mL/min or those on hemodialysis. However, in 2014, the manufacturer updated its package insert and stated that patients with a CrCl of < 15 mL/min and those on hemodialysis could receive the 5 mg twice daily dosing, which is the same dosing as those with normal renal function. This recommendation was based on pharmacokinetic studies.<sup>40-41</sup> However, the manufacturer does not recommend a dose reduction based on renal function alone. Per the manufacturer, apixaban should be dose-reduced to 2.5 mg twice daily if the patient meets two of the following criteria: age  $\geq$  80 years old, weight of < 60 kg and a SCr  $\geq$  2.5 mg/dL.<sup>14,15</sup>

The data for NOAC use in patients with severe renal dysfunction is limited; apixaban is currently the only NOAC with clinical data in patients with severe renal dysfunction. Until 2017, there were no published studies that evaluated the clinical efficacy and safety of apixaban in patients with severe renal impairment or those on hemodialysis. Steuber, Stanton, Sarratt and colleagues have set the stage for the use of apixaban in patients with atrial fibrillation and severe renal impairment through three studies. Steuber and colleagues, for example, conducted a multicenter cohort study to determine variables that were associated with bleeding events in hospitalized patients on chronic HD taking apixaban. This study found that bleeding occurred in 15 % of patients and the likelihood of bleeding increased as the total daily dose of apixaban increased, as well as with continuation of apixaban from the outpatient setting. Of the 17 patients who bled, 7 were on the 2.5 mg twice daily dose (median dose in the study), 3 were on 10 mg twice daily and the remaining were on 5 mg twice daily. Although the study demonstrated that apixaban was safe in 85 % of hospitalized patients on chronic hemodialysis, there are several limitations of this study, including a retrospective study design, a small sample size, short duration of follow-up and lack of efficacy outcomes. Furthermore, while apixaban was shown to be safe in patients with renal impairment, this study did not demonstrate the efficacy of these reduced doses.<sup>42</sup>

Sarratt and colleagues had similar limitations to their study, including a retrospective study design, a small sample size, a lack of efficacy outcomes and failure to meet power. Sarratt compared bleeding rates in patients with atrial fibrillation and on chronic hemodialysis taking either apixaban or warfarin. More than half of the patients taking apixaban were on 2.5 mg twice daily. This study found that there was no statistically significant difference in bleeding between apixaban and warfarin. Although apixaban had less major bleeding, it had a higher rate of clinically relevant non-major bleeding events when compared to warfarin. While apixaban appears to be safe in this patient population, similarly to the other studies, this study did not evaluate efficacy.<sup>43</sup>

Stanton and colleagues were the first to evaluate both efficacy and safety of apixaban compared to warfarin in patients with severe renal impairment. There was no statistically significant difference in efficacy or safety between warfarin and apixaban; however, apixaban had fewer bleeding events. Similarly to the patients in the study by Sarratt and colleagues, the majority of the patients taking apixaban



were on 2.5 mg twice daily. This study suggests that apixaban 2.5 mg twice daily may be just as safe as warfarin in patients with a CrCl < 25 mL/min, SCr > 2.5 mg/dL or on dialysis. However, there were several limitations to this study, such as the retrospective study design and small sample size. If the study had a higher power, a difference between the two study arms may have been detected. Despite the limitations of this study, there was a 5-month follow-up period, which makes this study unique compared to the studies by Steuber, Sarratt and colleagues, as the follow-up periods in those studies did not extend past hospitalization. Apixaban 2.5 mg twice daily appears to be safe; however, efficacy was not a primary outcome and therefore we are unable to definitively conclude if apixaban 2.5 mg twice daily is effective in this patient population.<sup>44</sup>

These studies assessed patients with renal impairment including patients with ESRD. There are several scenarios in which a patient's renal function can be acutely impaired, such as in settings of an adverse medication reaction, infections, and heart failure. Unfortunately, these studies did not specifically address acute kidney injury, however, anticoagulants should be dosed adjusted for the patient's renal function during the acute injury phase, as it is possible that the drug could accumulate and increase the patient's risk of bleeding. With the lack of evidence in patients with acute or transient renal impairment, comes a lack of direction on how to dose and how often renal function should be monitored in these patients. In addition, these studies, in addition to the original drug approval trials, used CrCl as a measure of kidney function. The different methods, including eGFR, that are used to measure a patient's kidney function are all estimates of kidney function; however, the estimates are not interchangeable. Therefore, CrCl should be used as a measure of kidney function in patients on anticoagulants as this was the method of measuring kidney function used in clinical trials.<sup>25-44</sup>

### Antidote Availability

Patients who are on anticoagulation with renal impairment are at an increased risk of experiencing a bleeding event. The ability to reverse anticoagulation or the ability to prevent further bleeding should be evaluated and taken into consideration when choosing an anticoagulation agent. Warfarin does not have a reversal agent currently on the market, however, in the event of a bleed, vitamin K can be given to prevent further bleeding.<sup>6</sup> Management of bleeding in patients on a NOAC, however, remains widely unknown and recommendations are based largely on expert opinion. In 2017, the American Heart Association (AHA) released a statement on the management of patients on NOACs in both acute care and periprocedural settings. For patients who experience a major bleed on dabigatran, the AHA recommends compression when possible, supportive care, and idarucizumab.<sup>45</sup> Idarucizumab, a monoclonal antibody fragment that binds specifically to and neutralizes dabigatran and its metabolites, was approved by the FDA in October of 2015 for the reversal of dabigatran in cases of emergency surgery and urgent procedures for uncontrollable or life-threatening bleeding.<sup>46</sup> In the Reverse-AD (Idarucizumab for Dabigatran Reversal) trial, idarucizumab was shown to completely reverse the anticoagulant effects of dabigatran, with a median time of 11.4 hours to cessation of bleeding.<sup>47</sup>

The AHA was unable to make a recommendation for patients with a bleed taking apixaban or rivaroxaban in their 2017 statement because the Andexxa-4 (Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors) trial was still in process at the time the AHA statement was released.<sup>45</sup> However, andexanet alfa (Andexxa), which binds and sequesters rivaroxaban and apixaban, has recently been FDA approved for anticoagulation reversal in patients on rivaroxaban or apixaban who have life-threatening or uncontrollable bleeding. In addition, andexanet alfa inhibits the tissue factor pathway inhibitor, which can increase tissue factor-initiated thrombin generation.<sup>48</sup> Although it was shown to reduce anti-factor-Xa activity and return patients to hemostasis in 79% of cases, andexanet alfa was only studied in patients on rivaroxaban and apixaban and thus should not be used for reversal of any other anticoagulant.<sup>49</sup> Edoxaban and betrixaban, the two newest NOACs on the market, do not have antidotes currently available on the market, and therefore supportive care is the only treatment option for patients who experience bleeding on these agents.

Patients with CKD and atrial fibrillation are at both an increased risk of bleeding and increased risk of stroke and thromboembolism.<sup>1-2, 4, 7-9,10,12</sup> Anticoagulants, such as warfarin and NOACs may be considered in these patients to prevent these complications.<sup>5</sup> NOACs provide healthcare providers and patients with an alternative option to warfarin, the use of which may result in a complicated regimen with its medication and food interactions, requirement for frequent monitoring, and high reliance on the kidney for elimination. However, for our patients with CKD choosing an anticoagulant can be difficult. All anticoagulants rely on the kidney to some extent, increasing the risk of bleeding in renal impairment due to accumulation. Apixaban is of particular promise because it has the least reliance on the kidney for elimination compared to other NOACs approved for the prevention of stroke and systemic embolism in patients with atrial fibrillation. In addition to apixaban, betrixaban, the newest NOAC approved in 2018, also has great potential in this patient population. Betrixaban is less reliant on the kidney for elimination as compared to apixaban, but currently it has only been studied and approved for extended duration thromboembolism prophylaxis in hospitalized patients who are acutely medically ill.<sup>15-24</sup> With additional studies, this medication may become a viable option for this patient population.

### Conclusion

There is a delicate balance between the risk of cardiovascular events and the risk of bleeding in this patient population. NOACs have been shown to be just as efficacious if not superior to warfarin in the prevention of stroke and systemic embolism in patients with atrial fibrillation. Although there are several retrospective studies that show promise with the use of apixaban in this patient population, the data is not robust enough to support its routine use in patients with severe renal impairment and ESRD over warfarin, with its long history of use and the availability of vitamin K to prevent further bleeding if needed. Choosing an anticoagulant in this patient population should be based on individual patient parameters, such as renal function, stroke risk, bleeding risk, adherence and affordability. The risks and benefits to the individual patient must be taken into consideration. For patients with atrial fibrillation and renal impairment that require anticoagulation but are unable to take warfarin, apixaban would be the

best alternative agent based on currently available data. In the future, large, long-term randomized control trials evaluating the efficacy and safety of NOACs in patients with severe renal impairment and ESRD are needed to determine appropriate doses and support their routine use in this patient population.

## Disclosure

None.

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