Direct Oral Anticoagulants in End-Stage Renal Disease

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Abstract

Patients with end-stage renal disease (ESRD) were excluded from pivotal clinical trials with oral anticoagulants. While such patients are at an increased risk of venous and arterial thromboembolism, their risk of bleeding is also elevated. It is thus of little surprise that stroke prevention with vitamin K antagonists (VKAs) in ESRD patients with atrial fibrillation is controversial, with observational evidence ranging from beneficial to harmful. This uncertainty extends to the less studied use of VKAs for venous thromboembolism in ESRD. The direct oral anticoagulants (DOACs) apixaban and rivaroxaban have now permissive labeling in the United States for atrial fibrillation in patients with ESRD; this expanded labeling has not yet occurred either in Europe or for venous thromboembolism. This review summarizes the current evidence for the pharmacology of DOACs in ESRD as well as their utilization and safety in patients with ESRD and atrial fibrillation.

Keywords

► anticoagulants
► renal dialysis
► kidney failure
► chronic
► venous thrombosis
► stroke

Chronic kidney disease (CKD), usually defined as glomerular filtration rate (GFR) < 60 mL/min/1.73 m² for at least 3 months,¹ affects ~7% of adults in the United States.²,³ Estimates of CKD prevalence vary by country and region and are associated with population aging and economic status.⁴ CKD is caused by four conceptual mechanistic pathways: glomerular diseases (e.g., diabetic nephropathy), tubulointerstitial diseases (e.g., myeloma), vascular diseases (e.g., hypertension), and cystic/congenital diseases (e.g., renal dysplasia).¹ A decline of GFR to < 15 mL/min/1.73 m² defines kidney failure, or end-stage renal disease (ESRD), which is an indication for renal replacement therapy (RRT; dialysis or renal transplantation). By 2014, more than a million individuals in the United States and Europe combined were receiving RRT, representing a marked increase in the prevalence of ESRD.⁵,⁶ Patients with ESRD and atrial fibrillation (AF) have an increased risk of stroke, compared with less severe renal impairment.⁶ Furthermore, the prevalence of AF in the hemodialysis population is 13 to 27%, or 10- to 20-fold higher than in the general population.⁷ The risk of venous thromboembolism (VTE) is also positively correlated with CKD, suggesting ESRD is a hypercoagulable state.⁸,⁹ Such thrombotic risk could be explained by various factors, including inherited thrombophilia,¹⁰ vascular access-related problems,¹¹ and increased concentrations of procoagulant factors.⁶ Thus, patients with ESRD have multiple indications for the use of oral anticoagulants. Nonetheless, data on oral anticoagulant use for VTE in patients with ESRD are scarce; thus, studies reviewed below are primarily in the AF population.

Search Strategy

Published studies and conference proceedings in English were searched using PubMed, EMBASE, and the Cochrane database. Search terms included: dialysis, end stage renal disease, vitamin K antagonists (VKAs), apixaban, dabigatran, rivaroxaban, edoxaban, atrial fibrillation, venous thromboembolism, and bleeding. In addition, reference lists of narrative and systematic reviews were manually searched for peer-reviewed publications. Where multiple publications...
Vitamin K Antagonists
Pharmacology in ESRD
Vitamin K antagonists (VKAs), including warfarin, reflect the mainstay of treatment and prevention of thromboembolic disease in ESRD. Warfarin has a near 100% bioavailability, and reaches peak concentration within 4 hours of absorption. Elimination of warfarin is almost entirely via metabolism, and renal clearance is negligible. However, in patients with ESRD, nonrenal clearance is diminished through downregulation of cytochrome P450 gene expression. A consequent increase in the S/R enantiomer ratio is the putative explanation for three important observations in ESRD patients: (1) reduced warfarin dose requirements; (2) diminished time in therapeutic range regardless of international normalized ratio (INR) intensity; and (3) increased time with excessive INR. Nonetheless, decreased protein binding in ESRD probably accounts for the 31% drop in warfarin concentration following hemodialysis, owing to partial filtration of unbound warfarin. Further, reduced protein binding is the likely cause of the shortened half-life of warfarin in patients with CKD, which is 30 hours compared with 45 hours in subjects with normal kidney function. Utilization Patterns in ESRD
The effectiveness and safety of VKA among patients with ESRD and AF is highly debated, as reflected in the wide variability of VKA use among patients with ESRD in different high-income countries. Similarly, studies from the United States preceding market availability of the direct oral anticoagulants (DOACs) report a 15.5 to 62.3% prevalence of VKA use in patients on dialysis with incident AF. One further concern with VKA use for stroke prevention is low persistence over time, or early discontinuation. Indeed, almost half of dialysis patients with AF initiated on VKA were found to discontinue the drug within less than 9 months of use and without switching to DOACs.

Safety in ESRD
The presence of ESRD confers a bleeding diathesis independent of oral anticoagulation, manifesting as major, but also as nonmajor bleeding events. In hemodialysis patients, repetitive activation of platelets is thought to lead to platelet “exhaustion” and consequent dysfunction. Several studies have been published on bleeding risk with VKA among patients with ESRD. While differing in study design and methodology, most of the larger (>100 VKA users) studies reported major bleeding rates of 10 per 100 person-years or higher. In comparison, the pivotal clinical trials with DOACs, which excluded patients with severe CKD or ESRD, reported bleeding rates of ~3 per 100 person-years in the VKA arm. This comparison emphasizes the bleeding diathesis in ESRD rather than the comparative risk of bleeding with VKA versus no use, which varies with reports.

A further safety concern with VKA use in ESRD is increased risk of calcific uremic arteriolopathy (or calcific vasculopathy), which leads to ischemic skin necrosis. This syndrome is prevalent in ~4% of hemodialysis recipients and is associated with a case-fatality rate of 27% at 6 months and 45% at 12 months. In a cohort of 1,030 patients on hemodialysis, the incidence rate of calcific uremic arteriolopathy was 6.24 versus 3.35 per 1,000 person-years in VKA users and nonusers, respectively.

Dabigatran
Pharmacology in ESRD
Dabigatran, a direct thrombin inhibitor, is the active metabolite of the prodrug dabigatran etexilate. Renal clearance is appropriately estimated with intravenous infusion; after such infusion, 81% of the dose is recovered in urine, with 80% renal contribution to the total clearance. Thus, dabigatran has the highest renal clearance among DOACs. Exposure to dabigatran is negatively correlated with renal function, and the area under the plasma concentration-time curve (AUC) is 6.3-fold higher in patients with severe CKD after a single oral dose, compared with healthy subjects. Accordingly, 150- or 110-mg dabigatran are not indicated in Europe in patients with severe CKD or ESRD. The Food and Drug Administration (FDA) has approved the use of a 75-mg dose in patients with GFR between 15 and 30 mL/min/1.73 m² based on pharmacokinetic studies, but offers no dosing recommendations for ESRD. Of note, a simulation study suggested that a 75- or 110-mg dose taken once daily would result in therapeutic exposure to dabigatran in hemodialysis patients. Dabigatran is dialyzable, and 50 to 60% of central compartment dabigatran can be removed by a single 4-hour dialysis. Whether this remains a viable option for dabigatran removal in urgent bleeding or need for urgent procedure (where anticoagulation should be stopped abruptly) following idarucizumab approval remains to be seen. Hemodialysis for dabigatran removal has been suggested when idarucizumab is not available, and caution should be exercised for a resumed anticoagulant effect at the end of the dialysis session.

Utilization Patterns in ESRD
Dabigatran was approved by the FDA for use in AF in October 2010, reaching this mark first among the DOACs. In the United States, the 75-mg dose is recommended in patients with GFR between 15 and 30 mL/min/1.73 m², while in Europe, the 110-mg dose is recommended for patients with GFR between 30 and 49 mL/min/1.73 m² and high risk for bleeding. As noted previously, dabigatran is not approved in Europe for patients with severe CKD. Prescription pattern analysis from Europe suggests CKD is a predictor for preferring VKA over DOACs for VTE, with dabigatran in either dose not prescribed at all in severe CKD. In the United States, the 75-mg dose was used in up to 3% of dialysis patients with AF who were being anticoagulated shortly after its approval. However, the
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Drug</th>
<th>Population</th>
<th>Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifudu and Dulin 199319</td>
<td>Single-arm</td>
<td>PO warfarin 10 mg</td>
<td>1 hemodialysis patient</td>
<td>31% drop in plasma warfarin concentration after dialysis</td>
<td></td>
</tr>
<tr>
<td>Bachmann et al 197720</td>
<td>Single-arm</td>
<td>PO warfarin 0.75 mg/kg</td>
<td>5 healthy subjects, 4 patients with GFR &lt; 50 (2 ESRD)</td>
<td>Half-life of warfarin was 44.8 vs 29.9 hours in healthy subjects and renal patients, respectively</td>
<td></td>
</tr>
<tr>
<td>Blech et al 200833</td>
<td>Single-arm</td>
<td>Single-dose PO Dabigatran etexilate 200 mg; IV dabigatran 5 mg</td>
<td>10 healthy males</td>
<td>77% unchanged dabigatran after IV infusion and 4% glucuronic derivatives, accounting to 81% renal contribution to elimination</td>
<td></td>
</tr>
<tr>
<td>Stangier et al 201034</td>
<td>Single-arm, parallel group</td>
<td>Single-dose, PO dabigatran etexilate 150 mg (non-ESRD) and 50 mg (ESRD)</td>
<td>6 healthy, 23 renal impairment (GFR 51–80, 31–50, and ≤ 30), 6 hemodialysis</td>
<td>AUC was increased 1.5-, 3.2-, and 6.3-fold in renal impairment; in ESRD twofold increase</td>
<td></td>
</tr>
<tr>
<td>Khadzhynov et al 201338</td>
<td>Single-arm, multiple dosing</td>
<td>PO dabigatran etexilate: 150 mg postdialysis, then 110 and 75 mg</td>
<td>7 hemodialysis patients</td>
<td>48.8% elimination with “catheter setting” dialysis and 59.3% with “shunt setting” dialysis</td>
<td>Experimental dose very high-flow dialysis session for 4 hours</td>
</tr>
<tr>
<td>Weinz et al 200946</td>
<td>Single-arm</td>
<td>PO rivaroxaban 10 mg</td>
<td>4 healthy subjects</td>
<td>66% of rivaroxaban excreted in urine (36% unchanged)</td>
<td>Renal clearance was not measured with intravenous infusion</td>
</tr>
<tr>
<td>Kubitza et al 201047</td>
<td>Single-arm, parallel group</td>
<td>PO rivaroxaban 15 mg</td>
<td>8 healthy, 8 GFR 50–79, 8 GFR 30–49, 8 GFR &lt; 30</td>
<td>AUC 1.35-, 2.16-, and 2.44-fold increased across renal impairment strata</td>
<td>Steady-state AUC differences may have been larger</td>
</tr>
<tr>
<td>Frost et al 200857</td>
<td>Randomized crossover</td>
<td>PO and IV apixaban at various doses</td>
<td>8 healthy male subjects</td>
<td>Renal clearance accounted for 17–30% of total clearance</td>
<td></td>
</tr>
<tr>
<td>Leil et al 201058</td>
<td>Population pharmacokinetics from a phase II randomized trial</td>
<td>PO apixaban (multiple dosing regimens)</td>
<td>1,298 hip and knee replacements patients</td>
<td>Minimal concentration increased and AUC in steady-state increased by 67 and 70% with moderate renal impairment, respectively</td>
<td></td>
</tr>
<tr>
<td>Wang et al 201659</td>
<td>Single-arm, parallel group</td>
<td>PO apixaban 5 mg before and after dialysis</td>
<td>8 healthy subjects and 8 hemodialysis patients</td>
<td>Postdialysis AUC decreased by 14%; AUC in dialysis was 36% increased vs. healthy subjects</td>
<td>Single-dose study</td>
</tr>
<tr>
<td>Mavrakanas et al 201760</td>
<td>Single-group crossover</td>
<td>PO apixaban 2.5 and 5 mg</td>
<td>7 hemodialysis patients</td>
<td>Steady-state AUC with apixaban 2.5 in dialysis patients mg is &lt; 10th percentile of 5 mg apixaban in healthy subjects; steady-state AUC with 5 mg</td>
<td>The effectiveness of the 2.5-mg dose in atrial fibrillation is unclear</td>
</tr>
</tbody>
</table>

(Continued)
The prevalence of dabigatran use in dialysis patients has subsequently dropped, reaching 0.3% in late 2015.

### Results

Data from the Outcomes Registry for Better Informed Therapy reflect this trend as well.

### Safety in ESRD

In the setting of a closely monitored phase-I study, three doses of dabigatran (150 mg, 110 mg, and 75 mg) once were associated with only one minor bleeding event. Nevertheless, very high rates of major and nonmajor bleeding with its use were associated with only one minor bleeding event. Data from shortly after the approval of dabigatran in the United States indicate very high rates of major and nonmajor bleeding with its use in hemodialysis patients (Table 4).

### Pharmacology in ESRD

Rivaroxaban, a factor Xa inhibitor, has a renal clearance of 66% after oral ingestion. Nevertheless, 36% of ingested rivaroxaban is excreted unchanged in the urine, indicating the renal clearance contribution out of total clearance (Table 1). In patients with mild, moderate, and severe CKD, the AUC was augmented by 44%, 52%, and 64%, respectively, representing significant drug accumulation.

Among patients receiving maintenance hemodialysis, a single 15-mg oral dose of rivaroxaban resulted in a 56% increase in post-dialysis AUC, compared with healthy subjects. This was concluded by the authors to reflect 35% decreased clearance in ESRD patients, which recapitulates the findings in patients with moderate CKD.

A further study conducted on 18 patients confirmed that rivaroxaban was not appreciably removed by dialysis. Further, this study examined a clinical steady state achieved after 7 days of rivaroxaban at 10 mg daily and demonstrated trough levels which were on par with those observed in patients with moderate CKD. Rivaroxaban was associated with mild and severe CKD, the AUC was augmented by 44%, 52%, and 64%, respectively, representing significant drug accumulation.
Table 2  Cohort studies reporting bleeding events with vitamin K antagonists in patients with end-stage renal disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Exposure (n)</th>
<th>Indication (AF/VTE/Other)</th>
<th>Follow-up, mean (d)</th>
<th>Exposed events</th>
<th>Incidence rate (per 100 PY)</th>
<th>Conclusions/ Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olesen et al 2011&lt;sup&gt;80&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 178) Warfarin + aspirin (n = 45)</td>
<td>223/0/0</td>
<td>725</td>
<td>243 major (all RRT)</td>
<td>8.9 (all RRT)</td>
<td>Person-time for exposure is nontransparent</td>
</tr>
<tr>
<td>Lai et al 2009&lt;sup&gt;81&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 78)</td>
<td>78/0/0</td>
<td>930</td>
<td>8 major</td>
<td>4.0</td>
<td>Event number in ESRD unclear</td>
</tr>
<tr>
<td>Phelan et al 2011&lt;sup&gt;82&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 141)</td>
<td>71/45/25</td>
<td>738</td>
<td>31 major</td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>Kai et al 2017&lt;sup&gt;83&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 989)</td>
<td>989/0/0</td>
<td>767</td>
<td>126 GIB 22 ICH</td>
<td>5.4 GIB 0.9 ICH</td>
<td>Potential exposure misclassification Immortal time bias</td>
</tr>
<tr>
<td>Winkelmayer et al 2011&lt;sup&gt;84&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 249)</td>
<td>249/0/0</td>
<td>552 GIB 646 ICH</td>
<td>48 GIB 11 ICH</td>
<td>13.4 GIB 2.6 ICH</td>
<td>Discrepancy between GIB and ICH results</td>
</tr>
<tr>
<td>Biggers et al 1977&lt;sup&gt;85&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 48)</td>
<td>0/0/48</td>
<td>715</td>
<td>50 major</td>
<td>53.2</td>
<td>Not time-to-event Prevention of circuit clotting</td>
</tr>
<tr>
<td>Vázquez et al 2003&lt;sup&gt;86&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 29)</td>
<td>7/14/8</td>
<td>600</td>
<td>13 major</td>
<td>26.0</td>
<td>Bleeding definition not compatible with ISTH</td>
</tr>
<tr>
<td>Khalid et al 2013&lt;sup&gt;87&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 34)</td>
<td>34/0/0</td>
<td>365</td>
<td>26 recurrent GIB</td>
<td>NA</td>
<td>Potential exposure misclassification Confounding by indication</td>
</tr>
<tr>
<td>Wang et al 2016&lt;sup&gt;88&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 59)</td>
<td>59/0/0</td>
<td>1242</td>
<td>22 events</td>
<td>9.1</td>
<td>Potential exposure misclassification Underpowered</td>
</tr>
<tr>
<td>Yodogawa et al 2016&lt;sup&gt;89&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 30)</td>
<td>30/0/0</td>
<td>1410</td>
<td>3 major</td>
<td>2.6</td>
<td>Potential exposure misclassification Bleeding definition unclear</td>
</tr>
<tr>
<td>Klil-Drori et al 2016&lt;sup&gt;90&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 467)</td>
<td>0/467/0</td>
<td>132</td>
<td>20 major</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>Shah et al 2014&lt;sup&gt;91&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 756)</td>
<td>756/0/0</td>
<td>662</td>
<td>149 major</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Shen et al 2016&lt;sup&gt;92&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 1,838)</td>
<td>1,838/0/0</td>
<td>497 GIB 533 ICH</td>
<td>153 GIB 29 ICH</td>
<td>5.9 GIB 1.0 ICH</td>
<td>Differences between ITT and AT approaches</td>
</tr>
<tr>
<td>Yoon et al 2017&lt;sup&gt;93&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 2,921)</td>
<td>2,921/0/0</td>
<td>477</td>
<td>215 GIB 89 ICH</td>
<td>5.6 GIB 2.3 ICH</td>
<td></td>
</tr>
<tr>
<td>Friberg et al 2015&lt;sup&gt;94&lt;/sup&gt;</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 164)</td>
<td>164/0/0</td>
<td>767</td>
<td>61</td>
<td>17.7</td>
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</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Exposure (n)</th>
<th>Indication (AF/VTE/Other)</th>
<th>Follow-up, mean (d)</th>
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<th>Incidence rate (per 100 PY)</th>
<th>Conclusions/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genovesi et al 2017</td>
<td>Prospective cohort</td>
<td>Warfarin (n = 134)</td>
<td>134/0/0</td>
<td>1461</td>
<td>55 events</td>
<td>17.0</td>
<td>Underpowered</td>
</tr>
<tr>
<td>Wakasugi et al 2014</td>
<td>Prospective cohort</td>
<td>Warfarin (n = 28)</td>
<td>28/0/0</td>
<td>700</td>
<td>3 major</td>
<td>5.3</td>
<td>Only prevalent use</td>
</tr>
<tr>
<td>Zellweger et al 2005</td>
<td>Prospective cohort</td>
<td>Low-intensity warfarin (n = 35)</td>
<td>0/0/35</td>
<td>126</td>
<td>0 major</td>
<td>NA</td>
<td>Prevention of catheter</td>
</tr>
<tr>
<td>Clark et al 2016</td>
<td>Prospective cohort</td>
<td>Warfarin (n = 42)</td>
<td>23/11/8</td>
<td>207</td>
<td>5 major</td>
<td>21.0</td>
<td>Pharmacist-led intervention</td>
</tr>
<tr>
<td>Knoll et al 2012</td>
<td>Prospective cohort</td>
<td>Warfarin (n = 46)</td>
<td>30/6/10</td>
<td>1,037</td>
<td>4 major (2 on treatment, 2 before treatment)</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Limdi et al 2009</td>
<td>Prospective cohort</td>
<td>Warfarin (n = 52)</td>
<td>29/23/0</td>
<td>730</td>
<td>32 major</td>
<td>30.5</td>
<td>47/52 hemodialysis</td>
</tr>
<tr>
<td>Crowther et al 2002</td>
<td>RCT</td>
<td>Low-intensity warfarin (n = 56)</td>
<td>0/0/56</td>
<td>199</td>
<td>5 major</td>
<td>16.4</td>
<td>Target INR 1.5–1.9</td>
</tr>
<tr>
<td>Mokrzycki et al 2001</td>
<td>RCT</td>
<td>Minidose warfarin (n = 41)</td>
<td>0/0/41</td>
<td>&lt; 365</td>
<td>1 event</td>
<td>NA</td>
<td>Bleeding event probably</td>
</tr>
<tr>
<td>Traynor et al 2001</td>
<td>RCT</td>
<td>Minidose warfarin (n = 10)</td>
<td>0/0/10</td>
<td>188</td>
<td>0 major</td>
<td>NA</td>
<td>Open label, small, and</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; AT, as-treated; GIB, gastrointestinal bleeding; ICH, intracranial hemorrhage; INR, international normalized ratio; ISTH, International Society on Thrombosis and Haemostasis; ITT, intention-to-treat; NA, not available; PY, person-years; RCT, randomized controlled trial; RRT, renal replacement therapy; TTR, time in therapeutic range; VTE, venous thromboembolism.
Table 3 Renal dosing recommendations for oral anticoagulants in the United States and Europe

<table>
<thead>
<tr>
<th>Warfarin</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonvalvular atrial fibrillation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>No renal dosing</td>
<td>GFR &gt; 30: 150 mg BID</td>
<td>GFR &gt; 50: 20 mg QD</td>
<td>At least 2/3: SCr ≥ 1.5 mg/dL, age ≥ 80, weight ≤ 60 kg; 2.5 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GFR 15–30: 75 mg BID</td>
<td>GFR 15–50: 15 mg QD</td>
<td>Otherwise: 5 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ESRD: contraindicated</td>
<td>ESRD: 5 mg BID (age &lt; 80 and weight &gt; 60 kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>No renal dosing</td>
<td>GFR &gt; 50: 150 mg BID</td>
<td>GFR &gt; 30: SCr ≥ 1.5 mg/dL and ½ (age ≥ 80, weight ≤ 60 kg): 2.5 mg BID;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GFR &lt; 30: contraindicated</td>
<td>Otherwise: 5 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GFR &lt; 15: contraindicated</td>
<td>GFR ≤ 20.5 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GFR &lt; 15: contraindicated</td>
<td></td>
</tr>
<tr>
<td><strong>Venous thromboembolism (treatment)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>No renal dosing</td>
<td>Same as NVAF</td>
<td>GFR ≥ 30: 15 mg BID for 21 d, then 20 mg QD</td>
<td>10 mg BID for 7 d, then 5 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GFR &lt; 30: C/I</td>
<td>No dose adjustments</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>No renal dosing</td>
<td>Same as NVAF</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>Same as US</td>
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<td></td>
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<td></td>
<td>GFR &gt; 15: same as US</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BID, twice daily; C/I, contraindicated; ESRD, end-stage renal disease; GFR, glomerular filtration rate; NVAF, nonvalvular atrial fibrillation; P-gp, p-glycoprotein; QD, once daily; US, United States.

Table 4 Cohort studies reporting bleeding events with direct oral anticoagulants in patients with end-stage renal disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Anticoagulant (n)</th>
<th>Indication (AF/VTE/Other)</th>
<th>Follow-up (d)</th>
<th>Exposed events</th>
<th>Incidence rate per 100 PY</th>
<th>Conclusions/Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarratt et al 2017</td>
<td>Inpatient cohort</td>
<td>Warfarin (n = 120)</td>
<td>81/39/0</td>
<td>9</td>
<td>7 major; 7 CRNMB</td>
<td>NA</td>
<td>57.6% of apixaban users had 2.5 mg BID dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apixaban (n = 40)</td>
<td>32/8/0</td>
<td>8.8</td>
<td>0 major; 5 CRNMB</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Steuber et al 2017</td>
<td>Inpatient cohort</td>
<td>Apixaban (n = 114)</td>
<td>75/39/0</td>
<td>6.2</td>
<td>7 major; 5 CRNMB</td>
<td>NA</td>
<td>Prevalent users</td>
</tr>
<tr>
<td>Stanton et al 2017</td>
<td>Retrospective cohort</td>
<td>Apixaban (n = 73)</td>
<td>53/19/1</td>
<td>369</td>
<td>7 major; 13 CRNMB</td>
<td>9.5 major; 17.6 CRNMB</td>
<td>Rates are for severe CKD rather than ESRD alone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Warfarin (n = 73)</td>
<td>53/19/1</td>
<td>562</td>
<td>13 major; 6 CRNMB</td>
<td>11.6 major; 5.3 CRNMB</td>
<td></td>
</tr>
<tr>
<td>Chan et al 2015</td>
<td>Retrospective cohort</td>
<td>Warfarin (n = 8,064)</td>
<td>8,064/0/0</td>
<td>0</td>
<td>1,858 major; 4,367 minor</td>
<td>47.1 major; 120.6 minor</td>
<td>Substantially shorter follow-up on rivaroxaban</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dabigatran (n = 281)</td>
<td>281/0/0</td>
<td>168</td>
<td>106 major; 153 minor</td>
<td>83.1 major; 58.8 minor</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rivaroxaban (n = 244)</td>
<td>244/0/0</td>
<td>106</td>
<td>46 major; 113 minor</td>
<td>68.4 major; 149.4 minor</td>
<td></td>
</tr>
<tr>
<td>Koretsune et al 2015</td>
<td>Prospective study</td>
<td>Edoxaban (n = 50)</td>
<td>50/0/0</td>
<td>98</td>
<td>0 major; 10 minor</td>
<td>NA</td>
<td>Patients with severe CKD and not ESRD</td>
</tr>
</tbody>
</table>

Abbreviations: AF, atrial fibrillation; BID, twice daily; CKD, chronic kidney disease; CRNMB, clinically relevant non-major bleeding; ESRD, end-stage renal disease; ISTH, International Society on Thrombosis and Haemostasis; NA, not available; PY, person-years; VTE, venous thromboembolism.
no clinical effectiveness data have been published in ESRD patients. Thus, there is some uncertainty whether the appropriate dose in ESRD patients is 10 or 15 mg daily. The explicitly recommended doses are presented in Table 3.

In Europe, rivaroxaban is contraindicated in ESRD. As of late 2015, rivaroxaban use was prevalent in 0.8% of dialysis patients on anticoagulants for AF in the United States. Similar to dabigatran, 41.3% of the non-ESRD patients with renal indication for dose reduction were overdosed. However, the large majority of rivaroxaban users with ESRD were receiving a 15-mg dose. Finally, in patients with severe CKD there has been a marked increase in the use of rivaroxaban in the United States.

Safety in ESRD

Very sparse information exists regarding the safety of rivaroxaban in ESRD patients, and no data on the 10-mg dose. The single study that examined the use of the 15- and 20-mg doses had a very short mean follow-up of 106 days (Table 4). Likely due to inappropriate use, a major bleeding rate of 68.4 per 100 person-years was recorded in this population. This rate is more than 18-fold higher than the rate observed in patients who experienced worsening renal function during the ROCKET-AF trial.

Apixaban

Pharmacology in ESRD

Between 24.5 and 28.8% of the parent drug apixaban, a factor Xa inhibitor, is recovered in the urine after oral ingestion (Table 1). After intravenous infusion, renal clearance contributes 17 to 30% of the total drug clearance. Renal function is an important predictor of steady-state drug exposure, which occurs after 3 to 4 days. Thus, patients with moderate renal impairment are likely to have a 70% higher AUC at steady state than twice those seen in healthy subjects. Further, dialysis has been found to have a marginal effect on apixaban exposure, reducing the maximal concentration by 13%. Thus, significant accumulation of apixaban at steady state was demonstrated in a subsequent study with six hemodialysis patients who received 2.5 mg apixaban twice a day for 7 days. This study is important in that it showed that the steady-state AUC and minimal concentration of apixaban at 2.5 mg twice a day taken by hemodialysis patients were well within the range in healthy subjects taking the 2.5-mg dose. However, the effectiveness of such a regimen may be questioned, as these values fall below the 10th percentile of the 5 mg twice a day dose in normal subjects. Finally, the same six hemodialysis patients underwent a washout period and then received 5 mg apixaban twice a day for 7 days with a consequent AUC and minimal concentration which were more than twice those seen in healthy subjects.

Utilization in ESRD

Apixaban was first approved by the FDA for AF in December 2012. The original label recommended dose reduction to 2.5 mg twice a day for patients with at least two factors out of: serum creatinine ≥ 1.5 mg/dL, age ≥ 80, and weight ≤ 60 kg. Following the single-dose pharmacokinetic study mentioned above, the label was changed in January 2014 such that the 5-mg twice a day dose was recommended in ESRD patients who are not older adults or underweight (Table 3). Of note, in direct reference to the findings from the steady-state study, a recommendation has been made to reconsider the 5-mg dose in hemodialysis patients. Concurrently, the use of apixaban is not approved in ESRD patients in Europe.

A large retrospective cohort study from the United States that excluded patients with ESRD has demonstrated that among patients with AF receiving apixaban with a renal indication for dose reduction, overdosing was very common at 48.5%; importantly, overdosing was associated with doubling of major bleeding rates. Further, among patients without renal indication for dose reduction, 16.5% were underdosed; such underdosing was associated with an increased risk of stroke (hazard ratio, 4.87; 95% confidence interval, 1.30–18.26).

Apixaban has been adopted very rapidly in the United States among patients with hemodialysis and AF, and has reached a point prevalence of 10.5% in this population in October 2015. There is currently paucity of information on utilization of off-label DOACs in the severe CKD or ESRD population in Europe. Nonetheless, among the DOACs, it appears that a larger proportion of apixaban users with AF have baseline CKD. In a survey among European electrophysiology centers, apixaban was indicated as the preferred anticoagulant in moderate CKD, and the lack of data on patients with severe CKD and/or RRT was emphasized.

Safety in ESRD

Bleeding risk with apixaban in ESRD has been assessed in three studies to date (Table 4). Two of these studies included only inpatient follow-up. With limited follow-up and selection of only events during admission, any rates of major bleeding in these studies are not comparable to clinical trials. In the third study, matched cohorts of patients with severe CKD who used apixaban or VKA were followed for major and clinically relevant nonmajor bleeding; each cohort comprised 73 patients (27 ESRD). Apixaban users received 2.5 mg twice a day primarily (61.6%) and were followed for 369 days. There were 9.5 major bleeding events per 100 person-years, which is 3.5-fold higher than the rate in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial where most of the study population received 5 mg twice a day. In ARISTOTLE, major bleeding rates in patients with GFR < 50 and > 80 mL/min/1.73 m² were 3.15 and 1.33 per 100 person-years, respectively. Thus, there is a suggestion for excessive bleeding with reduced-dose apixaban in patients with severe CKD or ESRD compared with full-dose apixaban in patients with nonsevere CKD or ESRD.

Edoxaban

Pharmacology in ESRD

Edoxaban, a factor Xa inhibitor, has a 50% renal clearance out of total clearance. After a single dose of 60 mg, 35.4% of edoxaban is recovered in urine (Table 1). With renal
Impairment, edoxaban exposure increases and is assessed as 1.93-fold higher in recipients of peritoneal dialysis than in healthy subjects. Edoxaban is not dialyzable and no supplemental dose is needed following a hemodialysis session.

Utilization in ESRD
Edoxaban (sold in the United States as Savaysa) was approved for use in AF by the FDA in January 2015. The recommended dose in patients with GFR 15 to 50 mL/min/1.73 m² is 30 mg once a day with no recommendation for ESRD. In Europe (where it is sold as Lixiana), there are similar recommendations. In Europe, there are similar recommendations (Table 3). These recommendations by the two regulatory authorities were based on population pharmacokinetic data only, as very few participants with GFR < 50 mL/min/1.73 m² were included in the ENGAGE-AF TIMI 48 trial. To date, there are few reports on the utilization of edoxaban in the ESRD population, and, by late 2015, it was probably negligible in the United States.

Safety in ESRD
A clinical trial in Japan reported on 50 patients with GFR 15 to 30 mL/min/1.74 m² who used edoxaban 15 mg daily in a nonrandomized fashion (Table 4). No major bleeding occurred during a 100-day follow-up.

Conclusion
VKAs are the most widely used oral anticoagulant among AF patients with ESRD. However, there are abundant reports on excessive bleeding risk associated with its use, as well as challenges in attaining therapeutic anticoagulation. These may have triggered rapid adoption of DOACs among ESRD patients in the United States, which initially may have led to inappropriate dosing and excessive bleeding. While apixaban and rivaroxaban have to date expanded labeling which allows use in ESRD, the dosing is based on single-dose studies which may have underestimated drug accumulation and foreseeable harm. Subsequently, steady-state studies have indicated in both cases a reduced dose. While recommending these doses for use in ESRD patients would align with current safety data, their effectiveness in preventing stroke in AF and recurrent VTE remains to be established. Nevertheless, it is very likely that with further increased use of DOACs in ESRD, more population-based safety and effectiveness data will allow informed dosing and choice of oral anticoagulant.

Conflicts of Interest
Dr. Tagalakis reports an investigator initiated grant from Sanofi, and consulting and speaker bureau fees from Pfizer, Bristol-Myers Squibb, Bayer, and Servier outside the submitted work. Dr. Kili-Drori reports personal fees from Bristol-Myers-Squibb, outside the submitted work.

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