



# ANTICOAGULANT TREATMENT IN PATIENTS WITH ATRIAL FIBRILLATION AND CHRONIC KIDNEY DISEASE

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**SUMMARY – Aim:** To investigate the efficacy and safety profile of oral anticoagulants and determine the best treatment for patients with atrial fibrillation (AF) and chronic kidney disease (CKD).

**Methods and materials:** A systematic assessment of literature from Pubmed/MEDLINE was performed in search of studies evaluating the efficacy, safety, pharmacokinetics, and pharmacodynamics of direct oral anticoagulants (DOACs) and warfarin in patients with CKD.

**Results:** According to guidelines, DOACs are the treatment of choice for patients with CKD 1–3 (Crcl  $\geq$  30 mL/min) due to their high efficacy, better safety profile, and fewer food/drug and drug/drug interactions than warfarin. For patients with CKD 4 (Crcl 15–29 mL/min), there are no such strong recommendations as to which group of anticoagulants is the better choice, and for those with CKD 5 (Crcl  $<$  15 mL/min), the choice is currently narrowed to warfarin or apixaban. However, there seem to be more negative effects of warfarin, including accelerated CKD progression and increased risk of bleeding compared to DOACs.

**Conclusion:** Considering their superior safety profile and the possibility of apixaban, rivaroxaban, and edoxaban to achieve an adequate anticoagulant effect even in severe kidney disease, DOACs seem to be a better option for anticoagulant treatment of patients with AF and CKD.

**Key words:** atrial fibrillation, anticoagulant treatment, chronic kidney disease

## Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a prevalence of 1% at the age of 60 years and increasing to more than 15% at the age of 85 years<sup>1</sup>. It is associated with a significantly increased risk of ischemic stroke and systemic thromboembolism (SSE) compared to healthy individuals<sup>2</sup>. To reduce this risk, in most AF cases, a life-long oral anticoagulant treatment should be initiated. There are currently two groups of oral anticoagulants – warfarin, which represents vitamin K antagonists, and direct oral anticoagulants (DOACs), which include dabigatran, rivaroxaban, apixaban, and edoxaban. Warfarin

has been used as an oral anticoagulant since 1954 and was the foundation of oral anticoagulant therapy<sup>3</sup>. On the other hand, the group of DOACs proved to be a good alternative to warfarin and are now the treatment of choice for AF patients due to their high efficacy, good safety profile, and fewer interactions with drugs or food than warfarin<sup>4</sup>. Choosing a specific anticoagulant drug for patients with AF can be further complicated by coexisting chronic kidney disease (CKD), which is relatively common in this group of patients<sup>5</sup>. Prevalence of both AF and CKD increases with age, as well as their simultaneous appearance<sup>6</sup>. Given that DOACs have a high level of renal clearance, their efficacy, safety, and dosing were not explored in randomized clinical trials (RCTs) on patients with severe CKD or kidney failure, which prompted some studies

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to conclude that warfarin is a better choice of treatment for this profile of patients<sup>7</sup>. However, new evidence has shown that warfarin has a significant association with acute kidney injury (AKI) and CKD progression, making its safety questionable in CKD patients. This study aimed to investigate each oral anticoagulant's efficacy and safety profile and determine the best anticoagulant treatment for patients with AF and CKD.

## Methods

A systematic assessment of the literature was performed. The main data sources included Pubmed/MEDLINE and Google Scholar in search of studies evaluating the efficacy, safety, pharmacokinetics, and pharmacodynamics of DOACs and warfarin in patients with CKD published from January 1, 2010, to January 14, 2021. A combination of the following terms was used: "warfarin, new oral anticoagulants, dabigatran, rivaroxaban, apixaban, edoxaban, chronic kidney disease, effectiveness, safety, anticoagulant related nephropathy". Pre-specified filters included: "meta-analysis, systematic reviews, observational studies, case reports".

## Results

Most cases of atrial fibrillation are treated with oral anticoagulants, either warfarin or DOACs. During the initiation of anticoagulant treatment in patients with AF and CKD, it is necessary to estimate the risk of thromboembolism, risk of bleeding, stage of CKD, and whether it is a case of valvular or nonvalvular atrial fibrillation (NVAF). The risk of thromboembolism is most commonly estimated by calculating CHA<sub>2</sub>DS<sub>2</sub>-VASc score (which includes TIA, age  $\geq$  75 years, heart failure, hypertension, diabetes, female sex, age 65 – 75 years, and atherosclerotic vascular disease)<sup>8</sup>. It is important to predict bleeding risk in all anticoagulated patients, but especially in those with CKD, considering CKD is by itself related to higher bleeding risk<sup>9</sup>. Bleeding is also the most common reason for stopping anticoagulation in the general population<sup>10</sup>. A frequently used tool to estimate the risk of bleeding is the HAS-BLED score, which predicts the yearly risk for major bleeding, defined by the International Society on Thrombosis and Haemostasis classification (ISTH)

criteria as the bleeding resulting in a decrease of hemoglobin by 2 g/dL or more, transfusion of two or more blood units, symptomatic bleeding in critical locations or organs, or bleeding with a deathly outcome<sup>11</sup>. The HAS-BLED score includes hypertension, kidney and/or liver dysfunction, former stroke, former bleeding, unstable INR, age  $>$  65 years, the use of antiplatelet or non-steroid antiinflammatory drugs, and alcohol consumption<sup>12</sup>.

The dosing regimen of all four DOACs approved by the Food and Drug Administration (FDA) in patients with AF is defined by the patients' kidney function (the level of serum creatinine, or creatinine clearance (Crcl) calculated by Cockcroft-Gault equation), with additional dosing criteria for apixaban in the cases of age  $\geq$  80 years and body mass  $\leq$  60kg<sup>13</sup>. The Cockcroft-Gault equation was used to calculate Crcl in original DOAC RCTs and pharmacokinetic studies, which preceded the drafting of clinical guidelines for the use of DOACs in patients with CKD. It is important to consider this because more commonly used equations for calculating renal functions such as MDRD or CKD-EPI equations could lead to the wrong estimation of the needed dose of DOACs for CKD patients<sup>14</sup>.

The kidney function needs to be monitored at least once a year in DOAC users. In the case of Crcl  $\leq$  60 mL/min, the recommended interval for follow-up is calculated by dividing the patients Crcl by 10, e.g., for Crcl 40 mL/min, kidney function should be tested every 4 months<sup>12,14</sup>. KDIGO guidelines define CKD stages according to the patients' estimated glomerular function (GFR) calculated using the CKD-EPI equation and expressed in milliliters per minute per 1.73 m<sup>2</sup> (mL/min/1.73 m<sup>2</sup>). There are five stages of CKD; CKD 1 (normal kidney function, GFR  $\geq$  90), CKD 2 (mild renal insufficiency GFR: 60 – 89), CKD 3 (moderate renal insufficiency, GFR: 30 – 59), CKD 4 (severe renal insufficiency, GFR: 15 – 29), CKD 5 (kidney failure, GFR:  $<$  15)<sup>15</sup>.

According to the available literature, the safety and efficacy of oral anticoagulants are different in the group of patients with CKD 1–3 (Crcl  $\geq$  30 mL/min) than in the group with CKD 4–5 (Crcl  $<$  30 mL/min) and will, therefore, be described separately below.

## Pharmacodynamics

Anticoagulant drugs inhibit the formation of fibrin clots by acting on different factors of coagulation path-

Table 1. Pharmacokinetic properties of DOACs.

	Bioavailability	Half-life	Standard dose	Reduced dose	Contraindications
Dabigatran	3 – 7% <sup>23,a</sup>	9 – 17 h <sup>23</sup>	150 mg BID <sup>23</sup>	110 mg BID, 75 mg <sup>23,b</sup>	Valvular atrial fibrillation, severe renal impairment (CrCl < 15 mL/min) <sup>12</sup>
Rivaroxaban	66% <sup>24,25</sup>	6 – 13 h <sup>25</sup>	20 mg OD <sup>23</sup>	15 mg OD <sup>23, b</sup>	Valvular atrial fibrillation, severe renal impairment (CrCl < 15 mL/min) or advanced liver disease <sup>26</sup>
Apixaban	50 % <sup>27</sup>	12 h <sup>27</sup>	5 mg BID <sup>12</sup>	2.5 mg BID <sup>c</sup>	Valvular atrial fibrillation, Serum creatinine >2.5 mg/dL or CrCl <25 mL/min <sup>12</sup>
Edoxaban	60 % <sup>12</sup>	12h <sup>12</sup>	60 mg OD <sup>12</sup>	30 mg OD <sup>d</sup>	Valvular atrial fibrillation, severe renal impairment (CrCl < 15 mL/min) or advanced liver disease <sup>12</sup>

<sup>a</sup> the oral bioavailability of dabigatran etexilate increases by 75%<sup>23</sup>

<sup>b</sup> in the presence of renal insufficiency (CrCl < 50 mL/min)<sup>23</sup>

<sup>c</sup> if patients have at least 2 of the following features: age ≥ 80 years, body mass ≤ 60 kg, or serum creatinine 1.5 mg/dL or more<sup>12</sup>

<sup>d</sup> if the CrCl is < 50 mL/min or body weight is less than 60 kg<sup>12</sup>

ways. Warfarin achieves its anticoagulant effect by inhibiting the C1 subunit of the vitamin K epoxide reductase enzyme complex, which reduces vitamin K epoxide into its active form<sup>16</sup>. Without enough reduced vitamin K, normal posttranslatic carboxylation of prothrombin (factor II) and other vitamin K dependant factors (VII, IX, and X) is not possible<sup>16</sup>. Dabigatran is a direct thrombin inhibitor. It attaches to a location on thrombin different from fibrin and can thus inhibit the free plasma thrombin as well as the form that is already attached in a thrombus<sup>17</sup>. Rivaroxaban, apixaban, and edoxaban are direct inhibitors of factor Xa, both the free plasmatic form and thrombus embedded one<sup>17</sup>.

### Pharmacokinetics

Warfarin is a small liposoluble molecule that is easily absorbed into the bloodstream, where 99% of it is bound to plasma proteins. Warfarin is metabolized by hepatic cytochrome P-450 enzyme complex, but severe renal impairment can significantly decrease both nonrenal clearance and bioavailability of warfarin<sup>18</sup>. Consequently, patients with severe CKD should receive a 20% lower dose of warfarin compared to those with a healthy kidney function<sup>19</sup>. This phenomenon was explained by animal studies, which showed a significant 40–85% downregulation of hepatic cytochrome P-450 in CKD<sup>20</sup>. As a result of being metabolized by cytochrome P-450, warfarin interacts with many other drugs that influence the cytochrome's ac-

tion, including cytochrome P-450 inducers (e.g., carbamazepine, barbiturates, rifampin) and cytochrome P-450 inhibitors (e.g., amiodarone, cimetidine)<sup>21</sup>.

DOACs too are well absorbed from the gastrointestinal tract, but during absorption interact with the P-glycoprotein (P-gp) transporter, which transfers a share of those molecules back into the intestine<sup>12</sup>. P-gp is also included in the renal clearance and its induction results in decreased plasma levels of DOACs, while inhibition of P-gp leads to increased levels of DOACs<sup>12</sup>. Many of those P-gp inhibitors are used in treating cardiac arrhythmias (e.g., verapamil, amiodarone, dronedarone)<sup>12</sup>. DOACs are also partially metabolized by cytochrome P-450, but interactions with other drugs are far less extensive than with warfarin<sup>12</sup>. Dabigatran is administered as a prodrug known as dabigatran etexilate and after absorption in the small bowel, it is activated by serum and hepatic esterases<sup>22</sup>. Bioavailability, half-life, and dosing of DOACs are described in Table 1. Pharmacokinetic properties of DOACs.

All DOACs are to some degree renally excreted and can accumulate in patients with CKD, which results in an increased risk of bleeding<sup>14</sup>. Edoxaban, rivaroxaban, and apixaban are all primarily bound to plasma proteins and can not be eliminated by hemodialysis<sup>14,28,29,30</sup>. Contrarily, dabigatran is successfully eliminated by dialysis<sup>7</sup>.

Dabigatran is mostly (80%) eliminated through renal excretion<sup>12</sup>, and its pharmacokinetics is the most

altered by CKD among DOACs<sup>7</sup>. In a pivotal pharmacokinetic study, dabigatran exposure was 1.5, 3.2, and 6.3 times greater in patients with mild, moderate, and severe renal insufficiency, respectively, compared with healthy individuals<sup>7</sup>.

Rivaroxaban is excreted renally (66%) and via biliary route<sup>7</sup>. Renal insufficiency only partially impacts the elimination of rivaroxaban, even in the cases of severe CKD<sup>31</sup>. A pharmacokinetic study showed that among patients with mild, moderate, and severe renal insufficiency, rivaroxaban exposure after a single dose of 10 mg was increased by 44%, 52%, and 64%, respectively, compared with healthy individuals<sup>7,25,31</sup>.

Apixaban elimination occurs via renal (27%) and nonrenal pathways<sup>7</sup>. A decrease in renal function increases apixaban systemic exposure with predicted increases of 16%, 29%, and 38%, corresponding to 24-hour creatinine clearance (Crcl) values of 65, 40, and 25 mL/min, respectively, compared with a reference Crcl of 100 mL/min<sup>7,32</sup>.

Edoxaban is eliminated 50% renally and 50% nonrenally<sup>7</sup>. Edoxaban plasma concentration increases with decreasing renal function, with 32%, 74%, and 72% higher levels of exposure reported in patients with mild, moderate, and severe renal impairment, respectively, compared with healthy individuals<sup>7,33</sup>.

### *Prevention of ischemic stroke and systemic thromboembolism*

The main indicator of the efficacy of anticoagulant drugs is their ability to prevent ischemic strokes and systemic thromboembolisms (SSE).

#### *CKD 1–3 (Crcl ≥ 30 mL/min)*

Warfarin decreases the risk of ischemic stroke by 60% in patients with atrial fibrillation and overall mortality by nearly 25% compared to patients who didn't receive any anticoagulant treatment<sup>34</sup>. It is equally effective in patients with CKD 1–3 (Crcl ≥ 30) as it is in the general population<sup>14,35,36</sup>, reducing the incidence of SSE in CKD 3 patients by as much as 76%<sup>36</sup>.

DOACs are as effective or superior to warfarin in decreasing the risk of SSE in the general population<sup>5</sup>. Patients with CKD 1–3 were included in the original DOAC RCTs (RE-LY, ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI), and their efficacy and safety profile have been further proved in many other

clinical research papers<sup>37,38,39</sup>. Among patients with CKD 1–3 and NVAf, all DOACs have been recognized as noninferior to warfarin in reducing SSE risk, except for dabigatran 150 mg BID, which was proven to be superior<sup>11,40,41</sup>. AHA, Canadian Cardiovascular Society, KDIGO, EHRA, CHEST, and ESC guidelines recommend DOACs as the treatment of choice for patients without contraindications, including those with CKD 1–3<sup>12,17,42,43,44</sup>.

Dabigatran given in 150 mg BID dose showed to be highly effective in the RE-LY trial<sup>41</sup>. It reduced the SSE risk in patients with Crcl 30–49 mL/min significantly more than warfarin (1.5% with dabigatran vs. 2.7% with warfarin per year, HR: 0.56 [95% CI, 0.37–0.85])<sup>45</sup>. The 110 mg BID dose had a similar SSE risk as warfarin (2.32% vs. 2.7% per year, HR: 0.85 [95% CI, 0.59–1.24])<sup>46</sup>.

ROCKET AF trial showed that 15 mg of rivaroxaban daily reduced the risk of SSE in patients with Crcl 30–49 mL/min as effectively as warfarin (2.32% with rivaroxaban vs. 2.7% with warfarin events/100 patient-years; HR: 0.84 [95% CI, 0.57–1.23])<sup>47,48</sup>.

Apixaban, according to ARISTOTLE trial, is related to significantly lower yearly SSE risk than warfarin in patients with Crcl 25–50 mL/min when given in a 5 mg BID dose (2.1% with apixaban vs. 2.67% with warfarin per year; HR: 0.79 [95% CI, 0.55–1.44])<sup>49,50</sup>. Along with high efficacy in SSE prevention, it also significantly reduces all-cause mortality compared to warfarin<sup>51</sup>. The reduced 2.5 mg BID dose is less effective than the regular dose of apixaban<sup>13</sup>.

The participants of ENGAGE AF-TIMI with Crcl ≥ 50 mL/min received the standard dose of 60 mg edoxaban, which resulted in a reduced risk of SSE compared to warfarin (1.2% with edoxaban vs. 1.6% with warfarin, HR: 0.79 [97.5% CI: 0.63–0.99];  $p < 0.001$  for noninferiority)<sup>52</sup>. Patients with Crcl 30–50 mL/min received a reduced dose of 30 mg, which proved to be equally effective in SSE prevention as warfarin (2.3% edoxaban vs. 2.7% warfarin per year; HR: 0.87 [95% CI, 0.65–1.18])<sup>37</sup>. Interestingly, edoxaban has an upper cutoff line for GFR of 95 mL/min because patients with higher GFR had a higher incidence of ischemic strokes compared to not treated patients<sup>53</sup>.

#### *CKD 4–5 (Crcl < 30 mL/min)*

Once creatinine clearance progressively declines to 15–30 mL/min, especially after dialysis is initiated,

weighing the negative side effects and benefit of anticoagulation treatment becomes especially problematic due to the lack of RCTs on efficacy and safety of warfarin and DOACs in these patients<sup>11</sup>. In patients with CKD 4, all clinical guidelines allow the use of warfarin, although the overall benefit of taking any kind of oral anticoagulant treatment isn't proved by prospective RCTs in this group of patients, but only with observational studies<sup>10</sup>.

Patients with kidney failure spend a significantly shorter time period within the therapeutic INR range compared to patients with CKD 1–3<sup>19</sup>, which could be the reason for the discrepancy of the results of clinical research on patients with CKD 5 using warfarin. Data from the Danish dialysis registry show that warfarin reduces the SSE risk even in CKD 5 patients (HR: 0.44 [95% CI, 0.26–0.74])<sup>54</sup>, while the US dialysis registry showed that the SSE risk could even increase in CKD 5 patients using warfarin compared to those not treated with anticoagulants (HR: 1.93 [95% CI, 1.29–2.90])<sup>55</sup>.

Although the original DOAC RCTs excluded patients with Crcl < 25 mL/min, FDA and European Medicines Agency support the use of DOACs in these patients with a dose reduction according to the results of pharmacokinetic and/or pharmacodynamic studies<sup>56,57</sup>.

FDA allows the use of a specific low dose of dabigatran (75 mg BID) in patients with NVAF and Crcl 15–30 mL/min, based on the pharmacokinetic research on this subgroup of CKD patients. When Crcl falls beneath 15 mL/min, the mathematical relation between glomerular function and dabigatran plasma levels vanishes, so there is no recommended dose of dabigatran that would be both effective and safe for these patients<sup>5,57,58</sup>.

A few small pharmacokinetic studies on the efficacy and safety of rivaroxaban in CKD 5 showed that it is possible to achieve stable plasma levels of rivaroxaban in these patients, similar to the rivaroxaban plasma levels of healthy controls. It was achieved by giving the patients with Crcl < 15 mL/min a reduced dose of 10 mg<sup>24</sup>. Currently, there are no clinical studies to confirm the efficacy of this dosing regime<sup>24</sup>.

Apixaban is the only DOAC approved by the FDA for the use in patients with Crcl < 15 mL/min<sup>59</sup>, and its use in these patients is also supported by AHA/ACC/HRS<sup>13</sup> and EHRA<sup>12</sup> guidelines. Pharmacokinetic stud-

ies showed that the dose of 5 mg BID apixaban achieves suprathreshold plasma levels in dialyzed patients, while the reduced dose of 2.5 mg results in apixaban plasma levels similar to those found in patients with a preserved kidney function<sup>22</sup>. On the other hand, a large observational study found that apixaban 5 mg BID was associated with significantly lower risks of SSE (HR, 0.64; 95% CI, 0.42–0.97;  $P=0.04$ ) and death (HR, 0.63; 95% CI, 0.46–0.85;  $P=0.003$ ) than warfarin in dialyzed patients, while the 2.5 mg BID dose had no difference in SSE incidence (HR, 1.11; 95% CI, 0.82–1.50;  $P=0.49$ ) or death (HR, 1.07; 95% CI, 0.87–1.33;  $P=0.52$ ) compared to warfarin.<sup>60</sup>

According to pharmacokinetic research, the reduced dose of 15 mg edoxaban given to patients with CKD 5 achieves similar plasma levels, risk of bleeding, and biomarker profile as does the 30 or 60 mg dose in patients with normal or mildly reduced kidney function<sup>59</sup>. However, edoxaban is currently not approved for use in patients with Crcl < 30 mL/min<sup>24</sup>.

### *Risk of bleeding*

The risk of bleeding is the main indicator of the anticoagulant treatment's safety, as it is a relatively common and potentially life-threatening side-effect of these drugs. Clinical studies most commonly monitor the occurrence of major bleeding and also often evaluate clinically relevant non-major bleeding leading to a need for hospitalization or a change of anticoagulant treatment<sup>10</sup>.

#### *CKD 1–3 (Crcl ≥ 30 mL/min)*

The risk of bleeding in warfarin users is notably higher in CKD patients than in those with a healthy kidney function (HR: 1.33 [95% CI, 1.16–1.53])<sup>54</sup>. Warfarin associated bleeding is in 44% of the cases related to a suprathreshold INR<sup>61</sup>.

DOACs have been recognized in most clinical research to have a lower major bleeding risk than warfarin in patients with Crcl 50–80 mL/min<sup>40,62</sup>. Taking into account the linear correlation between kidney function and bleeding risk, users of DOACs with CKD should be carefully monitored, especially those with fluctuations in renal clearance<sup>14</sup>.

There is marked heterogeneity in the results of clinical research, which studied the occurrence of major bleeding in dabigatran users with CKD 1–3. Some

of those results showed that dabigatran 150 mg BID users have the same risk of major bleeding as warfarin users (5.5% per year each; HR: 1.0 [95% CI, 0.79–1.30])<sup>63</sup>, others found that dabigatran was associated with a much higher major bleeding risk than warfarin<sup>64,65</sup> and finally, some noted that dabigatran was related to a lower major bleeding risk as opposed to warfarin<sup>65</sup>. A possible explanation for this heterogeneity is the fact that these studies were made in different countries with different methods of patient follow-up, definitions of treatment outcomes, and tools for measuring the bleeding risk<sup>63</sup>.

According to an analysis of the ROCKET AF trial, the risk of major bleeding in rivaroxaban users is similar to that of warfarin users (4.5% with rivaroxaban vs. 4.7% with warfarin /100-patient years; HR: 0.95 [95% CI, 0.72–1.26])<sup>46</sup>. The existence of moderate CKD did not affect the relative safety profile of rivaroxaban compared to warfarin<sup>7,63</sup>.

An analysis of the ARISTOTLE trial explored the risk of major bleeding in patients using apixaban with CKD 1–3 and found that apixaban users had a significant reduction in major bleeding risk compared to those treated with warfarin (3.2% vs. 6.44% per year; HR: 0.5 [95% CI, 0.38–0.66]), which makes apixaban the oral anticoagulant with the lowest risk of major bleeding in patients with CKD 1–3<sup>49</sup>.

Edoxaban (in both dosing regimens) was proven in the ENGAGE AF-TIMI trial to have a significantly lower major bleeding risk in CKD 1–3 patients compared to warfarin (3.43% per year with warfarin, 2.75% with 60 mg edoxaban [HR: 0.80; 95% CI, 0.71 to 0.91;  $P < 0.001$ ], 1.61% with 30 mg edoxaban [HR: 0.47; 95% CI, 0.41 to 0.55;  $P < 0.001$ ])<sup>52</sup>.

#### *CKD 4–5 (Crcl < 30 mL/min)*

Thrombocyte aggregation and coagulation are often impaired in severe CKD, which could lead to life-threatening bleeding in combination with anticoagulant treatment. The most dangerous source of bleeding in dialyzed patients is the gastrointestinal tract, accounting for 3–7% of total deaths in this population<sup>66</sup>. Renal dysfunction causes alterations in hemostatic systems that may result in both a prothrombotic state and a bleeding diathesis<sup>5</sup>.

Severe CKD is an independent factor for supratherapeutic INR, and owing to the slower carboxylation of the coagulation factors in severe CKD patients, the

recovery of therapeutic INR can also be slower<sup>19</sup>, which further increases the risk of bleeding in these patients. Tan et al. examined the use of warfarin in dialysis patients with atrial fibrillation and discovered a statistically significant increase in bleeding incidence in these patients compared to those with milder forms of CKD<sup>67</sup>.

The amount of available data on the safety of DOACs in CKD 5 patients is very limited. Bhatia et al. found that DOACs seem to be relatively safe in CKD 4–5 patients (Crcl < 30 mL/min) with a similar incidence of bleeding as it is in the CKD 3 group (Crcl 30 – 49 mL/min)<sup>10</sup>. Other research showed comparable bleeding risk with DOACs in patients with Crcl < 30 mL/min to that of warfarin users with the same stage of CKD<sup>14,68</sup>.

Most of the research on DOAC safety in CKD 4–5 is made with apixaban. One research showed that the incidence of bleeding in patients with Crcl < 25 mL/min is roughly the same with the use of apixaban as with the use of warfarin<sup>14</sup>, while others show a statistically significant decrease of major bleeding with apixaban<sup>67,68</sup>, or a decrease of bleeding without the statistical significance<sup>10</sup>.

The XANTUS study explored the difference in bleeding frequency in patients with severe CKD to those with mild or moderate CKD and concluded that patients with CKD 4–5 who received 15 mg of rivaroxaban experienced more major bleeding than those with Crcl  $\geq$  50 mL/min<sup>68</sup>.

#### *Progression of kidney disease and acute kidney injury*

Doubling of serum creatinine is considered a measure of kidney disease progression according to the FDA<sup>51</sup>. Since 2012, FDA and National Kidney Foundation approved an increase of GFR by 30% as a new measurement of kidney disease progression<sup>69</sup>. A progressive decrease of kidney function in patients using the anticoagulant treatment (either DOACs or warfarin) is relatively common. Yao et al. found that 1 out of 4 patients treated with anticoagulants has a 30% increase of GFR, while 1 out of 7 has an acute kidney injury (AKI) within 2 years of starting the anticoagulant treatment<sup>51</sup>.

Comparing the progression of kidney disease in DOAC users with warfarin users, most of the studies show that progression is more frequent and faster with

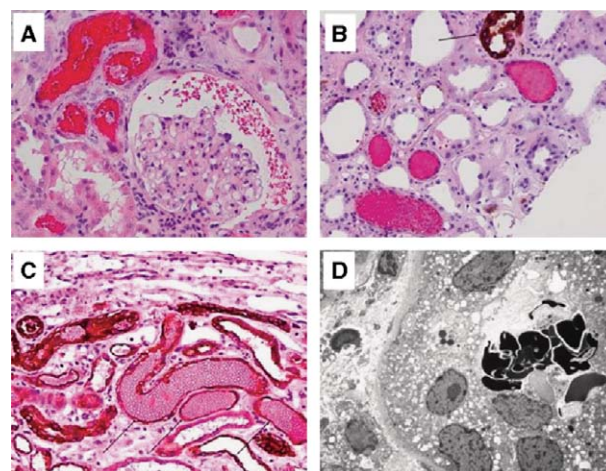
the use of warfarin than with DOACs<sup>2,51,70</sup>. Yao *et al.* observed that the frequency of 30% increase of GFR is highest in warfarin-treated patients whose INR was > 3 IU. However, the warfarin users with INR < 2 IU or 2 – 3 IU were also related to a greater GFR decline than patients treated with DOACs, which could indicate that warfarin related progression of CKD is not only attributable to poor INR control, but also may be influenced by off-target effects of warfarin<sup>51</sup>. AKI is also more common in warfarin users in comparison to DOAC users, with a difference of as much as 21% in the general population. This difference is seen only in patients with Crcl  $\geq$  30 mL/min, while those with Crcl < 30 mL/min AKI is more frequently related to DOAC use<sup>71</sup>.

As reported by a post hoc analysis of RCTs, dabigatran is related to the lowest risk of a 30% decline in GFR (HR: 0.72 [95% CI: 0.56–0.93]) and AKI (HR: 0.55 [95% CI: 0.40–0.77]) among DOACs. Rivaroxaban was also associated with a lower risk of 30% decline in GFR (HR: 0.73 [95% CI: 0.62–0.87]), doubling of serum creatinine (HR: 0.46 [95% CI: 0.28 – 0.75]), and AKI (HR: 0.69 [95% CI: 0.57–0.84]) compared to warfarin. Apixaban was associated with a lower risk of a 30% decline in GFR, AKI, and doubling of serum creatinine, but the difference was not statistically significant<sup>51</sup>. DOACs could have a potential protective effect on kidney function because they inhibit factor Xa and thrombin, which are associated with vascular inflammation<sup>51,72,73</sup>. However, this assumption is still highly speculative because the only renal outcome evaluated in the pivotal RCTs was GFR decline<sup>51,70</sup>.

### Anticoagulant related nephropathy

Anticoagulant related nephropathy (ARN) is a type of AKI affecting users of oral anticoagulants and is most commonly found in CKD patients, but can also occur in patients with a previously healthy kidney function<sup>74</sup>. It is far more common in warfarin users, but a few case reports of ARN related to DOAC use have been noted<sup>75,76,77</sup>. Histological findings of ARN in kidney parenchyma show glomerular hemorrhages with occlusive red blood cell casts, mostly in distal segments of nephrons, indicating glomerular hematuria<sup>78</sup>.

Since the diagnosis is predominantly made based on the increase in serum creatinine levels and a patient history of using oral anticoagulants, without the final



*Figure 1. Typical kidney biopsy findings in anticoagulant related nephropathy. (A) Red blood cells (RBC) in Bowman space and RBC occlusive tubule casts. (B) Immunohistochemical stain shows that most RBC casts do not contain Tamm-Horsfall protein. (C) Immunohistochemical stain for cytokeratin AE1/AE3 (arrows, dark brown) highlights distal tubules with occlusive RBC casts. (D) Dysmorphic RBCs seen in several tubules by means of electron microscopy. Represented with permission from Brodsky, S., Eikelboom J., Hebert LA. Anticoagulant-Related Nephropathy. JASN December 2018, 29 (12) 2787–2793<sup>79</sup>.*

confirmation by kidney biopsy and pathohistological analysis, the accurate incidence of ARN is not known. However, taking into account its high mortality rate and serious complications, it is an important factor to acknowledge while choosing anticoagulant treatment for CKD patients<sup>74</sup>. The exact mechanism of ARN development is not yet fully understood, but three theories suggest possible pathways of ARN occurrence. The first theory explains the mechanism of ARN development in warfarin users. Warfarin inhibits the activation of vitamin K by inhibiting the matrix Gla protein and a specific growth restriction gene (GAS-6). Matrix Gla protein and GAS-6 inhibit vascular calcification as well as migration and apoptosis of vascular smooth muscle cells<sup>80</sup>, while GAS-6 also regulates the proliferation of mesangial cells<sup>81</sup>. By inhibiting vitamin K, this protection of blood vessels (including glomerular capillaries) decreases, disrupting the glomerular hemodynamics and making it susceptible to glomerular bleeding and renal insufficiency<sup>81</sup>. The second proposed mechanism explains the development of ARN in dab-

igatran users and is achieved by thrombin and its receptor, Protease-activated receptor 1 (PAR-1)<sup>76</sup>. PAR-1 is found on endothelial cells where it regulates vascular permeability, leukocyte migration and adhesion<sup>82</sup>. Although warfarin and dabigatran act via different mechanisms, they both decrease thrombin activity<sup>83</sup> and, therefore, indirectly cause dysfunction of the glomerular barrier<sup>76</sup>. Glomerular barrier dysfunction enables erythrocytes to pass into the tubular system of the nephron and the surrounding interstitium. Additionally, hem derived from the erythrocytes damages the tubular epithelium through a toxic and proinflammatory effect<sup>84</sup>.

Patients with ARN recover to various extents. Some regain a normal kidney function, while more than two-thirds of patients require life-term hemodialysis<sup>3,78</sup>. At the moment, there are no available clinical guidelines for the treatment of ARN. Vitamin K has proven effective in preventing ARN in 5/6 nephrectomized rats. Cases of dabigatran-induced ARN have been reported where idarucizumab was administered and followed by recovery of kidney function<sup>84</sup>. However, high-quality evidence of effective treatment of ARN patients is still lacking<sup>2</sup>.

## Discussion

Choosing an anticoagulant drug that is both effective in preventing SSE and safe for patients with AF and CKD is highly challenging. For patients with valvular AF, the only anticoagulant option is warfarin because DOACs are contraindicated in this case<sup>13</sup>. Considering patients with CKD 1–3 were included in anticoagulant RCTs, there is high-quality evidence on the efficacy and safety of these drugs and clear guidelines on their usage. Contemporary guidelines suggest using DOACs as an anticoagulant treatment for patients with NVAF and CKD 1–3<sup>12,13,15,42,43,44</sup>, and it is up to the clinician to decide which specific drug to prescribe based on the patients' clinical characteristics and comorbidities. For patients with NVAF, CKD 1–3 (Crcl  $\geq$  30 mL/min), a high CHA<sub>2</sub>DS<sub>2</sub>-VASc score and a low risk of bleeding, a reasonable option would be dabigatran in the 150 mg BID dose<sup>41</sup> because of its high efficacy in preventing SSE<sup>46</sup> and a low risk of CKD progression<sup>51</sup>. On the other hand, patients with higher bleeding risk and CKD 1–3 could benefit more

from apixaban 5 mg BID, seeing it has the best safety profile among all anticoagulant drugs<sup>49</sup>. Choosing an anticoagulant drug becomes even more complex in patients with CKD 4–5 (Crcl < 30 mL/min). These patients have a greater risk of both SSE and bleeding as a result of the defect in hemostasis caused by uremia<sup>9</sup>. Experts' opinions differ, not only on which anticoagulant drug to use but also if it is even safe to initiate any kind of anticoagulant treatment in this group of patients<sup>13</sup>. Since patients with CKD 4–5 weren't included in the anticoagulant RCTs, there is no high-quality evidence on efficacy and safety of anticoagulants in patients with Crcl < 30 mL/min, which is why the guidelines recommendations are of lower strength<sup>13</sup>. Most of the guidelines approve the use of warfarin in patients with Crcl < 30 mL/min, although their INR is often outside of the therapeutic range, which is related to common and dangerous major bleeding<sup>67</sup>. The progression of CKD is faster in warfarin users compared to DOACs users, often leading to the need for hemodialysis<sup>51</sup>. Furthermore, warfarin users are much more likely to develop ARN, which in most cases leads to permanent kidney failure<sup>78</sup>. DOACs are rarely used in patients with CKD 4–5 because of their high proportion of renal clearance. However, pharmacokinetic studies have found reduced doses of each DOAC that should be effective in preventing SSE and safe in terms of bleeding risk for CKD 4 patients, as well as reduced doses of all DOACs, except for dabigatran, for CKD 5 patients. To conclude, there seem to be more negative effects of warfarin, including accelerated deterioration of renal function and increased risk of bleeding, than there are with DOACs, which suggests that DOACs are at least equally effective and a safer option for anticoagulant treatment of patients with both AF and CKD 1–4, while rivaroxaban, apixaban, and edoxaban could be a better option for CKD 5 patients.

There are some limitations to this study. During the literature assessment, no clinical studies comparing DOACs efficacy among themselves were found, only studies comparing an individual DOAC to warfarin. There were also no studies evaluating each anticoagulant agent in every stage of CKD. Finally, studies involved in this assessment had different outcome definitions and study designs, which could have influenced their results.



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## Sažetak

## ANTIKOAGULANTNA TERAPIJA U BOLESNIKA S FIBRILACIJOM ATRIJA I KRONIČNOM RENALNOM INSUFICIJENCIJOM

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Cilj: istražiti učinkovitost i sigurnost svakog pojedinog antikoagulantnog lijeka i odrediti najbolju terapijsku opciju za bolesnike s fibrilacijom atrijske (AF) i kroničnom bubrežnom bolešću (CKD-om).

Metode i materijali: Napravljen je pregled literature dostupne na Pubmedu/MEDLINEu u potrazi za istraživanjima o učinkovitosti, sigurnosti, farmakokinetici i farmakodinamici izravnih oralnih antikoagulanasa (DOAC) i varfarina u bolesnika s CKD-om.

Rezultati: DOAC-i su terapija izbora za bolesnike s CKD 1-3 (Crcl  $\geq$  30 mL/min) zahvaljujući visokoj učinkovitosti, dobrom sigurnosnom profilu i manje interakcija s lijekovima i hranom. Za bolesnike s CKD 4 (Crcl 15 - 29 mL/min) ne postoje tako snažne preporuke koji antikoagulantni lijek je najbolja opcija, a izbor antikoaguacije za bolesnike s CKD 5 (Crcl <15 mL/min) trenutno je ograničen na varfarin i apiksaban. Međutim, čini se da postoji više negativnih aspekata varfarina nego DOAC-a, uključujući ubrzanu progresiju CKD-a i povišen rizik krvarenja.

Zaključak: S obzirom na njihov dobar sigurnosni profil i mogućnost ostvarivanja zadovoljavajućeg antikoagulantnog učinka apiksabana, rivaroksabana te apiksabana i u teškoj CKD-u, DOAC-i bi mogli biti bolja terapijska opcija za bolesnika s AF-om i CKD-om.

Ključne riječi: *fibrilacija atrijske, antikoagulantna terapija, kronična bubrežna bolest*