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Original Scientific Paper

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 ≥ 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[1]. It is associated with a significantly increased risk of ischemic stroke and systemic thromboembolism (SSE) compared to healthy individuals[2]. 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[3]. 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[4]. 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[5]. Prevalence of both AF and CKD increases with age, as well as their simultaneous appearance[6]. 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[7]. 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_2DS_2-VASc score (which includes TIA, age ≥ 75 years, heart failure, hypertension, diabetes, female sex, age 65 – 75 years, and atherosclerotic vascular disease)[8]. 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[9]. Bleeding is also the most common reason for stopping anticoagulation in the general population[10]. 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[11]. 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 consummation[12].

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 Cockroft-Gault equation), with additional dosing criteria for apixaban in the cases of age ≥ 80 years and body mass ≤ 60kg[13]. The Cockroft-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[14].

The kidney function needs to be monitored at least once a year in DOAC users. In the case of Crcl ≤ 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[12,14]. 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^2 (mL/min/1.73 m^2). There are five stages of CKD; CKD 1 (normal kidney function, GFR ≥ 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)[15].

According to the available literature, the safety and efficacy of oral anticoagulants are different in the group of patients with CKD 1–3 (Crcl ≥ 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%[23, a]	9 – 17 h[23]	150 mg BID[23]	110 mg BID, 75 mg[23, b]	Valvular atrial fibrillation, severe renal impairment (Crcl < 15 mL/min)[12]
Rivaroxaban	66%[24,25]	6 – 13 h[25]	20 mg OD[23]	15 mg OD[23, b]	Valvular atrial fibrillation, severe renal impairment (Crcl < 15 mL/min) or advanced liver disease[26]
Apixaban	50 %[27]	12 h[27]	5 mg BID[12]	2.5 mg BID[c]	Valvular atrial fibrillation, Serum creatinine >2.5 mg/dL or Crcl <25 mL/min[12]
Edoxaban	60 %[12]	12h[12]	60 mg OD[12]	30 mg OD[d]	Valvular atrial fibrillation, severe renal impairment (Crcl < 15 mL/min) or advanced liver disease[12]

[a] the oral bioavailability of dabigatran etexilate increases by 75% [23]
[b] in the presence of renal insufficiency (Crcl < 50 mL/min) [23]
[c] 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 [12]
[d] if the CrCl is < 50 mL/min or body weight is less than 60 kg [12]

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[16]. 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[16]. 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[17]. Rivaroxaban, apixaban, and edoxaban are direct inhibitors of factor Xa, both the free plasmatic form and thrombus embedded one[17].

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[18]. Consequently, patients with severe CKD should receive a 20% lower dose of warfarin compared to those with a healthy kidney function[19]. This phenomenon was explained by animal studies, which showed a significant 40–85% downregulation of hepatic cytochrome P-450 in CKD[20]. As a result of being metabolized by cytochrome P-450, warfarin interacts with many other drugs that influence the cytochrome's action, including cytochrome P-450 inductors (e.g., carbamazepine, barbiturates, rifampin) and cytochrome P-450 inhibitors (e.g., amiodarone, cimetidine)[21].

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[12]. 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[12]. Many of those P-gp inhibitors are used in treating cardiac arrhythmias (e.g., verapamil, amiodarone, dronedarone)[12]. DOACs are also partially metabolized by cytochrome P-450, but interactions with other drugs are far less extensive than with warfarin[12]. 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[22]. 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[14]. Edoxaban, rivaroxaban, and apixaban are all primarily bound to plasma proteins and can not be eliminated by hemodialysis[14,28,29,30]. Contrarily, dabigatran is successfully eliminated by dialysis[7].

Dabigatran is mostly (80%) eliminated through renal excretion[12], and its pharmacokinetics is the most

altered by CKD among DOACs[7]. 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[7].

Rivaroxaban is excreted renally (66%) and via biliary route[7]. Renal insufficiency only partially impacts the elimination of rivaroxaban, even in the cases of severe CKD[31]. 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[7,25,31].

Apixaban elimination occurs via renal (27%) and nonrenal pathways[7]. 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[7,32].

Edoxaban is eliminated 50% renally and 50% nonrenally[7]. 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[7,33].

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[34]. It is equally effective in patients with CKD 1–3 (Crcl ≥ 30) as it is in the general population[14,35,36], reducing the incidence of SSE in CKD 3 patients by as much as 76%[36].

DOACs are as effective or superior to warfarin in decreasing the risk of SSE in the general population[5]. 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[37,38,39]. 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[11,40,41]. 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[12,17,42,43,44].

Dabigatran given in 150 mg BID dose showed to be highly effective in the RE-LY trial[41]. 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])[45]. 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])[46].

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])[47,48].

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])[49,50]. Along with high efficacy in SSE prevention, it also significantly reduces all-cause mortality compared to warfarin[51]. The reduced 2.5 mg BID dose is less effective than the regular dose of apixaban[13].

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)[52]. 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])[37]. 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[53].

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[11]. 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[10].

Patients with kidney failure spend a significantly shorter time period within the therapeutic INR range compared to patients with CKD 1–3[19], 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])[54], 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])[55].

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[56,57].

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[5,57,58].

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[24]. Currently, there are no clinical studies to confirm the efficacy of this dosing regime[24].

Apixaban is the only DOAC approved by the FDA for the use in patients with Crcl < 15 mL/min[59], and its use in these patients is also supported by AHA/ACC/HRS[13] and EHRA[12] guidelines. Pharmacokinetic studies showed that the dose of 5 mg BID apixaban achieves supratherapeutic 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[22]. 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.[60]

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[59]. However, edoxaban is currently not approved for use in patients with Crl < 30 mL/min[24].

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[10].

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])[54]. Warfarin associated bleeding is in 44% of the cases related to a supratherapeutic INR[61].

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[40,62]. 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[14].

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])[63], others found that dabigatran was associated with a much higher major bleeding risk than warfarin[64,65] and finally, some noted that dabigatran was related to a lower major bleeding risk as opposed to warfarin[65]. 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[63].

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])[46]. The existence of moderate CKD did not affect the relative safety profile of rivaroxaban compared to warfarin[7,63].

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[49].

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])[52].

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[66]. Renal dysfunction causes alterations in hemostatic systems that may result in both a prothrombotic state and a bleeding diathesis[5].

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[19], 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[67].

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)[10]. 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[14,68].

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[14], while others show a statistically significant decrease of major bleeding with apixaban[67,68], or a decrease of bleeding without the statistical significance[10].

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 ≥ 50 mL/min[68].

Progression of kidney disease and acute kidney injury

Doubling of serum creatinine is considered a measure of kidney disease progression according to the FDA[51]. Since 2012, FDA and National Kidney Foundation approved an increase of GFR by 30% as a new measurement of kidney disease progression[69]. 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[51].

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[2,51,70]. 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[51]. 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 ≥ 30 mL/min, while those with Crcl < 30 mL/min AKI is more frequently related to DOAC use[71].

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[51]. DOACs could have a potential protective effect on kidney function because they inhibit factor Xa and thrombin, which are associated with vascular inflammation[51,72,73]. However, this assumption is still highly speculative because the only renal outcome evaluated in the pivotal RCTs was GFR decline[51,70].

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[74]. It is far more common in warfarin users, but a few case reports of ARN related to DOAC use have been noted[75,76,77]. 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[78].

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 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[74]. 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[80], while GAS-6 also regulates the proliferation of mesangial cells[81]. 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[81]. The second proposed mechanism explains the development of ARN in dab-

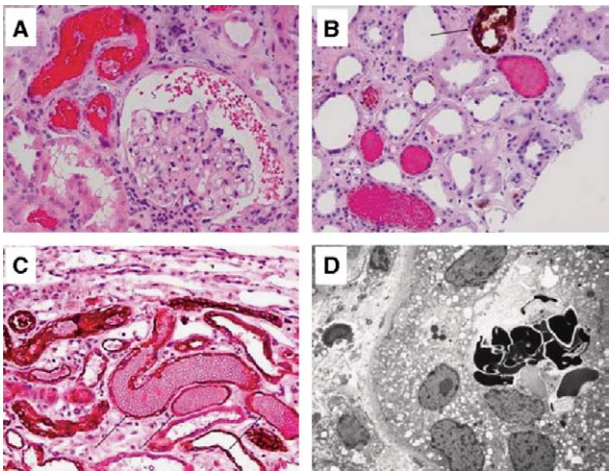

Figure 1. Typical kidney biopsy findings in anticoagulant related nephropathy. (A) Red blood cells (RBC) in Bowman space and RBC occlusive tubule casts. (B) Immunohistochemical stain shows that most RBC casts do not contain Tamm–Horsfall protein. (C) Immunohistochemical stain for cytokeratin AE1/AE3 (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[79].

igatran users and is achieved by thrombin and its receptor, Protease-activated receptor 1 (PAR-1)[76]. PAR-1 is found on endothelial cells where it regulates vascular permeability, leukocyte migration and adhesion[82]. Although warfarin and dabigatran act via different mechanisms, they both decrease thrombin activity[83] and, therefore, indirectly cause dysfunction of the glomerular barrier[76]. 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[84].

Patients with ARN recover to various extents. Some regain a normal kidney function, while more than two-thirds of patients require life-term hemodialysis[3,78]. 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[84]. However, high-quality evidence of effective treatment of ARN patients is still lacking[2].

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[13]. 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 [12,13,15,42,43,44], 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 ≥ 30 mL/min), a high CHA_2DS_2-VASc score and a low risk of bleeding, a reasonable option would be dabigatran in the 150 mg BID dose[41] because of its high efficacy in preventing SSE[46] and a low risk of CKD progression[51]. 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[49]. 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[9]. 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[13]. 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 strenght[13]. 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[67]. The progression of CKD is faster in warfarin users compared to DOACs users, often leading to the need for hemodialysis[51]. Furthermore, warfarin users are much more likely to develop ARN, which in most cases leads to permanent kidney failure[78]. 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.

References

1. Heeringa J, van der Kuip DA, Hofman A, Kors JA, van Herpen G, Stricker BH, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. Eur Heart J. 2006 Apr;27(8):949-53. doi: 10.1093/eurheartj/ehi825
2. Zhang C, Gu ZC, Shen L, Pan MM, Yan YD, Pu J, et al. Non-vitamin K Antagonist Oral Anticoagulants and Cognitive Impairment in Atrial Fibrillation: Insights From the Meta-Analysis of Over 90,000 Patients of Randomized Controlled Trials and Real-World Studies. Front Aging Neurosci. 2018 Oct 2;10:258. doi: 10.3389/fnagi.2018.00258.
3. Oliver T, Salman LA, Ciaudelli B, Cohen DA. Anticoagulation-Related Nephropathy: The Most Common Diagnosis You've Never Heard Of. Am J Med. 2019 Aug;132(8):e631-e633. doi: 10.1016/j.amjmed.2019.02.038
4. Almutairi AR, Zhou L, Gellad WF, Lee JK, Slack MK, Martin JR, L, et al. Effectiveness and Safety of Non-vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-analyses. Clin Ther. 2017 Jul;39(7):1456-1478.e36. doi: 10.1016/j.clinthera.2017.05.358.
5. Kumar S, Lim E, Covic A, Verhamme P, Gale CP, Camm AJ, et al. Anticoagulation in Concomitant Chronic Kidney Disease and Atrial Fibrillation: JACC Review Topic of the Week. J Am Coll Cardiol. 2019 Oct 29;74(17):2204-2215. doi: 10.1016/j.jacc.2019.08.1031.
6. Ananthapanyasut W, Napan S, Rudolph EH, Harindhanavudhi T, Ayash H, Guglielmi KE, et al. Prevalence of Atrial Fibrillation and Its Predictors in Nondialysis Patients with Chronic Kidney Disease. CJASN. 2009;5(2):173-181. doi: 10.2215/cjn.03170509
7. Weir MR, Kreutz R. Influence of Renal Function on the Pharmacokinetics, Pharmacodynamics, Efficacy, and Safety of Non-Vitamin K Antagonist Oral Anticoagulants. Mayo Clin Proc. 2018 Oct;93(10):1503-1519. doi: 10.1016/j.mayocp.2018.06.018.
8. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb;137(2):263-72. doi: 10.1378/chest.09-1584
9. Sohal AS, Gangji AS, Crowther MA, Treleaven D. Uremic bleeding: pathophysiology and clinical risk factors. Thromb Res. 2006;118(3):417-22. doi: 10.1016/j.thromres.2005.03.032.
10. Bhatia HS, Bailey J, Unlu O, Hoffman K, Kim RJ. Efficacy and safety of direct oral anticoagulants in patients with atrial fibrillation and chronic kidney disease. Pacing Clin Electrophysiol. 2019 Nov;42(11):1463-1470. doi: 10.1111/pace.13811.
11. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005 Apr;3(4):692-4. doi: 10.1111/j.1538-7836.2005.01204.x.
12. Steffel J, Verhamme P, Potpara TS, Albaladejo P, Antz M, Desteghe L, et al.; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018 Apr 21;39(16):1330-1393. doi: 10.1093/eurheartj/ehy136.
13. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019 Jul 9;74(1):104-132. doi: 10.1016/j.jacc.2019.01.011.
14. Shroff GR, Stoecker R, Hart A. Non–Vitamin K–Dependent Oral Anticoagulants for Nonvalvular Atrial Fibrillation in Patients With CKD: Pragmatic Considerations for the Clinician. AJKD. 2018;72(5):717–727. doi: 10.1053/j.ajkd.2018.02.360
15. Turakhia MP, Blankestijn PJ, Carrero JJ, Clase CM, Deo R, Herzog CA, et al. Chronic kidney disease and arrhythmias: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Eur Heart J. 2018 Jun 21;39(24):2314-2325. doi: 10.1093/eurheartj/ehy060.
16. Limdi NA, Limdi MA, Cavallari L, Anderson AM, Crowley MR, Baird MF, et al. Warfarin dosing in patients with impaired kidney function. Am J Kidney Dis. 2010 Nov;56(5):823-31. doi: 10.1053/j.ajkd.2010.05.023.
17. Manning WJ, Singer DE, Lip G. Atrial fibrillation: Anticoagulant therapy to prevent thromboembolism. In G. M. Saperia (Ed.), UpToDate.2019.
18. Holden RM, Clase CM. Use of Warfarin in People with Low Glomerular Filtration Rate or on Dialysis. Seminars in Dialysis. 2009;22(5):503-511.doi:10.1111/j.1525-139x.2009.00632.x
19. Limdi NA, Beasley TM, Baird MF, Goldstein JA, McGwin G, Arnett DK, et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. J Am Soc Nephrol. 2009 Apr;20(4):912-21. doi: 10.1681/ASN.2008070802.
20. Dreisbach AW, Lertora JJ. The effect of chronic renal failure on drug metabolism and transport. Expert Opin Drug Metab Toxicol. 2008 Aug;4(8):1065-74. doi: 10.1517/17425255.4.8.1065.
21. Vazquez SR. Drug-drug interactions in an era of multiple anticoagulants: a focus on clinically relevant drug interactions. Hematology Am Soc Hematol Educ Program. 2018 Nov 30;2018(1):339-347. doi: 10.1182/asheducation-2018.1.339.
22. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W. The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. Drug Metab Dispos. 2008 Feb;36(2):386-99. doi: 10.1124/dmd.107.019083.
23. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association

Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015 Oct;17(10):1467-507. doi: 10.1093/europace/euv309.

24. Kreutz R. Pharmacodynamic and pharmacokinetic basics of rivaroxaban. Fundam Clin Pharmacol. 2012 Feb;26(1):27-32. doi: 10.1111/j.1472-8206.2011.00981.x
25. Kubitza D, Becka M, Roth A, Mueck W. Dose-escalation study of the pharmacokinetics and pharmacodynamics of rivaroxaban in healthy elderly subjects. Curr Med Res Opin. 2008 Oct;24(10):2757-65. doi: 10.1185/03007990802361499
26. Diener HC, Aisenberg J, Ansell J, Atar D, Breithardt G, Eikelboom J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. Eur Heart J. 2017 Mar 21;38(12):860-868. doi: 10.1093/eurheartj/ehw069
27. Raghavan N, Frost CE, Yu Z, He K, Zhang H, Humphreys WG, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. Drug Metab Dispos. 2009 Jan;37(1):74-81. doi: 10.1124/dmd.108.023143
28. Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients. J Am Soc Nephrol. 2017 Jul;28(7):2241-2248. doi: 10.1681/ASN.2016090980
29. Dias C, Moore KT, Murphy J, Ariyawansa J, Smith W, Mills RM, et al. Pharmacokinetics, Pharmacodynamics, and Safety of Single-Dose Rivaroxaban in Chronic Hemodialysis. Am J Nephrol. 2016;43(4):229-36. doi: 10.1159/000445328
30. De Vriese AS, Caluwé R, Bailleul E, De Bacquer D, Borrey D, Van Vlem B, et al. Dose-finding study of rivaroxaban in hemodialysis patients. Am J Kidney Dis. 2015 Jul;66(1):91-8. doi: 10.1053/j.ajkd.2015.01.022
31. Kubitza D, Becka M, Mueck W, Halabi A, Maatouk H, Klause N, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. Br J Clin Pharmacol. 2010 Nov;70(5):703-12. doi: 10.1111/j.1365-2125.2010.03753.x
32. Chang M, Yu Z, Shenker A, Wang J, Pursley J, Byon W, et al. Effect of renal impairment on the pharmacokinetics, pharmacodynamics, and safety of apixaban. J Clin Pharmacol. 2016 May;56(5):637-45. doi: 10.1002/jcph.633
33. Parasrampuria, D.A., Truitt, K.E. Pharmacokinetics and Pharmacodynamics of Edoxaban, a Non-Vitamin K Antagonist Oral Anticoagulant that Inhibits Clotting Factor Xa. Clin Pharmacokinet 55, 641–655 (2016). https://doi.org/10.1007/s40262-015-0342-7
34. Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med. 2003 Sep 11;349(11):1019-26. doi: 10.1056/NEJMoa022913
35. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007 Jun 19;146(12):857-67. doi: 10.7326/0003-4819-146-12-200706190-00007.
36. Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. Clin J Am Soc Nephrol. 2011 Nov;6(11):2599-604. doi: 10.2215/CJN.02400311
37. Bohula EA, Giugliano RP, Ruff CT, Kuder JF, Murphy SA, Antman EM, et al. Impact of Renal Function on Outcomes With Edoxaban in the ENGAGE AF-TIMI 48 Trial. Circulation. 2016 Jul 5;134(1):24-36. doi: 10.1161/CIRCULATIONAHA.116.022361
38. Hijazi Z, Hohnloser SH, Andersson U, Alexander JH, Hanna M, Keltai M, et al. Efficacy and Safety of Apixaban Compared With Warfarin in Patients With Atrial Fibrillation in Relation to Renal Function Over Time: Insights From the ARISTOTLE Randomized Clinical Trial. JAMA Cardiol. 2016 Jul 1;1(4):451-60. doi: 10.1001/jamacardio.2016.1170
39. Eikelboom JW, Connolly SJ, Gao P, Paolasso E, De Caterina R, Husted S, et al. Stroke risk and efficacy of apixaban in atrial fibrillation patients with moderate chronic kidney disease. J Stroke Cerebrovasc Dis. 2012 Aug;21(6):429-35. doi: 10.1016/j.jstrokecerebrovasdis.2012.05.007
40. Ashley J, Sood MM. Novel oral anticoagulants in chronic kidney disease: ready for prime time? Curr Opin Nephrol Hypertens. 2018 May;27(3):201-208. doi: 10.1097/MNH.0000000000000410.
41. Hammwöhner M, Goette A. Kidney diseases and NOAC therapy: Is there a light at the end of the tunnel? International Journal of Cardiology. 2017;236:162–163.doi: 10.1016/j.ijcard.2017.01.066
42. Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest. 2018 Nov;154(5):1121-1201. doi: 10.1016/j.chest.2018.07.040
43. Andrade JG, Aguilar M, Atzema C, Bell A, Cairns JA, Cheung CC, et al. The 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society Comprehensive Guidelines for the Management of Atrial Fibrillation. Can J Cardiol. 2020 Dec;36(12):1847-1948. doi: 10.1016/j.cjca.2020.09.001
44. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2020 Aug 29:ehaa612. doi: 10.1093/eurheartj/ehaa612
45. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51. doi: 10.1056/NEJMoa0905561. Epub 2009 Aug 30. Erratum in: N Engl J Med. 2010 Nov 4;363(19):1877
46. Hijazi Z, Hohnloser SH, Oldgren J, et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY (Randomized Evaluation of Long-term Anticoagulation Therapy) trial analysis. Circulation. 2014 Mar;129(9):961-970. DOI: 10.1161/circulationaha.113.003628.

47. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91. doi: 10.1056/NEJMoa1009638

48. Fox KA, Piccini JP, Wojdyla D, Becker RC, Halperin JL, Nessel CC, et al. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in patients with non-valvular atrial fibrillation and moderate renal impairment. Eur Heart J. 2011 Oct;32(19):2387-94. doi: 10.1093/eurheartj/ehr342

49. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981-92. doi: 10.1056/NEJMoa1107039

50. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, et al. Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J. 2012 Nov;33(22):2821-30. doi: 10.1093/eurheartj/ehs274

51. Yao X, Tangri N, Gersh BJ, Sangaralingham LR, Shah ND, Nath KA, et al. Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation. J Am Coll Cardiol. 2017 Nov 28;70(21):2621-2632. doi: 10.1016/j.jacc.2017.09.1087

52. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013 Nov 28;369 (22):2093-104. doi: 10.1056/NEJMoa1310907.

53. Weber J, Olyaei A, Shatzel J. The efficacy and safety of direct oral anticoagulants in patients with chronic renal insufficiency: A review of the literature. Eur J Haematol. 2019 Apr;102 (4):312-318. doi: 10.1111/ejh.13208

54. Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012 Aug 16;367(7):625-35. doi: 10.1056/NEJMoa1105594

55. Chan KE, Lazarus JM, Thadhani R, Hakim RM. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol. 2009 Oct; 20(10):2223-33. doi: 10.1681/ASN.2009030319

56. Hariharan S, Madabushi R. Clinical pharmacology basis of deriving dosing recommendations for dabigatran in patients with severe renal impairment. J Clin Pharmacol. 2012 Jan;52 (1 Suppl):119S-25S. doi: 10.1177/0091270011415527

57. Lehr T, Haertter S, Liesenfeld K, Staab A, Clemens A, Reilly PA, et al. Dabigatran Etexilate in Atrial Fibrillation Patients With Severe Renal Impairment: Dose Identification Using Pharmacokinetic Modeling and Simulation. J. Clin. Pharmacol. 2012*; 52*(9): 1373-1378. doi: 10.1177/0091270011417716

58. Steuber TD, Shiltz DL, Cairns AC, Ding Q, Binger KJ, Courtney JR. A Multicenter Analysis of Factors Associated With Apixaban-Related Bleeding in Hospitalized Patients With End-Stage Renal Disease on Hemodialysis. Annals of Pharmacotherapy. 2017; 51(11): 954-960. doi:10.1177/1060028017717282

59. Koretsune Y, Yamashita T, Kimura T, Fukuzawa M, Abe K, Yasaka M. Short-Term Safety and Plasma Concentrations of Edoxaban in Japanese Patients With Non-Valvular Atrial Fibrillation and Severe Renal Impairment. Circ J. 2015;79(7): 1486-95. doi: 10.1253/circj.CJ-14-0942

60. Siontis KC, Zhang X, Eckard A, Bhave N, Schaubel DE, He K, et al. Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States. Circulation. 2018 Oct 9;138(15):1519-1529. doi: 10.1161/CIRCULATIONAHA.118.035418

61. Oake N, Fergusson DA, Forster AJ, van Walraven C. Frequency of adverse events in patients with poor anticoagulation: a meta-analysis. CMAJ. 2007 May 22;176(11):1589-94. doi: 10.1503/cmaj.061523.

62. Bai Y, Chen H, Yang Y, Li L, Liu XY, Shi XB, et l. Safety of antithrombotic drugs in patients with atrial fibrillation and non-end-stage chronic kidney disease: Meta-analysis and systematic review. Thromb Res. 2016 Jan;137:46-52. doi: 10.1016/j.thromres.2015.11.020.

63. Almutairi AR, Zhou L, Gellad WF, Lee JK, Slack MK, Martin JR, et al. Effectiveness and Safety of Non–vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-analyses. Clinical Therapeutics. 2017;39(7).doi:10.1016/j.clinthera.2017.05.358

64. Hernandez I, Baik SH, Piñera A, Zhang Y. Risk of bleeding with dabigatran in atrial fibrillation. JAMA Intern Med. 2015 Jan;175(1):18-24. doi: 10.1001/jamainternmed.2014.5398

65. Adeboyeje G, Sylwestrzak G, Barron JJ, White J, Rosenberg A, Abarca J, et al. Major Bleeding Risk During Anticoagulation with Warfarin, Dabigatran, Apixaban, or Rivaroxaban in Patients with Nonvalvular Atrial Fibrillation. J Manag Care Spec Pharm. 2017 Sep;23(9):968-978. doi: 10.18553/jmcp.2017.23.9.968.

66. Boyle JM, Johnston B. Acute upper gastrointestinal hemorrhage in patients with chronic renal disease. The American Journal of Medicine. 1983;75(3):409-412.doi:10.1016/0002-9343(83)90341-8

67. Tan J, Liu S, Segal JB, Alexander GC, Mcadams-Demarco M. Warfarin use and stroke, bleeding and mortality risk in patients with end stage renal disease and atrial fibrillation: A systematic review and meta-analysis. BMC Nephrology. 2016;17(1). doi:10.1186/s12882-016-0368-6

68. Camm AJ, Amarenco P, Haas S, Hess S, Kirchhof P, Kuhls S, et al. XANTUS: a real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. Eur Heart J. 2016 Apr 7;37(14):1145-53. doi: 10.1093/eurheartj/ehv466

69. Levey AS, Inker LA, Matsushita K, Greene T, Willis K, Lewis E, et al. GFR decline as an end point for clinical trials in CKD: a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis. 2014 Dec;64(6):821-35. doi: 10.1053/j.ajkd.2014.07.030

70. Böhm M, Ezekowitz MD, Connolly SJ, Eikelboom JW, Hohnloser SH, Reilly PA, et al. Changes in Renal Function in Patients With Atrial Fibrillation: An Analysis From the RE-LY Trial. J Am Coll Cardiol. 2015 Jun 16;65(23):2481-93. doi: 10.1016/j.jacc.2015.03.577
71. Shin JI, Luo S, Alexander GC, Inker LA, Coresh J, Chang AR, et al. Direct Oral Anticoagulants and Risk of Acute Kidney Injury in Patients With Atrial Fibrillation. J Am Coll Cardiol. 2018 Jan 16;71(2):251-252. doi: 10.1016/j.jacc.2017.10.089
72. Sparkenbaugh EM, Chantrathammachart P, Mickelson J, van Ryn J, Hebbel RP, Monroe DM, et al. Differential contribution of FXa and thrombin to vascular inflammation in a mouse model of sickle cell disease. Blood. 2014 Mar 13;123(11):1747-56. doi: 10.1182/blood-2013-08-523936
73. Lee IO, Kratz MT, Schirmer SH, Baumhäkel M, Böhm M. The effects of direct thrombin inhibition with dabigatran on plaque formation and endothelial function in apolipoprotein E-deficient mice. J Pharmacol Exp Ther. 2012 Nov;343(2):253-7. doi: 10.1124/jpet.112.194837
74. Brodsky SV, Nadasdy T, Rovin BH, Satoskar AA, Nadasdy GM, Wu HM, et al. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. Kidney Int. 2011 Jul;80(2):181-9. doi: 10.1038/ki.2011.44
75. Brodsky SV, Mhaskar NS, Thiruveedi S, Dhingra R, Reuben SC, Calomeni E, et al. Acute kidney injury aggravated by treatment initiation with apixaban: Another twist of anticoagulant-related nephropathy. Kidney Res Clin Pract. 2017 Dec;36(4):387-392. doi: 10.23876/j.krcp.2017.36.4.387
76. Ryan M, Ware K, Qamri Z, Satoskar A, Wu H, Nadasdy G, et al. Warfarin-related nephropathy is the tip of the iceberg: direct thrombin inhibitor dabigatran induces glomerular hemorrhage with acute kidney injury in rats. Nephrol Dial Transplant. 2014 Dec;29(12):2228-34. doi: 10.1093/ndt/gft380
77. Shafi ST, Negrete H, Roy P, Julius CJ, Sarac E. A case of dabigatran-associated acute renal failure. WMJ. 2013 Aug;112 (4):173-5; quiz 176.
78. Brodsky SV, Satoskar A, Chen J, Nadasdy G, Eagen JW, Hamirani M, et al. Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases. Am J Kidney Dis. 2009 Dec;54(6):1121-6. doi: 10.1053/j.ajkd.2009.04.024
79. Brodsky S, Eikelboom J, Hebert LA. Anticoagulant-Related Nephropathy. J Am Soc Nephrol. 2018 Dec;29(12):2787-2793. doi: 10.1681/ASN.2018070741
80. Chang CC, Liou HH, Wu CL, Chang CB, Chang YJ, Chiu PF, et al. Warfarin slows deterioration of renal function in elderly patients with chronic kidney disease and atrial fibrillation. Clin Interv Aging. 2013;8:523-9. doi: 10.2147/CIA.S44242
81. Ware K, Brodsky P, Satoskar AA, Nadasdy T, Nadasdy G, Wu H, et al. Warfarin-related nephropathy modeled by nephron reduction and excessive anticoagulation. J Am Soc Nephrol. 2011 Oct;22(10):1856-62. doi: 10.1681/ASN.2010101110
82. Coughlin SR. Protease-activated receptors in hemostasis, thrombosis and vascular biology. J Thromb Haemost. 2005 Aug;3(8):1800-14. doi: 10.1111/j.1538-7836.2005.01377.x
83. Narasimha Krishna V, Warnock DG, Saxena N, Rizk DV. Oral anticoagulants and risk of nephropathy. Drug Saf. 2015 Jun;38(6):527-33. doi: 10.1007/s40264-015-0290-z
84. Tracz MJ, Alam J, Nath KA. Physiology and pathophysiology of heme: implications for kidney disease. J Am Soc Nephrol. 2007 Feb;18(2):414-20. doi: 10.1681/ASN.2006080894
85. Awesat J, Sagy I, Haviv YS, Rabinovich A, Jotkowitz A, Shleyfer E, et al. Dabigatran-induced nephropathy and its successful treatment with Idarucizumab - case report and literature review. Thromb Res. 2018 Sep;169:120-122. doi: 10.1016/j.thromres.2018.07.019

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 atrija (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 antikoagulansa (DOAC) i varfarina u bolesnika s CKD-om.

Rezultati: DOAC-i su terapija izbora za bolesnike s CKD 1-3 (Crcl ≥ 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 teškom CKD-u, DOAC-i bi mogli biti bolja terapijska opcija za bolesnika s AF-om i CKD-om.

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