10.5152/turkjnephrol.2019.3448

Review

Turkish Journal of Nephrology

Oral Anticoagulant Treatment of Atrial Fibrillation in Chronic Kidney Disease Patients

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Abstract

Nonvalvular atrial fibrillation is the most prevalent sustained arrhythmia in chronic kidney disease patients. When compared to warfarin, new oral anticoagulants are found to be non-inferior or superior in safety and efficacy outcomes in the general population. The efficacy and safety of anticoagulation in mild chronic kidney disease is similar to the general population. Studies are yielding conflicting results in moderate to advanced chronic kidney disease and end stage renal disease. Due to hemostasis dysfunction in chronic kidney disease, both bleeding and thromboembolism risk increase. Advanced chronic kidney disease and end stage renal disease patients are excluded from randomized controlled trials. Our knowledge about the efficacy, safety and dose adjustments of warfarin and new oral anticoagulants are based on observational data. According to the recent studies, apixaban and edoxaban use in moderate chronic kidney disease with a glomerular filtration rate between 30-50 mL/min may be safer than warfarin. There are no high quality evidence to recommend the use of warfarin in advanced and end stage chronic kidney disease patients. The Food and Drug Administration approved the use of apixaban in end stage renal disease. Randomized controlled trials are needed to evaluate the use of oral anticoagulants in advanced chronic kidney disease.

Keywords: Anticoagulation, atrial fibrillation, chronic kidney disease

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Received: 07.07.2018 **Accepted:** 14.09.2018

Presented in: This study was presented at the "10th Capa Nephrology and Transplantation Days, 1-4 March 2018, Sapanca, Sakarya, Turkey".

Cite this article as: Artan AS, Gürsu M, Elçioğlu ÖC, Kazancıoğlu R. Oral Anticoagulant Treatment of Atrial Fibrillation in Chronic Kidney Disease Patients. Turk J Nephrol 2019; 28(3): 208-15.

INTRODUCTION

Nonvalvular atrial fibrillation (AF) is the most frequent, continuous rhythm disorder. The incidence in individuals with chronic kidney disease (CKD) is greater than in the non-CKD population. Its prevalence during predialysis in CKD is 16%-21%, while the prevalence during the end-stage renal failure (ESRD) is estimated to be 15%-40% (1).

The complications of AF are thromboembolic stroke and systemic embolization. In the general population, risk scoring systems were used to determine which patient was at a high risk for thromboembolism. It has been shown that anticoagulation in high risk patients significantly reduces the risk of stroke and embolization (2).

Anticoagulant treatment of patients with CKD and AF is difficult. While patients with CKD are at high risk for thromboembolic stroke and systemic embolization, the risks of major bleeding and bleeding-related death are also higher than in the healthy population (3). Data on anticoagulant use in CKD are less compared to the healthy population. Patients with advanced CKD or ESRD were excluded from large randomized AF trials. As the glomerular filtration rate (GFR) decreases, the data are based on observational studies and meta-analyses. In these analyses, patients on hemodialysis were represented with only a small number of patients (2).

The safety of anticoagulant drugs in primary prophylaxis of ischemic stroke in patients with CKD and its suitabil-

ity for clinical use are unknown (4). Recently, data deficiencies related to anticoagulant treatment of chronic kidney patients have been defined and tried to be eliminated.

The aim of this review is to summarize the recent data on anticoagulant applications and drugs used in patients with CKD and AF, a population frequently seen in nephrology clinics.

Atrial Fibrillation Treatment

Which patients should be treated?

The risk of thrombosis increases due to endothelial damage, platelet dysfunction, increased coagulation activity, and impaired fibrinolytic activity in CKD (5). Platelet adhesion and aggregation disorder and anemia increase the risk of bleeding. In addition, heparin administration during the sessions in patients on hemodialysis increases the risk of bleeding. As the renal dysfunction increases, the risk of thromboembolism increases (7). In the general population, anticoagulant therapy has been shown to significantly reduce the risk of stroke in elderly patients with AF. In the elderly CKD group, it is known that approximately 25% of patients discontinue treatment due to safety problems (8). It is also known that the risk of stroke in patients on hemodialysis is 10 times higher than in the general population. However, an important part of these are hemorrhagic strokes (9). A randomized study to evaluate the benefits and side effects of anticoagulation in the CKD group is not available today. Our knowledge on the treatment effectiveness and safety is based on numerous observational studies and meta-analyses. These studies have yielded conflicting results.

In the general population, risk scoring systems are used to identify patients who will benefit from AF treatment. According to these scoring systems, in patients with 2 or more points, treatment is initiated since the anticoagulant therapy is accepted to reduce the risk of stroke. The patient with 0 points will not receive anticoagulant therapy. In patients who receive 1 point, anticoagulant therapy may be given, not given, or aspirin may be used, taking into account the patient's clinical condition or the risk of bleeding in accordance with the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society (ACC/AHA/HRS) guide. The European Society of Cardiology recommends anticoagulation after evaluating the individual bleeding risk and patient preferences. In the CHA2DS2-VASc system, congestive heart failure (1 point), hypertension (1 point), advanced age (>75, 2 points), diabetes mellitus (1 point), stroke or transient ischemic attack history (2 points), vascular disease (1 point), age (>65, 1 point), and female gender (1 point) are scored. The 2014 ACC/AHA/HRS guidelines recommend the use of the CHA2DS2-VASc scoring system in the general population (10).

It is known that some treatments that are effective in normal patient groups do not exhibit efficiency in the CKD group. While it is clear that primary thromboembolism prophylaxis of patients with GFH >60 mL/min should be done in the same way as in the general population (9), there is a lack of data in intermediate and advanced renal failure. Whether any form of AT therapy is required in patients undergoing hemodialysis is a matter of debate.

It has been shown that current scoring systems are not as useful as in the general population in patients with CKD. It has been shown that the R2CHADS2 system, which is added 2 points in renal failure, has no additional benefit when it comes to predicting stroke risk in CKD. Since the criteria used in all current scoring systems such as hypertension, anemia, and heart failure do not provide an adequate definition of CKD (e.g., the hemoglobin level in CKD is lower than in the normal population which makes it difficult to define anemia, or which additional criteria should be used to differentiate congestive heart failure from hypervolemia), most patients with CKD are represented as at high risk in these systems, and this decreases the discrimination of scoring systems (2).

According to the KDIGO Controversies Conference report published this year, CHA2DS2-VASc is the most commonly recommended scoring system in CKD and it has been shown that CKD patients with a score greater than or equal to two benefit from oral anticoagulation (1).

Pharmacokinetic properties of oral anticoagulants

Warfarin binds to proteins by 99%. The half-life ranges between 20 and 60 hours. The urinary excretion is only 1%. Warfarin cannot be removed by dialysis. Vitamin K is its special antidote. The anticoagulant effect of warfarin can be eliminated with fresh frozen plasma and prothrombin complex concentrate.

Dabigatran binds to proteins at the rate of 35%. Its half-life is 7-17 hours, and 80% of the drug is excreted in the urine. It can be removed by dialysis. The special antidote approved by the US Food and Drug Administration (FDA) is idarucizumab. Apiksaban binds to proteins at 87%, its half-life is 8-15 hours, and 27% excretes in the urine. It cannot be removed by dialysis. Rivaroxaban binds to proteins at 95%, its half-life is 7-13 hours, and 36% can be excreted in the urine. It cannot be removed by dialysis. Edoxaban is bound to proteins at 54%. The half-life is 9-11 hours, and 50% is excreted via the kidney. It cannot be removed by dialysis. Apiksaban, rivaroxaban, and edoxaban have no approved antidotes. In case of bleeding, a prothrombin complex concentrate is used (11).

Warfarin

Warfarin disrupts the function of vitamin K by preventing vitamin K from returning to the epoxide state and blocks the gamma carboxylation of terminal regions of proteins linked to vitamin K. As a result, it leads to the decrease in the quantity of Factors 2, 7, 9, and 10 by preventing the production in the liver. Because of its interaction with the drug and foods based on the genetic structure of the individual, and the drug metabolism

varying from patient to patient, monitoring of the anticoagulant activity and dose adjustment are required (12).

In large randomized controlled trials investigating the efficacy of warfarin, patients with an advanced-stage CKD and ESRD were excluded from the study. Data on the efficacy of warfarin in reducing stroke in patients with CKD and safety in terms of bleeding are based on observational studies. In a retrospective cohort study published in 2016, patients who were taking and not taking anticoagulant were compared. A total of 6,544 patients with AFD aged over 66 and GFR <45 ml/min were included in the study. The 1,417 AF patients who were given anticoagulants were matched with 1,417 patients who were not given anticoagulants with similar characteristics using the trend score, and the pairs were evaluated. Thirty-two of 1,417 patients had GFR <15 mL/min (4). A total of 91.2% of the patients had taken warfarin, 2.8% heparin, and 6% new oral anticoagulants (NOACs). Endpoints were defined as ischemic stroke, bleeding, and mortality. Patients were followed for 267 and 268 days for ischemic stroke, and 254 and 269 days for bleeding. The most frequent hemorrhages were lower and upper gastrointestinal track bleedings, hematuria, hemoptysis, intracranial hemorrhage, and epistaxis. As a result, no significant difference was found between the two groups in terms of ischemic stroke, and bleeding was detected as higher in the anticoagulant group. Mortality was lower in the anticoagulant group. There may be several reasons for why no reduction was detected in ischemic stroke in the anticoagulant group. Anticoagulant use of risky patients excluded from randomized trials, including all CHADS2 scores to the study, thus evaluating patients with low-risk patients who will not benefit from anticoagulation, may have weaken the results. Warfarin was associated with vascular calcification, and vascular calcification may cause lacunar infarcts. Therefore, while the use of warfarin may reduce thromboembolic stroke, it may also increase stroke due to lacunar infarcts. Furthermore, the efficacy of anticoagulation, anticoagulant therapy compliance, and the absence of data on the number of patients using aspirin in addition to anticoagulant may have affected the results.

Studies on the efficacy and risk of warfarin have yielded conflicting results. Olesen found no reduction in the stroke risk and an increased risk of major bleeding in the nonfinal stage CKD (6); however, Carrero found that stroke decreased and that the risk of bleeding did not increase (13). In patients with ESRD, Chan showed that the risk of stroke increased and that the mortality did not decrease (14).

In the meta-analysis performed by Dahal in 2016, 13 studies including patients with CKD and ESRF were evaluated. Of the 48,500 patients, 11,600 were using warfarin. According to this meta-analysis, warfarin decreased the risk of ischemic stroke and thromboembolism and mortality in nonfinal stage CKD. The risk of bleeding did not increase (HR, 0.70; 95% p=0.004). It was shown that warfarin use does not reduce the risk of stroke and mortality in patients with ESRD. The risk of bleeding was significantly increased (7). The most important limitation of the studies on this subject is that they are observational studies. Therefore, deficiencies have emerged during the data collection phase. Diagnosis of the patients during the acceptance to the study was determined according to the International Classification of Diseases (ICD) codes, and the distinction between the acute renal failure and chronic renal failure was not sufficient. The definition of ischemic stroke varies according to the studies. Strokes without symptoms, which are found in many patients with ESRD, could not be detected. Data on patient compliance and international normalized ratio (INR) levels were not reported in some studies. Due to the selection of patients based on the clinical decisions of the physicians, patients who were prescribed warfarin were found to be healthier than those who were not prescribed anticoagulants (4, 6, 7, 13, 14).

In 2017, van der Meersch performed a meta-analysis of current studies to investigate warfarin use in patients on hemodialysis. A total of 11 observational studies, prospective or retrospective, were included into meta-analysis. The outcome of primary efficacy was determined as ischemic stroke and thromboembolic event, and the outcome of secondary efficacy was mortality. The primary safety outcome is major bleeding. Bleedings were defined as in the studies and hemorrhagic stroke. Of the 17,380 patients undergoing hemodialysis, 4,010 were using warfarin. While the average CHADS2 score was found to be 1.6-4, in one out of five patients, it was detected as <2. The efficacy of anticoagulation was reported in a small proportion of the studies included in meta-analysis, and the average INR value was found to range between 1.5 and 1.6. The diagnosis of ischemic stroke was defined by various criteria. These have been limited as ICD-9 and ICD-10 codes in patient files, records of hospitalized or deceased patients and radiological findings. While in some studies transient ischemic attack was defined within the scope of stroke, in others, it was excluded. In conclusion, the use of warfarin was shown to reduce the stroke risk by 26% compared to nontreated state; however, this result did not reach a statistical significance (HR=0.74; p<0.05). While there was no effects of warfarin on mortality, it was reported to increase the risk of bleeding significantly (HR=1.21). A correlation was found between bleeding and advanced age, diabetes mellitus, and male gender. One of the remarkable results of the study was that the risk of intracranial hemorrhage was significantly increased in patients using warfarin. Intracranial hemorrhage was thought to be related to the mechanism of action rather than the anticoagulant activity of warfarin. The findings suggest that warfarin inhibits the matrix G1a protein, resulting in a negative effect on angiogenesis (9).

While evaluating the results of this meta-analysis, it should be taken into consideration that the data are very heterogeneous. The low average of INR and the inclusion of patients with a lower risk according to the CHADS2 scoring system may have affected the statistical significance. While warfarin tends to decrease

the risk of ischemic stroke by 26%, it may not have reached statistical significance due to the data heterogeneity.

According to data from studies on warfarin use in patients with ESRD, warfarin use in patients with ESRF may be of no benefit when it comes to reducing the risk of thromboembolism, as in patients with normal renal function or mild CKD, or it may even be harmful according to some publications. In most publications, it is observed that warfarin increases the risk of bleeding in patients with ESRD. While interpreting these studies, it should be kept in mind that they are based on observational data.

Novel Oral Anticoagulants

Dabigatran

Dabigatran is the first oral anticoagulant to be produced, and it exhibits compete inhibitory effect to thrombin. A randomized controlled Phase III study published in 2009 included 18,113 patients with AF. Dabigatran at doses of 110 mg or 150 mg administered twice daily in a blinded study design was compared to open label, dose-adjusted warfarin. In conclusion, 110 mg dabigatran had similar prevalence with warfarin in stroke and systemic embolism, and less bleeding was observed in dabigatran. The risk of stroke and systemic embolism with dabigatran 150 mg was found to be lower than that of warfarin, and no difference was found between warfarin and dabigatran in terms of bleeding (15). Patients with advanced renal failure were not enrolled in the RE-LY study. In the study, the lower limit of GFH was determined as 30 mL/min. Dabigatran was approved by the FDA in October 2010 at a dose of 2x150 mg in normal renal function and 2x110 mg in GFH 30-50 mL/min.

In 2014, Hijazi published a secondary analysis of the RE-LY study related to patients with renal dysfunction. In this study, patients were divided into subgroups as GFR >80 mL/min, 50-80 mL/min, and 30-50 mL/min. Dabigatran 110 mg and 150 mg doses were found to be effectively independent of the level of renal function in the prevention of stroke. As the renal function calculated using the CKD-EPI equation was decreased, the risk of bleeding was increased. This difference was not observed with the Cockroft-Gault formula. When 150 mg of dabigatran was used, there was an increase in the risk of all-cause mortality (16).

In an observational study published by Chan in 2012, it was determined that the use of dabigatran increased bleeding, and the risk of death related to bleeding was increased in 281 ESRD patients (17).

The dose is recommended to be reduced to 2x75 mg, if GFR is between 15 and 30 mL/min. This information is based on pharmacological modeling studies, and to the best of our knowledge, there are no clinical studies confirming the efficacy and safety of this dose thus far (18).

Dabigatran is the only drug among NOACs that can be removed by dialysis (11).

Rivaroxaban

Rivaroxaban inhibits Factor 10a. In a double-blind, randomized controlled ROCKET-AF study, a total of 14,264 AF patients received 20 mg rivaroxaban or dose-adjusted warfarin daily. According to the results of this study, rivaroxaban was found to be equivalent to warfarin in preventing stroke and systemic embolism. There was no significant increase in bleeding in the group taking rivaroxaban compared to warfarin. The lower limit of GFR of the patients included in this study was determined as 30 mL/min according to the Cockroft-Gault formula (19). A secondary analysis of the ROCKET-AF study was conducted by Fox. Rivaroxaban 15 mg was used daily in the patients with GFH 30-49 mL/min. According to this study, the efficacy in preventing stroke and embolism risk in patients with moderate CKD is similar to that of warfarin, and no significant increase in the risk of bleeding was observed. Due to the lack of a sufficient number of patients, the equivalence could not be demonstrated (20). In an observational study published by Chan in 2015, the use of rivaroxaban in 244 patients on hemodialysis increased the risk of major bleeding and death associated with bleeding (17). The FDA approved the use of 20 mg of rivaroxaban daily. Based on the dose in the clinical trial, it is recommended to reduce the dose to 15 mg once a day when GFR is 15-30 mL/min. Confirmatory clinical data are few (18).

Apixaban

Apixaban inhibits Factor 10a. A randomized, double-blind, equivalence study in 2011 included a total of 18,201 patients with AF. Unlike other large studies on NOACs, patients with a GFR >25 ml/min were included into this study. Apixaban was used at a dose of 2x5 mg. Patients older than 80 years of age, weighing 60 kg or less, and having a serum creatinine level of 1.5-2.5 mg/dL were administered a dose of 2x2.5 mg. According to the study results, apiksaban was superior to warfarin in preventing stroke and systemic embolization. It has resulted in less bleeding and lower mortality. The risk of hemorrhagic stroke is significantly less than that of warfarin (21).

In the subgroup study published in 2012, apiksaban use was evaluated in patients with mild (GFR, 50-80 mL/min) and moderate to advanced (GFR, 25-50 mL/min) CKD. There was an improvement in the risk of efficacy, safety, and all-cause mortality, which did not reach statistical significance (22).

The apiksaban dose was approved by FDA as 5 mg twice a day, consistent with the clinical study. If there are 2 or more of the criteria, such as serum creatinine being 1.5-2.5 mg/dL, the patient age being >80, and the weight being <60 kg, a dose reduction by 2.5 mg twice a day is recommended. In 2014, the FDA approved the use of 2×5 mg or 2×2.5 mg in patients undergoing hemodialysis. This approval was based on the results of pharmacokinetic and pharmacodynamic studies. To the best of our knowledge, there were no validated clinical trials (18).

Edoxaban

Edoxaban inhibits Factor 10a. In a randomized controlled double-blind study performed by Guigliano (23), edoxaban was approved by the FDA at a dose of 60 mg once a day in accordance with the ENGAGE AF-TIMI 48 results. In this study, a low-dose of edoxaban (30 mg) and high doses of edoxaban (60 mg) or warfarin were given to patients at a moderate to high risk 21.105 AF. Both doses of edoxaban were found to be equivalent to warfarin in preventing stroke and systemic thromboembolism and superior to warfarin in terms of risk of bleeding. Bohula published a subgroup study of patients with GFH between 30 and 50 mL/min (24). In patients with moderate CKD, edoxaban is similar to warfarin in stroke prevention activity and safer in terms of bleeding risk. The FDA recommends reducing the dose to 30 mg per day, with GFR between 15 and 30 mL/min. This recommendation is based on pharmacokinetic modeling and simulation studies of patients with GFH 30-50 mL/min (25).

Intercomparison of New Oral Anticoagulants

To the best of our knowledge, there are no studies evaluating the comparison of NOACs in CKD. Data on the use of NOAC in CKD were obtained from the subgroup analyses of large randomized trials performed separately for each drug. Treatment of patients with GFR <50 mL/min in five randomized controlled trials on NOACs was compared with warfarin and each other in terms of efficacy and safety (26). In the first analysis, treatments were grouped into three groups as warfarin, low-dose NOAC (dabigatran 2×110 mg, edoxaban daily 30 mg or if GFH was <50 mL/min, the patient weight <60 kg, and nondihidropiridine calcium channel blocker was used, 15 mg daily was applied) and a single/high-dose NOAC (dabigatran 2x150 mg, rivaroxaban once a day 20 or if GFH was <50 mL min, dabigatran was applied once daily 15 mg, apisaban twice daily 2.5-5 mg, edoxaban 60 daily, or if GFH was <50 mL/min, the patient weight was <60 kg, and if nondihydropyridine calcium channel blocker was used, 30 mg was applied daily), and these three groups were compared with each other. In the second analysis, treatments were divided into two groups: warfarin, dabigatran 150 mg, dabigatran 110 mg, rivaroxaban, apixaban, edoxaban low-dose (30 mg), and high-dose (60 mg). The outcome of primary activity was determined as ischemic or hemorrhagic stroke. The definition of bleeding varied between studies. A total of 13,878 patients were evaluated. Of these, 5,604 used warfarin and 8,274 used NOAC. The patient age was generally >75 years.

Comparison of warfarin, low-dose new oral anticoagulants, and single-/high-dose new oral anticoagulants

When single-/high-dose NOACs were compared with warfarin, they were found to provide a 21% reduction in stroke and systemic embolism. When single-/high-dose and low-dose NOACs were compared with each other, a 29% decrease in stroke and systemic embolism was detected with a single/high-dose. When low-dose NOACs were compared with warfarin, an intention to decrease was detected with warfarin (OR 0.89). Major hemorrhage was found to decrease in a dose-dependent manner with NOACs compared to warfarin (OR 0.61 low-dose and 0.71 single/high-dose). As a result of these analyzes, it has been found that the treatment efficacy of NOACs in reducing bleeding is more than the treatment efficacy in preventing systemic embolism.

Intercomparison of treatments

Dabigatran 150 mg was found to be superior to warfarin to prevent stroke and systemic embolism (OR 0.56).

All other single-/high-dose NOACs showed statistically insignificant reductions compared to warfarin in the primary outcome. In the single-/high-dose group, no difference in efficacy was found between different NOACs. Apixaban and high-dose edoxaban significantly reduce bleeding compared to warfarin. Comparing NOACs with each other, bleeding with apiksaban was less than in other NOACs. There was no difference between high-dose edoxaban and apixaban in terms of the bleeding risk.

When all treatments for efficacy and safety were summarized, it was found that all single-/high-dose NOACs compared to warfarin significantly reduced the ischemic outcome and major bleeding. Warfarin tends to be more effective than low-dose NOACs. Single-/high-dose NOACs show no superiority over each other in terms of efficacy. With the exception of dabigatran, single-/high-dose NOACs have no significant advantage when it comes to efficacy than warfarin. Apixaban significantly reduces bleeding compared to all other single-/high-dose NOACs. Apixaban and high-dose edoxaban cause less bleeding than warfarin.

When the drugs were evaluated in terms of their efficacy and safety; dabigatran 150 was found to be the first and apixaban second with regard to efficiency; and low-dose edoxaban was the first and apixaban was the second with regard to safety. Low-dose edoxaban was last with regard to efficiency. Dabigatran 150 mg showed the highest risk of bleeding.

According to the results of this analysis, it was observed that the most preferred agents in the CKD group were apiksaban and high-dose edoxaban in terms of both the efficacy and safety.

One of the recent studies on the use of NOAC in patients with CKD and dialysis was published in *Nephrology Dialysis Transplantation* in March 2018 (27). This study is a meta-analysis of three retrospective cohorts and a case-control study together with large randomized controlled trials on NOACs. Patients with a GFH <60 mL/min and patients on hemodialysis were evaluated.

According to the results, when warfarin was compared to dabigatran 110 mg, rivaroxaban, and edoxaban in patients with moderate CKD with GFH <60 ml/min, there was no difference in stroke frequency. Dabigatran 150 mg and apiksaban significantly reduced the risk of stroke and systemic embolism compared to warfarin. Bleeding with edoxaban and apixaban was less than with warfarin. The doses of 110 and 150 mg of Rivarox-

aban and dabigatran were not significantly different in terms of bleeding compared to warfarin.

In patients on hemodialysis, there was no difference with regard to the risk of stroke when warfarin was compared to apixaban, dabigatran, and rivaroxaban. The risk of bleeding increased with rivaroxaban and dabigatran. There was no difference in the risk of bleeding with apixaban compared to warfarin. According to these results, apiksaban appears to be the safest NOAC in patients on hemodialysis. The most important limitation of the study was the heterogeneity in the definition of endpoints in the included studies and of patient inclusion or exclusion criteria. The same heterogeneity is also present in the definition of CKD.

Guideline Recommendations

The ACC/AHA/HRS released updated guidelines on AF treatment in 2014. According to these guidelines, the use of warfarin is recommended if anticoagulation is required in patients with creatinine clearance (CrCl1) <15 mL min or undergoing dialysis (Class 2A). If CrCl1 is >30 mL/min, dabigatran should be used at a dose of 150 mg twice a day; if CrCl1 is 15-30 mL/min, it should be used 75 mg twice a day. If CrCl1 is >50 ml/min, rivaroxaban should be used 20 mg daily; if CrCl1 is 15-50 mL/min, 15 mg daily should be used. There are no data available for the use of apixaban in ESRD. The dose is applied as 5 mg twice a day or in case of the presence of two of the three factors (age >80 years; weight <60 kg; creatinine, 1.5-2.5 mg/dL), it is used as 2.5 mg twice a day. In patients with CrCl1 51-95 mL/min, 60 mg of edoxaban is used daily, and 30 mg daily is used if CrCl1 is 15-50 mL/min (10).

Routine use of oral anticoagulants in the primary prophylaxis of stroke and systemic embolism in dialysis patients was not recommended in the Kidney Disease: Improving Global Outcomes (KDIGO) 2011 guideline and the use of these drugs was left to the nephrologist's decision (28).

According to the KDIGO Controversies Conference report published in March 2018, which summarized and updated the current information on CKD patients with AF, there are no randomized trial data with a GFR of <30 mL/min for the use of anticoagulants. The appropriate doses for rivaroxaban and apixaban in GFR less than 15 mL/min and in dialysis patients are unknown. For apixaban, 2×2.5 mg, and for rivaroxaban, 1×15 mg may be appropriate. Dabigatran and edoxaban are not recommended under 15 mL/min. According to observational data and meta-analysis results, data on warfarin use are in balance as to use or not to use.

The choice between warfarin or NOAC should be decided by an active interdisciplinary communication. It has been suggested that the renal function of patients using NOAC should be evaluated at certain intervals, and dose reduction should be made if necessary. To prevent bleeding in patients receiving anticoagulants, reduction of heparin use in dialysis, the use of citrate locks for catheters, prophylaxis of gastrointestinal bleeding, regulation of blood pressure, and discontinuation of antiaggregants were recommended (1).

The FDA does not approve the use of dabigatran, rivaroxaban, and edoxaban under 15 mL/min of GFR. Dabigatran was approved at a dose of 75 mg twice a day, with GFH between 15 and 30 mL/min. Rivaroxaban was approved at a dose of 15 mg per day, and edoxaban at a dose of 30 mg per day with GFR between 15 and 50 mL/min. The FDA approved the use of apiksaban 2.5-5 mg twice daily in mild, moderate, and advanced CKD and ESRD.

NOAC Use in Chronic Kidney Patients in Turkey

The prevalence of AF in Turkey was found to be 1.25%, according to the results from the *Heart Disease and Risk Factors in Turkish Adults* (29).

In a multicentre study published by Mert in 2017, anticoagulant therapies of patients with CKD and AF who applied to cardiology outpatient clinics were investigated (30). In 1,964, of 6,274 patients, GFR was found to be <60 mL/min according to the Cockroft-Gault formula. The average CHA2DS2-VASc score was 3.27±1.59. Patients with CKD are older and there are more women affected than individuals without CKD. The history of thromboembolic stroke or bleeding is significantly higher in the CKD group. A total of 69.9% patients with CKD use a type of anticoagulant therapy. No difference was found between the NOAC use in patients with and without CKD (37.4% in both groups, p=0.998). There was a significant difference between the two groups in terms of warfarin use (32.5% in the group with CKD and 36.2% in the non-CKD group, p=0.001). In 2.9% of patients with CKD, GFR is <30 mL/min, and 27.4% of these patients are treated with NOAC.

One of the most important findings of the study is that CKD patients, especially those with a GFH <30 mL/min, have a significantly increased history of bleeding and thromboembolic stroke.

With this study, it was shown that one-third of patients with CKD in our country did not use any type of anticoagulants. Furthermore, it was detected that guideline suggestions in terms of the NOAC use was not clear; NOACs were used in the patient group with GFR<30 mL/min. Low rates of anticoagulation may be explained by the high risk of bleeding in patients with CKD, but the results of the study show that the risk of thromboembolism is higher in patients with CKD than in non-CKD patients.

In a multicentre, cross-sectional study conducted by Altay in 2017, safety and efficacy of NOACs were evaluated in all indications such as AF, deep vein thrombosis, and pulmonary embolism (31). The study included 2,862 patients who had been using NOAC for at least 3 months due to AF, pulmonary thromboembolism, and/or venous thromboembolism. The GFR was calculated according to the MDRD formula, and values <60 mL/min were considered as CKD. The average GFR of patients was 78±23.1 mL/min. CKD

was detected in 224 patients (7.8%). In our country, rivaroxaban and dabigatran were found to be more preferred than apixaban. Thromboembolic events were seen in 37 of the patients (1.3%). Deep vein thrombosis, cerebrovascular accident, smoking, apiksaban use, and low-dose use of NOACs were associated with an increased risk of embolism. The use of rivaroxaban was found to be associated with a smaller number of thromboembolic events. The relation of CKD with the risk of thromboembolism was not detected. Hemorrhage was found in 217 (7.6%) of the patients, and the major bleeding rate was 1.1%. The use of dabigatran and rivaroxaban and the use of high doses of NOAC have been shown to be associated with bleeding. Apiksaban was associated with a lower risk of bleeding.

In this study, it was detected that approximately half of the patients were using low doses of NOACs. It was found that the patients who received low-dose treatment were older, the CHA2DS2-VASc scores were higher, and the GFR was lower. This is important because it shows that doctors in Turkey tend to use lower doses in high risk patients with bleeding concerns.

According to the results of the GFR mean, there were no patients with advanced CKD in this study. The risk of bleeding and thromboembolism not being associated with CKD can be explained by the absence of moderate- and advanced-stage CKD.

CONCLUSION

AF is more common in patients affected by CKD than in the normal population. AF- associated stroke and systemic embolism and AF-associated bleeding are more frequent in CKD. Anticoagulation recommendations in mild renal failure (GFR >60 mL/min) and efficacy and safety expected from anticoagulation are similar to the general population. As CKD progresses, the data on the indications for the use of anticoagulants, the efficacy of this treatment, and the risk of bleeding are conflicting and inadequate. The effectiveness and safety of NOACs shown via randomized trials and lack of need for follow-up of blood levels, lack of interaction with nutrients, and oral use make this treatment an attractive option. The presence of association between warfarin and intracranial hemorrhage and increased vascular calcification, especially in patients on hemodialysis, led to an alternative search for warfarin. It is known that treatment time with effective anticoagulation with warfarin is low in the CKD group. This may explain the extent of stroke and hemorrhage under anticoagulation in CKD. The experience of clinicians due to the prolonged use of warfarin and the fact that in case of any bleeding, the effect can fastly be removed by vitamin K and fresh frozen plasma are the strengths of warfarin therapy. Considering the results of the studies performed so far, it is understood that patients with mild renal failure who need anticoagulants for AF should be anticoagulated like patients without renal failure. NOACs can be used in these patients without dose restriction. When GFR falls below 50 mL/min, dose reductions should be initiated in NOAC therapies. Data on the efficacy and safety of anticoagulants in patients with GFH <15 mL/min are contradictory. At this stage, the safest NOACs according to the guidelines and study recommendations appear to be apixaban and a reduced dose of rivaroxaban. However, clinical trial data to support the use of these two drugs are insufficient. No NOAC except for apiksaban has been approved for use in patients undergoing hemodialysis. Although there are some contradictory results in the various studies conducted on the use of NOAC in CKD, the common result is that the use of these drugs in ESRD increases bleeding. Large randomized studies on the use of NOACs in patients with ESRD and GFR <15 mL/min should be conducted; a decision should be made based on the results of these studies. It should be kept in mind that not only bleeding, but the risk of thromboembolism is also increased in high risk patients. In advanced-stage kidney failure, the dose should be reduced and must be handled with utmost care, taking into account the benefit-to-risk ratio in the affected patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.S.A., R.K.; Design - M.G.; Supervision - Ö.C.E.; Resource - A.S.A.; Materials - Ö.C.E.; Data Collection and/or Processing - A.S.A.; Analysis and/or Interpretation - A.S.A., R.K.; Literature Search - M.G.; Writing - M.G., A.S.A.; Critical Reviews - Ö.C.E., R.K.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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