Oral anticoagulants in patients with Chronic Kidney Disease. A friend or foe?

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Abstract

Anticoagulant treatment of atrial fibrillation (AF) in patients with chronic kidney disease (CKD) is a common clinical problem as the prevalence of AF increases as kidney function deteriorates. Nevertheless, the risk-benefit ratio of anticoagulant treatment, especially warfarin, in patients with CKD and AF is unclear. Data analysis in patients with CKD stage III or lower, showed that well-adjusted doses of warfarin reduce the risk of ischemic stroke and systemic embolism. Regarding the use of DOACs, their administration is not inferior in efficacy for the prevention of ischemic stroke and thromboembolic events compared to warfarin in this particular group, while their safety profile is superior as they have been associated with a significant reduction in the risk of intracranial hemorrhage. In patients with end stage kidney disease on hemodialysis, warfarin administration has not been associated with a reduced risk of ischemic stroke. Moreover, there is a significant increase in the risk of hemorrhagic stroke. Regarding the use of DOACs in patients on hemodialysis and AF, treatment with DOACs has not been associated with a lower risk of new stroke or thromboembolic events. Concluding, in patients with AF and mild to moderate CKD without the need for renal replacement therapy, oral anticoagulation efficiently reduces the risk of ischemic stroke, while in those with advanced stage CKD or on hemodialysis the risk benefit ratio is still unidentified.

Key words: *Anticoagulants; direct oral anticoagulants; chronic kidney disease; hemodialysis*

INTRODUCTION

Anticoagulant treatment of atrial fibrillation (AF) in patients with chronic kidney disease (CKD) is a common and important daily problem that concerns both the cardiology and nephrology community as well as the general physician. The prevalence of AF (paroxysmal and permanent) increases as kidney function deteriorates and reaches up to 40% of patients with end-stage CKD (ESKD). In addition, these patients have an increased risk of both ischemic stroke - 1.5 times compared to patients without CKD - but also for severe bleeding episodes - 2 times higher than patients without CKD [1]. According to the revised 2019 AHA guidelines, patients with AF and CHA_2DS_2-VASc score, above 2 for men and above 3 for women, should receive oral anticoagulant therapy with one of the available agents (Warfarin, Dabigatran, Rivaroxaban, Apixaban or Edoxaban) [2].

Though, the prevalence of AF in patients with CKD is increased, the risk-benefit ratio of anticoagulant treatment, especially warfarin, in patients with CKD and AF is unclear. This is because initiation of such treatment, in this group of patients, greatly increases the risk of bleeding while at the same time controlling the therapeutic levels of warfarin (internal normalized ratio, INR) is difficult and its use is associated with increased risk of vascular calcification and cases of calciphylaxis es-

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pecially among those with ESKD [3]. Considering these data, in recent years, there has been an increase in the clinical use of newer direct oral anticoagulants (DOACs) in patients with CKD of all stages with concomitant AF without, however, sufficient data from randomized trials that confirm the safety and efficacy of these drugs in this group of patients. This uncertainty in the safety and efficacy of anticoagulant treatment in patients with CKD and especially ESKD is depicted in prescribing trends which show inter-country variation, as well as significant within-country variation between facilities ranging from 0 to 45% of the dialysis patients in the use of an oral anticoagulant, mostly warfarin (85%) [4]. Nevertheless, more recent data from the United States and Canada, report that just 24% to 46% of those with AF are prescribed warfarin while the use of DOACs is increasing with an average 23.5% of CKD patients taking them regularly for stroke prevention [5,6]. In line with these data, a Danish study with over 1500 patients with AF and CKD, describes that in recent years and especially since 2017 the rate of DOACs administration has exceeded that of coumarin anticoagulants, with apixaban being the most common substance [7]. Clinical ambiguity is further emphasized by a survey of Canadian nephrologists treating dialysis patients with nonvalvular AF, which revealed that warfarin was more likely to be recommended to patients with high stroke risk and low bleeding risk and less likely to be prescribed to patients with moderate stroke risk and high bleeding risk [8].

Moreover, despite such an increased incidence of AF in patients with CKD, the risk assessment for stroke is incomplete and problematic. The most commonly used tool for ischemic stroke risk assessment which is validated for patients with CKD (all stages) is the CHAD-VASC score which, however, does not show an acceptable accuracy in distinguishing high from low risk patients for stroke in those with established CKD (C statistic, 0.6 CKD-III, 0.7 CKD-IV / V and CKD-V Dialysis) [9]. Concerning bleeding risk assessment, the use of the HAS-BLED, ORBIT and ATRIA tools is not recommended by most of the published guidelines [1]. Thus, the aim of this review is to show the contemporary clinical data on the efficacy and safety of oral anticoagulation in patients with AF and established CKD.

METABOLISM OF ORAL ANTICOAGULANTS

Vitamin K antagonists (VKA) are still the most widely used anticoagulants for stroke prevention in patients with nonvalvular atrial fibrillation. From this group of drugs, warfarin is the one for which the majority of clinical evidence has been obtained. Warfarin is extensively metabolized by CYP2C9 in the liver, has a peak concentration (Cmax) at 2–6 h after administration, a t1/2 of 42 h, is protein bound by 97–99% and has a bioavailability of 99%. Other drugs that interact with warfarin and increase its anticoagulant effect include: amiodarone, verapamil, diltiazem, fluconazole, voriconazole, tigecycline, fluoroquinolones, NSAIDs, and SSRIs while drugs that decrease its effects include: rifampin, phenobarbital and carbamazepine [10]. Although the guidelines do not recommend VKA dose adjustment in CKD, clinical studies reveal an increased hemorrhagic risk, particularly within the first 3 months after initiation of treatment, most of them gastrointestinal [11]. For this reason, to reduce the risk of hemorrhage requires an average reduction of warfarin doses by 10% in patients with eGFR between 30 and 59 mL/min/1.73m^2 and by 19% in those with eGFR < 30 mL/min/1.73m^2, in order to maintain INR ≤ 4 [11]. Dose adjustment is also necessary in case of liver damage as then the renal clearance is enhanced. Warfarin administration is even more complicated in patients with ESKD as it is associated with an increased risk of thromboembolic events and hemorrhage.

All DOACs are excreted by the kidneys, so the presence of CKD greatly affects their metabolism. More specifically, renal involvement in the excretion of these drugs ranges from 27% for apixaban and can reach up to 80% for dabigatran. Table 1 details the hepatic and renal involvement of warfarin and DOACs metabolism [6]. The integrity of renal function in the pharmacokinetics of substances excreted by the kidneys is crucial. Renal excretion of drugs occurs primarily by glomerular filtration and occasionally by tubular secretion. When the glomerular filtration rate (GFR) and tubular function are reduced, the clearance of drugs eliminated by these mechanisms decreases and consequently the plasma half-life of these drugs is extended. This leads to increased exposure to drugs, as quantified by the area under the curve (AUC). In such cases, without proper dose adjustment, repeated dosing of a drug leads to bioaccumulation over time and toxicity [6]. The basic metabolic pathways of oral anticoagulants are presented in Table 1.

Therefore, as all DOACs show renal excretion, the presence of renal impairment will inevitably lead to their eventual accumulation. An additional problematic point in trying to adjust the appropriate therapeutic dosage of these drugs comes from the way renal function is assessed. It is noteworthy that all randomized

Table 1. *Basic metabolic pathways of oral anticoagulants.*

Substance	Kidney excretion (%)	Hepatic or other form of metabolism	Dialyzable
Warfarin	-	Predominantly via cytochrome P450 type 2C9 (CYP2C9)	No
Apixaban	27	CYP-3A4/5 P-glycoprotein	Partially (small)
Rivaroxaban	36	CYP-3A4/5 and CYP-2J2	No
Dabigatran	80	Metabolized by esterases	Yes
Edoxaban	50	CYP-3A4	No

trials (RCTs) using DOACs used eCrCl assay according to the Cockcroft-Gault formula to assess renal function. However, there are clinically significant dose deviation of DOACs based on this equation, especially considering that the proposed equation for the assessment of renal function is CKD-EPI and not the Cockcroft-Gault (CG) formula. These discrepancies are particularly significant for DOACs with greater dependence on renal clearance (dabigatran, rivaroxaban) and among elderly patients with dose discrepancies of up to 30%. In particular, mild to moderate CKD occurs in ~ 54% of patients with long-term anticoagulant therapy and approximately 25% of these patients develop severe CKD [12].

More specifically, compared to the CG equation, the MDRD and CKD-EPI equations in many cases overestimate eGFR and it is precisely this overestimation that can lead to an increased total dose of DOACs. By using the CKD-EPI or MDRD equations instead of CG, dosing discrepancies are higher with substances whose metabolism is more dependent on renal function such as dabigatran and rivaroxaban than with apixaban. Especially in patients with impaired renal function as calculated by the CG equation <60 ml / min and in elderly patients (> 75 years), the discrepancy between dabigatran and rivaroxaban doses is higher than in the general population (from 13.2% to 30.4%). In contrast, the dose mismatch of apixaban from the use of different equations to calculate eGFR is less than 5% [13]. The frequency of overdose of DOACs has also been seen in a large U.S. administrative database with over 14,000 patients with AF. In this, more than 40% of patients received a higher dose (for a given eGFR) than they normally should. More specifically, the proportion of patients receiving higher than the recommended dose was 48.5% for apixaban, 39.4% for dabigatran and 41.3% for rivaroxaban. Characteristically, the use of standard, but not appropriately reduced, doses of DOACs in patients with severe kidney impairment has been associated with a doubling of the risk of bleeding without any reduction in the risk of stroke [14]. DOACs dose adjustment according to CKD stage is presented in Table 2.

MONITORING OF THE ANTICOAGULATION EFFECT

Among patients treated with warfarin, INR is the most common test used to monitor warfarin response which should be determined at least weekly during initiation of anticoagulant therapy and at least monthly when anticoagulation (INR) is stable in order to keep the therapeutic range of an INR between 2.0 and 3.0 [2,10]. Clinical practice guidelines do not recommend dosage reduction for CKD or ESKD. Nevertheless, there are studies which show that dose reduction between 10-19% is required in patients with eGFR <60 ml/min/1.73m^2 and <30 ml/min/1.73m^2, respectively. It has not been established whether different dialysis procedures and methods result in changes in warfarin exposure and pharmacodynamics [10]. In contrast to VKAs, DOACs do not require routine monitoring as they have shown a predictable pharmacokinetic profile in patients though without high grade CKD. Monitoring of these agents, especially in CKD for assessing drug accumulation, relies on measurement for dabigatran, of thrombin time (TT) or ecarin clotting time (ECT), while for the factor Xa inhibitors, anti-Xa activity should be assessed [3]. There is a strong correlation between anti-Xa activity and factor Xa inhibitor concentration, however, it should be highlighted that there are no FDA-approved kits for universal standardization of the anti-Xa activity assay [15].

Reversal of the antithrombotic effect of oral anticoagulants is achieved using fresh frozen plasma, prothrombin complex concentrate, recombinant factor VIIa, factor VIII inhibitor by passing activity or a specific antidote. When warfarin is used, in patients with INR

Table 2. *DOACs dose adjustment according to CKD stage.*

CKD stage	eGFR (ml/min)	Apixaban	Rivaroxaban	Dabigatran	Edoxaban
I & II	> 60	Normal dose	Normal dose	Normal dose	Normal dose
III	30 - 59	Normal dose	reduced dose (eGFR < 49)	Reduced dose (eGFR < 49)	Reduced dose (eGFR < 49)
IV	15 - 29	normal or reduced dose (in patients with at least 2 of: age≥80, s. creatinine ≥1.5 mg/dl, weight ≤60 kg)	reduced dose	EMA: contraindicated FDA: reduced dose	reduced dose
V	< 15	EMA: contraindicated FDA: normal or reduced dose (in patients with at least 2 of: age≥80, s. creatinine ≥1.5 mg/dl, weight ≤60 kg)	contraindicated	contraindicated	contraindicated

value over 9, even with no major bleeding events, a single oral dose of vitamin K (2.5-5 mg) is needed, while in major bleeding regardless of INR value, vitamin K (10 mg) should be administered parenterally along with fresh frozen plasma, prothrombin complex concentrates or recombinant factor VIIa that shows a rapid effect. For dabigatran, the specific antidote Idarucizumab is indicated in case of life-threatening bleeding [16]. Idarucizumab has a rapid effect after a single dose of 5 g i.v. with no dose modification needed in CKD, though its efficacy and safety in ESKD has not been tested. For rivaroxaban, apixaban and edoxaban, FDA has recently approved Andexanet alfa as a reversal agent [10,11,16].

ANTICOAGULATION IN PATIENTS WITH NONVALVULAR AF AND ESTABLISHED CKD STAGE III (EGFR: 60 – 30 ML/MIN/1.73 M^2)

Patients' data from studies on VKAs primarily refer to warfarin and most of the evidence comes from extrapolation analysis of AF patient subgroups within larger groups of patients. There is only one randomized control study (Stroke Prevention in Atrial Fibrillation III study) that included patients with CKD stage III and patients with normal kidney function [17]. In this trial, high-risk participants were assigned to adjusted-dose warfarin (target INR 2 - 3) versus aspirin (325 mg) plus fixed, low-dose warfarin while low-risk participants received 325mg aspirin daily. Data analysis in CKD subgroup showed that well-adjusted doses reduce the risk of ischemic stroke and systemic embolism by 76% and 67%, respectively, without statistically significant differences in major bleeding rates [17]. Other data on warfarin derive from observational studies that include CKD subgroups, but overall, the results are consistent in terms of effectiveness in reducing the risk of stroke and thromboembolic episodes. A Cochrane database systematic review also favored the efficient and safe use of warfarin in patients with CKD stage III [18]. Finally, in a meta-analysis by Dahal et al, it was shown that the use of warfarin in non-dialysis dependent CKD reduces the risk of ischemic stroke and systemic embolism by 30% but at the cost of an insignificant 15% increase in major hemorrhages compared to the group not receiving warfarin [19].

Regarding the use of DOACs, the results of RCTs as well as their meta-analyses, have shown that their administration is not inferior in efficacy for prevention of ischemic stroke and thromboembolic events compared to warfarin in patients with estimated eCrCl (CG) 30-50 ml/min (apixaban, 25–50 ml/min). Recent evidence that derives from a meta-analysis of 8 RCTs and 46 observational studies, indicate the superiority of DOACs over warfarin in thromboembolic events prevention (HR 0.86, 95% CI 0.78-0.95) and bleeding risk reduction (HR

0.81, CI 0.66-0.99) in non-dialysis CKD population. In the same meta-analysis apixaban, in an eGFR accordingly adjusted dose, presents an advantage in thromboembolic events prevention compared to edoxaban [20]. However, there are insufficient data on the use of one particular DOAC over others, as there are no head-to-head studies in this CKD population. Although their efficacy is not inferior to warfarin, the safety profile of DOACs is superior. In all major RCTs, DOACs have been associated with a significant reduction (approximately 50%) in the risk of intracranial hemorrhage compared with warfarin [1]. More specifically, there was not any significant difference between DOACs and warfarin in reducing ischemic stroke in patients with moderate CKD, except for dabigatran (150 mg) and apixaban, which were superior in reducing the risk of ischemic stroke. In addition, in patients with moderate CKD, edoxaban and apixaban had a significantly reduced risk of bleeding compared to warfarin, while rivaroxaban and dabigatran showed no difference [21].

ANTICOAGULATION IN PATIENTS WITH NONVALVULAR AF AND ESTABLISHED CKD STAGE IV-V (EGFR: < 30 ML/MIN/1.73 M^2)

To date, there are no RCTs to explore the use of warfarin or other coumarin anticoagulants in patients with ESKD and AF, thus clinical practice is largely determined by retrospective studies. In a meta-analysis of 14 observational studies with 20,398 patients on hemodialysis, warfarin administration was not associated with a reduced risk of ischemic stroke (HR, 0.77; 95% CI, 0.55 to 1.07) compared with no warfarin use. In contrast, there was a significant increase in the risk of hemorrhagic stroke (HR, 1.93; 95% CI, 0.93 to 4.00) and gastrointestinal bleeding (HR, 1.19; 95% CI, 0.8 to 1.76) compared with no warfarin use [22,23]. In order to investigate the effectiveness of warfarin in the prevention of ischemic strokes and thromboembolic events in patients with ESKD and AF, a multicenter open label RCT (NCT02886962 - AVKDIAL) is in development, in which patients will be randomized to warfarin or no treatment. The results from this trial are expected in early 2023 and they will largely determine the effectiveness of warfarin treatment in patients with ESKD and AF.

Regarding the use of DOACs in patients with ESKD (on hemodialysis) and AF, in a retrospective study by the US renal data system covering the period between 2012–2015, patients receiving apixaban (521) were compared with 1561 patients with the same characteristics without treatment. In this study, treatment with apixaban was not associated with a lower risk of new stroke or thromboembolic events. However, there was a tendency to reduce ischemic strokes (insignificant) but this was accompanied by more hemorrhagic strokes when using apixaban at a dose of 5 mg bid in comparison to non-administration. At the 2.5 mg bid dose of apixaban, the incidence of intracranial hemorrhage was not significantly higher in comparison to the control group, however, at this dose, significantly more cases of ischemic strokes or thromboembolic events were observed [24]. In a meta-analysis of retrospective studies on the use of DOACs versus warfarin, the results showed that there was no difference in the prevention of ischemic strokes or arterial embolism. In particular, this result applied to all DOACs (apixaban, dabigatran and rivaroxaban) versus warfarin, in patients with ESKD on hemodialysis. However, the studies on which these results were based had significant limitations as they either involved a small sample size or a short follow-up [21]. It is noteworthy, however, that the same meta-analysis showed that patients in this group had a higher risk of major bleeding and higher mortality due to bleeding with dabigatran or rivaroxaban compared with warfarin. In contrast, administration of apixaban did not appear to increase the risk of bleeding in comparison to the use of VKA [21]. The only completed RCT to date which was designed to investigate the effectiveness of DOACs in patients with ESKD on hemodialysis, is RENAL - AF. Initially, this study, was planned to randomize 760 patients with nonvalvular AF on dialysis, to be treated with either warfarin or apixaban 5 mg twice daily or 2.5 mg twice daily in selected patients. The main endpoints included the risk of major and clinically significant bleeding, the risk of stroke, pulmonary embolism and death. The study was terminated prematurely due to insufficient patient participation. Finally, 154 patients were randomized (82 received apixaban and 72 warfarin). Apixaban appeared to be associated with fewer bleeding events than warfarin, but the difference was not significant. Therefore, even this initially well-designed study failed to be completed and bring clear results on the effectiveness of DOACs in patients with AF and ESKD.

IS THERE ANY BENEFIT FROM ORAL ANTICOAGULANT TREATMENT IN PATIENTS WITH AF AND CKD?

In patients with mild to moderate CKD (stage I to III) without the need for renal replacement therapy, oral anticoagulation treatment efficiently reduces the risk of ischemic stroke and thromboembolic events.

Moreover, all major prospective RCTs of different DOACs have shown that these agents are equally effective or even better in preventing ischemic stroke and thromboembolic events in comparison to warfarin [18,21]. Most importantly, the administration of these drugs reduces the risk of serious bleeding complications [18]. In addition, the ease of DOACs administration at predetermined doses which do not need to be adjusted should not be overlooked. On the contrary, VKA dose must be adjusted following frequent INR testing.

Overall, anticoagulant therapy increases the risk of bleeding by at least 20% in patients with advanced CKD or on dialysis, while the extent to which warfarin and DOACs reduce the risk of ischemic stroke in patients of this group remains unclear [11,21]. RCTs in the general population have shown warfarin to reduce the risk of ischemic stroke by 64% in patients with AF compared with placebo. However, there is evidence that anticoagulant therapy does not lead to a similar risk reduction in patients with advanced CKD and ESKD. There are several reasons for the ineffectiveness of VKA in patients with CKD-IV or V [21,25]. On the one hand, uremic induced platelet dysfunction may protect against thrombosis. On the other hand, increased comorbidity may reduce the chance to show a benefit (patients with ESKD have reduced life expectancy and follow-up time for stroke events) [6]. Furthermore, it should not be overlooked that all patients undergoing a chronic hemodialysis program are already receiving intravenous anticoagulation either with unfractionated heparin or more commonly with low molecular weight heparin which has a 24-hour effect and offers potential protection from thromboembolic events or may increase the risk of bleeding with concomitant administration of another anticoagulant.

WHAT ARE THE GUIDELINES RECOMMENDATIONS?

Cardiologists tend to extrapolate guideline recommendations for patients with CKD from studies and data of patients without CKD, while nephrologists are reticent in this respect. The latest 2011 KDIGO (Kidney Disease: Improving Global Outcomes) guidelines state that only nephrologists should recommend oral anticoagulants as primary prevention in ESKD and dialysis patients, based

Table 3. *Summary of guidelines about anticoagulation for stroke prevention in patients with established CKD and non-valvular AF.*

Association or approving authority	Summary of guidelines
Kidney Disease Improving Global Outcomes	"Team-based, multidisciplinary active communication, particularly involving the nephrologist, cardiologist (or cardiac electrophysiologist), primary care physician, and when possible, clinical pharmacist, may be useful to evaluate the risk-benefit of any decision regarding choice of VKA or a DOAC" [1]
American Heart Association	Dabigatran 150 mg twice daily in patients with CrCl > 30 mL/min Rivaroxaban 20 mg od for patients with CrCl > 50 mL/min Apixaban 5 mg twice daily for patients with no more than 1 of the following characteristics: age ≥ 80 years, serum creatinine ≥ 1.5 mg/dL, or body weight ≤ 60 kg Apixaban 2.5 mg twice daily for patients with at least 2 of the following: ≥ 80 years, body mass ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL74 CHA_2DS_2-VASc score ≥ 2 in men or ≥ 3 in women and eCrCl < 15 mL/min or on dialysis, reasonable to prescribe warfarin (INR 2.0-3.0) or apixaban For moderate to severe CKD (serum creatinine ≥ 1.5 mg/dL [apixaban], CrCl 15-30 mL/min [dabigatran], CrCl 15-50 mL/min [rivaroxaban], or CrCl 15-50 mL/min [edoxaban]) with an elevated CHA_2DS_2-VASc score, reduced doses of direct thrombin or factor Xa inhibitors should be considered [2]
European Society of Cardiology	Rivaroxaban 15 mg od if CrCl 30-49 mL/min Apixaban 2.5 mg twice daily if Cr ≥ 1.5 mg/dL, and age ≥ 80 years or weight ≤ 60 kg Edoxaban 30 mg daily if CrCl < 50 mL/min In dialysis patients: no consensus; controlled studies of anticoagulants (VKAs and NOAC) in AF patients receiving dialysis are needed [27]

on a strictly individualized algorithm [26]. The American Heart Association guidelines recommends warfarin even in dialysis patients with CHA_2DS_2-VASc score ≥ 2 for men and ≥ 3 for women and an INR target between 2 and 3 (class IIa, level of evidence B) and does not allow the use of dabigatran, edoxaban and rivaroxaban in ESKD and patients on dialysis [2]. For patients with AF who have a CHA_2DS_2-VASc score of 2 or greater in men or 3 or greater in women and who have end-stage chronic kidney disease (CKD; creatinine clearance [CrCl] <15 mL/min) or are on dialysis, it might be reasonable to prescribe warfarin (INR 2.0 to 3.0) or apixaban for oral anticoagulation [2]. The ESC guideline recommends that for patients with moderate or moderate-to-severe CKD (eGFR ≥ 15 ml/min/1.73 m^2) anticoagulation can be safely used in AF while for patients with ESKD on dialysis controlled studies of anticoagulants (both VKAs and NOACs) are needed [27]. These guidelines are summarized in Table 3.

ONGOING TRIALS

Currently ongoing studies include: the Strategies for the Management of Atrial Fibrillation in Patients Receiving Hemodialysis (SAFE HD; ClinicalTrials.gov identifier NCT03987711) trial, comparing warfarin, apixaban, and no anticoagulation (with a planned enrollment of 150 patients) and an estimated completion date on December 31, 2021; and the Compare Apixaban and Vitamin-K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease (AXADIA; ClinicalTrials.gov identifier NCT02933697), comparing phenprocoumon and apixaban (with a planned enrollment of 222 patients). A total of 222 patients will be randomized in an open-labelled, 1:1 design to receive either apixaban 2.5 mg twice daily or dose-adjusted vitamin K antagonist therapy (target INR 2.0–3.0). All patients will be treated and followed up for a minimum of 6 months up to a maximum of 24 months. The primary outcome is major or clinically relevant, non-major bleedings or death of any cause. Secondary outcomes include stroke, cardiovascular death and other thromboembolic events, thus exploring the efficacy of apixaban. The estimated completion date of AXADIA trial is in July 2023.

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REFERENCES

1. 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;39(24):2314-25.
2. 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;74(1):104-32.
3. Stamellou E, Floege J. Novel oral anticoagulants in patients with chronic kidney disease and atrial fibrillation. Nephrol Dial Transplant. 2018;33(10):1683-9.
4. Sood MM, Larkina M, Thumma JR, Tentori F, Gillespie BW, Fukuhara S, et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. Kidney Int. 2013;84(3):600-8.
5. Winkelmayer WC, Liu J, Patrick AR, Setoguchi S, Choudhry NK. Prevalence of atrial fibrillation and warfarin use in older patients receiving hemodialysis. J Nephrol. 2012;25(3):341-53.
6. Chan KE, Giugliano RP, Patel MR, Abramson S, Jardine M, Zhao S, et al. Nonvitamin K Anticoagulant Agents in Patients With Advanced Chronic Kidney Disease or on Dialysis With AF. J Am Coll Cardiol. 2016;67(24):2888-99.
7. Laugesen EK, Staerk L, Carlson N, Kamper AL, Olesen JB, Torp-Pedersen C, et al. Non-vitamin K antagonist oral anticoagulants vs. vitamin-K antagonists in patients with atrial fibrillation and chronic kidney disease: a nationwide cohort study. Thrombosis J. 2019;17:21.
8. Jegatheswaran J, Hundemer GL, Massicotte-Azarniouch D, Sood MM. Anticoagulation in Patients With Advanced Chronic Kidney Disease: Walking the Fine Line Between Benefit and Harm. Can J Cardiol. 2019;35(9):1241-55.
9. Donze J, Rodondi N, Waeber G, Monney P, Cornuz J, Aujesky D. Scores to predict major bleeding risk during oral anticoagulation therapy: a prospective validation study. Am J Med. 2012;125(11):1095-102.
10. Jain N, Reilly RF. Clinical Pharmacology of Oral Anticoagulants in Patients with Kidney Disease. Clin J Am Soc Nephrol. 2019;14(2):278-87.
11. Aursulesei V, Costache, II. Anticoagulation in chronic kidney disease: from guidelines to clinical practice. Clin Cardiol. 2019;42(8):774-82.
12. Shroff GR. NOAC Dosing in Atrial Fibrillation and Renal Dysfunction: What Measure Are You Using? J Am Coll Cardiol. 2017;70(21):2733-4.
13. Manzano-Fernandez S, Andreu-Cayuelas JM, Marin F,

Orenes-Pinero E, Gallego P, Valdes M, et al. Comparison of estimated glomerular filtration rate equations for dosing new oral anticoagulants in patients with atrial fibrillation. Rev Esp Cardiol (Engl Ed). 2015;68(6):497-504.
14. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-Vitamin K Antagonist Oral Anticoagulant Dosing in Patients With Atrial Fibrillation and Renal Dysfunction. J Am Coll Cardiol. 2017;69(23):2779-90.
15. Samuelson BT, Cuker A, Siegal DM, Crowther M, Garcia DA. Laboratory Assessment of the Anticoagulant Activity of Direct Oral Anticoagulants: A Systematic Review. Chest. 2017;151(1):127-38.
16. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):160S-98S.
17. Hart RG, Pearce LA, Asinger RW, Herzog CA. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. Am J Kidney Dis. 2011;6(11):2599-604.
18. Kimachi M, Furukawa TA, Kimachi K, Goto Y, Fukuma S, Fukuhara S. Direct oral anticoagulants versus warfarin for preventing stroke and systemic embolic events among atrial fibrillation patients with chronic kidney disease. Cochrane Database Syst Rev. 2017;11:CD011373.
19. Dahal K, Kunwar S, Rijal J, Schulman P, Lee J. Stroke, Major Bleeding, and Mortality Outcomes in Warfarin Users With Atrial Fibrillation and Chronic Kidney Disease: A Meta-Analysis of Observational Studies. Chest. 2016;149(4):951-9.
20. Su X, Yan B, Wang L, Lv J, Cheng H, Chen Y. Oral Anticoagulant Agents in Patients With Atrial Fibrillation and CKD: A Systematic Review and Pairwise Network Meta-analysis. Am J Kidney Dis. 2021.
21. Feldberg J, Patel P, Farrell A, Sivarajahkumar S, Cameron K, Ma J, et al. A systematic review of direct oral anticoagulant use in chronic kidney disease and dialysis patients with atrial fibrillation. Nephrol Dial Transplant. 2019;34(2):265-77.
22. Harel Z, Chertow GM, Shah PS, Harel S, Dorian P, Yan AT, et al. Warfarin and the Risk of Stroke and Bleeding in Patients With Atrial Fibrillation Receiving Dialysis: A Systematic Review and Meta-analysis. Can J Cardiol. 2017;33(6):737-46.
23. Garlo KG, Steele DJR, Nigwekar SU, Chan KE. Demystifying the Benefits and Harms of Anticoagulation for Atrial Fibrillation in Chronic Kidney Disease. Clin J Am Soc Nephrol. 2019;14(1):125-36.
24. Mavrakanas TA, Garlo K, Charytan DM. Apixaban versus No Anticoagulation in Patients Undergoing Long-Term Dialysis with Incident Atrial Fibrillation. Clin J Am Soc Nephrol. 2020;15(8):1146-54.
25. Kuno T, Takagi H, Ando T, Sugiyama T, Miyashita S, Valentin N, et al. Oral Anticoagulation for Patients With Atrial Fibrillation on Long-Term Hemodialysis. J Am Coll Cardiol. 2020;75(3):273-85.
26. Herzog CA, Asinger RW, Berger AK, Charytan DM, Diez J, Hart RG, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2011;80(6):572-86.
27. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893-962.

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