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Prescribing patterns of new oral anticoagulants in patients with atrial fibrillation and chronic kidney disease: A narrative review

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Abstract. *This study aimed to investigate the prescribing patterns of new oral anticoagulants in atrial fibrillation patients based on creatinine clearance. A thorough analysis of articles published between 2017 and 2021 in databases such as PubMed, Scopus, and Google Scholar was conducted.*

The review revealed distinctive features in the use of new oral anticoagulants concerning glomerular filtration rate. Apixaban was identified as a judicious choice for individuals with kidney disorders, with approximately 25% of its dose excreted in urine. American guidelines specifically recommend apixaban for those with a creatinine clearance of less than 15 mL/min, while European recommendations contraindicate all new oral anticoagulants for such rates.

In instances where the glomerular filtration rate ranges from 15 to 29 mL/min, apixaban or edoxaban may be preferred due to the substantial renal elimination of edoxaban. Reduced dose regimens of rivaroxaban, edoxaban, and apixaban are advised for individuals with chronic kidney disease and a creatinine clearance between 15 and 30 mL/min.

Dabigatran, characterized by an 80% renal elimination rate, is recommended for individuals with a creatinine clearance exceeding 30 ml/min according to European guidelines and those with a clearance of at least 15 ml/min according to American guidelines.

Keywords: atrial fibrillation, new oral anticoagulants, creatinine clearance, chronic kidney disease.

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Особливості призначення нових оральних антикоагулянтів пацієнтам з фібриляцією передсердь та хронічною хворобою нирок. Огляд літератури

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Резюме. Метою цього дослідження було охарактеризувати особливості застосування нових оральних антикоагулянтів у пацієнтів із фібриляцією передсердь відповідно до кліренсу креатиніну. Проаналізовано статті, опубліковані у 2017-2023 роках в електронних базах PubMed, Scopus та Google Scholar.

У результаті цього огляду можна виділити наступні особливості застосування нових оральних антикоагулянтів залежно від швидкості клубочкової фільтрації. Доцільно призначати апіксабан у пацієнтів з порушенням функції нирок оскільки лише четверта його частина екскретується з сечею. Тільки цей препарат рекомендований американськими дослідниками при меншій за 15 мл/хв. швидкості клубочкової фільтрації. Відповідно до Європейських рекомендацій усі нові оральні антикоагулянти протипоказані при зазначеному кліренсі креатиніну. Близько 50% едоксабану екскретується нирками. Апіксабан та едоксабан найбільш доцільні у пацієнтів із більшою за 15мл/хв. і меншою за 29 мл/хв. швидкістю клубочкової фільтрації. Знижені дози ривароксабану, едоксабану та апіксабану рекомендовані для хворих на хронічну хворобу нирок, що мають більший за 15мл/хв. і менший за 29 мл/хв. кліренс креатиніну. Дабігатран має найбільший відсоток (80 %) ниркової елімінації і доцільний при швидкості клубочкової фільтрації більший за 30 мл/хв. відповідно до Європейських та 15 мл/хв. – до Американських гайдлайнів.

Ключові слова: фібриляція передсердь, нові оральні антикоагулянти, кліренс креатиніну, хронічна хвороба нирок.

Introduction. According to class IA recommendations for patients with atrial fibrillation (AF), it is reasonable to prefer new oral anticoagulants (NOACs) over vitamin K antagonists when used in combination with antiplatelet therapy [1, 2, 3]. Treatment with NOACs showed to be associated with significant reductions of cardiovascular and bleeding events [4].

Unless contraindicated, an oral, long-term anticoagulant is recommended in all patients with heart failure and paroxysmal, persistent, or permanent AF. For prevention of thromboembolic events in patients with AF and without severe mitral stenosis and/or mechanical valve prosthesis NOACs are preferred, as they have similar efficacy to vitamin K antagonists but a lower risk of intracranial haemorrhages [5].

Respectively to European recommendations all NOACs are contraindicated if creatinine clearance (CrCl) is less than 15 ml/min and dabigatran can not be prescribed if this indicator is less than 30 ml/min [1].

Abnormal renal function is one of the criteria of HAS-BLED score which includes presence of dialysis, that is a modality of kidney replacement therapy, supporting approximately 10%-15% of patients with renal failure worldwide [6], kidney transplant and more than 200 mmol/L range of serum creatinine (for each factor

one point) [1]. High bleeding risk is determined if according to such score person have 3 points and more [7]. As a result creatinine clearance as an indicator of chronic kidney disease (CKD) is an important for the estimation of the dose of NOACs.

Chronic kidney disease (CKD) poses a substantial global public health challenge, exposing individuals to heightened risks of end-stage kidney disease, cardiovascular issues, and various mental and physical health complications associated with CKD, ultimately leading to premature mortality [8-10]. The situation in Ukraine is particularly complex, with citizens grappling not only with the challenges of living with kidney failure but also contending simultaneously with their diagnosis, the ongoing pandemic, and the impact of war [11].

The early changes in the kidneys and heart are explained by the development of microangiopathies, which is a typical feature of the pathogenesis of diabetes [12].

Albuminuria is the criteria of CKD too. Even the smallest degree of albuminuria increases risk for cardiovascular diseases and all-cause death [13]. Marushchak M., et al suggested that serum uric acid level is markedly elevated and positively associated with albuminuria in type 2 diabetic patients with comorbid obesity [14]. Furthermore, the degree of albuminuria is positively correlated with the level of low-density lipoproteins, triglycerides, total cholesterol [15], disorders of which are the risk factors for AF [1].

Reduced dose regimens of rivaroxaban, edoxaban, and apixaban are feasible options for severe CKD characterized by CrCl from 15 to 30 mL/min using the Cockcroft-Gault equation [1, 16, 17].

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CKD is defined as persistently elevated urine albumin excretion (more than 30 mg/g (3 mg/mmol) creatinine, persistently reduced estimated glomerular filtration rate (GFR) which is less than 60 ml/min per 1,73 m²), or both, for greater than 3 months, in accordance with KDIGO guidelines [18].

Prescribing patterns of apixaban in patients with atrial fibrillation and chronic kidney disease. The standard dose of apixaban for persons with AF is 5 mg twice a day. If serum creatinine is more than 1,5 mg/dL (133 mmol/L) the dose of apixaban must be 2,5 mg once daily [1].

Elimination occurs via multiple pathways including metabolism, biliary excretion, and direct intestinal excretion, with approximately 27% of total apixaban clearance occurring via renal excretion [19]. Finally about quarter of the orally administered dose of this drug is excreted in urine. As a result it is reasonable to use it for persons with kidney disorders. Unlike warfarin, apixaban does not need monitoring of the patient's international normalized ratio, offering an advantage [20]. Apixaban in a dose 2,5 mg twice daily based on a CrCl between 15 ml/min and 29 ml/min is recommended [21].

Reed D, et al. suggests that apixaban is a safe and effective alternative in patients with end stage renal disease maintained on dialysis [22]. As a result to American recommendation dialysis had a limited impact on apixaban clearance. Furthermore, limited data exist on single- and multiple dose apixaban (2,5 mg or

5 mg) in patients with AF and CKD on dialysis compared to healthy patients [23].

Mavrakanas TA, et al. wrote that apixaban 2,5 mg twice daily in patients on hemodialysis resulted in drug exposure comparable with that of the standard dose (5 mg twice daily) in patients with preserved renal function might be a reasonable alternative to warfarin for stroke prevention in patients on dialysis [24].

Siontis and colleagues retrospectively compared the rate of stroke/systemic embolism, major bleedings and death between patients on dialysis treated with apixaban versus warfarin [17]. The researchers concluded that both standard and reduced dose of apixaban (5 and 2.5 mg BID, respectively) were associated with a lower risk of major bleedings, but only the standard dose significantly reduced thromboembolic events and death compared to warfarin. However, they described also high rates of intracerebral bleedings and drug discontinuations, casting doubts on the real progress in the management of these complex patients [17].

Apixaban or edoxaban may be preferable in patients with GFR from 15 till 29 mL/min [25].

Prescribing patterns of edoxaban in patients with atrial fibrillation and chronic kidney disease. About 50% of the edoxaban is cleared through the kidneys in unchanged form and excreted in the urine, 50 % is eliminated through the biliary and intestinal system and excreted through feces. Edoxaban is contraindicated if glomerular filtration rate is less than 15 mL/min [26].

The standard dose of it for persons with AF is 60 mg once daily. If CrCl is more than 30 ml/min and less than 50 ml/min the dose of edoxaban must be 30 mg once daily [1]. The dose should be reduced to 30 mg daily in patients with moderate renal dysfunction (CrCl is from 15 to 50 mL per minute [27].

Prescribing patterns of rivaroxaban in patients with atrial fibrillation and chronic kidney disease. The standard dose of rivaroxaban for persons with AF is 20 mg once daily. If CrCl is more than 15 ml/min and less than 49 ml/min the dose of rivaroxaban must be 15 mg once daily [1]. Rivaroxaban has an intermediate renal clearance (33%) [25].

In patients at high bleeding risk rivaroxaban 15 mg once daily should be considered in preference to rivaroxaban 20 mg once daily for the duration of concomitant single or dual antiplatelet therapy, to mitigate bleeding risk [1, 28].

Rivaroxaban in reduced dose (15 mg) once daily is reasonable for prescription respectively to European and in US recommendation for persons with GFR more than 15 and less than 50 mL/min, in full dose (15 mg) once daily for all patients with CrCl more than 50 mL/min [1, 25]. This drug has 35% of renal elimination [25].

Prescribing patterns of dabigatran in patients with atrial fibrillation and chronic kidney disease. In patients at high bleeding risk, dabigatran 110 mg twice daily should be considered in preference to dabigatran 150 mg twice daily for the duration of concomitant single or dual antithrombotic therapy, to mitigate bleeding risk [1, 2].

Dabigatran has the highest renal elimination (80%) [25, 29].

Prescribing patterns of new oral anticoagulants in patients with acute coronary syndrome and chronic kidney disease. According to American trials a low dose dabigatran 75 mg twice daily has been approved for patients with severe CKD (a CrCl of 15–29 mL/min) respectively to pharmacokinetic simulations [25]. Based on European guidelines it is contraindicated in persons with such ranges [1].

Cockcroft-Gault formula for calculation of CrCl was adopted by a lot of randomized controlled trials [29].

According to the 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation it is recommended to apply the same diagnostic and therapeutic strategies in patients with CKD (dose adjustment may be necessary) as for patients with normal renal function. It is recommended to assess kidney function by GFR in all patients [30].

Rivaroxaban is a part of antithrombotic therapy in non-ST-segment elevation acute coronary syndrome patients without atrial fibrillation undergoing percutaneous coronary intervention [30].

In patients with atrial fibrillation without mechanical prosthetic heart valves or moderate-to-severe mitral stenosis undergoing percutaneous coronary intervention or

managed medically rivaroxaban monotherapy (15 mg or 10 mg once daily with CrCl from 15 to 49 mL/min was non-inferior to combination therapy for the primary efficacy composite endpoint of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or overall death. Regarding the need to continue with any antiplatelet agent beyond 12 months, the AFIRE trial AF patients treated with percutaneous coronary intervention more than 1 year earlier or with documented coronary artery disease to receive either monotherapy with rivaroxaban or combination therapy with rivaroxaban plus a single antiplatelet agent [30, 31].

Respectively to the algorithm for antithrombotic therapy in non-ST-segment elevation acute coronary

syndrome patients with atrial fibrillation undergoing percutaneous coronary intervention or medical management for both triple and dual antithrombotic therapy regimens, the recommended doses for the NOACs are as follows: apixaban 5 mg twice daily [3], dabigatran 110 mg or 150 mg twice daily [2], edoxaban 60 mg/d and rivaroxaban 15 mg or 20 mg/d [28].

Recommendations for the doses of NOACs respectively to GFR according to European and American guidelines.

Vio R, et al. discuss the current evidence regarding efficacy and safety profiles of NOACs according to different clinical setting and glomerular filtration rate [29], presented in Tables 1 and 2.

Table 1

Recommendations for direct oral anticoagulants dosing based on renal function according to European guidelines

Drug	GFR (ml/min)				
	> 95	50 – 95	30 – 50	15 – 30	< 15
Dabigatran	150 mg BID		110 mg BID or 150 mg BID	contraindicated	
Rivaroxaban	20 mg OD		15 mg OD		contraindicated
Edoxaban	60 mg OD	60 mg OD or 30 mg OD	30 mg OD		contraindicated
Apixaban	5 mg BID or 2,5 mg BID			2,5 mg BID	contraindicated

Notes: BID – twice daily; OD – once daily.

Table 2

Recommendations for direct oral anticoagulants dosing based of renal function according to American guidelines

Drug	GFR (ml/min)				
	> 95	50 – 95	30 – 50	15 – 30	< 15
Dabigatran	150 mg BID			75 mg BID	contraindicated
Rivaroxaban	20 mg OD		15 mg OD		contraindicated
Edoxaban	contraindicated	60 mg OD	30 mg OD		contraindicated
Apixaban	5 mg BID or 2,5 mg BID				

Notes: BID – twice daily; OD – once daily.

The standard dose of dabigatran is 150 mg twice daily, rivaroxaban – 20 mg once daily, edoxaban – 60 mg once daily, apixaban – 5 mg twice daily.

The reduced dose of dabigatran is 110 mg twice daily according to European and 75 mg twice daily according to American guidelines, rivaroxaban – 15 mg once daily, edoxaban – 30 mg once daily, apixaban – 2,5 mg twice daily [1, 5, 29].

The dose reduction criteria for dabigatran there high bleeding risk, for edoxaban – less than 60 kg of weight or concomitant potent P-Gp inhibitor. The dose reduction criteria for apixaban are at list 2 criteria. One of them are age more than 80 years old, other one is less

than 60 kg of weight, and the last one is more than 1,5 mg/dl [1, 5, 29].

As a result, if GFR is more than 95 ml/min according to European and American guidelines dabigatran and rivaroxaban is recommended in standard doses, apixaban – in standard or reduced doses. For such range of GFR according to European guidelines edoxaban is preferable in standard dose, American – it is contraindicated [1, 5, 29].

If GFR is more than 50 ml/min and less than 95 ml/min according to European and American guidelines it is recommended to use dabigatran and rivaroxaban in standard dose, apixaban – in standard or reduced

dose. For such range of GFR according to European guidelines edoxaban is preferable in standard or reduced dose, American – in standard dose [1, 5, 29].

If GFR is more than 30 ml/min and less than 50 ml/min according to European and American guidelines it is recommended to use rivaroxaban and edoxaban in reduced dose, apixaban – in standard or reduced dose. For such range of GFR according to European guidelines dabigatran is preferable in standard or reduced dose, American – in standard dose [1, 5, 29].

If GFR is more than 15 ml/min and less than 30 ml/min which is classified as fourth stage of CKD according to European and American guidelines it is recommended to use rivaroxaban and edoxaban in reduced dose. For such range of GFR according to European guidelines dabigatran is contraindicated, American – is preferable in reduced dose. Apixaban is recommended in reduced dose respectively to European and standard or reduced dose to American guidelines [1, 5, 29].

If GFR is less than 15 ml/min only apixaban can be prescribed in standard or reduced dose according to American guidelines. All other NOACs are contraindicated [1, 5, 29].

Conclusions. In conclusion, reduced dose regimens of rivaroxaban, edoxaban, and apixaban is recommended for persons with chronic kidney disease if creatinine clearance is more than 15 and less than 30 mL/min. Dabigatran has the highest renal elimination (80%) and is recommended for more than 30 ml/min according to European and 15 ml/min American guidelines. Only apixaban is recommended for persons with less than 15 mL/min CrCl respectively to American researches.

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