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Oral anticoagulation in end-stage CKD and atrial fibrillation

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Abstract---Leading cardiovascular diseases (arterial hypertension, coronary heart disease and diabetes mellitus) are often accompanied by such complications as atrial fibrillation (AF) and chronic kidney disease (CKD). As kidney function worsens, the risk of AF increases. The incidence of AF and CKD ranges from 5:1. At the same time, the risk of developing of end-stage CKD (ESCKD) increases in patients with AF. The combination of AF and ESCKD, on the one hand, increases the risk of thromboembolic complications, and on the other hand, it can cause hemorrhagic complications, which makes it difficult to decide whether to start oral anticoagulant therapy.

Keywords---atrial fibrillation, ESCKD, TEC, oral anticoagulation.

Implication for health policy/practice/research/medical education

In this mini review, we aimed to clarify main actions of direct oral anticoagulants compared with vitamin K antagonists, their effectiveness as a preventive measure of stroke and systemic embolism, and their safe use in the patients with CKD on hemodialysis and with atrial fibrillation. On the other hand, observational studies suggest that the use of direct OACs, compared to warfarin, decreases the risk of deterioration in kidney function and progression of CKD. The overall benefit-risk ratio must be carefully analyzed in the patients who are at high risk group, and the decision to anticoagulation must be conducted in a patient-specific manner.

Introduction

The high risk of thromboembolic complications (TEC) associated with CKD in patients with AF, regardless of the traditional risk factors for stroke, remains the most relevant today. In addition, the presence of AF complicates the management of advanced CKD. Patients with AF and ESKD require frequent vascular access and are prone to a variety of bleeding disorders, including strokes, making decisions to initiate oral anticoagulation (OAC) difficult. Oral anticoagulant therapy (ACT) is the standard for the prevention of thromboembolic complications, and especially acute cerebrovascular accident (ACVA) in AF. New oral anticoagulants (NOAC) are not inferior to vitamin K antagonists (VKA) in terms of efficiency and surpass them in safety parameters in chronic kidney disease stages 1–3 and atrial fibrillation (some representatives of this groups).

Patients with CKD stages 4-5 were not included in studies of NOAC for AF, however, based on pharmacokinetic studies, inhibitors of factor Xa rivaroxaban and apixaban were approved for use (with caution) at a glomerular filtration rate (GFR) of 15-30 ml/min/1.73m². The data of clinical trials on the use of NOAC in this category of patients are limited, which determines the relevance of these studies. The problem of complications of ACT and the algorithm for control of function have not been practically studied in patients with a newly diagnosed decrease in GFR of no more than 30 ml/min/1.73m² and "floating" GFR, which is often found in patients with cardiovascular diseases. Another under-explored area is dynamics of renal function during anticoagulant therapy in patients suffering AF and ESKD.

Materials and Methods

Articles related to this topic were searched in PubMed, Scopus, Web of Science, Embase, Directory of Open Access Journals (DOAJ) and Google Scholar, using the following keywords or their combinations: ESKD, atrial fibrillation, NOAC, TTR (Time in therapeutic range), INR (international normalized ratio), warfarin, rivaroxaban, ischemic stroke and bleeding complications.

Oral anticoagulation in end-stage CKD and atrial fibrillation

Today, the most common clinical combination among patients with end-stage CKD is an increased incidence of AF. In the general population under the age of 60, the prevalence of AF is 0.7%, while among patients with end-stage CKD, this indicator increases to 27%, which negatively affects the long-term prognosis of patients with various stages of CKD, and also causes a noticeable increase the frequency and duration of their hospitalizations (1). The well-known study Atherosclerosis Risk in Communities (ARIC) registered that in patients with a GFR of 30 ml/min/1.73m², the risk ratio for developing AF is 3.2 in comparison with those with normal GFR (2).

Favorable indicators of the safety and effectiveness of NOAC in AF, in particular, rivaroxaban, have been demonstrated in large clinical trials (3-5). NOAC has been recommended for use in AF and CKD based on a number of sub- and meta-analyzes. One such clinical study is the study by Weir et al. [17], which compared

patients with atrial fibrillation and in pre-dialysis stage of CKD (81.3%) and 5 (18.7%). Of these, 781 received rivaroxaban (469 (60.1%) - 15 mg/day, 115 (14.7%) - 20 mg/day and 165 (21.1%) - 10 mg/day) and 1536 - warfarin (mean "Time in therapeutic range" (TTR) was 38%), mean follow-up 12 months. The relative risk (RR) in the rivaroxaban group versus warfarin was 0.91 (95% CI: 0.65-1.28, $p=0.60$) for major bleeding and 0.93 (95% CI: 0.46-1.90, $p=0.85$) for the risk of TEC.

Chashkina M.I. and coauthors also studied the clinical outcomes of 12545 patients with CKD (12155 with grade 3 CKD, 390 with grade 4 CKD) who participated in randomized controlled trials (RCTs), demonstrated a rate of TEC comparable to warfarin (RR 0.81, 95% CI: 0.65-1.00) and major bleeding (RR 0.79, 95% CI: 0.59-1.04) while taking NOAC (6). CKD of late stages with a GFR decrease of no more than 30 ml/min/1,73m² (below 25 ml/min/1,73m² for apixaban) was an exclusion criterion in all studies. Direct inhibitors of factor Xa rivaroxaban and apixaban are approved for use (with caution) in GFR 15-30 ml/min as drugs with low renal clearance. The dabigatran, which is excreted by the kidneys up to 80%, can be assigned only if GFR is more than 30 ml/min/1,73m² (7).

The above mentioned study demonstrated that the incidence of ischemic events in two groups did not have significant difference. The high comorbidity in two groups explains the frequent readmission to hospital. About a third of all hospitalizations are associated with emergency reasons, among which decompensation chronic heart failure and paroxysmal AF prevailed. The above work is one of the examples of randomized prospective studies comparing rivaroxaban and VKA in patients with AF and a GFR of 15-29 ml/min/1,73m². It showed that while taking warfarin, the frequency of the development of minor clinically insignificant bleeding, mainly nasal and subcutaneous hemorrhages, as well as bleeding of the gums, significantly increased. It's worth noting that, according to the ISTH scale, both minor clinically significant and major bleeding also developed significantly more often in the warfarin group. The same trend was observed in the analysis of hemorrhagic complications according to the BARC scale (7-8).

It is known that achieving a target TTR>70% is difficult in advanced CKD (9). To increase the safety of therapy, the dose of warfarin will have to be dosed according to a new algorithm based on a low starting dose (2.5 mg/day) and more frequent (every 2-3 days) INR control at the dose selection stage. In some cases, dose selection can take up to six months, and each episode of significant changes in creatinine levels requires even more careful monitoring of INR, GFR and correction of therapy. Attention is directed to the phenomenon of "floating" GFR in a number of patients, which, naturally, reflects a natural transient deterioration of kidney function during the stage of decompensation of chronic heart failure, as evidenced by fluctuations the level of creatinine, which depends on the severity of it symptoms during hospitalization. And if for such patients the dose of rivaroxaban remains the same, then patients who received warfarin, in almost every case, have to adjust the dose.

It is important to analysis data from patients receiving warfarin, since the true state of renal function with the designation of the stage of CKD can be difficult to

determine. This is due to the rather frequent lack of anamnestic information about the level of creatinine in patients admitted to cardiology departments, and a clear idea of its further dynamics. In patients with a transient decrease in GFR after the hospital discharge, the creatinine level should be analyzed at least once every 3 weeks. Since in some cases, GFR can vary within a fairly wide range, varying until stabilization is reached, which allows to clearly define the stage.

All anticoagulants, to some extent, are excreted through the kidneys, which complicates their use in dialysis patients. This group of patients has the highest risk of drug accumulation and various bleeding between dialysis periods. Despite these problems, prospective randomized trials are currently underway that will clarify the problem of the superiority of reduced doses of NOAC over warfarin in patients with ESCKD and AF. The problem of the safety and efficiency of feasibility study prevention remains open to this day. Currently, it cannot be said that there is a good therapy option for the prevention of TEC in patients suffering AF and ESCKD. Doctors who begin VKA therapy for ESCKD should expect significant liability of anticoagulant activity for a long time and strictly monitor coagulation indicators. However, it must be admitted that the correct dose of NOAC may be the most appropriate therapeutic option for patients in advanced stage of CKD. They present a theoretical risk as there is no safety data available to be applied in dialysis patients with AF.

Conclusion

Based on the analysis of the conducted studies, data were obtained indicating a favorable safety profile of rivaroxaban in comparison with warfarin in patients suffering ESCKD and AF. Taking rivaroxaban was accompanied by an improvement in renal function, which may indicate a nephroprotective effect of the drug. Nevertheless, given the small sample of patients, large-scale studies are required to confirm the findings of various studies. Confirmation of these findings may be key in the choice of anticoagulant in patients suffering ESCKD and AF. We must make decisions to use NOAC or say no to drugs to prevent TEC in patients with ESCKD and AF.

Authors' contribution

RI and SA were the principal investigators of the study. RI was included in preparing the concept and design. SA revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Competing interests: The authors declare that they have no competing interests.

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