Dynamics of Kidney Function in Patients with Chronic Kidney Disease and Atrial Fibrillation Who Receive Dabigatran

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Atrial fibrillation (AF) is the most frequent type of supraventricular arrhythmias. The anticoagulant therapy should be prescribed to prevent thromboembolic events. According to randomized clinical trials, anticoagulants do not always prove their high efficiency in the real clinical practice. It is a complicated issue for any doctor to prescribe the anticoagulant therapy for patients with AF and CKD. 30 % of patients with atrial fibrillation are known to have chronic kidney disease, while 10–15% of patients with chronic kidney disease are diagnosed with atrial fibrillation. Currently, there are scarce studies into the use of direct oral anticoagulants in patients with atrial fibrillation and chronic kidney disease (in case of Glomerular Filtration Rate (GFR) below 45 ml/min/1.73 m^2).

Aim. To determine the dynamics of GFR in patients with AF and CKD (in case of GFR below 45 ml/min/1.73 m^2).

Material and Methods. The sub-analysis was carried out to examine a single-centre prospective study into the optimization of the anticoagulant therapy in the outpatient practice. Initially, 133 dabigatran taking patients were enrolled in the study, and 79 patients were included in the final analysis. Endpoints were changes in Glomerular Filtration Rate (CKD-EPI) formulae as of the inclusion date, in 6, 12, 24 and 60 months after the inclusion. Changes in the renal function shall mean a decrease or increase in GFR by ⩾5 ml/min.

Results. The average follow-up period for patients was 1785 ± 218 days. A GFR>45 ml/min/1.73 m^2 occurred in 116 (87.2%) patients, and a GFR <45 ml/min/1.73 m^2 was found in 17 (12.8%) patients. The average HAS-BLED score was 1.8, and CHA_2DS_2VASc score – 3.8. During the observation period, there were 3 cases of major bleeding and 133 cases of minor bleeding. Both major (p=0.025) and minor (p=0.012) bleeding were statistically significant more frequent in patients with GFR below 45 ml/min. During 5 years of follow-up, 66 (49.6%) patients had an average decrease in GFR of 3.32 ml/min/1.73 m^2 per year. Patients with the initially declined GFR (below 45 ml/min) did not demonstrate a significant dynamic of the renal function during the dabigatran therapy. The mortality rate in this group during the observation period was 61.5%.

Conclusion. In 49.6% of patients during 5 years of follow-up, GFR decreased by an average of 3.32 ml/min/1.73 m^2 per year, which does not exceed the indicators typical for patients with cardiovascular events and CKD.

Key words: atrial fibrillation, chronic kidney disease, anticoagulants, warfarin, bleeding.

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Introduction

Atrial fibrillation is the most common type of supraventricular heart rhythm disorder. Its prevalence is 1-2% in the general population [1,2]. According to domestic registries, the frequency of atrial fibrillation is 2.3% of observations when analyzing data from a regional polyclinic [2], 4.2% of all hospitalizations per year to a multidisciplinary hospital [3] and 21-31% of all hospitalizations per year to a cardiological branch [4,7]. Atrial fibrillation is one of the main pathogenetic factors in the development of ischemic stroke, which is currently becoming one of the leading causes of death and disability in the adult population in developed countries. [1,6].

Anticoagulant therapy is recommended for the prevention of thrombotic events. According to the data of randomized clinical trials, the high efficacy of anticoagulant drugs can't always be realized in real clinical practice. There are limited data on patient adherence to anticoagulant therapy after hospital discharge. According to a sample of patients with acute coronary syndrome and atrial fibrillation from the RECORD-3 register [7], anticoagulant therapy after discharge from the hospital is prescribed to 1/3 of patients, and adherence to treatment after 6-12 months decreases from 28% to 18%. Currently, antithrombotic therapy control rooms are widespread to improve these indicators.

A difficult clinical task of a physician is the appointment of anticoagulant therapy to patients with atrial fibrillation and concomitant diseases. The high risk of thrombotic complications, initially characteristic of patients with atrial fibrillation, increases when combined with coronary heart disease, chronic heart failure, cancer and chronic kidney disease [5,8]. One of the challenges for the physician is the prescription of anticoagulant therapy for patients with atrial fibrillation and chronic kidney disease. It's known that 30% of the population with atrial fibrillation is diagnosed with chronic kidney disease, and 10-15% of patients with chronic kidney disease have atrial fibrillation [9]. The combination of chronic kidney disease and atrial fibrillation in patients raises questions about changes in the pharmacokinetics and pharmacodynamics of prescribed drugs, as well as the effectiveness and safety of the therapy. This is of particular importance for the cardiologist when prescribing anticoagulant therapy as thromboprophylaxis in patients with atrial fibrillation and chronic kidney disease [9,10]. Currently, patients with atrial fibrillation are advised to use direct oral anticoagulants (apixaban, rivaroxaban and dabigatran) [11,12]. Dabigatran is limited to patients with a glomerular filtration rate <30 ml/min/1.73 m^2, and the use of factor Xa inhibitors (apixaban and rivaroxaban) is contraindicated in patients with a glomerular filtration rate <15 ml/min/1.73 m^2 [13,14].

Currently, in our country, insufficient research is being carried out on the use of direct oral anticoagulants in patients with atrial fibrillation and chronic kidney disease (with a glomerular filtration rate <45 ml/min/1.73 m^2). Several studies are available on the use of apixaban and rivaroxan in patients with advanced chronic kidney disease, but there are no results of using dabiratran in patients with a glomerular filtration rate <45 ml/min/1.73 m^2.

Objective: to study the dynamics of the glomerular filtration rate in patients with atrial fibrillation and chronic kidney disease (glomerular filtration rate less than 45 ml/min/1.73 m^2) taking dabigatran.

Material and methods

A subanalysis of a single-center prospective study to optimize anticoagulant therapy in outpatient practice was carried out. Patients over 18 years of age with atrial fibrillation and indications for anticoagulant therapy were included in the main study, who were observed in the anticoagulant therapy control room at the Cardiology Department of the Clinical Hospital No. 1 of the Sechenov University from 2013 to 2015. The study was approved by the local ethics committee. All patients signed an informed consent form.

Inclusion criteria for subanalysis: glomerular filtration rate at inclusion in the study <90 ml/min/1.73 m^2, dabigatran intake.

Information was collected during the first and subsequent consultations. All patients were assessed for the risk of thromboembolic complications using the CHA_2DS_2VASc scale, and the risk of bleeding was assessed using the HAS-BLED scale.

Endpoints - change in the glomerular filtration rate CKD-EPI at the time of inclusion and 6, 12, 24 and 60 months after inclusion. A decrease or increase

in glomerular filtration rate of ⩾5 ml/min/1.73 m^2 was taken under the change in renal function. All patients included in the study were assessed for the risks of cardiovascular complications according to the MACE scale, the number of major and minor bleeding according to the TIMI scale, systemic thromboembolism, and mortality. Serum creatinine and glomerular filtration rate after 3-5 years were also evaluated.

Statistical analysis of the results was performed using SPSS Statistics 23.0 software. The Kolmogorov-Smirnov test was performed to assess the normal distribution of the data. Data are presented as mean and standard deviation for normally distributed variables, and data are presented as median with interquartile range (25th and 75th percentile values in parentheses) for nonparametric variables. The main characteristics of the groups were compared using the χ^2 test and Fisher's exact test for ordinal variables, the Kruskal-Wallis test for independent samples for continuous variables with a non-normal distribution. The dynamics of indicators was assessed using the Wilcoxon signed rank test for related samples. Survival analysis was performed using Cox regression analysis. Differences were considered statistically significant at $p<0.05$.

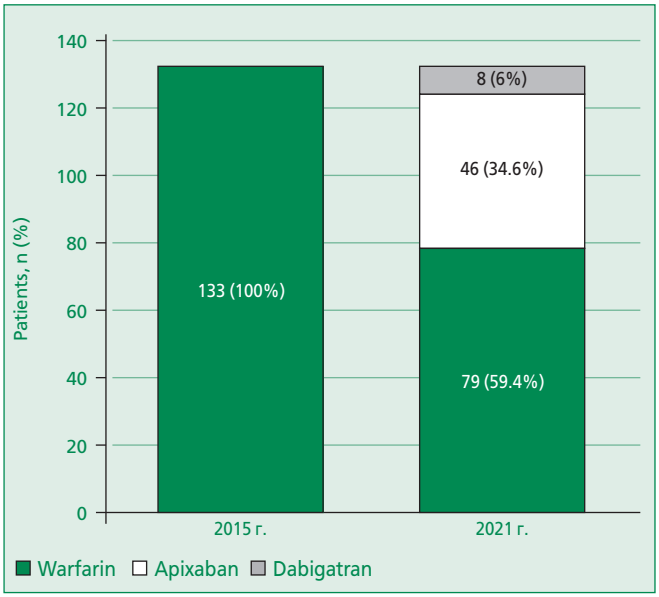

Figure 1. Anticoagulants prescribed by the doctor for patients with atrial fibrillation and decreased glomerular filtration rate at the beginning of the study and after 5 years of follow-up (n=133)

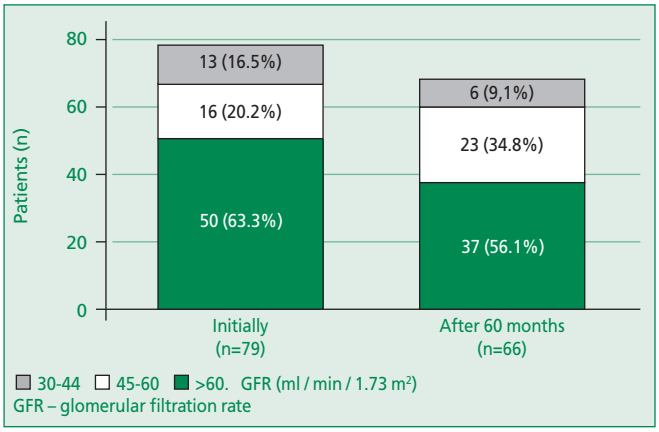

Figure 2. Distribution of stages of chronic kidney disease at baseline and after 60 months of follow-up in patients included in the subanalysis

Results

137 of 782 patients with atrial fibrillation and with indications for anticoagulant therapy took dabigatran. 133 patients met the criteria for inclusion in the subanalysis at the beginning of the study, some of whom changed their anticoagulant during the observation period for various reasons (Fig. 1). If the endpoint occurred in a patient before 2021, and he continued to take dabigatran, then this patient was included in the final analysis, and if there was a drug change, then the patient was excluded from the study. The final analysis included 79 patients (59.4%) treated with dabigatran with a glomerular filtration rate <90 ml/min/1.73 m^2 at inclusion in

Table 1. Clinical and demographic characteristics of patients included in the analysis (n=79)

Parameter	Value
Age, years	64±11
Mens, n (%)	29 (36,7)
Concomitant diseases	
Hypertonic disease, n (%)	51 (64.6)
History of myocardial infarction, n (%)	21 (26.6)
Chronic heart failure, n (%)	14 (17.7)
History of ischemic stroke, n (%)	49 (62)
Diabetes, n (%)	15 (19)
Glomerular filtration rate, ml/min/1.73m2	68 (54; 78)
CHA2DS2VASc, marks	3,8±1.6
HAS-BLED, marks	1,8±0.8
Pharmacotherapy	
Beta-blockers, n (%)	79 (100)
ACE inhibitors, n (%)	53 (67.1)
Diuretics, n (%)	31 (39.2)
Digoxin, n (%)	13 (16.5)
Acetylsalicylic acid, n (%)	20 (25.3)
Statins, n (%)	64 (81)

Data are presented as M±SD or Me (25%; 75%), unless otherwise indicated

ACE inhibitors – angiotensin converting enzyme inhibitors

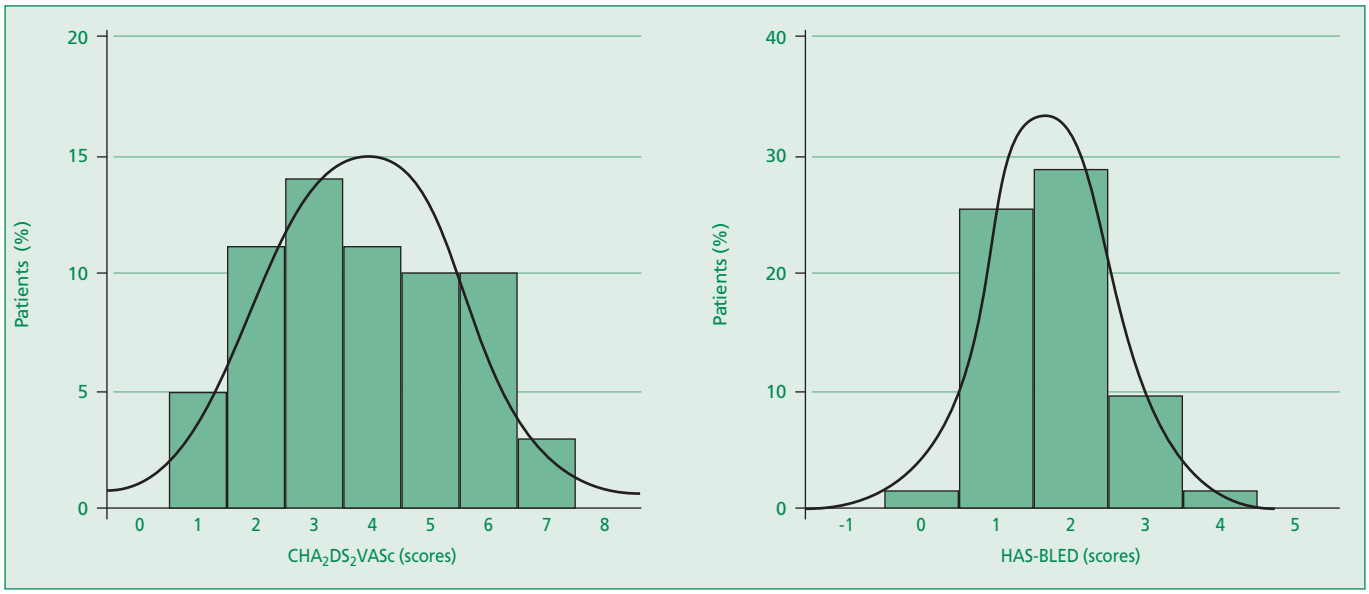

Figure 3. Risks of thromboembolic events (CHA_2DS_2VASc) and bleeding (HAS-BLED) in patients included in the subanalysis

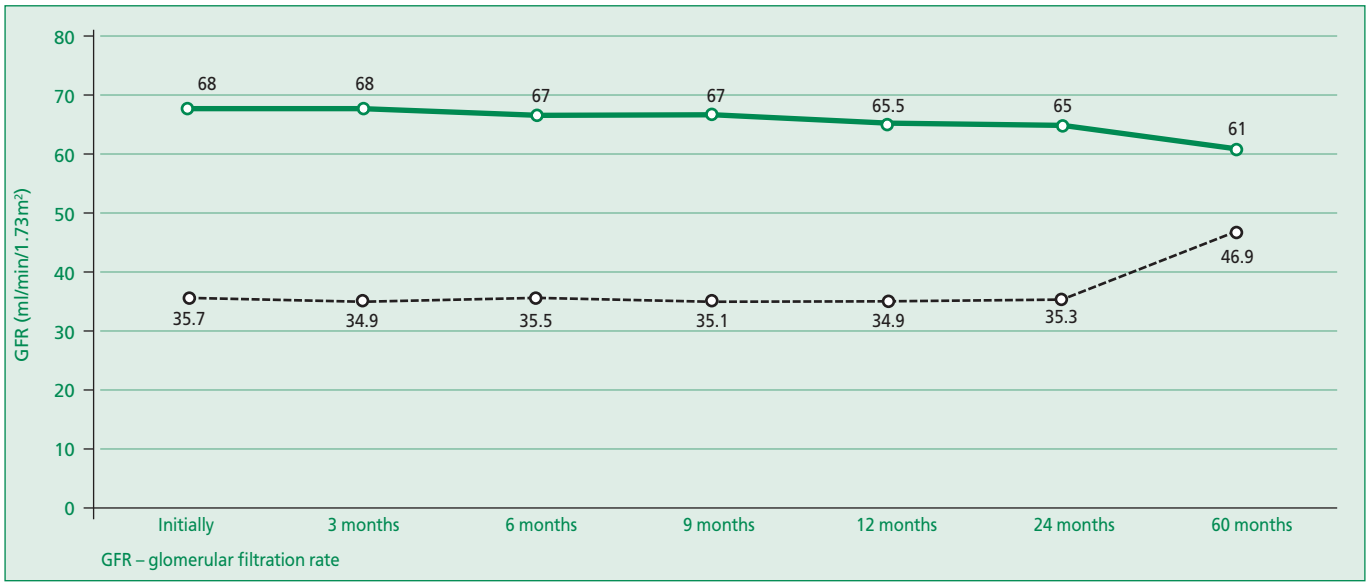

Figure 4. Changes in glomerular filtration rate in patients with atrial fibrillation and chronic kidney disease included in the study

the study. Clinical and demographic characteristics are presented in Table 1.

The glomerular filtration rate in 66 patients (83.5%) patients was ⩾45 ml/min/1.73 m², the glomerular filtration rate <45 ml/min/1.73 m² was observed in 13 (16.5%) patients (Fig. 2).

The risk of bleeding and thromboembolic events is shown in Fig. 3. The average score on the HAS-BLED scale was 1.8. The average score on the CHA_2DS_2VASc scale was 3.8.

The average follow-up period for patients was 1785±218 days (minimum 679 days, maximum 1849 days).

Renal function in patients with atrial fibrillation with a glomerular filtration rate <90 ml/min/1.73 m² significantly decreased from 68 (54; 78) ml/min to 61 (54.8; 74.4) ml/min during 5 years of follow-up (p <0.0001; Fig. 4). On average, the decrease in the glomerular filtration rate was 4.9 ml/min/1.73 m². During the observation period, the glomerular filtration rate decreased by more than 5 ml/min/1.73 m² in 50% (n=33) of patients. The glomerular filtration rate increased by more than 5 ml/min/1.73 m² in 24.2% (n=16) of patients, and the glomerular filtration rate didn't change in 25.8% (n=17) of patients.

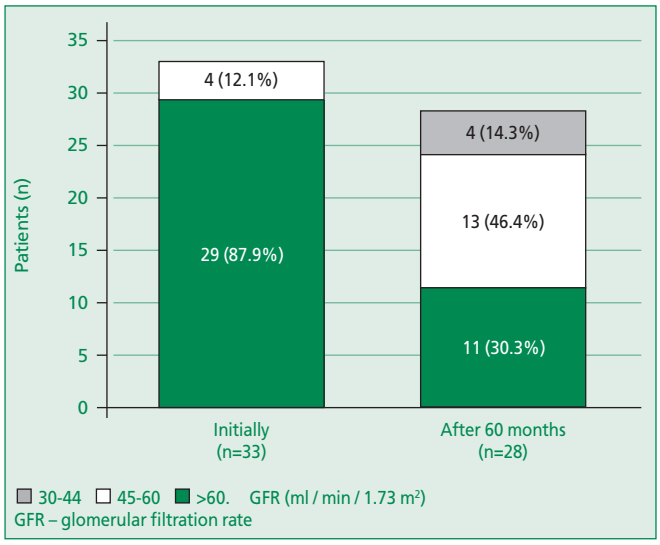

Figure 5. Distribution of stages of chronic kidney disease in patients with a decrease in glomerular filtration rate during the observation period

Comparison of patients with a worsening glomerular filtration rate during the observation period with the rest of the patients (the glomerular filtration rate is stable or increased) didn't reveal statistically significant differences in clinical and demographic characteristics.

The change in the glomerular filtration rate among patients with a decrease in renal function was -16.6±7.4 ml/min/1.73 m^2 (-3.32 ml/min/1.73 m^2/year). All patients who had a decrease in renal function were among patients with an initial glomerular filtration rate of ⩾45 ml/min (Fig. 5).

We also note that there was no statistically significant decrease in renal function among patients with an initially decreased glomerular filtration rate (<45 ml/min) (Fig. 4). An increase in the average glomerular filtration rate from 35.7 to 46.9 ml/min/1.73 m^2 in this group of patients after 5 years of follow-up is noteworthy. This is due to the fact that out of 8 out of 13 patients with a glomerular filtration rate <45 ml/min/1.73 m^2 included in the study, died from various causes during the observation period. The remaining 5 patients had an initially higher glomerular filtration rate, in which the glomerular filtration rate didn't decrease during the observation period.

During the observation period, the patients had 3 major and 133 minor bleeding. Both major (p=0.025) and minor (p=0.012) bleeding were observed statistically significantly more often among patients with a glomerular filtration rate <45 ml/min.

During 5 years of follow-up, 13 patients died (Table 2).

Cox regression analysis revealed that the risk of death is greater in patients with a more pronounced decrease in glomerular filtration rate at inclusion (Fig. 6).

It was not possible to assess whether decreased glomerular filtration rate is an independent predictor of poor prognosis in patients with atrial fibrillation and chronic kidney disease.

Discussion

The efficacy and safety of dabigatran for the prevention of thrombotic complications in atrial fibrilla-

Table 2. Causes of death among patients included in the study

Cause of death	Number of
Ischemic events, n (%) including	7 (8.9)
• acute cerebrovascular accident	3 (3.8)
• myocardial infarction	2 (2.5)
• pulmonary embolism	2 (2.5)
Oncological disease, n (%)	2 (2.5)
Flu, n (%)	1 (1.3)
COVID-19, n (%)	1 (1.3)
Accident, n (%)	1 (1.3)
Cause unknown, n (%)	1 (1.3)
General mortality – 3.3% per year	
Mortality from cardiovascular causes – 1.8% per year	
Mortality from myocardial infarction – 0.5% per year	
Mortality from thromboembolic events (acute cerebrovascular accident and pulmonary embolism) – 1.01% per year	

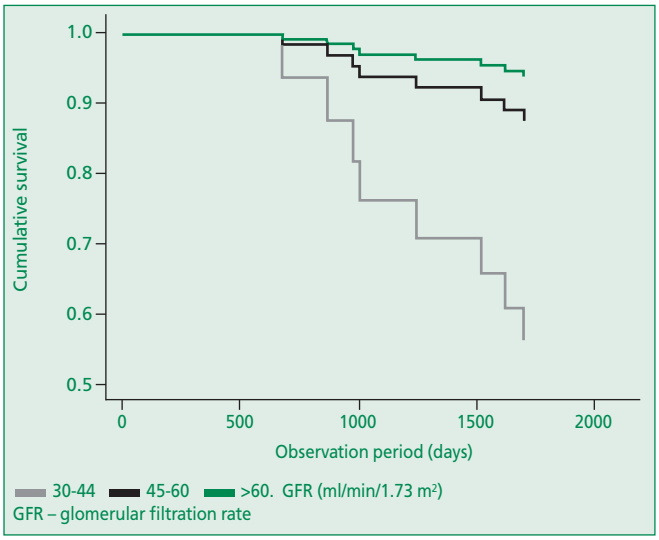

Figure 6. Survival of patients included in the study (n=79)

tion has been proven in a large, multicenter, blind, placebo-controlled, randomized study RE-LY [16], which included 18,113 patients with nonvalvular atrial fibrillation and indications for anticoagulant therapy. 20% of patients included in the study had creatinine clearance of 30-49 ml/min, patients with creatinine clearance <30 ml/min were not included in the study. Although 80% of dabigatran is excreted by renal excretion, the efficacy profile of both doses was maintained regardless of renal function, and the relative risk of major bleeding was lower or comparable to warfarin depending on renal function in the study [16].

In a prospective study IDEA [17], the incidence of nephropathy in patients taking dabigatran was assessed and the possible correlation between plasma dabigatran concentration and impairment of renal function was investigated. The researchers concluded that there was no lasting negative effect of dabigatran etexilate on kidney function, and there was no association between its high concentration and kidney damage.

It's also known that the glomerular filtration rate decreases with age by an average of 0.4 ml/min per year [18]. The decrease in the glomerular filtration rate is more pronounced in patients with concomitant cardiovascular diseases, and amounts to 1.83 ml/min/1.73 m^2 per year according to some authors [19]. The decrease in the glomerular filtration rate in patients with chronic kidney disease is 2.65 ml/min/1.73 m^2 per year [19].

A study by Y. Xiaoxi et al. [20] included 9769 patients with nonvalvular atrial fibrillation who were first prescribed anticoagulants (apixaban, dabigatran, rivaroxaban, or warfarin). The authors analyzed the incidence of renal endpoints (⩾30% decrease in glomerular filtration rate, doubling of creatinine levels, acute renal failure, onset of chronic kidney disease). The cumulative two-year risk of these events for dabigatran was 4%. Compared with warfarin, dabigatran was associated with a reduced risk of creatinine doubling and acute renal failure.

A feature of our study was the inclusion in the analysis of only patients with a reduced glomerular filtration rate (<90 ml/min/1.73 m^2) and a long follow-up period (5 years). During 5 years of observation, 50% of patients observed a decrease in the glomerular filtration rate by an average of 3.32 ml/min/1.73 m^2 per year, which doesn't exceed the indicators typical for patients with cardiovascular events and chronic kidney disease. Also, the features of the study are the absence of dynamics of the glomerular filtration rate among patients with an initially reduced glomerular filtration rate (<45 ml/min/1.73 m^2), which is probably associated with a small sample of patients.

The study also confirmed data on an increase in the incidence of bleeding and mortality among patients with chronic kidney disease (<45 ml/min/1.73 m^2). The mortality analysis showed data comparable to the large studies RE-LY and RELY-ABLE.

The main limitation of the study is the small sample size, which can affect the accuracy of the results obtained.

Conclusion

The glomerular filtration rate decreased on average by 3.32 ml/min/1.73 m^2 per year in 50% of patients during the 5-year the observation period, which doesn't exceed the rates typical for patients with cardiovascular events and chronic kidney disease. An increase in the average glomerular filtration rate from 35.7 to 46.9 ml/min/1.73 m^2 is observed in patients with a glomerular filtration rate <45 ml/min/1.73 m^2 after 5 years of the observation. This is due to the fact that 8 out of 13 patients with a glomerular filtration rate <45 ml/min/1.73 m^2 included in the study died from various causes during the observation period, the rest of the patients didn't observe a decrease in the glomerular filtration rate.

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