ORIGINAL ARTICLES

Chashkina M.I.1, Andreev D.A.1, Kozlovskaya N.L.2,3, Salpagarova Z.K.1, Suvorov A.Yu.1, Bykova A.A.1, Suchkova S.A.1, Syrkin A.L.1

1 I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia
2 City Clinical Hospital. A.K. Eramishantseva, Department of Health of Moscow, Russia
3 Peoples’ Friendship University of Russia (RUDN University), Moscow, Russia

SAFETY PERFORMANCE OF RIVAROXABAN VersUS WArfarIN IN PATIENTS WITH ATRIAL FIBRILLATION AND ADVANCED CHRONIC KIDNEY DISEASE

Aim
To evaluate safety of using rivaroxaban in patients with stage 4 chronic kidney disease (CKD) or transient, stable decline of glomerular filtration rate (GFR) to 15–29 ml/min/1.73 m² in the presence of atrial fibrillation (AF).

Material and methods
This multicenter prospective, randomized study included patients admitted to cardiology departments from 2017 through 2019. Of 10224 admitted patients 109 (3%) patients with AF and stage 4 CKD or a stable decline of GFR to 15–29 ml/min/1.73 m² were randomized at 2:1 ratio to the rivaroxaban 15 mg/day (n=73) treatment group or to the warfarin treatment group (n=36). The primary endpoint was development of BARC and ISTH major, minor, and clinically relevant minor bleeding. Mean follow-up duration was 18 months.

Results
Patients receiving warfarin had a significantly higher incidence of BARC (n=26 (72.2 %) vs. n=31 (42.4 %), p<0.01) and ISTH (n=22 (61.1 %) vs. n=27 (36.9 %), p<0.01) minor bleeding and all ISTH clinically relevant (minor clinically relevant and major bleedings) n=10 (27.7 %) vs. n=8 (10.9 %), p=0.03]. The number of repeated hospitalizations was 65 (43% of patients) in the rivaroxaban treatment group and 27 (48% of patients) in the warfarin treatment group (p=0.57), including 24 (36.9 %) and 11 (40.7 %) emergency admissions in the rivaroxaban and warfarin treatment groups, respectively (p=0.96). Significant improvement of changes in creatinine clearance and GFR (by CKD-EPI and Cockroft-Gault) was observed in the rivaroxaban treatment group.

Conclusion
The study provided evidence for a more beneficial safety profile of rivaroxaban compared to warfarin in patients with AF and advanced CKD.

Keywords
Atrial fibrillation; chronic kidney disease; anticoagulant therapy; rivaroxaban; warfarin

For citation
Chashkina M.I., Andreev D.A., Kozlovskaya N.L., Salpagarova Z.K., Suvorov A.Yu., Suchkova S.A. et al. Safety performance of rivaroxaban versus warfarin in patients with atrial fibrillation and advanced chronic kidney disease. Kardiologiia. 2020;60(11):94–100. [Russian: Чашкина М. И., Андреев Д. А., Козловская Н. Л., Салпагарова З. К., Суворов А. Ю., Сучкова С. А. и др. Показатели безопасности ривароксабана по сравнению с варфарином у пациентов с фибрилляцией предсердий и хронической болезнью почек поздних стадий. Кардиология. 2020;60(11):94–100].

Corresponding author
Chashkina M.I. E-mail: vebmar@mail.ru

Introduction
Atrial fibrillation (AF) and chronic kidney disease (CKD) are common complications of leading cardiovascular diseases, such as arterial hypertension, diabetes mellitus, and coronary heart disease. As kidney function deteriorates, the risk of AF increases [1]. At the same time, patients with AF are at a significantly increased risk of developing terminal CKD [2]. The combination of AF and CKD leads to an increased risk of thromboembolic complications, on the one hand, while on the other is a risk factor for bleeding [3]. Oral anticoagulant therapy (OAT) is the standard practice for the prevention of thromboembolic complications (TECs), and above all, cerebrovascular accident (CVA) in AF. In AF and CKD stage 1–3, direct oral anticoagulants (DOACs) are as effective as vitamin K antagonists (VKAs) (some of DOACs) and are safer [4]. Patients with CKD stage 4–5 were not included in the trials of DOAC in AF. However, direct Xa inhibitors rivaroxaban and apixaban have been approved (with caution) in a glomerular filtration rate of 15–30 mL/min/1.73 m² based on pharmacokinetic studies [5]. There is limited clinical data on the use of DOACs in this group of patients with AF, which makes the comparative studies with VKAs relevant. The complications of OAT and the algorithm for monitoring kidney function in patients with newly detected decrease in GFR less than 30 mL/min/1.73 m² and floating GFR, common in patients with cardiovascular diseases, remain almost unexplored. Changes in kidney function during anticoagulant therapy in patients with AF and late-stage CKD is another understudied area.
Objective
To assess the safety parameters of rivaroxaban in patients with CKD stage 4 or persistent reduction of GFR in AF up to 15–29 mL/min/1.73 m².

Material and methods
Patients
The study included patients hospitalized between 2017 and 2019 in the cardiology departments of five hospitals in Moscow which mainly provide emergency medical care. Inclusion criteria were age over 18 years; any form of nonvalvular AF, documented; the presence of indications for ACT; pre-diagnosed CKD stage 4 or transient reduction of GFR to 15–29 mL/min/1.73 m² newly detected at admission which continued throughout the inpatient period (at least 3 consecutive measurements during hospital stay). Exclusion criteria were myocardial infarction and unstable angina within the previous 12 months; ischemic CVA not older than one month and hemorrhagic CVA of any age; a history of bleeding requiring hospitalization; decrease in hemoglobin less than 80 g/L, platelet count less than 100×10⁹/L; indications for anti-platelet therapy; continuous use of drugs that increase the risk of bleeding (e.g., nonsteroidal anti-inflammatory drugs) and CYP3A4 inhibitors; and liver cirrhosis.

All patients included in the study signed informed consent. CKD was diagnosed following the KDIGO criteria. GFR was calculated using the currently recommended CKD-EPI (Chronic Kidney disease Epidemiology Collaboration) formula, as well as the Cockroft–Gault formula [6]. We used two formulas to correctly compare our results with those obtained in previous studies since the Cockroft-Gault formula was used, in order to evaluate kidney function in all large randomized controlled trials (RCTs) of DOACs [7–10]. ACT indications were determined in accordance with the Russian and European guidelines for AF using the TEC risk score CHA2DS2-VASc and the bleeding risk score HAS-BLED [11, 12]. Anemia was classified under the recommendations of the World Health Organization [13]. The time of international normalized ratio (INR) in therapeutic range (TTR) was estimated using the Rosendaal method. An individual INR table with automatic TTR calculation was generated for each patient. The target was TTR >70% [14]. All patients included in the study had received previously the best-possible DOAC therapy, or TTR was less than 60% with warfarin.

Study design
The study was open-label and randomized. Patients were randomized using MS Excel, at a ratio of 2:1 to receive rivaroxaban 15 mg or warfarin. Warfarin therapy was initiated using an algorithm based on a lower starting dose (2.5 mg/day) and more frequent (every 2–3 days) until the best possible dose was selected. Visits were scheduled every 3 months or more often, if necessary. Compliance was controlled, and adverse events were evaluated. Hemoglobin and creatinine levels were analyzed, and GFR was calculated following the available guidelines. Telephone calls and e-mail messages were used for monitoring of INR and for emergency consultations. INR was estimated in the certified laboratories. CoaguChek XS Plus and CoaguChek XS portable coagulometers were allowed.

Endpoint
The primary composite endpoint included the incidence of heavy, light, and clinically significant light bleeding events according to the BARC and ISTH scores [15, 16].

Statistical analysis
The data was processed using the R programming language. Standard methods of descriptive statistics were used: normality of the continuous variable distribution was estimated (Shapiro–Wilk test); normally distributed data was presented as the mean and the standard deviation, and non-normally distributed data as the median and the 25th and 75th percentiles; percentages of the categorical and ordinal variables were also defined. The comparative analysis of continuous numerical variables was performed using the Mann–Whitney U-test, of the ordinal and categorical ones using the Pearson χ² test. If it could not be applied due to small values, the Fisher exact test was used.

Linear mixed models were constructed for each group, in order to estimate the course of changes in creatinine and GFR levels over time. Time in months and the anticoagulant (rivaroxaban or warfarin) administered were chosen as fixed effects. The measure of differences in changes in each group was presented as a ratio of the interaction between the time and group variables. The significance of the ratio suggested different courses of changes in the creatinine and GFR levels in each group.

The ethics committee of the First Moscow State Medical University n.a. I. M. Sechenov approved the study.

Results
The data from 10,224 patients (medical records, anamnestic records) was analyzed, and 3,517 cases of nonvalvular AF were identified. 502 (15%) patients had CKD stage 4 or sustained decrease in GFR to 15–29 L/min/1.73 m² during hospital stay. Of them, 109 (3%) patients met the inclusion criteria and were randomized 2:1 to receive rivaroxaban 15 mg (n=73) or warfarin (n=36).

Patients did not significantly differ in terms of clinical and demographic characteristics except for the history of ischemic CVA, which was more common in the warfarin group. However, the risks of TECs (CHA2DS2 VASc) and bleeding (HAS-BLED) were comparable (Table 1).
The list of the drug classes and frequency of their use is given in Table 2.

The mean follow-up period was 18 months. Of the 109 patients included, 2 patients withdrew their consent, 9 patients were lost for follow-up, 8 patients started another DOAC, 4 patients had progression of CKD to stage 5, and 6 patients were given additional anti-platelet drugs.

In the warfarin group, TTR>70% was achieved in 34 (94%) patients. After obtaining at least three consecutive results for INR in the range of 2 to 3 in a public or commercial laboratory, some patients (n=17) were switched to INR control using a portable coagulometer. An average of 57 INR measurements over 18 months were needed to maintain target TTR in a single patient.

Patients taking warfarin were significantly more likely to develop light bleeding according to the BARC and ISTH scores. These were all clinically significant (heavy and clinically significant light) bleeding events (ISTH) (Table 3).

There are no significant differences in the incidence of any CVA, myocardial infarction, unstable angina, and all-cause deaths (Table 4).

The number of repeated all-cause hospitalizations was 65 (43% of patients) in the rivaroxaban group and 27 (48%) of patients in the warfarin group (p=0.57). Of these patients, 24 (36.9%) and 11 (40.7%) (in the rivaroxaban and warfarin groups, respectively) were hospitalized urgently (p=0.96).

Mixed linear models were constructed, in order to evaluate the course of changes in the levels of creatinine and GFR. The individual changes of the indicators for each patient were chosen as random effects, while time and the administration of warfarin or rivaroxaban were used as fixed effects. The graphical representation of the changes and differences is shown in Figures 1–3. The course of changes in creatinine and GFR (CKD-EPI and Cockroft–Gault) improved significantly in the rivaroxaban group compared to the warfarin group (Table 5, Figures 1–3): patients treated with rivaroxaban had increased GFR and decreased creatinine levels; whereas patients taking warfarin exhibited inverse changes in the renal function. Simultaneously, this trend was clear only when the CKD-EPI formula was used (Figure 3), while in cases when creatinine clearance was calculated using the Cockcroft–Gault formula, the values remained almost unchanged (Figure 2). It should be noted that 32 (43%) and 11 (34%) patients changed from CKD stage 4 to stage 3 in the rivaroxaban and warfarin group, respectively (p=0.26).

### Table 2. List of drug classes

| Pharmacological class            | Rivaroxaban group, n (%) | Warfarin group, n (%) | P   |
|----------------------------------|--------------------------|-----------------------|-----|
| ACE inhibitor/ARB                | 30 (41)                  | 15 (42)               | 0.67|
| Calcium channel blocker          | 51 (70)                  | 25 (69)               | 1.00|
| Loop diuretic                    | 30 (41)                  | 19 (53)               | 0.34|
| Thiazide diuretic                | 16 (22)                  | 11 (31)               | 0.45|
| Beta-blocker                     | 57 (78)                  | 33 (92)               | 0.13|
| Hypoglycemic drug                | 17 (23)                  | 8 (22)                | 1.00|
| Insulin                          | 7 (9.6)                  | 5 (13.9)              | 0.52|
| Statin                           | 63 (86)                  | 35 (97)               | 0.09|
| Erythropoietin                   | 8 (11)                   | 3 (8)                 | 1.00|
| Iron supplement                  | 45 (61)                  | 24 (67)               | 0.69|
| Proton pump inhibitor            | 34 (47)                  | 15 (42)               | 0.78|
| Uric acid-lowering drug          | 40 (55)                  | 26 (72)               | 0.12|

ACE, angiotensin-converting enzyme, ARB, angiotensin II receptor blocker.
The median levels of creatinine, GFR (CKD-EPI), and creatinine clearance (Cockroft–Gault) are presented in Tables 6–8.

Hemoglobin analysis showed no significant changes or differences between the groups: median baseline hemoglobin levels were 129 g/L [110; 136] in the rivaroxaban group; 123 g/L [112; 131] in the warfarin group (p=0.3); at 18 months – 130 g/l [112; 138]; and 121 g/l [114; 138], respectively (p=0.7).

### Discussion

The favorable safety and efficacy profile of DOACs in AF, particularly rivaroxaban, has been demonstrated in large clinical trials [7–9]. DOACs indicated for use in AF and CKD are based on several sub- and meta-analyses. For example, the clinical outcomes of 12,545 patients with CKD (12,155 patients with CKD stage 3 and 390 patients with CKD stage 4) were studied in the RCI. This showed the incidence of TECs (OR 0.81, 95% CI: 0.65–1.00, p=0.003) and heavy bleeding (OR 0.79, 95% CI: 0.59–1.04) during the use of DOACs comparable to warfarin [4]. Late-stage CKD with a decreased GFR of less than 30 mL/min/1.73 m² (less than 25 mL/min/1.73 m² for apixaban) was an exclusion criterion in all studies. Direct Xa inhibitors, rivaroxaban and apixaban, are approved to be used in GFR 15–30 mL/min (with caution) as drugs with low renal clearance. Direct thrombin inhibitors with CKD stage 3 and 390 patients with CKD stage 4) were studied in the RCI. This showed the incidence of TECs (OR 0.81, 95% CI: 0.65–1.00, p=0.003) and heavy bleeding (OR 0.79, 95% CI: 0.59–1.04) during the use of DOACs comparable to warfarin [4]. Late-stage CKD with a decreased GFR of less than 30 mL/min/1.73 m² (less than 25 mL/min/1.73 m² for apixaban) was an exclusion criterion in all studies. Direct Xa inhibitors, rivaroxaban and apixaban, are approved to be used in GFR 15–30 mL/min (with caution) as drugs with low renal clearance. Direct thrombin inhibitors
inhibitor dabigatran, which is excreted in urine up to 80%, can be administered only in GFR more than 30 mL/min.

This study is one of a few randomized prospective trials which compare rivaroxaban and vitamin K antagonists in patients with AF and GFR 15–29 mL/min/1.73 m². Light clinically insignificant bleeding (mainly nasal and subcutaneous hemorrhages and bleeding gums) was shown to be significantly common during the use of warfarin. It should be noted that, according to the ISTH score, clinically significant light and heavy bleeding also developed cumulatively to a significant degree more often in the warfarin group. The same trend was observed in the analysis of bleeding events using the BARC score.

Our findings are closest to the retrospective study by Weir et al. [17], who compared patients with AF and CKD stage 4 (81.3%) and stage 5 (18.7%). Of them, 781 patients received rivaroxaban (469 (60.1%) 15 mg/day, 115 (14.7%) 20 mg/day, and 165 (21.1%) <15 mg/day) and 536 patients received warfarin (mean TTR was 38%). The mean average follow-up time was 12 months. OR for rivaroxaban compared to warfarin was 0.91 (95% CI: 0.65–1.28; p=0.60) for heavy bleeding and 0.93 (95% CI: 0.46–1.90, p=0.85) for the risk of ischemic stroke and systemic embolism. In our study, the incidence of ischemic events in both groups did not differ significantly. High comorbidity in both groups explains the frequent and repeated hospitalizations. About one-third of all hospital admissions were associated with emergencies, including the most common events of decompensated CHN and paroxysmal of AF.

It is well known that the target TTR >70% is challenging to achieve in late-stage CKD [18]. In order to increase safety, warfarin was initiated using a new algorithm based on a lower starting dose (2.5 mg/day) and more frequent (every 2–3 days) INR monitoring until the best possible dose was selected. Each episode of significant change in the creatinine levels required even more thorough monitoring of INR (up to 14 measurements per month), GFR, and treatment corrections. Seventeen (17) patients used individual portable coagulometers, in order to reduce the number of visits to the laboratory. Patients and their relatives were briefed on how to use the device. Each INR measurement was reported to the investigator, and the anticoagulant dose was corrected, if necessary. The apparent convenience of measuring INR at home was offset by the need for more frequent monitoring of INR and remote physician visits. It was only such tactics that allowed the target TTR >70% in 94% of patients to be attained. This algorithm was developed in a study of anticoagulant therapy in outpatient practice in patients with AF, where TTR >70% was achieved in all patients taking warfarin (n=234) [19]. It should be noted that one

**Table 6. Changes in the creatinine levels according to the anticoagulant being used**

| Creatinine, μmol/L | Rivaroxaban (n=73) | Warfarin (n=36) | P   |
|--------------------|--------------------|----------------|-----|
| At inclusion       | 195 [180; 220]     | 203 [183; 229] | 0.39 |
| In 3 months        | 190 [176; 216]     | 202 [178; 222] | 0.2  |
| In 6 months        | 186 [170; 210]     | 206 [194; 223] | 0.01 |
| In 9 months        | 189 [165; 212]     | 204 [192; 230] | 0.02 |
| In 12 months       | 184 [160; 202]     | 221 [186; 250] | 0.003|
| In 18 months       | 180 [158; 205]     | 221 [192; 248] | <0.001|

**Table 7. Changes in glomerular filtration rate (CKD-EPI) according to the anticoagulant being used**

| GFR, mL/min/1.73 m² | Rivaroxaban (n=73) | Warfarin (n=36) | P   |
|---------------------|--------------------|----------------|-----|
| At inclusion        | 23.0 [20.0; 26.0]  | 22.0 [19.0; 24.2] | 0.16 |
| In 3 months         | 24.0 [21.0; 28.0]  | 22.0 [19.0; 25.0] | 0.03 |
| In 6 months         | 24.0 [21.0; 28.0]  | 21.0 [20.0; 24.2] | 0.02 |
| In 9 months         | 24.0 [21.0; 29.0]  | 22.0 [19.0; 24.0] | 0.03 |
| In 12 months        | 25.0 [21.0; 29.0]  | 20.0 [18.5; 24.0] | 0.007|
| In 18 months        | 25.5 [21.8; 30.0] | 20.0 [19.0; 23.5] | 0.002|

**Table 8. Changes in creatinine clearance (Cockcroft–Gault) according to the anticoagulant being used**

| Creatinine clearance, mL/min | Rivaroxaban (n=73) | Warfarin (n=36) | P   |
|-----------------------------|--------------------|----------------|-----|
| At inclusion                | 27.0 [23.0; 33.0]  | 25.0 [21.8; 29.2] | 0.2  |
| In 3 months                 | 29.0 [25.0; 33.0]  | 26.0 [21.0; 29.2] | 0.04 |
| In 6 months                 | 29.0 [24.0; 36.0]  | 25.0 [21.0; 31.2] | 0.02 |
| In 9 months                 | 30.0 [24.0; 35.5]  | 24.5 [20.0; 31.2] | 0.01 |
| In 12 months                | 31.0 [26.8; 36.5]  | 25.0 [19.5; 31.0] | 0.01 |
| In 18 months                | 31.0 [26.8; 38.0]  | 25.0 [19.5; 30.5] | 0.003|
patient with TTR 83% in the warfarin group developed fatal hemorrhagic CVA.

Another important aspect was the analysis of changes in creatinine levels and GFR levels during ACT. Mixed linear models were used to estimate the course of changes in GFR (creatinine clearance) and creatinine levels during the follow-up. The advantage of these models over traditional statistical tests is the ability to assess changes over time and minimize individual differences between patients. Changes in the creatinine levels and GFR in the rivaroxaban and warfarin groups differed significantly. Kidney function improved in the DOAc group, and the administration of warfarin was not accompanied by significant changes. The curves diverged after 6 months (Table 5, Figures 1–3). A comparison of GFR values calculated using both formulas enabled CKD-EPI to be recommended as most accurately characterizing glomerular filtration rate for the evaluation of kidney function in patients with AF. This is clearly demonstrated in Figures 1–3. It is surprising that when creatinine levels gradually increase (Figure 1) in patients receiving warfarin, the Cockcroft–Gault calculation demonstrates stable creatinine clearance tending towards increase (Figure 2), which seems to contradicts the real situation. The CKD-EPI equation eliminates this contradiction (Figure 3), demonstrating a downward trend in GFR.

The phenomenon of floating GFR in certain patients requires attention. It reflects the natural transient deterioration of kidney function in decompensated CHF, as evidenced by fluctuations in the creatinine levels and depends on the severity of symptoms during hospital stay. The dose of rivaroxaban remained the same for such patients. However, doses were adjusted almost in every case in the warfarin group. This sub-analysis is essential, since it can be difficult to determine the true state of kidney function and define the stage of CKD. This is due to the relatively frequent lack of medical history data on the levels of creatinine in patients admitted to cardiology units, or a clear idea of the further course of changes. In our study, creatinine levels were measured in the sub-group of patients with transient GFR at least once every 3 weeks after discharge. In some cases, the GFR varied quite widely, corresponding to different stages of CKD, several times within one month, until they stabilized during follow-up, allowing for a clear definition of the stage.

The transition from CKD stage 4 to stage 3 (CKD-EPI) was insignificantly more common in patients receiving rivaroxaban: 43% vs. 34% (p=0.26), which may generally indicate the positive effects of ACT on kidney function in patients with AF.

The prevalence of anemia among the patients included was 50%. No further decrease in hemoglobin was observed. Patients with severe anemia were not included in the study. Bleeding did not increase anemia.

The main limitation of our study is mainly the small patient sample (n=109), due to quite strict inclusion criteria and relatively low prevalence of patients with a similar combined pathology in the cardiology units. The post-hoc analysis showed a low statistical power achieved for estimating the primary endpoint: 62.3% and 35.5% for BARC and ISTH scores, respectively. Another limitation was the shorter follow-up period for some patients due to the exclusion criteria. Another important point to be noted was that it was often impossible to establish CKD duration due to the lack of medical history data on the creatinine levels, which could have an effect on the changes of this parameter and GFR.

Conclusion

The study produced data which showed a favorable safety profile for rivaroxaban compared to warfarin in patients with AF and late-stage CKD. The use of rivaroxaban was accompanied by improved kidney function, which may indicate its nephroprotective effect. For the assessment of renal function in patients with AF, the CKD-EPI formula is preferred. No significant changes in the hemoglobin levels were detected in either group. However, given the small sample of patients, large studies are required to confirm our findings. Confirming this data may be the key to selecting anticoagulant treatment for patients with AF and late-stage CKD.

No conflict of interest is reported.

The article was received on 12/08/2020

REFERENCES

1. Potpara TS, Ferro CJ, Lip GYH. Use of oral anticoagulants in patients with atrial fibrillation and renal dysfunction. Nature Reviews Nephrology. 2018;14(5):337–51. DOI: 10.1038/nrneph.2018.19
2. Leung KC-W, MacRae JM. Anticoagulation in CKD and ESRD, Journal of Nephrology. 2019;32(5):719–31. DOI: 10.1007/s40620-019-00592-4
3. Hwang HS, Park M-W, Yoon HE, Chang YK, Yang CW, Kim SY et al. Clinical Significance of Chronic Kidney Disease and Atrial Fibrillation on Morbidity and Mortality in Patients with Acute Myocardial Infarction. American Journal of Nephrology. 2014;40(4):345–52. DOI: 10.1159/000368422
4. 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 of Systematic Reviews. 2017;11(11):CD011373. DOI: 10.1002/14651858.CD011373.pub2
5. Weir MR, Kreutz R. Influence of Renal Function on the Pharmacokinetics, Pharmacodynamics, Efficacy, and Safety of Non–Vitamin K Antagonist Oral Anticoagulants. Mayo Clinic Proceedings. 2018;93(10):1503–19. DOI: 10.1016/j.mayocp.2018.06.018
6. KDIGO 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease. Kidney International supplements. 2013;3(1):1–150. [Available at: https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf]

7. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine. 2011;365(10):883–91. DOI: 10.1056/NEJ Moa1009638

8. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M et al. Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2011;365(11):981–92. DOI: 10.1056/NEJ Moa1107039

9. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A et al. Dabigatran versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2009;361(12):1139–51. DOI: 10.1056/NEJ Moa0905561

10. Fordyce CB, Hellkamp AS, Lokhnygina Y, Lindner SM, Piccinni JP, Becker RC et al. On-Treatment Outcomes in Patients With Worsening Renal Function With Rivaroxaban Compared With Warfarin Clinical Perspective: Insights From ROCKET AF. Circulation. 2016;134(1):37–47. DOI: 10.1161/CIRCULATIONAHA.116.021890

11. Kirchhoff F, Benussi S, Kotecha D, Ahlsson A, Attar D, Casadei B et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal. 2016;37(38):2893–962. DOI: 10.1093/eurheartj/ehw210

12. Ministry of Health of Russian Federation. Clinical recommendations: Atrial fibrillation and flutter in adults. (CP382). 2016. [Russian: Министерство Здравоохранения Российской Федерации. Клинические рекомендации: Фибрилляция и трепетание предсердий у взрослых. (МКБ-10: I148. КР382). Доступно на: http://webmed.irkutsk.ru/doc/pdf/fedaf.pdf]

13. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.1). Available at: https://www.who.int/vmnis/indicators/haemoglobin.pdf. 2011.

14. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thrombosis and Haemostasis. 1993;69(3):236–9. PMID: 8470047

15. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J et al. Standardized Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report From the Bleeding Academic Research Consortium. Circulation. 2011;123(23):2736–47. DOI: 10.1161/CIRCULATIONAHA.110.009449

16. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients: Definitions of major bleeding in clinical studies. Journal of Thrombosis and Haemostasis. 2005;3(4):692–4. DOI: 10.1111/j.1538-7836.2005.01204.x

17. Weir MR, Ashton V, Moore KT, Shrivastava S, Peterson ED, Ammann EM. Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and stage IV-V chronic kidney disease. American Heart Journal. 2020;223:3–11. DOI: 10.1016/j.ahj.2020.01.010

18. Yang F, Hellyer JA, Than C, Ullal AJ, Kaiser DW, Heidenreich PA et al. Warfarin utilisation and anticoagulation control in patients with atrial fibrillation and chronic kidney disease. Heart (British Cardiac Society). 2017;103(11):818–26. DOI: 10.1136/heartjnl-2016-309266

19. Salpagarova Z.K., Andreev D.A., Sychev D.A., Bykova A.A., Syrkin S.A., Suchkova S.A. Anticoagulant therapy control in primary healthcare setting. Sechenov Medical Journal. 2016;2(24):8–12. [Russian: Салпагарова З.К., Андреев Д.А., Сычев Д.А., Быкова А.А., Сыркин С.А., Сухкова С.А. Опыт работы кабинета по контролю антикоагулярной терапии в клинической практике. Сеченовский вестник. 2016;2(24):8–12]