https://doi.org/10.38109/2225-1685-2018-2-64-82

ISSN 2225-1685 (Print)
ISSN 2305-0748 (Online)

Kobalava Zh.D., Shavarov A.A.

ANTICOAGULANT THERAPY FOR CHRONIC KIDNEY DISEASE AND ATRIAL FIBRILLATION: THE AXIS OF ROTATION BETWEEN THE POLES OF RISK

"Peoples' Friendship University of Russia", Moscow, Russia

SUMMARY

The frequent comorbidity of atrial fibrillation (AF) and chronic kidney disease (CKD) in the general population is demonstrated in many epidemiological studies. Most patients with an established diagnosis of AF are recommended to use constant anticoagulant therapy (ACT) to prevent ischemic stroke and thromboembolic complications (TEC). With renal dysfunction, changes in the hemostatic system are observed at all stages of CKD, both related to an increase in prothrombogenic activity as well as to development of coagulopathy, which increases the threat of bleeding. Therefore, in patients with CKD and AF, an important aspect of ACT is the choice of the optimal anticoagulant, that will provide a balance between the risks of stroke and hemorrhagic complications, to which this article is dedicated.

Key words: *atrial fibrillation, chronic kidney disease, anticoagulants, warfarin-induced nephropathy, dabigatran*

Information about authors:

Kobalava Zhanna Davidovna	Ph.D., professor, head of the Department of Internal Diseases with the course of cardiology and functional diagnostics of the Peoples Friendship University of Russia, 117198, Moscow, ul. Miklukho-Maklaya, 6. E-mail: kobalava_zhd@rudn.university, Tel. 8(499)134-6591
The author responsible for communication with the editorial office: Shavarov Andrey Anatolievich	Candidate of medical science, associate professor, associate professor of the Department of Internal Diseases with the course of cardiology and functional diagnostics of the Peoples Friendship University of Russia, 117198, Moscow, ul. Miklukho-Maklaya, 6. E-mail: shavarov@yahoo.com, Tel. 8(499)135-9177

✉ **shavarov@yahoo.com**

For citation: Kobalava Zh.D., Shavarov A.A. Anticoagulant therapy for chronic kidney disease and atrial fibrillation: the axis of rotation between the poles of risk. Eurasian cardiological journal. 2018, May 25; 2:74-82.

The prevalence of atrial fibrillation (AF) in patients with terminal chronic kidney disease (CKD) is high, reaching 27% in patients on prolonged hemodialysis [1-3]. Advanced CKD is also interrelated with AF [4, 5]. Besides, CKD is often established in a concomitant diagnosis in patients with AF [6]. Renal dysfunction triggers a complex of pathophysiological reactions involving both hypo- as well as hypercoagulation [7]. There is a close connection between CKD and hemorrhagic complications caused by anticoagulant therapy (ACT). As a consequence, severe CKD is considered as a predictor of ACT-associated bleeding in many risk scales [8-13]. On the other hand, patients with AF in the presence of CKD in severe and even moderate stages are characterized by a higher risk of ischemic stroke and thromboembolic complications (TEC) compared to those with normal renal function [14, 15]. This article is devoted to the choice of oral anticoagulant (OAC) in patients with AF in combination with CKD.

Prevalence of chronic kidney disease and atrial fibrillation

The prevalence of CKD in the general population increases with age [16], and the development of CKD in patients increases morbidity and mortality [14].

In a number of population studies, it was shown that the prevalence of AF increases in proportion to the impairment of renal function [4, 5, 17]. For example, in the CRIC study (n = 3267), the prevalence of AF as a whole was 18%, and when comparing subgroups in patients with a glomerular filtration rate (GFR) <45, AF was 4.4% more likely than in individuals with a glomerular rate filtration (GFR) ≥45 ml/min (p <0.001) [5]. In the large Japanese study (n = 41417), depending on the upper, middle, or lower tertile of the glomerular filtration rate, the prevalence of AF was 0.9%, 1.2%, and 2.8%, respectively [17]. In the REGARDS study, which included 26917 patients with documented on an electrocardiogram (ECG) AF, the prevalence of cardiac arrhythmia was 1% in individuals without CKD, 2.8% in patients with CKD of 1-2 stages, 2.7% in CKD of Stage 3, 4.2% in CKD of stage 3, the odds ratio (OR) of AF development adjusted for age, race and sex was 2.67 (95% confidence interval [CI] 2.04-3.48), 1.68 (95% CI, 1.26-2, 24) and 3.52 (95% CI 1.73-7.15), respectively [4].

Albuminuria, as an indicator of kidney dysfunction, is also associated with an increased risk of AF development [18, 19]. In the work of McManus D. and co-authors, including 965 patients with ischemic heart disease (IHD), the ratio of albumin / creatinine

(A/C) in urine >15 mg / g increased the prevalence of AF by 4.6 times in comparison with the ratio (A/C) <7 mg / g [18]. In the Dutch study (n = 7546) in patients with microalbuminuria, the prevalence of AF was almost 2 times higher (relative risk [RR] 1.93, 95% CI 1.10-3.37, p <0.05) [19].

Although most of the studies that studied AF and CKD had a cross-sectional design, similar results were obtained in the longitudinal design of the study. In the Niigata study (n = 223877, average age 61 y.o.) during 6-year follow-up period, AF developed in 2947 (1.3%) patients, and the adjusted frequency of AF was 2.2 with GFR ≥60 ml/min and 5, 2 per 1000 man-years with GFR <60 ml/min (RR 1.38, 95% CI 1.14-1.66, p<0.001) [20]. The risk of developing of AF increased with a lower initial GFR, and this relationship was maintained even after patients with AH and diabetes mellitus (DM) were excluded from the analysis.

In the ARIC study (n = 10328), in which the observation period was 10 years, the beginning of AF de novo was observed in 788 (7.6%) patients [21]. After adjusting traditional risk factors including age, systolic blood pressure (SBP), body mass index, diabetes, compared with those without kidney dysfunction, the relative risk (RR) of AF development in CKD of 2, 3 and 4 stages was 1.29 (95% CI 1.05-1.58), 1.70 (95% CI 1.31-2.20), and 3.41 (95% CI 2.18-5.32), respectively [21]. In addition, the frequency of AF increased proportionally to the growth of albuminuria, reaching 5.8, 14.6 and 26.6 cases per 1000 man-years with an (A/C) ratio in urine <30, 30-299 and> 300, respectively (p <0,0001).

Albuminuria in combination with a decreased GFR increases the risk of AF. In the above-mentioned REGARDS study, albuminuria increased the odds ratio (OR) of AF development in subgroups with GFR> 60 and 30-59 ml/min, respectively, by 1.5 and 2.5 times, respectively [4]. Similarly, the frequency of AF increased with lower GFR for each stratum of the (A/C) ratio in the urine in the ARIC study [21]. For example, in patients with an (A/C) ratio of 30-299 mg / g, the frequency of AF increased from 8 to 30% as the GFR decreased from> 90 to 15-29 ml/min.

Prevalence of AF is usually higher in patients with severe CKD requiring hemodialysis, and ranges from 5 to 27%, depending on the duration of dialysis therapy, associated risk factors, and the clinical version of AF [22, 23]. According to the reports of the US National Database USRSD in patients on hemodialysis, the prevalence of AF increased from 3.5% in 1992 to 10.7% in 2006, which partly can be explained by the aging of the population, and therefore the proportion of patients ≥85 years for this time interval increased from 10 to 22.5% [23]. In addition, the mortality rate among patients receiving dialysis therapy, in the presence of AF increases by 2 times.

Thus, the prevalence of AF is higher in patients with, than without CKD. The increased risk of AF developing is associated with a decrease in GFR and the severity of albuminuria accompanying the development of CKD. The beginning of AF worsens the prognosis of patients with terminal CKD.

The effect of chronic kidney disease and atrial fibrillation on morbidity and mortality

Due to the close relationship of AF with structural pathology of the heart, the effect of the first on morbidity and mortality is not always clearly traced, because in a number of clinical situations it is difficult to determine whether the complication is caused by AF or by severe cardiac remodeling and arrhythmia , associated with it.

In comparison with GFR >59, in patients with GFR 45-59 ml/min, the adjusted relative risk (RR) of death is 1.2 times higher and the relative risk (RR) of hospitalization increases by 1.1 times, which increases with GFR <15 ml/min up to 5.9 and 3.1 times, respectively [24]. Analysis of the USRSD database showed that in patients with terminal CKD, the annual mortality rate is 5% with documented AF and only 2% in the absence of arrhythmia [14]. Three-year mortality in patients with terminal CKD who are hospitalized for AF is also significantly higher than in the control group (53 vs. 45%) [25]. Besides, in one single-center study with longitudinal design (n = 149), the death rate over the 4-year follow-up period in patients with terminal CKD and AF was even worse: 81 versus 29% in individuals without arrhythmia [26]. In the REPOSI study, it was shown that in patients with AF, higher values of calculated GFR were associated with a lower risk of hospital mortality (RR 0.96, 95% CI 0.94-0.99, P = 0.011), as well as of three-month mortality after discharge (RR 0.97, 95% CI 0.94-1.00, p = 0.038) [27].

Studies on the effect of AF on the mortality of patients with CKD of less severe stages than the terminal stage are not available, therefore, even without considering whether AF is an independent predictor or only a risk factor for death, clinicians should clearly understand the consequences of this arrhythmia in patients with CKD, associated with a significant increase in morbidity and mortality.

Risk of stroke in patients with chronic kidney disease and atrial fibrillation

Stroke and systemic thromboembolism are serious complications of AF, and some studies have demonstrated an increased risk of stroke and thromboembolic complications (TEC) in patients with CKD receiving dialysis therapy in case of beginning of AF [28-30], although other studies have shown no such correlation [16, 31].

In a retrospective ATRIA study (n = 10,908) in patients with AF, proteinuria increased the risk of thromboembolic complications (TEC) by 54%, and the progressive deterioration of GFR was associated with an increased risk of stroke in such a way that in patients with GFR <45 ml/min the risk of stroke was higher by 39% than in individuals with normal renal function [32].

Bonde A. and co-authors studied the relationship between CKD and risk of TEC depending of the index on the scale CHA2DS2VASc in patients with AF included in the Danish registry, as well as the clinical efficacy of ACT-produced warfarin. Out of 154229 patients with non-valvular AF, 11188 (7.2%) of patients had nonterminal CKD, and 1728 (1.1%) – terminal CKD, for which they received hemodialysis, pertonal dialysis, or renal transplantation was performed [33]. In patients with AF and terminal CKD, who had an index on the scale CHA2DS2VASc ≥2, warfarin significantly reduced the relative risk (RR) of death from all causes by 15% (95% confidence interval [CI] 0.72-0.99). In the group of patients with non-terminal CKD and index on the scale CHA2DS2VASc ≥2, warfarin reduced the relative risk (RR) of the combined endpoint, including fatal stroke and fatal bleeding by 29% (95% CI 0.57-0.88), relative risk (RR) of cardiovascular death - by 20% (95% CI 0.74-0.88), and death from all causes by 36% (95% CI 0.60-0.69) [33].

A combined analysis of three randomized clinical SPAF studies revealed an association between renal dysfunction and TEC in patients with AF who do not take warfarin. After 2 years of follow-up, the incidence of the combined endpoint, including stroke and TEC, was higher when comparing individuals with and without CKD (9.2 versus 4.1%, p = 0.004) [34]. In a small one-center study involving 387 patients with AF, it was shown that CKD was

associated with an increased risk of stroke regardless of the initial index on the CHADS2 scale [35].

In patients with a risk of thromboembolic complications on the CHADS2 = 6 scale, the annual stroke rate is 18.2% [36], but in the absence of all risk factors for this scale in a random sample of patients with AF and terminal CKD, stroke rates range from 17, 4 to 24% per year [8, 26]. Therefore, the CHADS2 scale may underestimate the risk of stroke and TEC in patients with CKD.

On the other hand, the results of some studies show that AF increases the risk of stroke and TEC in patients with CKD. In the DOPPS study, patients with terminal CKD with AF had an increase in the relative risk (RR) of stroke or cerebrovascular events by 28% (95% CI 1.01-1.62, p = 0.048) [37]. In a study of Vazquez E. and co-authors, in which 256 patients with terminal CKD on hemodialysis were observed for 4 years, AF was originally in 31 patients, and in 28 cases the arrhythmia developed during the 2-year follow-up period. In total, AF increased the risk of death by 1.7 times, and the risk of stroke - by 9.8 times [29]. In another longitudinal clinical study, which observed 488 patients on prolonged hemodialysis, in the presence of AF, mortality was higher by 21% [38].

Guo Y. and co-authors showed that in individuals with AF and GFR <60 ml/min, a subsequent deterioration in renal function was associated with an increased risk of serious clinical events [39]. Thus, an absolute or relative decrease in GFR ≥25 ml/min increased the risk of stroke by more than 2 times compared to those in whom the kidney function was stable for 6 months of follow-up.

Some authors have shown in their studies that GFR can not only be an independent predictor of mortality in stroke [40], but also predict unfavorable clinical outcomes in patients after stroke, such as increased neurological deficit, poor functional recovery [41, 42].

In total, the obtained data allow us to say that in patients with AF, renal dysfunction increases the risk of TEC, which is associated with changes in the coagulation system and platelet dysfunction in CKD, accompanied by an increase in both venous and arterial thrombosis [43].

The use of warfarin in patients with atrial fibrillation and chronic kidney disease

Current recommendations for the prevention of stroke and thromboembolic complications (TEO) are based on the conclusions of prospective cohort studies and suggest extrapolation of their results to the general population of patients with AF, while the evidence base for the efficacy of ACT in individuals with severe renal dysfunction is not sufficient. GFR <30 ml/min was the criterion for excluding patients from randomized studies. However, the administration of oral anticoagulants, especially warfarin, in patients with advanced CKD varies from 2% in Germany to 37% in Canada [37]. This heterogeneity reflects the uncertainty between risk and benefit in the use of ACT in this category of patients.

In most patients with AF, warfarin therapy is effective in reducing the risk of ischemic stroke and thromboembolic complications (TEO). However, the effect of renal dysfunction on the effects of warfarin in patients with AF for a long time remained unexplored.

Abbott K. and co-authors, in a retrospective study of 3,374 patients on hemodialysis, 123 of whom were hospitalized during the observation period for AF, found that cumulative mortality from all causes was significantly lower in patients receiving warfarin than in those who did not receive vitamin K antagonists (VKA) (RR 0.36, 95% CI 0.16-0.82, p = 0.014) [25]. Olesen J. and co-authors in patients with AF included in the Danish registry demonstrated a significant reduction in the risk of thromboembolic complications (TEC) both in general group and in the group of patients with terminal CKD. When comparing patients with and without CKD, warfarin reduced the relative risk (RR) of stroke and TEC by 24% (95% CI 0.64-0.91, p = 0.003) [44].

However, other studies have shown that warfarin can be potentially dangerous in patients with terminal CKD [23, 45, 46]. In large observational studies in patients with CKD who are on hemodialysis, the administration of warfarin increased the risk of ischemic stroke by more than 2 times compared to those who did not receive VKA.

In patients with AF and nonterminal CKD, the effectiveness of warfarin therapy in the prevention of stroke and TEC is obvious, as confirmed by the results of three observational studies [44, 47, 48]. However, in the Danish cohort study, anticoagulant therapy (ACT) with warfarin significantly increased the risk of bleeding by 36%, and with the combination of warfarin and aspirin this risk increased up to 63% [44].

Vazquez E. and co-authors in 2003 within the framework of a single-center study, that included 29 patients with terminal CKD, were among the first to establish a correlation between ACT with warfarin and bleeding [9]. It was shown that the annual frequency of bleeding in patients who didn't take oral anticoagulants was 11%, in patients receiving disaggregants – 16%, and in patients receiving VKA – 26%. Out of 13 patients who received warfarin, 10 had large bleeding, the source of which was mainly the gastrointestinal tract. The authors note that the international normalized ratio (INR) in these patients exceeded the therapeutic range, but none of the hemorrhagic complications was fatal.

Limdi N. and co-authors (n = 578) evaluated the effect of the functional state of the kidneys on the dosing regimen of warfarin, the adequacy of hypocoagulation and the risk of hemorrhagic complications [49]. The risk of TEC related to AF was an indication for ACT prescription in 134 (40%) patients with GFR ≥60 ml/min, 99 (56%) with GFR 30-50, 23 (43%) with GFR <30 ml/min. Patients with severe CKD received significantly lower doses of warfarin compared with patients with CKD of moderate and mild stages (3.9 [3.5-4.4] vs. 4.3 [4.0-4.6] vs. 4.8 [4.6-5.0] mg / day, respectively, p = 0.0002), regardless of the genotypes CYP2C9 and VKORC1, which determine the pharmacokinetic parameters of warfarin metabolism. Also, the results of this work showed that the time of INR finding within the 2-3 therapeutic range was the smallest in patients with severe CKD, which increased the risk of hypercoagulation (INR >4, p = 0.052). The proportions of patients with the target INR value where GFR ≥60, GFR 30-50 and GFR <30 ml/min were 49.7, 45.7 and 45.6%, respectively (p = 0.049). Patients with severe CKD had 2-4 times higher risk (95% CI, 1.1-5.3) of major bleeding than those with moderate and mild CKD. In actual clinical practice, CKD, especially in elderly patients, has an independent association with the rarer prescription of ACT.

The results of the REPOSI study demonstrated the correlation between reduced GFR and a lower percentage of oral anticoagulant prescription [27]. The possibility of ACT-associated bleeding in AF is particularly high in patients with terminal CKD. The data of the Italian nephrological register of patients with AF who are on chronic hemodialysis showed that the index on the CHADS2 scale is not the cause for the deployment of vitamin K antagonist therapy (AVK), and only the permanent form of AF serves as a factor having a positive correlation with the administration of warfarin. Therefore, less than 50% of patients with AF receives AVK therapy [50]. Such specific group of patients is characterized

by very high mortality, and AVK therapy improves their survival, while patients with the highest INR time in the therapeutic range had the lowest bleeding rate [51].

Despite the fact that an increased risk of bleeding often makes you doubt on the choice of oral anticoagulant (OAC), practitioners should remember that the clinical effect of ACT in reducing mortality and TEC exceeds the adverse risk of possible bleeding, especially in patients with senile asthenia, and with CKD [44].

Warfarin-induced nephropathy

The side effects associated with warfarin overdose in regard to renal function are well known and include hematuria, petechiae and ecchymosis, hemorrhagic vasculitis, interstitial nephritis [52, 53]. In recent years, another complication of AVC , the so-called warfarin-associated nephropathy, has been described, which is an increase in creatinine> 26.5 μmol / L within a week after an increase in INR >3 without obvious bleeding [54].

In one of the first observations of acute renal injury (acute renal failure), there was a correlation between coagulopathy, associated with warfarin administration and the thinning of the glomerular basal membrane (MBM) with following tubular obstruction [55]. Later, a similar syndrome was described in a patient with inactive systemic lupus erythematosus, which also had a thickening of MBM [56]. The mechanism of the development of warfarin-associated nephropathy in such patients includes excessive hypocoagulation (INR 6-9), in which patients develop pathological thinning or thickening of MBM, which in both cases determines spontaneous massive hematuria [57].

Brodsky S. and co-authors performed kidney biopsy in 9 patients with CKD who had acute renal injury (acute renal failure) with moderate hypocoagulation (INR 4.4±0.7) and hematuria that exhibited severe and widespread tubular obstruction with erythrocyte cylinders normal or minimally altered structure of the glomerular apparatus [58]. That is, the glomerular hematuria proved during biopsy was unforeseen. Besides, in most patients the kidney function did not recover or improved slightly. At the next stage, this group of authors performed a retrospective analysis of the data of the 4-year nephrological program, which observed 103 individuals with CKD of 2-4 stages, where 49 of them had at least one episode of INR> 3 [59].

Out of 49 individuals, 18 (37%) experienced an unexpected increase in creatinine> 26.5 μmol / L within the week when INR was> 3 while taking warfarin, and this group had a more rapid progression of CKD [59]. Similar results were obtained when analyzing a more representative sample of 4006 patients receiving warfarin [54]. Warfarin-associated nephropathy was noted in 33% of patients with established CKD and in 16.5% with preserved renal function. The risk factors for the development of warfarin-associated nephropathy included age, prior CKD, arterial hypertension (AH), diabetes, diabetic nephropathy, and chronic heart failure (CHF). Patients with warfarin-associated nephropathy often received aspirin (35 vs 28%, p = 0.001). Five-year survival was significantly lower in patients with warfarin-associated nephropathy than in those without this complication (58 vs. 73%, p<0.001). The highest risk of death was in the first weeks after an increase in INR >3 (relative risk in the first week – 3.65, 95% CI 2.81-4.75), after which the relative risk (RR) progressively decreased, losing statistical significance after 6 months.

Therefore, when prescribing vitamin K antagonist therapy (AVC), doctors should be alert for potential warfarin-associated acute kidney damage (CPD), which can develop in patients without a history of CKD and is associated with increased mortality.

Balancing between polar risks of stroke and bleeding

Patients with AF and CKD represent a specific group. Many pathophysiological mechanisms change with renal dysfunction [60, 61], which leads at all stages of CKD (but especially when terminal) to paradoxical shifts in the hemostasis system in the direction of increased prothrombogenic activity ,increasing the risk of TEO, as well as in the direction of coagulopathy with increased threat of bleeding [7, 9, 14, 26, 61]. This explains the high incidence of both ischemic strokes and hemorrhagic complications in this category of patients. In practice, the positive effect of oral anticoagulant therapy outweighs the risk of bleeding. Even in the general population of patients with AF there is a small zone of U-shaped distribution within the INR from 2 to 3 to prevent ischemic strokes and to avoid hemorrhagic events [62]. The optimal range of INR levels for patients with CKD remains unknown.

The use of dabigatran in patients with atrial fibrillation and chronic kidney disease

As we know, all new oral anticoagulants (new oral anticoagulants) are partially eliminated by the kidneys. Sardar P. and co-authors published the results of a meta-analysis of 10 large randomized phase III clinical studies that included 40693 patients with AF and mild (GFR 50-79 ml/min) or moderate (30-49 ml/min) renal dysfunction, and in which the effectiveness and safety of the new oral anticoagulants (dabigatran, rivaroxaban and apixaban) in comparison with warfarin were evaluated [63]. In patients with mild renal dysfunction, compared with warfarin, the new oral anticoagulants significantly reduced the risk of stroke and thromboembolic complications by 30% (95% CI 0.64-0.92), and the risk of large and clinically significant minor bleeding by 29% (95% CI 0,72-0.90). Patients with mild renal dysfunction experienced a significant decrease in the risk of thromboembolic complications (TEC) (RR 0.72, 95% CI 0.57-0.92) with no difference in the safety profile (RR 0.82, 95% CI 0.59-1.14). The sensitivity analysis of the two dose regimens of dabigatran 150 mg and 110 mg o 2 times a day showed comparability of the results with the initial studies of this drug.

In a retrospective analysis of RE-LY study in patients with AF, the efficacy and safety of two doses of dabigatran (n = 6004), prescribed according to the instructions for use, compared with warfarin (n = 6022). In case of individual dose choice, 110 mg (29% of cases) or 150 mg (71% of cases) 2 times a day, treatment with dabigatran was accompanied by a significant reduction in the risk of ischemic stroke and TEC (RR 0.74, 95% CI 0.60-0.91), hemorrhagic stroke (RR 0.22, 95% CI 0.11-0.44), death from all causes (RR 0.86, 95% CI 0.75-0.98) and death from vascular causes (RR 0.80, 95% CI 0.68-0.95), large bleeding (RR 0.85, 95% CI 0.73-0.98), life-threatening large bleeding (RR 0.72, 95% CI 0,58-0.91), intracranial bleeding (RR 0.28, 95% CI 0.17-0.45), any bleeding (RR 0.86, 95% CI 0.81-0.92), while the risk of large gastrointestinal bleeding was comparable (RR 1.23, 95% CI 0.96-1.59) [64].

In the subanalysis of the RE-LY study (n = 17951) according to pre-prescribed variables, Hijazi Z. and co-authors studied the frequency of clinical outcomes depending on renal function in patients with AF treated with dabigatran or warfarin [65]. There was an increase in the frequency of strokes, TEC, bleeding and deaths as the kidney function worsened. In comparison with warfarin, the incidence of ischemic strokes and TEC was lower when dabigatran was used at a dose of 150 mg 2 times daily and comparable

with dabigatran at a dose of 110 mg 2 d/day without significant heterogeneity in subgroups with GFR ≥80, 50-80 and GFR <50 ml/min (p = 0.1). Dabigatran therapy at a dose of 110 mg 2 r / day was associated with a lower risk of major bleeding in all subgroups of GFR, calculated by the Cockcroft-Gault formula (p = 0.06), and was associated with a significant reduction in this risk (RR 0.41, 95% CI 0.27-0.62, p = 0.0012) in patients in the subgroup with GFR ≥80 ml/min, calculated by the formula CKD-EPI.

With regard to dabigatran in a dosage of 150 mg 2 times a day, there is also no significant difference in the incidence of major bleeding in all GFR subclasses calculated by the Cockcroft-Gault formula in comparison with warfarin and a significant reduction in the risk of major bleeding (RR 0.59; 95% CI 0.41-0.84, p = 0.005) in the subgroup with GFR ≥80 ml/min calculated according to the formula CKD-EPI. In the RE-LY sub-study, which included 16,490 elderly patients with AF, it was revealed that during the 30-month follow-up period, GFR declined more significantly with warfarin therapy (-3.7±0.2 ml/min) than with dabigatran therapy in a dose of 110 mg (-2.6±0.2 ml/min, p = 0.0009) and in a dose of 150 mg (-2.5±0.2 ml/min, p = 0.0002) [66]. A decrease in GFR> 25% was less likely for dabigatran at the dose of 110 mg (RR 0.81, 95% CI 0.69-0.96, p = 0.017), and at the dose of 150 mg (RR 0.79, 95% CI 0.68-0.93, p = 0.006) compared with warfarin during more than 18 months period of follow-up. In general, patients with AF in the presence of diabetes had a lower GFR level than those without diabetes (64.0 vs. 66.4 ml/min, p<0.0001), and a more significant impairment of renal function. During a 30-month follow-up, a reduction in GFR with concomitant diabetes was higher in patients taking warfarin, rather than dabigatran (p <0.005). We should note the association of a faster reduction in GFR with prior ACT with warfarin and weak control of the level of hypocoagulation (the time of finding INR in the therapeutic range <65%). Patients with excessive hypocoagulation (INR >3) on the background of taking warfarin also had a more pronounced decrease in GFR than those with a target or low (<2) level of INR.

In one of the latest retrospective cohort studies using the Medicare medical database from November 2011 to December 2013, was included 18441 patients with AF for a comparative evaluation of the efficacy and safety of dabigatran 150 mg 2 times daily against rivaroxaban 20 mg once a day, dabigatran 75 mg 2 times a day against rivaroxaban 15 mg once a day [67]. There were no significant differences in the incidence of ischemic strokes between comparison groups. Rivaroxaban 20 mg in comparison with dabigatran 150 mg was associated with higher risks of development of other TEC (RR 1.28, 95% CI 1.14-1.44), large bleeding (RR 1.32, 95% CI 1.17-1.50) and death (RR 1.36, 95% CI 1.19-1.56). Risks of feasibility studies that do not include stroke (RR 1.37, 95% CI 1.15-1.62), large bleeding (RR 1.51, 95% CI 1.25-1.82), death (RR 1.21, 95% CI 1.04-1.41) with low doses were also higher in rivaroxaban than in dabigatran. Risks of TEC that do not include stroke (RR 1.37, 95% CI 1.15-1.62), large bleeding (RR 1.51, 95% CI 1.25-1.82), death (RR 1.21, 95% CI 1.04-1.41) with low doses were also higher in rivaroxaban than in dabigatran.

After correction by the compliance index in the optimal dose groups of dabigatran and rivaroxaban, the proportion of patients with CKD was 27%, and in safe dose groups – 52%. In the subgroups of patients with AF and CKD, the safety profile of rivaroxaban at a dose of 20 mg was less favorable than dabigatran 150 mg for the risk of major bleeding (RR 1.34, 95% CI 1.10-1.64), any bleeding RR 1.17, 95% CI 1.06-1.29) and death from all causes (RR 1.33, 95% CI 1.09-1.63), as well as rivaroxaban at a dose of 15 mg against dabigatran in a dose of 75 mg for the risk of major bleeding (RR 1.48, 95% CI 1.17-1.88) and any bleeding (RR 1.34, 95% CI 1.18-1.52).

Thus, in comparison with other new oral anticoagulants, dabigatran is the only drug which dosing regimens have been fully studied using the randomization method, which makes it possible to use an individual approach to the choice of dabigatran dose, based on the efficacy / safety ratio. Patients with AF who receive oral anticoagulant therapy have a decrease in renal function, which is less obvious in in patients taking dabigatran in comparison with patients taking warfarin. The effectiveness of dabigatran therapy at a dose of 150 and 110 mg of 2 times a day does not depend on the level of GFR. With comparable efficacy in the prevention of ischemic strokes, dabigatran is superior to rivaroxaban in reducing the risk of other TEC, death and large bleeding, while a more advantageous safety profile for dabigatran in both dosages is retained in patients with CKD.

Discussion

The combination of renal dysfunction and AF is frequent, and the competitive coexistence of these two pathologies leads to a paradoxical increase in the risk of TEC and bleeding.

As a parameter, severe renal dysfunction in patients with non-valvular AF is not included in the recommended scale for assessing the risk of cardioembolic stroke CHA2DS2VASc, whose acronym stands for two major risk factors (age ≥75 years and a prior stroke), for each of which 2 points are scored and six small risk factors (CHF with systolic dysfunction, hypertension, diabetes, vascular disease, age 65 to 74 years, and female sex) with a score of 1 each [68]. The last letter "c" in the acronym CHA2DS2VASc could be spelled out as "chronic" chronic kidney disease of a severe stage with an exception that the kidney function is not static and may worsen over time, especially in elderly patients with multiple comorbid pathologies and concomitant drug therapy.

At the same time, several risk factors for stroke of CHA2DS2VASc scale are similar for hemorrhages, and 3 common scales of the risk assessment for bleeding HAS-BLED, ATRIA and ORBIT as a parameter include renal dysfunction [69-71]. It is important to note that formally the risk of bleeding was not validated in the population of patients with AF with CKD of 4-5 stages, so it should be used with caution in this category of patients.

Focusing on the fact that patients with AF and moderate or severe renal dysfunction have an increased risk of both stroke and bleeding and lack of sufficient evidence, as patients with a glomerular filtration rate (GFR) <30 ml/min were not included in the randomized clinical studies [2], the choice of oral anticoagulants, providing a well-controlled hypocoagulation, is the best approach to their treatment. In the case of prescribing warfarin, the balance between the risks of stroke and bleeding is closely related to the quality of control of hypocoagulation, and from this position, the time of finding an INR, whose target level within 2.0-2.5 will be the most acceptable, within the therapeutic range should be more than 70% [72].

In many studies in patients with AF and CKD, warfarin therapy with individual dose selection has a more significant protective effect for strokes and TEC compared with placebo [15, 37, 39]. The results of randomized clinical studies have shown that in comparison with placebo or aspirin, ACT with warfarin reduces overall mortality by 26% [34]. Nevertheless, some authors identify factors that weaken the positive effect of warfarin, including the age of patients <65 years, the normal ECG, systolic arterial distillation <130 mm Hg, the absence of concomitant diabetes [2].

In patients with AF and terminal CKD who are on hemodialysis, in some studies, warfarin therapy was associated with an increased risk of ischemic stroke. As Winkelmayer W. and co-authors have shown, this increase in the incidence of ischemic strokes is rather secondary to hemorrhagic strokes and is not associated with thromboembolic cerebral events [23]. Another explanation for the increased risk of stroke among patients taking warfarin may be the lack of quality control of the INR level, which creates the background for reducing the time of finding INR within the therapeutic range [45]. However, further randomized studies are needed to fully understand such adverse effects of ACT with warfarin.

Warfarin is responsible for a third of emergency hospitalizations associated with the development of medicinal side effects in patients over 65 years of age, with about half of these hospitalizations occurring among people older than 80 years. (73). One of the complications caused by AVK is warfarin associated nephropathy, which can develop in any patient regardless of the original kidney function and is associated with higher mortality [54]. According to Brodsky S. and co-authors, warfarin associated nephropathy develops in a third of patients with a history of CKD and in 1/6 of patients with a preserved kidney function [54].

The use of new anticoagulants with moderate and severe renal dysfunction could simplify the management of patients with AF of such a high risk category. A recent meta-analysis demonstrated a higher efficacy and safety of dabigatran, rivaroxaban and apixaban in comparison with warfarin in mild to moderate renal dysfunction [63]. However, the benefits and safety of the new anticoagulants require further confirmation in randomized clinical studies.

Hijazi Z. and co-authors demonstrated the possibility of achieving effective and safe hypocoagulation with dabigatran in a comparison with ACT using the optimal dose of warfarin as part of a randomized study without the prescheduled reduction in the doses of oral anticoagulants, as was planned in the studies of ROCKET-AF and ARISTOTLE [74, 75]. The effect of dabigatran was independent of GFR level.

The frequency of bleeding increases with the progression of kidney dysfunction in patients on the background of taking warfarin or new oral anticoagulsnts regardness of the degree and variability of their renal excretion [13]. The risk of bleeding in patients with impaired renal function is determined by many factors, including platelet dysfunction, endothelial dysfunction, coagulopathy, concomitant diseases and drug interactions [2]. In addition to renal dysfunction, another significant risk factor for hemorrhagic complications in patients with AF and CKD considered age, which is included in the GFR calculation formulas [76].

The decrease in GFR according to the formula of calculating CKD-EPI is approximately 1 ml/min per year, although this decrease, as shown by Böhm M. and co-authors is more significant during the 30-month observation period on warfarin therapy than dabigatran [66]. Beginning with the 6-month follow-up, exceeding the therapeutic range, especially in cases of excessive INR increase, prior AVK therapy determined a more significant decrease in GFR in patients receiving warfarin, compared with two doses of dabigatran. This can be one of the reasons to recommend dabigatran instead of warfarin to patients with CKD of mild and moderate stages.

A more significant impairment of renal function was observed with concomitant diabetes, but the presence of this pathology did not affect the reliability of differences in the reduction of GFR between the warfarin and dabigatran groups. Progressive deterioration of kidney function is observed in elderly patients with AF, and this process is accelerated with diabetes [77]. In the study by B hm M. and co-authors, the annual decrease in GFR was -1.15 ml/min in the general population of patients with AF and -1.71 ml/min in individuals with diabetes, which is consistent with the data of other authors who studied this issue in elderly age.

An indirect comparison of the results of randomized studies RE-LY and ROCKET-AF showed that in patients with non-valvular AF, dabigatran more significantly reduces the risk of stroke and TEC than rivaroxaban (RR 1.35, 95% CI 1.02-1.78), with no significant differences between the two new anticoagulants compared in the incidence of ischemic strokes (RR 1.33, 95% CI 0.98-1.78) and bleeding (RR 1.12, 95% CI 0.92-1.37) [78, 79]. n real clinical practice, Hernandez I. and co-authors did not find significant differences in the reduction in the incidence of ischemic strokes between dabigatran and rivaroxaban, but found a lower risk of hemorrhagic complications (with the exception of intracranial hemorrhages, the frequency of which was comparable) when dabigatran was administered at a dose of 150 and 75 mg 2 times a day, and this risk ratio between dabigatran and rivaroxaban persisted even in patients with CKD [67].

The American Food and Drug Administration (FDA) approved the use of dabigatran at a dose of 75 mg 2 times a day in patients with AF and GFR 15-30 ml/min [80]. However, these recommendations differ from the European recommendations [68], which limit the administration of dabigatran, as well as rivaroxaban and apixaban, with GFR <30 ml/min due to the lack of randomized studies in this category of patients. With moderate renal dysfunction, the use of a reduced dose of dabigataran 110 mg 2 times a day is recommended only for certain groups of patients: individuals ≥80 y.o.; patients of 75-80 y.o. who have a high risk of bleeding (HAS-BLED ≥3 points); individuals initially receiving verapamil [68].

The four-hour session of dialysis therapy eliminates 68% of the dose of dabigatran [81]. Therefore, on the one hand, dabigatran is contraindicated in patients with terminal CKD, and on the other hand, hemodialysis can be used in case of hemorrhagic complications with thrombin inhibitor, reducing the duration and severity of bleeding.

Thus, due to the aging of the population and the increase in the proportion of elderly people, the need to treat patients with AF with accompanying CKD is steadily increasing in everyday clinical practice. In comparison with the preserved kidney function, patients with AF and CKD who receive ACT have an increased risk of stroke and bleeding regardless of the class of anticoagulants (AVK or new oral anticoagulants). The efficacy of AVK in patients with nonterminal CKD is evident, but in comparison with warfarin, dabigatran provides additional clinical benefits to this group of patients. Prospective, randomized studies are needed to establish clear guidelines for ACT in patients with CKD who require dialysis therapy or kidney transplantation.

Conclusion

Optimization of ACT in patients with AF and CKD is a difficult problem, because of the presence of CKD, on the one hand, increases the risk of stroke and TEC, on the other hand, increases the risk of death and bleeding, which puts the practicing physician before the necessity to resolve the conflict of two polar risks. Anticoagulants reduce the risk of cardioembolic stroke associated with AF, but at the same time exacerbate the risk of bleeding, which, even without oral anticoagulants, is high due to renal dysfunction. Therefore, oral anticoagulants in patients with AF and CKD should meet at least two requirements: optimal efficiency and maximum possible safety. Warfarin has proven its effectiveness

in patients with AF and nonterminal CKD, but to ensure quality control of hypocoagulation and maintain an acceptable risk of bleeding, certain efforts are needed, both from the patient's and physician's side. Excess hypocoagulation with AVK intake contains a potential threat of irreversible or partially reversible warfarin-associated nephropathy, which is detected in a third of patients with established CKD and increases mortality.

The decrease in GFR in time in patients with AF receiving oral anticoagulant therapy is less pronounced in those receiving dabigatran compared with warfarin. For the prevention of strokes and TEC in patients with non-valvular AF it is recommended to use the optimal dose of dabigatran 150 mg 2 times daily, which showed best results in reducing the risk of ischemic and hemorrhagic strokes, as well as in improving other clinical outcomes, in comparison with warfarin. Taking into account the age and functional state of the kidneys from the clinical point of view in order to improve safety, it is advisable to reduce the dose of dabigatran to 110 mg 2 times daily in patients at high risk of bleeding. The effectiveness of dabigatran therapy at a dose of 150 mg and 110 mg of 2 times daily does not depend on the level of GFR. With comparable efficacy in stroke prevention, the risk of bleeding with ACT with dabigatran is significantly lower than with rivaroxabano, and a more beneficial dabigatran safety profile in both dosages is maintained in patients with AF with concomitant CKD.

REFERENCES

1. *Banerjee A., Marin F., Lip G.Y. A new landscape for stroke prevention in atrial fibrillation: focus on new anticoagulants, antiarrhythmic drugs, and devices. Stroke, 2011;42: 3316–22.*
2. *Marinigh R., Lane D.A., Lip G.Y. Severe renal impairment and stroke prevention in atrial fibrillation: implications for hromboprophylaxis and bleeding risk. J Am Coll Cardiol. 2011;57:1339–48.*
3. *Reinecke H., Brand E., Mesters R., et al. Dilemmas in the management of atrial fibrillation in chronic kidney disease. J Am Soc Nephrol. 2009;20:705–11.*
4. *Baber U., Howard V.J., Halperin J.L., et al. Association of chronic kidney disease with atrial fibrillation among adults in the United States: REasons for Geographic and Racial Differences in Stroke (REGARDS) Study. Circ Arrhythm Electrophysiol. 2011;4:26–32.*
5. *Soliman E.Z., Prineas R.J., Go A.S., et al.; Chronic Renal Insufficiency Cohort (CRIC) Study Group. Chronic Renal Insufficiency Cohort (CRIC) Study Group. Chronic kidney disease and prevalent atrial fibrillation: the Chronic Renal Insufficiency Cohort (CRIC). Am Heart J. 2010;159:1102–7.*
6. *Pavord S., Myers B. Bleeding and thrombotic complications of kidney disease. Blood Rev. 2011;25:271–278.*
7. *Falga C., Capdevila J.A., Soler S., et al; RIETE Investigators. Clinical outcome of patients with venous thromboembolism and renal insufficiency: findings from the RIETE registry. Thromb Haemost. 2007;98:771–776.*
8. *Bos M.J., Koudstaal P.J., Hofman A., Breteler M.M. Decreased glomerular filtration rate is a risk factor for hemorrhagic but not for ischemic stroke: the Rotterdam study. Stroke. 2007;38:3127–32.*
9. *Vazquez E., Sanchez-Perales C., Garcia-Cortes M.J., et al. Ought dialysis patients with atrial fibrillation be treated with oral anticoagulants? Int J Cardiol. 2003;87:135–9.*
10. *Clark N. Low-molecular-weight heparin use in the obese, elderly, and in renal insufficiency. Thromb Res. 2008;123:58–61.*
11. *Lim W. Low-molecular-weight heparin in patients with chronic renal insufficiency. Intern Emerg Med. 2008;3:319–23.*
12. *Schmid P., Fischer A.G., Wuillemin W.A. Low-molecularweight heparin in patients with renal insufficiency. Swiss Med Wkly. 2009;139:438–52.*
13. *Hoffmann P., Keller F. Increased major bleeding risk in patients with kidney dysfunction receiving enoxaparin: a meta-analysis. Eur J Clin Pharmacol. 2012;68:757–65.*
14. *U.S. Renal Data System (USRDS) 2006 Annual Data Report. Volume 2: Atlas of End-Stage Renal Disease in the United States. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, 2006.*
15. *Apostolakis S., Guo Y., Lane D.A., et al. Renal function and outcomes in anticoagulated patients with non-valvular atrial fibrillation: the AMADEUS trial. Eur Heart J. 2013;34:3572–9.*
16. *Stevens L.A., Coresh J., Greene T., Levey A.S. Assessing kidney function-measured and estimated glomerular filtration rate. N Engl J Med. 2006;354:2473–83.*
17. *Iguchi Y., Kimura K., Kobayashi K., et al. Relation of atrial fibrillation to glomerular filtration rate. Am J Cardiol. 2008;102(8):1056–9.*
18. *McManus D.D., Corteville D.C., Shlipak M.G., et al. Relation of kidney function and albuminuria with atrial fibrillation (from the Heart and Soul Study). Am J Cardiol. 2009;104(11): 1551–5.*
19. *Asselbergs F.W., van den Berg M.P., Diercks G.F., et al. C-reactive protein and microalbuminuria are associated with atrial fibrillation. Int J Cardiol. 2005:98(1):73–7.*
20. *Watanabe H., Watanabe T., Sasaki S., et al. Close bidirectional relationship between chronic kidney disease and atrial fibrillation: the Niigata preventive medicine study. Am Heart J. 2009;158(4):629–36.*
21. *Alonso A., Lopez F.L., Matsushita K., et al. Chronic kidney disease is associated with the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2011;123(25):2946–53.*
22. *Atar I., Konas D., Acikel S., et al. Frequency of atrial fibrillation and factors related to its development in dialysis patients. Int J Cardiol. 2006;106(1):47–51.*
23. *Winkelmayer W.C., Patrick A.R., Liu J., et al. The increasing prevalence of atrial fibrillation among hemodialysis patients. J Am Soc Nephrol. 2011;22(2):349–57.*
24. *Go A.S., Chertow G.M., Fan D., et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351:1296–305.*
25. *Abbott K.C., Trespalacios F.C., Taylor A.J., Agodoa L.Y. Atrial fibrillation in chronic dialysis patients in the United States: Risk factors for hospitalization and mortality. BMC Nephrol. 2003;4:1–10.*
26. *Vazquez E., Sanchez-Perales C., Lozano C., et al. Comparison of prognostic value of atrial fibrillation versus sinus rhythm in patients on long-term hemodialysis. Am J Cardiol. 2003;92:868 –71.*
27. *Corrao S., Argano C., Nobili A., et al., REPOSI Investigators Brain and kidney, victims of atrial microembolism in elderly hospitalized patients? Data from the REPOSI study. Eur J Intern Med. 2015;26:243–9.*
28. *Go A.S., Hylek E.M., Phillips K.A., et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. JAMA. 2001;285:2370–5.*
29. *Vazquez E., Sanchez-Perales C., Garcia-Garcia F., et al. Atrial*

fibrillation in incident dialysis patients. Kidney Int. 2009;76:324–30.

30. *Schaeffner E.S., Ebert N., Delanaye P., et al. Two novel equations to estimate kidney function in persons aged 70 years or older. Ann Intern Med. 2012;157:471–81.*
31. *Levey A.S., de Jong P.E., Coresh J., et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int. 2011;80:17–28.*
32. *Go A.S., Fang M.C., Udaltsova N., et al.; ATRIA Study Investigators. Impact of proteinuria and glomerular filtration rate on risk of thromboembolism in atrial fibrillation: the anticoagulation and risk factors in atrial fibrillation (ATRIA) study. Circulation. 2009;119:1363–9.*
33. *Bonde A.N., Lip G.Y., Kamper A.L., et al. Net clinical benefit of antithrombotic therapy in patients with atrial fibrillation and chronic kidney disease: a nationwide observational cohort study. J Am Coll Cardiol. 2014;64:2471–82.*
34. *Hart R.G., Pearce L.A., Aguilar M.I. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have non-valvular atrial fibrillation. Ann Intern Med. 2007;146(12):857–67.*
35. *Nakagawa K., Hirai T., Takashima S., et al. Chronic kidney disease and CHADS(2) score independently predict cardiovascular events and mortality in patients with non-valvular atrial fibrillation. Am J Cardiol. 2011;107(6):912–6.*
36. *Gage B.F., Waterman A.D., Shannon W., et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864–70.*
37. *Wizemann V., Tong L., Satayathum S., et al. Atrial fibrillation in hemodialysis patients: clinical features and associations with anticoagulant therapy. Kidney Int. 2010;77:1098–106.*
38. *Genovesi S., Pogliani D., Faini A., et al. Prevalence of atrial fibrillation and associated factors in a population of long-term hemodialysis patients. Am J Kidney Dis. 2005;46(5):897–902.*
39. *Guo Y., Wang H., Zhao X., et al. Sequential changes in renal function and the risk of stroke and death in patients with atrial fibrillation. Int J Cardiol. 2013;168:4678–84.*
40. *Tsagalis G., Akrivos T., Alevizaki M., et al. Renal dysfunction in acute stroke: an independent predictor of long-term all combined vascular events and overall mortality. Nephrol Dial Transplant. 2009;24:194–200.*
41. *Kumai Y., Kamouchi M., Hata J., et al.; FSR Investigators. Proteinuria and clinical outcomes after ischemic stroke. Neurology. 2012;78:1909–15.*
42. *Yahalom G., Schwartz R., Schwammenthal Y., et al. Chronic kidney disease and clinical outcome in patients with acute stroke. Stroke. 2009;40:1296–303.*
43. *Dumaine R.L., Montalescot G., Steg P.G., et al. Renal function, atherothrombosis extent, and outcomes in high-risk patients. Am Heart J. 2009;158(1):141–8.e1.*
44. *Olesen J.B., Lip G.Y., Kamper A.L., et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012;367:625–35.*
45. *Chan K.E., Lazarus J.M., Thadhani R., Hakim R.M. Warfarin use associates with increased risk for stroke in hemodialysis patients with atrial fibrillation. J Am Soc Nephrol. 2009;20:2223–33.*
46. *Sood M.M., Larkina M., Thumma J.R., et al. Major bleeding events and risk stratification of antithrombotic agents in hemodialysis: results from the DOPPS. Kidney Int. 2013;84:600–8.*
47. *Hart R.G., Pearce L.A., Asinger R.W., Herzog C.A. Warfarin in atrial fibrillation patients with moderate chronic kidney disease. Clin J Am Soc Nephrol. 2011;6:2599–604.*
48. *Lai H.M., Aronow W.S., Kalen P., et al. Incidence of thromboembolic stroke and of major bleeding in patients with atrial fibrillation and chronic kidney disease treated with and without warfarin. Int J Nephrol Renovasc Dis. 2009;2:33–7.*
49. *Limdi N.A., Beasley T.M., Baird M.F., et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. J Am Soc Nephrol. 2009;20:912–21.*
50. *Genovesi S., Rossi E., Pogliani D., et al. The nephrologist's anticoagu- lation treatment patterns/regimens in chronic hemodialysis patients with atrial fibrillation. J Nephrol. 2014;27:187–92.*
51. *Genovesi S., Rossi E., Gallieni M., et al. Warfarin use, mortality, bleeding, and stroke in haemodialysis patients with atrial fibrillation. Nephrol Dial Transplant. 2015;30:491–98.*
52. *Kapoor K.G., Bekaii-Saab T. Warfarin-induced allergic interstitial nephritis and leucocytoclastic vasculitis. Intern Med J. 2008;38:281–3.*
53. *Wysowski D.K., Nourjah P., Swartz L. Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. Arch Intern Med. 2007;167:1414–19.*
54. *Brodsky S.V., Nadasdy T., Rovin B.H., et al. Warfarin-related nephropathy occurs in patients with and without chronic kidney disease and is associated with an increased mortality rate. Kidney Int. 2011;80:181–9.*
55. *Abt A.B., Carroll L.E., Mohler J.H. Thin basement membrane disease and acute renal failure secondary to gross hematuria and tubular necrosis. Am J Kidney Dis. 2000;35:533–6.*
56. *Kabir A., Nadasdy T., Nadasdy G., Hebert L.A. An unusual cause of gross hematuria and transient ARF in an SLE patient with warfarin coagulopathy. Am J Kidney Dis. 2004;43:757–60.*
57. *Spetie D.N., Nadasdy T., Nadasdy G., et al. Proposed pathogenesis of idiopathic loin pain-hematuria syndrome. Am J Kidney Dis. 2006;47:419–27.*
58. *Brodsky S.V., Satoskar A., Chen J., et al. Acute kidney injury during warfarin therapy associated with obstructive tubular red blood cell casts: a report of 9 cases. Am J Kidney Dis. 2009;54:1121–6.*
59. *Brodsky S.V., Collins M., Park E., et al. Warfarin therapy that results in an International Normalization Ratio above the therapeutic range is associated with accelerated progression of chronic kidney disease. Nephron Clin Pract. 2010;115:c142–146.*
60. *Kaw D., Malhotra D. Platelet dysfunction and end-stage renal disease. Semin Dial. 2006;19:317–22.*
61. *Boccardo P., Remuzzi G., Galbusera M. Platelet dysfunction in renal failure. Semin Thromb Haemost. 2004;30:579–89.*
62. *Hylek E.M., Skates S.J., Sheehan M.A., Singer D.E. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med. 1996;335:540–6.*
63. *Sardar P., Chatterjee S., Herzog E., et al. Novel oral anticoagulants in patients with renal insufficiency: a meta-analysis of randomized trials. Can J Cardiol. 2014;30:888–97.*
64. *Lip G.Y.H., Clemens A., Noack H., et al. Patient outcomes using the European label for dabigatran A post-hoc analysis from the RE-LY database. Thromb Haemost. 2014;111:933–42. doi:10.1160/TH13-09-0734.*
65. *Hijazi Z., Hohnloser S.H., Oldgren J., et al. Efficacy and safety of dabigatran compared with warfarin in relation to baseline renal function in patients with atrial fibrillation: a RE-LY trial analysis. Circulation. 2014;129(9):961–70. doi:10.1161/CIRCULATIONAHA.113.003628.*

66. *Böhm M., Ezekowitz M.D., Connolly S., et al. Changes in renal function in patients with atrial fibrillation: an analysis from the RE-LY trial. JACC. 2015;65(23):2481–93.*
67. *Hernandez I., Zhang Y. Comparing stroke and bleeding with rivaroxaban and dabigatran in atrial fibrillation: analysis of the US Medicare part D data. Am J Cardiovasc Drugs. 2017;17(1):37-47. doi: 10.1007/s40256-016-0189-9.*
68. *Kirchhof P., Benussi S., Kotecha D., et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016;18:1609–78.*
69. *Beyth R.J., Quinn L.M., Landefeld C.S. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. Am J Med. 1998;105:91–9.*
70. *Gage B.F., Yan Y., Milligan P.E., et al.. Clinical classification schemes for predicting haemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). Am Heart J. 2006;151:713–9.*
71. *Pisters R., Lane D.A., Nieuwlaat R., et al. Anovel userfriendly score (HAS-BLED) to assess 1-year risk of major bleeding in atrial fibrillation patients: the Euro Heart Survey. Chest. 2010;138:1093–10.*
72. *Ahrens I., Lip G.Y., Peter K. New oral anticoagulant drugs in cardiovascular disease. Thromb Haemost. 2010;104:49–60.*
73. *Budnitz D.S., Lovegrove M.C., Shehab N., Richards C.L. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011;365:2002–12.*
74. *Granger C.B., Alexander J.H., McMurray J.J., et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.*
75. *Patel M.R., Mahaffey K.W., Garg J., et al.; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.*
76. *Eikelboom J.W., Wallentin L., Connolly S.J., et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: An analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation. 2011;123:2363–72.*
77. *Hemmelgarn B.R., Zhang J., Manns B.J., et al. Progression of kidney dysfunction in the community-dwelling elderly. Kidney Int. 2006;69:2155–61.*
78. *Mantha S., Ansell J. An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. Thromb Haemost. 2012;108(9):476–84.*
79. *Lip G.Y., Larsen T.B., Skjoth F., Rasmussen L.H. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2012;60(8):738–46.*
80. *Hariharan S., Madabushi R. Clinical pharmacology basis of deriving dosing recommendations for dabigatran in patients with severe renal impairment. J Clin Pharmcol. 2012;52(Suppl 1):119S–125S.*
81. *Stangier J., Rathgen K., Stahle H., Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. Clin Pharmacokinet. 2010;49(4):259–68.*

Accepted for publication: April 18, 2018.