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THE INTERRELATION OF CYP2C9, CYP4F2, VKORC1 GENES POLYMORPHISMS WITH WARFARIN DOSE AND HEMORRHAGIC COMPLICATIONS RISK RISE IN PATIENTS WITH ATRIAL FIBRILLATION: A RETROSPECTIVE STUDY

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ВЗАИМОСВЯЗЬ ПОЛИМОРФИЗМОВ ГЕНОВ CYP2C9, CYP4F2, VKORC1 С ДОЗОЙ ВАРФАРИНА И ПОВЫШЕНИЕМ РИСКА ГЕМОРРАГИЧЕСКИХ ОСЛОЖНЕНИЙ У ПАЦИЕНТОВ С ФИБРИЛЛЯЦИЕЙ ПРЕДСЕРДИЙ: РЕТРОСПЕКТИВНОЕ ИССЛЕДОВАНИЕ

Abstract. The aim of the study was to identify the frequency of CYP2C9, CYP4F2, VKORC1 genes polymorphisms in patients with atrial fibrillation (AF) and to establish their interrelationship with warfarin (WF) dose and the hemorrhagic complications risk rise.

Materials and methods. A retrospective study was conducted in 60 AF patients receiving WF during one year. CYP2C9, CYP4F2, VKORC1 genes polymorphisms were studied by multiplex real time polymerase chain reaction.

Obtained results. The mean CHA2DS2-VASC score was 3.43 ± 0.18, HAS-BLED score – 2.2 ± 0.13; the WF dose median was 5 mg (3.75; 6.25). It was found out that the VKORC1 mutant allele A presence increased the probability of WF dose less than median in 7.00 times (95% CI 1.982-24.716; $p < 0.05$), and the CYP4F2 mutant allele T increased the probability of WF dose more than median in 6.263 times (95% CI 1.583-24.780). Statistically significant effect of CYP2C9 gene polymorphism on WF dosing was not observed. Bleeding was significantly more frequent in the group of patients with the VKORC1 gene mutation: 69.5% versus 37.5%, respectively ($\chi^2 = 5.331$; $p < 0.05$). The relative risk of bleeding in patients with the VKORC1 gene mutation was 1.97 (CI 1.039; 3.751; $p < 0.05$).

Conclusions. VKORC1 and CYP4F2 genes polymorphisms are associated with warfarin dose variation. VKORC1 gene mutation increases the risk of bleeding.

Аннотация. Целью исследования было выявить частоту полиморфизмов генов CYP2C9, CYP4F2, VKORC1 у пациентов с фибрилляцией предсердий (ФП) и установить их взаимосвязь с дозой варфарина (ВФ) и повышением риска геморрагических осложнений**.**

Материалы и методы. Ретроспективное исследование проведено у 60 пациентов с ФП, получавших ВФ в течение одного года. Полиморфизмы генов CYP2C9, CYP4F2, VKORC1 изучали методом мультиплексной полимеразной цепной реакции в режиме реального времени.

Полученые результаты. Средний балл CHA2DS2-VASC составил 3,43 ± 0,18, балл HAS-BLED - 2,2 ± 0,13; медиана дозы ВФ составила 5 мг (3,75; 6,25). Обнаружено, что наличие мутантного аллеля A VKORC1 увеличивало вероятность дозы ВФ меньше медианы в 7,00 раз (95% ДИ 1,982-24,716; p<0,05), а мутантный аллель T CYP4F2 увеличивал вероятность дозы ВФ больше медианы в 6,26 раза (95% ДИ 1,583-24,780). Статистически значимого влияния полиморфизмов гена CYP2C9 на дозу ВФ не наблюдалось. Кровотечения достоверно чаще возникали в группе пациентов с мутацией гена VKORC1: 69,5% против 37,5% соответственно (χ^2 = 5,331; p<0,05). Относительный риск кровотечения у пациентов с мутацией гена VKORC1 составил 1,97 (CI 1,039; 3,751; p <0,05).

Выводы. Полиморфизмы генов VKORC1 и CYP4F2 связаны с вариацией дозы варфарина. Мутация гена VKORC1 увеличивает риск возникновения кровотечений.

Key words: atrial fibrillation, warfarin, dosing, genes, bleeding.

Ключевые слова: фибрилляция предсердий, варфарин, дозировка, гены, кровотечение.

Introduction. Atrial fibrillation (AF) is one of the most common and widespread cardiac arrhythmias. It significantly increases the relative risk of general and cardiovascular mortality by 1.7 and 2 times, respectively, and doubles the risk of thromboembolic events [1, 2, 3, 4]. The incidence of ischemic stroke among patients with AF is 5% per year, which is 2–7 fold higher than in patients without AF [4, 5, 6, 7].

Despite the emergence of direct oral anticoagulants, warfarin (WF) continues to be a widely used drug in case to prevent thromboembolic complications [8, 9]. It is worth taking into account that WF is characterized with a narrow therapeutic range, and its dose, stability of anticoagulant effect and risk of bleeding depend on many factors, including genetic features related to the CYP2C9, CYP4F2, VKORC1 genes polymorphisms [10, 11, 12]. Genetically determined differences allow to identify patients with different activity of WF and vitamin K biotransformation enzymes and to apply an individual approach to management of these patients. [11, 12, 13, 14, 15] It should be noted that the frequency of gene mutations affecting WF sensitivity vary even in different regions of the same country [16]. The investigation of these genes polymorphisms was not conducted in Zaporizhzhia region.

The impact of genetic factors on the WF dosing and the incidence of hemorrhagic complications that require scientific research remains insufficiently studied.

The aim of the study was to identify the frequency of CYP2C9, CYP4F2, VKORC1 genes polymorphisms in patients with atrial fibrillation and to establish their interrelationship with warfarin dose and the hemorrhagic complications risk rise.

Materials and methods. A retrospective study was conducted in 60 AF patients (32 men, 28 women, median age – 70.5 (64.25; 76.75)) who after prescribing WF were observed at the specialized anticoagulant therapy monitoring office of the ZSMU University Clinic during one year. Patients were advised to take WF as they could not afford receiving up-to-date direct oral anticoagulants.

Inclusion criteria: verified atrial fibrillation; informed consent to participate in the study. Exclusion criteria: prosthetic heart valves, congenital and acquired heart defects, severe renal and hepatic dysfunction, acute coronary syndrome, acute cerebral circulation disorders, oncological and hematological diseases, mental health disorders, infections.

AF diagnosis was established according to ESC recommendations (2016) [17]. Coagulograms indexes with International Normalized Ratio (INR) were determined on a Coag Chrome 3003 monthly. The risk of thromboembolic and bleeding events was estimated according to CHA2DS2-VASC and HAS-BLED scales respectively. The selection and control of WF dose were carried out according to the standard method. Time in therapeutic range (TTR) was calculated by using Rosendaal method [18]. Hemorrhagic complications under the WF were divided into minor and major bleeding according to the Fihn S.D. classification. et al.[19]

The CYP2C9, CYP4F2, VKORC1 genes polymorphisms in AF patients were determined in the Department of Molecular Genetic Studies of the ZSMU Medical Laboratory Center (Director – Prof. AV Abramov). DNA samples were isolated from whole blood leukocytes using a set of PROBA-RAPID-GENETICA reagents (LLC "NPO DNA Technology"). Amplification of DNA fragments containing polymorphic regions was performed using multiplex real time polymerase chain reaction with Warfarin Pharmacogenetics kits (LLC NPO DNA Technology) in a CFX-96 thermocycler (BioRad) with a fluorescence detection scheme. 20 μl of pre-centrifuged appropriate amplification mixture was added to test tubes. Separately, a mixture of PCR buffer with Taq-AT polymerase in a ratio of 20: 1 was prepared and centrifuged for 1-3 sec. 10 μl of a mixture of PCR buffer with Taq-AT polymerase were added to the tubes with the mixture for amplification. 1 drop (20 μl) of mineral oil was added to each tube. 5 μl of DNA extracted from the sample drug tips with an aerosol barrier were added to the test tubes. The same manipulations were performed with the control sample. After 1-3 sec. centrifugation the amplification was carried out. PCR results were recorded automatically by the corresponding software.

The principles of bioethics were observed in the study: the basic provisions of the European Council Convention on Human Rights and Biomedicine (dated 04.04.1997), GCP (1996), the World Health Association's Helsinki Declaration on Ethical Principles for Scientific and Human Research (1964-2000) and the order of the Ministry of Health of Ukraine No. 281 of 01.11.2000.

Statistical data processing was performed using the Statistica 6.0 software package (StatSoftInc, No. AXXR712D833214FAN5) according to contemporary requirements. Comparison of qualitative indicators and assessment of conformity of genotypes distribution to the expected Hardy-Weinberg equilibrium values were performed using the Yates-adjusted criterion χ^2. To determine differences in the WF dose in patients with different genotypes a rank analysis according to Kruskal-Wallis was used. Hereafter paired comparison of groups of patients with different genotypes was performed using the Mann-Whitney U test, taking into account the Bonferroni correction for multiple comparisons. To determine the contribution of each polymorphic locus to the WF dosing regimen, the odds ratio with 95% CI of entering the group with a daily WF dose greater than or less than median was calculated. The differences were considered significant at $p < 0.05$.

Obtained results and discussion. The mean CHA2DS2-VASC score was 3.43 ± 0.18, HAS-BLED score – 2.2 ± 0.13. The median WF dose was 5.0 (3.75; 6.25) mg. The mean TTR was 70.02 ± 13.7%. Among the drugs affecting the WF metabolism 10 (16.7%) patients took amiodarone, 51 (85%) − statins.

During the year, hemorrhagic complications (minor bleeding) occurred in 29 (48.33%) patients (Figure 1), including subcutaneous hematomas in 11 (18.33%), hemophthalmia in 5 (8.33%), blood in the feces – in 4 (6.67%), nasal and gums bleeding – in 12 (20 %) patients, hematuria – in 2 (3%).

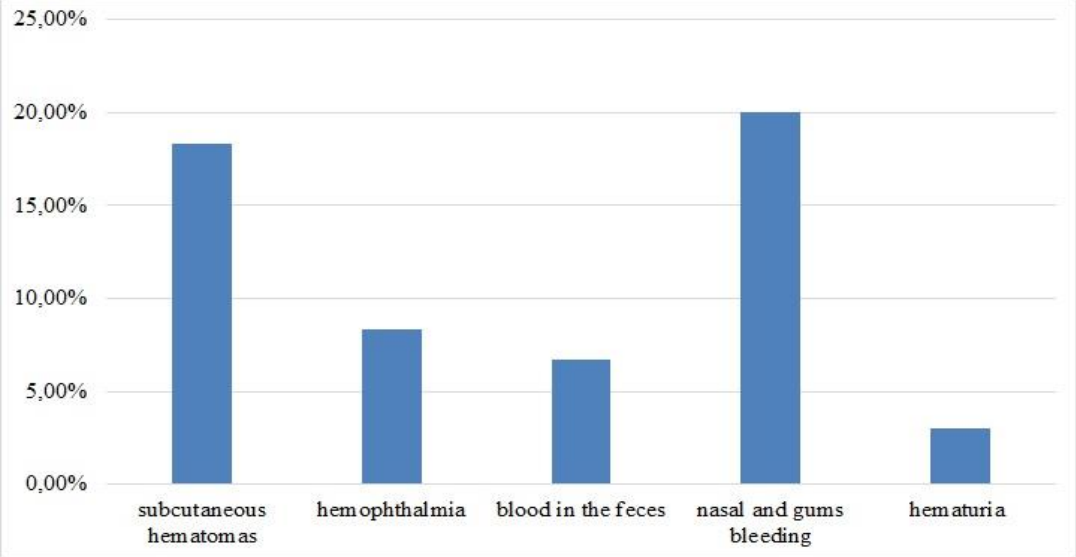

Figure 1. The structure of bleeding in AF patients receiving WF

No major bleeding was observed. Thromboembolic complications were not recorded, although the risk of stroke during the year for our patients was 4% (mean CHA2DS2-VASC score greater than 3).

The results of genetic analysis are shown in Table 1.

Table 1.

Frequency of genes polymorphism related to the WF metabolism in AF patients

Gene polymorphism	Homozygous for the wild-type allele	Heterozygous	Homozygous for the mutant allele
CYP2C9*2	46 (76.67%)	13 (21.67%)	1 (1.67%)
CYP2C9*3	52 (86.67%)	7 (11.67%)	1 (1.67%)
CYP4F2	40 (66.67%)	18 (30%)	2 (3.33%)
VKORC1	25 (41.67%)	28 (46.67%)	7 (11.67%)

According to the results of genotyping of the CYP2C9*2 gene, homozygous for the wild-type allele (genotype C/C) were found in 46 (76.67%) cases, heterozygous (C/T) − in 13 (21.67%), homozygous for the mutant (T/T) in 1 (1.67%) case. In the study of CYP2C9*3 gene polymorphism, homozygous for the wild-type allele (A/A) were detected in 52 (86.67%) cases, heterozygous (A/C) - in 7 (11.67%), homozygous for the mutant allele (C/C) – in 1 (1.67%) case. CYP4F2 gene polymorphism was detected in 20 (33.33%) patients, with heterozygous (C/T) in 18 (30%) patients and homozygous for the mutant allele (T/T) – 2 (3.33%), 40 (66.67%) patients had a wild-type genotype (C/C). The VKORC1 gene mutation was detected in 35 (58.34%) patients: 28 (46.67%) heterozygous (G/A) and 7 (11.67%) homozygous (A/A), respectively. No mutations were detected in 25 (41.67%) (G/G).

The distribution of CYP2C9, CYP4F2, VKORC1 genotypes were in accordance with Hardy-Weinberg equilibrium, indicating no errors in sample formation and genotyping (Table 2).

Table 2.

Comparison of genotype frequencies of CYP2C9, CYP4F2, VKORC1 genes polymorphisms with the calculated Hardy-Weinberg equilibrium frequencies

Genotypes	Cases	HWE	χ^2	p
	n = 60	n = 60		
CYP2C9 * 2 (C/T) polymorphic marker				
C/C	46 / 0.767	46 / 0.766	0.01	0.99
C/T	13 / 0.217	13 / 0.219		
T/T	1 / 0.017	1 / 0.016		
CYP2C9 * 3 (A/C) polymorphic marker				
A/A	52 / 0.867	51 / 0.856	1.52	0.47
A/C	7 / 0.117	8 / 0.139		
C/C	1 / 0.017	1 / 0.006		
CYP4F2 polymorphic marker (C/T)				
C/C	40 / 0.667	40 / 0.667	0.0002	0.99
C/T	18 / 0.300	18 / 0.299		
T/T	2/ 0.033	2/ 0.034		
VKORC1 (G/A) polymorphic marker				
G/G	25 / 0.417	25 / 0.423	0.04	0.98
G/A	28 / 0.467	28 / 0.456		
A/A	7 / 0.117	7 / 0.123		

A statistically significant difference in the daily WF dose was established depending on VKORC1 and CYP4F2 genotypes. For the VKORC1 G/G genotype patients the median daily dose was 6.25 (5.125; 7.5) mg, with G/A genotype − 4.75 (3.75; 6), with A/A genotype − 3.0 (2.5; 3.75) mg ($p < 0.05$). For the CYP4F2 genotype the median daily dose was 4.5 (3.25; 6.25) mg, with C/T genotype − 6.125 (5; 7.5), with T/T genotype – 5.625 mg. Significant difference in the daily dose of WF depending on CYP2C9 genotypes was not detected (Figure 2, 3).

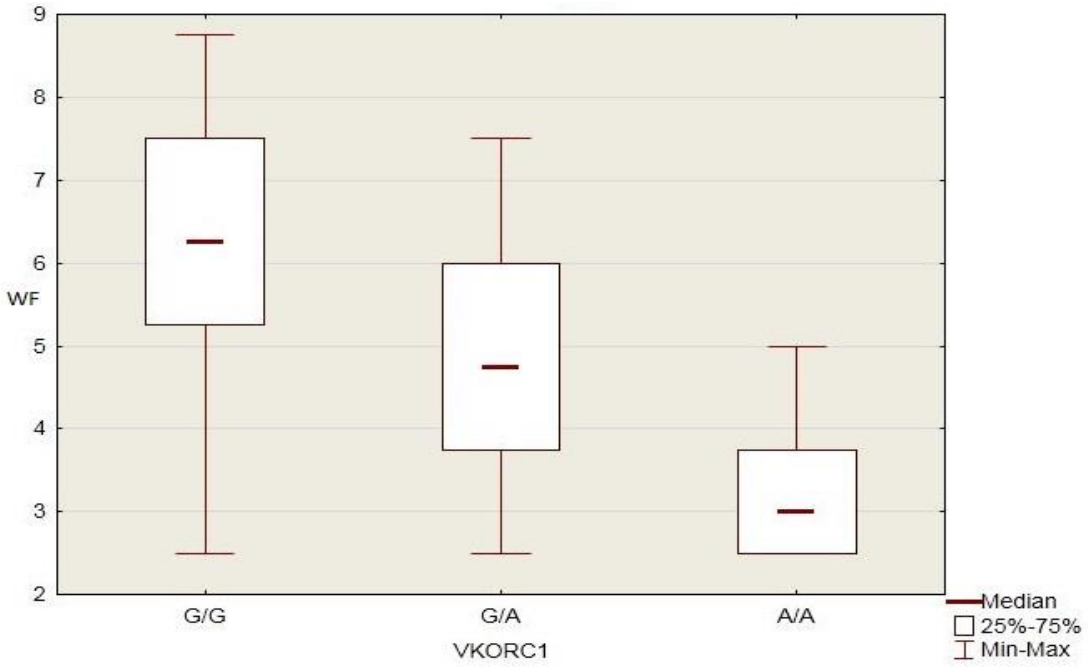

Figure 2. WF doses depending on VKORC1 polymorphism

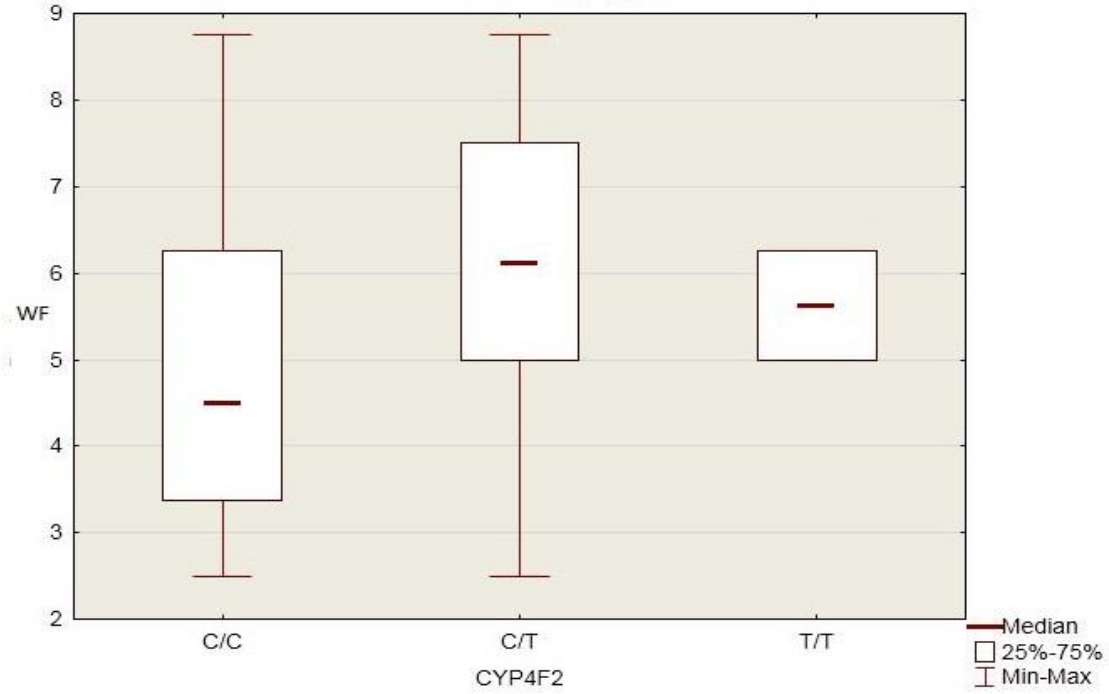

Figure 3. WF doses depending on CYP4F2 polymorphism

To determine the contribution of each polymorphic locus, the odds ratio of entering the group with a daily WF dose greater than or less than median was calculated. It was found out that a significant contribution to the therapeutic dose of WF is provided by the VCORC1 and CYP4F2 genes polymorphisms. The presence of VKORC1 A allele increases the probability of WF dose less than 5 mg by 7.00 times (95% CI 1.9823-24.716; p <0.05), while the CYP4F2 mutant allele T increased the probability of WF dose more than median in 6.263 times (95% CI 1.583-24.780). No statistically significant contributions of the CYP2C9 genes allelic polymorphism to the dosage of WF were observed.

In our study, bleedings occurred significantly more frequently in the group of patients with the VKORC1 gene mutation (Fig. 4): 60% versus 28%, respectively (χ^2 = 4.783; p <0.05). In this regard, we determined the relative risk of hemorrhagic complications in patients with a mutation of the VKORC1 gene. It was found that the relative risk of bleeding is 2.14 (CI 1.081; 4.248; p <0.05), which confirms the significant influence of the genetic factor on the probability of developing of this WF therapy complication. No relationship between bleeding frequency and other genes polymorphysms was found.

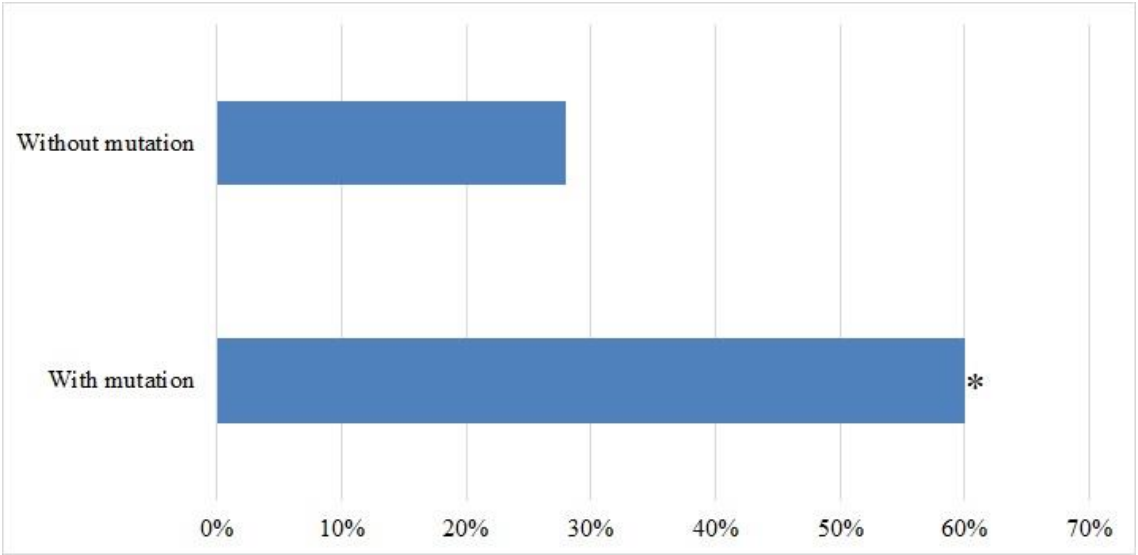

Figure 4. The incidence of bleeding, depending on the mutation of the VKORC1gene
*Note: * − the difference between the groups is probable by the criterion χ2.*

Discussion. The observed prevalence of CYP2C9, CYP4F2, VKORC1 genotypes found in AF patients living in Zaporizhzhia region was comparable to the results of studies conducted in the European population

[16,20], which indicates the feasibility of taking into account genetic polymorphism in WF dosing.

The obtained data about VKORC1 and CYP4F2 genes are confirmed with the results of scientific researches which have proved the influence of genes polymorphism related to WF and vitamin K metabolism on the frequency of hemorrhagic complications and WF doses [14,15,22]. Thus, the WARFAGEN study found out a correlation between the bleeding frequency and the genetically caused increased WF sensitivity [22]. According to meta-analyzes, the VKORC1 and CYP4F2 genes polymorphisms affects significantly on the WF dose: patients with VKORC1 GA and AA genotypes require lower doses of WF, while CYP4F2 C/T and T/T genotypes lead to higher WF doses [14, 15, 22], which was also confirmed in our study. Other studies have found that the allele A of VKORC1 gene is associated with high WF sensitivity and causes the development of excessive hypocoagulation in the first month of treatment, which contributes to the development of hemorrhagic complications, while allele G is associated with low WF sensitivity [23]. Most of the studies indicate the dependence of bleeding and WF dose on CYP2C9 polymorphisms [14,22,23]. In our study, this relationship was not identified; this may be related to the aggregate effect of other factors.

Therefore, it is important to implement pharmacogenetic testing to select the dose of warfarin, having regard to the genes polymorphisms that affect its metabolism, since it will significantly improve the efficiency and reduce the frequency of hemorrhagic complications during anticoagulant therapy.

Conclusions.

1. In AF patients, the prevalence of CYP2C9, CYP4F2, VKORC1 genotype frequencies is comparable to the European population.

2. In AF patients, the VKORC1 gene polymorphism was associated with a lower daily dose of warfarin while CYP4F2 gene polymorphism – with a higher dose. No statistically significant contribution of CYP2C9 gene mutations in the warfarin dosage was detected.

3. The presence of the VKORC1 gene mutant allele A in AF patients increases the relative risk of hemorrhagic complications under warfarin therapy by 2.14 times.

Prospects for further study: personalized approach to the WF dosing using pharmacogenetic testing is the next step in our study.

Compliance with Ethics Requirements: „The authors declare no conflict of interest regarding this article“

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law“.

References:

1. Morillo CA, Banerjee A, Perel P, Wood D, Jouven X. Atrial fibrillation: the current epidemic. J Geriatr Cardiol. 2017 Mar; 14(3): 195-203. DOI: 10.11909/j.issn.1671-5411.2017.03.011

2. Sankaranarayanan R., Kirkwood G., Visweswariah R., Fox D.J. How does Chronic Atrial Fibrillation Influence Mortality in the Modern Treatment Era? Curr Cardiol Rev. 2015 Aug;11(3):190–198. DOI: 10.2174/1573403X10666140902143020

3. Sychov OS, Borodai AO, Borodai ES. Predictors of cardiovascular outcomes in patients with non-valvular atrial fibrillation and flutter. Ukrainskyi kardiolohichnyi zhurnal. 2016;6:64-75. (in Ukr.).

4. Fox KAA, Lucas JE, Pieper KS, Bassand J-P, Camm AJ, Fitzmaurice DA, et al. Improved risk stratification of patients with atrial fibrillation: an integrated GARFIELD-AF tool for the prediction of mortality, stroke and bleed in patients with and without anticoagulation. BMJ Open. 2017;7(12):e017157. DOI: 10.1136/bmjopen-2017-017157

5. Tseluyko VI, Opolonskaya NA. The Prevalence of Risk Factors for Thromboembolic and Hemorrhagic Complications among Patients with Atrial Fibrillation. Medicyna neotlozhnykh sostoyanij. 2013;7(54):65-69. (in Russ.).

6. Oladirana O, Nwosub I. Stroke risk stratification in atrial fibrillation: a review of common risk factors. J Community Hosp Intern Med Perspect. 2019 Apr;9(2):113-120. DOI: 10.1080/20009666.2019.1593781

7. Cowan JC, Wu J, Hall M, Orlowski A, West RM, Gale CP. A 10 year study of hospitalized atrial fibrillation-related stroke in England and its association with uptake of oral anticoagulation. Eur Heart J. 2018;39(32):2975–2983. https://doi.org/10.1093/eurheartj/ehy411.

8. Andrade JG, Krahn AD, Skanes AC, Purdham D, Ciaccia A, Connors S. Values and preferences of physicians and patients with Nonvalvular atrial fibrillation who receive Oral anticoagulation therapy for stroke prevention. Can J Cardiol. 2016;32(6):747–53. DOI: 10.1016/j.cjca.2015.09.023

9. Kropacheva ES, Borovkov NN, Vavilova TV, Verenina NK, Vorob'eva NA, Galkina IS, et al. The rapid pace of saturation of warfarin - a predictor of excessive anticoagulation. Modernization algorithm dose adjustment of warfarin. Aterotromboz. 2015;1:75-86. (in Russ.).

10. Bader LA, Elewa H. The Impact of Genetic and Non-Genetic Factors on Warfarin Dose Prediction in MENA Region: A Systematic Review. PLoS One. 2016;11(12):e0168732. DOI: 10.1371/journal.pone.0168732

11. Geoffrey SG, Huntington FW, editors. Genomic and Precision Medicine: Cardiovascular Disease, Third Edition. Academic Press; 2017. Chapter 16, Cardiovascular Pharmacogenetics. p.291-307. https://doi.org/10.1016/C2015-0-06899-X

12. Francis Lam YW, Scott SA, editors. Pharmacogenomics: Challenges and Opportunities in Therapeutic Implementation, Second Edition. Academic Press; 2019. Chapter 6, Pharmacogenetics in Cardiovascular Diseases. p. 133-179. https://doi.org/10.1016/C2016-0-03878-0

13. Sychov OS, Borodai ES, Borodai AO. Recommendations for the use of pharmacogenetic testing in clinical practice. Ukrainian Journal of Cardiology. 2016;6:64–75 (in Russ).

14. Jorgensen AL, Richard J, Gerald F, Oyee J, Pirmohamed M, Williamson PR. Influence of CYP2C9 and VKORC1 on Patient Response to Warfarin: A Systematic Review and Meta-Analysis. PLoS One. 2012;7(8):e44064. DOI: 10.1371/journal.pone.0044064.

15. Sun X, Yu W-Y, Ma W-L, Huang L-H, Yang G-P. Impact of the CYP4F2 gene polymorphisms on the warfarin maintenance dose: A systematic review and meta-analysis. Biomed Rep. 2016 Apr;4(4):498–506. DOI: 10.3892/br.2016.599

16. Ross KA, Bigham AW, Edwards M, Gozdzik A, Suarez-Kurtz G, Parra EJ. Worldwide allele frequency distribution of four polymorphisms associated with warfarin dose requirements. J Hum Genet. 2010 Sep;55(9):582-9. DOI: 10.1038/jhg.2010.73.

17. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace. 2016;18(11):1609–1678. DOI: 10.1093/europace/euw295

18. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993; 69:236-239. DOI: 10.1055/s-0038-1651587

19. Fihn SD, McDonell M, Martin D, Henikoff J, Vermes D, Kent D, White RH. Risk factors for complications of chronic anticoagulation. A multicenter study. Warfarin Optimized Outpatient Follow-up Study Group. Annal of Internal Medicine. 1993;118(7):511–520. DOI: 10.7326/0003-4819-118-7-199304010-00005

20. Buzoianu AD, Trifa AP, Mureşanu DF, Crişand S. Analysis of CYP2C9*2, CYP2C9*3 and VKORC1 -1639 G>A polymorphisms in a population from South-Eastern Europe. J Cell Mol Med. 2012 Dec ;16(12):2919–2924. DOI: 10.1111/j.1582-4934.2012.01606.x

21. Levkovich NM, Gorovenko NG. Allele frequency distribution of CYP2C9 gene in Ukrainian population. Odeskyi medychnyi zhurnal. 2013;2:23-28. (in Ukr.).

22. Zhang J, Chen Z, Chen C. Impact of CYP2C9, VKORC1 and CYP4F2 genetic polymorphisms on maintenance warfarin dosage in Han-Chinese patients: A systematic review and meta-analysis. Meta Gene. 2016 Jul; 9:197-209. DOI: 10.1016/j.

23. Tomek A, Maťoška V, Kolářová T, Neumann J, Šrámek M, Šarbochová I., et al. The Bleeding Risk during Warfarin Therapy Is Associated with the Number of Variant Alleles of CYP2C9 and VKORC1 Genes. Cardiology. 2013;125:182-191.https://doi.org/10.1159/000350407

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EFFICIENCY AND SAFETY USING OF MODERN A2-AGONISTS IN ANESTHESIA FOR CORNEAL TRANSPLANTATION

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ЭФФЕКТИВНОСТЬ И БЕЗОПАСНОСТЬ ПРИМЕНЕНИЯ СОВРЕМЕННЫХ A_2-АГОНИСТОВ В АНЕСТЕЗИОЛОГИЧЕСКОМ ПОСОБИИ ПРИ ТРАНСПЛАНТАЦИИ РОГОВИЦЫ

Summary. In modern anesthesiology, there is a constant search for new adjuvants for anesthesia in order to improve postoperative comfort, control pain and reduce the number of complications. A2 agonists have pharmacological effects (sympatholytic, anxiolytic, antinociceptive) that contribute to the achievement of the above goals. The study involved 77 patients undergoing corneal transplantation. The patients were divided into 2 groups: control (group K) - 45 people and the main (group D) - 32 people. In both groups, multicomponent anesthesia was used, in group C, sibazone was used for sedation, in group D, dexmedetomidine. The main criteria for assessing the results were: stability of hemodynamics and gas exchange, the amount of opiates consumed, the severity of postoperative pain and the incidence of postoperative nausea and vomiting (PONV). Both schemes