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Способы контроля эффективности применения антикоагулянтов прямого действия при диабетической ретинопатии

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АННОТАЦИЯ

Применение антикоагулянтов является основой лечения многих заболеваний, вызывающих развитие артериальных и венозных тромбозов. Одно из таких заболеваний — диабетическая ретинопатия. До сих пор нет единого мнения, какой способ контроля эффективности данных препаратов наилучший. Именно поэтому ведётся активный поиск специфичных биомаркёров, отражающих качество проводимого лечения. С этой целью нами проанализированы научные работы, в которых исследовалось применение антикоагулянтов при лечении диабетической ретинопатии с помощью различных видов лабораторной диагностики.

Анализ научных публикаций выполнен в информационных базах PubMed и eLIBRARY.RU. В обзор включены опубликованные за последние 30 лет работы, содержащие описание основных групп антикоагулянтов и способы лабораторного контроля их применения. Проанализированы обзорные статьи, результаты экспериментальных исследований, монографии, учебные пособия и диссертационные работы.

Общеизвестно, что антикоагулянты разделяются на две основные группы — прямые и непрямые. В современной клинической практике применяют главным образом прямые. Для контроля их эффективности в основном используют традиционные методы определения коагулограммы, но всё чаще авторы прибегают к более детальному изучению реологических свойств крови (определение анти-Х-активности, агрегационной способности тромбоцитов с использованием индукторов, активности факторов свёртываемости). В то же время перспективным остаётся изучение влияния антикоагулянтов на концентрацию провоспалительных цитокинов и факторов роста в сыворотке крови и слёзной жидкости при диабетической ретинопатии.

Единое мнение о том, какие методы исследования наиболее точно отображают влияние антикоагулянтов на систему гемостаза и показатели воспалительной активности при различных заболеваниях, в частности при диабетической ретинопатии, пока не сформировано. Необходимо более детально изучить, какие лабораторные показатели способны изменяться под действием данных препаратов.

Ключевые слова: антикоагулянты; биомаркёры; гемостаз; диабетическая ретинопатия.

Как цитировать

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Methods for monitoring the effectiveness of direct-acting anticoagulants in diabetic retinopathy

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ABSTRACT

Anticoagulants are the basis for the treatment of various diseases that induces the development of arterial and venous thrombosis. One such disease is diabetic retinopathy. However, no consensus has been reached regarding the best way to control the effectiveness of these drugs. Thus, active search is ongoing for specific biomarkers that reflect treatment quality. To this end, this study analyzed scientific papers that presented the results of various laboratory diagnostics aimed at examining the use of anticoagulants in the treatment of diabetic retinopathy.

PubMed and eLIBRARY.RU were searched for legible studies. The review analyzed studies that describe the main groups of anticoagulants and methods of laboratory control of their use and published in the past 30 years. Review articles, results of experimental studies, monographs, study guides, and dissertations were analyzed.

Anticoagulants are divided into direct and indirect. In modern clinical practice, direct ones are mainly used. To control their effectiveness, traditional methods for determining the coagulogram are mainly used; however, increasingly more often, the authors resort to a more detailed study of the rheological properties of the blood, such as determination of anti-X activity, platelet aggregation using inductors, and activity of clotting factors. In addition, determining their effect on the concentration of pro-inflammatory cytokines and growth factors in the blood serum and lacrimal fluid in diabetic retinopathy remains promising.

However, no consensus has been established on which research methods most accurately reflect the effect of anticoagulants on the hemostatic system and indicators of inflammatory activity in various diseases, particularly in diabetic retinopathy. Therefore, a detailed analysis of what laboratory parameters can change under the influence of these drugs is necessary.

Keywords: anticoagulants; biomarkers; hemostasis; diabetic retinopathy.

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BACKGROUND

Anticoagulants are drugs that can influence hemostasis processes. These drugs are used in cases of a risk of arterial and venous thrombosis. Because increased thrombogenesis occurs in several diseases, anticoagulants are used in various fields of medicine [1]. Scientists have been actively searching for the most effective and safe anticoagulants with a convenient dosage regimen. The main requirement is the ability to effectively monitor the therapy by identifying specific biomarkers that reflect treatment quality [2].

INDIRECT ANTICOAGULANTS (VITAMIN K ANTAGONISTS)

There are two main groups of anticoagulants: direct and indirect. Indirect drugs include the vitamin K antagonist warfarin. This drug has long been the main drug for the treatment and prevention of venous thrombosis in various cardiovascular diseases [3]. However, the use of warfarin requires regular monitoring of the international normalized ratio (INR). Moreover, the INR range for warfarin is extremely small (2.0–3.0), and its efficiency can be influenced by several factors, from diet to the genetic characteristics of the body [3]. Some studies have revealed that warfarin may influence serum pro-inflammatory cytokine concentrations. Thus, Shafiq et al. [4] established that when low doses of warfarin are prescribed, the blood concentrations of interleukin (IL)-6 and cyclooxygenase 2 decrease significantly.

DIRECT ANTICOAGULANTS

Direct anticoagulants represent a much larger group than indirect ones. Its main representative is heparin and its derivatives. The main difficulties in using heparin are the parenteral route of administration and monitoring the activated partial thromboplastin time (aPTT) [5]. Low molecular weight heparins can block the action of factor Xa, which can serve as a biomarker of their effectiveness [1]. Heparinoid sulodexide is a relatively new drug that can significantly increase aPTT and thrombin time (TT) and reduce serum fibrinogen levels. Its effect on biochemical blood parameters was not noted [6]. Additionally, heparin and sulodexide have anti-inflammatory, antioxidant, and hypolipidemic properties [7, 8].

DIRECT ORAL ANTICOAGULANTS

Direct oral anticoagulants (DOACs) or new oral anticoagulants (NOACs) are the most current anticoagulants. Their main advantage is the absence of the need to monitor hemostasis parameters. However, there is evidence that their use increases the risk of minor bleeding. Therefore, the prescription of DOACs should be performed under dynamic monitoring [9]. Standard tests for monitoring coagulation activity cannot accurately characterize DOAC effectiveness but are modified by their influence [2]. The main DOACs are dabigatran etexilate and melagatran (thrombin inhibitors) and apixaban and rivaroxaban (factor Xa inhibitors) [10–13]. In the Russian Federation, the NOACs dabigatran, apixaban, and rivaroxaban are currently registered and recommended for use in medical practice [14].

Some experimental studies showed that dabigatran etexilate and melagatran may have a positive effect on the course of atherosclerosis. The use of thrombin inhibitors reduced the lipid content in plaque thickness and reduced the concentration of inflammatory cytokines and macrophages [11, 15]. However, at present, melagatran is not used in clinical practice because of its high negative effect on the liver with longterm use [16].

Antovic et al. [17] established that aPTT, INR, and TT cannot be biomarkers when taking dabigatran etexilate. They determined plasma drug concentrations using liquid chromatography–mass spectrometry (LS–MS/MS) and revealed that even at high doses of the drug, coagulation parameters did not change.

Additionally, Katoh et al. described that rivaroxaban and apixaban reduce inflammatory marker concentration and hemostatic system parameters [18]. Six months after the course of treatment, the activity of pro-inflammatory cytokines decreased, and coagulogram parameters increased significantly compared with those at the beginning of therapy. The authors conclude that factor Xa inhibitors have anticoagulant and anti-inflammatory effects.

Another study examined the role of rivaroxaban in angiogenesis in patients with diabetes mellitus. The experiment established that rivaroxaban stimulated the production of vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS), which triggered neovascularization processes [19].

Factor Xa inhibitors also reduce the development of atherosclerosis by reducing the concentration of lipids in plaques and production of inflammatory molecules (MMP-9, IL-1β, IL-6, and TNF-α) [20, 21].

Al-Aieshy et al. [22] compared the concentrations of apixaban and rivaroxaban, determined using LS–MS/MS, with parameters of the hemostatic system (anti-factor Xa, prothrombin time (PT)-INR, and aPTT). It was established that anti-Xa analysis is most sensitive to the use of these drugs, whereas PT-INR and aPTT changed only at high concentrations [22, 23].

Since standard coagulation tests do not enable the evaluation of hemostasis qualitatively and quantitatively when taking DOAC, attempts have been made to use a fundamentally new method, the thrombodynamics test. The study [24] analyzed parameters such as clot growth time (V), clot growth delay time (Tlag), initial clot growth velocity (Vi), steady-state clot growth velocity (Vst), clot size, and clot density (D). This test may be an extremely promising method for monitoring DOAC efficiency.

HIRUDINS

The use of hirudins in modern practice is not as widespread as that of other anticoagulants. Recombinant bivalirudin is an international drug used parenterally for acute cardiovascular events [25]. It is the only anticoagulant that can be used for heparin-induced thrombocytopenia [26]. Laboratory monitoring of the use of bivalirudin involves determining the activated coagulation time, which should be 365±100 s 5 min after drug infusion [27].

Furthermore, piyavit (not registered in the State Register of Medicines) is an oral drug from the hirudin group. The possibilities of using piyavit extend to various fields of medicine; however, there are no specific biomarkers of its efficiency.

Some authors have studied the effect of piyavit on various indicators of the hemostatic system during pregnancy. Thus, Kasennova [28] studied fibrinogen concentration, aPTT, platelet aggregation with adenosine diphosphate, prothrombin index, and thromboelastography in fetal growth retardation syndrome. Piyavit had a significant positive effect on all of these indicators. Piskunova [29] revealed a significant decrease in hyperaggregation induced by adrenaline, adenosine diphosphate, and collagen and a decrease in the concentration of fibrinogen and fibrin degradation products under the influence of piyavit.

Moreover, Mikhailova et al. [30] reported that piyavit has a positive effect on lipid metabolism, reduces blood hypercoagulation, and improves fibrinolytic activity. Thromboplastin and thrombin formation, coagulation time, total coagulation time, aPTT, prothrombin time, and clot lysis time increased significantly under the influence of piyavit, and fibrinogen concentration decreased. Thus, the authors concluded that piyavit can be recommended for use as part of complex therapy for diabetes mellitus.

Gilyazov and Samoilov [31] determined that in diabetic retinopathy (DR), with the use of piyavit, glycosylated hemoglobin and prothrombin index improved and clotting time decreased. Further, atherogenic low density lipoprotein concentration decreased and high density lipoprotein concentration increased.

BIOMARKERS OF DIABETIC RETINOPATHY

Diabetes mellitus is characterized by the development of metabolic disorders, hypercholesterolemia, and hemostatic system imbalance [32, 33]. As a result, microvasculature vessels, including the retina, are affected, leading to the development of DR [34]. Against this disease, some coagulogram parameters sharply increase (prothrombin index, fibrinogen concentration) and others decrease (INR, TT, aPTT). In addition, there is reliable evidence of a significant increase in the activity of the von Willebrand factor, antithrombin III, factor VIII, and protein C. The induced platelet aggregation test also reveals a high susceptibility to thrombogenesis [35]. Impaired blood flow in the retinal vessels leads to the appearance of vascular abnormalities in the form of microaneurysms, shunts that bypass ischemic areas, and neovascularization. Further, disruption of the integrity of the vascular walls causes diabetic macular edema [36, 37]. Using ophthalmoscopy, the area of edema is determined by the presence of a ring of "hard" exudates, which are deposits of proteins and lipids released from the retinal capillaries [38, 39]. Special research methods are used to assess these changes more accurately, namely, fluorescein angiography and optical coherence tomography, including in angiography mode. In DR, signs of chronic inflammation with the release of specific pro-inflammatory mediators are detected in the retinal tissues [40–46].

Thus, it should be noted that in treating DR, drugs prescribed to correct lipid status, particularly fenofibrate, are crucial [44]. Moreover, because disorders are registered in the blood coagulation system, anticoagulants are prescribed because they normalize the hemostasiogram and the content of specific hypercoagulation markers, which in turn leads to a decrease in the number of identified changes and, consequently, a decrease in the risk of permanent loss of visual functions [47]. Thus, the National Ophthalmology Manual recommends the international drug sulodexide (Vessel Due F) for the treatment of DR, which can be administered orally or intramuscularly [48]. The order of the Ministry of Health of the Russian Federation "On approval of the standard of primary health care for diabetic retinopathy and diabetic macular edema" also recommends the use of sulodexide as anticoagulant therapy[1].

Due to the development of a chronic inflammatory process in the microvasculature and ischemia in the retinal tissues, pro-inflammatory cytokines (IL-1β, IL-6, IL-8, IL-17) and VEGF in the internal environment of the eye (vitreous body, intraocular fluid) are crucial markers of retinal vascular damage in diabetes, as determined by enzyme immunoassay. To reduce the invasiveness of the study, it was proposed to use more accessible media, namely, lacrimal fluid, and blood serum [49]. However, it should be considered that it is challenging to identify the role of individual molecules in the development of DR because they have several pathogenetic effects that can overlap with each other [50].

Because anticoagulants are used for treating DR, there is an even greater need to control the rheological properties of blood in this disease. For this purpose, different indicators can be used depending on the type of drugs taken. Thus, the main aspects are INR control for warfarin [3] and aPTT for heparin and its derivatives [5, 6]. DOACs mainly affect the activity of factor Xa and the main indicators of the new

[1] Order of the Ministry of Health of the Russian Federation, dated December 24, 2012, N 1492n "On approval of the standard of primary health care for diabetic retinopathy and diabetic macular edema." Access mode: https://base.garant.ru/70344052

thrombodynamics test; however, they can also change the indicators of standard methods for determining coagulation activity [10, 11, 22–24]. Hirudins affect the coagulogram as a whole, anti-Xa activity, and platelet aggregation [27–31]. In addition, many anticoagulants tend to reduce the concentration of pro-inflammatory cytokines, growth factors, and final metabolites of nitric oxide in blood serum, which may be a promising direction for determining these markers in tear fluid [4, 18–21].

Therefore, patients with DR, depending on the medications taken, require monitoring of coagulogram, factor Xa activity, and platelet aggregation as the main biomarkers of hemostatic imbalance. Additionally, the determination of interleukins (IL-6, IL-8), VEGF, and NO metabolites (eNOS) in tears may provide broader insight into the pathogenesis of this hazardous complication of diabetes.

CONCLUSION

It is difficult to answer the question of which indicators (biomarkers) are critical in monitoring the efficiency of anticoagulants for treating diabetic retinopathy. Depending on the drug used, different tests are applied. In hospital therapy, heparins are used for which control of the activated partial thromboplastin time is significant. At home, the most popular drug is warfarin; therefore, monitoring of the international normalized ratio is required, including the use of special portable test systems. When administering DOACs, tests for factor Xa activity and a standard coagulogram can be used. According to several studies, hirudins have a positive effect on platelet aggregation.

In addition to studying the rheological properties of blood when using anticoagulants for the treatment of diabetic retinopathy, it is promising to determine the final stable metabolites of nitric oxide (eNOS), VEGF, and inflammatory activity (IL-6, IL-8) inducers in the lacrimal fluid. The listed research methods will help identify biomarkers necessary for a more accurate diagnosis of microvascular lesions in diabetes mellitus, including those in the retinal vessels.

ADDITIONAL INFORMATION

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REFERENCES

1. Netesin ES, Kuznetsov SM, Golub IE. Clinical-laboratory control of anticoagulant therapy. *Siberian Medical Journal (Irkutsk)*. 2007;70(3):109–113. (In Russ).

2. Mironova AI, Kropacheva ES, Dobrovolsky AB, et al. Modern possibilities and prospects in evaluating the anticoagulant effect of direct oral anticoagulants. *Atherothrombosis*. 2022;12(1):20–28. (In Russ). doi: 10.21518/2307-1109-2022-12-1-20-28

3. Antovic J, Kondratieva TB. Methods to monitor the therapy oral anticoagulants: the current problems. *Clinical Medicine (Russian Jornal)*. 2018;96(2):101–105. (In Russ). doi: 10.18821/0023-2149-2018-96-2-101-105

4. Shafiq H, Rashid A, Majeed A. Effects of different warfarin doses on IL-6 and COX-2 levels. *Pakistan Armed Forces Medical Journal.* 2016;66(5):673–675.

5. Smythe MA, Priziola J, Dobesh PP, et al. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism *J Thromb Thrombolysis.* 2016;41(1): 165–186. doi: 10.1007/s11239-015-1315-2

6. Ostapenko TV, Klimenko NJu, Ostapenko OV, i dr. Sulodeksid v korrekcii funkcii jendotelija i pokazatelej gemostaza u pacientov s postkovidnym sindromom. *Cardiovascular Therapy and Prevention.* 2022;21(S2):59–60. (In Russ).

7. Wang P, Chi L, Zhang Z, et al. Heparin: an old drug for new clinical applications. *Carbohydr Polym.* 2022;295:119818. doi: 10.1016/j.carbpol.2022.119818

8. Bignamini AA, Chebil A, Gambaro G, Matuška J. Sulodexide for diabetic-induced disabilities: a systematic review and meta-analysis. *Adv Ther.* 2021;38(3):1483–1513. doi: 10.1007/s12325-021-01620-1

9. Zlobina DS, Koroleva LYu, Kovaleva GV, Zlobin MV. Efficiency and safety of the long-term therapy with direct oral anticoagulants at thromboembolism of the pulmonary artery in real clinical practice. *University Proceedings. Volga Region. Medical Sciences*. 2019;(3): 5–18. (In Russ). doi: 10.21685/2072-3032-2019-3-1

10. Vinogradova AD, Malygin AS, Demidova MA. Anticoagulants in medical practice: literature review. *Volga Medical Journal.* 2020;19(4):27–31. (In Russ).

11. Bea F, Kreuzer J, Preusch M, et al. Melagatran reduces advanced atherosclerotic lesion size and may promote plaque stability in apolipoprotein E-deficient mice. *Arterioscler Thromb Vasc Biol.* 2006;26(12):2787–2792. doi: 10.1161/01.ATV.0000246797.05781.ad

12. Moiseev S. Direct oral anticoagulants for prevention of recurrent stroke in patients with atrial fibrillation. *Klinicheskaja farmakologija i terapija*. 2021;30(3):57–66. (In Russ). doi: 10.32756/0869-5490-2021-3-57-66

13. Bel'diev SN, Egorova IV, Platonov DJu. Recommendations on the use of oral anticoagulants in elderly patients: beers criteria and evidence-based medicine. *Medicina*. 2019;7(4):1–11. (In Russ). doi: 10.29234/2308-9113-2019-7-4-1-11

14. Vishnevskij VI, Panina JuN. Modern aspects of treatment of patients with atrial fibrillation with new oral anticoagulants. *Challenges in Modern Medicine*. 2020;43(1):65–72. (In Russ). doi: 10.18413/2687-0940-2020-43-1-65-72

15. Kadoglou NP, Moustardas P, Katsimpoulas M, et al. The beneficial effects of a direct thrombin inhibitor, dabigatran etexilate, on the development and stability of atherosclerotic lesions in apolipoprotein E-deficient mice: dabigatran etexilate and atherosclerosis. *Cardiovasc Drugs Ther*. 2012;26(5):367–374. doi: 10.1007/s10557-012-6411-3

16. Testa L, Bhindi R, Agostoni P, et al. The direct thrombin inhibitor ximelagatran/melagatran: a systematic review on clinical applications and an evidence based assessment of risk benefit profile. *Expert Opin Drug Saf*. 2007;6(4):397–406. doi: 10.1517/14740338.6.4.397

17. Antovic JP, Skeppholm M, Eintrei J, et al. Evaluation of coagulation assays versus LC-MS/MS for determinations of dabigatran concentrations in plasma. *Eur J Clin Pharmacol*. 2013; 69(11):1875–1881. doi: 10.1007/s00228-013-1550-4

18. Katoh H, Nozue T, Michishita I. Anti-inflammatory effect of factor-Xa inhibitors in Japanese patients with atrial fibrillation. *Heart Vessels*. 2017;32(9):1130–1136. doi: 10.1007/s00380-017-0962-y

19. Wu TC, Chan JS, Lee CY, et al. Rivaroxaban, a factor Xa inhibitor, improves neovascularization in the ischemic hindlimb of streptozotocin-induced diabetic mice. *Cardiovasc Diabetol*. 2015; 14:81. doi: 10.1186/s12933-015-0243-y

20. Hara T, Fukuda D, Tanaka K, et al. Rivaroxaban, a novel oral anticoagulant, attenuates atherosclerotic plaque progression and destabilization in ApoE-deficient mice. *Atherosclerosis*. 2015; 242(2):639–646. doi: 10.1016/j.atherosclerosis.2015.03.023

21. Zhou Q, Bea F, Preusch M, et al. Evaluation of plaque stability of advanced atherosclerotic lesions in apo E-deficient mice after treatment with the oral factor Xa inhibitor rivaroxaban. *Mediators Inflamm*. 2011;2011:432080. doi: 10.1155/2011/432080

22. Al-Aieshy F, Malmström RE, Antovic J, et al. Clinical evaluation of laboratory methods to monitor exposure of rivaroxaban at trough and peak in patients with atrial fibrillation. *Eur J Clin Pharmacol*. 2016;72(6):671–679. doi: 10.1007/s00228-016-2060-y

23. Skeppholm M, Al-Aieshy F, Berndtsson M, et al. Clinical evaluation of laboratory methods to monitor apixaban treatment in patients with atrial fibrillation. *Thromb Res*. 2015;136(1):148–153. doi: 10.1016/j.thromres.2015.04.030

24. Gebekova ZA, Ivanov II, Asambayeva A, et al. Thrombodynamics test in assessing the risk of thrombus formation in patients with atrial fibrillation taking direct oral anticoagulants. *Rational Pharmacotherapy in Cardiology*. 2022;18(5):544–552. (In Russ). doi: 10.20996/1819-6446-2022-09-07

25. Laine M, Lemesle G, Dabry T, et al. Bivalirudin during percutaneous coronary intervention in acute coronary syndromes. *Expert Opin Pharmacother*. 2019;20(3):295–304. doi: 10.1080/14656566.2018.1551361

26. Sun Z, Lan X, Li S, et al. Comparisons of argatroban to lepirudin and bivalirudin in the treatment of heparin-induced thrombocytopenia: a systematic review and meta-analysis. *Int J Hematol*. 2017;106(4):476–483. doi: 10.1007/s12185-017-2271-8

27. Averkov OV. bivalirudin and percutaneous coronary interventions in patients with acute coronary syndrome: theory and practice. *Russian Journal of Cardiology*. 2012;17(3):102–112. (In Russ).

28. Kazennova JuS. *Optimizacija diagnostiki i sposoby korrekcii zaderzhki razvitija ploda* [dissertation]. Novosibirsk; 2006. Available from: http://www.piyavit.ru/index.php?vm=20.view.126 (In Russ).

29. Piskunova JuA. *Principy girudofarmakoterapii dlja profilaktiki i lechenija sindroma poteri ploda i gestoza u beremennyh s trombofiliej* [dissertation]. Moscow; 2005. Available from: https://vivaldi.nlr.ru/bd000016531/details (In Russ).

30. Mihajlova EV, Chirkova LD, Balabolkin MI, Klebanova EM. Primenenie pijavita pri saharnom diabete. *Diabetes Mellitus*. 1999;(2):26–27. (In Russ).

31. Gilyazova AR, Samoilov AN. The study of the effect of the drug "piyavit" on the hemostatic system in patients with diabetic retinopathy. *Kazan Medical Journal*. 2011;92(4):516–519. (In Russ).

32. Cai X, Hu D, Pan C, et al. The risk factors of glycemic control, blood pressure control, lipid control in Chinese patients with newly diagnosed type 2 diabetes. A nationwide prospective cohort study. *Sci Rep*. 2019;9(1):7709. doi: 10.1038/s41598-019-44169-4

33. Schwartz SS, Epstein S, Corkey BE, et al. The time is right for a new classification system for diabetes: rationale and implications of the β-cell-centric classification Schema. *Diabetes Care*. 2016;39(2):179–186. doi: 10.2337/dc15-1585

34. Ivanova NV, Jarosheva NA. Disbalans v sisteme gemostaza i jendotelial'naja disfunkcija u bol'nyh s diabeticheskoj retinopatiej. *Journal of Ophthalmology*. 2008;(3):33–38. (In Russ).

35. Shelkovnikova TV, Shishljannikova NJu, Vavin GV, i dr. Izmenenija v sisteme gemostaza u pacientov s diabeticheskoj retinopatiej. *Medical Alphabet*. 2014;1(2):32–34. (In Russ).

36. Leley SP, Ciulla TA, Bhatwadekar AD. Diabetic retinopathy in the aging population: a perspective of pathogenesis and treatment. *Clin Interv Aging*. 2021;16:1367–1378. doi: 10.2147/CIA.S297494

37. Heng LZ, Comyn O, Peto T, et al. Diabetic retinopathy: pathogenesis, clinical grading, management and future developments. *Diabet Med*. 2013;30(6):640–650. doi: 10.1111/dme.12089

38. Mamedov TH, Narkevich AN. Detection of the signs of diabetic retinopathy using classification mathematical models. *Journal of New Medical Technologies*. 2021;28(2):107–110. (In Russ). doi: 10.24412/1609-2163-2021-2-107-110

39. Nguyen TT, Wang JJ, Sharrett AR, et al. Relationship of retinal vascular caliber with diabetes and retinopathy: the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care*. 2008;31(3): 544–549. doi: 10.2337/dc07-1528

40. Cai S, Liu TYA. Fluorescein angiography in diagnosis and treatment of diabetic retinopathy. *Curr Diab Rep*. 2021;21(9):30. doi: 10.1007/s11892-021-01398-0

41. Ashraf M, Sampani K, AbdelAl O, et al. Disparity of microaneurysm count between ultrawide field colour imaging and ultrawide field fluorescein angiography in eyes with diabetic retinopathy. *Br J Ophthalmol*. 2020;104(12):1762–1767. doi: 10.1136/bjophthalmol-2019-315807
42. Khalid H, Schwartz R, Nicholson L, et al. Widefield optical coherence tomography angiography for early detection and objective evaluation of proliferative diabetic retinopathy. *Br J Ophthalmol*. 2021;105(1):118–123. doi: 10.1136/bjophthalmol-2019-315365
43. Virgili G, Menchini F, Casazza G. et al. Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy. *Cochrane Database Syst Rev*. 2015;1:CD008081. doi: 10.1002/14651858.CD008081.pub3
44. Schmidt-Erfurth U, Garcia-Arumi J, Bandello F, et al. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA). *Ophthalmologica*. 2017;237(4):185–222. doi: 10.1159/000458539
45. Gildea D. The diagnostic value of optical coherence tomography angiography in diabetic retinopathy: a systematic review. *Int Ophthalmol*. 2019;39(10):2413–2433. doi: 10.1007/s10792-018-1034-8
46. Suciu CI, Suciu VI, Nicoara SD. Optical coherence tomography (angiography) biomarkers in the assessment and monitoring of diabetic macular edema. *J Diabetes Res*. 2020;2020:6655021. doi: 10.1155/2020/6655021
47. Yurova OV, Turova EA, Morozova NE, et al. Treatment and secondary prophylaxis integrated approach at non-proliferative diabetic retinopathy. *Ophthalmology in Russia.* 2011;8(3):9–12. (In Russ).
48. Avetisov SJe, Egorov EA, Moshetova LK, et al, editors. *Oftal'mologija. Nacional'noe rukovodstvo. Kratkoe izdanie.* Moscow: GJeOTAR-Media; 2014. 736 p. (In Russ).
49. Filippov VM, Petrachkov DV, Budzinskaya MV, Matyushchenko AG. The role of neurodegeneration biomarkers in the management of patients with diabetic retinopathy. *The Russian Annals of Ophthalmology*. 2021;137(5-2):314–322. (In Russ). doi: 10.17116/oftalma2021137052314
50. Jarilin AA. *Immunologija*. Moscow: GJeOTAR-Media; 2010. 752 p. (In Russ).

СПИСОК ЛИТЕРАТУРЫ

1. Нетесин Е.С., Кузнецов С.М., Голуб И.Е. Клинико-лабораторный контроль антикоагулянтной терапии // Сибирский медицинский журнал (Иркутск). 2007. Т. 70, № 3. С. 109–113.
2. Миронова А.И., Кропачева Е.С., Добровольский А.Б., и др. Современные возможности и перспективы в оценке антикоагулянтного эффекта прямых оральных антикоагулянтов // Атеротромбоз. 2022. Т. 12, № 1. С. 20–28. doi: 10.21518/2307-1109-2022-12-1-20-28
3. Антович Й., Кондратьева Т.Б. Методы контроля терапии прямыми оральными антикоагулянтами: состояние проблемы // Клиническая медицина. 2018. Т. 96, № 2. С. 101–105. doi: 10.18821/0023-2149-2018-96-2-101-105
4. Shafiq H., Rashid A., Majeed A. Effects of different warfarin doses on IL-6 and COX-2 levels // Pakistan Armed Forces Medical Journal. 2016. Vol. 66, N 5. P. 673–675.
5. Smythe M.A., Priziola J., Dobesh P.P., et al. Guidance for the practical management of the heparin anticoagulants in the treatment of venous thromboembolism // J Thromb Thrombolysis. 2016. Vol. 41, N 1. P. 165–186. doi: 10.1007/s11239-015-1315-2
6. Остапенко Т.В., Клименко Н.Ю., Остапенко О.В., и др. Сулодексид в коррекции функции эндотелия и показателей гемостаза у пациентов с постковидным синдромом // Кардиоваскулярная терапия и профилактика. 2022. Т. 21, № S2. С. 59–60.
7. Wang P., Chi L., Zhang Z., et al. Heparin: an old drug for new clinical applications // Carbohydr Polym. 2022. Vol. 295. P. 119818. doi: 10.1016/j.carbpol.2022.119818
8. Bignamini A.A., Chebil A., Gambaro G., Matuška J. Sulodexide for diabetic-induced disabilities: a systematic review and meta-analysis // Adv Ther. 2021. Vol. 38, N 3. P. 1483–1513. doi: 10.1007/s12325-021-01620-1
9. Злобина Д.С., Королева Л.Ю., Ковалева Г.В., Злобин М.В. Эффективность и безопасность длительной терапии прямыми оральными антикоагулянтами при тромбоэмболии легочной артерии в реальной клинической практике // Известия высших учебных заведений. Поволжский регион. Медицинские науки. 2019. № 3. С. 5–18. doi: 10.21685/2072-3032-2019-3-1
10. Виноградова А.Д., Малыгин А.С., Демидова М.А. Антикоагулянты в клинической практике: обзор литературы // Верхневолжский медицинский журнал. 2020. Т. 19, № 4. С. 27–31.
11. Bea F., Kreuzer J., Preusch M., et al. Melagatran reduces advanced atherosclerotic lesion size and may promote plaque stability in apolipoprotein E-deficient mice // Arterioscler Thromb Vasc Biol. 2006. Vol. 26, N 12. P. 2787–2792. doi: 10.1161/01.ATV.0000246797.05781.ad
12. Моисеев С.В. Прямые оральные антикоагулянты в профилактике повторного инсульта у пациентов с фибрилляцией предсердий // Клиническая фармакология и терапия. 2021. Т. 30, № 3. С. 57–66. doi: 10.32756/0869-5490-2021-3-57-66
13. Бельдиев С.Н., Егорова И.В., Платонов Д.Ю. Рекомендации по применению пероральных антикоагулянтов у пациентов пожилого возраста: критерии Бирса и доказательная медицина // Медицина. 2019. Т. 7, № 4. С. 1–11. doi: 10.29234/2308-9113-2019-7-4-1-11
14. Вишневский В.И., Панина Ю.Н. Современные аспекты лечения пациентов с фибрилляцией предсердий новыми пероральными антикоагулянтами // Актуальные проблемы медицины. 2020. Т. 43, № 1. С. 65–72. doi: 10.18413/2687-0940-2020-43-1-65-72
15. Kadoglou N.P., Moustardas P., Katsimpoulas M., et al. The beneficial effects of a direct thrombin inhibitor, dabigatran etexilate, on the development and stability of atherosclerotic lesions in apolipoprotein E-deficient mice: dabigatran etexilate and atherosclerosis // Cardiovasc Drugs Ther. 2012. Vol. 26, N 5. P. 367–374. doi: 10.1007/s10557-012-6411-3
16. Testa L., Bhindi R., Agostoni P., et al. The direct thrombin inhibitor ximelagatran/melagatran: a systematic review on clinical

applications and an evidence based assessment of risk benefit profile // Expert Opin Drug Saf. 2007. Vol. 6, N 4. P. 397–406. doi: 10.1517/14740338.6.4.397

17. Antovic J.P., Skeppholm M., Eintrei J., et al. Evaluation of coagulation assays versus LC-MS/MS for determinations of dabigatran concentrations in plasma // Eur J Clin Pharmacol. 2013. Vol. 69, N 11. P. 1875–1881. doi: 10.1007/s00228-013-1550-4

18. Katoh H., Nozue T., Michishita I. Anti-inflammatory effect of factor-Xa inhibitors in Japanese patients with atrial fibrillation // Heart Vessels. 2017. Vol. 32, N 9. P. 1130–1136. doi: 10.1007/s00380-017-0962-y

19. Wu T.C., Chan J.S., Lee C.Y., et al. Rivaroxaban, a factor Xa inhibitor, improves neovascularization in the ischemic hindlimb of streptozotocin-induced diabetic mice // Cardiovasc Diabetol. 2015. Vol. 14. P. 81. doi: 10.1186/s12933-015-0243-y

20. Hara T., Fukuda D., Tanaka K., et al. Rivaroxaban, a novel oral anticoagulant, attenuates atherosclerotic plaque progression and destabilization in ApoE-deficient mice // Atherosclerosis. 2015. Vol. 242, N 2. P. 639–646. doi: 10.1016/j.atherosclerosis.2015.03.023

21. Zhou Q., Bea F., Preusch M., et al. Evaluation of plaque stability of advanced atherosclerotic lesions in apo E-deficient mice after treatment with the oral factor Xa inhibitor rivaroxaban // Mediators Inflamm. 2011. Vol. 2011. P. 432080. doi: 10.1155/2011/432080

22. Al-Aieshy F., Malmström R.E., Antovic J., et al. Clinical evaluation of laboratory methods to monitor exposure of rivaroxaban at trough and peak in patients with atrial fibrillation // Eur J Clin Pharmacol. 2016. Vol. 72, N 6. P. 671–679. doi: 10.1007/s00228-016-2060-y

23. Skeppholm M., Al-Aieshy F., Berndtsson M., et al. Clinical evaluation of laboratory methods to monitor apixaban treatment in patients with atrial fibrillation // Thromb Res. 2015. Vol. 136, N 1. P. 148–153. doi: 10.1016/j.thromres.2015.04.030

24. Гебекова З.А., Иванов И.И., Асамбаева А., и др. Тест «Тромбодинамика» в оценке риска тромбообразования у пациентов с фибрилляцией предсердий, получающих прямые оральные антикоагулянты // Рациональная фармакотерапия в кардиологии. 2022. Т. 18, № 5. С. 544–552. doi: 10.20996/1819-6446-2022-09-07

25. Laine M., Lemesle G., Dabry T., et al. Bivalirudin during percutaneous coronary intervention in acute coronary syndromes // Expert Opin Pharmacother. 2019. Vol. 20, N 3. P. 295–304. doi: 10.1080/14656566.2018.1551361

26. Sun Z., Lan X., Li S., et al. Comparisons of argatroban to lepirudin and bivalirudin in the treatment of heparin-induced thrombocytopenia: a systematic review and meta-analysis // Int J Hematol. 2017. Vol. 106, N 4. P. 476–483. doi: 10.1007/s12185-017-2271-8

27. Аверков О.В. Теоретическое обоснование и практические аспекты использования бивалирудина при чрескожных внутрикоронарных вмешательствах у больных с острым коронарным синдромом // Российский кардиологический журнал. 2012. Т. 17, № 3. С. 102–112.

28. Казеннова Ю.С. Оптимизация диагностики и способы коррекции задержки развития плода : дис. ... канд. мед. наук. Новосибирск, 2006. Режим доступа: http://www.piyavit.ru/index.php?vm=20.view.126

29. Пискунова Ю.А. Принципы гирудофармакотерапии для профилактики и лечения синдрома потери плода и гестоза у беременных с тромбофилией : автореф. дисс. ... канд. мед. наук. Москва, 2005. Режим доступа: https://vivaldi.nlr.ru/bd000016531/details

30. Михайлова Е.В., Чиркова Л.Д., Балаболкин М.И., Клебанова Е.М. Применение пиявита при сахарном диабете // Сахарный диабет. 1999. № 2. С. 26–27.

31. Гилязова А.Р., Самойлов А.Н. Изучение влияния препарата «пиявит» на систему гемостаза у больных диабетической ретинопатией // Казанский медицинский журнал. 2011. Т. 92, № 4. С. 516–519.

32. Cai X., Hu D., Pan C., et al. The risk factors of glycemic control, blood pressure control, lipid control in Chinese patients with newly diagnosed type 2 diabetes. A nationwide prospective cohort study // Sci Rep. 2019. Vol. 9, N 1. P. 7709. doi: 10.1038/s41598-019-44169-4

33. Schwartz S.S., Epstein S., Corkey B.E., et al. The time is right for a new classification system for diabetes: rationale and implications of the β-cell-centric classification Schema // Diabetes Care. 2016. Vol. 39, N 2. P. 179–186. doi: 10.2337/dc15-1585

34. Иванова Н.В., Ярошева Н.А. Дисбаланс в системе гемостаза и эндотелиальная дисфункция у больных с диабетической ретинопатией // Офтальмологический журнал. 2008. № 3. С. 33–38.

35. Шелковникова Т.В., Шишлянникова Н.Ю., Вавин Г.В., и др. Изменения в системе гемостаза у пациентов с диабетической ретинопатией // Медицинский алфавит. 2014. Т. 1, № 2. С. 32–34.

36. Leley S.P., Ciulla T.A., Bhatwadekar A.D. Diabetic retinopathy in the aging population: a perspective of pathogenesis and treatment // Clin Interv Aging. 2021. Vol. 16. P. 1367–1378. doi: 10.2147/CIA.S297494

37. Heng L.Z., Comyn O., Peto T., et al. Diabetic retinopathy: pathogenesis, clinical grading, management and future developments // Diabet Med. 2013. Vol. 30, N 6. P. 640–650. doi: 10.1111/dme.12089

38. Мамедов Т.Х., Наркевич А.Н. Распознавание признаков диабетической ретинопатии с применением классификационных математических моделей // Вестник новых медицинских технологий. 2021. Т. 28, № 2. С. 107–110. doi: 10.24412/1609-2163-2021-2-107-110

39. Nguyen T.T., Wang J.J., Sharrett A.R., et al. Relationship of retinal vascular caliber with diabetes and retinopathy: the Multi-Ethnic Study of Atherosclerosis (MESA) // Diabetes Care. 2008. Vol. 31, N 3. P. 544–549. doi: 10.2337/dc07-1528

40. Cai S., Liu T.Y.A. Fluorescein angiography in diagnosis and treatment of diabetic retinopathy // Curr Diab Rep. 2021. Vol. 21, N 9. P. 30. doi: 10.1007/s11892-021-01398-0

41. Ashraf M., Sampani K., AbdelAl O., et al. Disparity of microaneurysm count between ultrawide field colour imaging and ultrawide field fluorescein angiography in eyes with diabetic retinopathy // Br J Ophthalmol. 2020. Vol. 104, N 12. P. 1762–1767. doi: 10.1136/bjophthalmol-2019-315807

42. Khalid H., Schwartz R., Nicholson L., et al. Widefield optical coherence tomography angiography for early detection and objective evaluation of proliferative diabetic retinopathy // Br J Ophthalmol. 2021. Vol. 105, N 1. P. 118–123. doi: 10.1136/bjophthalmol-2019-315365
43. Virgili G., Menchini F., Casazza G., et al. Optical coherence tomography (OCT) for detection of macular oedema in patients with diabetic retinopathy // Cochrane Database Syst Rev. 2015. N 1. P. CD008081. doi: 10.1002/14651858.CD008081.pub3
44. Schmidt-Erfurth U., Garcia-Arumi J., Bandello F., et al. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA) // Ophthalmologica. 2017. Vol. 237, N 4. P. 185–222. doi: 10.1159/000458539
45. Gildea D. The diagnostic value of optical coherence tomography angiography in diabetic retinopathy: a systematic review // Int Ophthalmol. 2019. Vol. 39, N 10. P. 2413–2433. doi: 10.1007/s10792-018-1034-8
46. Suciu C.I., Suciu V.I., Nicoara S.D. Optical coherence tomography (angiography) biomarkers in the assessment and monitoring of diabetic macular edema // J Diabetes Res. 2020. Vol. 2020. P. 6655021. doi: 10.1155/2020/6655021
47. Юрова О.В., Турова Е.А., Морозова Н.Е., и др. Комплексный подход при вторичной профилактике и терапии непролиферативной диабетической ретинопатии // Офтальмология. 2011. Т. 8, № 3. С. 9–12.
48. Офтальмология. Национальное руководство. Краткое издание / под ред. С.Э. Аветисова, Е.А. Егорова, Л.К. Мошетовой, и др. Москва : ГЭОТАР-Медиа, 2014. 736 с.
49. Филиппов В.М., Петрачков Д.В., Будзинская М.В., Матющенко А.Г. Роль биомаркеров нейродегенерации при диабетической ретинопатии // Вестник офтальмологии. 2021. Т. 137, № 5-2. С. 314–322. doi: 10.17116/oftalma2021137052314
50. Ярилин А.А. Иммунология: учебник. Москва : ГЭОТАР-Медиа», 2010. 752 с.

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