



## The role of pharmacogenetics in personalizing anticoagulant therapy: data from the Astrakhan region

A.N. Romanova, B.I. Kantemirova, O.V. Komarova, N.V. Timofeeva

Astrakhan State Medical University,  
121 Bakinskaya Str., Astrakhan, Russia, 414000

E-mail: alex973005@mail.ru

Received 09 Dec 2025

After peer review 16 June 2026

Accepted 06 July 2026

The metabolic characteristics of anticoagulants largely depend on the patient's genetic profile, determining the variability of pharmacological response to drugs and the risk of adverse reactions. Among the key genes encoding enzymes responsible for anticoagulant metabolism are *CES1*, *CYP2C9*, and *VKORC1*. They significantly influence the pharmacokinetics and pharmacodynamics of both indirect and direct oral anticoagulants, which dictates the effectiveness and safety of anticoagulant therapy. In clinical practice, the implementation of pharmacogenetic testing before prescribing anticoagulants will significantly reduce the risk of complications and improve therapeutic efficacy.

**The aim.** To assess the frequency of clinically significant polymorphisms of the *CYP2C9* (rs1799853), *VKORC1* (rs9912121), and *CES1* (rs2244613) genes in patients residing in the Astrakhan region.

**Materials and Methods.** The study sample consisted of 90 patients residing in the Astrakhan region who received inpatient treatment for confirmed coronavirus infection COVID-19 and were receiving anticoagulants. Venous blood collected in EDTA tubes was examined: diagnostic kits “*CYP2C9* gene Arg144Cys (rs1799853)” (NPF Sintol LLC, Russia), “*VKORC1* gene G1639A (G3673A) (rs9923231)” (NPF Sintol LLC, Russia), and “*CES1* gene C(-33)A (rs2244613) GenTest” (NMT LLC, Russia). After DNA isolation and amplification, blood samples were genotyped by PCR. The study was conducted with an assessment of Hardy–Weinberg equilibrium ( $p > 0.05$ ).

**Results.** The results showed that the frequency of *VKORC1* gene polymorphisms occurred in 60 (66.7%) patients (95% CI: [56.96–76.44];  $p > 0.05$ ), *CES1* gene in 55 (61.1%) (95% CI: [51.03–71.17];  $p > 0.05$ ), and *CYP2C9* gene in 24 (26.7%) (95% CI: [17.56–35.84],  $p > 0.05$ ).

**Conclusion.** The obtained results revealed a high frequency of distribution of polymorphic variants of genes associated with altered pharmacological response to anticoagulant therapy in patients residing in the Astrakhan region. This highlights the potential for implementing pharmacogenetic testing in the regional healthcare clinical practice for a personalized approach, optimized dosing, and reduced risks of adverse outcomes.

**Keywords:** pharmacogenetics; anticoagulants; warfarin; novel direct oral anticoagulants; *CES1*; *CYP2C9*; *VKORC1*

**Abbreviations:** ACT — anticoagulant therapy; ACDs — anticoagulant drugs; INR — international normalized ratio; NOACs — new oral anticoagulants.

## Роль фармакогенетики в персонализации антикоагулянтной терапии: данные Астраханского региона

А.Н. Романова, Б.И. Кантемирова, О.В. Комарова, Н.В. Тимофеева

Федеральное государственное бюджетное образовательное учреждение высшего образования  
«Астраханский государственный медицинский университет» Министерства здравоохранения  
Российской Федерации, Россия, 414000,  
г. Астрахань, ул. Бакинская, д. 121

E-mail: alex973005@mail.ru

Получена 09.12.2025

После рецензирования 16.06.2026

Принята к печати 06.07.2026

**For citation:** A.N. Romanova, B.I. Kantemirova, O.V. Komarova, N.V. Timofeeva. The role of pharmacogenetics in personalizing anticoagulant therapy: data from the Astrakhan region. *Pharmacy & Pharmacology*. 2026;14(4):377-386. DOI: 10.19163/2307-9266-2026-14-4-377-386

© А.Н. Романова, Б.И. Кантемирова, О.В. Комарова, Н.В. Тимофеева, 2026

**Для цитирования:** А.Н. Романова, Б.И. Кантемирова, О.В. Комарова, Н.В. Тимофеева. Роль фармакогенетики в персонализации антикоагулянтной терапии: данные Астраханского региона. *Фармация и фармакология*. 2026;14(4):377-386. DOI: 10.19163/2307-9266-2026-14-4-377-386

Особенности метаболизма антикоагулянтов во многом зависят от генетических характеристик пациента — обуславливают вариабельность фармакологического ответа на препараты и риск возникновения побочных реакций. Одними из ключевых генов, кодирующих работу ферментов, отвечающих за метаболизм антикоагулянтов, являются *CES1*, *CYP2C9* и *VKORC1*. Они оказывают значительное влияние на фармакокинетику и фармакодинамику как непрямых, так и прямых пероральных антикоагулянтов, что определяет эффективность и безопасность антикоагулянтной терапии. В условиях клинической практики имплементация фармакогенетического тестирования перед назначением антикоагулянтов значительно снижает риск развития осложнений и повышает терапевтическую эффективность.

**Цель.** Оценка частоты встречаемости клинически значимых полиморфизмов генов *CYP2C9* (rs1799853), *VKORC1* (rs9912121) и *CES1* (rs2244613) у пациентов, жителей Астраханского региона.

**Материалы и методы.** Исследуемую выборку составили 90 пациентов, жителей Астраханского региона, получивших стационарное лечение в связи с подтверждённой коронавирусной инфекцией COVID-19, которым назначали антикоагулянты. Исследовали венозную кровь, собранную в пробирки с ЭДТА: диагностические наборы «Arg144Cys гена *CYP2C9* (rs1799853)» (ООО «НПФ Синтол», Россия), «G1639A (G3673A) гена *VKORC1* (rs9923231)» (ООО «НПФ Синтол», Россия) и «ГенТест *CES1* C(-33)A (rs2244613)» (ООО «НМТ», Россия). После выделения ДНК и амплификации образцы крови генотипировали посредством ПЦР. Исследование проведено с оценкой соблюдения равновесия Харди-Вайнберга ( $p > 0.05$ ).

**Результаты.** В результате установлено, что частота полиморфизмов гена *VKORC1* встречается у 60 (66,7%) пациентов (ДИ 95%: [56,96–76,44];  $p > 0,05$ ), гена *CES1* — у 55 (61,1%) (ДИ 95%: [51,03–71,17];  $p > 0,05$ ), гена *CYP2C9* — у 24 (26,7%) (ДИ 95%: [17,56–35,84],  $p > 0,05$ ).

**Заключение.** Полученные результаты выявили высокую частоту распределения полиморфных вариантов генов, ассоциированных с изменённым фармакологическим ответом на антикоагулянтную терапию, у пациентов — жителей Астраханского региона. Это акцентирует внимание на возможности внедрения в клиническую практику регионального здравоохранения фармакогенетического тестирования для персонализированного подхода, оптимизации дозирования и снижения рисков неблагоприятных исходов.

**Ключевые слова:** фармакогенетика; антикоагулянты; варфарин; новые прямые пероральные антикоагулянты; *CES1*; *CYP2C9*; *VKORC1*

**Список сокращений:** АКТ — антикоагулянтная терапия; АКП — антикоагулянтные препараты; МНО — международное нормализованное отношение; НОАК — новые пероральные антикоагулянты.

## INTRODUCTION

In recent years, anticoagulant therapy (ACT) has become central to practical medicine due to its crucial role in the prevention and treatment of thromboembolic events. Impaired hemostasis and thrombosis, such as pulmonary embolism, systemic embolisms, venous thrombosis, atrial fibrillation, and acute coronary syndrome, ischemic stroke, are among the leading causes of mortality and disability worldwide, claiming 17.9 million lives annually<sup>1,2</sup>. Venous thromboembolism affects approximately 10 million people globally, with an incidence of 1–2 cases per 1000 population per year, while atrial fibrillation affects around 60 million people, increasing the risk of ischemic stroke by 4–5 times [1, 2]. The COVID-19 pandemic highlighted a key pathophysiological link in severe disease progression: the development of hemocoagulation complications associated with increased blood clotting [3–5]. The hypercoagulation syndrome observed in patients with coronavirus

infection was accompanied by increased levels of D-dimer, fibrinogen, and vascular thrombosis, necessitating a re-evaluation of approaches to the prevention and therapy of thrombotic complications. Consequently, during the pandemic, anticoagulant drugs (ACDs) became an integral part of treatment for both hospitalized and outpatient patients, as reflected in the temporary methodological recommendations “Prevention, Diagnosis, and Treatment of New Coronavirus Infection (COVID-19)” V revision<sup>3</sup> [6, 7]. ACD therapy plays a central role in clinical practice aimed at reducing cardiovascular diseases and improving prognoses in patients at high risk of adverse thrombotic events. Furthermore, a significant challenge is the selection of drug dosages, considering comorbid pathology of eliminating organs and systems, as well as clinically significant interactions with other medications.

For many decades, warfarin was the “gold standard” of ACT in the treatment of cardiovascular diseases. However, alongside its high efficacy,

<sup>1</sup> Healthcare in Russia. 2023: Statistical collection: Rosstat; Moscow, Z-46 2023. 179 p. Russian

<sup>2</sup> World Health Organization (WHO). Cardiovascular diseases. Available from: [https://www.who.int/ru/health-topics/cardiovascular-diseases#tab=tab\\_1](https://www.who.int/ru/health-topics/cardiovascular-diseases#tab=tab_1)

<sup>3</sup> Prevention, Diagnosis, and Treatment of New Coronavirus Infection (COVID-19): Interim Guidelines; Kraeva SA, Kostenko NA, Kamkin EG [et al.]. Version 3; Moscow: Ministry of Health of Russian Federation; 2020. 63 p. EDN: NKZMOV. Russian

warfarin use is associated with several limitations, such as a narrow therapeutic index, the need for constant monitoring of the international normalized ratio (INR), and multiple clinically significant drug interactions [8–10]. Under these circumstances, an individualized approach to warfarin dosing is crucial for achieving high efficacy and safety in ACT. The unpredictable pharmacokinetic and pharmacodynamic response to warfarin is determined, among other factors, by patients' genetic characteristics, which forms the basis for implementing pharmacogenetic strategies in ACD therapy [11, 12].

Currently, new oral anticoagulants (NOACs) such as dabigatran, apixaban, rivaroxaban, and edoxaban are actively used in clinical practice. These drugs have a more predictable pharmacological profile, do not require constant laboratory monitoring, are highly selective, and cause fewer clinically significant drug interactions [13, 14]. Overall, these advantages give NOACs benefits in many clinical situations, leading to their consideration as alternatives to warfarin. However, despite these advantages, individual sensitivity to them also affects the efficacy and safety of therapy, underscoring the need to study patients' pharmacogenetic, non-modifiable characteristics that influence the trajectory of pharmacological response.

For warfarin, the clinically significant genes are *CYP2C9* and *VKORC1*, polymorphisms of which lead to changes in the pharmacological response to the drug. The *CYP2C9* gene encodes an isoenzyme of the cytochrome P450 system involved in the metabolism of most drugs, including warfarin. The polymorphic variant of the *CYP2C9* gene, *CYP2C9\*2*, rs1799853 (430C>T), is associated with reduced functional activity of the enzyme, which can lead to drug accumulation, increased therapeutic concentration, and excessive anticoagulation [15], undoubtedly requiring dose titration downwards.

The *VKORC1* gene, in turn, encodes vitamin K epoxide reductase, a key enzyme in vitamin K metabolism. It converts the oxidized form of vitamin to its reduced form, which is necessary for the  $\gamma$ -carboxylation of blood clotting factors. Warfarin inhibits *VKORC1*, leading to reduced synthesis of these factors and hypocoagulation. The mutation rs9923231 (-1639G>A) is associated with the need for a reduced warfarin dose to achieve the target INR level, due

to slowed enzyme activity and increased sensitivity to the drug because of reduced levels of activated vitamin K [16, 17]. This is most significant for drugs with a narrow therapeutic index, such as warfarin, where even a slight dosage change can lead to adverse effects.

Among the NOACs, dabigatran is one of the most frequently used for the prevention and treatment of thrombotic complications. Dabigatran is a prodrug, administered as the inactive compound dabigatran etexilate, which is converted to its active form in the body by specific esterase enzymes, namely carboxylesterase 1 (CES1) and carboxylesterase 2 (CES2). CES1, primarily expressed in the liver, performs the main function, while intestinal CES2 partially compensates for reduced CES1 activity. Figure 1 illustrates the metabolism of dabigatran etexilate under the action of CES1 and CES2 enzymes [18].

Currently, the study of *CES1* gene polymorphisms, which can alter enzyme activity and thus affect ACT efficacy and safety, is of particular interest. Despite dabigatran's predictable pharmacological profile and its use at therapeutic doses, *CES1* polymorphisms can influence its pharmacokinetic and pharmacodynamic parameters. Carriage of the polymorphic allele rs2244613 (1168-33A>C) is associated with reduced metabolic activity of the enzyme, leading to slower conversion of dabigatran etexilate to its active form, dabigatran, which can result in lower drug concentration in the blood and reduced anticoagulation [19].

To date, the most well-known and clinically significant is the automated algorithm for warfarin dose adjustment via WarfarinDosing.org, which considers polymorphic variants of *CYP2C9* and *VKORC1* genes that slow drug metabolism [20]. When using therapeutic dosages, patients have an increased risk of bleeding, but with genetic information, the dose is reduced, leading to an effective and safe anticoagulant effect.

The implementation of pharmacogenetic testing (PGT) approaches into practice is a promising direction in pharmacology and medicine. Identifying genetic markers that influence a patient's individual sensitivity to ACDs can serve as a foundational basis for developing personalized therapy algorithms aimed at increasing treatment efficacy and safety.

**THE AIM** is to assess the frequency of clinically significant polymorphisms in the *CYP2C9* (rs1799853), *VKORC1* (rs9912121), and *CES1* (rs2244613) genes in patients with COVID-19 who received inpatient treatment.

## MATERIALS AND METHODS

### Study Design

A single-center retrospective cohort study was conducted.

### Ethics Approval

The study was conducted within the framework of a consortium between the Astrakhan State Medical University and the Russian Medical Academy of Continuous Professional Education "Ethnogenetic and Molecular Biological Basis of Complications After Post-COVID-19 Infection," approved by the Local Ethics Committee of the Astrakhan State Medical University, Protocol No. 3 dated December 30, 2021.

### Study Duration

Patient recruitment was conducted from December 2022 to August 2023.

### Study Conditions

The study was carried out at the multifunctional medical center of Astrakhan—a branch of the Astrakhan Regional City Clinical Hospital No. 3 named after S.M. Kirov, where patients received inpatient treatment for a confirmed diagnosis of coronavirus infection COVID-19.

### Eligibility Criteria

**Inclusion criteria:** confirmed diagnosis of coronavirus infection COVID-19, moderate or severe form of the disease, presence of voluntary informed consent, age 18 years and older, permanent residence in the Astrakhan region, administration of anticoagulant therapy (ACT) as part of inpatient treatment.

**Exclusion criteria:** patient's refusal to sign informed voluntary consent to participate in the study, presence of absolute contraindications for ACT prescription, unconfirmed COVID-19 diagnosis, bleeding at the time of inclusion, age under 18 years; incomplete set of laboratory parameters used in

the analysis (coagulogram, biochemical and clinical blood test data), repeated entries of the same patient (duplicate cases) identified during re-analysis of the database. The sample included patients with and without concomitant cardiovascular pathology. In accordance with the temporary methodological recommendations, ACT was prescribed to all patients with moderate and severe COVID-19 without exception, due to the presence of COVID-associated coagulopathy and etiopathogenetic damage to the vascular endothelium [21, 22].

### Study Methodology

For pharmacogenetic analysis, 3 mL of venous blood was collected into vacuum tubes with EDTA. Samples were stored according to regulatory documentation requirements at a temperature of -20°C in a vertical position on racks. DNA extraction was performed using the reagent kit "PROBA-RAPID-GENETIKA" (OOO "DNA-Tekhnologiya", Russia). Polymorphic variants of the *CYP2C9*, *VKORC1*, and *CES1* genes were identified by PCR using diagnostic kits "*CYP2C9* gene Arg144Cys (rs1799853)" (OOO "NPF Sintol", Russia), "*VKORC1* gene G1639A (G3673A) (rs9923231)" (OOO "NPF Sintol", Russia), and "*CES1* gene C(-33)A (rs2244613) GenTest" (OOO "NMT", Russia) according to the manufacturer's instructions.

### Statistical Analysis

Statistical analysis of the results was performed using the StatTech v. 4.12.5 software (OOO "Stattech", Russia). The conformity of allele and genotype distributions to Hardy-Weinberg equilibrium was assessed using the  $\chi^2$  (chi-square) test. Normality of quantitative indicators distribution was checked using the Shapiro-Wilk test. Categorical variables were presented as  $n$  (%) with a 95% confidence interval, and quantitative variables as  $M \pm SD$ . The critical significance level was set at  $p > 0.05$ . Additionally, a comparison of the obtained polymorphism frequencies with data from domestic and foreign studies was conducted.

## RESULTS

The study sample included 90 patients with a laboratory-confirmed diagnosis of coronavirus infection

COVID-19, presenting in moderate and severe forms. ACT was prescribed to all participants to prevent thromboembolic complications.

The distribution of patients by sex was characterized by a predominance of women—49 individuals (54.4%), while the number of men was 41 (45.6%). Patient age ranged from 24 to 70 years, with a mean age of  $62.81 \pm 11.19$  years (Table 1).

A moderate form of COVID-19 was diagnosed in 78 (86.7%) patients, and a severe form in 12 (13.3%). The average duration of hospitalization was  $12.06 \pm 4.99$  days. The average oxygen saturation level upon admission was  $93.23 \pm 2.12\%$ .

Analysis of laboratory parameters revealed pronounced signs of systemic inflammation and activation of the coagulation link of hemostasis. The average D-dimer level was  $0.82 \pm 3.28$   $\mu\text{g/mL}$  (normal  $< 0.5$   $\mu\text{g/mL}$ ), C-reactive protein— $74.12 \pm 8.67$   $\text{mg/L}$  (normal  $< 5.0$   $\text{mg/L}$ ), INR values reached the upper limits of normal— $1.16 \pm 0.68$ , while the average platelet count was within reference values— $237.43 \pm 155.10 \times 10^9/\text{L}$ .

All patients (100%) received ACT at therapeutic doses. Heparin was used in all cases (100%); additionally, apixaban was prescribed to 13 patients (14.4%), and rivaroxaban to 7 patients (7.8%). NOAC therapy was recommended to all patients without exception (100%) after discharge from the hospital for 3 months.

The study of the prevalence of polymorphisms in the *CYP2C9*, *VKORC1*, and *CES1* genes showed a high frequency of their carriage among residents of the Astrakhan region. The assessment of allele and genotype distributions showed conformity to expected values according to Hardy–Weinberg equilibrium ( $p > 0.05$ ). The obtained results indicate the genetic homogeneity of the study sample and confirm the reliability of the conducted analysis. Data on the prevalence of polymorphisms in the *CYP2C9*, *VKORC1*, and *CES1* genes in patients from the Astrakhan region are presented in Table 2.

Polymorphic variants of the *VKORC1* gene were found in 66.7% of patients (95% CI: [56.96–76.44],  $p > 0.05$ ), and the *CES1* gene—in 61.1% (95% CI: [51.03–71.17],  $p > 0.05$ ). *CYP2C9* gene polymorphism occurred less frequently—in 26.7% (95% CI: [17.56–35.84],  $p > 0.05$ ).

For the *CES1* gene (rs2244613), analysis of genotype distribution showed a high prevalence of CC and AC genotypes (61.1%), associated with a significant decrease in enzyme metabolic activity, which can lead to failure to achieve therapeutic dabigatran concentrations in plasma and be accompanied by an increased risk of thrombotic events [19, 23, 24].

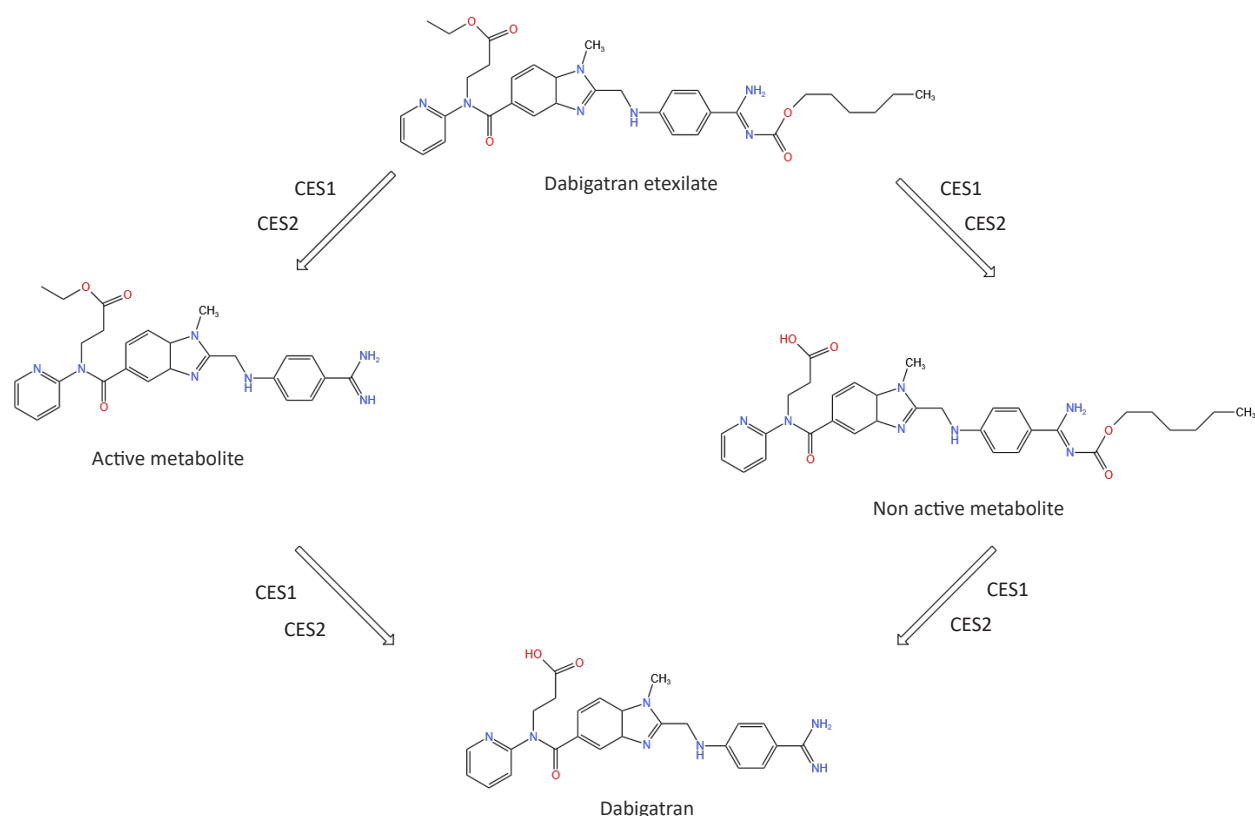
Analysis of genotype distribution for the *CYP2C9* gene (rs1799853) revealed that the most common genotype is CC, characterized by an unchanged rate of metabolic reactions. However, CT and TT genotypes were found in 26.7% of patients, which may indicate ACT inefficiency in every third patient. The presence of CT and TT genotypes demonstrates a reduced activity of the *CYP2C9* enzyme, responsible for warfarin metabolism. The presence of the T allele is associated with decreased drug clearance, increased INR at therapeutic doses, and an increased risk of hemorrhage [25, 26].

For the *VKORC1* gene, it was established that 60 (66.7%) patients had AA and GG genotypes, associated with slowed enzyme expression and high sensitivity to warfarin, which at standard doses can lead to major hemorrhages.

Analysis of these clinically significant gene polymorphisms showed that the study sample has a high proportion of carriers of genotypes affecting the pharmacokinetic and pharmacodynamic properties of anticoagulants. This distribution reflects the variability in metabolism and sensitivity to this group of drugs. Therapeutic doses may be inadequate for such patients, potentially leading to serious side effects.

Additionally, an assessment of the frequency of combinations of polymorphisms of the indicated genes was performed. The sample included patients with polymorphisms in one gene, as well as in combinations of two or all three genes.

Almost every second patient in the observation group (48.9%) has a combination of polymorphisms, meaning they have an atypical response to therapy, making the use of standard doses ineffective and unsafe. The detected high proportion of patients with multiple genetic predictors of altered drug metabolism indicates the significance of pharmacogenetic testing in the personalized selection of anticoagulants.



**Figure 1 — Metabolism of dabigatran etexilate under the influence of CES1 and CES2 enzymes.**

**Table 1 — Clinical and demographic data of patients**

| Indicator                                         | Value           |
|---------------------------------------------------|-----------------|
| Total number of patients, <i>n</i>                | 90              |
| Women, <i>n</i> (%)                               | 49 (54.4%)      |
| Men, <i>n</i> (%)                                 | 41 (45.6%)      |
| Age, M ± SD, years                                | 62.81 ± 11.19   |
| Moderate COVID-19, <i>n</i> (%)                   | 78 (86.7%)      |
| Severe COVID-19, <i>n</i> (%)                     | 12 (13.3%)      |
| Duration of hospitalization, M ± SD, days         | 12.06 ± 4.99    |
| O <sub>2</sub> saturation on admission, M ± SD, % | 93.23 ± 2.12    |
| D-dimer, M ± SD, µg/mL                            | 0.82 ± 3.28     |
| INR, M ± SD                                       | 1.16 ± 0.68     |
| C-reactive protein, M ± SD, mg/L                  | 74.12 ± 8.67    |
| Platelets, M ± SD, ×10 <sup>9</sup> /L            | 237.43 ± 155.10 |
| Anticoagulant prescription, M ± SD, <i>n</i> (%)  | 90 (100%)       |
| heparin                                           | 90 (100%)       |
| NOAC inpatient                                    | 20 (22.2%)      |
| NOAC outpatient after discharge                   | 90 (100%)       |
| Lethal outcome, <i>n</i> (%)                      | 6 (6.7%)        |

Note: INR, International Normalized Ratio; NOAC, Novel Oral Anticoagulants.

**Table 2 — Results of the frequency assessment of carrier status for polymorphic alleles of *CES1*, *CYP2C9* and *VKORC1* genes in patients, calculated by Hardy-Weinberg equilibrium**

| Genotypes                                 | Number<br>of patients, <i>n</i> (%) | Confidence Interval | $\chi^2$ | <i>p</i> |
|-------------------------------------------|-------------------------------------|---------------------|----------|----------|
| <b><i>CES1</i> (rs2244613)</b>            |                                     |                     |          |          |
| CC                                        | 18 (20.0%)                          | [11.74–28.26]       | 0.97     | 0.32     |
| AC                                        | 37 (41.1%)                          | [30.93–51.27]       |          |          |
| AA                                        | 35 (38.9%)                          | [28.83–48.97]       |          |          |
| <b><i>CES1</i> (rs2244613), alleles</b>   |                                     |                     |          |          |
| C                                         | 73 (40.6%)                          |                     |          |          |
| A                                         | 107 (59.4%)                         |                     |          |          |
| <b><i>CYP2C9</i> (rs2244613)</b>          |                                     |                     |          |          |
| TT                                        | 1 (1.1%)                            | [-1.05–3.25]        | 0.25     | 0.61     |
| CT                                        | 23 (25.6%)                          | [16.58–34.62]       |          |          |
| CC                                        | 66 (73.3%)                          | [64.16–82.44]       |          |          |
| <b><i>CYP2C9</i> (rs1799853), alleles</b> |                                     |                     |          |          |
| T                                         | 25 (13.9%)                          |                     |          |          |
| C                                         | 155 (86.1%)                         |                     |          |          |
| <b><i>VKORC1</i> (rs9923231)</b>          |                                     |                     |          |          |
| AA                                        | 27 (30.0%)                          | [20.53–39.47]       | 3.24     | 0.07     |
| GA                                        | 33 (36.7%)                          | [26.74–46.66]       |          |          |
| GG                                        | 30 (33.3%)                          | [23.56–43.04]       |          |          |
| <b><i>VKORC1</i> (rs9923231), alleles</b> |                                     |                     |          |          |
| A                                         | 87 (48.3%)                          |                     |          |          |
| G                                         | 93 (51.7%)                          |                     |          |          |

**Table 3 — Assessment of the frequency of occurrence of combinations of polymorphisms of *CES1*, *CYP2C9* and *VKORC1* genes in patients, residents of the Astrakhan region**

| Gene                                         | Number, %  | Total, %   |
|----------------------------------------------|------------|------------|
| Single polymorphism                          |            |            |
| CES1                                         | 18 (20.0%) | 40 (44.4%) |
| CYP2C9                                       | 2 (2.2%)   |            |
| VKORC1                                       | 20 (22.2%) |            |
| Combinations of polymorphisms of two genes   |            |            |
| CES1 + VKORC1                                | 21 (23.4%) | 33 (36.7%) |
| CYP2C9 + VKORC1                              | 8 (8.9%)   |            |
| CES1 + CYP2C9                                | 4 (4.4%)   |            |
| Combinations of polymorphisms of three genes |            |            |
| CES1 + CYP2C9 + VKORC1                       | 11 (12.2%) | 11 (12.2%) |

To evaluate the obtained data in the context of global patterns, a comparative analysis of the frequency of polymorphisms in the *CYP2C9*, *CES1*, and *VKORC1* genes with data from international studies was conducted. It was found that the frequencies of *CES1* polymorphisms vary significantly across global populations: among African Americans, it is 75.5%; among Latin Americans—77%; among East Asians—40.4%; among Europeans—81.6%; among South Asians—59.2%.

The frequency of *VKORC1* gene variants also varies depending on the population: 10% among African Americans, 39%—Latin Americans, up to 89% in East Asian populations, 38% in

Europeans, and about 18% in South Asians. *CYP2C9* gene polymorphism is characterized by lower and more heterogeneous prevalence: African Americans—2.2%, Latin Americans—8.5%, East Asians—0.07%, Europeans—12.8%, and South Asians—4.6% [27].

## DISCUSSION

The obtained data on the prevalence of polymorphisms in key anticoagulant (AKP) metabolism genes—*CYP2C9*, *CES1*, and *VKORC1*—among patients residing in the Astrakhan region differ from the results of genotype frequencies in other population groups of the Russian Federation.

In the European part of the Russian Federation, the prevalence of polymorphic variants of the *CYP2C9* gene is characterized by a relatively uniform distribution. In the Voronezh region, the frequency of the minor allele *CYP2C9\*2* is 10.5%, and the allele *CYP2C9\*3* reaches 6.7% [28]. Comparable indicators were recorded in Moscow, where the frequency of the *CYP2C9\*2* allele is 9.7%, and *CYP2C9\*3*—5.2%. The highest frequency of the *CYP2C9\*2* allele among the studied regions of the European part of the country was noted in the Stavropol Krai and reaches 12%, while the prevalence of the *CYP2C9\*3* allele is about 6% [29]. Similar values were found in St. Petersburg – the frequency of the *CYP2C9\*2* allele is 11.11%, and *CYP2C9\*3*—6.32% [30].

In the eastern regions of the Russian Federation, a change in the distribution structure of polymorphic variants of the *CYP2C9* gene is observed. In the Irkutsk region, the frequency of the *CYP2C9\*2* allele decreases to 6.1%, while the frequency of *CYP2C9\*3*, on the contrary, increases to 9.5%, which is one of the highest indicators among the studied regions [29]. In the Republic of Buryatia, the lowest prevalence of both minor alleles was found: the frequency of *CYP2C9\*2* is 2.3%, and *CYP2C9\*3*—1.7% [31]. In the Khabarovsk Krai, the frequency of the *CYP2C9\*3* allele remains at 5.7% [32].

Analysis of the regional distribution of *CYP2C9* gene polymorphisms indicates significant geographical variability. The results obtained in the Astrakhan region show the highest frequency of *CYP2C9* gene polymorphisms, with this indicator reaching 26.7%, which exceeds the corresponding values obtained in other regions of the Russian Federation. This can likely be attributed to the multi-ethnic composition of the Astrakhan region.

The prevalence of the rs2244613 polymorphism of the *CES1* gene in the populations of the Russian Federation is characterized primarily by ethnic differences, with relative stability of indicators among Russian populations in different regions.

Among Russian residents of various territories, the frequency of the minor allele C of the *CES1* gene shows similar values: in Moscow, it is 28.4%, and in the Irkutsk region, it is 28.3%, indicating the absence of significant regional differences within the European part of Russia and Siberia [33, 34].

Higher values of this indicator are observed in the populations of the Republic of Dagestan. Among Avars, the frequency of allele C is 38.3%, among Dargins, it is 40.0%, while among Laks, it is 29.3%, which is comparable to the level in Russian populations [34].

For the rs9923231 polymorphism of the *VKORC1* gene in the populations of the Russian Federation, significant regional differences have been identified,

with an increase in the frequency of the minor allele A in the eastern part of Russia.

In the European part of Russia, the indicators remain relatively stable; for example, in Moscow, the frequency of allele A is 38.1% [26]. Among Chuvash, the frequency of allele A of the *VKORC1* gene (–1639G>A) was 48.60% [35].

The highest values were recorded among the indigenous peoples of Eastern and Western Siberia. In the Republic of Buryatia, the frequency of allele A is 85.3%, in the Republic of Sakha (Yakutia), it reaches 83.1%, among Selkups, it is 71.8%, and among Nenets, it is 61.0% [26].

The high frequency of clinically significant polymorphisms identified in the Astrakhan region, combined with the results of international studies, creates prerequisites for discussing the possibility of developing and implementing a regionally adapted protocol for conducting FGT before prescribing ACT in each subject of the Russian Federation.

### Study Limitations

This study, despite the representativeness of the data and the identified trends, has several limitations that must be considered when interpreting the obtained results. The study has a relatively small sample size ( $n = 90$ ), and patients were not stratified by ethnicity.

### CONCLUSION

The conducted study revealed a high prevalence of polymorphisms in the *VKORC1*, *CES1*, and *CYP2C9* genes associated with altered sensitivity to ACT among patients residing in the Astrakhan region. The frequencies of the identified allelic variants were comparable to the data obtained in other subjects of the Russian Federation. A significant proportion of patients exhibited not only single but also combined polymorphisms, including combinations of two and three genes simultaneously, indicating potentially high variability in the pharmacokinetic profile of ACP in this population.

The dominance of combined genetic variants suggests an increased risk of hemorrhagic complications when using standard doses of ACP, especially in patients carrying multiple sensitive alleles. The totality of the obtained data underscores the necessity of implementing personalized approaches to ACT dosage selection and the use of pharmacogenetic testing before initiating treatment. Such an approach will enhance the safety and efficacy of therapy, minimize the risk of adverse reactions, and improve clinical outcomes in patients.

## FUNDING

This study did not have financial support from third-party organizations.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

Alexandra N. Romanova — formal analysis, writing—original draft; Bela I. Kantemirova — conceptualization, writing—review & editing; Olga V. Komarova, Natalia V. Timofeeva — formal analysis, visualization. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

## REFERENCES

1. Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. *Lancet*. 2021;398(10294):64–77. DOI: 10.1016/S0140-6736(20)32658-1
2. Yang X, Huang J, Huang Z, Xue Y, Deng H, Cao X. Screening for Atrial Fibrillation in Stroke Prevention: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Rev Cardiovasc Med*. 2025;26(7):36262. DOI: 10.31083/RCM36262
3. Nematzoda O, Gaibov AD, Kalmykov EL, Baratov AK. COVID-19-assotsirovanny arterial'nyy tromboz [COVID-19-related arterial thrombosis]. *Avicenna Bulletin*. 2021;23(1):85–94. DOI: 10.25005/2074-0581-2021-23-1-85-94. EDN APPDJJ.
4. Porembskaya OYa, Kravchuk VN, Galchenko MI, Deev RV, Chesnokov MSh, Avanesyan AV, Lobastov KV, Tsaplin SN, Laberko LA, Ermakov VS, Pashovkina OV, Schastlivtsev IV, Sayganov SA. Pulmonary Vascular Thrombosis in COVID-19: Clinical and Morphological Parallels. *Rational Pharmacotherapy in Cardiology* 2022;18(4):376–84. DOI: 10.20996/1819-6446-2022-08-01. EDN: HTTTBO
5. Lebedeva AA, Kulikov AN, Kovalchuk YuP, Kadinskaya MI, Ginzburg AM, Vlasov TD. Endothelial dysfunction and thrombotic events in patients with severe novel coronavirus infection COVID-19. *The Scientific Notes of Pavlov University*. 2021;28(4):38–47. DOI: 10.24884/1607-4181-2021-28-4-38-47
6. Sabirov I, Murkamilov I, Fomin V, Sabirova A. Prognostic value of d-dimer in the development of thromboembolic complications in New Coronavirus Infection (COVID-19). *The Scientific Heritage*. 2021;(60–2(60)):38–46. DOI: 10.24412/9215-0365-2021-60-2-38-46. EDN: CYFZAD
7. Makatsariya AD, Slukhanchuk EV, Bitsadze VO, Khizroeva JKh, Tretyakova MV, Shkoda AS, Akinshina SV, Makatsariya NA, Tsubizova VI, Gris J, Elalamy I, Ay C, Grandone E. Thrombotic storm, hemostasis disorders and thromboinflammation in COVID-19. *Obstetrics, Gynecology and Reproduction*. 2021;15(5):499–514. DOI: 10.17749/2313-7347/ob.gyn.rep.2021.247. EDN: TMZVTW
8. Fitzmaurice DA, Blann AD, Lip GY. Bleeding risks of antithrombotic therapy. *BMJ*. 2002;325(7368):828–31. DOI: 10.1136/bmj.325.7368.828
9. Romanova AN, Kantemirova BI, Komarova OV. Gene polymorphism: effectiveness and safety of anticoagulant therapy. *Caspian Journal of Medicine and Pharmacy*. 2025;6(1):6–18. DOI: 10.17021/2712-8164-2025-1-6-18. EDN: SPEEDL
10. Cross B, Turner RM, Zhang JE, Pirmohamed M. Being precise with anticoagulation to reduce adverse drug reactions: are we there yet? *Pharmacogenomics J*. 2024;24(2):7. DOI: 10.1038/s41397-024-00329-y
11. Sychev DA, Chernyaeva MS, Ostroumova OD. Genetic risk factors for adverse drug reactions. *Safety and Risk of Pharmacotherapy*. 2022;10(1):48–64. DOI: 10.30895/2312-7821-2022-10-1-48-64. EDN: AOKDTZ
12. Shi K, Deng J. Comparative performance of pharmacogenetics-based warfarin dosing algorithms in Chinese population: use of a pharmacokinetic/pharmacodynamic model to explore dosing regimen through clinical trial simulation. *Pharmacogenet Genomics*. 2024;34(9):275–84. DOI: 10.1097/FPC.0000000000000545
13. Gilyarevsky SR, Vereina NK, Golshmid MV. Current insights into the possible role of laboratory monitoring of effectiveness and safety of direct oral anticoagulants. *Rational Pharmacotherapy in Cardiology*. 2023;19(3):290–7. DOI:10.20996/1819-6446-2023-2922. EDN GUEZKX
14. Novikova TN. The risk of bleeding minimization with direct oral anticoagulants. *Atherothrombosis*. 2021;11(1):106–26. DOI: 10.21518/2307-1109-2021-11-1-106-126. EDN: AOSWXN
15. Sridharan K, Al Banna R, Malalla Z, Husain A, Sater M, Jassim G, Ootom S. Influence of CYP2C9, VKORC1, and CYP4F2 polymorphisms on the pharmacodynamic parameters of warfarin: a cross-sectional study. *Pharmacol Rep*. 2021;73(5):1405–17. DOI: 10.1007/s43440-021-00256-w
16. Georgieva KS, Pavlova SI, Bogdanova SM. Pharmacokinetic and pharmacodynamic features of the response to warfarin therapy on the example of excessive hypocoagulation development in a patient of the Chuvash population with a prosthetic heart valve. *Acta Medica Eurasica*. 2022;(4):97–102. DOI: 10.47026/2413-4864-2022-4-97-102. EDN: DENFCY
17. Zhang S, Zhao M, Zhong S, Niu J, Zhou L, Zhu B, Su H, Cao W, Xing Q, Yan H, Han X, Fu Q, Li Q, Chen L, Yang F, Zhang N, Wu H, He L, Qin S. Association between CYP2C9 and VKORC1 genetic polymorphisms and efficacy and safety of warfarin in Chinese patients. *Pharmacogenet Genomics*. 2024;34(4):105–16. DOI: 10.1097/FPC.0000000000000526
18. Savinova AV, Shnyder NA, Petrova MM, Nasyrova RF. Promising areas of research on the pharmacogenetics of dabigatran etexilate. *Pharmacogenetics and Pharmacogenomics*. 2020;(1):35–41. DOI: 10.37489/2588-0527-2020-1-35-41. EDN: FMWJLD
19. Li H, Zhang Z, Weng H, Qiu Y, Zubiaur P, Zhang Y, Fan G, Yang P, Vuorinen AL, Zuo X, Zhai Z, Wang C. Association between CES1 rs2244613 and the pharmacokinetics and safety of dabigatran: Meta-analysis and quantitative trait loci analysis. *Front Cardiovasc Med*. 2022;9:959916. DOI: 10.3389/fcvm.2022.959916

20. Asimwe IG, Zhang EJ, Osanlou R, Jorgensen AL, Pirmohamed M. Warfarin dosing algorithms: A systematic review. *Br J Clin Pharmacol.* 2021;87(4):1717–29. DOI: 10.1111/bcp.14608
21. Conway EM, Mackman N, Warren RQ, Wolberg AS, Mosnier LO, Campbell RA, Gralinski LE, Rondina MT, van de Veerdonk FL, Hoffmeister KM, Griffin JH, Nugent D, Moon K, Morrissey JH. Understanding COVID-19-associated coagulopathy. *Nat Rev Immunol.* 2022;22(10):639–49. DOI: 10.1038/s41577-022-00762-9
22. Makatsariya AD, Slukhanchuk EV, Bitsadze VO, Khizroeva JK, Tretyakova MV, Tsibizova VI, Shkoda AS, Grandone E, Elalamy I, Rizzo G, Gris J-C, Schulman S, Brenner B. COVID-19, Hemostasis Disorders and Risk of Thrombotic Complications. *Annals of the Russian Academy of Medical Sciences.* 2020;75(4):306–17. DOI: 10.15690/vramn1368. EDN: CFPGLT
23. Abdullaev SP, Mirzaev KB, Bochkov PO, Sychev IN, Sychev DA. The CES1 Gene rs2244613 Minor Allele Impact on the Safety Profile of Dabigatran Etexilate: Meta-Analysis. *Rational Pharmacotherapy in Cardiology* 2020;16(5):699–705. DOI: 10.20996/1819-6446-2020-10-09. EDN: UOKHYW
24. Sychev D, Skripka A, Ryzhikova K, Bochkov P, Shevchenko R, Krupenin P, Ivashchenko D, Kogay V, Listratov A, Krainyaya A, Gurinovich O, Sokolova A, Napalkov D, Fomin V. Effect of CES1 and ABCB1 genotypes on the pharmacokinetics and clinical outcomes of dabigatran etexilate in patients with atrial fibrillation and chronic kidney disease. *Drug Metab Pers Ther.* 2020;35(1):/j/dmpt.2020.35.issue-1/dmpt-2019-0029/dmpt-2019-0029.xml. DOI: 10.1515/dmpt-2019-0029
25. Biswas M, Murad MA, Ershadian M, Kali MSK, Shin Sim M, Ibrahim B, Sukasem C. Prevalence of risk phenotypes associated with CYP2C9\*2, \*3, and VKORC1 c.-1639G>A genetic polymorphisms in world populations: implications in clinical practice. *Front Pharmacol.* 2025;16:1597379. DOI: 10.3389/fphar.2025.1597379
26. Johnson M, Richard C, Bogdan R, Kidd R. Warfarin Dosing in a Patient with CYP2C9(\*)3(\*)3 and VKORC1-1639 AA Genotypes. *Case Rep Genet.* 2014;2014:413743. DOI: 10.1155/2014/413743
27. Whirl-Carrillo M, Huddart R, Gong L, Sangkuhl K, Thorn CF, Whaley R, Klein TE. An Evidence-Based Framework for Evaluating Pharmacogenomics Knowledge for Personalized Medicine. *Clin Pharmacol Ther.* 2021;110(3):563–72. DOI: 10.1002/cpt.2350
28. Sambyalovaa AYU, Bairovaa TA, Belyaevaa EV, Ershova OA, Sargaevab DS, Kolesnikov SI. CYP2C9, CYP4F2, VKORC1 Gene Polymorphism in Buryat Population. *Genetics.* 2020;56(12):1427–34. DOI: 10.31857/S0016675820120127. EDN: PLXTNE
29. Bairova TA, Novikova EA, Belyalov FI, Shchedreeva EA, levleva KD, Kalyuzhnaya OV, Ershova OA, Pustozarov VG, Kovaleva OA, Rasputina IV, Noskova IA, Batogova TV, Kuznetsova OV, Bogoslova OYu, Kolesnikov SI. Frequencies of polymorphisms in the cytochrome's P450 genes of warfarin transformation in a European population of EASTERN SIBERIA. *Acta Biomedica Scientifica.* 2018;3(5):39–48. DOI: 10.29413/ABS.2018-3.5.6. EDN: YMWRT
30. Sirotkina OV, Ulitina AS, Taraskina AE, Kadinskaya MI, Vavilova TV, Pchelina SN, Shvarts EI. CYP2C9\*2 and CYP2C9\*3 allele variants of CYP2C9 cytochrome gene in St. Petersburg population, and their clinical role in warfarin anticoagulant therapy. *Russian Journal of Cardiology.* 2004;9(6):47–50. EDN: ISVSNB
31. Makeeva O, Stepanov V, Puzyrev V, Goldstein DB, Grossman I. Global pharmacogenetics: genetic substructure of Eurasian populations and its effect on variants of drug-metabolizing enzymes. *Pharmacogenomics.* 2008;9(7):847–68. DOI: 10.2217/14622416.9.7.847
32. Shuev GN, Sychev DA, Suleymanov SSh, Ryzhikova KA, Mirzaev KB, Grishina EA, Snalina NE, Sozaeva ZhA, Il'ina ES, Grabuzdov AM, Matsneva IA. Comparison of CYP2C9, CYP2C19, CYP2D6, ABCB1, SLCO1B1 gene polymorphism frequency in Russian and Nanai populations. *Pharmacogenetics and pharmacogenomics.* 2016;(2):12–8. EDN: YHTQNF
33. Mirzaev KB, Osipova DV, Kitaeva EYu, Shprakh VV, Abdullaev ShP, Andreev DA, Sychev DA. CES1 gene polymorphism effect on the antiplatelet activity of clopidogrel. *Clin Pharmacol Ther* 2018;27(5):96–100. DOI: 10.32756/0869-5490-2018-5-96-100
34. Abdullaev ShP, Mirzayev KB, Mammaev SN, Gafurov DM, Kitaeva EYu, Shprakh VV, Ryzhikova KA, Shuyev GN, Grishina EA, Sozaeva ZhA, Sychev DA. The prevalence of the polymorphic marker rs2244613 of the CES1 gene associated with a lower risk of bleeding in patients using dabigatran in Russians and in the three ethnic groups of the Republic of Dagestan. *Clin Pharmacol Ther.* 2018;27(4):87–90. EDN: VACFNV
35. Georgieva KS, Pavlova SI. Polymorphisms of CYP2C9 and VKORC1 genes and their association with calcification of heart valves in Chuvash patients with chronic rheumatic heart disease. *Pharmacogenetics and Pharmacogenomics.* 2025;(1):17–23. DOI: 10.37489/2588-0527-2025-1-17-23. EDN: BXYGEA

## AUTHORS

**Alexandra N. Romanova** — postgraduate student of the Department of Pharmacology, Astrakhan State Medical University. ORCID ID: 0000-0002-6564-3408. E-mail: sasha.styles005@gmail.com

**Bela I. Kantemirova** — Doctor of Sciences (Medicine), Professor, Head of the Department of Pharmacology, Astrakhan State Medical University. ORCID ID: 0000-0003-3278-2556. E-mail: belakantemirova@rambler.ru

**Olga V. Komarova** — postgraduate student of the Department of Pharmacology, Astrakhan State Medical University. ORCID ID: 0000-0001-7011-0932. E-mail: olha437@yandex.ru

**Natalia V. Timofeeva** — Candidate of Sciences (Medicine), Assistant Professor of the Department of Pharmacology, Astrakhan State Medical University. ORCID ID: 0009-0002-0241-2327. E-mail: Natalitimofeeva@bk.ru