

## The best practices of the Russian Federation in the organization of anticoagulant therapy in patients with high risk of thromboembolic events

Vavilova T. V.<sup>1</sup>, Solovyova L. V.<sup>2</sup>, Bekoeva A. B.<sup>3</sup>, Zubkova P. Yu.<sup>1</sup>, Vorobyeva N. A.<sup>4, 5</sup>, Vorobyeva A. I.<sup>4</sup>, Melnichuk E. Yu.<sup>4</sup>, Khruslov M. V.<sup>1, 6</sup>, Vereina N. K.<sup>7</sup>, Safin D. D.<sup>8</sup>, Galyavich A. S.<sup>9</sup>, Sluiter M.<sup>10</sup>, Endubaeva G. V.<sup>1</sup>, Shlyakhto E. V.<sup>1</sup>

Organization of anticoagulant therapy control plays a key role in ensuring the effectiveness and safety of anticoagulant use. Currently, several models of organization are successfully used in the Russian Federation, which cover more than 23,000 patients at high risk for thromboembolic events. There are following common features of the models used: the maximum reduction in the time from the moment of international normalized ratio (INR) testing with a quick communication with a patient for the need to adjust the dose, the ability to sort patients depending on the degree of hypocoagulation and the risks of events with the creation of a personalized approach to treatment, the organization of a shared information space and maintaining a register of patients.

**Key words:** anticoagulant therapy, anticoagulant offices, vitamin K antagonists, time of the therapeutic margin.

**Relationships and Activities:** none.

Center of Hematology, Arkhangelsk, Russia; <sup>6</sup>Kursk Regional Clinical Hospital, Russia; <sup>7</sup>South Ural State Medical University, Chelyabinsk, Russia; <sup>8</sup>Interregional Clinical Diagnostic Center, Kazan, Russia; <sup>9</sup>Kazan State Medical University, Kazan, Russia; <sup>10</sup>OOO Portavita Health, Russia, Medical Facility Noorderboog, Netherlands.

Vavilova T. V. ORCID: 0000-0001-8537-3639, Solovyova L. V. ORCID: none, Bekoeva A. B. ORCID: none, Zubkova P. Yu. ORCID: 0000-0001-8292-2903, Vorobyeva N. A. ORCID: 0000-0001-6613-2485, Vorobyeva A. I. ORCID: 0000-0003-4817-6884, Melnichuk E. Yu. ORCID: 0000-0002-7000-5451, Khruslov M. V. ORCID: 0000-0001-9856-1284, Vereina N. K. ORCID: 0000-0001-6613-2485, Safin D. D. ORCID: 0000-0003-4412-9247, Galyavich A. S. ORCID: 0000-0002-4510-6197, Sluiter M. ORCID: 0000-0002-6063-0181, Endubaeva G. V.\* ORCID: 0000-0001-8514-6436, Shlyakhto E. V. ORCID: 0000-0003-2929-0980.

<sup>1</sup>Almazov National Medical Research Center, St. Petersburg, Russia; <sup>2</sup>Department of adult ambulatory care organization of the Health Committee of St. Petersburg, St. Petersburg, Russia; <sup>3</sup>City Consultative Diagnostic Center № 1, St. Petersburg, Russia; <sup>4</sup>Northern State Medical University, Arkhangelsk, Russia; <sup>5</sup>Northern branch of National Medical Research

\*Corresponding author:  
endubaeva.galina@yandex.ru

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Many cardiovascular complications are associated with thromboembolic events (TEE): cardioembolic stroke and systemic embolism in atrial fibrillation (AF) and deep vein thrombosis and pulmonary embolism in patients with mechanical valves. The basis of these complications are blood coagulation disorders. Risk of TEE is significantly reduced with anticoagulant therapy, which is prescribed for short and long term [1]. For more than 50 years, vitamin K antagonists (VKA) have been used to reduce the activity of vitamin K-dependent clotting factors. A meta-analysis of controlled studies showed that the use of such agents in patients with nonvalvular AF reduces the relative risk of all strokes by 64%, which corresponds to an absolute risk reduction of 2,7% per year [2]. In the last 10 years, novel inhibitors of clotting factors began to be used — direct oral anticoagulants (DOAC), which are not less effective than VKA but require careful monitoring of a patient [3]. One danger in using anticoagulants is the risk of bleeding events. A risk-benefit ratio is determined in each patient and specifies the drug selection.

Laboratory assessment and organization of outpatient monitoring is a key factor for the successful prevention of TEE using VKA. In world practice, various organizational models for monitoring patients receiving VKA and DOAC are used [4]. This study presents the Russian experience in monitoring patients with a high risk of TEE receiving anticoagulants.

The aim was to study the best practices of providing anticoagulant therapy in patients with high risk of TEE in different subjects of Russia.

### Material and methods

The study describes the experience of 5 Russian regions in the organization of anticoagulant therapy monitoring in outpatients with high risk of TEE: St. Petersburg, Arkhangelsk, Kursk, Chelyabinsk and Tatarstan. More than 23,000 patients took part in the implemented projects.

### Results

One of the first projects to structure work with patients receiving warfarin was the organization of offices for anticoagulant therapy control in **St. Petersburg**. It started in 2013 at the City Consultative and Diagnostic Center № 1. From the very beginning, the following principles were laid down: the shortest time from the moment of blood sampling for assessing the international normalized ratio (INR) to the doctor's consultation on test results, thorough identifying the risks TEE and bleeding events, work with modifiable risk factors, increasing patient motivation to improve medication adherence, a multidisciplinary team approach to solving individual prob-

lems. Since 2015, successful practices have been extended to city healthcare facilities and a network of eight offices was organized in St. Petersburg within the outpatient care system based on large hospitals and one federal institution — Almazov National Medical Research Center. In laboratory monitoring, the emphasis was on the use of portable INR analyzers, which significantly increased the efficiency and ensured the implementation of single window mode. INR measurement is carried out during a doctor's appointment in mentioned or another special office. A patient receives the result of a laboratory test and a doctor's consultation in one visit with the adjustment, if necessary, of the drug dose. Since 2018, a tariff for the study of INR using portable coagulation analyzer was provided, which, together with the tariff for a doctor's appointment, made it possible to fully ensure monitoring in anticoagulant office at the expense of the compulsory health insurance fund. Patient capacity of one such office is up to 2 thousand visits per year. During the implementation of the project, over 8 thousand patients were observed through network of offices. With the accumulation of experience and an increase in using DOAC, such patients also began to be referred to offices and amounted to 30% in 2019. The positive effect of anticoagulant offices is primarily to increase the INR time in therapeutic range to 75% (above the therapeutic range — 8,5%; below — 16,5%, mainly due to first-time visits). There were 0,6% of TEE events, 7% — minor bleeding events. No fatal bleedings or TEE were recorded. The work of multidisciplinary team, coordination of work with the Stroke Prevention Center allowed to monitor the most complex patients — with hereditary thrombophilia and antiphospholipid syndrome (2%), intracardiac thrombosis (2%), those requiring adjustment of antiplatelet therapy after stent implantation but having bleedings (5%).

Active and successful work on organizing monitoring of patients receiving long-term anticoagulation therapy is carried out in **Arkhangelsk**, which began in 2007. By 2016, it was implemented within a regional project to centralize monitoring of VKA therapy based on 28 medical organizations of the Arkhangelsk Oblast. In 2019, the number of offices increased to 38. A total of 6763 patients is monitored. An IT organizational structure based on a WEB server and network, coordinated by the Regional Center for Antithrombotic Therapy of the Arkhangelsk Oblast was created and implemented. This allowed to create a register of patients receiving long-term anticoagulation with a personalized approach to each patient.

The strategic goal of organizing a network of offices in the Arkhangelsk Oblast is to increase the availability, quality, safety and effectiveness of long-

term anticoagulation with VKA, and since 2020 — DOAC. There are following main tasks: determining indications for anticoagulant therapy; laboratory tests of INR; adjustment of VKA and DOAC therapy individually for each patient; patient-centered approach. Much attention is paid to education activity with the creation of programs for patients (1<sup>st</sup> level), the general medical community (doctors, nurses, pharmacists) (2<sup>nd</sup> level) and anticoagulation specialists, offices' staff (3<sup>rd</sup> level). 'Patient schools' for those receiving VKA and DOAC were organized, videos and audio presentations were prepared for nursing staff to help educate patients, a training manual on patient education based on questions and answers, and handouts were created. On the website of the Department of Clinical Pharmacology and Pharmacotherapy of the Northern State Medical University and the Regional Center for Antithrombotic Therapy, a section has been created for doctors and patients on the work of anticoagulant offices.

According to the analysis of anticoagulant office work in the Arkhangelsk Oblast for 2019, the INR time in therapeutic range amounted to 73% (Me 73 (65-82)). The advantages of WEB support were revealed and tested in actual clinical practice: accessibility for a larger number of patients in remote areas; implementation of a quality management system for medical workers; integration of various medical specialists and medical organizations into a single system; maintaining a register of patients receiving VKA therapy. In 2017, the project was awarded the M. V. Lomonosov prize as the best innovation and research work.

The original centralized VKA monitoring system was created in **Kursk**, which has been implemented since 2012. The model is based on the following principles: providing a qualitative and reliable determination of INR, creating conditions for the patient to quickly receive information and adjust therapy on the day of blood sampling, developing a software package that allows, under the under medical supervision, to monitor and interpret the INR value in real time with memorization of all results, test dates, and drug doses on the server in the electronic patient record. For the implementation of the project, conditions were created for the collection, transportation and analysis of INR in one centralized laboratory — a single center for determining INR. For emergency determination of INR and/or analysis on unplanned days, portable coagulation analyzers were additionally delivered to each medical institution. The software package "Warfarin manager" and "Warfarin manager 0.1.0" was developed as the central element of the centralized monitoring system. The patient monitoring system reduced the number of ischemic strokes from 8,06% at to 0,73% without fatal outcomes ( $p < 0,001$ ),

major bleedings requiring hospitalization from 3,0% to 0,9% without statistical significance, minor bleedings from 16,13% to 5,15% ( $p < 0,05$ ). The INR time in therapeutic range was increased from 40,1% to 73,2% ( $p < 0,01$ ). Thus, the clinical and laboratory model of monitoring of VKA therapy in the Kursk Oblast is a novel form of interaction between the doctor and cardiovascular patients, based on personalized medicine and innovative technologies. The authors proved the economic efficiency of model by preventing TEE and bleeding events, which are expensive in the treatment and further disability of patients.

The centralized system of anticoagulant offices was organized in **Chelyabinsk**. It includes 10 local offices based on medical organizations with a single coordinating center. The main aim at the organization phase was to improve control of VKA therapy. All offices were equipped with portable coagulation analyzers, consumables and software at the expense of the regional budget. This allowed to develop a single electronic database for patients taking VKA. The offices include 8 cardiologists and 2 therapists, nurses who have undergone special training. The work is carried out under the supervision of coordinating center. There are following functions of coordinating center: consultation of patients with difficulties in selecting a dose in the office; formation of a single city register; development and implementation of training programs for patients and medical staff; preparation of regular single reports on the operation results. Currently, 1830 people are in the general register. Indications for VKA therapy in 74,9% of patients were nonvalvular AF, in 17,4% — mechanical valves and valvular AF; in 6,4% — secondary prevention of venous thromboembolism (VTE); in 1,3% — other causes (intracardiac thrombosis, arterial thrombosis). Over 8 months, an increase in the average INR time in therapeutic range from 49% to 62%. There were 40% of patients with INR time in therapeutic range  $\geq 65\%$ . During the year, among the patients included in the register, 7 people died (0,38%), 6 (0,32%) had major bleeding, 3 — hemorrhagic strokes, 12 (0,7%) — thrombotic events, including ischemic strokes, myocardial infarction and VTE. High medication adherence within the implementation of this model is noted.

In the **Republic of Tatarstan**, the decision to introduce a centralized monitoring system for patients receiving anticoagulant therapy was made in 2018. To implement this project and solve a number of tasks, the Portavita Anticoagulation application was chosen as the most optimal and modern, evidence-based medical software. Extensive experience in its use has been gained in the Netherlands; the software was adapted for Russia together with the Almazov National

Medical Research Center in St. Petersburg and tested in actual clinical practice. The Anticoagulation module not only forms a register for dynamic monitoring of included patients, but also is the basis for selecting VKA dosage. Centralized monitoring system is based on anticoagulant offices, where patients are registered and monitored, with a staff of 1 therapist and 1 nurse. The expertise center coordinates with a staff of 2 cardiologists and 1 nurse, created on the basis of Interregional Clinical and Diagnostic Center. To date, 27 offices operate in the Republic of Tajikistan, where 4500 patients receiving VKA are monitored. There are 2207 patients (51,6%) with AF, 1692 (39,5%) — mechanical valves, 228 (5,3%) — VTE, 17(0,4%) — pulmonary hypertension. In the module, patients are divided into 3 dosing lists based on the algorithm taking into account ~40 parameters. The program prompts the recommended dose and the date of next visit. The recommendations are validated by the medical specialist. According to reports, 46% of patients belonged to the 3<sup>rd</sup> list, that is, they needed care of a highly qualified specialist due to bleeding vents, a planned surgery, which had out-of-range INR in last 3 tests. In general, INR time in therapeutic range, which is easily monitored by the program, increased in the region from 45% to 60%. During operation offices deaths were not recorded, and none of the patients needed hospitalization. During the pandemic, personal accounts were created for all interested patients for remote interaction.

## Conclusion

The system for anticoagulant therapy monitoring through the creation of specialized organizational models and software systems can significantly increase the effectiveness and safety of treatment in patients at high risk for TEE, reduce cardiovascular mortality and disability of the population from and is cost-effective.

Such a model provides support to primary care physicians and reduces the risk of bleeding; the doctor is “not afraid” to prescribe anticoagulants, delegating the authority to monitor the patient to specially trained medical workers. A patient-centered care is implemented as part of “patient schools”. The use of software systems makes it possible to maintain registers with full and operational monitoring of results. The implementation of the models gained particular importance during the COVID-19 epidemic, making it possible not to reduce the number of monitored patients.

Promising is the adaptation of DOAC programs. This program is a part of the Portavita Anticoagulation application, and can also become an additional solution in the Warfarin manager and Warfarin manager 0.1.0, which will fully cover this category of patients. The implementation of mobile applications is also a modern and effective addition to the centralized and remote monitoring system.

**Relationships and Activities:** none.

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