

## Directions for optimizing the organization of long-term anticoagulant treatment

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### Abstract

**Background:** In this study the organization of long-term anticoagulant treatment has been evaluated to estimate whether clinical practice is in accordance with current recommendations for optimal use and effective control of oral anticoagulant (OAC) treatment.

**Material and methods:** Mixed (quantitative and qualitative), transversal, descriptive, selective study. Samples: quantitative study – 394 adult patients, eligible for anticoagulant treatment; qualitative study – 39 family doctors.

**Results:** The rate of use of OAC treatment is 68%. The period from the diagnosis of the disease to the initiation of OAC treatment lasted one month or more in 59.1% of patients. 60.6% of patients do not have sufficient knowledge regarding the treatment of OAC. The high price is the most important barrier to direct oral anticoagulant administration (91.1%). Patients' satisfaction with OAC treatment control is low, mainly for vitamin K antagonists (59.8%). 75.5% of respondents claim that OAC treatment control and management is poor. 40.3% do not perform safe therapeutic International Normalized Ratio control, and 54.7% are not in the optimal therapeutic range.

**Conclusions:** The main barriers to adherence to OAC treatment: the burden of regular monitoring of blood parameters, perceived concern about complications, limited access to laboratory tests and specialist doctors, insufficient information about anticoagulation, and deficiencies in communication with medical staff. There is limited conviction, and uncertainty persists in the initiation and monitoring of OAC treatment by family doctors.

**Key words:** control of anticoagulant treatment, Warfarin management, oral anticoagulants, atrial fibrillation.

### Cite this article

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### Introduction

Thrombosis is a global public health problem, and the organization of anticoagulant therapy has evolved considerably, improving the management of OAC treatment [1]. The organization of effective long-term anticoagulant treatment must correspond to the correct and well-justified balance of providing quality services, by avoiding overuse, underuse or misuse [2]. The European and American Societies of Cardiology and Neurology recommend long-term (lifelong) anticoagulation with classical oral anticoagulants, vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs), with proven efficacy and safety, mainly in atrial fibrillation (AF) to prevent ischemic stroke (IS), as well as in other medical conditions that are associated with thromboembolic complications, such as deep vein thrombosis (DVT), pulmonary thromboembolism (PTE), and mechanical heart valves [3].

According to the Institute for Safe Medication Practices, anticoagulants are a high-priority drug family for optimal medication management, due to their established benefits in reducing the risk of IS due to AF by approximately 70%, the risk of recurrent venous thromboembolism by more than 90% and the risk of death by approximately 25% [4]. OAC is a socioeconomic burden that requires continuous

resources, taking into account the increasing demands arising from the aging of the population and the increase in the number of patients with increased thrombotic risk, being a treatment used throughout life, which currently involves approximately 2% of the western population [5].

Successful anticoagulation has always been defined as a scientific balance of the risk of thrombosis and bleeding complications. To maintain such optimal anticoagulation, rational prescription of drugs, institution of therapy monitoring, as well as active participation of patients receiving the therapy is required [6]. Inadequate anticoagulation control is often associated with major complications, such as bleeding, thromboembolic events, and mortality [5]. Most complications related to anticoagulation are preventable, and safety measures are encouraged or mandated [7].

In the Republic of Moldova there are no widely accessible anticoagulation clinics, there are no national disease registries, portable coagulometers are not accessible, and the health insurance fund does not reimburse the use of new OACs at the research stage. The management of anticoagulation (mainly Warfarin) in the long term is quite difficult, being officially assigned to family doctors. Adherence to regular OAC treatment monitoring and Warfarin dose adjustment are time-consuming and may be difficult to achieve in the outpatient setting, especially

for patients with limited mobility. Previous reports from other studies suggested that the use of OAC in the Republic of Moldova was poor [8], but there are no studies that provide a deeper insight into the use and management of OAC treatment in patients who require long-term anticoagulation, especially in the era of new OACs. A better understanding of utilization, treatment patterns, and factors that might influence treatment strategy is essential to know whether clinical practice is in line with current treatment recommendations.

### Material and methods

This study presents a mixed (quantitative and qualitative), transversal, descriptive, selective research.

The quantitative study was carried out using the survey as a method, and the questionnaire developed and adapted in the interests of the study as an instrument (it is based on the validated multinational questionnaire of barriers to the use of warfarin in AF, the multinational questionnaire for assessing patients' satisfaction in terms of regarding anticoagulant treatment "Anticoagulant Treatment Perception Questionnaire" (PACT-Q®), a new questionnaire for assessing the quality of life of patients treated with anticoagulants "Anticlotting Treatment Scale", the questionnaire for the Duke Anticoagulation Satisfaction Scale and the evaluation questionnaire of patients' knowledge about anticoagulant treatment).

The representative sample was calculated based on the reduced formula for large populations:

$$n = \frac{z_{\alpha}^2 * p(1-p)}{e^2} \quad n = \frac{z_{\alpha}^2 * p(1-p)}{e^2} \quad \text{where:}$$

- n** – minimum volume of the representative sample,
- p** – the probability of occurrence of the phenomenon (in case of 2% **p** will be equal to 0.02),
- e** – within the margin of error 2 % **e** will be equal to 0.02, at the 99% confidence level  $Z_{\alpha}$  will be equal to 2.58.

According to the data in literature, approximately 2% of the general population require long-term anticoagulant treatment. Using the respective formula, was obtained **n** approximately equal to 326 respondents. The non-response rate being estimated at 10% of probably invalid questionnaires, the minimum size of the representative sample will be approximately 359 respondents.

The sample of the study included 394 respondents from the entire territory of the Republic of Moldova. Inclusion criteria – adult patients, eligible for anticoagulant treatment from different regions of the Republic of Moldova, who agreed to participate in the survey. Exclusion criterion – people who refused to participate in the survey and incomplete questionnaires.

The tool used to carry out the qualitative study was the focus group interview guide, with the survey developed for this purpose. The research allowed the evaluation of the attitudes and practices of the use and control of anticoagulant treatment by family doctors, the identification of respondents' opinions and the reasons for selecting the answer. Family physicians working in Primary

Health Care Institutions (urban and rural) and consenting to participate in the study served as inclusion criteria in the study. The exclusion criterion was the family doctors who refused to participate in the discussions. The study sample consisted of 39 family doctors (24 from the urban regions and 15 from the rural regions).

Data collection period: November 1, 2022 – March 1, 2023. The data obtained were processed using the SPSS 23 (Statistical Package for the Social Sciences) application for statistical data analysis.

The study protocol was discussed and approved at the School of Public Health Management meeting (05.10.2022).

### Results and discussion

394 eligible patients were surveyed, selected uniformly throughout the territory of the Republic of Moldova. The average age of the investigated patients was 67 years, ranging between 33 and 84 years. The age of 65-74 years prevails. Of the diseases with thromboembolic risk, with an indication for long-term OAC treatment, the majority of patients in the sample were diagnosed with AF (the largest subset of patients requiring lifelong anticoagulation [9]), constituting 91.8% (CI 95% 81.7%-100%), 11.9% patients with heart valve prostheses, 7.2% with deep vein thrombosis and 3.4% with pulmonary embolism. Of the concomitant pathologies detected in the patients, arterial hypertension predominated, constituting 76.9% (CI 95% 72.6%-81.2%), diabetes 37.8% (CI 95% 33.2%-42, 9%) and chronic heart failure – 35.3% (95% CI 30.7%-40.1%). The obtained data allowed to evaluate the thromboembolic risk of stroke using the CHA<sub>2</sub>DS<sub>2</sub>-VASc score in patients with AF in this sample, demonstrating that the majority are at high thromboembolic risk – 72.9% or moderate – 17.5% and with indication for long-term OAC treatment. Particular attention was paid to the degree of use of OAC treatment. Patients eligible for OAC treatment were divided into four groups: patients undergoing OAC treatment – 68% (CI 95% 63.5%-71.6%), patients who were not indicated for OAC treatment – 8.6% (CI 95% 5.8%-11.4%), patients who did not follow the indicated treatment – 22.6% (CI 95% 18.8%-26.4%) and patients who did not consult a doctor for treatment until the moment of questioning – 0.8% (CI 95% 0%-1.8%), (fig. 1). Accordingly, in the given study, the degree of use of OAC treatment is 68% of the total eligible patients.

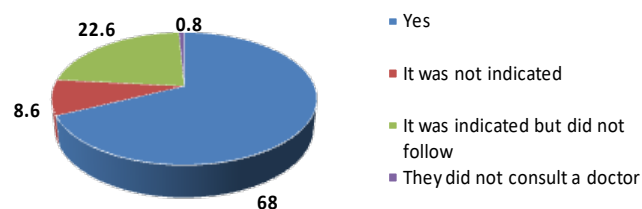


Fig. 1. Evaluation of the degree of use of OAC treatment (%)

The research analysis shows that patients from the rural region have a lower degree of use of OAC treatment

(63.8%), more often they do not follow the indicated OAC treatment (24.3%) or the treatment was not indicated (11%) ( $p < 0.05$ ), (fig. 2).

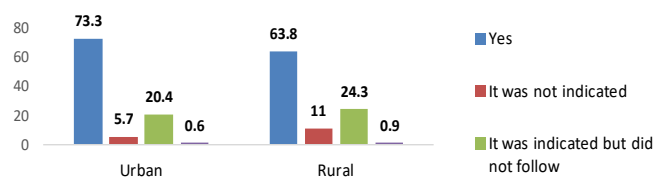


Fig. 2. Degree of use of OAC treatment by region of residence (%)

The age correlation highlights that younger patients have a better utilization rate of OAC treatment. In the category of patients under 75 years of age, the degree of use of OAC treatment is higher (70.1%), compared to those aged 75 and over (59.2%), (fig. 3).

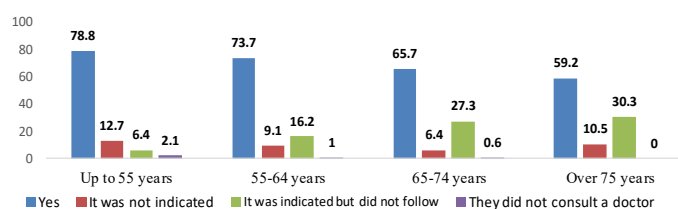


Fig. 3. Degree of use of OAC treatment by age (%)

The evaluation of the degree of use of the OAC treatment revealed a practically uniform use by regions, with a higher degree of use in the North of 71.1% ( $p < 0.05$ ), (fig. 4).

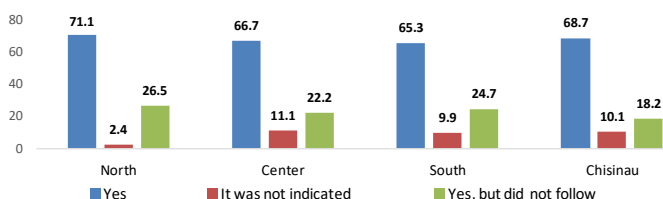


Fig. 4. Evaluation of the degree of use of OAC treatment by region (%)

In the examination group there was a prevalence of use of OAC treatment in women (73.1%) versus men (62.2%) ( $p < 0.05$ ). The period from the diagnosis of the disease to the initiation of OAC treatment lasted a month or more in more than half of the patients, constituting 59.1%, increasing the high thromboembolic risk of stroke or other thromboembolic complications (fig. 5).

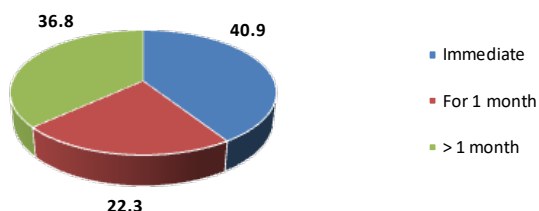


Fig. 5. Assessment of OAC treatment initiation time (%)

During the course of the research, many uncertainties arose regarding who it belongs to and who is responsible for prescribing OAC treatment. In this sample, the majority were cardiologists who indicated anticoagulant treatment, constituting 71.4% (CI 95% 65.2%-74.9%), (fig. 6).

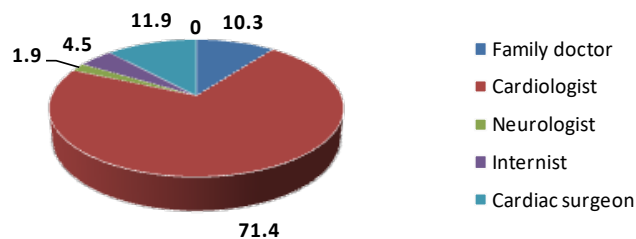


Fig. 6. Healthcare professionals involved in prescribing OAC treatment (%)

Was assessed the patients' level of responsibility in the treatment administering. From the total group of patients, practically half (46.7%) forgot 2-3 times a month or more to receive the medicine on time, and 31.7% of patients skipped (forgot) the treatment 2-3 times per month and more, which influences the degree of use, adherence and quality of AOC treatment. The rate of skipping (forgetting) one dose or more per month in correlation with age demonstrated that the rate of skipping one dose or more increases with age, and young patients, under 65 years of age, administer the medication daily at a higher level and have better treatment adherence ( $p < 0.005$ ), (fig. 7).

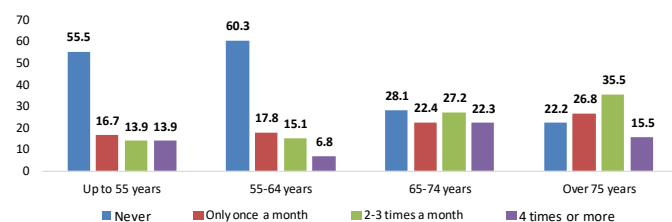


Fig. 7. Omission rate (forgetting) of the monthly dose depending on age (%)

To assess patients' knowledge of OAC treatment was assessed respondents' understanding of the purpose of OAC treatment. Of the respondents who receive OAC treatment, only 81% understand that the main action of OAC is to prevent the formation of blood clots, 53.7% see this treatment as one that can prolong life and 35.9% patients are informed that OAC can prevent stroke. The obtained results highlight that a large group of patients do not have sufficient knowledge related to OAC treatment and do not correctly perceive the purpose of this treatment, these factors being individual determinants in the treatment outcome (fig. 8).

The obtained data highlight that patients in the urban region are better acquainted with the treatment of OAC, constituting 69.2% versus 42.4% in the rural region, which results in the fact that access to information in the urban

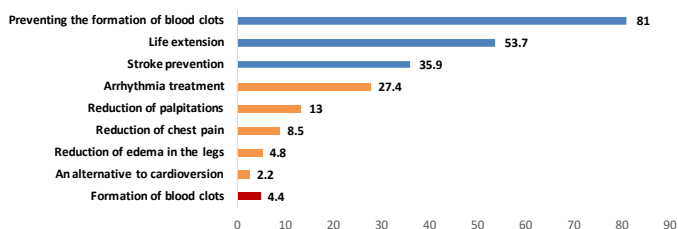


Fig. 8. Evaluation of respondents' understanding of the purpose of OAC treatment (%)

A multitude of factors was assessed with primordial negative impact on anticoagulant adherence, besides frequent blood monitoring, including perceived drug efficacy and safety, anxiety about real drug side effects, patient autonomy, quality of information provided to patients by physicians, the influence of the drug on physical activities and quality of life. Adherence barriers were compared between patients treated with VKAs (vitamin K antagonists) and DOACs (direct oral anticoagulants), demonstrating an increased preference for DOACs (in eligible patients) versus Warfarin among both patients and family doctors. The high price of DOAC, being the most important barrier to administration in 91.1%. Although antiplatelet therapy is not recommended simultaneously with OAC treatment in most cases [10], in the group of patients practically half (44%) received Aspirin or Clopidogrel simultaneously, being subject to an increased risk of bleeding. The complication rate of OAC treatment in the research group was 35.7% (mainly mild hemorrhagic complications, ecchymoses, superficial bleeding, blood in stool or urine), with prevalence in patients using VKA (38.7%), compared to DOAC (20%).

Patient satisfaction with anticoagulant treatment control is low in more than half of patients, mainly for VKA (59.8%). The majority of respondents claim that the task of controlling anticoagulant treatment is defective, and the management of OAC therapy in the medical institution where they are served is difficult (75.5%).

In patients using VKA were assessed preferences for the OAC treatment monitoring and control model. The majority of respondents wanted INR monitoring and control at home through self-monitoring (38.4%) or at specialized anticoagulation centers (36.4%), and only 25.2% claimed for monitoring at the family doctor. Considering that in the Republic of Moldova the management of OAC treatment is assigned to family doctors and there are no monitoring centers or the possibility of self-monitoring, patient preferences cannot be encouraged at the moment.

Time in therapeutic range (TTR) is a tool to assess the quality of treatment, and access to reliable INR monitoring is important for the optimal management of anticoagulation therapy of VKA, with the frequency of testing being assessed individually for each patient. The International Self-Monitoring Association for Oral Anticoagulation recommends a testing interval of no more

than 4 weeks for stable patients and no more than 2 weeks in unstable patients [11]. In the research carried out 40.3% of the respondents did not perform safe therapeutic control of International Normalized Ratio (INR), (fig. 9).

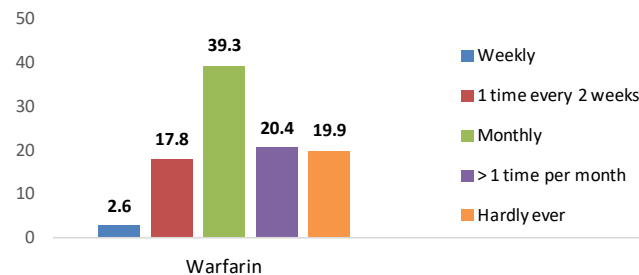


Fig. 9. Frequency of INR testing in the group of patients receiving VKA (%)

54.7% of patients are not in the optimal therapeutic range and do not have adequate treatment control, being subject to a high thromboembolic risk (fig. 10).

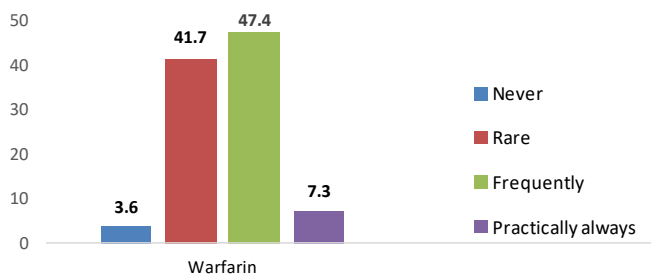


Fig. 10. INR values outside the therapeutic range (%)

Respondents mentioned that in 21.5% of cases the dose is changed practically after each INR test, with a negative impact on treatment adherence (fig. 11).

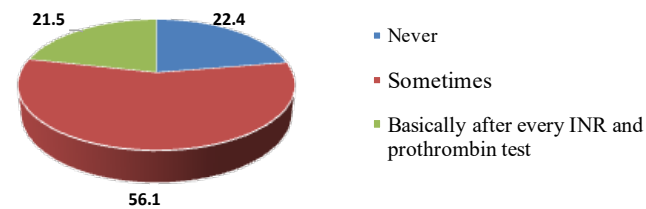


Fig. 11. Dose adjustment rate of respondents using VKA (%)

More than 1/3 of patients have a low level of trust and satisfaction in the healthcare provided (38.2%), which could also have a significant impact on adherence, persistence and therefore the effectiveness of OAC treatment, and 32.6% of patients were not explicitly informed about anticoagulant treatment, which indicates a low level of communication. The majority of respondents consider the cardiologist (224 respondents) and the family doctor (186 respondents) as the main source of information and communication.

## Conclusions

1. The study found that anticoagulant therapy is underused in the Republic of Moldova, especially among rural and elderly patients.
2. The main barriers to adherence to OAC treatment are the burden of regular monitoring of blood parameters imposed by Warfarin therapy, the perceived concern of complications and limited access to laboratory tests and specialist doctors.
3. The research conducted identified that there is limited confidence and uncertainty persists in the initiation and monitoring of OAC treatment by family doctors.
4. The use and control of OAC treatment are influenced by the technical-material and laboratory incapacity of the anticoagulation service to ensure the current rigors of diagnosis and treatment.
5. The application of DOAC treatment is associated with a higher level of patient satisfaction and compliance, as well as the safety of family doctors in the use of OAC treatment.
6. The monitoring model and applied practices of OAC treatment in the Republic of Moldova do not correspond to patients' preferences, at the same time there is no access to alternative monitoring and control models.
7. Some of the essential problems faced by patients with thromboembolic diseases are limited access to medical assistance, insufficient information about anticoagulation and deficiencies in communication with medical personnel.

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### Authors' contributions

NS conceptualized the project, drafted the first manuscript and interpreted the data. AB critically revised the manuscript. Both authors revised and approved the final version of the manuscript.

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This study was supported by the School of Public Health Management. The study was carried out as part of a master's program in Public Health Management. The authors are independent and take responsibility for the integrity of the data and accuracy of the data analysis.

### Ethics approval and consent to participate

The study protocol was discussed and approved at the School of Public Health Management meeting (05.10.2022).

### Conflict of interests

No competing interests were disclosed.