pharmacoepidemiology

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Direct Oral Anticoagulants' Consumption and Expenditure in the COVID-19 Pandemic in Russia and Clinical Practice Guidelines for Their Use

Elena A. Baybulatova [1,*], Mikhail S. Chenkurov [1], Elina A. Korovyakova [1], Sergey K. Zyryanov [1,2] and Liliya Eugenevna Ziganshina [1,3,4]

[1] Department of General and Clinical Pharmacology, Peoples' Friendship University of Russia named after Patrice Lumumba (RUDN University), 6 Miklukho-Maklaya St., 117198 Moscow, Russia; chenkurov-ms@rudn.ru (M.S.C.); korovyakova-ea@rudn.ru (E.A.K.); zyryanov-sk@rudn.ru (S.K.Z.); lezign@gmail.com (L.E.Z.)
[2] State Budgetary Institution of Healthcare of the City of Moscow "City Clinical Hospital No. 24 of the Moscow City Health Department", Pistzovaya St. 10, 127015 Moscow, Russia
[3] Department of Epidemiology and Knowledge Translation Cochrane, Russian Medical Academy for Continuous Professional Education of the Ministry of Health of the Russian Federation, 2/1 build. 1, Barrikadnaya St., 125993 Moscow, Russia
[4] Department of Pharmacology, Kazan State Medical University, 49 Butlerov St., 420012 Kazan, Russia
* Correspondence: baybulatova-ea@rudn.ru; Tel.: +7-(926)-047-89-88

Abstract: Background: The coronavirus pandemic has led to the creation of clinical guidelines by a large number of professional medical communities. However, the quality and methodology of development of Russian clinical guidelines has been little studied. The continued relevance of studying the use of DOACs (Direct oral anticoagulants) in patients with COVID-19 was the basis for conducting this study. Aim: The objective of this study was to assess DOAC consumption and expenditure in the Russian Federation during the COVID-19 pandemic and to analyze whether it was supported by the domestic evidence base for the use of DOACs in COVID-19 patients through identifying all publicly available Russian-produced CPGs (Clinical practice guidelines) for the treatment of COVID-19 and assessing their quality as the source of recommendations for the use of oral anticoagulants for the prevention of thrombotic complications in COVID-19 patients. We searched Russian databases for CPGs, published between 2020 and 2023. We identified seven relevant documents that met our inclusion criteria. Three authors analyzed Russian clinical guidelines using an AGREE II questionnaire. We calculated DOAC DDD (defined daily dose) consumption according to Russian clinical guidelines and DDD consumption in patients with COVID-19 for the period 2020–2022. Results: Seven clinical CPGs were analyzed with the AGREE II tool. It was revealed that experts gave the highest scores for the sections on scope and purpose (from 62.98% to 100%), and clarity of presentation (from 96.30% to 100%). The lowest scores were given for the sections on stakeholder involvement (33.33% to 64.81%), rigour of development (from 0% to 49.31%), applicability (from 23.61% to 50%), and editorial independence (from 0% to 50%). When comparing the total score, it was found that two clinical guidelines received the highest scores—ROPNIZ (Livzan), and ROPNIZ (Drapkina). The minimum score was registered with the NIIOZMM (Khripun) clinical guideline. No guideline received a total score of more than 70%. According to clinical recommendations, the consumption of apixaban and rivaroxaban is 15 DDD (30-day course of therapy), or 22.5 DDD (45-day course of therapy). Consumption of apixaban in the Russian Federation in 2020 and 2021 corresponds to the indicators presented in clinical recommendations (in 2020—26.59 DDD per patient with COVID-19; in 2021—15.75 DDD per patient with COVID-19), and in 2022—10.67 DDD, which is below the recommended values. In 2020, consumption of rivaroxaban in the Russian Federation was 26.59 which corresponds to data from clinical recommendations; in 2021, consumption decreased to 7.87 DDD; in 2022 it decreased to 5.48 DDD, which is 2.74 times less than recommended. Conclusions: Analysis of seven clinical recommendations revealed that such sections of clinical recommendations as scope, purpose, and clarity of presentation had the highest degree of assessment in accordance with AGREE II. The lowest scores were given for the sections on stakeholder involvement, rigour of development, applicability,

Citation: Baybulatova, E.A.; Chenkurov, M.S.; Korovyakova, E.A.; Zyryanov, S.K.; Ziganshina, L.E. Direct Oral Anticoagulants' Consumption and Expenditure in the COVID-19 Pandemic in Russia and Clinical Practice Guidelines for Their Use. *Pharmacoepidemiology* **2024**, *3*, 1–32. https://doi.org/10.3390/pharma3010001

Academic Editor: Hao Hu

Received: 1 November 2023
Revised: 8 December 2023
Accepted: 11 December 2023
Published: 29 December 2023

and editorial independence. When comparing the total score, it was found that two clinical guidelines received the highest scores—the Russian Society for the Prevention of Non-communicable Diseases (Livzan), and the Russian Society for the Prevention of Non-communicable Diseases (Drapkina). The minimum score was registered with the Research Institute for Healthcare Organization and Medical Management of Moscow Healthcare Department clinical guideline. No guideline received a total score of more than 70%. During the pandemic, the highest DDD consumption of DOACs was in 2020, which exceeded the DOACs' recommended DDD by Russian clinical guidelines. DOAC consumption had decreased by 2022. There was a decrease in the consumption of rivaroxaban, with an increase in apixaban's share in the structure of DOAC consumption during the coronavirus pandemic. Obtained data indicate that in 2021 the apixaban consumption in the Russian Federation corresponded to the recommended DDD in the national guidelines, which indicates the most correct use of apixaban according to Russian GPGs.

Keywords: COVID-19; DOACs; pharmacoepidemiology; pharmacoeconomics; clinical practice guidelines; clinical trials; AGREE II; CONSORT

1. Introduction

The global COVID-19 epidemic, officially recognized by the WHO on 11 March 2020, has become a serious test for global health. The most common manifestation of COVID-19 is damage to the respiratory system. However, this disease is characterized by high inflammatory activity and thrombotic complications leading to multiple organ damage. Management of a patient with COVID-19 involves not only the treatment of pneumonia and respiratory failure, but also the timely recognition and treatment of damage to other body systems. The risk of thrombosis in hospitalized patients with COVID-19 is an emerging issue that requires investigation. The occurrence of thrombosis in hospitalized patients with severe COVID-19 may be over 35% with a mortality rate of 45% [1,2].

To prevent thrombotic complications in patients with COVID-19, low molecular weight heparin (LMWH) preparations, and in some cases, unfractionated heparin (UFH) preparations, were used empirically. Direct oral anticoagulants (DOACs) or new oral anticoagulants (NOACs) are currently recognized as the standard of care for treatment of venous thrombosis and atrial fibrillation; however, the balance of benefits and risks of their use in hospitalized patients with COVID-19 is not clearly understood and hence the use of DOACs is not recommended. However, in patients with confirmed COVID-19 on an outpatient basis, DOAC therapy may be recommended [3]. Direct oral anticoagulants are used to improve the prognosis in patients with COVID-19, and are likely to reduce venous thrombosis and pulmonary embolism regardless of their dose compared with untreated patients and placebo patients. There is also no significant difference in the development of such outcomes as hospitalization, adverse events, death and major bleeding in patients receiving different doses of the same direct anticoagulant. The results of another systematic review of seven studies involving 16.185 people from Brazil, Iran, Italy, the USA, and a number of other countries, hospitalized with severe COVID-19, requiring intensive care and emergency care to be conducted, clearly demonstrated the benefits of using rivaroxaban. The authors found that there was little or no difference between using higher-dose or lower-dose rivaroxaban anticoagulants for 15 to 90 days in patients aged 55 to 68 years in all-cause mortality and increased minor bleeding. However, the data of direct anticoagulants reducing all-cause mortality in treated patients compared with untreated patients come from non-randomized studies and are very uncertain, which requires the continuation of new randomized trials and confirmation of these results. When used in the outpatient setting, anticoagulants (blood thinners) probably reduce venous thromboembolism (VTE) and pulmonary embolism (PE) when compared with a placebo or no treatment in people with COVID-19. However, these drugs seem to have little or no effect in reducing death, major bleeding, need for hospitalization, or adverse events [4,5].

The use of DOACs is associated with a risk of major bleeding (2–4%) most often with a mortality rate of 8–15% [6]. It was shown that the incidence rate of major bleeding increased with the severity of COVID-19: 0.5%, 2.3% and 12.3% in patients with mild, moderate, and severe forms of COVID-19, respectively, which was observed 1.5 times more often in patients during a pandemic with a mortality rate of 12.21% [7,8].

Taking into account the fact that DOACs are recommended at the outpatient stage of treatment of COVID-19 by various CPGs, including clinical recommendations of the Ministry of Health of the Russian Federation, the drugs of choice are the following: rivaroxaban (10 mg once daily), or apixaban (2.5 mg twice daily) for 30–45 days [9]. The authors of a systematic review with meta-analysis showed that the use of DOACs for the prevention of thromboembolic complications in hospitalized patients led to fewer deaths due to bleeding than [10]. According to one study [11], the use of DOACs helped reduce the risk of hospitalization to the ICU by 50% and COVID-associated mortality. Undoubtedly, during the COVID-19 pandemic and owing to recommendations of CPGs, DOACs have become one of the most sought-after groups of the pharmaceutical segment. In the Russian Federation in 2021, the sales of DOACs increased by 6.6%, and the market share for apixaban and rivaroxaban increased by 0.5% compared to 2020 [12]. The probability of prescribing rivaroxaban or apixaban was on average 33% per patient, and treatment with the above drugs cost RUB 911.08 and RUB 840.80 for a course of treatment [13].

CPGs are universally recognized to be an algorithm for clinical decision-making and advancing rational use of medicines aimed at achieving better health outcomes for patients [14]. We hypothesized that during the COVID-19 pandemic DOACs were overused and consumed in amounts exceeding those recommended by CPGs and evidenced to benefit patients. We also wanted to test the hypothesis whether the CPGs were of sufficient quality to be a reliable source of recommendation for the safe use of DOACs. To test these hypotheses, we conducted a comparative analysis of the domestic evidence base for the use of DOACs in COVID-19 patients and gross national DOAC consumption in pandemic years.

There are multiple organizations in Russia that publish clinical practice guidelines (CPGs). The demand for CPGs and appreciation of their role in healthcare provision has been steadily growing. However, the quality and methodology of rapid development of CPGs in the COVID-19 pandemic have not been systematically addressed, as well as whether national DOAC consumption followed CPG recommendations.

Aim

The objective of this study was to assess DOAC consumption and expenditure in the Russian Federation during the COVID-19 pandemic and to analyze whether it was supported by the domestic evidence base for the use of DOACs in COVID-19 patients through identifying all publicly available Russian-produced CPGs for the treatment of COVID-19 and assessing their quality as the source of recommendations for the use of oral anticoagulants for the prevention of thrombotic complications in COVID-19 patients.

2. Results for the DOAC Pharmacoepidemiology (See Appendices A and F, Table A3)

The defined daily doses (DDDs) of direct oral anticoagulants established by WHO are the following: for apixaban—10 mg (5 mg 2 times a day); rivaroxaban—20 mg; dabigatran etexilate—300 mg.

We calculated the hypothetical dosing load for a COVID-19 patient in DDDs as recommended by the CPGs for DOACs. As a result of detailed analysis of the available data in the Russian guidelines for the management of patients with COVID-19 which recommend DOAC use, we obtained the following recommended consumed doses of each DOAC to a patient for a course of prophylactic treatment:

The CPG of the Ministry of Health recommended preventive use of direct oral anticoagulants in patients with COVID-19 with the following dosage regime: rivaroxaban—10 mg once daily, apixaban—2.5 mg twice daily, dabigatran etexilate—110 mg twice daily for prevention of deep vein thrombosis of the lower extremities and pulmonary embolism. The duration of

anticoagulant use in COVID-19 outpatients was not described; however, it was recommended for up to 30–45 days depending on the patient's clinical condition and timing of recovery of motor activity. In accordance with this we calculated the recommended consumed doses of drugs in DDDs as shown in Appendix G, Table A4.

All studied CPGs were in agreement on recommending rivaroxaban, apixaban and dabigatran etexilate equally without preference for prophylaxis of deep vein thrombosis and pulmonary embolism in COVID-19 patients after discharge from hospitals in cases of concern of potential embolic complications. Outpatients with COVID-19 with persistent risk factors for deep vein thrombosis or pulmonary embolism (DVT/PE), elderly patients, patients undergoing treatment in the intensive care unit, patients with active cancer or a history of DVT/PE, patients with ongoing severe mobility limitation or with a D-dimer concentration in the blood 2 times the upper limit of normal and a low risk of bleeding are recommended to be treated with prophylactic doses of anticoagulants for 30 days, which can be extended to 45 days. The dabigatran dosage and mode of administration was not described in the ROPNIZ-2021 (Drapkina) recommendation. In the recommendations of MGNOT-2020, NIIOZMM 2021, FAR 2020 there is information about the equal doses of rivaroxaban, apixaban and dabigatran etexilate, but there is no description of the mode of their use in patients with COVID-19. The RSC-2020 guideline does not contain information about drug doses, indications, or the dosage regimen of direct oral anticoagulants, which makes it impossible to determine the consumer dose of the drugs; however, there are warnings of combination therapy with a protease and P-glycoprotein inhibitors.

The CGS of NIIOZMM-2021, MGNOT-2020, ROPNIZ-2021 and MoH-2022 contain the same information about combined prescribing anticoagulants and protease inhibitors. Simultaneous use of dabigatran with ritonavir is not recommended in patients with impaired renal function and correction of its dose is necessary, with monitoring of the patient for the development of bleeding. Simultaneous use of rivaroxaban with inhibitors of P-glycoprotein is contraindicated.

The lack of necessary information in the CGS of FAR-2020, NIIOZMM-2021, or MGNOT-2020 does not allow us to calculate the recommended consumption of drugs from the group of DOACs.

In the recommended regimens of DOAC use in COVID-19 patients in the Russian guidelines MoH 2022, ROPNIZ 2021 (Drapkina), and ROPNIZ 2021 (Livzan), we obtained equally comparable consumption rates of rivaroxaban, apixaban and dabigatran for the treatment and prevention of deep vein thrombosis and pulmonary thromboembolism in patients at high risk.

Recommended doses and calculated hypothetical DOAC dosing load are presented in Table 1.

Table 1. Recommended DOAC consumption per patient with COVID-19 by Clinical Practice Guidelines.

No	DOAC	DDD/Course of Treatment or Prophylaxis/Patient	CPG
1.	Rivaroxaban	15 DDDs (30 days of course); 22.5 DDDs (45 days of course)	[15–17]
2.	Apixaban	15 (30 days of course); 22.5 (45 days of course)	[15–17]
3.	Dabigatran etexilate	22 (30 days of course); 15 (with creatinine clearance 30–49 mL/min)	[16,17]
4.	Rivaroxaban	n/a	[18–20]
5.	Apixaban	n/a	
6.	Dabigatran etexilate	n/a	

DDD—Defined Daily Dose; CPG—Clinical Practice Guidelines, n/a—not available.

Gross national apixaban consumption varied through the years of 2020, 2021, and 2022 with the maximum consumption in 2021, which was nearly 2 times higher than in 2020. In 2022 national apixaban consumption decreased, but did not reach the level of 2020.

Gross national consumption of rivaroxaban demonstrated a steady downward trend through 2020, 2021, and 2022. Interestingly, in 2020 rivaroxaban consumption was equal to that of apixaban. In 2022, consumption of rivaroxaban in the Russian Federation decreased by 29.25% compared to 2021 and by 30.35% compared to 2020 (See Table 2).

Table 2. Gross national consumption of apixaban and rivaroxaban in the Russian Federation in 2020–2022 (number of DDDs per year).

Name of the Drug	2020 (DDDs/Year)	2021 (DDDs/Year)	2022 (DDDs/Year)
Apixaban	84,000,000 DDD	165,360,000 DDD	114,000,000 DDD
Rivaroxaban	84,000,000 DDD	82,680,000 DDD	58,500,000 DDD

DDD—Defined Daily Dose.

When studying the consumption of apixaban and rivaroxaban per patient with COVID-19, it was revealed that the maximum consumption of apixaban was in 2020, and the minimum in 2022. When analyzing the results of rivaroxaban consumption, similar results were obtained: the maximum consumption was in 2020, the minimum in 2022.

In 2021, apixaban consumption decreased by 40.77% compared to 2020. In 2022, the downward trend in consumption continued: DDD decreased by another 32.25% compared to 2021.

The highest consumption of rivaroxaban was observed in 2020—26.59 DDD per case of COVID-19. In 2021, we found a decrease in consumption by 70.40% compared to 2020. In 2022, this trend continued and the DDD per patient of rivaroxaban decreased by 30.37% compared to 2021 (See Table 3).

Table 3. DDDs/a case of COVID-19 of apixaban and rivaroxaban in the Russian Federation (2020 to 2022).

Name of the Drug	DDD (WHO), mg	2020	2021	2022
Apixaban	10	26.59	15.75	10.67
Rivaroxaban	20	26.59	7.87	5.48

DDD—Defined Daily Dose.

The hypothetical number of people taking the CPG-recommended course of apixaban in 2020 (if we consider a 30-day course of therapy) exceeds the number of officially registered COVID-19 patients by 1.77 times. If we consider a 45-day course of therapy, the results practically coincide with the estimated number of COVID-19 cases in 2020 of 3,733,333 patients.

In 2021, the hypothetical number of people taking the CPG-recommended course of apixaban was 11,024,000, which was 4.75% more than the number of COVID-19 patients (if we consider a 30-day course of therapy). If we consider a 45-day course of therapy, the hypothetical number of people taking the CPG-recommended course of apixaban in 2021 was 30.0% less than the number of officially registered 10,499,982 cases.

In 2022, 71.13% of patients with coronavirus infection received at least one 30-day course of apixaban therapy; If we consider a 45-day course, then 47.42% of patients received at least one course of apixaban.

The hypothetical number of people taking the CPG-recommended course of rivaroxaban in 2020 (if we consider a 30-day course of therapy) exceeds the number of COVID-19 patients by 43.58%; if we consider a 45-day course of therapy, the results obtained practically coincide with the number of COVID-19 cases in 2020 and amount to 3,733,333.

In 2021, the hypothetical number of people taking the CPG-recommended course of rivaroxaban was 5,512,000, which is 47.50% less than the number of COVID-19 patients (if we consider a 30-day course of therapy). If we consider a 45-day course of therapy, then the hypothetical number of people taking the CPG-recommended course of rivaroxaban in 2021 was 65.00% less than the number of cases.

In 2022, there was a decrease in rivaroxaban consumption compared to 2021: 36.5% of COVID-19 patients received rivaroxaban in 2022 (30-day course) or 24.3% if we consider a 45-day course of therapy (See Table 4).

Table 4. Estimated number of people taking a CPG recommended course of apixaban and rivaroxaban in the Russian Federation in 2020–2022 based on the assumption that only COVID-19 patients were responsible for gross national consumption.

Name of the Drug	DDD (According to Russian Clinical Guidelines)	2020	2021	2022
Apixaban	15 DDD (30 days)	5,600,000	11,024,000	7,600,000
	22.5 DDD (45 days)	3,733,333	7,349,333	5,066,667
Rivaroxaban	15 DDD (30 days)	5,600,000	5,512,000	3,900,000
	22.5 DDD (45 days)	3,733,333	3,674,667	2,600,000

DDD—Defined Daily Dose.

The largest number of COVID-19 patients was registered in 2021–2022. The smallest number of patients was registered in 2020. At the same time, the highest consumption of apixaban was in 2021, the lowest in 2020, and the largest amount of rivaroxaban was consumed in the Russian Federation in 2020; subsequently its consumption decreased and the lowest consumption was noted in 2022.

The above-presented calculations mean that, in 2020, each patient with COVID received more than 1 course of therapy with apixaban (1.77 courses of apixaban therapy (30-day)) and rivaroxaban (1.77 courses of rivaroxaban therapy (30-day)), which indicates serious overuse of DOACs at the beginning of the pandemic.

In 2021, almost every patient with COVID-19 received apixaban, and every second patient was prescribed rivaroxaban.

In 2022, DOAC consumption decreased, every third patient took rivaroxaban, and about ¾ of all patients took apixaban (30-day course).

This shows a more rational and targeted use of DOACs in patients with COVID in the 3rd year of the pandemic, which may be the result of both the accumulated experience and the emergence of clear algorithms for the management of patients with coronavirus infection (the CPGs) (See Table 5).

Table 5. Number of people taking apixaban and rivaroxaban in the Russian Federation in 2020–2022 (15 DDD, 30 days) and (22.5 DDD, 45 days).

	2020	2021	2022
COVID-19 patients	3,159,297	10,499,982	10,684,204
30 days			
Total consumption of Rivaroxaban and Apixaban (patients)	11,200,000	16,536,000	11,500,000
45 days			
Total consumption of Rivaroxaban and Apixaban (patients)	7,466,666	11,023,999	7,666,667

2.1. Results of CPGs Assessment Domain Scores

The domain scores differed between CPGs. The domains Scope and Purpose, and Clarity of Presentation, consistently received high scores across all seven CPGs. The domains Applicability, Editorial Independence and Rigour of Development received lower scores.

The domain Scope and Purpose deals with the main objective of CPGs, the health question and the population to whom the guideline is meant to apply. This domain includes three items (items 1–3). The range of scores for Scope and Purpose was 67–100% (See Appendix H—Section assessment results SCOPE AND PURPOSE)

Most CPGs received high scores for this domain (89–100%), while one CPG received a lower score—67%. The CPG by the FAR [18] obtained the lowest score for this domain. We attributed it to the guidelines having a vague and not clearly defined objective. The CPGs by ROPNIZ [16] and MGNOT [20] score for Scope and Purposes. The population was clearly described and the purpose was well defined and worded here.

The domain Stakeholder Involvement is focused on assessing whether all relevant clinical professionals participated in the development of the CPG and whether the target audience who would use the CPG is specified. This domain includes three items (items 3–6). The range of scores was 31–67% (See Appendix H—Section assessment results STAKEHOLDER INVOLVEMENT). The CPG by NIIOZMM [19] received the lowest score (31%) and the CPG by ROPNIZ [16] received the highest score—67%.

We assigned a relatively low score (31%) to the NIIOZMM [19] for the domain Stakeholder Involvement as it did not include any specifications about the target audience. The experts pointed out that epidemiologists and medical statisticians should have been included in the development of the CPGs of NIIOZMM [19]

The ROPNIZ CPGs [16] received the highest score (67%) for the domain Stakeholder Involvement (See Appendix H—Section assessment results STAKEHOLDER INVOLVEMENT). The variety of specialists involved in the development of these guidelines was better than in all other identified CPGs. A similar score (65%) for this domain was received by the ROPNIZ CPGs [15] and MGNOT [20] (See Appendix H—Section assessment results STAKEHOLDER INVOLVEMENT). These three CPGs received similar comments.

The domain Rigour of Development deals with the actual methods used to compose the CPGs. It is the largest domain in the AGREE II and consists of eight items (items 7–14). The range of scores for this domain was 0–49% (See Appendix H—Section assessment results RIGOUR OF DEVELOPMENT). Rigour of Development had the largest variation between the highest and the lowest scores, as it is the biggest and arguably the most important domain in the AGREE II. The scores for all CPGs varied.

The lowest score for the domain Rigour of Development we attributed to the ROPNIZ [16] (See Appendix H—Section assessment results RIGOUR OF DEVELOPMENT).

This CPG lacked a procedure of evidence search, strengths and limitations of this evidence and most other items of this domain. The only item in Rigour of Development that received a score above 1 from all three author-experts was item 14, which deals with a procedure for updating the guideline, which is described in the guideline.

The highest score (49%) for the domain Rigour and Development was attributed to the ROPNIZ [15] CPG (Appendix H). Section assessment results RIGOUR OF DEVELOPMENT). Even though this CPG had a high score, there were comments for this domain: the ROPNIZ [15] CPG did not include the methods for formulating the recommendations and these aren't clearly described, and the opinion of external experts and the update procedure are not described. It did not include a method for reviewing the strengths and limitations of the evidence (such as GRADE), or a Delphi method for formulating the recommendations.

The fourth domain Clarity of Presentation consists of three items (items 15–17). Clarity of presentation is focused on the way the CPG is written, specifically its language, format, and structure. This domain consistently received a high score in each of the CPGs (96–100%) (See Appendix H—Section assessment results CLARITY OF PRESENTATION). All CPGs scored high (96–100%). The comments stated that the recommendations are clear and unambiguous (See Appendix H—Section assessment results CLARITY OF PRESENTATION).

The domain Applicability includes four items (items 18–21). Applicability mostly assesses the way that the CPG can be used in society, including crucial factors such as assessment of cost, barriers, and facilitators of implementation, as well as possible tactics for uptake of the recommendations. Overall, Applicability received a low score from

the experts throughout all studied CPGs (24–50%) (See Appendix H—Section assessment results APPLICABILITY).

The lowest score (24%) for the Applicability domain we attributed to the MGNOT [20]. There was not enough information about the implementation factors in the CPG. On the other hand, the ROPNIZ [15] and its assumption received the highest score for the domain Applicability (See Appendix H—Section assessment results APPLICABILITY).

The last domain in the AGREE II is called Editorial Independence and it consists of two items (items 22–23). This domain score reflects whether the authors of a CPG could have had any conflicts of interest in the matter of creating the CPG. This domain received the lowest ratings from all experts. The range of the scores was 0–50%.

The lowest score of 0% was obtained for the ROPNIZ [15]. CPG (See Appendix H—Section assessment results EDITORIAL INDEPENDENCE), because no information about the potential conflicts of interest of the CPG authors was provided.

The highest score was received in the CPG for the diagnosis and treatment of circulatory diseases in the context of the COVID-19 pandemic (both received 50%; see Appendix H—Section assessment results EDITORIAL INDEPENDENCE).

2.2. Total Sum of Assessment Scores

The overall calculation of the total sum of scores was performed for each of the CPGs. Their comparison can be viewed in Appendix H—TOTAL SUM OF ASSESSMENT. It was used to assess the overall quality of the CPGs. Overall, the highest score (65%) was received in the CPG for the outpatient medical care in patients with chronic diseases under dispensary supervision in the conditions of the COVID-19 pandemic. These were temporary guidelines, Version 2 (Appendix H, Table A5) and Guidelines for the diagnosis and treatment of circulatory diseases in the context of the COVID-19 pandemic. Only the domains Stakeholder Involvement and Editorial Independence received low scores.

The lowest total sum score was given to the CPG by NIIOZMM [19]. (43%; (See Appendix H—TOTAL SUM OF ASSESSMENT). In four domains the score was less than 50%.

The peculiarity of the analyzed clinical recommendations was as follows: that they were all written during the pandemic of the new coronavirus infection, which certainly affected the quality of the work. All clinical recommendations were issued as soon as possible, despite the lack of any evidence base. Their main goal was to develop an algorithm for the doctors' actions and improve the quality of care provided to patients with the new coronavirus infection.

2.3. Comparison with U.S. Data in Consumption and Sales of DOACs

We examined the available publicly data on the costs of sold rivaroxaban and apixaban in 2020, 2021 in the USA and noted the dynamics shown in [21,22].

3. Discussion

The high level of consumption of DOACs and the growing cost of drugs in this group is a significant burden on the country's economy, given the fact that the effectiveness and safety of the use of DOACs in patients with COVID-19 still requires more careful study.

In Russia and the USA, there is a tendency for the cost of consumption of apixaban and rivaroxaban to have increased in 2021 compared to 2022.

In the USA, the consumption costs in 2021 compared to 2020 year of rivaroxaban increased by 8%, and apixaban by 23%, accordingly [21,22].

In Russia, the consumption costs for rivaroxaban in 2021 compared to 2020 increased by 90%, and for apixaban by 186%, accordingly. The consumption costs for rivaroxaban in the year 2020 were USD 89 million, in 2021 USD 171 million, and for apixaban USD 28/81 million in 2020/2021, accordingly.

Thus, the cost of consumption of rivaroxaban in Russia exceeded that of the USA by more than 12 times, and apixaban by more than 2 times, in 2020, and in 2021 rivaroxaban consumption was higher by 23 times, and apixaban by 5 times.

It should be noted that the dynamics of changes in costs by country differ. Despite the higher cost of rivaroxaban and apixaban consumption in Russia compared to the USA, the share of gross consumption of apixaban in both countries is comparably higher than rivaroxaban. See Figure 1.

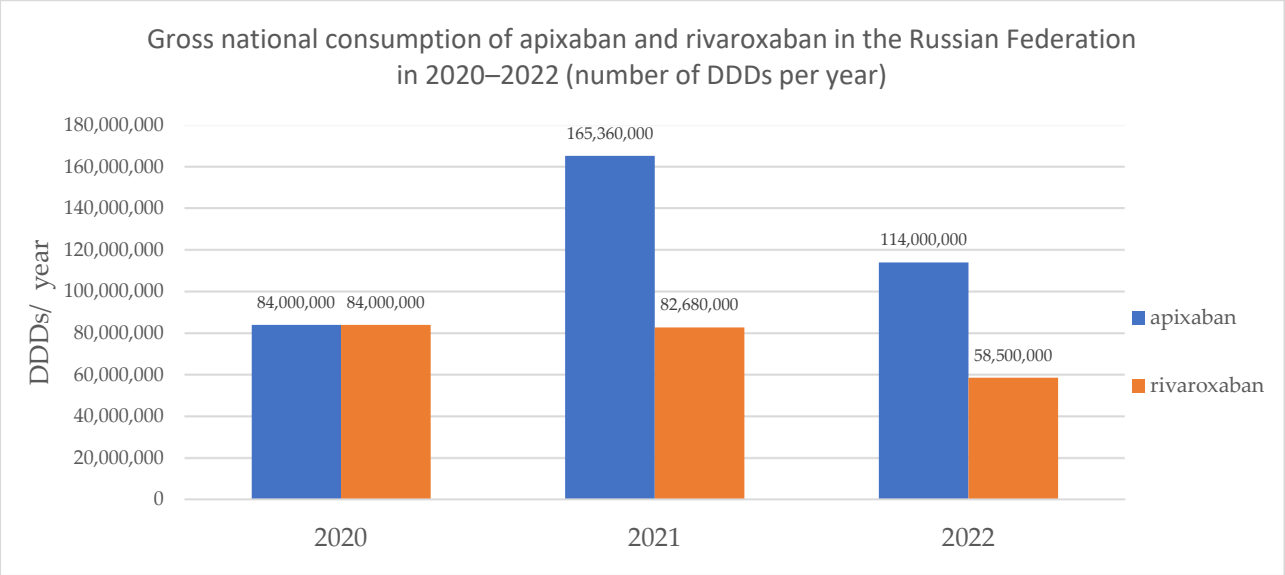

Figure 1. Gross national consumption of apixaban and rivaroxaban in the Russian Federation in 2020–2022 (number of DDDs per year).

The highest DDD consumption of DOACs was in 2020, which exceeded the DOACs recommended DDD by Russian clinical guidelines, which is probably due to polypragmasia.

The above-presented results mean that, in 2020, each patient with COVID-19 received more than one course of therapy with apixaban (1.77 courses of apixaban therapy (30-day)) and rivaroxaban (1.77 courses of rivaroxaban therapy (30-day)), which indicates a serious overdose of DOACs at the beginning of the pandemic. See Figure 2. Excessive prescribing and consumption of DOACs may have been dictated by the available data from a number of studies that established the benefits of treating patients with COVID-19 by DOACs for the prevention of deep vein thrombosis and pulmonary embolism compared to patients untreated with DOACs or receiving a placebo. At the same time, there was no significant difference in the effect of small and large doses of drugs on the risk of bleeding [4,5].

In 2020, there was a significant increase in demand for DOACs and apixaban consumption in our study was in the leading position what is comparable to the results of another study [22]. In 2021, when the highest gross national consumption of apixaban was noted, almost every patient with COVID-19 received apixaban, and every second patient was prescribed rivaroxaban, which is probably due to the growth of the disease and the advantage of the drug compared to rivaroxaban: higher efficiency in reducing the risk of secondary episodes of venous thrombosis and pulmonary embolism, better tolerability-lower risk of minor bleeding and a favorable price [23] See Figures 3 and 4.

Our results coincide with the data obtained in the study by Petrukhina I. et al. [23], where sales statistics were studied in the pharmacy market segment of the Samara region to assess the volume and structure of consumed cardiovascular and antithrombotic drugs during the COVID-19 pandemic, including DOACs. We can speculate that one of the reasons for the increased consumption of apixaban is due to its lower price compared to rivaroxaban.

We calculated the dynamics of the cost of one package of apixaban and rivaroxaban from 2020 to 2022. There was a trend towards an increase in the cost of DOACs, with the cost of one package of rivaroxaban exceeding the cost of apixaban. See Table 6.

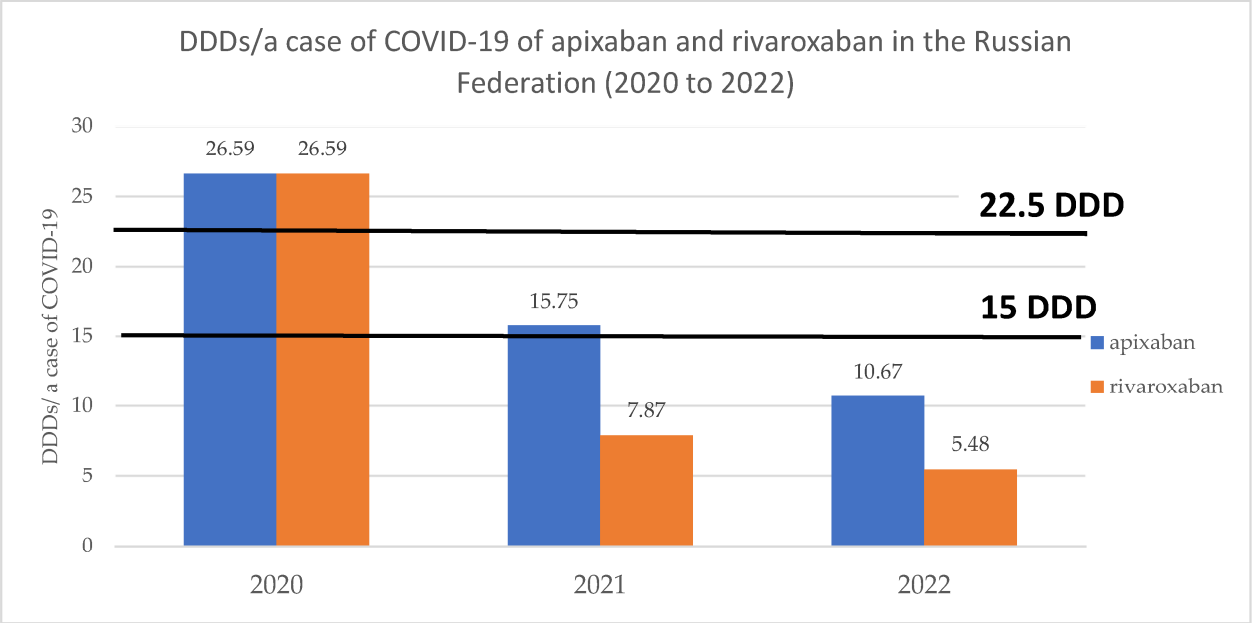

Figure 2. DDDs/a case of COVID-19 of apixaban and rivaroxaban in the Russian Federation (2020 to 2022).

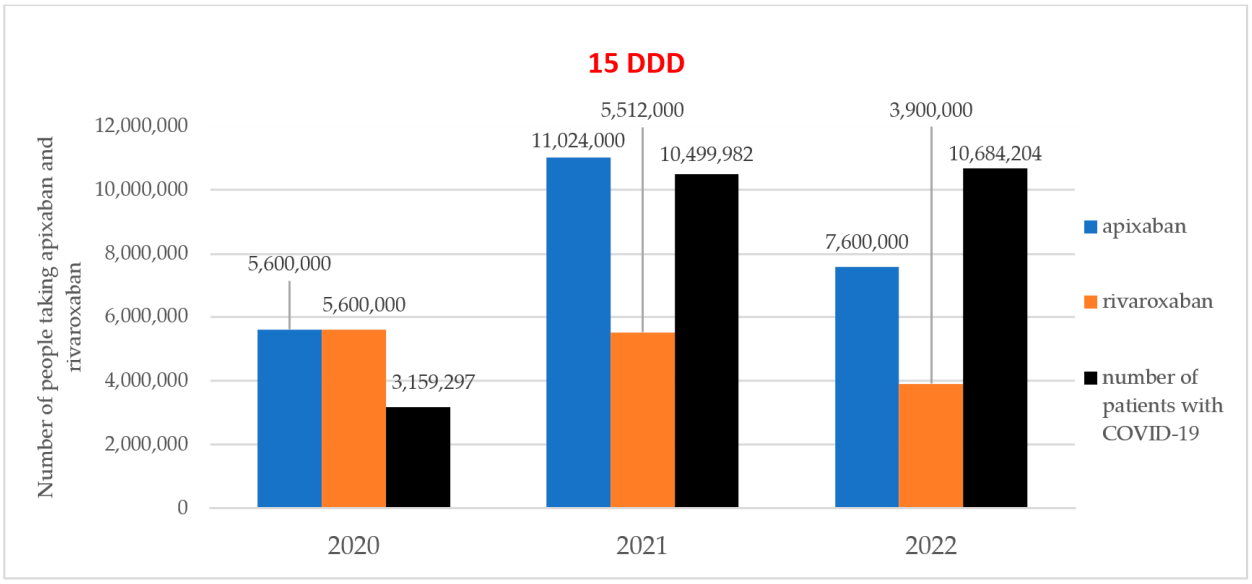

Figure 3. Number of people taking apixaban and rivaroxaban in the Russian Federation in 2020–2022 (15 DDD, 30 days).

Table 6. Dynamics of the cost of 1 DDD in the Russian Federation from 2020 to 2022 during the pandemic of a new coronavirus infection [24,25].

Name of Drug	2020	2021	2022
Apixaban	RUB 2,100,000,000:3,100,000 packages = RUB 677.42	RUB 6,000,000,000:11,024,000 packages = RUB 544.27	RUB 14,400,000,000:7,600,000 packages = RUB 1894.74
Rivaroxaban	RUB 6,600,000,000:3,100,000 packages = RUB 2129.03 (pharmacy market)	RUB 12,600,000,000:5,512,000 packages = RUB 2285.92 (pharmacy market)	16,200,000,000:3,900,000 packages = RUB 4153.85 (pharmacy market and government segment)

RUB—Russian Ruble.

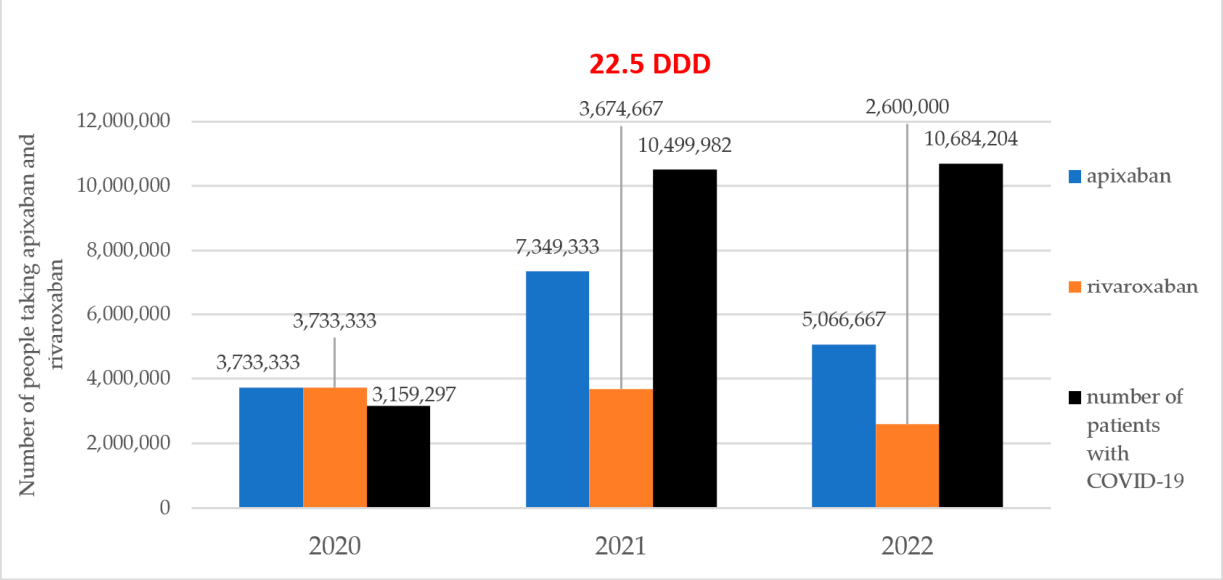

Figure 4. Number of people taking apixaban and rivaroxaban in the Russian Federation in 2020–2022 (22.5 DDD, 45 days).

We also believe that the increase in apixaban consumption is associated with the receipt of new information about the effectiveness and safety of the drug, which indicates the greater effectiveness and safety of apixaban compared to rivaroxaban.

For example, in this population-based cohort study, patients with VTE who were new users of apixaban had lower rates for recurrent VTE and bleeding than new users of rivaroxaban [26].

Also, in a systematic review and meta-analysis that examined the effectiveness and safety of apixaban in more than 3.9 million people with atrial fibrillation [27], apixaban was associated with a better overall safety and effectiveness profile compared to VKAs and other DOACs. Other studies have found similar results [28,29].

Currently, data on the effectiveness and safety of various drugs from the DOAC group in patients with COVID-19 are insufficient and contradictory, so this issue requires further study.

DOACs consumption had decreased by 2022 but every third patient took rivaroxaban, and about ¾ of all patients took apixaban (30-day course). The decrease in DOAC consumption occurred while maintaining a higher proportion of apixaban consumption during the coronavirus pandemic.

The dynamics of the decline in consumption of apixaban and rivaroxaban by 2022 may be a consequence of a more rational and targeted use of DOACs in patients with COVID-19 in the 3rd year of the pandemic, which may be the result of both the accumulated experience and the emergence of clear algorithms for the management of patients with coronavirus infection (the CPGs).

Clinical practice guidelines (guidelines or clinical practice guidelines) are systematically developed statements to assist existing regimens, practitioners, and patients on appropriate medical care in specific cases. The AGREE tool is a means of assessing the methodological rigor and transparency used in developing the guidelines.

We analyzed national guidelines using the AGREE II tool and obtained the following results.

Seven clinical guidelines were assessed. The quality of some CPGs really has to be questioned due to the complete lack of in-text citations. Only in two of the seven guidelines FAR 2020 [18]. and MGNOT 2021 [20] are references constantly cited throughout the text.

Each author reviewed the clinical guidelines using the AGREE II tool separately and independently. We did not compare each other's assessments. After each author rated the clinical guidelines and provided comments, we followed the same protocol described in

the Methods section to calculate item scores and total scores for each clinical guideline. We also created a summary table (see Appendix H) to easily visualize the differences in scores between clinical guidelines. We tried to analyze only the methodological quality of the guidelines and the possibility of their practical implementation in the Russian Federation, as provided for by the AGREE II tool.

When reviewing clinical guidelines, we found significant variability in the CPGs assessed. Each CPG differs in its structure, organization of content, use of evidence, etc. Two clinical guidelines (ROPNIZ-[15] and ROPNIZ-[16] were developed by a coalition of organizations, while all other guidelines were created by individual organizations and ministries. Interestingly, ROPNIZ-[15] and RSC 2020 [30] received the highest total score among the clinical guidelines studied (65%), and ROPNIZ 2021 [16] took fifth place in the overall rating of clinical recommendations, although the clinical recommendations of ROPNIZ [15] and ROPNIZ 2021 [16] were created by one group of organizations consisting of ROPNIZ and NIIOZMM [19]

One clinical guideline (Research Institute for Healthcare Organization and Medical Management of Moscow Healthcare Department 2021) has a low overall evaluation score.

We gave 0% points to three clinical guidelines [15,19,20] for the last domain "EDITORIAL INDEPENDENCE", as they did not indicate any funding or competing interests in the guideline text. Detailed scores for each domain can be found in the table in Appendix H.

In general, the authors' assessments differed slightly from each other. One of the reasons why the authors' answers were similar was that all the authors are specialists in the same field, pharmacology, so we may have the same points of view. The authors gave a low overall rating to certain clinical recommendations, but at the same time rated them 7 for overall quality (the last question of the AGREE II questionnaire, not used in calculating the total score). This may be explained by the fact that the authors took into account that the recommendations were created during a pandemic and were limited in information and time.

We do not know whether any of the developers of the clinical guidelines assessed in this study used AGREE II to develop their guidelines.

The low total scores we received when assessing Russian clinical guidelines can be explained by the fact that they were created during the COVID-19 pandemic, when there was still no clinical trial data and the time frame for creating guidelines was limited, since there was an urgent need to create algorithms for providing medical care to COVID-19 patients in order to simplify decision making by doctors.

Study Limitations

There were no data on adverse reactions associated with using DOACs in patients with COVID-19 in the Russian Federation. There was a limitation on pharmacoepidemiological and pharmacoeconomic indicators in patients with COVID-19 for the period 2020–2022. Only CPGs available online were analyzed. Institutional or any other CPGs were not analyzed.

Another limitation is that clinical guidelines for the treatment of COVID-19 were assessed by three appraisers, rather than four as recommended by the AGREE II guideline.

4. Materials and Methods

4.1. Design

It is a descriptive study. We used qualitative and quantitative methods. The study consisted of two parts: (1) analysis of DOAC consumption and expenditure at the all-Russia (National) level and (2) analysis of Russian CPGs, recommending DOAC use in COVID-19 patients.

4.2. DOAC Consumption and Expenditure (Pharmacoepidemiology of DOAC in Russia in the COVID-19 Pandemic)

We studied official data from open sources on medicine use and expenditure. We used data for the ATC class B01A, antithrombotic medicines. We used DDD values and guidelines of their use [31] to calculate national DOAC consumption. Aggregated data for

calculation of pharmacoepidemiological parameters and indicators of DOAC consumption in the Russian Federation 2020–2023 were obtained from the following information sources: annual reports by DSM Group and pharmaceutical sales in Russia by AlphaRM [24,25].

4.3. Consumption of Apixaban (Eliquis) in the Russian Federation, National Consumption: Example

(See Appendix A, Appendix F). We used sales data from these annual reports and calculated parameters of our interest. For example, the market share of rivaroxaban in 2021 was 0.1% in the pharmacy market in physical terms. Knowing the overall sales volume for Russia for 2021 (National), we calculated the sales volume of rivaroxaban (million packages) in 2021 using the published percentage of its market share:

5,512,000,000 packages × 0.001 = 5,512,000 packages of rivaroxaban sold in 2021

We calculated the total drug consumption per year in mg, as well as the amount of DDDs consumed. Total (National) drug consumption in mg = Dose per release form (package form in mg) × number of release forms per year.

The resulting value was used to calculate the number of DDDs consumed by patients: Number of DDDs consumed = Total drug consumption in mg/DDD in mg.

4.4. CPG Recommended Consumption

The recommended consumption of DOACs per one patient per one course of prophylactic treatment in patients with COVID was carried out in accordance with the data found in the Russian CPGs as follows:

1. Recommended doses of rivaroxaban, apixaban and dabigatran etexilate and the duration of the course of treatment were extracted from the text of each CPG;
2. These doses were multiplied by the duration of treatment;
3. Resultant dose was divided by DDD value.

Apixaban: 2.5 mg 2 times a day of 30 days = 150 mg; 150 mg: 10 (DDD) = 15 DDD—for one course of prophylactic treatment. Apixaban administration during 45 days leads to consumption of 22.5 DDD preparation: 2.5 mg 2 times a day of 450 days = 225 mg; 225 mg:10 (DDD) = 22.5 DDD—for one course of prophylactic treatment

Based on the results of these two series of calculations, the number of patients who completed at least 1 course of DOACs was determined by dividing the resulting national consumption in DDDs by the DDD equivalent of the CPG-recommended course of treatment/prophylaxis.

4.5. Consumption of Apixaban (Eliquis) in the Russian Federation for 2022 (January–August): Example

(See Appendix A, Appendix F).

1. Consumption of apixaban in the Russian Federation in 2022 was 7,600,000 packages [24,25]
2. 1 package of apixaban 2.5 mg contains 60 tablets; accordingly, 1 package contains 150 mg of apixaban.
3. Total amount of apixaban consumption in 2022 (in mg) = total number of packages consumed in 2022 in the Russian Federation × amount of apixaban in 1 package = 7,600,000 packages of apixaban × 150 mg = 1,140,000,000 mg
4. The number of DDDs of apixaban consumed in the Russian Federation in 2022 = 1,140,000,000 mg/ DDD (apixaban, mg) = 1,140,000,000/10 = 114,000,000 DDD of apixaban consumed in the Russian Federation in 2022.

Knowing the number of people with coronavirus infection in the period from 2020 to 2022, you can calculate the consumption of DOACs per person. Data on the number of cases of COVID-19 in the Russian Federation from 2020 to 2022 [25,32–34] are presented in Table 7.

Table 7. Population of the Russian Federation and the number of cases of COVID-19 in the period from 2020 to 2022.

Year	Population of the Russian Federation	Number of People with COVID-19 in the Russian Federation, People
2020	144,100,000 people	3,159,297 people
2021 October–November	143,400,000 people	10,499,982 people
2022 (1 January 2022)	146,980,000 people	10,684,204 people (10 January 2022)
2023 (1 January 2023)	146,447,000 people	4,718,854 people
Total		23,078,812 people (confirmed cases)

5. We analyzed DDDs/a case of COVID-19 of apixaban and rivaroxaban in the Russian Federation (2020 to 2022). (See Appendix B, Table A1).
6. We analyzed estimated number of people taking a CPG-recommended course of apixaban and rivaroxaban in the Russian Federation in 2020–2022 based on the assumption that only COVID-19 patients were responsible for gross national consumption. (See Appendix B, Table A1).

4.6. Eligibility Criteria for Inclusion of CPGs and Clinical Trials

We included Russian clinical practice guidelines (CPGs, the guidelines) for the treatment of new coronavirus infection with COVID-19 and Non-Infectious Diseases during the pandemic period which recommended use of new DOACs and Russian randomized clinical trials of COVID-19 patients with the use of DOACs. The guidelines and clinical trial reports had to be published between 2020 and 2023. The CPGs had to be written in the Russian language and to be intended for health care professionals and be freely available online.

4.7. Search Methods for Identification of CPGs and Clinical Trials

We searched for all guidelines that would meet our eligibility criteria regardless of their official standing (endorsement by either the Ministry of Health, or professional associations, or alternative health bodies or organizations. The guidelines could be endorsed, approved, or accepted for practical implementation, and published as draft consultations or documents in development). We searched for all randomized clinical trials of COVID-19 patients with the use of new oral anticoagulants.

We searched the following databases (See Appendix C):

- Official collection of clinical guidelines of the Ministry of Health (https://cr.minzdrav.gov.ru/; accessed on 1 September 2023);
- Russian Databases: eLIBRARY.RU (www.elibrary.ru; from 2020 to 2023; accessed on 1 September 2023);
- National Library of Medicine "(National Centre for Biotechnology Information, NCBI, https://pubmed.ncbi.nlm.nih.gov; from 2020 to 2023; accessed on 1 September 2023)";
- Google scholar "(https://scholar.google.ru; from 2020 to 2023; accessed on 1 September 2023)";
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov "(www.clinicaltrials.gov; from 2020 to 2023; accessed on 1 September 2023)";
- the Cochrane Library "(https://www.cochranelibrary.com; from 2020 to 2023; accessed on 1 September 2023)".

4.8. Description of the Databases and Websites Used for Search, Selection and Analysis of Clinical Practice Guidelines and Clinical Trials

1. The official collection of clinical practice guidelines of the Ministry of Health (MoH), named Rubricator

The Rubricator contains a searchable collection of guidelines, grouped according to the International Classification of Diseases 10 (ICD-10). With its first launch in October–November 2017 it established the system of National Clinical Guidelines. Rubricator operates in the Russian language only, and it allows for a simple search by a term, by a number of a CPG, by a year of publication, by the ICD position, and by official status (endorsed for implementation or approved, draft in development or outdated) with filters for adults and children.

2. eLIBRARY.RU

It is the open-access searchable Russian electronic database of scientific publications integrated with the Russian Scientific Citation Index (RSCI). It is the largest available database. The RSCI presents a tool for measuring publication activity both of individual researchers and of organizations; it is commissioned by the Ministry of Education and Science of the Russian Federation, and it is freely publicly available. The eLIBRARY.RU and RSCI were developed and are being supported by the Scientific Electronic Library Company. The detailed description of the eLIBRARY.RU platform is available elsewhere [35].

eLIBRARY.RU operates in Russian only; it contains publications in other languages, including English.

3. National Library of Medicine (National Centre for Biotechnology Information, NCBI, https://pubmed.ncbi.nlm.nih.gov); accessed on 1 September 2023.
4. Google scholar (https://scholar.google.ru); accessed on 1 September 2023.
5. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov); accessed on 1 September 2023.
6. The Cochrane Library (https://www.cochranelibrary.com) accessed on 1 September 2023.

We searched by the search terms of our research interest (COVID-19), and direct oral anticoagulants (DOAC) in above listed databases.

Search strategy.

We searched by the search terms of our research interest, COVID-19 and direct oral anticoagulants (DOAC) in above listed databases.

Search strategy for the following databases: PubMed.gov, Google scholar, Clinicaltrials.gov, Cochrane library and Official collection of clinical guidelines of the Ministry of Health search strategy was based on traditional Cochrane search method by combination of terms and Boolean operators OR and AND:

#1. "COVID-19" OR "SARS-CoV-2" OR "sars-cov-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR "coronavirus" OR "COV" AND

#2. "New" AND "mouth" OR "oral" AND "anticoagulants" OR "Anticoagulant Agent" OR "Anticoagulant Agents" OR "Anticoagulant Drug" OR "Anticoagulant Drugs" OR "Factor Xa Inhibitors" OR "Rivaroxaban" OR Xarelto" OR "rivaroxaban" OR "BAY 597939" OR "Apixaban" OR "Eliquis" OR "Edoxaban" OR "Savaysa" OR "Betrixaban" OR "Direct Thrombin Inhibitor" OR "Dabigatran Etexilate" OR "BIBR 1048" OR "Pradaxa" OR "Ximelagatran" AND Filter:

#3 #1 AND #2 AND

Russian language eLIBRARY.RU database search strategy was adapted taking into account its features based on the National Library of Medicine strategy. The time interval from 1 January 2020 to 1 September 2023 was taken as filter for all searched databases and "Russian Federation" was used as additional filter in Cochrane library and ClinicalTrials.gov databases. The detailed search strategies are presented in Appendix C.

The search strategies are presented in Appendix C.

Three review authors (EAB, EAK and MSC) independently examined titles and abstracts of records from the electronic searches and excluded those studies that were obviously irrelevant. Additionally, we used Microsoft Word auto-search and sorting program, EndNote's duplicate program, which allowed for duplicate removal. We analyzed the full texts of the remaining papers, and the same three review authors independently selected studies for inclusion based on the inclusion criteria. Disagreements were resolved by

discussion within the author team. We excluded articles that did not meet the inclusion criteria, providing reasons for their exclusion in the Appendix D, Table A2.

We used a PRISMA flow checklist to create the PRISMA diagrams for our literature searches (Checklist**)**. We conducted the searches in September 2023 (See Figure 5 and Appendix E).

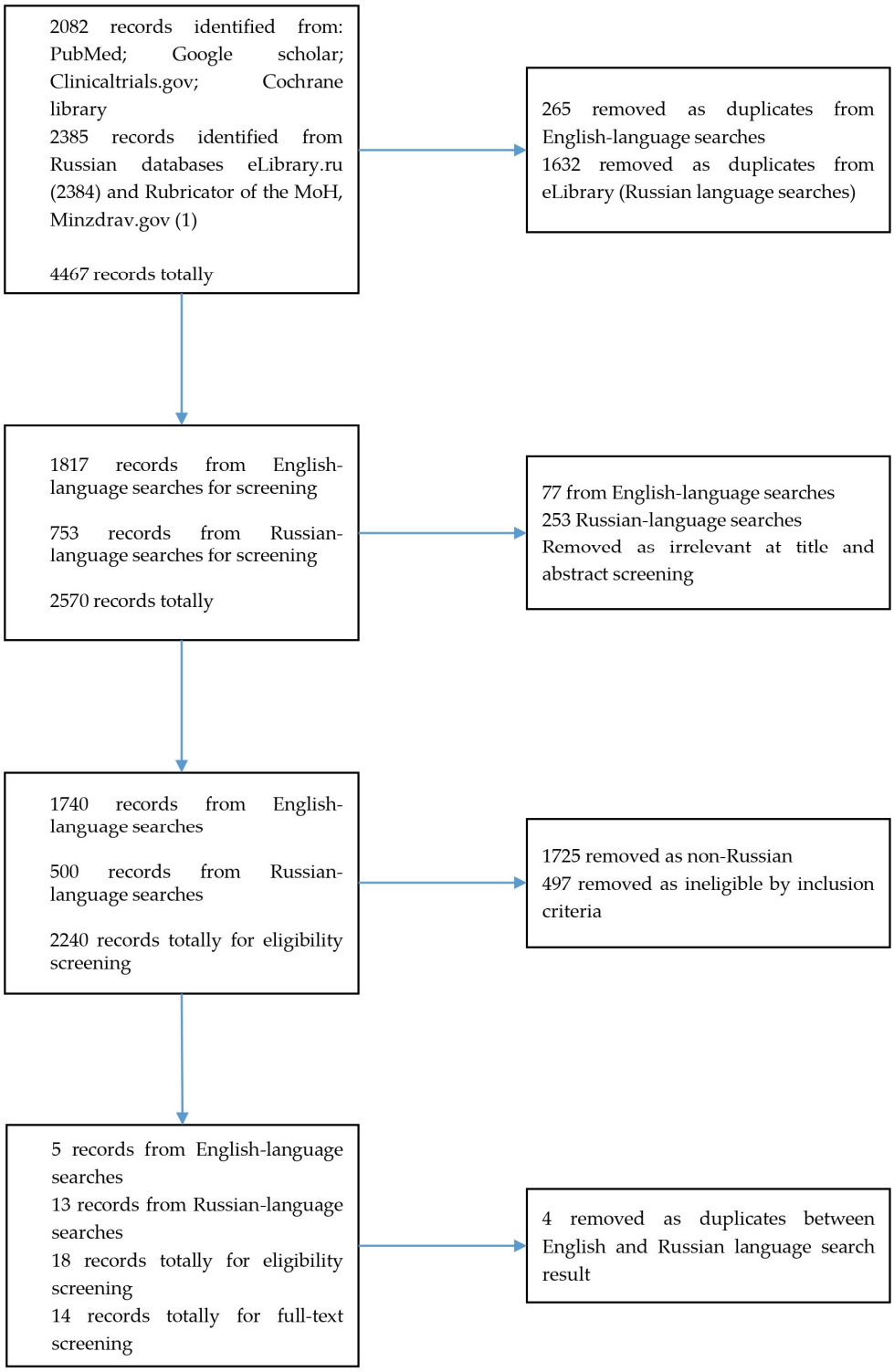

Figure 5. PRISMA flow diagram.

4.9. Results of the Searches

The initial searches yielded 2082 records from PubMed.gov, Google scholar, Clinicaltrials.gov, Cochrane library and 2384 from the Russian database eLibrary.ru and 1 record from the Minzdrav.gov collection of CPGs from 1 January 2020–1 September 2023. In total, we retrieved 4467 records.

After removing 1897 duplicates, a total of 2570 records were examined and 330 (77 foreign and 253 Russian) records were excluded as irrelevant, unrelated to the use of new anticoagulants in COVID-19.

The 2240 remaining records were screened after the title/abstract analysis, of which 1725 were removed as non-Russian and 497 records did not report our outcome of interest and were excluded as irrelevant by our inclusion criteria. The 5 foreign and 13 Russian remaining records were then screened for eligibility to be included in this review. Eighteen articles were included for having data of our interest. After quantitative evaluation of these articles in foreign and Russian databases, four common duplicates were excluded.

We searched 14 full-text articles included in the review by abstracts. Six records were removed after the qualitative assessment of these articles in foreign and Russian databases. The reasons for removing them were: two articles from the Russian database had the same information, so one of them was removed; five were irrelevant by our inclusion criteria: Tarlovskaya-2021, Kalinin-2023, Vorobyev-2020, Ruzhentsova-2021, and Krivoshchekov-2022.

Eight full-text articles were evaluated as meeting the inclusion criteria and were taken for further qualitative analysis. Articles included: one international clinical randomized trial conducted in Russia (Eikelboom J.W., Drapkina O.M.) [36] and seven Russian clinical guidelines for the management of COVID-19 patients with the use of direct oral anticoagulants (DOAC). The data are presented in Figure 5.

We report here on seven Russian clinical guidelines for the management of COVID-19 patients with the use of direct oral anticoagulants and one Russian clinical randomized trial running from 1 January 2020 to 1 September 2023, which met our inclusion criteria, and how we identified these trials. In eLibrary, we ran a series of searches by condition of interest (COVID-19) and direct oral anticoagulants (DOAC), which yielded finally six potential records of CPGs. In the Rubricator of the Ministry of Health of the Russian Federation we found one CPG which met our inclusion criteria (Table 8).

Table 8. Identified clinical practice guidelines to be assessed with AGREE II instrument.

Condition	Organization	Year	Organization Abbreviation with Expansion
COVID-19	Russian Society of Cardiology	2020	RSC 2020 (Shlyakhto E.V.) [30]
COVID-19	The All-Russia Public Organization «Federation of Anaesthesiologists and Reanimatologists»	2020	FAR 2020 (Zabolotskikh I.B.) [18]
COVID-19	Russian Society for the Prevention of Non-communicable Diseases	2021	ROPNIZ 2021(Drapkina O.M.) [15]
COVID-19	Russian Society for the Prevention of Non-communicable Diseases	2021	ROPNIZ 2021 (Livzan M.A.) [16]
COVID-19	Research Institute for Healthcare Organization and Medical Management of Moscow Healthcare Department	2021	NIIOZMM 2021 (Khripun A.I.) [19]
COVID-19	Moscow City Scientific Society of Physicians	2021	MGNOT 2021 (Vorobyev P.A.) [20]
COVID-19	Ministry of Health of the Russian Federation	2022	MoH 2022 [17]

Searches in PubMed.gov, Google scholar, Clinicaltrials.gov, and the Cochrane library databases, after the removal of duplicates, irrelevant records and ineligible studies through title/abstract screening and full text screening, identified only one Russian clinical randomized trial which was eligible to be included: Eikelboom 2022. It appeared to be an

open-label, factorial, randomized, multi-center [36] controlled trial, with one center in Russia led by Russian researcher Drapkina. We coded the study for the use in this project Drapkina-Eikelboom 2022 [36].

The identified CPGs are presented in Table 8 with the coding for them, which we use throughout the text.

4.10. CPG Assessment with AGREE II Instrument

The three experts of the team of authors independently performed the assessment with the AGREE II instrument.

The AGREE II is a questionnaire designed to assess the quality of health care guidelines and to be used as a tool to develop clinical practice guidelines.

AGREE II includes 23 questions in 6 different domains that address different aspects of guidelines. Those domains are Scope and Purpose (3 questions), Stakeholder Involvement (3 questions), Rigour of Development (8 questions), Clarity of Presentation (3 questions), Applicability (4 questions), and Editorial Independence (4 questions). For each question, the expert is asked to provide a numerical score between 1 and 7, 1 being the minimum score and 7 being the maximum score. Each question is presented as a statement and the experts should answer the questions based on how much they agree with the statement (1—strongly disagree, 7—strongly agree). Each CPG receives a raw score between 23 and 161 points from a single expert. It is recommended that at least two experts analyze the same guidelines using the AGREE II tool. Additionally, experts may leave comments for each question and state whether they would recommend the use of the guideline at the end of the questionnaire.

Next, the derived data was calculated by compiling the scores of all experts for each domain and scaling them as a percentage of a maximum possible score for that specific domain. That was done by using the formula (Equation (1)):

$$((\text{Obtained score} - \text{Minimum possible score})/(\text{Maximum possible score} - \text{Minimum possible score})) \times 100\% \quad (1)$$

Table 9 below provides a sample set of data for the Scope and Purpose domain for COVID-19 CPG by the Ministry of Health of the Russian Federation, in which we show sample calculations to illustrate how the AGREE II scoring was used in our study.

Table 9. Sample data set for the domain Scope and Purpose.

Scope and Purpose	EAB	EAK	MSC	Total (*n*)	Total (%)
	16	**21**	**21**	**58**	**90.7%**
The overall objective(s) of the guideline is (are) specifically described.	6	7	7	20	
The health question(s) covered by the guideline is (are) specifically described.	5	7	7	19	
The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	5	7	7	19	

The total obtained score is calculated by summing the individual scores of all experts (Equation (2)):

$$16 + 21 + 21 = 58 \quad (2)$$

The minimum possible score is calculated by attributing 1 to each question, as the minimum possible score is 1 for each question and multiplying it by the number of experts (Equation (3)):

$$(1 + 1 + 1) \times 3 = 9 \quad (3)$$

The maximum possible score is calculated by attributing 7 to each question, as the maximum possible score is 7 for each question and multiplying it by the number of experts (Equation (4)):

$$(7 + 7 + 7) \times 3 = 63 \quad (4)$$

The original formula is used to calculate the domain score (Equation (5)):

$$\text{((Obtained score} - \text{Minimum possible score)/(Maximum possible score} - \text{Minimum possible score))} \times 100\% = ((58 - 9)/(63 - 9)) \times 100 = 49/54 \times 100 = 0.907 \times 100 = 90.7\% \quad (5)$$

We performed this calculation in Microsoft Excel. We created a separate data sheet for each CPG and another sheet for the comparison of all guidelines. First, we created a table for each CPG with all 23 questions organized in the 6 domains. Each table included the data from three experts.

We added the scores for each question from the three experts. Next, we calculated minimum and maximum scores for each domain. Then, we calculated the difference between the maximum and the minimum score for each domain. We used the above formula to calculate a domain score for each domain and the total sum of assessment for each CPG.

Finally, we created a comparison table for all seven CPGs and made a bar graph to visualize the difference in the total sum of assessment between all the CPGs studied.

5. Conclusions

1. Analysis of seven clinical recommendations revealed that such sections of clinical recommendations as scope, purpose, and clarity of presentation had the highest degree of assessment in accordance with AGREE II. The lowest scores were given for the sections on stakeholder involvement, rigour of development, applicability, and editorial independence. When comparing the total score, it was found that two clinical guidelines received the highest scores—the Russian Society for the Prevention of Non-communicable Diseases (Livzan), and the Russian Society for the Prevention of Non-communicable Diseases (Drapkina). The minimum score was registered with the Research Institute for Healthcare Organization and Medical Management of Moscow Healthcare Department clinical guideline. No guideline received a total score of more than 70%.
2. During the pandemic, the highest DDD consumption of DOACs was in 2020, which exceeded the DOACs' recommended DDD by Russian clinical guidelines. DOAC consumption had decreased by 2022. There was a decrease in the consumption of rivaroxaban, with an increase in apixaban's share in the structure of DOAC consumption during the coronavirus pandemic.
3. Obtained data indicate that in 2021 the apixaban consumption in the Russian Federation corresponded to the recommended DDD in the national guidelines, which indicates the most correct use of apixaban according to Russian GPGs.

Author Contributions: Conceptualization, L.E.Z., S.K.Z. and E.A.B.; resources, L.E.Z. and S.K.Z.; data curation, L.E.Z. and E.A.B.; search of data sources—E.A.B., E.A.K. and M.S.C.; writing—original draft preparation, E.A.B., E.A.K. and M.S.C.; writing—review and editing, L.E.Z. and E.A.B.; supervision, S.K.Z. and L.E.Z. All authors have read and agreed to the published version of the manuscript.

Funding: This publication has been supported by the RUDN project No 0321040000. Sponsor: Peoples' Friendship University of Russia named after Patrice Lumumba.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Sources of information used in this review are listed in the References.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

AGREE II	Appraisal of Guidelines for REsearch & Evaluation
ATC	Anatomical Therapeutic Chemical code
CDSR	Cochrane Database of Systematic Reviews
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	COronaVIrus Disease 2019
CPG	clinical practice guidelines
DDD	Defined Daily Dose
DOAC	direct oral anticoagulants
DVT/PE	deep vein thrombosis/pulmonary embolism
FAR	The All-Russia Public Organization «Federation of Anaesthesiologists and Reanimatologists»
ICD-10	International Classification of Diseases 10
LMWH	Low molecular weight heparin
MGNOT (in Russian)	Moscow City Scientific Society of Physicians
MoH	Ministry of Health of the Russian Federation
NIIOZMM (in Russian)	Research Institute for Healthcare Organization and Medical Management of Moscow Healthcare Department
NOACs	new oral anticoagulants
PE	pulmonary embolism
PMC	Pubmed Central
ROPNIZ (in Russian)	Russian Society for the Prevention of Non-communicable Diseases
RSC	Russian Society of Cardiology
RSCI	Russian Scientific Citation Index
VTE	venous thromboembolism
WHO	World health organization

Appendix A. Consumption of Apixaban (Eliquis) and Rivaroxaban (Xarelto) in the Russian Federation for 2020–2022

Consumption of apixaban (Eliquis) in the Russian Federation for 2022 (January–August)

1. Consumption of apixaban in the Russian Federation in 2022—7,600,000 packages
2. 1 package of apixaban 2.5 mg contains 60 tablets; accordingly, 1 package contains 150 mg of apixaban.
3. Total amount of apixaban consumption in 2022 (in mg) = total number of packages consumed in 2022 in the Russian Federation × amount of apixaban in 1 package = 7,600,000 packages of apixaban × 150 mg = 1,140,000,000 mg
4. The amount of DDD of apixaban consumed in the Russian Federation in 2022 = 1,140,000,000 million mg/DDD (apixaban, mg) = 1,140,000,000/10 = 114,000,000 DDD of apixaban consumed in the Russian Federation in 2022

Consumption of apixaban (Eliquis) in the Russian Federation for 2021

1. Consumption of apixaban in the Russian Federation in 2021—11,024,000 packages
2. 1 package of apixaban 2.5 mg contains 60 tablets; accordingly, 1 package contains 150 mg of apixaban.
3. Total amount of apixaban consumed in 2021 (in mg) = total number of packages consumed in 2021 in the Russian Federation × amount of apixaban in 1 package = 11,024,000 packages of apixaban × 150 mg = 1,653,600,000 mg
4. The amount of DDD of apixaban consumed in the Russian Federation in 2021 = 1,653,600,000 million mg/ DDD (apixaban, mg) = 1,653,600,000/10 = 165,360,000 DDD of apixaban consumed in the Russian Federation in 2021.

Consumption of apixaban (Eliquis) in the Russian Federation for 2020

1. Consumption of apixaban in the Russian Federation in January–July 2020—3,100,000 packages Consumption of apixaban in the Russian Federation in 2020—5,600,000 packages

2. 1 package of apixaban 2.5 mg contains 60 tablets; accordingly, 1 package contains 150 mg of apixaban.
3. Total amount of apixaban consumed in 2020 (in mg) = total number of packages consumed in January–July 2020 in the Russian Federation × amount of apixaban in 1 package = 3,100,000 packages of apixaban × 150 mg = 465,000,000 mg

Total amount of apixaban consumed in 2020 (in mg) = total number of packages consumed in 2020 in the Russian Federation × amount of apixaban in 1 package = 5,600,000 packages of apixaban × 150 mg = 840,000,000 mg

4. The amount of DDD of apixaban consumed in the Russian Federation in January–July 2020 = 465 million mg/DDD (apixaban, mg) = 465,000,000/10 = 46,500,000 DDD of apixaban consumed in the Russian Federation in January–July 2020.

The amount of DDD of apixaban consumed in the Russian Federation in 2020 = 840 million mg/DDD (apixaban, mg) = 840,000,000/10 = 84,000,000 DDD of apixaban consumed in the Russian Federation in 2020.

Consumption of rivaroxaban (Xarelto) in the Russian Federation for 2022 (January–August)

1. Consumption of rivaroxaban in the Russian Federation in 2022—3,900,000 packages.
2. 1 package of rivaroxaban 10 mg contains 30 tablets; accordingly, 1 package contains 300 mg of rivaroxaban.
3. Total amount of rivaroxaban consumption in 2022 (in mg) = total number of packages consumed in 2022 in the Russian Federation × amount of rivaroxaban in 1 package = 3,900,000 packages of rivaroxaban × 300 mg = 1,170,000 000 mg
4. The amount of DDD of rivaroxaban consumed in the Russian Federation in 2022 = 1,170,000,000 mg/DDD (rivaroxaban, mg) = 1,170,000,000/20 = 58,500,000 DDD of rivaroxaban consumed in the Russian Federation in 2022.

Consumption of rivaroxaban (Xarelto) in the Russian Federation for 2021

1. Consumption of rivaroxaban in the Russian Federation in 2021—5,512,000 packages.
2. 1 package of rivaroxaban 10 mg contains 30 tablets; accordingly, 1 package contains 300 mg of rivaroxaban.
3. Total amount of rivaroxaban consumption in 2021 (in mg) = total number of packages consumed in 2021 in the Russian Federation × amount of rivaroxaban in 1 package = 5,512,000 packages of rivaroxaban × 300 mg = 1,653,600,000 mg
4. The amount of DDD of rivaroxaban consumed in the Russian Federation in 2021 = 1,653,600,000 million mg/DDD (rivaroxaban, mg) = 1,653,600,000/20 = 82,680,000 DDD of rivaroxaban consumed in the Russian Federation in 2021.

Consumption of rivaroxaban (Xarelto) in the Russian Federation for 2020

1. Consumption of rivaroxaban in the Russian Federation in January–July 2020—3,100,000 packages.
2. Consumption of rivaroxaban in the Russian Federation in 2020—5,600,000 million packages.
3. 1 package of rivaroxaban 10 mg contains 30 tablets; accordingly, 1 package contains 300 mg of rivaroxaban.

Total amount of rivaroxaban consumed in January–July 2020 (in mg) = total number of packages consumed in 2020 in the Russian Federation × amount of rivaroxaban in 1 package = 3,100,000 packages of rivaroxaban × 300 mg = 930,000,000 mg

Total amount of rivaroxaban consumed in 2020 (in mg) = total number of packages consumed in 2020 in the Russian Federation × amount of rivaroxaban in 1 package = 5,600,000 million packages of rivaroxaban × 300 mg = 1,680,000,000 mg

4. The amount of DDD of rivaroxaban consumed in the Russian Federation in January–July 2020 = 930,000,000 mg/DDD (rivaroxaban, mg) = 930,000,000/20 = 46,500,000 DDD of rivaroxaban consumed in the Russian Federation in January–July 2020.

The amount of DDD of rivaroxaban consumed in the Russian Federation in 2020 = 1,680,000,000 mg/DDD (rivaroxaban, mg) = 1,680,000 000/20 = 84,000,000 DDD of rivaroxaban consumed in the Russian Federation in 2020.

Appendix B. DDDs/a Case of COVID-19 of Apixaban and Rivaroxaban in the Russian Federation (2020 to 2022) and Estimated Number of People Taking a CPG-Recommended Course of Apixaban and Rivaroxaban in the Russian Federation in 2020–2022 Based on the Assumption That Only COVID-19 Patients Were Responsible for Gross National Consumption

Table A1. DDDs/a case of COVID-19 of apixaban and rivaroxaban in the Russian Federation (2020 to 2022).

Name of the Drug	DDD (WHO), mg	2020	2021	2022
Apixaban	10	84,000,000 DDD: 3,159,297 = 26.59	165,360,000 DDD: 10,499,982 = 15.75	114,000,000 DDD: 10,684,204 = 10.67
Rivaroxaban	20	84,000,000 DDD: 3,159,297 = 26.59	82,680,000 DDD: 10,499,982 = 7.87	58,500,000 DDD: 10,684,204 = 5.48

DDD—Defined Daily Dose.

Table: Estimated number of people taking a CPG-recommended course of apixaban and rivaroxaban in the Russian Federation in 2020–2022 based on the assumption that only COVID-19 patients were responsible for gross national consumption.

Appendix C. Search Strategy for the following Databases: PubMed.gov, Google Scholar, Clinicaltrials.gov, Cochrane Library, eLIBRARY

Search strategy for the following databases: PubMed.gov, Google scholar, Clinicaltrials.gov, Cochrane library was based on traditional Cochrane search method by combination of terms and Boolean operators OR and AND:

National Library of Medicine (PubMed) search strategy

#1. "COVID-19" OR "SARS-CoV-2" OR "sars-cov-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR "coronavirus" OR "COV" AND Filter: from 1 January 2020–1 September 2023.

#2. "New" AND "mouth" OR "oral" AND "anticoagulants" OR "Anticoagulant Agent" OR "Anticoagulant Agents" OR "Anticoagulant Drug" OR "Anticoagulant Drugs" OR "Factor Xa Inhibitors" OR "Rivaroxaban" OR "Xarelto" OR "rivaroxaban" OR "BAY 597939" OR "Apixaban" OR "Eliquis" OR "Edoxaban" OR "Savaysa" OR "Betrixaban" OR "Direct Thrombin Inhibitor" OR "Dabigatran Etexilate" OR "BIBR 1048" OR "Pradaxa" OR "Ximelagatran" AND Filter: from 1 January 2020–1 September 2023.

#3 #1 AND #2 AND Filter: from 1 January 2020–1 September 2023; Explode systematic reviews and randomized clinical trials/

Google scholar search strategy

#1. "COVID-19" OR "SARS-CoV-2" OR "sars-cov-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR "coronavirus" OR "COV" AND Filter: from 1 January 2020–1 September 2023.

#2. "New" AND "mouth" OR "oral" AND "anticoagulants" OR "Anticoagulant Agent" OR "Anticoagulant Agents" OR "Anticoagulant Drug" OR "Anticoagulant Drugs" OR "Factor Xa Inhibitors" OR "Rivaroxaban" OR "Xarelto" OR "rivaroxaban" OR "BAY 597939" OR "Apixaban" OR "Eliquis" OR "Edoxaban" OR "Savaysa" OR "Betrixaban" OR "Direct Thrombin Inhibitor" OR "Dabigatran Etexilate" OR "BIBR 1048" OR "Pradaxa" OR "Ximelagatran" AND Filter: from 1 January 2020–1 September 2023.

#3 #1 AND #2 AND Filter: Custom date range 2020 to 2023;
due to technical limitations, 998 records were studied.

Clinicaltrials.gov search strategy

#1. "COVID-19" OR "SARS-CoV-2" OR "sars-cov-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR "coronavirus" OR "COV".

#2. "New" AND "mouth" OR "oral" AND "anticoagulants" OR "Anticoagulant Agent" OR "Anticoagulant Agents" OR "Anticoagulant Drug" OR "Anticoagulant Drugs" OR "Factor Xa Inhibitors" OR "Rivaroxaban" OR "Xarelto" OR "rivaroxaban" OR "BAY 597939" OR "Apixaban" OR "Eliquis" OR "Edoxaban" OR "Savaysa" OR "Betrixaban" OR "Direct Thrombin Inhibitor" OR "Dabigatran Etexilate" OR "BIBR 1048" OR "Pradaxa" OR "Ximelagatran" AND Filter: from 1 January 2020– 1 September 2023.

#3 #1 AND #2 AND Filter: Russian Federation.

Cochrane library search strategy

#1. "COVID-19" OR "SARS-CoV-2" OR "sars-cov-2" OR "Severe Acute Respiratory Syndrome Coronavirus 2" OR "NCOV" OR "2019 NCOV" OR "coronavirus" OR "COV".

#2. "New" AND "mouth" OR "oral" AND "anticoagulants" OR "Anticoagulant Agent" OR "Anticoagulant Agents" OR "Anticoagulant Drug" OR "Anticoagulant Drugs" OR "Factor Xa Inhibitors" OR "Rivaroxaban" OR "Xarelto" OR "rivaroxaban" OR "BAY 597939" OR "Apixaban" OR "Eliquis" OR "Edoxaban" OR "Savaysa" OR "Betrixaban" OR "Direct Thrombin Inhibitor" OR "Dabigatran Etexilate" OR "BIBR 1048" OR "Pradaxa" OR "Ximelagatran" AND Filter: from 1 January 2020– 1 September 2023.

#3 #1 AND #2 AND Filter: Russian Federation.

Official collection of clinical guidelines of the Ministry of Health search strategy

#1. "SARS-CoV-2" OR "COVID-19" OR "new coronavirus infection".

#2. "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "lixiana" OR "betrixaban" OR "direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran".

#3 #1 AND #2. AND Filter: September 2023; Explode Clinical Practice Guidelines.

eLIBRARY search strategy

is based on specific search functions of the database.

Limitations: the system does not visualize a list of records over 10,000 either in search or in collections.

Because of the large number of publications devoted to COVID-19, we have broken down the search by years: 2020, 2021, 2022, 2023; and repeated the search every year.

These include:

1. search by term morphology, which means that the search is performed by a root of a word typed in the search box as a full word
2. search by combination of terms works as Boolean operator OR;
3. search within results of the previous search works as Boolean operator AND;
4. combining searches works in the automated way and removes duplicates.

In traditional search description our searches in eLIBRARY could be described as follows:

#1. "SARS-CoV-2" OR "COVID-19" OR "new coronavirus infection"

#2. "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "lixiana" OR "betrixaban" OR "direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran"

#3. #1 AND #2 Filter: 2020 or Filter: 2021 or Filter: 2022 or Filter: 2023

#4. "SARS-CoV-2" AND Filter: 2020

#5. "SARS-CoV-2" AND "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "lixiana" OR "betrixaban" OR "direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran" AND Filter: 2020

#6. "SARS-CoV-2" AND Filter: 2021

#7. "SARS-CoV-2" AND "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR

"lixiana" OR "betrixaban" OR "direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran" AND Filter: 2020 #7. "SARS-CoV-2" AND "factor Xa inhibitor" AND Filter: 2021

#8. "SARS-CoV-2" AND Filter: 2022

#9. "SARS-CoV-2" AND "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "lixiana" OR "betrixaban" OR "direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran" AND Filter: 2020 #7. "SARS-CoV-2" AND "factor Xa inhibitor" AND Filter: 2021#9. "SARS-CoV-2" AND "Xarelto" AND Filter: 2022

#10. "SARS-CoV-2" AND Filter: 2023

"SARS-CoV-2" AND "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "lixiana" OR "betrixaban" OR "direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran" AND Filter: 2020 #7. "SARS-CoV-2" AND "factor Xa inhibitor" AND Filter: 2023

#11. "COVID-19" AND Filter: 2020

#12. "COVID-19" AND "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "lixiana" OR "betrixaban" OR "direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran" AND Filter: 2020 #7. "SARS-CoV-2" AND "factor Xa inhibitor" AND Filter: 2021#9. "SARS-CoV-2" AND "Xarelto" AND Filter: 2020

#13. "COVID-19" AND Filter: 2021

#14. "COVID-19" AND "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "lixiana" OR "betrixaban" OR "direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran" AND Filter: 2020 #7. "SARS-CoV-2" AND "factor Xa inhibitor" AND Filter: 2021#9. "SARS-CoV-2" AND "Xarelto" AND Filter: 2021

#15. "COVID-19" AND Filter: 2022

#16. "COVID-19" AND "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "lixiana" OR "betrixaban" OR "direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran" AND Filter: 2020 #7. "SARS-CoV-2" AND "factor Xa inhibitor" AND Filter: 2021#9. "SARS-CoV-2" AND "Xarelto" AND Filter: 2022

#17. "COVID-19" AND Filter: 2023

#18. "COVID-19" AND "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "lixiana" OR "betrixaban" OR

"direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran" AND Filter: 2020 #7. "SARS-CoV-2" AND "factor Xa inhibitor" AND Filter: 2021#9. "SARS-CoV-2" AND "Xarelto" AND Filter: 2023

#19. "new coronavirus infection" AND Filter: 2020

#13. "new coronavirus infection" AND "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "lixiana" OR "betrixaban" OR "direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran" AND Filter: 2020 #7. "SARS-CoV-2" AND "factor Xa inhibitor" AND Filter: 2021#9. "SARS-CoV-2" AND "Xarelto" AND Filter: 2020

#14. "new coronavirus infection" AND Filter: 2021

#15. "new coronavirus infection" AND "New oral anticoagulants" OR "NOAC" OR "direct* factor Xa inhibitor" OR "rivaroxaban" OR "Xarelto" OR "apixaban" OR "Eliquis" OR "edoxaban" OR "lixiana" OR "betrixaban" OR "direct* thrombin inhibitor" OR "dabigatran" OR "Pradaxa" OR "ximelagatran" AND Filter: 2020 #7. "SARS-CoV-2" AND "factor Xa inhibitor" AND Filter: 2021

#16. "new coronavirus infection" AND Filter: 2022

#17. “new coronavirus infection” AND “New oral anticoagulants” OR “NOAC” OR “direct* factor Xa inhibitor” OR “rivaroxaban” OR “Xarelto” OR “apixaban” OR “Eliquis” OR “edoxaban” OR “lixiana” OR “betrixaban” OR “direct* thrombin inhibitor” OR “dabigatran” OR “Pradaxa” OR “ximelagatran” AND Filter: 2020 #7. “SARS-CoV-2” AND “factor Xa inhibitor” AND Filter: 2022

#18. “new coronavirus infection” AND Filter: 2023

#19. “new coronavirus infection” AND “New oral anticoagulants” OR “NOAC” OR “direct* factor Xa inhibitor” OR “rivaroxaban” OR “Xarelto” OR “apixaban” OR “Eliquis” OR “edoxaban” OR “lixiana” OR “betrixaban” OR “direct* thrombin inhibitor” OR “dabigatran” OR “Pradaxa” OR “ximelagatran” AND Filter: 2020 #7. “SARS-CoV-2”AND “factor Xa inhibitor” AND Filter: 2023

Appendix D

Table A2. Reasons for Exclusion.

	Reference	Reason
Journal paper 1 from eLIBRARY search 2021	Tarlovskaya E.I., Arutyunov A.G., Konradi A.O., et al. Analysis of influence of background therapy for comorbidities in the period before infection on the risk of the lethal COVID outcome. Data from the international ACTIV SARS-CoV-2 registry («Analysis of chronic non-infectious diseases dynamics after COVID-19 infection in adult patients SARS-CoV-2»). Kardiologiia. 2021;61(9):20-32. (In Russ.) https://doi.org/10.18087/cardio.2021.9.n1680 [37]	non-randomized clinical trial
Journal paper 2 from eLIBRARY search 2023	Kalinin RE, Suchkov IA, Agapov AB, Mzhavanadze ND, Povarov VO, Nikiforov AA. Analysis of Risk Factors of Venous Thromboembolic Complications and of Different Variants of Anticoagulant Therapy in Patients with New Coronavirus Infection. I. P. Pavlov Russian Medical Biological Herald. 2023;31(2):243–250. DOI: https://doi.org/10.17816/PAVLOVJ110956 [38]	non-randomized clinical trial
Journal paper 3 from eLIBRARY search 2020	Vorobyev P.A., Momot A.P., Krasnova L.S., et al. Pathogenesis, diagnosis, prevention and treatment of disseminated intra-vascular coagulation syndrome in COVID-19 infection. Therapeutic Archive. 2020; 92 (11): 51–56. DOI: 10.26442/00403660.2020.11.000887 [39]	non-randomized clinical trial
Journal paper 4 from eLIBRARY search 2021	Ruzhentsova T.A., Khavkina D.A., Chukhliaev P.V., Garbuzov A.A., Ploskireva A.A. Effect of anticoagulant therapy on the course of COVID-19 in comorbid patients. Problems of Virology (Voprosy Virusologii). 2021; 66(1): 40-46 (In Russ.). DOI: https://doi.org/10.36233/0507-4088-14 [40]	non-randomized clinical trial
Journal paper 5 from eLIBRARY search 2022	Krivoshchekov E.P., Poseryaev A.V., Romanov V.E., Elshin E.B. Treatment of varicothrombophlebitis in patients who have been new coronavirus infection COVID-19. Bulletin of the Medical Institute “REAVIZ”. Rehabilitation, Doctor and Health. 2022;12(2):5-13. https://doi.org/10.20340/vmi-rvz.2022.2.COVID.1 [41]	non-randomized clinical trial
Journal paper 6 from eLIBRARY search 2022	Krivoshchekov E.P., Kazantsev A.V., Poseryaev A.V. Optimization of therapy for varicothrombophlebitis in patients who have experienced a new coronavirus infection COVID-19. Theses of reports of the XIV Scientific-Practical Conference of the Association of Phlebologists of Russia, Kazan, May 26-29, 2022. Flebologiya. 2022;16(2-2):5-62. (In Russ.) https://doi.org/10.17116/flebo2022160225 [42]	non-randomized clinical trial and repeat of content

Appendix E. PRISMA-Checklist

Section/Topic	#	Checklist Item	Location(s) Reported
Information Sources and Methods			
Database name	1	Name each individual database searched, stating the platform for each.	Appendix C, page 6, 28–30
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	Appendix C, 28–30
Study registries	3	List any study registries searched.	Appendix C, page 28–30
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	Page 6–7
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	n/a
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	n/a
Other methods	7	Describe any additional information sources or search methods used.	n/a
Search Strategies			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	Appendix C,page 28–30
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	Appendix C, page 6–7, 28–30
Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	n/a
Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	n/a
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	n/a
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	1 September 2023
Peer Review			
Peer review	14	Describe any search peer review process.	n/a
Managing Records			
Total Records	15	Document the total number of records identified from each database and other information sources.	On request
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	Page 7

Appendix F

Table A3. Sales Data and Expenditures for National DOAC Consumption Calculations in 2020–2023.

Name of the Drug, Group	Year	Purchases (Expenditure is Billion Rubles (RUB))	Procurement (Packaging)
Total market size	2020	RUB 2,041,000,000	3,000,000,000 (January–July)—pharmacy sales [24] 5,600,000,000 packages (pharmacy sales in 2020) [24]
	2021	RUB 2,299,370,000 [25]	5,512,000,000 packages [25]
	2022	RUB 2,573,000,000 [25]	5,200,000,000 packages [25]

Table A3. *Cont.*

Name of the Drug, Group	Year	Purchases (Expenditure is Billion Rubles (RUB))	Procurement (Packaging)
	2020	RUB 6,600,000,000 (1.2% share of the pharmacy market in value terms) [24] RUB 1151 billion (pharmacy market in 2020) [24]	0.1% share of the pharmacy market in physical terms 3,100,000 packages [24] 3,100,000,000 × 0.001 = 3,100,000 (January–July) 5,600,000,000 packages (pharmacy sales in 2020) × 0.001 = 5,600,000 packages
	2021	RUB 12,600,000,000 (1.4% share of the pharmacy market in value terms) [24]	0.1% share of the pharmacy market in physical terms 5,512,000 packages [24]
	2022 (January–August)	RUB 6,500,000,000 (state segment) + 9.5 (pharmacies) = 16 billion rubles RUB 16.2 billion [25]	1.3 (government segment) + 2.6 (pharmacies) = 3,900,000 packages [25]
Apixaban	2020	RUB 2,100,000,000	0.1% share of the pharmacy market in physical terms 3,100,000 packages (January–July) [24] 5,600,000,000 packages (pharmacy sales for 2020) × 0.001 = 5.6 million packages [24]
	2021	RUB 6,000,000,000	0.2% share of the pharmacy market in physical terms 11,024,000 packages [24]
	January–August 2022	RUB 2,500,000,000 (government segment) + 9.8 (pharmacies) = 12.3 RUB 14,400,000,000 [25]	1,900,000 packages (government segment) + 5.7 (pharmacies) = 7,600,000 packages (January–August) [25]
Dabigatran	2020	ND	ND
	2021	ND	ND
	January–August 2022	ND	ND
[B] Drugs affecting hematopoiesis and blood Level I ATS groups	2020	ND	ND
	2021	ND	+6.6% compared to 2020 [24]
	2022	RUB 76,600,000,000 [25] RUB 63,300,000,000 (hospital purchases) [25]	150,700,000 packages [25] 6.24%—the group's share in physical volume [25] 129,400,000 packages (hospital purchases) [25]

Appendix G

Table A4. Indications and Dosage Regimen of DOACs Therapy in Patients with COVID-19.

Name of Clinical Recommendation	Name of the Drug	Indications	Recommended Dose	Duration of Use	Comments (Prophylactic Course)
MoH 2022	Rivaroxaban	Prevention of deep vein thrombosis of the lower extremities and pulmonary embolism	10 mg once daily	Duration of use of anticoagulants in outpatient treatment of COVID-19 may be continued up to 30–45 days depending on the dynamics of the patient's clinical condition and timing of recovery of motor activity.	Rivaroxaban (per os) 10 mg × 1 time a day × 30 days = 300 mg for one course of prevention 300 mg:20 mg (DDD) = 15 DDD for one course of prevention 10 mg × 1 time a day × 45 days = 450 mg for one course of prevention 450 mg:20 mg (DDD) = 22.5 DDD for one course of prevention
	Apixaban		2.5 mg twice daily		Apixaban (per os) 2.5 mg × 2 times a day × 30 days = 150 mg for one course of prevention; 150 mg:10 (DDD) = 15 DDD for one course of prevention 2.5 mg × 2 times a day ×45 days = 225 mg for one course of prevention; 225 mg:10 (DDD) = 22.5 DDD for one course of prevention
	Dabigatran etexilate		110 mg twice daily (for patients with clearance creatinine 30–49 mL/min—75 mg twice a day)		Dabigatran etexilate (per os) 110 mg × 2 times a day × 30 days = 6600 mg for one course of prevention; 6600 mg:300 mg (DDD) = 22 DDD for one course of prevention Patients with creatinine clearance 30–49 mL/min 75 mg × 2 times a day × 30 days = 4500 mg for one course of prevention; 4500 mg:300 mg (DDD) = 15 DDD for one course of prevention
ROPNIZ 2021 (Drapkina O.M.)	Rivaroxaban	Prevention of deep vein thrombosis of the lower extremities and pulmonary embolism	10 mg once daily	Outpatient patients with COVID-19 and patients after discharge from the hospital with persistent risk factors for deep vein thrombosis or pulmonary embolism (DVT/PE) and a low risk of bleeding up to 30–45 days	Rivaroxaban (per os) 10 mg × 1 time per day × 30 days = 300 mg for one course of prevention 300 mg:20 mg (DDD) = 15 DDD for one course of prevention 10 mg × 1 time a day × 45 days = 450 mg for one course of prevention 450 mg:20 mg (DDD) = 22.5 DDD for one course of prevention
	Apixaban		2.5 mg twice daily		Apixaban (per os) 2.5 mg × 2 times a day × 30 days = 150 mg for one course of prevention; 150 mg:10 (DDD) = 15 DDD for one course of prevention 2.5 mg × 2 times a day × 45 days = 225 mg for one course of prevention; 225 mg:10 (DDD) = 22.5 DDD for one course of prevention
RSC 2020 (Shlyakhto E.V.)	Anticoagulants	n/a	n/a	n/a	impossible to calculate
	Rivaroxaban				There is information about drug–drug interaction
	Apixaban				
	Dabigatran etexilate				

Table A4. *Cont.*

Name of Clinical Recommendation	Name of the Drug	Indications	Recommended Dose	Duration of Use	Comments (Prophylactic Course)
ROPNIZ 2021 (Livzan M.A.)	Rivaroxaban	Drug therapy for patients with COVID-19 on an outpatient basis with moderate course	10 mg once daily	Outpatient patients with COVID-19 and patients after discharge from the hospital with persistent risk factors for deep vein thrombosis or pulmonary embolism (DVT/PE) and a low risk of bleeding up to 30–45 days	Rivaroxaban (per os) 10 mg × 1 time per day × 30 days = 300 mg for one course of prevention 300 mg:20 mg (DDD) = 15 DDD for one course of prevention
	Apixaban		2.5 mg twice daily		Apixaban (per os) 2.5 mg × 2 times a day × 30 days = 150 mg for one course of prevention; 150 mg:10 (DDD) = 15 DDD for one course of prevention
	Dabigatran etexilate		110 mg twice daily (for patients with clearance creatinine 30–49 mL/min—75 mg twice a day)		Dabigatran etexilate (per os) 110 mg × 2 times a day× 30 days = 6600 mg for one course of prevention; 6600 mg:300 mg (DDD) = 22 DDD for one course of prevention Patients with creatinine clearance 30–49 mL/min 75 mg × 2 times a day × 30 days = 4500 mg for one course of prevention; 4500 mg:300 mg (DDD) = 15 DDD for one course of prevention
FAR 2020 (Zabolotskikh I.B.)	Oral anticoagulants	Persisnant hyperfibrinogenemia at the time of discharge (subject to discontinuation of Kaletra!)	n/a	discontinuation of Kaletra use is 2 weeks	impossible to calculate
	apixaban	Prevention of proximal deep vein thrombosis or pulmonary embolism in case of incompatibility with etiotropic drugs, dabigatran after initial parenteral therapy with low molecular weight heparins or unfractionated heparin		n/a	
	rivaroxaban				
	dabigatran				
NIIOZMM 2021 (Khripun A.I.)	Apixaban	prophylaxis	prophylactic dose—2.5 mg twice daily; intermediate dose—15 mg once daily.	n/a	impossible to calculate
		treatment	5 mg twice daily		
	Rivaroxaban	prophylaxis	prophylactic dose—10 mg once daily; intermediate dose—10 mg twice daily.		
		treatment	20 mg once daily		
	Dabigatran etexilate	prophylaxis	75 mg twice daily;		
		treatment	150 mg twice daily		
MGNOT 2021(Vorobyev P.A.)	Apixaban	prophylaxis	prophylactic effective daily dose—10 mg; 5 mg—twice daily	n/a	impossible to calculate
	Rivaroxaban		prophylactic effective daily dose—20 mg; 10 mg—twice daily		
	Dabigatran etexilate		prophylactic effective daily dose—220 mg; 110 mg—twice daily		

n/a—not available.

Appendix H

Table A5. Comparison of the Assessment of Seven CPGs for Treating COVID-19 with AGREE II.

Assessment of the Methodological Quality of CPG for Treating COVID-19 with the AGREE II Instrument, Comparison of Seven CPGs.							
	MoH 2022	**ROPNIZ 2021 (Drapkina)**	**ROPNIZ 2021 (Livzan)**	**RSC 2020 (Shlyakhto E.V.)**	**FAR 2020 (Zabolot-skikh)**	**NIIOZMM 2021 (Khripun)**	**MGNOT 2021 (Vorobyev)**
Scope and Purpose	58/90.74%	61/96.30%	62/98.15%	63/100%	45/66.67%	57/88.89%	62/98.15%
The overall objective(s) of the guideline is (are) specifically described.	20	21	21	21	3	19	20
The health question(s) covered by the guideline is (are) specifically described.	19	20	20	21	21	19	21
The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	19	20	21	21	21	19	21
Stakeholder Involvement	43/62.96%	44/64.81%	45/66.67%	27/33.33%	42/61.11%	26/31.48%	44/64.81%
The guideline development group includes individuals from all the relevant professional groups.	20	20	21	21	20	20	21
The views and preferences of the target population (patients, public, etc.) have been sought.	3	3	3	3	3	3	3
The target users of the guideline are clearly defined.	20	21	21	3	19	3	20
Rigour of Development	57/22.92%	95/49.31%	42/12.5%	93/47.92%	91/46.53%	24/0%	75/35.42%
Systematic methods were used to search for evidence.	3	17	3	3	3	3	3
The criteria for selecting the evidence are clearly described.	3	16	3	4	3	3	3
The strengths and limitations of the body of evidence are clearly described.	3	16	3	3	3	3	18
The methods for formulating the recommendations are clearly described.	3	3	3	3	19	3	3
The health benefits, side effects, and risks have been considered in formulating the recommendations.	20	18	3	21	21	3	21
There is an explicit link between the recommendations and the supporting evidence.	19	19	3	19	20	3	21
The guideline has been externally reviewed by experts prior to its publication.	3	3	3	20	3	3	3
A procedure for updating the guideline is provided.	3	3	21	20	19	3	3
Clarity of Presentation	63/100%	63/100%	63/100%	62/98.15%	63/100%	63/100%	61/96.30%
The recommendations are specific and unambiguous.	21	21	21	21	21	21	21
The different options for management of the condition or health issue are clearly presented.	21	21	21	21	21	21	21
Key recommendations are easily identifiable.	21	21	21	20	21	21	19
Applicability	48/50%	46/47.22%	48/50%	47/48.61%	30/25%	30/25%	29/23.61%
The guideline describes facilitators and barriers to its application.	3	3	3	3	3	3	3
The guideline provides advice and/or tools on how the recommendations can be put into practice.	21	19	21	20	3	3	3
The potential resource implications of applying the recommendations have been considered.	3	3	3	3	3	3	3
The guideline presents monitoring and/or auditing criteria.	21	21	21	21	21	21	20
Editorial Independence	6/0%	6/0%	21/41.67%	24/50%	22/44.44%	6/0%	23/47.22%
The views of the funding body have not influenced the content of the guideline.	3	3	3	3	3	3	3
Competing interests of guideline development group members have been recorded and addressed.	3	3	18	21	19	3	20
Total Sum of Assessment	275/56.94%	315/65.22%	281/58.18%	316/65.42%	293/60.66%	206/ 42.65%	294/60.87%

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