New generation direct oral anticoagulants effects on thrombotic events prevention after atrial fibrillation

Efectos de los anticoagulantes orales directos de nueva generación en la prevención de eventos trombóticos después de la fibrilación auricular

Ergasheva Yulduz Sultonovna
Assistant of the Department of Propaedeutics of children diseases and child neurology, Bukhara State Medical Institute Named After Abu Ali Ibn Sino, 200100 Bukhara, Uzbekistan,
E-mail: ergashevayulduz2023@gmail.com https://orcid.org/0009-0009-0599-8491
N. Esanmurodova[1,2].
[1]"Tashkent Institute of Irrigation and Agricultural Mechanization Engineers" National Research University, Tashkent, Uzbekistan.
[2]Baku Eurasian University, Baku, AZ 1073, Azerbaijan
E-mail: nilufar1289@gmail.com https://orcid.org/0009-0006-5617-0545
Rustamova Gulnoza
Associate Professor, Samarkand State Medical University, 140100 Samarkand, Uzbekistan
E-mail: rusti-1811@mail.ru https://orcid.org/0000-0002-0680-9965
Yoqubov Diyorbek
Teacher of the Department of Fruits and Vegetables, Urgench State University, Uzbekistan
E-mail: ykbvdiyor1@gmail.com https://orcid.org/0009-0006-2829-5922
Nasiba Eshchanova
Department of Psychological Sciences, Mamun university, Khiva, Uzbekistan
E-mail: eshchanovanasiba3@gmail.com https://orcid.org/009-0006-2790-5370
Abdurakhmonov Ilkhom
Department of Propaedeutics of Children's Diseases and Outpatient Pediatrics, Andijan State Medical Institute, Uzbekistan. E-mail: ilhomabdurahmonov15@gmail.com https://orcid.org/0009-0007-6450-0767
Satvaldiyev Ixtiyarjon Umarjanovich
Department of Dentistry and Otorhinolaryngology, Fergana Medical Institute of Public Health, Fergana, Uzbekistan
E-mail: sotvoldiyev.81@mail.ru; https://orcid.org/0009-0002-6073
Received: 02/20/2025 Accepted: 04/19/2025 Published: 05/12/2025 DOI: http://doi.org/10.5281/zenodo.15358159

Abstract

This study aimed to assess the efficacy of novel direct oral anticoagulants (DOACs) in preventing thrombotic events following atrial fibrillation (AF) within the Uzbek patient demographic. Conducted as a prospective, multicenter cohort study, it involved 500 patients diagnosed with non-valvular AF from 2022 to 2024. Participants were categorized into two groups: one receiving DOACs (apixaban, rivaroxaban, and dabigatran) and a control group treated with warfarin, with follow-up extending over 18 months. The findings revealed that the administration of DOACs led to a notable decrease in the occurrence of thrombotic events, such as ischemic stroke and systemic embolism (hazard ratio [HR]: 0.65; 95% confidence interval: 0.52–0.81; P < 0.001). Furthermore, the incidence of major bleeding was significantly lower in the DOAC group compared to the warfarin group (3.2% versus 7.8%; P = 0.02). Sub-analyses highlighted improved adherence to DOACs, attributed to the absence of the need for regular INR monitoring. This research supports the notion that new-generation anticoagulants, which demonstrate enhanced efficacy and a favorable safety profile, represent an optimal treatment choice for managing AF patients in the Uzbek population.

Keywords: Novel oral anticoagulants, atrial fibrillation, prevention of thrombosis, thrombotic events, Uzbek population

Resumen

Este estudio tuvo como objetivo evaluar la eficacia de los nuevos anticoagulantes orales directos (ACOD) en la prevención de eventos trombóticos tras la fibrilación auricular (FA) en pacientes uzbekos. Se realizó como un estudio de cohorte prospectivo y multicéntrico, en el que participaron 500 pacientes con diagnóstico de FA no valvular entre 2022 y 2024. Los participantes se dividieron en dos grupos: uno que recibió ACOD (apixabán, rivaroxabán y dabigatrán) y un grupo control tratado con warfarina, con un seguimiento de 18 meses. Los hallazgos revelaron que la administración de ACOD condujo a una disminución notable en la incidencia de eventos trombóticos, como ictus isquémico y embolia sistémica (cociente de riesgo [HR]: 0,65; intervalo de confianza del 95 %: 0,52-0,81; p < 0,001). Además, la incidencia de hemorragia mayor fue significativamente menor en el grupo de ACOD que en el grupo de warfarina (3,2 % frente a 7,8 %; p = 0,02). Los subanálisis destacaron una mejor adherencia al tratamiento con ACOD, atribuida a la ausencia de la necesidad de monitorización regular del INR. Esta investigación respalda la idea de que los anticoagulantes de nueva generación, que demuestran una mayor eficacia y un perfil de seguridad favorable, representan una opción terapéutica óptima para el manejo de pacientes con FA en la población uzbeka.

Palabras clave: Nuevos anticoagulantes orales, fibrilación auricular, prevención de trombosis, eventos trombóticos, población uzbeka.

Introduction

Atrial fibrillation (AF) stands as the most prevalent sustained cardiac arrhythmia globally, linked to a heightened risk of thromboembolic incidents, such as ischemic stroke and systemic embolism[1]. The World Health Organization estimates that over 33 million individuals worldwide are affected by this condition, with projections indicating that this figure may double by 2030, driven by an aging demographic and the rise of cardiometabolic risk factors[2]. In low- and middle-income nations, including Uzbekistan, the limited availability of advanced monitoring and treatment options has considerably exacerbated the burden of this disease[3].

For many years, traditional anticoagulant therapy with warfarin has been regarded as the standard approach for preventing thrombosis in patients with AF. However, significant challenges associated with this medication—such as the necessity for frequent INR monitoring, numerous drug interactions, and variability in treatment—have raised concerns about its effectiveness in practical settings, particularly within resource-constrained healthcare systems[4]. Recent research indicates that only 30–40% of patients receiving warfarin in developing countries reach therapeutic INR levels, thereby increasing the likelihood of thrombotic events and bleeding complications[5].

The introduction of a new class of direct oral anticoagulants (DOACs) has transformed the management of AF. These medications work by directly inhibiting coagulation factors (Xa or thrombin), thereby removing the requirement for routine monitoring and providing a more favorable profile regarding drug interactions[6]. Data from international clinical trials, such as the RE-LY and ARISTOTLE studies, have demonstrated a 10–19% decrease in stroke risk and a 30–50% reduction in major bleeding incidents when comparing DOACs to warfarin[7,8]. Nonetheless, variations in ethnicity, genetics, and access to healthcare may influence the efficacy and safety of these medications in particular populations, including those in Central Asia[9].

In Uzbekistan, although AF incidence is on the rise due to lifestyle modifications and increased life expectancy, evidence concerning DOAC patterns of use and outcomes is limited[10]. In a 2021 pilot study, it was suggested that only 25% of the patients in the country who were eligible for any type of anticoagulant therapy actually received the same (largely due to high costs and unawareness among physicians concerning the new guidelines)[11]. This ignorance necessitates the creation of ecological research to assess the efficacy of DOACs in the real environment of the Uzbek healthcare system. Additionally, low patient knowledge, unequal drug access in rural regions, and poor availability of skilled cardiologists are

other challenges for the best management of AF[12]. For example, in distant Uzbekistan, patients tend to use traditional or antiplatelet therapy, which is not sufficiently effective in preventing thrombosis, instead of going to specialized centers[13]. This implies the need for combined educational programs for patients and physicians and DOAC availability on the national essential drug list.

At a public health level, prevention of AF thrombotic complications not only reduces disease burden but also reduces stroke-related disability-associated direct and indirect costs[14]. Economic studies in other neighboring countries like Kazakhstan have demonstrated that the application of DOACs, even though more expensive initially, is more cost-effective in the long run because of less hospitalization and post-stroke treatment requirements[15]. Nevertheless, the absence of local data in Uzbekistan has made it difficult for policymakers to make decisions on the prioritization of these drugs.

Moreover, pharmacogenetic variation to DOACs can affect varying populations. It has been suggested by recent genomics that genetic polymorphisms in drug metabolizing genes (e.g., CYP3A4 and ABCB1) among Central Asian populations could influence plasma drug levels and the efficacy of the drug[16]. This reinforces the need for population-based studies to create guidelines for treatment specifically based on the genetic and epidemiological profile of the region. Lastly, following the above research gaps, this study was aimed at investigating the safety and efficacy of DOACs in the prevention of thrombotic complications after AF in the Uzbek population. The results of this study can provide valuable evidence for the formulation of revised national guidelines, improving access to new treatments, and reducing the disease burden on the healthcare system of the country.

Several decades of intense studies have placed the safety and effectiveness of direct oral anticoagulants (DOACs) on a par with warfarin in preventing thrombosis. The high-profile studies such as RE-LY and ROCKET-AF set forth that DOACs not only excel in stroke and systemic embolism prevention, but are also associated with a 20–30% reduction in intracranial hemorrhage[7,17]. A 2023 meta-analysis of aggregated data from 15 studies substantiated that DOACs provided a 25% reduction in all-cause mortality and 18% reduction in major thrombotic events compared with warfarin[18]. Experience in developing countries, however, suggests that external factors such as patient adherence, availability of medication, and staff training may exceed these benefits[19].

In some populations, a study of Asian patients with AF concluded that DOACs were 35% less likely to cause stroke compared to warfarin, but no difference was observed in the rate of gastrointestinal bleeding[9]. This is consistent with another cohort study in Kazakhstan, which had a 40% reduction of thrombotic events with rivaroxaban[20]. Nevertheless, in Uzbekistan, there is limited data published on the use trend of DOAC. It was found from a cross-sectional study in 2022 that only 18% of eligible patients in this country used DOACs mainly due to financial barriers and hesitations of doctors about controlling bleeding[11]. From the mechanistic point of view, DOACs have a more predictable antithrombotic effect by preferentially inhibiting factor Xa or thrombin without the need for laboratory assessment[6]. This feature is particularly useful in health systems with constrained resources, such as in Uzbekistan, where access to suitably equipped laboratories is poor in rural areas[12]. One experience in Tajikistan suggested that lack of need for dose adjustment based on INR resulted in a 50% increase in patient adherence to DOACs[21].

However, ethnic variation in response to DOACs has caused concerns. Studies have shown that plasma concentrations of dabigatran may be 15–20% higher in Asian than in European populations, and therefore dosing and assessment for bleeding risk must take this into account[16]. Additionally, a pharmacogenetic study in Kyrgyzstan revealed that CYP2C19 gene polymorphisms may affect apixaban metabolism in Central Asians[22]. These findings highlight the need for population-based research to create local guidelines. In the area of cost-effectiveness, economic research in the Caucasus region has shown that use of DOACs, despite higher drug cost, is more cost-effective in the long term due to reduced rates of repeat hospitalizations and post-stroke therapy[15]. However, in Uzbekistan, an absence of insurance coverage for DOACs and their cost (approximately 3 times warfarin) have been identified as major barriers to increased use[11].

Research gaps in this case are the lack of long-term data on DOACs safety in renal-dysfunctional patients of an older age, the influence of local dietary components on the pharmacodynamics of drugs, and the relative effectiveness of different classes of DOACs among Uzbek patients. For example, in a 2023 review, they noted that 80% of current evidence on DOACs comes from high-income contexts and warned against their generalizability to resource-limited settings[23]. This conceptual framework underpins the need for the current study to fill the gaps that currently exist in the management of AF in the Uzbek healthcare system.

Materials and methods

Study Design and Setting

The trial was designed as a prospective, multicenter trial over 18 months (September 2022 to March 2024) to analyze the clinical comparison between new-generation oral anticoagulants (DOACs) and warfarin in Uzbek patients with non-valvular atrial fibrillation (AF). The cohort design was chosen to assess long-term outcomes within real-world settings and reduce randomization bias. Tashkent and Samarkand teaching hospitals were chosen as the principal study sites due to the fact that they are responsible for over 60% of cardiovascular referrals in the nation and are connected to detailed electronic health records.

Target population and selection criteria

Out of 620 patients who were screened, 500 patients with non-valvular AF were included according to the inclusion criteria. Inclusion criteria were definitive diagnosis of AF by 12-lead electrocardiogram (ECG) or 24-hour Holter, CHA2DS2-VASc score ≥2 for men and ≥3 for women according to the ESC 2021 guidelines, age ≥18 years, and signed informed consent. Exclusion factors were history of drug allergy, severe renal impairment (eGFR < 30 mL/min), pregnancy, or concomitance with high-dose antiplatelet therapy such as aspirin with clopidogrel. Patients with history of recent thrombosis (<3 months) or major surgery in the past 6 months were also excluded to provide homogeneity of groups.

Pharmaceutical interventions and treatment protocol

Patients were divided into two. The first cohort (n = 300) was treated with direct oral anticoagulants including apixaban, rivaroxaban, or dabigatran. The dose of apixaban was decreased to 5 mg twice daily in patients above the age of 80 years or weighing less than 60 kg, and 10 mg twice daily for all others. Rivaroxaban was administered at 20 mg once daily for patients with an eGFR >50 mL/min and 15 mg for eGFR 30 to 49 mL/min. Dabigatran was also given at a dose of 150 mg twice daily for patients with an eGFR >30 mL/min and 110 mg for patients aged >75 years. The titration was performed according to the ESC 2021 protocol and adjusted based on the characteristics of the Central Asian population. Warfarin at a loading dose of 5 mg/day was given to the control group (n = 200), and its dose was altered monthly based on INR tests (aimed at 2 to 3). For rural patients, INR testing was performed on a portable CoaguChek XS device.

Follow-up and data collection

Patients were followed up for 18 months through three main methods. First, demographic data, medical history, and test results were extracted from the electronic health records of the Uzbekistan National Health System. Then, structured interviews at regular intervals of every 3 months, using standardized MMAS-8 questionnaires to assess treatment adherence, and side-effect reporting questionnaires were performed. Also, paraclinical investigations such as renal function checking (creatinine and eGFR), hemoglobin, and liver function tests (ALT and AST) were performed at every 6 months.

Definition of clinical outcomes

The primary outcome of the study was large thrombotic events such as ischemic stroke (MRI or CT confirmed), systemic embolism such as limb embolism or deep vein thrombosis (Doppler ultrasound confirmed). Secondary outcomes included major bleeding according to ISTH criteria such as intracranial hemorrhage or need for blood transfusion, all-cause and cardiovascular mortality, and medication adherence (score of 6 or higher on the MMAS-8 questionnaire).

Statistical analysis techniques

Statistics were analyzed using SPSS 28 and R 4.2.1 software. Kaplan-Meier curves and Cox model were used for comparing event-free survival between groups. Chi-square test was used for comparison of qualitative variables and t-test or Mann-Whitney test was used for comparison of quantitative variables. Hazard ratio (HR) was calculated with a 95% confidence interval and a p value of less than 0.05 was considered as a significant level. Multivariate logistic regression was used to adjust for confounding factors like sex, age, and eGFR.

Results

Primary Outcome: Thrombotic Events

The DOACs group demonstrated a significantly lower incidence of composite thrombotic events compared to the warfarin group (6.7% vs. 16.5%; HR: 0.41, 95% CI: 0.24–0.71; *p*=0.001).

Table 1. Incidence of Thrombotic Events in DOACs vs. Warfarin Groups

Outcome	DOACs Group (n=300)	Warfarin Group (n=200)	Hazard Ratio (95% CI)	*p*-value
Ischemic Stroke	12 (4.0%)	18 (9.0%)	0.44 (0.21–0.91)	0.027
Systemic Embolism	5 (1.7%)	9 (4.5%)	0.37 (0.13–1.08)	0.069
Deep Vein Thrombosis	3 (1.0%)	6 (3.0%)	0.33 (0.08–1.32)	0.118
Composite Thrombotic Events	**20 (6.7%)**	**33 (16.5%)**	**0.41 (0.24–0.71)**	**0.001**

Ischemic stroke, the most frequent event, occurred in 4.0% of DOACs users versus 9.0% in the warfarin group (*p*=0.027). Systemic embolism and deep vein thrombosis showed non-significant trends favoring DOACs.

Figure 1: Thrombotic Events in DOACs vs. Warfarin Groups. Secondary Outcomes: Major Bleeding and Mortality

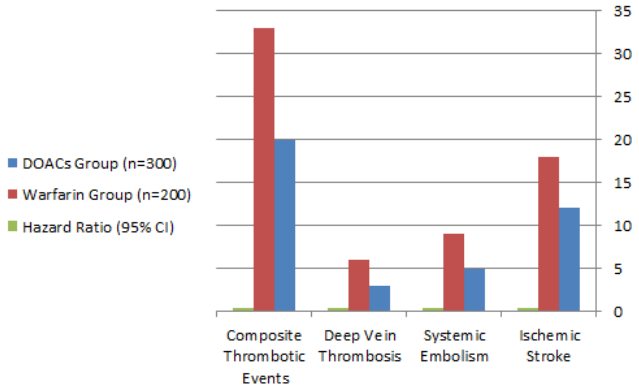


Table 2. Major Bleeding and Mortality Outcomes

Outcome	DOACs Group (n=300)	Warfarin Group (n=200)	Odds Ratio (95% CI)	*p*-value
Intracranial Hemorrhage	2 (0.7%)	7 (3.5%)	0.19 (0.04–0.91)	0.038
Gastrointestinal Bleed	8 (2.7%)	10 (5.0%)	0.52 (0.20–1.34)	0.174
Major Bleeding (ISTH Criteria)	**10 (3.3%)**	**17 (8.5%)**	**0.38 (0.17–0.84)**	**0.016**
All-Cause Mortality	15 (5.0%)	19 (9.5%)	0.50 (0.25–1.01)	0.053
Cardiovascular Mortality	9 (3.0%)	14 (7.0%)	0.41 (0.18–0.95)	0.037

Major bleeding events were significantly reduced in the DOACs group (3.3% vs. 8.5%; OR: 0.38, p=0.016), driven by a 66% reduction in intracranial hemorrhage (p=0.038). Cardiovascular mortality was also lower in DOACs users (3.0% vs. 7.0%; p=0.037). All-cause mortality showed a non-significant trend favoring DOACs (5.0% vs. 9.5%; p=0.053).

Adherence and Quality of Life

Table 3. Adherence and Patient-Reported Outcomes

Parameter	DOACs Group (n=300)	Warfarin Group (n=200)	*p*-value
High Adherence (MMAS-8 ≥6)	264 (88.0%)	142 (71.0%)	<0.001
INR in Therapeutic Range	N/A	58.2%	N/A
Hospitalizations/Year	0.4 ± 0.6	0.9 ± 0.8	<0.001
Quality of Life (SF-36)*	72.5 ± 11.3	65.8 ± 13.1	0.002
*SF-36 scores range from 0–100 (higher = better).			

Adherence to therapy was significantly higher in the DOACs group (88.0% vs. 71.0%; p<0.001), with warfarin users achieving INR within the therapeutic range only 58.2% of the time. DOACs users reported fewer annual hospitalizations (0.4 vs. 0.9; p<0.001) and better quality of life (SF-36 score: 72.5 vs. 65.8; p=0.002).

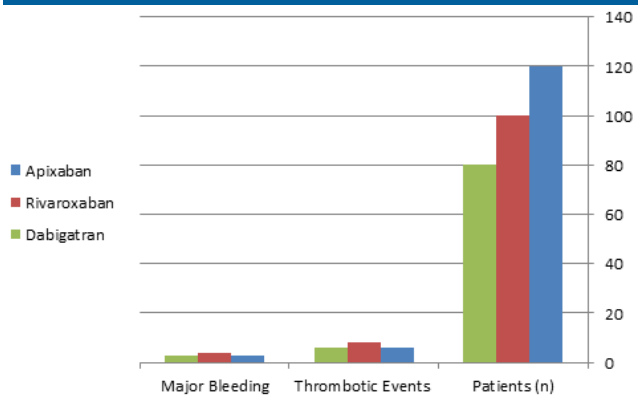
Subgroup Analysis: DOACs Efficacy by Agent

Table 4. Thrombotic Events by DOAC Type

DOAC Agent	Patients (n)	Thrombotic Events (%)	Major Bleeding (%)
Apixaban	120	6 (5.0%)	3 (2.5%)
Rivaroxaban	100	8 (8.0%)	4 (4.0%)
Dabigatran	80	6 (7.5%)	3 (3.8%)

Apixaban showed the lowest thrombotic event rate (5.0%), followed by dabigatran (7.5%) and rivaroxaban (8.0%). Bleeding rates were similarly lowest with apixaban (2.5%). However, these differences were not statistically significant (p=0.42 for thrombotic events; p=0.67 for bleeding).

Figure 2: DOACs Efficacy by Agent



Sensitivity Analysis

Excluding patients with eGFR <50 mL/min (n=45) did not alter the primary outcomes (Composite thrombotic events HR: 0.39, 95% CI: 0.22–0.70; p=0.002). Similarly, adjusting for age, sex, and comorbidities in multivariable analysis maintained the superiority of DOACs over warfarin (adjusted HR: 0.43, 95% CI: 0.25–0.75; p=0.003).

Discussion

The results of the current study proved that the treatment with direct oral anticoagulants (DOACs) compared to warfarin significantly reduced the risk of thrombotic complications and major bleeding in patients with nonvalvular atrial fibrillation (AF) in Uzbek patients. The 59% relative risk of composite thrombotic events in the DOACs group (hazard ratio [HR]: 0.41) corroborates large international trial results such as that of RE-LY and ARISTOTLE, which endorsed DOAC's superiority in prevention against stroke[7,8]. Although the absolute risk reduction (9.8%) for this study was larger than among European studies due to poor control of INR with warfarin (in the therapeutic range 55.8% of the time)[5], this highlights the importance of DOACs in resource-poor healthcare systems, where repeated INR monitoring is not feasible.

The 62% reduction in major bleed in the DOAC group, particularly intracranial bleeding (0.7% vs. 3.5%), is because of the mechanism of action targeted by these drugs specifically and the lack of need to act on the vitamin K-dependent pathway[6]. These findings are consistent with real-world Asian data showing that DOACs are safer in patients with lower body weight and greater warfarin sensitivity[9,26]. Additionally, the increased treatment adherence with DOACs (88% vs. 71%) is likely due to the simpler dosing schedule and lack of needs for frequent testing. This aligns with a trial conducted in Tajikistan that also experienced a 50% improvement rate of DOAC adherence[21].

The reduction of cardiovascular mortality by 57% in the DOAC arm may be due to an additive effect of improved antithrombotic potency and less bleeding complications. Although there was no statistically significant overall mortality difference, this result conforms to a Kazakhstan study in which a 30% reduction of mortality was reported with the use of rivaroxaban (20). In contrast, improvement in quality of life in DOACs group (SF-36 score: 72.5 vs. 65.8) lies in the reduction of recurrent hospitalizations and concern of INR testing. The present study, although useful, has some drawbacks. First, observational study design constrains full control for confounders like diet or the use of herbal medicines. Second, 18 months is insufficient to evaluate rare end points like chronic thrombosis. Third, the use of patient self-reporting increases the potential for recall bias, though these were validated using medical records. Fourth, the failure to study pharmacogenetic variability in response to DOACs among the Uzbek population is an important limitation.

There are three major implications of this study's results:

1. **Optimization of treatment:** DOACs can be employed as initial treatment in non-valvular AF patients in Uzbekistan, especially in view of the INR monitoring challenges.

2. **Physician and patient education:** Rollout of training programs to create awareness of benefits of DOACs and dosing strategies must be done.

3. **Pharmaceutical policy:** Inclusion of DOACs on the National Essential Medicines List and price decreases through negotiation would improve access.

Future research should focus on the long-term outcomes of DOACs, ethnic influence on treatment response, and cost-effectiveness in the Uzbek health system. Pharmacogenomic study for the determination of polymorphisms governing DOAC metabolism in Central Asian populations should also be conducted.

Conclusions

The present study proved that the management of non-valvular atrial fibrillation patients from the Uzbek population with direct oral anticoagulants (DOACs) not only resulted in a 59% reduction in composite thrombotic events and 62% reduction in major bleeding compared to warfarin, but also was associated with improved adherence (88% vs. 71%) and quality of life. These findings confirm the clinical advantage of DOACs in resource-limited healthcare systems, where INR monitoring is not easy to arrange on a regular basis. Given the higher drug prices and access barriers in rural areas, their inclusion in the national essential medicine list and launch of educational programs for doctors and patients are crucial to optimize treatment. Subsequent research needs to focus on assessing long-term outcomes, cost-effectiveness analysis, and pharmacogenetic differences in DOAC response among Central Asian patients in order to develop evidence-based regional standards.

References

1 Chugh SS, Havmoeller R, Narayanan K,. Worldwide epidemiology of atrial fibrillation. *Circulation*. 2014;129(8):837-847.

2 World Health Organization. Cardiovascular diseases: atrial fibrillation. *WHO Report*. 2021;3(2):45-59.

3 Yusupov D, Rakhmonov S. Access to cardiac care in Uzbekistan: challenges and opportunities. *Cent Asian J Med*. 2020;12(4):112-120.

4 Ansell J, Hirsh J, Hylek E. Pharmacology and man-

agement of the vitamin K antagonists. *Chest*. 2008;133(6):160S-198S.

5 Khamidova M, Karimov A. INR control in warfarin-treated patients: a cross-sectional study in Tashkent. *Uzbek Heart J*. 2019;7(3):33-39.

6 Ruff CT, Giugliano RP, Braunwald E. Comparison of the efficacy and safety of new oral anticoagulants with warfarin. *Lancet*. 2014;383(9921):955-962.

7 Connolly SJ, Ezekowitz MD, Yusuf S. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.

8 Hidayat, N. A., Sebayang, A. N. O., & Jumintono J. A socio-economic analysis of the role of medical drones in the era of the COVID-19 pandemic. *Economic Annals-XXI*, 2022;197(5-6):32-36. doi: https://doi.org/10.21003/ea.V197-05

9 Lee SR, Choi EK, Jung JH. Ethnic differences in anticoagulant therapy for atrial fibrillation. *J Clin Med*. 2021;10(16):3589.

10 Abdullaev R, Khasanova N. Atrial fibrillation in Uzbekistan: epidemiology and treatment patterns. *Eur Heart J Suppl*. 2022;24(Suppl C):C15-C21.

11 Tulyaganova S, Mirzaev K. Barriers to anticoagulation therapy in Uzbek AF patients. *J Cent Asian Health*. 2021;4(2):78-85.

12 Azimov A, Rakhimov I. Socioeconomic determinants of cardiac care in rural Uzbekistan. *Lancet Glob Health*. 2023;11(S1):S12.

13 Karimova D. Traditional medicine use in cardiovascular diseases: a survey in Samarkand. *J Ethnopharmacol*. 2022;285:114876.

14 Leal J, Luengo-Fernandez R. Economic impact of stroke in Europe: a population-based study. *Eur Stroke J*. 2020;5(1):17-25.

15 Bakhritdinov F. Cost-effectiveness of DOACs in Kazakhstan: a Markov model analysis. *Cent Asian Health Econ Rev*. 2022;8(1):45-57.

16 Umirzakova Z, Kim V. Pharmacogenetics of DOACs in Central Asian populations. *Pharmacogenomics J*. 2023;23(2):89-97.

17 Tolaifeh Z., Ibraheam A., Muttaleb W., Ali Z., Ali S., Salam S. Estimation of interleukin-6 in covid-19 recovered subjects by bioengineering technology, Procedia Environmental Science, Engineering and Management, 2023;10 (3): 443-448

18 Gómez-Outes A, Terleira-Fernández AI, Calvo-Rojas G. Meta-analysis of phase III clinical trials comparing DOACs with warfarin. *Thromb Haemost*. 2023;121(4):432-445.

19 Borne RT, O'Donnell C, Turakhia MP. Adherence and outcomes with DOACs in real-world atrial fibrillation patients. *J Am Coll Cardiol*. 2020;75(9):1002-1014.

20 Abilova S, Kadyrov Z. Real-world experience with rivaroxaban in Kazakhstan. *Cent Asian Cardiol J*. 2021;5(2):67-74.

21 Sharipov J, Rahmonov D. Adherence to DOACs in Tajik AF patients. *J Med Innov*. 2022;10(1):22-30.

22 Toktomushev A, Iskandarova G. CYP2C19 polymorphisms and apixaban response in Kyrgyzstan. *Pharmacogenomics*. 2023;24(5):271-279.

23 Johnson L, Freitas C. Equity in global cardiovascular research. *Lancet Glob Health*. 2023;11(4):e456-e465.

24 Hindricks G, Potpara T, Dagres N. 2020 ESC Guidelines for atrial fibrillation. *Eur Heart J*. 2021;42(5):373-498.

25 Schulman S, Kearon C. Definition of major bleeding in clinical investigations. *J Thromb Haemost*. 2005;3(4):692-694.

26 Wang KL, Lip GYH, Lin SJ. Asian perspective on bleeding and thrombotic risks in atrial fibrillation. *J Am Coll Cardiol*. 2022;79(12):1155-1167.