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# ANALYSIS OF THE EFFICACY AND SAFETY OF DIRECT ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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Chronic obstructive pulmonary disease (COPD) and atrial fibrillation (AF) are two widely prevalent conditions that often occur in patients over 60 years of age. These diseases have serious health consequences, increasing the risk of complications and worsening the quality of life of patients. Recent scientific studies indicate the adverse prognostic significance of AF in patients with COPD, requiring a comprehensive approach to diagnosis and treatment. For a long time, warfarin was the only oral anticoagulant for the prevention of thromboembolic complications and remains one of the main drugs to this day. Direct oral anticoagulants—rivaroxaban, apixaban, and dabigatran—have expanded the clinical arsenal for stroke prevention in atrial fibrillation. Our study showed that rivaroxaban is non-inferior to warfarin in clinical efficacy and superior warfarin in safety.

Keywords: atrial fibrillation, chronic obstructive pulmonary disease, stroke, oral anticoagulants, rivaroxaban, warfarin.

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death worldwide. According to the World Health Organization, the number of people with COPD continues to rise. The disease is characterized by progressive deterioration of lung function, leading to limitations in daily activities and reduced quality of life. Currently, more than 400 million people worldwide suffer from COPD, and the prognosis is concerning: by 2030, COPD is expected to become the third leading cause of mortality. Atrial fibrillation (AF), on the other hand, is the most common type of arrhythmia in adults [1]. According to research, AF occurs in 5-7% of the population and is significantly more common in people over 65 years of age. The frequency of its occurrence increases with the patient's age. In patients with COPD, the risk of developing AF increases 2-3 times compared to the general population. The presence of AF in patients with COPD worsens the prognosis, while the presence of COPD in patients with AF also has a certain impact on the progression of AF [2].

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For a long period, vitamin K antagonists (VKAs) and acetylsalicylic acid were the main drugs for the prevention of cardioembolic stroke associated with AF. A significant achievement was the introduction of oral anticoagulants (OACs) into clinical practice for stroke prevention in patients with AF. The main advantages of OACs over warfarin include the absence of the need for laboratory monitoring, a stable effect, minimal interaction with most drugs, no interaction with food, convenience of administration, and ultimately improved treatment adherence. Patients with non-valvular AF are recommended to be prescribed OACs (in the absence of contraindications), with the drugs of choice being rivaroxaban or apixaban (direct factor Xa inhibitors), as well as dabigatran etexilate (direct thrombin inhibitor) [3]. The individual choice of OAC is determined by the drug's efficacy and safety, as well as the presence of adverse effects during its use.

Study objective: To assess the efficacy and safety of warfarin and rivaroxaban therapy in patients with atrial fibrillation and chronic obstructive pulmonary disease.

Materials and Methods

A prospective study was conducted, monitoring 42 patients with non-valvular AF and COPD (GOLD stages II–III) aged 53 to 75 years, with a mean age of 62.8 ± 9.7 years. Among the participants, 66.7% (28) were men and 33.3% (14) were women. All patients received baseline COPD therapy, including long-acting anticholinergic drugs and/or a combination of long-acting β2-agonists and inhaled glucocorticosteroids. All patients were prescribed oral anticoagulants for the prevention of cardioembolic complications. The study included patients over 18 years of age with a creatinine clearance of at least 50 ml/min. Depending on the type of oral anticoagulant taken, all patients were divided into two comparable groups: Group 1—21 patients taking warfarin at a dose of 2.5-5 mg/day (with dose adjustment to achieve an international normalized ratio—INR of 2.0 to 3.0); Group 2—21 patients taking rivaroxaban at a fixed dose of 20 mg once daily. The formed groups were comparable in age, risk of thromboembolic and hemorrhagic complications.

Information about patients taking OACs was obtained through questionnaires completed by treating cardiologists in outpatient clinics. The observation period was 1 year from the start of drug administration. Quarterly follow-up examinations were conducted to identify thromboembolic and/or hemorrhagic complications, assess adherence to prescribed therapy, and all-cause mortality. Lung function tests, pulse oximetry, and Holter ECG monitoring were performed. Patients in the first group had their INR measured at least once a month.

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Data analysis was performed using the STATISTICA 10 statistical analysis software. Differences were considered statistically significant at $p < 0.05$.

Results and Discussion:

All 42 patients received baseline COPD therapy, including long-acting anticholinergic drugs and/or a combination of long-acting β2-agonists and inhaled glucocorticosteroids. All patients also received antiarrhythmic and anticoagulant therapy. Among all examined patients, the majority had moderate-severe COPD—76.2% of patients (32), while 23.8% of patients (10) had severe COPD.

The baseline characteristics of the patients in the two groups did not differ significantly (Table 1).

Table 1. Clinical and functional characteristics of patients

| Indicator | Number of patients taking warfarin (n=21) | Number of patients taking rivaroxaban (n=21) |
|---|---|---|
| Age, years | 59,7±7,2 | 61,3±6,8 |
| Males, % | 71,4% (15) | 61,9% (13) |
| Females, % | 28,6% (6) | 38,1% (8) |
| Duration of AF, years | 4,1±1,5 | 3,8±1,9 |
| Duration of COPD, years | 10,8±7,3 | 11,4±6,8 |
| COPD II | 76,2 % (16) | 81 % (17) |
| COPD III | 23,8 % (5) | 19% (4) |
| History of stroke or TIA, % | 14,3 % (3) | 9,5% (2) |
| FEV1, % | 62,3±6,4 | 64,1±5,9 |
| FEV1/FVC, % | 51,7±6,6 | 54,2±6,0 |
| $SpO_2$, % | 94±2,2 | 93±1,9 |
| Heart rate | 98±3,5 | 95±4,2 |

Note: Stroke—acute cerebrovascular accident; TIA—transient ischemic attack; FEV1—forced expiratory volume in the first second; SpO2—oxygen saturation; Heart rate—heart rate.

It was noted that in all groups examined over the 1-year observation period, adverse events occurred with a certain frequency (Table 2).

Table 2. Frequency of complications in the groups

| Complications | Number of patients taking | Number of patients taking |
|---|---|---|

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| | warfarin (n=21 | rivaroxaban (n=21) |
|---|---|---|
| Hematuria | 3 (14,3%) | 2 (9,5%) |
| Gastrointestinal bleeding | 4 (19%) | 0 |
| Uterine bleeding | 1 (4,8%) | 0 |
| Intracranial bleeding | 1 (4,8%) | 0 |
| Frequency of strokes | 1 (4,8%) | 1 (4,8%) |
| Frequency of venous thromboembolism | 0 | 0 |
| Fatal outcome, cause: stroke | 0 | 0 |
| Fatal outcome (myocardial infarction) | 1 (4,8%) | 0 |
| Fatal outcome (respiratory failure) | 1 (4,8%) | 0 |

A comparative analysis showed that in both the first and second groups of patients, stroke was observed in only 1 patient (4.8%). The development of venous thromboembolism was not noted in either group. No statistically significant differences in the number of cardioembolic complications or fatal outcomes between the groups were recorded. In no case was a fatal outcome due to stroke recorded. When comparing the efficacy of therapy, rivaroxaban outperformed warfarin, but not significantly ($p > 0.05$).

To assess the safety of OACs, an analysis of the frequency of gastrointestinal bleeding (GIB), uterine bleeding, and intracranial bleeding was conducted. Over the year of observation, in the first group of patients taking warfarin, gastrointestinal bleeding (GIB) was noted in 4 (19%) patients and uterine bleeding in 1 (4.8%) patient, while in the second group of patients taking rivaroxaban, no gastrointestinal or uterine bleeding was observed. These changes were statistically significant ($p < 0.05$).

Conclusion

Our study showed that OACs are preferable in terms of safety and are at least not inferior in efficacy to warfarin. Our data are consistent with the results of the ROCKET AF study (a study of rivaroxaban compared with vitamin K antagonists for the prevention of stroke and embolism in atrial fibrillation). The study showed a similar positive effect of rivaroxaban in patients with or without a prior stroke or transient ischemic attack [4]. The study included 14,264 patients, 40% of whom were women, with a mean age of 73 years. In a comparative assessment of efficacy,

rivaroxaban (20 mg once daily) was at least as effective as warfarin in preventing stroke and systemic embolism in patients with AF.

Over more than 60 years of using VKA therapy, it has been possible to identify both short-term and long-term effects in patients. The disadvantages of VKAs include a narrow therapeutic window and, consequently, safety and efficacy. Therefore, VKA therapy requires regular monitoring by measuring INR. Additionally, pharmacokinetics and pharmacodynamics are unpredictable due to interactions with other drugs, mechanisms dependent on cytochrome P450, and vitamin K intake with food [5]. In contrast to warfarin, due to the predictable pharmacokinetic and pharmacodynamic profiles of rivaroxaban, its monitoring is generally not recommended.

Thus, rivaroxaban and warfarin are the two main anticoagulants used for the prevention and treatment of thrombosis, including in patients with atrial fibrillation and chronic obstructive pulmonary disease. Our research demonstrated that rivaroxaban is at least as effective as warfarin in clinical outcomes and offers superior safety compared to warfarin.

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