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Safety and efficacy of apixaban in patients with glomerulonephritis and nephrotic syndrome: a prospective longitudinal cohort study

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Ключові слова: апіксабан, нефротичний синдром, гломерулонефрит, тромбоемболія, антикоагулянтна терапія, варфарин, кровотечі.

Aim. Assessment of the efficacy and safety of apixaban in preventing thromboembolic complications in patients with nephrotic syndrome caused by primary glomerulonephritis.

Materials and methods. We conducted a prospective longitudinal cohort study involving 125 patients with glomerulonephritis and nephrotic syndrome. According to the inclusion criteria, patients had to be over 18 years of age, diagnosed with nephrotic syndrome within the last month, and have an estimated glomerular filtration rate greater than 60 ml/min/1.73 m². The study population was divided into two cohorts for comparison: one group (62 patients) received prophylactic anticoagulation with warfarin, while the other group (63 patients) was administered apixaban at a dose of 5 mg twice daily. The observation period was 6 months.

Results. During the observation period, no thromboembolic events were reported in either group, indicating the effectiveness of both treatments. However, minor bleeding events were significantly more frequent in the warfarin group than in the apixaban group (p = 0.003). These findings suggest that apixaban is associated with a lower risk of bleeding while maintaining effective thromboembolic prevention.

Conclusions. This study highlights that apixaban is a potentially better alternative to warfarin for thromboprophylaxis in patients with nephrotic syndrome and glomerulonephritis, particularly in those at high thromboembolic risk. Further randomized controlled trials are recommended to confirm these findings and optimize anticoagulation strategies for this population.

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Безпека й ефективність апіксабану у пацієнтів із гломерулонефритом і нефротичним синдромом: проспективне поздовжнє когортне дослідження

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Мета роботи – оцінити ефективність і безпеку апіксабану у профілактиці тромбоемболічних ускладнень у пацієнтів із нефротичним синдромом, що розвинувся внаслідок первинного гломерулонефриту.

Матеріали і методи. Здійснили проспективне поздовжнє когортне дослідження за участю 125 пацієнтів із гломерулонефритом і нефротичним синдромом. Критерії залучення – вік понад 18 років; діагноз нефротичний синдром, встановлений протягом останнього місяця; розрахункова швидкість клубочкової фільтрації – понад 60 мл/хв/1,73 м². Популяцію дослідження поділили на дві когорти для порівняння: одна група (62 пацієнти) отримувала профілактичну антикоагулянтну терапію варфарином, інша група (63 пацієнти) одержувала апіксабан у дозі 5 мг двічі на добу. Період спостереження становив 6 місяців.

Результати. Протягом періоду спостереження тромбоемболічних ускладнень не зареєстровано в жодній із груп, що підтверджує ефективність обох методів лікування. Проте незначні кровотечі частіше виявляли в групі варфарину, ніж у групі апіксабану (p = 0,003). Ці результати свідчать, що апіксабан асоціюється з нижчим ризиком кровотеч при збереженні ефективної профілактики тромбоемболічних ускладнень.

Висновки. Апіксабан є потенційно кращою альтернативою варфарину для тромбопрофілактики у пацієнтів із нефротичним синдромом і гломерулонефритом, особливо серед тих, хто має високий ризик тромбоемболічних ускладнень. Доцільним є продовження рандомізованих контрольованих досліджень для підтвердження цих результатів та оптимізації стратегій антикоагулянтної терапії для таких пацієнтів.

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Nephrotic syndrome (NS), often a consequence of glomerulonephritis (GN), is a clinical condition characterized by significant proteinuria, hypoalbuminemia and edema [1]. One of the most serious complications of NS is an increased risk of thromboembolism, which is associated with a hypercoagulability. This state arises from several pathophysiological mechanisms, including the loss of antithrombotic proteins such as antithrombin III, elevated levels of prothrombotic factors like fibrinogen and factor VIII, enhanced platelet activity, and endothelial dysfunction [2]. The risk of thromboembolism is particularly high in patients with membranous nephropathy, with up to 36 % of these patients experiencing venous thromboembolic events [3].

Low serum albumin levels (<20–25 g/L) are a strong predictor of thromboembolic events, such as deep vein thrombosis and renal vein thrombosis [4]. Despite this recognized association, evidence is lacking to determine optimal strategies for prophylactic anticoagulant therapy in this patient group, including the identification of suitable candidates, timing of therapy initiation, and duration of treatment [5]. Current guidelines, such as those from KDIGO, suggest considering thromboembolic prophylaxis in patients with severe hypoalbuminemia, but these recommendations are not supported by reliable high-quality evidence [6].

Traditional anticoagulant therapies, such as warfarin and low-molecular-weight heparin, are commonly used to mitigate thromboembolic risk in patients with NS, but they have significant limitations. These include the need for constant monitoring, dietary restrictions, and variability in therapeutic effects, especially in patients with impaired renal function and proteinuria [7]. Warfarin, in particular, is associated with a narrow therapeutic window and an increased risk of bleeding, complicating its use in this patient population [8].

Direct oral anticoagulants (DOACs), including apixaban, have emerged as a promising alternative due to their convenience, fixed dosage, and predictable pharmacokinetics [9]. Apixaban, a factor Xa inhibitor, has minimal renal clearance and has demonstrated efficacy in reducing thromboembolic risk. However, studies assessing the efficacy and safety of apixaban in patients with NS, especially those with severe hypoalbuminemia, remain limited, highlighting the need for further research to confirm its suitability in this context [10,11].

Aim

This study aims to evaluate the efficacy and safety of apixaban in preventing thromboembolic complications in patients with nephrotic syndrome caused by primary glomerulonephritis.

Materials and methods

This prospective longitudinal cohort study included 125 patients with glomerulonephritis (GN) and nephrotic syndrome (NS) treated at the Ivano-Frankivsk Regional Clinical Hospital (Ukraine) between 2022 and 2024. The study adhered to international ethical standards, including obtaining informed consent, ethical considerations, and appropriate handling of biomaterials, in line with the WMA Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) and the UNESCO Universal Declaration on Bioethics and Human Rights. The research protocol was approved by the ethics committee of Ivano-Frankivsk National Medical University, and all participants provided written informed consent.

The study enrolled 125 patients, including 102 men (81.6 %; 95 % CI: 71.0–89.5) and 23 women (18.4 %; 95 % CI: 10.5–29.0), with a median age of 45 years (IQR: 40–49). Inclusion criteria were: age ≥18 years, diagnosis of NS within the past month, and an estimated glomerular filtration rate (eGFR) >60 ml/min/1.73 m^2. Exclusion criteria included: unwillingness to participate, age <18 years, systemic connective tissue diseases, systemic vasculitis, type 1 or type 2 diabetes mellitus, history of thromboembolic or cardiovascular events, chronic heart failure (NYHA class III–IV), acute infections of any origin, malignancies, acute or chronic liver failure, and mental health disorders.

The clinical diagnosis of GN and NS was established according to standard diagnostic criteria and guidelines for managing glomerular diseases, including the KDIGO 2021 recommendations [6]. All patients underwent comprehensive clinical examinations, laboratory tests, and imaging studies.

Morphological confirmation of GN revealed the following histological subtypes: 34 patients (27.2 %; 95 % CI 18.0–39.1) with membranous GN, 29 patients (23.2 %; 95 % CI 20.2–41.9) with mesangioproliferative GN, 27 patients (21.6 %; 95 % CI 10.5–29.0) with focal segmental glomerulosclerosis, 21 patients (16.8 %; 95 % CI 7.5–24.4) with minimal change disease, and 14 patients (11.2 %; 95 % CI 3.8–18.1) with membranoproliferative (mesangiocapillary) GN.

Treatment was selected depending on the histological variant of GN and included pathogenetic therapy such as glucocorticosteroids and cytostatics. Furthermore, all patients received either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Additionally, 56 patients (44.8 %; 95 % CI: 36.1–53.5) were treated with sodium-glucose cotransporter-2 inhibitors.

Prophylactic anticoagulation was guided by KDIGO recommendations [6] and the algorithm proposed by Lin et al., considering the underlying cause of NS, serum albumin levels, and bleeding risk. Bleeding risk was assessed using the HAS-BLED scoring system, categorizing patients into low, moderate, or high-risk groups. Anticoagulation was initiated in patients with low-to-moderate bleeding risk based on serum albumin thresholds: <30 g/L for membranous nephropathy and <25 g/L for other GN subtypes [12].

The studied patient population were divided into two groups:

– Group I (n = 62) received warfarin with regular international normalized ratio monitoring.

– Group II (n = 63) received apixaban at 5 mg twice daily. A reduced dose of 2.5 mg twice daily was prescribed for patients weighing ≤60 kg.

The duration of anticoagulation ranged from 1 to 6 months, based on the time required to achieve NS remission. Patients were followed up for six months, starting from the date of informed consent. The primary endpoint was mortality regardless of cause, while secondary endpoints included thromboembolic events, cardiovascular events, and major bleeding episodes.

Table 1. The main characteristics of the studied groups

Parameter, units of measurement	I group, n = 62	II group, n = 63	p-value
Age, years (Me (Q25; Q75))	42 (36; 48)	48 (42; 51)	0.369
Sex, male (%; 95 % CI)	80.6 (70.8–90.4)	82.5 (73.1–91.9)	0.821
Sex, female (%; 95 % CI)	19.4 (9.5–29.1)	17.5 (8.1–26.8)	0.821
Membranous GN (%; 95 % CI)	27.4 (17.8–39.5)	27.0 (17.5–39.0)	1.000
Mesangioproliferative GN (%; 95 % CI)	22.5 (13.9–34.4)	23.8 (15.0–35.6)	1.000
Focal segmental glomerulosclerosis (%; 95 % CI)	22.5 (13.9–34.4)	20.6 (12.5–32.2)	1.000
GN with minimal changes (%; 95 % CI)	16.1 (9.0–27.2)	17.4 (10.0–28.6)	1.000
Mesangiocapillary GN (%; 95 % CI)	11.2 (5.6–21.5)	11.1 (5.5–21.2)	1.000
Creatinine, μmol/L (Me (Q25; Q75))	98.5 (71.4; 112.3)	95.2 (75.2; 110,8)	0.738
Urea, mmol/L (Me (Q25; Q75))	7.4 (5.8; 8.7)	7.8 (6.1; 8.3)	0.842
Total cholesterol, mmol/L (Me (Q25; Q75))	7.2 (6.5; 8.8)	6.9 (6.2; 8.4)	0.687
Serum albumin, g/L	23 (18; 26)	22 (16; 25)	0.853
eGFR, ml/min/1.73 m^3 (Me (Q25; Q75))	62 (37; 92)	66 (43; 94)	0.761
DPE, g/day (Me (Q25; Q75))	5.6 (4.8; 7.5)	6.2 (5.2; 7.8)	0.424
D-dimer, mg/L (Me (Q25; Q75))	1.26 (0.85; 1.85)	1.35 (0.87; 2.13)	0.342
Platelet Count, $\times 10^9$/L (Me (Q25; Q75))	248 (187; 266)	252 (214; 315)	0.252
INR (Me (Q25; Q75))	0.9 (0.8; 1.0)	1.0 (0.9; 1.1)	1.000
APTT, s (Me (Q25; Q75))	45 (36; 50)	46 (41; 51)	0.843
PT, s (Me (Q25; Q75))	12 (11; 13)	12 (11; 14)	1.000
Fibrinogen, g/L (Me (Q25; Q75))	4.5 (3.8; 5.2)	4.8 (4.1; 5.4)	0.793

CI: confidence interval; **DPE:** daily protein excretion; **GFR:** glomerular filtration rate; **INR:** international normalized ratio; **APTT:** activated partial thromboplastin time; **PT:** prothrombin time.

Statistical analysis was performed using Statistica 8 software (StatSoft, Serial No. STA862D175437Q). Qualitative variables were presented as absolute and relative frequencies with 95 % confidence intervals (CI). Quantitative variables were analyzed using the Shapiro–Wilk test to assess distribution. Data with a normal distribution were expressed as mean ± standard deviation (M ± SD), and non-normally distributed data were reported as median and interquartile range (Me [Q25–Q75]). Comparisons between groups were conducted using: Student's t-test for normally distributed quantitative data, Mann–Whitney U-test for non-normally distributed data, Fisher's exact test for differences in qualitative variables. A p-value of <0.05 was considered statistically significant. Odds ratios were calculated with 95 % CIs to quantify differences between groups.

Results

The main demographic, clinical, and laboratory characteristics of the patients are presented in *Table 1*.

As presented in *Table 1*, the baseline demographic and clinical characteristics showed no significant differences between the two study groups.

The duration of prophylactic anticoagulation varied between 1 and 6 months, depending on the time required to achieve remission of NS, with a mean duration of 126 (95; 167) days in group I and 112 (84; 148) days in group II (p = 0.124).

No thromboembolic events were observed in any of the study groups during the observation period. However, bleeding episodes were reported in 9 patients (14.5 %; 95 % CI: 5.8–23.3) in the group I and 2 patients (3.2 %; 95 % CI: 0.0–7.5) in the group II, with a statistically significant difference between the groups (p = 0.03).

The incidence of bleeding events was significantly higher in the warfarin group compared to the apixaban group. Specifically, the probability of bleeding was 0.170 in the warfarin group and 0.033 in the apixaban group. The resulting odds ratio was 5.18 (95 % CI: 4.92–5.45: p = 0.03), this suggests that patients receiving warfarin were approximately 5.18 times more likely to experience a bleeding event compared to those receiving apixaban.

All bleeding events were classified as minor according to the criteria established by the International Society on Thrombosis and Haemostasis (ISTH). The reported episodes included cases of epistaxis, gingival bleeding, menorrhagia, and subcutaneous hemorrhage. It is important to note that none of these bleeding events required medical intervention or led to discontinuation of the study drug. Furthermore, no deaths were registered among the study participants during the entire observation period.

Discussion

The management of thromboembolic risk in patients with NS remains a significant clinical challenge, particularly in the context of hypoalbuminemia and impaired renal function [8]. Despite established recommendations for thromboprophylaxis in high-risk patients with NS, robust evidence from large-scale randomized controlled trials is lacking [13]. Current data on thromboprophylaxis largely originates from retrospective studies and case series, often involving traditional anticoagulants such as heparin and warfarin. For instance, a study by S. Kelddal et al. reported a complete absence of venous thromboembolic events in patients receiving anticoagulation compared to a 9 % incidence in non-anticoagulated patients. However, some patients treated with anticoagulants have experienced bleeding complications, although minor, highlighting the need to balance efficacy and safety [14].

Our findings demonstrate that both apixaban and warfarin were effective in preventing thromboembolic events during the 6-month observation period. These results align with previous studies suggesting that prophylactic anticoagulation significantly reduces thrombotic risk in patients with NS. The absence of thromboembolic events in our cohort underscores the importance of early and targeted anticoagulation therapy for high-risk patients.

DOACs offer multiple advantages, including fixed dosage, predictable pharmacokinetics, and a reduced need for routine monitoring. These characteristics are particularly advantageous in patients with NS, who often experience renal failure and variable anticoagulant responses due to hypoalbuminemia [15].

Apixaban stands out among DOACs due to its minimal renal clearance, making it particularly suitable for patients with impaired renal function. The ARISTOPHANES study demonstrated its efficacy and safety in reducing thromboembolic events in patients with atrial fibrillation and renal dysfunction [16].

Additionally, studies such as that by T. Van Meerhaeghe et al. emphasized apixaban's predictable pharmacokinetics, even in hypoalbuminemic condition, and demonstrated its ability to provide effective anticoagulation with a reduced risk of bleeding compared to traditional therapies [17]. Despite these encouraging findings, significant knowledge gaps persist. The pharmacodynamics and clinical efficacy of apixaban in extreme hypoalbuminemia (<20 g/L), a hallmark of severe NS, remain poorly understood. Furthermore, while observational studies suggest a favorable safety and efficacy profile, the lack of large-scale randomized controlled trials limits the generalizability of existing data [18,19]. Studies like those by M. Wei et al. have called for further exploration of DOAC pharmacokinetics in the context of severe proteinuria to better understand their behavior in this high-risk population [20]. Comparative studies with other DOACs, such as rivaroxaban, could provide further insights into the optimal choice of anticoagulant for this population.

Our study supports the use of apixaban as a viable alternative to warfarin for thromboprophylaxis in patients with NS, particularly those at high risk of thromboembolism and bleeding complications. By minimizing bleeding risks and simplifying treatment regimens, apixaban has the potential to improve adherence and outcomes in this vulnerable population.

Conclusions

1. This study highlights the favorable safety and efficacy profile of apixaban as a prophylactic anticoagulant in patients with GN and NS. During the follow-up period, no thromboembolic events were reported in either treatment group, emphasizing the effectiveness of anticoagulation in this high-risk population.

2. Bleeding complications, which were all classified as minor and did not require medical intervention or therapy discontinuation, were significantly more frequent in the warfarin group compared to the apixaban group ($p = 0.003$). These results indicate that apixaban offers a safer bleeding profile while maintaining effective thromboembolic prevention.

3. Overall, this study supports apixaban as a potentially better alternative to warfarin for thromboprophylaxis in NS, particularly in patients at elevated risk of thromboembolic events.

Limitations. This study was conducted at a single center with a relatively small sample size, which may limit the generalizability of the findings. Additionally, the follow-up period was limited to 6 months, which may not capture long-term outcomes such as delayed thromboembolic events or late-onset bleeding complications. Future multicenter studies with longer follow-up periods are recommended to address these limitations and provide more comprehensive data.

Prospects for further research. Future research should aim to evaluate the long-term effects of apixaban in this population, particularly regarding delayed thromboembolic events and late-onset bleeding complications. The study of biomarkers and individual patient factors influencing thromboembolic and bleeding risks could support the development of personalized anticoagulation strategies. Additionally, studies on new anticoagulants with enhanced safety and efficacy in hypoalbuminemic conditions could expand treatment options for high-risk patients.

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