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Apixaban in glomerulonephritis with nephrotic syndrome: thromboprophylaxis and pleiotropic effects in a prospective cohort study

I. S. Mykhaloiko[A,B,C,D,E], R. I. Yatsyshyn[A,C,E,F], N. V. Cherniuk[A,C,E,F], V. Ya. Kaminskyi[B,C,D], M. Ya. Humeniuk[B,C,D]

Ivano-Frankivsk National Medical University, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Keywords: apixaban, nephrotic syndrome, glomerulonephritis, thromboprophylaxis, inflammation, fibrosis, anticoagulation, biomarkers.

Aim: to assess the efficacy and safety of apixaban in preventing thromboembolic complications in patients with nephrotic syndrome (NS) due to primary glomerulonephritis, and to investigate its potential anti-inflammatory and antifibrotic effects.

Materials and methods. A prospective longitudinal cohort study included 85 adult patients with newly diagnosed NS and estimated glomerular filtration rate >60 mL/min/1.73 m^2. Patients were divided into two groups: 42 received warfarin and 43 received apixaban (5 mg twice daily). The follow-up period was 6 months. IL-6, TNFα, and TGF-β1 were measured in serum and urine at baseline, 1 month, and 6 months.

Results. No thromboembolic events occurred in either group. Minor bleeding events were significantly more common in the warfarin group ($p = 0.01$), confirming apixaban's better safety profile. After 6 months, the apixaban group showed a more pronounced decrease in IL-6, TNFα, and TGF-β1 levels in both serum and urine compared to the warfarin group ($p < 0.05$), suggesting anti-inflammatory and antifibrotic effects potentially associated with protease-activated receptor pathway modulation.

Conclusions. Apixaban ensures safe and effective thromboprophylaxis in NS with possible additional benefits in reducing inflammation and fibrosis. Further studies are needed to confirm these effects and define its role in nephrology.

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Ключові слова: апіксабан, нефротичний синдром, гломерулонефрит, тромбопрофілактика, запалення, фіброз, антикоагуляція, біомаркери.

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Роль апіксабану у запобіганні тромбозу та модуляції запалення при гломерулонефриті з нефротичним синдромом: результати проспективного повздовжнього когортного дослідження

І. С. Михалойко, Р. І. Яцишин, Н. В. Чернюк, В. Я. Камінський, М. Я. Гуменюк

Мета роботи – оцінити ефективність і безпеку апіксабану в профілактиці тромбоемболічних ускладнень у пацієнтів із нефротичним синдромом (НС), що спричинений первинним гломерулонефритом (ГН), а також вивчити його потенційні протизапальні та антифібротичні ефекти.

Матеріали і методи. Здійснили проспективне повздовжнє когортне дослідження за участю 85 дорослих пацієнтів із вперше діагностованим НС і швидкістю клубочкової фільтрації (ШКФ) >60 мл/хв/1,73 м^2. Учасників поділили на дві групи: 42 особи отримували варфарин, 43 – апіксабан у дозі 5 мг двічі на добу. Період спостереження становив 6 місяців. Рівні IL-6, TNFα і TGF-β1 визначено в сироватці крові та сечі на початку, через 1 і 6 місяців.

Результати. Тромбоемболічні ускладнення не зафіксовано в жодній із груп дослідження. Нетяжкі кровотечі частіше виникали в групі варфарину ($p = 0,01$), що підтверджує кращий профіль безпеки апіксабану. Через 6 місяців у групі апіксабану визначено більш виражене зниження рівнів IL-6, TNFα і TGF-β1 у сироватці та сечі порівняно з варфарином ($p < 0,05$). Це свідчить про можливі протизапальні та антифібротичні ефекти, ймовірно, пов'язані з модуляцією сигнальних шляхів, активованих протеазами.

Висновки. Апіксабан забезпечує ефективну та безпечну тромбопрофілактику у пацієнтів із НС і може додатково зменшувати запалення та фіброз. Необхідні наступні дослідження для підтвердження цих ефектів та визначення його ролі в нефрології.

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Nephrotic syndrome (NS), commonly resulting from primary glomerulonephritis (GN), is marked by significant protein loss with the urine, low serum albumin levels, edema, and elevated blood lipids [1]. A major and potentially life-threatening complication of NS is the occurrence of thromboembolic events – such as venous thrombosis, pulmonary embolism, and renal vein thrombosis – which may affect up to 44 % of patients, particularly those with membranous nephropathy [2,3]. The underlying mechanisms of thrombophilia in NS involve the urinary loss of natural anticoagulants (like antithrombin III and protein C), elevated levels of prothrombotic factors (such as fibrinogen and factor VIII), increased platelet activity, and endothelial dysfunction [4].

Hypoalbuminemia is recognized as an independent predictor of thrombotic risk. Nevertheless, the most effective prophylactic approach for managing this risk remains uncertain [5]. Although current KDIGO guidelines recommend considering anticoagulation in patients with marked hypoalbuminemia, robust clinical evidence regarding its safety and therapeutic benefit is still insufficient [6].

Traditional anticoagulants, such as warfarin and low-molecular-weight heparins (LMWHs), pose several challenges in patients with NS. Warfarin requires regular international normalized ratio (INR) monitoring and is affected by dietary vitamin K and drug interactions, complicating its use. In nephrotic patients, protein loss and impaired renal function can alter drug metabolism, increasing bleeding risk. LMWHs also accumulate in renal insufficiency, further elevating the risk of hemorrhage. Moreover, LMWHs may be less effective in NS due to the urinary loss of antithrombin III, a critical cofactor for their anticoagulant action. These limitations underscore the need for safer and more manageable anticoagulation strategies in this population [7,8].

In this context, direct oral anticoagulants (DOACs), particularly apixaban – a selective inhibitor of factor Xa – have become increasingly favored due to their stable pharmacokinetic profiles, fixed dosing regimens, and the absence of a need for routine coagulation monitoring [9]. Apixaban's low dependence on renal excretion makes it especially suitable for patients with compromised kidney function. Despite these advantages, data on its efficacy and safety in individuals with NS, especially those with marked hypoalbuminemia, is still scarce [10,11].

Beyond their primary anticoagulant activity, DOACs possess pleiotropic effects – including anti-inflammatory, antifibrotic, and antioxidant actions – that may hold therapeutic potential in GN and the progression of chronic kidney disease. Factor Xa and thrombin can activate protease-activated receptors (PAR-1 and PAR-2), which play key roles in mediating inflammation, fibrosis, cell proliferation, and tissue remodeling [12].

In vitro and in vivo studies indicate that apixaban can suppress the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), as well as pro-inflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). It also helps restore mitogen-activated protein kinase / extracellular signal-regulated kinase signaling balance, reduces the generation of reactive oxygen species (ROS), and influences transforming growth factor-β (TGF-β)-mediated fibrotic pathways [13]. Additionally, in experimental models of nephropathy, factor Xa inhibitors have demonstrated the ability to reduce glomerular fibrosis and crescent formation by blocking PAR-2 signaling mechanisms [14].

Therefore, apixaban may have a dual role – reducing the risk of thromboembolic complications while also influencing renal inflammation and fibrosis. This supports the scientific basis for investigating its effectiveness, safety, and potential nephroprotective benefits in patients with NS caused by primary GN.

Aim

To evaluate the efficacy and safety of apixaban in the prevention of thromboembolic complications in patients with NS due to primary GN, to investigate its potential anti-inflammatory and antifibrotic effects.

Materials and methods

This prospective longitudinal cohort study was conducted from 2022 to 2025 at the Ivano-Frankivsk Regional Clinical Hospital (Ukraine). A total of 85 patients with NS secondary to biopsy-proven primary GN were enrolled.

The study complied with international ethical standards, including the WMA Declaration of Helsinki and the UNESCO Universal Declaration on Bioethics and Human Rights. The study protocol was approved by the Ethics Committee of Ivano-Frankivsk National Medical University (Protocol No. 125/13 dated June 23, 2025), and all participants provided written informed consent.

A total of 85 patients were examined, including 68 men (80.0 %; 95 % CI: 71.5–88.5) and 17 women (20.0 %; 95 % CI: 12.5–28.5). The median age of the patients was 45 years, with an interquartile range (IQR) of 41 to 49 years.

Inclusion criteria: patients aged 18 years and older, with newly diagnosed nephrotic syndrome within the previous month and an estimated glomerular filtration rate (eGFR) greater than 60 mL/min/1.73 m^2.

Exclusion criteria included individuals younger than 18 years, those who refused to participate, or those with systemic connective tissue diseases, vasculitis, type 1 or type 2 diabetes mellitus, a history of cardiovascular events, chronic heart failure of New York Heart Association (NYHA) class III–IV, acute infections, malignancies, liver failure, or psychiatric illnesses.

The diagnoses of GN and NS were established based on standard clinical criteria in accordance with the KDIGO 2021 guidelines [6]. All patients underwent comprehensive clinical and laboratory evaluation, along with relevant imaging and diagnostic procedures. The histological subtypes of GN included: membranous GN – 24 patients (28.2 %; 95 % CI: 19.3–38.6 %), mesangioproliferative GN – 19 patients (22.4 %; 95 % CI: 14.2–32.3 %), focal segmental glomerulosclerosis – 17 patients (20.0 %; 95 % CI: 12.1–29.9 %), minimal change disease – 13 patients (15.3 %; 95 % CI: 8.4–24.8 %), membranoproliferative GN – 12 patients (14.1 %; 95 % CI: 7.5–23.3 %).

Treatment selection was based on the histological subtype of GN and included immunosuppressive therapy, as well as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. Additionally, 56 patients (65.9 %; 95 % CI: 55.0–75.6 %) received sodium-glucose cotransporter-2 inhibitors.

Prophylactic anticoagulation was carried out in line with KDIGO guidelines and the algorithm by R. Lin et al., which con-

Table 1. Baseline characteristics of the studied groups

Parameter, units of measurement	Group I, n = 42	Group II, n = 43	p-value
Age, years, Me (Q25; Q75)	43 (37; 48)	46 (40; 51)	0.378
Sex, male, (%; 95 % CI)	83.3 (69.8–91.5)	76.7 (62.8–87.0)	0.589
Sex, female, (%; 95 % CI)	16.7 (8.4–30.7)	23.3 (13.1–37.6)	0.589
Membranous GN, (%; 95 % CI)	28.6 (17.5–43.3)	27.9 (17.0–42.2)	0.875
Mesangioproliferative GN, (%; 95 % CI)	21.4 (11.7–35.9)	23.3 (13.1–37.6)	0.764
Focal segmental glomerulosclerosis, (%; 95 % CI)	21.4 (11.7–35.9)	18.6 (9.7–32.6)	0.683
GN with minimal changes, (%; 95 % CI)	14.3 (6.7–28.7)	16.2 (7.8–30.5)	0.742
Mesangiocapillary GN, (%; 95 % CI)	14.3 (6.7–28.7)	14.0 (6.2–27.9)	0.893
Creatinine, μmol/L, Me (Q25; Q75)	97.5 (73.6; 111.6)	94.3 (72.1; 109,8)	0.746
Urea, mmol/L, Me (Q25; Q75)	7.8 (5.6; 8.4)	7.4 (5.4; 8.5)	0.856
Total cholesterol, mmol/L, Me (Q25; Q75)	7.7 (6.8; 8.9)	7.4 (6.2; 8.5)	0.787
Serum albumin, g/L, Me (Q25; Q75)	22 (19; 25)	23 (18; 25)	0.812
eGFR, mL/min/1.73 m^2, Me (Q25; Q75)	75 (61; 92)	76 (63; 96)	0.754
DPE, g/day, Me (Q25; Q75)	5.2 (4.4; 6.5)	6.2 (5.1; 7.6)	0.576
D-dimer, mg/L, Me (Q25; Q75)	1.25 (0.95; 1.65)	1.32 (0.87; 1.74)	0.267
Platelet count (×10^9/L), Me (Q25; Q75)	214 (179; 263)	246 (194; 305)	0.342
INR, Me (Q25; Q75)	0.9 (0.8; 1.0)	1.0 (0.9; 1.1)	0.925
APTT, s, Me (Q25; Q75)	43 (34; 52)	46 (39; 53)	0.769
PT, s, Me (Q25; Q75)	12 (11; 13)	12 (11;14)	0.945
Fibrinogen (g/L), Me (Q25; Q75)	5.8 (4.1; 6.2)	6.2 (4.5; 7.1)	0.574

CI: confidence interval; **DPE:** daily protein excretion; **APTT:** activated partial thromboplastin time; **PT:** prothrombin time.

sider serum albumin concentration and bleeding risk (evaluated via the HAS-BLED score) [15]. Anticoagulant therapy was initiated in patients with low to moderate bleeding risk and serum albumin level below 25 g/L.

Patients were divided into two groups: Group I (n = 42) received warfarin with regular INR monitoring; Group II (n = 43) received apixaban at a dose of 5 mg twice daily; for patients weighing ≤60 kg, the dose was reduced to 2.5 mg twice daily.

A control group consisting of 20 healthy individuals was also included to establish reference values. The follow-up lasted 6 months from the initiation of treatment.

Markers of inflammation and fibrosis were measured in both serum and urine at three time points: at baseline, after 1 month, and after 6 months. The inflammatory markers analyzed included IL-6 and TNF-α, while TGF-β1 served as the indicator of antifibrotic activity. The concentration of human IL6 was quantified using a sandwich ELISA kit (MyBioSource, USA) with a detection range of 7.8–500.0 pg/mL and a sensitivity of less than 2.9 pg/mL. The concentration of human TNF-α was determined using a sandwich ELISA kit (MyBioSource, USA) with a detection range of 15.6–1000.0 pg/mL and a sensitivity of less than 7 pg/mL. The concentration of TGFβ1 was measured using a sandwich ELISA kit (MyBioSource, USA) with a detection range of 31.25–2000.00 pg/mL and a sensitivity of 18.75 pg/mL.

The primary endpoints of the study were the rates of thromboembolic events, including deep vein thrombosis, pulmonary embolism, and ischemic stroke, along with the incidence of clinically significant bleeding. Secondary endpoints involved monitoring dynamic changes in inflammatory biomarkers (IL-6, TNF-α) and the fibrotic marker TGF-β1 in both serum and urine. Renal function was also evaluated throughout the follow-up period by assessing changes in eGFR and levels of proteinuria.

Data analysis was performed using the Statistica 8 software package (StatSoft, license STA862D175437Q). Categorical variables were presented as absolute and relative frequencies with 95 % confidence intervals. The distribution of continuous variables was assessed for normality using the Shapiro–Wilk test. Normally distributed data were expressed as mean ± standard deviation (M ± SD), while non-normally distributed data were presented as median and interquartile range Me (Q25; Q75). Intergroup comparisons were performed using the following methods: Student's t-test for normally distributed variables; Mann–Whitney U test for non-normally distributed variables; Fisher's exact test for categorical variables. Differences were considered statistically significant at $p < 0.05$. In addition, odds ratios with 95 % confidence intervals were calculated to assess intergroup differences.

Results

The essential demographic, clinical, and laboratory characteristics of the patient cohort are summarized in *Table 1*.

Table 2. Baseline levels of inflammatory and fibrotic markers of the studied groups, Me (Q25; Q75)

Parameter, units of measurement	Control group, n = 20	Group I, n = 42	Group II, n = 43
IL-6 in serum, pg/mL	23.1 (18.3; 29.6)	87.2 (68.4; 112.7) p = 0.012	98.6 (75.9; 124.3) p = 0.008; p_1 = 0.573
IL-6 in urine, pg/mL	8.3 (7.1; 9.5)	56.3 (39.1; 74.5) p < 0.001	61.4 (43.8; 87.5) p < 0.001; p_1 = 0.738
TNF-α in serum, pg/mL	27.8 (25.3; 29.7)	123.5 (93.1; 137.6) p < 0.001	118.4 (88.2; 127.5) p < 0.001; p_1 = 0.312
TNF-α in urine, pg/mL	16.6 (15.1; 19.3)	47.9 (37.0; 52.3) p = 0.023	53.6 (39.8; 58.5) p = 0.016; p_1 = 0.475
TGF-β1 in serum, pg/mL	68.4 (51.7; 75.9)	265.3 (245.1; 312.6) p < 0.001	283.7 (251.1; 347.8) p < 0.001; p_1 = 0.147
TGF-β1 in urine, pg/mL	35.8 (31.5; 38.4)	894.6 (729.7; 932.6) p < 0.001	925.3 (798.7; 1032.2) p < 0.001; p_1 = 0.324

p: statistical significance of the difference between Group I and Group II in comparison with the control group; **p1:** statistical significance of the difference between Group II in comparison with Group I.

As shown in *Table 1*, there were no statistically significant differences in baseline demographic and clinical characteristics between the two groups.

Baseline concentrations of key inflammatory markers (IL-6, TNF-α) and the fibrotic marker TGF-β1 in serum and urine samples from the patients are summarized in *Table 2*.

As shown in *Table 2* both group I and group II demonstrated significantly elevated concentrations of all evaluated biomarkers in comparison with the control group, indicating a pronounced systemic and local inflammatory response. Specifically, serum IL-6 levels were significantly higher in Group I (p = 0.012) and Group II (p = 0.008) compared to the control group. A similar pattern was observed for urinary IL6 (p < 0.001 for both groups). For TNFα, significant differences were found in both serum (p < 0.001 for both groups) and urine (p = 0.023 and p = 0.016) compared to the control group. Likewise, levels of TGF-β1 were elevated in both serum (p < 0.001 for both groups) and urine (p < 0.001 for both groups) in Group I and Group II, respectively, compared to control.

In contrast, the comparison between Group I and Group II revealed no statistically significant differences for any of the assessed parameters, with all p_1 values exceeding 0.05. This indicates that, despite individual differences, both groups of patients had comparable baseline profiles of inflammatory and fibrotic activity.

The duration of prophylactic anticoagulation therapy ranged from 1 to 6 months, depending on the time needed to achieve remission of NS. The mean duration was 134 days (98–165) in Group I and 117 days (82–147) in Group II, with no statistically significant difference between the groups (p = 0.365).

No thromboembolic events were observed in either of the study groups during the observation period. However, bleeding episodes were reported in 12 patients (28.6 %; 95 % CI: 17.5–43.3) in the Group I and 3 patients (7.0 %; 95 % CI: 2.4–18.6) in the Group II, with a statistically significant difference between the groups (p = 0.01). The odds of bleeding events were significantly higher in the warfarin group compared to the apixaban group. Specifically, the odds of bleeding in the warfarin group were calculated to be 0.40, while in the apixaban group, the odds were 0.075. The resulting odds ratio was 5.33 (95 % CI: 1.32–21.48; p = 0.018), indicating that patients receiving warfarin were approximately 5.33 times more likely to experience a bleeding event compared to those receiving apixaban. All bleeding episodes observed during the study were categorized as minor based on the International Society on Thrombosis and Haemostasis criteria. These included instances of nosebleeds, gum bleeding, heavy menstrual bleeding, and subcutaneous bruising. Notably, none of the events required medical treatment or led to the discontinuation of anticoagulant therapy. Additionally, no deaths among participants were reported during the follow-up period.

In order to investigate the pleiotropic effects of apixaban, we analyzed inflammatory and fibrotic biomarkers at both 1 and 6 months of follow-up in both patient groups. This assessment aimed to evaluate potential non-anticoagulant effects of apixaban, including its influence on systemic inflammation and tissue remodeling processes.

In the course of the study, the dynamics of inflammatory (IL-6, TNFα) and fibrotic (TGF-β1) biomarker levels in blood serum and urine were analyzed in both patient groups after 1 and 6 months of treatment. IL-6 levels decreased in both serum and urine in both groups; however, by the 6-month follow-up, Group II exhibited significantly lower values compared to Group I (serum: p_2 = 0.012; urine: p_2 = 0.033). A similar trend was observed for TNFα and TGF-β1 levels. Both biomarkers showed a consistent and statistically significant decline in serum and urine in both groups. However, the reduction was more pronounced in Group II at 6 months. For TNFα, Group II demonstrated significantly lower levels compared to group I by the end of the observation period (serum: p_2 = 0.038; urine: p_2 = 0.028), indicating a stronger anti-inflammatory response. For TGF-β1, which reflects fibrotic activity, Group II also achieved significantly lower concentrations at 6 months (serum: p_2 = 0.035; urine: p_2 = 0.028). These findings suggest that the more pronounced reduction in both inflammatory and fibrotic biomarkers observed in Group II may be related to the pleiotropic effects of apixaban, beyond its primary anticoagulant action.

Table 3. Dynamics of inflammatory and fibrotic biomarkers in serum and urine at 1 and 6 months of follow-up in both studied groups, Me (Q25; Q75)

Treatment group	Baseline	1 month	6 months
IL-6 in serum, pg/mL			
Group I, n = 42	87.2 (68.4; 112.7)	73.4 (57.2; 96.4) p = 0.143	61.2 (43.2; 77.4) p = 0.042; p_1 = 0.041
Group II, n = 43	98.6 (75.9; 124.3)	48.6 (35.8; 54.6) p = 0.016	27.5 (18.7; 38.1) p = 0.001; p_1 = 0.025; p_2 = 0.012
IL-6 in urine, pg/mL			
Group I, n = 42	56.3 (39.1; 74.5)	45.6 (31.7; 62.6) p = 0.376	31.4 (25.2; 42.3) p = 0.031; p_1 = 0.154
Group II, n = 43	61.4 (43.8; 87.5)	32.6 (24.9; 47.6) p = 0.016	14.5 (9.8; 21.7) p = 0.001; p_1 = 0.024; p_2 = 0.033
TNF-α in serum, pg/mL			
Group I, n = 42	123.5 (93.1; 137.6)	88.3 (63.5; 102.5) p = 0.047	58.4 (35.4; 75.3) p = 0.012; p_1 = 0.031
Group II, n = 43	118.4 (88.2; 127.5)	67.4 (48.5; 81.6) p = 0.026	29.7 (18.4; 35.5) p = 0.001; p_1 = 0.027; p_2 = 0.038
TNF-α in urine, pg/mL			
Group I, n = 42	47.9 (37.0; 52.3)	32.6 (27.8; 45.4) p = 0.247	27.6 (21.2; 33.5) p = 0.042; p_1 = 0.071
Group II, n = 43	53.6 (39.8; 58.5)	28.2 (19.5; 36.6) p = 0.027	17.8 (12.3; 24.5) p = 0.002; p_1 = 0.035; p_2 = 0.028
TGF-β1 in serum, pg/mL			
Group I, n = 42	265.3 (245.1; 312.6)	187.4 (164.5; 212.7) p = 0.045	114.7 (96.8; 137.8) p = 0.001; p_1 = 0.021
Group II, n = 43	283.7 (251.1; 347.8)	135.8 (105.7; 157.9) p = 0.028	74.9 (58.2; 97.4) p = 0.001; p_1 = 0.018; p_2 = 0.035
TGF-β1 in urine, pg/mL			
Group I, n = 42	894.6 (729.7; 932.6)	436.2 (316.5; 545.7) p = 0.016	132.5 (89.6; 193.5) p = 0.001; p_1 = 0.001
Group II, n = 43	925.3 (798.7; 1032.2)	367.3 (294.3; 475.2) p = 0.001	56.5 (38.9; 98.3) p = 0.001 p_1 = 0.001; p_2 = 0.028

p: statistical significance of the difference between indicators before treatment and 1 and 6 months after treatment; **p_1:** statistical significance of the difference between indicators after 1 month and after 6 months after treatment; **p_2:** statistical significance of the difference between indicators after 6 months of treatment in Group II compared to Group I.

Discussion

In this prospective cohort study, we not only demonstrated the efficacy of apixaban in preventing thromboembolic complications in patients with nephrotic syndrome but also confirmed its potential pleiotropic properties, particularly its anti-inflammatory and antifibrotic effects.

Patients in the apixaban group showed a more pronounced reduction in IL-6, TNFα, and TGF-β1 levels in both serum and urine by the 6-month follow-up compared to those receiving warfarin. These differences reached statistical significance ($p_2 < 0.05$), suggesting that apixaban may influence PAR-1 and PAR-2 signaling pathways involved in inflammation, fibrosis, and oxidative stress [16,17].

Moreover, the incidence of bleeding episodes was significantly lower in the apixaban group compared to the warfarin group (p = 0.01), further confirming its safer profile in this high-risk group. All recorded bleeding events were minor and did not require discontinuation of therapy. No thromboembolic events were reported in either group, indicating that both anticoagulation regimens were effective in preventing thrombosis.

These findings are consistent with growing evidence that apixaban may exert pleiotropic effects by modulating inflammatory pathways, particularly through PAR-1 and PAR-2 signaling. Experimental studies have demonstrated that apixaban reduces the expression of VCAM-1, ICAM-1, TNF-α, IL-6, and markers of oxidative stress. Although the ARISTOTLE trial reported minimal impact on inflammatory biomarkers in patients with

atrial fibrillation, other condition-specific studies suggest that the anti-inflammatory potential of apixaban may depend on the clinical context [18,19].

Notably, S. Torramade-Moix et al. evaluated the effect of apixaban in vitro model of uremia-induced endothelial dysfunction. Exposure to uremic serum led to endothelial activation, characterized by increased VCAM1, ICAM1, and ROS levels, along with decreased nitric oxide synthase 3 and von Willebrand factor expression, platelet adhesion. Apixaban effectively reversed all these changes, demonstrating its ability to counteract uremia-induced vascular inflammation and oxidative stress. These results confirm the view that apixaban, beyond its anticoagulant activity, may act as an anti-inflammatory and antioxidant agent, providing additional benefits for patients with chronic kidney disease [20,21].

Overall, our results support the hypothesis that apixaban might be a safer alternative to warfarin with extra anti-inflammatory and antifibrotic properties – effects that could be clinically beneficial in slowing the progression of chronic kidney disease in GN.

Conclusions

1. Apixaban is an effective and safe alternative to warfarin in patients with NS due to primary GN, providing reliable prevention of thromboembolic events with a lower incidence of bleeding complications.

2. Apixaban demonstrated potential pleiotropic effects, including significant reductions in serum and urinary levels of inflammatory (IL-6, TNFα) and fibrotic (TGF-β1) biomarkers, which may reflect its anti-inflammatory and antifibrotic properties.

3. The dual action of apixaban – anticoagulant and anti-inflammatory / antifibrotic – may offer additional clinical benefits, potentially contributing to the slowing of chronic kidney disease progression in GN.

Prospects for further research. Future studies should aim to confirm the pleiotropic effects of apixaban in larger, multicenter trials with extended follow-up to evaluate its long-term impact on renal function and disease progression in nephrotic syndrome. Mechanistic research is needed to clarify the underlying pathways, including PAR signaling and inflammation modulation. The use of biomarker profiling and metabolomics could enhance understanding of its potential nephroprotective role. Comparative studies with other DOACs may also help determine whether these benefits are unique to apixaban or represent a class effect.

Limitations

This single-center study included a relatively small sample size, which may limit the generalizability of the results. The 6-month follow-up period was also relatively short and may not reflect long-term outcomes such as late thromboembolic events or bleeding complications. Additionally, the study lacked direct mechanistic investigations to confirm the pleiotropic effects of apixaban. Future multicenter trials with larger cohorts, longer follow-up, and molecular analyses are needed to validate and expand upon these findings.

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Information about the authors:

Mykhaloiko I. S., MD, PhD, Associate Professor of the Department of Internal Medicine 1, Clinical Immunology and Allergology named after Academician Ye. M. Neiko, Ivano-Frankivsk National Medical University, Ukraine.
ORCID ID: 0000-0002-7943-9029
Yatsyshyn R. I., MD, PhD, DSc, Professor, Rector of Ivano-Frankivsk National Medical University, Ukraine.
ORCID ID: 0000-0003-1262-5609
Cherniuk N. V., MD, PhD, DSc, Professor, Head of the Department of Internal Medicine 1, Clinical Immunology and Allergology named after Academician Ye. M. Neiko, Ivano-Frankivsk National Medical University, Ukraine.
ORCID ID: 0000-0001-8056-847X
Kaminskyi V. Ya., MD, PhD, Associate Professor of the Department of Internal Medicine 1, Clinical Immunology and Allergology named after Academician Ye. M. Neiko, Ivano-Frankivsk National Medical University, Ukraine.
ORCID ID: 0000-0002-1400-1018
Humeniuk M. Ya., MD, PhD, Associate Professor of the Department of Internal Medicine 1, Clinical Immunology and Allergology named after Academician Ye. M. Neiko, Ivano-Frankivsk National Medical University, Ukraine.
ORCID ID: 0000-0001-9545-3181

Відомості про авторів:

Михалойко І. С., канд. мед. наук, доцент каф. внутрішньої медицини № 1, клінічної імунології та алергології імені академіка Є. М. Нейка, Івано-Франківський національний медичний університет, Україна.
Яцишин Р. І., д-р мед. наук, професор, ректор Івано-Франківського національного медичного університету, Україна.
Чернюк Н. В., д-р мед. наук, професор, зав. каф. внутрішньої медицини № 1, клінічної імунології та алергології імені академіка Є. М. Нейка, Івано-Франківський національний медичний університет, Україна.
Камінський В. Я., канд. мед. наук, доцент каф. внутрішньої медицини № 1, клінічної імунології та алергології імені академіка Є. М. Нейка, Івано-Франківський національний медичний університет, Україна.
Гуменюк М. Я., канд. мед. наук, доцент каф. внутрішньої медицини № 1, клінічної імунології та алергології імені академіка Є. М. Нейка, Івано-Франківський національний медичний університет, Україна.

Mykhaloiko Iryna (Ірина Михалойко)
iralisn@gmail.com

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