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Apixaban versus warfarin in nephrotic syndrome: thromboembolic events, bleeding risk and changes in profibrotic and inflammatory cytokines

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Abstract. *Nephrotic syndrome (NS) is associated with a high risk of thromboembolic complications and activation of inflammatory and profibrotic pathways. The optimal anticoagulation strategy in NS remains uncertain.*
Objective. To compare the efficacy and safety of apixaban versus warfarin in patients with NS and to explore their effects on inflammatory, profibrotic, and coagulation biomarkers.
Methods. In this prospective observational cohort study, 67 adults with biopsy-proven primary glomerulonephritis and newly diagnosed NS were followed for 6 months. Patients received either warfarin (n=33) or apixaban (n=34) for thromboprophylaxis. Primary endpoints were thromboembolic and bleeding events. Secondary endpoints included longitudinal changes in serum and urinary IL-6, TNF-α, TGF-β_1, thrombin, proteinuria, and estimated glomerular filtration rate (eGFR).
Results. No thromboembolic events occurred in either group. Bleeding events were more frequent with warfarin (33.3%) than with apixaban (8.7%) (OR 5.17, 95% CI 1.28–20.9; p=0.021); all were minor. Both treatments were associated with reductions in inflammatory and profibrotic markers; however, apixaban demonstrated earlier and more pronounced decreases in serum and urinary IL-6, TNF-α, TGF-β_1, and urinary thrombin (all $p<0.05$ at 6 months vs warfarin). Proteinuria declined in both groups but was significantly lower in the apixaban group at 6 months (p=0.026). Decline in eGFR was less pronounced with apixaban (p=0.035 between groups).
Conclusions. Apixaban provided effective thromboprophylaxis with fewer bleeding events than warfarin and was associated with greater reductions in inflammatory and profibrotic biomarkers, alongside more favorable changes in proteinuria and eGFR. These findings suggest potential beneficial pleiotropic effects for apixaban requiring confirmation in randomized studies.

Keywords: *nephrotic syndrome, apixaban, warfarin, thromboprophylaxis, cytokines.*

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Апіксабан порівняно з варфарином пацієнтів з нефротичним синдромом: тромбоемболічні події, ризик кровотеч та зміни профібротичних і запальних цитокінів

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Резюме. *Нефротичний синдром (НС) асоціюється з високим ризиком тромбоемболічних ускладнень та активацією запальних і профібротичних шляхів. Оптимальна стратегія антикоагулянтної терапії при НС залишається невизначеною.*

Мета. Порівняти ефективність і безпеку апіксабану та варфарину у пацієнтів із НС, а також дослідити їх вплив на запальні, профібротичні та коагуляційні біомаркери.

Матеріали і методи. У проспективному обсерваційному когортному дослідженні 67 дорослих пацієнтів із біопсійно підтвердженим первинним гломерулонефритом і вперше діагностованим НС спостерігали протягом 6 місяців. Пацієнти отримували варфарин (n=33) або апіксабан (n=34) для тромбопрофілактики. Первинними кінцевими точками були тромбоемболічні події та кровотечі. Вторинні кінцеві точки включали динаміку рівнів IL-6, TNF-α, TGF-β_1, тромбіну в сироватці крові та сечі, а також зміни протеїнурії та розрахункової швидкості клубочкової фільтрації (рШКФ).

Результати. У жодній із груп не зареєстровано тромбоемболічних подій. Кровотечі частіше виникали у групі варфарину (33,3%) порівняно з апіксабаном (8,7%) (OR 5,17; 95% ДІ 1,28–20,9; p=0,021); усі випадки були незначними. Обидва препарати сприяли зниженню рівнів запальних і профібротичних маркерів; однак апіксабан забезпечував більш раннє та виражене зменшення IL-6, TNF-α, TGF-β_1 у сироватці та сечі, а також тромбіну в сечі (усі p<0,05 через 6 місяців порівняно з варфарином). Протеїнурія зменшувалася в обох групах, але через 6 місяців була достовірно нижчою у групі апіксабану (p=0,026). Зниження рШКФ було менш вираженим у групі апіксабану (p=0,035 між групами).

Висновки. Апіксабан забезпечував ефективну тромбопрофілактику з меншим ризиком кровотеч порівняно з варфарином і асоціювався з більш вираженим зниженням запальних та профібротичних біомаркерів, а також з покращенням показників протеїнурії та рШКФ. Отримані дані свідчать про потенційні плейотропні переваги апіксабану, які потребують підтвердження у рандомізованих дослідженнях.

Ключові слова: *нефротичний синдром, апіксабан, варфарин, тромбопрофілактика, запальні та профібротичні цитокіни.*

Introduction. Patients with nephrotic syndrome (NS) are known to have a markedly increased risk of thromboembolic complications due to a complex imbalance between procoagulant and anticoagulant factors [1–3]. Venous thromboembolism, encompassing deep vein thrombosis, pulmonary embolism, and renal vein thrombosis, constitutes one of the most clinically significant complications of NS [2].

The heightened thrombotic risk in these patients is indicative of a multifactorial process, characterized by the urinary loss of natural anticoagululants, including antithrombin III and protein C, increased production of procoagulant factors, platelet activation, and endothelial dysfunction [2, 3]. Severe hypoalbuminemia is widely recognized as a key determinant of thrombotic risk [1 ,4]. Current guidelines advocate for anticoagulation in specific high-risk patients; however, the most effective strategy for thromboprophylaxis in NS is still unclear and remains a topic of ongoing debate [3, 5].

Although warfarin and other vitamin K antagonists have long been used in this setting, their use is constrained by a limited therapeutic range, frequent monitoring requirements, and numerous drug and dietary interactions [6]. Changes in pharmacokinetics associated with hypoalbuminemia may exacerbate these restrictions in NS patients, potentially raising the risk of bleeding [5]. Additionally, low-molecular-weight heparins have significant disadvantages, particularly in patients with decreased antithrombin III levels and impaired renal function [3, 7].

Direct oral anticoagulants (DOACs) have gained popularity as a substitute for traditional treatment in recent years [8]. Patients with NS seem to find apixaban, a direct factor Xa inhibitor with comparatively low renal clearance, especially appealing. However, there is still a lack of clinical experience in this population, and it is unclear how heavy proteinuria and hypoalbuminemia affect medication disposition and clinical outcomes [7, 9].

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Factor Xa inhibitors may affect fibrotic and inflammatory processes in addition to their anticoagulant effects. According to experimental data, protease-activated receptors (PAR-1 and PAR-2) can be activated by both factor Xa and thrombin, resulting in intracellular pathways that stimulate the expression of adhesion molecules, profibrotic mediators, and pro-inflammatory cytokines [10, 11]. In preclinical models, inhibition of these pathways has been linked to a reduction in renal fibrosis and inflammation [12]. Nevertheless, there is still little and mostly indirect clinical evidence to support these effects in NS patients [13].

At the same time, most clinical studies of DOACs in NS have primarily addressed safety and thromboembolic outcomes, with considerably less attention given to their potential effects on inflammatory, profibrotic, and intrarenal coagulation pathways [1, 3, 9]. In particular, urinary thrombin, which may reflect intrarenal activation of coagulation, has rarely been evaluated in clinical studies. To our knowledge, this study is among the first to simultaneously assess clinical outcomes together with systemic and intrarenal biomarkers, including urinary thrombin, in patients with NS receiving anticoagulant therapy.

Against this background, we conducted a prospective observational study to compare apixaban and warfarin for thromboprophylaxis in patients with NS. In addition to clinical outcomes, we assessed changes in inflammatory and profibrotic cytokines, as well as thrombin levels in both serum and urine, in order to better characterize potential pleiotropic effects of factor Xa inhibition and to explore intrarenal coagulation activity in this patient population.

Materials and methods. *Study design and setting*. This prospective longitudinal cohort study was carried out at the Ivano-Frankivsk Regional Clinical Hospital (Ukraine) from 2022 to 2024 and included 67 patients with NS caused by biopsy-proven primary glomerulonephritis. No formal sample size calculation was performed, and the study size was determined based on available patients meeting the inclusion criteria. The study was conducted in accordance with international ethical standards, including the World Medical Association's 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, and written informed consent was obtained from all participants prior to enrollment.

Inclusion and exclusion criteria. Inclusion criteria were as follows: age ≥18 years; newly diagnosed NS (within the previous month) secondary to biopsy-confirmed primary glomerulonephritis (GN); and an estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2.

Exclusion criteria included: age <18 years; refusal to participate; presence of systemic connective tissue diseases, systemic vasculitis, type 1 or type 2 diabetes mellitus; history of cardiovascular events; chronic heart failure classified as New York Heart Association (NYHA) class III–IV; acute infections of any origin; malignancies; hepatic failure (acute or chronic); and psychiatric disorders.

The diagnoses of GN and NS were established based on standard clinical criteria in accordance with the KDIGO 2021 guidelines [4]. All patients underwent a comprehensive clinical and laboratory assessment, including relevant imaging and diagnostic procedures. Renal biopsy was performed to confirm the diagnosis and classify histological subtypes.

Treatment allocation and anticoagulation strategy. Prophylactic anticoagulation was administered in accordance with KDIGO recommendations and the decision-making algorithm proposed by R. Lin et al., which integrates serum albumin levels and bleeding risk assessment based on the HAS-BLED score [4, 8]. Anticoagulant therapy was initiated in patients with low to moderate bleeding risk, as assessed by the HAS-BLED score, and with a serum albumin concentration <25 g/L.

Patients were assigned to one of two treatment groups according to the anticoagulant prescribed in routine clinical practice: Warfarin group (n = 33): warfarin with regular monitoring of the international normalized ratio (INR) and dose adjustment to maintain therapeutic range.

Apixaban group (n = 34): apixaban administered at a standard dose of 5 mg twice daily. In patients weighing ≤60 kg, the dose was reduced to 2.5 mg twice daily in accordance with approved dosing recommendations.

As this was an observational study reflecting real-world clinical practice, treatment exposure was not blinded, and no protocol-mandated allocation sequence was applied. Treatment decisions were based on clinical judgment rather than random allocation; therefore, the potential for selection bias cannot be excluded.

The study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist. The completed STROBE checklist is provided in the Supplementary Materials (Supplementary Table S1).

Outcomes. The primary endpoints of the study were the incidence of thromboembolic events - including deep vein thrombosis, pulmonary embolism, and ischemic stroke - as well as the occurrence of clinically significant bleeding, as defined by the International Society on Thrombosis and Haemostasis (ISTH) criteria [6, 8].

Secondary endpoints included the longitudinal assessment of inflammatory biomarkers (IL-6, TNF-α), the profibrotic marker TGF-β_1, and thrombin levels in both serum and urine samples, along with evaluation of renal function dynamics through changes in eGFR and proteinuria during the follow-up period.

The duration of follow-up for both treatment groups was six months from therapy initiation.

Remission of NS was defined according to KDIGO 2021 criteria. Complete remission was defined as proteinuria <0.3 g/day with normalization of serum albumin

levels, whereas partial remission was defined as a ≥50% reduction in baseline proteinuria to a level <3.5 g/day [4].

ELISA. Thrombin levels in serum and urine were measured using a commercially available ELISA kit according to the manufacturer's instructions. Morning urine samples were collected under standardized conditions, centrifuged, and the supernatant was used for analysis. All samples were aliquoted and stored at −20 °C until batch testing.

Inflammatory and profibrotic cytokines (IL-6, TNF-α, and TGF-β_1) were measured using commercially available sandwich ELISA kits according to the manufacturers' protocols. All samples were analyzed in duplicate, and mean values were used for statistical analysis.

A control group of 20 apparently healthy individuals was included to establish reference biomarker levels. Controls were frequency-matched to patients by age and sex. Individuals with kidney disease, cardiovascular pathology, diabetes, inflammatory disorders, or active infection were excluded.

Statistical analysis. Statistical analysis was conducted using the Statistica 8 software package (StatSoft Inc., license STA862D175437Q). Categorical variables were reported as absolute numbers and percentages, accompanied by 95% confidence intervals (CIs). The distribution of continuous variables was assessed using the Shapiro–Wilk test to determine normality. Data with normal distribution were expressed as mean ± standard deviation (M ± SD), while non-normally distributed variables were presented as median and interquartile range (median, IQR). Between-group comparisons were carried out using Student's t-test for normally distributed variables and the Mann–Whitney U test for non-normally distributed variables. Categorical data were compared using Fisher's exact test. Time-to-event analysis for bleeding outcomes was performed using Kaplan–Meier survival curves, and differences between groups were assessed using the log-rank test. A p-value <0.05 was considered statistically significant. Additionally, odds ratios (ORs) with corresponding 95% confidence intervals were calculated to quantify between-group differences.

Results. *Baseline characteristics*. The study included 67 patients, 54 of whom were men (80.6% of the total). The study population had a median age of 47 years, with an interquartile range (IQR) of 39 to 52 years. At the beginning of the study, the renal and biochemical characteristics of both therapy groups were similar. The median eGFR was around 75 mL/min/1.73 m^2, the median proteinuria was about 6 g/day, and the median serum albumin levels were about 20 g/L. Table 1 shows the study population's detailed clinical and laboratory characteristics. There were no statistically significant differences between the Warfarin and Apixaban groups in terms of baseline demographic or clinical factors.

Table 1

Baseline demographic, clinical, and laboratory characteristics of the study groups (n = 67)

	Warfarin (n = 33)	Apixaban (n = 34)	p-value
Age, years; median (IQR)	45 (37–49)	48 (39–54)	0.378
Sex, male; % (95% CI)	75.8 (59.0–87.2)	85.3 (69.9–93.6)	0.368
Serum albumin, g/L; median (IQR)	19 (17–24)	20 (18–25)	0.884
eGFR mL/min/1.73 m^2; median (IQR)	75 (63–102)	73 (62–98)	0.672
Proteinuria g / day; median (IQR)	5.6 (4.1–6.8)	6.1 (4.8–7.3)	0.683
Urea, mmol/L; median (IQR)	7.3 (5.5–8.5)	7.2 (5.3–8.4)	0.839
Total cholesterol, mmol/L; median (IQR)	7.5 (6.6–8.7)	7.3 (6.4–8.6)	0.658
D-dimer, mg/L; median (IQR)	1.28 (0.91–1.57)	1.41 (0.98–1.73)	0.387
Platelet Count (*10^9/L); median (IQR)	226 (165283)	245 (189–315)	0.545
INR; median (IQR)	0.9 (0.8–1.0)	1.0 (0.9–1.1)	0.957
APTT (seconds); median (IQR)	45 (35–56)	42 (36–52)	0.775
Prothrombin time (seconds); median (IQR)	12 (11–13)	12 (11–14)	0.947
Fibrinogen (g/L); median (IQR)	5.5 (4.7–6.8)	6.4 (5.3–7.2)	0.647
Corticosteroids; % (95% CI)	29 87.9(76.8–99.0)	31 91.2 (81.7–100)	0.709
Cyclophosphamide; % (95% CI)	36.4 (20.0–52.8)	29.4 (14.1–44.7)	0.608
Cyclosporine; % (95% CI)	12.1 (1.0–23.2)	17.6 (4.8–30.4)	0.733
Mycophenolate mofetil; % (95% CI)	18.2 (5.0–31.4)	23.5 (9.3–37.7)	0.765
RAASi therapy; % (95% CI)	100 (89.4–100)	100 (89.7–100)	1.000
SGLT2i therapy; % (95% CI)	63.6 (45.1–79.6)	67.6 (49.5–82.6)	0.802

Note: *CI – confidence interval, eGFR, estimated glomerular filtration rate; INR, international normalized ratio; APTT, activated partial thromboplastin time; ICQ, interquartile range.*

Immunosuppressive medication was given based on the histological subtype and includes corticosteroids, cyclophosphamide, cyclosporine, and mycophenolate mofetil. There were no significant variations between the two treatment groups in how immunosuppressive regimens were given out. As clinically appropriate, treatment techniques also included inhibitors of the renin–angiotensin–aldosterone system (RAAS). Additionally, 44 patients (65.7%; 95% CI 53.7–76.0) were administered sodium–glucose cotransporter-2 (SGLT2) inhibitors as a component of their treatment regimen.

Cause of glomerular disease. Figure 1 shows the percentage of different types of glomerulonephritis (GN) in the two research groups. The predominant diagnosis was membranous glomerulonephritis (18 patients; 26.9%), followed by mesangioproliferative glomerulonephritis, focal segmental glomerulosclerosis (FSGS), minimal change disease (MCD), and membranoproliferative glomerulonephritis. Figure 1 shows that there were no statistically significant differences between the Warfarin and Apixaban groups in terms of the underlying GN etiology (all p> 0.05).

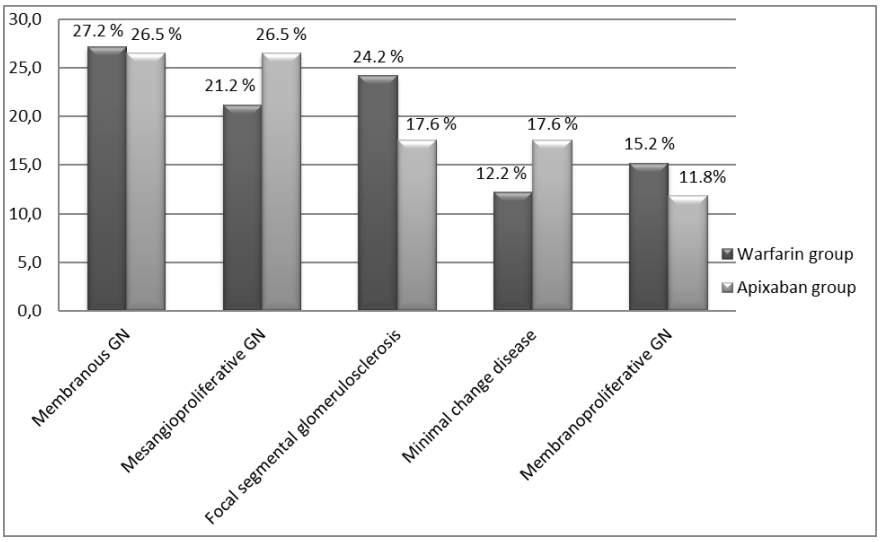

Fig. 1. Distribution of histological subtypes of primary glomerulonephritis in the warfarin (n = 33) and apixaban (n = 34) groups. No statistically significant differences were observed between the groups. Statistical comparisons were performed using Fisher's exact test (membranous GN, p = 1.000; mesangioproliferative GN, p = 0.577; focal segmental glomerulosclerosis, p = 0.562; minimal change disease, p = 0.515; membranoproliferative GN, p = 0.726).

Primary outcome: thromboembolic event and bleeding. The duration of prophylactic anticoagulation ranged from 1 to 6 months, depending on the time required to achieve remission of nephrotic syndrome (NS). The median treatment duration was 127 days (IQR 95–169) in the Warfarin group and 123 days (IQR 87–137) in the Apixaban group, with no significant between-group difference (p = 0.465).

Bleeding complications occurred more frequently in the Warfarin group than in the Apixaban group. Bleeding events were recorded in 11 of 33 patients (33.3%; 95% CI 19.5–50.9) receiving warfarin and in 3 of 34 patients (8.7%; 95% CI 3.0–23.1) treated with apixaban, corresponding to an odds ratio of 5.17 (95% CI 1.28–20.9; p = 0.021).

Time-to-event analysis using Kaplan–Meier curves demonstrated significantly lower bleeding-free survival in the Warfarin group compared with the Apixaban group (log-rank p = 0.015), indicating a higher cumulative incidence of bleeding over time among patients treated with warfarin (Fig. 2).

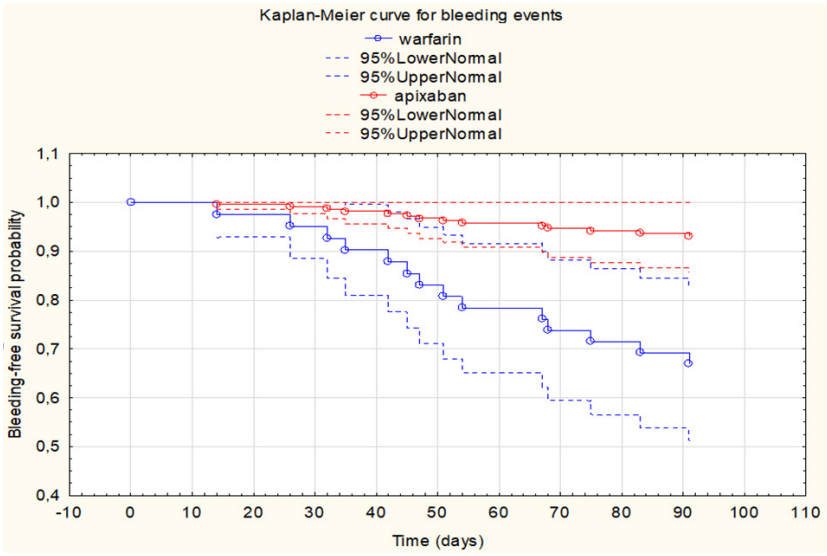

Fig. 2. Kaplan–Meier curves for bleeding-free survival in the warfarin and apixaban groups. The warfarin group showed a significantly higher cumulative incidence of bleeding. Statistical comparison between groups was performed using the log-rank test (p = 0.015).

All bleeding events were classified as minor according to the ISTH criteria and included epistaxis, gingival bleeding, menorrhagia, and subcutaneous bruising. No major bleeding events occurred. None of the bleeding episodes required hospitalization, invasive intervention, or permanent discontinuation of anticoagulant therapy. No deaths were reported during the observation period.

Secondary outcome: changes in proteinuria and eGFR, and changes in pro-inflammatory and profibrotic cytokines. A control group of 20 apparently healthy individuals was included to establish reference biomarker levels. Controls were frequency-matched to patients by age and sex. Compared to healthy controls, patients with nephrotic syndrome in both treatment groups had higher levels of inflammatory (IL-6, TNF-α), profibrotic (TGF-β_1), and coagulation (thrombin) proteins in serum and urine. At baseline, direct comparison between the warfarin group and the apixaban group showed no statistically significant differences for any assessed serum or urinary biomarkers (all $p_1 > 0.05$) (Table 2).

Table 2

Levels of pro-inflammatory and fibrotic markers and thrombin in serum and urine of the studied groups at baseline

	Control group (n=20)	Warfarin (n = 33)	Apixaban (n = 34)
IL-6 in serum, pg/mL; median (IQR)	23.1 (18.3–29.6)	84.6 (64.2–108.3) p=0.013	95.7 (77.3–118.6) p=0.009 p_1=0.686
IL-6 in urine, pg/mL; median (IQR)	8.3 (7.1–9.5)	61.5 (36.2–83.4) p<0.001	63.9 (44.6–88.3) p<0.001 p_1=0.842
TNFα in serum, pg/mL; median (IQR)	27.8 (25.3–29.7)	122.7 (98.4–147.8) p<0.001	119.4 (92.8–139.7) p<0.001 p_1=0.428
TNFα in urine, pg/mL; median (IQR)	16.6 (15.1–19.3)	43.8 (39.8–53.7) p=0.023	48.9 (41.5–62.5) p=0.016 p_1=0.475
TGFβ_1 in serum, pg/mL; median (IQR)	68.4 (51.7–75.9)	273.6 (225.4–335.6) p<0.001	289.8 (268.3–345.8) p<0.001 p_1=0.378
TGFβ_1 in urine, pg/mL; median (IQR)	35.8 (31.5–38.4)	679.6 (428.9–831.5) p<0.001	736.3 (497.2–912.3) p<0.001 p_1=0.647
Thrombin in serum, ng/ml; median (IQR)	0.68 (0.46–0.89)	0.97 (0.69–1.29) p=0.167	1.12 (0.73–1.35) p=0.173 p_1=0.562
Thrombin in urine, ng/ml; median (IQR)	0.38 (0.31–0.43)	9.8 (6.5–15.6) p<0.001	9.6 (6.2–14.7) p<0.001 p_1=0.562

Notes: *p-statistical significance of the difference between the Warfarin group and Apixaban group in comparison with the control group; p_1- statistical significance of the difference between the Apixaban group in comparison with the Warfarin group*

To explore the pleiotropic effects of apixaban, inflammatory and profibrotic biomarkers were evaluated in both treatment groups at 1 and 6 months of follow-up, alongside a longitudinal assessment of thrombin dynamics. The objective of this approach was to delineate the potential non-anticoagulant effects of apixaban, specifically its impact on factor Xa– and thrombin-mediated pathways associated with systemic inflammation and tissue remodeling.

Table 3 shows that a longitudinal analysis showed a steady decrease in inflammatory, profibrotic, and intrarenal coagulation markers in both groups over the 6-month follow-up period. However, patients taking apixaban showed changes earlier and more clearly.

Table 3

Longitudinal changes in serum and urinary inflammatory, fibrotic biomarkers, and thrombin levels at 1 and 6 months in both study groups

Treatment group	Baseline	1 month	6 months
IL-6 in serum, pg/mL (median, IQR)			
Warfarin (n = 33)	84.6 (64.2–108.3)	72.3 (56.8–98.1) p=0.254	53.5 (41.7–75.3) p=0.036 p_1=0.032
Apixaban (n = 34)	95.7 (77.3–118.6)	47.2 (34.2–52.5) p=0.024	24.7 (18.2–31.6) p=0.001 p_1=0.018 p_2=0.012
IL-6 in urine, pg/mL (median, IQR)			
Warfarin (n = 33)	61.5 (36.2–83.4)	41.7 (32.5–64.7) p=0.376	29.7 (24.7–45.4) p=0.039 p_1=0.165
Apixaban (n = 34)	63.9 (44.6–88.3)	31.7 (22.4–49.3) p=0.035	13.8 (9.5–20.9) p=0.001 p_1=0.037 p_2=0.039
TNFα in serum, pg/mL (median, IQR)			
Warfarin (n = 33)	122.7 (98.4–147.8)	85.5 (61.9–111.8) p=0.064	54.8 (31.8–79.4) p=0.024 p_1=0.039
Apixaban (n = 34)	119.4 (92.8–139.7)	63.2 (48.5–81.6) p=0.028	23.8 (17.8–36.2) p=0.001 p_1=0.024 p_2=0.039
TNFα in urine, pg/mL (median, IQR)			
Warfarin (n = 33)	43.8 (39.8–53.7)	31.6 (25.8–48.9) p=0.278	26.3 (22.6–34.6) p=0.045 p_1=0.134
Apixaban (n = 34)	48.9 (41.5–62.5)	27.5 (18.9–37.8) p=0.048	18.2 (13.3–26.6) p=0.001 p_1=0.042 p_2=0.048
TGFβ$_1$ in serum, pg/mL (median, IQR)			
Warfarin (n = 33)	273.6 (225.4–335.6)	192.5 (161.3–235.8) p=0.038	115.9 (95.6–139.4) p=0.001 p_1=0.025
Apixaban (n = 34)	289.8 (268.3–345.8)	126.7 (103.4–152.7) p=0.031	75.8 (56.7–98.5) p=0.001 p_1=0.013 p_2=0.027
TGFβ$_1$ in urine, pg/mL (median, IQR)			
Warfarin (n = 33)	679.6 (428.9–831.5)	426.6 (335.6–536.7) p=0.015	224.8 (182.4–275.8) p=0.001 p_1=0.001
Apixaban (n = 34)	736.3 (497.2–912.3)	343.5 (291.6–489.2) p=0.001	156.9 (88.9–198.3) p=0.001 p_1=0.001 p_2=0.038

Continuation of Table 3

Treatment group	Baseline	1 month	6 months
Thrombin in serum, ng/mL (median, IQR)			
Warfarin (n = 33)	0.9 (0.6–1.2)	0.9 (0.5–1.2) p=0.725	0.7 (0.5–0.9) p=0.534 p_1=0.342
Apixaban (n = 34)	1.1 (0.7–1.3)	0.6 (0.5–0.9) p=0.147	0.5 (0.3–0.8) p=0.046 p_1=0.082 p_2=0.067
Thrombin in urine, ng/mL (median, IQR)			
Warfarin (n = 33)	9.8 (6.5–15.6)	6.7 (4.5–8.6) p=0.147	4.8 (3.5–5.9) p=0.046 p_1=0.067
Apixaban (n = 34)	9.6 (6.2–14.7)	3.8 (2.2–4.6) p=0.034	1.6 (0.8–2.4) p=0.001 p_1=0.042 p_2=0.028

Note: *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 - the statistical significance of the difference between indicators 6 months after treatment in the Apixaban group in comparison with the Warfarin group.*

In the Apixaban group, serum IL-6 levels considerably dropped as early as 1 month ($p = 0.024$) and exhibited an additional substantial reduction at 6 months compared to baseline ($p = 0.001$). Conversely, in the Warfarin cohort, a significant reduction was noted solely after 6 months ($p = 0.036$). At the end of the follow-up, the levels of IL-6 in the blood were much lower in the Apixaban group than in the Warfarin group ($p_2 = 0.012$). A comparable trend was noted for urinary IL-6, exhibiting a significant decrease at 6 months in the Apixaban group ($p = 0.001$) and a more pronounced intergroup difference relative to the Warfarin group ($p_2 = 0.039$).

In both groups, the levels of TNF-α in the blood and urine went down over time, although they decreased to a greater extent in the Apixaban group. In the Apixaban group, serum TNF-α fell significantly at both 1 month ($p = 0.028$) and 6 months ($p = 0.001$). In the Warfarin group, however, a significant decrease was only seen at 6 months ($p = 0.024$). At month 6, TNF-α concentrations in both serum and urine were markedly decreased in the Apixaban group relative to the Warfarin group ($p_2 = 0.039$ and $p_2 = 0.048$, respectively).

Analysis of fibrotic activity revealed a consistent decline in TGF-β_1 concentrations during follow-up. Both groups demonstrated significant reductions in serum and urinary TGF-β_1 at 6 months (all $p < 0.001$); however, the magnitude of decrease was greater in the Apixaban group, resulting in significantly lower levels compared with the Warfarin group (serum $p_2 = 0.027$; urine $p_2 = 0.038$).

Regarding coagulation-related parameter, serum thrombin levels did not change significantly over time in either group (all $p > 0.05$). In contrast, urinary thrombin concentrations decreased progressively during follow-up. In the Apixaban group, urinary thrombin declined significantly at 1 month ($p = 0.034$) and further at 6 months ($p = 0.001$), whereas in the Warfarin group a significant reduction was observed only at 6 months ($p = 0.046$). At the end of follow-up, urinary thrombin concentrations were significantly lower in the Apixaban group compared with the Warfarin group ($p_2 = 0.028$).

Overall, the data indicate that although both anticoagulation strategies were associated with improvements in inflammatory, profibrotic, and intrarenal coagulation markers, apixaban treatment was characterized by earlier and more pronounced biomarker reductions, suggesting the presence of potential pleiotropic effects beyond anticoagulation.

These alterations were followed by positive changes in kidney parameters in the Apixaban group. Proteinuria decreased in both groups throughout follow-up; the decline was more noticeable in the Apixaban group at 6 months (Fig. 3).

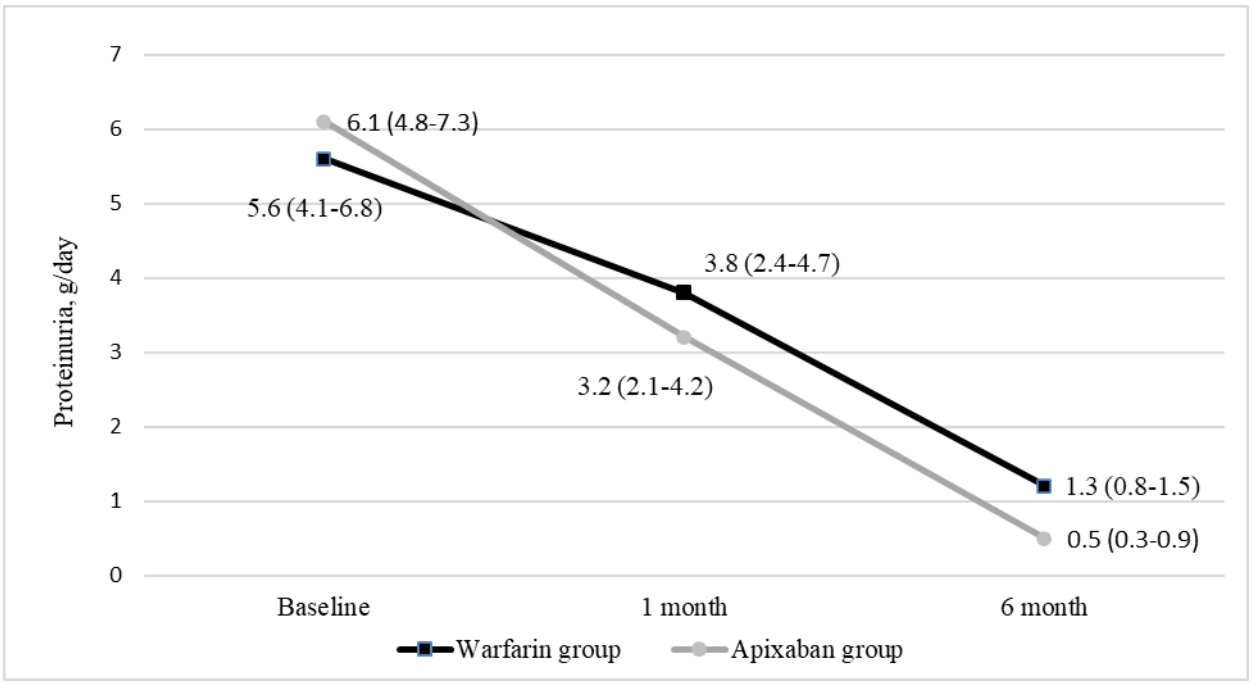

Fig. 3. Longitudinal changes in proteinuria levels in the Warfarin and Apixaban groups at baseline, 1 month, and 6 months of follow-up. Statistical comparisons between groups were performed using the Mann–Whitney U test (1 month: p = 0.647; 6 months: p = 0.026).

Similarly, whereas eGFR diminished with time in both groups, the reduction was less dramatic in patients administered apixaban, yielding a statistically significant difference between groups at month 6 (Fig. 4). These results indicate possible pleiotropic benefits of apixaban beyond anticoagulation; nevertheless, additional investigations are necessary to validate a direct renoprotective impact.

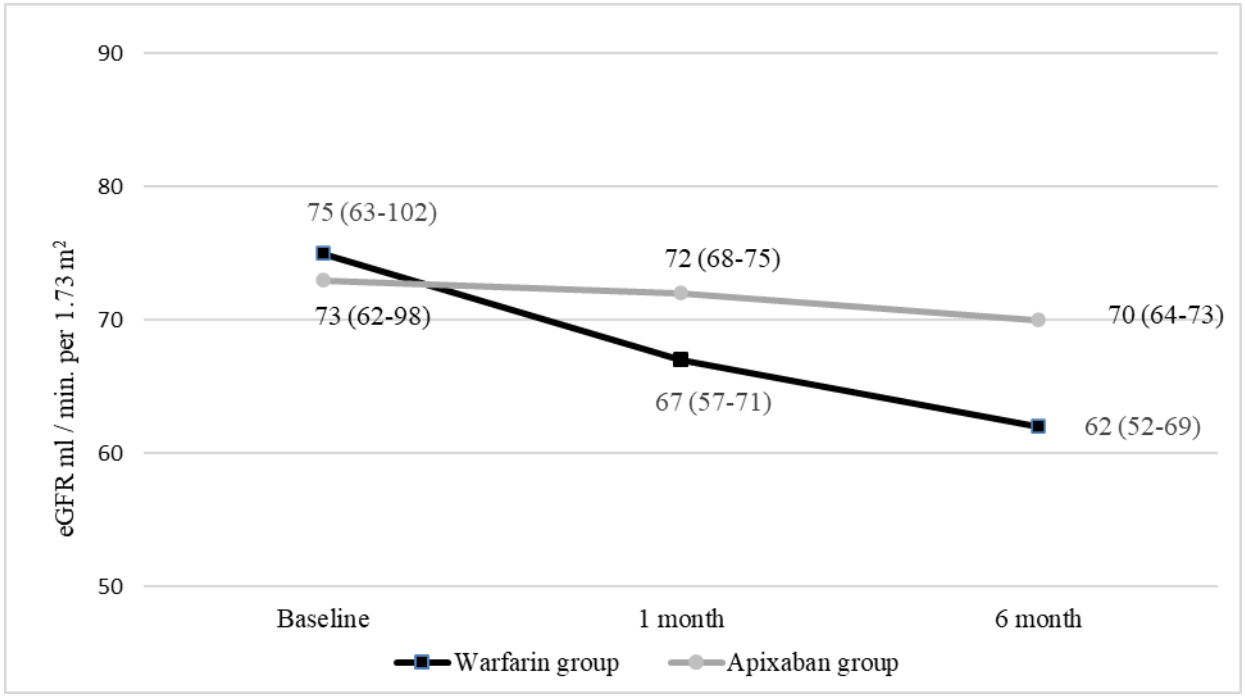

Fig. 4. Longitudinal changes in eGFR levels in the Warfarin and Apixaban groups at baseline, 1 month, and 6 months of follow-up. Statistical comparisons between groups were performed using the Mann–Whitney U test (1 month: p = 0.068; 6 months: p = 0.035).

Discussion. There were no thromboembolic events in either cohort of NS patients treated with warfarin or apixaban during the follow-up period. At the same time, it became clear that the treatment strategies were different in terms of safety and how biomarkers changed over time. Patients administered apixaban exhibited fewer bleeding incidents and exhibited more significant reductions in pro-inflammatory and profibrotic markers in comparison to those treated with warfarin. These observations warrant cautious interpretation, as they may indicate a more extensive biological influence of factor Xa inhibition beyond its anticoagulant properties, especially regarding kidney injury. Preliminary results of this work were reported previously [**14**]; the present analysis extends those findings by providing a more detailed assessment of both clinical outcomes and biomarker changes.

From a safety point of view, the lower rate of bleeding in the apixaban group is in line with data from other studies that have been published. Van Meerhaeghe et al. reported a favorable safety profile of apixaban in patients with severe nephrotic syndrome, without an increase in bleeding events despite marked hypoalbuminemia [**15**]. In our cohort, all bleeding incidents were minor and did not necessitate the cessation of therapy. Significantly, no thromboembolic events occurred in either group, reinforcing the overall efficacy of anticoagulation in this high-risk population. The study's small sample size and short follow-up period made it hard to find differences in thromboembolic outcomes. The lack of such events in our cohort restricts the direct comparison of the efficacy of the two anticoagulants. These findings indicate that apixaban may provide a more advantageous equilibrium between efficacy and safety in clinical practice.

The changes seen in inflammatory and profibrotic markers provide additional insight into the potential biological effects of anticoagulation. Patients who took apixaban had bigger drops in IL-6, TNF-α, and TGF-β_1 in both serum and urine after 6 months. Both treatment groups showed improvement over time, but the changes seemed to be more noticeable in the apixaban group. One possible explanation has to do with how factor Xa and thrombin activate PAR-1 and PAR-2, which are found on endothelial and renal cells. When these receptors are activated, they start signaling pathways inside cells that increase the production of pro-inflammatory cytokines and profibrotic mediators. Blocking factor Xa may slow down these processes, which would lower inflammation and fibrogenesis in the kidney. This idea is backed up by experimental data that show apixaban can lower oxidative stress, improve endothelial function, and stop inflammatory signaling [**10**, **17**]. In vitro studies have also shown that factor Xa inhibition lowers the expression of IL-6, TNF-α, VCAM-1, and ICAM-1 [**11**].

An important consideration is that the observed changes in inflammatory and profibrotic biomarkers may not be solely attributable to anticoagulant therapy. All patients received immunosuppressive treatment, which could have contributed to the improvement in these parameters. Due to the limited sample size and absence of multivariable analysis, the potential influence of confounding factors cannot be excluded.

These findings align with the expanding literature regarding DOACs in NS. Most of the studies that are available have looked at safety and pharmacokinetics. These studies have shown that anticoagulant activity is usually still present even when drug levels change [**9**]. At the same time, there isn't much information about inflammatory and profibrotic pathways. In this context, our findings build upon prior research by demonstrating concurrent decreases in cytokine levels and urinary thrombin, indicating that the biological effects of factor Xa inhibition may be more intricate, especially in conditions marked by active inflammation and intrarenal coagulation. Notably, large cardiovascular trials like ARISTOTLE found only small changes in circulating inflammatory markers [**18**]. This could mean that the size of these effects depends on the disease that is causing them.

One very important part of our study is measuring thrombin in both serum and urine. Even though systemic thrombin levels stayed about the same, urinary thrombin levels went down a lot over time, especially in patients who were taking apixaban. This pattern corroborates the hypothesis that NS is linked to predominant intrarenal thrombin generation rather than systemic coagulation activation [**16**]. Kelddal et al. have documented similar results, demonstrating that, despite diminished apixaban concentrations in the circulation of NS patients, thrombin production markers were inhibited, indicating the preservation of anticoagulant activity at the tissue level [**9**]. The more significant decrease in urinary thrombin noted in our study may indicate a more efficient regulation of intrarenal coagulation mechanisms, although this interpretation should be regarded as preliminary.

Changes in renal parameters followed a similar direction. Although proteinuria decreased in both groups, the reduction was greater in patients receiving apixaban, and the decline in eGFR appeared less pronounced. These findings may suggest a possible beneficial influence on renal function; however, they should be interpreted with caution. The relatively short follow-up period and the observational design of the study do not allow definitive conclusions regarding long-term nephroprotective effects.

Limitations. This study has several limitations that should be taken into account when interpreting the results. It was done at only one place and with a small number of patients, which may make it less applicable to other situations. Also, because of the observational design, we can't draw any conclusions about cause and effect, and there may still be some confounding factors. The 6-month follow-up period may be insufficient to evaluate long-term thromboembolic risk and sustained renal outcomes. Lastly, biomarker measurements were taken at set times, so they might not show how biologi-

cal processes change over time. Additional multicenter studies with larger cohorts and extended follow-up are required to validate these findings and elucidate their clinical significance.

Conclusions. In conclusion, apixaban was associated with a lower incidence of bleeding compared with warfarin while maintaining effective thromboprophylaxis in patients with NS. In addition, apixaban treatment was linked to more pronounced reductions in inflammatory, profibrotic, and intrarenal coagulation biomarkers, including urinary thrombin. These findings suggest potential pleiotropic effects of factor Xa inhibition; however, they should be interpreted with caution given the observational design and relatively short follow-up period. Their clinical significance and long-term impact on renal outcomes require confirmation in larger randomized studies.

Ethics approval and consent to participate. The study protocol was reviewed and approved by the Ethics Committee of Ivano-Frankivsk National Medical University, Ivano-Frankivsk, Ukraine (Protocol No. 124/21, November 29, 2021). All participants provided written informed consent prior to enrollment in the study and for the collection and analysis of their clinical and laboratory data.

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Availability of data and materials. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions.

I. Mykhaloiko: literature search, study design, data analysis, manuscript drafting, and manuscript submission.

R. Yatsyshyn: conceptualization and project administration.

Both authors read and approved the final manuscript.

Use of artificial intelligence. Artificial intelligence tools were used to improve the language, grammar, and readability of the manuscript. They were not used to create data, analyze results, or make scientific conclusions. The authors reviewed the final manuscript and take full responsibility for its content.

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