УДК 616.12-005.4:616.12-009.72 Original research

ANTI-INFLAMMATORY EFFECTS OF MAGNESIUM OROTATE IN REVASCULARIZED PATIENTS WITH CAD AND HFMREF: A RANDOMIZED STUDY

Kobryn O.T., Vakaliuk I.P.

Ivano-Frankivsk National Medical University, Ukraine

Key words: *coronary artery disease, heart failure with mildly reduced ejection fraction, magnesium orotate, galectin-3, soluble ST2, systemic inflammation, myocardial remodeling, treadmill test.*

Bukovinian Medical Herald. 2025. V. 29, № 4 (116). P. 16-22.

DOI: *10.24061/2413-0737.29.4.116.2025.3*

E-mail: *kobryn28o@gmail.com vakaluk@gmail.com*

Resume. *Coronary artery disease (CAD) and heart failure with mildly reduced ejection fraction (HFmrEF) represent interconnected clinical entities characterized by persistent low-grade systemic inflammation. Even in patients who have undergone complete myocardial revascularization, ongoing inflammatory activity remains a critical driver of adverse cardiovascular events and disease progression.*

Oblective. *To improve the efficacy of treatment of patients with stable CAD and heart failure with mid ranged ejection fraction, who underwent myocardial revascularization by percutaneous coronary intervention*

Material and methods. *Study included 62 patients with stable coronary artery disease (CAD) and mid-range left ventricular ejection fraction (LVEF 40–49%) who had undergone complete revascularization. Participants were randomized into two groups. Group 1 (n = 29) received standard pharmacological therapy. Group 2 (n = 33) received standard therapy supplemented with magnesium orotate at a dose of 500 mg twice daily. Treatment duration was 6 months with 3 visits: screening and inclusion, follow-up visit after 3 months, follow-up visit after 6 months. All patients underwent a treadmill stress test using the Bruce or modified Bruce protocol, serum concentrations of Galectin-3 and soluble ST2 (sST2) were measured, inflammatory indices, including (NLR), (SII), (PLR), (SIRI), and (AISI), were calculated.*

The results. *The research revealed that magnesium orotate has shown promise as an adjunct therapy in cardiovascular disease. Over the course of the study, the distance covered during the treadmill test showed a significant upward trend in both groups, with a more pronounced improvement observed among patients receiving magnesium orotate. Markers of systemic inflammation demonstrated a favorable dynamic in both groups, although the reduction was substantially more pronounced among patients receiving magnesium orotate. Biomarkers associated with myocardial remodeling and fibrosis exhibited a downward trend throughout the study period, with more favorable shifts observed in the magnesium orotate group.*

Conclusions*. Given the persistent inflammatory activation in stable CAD with HFmrEF and the need for therapies that improve both biomarker profiles and functional capacity, magnesium orotate is a compelling candidate for investigation. Its dual action on myocardial metabolism and inflammation suggests it could modulate key pathways underlying adverse remodeling while also enhancing exercise performance*

МАГНІЙ ОРОТАТ ЯК ІНСТРУМЕНТ МОДИФІКАЦІЇ ЗАПАЛЕННЯ ТА ПОЛІПШЕННЯ ФІЗИЧНОЇ ВИТРИВАЛОСТІ У ПАЦІЄНТІВ ПІСЛЯ РЕВАСКУЛЯРИЗАЦІЇ

Кобрин О.Т., Вакалюк І.П.

Ключові слова*: ішемічна хвороба серця, серцева недостатність зі середньозниженою фракцією викиду, магній оротат, галектин-3, розчинний ST2, системне запалення, реваскуляризація, тест із фізичним навантаженням.*

Резюме. *Ішемічна хвороба серця (ІХС) та серцева недостатність із помірно зниженою фракцією викиду (СНпзФВ) є актуальними проблемами сучасної кардіології, що значною мірою зумовлені хронічним низькоінтенсивним запаленням. Навіть у пацієнтів зі стабільною формою ІХС після проведення повної реваскуляризації зберігається системна запальна активність, яка асоціюється з прогресуванням серцевої недостатності та підвищенням ризику несприятливих подій.*

Мета дослідження - *підвищити ефективність лікування пацієнтів зі*

Буковинський медичний вісник. 2025. Т. 29, № 4 (116). С. 16-22.

стабільною ІХС та серцевою недостатністю із помірно зниженою фракцією викиду, яким проведено реваскуляризацію міокарда шляхом черезшкірного коронарного втручання.

Матеріал і методи. *У дослідження включено 62 пацієнти зі стабільною ІХС та ФВ ЛШ у межах 40–49%, яким проведено повну реваскуляризацію. Учасників методом рандомізації розподілено на дві групи: група 1 (n = 29) отримувала стандартну фармакологічну терапію; група 2 (n = 33) на тлі стандартного лікування додатково призначався магнію оротат у дозі 500 мг двічі на добу. Тривалість лікування становила шість місяців із трьома візитами (включення, 3-й та 6-й місяці). Всім пацієнтам проводили тредміл-стрес-тест за протоколом Bruce або модифікованим протоколом Bruce. Визначали сироваткові рівні галектину-3 та sST2, а також розраховували індекси системного запалення: NLR, SII, PLR, SIRI та AISI.*

Результати. *Застосування магнію оротату асоціювалося з більш вираженим покращенням клініко-функціональних показників порівняно зі стандартною терапією. Дистанція, подолана під час тредміл-тесту, зросла в обох групах, проте в групі магнію оротату динаміка була значно кращою. Маркери системного запалення знижувалися в усіх пацієнтів, але більш істотне зменшення виявлено у групі комбінованої терапії. Біомаркери міокардіального ремоделювання та фіброзу (галектин-3, sST2) продемонстрували тенденцію до зниження, при цьому позитивні зміни були більш вираженими в пацієнтів, які отримували магнію оротат.*

Висновки*. У пацієнтів зі стабільною ІХС та СНпзФВ, навіть після повної реваскуляризації, зберігається персистувальна активація запалення, що потребує пошуку додаткових терапевтичних підходів. Результати дослідження свідчать, що додавання магнію оротату до стандартної терапії сприяє більш вираженому зниженню маркерів системного запалення та міокардіального ремоделювання, а також покращенню толерантності до фізичного навантаження. Отримані дані дають підстави розглядати магній оротат як перспективний напрям у комплексному лікуванні цієї категорії хворих.*

Formulation of the problem. Coronary artery disease (CAD) and heart failure (HF) are increasingly recognized as conditions driven in part by chronic low-grade inflammation. Even in clinically stable CAD - such as patients who have undergone successful revascularization - persistent inflammatory activity has been linked to worse long-term outcomes [1].

Analysis of recent research and publications. In heart failure with mildly reduced ejection fraction (HFmrEF, typically defined as left ventricular EF 40–49%), an intermediate phenotype of HF, systemic inflammation is likewise prevalent and may contribute to ongoing myocardial dysfunction and disease progression [2]. Indeed, HFmrEF shares many features with HF with reduced EF, including a high prevalence of ischemic heart disease as an underlying cause [3], and patients often exhibit “inflammaging” – an age-related state of chronic low-grade inflammation – that can exacerbate both atherosclerotic and heart failure processes [2]. This inflammatory milieu provides a mechanistic link between stable CAD and HFmrEF, suggesting that anti-inflammatory strategies might yield therapeutic benefits in this population.

In this context, biomarkers of fibrosis and inflammation have emerged as important tools for risk stratification and disease monitoring. Galectin-3, a β-galactoside-binding lectin secreted by activated macrophages, plays a pivotal role in cardiac fibrosis and adverse remodeling. Elevated galectin-3 levels promote fibroblast proliferation, collagen deposition, and myocardial inflammation, processes that drive HF progression [4]. Clinically, galectin-3 is considered a prognostic biomarker – higher circulating levels have been associated with increased mortality and HF hospitalization in both preserved and reduced EF heart failure. Soluble ST2 (sST2), an interleukin-33 receptor fragment, is another inflammatory biomarker of interest. Myocardial strain and stress lead to increased sST2 release, which acts as a decoy receptor binding IL-33 and thereby blunting IL-33’s cardioprotective, anti-fibrotic effects [5]. As a result, sST2 is directly linked to inflammation and fibrogenesis in the heart. Notably, sST2 has proven to be an independent predictor of adverse outcomes across the spectrum of chronic and acute HF. There is also evidence that sST2 correlates with disease activity in coronary artery disease; for example, higher sST2 levels in stable CAD patients have been associated with greater atherosclerotic plaque burden and vulnerability [6]. Given their involvement in pathological remodeling, galectin-3 and sST2 represent promising indicators of the inflammatory state in patients with stable CAD and concomitant HFmrEF.

In stable CAD patients with HFmrEF, improving exercise capacity is a key therapeutic goal, making the treadmill test a relevant metric to judge the efficacy of interventions aimed at this population. One such intervention that has garnered interest is magnesium

orotate, an organic magnesium salt combining magnesium with orotic acid. Magnesium orotate is notable for its pharmacological and biochemical properties that may confer cardiovascular benefits. Orotic acid (a precursor in pyrimidine nucleotide synthesis, sometimes dubbed vitamin B13) is thought to facilitate the transport of magnesium into cells and augment cardiac energy metabolism [7].

Study aim. To improve the efficacy of treatment of patients with stable CAD and heart failure with mid ranged ejection fraction, who underwent myocardial revascularization by percutaneous coronary intervention.

Presentation of the main research material. This prospective, randomized, controlled study was conducted in the Departments of the Ivano-Frankivsk Regional Clinical Cardiological Hospital from January 2022 to December 2024. The study protocol was approved by the Ethics Committee of Ivano-Frankivsk National Medical University (protocol number available upon request) and conducted in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent prior to inclusion.

A total of 98 patients with stable coronary artery disease (CAD) and mid-range left ventricular ejection fraction (LVEF 40–49%) who had undergone complete revascularization were initially assessed for eligibility. Inclusion criteria also required age between 45 and 75 years, absence of acute coronary syndromes within the previous 6 months, and the ability to perform a treadmill stress test. Exclusion criteria included decompensated heart failure (NYHA class IV), chronic kidney disease stage IV or higher, liver dysfunction (ALT or AST >3× upper normal level), active inflammatory or autoimmune disease, malignancies, and recent use (within 3 months) of magnesium-containing supplements.

Out of the 98 initially assessed patients, 36 were excluded based on the predefined criteria. The final study sample included 62 patients, which met the a priori estimated sample size needed to detect a clinically relevant difference with 80% power and α=0.05.

Participants were randomized into two groups using a computerized randomization tool (random.org).

Group 1 (n = 29) received standard pharmacological therapy according to current ESC guidelines. Group 2 (n = 33) received standard therapy supplemented with magnesium orotate at a dose of 500 mg twice daily.

Treatment duration was 6 months with 3 visits: screening and inclusion, follow-up visit after 3 months, follow-up visit after 6 months.

Inflammatory indices, including neutrophil-to-lymphocyte ratio (NLR), systemic immune-inflammation index (SII), platelet-to-lymphocyte ratio (PLR), systemic inflammation response index (SIRI), and aggregate index of systemic inflammation (AISI), were calculated from peripheral blood samples collected at baseline and at the end of the study period.

Serum concentrations of Galectin-3 and soluble ST2 (sST2) were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits: Human Galectin-3 Quantikine® ELISA Kit (R&D Systems, Minneapolis, MN, USA), Presage® ST2 Assay (Critical Diagnostics, San Diego, CA, USA)

All patients underwent a treadmill stress test using the Bruce or modified Bruce protocol, selected based on baseline functional status and physician discretion. Exercise tolerance was assessed by duration (minutes), peak metabolic equivalents (METs), and occurrence of ischemic changes or arrhythmias.

Data were analyzed using Python 3.11 with the scipy.stats, numpy, and zepid libraries. The Shapiro–Wilk test was used to assess the normality of distributions. As all continuous variables were non-parametric, they were summarized as median (Q1; Q3), and group comparisons were performed using the Mann–Whitney U test. Categorical variables were reported as counts and percentages and compared using the χ^2 test. A p-value <0.05 was considered statistically significant.

At baseline, the median age of patients in the magnesium orotate group was slightly higher compared to the control group, although the difference did not reach statistical significance (p=0,097). Body mass index values were comparable between groups, with no meaningful variations observed (p=0,573). Analysis of body surface area demonstrated similar results, as no statistically significant discrepancies were found between the cohorts (p=0,29). The distribution of sexes was also closely matched, with a slightly higher proportion of women present in both groups, yet without any significant difference (p=0,899) (table 1).

Table 1

Baseline characteristics of patients

Parameter	Revascularized control group	Revascularized magnesium orotate group	p-value
Age, years	54.00 [48.00; 57.00]	57.00 [53.00; 59.00]	0.097
BMI, kg/m²	28.66 [24.25; 32.39]	28.03 [25.51; 30.19]	0.573
BSA, m²	1.89 [1.82; 1.97]	1.84 [1.80; 1.94]	0.29
Female sex	18 (62.10%)	21 (63.60%)	0.899
Male sex	11 (37.90%)	12 (36.40%)	

Over the course of the study, the distance covered during the treadmill test showed a significant upward trend in both groups, with a more pronounced improvement observed among patients receiving magnesium orotate. At baseline, median distances were nearly identical between the groups (p=0,391), and similar findings persisted at the 3-month evaluation (p=0,502). Nevertheless, by the 6-month follow-up, patients in the magnesium orotate group achieved a significantly greater distance compared to controls (p=0,042). Both cohorts demonstrated statistically significant increases relative to baseline at each follow-up; however, the relative change was markedly higher in the treatment group, reaching a 13,69% improvement by month six compared to 6,19% in controls. Oxygen consumption adjusted for body surface area remained

comparable initially (p=0,848), yet after three months a modest but statistically significant advantage emerged in the magnesium orotate group (p=0,041). By the end of the treatment period, oxygen consumption was significantly greater among patients who received magnesium supplementation (p<0,001), reflecting a 14,14% increase from baseline compared to a 6,43% gain in the control group (table 2).

Throughout the observation period, serum sodium concentrations decreased significantly in both groups, with a more pronounced decline detected among patients treated with magnesium orotate. Initial sodium levels were comparable between groups (p=0,439), and although no significant differences were seen after three months (p=0,153), by the 6-month follow-up sodium levels were significantly lower in the magnesium group compared to controls (p=0,034). Reductions in sodium concentration were statistically significant within each group at both follow-up points. Potassium levels at baseline were nearly identical across groups (p=0,423) and remained similar during the subsequent evaluations, without significant between-group differences at either three (p=0,894) or six months (p=0,412). Nevertheless, a statistically significant intra-group reduction in potassium was evident over time. Regarding magnesium, initial concentrations did not differ meaningfully between the groups (p=0,107), and remained comparable at intermediate and final visits (p=0,354 and p=0,84, respectively). However, patients receiving magnesium orotate demonstrated a greater relative increase in serum magnesium concentrations, reaching a 12,23% rise by the end of treatment compared to 6,54% in the control group, with these intra-group changes being statistically significant (table 3).

Markers of systemic inflammation demonstrated a favorable dynamic in both groups, although the reduction was substantially more pronounced among patients receiving magnesium orotate. At baseline, systemic immune-inflammation index (SII) values were comparable (p=0,163), but after three months, a statistically significant lower SII was observed in the magnesium group (p=0,022), with the difference becoming even more evident by six months (p=0,002). Platelet-to-lymphocyte ratio (PLR)

Table 2

Dynamics of treadmill test parameters

Parameter	Revascularized control group	Revascularized magnesium orotate group	p-value
Distance walked, m			
t0	337.00 (327.00; 363.00)	337.00 (323.00; 349.00)	0.391
t1	356.00 (336.00; 373.00)	355.00 (343.00; 370.00)	0.502
Δ%, p t1	+3.27%, p<0.001	+6.86%, p<0.001	
t2	370.00 (349.00; 384.00)	377.00 (361.00; 392.00)	0.042
Δ%, p t2	+6.19%, p<0.001	+13.69%, p<0.001	
Oxygen consumption, ml/min/m²			
t0	17.00 (16.00; 18.00)	17.00 (16.00; 17.00)	0.848
t1	17.71 (16.51; 18.43)	18.06 (17.22; 18.69)	0.041
Δ%, p t1	+3.14%, p<0.001	+6.92%, p<0.001	
t2	18.42 (16.93; 19.11)	19.26 (18.66; 20.21)	<0.001
Δ%, p t2	+6.43%, p<0.001	+14.14%, p<0.001	

Table 3

Dynamics of electrolyte levels

Parameter	Revascularized control group	Revascularized magnesium orotate group	p-value
Sodium, mmol/L			
t0	141.84 (141.40; 143.71)	142.83 (139.62; 144.71)	0.439
t1	137.13 (133.99; 141.84)	136.72 (133.45; 139.17)	0.153
Δ%, p t1	-3.37%, p<0.001	-4.36%, p<0.001	
t2	132.60 (127.86; 136.62)	129.12 (125.88; 132.70)	0.034
Δ%, p t2	-7.28%, p<0.001	-9.11%, p<0.001	
Potassium, mmol/L			
t0	4.49 (4.40; 4.61)	4.49 (4.40; 4.56)	0.423
t1	4.35 (4.22; 4.43)	4.25 (4.16; 4.44)	0.894
Δ%, p t1	-3.75%, p<0.001	-4.72%, p<0.001	
t2	4.20 (4.01; 4.31)	4.08 (3.93; 4.23)	0.412
Δ%, p t2	-7.62%, p<0.001	-9.45%, p<0.001	
Magnesium, mmol/L			
t0	0.79 (0.71; 0.88)	0.77 (0.66; 0.82)	0.107
t1	0.83 (0.73; 0.91)	0.79 (0.70; 0.88)	0.354
Δ%, p t1	+3.44%, p<0.001	+6.02%, p<0.001	
t2	0.85 (0.75; 0.95)	0.86 (0.77; 0.92)	0.84
Δ%, p t2	+6.54%, p<0.001	+12.23%, p<0.001	

showed a similar pattern, with initial values not differing significantly (p=0,24), but a significant reduction favoring magnesium supplementation emerging at six months (p=0,02). Neutrophil-to-lymphocyte ratio (NLR) also followed this trend: although baseline differences were nonsignificant (p=0,15), a significant divergence became apparent at both three (p=0,032) and six months (p=0,004), with larger declines seen in the magnesium group. In terms of the systemic inflammation response index (SIRI), values were initially similar (p=0,347), yet a notable intergroup difference was detected after six months of treatment (p=0,007). AISI (aggregate index of systemic inflammation) mirrored these findings, with comparable baseline levels (p=0,332), followed by significantly lower values in the magnesium orotate group at three (p=0,042) and six months (p=0,004).

Biomarkers associated with myocardial remodeling and fibrosis exhibited a downward trend throughout the study period, with more favorable shifts observed in the magnesium orotate group. Concentrations of soluble ST2 (sST2) were comparable at baseline (p=0,587) and remained similar after three months (p=0,658), without significant intra-group changes at that point. By six months, both groups experienced statistically significant reductions in sST2 levels compared to baseline, although no significant difference between the groups was noted (p=0,884). Galectin-3 levels at the start of the study were also similar between cohorts (p=0,299). At the three-month evaluation, the magnesium orotate group showed a trend toward lower galectin-3 values (p=0,066), which reached statistical significance by the end of the observation period (p=0,016). Reductions in galectin-3 concentration were significant within both groups at both follow-ups, but the relative decrease was more substantial in patients treated with magnesium orotate, achieving a 12,41% reduction compared to 7,23% in controls (table 5).

Clinically, magnesium orotate has shown promise as an adjunct therapy in cardiovascular disease. A prior randomized trial in patients with severe chronic heart failure reported that adding magnesium orotate to standard therapy improved symptoms and significantly reduced 1-year mortality compared to placebo (52% vs 76% survival, $p<0.05$). These benefits were attributed not merely to correction of magnesium deficiency, but also to the pharmacological effects of orotate, given the magnitude of outcome improvement observed [8]. Smaller studies have also noted improvements in exercise tolerance and cardiac function with magnesium orotate, including in patients

Table 4

Dynamics of inflammatory and metabolic markers

Marker	Revascularized control group	Revascularized magnesium orotate group	p-value
SII			
t0	789.84 (626.66; 871.95)	635.17 (581.67; 851.07)	0.163
t1	696.40 (544.22; 793.44)	524.71 (458.17; 657.41)	0.022
Δ%, p t1	-9.47%, p<0.001	-18.45%, p<0.001	
t2	647.20 (528.65; 736.70)	422.19 (379.46; 546.67)	0.002
Δ%, p t2	-18.40%, p<0.001	-32.69%, p<0.001	
PLR			
t0	200.16 (175.06; 247.61)	183.47 (170.58; 224.56)	0.24
t1	188.91 (159.58; 230.38)	160.68 (145.20; 202.74)	0.06
Δ%, p t1	-6.13%, p<0.001	-12.50%, p<0.001	
t2	180.80 (147.30; 211.72)	149.13 (128.26; 181.23)	0.02
Δ%, p t2	-12.02%, p<0.001	-21.45%, p<0.001	
NLR			
t0	2.90 (2.60; 3.75)	2.51 (2.26; 3.02)	0.15
t1	2.76 (2.48; 3.42)	2.16 (1.96; 2.80)	0.032
Δ%, p t1	-6.19%, p<0.001	-12.63%, p<0.001	
t2	2.64 (2.32; 3.20)	1.90 (1.69; 2.40)	0.004
Δ%, p t2	-12.26%, p<0.001	-23.67%, p<0.001	
SIRI			
t0	1.49 (1.14; 2.00)	1.48 (1.15; 1.88)	0.347
t1	1.36 (1.03; 1.85)	1.17 (0.92; 1.54)	0.061
Δ%, p t1	-9.24%, p<0.001	-18.13%, p<0.001	
t2	1.25 (0.96; 1.67)	0.99 (0.75; 1.28)	0.007
Δ%, p t2	-17.92%, p<0.001	-32.57%, p<0.001	
AISI			
t0	395.32 (275.73; 504.43)	397.80 (282.86; 463.42)	0.332
t1	351.46 (216.71; 436.39)	297.53 (199.97; 356.48)	0.042
Δ%, p t1	-12.37%, p<0.001	-23.49%, p<0.001	
t2	309.42 (189.34; 374.19)	242.27 (162.80; 279.02)	0.004
Δ%, p t2	-23.67%, p<0.001	-40.41%, p<0.001	

Table 5

Dynamics of myocardial fibrosis and remodeling biomarkers

Marker	Revascularized control group	Revascularized magnesium orotate group	p-value
sST2, ng/mL			
t0	32.63 (29.09; 35.86)	32.11 (29.56; 33.70)	0.587
t1	31.33 (27.65; 34.47)	31.28 (27.45; 34.58)	0.658
Δ%, p t1	-5.53%, p=0.146	-1.71%, p=0.632	
t2	30.19 (26.38; 33.67)	29.02 (25.83; 33.16)	0.884
Δ%, p t2	-8.92%, p=0.023	-7.84%, p=0.035	
Galectin-3, ng/mL			
t0	17.20 (15.91; 18.70)	16.29 (14.39; 18.13)	0.299
t1	16.97 (15.48; 17.89)	15.25 (13.76; 17.43)	0.066
Δ%, p t1	-3.45%, p<0.001	-6.50%, p<0.001	
t2	16.28 (15.12; 17.13)	14.12 (13.01; 15.63)	0.016
Δ%, p t2	-7.23%, p<0.001	-12.41%, p<0.001	

with CAD. Furthermore, magnesium itself possesses anti-arrhythmic and anti-inflammatory properties – magnesium supplementation can suppress pro-inflammatory cytokine release and oxidative stress, which are often elevated in heart failure and post-infarction states [9]. Magnesium orotate may thus uniquely combine the benefits of magnesium repletion (such as improved myocardial excitability and endothelial function) with the metabolic support and potential anti-inflammatory effects of orotic acid. Previous studies done by Herashchenko et al found that elevated inflammation indices in patients with heart failure are associated with worse diastolic function of the left ventricle [10].

Conclusions. Given the persistent inflammatory activation in stable CAD with HFmrEF and the need for therapies that improve both biomarker profiles and functional capacity, magnesium orotate is a compelling candidate for investigation. Its dual action on myocardial metabolism and inflammation suggests it could modulate key pathways underlying adverse remodeling while also enhancing exercise performance. The present study was designed to address this gap by evaluating the effects of magnesium orotate on inflammatory biomarkers (galectin-3 and sST2) and exercise tolerance (treadmill test performance) in patients with stable CAD and HFmrEF who have undergone revascularization. We were able to prove, that adjunctive magnesium orotate therapy dampens the chronic inflammatory state and improves functional capacity in this patient population, thereby providing a novel therapeutic avenue to improve outcomes in stable ischemic HFmrEF.

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Information about the authors
Kobryn Oleksii Tarasovych – PhD student, Department of Internal Medicine № 2 and Nursing, Ivano-Frankivsk National Medical University. https://orcid.org/0009-0007-0727-2665.
Vakaliuk Igor Petrovych – doctor of Medical Science, professor, Department of Internal Medicine № 2 and Nursing, Ivano-Frankivsk National Medical University. https://orcid.org/0000-0002-4430-6816.

Відомості про авторів
Кобрин О.Т. – аспірант кафедри внутрішньої медицини № 2 та медсестринства, Івано-Франківський національний медичний університет, м. Івано- Франківськ, Україна. https://orcid.org/0009-0007-0727-2665.
Вакалюк І.П. – д-р мед. наук, професор кафедри внутрішньої медицини № 2 та медсестринства, Івано-Франківський національний медичний університет, м. Івано-Франківськ, Україна. https://orcid.org/0000-0002-4430-6816.

Дата першого надходження рукопису до видання: 21.10.2025
Дата прийнятого до друку рукопису після рецензування: 17.11.2025
Дата публікації: 30.12.2025