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Efficacy of Losartan within a Multicomponent Secondary Prevention Strategy for Cardiovascular Events in Post-Ischemic Stroke Patients

Abstract

Aim. To assess the efficacy of adding losartan to standard therapy in patients with ischemic heart disease (IHD) and polyvascular atherosclerosis following ischemic stroke as part of a multicomponent secondary prevention strategy over a 4-month treatment period.

Materials and Methods. A prospective study enrolled 60 patients who were randomly assigned to two equal groups: standard therapy (including antiplatelet agents, statins, antihypertensive medications, and risk factor management) and standard therapy plus losartan. All patients underwent assessment of lipid profiles, as well as serum levels of the matrix metalloproteinases MMP-2 and MMP-9, interleukin-1β (IL-1β), plasminogen activator inhibitor-1 (PAI-1), thrombin-activatable fibrinolysis inhibitor (TAFI), and tumor necrosis factor-alpha (TNF-α), both at baseline and after 4 months of therapy.

Results. After 4 months of therapy, a significant reduction in the serum levels of lipids (TC, TG, LDL-C, HDL-C), MMP-2, MMP-9, IL-1β, PAI-1, TAFI, and TNF-α ($p<0.05$) was observed in both groups. However, compared with the standard therapy group, the addition of losartan was associated with a significant reduction in MMP-2 ($p = 0.008$) and TAFI ($p = 0.011$) in the intergroup ANCOVA analysis.

Conclusions. The addition of losartan to standard therapy in patients with IHD and polyvascular atherosclerosis following ischemic stroke over a 4-month period was associated with improved clinical outcomes, attenuation of inflammatory and proteolytic cascade activation, and enhanced hemodynamic parameters.

Keywords: *Ischemic heart disease, generalized atherosclerosis, ischemic stroke, losartan, secondary prevention, MMP-2, MMP-9, IL-1β, PAI-1, TAFI, TNF-α.*

Introduction. Ischemic stroke is one of the leading causes of death and disability worldwide. The INTERSTROKE study demonstrated that over 90 % of the risk for stroke is attributable to modifiable factors such as hypertension, dyslipidemia, and cardiac conditions [1]. Renin-angiotensin system inhibitors (ACE inhibitors) represent a cornerstone of secondary prevention strategies after stroke. Losartan possesses additional neuroprotective and vascular remodeling properties, including the suppression of matrix metalloproteinases (MMP-2 and MMP-9), which play key roles in vascular wall degradation and disruption of the blood-brain barrier [2]. Losartan, as a representative angiotensin II receptor blocker (ARB), has demonstrated superiority in reducing stroke risk compared with beta-blockers (atenolol) in the LIFE study [3].

Specifically, losartan was associated with a 25 % reduction in stroke risk (HR 0.75; p=0.001), as well as improved outcomes in terms of all-cause and cardiovascular mortality, with reductions of 13 % and 37-39 %, respectively, in the diabetic subgroup [4,5].

Losartan stands out among ARBs due to its ability to modulate key pathophysiological pathways beyond blood pressure reduction. Preclinical and clinical observations show that blocking the renin–angiotensin–aldosterone system (RAAS) – which losartan does effectively – attenuates both inflammatory and thrombotic processes in patients at high cardiovascular risk [6]. Moreover, a recent in vitro study demonstrated that losartan significantly suppresses TNF-α-induced pro-inflammatory and catabolic signaling in human cells, highlighting its anti-inflammatory and matrix-protective effects [7]. These properties make losartan especially suitable for geriatric patients with ischemic heart disease, polyvascular atherosclerosis, and prior ischemic stroke, as it addresses inflammation, extracellular matrix remodeling, and hemostatic balance – key contributors to recurrent cardio- and cerebrovascular events.

Biomarkers of inflammation and fibrinolysis – such as IL-1β, TNF-α, PAI-1, and TAFI – also have prognostic significance in patients with stroke and atherosclerosis. However, data on the impact of angiotensin II receptor blockers (ARBs) on these parameters in patients with polyvascular disease following ischemic stroke are limited.

Aim. To evaluate the impact of adding losartan to standard therapy in patients with a history of ischemic stroke, ischemic heart disease (IHD), and polyvascular atherosclerosis on lipid profile, biomarkers of vascular remodeling (MMP-2, MMP-9) and inflammation (IL-1β, TNF-α, PAI-1, TAFI).

Materials and Methods. This prospective, open-label, comparative, parallel clinical observation was conducted at the Municipal Non-Profit Enterprise "Kyiv City Clinical Hospital №12," Ukraine, between November 2023 and November 2024. The study was carried out in accordance with the principles of the Declaration of Helsinki (World Medical Association, 2013) and complied with the requirements of the Ethics Committee of Bohomolets National Medical University. The study protocol was reviewed and approved by the local ethics committee. Written informed consent was obtained from all participants prior to inclusion in the study.

Study design. A total of 60 patients with a confirmed diagnosis of ischemic stroke (acute cerebrovascular accident of ischemic type) were enrolled; all were in the chronic phase of the disease (ranging from 1 to 7 years post-event). The observation period lasted 4 months and included two assessment time points: baseline evaluation – within the first hours after hospital admission, and the treatment period lasting 4 months.

Patients were assigned to two comparable groups: the control group received standard therapy according to current national protocols, while the experimental group received the same standard therapy with the addition of losartan 50 mg, titrated individually.

Inclusion criteria: patients aged ≥60 years with stable coronary artery disease (including post-infarction cardiosclerosis); history of ischemic stroke or myocardial infarction 12 months to 7 years prior; confirmed ischemic stroke on CT/MRI; generalized atherosclerosis (IMT ≥1.2 mm, plaques, or ≥30 % stenosis in ≥2 vascular territories); heart failure ≤NYHA IIb; stable clinical condition; ability to follow the study protocol; written informed consent.

Exclusion criteria: congenital or acquired heart defects; cardiomyopathies; non-ischemic myocardial lesions; persistent AF/flutter; heart failure NYHA III–IV; haematologic disorders; coagulopathies; anaemia; thrombophilia; severe venous insufficiency; type 1 or 2 diabetes; recent trauma, surgery, or bleeding; chronic liver disease with impaired function; renal failure (eGFR <60); active infections; substance abuse; immunosuppressive therapy in the past 3 months; or age <60 years.

The study followed a structured sequence of phases, beginning with patient screening based on clearly defined inclusion and exclusion criteria. After the study cohort was finalized, the participants were randomized with consideration of clinical and demographic balance. At the initiation of the therapeutic intervention, each patient underwent a comprehensive assessment, which included clinical evaluation, echocardiography, Doppler ultrasound examination, Holter monitoring, and laboratory testing focused on inflammatory, hemostatic, and remodeling biomarkers. Over the course of four months, patients received standard therapy with or without the addition of losartan. Upon completion of the treatment period, follow-up assessments were performed using the same protocol. The collected data were then subjected to statistical analysis to compare within-group and between-group dynamics of the measured parameters.

Outcomes assessment and measurement. The main endpoints included changes in biomarkers of vascular remodeling (MMP-2, MMP-9) and inflammation (IL-1β, TNF-α, PAI-1, TAFI), as well as hemodynamic parameters. Echocardiographic examinations were performed using the HITACHI LTD, ALOKA Arietta S-70 system (Japan), utilizing B-mode, M-mode, color Doppler, and tissue Doppler imaging. Doppler ultrasonography of the extracranial arteries included B-mode, spectral, and color Doppler techniques. The following parameters were assessed: flow volume (FV), peak systolic velocity (PSV), mean velocity (MnV), end-diastolic velocity (EDV), pulsatility index (PI), resistance index (RI), intima-media thickness (IMT), and degree of stenosis. The methodology adhered to the Society for Vascular Ultrasound (SVU) Professional Performance Guidelines [8]. Twenty-four-hour Holter monitoring was performed using an ARNIKA device with standardized methods of data analysis.

Venous blood samples were collected immediately upon hospital admission and again after 4 months. The serum was prepared by centrifugation at 900 × g for 40 minutes and subsequently stored at -20 °C. The plasma concentrations of TAFI, PAI-1, MMP-2, MMP-9, IL-1β, and TNF-α were measured using enzyme-linked immunosorbent assay (ELISA) kits (Santa Cruz Biotechnology, CA, USA) following the methodology described by Aydin et al. [9]. The lipid profile was assessed using a standard enzymatic method.

Statistical Analysis. Statistical analysis was performed using SPSS software, version 20.0 (SPSS, Inc., Chicago, IL, USA), and GraphPad Prism, version 6.0 (GraphPad Software, Inc., La Jolla, CA, USA). Quantitative data were presented as the mean and standard deviation (M ± SD). To test the hypothesis of normal distribution, the one-sample Kolmogorov–Smirnov test was used. Changes in participants' outcomes between baseline and the end of treatment were compared using paired-sample t-tests (intragroup). Analysis of covariance (ANCOVA) was applied to identify any differences between the two groups after the intervention, adjusting for baseline measurements and confounders (intergroup).

Results. In this study, involving 60 patients with a balanced sex distribution, a comparative assessment was

conducted to evaluate the effectiveness of standard therapy versus its combination with losartan in the context of dynamic changes in key laboratory and instrumental parameters. The mean age of the study population was 75 years; 46.6 % were women, and 53.4 % were men. There were no statistically significant differences between the groups in terms of age, sex distribution, post-stroke duration, or baseline clinical or laboratory characteristics (p>0.05), confirming the comparability of the groups.

In both groups, a reduction in total cholesterol levels in intragroup analysis was observed; however, the decrease was more pronounced among patients receiving losartan (from 5.46 ± 1.09 mmol/L to 3.80 ± 0.54 mmol/L; p < 0.001) than in the control group, where cholesterol levels decreased from 5.31 ± 1.48 mmol/L to 4.30 ± 1.06 mmol/L (p<0.001) (Table 1, Figure 1A). This corresponded to an average reduction of 1.65 ± 0.94 mmol/L in the losartan group versus 1.01 ± 0.80 mmol/L in the control group, with a trend toward statistical significance between groups (p = 0.059) (Table 1).

A similar pattern was noted for low-density lipoprotein cholesterol (LDL-C). LDL-C, known for its direct atherogenic effect, showed a significant reduction in all subgroups, with a more pronounced trend observed in patients receiving losartan, indicating a more favorable achievement of target lipid values in patients receiving the modified treatment regimen. In the control group, the LDL-C level decreased from 2.98 ± 1.25 mmol/L to 2.36 ± 0.92 mmol/L (p=0.002). In the losartan group, levels decreased from 3.42 ± 0.91 mmol/L to 2.21 ± 0.50 mmol/L (p<0.001), corresponding to an absolute reduction of 1.21 mmol/L versus 0.62 mmol/L in the control group, with the between-group difference approaching significance (p=0.050) (Table 1, Figure 1B).

The level of high-density lipoprotein cholesterol (HDL-C), which is commonly considered the cardioprotective δ fraction due to its role in reverse cholesterol transport, increased in both groups after treatment. In the control group, HDL-C levels increased slightly from 1.05 ± 0.40 mmol/L to 1.23 ± 0.51 mmol/L (p=0.195) (Table 1, Figure 1C). On the other hand, in the losartan group, the elevation was more pronounced and differed significantly after 4 months (0.76 ± 0.42 vs 1.14 ± 0.58 mmol/L; p=0.020). Despite the approximately twofold higher elevation of HDL-C after losartan addition compared with standard therapy alone, changes in HDL-C in ANCOVA analysis were not significant (0.38 vs 0.18 mmol/L; p=0.355; Table 1).

Among the analyzed lipids, only triglyceride levels showed a more pronounced change in intragroup analysis in the standard care group. In the control group, triglycerides decreased from 2.34 ± 0.81 mmol/L to 1.77 ± 0.49 mmol/L (p=0.001), whereas in the losartan group, triglyceride levels decreased from 1.97 ± 0.65 mmol/L to 1.53 ± 0.68 mmol/L (p=0.015; Figure 1D). However, in ANCOVA analysis, the difference between groups was not significant (p=0.538; Table 1).

Although this trend may appear counterintuitive, it could reflect the multifaceted effects of losartan, including its anti-inflammatory activity and improvement of endothelial function. This finding is supported by in vivo evidence showing its regulatory influence on TNF-α and MMP-2 levels [10]. This effect is consistent with the concept of the pleiotropic properties of losartan, whereby AT_1-receptor blockade, attenuation of inflammation, and

Table 1

Analysis of outcomes with focus on lipid parameters (M ± SD)

Parameters	Standard treatment group (n=30)	p1	Standard treatment + Losartan group (n=30)	p2	p3	p4
Total cholesterol, mmol/L						
Baseline value	5.31±1.48		5.46±1.09		0.781	
Post-treatment value	4.30±1.06	<0.001	3.80±0.54	<0.001		
Mean changes	-1.01±0.80		-1.65±0.94			0.059
Triglycerides, mmol/L						
Baseline value	2.34±0.81		1.97±0.65		0.202	
Post-treatment value	1.77±0.49	0.001	1.53±0.68	0.015		
Mean changes	-0.57±0.64		-0.44±0.48			0.538
HDL, mmol/L						
Baseline value	1.05±0.40		0.76±0.42		0.068	
Post-treatment value	1.23±0.51	0.195	1.14±0.58	0.020		
Mean changes	0.18±0.59		0.38±0.45			0.355
LDL, mmol/L						
Baseline value	2.98±1.25		3.42±0.91		0.323	
Post-treatment value	2.36±0.92	0.002	2.21±0.50	<0.001		
Mean changes	-0.62±0.75		-1.21±0.76			0.050

Note: p1-2 – difference in standard care and losartan groups before and after intervention (intragroup analysis); p3 – differences between standard care and losartan groups baseline characteristics; p4 – difference between groups throughout the study (ANCOVA intergroup analysis). Significance was stated at p<0.05

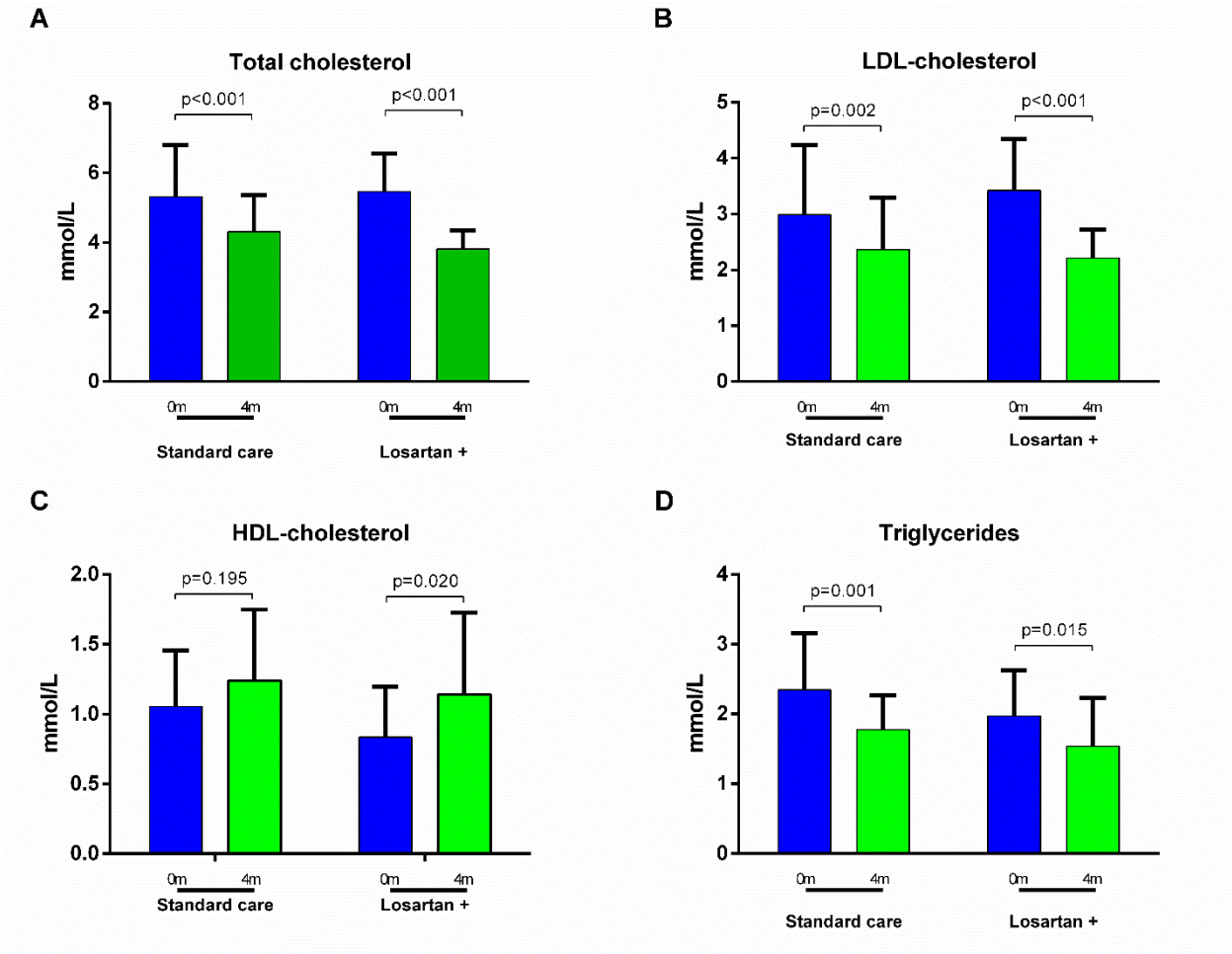

Figure 1. *Intra-group outcomes analysis with an accent on lipid parameters changes (A – total cholesterol; B – LDL-C; C – HDL-C; D – triglycerides). Data presented as M ± SD*

vascular wall remodeling contribute to a more profound correction of the atherogenic burden [10].

Particular attention in this study was devoted to the evaluation of vascular wall remodeling markers, as these biochemical indicators reflect the intensity of extracellular matrix degradation and structural alterations in the arterial wall – processes that play a key role in the progression of atherosclerosis and the development of its complications. In patients receiving modified therapy, including losartan, the level of MMP-2 decreased significantly from 5.90 ± 0.59 ng/mL to 4.27 ± 0.72 ng/mL (p<0.001), indicating substantial suppression of enzymatic activity. This dynamic was markedly greater than that in the control group, where the MMP-2 level decreased from 5.55 ± 0.73 ng/mL to 4.91 ± 1.00 ng/mL (p=0.005) (Table 2, Figure 2A). The between-group difference in absolute MMP-2 reduction was significant (p=0.008), confirming an additional effect of losartan on vascular wall stabilization and reduction in remodeling activity – likely attributable to its pleiotropic properties, including attenuation of endothelial dysfunction and suppression of chronic vascular inflammation.

A similar, albeit less pronounced, trend was observed for MMP-9, which, along with MMP-2, contributes to collagen and elastin degradation, thereby promoting structural destabilization of atherosclerotic plaques (Figure 2B). In the losartan group, the mean reduction in the MMP-9 level was 1.23 ± 0.83 ng/mL, whereas it was 0.68 ± 0.67 ng/mL in the control group. Although the between-group difference did not reach conventional statistical significance (p=0.078), it clearly indicates a trend toward better control of proteolytic activity under treatment with an angiotensin II receptor blocker (Table 2).

These findings are consistent with the well-established pleiotropic effects of losartan, which, in addition to its antihypertensive action, is capable of modulating inflammatory and remodeling processes within the vascular wall. The observed reductions in MMP-2 and MMP-9 activity may be considered one of the mechanisms contributing to atherosclerotic plaque stabilization and lowering the risk of rupture, thus supporting the prevention of acute coronary and cerebrovascular events in patients at high cardiovascular risk.

An important finding of this study was the ability of modified therapy, including losartan, to reduce systemic inflammation more effectively – a key pathogenic mechanism in the progression of atherosclerosis and destabilization of atherosclerotic plaques.

Table 2

Analysis of outcomes with focus on inflammatory and proteolytic cascade activation markers (M ± SD)

Parameters	Standard treatment group (n=30)	p1	Standard treatment + Losartan group (n=30)	p2	p3	p4
MMP-2, ng/mL						
Baseline value	5.55±0.73		5.90±0.59		0.190	
Post-treatment value	4.91±1.00	0.005	4.27±0.72	<0.001		
Mean changes	-0.63±0.86		-1.63±0.99			0.008
MMP-9, ng/mL						
Baseline value	4.77 ± 0.59		4.93 ± 0.49		0.462	
Post-treatment value	4.09 ± 0.54	>0.001	3.69 ± 0.63	0.001		
Mean changes	-0.68±0.67		-1.23±0.83			0.078
TNF-α, pg/mL						
Baseline value	6.88 ± 0.43		7.03 ± 0.20		0.304	
Post-treatment value	4.73 ± 0.51	>0.001	4.60 ± 0.32	<0.001		
Mean changes	-2.14±0.60		-2.43±0.35			0.180
IL-1β, pg/mL						
Baseline value	5.80 ± 0.72		5.66 ± 0.51		0.577	
Post-treatment value	4.21 ± 0.47	>0.001	3.92 ± 0.65	<0.001		
Mean changes	-1.59±0.82		-1.73±0.80			0.652
TAFI, μg/mL						
Baseline value	4.47 ± 0.78		4.88 ± 0.72		0.170	
Post-treatment value	4.07 ± 0.38	0.013	3.74± 0.18	0.001		
Mean changes	-0.40±0.63		-1.13±0.81			0.011
PAI-1, ng/mL						
Baseline value	5.23 ± 0.55		5.44 ± 0.59		0.353	
Post-treatment value	3.47 ± 0.64	>0.001	4.04 ± 0.68	0.001		
Mean changes	-1.76±0.69		-1.40±1.06			0.256

Note: p1-2 – difference in standard care and losartan groups before and after intervention (intragroup analysis); p3 – differences between standard care and losartan groups baseline characteristics; p4 – difference between groups throughout the study (ANCOVA intergroup analysis). Significance was stated at p<0.05

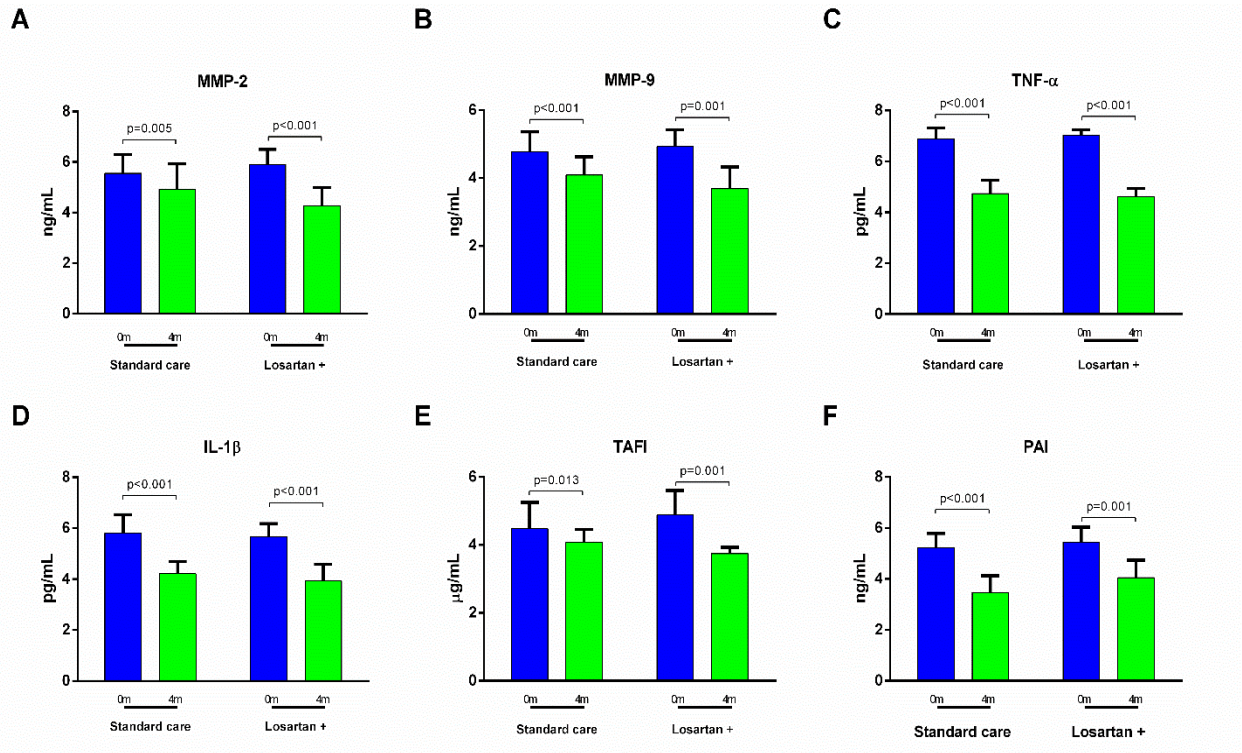

Figure 2. *Intra-group outcomes analysis with accent on inflammatory and proteolytic cascade activation markers changes (A – MMP-2; B – MMP-9; C – TNF-α; D – IL-1β; E – TAFI; F – PAI). Data presented as M ± SD*

Analysis of TNF-α concentrations revealed a marked decrease in patients receiving modified therapy with losartan, from 7.03±0.20 pg/mL to 4.60±0.32 pg/mL after treatment (p<0.001). The control group also presented a significant reduction in the levels of this proinflammatory cytokine – from 6.88 ± 0.43 pg/mL to 4.73 ± 0.51 pg/mL (p<0.001) – although the rate of change was less pronounced (Table 2, Figure 2C).

Both treatment regimens significantly reduced systemic inflammatory activity. However, the more pronounced dynamic observed in the losartan group suggests a potential additional anti-inflammatory effect of angiotensin II receptor blockade. This effect is likely mediated through reduced activation of NF-κB-dependent signaling pathways, suppression of pro-inflammatory cytokine production, and improvement of endothelial dysfunction, as supported by current research data.

In both study groups, a significant decrease in IL-1β, a key pro-inflammatory mediator involved in maintaining chronic low-grade vascular inflammation, was observed. In patients receiving therapy with losartan, the IL-1β level decreased from 5.66 ± 0.51 pg/mL to 3.92 ± 0.65 pg/mL (p<0.001). In the control group, the reduction was less pronounced, from 5.80 ± 0.72 pg/mL to 4.21 ± 0.47 pg/mL (p<0.001) (Table 2, Figure 2D). This difference in response supports the hypothesis that losartan exerts an additional anti-inflammatory effect beyond its classical antihypertensive action. On the other hand, changes in both cytokines (IL-1β: p=0.652; TNF-α: p=0.180) in the between-group analysis did not differ significantly (Table 2).

This is supported by contemporary experimental data: inhibition of the renin–angiotensin system by losartan under preclinical conditions has been shown to reduce IL-1β production in the adrenal cortex of mice. This was demonstrated in a study by AlSaad et al. (2020), where losartan significantly decreased the levels of IL-1β and TNF-α compared with the sustained increase observed in the control group [11].

Assessment of changes in the hemostatic system revealed distinct differences between the study groups, underscoring the added benefit of incorporating losartan into the standard treatment regimen. The level of TAFI in the modified therapy group significantly decreased from 4.88 ± 0.72 μg/mL to 3.74 ± 0.18 μg/mL (p=0.001), exceeding the degree of change observed in the control group, where levels declined from 4.47 ± 0.78 μg/mL to 4.07 ± 0.38 μg/mL (p = 0.013) (Table 2, Figure 2E). The between-group difference in the mean change was also significant (p=0.011), indicating a pronounced effect of losartan on reducing antifibrinolytic activity and potentially lowering the risk of thrombosis (Table 2).

A similar trend in intragroup analysis was observed in the dynamics of PAI-1, a key regulator of fibrinolysis whose elevated levels are associated with the progression of atherothrombosis. In patients receiving losartan, the PAI-1 level decreased from 5.44 ± 0.59 ng/mL to 4.04 ± 0.68 ng/mL (p=0.001), reflecting a substantial reduction in antifibrinolytic potential. The control group also showed favorable dynamics, with levels decreasing from 5.23 ± 0.55 ng/mL to 3.47 ± 0.64 ng/mL (p=0.001); however, the effect observed in the losartan group appeared to be more balanced in terms of concurrent correction of both TAFI and PAI-1 levels (Table 2, Figures 2E and 2F). The significant difference for PAI-1 in ANCOVA analysis was absent (Table 2).

Taken together, these findings indicate that the addition of losartan to baseline therapy not only modifies the lipid profile and inflammatory markers but also affects key components of the hemostatic system. This may reduce the risk of thrombotic complications in patients with IHD and generalized atherosclerosis [12-14].

Discussion. The inclusion of losartan in combination therapy for geriatric patients with IHD and polyvascular atherosclerosis demonstrated a pronounced, multicomponent positive effect that targeted key pathogenetic pathways involved in the progression of atherosclerosis and its complications. These results indicate that modified therapy significantly improves the lipid profile, reduces systemic inflammation, inhibits pathological vascular wall remodeling, and normalizes hemostatic parameters, surpassing the efficacy of standard treatment alone.

The pathophysiological rationale for the effects of losartan is grounded in its role as a selective AT_1 receptor blocker, which enables the inhibition of the renin–angiotensin system, reduction of oxidative stress, normalization of endothelial function, and downregulation of pro-inflammatory mediator expression. In vitro studies have confirmed the ability of losartan to suppress the synthesis of IL-1β and TNF-α, providing a strong anti-inflammatory effect through the inhibition of the NF-κB and MAPK signaling pathways [15-17]. Within the context of our study, this represents a key mechanism underlying the reduction in inflammation and the stabilization of atherosclerotic plaques.

The improvement in the lipid profile observed in the losartan group was significant after 4-month treatment. This effect is attributed not only to direct modulation of lipid metabolism but also to the capacity of losartan to reduce systemic inflammation and restore endothelial function -mechanisms supported by established pathophysiological evidence.

The results obtained highlight a close interrelationship between the impact of losartan on vascular wall remodeling markers, systemic inflammatory status, and hemostatic balance. This interplay is critical to understanding its clinical efficacy within the framework of secondary prevention of cardio- and cerebrovascular events. Particularly important are the findings related to remodeling markers: the statistically significant reduction in MMP-2 levels and the trend for decrease in MMP-9 in the losartan group as compared to standard care alone, underscore the drug's ability to suppress destructive processes within the fibrous cap of atherosclerotic plaques [18]. This is particularly important for the prevention of unexpected ischemic complications.

In our study, particular attention was given to the analysis of changes in biochemical markers of vascular wall remodeling, as they reflect the intensity of extracellular matrix degradation and structural alterations of the arterial wall – key processes in the progression of atherosclerosis and the development of its complications.

The more pronounced reduction in MMP-2 concentration and the greater decrease in MMP-9 levels in the losartan group compared with the standard therapy group indicate the suppression of extracellular matrix degradation and the potential slowing of destructive processes within the vascular wall. Excessive MMP activity is associated with destabilization of atherosclerotic plaques, increased susceptibility to rupture, and thrombus formation. Therefore, the observed changes may be regarded as a pathophysiological basis for a reduced risk of recurrent ischemic events.

These effects were accompanied by a more substantial decrease in the levels of the pro-inflammatory cytokines TNF-α and IL-1β, indicating attenuation of chronic inflammatory activity. The suppression of inflammatory mediators directly influences MMP expression, forming a reinforcing mechanism for atherosclerotic plaque stabilization. Consequently, the reduction in inflammation and inhibition of proteolytic activity are interrelated processes that collectively create favorable conditions for vascular remodeling in a more stable, less thrombogenic direction.

Moreover, the more pronounced reduction in TAFI and PAI-1 levels observed in the losartan group points to a decrease in antifibrinolytic activity and an increase in fibrinolysis – an effect of critical importance in atherosclerotic disease, where thrombus formation is a leading cause of acute events. Given the known influence of pro-inflammatory cytokines on the activation of the hemostatic system, it can be assumed that the reduction in TNF-α and IL-1β levels in patients treated with losartan contributed to the normalization of fibrinolytic potential via the downregulation of PAI-1 and TAFI.

The correction of hemostatic parameters – characterized by a marked reduction in TAFI and PAI-1 levels – indicates an increase in fibrinolytic potential and a reduction in thrombotic risk, which is consistent with our findings [7,19].

This comprehensive effect – rather than the isolated correction of individual laboratory parameters – likely underpins the clinical rationale for incorporating losartan into multicomponent therapy for high-risk patients, thereby increasing the relevance of our findings within the context of contemporary evidence-based medicine.

Conclusions. Under conditions of systemic vascular remodeling driven by chronic ischemia and low-grade inflammation, pharmacological intervention with losartan has the ability to slow the progressive destruction of the vascular wall through multilevel biochemical modulation. In addition to its conventional antihypertensive effects, losartan has been shown to reduce the expression of key proteolytic enzymes (MMP-2, MMP-9), suppress pro-inflammatory cytokine cascades (TNF-α, IL-1β), and normalize parameters of hemostatic homeostasis (TAFI, PAI-1), indicating its pronounced metabolic and endothelium-protective activity.

Throughout the observation period, laboratory biomarkers proved to be the most sensitive indicators of therapeutic response, capturing more profound changes than instrumental assessments. Thus, losartan, as part of a multicomponent therapeutic strategy, may be considered not only a means of blood pressure control but also a promising agent for active secondary prevention of cardio- and cerebrovascular events via targeted modulation of key pathogenic mechanisms.

Future research perspective. The prospects for further research include conducting long-term clinical studies to improve the evidence base for losartan's efficacy, determine optimal treatment regimens, expand the biomarker panel, and develop combined therapeutic approaches to enhance the effectiveness of secondary prevention of cardiovascular and cerebrovascular events.

Funding: The study was conducted within the framework of the department's research project.

Ethical Considerations: The study was conducted in accordance with the principles of the Declaration of Helsinki (World Medical Association, 2013) and complied with the requirements of the Ethics Committee of Bohomolets National Medical University. The study protocol was reviewed and approved by the local ethics committee. Written informed consent was obtained from all participants prior to their inclusion in the study.

Conflict of interest: The author declares no conflicts of interest.

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Ефективність лозартану у складі багатокомпонентної стратегії вторинної профілактики серцево-судинних подій у пацієнтів після ішемічного інсульту

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Резюме

Мета. Оцінити ефективність додавання лозартану до стандартної терапії у пацієнтів з ішемічною хворобою серця (ІХС) та поліваскулярним атеросклерозом після ішемічного інсульту як складової багатокомпонентної стратегії вторинної профілактики протягом 4-місячного періоду лікування.

Матеріали та методи. У проспективне дослідження було включено 60 пацієнтів, яких рандомізовано поділили на дві рівні групи: стандартна терапія (яка включала антитромбоцитарні засоби, статини, антигіпертензивні препарати та контроль факторів ризику) та стандартна терапія з додаванням лозартану. Усі пацієнти проходили оцінку ліпідного профілю (ЗХ, ТГ, ЛПНЩ, ЛПВЩ), а також визначення рівнів у сироватці матриксних металопротеїназ ММР-2 і ММР-9, інтерлейкіну-1β (IL-1β), інгібітора активатора плазміногену-1

(PAI-1), інгібітора фібринолізу, що активується тромбіном (TAFI), та фактора некрозу пухлин-α (TNF-α) на початку та після 4 місяців терапії.

Результати. Через 4 місяці лікування в обох групах спостерігалося достовірне зниження рівнів ліпідів, MMP-2, MMP-9, IL-1β, PAI-1, TAFI та TNF-α у сироватці крові ($p < 0,05$). Проте у порівнянні з групою стандартної терапії додавання лозартану асоціювалося з більш вираженим зниженням рівнів MMP-2 ($p = 0,008$) та TAFI ($p = 0,011$) за результатами міжгрупового аналізу ANCOVA.

Висновки. Додавання лозартану до стандартної терапії у пацієнтів з ІХС та поліваскулярним атеросклерозом після ішемічного інсульту протягом 4 місяців було пов'язане з покращенням клінічних результатів, зниженням активації запальних і протеолітичних каскадів та підвищенням показників гемодинаміки.

Ключові слова: *ішемічна хвороба серця, генералізований атеросклероз, ішемічний інсульт, лозартан, вторинна профілактика, MMP-2, MMP-9, IL-1β, PAI-1, TAFI, TNF-α.*

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