

Original article:

Clinical prospects for dyslipidemia treatment in patients with arterial hypertension.

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Abstract:

Background: Epidemiological research data shows that the prevalence of arterial hypertension among the adult population in the developed countries varies from 20% to 40% and increases with age. Hypertension is found in over 50% of men and women aged over 60. In Russia the structure of mortality patterns shows about 56% due to cardiovascular disease.

Methodology : We conducted an open prospective study of the lipid-lowering and antihypertensive efficacy of combined antihypertensive therapy using angiotensin-converting enzyme inhibitor Fozinopril (Fozinotec, Ranbaxy Laboratories Limited, India), starter dose: 10 mg per day and thiazide-like diuretic Indapamide (Retapres, Ranbaxy Laboratories Limited, India), starter dose: 1.5 mg per day, combined with diet therapy or administration of Simvastatin (Simvor, Ranbaxy Laboratories L The data we obtained demonstrates that combined therapy for patients presenting with dyslipidemic hypertension using angiotensin-converting enzyme inhibitor and statin can have a maximum effect on cardiovascular prognosis.

Results and conclusion: In case of an equal antihypertensive effect, the combination of Fozinopril and Simvastatin was much more effective than Fozinopril therapy in terms of decreasing the risk of major cardiovascular complications. An enhancement of the clinical effect in case of combining angiotensin-converting enzyme inhibitor with statins occurs, most likely, not due to the synergy of their hypotensive or hypolipidemic effects, but to their mutually enhancing angioprotective action on dyslipidemic hypertension .imited, India), starter dose: 20 mg per day. diseases associated with atherosclerosis.

Introduction:

Epidemiological research data shows that the prevalence of arterial hypertension among the adult population in the developed countries varies from 20%to 40% and increases with age.ⁱ Hypertension is found in over 50% of men and women aged over 60.ⁱⁱ [2] In Russia the structure of mortality patterns shows about 56% due to cardiovascular disease; the majority of cases are due to diseases associated with atherosclerosis.^{iiiv}

At this time the combination of arterial hypertension and dyslipidemia in patients is defined as a separate condition: - dyslipidemic hypertension. Obviously, for these patients the risk of cardiovascular disease co

morbidity due to dyslipidemic hypertension is much higher than for individual risk factors present.^v

Presentation of arterial hypertension combined with atherosclerosis results in exacerbation of both processes, partially due to synergy between elevated blood pressure (arterial hypertension) and other atherogenic stimuli triggering oxidative stress in arterial walls.^{vi}It has been proven that arterial hypertension triggers oxidative stress in the arterial wall, as does dyslipidemia. Arterial hypertension in and of itself is capable of damaging endothelium due to hemodynamic shock and triggering oxidative stress, result in gin increased levels of synthesis of collagen and fibronect in by endothelial cells;

nitrogen oxide synthesis regulation depends on vascular relaxation and increasing permeability for lipoproteins.^{viii} It was even proposed that superoxide anions may trigger hypertension in some models, presumably via the endothelium deactivating a vasodilator, such as nitrogen oxide.^{ix}

Atherosclerosis leads to structural changes, resulting in decreased elasticity of large arteries. Increased rigidity is considered to be the main pathophysiological change contributing to development of arterial hypertension.^{xi} Dyslipidemia disrupts endothelial function due to decreased synthesis of nitrogen oxide^{xii}, and that in turn may lead to increased blood pressure. Dyslipidemia may also enhance the effect of endothelin 1 and angiotensin II vasoconstrictors on endothelium, thus leading to hypertension.^{xiii} Increased plasma lipid levels, ectopic accumulation of lipids and presence of intracellular lipid droplets contribute to oxidative stress.^{xvii} Interaction of reactive oxygen and nitrogen with proteins, lipids and carbohydrates alters the structure and functioning of the cellular components.^{xviii} Therefore, decreased generation of nitrogen oxide combined with a heightened response of the vasoconstrictor mediators will lead to increased blood pressure in patients with dyslipidemia.

Primary prevention measures include lifestyle changes along with use of not just hypotensive therapy, but also intensive lipid-lowering therapy. The dependence of the efficacy of antihypertensive drugs on the plasma cholesterol levels determines the need to treat dyslipidemia in patients with arterial hypertension.

The study by *Morgado M. et al* demonstrates 54.9% blood pressure control in patients receiving combined treatment with antihypertensive drugs and

statins, which is significantly higher than in patients who received antihypertensive treatment only (21.4%).^{xx} Research by *Borghetti C. et al.*^{xxix} discovered that patients receiving add-on antihypertensive therapy combined with statins show a more significant effect of blood pressure decrease than can be accounted for solely by the hypolipidemic effect of statins or efficacy of antihypertensive drugs. These results demonstrate that the use of statins in combination with antihypertensive drugs may improve blood pressure control in patients with uncontrolled hypertension and high serum cholesterol levels.

Pathophysiology mechanisms that account for the effect of statins on blood pressure are most likely related to statins having a positive effect on endothelial cells and vascular smooth muscle cells. In addition to decreasing LDL levels, statins exhibit a number of pleiotropic effects associated with influencing the risk markers for cardiovascular disease; those include decrease of inflammation, increasing stability of atherosclerotic plaques, and improvement of endothelial function.^{xxix}

A number of sources report on the ability of statins to directly inhibit Rho/Rho kinase. The processes triggered by Rho-kinase play a central role in the development of endothelial dysfunction and hyperplasticity of vascular smooth muscle cells.^{xxix} Several other studies (in vitro, in vivo) have demonstrated that statins have a physiological effect regardless of the lowering of LDL cholesterol. For example, the positive vascular effects of statins may depend on their ability to alter the level of highly sensitive C-reactive protein. The latter induces cytokine synthesis, cellular adhesion molecules and platelet tissue factor in monocytes and endothelial cells^{xxxxxi} and activates type one angiotensin II

receptors in the vascular smooth muscle cells.^{xxxiii} Statin therapy in experimental models lowers the plasma level of IL-1 β highly sensitive C-reactive protein regardless of cholesterol decrease.^{xxxiii}

The renin-angiotensin-aldosterone system (RAAS) plays an important role in regulating the cardiovascular system by controlling the volume of extracellular fluid, sodium balance and functional and structural cardiovascular effects. RAAS hyperactivity is associated with the development of arterial hypertension, atherosclerosis, left ventricular hypertrophy and cardiovascular events such as myocardial infarction, stroke and congestive heart failure. Tissue hyperactivity of RAAS may lead to insulin resistance and disruptions in the lipid levels. High levels of free fatty acids (FFA), increased LDL levels and low HDL cholesterol levels may lead to further RAAS regulation disruption and promote the development of endothelial dysfunction and atherosclerosis due to lipotoxicity. Hypertension and dyslipidemia have a similar effect on artery walls. Both these processes increase oxidative stress, activating the genes involved in the inflammatory process, which in the presence of dyslipidemia results in formation of atherosclerotic plaque. Therefore, pharmacological blockage of RAAS is a promising direction for designing a treatment to improve both vascular and endothelial function. Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors are agents that affect the RAAS directly both by blocking binding of angiotensin II with AT1 receptors and decreasing production of angiotensin II respectively.^{xxxiv} Several large clinical studies demonstrated that use of angiotensin receptor blockers or angiotensin-converting enzyme inhibitors may significantly decrease glucose tolerance impairment, dyslipidemia and atherosclerotic

manifestations in hypertensive patients and / or patients presenting with metabolic syndrome.^{xxxxvxxxxvixxxxviixxxxviiixxxxixxlixlili}

Obviously, it is necessary to study patients with dyslipidemic hypertension in order to explore the effects of lipid-lowering therapy on blood pressure level and clarify the specific contribution to direct lowering of serum cholesterol, pleiotropic effects of lipid-lowering drugs or study possible drug interactions between lipid-lowering and antihypertensive drugs.

We conducted an open prospective study of the lipid-lowering and antihypertensive efficacy of combined antihypertensive therapy using angiotensin-converting enzyme inhibitor Fozinopril (Fozinotec, Ranbaxy Laboratories Limited, India), starter dose: 10 mg per day and thiazide-like diuretic Indapamide (Retapres, Ranbaxy Laboratories Limited, India), starter dose: 1.5 mg per day, combined with diet therapy or administration of Simvastatin (Simvor, Ranbaxy Laboratories Limited, India), starter dose: 20 mg per day.

Main eligibility criteria:

- Men and women aged 18 to 65
- Stage 1 or 2 arterial hypertension (systolic blood pressure 150-179 mmHg and/or diastolic blood pressure 90-109 mmHg);
- Confirmed dyslipidemia: cholesterol over 4.5 mmol/L and/or LDL over 2.5 mmol/L
- risk of death within 10 years due to cardiovascular events per SCORE table within 5-9%

The exclusion criteria included the following: presence of cardiovascular disease or very high risk thereof (over 10%), hyperkalemia (serum potassium level exceeding 5.7 mmol/L), patients with contraindications to angiotensin-converting enzyme inhibitor (angiotensin-converting enzyme inhibitor

intolerance, allergic reactions, bilateral stenosis of renal arteries or stenosis of the renal artery of a single kidney, pregnancy and lactation.

In accordance with the eligibility criteria, 16 patients were randomly allocated to the group treated with Fozinopril (Fozinotec, Ranbaxy Laboratories Limited, India) at 10 mg per day and Indapamide (Retapres, Ranbaxy Laboratories Limited, India) at 1.5 mg per day; 18 patients received Fozinopril (Fozinotec, Ranbaxy Laboratories Limited, India) at 10 mg per day, Indapamide (Retapres, Ranbaxy Laboratories Limited, India) at 1.5 mg per day, combined with Simvastatin (Simvor, Ranbaxy Laboratories Limited, India) at 20 mg per day. All the patients included in the study were briefed on adherence to the diet and medication schedule and dosage as well as the possibility of adverse reactions to medications.

Comparative clinical characteristics of the patients included in the study :

24-hour blood pressure monitoring was performed using the MEDIALOG PRIMA-OSCAR 2 system (UK) using data processing software. The measurements were taken at 15 minute intervals during the day and 30 minute intervals at night . Highest and lowest systolic and diastolic pressure levels were measured over 24 hours, average systolic and diastolic blood pressure during the daytime and at night, BP variation over 24 hours. Average systolic and diastolic blood pressure levels over a period of 24 hours were determined as well.

Biochemical blood analysis (albumin, creatinine , glucose, K, cholesterol, TAG, HDL) was performed in accordance with the standard methodologies.

Microalbuminuria in morning urine was measured using the immunochemical analyzer HemoCue

Albumin 201 (Sweden). Measurement range for this method is 5 - 150 mg/L of albumin.

Endothelial function was studied according to the methodology proposed by D.S. Celermajer et al. Using vasodilator testing with reactive hyperemia and nitroglycerin. The normal reaction of the brachial artery in the reactive hyperemia test was considered to be a dilation by 10% or more of the initial diameter. Normal response to 500 mg nitroglycerin test was considered to be an increase of the brachial artery diameter by 20% or more from the initial. Low concentrations of highly sensitive C-reactive protein (<6 mg/L) were measured using the immunoturbidimetric technique based on the ability of highly sensitive C-reactive protein to form antibody complexed antigens, fortified by latex particles. The measurements were performed using diagnostic reagent kits on protein analyzer Turbox plus, manufactured by Orion Diagnostika. ADMA was determined by a HPLC-tandem mass spectrometry technique with a measurement threshold of 1 ng/ml.

16 patients completed the study from the Fozinopril group (2 patients left the study) and 18 patients from the combined therapy (1 patient).

The reason for therapy termination with the drugs in the study were 2 cases of dry cough; 1 patient left the study due to a non-medical reason. There were no statistically significant differences between clinical and demographic parameters of the patients allocated to the comparison groups (Table 1).

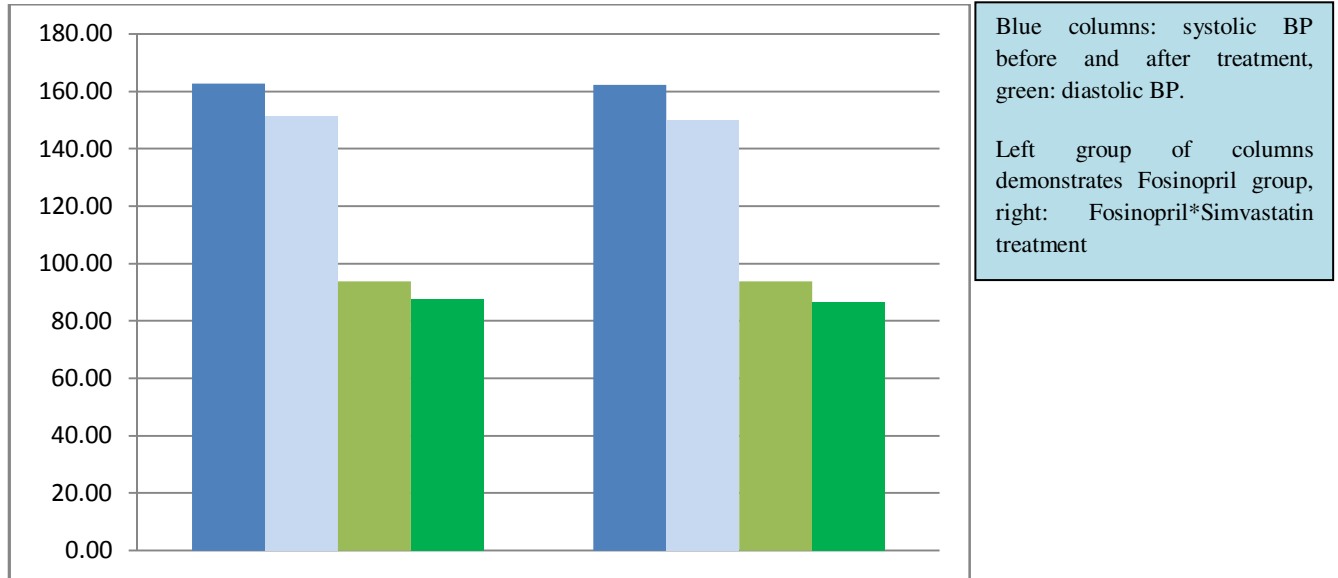
However, the patients from the combined therapy group with Fozinopril, Indapamide and Simvastatin had slightly higher SCORE andTAG values.

Table 1.

Variable	Fozinopril and Indapamide	Fozinopril,Indapamide and Simvastatin
N of patients	16	18
Male	9	8
	56.25%	44.44%
Female	7	10
	43.75%	55.56%
Age	57.06±5.39	57.72±4.04
Arterial hypertension duration, years		
Systolic BP (mmHg)	162.69±8.01	162.11±6.65
Diastolic BP (mmHg)	93.75±4.62	93.72±5.04
SCORE	5.71±0.64	6.20±0.83
Cholesterol (mmol/L)	5.96±1.55	5.91±1.03
TAG (mmol/L)	1.98±0.42	2.19±0.50
HDL (mmol/L)	1.17±0.35	1.32±0.19
LDL (mmol/L)	3.88±1.59	3.58±1.06
Highly sensitive C-reactive protein (mg/L)	2.43±1.26	2.54±1.22
Endothelium-independent vasodilation	14.69±4.41	15.22±3.89
Endothelium-dependent vasodilation	6.93±2.98	6.89±2.63
ADMA	0.47±0.22	0.43±0.25
MAU	39.63±33.31	35.72±33.09

By study end both groups showed a statistically significant comparable decrease for both systolic and diastolic blood pressure.

(Fig. 2).



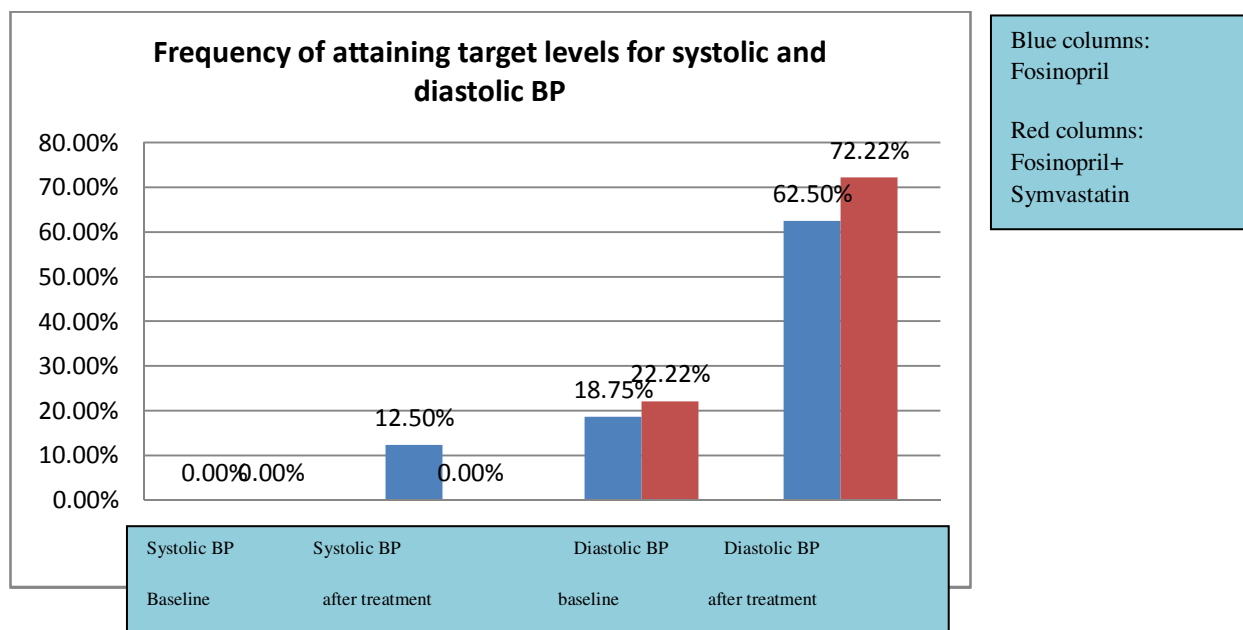
The group that received Fosinopril and Indapamide showed a decrease of systolic blood pressure by 11.44 ± 4.82 mmHg, and for the group treated with Fosinopril, Indapamide and Simvastatin systolic blood pressure decreased by 12.45 ± 3.22 mmHg. Diastolic pressure trends for the patients treated with Fosinopril and Indapamide showed a decrease of 6.25 ± 2.65 mmHg; in the group treated with Fosinopril, Indapamide and Simvastatin diastolic blood pressure decreased by 7.11 ± 3.92 mmHg.

The share of patients who attained the target BP levels of < 140 and 90 mmHg was very low. Only 12.5% patients from the group on Fosinopril therapy attained systolic blood pressure below 140 mmHg; at the same time 62.5% of patients treated with Fosinopril and Indapamide and 72.2% patients receiving add-on Simvastatin therapy attained diastolic blood pressure below 90 mmHg.

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Therapy effects on the levels of lipids and highly sensitive C-reactive protein are shown in Table 2.

Variable	Fozinopril and Indapamide			Fozinopril, Indapamide and Simvastatin		
	Initially	After 12 weeks	Δ	Initially	After 12 weeks	Δ
N patients	16			18		
Cholesterol (mmol/L)	5.96±1.55	5.71±1.47	-0.24±0.18	5.91±1.03	4.48±0.60	-1.41±0.84
TAG (mmol/L)	1.98±0.42	1.86±0.44	-0.12±0.18	2.19±0.50	1.87±0.28	-0.32±0.28*
HDL (mmol/L)	1.17±0.35	1.12±0.32*	-0.05±0.21*	1.32±0.19	1.38±0.14*	0.05±0.11*
LDL (mmol/L)	3.88±1.59	3.75±1.42*	-0.13±0.29*	3.58±1.06	2.26±0.58*	-1.33±0.87*
Highly sensitive C-reactive protein (mg/L)	2.43±1.26	2.33±0.91	-	2.54±1.22	2.11±0.99*	-

Both groups demonstrated a statistically significant decrease of total cholesterol and LDL cholesterol. However, this decrease was statistically significantly more pronounced among the patient group treated with Fozinopril, Indapamide and Simvastatin.

The share of patients who attained target cholesterol levels of < 4.5 mmol/L, LDL cholesterol < 2.5

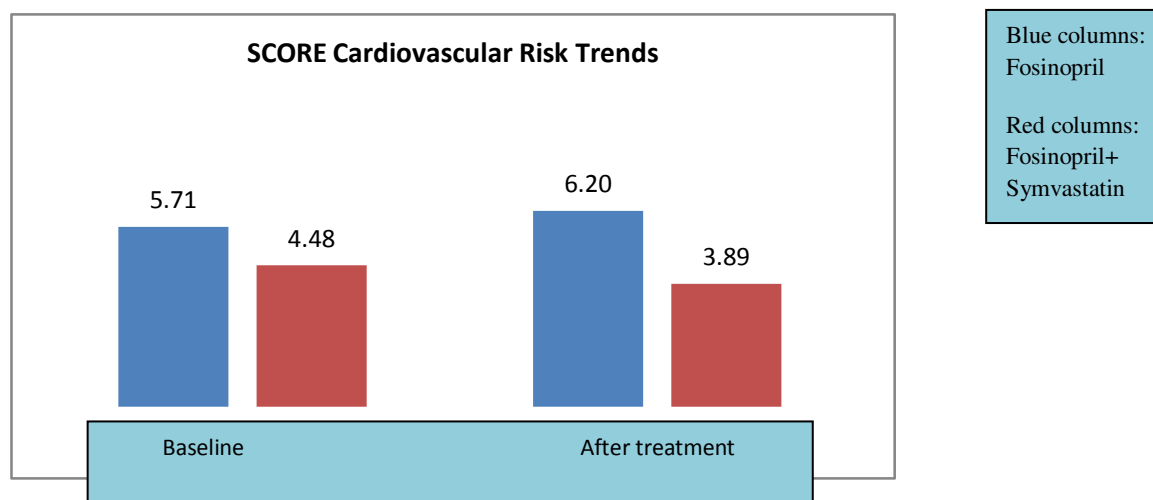
mmol/L and HDL over 1.0 for male and over 1.2 mmol/L for female patients was higher in the group on Fozinopril and Simvastatin therapy; at the same time the share of patients who attained the TAG target of < 1.7 mmol/L was higher in the group treated with Indapamide and Fozinopril only. Most likely this is associated with the benchmark data: in this

group the frequency of normal TAG levels was 3 times higher than among the group receiving additional Simvastatin therapy.

There were no statistically significant changes in the level of highly sensitive C-reactive protein in any of the groups; however, trend evaluation indicates that in the group treated with Fozinopril and Indapamide highly sensitive C-reactive protein decreased for 9 patients (56.25%) -1.10 ± 1.14 mg/L, and for 7 patients increased by 1.2 ± 0.76 mg/L; in the combined therapy group receiving Simvastatin decrease of highly sensitive C-reactive protein was observed in

13 patients (76.47%) by -0.56 ± 0.38 mg/L, while an increase was observed in only 4 patients, by 0.29 ± 0.21 mg/L. One patient from the group treated with Fozinopril, Indapamide and Simvastatin was excluded from data analysis due to an increase of highly sensitive C-reactive protein to 24 mg/L in the course of a viral infection manifestation.

The treatment entailed a significant decrease of the SCORE value in both groups; the decrease was significantly more expressed in the group receiving combination therapy with Simvastatin.



Data on therapy effects on the endothelial function is shown in Table 3.

Variable	Fozinopril and Indapamide			Fozinopril, Indapamide and Simvastatin		
	Initially	After 12 weeks	Δ	Initially	After 12 weeks	Δ
N patients	16			18		
Endothelium-dependent vasodilation	6.94±2.98	10.38±2.5*	3.44±1.97	6.89±2.63	11.17±2.07*	4.28±1.99
Endothelium-independent vasodilation	14.69±4.41	15.19±4.37*	0.5±0.63	15.22±3.89	15.94±3.76*	0.72±0.46
ADMA	0.47±0.22	0.43±0.23*	0.04±0.06	0.43±0.25	0.39±0.22*	0.04±0.09

Testing with reactive hyperemia following 3 months of treatment in both groups showed significant increase of the expansion of the brachial artery. However, the extent of the increase of vasodilation in the group on combined therapy with Simvastatin was greater than in the group that did not receive statins, even though the data is not significant. ADMA levels increase considerably in cases of arterial hypertension which contributes to rapid development of atherosclerosis; at this stage ADMA is an early predictor of the vascular damage in arterial hypertension cases, due to its ability to exacerbate endothelial dysfunction by decreasing bioavailability of nitrogen oxide.^{xliii} It has been demonstrated that RAAS blockade leads to a slight decrease of ADMA level.^{xliv} Nour study was noted identical ADMA decrease by 0.04 mmol/ml in both treatment groups.

Discussion

The data obtained by the study that we performed demonstrated that in patients with arterial hypertension and dyslipidemia therapy with angiotensin-converting enzyme inhibitor, Fozinopril and Indapamide leads to the expected blood pressure decrease. However, for patients with high cardiovascular risk it is necessary not only to improve blood pressure levels, but also to normalize lipid metabolism parameters; this is achieved by adding Simvastatin to the hypotensive therapy.^{xlv}

Combined Fozinopril, Indapamide and Simvastatin in therapy confers an advantage compared to therapy using Fozinopril and Indapamide. Combined treatment including Simvastatin provided a much more considerable decrease of the risk of cardiovascular events; also, it had a much more pronounced effect on lipid metabolism, highly sensitive C-reactive protein, ADMA, and endothelial function parameters.

A number of studies have demonstrated the ability of statins to decrease blood pressure. Meta-analysis of 20 randomized controlled clinical trials showed that systolic blood pressure was significantly lower on average by 1.9 mmHg in the group of patients receiving statins in addition to hypotensive therapy. In the group of patients whose initial systolic blood pressure was higher (>130 mmHg) the systolic blood pressure decrease was more pronounced (-4.0 mmHg). The antihypertensive effect of statins on diastolic blood pressure was also statistically significant: there was a decrease by 0.9 mmHg, and in the group with initially higher diastolic blood pressure (>80 mmHg) it was 1.2 mmHg. The effect of statins on decreasing arterial hypertension did not depend on the age of patients, duration of observation, initial and attained levels of total or LDL blood cholesterol levels, or add-on hypotensive treatment.^{xlvi} A recent meta-analysis demonstrates that systolic blood pressure levels in patients treated with statins is considerably lower than in the group receiving a placebo or other lipid-lowering drugs (average difference: -1.9 mm Hg with 95% confidence interval: -3.8 to -0.1). The effect is greater if the analysis is restricted to systolic blood pressure > 130 mmHg (systolic blood pressure change: -4.0; 95% confidence interval: -5.8 to -2.2 mmHg). The result tends to a decrease of diastolic blood pressure in patients receiving statins as compared to the controls: -0.9 mmHg (95% confidence interval: -2.0 to 0.2) in general and -1.2 mmHg (95% confidence interval: -2.6 to 0.1) in studies where diastolic blood pressure was > 80 mmHg. It is noted that the hypotensive effect of statins is expressed more with higher initial blood pressure levels. Lowering of blood pressure in statin treatment does not depend on age, change in serum cholesterol levels or duration of the trial.^{xlvii} In

the Brisighella Heart Study the Simvastatin effect on blood pressure control was limited to the two top quartiles for systolic blood pressure ≥ 140 mmHg. In particular, the average blood pressure decrease was better expressed in the fourth quartile patients whose level of blood pressure control was low despite administration of antihypertensive medications. On the other hand, no pronounced blood pressure changes were observed in patients in the two lower quartiles with normal levels of benchmark blood pressure (systolic blood pressure < 140 mmHg). Therefore, the use of statins could considerably improve blood pressure control in patients with dyslipidemia and uncontrolled arterial hypertension^{xlviii}. It is worth noting, however, that in the ASCOT and GREACE studies a combination of angiotensin-converting enzyme inhibitor and statins did not demonstrate an improvement for lowering blood pressure in comparison to monotherapy.^{xlix} In our study we were not able to demonstrate that adding Simvastatin results in an enhancement of the hypotensive effect of angiotensin-converting enzyme inhibitor.

The absence of an additional blood pressure decrease in our study could potentially be accounted for by the fact that the "hypotensive effect of the statins" is most likely not direct but endothelium-mediated, and thus a longer observation period is necessary for it to manifest.

Dyslipidemia and arterial hypertension are associated with endothelial dysfunction, and their concurrent presentation is associated with an increase of cardiac events in epidemiological studies. Dyslipidemia and arterial hypertension produce a synergistic negative effect on endothelial function which is associated with increased oxidative stress^{li}. It has been discovered that LDL and highly sensitive C-reactive

protein trigger activation of the angiotensin type 1 receptor^{liiii}. Angiotensin II activates superoxide anion thus further exacerbating endothelial dysfunction^{liv}. Accordingly, a combination of statins and angiotensin-converting enzyme inhibitor therapy may offer additional positive effects regardless of the influence of Simvastatin on the blood pressure level. During reactive hyperemia tests in our study after three months of treatment a significant increase in the diameter of the brachial artery was demonstrated in both groups. Even though the extent of the increase of vasodilation in the group using the combined therapy including Simvastatin was greater than in the group not treated with statin, this data is not statistically significant. The ability of statins to improve endothelial function has been confirmed in a large number of studies.^{lv} Statins are capable of directly influencing functional activity of eNOS, leading to an increase in its expression, mostly through posttranslational mechanisms.^{lvii} An increase of eNOS activity results in an increased output of nitrogen oxide, which is involved in regulating a variety of physiological processes on the luminal surface of the endothelium. Perhaps the lack of statistical significance of the data can be explained by the need for more prolonged treatment in order to attain an improvement in functional resources of the vascular endothelium due to the use of statins. Similarly, despite the correction of lipid levels during short-term observation in the study by J.A. Vita et al. (2000) in patients with coronary artery disease, there was no significant endothelium-dependent vasodilation improvement noted following Simvastatin therapy over a period of 6 months.^{lviii} Endothelial function to a great extent depends on the production and bioavailability of NO. The first factor to affect endothelial dysfunction is a disruption in

NO production due to the effect of coenzyme A isoforms. The other controlling process is the speed of NO inhibitor production –ADMA. Prolonged administration of angiotensin-converting enzyme inhibitor leads to a decrease in the ADMA level, increases NOx content and decreases the L-arginine/ADMA ratio in patients. It has been discovered that angiotensin-converting enzyme inhibitors lower ADMA plasma concentration independently of blood pressure.^{lix} Statins improve endothelial function by increasing eNOS activity; at the same time, statin therapy did not change ADMA level significantly in all studies^{lx}. Our study demonstrated a matching decrease of ADMA during Fozinopril therapy and add-on Simvastatin treatment. The decrease of total and LDL cholesterol observed in this study was significantly larger among the patients treated with Fozinopril, Indapamide and Simvastatin. Similar data was observed in the PHYLLIS trial during Fozinopril treatment; a decrease of total and LDL cholesterol levels was noted, even though not as considerable as with statin therapy. The anti-atherosclerotic effect of Fozinopril is most likely related to the blocking of tissue RAAS.^{lxii} The level of highly sensitive C-reactive protein, as the main anti-inflammatory marker, did not show a significant change in any of the groups; however, in its trend evaluation it is possible to note that in the group receiving combined therapy with

Simvastatin the trend was observed of a decrease in the level of highly sensitive C-reactive protein in 76.47% of patients, while in the group treated with Fozinopril it was observed only for 56.25%.

In clinical practice a plasma level of highly sensitive C-reactive protein at <1 mg/L is viewed as a low risk indicator, and >3 mg/L began, their ability to reduce C-reactive protein plasma levels by 20–30% has become viewed as one of the goals of therapy. In addition, statins promote a decrease in plasma level of highly sensitive C-reactive protein regardless of their hypolipidemic effect and this contributes to a positive prognosis for patients.

The data we obtained demonstrates that combined therapy for patients presenting with dyslipidemic hypertension using angiotensin-converting enzyme inhibitor and statin can have a maximum effect on cardiovascular prognosis. In case of an equal antihypertensive effect, the combination of Fozinopril and Simvastatin was much more effective than Fozinopril therapy in terms of decreasing the risk of major cardiovascular complications. An enhancement of the clinical effect in case of combining angiotensin-converting enzyme inhibitor with statins occurs, most likely, not due to the synergy of the antihypertensive or hypolipidemic effects, but to their mutually enhancing cardioprotective action on dyslipidemic hypertension.

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