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Angioprotective effects of antihypertensive therapy in patients with ischemic heart disease and chronic kidney disease stages 2–3 after coronary stenting

Aim	To study the condition of coronary vasculature by data of coronarography (CG) in patients with chronic ischemic heart disease (IHD) and arterial hypertension (AH) associated with stage 2–4 chronic kidney disease (CKD) and to evaluate the effect of a 12-week complex treatment with perindopril or with a combination of perindopril/amlodipine on changes in vascular wall stiffness, endothelial function, and structure and function parameters in this patient category after coronary stenting.
Material and methods	This study included 87 patients with chronic IHD and AH associated with stage 2–3 CKD for whom CG was performed due to ineffectiveness of the antianginal therapy. The patients were divided into three subgroups: subgroup 1 included 28 patients who received a conservative treatment with perindopril 10 mg/day; subgroup 2 consisted of 25 patients who underwent coronary stenting and were prescribed perindopril; subgroup 3 consisted of 34 patients who underwent stenting and were prescribed the perindopril/amlodipine combination. The reference group included 47 patients with IHD and AH with preserved kidney function. Anatomic and functional parameters of the heart, arterial stiffness, pulse wave velocity, cardio-ankle vascular index, augmentation index, central aortic systolic and pulse pressure, endothelium-dependent vasodilation, plasma concentration of endothelin-1 (ET-1), and plasma concentration of nitric oxide metabolites were evaluated at baseline and after 12 weeks of treatment.
Results	In patients with IHD, AH, and stage 2–3 CKD, arterial stiffness was more pronounced than in patients with preserved kidney function. Concentrations of ET-1 were significantly higher and levels of nitric oxide were lower in CKD. Supplementing the complex therapy with perindopril resulted in a considerable hypotensive effect in all subgroups, improvement of the kidney function, and positive dynamics of arterial stiffness and endothelial function. Changes in these parameters were more pronounced in patients after coronary stenting than in patients receiving only a conservative treatment. The use of perindopril/amlodipine following stenting exerted the most significant angioprotective and cardioprotective effect.
Conclusion	Patients with IHD and AH in combination with early CKD have pronounced impairment of the condition of arterial blood vessels and the heart. Addition of perindopril to the treatment not only exerted a hypotensive effect but also beneficially influenced mechanisms of progression of this combined pathology.

Keywords	Ischemic heart disease; chronic kidney disease; arterial stiffness; endothelin-1; perindopril/amlodipine
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Introduction

Today, cardiovascular diseases remain the leading cause of mortality [1]. Coronary artery disease (CAD) with concomitant arterial hypertension (AH) and chronic kidney disease (CKD) are increasingly understood as contributing to the structure of cardiovascular mortality. It has been previously shown that even initial renal dysfunction is associated with cardiovascular mortality: the relative risk of death increases with a decrease in glomerular filtration rate (GFR) by every 5 mL/min/1.73 m^2; moreover, the association persists after adjustments for significant

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risk factors (RF) [2]. Conversely, AH is known to accelerate atherosclerotic processes and cause kidney damage. Thus, progressing CAD and CKD mutually aggravate each other [3, 4]. The presence of CKD worsens the outcomes of surgical treatment of CAD [5].

Objective

Study the state of the coronary system using coronary angiography (CAG) in patients having chronic CAD and AH with concomitant CKD stage II–III; assess the effects of a 12-week combination therapy with perindopril and a fixed combination of perindopril and amlodipine on changes in vascular stiffness, endothelial function, as well as structural and functional parameters of the heart in patients of this category following coronary stenting.

Material and methods

The open, comparative, prospective and non-randomized study was conducted in the regional vascular center of the Kursk regional teaching hospital. The study was approved by the local ethics committee and carried out following the Declaration of Helsinki. All patients signed the informed consent to participate in the study.

Inclusion criteria: age from 50 to 75 years, presence of confirmed CAD: positive treadmill stress test and/or a documented history of myocardial infarction (MI), CAG data, uncontrolled AH, CKD stages II–III.

Exclusion criteria: obesity, diabetes mellitus, acute and chronic inflammatory kidney diseases; acute forms of CAD; severe concomitant pathology affecting the functions of the cardiovascular system and kidneys; inflammatory processes and mental disorders that can affect treatment adherence; therapy with angiotensin-converting enzyme (ACE) inhibitors or angiotensin II blockers within the past 3 months.

The study included 87 patients with chronic CAD and AH in combination with CKD stages II–III (Group 1, treatment group) and 47 patients with CAD and AH having preserved renal function (Group 2, control group). Patients of both groups had stable exertional angina of functional classes II–III. Target blood pressure (BP) levels were not achieved during previous treatment.

All patients received standard therapy (beta-blockers, statins, antiplatelet drugs). All patients underwent CAG due to elective surgical treatment for ineffective antianginal therapy.

Patients with chronic CAD and AH in combination with CKD stages II–III were divided after CAG into three subgroups: Subgroup 1: 28 patients who received conservative combination therapy with perindopril 10 mg/day; percutaneous coronary intervention (PCI) was not performed due to the lack of indications or for technical reasons; Subgroup 2: 25 patients who underwent coronary stenting and the same therapy with perindopril; Subgroup 3: 34 patients who underwent coronary stenting and received background therapy including a fixed combination of perindopril/amlodipine with dose titration.

Clinical and laboratory examinations as well as CAG were performed prior to the beginning of treatment and following 12 weeks of therapy.

Reduced GFR was diagnosed 1–5 years prior to index hospitalization and confirmed by calculation using the MDRD formula at admission with a reduction of at least 45 mL/min/1.73 m^2.

Regional arterial stiffness was assessed by volumetric sphygmography using a VS-1500 device (Fukuda Denshi, Japan). The following indicators of arterial wall stiffness were studied over time: pulse wave velocity (PWV), cardio-ankle vascular index (CAVI), aortic augmentation index (AIx), central systolic blood pressure (cSBP), and central pulse pressure (cPP).

Left ventricular (LV) diastolic function and pulmonary artery systolic pressure (PASP) was determined by echocardiography following the international guideline [6] using an Aloka SSD 1700 scanner.

The degree of endothelial dysfunction was estimated by flow-mediated dilation with post-occlusive reactive hyperemia (Celermajer, 1992) using a LOGIQ 500 MD scanner.

Stable nitric oxide metabolites were determined by spectrophotometry with the Griess reagent kit. The levels of endothelin-1 (ET-1) were determined by enzyme immunoassay using the Endothelin 1–21 reagent kit.

The data obtained were analyzed with the Statistica 10.0 software suite. The mean values and standard deviations (M±SD) were determined and the parametric Student's t-test was calculated. We used the nonparametric Wilcoxon rank test for dependent samples and the Mann–Whitney test for the independent samples. Pearson linear paired correlation and Spearman rank correlation coefficients were calculated. The differences were statistically significant at $p<0.05$.

Results

Clinical And laboratory characteristics of patients, CAG data are presented in Table 1. There were no statistically significant differences between patients with CKD and control patients without renal dysfunction

in total cholesterol, low-density lipoprotein cholesterol, triglycerides. However, the atherogenicity of lipid anomalies in patients with renal dysfunction was more pronounced due to the concentration of Apo-B lipoproteins being statistically significantly higher (144±10.2 mg/dL), which caused differences in the apoB/apoA1 ratio: 1.36% and 49.1%, respectively.

According to CAG, more pronounced atherosclerosis was observed in the control group (Table 1) in patients with CAD, AH, and preserved renal function. Accordingly, 18.4% of patients with CAD and CKD stages II–III and 6.4% of CAD patients without renal pathology had no hemodynamically significant coronary stenosis; single-vessel coronary disease was detected in 44.8% of patients with CAD and CKD and 21.3% of the control patients.

Coronary stenosis was more frequently detected in the proximal one-third of a vessel in the renal dysfunction group (42%) than in the control group (36%).

Thus, non-obstructive CAD was more common in the group of patients with early and moderate renal dysfunction with similar clinical severity of stable angina pectoris.

The study of arterial stiffness produced the following results (Table 2). PWV was increased in only 12.5% of the subjects in the control group but in 85% of the treatment group; PWV > 12 m/s was observed in 37% of subjects, which is considered as an independent RF for cardiovascular events in patients with AH. The baseline values of AIx, SLSI, cSBP, and cPP were statistically significantly higher in the treatment group. Thus, patients with CAD and AH with concomitant CKD stages II–III had higher baseline indicators of vascular wall stiffness, suggesting a significant contribution of arterial stiffness to the development of cardiovascular events in patients with renal dysfunction.

Increased PWV is known to be associated with the likelihood of CKD progression. There was a strong negative correlation between GFR and PWV in the group of patients with CAD, AH, and CKD (r= –0.75; p=0.001); in the control group, it was r = –0.43 (p<0.05). Negative correlations were found between GFR and cSBP (r = –0.58; p<0.01) and SADI (r = –0.39; p<0.05) in CKD. SADI was increased in all patients with CAD and CKD, but only in 40% of subjects in the control group. At the same time, a close relationship between

Table 1. Comparative characteristics of patient groups

Parameter	Group 1 (n=87)	Group 2 (n=47)
Age, years	68±5.7	68±8.5
Male patients, n (%)	57 (65.5)	37 (78.7)
History of myocardial infarction, n (%)	48 (55.2)	24 (51.1)
Duration of AH. years	15.3±4.4	11.3±2.7
Smoking, n (%)	37 (42.5)	19 (40.4)
Body mass index, kg/m^2	24.5±2.4	22.8±1.8
Creatinine, μmol/L	148±11*	73±14
GFR, mL/min/1.73m^2	51±1.4*	96±5.8
SBP, mm Hg	175±14	161±18
DBP, mm Hg	108±12*	93±8
Total cholesterol, mmol/L	6.2±0.8	5.9±0.5
Triglycerides, mmol/L	1.9±0.2	2.1±0.3
LDL-C, mmol/L	4.3±0.4	3.9±0.5
Apo-A lipoproteins, mg/dL	106±10.1	107±11.2
Apo-B lipoproteins, mg/dL	144±10.2*	120±9.8
CAG data, n (%)		
Without hemodynamically significant atherosclerosis	16 (18.4) *	3 (6.4)
Single-vessel coronary disease	39 (44.8) *	10 (21.3)
Two-vessel coronary disease	12 (13.8) *	14 (29.8)
Three-vessel coronary disease	20 (23.0) *	20 (42.6)

AH – arterial hypertension; GFR – glomerular filtration rate; SBP – systolic blood pressure; DBP – diastolic blood pressure; LDL-C – low-density lipoprotein cholesterol; CAG – coronary angiography; * – p<0.01.

Table 2. Indicators of arterial stiffness, endothelial dysfunction, diastolic function, and PASP in the study groups

Parameter	Group 1 (n=87)	Group 2 (n=47)
PWV, m/s	12.21±0.21*	8.67±0.30
AIx, n	1.39±0.14*	1.13±0.16
cSBP, mm Hg	156±9.1*	134±11.6
cPP, mm Hg	59±7.4*	39±6.4
R-CAVI	10.12±0.71*	8.64±0.32
L-CAVI	10.08±0.42*	8.73±0.23
R-ABI	1.18±0.12	1.16±0.17
L-ABI	1.18±0.10	1.15±0.12
Endothelin-1, fmol/mL	2.00±0.08*	1.03±0.06
Nitric oxide, μmol/L	4.81±0.22*	6.08±0.12
LVEDD, cm	4.6±0.30*	4.2±0.25
LVESD, cm	3.8±0.20	3.4±0.29
LVEF, %	62.2±3.71	63.4±4.84
E/A, units	2.2±0.03*	1.5±0.02
PASP, mm Hg	42.3±1.3*	30.2±1.4

* – p<0.05. PASP – pulmonary artery systolic pressure; PWV– pulse wave velocity; AIx – augmentation index; cSBP – central systolic blood pressure; cPP – central pulse pressure; CAVI – cardio-ankle vascular index; ABI – ankle-brachial index; LVEDD – left ventricular end-diastolic dimension; LVESD – left ventricular end-systolic dimension; LVEF– left ventricular ejection fraction; E/A – ratio of peak early diastolic filling velocity (E) and late diastolic filling velocity (A).

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Table 3. Changes in vascular stiffness, endothelial dysfunction, diastolic function, arterial and pulmonary hypertension in patients with chronic CAD and AH with concomitant CKD stage II–III after 12-week therapy

Parameter	Subgroup 1, background therapy + perindopril (n = 28)		Subgroup 2, background therapy + perindopril + coronary stenting (n = 25)		Subgroup 3, background therapy + perindopril/ amlodipine + coronary stenting (n = 34)	
	Baseline	In 12 weeks	Baseline	In 12 weeks	Baseline	In 12 weeks
Creatinine, μmol/L	138.2±10.3	118.0±10.1*	139.0±8.2	102.1±10.4*	158.0±8.2	98.0±2.5*
SBP, mm Hg	163±11.0	134±8.0*	173±8.0	131±9.0*	185±10.2	120±4.0*
DBP, mm Hg	106±8.0	85±7.6*	103±8.0	88±8.0*	118±3.1	85±1.5*
Endothelin-1, fmol/mL	1.97±0.04	1.50±0.04*	1.93±0.03	1.30±0.02*. **	2.01±0.01	0.61±0.01*.***
Nitric oxide, μmol/L	5.2±0.02	5.93±0.01*	5.01±0.02	6.71±0.03*	5.63±0.03	6.98±0.02*.***
PWV, m/s	9.97±0.08	8.62±0.07*	11.6±0.07	8.10±0.02*. **	12.4±0.03	8.22±0.07*
AIx	1.14±0.02	1.11±0.01	1.14±0.02	1.08±0.03*	1.16±0.02	1.06±0.02*
cSBP, mm Hg	152±12.4	138±6.2*	158±10.9	122±3.4*. **	156±10.2	110±3.4*.***
cPP, mm Hg	58±2.4	36±2.5*	60±5.0	38±1.4*	58±2.8	33±1.2*.***
LVEDD, cm	4.6±0.5	4.6±0.4	4.7±0.3	4.5±0.3	4.8±0.4	4.3±0.3
LVESD, mm	3.7±0.2	3.6±0.3	3.7±0.2	3.5±0.2	3.7±0.2	3.9±0.2
E/A	1.9±0.03	1.8±0.03	1.9±0.03	1.7±0.02*	2.4±0.04	1.9±0.03*.***
PASP, mm Hg	38±2.2	37±2.4	41±3.4	32±2.4*	42.2±3.4	25.2±2.4*.***

The differences are statistically significant ($p<0.01$) when comparing the results * – before and after 12-week treatment; ** – between Subgroup 1 and Subgroup 2; *** – after 12-week therapy with perindopril in Subgroup 2 and a fixed combination of perindopril and amlodipine in Subgroup 3. CAD – coronary artery disease; AH – arterial hypertension; CKD – chronic kidney disease; SBP – systolic blood pressure; DBP – diastolic blood pressure; PWV – pulse wave velocity; AIx – augmentation index; cSBP – central systolic blood pressure; cPP – central pulse pressure; LVEDD – left ventricular end-diastolic dimension; LVESD – left ventricular end-systolic dimension; E/A – ratio of peak early diastolic filling velocity (E) and late diastolic filling velocity (A); PASP – pulmonary artery systolic pressure.

SADI and coronary atherosclerosis was observed. When calculating the Spearman coefficient, it was shown to be characteristic only of patients in Group 2 ($r=0.75$; $p<0.001$). The findings confirm that severity of coronary atherosclerosis and the degree of clinical severity of CAD is not always directly proportional in patients with CAD, AH, and renal dysfunction.

When assessing the function of LV relaxation, we established a rigid type of LV diastolic dysfunction (LVDD) with an increased E/A ratio >2.0 in 42.5% of patients having CAD and AH with concomitant CKD but only in 20% of patients in the control group. E/A ≥2.0 indicates high left atrial pressure. The left atrial diameter was 4.8±0.4 cm with concomitant renal dysfunction and 4.3±0.3 cm in the control group. LVDD type I (E/A<0.8) was found in one-third of patients with CAD and CKD.

ET-1 was increased in both groups (0.25±0.01 fmol/mL in healthy subjects). ET-1 was 51% higher in CAD, AH, and CKD than in the control group. Nitric oxide levels were lower in the treatment group (4.81±0.22 μmol/L vs. 6.08±0.12 μmol/L; $p<0.05$). There was a positive correlation between nitric oxide and GFR ($r = 0.58$; $p<0.01$) and a negative correlation between ET-1 and GFR ($r = –0.72$; $p<0.001$).

Insufficient dilation of the brachial artery was observed in 80% of patients with a combination of CAD, AH, and CKD stages II–III and 68% in the control group, pathological vasoconstriction in 2.5% and 1.2%, respectively; normal function was registered in 17.5% and 30.8%, respectively ($p <0.001$).

Thus, patients with stable CAD and AH in CKD stages II–III had high-degree AH, deeper endothelial dysfunction, more pronounced arterial stiffness, and, consequently, morphological and functional remodeling of the heart.

The effects of combination therapy, which included perindopril A 10 mg/day or the fixed combination of perindopril/amlodipine with dose titration up to 10/10 mg/day, were studied in the second part of the study in patients with CAD, AH, and early CKD who underwent elective CAG followed by coronary stenting or who received only conservative therapy. A statistically significant decrease in systolic blood pressure was recorded in patients of all subgroups (Table 3).

The maximum hypotensive effect was observed in Subgroup 3, with all patients achieving the target BP levels. Creatinine levels decreased and renal function improved in all study subgroups.

During the 12-week treatment period, there were positive changes in the parameters of vascular stiffness along with a decrease in PWV, AIx, cSBP, cPP in all subgroups. Interestingly, patients who underwent coronary stenting showed more pronounced positive changes in the arterial stiffness indicators. For example, cSBP decreased by 9.2% in Subgroup 1 with the perindopril treatment and by 22.8% in Subgroup 2 ($p<0.01$). PWV decreased by 13.5% in Subgroup 1 and by 30.2% in Subgroup 2 ($p<0.01$).

During therapy with perindopril/amlodipine, the maximum decrease in aortic cSBP by 29.5% ($p<0.01$) and PWV by 33.7% ($p<0.01$) was recorded. PASP values were normalized in this subgroup. LV diastolic function improved only in the subgroup of patients receiving antihypertensive therapy with a fixed combination of perindopril and amlo dipine.

After 12 weeks, all three subgroups showed positive changes in endothelial function, such as a decrease in the plasma levels of ET-1 (from 23.9% in Subgroup 1 to 69.7% in Subgroup 3 ($p<0.01$). The levels of nitric oxide also improved (see Table 3).

Discussion

The accumulation of clinical and experimental data on the role of vascular endothelial dysfunction and the significance of arterial remodeling resulted in the parameters characterizing these processes being considered in some diseases as predictors of the risk of unfavorable outcomes, on the one hand, and as surrogate goals in the treatment of patients, on the other. Increased vascular stiffness was shown to be associated with a worse prognosis in patients with AH and those experiencing impaired renal function [7]. There is no doubt that worsening renal function as CKD progresses contributes to atherosclerosis, which further aggravates renal damage as it becomes more severe [8].

The attention of scientists is drawn to endothelial dysfunction as an early and integral process within the pathogenesis of atherosclerosis. AH is considered as a factor provoking the onset of endothelial dysfunction. AH and CKD were shown to mutually aggravate the prognosis [9]. More severe endothelial dysfunction is described in the combination of AH and CKD; here, wall stiffness of large and medium arteries is more pronounced [10]. We were also able to ascertain that patients with chronic CAD with stable angina pectoris with concomitant AH and early and moderate renal dysfunction, ET-1, nitric oxide levels, had statistically significantly more pronounced deviations as compared to patients with similar cardiovascular pathology and preserved renal function. The functional significance of these laboratory differences was confirmed by the test with post-occlusive reactive hyperemia: normal vasodilation was registered only in 17.5% of patients with CKD and in 30.8% of patients with preserved renal function.

Based on the results of many scientific researches, it is thought that more severe endothelial dysfunction and the degree of arterial remodeling are directly correlated with the severity of the atherosclerotic process. The design of our study, according to which patients with stable CAD were selected for the first time during ineffective antianginal therapy and with indications for CAG, allowed the following findings to be revealed. The results of CAG in the group of patients with early and moderate renal dysfunction showed that 18.7% did not have hemodynamically significant stenosis, while 44.5% had single-vessel coronary disease, which, however, led to the development of cardiovascular events, including MI, in 50% of these patients. The presence of non-obstructive CAD in CKD was reported by Keane et al. [11]. Thus, there was a statistically significant higher number of patients with non-obstructive CAD having similar clinical severity of stable angina pectoris in the group of patients with CKD stages II–III. In our opinion, this can be explained by the significant role of microvascular dysfunction as a manifestation of endothelial impairment in the genesis of ischemia in comorbid patients with CKD, which was studied by Charytan et al. [12], and LV diastolic dysfunction as a manifestation of morphofunctional remodeling of the heart in response to high stiffness of large arteries, which impairs coronary circulation.

As PCI has become an essential treatment for patients with chronic CAD, the problem of stent restenosis has arisen. Mazaev et al. [13] showed that the presence of CKD is a risk factor for late stent restenosis after elective PCI. Wu et al. [14] showed that increased aortic pressure, especially cPP, is the main predictor of all-cause death and repeated PCI (hazard ratios 2.46 and 1.41, respectively) in a cohort of 1,184 patients with CAD and AH who underwent PCI. The authors observed the highest cPP values in patients with CKD. Some researchers showed that the process of coronary angioplasty and stenting is accompanied by elevated blood levels of inflammation biomarkers and aggravated endothelial dysfunction due to artery wall trauma [15]. Cassese et al. [16] demonstrated in 10,004 patients that endothelial dysfunction and the severity of inflammation following stenting are independent RFs of restenosis.

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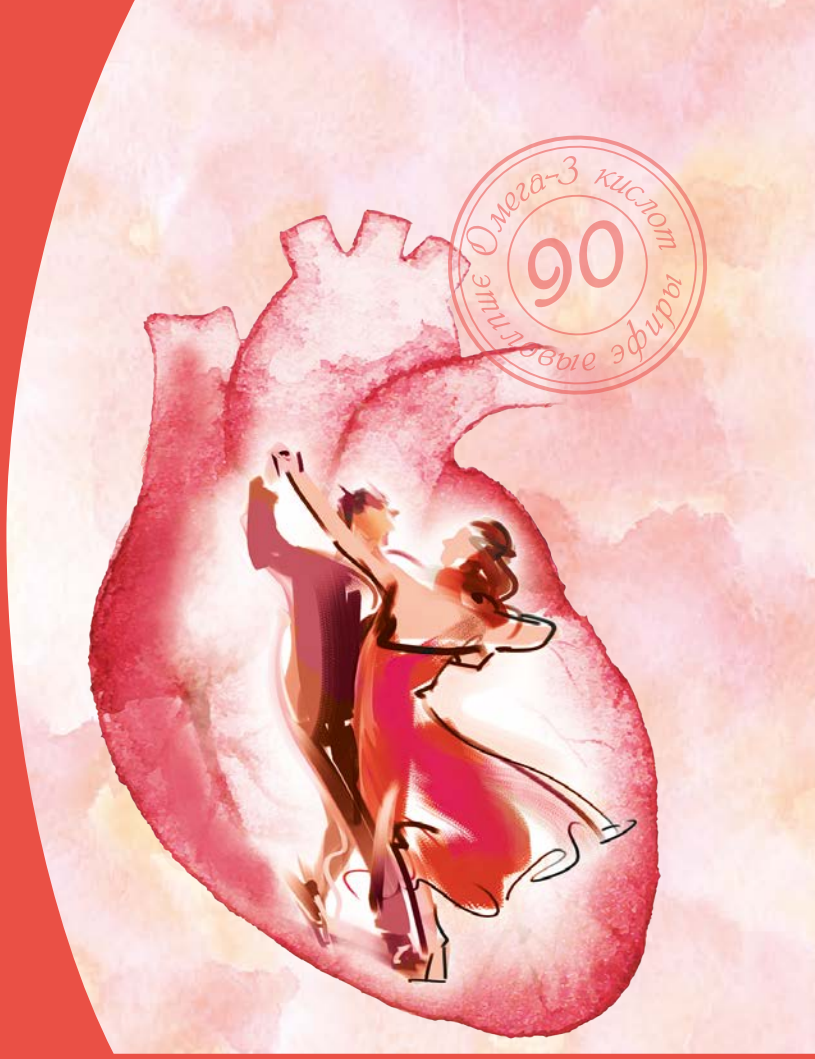
Abbott

- Способствует восстановлению клеток сердца*, 1, 2
- Снижает риск внезапной сердечной смерти на 45%*, 3
- Хорошо переносится при длительной терапии*, 4, 5



* У пациентов после инфаркта миокарда (в составе комбинированной терапии): в сочетании со статинами, антиагрегантными средствами, бета-адреноблокаторами, ингибиторами ангиотензинпревращающего фермента (АПФ).

ОМАКОР ДЕЛО ЖИЗНИ

ДЛЯ ВТОРИЧНОЙ ПРОФИЛАКТИКИ ПОСЛЕ ИНФАРКТА МИОКАРДА*, 6

Омакор. Регистрационный номер: ЛС-000559. **Международное непатентованное или группировочное наименование:** Омега-3 кислот этиловые эфиры 90. **Лекарственная форма:** капсулы, 1000 мг. **Фармакологические свойства*.** Полиненасыщенные жирные кислоты класса омега-3 – эйкозапентаеновая кислота (ЭПК) и докозагексаеновая кислота (ДГК) – относятся к незаменимым (эссенциальным) жирным кислотам (НЭЖК). Результаты клинического исследования GISSI-Prevenzione, полученные за 3,5 года наблюдений, показали существенное снижение относительного риска смертности от всех причин, нефатального инфаркта миокарда и нефатального инсульта на 15 % ([2-26] p=0,0226) у пациентов после недавно перенесенного инфаркта миокарда, принимавших препарат Омакор по 1 г в сутки. Дополнительно, относительный риск смерти по причине сердечно-сосудистой патологии, нефатального инфаркта миокарда и нефатального инсульта снижался на 20 % ([5-32] p=0,0082). Результаты клинического исследования GISSI-Heart Failure, в котором пациенты с хронической сердечной недостаточностью получали препарат Омакор по 1 г в сутки в среднем в течение 3,9 лет, показали снижение относительного риска смертности от всех причин на 9 % (p=0,041), снижение относительного риска смертности от всех причин и госпитализации по причине сердечно-сосудистых патологий на 8 % (p=0,009), снижение относительного риска первичной госпитализации по причине желудочковых аритмий на 28 % (p=0,013). **Показания к применению.** Гипертриглицеридемия: эндогенная гипертриглицеридемия IV типа по классификации Фредериксона (в монотерапии) в качестве дополнения к гиполипидемической диете при ее недостаточной эффективности; эндогенная гипертриглицеридемия IIb или III типа по классификации Фредериксона в комбинации с ингибиторами ГМГ-КоА редуктазы (статинами), когда концентрация триглицеридов недостаточно контролируется приемом статинов. Вторичная профилактика после инфаркта миокарда (в составе комбинированной терапии): в сочетании со статинами, антиагрегантными средствами, бета-адреноблокаторами, ингибиторами ангиотензинпревращающего фермента (АПФ). **Противопоказания.** Повышенная чувствительность к действующему веществу, сое, арахису или любому из вспомогательных веществ, входящих в состав препарата. Возраст до 18 лет (эффективность и безопасность не установлены). Беременность и период грудного вскармливания. Омакор не следует применять у пациентов с экзогенной гипертриглицеридемией (гиперхиломикронемией I типа). **С осторожностью.** Установленная гиперчувствительность или аллергия на рыбу; возраст старше 70 лет; нарушения функции печени; одновременный прием с пероральными антикоагулянтами; геморрагический диатез; пациенты с высоким риском кровотечений (вследствие тяжелой травмы, хирургической операции); вторичная эндогенная гипертриглицеридемия (особенно при неконтролируемом сахарном диабете). **Применение при беременности и в период грудного вскармливания*.** Назначать Омакор беременным следует с осторожностью, только после тщательной оценки соотношения риска и пользы, когда польза для матери превышает потенциальный риск для плода. Препарат не должен применяться в период грудного вскармливания. **Способ применения и дозы*.** Внутрь, независимо от приема пищи. Во избежание развития возможных нежелательных явлений со стороны желудочно-кишечного тракта (ЖКТ) препарат Омакор может приниматься во время приема пищи. Гипертриглицеридемия. Начальная доза составляет 2 капсулы в сутки. В случае отсутствия терапевтического эффекта возможно увеличение дозы до максимальной суточной дозы – 4 капсулы. Вторичная профилактика инфаркта миокарда. Рекомендуется принимать по 1 капсуле в сутки. **Побочное действие*.** Желудочно-кишечные расстройства (в том числе вздутие живота, боль в животе, запор, диарея, диспепсия, метеоризм, отрыжка, гастроэзофагеальная рефлюксная болезнь, тошнота или рвота). *Перечень всех побочных действий представлен в инструкции по медицинскому применению.* **Передозировка.** Особые указания отсутствуют. Должна быть проведена симптоматическая терапия. **Взаимодействие с другими лекарственными средствами*.** При одновременном применении препарата Омакор с пероральными антикоагулянтами или другими препаратами, влияющими на систему гемостаза (например, ацетилсалициловая кислота или НПВП), наблюдалось увеличение времени свертывания крови. При этом геморрагических осложнений не наблюдалось. Ацетилсалициловая кислота: пациенты должны быть проинформированы о возможном увеличении времени свертывания крови. Совместное применение препарата Омакор с варфарином не приводило к каким-либо геморрагическим осложнениям. Однако необходим контроль соотношения протромбинового времени/международного нормализованного отношения (ПТВ/МНО) при совместном применении препарата Омакор с другими препаратами, влияющими на соотношение ПТВ/МНО, или после прекращения терапии препаратом Омакор. **Особые указания*.** Омакор должен применяться с осторожностью у пациентов с установленной гиперчувствительностью или аллергией на рыбу. В связи с умеренным увеличением времени свертывания крови (при приеме в высокой дозе, т.е. 4 капсулы в сутки) требуется наблюдение за пациентами, имеющими нарушения со стороны свертывающей системы крови или получающими антикоагулянтную терапию или другие препараты, влияющие на систему гемостаза (например, ацетилсалициловую кислоту или НПВП); при необходимости, доза антикоагулянта должна быть скорректирована. Необходимо учитывать увеличение времени свертывания крови у пациентов с высоким риском развития кровотечения. При терапии препаратом Омакор снижается уровень образования тромбоксана А2. Существенного влияния на уровень других факторов свертывания крови не наблюдалось. У некоторых пациентов наблюдалось небольшое, но достоверное повышение активности АСТ и АЛТ (в пределах нормы), при этом отсутствуют данные, указывающие на повышенный риск приема препарата Омакор пациентами с нарушением функции печени. Необходим контроль активности АСТ и АЛТ у пациентов с любыми признаками нарушения функции печени (в частности, при приеме в высокой дозе, т.е. 4 капсулы в сутки). Опыт применения препарата для лечения экзогенной гипертриглицеридемии (гиперхиломикронемии типа 1) отсутствует. Опыт применения препарата при вторичной эндогенной гипертриглицеридемии ограничен (особенно при неконтролируемом сахарном диабете). **Влияние на способность управлять транспортными средствами, механизмами*.** Ожидается, что препарат не оказывает или оказывает несущественное влияние на способность управлять транспортными средствами и работать с механизмами. **Условия хранения.** Хранить при температуре не выше 25 °С. Не замораживать. Хранить в недоступном для детей месте! Условия отпуска. Отпускают по рецепту.

***Полная информация представлена в инструкции по медицинскому применению.**

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Информация предназначена для медицинских и фармацевтических работников.
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Thus, we were prompted to investigate whether the positive effects of ACE inhibitors would be reproduced in such a complex cohort of patients with correlated conditions, such as CAD, AH, CKD, soon after elective PCI with stenting.

Previous studies demonstrated the positive effects of ACE inhibitors on the development of atherosclerosis and nephroprotective effects in hypertension [17]. The ability of perindopril to improve the prognosis in patients with stable CAD was proven [18]. Bertrand et al. [19] showed that this drug is also effective in reducing cardiovascular mortality and the incidence of nonfatal myocardial infarction in patients with a history of MI and/or coronary revascularization, and that the protective effect persists in early renal dysfunction (mean GFR 76.2±18.1 mL/min/1.73 m^2) [20].

Panina et al. [21] described the practice of using antihypertensive therapy to correct endothelial dysfunction in patients at different stages of CKD. They identified a direct correlation between reduced GFR and indicators of vasodilating activity of the vascular wall. In our study, the 12-week combination therapy, including perindopril and especially perindopril in combination with amlodipine, in patients with CKD stage II–III (GFR ≥ 45 mL/min/1.73 m^2) and AH, CAD, improved endothelial function, which was shown by significantly decreased levels of the vasoconstrictor ET-1 and increased levels of the vasodilator nitric oxide. Svarovskaya et al. [22] found that ET-1 ≥ 0.852 fmol/L was a predictor of poor prognosis following stenting. Decreased levels of ET- 1 are associated with less pronounced severity of non-infectious vascular inflammation, which, according to some authors, plays an important role in the pathogenesis of AH and atherosclerosis and may thus help reduce the risk of adverse outcomes following coronary stenting [23, 24].

Following the results of the ASCOT-CAFE trial (2006), aortic blood pressure can be considered as a target for antihypertensive therapy due to a more significant correlation with the outcomes of AH than with brachial BP. Several authors showed that antihypertensive drugs produce different effects on aortic pressure and the augmentation index [25]. Pradhan et al. [26] observed in patients with AH that perindopril, especially in combination with a calcium channel blocker, reduces central blood pressure and PWV within 6 weeks more effectively than other ACE inhibitors ($p<0.05$). According to our data, the most pronounced antihypertensive effect on central pressure was achieved in patients with AH, CAD, and CKD in the subgroup of patients who received a fixed combination of perindopril and amlodipine. Considering the evidence, it seems especially significant that cPP is one of the main predictors of all-cause death and repeated PCI in patients with a history of elective PCI.

On the basis of the obtained materials, we show that 12-week therapy with perindopril and especially perindopril in combination with amlodipine can statistically significantly reduce vascular stiffness and improve endothelial function in patients with chronic CAD, AH and CKD, including those who underwent elective PCI with stenting. The practical relevance of this information is also determined by the fact that more than 40% of patients undergoing PCI have CKD [27], which offers the prospect for improving treatment outcomes in this category of patients.

Limitations

When interpreting the study results, it is necessary to consider the small number of patients in the treatment subgroups (from 25 to 34) and the short-term follow-up (12 weeks). These factors can affect the statistical significance of the study, and, hence, the accuracy of the results obtained.

Conclusion

Patients with coronary artery disease and arterial hypertension with concomitant early chronic kidney disease have more severe anatomical and functional impairments of arteries and heart than patients with chronic kidney disease and arterial hypertension where renal function is preserved.

The inclusion of the angiotensin-converting enzyme inhibitor perindopril in the combination therapy of patients with coronary artery disease and arterial hypertension with concomitant chronic kidney disease stages II–III had a good hypotensive effect and decreased the levels of creatinine. The use of perindopril for 12 weeks, especially the fixed combination of perindopril and amlodipine, in patients with coronary artery disease, arterial hypertension, and chronic stage II–III kidney disease decreases vascular stiffness and the severity of endothelial dysfunction, as well as improving the diastolic function of the heart, especially in patients who underwent coronary stenting.

No conflict of interest is reported.

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