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The Effect Of Arni On The Functional State Of The Kidneys In Patients With IHD

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ABSTRACT

Purpose of the study: comparative study of the effect of ARNI (combination of valsartan and sacubitrile) on the structural and functional state of the kidneys in patients with IHD after revascularization.

Material and research methods. The study included 320 patients with coronary artery disease. 37 patients underwent surgical revascularization (CABG), 283 patients underwent endovascular revascularization. On average, the concentration of creatinine was 90.08 ± 1.72 µmol /l. All patients were divided into 2 groups: patients who received the drug valsartan (group B, 160 people), patients who received a combination of valsartan and sacubitril a (ARNI - a combination of a molecule of valsartan and an inhibitor of neprilysin sacubitril in a molar ratio of 1: 1) (group C, 160 people). Also, all patients were divided into 2 subgroups depending on the degree of eGFR decrease by the 3rd month of observation: patients with a decrease in eGFR by the 3rd month of observation more than 20% (group 1 - 59 patients) and less than 20% (group 2 - 261 sick). In dynamics, three months later, at the end of the first and second years of follow-up after revascularization, the patients underwent determination of the blood creatinine concentration, with the calculation of GFR and ultrasound examination (US) of the kidneys with dopplerography of the segmental arteries.

Research results. The study showed that during 2 years of follow-up after coronary revascularization, there was a decrease in eGFR in both groups of patients, regardless of the therapy. Comparative analysis of the dynamics of eGFR between patients with different treatment regimens, depending on the severity of the decrease in eGFR, showed that the dynamics of the progression of CKD was significantly greater in patients with decreased eGFR by the 3rd month of therapy by 20% or more compared with patients who received sacubitril in the therapy regimen.The difference becomes significant only by the 1st year of observation and persists by the 2nd year of observation. Resistivity

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index of renal segmental arteries by the end of observation in-group C was significantly ($p < 0.05$) lower than in-group B.

Conclusion. The inclusion of ARNI (a combination of valsartan and sacubitril) in the IHD treatment regimen contributes to a significant decrease in the rate of progression of CKD in patients prone to rapid progression of type II cardiorenal syndrome. Against the background of ARNI application, there was a tendency to slow down the progression of pathological renal glomerular vascular remodeling.

KEYWORDS

Ischemic heart disease, chronic kidney disease, ARNI, sacubitril.

INTRODUCTION

Ischemic heart disease (IHD) is the most common non-infectious disease in people over 20 years old. Myocardial ischemia leads to pathological remodeling of the heart, the clinical manifestation of which is chronic heart failure (CHF) [1,2]. An increase in venous pressure is transmitted to the efferent arterioles of the renal glomeruli, intraglomerular pressure increases; hyperfiltration develops first, glomerular ischemia, followed by the accumulation of interstitial tissue and its sclerosis [3]. Glomerulosclerosis is clinically manifested by chronic renal failure (CKD) syndrome. CKD itself is the most important risk factor for cardiovascular events [4], and with an increase in the stage of CKD, the cardiovascular risk increases [5,6]. The combination of these pathologies in various variants is defined as cardiorenal syndrome [7,8].

Treatment of cardiorenal syndrome is carried out in two directions - coronary revascularization and pharmacological drugs. However, even after coronary revascularization, the started pathogenetic circles do not stop, and it is possible that the processes of myocardial fibrosis themselves increase the apoptosis of cardiomyocytes and glomerulosclerosis. Pharmacological correction of the second type of cardiorenal syndrome consists in the elimination / inhibition of trigger factors - the use of beta-blockers and drugs that inhibit the activity of RAAS (angiotensin converting enzyme inhibitors or angiotensin receptor blockers) [9,10]. According to trail studies, the use of these drugs is associated with a decrease in the risk of mortality and a slight decrease in the severity of cardiovascular remodeling; however, it is not possible to completely stop the progression of CHF and CKD [11]. Modern trends in the correction of CHF is the drug blockade of neurohumoral pathways of pathogenesis - beta-blockers and a combination of ARBs and the inhibitor neprilysin sacubitril [12,13].

PURPOSE OF THE STUDY

Comparative study of the effect of ARNI (combination of valsartan and sacubitrile) on the structural and functional state of the kidneys in patients with IHD after revascularization.

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MATERIAL AND RESEARCH METHODS

The study included 320 patients with coronary artery disease who were admitted to the Department of Interventional Cardiology of the Republican Specialized Scientific and Practical Medical Center for Therapy and Medical Rehabilitation for coronary angiography and a decision on the feasibility and choice of revascularization technique. In 94 patients, the cause of hospitalization was exertional angina of FC III-IV, in 60 - progressive angina, 6 patients were admitted due to heart failure as a clinical form of coronary artery disease. To achieve the goal of studying the pathogenetic features of type II cardiorenal syndrome, the study did not include patients with eGFR less than 60 ml / min. On average, the concentration of creatinine was 90.08 ± 1.72 μmol/l. According to the results of coronary angiography, 37 patients underwent surgical revascularization (CABG) within a month after CAG. Endovascular revascularization (stenting of the coronary arteries) was performed in 183 patients. Patients were prescribed standard IHD therapy: antiplatelet agent - aspirin 100mg / day or clopidogrel 75mg per day in case of contraindications to the appointment of aspirin (in the case of endovascular revascularization - double antiplatelet therapy aspirin + clopidogrel), beta blocker - bisoprolol (average dose of 7.8 0.27 mg / day), an acetyl-CoA reductase inhibitor - atorvastatin at an initial dose of 20 mg per day (the average dose of atorvastatin was 32.82 ± 1.83 mg / day, the achieved level of low-density lipoproteins was 2.18 ± 0.07 mmol / l). All patients were randomly divided into 2 groups according to the prescription of drugs that inhibit the mechanisms of CHF progression: patients who received valsartan in an individually selected dose depending on the hypotensive response, the average dose was 152.97 ± 9.21 mg / day (group B, 160 people), patients who received a combination of valsartan and sacubitril (ARNI is a combination of a molecule of valsartan and an inhibitor of neprilysin sacubitril in a molar ratio of 1:1), the average dose was 97.63 ± 3.26 mg / day of valsartan and 102.64 ± 4, Sacubitril 26mg / day (group C, 160 people).). Also, all patients were divided into 2 subgroups depending on the degree of eGFR decrease by the 3rd month of observation: patients with a decrease in eGFR by the 3rd month of observation more than 20% (group 1 - 59 patients) and less than 20% (group 2 - 261 sick). Group 1 included 28 patients from group B and 31 patients from group C. Group 2 included 129 patients from group B and 132 patients from group C. In dynamics after three months, at the end of the first and second years of observation after revascularization, all patients underwent examination, including the determination of the functional state of the kidneys: the concentration of creatinine in the blood, with the calculation of GFR and ultrasound examination (US) of the kidneys with dopplerography of the segmental arteries.

To assess the functional state of the kidneys, the concentration of blood creatinine was determined with the calculation of eGFR (Hojs R et al. Clin Nephrol. 2008). Ultrasound examination of the kidneys was performed from the lumbar approach to the prone position. The renal parenchymal volume (RPV) for both kidneys was determined and the obtained value was indexed to the body surface area (RPV), the maximum systolic and final diastolic blood flow velocity was recorded by Doppler at the level of the segmental arteries, and the Pursello resistance index (IR)

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was calculated for each kidney with subsequent averaging.

All the indicators obtained in the study were entered into the pivot tables of the Excel editor for Windows 2007, grouped according to the studied characteristics and, after checking the normal distribution, were summarized using the arithmetic mean values and the standard deviation of the arithmetic means. The reliability of intergroup comparisons was carried out using the Student's test for paired and unpaired differences.

RESEARCH RESULTS AND DISCUSSION

The study showed that during 2 years of follow-up after coronary revascularization, a progressive decrease in eGFR was observed in both groups of patients. Comparison of two groups of patients - the standard therapy group and the group of patients whose therapy included sacubitril - did not reveal a significant difference in eGFR levels both at baseline and at all stages of follow-up (Fig. 1). Accordingly, the relative dynamics of eGFR was also comparable in both groups (by the end of the 3rd month: -17.39 ± 1.17% in group B and -17.03 ± 1.13% in group C; by the end of the first year: -43.62 ± 1.28% and -40.99 ± 1.14%; by the end of the second year: -46.50 ± 1.79% and -44.80 ± 1.64%, respectively, differences in relative dynamics between groups - NR). These results of the study suggest that the advanced mechanism of progression of CHF and CKD, expressed in the development of myocardiosclerosis and glomerulosclerosis, is self-progressive. Along with this, it should be noted that the progression continues even after an adequately performed revascularization of the coronary bed. Perhaps, in some cases, even after coronary revascularization, started pathogenetic circles do not stop. Normally, to maintain renal oxygenation and glomerular filtration level, it is necessary to maintain an adequate difference between the arterial pressure of the bringing arteriole and the venous pressure of the outgoing arteriole. In heart failure, an increase in central venous pressure leads to a decrease in the perfusion gradient in the glomerular capillaries and, accordingly, a decrease in glomerular filtration [14,15].

Violation of glomerular hemodynamics and slowing of blood flow in the glomeruli is compensated by an increase in pressure in the afferent arteriole and its dilatation, an increase in filtration pressure (due to vasoconstriction of the outflow arteriole), hypertrophy of the glomerular capillaries, hyperfiltration (leads to proliferation of the mesangium, fibrosis and sclerosis of the vascular glomerulus) [16,17].

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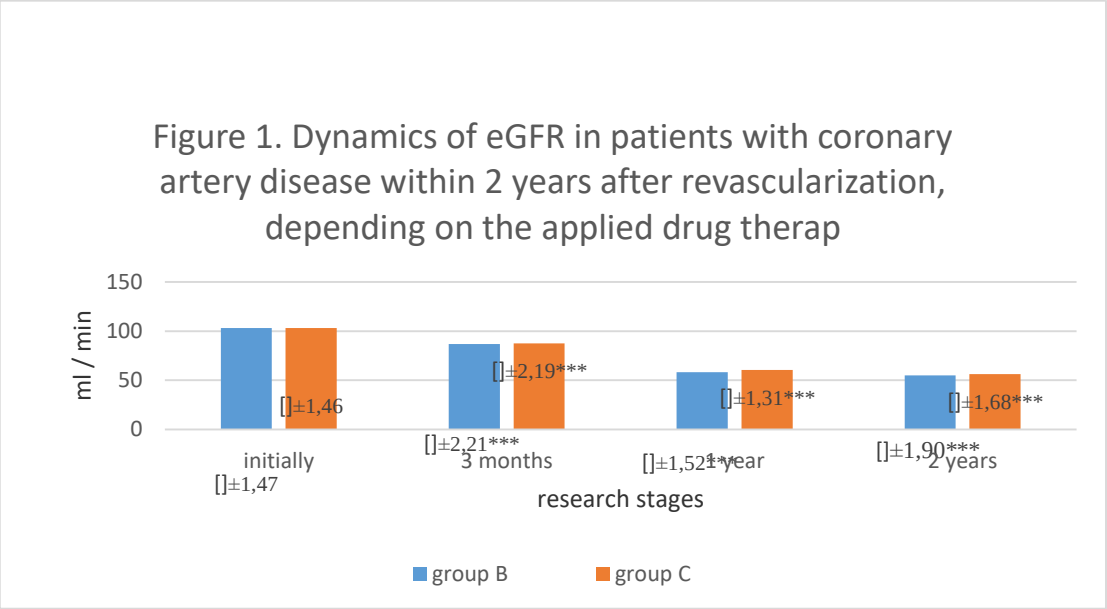

Note: * - reliability of differences with the initial data, ^ - reliability of differences between groups at the stages of observation. One sign - p <0.05, two signs - p <0.01, three signs - p <0.001.

In the course of the study, a comparative analysis of the eGFR dynamics between patients with different therapy regimens (groups B and C) was carried out depending on the severity of the eGFR decrease by the 3rd month of observation, that is, between groups 1 and 2. (Table 1). As a result, it was found that the dynamics of CKD progression (in terms of creatinine concentration and eGFR) was significantly greater in patients with decreased eGFR by the 3rd month of therapy by 20% or more compared with patients who received sacubitril in the therapy regimen. Moreover, the difference becomes significant only by the 1st year of observation and persists by the 2nd year of observation. In patients in whom the decrease in eGFR by the 3rd month of therapy was less than 20%, there were no differences in the progression of CKD depending on the use of sacubitril.

The improvement in GFR with the use of sacubitril is possibly associated with both an improvement in the structural and functional properties of the myocardium and the effect of ARNI on glomerulosclerosis processes. It is known that ARNI helps to reduce blood pressure, the diameter of the left chambers of the heart, and reduces intramyocardial tension, thereby reducing the production of ANP by ventricular cardiomyocytes [18]. In a number of studies, the use of the inhibitor neprilysin led to a decrease in proteinuria in patients with CHF [19, 20], an increase in eGFR by the 3rd month of therapy (from 50 to 53 ml / min), in patients with diabetic nephropathy, the use of ARNI was associated with a significant decrease in the albumin / urine creatinine [21].

Considering that the pathogenesis of type II cardiorenal syndrome is renal hemodynamic impairment, the research studied the dynamics

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of the renal segmental artery resistance index and the renal volume index against the background of the therapy regimens used (Table 2). IR in patients with coronary artery disease was significantly higher than in healthy individuals (0.62 ± 0.03 rel units, p <0.001). During the observation process, both in group B and in group C, there was no significant dynamics of IR (the relative dynamics was 1.45 ± 1.92% and 2.16 ± 3.07%, the difference in the relative dynamics between the groups was NR). However, by the end of the observation in-group C, the IR index was significantly (p <0.05) lower than in-group B.

The RPV index in patients with coronary artery disease was comparable to the index recorded in the control. For 2 years of follow-up, there was some insignificant decrease in RPV, comparable in both groups.

In our study, the use of ARNI was associated with an improvement in GFR and a lower progression of Doppler indicators of glomerulosclerosis - an increase in IR of renal segmental arteries. The improvement in GFR indicators when using sacubitril is possibly associated with both an improvement in the structural and functional properties of the myocardium, and with the effect of ARNI on glomerulosclerosis processes. It is known that ARNI helps to reduce blood pressure, the diameter of the left chambers of the heart, and reduces intramyocardial tension, thereby reducing the production of NP by ventricular cardiomyocytes [18]. In a number of studies, the use of the inhibitor neprilysin led to a decrease in proteinuria in patients with CHF [20], an increase in eGFR by the 3rd month of therapy (from 50 to 53 ml / min), in patients with diabetic nephropathy, the use of ARNI was associated with a significant decrease in the urine albumin / creatinine ratio [21].

Table 1.

Dynamics of eGFR and serum creatinine concentration in patients with coronary artery disease, depending on the therapy used (group B - in the numerator, group C - in the denominator) and the degree of decrease in eGFR by the 3rd month of observation

Groups	Group 1		Group 2	
indicators	Absolute values	Relative dynamics	Absolute values	Relative dynamics
Initially				
eGFR, ml/min	86,66±2,29 85,33±2,02		107,04±1,55 107,00±1,55	
Creatinine µmol /l	108,55±3,34 110,72±3,26		85,74±1,61 85,80±1,66	
3 months				
eGFR,	48,08±1,01***	-3,58±1,75	96,28±1,98***	-1,10±0,58

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ml / min	48,75±0,94***	-2,09±1,55	96,29±1,98***	-1,05±0,57
Creatinine µmol / l	188,16±7,40*** 182,19±6,56***	77,47±8,05 68,02±7,12	85,81±1,63*** 85,65±1,63***	0,06±0,06 -0,08±0,20
1 year				
eGFR, ml / min	32,86±0,79*** 37,37±1,05***^^^	- 61,30±1,46 - 5,58±1,58^^	64,18±1,43*** 65,78±1,17***	-39,38±1,29 -37,47±1,15
Creatinine, µmol / l	270,82±14,63*** 230,43±9,04***^	156,26±14,98 115,30±11,77^	140,35±3,77*** 131,90±2,33***	67,62±4,75 58,99±3,67
2 years				
eGFR, ml / min	26,27±1,78*** 32,12±2,25***^	-68,78±2,61 -61,36±3,14^	61,87±1,86*** 61,99±1,64***	-41,14±1,85 -40,70±1,72
Creatinine, µmol / l	346,85±24,84*** 260,50±8,91***^^	228,74±24,49 142,74±11,38^^^	190,77±7,11*** 173,66±4,11***^	129,99±9,39 112,56±7,23

Note: * - reliability of the difference with the initial data, ^ - reliability of the difference between groups B and C at the observation stages. One sign - p <0.05, two signs - p <0.01, three signs - p <0.001.

Table 2.

Dynamics of ultrasound of renal characteristics in patients with coronary artery disease, depending on the therapy used (group B - in the numerator, group C - in the denominator) and the degree of eGFR decrease by the 3rd month of observation

	Initially	3 months	1 year	2 years
IR, rel units	0,71±0,02 0,70±0,02	0,75±0,02 0,72±0,02	0,76±0,02 0,72±0,02*	0,79±0,02 0,73±0,02^**
RPV cm^2 / m^2	97,34±0,79 96,85±0,73	96,35±0,78 95,92±0,72	96,00±0,80 95,56±0,73	95,52±0,80 95,26±0,74

Note: * - reliability of the difference with the initial data, ^ - reliability of the difference between groups B and C at the observation stages. One sign - p <0.05, two signs - p <0.01, three signs - p <0.001.

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CONCLUSION

Thus, the present study has demonstrated that the inclusion of ARNI (a combination of valsartan and sacubitril) in the IHD treatment regimen contributes to a significant decrease in the rate of progression of CKD in patients prone to rapid progression of type II cardiorenal syndrome. Also, against the background of ARNI use, there was a tendency to slow down the progression of pathological renal glomerular vascular remodeling.

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