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Principles Of Treatment Of Patients With Chronic Kidney Disease And Arterial Hypertension.

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Annotation: Chronic kidney disease (CKD) is a progressive kidney injury, more common in the elderly, women, patients with diabetes mellitus (DM) and/or arterial hypertension (AH). Currently, CKD is recognized as one of the leading causes of death worldwide. Another medical and social problem is hypertension, which is the most important cardiovascular risk factor worldwide and one of the main causes of CKD. The high prevalence and comorbidity of CKD and hypertension, as well as an unfavorable prognosis, determine the need for effective prevention and treatment of these conditions. The use of nephroprotective approaches in the treatment of CKD can significantly improve the prognosis both in patients with risk factors for the development of renal dysfunction and in patients with existing kidney disease. According to modern recommendations for the treatment of hypertension, patients with high-risk hypertension, including from the standpoint of nephroprotection, are shown combination therapy with drugs from two groups, preferably in one tablet. The article presents data confirming the efficacy of a fixed combination of an angiotensin-converting enzyme inhibitor and a dihydropyridine calcium channel blocker.

Key words: chronic kidney disease, arterial hypertension, antihypertensive drugs, fixed combination, ramipril, amlodipine.

One of the main reasons for the development and increasing prevalence of CKD is arterial hypertension (AH), detected in 30–45% of the adult population [7, 8]. The incidence of AH in women is about 40%, in men it reaches 47% [9]. The disease is associated with age, in people over 60 years old it is detected more often, in about 60% of cases [1]. According to forecasts, by 2025 the number of patients with AH will increase to 1.5 billion [10]. An increase in systolic blood pressure (SBP) ≥140 mm Hg is accompanied by a 70% increase in the risk of mortality and disability. Damage to target organs, including the kidneys, against the background of AH aggravates the risks of developing cardiovascular complications (CVC) [7]. Impaired renal function or the appearance of an early marker of renal damage, microalbuminuria (MAU), is a prognostically unfavorable factor for both cardiovascular mortality and the development of non-fatal complications [11–13]. At the same time, 20% of patients with hypertension are diagnosed with chronic renal failure (CRF) of varying severity, as evidenced, in particular, by data from the NHANES (National Health and Nutrition Examination Survey) registry [14, 15]. End-stage renal failure (ESRF) as a consequence of renal damage in hypertension ranks second among the causes leading to RRT in the United States and third in Japan [16]. On the other hand, in patients with CKD, the prevalence and incidence of cardiovascular pathology are significantly higher compared to the general population, which is explained by such metabolic and hemodynamic shifts against the background of

renal dysfunction as the development of albuminuria/proteinuria, systemic inflammation, oxidative stress, anemia [1]. A decrease in the glomerular filtration rate calculated using the CKD-EPI formula (eGFR) below 60 ml/min/1.73 m2 is accompanied by the development of hyperuricemia, protein-energy malnutrition, electrolyte disturbances and secondary hyperparathyroidism [17]. The prognostic significance of new risk factors for the development of extrarenal complications cannot be ruled out: fibroblast growth factor 23 (FGF-23) and alpha-Klotho protein, which affect the processes of vascular calcification and oxidative stress [17], which is supported by a higher risk of death from CVE in stage 5 CKD. The above facts indicate a multifaceted, bidirectional nature of the relationship between the kidneys and the cardiovascular system, which underlie the cardiorenal continuum. Early diagnosis of kidney damage with the identification of signs of renal damage at the initial stages is necessary for timely measures to prevent the development and progression of renal pathology and the prevention of CVE.

Target BP values in patients with CKD

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Treatment of patients with CKD C1–C5, the purpose of which is to slow the rate of progression of renal dysfunction, prevent the development of ESRD and improve the prognosis, includes etiologic and pathogenetic directions. To optimize treatment and improve the prognosis, the management tactics are determined by the severity of renal dysfunction. Also, an important strategy for treating patients with CKD is cardioprotection due to the association of the risk of CVC with the severity of renal impairment.

Given that hypertension is one of the main causes of kidney damage and the progression of renal pathology, it is not surprising that adequate BP control slows the development of CKD [7].

Various national and international guidelines for the treatment of hypertension provide different target BP levels. Thus, in the current domestic clinical guidelines on hypertension in adults (approved in 2020) [7], all patients with hypertension are recommended to reduce blood pressure to values <140/90 mm Hg as the first target level, and, subject to good tolerance in the absence of CKD in individuals under 65 years of age, to a target level of 130/80 mm Hg or lower, which is associated with a proven improvement in prognosis. For patients with hypertension (without kidney damage) and under 65 years of age, a proven improvement in prognosis is associated with a SBP level of 120–130 mm Hg [7]. Target values of diastolic blood pressure (DBP) for all patients with hypertension, regardless of various factors, correspond to 70–79 mm Hg [7]. In Russian clinical guidelines for CKD (2021), the target BP level is determined by the stage of CKD and the level of albuminuria: in patients with CKD and elevated or high levels of albuminuria (<300 mg/day or <300 mg/g) and hypertension, a SBP of 130–139 mmHg is recommended as a target level [1]. Data from a meta-analysis of 18 RCTs (15,924 patients with CKD) indicate a statistically significant reduction in all-cause mortality with a decrease in SBP by 16 mmHg (from 148 to 132 mmHg) [1]. In order to slow the rate of CKD progression and the risk of developing ESRD

in patients with CKD C1–C5 and very high or nephrotic albuminuria (≥300 mg/day or ≥300 mg/g) or persistent proteinuria (total urine protein ≥500 mg/day or ≥500 mg/g) and hypertension, it is recommended to reduce SBP to 120–130 mmHg and DBP ≤80 mmHg (in the absence of contraindications) [1]. Long-term maintenance of BP at 125/75 mmHg (median >14 years) was accompanied by a reduction in the risk of developing ESRD (OR 0.77; 95% CI 0.64–0.92) in individuals with proteinuria, which justifies lower target BP levels in this category for the purpose of nephroprotection [1]. In 2021, new KDIGO clinical practice guidelines were released [28], in which a fundamentally important update, compared to the 2012 KDIGO guidelines [29], is the target SBP level of <120 mmHg for adult patients with hypertension and pre-dialysis CKD. With regard to DBP, KDIGO experts consider it appropriate to target DBP to <80 mmHg in young patients with CKD and patients with isolated diastolic hypertension. According to the experts, the benefits of intensive BP reduction (<120 mmHg) are more obvious in patients with CKD without diabetes. The new target level is based on the results of the Systolic Blood Pressure Intervention (SPRINT) study [30], which demonstrated the cardioprotective and cerebroprotective (impact on cognitive functions) effects of lower target BP levels. According to the results of this study, a decrease in SBP to <120 mmHg (compared to SBP <140 mmHg) is accompanied by a 25% reduction in the risk of CV events and a 27% reduction in all-cause mortality [30]. In addition, the guidelines emphasize that a decrease in SBP to <120 mmHg may be potentially dangerous in patients with a significant decrease in eGFR, initially low DBP (e.g., <50 mmHg), severe carotid artery stenosis, symptomatic postural hypotension, and concomitant coronary heart disease.

Treatment of hypertension and CKD.

In modern international and domestic clinical guidelines for hypertension in adults [7, 31], in the case of a combination of hypertension and CKD, the main group of drugs for the treatment of hypertension are renin-angiotensin-aldosterone system (RAAS) blockers — angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs). Also, an international consensus of experts recommends the use of ACEI for secondary prevention in all patients with high cardiovascular risk [32].

As a rule, ACEI and ARBs are as effective as other antihypertensive drugs, but have additional cardioprotective benefits in patients with heart failure, a history of myocardial infarction, and diabetes. In addition, both ACEI and ARBs have a nephroprotective effect, since they have an antiproteinuric effect. In this regard, the recommendations for the treatment of hypertension indicate that RAAS blockers are more effective in reducing albuminuria than other antihypertensive drugs and are indicated for patients with hypertension with MAU or proteinuria (the highest level of evidence is IA) [7].

Russian recommendations emphasize that all patients with CKD C3–C5, regardless of the presence of hypertension and in the absence of contraindications, are preferably prescribed ACE inhibitors or ARBs to effectively reduce proteinuria and the risks of progression of renal pathology (nephroprotection), cardiovascular events (cardioprotection) and death from all

causes [1, 7]. A meta-analysis of 119 RCTs (n=64,768) demonstrated significant advantages of ACE inhibitor or ARB therapy in patients with CKD (mainly pre-dialysis stages) in terms of reducing the rate of CKD progression to ESRD, CVE, and all-cause death compared to other classes of antihypertensive drugs, with treatment efficacy not dependent on the degree of hypertension, albuminuria level, decrease in eGFR, and presence of diabetes [1], but the antiproteinuric effect was dose-dependent. Among the drugs in the ACE inhibitor class, ramipril has a number of clinical and pharmacological advantages. It is a prodrug, characterized by high lipophilicity, and, due to increased affinity for tissue ACE, has a pronounced organoprotective effect [33]. Due to its long half-life (8–14 h), ramipril has high activity and a long duration of action (24 h). Thus, according to the results of the PRISMA I (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) study, the antihypertensive effect of ramipril develops 1–2 hours after administration and persists for 24 hours. At the same time, the persistent good antihypertensive effect in the morning and pre-morning hours has an important prognostic value given the association of this time of day with a higher risk of developing strokes and heart attacks [34].

Ramipril is also the drug of first choice for the treatment of patients with CKD. Significantly reducing total peripheral vascular resistance, ramipril has virtually no effect on renal blood flow. The absence of a sulfhydryl group eliminates nephrotoxic side effects [33]. The efficacy of ramipril in CKD has been confirmed in a number of clinical studies. Thus, the results of the MICRO-HOPE (Microalbuminuria, Cardiovascular and Renal Outcomes in the Heart Outcomes Prevention Evaluation) substudy [35], conducted as part of the large HOPE (Heart Outcomes Prevention Evaluation; 3577 patients with diabetes, average age 65.4 years), demonstrate a 25% reduction in the relative risk of cardiovascular death/nonfatal stroke/nonfatal myocardial infarction and a 24% reduction in the relative risk of death from all causes with ramipril compared to placebo. In the ramipril group, the frequency of increase in the urine albumin/urine creatinine ratio was also statistically significantly lower, which prevented the development of proteinuria. This study confirms the high efficacy of ramipril in patients with diabetes, especially in the presence of MAU.

It should be noted that treatment with ramipril reduces the likelihood of developing diabetes by 34%, which, in turn, is an independent risk factor for cardiovascular diseases and CKD [24, 36].

The goal of another clinical study REIN (Ramipril Efficacy in Nephropathy; 352 patients with chronic non-diabetic kidney diseases with proteinuria over 1 g/day) [37] was to assess the effect of ramipril on the level of proteinuria in these patients and the ability of the drug to affect the development and progression of the disease. According to the stated goal, the corresponding endpoints were also defined: change (decrease) in the glomerular filtration rate and the period before the manifestation of end-stage renal failure. The results of this study demonstrated a statistically significant decrease in the severity of proteinuria and a slowdown in the rate of progression of CKD during ramipril therapy compared with placebo. Moreover, the higher the degree of initial proteinuria, the more pronounced the nephroprotective effect of ramipril. The incidence of terminal

CKD in the ramipril group was almost 2 times lower, the risk of developing end-stage renal failure was reduced by 58% [37]. A subsequent 3-year follow-up of these patients after the completion of the REIN study revealed an increase in proteinuria by 15% and the development of CKD in 30% of patients in the placebo group, while in the ramipril group there was a further decrease in the level of proteinuria by 13% ($p = 0.003$) [38]. The REIN study showed that in patients with non-diabetic CKD, the use of ramipril leads to a two-fold decrease in the rate of progression of CKD compared with the placebo group. It is noteworthy that the most pronounced effect of ramipril was achieved at high initial levels of proteinuria [37].

The antiproteinuric effect of low doses of ramipril was also confirmed in the ATLANTIS (Ace-Inhibitor Trial to Lower Albuminuria in Normotensive Insulin-Dependent Subjects) study in patients with diabetic nephropathy against the background of type 1 diabetes and MAU [39].

The drug ramipril Hartil® (EGIS Pharmaceuticals, PLC, Hungary) is well known in Russia; its bioequivalence and therapeutic equivalence to the original drug have been demonstrated in a number of studies. In particular, therapeutic equivalence was proven in an open randomized crossover comparative study in patients with grade 1–2 hypertension and high cardiovascular risk [40]. Current clinical guidelines for hypertension in adults recommend a combination of antihypertensive drugs as initial therapy for all patients with hypertension (except for low-risk patients with BP<150/90 mmHg, patients ≥80 years old, patients with frailty syndrome). Preferred combinations should include a RAAS blocker (ACE inhibitor or ARB) and a dihydropyridine calcium channel blocker (CCB) or a diuretic [7].

Conclusion

The combination of hypertension and CKD in patients determines a high risk of developing cardiovascular and renal complications. For patients with a high risk of complications, a combination of antihypertensive drugs is recommended as initial therapy to achieve the target BP level and improve the prognosis, preferably in one tablet. The first drugs of choice are RAAS blockers, including ACE inhibitors, which have proven antihypertensive and nephroprotective effects. As a second drug, taking into account the proven advantages, the use of CCBs is indicated. FC RAAS blocker / CCB allows for effective control of BP, providing an organoprotective effect, which has a beneficial effect on the prognosis, while being characterized by a favorable safety profile and good tolerability.

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