SPECIFICITIES IN HYPERTENSION TREATMENT IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract

Today, it is believed that all over the world about 10% of the population has a kidney lesion, most often chronic kidney disease (CKD). Hypertension and diabetes mellitus are the most common causes of chronic kidney damage, and in everyday clinical practice, we often wonder whether hypertension is a consequence of a lesion of the kidney parenchyma and vasculature or is its cause. Patients with CKD have high cardiovascular (CV) morbidity and most often die from CV disease. The specificity of blood pressure treatment in patients with chronic kidney damage is that good control of hypertension not only leads to a reduction of CV risk but also to a slowing of the progression of chronic to terminal renal failure.

There is no doubt that the first line of treatment for hypertension in patients with CKD is angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-2 receptor blockers (ARB). They are recommended especially for those patients with diabetic nephropathy because, in addition to their antihypertensive effect, they reduce proteinuria, slow down the progression of chronic kidney failure, especially if given in the early stages of CKD, and reduce CV risk. However, for a long time, there have been controversial opinions about whether in the advanced stages of renal failure, when the glomerular filtration rate (GFR) is < 30 mL/min/1.73 m², these drugs should be excluded. According to the latest KDIGO guidelines in 2021, renin-angiotensin-aldosterone (RAAS) blockers are the first line in the treatment of proteinuric CKD patients, with and without diabetes mellitus, and in stage 4, with a note that these drugs should be continued in therapy unless there is marked hyperkalemia (potassium > 6 mmol/L), acute kidney damage or decrease in estimated glomerular filtration rate > 30%.

The most important thing is to individualize the optimal therapy for each patient.

In the guidelines for the treatment of hypertension in patients with CKD, there are no clear recommendations for the treatment of unregulated hypertension when target pressures cannot be achieved with RAAS blockade and when there are contraindications for the administration of this group of drugs. The addition of calcium channel blockers, diuretics, and beta blockers is based on expert opinion.

Keywords: chronic kidney disease, hypertension, renin-angiotensin-aldosterone blockers

Introduction

Today, it is considered that more than 850 million people in the world (about 10% of the world’s population) have some form of kidney function impairment, most often chronic kidney disease (CKD), and as many as 843 million. This number is two times higher than the number of people with diabetes mellitus and twenty times higher than the number of people with AIDS.

According to the Kidney Disease Improving Global Outcomes (KDIGO) guide from 2012 chronic kidney disease is defined as chronic kidney damage, characterized by albuminuria (≥ 30 mg/day) and/or a decrease in glomerular filtration rate (GFR) < 60 mL/min/1.73 m² lasting at least 3 months. Scheme 1 shows the KDIGO classification and prognosis of CKD from 2012 according to the stages of GFR (G1-5) and albuminuria (A1-3).

As can be seen from scheme 1, CKD is divided into five stages, according to GFR (G1-5) and albuminuria (A1-3) according to the amount of albumin in the urine. The high risk of the development of end-stage renal disease is represented in red (GFR < 15 mL/min/1.73 m² and albuminuria > 300 mg/g).

Chronic kidney disease is associated with a high prevalence of cardiovascular (CVD) diseases, primarily hypertension. On the one hand, hypertension can be a consequence of parenchymal and vascular kidney diseases, and on
the other, high blood pressure leads to the kidney’s small blood vessel damage - nephroangiosclerosis. So, there is a frequent dilemma in everyday clinical practice: is hypertension a consequence or a cause of chronic renal lesions? Apart from hypertension, the most common cause of chronic kidney damage is diabetic nephropathy, which occurs in 30% of patients with diabetes. Through numerous studies, it has been unequivocally shown that GFR < 60 mL/min/1.73 m² and the presence of albuminuria are two independent risk factors for general and CV mortality.

The specificity of the treatment of blood pressure in patients with chronic kidney damage is that good control of hypertension not only leads to a reduction of CV risk, but also to a slowing down of the progression of chronic to end-stage kidney disease (ESKD) and the moment of starting one of the renal replacement therapy. The latest guidelines for the treatment of hypertension in patients with chronic kidney damage was published in KDIGO 2021 (Clinical Practical Guideline for the Management of Blood Pressure in Chronic Kidney Disease). The KDIGO 2021 guidelines refer to the treatment of hypertension in patients with chronic kidney damage have updated the previous KDIGO guidelines (from 2012). Chapter 2 is directed to recommendations on diet, physical activity, and lifestyle (table 1), and chapter 3 is to blood pressure target values and antihypertensive therapy (table 3).

As can be seen in table 2, < 5 g of NaCl per day is recommended in patients with elevated blood pressure and chronic kidney damage. Mild to intense physical activity, adapted to CV status and physical tolerance, with a total weekly duration of 150 minutes is also recommended for these patients.

In chapter 3 of KDIGO 2021, is recommended that in patients with hypertension and CKD, the target systolic pressure should be < 120 mmHg in a routine measurement in the outpatient clinic, and RAAS inhibitors as the first line of therapy. These drugs are recommended as the first line of therapy both in patients with CKD stage 1-4 and albuminuria with and without diabetes. It has also been recommended to avoid any combination of ACEIs and ARBs, as well as combinations with direct renin inhibitors.
Target values of blood pressure

Although some large multicenter randomized studies have shown cardiovascular benefits in certain subpopulations, such as the frail and elderly, compared to the development of acute kidney injury, electrolyte imbalance, and cognitive dysfunction, one should be very cautious with these patients2-9. It is generally accepted that in patients with advanced CKD (stages 4 and 5), diabetes, with proteinuria > 1 g/day, elderly (> 90 years) and younger patients (< 50 years), as well as patients with severe hypertension and “white coat” hypertension one should not insist on systolic pressure < 120 mmHg. Randomized studies are needed to include these subpopulations. Also, in patients with coronary artery disease and low diastolic blood pressure, intensive lowering of blood pressure could lead to an increased risk of acute myocardial infarction, because myocardial perfusion depends on diastolic blood pressure.

It is generally accepted that lowering blood pressure is renoprotective and this has been demonstrated in large randomized trials in which systolic blood pressure is reduced from > 160 mmHg to < 140 mmHg, but this claim is less certain if it is reduced from 140 mmHg to < 120 mmHg. Thus, in the famous SPRINT study (Systolic Blood Pressure Intervention Trial Study) in long-term follow-up, in patients with intensive pressure reduction, chronic kidney disease progressed faster.

Antihypertensive drugs

Most patients with CKD and hypertension who have at least 20 mmHg higher blood pressure than the target, require a combination of two or more antihypertensive drugs. No randomized studies are comparing different drug combinations in patients with CKD, except for RAAS blocking drugs, calcium channel blockers (CCBs), and beta blockers compared to placebo, except for the SPRINT study. So, except for monotherapy, the schemes for the treatment of hypertension in patients with CKD are based on expert opinion.

Blockers of the renin-angiotensin-aldosterone system

In many large, strictly controlled randomized studies, drugs that block the renin-angiotensin-aldosterone system (RAAS) have shown beneficial effects not only in lowering blood pressure and preventing hypertensive target organ damage but also in reducing proteinuria and slowing the progression of CKD. Thus, these drugs with the proven properties mentioned, as well as proven good tolerance in the majority of people who take them in therapy, have found a place as the first line of antihypertensive therapy in many international guidelines for the treatment of hypertension, heart failure, diabetes, and kidney diseases.

However, both angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-2 receptor blockers (ARBs) have so-called “functional” side effects, which are associated with RAAS blockade, primarily hyperkalemia due to inhibition of aldosterone secretion and an initial acute reversible decrease in GFR by about 10-20% of the initial GFR. This slight worsening of renal function is caused primarily by a decrease in systemic blood pressure, but also by vasodilation of the efferent arteriole of the glomerulus, which leads to a decrease in intraglomerular pressure. A drop in GFR occurs in all stages of CKD, but it is more significant in people with already low GFR, that is advanced kidney failure. It is estimated that hyperkalemia (serum concentration ≥ 5.5 mmol/L) occurs in 30% of patients who are treated with RAAS blockers and have CKD stage 4 or 5.

Blocks of the RAAS system are not superior to other antihypertensive drugs in lowering blood pressure, but they have been unequivocally shown to slow down the progression of CKD, especially in patients with diabetes and proteinuria, if they are introduced in the earlier stages of CKD. However, there are controversial opinions about their beneficial effect in advanced stages of CKD, when GFR < 30 mL/min.

A recently published meta-analysis by Xie et al that included 119 randomized trials with nearly 65,000 patients with CKD, with or without diabetes mellitus, compared the effect of RAAS blocker therapy with other antihypertensive agents on renal and CV outcomes. It showed that both ACEi and ARBs reduced the risk of renal impairment and CV events, but the ACEi, not ARBs, reduced the risk of death compared with active control.

The benefit of the use of ACEi and ARB on the progression of CKD cannot be attributed only to the reduction of blood pressure in patients with proteinuria. It has already been noted that suppression of angiotensin II leads to vasodilation, predominantly the efferent arteriole, in the glomerulus, which results in a decrease of intraglomerular pressure and a significant antiproteinuric effect. The mechanism by which the reduction of albuminuria slows the progression of CKD cannot be attributed only to the reduction of blood pressure.
of renal disease is likely through altered permeability to macromolecules and consequently reduced exposure of large proteins to podocytes and tubule cells. Otherwise, this macromolecule exposure leads to progressive glomerulosclerosis and a decrease in GFR. Increased filtration of albumin and other macromolecules increases their reabsorption in the proximal tubules, which leads to the activation of vasoactive and proinflammatory cytokines that damage the tubulointerstitium, leading to fibrosis.

For years, there has been controversy about the even beneficial effect of excluding RAAS blockers from therapy in patients with advanced stages of CKD who have GFR < 30 mL/min. Thus, the study by Ahmed et al from 2010 showed that the exclusion of these drugs in 52 patients with CRF stage 4 led to an increase in eGFR by 10 mL/min/1.73 m², and the delay of ESKD, as well as an increase in blood pressure, while others studies did not have such conclusive evidence. While waiting for the results of a multicenter prospective randomized study on whether or not to exclude ACEi and ARB in advanced stages of CKD, without any clear views of this problem, many nephrologists lightly excluded ACEi and ARB in stages 4 and 5 of CKD, especially in cases of hyperkalemia, progression of CKD, hospitalization due to acute renal failure and the presence of numerous comorbid conditions. It is rare for such patients to return to this therapy after stabilization.

At the end of 2022 in NEJM (New England Journal of Medicine) the long-awaited randomized prospective three-year study of Bandar S et al with 411 patients with eGFR < 30 mL/min/1.73 m², which aimed to determine whether the exclusion of RAAS blockers leads to a slowing down of the decline in GFR, i.e. the progression of CKD. This study showed that the exclusion of these drugs did not affect the progression of CKD. This study did not aim to monitor CV events and mortality. On the other hand, a large Swedish national observational study published a year earlier showed that patients with advanced CKD who were excluded from RAAS blockers had a higher absolute risk of death, as well as a higher risk of major CV events but also a lower absolute risk for starting dialysis.

The recent post hoc analyzes of large randomized studies in the population of patients with diabetes have shown a long-term beneficial effect of RAAS blockade on reducing cardio-renal risk, regardless of acute deterioration of kidney function. Likewise, in some studies, it was shown that deterioration of kidney function and reduction of GFR was more frequent and pronounced in patients with heart failure, and it can be suggested that it is primarily due to deterioration of heart function rather than the intracranial effect of these drugs.

Based on previous studies, KDIGO 2021 recommended introducing RAAS blockers as the first line in the therapy of proteinuric CKD patients with and without diabetes mellitus and CKD stage 4, with a note that these drugs should be continued in therapy unless there is pronounced hyperkalemia (potassium > 6 mmol/L), acute renal damage or reduction of estimated GFR > 30%.

### Calcium channel blockers

Although large studies specifically analyzing the antihypertensive effect of dihydropyridine calcium channel blocker (DHP-CCB) in patients with CKD are lacking, these drugs have been used for comparison with RAAS blockers in significant studies. They have proven to be effective antihypertensives not only in all stages of CKD but also in ESRD. DHP-CCB are most often used in combination with ACEi or with ARB, and in cases of contraindications to the administration of drugs that block the RAAS, DHP-CCB are the first line of therapy. Since they are excreted by the liver, the dose of CCB should not be reduced with the progression of CKD. The most common side effects, such as tachycardia and leg swelling, resolve in patients in the general population without chronic renal impairment.

### Beta 2 blockers

Considering the high prevalence of CV diseases in patients with CKD, the use of beta blockers is very common. However, due to the lack of randomized prospective studies that would definitively find a place for beta blockers in the treatment of hypertension in CKD patients, they are currently not recommended as the first line of therapy, except in diastolic patients. Bradycardia as a side effect of beta blocker administration occurs more often in patients with impaired kidney function, so it is important to take care of the dose of the drug. As hydrophilic beta blockers (atenolol, bisoprolol, acebutolol, etc.) are excreted through the kidneys, their dose should be adjusted according to GFR. On the other hand, metoprolol, propranolol, and labetalol are metabolized in the liver and administered in the same doses as patients with normal kidney function.

### Diuretics

Due to the frequent occurrence of hypervolemia in CKD patients with hypertension, diuretics are a necessary integral part of the therapeutic scheme in these patients. However, there are few studies in the literature that analyze their effect on the outcome of the disease. Previously, it was generally accepted that thiazide diuretics were ineffective in the advanced stages of CKD and should be replaced by diuretics of the loop of Henle, but recent studies do not support this view. Both diuretics of the loop of Henle and thiazide diuretics act on the luminal side of the tubule epithelial cells, so with a decrease in nephron mass, their effect also decreases, which requires an increase in the dose of both. Loop diuretics are also given to patients who start extrarenal...
Table 4. Proposal of the introduction of the first, second, third, and fourth line of antihypertensive therapy by Sinha et al.

<table>
<thead>
<tr>
<th>PRESCRIBING ORDER</th>
<th>DRUG CLASS IN CRF</th>
<th>DRUG CLASS IN DIALYSIS</th>
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<tbody>
<tr>
<td>FIRST</td>
<td>ACEi or ARB</td>
<td>Beta blockers</td>
<td>Atenolol is long-acting and effective for hypertension on dialysis</td>
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<tr>
<td>SECOND</td>
<td>DHP-CCB or diuretic</td>
<td>DHP-CCB</td>
<td>DHP-CCB are effective and widely available</td>
</tr>
<tr>
<td>THIRD</td>
<td>Diuretic or DHP CCB</td>
<td>ACEi or ARB</td>
<td>No established role for diuretics in dialysis</td>
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<tr>
<td>FOURTH</td>
<td>MRB</td>
<td>Direct vasodilator</td>
<td>Evidence for MRB for resistant hypertension in the non-CKD population</td>
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</table>

Legend: ACEi - angiotensin-converting enzyme inhibitor; ARB - angiotensin II receptor blocker; DHP-CCB - dihydropyridine calcium channel blocker; MRB - mineralocorticoid receptor blocker

Depuration with chemo or peritoneal dialysis to preserve residual diuresis and better control hypervolemia.

Antagonists of mineralocorticoid receptors, which are a necessary “pillar” in modern protocols for the treatment of heart failure, should be carefully dosed in patients with CKD due to hyperkalemia, and frequent checks of the electrolyte status are necessary. Examination, in randomized studies, of the effects of new and more potent mineralocorticoid receptor antagonists (finerenone) on renal and CV outcome in patients with CKD and diabetes, showed its protective effect with hyperkalemia and a weaker effect on lowering systolic blood pressure (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease, FIDELIO-DKD) study. This drug has not yet entered the official KDIGO guidelines.

It has already been stated above that, apart from the highlighted recommendations on first-line therapy in the treatment of hypertension in patients with chronic kidney damage, there are no clear recommendations for the introduction of other antihypertensive drugs in unregulated hypertension in this patient population. Table 3 shows the expert opinion of Sinha et al. on the introduction of drugs in patients with chronic pre-dialysis renal failure and patients with end-stage renal failure on dialysis in the treatment of hypertension.

Conclusion

The specificity of the treatment of blood pressure in patients with chronic kidney damage is that good control of hypertension leads not only to a reduction in cardiovascular risk but also to a slowing down of the progression of chronic to terminal renal failure. According to KDIGO 2021, guidelines for the treatment of hypertension in patients with chronic kidney damage recommend the introduction of renin-angiotensin-aldosterone system (RAAS) blockers as the first line in the therapy of proteinuric patients with and without diabetes. The introduction of these drugs is recommended in both the early and late stages of chronic kidney disease, with the noted fact that these drugs should be continued in therapy unless there is marked hyperkalemia (potassium > 6 mmol/L), acute kidney injury, or a decrease in estimated GFR by > 30%. The discontinuation of RAAS blockers in advanced stages of chronic kidney disease does not lead to reduced risk and delay of end-stage renal disease and may increase CV morbidity and mortality. According to the new KDIGO guidelines for the treatment of hypertension in patients with chronic kidney disease (2021), it is recommended that the target systolic blood pressure be < 120 mmHg. However, it is necessary to be very careful with old and infirm patients, where such low pressure can lead to an acute exacerbation of chronic kidney damage and cognitive disorders. Unregulated blood pressure with RAAS blockers requires the inclusion of other antihypertensive drugs, such as calcium channel blockers, beta blockers, and diuretics, according to experts. The treatment of hypertension in patients with chronic kidney damage requires, above all, the individualization of therapy due to the often present numerous comorbidities.


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