DOI: https://doi.org/10.17816/KMJ626252

Treatment of arterial hypertension in patients with chronic kidney disease from the perspective of the 2023 European recommendations

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ABSTRACT

Hypertension is a common disease in the adult population with an increasing tendency, it leads to damage to target organs, including the kidneys, with the development of chronic kidney disease, and increases the risk of cardiovascular complications and mortality. The paper provides an overview of the European guidelines for the treatment of arterial hypertension, updated in 2023, approved by the European Kidney Association and the International Society of Hypertension, in the context of chronic kidney disease — in comparison with the previous European guidelines (2018) and the current National clinical guidelines (2021). The updated recommendations retain the main provisions of the strategy for the treatment of arterial hypertension with chronic kidney disease of the 2018 European recommendations. Updates have been made to the classification of the main and additional groups of drugs for the treatment of arterial hypertension. For the first time, a new group of "special drugs for the treatment of concomitant pathology" has been added, including three classes of drugs: (1) neprilysin receptor antagonists, (2) sodium-glucose transporter-2 inhibitors, (3) non-steroidal mineralocorticoid receptor antagonists. A step-by-step algorithm for choosing antihypertensive drugs for arterial hypertension depending on the stage of chronic kidney disease has been updated. Recommendations for the treatment of resistant arterial hypertension were covered in detail. Some new recommendations were included for blood pressure targets based on albuminuria levels and other factors. A slightly modified scale for assessing cardiovascular risk in patients with arterial hypertension was presented and the role of chronic kidney disease stages III–V as an independent factor of high or very high cardiovascular risk was confirmed.

Keywords: arterial hypertension; chronic kidney disease; European Clinical Guidelines 2023; cardiovascular risk; treatment methods; review.

To cite this article:
Sigitova ON. Treatment of arterial hypertension in patients with chronic kidney disease from the perspective of the 2023 European recommendations. *Kazan Medical Journal.* 2024;105(4):607–621. doi: https://doi.org/10.17816/KMJ626252

Received: 30.01.2024 **Accepted:** 27.04.2024 **Published:** 25.07.2024

DOI: https://doi.org/10.17816/KMJ626252
УДК 616.12-008.331.1: 616.61: 61608-035

Лечение артериальной гипертензии у пациентов с хронической болезнью почек с позиции Европейских рекомендаций 2023 г.

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АННОТАЦИЯ

Гипертоническая болезнь — распространённое заболевание взрослого населения с тенденцией к росту, приводит к поражению органов-мишеней, в том числе почек с развитием хронической болезни почек, повышает риск сердечно-сосудистых осложнений и смертности. В работе представлен обзор обновлённых в 2023 г. Европейских рекомендаций по лечению артериальной гипертензии, одобренных Европейской почечной ассоциацией и Международным обществом по артериальной гипертензии, в контексте хронической болезни почек — в сравнении с предыдущими Европейскими рекомендациями (2018) и актуальными Национальными клиническими рекомендациями (2021). В обновлённых рекомендациях сохраняются основные положения стратегии лечения артериальной гипертензии с хронической болезнью почек Европейских рекомендаций 2018 г. Внесены обновления в классификацию основной и дополнительной групп препаратов для лечения артериальной гипертензии. Впервые добавлена новая группа «специальных препаратов для лечения сопутствующей патологии», включающая три класса: (1) антагонисты рецепторов неприлизина, (2) ингибиторы натрий-глюкозного транспортёра-2, (3) нестероидные антагонисты минералокортикоидных рецепторов. Обновлён пошаговый алгоритм выбора антигипертензивных лекарственных препаратов при артериальной гипертензии в зависимости от стадии хронической болезни почек. Подробно освещены рекомендации лечения резистентной артериальной гипертензии. Включены некоторые новые рекомендации по целевому уровню артериального давления в зависимости от уровня альбуминурии и других факторов. Представлена несколько изменённая шкала оценки сердечно-сосудистого риска у пациентов с артериальной гипертензией и подтверждена роль хронической болезни почек III–V стадий как независимого фактора высокого или очень высокого сердечно-сосудистого риска.

Ключевые слова: артериальная гипертензия; хроническая болезнь почек; Европейские клинические рекомендации 2023 г.; сердечно-сосудистый риск; методы лечения; обзор.

Как цитировать:
Сигитова О.Н. Лечение артериальной гипертензии у пациентов с хронической болезнью почек с позиции Европейских рекомендаций 2023 г. // Казанский медицинский журнал. 2024. Т. 105, № 4. С. 607–621. doi: https://doi.org/10.17816/KMJ626252

Рукопись получена: 30.01.2024 **Рукопись одобрена:** 27.04.2024 **Опубликована:** 25.07.2024

Abbreviations

AH, arterial hypertension; BP, blood pressure; MRAs, mineralocorticoid receptor antagonists; BABs, beta adrenoblockers; CCBs, calcium channel blockers; ARBs, angiotensin II receptor blockers; HT, hypertension; DBP, diastolic blood pressure; ESH, European Society of Hypertension; ACEIs, angiotensin-converting enzyme inhibitors; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure; GFR, glomerular filtration rate; CKD, chronic kidney disease.

INTRODUCTION

Essential arterial hypertension (AH) or hypertension (HT) is one of the most common diseases affecting adults worldwide. Uncontrolled HT leads to target organ damage, including renal damage, which increases the risk of cardiovascular complications and cardiovascular mortality [1, 2]. Nephrosclerosis can develop in the kidneys, leading to chronic kidney disease (CKD), which often progresses to end-stage renal disease (ESRD). The risk of cardiovascular complications increases as the kidney function declines. For patients with stage III CKD or higher, the risk of progression to ESRD is ten times higher [2–4].

Due to the urgency of the issue of inadequate efficacy of AH treatments, numerous clinical trials have been conducted. Furthermore, cardiology societies and AH associations regularly publish updated clinical recommendations [5–8]. The latest clinical guidelines of the European Society of Hypertension (ESH) that were endorsed by the European Renal Association (ERA) and International Society of Hypertension (ISH) were presented at the congress in Milan in June, 2023 [5].

Herein, we have presented a review of the recommendations of the ESH-2023 in the context of CKD, recent Russian and foreign publications, and clinical trials on the treatment of AH with CKD. Furthermore, we have compared these recommendation with those of the 2018 European Recommendations and the 2021 National Clinical Recommendations that have been approved by the Ministry of Health of the Russian Federation. This review does not include recommendations on the treatment of symptomatic AH with CKD in patients with a primary kidney disease, which are outlined in the relevant publications [6].

Elevated systolic blood pressure (SBP) has the greatest negative impact on the development of cardiovascular complications and CKD. The risk of mortality and disability of patients increases by 70% when SBP ⩾ BP mmHg [9, 10].

Albuminuria in patients with AH with CKD is an independent risk factor for cardiovascular complications and mortality. However, CKD may occur in patients with AH without albuminuria. The PREVEND study demonstrated that the risk of cardiovascular complications in patients with CKD without albuminuria is the same as that in patients with albuminuria. Furthermore, the risk of cardiovascular complications increases with a decrease in glomerular filtration rate (GFR) to <40 mL/min/1.73 m^2 [11].

The frequency of essential AH is not declining. Recent epidemiological data indicates that its frequency is >40% in women, approximately 47% in men, and >60% in individuals over the age of 60 years [12]. Furthermore, the prevalence of AH is higher (67%–71%) in patients with CKD than in those without CKD. In older adults, the prevalence of AH reaches up to 82%, while in patients with late stages of CKD, the prevalence is 90%–95% [13, 14].

The proportion of patients with CKD whose blood pressure (BP) can be controlled remains low. Adequate BP control is achieved in only 30%–50% of the patients in European countries and in 24% of the patients in Russia [9]. In a presentation at the 30th Russian National Congress of Cardiologists in Moscow on September 20, 2023, Professor S.T. Matskeplishivili reported that up to 50% of patients exhibit low adherence to treatment, 53.5% have uncontrolled AH, and 27%–40% do not comply with the doctor's antihypertensive therapy recommendations. In the ESSE-RF3 study (2020–2022), only 27.9% of the patients demonstrated adequate AH control. Thus, the issue of AH control in Russia remains unresolved in the 21st century [8].

Given the high prevalence of CKD in patients with uncontrolled AH, patients with HT are at significant risk of developing CKD. In patients with AH and diabetes mellitus, the prevalence of CKD, as determined by the CHRONOGRAPH study using early markers of CKD (GFR < 60 mL/min/1.73 m^2 or urine albumin/creatinine ratio >30 mg/g), is 49.4%. The prevalence of CKD was 34.8% when the criterion was GFR < 60 mL/min/1.73 m^2, 32.6% when the criterion was albuminuria >30 mg/g, and 18% when both criteria were applied concurrently [2]. The study conducted by Kulakov et al. (2016) yielded comparable outcomes. The prevalence of CKD in patients with AH was 31% when criterion was GFR < 60 mL/min/1.73 m^2 and 30.5% when the criterion was high or very high albuminuria. Furthermore, the prevalence was 45% when at least one marker of CKD was considered. Finally, the authors hypothesized that the actual prevalence of CKD in adults with AH in the outpatient setting is 45% [3].

The results of another study indicate that the prevalence of CKD in outpatient working patients with stage II–III AH, using early markers of CKD, is 18.7% [4]. These findings align with those of the NHANES (National Health and Nutrition Examination Survey) registry, which indicates that approximately 20% of patients with AH have chronic renal failure [15, 16]. This likely reflects the comparable number of observed outpatients.

The presence of risk factors for CKD in patients with AH, such as an AH duration of >10.5 years, triglyceride levels >1.98 mmol/L, high-density lipoprotein cholesterol levels <0.73 mmol/L, and current smoking status, enables the stratification of these patients according to the risk of developing CKD [12]. In another study, the risk factors for the development of

CKD were a HT duration of ⩾ 11.3±1.3 years, early onset of HT (before the age of 40.5 years), increase in serum low-density lipoprotein level above the normal, SBP > 140 mmHg, body mass index > 29.5, and a smoking index of ⩾ 22.7 [4].

TREATMENT OF ARTERIAL HYPERTENSION IN PATIENTS WITH CHRONIC KIDNEY DISEASE

Non-medication methods of treatment of AH with CKD remain inviolable and entails the correction of all modifiable risk factors. The non-medication methods include salt restriction to <5 g/day, maintenance of physical activity, cessation of smoking, reduction of body weight, and correction of dyslipidemia and hyperglycemia [9, 17].

The ESH-2023 recommendations for the treatment of AH comprise a group of basic drugs (five classes), as seen in the previous European and current National Clinical Recommendations (2021). Additionally, the updated recommendations include a group of additional or reserve drugs (five classes), representing an increase from three to five. For the first time, the recommendations feature a group of drugs belonging to a distinct class for treating concomitant pathologies (three classes) [5].

The primary hypotensive drugs encompass the following five distinct classes: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), β-adrenoblockers (BABs), calcium channel blockers (CCBs), and diuretics. The revisions to the ESH-2023 guidelines impacted the type of diuretics to be used for the management of AH. The updated recommendations now include only thiazide drugs (hydrochlorothiazide) and thiazide-like drugs (chlorthalidone and indapamide). Loop diuretics (furosemide, torsemide, bumetanide, and etacrynic acid) have been reclassified as additional drugs [5, 18, 19].

According to numerous studies, renin-angiotensin system blockers are the drug of choice in patients with AH and CKD. They reduce the BP as well as proteinuria, which slows the progression of CKD and lowers the cardiovascular risk. They are the first drug of choice in several studies [20, 21] and patients with a pre-exiting high cardiovascular risk [22]. ACEIs and ARBs reduce intraventricular pressure and albuminuria with greater efficacy than other antihypertensive drugs. Consequently, they are indicated as a primary component of a nephroprotective strategy and are considered the preferred treatment option for AH in patients with CKD [9, 17].

ACEIs and ARBs are recommended for use in stages III–V of CKD, irrespective of the presence of AH, to reduce proteinuria and/or the risk of cardiovascular events and all-cause mortality. Some patients with stage II–III AH and target organ damage or associated diseases (e.g., postinfarction cardiosclerosis, chronic heart failure, and acute or chronic cerebral circulatory failure) may have normal BP levels [23, 24]. Furthermore, ACEIs and ARBs are the *drug of choice in any patients with pre-dialysis CKD*. Although the nephroprotective effect of ACEIs and ARBs in late stages of CKD (IV–V) is reduced or absent, the cardioprotective effect is preserved. Therefore, they are also recommended in stages IV–V of CKD [25]. This is particularly important because drugs of this group are not used sufficiently in real clinical practice. One study demonstrated that ACEIs are the fourth option for the treatment of patients with AH and CKD, while ARBs are the fifth option after BBs, calcium antagonists, thiazide, and thiazide-like diuretics [26]. Moreover, the frequency of their prescription significantly decreased in patients with CKD stages IV and V. The scientific medical literature contain recommendations of withdrawal of ACEIs and ARBs at stages IV–V of CKD that are not supported by evidence [27].

The latest iteration of the ESH-23 clinical guidelines has expanded the role of BABs, allowing for their prescription in both combination therapy and monotherapy for AH. However, in patients with CKD, they are not employed as monotherapy due to the absence of a nephroprotective effect and an impact on albuminuria. Its administration is only feasible in conjunction with other drugs from the primary category to augment BP reduction and cardioprotection, particularly when the efficacy of ACEIs or ARBs is inadequate or contraindicated.

The indications for the administration of BABs include, but are not limited to, the following conditions: angina pectoris, myocardial infarction, chronic heart failure with low ejection fraction, atrial fibrillation, aortic aneurysm, tachycardia, and AH in women of childbearing age. It is recommended that highly selective drugs with a long half-life, such as metoprolol, bisoprolol, and nebivolol, be given preference [28]. These can be used with caution in patients with severe CKD (creatinine clearance <20 mL/min). In patients with AH and CKD, carvedilol (BAB) may be used. In addition to its main property of blockade of α-adrenergic receptors, it improves renal function by increasing renal parenchymal perfusion [29].

The position of *CCBs* has not changed in the updated ESH-2023 clinical guidelines. Dihydropyridine CCBs are widely used as second-line therapy for AH in patients with CKD after renin-angiotensin-aldosterone system (RAAS) blockers. Although they effectively lower blood pressure, they do not have nephroprotective properties [30].

Thiazide and thiazide-like diuretics are other classes of drugs used for the treatment of AH, and they are recommended in stages I–III of CKD. In patients with stage IV CKD, these agents are typically substituted with loop diuretics because increasing the dosage of thiazide and thiazide-like diuretics does not enhance their natriuretic effect and may even precipitate adverse effects. Diuretics in general and thiazides in particular are associated with an increased risk of hyperuricemia. However, only gout is considered an absolute contraindication to the administration of hydrochlorothiazide. In patients with diabetes mellitus, the drug can be administered in a daily dose not exceeding 25 mg [1, 31].

Additional drugs, or reserve drugs, are prescribed in combination with ACEIs, ARBs, CCBs and/or diuretics as

a fourth drug for the treatment of resistant AH in patients in whom the classical combinations do not exhibit sufficient efficacy [32–34]. In addition to steroidal antagonists of mineralocorticoid receptors [35] such as α_1-adrenoblockers and imidazoline receptor agonists (moxonidine), loop diuretics and vasodilators have been included for the first time in ESH-2023 as an additional class of antihypertensive drugs.

Mineralocorticoid receptor antagonists (MRAs) are steroids that are used for the treatment of patients with AH without diabetes mellitus. Currently, the MRAs used in the Russian Federation are spironolactone and eplerenone. The diuretic effect of MRAs develops slowly, after 2–5 days, and is weakly expressed, with a decrease in sodium reabsorption of no more than 3%. Furthermore, the hypotensive effect does not depend on the plasma renin level and is not manifested in patients with normal BP. Eplerenone differs from spironolactone in its relative selectivity for mineralocorticoid receptors, better tolerance, and fewer side effects [36].

Randomized clinical trials of AH treatment with MRAs with robust endpoints have not been conducted. Nevertheless, since 2013, European guidelines have suggested prescribing MRAs as the third or fourth drug to overcome resistance to antihypertensive therapy. The ESH-2023 reiterated the risk of hyperkalemia when prescribing spironolactone, especially when the calculated GFR is <45 mL/min/1.73 m^2 and the potassium level is 4.5 mmol/L [5]. Similar conclusions were drawn from the secondary analysis of the ASCOT trial [37].

In most studies, MRAs have been used as part of a combination therapy. Treatment with MRAs reduce target organ damage, mainly via the blockade of aldosterone effects such as increased arterial stiffness and oxidative stress. Long-term (3 and 6 months) treatment with spironolactone in patients with resistant AH has been associated with a reduction in the severity of left ventricular hypertrophy [35].

In a 9-month long, double-blinded, randomized study of patients with left ventricular hypertrophy, eplerenone and enalapril were equally effective in producing left ventricular hypertrophy regression and lowering BP. Furthermore, their combined administration resulted in a greater regression of both parameters than isolated administration did [38].

MRAs are contraindicated when the estimated GFR is <30 mL/min or when the blood potassium levels are >5 mmol/L and the blood creatinine levels are >2 mg/dL (177 mmol/L) or >1.8 mg/dL (159 mmol/L) in men or women, respectively. The concomitant use of eplerenone with ACEIs and ARBs increases the plasma potassium levels and should be avoided in patients with an estimated GFR of <45 mL/min [39]. Serum potassium levels should be monitored not only at the start of treatment but also when the dose is altered. Episodic monitoring of potassium levels during MRA administration is also required. Patients with 30–60 mL/min of GFR should be started on a half dose of MRA every other day.

Alpha 1-adrenergic receptor blockers (e.g., prazosin, terazosin, doxazosin, alfuzosin, and tamsulosin) exert hypotensive and hypolipidemic effects and positively influence carbohydrate metabolism, as evidenced by a reduction in blood glucose concentration and insulin resistance. Additionally, these agents facilitate urination, reduce albuminuria, contribute to the regression of hyperplastic processes in the prostate gland, and alleviate left ventricular hypertrophy. They can be administered to patients with AH and concomitant obesity, diabetes mellitus, and benign prostatic hyperplasia [40].

The available evidence on the use of α-adrenoblockers in CKD is limited. Data from a Canadian population-based retrospective cohort study indicated that α-adrenoblockers (prazosin, terazosin, and doxazosin) are associated with an increased risk of renal disease progression. However, they are associated with a reduced risk of cardiac events and mortality when compared with other hypotensive drugs [41]. In patients with stage IIIb–V CKD and older adults who are prescribed α-adrenoblockers, it is essential to exclude episodes of arterial hypotension. However, reducing the dose is not necessary, as its pharmacokinetics remain unaltered with decreased renal function [27].

Imidazoline receptor agonists: The centrally acting adrenergic drug moxonidine, unlike other agonists (methyldopa and clonidine), is the drug of choice due to the absence or lesser severity of their side effects. In addition to its antihypertensive effect, moxonidine reduces the level of insulin resistance, glucose, and triglycerides in blood plasma, as well as the renal sodium reabsorption and body weight [42]. Moxonidine reduces the creatinine clearance in patients with baseline hyperfiltration, and it is well tolerated with only a few drug interactions. Moxonidine also reduces albuminuria and may slow the development of CKD in patients with AH [43, 44] or type 2 diabetes mellitus [45]. Moxonidine is indicated in patients with obesity and AH that is poorly controlled with standard therapy, as well as in patients with a metabolic syndrome [46].

Loop diuretics are the drugs of choice in stages IV–V of CKD. In advanced CKD (GFR < 20–30 mL/min/1.73 m^2), torsemide is preferred for the treatment of AH due to its higher and more stable bioavailability. Furthermore, it is administered once daily in compared to furosemide, which is administered 2–3 times daily [47].

Direct vasodilators for the treatment of AH include hydralazine, minoxidil, diazoxide, and sodium nitroprusside. The first three drugs only dilate small arteries (arterioles). Sodium nitroprusside dilates arterioles as well as veins. Direct vasodilators decrease the BP by decreasing the peripheral vascular resistance. The side effects of these drugs include fluid retention and palpitations [48].

Hydralazine is often used in combination with a diuretic and BAB for the treatment of severe AH. It is administered two times a day. *Minoxidil* is a more potent drug that is prescribed once daily for resistant AH in patients with CKD. To reduce the risk of side effects, these drugs should preferably be administered with diuretics and BABs to prevent sympathetic activation and reduce renin formation. *Sodium nitroprusside* has an immediate and short-lasting effect. Thus, it is used only intravenously to treat patients in hypertensive crisis.

The group of specific drugs used for the treatment of comorbidities in patients with AH and CKD include neprilysin receptor antagonists, sodium-glucose cotransporter-2 inhibitors, and non-steroidal MRAs.

Neprilysin receptor antagonists are used to treat chronic heart failure in patients with AH. The registered drug combination of valsartan and sacubitril (Juperio) is used for this purpose. However, this drug is contraindicated in patients with renal dysfunction.

Sodium-glucose cotransporter-2 inhibitors was recommended by the Kidney Disease: Improving Global Outcomes program in 2020 as the first-line therapy, in addition to metformin, for the treatment of type 2 diabetes mellitus in patients with CKD and a GFR of >30 mL/min/1.73 m^2. The main nephroprotective mechanism of sodium-glucose cotransporter 2 inhibitors is an increase in natriuresis, resulting in a decrease in intraglomerular pressure and hyperfiltration. The other nephroprotective mechanisms include reduction of albuminuria, inflammation, and oxidative stress as well as improvement of endothelial function [49, 50].

In August 2021, the sodium-glucose cotransporter-2 inhibitor dapagliflozin was approved for use in combination with an ACEI or ARB at its maximum tolerated dose for the treatment of patients with CKD regardless of the presence or absence of diabetes. Dapagliflozin reduces the risk of renal mortality and progression to ESRD [51, 52].

Non-steroidal MRAs: For the treatment of AH with CKD in patients with type 2 diabetes mellitus, the novel MRA finerenone has been approved in the European Union and has been included in the ESH-2023. Unlike spironolactone or eplerenone, finerenone is a non-steroidal MRA, and its administration is associated with a lower risk of hyperkalemia and cardiovascular mortality [53]. Finerenone is indicated for the treatment of stages I–IV of CKD with moderate to severe albuminuria (30–5000 mg/g) in adult patients with diabetes mellitus in combination with standard or maximum tolerated doses of ACEIs or ARBs [54].

The general recommendations for the treatment of AH in patients with CKD include avoidance of nephrotoxic drugs and adjustment of the doses of drugs that are eliminated by the kidney on the basis of renal function, until their withdrawal to prevent side effects. Thus, verospirone, eplerenone, thiazides, and thiazide-like diuretics are discontinued in patients with CKD stage IV or higher because their efficacy decreases at a GFR of <45 mL/min/1.73 m^2 and is absent at a GFR of <30 mL/min/1.73 m^2. ACEIs and ARBs are administered while controlling the GFR and serum potassium levels due to the risk of hyperkalemia.

The target BP in patients with CKD in the updated clinical guidelines remains changed. The target BP has been previously defined with the aim of reducing the risk of ERSD and cardiovascular complications, and it follows the pattern of a U-shaped curve.

ESH-2023 discusses different target BPs according to age in patients with cardiovascular diseases (e.g., coronary heart disease, HT without CKD, stroke, and thromboembolic attack). Only in patients with HT and CKD, the target SBP is independent of age and uniform across all age groups. In such patients the targets are SBP < 130 mmHg and diastolic BP (DBP) within 70–79 mmHg if tolerated. Because SBP reportedly exhibits a greater negative impact on target organ damage than DBP, ESH-23 recommends a target SBP of 130–139 mmHg and <130 mmHg, if well tolerated, in all patients of all ages (18–69 years and ⩾70 years) regardless of cardiac risk level and the presence of cardiovascular disease [5, 55–58].

The target BP in patients with CKD of any stage is contingent upon the degree of albuminuria. In patients with albuminuria of <300 mg/day, the target SBP id 130–139 mmHg [6]. In patients with albuminuria of ⩾300 mg/day, the target SBP is 120–130 mmHg, and the target DBP is ⩽80 mmHg in the absence of any contraindications. However, the ESH-2023 guidelines emphasize that it is not necessary to aim for a reduction of SBP to <120 mmHg and that of DBP to <70 mm Hg. In one study [58], maintaining the BP at 125/75 mm Hg for >14 years reduced the risk of ESRD development in patients with proteinuria, justifying the lower BP targets in patients with AH and CKD [58, 59].

The American College of Cardiology/American Heart Association guidelines, based on the results of the Systolic Blood Pressure Intervention study, adopted the a target SBP of <120 mmHg and target DBP of <80 mmHg in adult patients with AH and pre-dialysis CKD [60]. This target BP has been demonstrated to reduce the risk of cardiovascular complications by 25% and total mortality by 27%. Additionally, the risk of stroke and heart, kidney, and eye diseases is reduced. However, such a decrease in SBP is dangerous in patients with low calculated GFR and pre-exiting low DBP, significant carotid artery stenosis, postural arterial hypotension, and coronary artery disease [60]. In patients with an initially high pulse pressure, it should be monitored during treatment because it is an independent risk factor for cardiovascular events and mortality.

The treatment strategy for patients with AH and CKD in the ESH-2023 guidelines (Appendix 1) has not significantly changed when compared with the 2018 ESH guidelines and the current National Clinical Guidelines-2021. In most patients with AH and CKD, a target office (clinical) SBP of <140 mmHg and DBP of <90 mmHg are recommended. However, in several patients (young, with an albumin/creatinine ratio of >300 mg/g, and with high cardiovascular risk), the recommended target office BP is <130/80 mmHg if well tolerated. The same target BP is recommended for patients after renal transplantation. Furthermore, the need for BP control by daytime or home monitoring, as well as nocturnal BP control, which is often increased in patients with CKD, has been emphasized [5].

STEP-BY-STEP PRESCRIPTION OF ANTIHYPERTENSIVE THERAPY

The ESH-2023 clinical guidelines continue to recommend a combination of antihypertensive drugs. At the start of

therapy in patients with AH and CKD, (RAAS) inhibitors such as ACEIs or ARBs are generally prescribed with dihydropyridine CCBs or diuretics. The methodology employed in the step-by-step treatment of patients with AH and CKD has remained consistent. However, the selection of drugs at the outset of therapy may differ for patients with CKD stages I–III and those with CKD stages IV–V. The main difference lies in the use of distinct diuretic agents. In patients with CKD stages I–III, thiazide (hydrochlorothiazide) or thiazide-like (indapamide) diuretics are recommended. However, in patients with CKD stage IV–Vs, loop diuretics such as furosemide, torsemide, bumetanide, and etacrynic acid are indicated because of the diminished therapeutic effect of thiazide and thiazide-like diuretics in advanced CKD (see Appendix 2).

Step-by-step therapy involves the use of higher doses of drugs and a combination of drugs at each step to achieve renal protection. This is done because the antiproteinuric effect of RAAS blockers is dose-dependent. RAAS blocker administration should be monitored in the following situations: serum potassium > 5.0 mmol/L, serum creatinine > 221 μmol/L, estimated GFR < 30 mL/min/1.73 m^2, and SBP < 90 mm Hg. The dose can be doubled only after 2 weeks. Serum creatinine and potassium levels should be monitored 1–2 weeks after starting therapy, 1–2 weeks after the last dose increase, and thereafter, every 4 months. Achievement of target BP is recommended within 3 months with a dose titration interval of approximately 2–4 weeks.

In stages IV–V of CKD, treatment with RAAS blockers should be started at minimal doses under the control of GFR and serum potassium levels. RAAS inhibitors decrease the GFR and increase the creatinine level due to a hemodynamic effect. Nevertheless, if the elevated creatinine concentration returns to the baseline value within two weeks or its increase does not exceed 50% of the baseline, the calculated GFR decreases to 25 mL/min/1.73 m^2, and the potassium level does not exceed 5.5 mmol/L, the therapy need not be adjusted. If the creatinine level increases from 50% to 100% of the baseline level, the RAAS blocker dose should be reduced by a factor of 2. If the potassium level exceeds 5.5 mmol/L, the creatinine level is more than 100% of the baseline or >310 μmol/L, and the GFR is <20 mL/min/1.73 m^2, the drugs should be discontinued, and the patient should be referred to a nephrologist [61].

If the urea, creatinine, or potassium levels are elevated, withdrawal of the nephrotoxic potassium-containing and potassium-sparing drugs should be considered. However, if there is no evidence of congestion, the diuretic dose should be reduced.

If the target BP is not achieved with a dual combination therapy, a triple combination of a RAAS blocker, calcium antagonist, and diuretic is recommended. The following combinations are usually considered: ACEI + dihydropyridine CCB + BAB, ARB + dihydropyridine CCB + BAB, ACEI + CCB + diuretic, ARB + CCB + diuretic, ACEI + diuretic + BAB, ARB + diuretic + BAB, and dihydropyridine CCB + diuretic + BAB. In patients with resistant AH, the combination of a RAAS blocker, CCB, and diuretic at their full doses is considered the most effective.

Diuretics may cause hypokalemia. Therefore, the plasma potassium levels should be controlled during the first 10–14 days of therapy. Thus, potassium-sparing agents are indicated, possibly in combination with thiazides [9, 25].

When the BP is not controlled with triple therapy (in 15%–20% of the patients), the patients is considered to have resistant AH. Its prevalence is higher patients with CKD than in those without CKD, reaching 22.9%. In patients with resistant AH, a combination of four or more antihypertensive drugs is used. A four-component regimen is initiated if a triple combination therapy at maximum doses and with good tolerance does not produce any effect.

For resistant AH in patients with CKD stages I–III, the following drugs are recommended (in order of priority): (a) spironolactone or other MRA, (b) BAB or α1-blocker, or (c) centrally acting drug. Finally, renal denervation can be considered if the GFR is >40 mL/min/1.73 m^2.

For patient with stages IV–V of CKD (non-dialysis), the following drugs are recommended (in order of priority): (a) chlorthalidone (preferably) or another thiazide/thiazide-like diuretic, (b) BAB or α_1-adrenergic blocking agent, or (c) a centrally acting agent [9, 62, 63]. The combination of two RAAS blockers is still not recommended because of the increased risk of hyperkalemia, arterial hypotension, and worsening of renal function [64–66].

ADDITIONAL RECOMMENDATIONS

Renal artery denervation for the routine treatment of patients with resistant AH has not been included in the ESH-2018 guidelines and National Clinical Guidelines-2021. Moreover, further accumulation of data on its efficacy and safety is required. The efficacy of renal denervation to sufficiently lower BP remains controversial. In most studies, the reduction in SBP is insignificant (3%–5%). However, some individual studies have demonstrated that renal denervation is effective and safe in patients with resistant AH. In the Symplicity HTN-1 study, an SBP of <140 mmHg and <160 mmHg was achieved in 39% and 82% of the patients, respectively, after renal denervation [67]. Furthermore, complications rarely developed, and impairment of renal nitrogen excretion was not observed.

The updated guidelines recommend discussing the use of renal denervation in patients with resistant and uncontrolled essential hypertension (SBP > 160 mmHg or > 150 mmHg in patients with diabetes mellitus) despite triple therapy [5, 68]. More emphasis is being placed on prescribing polypills to improve adherence. Furthermore, the TIME trial did not prove the benefit of a chronotherapeutic approach (morning or evening dosing) in patients with AH. Thus, the choice of drug and time of administration should be based on the drug efficacy and the best adherence to treatment, which is slightly higher with a single morning dose. Furthermore, drugs with a stable effect over 24 h should be favored [69].

DOI: https://doi.org/10.17816/KMJ626252

Cardiovascular risk assessment in patients with AH with and without CKD in the ESH-2023 clinical guidelines: CKD in patients with AH can be a moderate, high, or very high risk factor of cardiovascular complications according to the degree of AH (Appendix 3). Stage III CKD corresponds to stage I HT. CKD stages IV–V correspond to stage III HT and is a very high risk factor for cardiovascular complications. In the updated recommendations, only the position of diabetes mellitus has changed when compared to the National Clinical Guidelines-2021. Diabetes mellitus, regardless of the presence or absence of target organ damage, corresponds to stage II HT, and the level of risk depends on the level of AH [5].

CONCLUSIONS

Essential AH is a prevalent disease among the adult population, with an inclination to worsen over time. It results in damage to target organs, including the kidneys, which can lead to the development of CKD. Additionally, essential AH increases the risk of developing cardiovascular complications and mortality.

In the recently updated ESH recommendations, which were approved by both the ERA and ISH, several changes have been noted. In the main category of antihypertensive drugs, only thiazide and thiazide-like diuretics have been retained. Loop diuretics have been reclassified as additional or reserve drugs. The number of drug classes in the additional group has increased from three to five due to the inclusion of loop diuretics and vasodilators.

For the first time, a dedicated group of drugs for the treatment of comorbidities has been included in the guidelines. This group includes three classes of drugs. Two of these drugs are used in the treatment of patients with CKD. They are dapagliflozin, a sodium-glucose transporter-2 inhibitor with a direct nephroprotective effect, and finerenone, a non-steroidal MRA for the treatment of AH with CKD in patients with diabetes mellitus.

In both the ESH-2023 and National Guidelines-2021, the combined prescription of RAAS blockers (ACEIs or ARBs) with CCBs or diuretics has been recommended for AH of any CKD stage at the start of treatment. The step-by-step therapy for AH in patients with CKD, the dosing recommendations that is contingent on the stage of CKD (I–III or IV–V), and the rational and non-recommended combinations of drugs is presented in Appendix 2. The guidelines for the treatment of resistant AH have been updated to include indications for renal denervation. Additionally, a new group of patients with a target BP of <130/70 mm Hg, dependent on the albuminuria level and other factors, has been incorporated into the treatment strategies for AH with CKD. Furthermore, polypills should be preferentially used to enhance patient adherence to therapy. Finally, in the cardiovascular risk assessment scale for patients with AH, the importance of diabetes mellitus has reduced, and CKD stages III–V are confirmed to be high/very high risk factors for cardiovascular complications.

ADDITIONAL INFORMATION

Appendix 1. https://doi.org/10.17816/KMJ626252-4212927.
Appendix 2. https://doi.org/10.17816/KMJ626252-4212928.
Appendix 3. https://doi.org/10.17816/KMJ626252-4212929.
Funding source. The study had no sponsorship.
Competing interests. The author declares that there is no conflict of interest in the presented article.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Приложение 1. https://doi.org/10.17816/KMJ626252-4210020.
Приложение 2. https://doi.org/10.17816/KMJ626252-4210021.
Приложение 3. https://doi.org/10.17816/KMJ626252-4210022.
Источник финансирования. Исследование не имело спонсорской поддержки.
Конфликт интересов. Автор заявляет об отсутствии конфликта интересов по представленной статье.

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