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ANTIHYPERTENSIVE AGENTS: MECHANISMS OF DRUG ACTION (ME ERNST, SECTION EDITOR)

Treatment of Hypertension in Chronic Kidney Disease

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Abstract

Purpose of Review Chronic kidney disease (CKD) is recognized as a worldwide epidemic. Hypertension commonly coexists with CKD and its prevalence is progressively increasing as kidney function declines.

Recent Findings For patients with established CKD and/or diabetes with albuminuria, the updated hypertension guidelines have recommended a blood pressure (BP) goal < 130/80 mmHg. Blood pressure level above 130/80 mmHg in CKD patients requires lifestyle modifications and multiple antihypertensive medications. According to recent guidelines, angiotensin-converting enzyme (ACE) inhibitors should be the drugs of first choice. Angiotensin II receptor blockers (ARBs) should be used if the ACE inhibitor is not tolerated. Non-dihydropyridine CCBs consistently reduce albuminuria and slow the decline in kidney function. Dihydropyridine CCBs should not be used as monotherapy in proteinuric CKD patients but always in combination with a RAAS blocker. Diuretics are commonly used and represent the cornerstone in the management of CKD patients. All the other agents are used when treatment with the other primary agents have failed.

Summary In patients with CKD, an intensive BP goal < 130/80 mmHg has been recommended. We review current treatment options.

Keywords Chronic kidney disease · Hypertension · Albuminuria · Antihypertensive therapy · RAAS blockers · ACE inhibitors

Introduction

Hypertension and chronic kidney disease (CKD) are two leading risk factors for cardiovascular (CV) disease. In the United States (U.S.), hypertension affects 80 million people [1] while the overall prevalence of CKD in the adult population was 14.8% in 2011–2014 [2]. Furthermore, in people older than 65 years, the annual incidence of CKD is more than 1200 individuals per million [3]. Thus, CKD was recognized as a worldwide epidemic. Since individuals with kidney failure treated by hemodialysis or peritoneal dialysis and transplantation continue to increase, it seems that by the year 2030, CKD patients with end-stage renal disease (ESRD) requiring dialysis should be more than 2.2 million [4].

Hypertension coexists in approximately 80–85% with CKD. In hypertensive patients about 15.8% have CKD [5]. On the other hand, in the Chronic Renal Insufficiency Cohort (CRIC) study, hypertension has been reported in 67 to 92% of patients [6]. Additionally, hypertension prevalence is progressively increasing as kidney function declines [7].

The coexistence of hypertension and CKD results in increased difficulties to control BP levels. In the U.S., about 52% of Americans adults had their BP levels controlled in 2011–2014 [1]. In CKD patients, hypertension control is suboptimal and control rates are very low (13.2%) [8]. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study resistant, hypertension was noticed in 28.1% of adults with concomitant hypertension and CKD [9]. These proportions increased with advancing stage of kidney disease and elevated systolic BP mainly accounted for the inadequate control [8]. However, the proportion of CKD individuals who were aware, treated, and disease-controlled rose steadily from approximately 8% in the early cohorts 1999–2002, to 28% in 2011–2014 [2].

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Although kidney disease is characterized by progressive scarring that ultimately affects all structures of the kidney regardless of the underlying cause, however, the presence of hypertension may accelerate further kidney injury; therefore, hypertension treatment is important for the prevention of further kidney damage in an apparent vicious circle that leads to a functional decline [7, 10]. In CKD patients, the level of BP may predict the development of ESRD. In the Kidney Early Evaluation Program (KEEP), database included 88,559 participants, baseline systolic BP independently was associated with the presence of kidney disease [11]. In the Multiple Risk Factor Intervention Trial (MRFIT), in more than 330,000 middle-aged men who participated in the over a 16-year period study, a strong, graded relation between both systolic and diastolic BP and ESRD was identified [12].Therefore, BP control in CKD patients has become one of the greatest challenges to improve kidney functional decline and consequently patients survival.

Blood Pressure Target in CKD Patients

The newly updated hypertension guidelines developed by the American Heart Association (AHA) and the American College of Cardiology [13] support an intensive BP control in patients with established CKD and the threshold for high BP has lowered to 130/80 mmHg. The guidelines suggest that antihypertensive treatment should be based on overall Atherosclerotic Cardiovascular Disease (ASCVD) risk assessment combined with BP levels [13]. The consensus report further supports a systolic BP goal between 125 and 130 mmHg for those who can tolerate this level [7, 13]. This strategy may prevent more CVD events compared with the treatment based on BP levels alone. The intensive BP goals are not in agreement with the former guidelines in the past, which recommended a BP goal < 140/80 mmHg for patients with CKD and/or diabetes, including those from the Eighth Report of the Joint National Committee (JNC-8) and the European Society of Hypertension–European Society of Cardiology committee, as well as the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Working Group on CKD [7, 14, 15]. The ADA recommendations suggest that in diabetic individuals at high risk of CV disease, a lower systolic and diastolic BP target (< 130/80 mmHg) may be appropriate, if it can be achieved without burden undue treatment [16••]. Intensification of antihypertensive therapy to target BP lower than < 130/80 mmHg may be beneficial for selected patients with diabetes such as those with a high risk of CV disease (Table 1) [16••].

This is best exemplified In The Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial were intensive BP control among people with type 2 diabetes to a target systolic BP < 120 mmHg did reduce the risk of stroke, at the expense of increased adverse events and may be reasonable in selected patients who have been educated about added treatment burden [17].

These data are also supported by The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation–Blood Pressure (ADVANCE BP) trial, where the active BP intervention arm, a fixed-dose combination of

Table 1 Major recommendations of treatment guidelines related to management of hypertension in patients with CKD and albuminuria

	2017 ACC/AHA [13]	2013 ESH/ESC [14]	2018 ADA [16••]	2012 NKF KDOQI [3, 7]
Type of CKD considered	Albuminuria ≥ 300 mg/d or ≥ 300 mg/g creatinine	Overt proteinuria	Urinary albumin-to-creatinine ratio ≥ 300 mg/g creatinine or 30–299 mg/g creatinine	Urine albumin excretion of 30 to 300 mg or > 300 mg per 24 h
Recommended BP target (mm Hg)	Lowering < 130/80	Lowering SBP to < 140 Lowering < 130/80 mmHg in individuals with overt proteinuria	Lowering < 140/90 Lowering < 130/80 mmHg, for individuals at high risk of cardiovascular disease	Lowering ≤ 130/80
Recommended initial antihypertensive treatment	ACE inhibitor or ARB if ACE inhibitor is not tolerated	ACE inhibitor or ARB	ACE inhibitor or ARB If one class is not tolerated, the other should be substituted	ACE inhibitor or ARB
Other comments	A 10 to 25% increase in serum creatinine may occur in some patients with CKD as a result of RAAS therapy	RAS blockade is more effective in reducing albuminuria than other antihypertensive agents and is also effective in preventing incident microalbuminuria	Patients and clinicians should engage in a shared decision-making process to determine individual BP targets Bedtime dosing: moving at least one antihypertensive medication to bedtime.	The antihypertensive and antialbuminuric effects ACE inhibitor or ARB are complemented by dietary sodium restriction or administration of diuretics.

ACC/AHA American College of Cardiology/American Heart Association; ACE inhibitors, angiotensin-converting enzyme inhibitors; *ADA*, American Diabetes Association; *ARBs*, angiotensin II receptor blockers; *CKD*, chronic kidney disease; *ESH/ESC*, European Society of Hypertension/European Society of Cardiology; *RAS*, renin angiotensin system; *NKF*, National Kidney Foundation

perindopril and indapamide, was compared with the placebo group [18]. Lower systolic BP levels during follow-up, even to < 110 mmHg, was associated with progressively lower rates of renal events without any BP threshold below which renal benefit was lost [19].

In non-diabetic patients, the available evidence was inconclusive for the CKD group as a whole because the existed appropriately randomized trials, including The Modification of Diet in Renal Disease (MDRD) trial [20], the African American Study of Kidney Disease [21], and the renoprotection in patients with non-diabetic chronic renal disease (REIN 2) study, failed to show any benefit with BP reduction < 130/80 mmHg. The MDRD trial examined whether two levels of BP (mean arterial pressure (MAP) < 92 vs. 102–107 mmHg would result in a slower decline in CKD and reduce the risk for renal replacement therapy with mean baseline glomerular filtration rate (GFR) 39 mL/min, and proteinuria more than 500 mg per day. The AASK study included over a 1000 African-American patients with a GFR between 20 and 65 mL/min/1.73m^2 and albuminuria in two BP levels, i.e., 140/82 vs. 128/77 mmHg. The REIN-2 trial included patients with proteinuria greater than 1000 mg/d randomly assigned in either conventional (diastolic < 90 mmHg) or intensified (systolic/diastolic < 130/80 mmHg) BP control [22]. These studies did not prove that a BP target of less than 130/80 mmHg improves clinical outcomes more than a target of less than 140/90 mmHg in adults with CKD [23]. Those with higher levels of proteinuria > 1000 mg might benefit from the intensive BP lowering [23]. The recent guidelines [13] were influenced by the Systolic Blood Pressure Intervention Trial (SPRINT) [24] published 3 years ago. The SPRINT trial was designed to test the benefits of a systolic BP target below 120 mmHg compared with < 140 mmHg in non-diabetic patients older than 55 years of age, including a substantial subgroup with CKD. The study showed that intensive treatment of systolic BP < 120 mmHg reduced the combined rate of having a heart attack, acute coronary syndrome, heart failure, or stroke by nearly one third, and reduced deaths from any cause by nearly a one-quarter compared to reducing BP to less than 140 mmHg [24]. The results of the SPRINT provide evidence that the goal of systolic BP should be closer to 120 than 140 mmHg. The cardiovascular benefits were also seen in the 30% of SPRINT patients with CKD [24]. Indeed, in prespecified subgroup analyses of outcomes in participants with CKD, intensive BP control < 120 mmHg compared with < 140 mmHg resulted in a substantial decrease in major CV events and all-cause death. Interestingly, in CKD patients, the intensive BP control did not correlate with a slower decline in kidney function. The overall rate of serious adverse events did not differ between treatment groups, although some specific adverse events occurred more often in the intensive group [25••]. In a recent systematic review and meta-analysis including more than 8000 patients with CKD without diabetes during a follow-up of 3.3 years, intensive BP control (< 130/80 mmHg) was compared with standard BP control (< 140/90 mmHg) on major renal outcomes. It was shown that targeting BP below the current standard did not provide additional benefit for renal outcomes compared with standard treatment. Even in this analysis, non-Black patients or those with higher levels of proteinuria might benefit from the intensive BP lowering and the risk of adverse events was mostly similar among different BP targets emphasizing the need for individualization of BP targets [26••].

BP Measurement in CKD Patients

CKD has been shown to be linked to alterations in circadian BP profile, such as greater nocturnal hypertension, non-dipping (blunting of nocturnal BP fall) profile, or increased BP variability. Therefore, an increasing emphasis should be given on the preferred method for recording BP and the usefulness of the Home Blood Pressure Self-monitoring (HBPM) and 24-h Ambulatory Blood Pressure Monitoring (ABPM) [27]. In the office, the preferred method for recording BP is Automated Office Blood Pressure Measurement (AOBPM) which has been shown that closely predict cardiovascular events [28•]. Furthermore, ACCORD BP and SPRINT studies measured BP using AOBPM which yields values that are generally lower than typical office BP readings by approximately 5–10 mmHg [29]. HBPM and 24-h ABPM may provide evidence of white-coat hypertension, masked hypertension, BP variability, or other discrepancies between office and "true" blood pressure [28•] usually noticed in CKD patients. The importance of excluding white-coat hypertension before initiating pharmacological therapy in CKD patients may be achieved by HBPM or ABPM as appropriate. Masked hypertension may occur in up to 30% of patients with CKD and is considered to be associated with further kidney injury [27]. In CKD patients, BP variability is associated with poor outcome [30••]. HBPM also may improve patient medication adherence and thus help reduce cardiovascular risk [31].

Lifestyle Modifications

Achievement of a BP target < 130/80 mmHg in CKD patients is difficult and requires lifestyle modifications and multiple antihypertensive medications. Individuals with nephropathy exhibit impaired salt excretion and sodium restriction may be appropriate, followed by smoking cessation and moderate alcohol consumption. Furthermore, weight loss if overweight or obese, regular exercise, and interventions for obstructive sleep apnea also should be part of a comprehensive strategy of effective treatment of hypertension in CKD [7]. Lifestyle

modifications enhance the effectiveness of some antihypertensive medications and probably reduce the appearance of adverse effects.

The Spectrum of Abuminuria

If urinary albumin-to-creatinine ratio (ACR) is < 30 mg/g creatinine, 30–300 or > 300 mg/g, abuminuria is characterized as normal to mild increased, moderately increased formerly named microalbuminuria, and severely increased formerly named macroalbuminuria respectively. In the U.S. population, the prevalence of ACR 30–300 mg/g creatinine was 8.5% and of ACR > 300 mg/g was 1.4% in 2011–2014 [2]. Approximately 20% of individuals had urinary ACR below the threshold for albuminuria 10–29 mg/g creatinine [2].

The presence of albuminuria is associated with a faster progression to renal failure and with increased risk of CVD. The risk for adverse outcomes, including mortality and ESRD, increases with increasing albuminuria and decreasing GFR [32••, 33••]. Therefore, in CKD patients with albuminuria, the proper BP medications should be carefully titrated to reduce albuminuria. Indeed, it is now fairly well established that albuminuria reduction supports a better preservation of renal function and a lower CV mortality [34]. It is suggested that the risk of ESRD in hypertensive patients with diabetic nephropathy is more likely related to the albuminuria reduction than to lowering BP [35]. Optimization of drug prescribing for hypertensive individuals with CKD and albumiuria remains a challenge and has become an important public-health issue worldwide. Incremental BP reduction may be appropriate with careful monitoring of kidney function.

The Renin Angiotensin-Aldosterone System Inhibitors

CKD as an important risk factor for CVD [36] belongs to the certain co-morbidities that may affect clinical decision making in hypertension. The majority of adults with CKD are likely to have a 10-year risk of ASCVD that exceeds 10%. Furthermore, selection of medications for use in treating high BP in patients with CKD is guided by the existed compelling indications (e.g., albuminuria). Agents that block the renin angiotensin-aldosterone system (RAAS) should be the drugs of choice in CKD patients because the role of RAAS in the pathogenesis of cardiovascular and renal disease is well documented [18, 37–40]. Strategies targeting RAAS interruption have shown to improve CKD outcomes in patients with albuminuria whether diabetic or not [40, 41] and in preventing microalbuminuria [42, 43].

The new hypertension guidelines suggest that if albuminuria > 300 mg/g is present, the preferred drug should be an ACE inhibitor or in case of ACE inhibitor intolerance, an ARB [13] (Fig. 1). RAAS inhibitors consistently reduce proteinuria and slow the decline in kidney function [44, 45]. In CKD patients without albuminuria, there is no evidence that the use of an ACE inhibitor or an ARB is more effective compared with other antihypertensive first-line agents. RAAS blockers are often discontinued or are administered at suboptimal doses to large proportion of patients with proteinuric CKD because of the increases in serum creatinine or due to incident hyperkalemia (Table 2). It should be emphasized that to achieve BP goals as well as to lower albuminuria, moderate to high doses of these drugs are often required. Inarguably, the side-effect profile of these agents is not affected to a large extent by their dose [7]. Substantial evidence from outcome trials has demonstrated a great benefit with the use of RAAS blockers on slowing CKD progression in

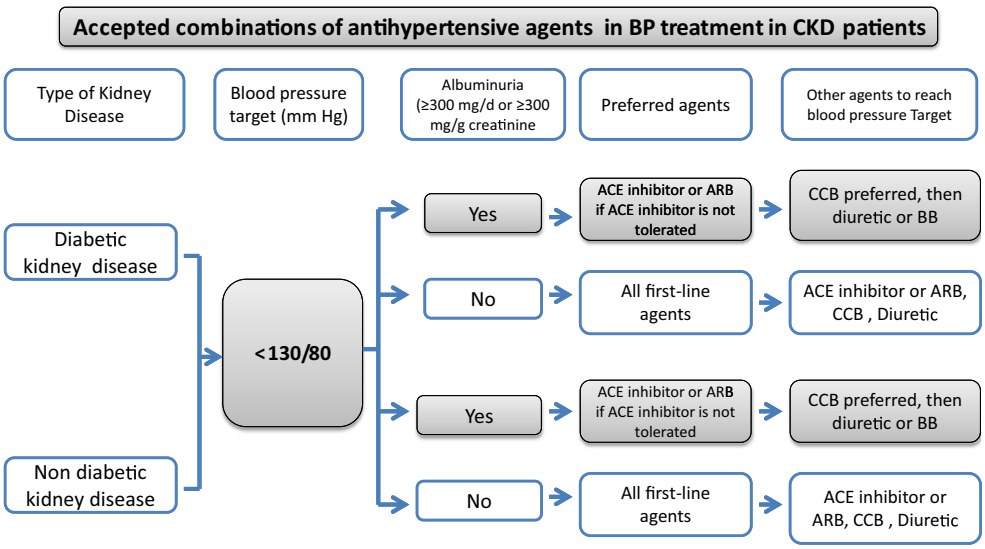

Fig. 1 Accepted combinations of antihypertensive agents for BP management in CKD patients. BP, blood pressure; CKD, chronic kidney disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BB, beta-blocker

patients with an eGFR less than 50 mL/min/1.73 m^2 albeit these agents are generally avoided by most physicians in these patients [3, 45, 46••, 47]. On the basis of current evidence, the administration of RAAS blockers could prevent both CKD progression to ESRD and premature mortality [48•]. An increase in serum creatinine with concurrent reduction in GFR often occurs because these agents reduce intraglomerular pressure. It has been suggested that the rise in serum creatinine in these patients within a few weeks of starting a RAAS inhibitor is associated with better CKD outcomes especially in those with proteinuric nephropathy and leads to a better preservation of kidney function over a mean follow-up period of 3 or more years [49]. With an increase of serum creatinine up to 30%, other causes should be carefully considered, such as volume contraction, bilateral renal artery stenosis, unsuspected left ventricular dysfunction, the use of non-steroidal anti-inflammatory agents, and/or other drugs affecting renal hemodynamics [50]. When serum creatinine rises from baseline values more than 30% within the first 3 to 4 months of therapy or incident hyperkalemia occurs (serum potassium > 5.2 mEq/L), a dose adjustment or withdrawn of RAAS-blocking therapy should be considered [49].

The combination of an ACE inhibitor with an ARB should be avoided and it is not supported by all recent guidelines [13, 14] due to an increased concern regarding the adverse events such as renal dysfunction, hyperkalemia, and symptomatic hypotension in high-risk CKD patients. RAAS inhibitors are contraindicated for use in pregnancy due to their extremely teratogenic effect. In addition, these agents should not be used in patients with a history of angioedema [7] (Table 2).

Aldosterone Receptor Antagonists

In patients with proteinuric CKD, aldosterone receptor antagonists, such as spironolactone or eplerenone in low-doses, may be also indicated. Indeed, a combination of a RAAS blocker with an aldosterone receptor antagonist may be beneficial in patients with proteinuric nephropathy and results in a further reduction of urine protein excretion [51]. However, aldosterone receptor antagonists in low doses are preferred. In fact, a dose-dependent increase in serum potassium levels after aldosterone receptor antagonists administration is commonly observed. Thus, serum potassium levels should be closely monitored during their administration [51]. In such cases, a dose adjustment of aldosterone receptor antagonist or a concomitant use of a loop diuretic therapy should be used. Consideration should be given with the use of spironolactone because the drug is associated with a greater risk of gynecomastia and impotence as compared with eplerenone, while eplerenone often requires twice–daily administration for adequate BP control [13] (Table 2).

Potassium-sparing diuretics are minimally effective antihypertensive agents and should be avoided in CKD patients with GFR < 45 mL/min [13]. Furthermore, spironolactone or eplerenone as well as amiloride and triamterene should be avoided if serum potassium concentration is > 5.2 mmol/L. On the contrary, in patients with CKD and hypokalemia, supposing that dietary causes have been excluded, combination

Table 2 Antihypertensive drugs and common side effects

Antihypertensive drugs	Common side effects
Thiazides and thiazide-like diuretics (e.g., hydroclorothiazide, indapamide chlorthalidone)	Hypovolemia Hypokalemia Hypomagnesemia Hypercalcemia Hyperuricemia Dyslipidemia Carbohydrate intolerance Sexual dysfunction
Loop diuretics (e.g., furosemide, torsemide)	Hypovolemia Ototoxicity (high doses) Hypokalemia Hypomagnesemia
Potassium-sparing diuretics (e.g., spironolactone, eplerenone amiloride, triamterene)	Hyperkalemia Hypotension Gynecomastia Impotence (in case of spirolactone)
B-blockers (e.g., metoprolol, atenolol, carvedilol, nebivolol)	Bradycardia Hypotension Tiredness Sexual function Hyperkalemia Dyslipidemia Bronchospasm Reduced exercise tolerance Cold hands and feet Carbohydrate intolerance (with all except nebivolol and carvedilol)
ACE inhibitors	Cough Hyperkalemia Angioedema Acute renal failure (in case of renal artery stenosis)
ARBs	Hyperkalemia Acute renal failure (in case of renal artery stenosis
Calcium channel blockers Diltiazem/Verapamil	Hypotension Sinus bradycardia
Dihydropyridines (e.g., amlodipine, nifedipine)	Hypotension Sinus tachycardia
Alpha(1)-blockers (doxazosin, terazosin)	Orthostatic symptoms
Central alpha-2 agonists (moxonidine, clonidine, alpha methyldopa)	Nausea Allergic skin reactions Dry mouth
Direct vasodilators such as minoxidil, hydralazine	Hirsutism Hypotension Reflex tachycardia

ACE inhibitors angiotensin-converting enzyme inhibitors, *ARBs* angiotensin II receptor blockers

therapy of an ACE inhibitor or an ARB, with low dose of potassium-sparing diuretic, can be considered in terms of correction of hypokalemia as well as proteinuria reduction [51].

New pharmacologic therapy for hyperkalemia management represents two novel agents for potassium lowering in patients with nephropathy. These agents, patiromer and sodium zirconium cyclosilicate, are ion exchange with promising results in treating hyperkalemia in patients with CKD without exhibiting serious adverse effects [52•].

Diuretics

Volume overload is often the hallmark in patients with kidney function deterioration. Thus, diuretics are the linchpin in the management of CKD. Thiazides and especially thiazide-like diuretics, such as chlorthalidone and indapamide, are preferred on the basis of their prolonged half-life. Thiazide diuretics may stimulate the RAAS system and a combination with ACE inhibitors or ARBs may be appropriate leading to an additive effect. These agents become less effective when GFR falls below 30 mL/min/1.73 m^2 [13]. On the other hand, loop diuretics exhibit a higher intrinsic efficacy compared to thiazides in patients with severe renal insufficiency. Furthermore, these agents are preferred in CKD patients with condomitant symptomatic heart failure. Thiazides should not be used in patients with a history of acute gout [13].

Calcium Channel Blockers

Calcium channel blockers (CCBs) are very effective antihypertensive drugs in patients with nephropathy. Different effects on proteinuria within the class of CCBs have been observed beyond their BP-lowering effects because of different effects on glomerular permeability. Non-dihydropyridine CCBs, verapamil and diltiazem, consistently reduce proteinuria and also slow the decline in kidney function among proteinuric CKD patients [42, 45]. Dihydropyridine CCBs, only when used in combination with a RAAS blocker, can reduce proteinuria among patients with advanced proteinuric nephropathy [3, 44]. Interestingly, manidipine, compared to amlodipine despite similar BP reductions [53], reduce intraglomerular pressure and thereby reduce albuminuria to a greater extent as compared to amlodipine [54].

In patients with CKD stage 3 to 5D, CCBs has similar effects on long-term BP reduction, mortality, heart failure, stroke or cerebrovascular events, and renal function to RAAS blocker agents [55•]. Moreover, as mentioned, dihydropyridine CCBs should not be used as monotherapy in proteinuric CKD patients but always in combination with a RAAS blocker (Fig. 1). Amlodipine or felodipine may be used if required in treating angina pectoris and heart failure in CKD patients with preserved ejection fraction [13]. It should be mentioned that non-dihydropyridine CCBs should not be used in CKD patients with heart failure with systolic dysfunction. These agents also increase the risk of bradycardia and heart block (Table 2), thus should not be used with beta-blockers [13]. According to the results of the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, a calcium antagonist, amlodipine, rather than a thiazide diuretic, should be considered as an add-on therapy to an ACE inhibitor, benazepril, because this combination is more effective in preventing the doubling of serum creatinine and ESRD, though less effective in preventing proteinuria [56]. These potential advantages should be kept in mind when selecting among possible agents to add to an antihypertensive treatment.

Agents Blocking the Sympathetic Nervous System

Beta-blockers

Beta-blockers are not first-line drugs in the treatment of hypertension particularly in patients over 60 years of age unless the patient has ischemic heart disease or heart failure. These agents have been shown to reduce cardiovascular mortality in high-risk patients, whereas their renoprotective effects have not been well established [57]. Beta-blockers with vasodilating properties such as nebivolol and carvedilol exhibit a better metabolic profile including lipid metabolism and insulin sensitivity compared to the traditional beta-blockers. Additionally, nebivolol induces nitric oxide-induced vasodilation [58]. Certain members of this class such as bisoprolol and metoprolol succinate are preferred in patients with heart failure with reduced ejection fraction [13]. Beta-blockers are not recommended in patients with bradycardia or with second- or third-degree heart block and should not be combined with a non-dihydropyridine CCB. In addition, it is important to point out that an abrupt cessation of these agents should be avoided [13].

Central Alpha-Adrenergic Agonists

Central alpha-adrenergic agonists reserve as last lines of therapy due to their adverse effects especially in older people. These agents exhibit a dose-dependent side effects profile and their tolerability is poor. The most obvious explanation of their use is to mitigate the increase in sympathetic activity observed in patients with nephropathy. The most commonly used is clonidine [59]. An abrupt discontinuation of clonidine may induce rebound hypertension thus clonidine must be carefully tapered to avoid hypertensive crisis [13]. Other members of this class include guanfacine and methyldopa, which are used primarily in pregnancy [60]. It is worth mentioning that moxonidine is an effective adjunctive therapy in combination with other antihypertensive agents. In fact, an improvement in the metabolic profile in hypertensive patients

with diabetes mellitus or impaired glucose tolerance has been shown after moxonidine administration [61]. However, a central alpha-adrenergic agonist and a β-blocker in combination can induce bradycardia and should be avoided [62].

Alpha 1-Adrenergic Blockers

Certain members of this class (doxazosin, prazosin, terazosin) are reserved as fifth-line agents in CKD patients. Since hypertension and benign prostatic hyperplasia often coexist in approximately 30% of adult men, alpha blockers might be used as add on therapy in hypertensive patients with benign prostatic hyperplasia [63]. These agents failed to slow renal disease progression or improve proteinuria in diabetic patients. Furthermore, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [64], a twofold higher incidence of congestive heart failure was noticed in the doxazosin arm compared with individuals receiving chlorthalidone [64].

Direct Vasodilators

Direct vasodilators, minoxidil or hydralazine, are used when treatment with the other primary agents has failed. Hydralazine is sometimes prescribed for acute BP lowering in hospitalized patients [65]. Some of the adverse effects related to hydralazine reported in the literature, include reflex tachycardia, hemolytic anemia, vasculitis, glomerulonephritis, and a lupus-like syndrome [66]. Minoxidil as a reserve antihypertensive agent still has a niche indication in a particular subgroup of CKD patients [67•]. It is associated with hirsutism and can induce pericardial effusion. Because these agents are associated with sodium and water retention, a combination with a beta-adrenergic blocker and/or a diuretic should be recommended and patients should always be closely monitor their body weight [13]. Antihypertensive therapy with direct vasodilators has not been shown to improve kidney outcomes.

Conclusions

Hypertension prevalence is progressively increasing as kidney function declines. In patients with CKD, an intensive BP goal < 130/80 mmHg has been recommended. The use of the HBPM and 24-h-ABPM may provide evidence of white-coat hypertension, masked hypertension, and BP variability that closely predict CV events. In patients with CKD and albuminuria > 300 mg/g, ACE inhibitors should be the drugs of first choice while ARBs should be used if the ACE inhibitor is not well tolerated. A CCB should be considered as an add-on therapy to the RAAS blocker. Non-dihydropyridines and manidipine can reduce intraglomerular pressure and thereby reduce albuminuria. Chlorthalidone and indapamide are preferred on the basis of their prolonged half-life, while a loop diuretic should be considered when GFR falls below 30 mL/min/1.73 m^2. Beta-blockers should be used preferably in patients with ischemic heart disease or heart failure. Central alpha-adrenergic agonists, alpha-adrenergic blockers, and direct vasodilators reserve as antihypertensive drugs in a particular subgroup of CKD patients when the primary agents are contraindicated and BP is not adequately controlled.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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- • Of importance
- •• Of major importance

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