Chapter 10
Management of Hypertension in Chronic Kidney Disease

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Blood Pressure Goals in Chronic Kidney Disease

Chronic kidney disease (CKD) and hypertension have an undeniably complex relationship. Hypertension is both a product of underlying kidney disease and a risk factor for the development and progression of CKD [1]. The complexity of this relationship likely contributes to disagreement in the literature, and thus among experts, regarding optimal blood pressure goals in patients with CKD. Sufficient blood pressure control can significantly reduce the rate of worsening renal function in patients with CKD [2]. Although there have been no blood pressure target trials specifically focused on cardiovascular events, patients with concomitant hypertension and CKD are at increased risk of adverse cardiovascular and cerebrovascular outcomes. Thus, careful attention to the management of blood pressure in these patients is critical [3].

In the 2014 Evidence-Based Management of Hypertension in Adults report, those empanelled as the Eighth Joint National Committee (JNC8) performed an intensive, systematic review of the existing literature; the 2014 report used data from Fair- to Good-quality randomized controlled trials (RCTs), and resorted to expert opinion in areas where RCTs were either not available, conflicting in their conclusions, or failed to address a particular question [4]. The report recommended that individuals <70 years of age with reduced kidney function (defined as an estimated glomerular filtration rate [eGFR] of <60 mL/min/1.73 m^2) and patients with albuminuria (defined as >30 mg/g) at any level of eGFR, with or without diabetes, should be initiated on antihypertensive therapy for a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg. Treatment should be titrated to achieve a goal systolic blood pressure of <140 mmHg and a goal diastolic

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blood pressure of <90 mmHg [4–7]. RCTs demonstrate no added benefit from stricter blood pressure control in patients with CKD with regard to progression of renal disease and adverse cardiovascular outcomes [8–10].

The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Management of Blood Pressure in CKD published in December 2012 provided comprehensive guidance regarding an extensive range of topics in the management of hypertension in patients with CKD (Table 10.1) [11]. The KDIGO guidelines systematically and transparently drew from a broader body of evidence, scrutinizing and denoting the quality of the available data for each subject addressed. The KDIGO guidelines have similar recommendations to those empanelled as JNC8 with regard to non-proteinuric patients with CKD. KDIGO recommends that non-diabetic and diabetic adults with CKD and no albuminuria (defined as <30 mg per 24 h) should be treated with antihypertensive medications to maintain a goal blood pressure of ≤140 mmHg systolic and ≤90 mmHg diastolic [11].

Blood Pressure Goals with Albuminuria

The increased risk of adverse cardiovascular and cerebrovascular outcomes in patients with concomitant hypertension and CKD is further exacerbated by the presence of proteinuria [3]. Post-hoc analysis of the MDRD study indicated that patients with >3 g per 24 h of proteinuria had greater renal benefit, defined as the slope of GFR change over time, from a blood pressure goal of <130/80 [8]. However, this finding was not consistent with primary analyses of other RCTs [9, 10]. As a result of the mixed available evidence, the recommendations regarding patients with albuminuria differ across treatment guidelines. Those empanelled as JNC8 recommend a goal systolic blood pressure of <140 mmHg and a goal diastolic blood pressure of <90 mmHg in these patients [4]. Acknowledging the limitations of the MDRD post-hoc analyses, the KDIGO report suggests that non-diabetic and diabetic adult CKD patients with any amount of albuminuria ≥ 30 mg per 24 h should be treated with antihypertensive medications to maintain a blood pressure of ≤130 mmHg systolic and ≤80 mmHg diastolic [8, 11].

Blood Pressure Goals in the Elderly

Those empanelled as JNC8 recommend that patients who are ≥60 years of age without CKD should be treated with antihypertensive therapy to achieve a goal systolic blood pressure of <150 mmHg and a goal diastolic blood pressure of <90 mmHg [4–7]. The group noted that there is no clear evidence regarding optimal blood pressure treatment goals in individuals with CKD who are ≥70 years of age. They recommend that elderly patients be evaluated and treated on an individualized

Table 10.1 Summary of the KDIGO 2012 guidelines for blood pressure management in CKD patients [11]

General guidelines
Individualize blood pressure targets and agents based on age, comorbidities, and side effects
Monitor for orthostatic hypotension, particularly in the elderly
Recommend lifestyle modification
Achieve or maintain a body mass index of 20–25 kg/m^2
Lower sodium intake to <2 g per day
Exercise at least 30 min 5 times per week
Limit alcohol intake to 2 drinks per day in men, 1 drink per day in women
Blood pressure management in diabetic and non-diabetic CKD patients
Urine Albumin Excretion <30 mg per 24 h
Initiate therapy for blood pressure >140 mmHg systolic or >90 mmHg diastolic
Maintain blood pressure consistently ≤140 mmHg systolic and ≤90 mmHg diastolic
Urine Albumin Excretion ≥30 mg per 24 h
Initiate therapy for blood pressure >130 mmHg systolic or >80 mmHg diastolic
Maintain blood pressure consistently ≤130 mmHg systolic and ≤80 mmHg diastolic
ARB or ACE-I is recommended
Blood pressure management in the elderly
Tailor blood pressure regimen based on age, comorbidities, and risk of medication interactions
Gradual escalation of therapy
Close monitoring for adverse effects
Orthostatic hypotension, acutely worsening azotemia, and electrolyte abnormalities

basis, taking into account other associated comorbidities and risk of adverse effects from treatment [4].

The KDIGO guidelines recommend a similar individualized approach to blood pressure targets according to age and coexisting comorbidities [11]. The authors noted that multiple studies in non-CKD elderly populations demonstrate a J-shaped

relationship between both systolic and diastolic blood pressure and survival [12–14], but that it appears to be safe to treat elevated blood pressures in elderly patients without CKD to a target level of <150/80 mmHg [5]. Much like JNC8, the KDIGO report states that the available data cannot be appropriately extrapolated to patients with CKD, and that it is not possible to provide a specific blood pressure target in elderly patients with CKD. The KDIGO report suggests an approach using the same goals as in younger patients with CKD, but emphasizes that treatment of hypertension in the elderly with CKD must be undertaken with greater caution and that treatment goals should be achieved gradually. The KDIGO guidelines also promote asking about dizziness and assessing for postural hypotension, noting that elderly patients with CKD undergoing treatment for hypertension are particularly prone to orthostatic hypotension, which can be exacerbated by volume depletion from diuretic therapy [11, 15].

Target Versus Achieved Blood Pressure

The disparity in recommendations regarding blood pressure goals in patients with CKD across different guidelines may be attributable in part to perceived differences in target versus achieved blood pressures. Achieved blood pressures in clinical practice may not consistently correlate with target blood pressures [16], raising concern that target blood pressures should be made lower in order to reach optimum blood pressure control in a greater number of patients and avoid treatment inertia. Critics of more lenient target blood pressures argue that observational data supporting lower blood pressure goals are evidence of the discrepancy between target and actually achieved blood pressures in "real world" settings. These critics also argue that RCT populations are not always generalizable to "real world" settings, where patients tend to have decreased motivation and adherence and increased heterogeneity compared to trial participants [11, 16].

Historically, some guidelines addressed the issue of achieved versus target blood pressure by recommending titration of treatment to a blood pressure that is lower than the recommended target blood pressure. The potential pitfalls of this approach include increased risk of adverse effects from medications, hypotension, and potential decreased survival in certain populations [12–14]. The KDIGO authors address the issue of achieved versus target blood pressure by recommending repeated office blood pressure measurements, and by wording their guidelines to recommend that patients *consistently* meet their target blood pressure [11]. Additionally, ambulatory blood pressure monitoring and home blood pressure monitoring are superior options to office-based measurements for prognostication of renal and cardiovascular outcomes in patients with chronic kidney disease, and allow for more reliable assessment of achieved blood pressure [17, 18].

Management of Hypertension in CKD

Non-Pharmacologic Therapy

RCT and observational data support lifestyle modifications such as decreased sodium intake [19], increased exercise [20], weight loss [21], and reduction in alcohol intake [22] for the management of blood pressure in the general population [23]. Existing evidence indicates that blood pressure reduction through lifestyle modifications can significantly improve cardiovascular and renal outcomes. Although mainly observational data are available in the CKD population, non-pharmacologic management with lifestyle modifications has become a key factor in the treatment of hypertension in patients with CKD. That said, most patients will require a combination of non-pharmacologic and pharmacologic treatment in order to achieve blood pressure targets (Table 10.2).

Reduced Sodium Intake

Excess sodium and water retention is a major contributing factor to elevated blood pressure in patients with CKD [24, 25]. Patients with reduced GFR have impaired filtering of sodium and water, resulting in expansion of the extracellular volume and thus an increase in systemic blood pressure. High amounts of sodium intake in patients with CKD contribute to volume expansion (which can occur in the absence of peripheral edema) [26], increased filtration fraction resulting in increased proteinuria [27], and hypo-responsiveness to pharmacologic antihypertensive therapies [28]. Since their elevated blood pressure is in part driven by this impairment in sodium excretion, patients with CKD tend to be sensitive to reductions in sodium intake. Although no RCTs have been performed evaluating the long-term effect of dietary sodium reduction in CKD patients, short duration RCTs have demonstrated that reduced sodium intake improves responsiveness to pharmacologic antihypertensive therapy in these patients [29–31].

There is no high-quality data on the ideal level of sodium intake in patients with CKD, however recent guidelines recommend a reduction in sodium intake to less than 2–2.3 g daily; more stringent sodium restriction does not appear to be beneficial [11, 32]. Patient education on interpreting food labels and provider-initiated feedback on sodium reduction using 24 h urine sodium collection are valuable tools in effectively implementing sodium reduction in hypertensive patients [33].

Potassium Supplementation

A number of studies in non-CKD patients demonstrate that low dietary potassium intake increases sodium sensitivity in patients with normal renal function, and that dietary potassium intake is inversely proportional to blood pressure [34, 35].

Table 10.2 Summary of non-pharmacologic and pharmacologic management options in CKD

Non-pharmacologic	Summary of the literature
Reduced sodium intake	Reduce sodium intake to less than 2–2.3 g per day
Potassium supplementation	Benefit in hypertension in inconclusive
	Not recommended in CKD due to risk of hyperkalemia
Exercise	Aerobic exercise 30 to 40 min, five to seven times weekly
Weight loss	Reduce or maintain body mass index <25 kg/m^2
Reduced alcohol intake	No studies in CKD
	Recommendations per KDIGO; limit to 2 drinks per day in men, 1 drink per day in women
Smoking cessation	No studies in CKD; strong evidence in diverse populations to support cessation
Pharmacologic	
ACE-I/ARB	Recommended as first-line therapy in most patients; best evidence is in the setting of proteinuria
	No benefit from dual ACE-I and ARB therapy, with increased risk of hyperkalemia and azotemia
Direct renin inhibition	Increased risk of nonfatal stroke, azotemia, hyperkalemia, and hypotension when given with ARB
	Not currently recommended in CKD in combination with ACE-I or ARB
Diuretics	Thiazides have long-term benefit in CKD, but are less effective than loop diuretics in advanced CKD
	Chlorthalidone is more potent than hydrochlorothiazide; electrolyte abnormalities persist in CKD
	Metolazone is useful for short-term adjunctive therapy along with loop diuretics
K-sparing diuretics and	Triamterene and amiloride not recommended due to risk of hyperkalemia
Mineralocorticoid antagonists	Spironolactone and eplerenone may be helpful as adjunct to ACE-I/ARB, however increase risk of hyperkalemia
Calcium channel blockers	Dihydropyridines may exacerbate extravascular volume expansion and albuminuria
	Non-dihydropyridines may reduce albuminuria; however, increase risk of bradycardia
Beta blockers	Avoid giving with non-dihydropyridines due to risk of atrioventricular block and bradycardia
	Atenolol and bisoprolol are renally eliminated
	Atenolol may have greater mortality benefit than metoprolol in older patients
Centrally acting alpha agonists	No interaction with other antihypertensives; useful as adjunctive therapy
	Moxonide accumulates in kidney disease, and has increased risk of mortality in heart failure
	Guanfacine has higher risk of sedation, postural hypotension, and sexual dysfunction

(continued)

Table 10.2 (continued)

Non-pharmacologic	Summary of the literature
Alpha blockers	Increased risk of heart failure in high-risk hypertensive patients
	High risk of postural hypotension, tachycardia, and falls, particularly in the elderly
Direct vasodilators	Hydralazine not generally recommended for long-term therapy due to need for frequent dosing
	Minoxidil is useful in very resistant hypertension; however, high risk of side effects
	Minoxidil should be administered with a beta blocker and diuretic due to risk of myocardial ischemia and volume expansion

Although some studies demonstrate that potassium supplementation can attenuate the effect of sodium on blood pressure, data on the effectiveness of potassium supplementation in the treatment of hypertension is inconclusive [36]. One proposed explanation for the inconsistent evidence is that both reduction in dietary sodium and increase in dietary potassium intake work synergistically to reduce sodium retention [37]. Regardless, potassium excretion is significantly impaired in the setting of reduced GFR, increasing the risk for hyperkalemia in patients with CKD. Given the limited evidence and potentially grave risk, there is no indication for potassium supplementation in the management of hypertension in patients with CKD.

Exercise

Multiple RCTs demonstrate that aerobic exercise lasting 30–40 min four to seven times weekly contributes to a significant reduction in blood pressure in the general population [20]. Resistance training at least 3 days per week, including three to four sets of eight to twelve repetitions, also significantly reduces blood pressure in non-CKD patients, but to a lesser degree than aerobic exercise [20]. Multiple RCTs exist evaluating the role of aerobic exercise in CKD populations. These studies demonstrated a significant though modest reduction in systolic blood pressure and no overall reduction in diastolic blood pressure in CKD patients who undergo at least 8 weeks of aerobic exercise intervention compared to controls [38]. No studies exist evaluating the role of resistance training in blood pressure reduction in patients with CKD.

Weight Loss

Excess adipose tissue contributes to increased sympathetic nervous activity and increased renin, angiotensin, and aldosterone activity [39–41]. Modest weight loss significantly decreases muscle sympathetic nerve activity [42] and renin-angiotensin activity [43] in non-CKD obese patients. Based on multiple RCTs,

remission of hypertension is observed in 75 % of non-CKD patients who lose weight after undergoing bariatric surgery [21]. Observational studies demonstrate a significant reduction in blood pressure with both surgical and non-surgical weight loss in patients with CKD (with 9 mmHg reduction and 22.6 mmHg reduction observed, respectively) [44]. Although elevated body mass index may be protective in dialysis populations [45], evidence suggests that increased adipose tissue increases the rate of progression of CKD in pre-dialysis patients [46]. Due to the role of excess adipose tissue in increased blood pressure and deterioration of renal function, current guidelines recommend normalization of body weight to a body mass index of less than 25 kg/m^2 in hypertensive patients with CKD [11].

Reduced Alcohol Intake

In non-CKD patients, reduction of alcohol intake results in a significant decrease in both systolic and diastolic blood pressure [22]. No studies have specifically evaluated the effect of reduction in alcohol intake on blood pressure in CKD patients, although there is also no evidence to suggest that the effect would vary significantly from non-CKD patients. The KDIGO guidelines recommend a maximum of two alcoholic drinks per day for men and one drink per day for women with CKD, consistent with current guidelines for the general population [11].

Smoking Cessation

Multiple observational studies demonstrate a significant improvement in systolic and diastolic blood pressure following smoking cessation in diverse non-CKD populations [47–49]. No studies specifically evaluate the effect of smoking cessation on blood pressure in patients with CKD. However, given the clear cardiovascular benefits of smoking cessation across all populations of patients, smoking cessation is strongly recommended in CKD patients to aid in the reduction of overall cardiovascular risk [11].

Pharmacologic Management

Patients with elevated blood pressure in CKD will likely benefit most from a stepwise approach to the management of their hypertension using a combination of lifestyle modifications and antihypertensive agents. Although adequate blood pressure control has clear renal, cardiac, and cerebrovascular benefits, selection of specific antihypertensive medications should be made on an individual patient basis, particularly taking into account the potential for adverse effects [11].

General Principles

Angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are strongly recommended as first-line therapy in patients with proteinuric CKD [4, 11, 50]; in patients with non-proteinuric CKD, there is no compelling evidence to support the use of ACE-Is or ARBs as first-line therapy, however these agents are still generally used for initial treatment of hypertension in most CKD patients [4]. The vast majority of patients with CKD will require a minimum of two to three antihypertensive medications in order to achieve target blood pressures [51]. No RCTs exist comparing different approaches to adjusting antihypertensive regimens in these patients. Based on expert opinion, if patients fail to meet the appropriate treatment goal within 1 month of initiation of an intervention, either the dose of the initial therapy should be increased as tolerated or an additional therapy may be introduced [4]. When selecting second and third-line therapies, patient-specific comorbidities and patient tolerance of the respective treatment should be taken strongly into consideration. Given the particularly high incidence of cardiac disease in patients with CKD, close attention should be paid to the coexistence of cardiovascular disease or congestive heart failure [52]. Treatment regimens should be tailored accordingly in order to optimize cardiac remodeling, afterload reduction, and other end organ effects of these frequently associated comorbidities.

Taking into account the often complex treatment regimens required to achieve adequate blood pressure control in these patients, certain combinations of medications should be addressed with caution or altogether avoided due to increased risks of adverse outcomes. Combination of ACE-I and ARB therapy is not currently recommended in patients with diabetic and non-diabetic CKD due to the amplified risk of hyperkalemia and azotemia, with no clear added benefit based on RCTs [53, 54]. Although there is anti-proteinuric benefit, the addition of an aldosterone antagonist to ACE-I or ARB therapy remains a point of controversy as well due to the potential increased risk of hyperkalemia [55]. The combination of non-dihydropyridine calcium channel blockers and beta blockers should be avoided due to the possibility of developing atrioventricular block or symptomatic bradycardia [56]. On the other hand, minoxidil should only be used in combination with both a beta blocker and high-dose loop diuretic due to the increased risk of tachycardia, myocardial ischemia, and tubular sodium retention when it is used as monotherapy [57].

ACE-Is, ARBs, and Renin Inhibitors

Reduction of proteinuria can be achieved both with adequate blood pressure control and blockade of the renin-angiotensin system, and plays a critical role in decreasing the rate of progression of CKD [2]. ACE-Is or ARBs significantly decrease the degree of proteinuria and delay the progression to end stage renal disease in diabetic and non-diabetic nephropathies when compared to both placebo and other antihypertensive therapies [58–61]. Additionally, ACE-Is and ARBs have greater renoprotective effect at higher degrees of baseline proteinuria [59, 60]. Consequently,

patients with proteinuria should receive an ACE-I or ARB as first-line therapy [4, 11, 50]. There is no strong evidence to support first-line treatment with ACE-Is or ARBs in non-proteinuric patients with CKD, however experts do generally recommend initial therapy with ACE-Is or ARBs in non-black patients with CKD. Black patients with non-proteinuric kidney disease may be initiated on treatment with a thiazide-type diuretic, calcium channel blocker, ACE-I, or ARB, with second-line addition of an ACE-I or ARB if not used as initial therapy [4, 62].

Aliskiren is a direct renin inhibitor that prevents the conversion of angiotensinogen to angiotensin I. There are limited data on the use of aliskiren in patients with CKD. One small RCT in patients with diabetic nephropathy demonstrated a slight improvement in proteinuria and no improvement in blood pressure when aliskiren was used as an adjunct to ARB therapy [63]. Another, larger scale RCT of combination aliskiren and ARB therapy in patients with diabetic nephropathy was terminated early due to an increased risk of adverse events (including nonfatal stroke, azotemia, hyperkalemia, and hypotension) in the absence of any clear benefit [64]. Accordingly, direct renin inhibition in combination with an ACE-I or ARB is not currently recommended in the management of hypertension in patients with chronic kidney disease [11].

Diuretics

Given the high sensitivity of CKD patients to sodium and water retention, diuretic therapy is a critical component of blood pressure management in these patients [24, 25]. Diuretic therapy augments the antihypertensive and renoprotective effects of ACE-I or ARB therapy [29–31]. Additionally, diuretics can help to attenuate the increased risk of hyperkalemia that occurs as a result of treatment with ACE-Is or ARBs. Patients with CKD require relatively high doses of diuretics due to decreased secretion of diuretics by the renal tubules in the setting of impaired renal function [25]. Although loop diuretics are the mainstay of treatment in patients with advanced CKD (i.e., GFR <30 mL/min/1.73 m^2), multiple small RCTs support the use of thiazide diuretics as monotherapy or in conjunction with loop diuretics in patients with CKD [65, 66]. Thiazides may also decrease peripheral vascular resistance, contributing to greater long-term benefit on blood pressure in addition to the acute improvement in volume expansion [25]. However, thiazide diuretics are overall less effective than loop diuretics in patients with more advanced CKD, likely due to decreased filtered sodium load reaching the distal tubule [67]. Additionally, thiazide diuretics may induce or exacerbate diabetes and hyperlipidemia [68].

Unlike traditional thiazide diuretics, metolazone remains effective in the setting of renal dysfunction [69]. However, the bioavailability of metolazone is unpredictable, and the medication should only be used for short durations of treatment, in combination with loop diuretics, and under close monitoring of serum electrolytes [67]. Observational data in patients with normal renal function demonstrates improved long-term cardiovascular outcomes with thiazide-like diuretics (chlorthalidone) compared to thiazide diuretics (hydrochlorothiazide) [70], though the results

are not upheld across all studies [71], and chlorthalidone is more highly associated with hypokalemia and hyponatremia in these patients. No evidence is available comparing the effectiveness of these medications in CKD patients; nonetheless, the increased potency of chlorthalidone is advantageous in the setting of reduced GFR, but the risk of hypokalemia persists [72, 73].

Potassium-Sparing Diuretics and Mineralocorticoid Antagonists

Potassium-sparing diuretics, including triamterene and amiloride, are not typically recommended in patients with CKD due to the added risk of hyperkalemia. Strong evidence supports the use of spironolactone, an aldosterone antagonist, and eplerenone, a mineralocorticoid receptor blocker, as adjunctive therapy in the treatment of resistant hypertension and congestive heart failure in the absence of CKD [25, 74, 75]. Eplerenone is favorable due to the absence of estrogen-like effects, though both medications are thought to be similarly effective. In patients with CKD, several RCTs demonstrate enhanced anti-proteinuric effects of ACE-Is or ARBs when given in combination with mineralocorticoid antagonists [55, 76], though the long-term efficacy of this combination of medications remains unclear. The added benefit of aldosterone antagonism in the treatment of CKD patients is thought to be due to a phenomenon identified as aldosterone escape, which occurs via non-ACE activation of angiotensin II [77]. Additionally, aldosterone is thought to play a role in renal fibrosis, which is attenuated by treatment with an aldosterone antagonist in animal studies [78]. Although many studies demonstrate no increased risk of adverse effects (specifically azotemia or hyperkalemia) from the use of aldosterone antagonists along with ACE-Is or ARBs [76], a meta-analysis suggests greater than twofold increase in relative risk of hyperkalemia with combination therapy [55]. If utilized, combination of aldosterone antagonism and renin-angiotensin system blockade should be handled with caution, including close monitoring of renal function and potassium.

Calcium Channel Blockers

Dihydropyridine calcium channel blockers, including amlodipine and nifedipine, are primarily selective for vascular smooth muscle, resulting in vasodilation. These medications are often associated with the development of peripheral edema. Dihydropyridine calcium channel blockers also primarily act on the afferent glomerular arteriole, resulting in increased albuminuria when used as monotherapy [79]. On the other hand, non-dihydropyridine calcium channel blockers, including diltiazem and verapamil, have a greater effect on the myocardium; these medications confer an increased risk of atrioventricular block or bradycardia, particularly when prescribed in combination with beta blockers [56]. Non-dihydropyridine calcium channel blockers have a vasodilatory effect on both the efferent and afferent glomerular arterioles, resulting in decreased albuminuria. While both

subclasses of medications have a similar capacity to lower blood pressure, non-dihydropyridines are preferred in patients with existing albuminuria, particularly if there is a contraindication to concomitant treatment with an ACE-I or ARB [79]. Due to the differential mechanisms of the calcium channel blocker subclasses, potential benefit of combination dihydropyridine and non-dihydropyridine therapy in hypertensive patients has been proposed [80]; however, this has not been studied in CKD patients.

Beta Blockers

Beta blockers are particularly useful in targeting specific cardiac comorbidities in patients with CKD, including cardiovascular disease, congestive heart failure, and tachyarrhythmias. Of note, elimination of atenolol and bisoprolol is highly dependent on renal function, extending their duration of action in patients with renal dysfunction [81]. Metoprolol and carvedilol have the greatest mortality benefit in non-CKD patients with congestive heart failure [81, 82]. Nonetheless, a recent large-scale observational study demonstrated that atenolol was associated with lower 90-day mortality than metoprolol in older patients, including patients with CKD; there was a similar risk of hospitalization for bradycardia or hypotension with both beta blockers, regardless of renal function [83].

Centrally Acting Alpha Agonists

Clonidine, methyldopa, guanfacine, and moxonidine are centrally acting $alpha_2$ agonists that act by decreasing central sympathetic outflow, resulting in vasodilation. While extensive data are not available in CKD patients, $alpha_2$ agonists do not tend to interact with other antihypertensive medications; they can therefore be used as relatively safe adjunctive therapy in CKD patients with resistant hypertension who are already being treated with multiple other medications [50]. Of note, moxonidine is associated with increased mortality in non-CKD patients with advanced heart failure [84]. Significant renal excretion of moxonidine requires dose-reduction in the setting of CKD [85]. Guanfacine, an $alpha_2$ agonist also utilized in the treatment of attention deficit hyperactivity disorder and anxiety, is associated with a higher frequency of sedation, orthostatic hypotension, and sexual dysfunction than the other $alpha_2$ agonists [86].

Alpha Blockers

$Alpha_1$ blockers cause peripheral vasodilation resulting in reduction in blood pressure. $Alpha_1$ blockers may be useful in men who also have symptoms of benign prostatic hyperplasia. However, $alpha_1$ blockers are highly associated with postural hypotension, tachycardia, and increased risk of falls, particularly in the elderly [87].

Additionally, the alpha$_1$ blocker arm of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was terminated early based on an increased risk of combined cardiovascular events, particularly congestive heart failure, in high-risk hypertensive patients who received an alpha$_1$ blocker as opposed to chlorthalidone [88]. Consequently, alpha$_1$ blockers are not recommended as first-line therapy in CKD patients due to an increased risk of adverse events compared to other antihypertensive agents.

Direct Vasodilators

Hydralazine and minoxidil have a direct vasodilatory effect on vascular smooth muscle, resulting in a reduction in blood pressure. Given its short duration of action and need for frequent dosing, hydralazine is not generally recommended in the treatment of chronic hypertension in patients with CKD [50]. Minoxidil may have a role in the treatment of CKD patients with highly resistant hypertension, however it is often poorly tolerated due to a considerable range of side effects, including hirsutism, pericardial effusion, severe volume expansion, and potentially myocardial ischemia. Minoxidil should only be administered along with a high dose diuretic and beta blocker, in order to limit adverse events [50, 57].

Pseudo-Resistant Hypertension in CKD

CKD patients frequently require complex antihypertensive regimens, resulting in a high pill-burden. Poor adherence is a common issue in these patients, and may result in misperceived resistance to medication. As a result, patients may be prescribed a greater number of medications, at higher doses than indicated by their degree of hypertension, increasing the risk of hypotension and other adverse effects when they do take their medications. Pill counting and monitoring of prescription renewals may provide clues into the occurrence of this phenomenon, but are suboptimal options in the usual treatment setting. Ambulatory blood pressure monitoring can be particularly helpful in the identification of these patients [89]. Additionally, providing empathy and carefully interviewing patients can shed light on specific barriers to appropriate use of medications, such as financial restraints, insufficient motivation, poor understanding of the benefits of medications, adverse effects, and high pill-burden [23]. Prescribers are encouraged to educate patients accordingly, and to employ strategies to try to help minimize pill-burden and maximize patient adherence. Examples of potential approaches include the use of less expensive or generic medications, as well as carefully coordinated and decreased frequency of dosing when possible, including the use of combination pills [11, 23, 89, 90].

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