Review

Hypertension in Cardiovascular and Kidney Disease

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Abstract

The relationship between hypertension and chronic kidney disease (CKD) is bidirectional in nature and, generally, management strategies for cardiovascular risk reduction also attenuate progression of CKD. Prevalent hypertension increases with diminishing kidney function, and the management strategy changes with level of kidney function. In this review, we will examine the evidence for management of hypertension, as a modifiable risk factor for cardiovascular disease in CKD, and the impact of this management on progression of CKD.

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Hypertension and Chronic Kidney Disease

Hypertension and chronic kidney disease (CKD) frequently exist together, though the influence of one upon the other is difficult to clarify. Hypertension is the number-two cause of end-stage renal disease (ESRD) following diabetes in the United States and is a comorbid condition in approximately 61–66% of those with an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 [1]. Prevalent hypertension in CKD increases with diminishing eGFR with a prevalence of 35.8% in CKD stage 1 and 84.1% in CKD stages 4–5 [1]. In comparison, CKD has a prevalence of 27.5% in patients with diagnosed hypertension and 22% among those with undiagnosed hypertension [2].

Treatment of hypertension is arguably the most important CKD and cardiovascular disease (CVD) risk reduction strategy. The overall mortality rate in CKD increases from 69.1 in

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CKD stages 1–2 to 89.7 in stages 3–5 per 1,000 patient-years at risk [1–4]. The relationship between CVD mortality and CKD is a graded one and increases linearly with diminishing GFR [1]. In a study of 18,597 participants aged 50–80 years treated for 3.8 years with aspirin and a protocol for blood pressure control, patients had progressively increasing rates of major CVD events as well as total mortality rates with decreasing GFR. Cardiovascular event rates were increased by 70–100% for every 50% decline of eGFR [3].

The coexistence of hypertension is associated with more rapid progression of CKD [4–6]. Several studies indicate treating hypertension in patients with CKD and proteinuria may slow the decline in GFR and progression of CKD [7–9]. Despite the evidence for control of blood pressure in reducing the risk of progressive CKD, blood pressure control is generally inadequate in the CKD population [10]. In patients with CKD stages 1–2, more than one third are unaware of having hypertension, 14% are not treated, and only 11% are treated adequately [1].

Therefore, in this review, we will examine the evidence for management of hypertension, as a modifiable risk factor for CVD in CKD, and the impact of this management on progression of CKD.

Approach to Therapy

A rational approach to the treatment of hypertension in those with CKD includes both non-pharmacologic and pharmacologic approaches. Figure 1 depicts a generalized approach to the pharmacologic management of hypertension in chronic kidney disease. Although currently being reviewed by the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for an eighth (JNC 8) report, current guidelines based on JNC 7 advocate a blood pressure goal of <130/80 mm Hg in those with CKD [11, 12]. This goal is supported by several studies suggesting a lower blood pressure may slow CKD progression. A meta-analysis in 2003 reported a lowered risk of CKD progression with a blood pressure goal of 110–129 mm Hg, and an increase in the relative risk for CKD progression at blood pressures >130 mm Hg. The beneficial results were most notable in those with proteinuria exceeding 1 g/d [13].

Lifestyle and Dietary Approaches
The evidence for non-pharmacologic intervention for hypertension in those without CKD is more compelling. The same interventions have largely been extrapolated to the CKD population. Importantly, compliance and patient interest are the biggest challenges for instituting lifestyle changes; however, they should be a component of all successful pharmacologic regimens. Lifestyle modifications recommended by the Kidney Disease Outcomes Quality Initiative (K/DOQI) and the Canadian Society of Nephrology include smoking cessation, weight reduction, exercise, and dietary sodium restriction [12, 14].

Low-Sodium Diet
Dietary sodium restriction is recommended to reduce extracellular fluid volume expansion and to lower blood pressure. Sodium intake has a dose-dependent relationship with blood pressure, and a modest reduction of 100 mmol/day (6 g of salt) will significantly reduce systolic and diastolic blood pressure in both hypertensive and normotensive subjects in as little as 4 weeks [15]. Blood pressure reduction with salt restriction can be seen across non-diabetic hypertensive ethnic groups, including Blacks, Hispanics, and Asians. Reduced sodium intake can lessen the incidence of hypertension by approximately 20% [16]. Excess sodium intake leads to resistance to renin-angiotensin-aldosterone system (RAAS) blockade,

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and sodium restriction can be as effective as the addition of a thiazide to a therapeutic regimen containing angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB) [17, 18].

Weight Loss

Weight loss, as in the non-CKD population, can augment blood pressure reduction. In this context, obesity is an independent risk factor for the development and progression of CKD [19]. Reductions in body mass index (BMI) in obese patients with CKD with non-surgical interventions can markedly decrease systolic blood pressure and proteinuria, along with cessation of GFR loss. Surgical intervention in morbidly obese individuals with a BMI >40 has the potential for normalization of GFR and reduction of systolic blood pressure and micro-albuminuria [20]. Unfortunately, many studies represent only short-term outcomes.

The National Kidney Foundation K/DOQI extends recommendations from JNC 7 for weight loss in CKD to a BMI <25 for those overweight and maintenance of weight for those with a BMI <25 [11, 12]. Avoidance of high-protein diets is advised in light of the exorbitant amounts of protein in Westernized diets and potential risk for enhancement of progression of CKD. Conversely, very restrictive diets may put CKD patients at overall health risk as these patients are already prone to protein-energy malnutrition.

Additionally, physical activity may provide a benefit. In the non-CKD population relatively modest amounts of physical activity, 30–60 min per week, lead to significant reductions in blood pressure in hypertensive subjects. The effect is graduated with increasing amounts of physical activity. Physical activity and the relationship with hypertension has not been well studied in the CKD population. Nevertheless, there appears to be a survival benefit in the CKD population that participates in regular physical activity [21].

Pharmacologic Interventions

Diuretics

Thiazide diuretics have become an integral element for treating hypertension in the early stages of CKD. While salt restriction has shown to be equivalent to thiazide diuretics for blood pressure reduction in the early stages of CKD, diuretics are essential when sodium restriction alone is unsatisfactory [22]. Thiazides induce a reduction in systolic and diastolic blood pressure between 10–15 and 5–10 mm Hg, respectively [23]. Along with chronic volume depletion, decreased systemic vascular resistance accounts for the long-term antihypertensive effects of thiazide diuretics. However, thiazide diuretics lose much of their antihypertensive effects as GFR falls below 50 ml/min/1.73 m^2 and are recommended only in patients with an eGFR of >30 ml/min/1.73 m^2 [12]. Although hydrochlorothiazide (HCTZ) is the most widely used thiazide for treating high blood pressure, clinical studies demonstrate that chlorthalidone is more efficacious in reducing blood pressure [24–27]. Side effects of thiazide diuretics include increases in blood glucose levels, hyperuricemia, hypercalcemia, and hypokalemia, which are dose dependent.

As the GFR declines, thiazide diuretics lose their utility in promoting natriuresis. Loop diuretics can be employed for effective volume management. Directed therapy with loop diuretics for volume control and hypertension comes in 2 stages, initiation and maintenance. Once the patient has achieved a maximum diuresis without symptoms of orthostatic hypotension, cramps, fatigue or decreased renal function, then the patient should be titrated to the lowest dose necessary to maintain established dry weight [28]. The pharmacokinetics and pharmacodynamics of loop diuretics change with advancing CKD and need to be continually monitored and adjusted to maintain dry weight. In this regard, increased doses of loop

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diuretics are required with diminishing kidney function, and inadequately dosed furosemide administration will result in sodium retention. Due to its short-acting nature, furosemide should be dosed at least twice daily.

RAAS Inhibition

RAAS inhibition is the cornerstone of management in patients with hypertension and CKD. RAAS inhibition is considered first-line therapy by both the K/DOQI and the JNC 7 [11, 12] and is achieved most commonly with ACE inhibitors and ARBs. ACE inhibitors competitively block the action of ACE, thereby reducing circulating levels of angiotensin II (Ang II). ARBs specifically block the binding of Ang II to the angiotensin type I receptor (AT_1R). By intervening in the RAAS, several actions are blunted, including direct vasoconstriction, release of noradrenaline from sympathetic nerve terminals, stimulation of proximal tubular reabsorption of sodium, stimulation of aldosterone secretion, and vasopressin release. ACE inhibition not only reduces blood pressure in the CKD patient, but also reduces the progression of CKD in non-diabetic kidney disease and proteinuria [29–31]. Like the ACE inhibitors, ARBs also reduce blood pressure, decrease proteinuria, and limit CKD progression in diabetic kidney disease [32, 33], and possibly non-diabetic kidney disease as well [34]. The utility of a combination of ARBs and ACE inhibitors becomes apparent by greater reductions in proteinuria than achieved by monotherapy; however, these comparisons are true with respect to conventional doses, and monotherapy at higher doses may be of equal benefit [34, 35]. A major limitation with the use of ACE inhibitor and ARB regimens in the CKD population is the risk for hyperkalemia. Both classes of agents increase the risk of hyperkalemia and the odds of mortality increase when hyperkalemia is present [36]. The risk of hyperkalemia can be mitigated by the concomitant use of diuretics [37], dietary potassium restriction, and potassium resin binders.

Mineralocorticoid receptor (MR) antagonists offer an additional opportunity for RAAS intervention in those with CKD and resistant hypertension, as defined by three or more maximally dosed anti-hypertensives including a diuretic. Similar to ACE and ARB use, the role of MR antagonism is also limited due to a potential risk for hyperkalemia in those with advanced CKD. Spironolactone and eplerenone are the MR antagonists that potentially prevent the aldosterone escape mechanism that occurs with ACE inhibitors and ARBs [38]. Mounting evidence supports a significant reduction in blood pressure and proteinuria when these MR antagonists are added to an ACE inhibitor or ARB [39, 40]. While these results would support improvements in mortality and kidney-related outcomes, data is lacking and future work is warranted. The beneficial cardiac effects of MR antagonists in patients with heart failure are well known, but have not been duplicated in patients with an eGFR <60 ml/min/1.73 m^2 [41]. Adverse effects associated with MR antagonists include breast tenderness, gynecomastia, hyperkalemia, prostatic hypertrophy, erectile dysfunction, and menstrual irregularities. Eplerenone has a more tolerable profile with reduced sexual side effects and gynecomastia. The incidence of hyperkalemia (>5.5 mmol/l) is approximately 5.7% in those with an eGFR <60 ml/min/1.73 m^2 and was more pronounced in those with an eGFR <45 ml/min/1.73 m^2 [42].

Direct renin inhibition became available with introduction of aliskiren, and limited evidence supports its use in CKD patients. In patients with type 2 diabetes mellitus, hypertension, and diabetic kidney disease, combination therapy with maximal doses of losartan and aliskiren led to a 20% reduction in albuminuria compared to losartan and placebo [43]. Long-term data regarding mortality and renal outcomes are not available. Serum potassium elevations >5.5 mmol/l were more frequent with aliskiren (22.5%) versus placebo (13.6%) in stage 3 CKD [44]. All other adverse event rates were similar between treatments, irrespective of CKD stage, except for an increased rate of renal dysfunction seen in the aliskiren group

in stage 3 CKD patients [44]. As additional studies and comparisons to other RAAS agents are performed, the role of aliskiren in clinical practice will be better understood. At this time, aliskiren is recommended to patients that have incomplete RAAS blockade with an eGFR >30 ml/min/1.73 m^2. Aliskiren, when used in combination with ACE inhibitors or ARBs, has greater blood pressure reduction than monotherapy. Additionally, when evaluated in type 2 diabetic patients with albuminuria, the combination is more antiproteinuric than monotherapy with ARB.
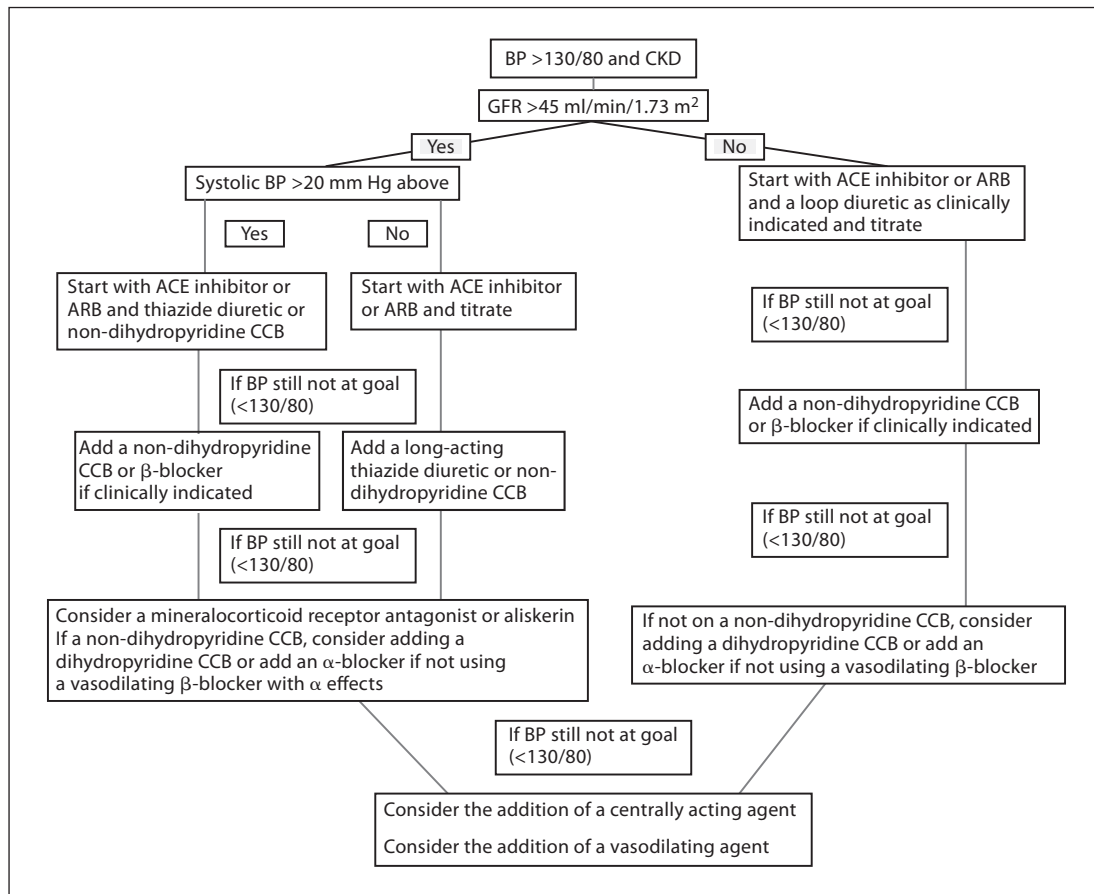
Calcium Channel Blockers

Calcium channel blockers (CCBs) are well-established blood pressure reduction agents in CKD. They can be used as second-line antihypertensive agents and are a good alternative for patients intolerant of ACE inhibitors and ARBs. They are proven safe and effective at reducing CKD progression and cardiovascular events when used in combination with other agents [45]. Of the two subclasses available, the non-dihydropyridines not only lower blood pressure, but decrease glomerular pressure and reduce proteinuria. Comparatively, the dihydropyridines reduce blood pressure, but have no effect on glomerular pressure and are inconsistent with the degree of reduction in proteinuria [46]. Treatment with either class of CCB in those with proteinuric nephropathies reduces proteinuria when coupled with an ACE inhibitor or an ARB. More importantly, CCBs will preserve renal function in both diabetics and non-diabetics with proteinuria [30, 43]. Synergism with other drug classes is an important feature. The ACE inhibitor trandolapril, and verapamil, a non-dihydropyridine, cause similar reductions in proteinuria. When verapamil and ramipril are combined, the level of protein reduction is nearly double when dosed for similar blood pressure reductions [46]. Thus, CCBs can be used either as monotherapy or to complement existing therapy in CKD hypertensive patients.

β-Blockers

Sympathetic over-activity in CKD contributes to the maintenance of hypertension; thus, β-blockers have a theoretical benefit in the treatment of hypertension in those with CKD. The most notable longitudinal data assessing CKD progression with a β-blocker is the African American Study of Kidney Disease (AASK) in which metoprolol was not as effective as ACE inhibitors in slowing GFR decline. However, metoprolol did have a reduced risk of ESRD and mortality benefit as compared to amlodipine [47]. Vasodilating β-blockers, labetalol and carvedilol, have been evaluated in hypertensive patients with renal impairment. While blood pressure reduction can be achieved, data are limited on the use of labetalol with regard to CKD progression and proteinuria [48]. Studies with carvedilol indicate that renal blood flow and GFR are preserved with reductions in microalbuminuria in both diabetic and non-diabetic hypertensives with microalbuminuria [49]. Carvedilol has a significant mortality benefit in ESRD patients with heart failure, but large prospective trials evaluating the use in CKD are lacking. Finally, the newest agent available, nebivolol, has proven to be safe in those with CKD stage 3 [50]. In animal models with kidney injury, nebivolol provides reductions in proteinuria and renal fibrosis [51]. Additional studies are needed to assess the role of β-blockers in CKD progression. Clearly, β-blockers play an important role in those with CVD and CKD, but they are not first-line agents and should be reserved for those with compelling indications.

Endothelin Antagonism

Endothelin has been implicated in CKD progression and podocyte injury; intervention has theoretical benefits. Two agents have been evaluated for use in hypertension: avosentan and darusentan [52]. The addition of avosentan in CKD stage 3 and 4 patients with diabetic

Fig. 1. Pharmacologic approach to hypertension management in CKD. BP = Blood pressure; CCB = calcium channel blocker; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker.

nephropathy as a complementary agent results in a significant reduction in proteinuria independent of decreased blood pressure. These findings have also been duplicated in non-diabetic CKD [53, 54]. The most notable adverse reaction is associated sodium and fluid retention that may lead to congestive heart failure; in fact, the ASCEND trial was prematurely ended for this reason. Additional studies evaluating CKD progression, mortality, and cardiovascular outcomes are needed before the role of endothelin antagonists are established.

α-Blockers

α-Blockers should not be considered as first-line therapy. However, they have a role in resistant hypertension by blocking vasoconstricting α-1 adrenoreceptors on vascular smooth muscles. Evidence supports the adjunctive role of the α-blocker doxazosin with ACE inhibitors, CCB, β-blockers, and diuretics in non-diabetic CKD patients in the Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA) whose blood pressure remained above 140/90 mm Hg. There was no apparent excess of heart failure among doxazosin users in that study, and plasma lipid profiles were improved [55]. However, when compared to chlorthalidone in ALLHAT, doxazosin had higher risks of heart failure with similar rates of stroke and combined CVD [56]. The decision to employ α-1 antagonists should balance these increased risks. Common adverse events include nasal congestion and

dizziness. α-Blockers do cause sodium retention, and diuretic therapy may need to be incorporated, but this may add to the orthostatic hypotensive effects of this class. In CKD patients treated with diuretics, doxazosin improves blood pressure [55].

Central Sympatholytic

Clonidine, the most widely used central sympatholytic, successfully reduces blood pressure. Clonidine stimulates both a2-adrenergic receptors and I1-imidazoline receptors in the rostral ventrolateral medulla nuclei resulting in decreased sympathetic outflow. Clonidine is typically administered orally or as a transdermal patch. Transdermal patches have several advantages that include continuous drug delivery, improved compliance, decreased rebound upon stopping, and decreased side effects including somnolence and dry mouth. Skin reactions are common with the transdermal patch. Sodium retention can occur with central sympatholytics, and diuretics may be required. Clonidine is generally considered to have neutral effects upon proteinuria.

Vasodilators

Two direct vasodilators, hydralazine and minoxidil, are available for blood pressure control. Both are considered fourth-line agents for resistant hypertension when hypertensive goals have not been reached with other agents. Despite the long history of experience with hydralazine, the effects of the agent on mortality, morbidity, and renal outcomes are poorly understood [57]. Notable reflexive tachycardia is associated with the use of hydralazine that can be controlled with β-blockers or a centrally acting α-agonist. When combined with a nitrate, significant reduction in mortality in Blacks with heart failure was seen, but this has not been specifically studied in the setting of CKD [58]. Minoxidil is another adjunctive agent in poorly responsive, severe hypertension associated with CKD. Minoxidil, while more efficacious in the degree of blood pressure reduction compared to hydralazine, has a more significant side effect profile [59]. Simultaneous administration of a diuretic with a β-blocker or a combined α/β-blocker is often required to control edema and mitigate the tachycardia associated with minoxidil use. Sodium retention following the start of minoxidil can be the cause of significant edema often resulting in temporary cessation of the medication. A loop diuretic will usually suffice, but the addition of metolazone is required in extreme cases [60].

Conclusion

Hypertension in the CKD population is an important clinical concern leading to increased risk of CKD progression and CVD mortality. Both non-pharmacologic and pharmacologic interventions are available to control and mitigate the associated increased risks. There is a wide range of therapeutic interventions clinicians can choose from, and therapy should be directed at achieving control of hypertension, keeping in mind the associated risk factors.

Disclosure Statement

There are no conflicts of interest.

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