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Hypertension with chronic kidney disease

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Abstract
Hypertension is a lifestyle disease affecting majority of population around the world. The prolonged elevation in blood pressure can damage the nephrons and subsequently lead to chronic renal failure. According to Joint National Committee in its 8th revision suggest Angiotensing receptor blockers or Angiotensin converting enzyme inhibitor as the first line drug, being a regulator of blood flow has shown favorable impact for a patient with hypertensive CKD. However, they may also produce few adverse drug reaction i.e. hyperkalemia, hypotension, intermittent claudication which needs medical attention. Acute renal failure is an ADR that has been reported by Indian Pharmacopoiea Commission. Being a drug that is supreme among all other antihypertensive agents which is safe in CKD, they can also cause renal damage. Hence, the data regarding the prescription, adherence and efficacy need to be analyzed.

Keywords: ACE inhibitors, ARBs, chronic kidney disease, hypertension

Introduction
Hypertension is a frequent finding in both acute and chronic kidney disease, particularly with glomerular or vascular disorders [1]

The pathogenesis and preferred treatment of hypertension vary with the type of renal disease and its duration. Progression of chronic kidney disease (CKD), as defined by a reduction in the glomerular filtration rate (GFR), occurs at a variable rate, ranging from less than 1 to more than 12 mL/min per 1.73 m2 per year, depending upon the level of blood pressure control, the degree of proteinuria, the previous rate of GFR decline, and the underlying kidney disease, including diabetes [2-6].

Pathogenesis of Hypertension in Kidney Disease
The pathogenesis of hypertension varies with the type of disease (eg, glomerular versus vascular) and with the duration of disease (acute versus chronic).

Acute glomerular disease
Patients with acute glomerular disease, such as poststreptococcal glomerulonephritis, tend to be volume expanded and edematous due to sodium retention [7]. As a result, the elevation in blood pressure is primarily due to fluid overload, as evidenced by suppression of the renin-angiotensin-aldosterone system and enhanced release of atrial natriuretic peptide [8]. Although these changes are most prominent with severe disease, the incidence of hypertension is increased even in patients with a normal serum creatinine concentration [9]. Both a familial predisposition to hypertension and subclinical volume expansion are thought to be important in this setting.

Experimental studies of the nephrotic syndrome or glomerulonephritis suggest that sodium retention in these disorders is due to increased reabsorption in the collecting tubules [10]. Two different abnormalities in collecting tubule function have been identified in glomerular disease, both of which could increase sodium reabsorption:

- Relative resistance to atrial natriuretic peptide due at least in part to more rapid degradation of the second messenger cyclic guanosine monophosphate (GMP) by the enzyme phosphodiesterase [9]. In an animal model of nephrotic syndrome, infusion of a phosphodiesterase inhibitor largely reverses this defect and restores the normal natriuretic response to volume expansion.
- Increased activity of the Na-K-ATPase pump in the cortical collecting tubule but not in other nephron segments [11]. This pump provides the energy for active sodium transport by pumping reabsorbed sodium out the cell into the peritubular capillary.

How these changes might be induced by the nephrotic syndrome or glomerulonephritis is not

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clear. They are not likely to be mediated by aldosterone, the secretion of which is reduced by volume expansion-mediated reductions in plasma renin activity [8].

Acute vascular disease
Hypertension is also common in acute vascular diseases, such as vasculitis or scleroderma renal crisis. In these settings, the elevation in blood pressure results from ischemia-induced activation of the renin-angiotensin system rather than volume expansion [13]. This difference in mechanism between glomerular and vascular disease may be of therapeutic importance.

Chronic kidney disease
Hypertension is present in approximately 80 to 85 percent of patients with CKD [13]. The prevalence of hypertension is elevated in patients with kidney damage and a normal glomerular filtration rate (GFR) and increases further as the GFR falls. Data from the Modification of Diet in Renal Disease Study, for example, showed that the prevalence of hypertension rose progressively from 65 to 95 percent as the GFR fell from 85 to 15 mL/min per 1.73 m2 [14]. As in patients without renal disease, the prevalence of hypertension is also higher in patients with higher body weight and in blacks. A variety of factors can contribute to the increased prevalence of hypertension in patients with CKD:

- Sodium retention is generally of primary importance, even though the degree of extracellular volume expansion may be insufficient to induce edema.
- Increased activity of the renin-angiotensin system is often responsible for at least part of the hypertension that persists after the restoration of normovolemia, particularly in patients with vascular disease since renal ischemia is a potent stimulus of renin secretion. Regional ischemia induced by scarring may also play a role.
- Hypertension can be a causative (eg, hypertensive nephrosclerosis) or contributory factor in the development of kidney disease.
- Hypertension may result from enhanced activity of the sympathetic nervous system [15]. The afferent signal may arise in part within the failing kidneys since it is not seen in patients who have undergone bilateral nephrectomy.
- Secondary hyperparathyroidism raises the intracellular calcium concentration, which can lead to vasoconstriction and hypertension [16]. Lowering parathyroid hormone secretion by the chronic administration of an active vitamin D analog can reduce both intracellular calcium and the systemic blood pressure.
- Treatment with erythropoietin may increase blood pressure, an effect that is in part related to the degree of elevation in the hematocrit.
- Impaired nitric oxide synthesis and endothelium-mediated vasodilatation has been demonstrated in patients with uremia [17]. Although the mechanisms are unclear, potential explanations include reduced nitric oxide availability due to a state of increased oxidative stress or cofactor deficiency-induced uncoupling of nitric oxide synthase.
- In addition to the factors that can raise the mean arterial pressure, two other factors may be important:
- Patients with end-stage renal disease (ESRD) are more likely to have an increase in central pulse pressure and isolated systolic hypertension [18]. Why this occurs is incompletely understood, but increased aortic stiffness

probably plays an important role.
- Patients with CKD may not demonstrate the normal nocturnal decline in blood pressure (such patients are called "nondippers"), a possible risk factor for hypertensive complications [19].

Treatment of Hypertension in Acute Glomerular or Vascular Disease
In view of the differences in pathogenesis, the mechanism and treatment of hypertension vary in patients with acute glomerular and vascular disease.
We prefer initial therapy with diuretics (particularly loop diuretics in patients with reduced glomerular filtration rates [GFRs]) to treat hypertension in patients with acute glomerular disease and edema since diuretics will also treat the hypervolemia and associated edema. If the hypertension persists, angiotensin-converting enzyme (ACE) inhibitors may be effective, even in the low-renin hypertension often In comparison with acute glomerulonephritis, we prefer ACE inhibitors as initial antihypertensive therapy in patients with acute vascular diseases since renal ischemia leads to activation of the renin-angiotensin system. Strong data support this approach in patients with scleroderma renal crisis, and we prefer angiotensin inhibition in polyarteritis nodosa and other vasculitides, as well. associated with acute glomerulonephritis [20]. This response may reflect activation of tissue renin-angiotensin systems, such as that in the kidney, vascular endothelium, and adrenal gland.

Treatment of Hypertension in Chronic Kidney Disease
Treatment of even mild hypertension is important in patients with CKD to protect against both progressive renal function loss and cardiovascular disease, the incidence of which is increased with mild to moderate CKD.

Goal blood pressure
Several observational studies have found that 24-hour ambulatory blood pressure is a stronger predictor of end-stage renal disease (ESRD), cardiovascular disease, and death than office-based measurements [21, 22]. In addition to blood pressure control, specific goals related to a reduction in urinary protein excretion have been formulated to slow the rate of progression of proteinuric CKD:

- We suggest a proteinuria goal of less than 1000 mg/day.
- In patients who are initially nephrotic and in whom this goal is unobtainable, we attempt to achieve a minimum reduction in proteinuria of at least 50 to 60 percent from baseline values **plus** protein excretion less than 3.5 g/day.

Importance of Proteinuria and Blood Pressure Control
Multiple studies in animals and humans have shown that progression of a variety of chronic kidney diseases may be largely due to secondary hemodynamic and metabolic factors, rather than the activity of the underlying disorder. The major histologic manifestations of these secondary causes of renal injury are interstitial fibrosis and focal segmental glomerulosclerosis (called secondary FSGS), which are superimposed upon any primary renal injury that may be present. [6]

Benefits of sodium restriction
Sodium restriction enhances the effect of many antihypertensive drugs. This is also true in patients with CKD, most of whom, as discussed below, are treated with

angiotensin inhibitors to slow disease progression. The potential benefits of sodium restriction were demonstrated in a crossover trial of 52 patients with proteinuric CKD (mean protein excretion of 1.6 g/day and mean creatinine clearance of 70mL/min), all of whom were taking lisinopril [23]. Four treatments were given in random order, each for six weeks: a low-sodium diet with placebo, a low-sodium diet with valsartan, a regular-sodium diet with placebo, and a regular-sodium diet with valsartan. Compared with a regular-sodium diet (mean urinary sodium excretion 184 mmol/day), a low-sodium diet (mean 106 mmol/day) decreased blood pressure to a greater degree than addition of valsartan (11 versus 3 mmHg). Addition of valsartan had a minimal additional effect (2 mmHg) on blood pressure beyond a low-sodium diet.

Use of diuretics and goal of therapy
Because of the reduction in renal function, higher doses of diuretics are typically required in patients with CKD who are usually volume expanded even in the absence of edema. Thiazide diuretics become less effective when the glomerular filtration rate (GFR) is less than 30 mL/min [24]. In such patients, loop diuretics are preferred as initial therapy. Torsemide, which has a longer duration of action than furosemide, may be preferred.

If edema persists, a thiazide diuretic can be added to the loop diuretic. The rationale for combined therapy is that most of the fluid leaving the loop of Henle after the administration of a loop diuretic is reabsorbed in the distal tubule, the site of action of thiazide diuretics. Thus, thiazides have an enhanced diuretic effect in patients treated with a loop diuretic.

The efficacy of combined diuretic therapy has been illustrated in a report of five patients with CKD (serum creatinine 2.3 to 4.9 mg/dL [203 to 433 micromol/L]) who had an inadequate response to 160 to 240 mg/day of furosemide in divided doses [25]. Increasing the furosemide dose had only limited efficacy. By contrast, the addition of 25 to 50 mg twice daily of hydrochlorothiazide produced a marked diuresis. Chlorthalidone is generally preferred to hydrochlorothiazide because it is more potent and has a longer duration of action [26].

In edematous patients with CKD, the initial goal is removal of edema. However, if hypertension persists once edema has been removed, plasma volume expansion may still be present and contribute to the hypertension. Thus, when diuretics are used to treat hypertension in patients with CKD without overt edema, the dose and/or frequency of diuretic should be increased when the antihypertensive response is inadequate.

Diuretic therapy should be increased until one of two endpoints is reached: the blood pressure goal is achieved or the patient has attained "dry weight," which, in the presence of persistent hypertension, is defined as the weight at which further fluid loss leads to symptoms (cramps, fatigue, orthostatic hypotension) or leads to decreased tissue perfusion as evidenced by an otherwise unexplained elevation in the serum creatinine concentration.

Choice of antihypertensive therapy
Attainment of goal blood pressure in patients with CKD typically requires multidrug therapy [27]. As with goal blood pressure discussed above, the choice of agent depends in part upon whether or not the patients have proteinuria.

Sequence of antihypertensive therapy in proteinuric CKD
In patients with CKD who have proteinuria, defined as a protein excretion greater than or equal to 500 mg/day,we recommend angiotensin inhibitors as first-line therapy. We suggest diuretics and non-dihydropyridine calcium channel blockers (eg, diltiazem, verapamil) as second-line and third-line agents, although loop diuretics would be a first-line therapy with angiotensin inhibitors in patients with edema. When using angiotensin inhibitors and diuretics in combination as first-line therapy, we titrate the dose of the second drug slowly to avoid hypotension since diuretics enhance the antihypertensive effect of angiotensin inhibitors.

First-line therapy in proteinuric CKD
High-quality evidence favors the use of an ACE inhibitor or angiotensin II receptor blocker (ARB) as first-line therapy in patients with proteinuric CKD (ie, protein excretion greater than 500 mg/day) because, in addition to lowering the blood pressure, these drugs slow the rate of progression of CKD.
Common side effects of angiotensin inhibition in patients with CKD include an acute reduction in GFR and hyperkalemia. In addition, both ACE inhibitors and ARBs are contraindicated in pregnancy.

Second- and third-line therapy in proteinuric CKD
Our suggestions for second- and third-line antihypertensive therapy in patients with proteinuric CKD depend upon whether overt volume overload is present:

- In patients with CKD who have proteinuria and **edema**, initial therapy usually consists of both an angiotensin inhibitor for renal protection and a loop diuretic for edema, which, by increasing renin release, may also enhance the antihypertensive effect of the angiotensin inhibitor. The use of a diuretic may also restore the antiproteinuric effect of ACE inhibitor therapy in patients without an adequate antiproteinuric response since volume expansion reduces angiotensin II release and makes the blood pressure less dependent upon angiotensin II [28, 29].

If further antihypertensive therapy is required, we suggest a non-dihydropyridine calcium channel blocker (eg, diltiazem or verapamil) since these drugs also lower proteinuria. By contrast, dihydropyridines (eg, amlodipine) have little or no effect on protein excretion [30].

Sequence of antihypertensive therapy in nonproteinuric CKD
In contrast to their renoprotective effects in proteinuric CKD, angiotensin inhibitors do **not** appear to be more beneficial than other antihypertensive agents in patients with nonproteinuric CKD [31].

In patients with nonproteinuric CKD, we suggest the following sequence, which depends upon the presence or absence of edema:

- In patients **with edema**, we prefer initial therapy with a loop diuretic. Once the edema is controlled, an angiotensin inhibitor or a dihydropyridine calcium channel blocker (eg, amlodipine) can be added in either order if hypertension persists.

- In patients **without edema**, we start with an angiotensin inhibitor and then add a dihydropyridine calcium channel blocker (eg, amlodipine) as second-line therapy. This approach has not been studied specifically in patients with nonproteinuric CKD. Rather, it is extrapolated from our recommendations for hypertensive patients in general, which are guided by the findings of the Avoiding

Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial. If needed, we suggest adding a diuretic as third-line therapy.

Possible benefit from nocturnal therapy
The average nocturnal blood pressure is approximately 15 percent lower than daytime values. Failure of the blood pressure to fall by at least 10 percent during sleep is called "nondipping" and is one of the strongest predictors of adverse cardiovascular outcomes. Many patients with CKD are nondippers [22]. Shifting one antihypertensive medication from the morning to the evening can restore the normal nocturnal blood pressure dip in these patients [32].

The effect of shifting at least one antihypertensive medication from the morning to the evening on the incidence of cardiovascular disease was evaluated in an open-label randomized trial of 661 patients with CKD (defined as an eGFR below 60 mL/min per 1.73 m2 or an albumin-to-creatinine ratio greater than 30 mg/g on two separate occasions) who were randomly assigned to take all medications in the morning or to take at least one at bedtime [33]. At baseline, the two groups had similar mean ambulatory blood pressure(135/77 versus 135/79 mmHg) and proportion of nondippers (68 versus 65 percent). The only medication classes permitted to be taken at bedtime were ACE inhibitors, ARBs, or long-acting calcium channel blockers.

Maintenance dialysis
The major therapeutic goal in hypertensive dialysis patients is gradual fluid removal to attain "dry weight."

Renin-Angiotensin System Inhibitors
A number of trials have identified a preferential benefit of renin-angiotensin system (RAS) inhibitors in reducing proteinuria, compared with other antihypertensive drugs. The rationale behind these studies is the observation that protein excretion varies directly with the intraglomerular pressure in animals with structural glomerular disease [34].

In addition to the reduction in intraglomerular pressure, a variety of other mechanisms may contribute to RAS inhibitor-induced reductions in proteinuria. These include:

- Direct improvement in the permselective properties of the glomerulus by ACE inhibitors, independent of changes in glomerular hemodynamics [35, 36]. The following findings support this hypothesis:
- Protein excretion progressively declines over weeks to several months, whereas the hemodynamic effects of ACE inhibition occur rapidly and are then stable [37].
- Acute administration of angiotensin II does not reverse the antiproteinuric effect, despite inducing renal and systemic vasoconstriction, and increasing intraglomerular pressure [38].
- In transgenic rats, overexpression of the angiotensin II receptor (type 1) in glomerular podocytes results in significant proteinuria, foot process effacement, and glomerulosclerosis [39].
- Angiotensin II reduces the expression of nephrin, a major component of the podocyte slit pore membrane and an important contributor to the glomerular filtration barrier [40]. By contrast, nephrin expression is increased by ACE inhibitor therapy [41].
- ACE inhibitors have an antifibrotic effect, which could contribute to the slowing of renal disease progression.

- The fall in protein excretion induced by RAS inhibitors (and some other antihypertensive drugs described below) may be associated with a reduction in serum lipid levels, which may reduce both the risk of systemic atherosclerosis and the rate of renal disease progression.

ACE inhibitors and ARBs have important side effects in patients with CKD, including the potential to induce hyperkalemia. The risk is low if the glomerular filtration rate is greater than 40 mL/min per 1.73 m2 and the initial serum potassium is in the low-normal range, and even lower if a diuretic is also given [18]. They can also acutely reduce the glomerular filtration rate, particularly if the patient is hypovolemic.

ACE inhibitors
ACE inhibitors generally reduce protein excretion by about 30 to 35 percent in patients with nondiabetic or diabetic CKD [42-46]. The antiproteinuric effect is most prominent in patients who are on a low-sodium diet or who are treated with diuretics since relative volume depletion results in greater angiotensin II dependence of the glomerular microcirculation [44, 47].

It is unclear whether the ACE inhibitor dose associated with a maximal antihypertensive effect is the same as that required for an optimal antiproteinuric effect. This issue was addressed in a study of 23 proteinuric patients with nondiabetic renal disease who were given increasing doses of spirapril for maximal antihypertensive effect (median dose of 6mg/day), as assessed by ambulatory blood pressure monitoring [48]. This dose reduced proteinuria from a mean of 2.56 to 1.73 g/day. An additional increase of spirapril to a supramaximal dose (median dose of 12 mg/day) failed to further decrease either blood pressure or proteinuria. In contrast to these findings, other studies have reported a dissociation between the doses required for optimal antihypertensive and antiproteinuric effects, suggesting that the amounts necessary for these two benefits are likely to vary among patients [49].

Angiotensin II receptor blockers
The antiproteinuric effect of angiotensin II receptor blockers (ARBs) has been demonstrated in patients with diabetic and nondiabetic CKD. Their effect on slowing progression of GFR decline was best demonstrated in diabetic renal disease. It seems likely that they will have a similar renoprotective effect as ACE inhibitors in nondiabetic CKD but supportive data are limited [50].

Studies in humans have found that ARBs are as effective as ACE inhibitors in reducing protein excretion in patients with CKD [42, 51-53]. In a 2008 meta-analysis of 49 randomized trials (mostly small), the reduction in proteinuria at 5 to 12 months was similar with ARBs and ACE inhibitors (ratio of means 1.08, 95% CI 0.96-1.22) [42].

As with ACE inhibition, there appears to be a dose effect, with greater reduction of proteinuria at higher (even supramaximal) doses in both nondiabetic and diabetic patients [54-57]. In the SMART trial, for example, 269 patients with proteinuria greater than 1 g/daydespite seven weeks of the maximum approved dose of candesartan (16 mg/day) were randomly assigned to candesartan at a dose of 16, 64, or 128 mg/day [57]. Patients who received 128 mg/day had a significantly greater reduction in proteinuria at 30 weeks compared with those who received 16 mg/day (mean difference 33 percent). The blood pressure was not different between groups. Although hyperkalemia required the

withdrawal of 11 patients from the trial, there was no difference in the incidence of hyperkalemia between groups. Further studies of the efficacy and safety are required before such high-dose therapy can be recommended.

ACE inhibitor plus ARB

The reduction in proteinuria appears to be greater when ACE inhibitors are used in combination with ARBs than with either drug alone, although no study has compared combination therapy with doubling the dose of a single agent [42]. However, it has not been proven that combination therapy improves renal outcomes and adverse effects may be more common.

Conclusion

The angiotensin converting enzyme inhibitors and angiotensin receptor blockers are widely used to treat hypertension with CKD. According to JNC8, the drug is prescribed for patient for early stage of CKD. The adverse drug reaction of these drugs are rare, however can aggravate the disease progress. Thus, ACE inhibitors and ARBs need to be administered to patients with cautions.

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