HYPERTENSION AND THE KIDNEY

Hypertension in Patients with Chronic Kidney Disease

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ABSTRACT

The prevalence of hypertension in chronic kidney disease (CKD) patients exceeds that of the general population. Uncontrolled hypertension plays a significant role in progression to end stage renal disease and results in increased cardiovascular morbidity and mortality. A complex interplay between various pathophysiologic mechanisms is responsible for the development of hypertension in this patient population. The major factors being extracellular volume overload, increased endothelin-1 release and excess renin-angiotensin-aldosterone system and sympathetic nervous system activity. Dietary and lifestyle modifications have synergistic effects to drug therapy in the control of hypertension. There is no single blood pressure target that is optimal for all CKD patients. It is important to individualize the treatment depending on age, the severity of albuminuria, and comorbidities. Drugs blocking the renin-angiotensin-aldosterone system are the recommended first-line antihypertensive agents for most CKD patients. Intradialytic hypertension may be prevented by individualizing the dialysis prescription and using nondialyzable antihypertensives. New onset of hypertension in the elderly or new onset of difficult to control hypertension in a previously well controlled hypertensive patient should prompt the work up for atherosclerotic renal vascular disease.

Keywords: Aldosterone, Angiotensin, Chronic, Hypertension, Kidney, Renin.

INTRODUCTION AND EPIDEMIOLOGY

Hypertension is an important cause of chronic kidney disease (CKD) and plays a significant role in its progression. On the contrary, hypertension is highly prevalent in CKD patients, which, if uncontrolled, results in high cardiovascular morbidity and mortality of this particular population. Data from the Indian Screening and Early Evaluation of Kidney Disease (SEEK) study show that prevalence of hypertension and CKD in the SEEK cohort is 43.5 and 17.2% respectively, and that the prevalence of hypertension in patients with CKD exceeds that of the general population (64.5% in CKD

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population *vs* 41.9% in non-CKD population).[1] The prevalence of hypertension is elevated in patients with kidney damage and a normal glomerular filtration rate, and increases further as the glomerular filtration rate falls. Data from the modification of diet in renal disease study, e.g., showed that the prevalence of hypertension rose progressively from 65 to 95%, as the glomerular filtration rate fell from 85 to 15 ml/min per 1.73 m^2.[2]

PATHOPHYSIOLOGY OF HYPERTENSION IN CHRONIC KIDNEY DISEASE

Although the kidney is involved in essential or primary hypertension, its insufficiency causes high blood pressure (BP), contributing to 2 to 5% of all cases of hypertension or half the cases of all forms of secondary hypertension.[3] The pathogenesis of hypertension related to CKD is complex and multifactorial, mainly in the late stages of the renal disease (Table 1).

Sodium and Volume Status

Hypertension in CKD is related to both increases in cardiac output and increased peripheral vascular resistance (Flow Chart 1). Positive sodium balance can affect either component and achieving sodium balance remains a primary target of managing hypertension in patients with CKD. Although alteration of either cardiac output or vascular resistance would initially be expected to affect BP in a concordant direction, a healthy kidney can adapt to short-term changes in BP to restore normotension. An increase in renal sodium excretion is the expected response to increased BP in healthy individuals. This pressure natriuresis allows for the restoration of extracellular volume and BP following an increase in cardiac output. However, in CKD, this homeostatic mechanism is impaired, and the

Table 1: Pathophysiologic mechanisms of hypertension in CKD

1. Extracellular volume overload
2. Excess renin-angiotensin-aldosterone system activity
3. Excess sympathetic nervous system activity
4. Increased endothelin-1 release
5. Decreased activity of renal dopaminergic system
6. Reduced renalase levels
7. Oxidative stress
8. High arginine vasopressin levels
9. Secondary hyperparathyroidism
10. Drugs: Erythropoietin
11. High levels of endogenous digitalis-like factors (EDLFs)

Flow Chart 1: Interplay between various pathophysiologic mechanisms causing hypertension in CKD
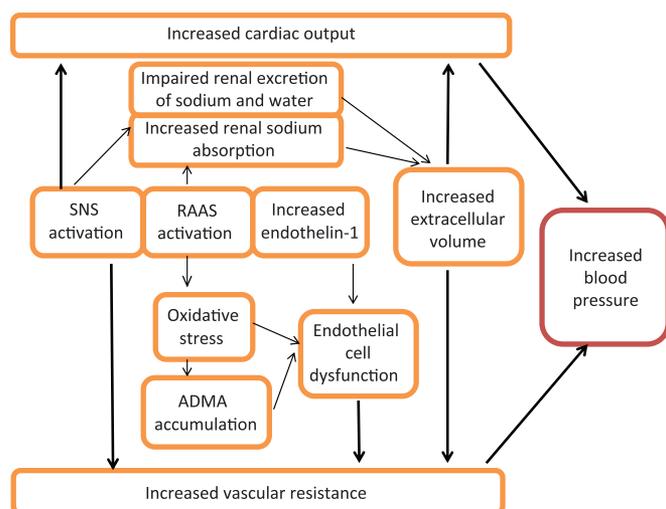
kidney fails to sufficiently excrete sodium loads. In CKD and end-stage renal disease (ESRD), it is hypothesized that an increase in cardiac output initiates the increase in BP, but ultimately, an increase in vascular resistance sustains the BP elevation.[4,5] Accordingly, addressing both volume status and the degree of peripheral vasoconstriction are necessary to control BP in these patient populations. The effects on BP related to sodium intake ("salt sensitivity") are augmented with the progression of renal disease.[6]

Role of Renin-Angiotensin-Aldosterone System

The renin-angiotensin-aldosterone system (RAAS) has local and systemic effects that control BP by altering renal sodium reabsorption and vascular resistance. Renin released from juxtaglomerular cells cleaves angiotensinogen to Angiotensin I (Ang I), which is ultimately converted into Angiotensin II (Ang II) by the angiotensin-converting enzyme (ACE). Angiotensin II causes vasoconstriction upon binding to angiotensin type 1 (AT1) receptors in vascular smooth muscle cells (VSMCs). Angiotensin II increases proximal tubular reabsorption of sodium and stimulates aldosterone release from the adrenal gland, which is responsible for further sodium reabsorption in the distal nephron. Although this proposed sequence applies to the levels and activity of RAAS components in the plasma, there is also local RAAS activity. In CKD, mainly secondary to vascular disease, diabetes, or polycystic kidney disease, in areas of renal injury or ischemia, there is a greater production of local and intrarenal Ang II, which then exacerbates systemic hypertension.[7,8]

Role of Renin and Aldosterone

Following the use of an ACE inhibitor or angiotensin receptor blocker (ARB), serum aldosterone levels typically decrease. However, in up to 40% of patients receiving these medications, aldosterone levels can rebound to pretreatment levels through a process referred to as "aldosterone escape."[9] Aldosterone increases BP via enhanced sodium reabsorption in the distal nephron, but it is also likely involved in vasoconstriction via interaction with the Ang II receptor.[10]

In contrast to the expected decrease in aldosterone following ACE inhibitor or ARB use, renin levels and plasma renin activity (PRA) are expected to increase as a result of the blockade in events downstream from the main actions of renin. It has been demonstrated *in vivo* that Ang II can be generated by enzymes other than ACE.[11] This presents a potential obstacle to complete RAAS blockade if renin levels are sufficiently elevated in the context of an ACE inhibitor or ARB administration, and the possible use of add-on therapy to ACE inhibitors or ARB with a direct renin inhibitor.

Sympathetic Nervous System and Hypertension

The sympathetic nervous system activity is hyperactive in CKD. The mechanisms responsible are thought to be related to an increased renal nerve activity. The kidney possesses baroreceptors and chemoreceptors that increase renal nerve firing secondary to pressure changes or metabolites produced in response to ischemia or uremia. Afferent signals from the diseased kidney are transmitted to the vasomotor control center in the brain increasing the BP.[12] Renal sympathetic nerve stimulation increases proximal tubular reabsorption of sodium and water.[13] In addition, the systemic effects of the SNS include increased cardiac output and vasoconstriction. Also, ESRD patients have increased muscle sympathetic nerve activity (MSNA) related to increases in RAAS activation.

Renal Dopaminergic System

Dopamine has a natriuretic effect by inhibiting Na-K-ATPase in proximal tubular segments. Patients suffering from CKD have reduced urinary excretion of dopamine and decreased activity of the renal dopaminergic system, thereby decreasing the sodium excretion.[14]

Renalase

Renalase is an amine oxidase, secreted into the circulation by kidneys, which contributes to catecholamine degradation. Patients with ESRD on hemodialysis have nearly undetectable levels, supporting the role of adequate renal function to maintain its presence.[15]

Oxidative Stress and Nitric Oxide Antagonism

Oxidative stress is a state of imbalance between oxidants and antioxidants in favor of the oxidants, which is detrimental to health.[16] In CKD, excess oxidant molecules

may directly stimulate vascular contraction or reduce nitric oxide, resulting in hypertension.[17] The endothelial-derived nitric oxide that causes vasodilatation is inhibited by increased levels of asymmetric dimethylarginine (ADMA) in CKD.[18]

Arginine Vasopressin

Arginine vasopressin (AVP) is a peptide released from the hypothalamus in response to increases in plasma osmolarity. Receptors for vasopressin include the V1a, V1b, and V2 receptors. Traditionally, V1a receptors were believed to be responsible for vasoconstriction via VSMC, and V2 receptors responsible for water reabsorption through the insertion of aquaporin channels in the collecting duct of the nephron. In CKD patients, AVP levels are higher and increase in response to osmolarity changes with a greater slope than in controls.[19]

Secondary Hyperparathyroidism

An association between increased BP and elevated serum parathyroid hormone (PTH) levels has been demonstrated in CKD patients. This could be due to higher cytosolic calcium in the subjects with elevated PTH levels.[20]

Drug Related: Erythropoietin-Stimulating Agents

Proposed mechanisms of erythropoietin-stimulating agent (ESA)-induced hypertension include increased endothelin-1 (ET-1) release and increased sensitivity to Ang II and adrenergic stimuli.[21]

Role of Endogenous Digitalis–like Factors

Endogenous digitalis–like factors (EDLFs) are substances, produced in the adrenal gland or in the hypothalamus, that inhibit the Na-K-ATPase in cell membranes, and also have natriuretic and vasoconstrictor properties.[22] The high levels of EDLFs in CKD, secondary to an increased sodium content and expanded blood volume, may also contribute to the hypertension in these patients.[23]

MANAGEMENT OF HYPERTENSION IN CHRONIC KIDNEY DISEASE

The major goals of controlling BP in CKD patients are to prevent the progression to ESRD and to reduce cardiovascular complications. Dietary and lifestyle modifications have synergistic effects to drug therapy and hence play a very important role. Patient education and regular counseling are pivotal in achieving the goals.

Salt Restriction and Lifestyle Modifications

Recent kidney disease improving global outcomes (KDIGO) guidelines recommend lowering salt intake to less than 90 mmol (<2 g) per day of sodium (corresponding to 5 g of sodium chloride), unless contraindicated.[24] The rationale of salt restriction is that it directly has an effect on BP reduction in CKD patients and also facilitates the antiproteinuric effects of RAAS-blocking drugs.[25] High-salt diet blunts kidney autoregulation, which exposes the glomerulus to higher filtration pressures.

Cigarette smoking can result in progression of CKD by worsening the hypertension through sympathetic nervous system activation and also by increasing the plasma endothelin levels.[26] The oxidative stress due to smoking can produce endothelial dysfunction and may result in the increase of BP. It is very important to counsel the patients regarding the consequences of smoking on renal function and to ensure strict abstinence.

Weight loss in CKD patients may result in reduction of proteinuria and better BP control. It also improves the long-term cardiovascular outcomes.[27]

Pharmacological Therapy

Antihypertensive drugs become mandatory as renal function worsens and patients usually need two or more drugs for hypertension control. There is no single BP target that is optimal for all CKD patients. It is important to individualize the treatment depending on age, the severity of albuminuria, and comorbidities. In general, the available evidence indicates that in CKD patients without albuminuria, the target BP should be ≤140 mm Hg systolic and ≤90 mm Hg diastolic. However, in most patients with an albumin excretion rate of ≥30 mg/24 h, a lower target of ≤130 mm Hg systolic and ≤80 mm Hg diastolic is suggested.[28] It is important to keep in mind that lowering the BP <120/70 mm Hg, mainly in older patients, can increase the progression of renal failure and enhance the probability of a cardiovascular event.

RAAS Blockade

Drugs blocking the RAAS system are the recommended first-line antihypertensive agents for most CKD patients, with the most commonly used agents being ACE inhibitors or ARBs. These agents should be titrated to the maximum recommended doses in order to achieve the greatest RAAS inhibition. The benefits of ACE inhibitors and ARB in CKD are much beyond hypertension control. They reduce the intraglomerular hydrostatic pressure, proteinuria and also the levels of Ang II.[29] Angiotensin II is an octapeptide with proinflammatory and profibrotic actions. It stimulates the production of transforming growth factor-β, which results in extracellular matrix deposition. As a result, these drugs also reduce cardiovascular morbidity and mortality. Patients must be closely followed up for hyperkalemia and for any rise in

serum creatinine after initiation of these drugs or every time the drug dose is increased. A slight increase of the creatinine level (<25% from baseline) is acceptable, as it reflects a decrease of the glomerular hyperfiltration and is beneficial in the long run. A significant increase of the creatinine level (>25% from baseline) is suggestive of volume depletion (concomitant use of diuretics) or of bilateral renal artery stenosis. Treating physician must counsel the patient regarding the need to avoid potassium-rich foods. Other hyperkalemic drugs, such as aldosterone antagonists or nonsteroid anti-inflammatory drugs, need to be avoided.

Limesh et al[30] devised a scoring system for RAAS blockade (RASB) wherein the amount of an ARB and ACE inhibitor was scored as the dose of that agent used in each patient divided by the maximum recommended antihypertensive dose (Table 2). For example, if a patient received 80 mg of enalapril and 50 mg of losartan simultaneously, RASB score in that patient would be 2.5 (80/40 + 50/100 or 2 + 0.5). The rate of change in estimated glomerular filtration rate (eGFR) was -1.5 ± 5.0 ml/min/1.73 m^2 per year in patients who received RASB (N = 168) and -6.0 ± 5.4 in those who did not (N = 97) (p < 0.001). In a subgroup of patients who received RASB, the incidence of decline of eGFR >50% was 17.8% in the low-dose RASB group (N = 84, RASB score 0.63 ± 0.38) and 4.8% in the high-dose group (N = 84, RASB score 2.5 ± 0.7) (p = 0.001). RASB was associated with significantly better renoprotection in CKD of diverse etiology, even in nonproteinuric diseases. This effect appeared to be dose-dependent, with higher supramaximal doses exhibiting better renoprotection than the lower conventional doses.

OTHER DRUGS

Single antihypertensive drug might not be sufficient for BP control in most CKD patients. The choice of another antihypertensive agent should be individualized according to patient condition and comorbidities (Flow Chart 2).
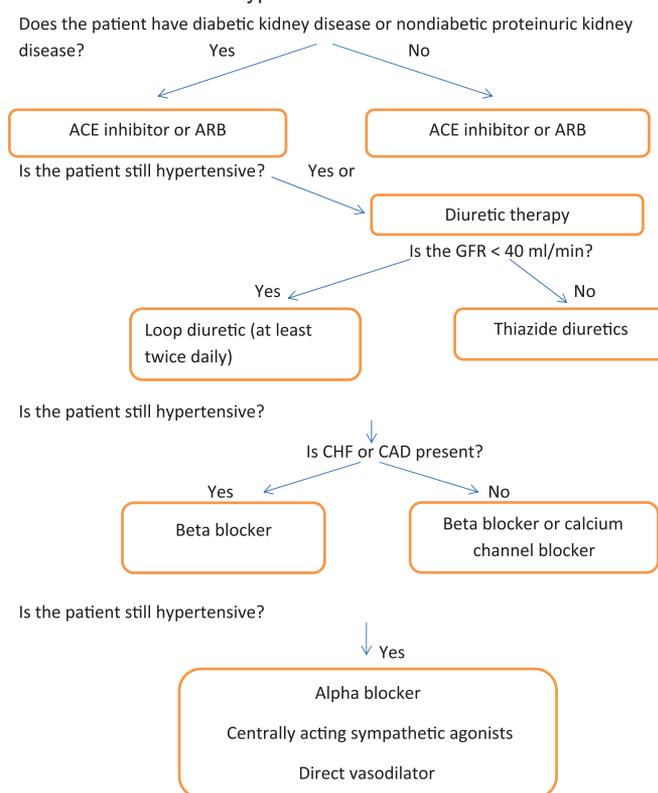
Diuretics

Diuretics are crucial drugs in controlling hypertension, as volume overload contributes significantly to high BP

Table 2: Definition of maximum dose of renin-angiotensin system blocking agent

Maximum dose defined for individual ARB agents were: Losartan 100, valsartan 320, telmisartan 80, irbesartan 300, and olmesartan 40 mg
Maximum dose defined for individual ACE inhibitor agents were: Enalapril 40, ramipril 20 and lisinopril 40 mg

Flow Chart 2: Algorithm for pharmacologic treatment of hypertension in CKD

as CKD progresses. Thiazides are usually used when the GFR > 30 ml/min/1.73 m^2 body surface area, being ineffective beyond this level. Loop diuretics such as indapamide or furosemide may be useful in advanced stages of CKD. It is important to dose loop diuretics at least twice daily and to consider increased doses in patients with significantly impaired GFR in order to optimize delivery of the drug to the site of action. Diuretics diminish sodium reabsorption, thereby decreasing blood volume and hence stimulate renin production. Hence, the effect of ACE inhibitors and ARB is intensified when diuretics are added along with them. On the contrary, care must be taken not to overdose, as diuretics are known to cause dehydration (more common during summer), acute interstitial nephritis, and directly reduce the GFR by increased delivery of solute to the loop of Henle resulting in tubuloglomerular feedback. Thiazides can cause hyponatremia, which is an important cause of falls in elderly people. Potassium-sparing agents should be used carefully, particularly if the patient is on ACE inhibitor or ARB, as they may result in life-threatening hyperkalemia.[31]

Dual Blockade of the Renin-Angiotensin-Aldosterone System

Currently, there is no conclusive evidence favoring combined RAAS-blockade in diabetic or nondiabetic

CKD. The sub-analysis of ONTARGET study reported an accelerated decline in estimated GFR (eGFR) and higher dialysis and mortality rates in a combined ARB and ACE inhibitor (ACE-I) therapy group.[32] However, there was a definite improvement in BP and proteinuria. Because RAAS blockade in the ONTARGET study was not titrated against BP or proteinuria level, generalizing the study conclusions to other populations or to other indications for RAAS blockade therapy may be inappropriate.

Calcium Channel Blockers

Calcium channel blockers (CCBs) may be used as an add-on therapy if the patient has angina or heart failure secondary to diastolic dysfunction.[31] Dihydropyridines such as amlodipine and nifidepine dilate only afferent arteriole, as they act only on L-type calcium channels, thereby resulting in glomerular hypertension, whereas cilnidipine also acts on N-type calcium channels that are present in nerve terminals, resulting in dilation of both afferent and efferent arterioles and hence reduces glomerular pressure and thereby proteinuria.[33] Hence, it is preferable to use cilnidipine in proteinuric CKD patients. Also, nondihydropyridine CCB may be added to an ACE inhibitor or ARB in patients with proteinuria. On the contrary, they should be avoided in patients with second and third-degree heart block or with congestive heart failure due to systolic dysfunction.[31]

Beta-Adrenergic Blockers

Chronic kidney disease is commonly associated with ischemic heart disease and hence beta-adrenergic blockers are particularly indicated in patients with prior angina or myocardial infarction or with atrial tachycardia or fibrillation.[31] Atenolol and sotalol are water soluble and excreted by the kidney, and thus may accumulate in CKD, whereas the lipid-soluble ones (propranolol, metoprolol) are metabolized in the liver and may be associated with central nervous system side effects. Both types can cause hyperkalemia. Carvedilol is a beta-adrenergic blocker with nonselective α1 activity that has beneficial effects on lipid profile, has an antioxidant activity, and also reduces albumin excretion.[34,35]

Aldosterone Antagonists

The addition of aldosterone antagonists with Ang II antagonists may be justified by the so-called aldosterone escape phenomenon.[9] The advantage of this add-on therapy is attributed to the antifibrotic and antihypertensive properties of aldosterone antagonists and there is also some reduction in proteinuria. However, the risk of hyperkalemia is increased.

Renin Inhibitors

Renin inhibitors block the conversion of angiotensinogen to Ang I. Aliskiren has been shown to reduce BP and albuminuria in type 2 diabetic patients, when given alone or in combination with losartan.[36,37] The ALTITUDE study was carefully designed to compare the effects of combination treatment of aliskiren on top of ACE inhibitors or ARB versus ACE or ARB alone on cardiovascular and renal outcomes in 8561 patients with type 2 diabetes. The trial was prematurely terminated due to renal complications, hyperkalemia, and hypotension in the aliskiren group.[38] Further studies are needed to determine whether aliskerin, alone or in combination, is able to reduce hard renal and cardiovascular end-points in CKD patients.

The α-adrenergic blockers, centrally acting sympathetic agonists, or the potent vasodilator minoxidil are used only if BP control was still not achieved with the previous described classes of antihypertensive drugs. Minoxidil must always be associated with a beta-adrenergic blocker and a diuretic in order to control the reflex tachycardia and the fluid retention induced by the former.[31]

α-adrenergic blockers may cause postural hypotension and should be used with caution.

Intradialytic Hypertension

There is no uniform definition of intradialytic hypertension (IDH). Intradialytic hypertension is defined as an increase in BP during or immediately after hemodialysis, which results in postdialysis hypertension. The frequency of IDH has been reported to be around 10 to 15% of the hemodialysis patients.[39,40] In addition to the pathophysiologic factors mentioned in Table 1, certain other factors may be responsible for IDH. Dialysate-specific factors such as high sodium and high calcium dialysate or a low potassium dialysate have been proposed to cause IDH. Antihypertensive drug removal (particularly metoprolol and atenolol) during dialysis and high doses of erythropoietin result in IDH.

Prevention of Intradialytic Hypertension

Adequate care should be taken to make sure that patients are at their ideal dry weight. Routine withholding of antihypertensive medications prior to hemodialysis should be avoided. In addition, antihypertensive agents (carvedilol, labetalol, amlodipine, ARB, clonidine, hydralazine), which are not removed during dialysis, should be preferred.[41] The dialysis prescription should be individualized to achieve adequate sodium solute removal. Routine use of high calcium dialysate should be avoided unless clinically indicated. The lowest possible dose of erythropoietin necessary should be used and

preferably subcutaneous dosing rather than intravenous dosing should be considered.

Hypertension in Chronic Kidney Disease Secondary to Atherosclerotic Renovascular Disease

Chronic kidney disease that results from atherosclerotic renal artery stenosis is frequently called ischemic nephropathy.[42] Findings that suggest the presence of renovascular disease include as follows:

- Severe hypertension that may be treatment resistant;
- An acute rise in serum creatinine following the administration of ACE inhibitors or ARB. This usually, but not invariably, resolves after withdrawal of the drug;
- Significant variability of serum creatinine concentration that may be due to changes in volume status (fluctuating renal parameters);
- Recurrent episodes of flash pulmonary edema and/ or refractory heart failure;
- Deterioration of renal function after placement of an endovascular aortic stent graft;
- New onset of hypertension in the elderly or new onset of difficult to control hypertension in a hypertensive patient who had a good control so far.

All patients should receive medical therapy to control their hypertension in addition to routine CKD care and surveillance. In addition to medical therapy and risk factor reduction, some but not all patients should undergo revascularization, depending upon the hemodynamic severity and likely recoverability of kidney function.

Results from studies of selected patients with ischemic nephropathy subjected to revascularization suggest that 25 to 30% will recover kidney function to a meaningful degree, sometimes avoiding progression to ESRD and/or the need for renal replacement therapy. Approximately 50% will have a little immediate change in kidney function but will "stabilize," whereas approximately 20% will have a progressive deterioration of kidney function, possibly related to the procedure.[43]

CONCLUSION

Hypertension is a prevalent comorbidity associated with CKD from the early stages to ESRD. A better understanding of the physiopathologic mechanisms is important to improve our treatment strategies. Irrespective of the etiology of CKD, controlling hypertension helps prevent its progression to ESRD. The target BP for CKD patients that optimally reduces the risk for both renal and cardiovascular outcomes remains unknown, but subjects with increased proteinuria derive more benefit from aggressive BP lowering. Salt restriction and lifestyle changes intensify the effects of pharmacologic antihypertensive agents, which will be required in most CKD patients. Inhibitors of RAAS appear to be the most beneficial in CKD patients with proteinuria. Intradialytic hypertension may be prevented by individualizing the dialysis prescription and using nondialyzable antihypertensives.

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