

**INTRODUCTION**

Chronic kidney disease (CKD) is a worldwide public health problem. The prevalence of CKD has steadily increased over the past two decades in US. The prevalence of CKD in India is largely undetermined. A recent study from western India showed CKD was found in 20.93% and eGFR  $<60$  mL/min/1.73 m<sup>2</sup> was noted in 8.29% of participants.

In India, it has been recently estimated that the age-adjusted incidence rate of end stage renal disease (ESRD) to be 229 per million population (pmp), and >100,000 new patients enter renal replacement programs annually. Hypertension (HTN) has been reported to occur in 85% to 95% of patients with CKD (stages 3–5). The relationship between HTN and CKD is cyclic in nature. Uncontrolled HTN, a risk factor for developing CKD, is associated with a more rapid progression of CKD, and is the second leading cause of ESRD in the U.S. Meanwhile, progressive renal disease can exacerbate uncontrolled HTN due to volume expansion and increased systemic vascular resistance. Multiple guidelines discuss the importance of lowering blood pressure (BP) to slow the progression of renal disease and reduce cardiovascular morbidity and mortality. However, in order to achieve and maintain adequate BP control, most patients with CKD require combination of antihypertensive agents; often up to three or four different medication classes.

**PATHOPHYSIOLOGY**

HTN - related mechanisms that are involved in the progression of renal damage include the systemic BP load, the degree to which it is transmitted to the renal microvasculature (i.e., renal autoregulation), and local susceptibility factors to barotrauma, which is the degree of damage for any degree of BP load. Among these proteinuria, glomerular hypertrophy, fibrogenic mediators, genetic factors, and age are the most important. Proteinuria is also important factor in progression of CKD. Therefore, drugs targeting proteinuria benefit in controlling HTN and overall retarding the progression of CKD.

The potential benefits of lower BP include a decreased risk of both cardiovascular disease (CVD) and progression of CKD. To assess the likely benefit in a given patient, the clinician needs to consider such issues as the prior rate of CKD progression, the expected course of the specific disease, the level of urinary albumin excretion and the presence or absence of other risks of CVD. Potential

adverse effects generic to treatment used to lower BP include decreases in cerebral perfusion (contributing to dizziness, confusion and falls) and acute deterioration in kidney function.

**BLOOD PRESSURE PATTERN IN CKD**

Masked uncontrolled HTN is more prevalent among individuals with CKD with rates ranging from 40% to 70%. The likelihood of having masked uncontrolled HTN rises in proportion to kidney dysfunction and the extent of proteinuria. Without an assessment of ambulatory or home BP, masked uncontrolled HTN will be missed, and this group of individuals is at a high risk for both cardiovascular events and initiation of dialysis. In healthy individuals, BP falls by 10% to 20% during sleep. A fall in nocturnal BP characterises a normal circadian pattern of BP. Individuals whose BP fails to drop or, instead, rises at night are at an increased risk of death compared with dippers. In addition, mean nocturnal systolic BP predicts ESRD or death, and non-dipping is associated with the severity of interstitial fibrosis and tubular atrophy. Therefore, the findings from Hermida and colleagues, that dipping patterns are blunted in individuals with CKD is a concern and particularly relevant for management of HTN in patients with CKD.

**SCREENING FOR SECONDARY CAUSES OF HYPERTENSION IN SPECIFIC GROUP OF CKD PATIENTS**

1. Renovascular hypertension- In patients in whom fibromuscular dysplasia (FMD) is suspected, an MR angiogram of the kidney should be performed. Routine screening for atherosclerotic renovascular disease is not recommended.
2. Pheochromocytoma- Plasma-free metanephrines levels may be falsely high in advanced CKD. In patients with CKD 5, plasma catecholamines (epinephrine and norepinephrine) may be a more appropriate screening test for pheochromocytoma.
3. Primary aldosteronism- 24-hr urine aldosterone  $>12$   $\mu$ g with a suppressed plasma renin activity in the setting of high dietary sodium intake along with MR of abdomen.
4. Glomerulonephritis- Urine microscopy should be performed in any patient who has sudden worsening of hypertension or renal functions.

**TARGETS OF BP CONTROL**

It is recommended that adults with CKD (diabetic/non-

diabetics) with urine albumin excretion <30 mg/day whose office BP is consistently >140mmHg systolic or >90mmHg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently <140 mm Hg systolic and <90 mm Hg diastolic. Also it is suggested that CKD (diabetic/non-diabetic) patients with urine albumin excretion >30mg/day whose office BP is consistently >130mmHg systolic or >80mmHg diastolic be treated with BP-lowering drugs to maintain a BP that is consistently <130 mm Hg systolic and <80 mm Hg diastolic. Furthermore, guidelines also recommend ACE-I or ARBs to be used as first line agents for such patients.

The recent publication of the Systolic Blood Pressure Intervention Trial (SPRINT) has again opened the debate on optimal BP targets. This trial, enriched with patients of CKD and the elderly, indicated superior cardiovascular and survival outcomes from a target systolic BP < 120 mm Hg versus the usual systolic BP target of < 140 mm Hg. At many levels, from primary care to subspecialty providers including nephrologists, there are calls for modifying current guidelines to consider new lower BP targets.

## MANAGEMENT

Individualise BP targets and agents according to age, co-existent CVD and other co-morbidities, risk of progression of CKD, presence or absence of retinopathy (in CKD patients with diabetes) and tolerance of treatment.

### Non pharmacological interventions to control blood pressure

Lifestyle modification offers the potential to lower BP in a simple, inexpensive, effective fashion while also improving a range of other outcomes (e.g., changes in lipid levels resulting from diet and exercise and liver function through moderation of alcohol intake). Various observational studies show that weight-loss strategies reduce BP in CKD patients. A BMI of 20-25 is recommended.

High dietary salt intake not only exacerbates HTN in patients with CKD but also has the potential to directly worsen kidney function. Rats receiving a high salt diet show sustained increases in kidney levels of transforming growth factor- $\beta$ , polypeptides associated with kidney fibrosis. High salt diet blunts kidney autoregulation, which exposes the glomerulus to higher filtration pressures. Over time, the high glomerular filtration pressure leads to glomerular sclerosis and nephron loss. Lowering salt intake reduces BP in the general population. In CKD patients with reduced GFR, salt retention is associated with an increase in BP. Lowering of salt intake to 90 mmol (2 g) per day of sodium (corresponding to 5 g of sodium chloride) is advisable unless there is contraindications.

Two larger studies from the US Renal Data System found that CKD 5 patients on dialysis who are sedentary have a higher risk of death than those who are active. Therefore undertaking an exercise program compatible with cardiovascular health and tolerance, aiming for at least 30minutes 5 times per week is recommended. Consumption of alcohol in moderation with cessation of

cigarette smoking is advisable, though there is no direct data regarding this.

## Pharmacological treatment

Data has shown that in CKD patients three or more agents are frequently needed for BP control. With the exception of ARBs or ACE-Is in CKD patients with high levels of urinary albumin or protein excretion, there is no strong evidence to support the preferential use of any particular agent(s) in controlling BP in CKD; nor are there data to guide the clinician in the choice of second- and third-line medications. CKD patients have relatively poor cardiovascular outcomes relating to their non dipper and reverse dipper status. At least one of the antihypertensive drug is suggested to be given at night. Also, to have maximum adherence and less of side effects, combination of drugs to have minimum pill burden is recommended whenever possible.

## RAAS BLOCKERS

ACE-Is and ARBs should be used with caution or even avoided in certain CKD subgroups, particularly in patients with bilateral renal-artery stenosis or with intravascular fluid depletion, because of the risk of a large reduction in GFR. The normal capacity of the kidney to auto-regulate GFR in the face of fluctuations in BP is impaired in CKD and further compromised by the use of ACE-Is or ARBs. If hyperkalemia occurs with them, then possible measures include lowering of potassium in diet, reducing dose or switching to fosinopril or trandolapril or adding potassium losing diuretic. The elderly diabetic patients should also be enquired about postural hypotension which may be increased by vasodilators and diuretics via volume depletion. Antihypertensive and anti-proteinuric effects of ACE-Is and ARBs are complemented by dietary sodium restriction or administration of diuretics. Co-administration of beta-blockers and calcium-channel blockers with ACE-Is or ARBs is also acceptable. Aldosterone antagonists like spironolactone and eplerenone have been shown to decrease urine albumin excretion when added to ACE-I or ARB therapy. Hyperkalemia is potential side-effect and plasma potassium levels and kidney function should be monitored closely during the introduction of aldosterone antagonists and during intercurrent illnesses, particularly those associated with a risk of GFR reduction, as occurs with dehydration.

## DIURETICS

Salt and water retention are major factors contributing to high BP in CKD patients and to morbidity and mortality through systemic or pulmonary edema. Thus, diuretics potentially have an important role in the control of hypertension in this clinical setting. Thiazides or thiazide like agents like chlorthalidone or indapamide are recommended as addition to ACE-I or ARBs for BP control especially in setting of edema. As the GFR falls below about 30–50ml/min/1.73m<sup>2</sup>, thiazides might not be effective in reducing edema. Their dose needs to be increased or switch to a loop diuretic like frusemide or

660 torsemide in patients with CKD 4, particularly if the BP is becoming resistant to therapy.

### CCBS

The major subclasses are the dihydropyridines (e.g., amlodipine, nifedipine, cilnidipine and lercanidipine), the non-dihydro-pyridine benzothiazepines (e.g., diltiazem) and the phenyl-alkylamines (e.g., verapamil). Studies have shown anti-proteinuric effect of cilnidipine. However, fluid retention, seen particularly with dihydropyridines, can be problematic in patients with CKD.

### BETA BLOCKERS

In patients with CKD, the accumulation of beta-blockers or active metabolites could exacerbate concentration-dependent side effects such as brady-arrhythmias. Such accumulation occurs with atenolol and bisoprolol, but not carvedilol, propranolol, or metoprolol. They can be combined with ACE-I or ARBs but should not be combined with verapamil or diltiazem as such combination can lead to life threatening brady-arrhythmias.

### ALFA BLOCKERS

Alpha-blockers reduce the symptoms of benign prostatic hyperplasia, which may be a co-morbidity to consider in older men with CKD. In general, alpha-blockers are not considered a first-line choice because of the common side effects of postural hypotension, tachycardia and headache. They should be commenced at a low dosage to avoid a first-dose hypotensive reaction.

### CENTRALLY ACTING ALPHA-ADRENERGIC AGONISTS

They decrease sympathetic outflow from brain and cause vasodilatation. The main agents in use are methyldopa, clonidine, and moxonidine. They are often required for BP control when other agents fail. Their important side-effect is fluid retention which often requires diuretic use.

### DIRECT VASODILATORS

Minoxidil is needed in cases of resistant hypertension. Side effects often limit its use. Hydralazine is used in hypertensive emergencies.

### HYPERTENSION IN DIALYSIS POPULATION

There have been no trials establishing an optimal level of BP control in patients on dialysis, and guidelines extrapolate trials in other high risk patients (e.g. diabetics). UK renal association guidelines suggest a BP goal of < 130/80 mmHg in both HD (post-dialysis) and PD patients.

Achieving BP targets in patients on HD is difficult:

1. HTN is multifactorial.
2. Volume overload is a major problem.
3. Timing of measurement of BP is controversial (pre or post-dialysis). Interdialytic measurement or ambulatory blood pressure monitoring (ABPM), are probably more useful but not easy to achieve in practice.
4. Compliance with salt and water intake and polypharmacy are major issues.

It is possible to achieve excellent BP control without the use of any drugs by normalising extracellular fluid volume and maintaining dry weight with ultrafiltration on dialysis. Salt and fluid intake between dialysis sessions must be kept low. Doses of antihypertensives should be kept low to avoid hypotension.

### BP CONTROL IN RENAL TRANSPLANT RECIPIENTS

HTN is well recognised as an important risk factor for both decline in transplant kidney function and development of CVD and an increased risk of graft loss and all-cause mortality. The aetiology of HTN in renal transplant is multifactorial:

- Native diseased kidneys
- Calcineurin inhibitors (cyclosporine, tacrolimus)
- Steroids
- Pretransplant HTN
- Donor HTN
- Transplant renal artery stenosis
- Chronic allograft injury

It is suggested that adult kidney transplant recipients whose office BP is consistently >130mmHg systolic or >80mmHg diastolic be treated to maintain a BP that is consistently <130mmHg systolic and <80mmHg diastolic, irrespective of the level of urine albumin excretion. In adult kidney transplant recipients, choose a BP-lowering agent after taking into account the time after transplantation, use of calcineurin inhibitors, presence or absence of persistent albuminuria, and other co-morbid conditions.

### CONCLUSION

No single BP target is optimal for all CKD patients. It is encouraged to individualise treatment depending on age, the severity of albuminuria, and co-morbidities. In general, the available evidence indicates that in CKD patients without albuminuria the target BP should be  $\leq 140$  mmHg systolic and  $\leq 90$  mmHg diastolic. However, in most patients with an albumin excretion rate of  $\geq 30$  mg/day (i.e., those with both micro- and macroalbuminuria), a lower target of  $\leq 130$  mmHg systolic and  $\leq 80$  mmHg diastolic is suggested. In achieving BP control, the value of lifestyle changes and the need for multiple pharmacological agents is acknowledged. Use of agents that block the RAAS is recommended or suggested in all patients with an albumin excretion rate of  $\geq 30$  mg/day. Recommendations are almost identical in CKD patients with and without diabetes.

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