Chapter

95 Hypertension in Patients with Renal Failure

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Chronic kidney disease, earlier known as chronic renal failure, is a major global public health problem, of high incidence and prevalence, prohibitive cost of treatment, particularly in a developing country like India, and poor outcomes. CKD is in epidemic proportion in India. It is estimated that every 5th patient with high blood pressure and every 7th patient with diabetes mellitus will develop CKD, and over the next 20 years, in India alone 25 million people will develop kidney failure. To create public awareness and as a wake up call for the pending crisis, the first ever World Kidney Day was celebrated on 9th March 2006, by nephrologists all over India.

Hypertension and CKD

Hypertension, present in more than 70-80% patients with CKD, is a risk factor for faster progression of kidney failure and greater cardiovascular morbidity and mortality. Substantial evidence indicates that HTN is a major contributor to the development of End Stage Renal Disease in most patients[1].

Which Comes First - Hypertension Or Kidney Disease?

It is a vicious cycle. With the possible exception of African-Americans, hypertension, in and of itself, is contributing to kidney disease, but it's not a "cause" of kidney disease itself. The most common secondary cause of hypertension is chronic kidney disease[2].

Significance of Glomerular Hypertension and Progression of CKD—The Dilemma of Nephrosclerosis

Hypertensive kidney disease or nephrosclerosis—this term is used by clinicians, when renal damage is thought to be secondary to essential hypertension. Systemic and intra-glomerular hypertension leads to changes in peri-glomerular vasculature. In a known hypertensive, uncontrolled or partially-controlled hypertension, the presence of co-morbid condition like Metabolic Syndrome, may lead to changes of nephrosclerosis, which may progress further to end stage renal disease[3].

Evaluation of Patients with Hypertension in CKD

Appropriate evaluation is the first step for achieving treatment goals. Several comprehensive guidelines, like JNC-7 and K/DOQI clinical practice guideline for CKD are clinically relevant and globally accepted[4-6].

First Confirm the Diagnosis of Chronic Kidney Disease

1. Assessment for the presence of CKD, defined as kidney damage as confirmed, by kidney biopsy or markers of damage > Proteinuria, shrunken kidneys, Uremia or GFR<60ml/1.73m^2 for >3 months.
2. Etiology of CKD: Type of CKD is important as some classes of antihypertensive agents are 'preferred agents' for certain type of CKD. Clinical relevant classification of diagnosis of CKD includes:
   - i. Diabetic kidney disease 30%
   - ii. Non-diabetic kidney diseases
     - a. Glomerular diseases - Chr. glomerulonephritis 20%
     - b. Chr. Tubulo Interstitial Nephritis - Chr. Pyelonephritis 10%
     - c. ADPKD 6%
     - d. Vascular disease HTN, RAS, Vasculitis 34%
3. Physical Examination: Special Consideration For Measurement of blood pressure in CKD patients.

Accurate measurement of blood pressure in CKD is especially important because JNC-7, identified CKD as a compelling indication for more aggressive anti hypertensive therapy, because of higher risk of CVD in CKD than in general population[11].

CKD patients differ from general population in having following pattern of high blood pressure:

1. *Altered Circadian Blood Pressure Rhythm—'Non-dipping pattern'.*

   It means a blunted sleep-related fall in mean SBP/DBP of less than 10%. This pattern is usually seen in CKD and connotes very high risk for end organ damage[12].

2. *Nocturnal Hypertension*

   High blood pressure drug sleep and normal during wakefulness. It places an already high risk patient into an ever higher risk level.

3. *Resistant Hypertension*

BP Measurement Techniques

i. Casual BP (CBP)
ii. Self-measured blood pressure (SMBP)
iii. Ambulatory BP monitoring (ABPM)[13]

Ambulatory BP monitoring is a popular diagnostic tool that has a close correlation with end organ damage-including progression of kidney disease and cardio and cerebro vascular outcomes in patients with CKD[14,15]. ABPM is becoming more widely used, yet important limitations remain such as expense of equipment, infrastructure, trained personnel and reimbursement.

Laboratory Evaluation

i. Serum Creatinine to estimate GFR
ii. Urinalysis/Proteinuria—24 hrs urinary albumin (UAE) or Spot Albumin to creatinine ratio (ACR)
iii. Coexistence of Renal Artery Disease and other identifiable causes of hypertension.

Evaluation for Renal Artery Disease

Renal Artery Disease is a cause of CKD and Hypertension both, and can be present in patients with other causes of CKD, such as diabetes or hypertensive nephrosclerosis. Renovascular hypertension (RVHC) is defined as systemic hypertension due to hemodynamically significant renal artery diseases, that is >75% stenosis of the lumen by renal angiography. Early intervention is required in all such cases, as it represents a potentially reversible form of hypertension and chronic kidney disease[10] (Table 1).

Table 1: Clinical clues predicting the RAD as the cause of hypertension and CKD

1. Age < 30 yrs or > 55 yr
2. Accelerated/malignant hypertension
3. Resistant hypertension to an appropriate three drug regimen
4. History of smoking
5. Systolic/diastolic renal Artery Bruit
6. Flash pulmonary edema
7. Decline in GFR with ACE/ARBs—in B/L stenosis.
8. Evidence of asymmetrical contracted kidney

Goals of Antihypertensive Therapy for HTN in CKD

In addition to dietary and lifestyle modification, Anti hypertensive therapy in CKD is used to:

1. Lower blood pressure
2. Slow progression of kidney disease to end stage renal disease
3. Reduce cardiovascular morbidity and mortality.

Dietary and Therapeutic Lifestyle Modification

Clinical and experimental studies clearly show that there is extreme salt-sensitivity of Blood pressure in patients with CKD and sodium retention leads to chronic expansion of ECF volume[15]. Based on the result of DASH and DASH sodium trials[16], NKF/DOQI Group recommended that most patients with CKD should take a low sodium diet of 100 m mol or 2.4 gm/day. Cessation of smoking, reduction of weight in obese and low cholesterol diet are other recommendations.

Use of Antihypertensive Agents in CKD: Guidelines and Recommendations

NKF-working group, taking into consideration the ALLHAT trial, ALLHAT CKD sub-group, and certain key clinical trials results included in JNC-7 recommendations, has formulated, General Guidelines[17-19].

Salient features of which are:

1. Target B.P. for CVD risk reduction in CKD should be <130/80 mmHg
2. Patients with CKD should be considered in the "highest risk" group for CVD, irrespective of cause of CKD.

3. All antihypertensive agents are effective and can be used to lower BP in CKD.
4. Multi drug regimen will be necessary in most patients with CKD to achieve therapeutic goal.
5. 'Preferred agent' for CKD should be used first.
6. Diuretics should be included in the antihypertensive regime, in most patients.

Preferred Class of Antihypertensive Agents

A "preferred agent" is a class of antihypertensive that has beneficial effect, to reduce the risk of CVD or slow the progression of kidney disease by mechanism, other than lowering blood pressure. A preferred agent should be the initial anti-hypertensive agent to be used for specific type of CVD/CKD.

Management of Hypertension in Diabetic Kidney Disease

Diabetes Mellitus is the most common cause of kidney failure in developed countries and is among the most common causes in the rest of the world. The natural history of diabetic kidney disease is characterized by the onset of micro-albuminuria, progress to macro-albuminuria then to massive proteinuria, Hypertension, declining GFR-↑ BUand S. Creatinine levels, and high risk of cardiovascular disease. Most patients with diabetic kidney disease are hypertensive. Onset of HTN in Type 1 DM, signifies the onset of kidney disease. In contrast, HTN in Type2 DM may occur in absence of kidney disease[7].

SUMMARY OF CLINICAL TRIALS AND CURRENT RECOMMENDATIONS: DIABETIC KIDNEY DISEASE

1. Most patients with diabetic kidney disease are hypertensive and higher levels of blood pressure are associated with more rapid progression to CKD (RENAAL, NKF-EDG)[20,21].
2. Multiple antihypertensive agents are usually required to reach target BP (IDNT)[22].
3. ACE Inhibitors and ARBs are effective in slowing the progression of Kidney disease with micro-albuminuria and Macroalbuminuria in Type 1 and Type 2 DM (AIPRI)[23,24].
4. ACE Inhibitors, ARBs and non-dihydrophyridine calcium channel blockers have a greater anti proteinuric effect than other antihypertensive classes[25,26].
5. Diuretics may potentiate the beneficial affects of ACE Inhibitors and ARBs (ALLHAT)[27].

Management of Hypertension in Non-Diabetic Kidney Disease

Non-diabetic kidney diseases include glomerular disease other than diabetes, vascular disease, other than Renal artery disease, tubulointerstitial nephropathies (Chr. Pyelonephritis, ADPKD). Level of proteinuria, is essential to the evaluation because of its important diagnostic, prognostic and therapeutic implications[8,9]. Glomerular disease are characterised by higher level and early onset of proteinuria than other diseases. Higher level of proteinuria are associated with faster progression of kidney diseases and increased risk of CVD[28].

SUMMARY OF CLINICAL TRIALS AND CURRENT RECOMMENDATIONS: NON-DIABETIC KIDNEY DISEASE

1. Most patients with non-diabetic kidney diseases are hypertensive (AIPRI, REIN, and MDRD Trials)
2. Higher SBP is more important than DBP or high pulse pressure for kidney disease progression (MRFIT, SHEP Trials)[29-31].
3. ACE Inhibitors are more effective than others in slowing the progression of non-diabetic kidney disease and beneficial effect is directly proportional to the level of proteinuria (AIPRD, COOPERATE)[32,33].
4. Diuretics may potentiate the beneficial effects of ACE Inhibitors and ARBs (AASK Trials)[34].
5. Calcium channel blockers are less effective than other agents in slowing progression of non-diabetic kidney disease with proteinuria (AASK, MDRD-Trials)[35] (Table 2).

PREFERRED CLASSES OF ANTIHYPERTENSIVES

Angiotensin-converting Enzyme Inhibitors and ARBs in CKD

ACE inhibitors and ARBs are preferred agents for diabetic kidney disease and non-diabetic kidney disease with significant proteinuria. They lower blood pressure, reduce proteinuria and slow the progress of kidney disease by 'Class Effect' mechanism in addition to their antihypertensive and antiproteinuric effects. ACE lnhibitors and ARBs can be used safely in most patient with CKD[38]. ACE inhibitors and ARBs have generally similar effects on BP, urinary protein excretion and slow progress of kidney disease and can be used as alternative for each other or combined with each other to lower the BP[39-41]. All the guidelines, worldwide advocate that maximal dosage, have more beneficial effects on kidney

Table 2: Recommendation for hypertension and antihypertensive agents in diabetic and non-diabetic kidney disease

	Diabetic kidney disease	*Non-diabetic kidney disease*
Target BP < 130/80	Add Diuretic first then CCB and β blockers	If initiated on ACE/ARB-add diuretic → CCB → β blockers
Diet and lifestyle modification	Sodium intake < 2.4 gm/day BMI < 25 kg/m^2	Sodium intake < 2.4 gm/day BMI < 25 kg/m^2
Albuminuria		
i. Microalbuminuria Albumin creatinine ratio = 30-300 mg/gm	ACE or ARB	Stage 1-3 = Thiazide diuretics Stage 4-5 = Loop diuretics
ii. Macroalbuminuria Albumin creatinine ratio ≥ 300 mg/gm	ACE for Type I DM ARB for Type II DM	ACE or ARB or Both in moderate to high dosages
iii. Significant proteinuria ≥ 500-1000 mg/gm	Lower target BP goal Increase dosage of ACE/ARB → Combine ACE+ARB → Add other agents	Lower SBP goal < 120/75 Increase dosage of ACE/ARB →Combine ACE+ARB →Add other agents

disease progression than low to moderate dosages, as prescribed till recently[42-45].

Adverse Effects

Beside dry cough and angioedema most common side effect especially in CKD patients—decrease in GFR, hypotension and hyperkalemia have to be monitored and treatment of disease is required. C/I— Absolutely contraindicated in Pregnancy—in 2nd and 3rd trimester.

Diuretics in CKD

Diuretics are useful in most patient, with CKD, they reduce ECF volume, lower BP, potentiate effects of ACE inhibitors/ARBs and other antihypertensive agents and reduce the risk of CVD in CKD. Selection of diuretics depends on level of GFR and ECF volume status.

a. Thiazide diuretics—used in stage 1-3 of CKD, when GFR > 30 ml/mt
b. Loop diuretics—Effective in all stages of CKD-GFR < 20 ml/mt
c. Potassium sparing diuretics—Avoided in CKD, high chance of hyperkalemia in CKD, more so if given with ACE or ARBs.

Patients monitoring in required for ↓ GFR, hypertension, hypokalemia and other electrolyte imbalances.

Diuretic Resistance

Failure to respond to adequately to a diuretic regimen in CKD may be due to increased tabular re-absorption of sodium and a high dietary sodium intake. A sodium excretion of >100 mmol/day suggests excessive dietary sodium intake[36].

Calcium Channel Blockers

The most preferred drug, after ACEI/ARBs and diuretics are non-dihydropyridine calcium channel antagonist verapamil and Dilitazem. Especially if the UAE is >300 ml/day, regardless of kidney function they reduce proteinuria, slow progression of renal failure, in addition to potent BP lowering effect[37].

Beta Blockers

In early stage CKD, certain β-blockers, like carvedilol and labetolol have vasodilating and anti-oxidant effects. In GEMINI trial, vasodilating beta blocker prevented development of microalbuminuria to a greater extent than the non-vasodilating ones. In multi drug regime, usually required for adequate BP control in CKD, ACEI +ARBs+ diuretic+ CCB may also require β-blocker.

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