Management of Hypertension in Chronic Kidney Disease: Consensus Statement by an Expert Panel of Indian Nephrologists

Georgi Abraham¹, KN Arun², N Gopalakrishnan³, S Renuka⁴, Dilip Kumar Pahari⁵, Pradeep Deshpande⁶, Rajan Isaacs⁷, Deodatta Shripad Chafekar⁸, Vijay Kher⁹, Alan Fernandes Almeida¹⁰, Vinay Sakhuja¹¹, Sankaran Sundar¹², Sanjeev Gulati¹³, Abi Abraham¹⁴, R Padmanaban¹⁵

Executive Summary

A 15-member panel comprising Indian nephrologists reviewed literature evidence on the complex association between hypertension and chronic kidney disease (CKD) and discussed strategies to manage hypertension in patients with CKD. The panel also discussed and debated the need for a checklist to gauge the risk of CKD occurrence in hypertensive individuals.

This consensus document aims to serve as a guide for the management of hypertension in CKD patients in India. A few salient points that emerged in this consensus are as follows:

- The cause-and-effect relationship between hypertension and CKD varies from one ethnic group to another. Therefore, the findings from different studies/ethnic groups cannot be extrapolated to the Indian context.
- Hypertension as a cause of kidney disease in India requires further study.
- Blood pressure, cholesterol, and estimated glomerular filtration rate are the three important parameters that should be evaluated while screening hypertensive patients for the presence of CKD.
- There is a need for intensive blood pressure targets in hypertensive patients, though the targets need to be individualized.
- Support staff and nurses measuring blood pressure should be thoroughly trained on accurate measurement of blood pressure.
- More than 2–3 antihypertensive agents may be required to lower blood pressure targets in patients with CKD.
- Weight control is crucial in patients with CKD, especially during the first three months after transplantation.

Background and Introduction

Hypertension has been recognized as a major factor responsible for a decline in kidney function in patients with diabetic and nondiabetic kidney disease. On the other hand, among patients with chronic kidney disease (CKD), high blood pressure may develop early during the course of the disease and contribute to adverse outcomes. Thus, hypertension can be a cause or a consequence of CKD.¹ Blood pressure control is an integral component in the care of patients with CKD.
Chronic Kidney Disease: An Overview

Definition and stages

According to the 2012 KDIGO clinical practice guidelines, CKD is defined as ‘abnormalities of kidney structure or function, present for >3 months, with implications for health.’ Further, the 2012 KDIGO guidelines recommend that CKD be staged based on the cause, glomerular filtration rate (GFR) category (Box 1), and albuminuria category (Box 2).

Prevalence of CKD: Global and Indian Data

Chronic kidney disease is a major public health concern worldwide with regard to the number of individuals affected and therapeutic costs involved. According to the results of the 2013 Global Burden of Disease Study, CKD contributed to 956,200 deaths, a 134% increase from 1990. Studies have reported that CKD affects >10% of the population in several countries and >50% of high-risk subpopulations. In developed countries, CKD affects nearly 7% of all individuals aged ≥30 years, which translates to greater than 70 million individuals. Furthermore, the prevalence of CKD increases with age and exceeds 20% in individuals aged more than 60 years and 35% in individuals aged more than 70 years. Globally, it has been estimated that more than 1.4 million individuals with ESRD receive renal replacement therapy with dialysis or transplantation.

Data on the prevalence of CKD in India are limited, since the glomerular filtration rate estimating equation and the Modification of Diet in Renal Disease (MDRD) formula have not been validated in the Indian population. Hence, different criteria are used to diagnose CKD in India. According to recent estimates from the International Society of Nephrology’s Kidney Disease Data Center (ISN-KDDC), the prevalence of CKD in India was 16.8%, using the Chronic Kidney Disease–Epidemiology Collaboration Equation (CKD–EPI). According to several other studies, the prevalence of CKD in India ranges from 6.3% to 17.2% (using the MDRD formula; Table 1). In India, diabetic nephropathy contributes to 30%
of cases of chronic renal failure, while hypertensive nephropathy and chronic pyelonephritis, each contribute to 10% cases of chronic renal failure.  

**Predictive risk factors involved in CKD**

Factors that predict the risk of CKD can be categorized into susceptibility factors, initiation factors, and progression factors. Susceptibility factors are those that increase the susceptibility to kidney damage and include older age, family history of CKD, reduced kidney mass, low birth weight, and low income or educational level. Initiation factors refer to factors that directly initiate kidney damage and include diabetes mellitus, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, and drug toxicity. Progression factors are those that worsen kidney damage and lead to a faster decline in kidney function after kidney damage has started. Examples of such factors include higher level of proteinuria, higher blood pressure, poor glycemic control in diabetes, and smoking.  

**Prognosis of CKD**

According to the 2012 KDIGO guidelines, it is important to identify the cause, GFR category, albuminuria category, and presence of other risk factors and comorbid conditions, to predict the prognosis of CKD. A heat map illustrating the prognosis of CKD, based on the GFR and albuminuria categories, is depicted in Figure 1. 

**Hypertension: A Cause and Consequence of CKD**

**Association between hypertension and CKD**

Hypertension is strongly associated with CKD. Several large, prospective, observational trials conducted in the general population have demonstrated that hypertension is a strong independent risk factor for ESRD and contributes to the disease itself, or most commonly, to its progression.

In the Multiple Risk Factor Intervention Trial, stage 4 hypertension (systolic blood pressure [SBP] >210 mmHg or diastolic blood pressure [DBP] >120 mmHg) compared to optimal blood pressure (SBP/DBP <120/80 mmHg) was associated with a 20-fold higher relative risk for ESRD. A 17-year follow-up study by Tozawa et al. has demonstrated that high normal blood pressure and mild, moderate, or severe hypertension, when compared to optimal blood pressure, are independent risk factors for ESRD in men and women. The study, which included 46,881 men and 51,878 women undergoing dialysis, categorized blood pressure as optimal (110±6/68±6 mmHg), normal (121±4/75±6 mmHg), high normal (131±4/79±6 mmHg), mild hypertension (142±8/86±7 mmHg), moderate hypertension (160±11/94±9 mmHg), and severe hypertension (181±16/105±12 mmHg). Figure 2...
Box 3: Selected factors that may contribute to hypertension in patients with CKD

<table>
<thead>
<tr>
<th>Factor</th>
<th>Dominant mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic activation</td>
<td>Direct vasoconstriction</td>
</tr>
<tr>
<td>Imbalance in prostaglandins or kinins</td>
<td>Stimulation of renin release</td>
</tr>
<tr>
<td>Endothelin</td>
<td>Direct vasoconstriction</td>
</tr>
<tr>
<td>Reduced nitric oxide</td>
<td>Renal injury</td>
</tr>
</tbody>
</table>

Hypertension as a consequence of CKD: Pathophysiology

In patients with CKD, impaired renal sodium handling leads to elevated blood pressure levels. Initially, the extracellular fluid (ECF) volume increases, leading to an increase in blood pressure, despite a reduction in total peripheral resistance. At this stage, an increase in cardiac output mediates a rise in blood pressure that manifests predominantly as systolic hypertension. Gradually, however, there is normalization of ECF volume and cardiac output, and elevated peripheral resistance leads to high blood pressure, which increases diastolic blood pressure. Further, it has been speculated that activation of the renin-angiotensin system may stimulate the sympathetic nervous system and contribute to hypertension. In addition to these, several other factors have been proposed to contribute to increased vascular resistance in patients with CKD (Box 3).

Prevalence of hypertension in patients with CKD

Hypertension is highly prevalent in patients with CKD. It has been reported that the prevalence of hypertension progressively increases as the severity of CKD increases. The national survey of a representative sample of noninstitutionalized adults in the US estimated that the prevalence of hypertension in patients with stages 1, 2, 3, and 4–5 CKD was 35.8%, 48.1%, 59.9%, and 84.1%, respectively, and 23.3% in individuals without CKD. In the screening and early evaluation of kidney disease (SEEK)-India cohort, hypertension, defined as systolic and diastolic blood pressure ≥140/90 mmHg, was noted in 64.5% of patients with CKD (using the MDRD equation) and in 64.6% of patients with CKD (using the CKD–EPI equation).

Secondary causes of hypertension and CKD

Drug-induced hypertension

Hypertension can develop following consumption of certain prescription or over-the-counter medications as well as exogenous substances. Drug-induced hypertension is the most common cause of secondary hypertension. A list of drugs that induce or exacerbate hypertension is presented in Box 4. Although the occurrence of drug-induced hypertension is quite frequent, primary care physicians usually miss the opportunity to...
Obstructive sleep apnea (OSA) is characterized by transient and repetitive complete or partial upper airway obstruction during sleep, causing sleep disturbances, intermittent hypoxemia, and daytime sleepiness. Patients with OSA are at increased risk of developing CKD, since OSA is associated with several risk factors for CKD progression, including glomerular hyperfiltration, proteinuria, and hypertension.

The pathophysiologic association between OSA and CKD has been depicted in Figure 3. As can be seen, OSA is associated with hypoxemia-induced reactive oxygen species (ROS) and systemic inflammation, which may contribute to atherosclerosis and even progression of CKD. Further, OSA is also associated with sleep fragmentation, which activates the sympathetic nervous system and the renin-angiotensin-aldosterone system, thereby altering cardiovascular hemodynamics, resulting in the generation of free radicals. These changes, in turn, trigger several deleterious processes, such as endothelial dysfunction, inflammation, platelet aggregation, atherosclerosis, and fibrosis, and thereby predispose an individual to adverse cardiovascular events and probably renal damage.

Furthermore, long-standing OSA induces chronic elevations in blood pressure and may thereby directly contribute to the progression of CKD. Obstructive sleep apnea may also increase sympathetic nerve discharge directed at the kidney and other vascular beds, increase blood pressure during episodes of upper airway occlusion, and chronically accelerate the progression of renal damage, with sustained increases in blood pressure during the awake state. Through these mechanisms, OSA could further contribute to the progression of CKD.

Hyperuricemia, defined as serum uric acid levels >7.0 mg/dL in males and >6.0 mg/dL in females, is usually a consequence of decreased excretion or increased production of uric acid, or a combination of both. It occurs frequently in CKD patients due to a reduction in the glomerular filtration rate.

The potential mechanisms through which increased serum uric acid levels may contribute to the development and progression of CKD are presented in Figure 4. Increased levels of uric acid may stimulate oxidative stress and endothelial dysfunction, and contribute to systemic and glomerular hypertension along with elevated renal vascular resistance and decreased renal blood flow. Obesity and metabolic syndrome,
Box 5: Recommended technique for measuring blood pressure

- Measurements should be obtained with a sphygmomanometer that is known to be accurate.
- A cuff with an appropriate bladder size that matches the patient’s arm size should be selected. If measurements are taken by auscultation, the width of the bladder should be close to 40% of the arm circumference and the length of the bladder should cover 80%–100% of the arm circumference. If an automatic device is selected, the cuff size should be chosen based on the manufacturer’s recommendations. The cuff should be placed such that the lower edge is at least 2.5 cm above the elbow crease and the crease of the bladder is over the brachial artery.
- The patient should be seated comfortably for 5 minutes with back support and without the legs crossed. The arm should be bare and supported such that the antecubital fossa is at the level of the heart, since a lower position leads to erroneously higher systolic and diastolic blood pressure measurements. Blood pressure should also be measured after two minutes of standing, with the arm supported, and when patients report symptoms suggestive of postural hypotension. It may also be helpful to obtain supine blood pressure measurements in elderly and diabetic patients.
- The cuff pressure should be increased rapidly to 30 mmHg above the level at which the radial pulse disappears, to exclude the likelihood of a systolic auscultatory gap.
- The bell or diaphragm of the stethoscope of the sphygmomanometer should be placed over the brachial artery.
- Next, the control valve should be opened such that the rate of cuff deflation is approximately 2 mmHg per beat or per second, if the patient’s heart rate is less than 60 beats/minute.
- The systolic level, i.e. phase I sound, and the diastolic level, i.e. phase V sound, should be recorded. Auscultation should be continued to at least 10 mmHg below phase V sound, to rule out a diastolic auscultatory gap. The patient’s blood pressure should be recorded to the closest 2 mmHg on the manometer or to 1 mmHg on electronic devices, along with information on the position of the patient and the arm chosen for measurement. The heart rate should also be recorded. Blood pressure measurements obtained with the patient in the seated position are used to determine and monitor treatment decisions, while those obtained with the patient in the standing position are used to examine postural hypotension.

The most common risk factors for CKD, are strongly associated with hyperuricemia probably due to insulin resistance and the effects of insulin on urinary urate. Retention of uric acid can also occur secondary to renal vasoconstriction, or low-level intoxication with lead and cadmium, which may block renal excretion of uric acid.

Panel Recommendations

- The cause-and-effect relationship between hypertension and CKD varies from one ethnic group to another and, hence, cannot necessarily be extrapolated to the Indian setting.
- Hypertension as a cause of kidney disease in India requires further study.
- The role of pharmacological therapy for asymptomatic hyperuricemia in preventing/treating hypertension, and for retarding CKD progression, has not yet been established by clinical studies.

Evaluation of Patients

Diagnostic clues in patient’s history

Typically, CKD evolves over several years, with a long latent period, during which time the disease is usually clinically silent. Therefore, it is essential to obtain a thorough history that can help establish a correct diagnosis.

Evaluation of patients at increased risk for CKD

In all patients at increased risk of CKD, clinical evaluation should include assessment of blood pressure, serum creatinine (to estimate GFR), and markers of kidney damage. The different markers of kidney damage include:

- proteinuria
- urine sediment abnormalities
- electrolyte and other abnormalities due to tubular disorders
- imaging abnormalities
- pathologic abnormalities directly observed on biopsy of kidney tissue

In patients with CKD, damage to the kidney can occur within the parenchyma, large blood vessels, or collecting systems. The markers of kidney damage usually provide a clue to the probable site of damage within the kidney, and when used in combination with other clinical findings, help to determine the cause of kidney disease.

In hypertensive patients, advanced age, low baseline eGFR, and the presence of diabetes are positively and significantly associated with the development of CKD. Therefore, it is important to evaluate the presence of these factors in hypertensive patients. In primary care settings, feasible tests for screening for CKD include testing the urine for protein and measuring serum creatinine levels to estimate GFR. The need to assess other markers of kidney damage should be decided based on clinical judgment and the presence/absence of CKD risk factors.

Measurement of blood pressure: Techniques, devices, and location

The auscultatory method has remained the mainstay of clinical blood pressure measurement for several years. In this method, a cuff is positioned around the upper arm to occlude the brachial artery, and is inflated to above systolic pressure. The onset of phase I sound corresponds to systolic pressure; however, it tends to underestimate the systolic pressure recorded by direct intra-arterial measurement. The disappearing sounds in phase V correspond to diastolic pressure; however, these sounds tend to occur before diastolic pressure is determined by direct intra-arterial measurement. The technique to be followed while measuring blood pressure is given in Box 5.
Table 2: Factors that may affect the accuracy of blood pressure values

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect on systolic blood pressure (mmHg)</th>
<th>Effect on diastolic blood pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold room vs. comfortable room temperature</td>
<td>114/115</td>
<td>115</td>
</tr>
<tr>
<td>Uncomfortably distended bladder</td>
<td>150</td>
<td>140</td>
</tr>
<tr>
<td>Full bladder</td>
<td>110–15</td>
<td>110–15</td>
</tr>
<tr>
<td>Heavy physical exercise before measurement</td>
<td>118–20</td>
<td>17–9</td>
</tr>
<tr>
<td>Heavy meal before measurement</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Smoking before measurement</td>
<td>110</td>
<td>18</td>
</tr>
<tr>
<td>Not resting at least 5 min before measurement</td>
<td>110–20</td>
<td>114</td>
</tr>
<tr>
<td>Supine vs. Sitting</td>
<td>13–10</td>
<td>11–5</td>
</tr>
<tr>
<td>Back/feet unsupported vs. Supported</td>
<td>15–15</td>
<td>16</td>
</tr>
<tr>
<td>Arm unsupported vs. supported</td>
<td>11–7</td>
<td>15–11</td>
</tr>
<tr>
<td>Legs crossed vs. uncrossed</td>
<td>15–8</td>
<td>13–5</td>
</tr>
<tr>
<td>Talking during measurement vs. being silent</td>
<td>117</td>
<td>113</td>
</tr>
<tr>
<td>Arm below heart level vs. at heart level</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>Cuff too large</td>
<td>110–30</td>
<td>110–30</td>
</tr>
<tr>
<td>Cuff too small</td>
<td>13–12 in obese individuals</td>
<td>12–8 in obese individuals</td>
</tr>
<tr>
<td>Diaphragm of stethoscope vs. bell (auscultation method)</td>
<td>10–2</td>
<td>10–2</td>
</tr>
</tbody>
</table>

Arterial pressure. This technique can be used for ambulatory and home blood pressure monitoring and offers several advantages. There is no need to place a transducer over the brachial artery, and hence cuff placement is not critical; the technique is less vulnerable to external noise, and the cuff can be removed and replaced by the patient. However, the disadvantage is that the amplitude of oscillations is dependent on factors other than blood pressure, such as the stiffness of the arteries. Thus, this technique may significantly underestimate the mean arterial pressure in older people with stiff arteries and wide pulse pressures. Further, the recorder does not work well during physical activity, during which time there may be considerable movement artifact. The mercury sphygmomanometer is the gold standard device for office blood pressure measurement. However, owing to the widespread implementation of the ban on mercury devices, these devices are being replaced by aneroid devices, hybrid sphygmomanometers, and oscillometric or electronic automatic devices. The accuracy of blood pressure measurement using automated devices is controversial. Automated devices have been shown to underestimate systolic and diastolic blood pressure in adults and overestimate systolic and diastolic blood pressure in children and adolescents aged 5 to 17 years.

The upper arm is the standard location for blood pressure measurement, with the stethoscope placed at the elbow crease over the brachial artery. However, measurement of blood pressure at several other sites such as the wrist and fingers is gaining popularity. Nevertheless, it is important to realize that there is substantial variation in systolic and diastolic pressures in different parts of the arterial tree. Generally, in more distal arteries, the systolic pressure increases, while the diastolic pressure decreases; and there is only a decrease of 1 to 2 mmHg in mean arterial pressure between the aorta and peripheral arteries.

Factors contributing to errors in blood pressure measurement

It is extremely important to obtain blood pressure measurements accurately. Clinical evidence indicates that underestimating diastolic blood pressure by 5 mmHg may deprive nearly two-thirds of hypertensive individuals of preventive therapy. On the contrary, overestimating the systolic blood pressure by 5 mmHg may increase the number of persons diagnosed with hypertension by nearly twofold. Several factors, such as the environment in which the measurement is obtained, the behavior of the subject, measurement protocol, and the device used can significantly influence the accuracy of the measured blood pressure (Table 2).

Visit-to-visit variability in blood pressure and renal outcomes in CKD patients

Recent evidence has demonstrated an association between the visit-to-visit variability of blood pressure and increased risk for coronary heart disease, stroke, and mortality. Furthermore, in some (but not all) studies, increased variability in blood pressure has been shown to be associated with rapid progression of CKD, as evidenced by a decrease in eGFR or increase in urinary albumin levels. Recently, Whittle et al. conducted an analysis to determine the association between the visit-to-visit variability of blood pressure and renal outcomes in 21,245 participants in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). The intrapatient SD of systolic blood pressure across visits (SD_SBP) was considered as a measure of variability of blood pressure. A higher SD_SBP was observed to be associated with an increased risk of renal outcomes. The risk of ESRD or a ≥50% decline in eGFR was greater in higher quintiles of SD_SBP. Further, the association was found to persist even after multivariable adjustment for vital potential confounders, such
as baseline eGFR and mean blood pressure. Based on the findings, the study concluded that greater visit-to-visit variability in blood pressure is associated with greater risk of renal outcomes; this association is independent of the mean blood pressure.31

White-coat hypertension and masked hypertension

The diagnosis and management of hypertension in patients with CKD relies almost entirely on clinic blood pressure measurements.34 However, clinic blood pressure measurements usually over- and underestimate the true blood pressure in patients with hypertension as well as in those with CKD.35 White-coat hypertension refers to a condition characterized by elevated blood pressure in the clinic, but normal ambulatory blood pressure. On the contrary, masked hypertension refers to a condition characterized by normal blood pressure in the clinic, but higher blood pressure values on ambulatory blood pressure monitoring.29,36

In the general population, compared to individuals with true hypertension, those with white-coat hypertension have a more benign prognosis and those with masked hypertension have worse outcomes.36

In people with CKD, masked hypertension is associated with lower eGFR, proteinuria, cardiovascular target organ damage, and increased likelihood of progression to ESRD and death.36,37 On the contrary, white-coat hypertension seems to be associated with better renal outcomes compared to persistent hypertension, in people with CKD.34 Evidence from a meta-analysis indicates that white-coat hypertension is prevalent in nearly 28% of CKD patients, while masked hypertension is prevalent in nearly 8% of CKD patients.35 Therefore, it is crucial to determine the presence of masked and white-coat hypertension in patients with CKD.36 Ambulatory blood pressure monitoring is an excellent diagnostic tool to diagnose WCH and masked hypertension in patients with CKD. It also provides a better measure of BP control compared to clinical BP measurements.38

Significance of central aortic pressure in CKD

Although the peripheral brachial blood pressure measured through a conventional sphygmomanometer is the gold standard for measurement of blood pressure, it does not accurately represent the central aortic pressure.36 The central aortic pressure, which is a more accurate representation of the pressure directly experienced by major organs, such as the brain, heart, and kidneys, is different from the blood pressure measured in the arm.36,38 Although the mean and diastolic blood pressure usually remain mostly unaltered, the systolic blood pressure and pulse pressure are amplified from the aortic root to the peripheral brachial artery. Noninvasive applanation tonometry can be used to reliably assess central aortic blood pressure and arterial compliance. The reproducibility of these measurements has been confirmed in the CKD population. Growing evidence suggest that measurements of central blood pressure and arterial compliance, compared to traditional peripheral brachial blood pressure, may serve as robust predictors of cardiovascular outcomes in several patients, including those with CKD.38

Screening for proteinuria and albuminuria in patients at risk for CKD

Proteinuria refers to the presence of increased amounts of protein in the urine.25 It is an early and sensitive marker of kidney damage in many types of CKD.24 Proteinuria may reflect abnormal loss of plasma proteins due to several conditions such as increased plasma concentration of low-molecular-weight proteins (overproduction proteinuria), increased permeability of glomeruli to large-molecular-weight proteins (albuminuria or glomerular proteinuria), or incomplete tubular reabsorption of normally filtered low-molecular-weight proteins (tubular proteinuria). It may also represent an abnormal loss of proteins derived from the lower urinary tract and kidney.25

Screening for proteinuria can alert the physician about the presence of CKD much before changes in GFR become apparent. Given that there is an association between proteinuria and a more rapid progression of CKD and higher likelihood of developing ESRD, it is essential to detect and quantify proteinuria in high-risk patients.40

Albuminuria refers to an abnormal loss of albumin, a type of plasma protein found normally in the urine. Albumin is found in larger quantities in patients with kidney disease. Although albuminuria is a common finding in patients with CKD, it is not uniformly observed in all patients. It serves as the earliest marker of glomerular diseases such as diabetic glomerulosclerosis, in which condition it usually manifests before the reduction in GFR.25

Proteinuria and albuminuria can be measured using excretion rates in timed urine collections, the ratio of concentrations to creatinine concentration in spot urine samples, and using reagent strips in spot urine samples. The normative values for proteinuria and albuminuria are usually expressed as the urinary loss rate, wherein the urinary loss rates of protein and albumin are referred to as protein excretion rate and albumin excretion rate, respectively. The relationship between the categories for albuminuria and proteinuria are presented in Table 3. A urinary albumin excretion rate of ≥30 mg/24 hours (approximately equivalent to an ACR of ≥30 mg/g or ≥3 mg/mmol in a random untimed urine sample) that is sustained for >3 months indicates CKD.25

Panel Recommendations

- Patients at high risk for developing CKD should be evaluated for end-organ damage. Fundus examination and urine examination are mandatory in this patient population.
- Blood pressure instrument standardization is needed, and an average of 3 blood pressure readings obtained 5 minutes apart should be taken into consideration.
- Digital devices are not recommended for measuring blood pressure.
Support staff and nurses measuring blood pressure should be thoroughly trained on the accurate measurement of blood pressure.

Blood pressure, cholesterol, and estimated glomerular filtration rate are the three important parameters that should be evaluated while screening hypertensive patients for the presence of CKD.

Home blood pressure monitoring is ideal, but is currently not reliable in Indian settings, since blood pressure-monitoring instruments are not standardized and are thus prone to calibration errors.

Ambulatory blood pressure monitoring is performed only in a small percentage of patients.

Patient education regarding blood pressure measurement is an important component in the management of hypertension.

White-coat hypertension can pose significant problems, especially in CKD patients.

Measurement of central aortic pressure is too cumbersome and impractical. Hence, it is not recommended in routine clinical practice.

Patients should be monitored for microproteinuria only in the absence of macroproteinuria.

Management of Hypertension in Patients with CKD

Optimal blood pressure target levels and management goals in CKD patients

In patients with CKD, guidelines from the Eighth Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure,41 the American Society of Hypertension/International Society of Hypertension (2014),42 the National Institute for Health and Care Excellence (2014),43 Canadian Hypertension Education Program (2014),44 and the European Society of Hypertension (2013)45 recommend a goal blood pressure of <140/90 mmHg. However, in patients with an albumin creatinine ratio of ≥70 mg/mmol, the 2014 National Institute for Health and Care Excellence guidelines recommend a goal blood pressure of <130/80 mmHg.43

The 2012 KDIGO guidelines have also recommended goal blood pressure in non-diabetic and diabetic adults with non-dialysis–dependent CKD. These recommendations are presented in Figures 5 and 6, respectively.2

Table 3: Relationship between categories for proteinuria and albuminuria25

<table>
<thead>
<tr>
<th>Measure</th>
<th>Normal to mildly increased (A1)</th>
<th>Moderately increased (A2)</th>
<th>Severely increased (A3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AER (mg/24 h)</td>
<td>&lt;30</td>
<td>30–300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>PER (mg/24 h)</td>
<td>&lt;150</td>
<td>150–500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>ACR (mg/mmol)</td>
<td>&lt;3</td>
<td>3–30</td>
<td>&gt;30</td>
</tr>
<tr>
<td>ACR (mg/g)</td>
<td>&lt;30</td>
<td>30–300</td>
<td>&gt;300</td>
</tr>
<tr>
<td>PCR (mg/mmol)</td>
<td>&lt;15</td>
<td>15–50</td>
<td>&gt;50</td>
</tr>
<tr>
<td>PCR (mg/g)</td>
<td>&lt;150</td>
<td>150–500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>Protein reagent strip</td>
<td>Negative to trace</td>
<td>Trace to + or greater</td>
<td></td>
</tr>
</tbody>
</table>

ACR: Albumin-to-creatinine ratio; AER: Albumin excretion rate; PCR: Protein-to-creatinine ratio; PER: Protein excretion rate.

Non-diabetic ND CKD patients

- Use antihypertensive drugs to maintain BP at ≤140/90 mmHg
- Use antihypertensive drugs to maintain BP at ≥130/80 mmHg (1B)
- Use antihypertensive drugs to maintain BP at ≥130/80 mmHg (2C)
- Use antihypertensive drugs to maintain BP at ≥130/80 mmHg (2D)

Intensive vs. standard blood pressure lowering: Clinical evidence

Although major guidelines recommend a blood pressure target of <140/90 mmHg in patients with CKD, recent evidence indicates that intensive blood pressure lowering may be beneficial.

According to the recent Systolic Blood Pressure Intervention Trial (SPRINT) results, among patients without diabetes but with a high risk of cardiovascular events, targeting a systolic blood pressure of <120 mmHg compared to <140 mmHg was associated with lower rates of fatal and nonfatal major cardiovascular events and death from any cause (Figure 7). However, significantly higher rates of some adverse events were observed in the intensive-treatment group. Participants in the intensive group, compared to those in the standard group, demonstrated a lower incidence of primary outcome, cardiovascular mortality, and all-cause mortality. The trial was stopped early after a median follow-up of 3.26 years, due to remarkable benefits demonstrated in the intensive arm compared to the standard arm. Among
Clinical evidence for blood pressure lowering: target of <140/90 mmHg in patients with CKD, recent non-diabetic and diabetic adults with non-dialysis-dependent CKD. The 2012 KDIGO guidelines have also recommended goal blood pressure in the number of participants with a reduction in the eGFR of 50% or more or reaching ESRD over the course of the trial between the two intervention groups. The authors also noted no evidence of significant permanent kidney damage with lower systolic blood pressure goals. However, they caution that the possibility of a long-term adverse renal outcome cannot be ruled out.46

According to a systematic review and meta-analysis by Xie et al. including 44,989 participants from 19 trials, intensive blood pressure lowering, compared to standard regimens, conferred greater cardiovascular protection, with net absolute benefits in high-risk individuals being large. The mean BP levels were 133/76 mmHg vs. 140/81 mmHg among patients in the more intensive blood pressure-lowering treatment group vs. less intensive treatment group, respectively.47

These findings have been confirmed by another systematic review and meta-analysis by Ettehad et al. The meta-analysis, which included 123 trials with 613,815 participants, has provided strong evidence supporting the benefits of lowering systolic blood pressure to levels less than 130 mmHg in individuals with a history of cardiovascular disease, coronary heart disease, stroke, diabetes, heart failure, and chronic kidney disease. Each 10-mmHg reduction in systolic blood pressure reduced the risk of major cardiovascular events by 20%, coronary heart disease by 17%, stroke by 27%, heart failure by 28%, and all-cause mortality by 13%. Significant reductions in relative risks were noted in patients with and without chronic kidney disease. The proportional risk reductions were smaller in patients with CKD than in those without CKD; however, given that CKD patients are at higher absolute risks, BP reduction in these patients can lead to significant absolute benefits.48

**Pharmacological therapy: Use of antihypertensive drugs**

According to the 2012 KDIGO guidelines, an angiotensin receptor blocker (ARB) organ angiotensin-converting enzyme inhibitor (ACE-I) is recommended in diabetic and non-diabetic adults with non-dialysis-dependent CKD and urine albumin excretion >300 mg/24 hours. Further, the guidelines suggest the use of an ARB or ACE-I in diabetic and non-diabetic adults with non-dialysis-dependent CKD and urine albumin excretion >300 mg/24 hours.
Management of Hypertension in Non-Dialysis-Dependent CKD Patients

General strategies for lowering blood pressure in non-dialysis–dependent CKD patients

A stepwise combination of lifestyle changes and pharmacological therapy should be used to lower blood pressure in patients with CKD. The 2012 KDIGO guidelines have put forth the following general management strategies for lowering blood pressure in non-dialysis–dependent CKD patients:2

- Individualize BP targets and agents based on the age, co-existence of cardiovascular disease and other co-morbidities, risk of CKD progression, presence or absence of retinopathy in patients with diabetes, and treatment tolerance.2
- Inquire about postural dizziness and regularly check for postural hypotension when treating CKD patients with antihypertensive drugs.2

Lifestyle recommendations for lowering blood pressure in non-dialysis–dependent CKD patients

It is well established that lifestyle-related factors exert an impact on blood pressure and the risk of cardiovascular and other diseases. Accordingly, the 2012 KDIGO guidelines recommend the following lifestyle changes to lower BP and improve long-term cardiovascular and other outcomes in non-dialysis–dependent CKD patients:2

- Achieve or maintain a healthy weight with a body mass index in the range of 20–25 kg/m².22
- Lower salt intake to <90 mmol (<2 g) per day of sodium, which corresponds to 5 g of sodium chloride, unless contraindicated.2
- Follow an exercise program compatible with cardiovascular health and tolerance, aiming for at least 30 minutes 5 times per week.2

Further, the guidelines suggest limiting alcohol intake to no more than two standard drinks per day for men and no more than one standard drink per day for women.2

Management of blood pressure in elderly individuals with non-dialysis–dependent CKD

Data from the Kidney Early Evaluation Program and NHANES indicate that as age advances, the prevalence and severity of CKD increase, thus confirming that there is a strong association between blood pressure and CKD in the elderly population. Despite these findings, there is limited evidence to offer recommendations for management of blood pressure in the elderly population with CKD.2

The 2012 KDIGO guidelines recommend that in individuals aged 265 years with non-dialysis–dependent CKD, blood pressure treatment should be tailored after carefully considering their age, other treatments, and presence of comorbidities. Furthermore, treatment should be gradually escalated and patients closely watched for adverse events related to blood pressure treatment, such as electrolyte disorders, orthostatic hypotension, acute deterioration in kidney function, and drug side effects.2 However, no particular drug class is recommended to reduce blood pressure in older patients with CKD. The severity of CKD, presence of albuminuria, and co-morbidities and their treatment should be taken into consideration when prescribing antihypertensive drugs.2

Proposed checklist to identify hypertensive patients at high risk for CKD

The panel has proposed a checklist to identify hypertensive patients at risk for CKD (Box 6).

Panel recommendations

The panel has proposed an algorithm for the management of blood pressure in CKD patients aged 18 years or older and lesser than 60 years (Figure 8). In patients aged more than 60 years, treatment should be individualized based on the presence of comorbidities and other treatments.
Management of Blood Pressure in Non-Dialysis and Pre-Dialysis CKD Patients

Management of resistant hypertension in CKD patients

Resistant hypertension is defined as blood pressure that remains above the target levels despite adherence to treatment with at least three antihypertensive agents prescribed at optimal doses, ideally including a diuretic. Although diuretics are essential to control blood pressure, treat fluid balance, prevent hyperkalemia, and regulate urine amount in patients with CKD, their use is associated with negative outcomes on renal function. Further, the use of diuretics or fluid overload in CKD patients can lead to hyponatremia. In patients with CKD, diuretic usage can lead to sodium imbalance, since as the renal disease progresses, the ability of the kidneys to regulate sodium dilution and concentration becomes impaired.

The management of resistant hypertension in patients with CKD should mainly aim to address several factors that contribute to the pathogenesis of hypertension, including impaired sodium handling and volume expansion, increased renin-angiotensin-aldosterone system activity, enhanced sympathetic activity, and decreased endothelium-dependent vasodilation. A physiology-based algorithm has been proposed by Drexler et al. for the identification and management of resistant hypertension in patients with CKD (Figure 9).

Patients with ESRD and uncontrolled hypertension can also be managed using open or laparoscopic nephrectomy. Compared to open nephrectomy, which is associated with significant morbidity and mortality; laparoscopic nephrectomy is associated with reduced rates of complication. Another safe and effective alternative for the management of uncontrolled hypertension in ESRD patients is renal artery embolization.

Panel recommendations

- Blood pressure targets should be individualized based on age, comorbidities, and presence of end-organ damage (cerebrovascular disease and retinopathy).
- Ideal blood pressure target attainment in the pre-dialysis stage is questionable; 130/80 mmHg appears to be a good target.
- Calcium channel blockers should be initiated to manage hypertension in the absence of proteinuria. In the presence of proteinuria, ARBs are the preferred option.
- The RAAS blockade should be optimized before increasing the dose of antihypertensive agents.
- Primary care physicians should be sensitized about the side effects of RAAS blockade, include hyperkalemia.
- Potassium levels should be monitored while administering ARBs.
- Serum creatinine levels should be monitored while optimizing the drug dose.
- If the patient requires antihypertensive agents from more than 4 drug classes for control of blood pressure, the timings of different drugs need to be planned.
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**Fig. 9: Physiology-based algorithm for initiation and management of resistant hypertension in patients with chronic kidney disease**

Initial diagnosis of resistant hypertension
- Office BP >130/80 mm Hg in proteinuric CKD or >140/90 mm-Hg in non-proteinuric CKD
- Prescribed ≥3 antihypertensive agents at optimal doses, ideally including a diuretic
- BP at goal but requires ≥4 antihypertensive agents to do so

Exlude pseudo-resistance
- Ensure proper blood pressure measurement
- Confirm adherence to prescribed treatment
- Evaluate the antihypertensive regimen for suboptimal dosing and combination of agents
- Avoid clinician inertia

Obtain 24-hour ambulatory blood pressure monitoring (ABPM)
- Rule out white-coat hypertension
- Identify the presence of a ‘non-dipper’ vs. ‘dipper’ pattern

Chronotherapy: Change ≥1 antihypertensive agents from AM to PM dosing
- For all patients vs. only non-dippers

Optimize diuretic regimen
- Change HCTZ to chlorthalidone
- Maintain thiazide and add MRB (spironolactone or eplerenone)
- Change thiaide to loop diuretic if eGFR <40 mL/min/1.73 m²
- Combined loop diuretic with distally acting diuretic (thiazide, amiloride)

Optimize RAAS blockade
- Uptitrat e ACE-I or ARB or ‘ultrahigh’ doses
- Add MRB (spironolactone or eplerenone)

Add or substitute β- or α- + β-blockade

Clues of hypertension mediated by the SNS
- Tachycardia
- Congestive heart failure
- Anxiety symptoms

Physiologic assessment of volume excess: indications for uptitrating diuretic regimen
- Low PRA
- 24-hour urine sodium >150 mmol/day
- Edema
- Reduced eGFR

Hyperactive RAAS
- High PRA
- Aldosterone breakthrough
- Reduced eGFR
- Refractory BP or proteinuria on escalating doses of ACE-I or ARB

from observational studies and lack of trial data, the 2005 NKF-KDOQI guidelines on hemodialysis have suggested a reasonable approach. Such an approach encompasses excluding any target blood pressure levels and focusing on patient education and hypertension prevention by restricting dietary sodium intake.56

Management of blood pressure in dialysis patients

The management of hypertension in patients undergoing dialysis is usually challenging. Lifestyle changes should remain an integral component of hypertension management in dialysis patients. According to the 2005 NKF KDOQI guidelines, careful attention to the management of fluid status and adjustment of antihypertensive medications are fundamental to the management of hypertension in dialysis patients. Approaches to managing excessive fluid accumulation between dialysis sessions include education and regular counseling by dietitians, low sodium intake (2–3 g/day), increased ultrafiltration, longer dialysis, drugs that reduce salt appetite, and more than 3 dialysis sessions per week.57

Antihypertensive drugs should be initiated when these measures are unsuccessful. The 2005 NKF KDOQI guidelines have put forth an algorithm for the management of hypertension in dialysis patients (Figure 10). Patients with compelling indications should be prescribed appropriate drugs for managing their compelling indications. Patients without compelling indications but with stage 1 hypertension should be started on an angiotensin-converting

![Diagram](image-url)
enzyme inhibitor or aldosterone receptor blocker. Patients with stage 2 hypertension should be started on a 2-drug combination, usually an angiotensin-converting enzyme inhibitor or aldosterone receptor blocker and a calcium channel blocker. If the patient is not at goal blood pressure, a β-blocker may be added to the previous combination and investigations carried out to determine secondary causes. If no secondary causes are identified, minoxidil should be added to the existing regimen. If despite a trial of minoxidil, the patient remains hypertensive, the patient should be considered for continuous ambulatory peritoneal dialysis. If continuous ambulatory peritoneal dialysis remains ineffective, the patient should be considered for surgical or embolic nephrectomy. Antihypertensive drugs should preferentially be administered at night, since they may decrease the nocturnal surge of blood pressure and minimize intradialytic hypotension, which may occur when these drugs are taken in the morning prior to a dialysis session.57

### Selection of antihypertensive drugs in dialysis patients

Angiotensin II-receptor blockers or ACE-I are preferred, since they are associated with greater regression of left ventricular hypertrophy; and reduction in sympathetic nerve activity and pulse wave velocity. Further, they may improve endothelial function and thereby decrease oxidative stress. However, in patients with compelling indications, it is important to follow certain criteria to select antihypertensive agents (Table 4).57 Additionally, it is important to consider the dialyzability of antihypertensive agents (Table 5) in patients with difficult-to-control hypertension.

### Panel recommendations

- A comprehensive exercise program in the dialysis unit, as shown in a few studies, and being practiced in certain centers, can prove to be beneficial for patients.
- The day after dialysis is the ideal time to record blood pressure; however, this may not always be practical.
- Hydralazine is still used by some nephrologists in the management of hypertension in dialysis patients.
- α-blockers are highly recommended in this category of patients as the third drug of choice.
- A 2D ECHO should be done at the beginning of dialysis as a baseline cardiac assessment tool.
- In patients with erythropoietin-related hypertension, CCBs can be used. It is recommended to first control the blood pressure and then initiate erythropoietin (if non-dialysis SBP>160). Carvedilol can be used to control blood pressures, since it is not removed by dialysis.

### Management of Hypertension in Post-Transplant Scenario

#### Prevalence of hypertension in post-transplant recipients

Hypertension has an adverse impact on transplant and patient survival outcomes. Prior to the approval of cyclosporine by the US Food and Drug Administration in 1983, it was reported that nearly 50% of all transplant recipients had hypertension, and this was attributed to activation of the renin-angiotensin
system of the native kidney or transplant derivation. Currently, it has been reported that hypertension is prevalent in >90% of calcineurin-inhibitor–treated kidney transplant recipients.58

Management of hypertension in post-transplant recipients

The 2012 KDIGO guidelines suggest that adult kidney transplant recipients with a consistent office BP of >130/80 mmHg be treated with antihypertensive agents to maintain the blood pressure consistently at ≤130/80 mmHg, regardless of the level of urine albumin excretion.2

Antihypertensive therapy in post-transplant recipients should mainly aim at preserving kidney function or retarding the progression of kidney disease and reducing the risk of cardiovascular disease.57 The choice of antihypertensive agent in adult kidney transplant recipients is generally based on several parameters such as:

- side effects noted in the general population as well as in kidney transplant recipients
- level of urine albumin

Table 5: Removal of antihypertensive drugs with dialysis57

<table>
<thead>
<tr>
<th></th>
<th>Percent removal with dialysis</th>
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<tbody>
<tr>
<td></td>
<td>HD</td>
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<tr>
<td>ACE inhibitors</td>
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<td>Benazepril</td>
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<td>Enalapril</td>
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<td>Fosinopril</td>
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<td>Lisinopril</td>
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<td>Ramipril</td>
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<tr>
<td>Calcium channel blockers</td>
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</tr>
<tr>
<td>Amlodipine</td>
<td>?</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>?</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Low</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>?</td>
</tr>
<tr>
<td>Felodipine</td>
<td>?</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Low</td>
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<td>Alebutolol</td>
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<tr>
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<td>Metoprolol</td>
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<td>Minoxidil</td>
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<tr>
<td>Angiotensin receptor blockers</td>
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<td>Valsartan</td>
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</tr>
<tr>
<td>Irbesartan</td>
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</table>

Evidence indicates that the use of calcium channel blockers is associated with a 25% lower rate of graft loss. Dihydropyridine calcium channel blockers are preferred for initial therapy after transplantation, since they dilate afferent arterioles and counteract the vasoconstrictive effect of calcineurin inhibitors. On the contrary, non-dihydropyridines may disrupt the metabolism and excretion of calcineurin inhibitors such as cyclosporine and tacrolimus, and mTOR inhibitors everolimus and sirolimus. Hence, renal transplant recipients who are prescribed non-dihydropyridine calcium channel blockers need careful monitoring of blood levels of CNIs and mTOR inhibitors if the drugs or dosages are changed.59

Angiotensin II receptor blockers and ACE-inhibitors are known to exert acute hemodynamic effects and increase levels of serum creatinine. Hence, these agents are frequently avoided during the first 3 to 4 months after transplantation, during which time acute rejection is a strong possibility, and increased creatinine levels can be difficult to interpret. However, ARBs and ACE inhibitors should be considered in the longer term, particularly in kidney-transplant patients with persistent albuminuria.2 Figure 11 presents an algorithm on the therapeutic approach for the management of hypertension in transplant patients.59

Panel recommendations

- Weight control is important during the first three months after transplantation.
- Steroid and CNI dose optimization is important to controlling hypertension.
- During the first year after transplantation, CCB (dihydropyridine) is the preferred antihypertensive agent over ACEi or ARB.
- In patients with mild graft dysfunction with proteinuria, ARB is the preferred drug.
- In patients with post-transplant hyperuricemia, losartan is the preferred drug.
- Loop diuretics may be used as add-on therapy.

Conclusion

- Hypertension is both a cause and consequence of CKD.
- All patients at increased risk of CKD should be evaluated for blood pressure, markers of kidney damage, and estimated GFR.
- Feasible tests for screening for CKD in primary care settings include testing the urine for protein and measuring serum creatinine levels to estimate GFR.
- Guidelines from across several international organization
The KDIGO guidelines suggest the following:

- The NKF-KDOQI guidelines recommend encouraging lifestyle modifications in CKD patients to reduce BP and improve long-term cardiovascular and other outcomes.

- In diabetic as well as non-diabetic, non-dialysis-dependent CKD patients with urine albumin excretion <30 mg per 24 hours or equivalent, and office BP consistently at >140/90 mmHg, antihypertensive agents are recommended to maintain BP at ≤130/80 mmHg.

- In elderly persons with CKD, BP management should be tailored carefully based on their age, other treatments, and presence of comorbidities.

**List of contributors**

1. Dr. Abi Abraham
2. Dr. Alan Almeida
3. Dr. Deodatta S. Chafekar
4. Dr. Dilip Pahari
5. Dr. Georgi Abraham
6. Dr. K.N. Arun
7. Dr. N. Gopalakrishnan
8. Dr. Pradeep Deshpande
9. Dr. Rajan Isaacs
10. Dr. Renuka S
11. Dr. R. Padmanaban
12. Dr. S. Sundar

**References**
