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Hypertension in Chronic Kidney Disease

Ashok L Kirpalani¹

Chronic Kidney Disease is mostly managed without definitive cure. It is rare that Chronic Kidney Disease patients get cured, although not impossible. Therefore, once the diagnosis of Chronic Kidney Disease is established, every effort has to be made by the treating physician/nephrologist to retard the progression of this disease. Even when incurable, it is essential that the cause of Chronic Kidney Disease be established when the patient presents first.

Kidneys and high blood pressure have a chicken and egg relationship. It is more often than not that, when the physician first makes the diagnosis of CKD, he is presented with the dilemma of having to decide whether kidney disease causes hypertension in this patient or the other way round, i.e. hypertension is the result of the kidney disease. It requires astute judgment and careful history-taking to distinguish one from the other. In an exhaustive review in this issue of the journal, Abraham et al, have laid down the principles of the management of hypertension in CKD. This review includes the methodology of approaching the patient of CKD with hypertension in order to establish what came first, the chicken or the egg. Quite often, however, one is left with the answer "I am not sure". Moreover, the patient with established Chronic Kidney Disease such as

Glomerulonephritis or Polycystic Kidneys or Diabetic Nephropathy, has a substantial overload burden of hypertension which is a result of the Chronic Kidney Disease. This BP overload additionally causes further kidney damage, per se, thereby causing progression of the already established CKD with increasing azotaemia. Thus, the vicious cycle is complete. The confused physician is left saying to himself, "Be that as it may, I have to reduce this patient's blood pressure so that the disease, which is now chronic, does not progress rapidly towards end stage and develop the need for renal replacements therapy i.e., dialysis or transplantation". In most cases, the management of hypertension demands exquisite and repeated attention from the physician in order to retard the progression of renal damage. Nephrologists are well aware, that in non-hypertensive renal diseases, progress is much slower towards end-stage than in hypertensive renal diseases.

The burden of CKD, as shown in this article, is anywhere between 10 and 15% in our country. Our country is socioeconomically challenged. We can ill afford to maintain a large population of patients on haemodialysis or peritoneal dialysis forever. The shortage of organs and the cost of immunosuppression post-transplant, also make transplantation of the kidneys very inaccessible for most of the Indian ESRD patients. The cost burden of ESRD is prohibitive. It is the need of the hour

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to make every effort to retard the progression of disease and delay the onset of Uraemia and End-Stage Renal Failure. There are 6 principles to be adopted in the management of CKD for reducing progression;

1. The most important is reduction of blood pressure.
2. Reduction of proteinuria.
3. Control of blood glucose in the diabetic.
4. Avoidance of infections and prompt treatment with appropriate antibiotics in the CKD patient.
5. Avoidance of nephrotoxic medications including allopathic, particularly pain killers, and the alternate medicines containing the heavy metals and,
6. Dietary modification and lifestyle modification in the CKD patient including salt, water, protein, and potassium restrictions.

Abraham et al have covered almost every aspect of blood pressure management in the CKD patients. The newer aspects covered are those of:

1. The limitations of standard office blood pressure in the management of treatment.
2. The role of aortic stiffness in causing target organ damage and clinical application of Applanation Tonometry to assess arterial stiffness.
3. The contribution of BP variability to the TOD damage done by hypertension in the CKD patients and the role of ambulatory blood pressure monitoring.
4. The controversies surrounding the “target” of BP control in CKD and Diabetes.

OFFICE MEASUREMENT OF BLOOD PRESSURE IN CKD

There is conflict between the recommendations for intensive control by the SPRINT group and the liberalisation in the JNC target recommendations. What needs to be emphasized about SPRINT is the method of measuring BP. The SPRINT trial was conducted using automated office blood pressure (AOBP) measurement

method, which is not how the earlier trials of antihypertensive medications were done. Automated office blood pressure measurement is a unique new oscillometric method. BP is recorded automatically after the patient is left alone in a quiet room having sat there for 5 minutes before the blood pressure recording starts. This is a very commonly used method in Canada with the BPTRU apparatus. It is important to emphasize that Canada, which generally tends to follow this AOBP method of office measurement of blood pressure, has the highest hypertension control rates of any country with more than 30% of their patients achieving “target”. The SPRINT trial used an Omron machine which records three reading and averages them out automatically in the absence of an operator. Given that the methodology is different, it is necessary to emphasize here that if the physician aims at this target of BP using “intensive treatment” guideline made by the SPRINT trial, then the method of measuring blood pressure should also be an automated office blood pressure rather than the manual method. In Canada, recording BP using a stethoscope and manual office sphygmomanometer is no longer a standard of care for the best medical practice and the Canadian physicians use AOBP, 24-hour ABPM, and home BP complementarily in the diagnosis and management of hypertension, particularly in CKD. When an oscillometric BP apparatus is used, the value for blood pressure is about 5 mm less than the Mercury Sphygmomanometer. Therefore, even in normal patients without CKD, the normal value of AOBP is 135/85, and not 140/90 as for Mercury Sphygmomanometer. Admittedly, the AOBP is difficult to implement in routine patient care. Devices currently available for recording AOBP are expensive and doctors do not have the time, patience, and the physical space to leave the patient alone in their consulting room without observation so as to get a more appropriate approximation of the patient’s average 24-hour day blood pressure. We conducted a study at the Bombay Hospital Institute of Medical Sciences, and subjected the patients of CKD to standard

Sphygmomanometric office BP, BPTRU measurement, and a 24-hour ABPM. The first reading of the BPTRU was in front of an operator and the remaining 5 readings were in the absence of the operator taken at two-minute intervals. We found that the daytime ABPM approximated much closely to the average BPTRU (last 5 readings) rather than the clinically observed manual BP. There was a justification for spending extra time, effort and space to provide for AOBP.

BLOOD PRESSURE VARIABILITY

Blood pressure patterns in CKD are similar to the patterns seen in non-CKD individuals, but the incidence of abnormalities is much higher in CKD patients. The incidence of variability of blood pressure is much more frequent. The CRIC study (Chronic Renal Insufficiency Cohort) has classified subjects as follows:

UNTREATED SUBJECT

- Sustained Normotension: Office – Normal. Home - Normal. ABPM - Normal.
- White Coat Hypertension: Office – High. Home – Normal. ABPM – Normal.
- Sustained Hypertension: Office – High. Home – High. ABPM – High.
- Masked Hypertension: Office – Normal. Home – High. ABPM – High

TREATED SUBJECT

- Good BP control: Office – Normal. Home – Normal. ABPM – Normal
- False/White Coat resistant uncontrolled hypertension: Office - High. Home - Normal. ABPM – Normal
- True resistant uncontrolled hypertension: Office – High. Home – High. ABPM – High
- Masked resistant uncontrolled hypertension (MUCH): Office – Normal. Home – High. ABPM – High.

The CRIC Study is an ongoing multicenter observational cohort study that enrolled 3939 participants aged 21–74 years with an eGFR

between 20 and 70 ml/min per 1.73 m². In this study, the following observations are being made about CKD patients:

1. Those on diuretics ACE-I, ARBS, had lower night time BP
2. Before ABPM recording – “controlled” BP was diagnosed in 77% by clinic BP; after ABPM recording only 49% turned out to have “controlled” BP. Therefore, 28% benefitted from the ABPM recording
3. Masked hypertension patients have:
 - Lower eGFR
 - More proteinuria
 - Higher LVM
 - More PWV
4. Night Risers (nocturnal hypertension) have low eGFR & more proteinuria
5. ABPM would help unveils covert TOD in CKD patients

In our own Hypertension Clinic at the Bombay Hospital Institute of Medical Sciences, while taking care of CKD patients, we found that non-selective ABPM monitoring i.e., monitoring each and every patient of CKD at first visit compared to selective monitoring i.e., doing ABPM only on those with clinical indications resulted in substantially higher detection of masked hypertension (30% versus 10%), white coat hypertension (35% versus 23%), and early morning surge (53% versus 20%) respectively. For various valid reasons, however, ABPM is an underutilized but a very useful investigation which should be more often, if not routinely, used in CKD patients.

ARTERIAL STIFFNESS IN CKD

Unlike the patient of essential hypertension, who has both, systolic and diastolic elevation of blood pressure, the patient with CKD behaves like an ageing old person and has much more systolic hypertension as compared to the degree of diastolic hypertension. It is not uncommon to find a 39-year-old patient of chronic glomerulonephritis in ESRD with blood pressure readings of 170/75 and a very

high pulse pressure. The arteries of a normal person will age, and there will be progressive arterial stiffness in the intima and reduction in compliance of the vessel wall. This is part of the natural ageing process and atherosclerotic stiffening of the arteries is expected with ageing. The CKD patient is subjected to similar arterial stiffening, but due to a sclerosis which takes place in the media of the arteries also known as Monckeberg's Sclerosis. Abraham et al have pointed out the role of arterial stiffening in CKD. CKD-MBD (CKD-Mineral Bone Disease) is multifactorial and is mostly attributed to the metamorphosis of the mesenchymal cells of the media of the arteries from mesenchymal cells to osteoblasts. These osteoblasts subsequently calcify due to deposition of calcium. Early intervention by medical management of CKD-MBD would significantly reduce the incidence of this arterial stiffening. Early laboratory markers of CKD-MBD such as Intact Parathormone (Serum i-PTH) and even earlier markers such as FGF-23, have now become clinical targets of manipulation by various medications to prevent the development of CKD-MBD. These will hopefully reduce cardiovascular arterial stiffening and its attendant morbidity and mortality in CKD.

In the past, assessing arterial stiffness by ankle-brachial index, augmentation index, aortic pulse wave velocity, and central aortic pressure were cumbersome and needed trained operators and sophisticated instruments such as Applanation Tonometers. With the development of newer simplified cuff-based technology to assess these internal parameters by transfer factor equations, which have been sufficiently validated by research, it is now possible to obtain these measurements using simple apparatus requiring marginally trained operators. This augers well and we can expect these investigations to become clinically relevant soon in the management of hypertension.

There are 2 components to arterial stiffening; A) The reversible component that can be reduced by various medications whereby there is enhancement of pliability of the

arterial vessel walls, and B) the non-reversible component due to calcium deposition which is permanent. While using antihypertensive medications, their effect on arterial stiffness over and above their ability to reduce brachial blood pressure have been studied.

The results of the CAFE study, which is part of the ASCOT Trial, are now widely accepted. This study shows that the beta-blockers, as a class of medications, do not qualify as being cardio-protective and organ-protective as compared to calcium-channel blockers and RAAS inhibitors because of their inability to lower central aortic pressure as effectively even though brachial blood pressure was equally lowered by all the medications. The Strong Heart Study outcomes revealed that central aortic pressure is a stronger predictor for CV morbidity and mortality than the brachial blood pressure and the Reason-Q study and Rotterdam-Q study concluded that pressure augmentation, a marker of arterial stiffness, is independently predictive of CV morbidity in asymptomatic individuals.

The day is not far when central aortic pressure would become a routine measurement in our clinical armamentarium while managing CKD hypertension.

MICROVASCULAR VERSUS MACROVASCULAR DISEASE IN DIABETES

More than 40% of CKD in India is Diabetic Kidney Disease, either non-diabetic nephropathy in the diabetic or K.W. type diabetic nephropathy. The blood pressure management of both types of patients is similar. The SPRINT trial has nicely shown that there are many advantages of lowering the blood pressure to the tight control of 120 systolic. Unfortunately, there are clearly two different types of target organ; those with microvascular disease such as neuropathy, retinopathy, and nephropathy and those with macrovascular disease such as brain strokes, coronary artery disease, and peripheral lower limb vascular claudication. It is still debated whether a very tight control is as useful in

microvascular disease as it is in the macrovascular disease which has now been clearly established by the SPRINT Trial.

IS SPRINT IMPORTANT FOR NEPHROLOGISTS?

For the nephrologist, the SPRINT trial has takeaway messages; the good, the bad and the indifferent. There are good outcomes of the SPRINT Trial as far as patients of CKD are concerned. SPRINT has shown reduction of CV morbidity and mortality in all types of hypertensive patients and similar reduction both, in non-CKD as well as in CKD patients. Additionally, it has shown no significant increase in AKI in patients who already have established CKD. However, the bad side, as far as CKD is concerned is,

1. That those without CKD had a significantly higher incidence of AKI (1% versus 0.3%) in intensive arm of treatment group i.e., systolic less than 120 mmHg (? Compromised microvasculature ?)
2. There is a greater overall incidence of hypotensive side effects such as syncope, hyponatremia and hypokalaemia. Although there was no higher incidence of patients having a fall, the older patients with such low pressure will have instability of gait and be predisposed to fall.
3. 50% of patients in intensive group failed to reach the intensive goal, which is a difficult goal. The intensive therapy requires an increase from an average of 1.8 medications in the standard treatment arm to 2.8 medications in the intensive goal arm. The increase of pill burden produces a major problem of cost and compliance. It bears worthwhile repetition to mention here, that there is a different AOBP time-consuming method of BP for SPRINT targeting. The physician who chooses to use the SPRINT target of intensive therapy must also use the AOBP method

of measuring office BP. Nephrologists must remember that the SPRINT Trial had the following limitations for CKD;

1. The SPRINT was never intended to be a CKD trial. It was aimed at reducing cardiovascular and cerebrovascular risk in selected cases of hypertension.
 2. It did not include patients below the age of 50.
 3. It excluded CKD patients who had more than 1 g proteinuria in 24 hours.
 4. It also excluded all CKD patients who had albuminuria more than 600 mg in 24 hours.
- Finally,
5. The results do not distinguish between the patients receiving different types of medications such as the Renin-Angiotensin System Blockers, diuretics, calcium-channel blockers and others.

The SPRINT Trial is not necessarily applicable to all CKD patients. In Indian patients, Abraham et al have, appropriately, made recommendation based mainly on the KDOQI guidelines rather than the SPRINT guidelines in the management of CKD hypertension.

This review is highly recommended for all those managing CKD.

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

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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.

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- 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 CKD patients, and is relevant at all stages of the disease, irrespective of the underlying cause.² Clinical evidence has demonstrated that antihypertensive agents from 3 or 4 medication classes may be needed to achieve blood pressure targets in most patients with CKD.³

In India, the incidence of CKD is rising, and

Box 1: GFR categories in CKD⁵

GFR category	GFR (mL/min/1.73 m ²)	Terms
G1	≥90	Normal or high
G2	60-89	Mildly decreased*
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

CKD: Chronic kidney disease; GFR: Glomerular filtration rate. *Relative to young adult level. In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

as per estimates from 2006, the age-adjusted incidence rate of end-stage renal disease (ESRD) is 229 per million population. Further, the number of new patients entering renal replacement programs annually is >100,000.⁴ The rising incidence of CKD in India is likely to burden health care and the economy in the future.⁴

Furthermore, owing to the lack of community-based programs, CKD is usually detected at an advanced stage. Early screening and intervention may retard the progression of kidney disease. Therefore, it should be impressed upon physicians taking care of hypertensive patients to screen for early kidney damage and to initiate early intervention to retard the progression of kidney disease. Additionally, it is imperative to plan for preventive health policies and allocate more resources for the treatment of patients with CKD/ESRD in India.⁴

Despite these findings, there is a lack of literature specific to the Indian scenario at present focusing on the management of hypertension in CKD. On the other hand, the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the Management of Blood Pressure in Chronic Kidney Disease is not a recent guideline and has not been updated since 2012. Additionally, these guidelines are not widely accepted or used by Indian physicians at present.

Therefore, an advisory board of leading

Box 2: Albuminuria categories in CKD⁵

Category	AER (mg/24 hours)	ACR (approximate equivalent)		Terms
		mg/mmol	mg/g	
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased*
A3	>300	>30	>300	Severely increased**

CKD: Chronic kidney disease; AER: Albumin excretion rate; ACR: Albumin-to-creatinine ratio. * Relative to young adult level. ** Including nephrotic syndrome (albumin excretion usually >2200 mg/24 hours [ACR>2220 mg/g; >220 mg/mmol]).

Table 1: Data on the prevalence of CKD in India^{4,11,12}

Study	Number of participants	Mean age (years)	Overall CKD prevalence	Criteria to diagnose CKD
KIDS project (Anupama <i>et al.</i> 2014)	2091	39.88±15.87	6.3%	MDRD
			16.69%	CG-BSA
SEEK (Singh <i>et al.</i> 2013)	5588	45.22±15.2	17.2%	MDRD
			16.4%	CKD-EPI
Cross-sectional study (Varma <i>et al.</i> 2010)	3398	35.64±8.72	15.04%	MDRD
			13.12%	CKD-EPI

CKD: Chronic kidney disease; KIDS: KIDney Disease Screening; SEEK: Screening and Early Evaluation of Kidney Disease; MDRD: Modification of Diet in Renal Disease; CKD-EPI: Chronic kidney disease-epidemiology collaboration equation; CG-BSA: Cockcroft-Gault equation corrected to Body Surface Area.

nephrologists in India was convened twice. At the first meeting, the advisory board members reviewed available literature evidence, provided insights based on their experience on the management of hypertension in CKD patients, and charted out key recommendations. At the second meeting, the advisory board members finalized the key recommendations as part of the consensus statement for the management of hypertension in CKD patients in India. The key discussion points and recommendations provided by the advisory panel are summarized here.

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.'⁵ 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).⁵

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.⁶ According to the results of the 2013 Global Burden of Disease Study, CKD contributed to 956,200 deaths, a 134% increase from 1990.⁷ Studies have reported that CKD affects >10% of the population in several countries and >50% of high-risk subpopulations.⁸ In developed countries, CKD affects nearly 7% of all individuals aged ≥30 years, which translates to greater than 70 million individuals.⁹ 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.⁸ Globally, it has been estimated that more than 1.4 million individuals with ESRD receive renal replacement therapy with dialysis or transplantation.⁷

**Prognosis of CKD by GFR
and albuminuria categories:
KDIGO 2012**

				Persistent albuminuria categories: Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/ 1.73 m ²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green boxes indicate low risk (if no other markers of kidney disease, no CKD); yellow boxes indicate moderately increased risk; orange boxes indicate high risk; red boxes indicate very high risk.

CKD: Chronic kidney disease; GFR: Glomerular filtration rate.

Fig. 1: Prognosis of CKD by GFR and albuminuria categories.^{5,15}

Green boxes indicate low risk (if no other markers of kidney disease, no CKD); yellow boxes indicate moderately increased risk; orange boxes indicate high risk; red boxes indicate very high risk. CKD: Chronic kidney disease; GFR: Glomerular filtration rate

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.^{10,11} Hence, different criteria are used to diagnose CKD in India.¹⁰ 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).⁷ According to several other studies, the prevalence of CKD in India ranges from 6.3% to 17.2% (using the MDRD formula; Table 1).^{4,11,12} 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.¹³

Predictive risk factors involved in CKD

Factors that predict the risk of CKD can

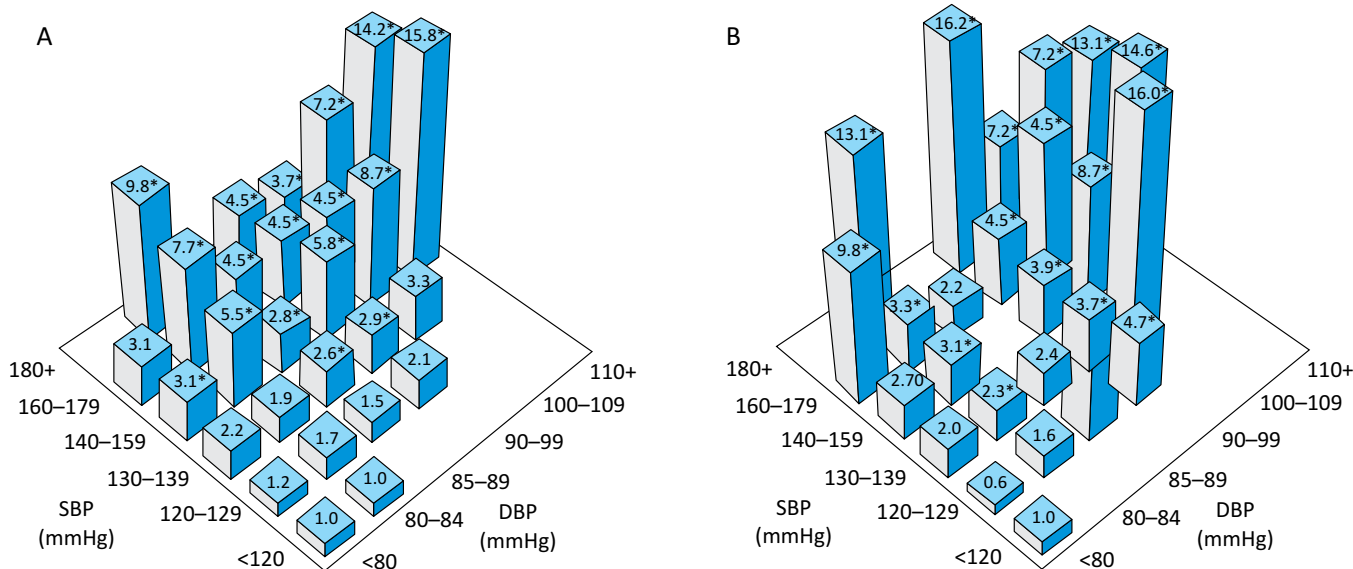


Fig. 2: Relative risk of ESRD development in men (A) and women (B), based on systolic and diastolic blood pressure.¹⁷

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.¹⁴

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.⁵ A heat map illustrating the prognosis of CKD, based on the GFR and albuminuria categories, is depicted in Figure 1.^{5,15}

HYPERTENSION: A CAUSE AND CONSEQUENCE OF CKD

Association between hypertension and CKD

Hypertension is strongly associated with CKD.¹⁶ 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.^{1,16}

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 BP (SBP/DBP <120/80 mmHg) was associated with a 20-fold higher relative risk for ESRD.¹ 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

Box 3: Selected factors that may contribute to hypertension in patients with CKD¹⁹

Factor	Dominant mechanism
Sympathetic activation	Direct vasoconstriction
	Stimulation of renin release
Imbalance in prosta- glandins or kinins	Vasoconstriction
Endothelin	Direct vasoconstriction
	Renal injury
Reduced nitric oxide	Loss of vasodilator effect

normal ($131\pm 4/79\pm 6$ mmHg), mild hypertension ($142\pm 8/86\pm 7$ mmHg), moderate hypertension ($160\pm 11/94\pm 9$ mmHg), and severe hypertension ($181\pm 16/105\pm 12$ mmHg). Figure 2 depicts the relative risk of ESRD development as per the systolic and diastolic blood pressure in the study participants after adjustment for age and body mass index. As can be seen, high normal blood pressure and hypertension are independent risk factors for the development of ESRD when compared with optimal blood pressure.¹⁷

On the other hand, patients with CKD may develop hypertension early during the disease, and hypertension may contribute to adverse outcomes, such as worsening of renal function, development of cardiovascular diseases, and high cardiovascular morbidity and mortality.^{1,16}

Hypertension as a risk factor for CKD: Pathophysiology

It has been proposed that chronic hypertension causes CKD through at least two pathways. As per the first pathway, chronic hypertension stimulates glomerular ischemia following damage to preglomerular arteries and arterioles. This leads to progressive luminal narrowing and a reduction in glomerular blood flow. Additionally, postglomerular renal ischemia occurs, contributing to the progressive loss of nephrons. As per the second pathway, chronic hypertension contributes to loss of autoregulation of afferent arterioles with subsequent transmission of high systemic blood pressure to the glomeruli. This leads to hyperperfusion

Box 4: Drugs that may induce or exacerbate hypertension²⁰

Nonsteroidal anti-inflammatory drugs
Oral contraceptives
Sympathomimetics
Mineralocorticoids
Glucocorticoids
Erythropoietin
Cyclosporine, tacrolimus
Vascular endothelial growth factor inhibitors
Illicit drugs
Herbal supplements

and hyperfiltration, which lead to structural glomerular damage (i.e. glomerulosclerosis) and progressive loss of renal function.¹⁸

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).¹⁹

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

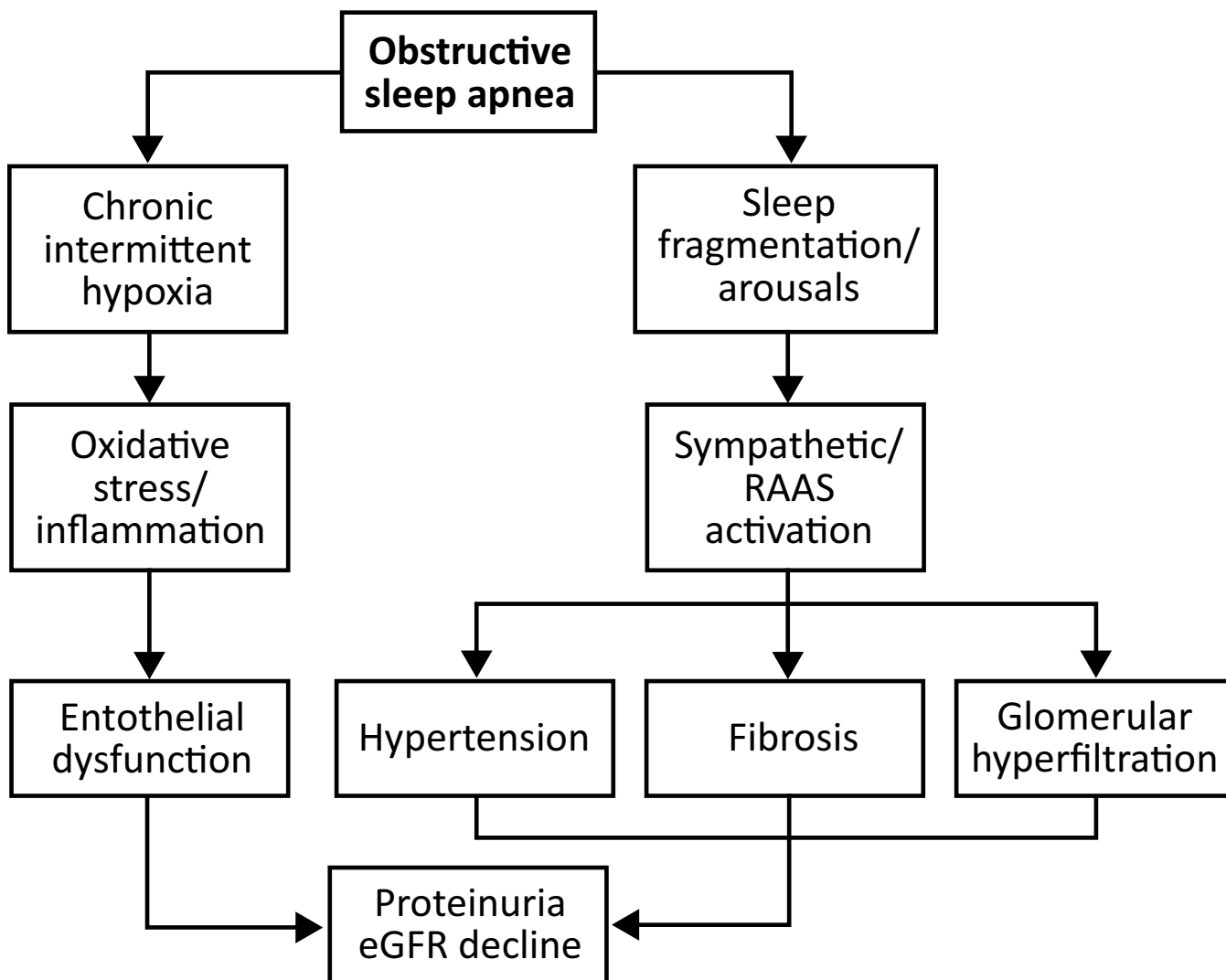


Fig. 3: Pathophysiologic association between obstructive sleep apnea and chronic kidney disease.²¹

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.¹⁹ In the Screening and Early Evaluation of Kidney Disease (SEEK)-India cohort, hypertension, defined as systolic and diastolic blood pressure $\geq 140/90$ 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).⁴ In the KIDS project conducted in rural India, hypertension was observed in 59.54% of subjects with CKD and in 31.83% of subjects without CKD.¹¹

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 detect and manage this condition.²⁰

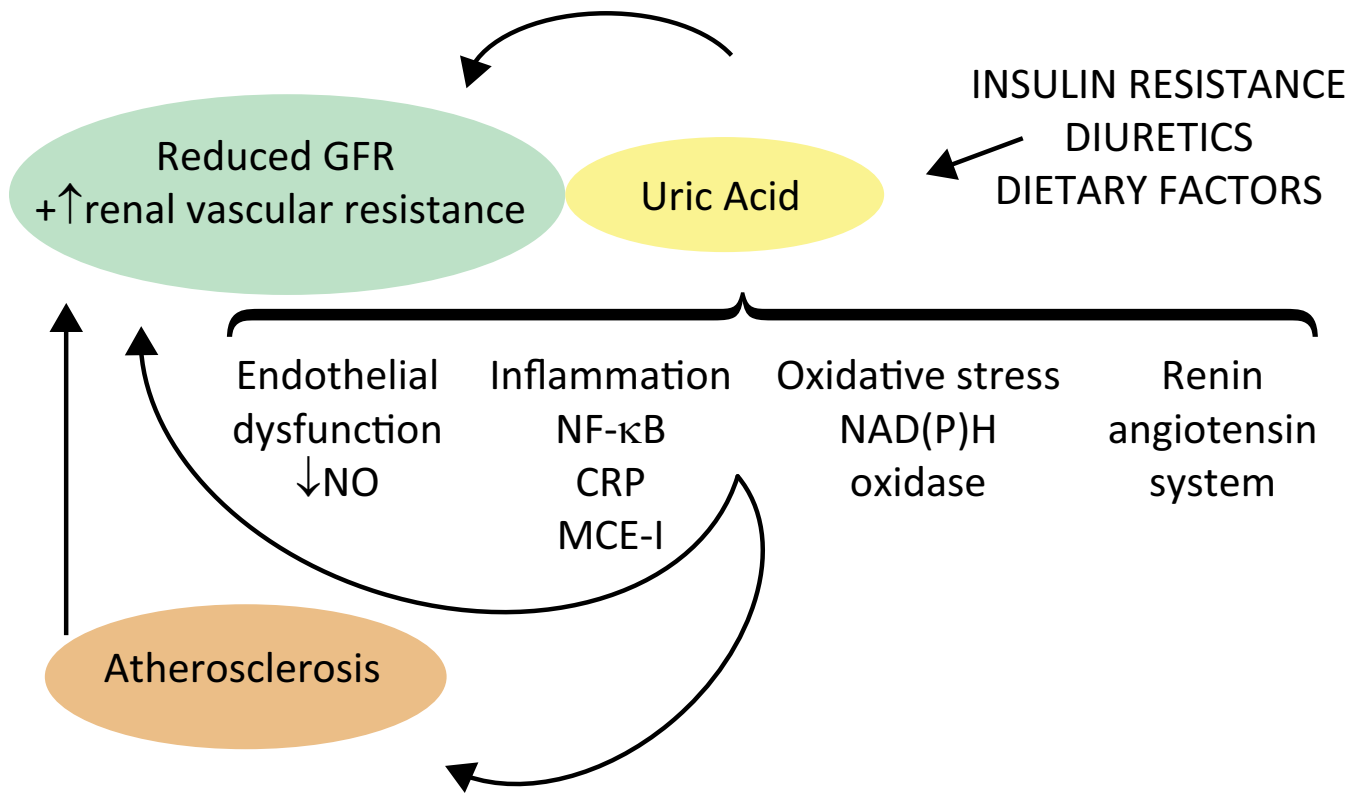


Fig. 4: Potential mechanisms through which elevated serum uric acid levels may contribute to the development and progression of CKD.²² GFR: Glomerular filtration rate; NO: Nitric oxide; NF- κ B: Nuclear factor- κ B; CRP: C-reactive protein

Obstructive sleep apnea and CKD

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.²¹

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 and

thereby alters 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.²¹

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.²¹

Box 5: Recommended technique for measuring blood pressure³⁰

- 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 heart 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.

Hyperuricemia and 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.²¹

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, 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.²²

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.²³ Therefore, it is essential to obtain a thorough history that can help establish a correct diagnosis.

Table 2: Factors that may affect the accuracy of blood pressure values³²

Factor	Effect on systolic blood pressure (mmHg)	Effect on diastolic blood pressure (mmHg)
Cold room vs. comfortable room temperature	↑14/↑15	↑15
Uncomfortably distended bladder	↑50	↑40
Full bladder	↑10–15	↑10–15
Heavy physical exercise before measurement	↓18–20	↓7–9
Heavy meal before measurement	↓20	↓20
Smoking before measurement	↑10	↑8
Not resting at least 5 min before measurement	↑10–20	↑14
Supine vs. Sitting	↑3–10	↑1–5
Back/feet unsupported vs. Supported	↑5–15	↑6
Arm unsupported vs. supported	↑1–7	↑5–11
Legs crossed vs. uncrossed	↑5–8	↑3–5
Talking during measurement vs. being silent	↑17	↑13
Arm below heart level vs. at heart level	↑10	↑10
Cuff too large	↓10–30	↓10–30
Cuff too small	↑3–12 in obese individuals ↑30	↑2–8 in obese individuals ↑30
Diaphragm of stethoscope vs. bell (auscultation method)	↓0–2	↓0–2

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.²⁴ 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.²⁵

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.²⁶ In primary care settings, feasible tests for screening for CKD include testing the urine for protein and measuring serum creatinine levels to estimate GFR.²⁷ The need to assess other markers of kidney damage should be decided based on clinical judgment and the presence/absence of CKD risk factors.²⁸

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.²⁹ The technique to be followed while measuring blood pressure is given in Box 5.³⁰

Although the auscultatory method has remained the mainstay of clinical blood pressure measurement, it is gradually being replaced by other techniques such as the Oscillometric technique, the finger cuff method of Penaz, ultrasound techniques, and tonometry.²⁹

In the oscillometric technique, oscillations of pressure in a sphygmomanometer cuff are recorded during gradual deflation. The point of maximal oscillation corresponds to the mean intra-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.²⁹

According to the American Heart Association, a minimum of 2 readings should be taken at intervals of at least 1 minute and the patient's blood pressure should be based on the average of these readings. If the difference between the first and second readings is greater than 5 mmHg, an additional 1 or 2 readings should be obtained and the average of these multiple readings used.²⁹

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.^{29,31} 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.³⁰

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.²⁹

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.³⁰ 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).³²

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 intraindividual 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 $\geq 50\%$ 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.³³

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.³⁸ 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.^{38,39} 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.

Table 3: Relationship between categories for proteinuria and albuminuria²⁵

Measure	Category		
	Normal to mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)
AER (mg/24 h)	<30	30–300	>300
PER (mg/24 h)	<150	150–500	>500
ACR (mg/mmol)	<3	3–30	>30
ACR (mg/g)	<30	30–300	>300
PCR (mg/mmol)	<15	15–50	>50
PCR (mg/g)	<150	150–500	>500
Protein reagent strip	Negative to trace	Trace to +	+ or greater

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

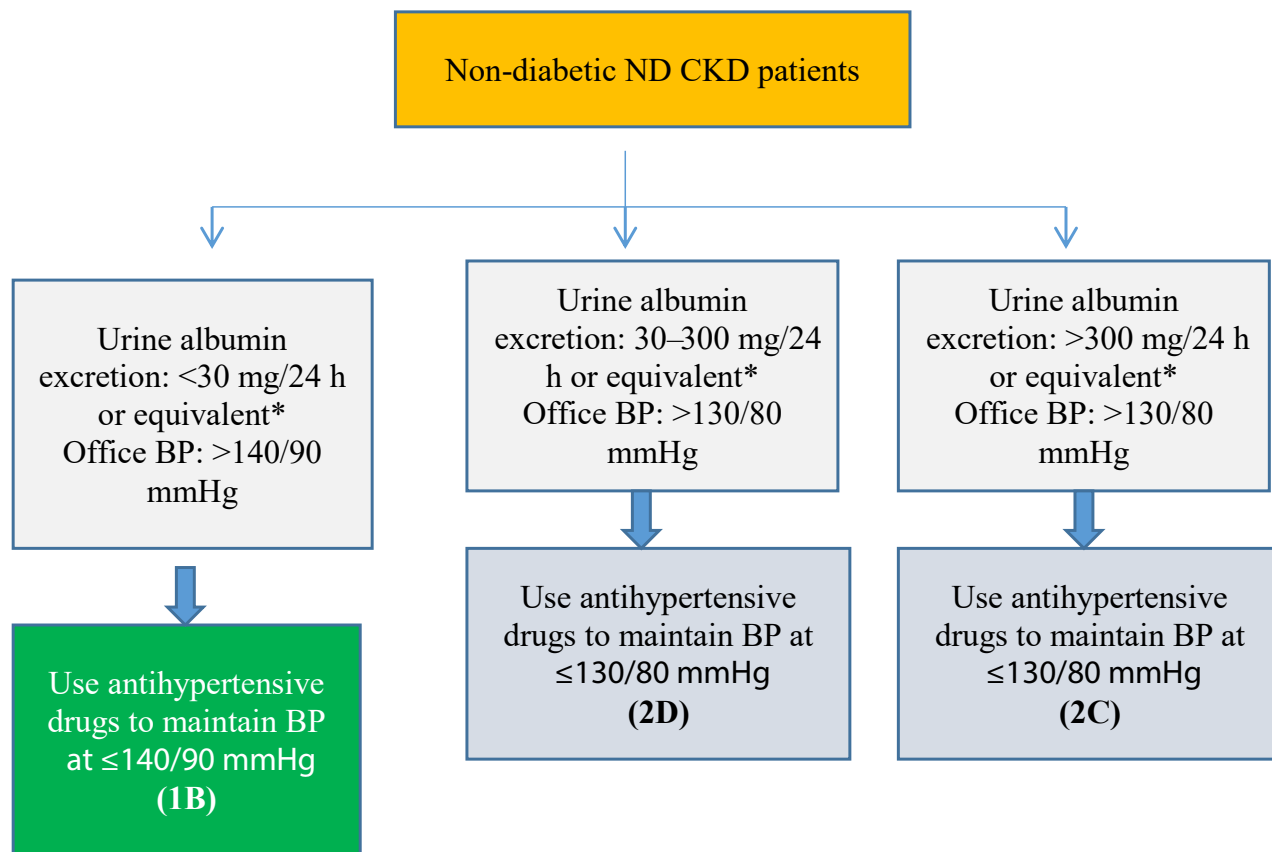


Fig. 5: 2012 KDIGO Guidelines on management of hypertension in non-diabetic non-dialysis-dependent CKD patients.² Green boxes indicate recommendations, and blue boxes indicate suggestions. BP: Blood pressure; CKD: Chronic kidney disease. * To know the approximate equivalents for albumin excretion rate per 24 h, refer to the 2012 KDIGO guidelines period

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),⁴² Canadian

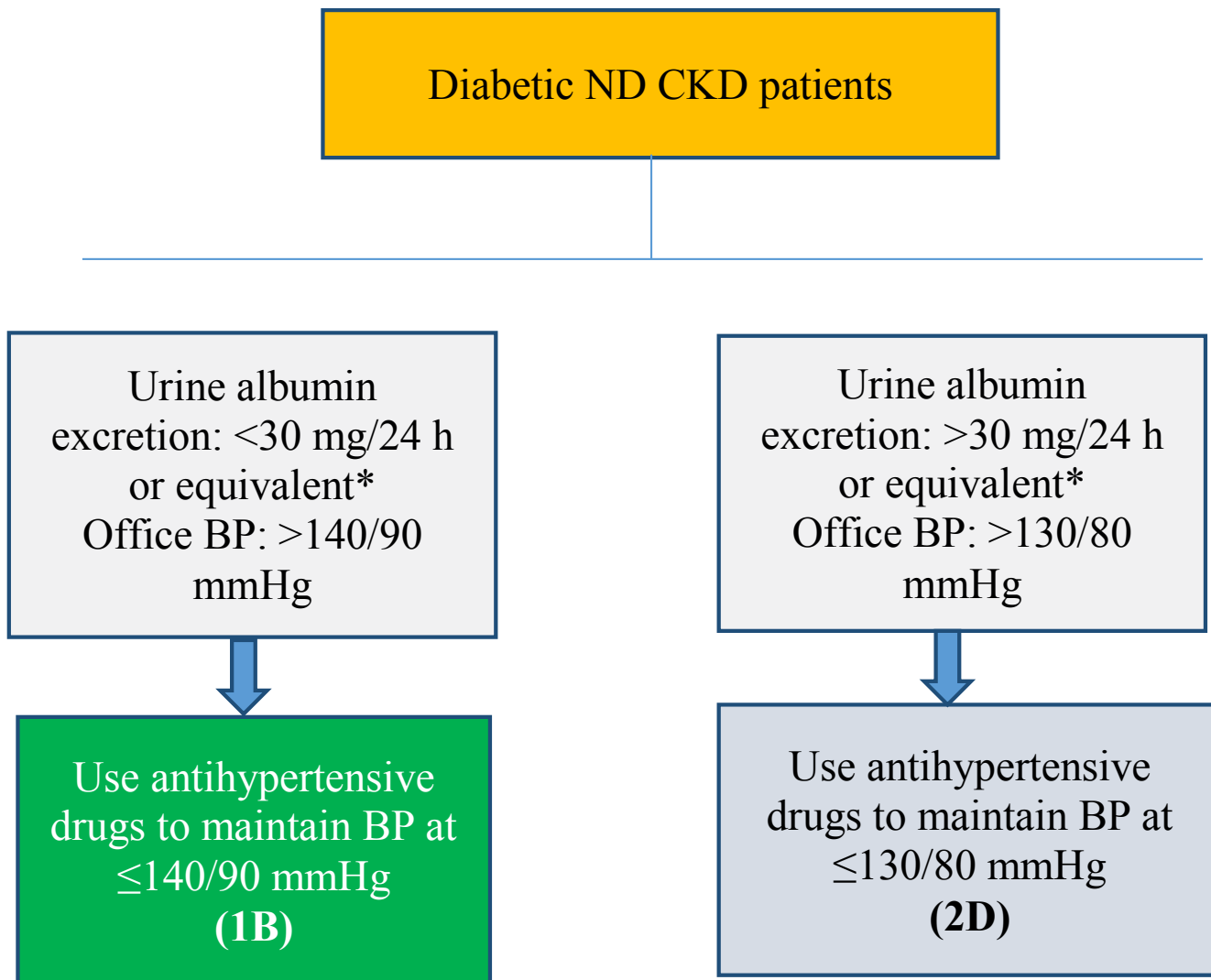


Fig. 6: KDIGO 2012 Guidelines on hypertension management in non-dialysis-dependent patients with diabetes mellitus.² Green boxes indicate recommendations, and blue boxes indicate suggestions. BP: Blood pressure; CKD: Chronic kidney disease. *To know the approximate equivalents for albumin excretion rate per 24 h, refer to the 2012 KDIGO guidelines end with a period

Hypertension Education Program (2014),⁴⁴ and the European Society of Hypertension (2013)⁴⁵ recommend a goal blood pressure of <math><140/90\text{ mmHg}</math>. However, in patients with an albumin creatinine ratio of $\geq 70\text{ mg}/\text{mmol}$, the 2014 National Institute for Health and Care Excellence guidelines recommend a goal blood pressure of <math><130/80\text{ mmHg}</math>.⁴³

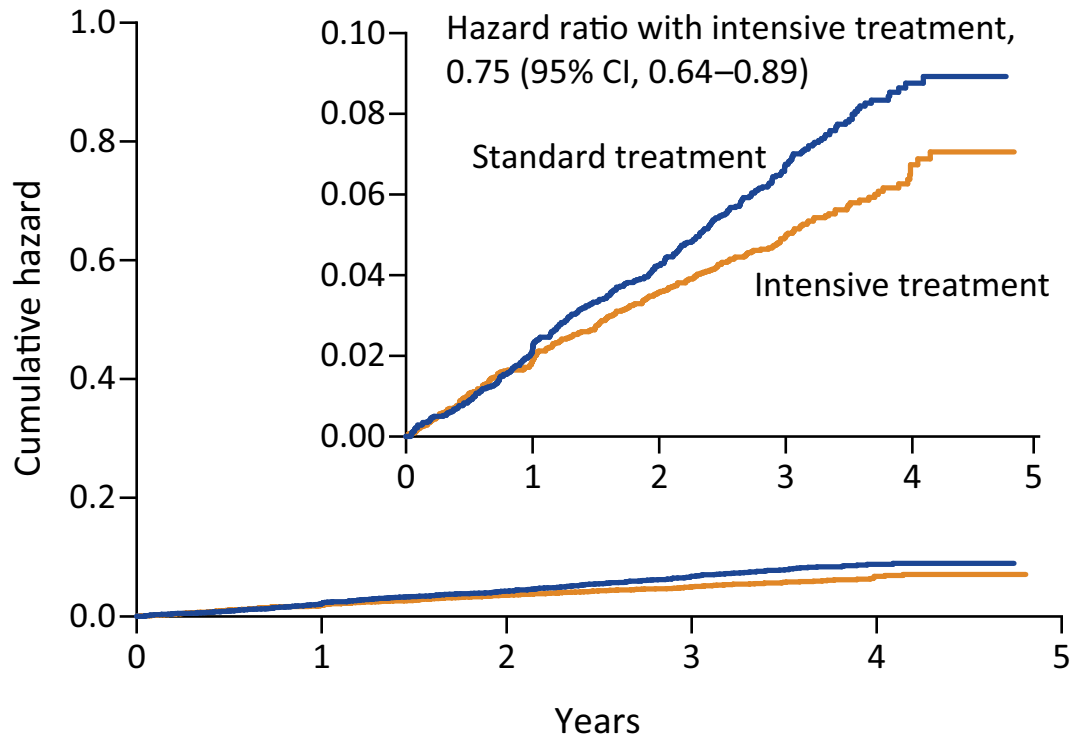
The 2012 KDIGO guidelines have also recommended goal blood pressure in non-diabetic and diabetic adults with non-dialysis-dependent CKD. These recommendations are

presented in Figures 5 and 6, respectively.²

Intensive vs. standard blood pressure lowering: Clinical evidence

Although major guidelines recommend a blood pressure target of <math><140/90\text{ mmHg}</math> 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



No. at risk

Standard treatment	4683	4437	4228	2829	721
Intensive treatment	4678	4436	4256	2900	779

Fig. 7: Cumulative hazard for primary outcome (composite of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes) among standard vs. intensive blood pressure-lowering groups.⁴⁶

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 subjects with CKD at baseline, no significant difference was observed 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

Box 6: Checklist for identifying hypertensive patients at risk for CKD

- Advanced age, i.e. greater than or equal to 50 years⁴⁹
- Presence of other comorbidities such as diabetes, metabolic syndrome, urinary stones, hyperlipidemia, etc.¹⁴
- History of or presence of anemia⁴⁹
- History of heart attack, stroke, or congestive heart failure⁴⁹
- Family history of CKD¹⁴
- Smoking¹⁴
- Abnormally increased levels of serum creatinine and cystatin C⁵⁰
- Two recent eGFR results obtained within the last 2 years, performed more than 90 days apart, with both showing values <60 mL/min/1.73m²⁵¹
- Presence of proteinuria, i.e. urine protein dipstick 1+ or greater, spot urine albumin-creatinine ratio >200 mg/g on two consecutive dates separated by at least 90 days with or without reduced GFR⁵²
- Albumin excretion rate >30 mg/24 hours in 24-hour samples, or albumin creatinine ratio 30–300 mg/g in at least two of three samples obtained within a period of 3–6 months²³
- Presence of red blood cells and white blood cells on urinalysis²⁵

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) or an 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 30–300 mg/24 hours.²

Panel Recommendations

- Blood pressure targets need to be individualized; in patients with proteinuria, the blood pressure targets can be lower.
- One or more antihypertensive agents can be prescribed to achieve blood pressure targets in CKD patients.
- α -blockers are effective add-on agents to achieve additional reduction in blood pressure in CKD patients.

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/m.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 ≥65 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.

- The blood pressure target in patients with CKD is less than 140/90 mmHg, and in patients with CKD and diabetes mellitus or albuminuria, the blood pressure target is less than 130/80 mmHg. If the blood pressure is below the target, the patient should be recommended lifestyle modifications to manage risk factors, and the blood pressure should be monitored. If the patient's blood pressure is above the target, then an ACE-I or ARB (ideally in patients with serum creatinine levels <3) or a calcium channel blocker (CCB) should be started. The patient's estimated glomerular filtration rate and serum potassium levels should be determined. Monitoring of blood pressure should be continued, and additionally, the patient should be recommended lifestyle modifications to manage risk factors.
- If during subsequent visits, the blood pressure is at the desired target, the patient should be encouraged to continue the recommendations for lifestyle modifications and blood pressure monitoring should be continued. If, however, the blood pressure is above the target, adherence to medication and lifestyle modifications should be reinforced; the dose of the prescribed ACE-I or

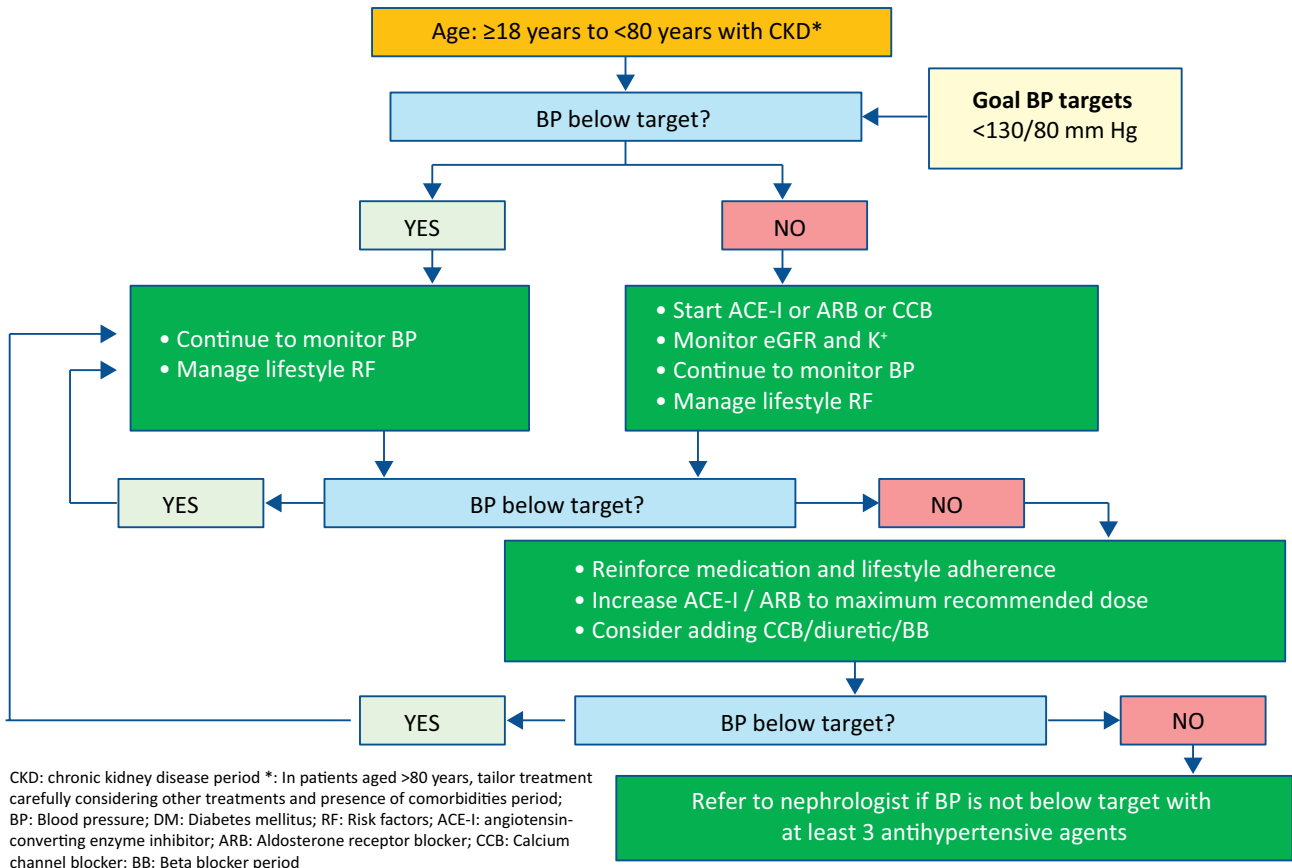


Fig. 8: Proposed algorithm for the management of blood pressure in patients with chronic kidney disease

ARB should be increased to the maximum recommended dose. The addition of a CCB, diuretic, α -blocker, or β -blocker may also be considered.

- If during subsequent visits, the blood pressure is at the desired target, the patient should be encouraged to continue the recommendations for lifestyle modifications and blood pressure monitoring should be continued. If, however, the blood pressure is above the target, adherence to medication and lifestyle modifications should be reinforced; the dose of the prescribed ACE-I or ARB should be increased to the maximum recommended dose. The addition of a CCB, diuretic, α -blocker, or β -blocker may also be considered.
- Women of reproductive age should be mandatorily educated on the need to use contraception, especially when they are on ACE-I or ARBs.
- Despite treatment with three antihypertensive agents, if the blood pressure does not remain at target levels, then the patient should be referred to a nephrologist.
- α -blockers are safe in CKD patients and are not associated with blood pressure variability, and can be used as add-on therapy.

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.⁵³ 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

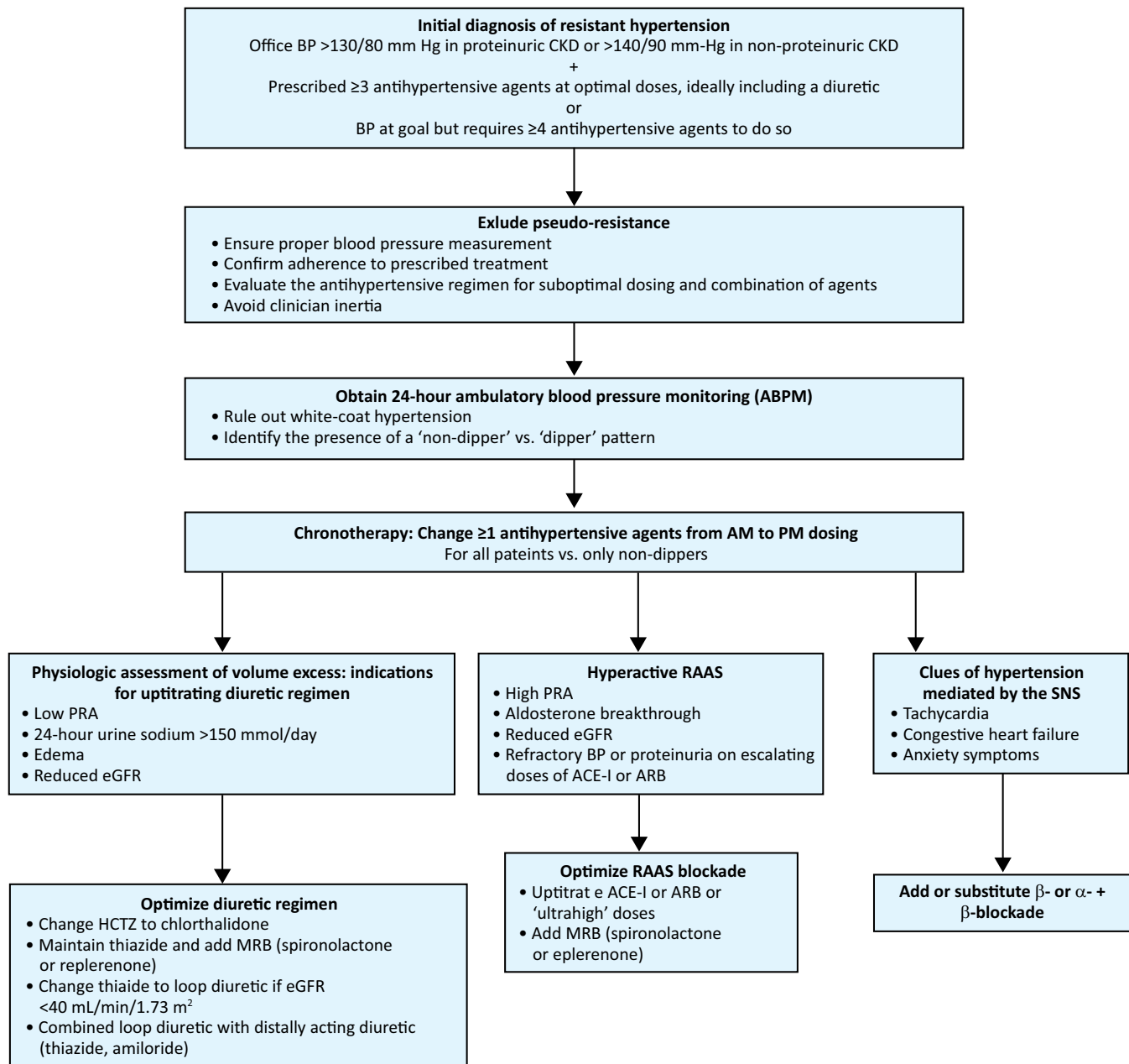


Fig. 9: Physiology-based algorithm for initiation and management of resistant hypertension in patients with chronic kidney disease⁵³

progresses, the ability of the kidneys to regulate sodium dilution and concentration becomes impaired.⁵⁴

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 sympa-

thetic 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).⁵³

Patients with ESRD and uncontrolled hypertension can also be managed using open or laparoscopic nephrectomy. Compared to open nephrectomy, which is associated with signif-

icant 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.⁵⁵

Panel recommendations

- Blood pressure targets should be individualized based on age, co-morbidities, 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.

MANAGEMENT OF BLOOD PRESSURE IN DIALYSIS-DEPENDENT CKD PATIENTS

Hypertension and mortality in dialysis patients

Evidence from large observational studies has demonstrated a U-shaped mortality curve with regard to blood pressure in patients undergoing dialysis. These studies failed to demonstrate an association between significant hypertension and worse outcomes; on the contrary, they demonstrated that lower blood pressure levels in dialysis patients are associated with increased mortality. In view of the contradictory findings 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 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

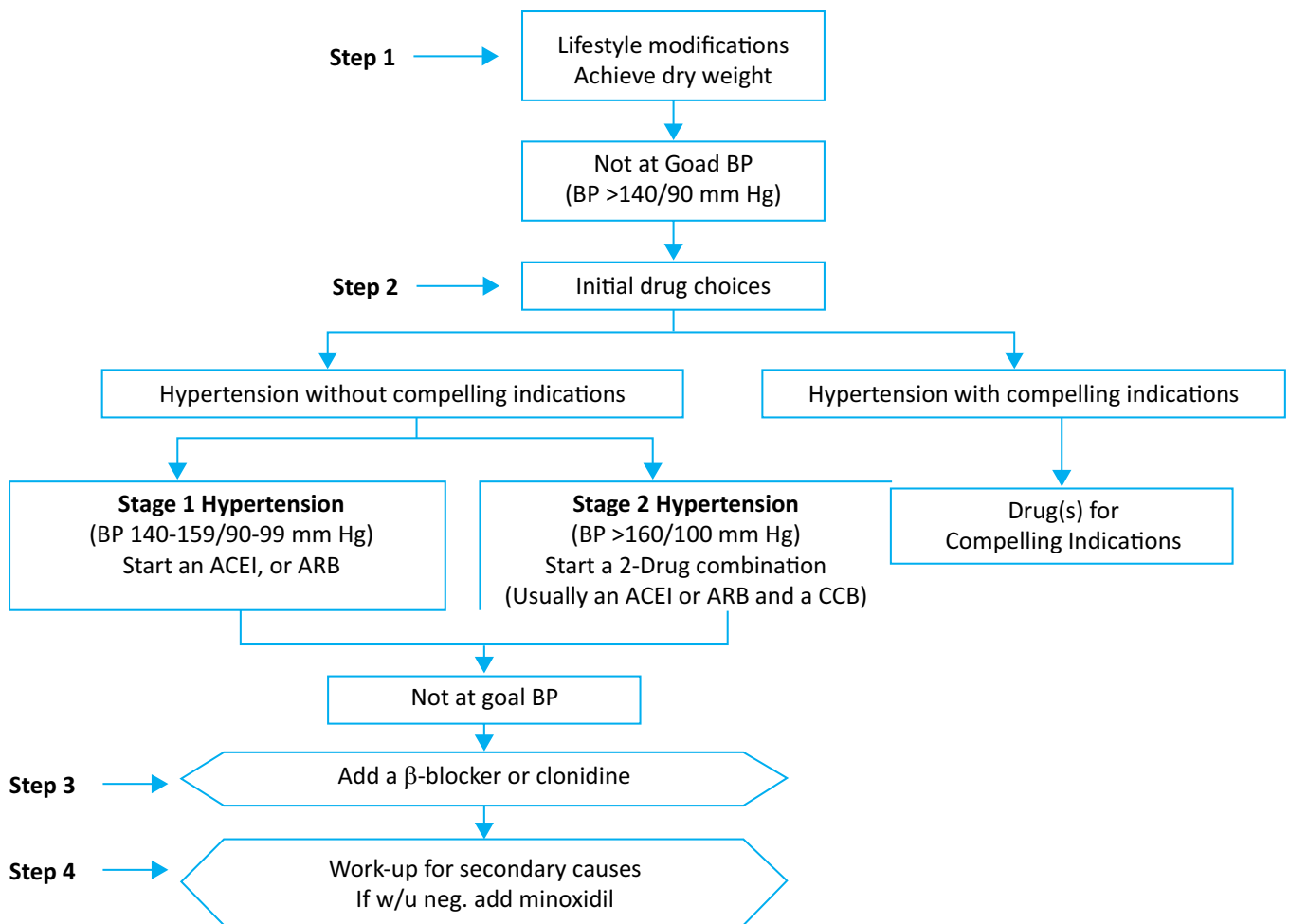


Fig. 10: Pharmacological approach for management of blood pressure in dialysis patients.⁵⁷

Table 4: Guidelines for selecting antihypertensive agents in dialysis patients⁵⁷

Clinical situation	Preferred	Relatively or absolutely contraindicated
Angina pectoris	β-blockers, CCBs	Direct vasodilators
Post-MI	Non-ISA β-blockers	Direct vasodilators
Hypertrophic cardiomyopathy with diastolic dysfunction	β-blockers, diltiazem, verapamil	Direct vasodilators, α1-blockers
Bradycardia, heart block, sick sinus syndrome		β-blockers, labetalol, verapamil, diltiazem
Heart failure (decreased LV ejection fraction)	ACE inhibitors, ARBs, β-blockers	CCBs
Peripheral vascular disease		β-blockers
Diabetes mellitus	ACE inhibitors, ARBs	
Asthma/COPD		β-blockers
Cyclosporine-induced hypertension	CCBs, labetalol	Nicadipine ^a , verapamil ^a , diltiazem ^a
Liver disease		Labetalol, methyldopa
Erythropoietin-induced hypertension	Calcium antagonists	ACE inhibitors ^b

^aMay increase serum levels of cyclosporine. ^bMay increase erythropoietin requirement. ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; COPD: Chronic obstructive pulmonary disease.

Table 5: Removal of antihypertensive drugs with dialysis⁵⁷

	Percent removal with dialysis	
	HD	PD
ACE inhibitors		
Benazepril	Yes	?
Enalapril	35	?
Fosinopril	2	?
Lisinopril	50	?
Ramipril	Yes	?
Calcium channel blockers		
Amlodipine	?	?
Diltiazem	?	?
Nifedipine	Low	Low
Nicardipine	?	?
Felodipine	?	?
Verapamil	Low	Yes
β-blockers		
Atenolol	75	53
Alebutolol	70	50
Carvedilol	None	None
Labetalol	<1	<1
Metoprolol	High	?
Antiadrenergic drugs		
Clonidine	5	?
Guanabenz	None	None
Methyldopa	60	3-40
Vasodilators		
Hydralazine	None	None
Minoxidil	Yes	Yes
Angiotensin receptor blockers		
Losartan	None	None
Cardesartan	None	?
Eprosartan	None	None
Telmisartan	None	?
Valsartan	None	None
Irbesartan	None	None

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 \leq 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:²

- side effects noted in the general population as well as in kidney transplant recipients
- level of urine albumin
- degree of hemodynamic stability
- presence of comorbid conditions that may indicate or preclude certain agents
- potential to alter graft perfusion, particularly during the period immediately after transplantation
- interactions with immunosuppressive agents or other medications specific to kidney transplant recipients
- and long-term impact on graft function, CVD, and all-cause mortality

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

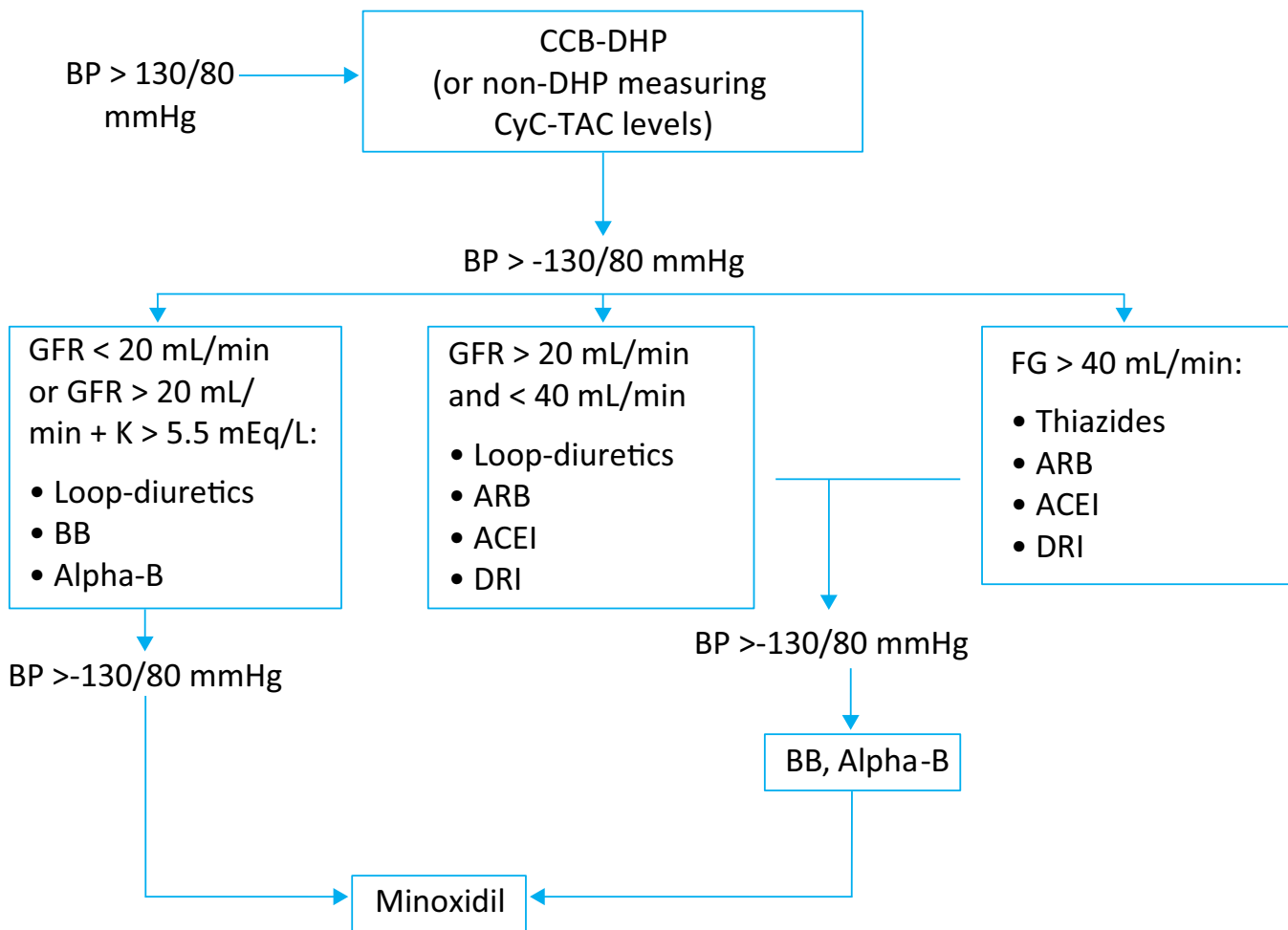


Fig. 11: Algorithm on therapeutic approach in transplant patients with hypertension⁵⁹

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 interna-

tional organization recommend a goal blood pressure of <140/90 mmHg in patients with CKD.

- The KDIGO 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 ≤140/90 mmHg.
- In diabetic as well as non-diabetic, non-dialysis-dependent CKD patients with urine albumin excretion >300 mg per 24 hours or equivalent in whom use of antihypertensive drugs is indicated, the use of an ARB or ACE-I is recommended.
- The NKF-KDOQI guidelines recommend a predialysis goal BP of <140/90 mmHg and a postdialysis goal BP of <130/80 mmHg in patients undergoing dialysis.
- The KDIGO guidelines suggest that irrespective of the level of urine albumin excretion, adult kidney transplant recipients with a consistent office BP of >130/80 mmHg be treated with antihypertensive agents to maintain the BP consistently at ≤130/80 mmHg.
- In children with non-dialysis-dependent CKD, BP-lowering treatment should be started when BP is consistently above the 90th percentile for age, sex, and height
- In elderly persons with CKD, BP management should be tailored carefully based on their age, other treatments, and presence of comorbidities.

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- Abstracts must be received by the date, 30th June, 2017.
- Each author may present only one free communication but may be co-author of additional abstracts.
- If accepted, your abstract will be reproduced exactly as it is typed and will appear in the Journal of H.S.I., which will be distributed to all the members.
- The decision of Scientific Committee will be final as to where to accommodate the paper.
- Approximate time allotted for each paper will be 5 minutes for presentation and 3 minutes for discussion on it.
- If authors of accepted papers remain absent without prior intimation to the Chairman of the Sc. Committee of HSI, their papers may not be considered for two subsequent conferences.
- The abstract should be as informative as possible to include Object of the study, Methodology, Summary of results and Conclusion reached.
- The abstract should be submitted to online www.hsindia.org / brbhsi1@gmail.com

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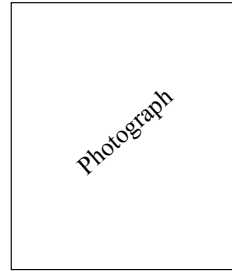
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