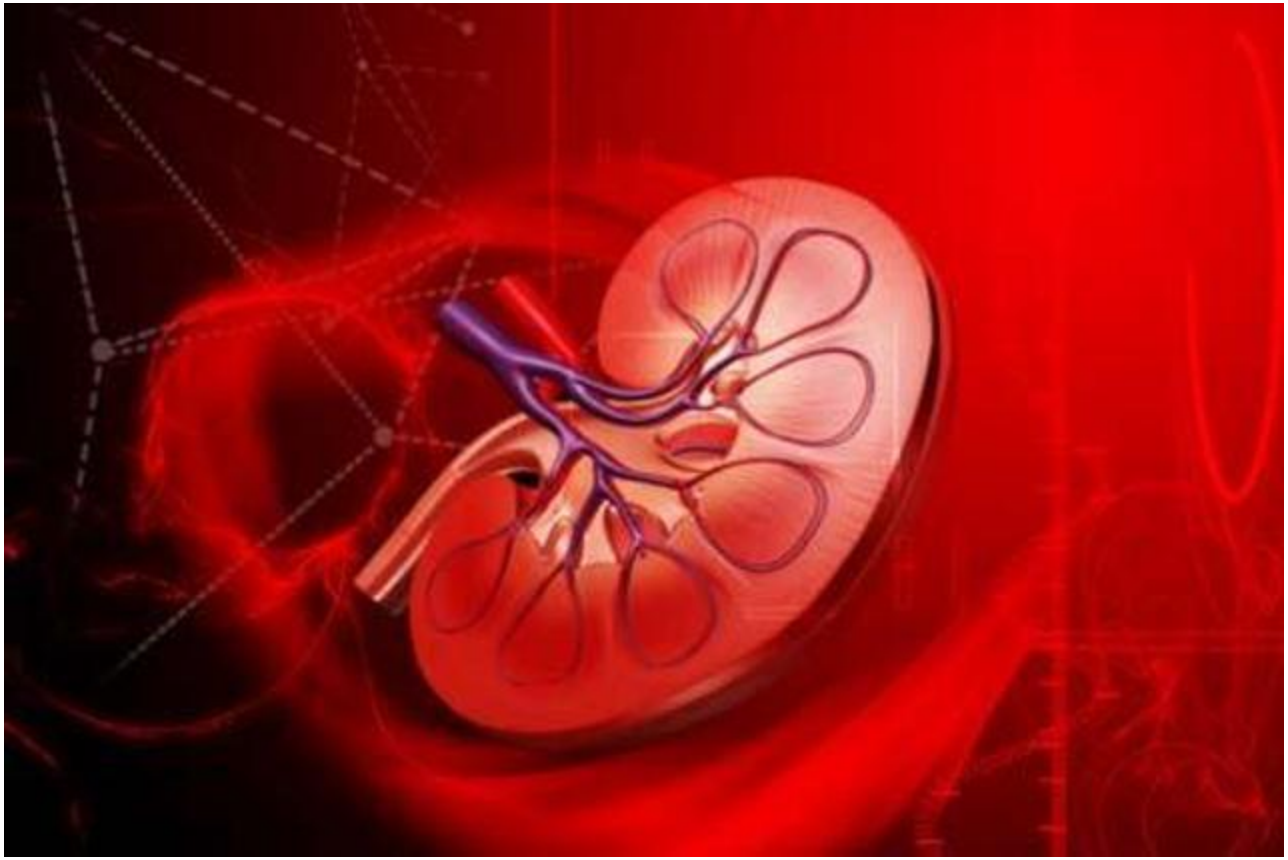


Management of Hypertension in CKD: An Insight

Hypertension Burden

970 million — Worldwide prevalence

60% — Increase in the number of adults with HTN globally by 2025

10% — Percent of all global healthcare spending attributable to HTN

$370 billion — Annual worldwide cost of hypertension

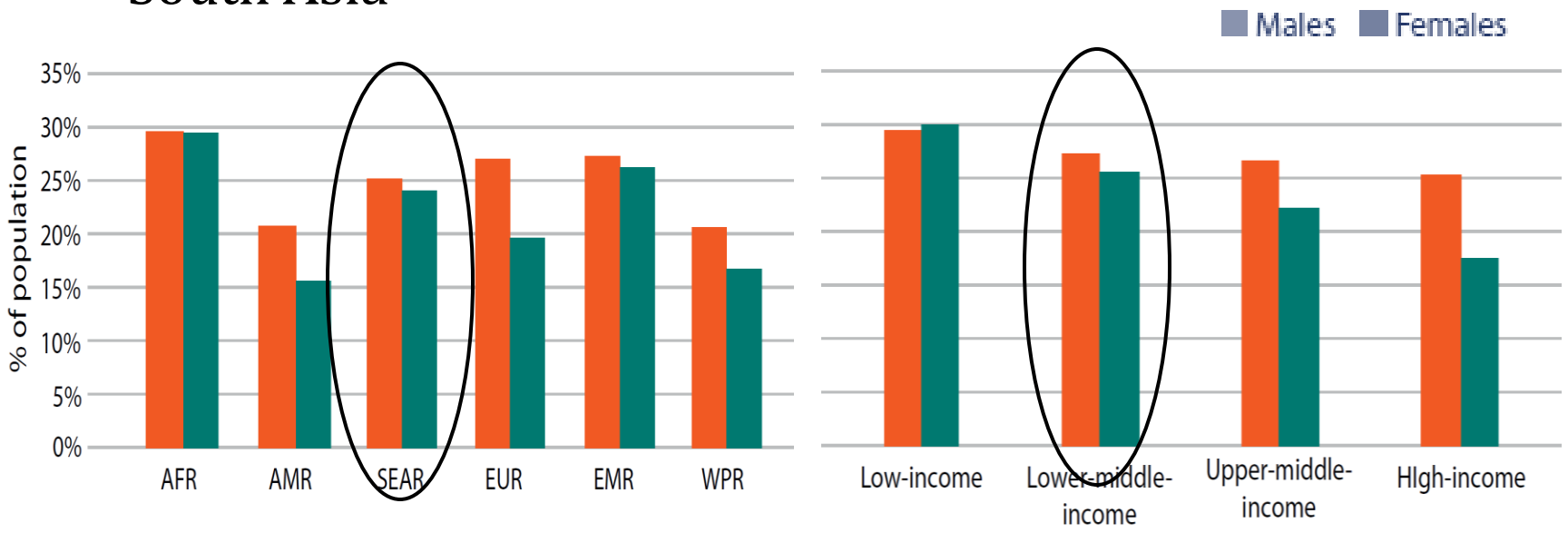
1.6 Billion HTN patients estimated by 2025

Singh PS et al. Int J Res Med Sci. 2017 Apr;5(4):1451-1455
World-heart-federation.org. [Accessed 10 May 2017]

Hypertension: WHO Estimates

- The global prevalence is ≈22%.

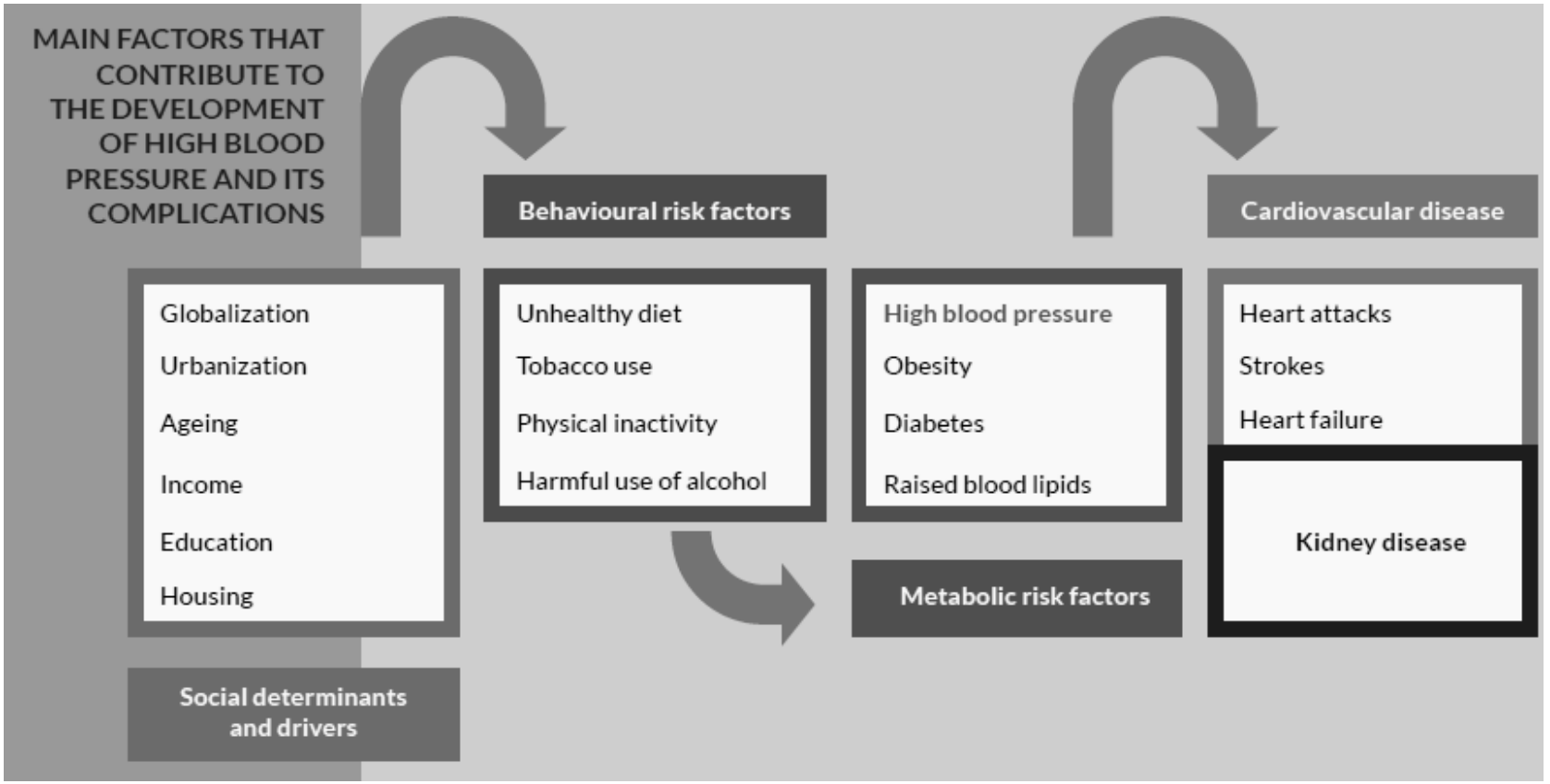
- **Ranked 3rd** most risk factor for hypertension burden in South Asia



AFR=African Region, AMR=Region of the Americas, SEAR =South-East Asia Region, EUR=European Region, EMR=Eastern Mediterranean Region, WPR=Western Pacific Region

Global Status Report, 2014. Apps.WHO.int.

Hypertension Risk Factors



Hypertension is a polygenic disease involving a major contribution of various factors

Who.int. WHO/ A global brief on hypertension

Gupta R et al. *J Hum Hypertens*. 2016 Feb;30(2):79-82.

CKD and Hypertension

- CKD and hypertension are closely associated with an overlapping and intermingled cause and effect relationship.

- Declines in kidney function are typically associated with rises in BP and sustained elevations in BP hasten the progression of kidney function decline

- In the Chronic Renal Insufficiency Cohort (CRIC) study (N= 3612) the prevalence of self-reported HTN was 86% compared with 29% in the general population

Judd A et al. Adv Chronic Kidney Dis. 2015 Mar; 22(2): 116–122.

CKD and Hypertension

- The prevalence rate of HTN rises, and BP becomes more difficult to control with advancing CKD stage.

- Worsening of kidney function as a consequence of an elevated BP is evident by a direct relationship between relative risk of developing end-stage kidney disease (ESKD) and BP severity.

- In a large health screening registry, individuals with a baseline BP close to 180/100 mm Hg were **approximately 15 times more likely to develop ESKD** than individuals with a baseline BP close to 110/70 mm Hg.

Tozawa M, et al. Hypertension. 2003;41(6):1341–1345

Hypertension and CKD

- Hypertension is a major risk factor for cardiovascular and renal disease.
- Conversely, chronic kidney disease (CKD) is the most common form of secondary hypertension
- Mounting evidence suggests it is an independent risk factor for CV morbidity and mortality
- Evidence from a large number of clinical trials has clearly demonstrated that effective treatment ameliorates the harmful effects of uncontrolled hypertension

Tedla FM et al. Int J Hypertens. 2011; 2011: 132405.

Defining BP Control by Ambulatory Monitoring in HTN

Defining BP Control in HTN

- For groups where an office BP less than 140/90 mm Hg defines control,
  - the overall 24-hour mean BP should be less than 130/80 mm Hg
  - with a corresponding mean daytime BP less than 135/85 mm Hg and mean night-time BP less than 120/70 mm Hg.

- Blood pressure control using self-measured BPs at home is identical to mean daytime BP with ambulatory monitoring (<135/85 mm Hg).

- Individuals with an office BP less than 140/90 mm Hg yet who are not controlled by home BP monitoring or 24-hour ambulatory monitoring are classified as masked HTN or masked uncontrolled HTN if he/she is receiving antihypertensive medications.

Judd A et al. Adv Chronic Kidney Dis. 2015 Mar; 22(2): 116–122.

Definition of Terms Associated With Hypertension

Hypertensive Term	Definition	Comments
Resistant hypertension	Uncontrolled BP despite maximal effective dosing of ≥3 medications of different classes, one ideally being a diuretic[41]	Includes patients controlled on ≥4 medications
Apparent resistant hypertension	Meeting criteria for resistant HTN, yet unable to exclude pseudoresistance[62]	Reported in observational studies
Pseudoresistance	Uncontrolled office BP while receiving ≥3 medications in the setting of medication nonadherence, improper BP measurement technique, and/or white coat HTN	Presumed to contribute to as much as 50% of resistant hypertension[62]
White coat hypertension	Uncontrolled office BP with a controlled overall average BP by 24-hr ABPM (<130/80 mm Hg) or home BP < 135/85 mm Hg[7]	
Masked uncontrolled hypertension	Controlled office BP (<140/90 mm Hg) with an elevated overall average BP by 24-hr ABPM (>130/80 mm Hg) or home BP > 135/85 mm Hg[7]	Present in as many as 40%–70% of patients with CKD and HTN[9,10]
Dipping	Fall in nocturnal systolic and diastolic BP of >10% of daytime values[7]	
Nondipping and rising	No reduction or an increase in nocturnal systolic and/or diastolic BP[7]	
Refractory hypertension	Uncontrolled BP despite maximal medical therapy (ie, ≥5 antihypertensive medications at maximal effective dosing and of different class)	

Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CV, cardiovascular; HTN, hypertension.

Masked uncontrolled HTN

- Masked uncontrolled HTN is more prevalent among individuals with CKD with rates ranging from 40% to 70%.

- The likelihood of having masked uncontrolled HTN rises in proportion to kidney dysfunction and the extent of proteinuria.

- Without an assessment of ambulatory or home BP, masked uncontrolled HTN will be missed, and this group of individuals is at a high risk for both cardiovascular events and initiation of dialysis.

Bangash F, Clin J Am Soc Nephrol. 2009 Mar; 4(3):656-64.

Masked uncontrolled Hypertension

- In a multicenter prospective study of 489 consecutive hypertensive patients with CKD.
- The group with masked uncontrolled HTN had a **3-fold higher risk** for fatal and nonfatal cardiovascular events
- Nearly **4-fold higher risk for dialysis** initiation after a median of 5.2 years of follow-up, compared with the group controlled both at home and in the clinic.
- No increase in risk was seen in the group who was uncontrolled in the office yet controlled at home

Minutolo R et al Am J Kidney Dis. 2014 Nov; 64(5):744-52.

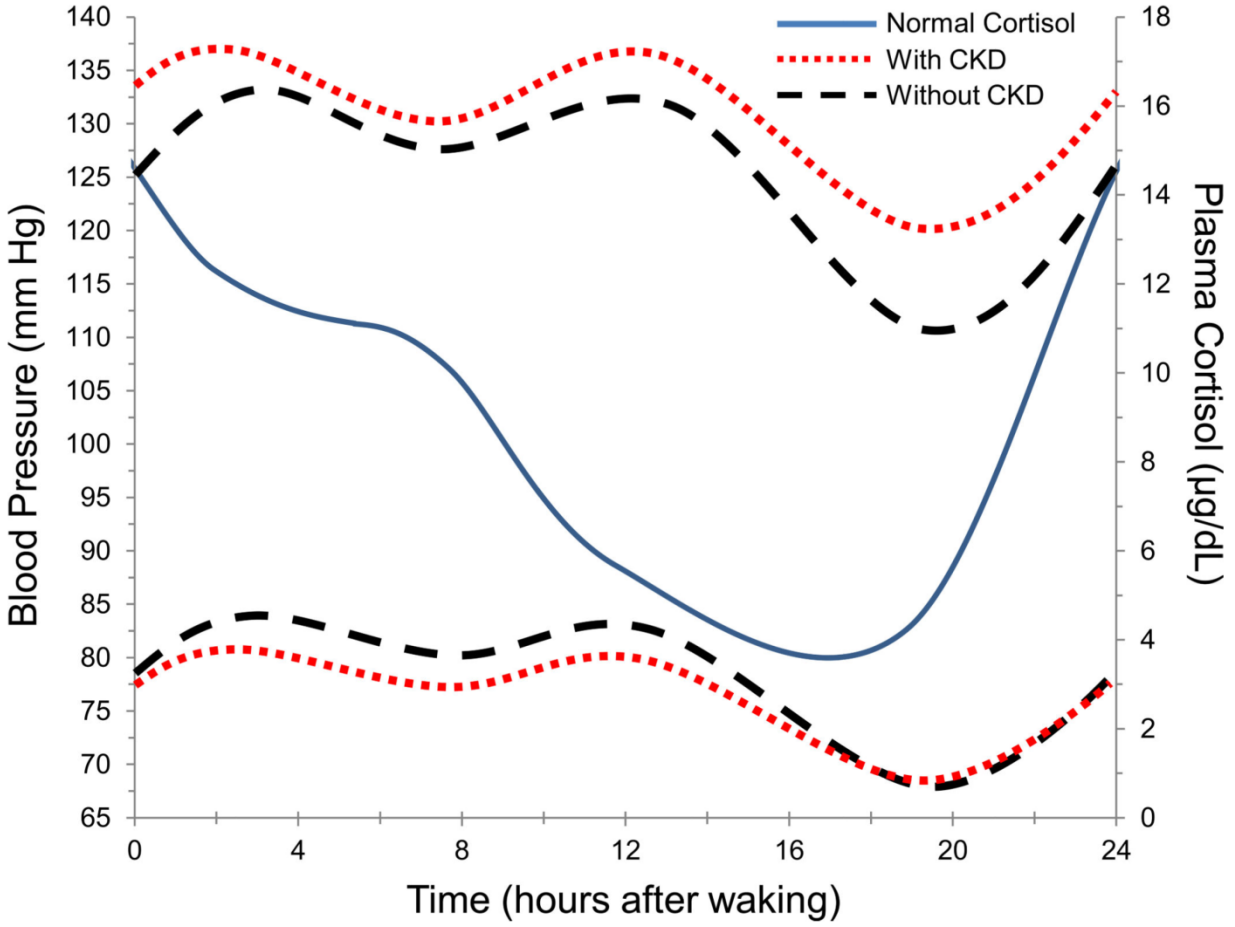
Circadian Rhythm of BP in Patients With CKD

- In healthy individuals, BP falls by 10% to 20% during sleep.
- A fall in nocturnal BP characterizes a normal circadian pattern of BP.
- Individuals whose BP fails to drop or, instead, rises at night are at an increased risk of death compared with dippers.
- In addition, mean nocturnal systolic BP predicts ESKD or death
- Nondipping is associated with the severity of interstitial fibrosis and tubular atrophy by kidney biopsy

Haruhara K et al Hypertens Res. 2015 Feb; 38(2):116-22.
Boggia J et al. Lancet. 2007 Oct 6; 370(9594):1219-29
Liu M et al. Nephrol Dial Transplant. 2003 Mar; 18(3):563-9.

Circadian Rhythm of BP in Patients With CKD

- The findings from Mojon and colleagues that dipping patterns are blunted in individuals with CKD is concerning and particularly relevant for management of HTN in patients with CKD.



Mojon et al. Chronobiol Int. 2013 Mar; 30(1-2):145-58.
Hermida RC et al. Nephrol Dial Transplant. 2014 Jun; 29(6):1160-7.

Comparison of ambulatory BP parameters of hypertensive patients with and without CKD

- Mojon and others were the first to examine circadian BP patterns in patients with HTN and CKD on a large scale.
- At the time of cross-sectional analysis by Mojon and colleagues, 10,271 hypertensive patients had been enrolled,
- 3227 had CKD defined by an estimated GFR less than 60 mL/min/1.73 m^2 and/or urine albumin-to-creatinine ratio of 30 mg/g or more.
- The prevalence of nondipping was higher in patients with CKD (60.6% vs 43.2%, $P < .001$)
- The largest difference was seen in the riser pattern where mean asleep systolic BP greater than mean awake systolic BP occurred in 17.6% of patients with CKD vs 7.1% of patients without CKD

Mojon et al. Chronobiol Int. 2013 Mar; 30(1-2):145-58.
Hermida RC et al. Nephrol Dial Transplant. 2014 Jun; 29(6):1160-7.

Nondipping among patients with CKD and HTN

- A cross-sectional analysis and small prospective study have shown an increased prevalence of nondipping among patients with CKD and HTN.

- Prevalence rates for nondipping were as high as 80% in a subgroup of the study participants of the African American Study of Kidney Disease and Hypertension (AASK) trial with baseline ambulatory BP monitoring.

- In 232 Veterans with CKD in stages ranging from 2 to 5, nondipping was detected more frequently in later stages of CKD (60% in Stage 2, 80% in Stage 3, and 72% in Stage 4).

Agarwal R, et al. Hypertension. 2005 Sep; 46(3):514-20.
Pogue V et al. Hypertension. 2009 Jan; 53(1):20-7.

Sleep-related increases in BP in CKD and Hypertension

- Although the mechanisms underlying sleep-related increases in BP and elevated pulse pressure in patients with CKD and HTN are not known,
- Impaired long-term balance of salt and water by the kidney is an attractive hypothesis.
- High salt intake diminishes night-time dipping of BP in salt-sensitive HTN.
- In a small clinical trial in patients with HTN and type 2 diabetes mellitus, the night-to-day ratio of mean BP by ambulatory monitoring correlated with 24-hour urine sodium excretion.

Uzu T et al. Clin Exp Nephrol. 2009 Aug; 13(4):300-6.

CKD and Hypertension

- An excess of total body salt likely also contributes to arterial stiffness, which is approximated by pulse pressure and known to be associated with worsened kidney function.
- Although it is difficult to disassociate BP-lowering effects on improvements in arterial stiffness with dietary restrictions of salt.
- The cause and effect relationship between total body salt and obstructive sleep apnea also remains undefined.
- However, the 2 are likely related given the high prevalence for both salt excess and obstructive sleep apnea in resistant HTN and CKD.
- Importantly, obstructive sleep apnea may contribute to nocturnal HTN and nondipping in individuals with CKD.

Townshed et al. Am J Hypertens. 2010 Mar; 23(3):282-9
Gates PE, et al. Hypertension. 2004 Jul; 44(1):35-41

The Central Role of Salt in CKD and HTN

- High dietary salt intake not only exacerbates HTN in patients with CKD but also has the potential to directly worsen kidney function.
- High salt diet blunts kidney autoregulation, which exposes the glomerulus to higher filtration pressures
- Over time, the high glomerular filtration pressure leads to glomerular sclerosis and nephron loss.
- A recent systematic review found worsened kidney function, defined as a decline in creatinine clearance, doubling of serum creatinine, or progression to ESKD, associated with high sodium intake in all 4 cohort studies that compared a low and high sodium intake

Fellner RC et al. Am J Physiol Renal Physiol. 2014 Jul 1; 307(1):F33-40.
Smyth A, et al. Am J Hypertens. 2014 Oct; 27(10):1277-84.

Blood Pressure Target in CKD

Blood Pressure Target in CKD

- Starting in 2011, there have been 8 clinical practice guidelines published that address the treatment of HTN.

- Although opinions differ in areas lacking large randomized controlled trials, consensus exists in setting a goal BP of less than 140/90 mm Hg for the majority of individuals.

The Kidney Disease Improving Global Outcomes BP work group Guidelines

- The Kidney Disease Improving Global Outcomes BP work group expanded their pool of evidence beyond long-term randomized controlled trials in HTN to include meta-analyses, systematic reviews, and selected randomized controlled trials with outcomes related to kidney disease progression.

- Review of this evidence base supported a lower BP goal of less than **130/80 mm Hg** for individuals with CKD and moderate-to-severe albuminuria (eg, urine albumin-to-creatinine ratio > 30 mg/g) either with or without diabetes mellitus

Am J Kidney Dis. 2013 Aug; 62(2):201-13

Screening for Secondary Causes of HTN in Patients With CKD

Special Conditions Arising in the Evaluation of Secondary Causes of Hypertension in Patients With CKD

CKD alone can lead to antihypertensive medication resistance; however, patients who remain uncontrolled on ideal doses of 3 different medication classes, including a diuretic, should undergo an evaluation for a separate secondary cause of HTN.

Secondary Cause	CKD-Specific Comment
Pheochromocytoma	Plasma-free metanephrines (normetanephrine and metanephrine) levels may be falsely high in advanced CKD. In patients with CKD Stage 5, plasma catecholamines (epinephrine and norepinephrine) may be a more appropriate screening test for pheochromocytoma.
Primary aldosteronism	MR imaging of the abdomen can replace the CT with contrast of the abdomen that is recommend as follow-up for positive biochemical testing for primary aldosteronism (eg, 24-hr urine aldosterone >12 μg with a suppressed plasma renin activity in the setting of high dietary sodium intake) if iodinated contrast cannot be given.
RVH	Following the results of the CORAL trial,[44] screening for atherosclerotic-related kidney artery stenosis is no longer recommended. However, in patients in whom FMD is suspected, an MR angiogram of the kidney should be performed.
Nephritic GN	Urinalysis with microscopy may be an early sign of GN in patients with both worsening hypertension and rising serum creatinine.

Abbreviations: CT, computed tomography; FMD, fibromuscular dysplasia; GN, glomerulonephritis; MR, magnetic resonance; RVH, renovascular hypertension.

Hypertension. 2008 Jun; 51(6):1403-19.

HTN Management in Patients With CKD

Salt Restriction

- The available evidence supports a large component of salt sensitivity to HTN in patients with CKD.
- Higher levels of sodium intake were associated with higher risk of cardiovascular disease.
- Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines recommend “lowering salt intake to < 90 mmol (<2 g) per day of sodium, unless contraindicated

Diuretic Use in Advanced CKD

- In general, as GFR falls, higher doses of diuretics are needed to achieve a natriuretic response.
- Diuretic dosing can be particularly challenging in late stages of CKD when the risk of over diuresis and its associated hastening of progression to dialysis outweighs the benefit of improved BP control.
- This is further complicated in patients with hypoalbuminemia as less protein-bound loop diuretic is available for tubular secretion.
- The short-acting effect of many loop diuretics hinders their efficacy in long-term BP control.
- For all these reasons, clinicians have reconsidered the use of thiazide diuretics as an alternative or additional medication to the use of loop diuretics in advanced CKD (estimated GFR < 30 mL/min/1.73 m^2)

Agarwal R, J Am Soc Hypertens. 2012 Sep-Oct; 6(5):299-308.

Diuretic Use in CKD

- Chlorthalidone, the long-acting thiazide used in many of the large clinical trials of HTN, has **twice** the potency of hydrochlorothiazide at similar doses and may hold some efficacy in advanced CKD.

- The combination of a thiazide and a loop diuretic may be most effective in patients with excess volume.

Carter BL, Hypertension. 2004 Jan; 43(1):4-9.

Night-time Antihypertensive Medication Dosing

- Multiple clinical trials have shown an improvement in nocturnal dipping of BP by dosing at least 1 antihypertensive medication at bedtime.

- Night-time medication dosing has been associated with reduced cardiovascular risk.

- American Diabetes Association included a level A recommendation to administer 1 or more antihypertensive medications at bedtime in the 2013 guidelines for the care of diabetes mellitus

- Future guidelines involving HTN management in patients with CKD will likely include recommendations for bedtime medication dosing

Hermida RC et al. Chronobiol Int. 2010 Sep; 27(8):1629-51.

Mineralocorticoid Antagonist Use in CKD

- Impressive reductions in BP for individuals receiving 3 or more antihypertensive medications have made mineralocorticoid antagonists an important fourth-line BP agent in the treatment of resistant HTN.
- Patients in later stages of CKD are likely to meet the classification of resistant HTN.
- Risks of hyperkalemia and acute kidney injury have limited mineralocorticoid antagonist use in advanced CKD.
- In proteinuric CKD and HTN, spironolactone effectively reduces both BP and urine protein levels.
- Caution is advised with starting spironolactone in patients who have a baseline serum potassium greater than 4.6 mEq/L.

Calhoun DA et al. Hypertension. 2008 Jun; 51(6):1403-19
Chapman et al. Hypertension. 2007 Apr; 49(4):839-45.

Mineralocorticoid Antagonist Use in CKD

- Spironolactone is contraindicated in patients with acute kidney injury and creatinine clearances less than 10 mL/min.

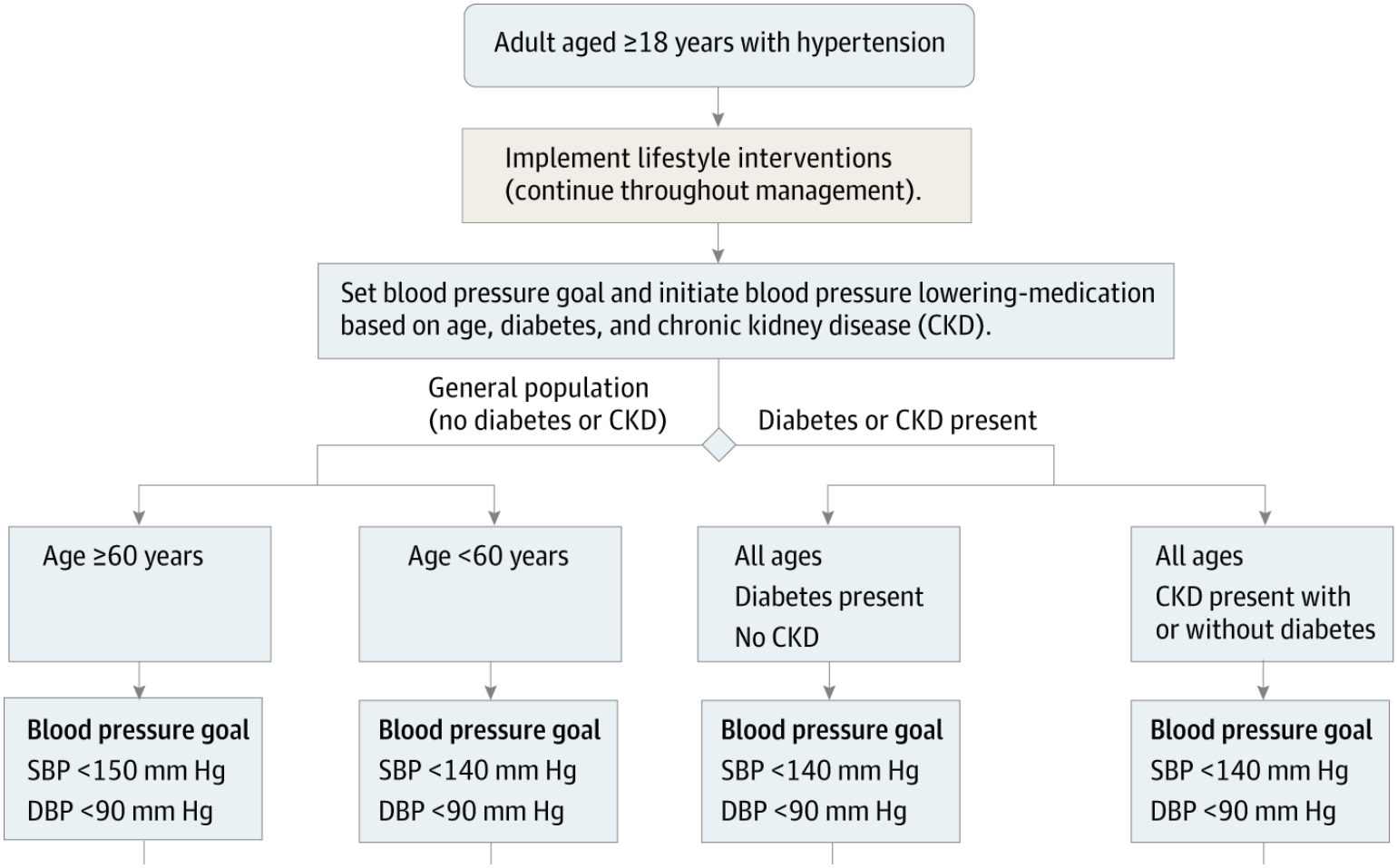
- Eplerenone, a more selective mineralocorticoid antagonist, is contraindicated for use when creatinine clearance falls less than 30 mL/min.

- Finerenone, which binds the mineralocorticoid receptor with a higher affinity than eplerenone, is currently undergoing clinical trials

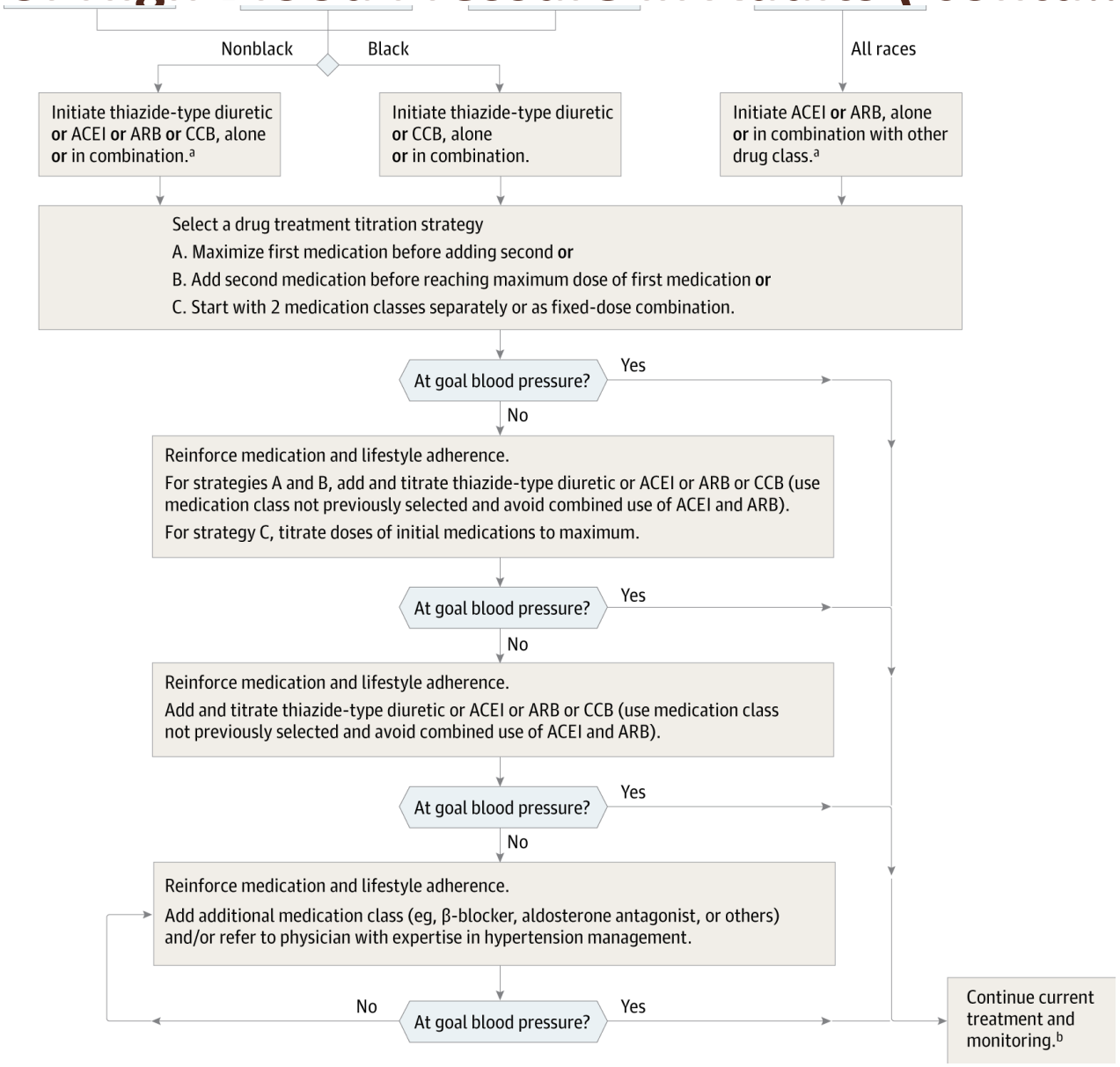
Judd A et al. Adv Chronic Kidney Dis. 2015 Mar; 22(2): 116–122.

Guidelines

2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

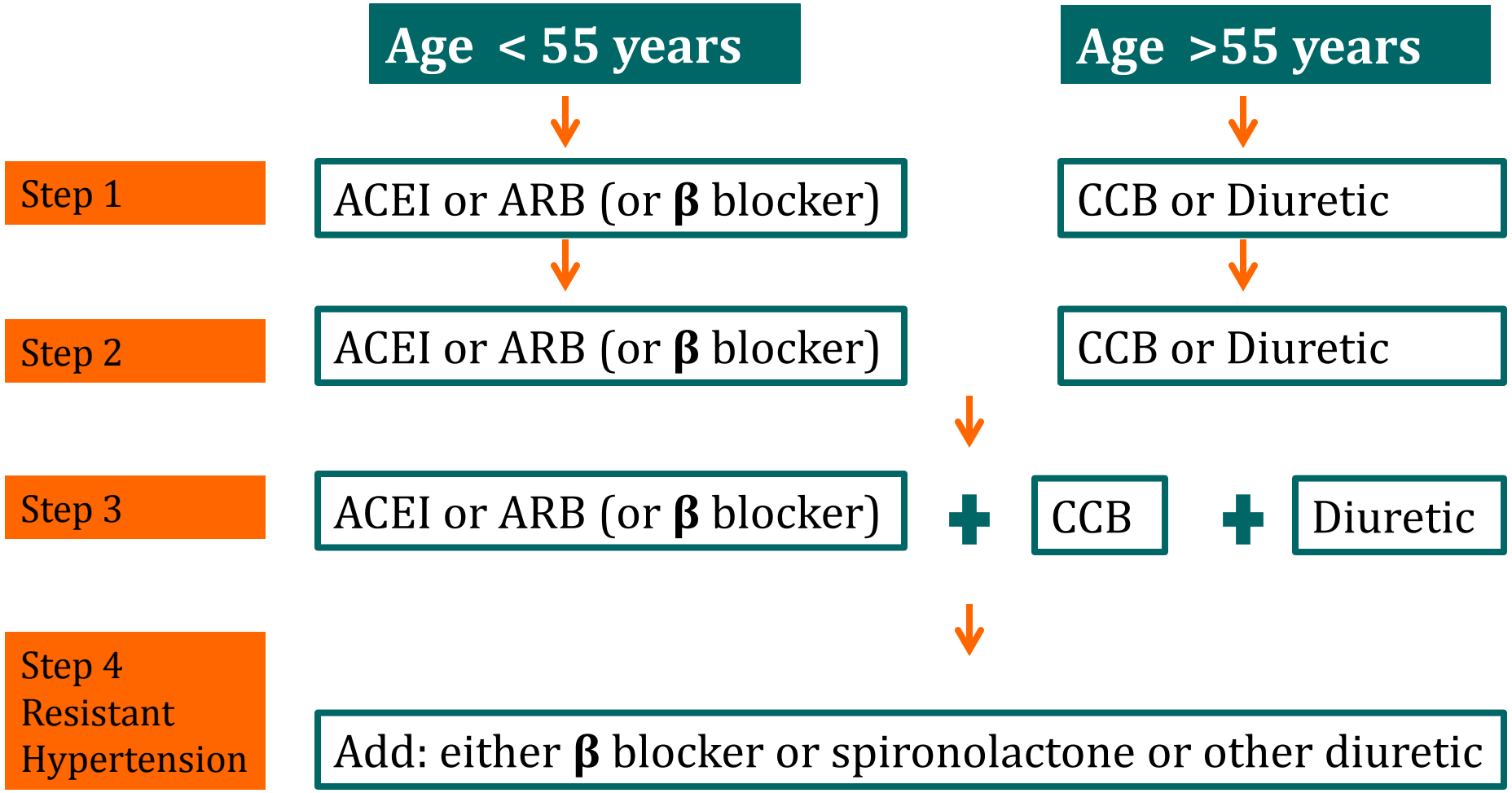


2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults (contd..)



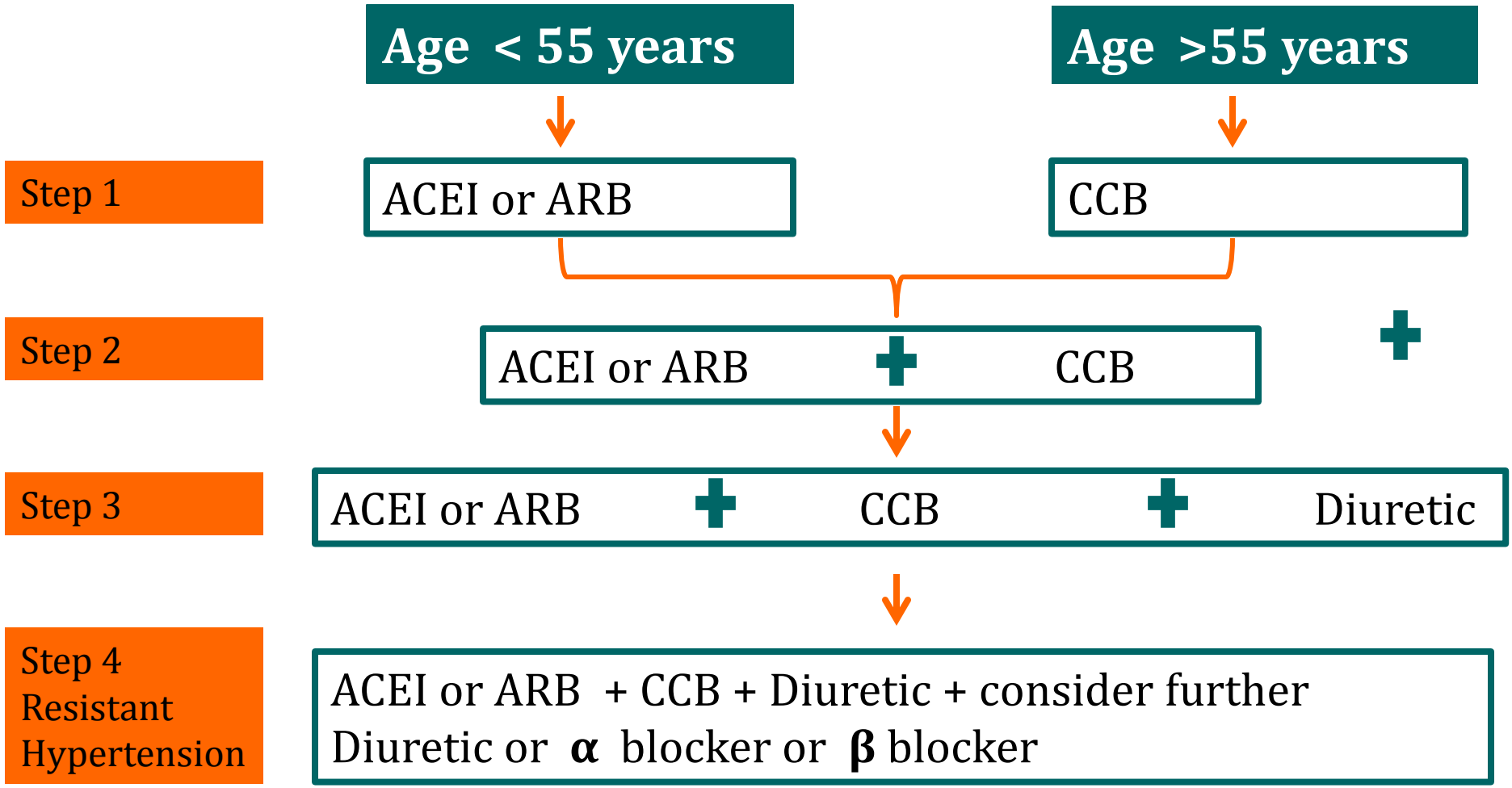
		KDIGO	JNC8
NON DIABETIC CKD	albuminuria <30 mg/d	>140/>90 (1B)	>140/>90 • E for SBP • A for DBP if over 30 • E for DBP if under 30 ACEi or ARB for all CKD regardless of diabetic or proteinuric status
	albuminuria 30-300 mg/d	>130/>80 (2D) ACEi or ARB (2D)	
	albuminuria >300 mg/d	>130/>80 (2C) ACEi or ARB (1B)	
DIABETIC CKD	albuminuria <30 mg/d	>140/>90 (1B)	
	albuminuria >30-300 mg/d	>130/>80 (2D) ACEi or ARB (2D)	
	albuminuria >300 mg/d	>130/>80 (2C) ACEi or ARB (1B)	

Association of Physicians of India (API) Guidelines



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCB- calcium channel blockers

NICE Clinical Guideline 2011



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blockers; CCB- calcium channel blockers

Conclusion

- In some forms of CKD, HTN may be the earliest sign of kidney dysfunction (eg, polycystic disease).
- Appropriate HTN management reduces both cardiovascular and kidney outcomes.
- Impaired dipping of BP during sleep, salt-sensitive HTN in animal models of kidney injury, and exaggerated BP responses to restrictions in dietary salt all highlight the importance of salt in patients with CKD and HTN.
- In addition to the well-established use of an ACEI or ARB, dietary salt restriction and appropriate diuretic therapy make up the mainstay of HTN treatment in patients with CKD.
- Lastly, future clinical practice guidelines may recommend bedtime dosing of 1 or more antihypertensive medications in patients with CKD.

Thank You