Management of Hypertension in Chronic Kidney Disease

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Introduction

- Chronic kidney disease (CKD) affects 10–15% of the population worldwide and its prevalence is increasing.
- CKD is defined as the presence of reduced kidney function (an estimated glomerular filtration rate [eGFR] < 60 mL/ min/1.73 m2) or kidney damage (often indicated by the presence of proteinuria) for ≥ 3 months duration.

Introduction

Hypertension, defined by the European Society of Cardiology and the European Society of Hypertension (ESC/ESH) as a blood pressure (BP) of ≥ **140/80** mmHg affects ~ 30% of the general adult population and up to 90% of those with CKD.

Introduction

- Hypertension is both a cause and effect of CKD and contributes to its progression.
- As eGFR declines, the incidence and severity of hypertension increase.
- Hypertension and CKD are both independent risk factors for cardiovascular disease.
- Importantly, from a therapeutic perspective, lowering BP can slow eGFR decline, delay progression to ESRD, and reduce the incidence of CVD in this patient group.

Proteinuria

Proteinuria is an important marker of renal damage and is incrementally and **independently associated with CKD progression** and incident CVD.

The most **practical way** to measure proteinuria is with a **protein-to creatinine** ratio (PCR) obtained from a spot urine sample.

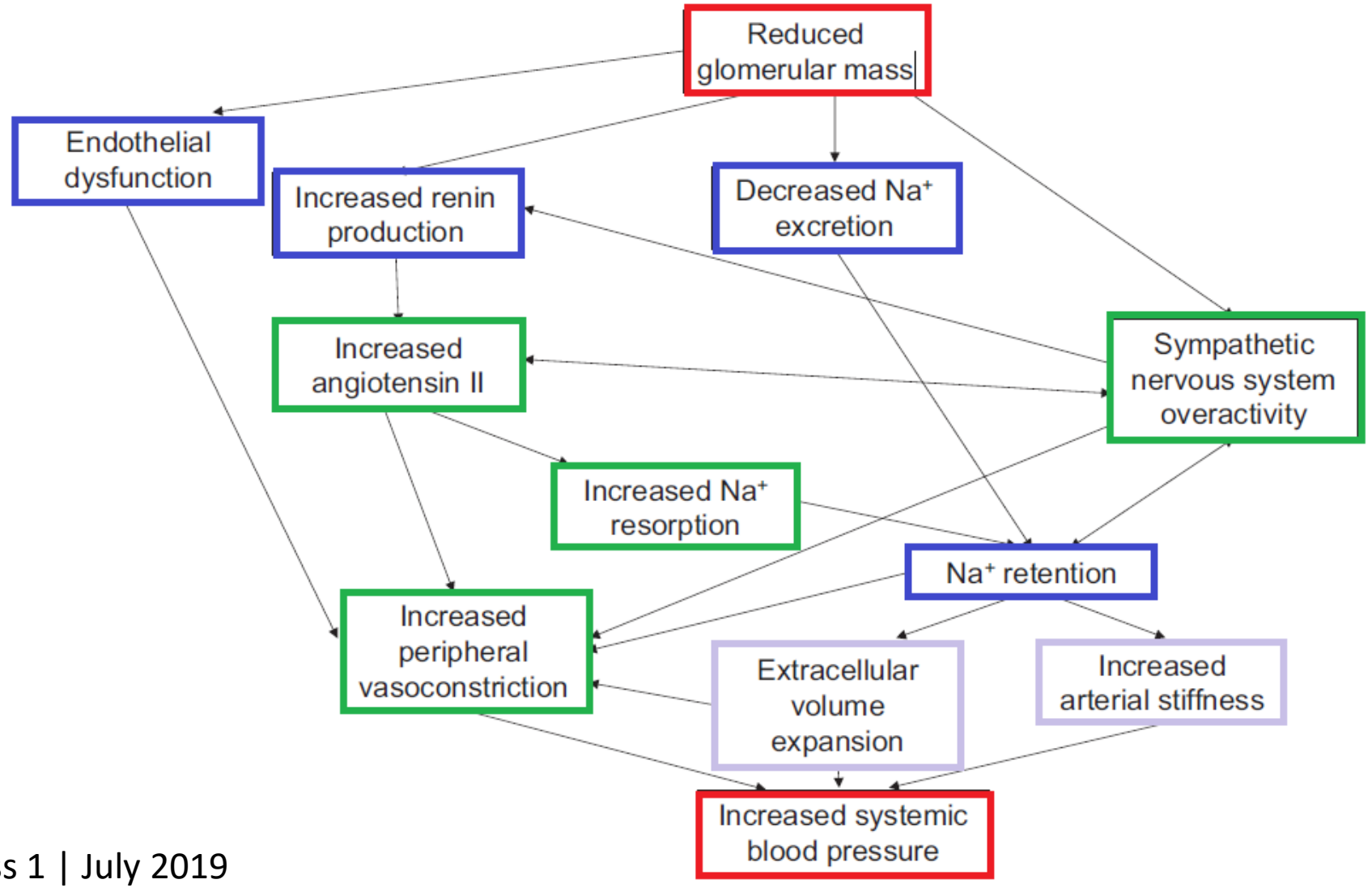
An **albumin-to-creatinine ratio** (ACR) is **more accurate** when protein leak is **minimal**, with an ACR value of ≥ 30 mg/g sufficient for a diagnosis of CKD regardless of eGFR.

Quantification of proteinuria (adapted from Kidney Disease: Improving Global Outcomes 2012 chronic kidney disease guidelines

Quantification method	Normal or mildly increased	Moderately increased	Severely increased	Nephrotic range
Dipstick	Negative to trace	Trace to +	+ or greater	+++ or greater
ACR				
mg/mmol	< 3	3–30	> 30	> 220
mg/g	< 30	30–300	> 300	> 2200
PCR				
mg/mmol	< 15	15–50	> 50	> 300
mg/g	< 150	150–500	> 500	> 3000
24-h urinary protein (g/day)	< 0.15	0.15–0.5	> 0.5	> 3

Drugs (2019) 79:365–379

Pathogenesis of Hypertension in Chronic Kidney Disease (CKD)



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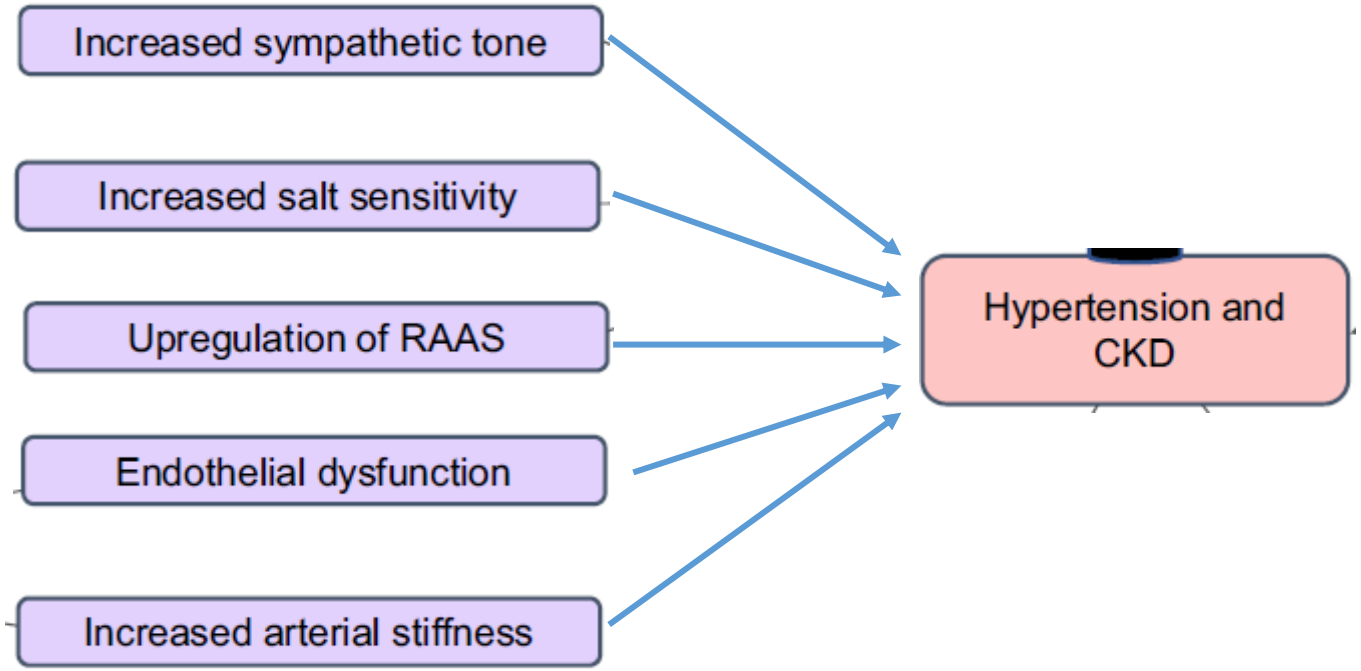


Drugs (2019) 79:365–379

Classification of BP

Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

*Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.
BP indicates blood pressure (based on an average of ≥2 careful readings obtained on ≥2 occasions, as detailed in DBP, diastolic blood pressure; and SBP systolic blood pressure.

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 3021–3104
doi:10.1093/eurheartj/ehy339

2018 ESC/ESH Guidelines for the management of arterial hypertension

Classification of office blood pressure and definitions of hypertension grade

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension[b]	≥140	and	<90

CENTRAL ILLUSTRATION **Comparison of American and European Society Definitions and Management of Hypertension**

Guideline Differences	American College of Cardiology/American Heart Association (ACC/AHA)			European Society of Cardiology/European Society of Hypertension (ESC/ESH)		
Level of blood pressure (BP) defining hypertension	Systolic (mm Hg)	and/or	Diastolic (mm Hg)	Systolic (mm Hg)	and/or	Diastolic (mm Hg)
Office/Clinic BP	≥ 130		≥ 80	≥ 140		≥ 90
Daytime mean	≥ 130		≥ 80	≥ 135		≥ 85
Nighttime mean	≥ 110		≥ 65	≥ 120		≥ 70
24-hour mean	≥ 125		≥ 75	≥ 130		≥ 80
Home BP mean	≥ 130		≥ 80	≥ 135		≥ 85
BP targets for treatment	< 130/80 mm Hg			Systolic targets < 140 mm Hg and close to 130 mm Hg		

BP Control for Renal Protection

MDRD
Interventions: Target MAP 107 vs 92 mmHg
Participants: eGFR 13–55 mL/min/1.73 m^2
Follow-up: 840 patients, mean 2.2 years
Results: Slowed eGFR decline in intensive group only if baseline proteinuria > 1 g/day

1994

AASK
Interventions: MAP 102–107 vs 97 mmHg
Participants: eGFR 20–65 mL/min/1.73 m^2, non-diabetic
Follow-up: 1094 patients, minimum 3 years
Results: Slowed eGFR decline in intensive group only if baseline proteinuria > 1 g/day

2002

REIN-2
Interventions: DBP < 90 vs BP < 130/80 mmHg with addition of CCB
Participants: Proteinuria > 1 g/day, eGFR < 70 mL/min/1.73 m^2, non-diabetic, on ACEi
Follow-up: 335 patients, median 1.6 years
Results: No difference in time to ESRD

2005

Drugs (2019) 79:365–379
https://doi.org/10.1007/s40265-019-1064-1

THERAPY IN PRACTICE

Management of Hypertension in Chronic Kidney Disease

Dan Pugh[1,2] · Peter J. Gallacher[1] · Neeraj Dhaun[1,2]

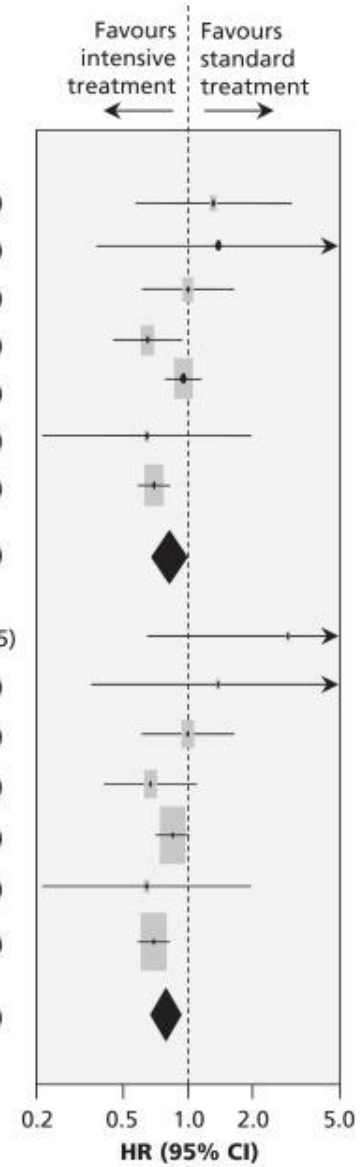
Review > CMAJ. 2013 Aug 6;185(11):949-57. doi: 10.1503/cmaj.121468. Epub 2013 Jun 24.

Effects of intensive blood pressure lowering on the progression of chronic kidney disease: a systematic review and meta-analysis

Jicheng Lv [1], Parya Ehteshami, Mark J Sarnak, Hocine Tighiouart, Min Jun, Toshiharu Ninomiya, Celine Foote, Anthony Rodgers, Hong Zhang, Haiyan Wang, Giovanni F M Strippoli, Vlado Perkovic

Interpretation: Intensive blood pressure lowering appears to provide protection against kidney failure events in patients with chronic kidney disease, particularly among those with proteinuria. More data are required to determine the effects of such a strategy among patients without proteinuria.

Study	Treatment, no. of events/patients: Intensive	Standard	Systolic BP, mm Hg, intensive/standard: Baseline	Achieved	HR (95% CI)
Composite outcome					
Toto et al.[21]	11/42	7/35	124/122	133/138	1.31 (0.57–3.02)
Schrier et al.[28]	5/41	3/34	143/142	90/101	1.38 (0.36–5.37)
Ruggenenti et al.[14]	38/169	34/169	137.0/136.4	129.6/133.7	1.00 (0.61–1.64)
Wühl et al.[18]	46/189	69/196	NA	NA	0.65 (0.45–0.94)
Appel et al.[13]	213/540	209/554	152/149	128/141	0.95 (0.78–1.15)
Hayashi et al.[27]	5/1230	8/1269	1717/171.8	135.9/145.6	0.64 (0.21–1.97)
Klahr et al.[17]	306/432	310/408	130/131	126.2/133.8	0.69 (0.59–0.83)
Overall (I^2 = 38.1%)	624/2643	640/2665	156.3/156.4	131.7/141.5	0.82 (0.68–0.98)
ESKD					
Toto et al.[21]	7/42	2/35	124/122	133/138	2.92 (0.65–13.15)
Schrier et al.[28]	5/41	3/34	143/142	90/101	1.38 (0.36–5.37)
Ruggenenti et al.[14]	38/169	34/169	137.0/136.4	129.6/133.7	1.00 (0.61–1.64)
Wühl et al.[18]	22/189	34/196	NA	NA	0.67 (0.41–1.10)
Appel et al.[13]	238/540	256/554	152/149	128/141	0.85 (0.71–1.02)
Hayashi et al.[27]	5/1230	8/1269	171.7/171.8	135.9/145.6	0.64 (0.21–1.97)
Klahr et al.[17]	306/432	310/408	130/131	126.2/133.8	0.69 (0.59–0.83)
Overall (I^2 = 21.6%)	621/2643	647/2665	156.3/156.4	131.7/141.5	0.79 (0.67–0.93)



Treatment

Non-Pharmacological Treatment

- Nonpharmacologic therapy should be the **first step** to the treatment of hypertension, even among patients with CKD.
- Diets rich in fruits and vegetables and low in saturated or unsaturated fats (such as the DASH [Dietary Approaches to Stop Hypertension] diet) can lead to moderate declines in BP by w10 mm Hg in hypertensive patients.
- Increasing potassium intake to 3 to 4 g/d and reducing sodium intake to <1.5 g/d can also lead to reductions in BP by ~5 mm Hg with both interventions inhypertensive patients, **although a high-potassium intake may be difficult to maintain without provoking hyperkalemia in patients with more advanced CKD (eg, stage 4 or 5).**

TABLE 1

The DASH Eating Plan

High in:

Fruits and vegetables (four or five servings each per day)

Fiber (seven or eight servings per day)

Low-fat dairy products (two or three servings per day)

Lean meat (two servings per day)

Calcium

Magnesium

Potassium

Low in:

Saturated fat

Cholesterol

Salt*

DASH = dietary approaches to stop hypertension.

American Family Physician
Volume 73, Number 11 June 1, 2006

Non-Pharmacological Treatment

- A restriction to a target < 100 mmol/ day (~ 6 g/day of salt) has also demonstrated a **reduction in proteinuria** by ~ 25%, an effect that is unlikely to be explained by BP reduction alone.
- Weight loss is effective in reducing **BP and proteinuria** and may slow CKD progression (~5 mm Hg for every 5-kg weight loss).
- For those with **sleep apnea**, treatment with continuous positive airway pressure may also lead to modest improvements in BP.
- Both **aerobic** and **isometric** resistance exercise can improve BPs in patients with hypertension. Currently, **90 to 150 minutes** of aerobic exercise is recommended per week.
- Use of over-the-counter medications such as **nonsteroidal anti-inflammatory** pain medications should **be avoided** because they may increase BP and also adversely affect kidney function.

Nonpharmacological Interventions

COR	LOE	Recommendations for Nonpharmacological Interventions
I	A	Weight loss is recommended to reduce BP in adults with elevated BP or hypertension who are overweight or obese.
I	A	A heart-healthy diet, such as the DASH (Dietary Approaches to Stop Hypertension) diet, that facilitates achieving a desirable weight is recommended for adults with elevated BP or hypertension.
I	A	Sodium reduction is recommended for adults with elevated BP or hypertension.
I	A	Potassium supplementation, preferably in dietary modification, is recommended for adults with elevated BP or hypertension, unless contraindicated by the presence of CKD or use of drugs that reduce potassium excretion.

Nonpharmacological Interventions (cont.)

COR	LOE	Recommendations for Nonpharmacological Interventions
I	A	Increased physical activity with a structured exercise program is recommended for adults with elevated BP or hypertension.
I	A	Adult men and women with elevated BP or hypertension who currently consume alcohol should be advised to drink no more than 2 and 1 standard drinks* per day, respectively.

*In the United States, 1 "standard" drink contains roughly 14 g of pure alcohol, which is typically found in 12 oz of regular beer (usually about 5% alcohol), 5 oz of wine (usually about 12% alcohol), and 1.5 oz of distilled spirits (usually about 40% alcohol).

TABLE 2 Best Proven Nonpharmacologic Interventions for Prevention and Treatment of Hypertension

Nonpharmacologic Intervention	Dose	Approximate Impact on SBP	
		Hypertension	Normotension
Physical activity			
Aerobic	• 90-150 min/week • 65%-75% heart rate reserve	−5/8 mm Hg	−2/4 mm Hg
Dynamic resistance	• 90-150 min/week • 50%-80% 1 repetition maximum • 6 exercises, 3 sets/exercise, 10 repetitions/set	−4 mm Hg	−2 mm Hg
Isometric resistance	• 4 × 2 min (hand grip), 1 min rest between exercises, 30%-40% maximum voluntary contraction, 3 sessions/week, • 8-10 weeks	−5 mm Hg	−4 mm Hg
Healthy diet			
DASH dietary pattern	Diet rich in fruits, vegetables, whole grains, and low-fat dairy products with reduced content of saturated and total fat	−11 mm Hg	−3 mm Hg
Weight loss			
Weight/body fat	Ideal body weight is best goal but ≥1 kg reduction in body weight for most adults who are overweight	−5 mm Hg	−2/3 mm Hg
Reduced intake of dietary [Na^+]			
Dietary sodium	<1,500 mg/day is optimal goal but ≥1,000 mg/day reduction in most adults	−5/6 mm Hg	−2/3 mm Hg
Enhanced intake of dietary [K^+]			
Dietary potassium	3,500-5,000 mg/day, preferably by consumption of a diet rich in potassium	−4/5 mm Hg	−2 mm Hg
Moderation in alcohol intake			
Alcohol consumption	In individuals who drink alcohol, reduce alcohol to • Men: <2 drinks/day • Women: <1 drink/day	−4 mm Hg	−3 mm Hg

Primary Prevention: Lifestyle Changes and Team-Based Care

DOI: 10.1016/j.jacc.2019.03.010

Pharmacological Treatment

RAAS blockade

- In general, for patients with CKD, **ACE inhibitors and ARBs** are considered **first-line antihypertensive agents** by most guidelines, especially in the presence of concurrent albuminuria (albumin excretion > 300 mg/d).They have both cardioprotective and renoprotective properties.
- ACE inhibitors and ARBs induce efferent arteriolar vasodilation, which leads to **reductions in intraglomerular pressure** and therefore suppresses proteinuria.
- This renal benefit is applicable to both patients **with and without diabetes**.

RAAS blockade

- However, the combination of ACE inhibitors with ARBs has **not** been shown to be effective at slowing the progression of CKD or reducing CV events in patients with CKD (with or without diabetes).
- Because this combination may **predispose to hyperkalemia** and **acute kidney injury**, dual blockade with ACE inhibitors and ARBs has generally fallen out of favor.
- ONTARGET study: Combination therapy was associated with an increased incidence of adverse effects with no significant reduction in the primary outcome of death from CVD, MI, stroke or heart failure

AJKD

Hypertension in CKD: Core Curriculum 2019

Elaine Ku, Benjamin J. Lee, Jenny Wei, and Matthew R. Weir

Medications	CKD-Related Indications	Other Potential Indications	Common Side Effects	Potential Contraindications	Other Considerations
RAS Blockade					
ACEi (first-line agents if proteinuria)	Proteinuria reduction; delays progression of CKD	Heart failure with reduced ejection fraction; post–myocardial infarction	Cough; angioedema; hyperkalemia; leukopenia; anemia	Pregnancy; bilateral renal artery stenosis	
ARBs (first-line agents if proteinuria)	Proteinuria reduction; delays progression of CKD	Uric acid lowering (losartan) or gout; similar to ACEi	Cough (less than with ACEi); angioedema; hyperkalemia	Pregnancy; bilateral renal artery stenosis	

Chronic Kidney Disease

COR	LOE	Recommendations for Treatment of Hypertension in Patients With CKD
I	SBP: B-R[SR]	Adults with hypertension and CKD should be treated to a BP goal of less than 130/80 mm Hg.
	DBP: C-EO	
IIa	B-R	In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio or the equivalent in the first morning void]), treatment with an ACE inhibitor is reasonable to slow kidney disease progression.
IIb	C-EO	In adults with hypertension and CKD (stage 3 or higher or stage 1 or 2 with albuminuria [≥300 mg/d, or ≥300 mg/g albumin-to-creatinine ratio in the first morning void]), treatment with an ARB may be reasonable if an ACE inhibitor is not tolerated.

SR indicates systematic review.

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journal homepage: www.elsevier.com/locate/tcm

Blood pressure and the new ACC/AHA hypertension guidelines ☆

John M. Flack[a,*], Bemi Adekola[b]

Table 1
Treating hypertension with selected comorbidities drug class.

Comorbidity	Favor	Avoid	Comment
Atrial fibrillation (AF)	ARB		ARBs may reduce AF recurrence
Aortic disease	Beta blockers		Patients with thoracic aorta disease
Chronic kidney disease (CKD)	ACEI or ARB		ARB if ACEI not tolerated
Diabetes	ACEI or ARB if albuminuria present		Consider usual first line drugs if no albuminuria
Heart failure (preserved EF)	Diuretics for volume overload		Add ACEI or ARB and beta blocker for incremental BP control; also consider angiotensin receptor – neprilysin inhibitor and mineralocorticoid receptor antagonists
Heart failure (reduced EF)	GDMT beta blockers	Non-DHP calcium antagonists	
Peripheral arterial disease			Consider usual first line drugs
Post-kidney transplant	Calcium antagonist	Use ACEI with caution	Calcium antagonist can improve kidney graft survival and GFR; 1st month post-transplant BP target (<160/90) to avoid hypotension – induced graft thrombosis

Diuretics

Diuretics are a reasonable choice for most patients with CKD, especially in the setting of volume overload.

Loop diuretics may be preferred as GFR declines, especially if there is evidence of volume overload, although higher doses are often required in those with a lower eGFR

Bumetanide or **torsemide** may be preferred due to its superior bioavailability. Torsemide also has a longer half-life than furosemide and bumetanide and can be administered once daily.

Diuretics

- There is evidence that **thiazide and thiazide-like diuretics** are effective antihypertensive agents, likely through indirect vasodilatory mechanisms.
- In non-proteinuric CKD, monotherapy with a thiazide-like diuretic (such as indapamide) may have a role and should be considered as a potential for first-line therapy .
- Treatment with a diuretic may also reverse the loss of physiological nocturnal dip in BP described in CKD

Diuretics

- Diuretics should generally be **avoided** in patients with **polycystic kidney disease** due to accelerated cyst growth and loss of excretory function associated with their use.
- Mineralocorticoid receptor antagonists (blockers) (such as spironolactone) effectively reduce BP in CKD but run the risk of exacerbating hyperkalaemia. These agents have been demonstrated to improve systolic and diastolic function in early CKD and therefore may be of particular value in patients with concomitant left ventricular dysfunction.

Calcium Channel Blockers

- Both dihydropyridine and non-dihydropyridine CCBs are useful in the management of hypertension in CKD. Dihydropyridine CCBs (such as amlodipine) can be used as first-line therapy in non-proteinuric CKD, either alone or in combination.
- In proteinuric CKD their effect is inferior to RAAS blockade.
- Nondihydropyridine calcium channel blockers (eg, diltiazem or verapamil) may also have antiproteinuric effects and may be useful in patients with CKD and proteinuria.

Therapeutic strategies for treatment of hypertension in CKD

Recommendations	Class[a]	Level[b]
In patients with diabetic or non-diabetic CKD, it is recommended that an office BP of ≥140/90 mmHg be treated with lifestyle advice and BP-lowering medication.[9,203,485]	I	A
In patients with diabetic or non-diabetic CKD: • It is recommended to lower SBP to a range of 130–139 mmHg.[9,487,489]	I	A
• Individualized treatment should be considered according to its tolerability and impact on renal function and electrolytes.	IIa	C
RAS blockers are more effective at reducing albuminuria than other antihypertensive agents, and are recommended as part of the treatment strategy in hypertensive patients in the presence of microalbuminuria or proteinuria.[487,489]	I	A
A combination of a RAS blocker with a CCB or a diuretic[c] is recommended as initial therapy.[175]	I	A
A combination of two RAS blockers is not recommended.[298]	III	A

ESC European Society of Cardiology
European Heart Journal (2018) **39**, 3021–3104
doi:10.1093/eurheartj/ehy339

ESC/ESH GUIDELINES

2018 ESC/ESH Guidelines for the management of arterial hypertension

β blockers

- β-Blockers (β-adrenoceptor antagonists) effectively reduce BP in CKD due to their effect on the dysregulated sympathetic nervous system. The cardioprotective benefits of these drugs are well-established.
- Among patients with cardiac disease, there may be indications for other classes of antihypertensive agents, such as β-blockers.
- Direct comparisons with ACE inhibitors have shown β-blockers to offer inferior renoprotection.

β blockers

- Underuse in patients with CKD may be partially explained by concerns regarding glycaemic control, reduced renal excretion and systemic accumulation (Atenolol).
- Although these are potential risks with certain classes of β-blockers, these drugs can be safely used in all degrees of renal impairment.
- Dosing adjustments may be required, and hepatically excreted β-blockers and those with additional vasodilatory properties (such as carvedilol) are likely to be of particular value.

α-blockers

- Peripherally acting α-blockers (such as prazosin, doxazosin) are commonly used as **part of combination therapy** for the management of hypertension in CKD.
- This may be due to a pharmacokinetic profile that is undisturbed by declining eGFR in addition to favourable effects on glycaemic control. Several studies have demonstrated their efficacy as **add-on** therapy in the management of hypertension in CKD .
- α-Blockers **should not, however, be considered for first-line therapy**, as they are less effective than other agents for reducing the incidence of CVD.

ACC/AHA Versus ESC/ESH on Hypertension Guidelines

JACC Guideline Comparison

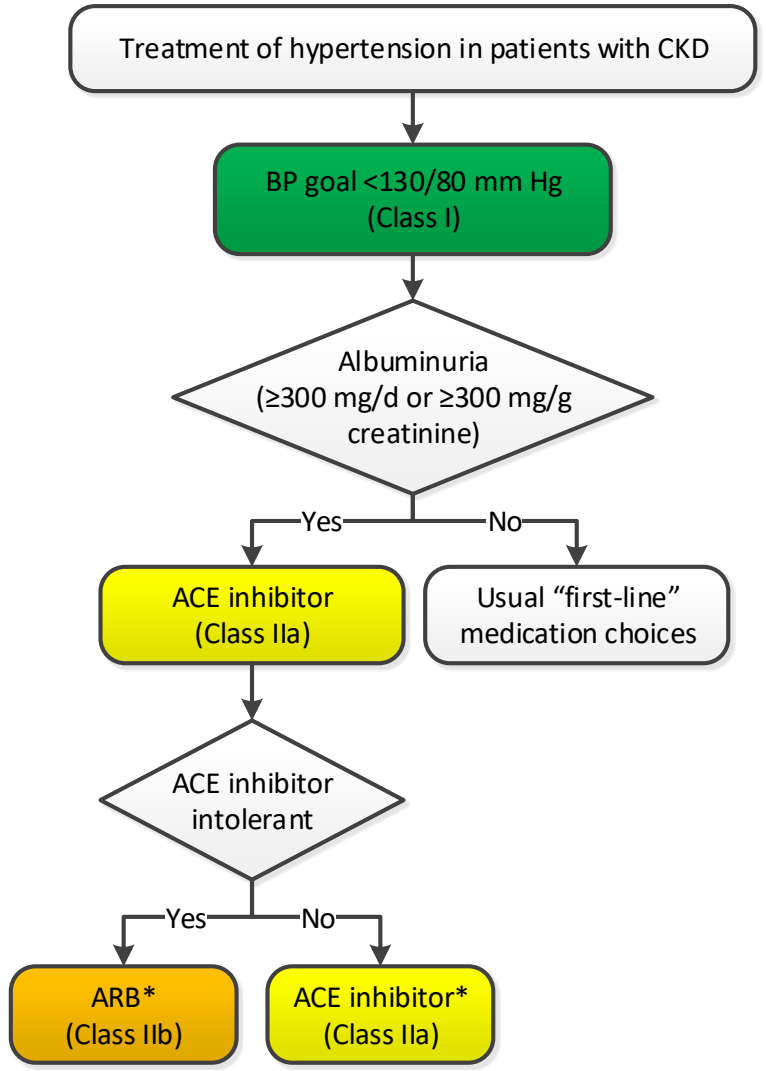
TABLE 4 Blood Pressure Goals in Patients With Hypertension According to Clinical Conditions

Category	ESC/ESH 2018	AHA/ACC 2017
Age ≥65 yrs	130 to <140/70 to 79 mm Hg	<130/<80 mm Hg
Diabetes	Close to 130 (or lower if tolerated/ 70 to 79 mm Hg	<130/<80 mm Hg
Coronary artery disease	Close to 130 (or lower if tolerated/ 70 to 79 mm Hg	<130/<80 mm Hg
Chronic kidney disease (eGFR <60 ml/min/1.73 m^2)	130 to <140/70 to 79 mm Hg	<130/<80 mm Hg
Post-stroke	Close to 130 (or lower if tolerated/ 70 to 79 mm Hg	<130/<80 mm Hg

Blood Pressure Goals in Patients With Hypertension According to Clinical Conditions

Bakris et al.
JACC VOL. 73, NO. 23, 2019 JUNE 18, 2019:3018–26

Management of Hypertension in Patients With CKD



•Colors correspond to Class of Recommendation in Table 1.

•*CKD stage 3 or higher or stage 1 or 2 with albuminuria ≥300 mg/d or ≥300 mg/g creatinine.

•ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP blood pressure; and CKD, chronic kidney disease.

Chronotherapy

As the diurnal variation of BP can be influenced by timing of antihypertensive medications, it has been hypothesized that **evening dosing** could reverse the **non-dipping nocturnal BP seen in CKD**. Chronotherapy would therefore seem to be one of the more straightforward methods of achieving improved outcomes for those with hypertension and CKD.

Antihypertensive Medication Adherence Strategies

COR	LOE	Recommendations for Antihypertensive Medication Adherence Strategies
I	B-R	In adults with hypertension, dosing of antihypertensive medication once daily rather than multiple times daily is beneficial to improve adherence.
IIa	B-NR	Use of combination pills rather than free individual components can be useful to improve adherence to antihypertensive therapy.

Managing Hypertension in the Context of Haemodialysis

- Hypertension in patients undergoing haemodialysis may be largely driven by sodium and water overload. However, hypertension often persists despite aggressive ultrafiltration.
- All classes of antihypertensive may be used, although data governing this are limited.
- Use of β-blockers is particularly attractive as they mitigate some of the arrhythmogenic effects of dialysis and reduce arterial stiffness and left ventricular hypertrophy, both of which are accelerated in ESRD. Choice of β-blocker remains contentious, in part due to variable degrees of drug clearance during haemodialysis.


دانشکده پزشکی