



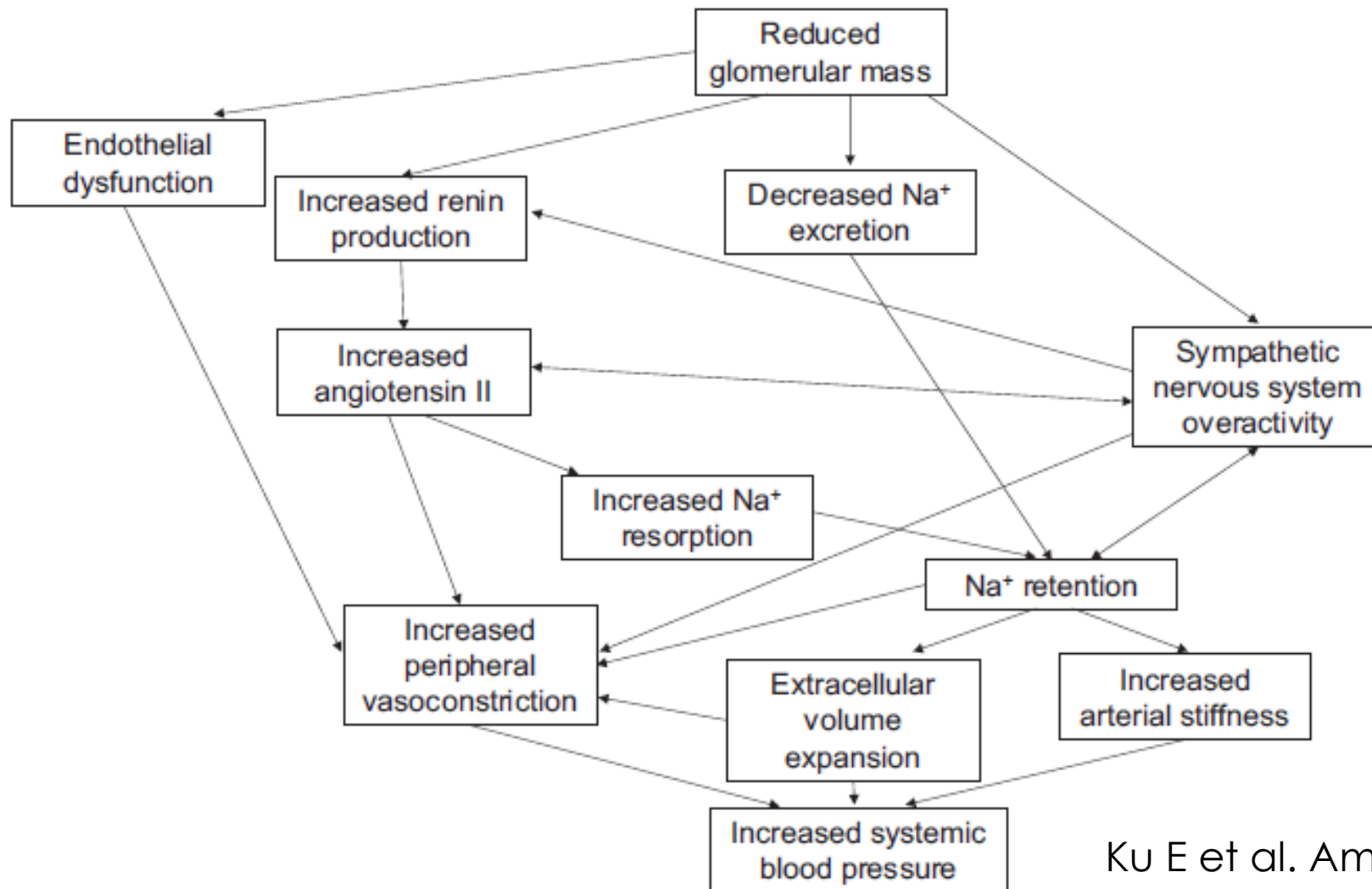
Hypertension and chronic kidney disease – New treatment perspectives



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 .
- ▶ Additionally, hypertension and CKD are both independent risk factors for cardiovascular disease (CVD).
- ▶ Inherent renal arterial myogenic responses also modify the response of the kidney to increased blood pressure.

Pathophysiologic mechanisms of hypertension in chronic kidney disease





Factors causing hypertension in chronic kidney disease

Factor	Dominant mechanism
Impaired sodium excretion	Expansion of ECF volume
Activation of RAS	Direct vasoconstriction Sympathetic activation
Sympathetic activation	Direct vasoconstriction Stimulation of renin release
Imbalance in prostaglandins or kinins	Vasoconstriction
Endothelin	Direct vasoconstriction Renal injury
Reduced nitric oxide	Loss of vasodilator effect

ECF: extracellular fluid; RAS: renin-angiotensin system.



Checklist for identifying hypertensive patients at risk for CKD

- Advanced age, i.e. greater than or equal to 50 years
- Presence of other comorbidities such as diabetes, metabolic syndrome, urinary stones, hyperlipidemia, etc.
- History of or presence of anemia
- History of heart attack, stroke, or congestive heart failure
- Family history of CKD
- Smoking
- Abnormally increased levels of serum creatinine



Checklist for identifying hypertensive patients at risk for CKD

- Two recent eGFR results obtained within the last 2 years, performed more than 90 days apart, with both showing values <60 mL/min/1.73m.
- 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 GFR
- 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 months
- Presence of red blood cells and white blood cells on urinalysis.

Normal and Abnormal BP based on the 2017 AHA/ACC Guideline in Patients With CKD

BP Classification	Office BP	Daytime ABPM or Home BP
Normal or elevated BP	<130/80 mm Hg	<130/80 mm Hg
Sustained hypertension	≥130/80 mm Hg	≥130/80 mm Hg
White coat hypertension	≥130/80 mm Hg	<130/80 mm Hg
Masked hypertension	<130/80 mm Hg	≥130/80 mm Hg

Difficult-to-Control BP	Definition
Resistant hypertension	Receiving ≥3 antihypertensive agents, 1 of which is a diuretic, without adequate BP control
Refractory hypertension	Receiving ≥3 antihypertensive agents, 1 of which is a thiazide-type diuretic and another of which is spironolactone, without adequate BP control

Abbreviations: ABPM, ambulatory blood pressure monitoring; AHA/ACC, American Heart Association/American College of Cardiology; BP, blood pressure; CKD, chronic kidney disease.

Whelton et al. J Am Coll Cardiol.

Factors affecting the accuracy of blood

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

Quantification of proteinuria 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

Relationship between measurement methods are not exact and will depend on multiple variables

ACR albumin-to-creatinine ratio, PCR protein-to-creatinine ratio

Albuminuria categories in CKD

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]).

GFR categories in CKD

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.

Abraham G et al. J Assoc Physicians India. 2017 ;65(2):6-22



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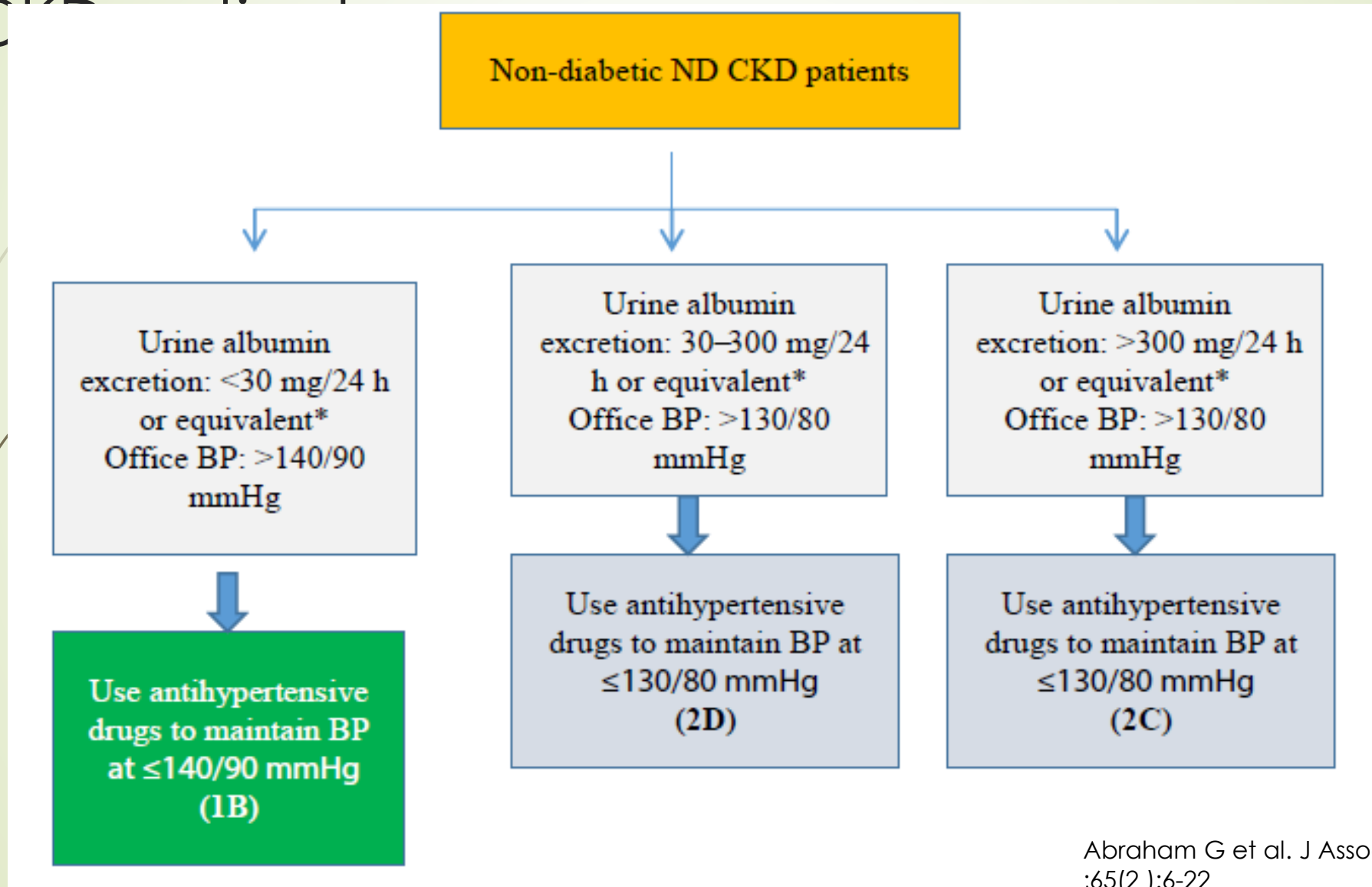
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Classification of hypertension stages according to BP levels, risk factors, hypertension mediated organ damage

Hypertension disease staging	Other risk factors, HMOD, or disease	BP (mmHg) grading			
		High-normal SBP 130–139 DBP 85–89	Grade 1 SBP 140–159 DBP 90–99	Grade 2 SBP 160–179 DBP 100–109	Grade 3 SBP ≥ 180 DBP ≥ 110
Stage 1 (uncomplicated)	No other risk factors	Low risk	Low risk	Moderate risk	High risk
	1 or 2 risk factors	Low risk	Moderate risk	Moderate to high risk	High risk
	≥ 3 risk factors	Low to moderate risk	Moderate to high risk	High risk	High risk
Stage 2 (asymptomatic disease)	HMOD, CKD grade 3, or diabetes mellitus without organ damage	Moderate to high risk	High risk	High risk	High to very high risk
Stage 3 (established disease)	Established CVD, CKD grade ≥ 4, or diabetes mellitus with organ damage	Very high risk	Very high risk	Very high risk	Very high risk

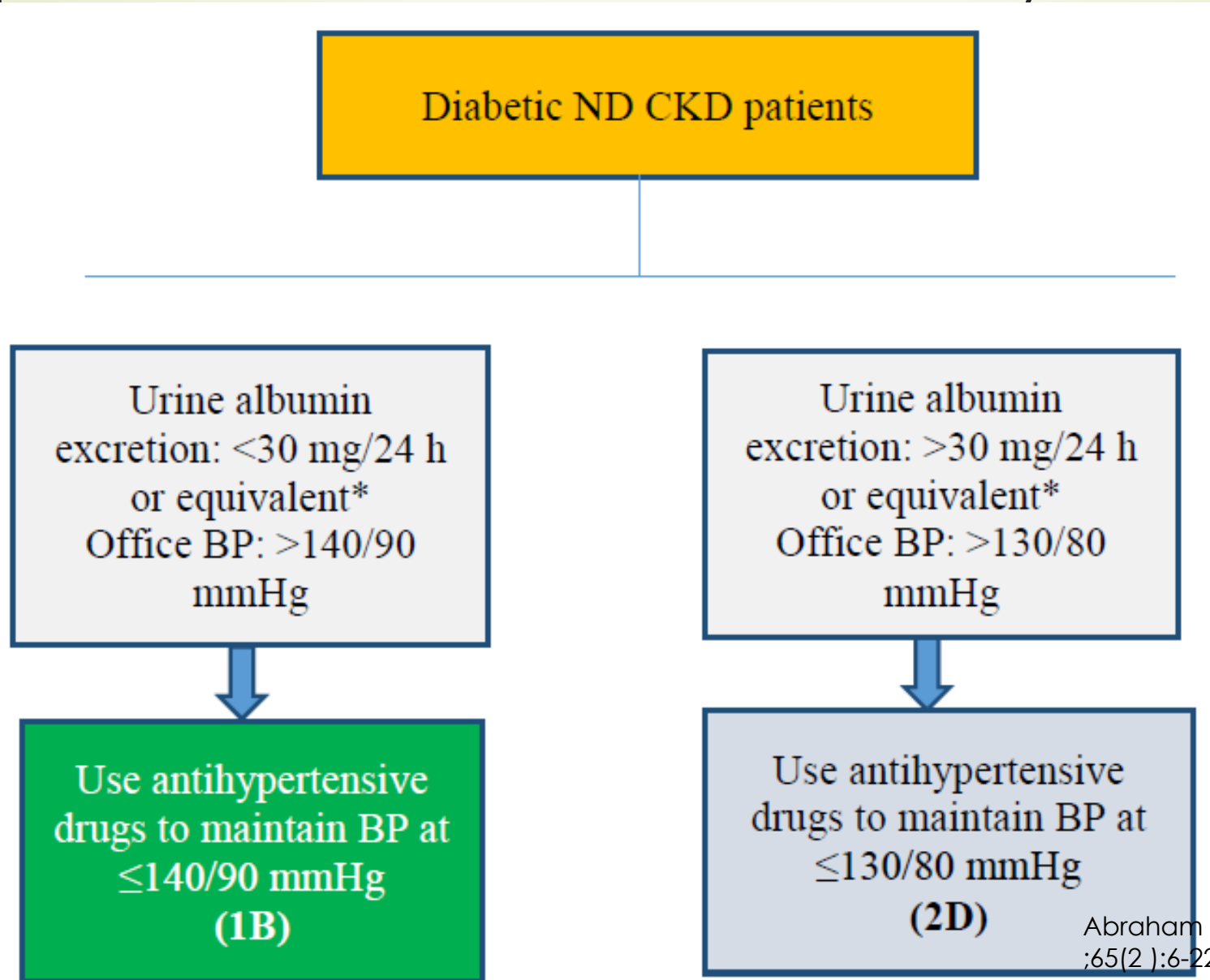
BP = blood pressure; CKD = chronic kidney disease; CV = cardiovascular; DBP = diastolic blood pressure; HMOD = hypertension-mediated organ damage; SBP = systolic blood pressure; SCORE = Systematic Coronary Risk Evaluation. CV risk is illustrated for a middle-aged male. The CV risk does not necessarily correspond to the actual risk at different ages. The use of the SCORE system is recommended for formal estimation of CV risk for treatment decisions.

2012 KDIGO Guidelines on management of hypertension in nondiabetic non-dialysis-dependent CKD patients

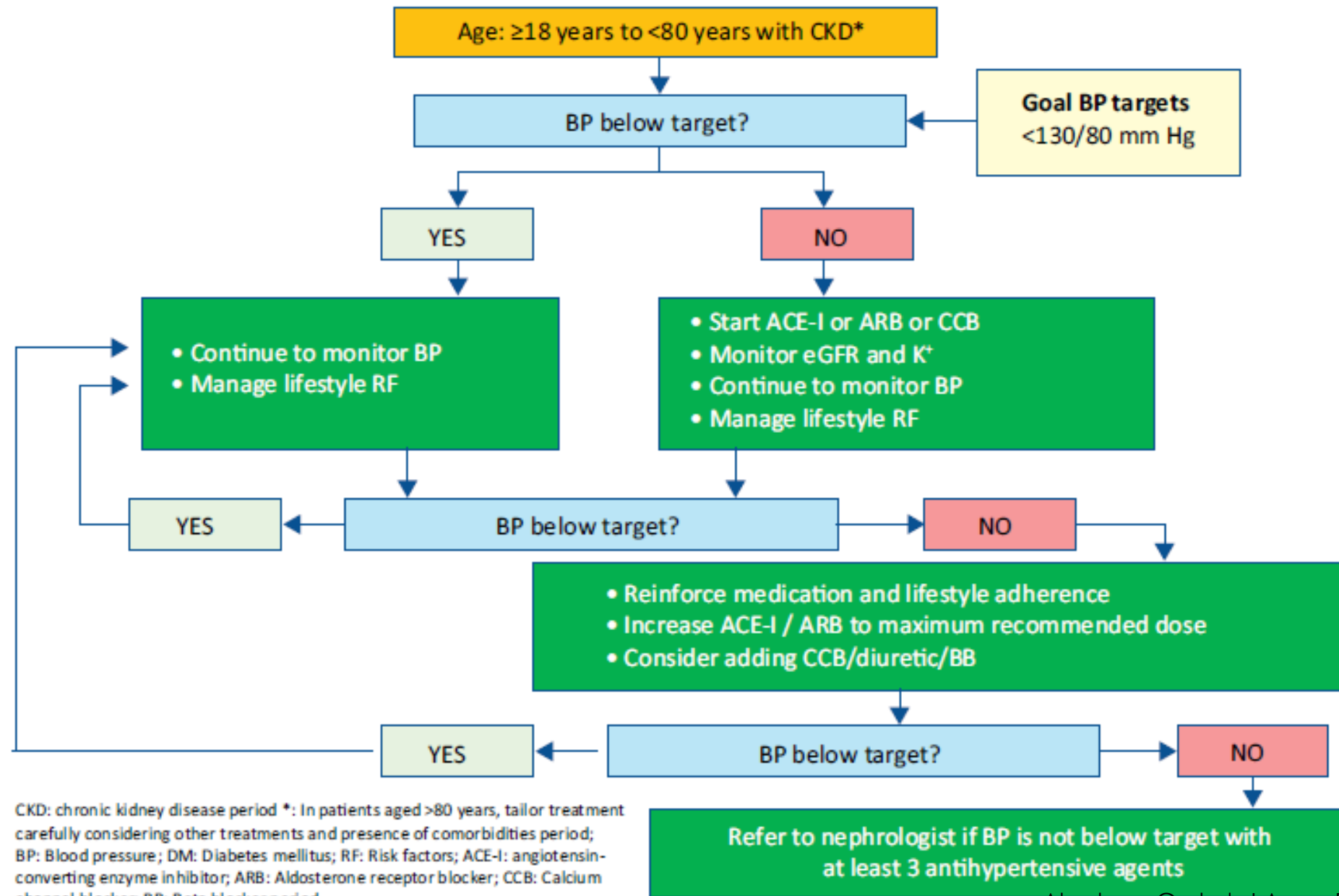


2012 KDIGO Guidelines on management of hypertension in diabetic non-dialysis-dependent

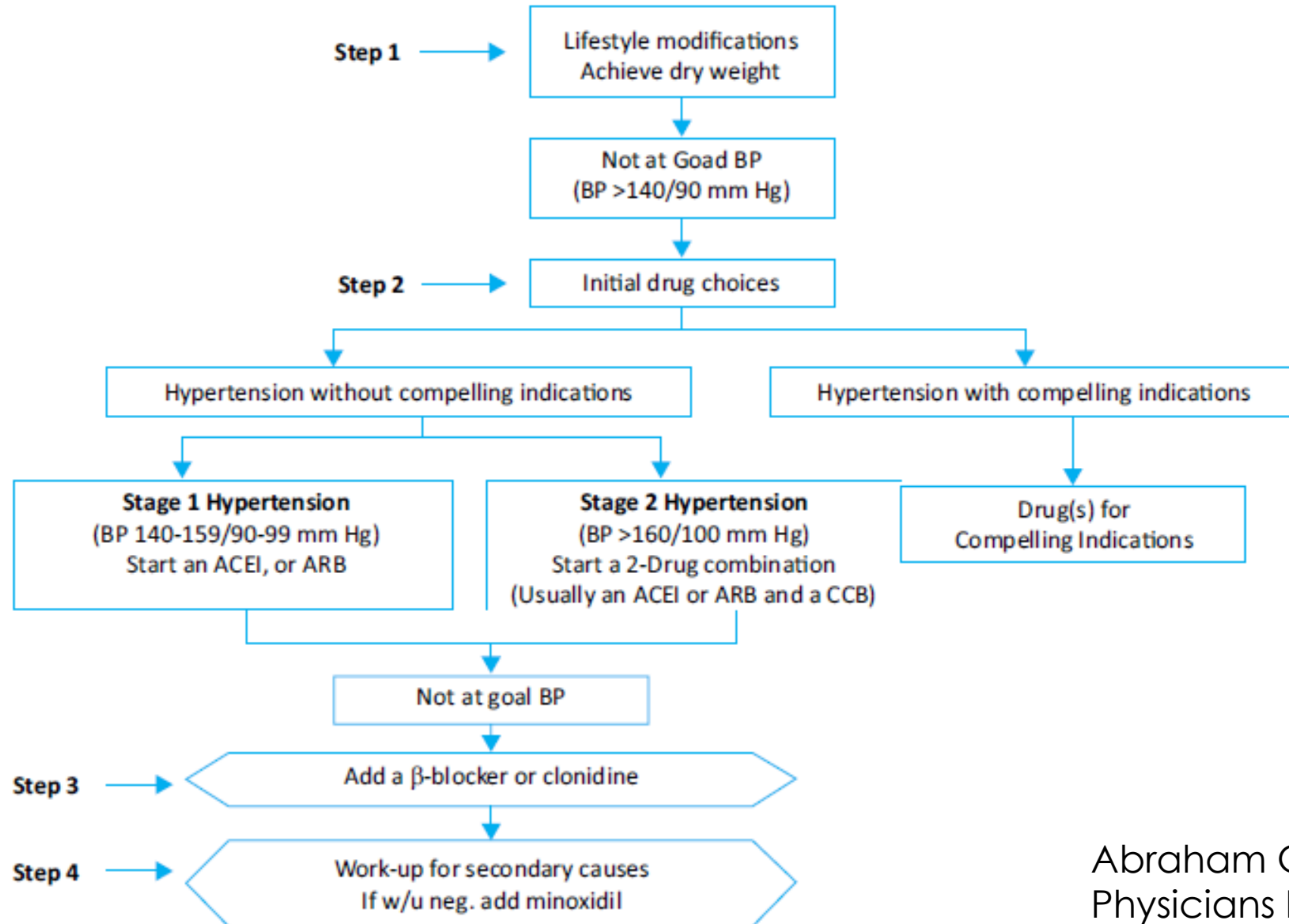
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Algorithm for the management of blood pressure in patients with CKD



Management of blood pressure in dialysis patients



Treatment guidelines related to management of hypertension in patients with CKD and albuminuria

	2017 ACC/AHA	2013 ESH/ESC	2018 ADA	2012 NKF KDOQI
Type of CKD considered	Albuminuria ≥ 300 mg/d or ≥ 300 mg/g creatinine	Overt proteinuria	Urinary albumin-to-creatinine ratio ≥ 300 mg/g creatinine or 30–299 mg/g creatinine	Urine albumin excretion of 30 to 300 mg or > 300 mg per 24 h
Recommended BP target (mm Hg)	Lowering < 130/80	Lowering SBP to < 140 Lowering < 130/80 mmHg in individuals with overt proteinuria	Lowering < 140/90 Lowering < 130/80 mmHg, for individuals at high risk of cardiovascular disease	Lowering ≤ 130/80
Recommended initial antihypertensive treatment	ACE inhibitor or ARB if ACE inhibitor is not tolerated	ACE inhibitor or ARB	ACE inhibitor or ARB If one class is not tolerated, the other should be substituted	ACE inhibitor or ARB
Other comments	A 10 to 25% increase in serum creatinine may occur in some patients with CKD as a result of RAAS therapy	RAS blockade is more effective in reducing albuminuria than other antihypertensive agents and is also effective in preventing incident microalbuminuria	Patients and clinicians should engage in a shared decision-making process to determine individual BP targets Bedtime dosing: moving at least one antihypertensive medication to bedtime.	The antihypertensive and antialbuminuric effects ACE inhibitor or ARB are complemented by dietary sodium restriction or administration of diuretics.

ACC/AHA American College of Cardiology/American Heart Association; ACE inhibitors, angiotensin-converting enzyme inhibitors; ADA, American Diabetes Association; ARBs, angiotensin II receptor blockers; CKD, chronic kidney disease; ESH/ESC, European Society of Hypertension/European Society of Cardiology; RAS, renin angiotensin system; NKF, National Kidney Foundation

Hypertension management in patients with type 2 diabetes, nephropathy and/or early CKD.

- In patients with type 2 diabetes and hypertension, salt intake of less than 90 mmol per day (less than 2 g per day of sodium – equivalent to 5 g of sodium chloride) (Grade 1C).
- In patients with type 2 diabetes, CKD and urine albumin excretion rate (AER) of less than 30 mg per 24 hours (albumin:creatinine ratio (ACR) less than 3 mg/mmol), target upright blood pressure should be less than 140/90 mmHg, using antihypertensive therapy in the maximum tolerated doses (Grade 1D).
- In patients with type 2 diabetes, CKD and urine AER of greater than 30 mg per 24 hours (ACR greater than 3 mg/mmol), target upright blood pressure is consistently less than 130/80 mmHg, using antihypertensive therapy in the maximum tolerated doses (Grade 2D)
- ACEIs (or ARBs if ACEIs are not tolerated) should be preferentially used in patients with type 2 diabetes and CKD who have urine AER above 30 mg per 24 hours (ACR greater than 3 mg/mmol).

Summary of Recommended Blood Pressure Targets by Comorbid Conditions and Age and by

	ADA (2018)	ACC/AHA (2017)	ACP/AAFP (2017)	Hypertension Canada (2017)	KHA-CARI (2013)	ESH/ESC (2013)	KDIGO (2012)	JNC8 (2014)	VA/DoD (2014)
Most adults	—	<130/80	<140/90	<140/90	—	—	—	<140/90	<140/90
CKD, no DM									
No proteinuria	—	<130/80	—	<140/90; SBP < 120 if high CV risk	<140/90	<140/90	<140/90	<140/90	<140/90
Proteinuria	—	<130/80	—	<140/90; SBP < 120 if high CV risk	<130/80	<140/90	<130/80	<140/90	<140/90
CKD and DM									
No proteinuria	<140/90; <130/80 or <120/80 if high CV risk & tolerated	<130/80	—	<130/80	<140/90	<140/85	<140/90	<140/90	<140/85
Proteinuria	<140/90; <130/80 or <120/80 if tolerated	<130/80	—	<130/80	<130/80	<140/85	<130/80	<140/90	<140/85
Kidney transplant recipients	—	<130/80	—	—	<130/80 <125/75 if proteinuria ^a	—	<130/80	—	—
Older population	—	<130/80	SBP < 150; <140 if h/o stroke or high CV risk ^a	<140/90; SBP < 120 if age ≥ 50 y & high CV risk or if age ≥ 75 y	—	<150/90	Individualize	<150/90	Unable to determine

Abbreviations: ACC/AHA, ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines; ACP/AAFP, American College of Physicians/American Academy of Family Physicians; ADA, American Diabetes Association; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; ESH/ESC, European Society of Hypertension and the European Society of Cardiology; h/o, history of; JNC8, Report from the Panel Members Appointed to the Eighth Joint National Committee workgroup; KDIGO, Kidney Disease: Improving Global Outcomes; KHA-CARI, Kidney Health Australia—Caring for Australians With Renal Impairment; SBP, systolic blood pressure; VA/DOD, Veterans Affairs/Department of Defense.

^aNo recommendations regarding diastolic blood pressure.

BP Target Studies in Populations With CKD

Study	Description	BP Groups	Mean f/u, y	Kidney End Point
SPRINT subgroup with CKD (N = 2,646)	Aged ≥50 y, high CVD risk, UPCR < 1 g/g; eGFR > 20 mL/min/1.73 m ² , no DM	SBP < 120 vs <140 mm Hg	3.3	HR, 0.90 (95% CI, 0.44, 1.83) for composite of ≥50% decline in eGFR or ESRD
REIN-2 (N = 338)	Aged 18-70 y, urine protein excretion 1-3 g/d with CL _{cr} < 45 mL/min or ≥3 g/d with CL _{cr} < 70 mL/min	SBP/DBP < 130/80 mm Hg vs DBP < 90 mm Hg	1.6	HR, 1.00 (95% CI, 0.61-1.64) for ESRD
AASK trial phase (N = 1,094)	18-70 y, African Americans with clinically attributed hypertensive CKD, GFR 20-65 mL/min/1.73 m ² , UPCR < 2.5 g/g, no DM	MAP ≤ 92 vs 102-107 mm Hg	4.1	HR, 1.06 (95% CI, 0.89-1.27) for ESRD
AASK trial phase with UPCR > 0.22 g/g (N = 357)			4.1	HR, 0.76 (95% CI, 0.55-1.04) for doubling of Scr or ESRD
AASK trial & cohort phases (N=691)			9.1	HR, 0.95 (95% CI, 0.78-1.15) for ESRD
AASK trial & cohort phases with UPCR > 0.22 g/g (N = 357)			9.1	HR, 0.76 (95% CI, 0.58-0.99) for doubling of Scr or ESRD
MDRD Study trial phase (N = 840)	Aged 18-70 y with GFR 13-55 mL/min/1.73 m ²	MAP < 92 mm Hg if age ≤ 60 y & MAP < 98 mm Hg if age ≥ 61 y vs 107 mm Hg if age < 60 y & <113 mm Hg if age ≥ 61 y	2.2	HR, 0.78 (95% CI, 0.66-0.93) for kidney failure
MDRD Study trial & cohort phases (N = 840)			9.2	HR, 0.68 (95% CI, 0.57-0.82) for ESRD

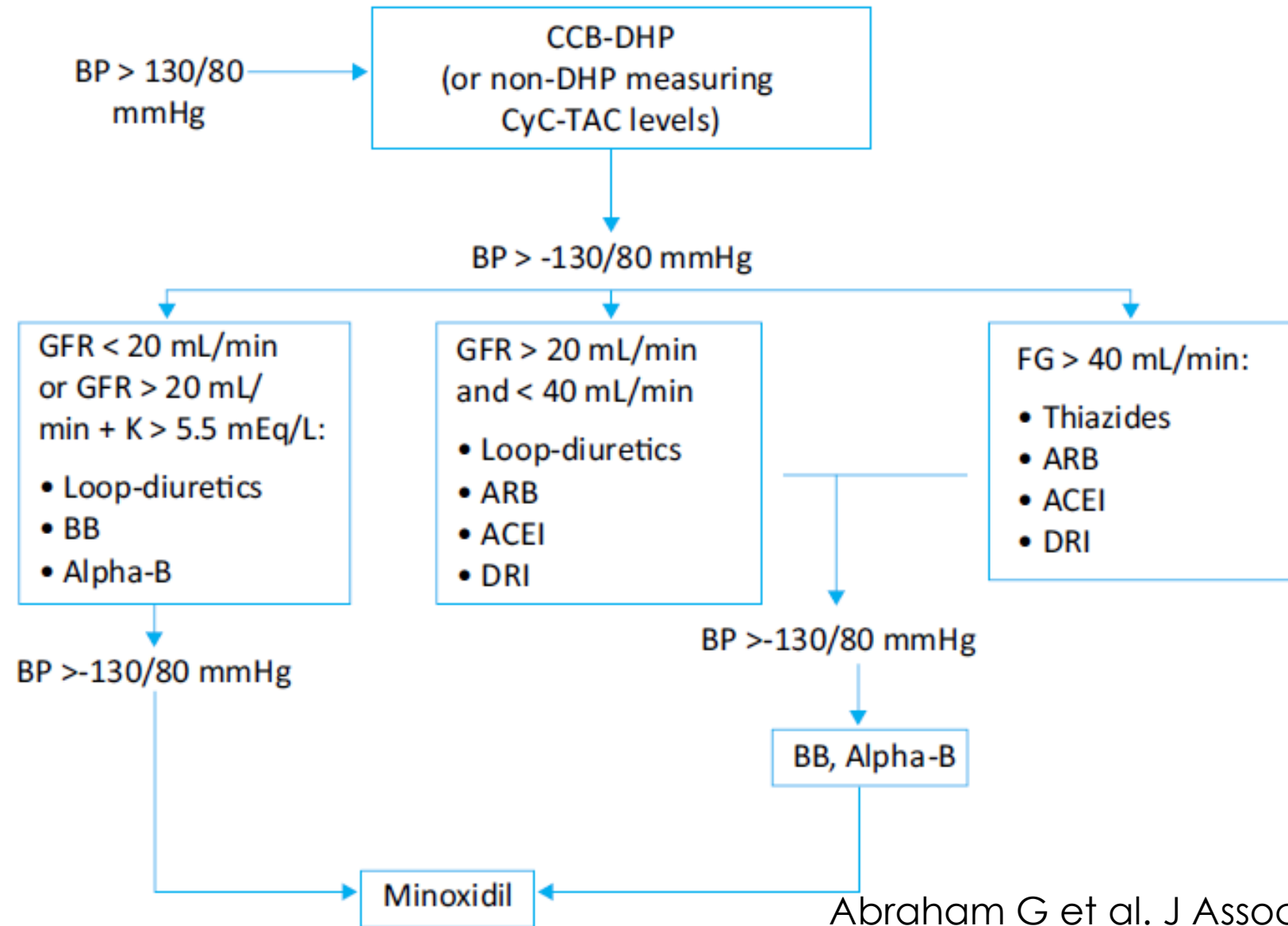
Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; BP, blood pressure; CI, confidence interval; CKD, chronic kidney disease; CL_{cr}, creatinine clearance; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; (e)GFR, (estimated) glomerular filtration rate; ESRD, end-stage renal disease; HR, hazard ratio; MAP, mean arterial pressure; MDRD, Modification of Diet in Renal Disease; REIN-2, Blood Pressure Control for Renoprotection in Patients With Non-Diabetic Chronic Renal Disease; SBP, systolic blood pressure; Scr, serum creatinine; SPRINT, Systolic Blood Pressure Intervention Trial; UPCR, urinary protein-creatinine ratio.

National Kidney foundation guidelines for selecting antihypertensive agents in dialysis

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, α_1 -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.

Therapeutic approach in transplant patients with hypertension



Indications & Choice of Antihypertensive Agents for Patients With CKD

Medications	CKD-Related Indications	Other Potential Indications	Common Side Effects	Potential Contraindications	Other Considerations
Diuretics					
Thiazide (eg, hydrochlorothiazide, chlorthalidone, metolazone)	Fluid overload; may improve proteinuria if used in combination with RAS inhibitors	Kidney stone prevention (hypercalciuria); Gordon syndrome; NDI	Hyperuricemia; hypercalcemia; hyponatremia; hypokalemia; hyperglycemia (with long-term use)	Gout; hypercalcemia	May be less effective when eGFR is <30 although some studies have shown these agents remain effective even with low eGFR
Loop (eg, furosemide, bumetanide, torsemide)	Fluid overload	Heart failure; hypercalcemia	Hearing loss; hypokalemia; hypocalcemia; hyponatremia	Gout; sulfonamide-related hypersensitivity	Bumetanide and torsemide have better intestinal absorption than furosemide
Potassium-sparing (triamterene, amiloride)	Fluid overload; hypokalemia	Refractory hypomagnesemia; lithium toxicity/NDI	Hyperkalemia; metabolic acidosis	Pregnancy	
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	

Ku E et al. Am J Kidney Dis.2019;

Indications & Choice of Antihypertensive Agents for Patients With CKD

Medications	CKD-Related Indications	Other Potential Indications	Common Side Effects	Potential Contraindications	Other Considerations
β-Blockers					
Selective (metoprolol, nebivolol)		Heart failure; atrial fibrillation; migraines; essential tremors; anxiety disorders; angina	Bradycardia; hyperkalemia; fatigue; depression; sexual dysfunction	Asthma; COPD; 2nd or 3rd degree heart block	
Combined α-β (carvedilol, labetalol)		Heart failure; atrial fibrillation	Bradycardia; hyperkalemia; fatigue; depression; sexual dysfunction	2nd or 3rd degree heart block	May be better tolerated in lung disease than selective β-blockers
Calcium Channel Blockers					
Dihydropyridine (amlodipine, nifedipine)		Raynaud, esophageal spasms	Lower-extremity edema; gingival hypertrophy		May worsen proteinuria
Nondihydropyridine (diltiazem, verapamil)	Proteinuria reduction	Atrial fibrillation	Constipation; gingival hyperplasia	2nd or 3rd degree heart block	↑ calcineurin and mTOR inhibitor levels
Other					
α-Blockers		Benign prostatic hypertrophy; kidney stone passage	Orthostasis		
Central α-adrenergic agonists (clonidine)			Sedation; bradycardia; dry mouth; rebound hypertension	Depression	

Indications & Choice of Antihypertensive Agents for Patients With CKD

Medications	CKD-Related Indications	Other Potential Indications	Common Side Effects	Potential Contraindications	Other Considerations
Vasodilators (minoxidil, hydralazine)			Headache; tachycardia; lupus-like syndrome (hydralazine); edema; pericardial effusion	Post-myocardial infarction; heart failure	
Direct renin inhibitors (aliskiren)	Proteinuria reduction; if not tolerating ACEi or ARB			Bilateral renal artery stenosis	Not recommended for use in combination with ACEi or ARBs
Aldosterone antagonists (spironolactone, eplerenone)	Proteinuria reduction	Cirrhosis with ascites; polycystic ovarian syndrome; hyperaldosteronism	Hyperkalemia; metabolic acidosis; gynecomastia		May be useful in addition to ACEi or ARB for proteinuria reduction

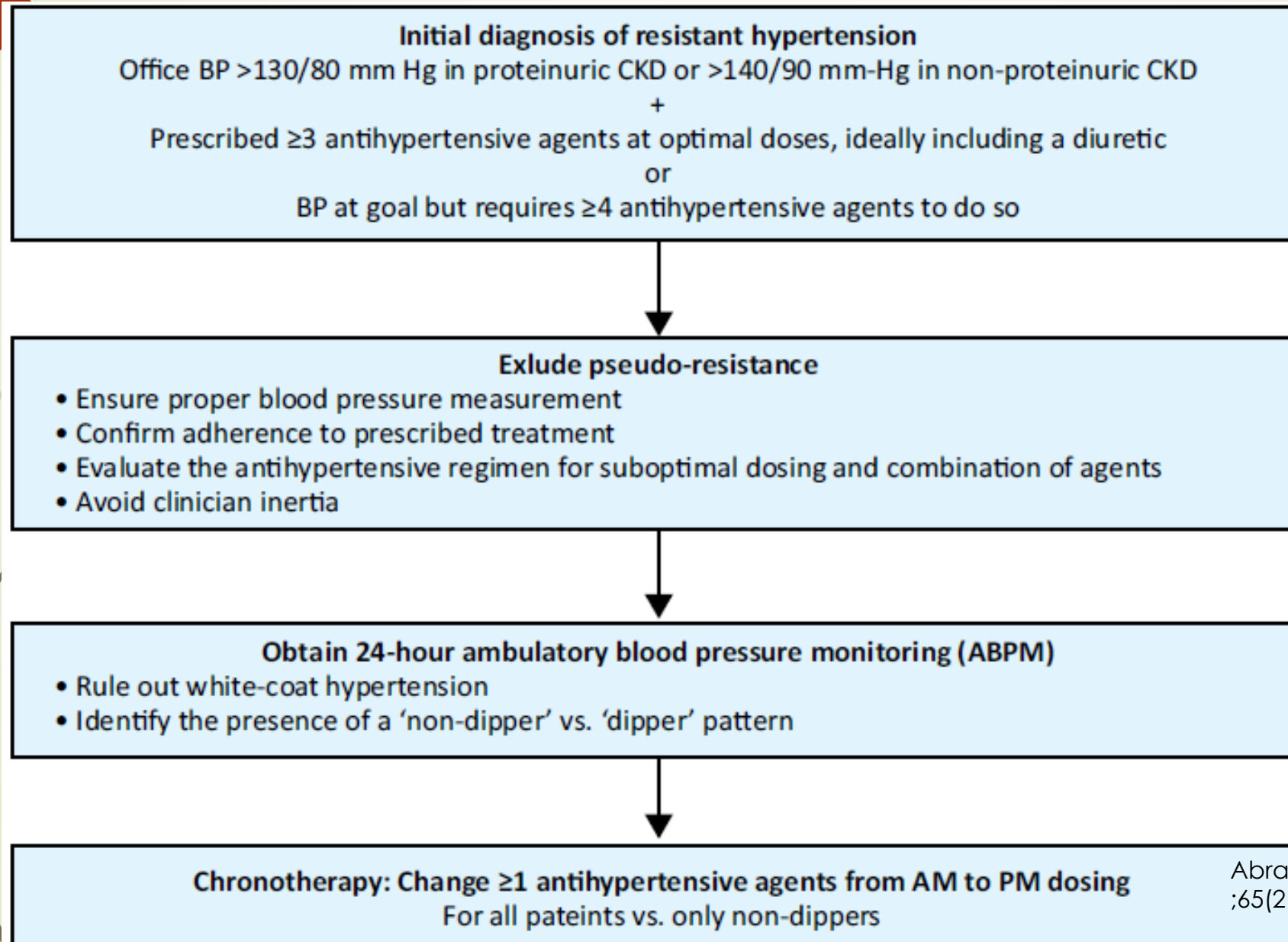
Caution in prescribing in patients with

Medication	Comments
Narrow therapeutic index drugs	
Aminoglycosides	Nephrotoxic (acute tubular necrosis, AKI). Ototoxic. Therapeutic drug monitoring recommended.
Digoxin	Increased for digoxin toxicity including arrhythmias. Therapeutic drug monitoring recommended.
Lithium	Diabetes insipidus, interstitial disease. Avoid concomitant use of thiazide diuretics and NSAIDs, maintain hydration. Therapeutic drug monitoring recommended.
Phenytoin	Low albumin will affect bound concentration. Monitor free phenytoin level.
Tacrolimus	Vasoconstriction, nephrotoxicity. Avoid concomitant use of CYP 3A4 inhibitors. Therapeutic drug monitoring recommended.
Warfarin	Increased risk of bleeding. Close INR monitoring recommended.
Analgesics	
NSAIDs	Hemodynamically mediated kidney injury, sodium and/or potassium retention, interstitial nephropathy. Avoid with concomitant use of diuretics or RAAS inhibitors, maintain hydration, consider alternate analgesic.
Meperidine	Active metabolite, normeperidine, increases risk of seizure. Avoid.
Morphine	Active metabolites, increased drug effect.
Contrast agents	
Iodinated contrast media	Nephrotoxic. Use lowest dose, maintain hydration with saline, can consider N-acetylcysteine or sodium bicarbonate, avoid concomitant nephrotoxins, avoid use of high-osmolality agents, avoid use of gadolinium-containing contrast media.
Bowel preparation	
Phosphate-containing bowel preparation	Increased risk for phosphate nephropathy and electrolyte disturbances. Avoid phosphate-based preparations.
Herbals	
Licorice	Increased risk of sodium and water retention, hypokalemia, hypertension. Avoid use.
Noni juice	Increased risk of hyperkalemia. Avoid use.
St. John's wort	CYP inducer. Increased risk of drug interactions. Avoid use.
Ginkgo biloba	Increased risk of bleeding. Avoid use.
Ephedra alkaloids (ma huang)	May potentiate hypertension. Avoid use.

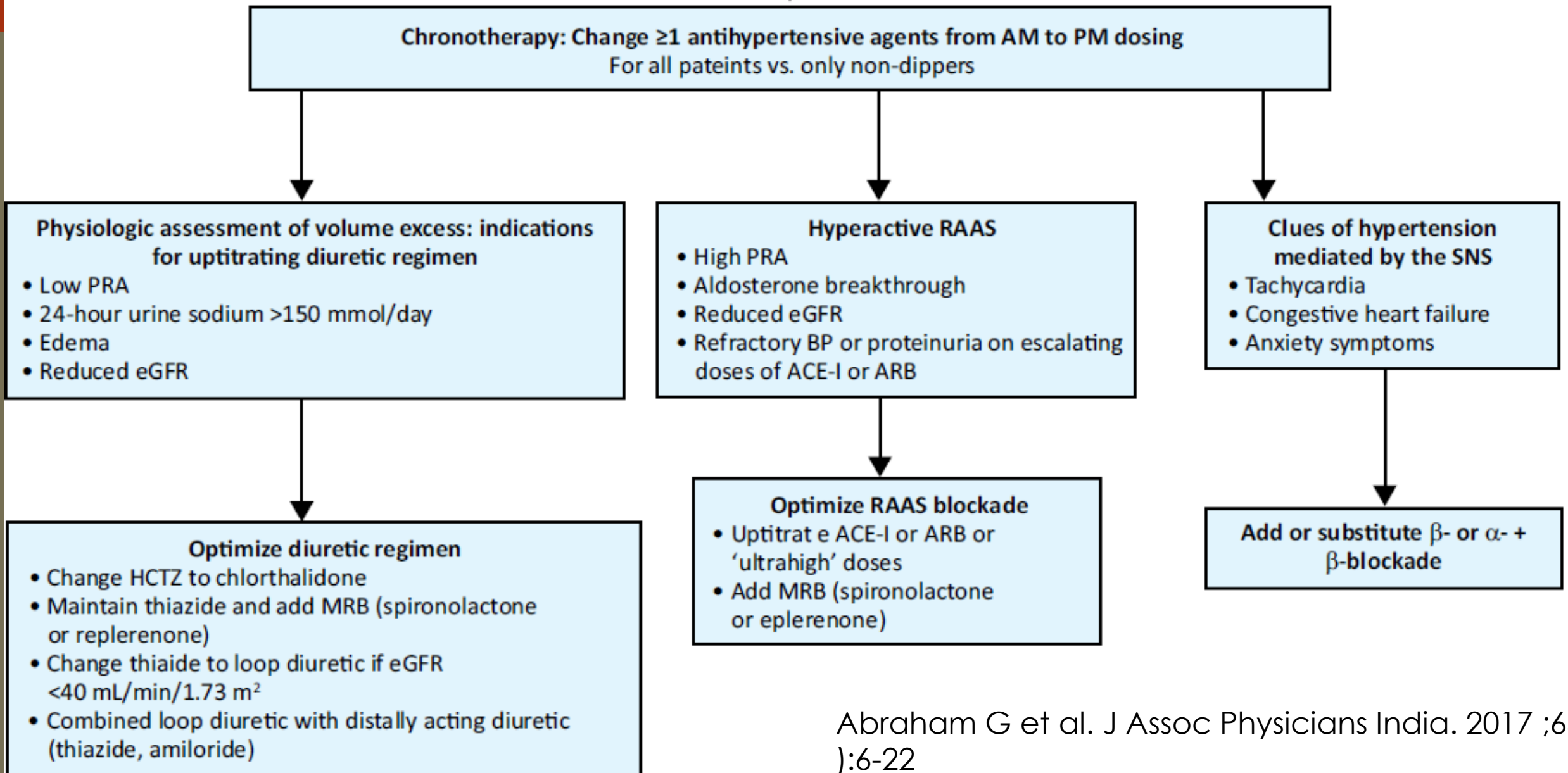
Excerpted from the 2012 Kidney Disease Improving Global Outcomes Guidelines on the management of CKD. NSAIDs, nonsteroidal anti-inflammatory drugs; CYP3A4, cytochrome p450 3A4; INR, International Normalized Ratio; RAAS, renin-angiotensin-aldosterone system; CYP, cytochrome p450.

Whittaker CF et al. Clin J Am Soc Nephrol. 2018; 13: 1738–1746

Resistant hypertension



Resistant hypertension - Management





Summary



- Hypertension is both a cause and consequence of CKD.
- All patients at increased risk of CKD should be evaluated for blood pressure, markers of kidney damage, and estimated GFR.
- Feasible tests for screening for CKD in primary care settings include testing the urine for protein and measuring serum creatinine levels to estimate GFR.
- Guidelines from across several international organization recommend a goal blood pressure of <140/90 mmHg in patients with CKD.
- In children with non-dialysisdependent 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.