Managing Difficult to Treat Hypertension

Jillian Hansen, DO

April 4, 2025

Disclosures

- None

Objectives

- Diagnostic criteria for resistant hypertension
- Recognize resistant hypertension and clinical inertia
- Evaluate specific agents to treat resistant hypertension using current guidelines and evidence-based practices
- Develop a therapeutic treatment plan for resistant hypertension considering patient specific factors

Blood Pressure Measurement

- Manual or automatic
- Preparation
  - Rest for 5 minutes
  - Avoid caffeine, smoking, exercise for 30 minutes prior
  - Empty bladder
  - Sit comfortably with back supported, feet on the floor, supported arm at heart level
- Correct cuff size
- Multiple readings
  - 2 readings at least 1-2 minutes apart and then average

Blood Pressure Measurement

- Ambulatory blood pressure monitoring
  - Measures BP over 24 hours
  - Variations
  - Nocturnal
- Home blood pressure monitoring
  - White coat hypertension
  - Masked hypertension

Definition of Hypertension

- 2017 ACC and AHA
  - American College of Cardiology
  - America Heart Association

Normal blood pressure	<120/80 mmHg
Elevated blood pressure	120-129/80 mmHg
Stage 1 hypertension	130-139/80-89 mmHg
Stage 2 hypertension	>140/90 mmHg

Guideline/Year	BP target	Office BP measurement	First-line therapy	Second-line therapy	Third-line therapy	Fourth-line therapy
AHA/ACC 2017	<130/80 mmHg	Standardized	ACEI or ARB in those with very high albuminuria	CCB or diuretic	Diuretic or CCB	Spironolactone*
ESH/ESC 2018	Systolic <140 down to 130 mmHg, if tolerated	Standardized	Initial combination of an ACEI or an ARB + CCB or diuretic		Combination therapy with ACEI or ARB + CCB + diuretic	Spironolactone*
ISH 2020	<130/80 mmHg (<140/90 mmHg in elderly patients)	Standardized	ACEI or ARB	CCB or diuretic	Diuretic or CCB	Spironolactone*
ESC 2021	Systolic <140 down to 130 mmHg, if tolerated	Standardized	Initial combination of an ACEI or an ARB + CCB or diuretic		Combination therapy with ACEI or ARB + CCB + diuretic	Spironolactone*
KDIGO 2021	Systolic <120 mmHg, when tolerated	Standardized	ACEI or ARB in those with very high albuminuria			

Nephrol Dial Transplant , 2023, Vol. 38, No. 12

Hypertension
Volume 71, Issue 6, June 2018; Pages e13-e115
https://doi.org/10.1161/HYP.0000000000000065

CLINICAL PRACTICE GUIDELINE

2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PC 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

Paul K. Whelton, MB, MD, MSc, FAHA, Robert M. Carey, MD, FAHA, Wilbert S. Aronow, MD, FACC, FAHA, Donald E. Casey, Jr, MD, MPH, MBA, FAHA, Karen J. Collins, MBA, Cheryl Dennison Himmelfarb, RN, ANP, PhD, FAHA, Sondra M. DePalma, MHS, PA-C, CLS, AACC, Samuel Gidding, MD, FAHA, Kenneth A. Jamerson, MD, Daniel W. Jones, MD, FAHA, Eric J. MacLaughlin, PharmD, Paul Muntner, PhD, FAHA, Bruce Ovbiagele, MD, MSc, MAS, MBA, FAHA, Sidney C. Smith, Jr, MD, MACC, FAHA, Crystal C. Spencer, JD, Randall S. Stafford, MD, PhD, Sandra J. Taler, MD, FAHA, Randal J. Thomas, MD, MS, FACC, FAHA, Kim A. Williams, Sr, MD, MACC, FAHA, Jeff D. Williamson, MD, MHS, and Jackson T. Wright, Jr, MD, PhD, FAHA

2017 AHA / ACC Guidelines Target <130/80

- Lifestyle modifications for everyone

- Weight loss
- Diet – low sodium, high potassium
- Physical activity
- Limit alcohol consumption to no more than 1-2 drinks per day

2017 AHA / ACC Guidelines
Target <130/80

- Single agent for stage 1 hypertension and cardiovascular disease risk (>130/90)
  - Primary prevention ASCVD risk >10%
  - Secondary prevention
- Two agents for stage 2 hypertension (>140/90)

- First line agents
  - Thiazide diuretics
  - Calcium channel blockers
  - ACEI or ARB

2017 AHA / ACC Guidelines
Target <130/80

- Preferred first agents based on comorbid conditions

- Diabetes and proteinuria: ACEI or ARB
- Chronic kidney disease: ACEI or ARB
- Heart failure: Beta-blockers, ACEI or ARB, mineralocorticoid receptor antagonists

Guideline/Year	BP target	Office BP measurement	First-line therapy	Second-line therapy	Third-line therapy	Fourth-line therapy
AHA/ACC 2017	<130/80 mmHg	Standardized	ACEI or ARB in those with very high albuminuria	CCB or diuretic	Diuretic or CCB	Spironolactone*
ESH/ESC 2018	Systolic <140 down to 130 mmHg, if tolerated	Standardized	Initial combination of an ACEI or an ARB + CCB or diuretic		Combination therapy with ACEI or ARB + CCB + diuretic	Spironolactone*
ISH 2020	<130/80 mmHg (<140/90 mmHg in elderly patients)	Standardized	ACEI or ARB	CCB or diuretic	Diuretic or CCB	Spironolactone*
ESC 2021	Systolic <140 down to 130 mmHg, if tolerated	Standardized	Initial combination of an ACEI or an ARB + CCB or diuretic		Combination therapy with ACEI or ARB + CCB + diuretic	Spironolactone*
KDIGO 2021	Systolic <120 mmHg, when tolerated	Standardized	ACEI or ARB in those with very high albuminuria			

Nephrol Dial Transplant , 2023, Vol. 38, No. 12

KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease

VOL 99 | ISSUE 3S | MARCH 2021

2021 KDIGO Guidelines

- Target <120 in those with chronic kidney disease
  - Evidence from SPRINT trial
  - Cardiovascular benefits from intensive BP lowering
  - Excluded those with diabetes
  - Has not been shown to significantly impact progression of kidney disease
- Less intensive therapy may be considered
  - Frailty
  - High risk of falls and fractures
  - Limited life expectancy
  - Symptomatic postural hypotension

2021 KDIGO Guidelines

- Preferred first line agents in those with chronic kidney disease with albuminuria

- ACEI or ARB
- Diuretics
- Calcium channel blockers

But the blood pressure is still high!

Hypertension
Volume 72, Issue 5, November 2018; Pages e53-e90
https://doi.org/10.1161/HYP.0000000000000084

AHA SCIENTIFIC STATEMENT

Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association

Robert M. Carey, MD, FAHA, Chair, David A. Calhoun, MD, FAHA, Vice Chair, George L. Bakris, MD, FAHA, Robert D. Brook, MD, FAHA, Stacie L. Daugherty, MD, MSPH, Cheryl R. Dennison-Himmelfarb, PhD, MSN, FAHA, Brent M. Egan, MD, John M. Flack, MD, MPH, FAHA, Samuel S. Gidding, MD, FAHA, Eric Judd, MD, MS, Daniel T. Lackland, DrPH, FAHA, Cheryl L. Laffer, MD, PhD, FAHA, Christopher Newton-Cheh, MD, MPH, FAHA, Steven M. Smith, PharmD, MPH, BCPS, Sandra J. Taler, MD, FAHA, Stephen C. Textor, MD, FAHA, Tanya N. Turan, MD, FAHA, and William B. White, MD, FAHA on behalf of the American Heart Association Professional/Public Education and Publications Committee of the Council on Hypertension; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Genomic and Precision Medicine; Council on Peripheral Vascular Disease; Council on Quality of Care and Outcomes Research; and Stroke Council

Diagnostic Criteria for Resistant Hypertension

- Blood pressure not at goal despite concurrent use of 3 antihypertensives drug classes
  - Long-acting calcium channel blocker
  - RAAS inhibition
  - Diuretic
- Blood pressure not at goal despite concurrent use of 4 or more antihypertensive medications
- Antihypertensives should be at maximum tolerated doses

- Exclude white coat hypertension and medication non-adherence

Why is this important?

- Higher risk for cardiovascular disease events and death

- >400,000 patients with resistant hypertension to those without resistant hypertension
- 33% increased risk of developing end stage kidney disease
- 24% increased risk of ischemic heart event
- 46% increased risk for heart failure
- 14% increased risk for stroke
- 6% increased risk of death

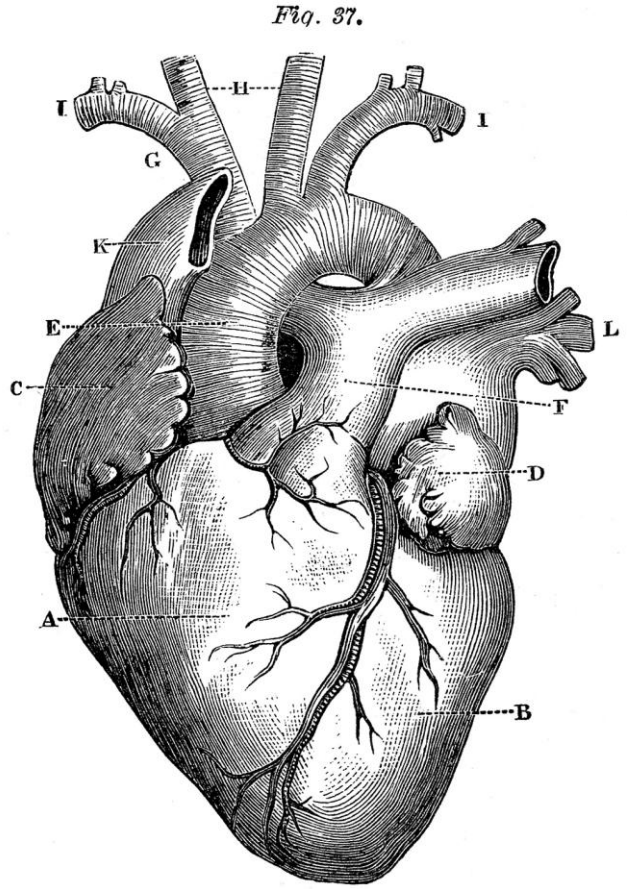
Tsioufis C, Kasiakogias A, Kordalis A, Dimitriadis K, Thomopoulos C, Tsiachris D, Vasileiou P, Doumas M, Makris T, Papademetriou V, Kallikazaros I, Bakris G, Stefanadis C.
Dynamic resistant hypertension patterns as predictors of cardiovascular morbidity: a 4-year prospective study.
J Hypertens. 2014;32:415–422.

Why is this important?

- More likely to have medication adverse effects
- Secondary cause of hypertension
- May benefit from special diagnostic or therapeutic approaches

Associated Co-Morbidities

- Obesity
- Left ventricular hypertrophy
- Albuminuria
- Diabetes mellitus
- Chronic kidney disease
- Obstructive sleep apnea
- Peripheral vascular disease



Prevalence of Resistant Hypertension

- 12-15% of adults treated for hypertension
  - NHANES data
- 15-18% based on clinic-based reports
  - European Study on Cardiovascular Risk Prevention and Management (EURIKA)
  - Spanish ABPM Registry
  - Chronic Renal Inefficiency Cohort (CRIC)
  - South Carolina Community*

*Egan BM, Zhao Y, Li J, Brzezinski WA, Todoran TM, Brook RD, Calhoun DA. *Hypertension*. 2013;62:691–697

American Heart Association®

Evaluation of Resistant Hypertension

Confirm Treatment Resistance

Clinic BP >130/80 mm Hg and patient taking 3 or more antihypertensive agents (including a long-acting calcium channel blocker, a blocker of the renin-angiotensin system [ACEI or ARB] and a diuretic) at maximal or maximally tolerated doses

↓

Exclude Pseudoresistance

- Confirm adherence to antihypertensive therapy
- Perform 24-hour ambulatory BP monitoring (if unavailable, use home BP monitoring) to exclude white-coat effect

↓

Assess for Secondary Hypertension

- Primary aldosteronism
- Renal parenchymal disease
- Renal artery stenosis
- Pheochromocytoma/paraganglioma
- Cushing syndrome
- Obstructive sleep apnea
- Coarctation of the aorta
- Other endocrine causes (**Table 3**)

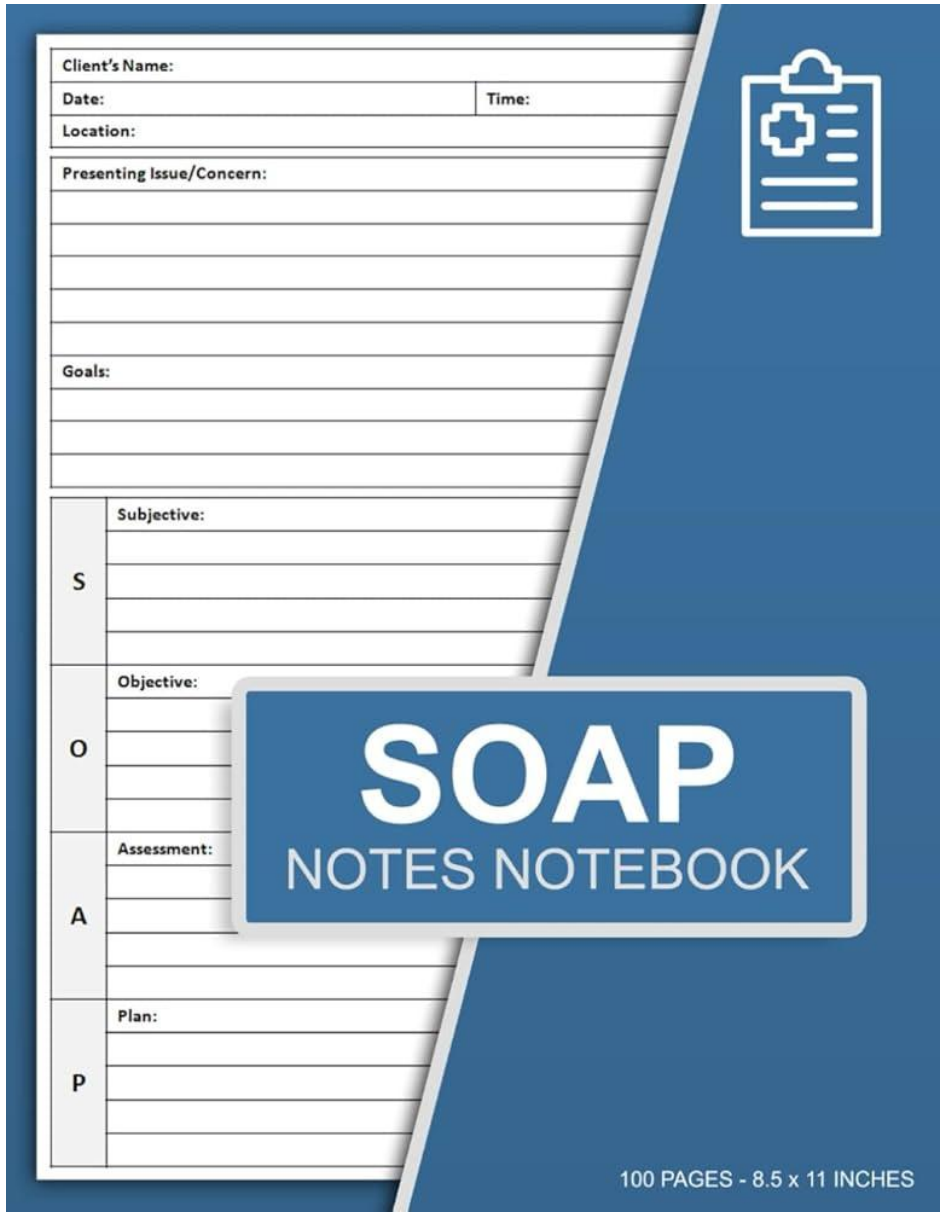
↓

Assess for Target Organ Damage

Ocular: funduscopic exam
Cardiac: left ventricular hypertrophy, coronary artery disease
Renal: proteinuria, reduced glomerular filtration rate
Peripheral arterial disease: ankle/brachial index

Evaluation

- History
- Exam – end organ damage
- Labs
- Imaging



Take a good history!

- Obesity
- Dietary sodium
- Alcohol
- Physical inactivity
- Illicit substance use

- Sleep disorders
  - Obstructive sleep apnea
  - Restless leg syndrome
  - Insomnia

- NSAIDs
- Oral contraceptives
- Sympathomimetics
- Calcineurin inhibitors
- Erythropoietin
- VEGF inhibitors
- Antidepressants
- Glucocorticoids
- Mineralocorticoids

Special Considerations

- Blood pressure in both arms and thigh if <30 years old
  - Evaluation for coarctation of the aorta
  - Pressure gradient greater than 20mmHg
- Evaluation for OSA with polysomnography is not indicated for all patients with resistant hypertension
  - STOP-BANG score

Secondary Hypertension

- Primary aldosteronism
- Chronic kidney disease
- Renal artery stenosis
- Coarctation of the aorta
- Pheochromocytoma
- Cushing syndrome
- Hypothyroidism
- Hyperthyroidism
- Hypercalcemia
- Congenital adrenal hyperplasia
- Mineralocorticoid excess syndromes
- Acromegaly

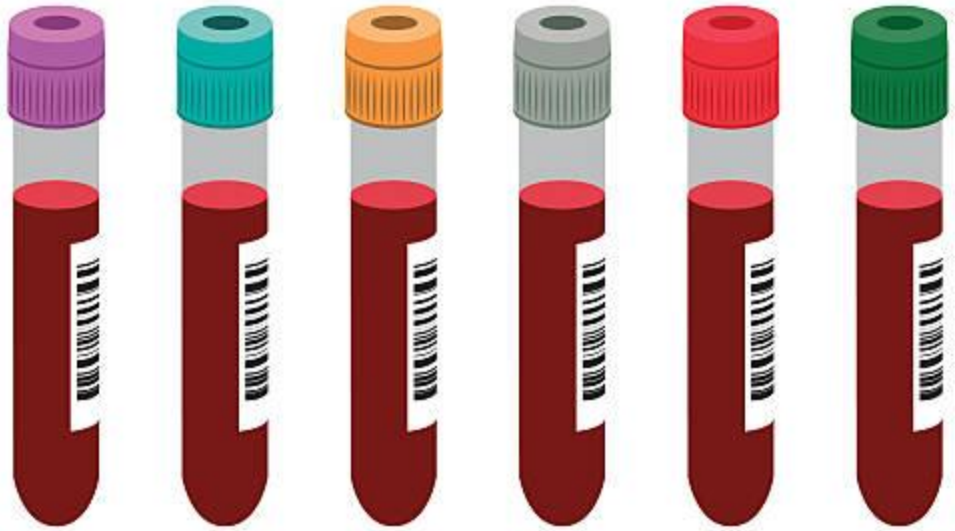
	Catecholamines	*Mineralocorticoid Excess or Effect*		*Other Endocrine Causes*
	Pheochromocytoma/ Paraganglioma	**Primary Aldosteronism**	**Excess DOC**	
When to consider	• Paroxysmal symptoms • Paradoxic BP responses • Resistant hypertension • Incidental adrenal mass • Previous PPGL • Family history PPGL • Syndromic features	• Sustained SBP ≥150 and/ or DBP ≥90 mm Hg • Resistant hypertension • Hypertension and: ✓ hypokalemia ✓ incidental adrenal mass ✓ OSA ✓ FHx of early onset hypertension or CVA at young age (≤40 yrs) • All first degrees relatives of patients with PA	**CAH - 11β or 17α-hydroxylase deficiency:** • Children, adolescents, and young adults who present with hypertension and hypo-kalemia and low levels of aldosterone and renin are present **DOC-Producing Tumor** • Hypertension and hypokalemia with low levels of aldosterone and renin **Primary Cortisol Resistance** • Hypertension and hypokalemia with low levels of aldosterone and renin	**Renovascular hypertension:** • Onset hypertension <30 yrs (think FMD) • Accelerated, resistant, malignant hypertension • Deterioration in renal function in response to treatment with an ACE-I or ARB • New onset of hypertension after age 50 yrs in smokers (think ASO) • Asymmetric kidneys and unexplained loss of renal function • Flash pulmonary edema **Other Endocrine Disorders** • Cushing syndrome • Hyperthyroidism • Hypothyroidism • Hypercalcemia and primary hyperparathyroidism • Acromegaly **Obstructive Sleep Apnea**
Case detection tests	Fractionated metanephrines measured in blood or 24-hr urine	Aldosterone/renin ratio	Plasma concentrations of DOC, 11-deoxycortisol, androstenedione, testosterone DHEA-S, cortisol, and 17-hydroxyprogesterone	**Renovascular hypertension:** • Image with renal artery duplex ultrasound or CT angiography or MR angiography or radionuclide scintigraphy **Obstructive Sleep Apnea:** • Polysomnography **Cushing syndrome:** • 1-mg DST, 24-hr UFC, late night salivary cortisol

ENDOCRINE SOCIETY

William F. Young, David A. Calhoun, Jacques W.M. Lenders, Michael Stowasser, Stephen C. Textor
Screening for Endocrine Hypertension: An Endocrine Society Scientific Statement
Endocrine Reviews, Volume 38, Issue 2, 1 April 2017, Pages 103–122

Labs and Imaging

- BMP
- UA
- Morning aldosterone and plasma renin activity
  - Aldosterone >16 ng/dL AND suppressed PRA
- Serum metanephrines
- 11pm salivary cortisol
- Renal artery duplex
- EKG and echocardiogram



Management of Resistant Hypertension

Medication Adherence

- Challenging since elevated blood pressure is generally symptomatic
- Resistant hypertension requires people to take multiple medications, multiple times per day

- Nonjudgmental discussion about barriers
- Simplify regimen, combination medications, pill boxes, alarms
- Diuretics in the morning (and afternoon if needing bid dosing)
- Education about prevention of cardiovascular disease

We need to be better too!

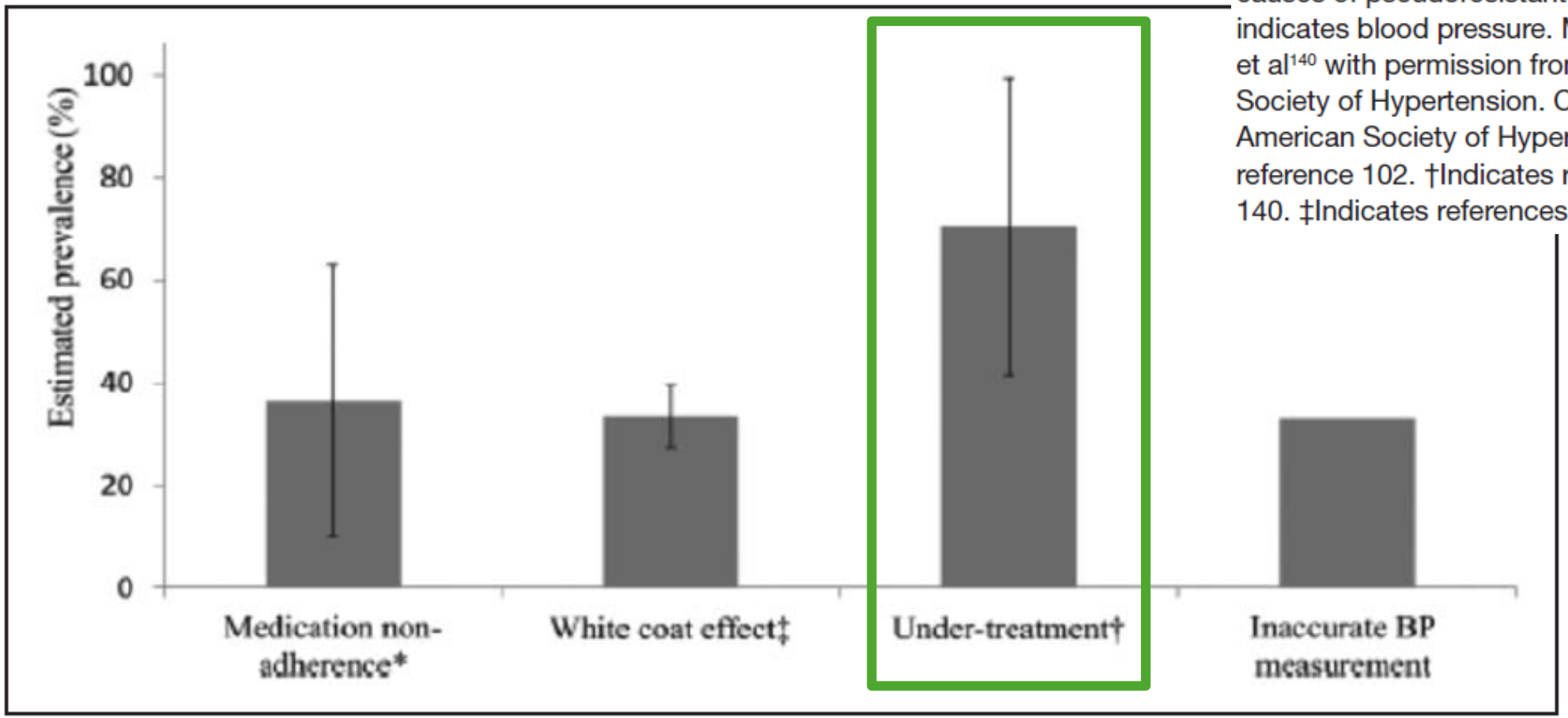


Figure 1. Estimated prevalence of each of the causes of pseudoresistant hypertension. BP indicates blood pressure. Modified from Bhatt et al[140] with permission from the American Society of Hypertension. Copyright © 2016, American Society of Hypertension. *Indicates reference 102. †Indicates references 20 and 140. ‡Indicates references 18, 32, and 145.

Hypertension
Volume 62, Issue 4, October 2013; Pages 691-697
https://doi.org/10.1161/HYPERTENSIONAHA.113.01448

American Heart Association.

EPIDEMIOLOGY/POPULATION

Prevalence of Optimal Treatment Regimens in Patients With Apparent Treatment-Resistant Hypertension Based on Office Blood Pressure in a Community-Based Practice Network

See Editorial Commentary, pp 680–681

Brent M. Egan, Yumin Zhao, Jiexiang Li, W. Adam Brzezinski, Thomas M. Todoran, Robert D. Brook, and David A. Calhoun

We need to be better too!

- 2007 to 2010
- 49.6% of patients with uncontrolled apparent resistant hypertension in a community-based practice network in the United States were prescribed an optimal antihypertensive regimen
- Antihypertensive medications were administered at <50% of their maximally recommended dose in 42.1% of patients with uncontrolled apparent resistant hypertension
- Patients were more likely to be prescribed optimal regimens were black, or diagnosed with chronic kidney disease, diabetes mellitus, or coronary artery disease

Egan BM, Zhao Y, Li J, Brzezinski WA, Todoran TM, Brook RD, Calhoun DA. *Hypertension*. 2013;62:691–697

Integrated Health Systems

- Hypertension control rates exceed the national average in the Kaiser Permanente and Veterans Affairs health systems
  - Approach to blood pressure control is systematic and multidisciplinary

- Identifying patients with hypertension, standardizing blood pressure measurements, and using a stepwise treatment algorithm have led to an increase in blood pressure control rates from 54% in 2004 to 84% in 2010 in the Kaiser Permanente Southern California health system*

*Sim JJ, Handler J, Jacobsen SJ, Kanter MH. Systemic implementation strategies to improve hypertension: the Kaiser Permanente Southern California experience. *Can J Cardiol*. 2014;30:544–552

Antihypertensives

Renin-Angiotensin-Aldosterone System (RAAS) Blockers

- ACE inhibitors
  - Lisinopril, Enalapril, Ramipril, Captopril
- Angiotensin II receptor blockers
  - Losartan, Valsartan, Irbesartan, Olmesartan
- First-line for CKD with albuminuria
- Potential contraindications: hyperkalemia, pregnancy, bilateral renal artery stenosis

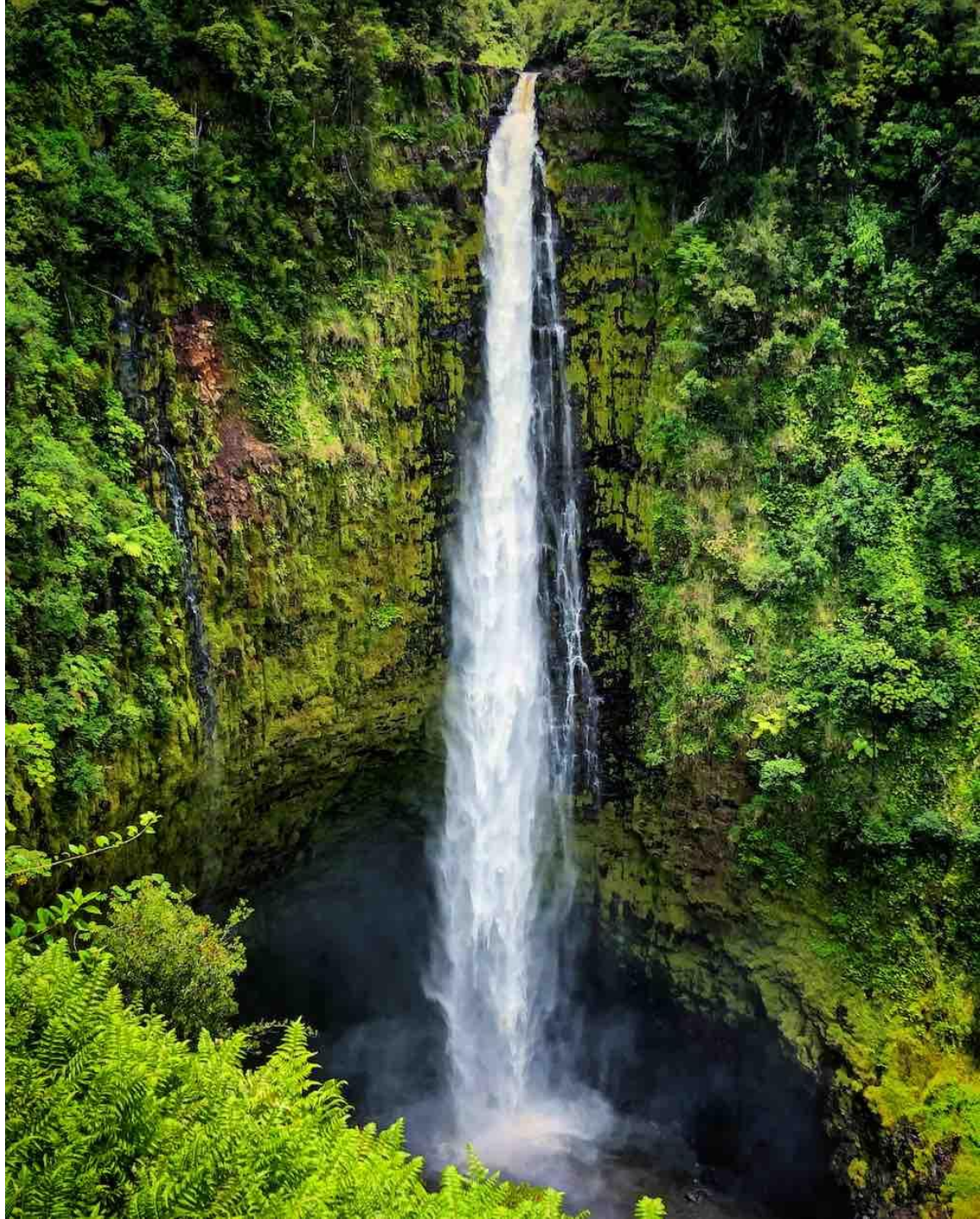
Calcium Channel Blockers

- Dihydropyridine
  - Amlodipine, Nifedipine, Felodipine
- Non-dihydropyridine
  - Diltiazem, Verapamil

- Do not use non-dihydropyridine CCB with heart block
- Medication interactions

Diuretics

- Thiazide and thiazide-like
  - Hydrochlorothiazide, Chlorthalidone, Indapamide
- Loop
  - Furosemide, Torsemide, Bumetinide
- Mineralocorticoid receptor antagonist
  - Spironolactone, Eplerenone
  - Finerenone (non-steroidal)
- SGLT-2 inhibitors
  - Dapagliflozin, Empagliflozin, Canagliflozin, Ertugliflozin



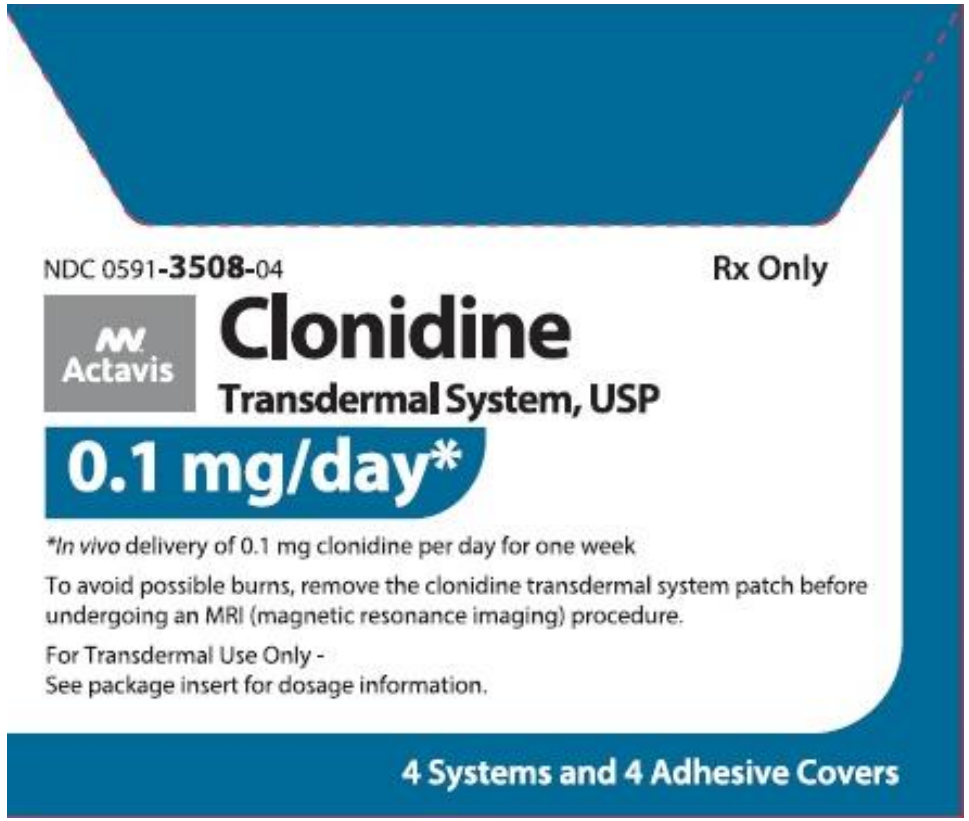
Beta Blockers

- Cardioselective
  - Metoprolol, Bisoprolol, Atenolol
- Non-cardioselective
  - Propranolol, Carvedilol, Labetalol

- Preferred in those with heart failure, coronary artery disease, and atrial fibrillation

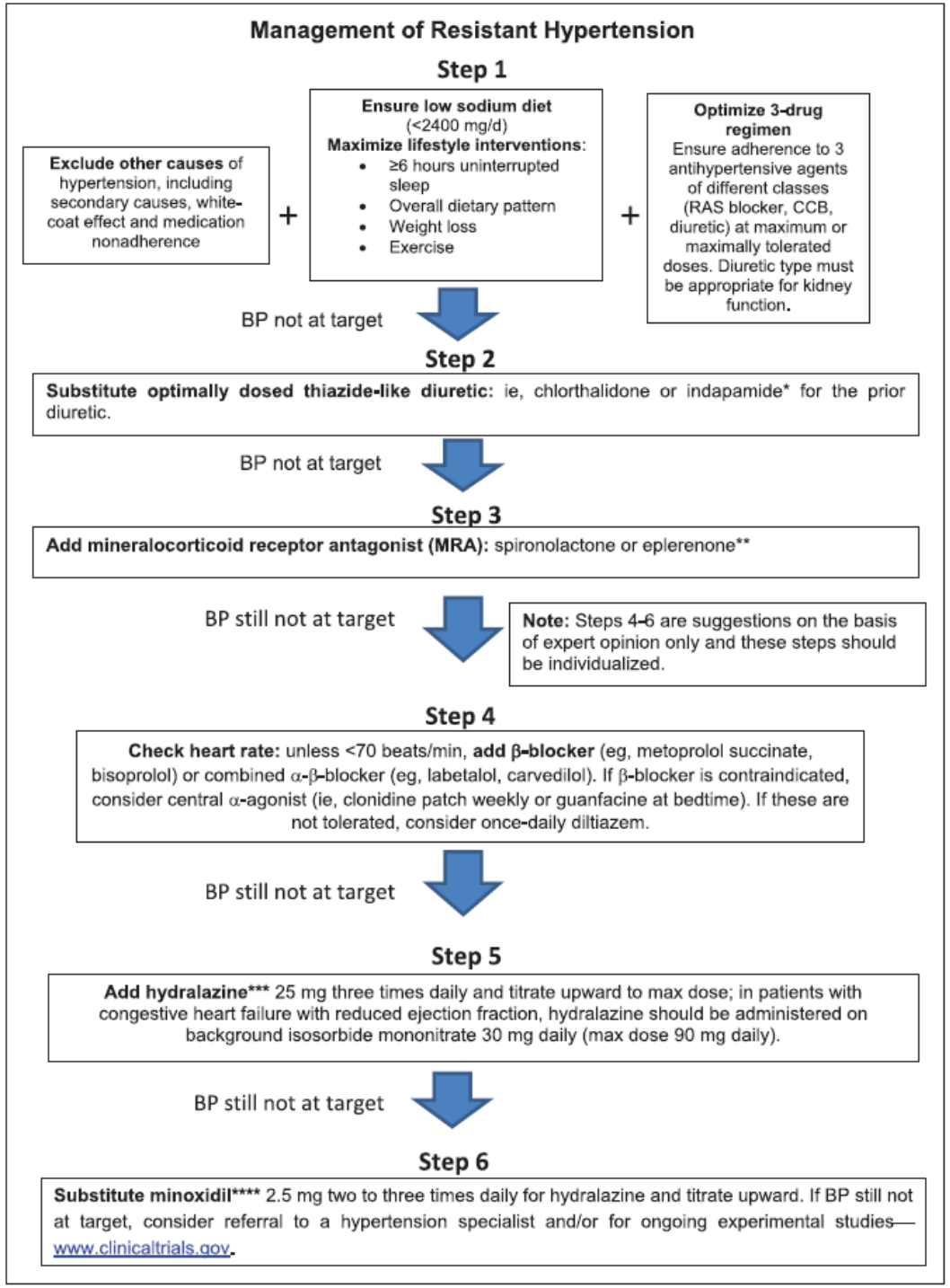
Other agents

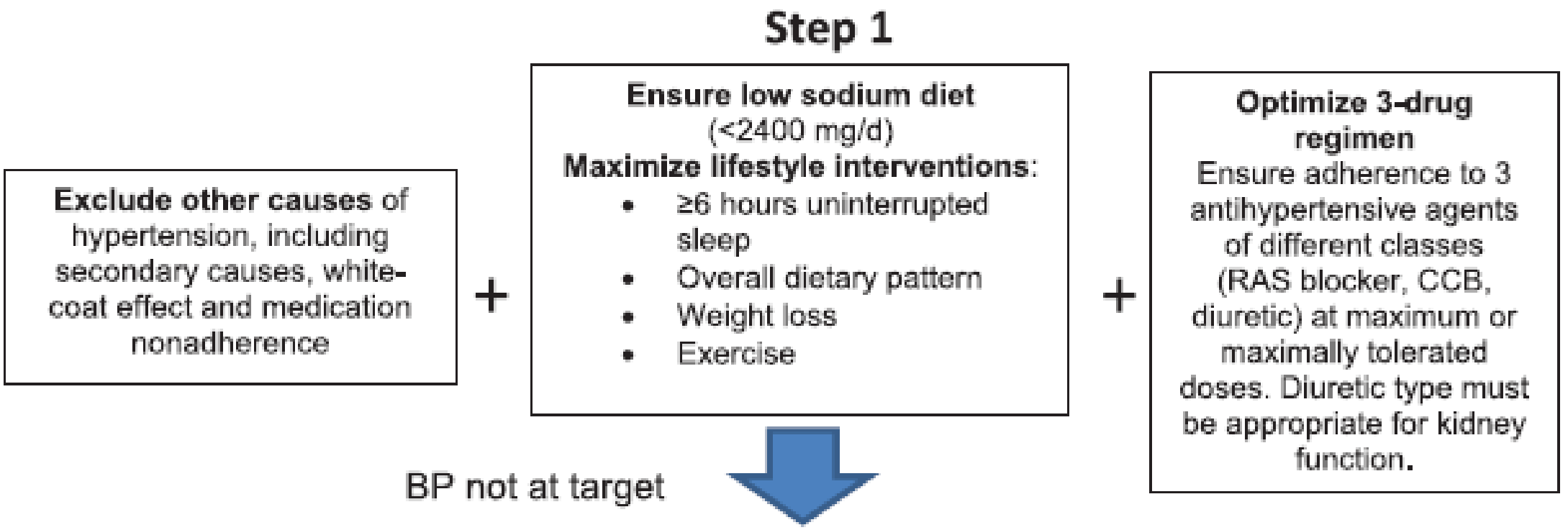
- Alpha-blockers
  - Doxazosin, Prazosin, Terazosin
- Vasodilators
  - Hydralazine, Minoxidil
- Centrally acting agents
  - Clonidine, Methyldopa
- Endothelin receptor antagonist
  - Aprocitentan




YOU ARE HERE
... And HERE Is A
Good Place To Start

American Heart Association®




Step 1
Exclude other causes of hypertension, including secondary causes, white-coat effect and medication nonadherence
+
Ensure low sodium diet
(<2400 mg/d)
Maximize lifestyle interventions:
≥6 hours uninterrupted sleep
Overall dietary pattern
Weight loss
Exercise
+
Optimize 3-drug regimen
Ensure adherence to 3 antihypertensive agents of different classes (RAS blocker, CCB, diuretic) at maximum or maximally tolerated doses. Diuretic type must be appropriate for kidney function.
BP not at target

Step 2

Substitute optimally dosed thiazide-like diuretic: ie, chlorthalidone or indapamide* for the prior diuretic.

BP not at target

*HCTZ does not induce a predictable natriuresis GFR <45ml/min
*Chlorthalidone induces natriuresis down to eGFR 30ml/min

Step 3

Add mineralocorticoid receptor antagonist (MRA): spironolactone or eplerenone**

BP still not at target

Note: Steps 4–6 are suggestions on the basis of expert opinion only and these steps should be individualized.

**Use caution if eGFR <30ml/min

PATHWAY-2

- Determine most effective add on therapy for patients with resista hypertension
- 285 patients with resistant hypertension
  - Already on ACEi/ARB + CCB + Thiazide
- Spironolactone, doxazosin, bisoprolol, placebo
- Reduction in home systolic blood pressure after 12 weeks

THE LANCET

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

Prof Bryan Williams, FRCP [a] · Prof Thomas M MacDonald, FRCP [b] · Steve Morant, PhD [b] · Prof David J Webb, FMedSci [c] · Prof Peter Sever, FRCP [d] · Prof Gordon McInnes, FRCP [e] · et al. Show more

Spironolactone wins!

- Spironolactone was superior to doxazosin and bisoprolol
- Hyperkalemia, gynecomastia in men

- Spironolactone 8.7mmHg
- Doxazosin 4.0mmHg
- Bisprolol 4.5mmHg
- Placebo No significant effect

Step 4

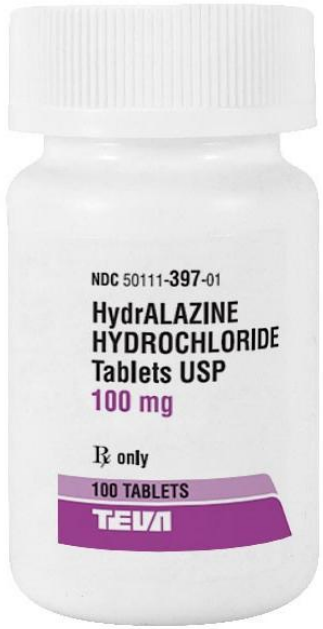
Check heart rate: unless <70 beats/min, **add β-blocker** (eg, metoprolol succinate, bisoprolol) or combined α-β-blocker (eg, labetalol, carvedilol). If β-blocker is contraindicated, consider central α-agonist (ie, clonidine patch weekly or guanfacine at bedtime). If these are not tolerated, consider once-daily diltiazem.

BP still not at target

*I will often do this before MRA if they have known heart disease

Step 5

Add hydralazine* 25 mg three times daily and titrate upward to max dose; in patients with congestive heart failure with reduced ejection fraction, hydralazine should be administered on background isosorbide mononitrate 30 mg daily (max dose 90 mg daily).



BP still not at target

***requires concomitant use of beta-blocker and diuretic

Step 6

Substitute minoxidil** 2.5 mg two to three times daily for hydralazine and titrate upward. If BP still not at target, consider referral to a hypertension specialist and/or for ongoing experimental studies—www.clinicaltrials.gov.

****requires concomitant use of beta-blocker and diuretic

Patient Specific Factors

American Heart Association®

Table 4. Specific Clinical Issues Associated With Treatment Resistance*

Issue Associated With Treatment Resistance	Management Consideration(s)
Volume control, edema resolution	Thiazide→chlorthalidone→loop diuretic
Heart rate control inadequate	β-Blocker, α,β-blocker, verapamil, diltiazem
Renin and aldosterone levels low	Low-salt diet, avoid nighttime shift work, amiloride
Renin low, aldosterone normal to high normal	Mineralocorticoid receptor antagonist
Would split dosing of medications improve control?	Evaluate BP pattern according to home and ambulatory BP monitoring
Medication adherence questionable	Initiate indirect or direct methods to detect nonadherence; if nonadherence is documented (partial or complete), discuss frankly, nonjudgmentally with patient and family
Pattern of BP response to medications outside clinician visit times unknown	Identify meal effects on BP, duration of medication effect, relationship of BP to side effects using out-of-office BP monitoring
Sleep disordered breathing; significant anxiety associated with highly variable hypertension	Initiate nondrug strategies concurrently with or separately from antihypertensive drug therapy

BP indicates blood pressure.

*Modified from White et al[334] with permission from the American Society of Hypertension. Copyright © 2014, American Society of Hypertension.

Volume first!

Time of day

Special Considerations

- Chronic kidney disease and diabetes mellitus
- Cardiovascular disease
- Heart failure

- Renal denervation
- Carotid baroreceptor activation

Evidence!!!

- CLICK Trial

- PATHWAY-2
- RALES

- FIGARO-DKD trial
- FIDELIGO-DKD trial

- EMPA-REG
- CANVAS
- DECLARE-TIMI 58

- DAPA-HF
- EMPOROR Reduced
- EMPOROR Preserved

- CREDENCE
- DAPA-CKD
- EMP-KIDNEY

CLICK Trial

The NEW ENGLAND JOURNAL of MEDICINE

Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

Authors: Rajiv Agarwal, M.D. , Arjun D. Sinha, M.D., Andrew E. Cramer, B.S., Mary Balmes-Fenwick, M.S., Jazmyn H. Dickinson, B.S., Fangqian Ouyang, M.S., and Wanzhu Tu, Ph.D. Author Info & Affiliations

Published November 5, 2021 | N Engl J Med 2021;385:2507-2519 | DOI: 10.1056/NEJMoa2110730
VOL. 385 NO. 27 | Copyright © 2021

- Assess weather chlorthalidone reduces blood pressures in patients with advanced CKD (eGFR 15-30ml/min) and uncontrolled hypertension.
- 160 patients with CKD. Uncontrolled hypertension. Already on one antihypertensive.
- Chlorthalidone 12.5mg or 25mg vs placebo.
- Change in 24-hour ambulatory BP at 12 weeks.
- Reduced ambulatory SBP by 11mmHg vs placebo.
- Higher risk of hypokalemia, mild increase in creatinine.

	Spironolactone	Finerenone
Class	Steroidal MRA	Non-steroidal MRA
Diuretic effect	Strong	Minimal
Gynecomastia risk	High	Low
Hyperkalemia risk	Moderate-High	Moderate-High
Primary use	Heart failure Hypertension Ascites PCOS	Chronic kidney disease Cardiovascular protection
Trial evidence	RALES, PATHWAY-2	FIGARO-DKD, FIDELIO-DKD
Cost	$10 for 30 day supply	$700 for 30 day supply

PATHWAY-2

- Determine most effective add on therapy for patients with resistant hypertension
- 285 patients with resistant hypertension
  - Already on ACEi/ARB + CCB + Thiazide
- Spironolactone, doxazosin, bisoprolol, placebo
- Reduction in home systolic blood pressure after 12 weeks
- Spironolactone was superior to doxazosin and bisoprolol

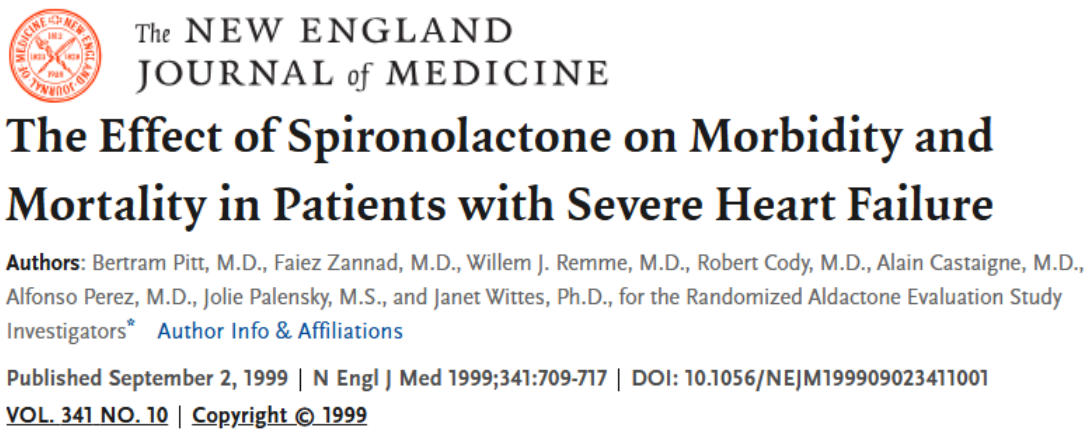
THE LANCET

Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial

Prof Bryan Williams, FRCP [a] · Prof Thomas M MacDonald, FRCP [b] · Steve Morant, PhD [b] · Prof David J Webb, FMedSci [c] · Prof Peter Sever, FRCP [d] · Prof Gordon McInnes, FRCP [e] · et al. Show more

RALES Trial

- Randomized Aldactone Evaluation Study
- HFrEF (<35%)
- Spironolactone 25mg daily vs placebo
- 30% reduction in all cause mortality (primary endpoint)
- 35% reduction in hospitalizations for heart failure (secondary endpoint)
- Better NYHA class improvement



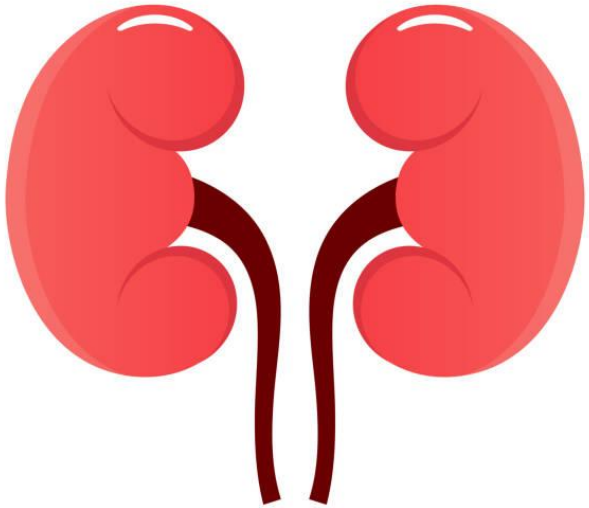
The NEW ENGLAND JOURNAL of MEDICINE

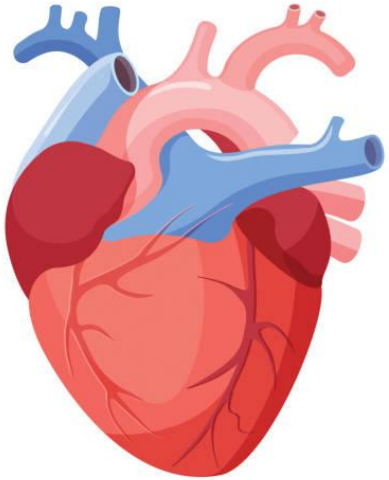
The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure

Authors: Bertram Pitt, M.D., Faiez Zannad, M.D., Willem J. Remme, M.D., Robert Cody, M.D., Alain Castaigne, M.D., Alfonso Perez, M.D., Jolie Palensky, M.S., and Janet Wittes, Ph.D., for the Randomized Aldactone Evaluation Study Investigators* Author Info & Affiliations

Published September 2, 1999 | N Engl J Med 1999;341:709-717 | DOI: 10.1056/NEJM199909023411001
VOL. 341 NO. 10 | Copyright © 1999

Finerenone





FIDELIO-DKD Trial

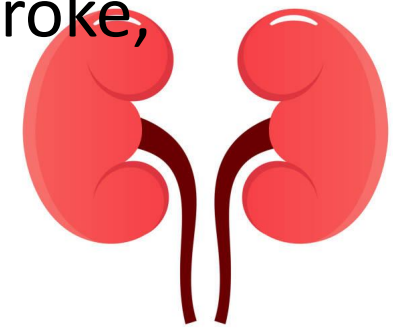
The NEW ENGLAND JOURNAL of MEDICINE

Effect of Finerenone on Chronic Kidney Disease Outcomes in Type 2 Diabetes

Authors: George L. Bakris, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., Bertram Pitt, M.D., Luis M. Ruilope, M.D., Peter Rossing, M.D., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., Amer Joseph, M.B., B.S., and Gerasimos Filippatos, M.D., for the FIDELIO-DKD Investigators* Author Info & Affiliations

Published October 23, 2020 | N Engl J Med 2020;383:2219-2229 | DOI: 10.1056/NEJMoa2025845
VOL. 383 NO. 23 | Copyright © 2020

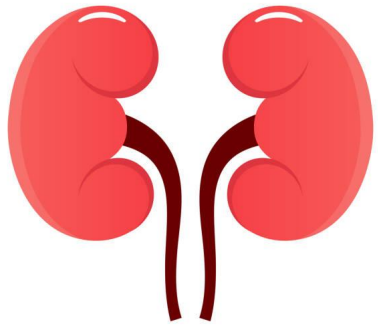
- Assess whether finerenone reduces kidney disease progression and cardiovascular outcomes in patient with CKD and T2DM
- CKD (eGFR 25-75ml/min), albuminuria, maximally tolerated RAAS blockade
- Finerenone 10-20mg daily vs placebo
- Kidney composite outcome – time to kidney failure, sustained >40% decline in eGFR, or kidney death
- Cardiovascular composite outcome – CV death, non-fatal MI, stroke, or hospitalization for heart failure



FIDELIO-DKD Trial

- 18% reduction in primary kidney outcome
  - Slower GFR progression compared to placebo
- 14% reduction in cardiovascular events

- 2.3% absolute increase in serious hyperkalemia evens compared to placebo



FIGARO-DKD Trial

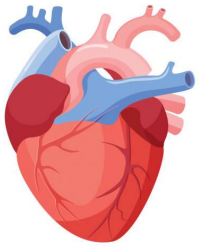
The NEW ENGLAND JOURNAL of MEDICINE

Cardiovascular Events with Finerenone in Kidney Disease and Type 2 Diabetes

Authors: Bertram Pitt, M.D., Gerasimos Filippatos, M.D., Rajiv Agarwal, M.D., Stefan D. Anker, M.D., Ph.D., George L. Bakris, M.D., Peter Rossing, M.D., Amer Joseph, M.B., B.S., Peter Kolkhof, Ph.D., Christina Nowack, M.D., Patrick Schloemer, Ph.D., and Luis M. Ruilope, M.D., for the FIGARO-DKD Investigators* Author Info & Affiliations

Published August 28, 2021 | N Engl J Med 2021;385:2252-2263 | DOI: 10.1056/NEJMoa2110956
VOL. 385 NO. 24 |

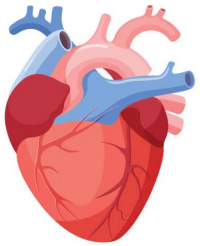
- Determine if finerenone reduces cardiovascular risk in patients with milder CKD and T2DM
- CKD (eGFR >25ml/min, lower albuminuria than FIDELIO-DKD), T2DM, RAAS blockade
- Finerenone 10-20mg daily vs placebo
- Cardiovascular composite outcome – CV death, MI, stroke, heart failure hospitalization
- Kidney composite outcome – eGFR decline, kidney failure, kidney death



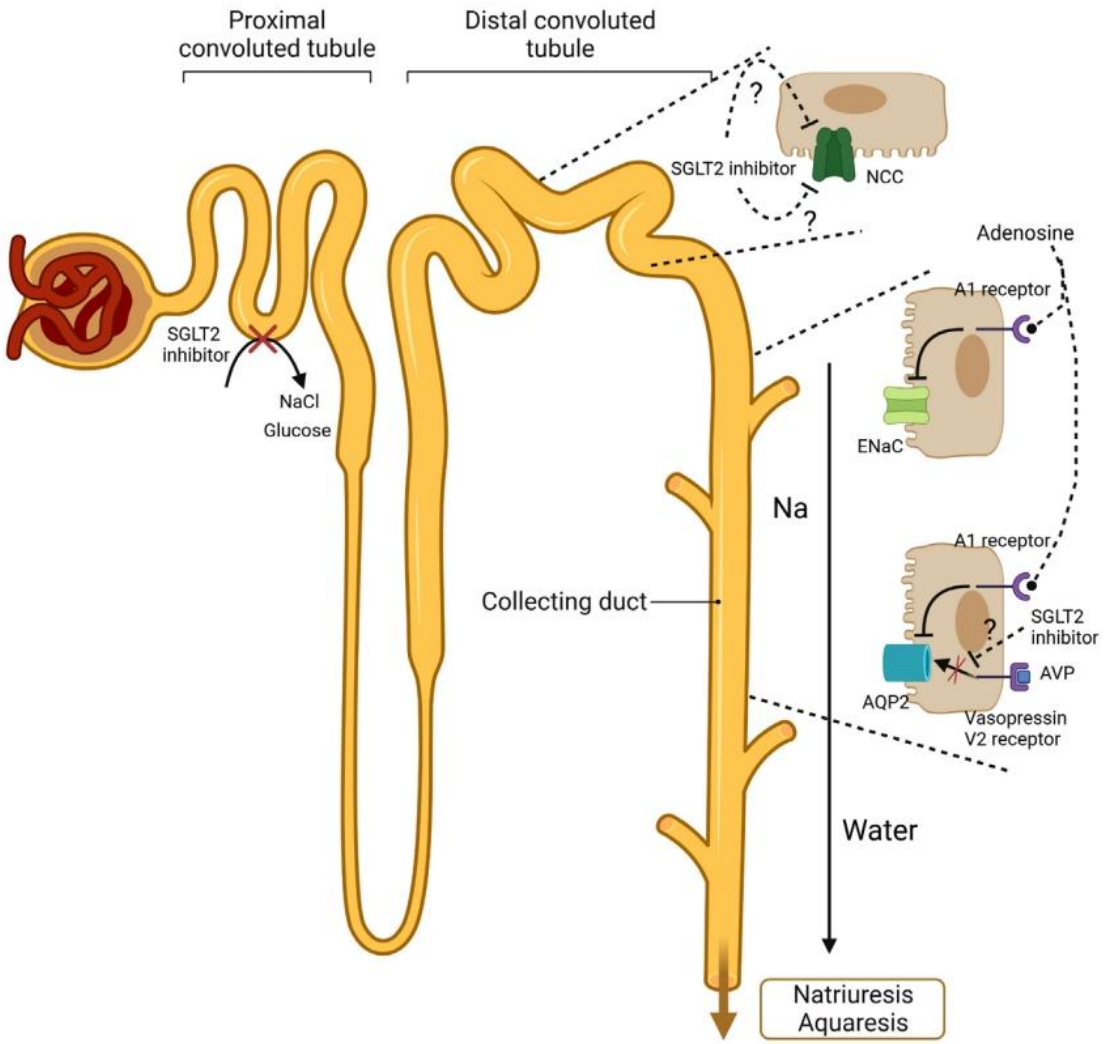
FIGARO-DKD Trial

- 13% reduction in cardiovascular events
  - Heart failure hospitalizations specifically
- No significant reduction in CKD progression (vs FIDELIO-DKD)

- Hyperkalemia higher than placebo

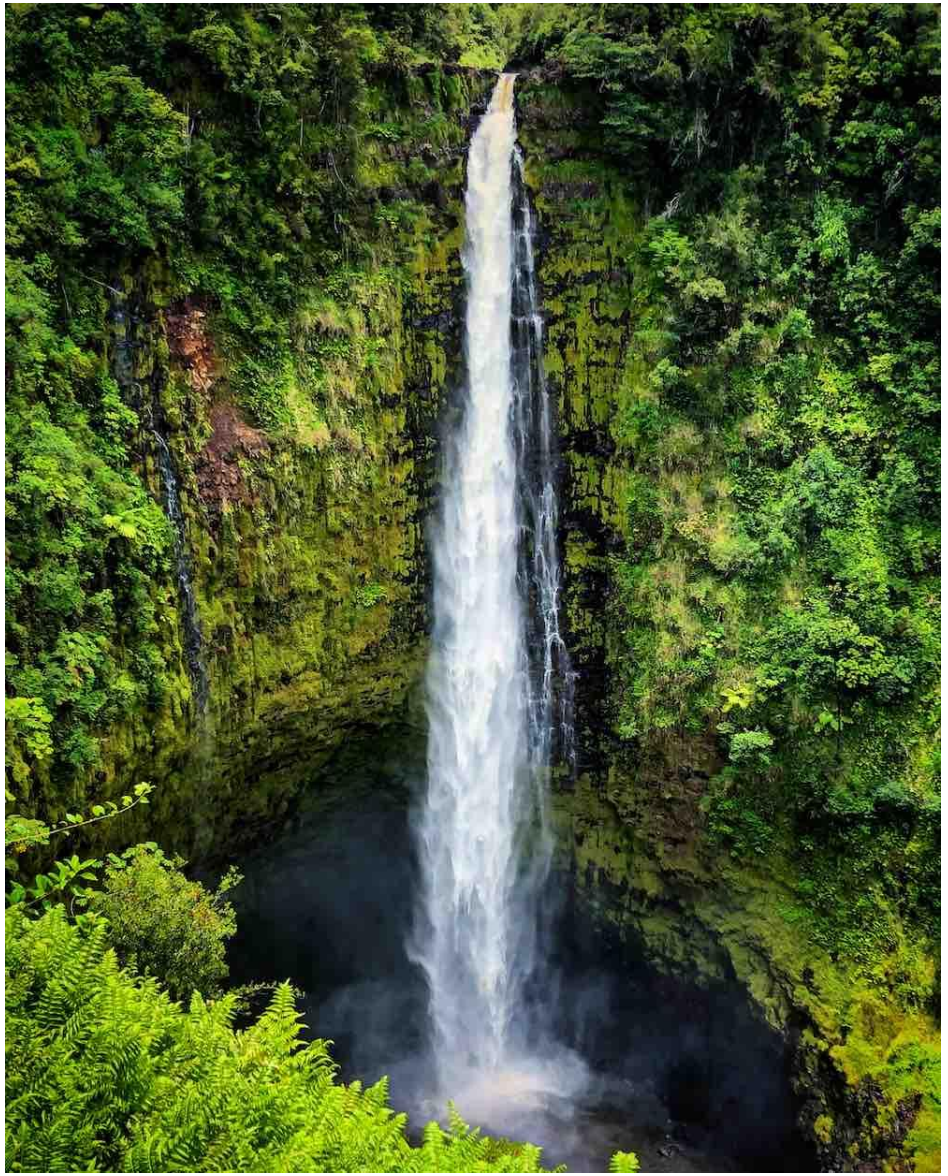


SGLT2 Inhibitors



Blood Pressure

- Osmotic diuresis and natriuresis
  - Increased sodium and water excretion reduces plasma volume
- Reduced arterial stiffness and vascular resistance
- Weight loss
- Reduces sympathetic activation



Blood Pressure

- Meta-analysis showing SGLT2i result in average reduction in SBP 3.62mmHg, and DBP 1.70mmHg
- Comparable with SBP-lowering effect of hydrocholorthiazide

Ambulatory Blood Pressure Reduction With SGLT-2 Inhibitors: Dose-Response Meta-analysis and Comparative Evaluation With Low-Dose Hydrochlorothiazide

Diabetes Care 2019;42:693–700 | https://doi.org/10.2337/dc18-2207

Clinical Impact and Guidelines

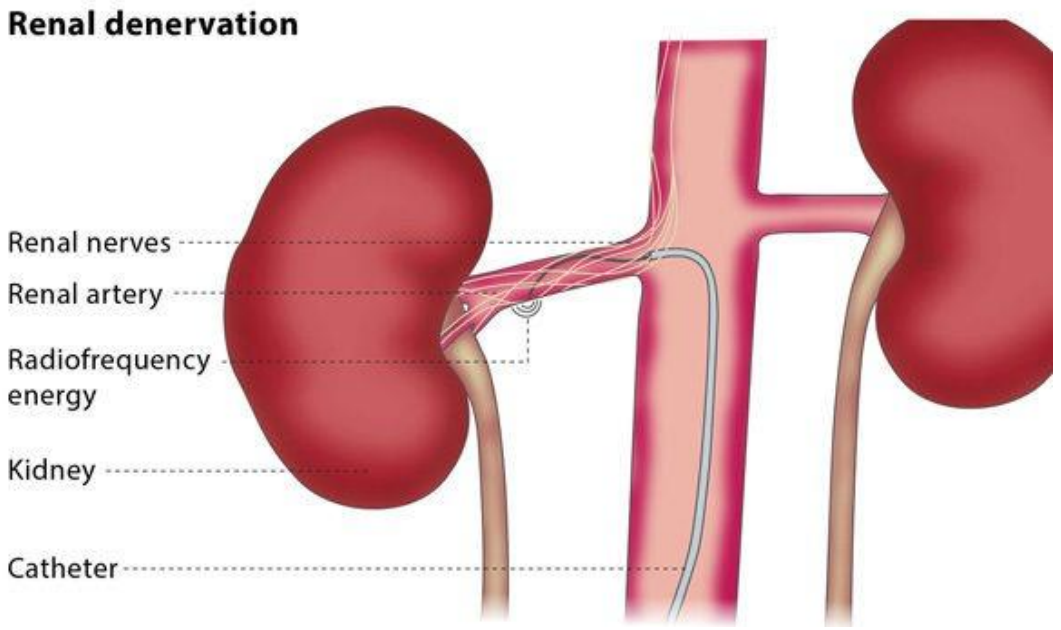
- ADA and ACC
  - SGLT2i are preferred in type 2 diabetes mellitus with cardiovascular disease, heart failure, or chronic kidney disease
- AHA / ACC / HFSA
  - SGLT2i are first-line therapy in HFrEF and recommended in HFpEF
- KDIGO
  - SGLT2i are recommended for patients with chronic kidney disease with eGFR >20ml/min, even without diabetes

Something a little different

Renal Denervation

- Catheter is inserted into the renal arteries
- Radiofrequency energy or ultrasound is used to destroy the sympathetic nerves to the arteries

- Result is disruption of the signals that cause kidneys to constrict blood vessels
- Can result in lowering of blood pressure



Renal Denervation

- SYMPLICITY HTN-3
  - First sham controlled prospective randomized trial
  - Little to no effect
  - Lead to new catheters and trial designs

- SPYRAL HTN-OFF MED and ON-MED
  - Most recent, different catheter, more extensive denervation
  - Patients enrolled didn’t have resistant hypertension
  - Confirmed blood pressure reduction of 8-10mmHg

- European Society of Hypertension adjunct therapy in some patients

Carotid Baroreceptor Activation

- Baroreflex activation leads placed adjacent to the carotid sinus, implantable pulse generator, and external programming system
- Electronically activates baroreceptors
- Multisystemic response for disorders associated with sympathetic overactivity
  - Hypertension, heart failure, arrhythmias
- Results in reduced sympathetic nervous system activity and enhanced vagal activity
- Initial trial results fail to meet primary endpoint (composite of 5 efficacy and safety points)
- Device is considered safe

Summary

- 2017 AHA / ACC guidelines
- 2021 KDIGO guidelines
- Resistant hypertension
  - Definition
  - Evaluation
  - Secondary hypertension
- Management
  - Patient and physician factors
  - Integrative care
- Medications
- Step-wise approach
- Special considerations
  - Chronic kidney disease
  - Heart failure
- Procedures

American Heart Association®