



COMMUNITY
HEALTH CARE
ASSOCIATION
of New York State

Resistant Hypertension

Hypertension Care & Management Webinar Series
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Erika Drury, MD

Associate Professor of Medicine

Division of Nephrology

University of Rochester School of Medicine



Resistant Hypertension: Diagnosis and Treatment Pearls

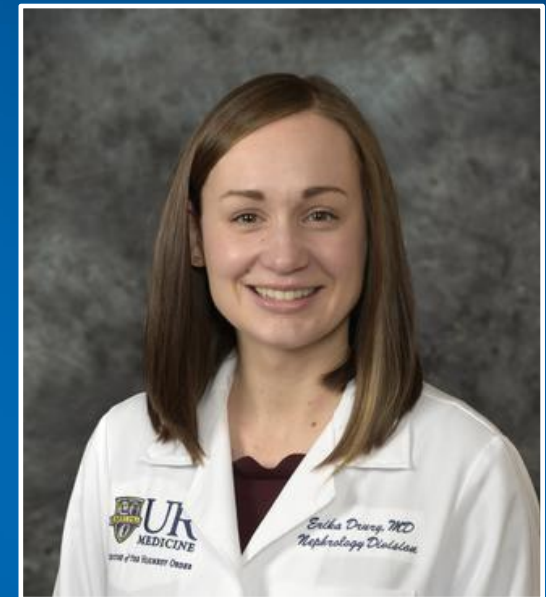
Erika R. Drury, MD

Assistant Professor of Medicine

Division of Nephrology

University of Rochester School of Medicine

Assistant Director University of Rochester AHA
Comprehensive Hypertension Center



MEDICINE *of* THE HIGHEST ORDER



Conflicts of Interest

I have no disclosures

Objectives

1. Define and diagnose true resistant hypertension
2. Describe the epidemiology of resistant hypertension and disparities in prevalence and control
3. Identify and appropriate workup for resistant hypertension and optimal treatment options

SETTING THE STAGE

Resistant Hypertension (RH)

Blood pressure elevated above goal ($>130/80$)

- Despite the use of 3 anti-hypertensive drug classes at maximum or maximally-tolerated doses, commonly:
 - Long-acting calcium channel blocker
 - Renin-angiotensin system blocker
 - Diuretic (*requirement; thiazide-like)



OR

Blood pressure controlled on ≥ 4 anti-hypertensive agents

Prognosis of Resistant Hypertension

Among hypertensives, those with resistant hypertension have:

32% increased risk of **ESRD**

24% increased risk of **ischemic heart event**

46% increased risk of **heart failure**

14% increased risk of **stroke**

More likely to have a **secondary cause** of HTN and experience
medication side effects

Sim JJ et al Comparative risk of renal, cardiovascular, and mortality outcomes in controlled, uncontrolled resistant, and nonresistant hypertension. *Kidney Int* 2015

Prevalence of Resistant Hypertension

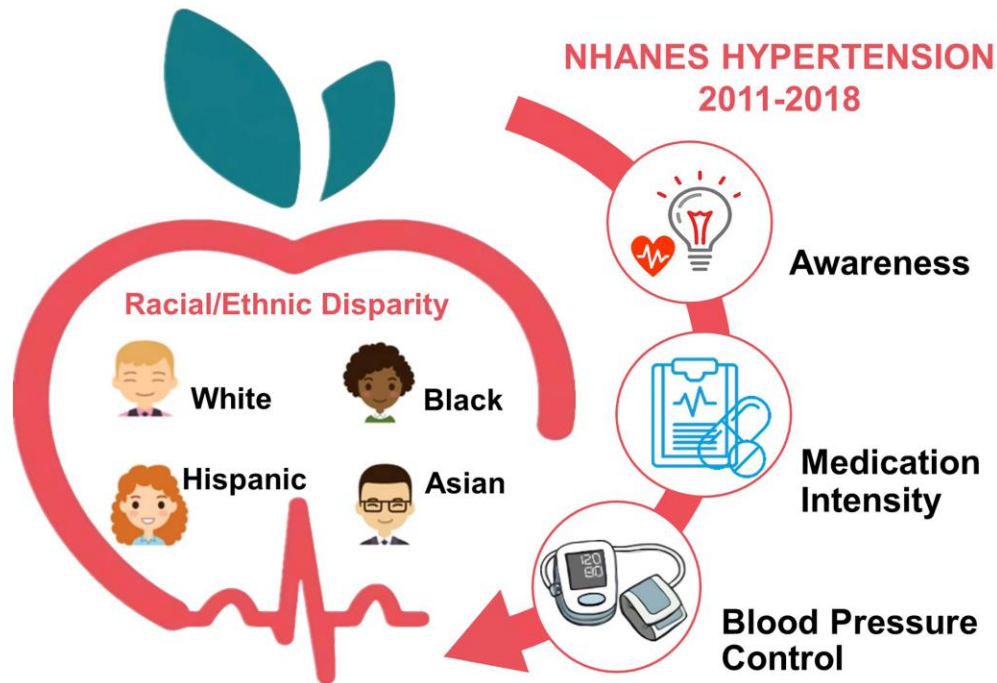
Population Based	Time Period	n	Uncontrolled With ≥ 3 BP Medications, %	Controlled With ≥ 4 BP Medications, %	aTRH, %
NHANES ¹³	1988–1994	2755	8.3	1.1	9.4
NHANES ¹³	1999–2004	3031	8.8	2.9	11.7
NHANES ¹⁴	2003–2008	3710	12.8
NHANES ¹³	2005–2008	2586	9.7	4.8	14.5
REGARDS ¹⁵	2003–2007	14731	9.1	5.0	14.1
REGARDS ¹⁶ (CKD)*	2003–2007	3134	28.1

NHANES 2005-2008: Resistant hypertension was more frequent in people who were older, obese, male, African American, and non-black Hispanic

Carey et al Resistant Hypertension: Detection, evaluation, and management. A scientific statement from the American Heart Association. Hypertension 2018.

Disparities in Hypertension

Trends in Racial Disparities in Hypertension



Main findings

- Despite receiving more antihypertensive medications, Black people have poorer hypertension control compared with White people.
- The poorer hypertension control among Asian and Hispanic people is associated with their lower hypertension awareness and treatment compared with White people

Reasons for Lower BP Control

- Social determinants of health
- Clinical factors
- Biologic factors

Data is less robust for resistant hypertension but follows similar trends

Lu Y et al Hypertension 2021

Characteristics of Resistant Hypertension in a Large, Ethnically Diverse Hypertension Population of an Integrated Health System

John J. Sim, MD; Simran K. Bhandari, MD; Jiaxiao Shi, PhD; In Lu A. Liu, MS; David A. Calhoun, MD; Elizabeth A. McGlynn, PhD; Kamyar Kalantar-Zadeh, MD, PhD; and Steven J. Jacobsen, MD, PhD

12.8% (60,327/470,386) with rHTN

Odds of rHTN greater for black race, older age, male sex, and obesity

NB comparing to White as referent group is problematic

Any trends in your practice?

TABLE 3. Unadjusted and Adjusted Logistic Regression Analyses for Resistant Hypertension (Simultaneously Adjusting for Variables Within Column)^{a,b}

Variable	OR (95% CI)	
	Unadjusted	Adjusted
Age, 5-y increase	1.17 (1.16-1.18)	1.11 (1.10-1.11)
Sex		
Female vs male	0.92 (0.89-0.95)	0.94 (0.91-0.97)
Male vs female	1.09 (1.05-1.12)	1.06 (1.03-1.10)
Black vs nonblack race	1.68 (1.62-1.74)	1.68 (1.62-1.75)
BMI ≥30 vs 0-29	1.31 (1.27-1.35)	1.46 (1.42-1.51)
CKD: eGFR <60 vs ≥60 mL/min/1.73 m ²	2.51 (2.44-2.58)	1.84 (1.78-1.90)
Diabetes mellitus	1.89 (1.84-1.94)	1.58 (1.53-1.63)
Ischemic heart disease	2.15 (2.09-2.22)	1.34 (1.30-1.39)
Congestive heart failure	3.04 (2.94-3.14)	1.78 (1.72-1.86)
Cerebrovascular disease	1.84 (1.77-1.90)	1.17 (1.13-1.22)

^aBMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; OR = odds ratio.

^bP<.001 for all.

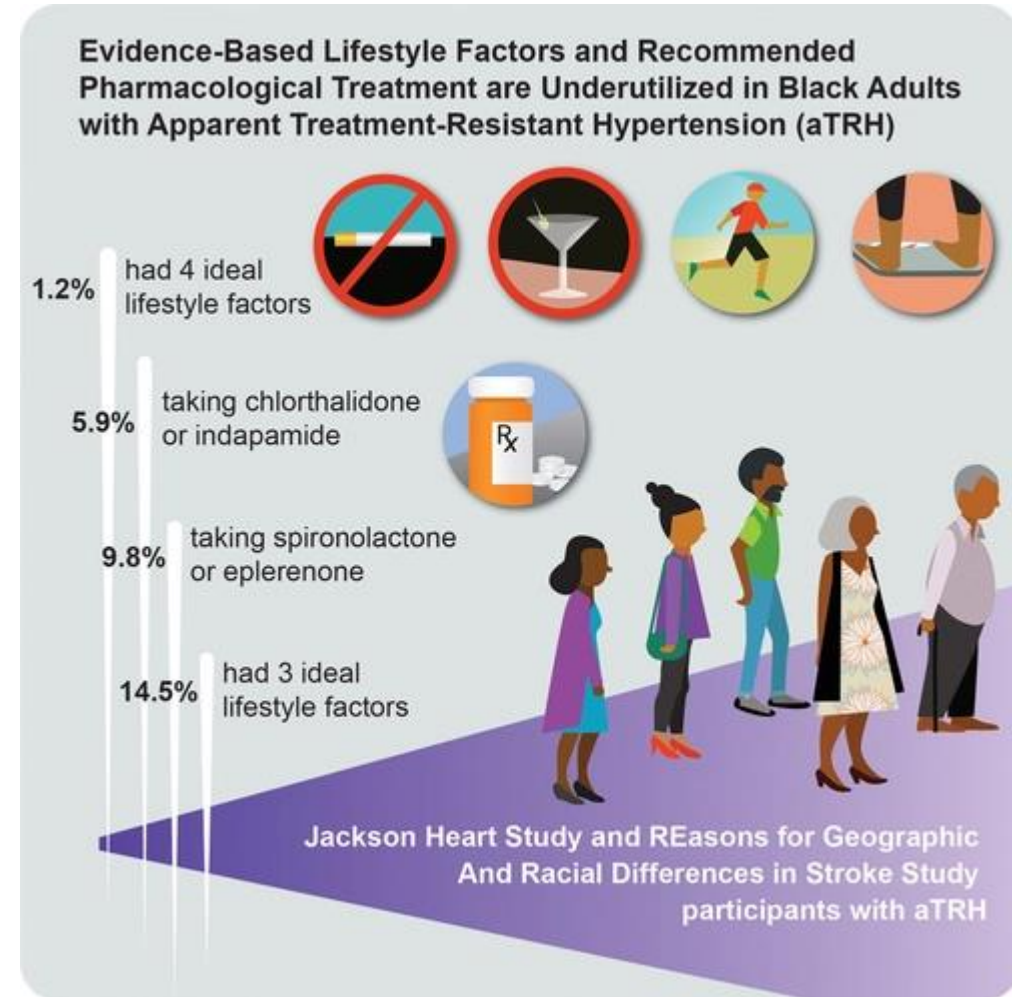
Sim JJ et al. Mayo Clinic Proc 2013.

Low use of recommended treatment for aTRH in Black adults

Self-identified Black adults in JHS and REGARDS with aTRH

NB: no comparison to non-Black adults

*low use of thiazide-like diuretics and MRAs

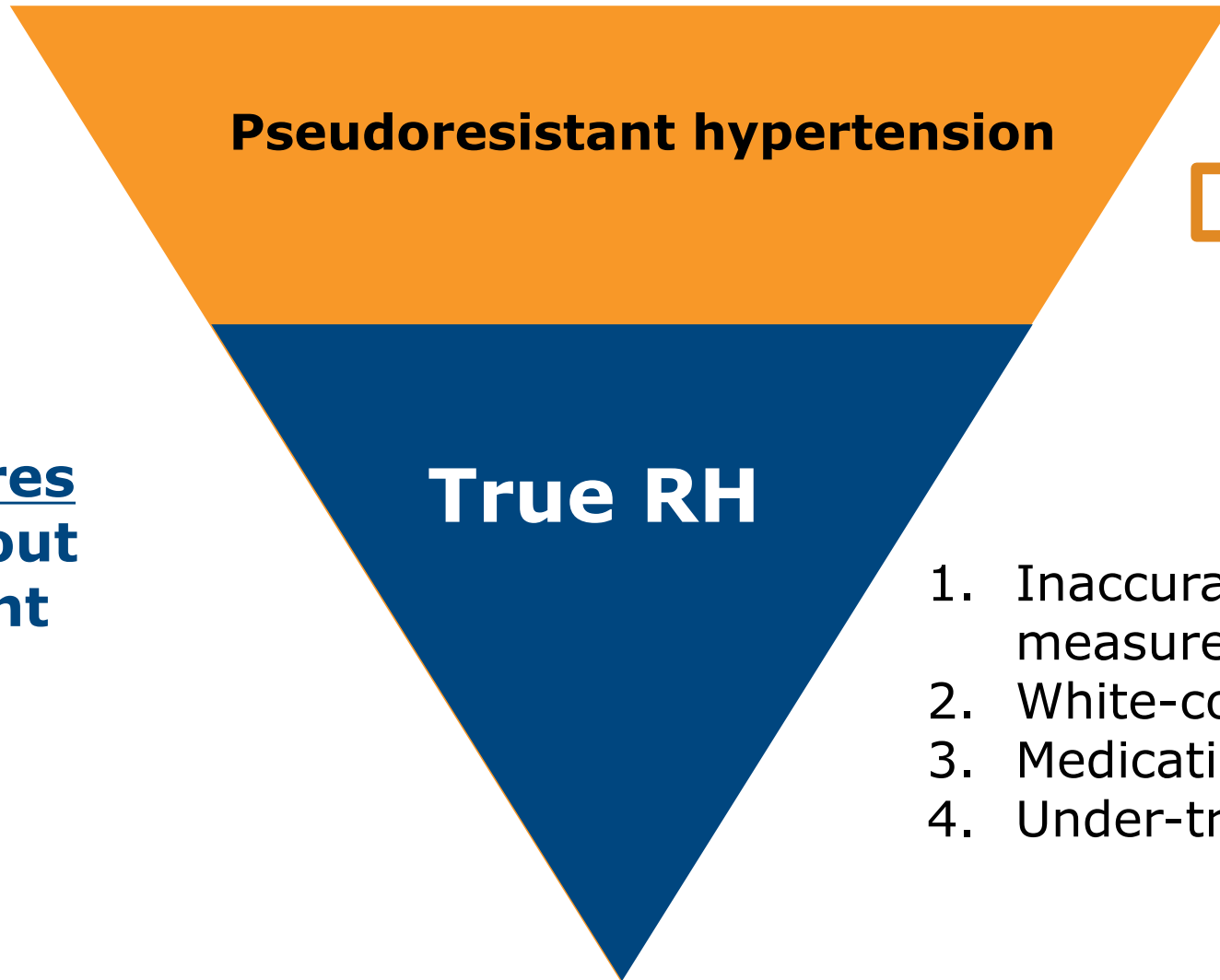


Langford AT et al Hypertension 2020

DIAGNOSIS OF RESISTANT HYPERTENSION

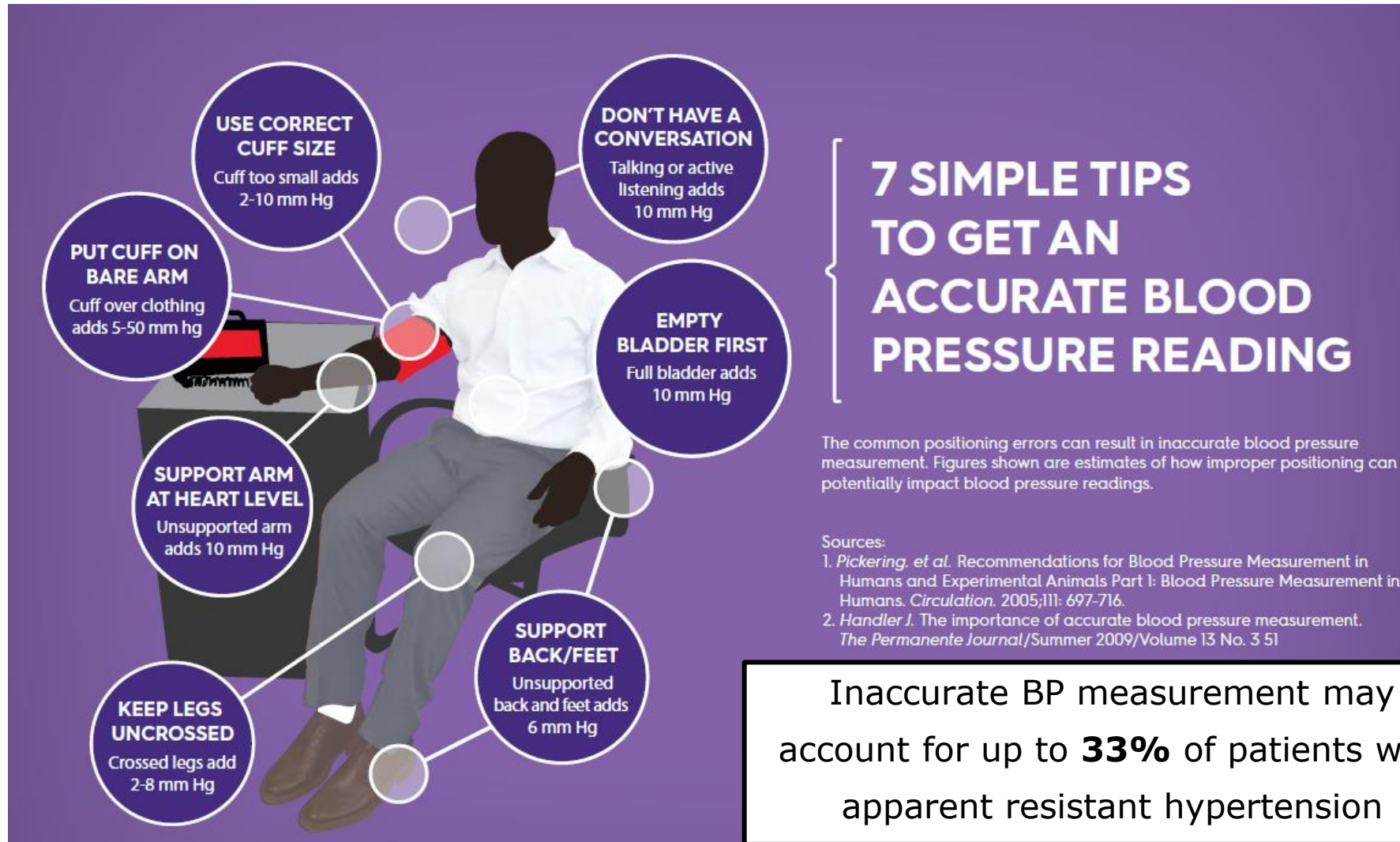
Apparent treatment-resistant hypertension (aTRH)

**True RH requires
that you rule-out
pseudoresistant
hypertension**



1. Inaccurate BP measurement
2. White-coat effect
3. Medication non-adherence
4. Under-treatment

Accurately Measure Blood Pressure



7 SIMPLE TIPS TO GET AN ACCURATE BLOOD PRESSURE READING

The common positioning errors can result in inaccurate blood pressure measurement. Figures shown are estimates of how improper positioning can potentially impact blood pressure readings.

Sources:

1. Pickering, et al. Recommendations for Blood Pressure Measurement in Humans and Experimental Animals Part 1: Blood Pressure Measurement in Humans. *Circulation*. 2005;111: 697-716.
2. Handler J. The importance of accurate blood pressure measurement. *The Permanente Journal/Summer 2009/Volume 13 No. 3 51*

Inaccurate BP measurement may account for up to **33%** of patients with apparent resistant hypertension

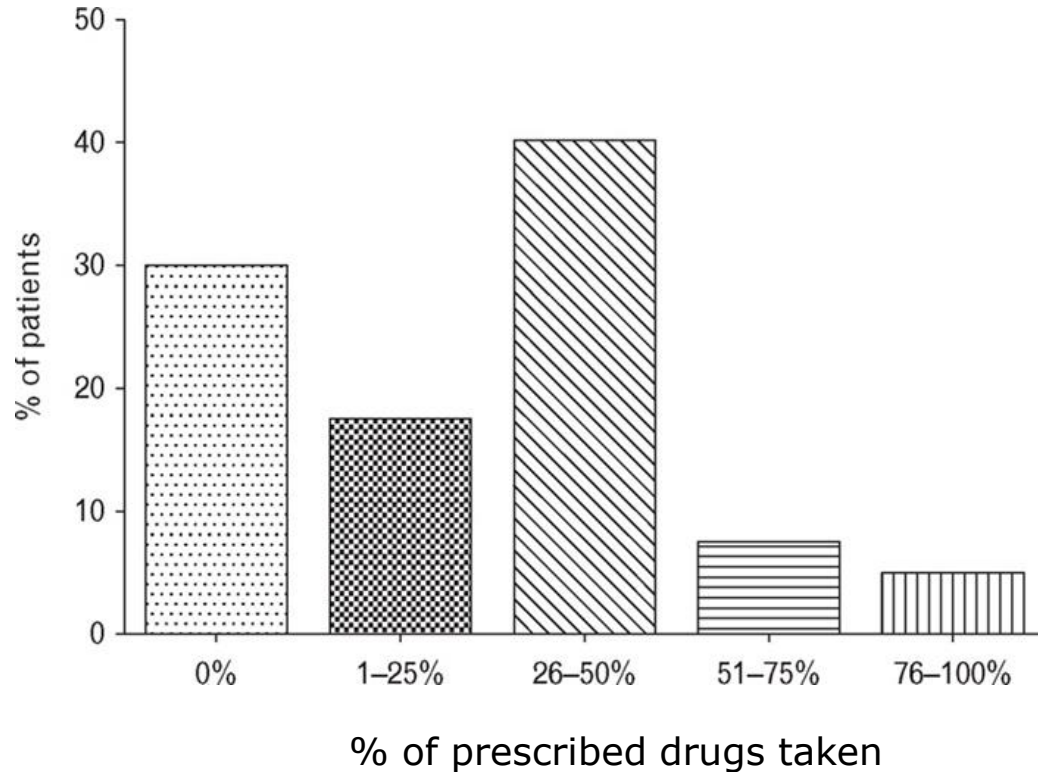
- USE CORRECT CUFF SIZE**
Cuff too small adds 2-10 mm Hg
- DON'T HAVE A CONVERSATION**
Talking or active listening adds 10 mm Hg
- EMPTY BLADDER FIRST**
Full bladder adds 10 mm Hg
- PUT CUFF ON BARE ARM**
Cuff over clothing adds 5-50 mm hg
- SUPPORT ARM AT HEART LEVEL**
Unsupported arm adds 10 mm Hg
- SUPPORT BACK/FEET**
Unsupported back and feet adds 6 mm Hg
- KEEP LEGS UNCROSSED**
Crossed legs add 2-8 mm Hg

Exclude the White Coat Effect

Use 24 hour ambulatory BP monitoring or appropriately-measured home BP



Identify and Address Medication Non-Adherence



Using urine toxicological analysis,
53% of patients with apparent RH
were non-adherent

Majority were taking **< 50%** of
prescribed drugs

30% were taking no drugs

Jung O et al J Hypertens 2013

Indirect methods to evaluate for adherence

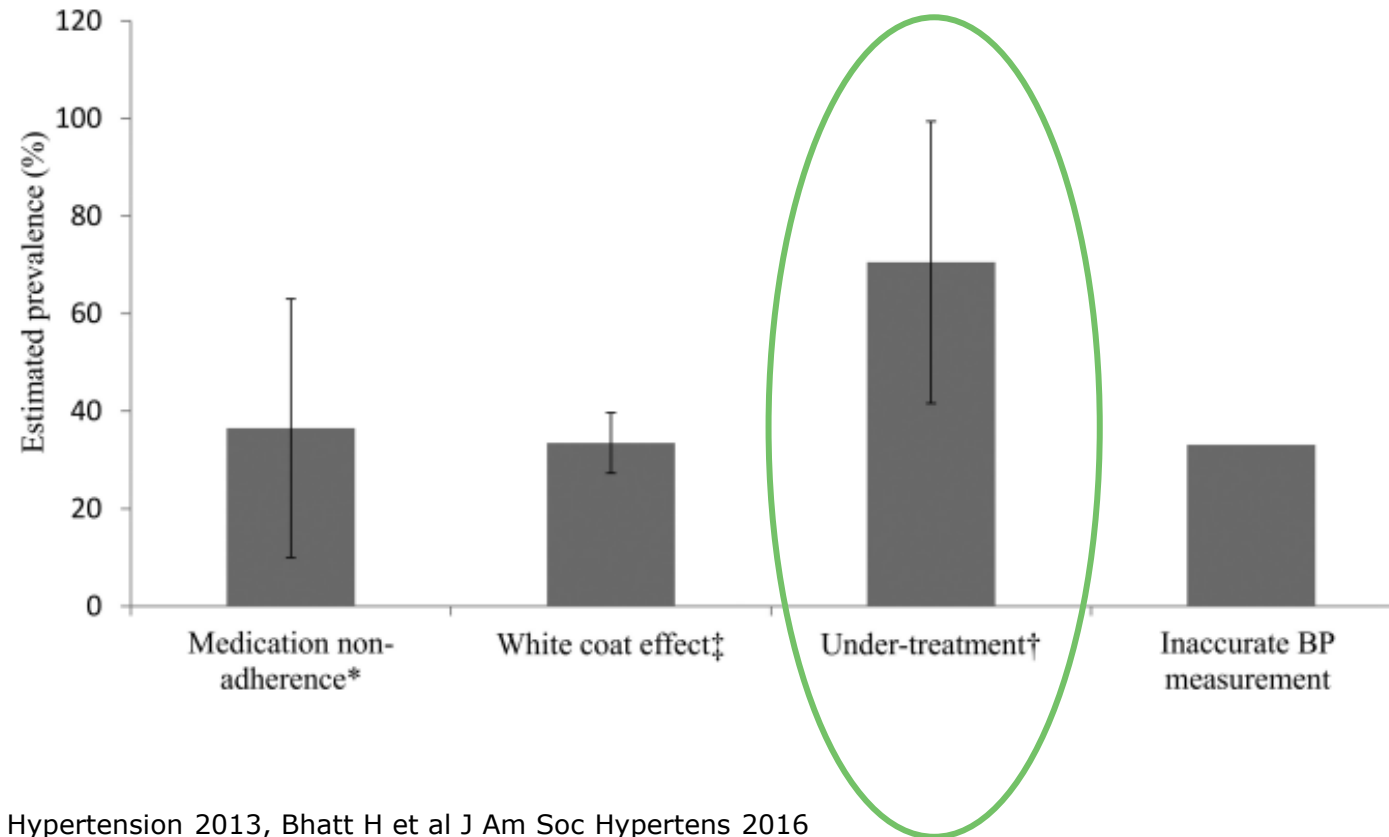
- Direct questioning in a non-threatening manner
- Pill counts
- Prescription refill data
- Validates assessment tools (e.g. Morisky Medication Adherence Scale)

Strategies to address non-adherence

- Team-based hypertension care
- SMBP programs
- Patient education
- Use of daily dosed medications, combination pills, 90-day refills

Assess for Undertreatment

Undertreatment is a common cause of pseudo-resistant hypertension



Egan BM et al Hypertension 2013, Bhatt H et al J Am Soc Hypertens 2016

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

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

147,635 uncontrolled hypertensives

30%

44,684 \geq 3 anti-HTN

15%

22,189 optimal therapy

Only **half** of patients with aTRH were actually prescribed optimal therapy

*Optimal therapy = diuretic and \geq 2 other BP meds at \geq 50% max doses

Once true RH has been identified, assess for causes of secondary hypertension



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**)

Resistant Hypertension: Detection, Evaluation, and Management, A Scientific Statement from the American Heart Association. 2018.

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Primary Aldosteronism (PA)

Defn: Renin-independent aldosterone secretion that is non-suppressible with sodium loading

Biochemically-overt PA can be seen across the entire spectrum of hypertensive disorders, but is highly prevalent in RH

All patients with RH need to be screened for PA (current screening rates are estimated to be <5%)

ORIGINAL RESEARCH

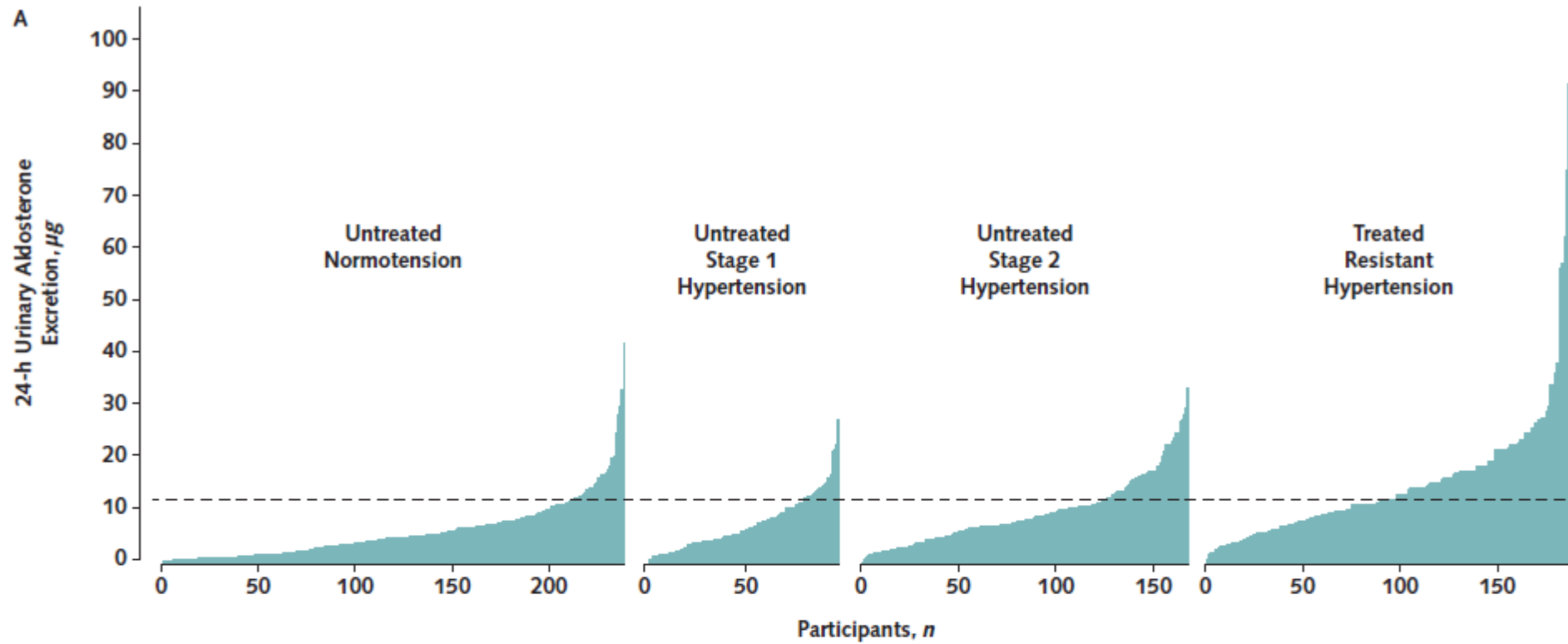
Annals of Internal Medicine

The Unrecognized Prevalence of Primary Aldosteronism

A Cross-sectional Study

Jenifer M. Brown, MD; Mohammed Siddiqui, MD; David A. Calhoun, MD; Robert M. Carey, MD; Paul N. Hopkins, MD, MSPH; Gordon H. Williams, MD; and Anand Vaidya, MD, MMSc

Figure 2. Distribution of renin-independent aldosterone production, by blood pressure category.



Adjusted prevalence of overt PA among the RH cohort was **22%**

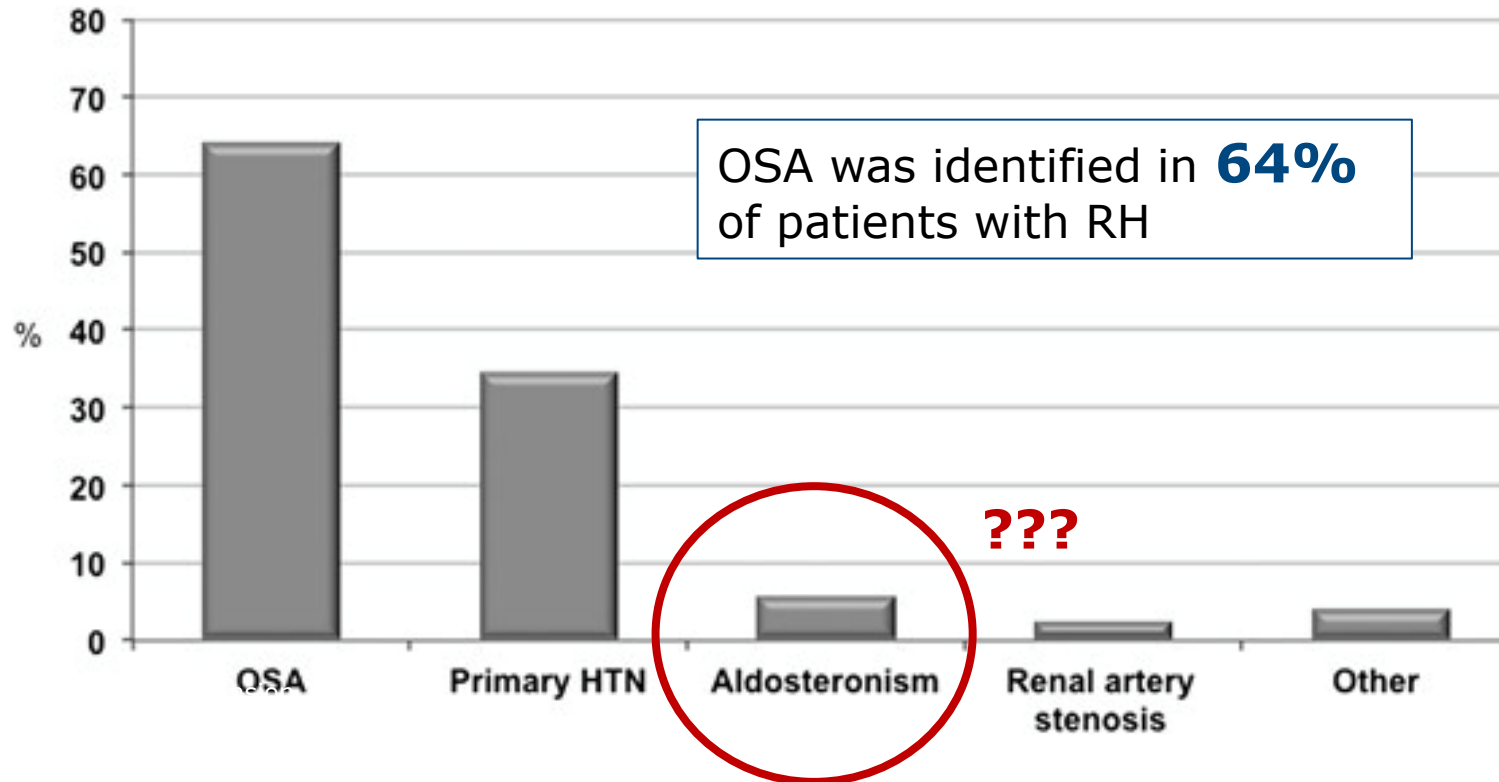
Screening for PA in RH

- Most Common Screening Test – ARR \geq 30 ng/dL per ng/ml/hr [morning, seated] in the context of a suppressed renin and an aldosterone concentration $>$ 15 ng/dL
 - BUT...Brown JM et al, among RH, 24.5% of confirmed cases had serum aldosterone $<$ 10 ng/dL
 - Updated Expert Opinion
 - Suppressed renin ($<$ 1 ng/mL/h), aldosterone $<$ 5 ng/dL – PA unlikely
 - Suppressed renin, aldosterone $>$ 15 – Overtly positive screen
 - Suppressed renin, aldosterone 5-15 – Requires confirmatory testing with sodium loading (urine sodium $>$ 150 mmol/day)
- * Stop MRAs, don't worry about other drugs initially
- * If a random PRA is suppressed $<$ 1 ng/mL/hour, strongly suggestive of PA

OSA in Resistant Hypertension

Prevalence of OSA in RH from prospective analyses of **55-83%**

(Gonzagga CC et al Clin Sleep Med 2010, Logan AG et al J Hypertens 2001, Muxfeldt ES et al Am J Hypertens 2014)



Treatment of OSA in RH lowers BP

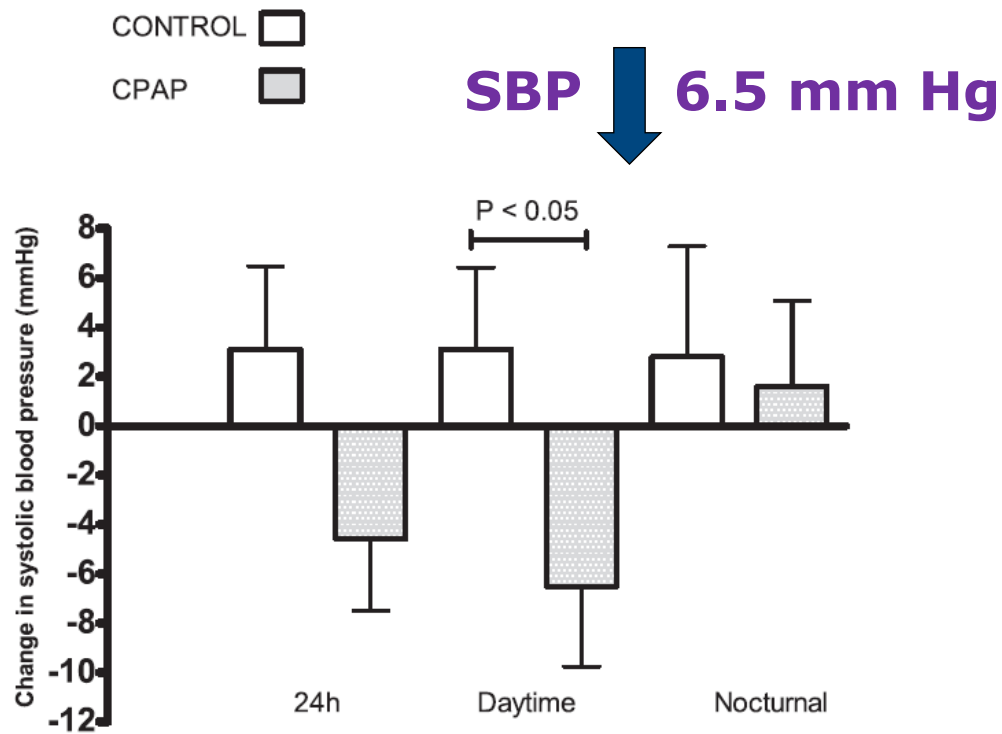


FIGURE 2. Effect of CPAP treatment on systolic BP in ambulatory BP. Data are presented as mean (SEM).

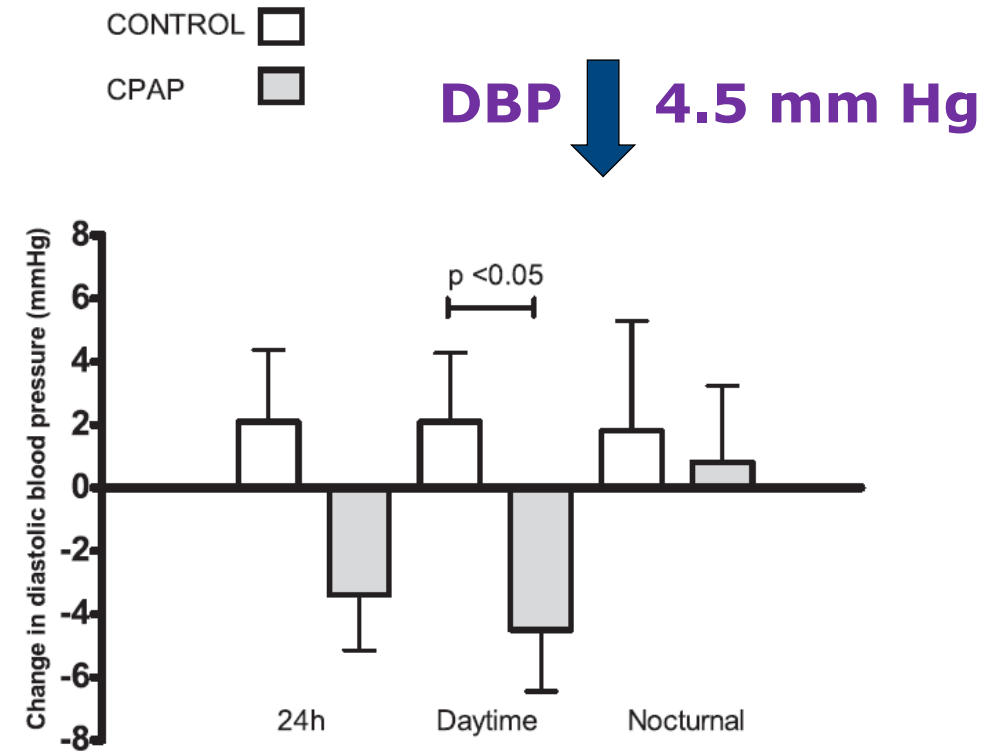


FIGURE 3. Effect of CPAP treatment on diastolic BP in ambulatory BP. Data are presented as mean (SEM).

Pedrosa RP et al Chest 2013

Don't forget about drugs...

Table 2. Drugs and Other Substances With Potential to Induce or Exacerbate Elevated BP and Hypertension

NSAIDs
Oral contraceptives
Sympathomimetic
Cyclosporine, tacrolimus
Erythropoietin
VEGF inhibitors
Alcohol
Cocaine
Amphetamines
Antidepressants
Glucocorticoids, mineralocorticoids

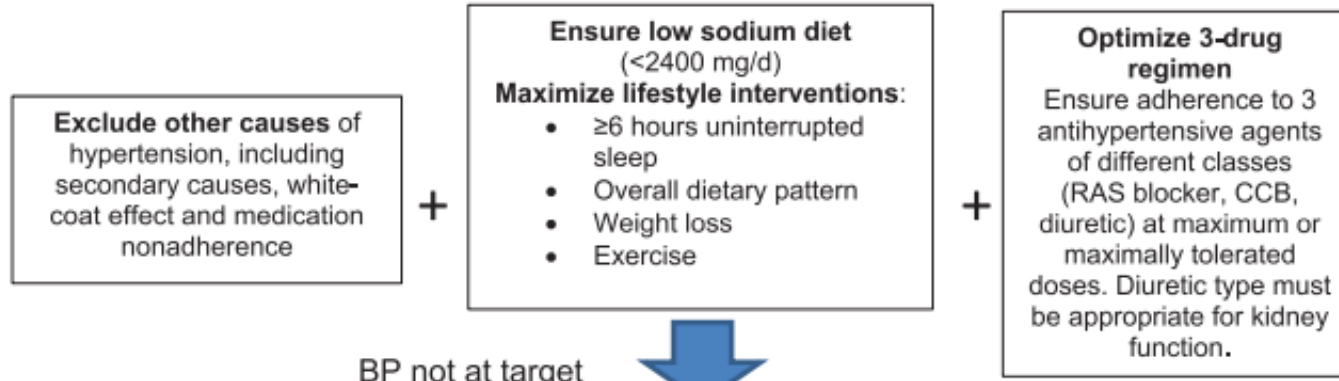
BP indicates blood pressure; NSAIDs, nonsteroidal anti-inflammatory drugs; and VEGF, vascular endothelial growth factor.



TREATMENT OF RH

Management of Resistant Hypertension

Step 1



Step 2

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

BP not at target

Step 3

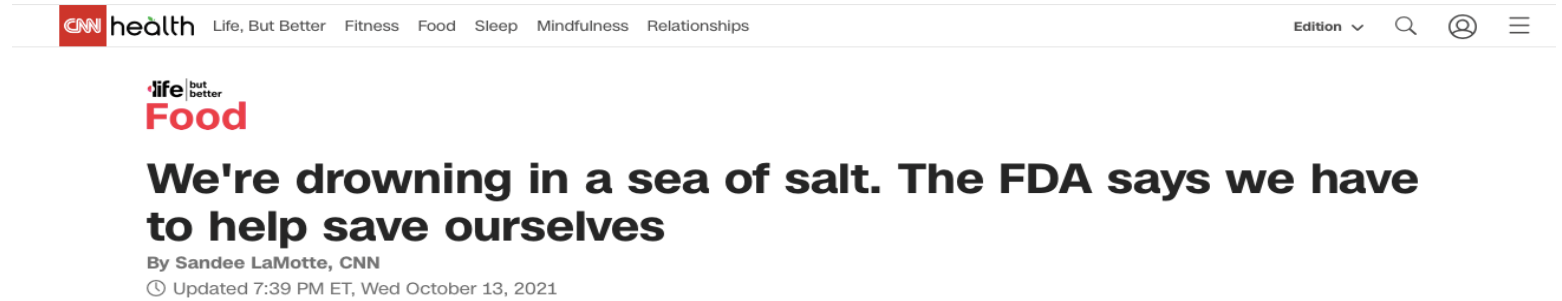
Add mineralocorticoid receptor antagonist (MRA): spironolactone or eplerenone**

BP still not at target

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

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

Maximize lifestyle and diet



- **Dietary sodium restriction**

- Limiting dietary sodium to 50 mmol/d (1,150 mg/d) decreased office BP by 22.7/9.2 mmHg in patients with RH

- **24-hour urine sodium excretion** can be used to evaluate daily sodium intake and guide dietary advice

- 2,400 mg Na/day = 104 mmol Na/24 hour urine

- **DASH diet** has not been studied specifically in RH

Optimize Diuretics

- **Thiazide-like diuretics: chlorthalidone (12.5-25 mg) or indapamide (1.25-2.5 mg)**
 - Greater potency and longer half lives (improved nighttime BP control?)
 - Meta analysis of 21 studies – reduction in CV events and heart failure was significant for thiazide-like diuretics irrespective of the adjustment for blood pressure (Olde Engberink RH et al. Hypertension 2015)
- **Loop diuretics added to or in place of thiazide-like diuretic when GFR<25-30 ml/min**
 - Once daily torsemide, bumetanide, or twice daily furosemide
 - Titrate to an effective “dry weight”
 - Some data chlorthalidone works at lower GFRs (Agarwal R et al. NEJM 2021)

Burnier M et al. J of Hypertens. 2019.

DiNicolantonio JJ et al. Future Cardiol. 2015.

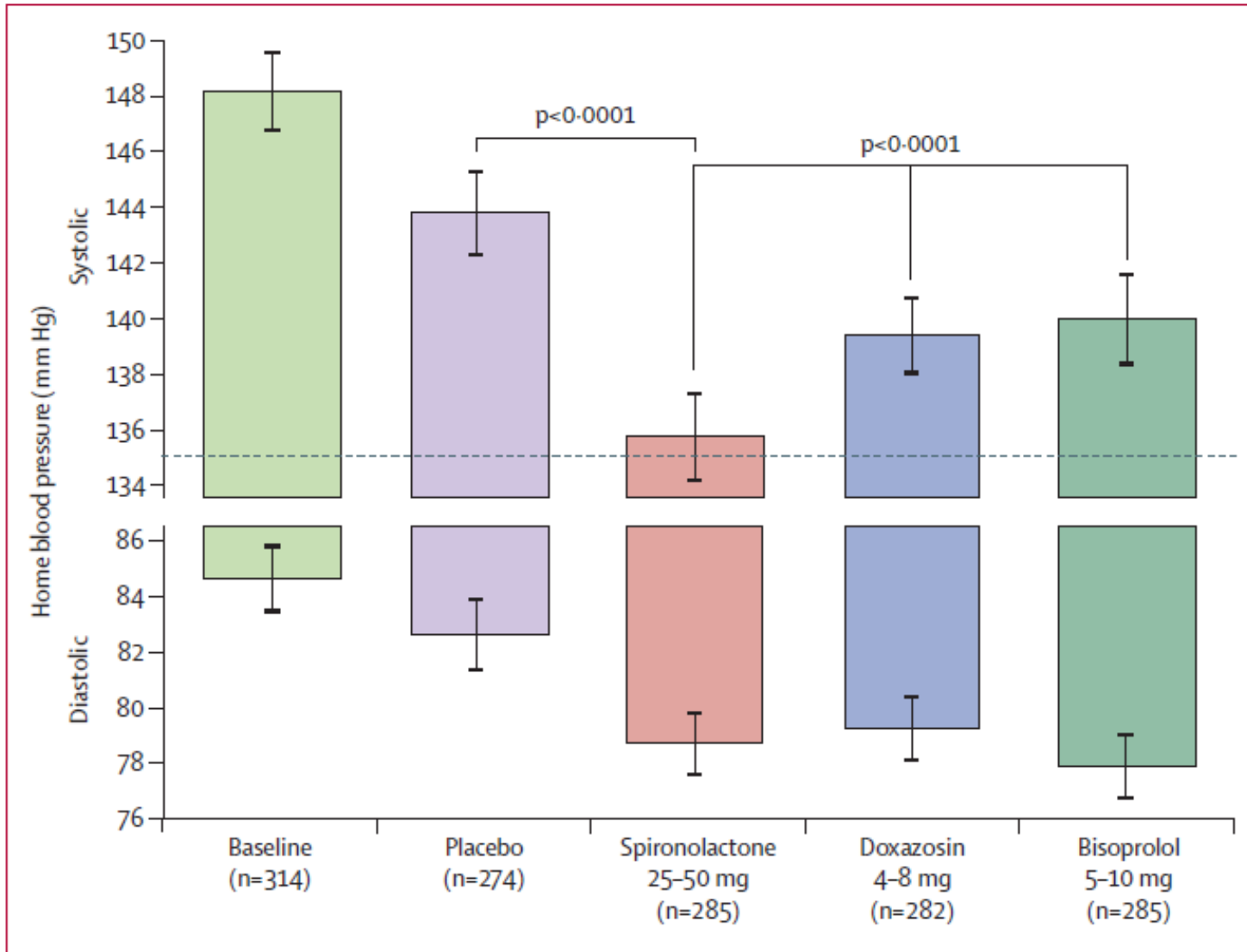
Fay KS and Cohen DL. Am J Kidney Dis. 2021

Add a mineralocorticoid receptor antagonist

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

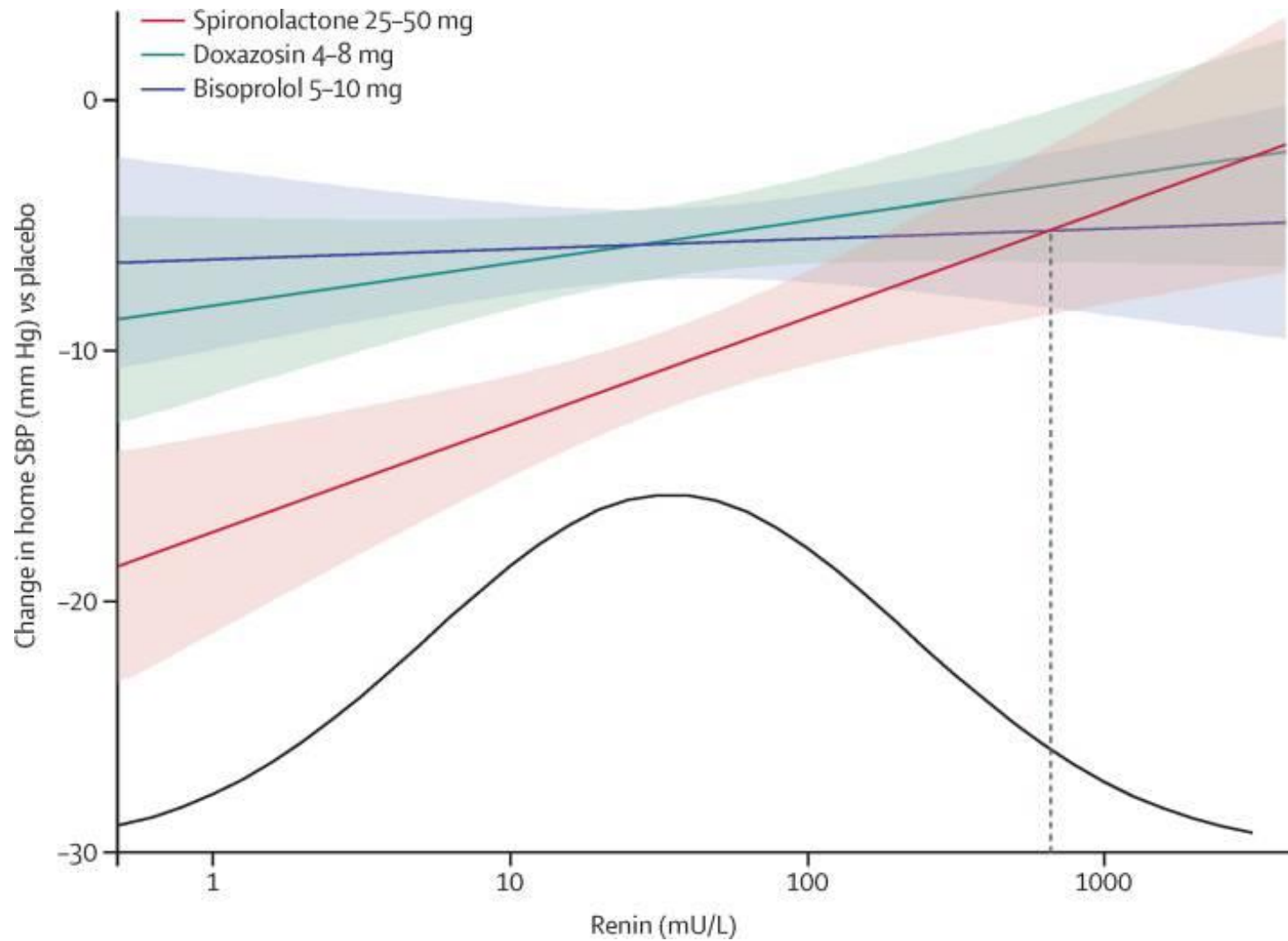
*Bryan Williams, Thomas M MacDonald, Steve Morant, David J Webb, Peter Sever, Gordon McInnes, Ian Ford, J Kennedy Cruickshank, Mark J Caulfield, Jackie Salsbury, Isla Mackenzie, Sandosh Padmanabhan, Morris J Brown, for The British Hypertension Society's PATHWAY Studies Group**

- RCT; evaluated which medication would be the most effective 4th drug for patients with RH already on maximum tolerated doses of 3 drugs
- Patients rotated through the addition of placebo, doxazosin, bisoprolol, or spironolactone for 12 weeks
- Excluded patients who were felt to have secondary hypertension



Spironolactone 25-50 mg/d by far the **most effective 4th drug**, achieved home SBP < 135 mm Hg in 60% of patients

Mean SBP reduction with spironolactone was **8.7 mm Hg**



Even in patients without overt PA, MRAs are the best 4th drug
 Bisoprolol was superior only in those with very high renin RH

Additional add-on therapy

- Beta blockers – prefer combination alpha/beta blockers [labetalol, carvedilol]
- Central Alpha antagonists – clonidine [patch] or guanfacine [at bedtime]
- Hydralazine or minoxidil – require use of a beta blocker and diuretic to counteract reflex tachycardia and fluid retention, respectively

Volume excess

Diuretics

Aldosteronism

Mineralocorticoid
receptor antagonists

Increased sympathetic
tone

Sleep disorders,
anxiety, obesity,
beta blockers

Take-Home Pearls

- Resistant hypertension (RH) is associated with poorer outcomes
- RH is more prevalent and sub-optimally controlled in Black individuals, with multiple factors contributing
- True RH requires the exclusion of pseudoresistant hypertension
- Screen for PA and OSA in all patients with RH
- Use thiazide-like diuretics
- Spironolactone (or eplerenone) is the best 4th line agent for RH

Questions?

