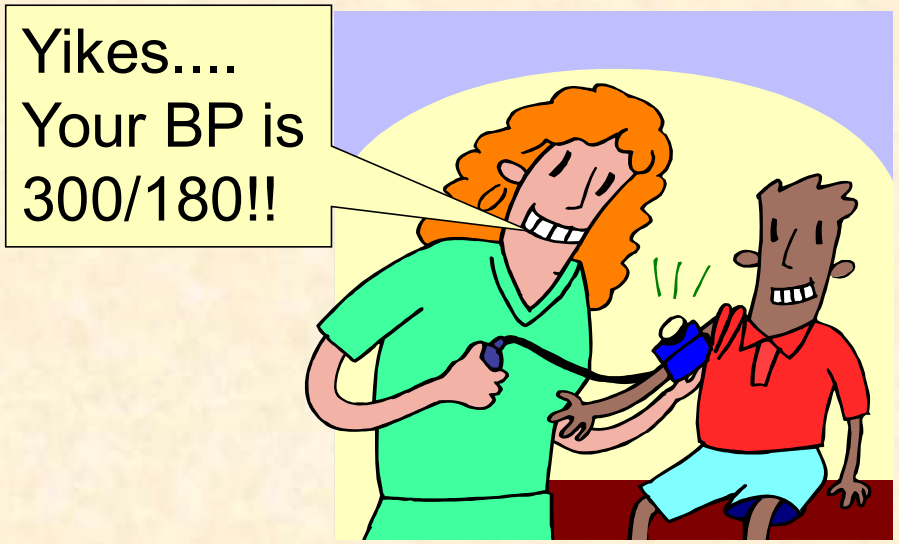
Pseudo, Apparent, or True – The Challenge of Resistant Hypertension



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Objectives

- Define pseudo-, apparent, and true treatment resistant hypertension.
- Identify the causes for pseudo-, apparent, and true treatment resistant hypertension
- Effectively evaluate patients to distinguish between these types of hypertension
- Apply the above to make appropriate management decisions for patients with these types of hypertension.

OUTLINE

- Definitions – true, apparent, pseudo RH
- Prevalence and prognosis of true RH
- Risk factors and causes
- Management (case scenarios)

Assuming maximum or maximally-tolerated doses of antihypertensive medications and good adherence, resistant hypertension can be diagnosed if:

A. Office BPs are above goal on four or more antihypertensive medications
B. Office BPs are above goal on three or more antihypertensive medications
C. Office and out-of-office BPs are above goal on ≥ three antihypertensive medications or controlled on ≥ four medications
D. Office and out-of-office BPs require at least three antihypertensive medications for control

Which of the following is the most frequent cause of pseudoresistant hypertension?

A. Incorrect blood pressure measurement
B. White coat effect
C. Under-treatment by clinician
D. Medication non-adherence by patient

Which of the following is most often found in patients with resistant hypertension?

A. Obstructive sleep apnea
B. Chronic kidney disease
C. Primary aldosteronism
D. Renal artery stenosis

OUTLINE

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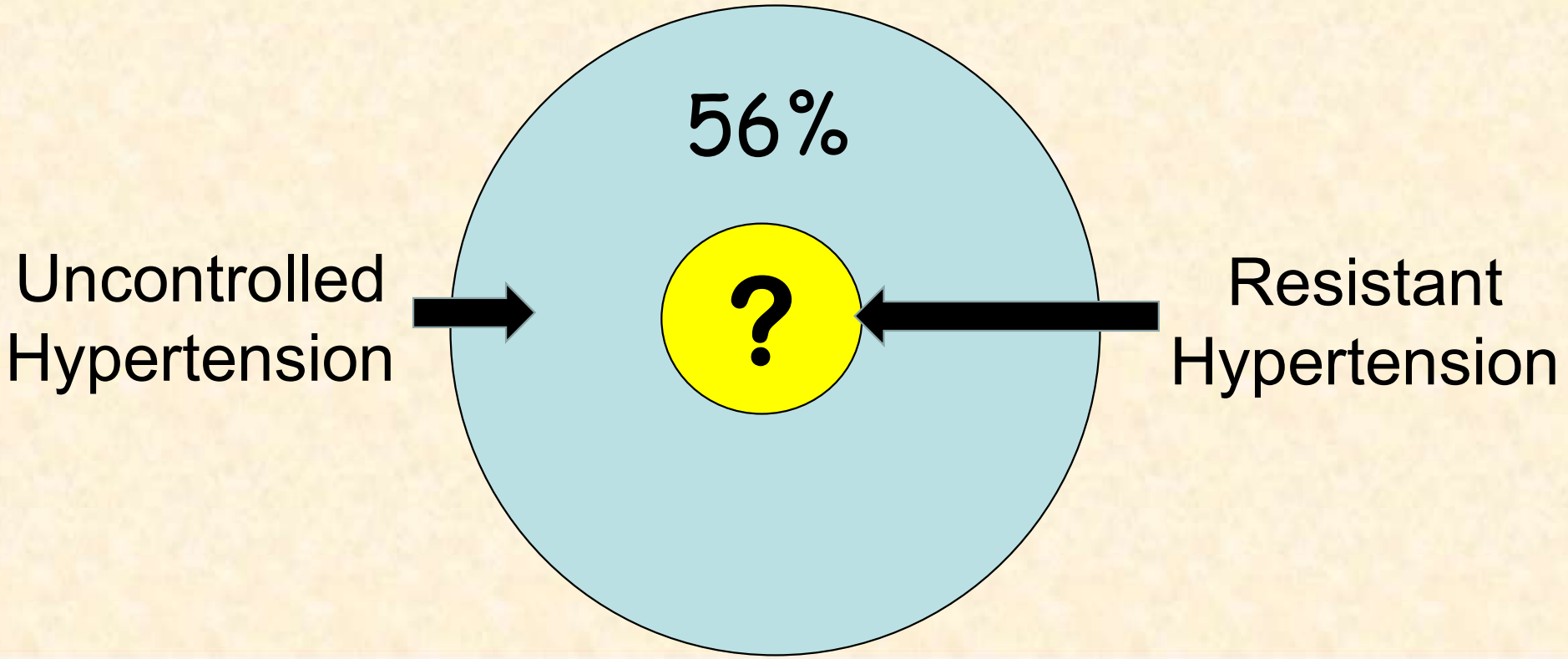
What is NOT resistant hypertension?

Resistant hypertension is **NOT** uncontrolled hypertension



What IS resistant hypertension?

- Blood pressure that remains above goal despite the use of three antihypertensive agents of different classes, preferably including a long-acting calcium channel blocker, a renin-angiotensin system blocker, and a diuretic at their maximum or maximally-tolerated doses.

or

- Blood pressure that is controlled on four or more antihypertensive drugs ("controlled resistant hypertension")

∴ RH includes both uncontrolled and controlled BP, depending on the number of antihypertensive drugs used.

A Case – 43-year-old female

Current medications:

Amlodipine 10 mg twice daily

Carvedilol 25 mg twice daily

Clonidine 0.1 mg twice daily

Hydrochlorothiazide 50 mg daily

Ramipril 15 mg twice daily

Nebivolol 15 mg daily

6 medications in therapeutic to supra-therapeutic doses

- She insists that she always takes her medications!!
- She does not add salt to her food, avoids high-sodium foods.
- Strong family history of hypertension

A Case – 43-year-old female

Automated office BP: 145/88

24-h ambulatory BP: 134/82

- 90% SBP ≥ 128
- 80% DBP ≥ 78

Fundi normal

Normal heart sounds and pulses; no edema; lungs clear

No abdominal bruits, + central obesity

Electrolytes normal; glucose 114; creatinine 1.0; TSH 3.0

Urinalysis normal; albumin:creatinine ratio normal

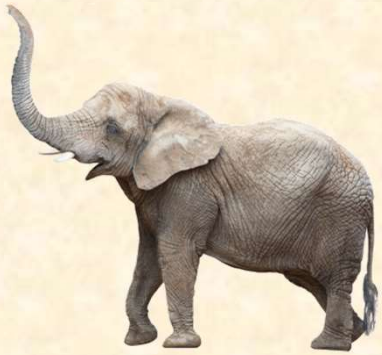
Does this patient have resistant hypertension?

A. Yes

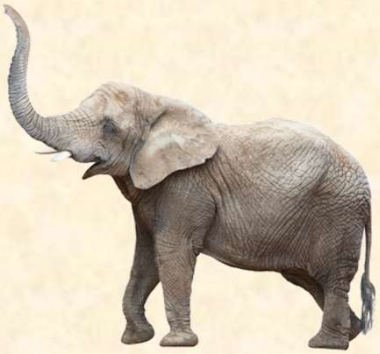
B. No

C. You got me on this one!

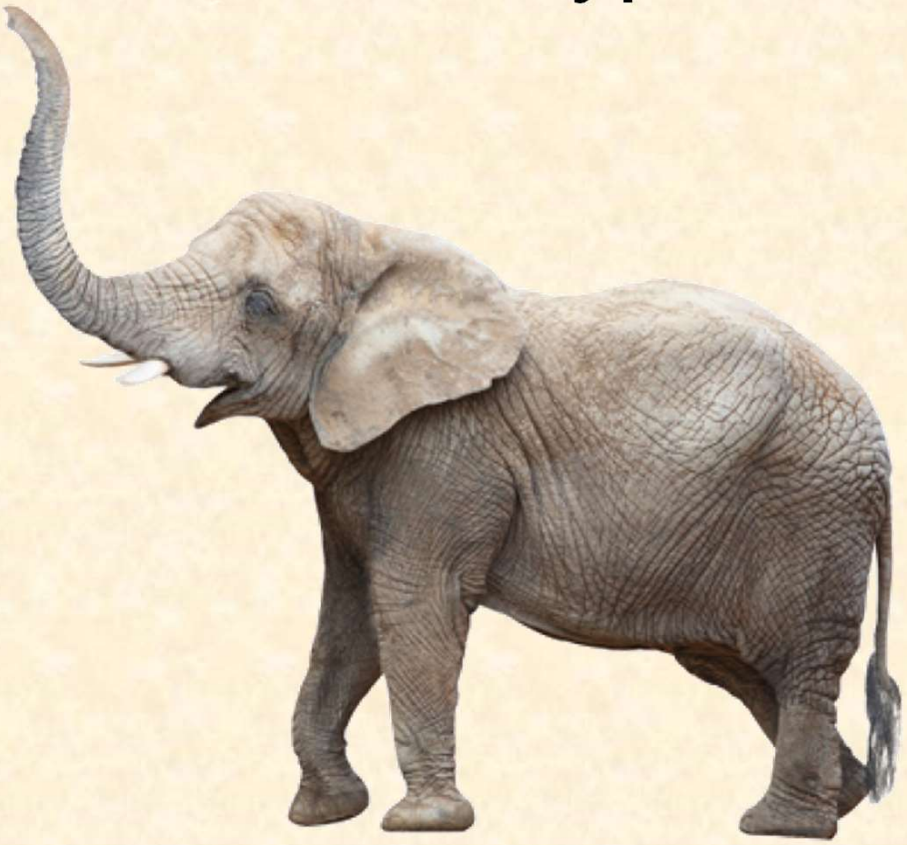
Pseudoresistant Hypertension

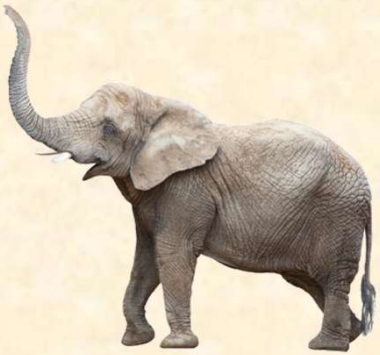


Poor BP technique

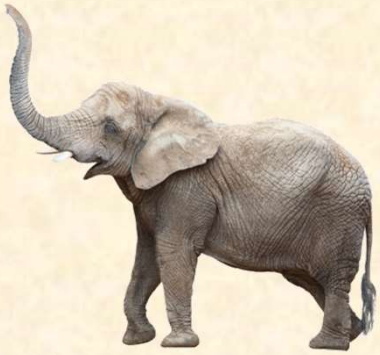


Undertreatment



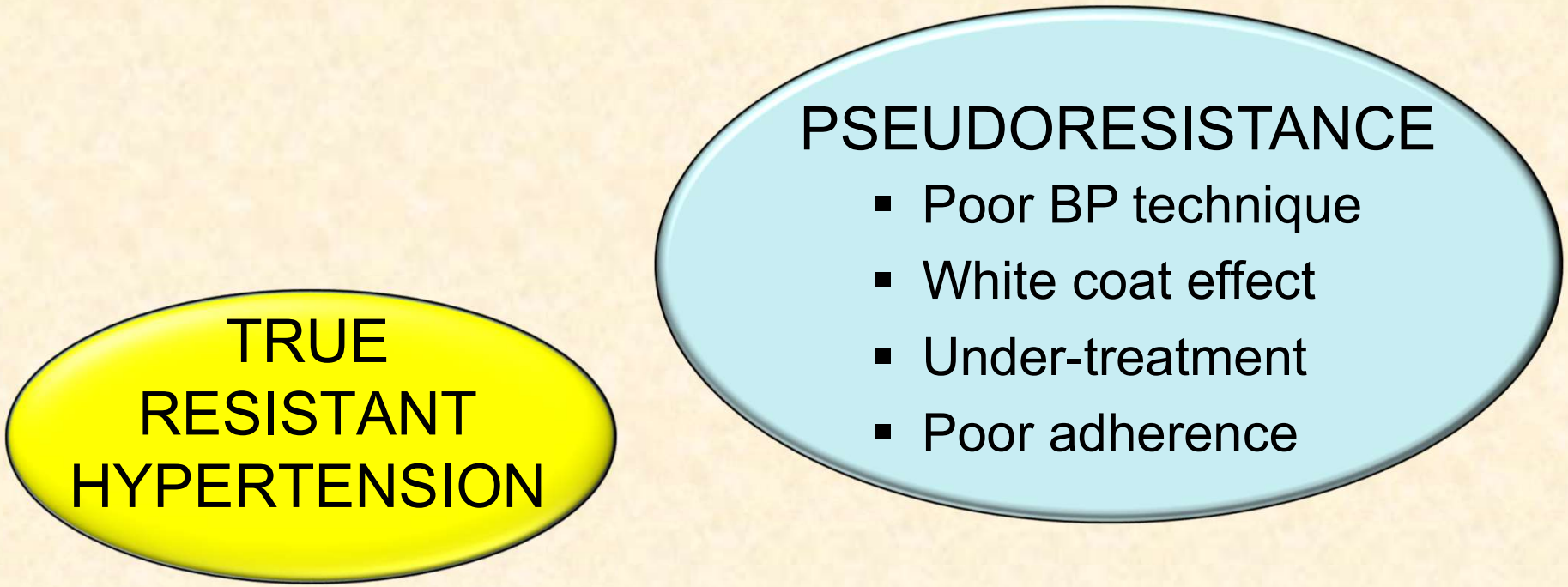


White coat effect

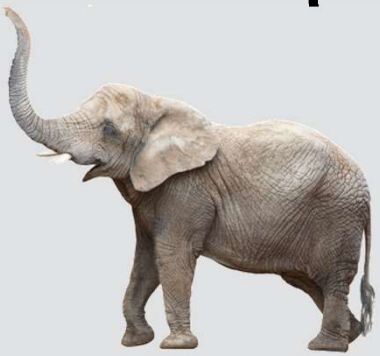


Poor adherence

RESISTANT HYPERTENSION



Poor Blood Pressure Technique



ACC/AHA Criteria for Accurate Office BP Measurement

- Mean of 2 or more BPs on 2 or more visits
- Seated ≥5 minutes with back support, feet on floor
- No smoking, exercise or caffeine for ≥30 minutes
- Empty bladder
- No speaking by patient or observer during rest period or BP determination
- Use a validated device; calibrate device periodically (dableducational.org)
- Proper cuff size placed directly on skin
- Arm supported at heart level
- Slow release of air from cuff: Deflate by 2 mm Hg per second
- Separate readings by 1-2 min.
- At first visit, check both arms; use higher arm for subsequent readings

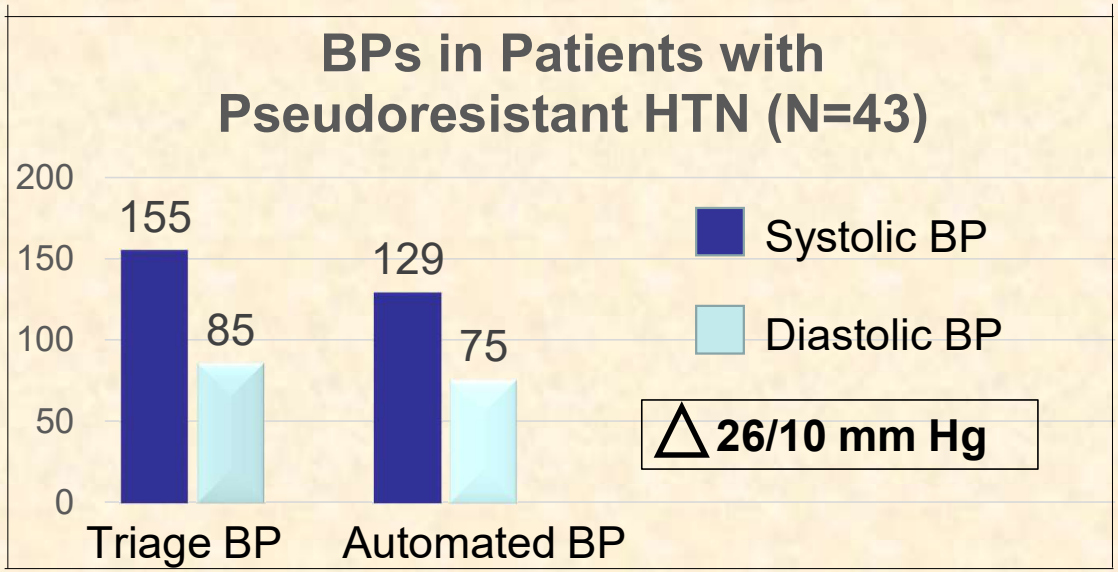
2017 ACC/AHA High Blood Pressure Clinical Practice Guidelines, Table 8

- Observer-free; starts automatically after 5-minute delay
- Takes 3-6 unattended readings 1-minute apart
- Averages the 3 readings

Misdiagnosis due to Improper Blood Pressure Measurement

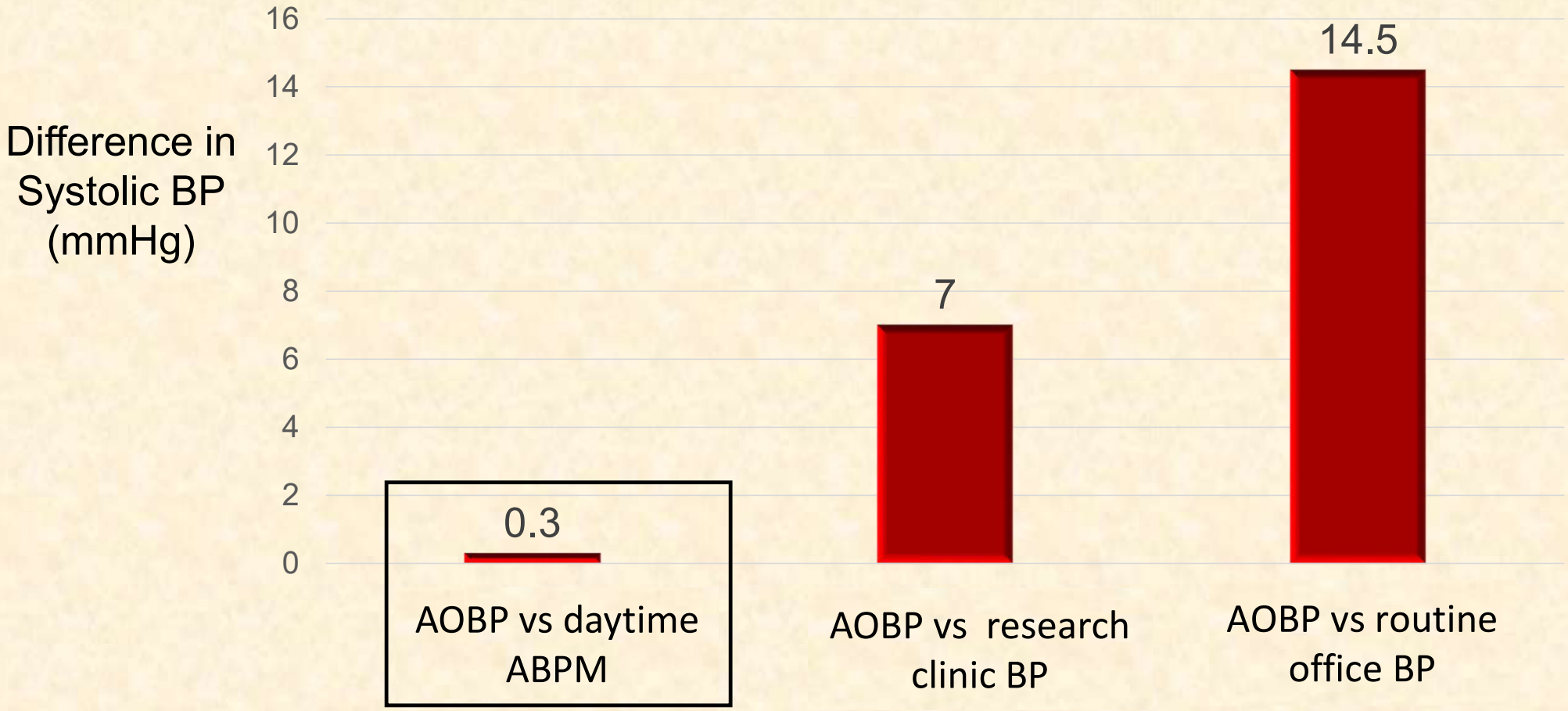
- University of Alabama, Birmingham Study
  - 130 patients with apparent treatment-resistant hypertension
  - Triage single BP compared with unattended automated BP, average of last 5 of 6 readings

33% (N=43) misdiagnosed by triage BP as uncontrolled true RH



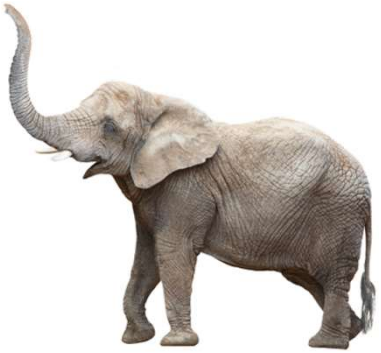
Bhatt H. J Am Soc Hypertens 2016;10:493-99

Automated Office BP (AOBP) vs. Other Methods



Roerecke M et al. JAMA Intern Med 2019;179:351-62

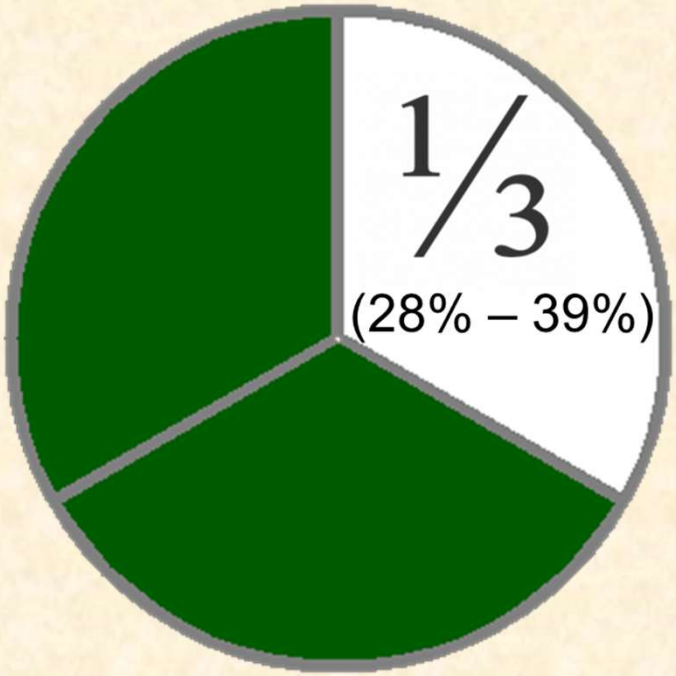
White Coat Effect



Definition: Elevated office BP with controlled or significantly lower BP outside the office in a hypertensive patient **on medication.**

Requires home BP measurements or 24-h ambulatory BP monitoring (ABPM). (Control by ABPM: <125/75 mm Hg)

What is the prevalence of White Coat Effect in apparent treatment-resistant hypertension by office blood pressure measurement?

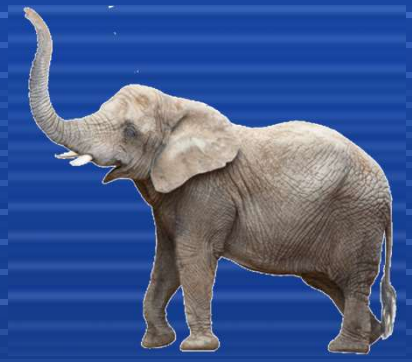


But…. patients with white coat effect often develop sustained hypertension, even within 18 months.

Carey RM et al. Hypertension. 2018;72:e53–e90

Under-treatment

Clinical inertia
Treatment inertia
Therapeutic inertia
(aka poor adherence by doctors, PAs, NPs)



Failure to initiate, intensify or change therapy in patients with uncontrolled BP.

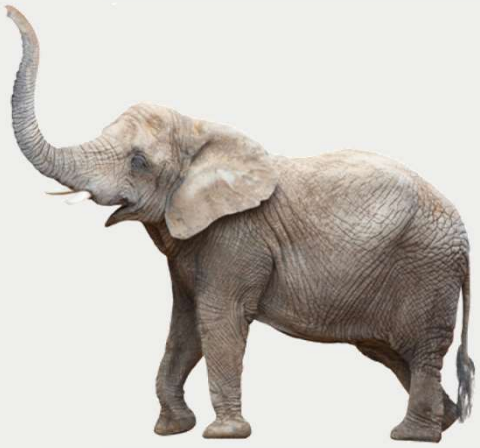
What is the prevalence of Under-treatment in apparent treatment-resistant hypertension by office blood pressure measurement?

468,000 patients with hypertension in >200 primary care practices.

45,000 with apparent treatment-RH.

22,000 treated optimally.

Egan BM et al. Hypertension 2013; 62:691–697



POOR MEDICATION ADHERENCE

What is the prevalence of Poor Adherence in apparent treatment-resistant hypertension by office blood pressure measurement?

…on method of assessment

How is poor adherence assessed?

- **Direct questioning of patient**

  Morisky Scale Questions

  1. Do you ever forget to take your medicine?
  2. Are you careless at times about taking your medicine?
  3. When you feel better, do you sometimes stop taking your medicine?
  4. Sometimes if you feel worse when you take the medicine, do you stop taking it?

Morisky DE. Medical Care 1986;24:67-74

How is poor adherence assessed?

- **Pill counts**
- **Pharmacy fill and refill data**
- **Urine/blood drug levels**
- **Directly observed therapy (DOT)**

Use of Directly Observed Therapy to Assess Treatment Adherence in Patients With Apparent Treatment-Resistant Hypertension

Ruzicka at al. JAMA Internal Medicine 2019;179:1433-1434

- 48 patients with apparent treatment-RH by ABPM
- All were adherent by questioning, pill count, and pharmacy records
- 71% remained hypertensive with directly observed therapy (DOT)
- 29% became normotensive on DOT and remained so 1 month later
  - Immediate decrease in BP: -26/3 mm Hg
  - One month decrease in BP: -22/6 mm Hg

Significant non-adherence remains missed with questioning, pill counts and pharmacy fill records.

A Case – 43-year-old female

Hypertensive on 6 medications, some in supra-therapeutic doses

Insists that she always takes her medications!!

No target organ damage

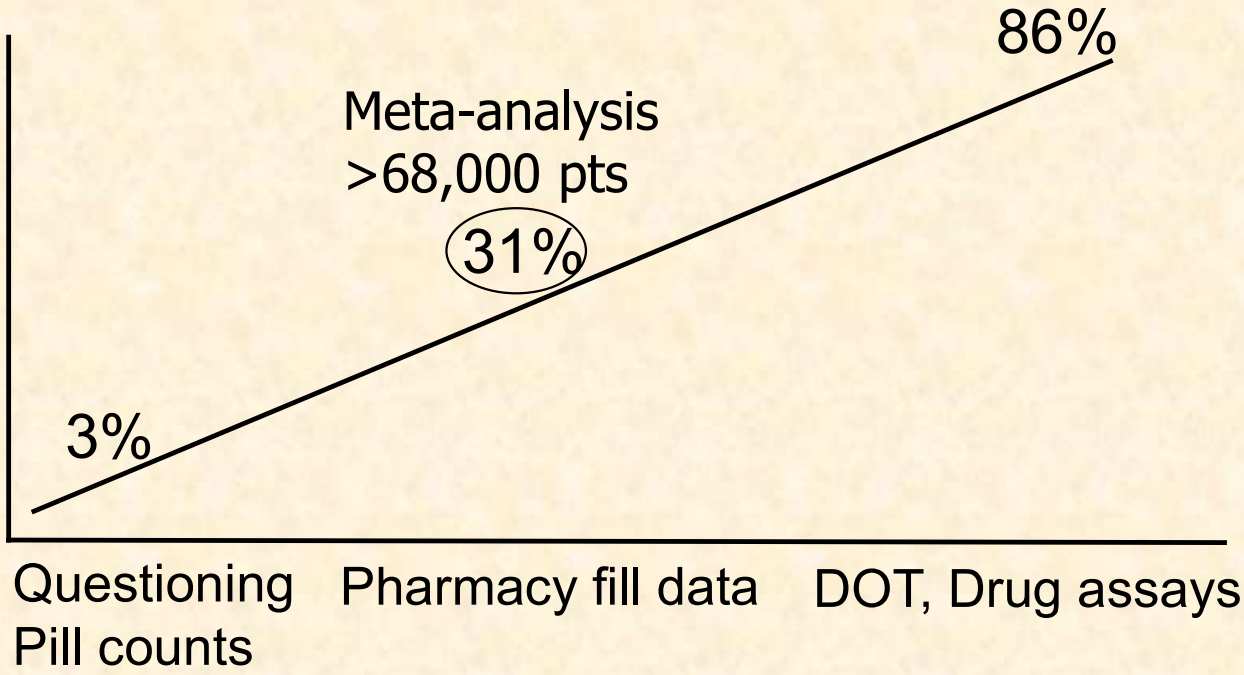
*The outcome of **DOT** for this patient:*

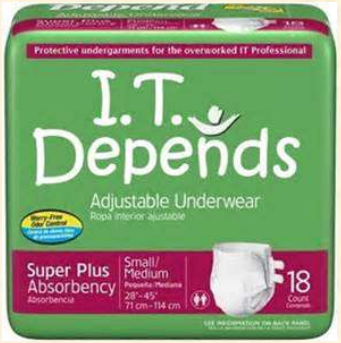
BP dropped dramatically.

She admitted non-adherence!

Her BP is controlled now for years on 2 antihypertensive drugs in small doses!

What is the prevalence of Poor Adherence in apparent treatment-resistant hypertension?

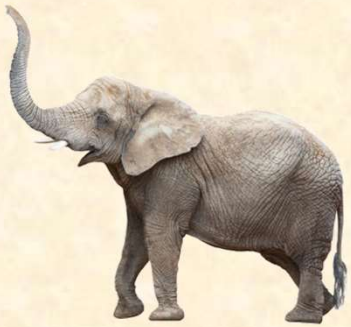




Durand H. J Hypertens 2017; 35:2346–2357

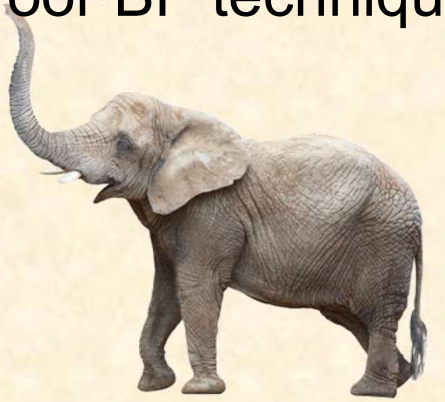
Summary: Causes of Pseudoresistant Hypertension

Prevalence Rates



33%

Poor BP technique



50%

Under-treatment

33%

White coat effect

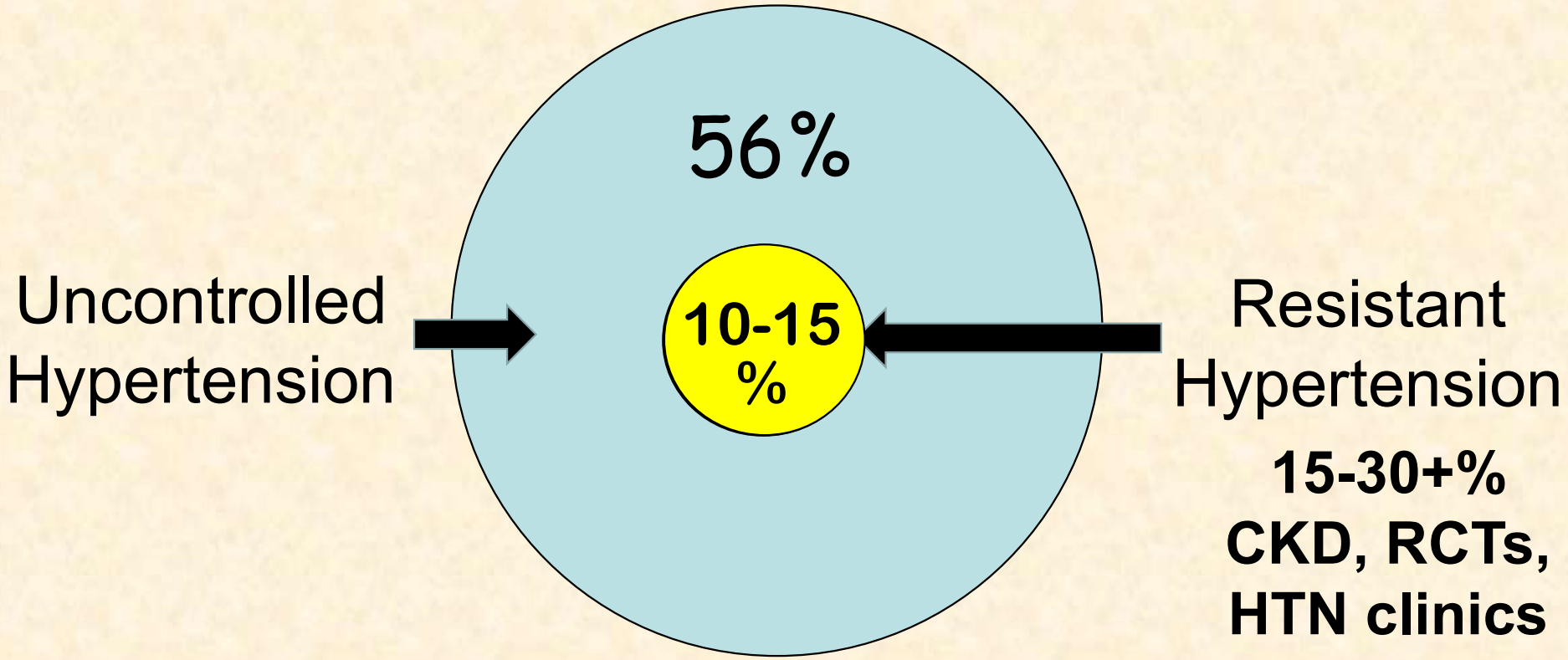
31%

Poor adherence

OUTLINE

- Definitions – true, apparent, pseudo RH
- Prevalence and prognosis of **true** RH
- Risk factors and causes
- Management (case scenarios)

What is the prevalence of **true** resistant hypertension?

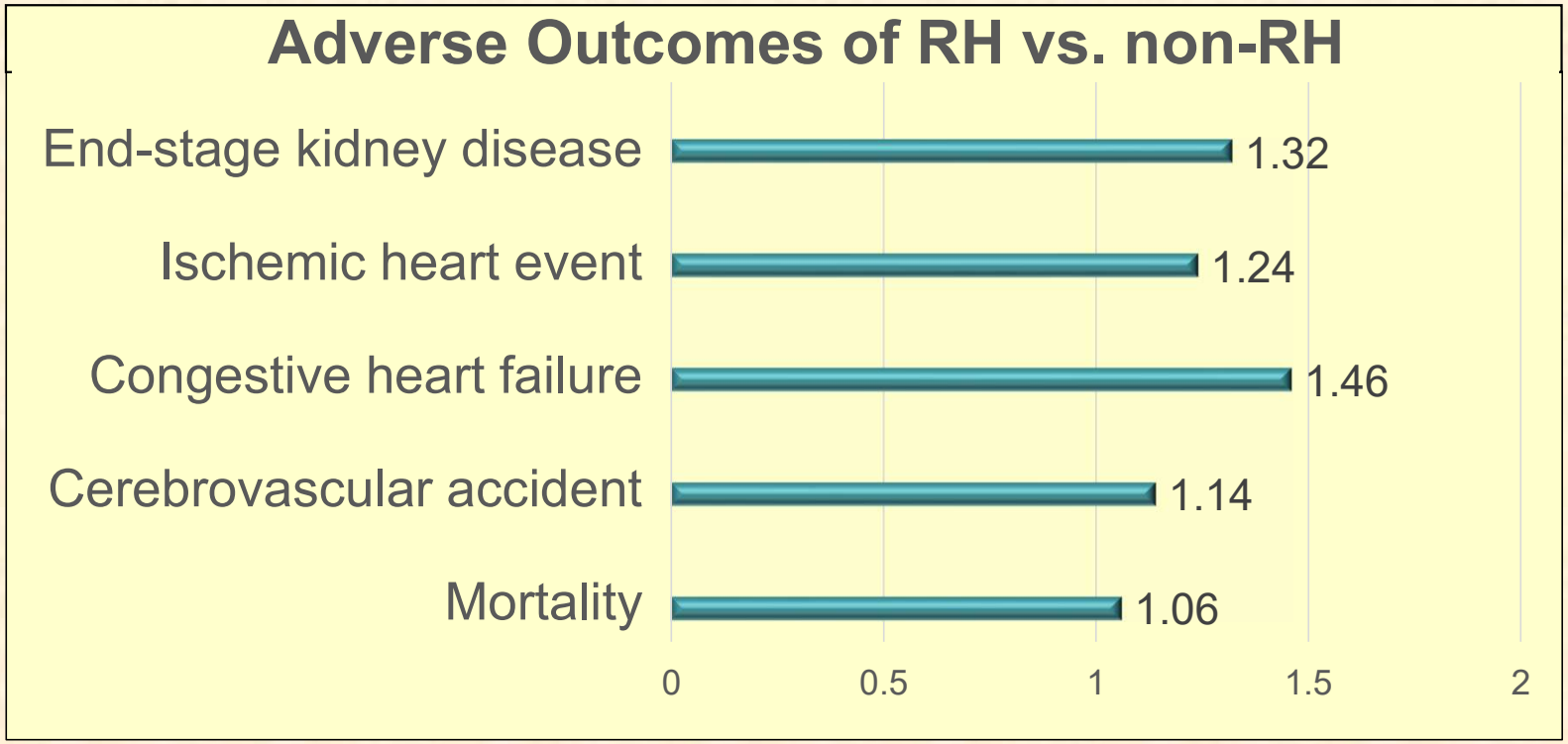


Nazarzadeh M et al. Heart 2019;105(2):96-7.

Prognosis of Resistant Hypertension

Kaiser Permanente retrospective cohort study:

470,386 patients with RH and non-RH



Sim JJ et al. Kidney Int 2015;88:622-632

OUTLINE

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Risk Factors for Resistant Hypertension

- Demographics
  - Older age
  - Male sex
  - Black race
- Comorbidities
  - Obesity
  - Diabetes
- Lifestyle
  - High salt intake
  - Heavy alcohol intake
  - Physical inactivity
  - Night-shift work
- Uncertain factors
  - Genetics
  - Pharmacogenetics

Carey RM et al. Hypertens 2018;72:e53-e90
Gupta AK et al. J Hypertens 2011;29:2004-13

Secondary Hypertension can cause Resistant Hypertension

COMMON	LESS COMMON OR RARE
Sleep apnea and other sleep disturbances	Coarctation of aorta
Hyperaldosteronism	Endocrine disorders
Drug-induced hypertension	Pheochromocytoma
Chronic kidney disease	Acromegaly, hyperparathyroidism
Renal artery stenosis	Hypo and hyperthyroidism

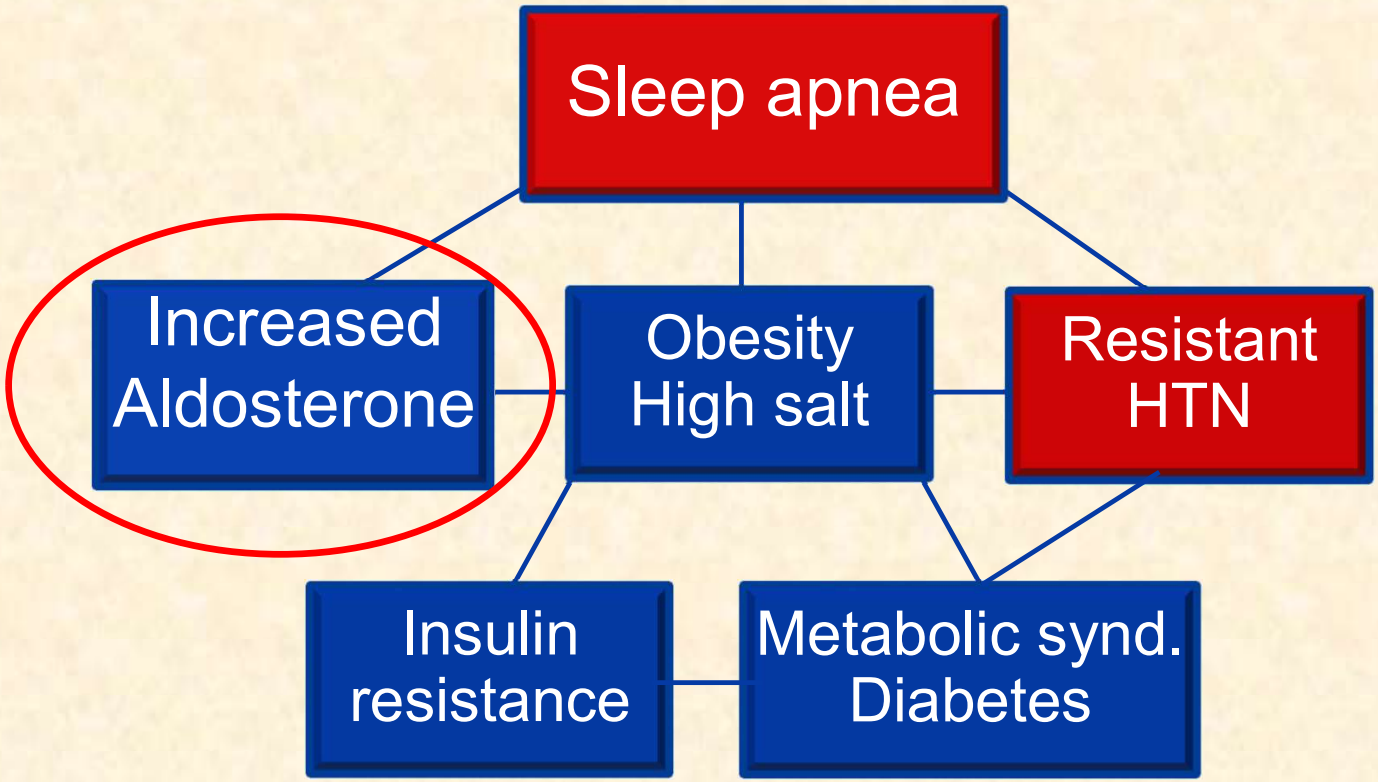
Obstructive Sleep Apnea and Resistant Hypertension

Prevalence of OSA in RH ⇨ 60-80%

∴ **All patients with RH should be screened for obstructive sleep apnea**

- Severity of OSA correlates with severity of HTN
- Association stronger for men than women
- BP response to CPAP is variable, modest, and mostly effective in lowering nocturnal BP

Conditions pathogenetically linked to sleep apnea



Goodfriend TL. Curr Hypertens Reports 2008;10:222226
Pimenta E et al. Prog in Cardiovasc Dis 2009;51(5):371-380

Role of Hyperaldosteronism in Resistant Hypertension

Prevalence of Primary Aldosteronism in RH ⇨ 15-20%

∴ **All patients with RH should be screened for primary aldosteronism**

Brown JM, et al. Ann Intern Med 2020;173:10-20

Drug-induced Resistant Hypertension

NSAIDs, COX-2 inhibitors	herbals (e.g., ma-huang)
sympathomimetic amines	tricyclic antidepressants
corticosteroids	cyclosporine, tacrolimus
anabolic steroids	licorice
alcohol	erythropoietin
cocaine, amphetamines	monoamine oxidase inhibitors
VEGF inhibitors	ergotamine

Always Think MEDIC!!

Chronic Kidney Disease and Resistant Hypertension

- Chronic Renal Insufficiency Cohort Study (CRIC)
  - Prevalence of apparent treatment-resistant hypertension = **40%**
  - Prevalence correlates with severity of renal impairment

GFR (ml/min/1.73m^2)	Prevalence of ATRH (%)
>60	22.3
30-60	39.4
<30	54.2

  - Adverse CV and renal outcomes more frequent than in non-RH

Thomas G et al. Hypertens 2016;67:387-396

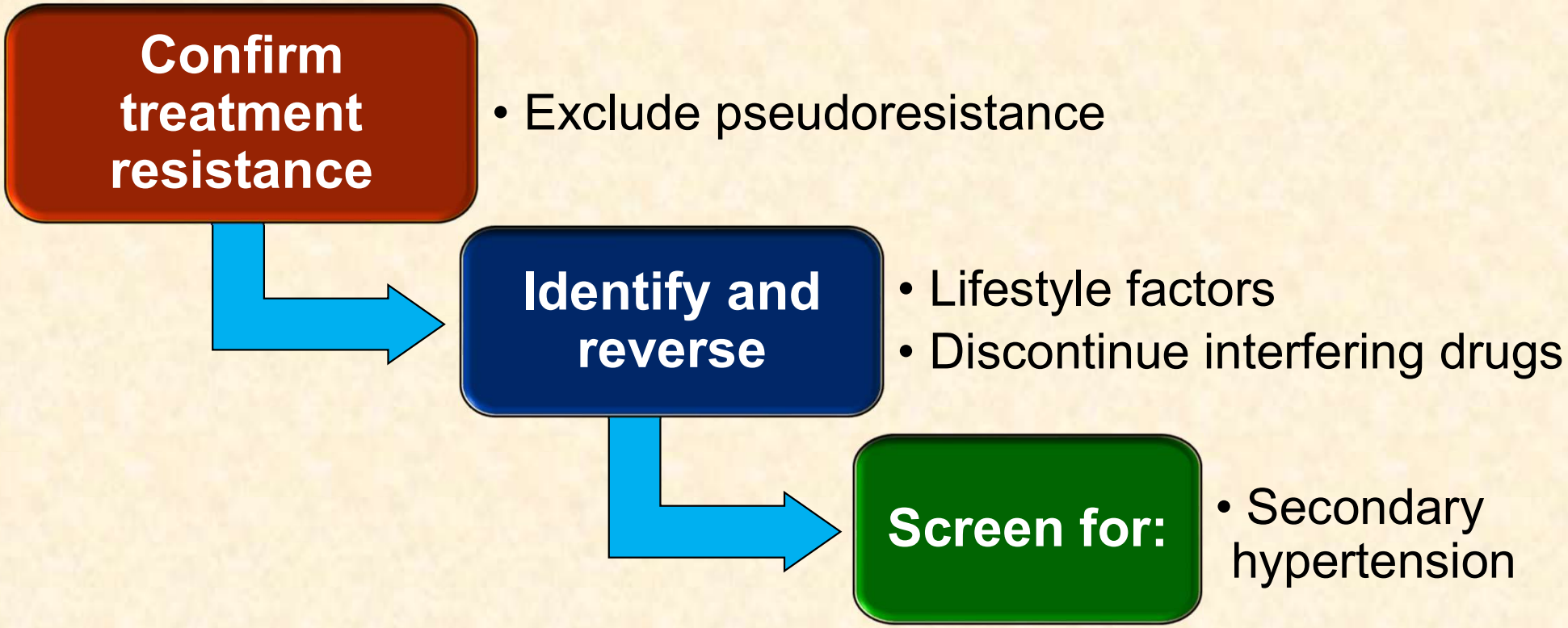
Renal Artery Stenosis and Resistant Hypertension

- Most caused by atherosclerotic disease
- Prevalence of RAS in older patients with RH (mean age 71) = **24%**
- Clues to RAS as a cause of RH
  - Generalized ASCVD
  - Recent acceleration of hypertension to RH
  - Flash pulmonary edema
  - Otherwise unexplained loss of renal function
  - Systolic-diastolic renal artery bruit

Benjamin MM et al. am J Cardiol 2014;113:687-690

Cause of secondary hypertension	Diagnostic tests
Obstructive sleep apnea	polysomnography/O2 saturation
Primary aldosteronism	aldo:renin ratio, saline loading, CT abd., adrenal vein sampling
Chronic kidney disease	UA, protein excretion, eGFR
Renal artery stenosis	CT or MR angiogram, doppler flow study, DS arteriogram
Cushing's syndrome	dexamethasone suppression test, ACTH, MR or CT scans
Thyroid disease (hypo, hyper)	T4, TSH
Pheochromocytoma	plasma or urine metanephrines, CT or MRI, MIBG scan (for mets)
Coarctation of aorta	CXR, CT angiography

Summary: Three Steps to Diagnosis Resistant Hypertension



Which of these patients is most likely to have secondary hypertension?

A. 30-year-old African-American male with BP 160/100 mmHg

B. 45-year-old Caucasian female with rheumatoid arthritis taking methotrexate

C. 35-year-old obese Native American male with propensity for driving accidents 

D. 40-year-old obese Mexican-American female, G1 P1, with acne and abdominal striae

Which of these patients is most likely to have secondary hypertension?

A. A 50-year-old female taking canagliflozin (Invokana™) for type 2 diabetes

B. A 60-year-old male taking leuprolide (Lupron™) for prostate cancer

C. A 28-year-old female consuming a box of Good & Plenty™ licorice candy (6 oz.) weekly

D. A 55-year-old male taking bevacizumab (Avastin™) for colon cancer

OUTLINE

- Definitions – true, apparent, pseudo RH
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Case 1: The “allergic” patient

- Sally is a 45-year-old female regional manager for Wal-Mart is taking benazepril/HCTZ 20/25 mg daily x 6 months and atenolol 50 mg daily x 2 months for hypertension. She complains of fatigue, orthostatic lightheadedness and difficulty concentrating at work.

  She tells you “I’m allergic to **all** medications. They all make me feel **bad**.”

  I’m not going to take those pills anymore!”

Translation: “Screw you!”

- P.E.: **BP 150/92**, P 70, BMI 22, rest of exam WNL
- Chem profile, UA, Ualb/creat ratio, CXR and EKG WNL

What do you do?

45-year-old female “allergic” to medications.
On benazepril/HCTZ + atenolol. She has fatigue, lightheadedness and difficulty concentrating. BP 155/92.
What do you do?

A. Taper off atenolol and increase benazepril/HCTZ
B. Taper off atenolol and switch to benazepril/amlodipine
C. Order home and work BP monitoring x 1 week
D. Stop all medications and monitor home and work BPs x 1 week
E. Refer her to a colleague you don’t like

You order either self-monitoring of BP and validate patient's technique in your office, or an ABPM so that you can see both daytime and nighttime blood pressures.

24-hour ambulatory BP Results

- 24-hour average BP 125/75
- Daytime average BP 128/80
- Nighttime average BP 118/72

HTN Threshold per ACC/AHA Guideline:

24-h BP 125/75 mm Hg

Daytime BP 130/80 mm Hg

Nighttime BP 110/65 mm Hg

What is her diagnosis?

What is her diagnosis?

A. White-coat effect

B. White-coat hypertension

C. Sustained hypertension

D. Masked hypertension

24-hour ambulatory BP Results

- 24-hour average BP 125/75
- Daytime average BP 128/80
- Nighttime average BP 118/72

Diagnosis: White-coat effect

Overtreatment based on office BPs

Eur Heart J 2018;39:3021-3104

New Engl J Med 2018;378:1509-20

Which, if any, of Sally's medications would you reduce or stop?

A. None, continue present treatment since home BP's are OK
B. Atenolol
C. HCTZ
D. Benazepril
E. Atenolol and HCTZ 
F. Benazepril-HCTZ combo

Which, if any, of Sally's medications would you reduce or stop?

- Taper off atenolol (fatigue, concentrating difficulty)
- Decrease HCTZ; change benazepril-HCTZ to 20/12.5 mg/day (orthostatic lightheadedness)
- If still having orthostatic Sxs, substitute amlodipine for HCTZ
- **Continue BP self-monitoring**
- **Adjust therapy according to <u>out-of-office BPs</u>**
- Repeat ABPM in one year or prn to verify control
  - White-coat hypertension and white-coat effect <u>often progress to sustained hypertension</u>

Case 2: A case of salty humor

- Ted is a 40-year-old bartender with uncontrolled hypertension on fosinopril-HCTZ 40 mg-25mg and nifedipine XL 90 mg daily.
- He denies salting his food, emphatically proclaiming "I don't even know what a saltshaker looks like!"

- Says he "drinks socially."
- Family history is positive for hypertension.
- A previous workup failed to reveal a secondary cause for his hypertension.

You enquire further…….

- He says he consumes 3-4 cans of beer a day during the week and up to 6 cans on weekends
- He's single and eats out for breakfast and lunch, usually at McDonalds, Kentucky Fried Chicken and/or Taco Bell
- He eats Healthy Choice meals and Campbell's soups for dinner

What test would you order to determine if Ted has true resistant hypertension?

A. 24-hour urine sodium excretion

B. 24-hour diet diary

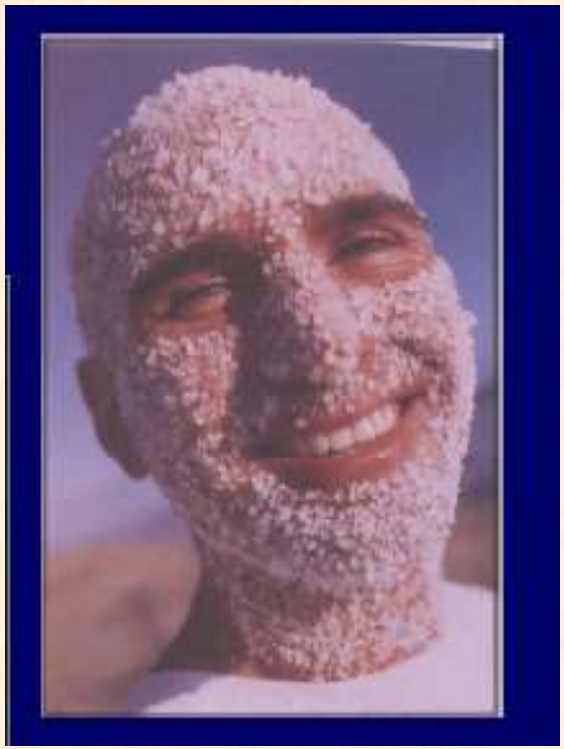
C. 24-hour urinary free cortisol

D. Plasma aldosterone/renin ratio

E. Renal artery doppler flow study

You order……

- A 24h urine for sodium
  - Result: 10 grams of sodium excretion/24h!



Your prescription…….

- Dietary counseling on salt intake
- Instruction +/- assistance regarding ETOH intake
- Likely reduction in BP meds if patient complies

Outcome……..

- Sodium intake decreases to 3 gm/day
- ETOH intake decreases to 2 beers/day
- BP decreases to WNL on fosinopril-HCTZ 20mg-12.5 mg daily; nifedipine D/C'd

Happy Ending!

Case 3: A sleepy tale

Ben, a 48-year-old used car salesman, weighs 196 lbs. with a BMI is 32 kg/m^2. He uses CPAP for OSA. His BP is consistently at or above 154/94 despite taking ramipril 20 mg daily, amlodipine 10 mg daily, and chlorthalidone 25 mg daily. Which of the following would be diagnostically the most helpful next step….and

(Would YOU buy a used car from Ben?)

A. Order a plasma aldosterone and renin levels
B. Order renal function studies
C. Order thyroid function studies
D. Order plasma cortisol level

You order…….

- Plasma aldosterone and renin levels
  - Plasma aldo in the middle of normal range
  - Renin low despite 3 drugs that can raise renin levels

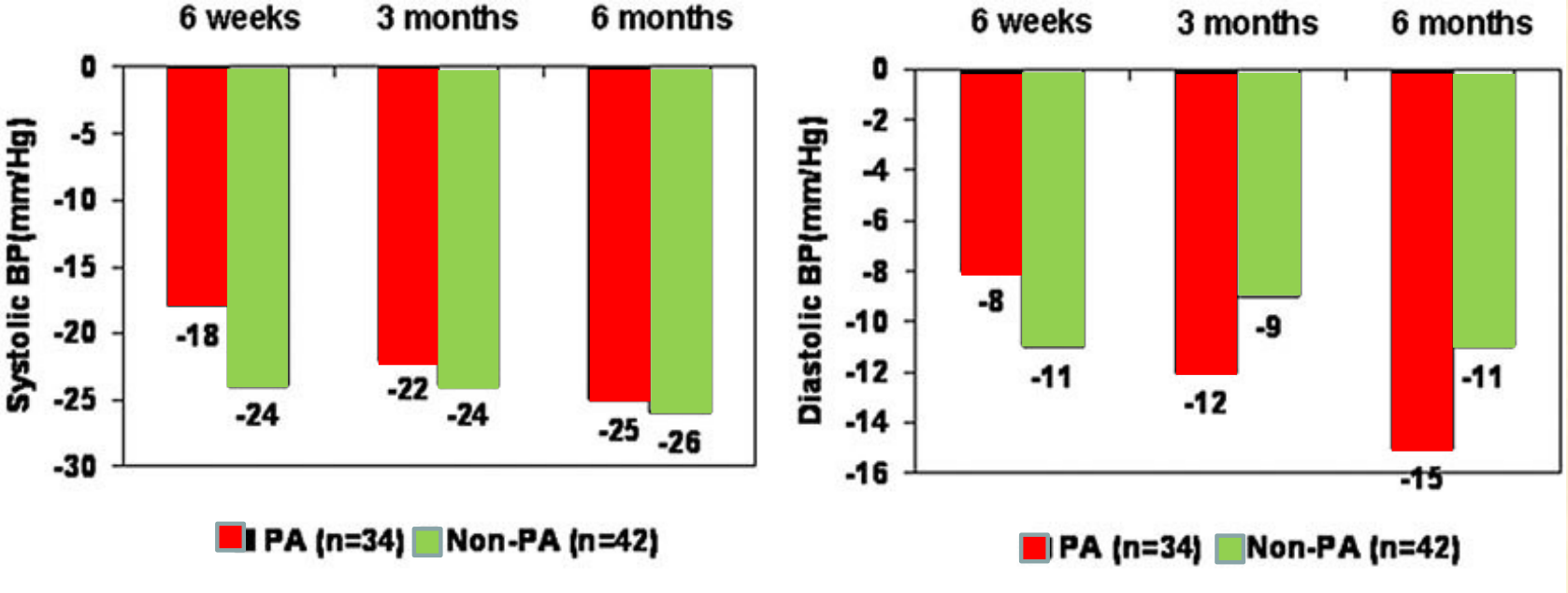
    His plasma aldo-renin ratio is hard to interpret.
- What drug do you add now to lower Ben's BP ?

What is the best drug to add to Ben's regimen?

A. Clonidine
B. Carvedilol
C. Spironolactone 
D. Irbesartan
E. Doxazocin

You order spironolactone 25 mg daily and titrate upward prn

- Rationale:
  - Mineralocorticoid inhibition has been shown to be <u>the best fourth-line agent for resistant hypertension</u>

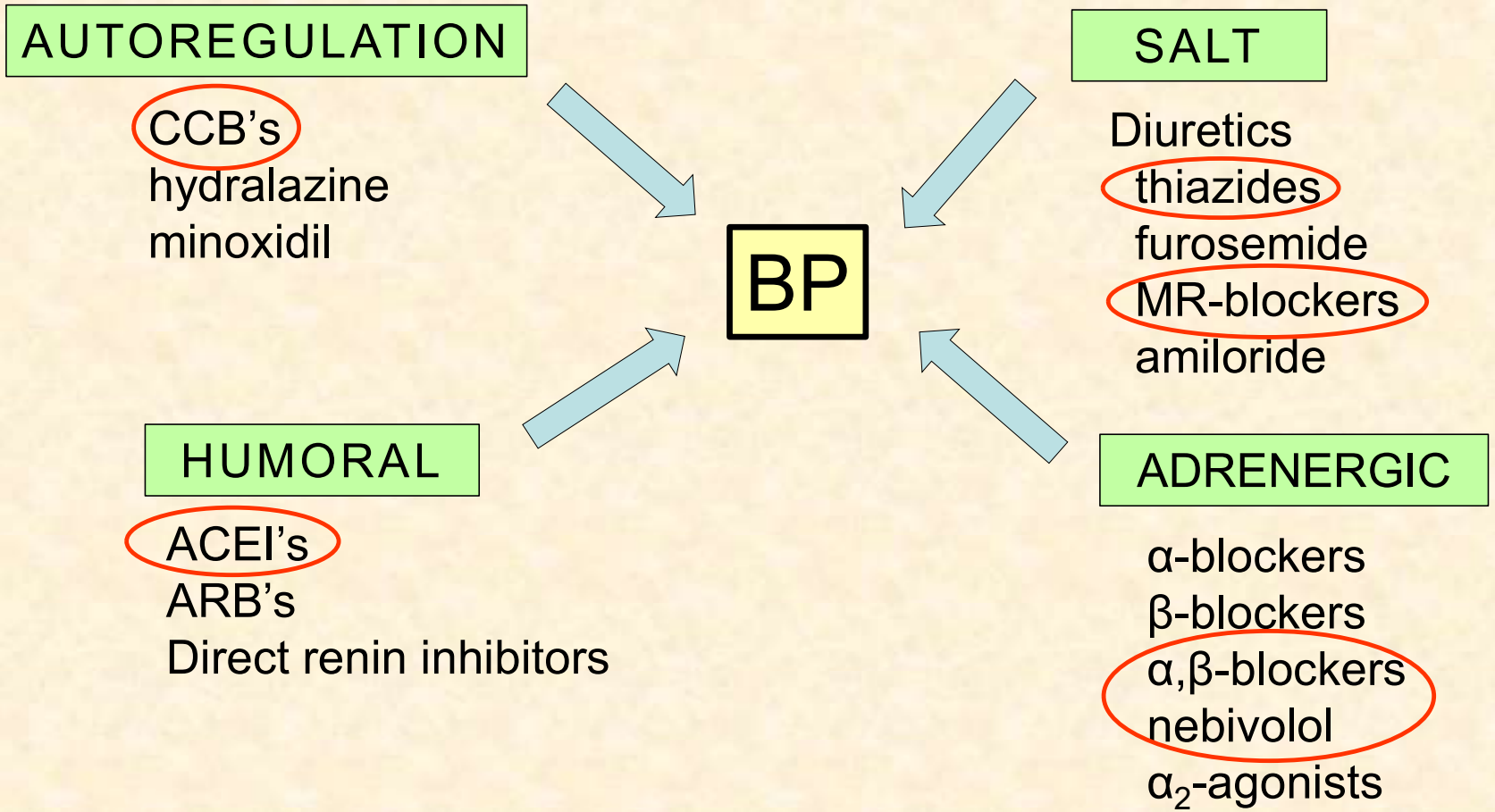


What if Ben’s BP is still above goal?

What drug class should be next?

Your options…….

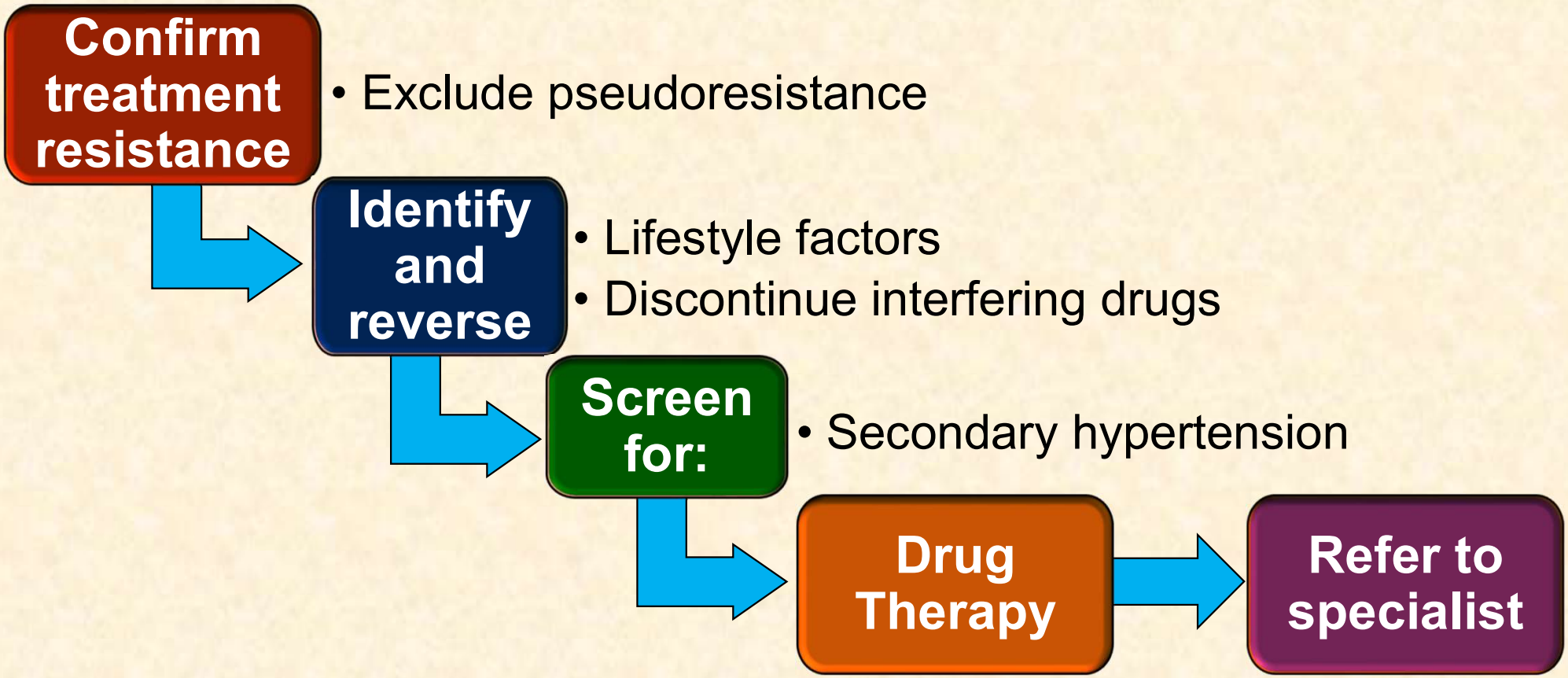
BUT….Be sure to monitor renal function and potassium!



Take-away Pearls on Drug Therapy for Resistant Hypertension

- ARBs are not created equal:
  - Losartan – weakest, shortest-acting; requires twice daily dosing
  - Azilsartan – strongest, longest-acting, but generic not available
    Lowers SBP by 4-8 mm Hg more than other ARBs or ACEi ramipril
- Diuretics: Chlorthalidone lowers SBP 7-8 mm Hg more than HCTZ at same daily dose. Indapamide is also preferable to HCTZ
- MR-blocking drugs: Eplerenone is half as potent as spironolactone and should be given twice daily vs. once-daily spironolactone
- Clonidine: Avoid tablets; use patch

Summary: Five Steps to Dx and Rx of Resistant Hypertension



Assuming maximum or maximally-tolerated doses of antihypertensive medications and good adherence, resistant hypertension can be diagnosed if:

A. Office BPs are above goal on four or more antihypertensive medications
B. Office BPs are above goal on three or more antihypertensive medications
C. Office and out-of-office BPs are above goal on ≥ three antihypertensive medications or controlled on ≥ four medications
D. Office and out-of-office BPs require at least three antihypertensive medications for control

Which of the following is the most frequent cause of pseudoresistant hypertension?

A. Incorrect blood pressure measurement
B. White coat effect
C. Under-treatment by clinician
D. Medication non-adherence by patient

Which of the following is most often found in patients with resistant hypertension?

A. **Obstructive sleep apnea**
B. Chronic kidney disease
C. Primary aldosteronism
D. Renal artery stenosis

References for suggested reading

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Questions…..

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