Approach to Resistant Hypertension

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Key Questions

1. What are the definition and prevalence of resistant hypertension?
2. What is pseudo-resistant hypertension?
3. What are the most common causes of resistant hypertension?
4. What is the optimal workup for resistant hypertension?
5. What is the optimal sequential approach to pharmacotherapy?
6. What is new in medications for resistant hypertension?
7. Does renal artery denervation work?

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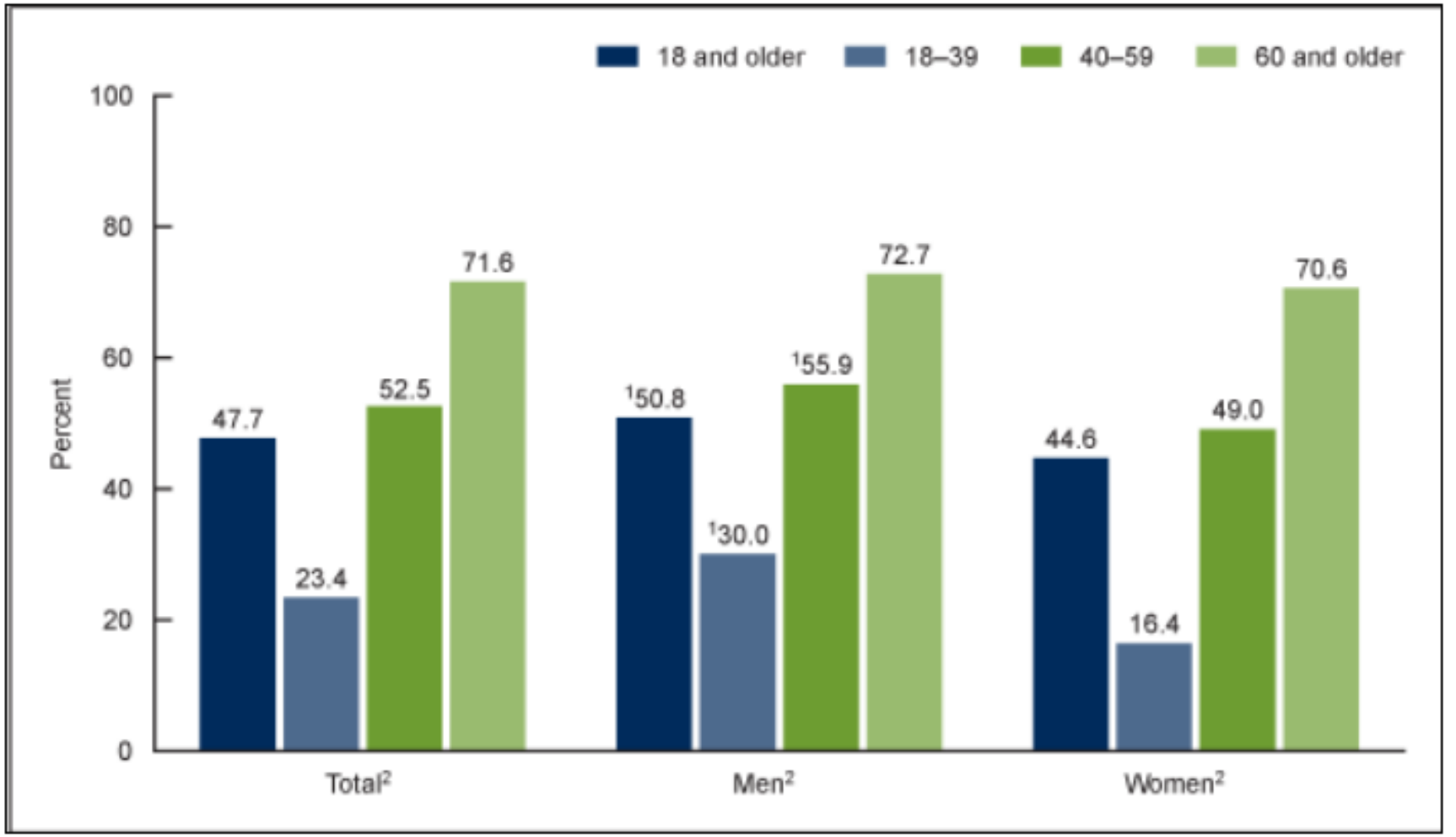
Question #1: What are The Definitions and Prevalence of Treatment Resistant Hypertension?

NHANES 2024: Nearly One Half of U.S. Residents are Hypertensive (>130/80 or on BP Meds)



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https://www.cdc.gov/nchs/products/databriefs/db511.htm

AHA/ACC Definition of “Apparent Treatment Resistant HTN (aTRH)”

- Blood pressure that is above goal (usually 130/80) in the office despite:
  - Three drugs
  - One of which should be a diuretic, if tolerated
  - Maximal recommended and/or tolerates doses
- OR any patient on 4 drugs regardless of bp
- AND patient is adherent to medications

Hypertension 2018;72:e53 Hypertension 2025;82:e212

How Common is aTRH? Prevalence among Patients Taking Antihypertensive Therapy

Subgroup	% of Patients
Overall	19.7%
Age group (years)	
• 20-49	10.8%
• 50-59	14.0%
• 60-69	19.9%
• ≥ 70	28.8%
Male sex	19.6%
Female sex	19.8%
Non-Hispanic white	18.9%
Non-Hispanic black	27.3%

Hypertension. 2019;73:424

Treatment Resistant Hypertension is Morbid When Compared to Controlled HTN and White Coat HTN

- Compared CV and all cause mortality between patients with controlled hypertension, resistant hypertension, white coat HTN, and ABPM confirmed resistant hypertension (i.e. white coat excluded)
- Multivariable analysis

Comparison	Total Mortality		CV Mortality	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Resistant vs. controlled	1.72	1.21	1.94	1.33
ABPM confirmed resistant vs. white coat resistant	1.47	1.45	1.69	1.68

Hypertension. 2024;81:2350

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Question #2: What is Pseudo-Resistant Hypertension?

How to Distinguish TRH from Pseudo-Resistant Hypertension?

- Measure bp properly in office with appropriately sized cuff:
  AOBP x 3 preferred
- Confirm that still uncontrolled by home measurements with validated cuff, or preferably 24-hour ABPM
- “Normal” values for 24-hour ABPM are 5-10 mg Hg lower than office values
- If controlled by home measurements, then this is white coat HTN or HTN with a white coat effect
- Be certain that patient is adherent to medication regimen
- Assess adherence to lifestyle recommendation
- The anti-hypertensive regimen may be sub-optimal (i.e., no diuretic)

Simple Strategies to Improve Adherence

- Choose low-cost generic
- Combination tablets may reduce copays
- Convert to once daily formulations when possible
- Combination tablets to reduce pill burden
- Blister packs
- 90-day refills
- Lowest effective doses to minimize side effects

- ACEi or ARB can reduce edema due to CCBs
- ACEi orARB minimize hypokalemia due to thiazides
- Multi-disciplinary teams when available
- Patient education
- Text message reminders
- Home bp monitoring with ongoing feedback connected to EMR

Don’t Forget OTC and Rx Medications and Substances that May Cause Pseudo-Hypertension

- Alcohol
- Caffeine
- Decongestants
- St. John’s wort
- Ephedra
- NSAIDs
- Cocaine
- Amphetamines
- MAO inhibitors
- Atypical antipsychotics
- OCPs
- Corticosteroids
- ADT for prostate cancer

Equivalent Bp Values for 24- Hour ABPM are Lower than That for Office bp or Casual HBPM

Office	HBPM	Daytime ABPM	Nighttime ABPM	24-Hour ABPM	
120/80	120/80	120/80	100/65	115/75	
130/80	130/80	130/80	110/65	125/75	Stage 1
140/90	135/85	135/85	120/70	130/80	
160/100	145/90	140/90	140/85	145/90	

How to Measure BP in the Office?

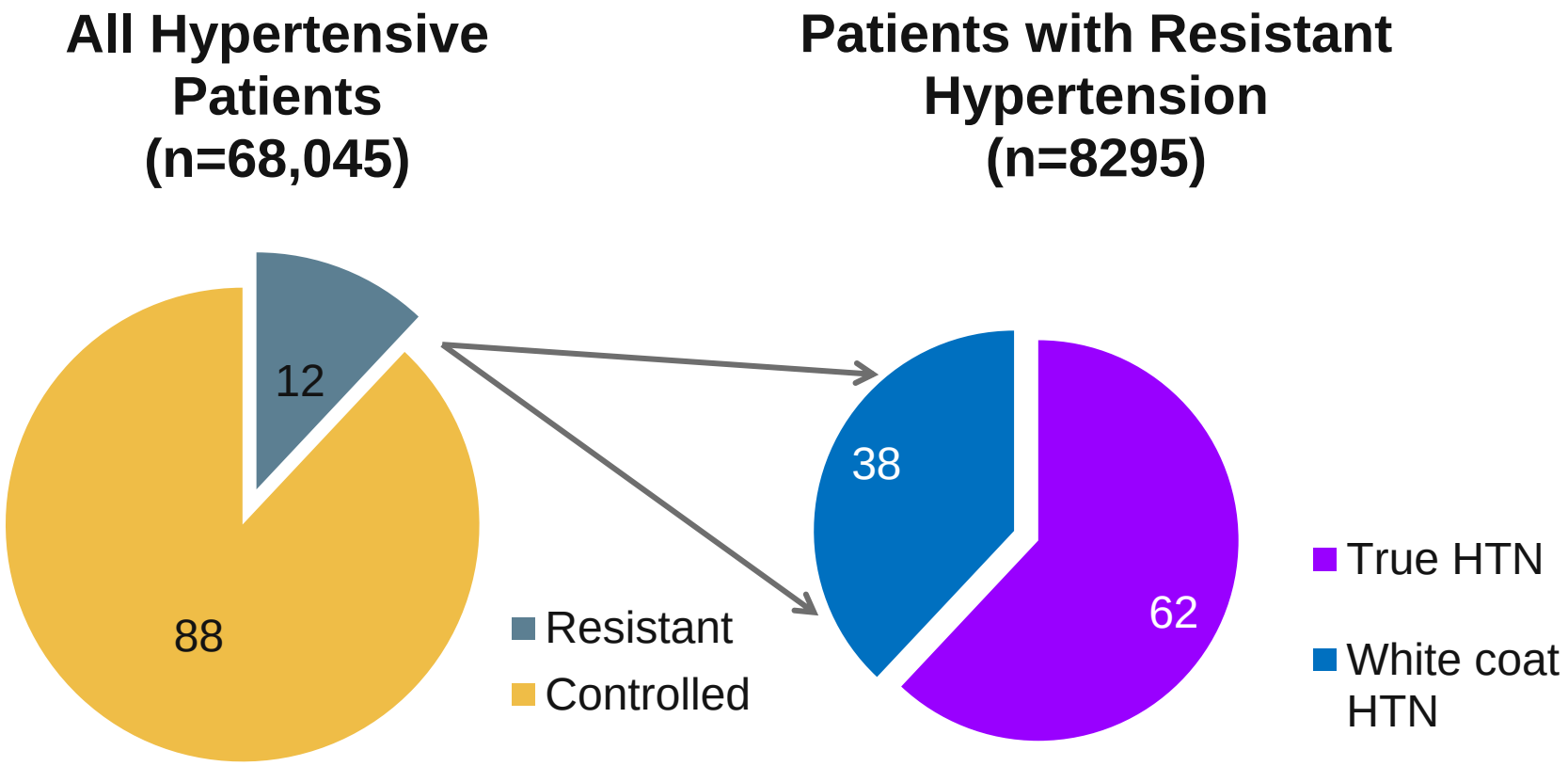
- A validated automated office blood pressure device (AOBP) preferred over clinician measurement
- Programmed to take 3 readings over 5 min. with patient resting alone
- Use the average of the three readings as the correct value
- AOBP is now preferred over traditional (casual) auscultatory method to measure blood pressure
- On average, sbp from AOBP 14 mm Hg lower than routine office measurement*
- Oscillometric values more reliable than auscultatory
- A substantial change from the way that many of us were trained and have practiced for years
- This is the ACC/AHA 2025 recommendation
- Use a cuff size appropriate for arm

If You Don’t Have AOBP? Checklist for Accurate Measurement

Office Blood Pressure Measurement

1. The patient should avoid caffeine, exercise, and smoking for at least 30 minutes before measurement. Ensure the patient has emptied their bladder.
2. Use a blood pressure device that has been validated for accuracy (validatebp.org).
3. Use the correct cuff size on a bare arm.
4. The patient’s arm should be supported at heart level.
5. Have the patient relax, sitting in a chair (feet on floor, legs uncrossed, and back supported) for more than 5 minutes of rest.
6. Neither the patient nor the clinician should talk during the rest period or during the measurement. The patient should not be using their phone.
7. Blood pressure measurement should be taken in a temperature-controlled room.
8. Take 2 or more blood pressure measurements at least 1 minute apart. Average the readings, and provide the patient their blood pressure readings both verbally and in writing.

Up to One Third of Patients with aTRH Actually Have White Coat Hypertension as the Basis



Hypertension 2011;57:898

White Coat Hypertension is the Most Comon Cause of Apparent Treatment Resistant Hypertension

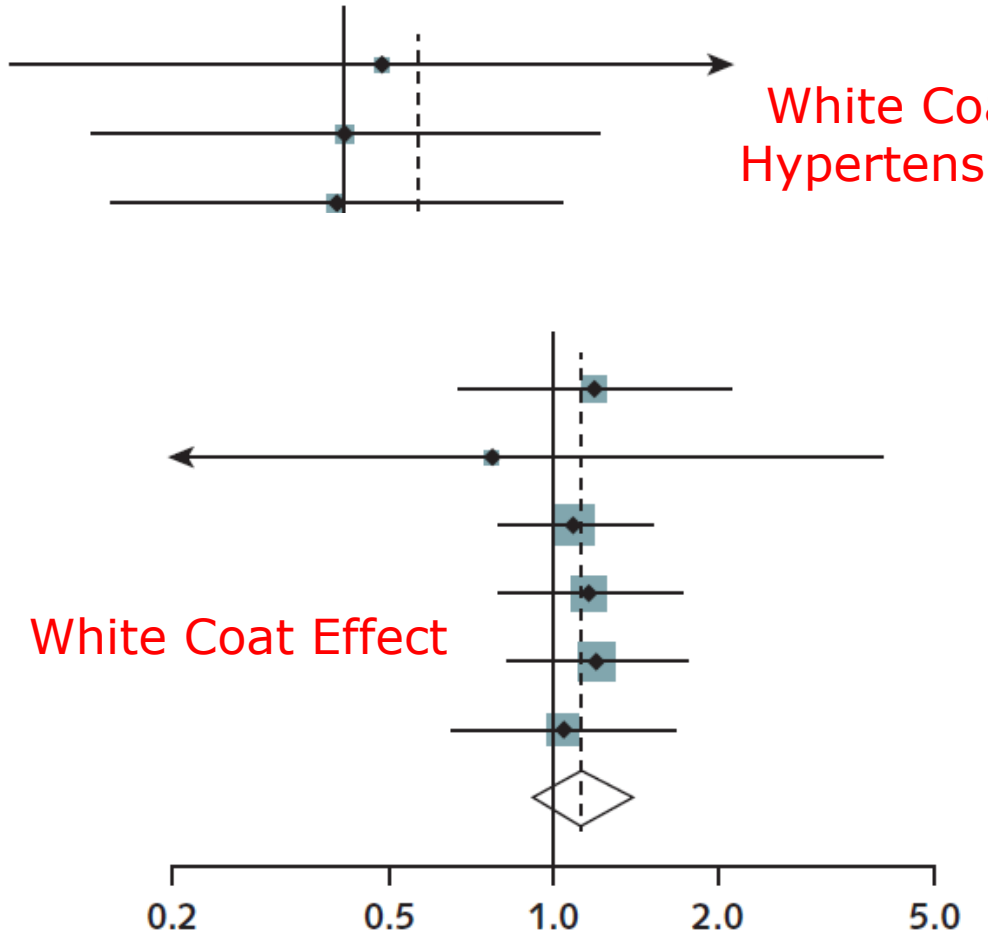
- Always need home measurements before making diagnosis of aTRH
- Ideally 24-hour ABPM
- Patients with pseudo-resistant hypertension due to white coat effect may not benefit from more antihypertensive drugs
- White coat effect = patients with treated hypertension who have reliable home bp readings < 130/80 despite persistent office elevations
- In this instance, use the home measurements to guide therapy
- Periodically reassess the accuracy of the home device

White Coat Hypertension, but not Treated White Coat Effect, is Potential Risk Factor for CV Events

White Coat Hypertension = Elevated Office bp, normal home bp, no Rx

White Coat Effect = Elevated Office bp, normal home bp and receiving antihypertensive Rx

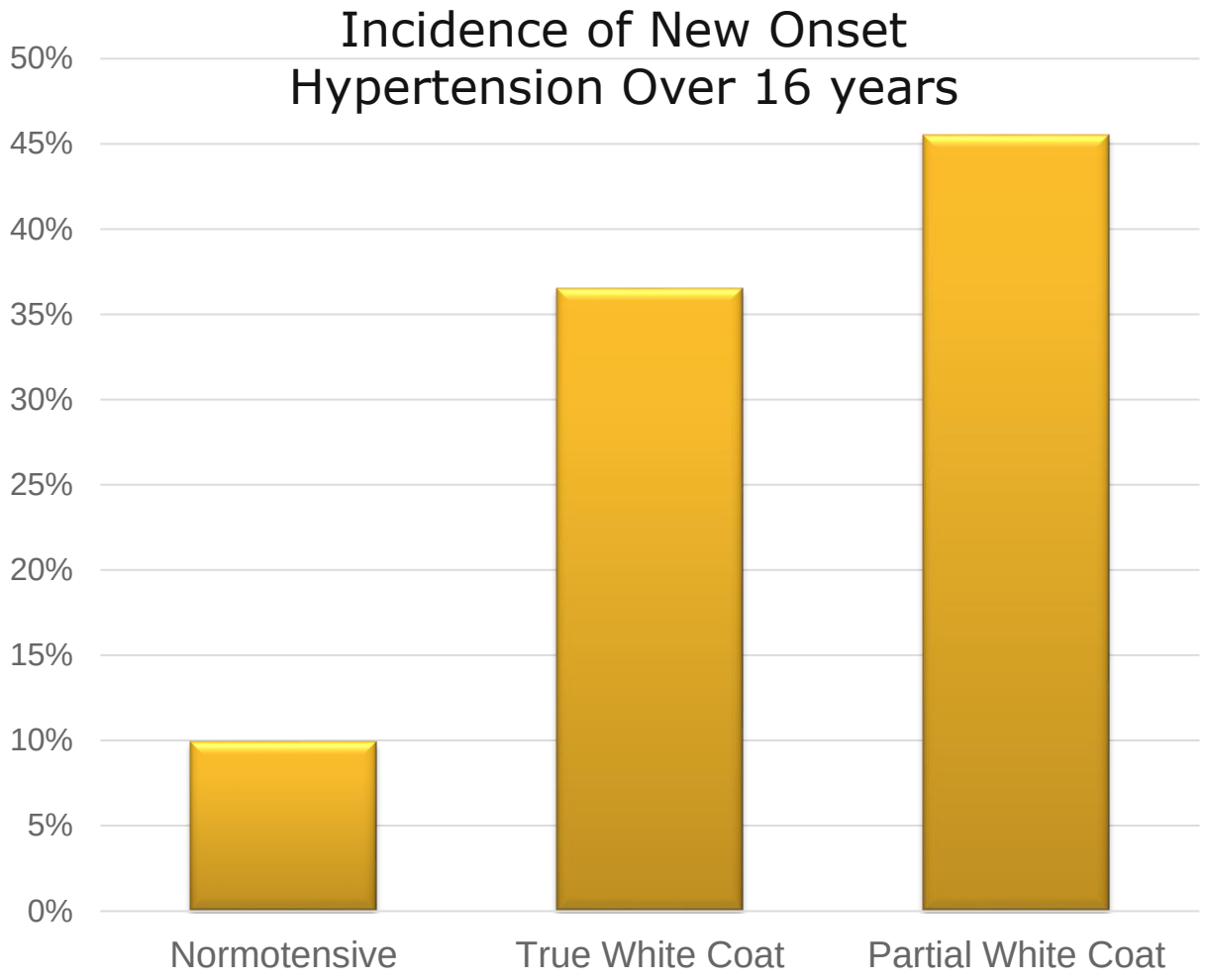
	HR (95% CI)
1.17 (0.25–5.33)	
1.00 (0.35–2.90)	
0.97 (0.38–2.46)	
1.45 (0.2	
5.59 (1.22	
1.20 (0.9	1.18 (0.67–2.10)
1.42 (1.0	0.77 (0.15–3.96)
1.96 (1.2	1.09 (0.79–1.52)
1.36 (1.0	1.16 (0.79–1.72)
	1.20 (0.82–1. 76)
	1.04 (0.65–1.66)
	1.12 (0.91–1.39)



Ann Intern Med. 2019;170:853-862

White Coat Hypertension: A Pre-Hypertensive State

- 2015 persons
- Normotensive (52%) Hypertensive (23%) White coat (25%)
- Divided white coat into true (all home reads normal) and partial (at least one home bp elevated)
- 16 years of followup



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Hypertension 2013;62:168

White Coat Hypertension: Current Approach

- UpToDate 2025
  - Do not treat with antihypertensive meds
- ACC/AHA 2025
  - No need for antihypertensive meds
  - Repeat ambulatory (24 hour) or home bp at least once yearly
  - When office bp ≥ 160/100, begin meds without needing home confirmatory values
- Masked hypertension
  - Elevated home readings with normal office readings
  - This is a CV risk factor
  - When present, use home values to guide therapy

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Question #3: What are the Most Common Causes of Resistant Hypertension?

Most Common Causes of Secondary Hypertension among Patients with Hypertension

- Pseudo-hypertension
- OSA – in as many as 25-50% of patients with TRH
- Primary aldosteronism 5-25%
  - Only ½ of patients will have spontaneous hypokalemia
- CKD 15%
- Drug or alcohol related
- Renovascular <5%
- Hyperthyroidism < 1%
- Pheochromocytoma <0.6%
- Cushing's syndrome < 0.1%

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Obstructive Sleep Apnea is the Most Common Cause of Resistant Hypertension

- In part related to obesity pandemic
- 15-30% of males and 10-15% of females in the U.S. have at least mild OSA (AHI >5)
- Risk factors are male sex, older age, obesity, crowded airway
- Screen with STOP Bang questionnaire (8-items)
- 50% of patients with OSA also have hypertension
- More severe OSA confers higher likelihood of co-existing HTN
- Patients with OSA are 4X more likely to have resistant hypertension than those without OSA*

*Ahmed AM, Nur SM and Xiaochen Y (2023) Front. Med. 10:1200952.

Does Rx of OSA with CPAP Lower Blood Pressure? Is This Worth Identifying, Particularly if no Symptoms?

- The impact of CPAP on bp is small compared to anti-hypertensive therapy
- In a meta-analysis of 75 trials (n=10,025), CPAP reduced 24-hour sbp by 2.5 mm Hg*
- CPAP was most effective in bp lowering for those with the most severe OSA (AHI > 30)
- To date, CPAP has not been shown to reduce CVD events in patients with OSA and HTN
- CPAP may be an adjunct to antihypertensive therapy, but usually does not allow reduction or d/c of meds

*Journal of Sleep Research, 2025; 34:e70072

What is New? Recommendation to Screen all Patients with TRH for Primary Aldosteronism

- Likely second most common cause of secondary HTN with a prevalence of 5-25%
- Only one half will be hypokalemic either spontaneously or after beginning a thiazide
- Hypokalemia does not need to be present in order to screen
- 2025 ACC/AHA recommends screening for aldosteronism in all patients with resistant HTN, hypokalemia, OSA, known adrenal mass, family h/o early onset hypertension
- This is now the first step in their flow chart for screening for secondary HTN

Other Clues that a Secondary Cause May Exist Besides TRH

- Stage 2 hypertension (≥140/90 mm Hg untreated)
- Sudden change in otherwise stable bp control on Rx
- Early onset < 30 years old
- Diastolic hypertension in older patients
- Severe HTN with non family h/o hypertension
- Hypokalemia, either spontaneous or elicited by diuretics
- Evidence of target organ damage out of proportion to degree of hypertension (LVH, albuminuria, retinal changes, diastolic dysfunction)

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Question #4: What is the optimal workup for resistant hypertension?

Optimal Workup When a Secondary Cause is Suspected in Resistant HTN

- This has evolved over recent decades
- More emphasis on identifying secondary causes that are common
- Consider rarer causes only if clinical features suggest
- Screen all patients with TRH for OSA by symptom screen such as STOP-BANG
- Baseline serum creatinine will identify patients with CKD as a cause
- Screen all patients with TRH for primary aldosteronism
- Review medication and alcohol history
- Many other causes are once in a lifetime diagnoses for primary care clinicians (pheo, Cushing's, etc.)

STOP-BANG Score to Assess for OSA

1. Do you snore loudly?
2. Are you often tired, fatigued, or sleep?
3. Has anyone observed you to stop breathing or gasp during sleep?
4. Do you have high blood pressure?
5. Is your BMI > 35?
6. Are you older than 50 years?
7. Is your neck size (shirt collar) > 16.5 inches?
8. Are you male (sex assigned at birth)?

Low risk of OSA:

0-2 points

Intermediate risk:

3-4 points

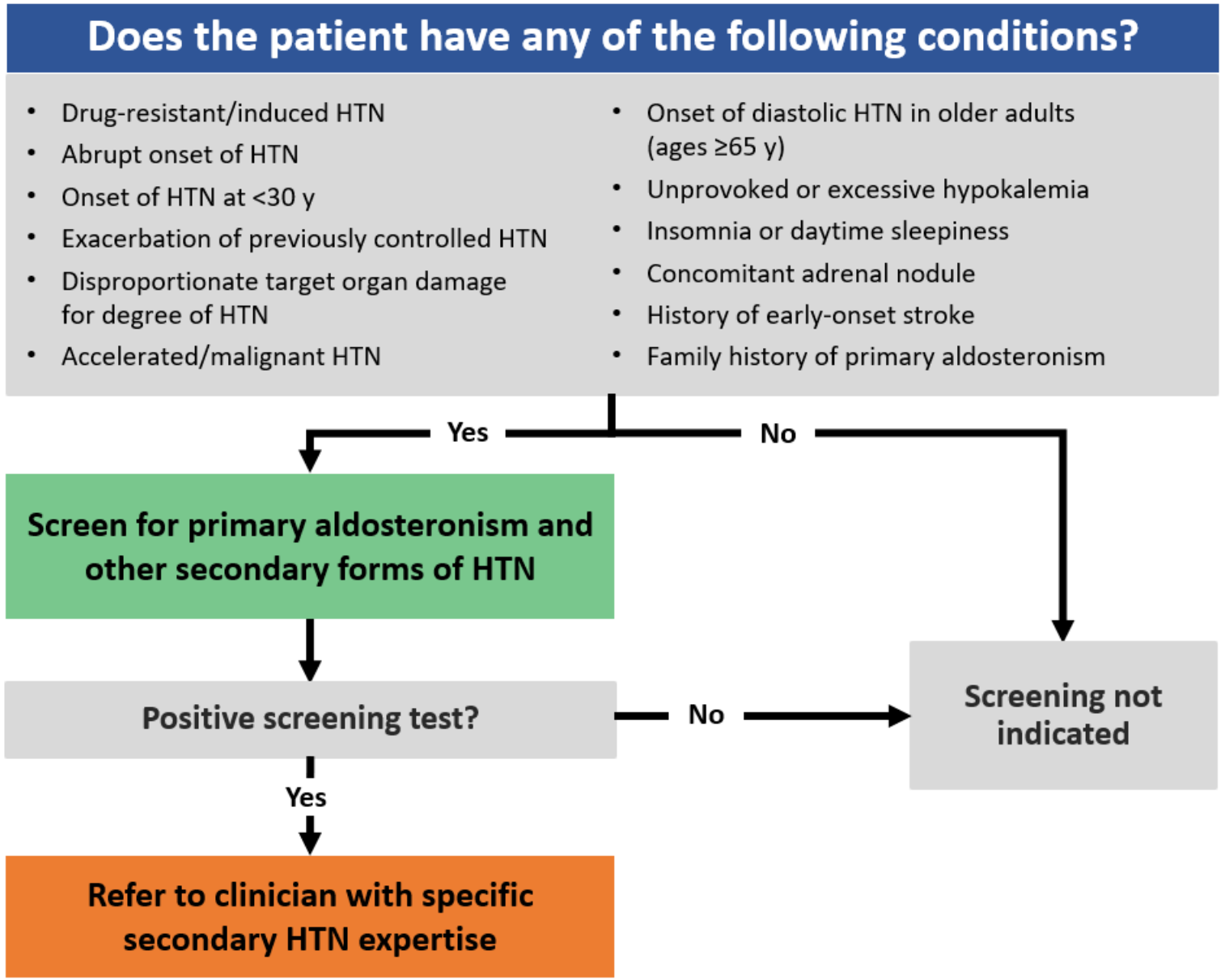
High risk:

5-8 points

Secondary Forms of Hypertension

ACC/AHA 2025 Secondary Causes:

Screening for Primary Aldosteronism is First Consideration



Source: AHA/ACC

Endocrine Society 2025 Guideline: How to Screen for Aldosteronism

- Measure plasma renin activity (PRA), aldosterone, and potassium
- Measure seated, in the morning
- Avoid dietary Na+ restriction for several days before testing
- Ideally hold MRA's, amiloride, triamterene, clonidine, 2-4 weeks before testing, but not absolutely required.
- A positive screen is:
  - PRA < 1
  - Aldosterone > 7.5-10 (depending on the assay type)
  - Aldosterone/PRA ratio > 20-70 (depending on assay type)
- Discusses meds that may cause false positive or negative results

Journal of Clinical Endocrinology & Metabolism, 2025, 110, 2453

Endocrine Society Controversial Guideline 2025

- Advises screening for primary aldosteronism in all patients with hypertension
- Not just those with TRH, hypokalemia, or other indication to screen
- Based on the premise that selected patients with aldosteronism will benefit more from a workup to find a lateralizing adrenal mass followed by adrenalectomy
- Rather than simply a trial of a mineralocorticoid antagonist (i.e. spironolactone) first
- Based on a single retrospective study that showed that screening for aldosteronism lowers sbp by 1.5 mm Hg
- And data indicating fewer CVD events among patients with aldosteronism who underwent adrenalectomy rather than MRA therapy alone long-term
- Despite no difference in HTN remission, CVD events, and CV mortality between patients who receive MRA and adrenalectomy

Screen for Rarer Causes of TRH only if Clinical Features Suggest Possibility

Common Causes

- Pseudo-hypertension
- OSA – in as many as 25-50% of patients with TRH
- Primary aldosteronism 5-25%
    - Only ½ of patients will have spontaneous hypokalemia
- CKD 15%
- Drug or alcohol related

Rarer Causes

- Renovascular <5%
- Hyperthyroidism < 1%
- Pheochromocytoma <0.6%
- Cushing's syndrome < 0.1%
- Aortic coarctation

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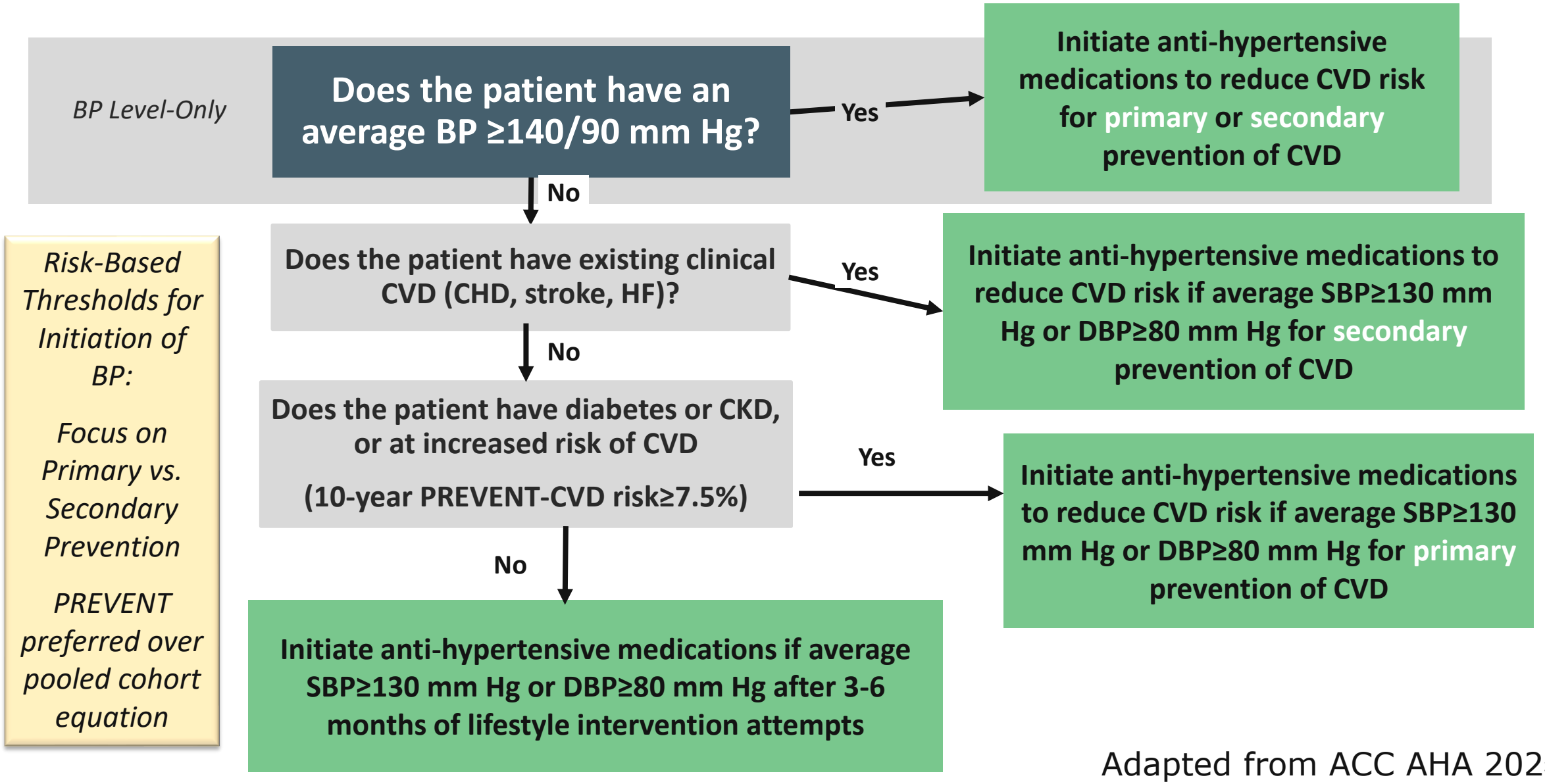
Question #5: What is the optimal sequential approach to pharmacotherapy in TRH?

Don’t Forget to Reinforce Lifestyle Modification

- DASH type diet (high in veggies, fruits, low fat dairy, whole grains, poultry, fish, nuts – similar to Mediterranean diet)
- Reduced Na+ intake
- Increase K+ intake if no significant CKD or meds that may cause hyperkalemia
- Weight loss if overweight or obese
- Regular exercise – ideally 40 minutes at least 3x per week
- Moderate alcohol for those who drink
- Occasionally, stress management can help
- Can employ colleagues and team members in your office to do some of this teaching, along with printed or web-based instructional materials

New for ACC AHA 2025: PREVENT Risk Based Thresholds for Initiation of BP Treatment: Primary vs. Secondary Prevention



Adapted from ACC AHA 2025

Resistant Hypertension: Treatment Strategies

- Effective combinations
  - ACEi/diuretic
  - ACEi/CCB
- Change HCTZ to chlorthalidone
- Add spironolactone
- Add furosemide if CKD

- Third line strategies for severe essential hypertension
  - Labetalol ***
  - Carvedilol
  - Clonidine
  - Dual CCB's
  - Hydralazine
  - Minoxidil

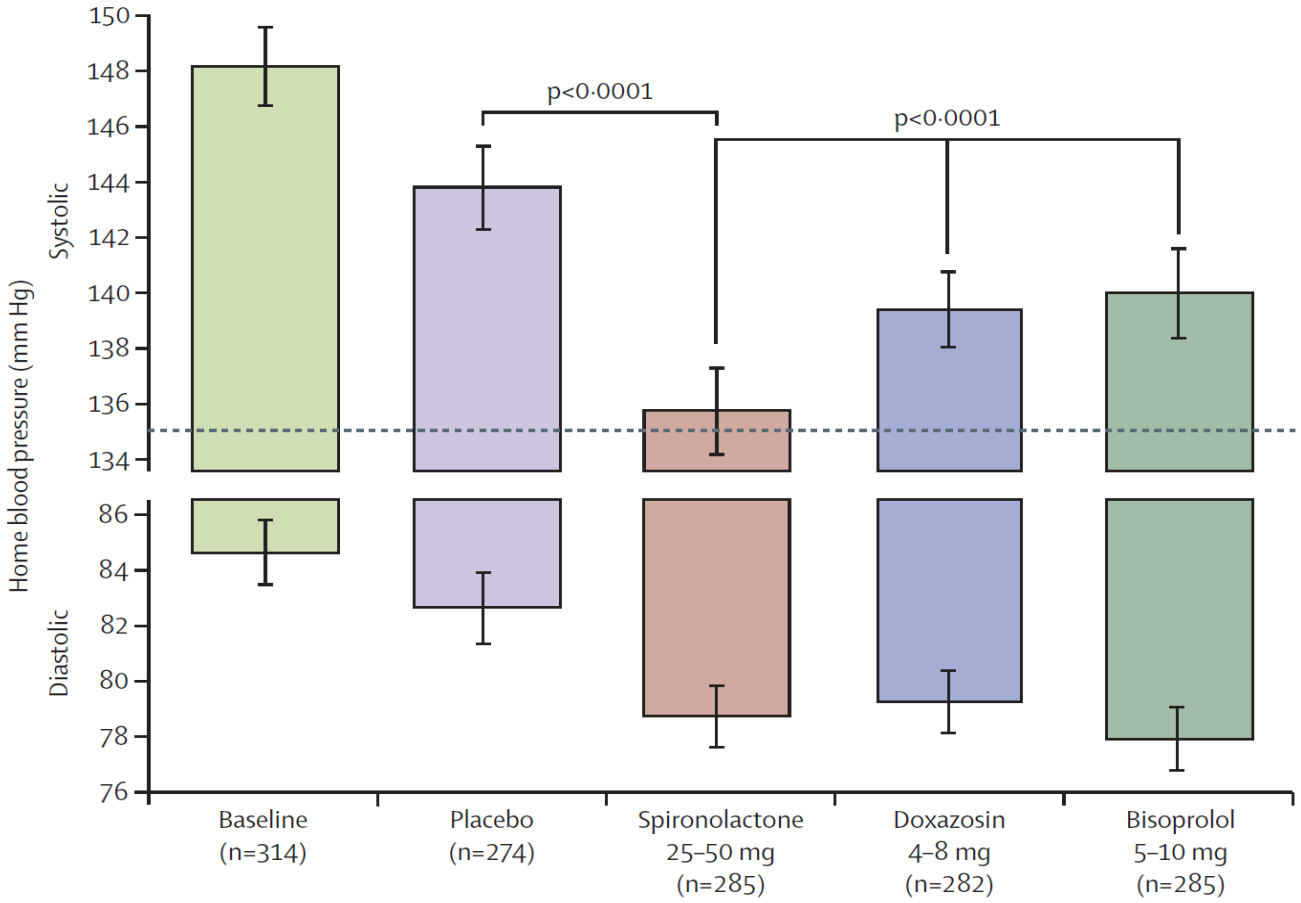
RCT: Spironolactone Superior to Bisoprolol and Doxazocin for Resistant Hypertension

N = 335

Resistant bp despite max tolerated of 3 drugs (ACEi or ARB, CCB, and Thiazide)

Rotated through each of 3 drugs as add-on Rx over 6 and 12 weeks

Note: 2% incidence of K^+ > 6.0



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Lancet: 2015;386:2059

Systematic Review: Spironolactone is Superior to Placebo, and Comparable to Other Drugs, and Renal Denervation in SBP Reduction in Treatment Resistant Hypertension

Medicine 2020;99:34

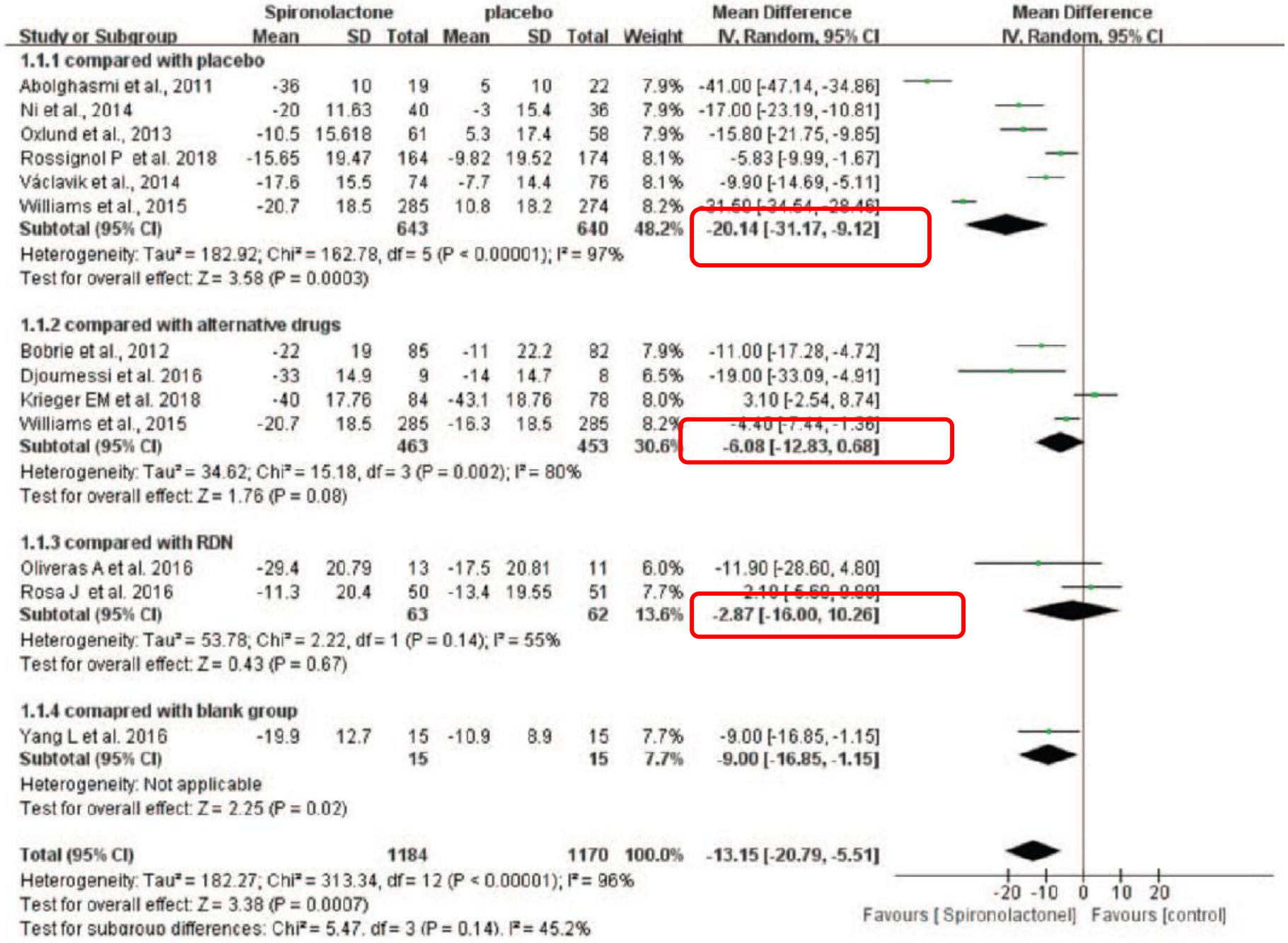

Figure 4. Forest plots comparing the office SBP between the spironolactone group and other groups.

ACC/AHA 2018 Guideline: Resistant Hypertension Management

Step 1	• Exclude white coat, 2nd causes. Maximize 3-drug regimen
Step 2	• Substitute chlorthalidone or indapamide for HCTZ
Step 3	• Add spironolactone or eplerenone
Step 4	• If HR > 70 add beta blocker or labetalol
Step 5	• Add hydralazine
Step 6	• Substitute minoxidil

Hypertension 2018;72:e53

Updated Management of Resistant Hypertension (ACC/AHA 2025)

Resistant Hypertension

- Office BP ≥ 130/80 on ≥ 3 antihypertensives (ACEi/ARB + CCB + thiazide diuretic)
- Office BP < 130/80 but requires ≥ 4 antihypertensives

Workup and Address Potential Causes

- Exclude pseudo-resistance (ambulatory BPs, medication adherence)
- Review and remove interfering medications
- Screen for secondary causes (primary aldosteronism, OSA, renal parenchymal disease and renovascular disease, etc.) Class 1

Contraindications or Intolerant of MRA?

No

Add MRA

In adults with uncontrolled resistant hypertension despite optimal treatment with first-line antihypertensive therapy and with an eGFR of ≥45 ml/min/1.73 m^2 Class 1

Yes

Adding an alternative second line agent is reasonable to control BP

- Amiloride
- Beta Blocker
- Alpha Blocker
- Class 2a
- Central sympatholytic drug
- Dual endothelin receptor antagonist
- Direct vasodilator

AHA/ACC Guidance on Medication Choices for TRH

1. Maximize diuretic Rx
2. Change HCTZ (if taking) to chlorthalidone or indapamide
3. Add spironolactone 25-50 mg qd (if tolerated) or eplerenone 25-50 mg bid if eGFR ≥ 45
4. If neither tolerated, add amiloride instead
5. Use chlorthalidone or loop diuretics if CKD stage 4 or greater (eGFR < 30)
6. Add drugs with different mechanism of action: beta blockers, central sympatholytic or non-dihydropyridine CCB if elevated HR
7. Add potent vasodilators: aprocitentan, hydralazine, or minoxidil, along with loop diuretic

Hypertension. 2025;82:e212–e316

Amiloride is as Effective as Spironolactone in TRH

- 112 adults with TRH despite fixed dose triple med with olmesartan, HCTZ, and amlodipine
- Randomly assigned to addition of spironolactone or amlodipine
- Primary endpoint SBP at 12 weeks
- SBP reductions:
  - Amiloride 13.6 mm Hg
  - Spironolactone 14.7 mm Hg
- Conclusion: Amiloride is an appropriate 4th line option for TRH in patients who cannot tolerate MRAs such as spironolacton

JAMA 2025;333;(23):2073

ACC/AHA 2025 Class of Recommendations for Resistant HTN

COR	Level of Evidence	Recommendation
1	B-NR	A more detailed evaluation for **secondary causes**, careful review of all medications and removal of those with interfering effects on BP, is beneficial for lowering BP
1	B-R	If resistant hypertension despite optimal treatment with first-line therapy (ie, a combination of ACEi or ARB plus CCB and thiazide-like diuretic [chlorthalidone or indapamide] and with an eGFR of ≥45, **addition of a MRA** is recommended to control BP
2a	B-NR	In patients who cannot tolerate or have contraindications to MRA, **add one of the following agents or classes**— amiloride, BBs, alpha-blockers, central sympatholytic drugs, dual endothelin receptor antagonists, or direct vasodilators

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Question #6: What is New in Medications for Resistant Hypertension?

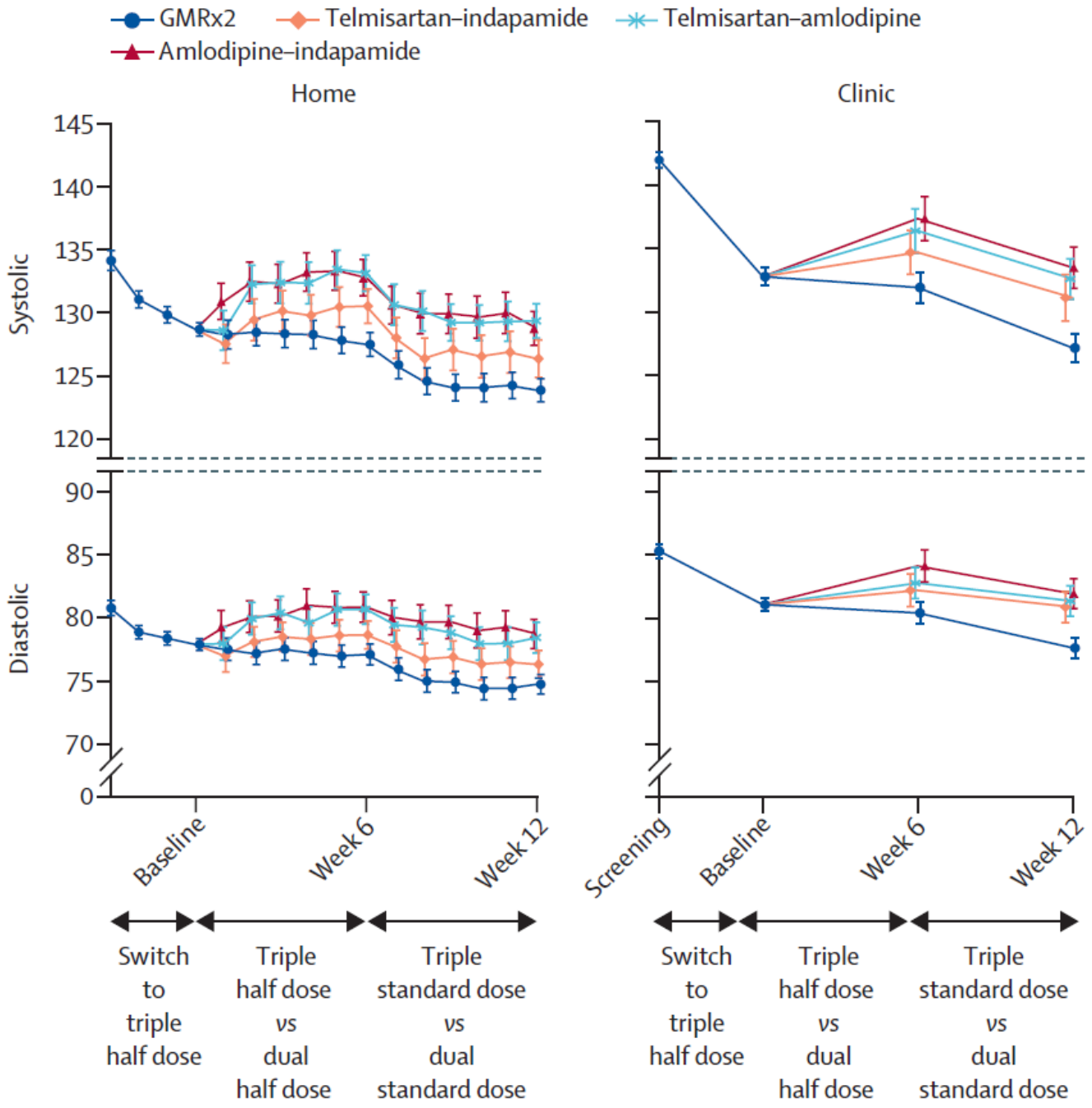
New Drug Option to Improve Adherence and BP? The First Triple Pill Containing Indapamide

- 1385 patients with untreated stage 2 hypertension or resistant hypertension
- Stopped taking all currently used medications
- Switched to GMRx2: a triple pill of telmisartan, amlodipine, indapamide at one half full dose
- Randomly assigned to double or triple pills
- Doses doubled at 6 weeks
- Primary outcome home sbp change
- Secondary outcome adverse events
- Mean baseline bp 142/85

Lancet 2024;404:1536

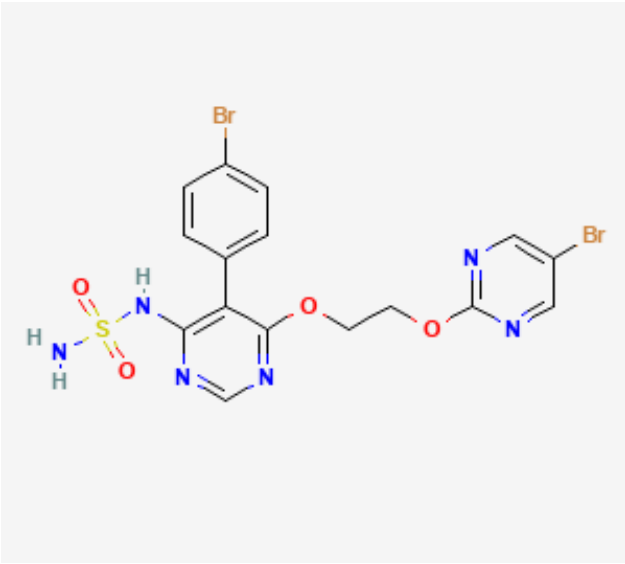
BP Lower with Triple Pill Compared to Each Double Pill Strategy

- Home sbp 2.5-5.5 mm Hg lower for triple pill than double pills
- No difference in Rx d/c due to adverse events between groups
- Modestly higher rates of symptomatic hypotension (6% vs. 1-4%)
- FDA approved June 2025
- Cost not yet disclosed
- (WIDAPLIK ®)

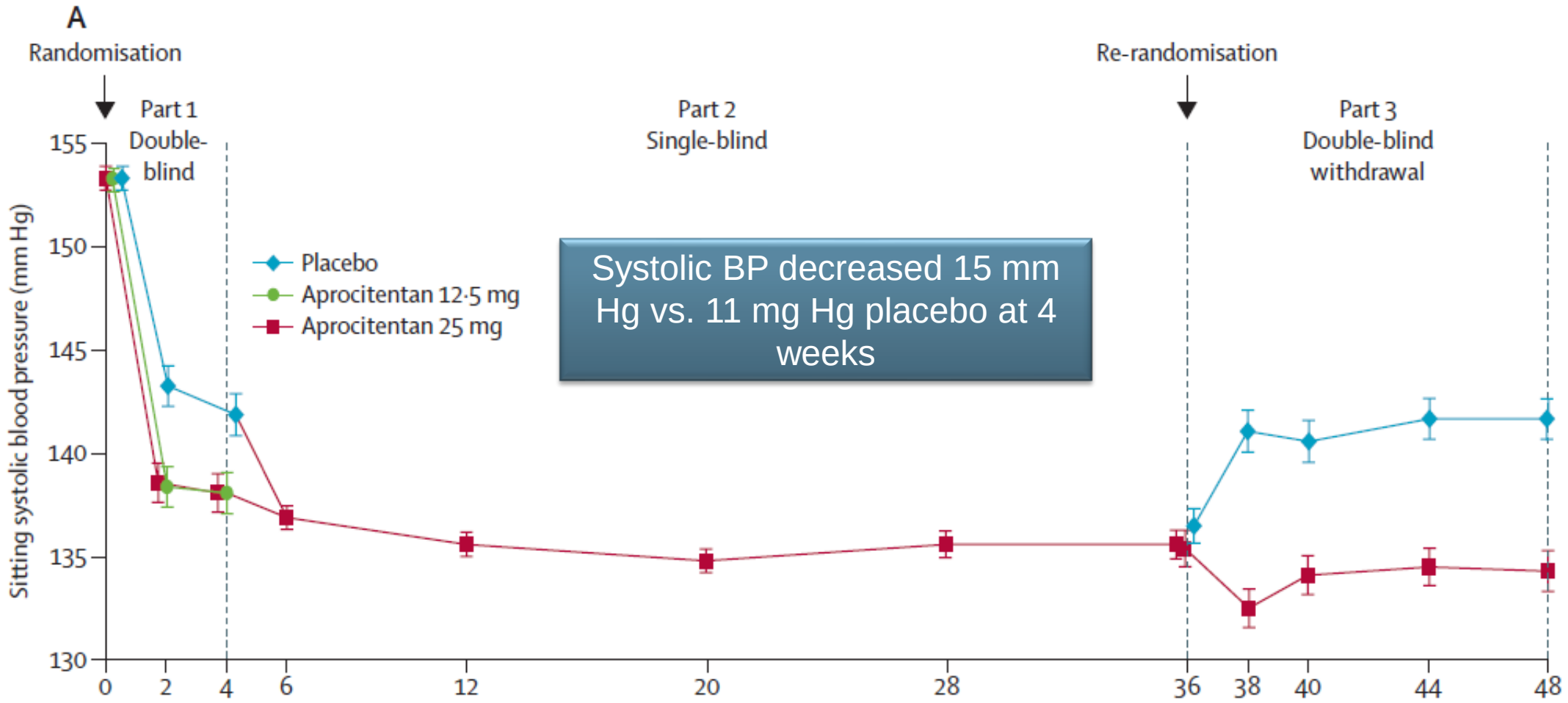


Aprocitentan is a Novel Dual Endothelin Receptor Antagonist for Resistant Hypertension

- Endothelin (ET-1) can cause vasoconstriction, fibrosis, inflammation, sympathetic activation
- Aprocitentan inhibits binding of ET-1to the ET_A and ET_B receptors
- Related to bosentan and other drugs used for Rx of pulmonary hypertension
- Half life of 48 hours
- Well tolerated in phase 2 dose-finding trials



PRECISION Trial: Aprocitentan was More Effective than Placebo in TRH but Absolute Effect was Modest



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Lancet 2022;400:1927

Aprocitentan is Much More Expensive than Other Drugs Used for Resistant Hypertension

Drug	Cost for 30-day supply
Indapamide 2.5 mg	$7
Spironolactone 50 mg	$4
Labetalol 200 mg bid	$8
Hydralazine 100 mg bid	$8
Minoxidil 2.5 mg bid	$14
Aprocitentan 12.5 mg	$800

FDA Approved 2024 for Resistant Hypertension

- Aprocitentan reduces systolic and diastolic bp only modestly by mean of 4 mm Hg in resistant hypertension
- Potential teratogenic risk: contraindicated if pregnancy possible
- Periodic LFT monitoring required
- Fluid retention is common (12-20%)
- Cost is a substantial barrier ($800 per month)
- This is another potential 4th line option for resistant HTN
- Has not been studied in direct comparison to spironolactone
- Labetalol and spironolactone should be tried first

On the Horizon: Aldosterone Synthase Inhibitors

- Lorundrostat is a selective aldosterone synthase inhibitor
- Has potential to provide same benefits as MRAs in TRA without the side effects of MRA such as gynecomastia.
- In a placebo-controlled phase 2 RCT (n=285), at 12 weeks reduced bp by mean of 7.9 mm Hg compared to placebo
- Severe hyperkalemia > 6.0 occurred in 5-7% of patients
- Similar results in the Target-HTN RCT
- Submitted to FDA Jan. 2026, may be approved this year
- Another aldosterone synthase inhibitor, baxdrostat, provided similar benefit with lower rates of hyperkalemia

NEJM 2025;392:1813 JAMA 2023;330:1140 NEJM 2025;393:1363

A Completely Novel Rx Approach: SC Injection of Interfering RNA: Zilebesiran

- Zilebesiran is a small interfering RNA that binds to hepatic receptors and reduces angiotensinogen messenger RNA thus reducing angiotensin levels
- Given as an infrequent SC injection
- Prolonged duration of action (up to 6 months) with single injection
- May be promising to improve adherence in challenging patients with TRH
- Previously shown in smaller studies to be effective as monotherapy in patients with hypertension and when given in combination with an ARB with side effects comparable to placebo*

*N Engl J Med 2023;389:228

KARDIA-2 RCT of Zilebesiran for Inadequately Controlled HTN

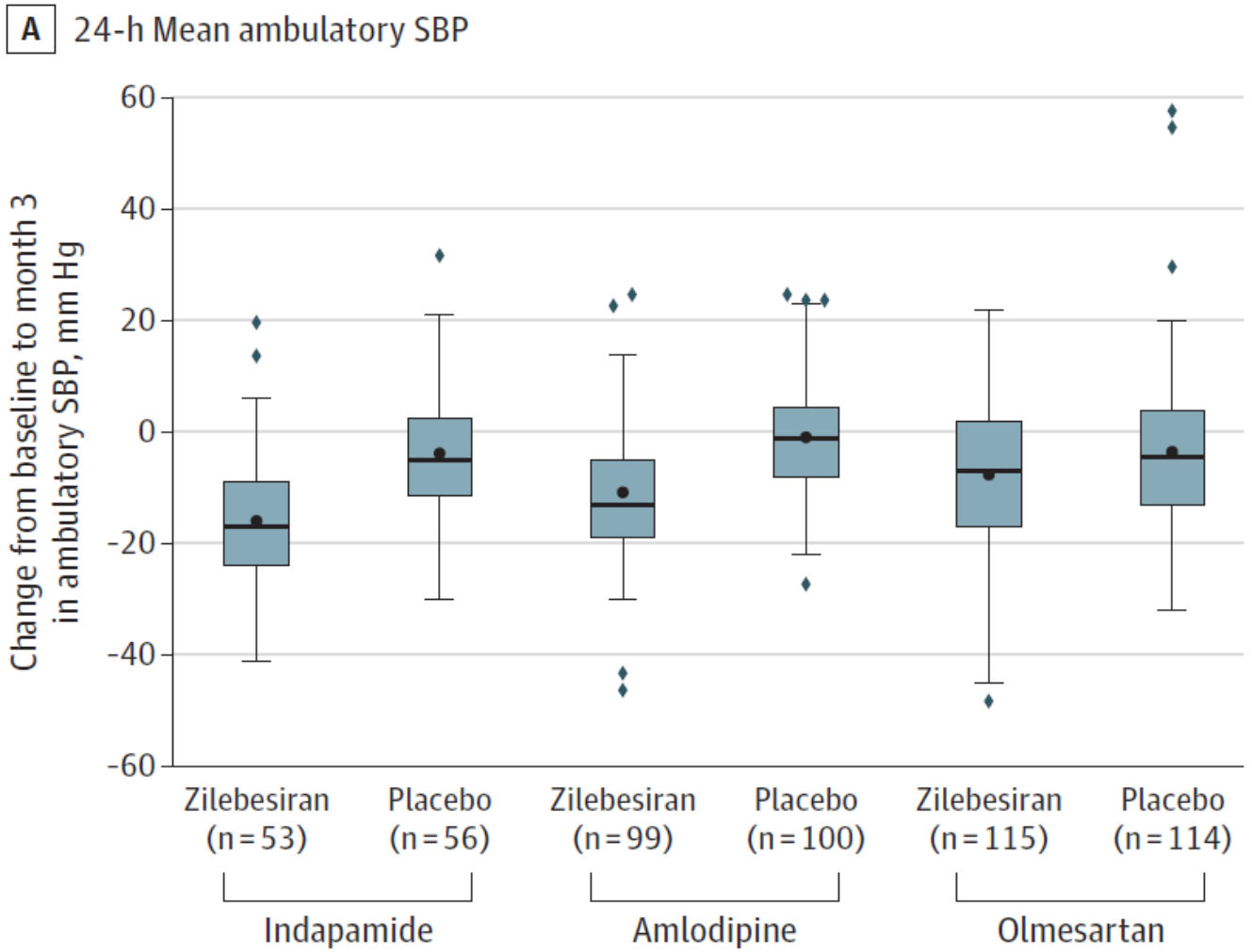
- 663 patients, aged 18-75 years, with uncontrolled hypertension (sbp 155-180 mm Hg) despite 1 or 2 drugs
- Excluded those with secondary hypertension, baseline K+ > 5.0, eGRFR < 30, HF, poorly controlled diabetes
- 4- week run in period with random assignment to monotherapy with indapamide, amlodipine, or olmesartan at moderate doses (no placebo group for oral monotherapy)
- Followed by random assignment to a single SC injection of zilebesiran 600 mg or placebo
- Rescue Rx with conventional meds allowed beginning at 3 months
- Primary outcome was change in 24-hour mean SBP at 3 months
- Trial too brief to measure CV outcomes

JAMA 2025 Jul 1;334(1):46

Zilebesiran Significantly Reduced SBP in all 3 Arms when compared to Placebo

- Mean reduction in SBP when zilebesiran was added to each monotherapy option (difference compared to placebo):

- Indapamide -12.1 mm Hg
- Amlodipine -9.7 mm Hg
- Olmesartan -4.5 mm Hg



Minor to Moderate Adverse Effects: Pooled Data from all Three Oral Monotherapy Arms

AE	Zilebesiran	Placebo
Injection site reaction	3.0	0.3
Orthostatic hypotension	4.3	2.1
K+> 5.0 confirmed on repeat	1.5	0
eGFR decrease by ≥ 30% confirmed on repeat measure	2.4	0.9
ALT > 3x ULN	2.1	0.6

- Impact: Zilebesiran holds great promise for second line Rx, and potentially TRH, when given with diuretic or CCB, but not ACEi or ARB
- Await more safety data in ongoing phase 3 trial.
- Can be dosed twice yearly for improved adherence
- Not yet FDA approved. Cost may be a factor

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Question #7: Does renal artery denervation work?

Renal Denervation: Conflicting Results

- Catheter-based RFA or catheter-based ultrasound ablation have both been studied
- Does not require a diagnosis of renovascular hypertension
- In short term trials of patients NOT on antihypertensive medications, benefits were modest
- Average bp reduction of 4-6/2-4 mm Hg at 2-3 months
- In a trial for patients with treated hypertension (but not TRH), greater benefit seen: 10/6 mm Hg reduction at 6 months
- Two large RCTs have compared denervation to sham Rx for TRH
- First FDA approved device in 2023

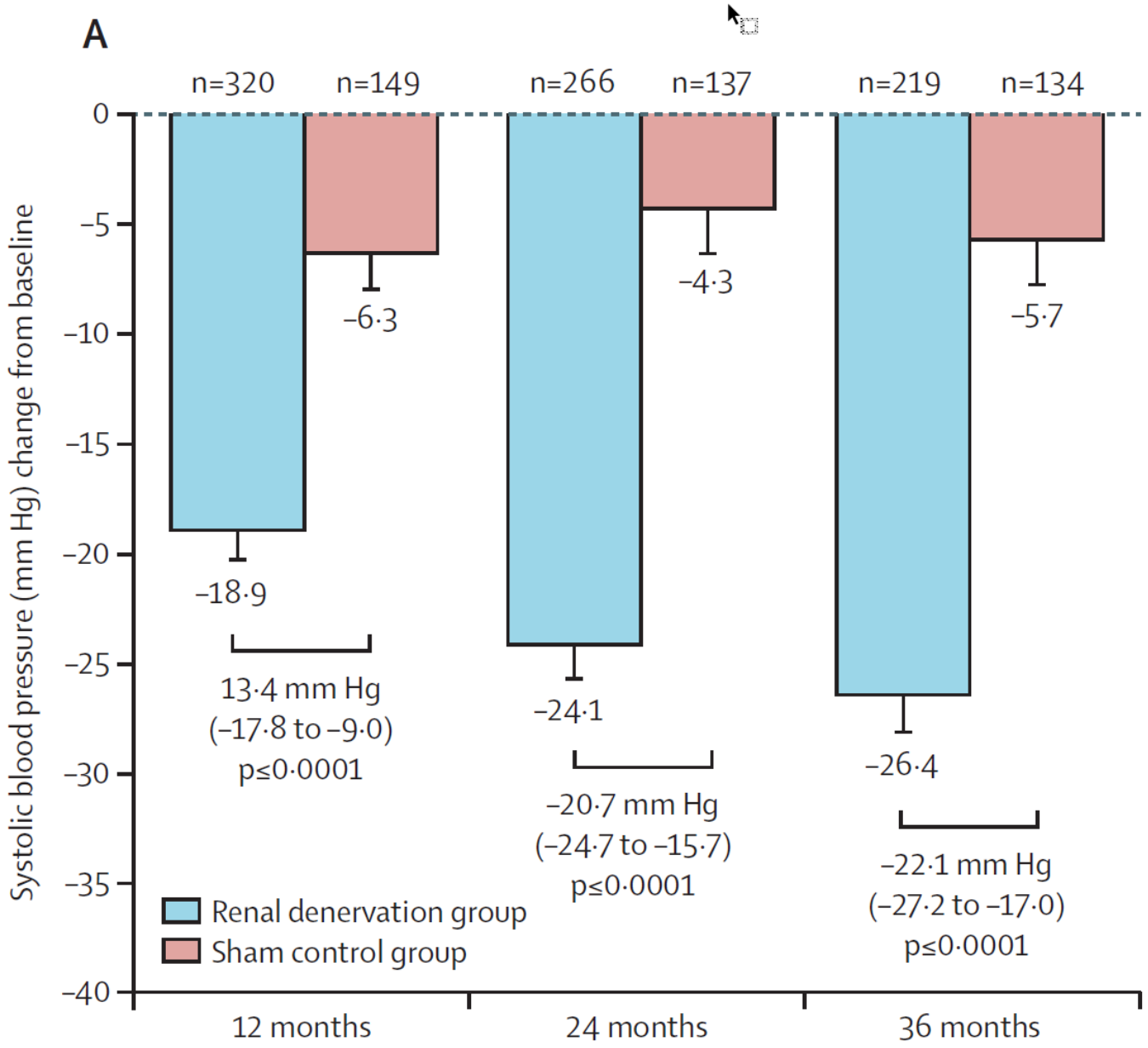
SYMPLICITY HTN-3: The Largest RCT of Renal Denervation in Treatment Resistant Hypertension

- 535 adults with TRH, 3 drugs including a diuretic
- Office sbp ≥ 160 mm Hg, 24-hour ABPM sbp ≥ 135 mm Hg
- Actual mean ABPM sbp at study entry was 161 mm Hg
- Excluded patients with secondary hypertension, renal artery stenosis > 50%
- Random assignment to catheter based RFA renal denervation or sham renal angiography alone
- Primary endpoint was change in office sbp at 6 months
- Crossover allowed after Rx unmasking at 6 months
- Additional followup data for 3 years after Rx

Lancet 2022; 400: 1405–16

Significant and Clinically Meaningful Reduction of office sbp > 20 mm Hg Compared to Sham by 2 years of followup

(Reduction in 24 hr ABPM sbp at 3 years was 16.5 mm Hg)



Favorable Safety Profile that Extended to 36 Months

- Composite safety outcome, death from any cause, hypertensive crises:
- All similar between denervation group, sham crossover, and sham non-crossover
- New onset ESRD more common in active Rx group (3% vs. 0%)
- Only one vascular complication and 3 renal artery re-interventions among 359 subjects receiving denervation

Meta-Analysis of 15 RCTs of Renal Denervation in TRH

- Total n = 2581
- Effects on sbp were more modest among 9 trials of patients with TRH on anti-hypertensive therapy than in SYMPLICITY 3
- Pooled results:
  - 6.4 mm Hg reduction in office sbp
  - 2.7 mm Hg reduction in 24-hour ABPM night-time sbp
- No difference in total number of required anti-hypertensive meds at 6 months
- No major procedural complications in any of the trials

J Am Heart Assoc. 2024;13:e034910

2024 AHA Scientific Statement: Candidate Selection for Renal Denervation

- All patients
  - Exclude white coat HTN with home values
  - Screen for CKD and aldosteronism
  - Maximize lifestyle modification
  - Shared decision making given modest benefits of denervation
- TRH
  - An option for TRH despite at least 3 medications
  - Bp not at goal and not able to tolerate additional meds
- Contraindications
  - Pregnancy, fibromuscular dysplasia, renal artery stent or significant stenosis
- Areas of uncertainty due to limited data
  - Stage 1 HTN, isolated systolic HTN, Stage 4 or 5 CKD

Hypertension. 2024;81:e135–e148

2025 ACC/AHA Final Recommendation for Renal Denervation

- Level 2b recommendation
- Consider in carefully selected patients with systolic and diastolic elevations
- Pseudo-hypertension, white coat, and secondary causes excluded
- eGFR ≥ 40
- TRH despite optimal medical Rx
- OR unable to tolerate optimal Rx due to side effects
- Renal denervation may be reasonable as an alternative to additional medications
- Only in specialty multi-disciplinary settings
- Shared decision making

Hypertension. 2025;82:e212–e316

7 Questions: What have We Learned that will Change Practice?

1. Treatment resistant HTN is bp > 130/80 despite three drugs including a diuretic
2. Ensure that measurement technique is proper, inquire about meds that may increase bp, rule out white coat hypertension with 24-hour ABPM
3. The most common causes of apparent TRH are pseudo-hypertension, obstructive sleep apnea, aldosteronism, and CKD
4. Initial workup for all patients with aTRH should include STOP BANG screen, baseline creatinine, a review of medication and alcohol use, and labs to screen for aldosteronism
5. For true TRH on 3 meds, the next drug should be spironolactone. Other options are eplerenone, amiloride, labetalol
6. New drug options include a triple pill to improve adherence, and a novel endothelin inhibitor: aprocitentan. Soon on the horizon: aldosterone synthase inhibitors, and interfering RNA injections.
7. The effect of renal artery denervation is modest. A 4th line option mostly for patients with multiple med intolerances. Requires a multidisciplinary team

A Final Thought Known to us All…

"The clinician must be able to tell the antecedents, know the present, and foretell the future — must mediate these things, and have two special objects in view with regard to disease, namely, to do good or to do no harm."

Hippocrates

from "Of the Epidemics," c. 420 BCE