CARDIOVASCULAR NURSING SYMPOSIUM

Hypertension: Responsive versus Resistant

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Objectives

1. Discuss detection and management of hypertension through screening
2. Review guideline directed medical therapy for responsive hypertension
3. Explore guideline directed medical therapy for non-responsive resistant hypertension

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RESISTANT HYPERTENSION (RHT)

RESISTANT HYPERTENSION

- Uncontrolled blood pressure (BP) ≥ 130/80 mm Hg despite concurrent prescription of ≥ 3 or ≥ 4 antihypertensive drugs in different classes or controlled BP despite prescription of ≥ to 4 drugs, at maximally tolerated doses, including a diuretic.

Carey RM et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. Hypertension. 2018 Nov;72(5):e53-e90. doi: 10.1161/HYP.0000000000000084. PMID: 30354828; PMCID: PMC6530990.

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RESISTANT HYPERTENSION

PSEUDORESISTANCE

- Suboptimal blood pressure control secondary to medication nonadherence, white-coat effect, or poor measurement technique.

APPARENT RESISTANCE

- *Apparent treatment-resistant hypertension (aTRH)* is the term used in epidemiologic studies to refer to cases in which patients meet the criteria for resistant hypertension but have unverified adherence or medication dosing or have not undergone out-of-office blood pressure monitoring to rule out the white-coat effect.

Carey RM et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. Hypertension. 2018 Nov;72(5):e53-e90. doi: 10.1161/HYP.0000000000000084. PMID: 30354828; PMCID: PMC6530990.

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aTRH

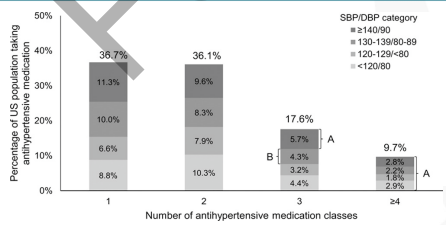
- 10.3M US Adults have aTRH
- Among US Adults Taking Antihypertensive Meds, 19.7% have aTRH
- Adults with aTRH were older, more likely to be non-Hispanic black, and more likely to have diabetes mellitus, CKD, ACR >30 mg/g, eGFR <60 mL/min per 1.73 m^2, a 10-year predicted ASCVD risk ≥20%, or a history of CVD compared with those without aTRH

Robert M. Carey. Hypertension. Prevalence of Apparent Treatment-Resistant Hypertension in the United States, Volume: 73, Issue: 2, Pages: 424-431, DOI: (10.1161/HYPERTENSIONAHA.118.12191)

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ANTIHYPERTENSIVE MED USE



Robert M. Carey. Hypertension. Prevalence of Apparent Treatment-Resistant Hypertension in the United States, Volume: 73, Issue: 2, Pages: 424-431, DOI: (10.1161/HYPERTENSIONAHA.118.12191)

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STEP 1: CONFIRM RESISTANT HTN

Office blood pressure above goal on at least 3 antihypertensive medications (typically ACEi or ARB, diuretic, and calcium channel blocker

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Confirm with out-of-office monitoring (ABPM or SMBP)

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START WITH PROPER BP MEASURMENT TECHNIQUE



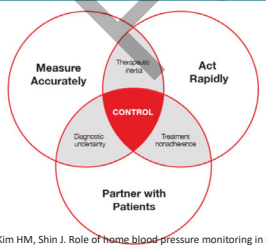
- Triage BP technique overestimated prevalence of uncontrolled TRH in 1/3 of patients
- About 1/3 of patients referred for aTRH have BP values well controlled at ABPM.
- "Spurious" (or "white-coat") TRH is associated with a better prognosis as compared to "true" TRH.

Bhatt H, Siddiqui M, Judd E, Oparil S, Calhoun D. Prevalence of pseudoresistant hypertension due to inaccurate blood pressure measurement. J Am Soc Hypertens. 2016 Jun;10(6):493-9. doi: 10.1016/j.jash.2016.03.186. Epub 2016 Mar 30. PMID: 27129931; PMCID: PMC4905807.

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SO, WHAT'S THE ROLE OF HMBP?



THERAPEUTIC INERTIA

SELF-MANAGEMENT

SHARED DECISION MAKING

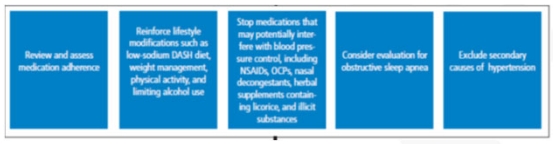
Kim HM, Shin J. Role of home blood pressure monitoring in resistant hypertension. Clin Hypertens. 2023 Jan 15;29(1):2. doi: 10.1186/s40885-022-00226-1. PMID: 36641498; PMCID: PMC9840827.

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STEP 2: RULE OUT PSEUDORESISTANCE



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STEP 3: OPTIMIZE MEDS

Optimize medications including dosing at maximal or maximally tolerated doses
Chlorthalidone or indapamide are preferred thiazide-like diuretics
Short-acting loop diuretics should be dosed at least twice daily
Avoid dual ACEi/ARB therapy

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STEP 4: ADDITIONAL AGENT

Add MRA (spironolactone preferred, eplerenone if not tolerated)

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STEP 5: ADDITIONAL AGENTS

Additional agents:

Vasodilatory beta-blockers are first-line therapy if compelling indications are present

Central alpha-receptor agonists such as clonidine patch or guanfacine, a longer-acting agent

Alpha-receptor antagonists such as prazosin, doxazosin, or terazosin

Vasodilators hydralazine or minoxidil

Expert Opinion

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AFTER 30+ YEARS …



FDA Okays New Drug for Resistant Hypertension

Megan Brooks
March 20, 2024

The US Food and Drug Administration (FDA) has approved aprocitentan (Tryvio) to lower blood pressure, in combination with other antihypertensive agents, in adults with treatment-resistant hypertension.

Aprocitentan is the first endothelin receptor antagonist approved for patients with hypertension. The recommended dose is 12.5 mg orally once daily, with or without food.

The efficacy and safety of aprocitentan were demonstrated in the phase 3 PRECISION study of 730 adults with systolic blood pressure ≥ 140 mmHg who were prescribed at least three antihypertensive medications.

Aprocitentan (12.5 mg daily) was well tolerated and statistically superior to placebo in lowering blood pressure at 4 weeks, with a sustained effect at 40 weeks.

Subgroup analyses showed that the blood pressure–lowering effect of aprocitentan appeared to be consistent among subgroups defined by age, sex, race, body mass index, baseline estimated glomerular filtration rate, baseline urine albumin-to-creatinine ratio, and medical history of diabetes, as well as between blood pressure measurement methods.

Aprocitentan

- Black-box warning regarding embryo–fetal toxicity (based on birth defects in animal studies)
- Available through a program called Risk Evaluation and Mitigation Strategy (REMS) restricted program

https://www.jwatch.org/na57341/2024/04/11/aprocitentan-newly-approved-drug-resistant-hypertension

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Patient Case #1

B.K.

Patient Case – Pseudoresistance
- Adherence, lifestyle, concurrent med issues?





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ADHERENCE

Estimated that 50% of patients do not take their medications as prescribed

Poor adherence leads to poor outcomes
- Disease state progression
- Increased healthcare costs
  - Provider visits, medications, hospital stays, lab testing
- Mortality

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BARRIERS TO MEDICATION ADHERENCE

- Access
  - Cost & Transportation
- Side effects
- Time Management
- Beliefs
  - Medication Related
  - Condition Related
- Trust

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ASSESSING MEDICATION ADHERENCE

- Ask patient to bring medication bottles to visit
  - If video visit, have patient show the medications
- **AVOID YES/NO questions,** use open ended questions
  - Tell me about your…
    - Blood pressure, medications, etc
  - How do you …
    - Check your blood pressure, manage your medications
  - What were told to expect from this medication?

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MEDICATIONS CAN INTERFERE WITH BP CONTROL

Prescription Medications

- Myrbetriq (Mirabegron)
- Antidepressants
  - SNRIs (Venlafaxine, Duloxetine), Bupropion
- Atypical Antipsychotics
  - Clozapine, Olanzapine
- Systemic Corticosteroids
- Chemotherapy / Immunosuppressive agents
  - Cyclophosphamide, Tacrolimus, Cyclosporine, Anastrozole, Letrozole

Over-the-Counter Medications & Supplements

- NSAIDs
- Decongestants
  - Pseudoephedrine, Phenylephrine
- Alcohol
- Caffeine
- Supplements
  - Ginseng, Licorice, St. Johns Wort, Vitamin E
- Illicit substances

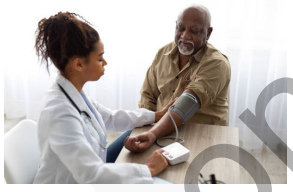
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Patient Case #2

J.B.

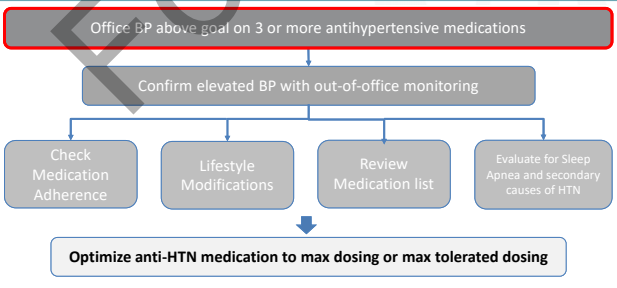
Patient Case #2 – HTN resistance on 3 maxed out meds with intolerability to one of the first line agents



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RESISTANT HTN



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RESISTANT HTN

Patient is on 3 drugs from each class, at the max dose, still with uncontrolled HTN

ACEI/ARBs
- Lisinopril
- Ramipril
- Losartan
- Valsartan
- Olmesartan

Thiazide Diuretics
- Hydrochlorothiazide
- Chlorthalidone

Calcium Channel Blockers*
- Dihydropyridine agents

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ANTI-HTN TREATMENT
ACEi/ARBs

Class	Medication	Initial dose, Max Daily Dose	Side effects and dosing considerations
ACEis	Lisinopril	5-10mg, 40mg	• Hyperkalemia • Renal function • Dizziness • Dry cough (ACEis) • Teratogenic– avoid in pregnancy and females of child-bearing age • DDIs: Lithium, Potassium sparing diuretics, ARNIs (Entresto), NSAIDs
	Ramipril	2.5mg, 20mg in 1 – 2 divided doses	
ARBs	Losartan	25-50mg, 100mg	
	Valsartan	80mg, 320mg	
	Olmesartan	20mg, 40mg	

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ANTI-HTN TREATMENT
Calcium Channel Blockers & Thiazide Diuretics

Class	Medication	Initial dose, Max Daily Dose	Side effects and dosing considerations
CCB's	Amlodipine	2.5mg, 10mg	• Lower extremity edema • Constipation • Avoid use in patients with HFrEF • DDI's: Simvastatin
	Nifedipine **ER**	30mg, 90mg	
Thiazide Diuretics	Hydrochlorothiazide	12.5mg, 50mg	• Electrolytes: Hyponatremia, Hypokalemia • Hyperuricemia • Diuresis reduced in CrCl <30 ml/min • DDI's: Avoid in those with a sulfa allergy, Lithium, Digoxin, NSAIDs
	Chlorthalidone	12.5mg, 25mg	
	Indapamide	1.25mg, 2.5mg	

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RESISTANT HTN

If patient on 3 drugs from each first line class (ACEi/ARB, CCB, Thiazide Diuretic), at the max dose or max tolerated dose, with BP still above goal

Considerations before adding a 4th agent!

Add 4th agent

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ANTI-HTN TREATMENT
Tips and Tricks to Trial before adding a 4th agent!

- **Consider switching to a more potent agent within the same medication class**
  - Losartan → Valsartan
  - HCTZ → Chlorthalidone or Indapamide (if eGFR > 30ml/min/1.73m^2)
- **Review lab values to ensure appropriate agents**
  - Thiazide diuretics natriuresis reduced with decreased renal function
    - HCTZ; eGFR <45ml/min/1.73m^2
    - Chlorthalidone: eGFR <30ml/min/1.73m^2
  - Long-acting loop diuretic (torsemide) preferred over Thiazide diuretics (or in addition to) when eGFR <30ml/min/1.73m^2 or when fluid overload

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RESISTANT HTN

If patient on 3 drugs from each first line class (ACEi/ARB, CCB, Thiazide Diuretic), at the max dose or max tolerated dose, with BP still above goal

Add 4th agent: *Mineralocorticoid receptor antagonist*
(Spironolactone, Eplerenone)

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ANTI-HTN TREATMENT
4th Line Agents: MRA

Not recommended for initial management, considered additional therapy for resistant HTN

Class	Medication	Initial dose, Max Daily Dose	Side effects and dosing considerations
MRA	Spironolactone	25mg, 50mg	• Hyperkalemia • Gynecomastia • Dose reduce in eGFR <50 • Not recommended for use in eGFR <30 • Mortality benefit in HFrEF
	Eplerenone	50mg once daily, 50mg twice daily	

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ANTI-HTN TREATMENT
5th Line Agents: MRA

Class	Medications	Side effects and dosing considerations
Beta Blockers	Vasodilating agents preferred (labetalol, bisoprolol, carvedilol, nebivolol)	• Bradycardia • Should not be first line for BP control but can be considered when other comorbidities present (HF, history of MI, IHD, elevated HR > 70 BPM)
Alpha blocker	Doxazosin, prazosin, terazosin	• High risk of orthostatic hypotension • Consider as 5th line agent if patient with BPH
Alpha Agonists	Clonidine, guanfacine	• **Rebound HTN with non-adherence** • Avoid with alcohol, and sedating medications • Significant Cardiovascular and CNS ADRs

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Summary

- BP Measurement Technique
- Stepwise Approach
- Shared Decision Making



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REFERENCES

1. Carey RM, Calhoun DA, Bakris GL, et al. Resistant hypertension: detection, evaluation, and management: a scientific statement from the American Heart Association. Hypertension 2018; 72(5):e53–e90. doi:10.1161/HYP.0000000000000084
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3. Izhar M, Alausa T, Folker A, Hung E, Bakris GL. Effects of COX inhibition on blood pressure and kidney function in ACE inhibitor-treated blacks and Hispanics. *Hypertension*. 2004;43:573–577. doi: 10.1161/01.HYP.0000115921.55353.e0

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