Baptist Health
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Drug Resistant Hypertension

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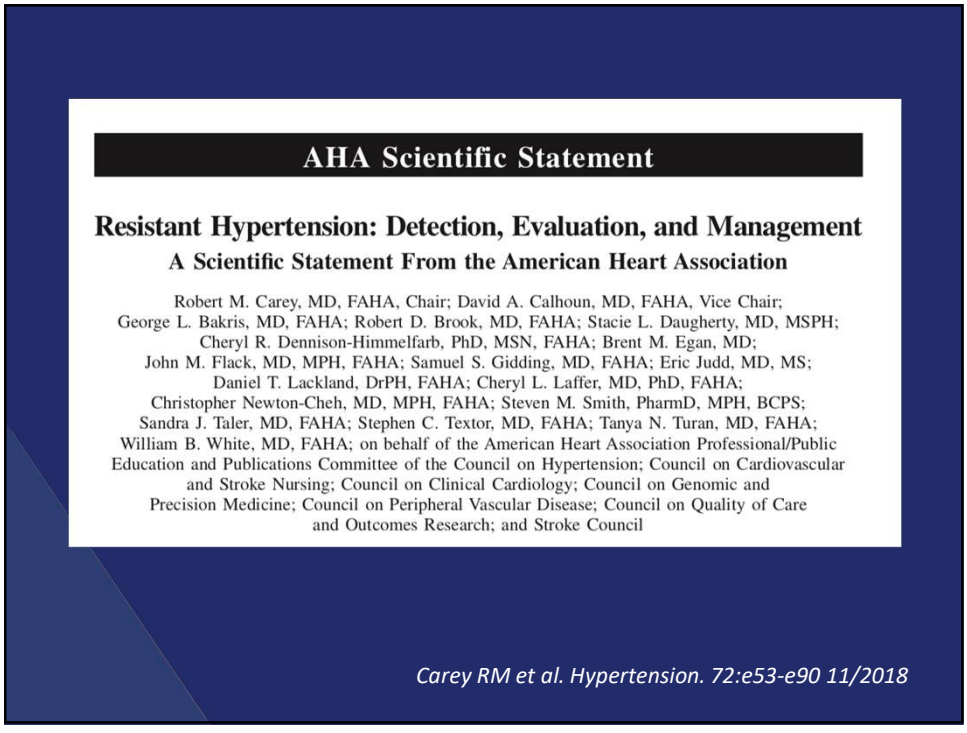
Disclosures: None

Outline

- Background
- Diagnosis and evaluation
- Secondary hypertension
- Treatment options
- Conclusions



Carey RM et al. Hypertension. 72:e53-e90 11/2018

Definitions of terms

- Uncontrolled hypertension
- Uncontrolled resistant hypertension (UCRH)
- Refractory hypertension
- Controlled resistant hypertension (CRH)
- Pseudoresistance
- **Apparent** treatment-resistant HTN (aTRH)
- White coat resistant hypertension (WCRH)

Acelajado et al. Circ Res 2019; 124:1061-1070

Definitions

- RH or uRH: BP above the goal despite 3 antihypertensive drugs including a diuretic
- cRH: controlled BP on ≥ 4 antihypertensives
- aTRH: pseudoresistance cannot be excluded given missing data such as: medication dose, adherence, or out-of- office BP.
- WCRH: uncontrolled office BP but controlled out-of-office BP on ≥3 antihypertensive agents

2017 HTN guidelines

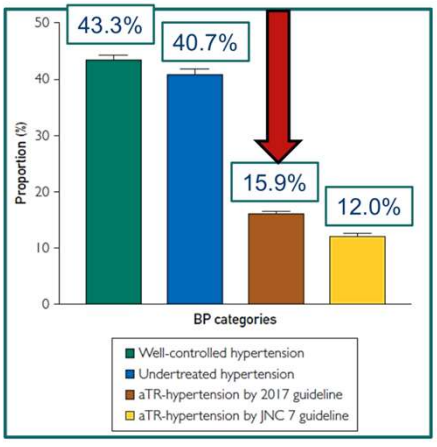
TABLE 6 Categories of BP in Adults*

BP Category	SBP		DBP
Normal	<120 mm Hg	and	<80 mm Hg
Elevated	120–129 mm Hg	and	<80 mm Hg
Hypertension			
Stage 1	130–139 mm Hg	or	80–89 mm Hg
Stage 2	≥140 mm Hg	or	≥90 mm Hg

Thresholds for diagnosis and treatment are in accordance with …

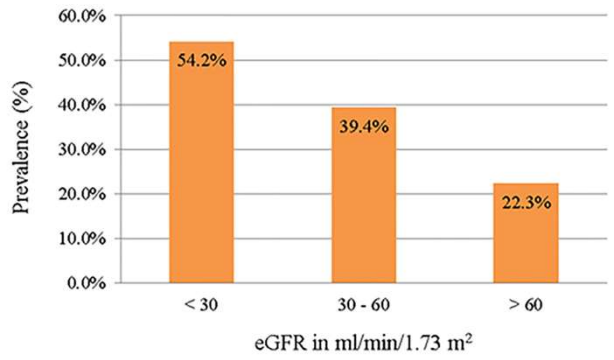
HTN: office SBP/DBP ≥ 130/80 mm Hg

Prevalence RH (aTRH)



Mayo Clin Proc. 2019;94(5):776-782

Prevalence of RH by eGFR status



Prevalence of ATRH increases as eGFR declines

Hypertension 2016; 67:387-396

Prognosis

- Patients with resistant HTN are
  - At increased risk of cardiovascular disease and other target organ damage
  - More likely to have adverse effects from medications
  - More likely to have a secondary cause of hypertension
  - Linked to metabolic derangements, including hyperuricemia, aldosterone excess and suppressed renin levels

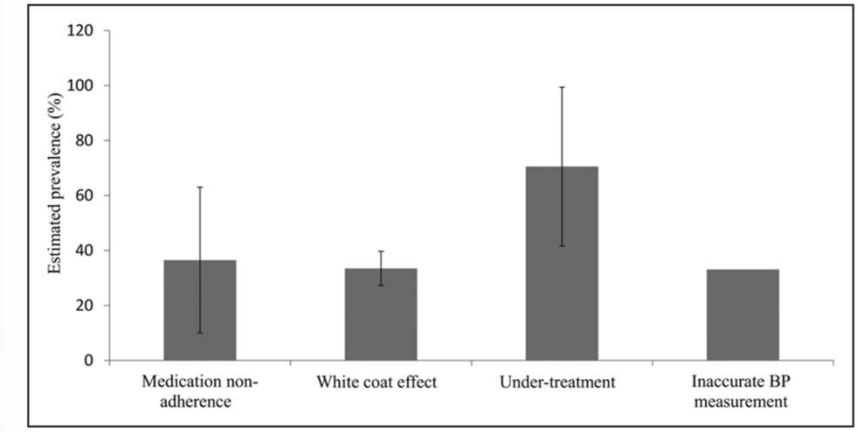
Evaluation of RH

1. Exclude pseudoresistance
2. Identify and reverse contributing lifestyle factors
3. Discontinue or minimize interfering substances
4. Undiagnosed condition (secondary hypertension)

Evaluation of RH

1. Exclude **pseudoresistance**
   - Ensure accurate office BP measurements
   - Assess for nonadherence
   - Exclude white coat effect
   - Inappropriate drug choices (suboptimal meds)

Estimated prevalence of common causes of Pseudo-resistance



Clinical inertia: the failure to establish appropriate targets and escalate treatment to achieve treatment goals

Pseudoresistance

- Incorrect BP measuring technique

Accurate measurement of BP

- Properly prepare the patient
  - **Relax (> 5 min),** in chair with feet on the floor and uncrossed, supported back & arm
  - Avoid caffeine, exercise, smoking > 30 min
  - Empty bladder
  - No conversation during rest or measurement
  - Remove clothing over arm
- Use proper technique …

Wrong size cuff

TABLE 9 Selection Criteria for BP Cuff Size for Measurement of BP in Adults

Arm Circumference	Usual Cuff Size
22–26 cm	Small adult
27–34 cm	Adult
35–44 cm	Large adult
45–52 cm	Adult thigh

Arm supported
Correct cuff size (**encircles 80% of the arm**)
Cuff on upper arm at level of right atrium (not the wrist)

Auscultatory

Observer variability
Inaccurate in hypotensive pts
Variability in correlation with intra-arterial pressure, specially in the elderly with calcified brachial artery (pseudo-hypertension)

Oscillometric

Use devices with **validated** measurement protocol
Ensure that the device is calibrated periodically
Automated office BP (AOBP)
Validated BP monitor for home use
https://bihsoc.org/bp-monitors/for-home-use/

Pseudoresistance

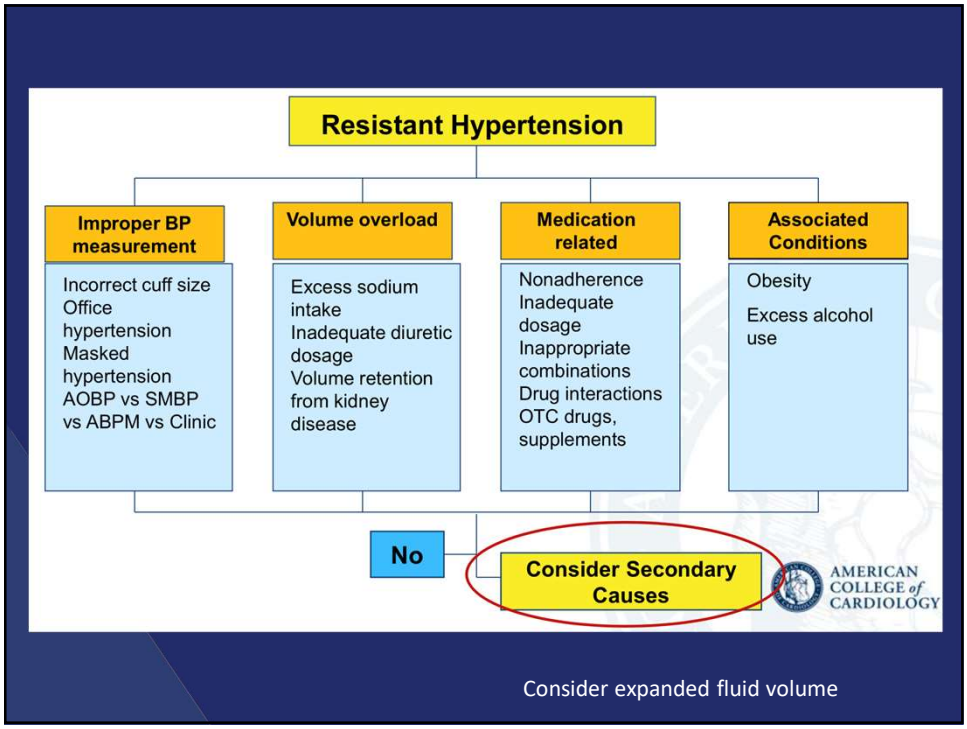
- Incorrect BP measuring technique
- Exclude white coat hypertension
  - Often superimposed on essential hypertension
  - Needs continue surveillance

Pseudoresistance

- Incorrect BP measuring technique
- Exclude white coat hypertension
- Exclude nonadherence
  - Role of urine drug assay
  - Other medications issues:
    - Drug interactions
    - **Inadequate dosages or combinations (suboptimal medications)**
    - Overlapping mechanisms of action

Drugs that may elevated BP

- Sympathomimetic: amphetamines, decongestants
- Antidepressants: Venlafaxine, Duloxetine, Amitriptyline, Nortriptyline, Buspirone
- Clozapine, Olanzapine
- Carbamazepine
- Cyclosporine, Tacrolimus, Sirolimus
- Oral contraceptives
- NSAIDs, steroids
- Methamphetamines, Cocaine, EtOH



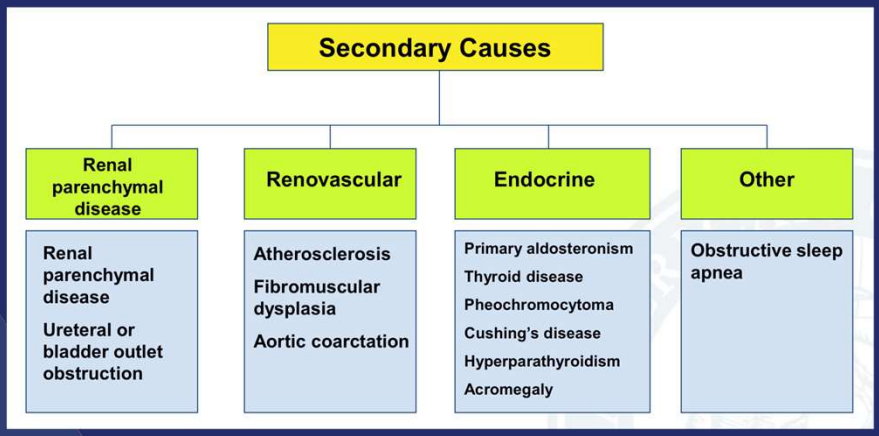
Consider expanded fluid volume

Secondary hypertension

- The presence of a specific condition known to cause hypertension (~ 10%)
- May be the primary and sole cause
- May be a contributing cause
- Presence may not always require invasive or corrective treatment

When to evaluate for secondary HTN

- Resistant hypertension
- Sudden onset of hypertension
- Worsening of previously controlled BP
- Unexplained or disproportionate target organ damage for degree of hypertension
- Onset of diastolic hypertension in older adults
- Early-onset hypertension (<30 y, except blacks)

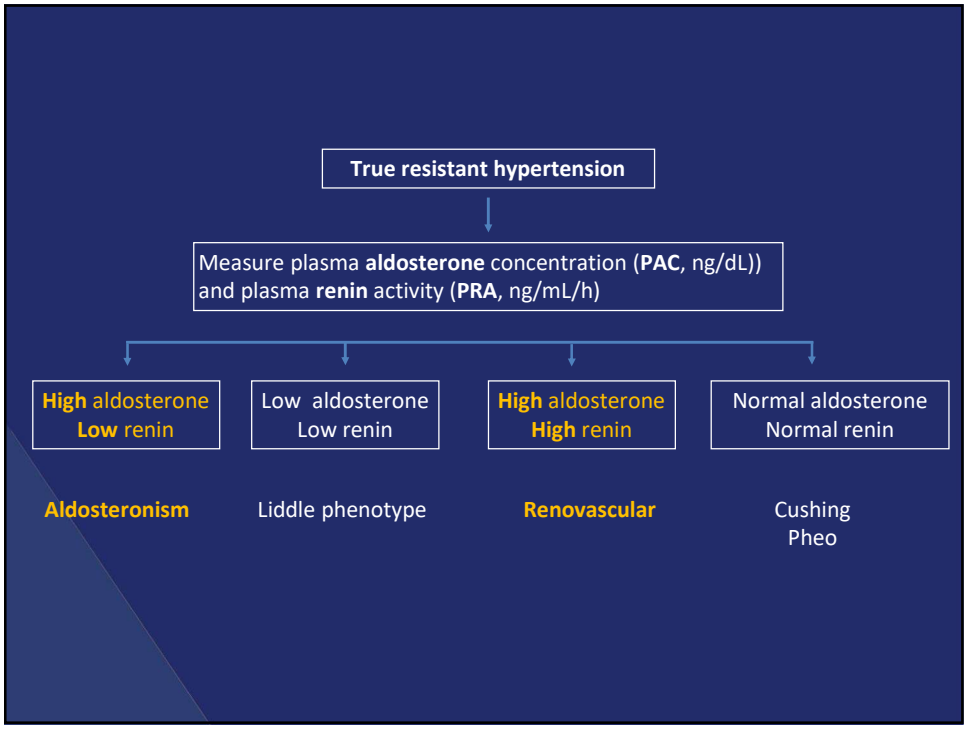


Syndromes of Aldosterone Excess

- Primary aldosteronism: 5-10%, 30% if suggestive features, 50% if unprovoked low K
- Clinical indications: Hypertension +
  - Hypokalemia (spontaneous or induced)
  - Muscle cramps or weakness
  - Incidentally discovered adrenal mass (incidentaloma)
- Screening test: elevated ARR = aldosterone/renin (PAC/PRA) > 30

Primary Aldosteronism

- Hypokalemia is absent in the majority of cases and has a low negative predictive value
- Correction of hypokalemia & withdrawal of MRA for 4-6 weeks.
- Also withdrawn BB & DHP-CCB for 2 wks.
- 50% due to bilateral adrenal hyperplasia
- Confirmatory test: oral sodium loading test or intravenous saline suppression test
- Surgery or MRA (spironolactone or eplerenone)



Renovascular hypertension

- High aldosterone & high renin phenotype
- Atherosclerosis (90%)
- FMD in younger, healthier pts
- Renal duplex US, MRA with gadolinium or CTA
- CORAL trial
- RAS blocker, HIST, ASA
- Revascularization for those who do not respond to medical therapy and for those who have nonatherosclerotic disease (Takayasu, FMD)

Obstructive sleep apnea

- Consider the diagnosis in every RH patient (> 80%)
- Symptoms – chronic fatigue (sleepiness) with dramatic effect from CPAP
- Exam – narrow oral-pharyngeal opening, large neck (Mallampati score)
- The role of aldosterone in promoting OSA
- Polysomnography is used for diagnosis
- Whether fully corrected by CPAP is unclear, only modest reductions in BP.

Pheochromocytoma

- Rare (0.01 % to 0.2%)
- Paroxysmal or episodic hypertension, headache, palpitations and sweating (piloerection)
- Adrenal incidentaloma
- Metanephrines in 24-hour urine sample or plasma free metanephrines
- Imaging (CT)
- Surgery

Pharmacological treatment

- Initial 3-drug regimen
  - Available in multiple combination products
- Fourth drug
  - Spironolactone (PATHWAY-2 study)
  - Beta-blockers
- Others

Initial 3-drug regimen

- The initial drug choice should be RAS blocker or long-acting CCB
  - ACEI/ARB
  - Amlodipine
  - Strongly consider starting therapy with combination AML/Benazepril
    - Clinical trial (ACCOMPLISH) shows superiority of this regimen as initial mgmt.

- Second drug of choice
  - Should be ACEI/ARB or amlodipine
- Third drug of choice
  - Should be a diuretic
  - **AML/Benazepril** vs. HCTZ/Benazepril
  - Common SE: hypokalemia, hyperuricemia, hyperglycemia and exacerbation of metabolic syndrome

Which diuretic?

- All JNC7 clinical trials which supported diuretic therapy used CHLOR, **not** HCTZ
- Chlorthalidone has improved outcomes in every large clinical trial
- Longer half-life
  – 45–60 h compared to 8–15 h for HCTZ
- More hypokalemia and hyponatremia
- Alternative **indapamide**

Fourth Drug

- **Spironolactone**
  - Regress LVH and reduce proteinuria
  - Improves endothelial function
  - Decreases myocardial and vascular fibrosis
  - Irrespective of aldosterone/renin ratio
  - Hyperkalemia is uncommon (1-7%), higher risk in CKD pts, avoid MRA if GFR < 30

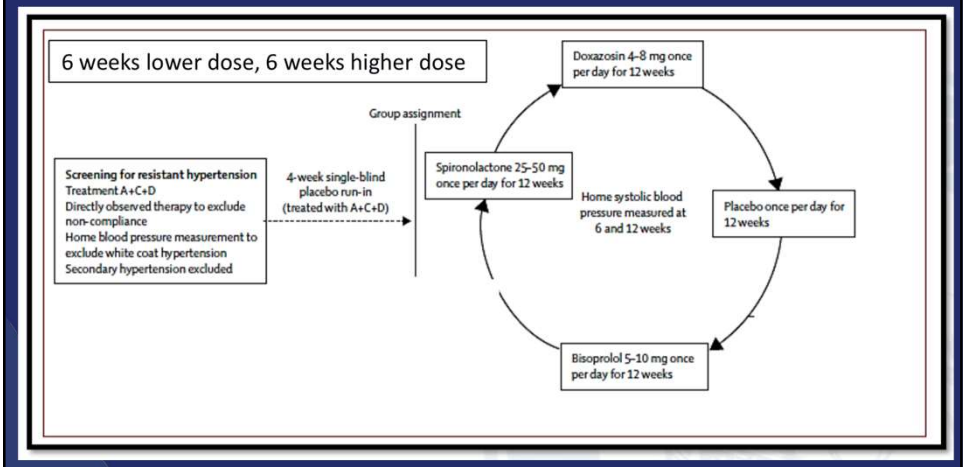
PATHWAY-2 STUDY

Prevention and treatment of hypertension with algorithm based therapy

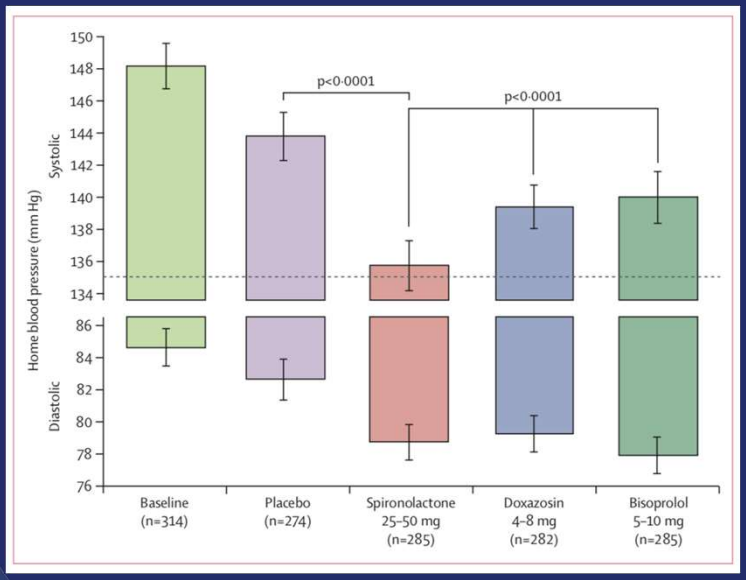
- Prospective randomized double blind crossover trial (Landmark study)
- 314 subjects with office SBP ≥140 mm Hg, ≥135 mm Hg if diabetic, or home SBP ≥130 mm Hg on 3 drugs (ACEI/ARB, CCB and a diuretic)
- **Aldactone** versus Placebo, Bisoprolol, and Doxazosin for Drug Resistant Hypertension
- Primary endpoint was change in home SBP

Williams B. Lancet 2015; 386: 2059-2068

3 months of treatment MRA/BB/@B as add-on therapy for RH



Spironolactone was titrated to 50 mg
Enhanced benefit in pts with suppressed renin levels
Significant reduction of thoracic fluid content, an index of fluid retention

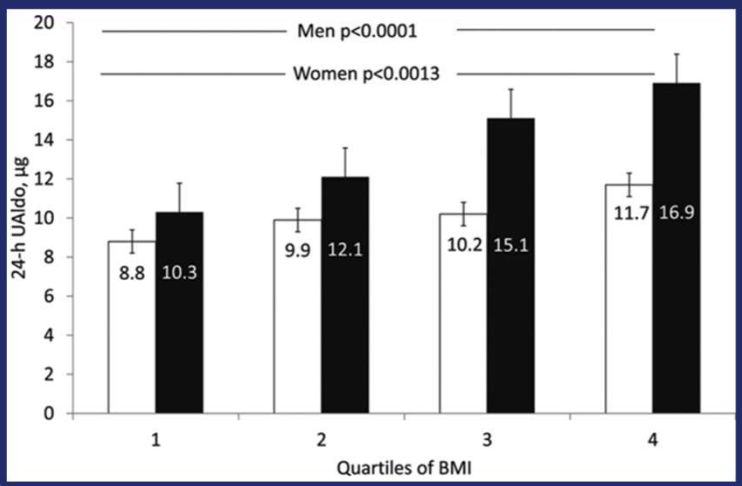


Spironolactone was superior and had largest additional effect at higher dose
58% achieved BP target with spironolactone (3x greater than other agents)
No difference in the occurrence of adverse events

PATHWAY-2 STUDY

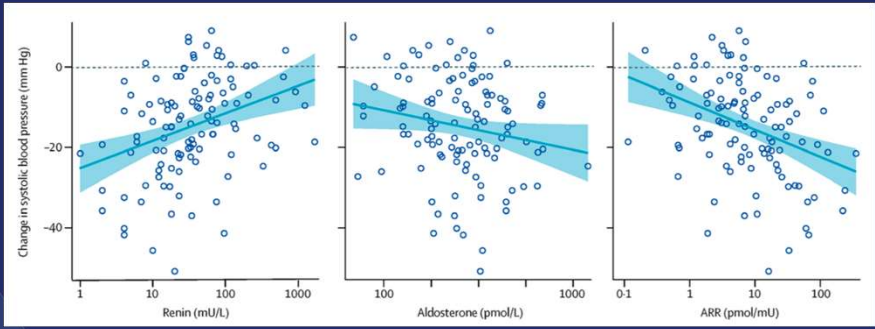
Prevention and treatment of hypertension with algorithm based therapy

- Aldosterone excess is a common cause of RH, usually related to being overweight or obese
- RH is attributable to excess fluid retention mediated by aldosterone excess
- MR blockade are effective for treatment of RH
- Amiloride (10 to 20 mg) reduced clinic SBP comparable to spironolactone
- If spironolactone is not tolerated, amiloride can be an effective alternative



Positive relationship between weight gain and aldosterone levels, more pronounced in men

Mechanism substudies



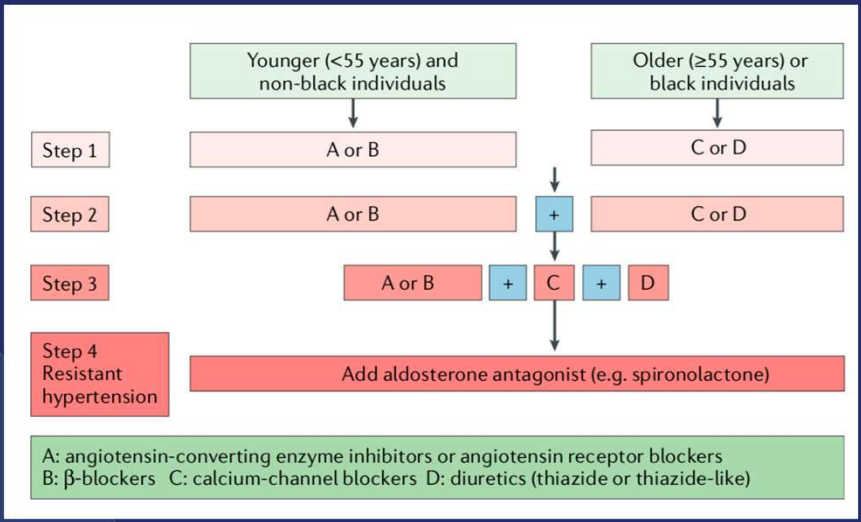
BP response to spironolactone in patients with RHTN is strongly predicted by a **suppressed PRA**.

These data support measuring the PRA in patients with resistant hypertension to guide therapy

What about beta blockers?

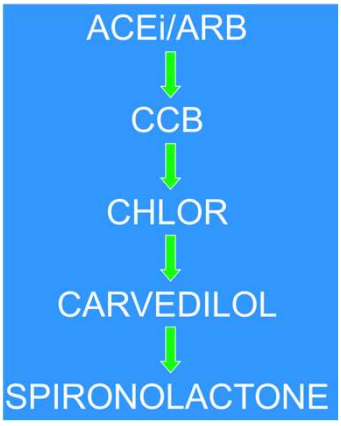
- **Beta blocker**
  - Carvedilol: BID dose, is generic, has alpha blocker
  - Nebivolol: very effective, but brand name
  - Metoprolol XL
- Although β-blockers reduce CV end points in clinical trials, meta-analyses suggest that they are less effective than diuretics, ACEI/ARBs, and CCBs
- SE: fatigue, sexual dysfunction, glucose intolerance

AB/CD algorithm



Higher renin concentration in younger (< 55) and white

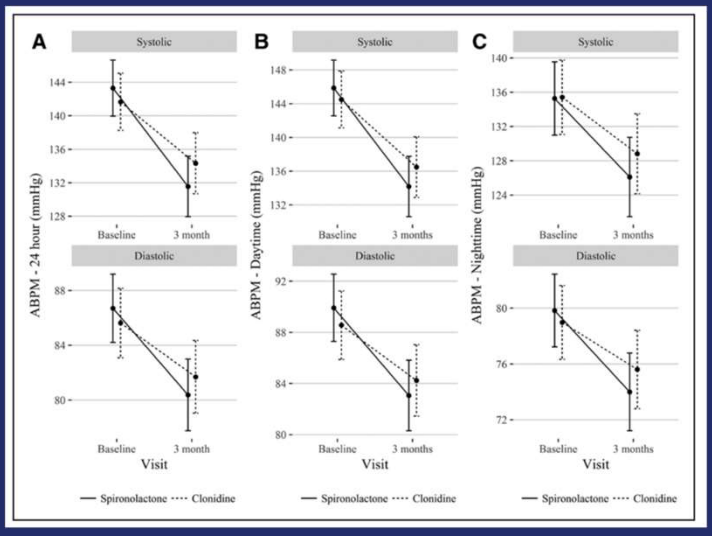
Suggested Algorithm



Standard 3-drug regimen
4th agent: beta blocker
5th agent: MRA

Other agents

- Clonidine
  - Associated with rebound hypertension
  - The ReHOT study
- Minoxidil
  - Hypertrichosis, pericardial effusion
- Hydralazine



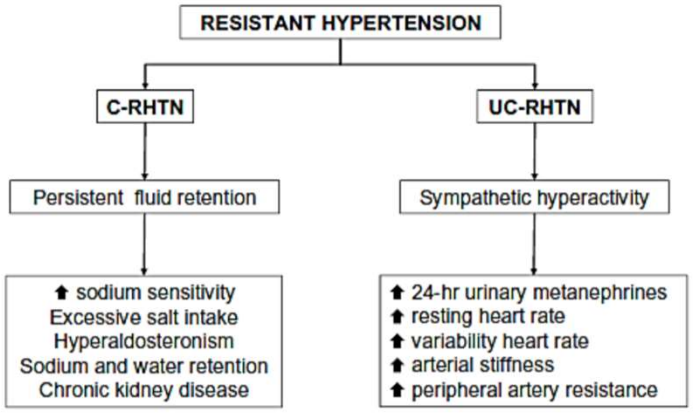
187 pts taking 3 agents randomized to 12 weeks spironolactone 12.5-50 mg/d or clonidine 0.1- 0.3 mg bid. **Clonidine not superior** . Spironolactone preferred for easier dosing and better secondary endpoints

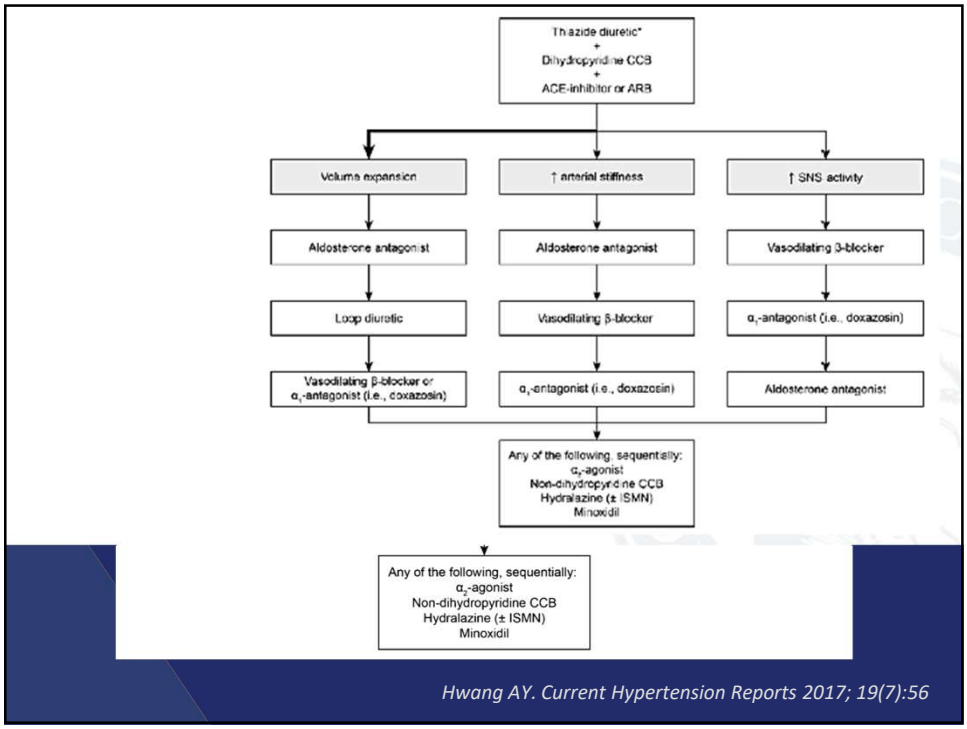
Krieger EM. Hypertension 2018; 71(4): 681-690

Refractory hypertension

- Rare, less than 5% of patients
- BP not controlled to target using ≥5 antihypertensive medications (CTD, MRA)
- Refractory hypertension may be more than volume expansion and include sympathetic activation/hyperactivity and possibly inflammatory activation
- Ongoing debate on whether these are different conditions

Refractory Hypertension





Hwang AY. Current Hypertension Reports 2017; 19(7):56

CONCLUSIONS

Resistant Hypertension

- Uncontrolled hypertension is not synonymous with resistant hypertension
- Needs to exclude pseudoresistance
- Resistant hypertension does not necessarily indicate secondary hypertension
- Spironolactone as a fourth medication, but be mindful of compelling indications

CONCLUSIONS

Obstacles to BP control

- Treatment of asymptomatic disease
- Nonadherence is common and difficult to detect
  - Including lifestyle factors
- Variability of pt response – by race, gender, age
- Side effects, drug intolerances
- Complexity of choosing beyond the 3rd agent
- Decision making on when remove an agent
- Clinical inertia (status quo)

Thank You