Resistant Hypertension

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Disclosures

- None

Learning objectives

Upon completion of this activity, participants will be able to:

1. Define resistant hypertension
2. Recognize when to suspect a secondary cause of resistant hypertension
3. Demonstrate an approach to managing patients with resistant hypertension

Resistant Hypertension: Current AHA guideline

- Carey RM, et al. Resistant Hypertension: Detection, Evaluation and Management. A Scientific Statement from the American Heart Association. Hypertension. 2018;72:00-00

Resistant hypertension (RH): 2018 definition

1. Above goal elevated BP despite concurrent use of 3 antiHTN drug classes, including a long-acting calcium channel blocker, an ACEi or ARB and a diuretic, at maximum or maximally tolerated doses
2. BP at goal on $\geq$ 4 antiHTN meds
3. Aim for the goals set by ACC/AHA in 2017:
   - Office BP < 130/80
   - Home BP < 130/80

Home BP is stronger predictor of CV risk than office BP

- Prospective study of 2081 subjects aged 45-74 followed for 6.8 yrs
- **Results:**
  - Only home BP was predictive of CV events
  - Only systolic home BP was predictive of total mortality

Hypertension 2010;55:1346

R/O Pseudoresistant hypertension

- Poorly controlled HTN that appears resistant but is due to other factors
- Five most common causes:
  - Inaccurate measurement of BP
  - Poor adherence to lifestyle approaches
  - Poor adherence to treatment
  - Suboptimal treatment
  - White coat hypertension

Heart 2014;100:855

White-coat hypertension

- Office BPs ≥130/80; reliable home BPs <130/80
- Suspect if no target organ damage
- **Diagnosis:** repeated home measurements or 24-hour ambulatory monitoring
- **Prognosis:** minimal increase in CVD risk and all-cause mortality
- **Recommendation:** lifestyle modification, annual home BP monitoring

Drugs that can cause elevated BP

- NSAIDS and cox-2 inhibitors
  - Raise systolic and diastolic BP
  - Cause sodium and fluid retention
  - Inhibit production of renal vasodilative prostaglandins
  - Interfere with efficacy of diuretics, ACE-inhibitors, ARBs, B-blockers
- Others
  - Estrogen-containing contraceptives
  - Sympathomimetic drugs: phenylephrine, phentermine, cocaine
  - Chemotherapeutic agents: gemcitabine, antiangiogenic agents
  - Herbal supplements: ginseng
  - Anabolic steroids
  - Erythropoietin

Evaluate for medication nonadherence

- **Prevalence:**
  - 8-40% in studies using questionnaires or pharmacy refill data
  - 50-60% when checking blood levels
- **Patient self-report** can be helpful
- **Reasons:** economic, side effects, literacy, miscommunication, too complicated

JAMA 2018;320(23):2461

Recommendation:
Simplify the drug regimen

- Use **minimum effective doses**: once a day
- Use **minimum number of pills**: fixed dose combinations
  - Meta-analysis: 24% decrease in risk of non-compliance

When should we suspect a secondary cause?

- Resistant hypertension
- Acute rise in BP in patient with previously stable values
- Malignant or accelerated HT: severe HT, end-organ damage
- Age less than 30 in non-obese, non-black patient with negative FH and no other risk factors
- Onset before puberty

Ms. Resista is a 45 year old woman with BP 150/90 despite treatment with hctz 25 mg qd, amlodipine 10 mg qd, and lisinopril 20 mg qd. Her potassium is 3.4. An abdominal USG is normal.
What secondary cause of hypertension is most likely?

A. Sleep apnea
B. Renal artery stenosis
C. Primary aldosteronism

Common secondary causes

Primary aldosteronism: prevalent and unrecognized

- Recent cross-sectional study at 4 U.S. academic medical centers
- **Evaluation:** patients with nl BP (n = 289), stage 1 HTN (n = 115), stage 2 HTN (n =203), resistant HTN (n = 408)
- **Measurement:** 24-hour urinary aldosterone after oral sodium load. **Primary aldo** diagnosed when 24-hour urinary aldo >12 ug/24 hours

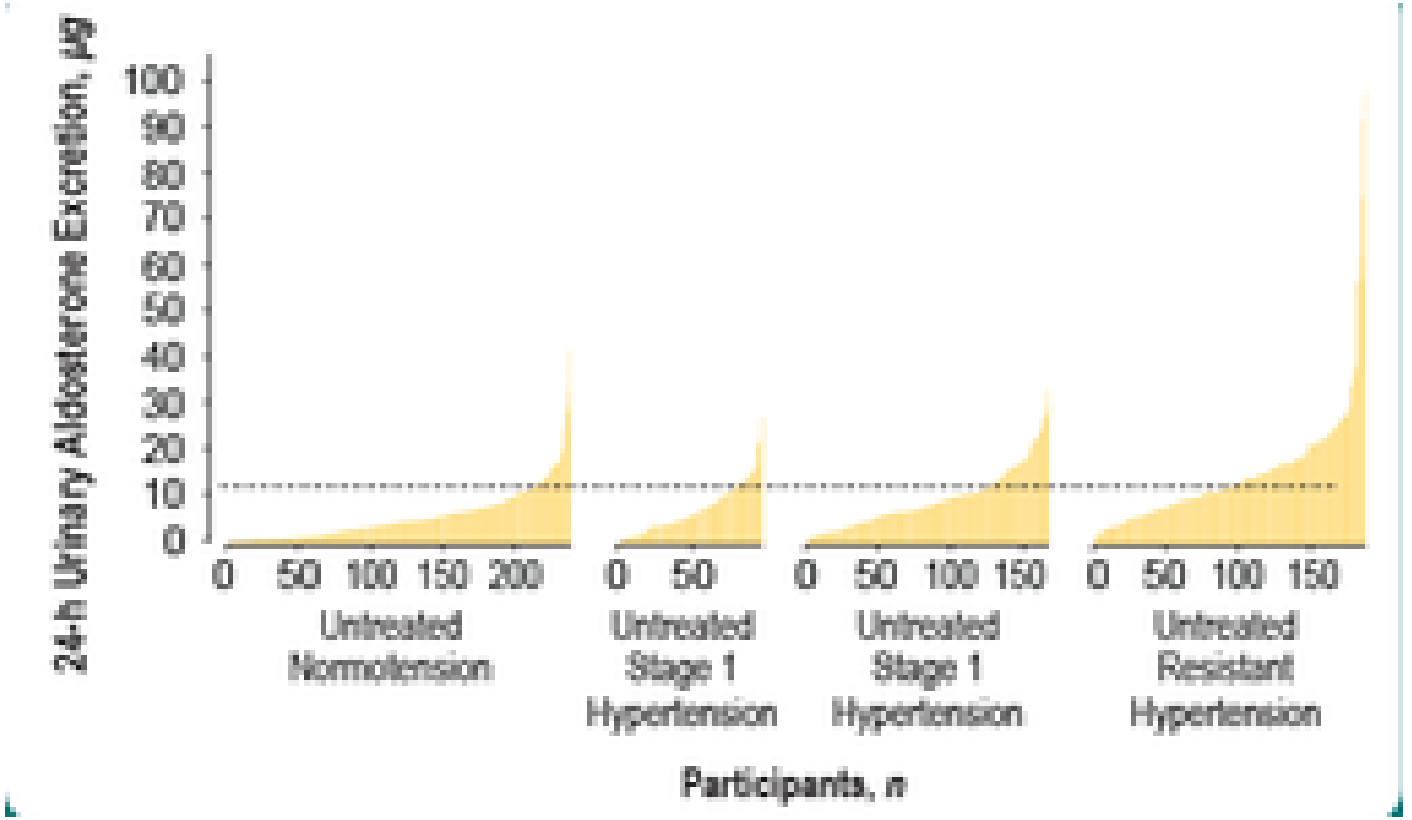
Ann Intern Med 2020;173:10

Unrecognized prevalence of primary aldosteronism: results

- Continuum of renin-independent aldosterone production that parallels the severity of HTN
- Prevalence of elevated aldosterone
  - 11.3% in normotension
  - 22% in resistant HTN

Ann Intern Med 2020; 173: 10

Distribution of renin-independent aldosterone production by BP category



Ann Intern Med 2020; 173: 10

Prevalence of primary aldosteronism: conclusions

- Primary aldo may be the underlying cause of “essential” hypertension in many of our patients
- Primary aldo is much more common than we realize

Ann Intern Med 2020;173:10-20

Aldosteronism: diagnosis

1. Abnormal AM plasma aldosterone to renin ratio (>20:1)
2. Confirm with aldosterone suppression test:
   - 3 day salt load, then 24 hour urine for aldosterone, sodium, creatinine
   - confirmatory result: urinary aldosterone > 12 mcg
3. Do adrenal venous sampling

Outpatient salt-loading test

- Give your patient 12 of these:
- **Day 0**: make sure K is normal
- **Day 1:** take 4 packets
- **Day 2:** take 4 packets, check/correct K
- **Day 3:** take 4 packs, collect 24 hour urine for creatinine, aldosterone, sodium
- **Day 4:** Return urine, check K
- Sodium > 200 mEq/24 hr and aldosterone > 12 mcg/24 hr confirms diagnosis

Whom would you test for primary aldosteronism?

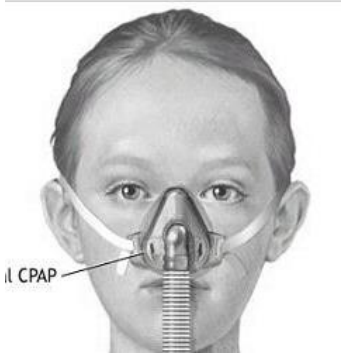
Patients with:

- HTN and spontaneous or low-dose diuretic-induced hypokalemia
- Severe HTN (greater than 150/100) or drug resistant HTN
- HTN with adrenal incidentaloma
- HTN and atrial fib

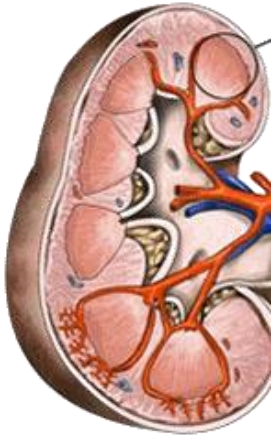
When not to screen

- Older normokalemic patient with mild hypertension
- Patient in whom the diagnosis would not change management: Older patient, BP easily controlled on one drug

Sleep apnea



- **Prevalence:** 5% of middle-aged population
  - 30-40% of patients with hypertension
  - 60-70% of patients with resistant hypertension
- **Symptoms/signs:** interrupted sleep, snoring, daytime somnolence, obesity
- **Dx:** sleep study
- **Treatment:** CPAP, wt. loss. Leads to modest BP reductions



Chronic renal parenchymal disease (CKD)

- Common cause of secondary hypertension
- From diabetic nephropathy or hypertensive nephrosclerosis
- **Dx:** proteinuria, elevated creatinine

Renal artery stenosis: prevalence and clues

- **Prevalence**: 2-24% patients with resistant hypertension
- **Clues:**
  - Sustained increase in creatinine by more than 30% within 2 weeks of starting ACE or ARB
  - Severe HTN with unexplained atrophic kidney
  - Severe HTN with episodes pulmonary edema
  - Severe HTN with systolic-diastolic abdominal bruit lateralizing to 1 side

Renal artery stenosis: causes

- **Atherosclerosis**
  - Common in elderly smokers
- **Fibromuscular dysplasia**
  - Non-atherosclerotic, non-inflammatory disorder leading to arterial stenosis
  - Causes most cases of renal artery stenosis in adults under age 50

Atherosclerotic renal artery stenosis: treatment

- **Recent trials:** medical therapy especially with ACE inhibitors/ARBs often effective
- **Current practice:** optimize drug rx before considering interventional strategy

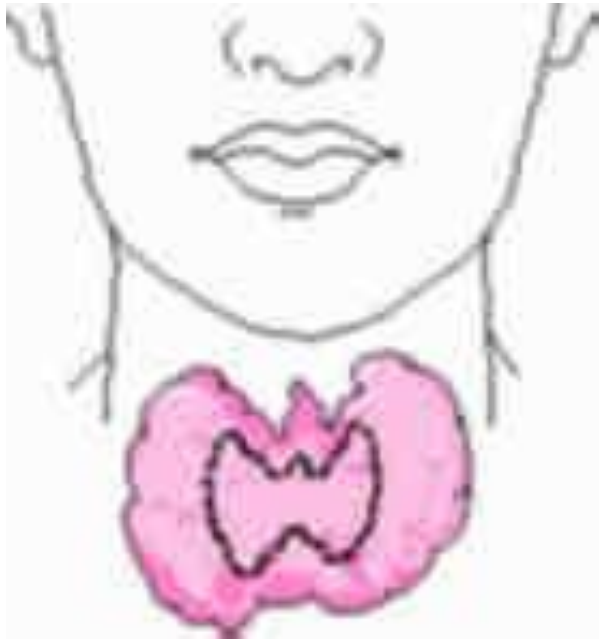
Fibromuscular dysplasia: treatment

- **Medical:** 1st step: ACE or ARB
- **Imaging:**
  - Consider if high likelihood of cure or improved control with revascularization
  - Duplex USG
- **Revascularization:** Consider in younger patients
  - Angioplasty
  - Surgical revascularization if needed

Less frequent secondary causes

Thyroid disease

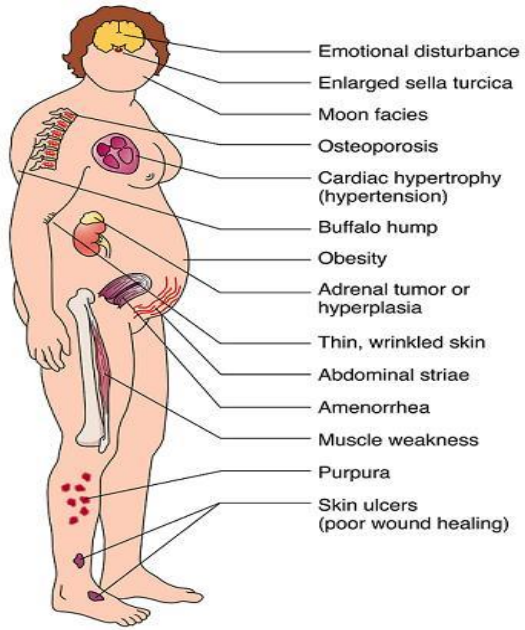
- Prevalence: 2%
- **Hyperthyroid:** tachycardia,
  increased systolic BP
- **Hypothyroid:** weight gain, fatigue,
  increased diastolic BP



Pheochromocytoma

- **Prevalence:** < 0.5%
- **Symptoms**: palpitations, diaphoresis, paroxysms of HTN
- **Finding:** consider eval if adrenal incidentaloma
- **Diagnosis:**
  - Plasma fractionated metanephrines: high false positive rate. Reserve for cases with high index of suspicion
  - 24-hour urine fractionated metanephrines and catecholamines: cases with low index of suspicion
  - Adrenal/abdominal CT or MRI
- **Treatment:** surgery

Cushing's syndrome



- **Prevalence:** < 0.5%
- **Symptoms/signs:** obesity, striae, increased glucose
- **Finding:** consider eval if adrenal incidentaloma
- **Diagnosis:** Do at least 2 first-line tests
  - Low dose dexamethasone suppression test
  - 24-hour urinary cortisol: >3x upper limit of nl
  - Late night salivary cortisol

Management of resistant hypertension

- A **six-step** approach
- **Steps 1-3:** recommendations based on high quality evidence
- **Steps 4-6:** suggestions based on expert opinion only

Management of Resistant Hypertension: Step 1

- **Maximize lifestyle interventions**
- **Exclude other causes:** white-coat, nonadherence to meds, secondary
- **Optimize 3-drug regimen:** maximum or maximally tolerated doses: ACEi or ARB, CCB, diuretic

Maximize lifestyle interventions

- Weight loss: >5-10% wt loss can lower BP by 4.5 mm Hg
- Salt restriction: <2.3 g/d
- DASH diet; fruits, vegetables, low-fat dairy
- Physical activity: ≥ 150 min/wk of moderate-intense aerobic exercise: 5-8 mm Hg
- Decrease alcohol: men: no more than 2 drinks qd, women: no more than 1 drink qd
- Sleep: need more than 6 hours of uninterrupted sleep

Controversy over optimal timing for daily antihypertensive meds

- Hygia Chronotherapy Trial, 2019: RTC of 19,084 patients: all HTN meds at bedtime vs. on awakening
  - Patients on bedtime meds: lower hazard ratio for primary CVD outcomes
- New: the TIME study in the UK
  - 21,000 adults with treated HTN randomized to take usual daily meds in morning or night.
  - Median f/u of 5 years
  - Morning and night dosing groups had similar rates of composite CV outcomes
  - Recommendation: Take meds at time convenient for patient

Lancet 2022; 400: 1417-25

Step 2: intensify diuretics

- Consider changing HCTZ to **optimally dosed thiazide-like diuretic**: chlorthalidone, indapamide
  - Longer acting, more potent than HCTZ
- Titrate to BP goal
  - or to maximum recommended dose
  - or until signs of overdiuresis: orthostatic hypotension, elevated creatinine

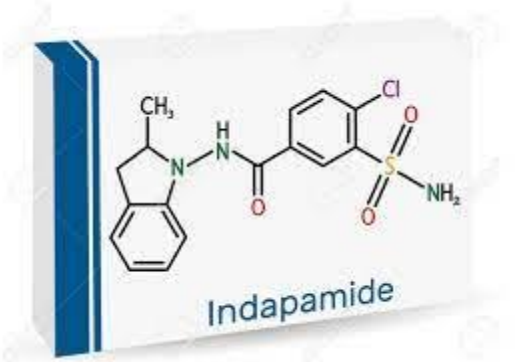
Controversy about chlorthalidone vs. hctz for preventing major adverse CV events in patients with HTN

- The Diuretic Comparison Project Writing Group: pragmatic trial of adults 65 years of age or older in the VA health system on hctz 25 or 50 mg
  - Continue rx with hctz or switch to chlorthalidone 12.5 or 25 mg qd
  - Primary outcome: composite nonfatal MI, stroke, heart failure leading to hospitalization, urgent coronary revascularization, non-cancer-related death, safety
  - Results: Mean baseline systolic BP in each group: 139
    - Median f/u of 2.4 yrs: no sig difference in major CV outcome events or non-cancer-related deaths; more hypokalemia in chlorthalidone group
  - Limitation: Primary comparison was between hctz 25 mg and 12.5 mg chlorthalidone. Trials that showed chlorthalidone benefits on CV outcomes used higher doses: hctz 50 mg or chlorthalidone 25 mg

N Engl J Med 2022; 387: 2401-10

Why and how to use chlorthalidone

- **Duration of action**: 30 hours vs. 12 hours for HCTZ
  - Greater fall in nighttime BP
- Studies: **systolic blood pressure reduction of 7-8 mm Hg** by switching from HCTZ to same dose of chlorthalidone
- Start with chlorthalidone dose of 12.5 mg qd, increase to 25 mg qd if needed
- Exception: Frail, elderly patient less than 10 mm above goal: stick with HCTZ



Indapamide: thiazide-like diuretic

- Longer acting, more potent than HCTZ
- Shown to reduce CV events in the HYVET and ADVANCE trials
- Start with low dose: 1.25-2.5 mg/day
- Increase to 5 mg/day if needed

Carey et al. Hypertension 2018;72:00

Patients with eGFR ≥30, on thiazide-like diuretic, with persistent signs of hypervolemia

- ADD a loop diuretic to the thiazide-like diuretic (i.e. sequential nephron blockade)

Patients with eGFR < 30 ml/min. or creatinine > 2 mg

- SWITCH to a loop diuretic
- If already taking a loop diuretic, intensify the dose, unless patient develops signs of hypovolemia

Loop diuretics

- **Short-acting** ones: give twice a day
  - Furosemide 20-80 mg bid
  - Once daily leads to reactive sodium retention -> inadequate BP control
- **Long-acting**: give once a day
  - Torsemide 2.5-10 mg qd

Assess for orthostatic hypotension

- Patients at increased risk: elderly, DM
- Check sitting and standing BP
- **Orthostatic hypotension**: within 2 minutes of standing:
  - 20 mm fall in systolic BP, or
  - 10 mm fall in diastolic BP, or
  - dizziness

Monitor for hypokalemia

- Occurs in 7% patients
- More common in patients with resistant hypertension due to higher aldosterone levels
- More common with chlorthalidone than HCTZ
- Low salt diet decreases risk of hypokalemia
- Potassium loss occurs during 1st two weeks of rx
- Check potassium after 2 weeks of rx

Mr. Hyperten is a 50 year old man with BP 145/95 despite treatment with chlorthalidone 12.5 mg qd, amlodipine 10 mg qd, and lisinopril 40 mg qd. His potassium is 3.6.
What treatment would you add?

A. Increase chlorthalidone to 25 mg qd
B. Add spironolactone 25 mg qd
C. Add furosemide 10 mg po bid

Step 3: Add spironolactone, mineralocorticoid receptor antagonist

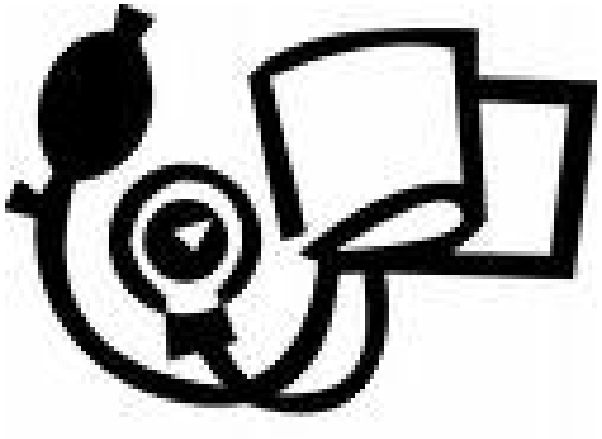
ASCOT-BPLA trial: design

- Analysis of effect of spironolactone as 4th line rx in patients not controlled on 3 drugs
- 1411 participants
  - Mean age 63
  - 77% men
  - 40% had diabetes
- Median spironolactone dose: 25 mg

Hypertension 2007;49:839

ASCOT-BPLA trial: results

- Mean BP fell by 22/10 mm Hg
- Adverse effects
  - Gynecomastia 6%
  - Hyperkalemia 2%



PATHWAY-2 trial

- 3 month long RCT in 285 patients with resistant hypertension on ACEi or ARB, calcium channel blocker and diuretic
- Compared efficacy of adding:
  - Spironolactone 25-50 mg qd, or
  - Placebo, or
  - Doxazosin, or
  - Bisoprolol

Lancet 2015;386(Nov 21):2059

PATHWAY-2 trial: results

Drug	Average reduction in systolic BP (mm HG)
Placebo	- 4.1
Bisoprolol	- 8.3
Doxazosin	- 8.7
Spironolactone	- 12.8

Implications for practice

- Spironolactone is the most effective add-on drug for treatment of resistant hypertension
- Consider truly resistant HTN as BP not controlled by A + C + D + spironolactone
- Start with 12.5 mg, titrate up to 50 mg
- DON'T use in patients with renal insufficiency (GFR < 30)
- Recheck creatinine, electrolytes after 1 week

A = ACEi or ARB C = calcium channel blocker

D = diuretic

Alternatives if spironolactone is not tolerated

- Try:
  - **Eplerenone 25 mg bid -> 50 mg bid**
    - Mineralocorticoid receptor antagonist, OR
  - **Amiloride 5-10 mg**
    - Potassium-sparing diuretic,
    - Blocks collecting tubule sodium channels normally opened by aldosterone

Step 4: If still hypertensive, add vasodilating beta- blocker

- **Labetalol**: wide dosing range
  - Start at 100 mg bid
  - Titrate to 1200 mg bid
- **Carvedilol:**
  - Start at 6.25 mg bid
  - Titrate to 20 mg bid

If B-blocker contraindicated, consider centrally acting agent

- **Clonidine**
  - Use transdermal patch q week: initial: 0.1 mg/24-hour patch applied once every 7 days. Increase by 0.1 mg at 1 to 2-week intervals.
  - Usual dose range: 0.1 to 0.3 mg/24-hour patch applied once every 7 days
  - Avoid tablets: need for frequent dosing, risk of rebound HTN
- **Guanfacine immediate release** 0.5-1 mg at bedtime

Step 5: If patient remains hypertensive: add hydralazine

- Start 10 mg qid -> 25 mg qid -> 50 mg qid.
  Usual range 100-200 mg qd
- Direct vasodilator
- Causes increased sympathetic tone:
  use with **beta-blocker**
- Causes sodium avidity:
  use with **loop diuretic**
- In patient with CHF:
  use with **nitrate**

Step 6: Try minoxidil instead of hydralazine

- Dose: 2.5 mg two-three times qd, titrate up q 3 days. Usual effective dose: 10 to 40 mg/day in 1 to 3 divided doses
- Not well tolerated
  - Causes hirsutism
  - Causes fluid retention and increased sympathetic tone: need loop diuretic and B-blocker
- BUT often lowers BP effectively

Check list: Combine agents from different classes

1. Reduce volume overload: diuretic
2. Decrease vascular resistance: ACE or ARB
3. Smooth muscle relaxation: calcium channel blocker
4. Aldosterone antagonist
5. Reduce sympathetic overactivity: beta-blocker
6. Direct vasodilation: hydralazine

Work with the patient's current regimen

- If current regimen does not include a drug from the 3 recommended drug classes, ADD the missing preferred drug and assess response
- Don't discontinue any drugs, as long as they are well tolerated, before achieving BP control

If BP is still not controlled…

- Refer to a hypertension specialist
- Ask about referral to a clinical trial

What's new: positive data about renal denervation

- Usefulness of renal denervation in patients with resistant hypertension has been unclear
- SYMPLICITY HTN-3 trial: renal denervation compared with sham-control procedure
  - 6 months: No sig improvement in amb BP
  - 12 months: Larger decrease in amb systolic BP (- 7.5 vs. -0.1 mmHg)
  - 36 months: -15.6 vs. -0.3 mmHg
  - Suggests that renal denervation can effectively lower BP in patients with resistant HTN

Lancet 2022; 400: 1405-16

What's very new: dual endothelin antagonist aprocitentan for resistant HTN

- Blockade of the endothelin pathway to lower BP was suggested in late 1990s: 1 positive phase 3 trial, not confirmed
- PRECISION: multicenter, randomised, phase 3 trial: 730 patients with resistant HTN
- 4-wk double-blind, placebo-controlled phase;

  32-wk single-blind, active-treatment phase;

  12-wk double-blind, placebo-controlled withdrawal phase
- Supports role of endothelin receptor blockade in rx of resistant HTN after triple antihypertensive rx
- Well tolerated, effective. Stay tuned!!

Lancet 2022; 400: 1927-37

Key points

- **Common reasons** for inadequate control of HTN:
  obesity, high salt diet, too much alcohol, nonadherence, suboptimal doses of meds
- **Most common treatment-related cause:** Inadequate diuretic therapy
- **Best treatment:**

  ACEi or ARB + CCB + chlorthalidone
- **Best next step:** spironolactone

Next best steps

- Try to intensify lifestyle management
- Use maximum doses of an ACEi or ARB and a calcium channel blocker
- Do aggressive diuretic therapy: switch to chlorthalidone with careful monitoring for side effects
- Next best step: add spironolactone