

## Resistant Hypertension

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A 56-year-old man with type 2 diabetes mellitus is referred for blood pressure evaluation. He was diagnosed with hypertension 15 years ago but still has persistent hypertension despite adherence to his medication regimen. His family history is significant for hypertension in multiple family members, most of whom were diagnosed between the ages of 40-50 years. The patient's home blood pressure readings are from 150-160 systolic and 80-90 diastolic.

Medications include Hydrochlorothiazide 25 mg daily, Valsartan 160 mg daily, Diltiazem long-acting 300 mg daily, Clonidine 0.2 mg BID, and Metoprolol long-acting 100 mg daily.

Physical exam shows blood pressure 158/92 in both arms, after 5 minutes of rest. The blood pressure did not change on standing. His heart and lung examinations were normal, and there was no noted edema.

Laboratory studies show sodium of 138 mEq/L, serum potassium 4.9 mEq/L, chloride 103 mEq/L, bicarbonate 25 mEq/L, BUN 14 mg/dl, and creatinine 0.9 mg/dl. Urine dipstick was unremarkable.

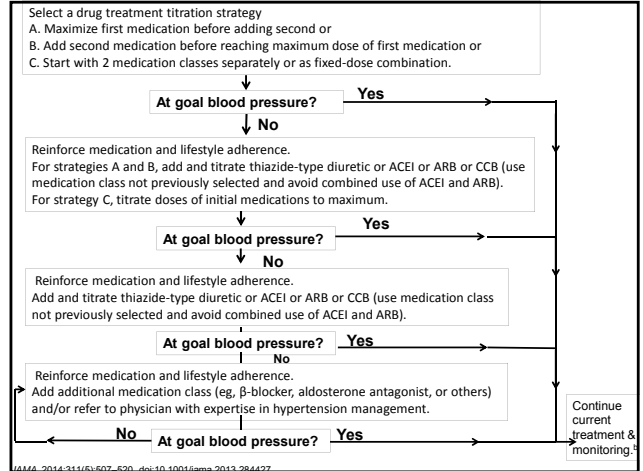
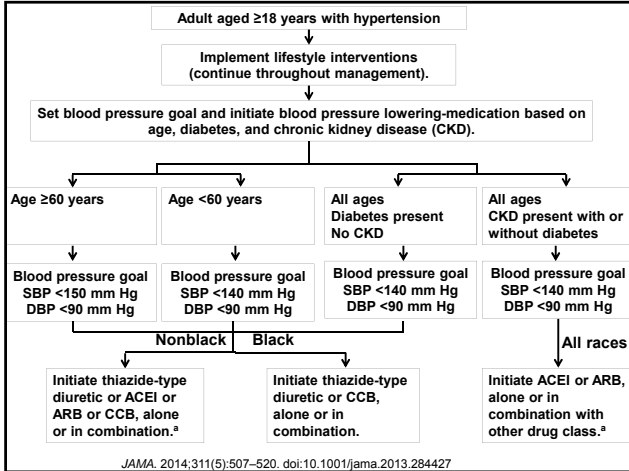
## Objectives

- Diagnose resistant hypertension
- In those who are noted to have resistant hypertension, identify those who require screening for secondary workup
- Understand appropriate testing measures for secondary hypertension
- Understand management of resistant hypertension and secondary hypertension

## What is resistant hypertension?

- Blood pressure that remains above goal despite the use of three anti-hypertensives in different classes at optimal doses. One of the three agents should be a diuretic.
- Goal blood pressure less than 140/90 (in general) but this is also individualized based on patient population
- Goal blood pressure less than 130/80 in patients with diabetes, established CV or cerebrovascular disease, or chronic kidney disease

Calhoun, et al. *Hypertension*. 2008;51: 1403-1419



Initial Drugs of Choice for Hypertension	
ACE inhibitors (ACEI)	
Angiotensin receptor blockers (ARB)	
Thiazide-type diuretics	
Calcium channel blockers (CCB)	

Strategy	Description
A	Start one drug, titrate to maximum dose, and then add a second drug
B	Start one drug and then add a second drug before achieving maximum dose of the initial drug
C	Begin with 2 drugs at the same time, either as 2 separate pills or as a single pill combination

JAMA. 2014;311(5):507-520. doi:10.1001/jama.2013.284427

Lifestyle changes:
• Smoking Cessation
• Control blood glucose and lipids
• Diet
– Eat healthy (i.e. DASH diet)
– Moderate alcohol consumption
– Reduce sodium intake to no more than 2,400 mg/day
• Physical activity
– Moderate-to-vigorous activity 3-4 days a week averaging 40 min per session

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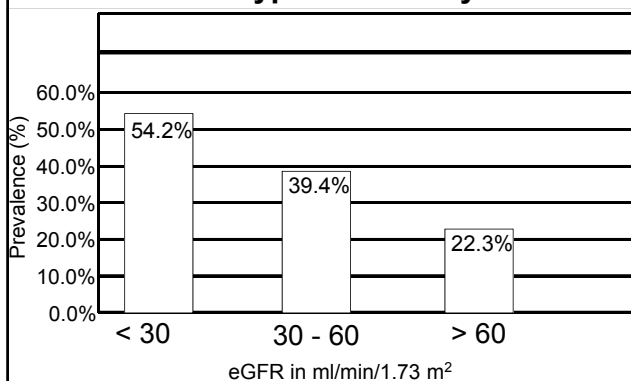
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## Prevalence of Resistant Hypertension

- Relatively unknown and highly variable. Some studies report a prevalence between 2%-40%
- According to NHANES (2003-2008), the prevalence was reported to be 11.8%
- According to ALLHAT (1996-2000), the prevalence was 12.7%
- CRIC study estimated a prevalence of 40% in hypertensive patients with chronic kidney disease
- We must have a consistent definition for resistant hypertension to limit this variability

Braam, et al. *Clin J Am Soc Nephrol* 12: 524-535, 2017

## Prevalence of Apparent Treatment Resistant Hypertension by eGFR

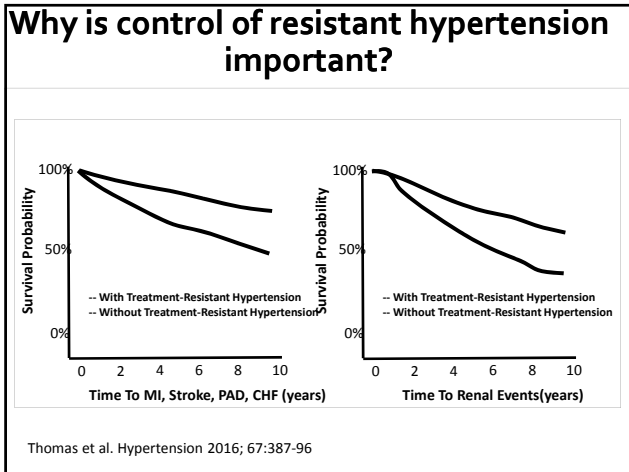


Thomas et al. *Hypertension* 2016; 67: 387-396

## Risk Factors for Resistant Hypertension

- Older age
- Male sex
- African Americans
- Proteinuria
- Diabetes Mellitus
- Higher BMI/obesity [1]
- Chronic kidney disease defined as serum creatinine greater than or equal to 1.5 mg/dL [2]

1. Thomas et al. *Hypertension* 2016; 67: 387-396  
2. Calhoun, et al. *Hypertension*. 2008;51: 1403-1419



### Steps in Evaluating rHTN in the Outpatient Setting

#### 7 Steps at a Glance

1. Confirm Treatment Resistance
2. Exclude Pseudoresistance
3. Identify & Reverse Lifestyle Factors
4. Discontinue Interfering Substances
5. Screen for Secondary HTN
6. Pharmacological Treatment
7. Refer to a Specialist

Townsend. Clin J Am Soc Nephrol 6: 2301-2306, 2013.

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### 1. Confirm Treatment Resistance

- Confirm adherence
  - “Resistant hypertension? Assessment of adherence by toxicological urine analysis”
    - Used mass spectrometry to analyze urine samples of patients with ATRH and whether they were adherent to medications
    - 47.4% (36 patients) of patients were adherent to all medications
    - 52.6% (40 patients) showed nonadherence
      - Of the non-adherent patients, 30% (12 out of 40) had complete nonadherence
      - 70% (28 out of 40 patients) had incomplete adherence
- Address barriers to adherence

Jung, et al. J Hypertens 31: 766-774, 2013

## 2. Exclude Pseudoresistance

- **Poor Blood Pressure Technique**
  - Too small a cuff results in falsely high readings
  - Cuff bladder should encircle at least 80% of the arm circumference [1]
  - Taking blood pressure too early (ideally after 5 min of rest) or wrong position
  - If applicable, have patient demonstrate use of home cuff
- **White-Coat Effect**
  - Prevalence in the range of 20-30% [2]
  - Consider 24 hour Ambulatory BP monitoring

1. Calhoun, et al. *Hypertension*. 2008;51: 1403-1419  
2. Brown, et al. *Am J Hypertens*. 2001; 14: 1263-1269

## Our case

Patient shows us his technique with his home cuff and is appropriate. BP readings are consistent with our office readings.

Home cuff and office cuff are appropriate size and measurements were performed appropriately in the office.

He reports no irregularity with medication dosing and uses a weekly pill box to remind him.

## 3. Lifestyle Factors

- **Obesity**
  - 8 kg weight loss results in drop of 6-10 mmHg [1]
- **Dietary Salt [2]**
  - Particularly important in salt-sensitive patients
    - Elderly
    - African Americans
    - Patients with CKD
  - Low salt had 23/9 mmHg difference in one trial
- **Alcohol**
  - Abstinence of heavy drinking can result in a drop of about 7 mmHg [3]

Townsend. *Clin J Am Soc Nephrol* 6: 2301-2306, 2011.  
2. Boudville, et al. *American journal of hypertension*. 2005;18:1300-1305.  
3. Aguilera, et al. *Hypertension*. 1999;33:653-657

## 4. Interfering Substances/ Drug related causes

### Medications that can interfere with Blood Pressure Control

- **Nonnarcotic Analgesics**
  - NSAIDs including Aspirin
  - Selective COX-2 inhibitors
- **Sympathomimetic agents**
  - Decongestants
  - Diet Pills
  - Cocaine
- **Alcohol**
- **Oral Contraceptives**
- **Cyclosporine**
- **Erythropoietin**
- **Natural licorice**
- **Herbal Compounds**
  - Ephedra
  - Ma huang

Calhoun, et al. *Hypertension*. 2008;51: 1403-1419

## Our case

He has a BMI of 30 and discussion of lifestyle modifications, dietary changes and exercise are done. He generally does not add salt to his meals and does not eat out frequently. He does not drink any alcohol because it used to exacerbate his heartburn.

In addition to his prescribed medications, he only uses ibuprofen occasionally for his osteoarthritis. He estimates only 1-2 times in the last month.

## Resistant Hypertension

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### 5. Screen for Secondary Hypertension

#### Common Causes

Obstructive Sleep Apnea  
Obesity  
Renal parenchymal disease  
Primary aldosteronism  
Renal Artery Stenosis

#### Uncommon Causes

Pheochromocytoma  
Cushing's Disease  
Hyperparathyroidism  
Hyper or hypothyroidism  
Aortic Coarctation  
Intracranial Tumor/neurogenic hypertension  
Inherited disorders of sodium handling (Liddle Syndrome, Gordon Syndrome, Apparent mineralocorticoid excess, Glucocorticoid remediable aldosteronism)

### Renal Parenchymal Disease

- Achievement of goal blood pressure in the CKD population was uncommon according to NHANES
- Despite use of 3 different antihypertensive, less than 15% of patients followed in nephrology clinic were controlled to less than 130/80 mm Hg
- What accounts for treatment resistance is likely increased sodium and fluid retention in CKD patients
- Special considerations for using diuretics in patients with impaired GFR

Calhoun, et al. *Hypertension*. 2008;51: 1403-1419

## Renal Artery Stenosis

- Most cases are atherosclerotic
- Older age
- Smokers
- Patient's with known atherosclerotic disease: PAD
- Bilateral RAS should be suspected in the presence of flash pulmonary edema

Calhoun, et al. *Hypertension*. 2008;51: 1403-1419

## Diagnosis of Renal Artery Stenosis

- Diagnosis of renovascular hypertension requires stenotic vascular lesion and activation of RAAS
- Imaging Options:
  - Duplex Ultrasound
  - Captopril renography
  - MRA
  - CTA

## Treatment of Renal Artery Stenosis

- Conventional RAAS blockade: ACE inhibitors, renin inhibitors, ARBs
- Other medications that interfere with RAAS: dihydropyridine CCBs, diuretics
- Typically, angiotensin II maintains GFR by efferent arteriolar vasoconstriction
- The caveat: RAAS inhibitors can cause AKI due to a drop in filtration pressure
- Revascularization: permanent cure in fibromuscular dysplasia. Should be considered in patients with bilateral disease, high-grade stenosis, or progressive worsening of renal function.

## Primary Aldosteronism

- Common in patient with resistant hypertension with prevalence of about 20%
- Serum potassium is uncommonly low, and this may be a late presentation of the disorder
- Unclear stimulus for aldosterone excess, but obesity may be linked

## Diagnosis of Primary Aldosteronism

- Aldosterone > 15 ng/dl (mineralocorticoid receptor blockers can be used for any level above 10)
- Aldosterone:Renin ratio of 25-50 (>50 is more suggestive)
- If the ratio is 25-50, confirmatory testing required
  - PO NaCl loading
  - Saline infusion test
  - Fludrocortisone suppression test
  - Captopril challenge test
- Once primary aldosteronism is confirmed:
  - CT
  - If adenoma is identified, obtain adrenal vein sampling to determine functionality/lateralization

## Medications that Interfere with Diagnosis of Primary Aldosteronism

- Beta blockers
- Ace inhibitors/ARBs
- Diuretics
- Spironolactone/Eplerenone

## Obstructive Sleep Apnea

- Common in patients with resistant hypertension
- More common and severe in males
- Mechanism is not perfectly understood, but likely involves upper airway resistance leading to increased sympathetic nervous system activity
- Patients with ESRD are susceptible to OSA

## Pheochromocytoma

- Rare; 0.1-0.6% of patients with HTN
  - Despite this, many cases are missed
- Blood pressure can be variable depending on NE secretion by the tumor
- Diagnosis involves the following constellation of symptoms: headache, palpitations, sweating, episodic
- Screen with plasma free metanephrines

Calhoun, et al. *Hypertension*. 2008;51: 1403-1419



## Cushing's Syndrome

- Cortisol stimulates the mineralocorticoid receptor, leading to hypertension
  - cortisol excess from adrenal adenoma or carcinoma
  - rarely ectopic ACTH
  - or exogenous steroid administration
- End organ damage is typically more severe in Cushing's Syndrome
- Cardiovascular risk is high because the condition is associated with diabetes, metabolic syndrome, OSA, obesity, and dyslipidemia

## Diagnosis of Cushing's Syndrome

- Elevated urine free cortisol level
- Dexamethasone suppression: 1 mg administered at midnight
  - If 8 am plasma cortisol is not suppressed, this helps confirm the diagnosis
- Imaging: CT and MRI of pituitary/adrenals
- Treatment: adrenalectomy if adenoma is confirmed or tumor removal if ectopic ACTH

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## Our case

As mentioned previously, patient was noted to have elevated BMI. After some history taking, patient tells us that his wife tells him that he snores very loudly and she is fearful that he stops breathing sometimes while sleeping. He endorses non-restorative sleep and feels tired every morning despite getting 8 hours consistently.

Patient is sent for sleep study and diagnosed with Obstructive Sleep Apnea and started on CPAP.

He returns to your office with improved BP readings but still not at goal.

## 6. Pharmacologic Treatment

- Initiate or optimize diuretic therapy
  - In most individuals, thiazides are effective. Long-acting thiazides have shown to be more efficacious so preferentially, one should use Chlorthalidone as opposed to Hydrochlorothiazide in resistant hypertension.
  - Loop diuretics may be necessary in patients with CKD
- Combination therapy in three classes is generally effective
- Aldosterone antagonists can be effective in patients with uncontrolled HTN despite several medications
- Ultimately, therapy needs to be tailored depending on the patient's medical history (diabetes, heart disease, CKD)

## Mineralocorticoid Receptor Blockers

- The addition of mineralocorticoid receptor antagonists irrespective of plasma aldosterone levels, plasma renin activity, or aldosterone renin ratios improved blood pressure control
- On average, the systolic blood pressure was lowered by 25 mm Hg and diastolic 12 mm Hg
- On average, the patients were on 4 antihypertensive medications
  - All patients studied were on a diuretic and ACEi/ARB

Nishizaka MK, et al. *Am J Hypertens*, 2003 Nov;16(11 Pt 1):925-30

## Our Case

Patient is switched from Hydrochlorothiazide to Chlorthalidone. His chemistries are monitored closely after initiation and remain stable. He is successfully weaned from clonidine

A few years go by and patient's blood pressure slowly rises again and now his serum creatinine also creeps up as well. He now qualifies as Stage 4 Chronic Kidney Disease.

Referral to nephrology is made.

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### **Special Considerations in the CKD population**

- Optimize volume status and ensure the patients are on RAAS inhibition
- Patient's dietary sodium intake can be measured by 24 hour urine collection for sodium excretion
- OSA is common
- In patients with stable CKD, renal angioplasty/stenting is not of benefit
  - Routine screening for atherosclerotic renal disease is not recommended
- KDIGO guidelines recommend sodium intake 2 g/d for those not on dialysis
  - DASH diet confers increased risk for hyperkalemia, especially in those on RAAS inhibition

Braam, et al. *Clin J Am Soc Nephrol* 12: 524-535, 2017

### **Our Case**

Patient was switched from Chlorthalidone to Lasix BID and started on Spironolactone. His blood pressure became well controlled.

He will continue to follow-up with Nephrology every 3-4 months.