Disclosures

Research Grant: Eli Lilly (REWIND), ReCor (RADIANCE I and II)

Ablative Solutions: (Target BP I)

Consultant: Medtronic Adjudication Committee (AF

Ablation-Hypertension Renal Denervation Study), Up-to-Date

(Hypertension Section)
Case 1

- 28 year old married obese white female comes for a first office visit.
- History: Hypertension for 2 years that has been well controlled on Lisinopril 20 mg qam.
- No family history of premature ASCVD but mother has a hx of hypertension and 30 yr old sister has a history of pre-eclampsia.
- BP: 128/84 mm Hg in the office (average of 3 values).
- BP’s at home taken properly have been similar to the BPs taken in the office.
- She states she and her husband are actively trying to get pregnant for the first time and wants to know if there is anything to do now.

What Would You Do Now?

A. Continue the lisinopril as she has time to stop it.
B. Begin labetalol 200 mg bid and stop lisinopril this visit.
C. Refer the patient to a high-risk OB clinic.
D. Begin aspirin 81 mg qd and calcium supplementation now
E. B,C
F. B,C,D
**Pregnancy**

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations for Treatment of Hypertension in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-LD</td>
<td>Women with hypertension who become pregnant, or are planning to become pregnant, should be transitioned to methyldopa, nifedipine, and/or labetalol during pregnancy.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-LD</td>
<td>Women with hypertension who become pregnant should not be treated with ACE inhibitors, ARBs, or direct renin inhibitors.</td>
</tr>
</tbody>
</table>

Adapted from 2017 ACC-AHA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Hypertension; JACC Nov 2017

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**Oral Antihypertensive Therapy**

- **Labetalol 100-200mg BID**, increase Q2-3d; max 2400 mg/24h
- **Nifedipine ER 30-60mg QD**, increase Q7-14d; max 120 mg/24h
- **Methyldopa 250 mg BID-TID**, increase Q2d; max 3000 mg/24h

**Hydralazine** *10mg QID*, increase Q2-5d; max 200 mg/24h

**Thiazide diuretics**-Hctz 12.5-50 mg daily, second or 3rd line agent

**CONTRAINDICATED**: ACEI/ARB, Renin Inhibitors, MRAs

*Hydralazine should not be used in isolation due to reflex tachycardia*

Hypertensive Disorders of Pregnancy: A spectrum of peri-partum conditions that include:

- **Chronic Hypertension** - hypertension that either starts before pregnancy, before 20 weeks gestation, or persists longer than 6-12 weeks postpartum.
- **Gestational hypertension** - first manifests after 20 weeks of pregnancy without proteinuria or other end-organ damage and resolves within 12 weeks of delivery.
- **Pre-eclampsia** - new onset hypertension and proteinuria after 20 weeks gestation. In addition to hypertension, there must be liver or kidney injury, pulmonary edema, cerebral or visual sx, or thrombocytopenia.
- **Superimposed pre-eclampsia on chronic hypertension**
- **Eclampsia** - presence of seizures in a patient with pre-eclampsia.


Classifying Hypertension in Pregnancy

- SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg
- < 20 weeks gestation or Persistent >6-12 weeks postpartum
- ≥ 20 weeks gestation

Risk Factors Associated with an Increased Risk for Pre-Eclampsia In Our Patient Include?

A. Obesity.
B. Nulliparity
C. Smoking
D. Family History
E. None of the above
F. All of the above

Risk Factors That Increase The Risk of a Pregnancy Being Complicated By Preeclampsia

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Mean RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid syndrome</td>
<td>9.72 (4.34–21.75)</td>
</tr>
<tr>
<td>Previous preeclampsia</td>
<td>7.19 (5.85–8.83)</td>
</tr>
<tr>
<td>Insulin-dependent diabetes</td>
<td>3.56 (2.54–4.99)</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>2.93 (2.04–4.21)</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>2.91 (1.28–6.61)</td>
</tr>
<tr>
<td>Family history of preeclampsia</td>
<td>2.90 (1.70–4.93)</td>
</tr>
<tr>
<td>Obesity</td>
<td>2.47 (1.66–3.67)</td>
</tr>
<tr>
<td>Age &gt;40 years</td>
<td>1.96 (1.34–2.87)</td>
</tr>
<tr>
<td>Preexisting hypertension</td>
<td>1.38 (1.01–1.87)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

ACOG Treatment Initiation & BP Goals: What a Puzzlement??

<table>
<thead>
<tr>
<th>Severe Chronic HTN*</th>
<th>Gestational HTN</th>
<th>Preeclampsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>SBP ≥ 160 mm Hg</td>
<td>SBP ≥ 160 mm Hg</td>
</tr>
<tr>
<td></td>
<td>DBP ≥ 105 mm Hg</td>
<td>DBP ≥ 110 mm Hg</td>
</tr>
<tr>
<td>Goal?</td>
<td>SBP 120-160 mm Hg</td>
<td>NO DATA</td>
</tr>
<tr>
<td></td>
<td>DBP 80-110 mm Hg</td>
<td></td>
</tr>
</tbody>
</table>

* In the setting of co-morbidities or renal dysfunction, treating to a lower threshold may be appropriate

- Weight loss and extremely low sodium diets (<100 mEq/day) are not recommended for BP management in pregnancy
- Moderate exercise can be continued


ADA 2020 Standards of Hypertension and BP Control in Diabetes

Key Recommendations-Rx Goals in Pregnancy:

- In pregnant patients with diabetes and preexisting hypertension, a BP target of ≤ 135/85 mm Hg is suggested in the interest of reducing the risk of accelerated maternal hypertension (Grade A) and minimizing impaired fetal growth (Grade E).

ADA Standards of Medical Care in Diabetes. Diabetes Care 2020 Jan; 43 (Suppl.1):S112.
The 4th Trimester

• Pregnancy related hypertension should resolve within 6 to at most 12 weeks.

• Women with gestational HTN and preeclampsia have >2x higher rates of developing chronic HTN usually in the first 1-5 years post-pregnancy compared to normotensive women.


Lifetime Considerations for CV Surveillance in Women at Increased CVD Risk

• Premature menarche (< 12 years old)
• Polycystic ovarian syndrome
• Multiple miscarriages
• Gestational diabetes
• Pre-eclampsia; gestational hypertension
• Preterm delivery; small for gestational age infant
• Premature ovarian failure or early menopause

Case 2

- 55 year Old AA male comes for a first office visit.
- History: Hypertension for 10 years that has been “controlled” with lifestyle modification but never Rx’d with drug therapy. No hx of smoking.
- Strong family history of hypertension but no family hx of premature ASCVD or stroke.
- BP: 138/84 mm Hg (average of 3), BMI 30 kg/m², WC = 37 inches.
- BP’s at home taken properly have been similar to the BPs taken in the office.

Case 2 (Cont.)

- Meds: Atorvastatin 40 mg qd. Not on Aspirin.
- Exam unremarkable.
- EKG-NSR, LVH, otherwise unremarkable.
- Labs-Na++ 136, K+ 4.2, Creatinine 0.9, eGFR 82, LDL-C 64 mg/dl, Total-C 130 mg/dl, HDL-C 40 mg/dl, TG-130 mg/dl, urine for microalbumin 18 mg albumin/g creatinine, A1C 5.6%
One of the Most Important Things to Do in This 55 Year Old with Hypertension Is?

A. A Coronary Calcium Score  
B. A Hs-CRP  
C. An Lp(a)  
D. Carotid Intimal Medial Thickness  
E. 10-year ASCVD Risk Score Using PCE

CVD Risk Prediction Does Not Need To Be Complicated

http://tools.acc.org/ASCVD-Risk-Estimator/
Case 2 (Cont.)

- Current 10-year ASCVD Risk: 3.8%
- Lifetime ASCVD Risk: 27%
- Optimal ASCVD Risk: 1.8%

Characteristics of Hypertension in African-American Patients Compared to White Americans

- Premature Onset of Hypertension
- Greater Severity of Hypertension
- Greater likelihood of target-organ disease
  - LVH
  - ESRD (4.2x)
  - Heart Failure (1.5x)
  - NF Stroke (1.3x) and Fatal Stroke (1.8x)
- Heart Disease and Overall Mortality
What Goal BP Would You Try to Achieve in This 55 Year Old with Hypertension?

A. < 120/80 mm Hg
B. < 130/80 mm Hg
C. < 140/90 mm Hg
D. < 150/90 mm Hg
E. Shared patient-provider informed decision as to the best BP goal
### BP Thresholds for and Goals of Therapy in Patients With Hypertension According to Clinical Conditions

<table>
<thead>
<tr>
<th>Clinical Condition(s)</th>
<th>BP Threshold, mm Hg</th>
<th>BP Goal, mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical CVD or 10-year ASCVD risk ≥10%</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>No clinical CVD and 10-year ASCVD risk &lt;10%</td>
<td>≥140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)</td>
<td>≥130 (SBP)</td>
<td>&lt;130 (SBP)</td>
</tr>
<tr>
<td>Specific comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic kidney disease after renal transplantation</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Heart failure</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Stable ischemic heart disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Secondary stroke prevention</td>
<td>≥140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Secondary stroke prevention (lacunar)</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>≥130/80</td>
<td>&lt;130/80</td>
</tr>
</tbody>
</table>

ASCVD-atherosclerotic cardiovascular disease                                          BP-blood pressure
CVD-cardiovascular disease                                                             SBP-systolic blood pressure.

BP Thresholds and Recommendations for Treatment and Follow-Up

- **Normal BP** (<120/80 mmHg)
  - Promote optimal lifestyle habits
  - Reassess in 1 year (class IIa)
- **Elevated BP** (120-129/<80 mmHg)
  - Nonpharmacologic therapy (class I)
  - Reassess in 3-6 months
- **Stage 1 HTN** (>130-139/80-89 mmHg)
  - Clinical ASCVD, CKD, or DM or estimated 10-y CVD risk ≥10%
  - Nonpharmacologic therapy (class I)
  - Reassess in 3-6 months
  - Reassess in 1 month
- **Stage 2 HTN** (≥140/90 mmHg)
  - Nonpharmacologic therapy and BP-lowering medication (class I)
  - Reassess in 1 month


### Nonpharmacological Interventions

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations for Nonpharmacological Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>A</td>
<td><strong>Weight loss</strong> is recommended to reduce BP in adults with elevated BP or hypertension who are overweight or obese.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>A heart-healthy diet, such as the <strong>DASH</strong> (Dietary Approaches to Stop Hypertension) diet, that facilitates achieving a desirable weight is recommended for adults with elevated BP or hypertension.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td><strong>Sodium reduction</strong> is recommended for adults with elevated BP or hypertension.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td><strong>Potassium supplementation</strong>, preferably in dietary modification, is recommended for adults with elevated BP or hypertension, unless contraindicated by the presence of CKD or use of drugs that reduce potassium excretion.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Increased physical activity with a structured exercise program is recommended for adults with elevated BP or hypertension.</td>
</tr>
<tr>
<td>I</td>
<td>A</td>
<td>Adult men and women with elevated BP or hypertension who currently consume <strong>alcohol</strong> should be advised to drink no more than 2 and 1 standard drinks per day, respectively.</td>
</tr>
</tbody>
</table>

### LIFESTYLE MODIFICATION: THE CORNERSTONE FOR PREVENTION AND TREATMENT OF HYPERTENSION

<table>
<thead>
<tr>
<th>Lifestyle Intervention</th>
<th>Dose</th>
<th>Impact on SBP Hypertension</th>
<th>Normotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss</td>
<td>Best goal is ideal body weight, but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.</td>
<td>-5 mm Hg</td>
<td>-2/3 mm Hg</td>
</tr>
<tr>
<td>Healthy diet</td>
<td>Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat. DASH is high in Ca++, K++, and Mg++.</td>
<td>-11 mm Hg</td>
<td>-3 mm Hg</td>
</tr>
<tr>
<td>Reduced intake of dietary sodium</td>
<td>Optimal goal is &lt;1500 mg/d, but aim for at least a 1000-mg/d reduction in most adults.</td>
<td>-5/6 mm Hg</td>
<td>-2/3 mm Hg</td>
</tr>
<tr>
<td>Enhanced intake of dietary potassium</td>
<td>Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium.</td>
<td>-4/5 mm Hg</td>
<td>-2 mm Hg</td>
</tr>
</tbody>
</table>

All 4 Recommendations COR:1; LOE:A


---

### LIFESTYLE MODIFICATION: THE CORNERSTONE FOR PREVENTION AND TREATMENT OF HYPERTENSION

<table>
<thead>
<tr>
<th>Nonpharmacological Intervention</th>
<th>Dose</th>
<th>Effect on SBP Hypertension</th>
<th>Normotension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aerobic</td>
<td>● 90–150 min/week</td>
<td>-5/6 mm Hg</td>
<td>-2/4 mm Hg</td>
</tr>
<tr>
<td>● 65%–75% heart rate reserve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dynamic resistance</td>
<td>● 90–150 min/week</td>
<td>-4 mm Hg</td>
<td>-2 mm Hg</td>
</tr>
<tr>
<td>● 50%–80% 1 rep maximum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>● 6 exercises, 3 sets/exercise, 10 repetitions/set</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isometric resistance</td>
<td>● 4 ± 2 min (hand grip), 1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/week</td>
<td>-5 mm Hg</td>
<td>-4 mm Hg</td>
</tr>
<tr>
<td>● 8–10 week</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderation in alcohol intake</td>
<td>Alcohol consumption</td>
<td>-4 mm Hg</td>
<td>-3 mm</td>
</tr>
<tr>
<td>Men: ≤2 drinks daily</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women: ≤1 drink daily</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Both Recommendations COR:1; LOE:A

If Patient had Stage 2 Hypertension, What Antihypertensive Agent(s) Would You Now Start?

A. Start an ACE inhibitor (ACEi) or ARB.
B. Start a CCB or Thiazide/thiazide-type diuretic
C. Start either an (ACEi or ARB) + (CCB or thiazide/thiazide-type diuretic)
D. Start a Beta Blocker
E. Start an Alpha Blocker

Choice of Initial Medication

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation for Choice of Initial Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>ASR</td>
<td>For initiation of antihypertensive drug therapy, first-line agents include thiazide diuretics, CCBs, and ACE inhibitors or ARBs.</td>
</tr>
</tbody>
</table>

SR indicates systematic review.

Whelton et al., Hypertension 2018; 71:e13-e115.
Racial and Ethnic Differences in Treatment

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations for Race and Ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B-R</td>
<td>In black adults with hypertension but without HF or CKD, including those with DM, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.</td>
</tr>
<tr>
<td>I</td>
<td>C-LD</td>
<td>Two or more antihypertensive medications are recommended to achieve a BP target of less than 130/80 mm Hg in most adults with hypertension, especially in black adults with hypertension.</td>
</tr>
</tbody>
</table>


AllHAT Hypertension Trial

- 42,418 high-risk hypertensive patients
- 90% previously treated
- 10% untreated

**STEP 1 AGENTS**

<table>
<thead>
<tr>
<th>Chlorthalidone 12.5-25 mg</th>
<th>Amlodipine 2.5-10 mg</th>
<th>Lisinopril 10-40 mg</th>
<th>Doxazosin 1-8 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=15,255</td>
<td>N=9,048</td>
<td>N=9,054</td>
<td>N=9,061</td>
</tr>
</tbody>
</table>

**STEP 2 AND 3 AGENTS (5 years)**

<table>
<thead>
<tr>
<th>Atenolol 28.0%</th>
<th>Clonidine 10.6%</th>
<th>Reserpine 4.3%</th>
<th>Hydralazine 10.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.0%</td>
<td>10.6%</td>
<td>4.3%</td>
<td>10.9%</td>
</tr>
</tbody>
</table>

JAMA 2002;288:2981-97
### Initial Medications For The Management of Hypertension

**Initial Rx Thiazide-type Diuretics or CCBs in Blacks unless HF or CKD where RAS Blocker is indicated**

- **Thiazide and Thiazide-like Diuretics**
- **ACE Inhibitors or ARBs***
- **Calcium Channel Blockers**

*Recommended for Stage 3 or higher CKD or with albuminuria (>300 mg/day)
Combining ACEI with ARB discouraged

---

**Relative Risk and 95% Confidence Intervals**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>1.10</td>
<td>(0.94 - 1.28)</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>1.06</td>
<td>(0.95 - 1.18)</td>
</tr>
<tr>
<td>Combined CHD</td>
<td>1.15</td>
<td>(1.02 - 1.30)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>1.19</td>
<td>(1.09 - 1.30)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.40</td>
<td>(1.17 - 1.68)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.32</td>
<td>(1.11 - 1.58)</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.29</td>
<td>(0.94 - 1.75)</td>
</tr>
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JAMA 2002;288:2981-97
Racial and Ethnic Differences in Treatment

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</tr>
</tbody>
</table>


ESC/ESH 2018

Combining Drugs from Different Classes is Approximately 5 Times More Effective in Lowering BP than Doubling the Dose of 1 Drug

Value of Low-Dose Combination Therapy: Fewer Side Effects
Case 3

• 65 year old white male lawyer is referred for difficult-to-control BP.
• He feels well, being asx, playing golf 2 times a week w/o difficulty.
• History: Hypertension for 10 years initially well controlled on Lisinopril/hctz 20mg/12.5 mg qam.
• Over the past 2-3 years his BP has been difficult to control now on hctz 12.5 mg at 9 pm, losartan 100 mg at 9 pm, and nebivolol 10 mg given at 9 am and 9 pm. He also takes terazosin 5 mg at bedtime for BPH.
• He also takes KCL 40 meq qam.
• No hx of stroke, MI, kidney disease, or diabetes, he had a normal nuclear stress test 1 year ago as a routine procedure.
• Stopped smoking in 1982, he doesn’t abuse salt or alcohol.

Case 3 (Con’t)

• A renal ultrasound for unclear reasons in 2016 was normal with no evidence of renal artery stenosis. The right kidney was 12.3 cm and the left kidney was 11.7 cm.
• Recently his BP at home has been as high as 190-200/90-98 mm Hg with no specific pattern and home BPs average 168/96.
• Past surgery-uvulopalatopharyngoplasty (UPPP) for sleep apnea in 2014. Felt to be resolved.
• BP: 168/96 mm Hg in the office supine, standing, and sitting (average of 3 values) without orthostasis.
Case 3 (Con’t)

• Exam-unremarkable for hypertensive changes in the retina, no abdominal striae, moon facies, or buffalo hump. No abdominal bruits, no difference between arms and arm and leg BP’s, and no delay in femoral pulses.
• EKG-SB, Incomplete RBBB (unchanged), otherwise unremarkable.
• Labs-Sodium 141, Potassium 2.9, Chloride 101, CO2 29, BUN 17, glucose 104. Creatinine 0.86, eGFR >60, Ca++ 9.1, urine for microalbumin 24 mg/g creatinine.

Which of the Following Tests Would You Order?

A. TSH
B. Plasma metanephrines, normetanephrines
C. Plasma aldosterone, plasma renin
D. Plasma cortisol
E. A,B,C
F. All of the above
G. None of the above
Screening for Secondary Hypertension

New onset or uncontrolled hypertension in adults

CONDITIONS:
- Resistant hypertension; drug-associated htn
- Abrupt onset of hypertension;
- Onset of hypertension at <30 years of age;
- Unprovoked or excessive hypokalemia
- Exacerbation or previously controlled hypertension;
- Disproportionate TOD for degree of hypertension;
- Accelerated/malignant hypertension

Yes No

Screen for secondary HTN (Class I)

Screening not indicated

Positive screening test

Yes No

Refer to clinician with specific expertise (Class IIb)

Referral not necessary

Screening not indicated

Whelton P et al. Hypertension 2017

Secondary Forms of Hypertension

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations for Secondary Forms of Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C EO</td>
<td>Screening for specific form(s) of secondary hypertension is recommended when the clinical indications and physical examination findings are present or in adults with resistant hypertension.</td>
</tr>
</tbody>
</table>

Screening Tests for 2° HTN

<table>
<thead>
<tr>
<th>Condition</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓, ↑ thyroid</td>
<td>TSH, free T4</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>plasma free or 24-hr urinary fractionated metanephrines</td>
</tr>
<tr>
<td>1° aldosteronism</td>
<td>↓ or nl K⁺, ↑ plasma aldo (&gt; 15) with Aldo/PRA &gt;20-30</td>
</tr>
<tr>
<td>Cushing’s disease</td>
<td>24 hr urinary free cortisol, Overnight dex supp</td>
</tr>
<tr>
<td>Hyperparathyroid</td>
<td>Ca⁺⁺, alb, Cl/P, iPTH</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>Duplex Ultrasound, MRA or CTA</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>Hx*, polysomnography, overnight oximetry</td>
</tr>
</tbody>
</table>

*Positive Epworth Sleepiness Score

Which of the Following Would You Now Do?

A. Increase KCL to 40 meq bid
B. Change HCTZ 12.5 mg to Chlorthalidone 12.5 mg
C. Change Losartan from 100 mg qhs to 50 mg qam and qhs
D. Start spironolactone 12.5 mg qam
E. A, B
F. A, B, C
G. A, B, C, D
Case 3 (Con’t)

- Results of tests:
  - TSH 2.5
  - plasma metanephrine 0.13 nmol/L (0.00-0.49)
  - plasma normetanephrine 0.53 nmol/L (0.00-0.89)
  - plasma aldosterone 35.7 (0.00-30.00 ng/dL)
  - plasma renin <0.167 (nl 0.167-5.380 ng/ml/hour)
- Based on these you order a 24 hour urine for sodium and aldosterone which come back with a sodium of 280 meq and an aldosterone level of 18 micrograms (adequate sample).

The Most Likely Diagnosis is:

A. Pheochromocytoma
B. Cushing’s Syndrome
C. Hyperthyroidism
D. Hyperparathyroidism
E. Primary Aldosteronism
F. None of the above
Causes of Secondary Hypertension With Clinical Indications

<table>
<thead>
<tr>
<th>Common causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal parenchymal disease-CKD</td>
</tr>
<tr>
<td><strong>Renovascular disease-RVH and Fibromuscular Disease</strong></td>
</tr>
<tr>
<td>Primary aldosteronism (MOST COMMON)</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
</tr>
<tr>
<td>Drug or alcohol induced-Interfering Substances</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncommon causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheochromocytoma/paraganglioma</td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
</tr>
<tr>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Aortic coarctation (undiagnosed or repaired)</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
</tr>
<tr>
<td>Congenital adrenal hyperplasia</td>
</tr>
<tr>
<td>Mineralocorticoid excess syndromes other than primary aldosteronism</td>
</tr>
<tr>
<td>Acromegaly</td>
</tr>
</tbody>
</table>


PRIMARY ALDOSTERONISM

**Definition**

A group of disorders in which aldosterone production is:

- inappropriately high
- relatively autonomous
- independent of the renin-angiotensin system
- not suppressed by sodium loading.
Primary Aldosteronism (PA)

Why is PA important for the clinician?

1. PA is the most common cause of secondary hypertension: ≈8% of all people with high blood pressure and up to 20% with Resistant Hypertension.

2. The diagnosis of PA provides the clinician with a unique opportunity—to either cure hypertension or to use targeted pharmacotherapy and prevent end stage PA: renal, cerebral, and cardiac disease.

CARDIOVASCULAR DISEASE & EVENTS
IN PRIMARY ALDOSTERONISM

- Striking increase in the relative risk of:
  - stroke (4.2x)
  - myocardial infarction (6.5x)
  - atrial fibrillation (12.1x)
- Increased LVH & diastolic dysfunction
- Increased stiffness of large arteries
- Widespread tissue fibrosis
- Increased remodeling of resistance vessels

Primary Aldosteronism

- Autonomous hypersecretion of aldosterone – independently of the renin-angiotensin system and K⁺ (the major normal aldo stimulators):
  - Hypertension, ↑ plasma aldosterone & ↓ plasma renin activity (PRA)
- Two most common causes:
  - Unilateral aldosterone-producing adenoma (APA)
  - Idiopathic hyperaldosteronism (IHA) with bilateral adrenal hyperplasia
WHO TO CONSIDER AND HOW SHOULD I SCREEN FOR PRIMARY ALDOSTERONISM?

Step 1. Who to Consider Testing for Primary Aldosteronism:
- Hypertension and hypokalemia
- All with Resistant hypertension
- Adrenal incidentaloma on CT and hypertension
- Onset of hypertension at a young age (<30 y)
- Marked hypertension (≥150 mm Hg systolic or ≥100 mm Hg diastolic)
- Whenever considering secondary hypertension

Step 2. Case Detection Testing (screen):
Morning blood sample in ambulant patient, seated x 5
- Plasma aldosterone concentration (PAC)
- Plasma renin activity (PRA) or plasma renin concentration (PRC)

NOTE: only 30% of patients with PA are hypokalemic! Most are Normokalemic and hypertensive

PAC (≥10-15 ng/dL; ≥277 - 416 pmol/L) and
↓ PRA (<1.0 ng/mL/hr) or ↓ PRC (< lower limit of detection for the assay)

*UpToDate: “Approach to the patient with hypertension and hypokalemia” WF Young, NM Kaplan. Accessed January 1, 2017
Improving the Diagnostic Accuracy of the Plasma Aldosterone:Plasma Renin Activity (PA:PRA) Ratio

- Better diagnostic accuracy is obtained if the absolute plasma aldosterone concentration is included as a second criterion in combination with PA:PRA ratio.
- The combination of a PA:PRA ratio >30 and a PA value >20 ng/dL had a sensitivity of 90% and specificity of 91% for APA (Myron Weinberger 1993)
- A PA:PRA ratio ≥20 and PA >15 ng/dL were found in >90% of patients with surgically-confirmed APA (William Young 1999)

Antihypertensive Drugs Can Affect the Plasma Aldosterone:Plasma Renin Activity (PA/PRA) Ratio (ARR)

- Ideally, drugs that markedly affect ARR such as spironolactone, eplerenone, and high-dose amiloride should be withdrawn for at least 4-6 weeks before testing.
- Drugs that can suppress plasma renin including B-Blockers, central α₂ receptor agonist (e.g. Clonidine), and Aliskiren should be kept in mind when interpreting the ARR.
- Drugs that can elevate plasma renin including ACEi, ARBs, thiazide and loop diuretics and dihydropyridine CCBs should be kept in mind as well.
Antihypertensive Drugs that Affect the Plasma Aldosterone:Plasma Renin Activity (PA:PRA) Ratio

- If the initial Case Detection (screening) test results are not convincing, those antihypertensive medications that affect plasma renin can be selectively withdrawn for at least 2 weeks, while BP is controlled with other agents that do not influence the renin-angiotensin-aldosterone system, including:
  - slow release verapamil
  - hydralazine
  - Doxazosin (an α₁-adrenergic receptor antagonist)
  - alpha-methyl dopa.

Step 1. Who to Consider Testing for Primary Aldosteronism:
- Hypertension and hypokalemia
- Resistant hypertension (3 drugs and poor BP control)
- Adrenal incidentaloma and hypertension
- Onset of hypertension at a young age (<30 y)
- Marked hypertension (≥150 mm Hg systolic or ≥100 mm Hg diastolic)
- Whenever considering secondary hypertension

Step 2. Case Detection Testing:
Morning blood sample in ambulant patient, seated x 5
- Plasma aldosterone concentration (PAC)
- Plasma renin activity (PRA) or plasma renin concentration

\[ \text{PAC} \geq 10-15 \text{ ng/dL;} \geq 277 - 416 \text{ pmol/L} \]

\[ \downarrow \text{PRA} < 1.0 \text{ ng/mL/hr} \text{ or } \downarrow \text{PRC} (< \text{lower limit of detection for the assay}) \]

Step 3. Confirmatory Testing

*UpToDate: “Approach to the patient with hypertension and hypokalemia” WF Young, NM Kaplan. Accessed January 1, 2017*
Primary Aldosteronism—Step 3 Confirmatory Testing:

- IV Saline Suppression Test*
- Oral sodium loading test
- Captopril challenge (stimulation) test
- Fludrocortisone suppression test

* preferred

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Confirmatory Testing

<table>
<thead>
<tr>
<th>Oral Sodium Loading Test</th>
<th>Fludrocortisone Suppression Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 6 gm NaCl/day x 3-5 days, assay 24-hour urine for Na*, aldo</td>
<td>• 0.1 mg fludrocortisone q 6 hr x 4 days; assay plasma aldo while upright</td>
</tr>
<tr>
<td>• Confirmatory if urinary aldo excretion &gt;12 or 14 µg/day</td>
<td>• Confirmatory if plasma aldo &gt;6 ng/dL (and PRA and cortisol are low)</td>
</tr>
<tr>
<td>• Not recommended for patients with heart failure, CKD, uncontrolled BP</td>
<td>• Difficult for outpatients who come from a distance</td>
</tr>
</tbody>
</table>

**IV Saline Suppression Test**

- 2 L of normal saline over 4 hours (8 AM to noon); assay plasma aldo
- Confirmatory if post-infusion plasma aldo >10 ng/dL
- Not recommended for patients with heart failure, CKD, uncontrolled BP

Captopril Challenge Test

- 25–50 mg of captopril p.o.; assay plasma aldo after 0, 1 and 2 hours
- Confirmatory (?) if plasma aldo remains elevated and unchanged
- Many false-negative or equivocal results
Aldosterone Excretion Rate After Three Days of Oral Sodium Loading (250 mEq urinary Na per 24 hr)

The Most Important Thing to do Now is:

A. Order a abdominal CT scan focusing on the adrenals
B. Call your favorite surgeon
C. Start spironolactone
D. Refer him to someone smarter than you
E. None of the above
Case 3 (Con’t)

• Results: Abdominal CT scan

Liver: Hepatic parenchyma is unremarkable. Gallbladder/Biliary: GB is unremarkable. No biliary ductal dilatation.
Adrenal glands: 1.5 cm right adrenal nodule which measures -3 Hounsfield units on non-contrast exam. The left adrenal gland is normal.
Kidneys: No hydronephrosis.
GI tract: No evidence of bowel obstruction. Normal appendix. Colonic diverticulosis
Lymph nodes: No lymphadenopathy.
Vasculature: No evidence of AAA. Atherosclerotic calcification of the aorta

IMPRESSION:
1.5 cm right adrenal adenoma.

The Patient Asks if He Should have Surgery to Remove the Growth or Just Go on the Specific Medication that Blocks its Hormonal Effects. You:

A. Tell him to remain on medication because meds are as good as surgery.
B. Tell him that those that have surgery for a unilateral aldosteronoma have a better long-term quality of life and early evidence suggests a better effect on the heart and kidneys.
C. Tell him the jury is still out on this question
D. Tell him you will refer him to someone smarter than you
The Patient Wants to Have the Surgery. The Next Most Important Thing to Do is to:

A. Call the interventional radiologist
B. Call your favorite surgeon
C. Start spironolactone and treat him medically
D. Refer him to someone smarter than you
E. None of the above

Case 3 (Con’t)

- He undergoes selective adrenal vein sampling for renin/aldosterone and cortisol.
- Results show:
  - IVC aldosterone-64, cortisol 38
  - right adrenal vein-aldosterone-12,784, cortisol 1133
  - left adrenal vein-aldosterone-80, cortisol 899
- Based on the specificity index, localization index, and contralateral suppression index this is highly consistent with a right sided adrenal adenoma

Kline et al. Clinical Endocrinology 2015. PMID 25400021
Case 3 (Con’t)

- He is treated with chlorthalidone 25 mg qam, losartan 50 mg qam and qpm, amlodipine 10 mg qhs, spironolactone 25 mg qam and qpm, hytrin 5 mg qhs (for prostate) and potassium 20 meq bid until surgery can be arranged.
- His BPs are sitting 117/52 pulse 66
  standing 114/54 pulse 64
  supine 115/48 pulse 62
- 5 weeks later he undergoes a right posterior retroperitoneoscopic adrenalectomy.
**Case 3 (Con’t)**

- He stays in the hospital < 24 hours and the first night at home his BPs are 140/65, 130/62 and 126/60 off chlorthalidone (held the morning of surgery) and off potassium. 1 week post surgery his BMP is normal.
- 3 weeks post-surgery his BPs continued to be extremely well controlled at home on losartan 25 bid and hytrin 5 mg qhs for the prostate. His BPs in the office that day are:
  - sitting 120/73 pulse 63, standing 126/74 pulse 70
  - supine 123/71 pulse 64
- His plasma renin is now 3 ng/ml/hr (no longer suppressed), aldosterone is 8.7 ng/dL, and potassium 4.2 mg/dL.
- He is doing very well and is to be seen in 6 months for f/up.

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**2020 Take Home Points:**

- **Primary aldosteronism:**
  - It is most common cause of secondary hypertension (8% overall, 20% RH)
  - Most have normal serum K⁺ (50-70%)
  - Screen for it!! – Morning PAC & PRA
  - Don’t trust CT alone for surgery clearance except in a rare circumstance
  - If your AVS program is not optimal, you will have poor AVS-directed outcomes
Screening for Endocrine Hypertension: An Endocrine Society Scientific Statement

William F. Young Jr.,1 David A. Calhoun,2 Jacques W.M. Lenders,4,5 Michael Stowasser,6,7,8 and Stephen C. Textor9

The Management of Primary Aldosteronism: Case Detection, Diagnosis, and Treatment: An Endocrine Society Clinical Practice Guideline

John W. Funder (chair), Robert M. Carey, Franco Mantero, M. Hassan Murad, Martin Reincke, Hirotaka Shibata, Michael Stowasser, and William F. Young, Jr.