Resistant Hypertension:
Tricks of the Trade for Improving BP Control in Your Practice

59th Annual Greenville Postgraduate Assembly
Embassy Suites Hotel
Greenville, South Carolina
April 22, 2015

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<tr>
<th>Role</th>
<th>Companies/Institutions</th>
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<tr>
<td>Grant/Research support</td>
<td>NHLBI (SPRINT)</td>
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<tr>
<td>Consultant</td>
<td>Amgen, Arbor, Eli-Lilly, Forest, Janssen, Lundbeck, Medtronic, Novartis</td>
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<td>Speakers Bureau</td>
<td>Arbor, Janssen</td>
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<td>Major stock shareholder</td>
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LEARNING OBJECTIVES

After participating in this educational activity, clinicians should be better able to:

• Understand the definition and burden of resistant hypertension
• Discuss the clinical evaluation of resistant hypertension, including approaches to rule out identifiable [secondary or reversible] causes
• Recognize the importance of 24-hour ambulatory blood pressure monitoring (ABPM) in confirming the diagnosis of resistant hypertension and ruling out white-coat hypertension
• Employ effective combinations of lifestyle interventions and pharmacotherapy to maximize BP control in patients with resistant hypertension
Issues in the Diagnosis and Management of Resistant Hypertension:

- Sam is a 58 y.o man with a 20 yr history of hypertension who is new to your practice. With a BMI of 32.2 kg/m2, he has no history of ASCVD, diabetes, or other vascular disease. He has been treated with antihypertensive drugs for the past 10+ years including a combination diuretic/ACE inhibitor which had to be stopped due to a cough. He states his BP has never been well controlled and his physicians have always been concerned over this issue. When seen by you, he is on losartan/Hctz 100/25 and amlodipine 10 mg. His BP today in your office is 144/94.
- His physical exam is unremarkable including his eyeground exam.
- He has normal renal function, a potassium of 4.2, and his EKG reveals a NSR and voltage suggestive of LVH.
AHA Scientific Statement

Resistant Hypertension: Diagnosis, Evaluation, and Treatment

A Scientific Statement From the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research

David A. Calhoun, MD, FAHA, Chair; Daniel Jones, MD, FAHA; Stephen Textor, MD, FAHA; David C. Goff, MD, FAHA; Timothy P. Murphy, MD, FAHA; Robert D. Toto, MD, FAHA; Anthony White, PhD; William C. Cushman, MD, FAHA; William White, MD; Domenic Sica, MD, FAHA; Keith Ferdinand, MD; Thomas D. Giles, MD; Bonita Falkner, MD, FAHA; Robert M. Carey, MD, MACP, FAHA
Questions to discuss:

- Does Sam have resistant hypertension?
- How important is “pseudo-resistant” vs. true resistant hypertension?
- How important is it to control resistant hypertension?
Resistant Hypertension

• JNC 7 definition
  – BP that remains above 140/90 in patients adhering to an adequate and appropriate triple-drug regimen (including a diuretic), with all drugs prescribed at near-maximum or maximum recommended doses.

• AHA Scientific Statement definition adds to the above definition
  – Uncontrolled BP despite use of 3 medications
  – BP controlled but requiring at least 4 medications—"controlled resistant hypertension"

Questions to discuss:

- Does Sam have resistant hypertension? - Yes
Prevalence of Resistant Hypertension

- True prevalence of resistant hypertension is not known\(^1\)
- Depending on locale, studies estimate the prevalence around
  - 10-30% in general practice
  - ≥ 50% in nephrology referral clinics\(^2\)
- NHANES (2003-2008) estimated prevalence of resistant hypertension
  - 8.9% (1 in 11) of US adults with hypertension
  - 12.8% (1 in 8) of all antihypertensive drug-treated US adults with hypertension\(^3\)
  - More recent 2005-2008 estimates show the prevalence of resistant hypertension continues to increase\(^4\)

Questions to discuss:

- How important is “pseudo-resistant” or “apparent” resistant hypertension vs. true resistant hypertension?
Uncontrolled Blood Pressure

Apparent Resistant HTN

Pseudo-resistance
- Improper BP measurement
- White coat effect—consider 24-hr ABPM
- Poor Medication Adherence

Resistant Hypertension

True Resistant HTN

BP Measurement in the Office in Established Patient

1. Preferably taken before the patient ever sees the clinician caring for the patient

2. - 5 minutes of rest
   - no conversation
   - seated comfortably with feet on the floor, back supported
   - arm at heart level
   - no tobacco or caffeine for 30 minutes before BP taken

3. Two to Three seated readings (averaged)

4. An upright reading (taken after 1 minute of standing)
Uncontrolled Blood Pressure

Apparent Resistant HTN

Pseudo-resistance
- Improper BP measurement
- White coat effect—consider 24-hr ABPM
- Poor Medication Strategy or Adherence

Resistant Hypertension

True Resistant HTN

1/3 of “Resistant Hypertension” Is Actually White-Coat Hypertension by ABPM

Spanish APBM Registry of 8295 Patients

Percentage of treated hypertensives

Entire Cohort

- Office Resistant: 12.20%
- True resistant: 62.50%
- White coat resistant: 37.50%

de la Sierra, A. Hypertension 2011; 57:898-902
Uncontrolled Blood Pressure

Apparent Resistant HTN

Pseudo-resistance
- Improper BP measurement
- White coat effect - consider 24-hr ABPM
- Poor Medication Strategy or Adherence

Resistant Hypertension

True Resistant HTN

375 Patients Referred for Uncontrolled HTN on 3 Drugs

Maximized Doses
Excluded White Coat

108 Uncontrolled

15 with Secondary HTN
17 Controlled on 4 Drugs

76 Uncontrolled

40 Non-Adherent
(30% taking no meds and 85% <half)

36 True Resistant HTN (3.5% of all 375 referred patients)

Exclude Pseudo-resistant

Types of “Pseudo”-resistance-”apparent resistant htn”

- **Inaccurate BP measurement**
  - Can repeat BP measurement yourself, including standing BP and BP in both arms using device technique but initial BP is best w/o the health care provider in the room

- **Poor Med adherence**
  - Look at pill bottles or call pharmacy, blood or urine drug levels, MEMS

- **White coat hypertension (WCH)**
  - Do out of office BP measurement and have a low threshold for a 24-hour ABPM being placed on the morning after the clinician administers the patients’ BP meds to the patient

MEMS=Medication Event Monitoring System
Questions to discuss:

- Does Sam have resistant hypertension? - Yes

- How important is “pseudo-resistant” hypertension? - Very important accounting for up to 50% of those who appear to be resistant

- Do we believe there is a benefit to controlling resistant hypertension?
Uncontrolled Blood Pressure

- Improper BP measurement
- White coat effect
- Poor Adherence

True Resistant Hypertension

Questions to discuss:

- Do we believe there is a benefit to controlling resistant hypertension?
Consequences of Resistant Hypertension

• The degree to which CV risk is reduced with treatment is unknown, however the benefits of successful treatment are likely substantial.\(^1\)

• In fact, two recent studies found that resistant hypertension was associated with a 2.2-fold increased risk for cardiovascular morbidity\(^2\) and a 50% higher risk for cardiovascular events\(^3\).

• Furthermore, the TNT study\(^4\) and recent ALLHAT post-hoc sub-study found significant increases in CHD, stroke, all cause mortality and HF in the 1/3 within the ALLHAT study who had resistant hypertension\(^5\).

Questions to discuss:

- Do we believe there is a benefit to controlling resistant hypertension? - Yes
Causes of True Resistant Hypertension

Identifiable (Secondary-Reversible) Causes of Hypertension

Drug-Induced or Other Causes

Volume Overload-high sodium intake, CKD, inadequate diuretic therapy

Aldosterone Excess

Associated Conditions

• Obesity
• Excess alcohol intake
• Sleep apnea

Clinical Inertia

Suboptimal antihypertensive drug combinations

Secondary Causes of Resistant Hypertension

- Etiologies of Secondary Hypertension
  - Sleep apnea
  - Intrinsic renal disease
  - Thyroid disease
  - Cushing’s syndrome
  - Primary aldosteronism
  - Pheochromocytoma
  - Renal artery disease

- When to evaluate for a secondary cause?
  1. Unusual presentation of hypertension
     - very severe
     - very sudden
     - very young or very old
     - resistant
  2. Clinical clues suggesting a particular form of secondary hypertension

Calhoun D et al. AHA Scientific Statement: Circulation 2008;117;E510-526
# Screening Tests for 2° HTN

<table>
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<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 metanephrines</td>
</tr>
<tr>
<td>1° aldosteronism</td>
<td>↓ or nl K⁺, ↑ plasma aldo (&gt;15) with Aldo/PRA &gt;20-30</td>
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<tr>
<td>Cushing’s disease</td>
<td>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</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>Hx*, polysomnography</td>
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</tbody>
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*Positive Epworth Sleepiness Score
Drug-Induced (Medications) that Can Interfere with BP Control

- NSAIDs/COX-2 inhibitors
- Oral contraceptives (estrogen predominant)
- Sympathomimetic agents (decongestants, diet pills, cocaine)
- Stimulants (amphetamines, methylphenidate)
- Alcohol
- Anti-depressants (TCAs and SNRIs)
- Cyclosporine
- Erythropoietin
- Natural licorice
- Herbal compounds (ephedra or ma huang)

Calhoun et al. AHA Scientific Statement: *Hypertension* 2008;51:1403-1419
Causes of True Resistant Hypertension

Identifiable (Secondary) Causes of Hypertension
Drug-Induced or Other Causes
Volume Overload-High Sodium Intake
  CKD
  Inadequate Diuretic Therapy
Aldosterone Excess
Associated Conditions
  • Obesity
  • Excess alcohol intake
  • Sleep apnea
Clinical Inertia
Suboptimal antihypertensive drug combinations

Resistant Hypertension: High/Low Dietary Salt Cross-Over Evaluation

Seated Blood Pressure/ ABPM

12 patients

3.4 BP meds
Office BP = 146/84 mm Hg

6 patients low-salt diet 1 week
Low Na 50 mmol/d

wash-out 2 weeks

6 patients low-salt diet 1 week
Low Na 50 mmol/d

6 patients high-salt diet 1 week
High Na 250 mmol/d

24-hr Urine for Na, K, Aldo
BNP, PRA
PWV, AIx

6 patients high-salt diet 1 week
High Na 250 mmol/d

Pimenta, E et al. Hypertension 54: 475-481, 2009
Large Reduction in Systolic and Diastolic BP with Dietary Na Restriction

Pimenta, E et al. Hypertension 54: 475-481, 2009
Initial Medications For The Management of Hypertension

Lifestyle Modification—Especially Diet and Exercise

β-blockers should be included in the regimen if there is a compelling indication for a β-blocker

Diuretics

ACE inhibitors or ARBs

Black population

Calcium antagonists

Which “Thiazide”? 

- Thiazide
  - Hydrochlo-rothiazide
  - Chlorthiazide
  - Bendro-flumethiazide

- Thiazide-like
  - Chlorthalidone
  - Metolazone
  - Indapamide
Switching Hctz to Chlorthalidone at Same Dose Now Controls Those with Resistant Hypertension

Study Design
(Chlorthalidone vs Hctz as Add-On)

Phase 3, multicenter, double-blind randomized study

Screening, washout, placebo run-in

AZL 40 mg

Monotherapy

Day -1 Randomization, baseline ABPM

Forced addition of CLD or HCTZ

Week 2

Optional titration

Week 6 ABPM

AZL–CLD 40 mg + 25 mg

Week 10 Final ABPM

AZL + HCTZ 40 mg + 25 mg

Follow-up

AZL + HCTZ 40 mg + 12.5 mg

Primary Efficacy Endpoint

Change in Trough Sitting Clinic SBP (mm Hg) at 6 and 10 weeks

<table>
<thead>
<tr>
<th>Week 6</th>
<th>Week 10</th>
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<tbody>
<tr>
<td>164.7 ± 9.1</td>
<td>164.7 ± 9.1</td>
</tr>
<tr>
<td>-35.1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-37.8&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>164.4 ± 9.9</td>
<td>164.4 ± 9.9</td>
</tr>
<tr>
<td>-29.5</td>
<td>-32.8</td>
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<sup>a</sup> P<0.001

AZL–CLD  (N=303)
AZL + HCTZ  (N=306)

Diuretic Use: Practical Considerations

Chlorthalidone

- Dosing 12.5-25 mg daily

- Metabolic complications slightly worse, especially hypokalemia, but greatly lessened when used with RAS blocker

- May be given with spironolactone (but watch out for hyponatremia)
Diuretic Use: Practical Considerations

Spironolactone

- Dosing 12.5–25 mg daily

- Hyperkalemia uncommon if good renal function

- CKD, ACEI or ARB or Renin inhibitor, NSAIDs increase risk of hyperkalemia

- Generally well tolerated up to 25 mg

- Breast tenderness/gynecomastia dose dependent, more common in dig era
Diuretic Use: Practical Considerations
Loop diuretics (LD)

- Venodilators
- Usually not needed until GFR < 30-35 mL/min/1.73m²
- Combine LD along with BB when using minoxidil or hydralazine
- Use Long acting agent (torsemide) or at least twice-3X daily dosing if using furosemide to avoid distal paradoxical sodium reclamation
Prevalence of Idiopathic Hyperaldosteronism in Subjects With Resistant Hypertension

PA = primary aldosteronism.
BP Response with Spironolactone 25-50 mg as 4th Drug: ASCOT Results

- SBP: Pre 156.9, Post 135.1, Δ SBP = -21.9
- DBP: Pre 85.3, Post 75.8, Δ DBP = -9.5

6% discontinuation rate due to adverse effects

N=1411

Causes of True Resistant Hypertension

Identifiable (Secondary) Causes of Hypertension
Drug-Induced or Other Causes
Volume Overload-high sodium intake, CKD, inadequate diuretic therapy

Aldosterone Excess

Associated Conditions- assoc w Increased SNS and MRA
  • Obesity - excess volume and SNS overactivity
  • Excess intermittent alcohol intake-SNS overactivity
  • Sleep apnea - CPAP reduces BP but does not cure HTN

Clinical Inertia
Suboptimal antihypertensive drug combinations

The Effect of CPAP on Resistant Hypertension is Modest, At Best
HIPARCO Randomized Clinical Trial

Methods:
- Spanish Study in 194 patients with resistant htn and OSA (AHI >15)
- CPAP vs no CPAP
- Primary Endpoint = Change in 24 hour mean BP as measured by ABPM

Mean Change in BP with CPAP modest
- Diastolic BP – 3.2 mm Hg
- Systolic BP – 3.1 mm Hg
- Greater prevalence of dipping (35.9% vs 21.6%)

Martinez-Garcia et al. JAMA 2013; 310: 2407
Causes of True Resistant Hypertension

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Associated Conditions
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• Sleep apnea

Clinical Inertia
Suboptimal antihypertensive drug combinations

What Is Clinical Inertia?

The failure of healthcare providers to initiate or intensify therapy when indicated.
Poorly Controlled Hypertension in NHANES, 2005-2008

- 52% Untreated
- 34% Taking <3 meds
- 14% Clinical Inertia
- 52% Apparent Treatment Resistant

The Effect of Therapeutic Inertia

- 62 practices in N.C., S.C., Ga. Part of the Hypertension Initiative
- N=7,253 hypertensive patients that had ≥4 visits and ≥1 elevated BP
- Therapeutic inertia = SBP ≥140 mm Hg and/or DBP ≥90 mm Hg with no change in antihypertensive therapy
- Occurred in 86.9% of visits

Okonofua EC et al. Hypertension 2006;47:1-7
Causes of True Resistant Hypertension

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Drug-Induced or Other Causes
Volume Overload—high sodium intake, CKD, inadequate diuretic therapy
Aldosterone Excess
Associated Conditions
• Obesity
• Excess alcohol intake
• Sleep apnea
Clinical Inertia
Suboptimal antihypertensive drug combinations
  ACE + ARB
  Beta Blocker + Clonidine
  Aliskerin + ACE/ARB in Type 2 AODM or when eGFR < 60 mL/min/1.73 m²

Combining ACEI and ARB: Harm in Clinical Trials

• 1ALTITUDE Study: Combined ACEi or ARB with a Direct Renin Inhibitor in Type 2 diabetes: No benefit, more hyperkalemia

• 2NEPHRON-D Study: Combined ACEi and ARB in type 2 diabetes: Stopped for futility, acute hyperkalemia, and acute kidney injury

• 3ONTARGET Study: Combined ACEi and ARB: No benefit, more acute kidney injury, hypotension and hyperkalemia

1 N Engl J Med 2012; 367:2204-2213
4Curr Opin Nephrol Hypertens. 2014;23(5):449-455
Device-Based Therapy for Resistant Hypertension - Not Ready for Prime Time 
Not FDA Approved

• **Baroreflex Activation Therapy**
  - back to the drawing board

• **Renal Denervation Therapy**
  - re-evaluating the data

We will have to wait to see if either of these devices meet with Future FDA approval
Conventional, 24-hr, Daytime and Night-time SBP as Predictors of Cardiovascular Endpoints – Syst-Eur

Bedtime Dosing of One BP Medication in Resistant Hypertension
Best for RAS Blocker or CCB

- Change in SBP (mm Hg):
  - 12 - 15
  - 8
  - 6
  - 4
  - 2
  - 0
- Change in DBP (mm Hg):
  - 12 - 15
  - 8
  - 6
  - 4
  - 2
  - 0

Diurnal mean: $P < 0.001$
Nocturnal mean: $P < 0.001$
24-hr mean: $P < 0.001$

3 drugs on awakening
One of the drugs at bedtime

Hermida Am J HTN 2010, 23: 432
Hermida et al. *Chronobiol Intern* 2010; 27: 1629
Final Points:

• In the future we may define resistant hypertension as an elevated BP in patients fully adherent to maximally tolerated doses of multiple-drug regimens, including a long-acting thiazide diuretic (chlorthalidone preferred) and a mineralocorticoid receptor antagonist (MRA), like spironolactone, while on a low-salt diet. In addition, patients should have a 24-hr ABPM placed in the morning after personally administering their medications to confirm true resistant and not white-coat resistant hypertension.
Issues in the Diagnosis and Management of Resistant Hypertension:

- Sam is a 58 y.o man with a 20 yr history of hypertension who is new to your practice. When seen by you, he is on losartan/Hctz 100/25 and amlodipine 10 mg. His BP today in your office is 144/94.

- Change Losartan/Hctz to another ARB/chlorthalidone
- Add spironolactone 12.5 mg q day
- Watch K+, creatinine, and sodium on follow-up
- BP falls to 128/82 mm Hg
Summary

- Resistant hypertension is a medical problem that is increasing in prevalence and of clinical concern.

- Mechanisms are multiple, but aldosterone excess and high dietary salt ingestion contributing to persistent intravascular fluid retention w/o edema appears to be an important underlying factor.

- Treatment is predicated upon lifestyle changes, combining agents from different classes at effective doses, with effective use of diuretics, including Mineralocorticoid antagonists (MRA’s).

- Future approval of device therapy in the US to treat resistant hypertension remains uncertain but is being studied.