Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

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FACULTY DISCLOSURES

Jan N. Basile, MD
- Consultant – Lilly, Medtronic
- Speaker - Arbor

William Elliott, MD, PhD
- Editor - Elsevier

Keith C. Ferdinand, MD, FACC, FAHA
- Consultant - Boehringer Ingelheim, Sanofi, Amgen, Eli Lilly
- Speaker/Consultant - Astra Zeneca
LEARNING OBJECTIVES

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

• Describe the burden of resistant hypertension
• Discuss the clinical evaluation of resistant hypertension, including approaches to rule out identifiable [secondary, reversible] causes
• Recognize the importance of 24-hour ambulatory blood pressure monitoring (ABPM) in the diagnosis of resistant hypertension
• Employ effective combinations of lifestyle interventions and pharmacotherapy to maximize BP control in patients with resistant hypertension

PRE-TEST QUESTION 1

ON A SCALE OF 1 TO 5, PLEASE RATE HOW CONFIDENT YOU ARE IN DIAGNOSING AND TREATING PATIENTS WITH RESISTANT HYPERTENSION

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
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PRE-TEST QUESTION 2

A 50 yr old female presents on maximum doses of 3 antihypertensive agents, one of which is a thiazide diuretic, and a BP of 150/98.

While the prevalence of resistant hypertension can be seen in up to 50% of those referred to a specialty hypertension clinic, it more likely occurs in:

1. 1 in 25 drug treated patients with hypertension
2. 1 in 12 drug treated patients with hypertension
3. 1 in 8 drug treated patients with hypertension
4. 1 in 5 drug treated patients with hypertension
5. 1 in 3 drug treated patients with hypertension

PRE-TEST QUESTION 3

A 62 year old AA male on 4 antihypertensive medications including a diuretic presents with a BP of 154/98 mm Hg. A test that is not indicated in his workup for resistant hypertension is:

1. Polysomnography after a positive Epworth Sleepiness Score
2. Plasma Metanephrines to rule out pheochromocytoma
3. Plasma aldosterone (A) and renin (R) levels to calculate the (A/R) ratio when considering an adrenal aldosteronoma
4. An echocardiogram to rule out LVH
5. A TSH to rule out hyper and hypothyroidism
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PRE-TEST QUESTION 4

A 48 yr old WF is being treated with lisinopril 40 mg, amlodipine 10 mg, and chlorthalidone 25 mg every day and has an office BP of 148/94 mm Hg. Up to what percentage of patients thought to have resistant hypertension actually have unrecognized white-coat hypertension on 24-hr ABPM?

1. 5%
2. 10%
3. 15%
4. 25%
5. 33%

PRE-TEST QUESTION 5

A 72 year old woman with resistant hypertension on 5 medications including 12.5 mg HCTZ remains uncontrolled on a 24-hour ABPM. Which is a frequently seen error in her treatment?

1. Failure to appreciate sodium excess
2. Failure to use adequate doses of medications
3. Failure to consider non-adherence
4. Failure to use the most effective diuretics
5. All of the above
### 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 F. 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 Faulkner, MD, FAHA; Robert M. Carey, MD, MACP, FAHA

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**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. Although obese, with a BMI of 32.2 kg/m2, he states he has been more adherent to a diet and exercise program of late. He has no history of ASCVD and 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. Most recently he is on olmesartan/HCTZ 40/25 and amlodipine 10 mg. His BP today in your office is 144/94.
Questions to discuss:

- Does Sam have resistant hypertension?

- How important is “pseudo-resistant” or treatment resistant hypertension?

- Do we believe there is a benefit to controlling 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

Questions to discuss:

- Does Sam have resistant hypertension? - Yes
- How important is “pseudo-resistant” hypertension?
- Do we believe there is a benefit to controlling resistant hypertension?

Prevalence of Resistant Hypertension

- True prevalence of resistant hypertension is not known
- Small studies estimate the prevalence at approximately
  - 10-30% in general practice
  - ≥ 50% in nephrology referral clinics
- 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
  - More recent 2005-2008 estimates show the prevalence of resistant hypertension continues to increase

Questions to discuss:

- Does Sam have resistant hypertension? - Yes
- How important is “pseudo-resistant” hypertension?
- Do we believe there is a benefit to controlling 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

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Pseudo-resistance

Types of “Pseudo”-resistance

- 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 24-hour ABPM placed the morning the clinician administers meds to patient

Suspect WCH when

- There is marked hypertension w/out TOD
- BP therapy produces symptoms suggestive of hypotension w/out much decrease in office BP

MEMS=Medication Event Monitoring System

Poor BP Measurement Technique May Be A Problem

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**Only Use an Acceptable Device**

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

**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

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

Entire Cohort

Apparent Treatment Resistant

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

True Resistant HTN

Don’t Forget About Clinical Inertia!

Prevalence of Optimal Treatment Regimens in Patients With Apparent Treatment-Resistant Hypertension Based on Office Blood Pressure in a Community-Based Practice Network
Brent M. Egan, Yumin Zhao, Jiexiang Li, W. Adam Brzezinski, Thomas M. Todoran, Robert D. Brook and David A. Calhoun

Resistant hypertension? Assessment of adherence by toxicological urine analysis
Oliver Jung\(^a\), Janis L. Gechter\(^a\), Cora Wunder\(^a\), Alexander Pauker\(^a\), Christine Bartel\(^a\), Helmut Geiger\(^a\), and Stefan W. Toennes\(^a\)

375 Patients Referred for Uncontrolled HTN on 3 Drugs

Maximized Doses
Excluded White Coat
Exclude Pseudo-resistant

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)
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?

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Uncontrolled Blood Pressure

![Diagram of Uncontrolled Blood Pressure]

True Resistant Hypertension

Questions to discuss:

- Does Sam have resistant hypertension?
- How important is “pseudo-resistant” hypertension?
- 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.\(^1\)
- However 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\(^3\)

Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

Treat to New Targets (TNT)-Resistant Hypertension

- 11.1% of 10,001 coronary artery disease (CAD) patients in the TNT Study had treatment resistant hypertension (TRH) defined as BP < 140 mm Hg on > 4 agents or ≥ 140 mm Hg on 3 antihypertensive agents. Mean f/up 4.9 years.

- The primary outcome was major CV events (composite of fatal CHD, nonfatal MI, resuscitated cardiac arrest, and stroke).

- TRH was associated with a 64% \( \overline{\text{in the primary outcome}} \) (hazard ratio [HR], 1.64; \( P < .001 \)), driven by a 69% \( \overline{\text{in CHD death}} \) (HR, 1.69; \( P = .001 \)) and a 73% \( \overline{\text{in nonfatal MI}} \) (HR, 1.73; \( P < .0001 \)).

- Patients with TRH also had a 45% \( \overline{\text{in death}} \) (\( P = .001 \)).

- In patients with CAD and HTN, TRH is associated with a marked increase in the risk of CV morbidity and mortality, including an increase in all-cause death.


Questions to discuss:

- Does Sam have resistant hypertension?

- How important is “pseudo-resistant” hypertension?

- Do we believe there is a benefit to controlling resistant hypertension? - Yes (TNT study and recent ALLHAT post-hoc sub-study in those with resistant hypertension\(^1\))

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

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
   • severe
   • sudden
   • very young or very old
   • resistant

2. Clinical clues suggesting a particular form of secondary hypertension

Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

### 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 metanephrines</td>
</tr>
<tr>
<td>1° aldosteronism</td>
<td>↓ or nl K⁺, ↑ plasma aldo (&gt; 15) with Aldo/PRA &gt;20</td>
</tr>
<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></td>
<td>Hx*, polysomnography</td>
</tr>
</tbody>
</table>

*Positive Epworth Sleepiness Score

### 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

### 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**

Questions to discuss:

- How important is lifestyle modifications in treating resistant hypertension?

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

Seated Blood Pressure/ ABPM

6 patients low-salt diet 1 week

6 patients high-salt diet 1 week

wash-out 2 weeks

12 patients

3.4 BP meds
Office BP = 146/84 mm Hg

Low Na 50 mmol/d

Low Na 50 mmol/d

High Na 250 mmol/d

High Na 250 mmol/d

Pimenta, E et al. Hypertension 54: 475-481, 2009

24-hr Urine for Na, K, Aldo
BNP, PRA
PWV, AIx
Large Reduction in Systolic and Diastolic BP with Dietary Na Restriction

Pimenta, E et al. Hypertension 54: 475-481, 2009

Questions to discuss:

- How important is lifestyle modification in treating resistant hypertension? - Very important, especially sodium excess which is often unappreciated.
Issues in the Diagnosis and Management of Resistant Hypertension:

- Mary is a 58 y.o woman with a 25 yr history of hypertension. She has CKD with an eGFR of 48 mL/min/1.73m2 for the past 2 years. Her BP was controlled up to 1 year ago on losartan 50 mg twice daily, amlodipine 10 mg daily and HCTZ 25 mg daily but she started taking a NSAID for joint aches.
  
  Her current BP sitting is 146/96 w/o orthostasis on a low-salt diet, eating no processed foods and not adding salt at the table. She has stopped the NSAID. Her 24-hour ABPM confirms her treatment resistance after giving her BP medications to her the morning of the test.

Which would not be an appropriate therapy for this patient?

1. Substituting chlorthalidone for HCTZ at the dose currently being used watching the serum potassium, sodium, and renal function
2. Consider using a different ARB for treating the patient
3. Add an ACE inhibitor to further inhibit the renin-angiotensin system
4. As a fourth drug, consider adding a mineralocorticoid-receptor antagonist (spironolactone or eplerenone) in addition to # 1.
5. Continue to reinforce the importance of a low-salt diet, daily exercise, and NSAID avoidance.
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### Initial Medications For The Management of Hypertension

**Lifestyle Modification—Especially Diet and Exercise**

- **Diuretics**
- **β-blockers** should be included in the regimen if there is a compelling indication for a β-blocker
- **ACE inhibitors** or **ARBs**
- **Calcium antagonists**

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**Diuretic Use: Practical Considerations**

**Chlorthalidone**

- Dosing 12.5-25 mg daily
- Metabolic complications worse, especially hypokalemia but lessened with RAS blocker
- May be dosed with spironolactone (watch out for hyponatremia)

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## Diuretic Use: Practical Considerations

### Spironolactone

- **Dosing**: 12.5–25–50 mg daily
- **Hyperkalemia**: uncommon if good renal function
- **Risk Factors**: CKD, ACEI or ARB, renin inhibitor, NSAIDs increase risk of hyperkalemia
- **Tolerance**: Generally well tolerated up to 25 mg
- **Side Effects**: Breast tenderness/gynecomastia dose dependent, more common in dig era

### Loop diuretics (LD)

- **Use**: Usually not needed until GFR < 30-35 mL/min/1.73m2
- **Combination**: Use LD often with BB when using minoxidil or hydralazine
- **Dosage**: Use Long acting agent or at least twice-3X daily dosing if using furosemide
Tricks of the Trade on Diuretics

• Maximize Diuretic Therapy
  – “Chlorthalidone should be preferentially used in patients with resistant hypertension”
  – Consider addition of mineralocorticoid receptor antagonist (spironolactone 25-50 mg, eplerenone (when > 50 mg use it bid), amiloride (5-10 mg qd) as a 4th drug

Calhoun et al. AHA Scientific Statement: Hypertension 2008;51:1403-1419

Chlorthalidone Has a Longer Half-life and Duration of Action vs. HCTZ

<table>
<thead>
<tr>
<th></th>
<th>Half-life, hours</th>
<th>Duration of Action, hours</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single dose</td>
<td>Long-term dosing</td>
</tr>
<tr>
<td></td>
<td>Single dose</td>
<td>Long-term dosing</td>
</tr>
<tr>
<td>HCTZ</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>CLD</td>
<td>40</td>
<td>45-60</td>
</tr>
<tr>
<td></td>
<td>24-48</td>
<td>48-72</td>
</tr>
</tbody>
</table>

Chlorthalidone 25 mg Has Greater BP-Lowering Efficacy vs HCTZ 50 mg, Especially at night

Daytime was 6:00 AM to 10:00 PM; night-time, 10:00 PM to 6:00 AM.

CLD=chlorthalidone; HCTZ=hydrochlorothiazide.


Switching Hctz to Chlorthalidone at Same Dose Now Controls Those with Resistant Hypertension

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Study Design

Phase 3, multicenter, double-blind randomized study

AZL–CLD

AZL–CLD

AZL + HCTZ

AZL + HCTZ

Screening, washout, placebo run-in

AZL 40 mg

Week 2

Week 6

Week 10

Final ABPM

Montotherapy

Forced addition of CLD or HCTZ

Optional titration

Day -1
Randomization, baseline ABPM

Follow-up

AZL 40 mg

AZL 40 mg

AZL 40 mg

AZL 40 mg

AZL–CLD 40 mg + 12.5 mg

AZL–CLD 40 mg + 25 mg

AZL + HCTZ 40 mg + 12.5 mg

AZL + HCTZ 40 mg + 25 mg


Primary Efficacy Endpoint

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

Week 6

Week 10

0

164.7± 9.1

164.7± 9.1

164.4± 9.9

164.4± 9.9

-30

-20

-10

0

-10

-20

-30

-40

AZL–CLD

(A=303)

AZL + HCTZ

(A=306)

-35.1

-29.5

-32.8

-37.8

P<0.001

Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

Prevalence of Idiopathic Hyperaldosteronism in Subjects With Resistant Hypertension

![Prevalence of PA (%)](image)

PA = primary aldosteronism.

BP Response with Spironolactone 25-50 mg as 4th Drug: ASCOT Results

![BP Response with Spironolactone](image)

△ SBP = -21.9
△ DBP = -9.5

6% discontinuation rate due to adverse effects

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 volume and SNS overactivity
• Excess alcohol intake
• Sleep apnea - CPAP reduces BP but does not cure HTN

Clinical Inertia

Suboptimal antihypertensive drug combinations


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Sleep Apnea Patient
Obstructive Sleep Apnea (OSA) and Resistant Hypertension: General Considerations

- OSA is common in resistant hypertension (RH)
  - Incidence 56-90% in observational studies
  - Incidence depends on diagnostic cut-off (AHI index)
  - Incidence higher in RH than in controlled hypertension
    - 71% vs 38%
- Often associated with a non-dipping pattern at night
- OSA increases activation of the sympathetic nervous system (SNS) and is associated with increased serum aldosterone

1. Isaksson H, Cin and Exp Hypertens, 1991
2. Logan AG, J of Hypertens 2001
4. Lloberes P, J of Sleep Research, 2010
5. Goncalves SC, Chest 2007

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 mmHG
- Systolic BP – 3.1 mmHg
- Greater prevalence of dipping (35.9% vs 21.6%)

Martinez-Garcia et al. JAMA 2013; 310: 2407
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

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

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Associated Conditions
• Obesity
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Clinical Inertia

Suboptimal antihypertensive drug combinations

What Is Clinical Inertia?

The failure of healthcare providers to initiate or intensify therapy when indicated

Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

Poorly Controlled Hypertension in NHANES, 2005-2008

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

BP (mm Hg)

<table>
<thead>
<tr>
<th>BP Control Rate (%)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP &lt;140/90 mm Hg</td>
<td>100</td>
</tr>
</tbody>
</table>

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

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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
Device-Based Therapy for Resistant Hypertension—Not Ready for Prime Time

- **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.

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**Baroreflex Activation Therapy (BAT)**
Continuously Modulates the Autonomic Nervous System

De Leeuw. ESC. 2011.
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

### Rheos Trial: Primary Endpoint Negative

<table>
<thead>
<tr>
<th>Description</th>
<th>Timeframe</th>
<th>N</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short Term Acute Efficacy</td>
<td>6 months</td>
<td>265</td>
<td>0.97</td>
</tr>
<tr>
<td>Long Term Sustained Efficacy</td>
<td>12 months</td>
<td>97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Short Term Procedure Adverse Events</td>
<td>30 days</td>
<td>265</td>
<td>1.00</td>
</tr>
<tr>
<td>Short Term BAT Adverse Events</td>
<td>6 months</td>
<td>265</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Long Term Device Adverse Events</td>
<td>12 months</td>
<td>265</td>
<td>&lt;0.001</td>
</tr>
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</table>


### Device-Based Therapy for Resistant Hypertension

- Renal Denervation Therapy
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

**Renal Sympathetic Afferent Nerve Activity:**
Kidney as Origin of Central Sympathetic Drive

- Vasoconstriction
- Insulin Resistance
- Hypertrophy
- Arrhythmia
- Oxygen Consumption
- Heart Failure Systolic
- Heart Failure p EF
- Renin Release → RAAS activation
- Sodium Retention
- Renal Blood Flow


**Symplicity Trials-Three so Far**

- **SYMPLICITY HTN-1 Study**
  - Pilot Study (n=45)
  - Catheter-based renal sympathetic denervation for resistant hypertension: a multicenter safety and proof-of-concept cohort study

- **SYMPLICITY HTN-2 Study**
  - Initial Randomized Study Performed Outside of the US
  - An international, multicenter, prospective, randomized, controlled study on the safety and effectiveness of renal denervation in patients with resistant hypertension

- **SYMPLICITY HTN-3 Study**
  - A multicenter, prospective, single-blind, randomized, sham-controlled study on the safety and effectiveness of renal denervation in patients with uncontrolled hypertension

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*** NEJM 2014; 370: 1393-1401.
Resistant Hypertension: Tricks of the Trade for Controlling Blood Pressure

**Symplicity HTN-3**

- Prospective, randomized, blinded, sham-controlled study in 535 TRH patients aged 18-80 years of age
- Office SBP $> 160$ mm Hg
- $\geq 3$ antihypertensive medications (one must be a diuretic) at maximally tolerated dose.
- On stable regimen for at least 2 weeks
- No significant renal insufficiency (eGFR $< 45$ mL/min)
- No known renal artery anatomy exclusion (i.e. dual renal arteries, known RA stenosis $> 50\%$)
- Until 6 month primary endpoint:
  - Change in OBP from baseline to 6 months post-randomization (sup margin of 5 mm Hg in renal denervation)
  - Incidence of major adverse events through 1 month post-randomization
  - Incidence of RAS at 6 months post-randomization.
- Major Secondary Outcome - change in average 24-hr ABPM from baseline to 6 months (superiority margin of 2 mm Hg)

**Primary Efficacy Endpoint**

$\Delta = -2.39$ (95% CI, -6.89 to 2.12)

$P = 0.26^*$

$\Delta = -14.1 \pm 23.9$

$P < 0.001$

$\Delta = -11.7 \pm 25.9$

$P < 0.001$

Office SBP (mm Hg)

180 mm Hg 166 mm Hg 180 mm Hg 168 mm Hg

(N=364) (N=353) (N=171) (N=171)

$*P$ value for superiority with a 5 mm Hg margin; bars denote standard deviations

**Symplicity HTN-3 STOPPED Jan 2014**

Lack of BP-efficacy
### Bedtime Dosing of One BP Medication in Resistant Hypertension

**Best for RAS Blocker or CCB**

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<tr>
<th>Drug Timing</th>
<th>SBP Change (mm Hg)</th>
<th>P-Value</th>
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<tbody>
<tr>
<td>Awakening</td>
<td>-12</td>
<td>&lt;0.001</td>
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**DBP Change (mm Hg)**

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**Diurnal mean**

**Nocturnal mean**

**24-hr mean**

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### Take Home Messages

**Resistant Hypertension**

1) Confirm treatment resistance
2) Exclude pseudoresistance
   - Including white coat hypertension and poor adherence
3) Identify and reverse contributing lifestyle factors
   - Including reduction in sodium consumption
4) Discontinue or minimize interfering substances

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Hermida Am J HTN 2010, 23: 432
Hermida et al. Chronobiol Intern 2010; 27: 1629
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Take Home Messages (Con’t)  
Resistant Hypertension

5) Consider (and then screen) for secondary causes of HTN
6) Rationalize/Intensify pharmacological treatment
   - Preferential use of chlorthalidone (or loop diuretic if CKD)
   - Consider spironolactone or eplerenone if side effects to spironolactone
   - Consider adding peripheral alpha blocker or beta-blocker [BB] (5th or 6th) unless there is a compelling indication for the BB (where used earlier)
   - Consider using DHP and non-DHP CCB together
   - Consider bed-time dosing of at least one agent

Final Points:

Distinguishing “apparent or pseudo- resistant” from “true” resistant hypertension will be a necessary part of any clinical assessment

• 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, while on a low-salt diet. In addition, they should have a 24-hr ABPM placed after administering their medications to confirm true resistant and not white-coat hypertension.
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Summary

• Resistant hypertension is a medical problem that is increasing in prevalence

• Mechanisms are multiple, but aldosterone excess and high dietary salt ingestion contributing to persistent intravascular fluid retention 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

• Future approval of device therapy in the US to treat resistant hypertension remains uncertain

POST-TEST QUESTION 1

A 50 yr old female presents on maximum doses of 3 antihypertensive agents, one of which is a thiazide diuretic, and a BP of 150/98.

While the prevalence of resistant hypertension can be seen in up to 50% of those referred to a specialty hypertension clinic, it more likely occurs in:

1. 1 in 25 drug treated patients with hypertension
2. 1 in 12 drug treated patients with hypertension
3. 1 in 8 drug treated patients with hypertension
4. 1 in 5 drug treated patients with hypertension
5. 1 in 3 drug treated patients with hypertension
POST-TEST QUESTION 2

A 62 year old AA male on 4 antihypertensive medications including a diuretic presents with a BP of 154/98 mm Hg. A test that is not indicated in his workup for resistant hypertension is:

1. Polysomnography after a positive Epworth Sleepiness Score
2. Plasma Metanephrines to rule out pheochromocytoma
3. Plasma aldosterone (A) and renin (R) levels to calculate the (A/R) ratio when considering an adrenal aldosteronoma
4. An echocardiogram to rule out LVH
5. A TSH to rule out hyper and hypothyroidism

POST-TEST QUESTION 3

A 48 yr old WF is being treated with lisinopril 40 mg, amlodipine 10 mg, and chlorthalidone 25 mg every day and has an office BP of 148/94 mm Hg. Up to what percentage of patients thought to have resistant hypertension actually have unrecognized white-coat hypertension on 24-hr ABPM?

1. 5%
2. 10%
3. 15%
4. 25%
5. 33%
A 72 year old woman with resistant hypertension on 5 medications including 12.5 mg HCTZ remains uncontrolled on a 24-hour ABPM. Which is a frequently seen error in her treatment?

1. Failure to appreciate sodium excess
2. Failure to use adequate doses of medications
3. Failure to consider non-adherence
4. Failure to use the most effective diuretics
5. All of the above

ON A SCALE OF 1 TO 5, PLEASE RATE HOW CONFIDENT YOU ARE IN DIAGNOSING AND TREATING PATIENTS WITH RESISTANT HYPERTENSION

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
POST-TEST QUESTION 6

WHICH OF THE STATEMENTS BELOW DESCRIBES YOUR APPROACH TO DIAGNOSING AND TREATING PATIENTS WITH RESISTANT HYPERTENSION (RH)?

1. I do not manage RH, nor do I plan to this year.
2. I did not manage RH before this course, but as a result of attending this course I’m thinking of managing it now.
3. I do manage patients with RH and this course helped me change my treatment methods.
4. I do manage patients with RH and this session confirmed that I don’t need to change my treatment methods.