Resistant Hypertension: Management Strategies

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Presenter Disclosure Information

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“Resistant Hypertension: Management Strategies”

FINANCIAL DISCLOSURE:
Institutional Grants: Lilly
Uncompensated Consulting: Takeda

Hypertension

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. Cushman, MD, FASA, Chair; Daniel Jones, MD, FASA; Stephen Turner, MD, FASA; David C. Goel, MD, FASA; Timothy P. Murphy, MD, FASA; Robert D. Tonin, MD, FASA; Anthony White, PhD; William C. Cushman, MD, FASA; William White, MD; Domenic A. Izzo, MD, FASA; Keith Nishiyama, MD; Thomas D. Gius, MD; Brian Finkler, MD, FASA; Robert M. Carey, MD, MACP, FAMA

Cahoon et al. AHA Scientific Statement: Hypertension 2008;51:1403-1419
Resistant Hypertension
Definition

- BP remaining above goal in spite of concurrent use of 3 antihypertensive agents of different classes.
- Ideally, 1 of the 3 agents should be a diuretic & all agents should be prescribed at optimal dose amounts.
- Resistant hypertension includes patients whose BP is controlled with use of >3 medications.

SBP Response to 2-Drug Combinations That Include or Do Not Include a Diuretic


Definition
Rationale

Resistant HTN is thus defined in order to identify patients who are at high risk of having reversible causes of HTN and/or patients who, because of persistently high BP levels, may benefit from special diagnostic and therapeutic considerations.
Prevalence of Resistant Hypertension

- True prevalence of resistant hypertension is not known¹
- Depending on locale, studies estimate the prevalence around
  - 10-30% in general practice
  - ≥ 50% in nephrology referral clinics²
- 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 hypertension³
- More recent 2005-2008 estimates show the prevalence of resistant hypertension continues to increase⁴

3. Persell SD. Hypertension. 2011;57:1076-1080

Treatment-Resistant Hypertension and the Incidence of CVD and ESRD in ALLHAT
[Prevalence: 14%]

Cumulative Percent Controlled (BP < 140/90) at Five Years by Number of Drugs Prescribed

Patient Characteristics Associated With Resistant Hypertension

- High baseline BP
- Older age
- Obesity
- Excessive dietary salt ingestion
- Chronic kidney disease
- Diabetes
- Left ventricular hypertrophy
- African American race
- Female gender
- Residence in southeastern United States

Lifestyle Factors Contributing to Resistant Hypertension

- Obesity or overweight
- High salt diet
- Physical inactivity
- Ingestion of low-fiber, high-fat diet
- Heavy alcohol ingestion

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

Seated Blood Pressure/ ABPM

- Low Na 50 mmol/d
- 6 patients low-salt diet 1 week
- wash-out 2 weeks
- Low Na 50 mmol/d
- 6 patients low-salt diet 1 week

- High Na 250 mmol/d
- 6 patients high-salt diet 1 week
- 24-hr Urine for Na, K, Aldo
- BNP, PRA
- PWV, Arx

Pimenta, E et al. Hypertension 54: 475-481, 2009
Large Reduction in Systolic and Diastolic 24h BP with Dietary Na Restriction

Causes of Resistance to Hypertension Treatment

- Poor adherence with prescribed medications
- Inaccurate BP measurement
- White coat hypertension

Overestimation of BP in VA:
Routine Clinic BPs (CPRS) vs Random Zero Mercury Manometers (Standard Technique with Trained Observers)
BP Measurement:
Of Paramount Importance!
- Patient seated with back supported and arm bared and supported at heart level.
- Patient should refrain from smoking or ingesting caffeine for 30 minutes prior to measurement.
- Measurements should begin ≥5 minutes of rest (patient should not talk and not be spoken to).
- Use appropriate cuff size and validated equipment.
- If manual determination:
  - Determine pulse obliteration pressure (POP) for SBP estimate: then inflate to about 30 mm Hg above POP.
  - Rate of "column" drop: 2 mm Hg/second or beat initially.
- Both SBP and DBP should be recorded.
- >2 readings: averaged or use median of 3 readings.

Substances that Can Interfere with Blood Pressure Control
- Non-Narcotic Analgesics
  - Non-steroidal anti-inflammatory agents including aspirin
  - Selective COX-2 inhibitors
- Sympathomimetic agents
  - decongestants
  - diet pills
  - cocaine
- Stimulants
  - methylphenidate
  - dextroamphetamine
  - dextroamphetamine
  - amphetamine, methamphetamine
  - modafinil

Substances that Can Interfere with Blood Pressure Control
- Alcohol
- Oral contraceptives
- Cyclosporine
- Erythropoietin
- Natural licorice
- Herbal compounds
  - ephedra
  - ma huang
Secondary Causes of Resistant Hypertension

Common

- Obstructive sleep apnea
- Renal parenchymal disease
- Primary aldosteronism
- Renal artery stenosis

Secondary Causes of Resistant Hypertension

Uncommon

- Pheochromocytoma
- Cushing’s disease
- Hyperparathyroidism
- Aortic coarctation
- Intracranial tumor

The Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) study

Original Article
Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Stoffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D’Agostino, Sr., Ph.D., Lance D. Dworkin, M.D., for the CORAL Investigators

N Engl J Med
Volume 370(1):13-22
January 2, 2014
CORAL: Kaplan–Meier Curves for the Primary Outcome


$N=947$

$\text{SBP 2.3 mm Hg lower in stent group; } P = 0.03$

Initial Choices of Medications

Diuretics

Diuretics or CCBs in Blacks

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

ACE inhibitors or ARBs

Calcium antagonists

* Recommended for CKD
Combining ACEI with ARB discouraged

Chlorthalidone 25 mg Vs. HCTZ 50 mg:
Change in 24-Hour Mean Systolic Blood Pressure


-15
-10
-5
0
24-Hour Mean
Daytime Mean
Nighttime Mean

HCTZ 50 mg/d, n=16
Chlorthalidone 25 mg/d, n=14

P=0.054
P=0.230
P=0.009
Treatment of Resistant Hypertension

- Consider addition of mineralocorticoid receptor antagonist [or amiloride]
- Use of loop diuretic may be necessary in patients with [stage 4] CKD (eGFR <30 mL/min)

Calhoun et al. Hypertension 2008;51:1403-19

Prevalence of Primary Aldosteronism in Subjects With Resistant Hypertension

<table>
<thead>
<tr>
<th>City</th>
<th>Prevalence of PA, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seattle</td>
<td>17%</td>
</tr>
<tr>
<td>Birmingham</td>
<td>20%</td>
</tr>
<tr>
<td>Oslo</td>
<td>22%</td>
</tr>
<tr>
<td>Prague</td>
<td>19%</td>
</tr>
</tbody>
</table>

PA = Primary aldosteronism


PATHWAY-2 Study Design

The Prevention And Treatment of Hypertension With Algorithm based therapy (PATHWAY)

Double blind, Randomised, Placebo-Controlled, Cross-over Study

Screening for Resistant Hypertension
- Rx A + C + D
- DOT* to exclude non-compliance
- Home BP to exclude white coat hypertension
- Secondary hypertension excluded

4 week
Single blind placebo run in
Treated with A+C+D
Randomisation

Double blind, Randomised, Placebo-Controlled, Cross-over Study
- 12 weeks per treatment cycle
- Forced titration; lower to higher dose at 6 weeks
- No washout period between cycles
- Home Systolic BP measured at 6 and 12 weeks

Amiloride
Open-label
Run-out
10 - 20mg o.d.

Plasma
Renin

Doxazosin MR
4 - 8mg o.d.

Bisoprolol
5 - 10mg o.d.

Placebo

Spironolactone
25 - 50mg o.d.

Sodium MR
0 - 8mg o.d.

Fluvastatin
10 - 40mg o.d.

Flurbiprofen
1 - 300mg o.d.
The Prevention And Treatment of Hypertension With Algorithm based therapy (PATHWAY) 2: Primary Outcome (Average Home SBP)

Improvement in BP in Blacks Uncontrolled with Diuretic+CCB

2X2 factorial design (n=98):
- amiloride (10 mg/d)
- spironolactone (25 mg/d)
- combination of both drugs
- placebo


Combinations of Medications*

- Diuretics
- ACE inhibitors or ARBs
- Calcium antagonists

Can add: mineralocorticoid antagonist or amiloride, α-blocker, alternative CCB, vasodilator, β-blocker, α-β-blocker, and/or central agonist

* Compelling indications may modify this.
If a specific secondary cause of HTN is suspected in a patient with resistant HTN, referral to the appropriate specialist is recommended as needed.

In the absence of suspected secondary causes of HTN, referral to a HTN specialist is recommended if the BP remains elevated in spite of 6 months of treatment. [Note: I would not recommend waiting 6 months, but refer whenever BP is not controlled and provider is unsure what to do next – this is what most do in VA because of BP performance measure]
Device-Based Therapy for Resistant Hypertension: Not Ready for Prime Time

- Baroreflex Activation Therapy still being investigated
- Renal Denervation Therapy re-designed the trials which are ongoing

We will have to wait to see if either of these devices meet with future FDA approval

Summary/Take Home Messages

- Resistant HTN is a common clinical problem, and is a marker of increased CVD risk
- Common factors related to resistant HTN include older age, obesity, DM, CKD, high salt diet, African American race, inconsistent adherence, and living in the southeastern U.S.
- Patients with resistant HTN may benefit from further evaluation, intensification of antihypertensive lifestyle and drug regimen, and/or referral to a hypertension specialist.
- Intensify regimen by combining agents from 3 major classes (diuretic, RAS blocker, CCB) at effective doses, with effective use of thiazide-type diuretics such as chlorthalidone, then, if necessary, add spironolactone or amiloride and/or a vasodilator.

Questions?