Best Therapy for Resistant Hypertension: The PATHWAY-2 Study

Antonio Coca MD, PhD, FRCP, FESC

Council on Hypertension. European Society of Cardiology
Hypertension and Vascular Risk Unit. Department of Internal Medicine
Hospital Clínic (IDIBAPS). University of Barcelona, Spain

Conflict of interest concerning this presentation: None

Joint Session ESC Council on HT & WG Cardiovascular Pharmacotherapy
EuroCVP 2016 Congress. Tel Aviv (Israel), May 29th, 2016
Definition of Resistant Hypertension

BP > 140/90 mmHg despite:

- Attention to lifestyle measures
- Treatment with 3 antihypertensive drugs in adequate doses (including a diuretic)


BP < 140/90 mmHg

- Requiring 4 or more antihypertensive drugs

The prevalence is unknown. Most data come from observational studies and retrospective analyses of clinical trials on prevention of morbidity and mortality.

Resistant hypertension is not synonymous with uncontrolled hypertension (which includes all patients not at BP goal independently of the cause and type of treatment).

Persell SD. Hypertension 2011;57:1076-1080
## Estimated Prevalence of Resistant Hypertension in Trials on Prevention of Morbidity and Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Uncontrolled patients (%)</th>
<th>Patients with ≥3 drugs (%)</th>
<th>Estimated prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT</td>
<td>34%</td>
<td>27%</td>
<td>15%</td>
</tr>
<tr>
<td>CONVINCE</td>
<td>33%</td>
<td>18%</td>
<td>12%</td>
</tr>
<tr>
<td>VALUE</td>
<td>40%</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

*Epstein M. J Clin Hypertens 2007; 9 (Suppl 1): 2-6*
Prevalence of Resistant Hypertension

Data from the US National Health and Nutrition Examination Survey from 2003 – 2008 including 15,968 adults with BP ≥ 140/90

- Resistant Hypertension: BP ≥ 140/90 despite using 3 different antihypertensive drug classes or using ≥ 4 drugs regardless of BP
- 539 patients (12.8% of drug treated patients) met criteria for resistant hypertension

Persell SD. Hypertension 2011;57:1076-1080
Resistant hypertension: a frequent and ominous finding among hypertensive patients with atherothrombosis

Dharam J. Kumbhani, P. Gabriel Steg, Christopher P. Cannon, Kim A. Eagle, Sidney C. Smith Jr, Kevin Crowley, Shinya Goto, E. Magnus Ohman, George L. Bakris, Todd S. Perlstein, Scott Kinlay, and Deepak L. Bhatt, on behalf of the REACH Registry Investigators

- The REACH registry is an international cohort of 53,530 patients with clinical atherosclerosis (5,587 physicians from 44 countries)
- The prevalence of resistant hypertension is estimated at 12.7% (6.2% treated with 3 drugs, 4.6% with 4 and 1.9% with ≥ 5 drugs)

© A. Coca
Hospital Clinico. IDIBAPS
Universidad Barcelona

Kumbhani et al. Eur Heart J 2013; 34; 1204-1214
Prevalence of Resistant Hypertension

Summary

- Accepting the reported prevalence of patients uncontrolled despite treatment with ≥ 3 antihypertensives of about 12.5% (RHT)
- Assuming that no more than 10% of all evaluated patients with apparent RHT have “true essential resistant HT”
- Hypertensive patients with true essential resistant resistant HT represent no more than 1% of all hypertensive patients
- Therefore, RHT may be considered an “infrequent” clinical condition

Jung et al. J Hypertens 2013; 31: 766-774
Kumbhani et al. Eur Heart J 2013; 34; 1204-1214
Egan BM et al. Circulation 2011;124:1046-1058
Causes of Resistant Hypertension

- **Apparently Resistant Hypertension**
  - Non compliance with treatment
  - White coat hypertension
  - Pseudohypertension

- **True Resistant Hypertension**
  - Medications and illicit drug use
    - Drugs (weight loss medicines..)
    - Herbal medicines
    - Illicit drugs (cocaine,..)
  - Associated clinical factors
    - Excessive salt and alcohol consumption
    - Obesity
    - Obstructive sleep apnea

- **Identifiable causes**
  - Primary aldosteronism
  - Renovascular disease
  - Chronic kidney disease
  - Pheochromocytoma, Cushing’s
  - Aortic coarctation

- **No identifiable causes**
  - “Essential” Resistant Hypertension

**Resistant Hypertension due to incorrect diagnosis or inadequate treatment**
Causes of Resistant Hypertension

141 patients (11%) with RH out of 1281 HT attended by the Hypertension Unit, RUSH University (Chicago) between 1993 and 2001

- "White coat" RH: 6%
- "essential" RH: 6%
- Nonadherence: 16%
- Drug-related (inadequate treatment): 58%
- Interfering substances: 1%
- Psychological: 9%
- Secondary HT: 5%
- Essential RH: 6%

375 patients referred to the Hypertension Unit of Goethe University Hospital (Frankfurt) between January 2004 and December 2011

Causes of Resistant Hypertension

- "White Coat" 2.5%
- "esencial" RH 9.8%
- Secondary HT 4%
- Inadequate treatment 68.1%
- Total or partial non-adherence 10.9%

Jung et al. J Hypertens 2013; 31: 766-774
Compliance with Antihypertensive Treatment in Resistant Hypertensive Patients

Compliance assessed by unplanned blood sampling for measurement of serum antihypertensive drug concentrations in all patients

163 men with RHT investigated for first time in the Out-patients Clinic

- Total noncompliance: 23%
- Partial noncompliance: 24%
- Full compliance: 53%

176 men with RHT admitted for hospitalization to exclude secondary HT

- Total noncompliance: 10%
- Partial noncompliance: 9%
- Full compliance: 81%

Compliance assessed by unplanned blood sampling for measurement of serum antihypertensive drug concentrations in all patients

 Strauch et al. J Hypertens 2013; 31: 2455-2461
Hemodynamic Treatment of Resistant Hypertension

Taler et al. Hypertension 2002; 39: 982-988
Low-dose Spironolactone in the Management of Resistant Hypertension


© A. Coca
Hospital Clinico. IDIBAPS
Universidad Barcelona

SBP

1.5 m 3 m 6 m

PA  Non PA

-18 -24 -24

-22 -24 -25

-26

DBP

1.5 m 3 m 6 m

-8 -11 -11

-12 -9

-15

Spironolactone 12.5 to 50 mg during 6 months
42 patients with true Resistant hypertension

Prospective, open-label, crossover design, with two treatment strategies:

- Phase 1: ARB + ACEI for 12 w
- Wash-out: 4 w
- Phase 2: ARB + Spironolactone 25-50 mg for 12 w

Mean age: 67 ± 9
Gender: 50% male
Baseline office SBP: 158.4 ± 15.3
Baseline office DBP: 80.4 ± 11.4

© A. Coca
Hospital Clínic. IDIBAPS
Universidad Barcelona

Alvarez et al. J Hypertens 2010; 28: 2329-2335
Spironolactone in the Management of Resistant Hypertension: ASCOT Study

- Prospective, open, randomized, two treatment groups:
  - Group 1: AML 5-10 + PERIND 4-8 + DOXAZ 4-8
  - Group 2: ATL 50-100 + DIU 1.2-2.5 + DOXAZ 4-8
- 1411 uncontrolled patients out of 19257 (7%) received 25-50 mg/d of spironolactone
- Mean age: 63 ± 8 years
- 40% with type 2 Diabetes
- Baseline BP 156.9 ± 18 / 85.3 ± 11.5

- K⁺: ↑ 0.41 mmol/L
- 4% K⁺ > 5.5 mmol/L
- 2% K⁺ > 6.0 mmol/L
- Cr: ↑ 0.1 mg/dL
- Side effects 6%
- Final mean dose of spironolactone 41 mg
- Follow-up 1.3 years (0.6-2.6)

Resistant Hypertension, Aldosterone, and Intravascular Volume Expansion

- RH all patients (n=279)
- RH high Aldo status (n=81) (UAld ≥ 12µg/ml and PRA ≤ 1 ng/ml/h)
- RH normal Aldo status (n=198)
- HT control group (n=53)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Aldo Status</th>
<th>High Aldo Status</th>
<th>All Patients</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP</td>
<td>P=0.008</td>
<td>P=0.002</td>
<td>P=0.001</td>
<td></td>
</tr>
<tr>
<td>ANP</td>
<td>P=0.002</td>
<td>P=0.01</td>
<td>P=0.001</td>
<td></td>
</tr>
</tbody>
</table>

The Prevention And Treatment of Hypertension With Algorithm based therapy
PATHWAY

Optimal Treatment of Drug Resistant Hypertension
PATHWAY-2

Principal Results

Bryan Williams, Tom MacDonald and Morris Brown
on behalf of the PATHWAY Investigators

Background

• The optimal drug treatment of resistant hypertension remains undefined
• Recent meta-analysis, 3 small RCTs, and several open/observational studies suggests that spironolactone is an effective treatment versus placebo
• There have been no RCTs directly comparing spironolactone with other BP-lowering drugs to determine whether spironolactone is the most effective treatment for resistant hypertension

Hypothesis

• Resistant hypertension is a sodium retaining state that is characterised by an inappropriately low plasma renin level despite treatment with a RAS-blocker + CCB + Thiazide Diuretic
• Further diuretic therapy with spironolactone will be more effective at lowering BP than alternative treatments, targeting different mechanisms, i.e. bisoprolol (β-sympathetic blockade and renin suppression) or doxazosin MR (α-sympathetic blockade and vasodilatation)
• Plasma renin level will be inversely related to the response to spironolactone

PATHWAY-2 Study Design

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

Doxazosin MR 4 – 8mg o.d.

Spironolactone 25 – 50mg o.d.

Bisoprolol 5 – 10mg o.d.

Placebo

Home Systolic BP measured at 6 and 12 weeks

Plasma Renin

*DOT = Directly Observed Therapy

- 12 weeks per treatment cycle
- Forced titration; lower to higher dose at 6 weeks
- No washout period between cycles

Primary outcome measures

Hierarchical Primary End-point:

1) Difference in average home systolic BP (HSBP) between spironolactone and placebo

followed, if significant by;

2) HSBP difference between spironolactone and the average of the other two active drugs (bisoprolol and doxazosin MR)

followed, if significant by;

3) HSBP difference between spironolactone and each of the other two active drugs

### Primary Outcome

<table>
<thead>
<tr>
<th>Comparators (N=314)</th>
<th>Home Systolic BP difference (mmHg)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone vs placebo</td>
<td>-8.70 (-9.72, -7.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone vs mean Bisoprolol/Doxazosin</td>
<td>-4.26 (-5.13, -3.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone vs Doxazosin</td>
<td>-4.03 (-5.04, -3.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spironolactone vs Bisoprolol</td>
<td>-4.48 (-5.50, 3.46)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Home Systolic BP (mmHg)</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>134.9 (134.0,135.9)</td>
<td>-12.8 (-13.8,-11.8)</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>139.0 (138.0,140.0)</td>
<td>-8.7 (-9.7,-7.7)</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>139.4 (138.4,140.4)</td>
<td>-8.3 (-9.3,-7.3)</td>
</tr>
<tr>
<td>Placebo</td>
<td>143.6 (142.6,144.6)</td>
<td>-4.1 (-5.1,-3.1)</td>
</tr>
</tbody>
</table>

Primary Outcome

# BP Control Rates

<table>
<thead>
<tr>
<th></th>
<th>Home Systolic BP (mmHg)</th>
<th>Patients</th>
<th>Met target</th>
<th>Least Squares Estimates</th>
<th>Odds ratio</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td>(n)</td>
<td>(r)</td>
<td>r/n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Spironolactone</strong></td>
<td>148.3</td>
<td>282</td>
<td>163</td>
<td>57.8</td>
<td>58.0 (52.0,63.7)</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>133.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Doxazosin</strong></td>
<td>147.8</td>
<td>276</td>
<td>115</td>
<td>41.7</td>
<td>41.5 (35.8,46.5)</td>
<td>0.52 (0.37,0.73)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>138.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bisoprolol</strong></td>
<td>147.7</td>
<td>280</td>
<td>122</td>
<td>43.6</td>
<td>43.3 (37.5,49.2)</td>
<td>0.55 (0.39,0.78)</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final</td>
<td>139.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>147.8</td>
<td>270</td>
<td>66</td>
<td>24.4</td>
<td>23.9 (19.1,29.4)</td>
<td>0.23 (0.16,0.33)</td>
</tr>
</tbody>
</table>

BP control rates refer to patients achieving a home systolic BP of <135mmHg. Odds ratios from logistic regression models adjusted for baseline.

# Serious Adverse Events and Withdrawals

<table>
<thead>
<tr>
<th></th>
<th>Bisoprolol</th>
<th>Spironolactone</th>
<th>Doxazosin</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events</strong></td>
<td>8 (2.6%)</td>
<td>7 (2.3%)</td>
<td>5 (1.7%)</td>
<td>5 (1.7%)</td>
<td>0.831</td>
</tr>
<tr>
<td><strong>Any adverse event</strong></td>
<td>68 (11.3%)</td>
<td>67 (10.4%)</td>
<td>58 (10.1%)</td>
<td>42 (9.1%)</td>
<td>0.711</td>
</tr>
<tr>
<td><strong>Withdrawals for adverse events</strong></td>
<td>2 (2.9%)</td>
<td>3 (3.4%)</td>
<td>8 (10.0%)</td>
<td>2 (2.6%)</td>
<td>0.084</td>
</tr>
</tbody>
</table>

*p values for Fisher’s exact test*

PATHWAY 2

Implications for Clinical Practice

- PATHWAY-2 is the first RCT to directly compare spironolactone with other active BP-lowering treatments in patients with well characterised resistant hypertension.

- The result in favor of spironolactone is unequivocal – Spironolactone is the most effective treatment for resistant hypertension, and these results should influence treatment guidelines globally.

- Patients should not be defined as resistant hypertension unless their BP remains uncontrolled on spironolactone.

How to Manage Resistant Hypertension

Confirm Treatment Resistance
Office BP ≥ 140/90 or ≥ 130/80 (Dm2, CRF) receiving 3 antiHT drugs (diuretic) or office BP at goal but requiring 4 or more antiHT drugs

Exclude Pseudoresistance

Identify and Reverse Contributing Lifestyle Factors

Discontinue or Minimize Interfering Substances

Screen for Secondary Causes of HT

RAS blockade
Diuretic
Calcium Channel Blocker
Spironolactone

How to Manage Resistant Hypertension

Confirm Treatment Resistance
Office BP ≥ 140/90 or ≥ 130/80 (Dm2, CRF) receiving 3 antiHT drugs (diuretic) or office BP at goal but requiring 4 or more antiHT drugs

Exclude Pseudoresistance

Identify and Reverse Contributing Lifestyle Factors

Discontinue or Minimize Interfering Substances

Refer to Hypertension Specialist

Pharmacological Treatment

Screen for Secondary Causes of HT

© A. Coca
Hospital Clínico. IDIBAPS
Universidad Barcelona