Resistant hypertension: fact or fiction?

Wilko Spiering, internist-vascular medicine specialist
Department of Vascular Medicine
University Medical Center Utrecht
The Netherlands
Hypertension is a silent killer

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>High-income regions</th>
<th>Central Asia and central and eastern Europe</th>
<th>Latin America and Caribbean</th>
<th>Middle East and North Africa</th>
<th>East and Southeast Asia and Oceania</th>
<th>South Asia</th>
<th>Sub-Saharan Africa</th>
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<tbody>
<tr>
<td>Deaths</td>
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<td>High Blood Pressure</td>
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<td>Smoking and Secondhand Smoke</td>
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<td>Diets Low in Fruits</td>
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<td>High BMI</td>
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<td>High Blood Glucose</td>
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<tr>
<td>Physical Inactivity and Low Activity</td>
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<td>High Dietary Salt</td>
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<td>Alcohol Use</td>
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<td>Diets Low in Nuts and Seeds</td>
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<td>High Serum Cholesterol</td>
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<td>Diets Low in Vegetables</td>
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<td>Diets Low in Whole Grains</td>
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<tr>
<td>Diets Low in Fish and Seafood</td>
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</tr>
</tbody>
</table>

Deaths Attributable to Individual Risk Factors

Ezzati, N Engl J Med 2013
Effects on global deaths and DALYs in 2010

Lim, Lancet 2013
Definition of resistant hypertension

• 2008 AHA and 2013 ESH/ESC definition\textsuperscript{1,2}:
  – Uncontrolled BP, despite ≥3 optimally dosed drugs of different classes, ideally including diuretic, OR
  – Controlled BP with ≥4 optimally dosed drugs of different classes, ideally including diuretic

• Subtypes:
  – Apparent resistant hypertension
  – True resistant hypertension
  – Pseudoresistant hypertension
  – Refractory resistant hypertension

\textsuperscript{1}Calhoun, Circulation 2008
\textsuperscript{2}Mancia, J Hypertens 2013
Prevalence of resistant hypertension

- **8.9%** (n = 539) 'Resistant hypertensives'
- **37.0%** (n = 1520) 'Uncontrolled, untreated'
- **40.8%** (n = 2025) 'Controlled, ≤3 drugs'
- **19.6%** (n = 1135) 'Uncontrolled, ≤2 drugs'

**Percent of US hypertensives**

**Years of National Health and Nutrition Examination Surveys**

- **1988-94**
  - Controlled on ≥ 4 medications: 2.3 ± 0.5% (n = 89)
  - Uncontrolled on ≥ 3 medications: 6.5 ± 0.7% (n = 252)
- **1999-2004**
  - Controlled on ≥ 4 medications: 5.2 ± 0.8% (n = 180)
  - Uncontrolled on ≥ 3 medications: 9.3 ± 0.7% (n = 322)
- **2005-08**
  - Controlled on ≥ 4 medications: 7.3 ± 1.1% (n = 162)
  - Uncontrolled on ≥ 3 medications: 13.4 ± 1.1% (n = 298)
Prevalence of resistant hypertension

- Spanish ABPM cohort (n=68,045)
- Definition: office blood pressure ≥140 and/or 90 mmHg with ≥3 antihypertensives, 1 of them a diuretic
- Resistant hypertension: 12.2%
- After ABPM:
  - True resistant hypertension 62.5%
  - White coat resistant hypertension 37.5%
Resistant hypertension: fact or fiction?

- Prevalence hypertension\(^1\):
  - 2000: 972 million
  - 2025: 1.5 billion

- Prevalence true resistant hypertension:
  - ~8-10\% all hypertensives
  - ~100 million worldwide in 2015

- Associated with increased long-term cardiovascular events\(^2\)

\(^1\)Kearney, Lancet 2005
\(^2\)Daugherty, Circulation 2012
Workup in resistant hypertension

1. Exclude pseudoresistant hypertension
2. Reverse contributing factors
3. Screen for secondary hypertension
4. Optimize pharmacotherapy
5. Consider device-based therapy
Workup in resistant hypertension

1. Exclude pseudo-resistant hypertension
2. Reverse contributing factors
3. Screen for secondary hypertension
4. Optimize pharmacotherapy
5. Consider device-based therapy
Causes of pseudo-resistant hypertension

- Inaccurate BP measurement
- Poor adherence to antihypertensive therapy
- Suboptimal antihypertensive therapy
- Poor adherence to lifestyle aspects
- White coat resistant hypertension
Nonadherence in resistant hypertension

FIGURE 3 Percentage of prescribed drugs taken by nonadherent patients.

Jung, J Hypertens 2013
Workup in resistant hypertension

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Effects of dietary salt reduction

Pimenta, Hypertension 2009
Drug-related causes in resistant HT

- Nonnarcotic analgesics (NSAID’s, selective COX-2 inhibitors)
- Sympathomimetic agents (decongestants, diet pills, cocaine)
- Stimulants (methylphenidate, amphetamines, modafinil)
- Oral contraceptives
- Glucocorticoids
- Cyclosporine
- Erythropoietin
- Angiogenesis inhibitors
- Herbal preparations (ephedra)
Workup in resistant hypertension

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Secondary causes of resistant hypertension

- Primary aldosteronism
- Obstructive sleep apnea
- Renal parenchymal disease
- Renal artery stenosis
- Insulin resistance
- Pheochromocytoma
- Cushing’s syndrome
- Hyperparathyroidism
- Aortic coarctation
- Intracranial tumor
### Secondary causes of resistant hypertension

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Prevalence in Resistant Hypertension, %</th>
<th>Diagnostic Tests</th>
<th>Treatment</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive sleep apnea</td>
<td>60-70</td>
<td>Polysomnography</td>
<td>Continuous positive airway pressure</td>
<td>High</td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>7-20</td>
<td>Serum aldosterone, plasma renin activity</td>
<td>Spironolactone, eplerenone, or surgical resection of tumor in unilateral aldosterone-producing adenoma</td>
<td>High</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>2-24</td>
<td>Duplex Doppler ultrasonography, computed tomographic angiography, or magnetic resonance angiography</td>
<td>Renal revascularization in selected patients</td>
<td>High</td>
</tr>
<tr>
<td>Renal parenchymal disease</td>
<td>1-2</td>
<td>Serum creatinine</td>
<td>Correction of underlying causes if possible</td>
<td>High</td>
</tr>
<tr>
<td>Drug-induced or heavy alcohol</td>
<td>2-4</td>
<td>History taking</td>
<td>Discontinuation of offending agents</td>
<td>Moderate</td>
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<tr>
<td>Alcohol use</td>
<td></td>
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<tr>
<td>Thyroid disorders</td>
<td>&lt;1</td>
<td>Thyrotropin, free thyroxine</td>
<td>According to underlying disorders</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

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*a Level of evidence based on evidence strength and consistency.*
Reasons for excluding patients for renal denervation

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Office SBP &lt; 160 mmHg</td>
<td>23 (19%)</td>
</tr>
<tr>
<td>Mean 24-h ambulatory SBP &lt; 150 mmHg without antihypertensive treatment or SBP &lt; 140 mmHg during antihypertensive treatment</td>
<td>26 (22%)</td>
</tr>
<tr>
<td>Secondary cause of hypertension</td>
<td></td>
</tr>
<tr>
<td>Primary aldosteronism</td>
<td>14 (12%)</td>
</tr>
<tr>
<td>Primary hyperparathyroidism</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Pseudo-hyperaldosteronism</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Coarctatio aortae</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>10 (8%)</td>
</tr>
<tr>
<td>Renal artery anatomy is ineligible for treatment with pRDN</td>
<td>9 (7%)</td>
</tr>
<tr>
<td>History of renal artery stenting</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Renal artery stenosis</td>
<td>6 (4%)</td>
</tr>
<tr>
<td>Options for pharmaceutical treatment of hypertension</td>
<td></td>
</tr>
<tr>
<td>Other reasons</td>
<td></td>
</tr>
<tr>
<td>Patient did not want to be treated with pRDN</td>
<td>24 (20%)</td>
</tr>
<tr>
<td>Referring physician did not want his patient to be treated</td>
<td>12 (10%)</td>
</tr>
<tr>
<td>Patient is expected not to be compliant</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Severe claustrophobia</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Adequate regulation of BP after lifestyle adjustments</td>
<td>1 (1%)</td>
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<tr>
<td></td>
<td>2 (1%)</td>
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</tbody>
</table>
Workup in resistant hypertension

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5. Consider device-based therapy
Optimize pharmacotherapy in resistant HT

• Withdrawal interfering medications
• Diuretic therapy
  • Higher doses
  • Chlorthalidone in stead of hydrochlorothiazide
  • Loop diuretics when eGFR $<30$ ml/min/1.73 m$^2$
• Combination therapy
  • Low dose combination vs. maximal uptitration
  • Triple FDC vs. dual FDC
• Mineralocorticoid receptor antagonists
### Spironolactone in resistant hypertension

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Spironolactone (n=55)</th>
<th>Placebo (n=56)</th>
<th>Between-Group Difference*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic BP</strong></td>
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<tr>
<td>ABPM daytime systolic BP, mm Hg</td>
<td>$-9.3 (±12.6)$</td>
<td>$-3.9 (±12.1)$</td>
<td>$-5.4 (±10.0; -0.8)$</td>
<td>0.024</td>
</tr>
<tr>
<td>ABPM nighttime systolic BP, mm Hg</td>
<td>$-11.2 (±17.6)$</td>
<td>$-2.6 (±17.7)$</td>
<td>$-8.6 (±15.2; -2.0)$</td>
<td>0.011</td>
</tr>
<tr>
<td>24-h ABPM systolic BP, mm Hg</td>
<td>$-13.8 (±11.8)$</td>
<td>$-4.0 (±12.7)$</td>
<td>$-9.8 (±14.4; -5.2)$</td>
<td>0.004</td>
</tr>
<tr>
<td>Office systolic BP, mm Hg‡</td>
<td>$-14.6 (±15.6)$</td>
<td>$-8.1 (±14.8)$</td>
<td>$-6.5 (±12.2; -0.8)$</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
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</tr>
<tr>
<td>ABPM daytime diastolic BP, mm Hg</td>
<td>$-4.2 (±8.0)$</td>
<td>$-3.2 (±8.2)$</td>
<td>$-1.0 (±4.0; 2.0)$</td>
<td>0.358</td>
</tr>
<tr>
<td>ABPM nighttime diastolic BP, mm Hg</td>
<td>$-5.6 (±10.5)$</td>
<td>$-2.6 (±11.0)$</td>
<td>$-3.0 (±7.0; 1.0)$</td>
<td>0.079</td>
</tr>
<tr>
<td>24-h ABPM diastolic BP, mm Hg</td>
<td>$-4.2 (±7.0)$</td>
<td>$-3.2 (±7.7)$</td>
<td>$-1.0 (±3.7; 1.7)$</td>
<td>0.405</td>
</tr>
<tr>
<td>Office diastolic BP, mm Hg‡</td>
<td>$-6.6 (±9.6)$</td>
<td>$-4.1 (±8.6)$</td>
<td>$-2.5 (±5.9; 0.9)$</td>
<td>0.079</td>
</tr>
<tr>
<td><strong>Pulse Pressure§</strong></td>
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<tr>
<td>ABPM daytime pulse pressure, mm Hg</td>
<td>$-5.1 (±8.4)$</td>
<td>$-0.7 (±8.3)$</td>
<td>$-4.4 (±7.5; -1.3)$</td>
<td>0.007</td>
</tr>
<tr>
<td>ABPM nighttime pulse pressure, mm Hg</td>
<td>$-5.6 (±12.9)$</td>
<td>$0.0 (±10.4)$</td>
<td>$-5.6 (±10.0; -1.2)$</td>
<td>0.005</td>
</tr>
<tr>
<td>24-h ABPM pulse pressure, mm Hg</td>
<td>$-6.5 (±7.2)$</td>
<td>$-0.8 (±7.6)$</td>
<td>$-5.7 (±8.5; -2.9)$</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Office pulse pressure, mm Hg‡</td>
<td>$-8.0 (±11.2)$</td>
<td>$-4.0 (±11.8)$</td>
<td>$-4.0 (±8.3; 0.3)$</td>
<td>0.056</td>
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<tr>
<td><strong>Other Characteristics</strong></td>
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<tr>
<td>Weight, kg</td>
<td>$0.3 (±1.6)$</td>
<td>$0.5 (±2.6)$</td>
<td>$-0.2 (±1.0; 0.6)$</td>
<td>0.772</td>
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<td>Serum Na, mmol/L</td>
<td>$-1 (-6; 3)$</td>
<td>$-1 (-5; 4)$</td>
<td>0.0</td>
<td>0.135</td>
</tr>
<tr>
<td>Serum K, mmol/L</td>
<td>$0.3 (-0.5; 1.5)$</td>
<td>$0.0 (-0.8; 0.6)$</td>
<td>0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum creatinine, μmol/L</td>
<td>$7 (-11; 22)$</td>
<td>$0 (-11; 18)$</td>
<td>7.0</td>
<td>&lt;0.001</td>
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<tr>
<td>Microalbuminuria, mg/day</td>
<td>$-4.4 (-257.0; 11.0)$</td>
<td>$0.0 (-87.0; 98.0)$</td>
<td>$-4.4$</td>
<td>0.023</td>
</tr>
<tr>
<td>Proteinuria, g/day</td>
<td>$0.0 (-0.5; 0.1)$</td>
<td>$0.0 (-0.3; 1.7)$</td>
<td>0.0</td>
<td>0.221</td>
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</tbody>
</table>
Workup in resistant hypertension

1. Exclude pseudoresistant hypertension
2. Reverse contributing factors
3. Screen for secondary hypertension
4. Optimize pharmacotherapy
5. Consider device-based therapy
Device-based therapy of hypertension

- Renal denervation
- Baroreflex activation therapy (‘barostimulation’)
- Central arteriovenous anastomosis
- Endovascular baroreceptor amplification (‘barostenting’)

Catheter-based renal denervation – *Symplicity catheter*

- Renal artery access via standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary radiofrequency generator
- Automated
- Low power
- Built-in safety algorithms
SYMPPLICITY HTN-3 study

Office Systolic Blood Pressure (mm Hg)

- **Denervation**
  - Baseline: 180 (N=364)
  - 6 Months: 160 (N=353)
  - Change: -14.13±23.93 mm Hg
  - P<0.001

- **Sham**
  - Baseline: 180 (N=171)
  - 6 Months: 174 (N=171)
  - Change: -11.74±25.94 mm Hg
  - P<0.001

Ambulatory 24-Hr Average Systolic Blood Pressure (mm Hg)

- **Denervation**
  - Baseline: 150 (N=360)
  - 6 Months: 140 (N=329)
  - Change: -6.75±15.11 mm Hg
  - P<0.001

- **Sham**
  - Baseline: 150 (N=167)
  - 6 Months: 140 (N=162)
  - Change: -4.79±17.25 mm Hg
  - P<0.001

Difference in change, -2.39 mm Hg (95% CI, -6.89 to 2.12)

P=0.26

Difference in change, -1.96 mm Hg (95% CI, -4.97 to 1.06)

P=0.98

Baroreflex activation therapy with Barostim neo

- Carotid Baroreceptor Activation
- Brain
- Autonomic Nervous System:
  - Reduces Sympathetic Activity
  - Increases Parasympathetic Activity

- Heart:
  - HR: Irritability
- Vessels:
  - Vasodilation
  - Venous capacitance
  - Stiffness
- Kidneys:
  - Diuresis
  - Natriuresis
  - RAAS activity

- Reduces excessive blood pressure
- Reduces myocardial work and oxygen consumption
- Reduces neurohormonal stimulus
- Reduces arrhythmogenesis
Baroreflex activation therapy with Barostim neo

Heusser, Hypertension 2010
Effects of baroreflex activation therapy on BP

Bisognano, J Am Coll Cardiol 2011
Central arteriovenous anastomosis with ROX Coupler
Effects of ROX Coupler on BP

Lobo, Lancet 2015
Endovascular baroreceptor amplification with MobiusHD
Device deployment reshapes the artery

Reshaped artery leads to increased effective radius of curvature of the artery

Increased effective radius amplifies the signals detected by the baroreceptors

\[
\varepsilon = \frac{p}{t/E}
\]

\( r_2 > r_1 \)

\( \varepsilon \) = wall strain
\( p \) = pressure inside artery
\( r \) = artery internal radius
\( t \) = artery wall thickness
\( E \) = Young’s Modulus
\( C \) = perimeter
Effects of MobiusHD on BP in canine model

- First implant
- Contralateral implant

BP (mmHg):
- Systolic
- Diastolic

Heart rate (bpm)

Time (h)
Conclusions

• Around 8-10% of patients with hypertension have resistant hypertension

• Apparent resistant hypertension needs a thorough workup

• Nonadherence to therapy is major issue

• Consider device-based therapy when optimization of therapy has failed

• So far baroreflex activation therapy seems to be most effective device-based therapy