Newer therapies in management of hypertension

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Glickman Urological & Kidney Institute
Objectives

• Discuss new guidelines (“JNC 8”)
• Discuss approach to “resistant hypertension”
• Discuss experimental therapies

* Focused on outpatient management of HTN
The hypertension story…

• 1930s – 1940s
  – “The greatest danger to a man with high blood pressure lies in its discovery, because then some fool is certain to try and reduce it” – J.H. Hay, 1931
  – Sedatives (Goodman and Gilman, 1941)
  – Kempner rice diet, typhoid bacilli, pentaquine
  – Radical sympathectomy
  
  – FDR (died 1945 – stroke, “BP… >300/195”)
  – National Heart Lung Blood Institute – NHLBI (est. 1948)
  – Framingham Heart Study (started 1948)
The hypertension story…

- 1950s –
  - “Those with chest pain or other overt signs of disease should have their hypertension treated; others should not.”
    *Harrison, Principles of Internal Medicine, 1st Edition, 1950*
  - Ganglion blockers, Reserpine, Hydralazine

- Then… in 1957
  - Clinical trials on Chlorothiazide
  - Harriet Dustan, Cleveland Clinic
  - Mosaic theory of hypertension
    - Irvine Page, Cleveland Clinic

*Page, Gifford, and Dustan*
The hypertension story…

• 1960s onwards…
  – VA study 1967
    • Thiazide + reserpine + hydralazine
  – Framingham heart study (first report) 1969
  – National High Blood Pressure Education program 1972
  – JNC 1 1976
  – Progress in pharmacology
    • 1960s… Propranolol
    • 1970s… Verapamil, methyldopa
    • 1980s… ACEIs
    • 1990s… ARBs
    • 2000s… Direct renin inhibitors
## JNC – a brief publication history

<table>
<thead>
<tr>
<th>JNC</th>
<th>Year</th>
<th>Pages</th>
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<tbody>
<tr>
<td>1</td>
<td>1976</td>
<td>6</td>
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<tr>
<td>2</td>
<td>1980</td>
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<td>3</td>
<td>1984</td>
<td>13</td>
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<td></td>
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<td>(Chair: Harriet Dustan)</td>
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<td>4</td>
<td>1988</td>
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<td>5</td>
<td>1992</td>
<td>30</td>
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<td></td>
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<td>(Chair: Ray Gifford)</td>
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<tr>
<td>6</td>
<td>1997</td>
<td>34</td>
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<td>7</td>
<td>2003</td>
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Appointed by NHLBI/NIH – National High Blood Pressure Education Program
“JNC 8”

• JNC 8 panel report, 2013
  – 14 pages (with 300+ page suppl.)
  – Strictly evidence-based
  – Narrow scope

• Controversial
  – Not sanctioned by NIH/NHLBI
  – Not endorsed by any professional society
“JNC 8” – guidelines in a nutshell

<table>
<thead>
<tr>
<th>Goals</th>
<th>≥ 60</th>
<th>&lt; 150/90</th>
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<tbody>
<tr>
<td></td>
<td>&lt; 60</td>
<td>&lt; 140/90</td>
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<tr>
<td>DM</td>
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<td>&lt; 140/90</td>
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<tr>
<td>CKD</td>
<td></td>
<td>&lt; 140/90</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Initial therapy</th>
<th>General</th>
<th>A/C/D or C/D</th>
</tr>
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<tbody>
<tr>
<td>DM</td>
<td>A/C/D or C/D</td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>A</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>How to reach goal</th>
<th>Increase or add from other classes</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No ACEI + ARB combination</td>
</tr>
<tr>
<td></td>
<td>Refer to HTN specialist if difficult control</td>
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</table>

A = ACEI/ARB  
C = CCB  
D = thiazide-type diuretic
Resistant Hypertension: definition

• “Blood pressure that remains above goal in patients who are adhering to optimal doses of an appropriate 3-drug regimen of different classes that includes a diuretic…”

• BP controlled but on > 3 medications is also considered resistant hypertension
Apparent Resistance
(Pseudo-resistant Hypertension)

• Improper BP measurement
• Pseudo-hypertension (in the elderly)
  – Due to calcified brachial artery which does not compress
• White-coat effect
  – 1/3 of “resistant” hypertension was white coat hypertension (Spanish ABPM registry of > 68000 patients)
• Poor patient adherence to therapeutic regimen
BP measurement in the office – far from ideal

“I’m going to take your blood pressure, so try to relax and not think about what a high reading might mean for your chances of living a long, healthy life.”
Automated office BP devices (AOBP)

- **Multiple consecutive** BP readings in the office with the patient sitting and resting **alone**

- Decreased white coat response with AOBP

- CAMBO trial (with BpTRU device)
  - BpTRU readings significantly closer to daytime ambulatory blood pressure (ABPM) readings than conventional manual readings
Ambulatory blood pressure monitoring

- Stronger predictor of CV mortality than conventional office BP measurement.

  24-hour average BP $\geq 130/80$ mmHg  
  Daytime (awake) BP $\geq 135/85$ mmHg  
  Nighttime (asleep) BP $\geq 120/70$ mmHg
  Normal nocturnal dipping 10-20%

- Nocturnal “non-dipping” associated with increased risk of target organ damage and all-cause mortality
Factors associated with true resistant hypertension

• Drug-induced
  • NSAIDs most common

• Volume overload
  • Excessive sodium intake, inadequate diuretic therapy

• Associated conditions
  • Obesity
  • Excess alcohol intake
  • Obstructive sleep apnea
Factors associated with true resistant hypertension

- Provider inertia
- Inadequate doses or inappropriate drug combinations
- Identifiable (secondary) causes of hypertension
Patient compliance

• Difficult to assess
• Cost, complexity, side effects, lack of understanding

Clues:
• Missed office visits
• Vagueness about the names, descriptions of tablets and how often they are taken
• Lack of physiologic evidence of therapy

Strategies:
• Pill bottles, call patient’s pharmacy
• Urine diuretic screen
• 24 hr urine sodium (> 100 mEq translates to > 2.3 g sodium)
• Observed administration of medications
Key points on medications...

• Chlorthalidone is more potent than HCTZ (longer half-life → better nocturnal control)

• Use loop diuretics instead of thiazide diuretics if GFR < 30

• Short-acting loop diuretics (furosemide/bumetanide) should be dosed at least twice daily
Key points on medications…

• Short-acting CCBs not recommended
• CCB edema – due to arteriolar dilation; diuretics may not help much. ACEI/ARB may be beneficial.

• Use **vasodilating beta blockers** instead of atenolol or metoprolol (like Coreg, Nebivolol…)

• Direct vasodilators like hydralazine and minoxidil will need concomitant diuretic and beta blockade (to offset fluid retention and tachycardia)
Key points on medications…

• **ACEI + ARB combination not recommended** for HTN management

• **Aliskiren (Direct Renin Inhibitor) + ACEI/ ARB** not recommended for HTN management

• If you see hypokalemia, ask why?...

• Consider use of **aldosterone antagonists (spironolactone)** in resistant hypertension
Spironolactone

- Analysis of ASCOT trial, when spironolactone was added as 4th drug
- Median starting dose 25 mg (range 25 – 50 mg)
- Also useful in patients with obesity and OSA

*Hypertension 2007*
Counsel about lifestyle changes…

<table>
<thead>
<tr>
<th>Modification</th>
<th>Comment</th>
<th>Approx. SBP reduction (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium restriction</td>
<td>No added salt. Limit sodium to <strong>less than 2.4 g/day</strong></td>
<td>2 - 8</td>
</tr>
<tr>
<td>DASH (Dietary Approaches to Stop Hypertension)</td>
<td>Diet rich in <strong>fruits, vegetables</strong>, low fat dairy, low in saturated fat</td>
<td>8 - 14</td>
</tr>
<tr>
<td>Weight reduction</td>
<td>If over ideal BMI</td>
<td>5 – 20/ 10 kg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Aerobic activity for <strong>at least 30 minutes most days of the week</strong></td>
<td>4 - 9</td>
</tr>
<tr>
<td>Limit alcohol</td>
<td>Limit to <strong>2 drinks in men</strong> and <strong>1 drink in women</strong> and lighter-weight persons</td>
<td>2 - 4</td>
</tr>
</tbody>
</table>

JNC 7, AHA/ ACC Lifestyle Working Group, ASH/ISH
Chicken Caesar Salad, Costco
Sodium: **2680 mg**

Double whopper, Burger King
Sodium: **980 mg**
Illustrative case

- 58 year old male engineer referred for resistant hypertension. History of DM for 5 years and **hypertension for 12 years**. No CAD or stroke
- Seated office BP **168/94 mm Hg** (similar in both arms); not orthostatic; **HR 50 bpm**; BMI 32
- Exam: PMI is displaced laterally, S4 is present, mild arteriolar narrowing in fundus without hemorrhages or exudate, no peripheral edema, no bruit
- Urine analysis unremarkable, EKG – voltage criteria for LVH
- Labs: Na 139, K 4.0, Cr 1.1
- Strong family history of hypertension
- Non-smoker, drinks a glass of wine almost every night
Medications (of interest)

- HCTZ 25 mg daily
- Valsartan 160 mg daily
- Felodipine 10 mg daily
- Clonidine 0.2 mg twice daily
- Metoprolol, long acting 100 mg daily
- Aleve twice daily (for knee pain)

Complaints include fatigue and dry mouth.
Notes daytime sleepiness, wife notes snoring
A) Confirm resistance

- Proper measurement
  - Automated office BP (average of 5 readings)
  - Review of home BP log (his machine was checked and he demonstrated correct technique)
  - ABPM? (not done)
- Target organ involvement
- No reason to suspect non-compliance
B) Identify and reverse factors contributing to true resistance

 ✓ Stop NSAIDs
 ✓ Diet reviewed – “does not add salt” but... eats processed foods and eats out often (reviewed low sodium diet)
 ✓ Alcohol – counseled to limit to no more than 2 drinks/day
 ✓ Physical activity and weight loss
 ✓ Normal kidney function, no proteinuria
 ✓ Work up for secondary causes? (was previously done)
   ✓ Normal plasma metanephrines
   ✓ Normal duplex US of renal arteries
   ✓ Renin 1.1 ug/l/hr; aldosterone 8 ng/dl
 ✓ Sleep study
C) Pharmacologic principles

Current regimen...
- HCTZ 25 mg daily
- Valsartan 160 mg daily
- Felodipine 10 mg daily
- Clonidine 0.2 mg twice daily
- Metoprolol, long acting 100 mg daily

Changes made...
- Switched HCTZ to chlorthalidone 25 mg daily
- Continue valsartan 160 mg daily
- Switched felodipine to amlodipine 10 mg daily
- Start clonidine taper
- Decrease metoprolol to 50 mg daily
Follow-up…

Started CPAP for OSA, stopped NSAIDs
Weight loss of 7 lbs. in 2 months
Low sodium diet (but difficult when he travels, which is often)
Clonidine was tapered off.

BP 153/90 mm Hg, HR 60 bpm
Symptoms better but still notes fatigue
Discussed addition of aldosterone antagonist – spironolactone vs. eplerenone
Started on eplerenone 50 mg daily
Stopped metoprolol

BP 122/88 mm Hg, HR 72 bpm
Follow up labs – Cr 1.3, K 4.2
Feels well.
At this point, BP at goal on 4 drugs (caution: monitor K closely…)
# Alternative therapies?

<table>
<thead>
<tr>
<th>Alternative Treatments</th>
<th>LOE</th>
<th>COR</th>
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<tbody>
<tr>
<td><strong>Behavioral therapies</strong></td>
<td></td>
<td></td>
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<tr>
<td>Transcendental Meditation</td>
<td>B</td>
<td>IIIB</td>
</tr>
<tr>
<td>Other meditation techniques</td>
<td>C</td>
<td>III (no benefit)</td>
</tr>
<tr>
<td>Biofeedback approaches</td>
<td>B</td>
<td>IIIB</td>
</tr>
<tr>
<td>Yoga</td>
<td>C</td>
<td>III (no benefit)</td>
</tr>
<tr>
<td>Other relaxation techniques</td>
<td>B</td>
<td>III (no benefit)</td>
</tr>
<tr>
<td><strong>Noninvasive procedures or devices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acupuncture</td>
<td>B</td>
<td>III (no benefit)</td>
</tr>
<tr>
<td>Device-guided breathing</td>
<td>B</td>
<td>IIA</td>
</tr>
<tr>
<td><strong>Exercise-based regimens</strong></td>
<td></td>
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<tr>
<td>Dynamic aerobic exercise</td>
<td>A</td>
<td>I</td>
</tr>
<tr>
<td>Dynamic resistance exercise</td>
<td>B</td>
<td>IIA</td>
</tr>
<tr>
<td>Isometric handgrip exercise</td>
<td>C</td>
<td>IIIB</td>
</tr>
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*(Hypertension 2013)*
Experimental therapies
Sympatho-renal axis

Schlaich et al. Hypertension. 2009
Renal denervation

The nerves arborize around the artery and lie within the adventitia
Symlicity Investigational Catheter Device

• RF energy (5-8W)
• 4 to 6 treatments per artery
• 2 minutes for each treatment
• Median procedure time 38 min
• IV narcotics/ sedatives

Investigational device. Limited by US law to investigational use
**Proof of concept – decreased sympathetic activity after renal denervation**

<table>
<thead>
<tr>
<th></th>
<th>MSNA (burst/min)</th>
<th>BP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>56</td>
<td>161/107</td>
</tr>
<tr>
<td><strong>1 month</strong></td>
<td>41</td>
<td>141/90 (-20/-17)</td>
</tr>
<tr>
<td><strong>12 months</strong></td>
<td>19</td>
<td>127/81 (-34/-26)</td>
</tr>
</tbody>
</table>

59-year-old male on antihypertensive medications.

*NEJM 2009*
Symplicity HTN-I Trial: non-randomized

36 month results

BP Change (mm Hg)

<table>
<thead>
<tr>
<th>Time</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mo</td>
<td>-19</td>
<td>-9</td>
</tr>
<tr>
<td>3 Mo</td>
<td>-21</td>
<td>-10</td>
</tr>
<tr>
<td>6 Mo</td>
<td>-22</td>
<td>-10</td>
</tr>
<tr>
<td>12 Mo</td>
<td>-26</td>
<td>-13</td>
</tr>
<tr>
<td>24 Mo</td>
<td>-33</td>
<td>-15</td>
</tr>
<tr>
<td>36 Mo</td>
<td>-33</td>
<td>-19</td>
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P < 0.01 for ∆ from baseline for all time points
Symplicity HTN-2 Trial: *non-randomized*

6 month primary end-point

39% of patients in the RDN group had SBP < 140 mm Hg at 6 mos.
Safety

Short-term peri-procedure safety
• No catheter or generator malfunctions
• Renal artery dissection during catheter delivery (prior to RF energy delivery)
• Access site-complications (pseudoaneurysm/hematoma)

Vascular safety (duplex/CTA/MRA)

No change in renal function
Smaller studies reporting other favorable effects

- Improved **glucose metabolism** (37 RDN patients)
  
  *Circulation 2012*

- Improvement in LVH and diastolic function (46 RDN patients)
  
  *JACC 2012*

- Decrease in apnea-hypopnea index in **obstructive sleep apnea** (10 RDN patients)
  
  *Hypertension 2011*

- Improved insulin sensitivity in **PCOS** (2 RDN patients)
  
  *J Hypertension 2011*
Smaller studies reporting other favorable effects

• Efficacy in **CKD stage 3 and 4** (15 RDN patients, mean GFR 31 ml/min/1.73m²)
  *JASN 2012*

• Improvement in **central hemodynamics and arterial stiffness** (110 RDN patients)
  *JACC 2012*

• Reduced recurrences of **atrial fibrillation** (13 patients)
  *JACC 2012*
SYMPLICITY HTN-3

• First US trial - IDE trial, so greater oversight
  – Larger trial because powered for the safety endpoint
  – More centers

• SBP ≥160 mm Hg on ≥3 antihypertensive meds
• 24° ABPM SBP >135 mmHg inclusion criteria
• Sham procedure
• Patient and follow-up assessor and study management blinding
• “Clinically significant” superiority margin (>5 mmHg)
SYMPLICITY HTN-3: Schematic

- 2:1 randomization
- Treatment
  - 1 mo
  - 3 mo
  - 6 mo
- Control (only renal angio)
  - 1 mo
  - 3 mo
  - 6 mo
- Patient can crossover
- Follow-up to 3 years
  - 12, 18, 24, 30, 36
  - +1, 3, 6, 12, 18, 24, 30
  - 12, 24, 36

1441 enrolled
535 subjects Randomized
(63% Screen Failure Rate)
Symplicity HTN-3 Trial: *randomized*
6 month primary end-point

**Office Systolic Blood Pressure (mm Hg)**

- **Baseline**
  - Denervation: ~180 mm Hg
  - Sham: ~180 mm Hg

- **6 Months**
  - Denervation: ~200 mm Hg
  - Sham: ~200 mm Hg

**Change from baseline**

- Denervation: ~20 mm Hg
  - Baseline: ~160 mm Hg
  - P < 0.001

- Sham: ~160 mm Hg
  - Baseline: ~160 mm Hg
  - P < 0.001

**Ambulatory 24-hr Average Systolic Blood Pressure (mm Hg)**

- **Baseline**
  - Denervation: ~160 mm Hg
  - Sham: ~160 mm Hg

- **6 Months**
  - Denervation: ~140 mm Hg
  - Sham: ~140 mm Hg

**Change from baseline**

- Denervation: ~4 mm Hg
  - Baseline: ~160 mm Hg
  - P < 0.001

- Sham: ~4 mm Hg
  - Baseline: ~160 mm Hg
  - P < 0.001

**Difference in change**

- Office blood pressure: ~2.39 mm Hg (95% CI, ~6.89 to 2.12)
  - P = 0.26

- ABPM: ~1.96 mm Hg (95% CI, ~4.97 to 1.06)
  - P = 0.98

**NO significant difference from controls for office blood pressure and ABPM**

*NEJM 2014*
Medtronic Blood Pressure Device Misses Goal in Study
Future of Technology Seen as Source of Revenue Growth Thrown Into Doubt

Bloomberg Businessweek
News From Bloomberg

Bloomberg News
Medtronic Nerve-Burning Failure ‘Colossal’
Loss for Industry (1)

REUTERS
Medtronic to form panel after blood pressure device fails study
Hawthorne Effect

Placebo Effect

Patient Demographics

Heterogeneity of U.S. Operator Experience

Catheter Design
Single electrode vs. Multi-electrode...

Medication Changes or Adherence

Trial Design/Conduct

Hawthorne Effect

Regression to the Mean

Placebo Effect
Current status of renal denervation

- Not available for clinical use in US
- Still available for clinical use outside the US
- Other renal denervation devices…
  - Multi-electrode devices
  - Ultrasound-based therapy (non-invasive)
Rheos Baroreflex Activation Therapy (BAT)

DEBuT-HT trial
18 patients completed mean duration of 58 ± 6 mos
Mean reduction in SBP -53 ± 9 mm Hg, DBP -30 ± 6 mm Hg, HR -5 ± 2 bpm

Rheos Pivotal Trial
Take home points…

• Correct measurement is key
• Emphasize lifestyle changes
• Medications – choice, dosing
• Compliance
• Think secondary causes
• Refer to hypertension specialist if difficult blood pressure control
• Experimental device therapies are… experimental at this time
Resistant Hypertension clinic

Appointments line: 216 444-6771
Thank you!