10:45–11:45am

Hypertension Management: A Moving Target

SPEAKER
Karol Watson, MD, PhD, FACC

Presenter Disclosure Information

The following relationships exist related to this presentation:
► Karol Watson, MD, PhD, FACC, receives fees for non-CME/CE services as a Merck Clinical Trials Adjudicator.

Off-Label/Investigational Discussion
► In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Important to Note…

► JNC 7 was “The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)”
► JNC 8 is the “2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)”
► In JNC 8 they give 9 Evidence-Based Recommendations
► “... these recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient.”
Strength of Recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Strength of Recommendation</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Strong recommendation: There is high certainty based on evidence that the net benefit is substantial.</td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>Moderate recommendation: There is moderate to high certainty based on evidence that the net benefit is moderate to substantial</td>
<td>3</td>
</tr>
<tr>
<td>C</td>
<td>Weak recommendation: There is at least moderate certainty based on evidence that there is a small net benefit.</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Recommendation against: There is at least moderate certainty based on evidence that it has no net benefit or that risks/harms outweigh benefits.</td>
<td>0</td>
</tr>
<tr>
<td>E</td>
<td>Expert opinion (&quot;There is insufficient evidence or evidence is unclear or conflicting, but this is what the Panel recommends.&quot;)</td>
<td>5</td>
</tr>
<tr>
<td>N</td>
<td>No recommendation for or against (&quot;There is insufficient evidence or evidence is unclear or conflicting.&quot;) Net benefit is unclear. Balance of benefits and harms cannot be determined because of no evidence, insufficient evidence, unclear evidence, or conflicting evidence, and the Panel thought no recommendation should be made. Further research is recommended in this area.</td>
<td>0</td>
</tr>
</tbody>
</table>

Recommendation #1

1. In patients aged ≥60 years, initiate pharmacologic treatment in systolic BP ≥150mmHg or diastolic BP ≥90mmHg and treat to a goal systolic BP <150mmHg and goal diastolic BP <90mmHg.

(Strong Recommendation – Grade A)

In other words:
Ease up on Hypertension Treatment in Older Adults (60 years of age or older)

Treat if BP >150/90
Aim for <150/90

Recommendations #2 and #3

2. In patients aged <60 years, initiate pharmacologic treatment at DIASTOLIC BP ≥90mmHg and treat to a goal <90mmHg.

For ages 30–59 years, Strong Recommendation–Grade A
For ages 18–29 years, Expert Opinion–Grade E

3. In patients aged <60 years, initiate pharmacologic treatment at SYSTOLIC BP ≥140mmHg and treat to a goal <140mmHg.

Expert Opinion–Grade E

For Adults under 60 years of age
Treat if BP >140/90; Aim for <140/90
There's strong evidence for treating high diastolic BP in patients 30–59 years of age.
Everything else is "Expert Opinion"

Recommendations # 4 & 5

In patients aged ≥18 years with chronic kidney disease, initiate pharmacologic treatment at systolic BP ≥140mmHg or diastolic BP ≥90mmHg and treat to goal systolic BP <140mmHg and goal diastolic BP <90mmHg.

(Expert Opinion–Grade E)

Earlier HTN guidelines lowered treatment goals for adults with CKD and DM; but JNC 8 gives the same BP goals in these patients as in the general population.

BP goal <140/90
Hypertension in CKD

Modification of Diet in Renal Disease (MDRD)
• Randomized to a MAP < 93 (120/80) vs MAP < 107 (140/90)
• RESULT: No CV or renal benefit

African American Study of Kidney Disease
• randomized to a MAP < 93 vs MAP 102-107; Achieved BP 130/78 vs 141/86
• RESULT: No CV or renal benefit


Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial

• NHLBI 10,251 Type 2 diabetics
• Three Trial arms
  • Glycemic control
  • BP
  • Lipids
• BP arm 4,773 randomized to SBP<120 or <140


ACCORD Trial: Outcomes

Primary Outcome
Nonfatal MI, Nonfatal Stroke or CVD Death

Total Stroke

Patients with Events (%) Years Post-Randomization

Intensive Standard

Intensive Standard

Patients with Events (%) Years Post-Randomization

Intensive Standard


ACCORD Trial: Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AE</td>
<td>77 (3.3)</td>
<td>39 (1.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypotension</td>
<td>17 (0.7)</td>
<td>1 (0.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Syncope</td>
<td>12 (0.5)</td>
<td>5 (0.2)</td>
<td>0.10</td>
</tr>
<tr>
<td>Bradycardia or Arrhythmia</td>
<td>12 (0.5)</td>
<td>3 (0.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>9 (0.4)</td>
<td>1 (0.04)</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>5 (0.2)</td>
<td>1 (0.04)</td>
<td>0.12</td>
</tr>
<tr>
<td>eGFR ever &lt;30 mL/min/1.73m²</td>
<td>99 (4.2)</td>
<td>52 (2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any Dialysis or ESRD</td>
<td>59 (2.5)</td>
<td>58 (2.4)</td>
<td>0.93</td>
</tr>
<tr>
<td>Dizziness on Standing</td>
<td>217 (44)</td>
<td>188 (40)</td>
<td>0.36</td>
</tr>
</tbody>
</table>


Recommendation #6

6. In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CCB, ACE inhibitor, or ARB. (Moderate Recommendation–Grade B) This recommendation is different from the JNC 7 in which the panel recommended thiazide-type diuretics as initial therapy for most patients.

While JNC 7 recommended thiazide-type diuretics as the initial antihypertensive choice for all, JNC 8 broadens the choices to also include CCB, ACE-I, and ARBs along with thiazide-type diuretics.

NOTE: βblockers are OUT

ALLHAT Hypertension Trial

42,418 high-risk hypertensive patients
90% previously treated
10% untreated

Step 1 agents titrated and atenolol, clonidine, reserpine, and/or hydralazine added as needed to achieve BP goal

JAMA 2002; 288: 2981-2997
**Cumulative Event Rates for the Primary Outcome (Fatal CHD or Nonfatal MI) by ALLHAT Treatment Group**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/C</td>
<td>0.98 (0.90-1.07)</td>
<td>0.85</td>
</tr>
<tr>
<td>L/C</td>
<td>0.99 (0.91-1.08)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

**Recommendation #7**

7. In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.

For general black population: Moderate Recommendation - Grade B

For black patients with diabetes: Weak Recommendation - Grade C

JNC 8 recommends a thiazide-type diuretic or CCB as the initial choice in African Americans, but there's less certainty about African Americans with diabetes due to lack of data (they were torn about not including ACE/ARB).

**ALLHAT**

**BP Results by Treatment Group in Black Participants**

**Recommendation #8**

8. In the population aged ≥ 18 years with chronic kidney disease, initial (or add-on) antihypertensive treatment should include an ACE inhibitor or ARB to improve kidney outcomes. (Moderate Recommendation – Grade B)

In adult patients with CKD, make sure an ACE-I or an ARB is part of the antihypertensive regimen.
ACE-I or ARB in CKD reduces progression of kidney disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Pts</th>
<th>Design</th>
<th>RR for kidney disease progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maschio et al 1996</td>
<td>583</td>
<td>Benazepril v. placebo</td>
<td>53%</td>
</tr>
<tr>
<td>Dissen group 1997</td>
<td>188</td>
<td>Ramipril v. placebo</td>
<td>48%</td>
</tr>
<tr>
<td>Hou et al 2006</td>
<td>224</td>
<td>Benazepril v. placebo</td>
<td>43%</td>
</tr>
<tr>
<td>Brenner et al 2001</td>
<td>1513</td>
<td>Losartan v. placebo</td>
<td>22%</td>
</tr>
</tbody>
</table>

**Recommendation # 9**

9. If goal BP cannot be reached using only the drugs in Recommendation 6, antihypertensive drugs from other classes can be used. (Expert Opinion–Grade E)

Don’t dilly dally. If BP is not at goal within a month, use one of these 3 strategies:

1. Increase the dose of the initial drug
2. Add a 2nd, then a 3rd drug (Rec #6)
   *Not an ACE + ARB together*
3. Add a drug from other classes

**Telmisartan vs. Telmisartan + Ramipril:**

Primary Outcome (MI, Stroke, CV death, CV hospitalization)

<table>
<thead>
<tr>
<th>Event</th>
<th>Ram</th>
<th>Ram + Tel</th>
<th>RR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>149</td>
<td>406</td>
<td>2.75</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Syncope</td>
<td>15</td>
<td>29</td>
<td>1.95</td>
<td>0.032</td>
</tr>
<tr>
<td>Cough</td>
<td>360</td>
<td>392</td>
<td>1.10</td>
<td>0.1885</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>39</td>
<td>3.28</td>
<td>0.0001</td>
</tr>
<tr>
<td>Angioedema</td>
<td>25</td>
<td>18</td>
<td>0.73</td>
<td>0.30</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>60</td>
<td>94</td>
<td>1.58</td>
<td>0.0050</td>
</tr>
<tr>
<td>Any Discontinuation</td>
<td>2099</td>
<td>2495</td>
<td>1.20</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**JNC 8 Algorithm**

**Managing Difficult to Treat Hypertension**
General Principles about HTN

- Two main physiologic systems control blood pressure
- There is a characteristic circadian rhythm to blood pressure

Renin-Angiotensin-Aldosterone Regulation of Blood Pressure

- Renin-angiotensin-aldosterone system plays a crucial role in regulating blood pressure.
- Angiotensin I is converted to Angiotensin II by Angiotensin Converting Enzyme (ACE).
- Aldosterone, produced by the adrenal cortex, regulates sodium and water reabsorption.

Sympathetic Nervous System Regulation of Blood Pressure

- The sympathetic nervous system releases catecholamines (noradrenaline and adrenaline) to increase blood pressure.
- Adrenergic tone, cardiac output, resistance arteries, and afterload are all regulated by the sympathetic nervous system.

Blood Pressure Distribution in the Population According to Age

- The graph shows the distribution of blood pressure in the population, with different levels for men and women by age group.
- The pulse pressure (PP) is also indicated.

CLINICAL PEARL # 1

- Avoid lowering the diastolic blood pressure below 60-65 mm Hg as coronary perfusion may be compromised if DBP is too low.

Adapted from: Third National Health and Nutrition Examination Survey, Hypertension 1995;25:105-13
General Principles about HTN

- Two main physiologic systems control blood pressure
- There is a characteristic circadian rhythm to blood pressure
- There is a characteristic life-cycle pattern to blood pressure
- Vascular changes of aging will lead nearly everyone to develop hypertension at some point and predispose to orthostasis

Postural Changes in Blood Pressure are more common as we Age

CLINICAL PEARL # 2

Always measure BP in the standing as well as the sitting position in the very elderly as orthostatic hypotension is common

Most cases of Resistant Hypertension are caused by:

- Sodium excess
- Extracellular volume expansion
- Sympathetic overactivation

Medications that can exacerbate HTN

- Salt, H₂O retention
  - NSAIDs, COX-2 inhibitors (Celecoxib)
  - Hormone therapy, Oral Contraceptive Pills (OCPs)
  - Steroids
  - Cyclosporine
  - Excessive black licorice ingestion (aldosterone-like)
- Sympathetic Overactivity
  - Sympathomimetic agents (decongestants)
  - Diet pills, Cocaine, Ephedrine
  - Stimulants (Methylphenidate, Amphetamine)
  - herbal compounds (ephedra)
  - SSRIs (parasympathetic withdrawal = sympathetic overactivity)
  - Alcohol (binge drinking, >30 ml/day) ?
  - Erythropoietin ?

Causes of Secondary Hypertension

CONGENITAL
- Coarctation of aorta

RENEAL
- Renal Artery Stenosis
- Renin tumor
- Glomerulonephritis
- DM nephrosclerosis
- Polycystic disease
- Collagen disease
- Chronic Pyelonephritis

ENDOCRINE
- Hyperaldosteronism
- Cushing syndrome
- Thyroid Disease
- Acromegaly
- Hyperparathyroidism
- Pheochromacytoma

OTHER
- Drug Induced
- Sleep Apnea
- Preeclampsia
Effect of CPAP on Blood Pressure

Changes in blood pressure with effective (blue bars) vs subtherapeutic (orange bars) nCPAP.

Becker et al, 2003

CLINICAL PEARL # 3

Obstructive Sleep Apnea is a Common Cause of Resistant Hypertension which can be improved with effective OSA therapy

Hyperaldosteronism

- Most cases of Primary Hyperaldosteronism (PH) are caused by bilateral adrenal hyperplasia
- PH often causes spontaneous hypokalemia (<3.5 mmol/L), profound diuretic-induced hypokalemia (<3.0 mmol/L), or hypertension refractory to treatment with 3 or more drugs.
- Screening for Primary Aldosteronism:
  - Aldosterone >15 ng%
  - Aldosterone / Renin Ratio (ARR) > 20

Spironolactone

EXTREME Caution if K+ > 5.0 or Cr > 2.5; monitor K+

CLINICAL PEARL # 4

Aldosterone excess is seen even in the absence of Primary aldosteronism, thus many patients with resistant hypertension benefit from a trial of an aldosterone antagonist

personal communication Franz Messerli

Multiple BP Lowering Agents are needed to reach Goal

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target BP (mm Hg)</th>
<th>Number of antihypertensive agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT</td>
<td>&lt;140/90</td>
<td>1</td>
</tr>
<tr>
<td>UKPDS</td>
<td>DBP &lt;85</td>
<td>2</td>
</tr>
<tr>
<td>ABCD</td>
<td>DBP &lt;75</td>
<td>3</td>
</tr>
<tr>
<td>MDRD</td>
<td>MAP &lt;92</td>
<td>4</td>
</tr>
<tr>
<td>HOT</td>
<td>DBP &lt;80</td>
<td></td>
</tr>
<tr>
<td>AASK</td>
<td>MAP &lt;92</td>
<td></td>
</tr>
<tr>
<td>IDNT</td>
<td>&lt;135/&lt;85</td>
<td></td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.
Diuretics and BP Control

- In states of sodium (and water) excess, diuretics are essential
- Most classes of antihypertensive agents lead to sodium retention, as compensation for lower BP
- JNC 8 recommends a thiazide-type diuretic, as one of four initial antihypertensive choices in the general population
- JNC 8 recommends a thiazide-type diuretic, as one of two initial antihypertensive choices in the Black patients

Thiazide Diuretics Differ in Their Antihypertensive Effects

<table>
<thead>
<tr>
<th>Office Blood Pressure*</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide 50 mg daily</td>
<td>(-10.6 \pm 3.2)</td>
<td>(-10.8 \pm 3.8)</td>
<td>(-10.8 \pm 3.3)</td>
<td>(-10.6 \pm 3.6)</td>
</tr>
<tr>
<td>Chlorthalidone 25 mg daily</td>
<td>(-10.4 \pm 3.2)</td>
<td>(-10.7 \pm 3.2)</td>
<td>(-10.4 \pm 3.3)</td>
<td>(-10.3 \pm 3.1)</td>
</tr>
</tbody>
</table>


CLINICAL PEARL # 5

Failure to use enough medication is a common cause of “resistant” hypertension

CLINICAL PEARL # 6

In many patients with HTN, adequate diuresis is ESSENTIAL for BP control

CLINICAL PEARL # 7

In patients with Resistant Hypertension switching the diuretic from HCTZ to Chlorthalidone may improve BP control (but watch electrolytes!)
Sodium (Salt)

Effects of Reduced Na+ on BP and CVD Events: Results from 3 Randomized Trials

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>OUTCOME</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>TONE</td>
<td>21% CV events</td>
<td>2.3 y</td>
</tr>
<tr>
<td>639 elderly pts - weight loss and sodium restriction, following withdrawal of BP medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan Veterans</td>
<td>41% CV Mortality</td>
<td>2.6 y</td>
</tr>
<tr>
<td>1,981 elderly Taiwanese, living at a Veteran’s home; table salt substituted with a potassium salt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOHP Follow-up</td>
<td>30% CV events</td>
<td>10-15 y</td>
</tr>
<tr>
<td>3,126 pts with Prehypertension (30-54 y.o.) dietary sodium reduction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Appel, Arch Int Med, 2001; *Chang, AJCN, 2006; *Cook, BMJ, 2007

CLINICAL PEARL # 8

A 24 hour urine Na+ measurement will give you a good idea of how much salt your patient is eating.

Na (mg/day) = Na (mmol/day) x 23

Salt Sensitivity can be decreased with increased potassium intake

- Salt sensitivity was measured in AA and white men.
- Following this they were maintained on diets of varying K+ levels.
- On a low K+ diet, 80% of AA and 35% of white men were salt sensitive
- As potassium intake was increased, salt sensitivity decreased.
- On a high K+ diet, only 20% of the AA men, and no white men were still salt sensitive

The Role of Potassium in Hypertension

- How low potassium leads to HTN:
  - Potassium deficit triggers cells to gain sodium in order to maintain cell tonicity and volume
  - Sodium depolarizes cell membranes, leading to vasoconstriction
- How Potassium reduces blood pressure:
  - Potassium hyperpolarizes cell membranes, thereby relaxing blood vessels.
  - Potassium increases Na+ excretion (as above). Water follows, thus there is a diuretic effect.
  - This is the basis for the DASH diet which is high in potassium rich fruit and vegetables

CLINICAL PEARL # 9

In patients with Hypertension it is very difficult to control BP unless the serum K+ can be maintained above 4.0 mmol/l. DASH diet is a great way to increase K+ levels

Hypertension 2014

- Hypertension is common and will likely affect most individuals at some point in their lifetime
- Guidelines on how best to treat hypertension are evolving and sometimes contradictory
- For information on prevention, detection and evaluation of hypertension, JNC 7 and international guidelines offer guidance
- OSA and hyperaldosteronism are the most common secondary causes of resistant HTN
- Inadequate treatment is also a common cause of resistant HTN (rule of 10s)
- Potassium sufficiency is critical to BP control