Hypertension: JNC-8 and beyond

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Disclosure

• No real or potential conflict of interest to disclose.
• No off-label, experimental or investigational use of drugs or devices will be presented.

Objectives

• Upon completion of the learning activity the participant will be able to:
  – Describe the clinical consequences of hypertension.
  – Identify the recommended use of antihypertensive medications per current recommendation for adults and elders.
  – Discuss recommendations for antihypertensive therapy with select comorbid conditions.
Evidence-based Guideline for the Management of High BP in Adults: Report from the Panel Members Appointed to the Eighth Joint National Committee (JNC-8)


BP=HR (Heart Rate) x SV (Stroke Volume) x PR (Peripheral Resistance, Also Known as Peripheral Vascular Resistance {PVR})

Definition of Hypertension

Definition of HTN unchanged from through JNC-1, JNC-2, JNC-3, JNC-4, JNC-5, JNC-6, JNC-7, JNC-8 (one exception)
HTN: A Complex Disease with a Core Defect of Vascular Dysfunction that Leads to Select Target Organ Damage (TOD)

Treating HTN Goal=Reach BP goal while minimizing risk of HTN TOD

HTN TOD
- Brain
  - Stroke
    - 35–40% rate reduction with HTN treatment
  - Vascular (multi-infarct) dementia

HTN TOD (continued)
- Eye
  - HTN retinopathy with risk of blindness
HTN TOD (continued)

- Kidney
  - HTN nephropathy
  - Renal failure

HTN TOD (continued)

- Cardiovascular system
  - Atherosclerosis
  - MI
    - 25% rate reduction with HTN therapy
  - LVH
  - HF
    - 50% rate reduction with HTN therapy
Hypertension TOD
Atrial Fibrillation

• HTN = Major AF development risk factor
  – New onset of AF approx. 2% per year age ≥65 years
  – Evidence that HTN control prevents its development/recurrence

Establishing the Diagnosis of HTN

Key to Effective Practice
An Accurate BP Measurement

• ≥2 measurements per visit
  • Auscultatory method preferred
  – Patient seated comfortably for ≥5 minutes with back supported, feet on floor, arm supported in horizontal position
  – BP cuff at heart level
  • Technique for home or clinic
Key to Effective Practice
An Accurate BP Measurement (continued)

• BP cuff size
  - Covers more than 80% of upper arm
  - Cuff’s bladder approximately 40% of arm circumference
  • Use of too small cuff can lead to a falsely elevated BP
    - Source: http://hyper.ahajournals.org/content/24/6/786.abstract

Key to Effective Practice
An Accurate BP Measurement (continued)

• Additional measure
  - Measured with patient standing for 1–3 minutes to evaluate for postural hypotension or hypertension

What about lifestyle modification in treatment of hypertension?
Available at http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437740.48606.d1.citation

Advise adults who would benefit from BP lowering to:

- Preferable diet
  - Vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes
  - Nontropical vegetable oils and nuts
  - Limits intake of sweets, sugar-sweetened beverages, and red meats

(continued)

- Engage in aerobic physical activity
  - 3 to 4 sessions a week
  - Lasting on average 40 minutes per session
  - Involving moderate-to-vigorous intensity physical activity
What is the effect of different levels of dietary sodium intake on BP?

• In adults 30 to 80 years of age with or without HTN, counseling to reduce sodium intake by an average 1,150 mg/day reduces BP by 3−4/1−2 mm Hg.

What is the effect of dietary intake of potassium on BP and CVD outcomes?

• There is insufficient evidence to determine whether increasing dietary potassium intake lowers BP.

What is the effect of dietary intake of potassium on BP and CVD outcomes? (continued)

• In observational studies with appropriate adjustments (BP, sodium intake, etc.), higher dietary potassium intake is associated with lower stroke risk.
What is the effect of dietary intake of potassium on BP and CVD outcomes? (continued)

- There is insufficient evidence to determine whether there is an association between dietary potassium intake and CHD, HF, and cardiovascular mortality.

When to initiate pharmacologic therapy, establishing treatment goals per JNC-8
Recommendations for Management of Hypertension

- General population age < 60 years
  - Initiate pharmacologic treatment to lower BP at DBP 90 mm Hg and treat to a goal DBP < 90 mm Hg, lower BP at SBP 140 mm Hg and treat to a goal SBP < 140 mm Hg.
    - Grade A evidence for ages 30–59 years, Grade E evidence for ages 18–29 years

Recommendations for Management of Hypertension (continued)

- General population age ≥ 60 years (cont.)
  - Threshold to start meds = 150/90 mm Hg (Grade A)
  - BP goal with treatment goal SBP < 150 mm Hg and goal DBP < 90 mm Hg (Grade A)
    - Yields reduction in stroke, HF, CHD

Recommendations for Management of Hypertension (continued)

- Diabetes mellitus age ≥ 18 years
  - Start pharmacologic treatment to lower BP at SBP 140 mm Hg or DBP 90 mm Hg and treat to this goal
    - Expert opinion – Grade E
    - Insufficient evidence to support a lower threshold (or goal) based on outcomes
Recommendations for Management of Hypertension (continued)

- Chronic kidney disease (CKD) age≥18 years
  - Start pharmacologic treatment to lower BP at SBP 140 mm Hg or DBP 90 mm Hg, treat to goal SBP<140 mmHg and goal DBP<90 mm Hg
  - Expert opinion – Grade E

Are there benefits of additional lowering BP?

- In adults age<60 years
  - DBP 90 mm Hg based on evidence that DBP<85 or 80 mm Hg=No additional benefit noted
- In adults age≥60 years
  - Lowering to <140/<90 mm Hg showed no additional benefit, compared to 140−160 or 140−149 mm Hg

What if already at lower BP with current therapy?

- In general population
  - Treatment is well tolerated without adverse effects to QoL (quality of life).
  - Treatment does not need to be adjusted.
  - Expert opinion – Grade E
JNC-7 vs. JNC-8: Medication Recommendations

- **JNC-7**
  - 5 drug classes to be considered as initial therapy, thiazide-type diuretics as initial therapy for most patients without compelling indication for another class, dose ranges mentioned

- **JNC-8**
  - 4 specific medication classes and doses based on RCT evidence, racial, CKD, and diabetic subgroups, created table of drugs and doses used in the outcome trials

How many medications?

When BP is >20/10 mm Hg above goal, consideration should be given to starting with 2 drugs.

References

- Combination Therapy Versus Monotherapy in Reducing Blood Pressure: Meta-analysis on 11,000 participants from 42 trials, available at www.ncbi.nlm.nih.gov/pubmed/19272490
The Major AntiHTN Drug Groups

- ACEI, ARB
- CCB
- Thiazide-like diuretics
  - Thiazide diuretics (HCTZ)
  - chlorthalidone, indapamide

Why these drug classes?
- Comparable outcomes, particularly in general population
  - Grade B evidence (moderate amount)
- Lower overall death rates
- Improved CV (with exception of heart failure), cerebrovascular, renal outcomes

Ethnic Differences in Cardiovascular Drug Response: Potential Contribution of Pharmacogenetics

<table>
<thead>
<tr>
<th>Drug category</th>
<th>Mean BP reduction (SBP/DBP)</th>
<th>White-Black difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics</td>
<td>11.5/9.1</td>
<td>15.0/10.7</td>
</tr>
<tr>
<td>CCBs</td>
<td>15.3/12.6</td>
<td>16.9/13.3</td>
</tr>
<tr>
<td>β-blockers</td>
<td>11.7/11.3</td>
<td>5.9/9.5</td>
</tr>
<tr>
<td>ACEI/ARB</td>
<td>12.8/11.4</td>
<td>8.5/8.0</td>
</tr>
</tbody>
</table>

Source: [www.ncbi.nlm.nih.gov/pmc/articles/PMC2730023/table/T2/](www.ncbi.nlm.nih.gov/pmc/articles/PMC2730023/table/T2/)
How often should you titrate medication?

- If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendations.
  
  - Expert opinion – Grade E

Dosing for Antihypertensive Drugs

Per JNC-8, medications should be dosed adequately to achieve results similar to those seen in RCTs. These RCTs excluded certain patient groups including individuals with established CVD, heart failure.
Effect of Adding BP Medications vs. Increasing Single Drug

• “Comparison of our results with those of a published meta-analysis of different doses of the same drug showed that doubling the dose of 1 drug had approximately one fifth of the equivalent incremental effect (0.22 [95% CI, 0.19–0.25]).”


Thiazide-like diuretics
Examples- HCTZ, chlorthalidone, indapamide
• MOA- Low volume sodium depletion that leads to PVR reduction

\[ \text{BP} = \text{HR} \times \text{SV} \times \text{PVR} \]

- Thiazide diuretic use is an independent risk factor of T2DM development.
- Monitor for K+, Na+, Mg+ depletion. Calcium sparing. Elders particularly sensitive to hyponatremia induced by thiazide diuretic use.

### Antihypertensive medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide-like diuretics</td>
<td>Thiazide diuretic use is an independent risk factor of T2DM development.</td>
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<tr>
<td>Examples- HCTZ, chlorthalidone, indapamide</td>
<td>Monitor for K+, Na+, Mg+ depletion. Calcium sparing. Elders particularly sensitive to hyponatremia induced by thiazide diuretic use.</td>
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</tbody>
</table>

### Thiazide-type Diuretics

<table>
<thead>
<tr>
<th>Antihypertensive medication</th>
<th>Initial daily dose, mg</th>
<th>Target dose in RCTs, mg/d</th>
<th>No. of doses per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorthalidone (Hygroton®)</td>
<td>12.5</td>
<td>12.5–25</td>
<td>1</td>
</tr>
<tr>
<td>Hydrochlorothiazide (HydroDiuril®)</td>
<td>12.5–25</td>
<td>25–100*</td>
<td>1–2</td>
</tr>
<tr>
<td>Indapamide (Lozol®)</td>
<td>1.25</td>
<td>1.25–2.5</td>
<td>1</td>
</tr>
</tbody>
</table>

*Current recommended evidence-based dose that balances efficacy and safety is 25–50 mg daily.
Thiazide Diuretic Use

- Less effective when GFR<30 mL/min/1.73 m²
  - Loop diuretics will likely remain effective.
- Be vigilant for evidence of overdiuresis in older adult.
  - Postural hypotension
  - BUN: Cr ratio≥20
  - Hyponatremia

K+ Monitoring with Diuretic Use

- Thiazide without K+ sparing medication
  - K+ usually at its lowest point 1 mo after starting or adjusting dose
- Loop without K+ sparing medication
  - K+ wasting typically
    - Dose dependent
    - Worse in first weeks of use
  - Check at least weekly for first month

Renin-angiotensin Cascade

- Angiotensinogen
- Non-renin (e.g. tPA)
- Non-ACE (e.g. chymase)
- Angiotensin I
- Angiotensin II
- ACE
- Bradykinin
- Inactive peptides
- AT1
- AT2
- ATn
**Angiotensin converting enzyme inhibitors (ACEI)**

- ACEI examples: Lisinopril, enalapril, all with -pril suffix
- Angiotensin receptor blockers (ARB): ARB examples- Losartan, telmisartan, all with -sartan suffix

**Comments**

- Adjust dose in renal insufficiency. Do not use in presence of bilateral renal artery stenosis.
- Hyperkalemia risk, especially with inadequate fluid intake, excessive diuresis, when used with aldosterone antagonist.

**Angiotensin receptor blockers (ARB)**

- ARB examples- Losartan, telmisartan, all with -sartan suffix

**BP=HR x SV x PVR↓**

(without increase in HR, SV)

**MOA- Attenuate angiotensin II (Ag II, a potent vasoconstrictor that stimulates adrenal catecholamine release) effect by minimizing its production (ACEI) or blocking its action (ARB)**

- ACEI-induced cough- Can use ARB as alternative.
- Angioedema risk with ACEI use, less so with ARB use
- Do not use during pregnancy (category D).

**ACE Inhibitors**

<table>
<thead>
<tr>
<th>Antihypertensive medication</th>
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<th>Target dose in RCTs reviewed, mg/d</th>
<th>No. of doses per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>50</td>
<td>150–200</td>
<td>2</td>
</tr>
<tr>
<td>Enalapril</td>
<td>5</td>
<td>20</td>
<td>1–2</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10</td>
<td>40</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; RCT, randomized controlled trial.
### Angiotensin Receptor Blockers

<table>
<thead>
<tr>
<th>Antihypertensive medication</th>
<th>Initial daily dose, mg</th>
<th>Target dose in RCTs reviewed, mg</th>
<th>No. of doses per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eprosartan</td>
<td>400</td>
<td>600-800</td>
<td>1-2</td>
</tr>
<tr>
<td>Candesartan</td>
<td>4</td>
<td>12-32</td>
<td>1</td>
</tr>
<tr>
<td>Losartan</td>
<td>50</td>
<td>100</td>
<td>1-2</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40-80</td>
<td>160-320</td>
<td>1</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>75</td>
<td>300</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; RCT, randomized controlled trial.

### Monitoring K+ in Person on ACEI/ARB with CKD

- Check K+ and SCr within 1 to 2 weeks of initiation (1 week in elderly) and after dosage increases.
- Recheck in 3 to 4 weeks if stable, then 1–2 times per year or as dictated by patient comorbidities or status change.

### Per JNC-8

- “ACEI or ARB improves kidney outcomes for patients with CKD. This recommendation applies to CKD patients with and without proteinuria, as studies using ACEIs or ARBs showed evidence of improved kidney outcomes in both groups.”
Calcium Channel Blockers

<table>
<thead>
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<th>Target dose in RCTs reviewed, mg</th>
<th>No. of doses per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>2.5</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Diltiazem extended release</td>
<td>120−180</td>
<td>360</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; RCT, randomized controlled trial.
Current recommended evidence-based dose that balances efficacy and safety is 25–50 mg daily.

What does this mean in practice?

• 58-year-old African-American man with T2DM, HTN and dyslipidemia, BP=170/105 mm Hg
  • Clear need for 2+ meds
    • JNC-7=Thiazide, ACEI, CCB
    • BP goal ≤130/<80 mm Hg
    • JNC-8=Thiazide, ACEI, CCB
    • BP goal ≤140/<90 mm Hg
What does this all mean in practice? (continued)

- 66-year-old woman of European ancestry with HTN, BP=162/92 mm Hg
  - Possible control with 1 med
    - JNC-7=Thiazide as 1st line, BB, ACEI, CCB as 2d line
  - Goal BP<140/<90 mm Hg
  - JNC-8=Thiazide, ACEI, CCB
  - BP goal≤150/<90 mm Hg

Beta blockers as a 4th line therapy?

Meta-analysis Results
Beta Blockers in Uncomplicated HTN

- Stroke
  - Significantly higher with beta blockers than with other antiHTN (relative risk, 1.16; 95% CI, 1.04–1.30)
  - Most problematic w/ atenolol than w/ other non-beta blocker antiHTN (RR, 1.26; 95% CI, 1.15–1.38)

### Beta Blockers

<table>
<thead>
<tr>
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<th>Initial daily dose, mg</th>
<th>Target dose in RCTs reviewed, mg</th>
<th>No. of doses per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>25−50</td>
<td>100</td>
<td>1−2</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>50</td>
<td>100−200</td>
<td>1−2</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; RCT, randomized controlled trial.

*Current recommended evidence-based dose that balances efficacy and safety is 25−50 mg daily.

### Aldosterone antagonist as a 4th line drug?

**Medication**

- Aldosterone antagonist Examples: Spironolactone (Aldactone®), eplerenone (Inspra®)

**Comment**

- Hyperkalemia risk, particularly w/ ACEI, ARB use or volume depletion, including excessive diuresis. Most often used in heart failure treatment.
- Gynecomastia risk with prolonged use
- Use with caution in renal impairment, especially when GFR<30 mL/min/1.73 m²
Anticipated BP Response with Spironolactone Use

- SBP reduction: 22 mm Hg
- DBP reduction: 10 mm Hg
- Average dose: 25 mg per day

You start a patient...

...on spironolactone who is also on an angiotensin-converting enzyme inhibitor. You advise the patient to return in 4 weeks to check which of the following laboratory parameters?

Why not check the labs sooner?

A. Sodium
B. Calcium
C. Potassium
D. Chloride
Why not check the labs sooner?
A. Sodium
B. Calcium
C. Potassium
D. Chloride

Per JNC-8 Medications that are Not Mentioned
- Centrally-acting agents
  - Clonidine, methyldopa
- Direct renin inhibitor
  - Aliskiren

Hypertension in the Elderly
ACCF/AHA Expert Consensus Document
Available at http://content.onlinejacc.org/article.aspx?articleid=1146473

Developed in collaboration with the American Academy of Neurology, Association of Black Cardiologists, American Geriatrics Society, American Society of Hypertension, American Society of Nephrology, American Society for Preventive Cardiology, and the European Society of Hypertension
Hypertension in the Elderly
Therapeutic Options

- Per ACCF/AHA
  - Diuretics, ACEI, calcium antagonists, beta blockers
- All shown benefit on CV outcomes in randomized trials among elderly cohorts
- Specific agents choice dictated by efficacy, tolerability, comorbidities, and cost

Compelling Indications
- Heart failure
- Post MI
- CAD or high CVD risk
- Angina pectoris
- Aortopathy/AAA
- Diabetes
- Chronic kidney disease
- Recurrent stroke prevention
- Early dementia

Initial Drug Choices

Stage 1 Hypertension
- SBP 140–159 mm Hg or DBP 90–99 mm Hg
- ACEI, ARB, CA, diuretic, or combination

Stage 2 Hypertension
- SBP ≥160 mm Hg or DBP ≥100 mm Hg
- Majority will require ≥2 drugs to reach goal if ≥20 mm Hg above target. Initial combinations should be considered. Combination of amlodipine with an RAAS blocker (ACEI, ARB) may be preferred to a diuretic combination, though either is acceptable.

Compelling Indications for Use of Select Meds in Elder w/HTN
- Heart failure
  - Thiazide diuretic, beta blocker, ACEI, ARB, CCB, aldosterone antagonist
- Post myocardial infarction
  - Beta blocker, ACEI, ARB, aldosterone antagonist

Not at target BP
- Optimize dosages or add additional drugs until goal BP is achieved.
- Refer to a clinical hypertension specialist if unable to achieve control.
Compelling Indications for Use of Select Meds in Elder w/HTN (continued)

- CAD or high CVD risk
  - Thiazide diuretic, beta blocker, ACEI, CCB
- Angina pectoris
  - Beta blocker, CCB

Compelling Indications for Use of Select Meds in Elder w/HTN (continued)

- Aortopathy/aortic aneurysm
  - Thiazide diuretic, beta blocker, ACEI, CCB

Compelling Indications for Use of Select Meds in Elder w/HTN (continued)

- Diabetes mellitus
  - Thiazide diuretic, beta blocker, ACEI, ARB, CCB
- Chronic kidney disease
  - ACEI, ARB
Compelling Indications for Use of Select Meds in Elder w/HTN (continued)

- Recurrent stroke prevention
  - Thiazide diuretic, ACEI, ARB, CCB

Postural Hypotension in Older Adult: Major Etiology

- Age-related changes
- Low circulating volume
  - Overdiuresis
  - Poor oral intake
- Use of medications with vasodilating capability

Postural Hypotension
AKA Orthostatic Hypotension or Orthostasis

- Defined
  - Abnormal fall in blood pressure, ≥20 mm Hg systolic, ≥10 mm Hg diastolic or both, within three minutes of standing upright
- Usually associated with symptoms
Postural Hypotension
AKA Orthostatic Hypotension or Orthostasis
(continued)
• Origin of postural hypotension
  – Age-associated reduction in baroreflex function
  – Increase in venous insufficiency
• Risk for falls, syncope, CV events

Postural Hypotension
AKA Orthostatic Hypotension or Orthostasis
(continued)
• Postural hypotension symptoms
  • Faintness, light-headedness
  • Dizziness
  • Confusion
  • Blurred vision
  – Occur within seconds to a few minutes of standing and resolve rapidly on lying down

Antihypertensive
Treatment-related Adverse Effects
• The high prevalence of both CV and non-CV comorbidities among the older adults dictates need for great vigilance to avoid treatment-related adverse effects such as
  – Electrolyte disturbances
  – Renal dysfunction
  – Excessive orthostatic BP decline
Difficulty in HTN Control
Possible Contributors

• Use of select medications
  – NSAIDs in dose-dependent manner
    • Partial reversal of antiHTN effect of beta blockers (most potent), diuretics, ACEI, ARB but not CCB
    • Use associated w/renal impairment, sodium retention, decreased GFR, edema, hyperkalemia, and/or papillary necrosis

Difficulty in HTN Control
Possible Contributors
(continued)

• Use of select medications (cont.)
  – Cyclooxygenase-2 (COX-2) inhibitors
    • An NSAID form
  – Systemic corticosteroids
    • Mechanism similar to NSAIDs, as much 15 mm Hg rise within 24 h of starting medication
  – Certain DMARDs
    • Cyclosporine, leflunomide

Conclusion
End of Presentation
Thank you for your time and attention.

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