Reviewing the Different Guidelines for BP Control: 2015

59th Annual Postgraduate Seminar
Embassy Suites Hotel
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DISCLOSURE OF FINANCIAL RELATIONSHIPS

Jan N. Basile, MD

Grant/Research support: NHLBI (SPRINT)
Consultant: Actavis, Amgen, Arbor, Eli-Lilly, Janssen, Medtronic
Speakers Bureau: Arbor, Janssen
Major stock shareholder: None
Other: None
Objectives:

1. Understand the epidemiology of hypertension and recent improvements in control rates for hypertension.

2. Understand the current state of office, home, and 24-hr ambulatory blood pressure monitoring (24-hr ABPM)

3. Summarize recent HTN guidelines dealing with BP levels achieved to improve CV and renal outcomes and which classes of antihypertensive agents are recommended as first-line agents.
Objectives:

1. Understand the epidemiology of hypertension and recent improvements in control rates for hypertension.
The Impact of Hypertension

- Approximately 77.9 million (33.3%) US adults 20 years of age and older have hypertension.

- Approximately 69% of people who have a first heart attack, 77% of those who have a first stroke, and 74% of those who have HF have BP >140/90 mm Hg.

- From 1998 to 2008, the death rate caused by HTN increased 20.2% and the actual number of deaths rose 49.7%.

- HTN is associated with shorter overall life expectancy.


Egan BM et al. JAMA. 2010;303:2043.
Objectives:

2. Understand the current state of office, home, and 24-hr ambulatory blood pressure monitoring (24-hr ABPM)
BP Measurement in the Office in Established Patient: A Systems Approach In The Office

1. Preferably taken before the patient ever sees the clinician caring for the patient

2. - 5 minutes of rest
   - no conversation
   - seated comfortably with feet on the floor
   - arm at heart level
   - no tobacco or caffeine for 30 minutes before BP

3. Two to Three seated readings (averaged)

4. An upright reading (taken after 1-3 minutes of quiet standing)
Only Use an Acceptable Device
Poor BP Measurement Technique May Be A Problem

“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.”

<table>
<thead>
<tr>
<th>Office BP</th>
<th>Home BP</th>
<th>24h ABPM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The time-proven measure</strong></td>
<td><strong>Easy to perform and widely available</strong></td>
<td></td>
</tr>
<tr>
<td>More reproducible than office BP</td>
<td>Assessment of White Coat and Masked HTN/Effect</td>
<td></td>
</tr>
<tr>
<td>No hard-outcomes thru clinical trials but consistently better marker of organ damage and prognosis in observational studies</td>
<td>Assessment of sleep BP, morning surge and BP variability; required for dx of resistant hypertension</td>
<td></td>
</tr>
</tbody>
</table>
Conventional, 24-hr, Daytime and Night-time SBP as Predictors of Cardiovascular Endpoints – Syst-Eur

The Concept of White-Coat Hypertension

- **True Normotensive**
- **True Hypertensive**
- **Masked Hypertension**
- **White Coat HTN**

 Derived from Pickering et al. *Hypertension* 2002:40:795-796
Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial

Richard J McManus, Jonathan Mant, Emma P Bray, Roger Holder, Mireni Jones, Sheila Greenfield, Billingsley Kaambwa, Miriam Banting, Stirling Bryan, Paul Little, Bryan Williams, FD Richard Hobbs

<table>
<thead>
<tr>
<th>Effect size, mm Hg (95% CI)</th>
<th>Subgroup comparison pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMD 2007</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>1.6 (-4.4 to 7.6)</td>
</tr>
<tr>
<td>Low</td>
<td>7.0 (3.4 to 10.5)</td>
</tr>
<tr>
<td>Diabetes and chronic kidney disease status</td>
<td></td>
</tr>
<tr>
<td>Either disease</td>
<td>13 (-8.5 to 11.0)</td>
</tr>
<tr>
<td>Neither disease</td>
<td>5.8 (2.6 to 9.0)</td>
</tr>
<tr>
<td>Baseline systolic blood pressure</td>
<td></td>
</tr>
<tr>
<td>&gt;150 mm Hg</td>
<td>3.6 (-1.2 to 8.5)</td>
</tr>
<tr>
<td>≤150 mm Hg</td>
<td>7.0 (3.2 to 10.8)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>5.8 (1.4 to 10.2)</td>
</tr>
<tr>
<td>≤65 years</td>
<td>5.0 (0.8 to 9.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>4.4 (0.1 to 8.7)</td>
</tr>
<tr>
<td>Male</td>
<td>6.3 (2.0 to 10.5)</td>
</tr>
<tr>
<td>Overall</td>
<td>5.4 (2.4 to 8.4)</td>
</tr>
</tbody>
</table>

N=527 (263v264)   F/U 6 + 12 months  ↓BP 13 vs 9 and 17 and 12 mmHg  AEs equal

*Lancet* 2010; 376: 163-172
Objectives:

3. Summarize recent HTN guidelines dealing with BP levels achieved to improve CV and renal outcomes and which classes of antihypertensive agents are recommended as first-line agents.
# The Seventh Report on the Prevention, Detection, Evaluation, and Management of High Blood Pressure (JNC 7): Classification and Management

<table>
<thead>
<tr>
<th>BP Classification</th>
<th>SBP* (mm Hg)</th>
<th>DBP* (mm Hg)</th>
<th>Lifestyle Modification</th>
<th>Without Compelling Indications</th>
<th>With Compelling Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>&lt;80</td>
<td>Encourage</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pre-HTN</td>
<td>120–139</td>
<td>80–89</td>
<td>Yes</td>
<td>No antihypertensive drug indicated</td>
<td>Drug(s) for the compelling indications†</td>
</tr>
<tr>
<td>Stage 1 HTN</td>
<td>140–159</td>
<td>90–99</td>
<td>Yes</td>
<td>One-drug therapy Indicated</td>
<td>Drug(s) for the compelling indications Other antihypertensive drugs as needed to control BP</td>
</tr>
<tr>
<td>Stage 2 HTN</td>
<td>≥160</td>
<td>≥100</td>
<td>Yes</td>
<td>Two-drug combination indicated for most‡</td>
<td>Drugs for the compelling indications Other antihypertensive drugs as needed to control BP</td>
</tr>
</tbody>
</table>

*Treatment determined by the highest BP category. SBP, systolic blood pressure; DBP, diastolic blood pressure;
†Treat patients with CKD or DM to BP goal of <130/80 mm Hg.
‡Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

Development of Hypertension Guidelines: the JNCs and Drug Therapy

- **Earliest Guidelines**: 1972
- **JNC I**: 1973
- **JNC II**: 1976
- **JNC III**: 1980
- **JNC IV**: 1984
- **JNC V**: 1988
- **JNC VI**: 1993
- **JNC VII**: 1997
- **JNC VIII**: 2003
- **8th Report**: December 18, 2013

- **28 drugs**
  - DBP $\geq 105$
  - Diuretics
- **34 drugs**
  - Diuretics
- **43 drugs**
  - Low dose diuretics, β-blockers Added
- **50 drugs**
  - ACEI, CAs added
- **68 drugs**
  - Diuretics/β-blockers
- **84 drugs**
  - 7 options
- **>125 drugs**
  - Diuretics “for most” (ALLHAT)
What to Make of The Hypertension Guidelines?

- The NHLBI originally commissioned a writing panel in 2008 to develop the JNC 8 hypertension guidelines as part of an entire prevention portfolio.
- In 2013, the NHLBI got out of the guideline area and asked the ACC/AHA Joint Task Force to assume the guideline process.
- The writing panel (JNC 8) declined to be a part of the process and published their own document in JAMA.
- Accordingly, “JNC 8” was a “stand alone document” not endorsed by any other group.
- We expect the AHA/ACC Joint Task Force guideline to be published sometime in 2015.
Four Decision-Point Variables

1. Age (>59?)
2. CKD (yes?)
3. Diabetes (yes?)
4. Ethnicity/Race (AA?)

The Document Referred to as “JNC 8”

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Questions Guiding the Evidence Review

What should be your specified BP goal?
How low should you go with BP?
### Guidelines Have Set Clear Treatment Goals

**JNC7/ADA/NKF/ISHIB Guidelines for Hypertension**

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ADA, American Diabetes Association; NKF, National Kidney Foundation; ISHIB, International Society on Hypertension in Blacks

Flack JM et al. *Hypertension* 2010;56:780.
JNC 8 Hypertension Guideline Management Algorithm

Adult (age ≥ 18 years)

Lifestyle Interventions to be applied throughout Treatment Algorithm

Set Blood Pressure Goal and Initiate Blood Pressure Lowering Medication Based on Age, Diabetes, and CKD

- Age ≥ 60 years and No Diabetes and No CKD
  - Goal SBP < 150 mm Hg
  - Goal DBP < 90 mm Hg
- Age < 60 years and No Diabetes and No CKD
  - Goal SBP < 140 mm Hg
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- All Ages with Diabetes and No CKD
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Black

- Initiate thiazide-type diuretic or CCB alone or in combination

Nonblack

- Initiate thiazide-type diuretic or ACEI or ARB or CCB alone or in combination

Other Races

- Initiate ACEI or ARB alone or in combination with other class

Select a treatment titration strategy: A: maximize first medication before adding second, B: add second medication before reaching maximum dose of first, or C: start with 2 medication classes separately or as fixed dose combination

### Benefit of Treatment of Stage 2 Isolated Systolic HTN:
Final BP <150 mm Hg but not < 140 mm Hg

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<tr>
<th>Trial</th>
<th>Bp</th>
<th>BP</th>
<th>Change in BP v P</th>
<th>Change in CVE</th>
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<tbody>
<tr>
<td>SHEP</td>
<td>170/77</td>
<td>143/68</td>
<td>12/4</td>
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BP = initial BP
BP = treatment BP
P = placebo
CVE = cardiovascular event

## Benefit of Treatment of Stage 2 Isolated Systolic HTN:
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Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in Patients Aged 60 Years or Older: The Minority View

Jackson T. Wright Jr., MD, PhD; Lawrence J. Fine, MD, DrPH; Daniel T. Lackland, DrPH; Gbenga Ogedegbe, MD, MPH, MS; Cheryl R. Dennison Himmelfarb, PhD, RN, ANP

Conclusion: These five dissenters believe that the threshold and goal BP should be < 140 mm Hg and not < 150 mm Hg in those ≥ 60 years of age

**Major Randomized Trials Testing SBP Goals in General (Older) Populations**

<table>
<thead>
<tr>
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<th>SHEP</th>
<th>Syst-Eur</th>
<th>HYVET</th>
<th>JATOS</th>
<th>VALISH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>≥60</td>
<td>≥60</td>
<td>≥80</td>
<td>65-85</td>
<td>70-84</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>4,736</td>
<td>4,695</td>
<td>3,845</td>
<td>4,418</td>
<td>3,260</td>
</tr>
<tr>
<td><strong>Entry SBP</strong></td>
<td>160-219</td>
<td>160-219</td>
<td>160-199</td>
<td>≥160</td>
<td>≥160</td>
</tr>
<tr>
<td><strong>Goal SBP</strong></td>
<td>&lt;148</td>
<td>&lt;150</td>
<td>&lt;150</td>
<td>&lt;140</td>
<td>&lt;140</td>
</tr>
<tr>
<td><strong>Achieved</strong></td>
<td>142</td>
<td>151</td>
<td>144</td>
<td>136</td>
<td>137</td>
</tr>
<tr>
<td><strong>Stroke ↓</strong></td>
<td>36%</td>
<td>42%</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>CVD ↓</strong></td>
<td>32%</td>
<td>31%</td>
<td>34%</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Mortality ↓</strong></td>
<td>ns</td>
<td>ns</td>
<td>21%</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
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SBP = systolic blood pressure; CVD = cardiovascular disease
Risk of Adverse Outcomes Among Elderly CAD Patients by Age and BP—“Is There a Sweet Spot for BP”

## Contrasts in Goal BP Recommendations

<table>
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<tr>
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<th>&gt;60 years</th>
<th>≥80 years</th>
<th>CKD</th>
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<tbody>
<tr>
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<td>130-140/80-90</td>
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</tr>
<tr>
<td>2014 HTN guidelines</td>
<td>&lt;150/90</td>
<td>&lt;150/90</td>
<td>&lt;140/90</td>
</tr>
<tr>
<td>ADA 2015</td>
<td>-</td>
<td></td>
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Guidelines Have Set Clear Treatment Goals

**JNC7/ADA/NKF/ISHIB Guidelines for Hypertension**

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JNC 8 Hypertension Guideline Management Algorithm

Adult (age ≥18 years)

Lifestyle Interventions to be applied throughout Treatment Algorithm

Set Blood Pressure Goal and Initiate Blood Pressure Lowering Medication Based on Age, Diabetes, and CKD

- Age ≥60 years and No Diabetes and No CKD
  - Goal SBP <150 mm Hg
  - Goal DBP <90 mm Hg
  - Black: Initiate thiazide-type diuretic or CCB alone or in combination
  - Nonblack: Initiate thiazide-type diuretic or ACEI or ARB or CCB alone or in combination
- Age <60 years and No Diabetes and No CKD
  - Goal SBP <140 mm Hg
  - Goal DBP <90 mm Hg
- All Ages with Diabetes and No CKD
  - Goal SBP <140 mm Hg
  - Goal DBP <90 mm Hg
- All Ages with CKD
  - Goal SBP <140 mm Hg
  - Goal DBP <90 mm Hg
  - All Races
    - Select a treatment titration strategy: A: maximize first medication before adding second, B: add second medication before reaching maximum dose of first, or C: start with 2 medication classes separately or as fixed dose combination

Initiate ACEI or ARB alone or in combination with other class
## Contrasts in Goal BP Recommendations

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<th>Diabetes</th>
<th>CKD</th>
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<tr>
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### Guidelines Have Set Clear Treatment Goals

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Flack JM et al. *Hypertension* 2010;56:780.
**Recommendation 5**

In the population aged ≥18 years with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to a goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Expert Opinion – Grade E)
People with Diabetes and Hypertension should be treated to a systolic BP goal of < 140 mm Hg. (Level of Evidence A)

Lower systolic targets, such as < 130 mm Hg, may be appropriate for certain individuals, such as younger patients or those in whom stroke risk is a concern, if it can be achieved without undue treatment burden (Level of Evidence C).

Patients with diabetes should be treated to a diastolic BP goal of < 90 mm Hg although lower targets may be appropriate in certain individuals. (Level of Evidence A).

This is in harmonization with the 8th JNC
UKPDS, ADVANCE, and ACCORD BP reduction in context: UK Prospective Diabetes Study Epidemiologic Data

Adapted from UK Prospective Diabetes Study, BMJ Volume 321, August 12, 2000.
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Which class(es) of antihypertensive agents are recommended as initial therapy?
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- All Ages with Diabetes and No CKD
  - Goal SBP < 140 mm Hg
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- All Ages with CKD

- All Races
  - Initiate ACEI or ARB alone or in combination with other class

Select a treatment titration strategy: A: maximize first medication before adding second, B: add second medication before reaching maximum dose of first, or C: start with 2 medication classes separately or as fixed dose combination

## Compelling Indications for Individual Drug Classes

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<thead>
<tr>
<th></th>
<th>Diuretic</th>
<th>β-blocker</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
<th>Aldo Antag.</th>
<th>Clinical Trial Basis</th>
</tr>
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<tbody>
<tr>
<td><strong>HF</strong></td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>ACC/AHA HF guideline; MERIT-HF; COPERNICUS, CIBIS, SOLVD; AIRE, TRACE, Val-HeFT; RALES</td>
</tr>
<tr>
<td><strong>Post-MI</strong></td>
<td></td>
<td></td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>ACC/AHA post-MI guideline; BHAT; SAVE, CAPRICORN, EPHESUS/VALIANT</td>
</tr>
<tr>
<td><strong>High CAD Risk</strong></td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>ALLHAT; HOPE, ANBP2; LIFE; CONVINCE, ONTARGET</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>NKF-ADA guideline; UKPDS; ALLHAT</td>
</tr>
<tr>
<td><strong>CKD</strong></td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td>NKF guideline; CAPPP; RENAAL, IDNT, REIN, AASK</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td>PROGRESS, LIFE</td>
</tr>
</tbody>
</table>

MI=myocardial infarction  
CKD=chronic kidney disease

Adapted from Chobanian AV et al. JAMA. 2003;289:2560-2572.
1° Endpoint: Nonfatal MI + CHD Death – Subgroup Comparisons – RR (95% CI)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Amlodipine</th>
<th>Chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.98 (0.90, 1.07)</td>
<td>0.99 (0.91, 1.08)</td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>0.99 (0.85, 1.16)</td>
<td>0.95 (0.81, 1.12)</td>
</tr>
<tr>
<td>Age &gt;= 65</td>
<td>0.97 (0.88, 1.08)</td>
<td>1.01 (0.91, 1.12)</td>
</tr>
<tr>
<td>Men</td>
<td>0.98 (0.87, 1.09)</td>
<td>0.94 (0.85, 1.05)</td>
</tr>
<tr>
<td>Women</td>
<td>0.99 (0.85, 1.15)</td>
<td>1.06 (0.92, 1.23)</td>
</tr>
<tr>
<td>Black</td>
<td>1.01 (0.86, 1.18)</td>
<td>1.10 (0.94, 1.28)</td>
</tr>
<tr>
<td>Non-Black</td>
<td>0.97 (0.87, 1.08)</td>
<td>0.94 (0.85, 1.05)</td>
</tr>
</tbody>
</table>

Diabetic

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Lisinopril</th>
<th>Chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>0.99 (0.88, 1.11)</td>
<td>0.99 (0.88, 1.11)</td>
</tr>
<tr>
<td>Age &lt; 65</td>
<td>0.99 (0.87, 1.13)</td>
<td>1.00 (0.87, 1.14)</td>
</tr>
<tr>
<td>Age &gt;= 65</td>
<td>0.99 (0.87, 1.13)</td>
<td>1.00 (0.87, 1.14)</td>
</tr>
<tr>
<td>Men</td>
<td>1.06 (0.92, 1.23)</td>
<td>1.06 (0.92, 1.23)</td>
</tr>
<tr>
<td>Women</td>
<td>1.06 (0.92, 1.23)</td>
<td>1.06 (0.92, 1.23)</td>
</tr>
<tr>
<td>Black</td>
<td>1.10 (0.94, 1.28)</td>
<td>1.10 (0.94, 1.28)</td>
</tr>
<tr>
<td>Non-Black</td>
<td>0.94 (0.85, 1.05)</td>
<td>0.94 (0.85, 1.05)</td>
</tr>
</tbody>
</table>
Four Decision-Point Variables

1. Age (>59?)
2. CKD (yes?)
3. Diabetes (yes?)
4. Ethnicity/Race (AA?)

The Document Referred to as “JNC 8”

JNC 8 Hypertension Guideline Management Algorithm

Adult (age ≥18 years)

Lifestyle Interventions to be applied throughout Treatment Algorithm

Set Blood Pressure Goal and Initiate Blood Pressure Lowering Medication Based on Age, Diabetes, and CKD

- Age ≥60 years and No Diabetes and No CKD
  - Goal SBP <150 mm Hg
  - Goal DBP <90 mm Hg
  - Initiate thiazide-type diuretic or CCB alone or in combination

- Age <60 years and No Diabetes and No CKD
  - Goal SBP <140 mm Hg
  - Goal DBP <90 mm Hg
  - Initiate thiazide-type diuretic or ACEI or ARB or CCB alone or in combination

- All Ages with Diabetes and No CKD
  - Goal SBP <140 mm Hg
  - Goal DBP <90 mm Hg
  - Initiate ACEI or ARB alone or in combination

- All Ages with CKD
  - Goal SBP <140 mm Hg
  - Goal DBP <90 mm Hg
  - All Races
    - Initiate ACEI or ARB alone or in combination with other class

Select a treatment titration strategy: A: maximize first medication before adding second, B: add second medication before reaching maximum dose of first, or C: start with 2 medication classes separately or as fixed dose combination
JNC 8 Hypertension Guideline Management Algorithm

**Age (>59?)**; **CKD (yes?)**; **Diabetes (yes?)**; **Ethnicity/Race (AA?)**

- **General population (no diabetes or CKD)**
- **Diabetes or CKD present**

**All Ages**
- **CKD present with or without diabetes**
- **Diabetes present**
- **No CKD**

**Blood Pressure Goal**
- **SBP <140 mm Hg**
- **DBP <90 mm Hg**

**Nonblack**
- **Black**

- **Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination**
- **Initiate thiazide-type diuretic or CCB, alone or in combination**

**All races**
- **Initiate ACEI or ARB, alone or in combination with other drug class\(^a\)**

---

JNC 8 Hypertension Guideline Management Algorithm

Age (>59?); CKD (yes?); Diabetes (yes?); Ethnicity/Race (AA?)

General population (no diabetes or CKD)

Diabetes or CKD present

Age ≥60 years
- Blood Pressure Goal
  - SBP <150 mm Hg
  - DBP <90 mm Hg
- Nonblack
  - Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination

Age <60 years
- Blood Pressure Goal
  - SBP <140 mm Hg
  - DBP <90 mm Hg
- All Ages
  - Diabetes present
  - No CKD
  - Black
  - Initiate thiazide-type diuretic or CCB, alone or in combination

All Ages
- CKD present with or without diabetes
- All races
  - Initiate ACEI or ARB, alone or in combination with other drug class

JNC 8: Initial Medications For The Management of Hypertension

Lifestyle Modification—Especially Diet and Exercise

- Diuretics
- ACE inhibitors or ARBs
- Calcium antagonists

β-blockers should be included in the regimen if there is a compelling indication for a β-blocker for the Black population.

The available evidence does not support the use of beta-blockers as first-line drugs in the treatment of hypertension.
Main benefits of treatment depend on BP lowering per se

Confirmation that initiation / maintenance of treatment can make use of

- Diuretics
- Beta-blockers
- Calcium antagonists
- ACE-inhibitors
- Angiotensin receptor blockers
Which “Thiazide” to Use?

• Thiazide
  – Hydrochlorothiazide
  – Chlorthiazide
  – Bendroflumethiazide

• Thiazide-like
  – Chlorthalidone
  – Metolazone
  – Indapamide
# Diuretics Used to Treat Hypertension

<table>
<thead>
<tr>
<th>Thiazide and Thiazide-like Diuretics</th>
<th>BA (%)</th>
<th>T$_\frac{1}{2}$ (hours)</th>
<th>DOA (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide</td>
<td>65 – 75</td>
<td>3.0 – 10.0</td>
<td>6 – 12</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>30 – 50</td>
<td>15.0 – 25.0</td>
<td>6 – 12</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>65</td>
<td>24.0 – 55.0</td>
<td>24 – 72</td>
</tr>
<tr>
<td>Indapamide</td>
<td>90</td>
<td>6.0 – 15.0</td>
<td>24 – 36</td>
</tr>
<tr>
<td>Metolazone</td>
<td>65</td>
<td>14</td>
<td>12 – 24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Loop Diuretics</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide</td>
<td>80 – 90</td>
<td>0.3 – 1.5</td>
<td>4-6</td>
</tr>
<tr>
<td>Furosemide</td>
<td>10 – 100</td>
<td>0.3 – 3.4</td>
<td>6-8</td>
</tr>
<tr>
<td>Torsemide</td>
<td>80 – 100</td>
<td>3.0 – 4.0</td>
<td>6-8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Potassium-Sparing Diuretics</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiloride</td>
<td>15-20</td>
<td>17.0 – 26.0</td>
<td>24</td>
</tr>
<tr>
<td>Triamterene</td>
<td>83 (55)*</td>
<td>3.0 (3.0)*</td>
<td>7-9</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>&gt;90</td>
<td>1.5 – 15.0†</td>
<td>48-72</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>69</td>
<td>2.2 – 9.4</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Parentheses denote active metabolite. †The half-life of one active metabolite, potassium canrenoate, is 15 h.

BA = bioavailability; T$_\frac{1}{2}$ = half-life; DOA = duration of action; NA = unknown.

### Representative Outcome Studies Using Chlorthalidone vs HCTZ

<table>
<thead>
<tr>
<th>Chlorthalidone</th>
<th>HCTZ (dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MRFIT</strong>&lt;br&gt;(50–100 mg)</td>
<td><strong>MRFIT</strong>&lt;br&gt;(50–100 mg)</td>
</tr>
<tr>
<td><strong>SHEP</strong>&lt;br&gt;(12.5–25 mg)</td>
<td><strong>ACCOMPLISH</strong>&lt;br&gt;(2.5–25 mg)</td>
</tr>
<tr>
<td><strong>ALLHAT</strong>&lt;br&gt;(12.5–25 mg)</td>
<td><strong>Medical Research Council trial in the Elderly (MRC-E)</strong>&lt;br&gt;(25–50 mg)</td>
</tr>
<tr>
<td>Treatment of Mild Hypertension trial (TOMHS)&lt;br&gt;(12.5–25 mg)</td>
<td>VA Cooperative Study Group on antihypertensive agents&lt;br&gt;(50–100 mg)</td>
</tr>
<tr>
<td>Hypertension Detection and Follow-up Program (HDFP)&lt;br&gt;(25–100 mg)</td>
<td></td>
</tr>
</tbody>
</table>

HCTZ=hydrochlorothiazide.

Major Outcomes
Relative Risks and 95% Confidence Intervals

### Amlodipine/Chlorthalidone

- **CHD**: 0.98 (0.90-1.07)
- **All-Cause Mortality**: 0.96 (0.89-1.02)
- **Stroke**: 0.93 (0.82-1.06)
- **Combined CVD**: 1.04 (0.99-1.09)
- **Heart Failure**: 1.38 (1.25-1.52)
- **ESRD**: 1.12 (0.89-1.40)

### Lisinopril/Chlorthalidone

- **CHD**: 0.99 (0.91-1.08)
- **All-Cause Mortality**: 1.00 (0.94-1.08)
- **Stroke**: 1.19 (1.07-1.31)
- **Combined CVD**: 1.10 (1.05-1.16)
- **Heart Failure**: 1.15 (1.02-1.30)
- **ESRD**: 1.11 (0.88-1.38)

Favors
- **Amlodipine**
- **Chlorthalidone**
- **Lisinopril**
- **Chlorthalidone**

JAMA 2002;288:2981-2997
ALLHAT
Stroke in Black vs Nonblack Patients

ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. JAMA. 2002;288:2981-2997.[15]
JNC 8

Initial Medications for the Management of Hypertension

Lifestyle Modification—Especially Diet and Exercise

Diuretics

Black population

ACE inhibitors or ARBs

Calcium antagonists

Meta-analysis: 24 Hr ABPM Antihypertensive: Efficacy of HCTZ and Comparison of HCTZ Doses

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Number of Studies</th>
<th>Total Participants</th>
<th>BP Change Systolic ABP</th>
<th>BP Change Diastolic ABP</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 Studies</td>
<td>12.5mg</td>
<td>232</td>
<td>-5.7</td>
<td>-3.7</td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td>715</td>
<td>-7.5</td>
<td>-5.3</td>
</tr>
<tr>
<td></td>
<td>50 mg+</td>
<td>207</td>
<td>-12.9</td>
<td>-6.4</td>
</tr>
</tbody>
</table>

P = NS vs 12.5mg (Both Systolic and Diastolic)

P = 0.0005 vs 25mg systolic
P = NS vs 25mg diastolic

Messerli, et al. JACC. 2011;57:590-600
Chlorthalidone 25 mg Has Greater BP-Lowering Efficacy vs HCTZ 50 mg, Especially at night

Reduction in Mean SBP
Baseline to Week 8, mm Hg

-20
-18
-16
-14
-12
-10
-8
-6
-4
-2
0

24-hour Mean SBP
Daytime Mean SBP
Night-time Mean BP

-12.4
-11.4
-13.5

P=0.054  P=0.230  P=0.009

CLD 25 mg  HCTZ 50 mg

Daytime was 6:00 AM to 10:00 PM; night-time, 10:00 PM to 6:00 AM.

CLD=chlorthalidone; HCTZ=hydrochlorothiazide.

Summary

- Thiazide-type diuretic class (at appropriate doses) has well demonstrated benefits on reduction of BP and CV events – unsurpassed by other classes at appropriate dose.

- Chlorthalidone appears to be more effective than HCTZ for BP and CV event reduction at the similar and often used doses of 12.5 mg to 25 mg a day.

- Since 97% of patients are currently on HCTZ, in established patients if BP is not controlled with HCTZ, replacing HCTZ with CTD often is effective and well-tolerated.

- Based on outcomes, newly diagnosed patients with hypertension should be considered for chlorthalidone as initial therapy.
Objectives:

1. Understand the epidemiology of hypertension and recent improvements in control rates for hypertension.

2. Understand the current state of office, home, and 24-hr ambulatory blood pressure monitoring (24-hr ABPM).

3. Summarize recent HTN guidelines dealing with BP levels achieved to improve CV and renal outcomes and which classes of antihypertensive agents are recommended as first-line agents.
Thank you!