Hypertension Management: JNC 8’s Evidence and Recommendations

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Learning Objectives

• Describe the main recommendations of the JNC 8 panelists’ guideline for the treatment of hypertension
• Review the rationale for the recommendations
• Review dissenting opinions about blood pressure targets and their evidence

Comparing JNC 8 to JNC 7

<table>
<thead>
<tr>
<th>Topic</th>
<th>JNC 7</th>
<th>JNC 8</th>
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<tbody>
<tr>
<td>Methodology</td>
<td>Non-systematic review</td>
<td>Critical questions</td>
</tr>
<tr>
<td></td>
<td>All available evidence</td>
<td>Systematic review by</td>
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<tr>
<td></td>
<td></td>
<td>methodologists</td>
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<tr>
<td></td>
<td></td>
<td>Restricted to RCT</td>
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<tr>
<td>Treatment Goals</td>
<td>Separate goals for</td>
<td>Similar goals for all HTN</td>
</tr>
<tr>
<td></td>
<td>“uncomplicated HTN” vs.</td>
<td>populations unless evidence</td>
</tr>
<tr>
<td></td>
<td>with comorbidities</td>
<td>supports otherwise</td>
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<tr>
<td>Drug Therapy</td>
<td>5 drug classes – favor</td>
<td>4 drug classes based on</td>
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<td></td>
<td>thiazides</td>
<td>RCT evidence</td>
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<td></td>
<td>Recommended drug classes</td>
<td>More clinician discretion</td>
</tr>
<tr>
<td></td>
<td>by comorbidity</td>
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</table>
Evidence Review

• RCTs
  – Hypertensive adults ≥ 18 years old
  – N ≥ 100
  – Follow up ≥ 1 year
  – Health outcomes: mortality, MI, HF, CVA, ESRD

Guiding Questions

1. At what BP should treatment be initiated to improve outcomes?
2. What should the target BP be for those undergoing treatment?
3. Which antihypertensive medications are best to use?
BP Treatment Thresholds/Targets

- **Age ≥ 60**
  - CKD, Age ≥ 18
    - SBP: 150
    - DBP: 90
  - Age ≤ 60
    - SBP: 140
    - DBP: 90

- **Diabetes, Age ≥ 18**
  - SBP: 140
  - DBP: 90

- **Age < 60**
  - SBP: 140
  - DBP: 90

**Emphasis on two particular comorbidities that increase risk**
- Diabetes
- CKD

**Thresholds/targets differ by age and presence of these comorbidities**

**Everyone <60 years regardless of comorbidity and people ≥60 have goal <140/90**

**People ≥60 w/o DM/CKD have goal <150/90**

**Evidence from 4 trials favoring treatment at SBP≥160**
- HYVET
- SHEP
- Syst-Eur
- EWPHE (fair)

**Reduces CVA morbidity and mortality**
**Reduces CHF**
**Reduces CHD**

**Selected Trial Results: % Reduction**

<table>
<thead>
<tr>
<th>Trial</th>
<th>All cause mortality</th>
<th>CV death</th>
<th>Fatal/ non-fatal Stroke</th>
<th>Fatal/ non-fatal Coronar y Event</th>
<th>CHF</th>
<th>CV combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYVET</td>
<td>21</td>
<td>23 (NS)</td>
<td>30</td>
<td>31</td>
<td>64</td>
<td>34 (NS)</td>
</tr>
<tr>
<td>SHEP</td>
<td>13 (NS)</td>
<td>20 (NS)</td>
<td>36</td>
<td>27</td>
<td>49</td>
<td>23</td>
</tr>
<tr>
<td>Syst-Eur</td>
<td>14 (NS)</td>
<td>27 (NS)</td>
<td>42</td>
<td>30 (NS)</td>
<td>25</td>
<td>31</td>
</tr>
</tbody>
</table>
Age < 60: Lack of evidence for SBP threshold

- Insufficient evidence for reduction of CVA, CHD, mortality with starting treatment at any SBP threshold.
- Lack of trials meeting criteria for inclusion
- Oslo Study, 785 men age 40-49 started treatment at SBP 150
  - Data was rated poor due to high crossover between treatment and control groups.
  - No difference in CHD events, mortality, total CVD events
  - Significant decrease in strokes but only 7 events.

Age < 60: Evidence for DBP threshold of 90

- Treating patients age 30-59 at DBP of 90 reduces CVD morbidity and mortality, CHF,
- Up to 6 trials included:
  - EWPHE, HDFP, Hypertension-Stroke Cooperative, HYVET, MRC, and VA cooperative
  - All showed reduction in CVD morbidity/ mortality
  - Consistent magnitude of effect

Age < 60: Evidence for DBP threshold of 90

- Fatal or non-fatal stroke: -30-45%
- Fatal stroke: -32-39%
- Non-fatal stroke: -11-49%
- Fatal or non-fatal heart failure: -64% (HYVET)
- Overall mortality: -1.3% (absolute decrease) at 5 years (HDFP)

Age < 60: Evidence for DBP threshold of 90

- No qualifying study assess effect of BP treatment at DBP of 90 for people< 30 years.
- No benefit found to treating to lower DBP target of <85 or <80.
  - HOT trial showed no improvement in CVD events, mortality
Age < 60: Evidence for DBP threshold of 90

- Elevated DBP is more important cardiovascular risk factor than elevated SBP
- No need to change the SBP threshold

Patients with CKD

- 3 trials included: AASK, MDRD, REIN-2
- 1 post-hoc analysis showing possible benefit of lower target at 130/80
- 2 other primary analyses did not show significant benefit of 130/80 over 140/90
- AASK: No benefit to CHD or CVD outcomes
  - Follow up in cohort phase 8-12 years did not show differences in serum creatinine doubling, ESRD, death

Patients with CKD

- No benefit of target 130/80 over 140/90 in progression of kidney disease
  - No reduction in ESRD, GFR by 50%, death
  - Consistent finding across all three studies
- Trend of benefit of lower goal for patients with severe proteinuria (> 3 gm/ day baseline)

Patients with DM

- No RCTs to support goal of < 140/90
- Treatment at SBP of 150 resulted in decreased mortality, CVD and CHD events.
- HOT trial compared DBP<80 to <90 found reduction of composite CVD outcome in post-hoc analysis of subgroup of 8% of study population
Choosing BP medications

- First-line and later line treatments should be:
  - Thiazides
  - CCBs
  - ACEIs
  - ARBs

- Second-line and third-line:
  - Maximize dose of initial medication
  - Addition of second medication of above 4 classes

Choosing BP medications

- Later-line alternatives
  - Beta-blockers
  - Alpha-blockers
  - Alpha1/beta-blockers (carvedilol)
  - Vasodilating beta-blockers (nebivolol)
  - Central alpha2-adrenergic agonists (clonidine)
  - Direct vasodilators (hydralazine)
  - Loop diuretics
  - Aldosterone antagonists
  - Peripherally acting adrenergic antagonists

Treatment strategies

- Start with one of the 4 first-line medications
- Attain goal within 1 month of treatment
- If not at goal, increase dose or add second medication
- Add 3rd medication if needed to reach goal
- Consider specialist consultation, work up for secondary causes if still not at goal
Special considerations

- Pts of African descent should start with thiazide or CCB
- Pts of any ethnicity with CKD should use ACEIs or ARBs initially
- Do not combine ACEIs and ARBs
- Prefer CCB and thiazides in pts >75 with renal dysfunction due to risk of hyperkalemia/further renal impairment

Controversy re: SBP threshold/target for low risk patients

- 2012 Cochrane review finds no benefit of treating health patients with mild hypertension (140-159/90-99)
- Data from 4 RCTs (8912 participants)
- Treated for 4-5 years with antihypertensive medications

Controversy re: SBP threshold/target for low risk patients

- Total mortality: RR 0.85 (0.63-1.15)
- CHD: RR 1.12 (0.8-1.57)
- Stroke: RR 0.51 (0.24 – 1.08)

Controversy re: SBP threshold/target for low risk patients

- Critique of Cochrane review
  - Most patients came from one study of 4 which were included
  - Many of the patients were taking only a beta blocker
  - Total number of events in the studies were low
  - Would need a large study using thiazides, ACEI with placebo would be needed to answer the question
Dissenting Opinions

Evidence Supporting a Systolic Blood Pressure Goal of Less Than 150 mm Hg in Patients Aged 60 Years or Older: The Minority View

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)" demonstrated several major changes from the JNC 7 report (1, 2). The 2014 guideline is based on a systematic review of randomized, controlled trials (RCTs) by a multidisciplinary panel using a process informed by Institute of Medicine recommendations for guideline development (3). Although there was almost unanimous agreement on nearly all recommendations, a minority of the panel (the authors of this commentary) disagreed with the recommendation to increase the target systolic blood pressure (SBP) from 140 to 150 mm Hg in persons aged 60 years or older without diabetes mellitus (DM) or chronic kidney disease (CKD). This target guides both the initiation of therapy and treatment goals. Although this issue has major clinical and public health implications, the evidence and biases associated with expert panel group reviewing similar evidence have recommended a goal of less than 140 mm Hg, particularly in persons aged 80 years or younger (3-5).

**Figure Legend:**


**Impact of JNC 8 Recommendations**

- NHANES data from 2005-2010 (n= 16372)
- Compared proportions meeting targets of JNC 7 and JNC 8
- Adults < 60 eligible for treatment: 20.3% to 19.2%
- Adults ≥ 60 eligible for treatment: 68.9% to 61.2%
- Adults < 60 at goal: 41.2% to 47.5%
- Adults ≥ 60 at goal: 40% to 65.8%

**Impact of JNC 8 recommendations**

- NCDR PINNACLE Registry
- Compared proportion of patients who met the JNC 7 and JNC 8 guidelines
- 1.2 million patients
  - 59.6% achieved JNC 7 goals
  - 74.3% achieved JNC 8 goals
- 14.6% (174k): goals changed
  - 23.2% had had prior stroke or TIA
  - 64.6% had CAD
  - 10 year of MI/CHD death: 8.5% ASCVD risk score: 28%
Impact of JNC 8 Recommendations

- About 15% (13.5 million) patients eligible for initiation or intensification of blood pressure therapy under JNC 7 would not be under JNC 8

Controversy re: SBP threshold/target 150 v 140

- > 50% of pts with hypertension are ≥ 60
- Trend of adequate BP control has been increasing over last 50 years
- Clinicians may interpret that they can be less aggressive with treating hypertension
- Pts ≥ 60 have 10 year CVD risk > 20%, higher than younger pts with diabetes.
- May be reducing benefits of current BP goals

Controversy re: SBP threshold/target 150 v 140

- The SBP achieved by both HYVET and SHEP was closer to 140 than 150
- Trials not showing benefit were underpowered
- FEVER trial showed 27% reduction in all CVD outcomes.
- Strict trial inclusion criteria excluded 98% of available evidence
- Evidence from more recent trials indicating increased benefit with SBP threshold of 140

Results of the INVEST Trial

- Observational subgroup analysis of 6400 of 22576 participants
- Age 50 or greater
- Diabetes and CAD
- Followed for at least 3 years. Extended follow up through National Death Index up to 11 years after recruitment.
- First line treatment with CCB, BB then ACEI, diuretic
- Tight control SBP< 130, usual control < 140, uncontrolled 140 or higher
Results of INVEST Trial

![Graph showing systolic blood pressure and event rate over time for the INVEST Trial.]

Results of the INVEST Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Tight Control</th>
<th>Usual Control</th>
<th>Uncontrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>% Event rate/100 pt-years</td>
<td>% Event rate/100 pt-years</td>
<td>% Event rate/100 pt-years</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>11.0</td>
<td>10.2</td>
<td>15.4</td>
</tr>
<tr>
<td>Total MI</td>
<td>4.8</td>
<td>5.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Total stroke had to take place in the event of death.</td>
<td></td>
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</tbody>
</table>

Results of VALUE Trial

Table.

<table>
<thead>
<tr>
<th>Hazard ratios for events in immediate blood-pressure responders compared with non-immediate responders to initial treatment, and in controlled compared with non-controlled patients, respectively</th>
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<tbody>
<tr>
<td>Immediate responders vs non-immediate responders to initial therapy*</td>
</tr>
<tr>
<td>Combined</td>
</tr>
<tr>
<td>Fatal and non-fatal cardiac events</td>
</tr>
<tr>
<td>Fatal and non-fatal stroke</td>
</tr>
<tr>
<td>All-cause death</td>
</tr>
<tr>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Heart failure hospitalisations</td>
</tr>
</tbody>
</table>

Controlled compared with non-controlled patients

| Fatal and non-fatal cardiac events | 0.75 (0.67-0.83) | 0.76 (0.66-0.88) | 0.73 (0.63-0.85) |
| Fatal and non-fatal stroke | 0.55 (0.46-0.64) | 0.60 (0.48-0.74) | 0.50 (0.39-0.64) |
| All-cause death | 0.79 (0.71-0.88) | 0.79 (0.69-0.91) | 0.79 (0.69-0.92) |
| Myocardial infarction | 0.86 (0.73-1.02) | 0.83 (0.66-1.03) | 0.91 (0.71-1.27) |
| Heart failure hospitalisations | 0.64 (0.55-0.74) | 0.62 (0.50-0.77) | 0.64 (0.52-0.78) |

Results of ACCOMPLISH Trial

![Graph showing event rates for major clinical outcomes in patients in ACCOMPLISH categorized according to their achieved systolic blood pressures.]

Michael A. Weber, George L. Bakris, Allen House, Matthew R. Weir, Tsushung A. Hua, Dion Zappone, Bijan Danks,
Systolic Blood Pressure and Cardiovascular Outcomes During Treatment of Hypertension
The American Journal of Medicine, Volume 126, Issue 6, 2013, 501 - 508
http://dx.doi.org/10.1016/j.amjmed.2013.01.007
### Results of ACCOMPLISH Trial

![Figure 4](image-url)

Figure 4. Event rates (per 1000 patient years) for major clinical outcomes in patients in ACCOMPLISH categorized according to their achieved systolic blood pressures. The P-values for differences between adjacent groups are shown on...Michael A. Weber, George L. Bakris, Allen Hester, Matthew R. Weir, Tsushung A. Hua, Dion Zappe, Bjorn Dahlo...Systolic Blood Pressure and Cardiovascular Outcomes During Treatment of Hypertension

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http://dx.doi.org/10.1016/j.amjmed.2013.01.007

### Comparison of Guidelines

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</thead>
<tbody>
<tr>
<td>Definition of hypertension</td>
<td>≥140/90 and daytime ambulatory BP or home BP ≥135/85</td>
<td>≥140/90</td>
<td>≥140/90</td>
<td>≥140/90</td>
</tr>
<tr>
<td>BP targets</td>
<td>≥160/100 or daytime ambulatory BP ≥150/95</td>
<td>≥140/90</td>
<td>≥140/90</td>
<td>≥140/90</td>
</tr>
<tr>
<td>β-Blockers as first-line drug</td>
<td>No (Step 4)</td>
<td>Yes</td>
<td>No (Step 4)</td>
<td>No (Step 3)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Chlorothalidone, indapamide</td>
<td>Thiazide, chlorothalidone, indapamide</td>
<td>Thiazide, chlorothalidone</td>
<td>Thiazide, chlorothalidone, indapamide</td>
</tr>
<tr>
<td>Diuretic +/– ACEI for patients with diabetes mellitus or chronic kidney disease</td>
<td>Not addressed</td>
<td>Thiazide</td>
<td>Not addressed</td>
<td>Thiazide, chlorothalidone, indapamide</td>
</tr>
</tbody>
</table>

### Recommendations

- **Do not relax in treating hypertension**
- **Increasing evidence that 140/90 may be a better threshold for BP treatment than 150/90 for people over 60.**
- **May be reasonable to use higher threshold with patients over 80.**
- **Lots of flexibility given for clinical judgment.**

### Recommendations

- **JNC 8 does not provide guidance for pts with HF, CAD, or multiple comorbidities**
- **ACC/AHA guidelines**
  - Beta blockers and ACEI for patients with stable HF, LVEFs ≤ 40%
  - Beta blockers, ACEI or ARB for patients with hx of MI/ ACS and reduced EF
  - Avoid non-dihydropyridine CCBs for post-MI pts with reduced EF
  - Diuretics for patients with fluid retention
  - Diuretics +/- ACEI may be helpful for secondary stroke prevention