
Diana Isaacs, PharmD, BCPS, BC-ADM, CDE
Clinical Pharmacy Specialist
Cleveland Clinic

Andrew Straw, PharmD, BC-ADM
Assistant Professor of Pharmacy Practice
Cedarville University
Disclosures

• The presenters do not have anything to disclose
Learning Objectives

• Review the evidence that led to lower blood pressure goals in the 2017 ACC/AHA Hypertension guidelines compared to previous guidelines.

• Describe how the new recommendations affect specific populations including older patients and patients with diabetes.

• Explain medication safety concerns when intensifying therapy to achieve more stringent blood pressure targets.
Patient Case

- 83 year old African American woman
- PMH: HTN, osteoporosis, anxiety, dementia, gout
- Current Meds:
  - sertraline
  - alprazolam
  - alendronate
  - memantine
  - allopurinol
  - lisinopril-stopped due to cough
- Social History:
  - (-) smoking
  - (-) exercise
  - Diet: reduced Na, controlled by assisted living
- Vitals:
  - BP 157/78mmHg, 156/76mmHg on repeat
- Lab values:
  - Scr= 0.90mg/dL, eGFR 65ml/min/1.73m2
  - K+ = 4.5 meq/L, No albuminuria
  - Uric Acid= 7.1
Questions to Think About

• What is this patient’s BP goal?

• What antihypertensive med(s) are best to initiate?

• How should these additional med(s) be monitored?
Pre-Hypertensive Patients Are at Risk

- Meta-analysis of 29 articles including 1,010,858 participants demonstrated “pre-hypertension” is a risk for CVD

![Risk of CVD Event Compared to Normal BP](image)

Blood Pressure through the Ages

## Literature Review: Lower is Better

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Intervention</th>
<th>Achieved SBP</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEVER</td>
<td>9,711 Chinese patients Age 50-79 Mean Age: 61.5</td>
<td>Randomized to felodipine 5mg/day or placebo</td>
<td>Felodipine Mean BP 137.3 mmHg&lt;br&gt;Placebo Mean BP: 142.5 mmHg</td>
<td>Incidence of stroke and CV events reduced in felodipine group by 27% (p=0.001)&lt;br&gt;Subgroup analysis: patients ≥65 44% reduction in all strokes (p&lt;0.0010)</td>
</tr>
<tr>
<td>SPS3</td>
<td>3,020 patients ≥30 Mean Age: 63&lt;br&gt;Recent, symptomatic, MRI-confirmed lacunar stroke</td>
<td>Treatment to SBP target of 130-149mmHg or &lt;130mmHg</td>
<td>Lower Target Mean SBP: 127mmHg&lt;br&gt;Higher Target Mean SBP: 138mmHg</td>
<td>Lower SBP target reduced subsequent strokes by 19% (p = 0.08) and hemorrhagic strokes by nearly 50% (p &lt; 0.01)</td>
</tr>
<tr>
<td>INVEST</td>
<td>8,354 patients ≥60 with a baseline SBP ≥150mmHg Mean Age: 70.7</td>
<td>Randomized to verapamil-SR/trandolapril – OR- atenolol/hctz</td>
<td>SBP &lt;140 (n=4787)&lt;br&gt;SBP 140-149 (n=1747)&lt;br&gt;SBP ≥ 150 (n=1820)</td>
<td>Lower rates primary outcome (all cause death, nonfatal MI, nonfatal stroke) SBP &lt;140 vs. higher SBPs (9.36% vs. 12.71% vs. 21.32%; p&lt;0.0001)</td>
</tr>
</tbody>
</table>

**SPRINT Trial: Intensive vs Standard SBP**

| Inclusion | 9361 patients, age ≥ 50 years (mean age: 67.9 years)  
|           | Risk (1 or more of the following)  
|           | - Presence of clinical or subclinical CVD (not stroke)  
|           | - Chronic Kidney Disease (CKD), defined as eGFR 20 – 59 ml/min/1.73m²  
|           | - Framingham Risk Score for 10-year CVD risk ≥ 15%  
|           |   - Not needed if eligible based on preexisting CVD or CKD  
|           | - Age ≥ 75 years  
|           | - Systolic blood pressure  
|           |   - SBP: 130 – 180 mm Hg on 0 or 1 medication  
|           |   - SBP: 130 – 170 mm Hg on up to 2 medications  
|           |   - SBP: 130 – 160 mm Hg on up to 3 medications  
|           |   - SBP: 130 – 150 mm Hg on up to 4 medications |

| Intervention | Open-label treatment to SBP <120 (intensive group) or <140 (standard group) |

| Endpoints | Primary composite: ACS, stroke, HF, or death from CV causes |

| Excluded patients | Stroke, diabetes, congestive heart failure (symptoms or EF < 35%), proteinuria >1g/d, CKD with eGFR < 20 mL/min/1.73m² (MDRD), adherence flags |
SPRINT Results: Intensive vs Standard SBP

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive Treatment</th>
<th>Standard Treatment</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Intersection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>243/4678 (5.2)</td>
<td>319/4633 (6.8)</td>
<td>0.75 (0.64–0.85)</td>
<td>0.36</td>
</tr>
<tr>
<td>Previous CKD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>135/3348 (4.0)</td>
<td>193/3367 (5.7)</td>
<td>0.70 (0.56–0.87)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>108/1330 (8.1)</td>
<td>126/1318 (9.5)</td>
<td>0.82 (0.63–1.07)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>≤75 yr</td>
<td>142/3351 (4.2)</td>
<td>175/3364 (5.2)</td>
<td>0.80 (0.64–1.00)</td>
<td></td>
</tr>
<tr>
<td>≥75 yr</td>
<td>101/1317 (7.7)</td>
<td>144/1319 (10.9)</td>
<td>0.57 (0.31–0.86)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>Female</td>
<td>77/1664 (4.6)</td>
<td>89/1648 (5.4)</td>
<td>0.84 (0.62–1.14)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>166/2994 (5.5)</td>
<td>230/1035 (7.0)</td>
<td>0.72 (0.59–0.88)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Black</td>
<td>62/1454 (4.3)</td>
<td>85/1493 (5.7)</td>
<td>0.77 (0.55–1.06)</td>
<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td>181/2224 (5.6)</td>
<td>234/2190 (7.3)</td>
<td>0.74 (0.61–0.90)</td>
<td></td>
</tr>
<tr>
<td>Previous cardiovascular disease</td>
<td></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>No</td>
<td>149/3738 (4.0)</td>
<td>208/3754 (5.6)</td>
<td>0.71 (0.57–0.88)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>94/940 (10.0)</td>
<td>111/937 (11.8)</td>
<td>0.83 (0.62–1.03)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
<td>0.77</td>
</tr>
<tr>
<td>≤112 mm Hg</td>
<td>71/1383 (4.5)</td>
<td>98/1353 (6.3)</td>
<td>0.70 (0.51–0.95)</td>
<td></td>
</tr>
<tr>
<td>&gt;112 to ≤145 mm Hg</td>
<td>77/1489 (5.2)</td>
<td>106/1449 (6.8)</td>
<td>0.77 (0.57–1.03)</td>
<td></td>
</tr>
<tr>
<td>≥145 mm Hg</td>
<td>95/1606 (5.9)</td>
<td>115/1381 (7.3)</td>
<td>0.83 (0.63–1.09)</td>
<td></td>
</tr>
</tbody>
</table>

Take Away Points: SPRINT

Results

- Mean SBP 121.5mmHg (intensive) vs. 134.6mmHg (standard) at 3.26 years
- 25% decrease in primary outcomes in lower SBP group
- NNT to prevent one primary outcome event: 61; death any cause: 90
- No difference: serious adverse event, injurious falls, bradycardia, orthostatic hypotension with dizziness
  \[^{1}\] in hypotension, syncope, electrolyte abnormality, AKI/ARF in intensive treatment group (NNH of 71, 91, 100, and 56 respectively)

Limitations

- Exclusion of patients with prior stroke and patients residing in nursing homes or assisted-living facilities
- Early cessation of trial
- Baseline use of statin 43%, aspirin 51%
- Open label
- Difficult to replicate BP monitoring techniques

Practical Application: SPRINT

• Treatment to SBP <140mmHg
  • Only achieved in 50% of population

• Treatment to SBP <120mmHg
  • Required ~1 additional medication
  • Achieved in less than half of strict treatment group
  • More demanding, time-consuming, and costly in practice
SPRINT-Senior

- Pre-specified subgroup for analysis
- Objective: evaluate effects of intensive vs standard SBP in patients ≥ 75yr with HTN but without DM
  - 815 participants (30.9%) were classified as frail and 1456 (55.2%) as less fit
  - Exclusion criteria: dementia, expected survival <3 years, SBP <110mmHg after 1 min standing, unintentional weight loss >10% 6 months prior, nursing home residents
- Outcomes:
  - Primary: composite of MI, ACS not resulting in MI, nonfatal stroke, nonfatal acute decompensated HF, death from CV causes

JAMA. 2016;315(24):2673-82.
Take Away Points: SPRINT-Senior

**Results**
- Mean SBP 123.4mmHg (intensive) vs. 134.8mmHg (standard)
- NNT estimate for the primary outcome was 27 (95% CI, 19-61) and for all-cause mortality it was 41 (95% CI, 27-145) at 3.14 years
- Intensive group required 1 more medication to reach the achieved lower BP

**Safety**
- Intensive treatment group SAEs occurred in 637 participants (48.4%) compared with 637 participants (48.3%) in standard treatment group
- Absolute rate of injurious falls was lower in the intensive treatment group (4.9% vs 5.5% in the standard treatment group; HR, 0.91 [95% CI, 0.65-1.29])

JAMA. 2016;315(24):2673-82.
New BP Classification

<table>
<thead>
<tr>
<th>SBP</th>
<th>DBP</th>
<th>JNC7</th>
<th>2017 ACC/AHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;120</td>
<td>&lt;80</td>
<td>Normal BP</td>
<td>Normal BP</td>
</tr>
<tr>
<td>120–129</td>
<td>&lt;80</td>
<td>Prehypertension</td>
<td>Elevated BP</td>
</tr>
<tr>
<td>130–139</td>
<td>80–89</td>
<td>Prehypertension</td>
<td>Stage 1</td>
</tr>
<tr>
<td>140–159</td>
<td>90–99</td>
<td>Stage 1</td>
<td>Stage 2</td>
</tr>
<tr>
<td>≥160</td>
<td>≥100</td>
<td>Stage 2</td>
<td>Stage 2</td>
</tr>
</tbody>
</table>

### BP Threshold for Drug Therapy

**Correlation (COR)** | **Level of Evidence (LOE)** | **Recommendations for BP Treatment Threshold and Use of Risk Estimation to Guide Drug Treatment of HTN**
--- | --- | ---
**I** | **SBP: A**<br>**DBP: C-EO** | • Secondary prevention (ASCVD): ≥130/80 mm Hg<br>• High Risk Primary Prevention (estimated 10-year ASCVD risk ≥10%): ≥130/80 mm Hg

**I** | **C-LD** | • Primary prevention and estimated 10-year ASCVD risk <10%: ≥140/90 mm Hg

## Comparison of BP Thresholds for Drug Therapy

<table>
<thead>
<tr>
<th>Clinical Condition(s)</th>
<th>JNC 7</th>
<th>JNC 8</th>
<th>2017ACC/AHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical CVD or 10-yr ASCVD risk ≥10%</td>
<td>≥140/90</td>
<td>≥140/90</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>No clinical CVD and 10-yr ASCVD risk &lt;10%</td>
<td>≥140/90</td>
<td>≥140/90</td>
<td>≥140/90</td>
</tr>
<tr>
<td>Older persons</td>
<td>≥140/90</td>
<td>≥150 (SBP)*</td>
<td>&lt;130 (SBP)†</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>&lt;130/80</td>
<td>≥140/80</td>
<td>&lt;130/80</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>&lt;130/80</td>
<td>≥140/80</td>
<td>&lt;130/80</td>
</tr>
</tbody>
</table>

* ≥60 years of age
† ≥65 years of age; noninstitutionalized, ambulatory, community-living adults

## BP Measurement Considerations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>For diagnosis and management of high BP, proper methods are recommended for accurate measurement and documentation of BP.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| I   | A<sup>S</sup>R | Out-of-office BP measurements recommended to:  
  • Confirm diagnosis of HTN  
  • Titration of BP-lowering medication  
Used in conjunction with telehealth counseling or clinical interventions |

New Guidelines=More Treated Patients

How Might these Guideline Changes Affect Older Patients or Patients with Diabetes?
Did We Forget Something?

2017 ACC/AHA is >400 pages, yet lacks meaningful discussion of potential harms of targeting this BP goal

• Will this goal affect certain populations differently?

• Could this goal lead to a pattern where practitioners leave out consideration of other factors?


The Cost of Stricter Goals

Projection of SPRINT results on all eligible US population would prevent:
• 107,500 deaths
• 46,100 cases of heart failure

This would come at a cost of:
• 56,100 episodes of hypotension
• 34,400 episodes of syncope
• 43,400 serious electrolyte disorders
• 88,700 acute kidney failures per year

Careful consideration of risk vs. benefit ratio is central to applying new guideline changes.

Benefits and Harms of Intensive BP Control in Adults Aged 60 Years and Older

<table>
<thead>
<tr>
<th>Primary Objective</th>
<th>To systematically review the risk and benefits of more versus less intensive BP control in older adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion</td>
<td>Randomized studies of adults with hypertension with a mean age of at least 60 years that directly compared 2 or more blood pressure targets</td>
</tr>
<tr>
<td>Total Studies</td>
<td>Selected 21 randomized, controlled trials comparing BP targets&lt;br&gt;Selected 3 observational studies assessing harms</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Comparing intensive goal with less intensive goal:&lt;br&gt;↑ medication burden&lt;br&gt;↑ hypotension&lt;br&gt;↑ syncope RR 1.52, CI:1.22-2.07&lt;br&gt;No significant evidence of difference in falls, fractures, cognitive, or renal outcomes</td>
</tr>
</tbody>
</table>

Greater Medication Burden

<table>
<thead>
<tr>
<th>Trial</th>
<th>Avg Meds Intensive</th>
<th>Avg Meds Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>3.5</td>
<td>2.2</td>
</tr>
<tr>
<td>SPRINT</td>
<td>2.8</td>
<td>1.8</td>
</tr>
<tr>
<td>SPS3</td>
<td>2.4</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Medication burden could be significant given propensity to cause drug interactions, additional cost, and adherence issues.

Hypotension

One of the most commonly cited reasons for trial withdrawal (along with cough) across 10 trials

Other meta-analyses found those in the intensive regimen were three times more likely to experience severe hypotension (0.3% vs 0.1%)

- This was also the only adverse event to be statistically different than the conventional regimen group

**SPRINT- Senior**

<table>
<thead>
<tr>
<th>Primary Objective</th>
<th>To evaluate the effectiveness of intensive blood pressure target versus standard blood pressure target</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>Age 75 and older with hypertension</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
<td>Diabetes, diagnosis or treatment of dementia, expected survival &lt; 3 years, SBP &lt;110mmHg after 1 min of standing, nursing home resident</td>
</tr>
<tr>
<td><strong>Selected Safety Outcomes</strong></td>
<td>No significant difference in serious adverse events. No significant difference in syncope, bradycardia, or injurious fall</td>
</tr>
<tr>
<td></td>
<td>• Hypotension, HR 1.67 (&lt;0.001), NNH = 100</td>
</tr>
<tr>
<td></td>
<td>• Electrolyte abnormality, HR 1.35 (0.02), NNH = 125</td>
</tr>
<tr>
<td></td>
<td>• Acute kidney injury or acute renal failure, HR 1.66 (&lt;0.001), NNH = 56</td>
</tr>
</tbody>
</table>

Take-Aways

Significant differences tend to occur only in medication burden, hypotension, and syncope

Lower blood pressure goals were not associated with decreased quality of life, dementia, fractures, or falls

Little to no data to apply intensive blood pressure goal to nursing home residents or those with dementia
Back to the Patient Case

• 83 year old African American woman
• PMH: HTN, osteoporosis, anxiety, dementia, gout
• Current Meds:
  • sertraline
  • alprazolam
  • alendronate
  • memantine
  • allopurinol
  • lisinopril-stopped due to cough
• Social History:
  • (-) smoking
  • (-) exercise
  • Diet: reduced Na, controlled by assisted living
• Vitals:
  • BP 157/78mmHg, 156/76mmHg on repeat
• Lab values:
  • Scr= 0.90mg/dL, eGFR 65ml/min/1.73m2
  • K+=4.5 meq/L, No albuminuria
  • Uric Acid=7.1

What is the Optimal BP Goal for this Patient?
Treating HTN in Patients with Diabetes

• Diabetes patients were excluded from SPRINT trials

• ACCORD-BP trial
  • Rate of serious adverse events was 2.5 times higher in intensive treatment group compared with the control group
  • Absolute rate of these events was low (0.7% per year vs 1.87% per year)

• A “J-Curve” effect has been proposed
**SPRINT-Eligible Participants of ACCORD-BP**

<table>
<thead>
<tr>
<th>Primary Objective</th>
<th>To determine the effect of intensive blood pressure control on cardiovascular outcomes in participants with type 2 diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion</strong></td>
<td>Standard glucose arm of ACCORD-BP CVD risk factors required for SPRINT eligibility</td>
</tr>
<tr>
<td><strong>Exclusion</strong></td>
<td>ACCORD-BP intensive glucose arm</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>↓ risk of composite CVD death, nonfatal MI, nonfatal stroke, heart failure by 21%, HR 0.79; CI 0.65-0.96</td>
</tr>
<tr>
<td></td>
<td>↑ risk of serious adverse events, 4.1% vs 2.1% (0.003)</td>
</tr>
<tr>
<td></td>
<td>Authors suggest that intensive BP goal may only be beneficial for those with additional CVD risk (SPRINT eligible)</td>
</tr>
</tbody>
</table>

Potential “J Curve” Effect

• Meta-analysis of studies focused on blood pressure lowering in those with diabetes:
  • Confirmed cardiovascular benefit of anti-hypertensive therapy when baseline systolic BP is >140mmHg
  • Identified patterns of harm of anti-hypertensive treatment when systolic pressure is already <140mmHg

• Proposed explanation is “J-curve” effect
  • Intensive treatment may impair blood flow to end organs leading to ischemia
  • Arterial stiffening seen in diabetes may cause perfusion to be more dependent on SBP

### Stratified by Baseline Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All cause mortality</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 150 mm Hg</td>
<td>0.89 (0.80 to 0.99)</td>
</tr>
<tr>
<td>140-150 mm Hg</td>
<td>0.87 (0.78 to 0.98)</td>
</tr>
<tr>
<td>&lt; 140 mm Hg</td>
<td>1.05 (0.95 to 1.16)</td>
</tr>
<tr>
<td>Test for interaction: P = 0.019</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 150 mm Hg</td>
<td>0.75 (0.57 to 0.99)</td>
</tr>
<tr>
<td>140-150 mm Hg</td>
<td>0.87 (0.71 to 1.05)</td>
</tr>
<tr>
<td>&lt; 140 mm Hg</td>
<td>1.15 (1.00 to 1.32)</td>
</tr>
<tr>
<td>Test for interaction: P = 0.002</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 150 mm Hg</td>
<td>0.74 (0.63 to 0.87)</td>
</tr>
<tr>
<td>140-150 mm Hg</td>
<td>0.84 (0.76 to 0.93)</td>
</tr>
<tr>
<td>&lt; 140 mm Hg</td>
<td>1.00 (0.87 to 1.15)</td>
</tr>
<tr>
<td>Test for interaction: P = 0.017</td>
<td></td>
</tr>
</tbody>
</table>

### Stratified by Attained Systolic Blood Pressure

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All cause mortality</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 140 mm Hg</td>
<td>0.96 (0.86 to 1.06)</td>
</tr>
<tr>
<td>130-140 mm Hg</td>
<td>0.86 (0.79 to 0.93)</td>
</tr>
<tr>
<td>&lt; 130 mm Hg</td>
<td>1.10 (0.91 to 1.33)</td>
</tr>
<tr>
<td>Test for interaction: P = 0.009</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular mortality</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 140 mm Hg</td>
<td>0.87 (0.71 to 1.07)</td>
</tr>
<tr>
<td>130-140 mm Hg</td>
<td>0.86 (0.72 to 1.04)</td>
</tr>
<tr>
<td>&lt; 130 mm Hg</td>
<td>1.26 (0.89 to 1.77)</td>
</tr>
<tr>
<td>Test for interaction: P = 0.010</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td></td>
</tr>
<tr>
<td>&gt; 140 mm Hg</td>
<td>0.82 (0.72 to 0.92)</td>
</tr>
<tr>
<td>130-140 mm Hg</td>
<td>0.88 (0.79 to 0.97)</td>
</tr>
<tr>
<td>&lt; 130 mm Hg</td>
<td>0.94 (0.76 to 1.15)</td>
</tr>
<tr>
<td>Test for interaction: P = 0.476</td>
<td></td>
</tr>
</tbody>
</table>

## BP Goals Guideline Comparison

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>JNC 7</th>
<th>JNC 8</th>
<th>2017 ACC/AHA</th>
<th>2018 ADA</th>
<th>2012 KDIGO</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>&lt;140/90</td>
<td>&lt;140/90</td>
<td>&lt;130/80*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older Patients</td>
<td>&lt;140/90</td>
<td>&lt;150/90†</td>
<td>&lt;130/80‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>&lt;130/80</td>
<td>&lt;140/90</td>
<td>&lt;130/80</td>
<td>&lt;140/90;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;130/80</td>
<td></td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>&lt;130/80</td>
<td>&lt;140/90</td>
<td>&lt;130/80</td>
<td></td>
<td>&lt;140/90§ or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;130/80</td>
</tr>
</tbody>
</table>

Take-Aways

Patients with diabetes and additional CVD risk factors may benefit from a more intensive goal

Adverse events occurred at a higher rate among patients with diabetes treated to a goal of <130, but at a low absolute risk
Intensifying Medication Therapy & Medication Safety
Hypertension Medication Options

**Primary Agents**
- Thiazide or thiazide-type diuretic
- ACE inhibitor
- Angiotensin receptor blocker (ARB)
- Calcium channel blocker (CCB)
  - Dihydropyridine
  - Nondihydropyridine

**Secondary Agents**
- Loop diuretic
- Potassium sparing diuretic
- Aldosterone antagonist
- Beta blocker
- Direct renin inhibitor
- Alpha-1 blocker
- Centrally acting
- Direct vasodilator
Medication Selection

• First line agents
  • Thiazide diuretic, ACE inhibitor or ARB, CCB
• Avoid combination of ACE inhibitor, ARB, and/or renin inhibitor
• Patient considerations
  • Age, concurrent medications, adherence, drug interactions, out-of-pocket costs, comorbidities
  • Shared decision making with the patient
• Many patients started on a single agent will subsequently require ≥2 drugs from different pharmacological classes to reach BP goals
  • Choose agents with complementary actions
  • Avoid 2 medications from the same drug class

## Compelling Indications

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>1st Line Agent(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Thiazide, CCB, ACE-I or ARB</td>
</tr>
<tr>
<td>Diabetes with albuminurea</td>
<td>ACEI-I or ARB</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>ACEI-I or ARB</td>
</tr>
<tr>
<td>Heart failure with reduced EF</td>
<td>Beta-blocker, ACE-I or ARB, aldosterone antagonist</td>
</tr>
<tr>
<td>Heart failure with preserved EF</td>
<td>Beta-blocker, ACE-I or ARB</td>
</tr>
<tr>
<td>Stable ischemic heart disease</td>
<td>Beta-blocker, ACE-I or ARB, CCB (if angina)</td>
</tr>
<tr>
<td>Secondary stroke prevention</td>
<td>Thiazide, ACE-I or ARB</td>
</tr>
</tbody>
</table>

### Thiazide – Dosing in HTN

<table>
<thead>
<tr>
<th>Thiazide Diuretic</th>
<th>Usual Hypertension Dose Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrochlorothiazide (HCTZ)</td>
<td>25-50mg daily</td>
</tr>
<tr>
<td>Chlorthalidone</td>
<td>12.5 – 25 mg daily</td>
</tr>
<tr>
<td>Indapamide</td>
<td>1.25 – 2.5 mg daily</td>
</tr>
<tr>
<td>Metolazone</td>
<td>2.5 – 10 mg daily</td>
</tr>
</tbody>
</table>

- Chlorthalidone preferred over HCTZ

Thiazide—Adverse Effects

• Electrolyte abnormalities (hyponatremia, hypokalemia, hypomagnesemia)
• Muscle cramps/weakness
• Increased uric acid
• Increased calcium
• Slight Increase in LDL and TG
• Increased glucose
• Increased urination

Thiazide – Clinical Pearls

• Dose in the morning to avoid nocturnal diuresis
• Generally not effective when CrCL<30
  • *Loop diuretics are preferred*
• Diuresis decreases over time (not BP effect)
• Benefits in patients with osteoporosis
• Use caution in patients with gout
• Recommend to keep potassium between 4-5 meq/L
# ACE-Inhibitor – Dosing in HTN

<table>
<thead>
<tr>
<th>ACE Inhibitor Agent</th>
<th>Usual Dose Range (mg/day)</th>
<th>Daily Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>12.5-150</td>
<td>2-3</td>
</tr>
<tr>
<td>Enalapril</td>
<td>5-40</td>
<td>1-2</td>
</tr>
<tr>
<td>Quinapril</td>
<td>10-80</td>
<td>1-2</td>
</tr>
<tr>
<td>Perindopril</td>
<td>4-16</td>
<td>1</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>10-40</td>
<td>1</td>
</tr>
<tr>
<td>Benazepril</td>
<td>10-40</td>
<td>1-2</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>10-40</td>
<td>1</td>
</tr>
<tr>
<td>Moexepril</td>
<td>7.5-30</td>
<td>1-2</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5-10</td>
<td>1-2</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>1-4</td>
<td>1</td>
</tr>
</tbody>
</table>

ACE Inhibitor – Adverse Effects

• Dry cough
• Hyperkalemia
• Angioedema
• Bump in SCr
  • Up to 30% is acceptable
• Orthostatic hypotension (initial dose)
• Skin rash (captopril)
• Avoid use:
  • Pregnancy
  • Bilateral renal artery stenosis
  • Patients on ARB or direct renin inhibitor

ACE Inhibitor – Clinical Pearls

- First line in CAD, MI, heart failure, CKD, DM with albuminurea
- Consider stopping if Scr increases >30% from baseline
- Use caution in combination with NSAIDs
- Consider ↓ initial dose by 50% in patients on a diuretic, volume depleted, or very elderly
- Potential adverse effects often not dose dependent except hyperkalemia
- Less effective in certain groups of patients

<table>
<thead>
<tr>
<th>ARB Agent</th>
<th>Usual HTN Dose Range (mg/day)</th>
<th>Daily Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>8-32</td>
<td>1</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>600-800</td>
<td>1-2</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>150-300</td>
<td>1</td>
</tr>
<tr>
<td>Losartan</td>
<td>50-100</td>
<td>1-2</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>20-40</td>
<td>1</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>20-80</td>
<td>1</td>
</tr>
<tr>
<td>Valsartan</td>
<td>80-320</td>
<td>1</td>
</tr>
<tr>
<td>Azilsartan</td>
<td>40-80</td>
<td>1</td>
</tr>
</tbody>
</table>

ARB – Clinical Pearls

• Similar CV and renal benefits as ACE inhibitors
• Most adverse effects similar to ACEI except
  • No cough
  • Less angioedema
• Consider ↓ by 50% in pts on a diuretic, are volume depleted, or very elderly
• Patients with a history of angioedema with an ACE inhibitor can receive an ARB beginning 6 weeks after ACE inhibitor is discontinued
• Less effective in certain groups of patients

### Calcium Channel Blockers

<table>
<thead>
<tr>
<th>Non-Dihydropyridine</th>
<th>Usual Dose (mg/day)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diltiazem SR</td>
<td>180-360</td>
<td>2</td>
</tr>
<tr>
<td>Diltiazem ER</td>
<td>120-480</td>
<td>1</td>
</tr>
<tr>
<td>Verapamil IR</td>
<td>40-80</td>
<td>3</td>
</tr>
<tr>
<td>Verapamil SR</td>
<td>180-480</td>
<td>1-2</td>
</tr>
<tr>
<td>Verapamil delayed-onset ER</td>
<td>100-480</td>
<td>1 (evening)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dihydropyridine</th>
<th>Usual Dose (mg/day)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amlodipine</td>
<td>2.5-10</td>
<td>1</td>
</tr>
<tr>
<td>Felodipine</td>
<td>5-20</td>
<td>1</td>
</tr>
<tr>
<td>Isradipine</td>
<td>5-10</td>
<td>2</td>
</tr>
<tr>
<td>Nicardipine SR</td>
<td>5-20</td>
<td>1</td>
</tr>
<tr>
<td>Nifedipine LA</td>
<td>60-120</td>
<td>1</td>
</tr>
<tr>
<td>Nisoldipine</td>
<td>30-90</td>
<td>1</td>
</tr>
</tbody>
</table>

Nondihydropyridine CCB – Clinical Pearls

• Also used to treat atrial fibrillation, atrial flutter, supraventricular arrhythmias
• Verapamil beneficial in migraine prophylaxis
• No electrolyte disturbances expected
• Multiple formulations that are NOT interchangeable or equipotent due to different release mechanisms and bioavailability
• Adverse effects
  • Bradycardia, heart block, constipation (verapamil), dizziness
• Numerous drug interactions with verapamil (CYP-450 3A4 substrate) and diltiazem (CYP-450 3A4 inhibitor)
• Avoid use:
  • Heart failure, second or third degree heart block, in combination with $\beta$-blockers for HTN
Dihydropyridine CCB – Clinical Pearls

• More potent peripheral vasodilators, minimal effect on cardiac tissue

• Vasodilatory side effects
  • Reflex tachycardia, peripheral edema, headache, dizziness

• Also used to treat angina and Raynaud’s syndrome

• Can be used in combination with β-blockers or in patients with heart block (unlike non-dihydropyridines)

• No electrolyte disturbances expected

β-Blocker Types

- Cardioselective
  - Bisoprolol
  - Metoprolol tartrate
  - Metoprolol succinate

- Cardioselective and vasodilatory
  - Nebivolol

- Combined alpha and beta activity
  - Carvedilol
  - Carvedilol phosphate
  - Labetolol

- Non cardioselective
  - Propranolol IR
  - Propranolol LA
  - Nadolol

- Intrinsic sympathomimetic activity (ISA)
  - Acebutolol
  - Carteolol
  - Penbutolol
  - Pindolol

**β-Blocker-Medication Selection**

- **Cardioselective**
  - Preferred in COPD/asthma
  - Preferred in HF with reduced EF

- **Cardioselective and vasodilatory**
  - Nebivolol induces nitric oxide–induced vasodilation

- **Combined alpha and beta activity**
  - Carvedilol preferred in patients with HF or IHD
  - Increased BP lower effects

- **Non cardioselective**
  - Avoid use in COPD/asthma

- **Intrinsic sympathomimetic activity (ISA)**
  - Avoid in patients with heart failure or IHD

---

IHD: ischemic heart disease
HF: heart failure
COPD: chronic obstructive pulmonary disease

β-Blocker – Clinical Pearls/Adverse Effects

• Potential adverse effects
  • Bradycardia, bronchospasm
  • Fatigue, exercise intolerance
  • CNS (dizziness, drowsiness, vivid dreams, depression)
  • Impotence/sexual dysfunction
  • Lipids: Increase TG, decrease HDL

• Mask symptoms of hypoglycemia

• Do not abruptly stop

• Avoid use:
  • Sinoatrial or atrioventricular node dysfunction, decompensated HF, severe bronchospastic disease

• Less effective for certain patient populations

Loop Diuretic

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual Daily Dose Range (mg/day)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bumetanide (Bumex®)</td>
<td>0.5-4</td>
<td>2</td>
</tr>
<tr>
<td>Furosemide (Lasix®)</td>
<td>20-80</td>
<td>2</td>
</tr>
<tr>
<td>Torsemide (Demadex®)</td>
<td>5-10</td>
<td>1</td>
</tr>
</tbody>
</table>

- Dose in the morning and late afternoon
  - Avoid evening dosing
- Preferred instead of thiazides when CrCl <30mL/min and symptomatic heart failure
- Electrolyte disturbances
  - Decreased potassium, sodium, magnesium, calcium
- Monitor chem7, weight

Potassium Sparing Diuretic

• Amiloride, Triamterene, Triamterene/HCTZ, Amiloride/HCTZ

• Dosing
  • Amiloride, 5-10mg/day
  • Triamterene, 50-100mg/day

• Weak diuretics generally used in combo with thiazides to minimize hypokalemia

• Avoid in patients with eGFR<45

• Does not significantly lower BP alone

• Monitor K+ closely

Aldosterone Antagonist

• Medications
  • Eplerenone 50-100mg/day divided 1-2 times daily
  • Spironolactone 25-100mg/day divided 1-2 times daily

• Preferred in primary aldosteronism and resistant hypertension

• Adverse effects
  • Hyperkalemia
  • Gynecomastia (spironolactone > eplerenone)
  • Impotence (spironolactone > eplerenone)

• Contraindications/Precautions
  • CrCL<50ml/min eplerenone
  • CrCL<30ml/min spironolactone

• Monitor K+, Scr

Direct Renin Inhibitor (Aliskiren)

• Dosing
  • 150mg starting dose; up to 300mg daily

• Take consistently with regard to meals; high fat meals decrease absorption

• Similar adverse effect profile to ACEI and ARB
  • Angioedema, Increased SCr, hyperkalemia
  • Cough (unclear if there are effects on bradykinin)
  • Avoid in pregnancy and bilateral renal artery stenosis

• Lacks outcome data compared to ACEI and ARB

• Monitoring: similar to ACEI and ARB
\( \alpha_1 \)-blocker

- Symptomatic benefit in BPH

- Adverse effects
  - Orthostatic hypotension
  - First dose syncope
  - Take at bedtime
  - Sexual dysfunction relatively common
  - Dizziness

- ALLHAT trial
  - 25% relative increase in heart failure incidence
  - Two-fold increase in hospitalizations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual Dose Range (mg/day)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxazosin</td>
<td>1-8</td>
<td>1</td>
</tr>
<tr>
<td>Prazosin</td>
<td>2-20</td>
<td>2-3</td>
</tr>
<tr>
<td>Terazosin</td>
<td>1-20</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Direct Vasodilator

<table>
<thead>
<tr>
<th>Agent</th>
<th>Usual Dose Range (mg/day)</th>
<th>Daily Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minoxidil</td>
<td>5-40</td>
<td>1-2</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>20-200</td>
<td>2-3</td>
</tr>
</tbody>
</table>

- Most commonly used for resistant HTN in patients with severe CKD

- **Adverse effects:**
  - Reflex tachycardia
  - Headache
  - Fluid retention
  - Drug-induced lupus-like syndrome (hydralazine)
  - Hirsutism (minoxidil)
  - Pericardial effusion (minoxidil)

- Use in combination with a diuretic to diminish fluid retention and with a beta-blocker to reduce reflex tachycardia

Webber et al. ASHI/ISH Hypertension Guideline
Central $\alpha_2$-Agonist

• Agents: clonidine, guanfacine, guanabenz, methyldopa

• Most commonly used for resistant HTN

• Adverse effects: (Anticholinergic)
  • Sedation
  • Dry mouth
  • Orthostatic hypotension
  • Constipation
  • Urinary retention
  • Blurred vision
  • Depression (high doses)

• Better to avoid in the elderly
  • More side effects, fall risk

• Taper clonidine to avoid rebound hypertension/hypertensive crisis

Combining Antihypertensive Agents

• Initiate with 2 agents if SBP >20 or DBP>10 above goal
  • Use caution in elderly

• Better BP reduction by combining 2 or more agents versus doubling dose of 1 agent

• Better BP reduction when 1 agent is a diuretic

• Best combos: combining 1st line agents: thiazide + CCB + ACEI or ARB

• The more agents used, the more potential for adverse effects

• Aldosterone antagonist good option for resistant HTN (monitor K+)

• Vasodilators must be used with beta blocker + diuretic

Avoid Certain Combinations

• Avoid 2 drugs from the same class

• Avoid loop + thiazide
  • However, K+ sparing diuretic can be used with other diuretics (Ex. HCTZ/Triamterene)

• Other combinations to avoid for HTN
  • ACE+ARB, ACE or ARB +direct renin inhibitor
  • BB + non-dihydropyridine CCB
Back to the Patient Case

- 83 year old African American woman
- PMH: HTN, osteoporosis, anxiety, dementia, gout
- Current Meds:
  - sertraline
  - alprazolam
  - alendronate
  - memantine
  - allopurinol
  - lisinopril-stopped due to cough

- Social History:
  - (-) smoking
  - (-) exercise
  - Diet: reduced Na, controlled by assisted living

- Vitals:
  - BP 157/78mmHg, 156/76mmHg on repeat

- Lab values:
  - Scr= 0.90mg/dL, eGFR 65ml/min/1.73m2
  - K+=4.5 meq/L, No albuminuria
  - Uric Acid=7.1

What antihypertensive med(s) are best to initiate? How should these additional med(s) be monitored?
In Summary

• Recent clinical trial evidence suggests a BP target of <130/80mmHg is preferred for most patients.

• This more stringent goal may not be appropriate for ALL patients; clinical judgment is necessary especially for older patients and patients with diabetes.

• Several safety concerns when adding multiple medications for HTN including drug interactions, side effects, adherence and polypharmacy.