Hypertension Update
Clinical Controversies Regarding Age and Race

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I, Allison Helmer, have no actual or potential conflict of interest in relation to this program.
OBJECTIVES

- Differentiate hypertension treatment recommendations based on patient specific factors such as age and race
- Evaluate the hypertension literature to understand the rationale for these recommendations
- Recommend hypertension therapy for elderly and African American patients
ABBREVIATIONS

ACEI: Angiotensin converting enzyme inhibitor
ARB: Angiotensin receptor blocker
JNC8: 8th Joint National Committee
ASH/ISH: American Society of Hypertension/International Society of Hypertension
ESH/ESC: European Society of Hypertension/European Society of Cardiology
CHEP: Canadian Hypertension Education Program
CCB: Calcium channel blocker
BB: Beta-blocker
ACP: American College of Physicians
SBP: Systolic blood pressure
HF: Heart failure
CVD: Cardiovascular disease
CHD: Coronary heart disease
RCT: Randomized controlled trial
MI: Myocardial Infarction
ACS: Acute coronary syndrome
ISHIB: International Society of Hypertension in Blacks
HTN: Hypertension
HCTZ: Hydrochlorothiazide
Which of the following statements is correct regarding hypertension guideline recommendations?

A. All hypertension guidelines agree on increasing the blood pressure goal in elderly patients

B. JNC8 guidelines recommend a blood pressure goal of <150/90 in all patients greater than 80 years of age

C. ASH/ISH guidelines recommend a blood pressure goal of <150/90 in all patients greater than 80 years of age

D. All hypertension guidelines agree that ACEI/ARB are contraindicated in black patients
## Reviewing the Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>General Population</th>
<th>Elderly</th>
<th>Black</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>JNC8 2014</strong></td>
<td>&lt;140/90</td>
<td>&gt;60 years: &lt;150/90</td>
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Elderly Patients

When should we raise the BP goal?
# ACP Guidelines 2017

**HTN Treatment in Adults ≥ 60 Years**

<table>
<thead>
<tr>
<th>Adults ≥ 60 years</th>
<th>SBP goal &lt; 150 mmHg to reduce mortality, stroke, and cardiac events</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of stroke</td>
<td>Consider SBP goal &lt; 140 mmHg to reduce recurrent stroke</td>
</tr>
<tr>
<td>High CV risk</td>
<td>Consider SBP goal &lt; 140 mmHg to reduce stroke or cardiac events</td>
</tr>
</tbody>
</table>

JNC8 RECOMMENDATIONS

General population ≥ 60 years

- Blood pressure target < 150/90 mmHg reduces stroke, HF, CHD

SBP < 140 mmHg not recommended

- No additional benefit vs. higher goal
- 2 underpowered Japanese studies – JATOS, VALISH

## JNC 8 Evidence for Elderly BP Target

<table>
<thead>
<tr>
<th>Trial</th>
<th>Age</th>
<th>Intervention</th>
<th>Primary Endpoint Result</th>
<th>Mean SBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYVET 2008</td>
<td>≥ 80 years</td>
<td>Indapamide vs. placebo</td>
<td>Indapamide reduces fatal stroke</td>
<td>2 years: 144 vs. 159</td>
</tr>
<tr>
<td>Syst-Eur 1997</td>
<td>≥ 60 years</td>
<td>Nitrendipine vs. placebo</td>
<td>Nitrendipine reduces fatal and nonfatal stroke</td>
<td>2 years: 150 vs. 160</td>
</tr>
<tr>
<td>SHEP 1991</td>
<td>≥ 60 years</td>
<td>Chlorthalidone vs. placebo</td>
<td>Chlorthalidone reduces fatal and nonfatal stroke</td>
<td>5 years: 143 vs. 155</td>
</tr>
</tbody>
</table>

5 of 17 panel members disagreed with BP recommendation in elderly.

Concern for reducing intensity of antihypertensive therapy in high risk population.

Concern that higher BP goal may reverse progress made in reducing CVD, particularly stroke mortality.

Evidence inconsistent and insufficient to warrant the change.

Observational studies and RCT data not included → support SBP goal of <140 mmHg, especially in high risk population.

Support SBP < 150 mmHg in frail patients > 80 years old.

Similar to European guideline recommendations.

No longer support increasing BP goal in elderly patients

“Evidence suggest[s] that older individuals with hypertension benefit from BP reduction irrespective of baseline frailty.”

Post-hoc analysis of HYVET

Pre-specified subgroup of SPRINT

Recommend caution in those with orthostasis
HYVET

- 3845 hypertensive patients > 80 years old and SBP > 160 mmHg
- Europe, China, Australasia, Tunisia
- Indapamide SR 1.5 mg or placebo
  - Perindopril 2-4 mg or placebo added if necessary to achieve SBP < 150 mmHg
- Primary endpoint: fatal or nonfatal stroke

NEJM 2008;358(8):1887-1898.
HYVET Results

- Median follow-up: 1.8 years
- Primary endpoint (fatal or nonfatal stroke)
  - Lower but not significantly reduced with indapamide (12.4% vs. 17.7%)
  - **Fatal stroke was significantly reduced (p=0.046)**
- Seated blood pressure after 2 years
  - 143.5/77.9 mmHg indapamide
  - 158.5/84 mmHg placebo

NEJM 2008;358(8):1887-1898.
HYVET
POST-HOC ANALYSIS

- Frailty index (FI) calculated for 69% of patients in study
- After adjustment for FI, sex, and age, BP treatment significantly reduced the risk of fatal and nonfatal stroke (p=0.03)
- No interaction between baseline FI and BP treatment on risk of stroke, death from any cause, or CV events
- Evidence used to remove age qualifier for BP goal in Canadian guidelines
SPRINT

- 9361 patients with SBP > 130 mmHg, high CV risk, no diabetes
- Intervention
  - SBP < 120 mmHg vs. SBP < 140 mmHg
- Primary outcome
  - MI, other ACS, stroke, heart failure, CV death

NEJM 2015;373(22):2103-2116
SPRINT RESULTS

- Stopped early, mean follow-up: 3.26 years
- Intensive treatment significantly reduced primary endpoint (5.5% vs. 6.5%, p < 0.001)
- Mean SBP achieved
  - 121.5 mmHg vs. 134.6 mmHg
- Mean number of medications: 2.8 vs. 1.8
- Subgroup analysis
  - Potentially better results in those > 75 years, mean 79.9 years

NEJM 2015;373(22):2103-2116
SPRINT
ELDERLY SUBGROUP

- Primary outcome:
  - MI, other ACS, stroke, heart failure, CV death
  - 7.74% (intensive) vs. 11.2% (standard), p=0.001
  - Significant reduction in HF and all-cause mortality

- Nonsignificant increases in hypotension, syncope, electrolyte abnormalities, AKI/renal failure in intensive group

JAMA 2016;315(24):2673-2682
Stratified results by baseline frailty – higher events with increasing frailty, lower rates overall in intensive group

<table>
<thead>
<tr>
<th>Frailty Status</th>
<th>Intensive</th>
<th>Standard</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fit</td>
<td>4/159</td>
<td>10/190</td>
<td>p=0.20</td>
</tr>
<tr>
<td>Less Fit</td>
<td>48/711</td>
<td>77/745</td>
<td>p=0.01</td>
</tr>
<tr>
<td>Frail</td>
<td>50/440</td>
<td>61/375</td>
<td>p=0.06</td>
</tr>
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2017 Systematic Review and Meta-Analysis

Risk vs. benefit of intensive BP control in adults ≥ 60 years

21 RCTs comparing BP targets or intensity of treatment

3 observational studies assessing safety

2017 Systematic Review and Meta-Analysis - Results

- High-strength evidence from 9 trials $\rightarrow$ BP $<$ 150/90 mmHg reduces mortality, cardiac events and stroke
- Low-to moderate-strength evidence from 6 trials
  - BP $\leq$ 140/85 mmHg
    - Reduces cardiac events and stroke
    - Nonsignificantly reduces mortality
  - Results largely weighted by SPRINT
- No increase in falls or cognitive impairment

2016 Systematic Review and Meta-Analysis

- **Purpose:** evaluate safety and efficacy of intensive BP lowering in high risk patients
- 19 RCTs comparing BP targets or intensity of treatment
- Intensive lowering (mean BP 133/76 mmHg vs. 140/81 mmHg in less intensive groups)
  - Reduces major CV events, MI, stroke, albuminuria, retinopathy progression
  - Minimal difference in serious adverse events
- Sub-group of 7 trials with mean age ≥ 62 years → significant reduction in major CV events

* Lancet 2016; 387: 435-43
How should we treat elderly patients in clinical practice?
Conflicting guideline recommendations
- Many agree to raise BP target in elderly
- Age to increase target and impact of frailty unclear
- Treating intensively may not increase adverse events and may reduce incidence of stroke and possibly other cardiovascular events
- Reasonable to consider lower goal (<140/90mmHg) in high risk patients
Rose is a 77 year old white female with a PMH of hypertension as well as a stroke last year. Current medications include: atorvastatin 80 mg daily, lisinopril 20 mg daily, and aspirin 81 mg daily.

Vitals:
BP 148/84 mmHg (last visit 146/84 mmHg)
HR 82 bpm
Recent labs are stable and within normal limits
What would you recommend for Rose today?

A. **Continue current therapy.** Evidence is clear that SBP should not be lowered below 140 mmHg in the elderly

B. **Continue current therapy.** The SPRINT subgroup analysis showed that frail elderly patients had higher CV risk if treated intensively

C. **Continue current therapy based on JNC8 recommendations for BP goal < 150/90 mmHg**

D. **Increase lisinopril to 40 mg daily based on ACP recommendations and results of meta-analyses**
Black Patients
Should ACEI and ARBs be avoided?
James is a 51 year old black male with no past medical history. He presents to your internal medicine clinic after having an elevated blood pressure at a recent health fair (BP 148/92 mmHg).

Vitals in clinic: BP 146/92 mmHg    HR 88 bpm
All labs are within normal limits
What is the best option to treat this patient’s hypertension?

A. Lisinopril 10 mg daily
B. Amlodipine 5 mg daily
C. Metoprolol succinate 12.5 mg BID
D. Hydrochlorothiazide 50 mg daily
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<td></td>
<td></td>
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HYPERTENSION IN BLACK PATIENTS

- Higher prevalence of hypertension
- Higher prevalence of severe hypertension
- Difficult to control
- Many comorbid conditions

High risk of blood pressure-related CV and renal outcomes

Hypertension 2010;56:780-800
RAAS System in Black Patients

- Historically thought to be less active in blacks vs. whites
- Most blacks do not have fully suppressed renin levels
- Sodium sensitivity more predictive of BP response to RAAS blockers
  - Sodium intake in salt-sensitive people → angiotensin II production → elevated BP
  - Present in >50% of black and white hypertensive patients
  - More common in blacks vs. whites

Hypertension 2010;56:780-800
Effectiveness of ACEI and ARB in Black Patients

Blood Pressure Lowering and Cardiovascular Outcomes
Review of ACEI in Blacks vs. Whites

**Purpose:** Identify similarities in BP response between blacks and whites

Significant overlap in BP responses to ACEI in blacks and whites

> 80% of patients had similar changes in BP after treatment with ACEI

Hypertension 2010;56:780-800; Hypertension 2004;43:566-572
Purpose: Determine difference in BP response to quinapril in blacks vs. whites

BP 4.7/2.4 mmHg higher in blacks
BP 2.3/1.9 mmHg higher after adjustments

Numerous confounders: age, gender, body size, pretreatment blood pressure

**Bottom line:** race may not be best predictor of BP response to ACEI

Hypertension 2010;56:780-800; Hypertension 2004;43:1202-1207
# ARB vs. Combination Therapy in Blacks

<table>
<thead>
<tr>
<th>Mean Baseline BP</th>
<th>Interventions</th>
<th>Duration</th>
<th>BP Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>150/100 mmHg</td>
<td>Losartan</td>
<td>12 weeks</td>
<td>-6.4/-6.6 mmHg</td>
</tr>
<tr>
<td></td>
<td>Losartan + HCTZ</td>
<td></td>
<td>-16.8/-10.8 mmHg</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>-2.2/-3.9 mmHg</td>
</tr>
<tr>
<td>170/98 mmHg</td>
<td>Amlodipine</td>
<td>8 weeks</td>
<td>-26.6/-11.2 mmHg</td>
</tr>
<tr>
<td></td>
<td>Amlodipine + Valsartan</td>
<td></td>
<td>-33.3/-14 mmHg</td>
</tr>
<tr>
<td>155/101 mmHg</td>
<td>Telmisartan</td>
<td>8 weeks</td>
<td>-7.8/-8.7 mmHg</td>
</tr>
<tr>
<td></td>
<td>HCTZ</td>
<td></td>
<td>-9.2/-8.2 mmHg</td>
</tr>
<tr>
<td></td>
<td>Telmisartan + HCTZ</td>
<td></td>
<td>-21.5/-13.3 mmHg</td>
</tr>
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ALLHAT

33,357 patients, ≥ 55 years, HTN plus 1 additional risk factor for CHD

Chlorthalidone vs. amlodipine vs. lisinopril

Primary outcome: combined fatal CHD or non-fatal MI

32% black patients

JAMA. 2002;288:2981-2997
SUB-GROUP ANALYSES OF ALLHAT BLOOD PRESSURE CHANGES

- Black vs. nonblack (with vs. without metabolic syndrome)
- Essentially no BP change in nonblack patients among 3 treatment groups
- Less BP reduction in blacks on lisinopril

<table>
<thead>
<tr>
<th>Agent</th>
<th>Lisinopril</th>
<th>Amlodipine</th>
<th>Chlorthalidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>-6.8 mmHg</td>
<td>-8.8 mmHg</td>
<td>-10.5 mmHg</td>
</tr>
<tr>
<td>DBP</td>
<td>-5.6 mmHg</td>
<td>-6.6 mmHg</td>
<td>-6.6 mmHg</td>
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SUB-GROUP ANALYSES OF ALLHAT CARDIOVASCULAR OUTCOMES

Primary Outcome
• Fatal CHD or nonfatal MI
• No difference in main study or subgroup analysis

Secondary Outcomes
• Combined CHD, combined CVD, stroke
• Higher in blacks on lisinopril with metabolic syndrome

<table>
<thead>
<tr>
<th>Cohort study</th>
<th>LIFE sub-group</th>
<th>VALUE sub-group</th>
</tr>
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<tr>
<td>• ACEI vs. CCB, thiazide or BB in black patients</td>
<td>• Lisinopril vs. atenolol in patients with HTN and LVH</td>
<td>• Valsartan vs. amlodipine in high risk hypertensive patients</td>
</tr>
<tr>
<td>• Death, MI, stroke</td>
<td>• CV death, stroke, MI</td>
<td>• Cardiac morbidity and mortality</td>
</tr>
<tr>
<td>• Higher in black patients taking lisinopril</td>
<td>• Higher in black patients taking lisinopril</td>
<td>• No difference</td>
</tr>
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LIMITATIONS IN TRIAL DATA

- Limited high quality evidence for BP response and CV outcomes in black patients with hypertension.
- No high quality studies in 100% black hypertensive patients.
  - Most data → cohort studies, subgroup analyses.
- Larger hypertension landmark trials → very low percentage of black patients.
  - Difficult to interpret outcomes in subgroup analyses.
Salt-sensitivity and other factors likely more predictive of BP response to ACEI/ARB compared to race

Black patients may have reduced response to ACEI or ARB compared to nonblack patients, though overlap exists
- Likely diminished with combination therapy

CV outcomes may be worse in black patients taking ACEI or ARB monotherapy
- Data from subgroup analyses or cohort studies
- No clear evidence in combination therapy

Reasonable to choose CCB or thiazide as initial therapy for HTN in black patients
WHEN TO USE ACEI OR ARB IN BLACKS?

Add on Therapy for HTN

Heart Failure/ACS

Diabetic CKD

Non-Diabetic CKD
Rachel is a 54 year old black female with a PMH of diabetes and hypertension. Current medications include metformin 1000 mg BID and amlodipine 10 mg daily.

Labs: SCr 1.17 mg/dL  eGFR 58 mL/min/m²  K 4.2 mg/dL
Albumin to creatinine: 125 mg/g (normal < 30 mg/g)

Vitals: BP 144/86 mmHg (148/88 mmHg last visit)
HR 74 bpm
What is the best option for managing her hypertension?

A. Increase amlodipine to 20 mg daily. Always increase current doses before adding additional medications

B. Add hydrochlorothiazide 12.5 mg daily. Evidence is clear that ACEI are contraindicated in black patients

C. Add lisinopril 10 mg daily. Evidence is clear that ACEI reduce CV events in black patients

D. Add lisinopril 10 mg daily. Rachel has CKD and albuminuria
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