Disclosure:
Relationships with Industry
Conflicts of Interests

- None

- I have provided academic consultations to University Departments of Family Medicine in the United States.
Learning Objectives:
Participants will be able to:

• Describe the Process for creating an evidence-based Guideline such as the 2014 HTN Guidelines and how it differs from a Consensus Guideline.

• Establish goal BP’s for patients based on their age, race and presence of Diabetes or Kidney Disease

• Select initial medications of choice for treating high blood pressure.
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)


*4 members had relationships to disclose; 13 had no relationships to disclose. Panel members disclosed their relationships and recused themselves from voting on evidence statements and recommendations relevant to their relationships.
The Panel Process

- Strictly evidence-based
- Focus only on randomized controlled trials assessing important health outcomes (no use of intermediate/surrogate measures)
- Every included study is rated for quality by two independent reviewers using standardized tools
- Evidence statements graded for quality using prespecified criteria
- Separate grading strength of recommendations
- Independent methodology team to ensure objectivity of the review
- Initial set of recommendations focused on 3 key questions
NHLBI Systematic Review and Guideline Development Process

1. **Topic Area Identified**
2. **Expert Panel Selected**
3. **Critical Questions & Study Eligibility Criteria Identified**
4. **Literature Searched; Eligible Studies Identified**
5. **Studies Quality Rated; Data Abstracted**
6. **Evidence Tables Developed; Body of Evidence Summarized**
7. **External Review of Guideline Drafts; Revised as Needed**
8. **Graded Evidence Statements & Recommendations Developed**
9. **Guidelines Disseminated & Implemented**
NHLBI Evidence Quality Grading and Recommendation Strength

**Evidence Quality**

- **High**
  - Well-designed and conducted RCTs

- **Moderate**
  - RCTs with minor limitations
  - Well-conducted observational studies

- **Low**
  - RCTs with major limitations
  - Observational studies with major limitations

**Recommendation Strength**

- **A** – Strong
- **B** – Moderate
- **C** – Weak
- **D** – Against
- **E** – Expert Opinion
- **N** – No Recommendation
The 3 Most Important Questions in managing patients with high blood pressure

1. In adults with HTN, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?

Or put another way:

At what BP should medication be started?
The 3 Most Important Questions in managing patients with high blood pressure

2. In adults with HTN, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes? Or put another way:

How low should you set the goal for BP targets?
3. In adults with HTN, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

Or put another way:

What are the best drugs to start treatment with to achieve goal BP?
What is different about the New Guidelines?

- Strict adherence to an evidence-based process (Not consensus panel)
- Limited scope- it does not answer all questions about the management of high blood pressure.
- New BP Goals for treatment and different first-line medications
We examined studies for both Thresholds for treatment and Goals for treatment

- Although some trials had higher thresholds for eligibility than the goals tested, the panel elected to simplify treatment by making the same thresholds and goals for blood pressure treatment.
New Goal Blood Pressures for Adults: Quick Summary

• For age 60 years and older without diabetes or kidney disease, strong evidence to support Goal BP < 150/90 based on Grade A level evidence

• For all others, we recommend Goal BP < 140/90 based on expert opinion
Initial Drug Treatment Recommendations for High Blood Pressure

- **Non-Black Population without CKD:** Thiazide-type diuretic, CCB, ACEI or ARB
  - B Level Evidence
- **Black Population including those with DM:** Thiazide-type diuretic or CCB
  - B Level Evidence for general Population and C Level Evidence for DM
Initial Drug Treatment Recommendations for High Blood Pressure

- CKD* Population (Black and non-Black, DM or not DM): ACEI or ARB (but not both together in any circumstance)
  - B Level Evidence

*CKD based on eGFR < 60 ml/min/1.73m² and age less than 70 years old.
Drug Therapy Recommendations

**BLOOD PRESSURE GOALS**

≥ 60 YO:
SBP < 150mmHg
DBP < 90mmHg

<60 YO, DM, CKD:
SBP < 140mmHg
DBP < 90mmHg

**SPECIFIC RECOMMENDATIONS**

African Americans:
Diuretic/CCB

CKD:
ACEI/ARB

- Don’t use ACEI + ARB
- Use evidence-based dosing (HCTZ!)
- Only use Beta Blockers with compelling indication
Adult aged ≥18 years with hypertension

Implement lifestyle interventions (continue throughout management).

Set blood pressure goal and initiate blood pressure lowering-medication based on age, diabetes, and chronic kidney disease (CKD).

General population (no diabetes or CKD) vs. Diabetes or CKD present

Age ≥60 years vs. Age <60 years

Blood pressure goal
SBP <150 mm Hg DBP <90 mm Hg vs. SBP <140 mm Hg DBP <90 mm Hg

All ages

Diabetes present vs. No CKD

Blood pressure goal
SBP <140 mm Hg DBP <90 mm Hg vs. SBP <140 mm Hg DBP <90 mm Hg

All ages

CKD present with or without diabetes

Blood pressure goal
SBP <140 mm Hg DBP <90 mm Hg

Nonblack vs. Black

Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination.\(^3\)

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

Initiate ACEI or ARB, alone or in combination with other drug class.\(^3\)

Select a drug treatment titration strategy
A. Maximize first medication before adding second or
B. Add second medication before reaching maximum dose of first medication or
C. Start with 2 medication classes separately or as fixed-dose combination.
At goal blood pressure?

Yes

Reinforce medication and lifestyle adherence.
For strategies A and B, add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB).
For strategy C, titrate doses of initial medications to maximum.

No

At goal blood pressure?

Yes

Reinforce medication and lifestyle adherence.
Add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB).

No

Reinforce medication and lifestyle adherence.
Add additional medication class (eg, β-blocker, aldosterone antagonist, or others) and/or refer to physician with expertise in hypertension management.

Continue current treatment and monitoring.\(^b\)

No

At goal blood pressure?
Case Study:

- 76 yo black male in your clinic with HTN, CAD but no MI, and Stage 2 CKD w/o proteinuria (eGFR 68 mL/min/1.73 m²) for follow-up.
- Meds: ASA 81 mg, atorvastatin 20 mg, HCTZ 25 mg, lisinopril 40 mg & metoprolol succinate 25 mg all daily.
- He reports good health w/o angina or dyspnea, denies adverse drug effects and denies orthostatic light-headedness. Is active though does not exercise.
- Exam: P= 67, BP = 108/62. BMI = 24 kg/m² with normal findings otherwise.
How would you proceed with further management of this gentleman?
Questions?
Addendum Slides
“Guidelines We Can Trust” from IOM Report

1. Transparent
2. Manage COI
3. Group Composition
4. Guideline development – Systematic review intersection
“Guidelines We Can Trust” from IOM Report

5. Establish Evidence rating system and Strength of Recommendation system
6. Clear articulation of Recommendations
7. External Review
8. Updating
Inclusion/Exclusion Criteria

• Randomized Controlled Trials
  ▪ RCTs are subject to less bias and represent the gold standard for determining efficacy and effectiveness\(^1\)

• Search dates: 1966 to present

• Minimum one-year follow-up period

• Studies with sample sizes less than 100 excluded

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Outcomes Required to Include a Randomized Controlled Trial

• Overall mortality, CVD-related mortality, CKD-related mortality, myocardial infarction, heart failure, hospitalization for heart failure, stroke

• Coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement), peripheral revascularization (includes carotid, renal, and lower extremity revascularization)

• End stage renal disease (i.e., kidney failure resulting in dialysis or transplant), doubling of creatinine, halving of eGFR
Standardized Scoring Used by the Independent Methodology Team

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes</th>
<th>No</th>
<th>Other (CD, NR, NA)*</th>
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</thead>
<tbody>
<tr>
<td>1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?</td>
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<td>2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?</td>
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<td>3. Was the treatment allocation concealed (so that assignments could not be predicted)?</td>
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<td>4. Were study participants and providers blinded to treatment group assignment?</td>
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<tr>
<td>5. Were the people assessing the outcomes blinded to the participants’ group assignments?</td>
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<td>6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?</td>
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<td>7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?</td>
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<td>8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?</td>
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<td>9. Was there high adherence to the intervention protocols for each treatment group?</td>
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<td>10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?</td>
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<tr>
<td>11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?</td>
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<tr>
<td>12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?</td>
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<tr>
<td>13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?</td>
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<tr>
<td>14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?</td>
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Quality Rating (Good, Fair, Poor) (see guidance)

Rater #1 initials: ___________________________  Rater #2 initials: ___________________________

Additional Comments (If POOR, please state why):

*CD: cannot determine; NA: not applicable; NR: not reported
Question 1: Among adults with hypertension, does initiating antihypertensive pharmacological therapy at specific BP thresholds improve health outcomes?

Articles Screened = 1496

Included = 44

Good = 8  Fair = 18  Poor = 18

Excluded = 1452 (Did not meet prespecified inclusion criteria)

Total Abstracted = 26
Question 2: Among adults, does treatment with antihypertensive pharmacological therapy to a specified BP goal lead to improvements in health outcomes?

Articles Screened = 1978

Included = 92

Good = 17
Fair = 39
Poor = 36

Excluded = 1886
(Did not meet prespecified inclusion criteria)

Total Abstracted = 56
Question 3: In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

Articles Screened = 2662

Included = 101

- Good = 15
- Fair = 51
- Poor = 35

Excluded = 2561
(Did not meet prespecified inclusion criteria)

Total Abstracted = 66
Several trials used DBP goal <90 mm Hg and demonstrated consistent reduction of CVD events, e.g., VA morbidity trial, HDFP, MRC trial, …
Recommendation 1

- In the general population ≥60 years of age, initiate pharmacologic treatment to lower BP at SBP ≥150 mm Hg or DBP ≥90 mm Hg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg.

  Strong Recommendation – Grade A


Corollary Recommendation: In the general population ≥60 years of age, if pharmacological treatment for high BP results in lower achieved SBPs (for example, <140 mm Hg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted.

- Expert Opinion – Grade E
Recommendation 2

- In the general population <60 years of age, initiate pharmacologic treatment to lower BP at DBP $\geq 90$ mm Hg and treat to a goal DBP $<90$ mm Hg.
  - For ages 30-59 years,
    - Strong Recommendation – Grade A
  - For ages 18-29 years,
    - Expert Opinion – Grade E
Recommendation 3

- In the general population <60 years of age, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg and treat to a goal SBP <140 mm Hg.
  - Expert Opinion – Grade E
Recommendation 4

- In the population ≥18 years of age with CKD, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to goal SBP <140 mm Hg and goal DBP <90 mm Hg.
  - Expert Opinion – Grade E
  - Trials Considered: REIN-2, 2005; AASK, 2002; MDRD, 1994
Recommendation 5

• In the population ≥18 years of age 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)

• Trials Considered: ACCORD, 2010; SHEP, 1996; Syst-Eur, 1999; ABCD- HTN Cohort, 2000; ABCD- Normotensive Cohort, 2002; HOT, 1998; UKPDS, 1998;
Why is it important not to recommend intensifying medications to reduce BP below the level proven in trials?

- Lower thresholds/goals identify a much larger population as having “HTN” and presumably needing drug therapy. (e.g., reducing definition of HTN from 140/90 to 120/80 mm Hg doubles those with “HTN”)
- Millions classified as “HTN” based on higher BP goals require more drugs to achieve lower BP goals.
- Treating to lower BP levels may be harmful (J-curve?).
- If neither beneficial nor harmful, resources would be wasted and patient adherence may suffer.
This 2014 HTN evidence-based guideline focuses on the panel’s 3 highest ranked questions related to HTN management

1. In adults with HTN, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?

2. In adults with HTN, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?

3. In adults with HTN, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?
Comparisons of Diuretics and ACE Inhibitors

Legend:  *Circle* = Primary outcome; *Triangle* = Secondary outcome or not specified,  - Color: *Green* = Statistically significant where the ACE inhibitor did better ($p < 0.05$), *Red* = Statistically significant where the ACE inhibitor did worse, *Yellow* = $p \geq 0.05$ and $\leq 0.10$ *Clear* = $p > 0.10$

<table>
<thead>
<tr>
<th>Study Criteria and Characteristics</th>
<th>Mortality Outcomes</th>
<th>CHD Outcomes</th>
<th>Cerebrovascular</th>
<th>Heart Failure Outcomes</th>
<th>Composite Outcomes</th>
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<tbody>
<tr>
<td><strong>ANBP2, 2003</strong></td>
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<tr>
<td>Adults, ages 65 to 84, with absence of recent CV events</td>
<td>▲ Death from any cause</td>
<td>▲ Non-fatal MI HR (95% CI) for ACE: 0.68 (0.47, 0.99) $p = 0.05$</td>
<td>▲ Non-fatal stroke HR (95% CI) for ACE: 0.93 (0.70, 1.26) $p = 0.65$</td>
<td>▲ Non-fatal HF HR (95% CI) for ACE: 0.85 (0.62, 1.17) $p = 0.32$</td>
<td>▲ Non-fatal CV event HR (95% CI) for ACE: 0.86 (0.74, 0.99) $p = 0.03$</td>
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<tr>
<td>ACE: ACE Inhibitor: Enalapril recommended; dose not specified</td>
<td>▲ Non-fatal coronary event HR (95% CI) for ACE: 0.92 (0.73, 1.16) $p = 0.49$</td>
<td>▲ Stroke HR (95% CI) for ACE: 1.02 (0.78, 1.33) $p = 0.91$</td>
<td>▲ HF HR (95% CI) for ACE: 0.85 (0.62, 1.18) $p = 0.33$</td>
<td>▲ All CV events or death from any cause HR (95% CI) for ACE: 0.89 (0.79, 1.00) $p = 0.05$</td>
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<td>DIU: Diuretic: HCTZ recommended; dose not specified</td>
<td>▲ MI HR (95% CI) for ACE: 0.68 (0.47, 0.98) $p = 0.04$</td>
<td>△ Fatal stroke events HR (95% CI) for ACE: 1.91 (1.04, 3.50) $p = 0.04$</td>
<td>▲ Fatal HF events HR (95% CI) for ACE: 0.24 (0.03, 1.94) $p = 0.18$</td>
<td>▲ Fatal CV events HR (95% CI) for ACE: 0.99 (0.72, 1.35) $p = 0.94$</td>
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<td>N: 6,083</td>
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<td>Median 4.1 years</td>
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<td><strong>Fair</strong></td>
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</table>
### Exhibit J: Evidence from randomized controlled trials of initial antihypertensive drug therapy with beta blockers versus other drugs

<table>
<thead>
<tr>
<th>Study Criteria and Characteristics</th>
<th>Mortality Outcomes</th>
<th>Coronary Heart Disease Outcomes</th>
<th>Cerebrovascular Outcomes</th>
<th>Heart Failure Outcomes</th>
<th>Composite Outcomes</th>
<th>Kidney Outcomes</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCOT-BPLA, 2005</td>
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<tr>
<td>Adults, age 40-79 years, with HTN and at least 3 CV risk factors</td>
<td>All-cause mortality 15.5 per 1000 pts ATN vs 13.9 per 1000 pts AML HR (95% CI): 0.89 (0.61, 0.99) p = 0.0247</td>
<td>Total coronary endpoint 10.8 per 1000 pts ATN vs 14.6 per 1000 pts AML HR (95% CI) for AML: 0.87 (0.79, 0.96) p = 0.0070</td>
<td>Fatal and non-fatal stroke 8.1 per 1000 pts ATN vs 6.2 per 1000 pts AML HR (95% CI) for AML: 0.77 (0.66, 0.89) p = 0.0003</td>
<td>Fatal and non-fatal HF 3.0 per 1000 pts ATN vs 2.5 per 1000 pts AML HR (95% CI) for AML: 0.84 (0.66, 1.06) p = 0.1257</td>
<td>Composite of 1 Non-fatal MI (including silent MI) and fatal CHD 9.1 per 1000 pts ATN vs 8.2 per 1000 pts AML HR (95% CI) for AML: 0.90 (0.79, 1.02) p = 0.1052</td>
<td></td>
<td>Development of DM 15.9 per 1000 pts ATN vs 11.0 per 1000 pts AML HR (95% CI) for AML: 0.70 (0.63, 0.78) p &lt; 0.0001</td>
</tr>
</tbody>
</table>
Drug Therapy RCTs Considered

- **ACEs**: CAPPP, 1999; ANBP2, 2003; ALLHAT, 2002; JMIC-B, 2004; STOP Hypertension-2, 1999;
- Combination TX: ACCOMPLISH, 2008; ACCOMPLISH, 2010;
Recommendation 6

- In the general non-Black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, CCB, ACEI or ARB.
  - Moderate Recommendation – Grade B
Drug Considerations

• Each of the 4 drug classes recommended by the panel yielded comparable effects on overall mortality and CV, cerebrovascular, and kidney outcomes, with one exception: HF.

• Initial treatment with a thiazide-type diuretic was more effective than a CCB or ACEI, and an ACEI was more effective than a CCB in improving HF outcomes.

• While the panel recognized that improved HF outcomes was an important finding that should be considered when selecting a drug for initial therapy for HTN, the panel did not conclude that it was compelling enough within the context of the overall body of evidence to preclude the use of the other drug classes for initial therapy.
Recommendation 7

- In the general Black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.
  - For general Black population: Moderate Recommendation – Grade B
  - For Blacks with diabetes: Weak Recommendation – Grade C
Recommendation 8

- In the population ≥18 years of age with CKD and HTN, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with HTN regardless of race or diabetes status.
  - Moderate Recommendation – Grade B
Recommendation 9

- The main objective of HTN treatment is to attain and maintain goal BP.
- If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a 2\textsuperscript{nd} drug from one of the classes in Recommendation 6 (thiazide-type diuretic, CCB, ACEI or ARB). Continue to assess BP and adjust the treatment regimen until goal BP is reached.
- If goal BP cannot be reached with 2 drugs, add and titrate a 3\textsuperscript{rd} drug from the list provided. Do not use an ACEI and an ARB together in the same patient.
• If goal BP cannot be reached using the drugs in Recommendation 6 because of a contraindication or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used.

• Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients where additional clinical consultation is needed.

  - Expert Opinion – Grade E
Hypertension: A Moving Target
JNC Classifications: Diastolic Blood Pressure

JNC II. Arch Intern Med. 1980;140:1280-1285.
JNC III. Arch Intern Med. 1984;144:1045-1057.