New Recommendations for the Treatment of Hypertension:
From Population Salt Reduction to Personalized Treatment Targets

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Nothing to Disclose
“In its **current form**, habits, and environment, American health care is **incapable** of providing the public with the **quality** health care it expects and deserves.”

**Design Rule 5:**

**Current:** Decision making is based on training and experience. **New:** Decision making is based on **evidence**. Patients should receive care based on the best available scientific knowledge. Care should not vary illogically from clinician to clinician or from place to place.

Institute of Medicine, *Crossing the Quality Chasm: A New Health System for the Twenty-first Century.*
The landscape for developing clinical practice guidelines has changed.
Development of clinical practice guidelines was a key role for NHLBI in past years.

Joint National Committee on Prevention, Detection, Evaluation, & Treatment of High Blood Pressure (JNC)

- JNC 7: 2003
- JNC 6: 1997
- JNC 5: 1992
- JNC 4: 1988
- JNC 3: 1984
- JNC 2: 1980
- JNC 1: 1976

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP, Adult Treatment Panel)

- ATP III Update: 2004
- ATP III: 2002
- ATP II: 1993
- ATP I: 1988

Clinical Guidelines on the Identification, Evaluation, & Treatment of Overweight and Obesity in Adults

- Obesity 1: 1998
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)


How the Process Has Evolved

- Strictly evidence-based
- Committee includes cardiovascular specialists and primary care
- 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 pre-specified criteria
- Separate grading for recommendations
- Independent methodology team to ensure objectivity of the review
- Initial set of recommendations focused on 3 key questions
Does Hypertension Treatment Effect In RCTs Mirror Observational Data?

![Graph showing the relationship between systolic blood pressure and incidence of cardiovascular disease. The graph compares observational data with treatment effect.](image-url)
Relative Risk Reduction in Patients on Active Antihypertensive Treatment vs Placebo or No Treatment

Systolic/Diastolic Hypertension

<table>
<thead>
<tr>
<th>Fatal and nonfatal events</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke CHD</td>
<td>All-cause CV</td>
</tr>
<tr>
<td></td>
<td>Non-CV</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Isolated Systolic Hypertension

<table>
<thead>
<tr>
<th>Fatal and nonfatal events</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke CHD</td>
<td>All-cause CV</td>
</tr>
<tr>
<td></td>
<td>Non-CV</td>
</tr>
<tr>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

CHD = coronary heart disease; CV = cardiovascular.
Achieved BP and Benefit in Hypertension Trials

3 Major Guidelines differ after 1st ALLHAT
- JNC 7 diuretics as first step
- ESH/ESC use any of 5 drug classes
- British discourage diuretics and BBs
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?
Thresholds

The panel decided that, although some trials had higher thresholds for eligibility than the goals tested, translation into practice should make the threshold for initiating antihypertensive treatment the same as the BP treatment goal.
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.
### Lifestyle Modifications for BP Control

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Approximate SBP Reduction Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight reduction</td>
<td>Maintain normal body weight (BMI=18.5-25)</td>
<td>5-20 mmHg/10 kg weight lost</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>2013 ACC/AHA Lifestyle Guidelines</strong></td>
</tr>
<tr>
<td></td>
<td><strong>3. Advise adults who would benefit from BP lowering to:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a. Consume no more than 2,400 mg/day of sodium;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. Further reduction of sodium intake to 1,500 mg/day is desirable since it is associated with an even greater reduction in BP; and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>c. Reduce sodium intake by at least 1,000 mg/day since that will lower BP, even if the desired daily sodium intake is not yet achieved.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>NHLBI Grade: B (moderate); ACC/AHA COR: IIa, LOE: B</strong></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td>Regular aerobic exercise for at least 30 minutes most days of the week</td>
<td>4-10 mmHg</td>
</tr>
<tr>
<td>Moderate alcohol</td>
<td>≤2 drinks/day for men and ≤1 drink/day for women</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

BMI=Body mass index, SBP=Systolic blood pressure

Chobanian AV et al. *JAMA* 2003;289:2560-2572
Diastolic BP Goal Trials

Several trials used DBP goal <90 mm Hg and demonstrated consistent reduction of CVD events, e.g., VA morbidity trial, HDFP, MRC trial, ...
**Hypertension Optimal Treatment (HOT) Trial**

- Only one randomized controlled trial examined whether diastolic BP goals below 90 mm Hg reduced or increased major CVD events: HOT

- HOT randomized 18,790 participants to diastolic BP goals ≤90 mm Hg, ≤85 mm Hg or ≤80 mm Hg:
  - aged 50–80 years (mean 61.5 years)
  - HTN and diastolic BP 100-115 mm Hg (mean 105 mm Hg)
  - CCB felodipine + other agents as needed to reach goal diastolic BP
# Major Trials Testing SBP Goals in General Populations

<table>
<thead>
<tr>
<th>Age</th>
<th>SHEP</th>
<th>Syst-Eur</th>
<th>HYVET</th>
<th>JATOS</th>
<th>VALISH</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60</td>
<td>&gt; 60</td>
<td>≥ 80</td>
<td>65-85</td>
<td>&gt;70, &lt;85</td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>4,736</td>
<td>4,695</td>
<td>3,845</td>
<td>4,418</td>
<td>3,260</td>
</tr>
<tr>
<td>Entry SBP</td>
<td>160-219</td>
<td>160-219</td>
<td>160-199</td>
<td>≥160</td>
<td>≥160</td>
</tr>
<tr>
<td>Goal SBP</td>
<td>&lt;148</td>
<td>&lt;150</td>
<td>&lt;150</td>
<td>&lt;140</td>
<td>&lt;140</td>
</tr>
<tr>
<td>Achieved SBP</td>
<td>142</td>
<td>151</td>
<td>144</td>
<td>136</td>
<td>137</td>
</tr>
<tr>
<td>Stroke</td>
<td>36%</td>
<td>42%</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>CVD</td>
<td>32%</td>
<td>31%</td>
<td>34%</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mortality</td>
<td>ns</td>
<td>ns</td>
<td>21%</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure  
CVD = cardiovascular disease

The table shows the number of participants, the entry systolic blood pressure (SBP), the goal SBP, and the achieved SBP in several trials. The outcomes for stroke, CVD, and mortality are also provided, with some showing a significant decrease (↓) compared to others. The last two columns indicate whether the observed difference is statistically significant (ns = not significant).
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 ≥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
## RCTs Testing BP Goals In Hypertensive Diabetic Patients

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Duration (years)</th>
<th>SBP goal, mmHg</th>
<th>DBP goal, mmHg</th>
<th>Mean BP, less intense, mmHg</th>
<th>Mean BP, more intense, mmHg</th>
<th>Outcome Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP</td>
<td>583</td>
<td>5</td>
<td>&lt;148</td>
<td>none</td>
<td>155/72°</td>
<td>146/68°</td>
<td>Stroke CVD CHD 22% (ns) 34% 56%</td>
</tr>
<tr>
<td>Syst-Eur</td>
<td>492</td>
<td>2</td>
<td>&lt;150</td>
<td>none</td>
<td>162/82</td>
<td>153/78</td>
<td>Stroke CVD 69% 62%</td>
</tr>
<tr>
<td>HOT</td>
<td>1,501</td>
<td>3</td>
<td>none</td>
<td>&lt;80</td>
<td>148/85</td>
<td>144/81</td>
<td>CVD MI CV death 51% 50% 30% (ns) 67%</td>
</tr>
<tr>
<td>UKPDS</td>
<td>1,148</td>
<td>8.4</td>
<td>&lt;150</td>
<td>&lt;85</td>
<td>154/87</td>
<td>144/82</td>
<td>DM-related deaths Stroke Microvasc 34% 32% 44% 37%</td>
</tr>
<tr>
<td>ABCD</td>
<td>470</td>
<td>5.3</td>
<td>none</td>
<td>&lt;75</td>
<td>138/86</td>
<td>132/78</td>
<td>Renal (1º) Microvasc Death CVD nc nc 49% ns</td>
</tr>
<tr>
<td>ACCORD</td>
<td>4,733</td>
<td>4.7</td>
<td>&lt;120</td>
<td>none</td>
<td>134</td>
<td>119</td>
<td>CVD (1º) Stroke 12% (ns) 41%</td>
</tr>
</tbody>
</table>

BP Targets in Chronic Kidney Disease (CKD)

- 3 RCTs (8 reports), total of 2272 participants:
  - **MDRD** (Modification of Diet in Renal Disease) Study
  - **AASK** (African American Study of Kidney Disease and Hypertension) Trial
  - **REIN-2** (Ramipril Efficacy in Nephropathy 2) trial

- No conclusive evidence favoring a BP target of **<125/75** to **130/80** mm Hg rather than **<140/90** mm Hg.

ALLHAT

Only Subgroup Differences: Lisinopril vs Chlorthalidone in Blacks/Non-Blacks for CVD & Stroke

<table>
<thead>
<tr>
<th>Condition</th>
<th>Blacks</th>
<th>Non-Blacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>1.10 (0.94 - 1.28)</td>
<td>0.94 (0.85 - 1.05)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.06 (0.95 - 1.18)</td>
<td>0.97 (0.89 - 1.06)</td>
</tr>
<tr>
<td>Combined CVD</td>
<td>1.19 (1.09 - 1.30)</td>
<td>1.06 (1.00 - 1.13)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.40 (1.17 - 1.68)</td>
<td>1.00 (0.85 - 1.17)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>1.32 (1.11 - 1.58)</td>
<td>1.15 (1.01 - 1.30)</td>
</tr>
<tr>
<td>ESRD</td>
<td>1.29 (0.94 - 1.75)</td>
<td>0.93 (0.67 - 1.30)</td>
</tr>
</tbody>
</table>

Favors Lisinopril  Favors Chlorthalidone  Favors Lisinopril  Favors Chlorthalidone
LIFE: Individual Endpoint Results

- **Cardiovascular Death**
  - Losartan: 4.4%
  - Atenolol: 5.1%
  - Adjusted HR: 0.89
  - P = 0.206

- **Myocardial Infarction**
  - Losartan: 4.3%
  - Atenolol: 4.1%
  - Adjusted HR: 1.07
  - P = 0.491

- **Stroke**
  - Losartan: 5.0%
  - Atenolol: 6.7%
  - Adjusted HR: 0.75
  - P = 0.001
LIFE: New-onset diabetes

Rate 13.0/1,000 patient yrs

Rate 17.4/1,000 patient yrs

Adjusted Hazard Ratio = 0.75

P=0.001

Losartan: 5.2%
n=241

Atenolol: 7.0%
n=319
2014 Hypertension Guideline Management Algorithm

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)

Age ≥60 years

Blood pressure goal SBP <150 mm Hg DBP <90 mm Hg

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

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

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

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

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

All ages

Diabetes present

No CKD

All ages

CKD present with or without diabetes

Diabetes or CKD present

Nonblack

Black

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.

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

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

Initiate ACEI or ARB, alone or in combination with other drug class.

Nonblack

Black

All races
Initial Combinations of Medications (LIFE)

- 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

* Combining ACEI with ARB discouraged
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.
Recommendation 9, cont

• 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