Current Therapy for Hypertension
JNC-8

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Epidemiology

- Affects 60.5 million American adults
- Hypertension (HTN) is the most common primary diagnosis in America
- 35 million office visits each year account for the primary diagnosis of HTN
- Prevalence increases with age
- More common in African Americans than in Caucasians
- BP control rates remain poor with only 34% of treated hypertensive patients below their goal BP level

Wong, N.D. Arch Intern Med, 2007; 167:2431-2436

Epidemiology

- The BP relationship to risk of CVD is continuous, consistent, and independent of other risk factors.
- Each increment of 20/10 mmHg doubles the risk of CVD across the entire BP range starting from 115/75 mmHg.
- Prehypertension signals the need for increased education to reduce BP in order to prevent hypertension.
- Risk of CHD/stroke begins to rise when BP >115/75 mm Hg
- Risk doubles for each 20/10 mm Hg increase
- Therefore in the Prehypertensive patient 135/85 = 2 fold risk

JNC VII report
The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to CVD by following its development over a long period of time in a large group of participants who had not yet developed overt symptoms of CVD or suffered a heart attack or stroke.

Results:

- Hypertensive patients have a fourfold increase in cerebrovascular accidents
- Hypertensive patients have a sixfold increase in CHF when compared to normotensive control subjects
Hypertension

- Hypertensive patients compared to normotensive patients have
  - A 2-fold risk of peripheral artery disease
  - A 3-fold risk of coronary artery disease
  - A 4-fold risk of congestive heart failure
  - A 7-fold risk of stroke
# Types of Hypertension

<table>
<thead>
<tr>
<th>Primary (Essential) HTN</th>
<th>Secondary HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 95% of the hypertensive patients in which no single cause can be identified</td>
<td>• ~ 5% of patients with HTN have identifiable causes</td>
</tr>
<tr>
<td>• HTN results from complex interactions between multiple genetic and environmental factors</td>
<td>• Suspect in patients who develop HTN at an early age, who first exhibit HTN when over age 50, or those who were well controlled but became refractory to treatment</td>
</tr>
</tbody>
</table>
Patient Evaluation

- 3 objectives

- To assess lifestyle and identify other cardiovascular risk factors or concomitant disorders that may affect prognosis and guide treatment

- To reveal identifiable causes of high BP

- To assess the presence or absence of target organ damage and CVD
Target Organ Damage

- Heart
  - Left ventricular hypertrophy
  - Angina or prior myocardial infarction
  - Prior coronary revascularization
  - Heart failure

- Brain
  - Stroke or transient ischemic attack

- Chronic kidney disease
- Peripheral arterial disease
- Retinopathy
Identifiable Causes of HTN

- Sleep apnea
- Drug-induced or related causes
- Chronic kidney disease
- Primary aldosteronism
- Renovascular disease
- Chronic steroid therapy and Cushing’s syndrome
- Pheochromocytoma
- Coarctation of the aorta
- Thyroid or parathyroid disease
History

- Seek to discover secondary causes of HTN
- Angina/MI Stroke: Complications of HTN, Angina may improve with b-blockers
- Asthma, COPD: Preclude the use of b-blockers
- Heart failure: ACE inhibitors indication
- DM: ACE preferred

- Claudication: May be aggravated by b-blockers, atheromatous RAS may be present
- Gout: May be aggravated by diuretics
- Use of NSAIDs: May cause or aggravate HTN
- Polyuria and nocturia: Suggest renal impairment
History

- Cigarette smoker: Aggravate HTN, independently a risk factor for CAD and stroke

- High alcohol intake: A cause of HTN

- High salt intake: Advice low salt intake
Examination

- Appropriate measurement of BP in both arms
- Investigation for target organ damage or a secondary cause of HTN
- Optic fundi
- Calculation of BMI (waist circumference also may be useful)
- Auscultation for carotid, abdominal, and femoral bruits
- Thorough examination of the heart and lungs
- Abdomen for enlarged kidneys, masses, and abnormal aortic pulsation
- Lower extremities for edema and pulses
- Neurological assessment
- Palpation of the thyroid gland
## Diagnostic Testing

<table>
<thead>
<tr>
<th>Laboratories</th>
<th>Diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• UA</td>
<td>• ECG</td>
</tr>
<tr>
<td>• CBC</td>
<td>• Chest Radiography</td>
</tr>
<tr>
<td>• Chemistry</td>
<td>• Echocardiogram</td>
</tr>
<tr>
<td>• Uric Acid</td>
<td></td>
</tr>
<tr>
<td>• Fasting Lipid Panels</td>
<td></td>
</tr>
</tbody>
</table>
Treatment Overview

• Goals of therapy
  • Lifestyle modification

• Pharmacologic treatment

• Algorithm for treatment of hypertension

• Classification and management of BP for adults

• Follow-up and monitoring
Benefits of Treatment

- Over past 3 decades, aggressive treatment of HTN has resulted in a decrease in death rates from stroke and coronary heart disease
- Reductions in stroke incidence, averaging 35-40%
- Reductions in MI, averaging 20-25%
- Reductions in HF, averaging >50%

http://www.nhlbi.nih.gov/
Lifestyle modifications

<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 (body mass index 18.5–24.9 kg/m²).</td>
<td>5–20 mmHg/10kg³²,³³</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>Consume a diet rich in fruits, vegetables, and lowfat dairy products with a reduced content of saturated and total fat.</td>
<td>8–14 mmHg³⁴,³⁵</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).</td>
<td>2–8 mmHg³⁴,³⁶</td>
</tr>
<tr>
<td>Physical activity</td>
<td>Engage in regular aerobic physical activity such as brisk walking (at least 30 min per day, most days of the week).</td>
<td>4–9 mmHg³⁷,³⁸</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>Limit consumption to no more than 2 drinks (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) per day in most men, and to no more than 1 drink per day in women and lighter weight persons.</td>
<td>2–4 mmHg³⁹</td>
</tr>
</tbody>
</table>
Pharmacologic Treatment

- A large number of drugs are currently available

- > 2/3 of HTN patients cannot be controlled on one drug & will require 2 or more antihypertensive agents

- ALLHAT
  - 60% of patients with BP <140/90 received ≥ 2 agents
  - 30% were controlled with one drug
Pharmacologic Treatment

- Thiazide-type diuretics have been the basis of antihypertensive therapy in the majority of placebo-controlled outcome trials.

- Excellent clinical trial data proving that reducing BP with other classes of drugs reduced the complication of HTN:
  - ACEIs
  - ARBs
  - CCBs
## JNC 7 and Since: Compelling Indications for Individual Drug Classes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diuretic</th>
<th>β-blocker</th>
<th>ACEI</th>
<th>ARB</th>
<th>CCB</th>
<th>Aldo Antag.</th>
<th>Clinical Trial Basis</th>
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</thead>
<tbody>
<tr>
<td>HF</td>
<td></td>
<td></td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>ACC/AHA HF guideline; MERIT-HF; COPERNICUS, CIBIS, SOLVD; AIRE, TRACE, Val-HeFT; RALES</td>
</tr>
<tr>
<td>Post-MI</td>
<td></td>
<td>❌</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>ACC/AHA post-MI guideline; BHAT; SAVE, CAPRICORN, EPESUS/VALIANT</td>
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<tr>
<td>High CAD Risk</td>
<td>●</td>
<td></td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>ALLHAT; HOPE, ANBP2; LIFE; CONVINCE, ONTARGET</td>
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<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>NKF-ADA guideline; UKPDS; ALLHAT</td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>NKF guideline; CAPP; RENAAL; IDNT, REIN, AASK</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
<td>PROGRESS, LIFE</td>
</tr>
</tbody>
</table>

- ● Published after JNC 7

*Chobanian AV et al. JAMA. 2003;289:2560-2572.*
So What Was Next

- JNC-1 published in 1978
- JNC-7 published in 2003
- 10 years without an update??
- JNC-8 published 2014
Questions to Answer???

- Treatment of the Elderly?
- Diuretics are Frontline??
- Beta Blockers Frontline?
- Combination Therapy to start?
- Goals for Diabetics change?
**HYVET**

**Trial design:** Hypertensive geriatric (age > 80 years) patients were randomized to indapamide SR 1.5 mg or to placebo. Clinical outcomes were evaluated at 2 years.

**Results**
- Trial was terminated early
- Stroke ↓ 30% (p = 0.06), mortality ↓ 21% (p = 0.02), heart failure ↓ 64% (p < 0.001) in indapamide arm compared with placebo
- Number needed to treat at 2 years: 94 for stroke, 40 for mortality

**Conclusions**
- Significant mortality benefit with treatment of BP >160 mm Hg in patients older than 80 years
- Newer guidelines will need to consider this group of patients specifically

Presented by Dr. Nigel Beckett at SCAI-ACC i2 Summit/ACC 2008
Questions to Answer???

- Treatment of the Elderly?
- Diuretics are Frontline??
- Beta Blockers Frontline?
- Combination Therapy to start?
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ALLHAT

Trial Design: ALLHAT was a NHLBI sponsored, 623 site, blinded randomized trial of the diuretic chlorthalidone vs the calcium channel blocker amlodipine and the ACE inhibitor lisinopril in patients with hypertension. Patients were followed for a mean of 4.9 yrs. Primary endpoint (EP) was fatal heart disease or nonfatal MI.

Results
- No difference in prespecified 1° endpoint
- Lower heart failure rate (2° EP) with chlorthalidone vs amlodipine or lisinopril
- Lower stroke rate (2° EP) with chlorthalidone vs lisinopril (RR 1.15 p=0.02)
- Higher glucose levels with chlorthalidone vs amlodipine or lisinopril
- All 3 drugs reduced blood pressure from baseline, but SBP reduction greater with chlorthalidone

Conclusions
- No difference in fatal heart disease or MI
- Benefit for chlorthalidone in heart failure EP

Limitations
- Important side effect in the chlorthalidone arm was higher fasting glucose levels
- Impact of chlorthalidone on diabetes and CV disease may not be fully manifested in the relatively short follow-up of 4 years
- ACE-I arm may be disadvantaged since the 1st add-on therapy specified was beta-blocker rather than diuretic or Ca blocker
- Relatively large crossover rate

JAMA 2002;288:2981-2997

www.cardiosource.com
Additional BP Reduction with Spironolactone in Resistant Hypertension

- Reims
- Dublin
- Birmingham
- ASCOT

Blood pressure reduction (mm Hg)

- Systolic
- Diastolic

Reims: -24
Dublin: -13
Birmingham: -12
ASCOT: -9.5
Questions to Answer???

- Treatment of the Elderly?
- Diuretics are Frontline??
- Beta Blockers Frontline?
- Combination Therapy to start?
- Goals for Diabetics change?
There May Be Less Emphasis on BBs as Initial Therapy in the Absence of Established Heart Disease

• End point data (largely with atenolol)
  – In comparison with other antihypertensive drugs, the effect of BBs is less than optimal, with a raised risk of stroke with Atenolol
• Recent guidelines have suggested that, in the absence of established CAD or HF, BBs should not be used as initial therapy
  – Unclear whether this should apply to “newer” BBs like carvedilol and nebivolol and whether it mainly applies to atenolol.

National Collaborating Centre for Chronic Conditions and British Hypertension Society.
Questions to Answer???

- Treatment of the Elderly?
- Diuretics are Frontline??
- Beta Blockers Frontline?
- Combination Therapy to start?
- Goals for Diabetics change?
# 2 or More Medications Are Required to Achieve BP Control in Clinical Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>SBP achieved (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>ALLHAT</td>
<td>138</td>
</tr>
<tr>
<td>HOT</td>
<td>138</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
</tr>
<tr>
<td>ACCORD (intensive)*</td>
<td>119</td>
</tr>
<tr>
<td>ACCORD (standard)*</td>
<td>133</td>
</tr>
<tr>
<td><strong>Diabetes with and without renal disease</strong></td>
<td></td>
</tr>
<tr>
<td>IDNT</td>
<td>138</td>
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<tr>
<td>RENAAL</td>
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</tr>
<tr>
<td>ABCD</td>
<td>132</td>
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<tr>
<td>UKPDS</td>
<td>144</td>
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<tr>
<td><strong>Kidney disease</strong></td>
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<tr>
<td>AASK</td>
<td>128</td>
</tr>
<tr>
<td>MDRD</td>
<td>132</td>
</tr>
</tbody>
</table>

SBP=systolic blood pressure. *Target blood pressure control groups in ACCORD defined as $<120$ mm Hg (intensive) and $<140$ mm Hg (standard).

Combining Drugs from Different Classes is Approximately 5 Times More Effective in Lowering BP than Doubling the Dose of 1 Drug

- Adding a drug from another class (on average standard doses)
- Doubling dose of same drug (from standard dose to twice standard)

Bar chart showing the incremental SBP reduction ratio of observed to expected additive effects for different classes of drugs:
- Thiazide: 1.04
- Beta blocker: 1.00
- ACE inhibitor: 1.16
- Calcium channel blocker: 0.89
- All classes: 1.01

**ACCOMPLISH**

**Trial design:** Patients with hypertension were randomized to fixed dose amlodipine / benazepril or hydrochlorothiazide (HCTZ) / benazepril. Patients were followed for 5 years. Trial was terminated early.

**Results**
- Primary endpoint (CV mortality, stroke, MI, revascularization, unstable angina, resuscitation from death 9.6% in amlodipine/benazepril arm, compared with 11.8% in HCTZ/benazepril arm ($p < 0.001$)
- MI was reduced with amlodipine/benazepril arm ($p = 0.04$); CV mortality and stroke, similar
- Adverse events were similar

**Conclusions**
- Fixed dose combination of amlodipine/benazepril better than HCTZ/benazepril in reduction in blood pressure as well as CV endpoints in patients with high-risk hypertension
- Important study—may require revision of current JNC-7 guidelines

Trial design: Patients at high risk for cardiovascular events, but without heart failure, were randomized to telmisartan, ramipril, or the combination. Patients were followed for a median of 56 months.

Results
- Telmisartan (16.7%) noninferior; combination (16.3%) not superior to ramipril (16.5%) for primary endpoint (CV death, MI, stroke, heart failure)
- Greater incidence of hypotension in combination (4.8%) and telmisartan (2.7%) groups, compared with ramipril group (1.7%) (p < 0.001)

Conclusions
- Either telmisartan or ramipril, but not both, can be used in hypertensive patients at high risk for cardiovascular events
- Side effects greater with combination therapy

* Telmisartan vs. ramipril for noninferiority

Questions to Answer???

- Treatment of the Elderly?
- Diuretics are Frontline??
- Beta Blockers Frontline?
- Combination Therapy to start?
- Goals for Diabetics change?
ACCORD BP Protocol

- Many drugs/combinations provided to achieve goal BP according to randomized assignment.

- Intensive Intervention:
  - 2-drug therapy initiated: thiazide-type diuretic + ACEI, ARB, or b-blocker.
  - Drugs added and/or titrated at each visit to achieve SBP <120 mm Hg.
  - At periodic “milepost” visits: addition of another drug “required” if not at goal.

- Standard Intervention:
  - Intensify therapy if SBP ≥160 mm Hg @ 1 visit or ≥140 mm Hg @ 2 consecutive visits
  - Down-titration if SBP <130 mm Hg @ 1 visit or <135 mm Hg @ 2 consecutive visits
Primary Outcome
Nonfatal MI, Nonfatal Stroke or CVD Death

Patients with Events (%)

Years Post-Randomization

HR = 0.88
95% CI (0.73-1.06)
Conclusions

- The ACCORD BP trial evaluated the effect of targeting a SBP goal of 120 mm Hg, compared to a goal of 140 mm Hg, in patients with type 2 diabetes at increased cardiovascular risk.

- The results provide no conclusive evidence that the intensive BP control strategy reduces the rate of a composite of major CVD events in such patients.
Figure: 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)

<table>
<thead>
<tr>
<th>Age ≥60 years</th>
<th>Age &lt;60 years</th>
<th>All ages</th>
<th>Diabetes present</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure goal SBP &lt;150 mmHg DBP &lt;90 mmHg</td>
<td>Blood pressure goal SBP &lt;140 mmHg DBP &lt;90 mmHg</td>
<td>Blood pressure goal SBP &lt;140 mmHg</td>
<td>Blood pressure goal SBP &lt;140 mmHg DBP &lt;90 mmHg</td>
<td></td>
</tr>
<tr>
<td>Nonblack</td>
<td>Black</td>
<td>All races</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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?

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 combination use of ACEI and ARB).

At goal blood pressure?

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 combination use of ACEI and ARB).

At goal blood pressure?

Reinforce medication and lifestyle adherence.
Add additional medication class (e.g., β-blockers, aldosterone antagonists, or others) and/or refer to physician with expertise in hypertension management.

At goal blood pressure?

Continue current treatment and monitoring.

**SBP** indicates systolic blood pressure; **DBP** diastolic blood pressure; **ACEI**, angiotensin-converting enzyme; **ARB**, angiotensin receptor blocker; and **CCB**, calcium channel blocker.

ACEIs and ARBs should not be used in combination.

If blood pressure fails to be maintained at goal, reenter the algorithm where appropriate based on the current individual therapeutic plan.
Box. Recommendations for Management of Hypertension

Recommendation 1
In the general population aged ≥60 years, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) ≥150 mm Hg or diastolic blood pressure (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 aged ≥60 years, if pharmacologic treatment for high BP results in lower achieved SBP (eg, <140 mm Hg) and treatment is well tolerated and without 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, 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, 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 aged ≥18 years with chronic kidney disease (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)

Recommendation 5
In the population aged ≥18 years 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)

Recommendation 6
In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation – Grade B)
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 black patients with diabetes: Weak Recommendation – Grade C)

Recommendation 8
In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. (Moderate Recommendation – Grade B)

Recommendation 9
The main objective of hypertension 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 second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should 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 third 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 only 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 for whom additional clinical consultation is needed. (Expert Opinion – Grade E)