Evidence Based Practice Guidelines on the Treatment of Hypertension

David Stewart, Pharm.D., BCPS
Assistant Professor, Pharmacy Practice
stewardw@etsu.edu

Objectives:
After this program, the audience should be able to:

• Summarize the 7th Report of the Joint National Committee on the prevention, detection, evaluation, and treatment of high blood pressure (JNC-7) and current American Heart Association (AHA)/American College of Cardiology (ACC) guidelines dealing with the treatment of hypertension.

• Interpret and apply current primary literature relating to the treatment of hypertension.

• Apply evidence based guidelines and current primary literature to specific patient care situations.
Introduction to Hypertension

BP as Risk Factor for CV Mortality

Relative Risk of CV Mortality

Age-adjusted prevalence of hypertension in adults: US 1999-2006

% of US Adults With:

- Hypertension: 29%
- Pre-hypertension: 37%
- Unaware of dx: 7%
- Treated hypertension: 68%
- BP at goal: 64%

Population of United States 308.9 million
With hypertension 89.6 million
With inappropriate treatment 32.3 million

www.census.gov (accessed 3/17/10)
Cardiovascular Risk Factors

- Hypertension*
- Diabetes*
- LV Hypertrophy*
- Increased LDL*
- Smoking*
- Family hx of premature CVD (< 55/65, M/F)
- Obesity (BMI > 30 kg/m²)
- Chronic Renal Disease
- Age (> 55 for men, > 65 for women)

* Primary Risk Factor

JNC VII;2004;NHLBI.

Key Point

Hypertension is a modifiable risk factor for the development of cardiovascular disease.
JNC VII Key Points

- < 120/80 Normal
- 120/80 – 139/89 Prehypertension
  - Not a disease category
  - Identifies individuals at high risk for hypertension
  - Not candidates for medication therapy
- 140/90 – 159/99 Stage 1
- ≥ 160/100 Stage 2

ACC/AHA Statement on Hypertension with Ischemic Heart Disease

- < 140/90 mmHg
  - Framingham Risk < 10%
- < 120/80 mmHg
  - LVD
- < 130/80 mmHg
  - Framingham Risk ≥ 10%
  - DM
  - CKD
  - CAD (or equivalent)

Modified Goal
(Collective Recommendations)\(^1-4\)

- **< 130/80 mmHg**
  - Diabetes\(^1,2,4\)
  - Renal Disease\(^1,3\)
  - Renal Disease & Diabetes\(^1-4\)
  - Coronary artery disease (CAD)\(^4\)
  - CAD risk equivalents\(^4\)
  - Carotid artery disease\(^4\)
  - Peripheral artery disease\(^4\)
  - Abdominal aortic aneurysm\(^4\)
  - High risk (≥ 10% 10-yr Framingham risk)\(^4\)
- **< 120/80 mmHg**
  - Left ventricular dysfunction\(^4\)


---

**ACCORD**

- Randomized, uncontrolled, non-blinded study
- 77 centers in US and Canada
- Began recruitment in 2001
- 10,251 high-risk participants with type 2 DM
- Evaluated glycemic, BP, and lipid control
- 4,733 participants enrolled in BP arm
- Sponsored by NHLBI
- Participants
  - Type II DM with HbA1c ≥ 7.5%
  - 40 YOA & CV disease and
  - 55 YOA & anatomical evidence of CVD or 2 risk factors
  - Elevated BP values
- 5 year follow-up

**ACCORD**

• **BP Study Design**
  – Tested goal BP, not regimen
  – Randomized to:
    • Intensive BP Goal (< 120 mmHg SBP)
    • Standard BP Goal (< 140 mmHg SBP)

• **Outcomes**
  – **Primary**
    • Major CV event
      – Nonfatal MI
      – Nonfatal stroke
      – CV death
  – **Secondary**
    • Many additional CV secondary outcomes including some additional composites were evaluated


---

**ACCORD**

• **Results**
  – **Achieved targets of:**
    • Intensive arm – 119.3/64.4 mmHg
    • Standard arm – 133.5/70.5 mmHg
  – **Only significant differences were:**
    • Any stroke
      – n = 36 of 2,363 (0.32%/yr) vs 62 of 2,371 (0.53%/yr)
      – HR 0.59 [0.39-0.80]
    • Nonfatal stroke
      – n = 34 of 2,363 (0.30%/yr) vs 55 of 2,371 (0.47%/yr)
      – HR 0.63 [0.41-0.96]
  – **Any stroke**
    • NNT = 92 pts for 5 years to prevent 1 stroke
  – **Fatal stroke**
    • NNT = 476 pts for 5 years to prevent 1 stroke
  – **All other outcomes were not statistically significant**

ACCORD - Discussion

• Did not evaluate regimens
  – ACE-I/ARB usage at last visit:
    • Intensive arm – 90%
    • Standard arm – 80%
    • Chi square p-value – 0.0002
  – Did not compare current recommended goal
    • < 130/80 mmHg recommended by JNC 7/AHA/ADA
    • < 130/85 mmHg was current JNC 6 recommendation
• Calls into question “goal” values not supported by clinical evidence
• Largest trial to date to evaluate BP goal of DM pts

Case Study
(what not to do)

• FM is a middle-aged obese WM who went to the dentist for tooth extraction
• He was found to have stage 1 hypertension (144/92)
• Referred for medical treatment
• Prescribed lisinopril 20 mg/HCTZ 25 mg daily
• Became orthostatic and called EMS
• At ED the patient had BP of 80/48 after fluid boluses

When Should One Start Treatment?

Table 4. Recommendations for followup based on initial blood pressure measurements for adults without acute end organ damage

<table>
<thead>
<tr>
<th>Initial Blood Pressure (mmHg)</th>
<th>Followup Recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Redcheck in 2 years</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>Redcheck in 1 year</td>
</tr>
<tr>
<td>Stage 1 Hypertension</td>
<td>Confirm within 2 month</td>
</tr>
<tr>
<td>Stage 2 Hypertension</td>
<td>Evaluate or refer to source of care within 1 month. For those with higher pressures (e.g., &gt;160/110 mmHg), evaluate and treat immediately or within 1 week depending on clinical situation and complications.</td>
</tr>
</tbody>
</table>

JNC VII, 2004; NHLBI.
Drugs or No Drugs?

- Prehypertension
  - Counsel patient on lifestyle modifications
- Stage 1
  - Counsel patient on lifestyle modifications
  - Recheck in 2 months
  - If still elevated, begin antihypertensives (mono or combo therapy)
- Stage 2
  - Counsel patient on lifestyle modifications
  - Begin antihypertensives (2 drug therapy)
    - Base on patient specific factors (compelling indications)
- A large proportion of patients will require multiple drug therapy to reach set BP targets. These data led experts to recommend initiating 2-drug therapy for stage 2 hypertension.
- Average patient will require > 2 antihypertensives

JNC VII;2004;NHLBI.

Targets of Drug Therapy

- $\alpha_1$-receptors (blockade)
- *$\beta$-receptors (blockade)
- *Calcium channels (blockade)
- Central $\alpha_2$-receptors (stimulation)
- *Nephron (diuresis)
- *Renin Angiotensin-Aldosterone System
- Vascular endothelium (vasodilation)

*Common 1st-2nd line antihypertensives, others are used in refractory disease or no longer have a place in therapy.

**A complete listing of common medications including usual dosages and frequencies can be found in JNC 7, Table 10.
Which Medication Should I Choose?

- > 66 Antihypertensives
- Factors to consider
  - Cost
  - Compliance
  - Common adverse effects
  - Compelling indications

JNC 7 Guidelines

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Initial Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>No compelling indication</td>
<td></td>
</tr>
<tr>
<td>Stage 1</td>
<td>Thiazide diuretic (favors this option), ACE-I or ARB, beta-blocker, CCB</td>
</tr>
<tr>
<td>Stage 2</td>
<td>2-drug combination of above agents</td>
</tr>
<tr>
<td>Compelling indication</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>ACE-I or ARB</td>
</tr>
<tr>
<td>CKD</td>
<td>ACE-I or ARB</td>
</tr>
<tr>
<td>CAD</td>
<td>Beta-blocker, ACE-I or ARB</td>
</tr>
</tbody>
</table>

JNC VII; 2004; NHLBI.
Should β-Blockers be 1st Line?

- Are currently listed as a first line agent in JNC 7
- No mortality or outcomes data
- Based on standard of practice
- Less BP reduction than other agents
- May have less effect on central aortic pressure compared to RAAS blocking agents, diuretics, and CCBs
- Not always tolerated well
- Appropriate role
  - 2nd prevention MI
  - HF (metoprolol, carvedilol, bisoprolol)


ACC/AHA Guidelines

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Prevention</td>
<td>ACE-I or ARB, CCB, thiazide diuretic</td>
</tr>
<tr>
<td>High CAD Risk</td>
<td>1st – ACE-I or ARB</td>
</tr>
<tr>
<td></td>
<td>2nd – thiazide diuretic</td>
</tr>
<tr>
<td></td>
<td>3rd – CCB or beta-blocker</td>
</tr>
<tr>
<td>CAD</td>
<td>1st – beta-blocker, ACE-I or ARB</td>
</tr>
<tr>
<td></td>
<td>2nd – thiazide diuretic</td>
</tr>
<tr>
<td></td>
<td>3rd – CCB</td>
</tr>
<tr>
<td>CAD Risk Equivalent</td>
<td>1st – ACE-I or ARB, thiazide diuretic</td>
</tr>
<tr>
<td></td>
<td>2nd – CCB</td>
</tr>
<tr>
<td>LVD</td>
<td>Stage B – ACE-I or ARB &amp; beta-blocker</td>
</tr>
<tr>
<td></td>
<td>Stage C/D – ACE-I or ARB, beta-blocker, diuretic,</td>
</tr>
<tr>
<td></td>
<td>aldosterone antagonist, hydralazine + isosorbide</td>
</tr>
<tr>
<td></td>
<td>dinitrate</td>
</tr>
</tbody>
</table>

Thiazide Diuretics

• Have been shown to reduce outcomes
  – Stroke
  – CAD
  – HF
• Very cost effective
• Effective add-on therapy with ACE-I/ARB
• May increase risk of diabetes
• Should keep K+ concentrations ≥ 3.9
  – Levels < 3.5 increase risk of CV events
  – Levels < 3.8 ↓ utilization of endogenous insulin


ACCOMPLISH

• >11,500 patients, multi-center, randomized, controlled trial
• 2 treatment arms (mean dose)
  – Benazepril (36.1 mg) + HCTZ (19.3 mg)
  – Benazepril (36.3 mg) + amlodipine (7.7 mg)
• Mean duration approximately 30 months
• Patient population
  – Hypertension & high risk for cardiovascular events
  – Coronary events, MI, revascularization, or stroke
  – Impaired renal function
  – LVH
  – DM
• Primary endpoint
  – Composite of cardiovascular events and death from cardiovascular causes

ACCOMPLISH – Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>B+A Group</th>
<th>B+H Group</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite&lt;sup&gt;3&lt;/sup&gt;</td>
<td>552 (9.6)</td>
<td>679 (11.8)</td>
<td>0.80 (0.72-0.90)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Death from CV causes</td>
<td>107 (1.9)</td>
<td>134 (2.3)</td>
<td>0.80 (0.62-1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Fatal &amp; nonfatal MI</td>
<td>125 (2.2)</td>
<td>159 (2.8)</td>
<td>0.78 (0.62-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Fatal &amp; nonfatal stroke</td>
<td>112 (1.9)</td>
<td>133 (2.3)</td>
<td>0.84 (0.65-1.08)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospitalization for UA</td>
<td>44 (0.8)</td>
<td>59 (1.0)</td>
<td>0.75 (0.50-1.10)</td>
<td>0.14</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>334 (5.8)</td>
<td>386 (6.7)</td>
<td>0.86 (0.74-1.00)</td>
<td>0.04</td>
</tr>
<tr>
<td>Resuscitation after arrest</td>
<td>14 (0.2)</td>
<td>8 (0.1)</td>
<td>1.75 (0.73-4.17)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Selected secondary

- All cause mortality                   | 236 (4.1) | 262 (4.5) | 0.90 (0.76-1.07) | 0.24    |

<sup>1</sup>B+A Group = benazepril + amlodipine group;  <sup>2</sup>B+H Group = benazepril + HCTZ group;  <sup>3</sup>Primary composite endpoint includes all individual endpoints listed below in that section


ACCOMPLISH – Discussion

- Reduction in primary endpoint
- No reduction in all cause mortality or stroke
- Blood pressure 131.6/73.3 mmHg vs 132.5/74.4 mmHg (BA vs BH) (p < 0.001)
- Only 37.3% had controlled hypertension at enrollment
- High risk population with goals < 130/80 mmHg
- Bottom line
  - Amlodipine + ACE-I is effective in reducing adverse outcomes associated with hypertension
  - Amlodipine + ACE-I is an effective option for the treatment of hypertension
- Can these results be extrapolated to monotherapy?
- Even with generic amlodipine, patient cost can still be an issue
ONTARGET

• 25,620 patients
  – CAD
  – Cerebrovascular disease
  – Diabetes
• Treatment groups (3)
  – Ramipril 10 mg
  – Telmisartan 80 mg
  – Combination Therapy (Ramipril 10 mg/Telmisartan 80 mg)
• Endpoints
  – 1° - CV Death, MI, Stroke, HF hospitalization
  – Main 2° - CV Death, MI, Stroke (same as HOPE)

Conclusions

• ACE-I/ARB no better than monotherapy at reducing CV events in high-risk patients
• Combination therapy increased risk of AEs
  – Renal impairment (p < 0.001)
  – Hypotensive symptoms (p < 0.001)
  – Hyperkalemia (p < 0.001)
Practical Considerations for Primary Care

• Get patient involved with home monitoring
• Educate patient about disease
  – Intense education by pharmacists as part of a systematic education program has shown improved BP reduction
• Medication selection
  – Consider compliance rates
    • Highest for ARBs & ACE-1’s
  – Consider adverse effects
    • May play a role in compliance
  – Combination tablets
    • Generic components
    • Convert once titration has occurred if possible

Conclusion & Summary of Treatment Recommendations

• Consider lower goal BP targets for some high-risk patients
• Goal BP target of < 130/80 may not be warranted in all patients with DM
• Avoid beta blockers as first line treatment for essential hypertension without CAD
• Thiazide diuretics are linked to a higher rate of development of DM
• ACE-I/ARB combination therapy should not be used for the treatment of hypertension
On the Horizon

Other Potential Therapies

• Endothelin type A Receptor Antagonist
  – Phase II trials currently ongoing
  – Adverse effects may limit use to resistant hypertension only

• Angiotensin II type 1/Endothelin type A antagonist
  – Phase II trial ongoing

• Angiotensin II Vaccine
  – Phase II trial showed modest BP reduction
  – Long-term duration may limit use
  – Clinical application questionable at this point
Information on DOIs

• DOI
  – Digital object identifier
  – More reliable than web addresses as they do not change overtime
  – Unique to the work, not the web address
  – May find works by using a DOI Resolver
• www.doi.org

Evidence Based Practice Guidelines on the Treatment of Hypertension

David Stewart, Pharm.D., BCPS
Assistant Professor, Pharmacy Practice
stewardw@etsu.edu