Hypertension Update: Focus on Pharmacotherapy

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Learning Objectives:
At the end of the presentation, learners should be able to:

1) Describe and define several basic facts about the epidemiology and pathophysiology of hypertension

2) Describe and explain fully the goals and overall approach to managing patients with hypertension with an emphasis on pharmacotherapeutic issues

3) Discuss current JNC 7 issues and evidenced-based support for their recommendations (and modifications based on recent studies)

4) Outline salient features of pharmacotherapeutic agents commonly used to treat patients with hypertension and be able to develop a rationale for their selection for specific patients
JNC 7 Guidelines for Hypertension

- Goal: To reduce CV morbidity and mortality through prevention and management of hypertension
- JNC 7 Guidelines (2003)

<table>
<thead>
<tr>
<th>Category</th>
<th>SBP (mm Hg)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Prehypertension</td>
<td>120-139</td>
<td>80-89</td>
</tr>
<tr>
<td>Hypertension, Stage 1</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Hypertension, Stage 2</td>
<td>≥ 160</td>
<td>≥ 100</td>
</tr>
</tbody>
</table>

Classification of Blood Pressure

Adapted from the JNC 7 Slide Deck. Available at: http://www.nhlbi.nih.gov.

Framingham Study - CV Events and BP

Women

Optimal: <120 and <80,
Normal <130 and <85,
High normal 130-139 or 85-89 (JNC VI)

**BP Category and 1st Major CV Event**

- **Women**
  - Optimal: [Data Point]
  - Normal: [Data Point]
  - High Normal: [Data Point]
- **Men**
  - Optimal: [Data Point]
  - Normal: [Data Point]
  - High Normal: [Data Point]


**Opt: <120/80**

**NL: 120-129/80-84**

**High NL: 130-139/85-89**

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**Age-Adjusted Relative Risk for CHD Death**

Multiple Risk Factor Intervention Trial

---
Estimated 10-Year Risk (%) of Coronary Artery Disease for Various Combinations of Risk Factors for Men and Women

<table>
<thead>
<tr>
<th>BP Systolic</th>
<th>Cholesterol</th>
<th>HDL-C</th>
<th>Diabetes</th>
<th>Cigarettes</th>
<th>LVH by ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>220</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>160</td>
<td>260</td>
<td>50</td>
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<td>35</td>
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<td>+</td>
<td>+</td>
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<td>260</td>
<td>35</td>
<td>+</td>
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MRFIT: Impact of Elevated SBP and Total Cholesterol on CHD Mortality (N=316,099)

Target Organ Damage in Hypertension

- Stroke
- Retinopathy
- Decreased arterial compliance
- Renal impairment

Adapted from JNC V. Arch Intern Med. 1993;1563:154.

Lowering BP Is Imperative in Reducing Cardiovascular Risk

In clinical trials, antihypertensive therapy has been associated with reductions in:

- Myocardial Infarction: 20%-25%
- Stroke: 35%-40%
- Heart Failure: >50%

JNC 7 Express. 2003. NIH Publication 03-5233.
JNC - 7

The Seventh Report
of the
Joint National Committee on Prevention, Detection, Evaluation, and Treatment of
High Blood Pressure
Web Site

JNC 7 Highlights

• For patients older than 50 years, SBP >140 mm Hg is a more important CVD risk factor than DBP
• Patients with pre-hypertension require health-promoting lifestyle modifications to prevent CVD
• Thiazide-type diuretics should be used in drug treatment for most patients with uncomplicated hypertension, either alone or in combination with drugs from other classes
• High-risk conditions are compelling indications for the initial use of specific antihypertensive drug classes
• Most patients will require 2 or more antihypertensive agents to reach their goal blood pressure
• If BP is >20/10 mm Hg above goal, consideration should be given to initiating therapy with 2 agents, one of which should usually be a thiazide-type diuretic

JNC 7 Guidelines for Hypertension

- Goal: To reduce CV morbidity and mortality through prevention and management of hypertension
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</table>

Benefits of Lowering BP

- In stage 1 HTN and additional CVD risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated

<table>
<thead>
<tr>
<th></th>
<th>Average Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Incidence</td>
<td>35-40%</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>20-25%</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>50%</td>
</tr>
</tbody>
</table>
Patient Evaluation

Evaluation of patients with documented HTN has three objectives

1. Assess lifestyle and identify other CV risk factors or concomitant disorders that affects prognosis and guides treatment

2. Reveal identifiable causes of high BP

3. Assess the presence or absence of target organ damage and CVD

*Controlled BP = SBP <140 mm Hg and DBP <90 mm Hg.

Adapted from JNC 7. JAMA. 2003;289:2560-2572.
Major CVD Risk Factors: JNC 7

- Hypertension*
- Cigarette smoking
- Physical inactivity
- **Obesity (body mass index ≥30 kg/m²)***
- Dyslipidemia*
- Diabetes mellitus*
- **Microalbuminuria or estimated GFR <60 mL/min**
- Age (>55 years for men, >65 for women)
- Family history of premature CVD (men aged <55 or women aged <65 years)

*Components of the metabolic syndrome.
Yellow = modifiable, Underline = new from JNC 6

Identifiable Causes and Target Organ Damage

**Identifiable Causes:**
- Sleep apnea, drug induced, chronic kidney disease, primary aldosteronism, renovascular disease, chronic steroid therapy and Cushing’s syndrome, pheochromocytoma, coarctation of the aorta, thyroid or parathyroid disease.

**Target Organ Damage:**
- Heart: (LVH, Angina or prior MI, Prior revascularization, Heart failure)
- Brain: (Stroke or TIA)
- Chronic Kidney Disease
- Peripheral Arterial Disease
- Retinopathy

Laboratory Tests

- **Routine Tests:**
  - ECG
  - UA
  - Blood glucose, and hematocrit
  - Serum Potassium, creatinine, or the corresponding estimated GFR and Ca
  - Lipid profile, after 9-12 hour fast, that includes HDL, LDL and TG

- **Optional Tests:**
  - Measurement of Urinary albumin excretion or albumin/creatinine ratio
  - More extensive testing for identifiable causes not generally indicated unless BP control is not achieved

Adapted from the JNC 7 Slide Deck. Available at: http://www.nhlbi.nih.gov.

Goals of Therapy

- **Reduce CVD and renal morbidity and mortality**
- **Treat to BP < 140/90 mmHg or BP < 130/80 mmHg in patients with diabetes or chronic kidney disease**
- **Achieve SBP goal especially in persons ≥50 years of age**

Adapted from the JNC 7 Slide Deck. Available at: http://www.nhlbi.nih.gov.
JNC 7: Lifestyle Modification

<table>
<thead>
<tr>
<th>Modification</th>
<th>Approximate SBP reduction (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Reduction</td>
<td>5-20 mmHg/10Kg wt loss</td>
</tr>
<tr>
<td>Adopt DASH eating plan</td>
<td>8-14 mmHg</td>
</tr>
<tr>
<td>Dietary sodium reduction</td>
<td>2-8 mmHg</td>
</tr>
<tr>
<td>Physical activity</td>
<td>4-9 mmHg</td>
</tr>
<tr>
<td>Moderation of alcohol consumption</td>
<td>2-4 mmHg</td>
</tr>
</tbody>
</table>

Adapted from the JNC 7 Reference Card. Available at: http://www.nhlbi.nih.gov.

JNC 7 Algorithm for Treatment

- Algorithm for Treatment of Hypertension
- Lifestyle Modifications
- Not at Goal Blood Pressure (<140/90 mmHg)
- (<130/80 mmHg for patients with diabetes or chronic kidney disease)
- Initial Drug Choices
- Without Compelling Indications
- With Compelling Indications
- Drug(s) for the compelling indications
- See Compelling Indications for Individual Drug Classes
- Other antihypertensive drugs (diuretics, ACEI, ARB, BB, CCB) as needed.
- Not at Goal Blood Pressure
- Optimize dosages or add additional drugs until goal blood pressure is achieved. Consider consultation with hypertension specialist.

Adapted from the JNC 7 Slide Deck. Available at: http://www.nhlbi.nih.gov
JNC 7: Compelling Indications for Individual Drug Classes

<table>
<thead>
<tr>
<th>Compelling Indication</th>
<th>Recommended Drug Classes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>THIAZ, BB, ACEI, ARB, ALDO ANT</td>
</tr>
<tr>
<td>Post-myocardial infarction</td>
<td>BB, ACEI, ALDO ANT</td>
</tr>
<tr>
<td>High CVD risk</td>
<td>THIAZ, BB, ACEI, CCB</td>
</tr>
<tr>
<td>Diabetes</td>
<td>THIAZ, BB, ACEI, ARB, CCB</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>ACEI, ARB</td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>THIAZ, ACEI</td>
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Adapted from the JNC 7 Reference Card. Available at: http://www.nhlbi.nih.gov.

Compelling Indications for Individual Drug Classes: JNC 7

<table>
<thead>
<tr>
<th>Compelling Indication</th>
<th>Recommended</th>
<th>Clinical Trial Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>DIUR, BB, ACEI, ARB, ALDO-ANT</td>
<td>ACC/AHA Heart Failure Guideline, MERIT-HF, COPERNICUS, CIBIS, SOLVD, AIRE, TRACE, ValHEFT, RALES, CHARM</td>
</tr>
<tr>
<td>Post-myocardial infarction</td>
<td>BB, ACEI, ALDO ANT</td>
<td>ACC/AHA Post-MI Guideline, BHA, SAVE, Capricorn, EPHEUS</td>
</tr>
<tr>
<td>High CAD risk</td>
<td>ALLHAT, HOPE, ANBP2, LIFE, CONVINCE</td>
<td>DIUR, BB, ACE, CCB</td>
</tr>
</tbody>
</table>

Adapted from Chobanian et al. JAMA. 2003; Vol 289, No 19: 2560-2572.
## Compelling Indications for Individual Drug Classes: JNC 7

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<th>Clinical Trial Basis</th>
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</thead>
<tbody>
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<td>Diabetes</td>
<td>DIUR, BB, ACE, ARB, CCB</td>
<td>NKF-ADA Guideline, UKPDS, ALLHAT</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>ACEI, ARB</td>
<td>NKF Guideline, Captopril Trial, RENAAAL, IDNT, REIN, AASK</td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>DIUR, ACEI</td>
<td>PROGRESS</td>
</tr>
</tbody>
</table>

Adapted from Chobanian et al. JAMA. 2003; Vol 289, No 19: 2560-2572.

## Studies Supporting the Guidelines

- ALLHAT, ANBP2, VALUE ASCOT-BPL
- MERIT-HF, VALHFT, CHARM
- LIFE, LIFE Substudy
- HOPE, Micro-HOPE
- IDNT RENAAAL
- AASK
Treatment Diabetes: Diabetes Care 29;S4-S42:2006

- Initial drug therapy for those with a blood pressure >140/90 should be with a drug class demonstrated to reduce CVD events in patients with diabetes (ACE inhibitors, ARBs, β-blockers, diuretics, calcium channel blockers). (A)
  - All patients with diabetes and hypertension should be treated with a regimen that includes either and ACE inhibitor or ARB (E)

Hypertension Management in Adults with Diabetes (Diabetes Care, Vol 29 S4-S42, Supplements Jan 2006)

Treatment Cont.

- If ACE inhibitors or ARBs are used, monitor renal function and serum potassium levels. (E)

- While there are no adequate head-to-head comparisons of ACE inhibitors and ARBs, there is clinical trial support for each of the following statements:
  - In patients with type 1 diabetes with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. (A)
  - In patients with type 2 diabetes, hypertension, and microalbuminuria, ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. (A)
  - In those with type 2 diabetes, hypertension, macroalbuminuria (>300 mg/day), and renal insufficiency, an ARB should be strongly considered. (A)

Hypertension Management in Adults with Diabetes (Diabetes Care, Vol 29, S4-S42, Jan 2006)
Diagnostic Criteria for Albuminuria

- Standard urine dipsticks are not sensitive enough to detect microalbuminuria

<table>
<thead>
<tr>
<th>Albuminuria</th>
<th>Spot Specimen (mcg/mL)</th>
<th>Spot Specimen (mcg/mg Cr)</th>
<th>24-hr Timed Specimen (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normo-</td>
<td>&lt; 20</td>
<td>&lt; 30</td>
<td>&lt; 30</td>
</tr>
<tr>
<td>Micro-</td>
<td>20-200</td>
<td>30-299</td>
<td>30-299</td>
</tr>
<tr>
<td>Macro-</td>
<td>&gt; 200</td>
<td>≥ 300</td>
<td>≥ 300</td>
</tr>
</tbody>
</table>


JNC 7: Goals for Prevention and Management of Hypertension

- Reduce morbidity and mortality by least intrusive means possible
  - SBP <140 mm Hg and DBP <90 mm Hg (<130/80 for diabetics)
  - SBP/DBP below these levels if treatment is tolerated
  - Control other modifiable risk factors

Follow-up and Monitoring

- Patients should return for follow-up and adjustment of medications until the BP goal is reached
- More frequent visits for stage 2 HTN or with complicating comorbid conditions
- Serum potassium and creatinine monitored 1-2 times per year
- After BP at goal and stable, follow-up at 3-6 month intervals
- Comorbidities, such as heart failure, associated diseases, such as diabetes, and the need for laboratory tests influence the frequency of visits

HOT: Cardiovascular Events in Diabetes Patients and DBP Level


<table>
<thead>
<tr>
<th>Event</th>
<th>≤90 mm Hg DBP</th>
<th>≤85 mm Hg DBP</th>
<th>≤80 mm Hg DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>7.5</td>
<td>4.3</td>
<td>3.7</td>
</tr>
<tr>
<td>Stroke</td>
<td>9.1</td>
<td>7.0</td>
<td>6.4</td>
</tr>
<tr>
<td>CV Mortality</td>
<td>11.1</td>
<td>11.2</td>
<td>3.7</td>
</tr>
<tr>
<td>All Mortality</td>
<td>15.9</td>
<td>15.5</td>
<td>9.0</td>
</tr>
</tbody>
</table>

*P* = .016
### Additional Considerations in Antihypertensive Drug Choices

**Potential favorable effects:**
- Thiazide diuretics useful in slowing demineralization in osteoporosis
- BBs useful in the treatment of atrial tachyarrhythmias/fibrillation, migraine, thyrotoxicosis (short term), essential tremor, or perioperative HTN
- CCBs useful in Raynaud’s syndrome and certain arrhythmias
- Alpha-blockers useful in prostatism.

### Additional Considerations in Antihypertensive Drug Choices

**Potential unfavorable effects:**
- Thiazide diuretics should be used cautiously in gout or history of significant hyponatremia
- BBs should be generally avoided in patients with asthma, reactive airway disease or second or third-degree heart block
- ACEIs and ARBs are contraindicated in pregnant women or those likely to be come pregnant
- ACEIs should not be used in individuals with a history of angioedema
- Aldosterone antagonists and K-sparing diuretics can cause hyperkalemia
Selected Side Effects With Hypertensive Medications

- **Beta Blockers**
  - Bronchospasm
  - Bradycardia
  - Heart failure
  - May mask insulin-induced hypoglycemia

- **Calcium Channel Blockers**
  - Edema of the ankle
  - Headache
  - Gingival hypertrophy

- **ACE Inhibitors**
  - Cough (common)
  - Angioedema (rare)
  - Hyperkalemia (rare)
  - Rash (rare)
  - Loss of taste (rare)

- **ARBs**
  - Angioedema (very rare)

**Less Serious:**
- Impaired peripheral circulation
- Insomnia
- Fatigue
- Decreased exercise tolerance
- Hypertriglyceridemia
  *Dihydropyridine
  *Except agents with intrinsic sympathomimetic activity


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Multiple Antihypertensive Agents Are Often Needed to Achieve Target BP

<table>
<thead>
<tr>
<th>Trial</th>
<th>Target BP (mm Hg)</th>
<th>No. of antihypertensive agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>DBP &lt;85</td>
<td>1</td>
</tr>
<tr>
<td>ABCD</td>
<td>DBP &lt;75</td>
<td>2</td>
</tr>
<tr>
<td>MDRD</td>
<td>MAP ≤92</td>
<td>3</td>
</tr>
<tr>
<td>HOT</td>
<td>DBP ≤80</td>
<td>4</td>
</tr>
<tr>
<td>AASK</td>
<td>MAP ≤92</td>
<td></td>
</tr>
<tr>
<td>IDNT</td>
<td>SBP ≤135/DBP ≤85</td>
<td></td>
</tr>
<tr>
<td>ALLHAT</td>
<td>SBP ≤140/DBP ≤90</td>
<td></td>
</tr>
</tbody>
</table>

DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure.

1. UKPDS 38. BMJ. 1998;317:703-713.
Benefits of Combination Therapy

- Combinations of low-dose agents from different classes have been shown:
  - to provide additional antihypertensive efficacy\textsuperscript{1,2}
  - to minimize the likelihood of dose-dependent adverse events\textsuperscript{2,3}
- Patient adherence is better with once-daily dosing\textsuperscript{2}


Antihypertensive Drug Classes

- Diuretics
- Adrenergic inhibitors (β-blockers, α-blockers, central α-agonists, combined α-β blockers, peripheral agents)
- Direct vasodilators
- CCBs (dihydropyridines, nondihydropyridines)
- ACE inhibitors
- Angiotensin II receptor antagonists
- Drug combinations

Diuretics

- Well studied: Class of agents for HTN (SHEP, ALLHAT etc), useful in CHF
- Low acquisition cost
- Proven Mortality benefit (HTN) (SHEP Study)
- MOA: Decrease PVR in the long term
- Monitor for: Hypokalemia, hyperuricemia, hyperglycemia, hypercalcemia, Lipids, gynecomastia (spirionlactone) etc.
- Which Agent?
  - ClCr > 30 ml/min thiazide (all probably work equally well)
  - ClCr < 30 ml/min loop diuretics or combination

Diuretics in Patients With Hypertension

**Advantages**
- Clinical trials showed decre. in cardiovascular morbidity and mortality
- Efficacious in white and African American patients
- Cost-effective

**Disadvantages**
- Require monitoring for adverse effects on serum potassium/glucose/lipids
- In high doses, incr. risk for hyperglycemia/other metabolic abnormalities

GFR= glomerular filtration rate.
**β-Blockers for Hypertension**

- **Mechanism:** reduce cardiac work by negative inotropic, negative chronotropic and hypotensive (central and renin blocking) effects
- **Pharmacologic Issues:** High first pass, modest half-life, variable protein binding, cardioselectivity (dose dependent), intrinsic sympathomimetic activity, alpha-blockade
- **Monitor:** SE’s are extension of pharmacologic effects, bradycardia, hypotension, CHF, depression, abrupt withdrawal, impotence, diabetes *(Signs and Symptoms)* lipid effects (decrease HDL, incr. trigs), reactive airway disease
- **Outcomes:** Several studies on outcomes in the area of Hypertension with/without diuretics or other agents (STOP-hypertension) and with post AMI, in CHF etc.

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**Beta Blocking Agents**

- **Non-Selective**
  - - ISA
  - + ISA
  - Nadolol
  - Propranolol
  - Timolol
  - Pindolol
  - Carteolol
  - Penbutolol

- **Selective**
  - - ISA
  - + ISA
  - Atenolol
  - Metoprolol
  - Esmolol
  - Betaxolol
  - Bisoprolol
  - Acebutolol
  - Labetalol
  - Carvedilol

*Beta-1 Cardioselective*
β-Blockers in Patients With Hypertension

Advantages

- Clinical trials have showed cardiovascular morbidity and mortality reductions in non-elderly
- Non-ISA b-blockers risk of re-infarction/sudden death in post-MI patients has been demonstrated to be reduced

Disadvantages

- Insulin sensitivity: may lead to glucose intolerance masking signs/symptoms of hypoglycemia
- Non-ISA b-blockers incr. triglycerides
- Contraindicated in patients with asthma, COPD, or 2°/3° heart block
- Meta-analysis: Lindholm Lancet 2005;345:1545-53 comparing beta-blockers with other hypertensives: Risk of stroke was 16% higher than other antihypertensives (sign)


Meta-analysis: Diuretics and β-Blockers in Older Patients

<table>
<thead>
<tr>
<th>Outcome First Drug</th>
<th>No. of Trials</th>
<th>Active Treatment Events/ No. of Patients</th>
<th>Control Events/ No. of Patients</th>
<th>Odds Ratio and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>8</td>
<td>222/5876</td>
<td>412/6661</td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>2</td>
<td>79/1521</td>
<td>178/2678</td>
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<tr>
<td>Stroke Mortality</td>
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<tr>
<td>Diuretics</td>
<td>7</td>
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<td>122/6618</td>
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<td>Cardiovascular Mortality</td>
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<td>227/1521</td>
<td>384/2678</td>
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CCBA’s for Hypertension

- Mechanism: reduce cardiac work by negative chronotropic, negative inotropic and systemic (as well as coronary) vasodilation
- Pharmacologic Issues: relative effects on conduction system, negative inotropism, vasodilatation
- Monitor: EKG intervals, HR, BP, PK-PD interactions with drugs
- Issues: Edema with higher doses of Dihydropyridines, CYP3A4 inhibition of verapamil/diltiazem?
- Outcomes: Several studies (Syst-EUR, Syst-China, HOT, ASCOT-BPL) favoring CCBAs of dihydropyridine type over placebo for ISH, however others (AASK, IDNT may call to question benefits in specific patient populations)

Calcium Channel Blockers in Patients With Hypertension

**Advantages**
- Clinical trials with long-acting DHP CCB showed reduced CV morbidity/mortality in ISH
- Antianginal efficacy (long-acting CCBs)
- Useful in pts with contraindications (COPD, gout) to other drug classes
- Effective in white and African American patients
- ALLHAT- Amlopidine had similar primary outcome to Chlortalidone and superior to beta-blockers and diuretics? (ASCOT-BPL)

**Disadvantages**
- Cardiac conduction abnormalities more common with non-DHP CCBs
- Non-DHP CCBs may have negative effect in heart failure
- Short-acting CCBs should not be used in hypertension
- DHP (and sometimes all) CCBs in higher doses may likely cause edema
  
  **ALLHAT –** Amlodipine had more CHF than Chlortalidone

CCBA’S Chemical Classification

• Benzothiazepines
  – Diltiazem (Cardizem™, Dilacor™, Tiazac™, Others)

• Phenylalkylamines
  – Verapamil (Calan™, Isoptin™, Covera-HS™, others)

• Dihydropyridines
  – Nifedipine (Procardia™, Adalat™)
  – Nicardipine (Cardene™)  Felodipine (Plendil™)
  – Isradipine (DynaCirc™)  Nimodipine (Nimotop™)
  – Amlodipine (Norvasc™)  Bepridil (Vascor™)
  – Nisoldipine (Sular™)

ACE Inhibitors in Patients With Hypertension

Advantages
• Preferred in hypertensive patients with
  – Heart failure due to systolic dysfunction
  – Diabetes (1+2?) proteinuria (see notes)
• Useful after MI with low ejection fraction

Disadvantages
• Cough, especially in women and elderly
• Hyperkalemia, rash, reversible acute renal failure relatively infrequent
• Decr. efficacy in older African Americans
ACE Inhibitors

Practical Notes:
- Initiate with small doses
- continue for > 2-4 wks before assessing benefit
- may take 3-6 months before max. benefit (CHF) but 1-2 months for HTN
SE's – Hypotension (monitor BP)
- Renal Insufficiency (monitor Scr)
- Potassium retention (monitor K)
- Cough
Contraindicated with RAS, angioedema
Conclusions:
- ACE I's represent a significant opportunity for CHF, post-AMI, diabetic nephropathy and HTN

ACE Inhibitors

Non-renin

\[ \text{ANGIOTENSINOGEN} \]

\[ \text{Renin} \]

\[ \uparrow \text{Angiotensin I} \]

\[ \text{ACE} \]

\[ \downarrow \text{ANGIOTENSIN II} \]

\[ \text{ACEI} \]

\[ \downarrow \text{AT}_1 \]

\[ \downarrow \text{AT}_2 \]

\[ \text{AT}_n \]

\[ \uparrow \text{Bradykinin} \]

Inactive peptides
Angiotensin Receptor Blockers (ARBs)

Non-renin

Non-ACE

ANGIOTENSINOGEN

↑Angiotensin I

↑ANGIOTENSIN II

Renin

ACE

Bradykinin

Inactive peptides

AT₁ receptor stimulates:
Vasoconstriction, Cell growth,
Na⁺ retention, Sympathetic activation

ARBs

AT₁

AT₂

ATₙ

Angiotensin Converting Enzyme

RENIN INHIBITORS

ACE INHIBITORS

All ANTAGONISTS

AT₁ Receptor
Classification of Angiotensin II Receptors

AT₁
Sensitive to blockade by:
Losartan, Valsartan, etc.

AT₂
Sensitive to blockade by:
CGP 42112A, PD123177

- Vasoconstriction
- Aldosterone Release
- Cardiac Inotropic Effect
- Vasopressin Release
- Increase SNS Activity
- Decrease Renin Release
- Renal Na⁺ & H₂O Reabsorption
- Cell Growth & Proliferation

- Vasodilation
- Antiproliferation
- Apoptosis
- Bradykinin Release
- Nitric Oxide Release

Angiotensin II Receptor Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>% Bio- available</th>
<th>Effect of Food</th>
<th>T₁/₂ (hrs)</th>
<th>Protein Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan</td>
<td>Cozaar®</td>
<td>33</td>
<td>No</td>
<td>2</td>
<td>99%</td>
</tr>
<tr>
<td>(Metabolite E-3174)</td>
<td></td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>99%</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan®</td>
<td>25</td>
<td>50%↓</td>
<td>6</td>
<td>95%</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Avapro®</td>
<td>60</td>
<td>No</td>
<td>15</td>
<td>90%</td>
</tr>
<tr>
<td>Candesartan</td>
<td>Atacand®</td>
<td>40</td>
<td>No</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(Metabolite CV-11974)</td>
<td></td>
<td>-</td>
<td>-</td>
<td>9</td>
<td>99%</td>
</tr>
<tr>
<td>Telisartan</td>
<td>Micardis®</td>
<td>50</td>
<td>20%↓</td>
<td>13</td>
<td>99%</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>Teveten®</td>
<td>13</td>
<td>25%↓</td>
<td>9</td>
<td>98%</td>
</tr>
</tbody>
</table>
### Angiotensin II Receptor Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand Name</th>
<th>% Bio-available</th>
<th>Effect of Food</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; (hrs)</th>
<th>Protein Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan (Cozaar® Merck, 25 + 50 mg tabs qd-bid)</td>
<td>Cozaar®</td>
<td>33%</td>
<td>No</td>
<td>29</td>
<td>99%</td>
</tr>
<tr>
<td>Valsartan (Diovan®, Novartis, 80 and 160 mg caps qd)</td>
<td>Diovan®</td>
<td>50%</td>
<td>↓</td>
<td>69</td>
<td>95%</td>
</tr>
<tr>
<td>Irbesartan (Avapro® BMS, 150-300mg/d tabs qd)</td>
<td>Avapro®</td>
<td>No</td>
<td>15</td>
<td>90%</td>
<td>99%</td>
</tr>
<tr>
<td>Candesartan (Atacand®, Astra Merck, 4, 8, 16, 32mg tabs (qd-bid))</td>
<td>Atacand®</td>
<td>40%</td>
<td>No</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Telmisartan (Micardis® Boehringer Ing, Glaxo Welcome, 20-80mg tabs qd)</td>
<td>Micardis®</td>
<td>20%</td>
<td>↓</td>
<td>13</td>
<td>99%</td>
</tr>
<tr>
<td>Eprosartan (Teveten®, Astra Merck)</td>
<td>Teveten®</td>
<td>25%</td>
<td>↓</td>
<td>9</td>
<td>98%</td>
</tr>
</tbody>
</table>

**Angiotensin II Receptor Blockers (ARBs)**

- Losartan (Cozaar® Merck, 25 + 50 mg tabs qd-bid)
- Valsartan (Diovan®, Novartis, 80 and 160 mg caps qd)
- Irbesartan (Avapro® BMS, 150-300mg/d tabs qd)
- Telmisartan (Micardis® Boehringer Ing, Glaxo Welcome, 20-80mg tabs qd)
- Candesartan (Atacand®, Astra Merck, 4, 8, 16, 32mg tabs (qd-bid))
- All of available agents are approved for hypertension
  - Hyzaar® is losartan 50 mg/HCT 12.5 mg tablet
  - Diovan HCT® is valsartan + HCT 80/12.5 or 160/12.5 capsules
  - Avilide® is irbesartan + HCT 12.5 or 25mg tablets
Angiotensin II Receptor Blockers (ARBs)

- Similar anti-HTN efficacy to ACE inhibitors and atenolol (perhaps less SE’s and D/C rates)
- Advantages may be in reduced incidence of cough and angioedema (vs. ACE inhibitors) although angioedema has been reported
- Apparently no effects on lipids, fasting glucose although have a significant uricosuric effect
- Hyperkalemia can occur to comparable level as with ACE inhibitors

Angiotensin II Receptor Blockers in Patients With Hypertension

**Advantages**
- Decreased incidence of cough vs. ACE inhibitors
- Alternative for ACE intolerant patients
- Significant uricosuric effect
- Benefits in Type 2 Diabetics
- Benefit in CHF patients (CHARM)

**Disadvantages**
- Limited data on long-term efficacy/safety in clinical practice
- Questions remain about efficacy vs ACE’s in heart failure (ELITE II, Val-HeFT, CHARM)
- Similar to ACE inhibitors wrt K+ sparing
Cough: ARBs vs Enalapril

**Percent of patients experiencing cough**

<table>
<thead>
<tr>
<th></th>
<th>Enalapril</th>
<th>Irbesartan</th>
<th>Losartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (%)</td>
<td>13.1*</td>
<td>2.5</td>
<td>15.1*</td>
<td>4.3</td>
</tr>
<tr>
<td>n = 61</td>
<td>n = 121</td>
<td>n = 199</td>
<td>n = 200</td>
<td>n = 60</td>
</tr>
<tr>
<td>Patients (%)</td>
<td>0.7</td>
<td>4.3</td>
<td>3.0</td>
<td>0.7</td>
</tr>
<tr>
<td>n = 137</td>
<td>n = 199</td>
<td>n = 200</td>
<td>n = 60</td>
<td>n = 137</td>
</tr>
</tbody>
</table>

* P < .01


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Irbesartan Safety Profile: Comparable to Placebo

Selected adverse events often associated with antihypertensive therapy occurring in more than 1% of patients in placebo-controlled trials

![Graph showing adverse event comparison](#)

- **Placebo** (n = 641)
- **Irbesartan** (n = 1,965)

Selected adverse events:

- Headache
- Musculo-skeletal pain
- Dizziness
- Cough
- Nausea/vomiting
- Edema

Data on file.
### $\alpha_1$-Blockers in Patients With Hypertension

**Agents:** Doxazosin (Cardura®), Prazosin (Minipress®), Terazosin (Hytrin®), Tamsulosin (Flomax®)

**Advantages**
- Useful in patients with dyslipidemia: neutral or beneficial effect on lipids
- Useful in patients with hypertension and benign prostatic hypertrophy

**Disadvantages**
- Can produce 1st dose syncope
- Common SEs (5-20%): Dizziness, headache, lethargy, palpitations
- Orthostatic hypotension can occur
- Early termination of doxazocin arm of ALLHAT due to negative outcome (higher HF, stroke, CVD risk) of doxazocin vs. chlorthalidone (JAMA 2000:283;1967-75)
Centrally acting $\alpha_2$-Agonists in Patients With Hypertension

- **Agents:** Clonidine (Catapress®), Guanabenz, Guanfacine, Methyldopa (Aldomet®)
- **Advantages**
  - Clonidine has a very quick onset and useful for hypertensive urgencies
  - Clonidine also has a patch form that is applied once a week improving adherence to therapy for select patients
  - Methyldopa is a useful antihypertensive during pregnancy
- **Disadvantages**
  - Many frequent (5-40%) SEs limit the use of these agents (e.g. Dry mouth, drowsiness, dizziness, constipation, weakness, nausea & vomiting, agitation, orthostatic hypotension)
  - Abrupt withdrawal of therapy results in a rapid (24-48hr) rebound hypertension

Peripherally Acting Adrenergic Blockers

- **Agents:** Guanadrel, Guanethidine, Reserpine
- **Advantages**
  - Reserpine is generally well tolerated at low doses
  - Low Cost
- **Disadvantages**
  - Common SEs (5-40%) for Guanadrel, Guanethidine: significant orthostatic hypotension, syncope, diarrhea, drowsiness, fatigue, decreased ejaculation, peripheral edema, nasal stuffiness, cough, palpitations, SOB, leg cramps
  - Reserpine SEs: Nasal congestion, activation of PUD \(\rightarrow\) Avoid in PUD patients. Dose related depression \(\rightarrow\) Avoid in patients with depression history
Direct Vasodilators

- **Agents**: Hydralazine, Minoxidil

- **Advantages**
  - Both are potent vasodilators
  - Hydralazine IV is a safe choice for eclampsia
  - Minoxidil could be added to a regimen in case of a resistant hypertension

- **Disadvantages**
  - Minoxidil SEs: Hirsutism, transient ECG (T wave) changes
  - Hydralazine common SEs: Headache, nausea / vomiting, diarrhea,
  - Reflex tachycardia and RAAS activation for both

Combination Drug Therapy

Rational for the use of combination agents:

1. Maximize antihypertensive efficacy
   - utilizing different pharmacologic agents
   - block opposing actions of each entity
2. Minimize side effects
   - block the predictable side effects from the single entity buy using dual therapy
3. Rarely cost more than individual agents (reduces co-pay)
4. Improves compliance (less # of drugs to take)
### Summary by Drug Class

- **Diuretics:**  
  - Supported by JNC 7 and evidence (SHEP, STOP-HTN ALLHAT etc.)
- **Beta-Blockers:**  
  - Supported by JNC VI and evidence (SHEP, STOP-HTN etc.)  
  - Supported by evidence of co-morbidities (AMI, CHF)  
- **ACE Inhibitors:**  
  - Supported by ADA Guidelines (general for Diabetics) and Evidence (HOPE, AASK)  
- **Calcium Channel Blockers**  
  - Supported by Evidence (Syst-Eur, Syst-China, ASCOT-BPL)  
- **ARBs:**  
  - Supported by guidelines (ADA for type 2 diabetics with microalbuminuria-IDNT, IRMA 2, RENAAL), Alternative to ACE inhibitors for CHF (if intolerant to ACE I’s, some comparative HTN data with b-blockers-LIFE)  
- **Others:**  
  - alpha blockers (not for HTN only- ALLHAT)

### Essentials of Hypertension: Summary

- Fundamental basis for aggressive management of blood pressure is established  
- Guidelines for selection of drug classes must be considered as guide for most patients  
- Special populations (eg. Diabetics) may require specific approaches with multiple drugs  
- Too many patients are less than optimally managed for hypertension and other risk factors for CVD