Hypertension 2013: Latest Diagnostic and Treatment Options

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Objectives

• Upon completion of this lecture, the participant will be able to:
  – Identify complications associated with hypertension
  – Discuss the JNC VII guidelines
  – Discuss pharmacologic options for the treatment of hypertension

CVD Is the Most Common Health Problem in the United States

Evolution in Understanding Cardiovascular Disease: Total Risk Perspective

CVD disease mortality trends for males and females

Evolution in Understanding Cardiovascular Disease Is an Interplay of Risk Factors

Disclosures

• Speaker Bureau: GSK, Sanofi-Pasteur, Merck, Takeda, Vivus, Boehringer
• Consultant: Vivus, Sanofi-Pasteur, Takeda
Hypertension and Dyslipidemia Contribute to Atherogenesis

- Hypertension
- Dyslipidemia
  - Smooth Muscle Cell Contraction
  - Impaired Vasodilation
  - Endothelial Dysfunction
  - Atherosclerosis

Impact of Elevated SBP and Total Cholesterol on CHD Mortality in MRFIT

- Age-Adjusted CHD Death Rates Per 10,000 Person-Years

<table>
<thead>
<tr>
<th>Cholesterol Quintile (mg/dL)</th>
<th>SBP Quintile (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.7</td>
<td>182-202</td>
</tr>
<tr>
<td>22.6</td>
<td>203-220</td>
</tr>
<tr>
<td>12.3</td>
<td>221-244</td>
</tr>
<tr>
<td>8.3</td>
<td>245+</td>
</tr>
<tr>
<td>5.5</td>
<td>&lt;182</td>
</tr>
</tbody>
</table>

Hypertension and Dyslipidemia: A Significantly Undertreated Syndrome

- 27 million affected by both hypertension and dyslipidemia
- 14.7 million undiagnosed
- 3 million treated for both
- 9 million diagnosed with both

Impact of Hypertension

- 50 million individuals in the United States have hypertension
- 277,000 deaths annually in US due to hypertension

Hypertension Remains One of the Most Important Multipliers of CV Risk

- BP >140/90 mm Hg is associated with:
  - 277,000 deaths in 2003

It is currently estimated that...

- 90% of normotensive 55 year olds will develop hypertension at some point in his/her lifetime
Statistics

• Nearly 30% of all hypertensive individuals are unaware of their condition
  – 42% are not being treated with antihypertensive medication
  – 69% do not have their blood pressure (BP) controlled to the level recommended by JNC 7. 1,2
• The prevalence of hypertension will continue to increase as the population ages unless effective preventive actions are implemented.

Hypertension and Management: Old School

Hypertension = Systemic disease
Hemodynamics altered
Treat the blood pressure

Therapeutic options

Beta Blockers ACE ARB Diuretics CCB Others

Hypertension and Management: New School

Hypertension = Disease of the blood vessels
Vascular biology altered
Treat the vasculature

Therapeutic options

Beta Blockers ACE ARB Diuretics CCB Others

Physiology of the Renin Angiotensin System

RAAS and Adipose Tissue

• All components of the RAAS system are expressed in adipose tissue, especially the visceral adipose tissue1,2,3
• Visceral adipose tissue of patients with insulin resistance and Type 2 diabetes is dysfunctional and is a source of chronic low-grade inflammation4

1 Sowers, James R. Insulin Resistance and Hypertension Physiol Heart Circ Physiol 2004;206: H1597-H1602
3 Kershaw EE, Flier JS. Adipose Tissue as an Endocrine Organ Clin Endocrinol Metab. 2004; 98:2548-2556.

RAAS and Endothelial Dysfunction

• Growing body of evidence
  – Promotion of endothelial dysfunction
  – Microalbuminuria1-2
• RAAS Inhibition (ACE, ARB and Direct Renin Inhibitor)
  – Decreased incidence of new onset Type 2 diabetes
  – Improvement in CVD outcomes3

1 Wright, 2013
2 Wright, 2013
3 Wright, 2013
4 Wright, 2013
Today –
The Hypertensive Patient Exhibits...
• More insulin resistance
• More hyperinsulinemia
• Dyslipidemia
• Microalbuminuria
• Obesity
...as compared to nonhypertensive patients!


Blocking the RAAS has been shown to be beneficial in...

Cardiovascular Disease
Hypertension
Diabetes

JNC VII:
Messages to Clinicians


New Messages JNC VII
• The risk of CVD, beginning at 115/75 mm Hg, doubles with each increment of 20/10 mm Hg.


CV Disease Risk Doubles with Each 20/10 mm Hg BP Increment*

CV Disease Risk

SBP/DBP (mm Hg)
115/75 135/85 155/95 175/105
0 1 2 3 4 5 6 7 8

*Individuals aged 40-70 years, starting at BP 115/75 mm Hg.
CV, cardiovascular; SBP, systolic blood pressure; DBP, diastolic blood pressure

Diagnosis
• 2 readings; separated apart
• Patient should not ingest caffeine or smoke for 30 minutes before readings
• Patient should sit for 5 minutes with arm at heart level before blood pressure is checked
**JNC 7: New Blood Pressure Classification**

<table>
<thead>
<tr>
<th>Blood Pressure Classification</th>
<th>SBP*</th>
<th>DBP* (mm Hg)</th>
</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>Stage 1 hypertension</td>
<td>140-159</td>
<td>90-99</td>
</tr>
<tr>
<td>Stage 2 hypertension</td>
<td>≥160</td>
<td>or ≥100</td>
</tr>
</tbody>
</table>

*Treatment determined by highest BP category (SBP or DBP).


**Prehypertension**

- Individuals with a systolic BP of 120-139 mm Hg or a diastolic BP or 80-89 mm Hg should be considered as prehypertensive and lifestyle modification initiated.

**Most Cases of Hypertension**

- Primary hypertension
  - Also called essential
  - Responsible for 90-95% of all hypertension diagnoses

**Consider Secondary Causes of HTN**

- Sleep apnea
- Drug-induced or drug related
  - Including OTC medications
- Chronic kidney disease
- Polycystic kidneys
- Renal artery stenosis
- Primary aldosteronism
- Renovascular disease
- Chronic steroid therapy and Cushing’s disease
- Pheochromocytoma
- Coarctation of the Aorta
- Thyroid or parathyroid disease

**What about White-Coat Hypertension?**

- Patient involvement in the measurement of his/her blood pressure is recommended, particularly for those individuals whose blood pressure is normal out of the office but consistently elevated in the office
- The office blood pressure of elders is 5 mm Hg higher than their ambulatory blood pressure
- Older the individual, the greater the discrepancy between home and office blood pressures
- No longer considered a benign condition

**Initial Work-up**

- History and review of systems
  - Medications and risk factors
- Consider home blood pressure readings with validated blood pressure cuff
- Laboratory workup: CBC, BUN, Creatinine, Glucose, Lipids, GFR, urine - protein
- EKG and/or Echocardiogram, if indicated
- Urine for microalbuminuria

Treatment of Hypertension

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How Helpful is control of BP?
In stage 1 HTN, combined with additional CVD risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated.

JAMA. 2003;289:2560-2577.

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Benefits of Lowering Blood Pressure
Average Percent Reduction

Stoke: 35% - 40%
MI: 20% - 25%
CHF: 50%

Assessed 5-1-08

Treatment Goals
• < 140/90 mm Hg for those with no complications
• < 130/80 mm Hg for those with diabetes or CRF (per ADA)
• < 130/80 mm Hg – all individuals per NKF

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AHA 2011 Expert Consensus Document on Hypertension in Elderly
• Age 65 - 79 years:
  – 140/90 mm Hg systolic blood pressure is reasonable
• Age 80 years of age and older:
  – Systolic BP of 150 mm Hg in people
• Lower blood pressure goals is also reasonable, if well tolerated

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JNC 7: Algorithm for Treatment of Hypertension

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LIFESTYLE MODIFICATIONS
If not at goal BP, optimize dosages or add additional drugs until goal BP is achieved. Consider consultation with hypertension specialist.
Therapeutic Lifestyle Changes

Lifestyle Modifications to Manage Hypertension

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Systolic Diastolic Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Reduction</td>
<td>BMI 18.5-24.9 Diet rich in fruits and low fat</td>
<td>5-20mm/10 kg wt loss 8-14 mm Hg</td>
</tr>
<tr>
<td>Adopt DASH eating</td>
<td>vegetables and low fat with reduced saturated and total fat</td>
<td>2-8 mm Hg 4-9 mm Hg</td>
</tr>
<tr>
<td>Dietary Sodium</td>
<td>2.4g Na Brisk exercise 30” day most days of week</td>
<td>2-4 mm Hg</td>
</tr>
<tr>
<td>Physical Inactivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderation of Alcohol intake</td>
<td>2 drinks day max 24 oz beer; 10 oz wine 2 oz 100 proof whiskey</td>
<td></td>
</tr>
</tbody>
</table>


Lifestyle Modifications

- Dietary sodium reduction
  - Most helpful in African Americans and patients with diabetes
  - Recommend limiting sodium to < 2000 mg/day for these individuals
    - Average individual ingests 4000 mg / day
  - ACE inhibitors and diuretics work best with a relatively low sodium diet

How Successful Is It?

- Combination of the DASH diet and a dietary sodium reduction to 1600 mg/day is as effective as 1 medication

New Messages JNC VII

- The most effective therapy prescribed by the most careful clinician will control hypertension only if the patient is motivated.


Alcohol Intake

- Limit alcohol intake to < 30 mL or 1 ounce of ethanol/day
  - Translation: 2 ounces of whiskey
  - 10 ounces of wine
  - 24 ounces of beer

- Excessive amounts increases treatment resistance
- Also increases risk of a CVA
  - Women: ½ this amount
Electrolytes

- Diets high in potassium, calcium and magnesium are associated with a lower blood pressure
- JNC VII recommends an adequate dietary intake of these but does not recommend supplementing from an outside source to lower blood pressure

Additional Recommendations

- Omega-3 fatty acids may lower blood pressure
- Caffeine may increase it but tolerance often develops
  - Most studies do not support a relationship between hypertension and caffeine
- Smoking: discontinuation is important
- Exercise: 30 minutes daily recommended

Pharmacologic Treatments

New Messages JNC VII

- Thiazide diuretics should be used in drug treatment for patients with uncomplicated hypertension.

Thiazide Diuretics

- Dosing:
  - Start @ 12.5 mg of HCTZ
  - Increase to 25 mg at 6 weeks
- Benefits
  - 55% reduction in CHF
  - 37% reduction in CVA
  - 27% reduction in cardiac events
- If not adequately controlled, add additional agents

Chlorthalidone

- Making a come back into thiazide arena
- Dosage: 25 mg once daily
- May increase dosage to 100 mg once daily
Decreased Efficacy

- When GFR decreases below 30 mL/min, thiazide diuretics are likely ineffective
- Consider changing to loop diuretic at that time

Diuretic Precautions

- Electrolyte imbalances
- Syncope/presyncope when combined with ACE/ARB
- Hemoconcentration
- Decrease in urate excretion
- Worsening of insulin resistance at higher doses
- Fatigue

Angiotensin Converting Enzyme (ACE) Inhibitors

- Increased nitric oxide at vessel for vasodilatation
- Improved glucose disposal
- Reduction in LV geometry changes
- Reduction in inflammation
- Stabilization of fibrous cap of lipid lesion
- Decreased proteinuria
- Improves endothelial function
- Reduced mortality in patients with CHF
- Decreases post-MI mortality

ACE Inhibitor Trials

<table>
<thead>
<tr>
<th>Year</th>
<th>CHF</th>
<th>LVD</th>
<th>Post-AMI</th>
<th>AMI</th>
<th>CAD</th>
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<tr>
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<td>2001</td>
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</table>

ACE Inhibitors Precautions

- Hyperkalemia
- Increase in creatinine
- May improve insulin sensitivity
- Decrease in serum Na+ may result in syncope and dizziness when used with diuretics
- Angioedema
- Cough

Effects on Hypoglycemia

- Several studies have shown the ability of ACE inhibition to improve glycemic control – even decrease the risk of hypoglycemia in patients using sulfonylureas.

ACE Inhibitors Are Highly Effective.. But...

If you block the receptor site, you don’t have to worry about the angiotension levels...

Angiotensin Receptor Blockers (ARB’s)

- Utilized since April 1995
- Blocks uptake at receptor site
- Angiotension II produced in locations other than in the lungs
- BP decreased by reducing vascular tone and enhancing NA+ and water clearance

Metabolic Effects of ARB’s

- Metabolically neutral
- No impact on lipids
- No impact on insulin
- No impact on K+
- Lowers uric acid levels
- Minimal side effect profile

Product Inserts accessed 04-20-2009
**ACE vs ARB ONTARGET Trial**

1. **Assess the effects of ACE VS ARB in terms of efficacy**
2. **Assess if the combination ACE & ARB was superior**

**Results:**
- Telmisartan was found to be “noninferior” to ramipril in patients with vascular disease or high risk diabetes
- Combination of these two agents was associated with more adverse events without an increase in benefit.


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**Beta Blockers**

- Reduction in blood pressure
- Decreased contractility
- Decreased heart rate
- Decreased myocardial oxygen demand
- Reduction in LVH
- Reduced arrhythmias

**Beta Blocker Trials**

<table>
<thead>
<tr>
<th>SHEP</th>
<th>Systolic Hypertension in the Elderly Program</th>
<th>Step Approach</th>
<th>Chlorothalidone/Atenolol</th>
<th>Reduced incidence of major CV events and CVA; chlorthalidone decreased CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>STOP HTN 2</td>
<td>Swedish Trial in Old Persons with Hypertension</td>
<td>Beta Blocker Vs CCB VS ACE on CV Morbidity</td>
<td>ACE BB similar efficacy in preventing CV mortality.</td>
<td></td>
</tr>
<tr>
<td>CAPP Project</td>
<td>Captopril Prevention Project</td>
<td>Beta Blocker + Diuretic vs Captopril</td>
<td>Captopril not better than conventional HTN Rx in prevention of CV mortality and mortality; Diabetic patients on captopril did better than BB +Diuretics in decreasing mortality</td>
<td></td>
</tr>
</tbody>
</table>


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**Calcium Channel Blockers**

- Effectively treat systolic hypertension
- May be superior to other antihypertensives for stroke prevention
- Effective in patients with:
  - Comorbid conditions (Raynauds, migraine)
  - Particularly effective in
    - Elderly and African American's

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The Calcium Blockers

**Dihydropyridines**
- Studies of DPH's effects on proteinuria have produced conflicting results.
- NKF recommends that in patients who have diabetes and kidney disease, DPH's should only be used in combination with and ACE or ARB.


**Nondihydropyridines**
- Regression of proteinuria
- Combination of Verapamil + ACE, reduction in proteinuria can be greater than achievable with verapamil alone.
- NKF now recommends adding a NDH to treat hypertension with an ACE inhibitor or an ARB to slow the progression of kidney disease.


Alpha Blockers

- Block postsynaptic $\alpha_1$ Receptors
- Results in vasodilatation
- Relatively inexpensive
- Fair tolerability; May cause postural effects
- Additive agent for Older men to decrease BPH symptomatology
- Add-on agent only
- Should never be used as monotherapy due to increased risk of stroke and CHF


Centrally Acting Blockers

- Stimulates central $\alpha_2$ receptors which results in:
  - Inhibiting efferent sympathetic activity
- Additive agents
- Should be used 3rd or 4th line
  - Examples: Clonidine (catapress, catapress TTS); methyldopa
- Caution: sedation, orthostatic hypotension


Aldosterone Agonists

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Aldosterone Antagonists

- Spironolactone (Aldactone)
- HCTZ / spironolactone (Aldactazide)
- Eplerenone (Inspra)

Aldosterone as a Therapeutic Target

- Aldosterone promotes:
  - Retention of sodium
  - Loss of magnesium and potassium
  - Sympathetic activation
  - Parasympathetic inhibition
  - Baroreceptor dysfunction
  - Impaired arterial compliance


Precautions

- Must monitor electrolytes
- Must obtain baseline renal function
- Should discontinue the K+ supplement
- Should limit to use in severe heart failure and post MI patients


New Classes/Agents

Direct Renin Inhibitor

Renin is the enzyme at the beginning of the RAAS, one of the key regulating centers for blood pressure. Blocking this enzyme can decrease the downstream impact of the RAAS system.

Suppression of the RAAS has been shown to treat hypertension and reduce target organ damage.
Direct Renin Inhibition
Inhibits the Entire Renin System\textsuperscript{1-4}

<table>
<thead>
<tr>
<th>Class</th>
<th>PRA</th>
<th>Ang I</th>
<th>Ang II</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct Renin Inhibitor (DRI)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Increased peptide levels have not been shown to overcome the blood pressure-lowering effect of these agents.


Aliskiren

- **Dosage:**
  - 150 mg or 300 mg once daily
- **Indications:**
  - Adults with hypertension

Warning re: Aliskiren

- Do not combine with ACE or ARB
- Avoid use of valsartan
  - Aliskiren and valsartan
- Warning followed after early termination of the ALTITUDE trial
  - Offered no benefit and was associated with an increased risk of CVA’s

European Medicines Agency

- The EMA has announced plans to review all aliskiren products and, until the results of this review are available, it has recommended that:
  - Aliskiren-containing medicines should not be prescribed to diabetic patients who are also taking an ACE inhibitor or an ARB
  - Prescribers should review patients taking aliskiren at a routine (non-urgent) appointment and, if patients are diabetic and are also taking ACE inhibitors or ARBs, aliskiren should be stopped and alternative treatments considered

New Messages JNC VII

- Certain high risk conditions are compelling indications for the initial use of other antihypertensive drug classes.
  - Angiotensin-converting enzyme inhibitors
  - Angiotensin-receptor blockers
  - Beta blockers
  - Calcium channel blockers

JNC 7: Compelling Indications for Individual Antihypertensive Drug Classes

<table>
<thead>
<tr>
<th>Compelling Indication*</th>
<th>Recommended Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DIURETIC</strong></td>
<td><strong>BB</strong></td>
</tr>
<tr>
<td>Heart failure</td>
<td>●</td>
</tr>
<tr>
<td>Post-MI</td>
<td>●</td>
</tr>
<tr>
<td>High coronary disease risk</td>
<td>●</td>
</tr>
<tr>
<td>Diabetes</td>
<td>●</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>●</td>
</tr>
<tr>
<td>Recurrent stroke prevention</td>
<td>●</td>
</tr>
</tbody>
</table>

*Compelling indications are based on benefits from outcome studies or existing clinical guidelines; the compelling indication is managed parallel with the BP.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; Aldo ANT = aldosterone antagonist; BB = beta-blocker; CCB = calcium channel blocker.

Adapted from NHBPEPCC. 2003. NIH Publication No. 03-5233.
Combination Therapy

JNC 7 (2003)
Combination Therapy

- Most hypertensive patients will require two or more antihypertensive medications to achieve goal BP (<140/90 mm Hg or <130/80 mm Hg in patients with diabetes/renal disease)
- Initiating therapy with combination therapy should be considered when BP is >20/10 mm Hg above goal.

Assessed 5-1-08

JNC 7 (2003)
Combination Therapy

- "When BP is more than 20/10 mm Hg above goal, consideration should be given to initiating therapy with two drugs, either as separate prescriptions or in fixed-dose combinations."
- "Failure to titrate or combine medications, despite knowing the patient is not at goal BP, represents clinical inertia and must be overcome."

Multiple Antihypertensive Agents Are 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 &lt;92</td>
<td>3</td>
</tr>
<tr>
<td>HOT</td>
<td>DBP &lt;80</td>
<td>4</td>
</tr>
<tr>
<td>AASK</td>
<td>MAP &lt;92</td>
<td></td>
</tr>
<tr>
<td>IDNT</td>
<td>SBP &lt;135/DBP &lt;86</td>
<td></td>
</tr>
</tbody>
</table>

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

Target Organ Damage

- Heart
  - LVH, Angina, CHF, MI
- Brain
  - Stroke or TIA
  - Dementia
- Chronic Kidney Disease
- Peripheral Vascular Disease
- Retinopathy

JAMA. 2003;289:2560-2577.
Pick the agent wisely

• Benefits are not the same in antihypertensive therapy at the same commensurate blood pressure control.

American Heart Association Scientific Sessions 2003; November 9-12, 2003, Orlando, Florida, USA.

Thank You For Your Time and Attention!

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