Hypertension and Hyperlipidemia: Latest Diagnostic and Treatment Options

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Disclosures
• Grants: Novartis, Daiichi-Sankyo
• Speaker Bureau: Ortho-McNeil, Abbott, Novartis, GSK, Sanofi-Pasteur, Daiichi-Sankyo, Merck

Objectives
• Upon completion of this lecture, the participant will be able to:
  – Identify the various classifications of prehypertension, Stage 1 and Stage 2 hypertension; and the optimal ranges for various lipid parameters
  – Discuss nonpharmacologic treatment options for the patient with hypertension and hyperlipidemia
  – Discuss pharmacologic treatment options for the patient with hypertension and hyperlipidemia
CVD Is the Most Common Health Problem in the United States

More than 60 million Americans (20%) have some form of cardiovascular disease.


CVD disease mortality trends for males and females


Source: NCHS and NHLBI.

Evolution in Understanding Cardiovascular Disease: Total Risk Perspective

Cardiovascular Disease Is an Interplay of Risk Factors

Hypertension and Dyslipidemia Contribute to Atherogenesis

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

Hypertension and Dyslipidemia: A Significantly Undertreated Syndrome

Adapted from Neaton JD et al. Arch Intern Med. 1992;152:56-64.
MRFIT = Multiple Risk Factor Intervention Trial.
Adapted from American Heart Association.
Impact of Hypertension

- 50 million individuals in the United States have hypertension\(^1\)
- 277,000 deaths annually in US due to hypertension\(^2\)

1. American Association of Clinical Endocrinologists Medical Guidelines For Clinical Practice for the Diagnosis and Treatment of Hypertension. Endocrine Practice, Vol 12 No. 2 March/April 2006

Hypertension Remains One of the Most Important Multipliers of CV Risk

BP >140/90 mm Hg is associated with:

- 277,000 deaths in 2003

BP, blood pressure; CHF, congestive heart failure; MI, myocardial infarction.

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It is currently estimated that...

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

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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

Adapted from Vascular Biology Working Group, University of Florida College of Medicine, Carl Pepine, MD, Director

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

Adapted from Vascular Biology Working Group, University of Florida College of Medicine, Carl Pepine, MD, Director
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 tissue.1,2,3
- Visceral adipose tissue of patients with insulin resistance and Type 2 diabetes is dysfunctional and is a source of chronic low-grade inflammation4

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

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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.

JAMA. 2003;289:2560-2577.

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

![Graph showing CV disease risk increase with BP increments](graph.png)

*Individuals aged 40-70 years, starting at BP 115/75 mm Hg.

3. Wright, 2012

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* DBP* (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>≤120 and ≤80</td>
</tr>
<tr>
<td><strong>Prehypertension</strong></td>
<td>120-139 or 80-89</td>
</tr>
<tr>
<td><strong>Stage 1 hypertension</strong></td>
<td>140-159 or 90-99</td>
</tr>
<tr>
<td><strong>Stage 2 hypertension</strong></td>
<td>≥160 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.

*JAMA. 2003;289:2560-2577.*

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

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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

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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

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Treatment of Hypertension

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.

1 in 11 Treated!

Benefits of Lowering Blood Pressure

Average Percent Reduction

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

JNC 7: Algorithm for Treatment of Hypertension

LIFESTYLE MODIFICATIONS

Not at Goal BP (<140/90 mm Hg, or <130/80 mm Hg for patients with diabetes or chronic kidney disease)

INITIAL DRUG CHOICES

Stage 1 Hypertension (SBP 140-159 or DBP 90-99 mm Hg)
- Thiazide-type diuretics for most; may consider ACEI, ARB, BB, CCB, or combination.

Stage 2 Hypertension (SBP ≥160 or DBP ≥100 mm Hg)
- 2-drug combinations for most (usually thiazide-type diuretics and ACEI, or ARB, or BB, or CCB).

Drug(s) for compelling indications
- Other antihypertensive drugs (diuretic, ACEI, ARB, BB, CCB) as needed.

If not at goal BP, optimize dosages or add additional drugs until goal BP is achieved. Consider consultation with hypertension specialist.
New Messages JNC VII

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


Lifestyle Modifications to Manage Hypertension

<table>
<thead>
<tr>
<th>Modification</th>
<th>Recommendation</th>
<th>Systolic Diastolic Chgs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Reduction</td>
<td>BMI 18.5-24.9 Diet rich in fruits vegetables and low fat with reduced saturated and total fat</td>
<td>5-20mm/10 kg wt loss 8-14 mm Hg</td>
</tr>
<tr>
<td>Adopt DASH eating</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dietary Sodium</td>
<td>2.4g Na Brisk exercise 30” day most days of week</td>
<td>2-8 mm Hg 4-9 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>2-4 mm Hg</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

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.
  
  *JAMA. 2003;289:2560-2577.*
**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

**Diuretic Precautions**

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

*Product inserts accessed 04-20-2008*
Angiotensin Converting Enzyme (ACE) Inhibitors

- Increased nitrous 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>Anterior</th>
<th>AMI</th>
<th>AMI</th>
<th>CAD</th>
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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

Product inserts accessed 04-20-2009

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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...

Long Term Effect of Enalapril (20mg) on Plasma ACE and Angiotensin II

* = p<0.001 versus placebo

Modified from: Journ Cardiovasc Pharm 1982; 966-72
If you block the receptor site, you don’t have to worry about the angiotension levels…

Angiotensin Receptor Blockers

- 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

* Angiotensin II Receptor Blockers
  * 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

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ARB Trials

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<td>Renal/CV</td>
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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.

Blockers

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


Beta Adrenergic Receptors

- 3 receptors are found in human cardiac myocytes that are coupled to a positive inotropic response and cell growth.
  - Beta_1
  - Beta_2
  - Alpha_2

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Beta Blocker Trials

<table>
<thead>
<tr>
<th>SHEP</th>
<th>Systolic Hypertension in the Elderly Program</th>
<th>Step Approach 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-BS similar efficacy in preventing CV mortality.</td>
</tr>
<tr>
<td>CAPPP</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 morbidity and mortality; Diabetic patients on captopril did better than BP +Diuretics in decreasing mortality</td>
</tr>
</tbody>
</table>

Wright, 2012
Calcium Channel Blockers

- Effectively treat systolic hypertension
- May be superior to other antihypertensives for stroke prevention
- Effective in patients with:
  - Comorbid conditions (Raynauds, migraine) ¹
- Particularly effective in
  - Elderly and African American’s ²


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 Alpha1 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

Assessed 5-1-08

Wright, 2012
Centrally Acting Agents

- 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

Direct Vasodilators

- Direct smooth muscle vasodilatation, primarily arteriolar
- Two agents
  - Apresoline (Hydralazine)
  - Minoxidil
  **Precautions include: tachycardia, significant peripheral edema and hair growth
  **Agents to reduce heart rate may be needed
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

Aldosterone Antagonists

- May be recommended in the following individuals:
  - Post MI
  - NYHA Class III or IV
  - Ejection fraction of < 35%
  - Serum creatinine of < 2.5 mg/dl
  - K+ < 5.0 mmol/L

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>
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<tr>
<td>ARB</td>
<td></td>
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<tr>
<td>Direct Renin Inhibitor (DRI)</td>
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</tbody>
</table>

Increased peptide levels have not been shown to overcome the blood pressure-lowering effect of these agents. ACEI, angiotensin-converting enzyme inhibitor; Ang, angiotensin; ARB, angiotensin receptor blocker; PRA, plasma renin activity.


Aliskiren

- **Dosage:**
  - 150 mg or 300 mg once daily

- **Indications:**
  - Adults with hypertension
New Warning re: Aliskiren

- Do not combine with ACE or ARB
- Avoid use of valturin
  - Aliskiren and valdastaran
- 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></td>
<td>DIURETIC</td>
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<tr>
<td>Heart failure</td>
<td>●</td>
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<tr>
<td>Post-MI</td>
<td>●</td>
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<tr>
<td>High coronary disease</td>
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<td>risk</td>
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<td>Diabetes</td>
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<td>Chronic kidney disease</td>
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<tr>
<td>Recurrent stroke</td>
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</tbody>
</table>

*Compelling indications for antihypertensive drugs 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**

When you put your hand in the cabinet...
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.


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>
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<tr>
<td>ABCD</td>
<td>DBP &lt;75</td>
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<tr>
<td>MDRD</td>
<td>MAP &lt;92</td>
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<td>AASK</td>
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<tr>
<td>IDNT</td>
<td>SBP &lt;135/DBP &lt;85</td>
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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

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

Pick the agent wisely

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

Many Patients Are Not Reaching Their LDL-C Goal

LDL Is the Primary Target

- LDL is the primary target of reduction
  - All should be < 100
- Anyone with an LDL > 160 – candidate for pharmacotherapy
- Only exception is the patient with triglycerides > 400 – 500
  - Then...target triglycerides first
  - Reduce LDL as second goal
ATP III Recommendations

- Persons with diabetes without CHD raised to level of CHD risk equivalent
- Same for patients with CVD, PVD, aortic aneurysm and chronic renal failure
  - This means LDL must be reduced to under 70


Landmark Statin Trials: LDL-C Levels vs Events

- Primary prevention
- Pravastatin: 5.4 (210) vs 2.3 (90) 2.8 (110) 3.4 (130) 3.9 (150) 4.4 (170) 4.9 (190)
- Lovastatin: 9
- Atorvastatin: 10

[Modified from Kastelein JJP. Atherosclerosis. 1999;143(suppl 1):S17-S21]

The Problem with Estimating LDL-C

Estimated or Friedewald LDL-C = TC – HDL-C – TG/5
- Assumes TG to Cholesterol ratio in each VLDL particle is a constant
- Breaks down when TG > 200 or < 100
- Breaks down if you do not fast
- Breaks down when LDL is low

When LDL is 93 mg/dL, then Friedewald is 15% falsely low*
When LDL is 61 mg/dL, then Friedewald is 19% falsely low*

What About HDL?

- Low HDL-C: <40 mg/dL in men
  - < 50 mg/dL in women
- Targets of therapy:
  - all persons with low HDL-C: achieve LDL-C goal; then decrease weight, increase physical activity
  - those with TG <200 mg/dL: consider drugs for raising HDL-C (fibrates, nicotinic acid)

Important To Talk About Latest AHA Addendum

- HDL elevated to > 50 as optimal for women
  - For women whose HDL is < 50; Niacin is recommended or fibrate therapy
  - Guidelines also say...dietary supplement niacin "must not be substituted for prescription niacin"

Emerging Risks

- Particle size
  - Provides us with the size and total number of the LDL lipoproteins
  - Small dense LDL
    - Susceptible to oxidation
    - Associated with increased vascular permeability
  - Associated with insulin resistance syndrome
  - What about HDL?
    - Size matters also HDL_2 (Larger): Most protective
    - HDL_3 (Small) – Less protective
Basic Lipid Panel – Abnormal
TC= 123
LDL = 77
HDL = 24
Trigs = 162
Advanced Lipoprotein Panel Highly Abnormal

**Insulin Resistant**
Abundance of Lg VLDL
Abundance of LDL Small
Abundance of HDL Small

Highly Atherogenic

Insulin Resistance Syndrome
Structure of HDL

Surface
Monolayer of Phospholipids and Free Cholesterol

Hydrophobic Core
of Triglyceride and Cholesterol Esters


The HDL Molecules(s)

Industrial Strength
Most protective

Dust Buster
Least protective

Wright, 2012
hsCRP

- CRP is hepatically derived family of proteins that are nonspecific, acute-phase reactant proteins
  - CRP normally circulates at very low levels
  - Acute inflammatory processes, infections, or tissue injuries induce a marked increase in hepatic synthesis of CRP, which can induce a 100-fold serum increase

hsCRP

• Atherosclerosis is now linked in part to chronic, low-level inflammation of the vascular endothelium
• Hence, the association with elevated levels of hsCRP


Studies Regarding C-reactive Protein

• 3 year study
• 28,000 postmenopausal healthy women
• High-sensitivity CRP: strongest single predictor of future cardiac events
• Highest levels of ultrasensitive CRP: 5 fold increased risk of developing CHD and a 7 fold increase of having an MI or stroke


Additional Studies

• Ridker et al. 1998 found an increased risk of cardiovascular events in patients with a baseline hsCRP of 6.6 when compared with a level of 1.2 mg/L
  –75% greater risk of cardiovascular events
Study Regarding Obesity and hsCRP

• Human fat cells produce a protein that is linked to both inflammation and an increased risk of heart disease and stroke
• Explains why people who are overweight generally have higher levels of the C-reactive protein (CRP)

Willerson, J.T. et. al. Journal of the American College of Cardiology; September 2005

Who Should Be Tested for hsCRP?

• Individuals who, according to the Framingham Risk Assessment Tool, are at an intermediate risk for the development of cardiovascular disease (10 – 20% risk)

www.aha.org accessed 01/28/07

Who Should Be Tested for hsCRP?

• Not for widespread screening of the general adult population; continue to focus on major risk factors, such as high blood pressure, high cholesterol, smoking and diabetes
• Useful as an independent marker of risk and as a “discretionary tool” in the evaluation of those with moderate cardiovascular disease risk to determine treatment course

www.aha.org accessed 01/28/07
Other Expert’s Disagree....

- Many experts believe that this test should be conducted on all patients
  - 36 studies to date have been conducted on the link between hsCRP and CAD
  - All 36 studies have shown a positive relationship
    - PHS, WHS, MONICA, ARIC, NHS, HPFS, CHS, EPIC-Norfolk, PIMA are just a few of the studies to show a positive correlation between elevated hsCRP and increased risk for CAD

Laboratory Measurements

- hsCRP
  - < 1.0 mg/L - low risk of developing cardiovascular disease
  - 1.0 and 3.0 mg/L - average risk
  - > 3.0 mg/L - high risk
  - In the past, it was said that if hsCRP is > 10 mg/L; it was unlikely to be related to cardiovascular inflammation

  **NO LONGER BELIEVED TO BE TRUE!!**

- High vs. Low hsCRP

  - This study showed that approximately 10% of the population has an hsCRP level that is undetectable.
  - These individuals have an incredibly low event rate and low plaque rupture rate
  - Individuals with hsCRP > 10 – 20 had the highest event rate (about 7 fold higher than the individual with a low hsCRP)
How Do We Treat hsCRP?

- **Lifestyle modification**
  - Dietary and exercise modifications leading to weight reduction
  - Smoking cessation

- **Weight loss**
  - 12 weeks of a low-fat diet, hsCRP decreased by 26% in healthy obese women
  - Does this reduce events?? Stay tuned.....


How Do We Treat hs-CRP?

- **Statins**
  - Can reduce hsCRP by 29% - 50% (fluvastatin ER)
  - In another study, simvastatin, pravastatin and fluvastatin all reduced CRP by 45%, 66% and 76%
  - Best outcomes may be LDL < 70 mg/dL and hsCRP < 2 mg/L


What is the Target?

- **PROVE-IT TIMI 22 Trial**
  - Patients were randomized to 40 mg/day of pravastatin vs. 80 mg/day of atorvastatin
  - Reducing hsCRP to < 2 mg/L improved event-free survival in all patients with ACS regardless of LDL levels
  - Lowering hsCRP < 2 was protective even when the LDL was > 70 mg/dL

Internal Medicine World Report, March 2005
What is the Target?

- **REVERSAL** Trial
  - 502 patients with documented CHD
  - Randomized to 40 mg/day of pravastatin vs. 80 mg/day of atorvastatin
    - Patients randomized to atorvastatin had less progression of atherosclerosis
  - Reducing hsCRP levels provided a benefit in atherosclerosis progression that was independent of the LDL lowering


Treating hsCRP

- Niacin has been shown to reduce hsCRP
- Aspirin has also been shown to reduce hsCRP
- TZD’s and ACE inhibitors can reduce hsCRP
- Omega-3 fatty acids can reduce hsCRP

HMG CoA Reductase Inhibitors

- **Action**
  - Inhibit the HMG CoA reductase enzyme
  - Enzyme is essential for the synthesis of cholesterol
  - Also increases the uptake of LDL by the liver
  - Additional properties:
    - Smooth muscle cell proliferation, platelet aggregation and deposition, fibrinogen, endothelial vasodilation and blood viscosity are also affected by the statins
    - May indicate that these medications should be used with diabetes, hypertriglyceridemia, and for stroke prevention

Recent Landmark Coronary Prevention Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Duration (Years)</th>
<th>Main Findings</th>
<th>Event Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>simvastatin</td>
<td>5</td>
<td>↓↓ ↓↓ 30% total mortality ↓↓ ↓↓ 34% coronary events*</td>
<td>69</td>
</tr>
<tr>
<td>WOS</td>
<td>pravastatin</td>
<td>5</td>
<td>↓↓ ↓↓ 31% coronary events</td>
<td>70</td>
</tr>
<tr>
<td>CARE</td>
<td>pravastatin</td>
<td>5</td>
<td>↓↓ ↓↓ 24% coronary events ↓↓ ↓↓ 31% stroke</td>
<td>77</td>
</tr>
<tr>
<td>AFCAPS/TexCAPS</td>
<td>lovastatin</td>
<td>5</td>
<td>↓↓ ↓↓ 37% coronary events/ unstable angina</td>
<td>76</td>
</tr>
<tr>
<td>LIPID</td>
<td>pravastatin</td>
<td>6</td>
<td>↓↓ ↓↓ 22% total mortality ↓↓ ↓↓ 24% death from CHD</td>
<td>78</td>
</tr>
</tbody>
</table>

Events* in the Major Prevention Trials

<table>
<thead>
<tr>
<th>Event % Reduction</th>
<th>Event % Not Avoided</th>
</tr>
</thead>
<tbody>
<tr>
<td>69</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td></td>
</tr>
<tr>
<td>77</td>
<td></td>
</tr>
<tr>
<td>76</td>
<td></td>
</tr>
<tr>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>
Important Information

- Statins may increase risk of diabetes
  - Studies now confirm this in both men and women
- Statins may be administered to children age 10 and up with markedly elevated LDL's unresponsive to traditional therapy
- Rule of 6's
- Newest statin: pitavastatin (Livalo)
- No longer need to monitor liver enzymes on scheduled basis; clinician judgement

Why Are We Reducing Events By Only 24%

- 80% of individuals are on monotherapy with statins
  - Majority of individuals are in need of combination therapy
- Must consider each component of the lipid panel independently
  - A great LDL does not negate the risks associated with a low HDL
  - A great HDL does not negate the risks associated with a high LDL
- Target LDL 1st – unless trigs > 400 – 500
- Then target - HDL

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CORONARY HEART DISEASE RISK
HDL vs. LDL as a Predictor

Data from Framingham Study

Risk of CHD After 4 Yrs

HDL (mg/dl)

LDL (mg/dl)

---

Risk of coronary heart disease over 4 years of follow-up for men ages 50 to 70.
Framingham Data...

- This landmark study very clearly demonstrated that for every 4 mg/dL HDL is decreased, there is a 10% increase in CAD
- This is independent of any other risk factors

Framingham Offspring Study: Multiplier for HDL-Cholesterol Level*

<table>
<thead>
<tr>
<th>HDL cholesterol</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>1.82</td>
<td>—</td>
</tr>
<tr>
<td>35</td>
<td>1.49</td>
<td>—</td>
</tr>
<tr>
<td>40</td>
<td>1.22</td>
<td>1.94</td>
</tr>
<tr>
<td>45</td>
<td>1.00</td>
<td>1.55</td>
</tr>
<tr>
<td>50</td>
<td>0.82</td>
<td>1.25</td>
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<tr>
<td>55</td>
<td>0.67</td>
<td>1.00</td>
</tr>
<tr>
<td>60</td>
<td>0.55</td>
<td>0.80</td>
</tr>
<tr>
<td>65</td>
<td>0.46</td>
<td>0.64</td>
</tr>
<tr>
<td>70</td>
<td>—</td>
<td>0.52</td>
</tr>
</tbody>
</table>

*Relative increase or decrease of CHD risk according to HDL cholesterol value. Multiply the patient’s general risk by the number opposite the HDL cholesterol value.

Nicotinic Acid

- Examples
  - Niacin (Immediate release)
  - Niaspan (Extended release)
Niacin – OTC Preparations

- Recent study of "NO flush Niacin" products revealed:
  - None of the 8 products marketed as no flush niacin had any niacin in them

Mechanism of Action of Niacin

\[ \text{Niacin} \quad \downarrow \quad \text{Adipose tissue} \quad \downarrow \quad \text{FA mobilization} \quad \downarrow \quad \text{FA synthesis/esterification} \quad \downarrow \quad \text{TG synthesis} \quad \downarrow \quad \text{Assembly of Apo B containing Lipoproteins} \quad \uparrow \quad \text{Apo B degradation} \quad \downarrow \quad \text{VLDL, LDL} \]

\[ \text{Niacin} \quad \downarrow \quad \text{HDL-catabolism} \quad \downarrow \quad \text{HDL-Apo A-1 Uptake/removal} \quad \uparrow \quad \text{Apo A-1/reverse Cholesterol Transport} \]

VA-HIT Results: Major Study Showing HDL Improvement Does Matter!

\[ \begin{array}{c|c|c|c|c|c|c}
\% \text{ Change} & \% & 6\% & 4\%* & -23\%* & -22\%** & -29\%* \\
\end{array} \]

* \text{p} \leq 0.05
** \text{p} = 0.07
† Investigator designated


Wright, 2012
**Not Everyone Deserves Niacin**

- Recent information:
  - Individuals with heart disease and LDL < 70 mg/dL show no benefit from increasing HDL with niacin (AIM HIGH TRIAL)
  - High dose Niacin was added to simvastatin
  - Studied was concluded at 18 months when no benefit was seen; followed for 36 months
  - Despite raising HDL, no improved outcomes

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**What About Combination Therapy?**

- Increasingly becoming the norm
- Particularly in individuals with insulin resistance syndrome
- HATS Trial addressed this issue

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**HATS Trial:**

- **HDL--Atherosclerosis Treatment Study**
- 160 CAD patients
  - HDL < 40 mg/dL in women
  - HDL < 35 mg/dL in men
- Randomized
  - Simvastatin (13 mg/d) and niacin (mean 2.4 g/d)
  - Antioxidants (Vitamin E, vitamin C, Beta-carotene, selenium)
- Outcomes
  - CV events (death, MI, stroke, revascularization)
  - Arteriographic change in coronary stenosis
- Follow-up, 3 years
HATS: Conclusions

- In patients with CHD and low HDL-C, combination simvastatin and niacin:
  - Decreased LDL-C by 42% and raised HDL-C by 26%
  - Resulted in a significant regression in mean coronary stenosis (0.4%) and a reduction of coronary events by 89% over 3 years of treatment
  - The combination of simvastatin plus niacin may be beneficial in patients with diabetes

HATS: Clinical Endpoints

- 89% reduction in coronary death, MI, stroke, or revascularization

Wright, 2012
Bile Acid Sequestrants

• “Resins”
• Indications: Hyperlipidemia; Particularly LDL
• Examples:
  – Cholestyramine (Questran)
  – Colestipol (Colestid)
  – Colesevelam HCL (Welchol)

Welchol

• Welchol (Colesevelam HCL)
• Dosage: 625 mg
  – 3 tablets bid or 6 tablets qd; Maximum 7 tablets/day
  • With a statin: 4 – 6 tablets daily
  – Take with food
• Indications
  – Adjunct to diet and exercise to reduce LDL cholesterol
  – May be used alone or in combination with a statin

Welchol

• Results
  – LDL reduction: 2% - 20% (lowest – highest doses)
  – Total cholesterol reduction (8%)
  – HDL improvement (8 – 11%)
  – May increase triglycerides
Bile Acid Sequestrants

- Side effects
  - GI side effects are the most common
  - Elders: may be at risk for a fecal impaction
  - Decreased vitamin/medication absorption
  - May also increase bleeding tendencies

Bile Acid Sequestrants

- Precautions
  - Decreased absorption of thyroxine, digoxin, anticoagulants, thiazide diuretics, propranolol, furosemide, statin drugs
  - Dose these medications 1 hour before or 4 hours after the bile acid binding resins

Fibric Acid Derivatives

- “Fibrates”
- Indications
  - Hypertriglyceridemia with a family history of atherosclerosis
- Examples
  - Lopid (gemfibrozil)
  - Tricor (fenofibrate)
Fibric Acid Derivatives

• Mechanism of Action
  – Increase the clearance of VLDL from the plasma and therefore increase the secretion of cholesterol into bile
• Dosing
  – Lopid (gemfibrozil): 600mg bid
  – Tricor (fenofibrate):
    • 48 mg and 145 mg once daily

Fibric Acid Derivatives

• Results
  – Triglyceride reduction: 20-50%
  – HDL increase: 10-15%
  – LDL +/-
  – Limited data regarding long-term benefits of fibrate therapy
• Side effects
  – Generally well tolerated

Fibric Acid Derivatives

• Side effects
  – Gastrointestinal complaints including nausea, dyspepsia, abdominal and epigastric pain, vomiting
  – Rash
  – Accentuates anticoagulants
  – Elevated LFTs
Significant FDA Warnings

- Combination of fibrate including fenofibric acid (Trilipix) in combination with statin
- Increased risks of rhabdomyolysis

Ezetamibe (Zetia): A Cholesterol Absorption Inhibitor

- Dosage: 10 mg once daily
- Efficacy: 18% reduction in LDL when used as monotherapy
  - When added to a statin – 25% reduction in LDL

Other Therapies
Formerly - Omacor
Now - Lovaza

- Omega-3 Fatty Acids
- 1 gram capsules
- Dosages: 4 capsules daily
- Indications: reduce triglyceride levels in excess of 500 mg/dL
- Precautions: bleeding, anticoagulants
- Side effects: Burping

Fish Oils

- AHA recommending 1 gram per day of fish oils for those with heart disease
- First prescription drug containing omega – 3 fatty acids (EPA and DHA)
- Lowers triglycerides as much as 45%
  - More concentrated (meaning they contain 3x more EPA and DHA than OTC products)

One Regimen

- Flax Seed daily
  - Shown to reduce total cholesterol and LDL
  - No research to support lower morbidity and mortality
- Red Yeast Rice daily
  - Previously equivalent to approximately 10 mg of lovastatin (Mevacor)
  - No longer the case
  - No statin-like active ingredient
Benecol

- Benecol, Right Start, Take Control
  - All spreadable “margarine” like products that have been shown to reduce LDL by approximately 15%
  - Can certainly be added to statin, niacin, fibrate or bile acid sequestrant
- Dosage: 2 – 3 tbsp per day

Advances in the Prevention of CHD

- LDL-C
- HDL-C
- Lipid subclasses
- C-reactive protein
- Combination therapy

Thank You For Your Time and Attention!