Hypertension and Hyperlipidemia 2014: What’s New in the Treatment Guidelines

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Disclosures

• Speaker Bureau: Novartis, GSK, Sanofi-Pasteur, Merck, Takeda, Vivus

• Consultant: Vivus, Sanofi-Pasteur, Takeda
Objectives

- Upon completion of this lecture, the participant will be able to:
  - Identify complications associated with hypertension and hyperlipidemia
  - Discuss the AHA guidelines and JNC VIII guidelines
  - Discuss nonpharmacologic and pharmacologic options for the treatment of hyperlipidemia and hypertension
CVD Is the Most Common Health Problem in the United States

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

Wright, 2014
Evolution in Understanding Cardiovascular Disease: Total Risk Perspective

Cardiovascular Disease is an Interplay of Risk Factors


Wright, 2014
Impact of Hypertension

- Hypertension is the most common condition seen in primary care
- 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.


Wright, 2014
It is currently estimated that...

- 90% of normotensive 55 year olds will develop hypertension at some point in his/her lifetime
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 Wright, 2014
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 Wright, 2014
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 VIII

- Made numerous recommendations regarding treatment
- The following slides will present these recommendations:
Recommendation 1

• In the general population aged ≥ 60 years, initiate pharmacologic treatment to lower BP at systolic blood pressure (SBP) of 150 mmHg or higher or diastolic blood pressure (DBP) of 90 mmHg or higher and treat to a goal SBP lower than 150 mmHg and goal DBP lower than 90 mmHg.

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Recommendation 2

• In the general population < 60 years, initiate pharmacologic treatment to lower BP at DBP of 90 mm Hg or higher and treat to a goal DBP of lower than 90 mmHg
Recommendation 3

- In the general population < 60 years, initiate pharmacologic treatment to lower BP at SBP of 140 mm Hg or higher and treat to a goal SBP of lower than 140 mm Hg.

Wright, 2014
Recommendation 4

- In the population ≥ 18 years or older with CKD, initiate pharmacologic treatment to lower BP at SBP of 140mmHg or higher or DBP of 90mmHg or higher and treat to goal SBP of lower than 140mm Hg and goal DBP lower than 90mmHg.
Recommendation 5

- In the population $\geq$ 18 years or older with diabetes, initiate pharmacologic treatment to lower BP at SBP of 140mmHg or higher or DBP of 90 mm Hg or higher and treat to a goal SBP of lower than 140mmHg and goal DBP lower than 90mmHg.
Treatment of Hypertension
Benefits of Lowering Blood Pressure

Average Percent Reduction

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

Therapeutic Lifestyle Changes
## 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</td>
<td>5-20mm/10 kg wt loss</td>
</tr>
<tr>
<td>Adopt DASH eating</td>
<td>Diet rich in fruits vegetables and low fat with reduced saturated and total fat</td>
<td>8-14 mm Hg</td>
</tr>
<tr>
<td>Dietary Sodium</td>
<td>2.4g Na</td>
<td>2-8 mm Hg</td>
</tr>
<tr>
<td>Physical Inactivity</td>
<td>Brisk exercise 30” day most days of week</td>
<td>4-9 mm Hg</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>


Wright, 2014
2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Adult aged ≥18 years with hypertension
Implement lifestyle interventions (continue throughout management).
Set blood pressure goal and initiate blood pressure lowering medication based on age, diabetes, and chronic kidney disease (CKD).

General population (no diabetes or CKD) → Diabetes or CKD present

Age ≥60 years → Age <60 years

Blood pressure goal SBP < 140 mm Hg DBP < 90 mm Hg
Blood pressure goal SBP < 140 mm Hg DBP < 90 mm Hg
Blood pressure goal SBP < 140 mm Hg DBP < 90 mm Hg
Blood pressure goal SBP < 140 mm Hg DBP < 90 mm Hg

Nonblack → Black

Initiate thiazide-type diuretic or CCB, alone or in combination.
Initiate thiazide-type diuretic or ACEI or ARB or CCB, alone or in combination.
Initiate ACEI or ARB, alone or in combination with other drug class.

Select a drug treatment titration strategy
A. Maximize first medication before adding second or
B. Add second medication before reaching maximum dose of first medication or
C. Start with 2 medication classes separately or as fixed-dose combination.

At goal blood pressure?
Yes
No

Reinforce medication and lifestyle adherence.
For strategies A and B, add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB).
For strategy C, titrate doses of initial medications to maximum.

At goal blood pressure?
Yes
No

Reinforce medication and lifestyle adherence.
Add or titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB).

At goal blood pressure?
Yes
No

Reinforce medication and lifestyle adherence.
Add and titrate additional medication class (eg, β-blocker, aldosterone antagonist, or others) and/or refer to physician with expertise in hypertension management.

At goal blood pressure?
No
Yes

Continue current treatment and monitoring.

Treatment Recommendation

• In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB).

Downloaded From: http://jama.jamanetwork.com/ on 01/19/2014
Treatment Recommendation

- In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB
Treatment Recommendation

• In the population aged 18 years or older with CKD and hypertension, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes.

• This applies to all CKD patients with hypertension regardless of race or diabetes status.

Downloaded From: http://jama.jamanetwork.com/ on 01/19/2014
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

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

Wright, 2014
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
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

Plasma ACE (mmol/ml/min)

Plasma ANG II (pg/ml)

* = p<0.001 versus placebo

Placebo     4h        24h          1           2           3           4           5            6

Hospital Months

Modified from Journ Cardiovasc Pharm 1982; 966-72
If you block the receptor site, you don’t have to worry about the angiotension levels…
Long Term Effect of Enalapril (20mg) on Plasma ACE and Angiotensin II

Plasma ACE (mmol/ml/min)

* = p<0.001 versus placebo

Plasma ANG II (pg/ml)

Placebo 4h 24h 1 2 3 4 5 6

Modified from *Journ Cardiovasc Pharm* 1982; 966-72
**Angiotension 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

Wright, 2014
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
Wright, 2014
<table>
<thead>
<tr>
<th>Year</th>
<th>Trial</th>
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</thead>
<tbody>
<tr>
<td>1995</td>
<td>ELITE I</td>
</tr>
<tr>
<td>1996</td>
<td>ValHeFT</td>
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<td>ELITE II</td>
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<td>1998</td>
<td>CHARM</td>
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<td>MARVAL</td>
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<td>VALUE</td>
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<td>2006</td>
<td>IDNT</td>
</tr>
<tr>
<td>2007</td>
<td>RENAAL</td>
</tr>
<tr>
<td>2008</td>
<td>IPreserve</td>
</tr>
</tbody>
</table>

Wright, 2014
# 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.


Wright, 2014
Calcium Channel Blockers
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\(^2\)


Wright, 2014
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.

Treatment Recommendation

- If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the following:
  - Thiazide-type diuretic, CCB, ACEI, or ARB
What About Other Antihypertensives? When Do You Use?
Select a drug treatment titration strategy
A. Maximize first medication before adding second or
B. Add second medication before reaching maximum dose of first medication or
C. Start with 2 medication classes separately or as fixed-dose combination.

At goal blood pressure? Yes
No
Reinforce medication and lifestyle adherence.
For strategies A and B, add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB). For strategy C, titrate doses of initial medications to maximum.

At goal blood pressure? Yes
No
Reinforce medication and lifestyle adherence.
Add and titrate thiazide-type diuretic or ACEI or ARB or CCB (use medication class not previously selected and avoid combined use of ACEI and ARB).

At goal blood pressure? Yes
No
Reinforce medication and lifestyle adherence.
Add additional medication class (eg, β-blocker, aldosterone antagonist, or others) and/or refer to physician with expertise in hypertension management.

At goal blood pressure? Yes
No
Continue current treatment and monitoring.
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>Study</th>
<th>Description</th>
<th>Approach</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP</td>
<td>Systolic Hypertension in the Elderly Program</td>
<td>Step Approach Chlorthalidone/Atenolol</td>
<td>Reduced incidence of major CV events and CVA; chlorthalidone decreased CHF</td>
</tr>
<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>
</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 BB +Diuretics in decreasing morbidity</td>
</tr>
</tbody>
</table>

Wright, 2014
Alpha Blockers
**Alpha Blockers**

- Block postsynaptic $\text{Alpha}_1$ 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

Assessed 5-1-08

Wright, 2014
Centrally Acting Blockers
Centrally Acting Agents

- Stimulates central alpha$_2$ receptors which results in:
  - Inhibiting efferent sympathetic activity
- Additive agents
- Should be used 3$^{rd}$ or 4$^{th}$ line
  - Examples: Clonidine (catapress, catapress TTS); methyldopa
- Caution: sedation, orthostatic hypotension


Wright, 2014
Aldosterone Agonists

Wright, 2014
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


Wright, 2014
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

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.

Wright, 2014
**Direct Renin Inhibition Inhibits the Entire Renin System**

<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><img src="up.png" alt="Up" /></td>
<td><img src="up.png" alt="Up" /></td>
<td><img src="down.png" alt="Down" /></td>
</tr>
<tr>
<td>ARB</td>
<td><img src="up.png" alt="Up" /></td>
<td><img src="up.png" alt="Up" /></td>
<td><img src="up.png" alt="Up" /></td>
</tr>
<tr>
<td>Direct Renin Inhibitor (DRI)</td>
<td><img src="down.png" alt="Down" /></td>
<td><img src="down.png" alt="Down" /></td>
<td><img src="down.png" alt="Down" /></td>
</tr>
</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.

Warning re: Aliskiren

- Do not combine with ACE or ARB
- Avoid use of valturna
  - Aliskiren and valdasartan
- 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

http://www.pjonline.com/clinical-pharmacist/2012_jan/avoid_aliskiren_with_ACE_inhibitors_and_ARBs accessed 01-12-2012
Combination Therapy

Wright, 2014
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;85</td>
<td></td>
</tr>
</tbody>
</table>

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

Treatment Recommendation: Combination Therapy

- Initiate therapy with 2 drugs simultaneously, either as 2 separate drugs or as a single pill combination
  - For instance: start therapy with $\geq 2$ drugs when SBP is $>160$ mm Hg and/or DBP is $>100$ mm Hg, or if SBP is $>20$ mm Hg above goal and/or DBP is $>10$ mm Hg above goal
- If goal BP is not achieved with 2 drugs, select a third drug from the list (thiazide-type diuretic, CCB, ACEI, or ARB)
- Avoid the combined use of ACEI and ARB
- Titrate the third drug up to the maximum recommended dose.
Target Organ Damage

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

Hyperlipidemia
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and WomenHeart: The National Coalition for Women with Heart Disease

Major Recommendations

Figure 2. Major recommendations for statin therapy for ASCVD prevention

- **ASCVD Statin Benefit Groups**
  - Healthy lifestyle habits are the foundation of ASCVD prevention.
  - In individuals not receiving cholesterol-lowering drug therapy, reevaluate estimated 10-year ASCVD risk every 4-6 years.

- **Clinical ASCVD**
  - Yes → Age ≤ 75 y High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
  - No → Age > 75 y OR if not candidate for high-intensity statin Moderate-intensity statin

- **LDL-C ≥ 190 mg/dL**
  - Yes → High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)
  - No → Moderate-intensity statin

- **Diabetes**
  - Type 1 or 2
    - Age 40-75 y
      - Yes → Estimate 10-year ASCVD risk with Framingham Cohort Equations*
        - Yes → High-intensity statin
        - No → Moderate-to-high intensity statin
      - No → Moderate-intensity statin
    - No → Estimated 10-year ASCVD risk ≤ 27.5% High-intensity statin

- **ASCVD prevention benefit of statin therapy may be less clear in other groups**
  - In selected individuals, consider additional factors influencing ASCVD risks and potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment.
What’s New?

1. *Focus on ASCVD Risk Reduction: 4 statin benefit groups*
   - Based on a comprehensive set of data from RCTs that identified 4 statin benefit groups which focus efforts to reduce ASCVD events in secondary and primary prevention.
   - Identifies high-intensity and moderate-intensity statin therapy for use in secondary and primary prevention.

2. *A New Perspective on LDL–C and/or Non-HDL–C Treatment Goals*
   - The Expert Panel was unable to find RCT evidence to support continued use of specific LDL–C and/or non-HDL–C treatment targets.
   - The appropriate intensity of statin therapy should be used to reduce ASCVD risk in *those most likely to benefit*.
   - Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared to their potential for adverse effects in the routine prevention of ASCVD.

What’s New?

Global Risk Assessment for Primary Prevention

- This guideline recommends use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women.
- By more accurately identifying higher risk individuals for statin therapy, the guideline focuses statin therapy on those most likely to benefit.
- It also indicates, based on RCT data, those high-risk groups that may not benefit.
- Before initiating statin therapy, this guideline recommends a discussion by clinician and patients.

What’s New?

### Safety Recommendations
- This guideline used RCTs to identify important safety considerations in individuals receiving treatment of blood cholesterol to reduce ASCVD risk.
- Using RCTs to determine statin adverse effects facilitates understanding of the net benefit from statin therapy.
- Provides expert guidance on management of statin-associated adverse effects, including muscle symptoms.

### Role of Biomarkers and Noninvasive Tests
- Treatment decisions in selected individuals who are not included in the 4 statin benefit groups may be informed by other factors as recommended by the Risk Assessment Work Group guideline.

Major Recommendations

Four Major Statin Benefit Groups

- Those with clinical ASCVD
- Those with primary elevations of LDL–C > 190 mg/dL
- Those with diabetes aged 40 to 75 years with LDL–C 70 to 189 mg/dL and without clinical ASCVD
- And...those without clinical ASCVD or diabetes with LDL–C 70 to 189 mg/dL and estimated 10-year ASCVD risk >7.5%

Wright, 2014
Let’s Start with Clinical ASCVD

• Definition:
  – Acute coronary syndromes
  – History of MI
  – Stable or unstable angina
  – Coronary or other arterial revascularization
  – Stroke or TIA
  – Peripheral arterial disease presumed to be of atherosclerotic origin


Wright, 2014
Let’s Start with Clinical ASCVD

- What to do....

**Figure 2. Major recommendations for statin therapy for ASCVD prevention**

ASCVD Statin Benefit Groups
Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C 70-189 mg/dL.

- Adults age >21 y and a candidate for statin therapy
  - Yes
  - Clinical ASCVD
  - No

  **Age ≤75 y**
  - Yes
  - High-intensity statin
  - (Moderate-intensity statin if not candidate for high-intensity statin)

  **Age >75 y OR if not candidate for high-intensity statin**
  - Moderate-intensity statin

---

High and Moderate Intensity Statins

- Definitions:

  ![Definitions of High- and Moderate-Intensity Statin Therapy](image)

  - **High**
    - Daily dose lowers LDL–C by approx. ≥50%

  - **Moderate**
    - Daily dose lowers LDL–C by approx. 30% to <50%


Wright, 2014
High, Moderate and Low-Intensity Statins

Let’s operationalize:

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL-C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL-C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL-C on average, by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin (40†)–80 mg Rosuvastatin 20 (40) mg</td>
<td>Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg† Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg</td>
<td>Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

LDL-C > 190 mg/dL

• If yes….high intensity statin:

Diabetes Aged 40 - 75 years with LDL–C 70 to 189 mg/dL and without clinical ASCVD

• What to do:

So How Do You Calculate 10-Y ASCVD Risk?

- Tools available to calculate risk:
  - http://my.americanheart.org/cvriskcalculator

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
## Statins:
### LDL Lowering at Various Doses From Package Inserts

<table>
<thead>
<tr>
<th>Drug</th>
<th>10 mg</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lova Mevacor®</td>
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<tr>
<td>Pravachol®</td>
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<tr>
<td>Simva Zocor®</td>
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<tr>
<td>Fluva Lescol®</td>
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<tr>
<td>Pitava Livalo®</td>
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</tr>
</tbody>
</table>

- **Lova Mevacor®**
  - 20 mg: 29%
  - 40 mg: 31%
  - 80 mg: 48%

- **Pravachol®**
  - 10 mg: 19%
  - 20 mg: 29%
  - 40 mg: 34%
  - 80 mg: 48%

- **Simva Zocor®**
  - 10 mg: 28%
  - 20 mg: 35%
  - 40 mg: 40%
  - 80 mg: 48%

- **Fluva Lescol®**
  - 20 mg: 17%
  - 40 mg: 23%
  - 80 mg: 33%

- **Atorva Lipitor®**
  - 10 mg: 38%
  - 20 mg: 46%
  - 40 mg: 51%
  - 80 mg: 54%

- **Rosuva Crestor®**
  - 5 mg: 43%
  - 10 mg: 50%
  - 20 mg: 53%
  - 40 mg: 62%

- **Pitava Livalo®**
  - 1 mg: 30%
  - 2 mg: 36%
  - 4 mg: 45%

*Wright, 2014*
**Recent Landmark Coronary Prevention Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>Duration (Years)</th>
<th>Main Findings</th>
</tr>
</thead>
</table>
| **4S†**      | simvastatin| 4,444 | 5                | ↓30% total mortality  
|              |            |       |                  | ↓34% coronary events*                                |
| **WOS‡**     | pravastatin| 6,595 | 5                | ↓31% coronary events  
|              |            |       |                  | ↓22% total mortality                                  |
| **CARE† **   | pravastatin| 4,159 | 5                | ↓24% coronary events  
|              |            |       |                  | ↓31% stroke                                          |
| **AFCAPS/ TexCAPS‡ ** | lovastatin | 6,605 | 5                | ↓37% coronary events/unstable angina  
|              |            |       |                  | Low HDL population                                    |
| **LIPID†**   | pravastatin| 9,014 | 6                | ↓22% total mortality  
|              |            |       |                  | ↓24% death from CHD                                   |

* Nonfatal MI/CHD death  
‡ Primary Prevention  
† Secondary Prevention  
** Normal cholesterol levels

* The Lancet 1994;344:1383-1389  
† JAMA 1998;279:1615-1622.  
Wright, 2014
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
CK Measurement

- Baseline measurement of CK is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy.

NO Longer Are We….

- Treating to a target LDL, HDL or triglycerides
- The RCT evidence clearly shows that ASCVD events are reduced by using the maximum tolerated statin intensity in those groups shown to benefit.
- After a comprehensive review, no RCTs were identified that titrated drug therapy to specific LDL–C or non-HDL–C goals to improve ASCVD outcomes.

What About Other Agents??

- The Expert Panel did find RCT evidence that use of therapy (e.g., niacin) to additionally lower non-HDL–C, once an LDL–C target was achieved, did not further reduce ASCVD outcomes.

Essentially….

- The following medications should be used for those who are completely statin intolerant
- Or….who have poor response to statins, despite maximal therapy and are in the highest risk groups (ASCVD, Diabetes, LDL-C ≥190 mg/dL)
  - If benefits outweigh risk and keeping in mind, no evidence to support risk reduction


Wright, 2014
Nicotinic Acid

- Examples
  - Niacin (Immediate release)
  - Niaspan (Extended release)
Mechanism of Action of Niacin

Niacin

↓ Adipose tissue
FA mobilization

↓ FA synthesis/
esterification

↓ TG Synthesis

↓ Large TG-rich
VLDL

↓ Small dense LDL

↓ HDL-catabolism
receptor

↓ HDL Apo A-1
Uptake/removal

↓ Assembly of Apo B containing
Lipoproteins / ↑ Apo B
degradation

↑ Apo A-1/reverse
Cholesterol
Transport

Wright, 2014
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
Recent information:

- HPS2-THRIVE Trial
- The addition of extended-release niacin–laropiprant to statin-based LDL cholesterol–lowering therapy did not significantly reduce the risk of major vascular events but did increase the risk of serious adverse events
- Laropiprant has no cholesterol-lowering effect and is used mainly to decrease flushing associated with niacin (prostaglandin receptor antagonist)

Bile Acid Sequestrants

- "Resins"
- Indications: Hyperlipidemia; Particularly LDL
- Examples:
  - Cholestyramine (Questran)
  - Colestipol (Colestid)
  - Colesevelam HCL (Welchol)

Wright, 2014
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
Fibric Acid Derivatives

• “Fibrates”
• Indications
  – Hypertriglyceridemia with a family history of atherosclerosis
• Examples
  – Gemfibrozil (Lopid)
  – Fenofibrate (Tricor)
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

Wright, 2014
Significant FDA Warnings

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

Wright, 2014
Ezetimibe (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
Combination Therapy

- Ezetimibe and simvastatin (Vytorin)
- Ezetimibe and atorvastatin (Liptruzet)
  - Dosages: 10/10, 10/20, 10/40
- No indication of improved outcomes with ezetimibe

Wright, 2014
Other Therapies
Omega-3 Fatty Acids

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

Wright, 2014
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

Wright, 2014
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
Thank You For Your Time and Attention!
Wendy L. Wright, ARNP
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Thank You

I Would Be Happy To Entertain Any Questions