What’s New in Lipid Therapy?

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Disclosure Statement

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- Brooke Hudspeth, PharmD, has nothing to disclose.
Objectives

- Review current dyslipidemia management strategies and discuss the role of lipoprotein parameters other than LDL or non-HDL in lipid management
- Discuss the results of the ENHANCE trial and how this will effect therapy decisions
- Examine new therapies for treating dyslipidemia that are under active development

Background

- Coronary heart disease (CHD) is the single largest killer of both men and women in the US
- Dyslipidemia (specifically elevated LDL) = major modifiable risk factor for the development and progression of CHD. Thus, LDL-lowering therapy reduces risk for CHD.
- Estimated that > 65 million Americans eligible for lipid modification

Pharmacists’ Role in Lipid Management

- Pharmacy-based lipid management services:
  - 60%-70% of patients at lipid goal
  - *National average ~20%-30%
  - >90% compliance with lipid-lowering therapy
  - *National average ~30%-40%


Lipoprotein Review

- Lipids derived from dietary sources or synthesized by body
  - Cholesterol: Primarily synthesized in liver
  - Triglycerides (TG): Dietary triglycerides account for >75% of total
- These lipids transported to sites of use or storage via Lipoproteins (chylomicrons, VLDL, IDL, LDL, and HDL)
Lipoprotein Review

- **Exogenous Pathway**: Transport system for cholesterol and TG from dietary sources
  - Chylomicrons
    - Primarily TG-bearing lipoproteins

- **Endogenous Pathway**: Transport system for cholesterol and TG secreted by liver
  - VLDL
    - Produced by liver
    - Primary carriers of circulating TG
  - LDL
    - By-products of VLDL metabolism
    - Primary carriers of plasma cholesterol
  - HDL
    - Promotes reverse cholesterol transport
    - Anti-inflammatory

Apolipoproteins

- Provide structural integrity to lipoproteins
- Help to activate certain enzymes
- Bind or dock to specific receptors on surfaces of cells
- apoB
  - Carried by chylomicrons, VLDL, and LDL
- apoAI and apoAII
  - Carried by HDL
Atherosclerosis

- LDL accumulates in subendothelial space of artery and initiates inflammatory response.
- Eventually leads to the formation of foam cells which turn into fatty streaks (initial lesion of atherosclerosis) covered by fibrous caps.
- When the fibrous cap becomes unstable and ruptures, a thrombus develops which leads to CHD.

Derived from http://www.nutrizone.co.za/slides/100/images/ss2s3_JPG.jpg

Comprehensive Evaluation

- Objectives
  1. Determine the magnitude of the future risk of CVD events
  2. Identify the presence of possible modifiable prognostic factors
  3. Establish a treatment plan

Lipid Risk Factors

ATP III Guidelines for Optimal Cholesterol Levels

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Less than 200 mg/dL</th>
<th>200 – 239 mg/dL</th>
<th>Greater than 240 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>Desirable</td>
<td>Borderline High</td>
<td>High</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>Optimal</td>
<td>Above Optimal</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Borderline High</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Very High</td>
<td></td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>Greater than 60 mg/dL</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Less than 40 mg/dL</td>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>

Source: National Cholesterol Education Program, National Institutes of Health

Nonlipid Risk Factors for CHD

- Modifiable
  - Atherogenic Diet
  - Hypertension
  - Hyperglycemia
  - Cigarette smoking
  - Obesity
  - Physical Inactivity

- Non-modifiable
  - Age
    - Men ≥ 45 years
    - Women ≥ 55 years
  - Sex
    - Male gender
  - Ethnicity
  - Family History
    - MI or sudden death in 1st degree
      - Male relative <55
      - Female relative <65
Emerging Risk Factors

- Biomarkers
  - C-reactive protein (CRP)
  - Homocysteine
  - Fibrinogen
  - Lipoprotein(a)

Classification

- Primary
  - Genetic
- Secondary
  - Drugs (i.e. progestins, steroids, protease inhibitors)
  - Diet (i.e. excessive alcohol, saturated fats)
  - Metabolic Disorders (i.e. diabetes, weight gain, anorexia, hypothyroidism)
  - Disease States (i.e. nephrotic syndrome, chronic liver disease)

Stone NJ. Med Clin North Am.1994;78:120
Stone and Blum. Management of Lipids in Clinical Practice. 6th edition. 2006
Risk Assessment and Strategies

- American Diabetes Association
  - DiabetesPHD (Personal Health Decisions)
  - http://www.diabetes.org/diabetesphd/default.jsp
  - Calculates current risk for diabetes and complications (i.e. heart attack, stroke, kidney failure, eye and foot complications) based on patient health history and how making healthy changes could affect future health
- ATP III Guidelines At-A-Glance Quick Desk reference
  - Treatment algorithm for treating lipid disorders
  - 9 step process

Step 1

Determine lipoprotein levels
ATP III Guidelines

- Obtain complete lipoprotein profile after 9- to 12-hour fast
- ATP III recommends that all Americans ≥ 20 have fasting lipid panel performed every 5 years
- More frequent measurements in people with multiple CHD risk factors

Step 2

Identify presence of CHD or CHD risk equivalents
CHD and CHD Risk Equivalents

- Established CHD
- Abdominal Aortic Aneurysm
- Peripheral Arterial Disease
- Carotid Artery Disease
- Diabetes

Step 3
Determine the presence of major risk factors
Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Any cigarette smoking in the past month</td>
</tr>
<tr>
<td>Hypertension</td>
<td>BP $\geq$ 140/90 mmHg or on antihypertensive medication</td>
</tr>
<tr>
<td>Low HDL cholesterol</td>
<td>$&lt;40$ mg/dl</td>
</tr>
<tr>
<td>Family history of premature CHD</td>
<td>CHD in male first degree relative $&lt;55$ years; CHD in female first degree relative $&lt;65$ years</td>
</tr>
<tr>
<td>Age</td>
<td>men $\geq$ 45 years; women $\geq$ 55 years</td>
</tr>
</tbody>
</table>

**Negative Risk Factor**

- High HDL cholesterol $\geq 60$ mg/dl

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Step 4

Assess Short-Term CHD risk
Framingham Point Scores

- If person has $\geq 2$ risk factors (from Step 3) without CHD risk equivalents, perform 10-year risk assessment using Framingham point scores
- Scores based on age, total cholesterol, systolic BP, treatment of hypertension and smoking status
- 3 levels of 10-yr risk:
  - High: $>20\%$ -- CHD risk equivalent
  - Moderate: 10-20\%
  - Low: $<10\%$

Step 5
Determine Risk Category
ATP III Update

- Establish LDL goal of therapy
- Determine need for therapeutic lifestyle changes (TLC)
- Determine level for drug consideration

ATP III Update 2004

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL Goal</th>
<th>LDL level at Which to Initiate TLC</th>
<th>LDL level at Which to Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD or CHD risk equivalents (10-yr risk &gt;20%)</td>
<td>&lt;100 mg/dl (optional goal &lt;70 mg/dl)</td>
<td>≥100 mg/dl</td>
<td>≥100 mg/dl (&lt;100 mg/dl: Consider drug options)</td>
</tr>
<tr>
<td>2+ Risk Factors (10-yr risk ≤20%)</td>
<td>&lt;130 mg/dl (optional goal &lt;100 mg/dl)</td>
<td>≥130 mg/dl</td>
<td>10-yr risk 10-20%: ≥ 130 mg/dl (100-129 mg/dl: Consider Drug options)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10-yr risk &lt;10%: ≥ 160 mg/dl</td>
</tr>
<tr>
<td>0-1 Risk Factor</td>
<td>&lt;160 mg/dl</td>
<td>≥ 160 mg/dl</td>
<td>≥ 190 mg/dl (160-189 mg/dl: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>
Based upon information from 5 recent clinical trials (PROSPER, ALLHAT-LLT, ASCOT-LLA, PROVE IT, HPS), a modified scheme of LDL cholesterol goals and treatment cutpoints were proposed

- No modifications in low-risk patients
- Most recommendations pertaining specifically to patients in high-risk category

**Key Changes**

- **High Risk**
  - LDL cholesterol goal <70 mg/dl therapeutic option, especially in very high risk patients
  - If baseline LDL >100 mg/dl, an LDL-lowering drug is indicated
  - If baseline LDL <100 mg/dl, LDL-lowering drug is therapeutic option
- **Moderately High Risk**
  - LDL goal <100mg/dl therapeutic option
  - LDL 100-129mg/dl, LDL-lowering drug is therapeutic option
- **High Risk and Moderately High Risk**
  - Intensity of LDL-lowering drug therapy sufficient to achieve at least 30% reduction in LDL cholesterol
Step 6

Initiate Therapeutic Lifestyle Changes (TLC)

TLC

- Weight Management
- TLC Diet
  - Saturated fat <7% of calories, cholesterol <200mg/day
  - Increase soluble fiber (10-25g/day) and plant stanols/sterols (2g/day)
- Increased Physical Activity
- Smoking Cessation
### Table 7. Drugs Affecting Lipoprotein Metabolism

<table>
<thead>
<tr>
<th>Drug Class, Agents and Daily Doses</th>
<th>Lipid/Lipoprotein Effects</th>
<th>Side Effects</th>
<th>Contraindications</th>
<th>Clinical Trial Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA reductase inhibitors (statins)*</td>
<td>LDL ↓10-15% HDL ↓5-15% TG ↓15-30%</td>
<td>Myopathy Increased liver enzymes</td>
<td>Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs*</td>
<td>Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality</td>
</tr>
<tr>
<td>Bile acid Sequestrants*</td>
<td>LDL ↓15-30% HDL ↓3-5% TG No change or increase</td>
<td>Gastrointestinal distress Constipation Decreased absorption of other drugs</td>
<td>Absolute: • Dysbeta-lipoproteinemia • TG &gt;400 mg/dl Relative: • TG &gt;200 mg/dl</td>
<td>Reduced major coronary events and CHD deaths</td>
</tr>
<tr>
<td>Nicotinic acid*</td>
<td>LDL ↓5-25% HDL ↓15-35% TG ↓20-50%</td>
<td>Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity</td>
<td>Absolute: • Chronic liver disease • Severe gout Relative: • Diabetes • Hyperuricemia • Peptic ulcer disease</td>
<td>Reduced major coronary events and possibly total mortality</td>
</tr>
<tr>
<td>Fibric acid*</td>
<td>LDL (may be increased in patients with high TG) HDL ↓10-20% TG ↓20-50%</td>
<td>Dyspepsia Gallstones Myopathy Unexplained non-CHD deaths in WHO study</td>
<td>Absolute: • Severe renal disease • Severe hepatic disease</td>
<td>Reduced major coronary events</td>
</tr>
</tbody>
</table>

**Chart**

**Drugs That Affect Lipoprotein Metabolism**
HMG-CoA Reductase Inhibitors (Statins)

- Most effective class of drugs for lowering LDL-cholesterol
- Mainstay of lipid-modifying therapy (in combination with TLC)
- MOA: catalyze the rate limiting step in cholesterol synthesis
- Also have ability to decrease CRP

Bile Acid Sequestrants

- 2nd most effective class of drugs for lowering LDL
- Add to the LDL-lowering effects of other drugs (statins)
- MOA: lead to conversion of cholesterol to bile acids in the liver
- Not absorbed by the GI tract; do not act systemically
- Caution: May increase TG
- Space other medications
Nicotinic Acid (Niacin)

- Oldest known lipid-lowering agent still in use
- Usually secondary agent in combination with other drugs due to intolerability
- MOA: Exact mechanism not known. Appears to decrease hepatic synthesis of VLDL particles by inhibition of mobilization of free fatty acids from peripheral tissues. Also causes a shift in LDL particles from small, dense particles to larger particles.
- Available in 2 formulations:
  - Immediate Release (crystalline) preparations
  - Extended Release tablets
- Only agent known to reduce levels of lipoprotein A

Fibric Acids

- Primarily used as monotherapy or combination therapy to decrease triglycerides and increase HDL
- MOA: Enhance the catabolism of triglyceride-rich remnant lipoproteins and decrease hepatic synthesis of VLDL particles
Cholesterol Absorption Inhibitors

- Ezetimibe (Zetia®) first member of this class of medications
- MOA: Selectively inhibits the intestinal absorption of dietary and biliary cholesterol at the brush border of the small intestine
- Primary use as combination therapy with statins for LDL-lowering (monotherapy for selected patients)

ENHANCE Trial

- Effect of Combination Ezetimibe and High-Dose Simvastatin vs. Simvastatin Alone on the Atherosclerotic Process in Patients with Heterozygous Familial Hypercholesterolemia
- Study evaluated carotid intimal thickness in patients with familial hypercholesterolemia who were taking Vytorin® 10/80 mg vs. simvastatin 80 mg alone
- No difference in two groups in regard to intimal thickness
- 18-20% greater decrease in LDL in patients taking Vytorin® vs. simvastatin alone

ENHANCE Trial (cont’d)

- No difference in the incidence of cardiovascular mortality, non-fatal MI, non-fatal stroke or need for revascularization
  - This trial not adequately powered to study these clinical outcomes
- Overall incidence of treatment-related adverse events was similar between the two groups
- Impact on Therapy
  - Clinical decisions to stop Vytorin® should not be made on the ENHANCE trial alone and should still be considered a treatment option
  - See College of Cardiology’s (ACC) Statement on the ENHANCE trial

http://www.acc.org/enhance.htm

Omega-3-Acid Ethyl Esters

- Lovaza® (previously Omicor®)
  - Used as an adjunct to reduce very high TG levels (>500 mg/dl) in adult patients
- MOA: May reduce synthesis of triglycerides in the liver
New Therapies - Cholesteryl Ester Transfer Protein (CETP) Inhibitor

- Increase HDL
- Phase 3 clinical trial of torcetrapib (ILLUMINATE) terminated early due to excess CV events
  - Question of safety of drug itself vs. safety of target of therapy (CETP inhibition)
- Newer CETP inhibitors have different chemical structures
  - RO4607381
    - Phase 2 safety data positive
    - Currently being evaluated in Phase 3 clinical trial
  - Anacetrapib
    - Studied in phase 2 clinical trials

New Therapies - Phospholipase A$_2$ (PLA$_2$) Inhibitors

- Phospholipase A$_2$ (PLA$_2$) Inhibitors
  - PLA$_2$ modifies LDL particles in vitro
    - Hydrolyze phospholipids
    - Enhanced uptake by macrophages
    - Reaction products lead to activation of immunoinflammatory processes related to the pathogenesis and complications of atherosclerosis
  - Lipoprotein-associated (Lp)-PLA$_2$ and Secretory (s)PLA$_2$
  - High plasma levels of Lp-PLA$_2$ associated with increased CV risk
  - Inhibition of PLA$_2$
    - Anti-inflammatory effects
    - Reduction of CV events
New Therapies - Phospholipase A$_2$ (PLA$_2$) Inhibitors

- Darapladib
  - Selective LpPLA$_2$ Inhibitor
  - In Phase 2/3 development with GlaxoSmithKline
    - No major safety concerns
    - Did not modify levels of LDL, HDL, TC or TG
    - Significant reductions in inflammatory biomarkers
  - IBIS-2 study
    - Designed to assess impact of darapladib on arterial plaque composition
    - Decision on whether to advance to Phase 3 trials will be made


New Therapies - Phospholipase A$_2$ (PLA$_2$) Inhibitors

- Varespladib
  - Potent inhibitor of sPLA$_2$
  - Phase 2 PLASMA trial
    - Marked reduction sPLA$_2$ mass and reduced LDL
    - Treatment with statin: significantly greater reductions in LDL
    - Twice daily administration
  - Phase 2b clinical trial
    - Reduction in sPLA$_2$ and LDL
    - Once daily administration

New Therapies – New Formulation of Fenofibric Acid

- Choline fenofibrate (ABT-335): active metabolite of fenofibric acid
  - Pharmacokinetetic profile differs from fenofibrate
  - Combo therapy with statin has shown improved lipid levels compared with corresponding monotherapies
  - If approved, will be marketed as TriLipix™


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Step 8

Identify and Treat Metabolic Syndrome
Step 9

Treat Elevated Triglycerides

ATP III Classification of Serum Triglycerides

<table>
<thead>
<tr>
<th>Category</th>
<th>ATP III Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;150 mg/dl</td>
</tr>
<tr>
<td>Borderline High</td>
<td>150-199 mg/dl</td>
</tr>
<tr>
<td>High</td>
<td>200-499 mg/dl</td>
</tr>
<tr>
<td>Very High</td>
<td>≥500 mg/dl</td>
</tr>
</tbody>
</table>
Non-HDL as Secondary Target

- Non-HDL = Total Cholesterol – HDL
- Reflects the concentration of cholesterol within atherogenic lipoprotein particles
  - i.e represents apo B carrying lipoproteins
  - VLDL, chylomicron remnants, VLDL remnants, IDL, LDL
- Used as secondary target (after targeting LDL) in patients with elevated TG
  - If LDL goals met and TG ≥ 200, calculate non-HDL
  - Set non-HDL goal at 30 points higher than LDL goal

APhA. Pharmacy-Based Lipid Management. 2005

Non-HDL as Secondary Target

- May be a better predictor of CVD risk than is LDL cholesterol
  - Especially in statin-treated patients
- Lack of additional expense in patients already getting lipid panel measurements

Diabetes Care 2003;26:16-23
Diabetes Care 2005;28:1916-1921
Circulation 2005;112:3375-3383
Other targets—LDL Particle Number and Size

- LDL particle concentration and size important predictors of CVD
  - Concentration
    - Direct measure of the # of LDL particles using nuclear magnetic resonance (NMR)
  - Size
    - LDL particle size can also be measured
    - Atherogenic properties of small dense LDL particles
    - Unclear if particle size measurement of value

- Limitations of NMR measurement
  - Technique not widely available
  - Relatively expensive
  - Need for more data confirming the accuracy of the method


Other Targets—ApoB-100

- Represent total burden of particles considered most atherogenic
  - Chylomicrons, VLDL, IDL, LDL, Lp(a) particles each contain a single apoB molecule

- Some studies suggest that once LDL lowered, apoB may be more effective way to assess residual CVD risk and determine therapy adjustments

- ApoB measurements
  - Do not require fasting sample
  - Standardized but not widely available

Lipoprotein Management in Patients With Cardiometabolic Risk:

Consensus Statement from the American Diabetes Association and the American College of Cardiology Foundation.

Residual Risk on Statin Therapy

- Proven evidence that statin therapy reduces cardiovascular risk
  - However, residual risk remains in treated patients
- Studies needed
  - To determine whether residual risk can be decreased by interventions effecting other lipoproteins (i.e. HDL, small dense LDL)
  - To directly determine if other therapeutic targets (i.e. apoB, other lipoproteins) are superior to LDL

Summary of Recommendations

- Statin therapy for the majority of dyslipoproteinemic adult patients with cardiometabolic risk (CMR)
- In patients with CMR on statin therapy, therapy should be guided with apoB measurements and treatment to apoB goals as well as LDL cholesterol and non-HDL cholesterol assessments
- Treatment goals that address high lifetime risk of patients with dyslipoproteinemia and CMR (see table)
- Clinical trials to determine whether pharmacologic therapy required to achieve very low levels of atherogenic lipoproteins is safe and cost-effective


Suggested Treatment Goals in Patients with CMR and Lipoprotein Abnormalities

<table>
<thead>
<tr>
<th></th>
<th>LDL Goal (mg/dl)</th>
<th>Non-HDL Goal (mg/dl)</th>
<th>ApoB Goal (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest-risk patients(^1)</td>
<td>&lt;70</td>
<td>&lt;100</td>
<td>&lt;80</td>
</tr>
<tr>
<td>High-risk patients(^2)</td>
<td>&lt;100</td>
<td>&lt;130</td>
<td>&lt;90</td>
</tr>
</tbody>
</table>

\(^1\)Including those with: 1) known CVD or 2) diabetes plus ≥ 1 additional major CVD risk factors

\(^2\)Including those with: 1) no diabetes or known clinical CVD but ≥ 2 additional major CVD risk factors or 2) diabetes but no other major CVD risk factors

*Other major risk factors = smoking, HTN, family history of premature CAD
Questions?

References

- APhA. Pharmacy-Based Lipid Management. 2005
- Stone and Blum. Management of Lipids in Clinical Practice. 6th edition. 2006
References

- http://www.acc.org/enhance.htm