Lipid Management:
A Primary Care Perspective

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Content Collaborator
Session 5: Lipid Management: A Primary Care Perspective

Learning Objectives
1. Utilize evidence-based lipoprotein management strategies for non-LDL-C lipid targets.
2. Describe the risk factors, disease spectrum, and appropriate management of familial hypercholesterolemia.

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Dr. Alan Brown has been the director of the prevention center/lipid clinic for Midwest Heart Specialists, a group of 52 cardiologists located in Chicago's western suburbs, since its inception in 1985. He has served as clinical associate professor of medicine and cardiology at Loyola University since 1993. Dr. Brown is board certified in internal medicine, cardiology, echocardiography, and clinical lipidology. Dr. Brown has served as governor/president of the Illinois chapter of the American College of Cardiology (ACC) and subsequently was elected chairman of the board of governors for the ACC in 2004. He is a fellow of the ACC and also has been a member of the ACC's prevention of cardiovascular disease committee, the annual scientific program committee, and served as a member of the ACC board of trustees from 2003 through 2006. He is a fellow of the National Lipid Association and serves on their board of directors.

Faculty Financial Disclosure Statement
The presenting faculty reports the following:

Alan S. Brown, MD, FACC, FNLA, serves as a speaker for Kowa Pharmaceuticals America, Inc.; and is a consultant for Aegerion Pharmaceuticals, Kowa Pharmaceuticals America, Inc., and Merck & Co., Inc.
SESSION 5
3–4pm

Lipid Management:
A Primary Care Perspective

SPEAKER
Alan S. Brown, MD, FACC, FNLA

Learning Objectives

• Utilize evidence-based lipoprotein management strategies for non-LDL-C lipid targets
• Describe the risk factors, disease spectrum, and appropriate management of familial hypercholesterolemia (FH)

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

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

Stone NJ et al. Circulation. 2013;01.cir.0000437738.63853.7apublished online before print November 12 2013

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NHLBI Charge to the Expert Panel

Evaluate higher quality randomized controlled trial (RCT) evidence for cholesterol-lowering drug therapy to reduce ASCVD risk

➢ Use Critical Questions (CQs) to create the evidence search from which the guideline is developed
➢ RCTs and systematic reviews/meta-analyses of RCTs independently assessed for quality
➢ Less expert opinion than in prior guidelines

Presenter Disclosure Information

The following relationships exist related to this presentation:

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Off-Label/Investigational Discussion

➢ In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

*Ex-Officio Members:

Ken LaBresh, MD
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Janusz Wnek, PhD
Glen Bennett, M.P.H.
Denise Simons-Morton, MD, PhD

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Systematic Review Process

- The Expert Panel constructed CQs relevant to clinical practice.
- The Expert Panel identified (a priori) inclusion/exclusion (I/E) criteria for each CQ.
- An independent contractor developed a literature search strategy, based on I/E criteria, for published clinical trial reports for each CQ.
- Executed a systematic electronic search of the published literature from relevant bibliographic databases for each CQ.

The date for the overall literature search was from January 1, 1995 through December 1, 2009. However, RCTs with the ASCVD outcomes of MI, stroke, & cardiovascular death published after that date were eligible for consideration until July 2013.

3 Clinical Questions (CQ’s)

1. What is the evidence for LDL-C and non-HDL-C goals for secondary prevention of ASCVD?
2. What is the evidence for LDL-C and non-HDL-C goals in primary prevention?
3. For primary and secondary prevention, what is the impact on lipid levels, effectiveness, and safety of specific lipid meds, in general and in specific subpopulations

Synopsis of Recommendations*

1. Encourage adherence to a healthy lifestyle
2. Statin therapy recommended for adult groups demonstrated to benefit
3. Statins have an acceptable margin of safety when used in properly selected individuals and appropriately monitored
4. Engage in a clinician-patient discussion before initiating statin therapy – especially for primary prevention in patients with lower ASCVD risk


The 4 Statin Benefit Groups

High risk groups:
1. Clinical atherosclerotic cardiovascular disease (ASCVD)
2. LDL–C ≥190 mg/dL, Age ≥21 years (FH)
3. Diabetes: Age 40-75 years, LDL–C 70-189 mg/dL
4. Primary prevention – Clinician-patient risk discussion required:
   – No diabetes and ≥7.5% 10-year ASCVD risk
   – Age 40-75 years, LDL–C 70-189 mg/dL

Primary Prevention Statin Therapy

- Thresholds for initiating statin therapy derived from 3 exclusively primary prevention RCTs
- Before initiating statin therapy, clinicians and patients engage in a discussion of the potential for ASCVD risk reduction benefits, potential for adverse effects, drug-drug interactions, and patient preferences

Synopsis of Recommendations, cont’d

5. Use the newly developed pooled cohort equations for estimation 10-year ASCVD risk
6. Initiate proper intensity of statin therapy
7. Evidence is inadequate to support treatment to specific LDL-C or non-HDL-C goals
8. Regularly monitor patients for adherence to lifestyle and statin therapy

ASCVD Risk Calculator
55 y/o AA and White Women

![Risk Calculator Diagram]

**Why Not Continue to Treat to Target?**

**Major difficulties:**
1. Current RCT data do not indicate what the target should be
2. Unknown magnitude of additional ASCVD risk reduction with one target compared to another
3. Unknown rate of additional adverse effects from multidrug therapy used to achieve a specific goal
4. Therefore, unknown net benefit from treat-to-target approach

**Focus on Appropriate Intensity of Statin Therapy to Reduce ASCVD Risk**

- Lack of RCT evidence to support titration of drug therapy to specific LDL–C and/or non-HDL–C goals
- Strong evidence that **appropriate intensity of statin therapy** should be used to reduce ASCVD risk in those most likely to benefit
- Quantitative comparison of statin benefits with statin adverse effects
- Nonstatin therapies – did not provide ASCVD risk reduction benefits or safety profiles comparable to statin therapy

**Individuals Not in a Statin Benefit Group**

In those for whom a risk decision is uncertain:

- These factors may inform clinical decision making in context of clinician-patient discussion.
  - LDL–C ≥160 mg/dL
  - Elevated lifetime risk of ASCVD (below added from risk assessment guideline)
  - Family history of premature ASCVD
  - hs-CRP ≥2.0 mg/L
  - Coronary artery calcium score ≥300 Agatston units
  - Ankle brachial index (ABI)<0.9

**Statin-Treated Individuals Nonstatin Therapy Considerations**

- Use the maximum tolerated intensity of statin
- Consider addition of nonstatin cholesterol-lowering drug
  - If a less-than-anticipated therapeutic response persists
  - Only if ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
    - **Clinical ASCVD** <75 years of age
    - Baseline LDL–C ≥190 mg/dL
    - Diabetes mellitus 40 to 75 years of age
- Nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs are preferred

**To Reduce ASCVD by Treating Blood Cholesterol**

1. Favor proven therapy for those shown to benefit.
2. Use statins as drugs of choice; they are inexpensive (most are generic) & safe when taken as tolerated.
3. Focus on proper intensity of statin therapy & monitor for adherence to optimal lifestyle and statin Rx
4. Insist on a clinician-patient discussion in primary prevention:
   - Discuss a global risk reduction strategy
   - Discuss potential for benefit and adverse effects of statin therapy including drug-drug interactions
   - Patient preferences (shared decision making)
Will such a simple strategy work to achieve lipid goals?

"However beautiful the strategy, occasionally you should look at the results!"

Sir Winston Churchill

Electronic Medical Records and Computer Assisted Lipid Management

Year One: 11,263 Consecutive Patients


Effects of EMR on Lipid Management (Year 1 – 11,263 Patients)

At the End of 2 Years, for 20,000 Consecutive Patients with CAD:

• 70% had LDL < 100 mg/dL
• Of those with triglycerides over 200 mg/dL but LDL at goal, 89% were also at non-HDL goal on statin monotherapy alone

Future Updates to the Blood Cholesterol Guideline

• These guidelines represent a change from previous guidelines. They align recommendations more closely to the evidence
• The focus is on assessment of global ASCVD risk; “proven therapy” as appropriate and followup that stresses adherence
• For primary prevention, they are “patient-centered”
• Guidelines will change in the future as quality data becomes available to improve them

Conclusions

• The new Guideline process was significantly different from that of the past
• Statin therapy remains the mainstay for treatment of dyslipidemia with intensity of therapy based on current evidence
• Clinical judgement remains critical for treating those patients with lipid abnormalities where evidence is pending or not available
• A new simple strategy may get more patients to goal than complex prior guidelines
Case Study: Pat

- 62-year-old woman with family history of maternal uncle having MI at age 39
- Physical exam normal except thickening of Achilles tendons bilaterally

Labs
Patient is euthyroid
Chemistries: normal
Total cholesterol: 305 mg/dL
HDL-C: 50 mg/dL
LDL-C: 210 mg/dL
Triglycerides: 175 mg/dL

Genetic Etiologies for Very High LDL Familial Hypercholesterolemia (FH)

- LDL receptor mutation (heterozygous, homozygous, compound homozygous)
- Mutations in the gene for apo B can also give rise to FH (familial defective apo B).
- Deficiency of 7-alpha hydroxylase (cyp7A1 mutation)
- Autosomal recessive hypercholesterolemia (due to reduced expression of adaptor protein that facilitates association of LDLR with clathrin in cell surface coated pits).
- Autosomal dominant hypercholesterolemia attributable to gain of function mutations in PCSK9

Genetics

- Affected subjects are at increased risk for all forms of atherosclerotic disease and premature death secondary to lifelong pathogenic elevations in serum LDL-C.
- The Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff lists 1614 mutations in the LDL receptor gene.

FH Prevalence

Heterozygotes
- Frequency ≈ 1 in 300-500
- One of most common congenital metabolic disorders
- Serum cholesterol: 300-550 mg/dL
- Since patients have one normal LDL-R gene, their hepatocytes take up LDL-C at approximately one-half the rate of unaffected patients.

Homozygotes
- Frequency ≈ 1 in 1 million
- Serum cholesterol: 650-1000 mg/dL
- Have near total or total loss of LDL-R functionality
- Can inherit 2 copies of same mutant allele, or may be classified as compound homozygotes due to inheritance of 2 different mutant alleles

Physical Findings in Familial Hypercholesterolemia

- Yellow-orange cutaneous xanthomas
- Tendon xanthomas
- Xanthelasma
- Corneal arcus
- Heart murmur stemming from aortic stenosis
- Can develop supravalvular stenosis of the aorta
- Arterial bruits (carotid, femoral) arising from diffuse, systemic atherosclerosis
- Polyarthritis
- Tendinitis
Screening for FH

<table>
<thead>
<tr>
<th>Screening Recommendations</th>
<th>Adults (≥20 years)</th>
<th>LDL cholesterol ≥190 mg/dL or non-HDL cholesterol ≥220 mg/dL</th>
<th>Ask about family history of high cholesterol and heart disease in first-degree relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children, adolescents and young adults (&lt;20 years)</td>
<td>LDL cholesterol ≥160 mg/dL or non-HDL cholesterol ≥190 mg/dL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Higher likelihood of FH with positive family history of hypercholesterolemia or CHD onset < 55 years (men), < 65 years women
- Consider cholesterol screening starting at age 2 for children with a family history of premature CHD or elevated cholesterol
- All individuals should be screened by age 20


Treat All FH Patients

- Very high lifetime risk of coronary heart disease
- Very high risk of premature onset CHD
- Early and long term treatment is highly beneficial
- Long term drug therapy in patients with FH removes excess lifetime risk of CHD due to the genetic disorder, with a goal of reducing CHD risk to a level similar to that of the general population
- LDL apheresis: LDL>200 mg/dL; 130 mg/dL with Lp(a) >50-60 mg/dL


Treat All FH Patients

- Untreated FH
  - Mean onset CVD
    - Men early 40’s
    - Women in early 50’s
  - 24 times higher risk of MI before age 40
- Long-term statin treatment largely ameliorates excess CVD risk due to FH
- Risk of long-term statin treated FH patients = Risk of general population

Versmissen J, et al. BMJ. 2008; 337: a2423

Kaplan-Meier curve estimates cumulative CHD-free survival among FH patients (P<0.001)

Aggressive Approaches to LDL Lowering and Novel agents

- LDL apheresis
- ApoB mRNA antisense oligonucleotides (indicated for HoFH)
- Microsomal triglyceride transfer protein (MTP) inhibitors (indicated for HoFH)
- Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors

HoFH=homozygous familial hypercholesterolemia

ApoB (LDL-C, Non-HDL-C) Lowering

<table>
<thead>
<tr>
<th>Current</th>
<th>Future?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins – Maximize or optimize</td>
<td>ApoB formation inhibitors</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>PCSK9 inhibitors</td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>MTP inhibitors</td>
</tr>
<tr>
<td>Niacin</td>
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<tr>
<td>Fibrates</td>
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</tbody>
</table>

Current Future?

- Statins
- Ezetimibe
- Bile acid sequestrants
- Niacin
- Fibrates

- ApoB formation inhibitors
- PCSK9 inhibitors
- MTP inhibitors

Antisense Mechanism of Action

An antisense oligonucleotide (ASO) blocks the mRNA translation into protein, therefore blocking protein synthesis

- ApoB-100 as a target
- Essential for the synthesis and transport of VLDL and LDL-C
- Plays a crucial role in lipid management
Apo B-100 as a Target

DNA → mRNA → Disease-Associated Protein

Transcription → Translation → Traditional Drug

No Disease-Associated Proteins Produced

Antisense Drug (Oligonucleotide)


Mipomerson*: An ApoB Antisense Oligonucleotide

Dose-dependent reductions in LDL-C in health volunteers over 83 days (12 weeks)

Baseline LDL-C mg/dL (mean (SD))
- Placebo (n = 7): 131 (27)
- 50 mg (n = 8): 126 (24)
- 100 mg (n = 8): 131 (24)
- 200 mg (n = 9): 123 (16)
- 400 mg (n = 4): 133 (23)

Reductions in LDL-C and Lp(a) Levels in Ho-FH (n=51) with Mipomersen

Reduction in LDL-C over 28 weeks

Reduction in Lp(a) over 28 weeks

Mipomersen Safety

- Injection site reactions (84%), flu-like symptoms (30%), nausea, headache
- 8.4% of mipomersen-treated patients had ALT > 3x ULN on two consecutive measures 7 days apart (vs 0% for placebo)
- Reversible, median increase in hepatic fat with no effects noted on liver synthetic function (total bilirubin, PT, albumin)
  - Hepatic steatosis is a risk factor for progressive liver disease

Human Monoclonal Antibody to PCSK9*

Changes in Apo B, Non-HDL-C, and Lipoprotein(a) from Baseline to Week 12 by Treatment Group

<table>
<thead>
<tr>
<th>Intervention</th>
<th>% Change Apo B</th>
<th>% Change Non-HDL-C</th>
<th>% Change Lipoprotein(a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>2.2</td>
<td>-2.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Alirocumab 50 mg/2 weeks</td>
<td>-27.3*</td>
<td>-33.6*</td>
<td>-13.3**</td>
</tr>
<tr>
<td>Alirocumab 100 mg/2 weeks</td>
<td>-48.1*</td>
<td>-55.8*</td>
<td>-26.1*</td>
</tr>
<tr>
<td>Alirocumab 150 mg/2 weeks</td>
<td>-56.1*</td>
<td>-62.3*</td>
<td>-28.8*</td>
</tr>
<tr>
<td>Alirocumab 200 mg/2 weeks</td>
<td>-20.7*</td>
<td>-37.4*</td>
<td>-6.3*</td>
</tr>
<tr>
<td>Alirocumab 300 mg/4 weeks</td>
<td>-33.17*</td>
<td>-40.2**</td>
<td>-7.9**</td>
</tr>
</tbody>
</table>

*P < 0.0001 for % change Alirocumab vs. placebo
** P = 0.05 for % change Alirocumab vs. placebo


Microsomal Transfer Protein Inhibitors

- Dose-escalation study in 6 patients with homozygous familial hypercholesterolemia
  - Lomitapide,* 1 mg/kg daily, decreased LDL-C by 50.9% and Apo B by 55.6% from baseline
  - Markedly reduces Apo-B production
  - Adverse effects were elevated aminotransferase levels and hepatic fat accumulation in 10-40% of patients at the 1.0 mg/kg dose range


* Lomitapide is only approved for use in patients with homozygous familial hypercholesterolemia.
**Key Clinical Take Home Points**

- LDL-C remains the principle target of therapy for patients at risk for CAD. (Evidence Level A)
- The evidence for HDL-C raising/TG lowering providing additional benefit on top of statins to reduce CHD risk is disappointing. (FIELD, AIM HIGH, ACCORD)
- Non-HDL-C and ApoB are better predictors of CHD risk than LDL-C in patients with elevated TG. (Evidence Level A)
- We still need a trial of patients with high non-HDL-C who are at LDL-C targets to prove treatment benefit.

**Getting Non-HDL to Target in Mixed Dyslipidemia**

- Consider the patient: age, finances, side effects
- Intensify LDL-C lowering or use combination therapy to adjust HDL-C/TG
- TG level > 200 with LDL-C/HDL-C ratio >5? 
  - This patient will likely benefit from niacin or fibrate
- Follow NCEP guidelines, until trial evidence suggests differently!

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**Conclusions: LDL, HDL, TG, non-HDL**

- Benefit of adding niacin or fenofibrate to statin to raise HDL-C in patients with T2DM, mixed dyslipidemia and CAD?  
  [Current evidence is lacking.]

- Clinical benefits of novel therapies to increase HDL-C?  
  [Jury remains out.]

- Last 2 decades focused on LDL lowering.  
  [Next decade will likely focus on HDL-C, TG, non-HDL-C, Apo B, FBS, BP and obesity.]

  In order to adequately reduce "residual risk" we will need to be more aggressive at treating all the risk factors for CHD and to develop systems to provide better treatment to large numbers of patients.

**Conclusions: Familial Hypercholesterolemia**

- FH is a common genetic disorder
- Diagnosis is critical not only for the patient but also for family members
- Cascade screening is mandatory
- Aggressive treatment of LDL is necessary
- Several new therapeutic agents are under development that will likely be effective for treatment of FH and statin-intolerant patients

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**Questions**

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