Current Perspectives and Emerging Approaches in Lipid Management

Wednesday, March 26, 2014
7:45–9:15am

Anaheim Convention Center
800 W. Katella Avenue
Anaheim, California

C. Noel Bairey Merz, MD
Professor of Medicine
Cedars-Sinai Medical Center
Los Angeles, California

Eliot A. Brinton, MD
Director, Atherometabolic Research
Utah Foundation for Biomedical Research
Salt Lake City, Utah

Educational Partner:
Voxmedia, LLC
Session 1: Current Perspectives and Emerging Approaches in Lipid Management

Learning Objectives

1. Evaluate primary and secondary prevention evidence with statins.
2. Explain the importance of lowering LDL-C for reducing cardiovascular risk, interpret statin safety data, assess benefit/risk with statins, and discuss current guideline recommendations.
3. Explain the association of hypertriglyceridemia with increased risks and identify currently available therapies for reducing elevated triglycerides.
4. Discuss similarities and differences between currently available and emerging omega-3 fatty acid agents, and indicate patient populations for potential incorporation of omega-3 fatty acids in clinical practice.

Faculty

C. Noel Bairey Merz, MD
Professor of Medicine
Cedars-Sinai Medical Center
Los Angeles, California

Dr. C. Noel Bairey Merz is professor of medicine, the Women’s Guild endowed chair in women’s health, and director of the Women’s Heart Center and the Preventive and Rehabilitative Cardiac Center in the Cedars-Sinai Heart Institute. Dr. Bairey Merz received her medical degree from Harvard University. She completed her residency at the University of California, San Francisco, and completed fellowships in clinical cardiology and nuclear cardiology at Cedars-Sinai Medical Center. Her research interests include women and heart disease, mental stress and heart disease, the role of exercise and stress management in reversing disease, and the role of nutrition in heart disease. Currently, she is chair of the National Institutes of Health (NIH) sponsored Women’s Ischemic Syndrome Evaluation (WISE) initiative. Dr. Bairey Merz has received investigational grants from the NIH National Heart, Lung and Blood Institute (NHLBI), NIH National Center for Alternative and Complementary Medicine (NCCAM), the Pfeiffer Foundation, the Eli and Edythe Broad Foundation, the Barbra Streisand Foundation, and the Women’s Guild. Dr. Bairey Merz served on the board of trustees of the American College of Cardiology as well as the American Heart Association; where she is past chair of the women in cardiology committee. Dr. Bairey Merz has over 500 scientific publications including the New England Journal of Medicine, the Journal of the American Medical Association, Circulation, the Journal of the American College of Cardiology, and the Journal of Women’s Health. Dr. Bairey Merz received the 2012 American College of Cardiology distinguished scientist award, the 2009 American Heart Association women in cardiology mentoring award, the 2008 McCue female cardiologist of the year, the 2005 Red Dress Award for leadership in cardiovascular research in women, the 2005 Women of the 21st Century award from the Women’s Guild of Cedars-Sinai Medical Center, and the 2006 Alvin P. Shapiro award by Psychosomatic Society for excellence in clinical research.

Eliot A. Brinton, MD
Director
Atherometabolic Research
Utah Foundation for Biomedical Research
Salt Lake City, Utah

Dr. Eliot Brinton is director of atherometabolic research at the Utah Foundation for Biomedical Research, president of the Atherometabolism Institute, and president of the Utah Lipid Center, Salt Lake City, Utah. He is president and founding board member of the American Board of Clinical Lipidology and is a founding board member of the National Lipid Association. He is also president of the Utah Atherosclerosis Society and past president of the Pacific Lipid Association. Dr. Brinton obtained his medical
degree from the University of Utah, Salt Lake City, his residency at Duke University, and his fellowship in metabolism, endocrinology, and nutrition at the University of Washington, Seattle. He has served on faculty at the Rockefeller University in New York, New York, Wake Forest University, Winston-Salem, North Carolina, the University of Arizona, Phoenix, and the University of Utah. He served as chief of metabolism, endocrinology, and nutrition at the Carl T. Hayden VA Medical Center and as director of the Phoenix Crosstown Endocrinology Fellowship, Phoenix, Arizona. Dr Brinton is an editor of Lipids Online, an assistant editor of the Journal of Clinical Lipidology and of the Journal of Obesity; and serves on the editorial boards of the Journal of Clinical Endocrinology and Metabolism, the Journal of Managed Care Pharmacy, and Clinical Lipidology. He has authored numerous original scientific article for publications such as the New England Journal of Medicine, Science, Circulation, the Journal of Clinical Investigation and Arteriosclerosis, Thrombosis and Vascular Biology. Dr Brinton received the Alpha Omega Alpha, a national research service award and clinical investigator award from the NIH, and a merit review award from the Veterans Administration. Dr Brinton is corecipient of the 2012 Robert I. Levy award of the Kinetics and Metabolism Society.

Faculty Financial Disclosure Statements
The presenting faculty reports the following:

Dr Bairey Merz has received consultant and/or honorarium fees from the Mayo Foundation, the Research Triangle Institute, Amgen, Practice Point Communications, Bristol-Myers Squibb, Amgen, Gilead, Pri-Med, Voxmedia, BCB Communications, NIH-SEP, and ACC-SAP.

Dr Brinton has received consultant and/or honorarium fees from AstraZeneca and Merck.

Education Partner Financial Disclosure Statements
The content collaborator at Voxmedia reports the following:

John F. Kocsis, PhD, has no financial relationships to disclose.
Meghna Jhaveri, PharmD, has no financial relationships to disclose.

Suggested Reading List


Fish oil and omega-3 fatty acid supplements (EPA and DHA from fish, algae, and krill). Consumer Lab; Available from: https://www.consumerlab.com/reviews/fish_oil_supplements_review/omega3.


SESSION 1
7:45–9:15am
Current Perspectives and Emerging Approaches in Lipid Management

SPEAKERS
C. Noel Bairey Merz, MD
Eliot A. Brinton, MD

Drug List

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>Lipitor</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Lescol, Lescol XL</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>Mevacor, Altosprev</td>
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<td>Pravastatin</td>
<td>Pravachol</td>
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<td>Rosuvastatin</td>
<td>Crestor</td>
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<td>Pitavastatin</td>
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<td>Tiopronin</td>
<td>Aggrastat</td>
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<td>Ezetimibe</td>
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<td>Itraconazole</td>
<td>Sporanox</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Nitrazol, Extina, Xolgel, Kuric</td>
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<tr>
<td>Erythromycin</td>
<td>E-mycin, Eryc, Ery-tab, PCE, Ilusone, Pestazol</td>
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</tbody>
</table>

Drug List (cont’d)

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>Biaxin, Biaxin XL</td>
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<td>Nafazadone</td>
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<td>Verapamil</td>
<td>Calan, Verelan, Verelan PM, Isupin, Isupin SR, Covera-HS</td>
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<td>Amiodarone</td>
<td>Pacerone, Cordarone, Cordarone IV, Nestorone</td>
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<td>Nicotinic acid</td>
<td>Niacor, Niazen, Bio-Niacin</td>
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<td>Bezaflurate</td>
<td>Bezalip</td>
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<tr>
<td>Fenofibrate</td>
<td>Tricor, Lipidil, Antara, Triglide, Trilipix</td>
</tr>
<tr>
<td>Omega-3 acid ethyl esters</td>
<td>Lovaza</td>
</tr>
<tr>
<td>Icosapent ethyl</td>
<td>Vascepa</td>
</tr>
<tr>
<td>Omega-3 free fatty acids</td>
<td>Epanova</td>
</tr>
</tbody>
</table>

Educational Objectives

- Evaluate primary and secondary prevention evidence with statins.
- Explain the importance of lowering LDL-C for reducing cardiovascular risk, interpret statin safety data, assess benefit/risk with statins, and discuss current guideline recommendations.
- Explain the association of hypertriglyceridemia with increased risks and identify currently available therapies for reducing elevated triglycerides.
- Discuss similarities and differences between currently available and emerging omega-3 fatty acid agents, and indicate patient populations for potential incorporation of omega-3 fatty acids in clinical practice.

Reducing Cardiovascular Risk: Taking a Closer Look at Statin Efficacy and Safety

C. Noel Bairey Merz, MD, FACC, FAHA
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Dr Bairey Merz has received consultant and/or honorarium fees from the Mayo Foundation, the Research Triangle Institute, Amgen, Practice Point Communications, Bristol-Myers Squibb, Amgen, Gilead, Pri-Med, Voxmedia, BCB Communications, NIH-SEP, and ACC-SAP.
- Dr Brinton has received consultant and/or honorarium fees from AstraZeneca and Merck.

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.
Educational Objectives

1) Provide primary and secondary prevention evidence with statins

2) Explain the importance of lowering LDL-C for reducing cardiovascular risk, interpret statin safety data, and describe benefit/risk with statins

3) Provide current guideline recommendations

Primary Prevention: Fixed Dose High Intensity Statin
JUPITER: MI, Stroke, UA/Revascularization, CV Death

- 44 %

Rosuvastatin 142 / 8901
Placebo 251 / 8901

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

Secondary Prevention: Fixed Dose High Intensity Statin
Treating to New Targets (TNT) Trial
10,001 patients with stable CHD randomized to atorvastatin (80 mg) or atorvastatin (10 mg) for 4.9 years

High-dose statins provide benefit in chronic CHD

CHD=Coronary heart disease, CV=Cardiovascular, MI=Myocardial infarction, RRR=Relative risk reduction

Includes CHD death, nonfatal MI, resuscitation after cardiac arrest, or stroke

LaRossa JC et al. NEJM 2005;352:1425-35

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
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Educational Objectives

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2) Explain the importance of lowering LDL-C for reducing cardiovascular risk, interpret statin safety data, and describe benefit/risk with statins

3) Provide current guideline recommendations
Why Risk Discussion Important

- About 1/3rd of US adults 40-79 (~32M) will have risk ≥ 7.5% and merit risk discussion & statin consideration for primary prevention.

Context
- ~1/3rd of Americans die from heart disease & stroke
- ~60% have a major vascular event during life
- ~70M US adults qualify for BP lowering therapy
- Other tests may be considered when risk-based treatment uncertain

ASCVD Risk Calculator

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Units</th>
<th>Acceptable range of values</th>
<th>Optimal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M or F</td>
<td>M or F</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>20-79</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>AA or WH</td>
<td>AA or WH</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>mg/dL</td>
<td>130-320</td>
<td>170</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>mg/dL</td>
<td>20-100</td>
<td>50</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>mm Hg</td>
<td>90-200</td>
<td>110</td>
</tr>
<tr>
<td>Treatment for High Blood Pressure</td>
<td>Y or N</td>
<td>Y or N</td>
<td>Y or N</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y or N</td>
<td>Y or N</td>
<td>Y or N</td>
</tr>
<tr>
<td>Smoker</td>
<td>Y or N</td>
<td>Y or N</td>
<td>Y or N</td>
</tr>
</tbody>
</table>

ASCVD Risk Calculator

55 yo AA and White Women

Baseline Safety Labs

- Obtain ALT as a baseline; if normal liver test (s), no need for routine monitoring
- Obtain CK as a baseline if a personal or family history of muscle problems/disorders. Routine CK not needed at baseline.
- Screen and treat type II diabetes according to current practice guidelines.
Safety

- Allow estimation of net benefit from statin therapy
  - ASCVD risk reduction versus adverse effects
  - In benefit groups, statin benefits outweigh small risk of new diabetes diagnoses
- Expert guidance on management of statin-associated adverse effects, including muscle symptoms
- Recommendations on nonstatin safety issues
- Advise use of additional information including pharmacists, manufacturers prescribing information, & drug information centers for complex cases

Management of Muscle Symptoms on Statin Therapy

- It is reasonable to evaluate and treat muscle symptoms including pain, cramping, weakness, or fatigue in statin-treated patients according to the management algorithm
- To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy

Management of Muscle Symptoms on Statin Therapy (con’t)

If mild-to-moderate muscle symptoms develop during statin therapy:
- Discontinue the statin until the symptoms are evaluated
- Evaluate the patient for other conditions* that might increase the risk for muscle symptoms
- If after 2 months without statin Rx, muscle symptoms or elevated CK levels do not resolve completely, consider other causes of muscle symptoms
*Hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency or primary muscle diseases

Management of Muscle Symptoms on Statin Therapy (con’t)

If unexplained severe muscle symptoms or fatigue develop during statin therapy:
- Promptly discontinue the statin
- Address possibility of rhabdomyolysis with:
  - CK
  - Creatinine
  - urine analysis for myoglobinuria

Educational Objectives

1) Provide primary and secondary prevention evidence with statins
2) Explain the importance of lowering LDL-C for reducing cardiovascular risk, interpret statin safety data, and describe benefit/risk with statins
3) Provide current guideline recommendations

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
**ACC/AHA Blood Cholesterol Guideline**

**Panel Members**

Neil J. Stone, MD, MACP, FAHA, FACC, Chair
Jennifer G. Robinson, MD, MPH, FAHA, Vice Chair
Alice H. Lichtenstein, DSc, FAHA, Vice Chair

Anne C. Goldberg, MD, FACP, FAHA
Conrad B. Blum, MD, FAHA
Robert H. Eckel, MD, FAHA, FACC
Daniel Levy, MD
David Gordon, MD*
C. Noel Bairey Merz, MD, FAHA, FACC

**Acknowledgements**

**Methodology Members**

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Lev Nevo, MD
Janusz Wnek, PhD

**National Heart, Lung, and Blood Institute**

Glen Bennett, M.P.H.
Denise Simons-Morton, MD, PhD

**Conflict of Interest/Relationships With Industry**

1) All panel members disclosed conflict of interest information to the full panel in advance of the deliberations

2) Members with conflicts recused themselves from voting on any aspect of the guideline where a conflict might exist

3) All 16 members of the NHLBI ATP IV Panel transitioned to the ACC/AHA guideline Expert Panel

4) Independent contractors performed the systematic review with the assistance of the Expert Panel and provided methodological guidance to the Expert Panel

**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

**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

*Stone NJ et al Ann Int Med 2014

**4 Statin Benefit Groups**

High risk groups:
1. Clinical atherosclerotic cardiovascular disease (ASCVD)
2. LDL–C ≥190 mg/dL, Age ≥21 years
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,

**Vignettes Statin Benefit Groups**

1. 63 yo man with STEMI
2. 26 yo woman w/elevated LDL–C of 260 mg/dL, noted in teens + family history CHD
3. 44 yo woman with diabetes, well-controlled hypertension and micro-albuminuria
4. 55 yo AA woman with 7.7% 10 yr CVD risk

Key issue for each case is optimal intensity of statin therapy!
Synopsis of Recommendations

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


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

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 a nonstatin cholesterol-lowering drug(s)
  • 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:
   a. Discuss a global risk reduction strategy
   b. Discuss potential for benefit and adverse effects of statin therapy including drug-drug interactions
   c. Patient preferences (shared decision making)

Application of New Cholesterol Guidelines to a Population Based Sample

➢ National Health and Nutrition Examination Surveys 2005 – 2010
➢ As compared with ATP-III guidelines, the new guidelines would increase # of US adults receiving or eligible for statin therapy from 43.2 million (37.5%) to 56.0 million (48.6%).
  • Most of this increase in numbers (10.4 million of 12.8 million) would occur in adults without CVD.
  • Among adults, 60-75 yrs without CVD who are not receiving statin therapy, % that would be eligible would increase from 30.4% to 57.4% among men and from 21.2% to 53.6% among women.
  • This effect would be largely driven by increased # of adults who would be classified solely by their 10-year risk of a CV event.

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 follow-up that stresses adherence.
- For primary prevention, they are “patient-centered”
- Guidelines will change in the future as quality data becomes available to improve them

Hypertriglyceridemia and Omega-3 Fatty Acids: Current and Emerging Treatment Options

PriMed Anaheim, CA
March 26, 2014

Eliot A. Brinton, MD, FAHA, FNLA
President, American Board of Clinical Lipidology
Director, Atherometabolic Research
Utah Foundation for Biomedical Research
President, Utah Lipid Center
Salt Lake City
eliot.brinton@utah.edu

Educational Objectives

At the end of this presentation, listeners will be able to:
- Explain
  - The pathophysiology of hypertriglyceridemia (HTG)
  - The association of HTG with pancreatitis and cardiovascular disease (CVD)
  - Measurement of triglycerides (TG) and clinically important degrees of HTG
- Discuss settings appropriate for use of currently available TG-lowering treatments
- Compare and contrast currently available and emerging HTG therapies

TG Levels Predict CHD Risk
(Meta-analysis of 29 Studies, N=262,525*)

<table>
<thead>
<tr>
<th>Groups</th>
<th>CHD Cases</th>
<th>CHD Risk Ratio* (95% CI)</th>
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<tbody>
<tr>
<td>Duration of Follow-up</td>
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<td></td>
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<tr>
<td>≥10 years</td>
<td>5092</td>
<td>1.72 (95% CI 1.56-1.90)</td>
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<td>Sex</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>7728</td>
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<tr>
<td>Female</td>
<td>1994</td>
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<tr>
<td>Nonfasting</td>
<td>2674</td>
<td>*</td>
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<tr>
<td>Adjusted for HDL-C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4469</td>
<td>*</td>
</tr>
<tr>
<td>No</td>
<td>5689</td>
<td>*</td>
</tr>
<tr>
<td>Overall CHD Risk Ratio*</td>
<td></td>
<td>1.72 (95% CI 1.56-1.90)</td>
</tr>
</tbody>
</table>

*Also: 22% ↑ CV/↑ 88 mg/dL ↑ TG (61 studies N=330,566) Liu, J. Lipids in Health and Disease. 2013, 12:159.

CHD Risk Is Increased With TG Levels ≥ 200 mg/dL

TGs are independently associated with premature familial CHD*

*Triglyceride odds ratio adjusted for HDL-C; n=653 (FHx early CHD), n=1029 (control)
TG Categories: Names, Disease Risks, and Drug Approval Pathways

<table>
<thead>
<tr>
<th>TG Range (mg/dL)</th>
<th>NCEP ATP-III 1</th>
<th>AHA Statement 2</th>
<th>Disease Risk</th>
<th>FDA</th>
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</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>Desirable</td>
<td>Optimal</td>
<td>None</td>
<td></td>
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<tr>
<td>150-199</td>
<td>Borderline High</td>
<td>Borderline</td>
<td>More dyslipidemia</td>
<td>No Rx interest</td>
</tr>
<tr>
<td>200-499</td>
<td>High</td>
<td>High</td>
<td>↑CVD</td>
<td>Approve if CVD likely</td>
</tr>
<tr>
<td>≥500</td>
<td>Very High</td>
<td>Very High</td>
<td>↑CVD &amp; ↑ ApoC &amp; ↑ CE particle (esp if &gt;2000)</td>
<td>Approve if reasonable safety</td>
</tr>
</tbody>
</table>


TG Measurement

LDL-C Doubly Underestimates ↑CVD Risk With HTG/low HDL-C & Small, Dense LDL

HG As a Cause of Atherosclerosis & CVD

**Biological mechanisms** (selected)
- TGRLp Remnants → senescence of endothelial precursors
- pTG → ↑ endothelial microparticles, inflammatory cytokines, apoptosis
- TG lipolysis → FFA → ↑ endothelial cell inflammation
- Apo C-III → vascular endothelial activation & monocyte adhesion
- Apo C-III deficiency → ↓athero & ↑longevity

**Incidence of Pancreatitis by TG Level**

<table>
<thead>
<tr>
<th>TG Level vs Acute Pancreatitis Risk</th>
<th>Incidence of Acute Pancreatitis by TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-response of TG vs. Pancreatitis (adjusted HR, 1.04 [95% CI, 1.02-1.05])</td>
<td>Group 1</td>
</tr>
<tr>
<td>Pancreatitis ↑4%/100 mg/dL ↑TG</td>
<td>Group 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Triglycerides (mg/dL)</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
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<tbody>
<tr>
<td>≤150 (&lt;150 mg/dL)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>150-499 (150-499 mg/dL)</td>
<td>0.5</td>
<td>0.5</td>
<td>2.5</td>
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<tr>
<td>≥500 (≥500 mg/dL)</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

After adjustment for covariates and removal of patients hospitalized for gallstones, chronic pancreatitis, alcohol-related morbidity, renal failure, and other biliary disease


**TG Measurement**

**Incidence of Pancreatitis by TG Level**

- Only factor specific for TG rather than TG-rich Lp

**Lipid profile:**
- TC 198 mg/dL
- LDL-C 130 mg/dL
- TG 90 mg/dL
- HDL-C 50 mg/dL
- Non-HDL-C 148 mg/dL

**Lipid profile:**
- TC 210 mg/dL
- LDL-C 130 mg/dL
- TG 250 mg/dL
- HDL-C 30 mg/dL
- Non-HDL-C 180 mg/dL

Non–HDL-C Is Stronger than LDL-C in Predicting CHD Risk

Non–HDL-C: A Neglected CVD Risk Factor/Rx Goal

TG Measurement

- 12-h fast (water and other non-caloric beverages ok/encouraged)
- Non-fasting TG predicts CVD risk in populations but variable in individuals
- NF TG < 200 mg/dL implies normal TG, may NOT require fasting TG
- Total TG is standard
- Remnant particle testing controversial
  - Post-prandial (cumbersome, no standards)
  - RLP-C—easy but ?accuracy ?validation
  - DGUC—harder but better? Remnant Lp-C an emerging RF (as A-I/Rem)?

Non–HDL-C incorporates LDL-C + cholesterol content of TG-rich lipop (both atherogenic)
Non–HDL-C is much less variable
- Day to day
- Fasting vs non-fasting
More consensus re: Rx goals for non-HDL-C vs TG
TG/5 estimates VLDL-C (≈remnant chol), but direct-measure is intuitively more informative
TG might be directly atherogenic but remnant cholesterol is especially so (+ other non-lipid mechanisms? e.g. apo C-III—how to measure?)

Treatment of HTG: Begin with 2° Causes

- High fructose/sucrose/carbohydrate intake
- Low fiber intake
- Ethanol
- Sedentary lifestyle
- Central obesity/insulin resistance
- DM (especially if poorly controlled)
- Hypothyroidism
- Nephrotic syndrome
- Medications:
  - Antiretrovirals
  - Oral estrogens
  - Systemic glucocorticoids
  - Retinoic acid derivatives
  - Minor effects (some antipsychotics, nonselective beta-blockers, thiazide diuretics, etc.)

AHA Scientific Statement: Treatment Effect by Drug Class for Lowering Triglyceride Levels

<table>
<thead>
<tr>
<th>Drug</th>
<th>% TG Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrates</td>
<td>30-50</td>
</tr>
<tr>
<td>Immediate-release niacin</td>
<td>20-50</td>
</tr>
<tr>
<td>Omega-3 Fatty Acids</td>
<td>20-50</td>
</tr>
<tr>
<td>Extended release niacin</td>
<td>10-30</td>
</tr>
<tr>
<td>Statins</td>
<td>10-30</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>5-10</td>
</tr>
</tbody>
</table>

The 2013 ACC/AHA Cholesterol Guidelines Focus Only on Statins—Isn’t Statin Monotherapy Enough?

No!

• Statins don’t eliminate CVD (~2/3 remains)
• Statins don’t lower TG enough (most pts)
• Residual HTG during statin Rx predicts CVD risk
• Those guidelines did not address HTG; they refer to the 2011 AHA TG guidelines

↑Residual CHD Risk in HTG Despite LDL-C <70 w/ Statin Rx

(67%↑ coronary events* if TG ≥200 mg/dL despite LDL-C <70 mg/dL with a high-dose statin)

ACCORD-LIPID: 1st Endpoint in HTG + Low HDL-C vs. All Others (Pre-specified Subgroups)

Statin + EPA/DHA (TG 200-500):
COMBOS Lipid Endpoints

Statin + EPA (TG 200-500):
ANCHOR Lipid Endpoints

Bottom line: EPA+DHA better for ↓TG & ↑HDL-C.
EPA better for ↓LDL-C, ↓Non-HDL-C, ↓Apo B (↓CVD?)
Available Forms of Omega-3 Fatty Acids for Supplement and Pharmaceutical use

<table>
<thead>
<tr>
<th>Form</th>
<th>Absorption</th>
<th>Consistency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epanova (OM3-FFA)</td>
<td>Good Conc.</td>
<td>EE Om-3</td>
</tr>
<tr>
<td>Lipid inclusion</td>
<td>200 mg/dL ≥ TG</td>
<td>2 g/d*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>0.7 - 2%</td>
<td>1.0 - 2%</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>2 - 3%</td>
<td>2 - 3%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>2 - 3%</td>
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</tr>
</tbody>
</table>

Values are n (%).

Epanova not FDA approved

---

**EVOLVE: Om3-FFA Lipid Effects (1st & 2nd Endpoints)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OO, 4 g/d</th>
<th>OM3-FFA, 2 g/d*</th>
<th>OM3-FFA, 3 g/d*</th>
<th>OM3-FFA, 4 g/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint TGL mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>148 (418, 2855)</td>
<td>177 (445, 2017)</td>
<td>220 (448, 2329)</td>
<td>655 (445, 2998)</td>
</tr>
<tr>
<td>End of treatment</td>
<td>142 (119, 563)</td>
<td>154 (179, 237)</td>
<td>154 (145, 2051)</td>
<td>513 (115, 721)</td>
</tr>
<tr>
<td>%Δ LDL-C (55% CI)</td>
<td>(-13.1 to 5.4)</td>
<td>(-13.2 to -18.3)</td>
<td>(-13.4 to -17.8)</td>
<td>(-17.3 to -23.4)</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C mg/dL Baseline</td>
<td>215 (179, 586)</td>
<td>220 (165, 517)</td>
<td>225 (115, 600)</td>
<td>200 (107, 548)</td>
</tr>
<tr>
<td>End of treatment</td>
<td>217 (186, 443)</td>
<td>209 (65, 138)</td>
<td>97 (77, 163)</td>
<td>211 (91, 430)</td>
</tr>
<tr>
<td>%Δ HDL-C, mg/dL Baseline</td>
<td>2.1 (2.0 to 7.4)</td>
<td>7.6 (12.0 to 3.0)</td>
<td>4.1 (13.4 to 2.2)</td>
<td>9.6 (14.6 to 5.1)</td>
</tr>
</tbody>
</table>

TRIG CVD significant difference vs control: *p < 0.01, **p < 0.001, ***p < 0.0001

Lipid: Mean change from baseline (%) vs control: -4.5% (10.0% CI) vs placebo.

Epanova (OM3-FFA) not FDA approved

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**Om-3 + Statins (TG 200-500)**

<table>
<thead>
<tr>
<th>EPA+DHA EE</th>
<th>EPA EE</th>
<th>EPA+DHA FFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>COMBO (n=296)</td>
<td>ANCHOR (n=702)</td>
</tr>
<tr>
<td>Lipid profile</td>
<td>200 mg/dL &gt; TG &gt; 500 mg/dL</td>
<td>200 mg/dL &gt; TG &gt; 500 mg/dL</td>
</tr>
<tr>
<td>Duration</td>
<td>8 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment</td>
<td>6 g plus Simva 40mg</td>
<td>3 g plus Simva 100mg</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-26%</td>
<td>-17.1%</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-3.7</td>
<td>-2.8</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-2.2</td>
<td>-2.2</td>
</tr>
<tr>
<td>TC</td>
<td>-1.7</td>
<td>-5.2</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-1.2</td>
<td>-1.2</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>-0.2</td>
<td>-0.2</td>
</tr>
</tbody>
</table>


**Lipid Effects of Prescription Om-3 in TG >500 mg/dL**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OO, 4 g/d</th>
<th>OM3-FFA, 2 g/d*</th>
<th>OM3-FFA, 3 g/d*</th>
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Lipid: Mean change from baseline (%) vs control: -4.5% (10.0% CI) vs placebo.

Epanova (OM3-FFA) not FDA approved

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**Selected Om-3 CVD Outcome Studies**

<table>
<thead>
<tr>
<th>Om-3 Treatment</th>
<th>EPA+DHA EE</th>
<th>EPA EE</th>
<th>EPA+DHA FFA</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPA+DHA EE</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>EPA EE</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
</tr>
<tr>
<td>EPA+DHA FFA</td>
<td>5%</td>
<td>10%</td>
<td>15%</td>
</tr>
</tbody>
</table>

**Low-dose Om-3 doesn’t lower CVD in statin-era. Mid-dose Om-3 does (CVD)**

Epanova (OM3-FFA) not FDA approved
Reduction of Cardiovascular Events with EPA – Intervention Trial: REDUCE-IT

- N=8000 M&F ≥45 y/o
- High CVD risk:
  - Prior CHD (70% pts), or
  - DM-2 & ≥1 RF
- Dyslipidemic:
  - H/O Chol, but at LDL-C goal on statin, and
  - TG 150-500 mg/dL
- Randomized, double-blind, multinational
- 2 outcomes: individual CVD events, lipid/lipoprotein levels, safety, subgroup analyses (diabetics, etc.)
- Completion ~Nov 2016

Primary endpoint:
- 1st major CV event composite

AMR101 = icosapent ethyl = Vascepa

Fibrates vs. Omega-3 for Atheroprevention in HTG

Favoring Fibrates
- More conventional
- Generics available
- Slightly better HDL-C, LDL-C and TG effects?
- Other PPAR α benefits?
- More convenient
- Formulary coverage
- No fishy burping
- No ↑glucose
- ↑Microvasc dis (DM and pre-DM pts)?

Favoring Omega-3
- ↓CVD (and total mortality)?
- Greater range of ↓CVD MoA?
  - antiplatelet
  - anti-inflammatory
  - anti-arrrhythmic, etc.
- More “natural”
- Less drug-drug interaction
- No transaminase contraindicated.
- No statin precaution/warning
- Fewer GI Sx (?)
- No warfarin interaction
- No DVT or PE

Bottom line
- Both are good as first-line mono Rx
- Both often needed in combination!

Hypertriglyceridemia
Drug Treatment: Summary

When (after diet and Rx, 2° factors) use meds for:
- TG >500 for pancreatitis & athero—treat ALL
- TG 200-500 mg/dL; Rx to lower non-HDL-C to goal, esp. if 2° prevention or ↑ CVD risk

How?
- Diet ([sugar, fat, calories, EtOH] and lifestyle ([exercise]—do this in all patients!
- Fenofibrate—easy and effective
- Prescription Om-3—excellent fibrate alternative/adjunct
- Niacin—less well tolerated, good if HDL-C low?
- Statins—less effective, good if LDL-C high
- Pioglitazone useful in DM-2 (DM-2 prevent in pre-DM?)
- Combinations—any 2 (or 3) of above for greater TG ↓ and/or other lipid benefits (don’t do gemfib + statin)

Case
48-year-old man relocates to your town, and sees you for a physical
- F Hx +
  - No history of cardiovascular disease
- Tobacco
  - 20 pack years but quit 5 years ago
- Diet
  - 6 servings of fruits and vegetables daily
  - 5 servings of whole grains daily
  - Fish thrice weekly
  - Fats are nearly all PUFAs and MONOs
- Exercise
  - Sporadic twice weekly

Thank You!
**Case**

**Drugs**
- Lisinopril 10 mg (for HTN)

**Physical Exam**
- Vital Signs
  - Pulse: 64
  - BP: 146/86
  - Weight: 74.3 kg
  - Waist circ: 99 cm
  - BMI: 28.8 kg/m²
  - No other abnormalities

**Metabolic Panel**
- Total cholesterol: 232 mg/dL
  - TG: 330 mg/dL
  - HDL-C: 31 mg/dL
  - LDL-C: 135 mg/dL
- ALT normal
- FPG 110 mg/dL; AIC 6.2

**ACC/AHA Cholesterol Treatment Guidelines**

- **Clinical ASCVD** → < 75 yrs, high intensity statin
- **LDL-C > 190 mg/dL** → High Intensity Statin
- **Diabetes in age 40-75, LDL-C ≥ 75** → Moderate Intensity Statin
- **≥ 75 yrs or LDL-C ≥ 75** → Moderate to High Intensity Statin

**Primary Prevention**

**Global Risk Assessment**
- To estimate 10-year ASCVD risk
  - New Pooled Cohort Risk Equations
  - White and Black men and women
  - Heart Attack AND Stroke Risk included
- More accurately identifies higher risk individuals for statin therapy
  - Focuses statin therapy on those most likely to benefit
  - Avoid statin therapy in high-risk groups found not to benefit (heart failure, hemodialysis)

**Using the Risk Estimator**
- Gender: Male
- Age: 48
- Race: White
- Total Cholesterol: 232 mg/dL
- HDL-Cholesterol: 31 mg/dL
- SBP: 146 mm Hg
- Treatment for Hypertension: Yes
- Diabetes: No
- Smoker: Yes

**2013 Pooled Cohort Equations ASCVD Risk Calculator**
- By Nathaniel Lee, MD
  - Gender
  - Age
  - Race
  - Total Cholesterol
  - HDL Cholesterol
  - Systolic BP
  - Treatment for BP?
  - Diabetes
  - Smoking

Scan code or visit [http://tinyurl.com/ttm2vt](http://tinyurl.com/ttm2vt)

or google: 2013 pooled cohort risk calculator app
Using the Risk Estimator

- 10-Year ASCVD Risk: 20.0% calculated risk
- 1.7% with optimal risk factors
- Optimal risk factors include:
  - Total cholesterol 170 mg/dL
  - HDL-C 50 mg/dL
  - SBP 110 mm Hg
  - Not taking meds for hypertension
  - Not diabetic
  - Non smoker

Case

- Atorvastatin 10 mg initiated

Statins: Myopathy

- Abnormal AST and ALT
  - < 3X ULN: ~1.3%
  - > 3X ULN: <1.0%
  - Dose related
- Myopathy: Any disease of muscles
  - Myalgias: pain in a muscle of group of muscles
    - ~10%
  - Myositis: muscle symptoms with ↑ CK
    - ~2.5%
  - Rhabdomyolysis: > 50 fold ↑ in CK + renal impairment
    - <0.1%

ACC/AHA Cholesterol Treatment Guidelines

Case

- Patient returns to the office 6 weeks later, complaining of muscle aches. You discontinue the statin and investigate.

Case

- Patient labs:
  - CPK 122
  - Creatinine
  - Urinalysis negative for myoglobinuria

Bruckert E et al, Cardiovasc Drugs Ther 19:403, 2005
Otusko E, J Fam Pract 57:449, 2008
What the Clinician Needs to Consider

- Hypothyroidism
- Other drugs
  - Fibrates, azole anti-fungals, cyclosporine, macrolides, diltiazem, HIV protease inhibitors
- Genetic differences in drug-metabolizing enzymes, e.g. OATP1B1
  - SLCO1B1, CYP2D2, 3A4
- Neuromuscular diseases
  - Mitochondrial myopathy, McArdles disease, myotonic dystrophy, polymyositis

Case

You decide to add a low dose of a different statin (i.e. 5 mg rosuvastatin). The patient tolerates this dose and does not report any muscle symptoms. Due to prior muscle symptoms, the patient is unwilling to have his dose titrated up. His lipids are shown on the next slide.

Laboratory Assessment

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>6 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>232</td>
<td>181</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>135</td>
<td>95</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>330</td>
<td>265</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>201</td>
<td>148</td>
</tr>
</tbody>
</table>

What are the next steps according to the NCEP III guidelines?

Final Laboratory Assessment--Prescription Omega 3 Added to Statin Therapy

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>6 weeks</th>
<th>12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>232</td>
<td>181</td>
<td>158</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>31</td>
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<td>125</td>
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</tbody>
</table>

According to NCEP III, the patient is now at his LDL-C and non-HDL-C goal of <100 mg/dL and <130 mg/dL respectively

Question & Answer