Current Perspectives and Emerging Approaches in Lipid Management

Friday, November 21, 2014
3:15–4:45pm

The Henry, Autograph Collection
300 Town Center Dr.
Dearborn, MI

Eliot A. Brinton, MD
Associate Professor of Medicine
University of Utah School of Medicine
Salt Lake City, Utah

JoAnne M. Foody, MD
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Educational Partner:
Voxmedia, LLC
Session 6: 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

Eliot A. Brinton, MD
President
Atherometabolism Foundation
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 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 scientific publications in 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 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.

JoAnne M. Foody, MD
Assoc. Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Dr. JoAnne Foody is an associate professor of medicine at Harvard Medical School and the medical director of the Pollin Cardiovascular Wellness Center at Brigham and Women’s Hospital, Boston, Massachusetts. She earned her medical degree from the University of Chicago Pritzker School of Medicine, completed her internship and a residency in internal medicine at Brigham and Women’s Hospital, and held a fellowship in cardiology at the Cleveland Clinic Foundation. Dr. Foody’s research focuses on identifying and fostering greater use of clinical strategies that prevent adverse cardiovascular events in people with and without coronary artery disease. She has had leadership roles in multiple quality improvement projects of the Centers for Medicare & Medicaid Services.

Session 6
fellow of the American College of Cardiology (ACC) and the American Heart Association, Dr Foody is the author of over 100 peer reviewed articles, is editor of the authoritative text “Preventive Cardiology”, and serves as editor-in-chief of CardioSmart.org: the ACC’s patient website.

Faculty Financial Disclosure Statements
The presenting faculty reports the following:

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

Dr Foody has nothing to disclose.
Dr Foody will discuss unlabeled/unapproved uses of drugs in her presentation.

Education Partner Financial Disclosure Statements
The content collaborator at Voxmedia has no financial relationships to disclose.

Suggested Reading List


SESSION 6
3:15pm – 4:45pm

Current Perspectives and Emerging Approaches in Lipid Management

SPEAKERS
Eliot Brinton, MD
JoAnne Foody, MD, FACC, FAHA

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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.

Drug List

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
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<tbody>
<tr>
<td>Atorvastatin</td>
<td>Lipitor</td>
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<tr>
<td>Fluvastatin</td>
<td>Lescol, Lescol XL</td>
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<td>Lovastatin</td>
<td>Mevacor, Altoprev</td>
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<td>Tirofiban</td>
<td>Aggrastat</td>
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<tr>
<td>Cholestyramine</td>
<td>Questran, Questran Light, Prevalite, Locholest, Locholest Light</td>
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<td>Welchol</td>
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<td>Itraconazole</td>
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<tr>
<td>Ketoconazole</td>
<td>Nizoral, Extina, Xolegel, Kuric</td>
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<tr>
<td>Erythromycin</td>
<td>E-mycin, Eryc, Ery-tab, PCE, Ilosone, Pediazole</td>
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<td>Verapamil</td>
<td>Calan, Verelan, Verelan PM, Isoptin, Isoptin SR, Covera-HS</td>
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<td>Amiodarone</td>
<td>Pacerone, Cordarone, Cordarone IV, Nexterone</td>
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<td>Niacin/Nicotinic acid</td>
<td>Niacor, Niaspan, Slo-Niacin</td>
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<tr>
<td>Gemfibrozil</td>
<td>Lopid</td>
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<td>Bezafibrate</td>
<td>Bezalip</td>
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<tr>
<td>Fenofibrate</td>
<td>Tricor, Lipidil, Antara, Triglide, Triglide, Trilipix</td>
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<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>
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Educational Objectives

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• 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.
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• 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

JoAnne M. Foody, MD
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts
CHD Risk According to LDL-C Level

Relative Risk for Coronary Heart Disease (Log Scale)

CHD=Coronary heart disease, LDL-C=Low-density lipoprotein cholesterol


A Meta-analysis of 164 Trials

<table>
<thead>
<tr>
<th>Statin</th>
<th>10 mg/d</th>
<th>20 mg/d</th>
<th>40 mg/d</th>
<th>80 mg/d</th>
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<tbody>
<tr>
<td>Atorvastatin</td>
<td>69 (37)</td>
<td>80 (43)</td>
<td>91 (49)</td>
<td>102 (55)</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>29 (15)</td>
<td>39 (21)</td>
<td>50 (27)</td>
<td>61 (33)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>39 (21)</td>
<td>54 (20)</td>
<td>68 (37)</td>
<td>83 (46)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>37 (20)</td>
<td>45 (24)</td>
<td>53 (29)</td>
<td>62 (33)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>80 (43)</td>
<td>90 (48)</td>
<td>99 (53)</td>
<td>108 (58)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>51 (27)</td>
<td>60 (32)</td>
<td>69 (37)</td>
<td>78 (42)</td>
</tr>
</tbody>
</table>

Data presented as absolute reductions in LDL-C* (mg/dL) and percent reductions in LDL-C (in parentheses)

*Standardized to LDL-C 186 mg/dL (mean concentration in trials) before Rx.
† Independent of pre-Rx LDL-C.
‡Maximum dose of 80 mg/d administered as two 40-mg tablets.
§Not FDA approved at 80 mg/d.

HMG-CoA Reductase Inhibitor: Primary Prevention

Relationship between LDL-C Levels and Event Rates in Primary Prevention Statin Trials

AFCAPS= Air Force/Texas Coronary Atherosclerosis Prevention Study; ASCOT= Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm; WOSCOPS= West of Scotland Coronary Prevention Study.


JUPITER – Study Design

No history of CAD men ≥ 50 yrs women ≥ 60 yrs
LDL-C <130 mg/dL CRP ≥ 2.0 mg/L

CAD=coronary artery disease, LDL-C=low-density lipoprotein cholesterol; CRP=C-reactive protein; HbA1c=glycated haemoglobin

Ridker PM. Circulation 2005;111: 2590-2597.
Ridker PM. Am J Cardiol 2007; 100: 1659–1664.

JUPITER - Primary Endpoint

Time to first occurrence of a CV death, non-fatal stroke, non-fatal MI, unstable angina or arterial revascularization

Hazard Ratio 0.56
(95% CI 0.46-0.69)
P<0.00001

JUPITER - Total Mortality

Death from any cause

Hazard Ratio 0.80
(95% CI 0.67-0.97)
p=0.02

### HMG-CoA Reductase Inhibitor: Secondary Prevention

#### Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)—TIMI 22 Study

4,162 pts with an ACS randomized to atorvastatin (80 mg) or pravastatin (40 mg) for 24 months

- **Follow-up (months):** 3 6 9 12 15 18 21 24 27 30
- **RRR:** 16%

**Acute intensive treatment significantly reduces event rates**

ACS=Acute coronary syndrome, CV=Cardiovascular, MI=Myocardial infarction, UA=Unstable angina


### HMG-CoA Reductase Inhibitor: Secondary Prevention

#### Scandinavian Simvastatin Survival Study (4S)

- **Mortality (%):**
  - Placebo: 11.5
  - Simvastatin: 8.2

- **RRR:** 30%

**Statins provide significant benefit in those with average LDL-C levels**

4,444 patients with angina pectoris or previous MI randomized to simvastatin (20-40 mg) or placebo for 5.4 years

**Statins provide significant benefit across a broad range of LDL-C levels**

CAD=Coronary artery disease, CI=Confidence interval, DM=Diabetes mellitus


### HMG-CoA Reductase Inhibitor: Secondary Prevention

#### 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

- **RRR:** 32%

**High-dose statins provide benefit in chronic CHD**

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

1.4% incidence of elevated hepatic transaminases (1.1% incidence in control arm)

- Dose-dependent phenomenon that is usually reversible
- 15.4% incidence of myalgias* (18.7% incidence in control arm)
- 0.9% incidence of myositis (0.4% incidence in control arm)
- 0.2% incidence of rhabdomyolysis (0.1% incidence in control arm)


74,102 subjects in 35 randomized clinical trials with statins

Risk Factors for the Development of Myopathy*

<table>
<thead>
<tr>
<th>Concomitant Use of Meds</th>
<th>Other Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrate</td>
<td>Advanced age (especially &gt;80 years)</td>
</tr>
<tr>
<td>Nicotinic acid (Rarely)</td>
<td>Women &gt; Men especially at older age</td>
</tr>
<tr>
<td>Cyclopentolate</td>
<td>Small body frame, frailty</td>
</tr>
<tr>
<td>Anti fungal azoles**</td>
<td>Multisystem disease†</td>
</tr>
<tr>
<td>Macrolide antibiotics†</td>
<td>Multiple medications</td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td>Perioperative period</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Verapamil, Amiodarone</td>
<td>Grapefruit juice (&gt;1 quart/day)</td>
</tr>
</tbody>
</table>

*General term to describe diseases of muscles
**Itraconazole, Ketoconazole
†Erythromycin, Clarithromycin
‡Chronic renal insufficiency, especially from diabetes mellitus

2013 ACC / AHA Cholesterol Guideline: 4 Statin Benefit Groups

- Clinical Atherosclerotic Cardiovascular Disease (ASCVD)
- LDL-C ≥ 190 mg/dL, Age ≥ 21 years
- Primary Prevention--Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary Prevention--No Diabetes†: ≥ 7.5% ‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

† Requires risk discussion between clinician and patient before statin initiation
‡ Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator

2013 ACC / AHA Cholesterol Guideline: Primary Prevention Global Risk Assessment

- To estimate 10-year ASCVD* risk
  - New Pooled Cohort Risk Equations
  - White and black men and women
- More accurately identifies higher risk individuals for statin therapy
  - Focuses statin therapy on those most likely to benefit
  - You may wish to avoid initiating statin therapy in high-risk groups found not to benefit (higher grades of heart failure and hemodialysis)

*10-year ASCVD: Risk of first nonfatal myocardial infarction, coronary heart disease death, nonfatal or fatal stroke

Individuals Not in a Statin Benefit Group

- In those for whom a risk decision is uncertain, these factors may inform clinical decision making:
  - Family history of premature ASCVD
  - Elevated lifetime risk of ASCVD
  - LDL-C ≥160 mg/dL
  - hs-CRP ≥2.0 mg/L
  - CAC score ≥300 Agaston units
  - ABI <0.9
- Statin use still requires discussion between clinician and patient

ABI, ankle brachial index

Safety

- RCTs & meta-analyses of RCTs used to identify important safety considerations
- Allow estimation of net benefit from statin therapy
- ASCVD risk reduction versus adverse effects
- Expert guidance on management of statin-associated adverse effects, including muscle symptoms
- 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 (cont.)

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


Association between statins and development of diabetes

<table>
<thead>
<tr>
<th>Statin</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=91 140)</td>
<td>1.09 (1.02–1.17)</td>
</tr>
<tr>
<td>Atorvastatin only (n=7773)</td>
<td>1.14 (0.89–1.46)</td>
</tr>
<tr>
<td>Simvastatin only (n=18 815)</td>
<td>1.11 (0.97–1.26)</td>
</tr>
<tr>
<td>Rosuvastatin only (n=24 714)</td>
<td>1.18 (1.04–1.33)</td>
</tr>
<tr>
<td>Pravastatin (n=33 627)</td>
<td>1.03 (0.90–1.19)</td>
</tr>
<tr>
<td>Lovastatin (n=6211)</td>
<td>0.98 (0.70–1.38)</td>
</tr>
</tbody>
</table>


FDA reports on the Risk of Diabetes with statins

February 2012

• A small increased risk of elevated blood sugar levels and the development of Type 2 diabetes have been reported with the use of statins.

• “Clearly we think that the heart benefit of statins outweighs this small increased risk” But blood-sugar levels may need to be assessed after instituting statin therapy.

www.fda.gov/ForConsumers/ConsumerUpdates

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

Three Principles

- Do not focus on LDL-C or non-HDL-C cholesterol levels as treatment goals
- Although continue to obtain a lipid panel to monitor adherence
- Use medications proven to reduce ASCVD risk
- Risk decisions in primary prevention require a clinician-patient discussion to evaluate the benefits and harms for the individual patient
- Optimal lifestyle emphasized
- Clinician-patient discussion needed for appropriate shared decision-making

Application of New Cholesterol Guidelines to a Population Based Sample

- 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.

Summary

- LDL linked to CV events
- Robust evidence that statins improve outcomes in wide range of patients
- New guidelines support moderate to high intensity statins in significant majority of patients
- Adverse side effects may limit utility and add to nonadherence, particularly at high dose
- While guidelines suggest not treating to target, LDL levels important to monitor for response and adherence

Educational Objectives

At the end of this presentation, listeners will be able to:

- Explain
  - HTG prevalence and pathophysiology of the “atherogenic dyslipidemia” of insulin resistance
  - Likely causal associations of HTG with
    - Acute pancreatitis
    - Cardiovascular disease (CVD)
- Discuss measurement of TG and related levels
- Assess prescription vs dietary supplement omega-3 treatments
- Choose from available prescription omega-3 treatments according to clinical circumstances
- Implement appropriate omega-3 treatment in context of other TG-lowering medications

Hypertriglyceridemia Management: Focus on Omega-3 Fatty Acids

PriMed Dearborn, MI
November 21, 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
**Causes and Atherogenic Consequences of Hypertriglyceridemia**

- Central Adiposity
- Insulin Resistance
- Fatty Liver
- Triglycerides (TG)
- Very Low-Density Lipoprotein (VLDL)
- Cholesterol Ester Transfer Protein (CETP)
- HDL
- Hepatic Lipase
- Kidneys
- Rapid Loss of Apo A-I
- Fatty Liver & ↑ VLDL synth are key to moderate HTG & its athero consequences

**Fatty Liver & ↑ VLDL synth are key to moderate HTG & its athero consequences**

- TG
- VLDL-C
- LDL size
- Apo B & LDL-P
- HDL
- Apo A-I

**Incidence of Pancreatitis by TG Level**

- **TG Level vs Acute Pancreatitis Risk**
  - Dose-response of TG vs. Pancreatitis (adjusted HR, 1.04 [95% CI, 1.02-1.05])
  - Pancreatitis: ↑4%/100 mg/dL ↑TG*

**TG Levels Predict CHD Risk**

- **(Meta-analysis of 29 Studies, N=262,525*)**

<table>
<thead>
<tr>
<th>Groups</th>
<th>CHD Cases</th>
<th>Duration of Follow-up</th>
<th>CHD Risk Ratio† (95% CI)</th>
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<tbody>
<tr>
<td>≤150 (unit TG)</td>
<td>5902</td>
<td>&lt;10 years</td>
<td>4266</td>
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<tr>
<td>150-499 (unit TG)</td>
<td>7728</td>
<td>Female</td>
<td>1094</td>
</tr>
<tr>
<td>≥500 (unit TG)</td>
<td>7484</td>
<td>Nonfasting</td>
<td>2674</td>
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<tr>
<td>Adjusted for HDL-C</td>
<td>4469</td>
<td>Yes</td>
<td>5689</td>
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<td>Overall CHD Risk Ratio†</td>
<td>1.72 (95% CI, 1.56-1.90)</td>
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*Only factors specific for TG rather than TG-rich Lp

**Mechanisms & Evidence for HTG As a Cause of Atherosclerosis & CVD**

- "Atherogenic dyslip": SD LDL, ↓A-I, ↑TGRLp Chol
- ↑TGRLp remn → endoth precursors senescence
- ↑ppTG → ↑endothelial microvesicles, inflammatory cytokines, apoptosis
- Lipolysis of ↑TG → ↑FFA → ↑endothelial inflammation
- ↑Apo C-III → endoth activation & monoc. adhesion
- Mendelian randomization suggests HTG → CVD


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**Incidence of Acute Pancreatitis by TG**

- Group 1: ≤150 mg/dL
- Group 2: 150-499 mg/dL
- Group 3: ≥500 mg/dL

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


**Mechanisms & Evidence for HTG As a Cause of Acute Pancreatitis**

- Large, TG-rich chylomicrons
- Impaired pancreatic capillary blood flow
- Modest pancreatic lipase leak → ↑FFA production
- Ischemia
- Inflammation
- Pancreatic acinar cell injury

**Proposed Mechanisms of VHTG-Induced Acute Pancreatitis**


**HTG as a cause of Acute Pancreatitis and ASCVD**

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

**Groups CHD Cases**

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*Only factors specific for TG rather than TG-rich Lp
Lipid Measurement in HTG

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

Large LDL
- Fewer Particles & Less Risk/Particle

Small, Dense LDL
- More Particles & More Risk/Particle

Lipid profile: TC 108 mg/dL LDL-C (130 mg/dL) Apo B

Lipid profile: TC 210 mg/dL LDL-C 130 mg/dL Apo B

TC 108 mg/dL LDL-C 130 mg/dL Apo B

TC 210 mg/dL LDL-C 130 mg/dL Apo B

Other Non–HDL-C benefits:
- Valid in non-fasting samples
- Valid in HTG patients
- Counts most ↑CVD risk from HTG

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

Non–HDL-C, mg/dL

Relative CHD Risk

<130 130-159 ≥160 160-189 ≥190

*Lipid profile:
- TG 90 mg/dL HDL-C 50 mg/dL Non–HDL-C 148 mg/dL
- TG 250 mg/dL HDL-C 30 mg/dL Non–HDL-C 180 mg/dL

Treatment of HTG:

Address 2o Causes 1st

- High fructose/sucrose/carbohydrate intake
- High fat intake (need to ↓only if TG >~700 mg/dL)
- Low fiber intake
- Ethanol (may →↑TG even in moderation)
- Sedentary lifestyle
- Central obesity/insulin resistance
- DM (especially if poorly controlled)
- Hypothyroidism
- Nephrotic syndrome

Medications:
- Oral estrogen (contraceptives or HRT)
- Systemic glucocorticoids
- Antiretrovirals (for HIV)
- Retinoic acid derivatives
- Various with minor effects (some antipsychotics, nonselective beta-blockers, thiazide diuretics, etc.)

Diet & Lifestyle for HTG

- TG is the most responsive of all lipids!
- ↓Caloric balance → ↓ins. resist → ↑LPL
  - ↓Calories (generally more effective)
  - ↑Exercise (broader benefits?)
- "Continental Divide" re: food type
  - If TG <~700: ↓Sugar (fructose) → ↓VLDL synth (similar benefits from ↓EtOH, ↓oral estrogen?)
  - If TG >~700: ↓Fat → ↓chylomicron synthesis


Prescription Medications for HTG

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


Statin Monotherapy Leaves ↑Residual CHD Risk w/ HTG
(67% ↑ coronary events* if TG ≥200 mg/dL despite LDL-C <70 mg/dL with a high-dose statin)

These data imply adding TG-Rx to a statin may reduce this residual risk, AND recent trials of om-3, fibrates & niacin show ↓CVD in HTG/low HDL-C patients!

Omega -3 Dietary Supplements are NOT forTreating Disease!

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

Drugs | % Triglyceride Reduction
--- | ---
Fibrates | 30-50
Omega-3 Fatty Acids | 20-50
Immediate-release niacin | 20-50
Extended release niacin | 10-30
Statins | 10-30
Ezetimibe | 5-10


EPA+DHA EE

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

EPA+DHA EE

EPA/DHA FFA


*P<0.05
### Om-3 + Statins (TG 200-500)

<table>
<thead>
<tr>
<th>Study</th>
<th>COMBO (n=256)</th>
<th>ANCHOR (n=702)</th>
<th>ESPRIT (n=647)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid inclusion</td>
<td>200 mg/dL ≥ TG = 500 mg/dL</td>
<td>200 mg/dL ≥ TG = 500 mg/dL</td>
<td>Patients with high risk for CV events with 200 mg/dL ≥ TG = 500 mg/dL</td>
</tr>
<tr>
<td>Duration</td>
<td>8 weeks</td>
<td>12 weeks</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Treatments</td>
<td>4 g/d plus Simva 40mg</td>
<td>Placebo plus Simva 40mg</td>
<td>4 g/d plus statin</td>
</tr>
</tbody>
</table>

### CVD Endpoint Trials of Omega-3 Treatment

**Recent Results: CVD Endpoint Trials**

<table>
<thead>
<tr>
<th>CVD Endpoint Trials</th>
<th>Om-3 Type/dose</th>
<th>Population</th>
<th>N/yr pub</th>
<th>Gender</th>
<th>Risk Profile</th>
<th>Follow-up</th>
<th>Statin Use</th>
<th>Primary End Point</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>REDUCE-IT</td>
<td>EPA/DHA 1 g/day</td>
<td>International</td>
<td>~8,000</td>
<td>70%</td>
<td>1RF; H/O ↑TC</td>
<td>4-6 y (event driven)</td>
<td>100%</td>
<td>CV death, NFMI or stroke, cor revasc, hosp for USA</td>
<td>HR=0.98, P=0.72</td>
</tr>
<tr>
<td>STRENGTH</td>
<td>4g/d bid</td>
<td>Japanese</td>
<td>~29,000</td>
<td>61%</td>
<td>100%</td>
<td>4 y median</td>
<td>100%</td>
<td>CV death, NFMI or stroke, cor revasc, hosp for USA</td>
<td>HR=0.97, P=0.58</td>
</tr>
</tbody>
</table>

### TG Treatment Choices: Omega-3 vs Others

**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?
- anti-platelet
- anti-inflammatory
- anti-arrhythmic, etc.
- More “natural”
- Less drug-drug interaction
- No transaminase contraind.
- 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!
**Choice of Prescription Om-3**

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>EPA/DHA (total)</th>
<th>Bioavailability (short-term)</th>
<th>Regimen</th>
<th>Tolerability issues</th>
<th>LDL-C effects (VHITG/HTG)</th>
<th>CVD?</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERADCA</td>
<td>55/45 (84%)</td>
<td>Good</td>
<td>2 bid w/ meals</td>
<td>Fishy taste &amp; eruct, dyspeps</td>
<td>↑↑/±</td>
<td>No data, but ongoing trial</td>
</tr>
<tr>
<td>EPA+DHA*</td>
<td>100/0 (98%)</td>
<td>Good</td>
<td>2 bid w/ meals</td>
<td>Fishy urtica, dyspeps, diarrhea, nausea</td>
<td>↑↑/±</td>
<td>Probably (mid-dose) ongoing trial</td>
</tr>
<tr>
<td>FFA EPA+DHA***</td>
<td>73/27 (75%)</td>
<td>Excellent</td>
<td>2 or 4 qd meal indep.</td>
<td>Arthralgia only</td>
<td>↑↑/±</td>
<td>No data, but ongoing trial</td>
</tr>
</tbody>
</table>


**Hypertriglyceridemia Drug Treatment: Summary**

When (after diet and R, 2nd 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 2nd 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

**Case Presentation**

Developed by Joanne Foody, MD and Terry A. Jacobson, MD

**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

**Case**

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
Clinical ASCVD
LDL-C > 190 mg/dL
Diabetes w/ age 40-75, LDL-C > 70
< 75 yrs, high intensity statin
≥ 75 yrs, moderate-intensity statin

Diabetes w/ age 40-75, LDL-C > 70
≥ 75 yrs, moderate-intensity statin
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)

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/ltmm2vt
or google: 2013 pooled cohort risk calculator app

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: No

Using the Risk Estimator
• 10-Year ASCVD Risk: 8.8% 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

ACC/AHA Cholesterol Treatment Guidelines
Clinical ASCVD
LDL-C ≥ 190 mg/dL
Diabetes w/ age 40-75, LDL-C ≥ 70
< 75 yrs, high intensity statin
≥ 75 yrs, moderate-intensity statin
High Intensity Statin
Moderate Intensity Statin
Moderate to High Intensity Statin
Case

- Atorvastatin 10 mg initiated

Case

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

Statins: Myopathy

- 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%

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

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

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?

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

<table>
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<tr>
<th>Measurement</th>
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<th>6 weeks</th>
<th>12 weeks</th>
</tr>
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<tbody>
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<td>TC (mg/dL)</td>
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