Current Perspectives and Emerging Approaches in Lipid Management

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2–3:30pm

George R. Brown Convention Center
1001 Avenida De Las Americas
Houston, Texas

Terry Jacobson, MD
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Emory University
Atlanta, Georgia

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

Educational Partner:
Voxmedia, LLC
Session 5: 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

Terry Jacobson, MD
Professor of Medicine
Emory University
Atlanta, Georgia

Dr Terry Jacobson is a professor of medicine at Emory University and director of the office of health promotion and disease prevention at Grady Health Systems, Atlanta, Georgia; where he also serves as codirector of the lipid and cardiovascular risk reduction program. Dr Jacobson is a graduate of Cornell University and Cornell University Medical College and completed a Robert Wood Johnson clinical scholar’s fellowship at the University of Pennsylvania. His specific expertise is in hyperlipidemia, nutrition and drug management of hypercholesterolemia, coronary heart disease (CHD) risk reduction, and translating cardiovascular prevention into practice. He has published articles in the Journal of the American Medical Association, Lancet, the American Journal of Cardiology, Archives of Internal Medicine, Annals of Internal Medicine, the American Journal of Medicine, Current Opinion in Lipidology, and others. Dr Jacobson is a member of the Southeast Lipid Association board of directors.

JoAnne M. Foody, MD
Associate 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. A fellow of the American College of Cardiology (ACC) and the American Heart Association, Dr Foody is the author of over 100 peer-reviewed articles, 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 Jacobson has received honoraria and consultant fees from AstraZeneca.

Dr Foody has no financial relationship to disclose.

Education Partner Financial Disclosure Statement
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.


Learning 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

JoAnne M. Foody, MD
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts
**HMG-CoA Reductase Inhibitor: Reduction in LDL-C**

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>
</tr>
</thead>
<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 (29)</td>
<td>68 (37)</td>
<td>83 (45)</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>83 (45)</td>
<td>68 (37)</td>
<td>54 (29)</td>
<td>39 (21)</td>
</tr>
<tr>
<td>Simvastatin‡</td>
<td>51 (27)</td>
<td>60 (32)</td>
<td>69 (37)</td>
<td>82 (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.

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**HMG-CoA Reductase Inhibitor: Primary Prevention**

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

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**JUPITER – Study Design**

No history of CAD

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Rosuvastatin 20 mg (n=8900)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run-in</td>
<td>1 2 3 4 6-month intervals</td>
</tr>
<tr>
<td>Final</td>
<td>3-4 y</td>
</tr>
</tbody>
</table>

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


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**JUPITER - Primary Endpoint**

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

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**JUPITER - Total Mortality**

Death from any cause

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**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

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)

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

Mortality (%)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.5</td>
<td>8.2</td>
</tr>
</tbody>
</table>

30% RRR

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

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

Heart Protection Study (HPS)

20,536 patients with CAD, other occlusive arterial disease, or DM randomized to simvastatin (40 mg) or placebo for 5.5 years

Event Rate Ratio (95% CI)

<table>
<thead>
<tr>
<th>Statin Better</th>
<th>Statin Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.76 (0.72–0.81)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

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

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER)

5,804 patients aged 70-82 years with a history of, or risk factors for, vascular disease randomized to pravastatin (40 mg) or placebo for 3.2 years

CHD death, non-fatal MI, stroke (%)

Years

Placebo

Pravastatin

15% RRR, P=0.014

Statins provide benefit in older men

Heart Protection Study (HPS)

20,536 patients with CAD, other occlusive arterial disease, or DM randomized to simvastatin (40 mg) or placebo for 5.5 years

Event Rate Ratio (95% CI)

<table>
<thead>
<tr>
<th>Statin Better</th>
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<td>0.76 (0.72–0.81)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

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

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

22% RRR

High-dose statins provide benefit in chronic CHD

Relationship between LDL-C Levels and Event Rates in Secondary Prevention Statin Trials of Patients with Stable CHD

LDL-C=Low density lipoprotein cholesterol

CARE=Cholesterol and Recurrent Events Trial

HPS=Long-term Intervention with Pravastatin in Ischaemic Disease

HPS=Scandinavian Simvastatin Survival Study

TNT=Treating to New Targets

LDL-C=Low density lipoprotein cholesterol


SI conversion factor: To convert LDL-C to mmol/L, multiply by 0.0259

ACS=Acut coronary syndrome

CAD=Coronary artery disease

CHD=Coronary heart disease

CARE=Cholesterol and Recurrent Events Trial

HPS=Long-term Intervention with Pravastatin in Ischaemic Disease

HPS=Scandinavian Simvastatin Survival Study

TNT=Treating to New Targets

LDL-C=Low density lipoprotein cholesterol


Cannon CP et al. JAMA 2005;294:2492-2494
HMG-CoA Reductase Inhibitor: Adverse Effects

- 74,102 subjects in 35 randomized clinical trials with statins
  - 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)


**The rate of myalgias leading to discontinuation of atorvastatin in the TNT trial was 4.8% and 4.7% in the 80 mg and 10 mg arms, respectively.

**HMG-CoA Reductase Inhibitor: Adverse Effects

Concomitant Use of Meds
- Fibrate
- Nicotinic acid (Rarely)
- Cyclosporine
- Antifungal azoles**
- Macrolide antibiotics†
- HIV protease inhibitors
- Neofazadone
- Verapamil, Amiodarone

Other Conditions
- Advanced age (especially >80 years)
- Women > Men especially at older age
- Small body frame, frailty
- Multisystem disease‡
- Multiple medications
- Perioperative period
- Alcohol abuse
- Grapefruit juice (>1 quart/day)

*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


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.


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


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

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


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

Lessons From the Vignettes

None of these need ASCVD risk calculation:
- **Case 1:** ASCVD ≤75 years of age
  - High-intensity statin therapy
  - For optimal risk reduction in those who tolerate it
  - Moderate-intensity statin therapy
  - If >75 yo may be initiated or continued
  - Also use if high-intensity Rx not safe or not tolerated

Lessons From the Vignettes

None of these need ASCVD risk calculation:

• **Case 2**: LDL-C ≥190 mg/dL with secondary causes ruled out:
  - High-intensity statin therapy for optimal risk reduction in those who can tolerate it
  - If LDL-C levels remain very high after the intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to lower LDL-C further


Lessons From the Vignettes

ASCVD risk calculation useful here:

• **Case 3**: Diabetes, 40-75 yo, LDL-C 70-189 mg/dL
  - Evidence supports moderate-intensity statin Rx to be initiated or continued
  - High-intensity statin Rx reasonable if estimated 10-year ASCVD risk calculated to be >7.5%


Lessons From the Vignettes

ASCVD risk calculation useful here:

• **Case 4**: Primary prevention 40-75 yo; LDL-C 70-189 mg/dL; not low risk for ASCVD
  - Use Pooled Cohort Equations (risk calculator) to est.10-y ASCVD risk for African American & white individuals
  - Clinician-patient discussion before statin Rx initiated
  - Moderate- or high-intensity statin when ≥7.5% 10-y ASCVD risk
  - Moderate-intensity statin therapy reasonable when ≥5% 10-y ASCVD risk or when other characteristics that increase ASCVD risk are present


Lessons From the Vignettes: Primary Prevention

• **Case 5**: LDL-C <190 mg/dL
  - Not otherwise identified in a statin benefit group OR
  - After quantitative risk assessment, a risk-based treatment decision is uncertain
  - Additional factors that increase risk may be considered. In our case, can use LDL ≥160 mg/dL and family history of premature ASCVD as factors to inform the decision about statin Rx.


Lessons From the Vignettes

• **Case 5 (cont.)**
  - In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preferences.
  - Example of where guidelines inform clinical judgment, but do not replace it.


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

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

Terry A. Jacobson, MD, FAHA, FNLA
Director, Office of Health Promotion and Disease Prevention
Professor of Medicine
Emory University
Atlanta, GA

Outline

• Understand Hypertriglyceridemia and Other Atherogenic Lipids (Non-HDL-C and Apo B)
• Guidelines for HTG Management
• HTG Management: Lifestyle and Drug Therapy
• Omega 3 Fatty Acids: Evidence and Clinical Trials
• New Omega 3 Therapies

HTG, hypertriglyceridemia

AHA Scientific Statement on Triglycerides (TG) Classification

TG Revisions between 1984 and 2001

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Desirable</td>
<td>&lt; 250</td>
<td>&lt; 200</td>
<td>&lt; 150</td>
</tr>
<tr>
<td>Borderline High</td>
<td>250-499</td>
<td>200-399</td>
<td>150-199</td>
</tr>
<tr>
<td>High</td>
<td>500-999</td>
<td>400-999</td>
<td>200-499</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt; 1000</td>
<td>&gt;1000</td>
<td>&gt;500</td>
</tr>
</tbody>
</table>


TG and CHD Risk: Meta-Analysis of 29 Studies

<table>
<thead>
<tr>
<th>Groups</th>
<th>CHD Cases (≥10 years)</th>
<th>CHD Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥10 years</td>
<td>5902</td>
<td></td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>4256</td>
<td></td>
</tr>
</tbody>
</table>

Sex

Male 7278
Female 1994

Fasting Status

Fasting 7494
Nonfasting 2674

Adjusted for HDL

Yes 4409
No 5689

Overall CHD Risk Ratio*: 1.72 (95% CI, 1.56-1.90)

Increased Risk

Decreased Risk

* Individuals in top versus bottom third of usual log-TG values, adjusted for at least age, sex, smoking status, lipid concentrations, and (in most studies) blood pressure.


TG < 150 mg/dL Associated With Lower Risk of CHD Events Independent of LDL-C Level

PROVE IT-TIMI 22 Trial

N = 4162

• Achieving both low LDL-C and low TG (<150 mg/dL) may be important therapeutic strategies in patients after an ACS


Atherogenic Dyslipidemia Associated with Hypertriglyceridemia

Liver

FFA/TG

VLDL

LDL

HDL

CETP

HDL Lipase

Insulin Resistance: MetSyndrome and DM-2

Also, ↑ VLDL synthesis is assoc. w/ ↑ plasma apo B

Also, ↑ VLDL synthesis is assoc. w/ ↑ plasma apo B
What is Non–HDL-C?

- Non-HDL-C = TC – HDL-C
- Non-HDL-C = LDL-C + VLDL-C + IDL-C + Lp(a)
- Non-HDL-C goal
  - Normal VLDL-C defined as value when TG < 150 mg/dL
  - Non-HDL-C goal is 30 mg/dL above goal for LDL-C

Rationale for Non-HDL-C Assessment

- In the presence of high serum TG, non-HDL-C may better represent the concentration of all apoB-containing lipoproteins than does LDL-C.1
- Unlike calculated LDL-C, non-HDL-C can be accurately measured in nonfasting patients.2,3
- Non-HDL-C is highly correlated with total apoB.1
- Serum total apoB has been shown to have a strong predictive power for severity of coronary atherosclerosis and CHD events.1
- Non-HDL-C is calculated using subtraction of 2 values provided in a standard lipid panel (i.e., TC – HDL-C) and therefore incurs no additional costs.1,4

Apo B-containing Lipoproteins

Non–HDL-C

LDL-C

VLDL-C

IDL-C

Lp(a)

ATP III Treatment Recommendations for Elevated TGs

<table>
<thead>
<tr>
<th>TG (mg/dL)</th>
<th>ATP III Classification</th>
<th>Primary Target of Therapy</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>150–199</td>
<td>&quot;Borderline&quot; High TG</td>
<td>LDL-C goal</td>
<td>Weight reduction, increased physical activity</td>
</tr>
<tr>
<td>200–499</td>
<td>&quot;High&quot; TG</td>
<td>LDL-C goal</td>
<td>Weight reduction, increased physical activity; consider drug therapy to achieve non–HDL-C goal (intensify LDL-C–lowering with statin or lower VLDL-C by adding niacin or fibrates)</td>
</tr>
<tr>
<td>≥500</td>
<td>&quot;Very High&quot; TG</td>
<td>Reduce TG to prevent acute pancreatitis</td>
<td>Very low fat diet (fat ≤15% of total calories), weight reduction, increased physical activity, and drug therapy with niacin or fibrates</td>
</tr>
</tbody>
</table>

ATP III Update 2004:

LDL-C Goals and Cutpoints for Therapy in Different Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Non-HDL-C Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high risk: ACS, or CHD w/ DM, multiple CHD risk factors</td>
<td>&lt;70 mg/dL</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>High risk: CHD or CHD risk equivalents (DM) (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL</td>
<td>&lt;100 mg/dL (optional)</td>
</tr>
<tr>
<td>Moderately high risk: 2+ risk factors (10-year risk 10% to 20%)</td>
<td>&lt;130 mg/dL</td>
<td>&lt;160 mg/dL (optional)</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors (risk &lt;10%)</td>
<td>&lt;130 mg/dL</td>
<td>&lt;160 mg/dL</td>
</tr>
<tr>
<td>Lower risk: 0-1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>&lt;190 mg/dL</td>
</tr>
</tbody>
</table>

Lifestyle and Diet Can Improve Triglycerides and HDL-C

<table>
<thead>
<tr>
<th>Diet/Lifestyle Change</th>
<th>Lipid Profile Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>↑ HDL-C 4 mg/dL</td>
</tr>
<tr>
<td>Weight loss (5-10%)</td>
<td>↓ TG 20%, ↑ HDL-C 10%</td>
</tr>
<tr>
<td>Diet</td>
<td>¬Total carb &amp; ¬fat (to 33-50% of calories)</td>
</tr>
<tr>
<td>Implement a Mediterranean-style diet vs a low-fat diet</td>
<td>↓ TG 5%</td>
</tr>
<tr>
<td>Brisk 30-min walk, 3x/wk</td>
<td>↑ HDL-C 5-10%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Triglyceride 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>

TC = total cholesterol
Prescription Omega-3 Fatty Acids (EPA and DHA Ethyl Esters)

- Omega-3-acid ethyl esters (Lovaza®) is a combination of ethyl esters of omega-3-fatty acids containing 465 mg EPA and 375 mg DHA in 1 gram capsule
- Omega-3-acid ethyl esters is FDA approved for Very High TG (>500 mg/dL)
- The daily dose of omega-3-acid ethyl esters is 4 g per day taken as a single 4-gram dose (4 capsules) or as two 2-gram doses (2 capsules given twice daily).


Omega-3 free fatty acids (Epanova®) not approved by FDA

New Research in Omega 3 Formulations

- Is there a difference in bioavailability between Omega 3 fatty acids taken orally as “free fatty acids” (Epanova) versus their “acid ester form” (Lovaza and Vascepa)?
- Would these differences in formulation be clinically significant in terms of triglyceride reduction or effectiveness on a low fat diet?

EVOLVE: Primary and Secondary End Points

<table>
<thead>
<tr>
<th>Variable</th>
<th>OO, 4 g/d</th>
<th>OMEGA-3, 2 g/d*</th>
<th>OMEGA-3, 3 g/d*</th>
<th>OMEGA-3, 4 g/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>Baseline</td>
<td>152 (148, 153)</td>
<td>152 (148, 153)</td>
<td>152 (148, 153)</td>
</tr>
<tr>
<td>Non-HDL-C mg/dL</td>
<td>125 (120, 130)</td>
<td>125 (120, 130)</td>
<td>125 (120, 130)</td>
<td>125 (120, 130)</td>
</tr>
<tr>
<td>HDL-C mg/dL</td>
<td>57 (53, 61)</td>
<td>57 (53, 61)</td>
<td>57 (53, 61)</td>
<td>57 (53, 61)</td>
</tr>
<tr>
<td>LDL-C mg/dL</td>
<td>71 (65, 79)</td>
<td>71 (65, 79)</td>
<td>71 (65, 79)</td>
<td>71 (65, 79)</td>
</tr>
<tr>
<td>Apo B mg/dL</td>
<td>89 (86, 93)</td>
<td>89 (86, 93)</td>
<td>89 (86, 93)</td>
<td>89 (86, 93)</td>
</tr>
</tbody>
</table>

Secondary end points

- Non-HDL-C, mg/dL
- HDL-C, mg/dL
- LDL-C, mg/dL
- Apo B, mg/dL
- % LSQG CI

EVOLVE: A Trial of Omega-3 Free Fatty Acids (Epanova®: 2,3,4 g/d) versus Olive Oil Placebo (4g/day) in Patients with Triglycerides between 500 mg/dL to 2000 mg/dL, for 12 weeks

A randomized, double-blind, placebo controlled trial in men and women with triglycerides (TG) 500 mg/dL versus control placebo (OO 6 g/d; n=198), OO+4% P (EPA 2 g/d; n=201), OMEGA-3 FFA 2 g/d (EPA and DHA ethyl esters 47% capsaicin) for 12 weeks in combination with the National Cholesterol Education Program Therapeutic Lifestyle Changes diet.


Omega-3 free fatty acids (Epanova®) not approved by FDA
Summary

• If TG remain between 200-499 mg/dL on statin therapy and LDL is at goal, aim to reduce Non-HDL-C to goal, by either using a TG lowering drug with proven outcomes data or by further reducing LDL-C
• Although the clinical trial data is post-hoc, there is a suggestion of more benefit of triglyceride lowering therapies on top of statin therapy, in patients with both low HDL-C and high TG, on either omega 3’s, fibrates, and niacin
• New omega 3 fatty acid formulations offer new options in the treatment of hypertriglyceridemia

Case Presentation

Joanne Foody, MD
Terry A. Jacobson, MD

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

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: 225 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

Stone NJ. Circulation 2013 (online)
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)

Stone N et al. 2013 Circulation

Using the Risk Estimator

- Gender: Male
- Age: 48
- Race: White
- Total Cholesterol: 225 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: 8.4% 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

<table>
<thead>
<tr>
<th>Clinical ASCVD</th>
<th>LDL-C ≥ 190 mg/dL</th>
<th>Diabetes w/ age 40-75, LDL-C ≥ 75</th>
<th>&lt;75 yrs, high intensity statin ≥75 yrs, moderate-intensity statin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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

• 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%

Bruckert E et al, Cardiov Drugs 19:403, 2005
Onusko E, J Fam Pract 57:449, 2008

Case

• Patient labs:
  – CPK 122
  – Creatinine
  – Urinalysis negative for myoglobinuria

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>Statin Added</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC (mg/dL)</td>
<td>225</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>194</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>225</td>
<td>181</td>
<td>158</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>31</td>
<td>33</td>
<td>33</td>
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<td>LDL-C (mg/dL)</td>
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<td>95</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>330</td>
<td>265</td>
<td>150</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>194</td>
<td>148</td>
<td>125</td>
</tr>
</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.

The 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults indicates that statin therapy is indicated for:

1) Primary prevention in a 35 year old woman with a 20 year history of type 1 diabetes
2) Primary prevention in a 40-75 year old patient with a 5-7.5% 10 year risk of a CVD event with a lipoprotein (a) >30 mg/dL
3) Primary prevention in a 40-75 patient with a 5-7.5% 10 year risk of a CVD event with a hsCRP ≥2.0 mg/dL
4) Primary prevention in patients with a LDL-C > 220 mg/dL

Question & Answer