Current Perspectives and Emerging Approaches in Lipid Management

Thursday, March 20, 2014
2–3:30pm

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

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Voxmedia, LLC

Session 5: Current Perspectives and Emerging Approaches in Lipid Management

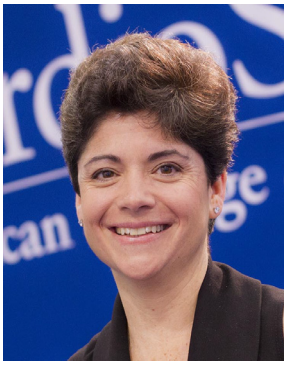
Learning Objectives

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

Goff DC, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013 Nov 12. [Epub ahead of print]

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Drug List

Generic	Trade
Atorvastatin	Lipitor
Fluvastatin	Lescol, Lescol XL
Lovastatin	Mevacor, Altoprev
Pravastatin	Pravachol
Rosuvastatin	Crestor
Simvastatin	Zocor
Pitavastatin	Livalo
Tirofiban	Aggrastat
Cholestyramine	Questran, Questran Light, Prevalite, Locholest, Locholest Light
Colesevelam	Welchol
Colestipol	Colestid
Ezetimibe	Zetia
Itraconazole	Sporanox
Ketoconazole	Nizoral, Extina, Xolegel, Kuric
Erythromycin	E-mycin, Eryc, Ery-tab, PCE, Ilosone, Pediazole

Drug List (cont'd)

Generic	Trade
Clarithromycin	Biaxin, Biaxin XL
Nefazadone	Serzone
Verapamil	Calan, Verelan, Verelan PM, Isoptin, Isoptin SR, Covera-HS
Amiodarone	Pacerone, Cordarone, Cordarone IV, Nexterone
Niacin/Nicotinic acid	Niacor, Niaspan, Slo-Niacin
Gemfibrozil	Lopid
Bezafibrate	Bezalip
Fenofibrate	Tricor, Lipidil, Antara, Triglide, Trilipix
Omega-3-acid ethyl esters	Lovaza
Icosapent ethyl	Vascepa
Omega-3 free fatty acids	Epanova

Learning Objectives

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- **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
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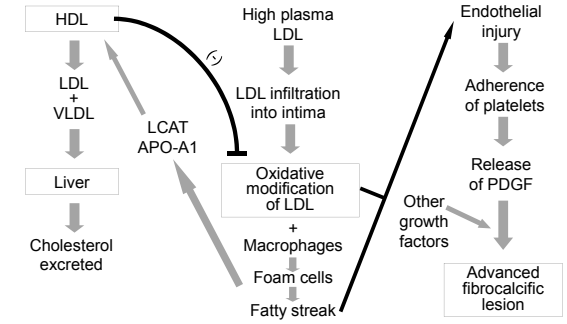
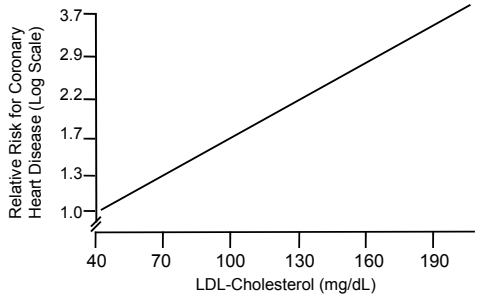
The Role of Lipoproteins in Atherogenesis



APO-A1=Apolipoprotein A1, HDL=High density lipoprotein, LCAT=Lecithin cholesterol acyltransferase, LDL=Low density lipoprotein, PDGF=Platelet-derived growth factor, VLDL=Very low density lipoprotein

CHD Risk According to LDL-C Level



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

Grundy S et al. *Circulation* 2004;110:227-39.

HMG-CoA Reductase Inhibitor: Reduction in LDL-C

A Meta-analysis of 164 Trials*†

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

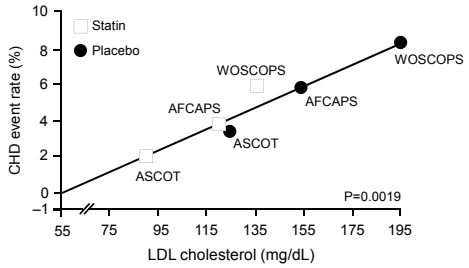
Data presented as absolute reductions in LDL-C* (mg/dL) and percent reductions in LDL-C (in parentheses)
*Standardized to LDL-C 186 mg/dL (mean concentration in trials) before Rx.
† Independent of pre-Rx LDL-C.
‡Maximum dose of 80 mg/d administered as two 40-mg tablets.
§Not FDA approved at 80 mg/d.

FDA=Food and Drug Administration, LDL-C=Low density lipoprotein cholesterol, Rx=Treatment

Law MR et al. *BMJ* 2003;326:1423-1427.

HMG-CoA Reductase Inhibitor: Primary Prevention

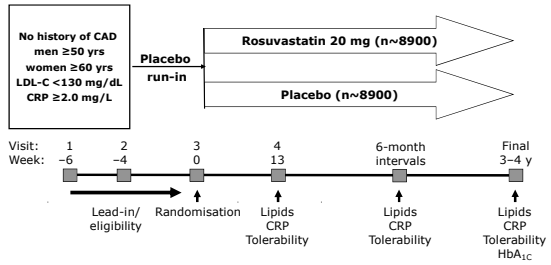
Relationship between LDL-C Levels and Event Rates in Primary Prevention Statin Trials



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

O'Keefe JH Jr et al. *JACC* 2004;43:2142-6.

JUPITER – Study Design

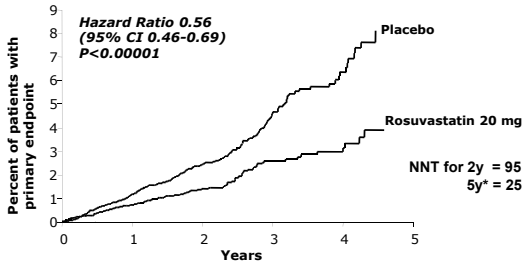


CAD=coronary artery disease; LDL-C=low-density lipoprotein cholesterol; CRP=C-reactive protein; HbA_{1C}=glycated haemoglobin

Ridker PM. *Circulation* 2003; 108: 2292–2297.
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



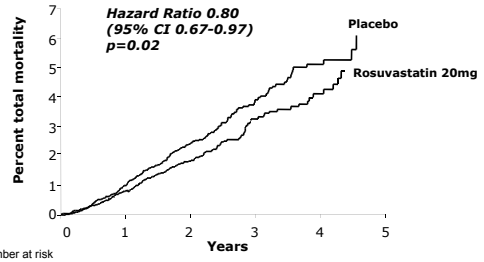
Number at risk

RSV	8901	8412	3893	1353	538	157
Placebo	8901	8353	3872	1333	531	174

*Extrapolated figure based on Altman and Andersen method

Ridker P *et al. N Eng J Med* 2008;**359**: 2195-2207

JUPITER - Total Mortality
Death from any cause



Number at risk

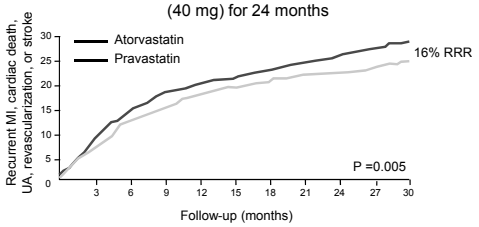
RSV	8901	8787	4312	1602	676	227
Placebo	8901	8775	4319	1614	681	246

Ridker P *et al. N Eng J Med* 2008;**359**: 2195-2207

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

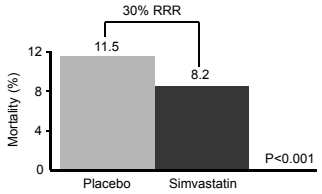
ACS=Acute coronary syndrome, CV=Cardiovascular, MI=Myocardial infarction, UA=Unstable angina

Cannon CP et al. *NEJM* 2004;350:1495-1504.

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



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

MI=Myocardial infarction, RRR=Relative risk reduction

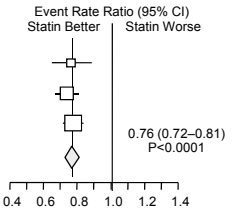
4S Group. *Lancet* 1994;344:1383–1389.

HMG-CoA Reductase Inhibitor: Secondary Prevention

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

Baseline LDL-C (mg/dL)	Statin (n = 10,269)	Placebo (n = 10,267)
<100	282 (16.4%)	358 (21.0%)
100–129	668 (18.9%)	871 (24.7%)
≥130	1083 (21.6%)	1356 (26.9%)
All patients	2033 (19.8%)	2585 (25.2%)



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

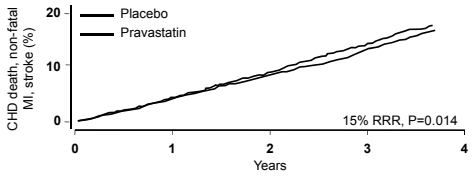
CAD=Coronary artery disease, CI=Confidence interval, DM=Diabetes mellitus

HPS Collaborative Group. *Lancet* 2002;360:7-22.

HMG-CoA Reductase Inhibitor: Secondary Prevention

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



Statins provide benefit in older men

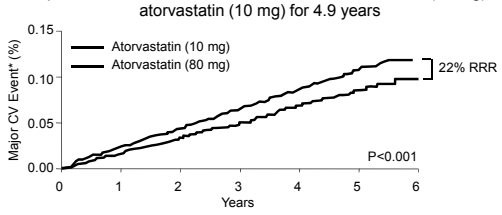
CHD=Coronary heart disease, MI=Myocardial infarction, RRR=Relative risk reduction

Shepherd J et al. *Lancet* 2002;360:1623-1630.

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



High-dose statins provide benefit in chronic CHD

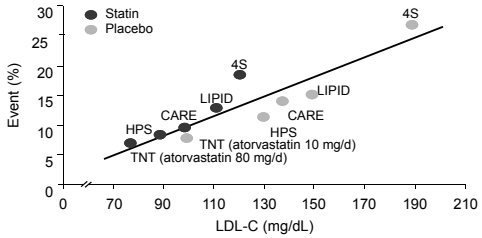
CHD=Coronary heart disease, CV=Cardiovascular, MI=Myocardial infarction, RRR=Relative risk reduction

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

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

HMG-CoA Reductase Inhibitor: Secondary Prevention

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



CARE=Cholesterol and Recurrent Events Trial, HPS=Heart Protection Study, LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; 4S=Scandinavian Simvastatin Survival Study, TNT=Treating to New Targets

LDL-C=Low density lipoprotein cholesterol

LaRosa JC et al. *NEJM* 2005;352:1425-1435.

HMG-CoA Reductase Inhibitor: Intensive Therapy

Trial	Population	Duration (years)	LDL-C Reduction (mg/dL)	RR in Primary End Point (%)	RR in MI or CHD Death (%)
PROVE IT-TIMI 22	ACS (N = 4162)	2	33	16	16
A to Z	ACS (N = 4497)	2	14	11	15
TNT	Stable CAD (N =10,001)	5	24	22	21
IDEAL	Stable CAD (N = 8888)	5	23	11	11

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

ACS=Acute coronary syndrome, CAD=Coronary artery disease, CHD=Coronary heart disease, LDL-C=Low density lipoprotein cholesterol, MI=Myocardial infarction, RR=Relative reduction

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.

Kashani A et al. *Circulation* 2006;114:2788-97.

HMG-CoA Reductase Inhibitor: Adverse Effects

Risk Factors for the Development of Myopathy*

Concomitant Use of Meds
Fibrate
Nicotinic acid (Rarely)
Cyclosporine
Antifungal azoles**
Macrolide antibiotics†
HIV protease inhibitors
Nefazadone
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

Pasternak RC et al. *Circulation* 2002;106:1024-1028.

2013 ACC / AHA Cholesterol Guideline: 4 Statin Benefit Groups

- Clinical Atherosclerotic Cardiovascular Disease (ASCVD)
- LDL-C $\geq$ 190 mg/dL, Age $\geq$ 21 years
- Primary Prevention--Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary Prevention--No Diabetes†: $\geq$ 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

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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 ASVD: Risk of first nonfatal myocardial infarction, coronary heart disease death, nonfatal or fatal stroke.

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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

CK, creatine kinase

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

Management of Muscle Symptoms on Statin Therapy (cont.)

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

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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%

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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.

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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.

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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

Stone NJ et al. *Circulation*. 2013 Nov 12 (epub ahead of print).

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

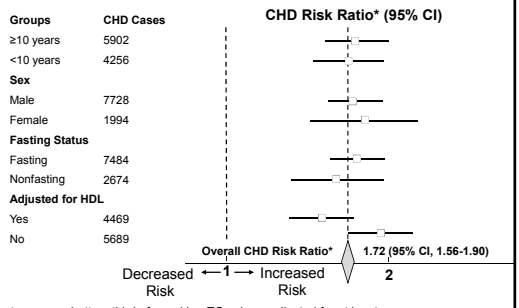
AHA Scientific Statement on Triglycerides (TG) Classification

TG Revisions between 1984 and 2001

TG Designate	1984 NIH Consensus Panel	1993 NCEP ATP II	NCEP ATP III 2001
Desirable	< 250	< 200	**< 150**
Borderline High	250-499	200-399	**150-199**
High	500 -999	400-999	**200-499**
Very High	> 1000	>1000	**> 500**

Miller M et al. Circulation. 2011;123(20):2292-2333.

TG and CHD Risk: Meta-Analysis of 29 Studies



*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.

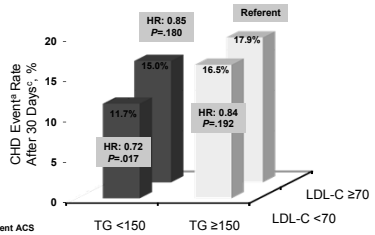
Sarwar N, et al. *Circulation.* 2007;115:450-458. N=262,525

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

PROVE IT-TIMI 22 Trial[b]

N = 4162

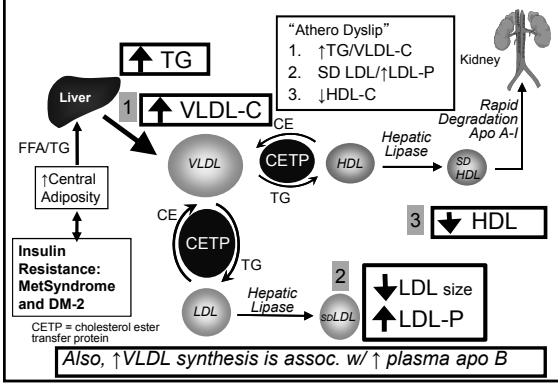
- Achieving both low LDL-C and low TG (<150 mg/dL) may be important therapeutic strategies in patients after an ACS



[a]Death, MI, and recurrent ACS
[b]ACS patients on atorvastatin 80 mg or pravastatin 40 mg
[c]Adjusted for age, gender, low HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment
Lipid values are in mg/dL

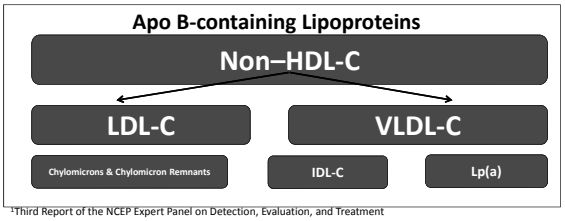
Miller M, et al. *J Am Coll Cardiol.* 2008;51:724-730.

Atherogenic Dyslipidemia Associated with Hypertriglyceridemia



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



[1]Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III). *Circulation*. 2002;106:3143-3421.

VLDL, very-low-density lipoprotein

Greenfield RS. *LipidSpin*. 2011;9:6-7.

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]**

TC = total cholesterol

1. NCEP ATP III. *Circulation*. 2002;106:3143-3421.
2. Miller M et al. *Circulation*. 2011;123:2292-2333.
3. Brunzell JD et al. *J Am Coll Cardiol*. 2008;51:1512-1524.
4. Mora S et al. *Circulation*. 2009;119:2396-2404.

ATP III Treatment Recommendations for Elevated TGs

TG (mg/dL)	ATP III Classification	Primary Target of Therapy	Treatment Recommendations
150–199	"Borderline" High TG	LDL-C goal	Weight reduction, increased physical activity
200–499	"High" TG	LDL-C goal	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 fibrate)
≥500	"Very High" TG	Reduce TG to prevent acute pancreatitis	Very low fat diet (fat ≤15% of total calories), weight reduction, increased physical activity, and drug therapy with niacin or fibrate

ATP III Panel. *Circulation* 2002; 106(25):3143-3421.

ATP III Update 2004:

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

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

Grundy S, et al. *Circulation* 2004;110:227.

Lifestyle and Diet Can Improve Triglycerides and HDL-C

Diet/Lifestyle Change	Lipid Profile Change
Smoking cessation	↑ HDL-C 4 mg/dL
Weight loss (5-10%)	↓ TG 20%, ↑ HDL-C 10%
Diet ↓Total carb & ↓fat (to 33-50% of calories)	↓ TG 5%
Implement a Mediterranean-style diet vs a low-fat diet	↓ TG 10–15%
Brisk 30-min walk, 3x/wk	↑ HDL-C 5-10%

Adapted from Miller M, et al. *J Am Coll Cardiol*. 2008;51:724-730.

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

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

Miller M et al. Circulation. 2011;123:2292-2333.

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Clinical Trial Evidence for Combination Therapy With Statins

	Impact of Therapy on Top of Statin Therapy		
	Fenofibrate	Niacin	Omega-3 ethyl esters (EPA+DHA) (EPA)
Clinical Trial	ACCORD FIELD	AIM-HIGH HPS-2 THRIVE	ORIGIN JELIS OMEGA (1.8g)(1gm)
Trial Results	Negative	Negative	Negative Positive

ACCORD Study Group. *N Engl J Med.* 2010;362:1563-74. FIELD: Keech A et al. *Lancet.* 2005;366:1849-61.
AIM HIGH Investigators. *N Engl J Med.* 2011;365:2255-67. Armitage J, ACC Scientific Sessions, March 2013. Yokoyama M et al. *Lancet.* 2007;369:1090-1098. ORIGIN Trial Investigators, et al. *N Engl J Med.* 2012;367:309-18.

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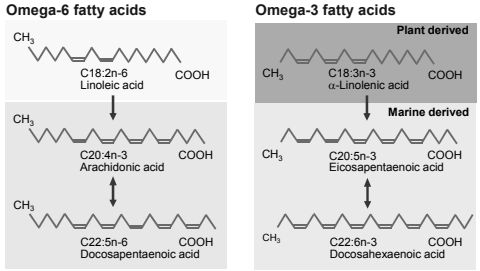
Clinical Outcome Studies Evaluating High TG Subgroups

	Trial (Drug)	Primary Endpoint: Entire Cohort (P-value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup (P-value)
Pre-statin era	HHS (Gemfibrozil)	-34% (0.02)	TG > 204 mg/dl LDL-C/HDL-C > 5.0	-71% (0.005)
	BIP (Bezafibrate)	-9.4% (0.26)	TG ≥ 200 mg/dl HDL-C <35 mg/dl	-42% (0.02)
Some statin use	FIELD (Fenofibrate) (no statins at entry)	-11% (0.16)	TG ≥ 150 mg/dl	-12% (0.07)
Statin add-on	ACCORD (Fenofibrate/simva)	-8% (0.32)	TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl	-31% (0.0567)
	JELIS (ethyl EPA) (simva & prava)	-19% (0.011)	TG ≥ 150 mg/dl HDL-C ≤ 40 mg/dl	-53% (0.043)

ACCORD Study Group. *N Engl J Med.* 2010;362:1563-74. FIELD: Keech A et al. *Lancet.* 2005;366:1849-61. Frick MH et al. *N Engl J Med*. 1987;317:1237-45. The BIP Study Group. *Circulation*. 2000;102:21-27. Yokoyama M et al. *Lancet*. 2007;369:1090-1098

Structure of Omega-3 and Omega-6 Fatty Acids



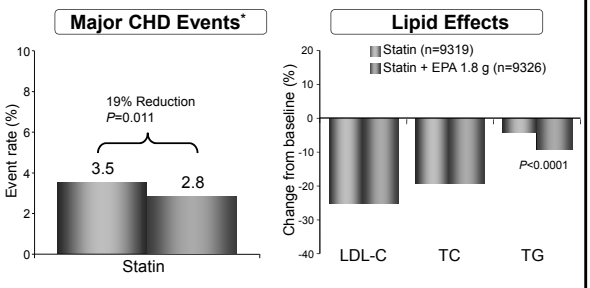
Din JN et al. *BMJ.* 2004;328:30-35.
Reprinted with permission from BMJ Publishing Group.

AHA Recommendations for Omega-3 FA Intake

Population	Recommendation
Patients without documented CHD	Eat a variety of (preferably oily) fish at least twice a week. Include oils and foods rich in α-linolenic acid (flaxseed, canola, and soybean oils; flaxseeds; and walnuts)
Patients with documented CHD	Consume ~1 g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician
Patients needing triglyceride lowering	2–4 grams of EPA+DHA per day provided as capsules under a physician's care

Kris-Etherton PM et al. *Circulation* 2002;106:2747-2757.

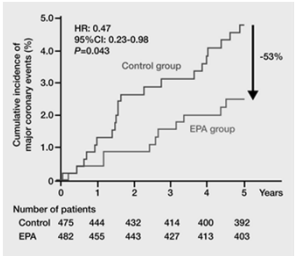
Addition of Eicosapentaenoic Acid (EPA) to Statin Therapy in Japanese Patients



*Sudden cardiac death, fatal and non-fatal MI, unstable angina, angioplasty, stenting, or CABG. CHD=coronary heart disease; LDL-C=low-density lipoprotein cholesterol; TC=total cholesterol.
Yokoyama M et al. *Lancet.* 2007;369:1090-8.

Patient Subgroup – TG >150 mg/dL and HDL <40 mg/dL: JELIS

Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS)



Saito S, et al. *Atherosclerosis.* 2008;199:378-383.

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).

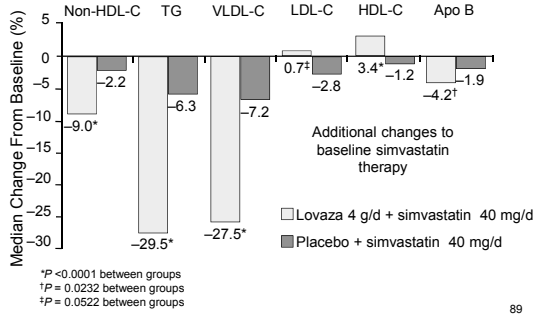
http://www.pdr.net/full-prescribing-information?druglabelid=211

Prescription Omega-3 Fatty Acids (EPA Ethyl Esters Only)

- Icosapent ethyl (Vascepa®) is a 96% pure ethyl ester of eicosapentaenoic acid (EPA)
- Icosapent ethyl is FDA approved for Very High TG (>500 mg/dL)
- The daily dose is 4 g per day taken as 2 capsules twice daily

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202057s002lbl.pdf

Combination Omega-3 and Simvastatin (COMBOS): Primary and Secondary Efficacy Results



*P <0.0001 between groups
†P = 0.0232 between groups
‡P = 0.0522 between groups

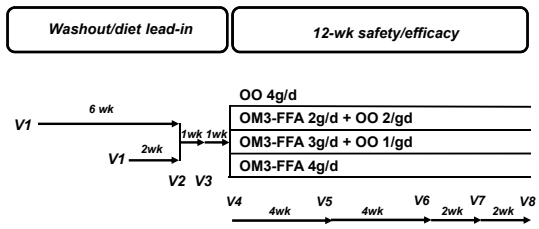
Davidson MH et al. *Clin Ther.* 2007;29(7):1354-1367.

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?**

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

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



OM3-FFA, omega-3 free fatty acids; OO, olive oil; V, visit; g/day, grams per day

A multinational, double-blind, randomized study in men and women with triglycerides (TGs) >500 mg/d to <2000 mg/dLversus control (olive oil [OO] 4 g/d; n=99), OM3-FFA 2 g/d (plus OO 2 g/d; n=100), OM3-FFA 3 g/d (plus OO 1 g/d; n=101), or OM3-FFA4 g/d (n=99) capsules for 12 weeks in combination with the National Cholesterol Education Program Therapeutic Lifestyle Changes diet.

Kastelein JJP et al. J. Clin. Lipidol. 2014;8:94-106

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

EVOLVE: Primary and Secondary End Points

Variable	OO, 4 g/d (n = 98)	OM3-FFA, 2 g/d* (n = 99)	OM3-FFA, 3 g/d* (n = 97)	OM3-FFA, 4 g/d (n = 99)
Primary end point				
TG, mg/dL				
Baseline	682 (418, 2007)	717 (415, 1578)	728 (439, 2158)	655 (435, 2095)
End-of-treatment	642 (190, 5655)	554 (73.5, 1723)	544 (141, 10317)	513 (138, 2013)
%Δ LSGM (95% CI)	-4.3 (-13.1 to 5.4)	-25.9 (-32.8 to -18.3)‡	-25.5 (-32.4 to -17.8) ‡	-30.9 (-37.3 to -23.)§
Secondary end points				
Non–HDL-C, mg/dL				
Baseline	215 (109, 380)	205 (106, 517)	215 (115, 609)	225 (107, 536)
End-of-treatment	217 (98.0, 473)	209 (64.5, 538)	197 (77.5, 1161)	211 (91.0, 435)
%Δ LSGM (95% CI)	2.5 (-2.3 to 7.6)	-7.6 (-12.0 to -3.0)†	-6.9 (-11.4 to -2.2) †	-9.6 (-14.0 to -5.1) ‡
HDL-C, mg/dL				
Baseline	28.7 (14.0, 60.0)	27.3 (13.3, 47.3)	28.0 (15.3, 58.7)	28.7 (12.7, 69.3)
End-of-treatment	30.0 (12.0, 64.5)	29.0 (15.0, 63.5)	28.5 (14.0, 62.0)	29.0 (14.0, 93.5)
%Δ LSGM (95% CI)	1.9 (-2.0 to 6.0)	7.4 (3.2 to 11.7)	3.8 (-0.3 to 8.0)	5.8 (1.7 to 10.1)

LSGM, Least squares geometric mean; *, Subjects in the OM3-FFA 2 g/d and 3 g/d arms also received OO capsules at dosages of 2 g/d and 1 g/d, so that each treatment group received a total of 4 g/d oil. †, Significantly different from the OO group, P < 0.05 ‡, Significantly different from the OO group, P < 0.001 §, Significantly different from the OO group,

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

Kastelein JJP et al. J. Clin. Lipidol. 2014;8:94-106

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

Case

Drugs

- Lisinopril 10 mg (for HTN)

Physical Exam

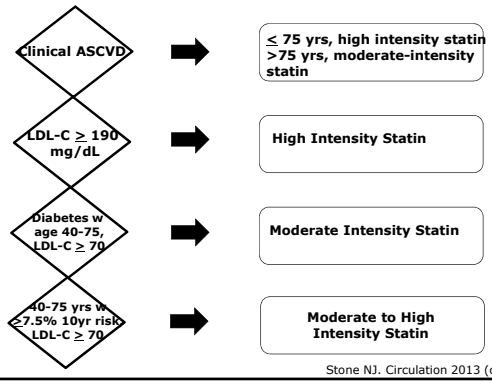
- Vital Signs
  - Pulse: 64
  - BP: 146/86
  - Weight: 74.3 kg
  - Waist circ: 99 cm
  - BMI: 28.8 kg/m^2
    - No other abnormalities

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

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

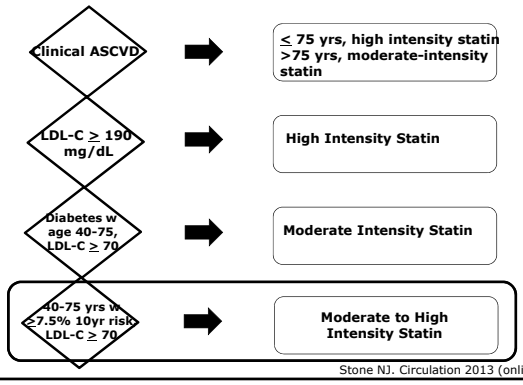
Using the Risk Estimator

- Gender: Male
- Age: 48
- Race: White
- Total Cholesterol: 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



Stone NJ. Circulation 2013 (online)

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
Brown WV, *Curr Opin Lipid* 19:558, 2008
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

Measurement	Baseline	6 weeks
		Statin Added
TC (mg/dL)	225	181
HDL-C (mg/dL)	31	33
LDL-C (mg/dL)	135	95
TG (mg/dL)	330	265
Non-HDL-C (mg/dL)	194	148

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

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

Measurement	Baseline	6 weeks	12 weeks
		Statin Added	Omega 3 Added
TC (mg/dL)	225	181	158
HDL-C (mg/dL)	31	33	33
LDL-C (mg/dL)	135	95	95
TG (mg/dL)	330	265	150
Non-HDL-C (mg/dL)	194	148	125

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

? Post

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