

The Complex Patient with Mixed Hyperlipidemia

Susan Schima, MD

April 30, 2011

Disclosures

- None

Objectives

- Identify the complex patient with dyslipidemia
- Recognize residual risk
- Discuss available treatment options, including therapeutic lifestyle changes and pharmacological options

Defining the Complex Patient

- Mixed Hyperlipidemia
 - High LDL, High triglycerides, Low HDL
- Metabolic Syndrome
 - Waist circ $> 40''$ m, $> 35''$ w, trig > 150 ,
HDL < 40 m, < 50 w, BP $> 130/85$, FBS > 100
- Residual Risk
 - Controlling LDL insufficient to prevent events

ATPIII Goals

- LDL < 100 (highest risk < 70 mg/dL)
- HDL > 40 mg/dL in men, > 50 in women
- Triglycerides < 150 mg/dL
- Non-HDL < 130 mg/dL
 - Total Cholesterol-HDL
 - Should be within 30 mg/dL of LDL

Non-HDL cholesterol

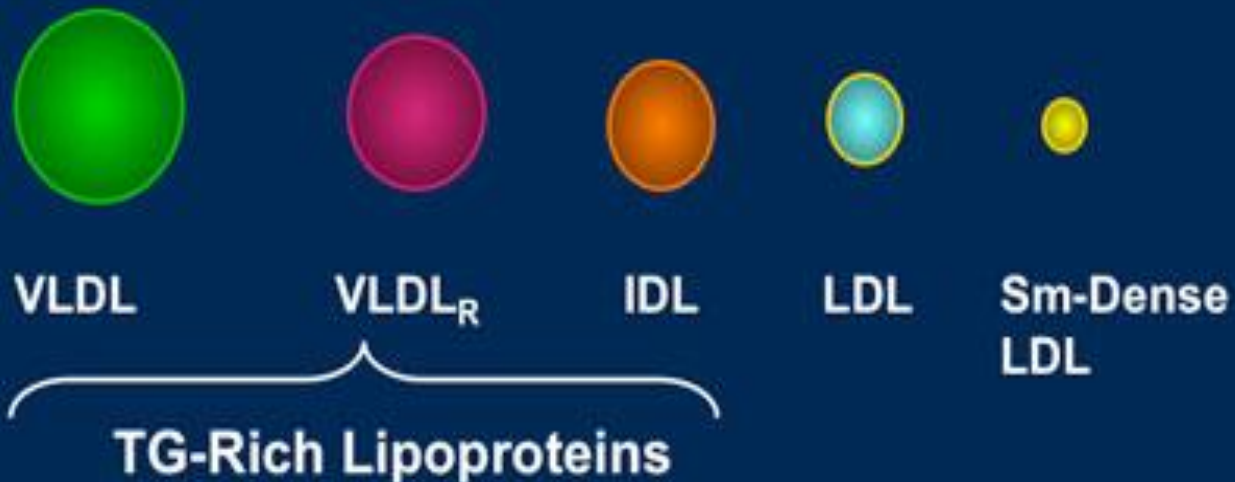
- LDL does not tell the number of atherogenic particles present
- Smaller particle size generally means more particles required to carry cholesterol

Apolipoprotein B

- Each atherogenic particle has 1 apoB protein attached
- Additional test
- Some studies suggest non-HDL and apolipoprotein B levels more predictive of future CV events than LDL-C

Atherogenic Particles

Measurements: Apolipoprotein B
Non-HDL-C (TC-HDL)



TC=total cholesterol; IDL=intermediate density lipoprotein; VLDL=very low-density lipoprotein; VLDL_R=very low-density lipoprotein receptor

HDL

- HDL-C promotes reverse cholesterol transport, delivering systemic cholesterol back to liver where it's discarded
- Decreases atherogenicity of LDL-C by reducing its oxygenation
- Increases NOS activity, increases NO, which protects against inflammation.

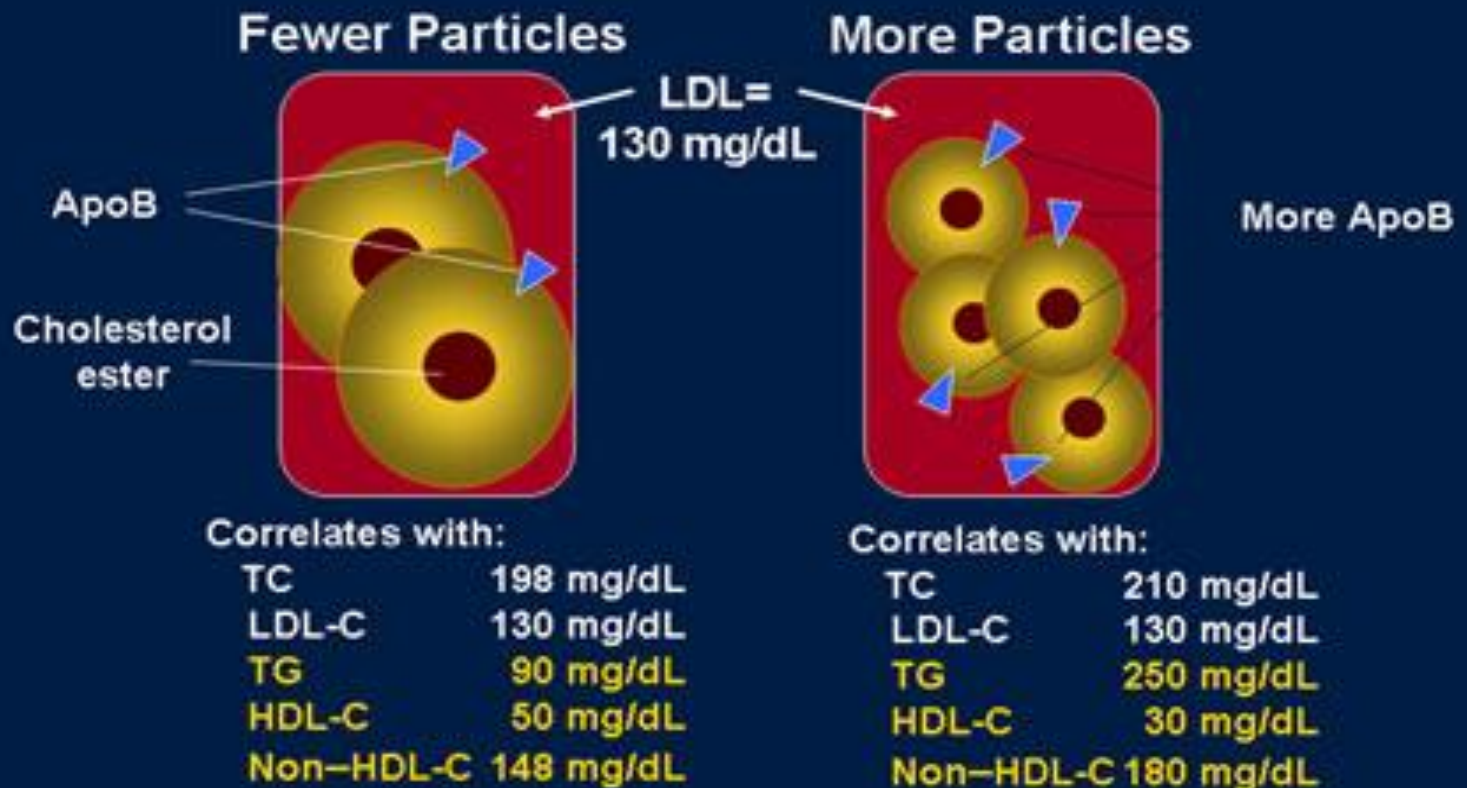
HDL

- Framingham Heart Study
 - Risk of CHD lower among those with higher HDL-C levels
 - 1 mg/dL higher HDL-C associated with a 2-3% lower risk of CHD

Triglycerides

- Marker for other highly atherogenic substances, such as VLDL and chylomicrons
- Prospective Munster CV Study: incr triglycerides increased risk for CAD independent of HDL and LDL
- Copenhagen Male Study

Elevated Triglycerides Are Associated With Increased Small LDL Particle Number



- Do low HDL-C and high triglycerides contribute to residual cardiovascular risk?

Clues

- Low HDL is the most common lipid abnormality in patients with premature CAD
- Statin trial meta-analyses have shown the highest placebo event rate and greatest absolute reduction in clinical events in patients with the lowest baseline HDL-C

Evidence

- VA-HIT: gemfibrozil reduced mortality and non fatal MI independent of changes in LDL
- BECAIT: decrease in disease progression when HDL and triglyceride profile improved despite no change in LDL
- Helsinki Heart Study: decr CAD if successfully treated for non-HDL goal

Treating to New Targets (NEJM 2007)

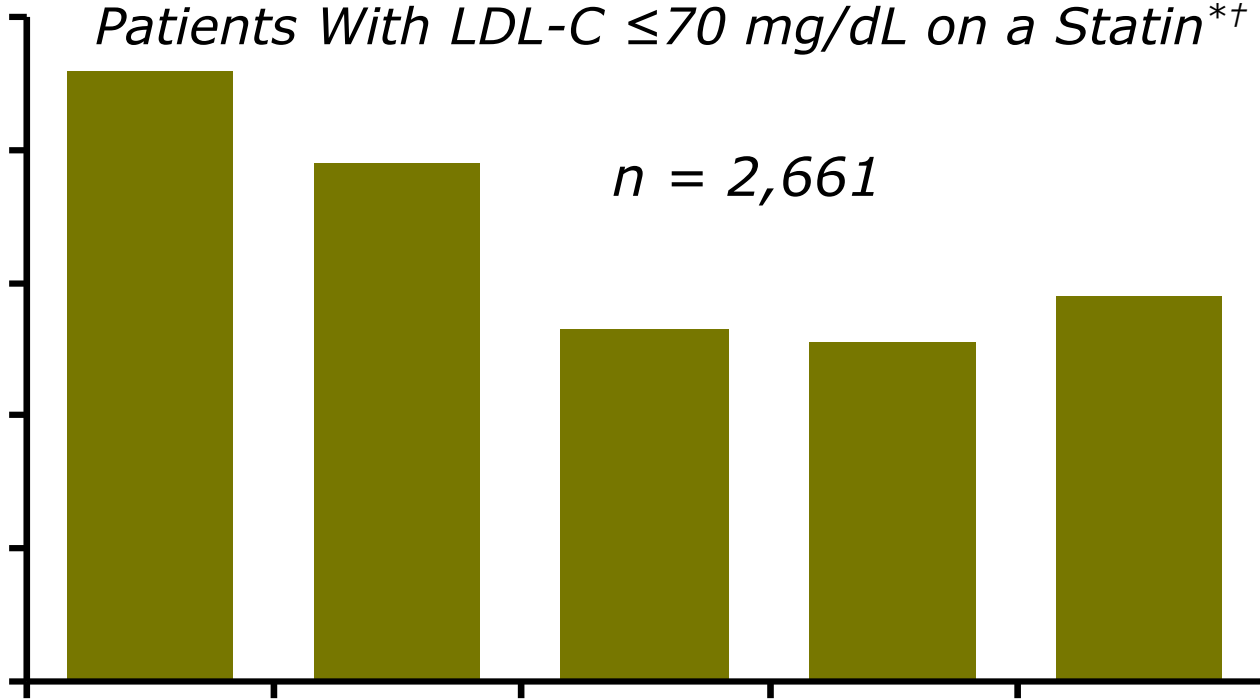
- High v low dose statin in stable patients with CHD
- LDL < 70
- When HDL > 42, flattening out of event rates in high dose statin group
- When HDL < 42, higher event rate even with LDL < 70

Low HDL-C Increases CVD Risk Even When LDL-C Levels Are Well Controlled

5- Year Risk of Major CVD Events (%)

Patients With LDL-C ≤ 70 mg/dL on a Statin^{*†}

n = 2,661



HDL-C Quintiles*
 mg/dL

Q1
 <37

Q2
 37 to <42
 0.85

Q3
 42 to <47
 0.57

Q4
 47 to <55
 0.55

Q5
 ≥55
 0.61

Hazard Ratio vs. Q1[‡]

*On-treatment level (3 months statin therapy); †mean LDL-C = 58 mg/dL and mean triglycerides = 126 mg/dL; ‡P = 0.03 for differences among quartiles of HDL-C

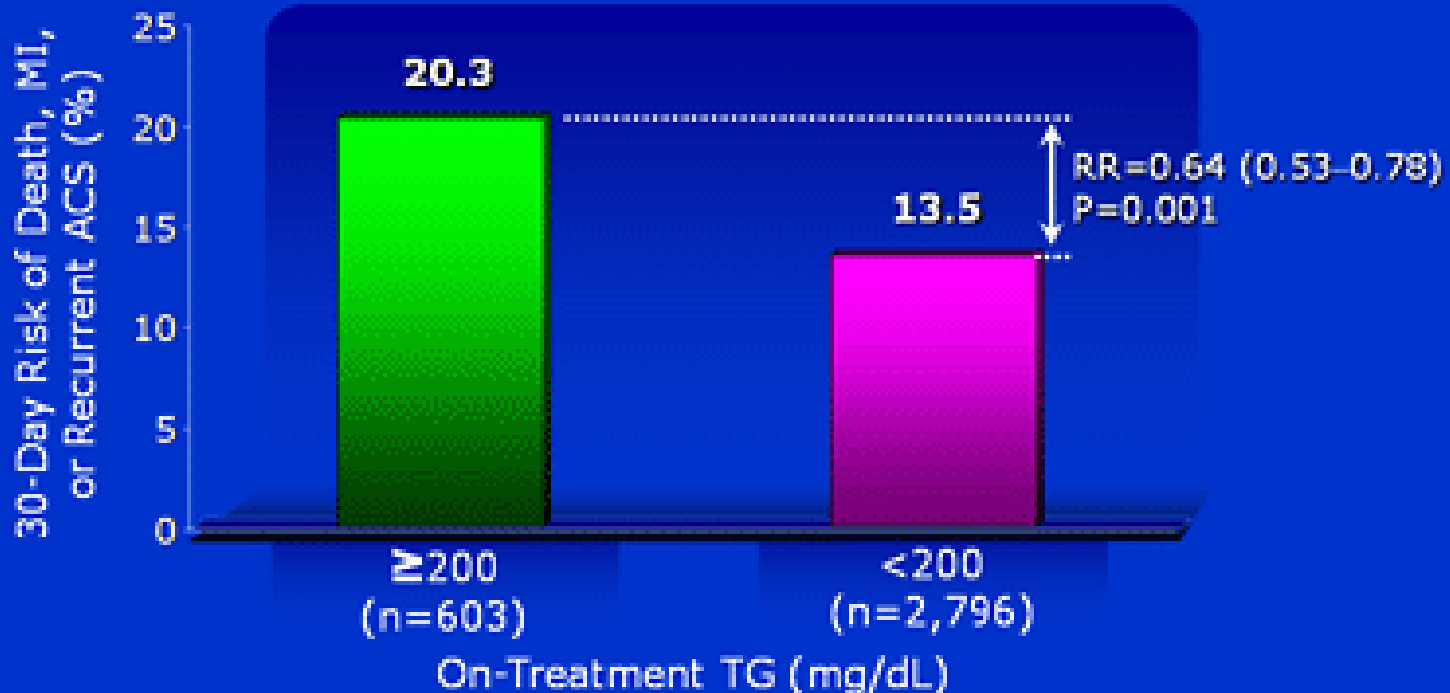
CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol

Reprinted from Barter P, et al. *N Engl J Med.* 2007;357:1301-1310.
 Copyright © 2007 Massachusetts Medical Society. All rights reserved.

PROVE-IT TIMI 22

- Best outcomes when LDL < 70 and triglycerides < 150

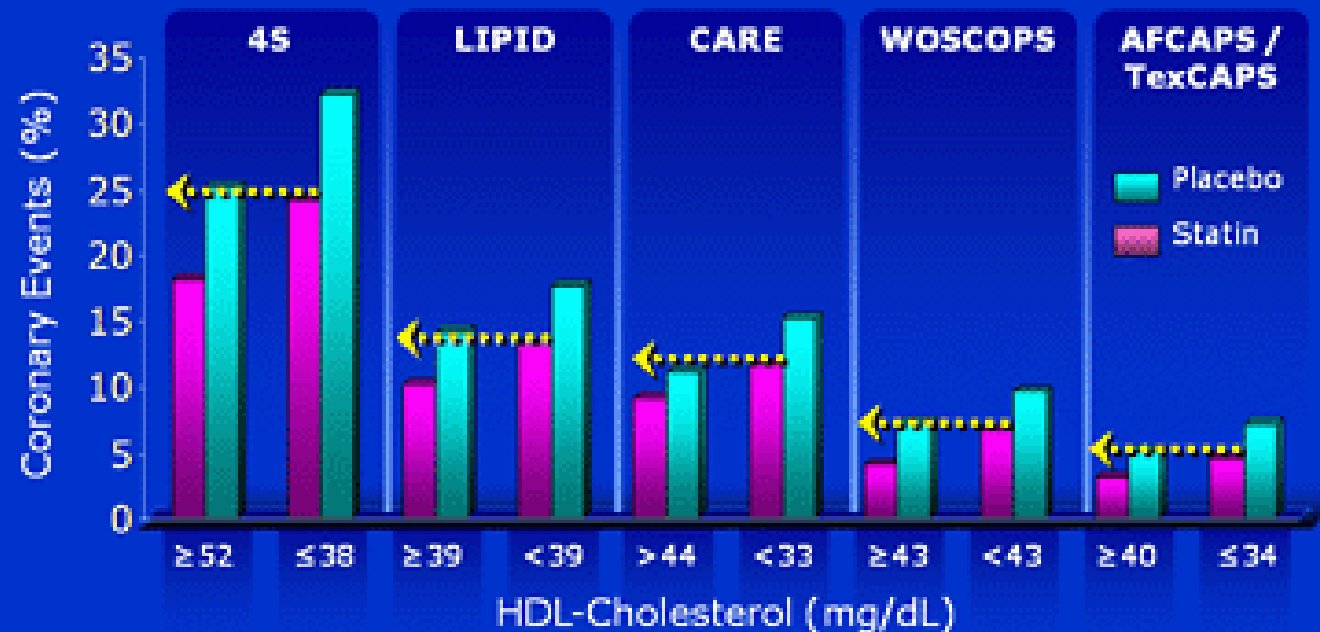
High Triglycerides Contribute to the Residual Risk After Statin Treatment: PROVE IT-TIMI-22 Post-Hoc Analysis



ACS = acute coronary syndrome; MI = myocardial infarction;
RR = relative risk; TG = triglycerides

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

Statin Trials and Coronary Risk Associated With Low HDL-Cholesterol



STATINS DECREASE CARDIOVASCULAR DISEASE IN PATIENTS WITH DIABETES BUT DO NOT ELIMINATE THE RISK ASSOCIATED WITH LOW HDL-CHOLESTEROL

Reprinted in an adapted form from Ballantyne CM, et al. *Circulation*. 1999;99:736-743, with permission from Wolters Kluwer Health.

Slide Source:
Lipids Online Slide Library
www.lipidsonline.org

Evidence

- FIELD study
 - effect of fenofibrate on CV outcomes in patients with T2DM
 - Primary outcome of major coronary events not reduced
 - Coronary revascularization and nonfatal MI reduced (slightly)
 - Microvascular complications of DM (need for laser retinopathy and albuminuria) were reduced

FIELD Study

- Criticized for including patients with normal lipid profiles and high drop in rate of statins

Evidence

- Accord Lipid Study
 - Simvastatin + fenofibrate v simvastatin + placebo in T2DM
 - N=5518
 - Primary outcome: 1st non-fatal MI or CVA or death from CV cause
 - Baseline triglycerides 162 mg/dL, HDL 38.1 mg/dL
 - Mean follow up 4.7 yrs

ACCORD lipid study

- Combination therapy did not reduce event rate for primary outcomes
- Results do not support routine use of combination therapy to reduce CV risk in majority of high risk T2DM patients
- Caveat....baseline lipids not too bad

ACCORD lipid study

- Subgroup analysis in pts with triglycerides >204 and HDL < 34
 - Primary outcome 12.4% in fenofibrate group v 17.3% in placebo group

Where do we stand?

- LDL-C reduction with statin therapy has demonstrated benefit in CVD risk reduction
- HDL-C, apo B, Triglycerides, non-HDL helpful for risk stratification
- Suggestion that therapies targeting these lipid parameters may be beneficial
- Studies mixed

Treatment

- Pharmacologic v Non-pharmacologic
- Statins first line pharmacologic
- Intolerance
- Additional Options
 - Fish Oil
 - Niacin
 - Fibrates
 - Cholesterol binders

Therapeutic Lifestyle Changes

- Dietary modifications
- Exercise
- Tobacco Cessation
- Alcohol

Lifestyle Modification

- “Western dietary patterns warm up inflammation, while prudent dietary patterns cool it down.”
- Refined starches, sugar, saturated and trans-fatty acids, low in fruits, vegetables, omega-3 fa, and whole grains
- Associated with higher CRP, metabolic syndrome, DM, obesity

Dietary Modifications

- Saturated fats promote atherosclerosis and diminish protective effects of HDL
- Polyunsaturated fats may enhance protective effects of HDL
- Purely low fat diets decrease HDL levels to similar levels of LDL. When unsat fats replace sat, LDL decreased proportionally more

Dietary Modifications

- Diets high in monounsaturated fats (olive and canola oil) decrease LDL without adversely affecting HDL
- Poly-unsat fats, including omega 3 FA (fish oil) can increase HDL, esp in those with high triglycerides
- Grapeseed oil (by-prod of wine making) can incr HDL 13%

Lifestyle Modifications

Saturated fat	<7% total calories
Polyunsaturated fat	Up to 10%
Monounsaturated fat	Up to 20%
Total fat	25-35%
Carbohydrate	50-60%
Fiber	20-30g/d
Protein	15%
Cholesterol	< 200 mg/d
Total calories	Balance intake and expenditure

GOALS	Trig 150-199 (borderline)	Trig 200-499 (High)	Trig > 500 (very high)
Weight Loss (%)	<5	5-10	5-10
Carbohydrate (%daily caloric intake)	50-60	50-55	45-50
Fructose (g/day)	<100	50-100	<50
Sat FA (% cal intake)	<7	<5	<5
Mono/poly unsat FA	10-20	10-20	10-20
DPA/DHA (g/day)	.5-1	1-2	>2

Lifestyle Modifications

- Obesity is the central abnormality that contributes to the Metabolic Syndrome and dyslipidemia
- Weight loss through diet or exercise equally result in increase in HDL
- Those with dietician consult do better

Diet and Weight Loss

- 5-10% weight loss
 - 20% decrease in triglycerides
 - 15% decrease in LDL
 - 8-10% increase in HDL

Weight Loss

- Those actively losing weight initially have decr HDL levels, but once at stabilized reduced wt, have HDL levels inversely proportionate to their weight
- Lipoprotein lipase decreases with acute caloric restriction but increases with stable weight loss

Weight Loss and Exercise

- Exercise (one hour a day) for weight loss
- All should exercise at moderate intensity for 150 min/wk

Tobacco Cessation

- Cigarette smoking decreased HDL levels by 4 mg/dL in men and 6 mg/dL in women in FHS
- Overall, smokers have 9% lower HDL
- CETP- enzyme that increases transfer of cholesterol esters from HDL to apo B particles. CETP increased in smokers

Tobacco Cessation

- Smoking cessation improves HDL levels and increases Apo 1
- Favorable effects seen within 30d of quitting

Alcohol intake

- Moderate intake protective on CHD, partly due to incr HDL
- Wine has flavinoids that act as lipoprotein anti-oxidants
- Recommendation for ETOH limited by potential for abuse, dependence and caloric intake

Success of Lifestyle Modifications

- Low-sodium diet: Decr BP 4.8/2.5 mmHg in HTN pts, 1.9/1.1 mmHg in others
- Wt loss: for every kg lost, BP decr 1mmHg. Hard to sustain results
- Decr # of meds, improve/ prevent DM
- Exercise: can decr BP, incr HDL, improve endothelial function

Success of Lifestyle Modifications

- EUROACTION
 - Focus on lifestyle changes during 16 wk program
 - Significant improvements in those attending the program when re-examined at 1 year

EUROACTION

- Couples who attended a preventive cardiology program together after one had suffered a coronary event changed their dietary and exercise habits in tandem

Fish Oil

- Omega 3 fatty acids
- Long chain
- EPA (eicosapentaenoic acid)
- DHA (docosahexaenoic acid)
- ALA (alpha linoleic acid)
 - Flaxseed or soybean
 - Small proportion converted to EPA/DHA

Fish Oil

- Polyunsaturated fat
- First double bond counting from the omega (or methyl) carbon is at position 3

Fish Oil

- Most clinical benefit inferred from data on fish consumption (eskimos)
- Essential in diet, can't be synthesized de novo
- Fish don't produce omega 3 FA, obtain from ingestion of marine microorganisms

Studies

- GISSI
 - >11,000 pts within 3 m MI
 - Vit E v omega 3 FA v placebo
 - Only omega 3 FA decreased primary endpoint (15%)
 - Decrease in SCD (membrane stabilization?)

GISSI-HF

- Pts with Class II-IV HF
- Same arms as GISSI
- Primary endpoints
 - Time to death or admit to hospital
 - Omega 3 FA decr 8-9%
 - Substudy showed rosuvastatin had no effect

JELIS

- >18,000 pts with TC > 250 mg/dL placed on statin and either 1800 mg/d EPA or usual care
- Primary endpoint MACE
- Most pts no history CAD
- Decreased stroke rate (concern due to higher incidence hemorrhagic CVA in Japan and mild antiplatelet effect of fish oil)

JELIS

- Risk for MACE increased by 71% in those with low HDL and high triglycerides
- In this group, EPA decreased MACE 53% (even on statin)
- No significant change in lipids, glycemic measures or BP observed (triglycerides decr 7-8%)

Supplementation

- OTC usually contains 1000 mg, but only 300-400 mg of DHA and EPA
- Lovaza has close to 1000 mg EPA and DHA
 - Larger capsule (1200-1300 mg)
 - 465 mg EPA, 375 mg DHA, 60 mg other
 - FDA approved
 - \$\$\$\$

Supplementation

- The higher the baseline triglycerides, the greater the effect
- Lovaza approved for trig > 500 at dose of 4g/d
- Safe in combination
- MOA?
 - Decreases hepatic secretion of triglycerides into blood
 - Decrease afib? Anti-inflammatory?

AHA Recommendations

- 2 meals oily fish/wk (400-500 mg EPA + DHA/day)
- If CHD, 1 g/day omega 3 FA
- If CHF, 1 g/day may benefit
- If increased triglycerides, 1-2 g/d
- If triglycerides > 500 mg/dL, 4 g/d

Fish Oil

- Fish allergic pts can take
- Salmon, tuna
- Tilapia, cod, bass, perch not good sources of omega 3, but prob better than red meat
- PLB/dioxin concerns
 - Known benefits of eating farmed salmon outweighs risk of CA by 400:1

Niacin

- Potently increases HDL levels by 23%
- More mild effect on decreasing LDL and triglyceride levels
- Side effects limit compliance (skin flushing in up to 85%)
- Sustained release formulations with lower incidence of flushing (26%) but also less efficacious (13%)

Ezetimibe

- Cholesterol absorption inhibitor
- Incremental benefit in increasing HDL (nominal -2.7%)
- Allows lower statin dose to achieve similar effects on LDL

Cholesterol binders

- Relatively effective, but limited by side effects (abdominal pain, bloating, diarrhea)

Fibrates

- Increase HDL and decrease triglycerides
- PPAR agonists
- Receptor regulates gene transcription relating to lipoproteins and fatty acid metabolism
- Stimulates apo A-I and A-II which increase production of HDL
- Stimulate metabolism of triglycerides by reducing production of apo C-III

Fibrates

- Historically, concern regarding interaction with statins
- Gemfibrozil decreased elimination of statins. Increased statin toxicity
- Fenofibrate does not interfere significantly with statins
- New formulation, fenofibric acid, has proven safety with low and moderate dose statins

CETP Inhibitors

- **DEFINE**
 - Anacetrapib found to increase HDL 138% and decrease LDL 40%
 - Previous drug in this class (torcetrapib) led to increased BP, mortality and CV events

Summary

- Treat LDL, proven benefit in CV disease
- Triglycerides, HDL, non-HDL secondary targets- clinical outcomes lacking
- Recurrent events? Consider aggressive treatment of secondary targets
- New targets- hsCRP, apoB?
- Await ATP IV Spring 2012