

Case Study in Lipid Management 2011

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Lipid Management 2011

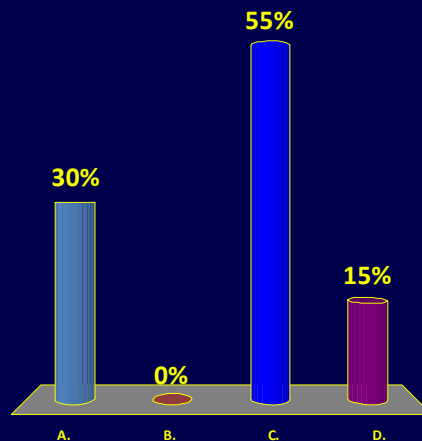
- Secondary Prevention vs Primary Prevention?
- High Risk Patients without CAD
 - Risk equivalents: PVD, AAA, DM, > 20% 10 yr FRS
- What is the therapeutic TARGET??
- Achieve goals!!

Patient Sam

- 60 y.o. male with prior IWMI 2008, EF NL feels “achy”
- Former smoker
- BMI: 28, exercises occasionally, low fat diet
- Meds: ASA, lipitor 40 mg/d, metoprolol, fish oils 1gm
- TC 141, LDL 69, TG 220, HDL 28, CPK normal

What is the best next option?

- A. Reduce lipitor to 20 mg
- B. Stop lipitor, start zocor 40 mg, add Co Q 10
- C. Stop lipitor, start crestor 20mg, start Co Q-10
- D. Start gemfibrozil

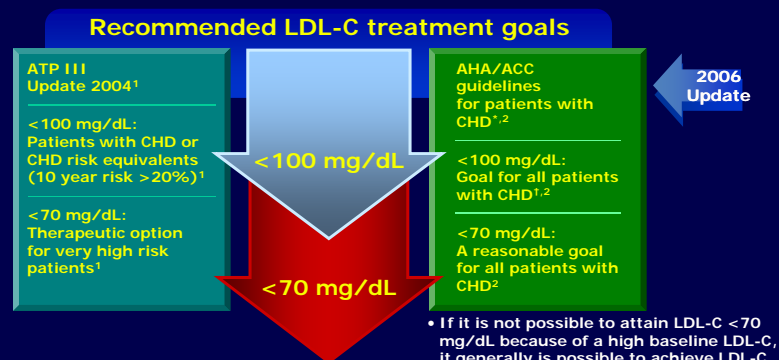


Therapeutic Goals for LDL-C NCEP, ATP III

Patient Category	LDL-C Goal (mg/dL)
No CHD, 0-1 risk factors	<160
No CHD, 2+ risk factors	<130 (optional <100)
CHD/CHD risk equivalent (DM)	<100
CVD + DM/MS/Cigs/ACS	<70 (optional)

Adapted from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497. | Grundy SM, et al. *Circulation*. 2004;110:227-239.

Intensive LDL-C Goals for High Risk Patients



• If it is not possible to attain LDL-C <70 mg/dL because of a high baseline LDL-C, it generally is possible to achieve LDL-C reductions of >50% with more intensive LDL-C-lowering therapy, including drug combinations.

* And other forms of atherosclerotic disease.²

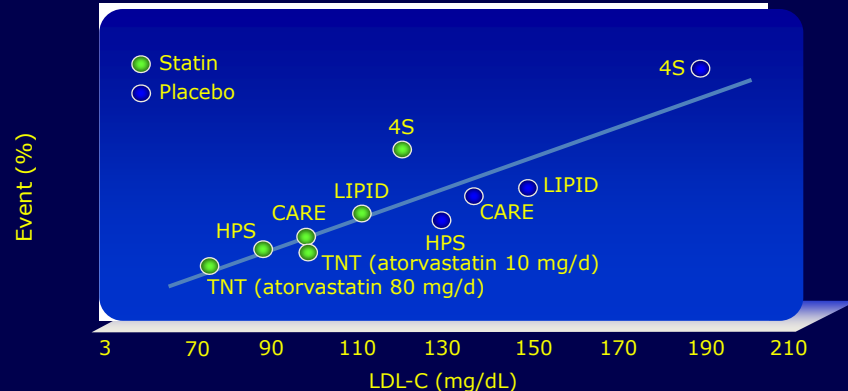
[†] Factors that place a patient at very high risk: established cardiovascular disease plus: multiple major risk factors (especially diabetes); severe and poorly controlled risk factors (e.g., cigarette smoking); metabolic syndrome (triglycerides ≥200 mg/dL + non-HDL-C ≥130 mg/dL with HDL-C <40 mg/dL); and acute coronary syndromes.¹

1. Grundy SM et al. *Circulation* 2004;110:227-239.

2. Smith SC Jr et al. *Circulation* 2006; 113:2363-2372.

HMG-CoA Reductase Inhibitor: Secondary Prevention

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



LDL-C=low-density lipoprotein cholesterol; CHD=coronary heart disease; TNT=Treating to New Targets; HPS=Heart Protection Study; CARE=Cholesterol and Recurrent Events Trial; LIPID=Long-term Intervention with Pravastatin in Ischaemic Disease; 4S=Scandinavian Simvastatin Survival Study.

LaRosa et al. *N Engl J Med* 2005;352:1425-1435.

Discussion: Pt Sam

- Secondary Prevention: Prior IWMI
- Goal : Pt with known CAD, LDL < 70 mg/dl
- Tools/tricks to approach statin intolerance
 - Myalgias leading cause of statin discontinuation in the U.S. 2011



Treating statin myalgias

- Proper history: ? True statin myalgia vs osteoarthritis, fibromyalgia,
- Check TSH: Hypo/Hyperthyroidism increases risk for myopathy
- Check for medication interactions
- CPK may or may not be elevated

Statin Differences

- Lipitor, Zocor, Lovastatin: P450/CYP3A4 elimination
 - Lipophilic
 - Beware azole antifungals, macrolides, calcium channel blockers, amiodarone, amlodipine, ranolazine
- Crestor, Pravachol, Fluvastatin (Ilescol): CYP2C9 pathway
 - Hydrophilic
- Gemfibrozil with any statin risky, use fenofibrate with statins
- An evening dose of statin and one glass grapefruit juice in am has minimal effect on statins (need > 1 quart/day)

2011 Simvastatin: FDA

- 80 mg dose only if taking > 12 mo
- No new 80 mg dosing
- Do not exceed 20 mg: amlodipine, ranolazine
- Do not exceed 10 mg: amio, verapamil, dilt
- Do not use
 - Itraconazole, ketoconazole, any “zole” drug, EES, clarithromycin or any “mycin” drug, HIV protease drugs, Nefazodone, gemfibrozil, CSA, danazole

Statin Myalgias RX

- Initial strategy: Statin choice/class
 - If renal failure, favor Lipitor (no renal clearance)
 - If no renal failure, favor hydrophilic statins (prava, rosuva, lescol)
 - Best LDL lowering with Atrovastatin 80 or Crestor 40 (up to 60% LDL lowering)
 - Continue to try alternate statin despite intolerance to priors
- Dosing
 - Try reduced dosing or alternate day dosing
 - Should be dosed at night: most hepatic cholesterol synthesis takes place while we sleep
- Labs
 - Only need to hold statin if LFT's > 3x NL or CPK > 5-10X NL (with Sx)

Supplements Statin Myalgias

- Consider trial CoQ-10, 200 mg BID/TID or more to correct depleted levels
- Measure vitamin D level, treat to level > 60

Summary: Statins/Myalgias

- Try multiple statins
- Initial tactic: move to other class statin
- Favor dose reductions over d/c
- Take at night, with supplements (co-Q, Vit D)
- Add Plant sterols, soluble fiber aid LDL lowering
 - Cholest-off

Pt Sam: Statin intolerance

- 60 y.o. male with prior IWMI 2008, EF NL feels “achy”
- Former smoker
- BMI: 29, exercises occasionally, low fat diet
- Meds: ASA, lipitor 40 mg/d, metoprolol, fish oils 1gm
- TC 141, LDL 69, TG 220, HDL 28, CPK normal

What is the best next option?

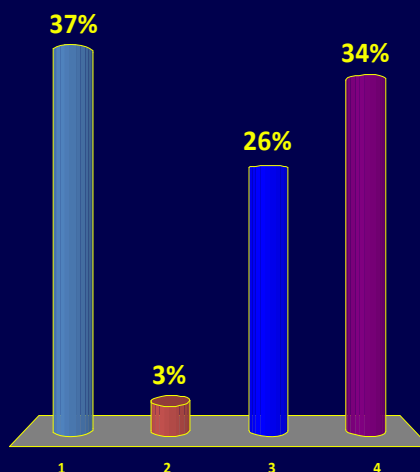
- A. Reduce lipitor to 20 mg (NO should switch drugs)
- B. Stop lipitor, start zocor 40 mg, add co Q-10 (should switch to hydrophilic)
- C. Stop lipitor, start crestor 20mg, start Co Q-10 (BEST OPTION)
- D. Start gemfibrozil (no, will increase risk of myalgias)

Pt Sam

- Switched to crestor 20 mg daily
- Fish oils increased to 1,000 mg DHA/EPA
- Exercise increased to 150 min/wk
- Six months later:
 - TC 137 LDL 65 TG 210 HDL 30

What would you do next?

1. No changes, we are at goal
2. Add gemfibrozil 600 mg bid
3. Add tricor (fenofibrate) 145 mg daily
4. Add niacin ER 500 mg/day



Therapeutic Goals for LDL-C and Non-HDL-C

<i>LDL-C Goal + 30 mg/dL = Non-HDL-C Goal</i>		
<i>Patient Category</i>	<i>LDL-C Goal (mg/dL)</i>	<i>*Non-HDL-C Goal (mg/dL)</i>
<i>No CHD, 0-1 risk factors</i>	<i><160</i>	<i><190</i>
<i>No CHD, 2+ risk factors</i>	<i><130 (optional <100)</i>	<i><160</i>
<i>CHD/CHD risk equivalent</i>	<i><100</i>	<i><130</i>
<i>CVD + DM/MS/Cigs/ACS</i>	<i><70 (optional)</i>	<i><100 (optional)</i>

* When TG > 200

Adapted from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA. 2001;285:2486-2497. | Grundy SM, et al. Circulation. 2004;110:227-239.

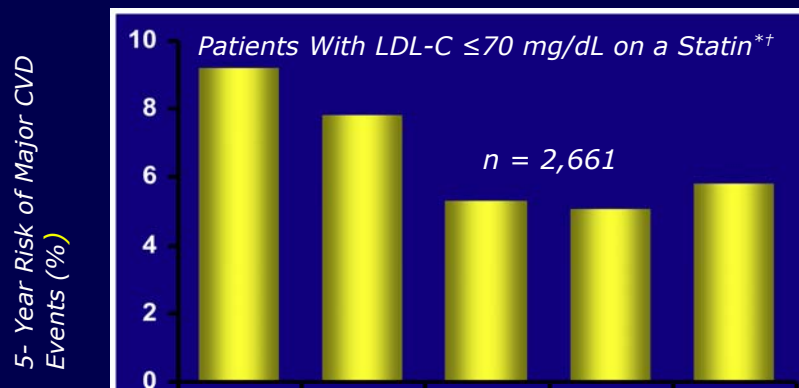
Limitations of Statin Monotherapy on CHD Events

Trial	Drug	N	Events, * n		Risk Reduction, %†	Events not Avoided, %
			Control Group	Statin Group		
4S WOSCOPS CARE AFCAPS LIPID	Simvastatin Pravastatin Pravastatin Lovastatin Pravastatin	30,817	2,042	1,490	26	74
HPS	Simvastatin	20,586	1,212	898	26	74
PROSPER	Pravastatin	5,804	356	292	19	81
ASCOT-LLA	Atorvastatin	10,305	154	100	36	64
Total		67,462	3,764	2,780	27	73

* Nonfatal MI and CHD death; AFCAPS also included unstable angina
 † Weighted average

Reprinted from Bays H. *Expert Rev Cardiovasc Ther* 2004; 2:89-105, with permissions from Future Science Group.

Low HDL-C Increases CVD Risk Even When LDL-C Levels Are Well Controlled: **Treating to New Targets Study**



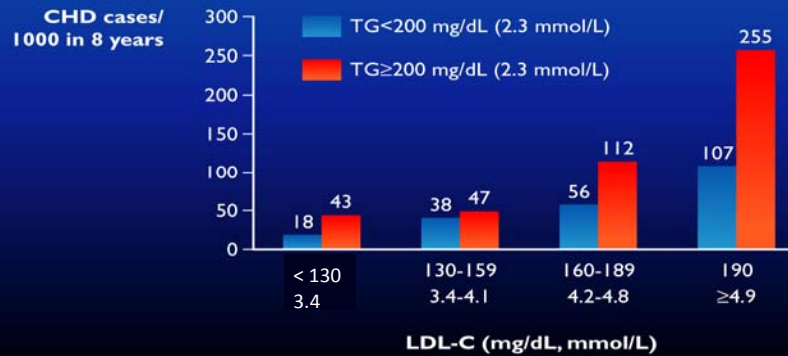
HDL-C Quintiles* mg/dL	Q1 <37	Q2 37 to <42	Q3 42 to <47	Q4 47 to <55	Q5 ≥55
Hazard Ratio vs. Q1*		0.85	0.57	0.55	0.61

*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

Reprinted from Barter P, et al. *N Engl J Med.* 2007;357:1301-1310.
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PROCAM Study

CHD risk according to LDL-C and TG
increased TG confers raised CHD risk at all levels of LDL-C



Pt Sam: Non HDL Cholesterol Goal

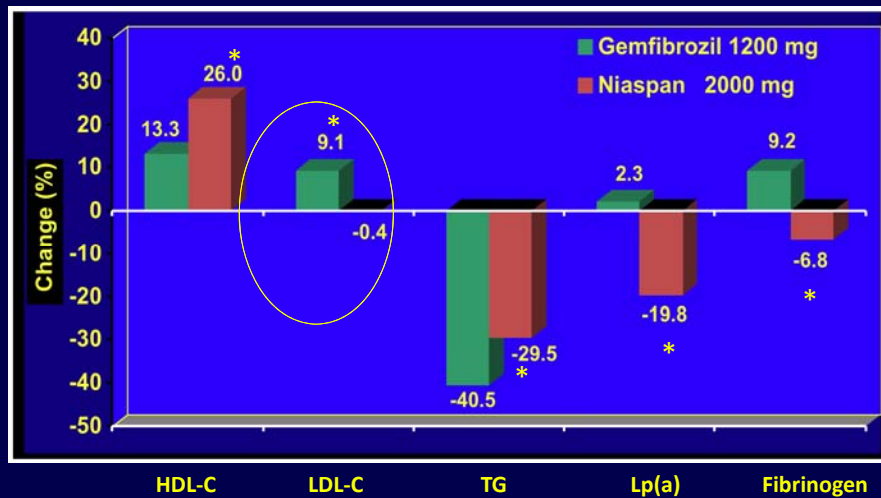
- Total – HDL
 - Represents Apo B Particles (atherogenic)
 - Commonly elevated when HDL low, TG high
 - Goal <30 points above LDL goal
- TC 137 LDL 65 TG 210 HDL 30
 - Non HDL Chol : $137 - 30 = 107$

Lipid-Modifying Drugs That Affect High-Density Lipoprotein Cholesterol Levels

Niacin	↑ 15–35%
Fibrates	↑ 10–15%
Statins	↑ 5–10%
Omega-3 Fatty Acids	↑ 3–15%
Ezetimibe	↑ 1–3%

Belalcazar LM, et al. Progr Cardiovasc Dis. 1998;41:151–174.

Niaspan® vs Gemfibrozil in Patients With Isolated Low HDL-C

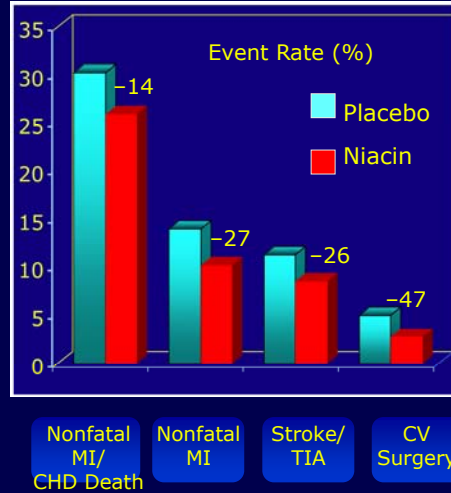


* $P < 0.03$ vs comparator drug

Adapted from Guyton JR et al. *Arch Intern Med.* 2000;160:1177

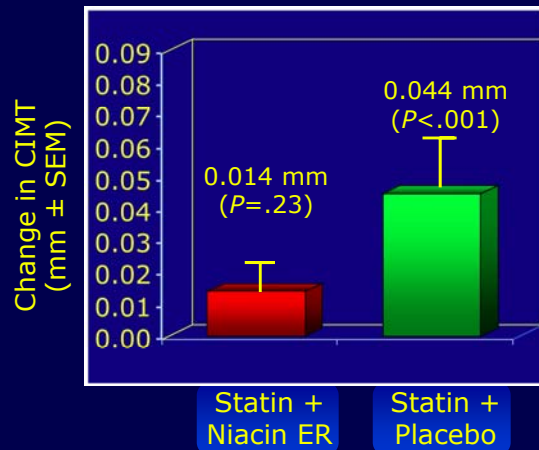
Coronary Drug Project

- 1966–1975, men with prior MI
- 5 lipid-influencing drugs
 - Estrogen (2 arms), dextrothyroxine, clofibrate, niacin
 - 1 g TID (n=1119)
- 6 years: reduction in MI
 - Only in niacin group
- 15 years: 4% absolute reduction in mortality
 - NNT = 25



Coronary Drug Project. *JAMA* 1975; 231:360-381. | Canner PL et al. *J Am Coll Cardiol* 1986;8:1245-1255.

ARBITER 2: Δ CIMT at 12 Months



Statin + Niacin ER

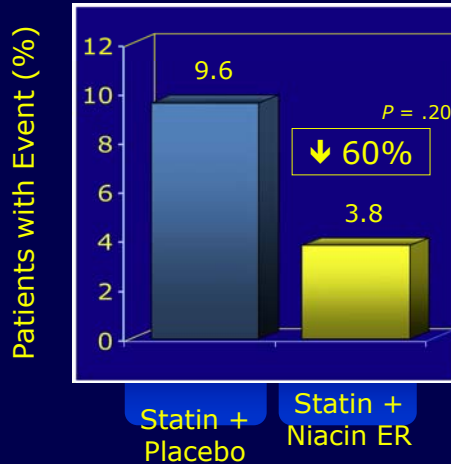
- Safe
- Flushing common, occurred in 2/3 of patients
- Adherence >90%

Between-group comparison: $P = .08$, intent-to-treat analysis of placebo > niacin ER, $P = .048$.

Taylor AJ et al. *Circulation* 2004;110:3512-3517.

ARBITER 2: Secondary Efficacy Endpoint—Clinical Events

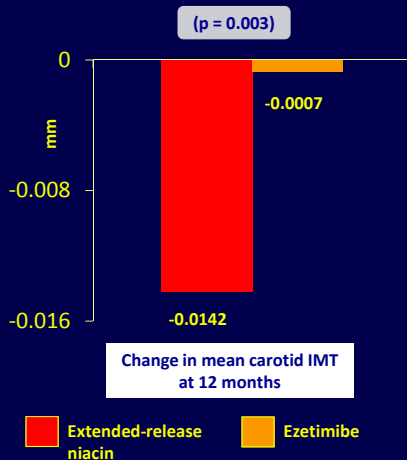
- Composite clinical event endpoint
 - Unstable angina/MI hospitalization
 - Stroke
 - Sudden cardiac death
 - Percutaneous coronary revascularization, CABG, or peripheral revascularization



Taylor AJ et al. *Circulation* 2004;110:3512-3517.

ARBITER 6-HALTS

Trial design: Patients with CHD (or risk equivalent) on statin therapy and with low HDL cholesterol were randomized to extended-release niacin 2000 mg daily (n = 97) versus ezetimibe 10 mg daily (n = 111). Follow-up was 14 months.



Results:

- Change in LDL cholesterol: -10.0 mg/dl vs. -17.6 mg/dl (p = 0.01), respectively
- Change in HDL cholesterol: 7.5 mg/dl vs. -2.8 mg/dl (p < 0.001), respectively
- MACE: 1% niacin vs. 5% zetia (p = 0.04),

Taylor AJ, et al. *N Engl J Med* 2009;Nov 15

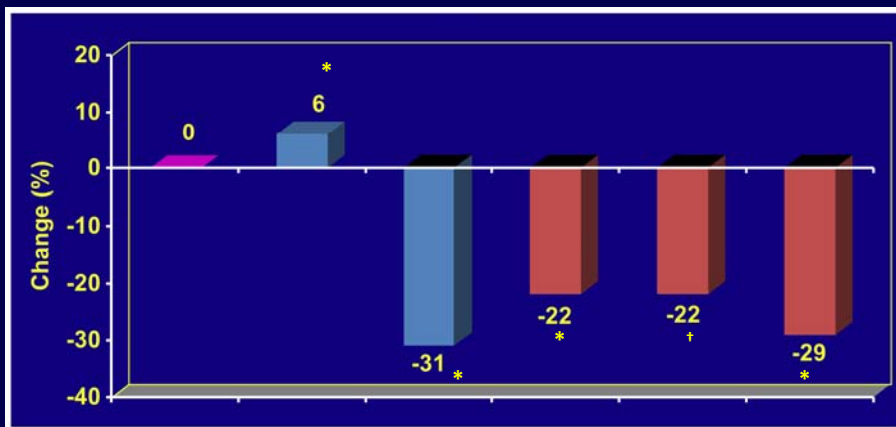
AIM HIGH

- 3414 pts
- US and Canada, 90 centers
- Simva to LDL < 80 plus Niaspan vs placebo
- Study terminated early May 2011
- Increase strokes Niacin group
 - 28 (1.6%) vs 12 (.7%) placebo group
 - ? Related to increase glucose

HPS2-THRIVE

- 25,000 pts with CAD
- Adding ER Niacin (and Laropipriant) to statin in metabolic syndrome
- Laropipriant-reduced prostaglandin mediated side effects of Niacin
- Will evaluate increase Diabetes/Blood sugars

VA-HIT: Results: Lopid vs Placebo, no Statin



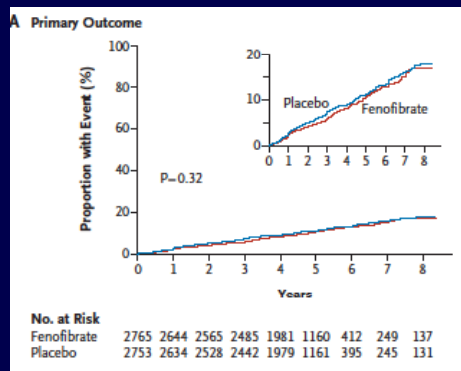
* $P \leq 0.05$

† $P = 0.07$

‡Investigator designated

Rubins HB et al. *N Engl J Med.* 1999;341:410

ACCORD study: No benefit Tricor added to Simvastatin



5518 Pts

Fenofibrate (Tricor) + statin vs statin + placebo

NEJM April 2010

Simva/Zetia (Vytorin)

- SHARP: Vytorin vs Placebo
 - 9,000 pts with renal failure
 - Vytorin reduced major CV events by 17% vs placebo
- SEAS: Vytorin vs Placebo
 - 1800 pts with severe Aortic Stenosis
 - 20% reduced ischemic events
 - Many more cancers with Vytorin
- IMPROVE-IT: Simvastatin vs Vytorin
 - Study extended, pts added, due 2012

CETP Inhibitors

- Torcetrapib: Pfizer ILLUMINATE study
 - Raised HDL markedly (up to 100%)
 - 25% Increased CV death, 60 % increase all cause mortality
 - Increased serum sodium, aldosterone stimulation, cortisol
 - Small increases in BP (2-4 mmHg)
- More recent: Dalcetrapib
 - More modest increases in HDL(25-40%)
 - NO upregulation of aldosterone

ADA/ACC Consensus Statement on Lipoprotein Management in Patients With Cardiometabolic Risk

- In patients who are taking statins and continuing to have low HDL-C or elevated non-HDL-C, especially if apo B remains elevated, combination therapy is recommended.
- The preferred agent to use in combination with a statin is niacin because there is somewhat better evidence for reduction in cardiovascular disease events with niacin than there is for fibrates.

ACC = American College of Cardiologists; ADA = American Diabetes Association; apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol

Brunzell JD et al. Diabetes Care. 2008;31:811-822.

Pt Sam

- Switched to crestor 20 mg daily
- Fish oils increased to 1,000 mg DHA/EPA
- Exercise increased to 150 min/wk
- Six months later:
 - TC 137 LDL 65 TG 210 HDL 30

What would you do next:

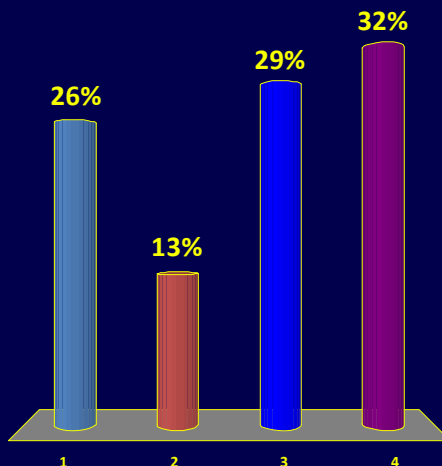
1. No changes, we are at goal (NO not at Non HDL chol, HDL low)
2. Add gemfibrozil 600 mg bid (NO don't combine statin and gemfibroz)
3. Add tricor (fenofibrate) 145 mg daily (NO primary issue low HDL, ACCORD data)
4. Add niacin ER 500 mg/day (Reasonable given data, low HDL)

Case 1: Niaspan added

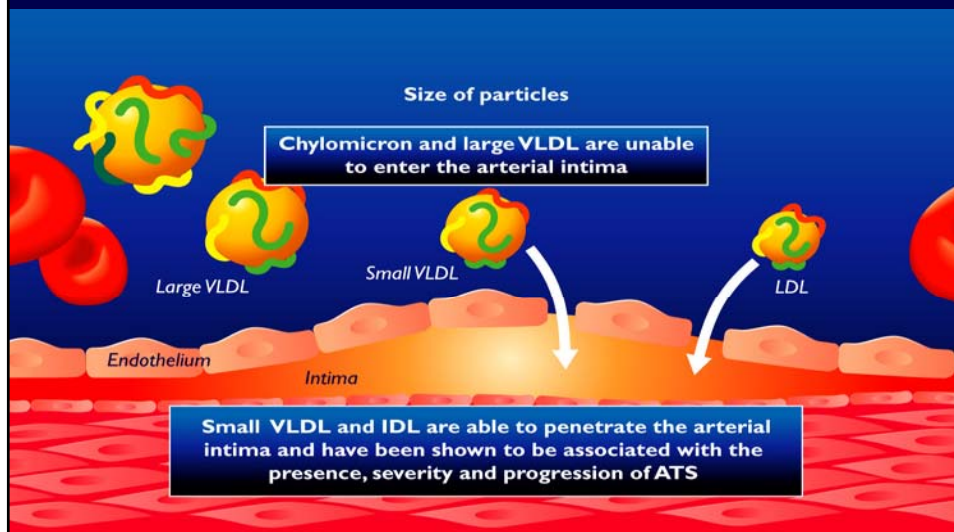
- 500 mg Niaspan ER added
- Since last visit had recurrent CP and PCI
- Repeat Lipid Profile:
 - TC 131 LDL 60 TG 150 HDL 41

Any other steps to be considered?

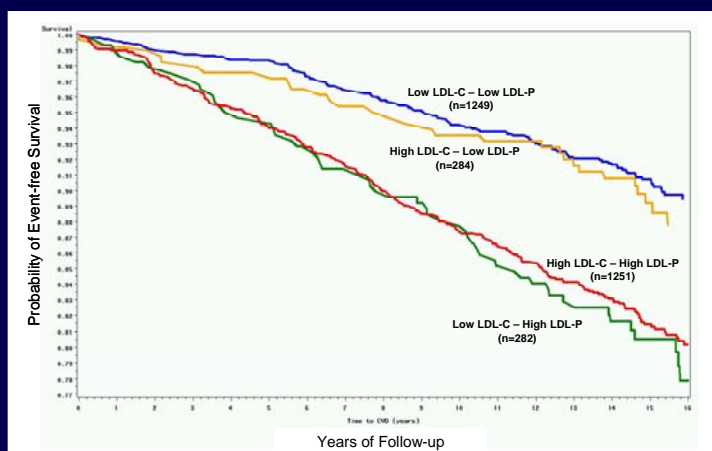
1. No, we are done
2. Add fibrate
3. Calcium score
4. NMR profile



Size and apolipoprotein composition are the main factors determining atherogenicity of triglyceride-rich particles

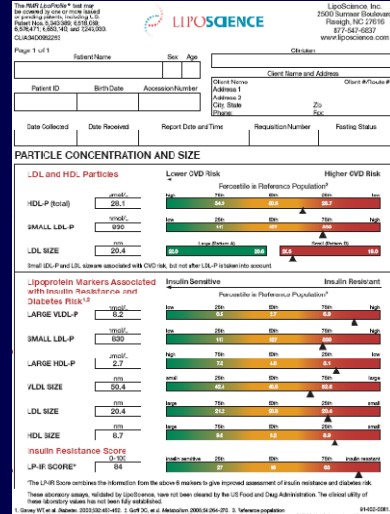
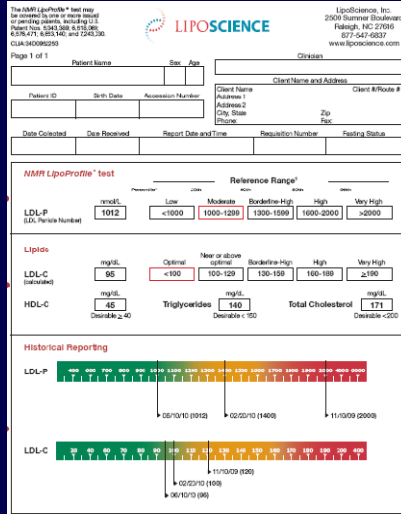


Associations Between CHD Events and LDL Particle Number* Versus LDL Cholesterol



*Measured by nuclear magnetic resonance.
 CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol;
 LDL-P = low-density lipoprotein particles

Reprinted from Cromwell WC, et al. J Clin Lipidol. 2007;1: 583-592, with permission from Elsevier Limited.



Pt Sam

- NMR Lipoprofile test
- LDL-C: 60
- LDL-P: 1250, moderately increased
- Pattern: "Type B", small dense LDL
- Niaspan titrated to 1500 mg/day
- LDL-C: 58
- LDL-P: 889, optimal
- Pattern: "Type A", large buoyant LDL

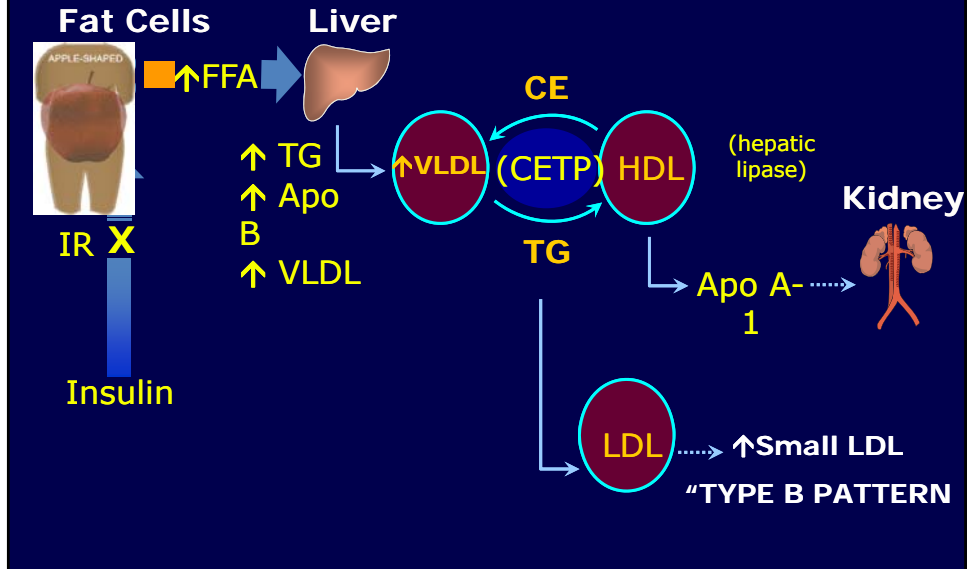
MHI Medical Treatment of Hyperlipidemia: General Principles

- Statins are the mainstay of therapy in both Primary and Secondary prevention
- Achieve LDL goals FIRST before RX non HDL cholesterol, Lp (a), particle sizes
- Meds:
 - Additional LDL lowering: Bile Acid Seq (Welchol), Zetia
 - Treat non HDL cholesterol, Lpa, particle sizes: Niacin, fish oils, fibrates (w/high TG >500)

Bile Acid Seq: Welchol

- Colesevelam plus statin
- Lowers LDL additional 10-16%
- Raises HDL additional 5-7%
- Can increase TG levels
- Welchol water insoluble, best tolerated
- No outcome trials

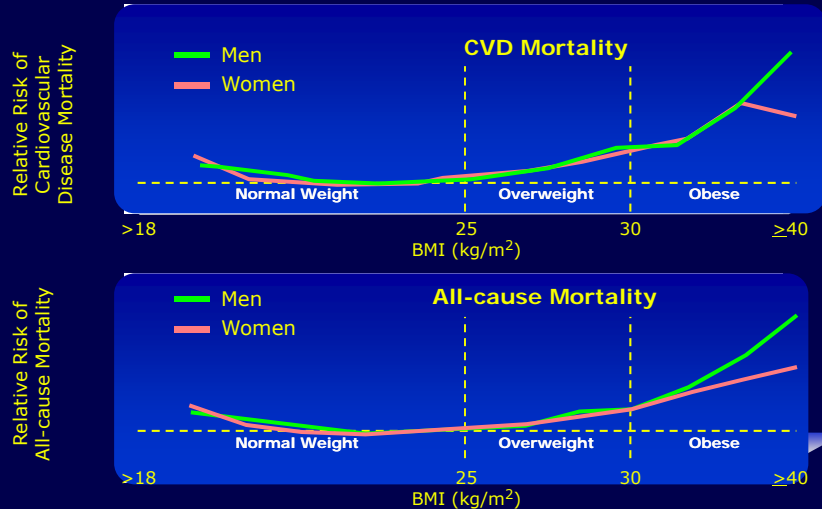
Two Atherogenic Consequences of Metabolic Syndrome



Lp(a): Lipoprotein "little a"

- A modified Apo B LDL with an apolipoprotein (a) attached
- Apo a genetically similarities to plasminogen
- Therefore, both atherogenic (LDL) and pro thrombotic (plasminogen)
- Genetically determined: Autosomal Dominant
- Difficult to Rx: Niacin, lifestyle

Overweight and Obesity Increase the Risk of Cardiovascular Disease Mortality and All-Cause Mortality



Data are from 1 million men and women followed for 16 years with an average age of 57 who never smoked and had no history of disease at enrollment.

Calle et al. *N Engl J Med* 1999;341:1097-1105.

Fish Oils: The Trials

- GISSI-Prevenzione Study 1mg DHA/EPA post MI reduced cardiac mortality 17-30%
- GISSI-HF Study: 1gm DHA/EPA reduced all cause mortality in CHF pts by 9%
- JELIS Study 1.8 gm EPA benefit in both primary and secondary prevention 19% reduction in coronary events
- Prescriptive: LOVAZA: more effective at lowering TG than Gemfibrozil

Niacin : A B3 Vitamin

- OTC B3, inositol nicotinate, are not Niacin and do not flush or work
- Flushing related to hepatic metabolism: High capacity pathway: flushing (immediate release), Low capacity pathway: no flush but more liver toxicity
- Slow, controlled, sustained, long release... reduce flushing at the expense of increased LFT elevation
- Niaspan (high capacity pathway) ER formulation in the middle, slows metabolism but not so much as to markedly increase LFTs
- Flushing avoided by taking 325 mg ASA 30 minutes prior to niacin (take with food)
- Promote larger, buoyant LDL particles, less atherogenic
- Modestly increase glucose and uric acid levels

Zetia: ENHANCE

ENHANCE: Primary end point

End point	Ezetimibe plus simvastatin	Simvastatin alone	p
Change in mean carotid IMT after 2-y treatment (mm)	0.0111	0.0058	0.29

Zetia plus simvastatin vs simvastatin alone: no improvement in CIMT