

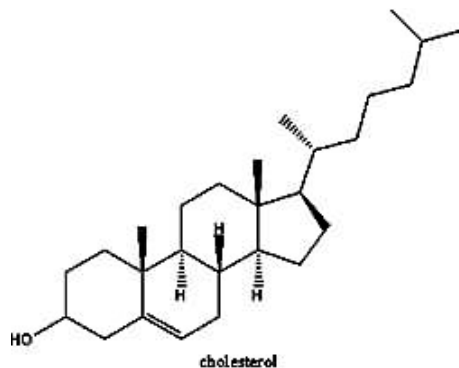
# Lipid Management Manual

## A Guide to the Management of Patients with Lipid Disorders

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## Evaluation of Patients with Possible Lipid Disorders

### History:

1. Basic cardiovascular history: Chest pain, heart failure symptoms, etc.
2. Other Vascular beds: Claudication, CVA symptoms
3. Past medical history: Focus on possible secondary cause for dyslipidemia: obesity (especially visceral obesity), diabetes, renal disease, nephrotic syndrome, HIV on antiretrovirals, hypothyroidism, transplant, liver disease
4. Past cardiac, vascular history: Any history of known HTN, CAD/PVD/CVD. History of revascularizations? Family History: Anyone with CAD, CVD, PVD. Anyone with known lipid disorders, taking cholesterol lowering medication
5. Medications: alcohol, hormone replacement, diuretics, betablockers, alpha-blockers, glucocorticoids, protease inhibitors, cyclosporine (+statin increases risk of rhabdomyolysis), statin, fibrates, bile acid resin binders, niacin, etc. vitamins, supplement use like omega-3 fatty acids
6. Diet: Evaluate amount of saturated fat vs. polyunsaturated fats, simple carbohydrates, excess calories
7. Exercise: Amount of physical activity per day

### Physical Exam:

1. HEENT: examine eyes for arcus senilis, xanthelesmas
2. Neck: examine carotids for bruits, upstroke, thyromegaly
3. Lungs: Crackles
4. CV: routine cardiac exam (especially isolated aortic area systolic ejection murmur)
5. Abd: bruits, hepatomegaly, hepatic tenderness
6. Ext: femoral bruits, all pulses, edema, tendons for xanthomas, loss of pinprick awareness or vibratory sense

### Laboratory Evaluation:

Baseline: TSH, Chemistry panel, LFTs, Lipid panel (total cholesterol, LDL, HDL, triglycerides, VLDL, apo-B, apo-A1) Lp(a), homocysteine, urine microalbumin/creatinine, CRP, HbA1C, CPK

\*\*LDL can be directly measured or calculated.

$LDL-C = \text{Total cholesterol} - HDL-C - (\text{triglycerides}/5)$

Converting LDL and total cholesterol from mg/dL to mmol/L multiple by 0.0259.

For example  $LDL = 143 \text{ mg/dL} \times 0.0259 = 3.7 \text{ mmol/L}$

12 lead ECG: evidence of prior infarct, LVH, ischemic changes

## **Etiologies for lipoprotein abnormalities**

### **Causes of elevated LDL**

#### Genetic:

Heterozygous familial hypercholesterolemia  
Familial defective B-100  
Polygenic hypercholesterolemia  
Familial combined hyperlipidemia  
Lp(a) excess

#### Drugs:

Cyclosporine  
Loop diuretics  
Thiazide diuretics  
Glucocorticoids  
Protease inhibitors (increase Lp(a))

#### Diseases:

Nephrotic syndrome (hypoalbuminemia results in increased hepatic lipoprotein synthesis and clearance is altered)  
Hypothyroidism (decrease cell surface LDL receptors and LDL catabolism)

### **Causes of small dense LDL**

\*Seen with low HDL, elevated triglycerides, abdominal obesity, and insulin resistance

#### Genetic:

Familial combined hyperlipidemia

#### Diseases:

Metabolic Syndrome  
Diabetes  
Obesity

#### Drugs:

Protease Inhibitors

### **Causes of increased remnants**

#### Genetic:

Familial dysbetalipoproteinemia (apoE2/E2 deficiency, hepatic lipase deficiency)

#### Diseases:

Diabetes  
Hypothyroidism

Dysglobulinemia

### **Causes of increased VLDL**

#### Genetic:

Familial Hypertriglyceridemia +/- hyperchylomicronemia  
Familial combined hyperlipidemia +/- hyperchylomicronemia  
Lipoprotein lipase (LPL) deficiency  
Apo C-2 deficiency  
Apo C-3 inhibitor excess

#### Diseases:

DM (+increased chylomicrons)  
Dysglobulinemias (+increased chylomicrons)  
Hypothyroidism  
Uremia  
Nephrotic syndrome (+increased chylomicrons)  
Chronic Renal disease  
Stress (+increased chylomicrons)  
Pregnancy

#### Drugs

Glucocorticoids  
Etoh use  
Estrogen

### **Causes of low HDL**

#### Genetic:

Primary hypoalphalipoproteinemia

#### Diseases/Habits:

Cigarette Smoking  
Physical Inactivity  
Metabolic Syndrome  
Diabetes type 2  
Androgens  
Beta-blockers

### **Causes of elevated triglycerides**

#### Genetic:

Familial hypertriglyceridemia  
Familial combined hyperlipidemia

### Diseases/Habits

Obesity  
Diabetes  
Acromegaly  
Burns  
Chronic renal failure  
Cigarette smoking  
Glycogen storage diseases  
Hepatitis  
Hyperandrogenism in women  
Hypothyroidism  
Lipodystrophy  
Nephrotic syndrome  
Polyclonal gammopathy  
Pregnancy  
Systemic lupus erythematosus  
Metabolic syndrome  
Transplantation

### Drugs

Alcohol  
Anti-psychotics (olanzapine, clozapine)  
Beta-blockers  
Didanosine  
Thiazides  
Estrogen  
Glucocorticoids  
Protease inhibitors  
Retinoids  
Tamoxifen

## Primary Lipoprotein Abnormalities

Adapted from Table 1. Knopp RH. NEJM 1999.

Disorder	Mechanism	Complication
Familial hypertriglyceridemia	Decreased serum triglycerides removal secondary to decreased LPL activity  Increased hepatic secretion of triglyceride-rich VLDL	Pancreatitis (Triglycerides >2000 mg/dL)
Familial combined hyperlipidemia	Increased hepatic secretion of apolipoprotein B containing VLDL and conversion to LDL  Accumulation of VLDL, LDL, or both, depending on efficiency of their removal	CAD, PVD, CVD
Remnant removal disease (familial dysbetalipoproteinemia)	Increased secretion of VLDL  Impaired removal of remnant lipoproteins resulting from homozygosity ( <i>e2/e2</i> ) or heterozygosity ( <i>e2/e3</i> or <i>e2/e4</i> ) for lipoprotein E <i>e2</i>	PVD, CAD, CVD
Familial or polygenic hypercholesterolemia	Diminished LDL-receptor activity  Defective apolipoprotein B that is poorly recognized by LDL receptor	CAD, occasionally PVD, CVD
Familial hypoalphalipoproteinemia (low HDL syndrome)	Diminished apolipoprotein A1 formation  Increased removal of apolipoprotein A1  Increased CETP or hepatic lipase activity	CAD, PVD

CAD= Coronary artery Disease  
PVD= Peripheral Vascular Disease  
CVD= Cerebrovascular Disease, Stroke  
CETP: Cholesterol-ester transfer protein

# Determining Treatment in Moderate and High Risk Individuals for Coronary Heart Disease

Does patient have documented atherosclerotic disease or equivalent: CHD, CVD, PVD, DM, or 10 year risk of hard CHD events of >20%?  
 \*See next page to determine 10 year risk\*

YES

NO

1. Begin Statin Therapy
2. Goal <100 mg/dL
3. Goal <70 mg/dL if high risk features (DM+CVD)

At goal?

NO

YES

Increase statin or add another agent like zetia to achieve goal  
 Monitor for toxicity

If at goal monitor for toxicity.  
 See Statin Management sheet.

## Everyone should

1. Stop smoking
2. Treat hypertension per JNC VII guidelines
3. Maintain BMI <25 (less depending on ethnic background)
4. Regular Activity (evaluate first for unstable CHD or vascular disease before prescribing exercise program)
5. Treat DM aggressively
6. TLC Diet (See diet sheet)

Moderate Risk 2+ risk factors (10 year risk for CHD 10 to 20%)? Begin statin for LDL  $\geq$  130

At goal?

NO

YES

Increase statin or add another agent like zetia to achieve goal  
 Monitor for toxicity

If at goal monitor for toxicity  
 See Statin Management sheet.

Are fasting triglycerides > 200 mg/dL?

YES

Is non HDL-C > 130 mg/dL (high risk), >160 mg/dL (moderate risk)?

YES

Begin Niacin, Fibrate, or Fish oil See Fibrate and Niacin Management Sheet. Monitor for toxicity

## Metabolic Syndrome

- Meets 3 of the following criteria:
  1. Waist circumference  $\geq 35$  (88 cm) inches for women  
 $\geq 40$  (102 cm) inches for men
  2. Fasting triglycerides  $\geq 150$  mg/dL
  3. HDL  $\leq 40$  for men  $\leq 50$  for women
  4. Elevated fasting blood glucose  $\geq 110$  mg/dL
  5. Hypertension: Blood Pressure  $>130/85$
  6. Microalbuminuria
- People with metabolic syndrome have elevated thrombotic factors such as PAI-1 , and inflammatory markers such as CRP.
- The pathophysiological derangements of metabolic syndrome such as insulin resistance, atherogenic dyslipidemia, raised blood pressure, proinflammatory state, and prothrombotic state puts people with metabolic syndrome at significant increased risk of diabetes and heart disease
- Estimated 47 million people have metabolic syndrome (from NHANES data)
- Age-adjusted prevalence for metabolic syndrome for US adults is 23.7%
- True risk of coronary disease may be underestimated using traditional risk factor calculations (e.g. Framingham)

### FOR EXAMPLE:

A 54 y.o post-menopausal woman without any known vascular disease or diabetes has metabolic syndrome.

Waist Circumference	37 inches
Triglycerides	220 mg/dL
HDL	38 mg/dL
Blood Pressure	135/90
Fasting Blood Glucose	112 mg/dL
Microalbuminuria	yes

She also has a total cholesterol of 222 mg/dL, LDL 134 mg/ dL, Non-HDL is 182 mg/dL, She is a nonsmoker with a family history of premature CHD (mother had an MI at 50 and father had an MI at 48).

Her Framingham 10-year risk for CHD events is only **2%**. According to Framingham risk score she is in a **low risk** category despite having greater than 2+ risk factors for heart disease. Therefore, according to ATP III/NCEP Guidelines you would not initiate drug therapy unless her LDL was > 160 mg/ dL. If you take it a step further using these guidelines her Non-HDL goal is 190 mg/dL and she still would not meet criteria to initiate drug therapy. In fact you would not start drug therapy on her (assuming all of the numbers remain the same) until she was 75 years old!

Of course you would “intensify weight management and counsel her to increase physical activity” per guidelines. These changes are very important. How many people would feel safe not treating this woman with lipid lowering therapy? We are not advocating you to not follow national guidelines. However, this patient needs special consideration for lipid lowering therapy and aggressive counseling regarding weight loss and activity. Furthermore this patient would qualify for ASA therapy per NCEP/ATP III guidelines. Other therapies such as increasing omega-3 fatty acid intake in terms of fatty fish should also be considered.

- Therapies to Consider in Metabolic Syndrome:

Weight Loss

TLC diet (see familial combined hyperlipidemia section for % nutrients)

Increase fiber in diet

Increase activity (at least 30 minutes of vigorous walking/day)

Baby ASA

Fatty fish meal (at least two per week) or omega-3 fatty acid supplementation in form of fish oil

Multivitamin per day to ensure adequate folate, B vitamin intake

Statin therapy per guidelines

Fibrate

Niacin

## LIPID-LOWERING AGENTS

DRUG		INDICATIONS (HYPERLIPIDEMIA)	PRIMARY LIPOPROTEIN EFFECTS	MAJOR MECHANISMS OF ACTION (KNOWN OR SUSPECTED)	PRINCIPAL ADVERSE REACTIONS AND DRUG INTERACTIONS	DOSAGE	LAB TESTS
STATINS	Fluvastatin (Lescol®) Novartis	HC CHL	Triglycerides ↓ Cholesterol ↓↓ VLDL ↓ LDL ↓↓ HDL ↑	HMG CoA reductase inhibition:  1. Reduces endogenous cholesterol synthesis  2. Increases LDL receptor activity	Abnormal liver function tests Myositis w/↑ CPK Occasional insomnia GI upset, gas Difficulty thinking Daytime inattention Rash Headache Rhabdomyolysis (rare) Myoglobinuria (rare) Proteinuria	20-80 mg	AST (SGOT)
	Lovastatin (Mevacor®) Merck					10-80 mg	
	Pravastatin (Pravachol®) Squibb					10-40 mg (80mg)	
	Simvastatin (Zocor®) Merck					10-80 mg	
	Atorvastatin (Lipitor®) Pfizer					10-80 mg	
	Rosuvastatin (Crestor®) AstraZeneca					5-40 mg	
FIBRATES	Gemfibrozil (Lopid®) Pfizer	HTG, CHL	Triglycerides ↓↓ Cholesterol ↓ VLDL ↓↓ LDL ↓ HDL ↑↑	VLDL synthesis ↓ Apo B synthesis ↓ Lipoprotein lipase ↑	Abdominal and epigastric pain (Lopid only) Prolongs coumadin effect; decrease dose 30%	600 mg twice daily	AST (SGOT)
	Fenofibrate (Tricor®) Abbott					54 mg, 1-3 tabs daily (54, 108, or 160 mg)	
RESINS	Colesevelam (WelChol®) Sankyo	HC	Triglycerides ↑ Cholesterol ↓ VLDL ↑ LDL ↓ HDL slightly ↑	Binds intestinal bile acids - preventing their reabsorption VLDL and triglyceride synthesis	Constipation, nausea, bloating, abdominal pain, heartburn, belching Decreased absorption of fat-soluble vitamins (A, D, and K) and other drugs, delaying or reducing their absorption	625 mg tablets, 3 bid	
	Cholestyramine resin (Prevalite®) Upsher-Smith					4 grams, 1-4 times daily. 4 grams = 1 scoop	
	Colestipol (Colestid®) Pharmacia					5 grams, 1-4 times daily. 5 grams = 1 scoop	
NIA CIN	Niacin tablets (plain or crystalline)	HC, CHL, HTG, and remnant removal disease	Triglycerides ↓↓ Cholesterol ↓ VLDL ↓↓ LDL ↓ HDL ↑ or ↓ ↓ Lp (a)	Adipose lipolysis ↓ VLDL synthesis ↓ Hepatic secretion of biliary cholesterol ↑ Cholesterol synthesis ↓	Severe generalized flushing Pruritis/dry skin/dry eyes GI disorders Hyperuricemia, glucose intolerance Abnormal liver function tests	1-2 grams, 3 times daily. Start low, increase slowly.	Glucose Uric acid AST (SGOT)
	Niaspan® (extended release)					1000 -1500 mg qd @ HS Titrate: 500 mg qd x 1 mo 1000 mg qd x 1 mo, etc (500 mg tabs release over more time)	
	Slo-niacin (OTC)						
CHOL. ABSORPTION INHIBITOR	Zetia® (ezetimibe) Merck-Schering Plough	Mild HC or CHL, Unattained LDL target with statins	LDL ↓ HDL slightly ↑ Triglyceride ↓	Inhibits cholesterol absorption by the intestine	Occasional SGOT rise with statins Bound by resins, Fibrates increase ezetimibe levels	10 mg qd	SGOT

Apo: apolipoprotein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein; Chol: Cholesterol

↑: increase; ↑↑: greater increase; ↓: decrease; ↓↓: greater decrease; ↔: no effect; HC: hypercholesterolemia; CHL: Combined Hyperlipidemia; HTG: Hypertriglyceridemia.

## COMBINED LIPID LOWERING DRUG THERAPY

SUPPLEMENT OR TREATMENT		INDICATIONS (HYPERLIPIDEMIA)	PRIMARY LIPOPROTEIN EFFECTS	MAJOR MECHANISMS OF ACTION (KNOWN OR SUSPECTED)	PRINCIPAL ADVERSE REACTIONS AND DRUG INTERACTIONS	DOSAGE	LAB TESTS
STATIN/NIACIN	Advicor® (Nicostatin) (Niaspan®/lovastatin) KOS Pharmaceuticals	CHL	LDL ↓↓ Triglyceride ↓ HDL ↑	Statin, niacin effects combined	Skin flushing Hepatotoxicity GI upset	Niaspan/Lovastatin doses: 500/20 mg (1-2 tablets/day) 1000/20mg (1-2 tablets/day) (maximum 2000/40 mg daily)	SGOT
	Any statin with any niacin						
STATIN/CHOL. ABSORB. INHIBIT.	Vytorin™ (simvastatin/ezetimibe) (Zocor®/Zetia™)	Insufficient response to statin alone	Triglycerides ↓ Cholesterol ↓↓ VLDL ↓ LDL ↓↓ HDL ↑	Dual inhibition: decreased synthesis, decreased absorption	<u>Statin:</u> Abnormal liver function tests Myositis w/↑ CPK Occasional insomnia GI upset, gas, rash, Headache Difficulty thinking Daytime inattention Rhabdomyolysis (rare) Myoglobinuria (rare) Proteinuria <u>Ezetimibe:</u> Diarrhea (?)	Simvastatin/ezetimibe (mg/mg): 10/10 20/10 40/10 80/10	SGOT: 2-3 times more likely to increase compared to each agent alone.

## OTHER LIPID LOWERING TREATMENTS

SUPPLEMENT OR TREATMENT		INDICATIONS (HYPERLIPIDEMIA)	PRIMARY LIPOPROTEIN EFFECTS	MAJOR MECHANISMS OF ACTION (KNOWN OR SUSPECTED)	PRINCIPAL ADVERSE REACTIONS AND DRUG INTERACTIONS	DOSAGE	LAB TESTS
OMEGA-3 Fatty Acids	Fish Oil	HTG	Triglycerides ↓↓ Cholesterol ↓ or ↔ VLDL ↓↓, LDL ↑↓, HDL ↑	Inhibits synthesis of triglycerides	Fishy smell in high doses Potential inhibition of platelet aggregation	1-10 grams, average is 2-4 grams daily	
STANOL/STEROL ESTERS	Benecol® spread (plant stanol esters) McNeil	Mild HC or CHL, Unattained LDL target with other drugs	LDL mildly ↓ (14% if full dose)	Inhibits cholesterol absorption (not absorbed itself)		1½ teaspoons tid	
	TakeControl® spread (plant sterol esters) Unilever		LDL mildly ↓ (10% if full dose)	Inhibits cholesterol absorption (partly absorbed itself)		1 tablespoon bid	

Apo: apolipoprotein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein; Chol: Cholesterol

↑: increase; ↑↑: greater increase; ↓: decrease; ↓↓: greater decrease; ↔: no effect; HC: hypercholesterolemia; CHL: Combined Hyperlipidemia; HTG: Hypertriglyceridemia.

## How much reduction in LDL cholesterol can I expect with the different statins?

**Absolute reductions\*** in **mg/dL** and **% change** in serum **LDL** cholesterol concentrations according to statin and daily dose (summary estimates from 164 randomized placebo controlled trials)\*

Statin	mg/dL Decrease				
	5 mg	10 mg	20 mg	40 mg	80 mg
Lovastatin (Mevacor)		39	54	68	83
Pravastatin (Pravachol)	28	37	45	53	62
Fluvastatin (Lescol)	18	29	39	50	61
Simvastatin (Zocor)	42	51	60	69	78
Atorvastatin (Lipitor)	58	69	80	91	102
Rosuvastatin (Crestor)	71	80	90	99	108

Statin	Percent (%) Decrease				
	5 mg	10 mg	20 mg	40 mg	80 mg
Lovastatin (Mevacor)		21	29	37	45
Pravastatin (Pravachol)	15	20	24	29	33
Fluvastatin (Lescol)	10	15	21	27	33
Simvastatin (Zocor)	23	27	32	37	42
Atorvastatin (Lipitor)	31	37	43	49	55
Rosuvastatin (Crestor)	38	43	48	53	58

\* Absolute reductions are standardized to usual serum LDL cholesterol before treatment (mean concentration in trials).

\*\* Adapted from: Table 2: Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326:1423-1430

\*\*\* Percentage reductions are independent of pretreatment LDL cholesterol concentration

Statin	mg Equivalence
Lovastatin (Mevacor)	80 mg
Pravastatin (Pravachol)	80 mg
Fluvastatin (Lescol)	80 mg
Simvastatin (Zocor)	40 mg
Atorvastatin (Lipitor)	20 mg
Rosuvastatin (Crestor)	10 mg

## Major Prevention Trials with Statins with Hard Clinical Outcomes

Trial	Population	Drug	N	Duration (yrs)	Major Findings
4S <sup>1</sup>	Adults aged 35- 70 with history of angina or MI and cholesterol 213-309 mg/dL	Simvastatin 20 mg (titrate up to 40 mg to meet goal) vs. placebo	4444	5	Decrease 30% total mortality Decrease 34% coronary events*
WOSCOPS <sup>2</sup> (Primary Prevention)	Men aged 45-64 LDL >250 mg/dL No history of MI	Pravastatin 40 mg vs. placebo	6595	5	Decrease 22% total mortality Decrease 31% coronary events*
CARE <sup>3</sup>	Adults aged 21- 75 with history of MI 3-20 months prior to randomization, Total cholesterol <240 mg/dL	Pravastatin 40 mg vs. placebo	4159	5	Decrease 24% coronary events Decrease 31% stroke
AFCAPS/TexCAPS <sup>4</sup> (Primary Prevention)	Adults average levels of cholesterol and below average HDL No history of MI	Lovastatin 20 –40 mg vs. placebo	6605	5	Decrease 37% coronary events*/unstable angina
LIPID <sup>5</sup>	Adults aged 31-75 with history of MI or UsA and cholesterol levels of 155-271 mg/dL	Pravastatin 40 mg vs. placebo	9014	6	Decrease 22% total mortality Decrease 24% coronary events*
AVERT <sup>6</sup>	Adults with stable coronary artery disease with $\geq 50\%$ stenosis of at least one coronary artery who had been recommended for treatment with angioplasty, nl LV function, LDL $\geq 115$ mg/dL	Atorvastatin 80 mg vs. PTCA +usual care (could include statin)	341	18 months	Decrease 36% ischemic events+ with atorvastatin 80 (but not statistically significant after adjustment for interim analyses)
MIRACL <sup>7</sup>	Adults >18 with admission for acute coronary syndrome (started study drug 24-96 hours after admission), several exclusions	Atorvastatin 80 mg vs. placebo	3086	16 weeks	Decrease of 16% in death and nonfatal ischemic event++ (death not statistically different, driven by nonfatal ischemic events)

HPS <sup>8</sup>	Adults age 40-80 with CAD, other occlusive arterial disease, or DM	Simvastatin 40 mg vs. placebo	20,536	5	Decrease 13% total mortality Decrease 27% coronary events* Decrease 25% Stroke
ALLHAT-LLT <sup>9</sup>	Adults age ≥55, stage 1 or 2 htn, at least one additional CHD risk factor and moderately elevated cholesterol (+/- history of MI)	Pravastatin 40 mg vs. usual care	10,355	5	No statistical difference in total mortality and coronary events* between both groups
ASCOT-LLA <sup>10</sup>	Adults with HTN with total cholesterol < 6.5 mmol/L and >3 risk factors (no MI in previous 3 months)	Atorvastatin 10 mg vs. Placebo	10,305	3.3	No statistical difference in total mortality Decrease 36% coronary events* Decrease stroke 27%
CARDS <sup>11</sup>	Diabetics aged 40- 75 without known CHD With LDL <160 mg /dL + one other risk factor	Atorvastatin 10 mg vs. Placebo	2838	4	Decrease 34% coronary events, revascularization, or stroke Decrease total mortality by 27% but not statistically significant

\*Coronary events= Nonfatal MI and CHD death

+Ischemic events =Death from cardiac causes, resuscitation after cardiac arrest, nonfatal MI,CVA, CABG, PCI, Worsening angina with objective evidence of ischemia resulting in hospitalization

++Nonfatal ischemic events: nonfatal acute MI, cardiac arrest with resuscitation, recurrent symptomatic ischemia with objective evidence requiring emergent hospitalization

## Major Prevention Trials with Fibrates/Gemfibrozil/Niacin with Hard Clinical Outcomes

Trial	Population	Drug	N	Duration (yrs)	Major Findings
VA-HIT <sup>12</sup>	Men with CHD with LDL $\leq$ 140 mg/dL and HDL $\leq$ 40 mg/dL	Gemfibrozil 1200 mg vs. placebo	2531	5	Decrease 22% coronary events and 24% including stroke
BIP <sup>13</sup>	Adults with CHD total cholesterol 180-50 mg/dL, HDL-C $\leq$ 45 mg/dL, TG $\leq$ 300 mg/dL	Bezafibrate vs. placebo	3090	6	Not statistically significant reduction in coronary events*
CDP <sup>14,15</sup>	Adults with CHD	Niacin 3 g/day vs. placebo	3908	6,9	Decrease 27% nonfatal MI at 6 years Decrease 11% total mortality at 9 years
FATS <sup>16</sup>	Men with CHD, family hx CHD, apoB >125 mg/dL	Lovastatin 20 mg qd vs. niacin 1gm +colestipol 10 g tid vs. conventional therapy (placebo or colestipol)	146	2.5	Decrease 83% coronary events* + revascularization (lovastatin and niacin+colestipol group vs. conventional) Coronary regression also seen in these groups vs. conventional
HATS <sup>17</sup>	Adults <63 for men <70 for women with CHD, $\geq$ 3 coronary lesions $\geq$ 30% stenosis or $\geq$ 1 coronary lesion with $\geq$ 50% stenosis, LDL $\leq$ 145 mg/dL, TG $\leq$ 400 mg/dL, Men HDL $\leq$ 35, Women HDL $\leq$ 40	Simvastatin (adjusted to achieve LDL of 40-90 mg/dL + Niacin (500 mg-4g/d) or placebo (received simvastatin 10 mg if LDL $\geq$ 140 mg/dL) and (antioxidants or placebo)	160	3	Regression of diameter stenosis by 0.4% in simvastatin +niacin group Decrease of coronary events, stroke, or revascularization by 90% in simvastatin-niacin (no antioxidants) vs. all placebos decreased to 48% with addition of antioxidants
Stockholm <sup>18</sup>	Adults with CHD	Niacin (4.5 g/d) +clofibrate (1.5 g/d) vs. placebo	555		Decrease 26% total mortality Decrease 36% ischemic heart disease mortality

\*Coronary events= Nonfatal MI and CHD death

+Ischemic events =Death from cardiac causes, resuscitation after cardiac arrest, nonfatal MI,CVA, CABG, PCI, Worsening angina with objective evidence of ischemia resulting in hospitalization

++Nonfatal ischemic events: nonfatal acute MI, cardiac arrest with resuscitation, recurrent symptomatic ischemia with objective evidence requiring emergent hospitalization

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## Statin Management

Adapted from: ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins.  
*JACC.* 2002; 40: 567-572

### I. Management and Screening

- a. Baseline tests: LFTS, CK
  - i. Repeat LFTS at 12 weeks and then annually if no symptoms or indication of liver disease (some prefer to check at each visit)
  - ii. Repeat CK for any symptoms of myositis
    1. Also check TSH if symptoms of myositis because of hypothyroid induced myopathies
    2. Routine CK screening up to physician discretion
- b. Discontinue drug therapy
  - i. CK elevation  $>10$  X ULN + symptoms
  - ii. CK  $>3$ X to  $10$ X ULN; follow weekly but do not have to discontinue
  - iii. LFTS  $>3$ X ULN but ok to rechallenge or start another statin (especially consider water soluble (hydrophilic) statins like pravastatin or rosuvastatin) in future with close monitoring
  - iv. Do NOT need to discontinue if symptoms but no change in CK or LFTS from baseline as long as patient can tolerate
- c. Drug Interactions
  - i. Amiodarone, cyclosporine, fibrates, niacin, and verapamil may increase the risk of myopathy and rhabdomyolysis (lower doses of statins needed)
  - ii. Other drug interactions
  - iii. Statin concentration may be increased when taken with  $>1$  quart of grapefruit juice
  - iv. Avoid excessive etoh consumption due to potential hepatic effects
  - v. Pregnancy Class X (contraindicated)

### II. Increased LFTs

- a. Incidence: 0.5%- 2%
- b. Dose dependent
- c. No evidence statins exacerbate existing liver disease
- d. If mild to modest increase (LFTs  $<3$  X ULN) NOT contraindication to initiate, continue, or advance statin use but need to follow very closely.
- e. LFT elevations should reverse with decreasing dose or discontinuation of statin
- f. Ok to re-challenge or select another statin with close monitoring
- g. Progression to liver failure very rare if occurs at all

- h. LFT increase may be secondary to NASH (fatty infiltration of liver) and LFTS may improve if fatty liver improves

### III. Myopathy

#### a. Definitions

- i. Myopathy: any disease of muscles (inherited or acquired)
- ii. Myalgias: muscle aches or weakness without CK elevation
- iii. Myositis: muscle symptoms with CK elevation
- iv. Rhabdomyolysis: muscle symptoms (usually weakness ascending from the legs) with CK elevation (usually >10X ULN) with increased urine creatinine (usually with brown urine, urine hematest positive without red cells, and urinary myoglobin)

#### b. Risk Factors

- i. Older age
- ii. Female
- iii. Small frail frame
- iv. Multisystem organ disease (especially azotemia)
- v. Multiple RX
- vi. Perioperative steroid use
- vii. Medications
  - 1. Fibrates
  - 2. Nicotinic acid
  - 3. Cyclosporine
  - 4. Azole antifungals
  - 5. Macrolide antibiotics
  - 6. HIV protease inhibitors
  - 7. Nefazadone (antidepressant)
  - 8. Verapamil
  - 9. Amiodarone
  - 10. >1 qt. Grapefruit juice/day
  - 11. Alcohol abuse
- viii. Hospitalization for major surgery
- ix. Statins may exacerbate exercise induced muscle injury

#### c. Rates of myositis

- i. Cervistatin monotherapy resulted in 1.9 deaths/ million prescriptions due to rhabdomyolysis
  - 1. 10- 50X rate if any other statin
  - 2. No longer available as of August 8, 2001
  - 3. 60% of deaths were at highest dose
- ii. Lovastatin and simvastatin incidence of severe myositis is 0.08%

- iii. Statin-Fibrate combination 600 trials with 1% rate of CK >3X ULN without symptoms and 1% muscle symptoms and no cases of rhabdomyolysis (trials do not reflect routine practice)

Abbreviations:

LFTs: liver function tests

CK: creatinine kinase

ULN: upper limit of normal

TSH: thyroid stimulating hormone

## Fibrate Management

### Fibrate Effects

Enhance the oxidation of fatty acids in liver and muscle  
Decrease rate of lipogenesis in the liver  
Increased lipoprotein lipase (LPL) activity  
Decrease triglycerides, increase HDL, decrease or increase LDL  
Activate PPARalpha and can increase size of LDL particles and decrease PAI-1  
Fenofibrate decreases LDL-C 6- 20%, Gemfibrozil decreases LDL-C 0 to 15%, Fenofibrate increases HDL 18 to 33%, Gemfibrozil increases HDL 15 to 25%, Fenofibrate decreases triglycerides 41 to 53%, Gemfibrozil decreases triglycerides 35 to 50%  
(Knopp. NEJM. 1999)

### Different types of Fibrates

#### Gemfibrozil

Doses: 600 mg- 1200 mg  
Contraindicated in hypersensitivity to fibrates, severe liver and renal dysfunction, primary biliary cirrhosis, gallbladder disease  
Interacts with warfarin; Requires reduction of warfarin by 30%  
Other medication interactions  
Pregnancy Class C

#### Fenofibrate

Doses: Capsule: 67 mg/day - 200 mg/day  
Tablet: 48 mg/day- 145 mg/day  
Decrease dose in renal impairment: Decrease dose or increase dosing interval for patients with renal failure: Initial: 67 mg/day (capsule) or 48 mg/day (tablet)  
Contraindicated in hypersensitivity to fibrates, severe liver and renal dysfunction, primary biliary cirrhosis, gallbladder disease  
Interacts with warfarin; Requires reduction of warfarin by 30%  
Other medication interactions  
Pregnancy Class C

### Side Effects

Myositis with impaired renal function (increased risk in combination with statin)  
Increased LFTs (increased risk in combination with statin)  
Other: rash, increases 1-2% gallstones, GI symptoms, anemia, leukopenia

### Management and Screening

Baseline tests: LFTs, CPK

- i. Repeat LFTs, CPK at 4-12 weeks and then annually if no symptoms or indication of liver disease (some prefer to check at each visit)
- ii. Discontinue therapy
  1. Rhabdomyolysis
  2. Myositis (increased CPK with symptoms)
  3. LFTS > 3X ULN

# Niacin Management

## Niacin Effects

- a. Decreases Apo B lipoproteins (VLDL, IDL, LDL-C, Apo B, small dense LDL, Lp(a) (only agent which decreases Lp(a) is niacin)
- b. Increases Apo A lipoproteins (Increases HDL-C, Increases HDL<sub>2</sub>>HDL<sub>3</sub>, increases Apo A1)
- c. Average decrease of LDL 10 to 25%, average increase HDL 15 –35%, Average decrease triglycerides 10 to 33%

## II. Different types of Niacin

- a. Niacin Immediate Release
  - i. High rate of flushing
  - ii. Give up to 6 grams
  - iii. Over the counter
- b. Niacin Extended Release
  - i. Decreased rate of flushing
  - ii. Give up to 2 grams
  - iii. Over the counter (Slo-Niacin)
  - iv. Prescription (Niaspan)

## Side Effects

- c. Flushing
  - i. Give asa 30 minutes before to minimize flushing
  - ii. Eat with meal but do not take with hot drinks
- d. Pruritis/dry skin/dry eyes
- e. GI upset
- f. Hyperuricemia
- g. Glucose Intolerance (Usually seen at higher doses > 4grams), Diabetes is NOT a contraindication to niacin
- h. Abnormal LFTs (Dramatic LDL lowering, symptoms of nausea, anorexia, and fatigue may be signs of niacin hepatotoxicity)

## III. Management and Screening

- a. Baseline tests: LFTS
  - iii. Repeat LFTS at 4-12 weeks and then annually if no symptoms or indication of liver disease (some prefer to check at each visit)
  - iv. Discontinue therapy
    1. Intolerable flushing but first try adding asa, or switching to extended release niacin
    2. Significant LFT abnormality >3 ULN; may first decrease dose; follow LFTs closely
- d. Drug Interactions
  - i. Effect of oral hypoglycemics may be decreased with niacin
  - ii. Increased risk of myopathy, rhabdomyolysis, LFT abnormalities when used in combination with statins
  - iii. Other drug interactions

- iv. Pregnancy Class A (if do not exceed RDA recommendations otherwise Class C)

## Therapeutic Lifestyle Change (TLC) Diet From the American Heart Association

### Summary of Dietary Guidelines from AHA Dietary Guidelines. (Circulation 2000;102:2284-2299)

	Overall healthy eating pattern	Appropriate Body Weight	Desirable Cholesterol Profile	Desirable Blood Pressure
Major Guidelines	Variety of fruits, vegetables, grains, low-fat or nonfat dairy products, fish, legumes, poultry, lean meats	Match energy intake to energy needs, with appropriate changes to achieve weight loss when indicated	Limit foods high in saturated fat and cholesterol; and substitute unsaturated fat from vegetables, fish, legumes, nuts	Limit salt and alcohol; maintain a healthy body weight and a diet with emphasis on vegetables, fruits, and low fat or non-fat dairy products.

#### Diet Composition

	<b>Hypercholesterolemia</b>	<b>Familial Combined Hyperlipidemia (Includes Metabolic Syndrome / Diabetics/Insulin Resistant)</b>
<b>Nutrient</b>	<b>Recommended Intake as Percent of Total Calories</b>	<b>Recommended Intake as Percent of Total Calories</b>
<b>Total Fat</b> <sup>1</sup>	25–35%	30–40%
Saturated	Less than 7%	Less than 7%
Polyunsaturated	Up to 10%	Up to 20%
Monounsaturated	Up to 20%	Up to 20%
<b>Carbohydrate</b>	50–60% of total calories	40–50% of total calories
<b>Protein</b>	Approximately 15%	Approximately 15- 20 %
<b>Cholesterol</b>	Less than 200 mg per day	Less than 200 mg per day
<b>Total Calories</b> <sup>2</sup>	Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain	Balance energy intake and expenditure to maintain desirable body weight and prevent weight gain
	<b>From AHA</b>	<b>Per Dr. Knopp</b> <sup>3</sup>

1. Carbohydrate should come mainly from foods rich in complex carbohydrates. These include grains (especially whole grains), fruits and vegetables.
  
2. Daily energy expenditure should include at least moderate physical activity (contributing about 200 Kcal a day).
  
3. These recommendations based on interpretation of data from: Dansinger ML, Gleason JA, Schaefer EJ. Comparison of the Atkins, Ornish, Weight Watchers, and Zone Diets for Weight Loss and Heart Disease Risk Reduction: A Randomized Trial. *JAMA*. 2005;293:43-53.

### **LDL Recommendations**

<b>Component</b>	<b>Recommendation</b>
<b>LDL-Raising Nutrients</b>	
Saturated Fats	Less than 7% of total calories
	Trans fatty acids also raise LDL and should be kept at a low intake
Dietary Cholesterol	Less than 200 mg/day
<b>LDL-Decreasing</b>	
Plant stanols/sterols	2 grams per day
Increased viscous (soluble) fiber	10–25 grams per day

## Selected Reading

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