

Current Treatment of Lipid Disorders – an Update

GPEA meeting 21 June 2003

James Best

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Hyperlipidaemia

What is it?

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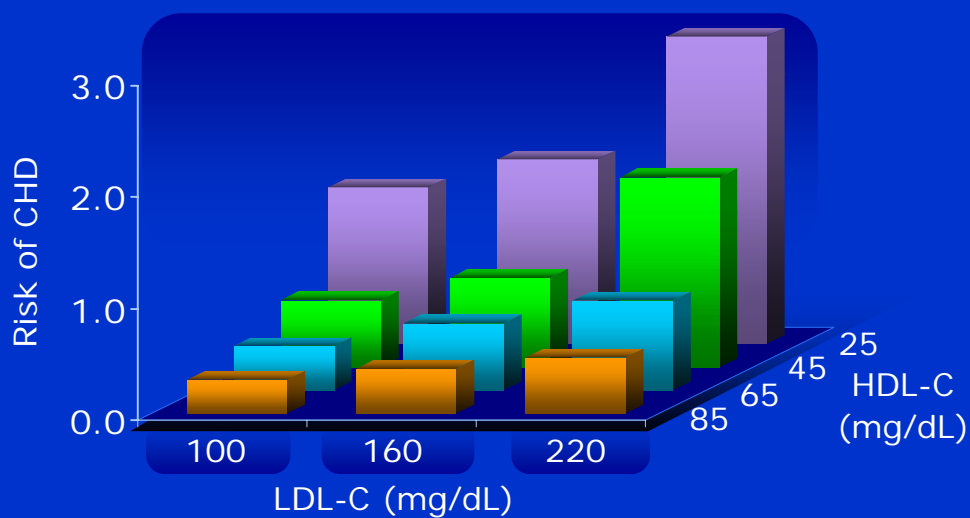
Hyperlipidaemia

Primary causes

- Familial Hypercholesterolaemia
- Familial Combined Hyperlipidaemia
- Familial Hypertriglyceridaemia
- Isolated Low HDL cholesterol

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Low HDL-C is an Independent Predictor of CHD Risk Even When LDL-C is Low



Gordon T et al. *Am J Med* 1977;62:707-714.

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ATP III: New Definition of Low HDL-C

Low HDL-C was redefined as <40 mg/dL
(< 1.0 mmol/L)

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001; 285:2486-2497.

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Hyperlipidaemia

Secondary causes

Hypothyroidism
Hypopituitarism
Renal disease
Alcohol
Oestrogen
Diabetes
Metabolic syndrome

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Metabolic Syndrome as a Secondary Goal after LDL-C

Risk Factor (≥ 3)	Defining Level
Abdominal obesity	Waist circumference*
Triglycerides	≥ 150 mg/dl
HDL-C	< 40 mg/dl in men; < 50 mg/dl in women
Blood pressure	$\geq 130/\geq 85$ mm Hg
Fasting glucose	≥ 110 mg/dl

* Men: >40 in (102 cm); women > 35 in (88 cm)

Expert Panel. *JAMA* 2001;285:2486-2497.

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Metabolic Syndrome as a Secondary Goal after LDL-C

Risk Factor	Defining Level
Abdominal obesity	> 100 cm waist circ. in men > 90 cm waist circ. in women
HDL-C	< 1.0 mmol/L in men < 1.25 mmol/L in women

Circ. = circumference measured at level of the iliac spine

Expert Panel. *JAMA* 2001;285:2486-2497.

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Clustering of Risk Factors Incorporated into the Metabolic Syndrome

- Includes risk factors not routinely measured
 - Insulin resistance
 - Small dense LDL
 - Endothelial dysfunction
 - Abnormal sympathetic nervous activity
 - Prothrombotic markers—PAI-1, fibrinogen
 - Proinflammatory markers such as CRP

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Hyperlipidaemia

Why treat?

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Non-Pharmacological Treatment

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Non-Pharmacological Treatment

Thiazides
Beta-blockers

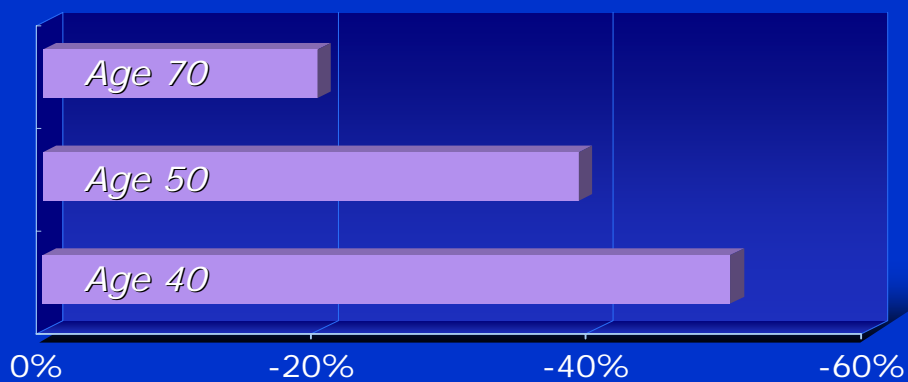
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Non-Pharmacological Treatment

**Diabetes
Hypertension
Metabolic Syndrome**

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Primary Prevention: Crucial Opportunity to Reduce the Burden of CHD



Reduction in risk in men with 10% reduction in total cholesterol (10 cohort studies)

Law MR et al. *BMJ* 1994; 308: 367-372.

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Primary Prevention: *Adverse Life Habit Changes*

- Atherogenic diet
- Sedentary lifestyle
- Obesity

Expert Panel. *JAMA* 2001;285:2486-2497.

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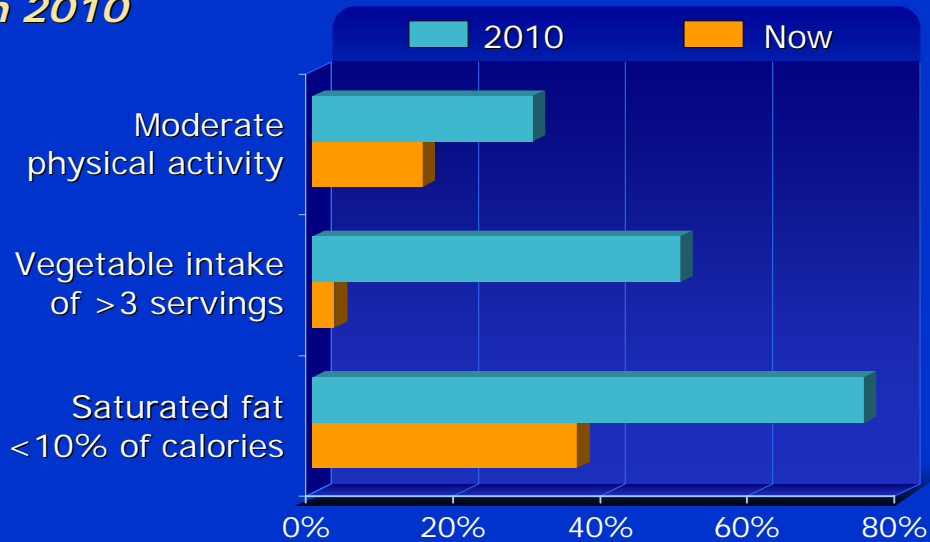
Primary Prevention—Rx: *Therapeutic Lifestyle Changes (TLC)*

- Therapeutic diet to lower LDL-C
- Physically active on a daily basis
- Weight control

Expert Panel. *JAMA* 2001;285:2486-2497.

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Primary Prevention: *Status and Goals in 2010*



NCEP. Adult Treatment Panel III Report. 2001.

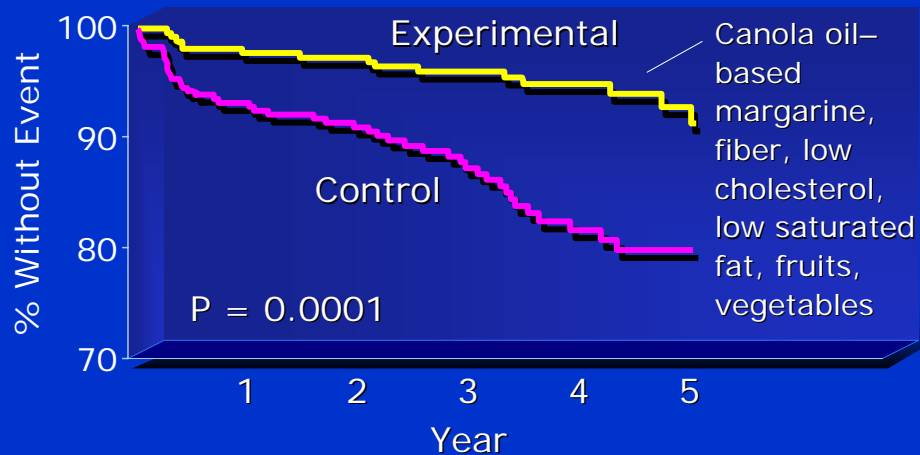
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Total Fat

- Primary emphasis is to reduce saturated fats
 - Total fat should range 25–30% for most cases
- Those with metabolic syndrome
 - Avoid very high fat intakes
 - Avoid very low fat intake (low HDL-C, high TG)
 - Total fat intake can range from 30–35% if extra fat is unsaturated
 - May reduce some lipid and nonlipid risk factors
 - Clinical judgment required.

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Lyon Diet Heart Study: *Cumulative Survival without Cardiac Death and Nonfatal MI*



de Lorgeril M et al. *Circulation* 1999;99:779-785.
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Comparison of the Diets

Item	Experimental	Control
Total calories	1947	2088*
Total fat	30.4%	33.6%*
Saturated fat	8%	11.7%
Dietary cholesterol	203 mg/dl	312 mg/dl*
Alcohol	Same	Same
Olive oil	None	None
MUFA n-9	Increased*	
PUFA	Increased*	
n-3/n-6 fatty acids	Increased*	
Fiber	18.6	

*Significantly different
de Lorgeril M et al. *Circulation* 1999;99:779-785.

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Primary Prevention—Rx: *TLC Measures to Lower LDL-C*

- Saturated fats (<7% total calories) and cholesterol (<200 mg/d)
- Also therapeutic options:
 - Plant stanols/sterols (2 g/d)
 - Increased viscous fiber (10–25 g/d)

Expert Panel. *JAMA* 2001;285:2486-2497.

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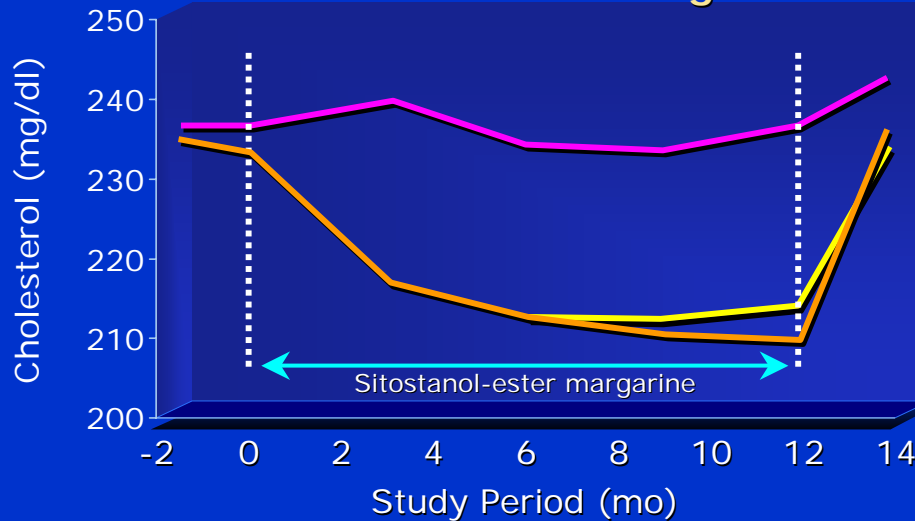
Plant Sterol/Stanol Esters

- If 2 g of plant sterol or stanol is added to average daily portion of margarine, it has variable effect on LDL-C by age group:
- Age LDL-C reduced by:
 - 50–59 21 mg/dl or 0.54 mmol/l
 - 40–49 17 mg/dl or 0.43 mmol/l
 - 30–39 13 mg/dl or 0.33 mmol/l

Law MR et al. *BMJ* 2000;320:861-864.

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Treatment with Stanol Ester Margarine



Miettinen TA et al. *N Engl J Med* 1995; 333:1308-1312.
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Suggestions on Activity

1. Scheduled physical activity

- Walking, treadmill, jogging, walking dog
- Swimming, biking, volleyball

2. Lifestyle physical activity

- Walk more stairs at work, walking for errands, parking farther away in parking lots
- Housework, gardening

U.S. Dept. of Health and Human Services. *Physical Activity and Health: A Report of the Surgeon General*. Atlanta, Ga: Centers for Disease Control and Prevention, 1996.

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Goals of Weight Loss

1. Reduce body weight in the short term
2. Maintain a lower body weight for the long term
3. Prevent further weight gain — minimum goal

Obesity Education Initiative. *Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults: the Evidence Report*. Bethesda, Md.: NIH, 1998

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Further Goals of Weight Loss

1. Rate of weight loss
 - 10% reduction in body weight in 6 months of therapy
 - Rate is 1–2 lbs per week

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Metabolic Benefits of Weight Loss

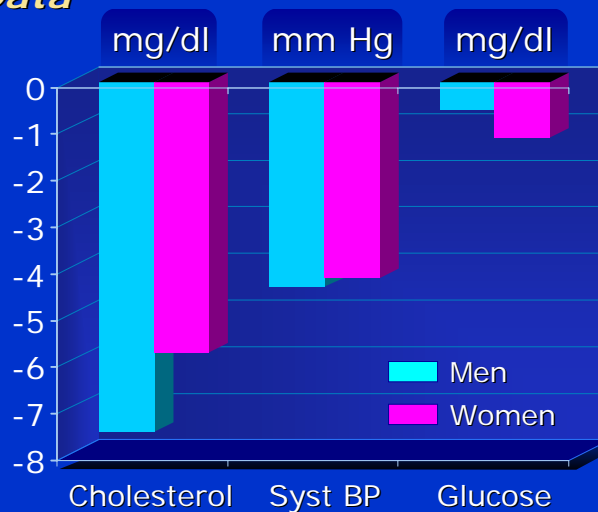
- Reverse changes of insulin resistance and metabolic syndrome
- Raise HDL-C (can see increase of 1.6 mg/dl from a 10-lb weight loss)

Dattilo AM et al. *Am J Clin Nutr* 1992;56:320-328.

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Metabolic Response to 10-lb Weight Loss: *Framingham Data*

Small changes can add up to significant changes in long-term risk



Higgins M et al. *Acta Med Scand Suppl* 1988;723:23-36.

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Primary Prevention with TLC

- Therapeutic Lifestyle Changes can lower LDL-C so medication not required or increase not needed
- Can treat metabolic syndrome
 - Lowers TG
 - Raises HDL-C
 - Reduces risk of diabetes
- Provides overall healthful lifestyle

Expert Panel. *JAMA* 2001;285:2486-2497.

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Pharmacological Treatment

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Treatment of Hyperlipidemia

High LDL-C

Therapeutic Lifestyle Change

Drug Therapy

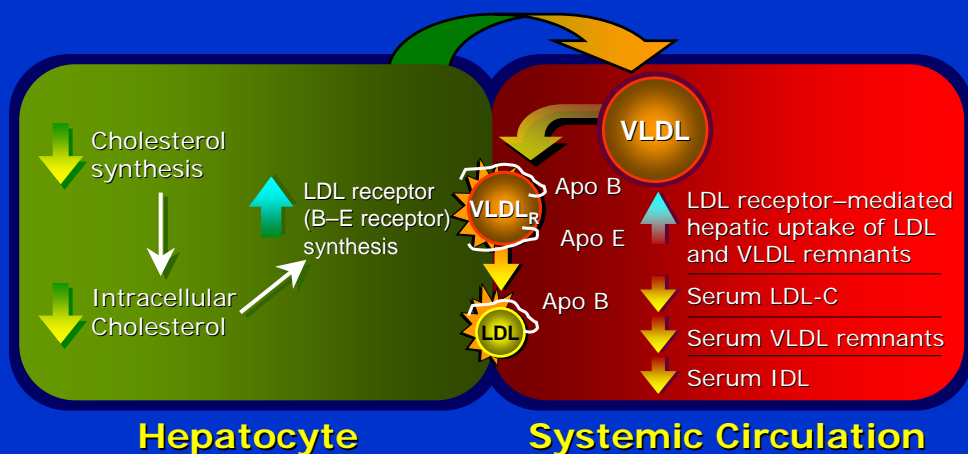
Therapy of Choice: **Statin**

Alternative: **Resin or niacin**

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001; 285: 2486-2497.

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Statins: Mechanism of Action



Reduce hepatic cholesterol synthesis, lowering intracellular cholesterol, which stimulates upregulation of LDL receptor and increases the uptake of non-HDL particles from the systemic circulation.

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The LDL-C–Lowering Efficacy of the Currently Available Statins

Daily Dose	Atorva	Fluva	Lova	Prava	Simva
10 mg	–39%			–22%	–30%
20 mg	–43%	–22%	–27%	–32%	–38%
40 mg	–50%	–25%	–32%	–34%	–41%
80 mg	–60%	–36%	–42%		–47%

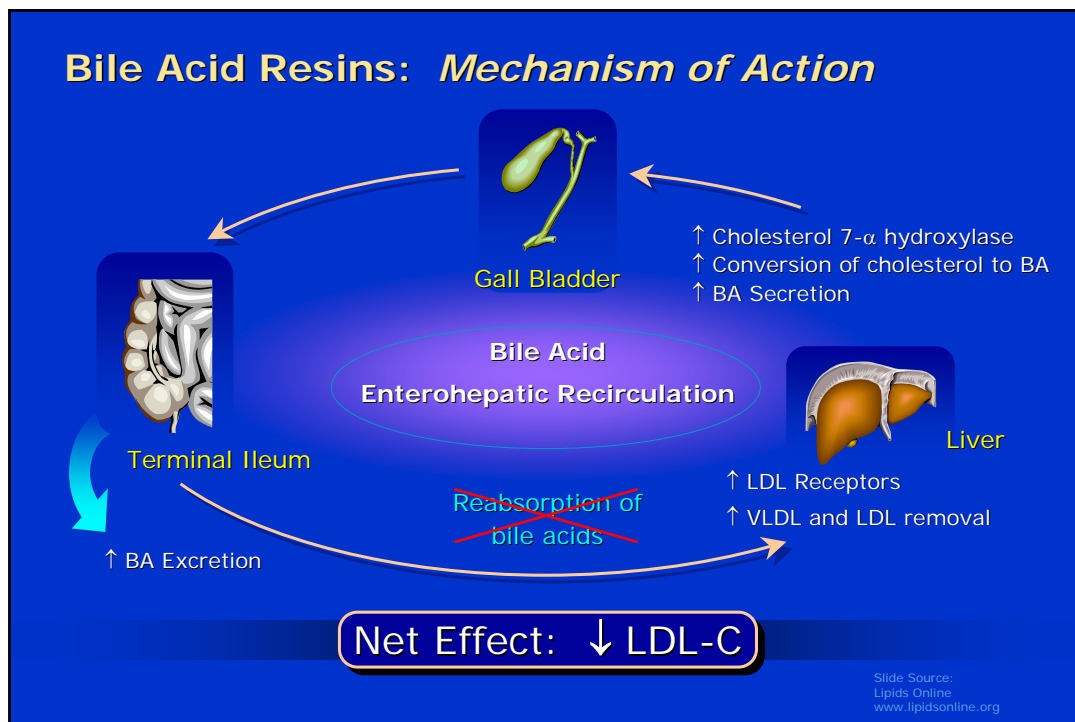
Physician's Desk Reference. 55th ed. Montvale, NJ: Medical Economics, 2001.

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Statin Adverse Events

- **Common side effects**
 - Headache – Myalgia – Fatigue
 - GI intolerance – Flu-like symptoms
- **Increase in liver enzymes**
 - Occurs in 0.5 to 2.5% of cases in dose-dependent manner
 - Serious liver problems are exceedingly rare
 - Manage by reducing statin dose or discontinue until levels return to normal
- **Myopathy**
 - Occurs in 0.2 to 0.4% of patients
 - Rare cases of rhabdomyolysis
 - Reduce by
 - Cautiously using statins in patients with impaired renal function
 - Using the lowest effective dose
 - Cautiously combining statins with fibrates
 - Avoiding drug interactions
 - Careful monitoring of symptoms
 - Presence of muscle toxicity requires the discontinuation of the statin

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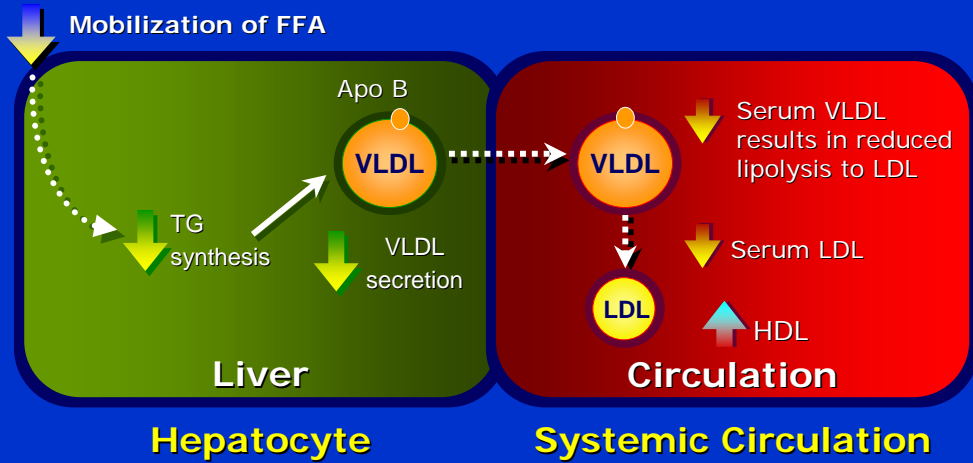


Clinical Features of BARs

- **Products available:**
 - Cholestyramine (Questran), 4–16 g/d
 - Colestipol (Colestid), 5–20 g/d
 - Colesevelam (WelChol) 625 mg tablets, 6–7 tablets/d
- **Reduce coronary events (LRC-CPPT)**
- **Adverse effects**
 - GI intolerance: constipation, bloating, abdominal pain, flatulence
 - Lack systemic toxicity
- **Drug interactions** (colestipol and cholestyramine)
 - Bind other negatively charged drugs
 - Impede the absorption of drugs and/or fat-soluble vitamins
 - Must give other drugs 1 hour before or 4–6 hours after

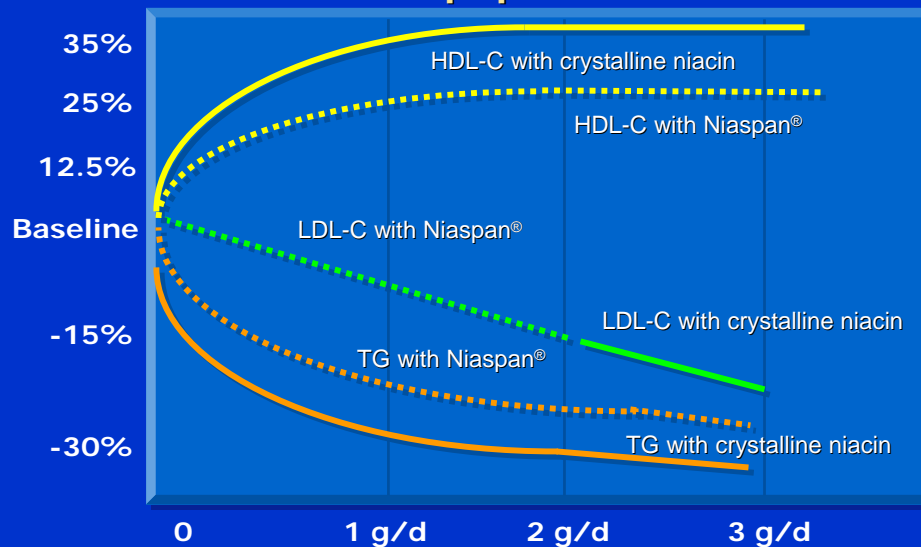
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Nicotinic Acid: Mechanism of Action



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Effect of Niacin on Lipoproteins



Adapted from Knopp RH. *N Engl J Med* 1999; 341: 498-511.
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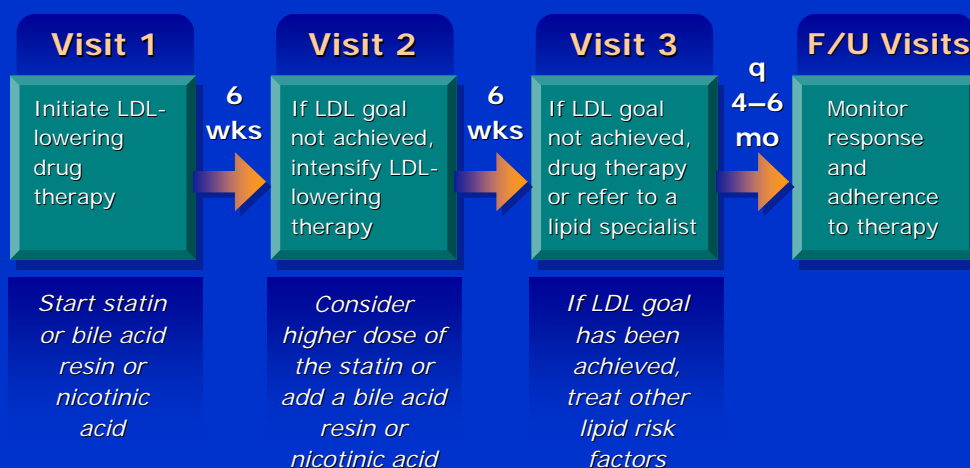
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Clinical Features of Nicotinic Acid

- **Products available** (daily dose)
 - Immediate-release, 2–4 g/d
 - Extended-release (Niaspan®), 1–2 g/d
 - OTC products, sustained-release, ≤2 g/d
- **Best agent to raise HDL-C**
- **Reduces coronary events (Coronary Drug Project)**
- **Adverse effects**
 - Flushing, itching, headache (immediate-release, Niaspan®)
 - Hepatotoxicity, GI (sustained-release)
 - Activation of peptic ulcer
 - Hyperglycemia and reduced insulin sensitivity
- **Contraindications**
 - **Active liver disease or unexplained LFT elevations**
 - Peptic ulcer disease

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Progression of Drug Therapy for LDL-C Lowering



Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001; 285: 2486–2497.

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Rationale for Change in the Categorization of Triglyceride Levels in ATP III

- ATP III gives additional emphasis to moderate elevations of triglycerides (150–200 mg/dL) for the following reasons:
 - New meta-analysis suggests that raised triglyceride levels may be an independent risk factor for CHD.¹⁻²
 - Elevated triglycerides are associated with components of the metabolic syndrome such as glucose intolerance, low HDL, inflammation, and prothrombotic state.³
 - Subjects with modestly elevated triglyceride levels have atherogenic remnant lipoproteins.³

¹ Austin MA. *Can J Cardiol* 1998;14:14B-17B. ² Assmann G et al. *Eur Heart J* 1998;19:M8-M14. ³ Grundy SM. *Am J Cardiol* 1998;81:18B-25B.

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Treatment of Mixed Hyperlipidemia

High LDL-C and TGs

Therapeutic Lifestyle Change

Drug Therapy

STEP 1 Achieve the LDL-C goal

STEP 2 Increase statin dose or
Add a fibrate, niacin or fish oils

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285:2486-2497.

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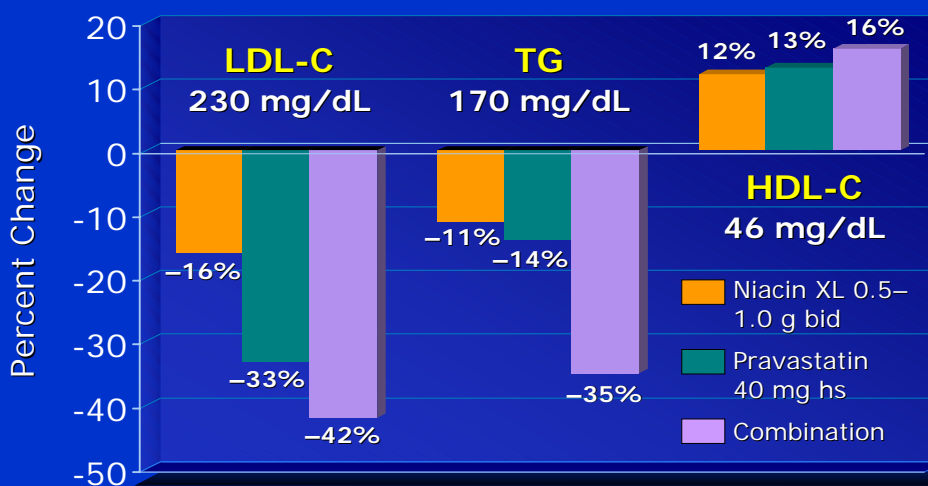
The Triglyceride-Lowering Effects of Statins

	Baseline TG (mg/dL)		
	<150	150–250	>250
Lova 20 mg	1%	–9%	–32%
Prava 10 mg	6%	–11%	–22%
Simva 10 mg	1%	–20%	–28%

Stein EA et al. *Am J Cardiol* 1998;81:66B-69B.

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Pravastatin and Niacin Alone and Together



Davignon J et al. *Am J Cardiol* 1994;73:339-345.

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Fish Oils

Indications: Adjunctive therapy to diet
Hypertriglyceridemia (Type IV and V)
With statins or other LDL-C-lowering drugs
in mixed hyperlipidemia

Efficacy: Decrease TG 30–40%
LDL-C remains the same or increases
No change in HDL-C

Side Effects: GI upset and a “fish burp”

Intervention Trials: Lyon Heart Study (dietary), GISSI
Prevenzione Trial, others

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Fibric Acid Derivatives

Indications: Adjunctive therapy to diet
Hypertriglyceridemia (Type IV and V)
Combined hyperlipidemia (Type IIb) with low HDL-C
who do not respond to nicotinic acid

Mechanism of Action: Increase peripheral lipolysis and decrease hepatic
TG production

Efficacy: Decrease TG 25–50%
LDL-C decreases, remains the same, or increases
Increase HDL-C 15–25% in hypertriglyceridemia

Side Effects: GI upset (8%), cholelithiasis, myositis, abn LFTs

Contraindications: Hepatic or renal dysfunction
Pre-existing gallbladder disease

Intervention Trials: HHS, VA-HIT, BIP, LOCAT, BECAIT, DAIS

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Effects of Fenofibrate on Plasma Lipids

Double-Blind, Multicenter, 24-Week Study in Patients with Primary Hypercholesterolemia or Mixed Hyperlipidemia (HPL)

	Hypercholesterolemia (%)		Mixed HPL (%)	
	Feno n=92	Plb n=88	Feno n=24	Plb n=22
Total Cholesterol	-17.5	-0.4	-15.8	+4.6
LDL-C	-20.3	+0.4	-6.1	-0.5
HDL-C	+11.1	-1.2	+15.3	-3.5
Total Triglycerides	-37.9	-4.2	-44.6	+22.3
LDL-C/HDL-C	-27.1	-1.9	-13.3	0.0
VLDL-C	-38.4	-2.5	-52.7	+8.4

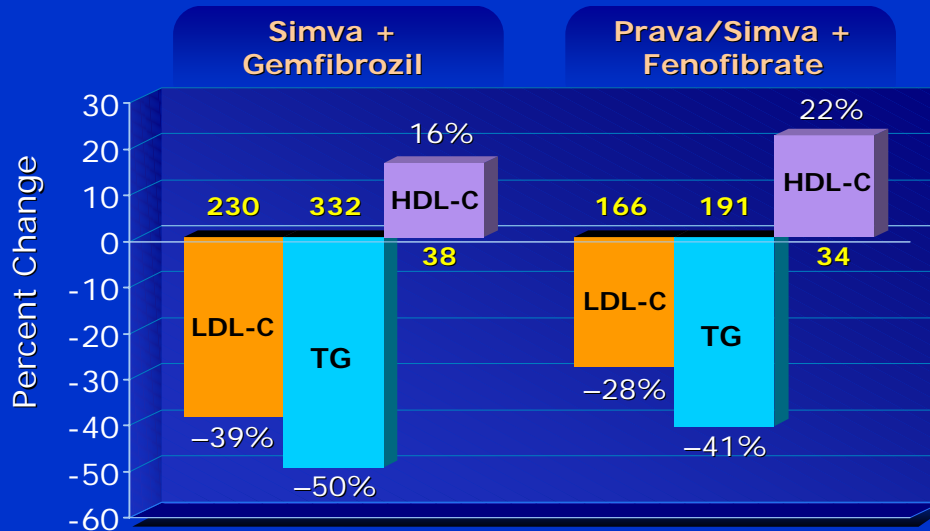
p<0.01 except for LDL-C in Type IIb, where p>0.10

Brown WV et al. *Arteriosclerosis* 1986;6:670-678.

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Statin + Fibrate



Da Col PG et al. *Curr Ther Res Clin Exp* 1973;53:473-482. | Ellen RL et al. *Am J Cardiol* 1998;81:60B-65B.

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Steps to Minimize the Risk of Muscle Toxicity with Fibrate–Statin Combination Therapy

- Use statin alone for non-HDL-C goals
- Use fish oils or niacin rather than fibrates
- Keep the doses of the statin and fibrate low
- Dose the fibrate in the AM and the statin in the PM
- Avoid (or cautiously use) combo in renal impairment
- Assure no interactions
- Teach the patient to recognize muscle symptoms
- Discontinue therapy if muscle symptoms are present and CK is >10 times the upper limit of normal

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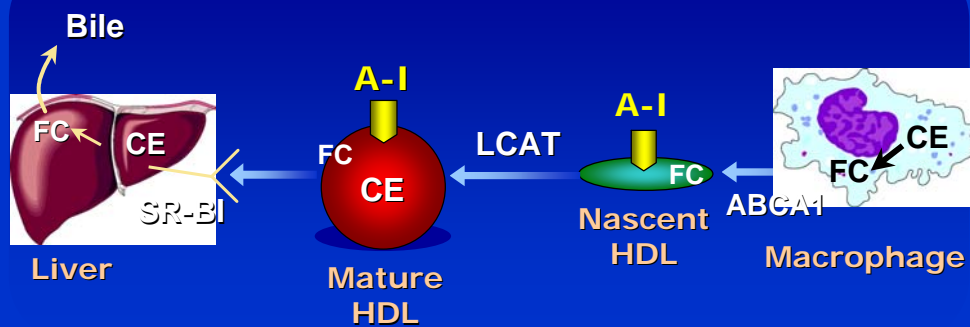
HDL-C is Associated with Increased Cardiovascular Risk

Low HDL-C levels are commonly found in patients who:

- Smoke
- Are sedentary
- Are obese
- Are insulin resistant or diabetic
- Have hypertriglyceridemia
- Have chronic inflammatory disorders

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HDL and Reverse Cholesterol Transport



Management of Low HDL-C

- Therapeutic lifestyle changes
 - Smoking cessation
 - Regular aerobic exercise
 - Weight loss
 - Alcohol use?

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Management of Low HDL-C

- Therapeutic lifestyle changes
- Pharmacologic therapy
 - Statins

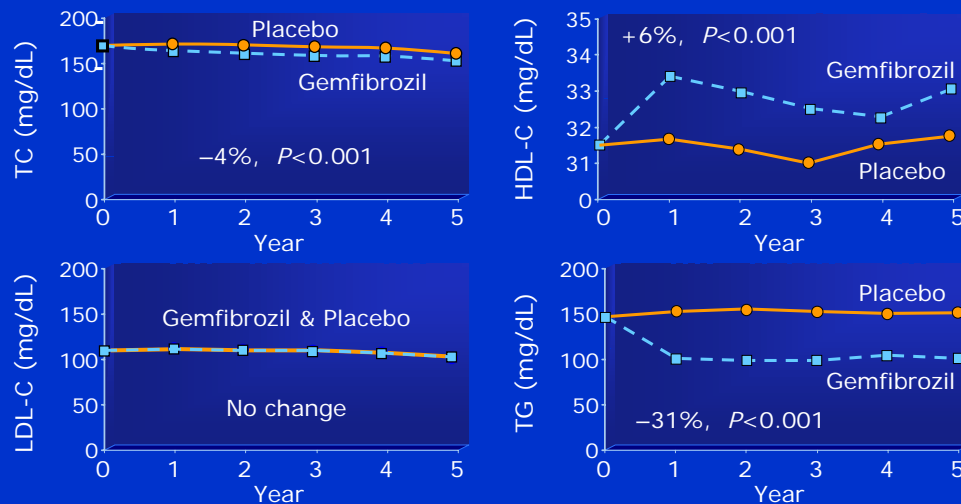
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Management of Low HDL-C

- Therapeutic lifestyle changes
- Pharmacologic therapy
 - Statins
 - Fibrates

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VA-HIT: Lipid Concentrations According to Year of Study and Treatment Group



Rubins HB et al. *N Engl J Med* 1999;341:410-418.

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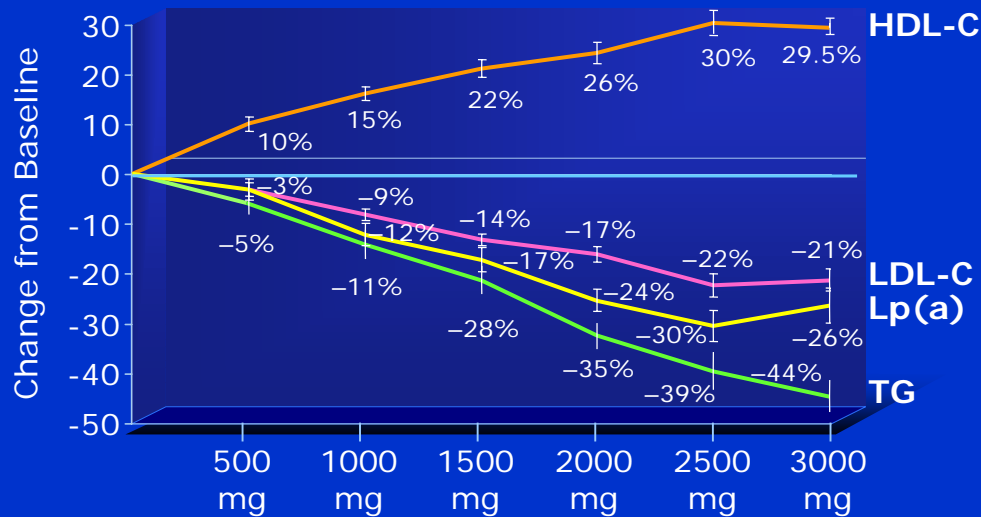
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Management of Low HDL-C

- Therapeutic lifestyle changes
- Pharmacologic therapy
 - Statins
 - Fibrates
 - Niacin

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Efficacy of Extended-Release Niacin



Goldberg A et al. *Am J Cardiol* 2000; 85: 1100-1105.

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Management of Low HDL-C

- Lifestyle changes and secondary causes
- Pharmacologic therapy
 - If LDL-C elevated: statin
 - If TG elevated: fibrate
 - If isolated low HDL-C: niacin
- Combination therapy

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Addition of Extended-Release Niacin to a Statin because of Persistently Low HDL-C



Wolfe ML et al. *Am J Cardiol* 2001;87:476-479.
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Summary

- LDL-C remains the primary target of lipid-altering therapies
- HDL-C is an important CHD risk factor
- Even small increases in HDL-C may confer substantial benefit
- Intervention to raise HDL-C levels should be considered in high-risk patients

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