Drugs for Dyslipidemias

HMG CoA reductase inhibitors (statins):

atorvastatin, lovastatin, pravastatin, simvastatin

Bile acid-binding resins:

cholestyramine, colestipol, colesevelam

Fibric acid derivatives (fibrates):

gemfibrozil, fenofibrate

(clofibrate is the prototype but use is discontinued)

Niacin (nicotinic acid)

Cholesterol Absorption Inhibitor:

ezetimibe

Others:

Antioxidants (vitamin E)

Omega 3 fatty acids (fish oil)

AJ Davidoff '09

Medical Letters Treatment Guidelines February 2008

Dyslipidemias

Abnormal blood lipids

e.g., ↑ cholesterol (CHL)
↑ triglycerides (TG)
↑ low density lipoprotein (LDL)
↓ high density lipoprotein (HDL)

↑ Risks of atherosclerosis (e.g., ↑ CAD)
↑ Risk of pancreatitis (due to ↑ TGs)
↑ Risk of liver disease

Often part of a cluster of risk factors for CAD:

- obesity, sedentary lifestyle, hypertension, diabetes
- elderly and postmenopause ↑ risk of ↑ CHL

Therapeutic goals

↓ blood LDL and TG, ↑ HDL

Ideal:	total CHL	180-200 mg/dL
	LDL	<130 mg/dL
	HDL	> 60 mg/dL (may be protective)
	TG	< 150 mg/dL
HDL		< 40 mg/dL risk factor in men
		< 50 mg/dL risk factor in women

Manage with diet and life style changes (preferably)

Control other risk factors (e.g., BP, diabetes)

Caution with certain drugs causing lipid changes:

- Diuretics (thiazides)
- β-blockers (non-selective; propranolol)
- Oral contraceptives

Lipid Management Goals: National Cholesterol Education Program

Risk Category	LDL-C and non-HDL-C Goal	Initiate TLC	Consider Drug Therapy
High risk: CHD or CHD risk equivalents (10-year risk >20%) and	<100 mg/dL if TG >200 mg/dL then, non-HDL-C should be <130 mg/dL	≥100 mg/dL	≥100 mg/dL (<100 mg/dL: consider drug options)
Very high risk: ACS or established CHD plus: multiple major risk factors (especially diabetes) or severe and poorly controlled risk factors	<70 mg/dL non-HDL-C <100 mg/dL	All patients	≥100 mg/dL (<100 mg/dL: consider drug options)

CHD = coronary heart disease, ACS = acute coronary syndrome
TLC = therapeutic lifestyle changes

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

Types of hyperlipidemias

Primary (genetically determined)

−plasma CHL and/or TG

Try to establish etiology

e.g., familial hypercholesterolemia

↓LDL receptors

Secondary forms

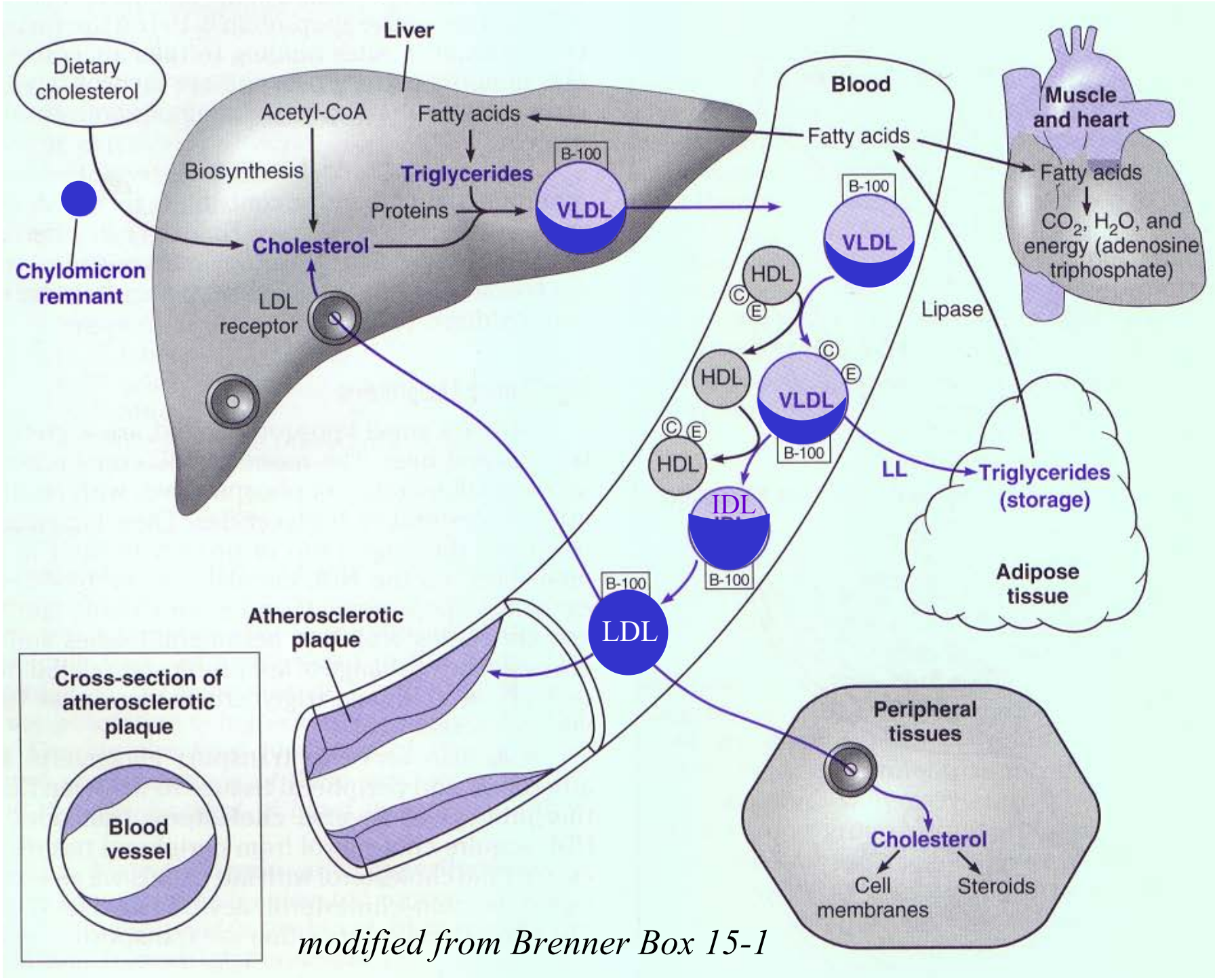
Consequence of other conditions

e.g., diabetes mellitus

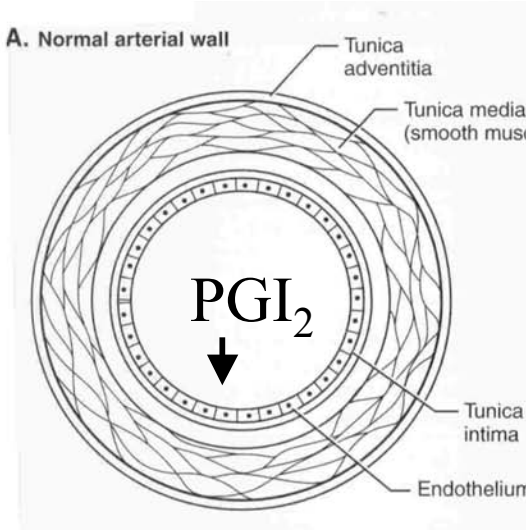
hypothyroidism

alcoholism

renal or hepatic disease



modified from Brenner Box 15-1

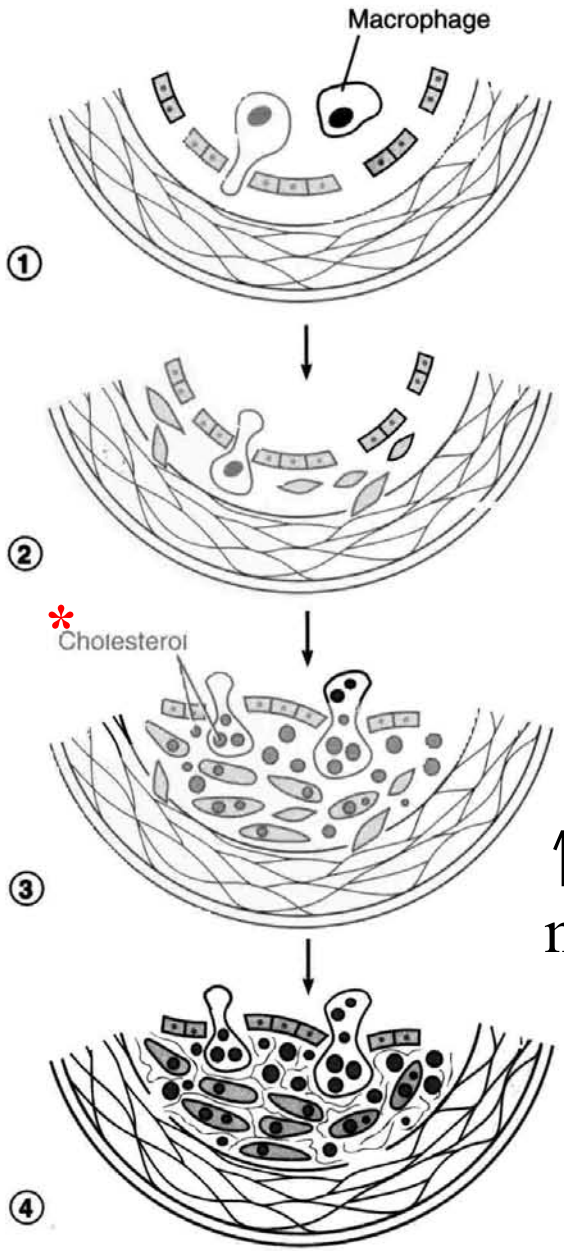


endothelial cell
prostacyclin (PGI_2)
(-) platelet aggregation

Pathogenesis of atherosclerosis

plaque_development.exe

Brenner Fig 15-1



endothelial dysfunction

↓

macrophage infiltration

↓

*LDL oxidation (activation)

↓

↑ platelet aggregation
macrophage→ foam cells

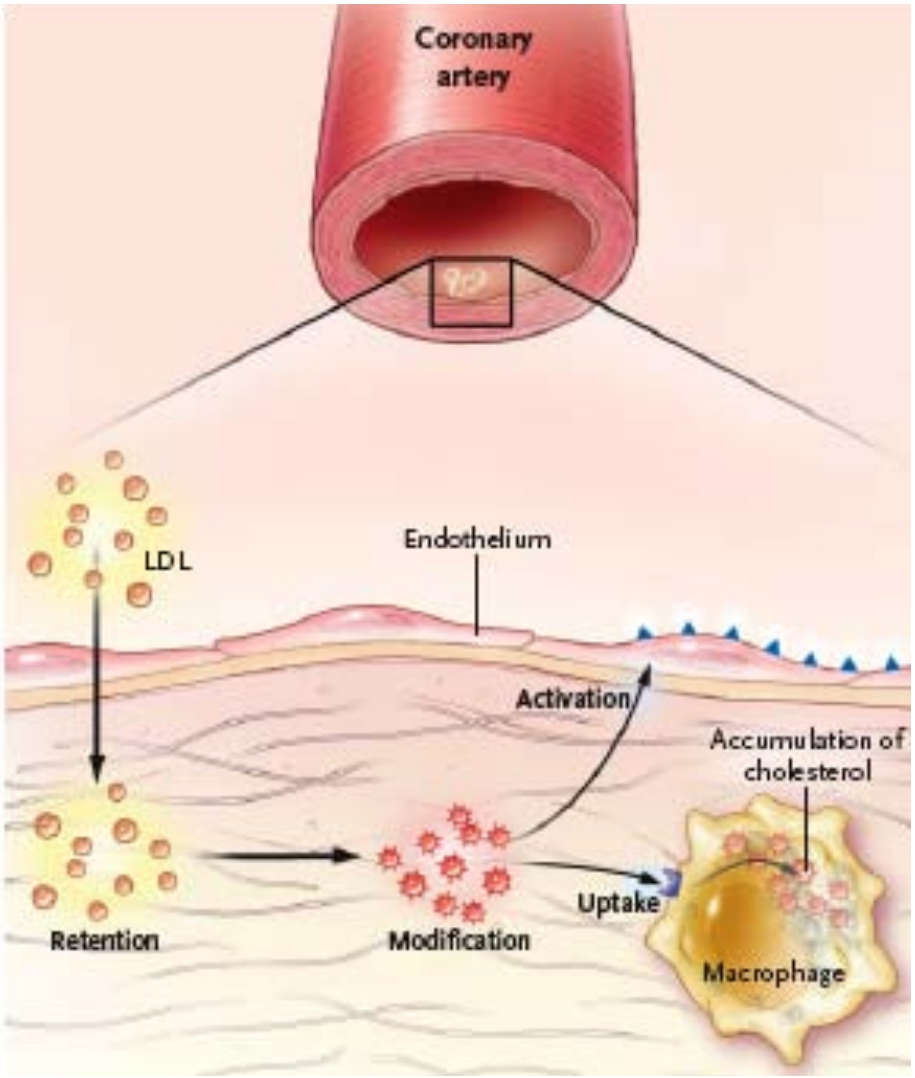
↓

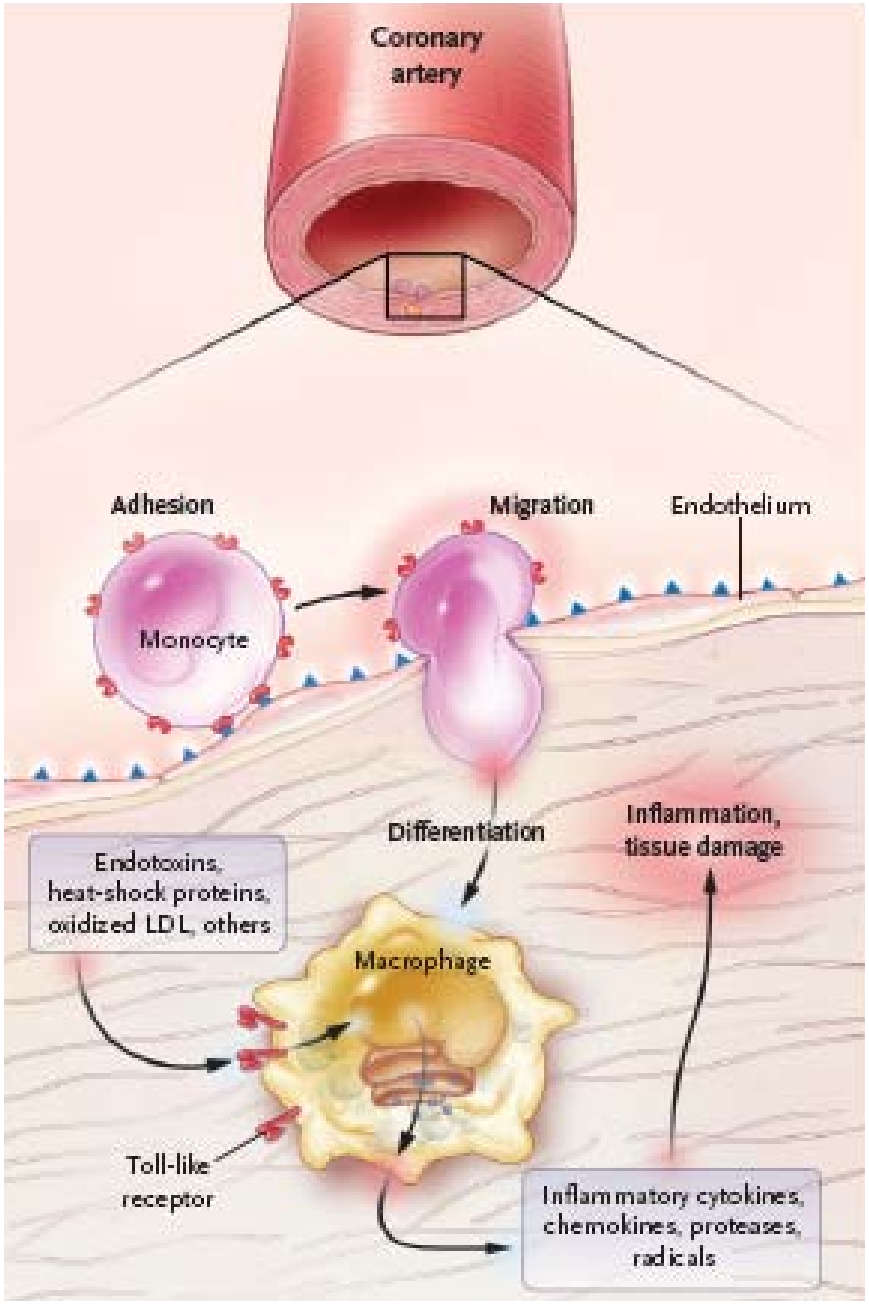
release of chemotaxins
growth factors

↙

VSMC proliferation
deposition of tissue

Inflammation, Atherosclerosis and CAD





Hansson NEJM (April) 352:16, 2005

Inflammation in Cardiovascular Disease including Atherosclerosis

Innate or natural immune response – first line of defense

- limits vascular damage
- confines pathogens
- initiates vascular repair

Inflammatory biomarkers used for risk stratification:

- Cytokines (IL-1, IL-6, TNFα, IL-18, MCP-1)
- Acute-Phase Reactants (hs-CRP)
- Endothelial Cell Activation (dysfxn) (vWF, ICAM-1, V(
- Oxidative Stress (MPO, oxLDL, PLA_2)

see note page for definitions

Inflammation is also associated with:

- **Hypertension**
- **Insulin resistance/Obesity**
- **Diabetes**

Strategies for treating hyperlipidemias

↓ Food intake containing CHL

↑ Exercise

↓ Production of lipoproteins

statins, niacin, fibrates

(antioxidants?)

↑ Degradation of lipoproteins

fibrates

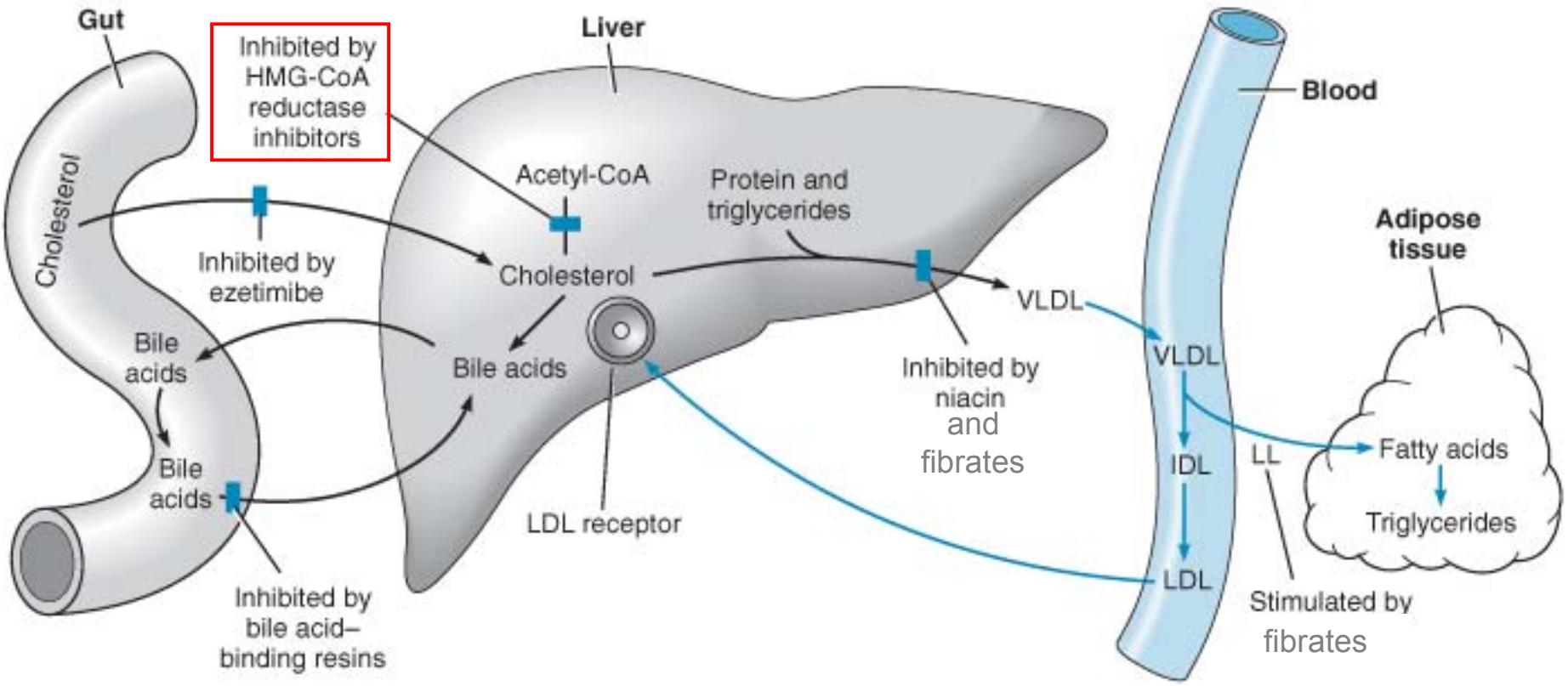
↑ CHL clearance

statins (↓ *de novo* synthesis)

resins (↑ bile secretion, ↓ intestinal absorption)

↓ CHL absorption inhibitor (new class)

Ezetimibe (↓ intestinal absorption)



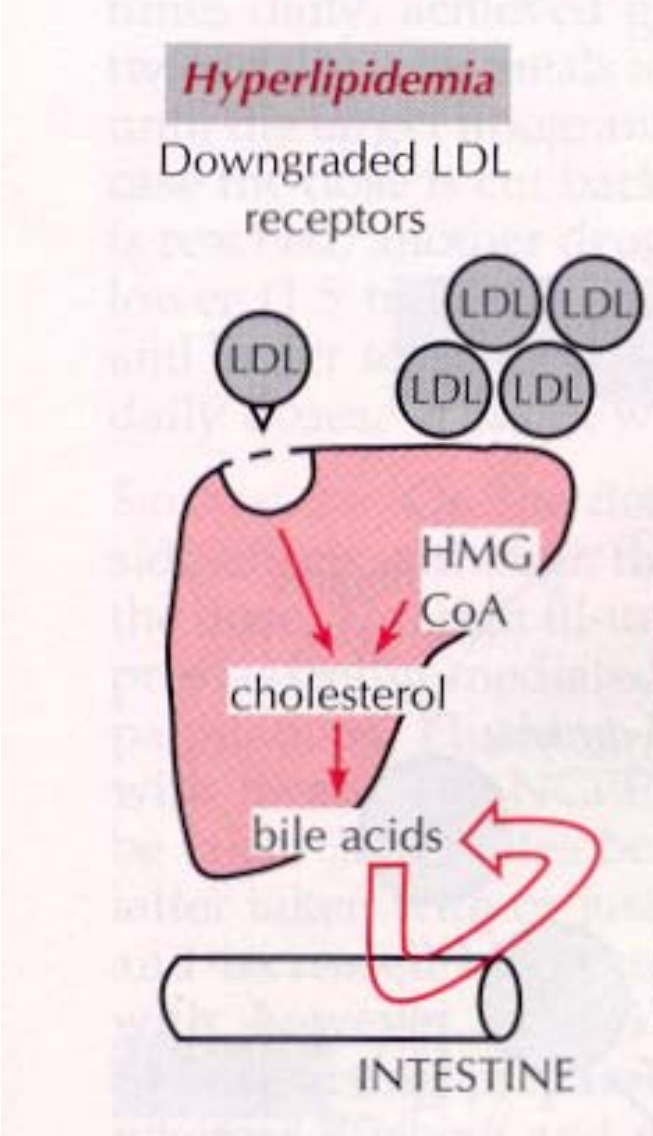
Statins

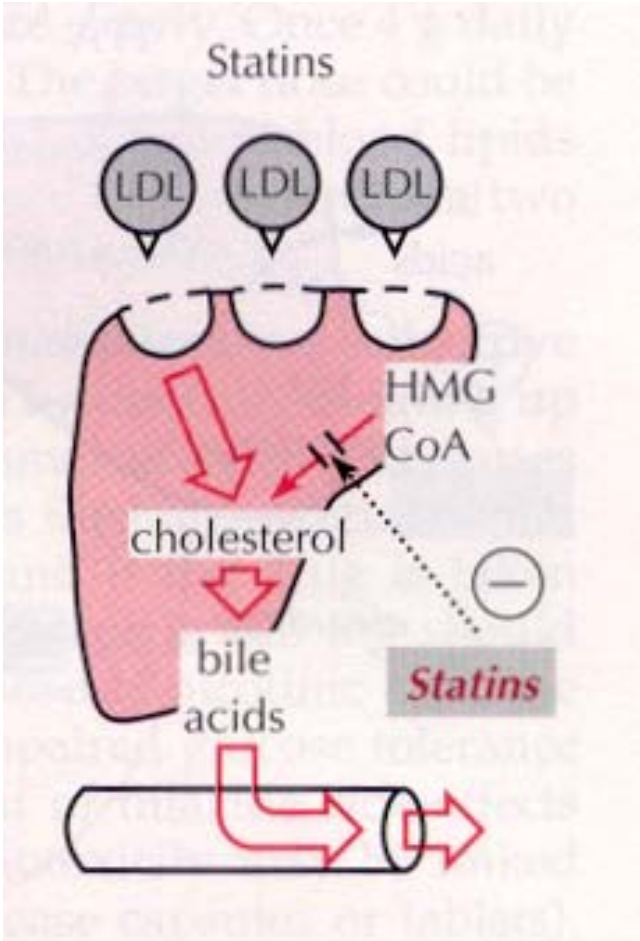
3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors

Indicated for hypercholesterolemia
(some also effective for hypertriglyceridemia)

modified from Brenner Fig 15-2

LDL-receptors and CHL





Opie 1997

Therefore, individuals who lack LDL receptors may not benefit from therapy

HMG CoA reductase inhibitors (statins):

atorvastatin, lovastatin, pravastatin, simvastatin, rosuvastatin, fluvastatin

Differ in pharmacokinetics

- Lovastatin and simvastatin are pro-drugs
- Others are active parent compounds
- Most have short $T_{1/2}$ (except atorvastatin)
- Most metabolized by CYP450 enzymes

Adverse effects *(cerivastatin (Baycol) recalled in 2001)*

- Typically dose dependent
- Potential hepatic toxicity (but still considered very safe) – need to do LFT first, during and until good mx dose achieved
- Myopathies (range from muscle weakness to rhabdomyolysis)
- Drug interactions (e.g., interfere with warfarin metabolism)

Contraindications

- pregnancies and children/teenagers ← **WHY? Hormones amu**

Drug Interactions with Statins

Optional information – for now!

Table 1. Some Inhibitors and Inducers of CYP3A4

Strong Inhibitors	Moderate Inhibitors	Inducers
Atazanavir (*Reytataz*)	Amiodarone (*Cordarone*)	Bosentan (*Tracleer*)
Clarithromycin (*Biaxin*)	Amprenavir (*Agenerase*)	Carbamazepine (*Tegretol*)
Conivaptan (*Vaprisol*)	Aprepitant (*Emend*)	Efavirenz (*Sustiva*)
Imatinib (*Gleevec*)	Cyclosporine (*Neoral*)	Fosphenytoin (*Cerebyx*)
Indinavir (*Crixivan*)	Darunavir (*Prezista*)	Nafcillin
Isoniazid	Delavirdine (*Rescriptor*)	Nevirapine (*Viramune*)
Itraconazole (*Sporanox*)	Diltiazem (*Cardizem*)	Oxcarbazepine (*Trileptal*)
Ketoconazole (*Nizoral*)	Erythromycin (*Erythrocin*)	Phenytoin (*Dilantin*)
Nefazodone (*Serzone*)	Fluconazole (*Diflucan*)	Phenobarbital
Nelfinavir (*Viracept*)	Fosamprenavir (*Lexiva*)	Primidone (*Mysoline*)
Posaconazole (*Noxafil*)	Grapefruit juice (8oz, 24-48 hrs)*	Rifabutin (*Mycobutin*)
Ritonavir (*Norvir*)	Verapamil (*Calan*)	Rifapentine (*Priftin*)
Saquinavir (*Invirase*)		Rifampin (*Rifadin*)
Telithromycin (*Ketek*)		Saint John's wort
Voriconazole (*Vfend*)		

The Medical Letter Oct 20, 2008

*Wilkinson GR. Drug metabolism and variability among patients in drug response. NEJM 2005, 352:2211-2221

Beneficial cardiovascular effects of statins:

- Most effective drugs for lowering LDL-C (CHL)
- Slow progression of atherosclerosis
- Reduce risk of CAD and other vascular diseases
- Reduce risk of cardiac mortality

Lipid lowering, anti-inflammatory, and reduce: plasma viscosity, platelet aggregation, thrombin formation, C reactive protein*

(NEJM Jan. 2005; Nat Rev Drug Discov Dec. 2005; Int J Cardiol Jan. 2006)

*JUPITER trial, treated patients with normal LDLs (<130mg/dl) but high hsCRP (≥2 mg/L), rosuvastatin (20 mg/daily) vs placebo. Findings: hsCRP (1.8 vs 3.3mg/L) and LDLs (55 vs 109mg/dl), Tg (99 vs 118mg/dl), no change HDLs, reduced major CV events in healthy people with high hsCRP
(AHA Nov 2008, Med Letters Dec 2008)

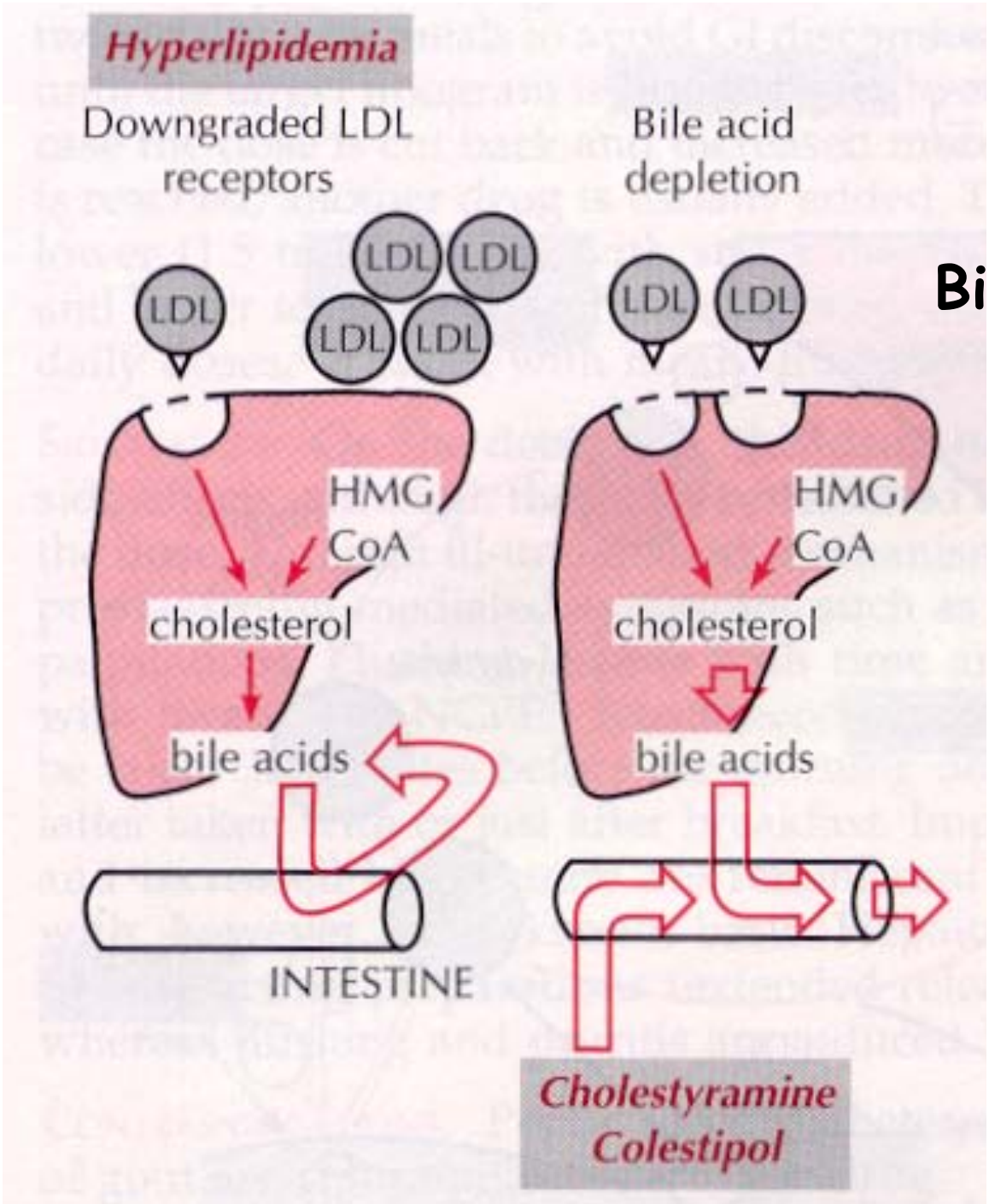
Beneficial non-cardiovascular effects of statins:

- Anticancer effects *(Nat. Rev Cancer Dec. 2005, Feb. 2007)*

- Potentially osteogenic *(J Pharm Pharmacol Jan. 2006)*

- May attenuate development of type 2 diabetes but not as a monotherapy *(Am Heart J Nov. 2005)*

- May reduce amyloid-β protein deposits associated with Alzheimer's disease *(Am J Med Dec. 2005)*



Resins

(aka)

Bile-Acid Sequestrants

Indicated for hypercholesterolemia

Bile acid binding resins:

cholestyramine, *colestipol*, colesevelam

Anion exchange resins

Bind to bile acids and salts in small intestine prevents CHL reabsorption

–LDL receptors (liver) → ↓ blood LDL

<u>Differ in formulation</u>

Colesevelam (tablet), others are powders

<u>Adverse effects and interactions</u>

- ↓ absorption of fat soluble vitamins
- GI disturbances
- May increase TG (need to combine with nicotinic acid or fibrates)
- Cholestyramine and colestipol can bind to a number of drugs (e.g., digoxin, warfarin, T4, statins) – stagger dosing by 2 hrs
- Colesevelam (newer drug) does not interfere with drug

Cholesterol Absorption Inhibitor (new class)

Ezetimibe

(only one on US market as of 2004)

- Inhibits intestinal absorption of dietary and biliary CHL
  - blocks uptake mechanism
- Metabolized to active glucuronide in small intestine and liver
- Excreted in stool (mostly)
- Decrease in total CHL (12%), LDL (17%) and TG (6%) as monotherapy
- Augments effects of statins on LDL lowering

(e.g. combined with simvastatin 57%, compared to 44% with statin alone)

Advantages:

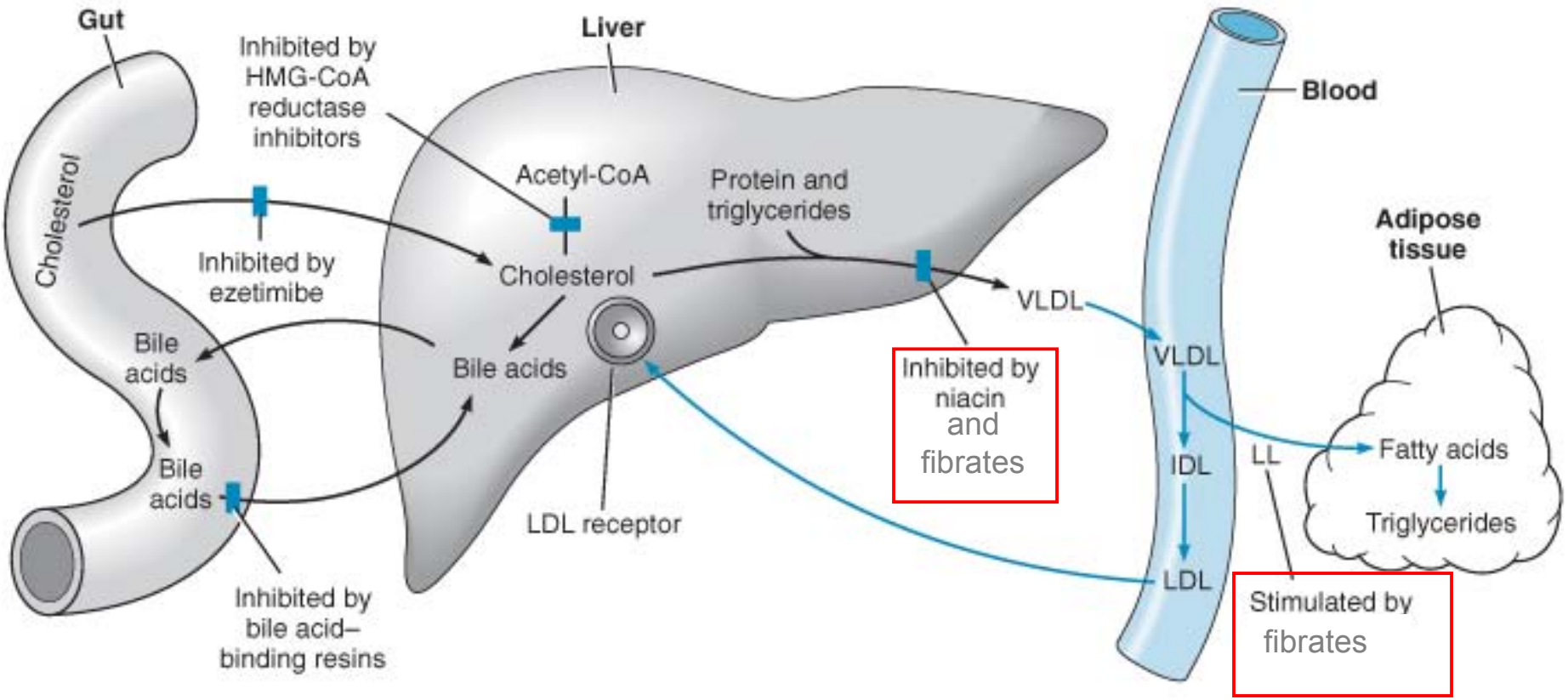
Well tolerated compared to resins

No GI disturbances

Does not interfere with drug absorption

No long-term data yet!!!

*ENHANCE trial (see notes pg)



Fibrates and Niacin

Indicated for hypertriglyceridemia

In Maine, large French Canadian population with severe hyperTG (>1000 mg/dL) -impaired lipoprotein lipase (LL)

Fibrates:

gemfibrozil, fenofibrate

(+) lipoprotein lipase and (-) VLDL synthesis → ↓↓↓↓ blood TGs
↑↑HDLs

(+) PPARα agonist (peroxisome proliferator activated receptor)
(transcription factor which +LL synthesis)

(+) stimulates fatty acid oxidation

Adverse effects

myopathies similar to statins; gemfibrozil (but not fenofibrate) inhibits statin metabolism, therefore ↑risk

Contraindicated

pregnancy, nursing

hepatic disease

Niacin (nicotinic acid, vit B_3)

Vitamin with broad lipid lowering activity

(-) TG breakdown

↓ VLDL synthesis and release

↓ CHL (a little)

Also: ↑↑↑ HDL

<u>Adverse effects</u>

Prostaglandin mediated effects

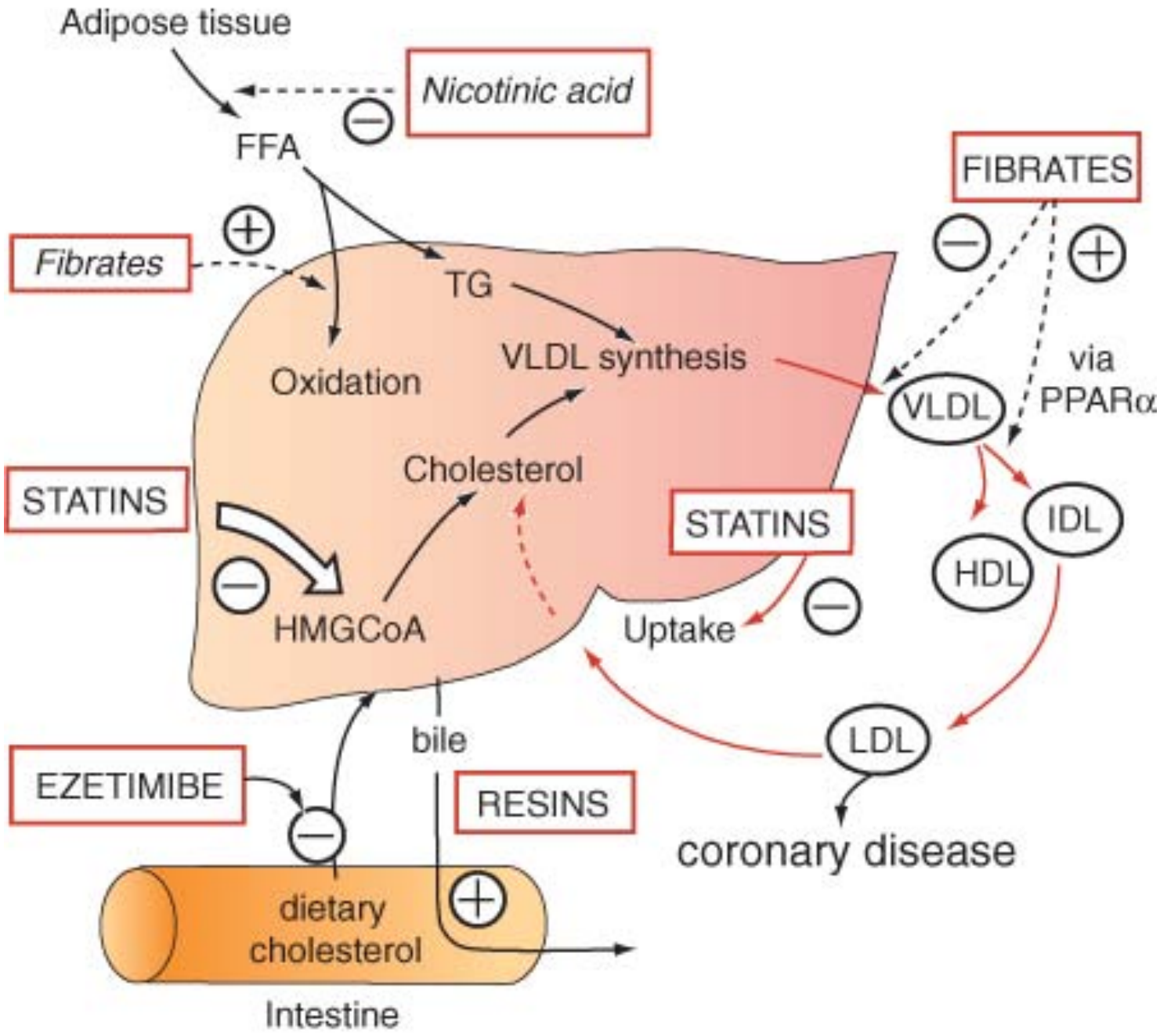
Intense flushing

Pre-administer aspirin to reduce, or use extended-release niacin

(-) tubular secretion of uric acid: ↑ hyperuricemia (gout)

May exacerbate hyperglycemia (caution with diabetics)

Risk of myopathies and hepatoxicity may increase in combination with statins



(L.H. Opie, Drugs for the Heart, 2004.)

Antioxidants:

vitamin E, ascorbic acid, β-carotene

Concept:

(-)LDL oxidation → (-)foam cell formation → (-) plaque formation

Efficacy to reduce CV disease has not been demonstrated

Have been shown to improve some cognitive dysfunctions

(blueberries also efficacious – Jim Joseph, Tufts Medical Sch.)

American Heart Association advisory statement 2004

(*Circulation*. 2004;110:637–641.)

AHA Science Advisory

Antioxidant Vitamin Supplements and Cardiovascular Disease

Penny M. Kris-Etherton, PhD, RD; Alice H. Lichtenstein, DSc; Barbara V. Howard, PhD; Daniel Steinberg, MD, PhD; Joseph L. Witztum, MD; for the Nutrition Committee of the American Heart Association Council on Nutrition, Physical Activity, and Metabolism

As reviewed in the first AHA Science Advisory[2] on antioxidant vitamins, epidemiological and population studies reported that some micronutrients may beneficially affect CVD risk (ie, antioxidant vitamins such as vitamin E, vitamin C, and β-carotene).

Collectively, for the most part, clinical trials have failed to demonstrate a beneficial effect of antioxidant supplements on CVD morbidity and mortality.

Summary

At this time, the scientific data do not justify the use of antioxidant vitamin supplements for CVD risk reduction.

Others:

Efficacy against dyslipidemia has been shown. However, always be aware of distinguising risk reductions (e.g., lower TGs) vs outcome reductions

- Mediterranean-type diet
  (e.g., breads, fiber, fruits, vegetables)
- Fish oil; 3 omega fatty acids (↓TGs)
  - *no adverse effects in combination with statins (Med Letters Nov. 2005)*
  - *>4g/day significantly lower Tgs, but primary end points (e.g., CVD) have not been measured (JACC 2008)*
- Modest alcohol consumption
- Red juices, black tea, nuts (almonds)
- Estrogens (↑HDL) BUT no evidence of CV benefits, in fact may increase risk of deep vein thrombosis

Note: Dietary fish oil reverses insulin resistance and cardiomyopathy in rats (Davidoff et al. Am J Physiol, Endo and Metabolism (2004))

Summary of drug effects

Intervention	Change in plasma levels			
	CHL (total)	LDL	HDL	TG
Diet alone	↓	↓	↔	↓
Exercise	↔	↔	↑	↓↓↓
Resins	↓	↓	~↑	~↑
Statins	↓↓	↓↓↓	↑	↓
Fibrates	↓	↓	↑↑	↓↓
Niacin	↓	↓	↑↑↑	↓↓↓

Lipid Management Pharmacotherapy
(monotherapy)

Therapy	Total CHL	LDL	HDL	TG	Patient tolerability
Statins	↓ 19-37%	↓ 25-50%	↑ 4-12%	↓ 14-29%	Good
Ezetimibe	↓ 13%	↓ 18%	↑ 1%	↓ 9%	Good
Bile acid sequestrants	↓ 7-10%	↓ 10-18%	↑ 3%	Neutral or ↑	Poor
Nicotinic acid	↓ 10-20%	↓ 10-20%	↑ 14-35%	↓ 30-70%	Reasonable to Poor
Fibrates	↓ 19%	↓ 4-21%	↑ 11-13%	↓ 30%	Good

AHA/ACC Guidelines for Secondary Prevention for Patients with Coronary and Other Atherosclerotic Vascular Disease: 2006 Update

Antihypertensive drugs affecting lipid profiles

Adverse lipid effects:

High dose thiazides increase TG

(low doses do not affect lipids)

β-blockers reduce HDL and increase TG

Beneficial lipid effects:

α-blockers (prazosin)

improves all lipid profiles

α-β-blockers (carvedilol not labetalol)

reduces TG, increases HDL and reduces TCHL

Lipid neutral cardiac drugs:

ACE inhibitors (captopril, lisinopril)

ARBs (losartan)

CCBs (calcium channel blockers)

Centrally active (methyldopa, clonidine)

Direct vasodilators (nitrates and hydralazine)

Website resources:

American Heart Association

http://www.americanheart.org

National Heart Lung and Blood Institute (NIH)

http://www.nhlbi.nih.gov/health/prof/heart/index.htm

ATP III at a glance

Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf

Guidelines at a glance

American College of Cardiology

Clinical Statements/Guidelines

http://www.acc.org/qualityandscience/clinical/statements.htm

Clinical Statesments ACC

American Diabetes Association

http://www.diabetes.org/home.jsp