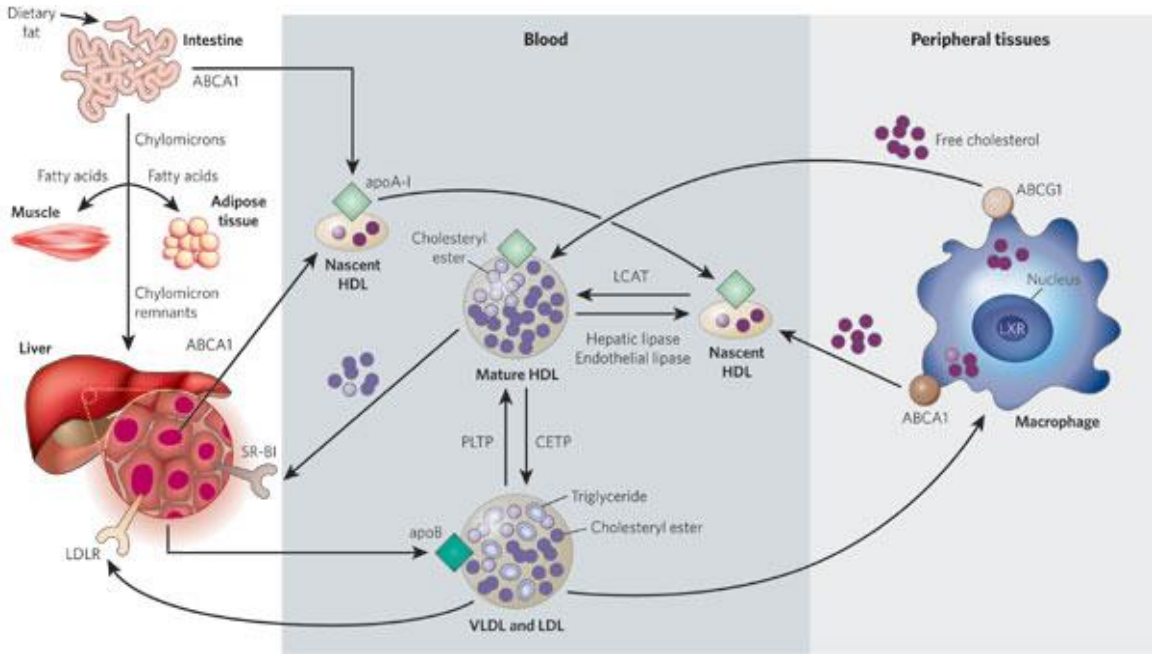
Team Medicine

15# Hyperlipidemia

Writer: Lamia Alghamdi
Reviser1:Abdulelah Al-Kaboor
Reviser 2: Abeer Al-Suwailem

Leader: Sama Al Ohali

Lipid Transport



The following sites are involved in lipid transport:
Intestines, muscle, adipose tissue, liver, macrophages in peripheral vessels and blood.

- The intestines package lipids into chylomicrons, which are then broken down by lipoprotein lipase into FFAs that are released to the blood, the remnant of the chylomicron goes back to the liver.
- The liver forms lipoproteins, which carry TGs and cholesterol.
- The liver releases VLDL, LDL, and HDL to the blood.
- LDL (the most atherogenic) transports fat from the liver to the macrophages (foam cells) in the rest of the body's cells.
- Pre or nascent HDL takes up cholesterol from the macrophages to the liver

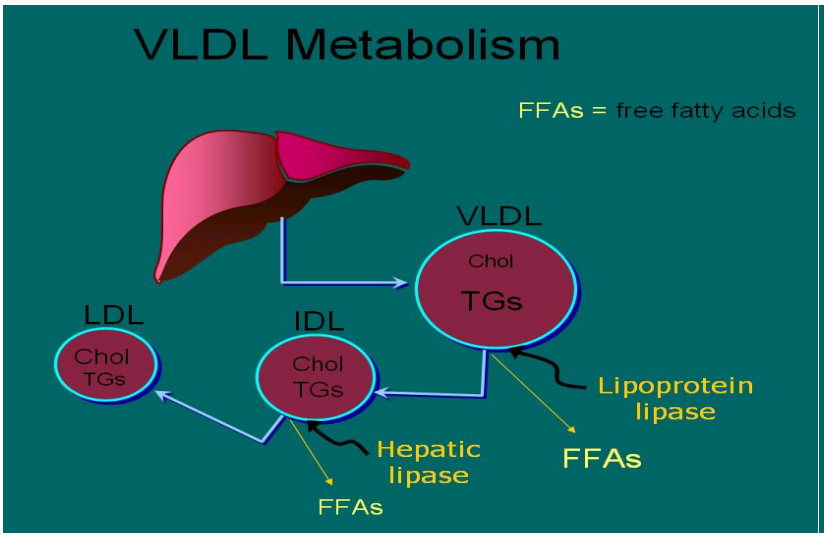
LDL and HDL work in opposite directions.

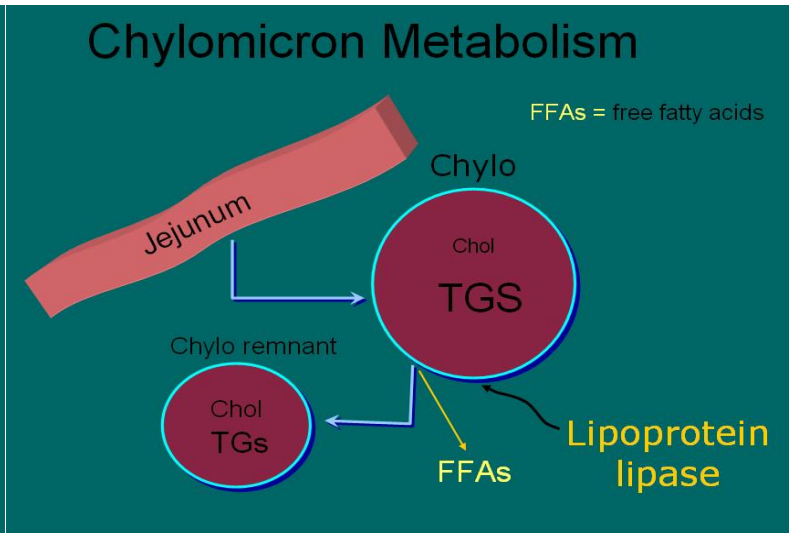
What can be done to reduce cholesterol levels in the body?

- Decrease the absorption of cholesterol
- Prevent the bile from being reabsorbed

- VLDL (high TGs concentration) comes from the liver, tissue lipoprotein lipase releases free fatty acids, the result from this process is the formation of a new lipoprotein 'IDL' (because the concentration of the TGs became lower, cholesterol ester is now higher), by hepatic lipase (which frees more FFAs) IDL will form LDL (containing more cholesterol ester and less TGs).
- Nascent HDL takes up cholesterol from macrophages and then it becomes mature HDL that transports fat to the liver, to spare the vessels from high concentrations of cholesterol ester; therefore, preventing atherosclerosis.

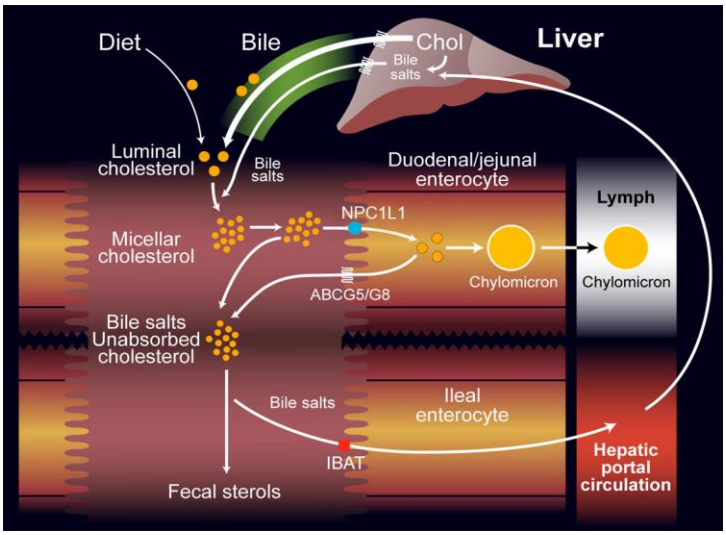
Some medications increase the levels of mature HDL, but they do not affect the level of cholesterol in the blood, why? Because nascent is HDL in needed to take up fat from the cells, which in turn will be transported to the liver.



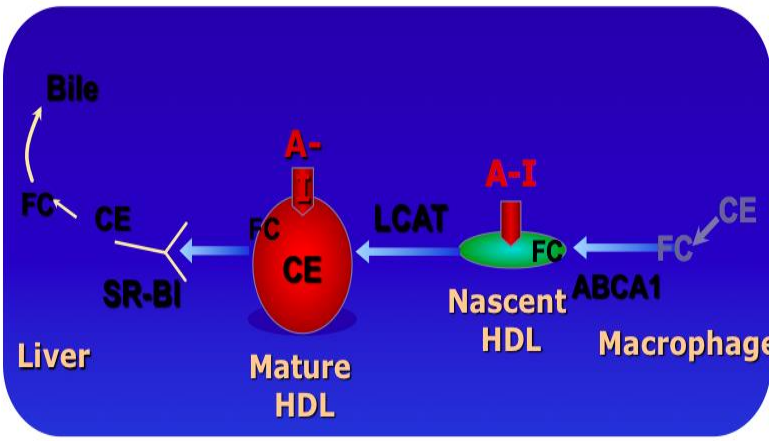


The story of lipids

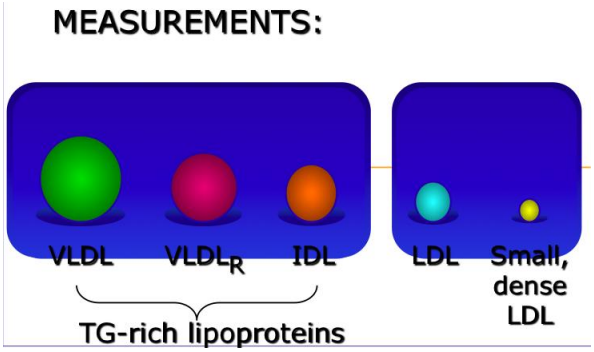
- Chylomicrons transport fats from the intestinal mucosa to the liver
- In the liver, the chylomicrons release triglycerides and some cholesterol and become low-density lipoproteins (LDL).
- LDL then carries fat and cholesterol to the body's cells.
- High-density lipoproteins (HDL) carry fat and cholesterol back to the liver for excretion.
- When oxidized LDL cholesterol gets high, atheroma formation in the walls of arteries occurs, which causes atherosclerosis.
- HDL cholesterol is able to go and remove cholesterol from the atheroma.
- Atherogenic cholesterol → LDL, VLDL, IDL



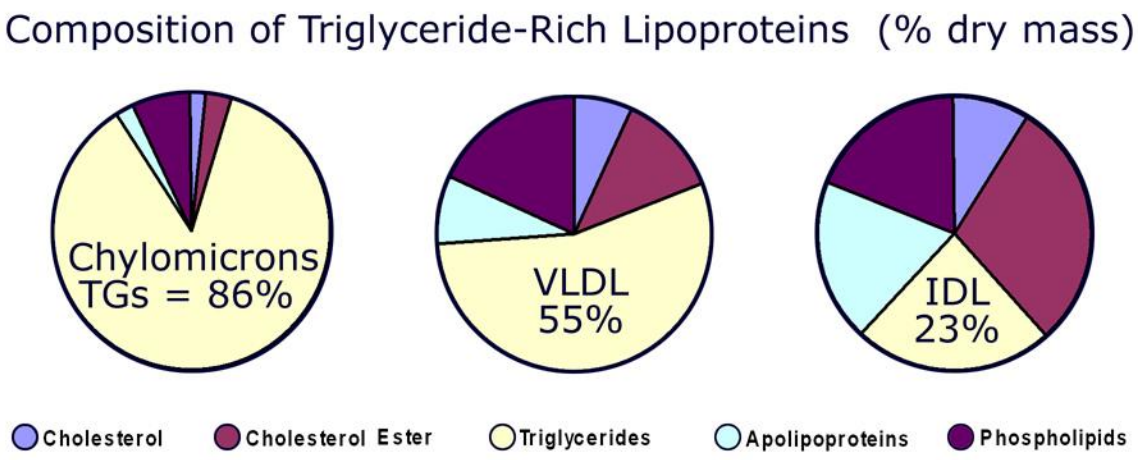
HDL and Reverse Cholesterol Transport



Atherogenic Particles:



-IDL, LDL have high concentrations of cholesterol ester; therefore, they are very atherogenic.
-HDL contains small concentrations of cholesterol but it acts differently, not atherogenic.



Plasma lipoproteins

Type	Source	Major lipid	Apoproteins	ELFO	Athero-genicity
Chylomicrons	Gut	Dietary TGs	A-I, B-48, C-I, C-III, E	no mobility	– (pancreatitis)
VLDL	Liver	Endogenous TGs	B-100, E, C-II, C-III,	Pre-β	+
IDL	VLDL remnant	Ch esters, TGs	B-100, C-III, E	Slow pre- β	+
LDL	VLDL, IDL	Ch esters	B-100	β	+++
HDL	Gut, liver	Ch esters, PLs	A-I, A-II, C-II, C-III, D, E	α	Anti atherogenic

Hereditary Causes of Hyperlipidemia

- Familial Hypercholesterolemia
  - Codominant genetic disorder, coccurs in heterozygous form
  - Occurs in 1 in 500 individuals
  - Mutation in LDL receptor, resulting in elevated levels of LDL at birth and throughout life
  - High risk for atherosclerosis, tendon xanthomas (75% of patients), tuberous xanthomas and xanthelasmas of eyes.

Familial Hypercholesterolemia is a common autosomal dominant disorder (1 allele is enough to cause the disorder, 2 alleles results in a very bad case causing MI before the age of 12 "rare:1 in a million"), it causes premature ischemic heart disease, the problem is in the LDL receptor resulting in failure of LDL uptake by the liver → high LDL concentration in the blood vessels. Patients have MI before the age of 45.
Diagnosed clinically by the presence of tendon xanthoma (usually at the Achilles tendon, on the heel bone).
Cholesterol levels:
Heterozygous (1 allele): 7-13
Homozygous (2 alleles): more than 13
high LDL levels, Heterozygous up to 9, homozygous up to 12

- Familial Combined Hyperlipidemia
    - Autosomal dominant
    - Increased secretions of VLDLs
- Dysbetalipoproteinemia
    - Affects 1 in 10,000
    - Results in apo E2, a binding-defective form of apoE (which usually plays important role in catabolism of chylomicron and VLDL)
    - Increased risk for atherosclerosis, peripheral vascular disease
    - Tuberous xanthomas, striaepalmaris

Fredrickson classification of hyperlipidemias (not commonly used anymore)

Phenotype	Lipoprotein(s) elevated	Plasma cholesterol	Plasma TGs	Athero-genicity	Rel. freq.	Treatment
I	Chylomicrons	Norm. to ↑	↑↑↑↑	– pancreatitis	<1%	Diet control
IIa	LDL	↑↑	Norm.	+++	10%	Bile acid sequestrants, statins, niacin
IIb	LDL and VLDL	↑↑	↑↑	+++	40%	Statins, niacin, fibrates
III	IDL	↑↑	↑↑↑	+++	<1%	Fibrates
IV	VLDL	Norm. to ↑	↑↑	+	45%	Niacin, fibrates
V	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	+ pancreatitis	5%	Niacin, fibrates

Primary hypercholesterolemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial hyper-cholesterolemia	LDL receptor	dominant	heteroz.:1/500 5% of MIs <60 yr homoz.: 1/1 million	premature CAD (ages 30–50) TC: 7-13 mM CAD before age 18 TC > 13 mM
Familial defective apo B-100	apo B-100	dominant	1/700	premature CAD TC: 7-13 mM
Polygenic hypercholesterolemia	multiple defects and mechanisms	variable	common 10% of MIs <60 yr	premature CAD TC: 6.5-9 mM
Familial hyper-alphalipoproteinemia	unknown	variable	rare	less CHD, longer life elevated HDL

The main concern in hypertriglyceridemia is pancreatitis.
High chylomicrons → problems in lipoprotein lipase production in the liver, resulting in failure of chylomicron breakdown.
Chylomicrons are not very atherogenic but they may cause lethal pancreatitis.

Primary hypertriglyceridemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
LPL deficiency	endothelial LPL	recessive	rare 1/1 million	hepatosplenomegaly abd. cramps, pancreatitis TG: > 8.5 mM
Apo C-II deficiency	Apo C-II	recessive	rare 1/1 million	abd. cramps, pancreatitis TG: > 8.5 mM
Familial hyper-triglyceridemia	unknown enhanced hepatic TG-production	dominant	1/100	abd. cramps, pancreatitis TG: 2.3-6 mM

Primary mixed hyperlipidemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial dysbeta-lipoproteinemia	Apo E high VLDL, chylo.	recessive rarely dominant	1/5000	premature CAD TC: 6.5 -13 mM TG: 2.8 – 5.6 mM
Familial combined	unknown high Apo B-100	dominant	1/50 – 1/100 15% of MIs <60 yr	premature CAD TC: 6.5 -13 mM TG: 2.8 – 8.5 mM

Dietary sources of Cholesterol

Type of Fat	Main Source	Effect on Cholesterol levels
Monounsaturated	Olives, olive oil, canola oil, peanut oil, cashews, almonds, peanuts and most other nuts; avocados	Lowers LDL, Raises HDL
Polyunsaturated	Corn, soybean, safflower and cottonseed oil; fish	Lowers LDL, Raises HDL
Saturated	Whole milk, butter, cheese, and ice cream; red meat; chocolate; coconuts, coconut milk, coconut oil , egg yolks, chicken skin	Raises both LDL and HDL
Trans	Most margarines; vegetable shortening; partially hydrogenated vegetable oil; deep-fried chips; many fast foods; most commercial baked goods	Raises LDL

Causes of Hyperlipidemia

- Diet
- Hypothyroidism
- Nephrotic syndrome
- Anorexia nervosa: Down regulation of hepatic lipase (7-cholesterol-lipase) → high LDL levels due to failure of reuptake by the liver → MI.
- Obstructive liver disease
- Obesity
- Diabetes mellitus

  VLDL is high due to the down regulation of lipoprotein lipase in a patient with insulin resistance or insulin deficiency

  LDL is mildly elevated, HDL is mildly lower. The main concern is high VLDL levels.
- Pregnancy
- Obstructive liver disease
- Acute heaptitis
- Systemic lupus erythematousus
- AIDS (protease inhibitors)

AIDs medication causes hyperlipidemia (mainly high TGs)

In a lipid profile of a diabetic patient (uncontrolled):
- VLDL (TGs) will be very high, the first step here is to control diabetes (blood sugar) to increase insulin sensitivity, not to treat TGs, it will drop by itself.
- If there are high levels of LDL initially in a diabetic patient (uncontrolled): must treat and correct LDL levels, even after controlling diabetes, LDL levels do not drop on their own.
- If high LDL + HTN: must correct hyperlipidemia
- In a diabetic patient or a patient with IHD, LDL levels must be checked first.
- Lowering LDL levels is the goal for preventing IHD.
- Each patient has his or her own normal levels (depending on the risk factors)

Secondary hyperlipidemias

Disorder	VLDL	LDL	HDL	Mechanism
Diabetes mellitus	↑ ↑ ↑	↑	↓	VLDL production ↑, LPL ↓, altered LDL
Hypothyroidism	↑	↑ ↑ ↑	↓	LDL-rec.↓, LPL ↓
Obesity	↑ ↑	↑	↓	VLDL production ↑
Anorexia	-	↑ ↑	-	bile secretion ↓, LDL catab. ↓
Nephrotic sy	↑ ↑	↑ ↑ ↑	↓	Apo B-100 ↑ LPL ↓ LDL-rec. ↓
Uremia, dialysis	↑ ↑ ↑	-	↓	LPL ↓, HTGL ↓ (inhibitors ↑)
Pregnancy	↑ ↑	↑ ↑	↑	oestrogen ↑ VLDL production ↑, LPL ↓
Biliary obstruction PBC	-	-	↓	Lp-X ↑ ↑ no CAD; xanthomas
Alcohol	↑ ↑ chylomicr. ↑	-	↑	dep. on dose, diet, genetics

Checking lipids

- Nonfasting lipid panel
  - measures HDL and total cholesterol
- Fasting lipid panel
  - Measures HDL, total cholesterol and triglycerides
  - LDL cholesterol is calculated:
    - LDL cholesterol = total cholesterol – (HDL + triglycerides/5)

Patients fast 12 hrs before measuring lipid profile
You don't need to know about the measurement

When to check lipid panel

- Different Recommendations
  - Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP)
    - Beginning at age 20: obtain a fasting (9 to 12 hour) serum lipid profile consisting of total cholesterol, LDL, HDL and triglycerides
    - Repeat testing every 5 years for acceptable values
  - United States Preventative Services Task Force
    - Women aged 45 years and older, and men ages 35 years and older undergo screening with a total and HDL cholesterol every 5 years.
    - If total cholesterol > 200 or HDL <40, then a fasting panel should be obtained
    - Cholesterol screening should begin at 20 years in patients with (premature IHD) a history of multiple cardiovascular risk factors, diabetes, or family history of either elevated cholesteral levels or premature cardiovascular disease.

Treatment Targets

- LDL: To prevent coronary heart disease outcomes (myocardial infarction and coronary death)
- Non LDL(TC/HDL): To prevent coronary heart disease outcomes (myocardial infarction and coronary death)
- Triglyceride: To prevent pancreatitis and may be coronary heart disease outcomes (myocardial infarction and coronary death)

LDL and Non-LDL(HDL/TC)

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

Framingham Heart Study to estimate 10-year risk for coronary heart disease outcomes

http://hp2010.nhlbihin.net/atpiii/CALCULATOR.asp?usertype=prof

- Age
- LDL-C
- T. Chol
- HDL-C
- Blood Pressure
- Diabetes
- Smoking

Adult Treatment Panel III Guidelines for Treatment of Hyperlipidemia

Risk Category	***Begin Lifestyle Changes If:***	***Consider Drug Therapy If:***	***LDL Goal***
High: CAD or CAD equivalents (10-yr risk > 20%)	**LDL ≥ 2.58 mM**	**LDL ≥ 2.58 mM (drug optional if < 2.58 mM)**	**< 2.58 mM; < 1.8 mM optional**
Moderate high: ≥ 2 risk factors with 10-yr risk 10 to 20%*	**LDL ≥ 3.36 mM**	**LDL ≥ 3.36 mM**	**< 3.36 mM; < 2.58 mM optional**
Moderate: ≥ 2 risk factors with 10-yr risk < 10%*	**LDL ≥ 3.36 mM**	**LDL ≥ 4.13 mM**	**< 3.36 mM; < 2.58 mM optional**
Lower: 0–1 risk factor	**LDL ≥ 4.13 mM**	**LDL ≥ 4.91 mM (drug optional if 4.13–4.88 mM)**	**< 4.13 mM**

- **High risk:** patient with diabetes, previous MI or IHD, more than 3 risk factors of IHD, or peripheral vascular disease.
- **High risk:** the target of LDL is less than 2, total cholesterol less than 4
- **Low risk:** do not treat unless LDL is more than 5, total cholesterol more than 6
- The target is to reduce the LDL by 50%

Canadian New Guideline

Risk categories

Risk level	10-year CAD risk	Recommendations
High	≥20%	*Treatment targets:* Primary target: LDL-C <2.0 mmol/L Secondary target: TC/HDL-C <4.0
Moderate	10% - 19%	*Treat when:* LDL-C ≥3.5 mmol/L *or* TC/HDL-C ≥5.0
Low	<10%	*Treat when:* LDL-C ≥5.0 mmol/L *or* TC/HDL-C ≥6.0

High risk includes coronary artery disease (CAD), peripheral artery disease, cerebrovascular disease and most patients with diabetes.

Treatment of Hyperlipidemia

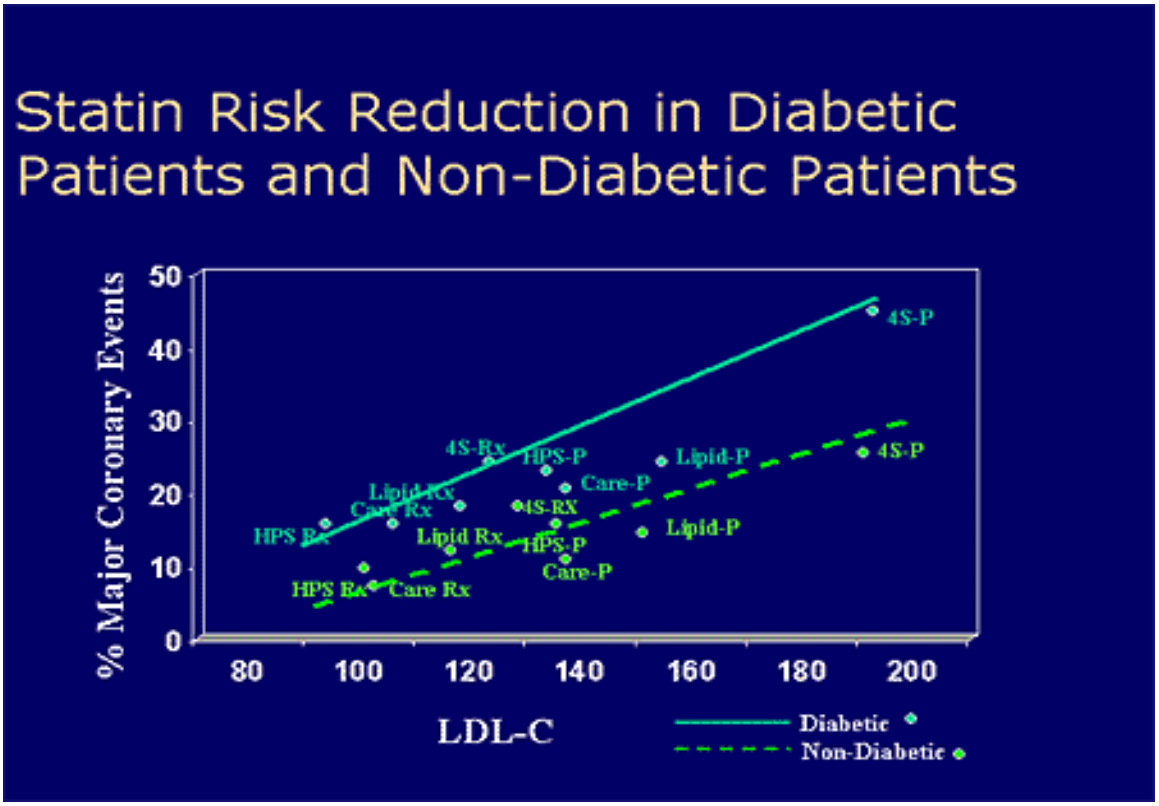
- Lifestyle modification
  - Low-cholesterol diet
  - Exercise

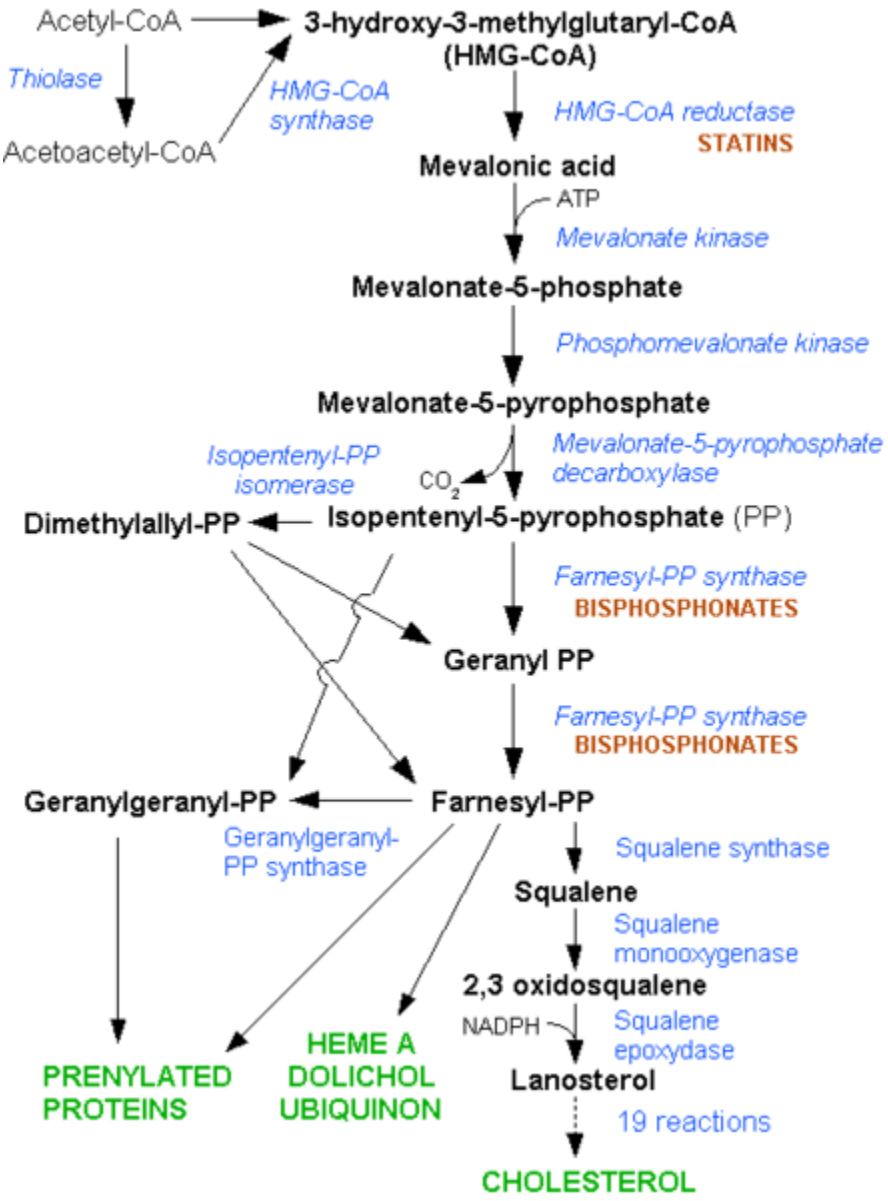
Medications for Hyperlipidemia

-Nicotinic acid is not used due to side effects (flushing, hyperglycemia, hyperuricemia)
- Fibrates are used to treat hypertriglyceridemia

Drug Class	*Agents*	*Effects (% change)*	*Side Effects*
HMG CoA reductase inhibitors	**Statins**	**↓LDL (18-55),↑ HDL (5-15) ↓ Triglycerides (7-30)**	**Myopathy, increased liver enzymes**
Cholesterol absorption inhibitor	**Ezetimibe**	**↓ LDL(14-18), ↑ HDL (1-3) ↓Triglyceride (2)**	**Headache, GI distress**
Nicotinic Acid		**↓LDL (15-30), ↑ HDL (15-35) ↓ Triglyceride (20-50)**	**Flushing, Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity**
Fibric Acids	**Gemfibrozil Fenofibrate**	**↓LDL (5-20), ↑HDL (10-20) ↓Triglyceride (20-50)**	**Dyspepsia, gallstones, myopathy**
Bile Acid sequestrants	**Cholestyramine**	**↓ LDL ↑ HDL No change in triglycerides**	**GI distress, constipation, decreased absorption of other drugs**

Example:
A young female with low risk of IHD → LDL level target (threshold) is higher
Male, 40 Y/O, total cholesterol 450, low HDL, BP 160, diabetic, smoker = very high risk, meaning LDL levels should be on the lowest margin of the range.
21, non smoker, cholesterol 160, BP 120/80, non-diabtei, non-smoker = very low risk, no need to treat unless LDL levels are very high (such as in familial hypercholesterolemia)





- Statins block the HMG CoA pathways → prevent cholesterol synthesis in the hepatocytes → low concentrations of cholesterol ester →upregulation of LDL receptors → more affinity to LDL → pulls down LDL from the blood to hepatocytes.
- Only strong types of statins can treat familial hypercholesterolemia

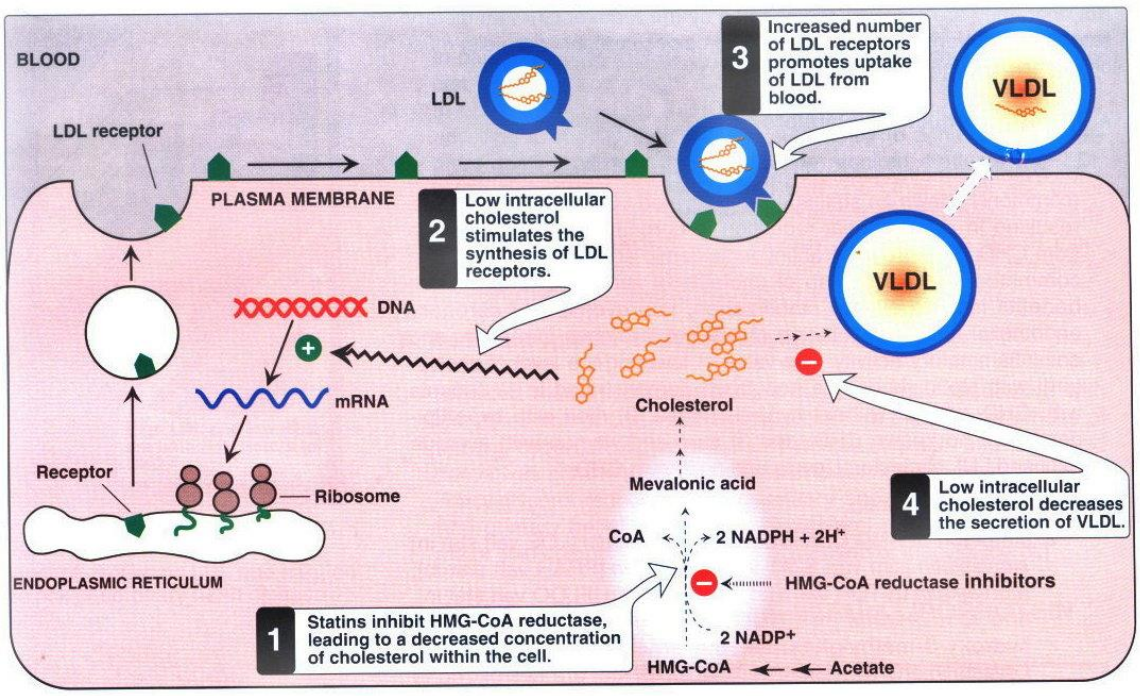


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.

Table 1: Assessment and action strategies for elevated plasma triglyceride concentrations [TG]

[TG], mmol/L	Step	Action and comments	Retest interval, mo*
< 2		Continue current management • Reassess lipid profile regularly, to ensure that [LDL-C] is at target	6-12
≥ 2, < 5	1.	Therapeutic lifestyle measures • Weight control • Reduce dietary fat, simple sugars • Reduce alcohol intake • Increase physical activity Reassess lipid profile regularly, to ensure that [LDL-C] is at target	3-6
	2.	Manage other secondary factors • Control glycemia, if diabetic • Reassess medications; consider lipid-neutral alternatives	
	3.	Consider pharmacologic treatment • Intensify LDL-lowering (e.g., statin therapy) • Fish oil (omega-3 fatty acid) • Niacin (e.g., extended release)	

≥ 5, < 10	4. Intensify steps 1-3, above • [LDL-C] cannot be estimated when [triglycerides] > 5 mmol/L • Apolipoprotein B determination might be helpful	2-3
	5. Consider fibrate therapy, e.g., • Bezafibrate (Bezalip) 400 mg/d • Fenofibrate — Lipidil micro 200 mg/d — Lipidil supra 160 mg/d — Lipidil EZ 145 mg/d • Gemfibrozil (Lopid) 600-1200 mg/d	
≥ 10	6. Further intensify steps 1-3 With acute pancreatitis: • Very-low-fat diet (10%-15% of energy intake) • Cessation of alcohol • Insulin, if indicated for glycemic control • Admit patient to hospital — Nothing by mouth: IV fluid replacement — Plasma exchange is unhelpful	1-2
	7. Initiate fibrate therapy • Monitor serum [creatinine]	
	8. Consider specialist referral	

-Triglycerides (more than 2 is considered high)

- between 2 – 5.6 : is considered high with no risk of pancreatitis, with a small risk of IHD.

fenofibrates do not prevent IHD, statins must be used if the aim is the prevention of IHD, although the effect of statins on TGs is lower than fibrates.

START with statins (your aim is IHD prevention)

- More than 5.6: high risk of pancreatitis (start with fibrates)

TGs more than 10? Very high risk of pancreatitis (admit the patient ,NPO, start fibrates)

Summary:

- Small dense LDL, which contains high levels of CE, is the most athrogenic form.
- High chylomicrons, which contain high levels of TGs, can cause pancreatitis.

- **Familial disorders:**

Familial Hypercholesterolemia

- LDL mutated receptor , Autosomal Dominant
- Heterozygous:
    - 1:500
    - Cholesterol levels: 7-13
    - CAD at age of: 30-50
- Homozygous:
    - 1:1000,000
    - Cholesterol levels: >13
    - CAD at age of: 18

- **DM or HTN:**
    - LDL high treat the pt for hyperlipidemia
    - TG high do NOT treat, it will come back to normal with treatment of DM or HTN.

- **When to check lipid panel** (Different Recommendations)
    - Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP)
        - **Beginning at age 20**
        - **Repeat testing every 5 years** for acceptable values

    - United States Preventative Services Task Force
        - **Women aged 45 years** and older, and **men ages 35 years** and older undergo screening with **a total and HDL cholesterol every 5 years**.
        - Cholesterol screening **should begin at 20 years in patients with (premature IHD)**

- **Treatment Targets**
    - **LDL and Non LDL (TC/HDL) :** To prevent coronary heart disease outcomes (myocardial infarction and coronary death)
    - **Triglyceride:** To prevent pancreatitis
    - Tx: statin (Mainly reduce LDL through blocking the HMG CoA pathways)
    - TG is high in DM so if a diabetic had TG levels of:
        - 2- 5.6 = high but **no risk of pancreatitis** but only small risk of IHD, start **statins.**
        - >5.6 = high and there is a **risk of pancreatitis**, start **fibrates.**

Risk categories

Risk level	10-year CAD risk	Recommendations
High	≥20%	*Treatment targets:* Primary target: LDL-C <2.0 mmol/L Secondary target: TC/HDL-C <4.0
Moderate	10% - 19%	*Treat when:* LDL-C ≥3.5 mmol/L *or* TC/HDL-C ≥5.0
Low	<10%	*Treat when:* LDL-C ≥5.0 mmol/L *or* TC/HDL-C ≥6.0

High risk includes coronary artery disease (CAD), peripheral artery disease, cerebrovascular disease and most patients with diabetes.

Questions:

http://www.courses.ahc.umn.edu/pharmacy/5822/casehyperlipid3.html
http://www.courses.ahc.umn.edu/pharmacy/5822/casehyperlipid2.html
http://www.courses.ahc.umn.edu/pharmacy/5822/casehyperlipid1.html