Dyslipidemia

Objectives:

- **Not given.**

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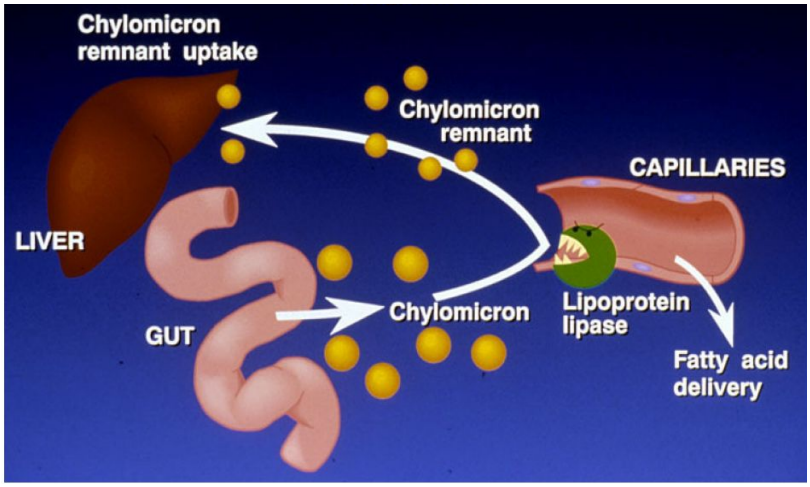
Resources: 435 team + Davidson + kumar + Kaplan "USMLE™ Step 2 CK Qbook."

- Editing file
- Feedback

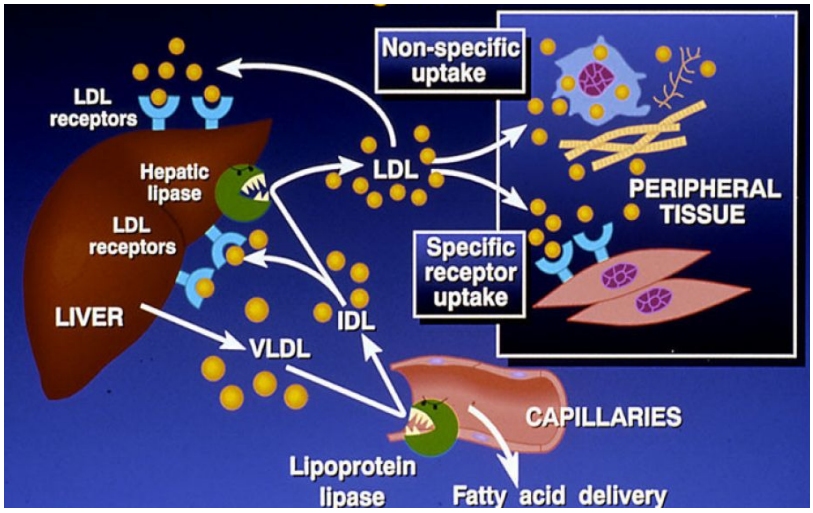
Lipoprotein[1] Pathway (helpful video)

★ Exogenous Pathway:



Chylomicron comes from the gut.
↓
it's metabolized by Lipoprotein Lipase.
↓
Lipoprotein lipase releases fatty acids from the chylomicrons, leaving Chylomicron remnant that goes back to the Liver.

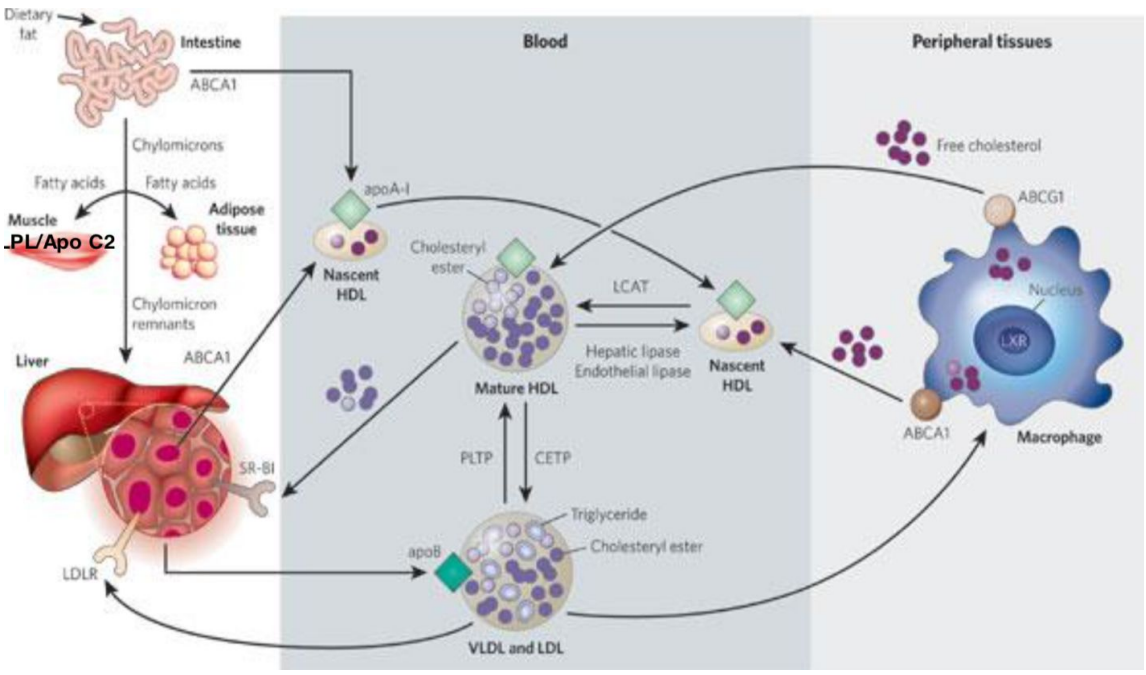
★ Endogenous Pathway:



In the liver, Hepatic lipase breaks down IDL to LDL outside of the liver. Then, LDL binds with LDL receptors that will bring it back into the liver.

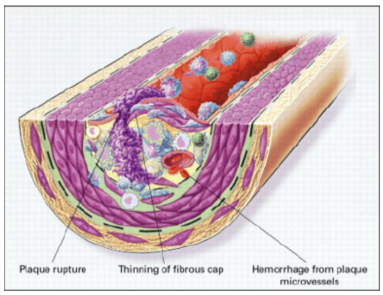
[1] Lipoprotein is a substance that carries cholesterol throughout your system

Lipid transport



1. Chylomicrons[2] transport fats from the intestinal mucosa to the liver.
2. In the liver, the chylomicrons release triglycerides and some cholesterol and becomes low-density lipoproteins (LDL).
3. LDL then carries fat and cholesterol to the body's cells. LDL receptors[3] in the Liver take up the LDL into the Liver.
4. High-density lipoproteins (HDL) carry fat and cholesterol back to the liver for excretion.
5. When oxidized LDL cholesterol gets high, atheroma formation in the walls of arteries occurs, which causes atherosclerosis.
6. HDL cholesterol is able to go and remove cholesterol from the atheroma.
7. Atherogenic cholesterol → LDL, VLDL, IDL.

Which one among them is the most atherogenic? LDL (LDL small particles) , because it's small enough to get through the vessel intima.



Atherosclerosis →

HDL can also remove the TG's from the atheroma.

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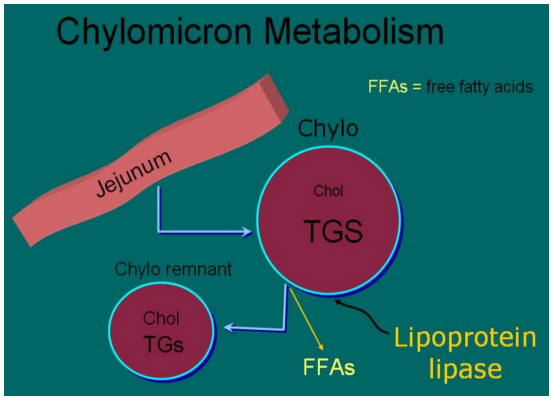
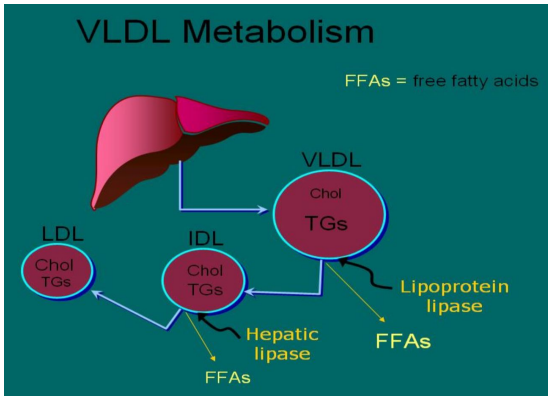
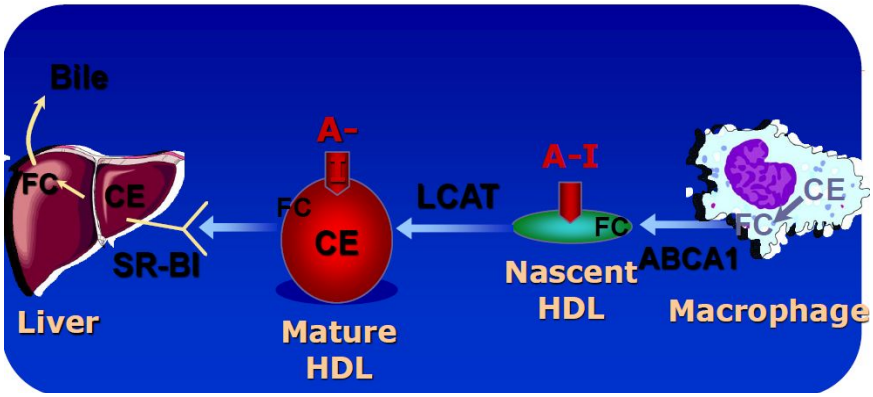
[2] A small fat globule composed of protein and lipid. made up of chylo → milky and micron → small = small milky (globules). The chylomicrons are synthesized in the mucosa of the intestine.

[3] LDL receptors are present only in the liver, otherwise LDL can go through blood vessels and into tissues without a receptor.





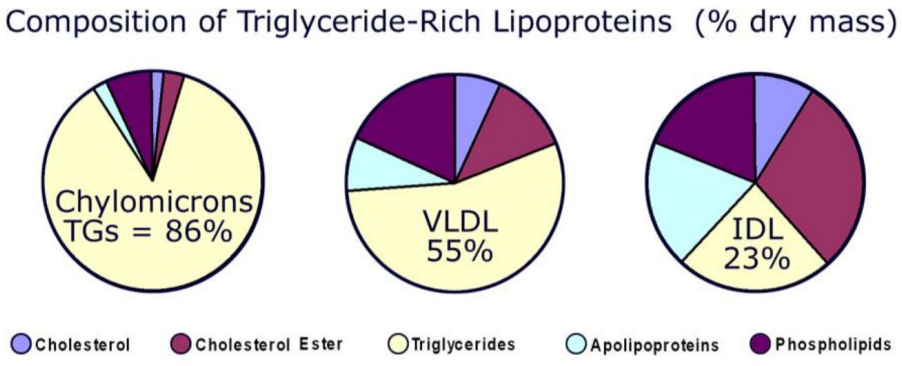
High TGs leads to higher risk of having pancreatitis.



If we had to choose between Mature (full bus) and Premature (empty bus) HDL
Which one should we choose to treat pancreatitis? Premature because it will take up the cholesterol.

Difference between LDL and LDL particles:

Total LDL is Low, LDL particles are High > Higher incidence of cardiovascular disease
the more the small LDL particles the more dangerous and higher risk of cardiovascular disease..



Plasma lipoproteins

Type	Source	Major lipid	Apoproteins	ELFO	Atherogenicity
Chylomicrons	Gut	Dietary TGs	A-I B-48 C-I, C-III E	No mobility	- Pancreatitis
VLDL[4]	liver	Endogenous TGs	B-100 E C- II, C-III	Pre-β	+
IDL[5]	VLDL remnant	Ch esters, TGs	B-100 C-III E	Slow pre- β	+
LDL[6]	VLDL, IDL	Ch esters	B-100	β	+++
HDL[7]	Gut, liver	Ch esters, PLs	A-I, A-II C-II, C-III D E	α	Antiatherogenic cardioprotective

Causes of Hyperlipidemia

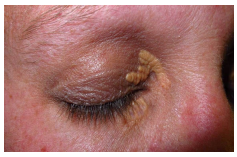
★ General causes:

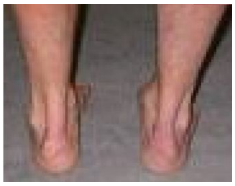
- Diet
- Hypothyroidism
- Nephrotic syndrome
- Anorexia nervosa[8]
- Obstructive liver disease
- Obesity
- Diabetes mellitus
- Pregnancy
- Acute hepatitis
- Systemic lupus erythematosus (SLE)
- AIDS (protease inhibitors)

[4] Very-low-density lipoprotein
[5] Intermediate-density lipoproteins
[6] Low-density lipoprotein
[7] High-density lipoprotein
[8] psychological and potentially life-threatening eating disorder

★ Hereditary Causes:

- **Familial Hypercholesterolemia**





  - Codominant (autosomal dominant) genetic disorder, occurs in heterozygous form (needs only one allele)
  - Occurs in 1 in 500 individuals
  - **Mutation in LDL receptor,** resulting in elevated levels of LDL at birth and throughout life (it means that LDL will not be taken up by the liver, so it will be elevated)
  - Lipoprotein lipase deficiency will lead to elevation in Chylomicron + VLDL that has TGs , so there will be elevated TGs as well
  - High risk for atherosclerosis, tendon xanthomas (75% of patients), tuberous xanthomas, Corneal arcus and xanthelasmas of eyes.
- **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, striae palmaris

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 and avocados.	↓ LDL ↑ HDL
Polyunsaturated	Corn, soybean, safflower and cottonseed oil and fish.	↓ LDL ↑ HDL
Saturated	Whole milk, butter, cheese, and ice cream; red meat; chocolate; coconuts, coconut milk, coconut oil, egg yolks, chicken skin.	↑ LDL & HDL
Trans	Most margarines; vegetable shortening; partially hydrogenated vegetable oil; deep-fried chips, many fast foods; most commercial baked goods.	↑ LDL

Fredrickson classification of hyperlipidemias

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

Primary hypercholesterolemia

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial hypercholesterolemia (Important) - LDL level >190	LDL receptor	dominant	**hetero** :1/500 5% of MIs <60 yr	- Premature CAD [9](ages 30–50) - TC: 7-13 mM
			homoz.: 1/1 million	- 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 hyperalphalipoproteinemia	unknown	variable	rare	- Less CHD, longer life elevated HDL

[9] Coronary Artery disease

Primary hypertriglyceridemia

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
LPL deficiency (Important)	endothelial LPL	recessive	rare 1/1 million	- Hepatosplenomegaly, abdominal cramps and pancreatitis. - TG: >8.5 mM
Apo C-II deficiency (Important)	Apo C-II	recessive	rare 1/1 million	- Abdominal cramps, pancreatitis. - TG: >8.5 mM
Familial hypertriglyceridemia	unknown enhanced hepatic TG-production	dominant	1/100	- Abdominal 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 rerley dominant	1/5000	- Premature CAD - TC: 6.5 -13 - mMTG: 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 - mMTG: 2.8 –8.5 mM

Secondary hyperlipidemias (don't skip this table)

Disorder	VLDL	LDL	HDL	Mechanism
DM	↑↑↑	↑	↓	- Increase VLDL production - Decrease LPL and Altered LDL
Hypothyroidism **Exam question** **المشكلة في ايش ؟ LDL**	↑	↑↑↑ **Mainly LDL**	↓	Decrease LDL-rec. and LPL
Obesity	↑↑	↑	↓	Increase VLDL production
Anorexia **Exam question** **المشكلة في ايش ؟ LDL**	-	↑↑ **ONLY LDL**	-	Decreased bile secretion and LDL catabolism.
Nephrotic syndrome	↑↑	↑↑↑	↓	- Increase Apo B-100 - Decrease LPL and LDL-rec.
Uremia, dialysis	↑↑↑	-	↓	Decrease LPL and HTGL[10] (by increase inhibitors)
Pregnancy	↑↑	↑↑	↑	- Increase oestrogen and VLDL production. - Decrease LPL
Biliary obstruction	-	-	↓	- Increase Lp-X - No CAD; xanthomas
Alcohol	↑↑ Increase Chylomicrons	-	↑	- dep. on dose - Diet - Genetics

[10] hepatic triglyceride lipase

Checking lipids

★ Nonfasting lipid panel:

- Measures HDL and total cholesterol

● Fasting lipid panel:

- **Measures HDL, total cholesterol and triglycerides**
- LDL cholesterol is calculated: total cholesterol – (HDL + triglycerides/5)

● When to check lipid panel? Two different recommendations

1. Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP)
    a. Beginning at age 20: obtain a fasting (9 to 12 hour) serum lipid profile consisting of total cholesterol, LDL, HDL and triglycerides.
    b. Repeat testing every 5 years for acceptable values.

★ United States Preventive 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 a history of multiple cardiovascular risk factors, diabetes, or family history of either elevated cholesterol levels or premature cardiovascular disease.

★ Treatment (first, lifestyle modification is needed)

Target	Aim
LDL[11]	To prevent coronary heart disease outcomes (myocardial infarction and coronary death)
Non LDL (TC/HDL)[12]	To prevent coronary heart disease outcomes (myocardial infarction and coronary death)
Triglyceride	To Mainly prevent pancreatitis and may be coronary heart disease outcomes (myocardial infarction and coronary death) If the TGs is more than 10, the risk for pancreatitis is sky high.

[11] You target lowering LDL level.
[12] You target lowering lowering Total cholesterol (All types) except the HDL (the good one).

- ## How to estimate 10-year risk for ASCVD?

By:

1. AGE
2. SBP/DBP
3. T cholesterol, HDL, LDL
4. DM, Smoking
5. On Anti HTN, On statin, On aspirin?

What you need to know:

1- Lifestyle modification.

2- Does this patient have established coronary artery disease? (Had MI…)

✓ If yes? High intensity statin!
except if pt is old >75.

3- Is his LDL more than 190?

✓ If yes? High intensity statin!
No need for further questions

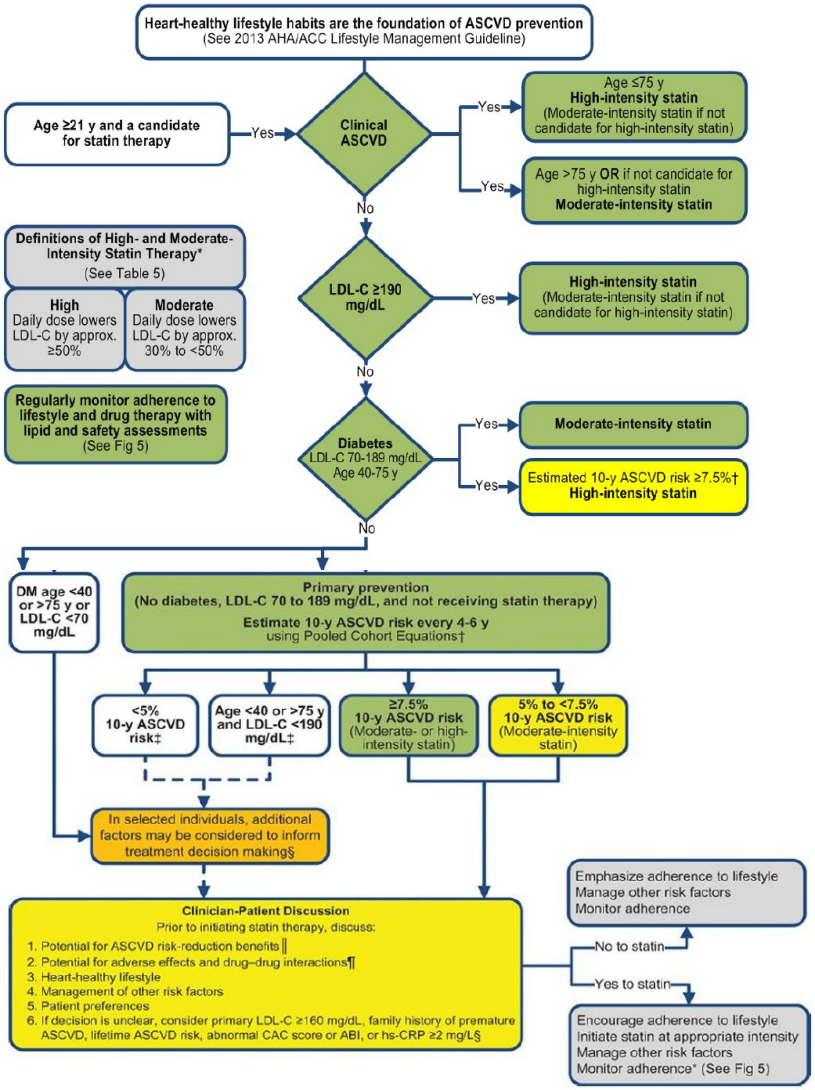
4- Has DM?

- More than 40 years?

✓ If yes? High intensity statin!

5- Anything other than that (2,3,4), we apply the 10 year risk assessment (done by websites and applications):-

- If its less than 5% > No need for meds.
- between 5%-7.5% > needs moderate intensity statin.
- More than 7.5% > needs High intensity statin.



If you know this ↑ you can skip the next 2 tables.

★ Guideline of therapy

Age	Risk factors	Statin intensity
> 29 Age	ASCVD[13]	High
> 29 years	LDL >190 mg/dl (4.9 mmol/l)	High
NO DM LDL <190	Estimate 10-year risk for ASCVD <5%	No
	Estimate 10-year risk for ASCVD 5-7.5%	Moderate
	Estimate 10-year risk for ASCVD >7.5%	High

- **Recommendations in DM**

Age	risk factors	Statin intensity
< 40 years	None	None
	ASCVD risk factor(s)	Moderate or high
	ASCVD	High
40 – 75 years	None	Moderate
	ASCVD risk factor(s)	High
	ACS & LDL +50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe
> 75 years	None	Moderate
	ASCVD risk factor(s)	Moderate or high
	ASCVD	High
	ACS & LDL +50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe

[13] Atherosclerotic Cardiovascular Disease

• Statin Treatment (After patient had IHD he should be on Statin)

	High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Dose	- Daily dose **lowers LDL-C**, on average, **by approximately +50%**	- Daily dose lowers LDLC, on average, by approximately 30% to <50%	- Daily dose lowers LDLC, on average, by <30%
Medications	**- Atorvastatin (40+) 80 mg** **- Rosuvastatin (20-40) mg**	- Atorvastatin 10 (20) mg - Rosuvastatin (5) 10 mg - Simvastatin 20–40 mg - Pravastatin 40 (80) mg - Lovastatin 40 mg - Fluvastatin XL 80 mg - Fluvastatin 40 mg BID - Pitavastatin 2–4 mg	- Simvastatin 10 mg - Pravastatin 10–20 mg - Lovastatin 20 mg - Fluvastatin 20–40 mg - Pitavastatin 1 mg

• Treatment of Hyperlipidemia

1. Lifestyle modification:

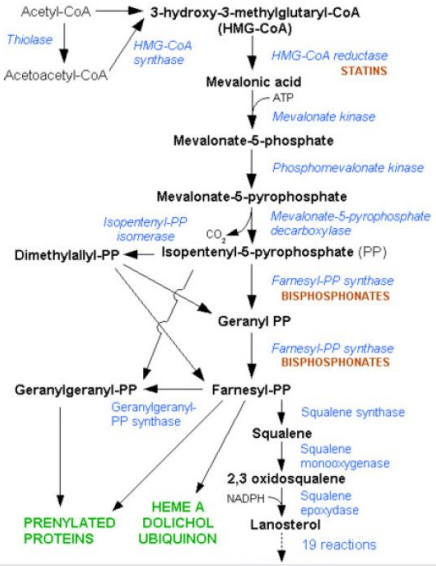
- Low-cholesterol diet
- Exercise
- Smoking
- No Alcohol

2. Medications:

Drug Class	Agents	Effects (% change)	Side Effects
HMG CoA reductase inhibitors	Statins	- Decrease LDL (18-55) - Decrease Triglycerides (7-30) - Increase HDL (5-15)	Myopathy, increased liver enzymes
Cholesterol absorption inhibitor	**Ezetimibe**[14]	- Decrease LDL (14-18) - Decrease Triglycerides (2) - Increase HDL (1-3)	Headache, GI distress
Nicotinic Acid[15]	-	- Decrease LDL (15-30) - Decrease Triglycerides (20-50) - Increase HDL (15-35)	Flushing, Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity

[14] used if pt is resistant to statins
[15] Very effective! but not used due to its intense side effects.

Fibric Acids	- Gemfibrozil - Fenofibrate	- Decrease LDL (5-20) - Decrease Triglycerides (20-50) - Increase HDL (10-20) The most appropriate treatment to prevent pancreatitis is to correct TGs by Fenofibrate	Dyspepsia, gallstones, myopathy
Bile Acid sequestrants	Cholestyramine	- Decrease LDL - Increase HDL - No change in Triglycerides	GI distress, constipation, decreased absorption of other drugs
PCSK9	- Evolocumab - Alirocumab	Decrease LDL (50-60%)	Injection-site reactions, muscle pain, neurocognitive adverse events. These included memory impairment and confusion



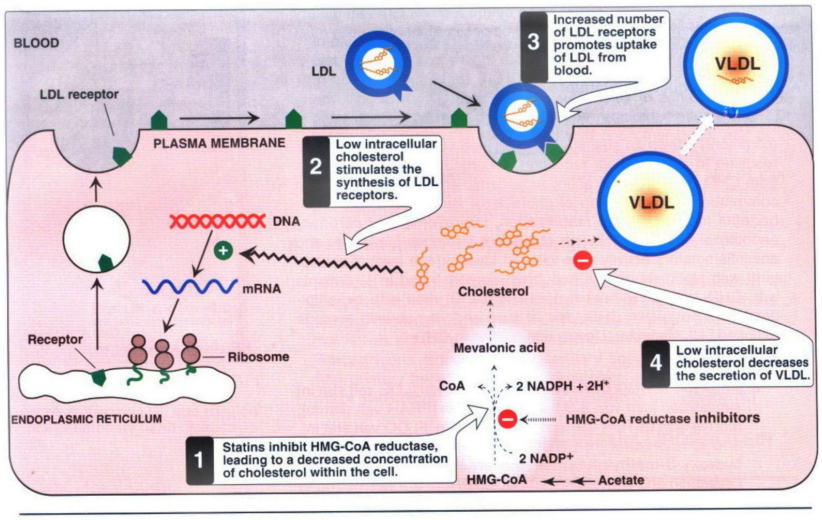


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.

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	

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

Summary

Primary hypercholesterolemia

- **Familial hypercholesterolemia**: **LDL receptor mutation -> Elevated LDL + Family hx of premature CVD death**
  - High risk for atherosclerosis, tendon xanthomas, tuberous xanthomas and xanthelasmas of eyes.

Primary hypertriglyceridemia

- LPL deficiency
- Familial hypertriglyceridemia: enhanced hepatic TG-production
- Apo-CII deficiency

All can lead to pancreatitis

Secondary hyperlipidemia

- DM: VLDL increased production
- Obesity: VLDL increased production
- Hypothyroidism: Mainly LDL increased production
- Anorexia : increased LDL ONLY

Aims of dyslipidemia treatment

LDL: prevent coronary heart disease (statins)
Non LDL (TC/HDL): prevent coronary heart disease
Triglyceride: prevent pancreatitis and may be coronary heart disease outcomes (fibrates)

Guidelines of Therapy

1- Lifestyle modification.

2- Does this patient have established coronary artery disease? (Had MI…)

✓ If yes? High intensity statin!
except if pt is old >75.

3- Is his LDL more than 190?

✓ If yes? High intensity statin!
No need for further questions

4- Has DM?

- More than 40 years?

✓ If yes? High intensity statin!

5- Anything other than that (2,3,4), we apply the 10 year risk assessment (done by websites & applications):-

- If its less than 5% > No need for meds.
- between 5%-7.5% > needs moderate intensity statin.
- More than 7.5% > needs High intensity statin.

- **Best to prevent CAD/MI : Statins (reduce LDL)**
- **Best to prevent Pancreatitis: Fibrate (reduce TGs)**

Questions (Click here for Important Q's)

1.Which of the following is the most dangerous to a patient in terms of risk for CAD?

A. Elevated triglycerides.
B. Elevated total cholesterol.
C. Decreased high density lipoprotein(HDL).
D. Elevated low density lipoprotein(LDL).

2.Which of the following is the most common adverse effect of statin medications?

A. Liver dysfunction.
B. Renal failure.
C. Encephalopathy.
D. Hyperkalemia.

3.**A 30-year-old man is brought to the emergency department because of acute chest pain for 1 hour. He is admitted with a diagnosis of myocardial infarction, which is confirmed by imaging and serum marker studies. The patient's family history is significant for early myocardial infarctions in several of his relatives. Nodular lesions are noted in his eyelids and several tendons, which are diagnosed as xanthomas by biopsy examination. Serum cholesterol level is 350 mg/dL, and triglycerides are within the normal range. An abnormality in which of the following proteins most likely accounts for this patient's condition?**

A. Apolipoprotein CII
B. Apolipoprotein E
C. Lipoprotein lipase
D. LDL receptor

Answers:

1.D

2.A

3.D (The constellation of high cholesterol level, MI at a young age, positive family history for early-onset MI, and multiple xanthomas is consistent with familial hypercholesterolemia. This autosomal dominant disorder is caused by mutations in the gene for the LDL receptor.