MEDICINE

432 Team

43 Dyslipidemia

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COLOR GUIDE: • Females' Notes • Males' Notes • Important • Additional

Objectives

Not given

Hyperlipidemia

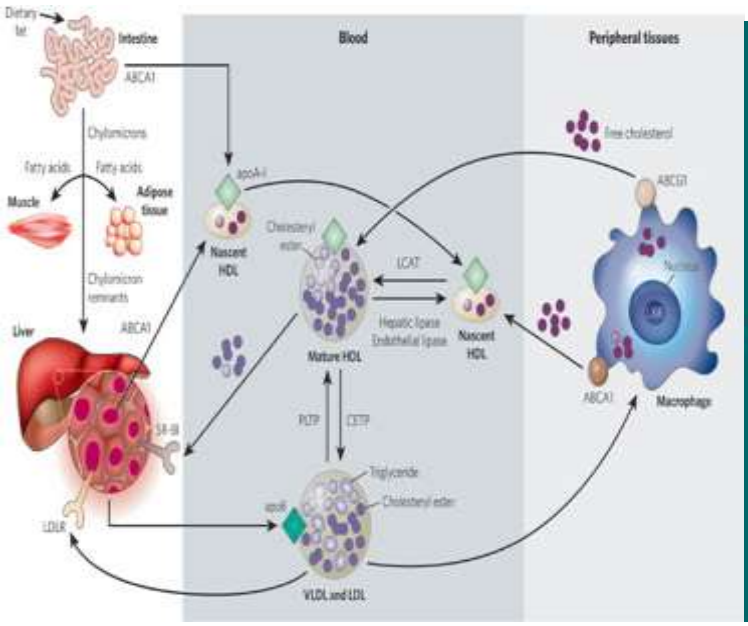
Lipid Transport:

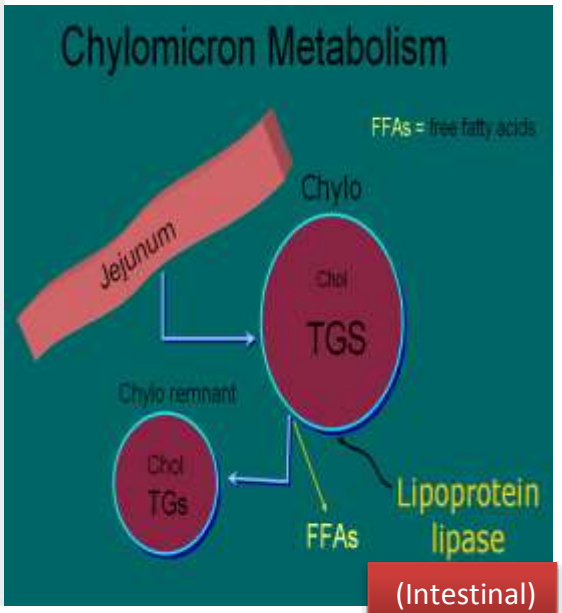
Lipoprotein metabolism has a key role in **atherogenesis**. It involves the transport of lipids, particularly cholesterol and triglycerides, in the blood. The intestine absorbs dietary fat and packages it into chylomicrons (large triglyceride-rich lipoproteins), which are transported to peripheral tissues through the blood. In muscle and adipose tissues, the enzyme lipoprotein lipase breaks down chylomicrons, and fatty acids enter these tissues. The chylomicron remnants are subsequently taken up by the liver. The liver loads lipids onto apoB and secretes very-low-density lipoproteins (VLDLs), which undergo lipolysis by lipoprotein lipase to form low-density lipoproteins (LDLs). LDL is then taken up by the liver through binding to the LDL receptor (LDLR), as well as through other pathways.

Note(s):

-Lipoprotein is made of **protein** *carrying* **cholesterol**

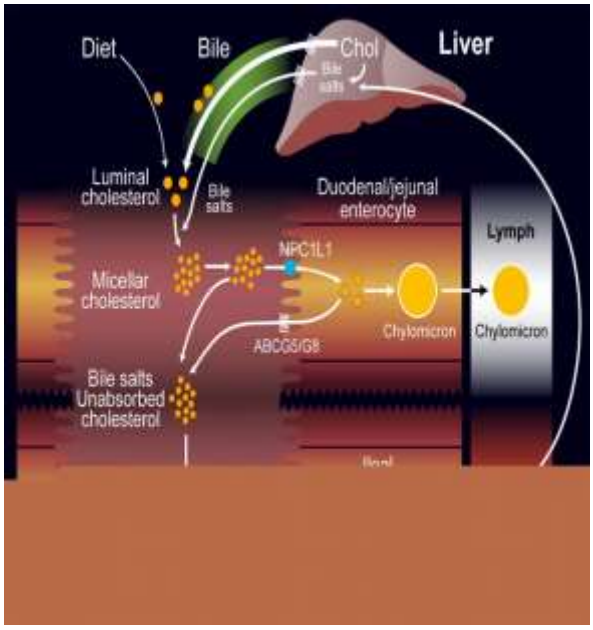
- Plasma cholesterol levels depend on the balance of cholesterol production and intestinal absorption.[1]





There are three important type of lipoprotein:
1-LDL: protein + cholesteryl ester it moves from the liver to the blood vessel
2-HDL: protein + cholesterol it moves from the blood vessel to the liver
3-chylomicron: cholesterol + protein (mainly) it moves from the intestine to the liver

1. 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.
2. The liver forms lipoproteins, which carry TGs and cholesterol.
3. The liver releases VLDL, LDL, and HDL to the blood.
4. LDL (the most **atherogenic**) transports fat from the liver to the macrophages (foam cells) in the rest of the body's cells.
5. Pre or nascent HDL takes up cholesterol from the macrophages to the liver LDL and HDL work in opposite directions.



VLDL:

The LDL will form internally (intrinsic cholesterol VLDL mainly) it's made and released in the liver mainly TGS.

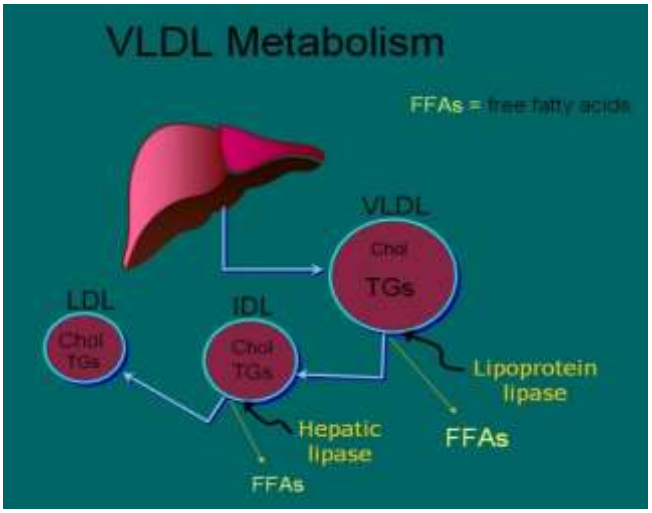
Note(s):

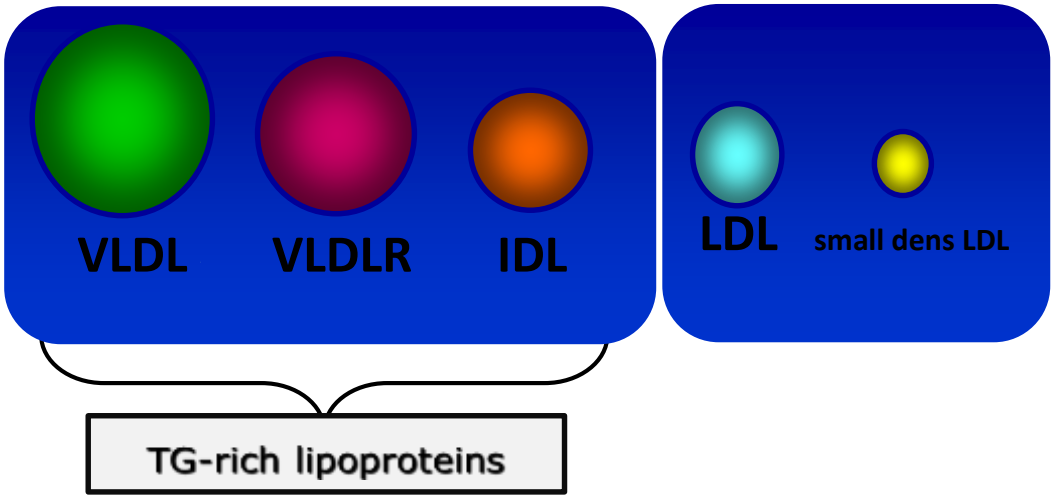
VLDL *is the body's main* source of energy during prolonged fasting

There are two lipoprotein lipase:

1. In the chylomicron (intestinal lipoprotein lipase)
2. **In the VLDL (tissue lipoprotein lipase)**

breakdown the VLDL to IDL then to LDL (happened in the liver and blood).





Note(s):

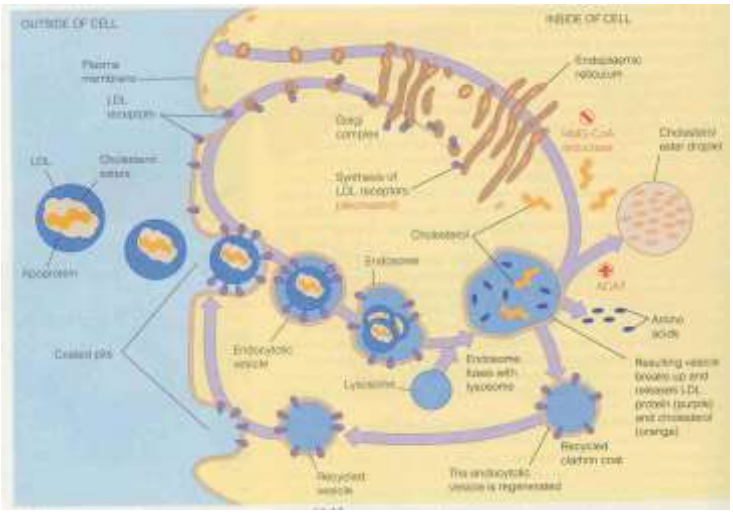
The larger the lipoprotein the higher amount of TGS and lesser amount of cholesterol And vice versa

Explanation:

LDL almost 100% cholesteryl ester which mean its an atherogenic (the higher the cholesterol percent the smaller the lipoprotein the more it become atherogenic)

LDL:

LDL is the main carrier of cholesterol, and deliver it both to liver and peripheral cell, the number of hepatic LDL clearance receptor regulate the circulating LDL concentration, which is also influenced by controlling the activity of the rate-limiting enzyme in the cholesterol synthetic pathway, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase.

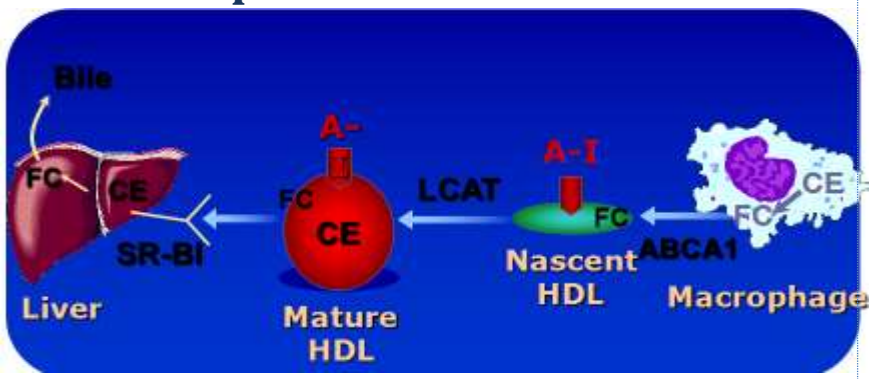


Atherogenic particles:

Not only is LDL-C a risk factor for cardiovascular disease, but triglyceride-rich lipoproteins—very low-density lipoprotein (VLDL), VLDL remnants, and intermediate-density lipoprotein (IDL)—may also increase the risk of heart disease.

HDL and reverse cholesterol transport:

HDL is believed to protect against atherosclerosis at least in part through the process of reverse cholesterol transport, whereby excess free cholesterol (FC) is removed by the HDL from cells in peripheral tissues, such as macrophages within the arterial wall, and returned to the liver for excretion in the bile. (**Nascent HDL**)



Hereditary (primary) Causes of Hyperlipidemia:

- **Familial Hypercholesterolemia** (autosomal dominant):

It's a disease affecting young people present to you with myocardial infarction in younger age

- Co-dominant genetic disorder occurs in heterozygous form.
- Occurs in 1 in 500 individuals.
- Mutation in LDL receptor (in the liver), 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.

It has two types:

1. Heterozygous Familial Hypercholesterolemia:

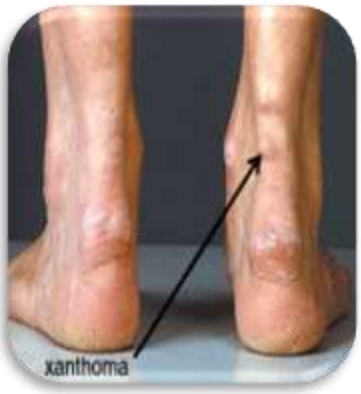
Autosomal dominant disorder present in 1 in 500 of normal population (common) one allele affected, the genetic defect is underproduction or malproduction of the LDL receptor in the liver.

2. Homozygous Familial Hypercholesterolemia:

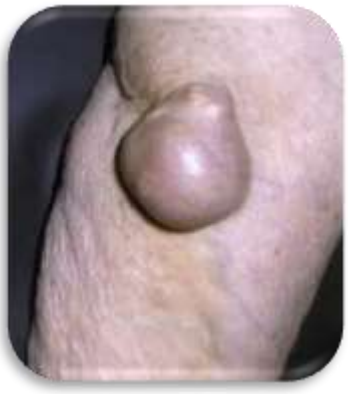
Its very rare (one in a million) affect children have no LDL receptor in the liver , the LDL here is sky-high and they suffer from myocardial infarction since the childhood (12 – 14 age) even younger .

Clinical Presentation:

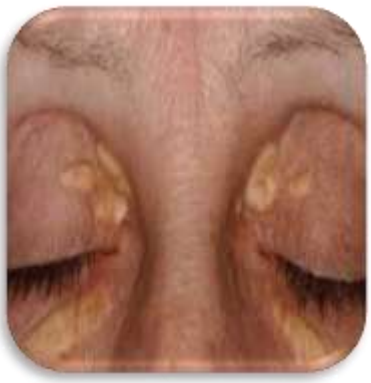
- Atherosclerosis.
- Tendon xanthomas.
- Tuberous xanthomas.
- Xanthelasmas of eyes.



Tendon xanthomas



tuberous xanthomas



xanthelasmas of eyes

- **Familial hyper-triglyceridemia:**

The problem in this disease is in the lipoprotein lipase enzyme so they have: high VLDL + high TGS, and they have also pancreatitis (as a result of high TGS).

- **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.

Secondary Causes of Hyperlipidemia:

- Diet
- Hypothyroidism
- Nephrotic syndrome
- Anorexia nervosa
- Obstructive liver disease
- Obesity
- Diabetes mellitus
- Pregnancy
- Obstructive liver disease
- Acute hepatitis
- Systemic lupus erythematousus
- AIDS (protease inhibitors

Disorder	VLDL	LDL	HDL	Mechanism
Diabetes mellitus	↑ ↑ ↑	↑	↓	VLDL production ↑, LPL ↓, altered LDL
Hypothyroidism	↑	↑ ↑ ↑	↓	LDL-rec.↓, LPL ↓
Obesity	↑ ↑	↑	↓	VLDL production ↑
Anorexia	-	↑ ↑	-	bile secretion ↓, LDL catab. ↓
Pregnancy	↑ ↑	↑ ↑	↑	oestrogen ↑ VLDL production ↑, LPL ↓

Checking lipids:

- **Non-fasting 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).

When to check lipid panel:

Different Recommendations:

- 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 (Because of the estrogen and its protective actions) .
  - 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.

- 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.

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.

Risk factors:

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

Note(s):

***C in** the **LDL-C** and **HDL-C** stand for cholesterol.*

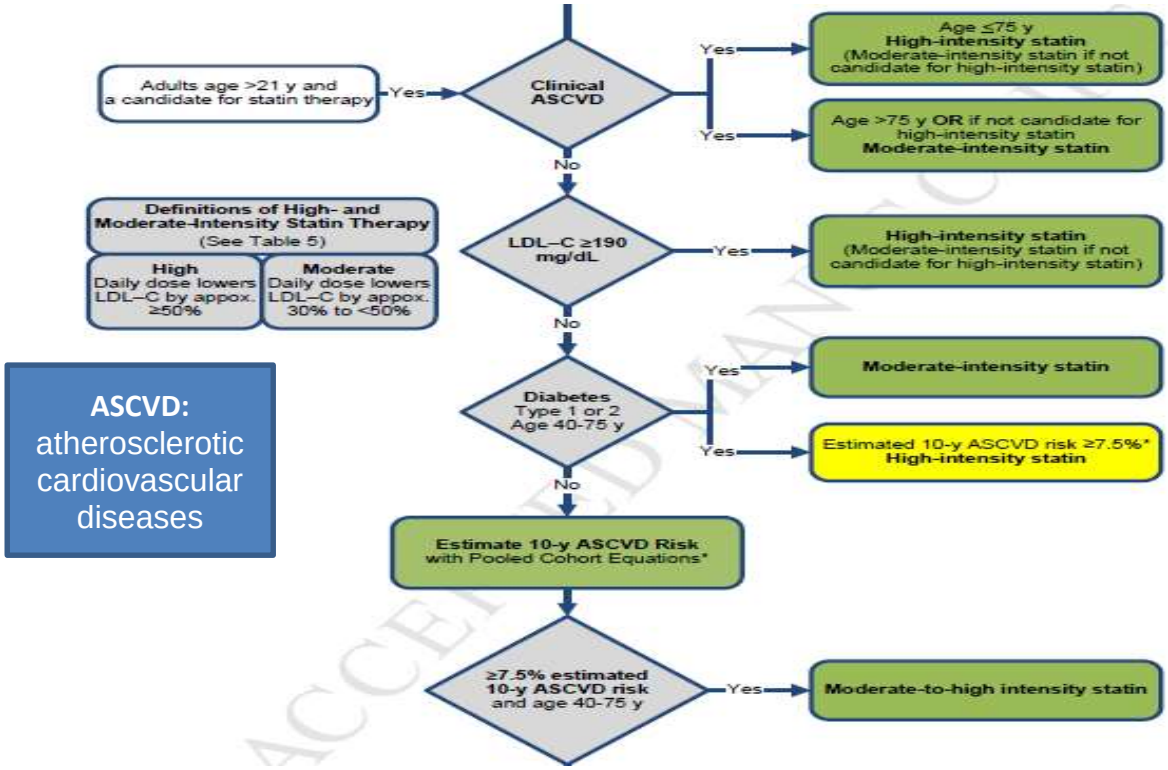
Canadian New Guideline (doctor recommended this one)

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.

The new guideline made by the American heart association



ASCVD: atherosclerotic cardiovascular diseases

This algorithm summarizes the major guidelines in one page:

- You see the 4 statin benefit groups in the middle: on top, you see the patient's group with clinical ASCVD, below that you see the group with LDL >190, below that you see the patient's with history of DM 40-75 years old, and in the bottom, you see patients who don't have the characteristics of the first 3 groups but their 10 year ASCD risk is greater than 7.5%

- For the first group: based on the guideline, if you have clinical ASCD, are younger than 75 and don't have any history of intolerance to statin, you should be started on high intensity statin. On the other hand, if you are older than 75, or not a candidate for high intensity statin due to lets say intolerance to statins, you are a candidate for moderate-intensity statin
- For the second group, if your LDL is greater than 190, you need to be started on high-intensity statin, unless you have contra-indication to high dose →start on moderate dose
- For the third group, individuals with diabetes with above mentioned group age, you need to calculate the 10 year ASCVD risk using a new equation/calculator called "pooled Cohort Equations" →if the 10 year risk is greater than 7.5%, start them on high-intensity, otherwise, you can start them on moderate-intensity statin
- For the last group, you need to calculate patient's risk factor and start them on moderate-to-high intensity statin if their estimated 10-y ASCVD risk is greater than 7.5%
- Keep that in mind that what we mean by "high intensity" statin, is the daily dose of statin that lowers the LDL by approx. greater than 50%, and what we mean by moderate intensity statin, is the daily dose of statin that lowers the LDL by approx. 30-50%.

Intensity of Statin Therapy in primary and secondary prevention:

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL–C on average, by approximately ≥50%	Daily dose lowers LDL–C on average, by approximately 30% to <50%	Daily dose lowers LDL–C on average, by <30%
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*

Table 8.1—Recommendations for statin treatment in people with diabetes

Age	Risk factors	Recommended statin dose*	Monitoring with lipid panel
<40 years	None CVD risk factor(s)** Overt CVD***	None Moderate or high High	Annually or as needed to monitor for adherence
40–75 years	None CVD risk factors Overt CVD	Moderate High High	As needed to monitor adherence
>75 years	None CVD risk factors Overt CVD	Moderate Moderate or high High	As needed to monitor adherence

*In addition to lifestyle therapy.
**CVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, and overweight and obesity.
***Overt CVD includes those with previous cardiovascular events or acute coronary syndromes.

Note:

The goal of LDL in a diabetic patient is 100mg/dl

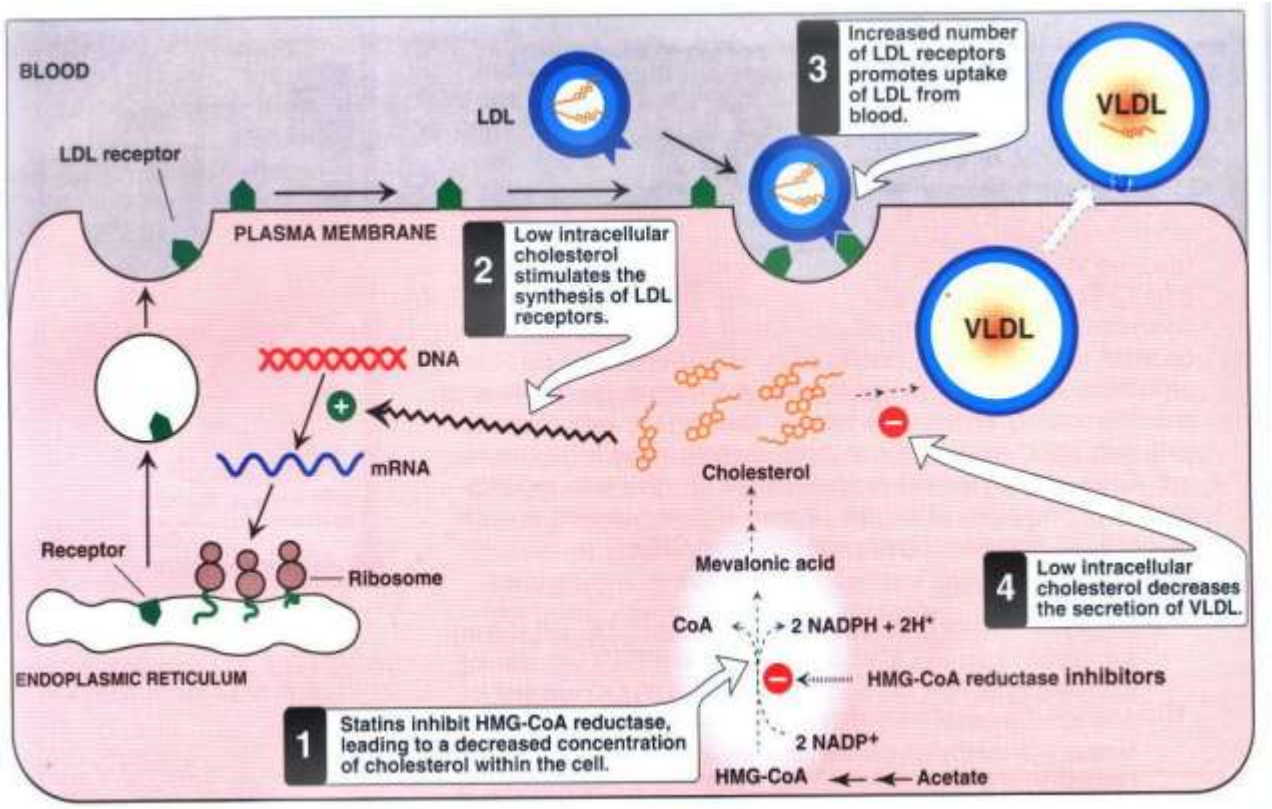
Drug Class	*Agents*	*Effects (% change)*	*Side Effects*
HMG CoA reductase inhibitors		Statins	↓LDL (18-55),↑ HDL (5-15) ↓ Triglycerides (7-30)	Myopathy, increased liver enzymes
Cholesterol absorption inhibitor		Ezetimibe	↓ LDL(14-18), ↑ HDL (1-3) ↓Triglyceride (2)	Headache, GI distress
Nicotinic Acid			↓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

The most common treatments used:

1. **Statins** 2- Cholesterol absorption inhibitor 3- Fibric Acids (mainly for TGS)

The mechanism of action of statins:

1. **Inhibition of HMG CoA reductase** (reduce the cholesterol in the hepatocyte)
2. **Up-regulation of the LDL receptor**.



Triglyceride:

[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	

SUMMARY

1. Hyperlipidemia is one of the most important (and modifiable) risk factor for CAD. It causes accelerated atherosclerosis
2. There a different type of lipoprotein but the most important is :
   A. LDL cholesterol: two third of the total cholesterol. CAD risk is primarily due to the LDL component (most atherogenic)
   B. HDL cholesterol: it's a protective effect (removes excess cholesterol from the arterial walls).
   C. Triglyceride: elevated TGs are associated with coronary risk and pancreatitis.
3. Most patients are asymptomatic but in sever hyperlipidemia the have: tendon xanthomas, tuberous xanthomas, and xanthelasmas of eyes.
4. Lipid screening is either by Non-fasting lipid (measures HDL and total cholesterol) Fasting lipid panel (Measures HDL, total cholesterol and triglycerides LDL cholesterol is calculated).
5. The long-term goal of treatment is to reduce the coronary heart disease the short-term goal is to reduce the LDL level.
6. Rather than LDL–C or non-HDL– C targets, new guideline uses the intensity of statin therapy as the goal of treatment.
7. Know the 4 Statin Benefit Groups:
   i. Individuals with clinical ASCVD
   ii. Individuals with primary elevations of LDL–C ≥190 mg/dL
   iii. Individuals 40 to 75 years of age with diabetes and LDL–C 70 to189 mg/dL without clinical ASCVD
   iv. Individuals without clinical ASCVD or diabetes who are 40 to 75 years of age with LDL–C 70 to 189 mg/dL and have an estimated 10-year ASCVD risk of 7.5% or higher. (**Using the Pooled Cohort Equations for ASCVD risk prediction**)

Questions

1. 50 year old white female

Total cholesterol 180
HDL: 50
SBP: 130
Taking anti-hypertension medication
+Diabetic
+Smoker
Calculated 10 years ASCVD: 9.8%

What are you going to treat her with?

A. High intensity statin

B. Moderate intensity statin

C. Low intensity statin

D. Statin therapy NOT recommended

2. 48 year old white female

Total cholesterol 180
HDL: 55
SBP: 130
Not taking anti-hypertension medication
+Diabetic
Non-smoker
Calculated 10 years risk ASCVD : 1.8%

What are you going to treat her with?

A. High intensity statin

B. Moderate intensity statin

C. Low intensity statin

D. Statin therapy NOT recommended

3. 22 year old white male

LDL: 195
SBP: 120
Not taking anti-hypertension medication
Non-diabetic
Non-smoker

What are you going to treat him with?

A. High intensity statin

B. Moderate intensity statin

C. Low intensity statin

D. Statin therapy NOT recommended

4. 66 year old white female

High Total cholesterol: 230
HDL: 55
SBP: 150
Taking anti-hypertension medication
Non-diabetic
Non-smoker
Calculated 10 years risk of ASCVD: 2.0 %

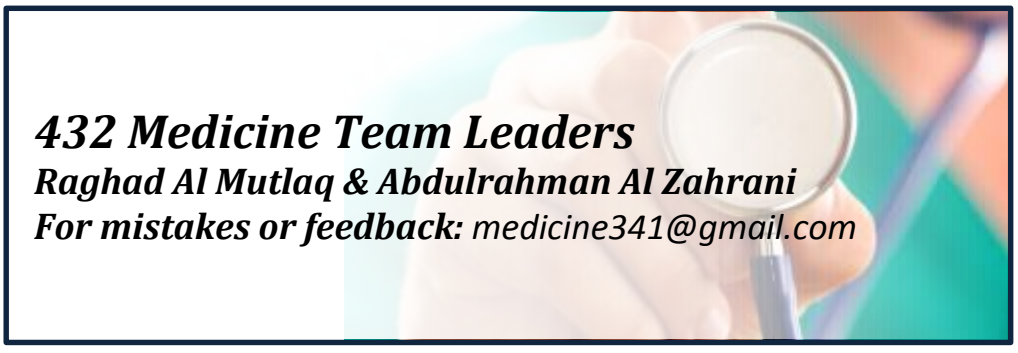
What are you going to treat her with?

A. High intensity statin

B. Moderate intensity statin

C. Low intensity statin

D. Statin therapy NOT recommended



Answers:

1st Questions: A

2nd Questions: B

3rd Questions: A

4th Questions: D