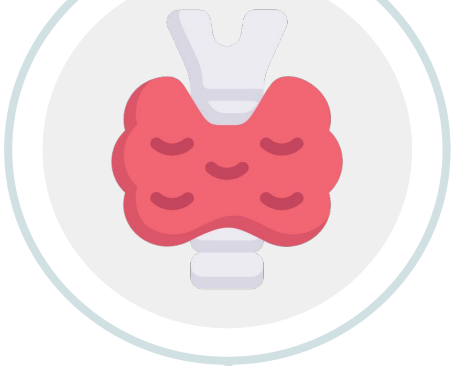
Hyperlipidaemia



Objectives :

- ★ Know the Physiology of lipid and lipoprotein cycles
- ★ Know the most important hereditary diseases related to lipid
- ★ Know the 2ndary causes of hyperlipidemia
- ★ Approach the patient with hyperlipidemia
- ★ Discussion around the therapy

Editing file

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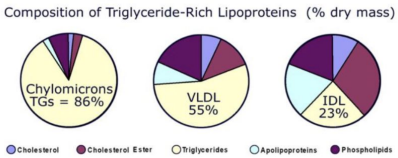
◄ Introduction:

- Lipids are insoluble in water, and are **transported in the bloodstream as lipoprotein** particles composed of:

- **Lipids:**
  - Mainly triglycerides, cholesterol and cholesterol esters
  - surrounded by a coat of phospholipids.
- **Proteins:**
  - Called apo- proteins
  - Embedded into the phospholipid coating exert a stabilizing function and allow the particles to be recognized by receptors in the liver and peripheral tissues.



◄ Plasma lipoproteins:

Feel lost?
Click for a nice summary

Type	Source	Major lipid	Apoproteins	ELFO	Atherogenicity
Chylomicron	• **Function:** transport the digestion products of dietary fat to the liver and peripheral tissues.				
	Gut	Dietary TAGs and a small amount of cholesterol and its ester	A-I, B-48, C-I, C-III, E	no mobility	**Not atherogenic** (doesn't cause MI) **but causes pancreatitis**
VLDL	• Contain **most of the body's endogenous triglyceride** and a smaller quantity of cholesterols • Very raised triglyceride concentrations (>6 mmol/L) cause a greatly increased risk of acute pancreatitis and retinal vein thrombosis. Hypertriglyceridemia tends to occur in association with a reduced HDL concentration.				
	Liver	Endogenous TAGs	B-100, E, C-II, C-III	Pre-β	+
IDL	VLDL remnant	Ch esters, TAGs	B-100, C-III, E	Slow pre- β	+
LDL	• The main carrier of cholesterol, and deliver it both to the liver and to peripheral cells. And can deposit lipid into the walls of the peripheral vasculature				
	VLDL, IDL	Ch esters	B-100 and E	β	+++
★ **HDL**	• Nascent HDL become mature particles by the acquisition of phospholipids, and the E and C apoproteins from chylomicrons and VLDL in the circulation • **Function:** transports cholesterol away from the periphery either indirectly to other particles such as VLDL in the circulation or directly to the liver and steroid-synthetic tissues (ovaries, testes, adrenal cortex)				
	Gut, liver	Ch esters, PLs	A-I, A-II, C-II, C-III, D, E	α	**Anti-atherogenic**

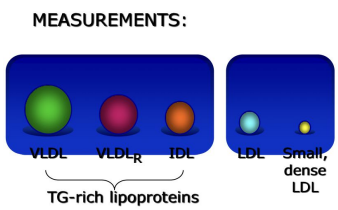
◀ The history of lipids

- Chylomicrons transport fats from the intestinal mucosa to the liver
- In the liver, VLDL released to blood stream to form IDL and LDL.
- LDL then carries fat and cholesterol to the body's cells. LDL receptors in Liver take the LDL to Liver.
- High-density lipoproteins (HDL) released from intestine and liver and carry fat and cholesterol from blood vessels to the liver.

◀ Atherogenic particles

Atherogenic cholesterol → LDL, VLDL, IDL

- When oxidized LDL cholesterol gets high → atheroma formation in the walls of arteries occurs → atherosclerosis.
- **HDL** cholesterol is able to go and **remove cholesterol from the atheroma.**
- ★ **Which one has the most atherogenic effect? Small dense LDL.** Because it's very small and can easily penetrate the intima of the blood vessels, can easily concentrate there and easily taken by macrophages. Even though it has the least amount of cholesterol!



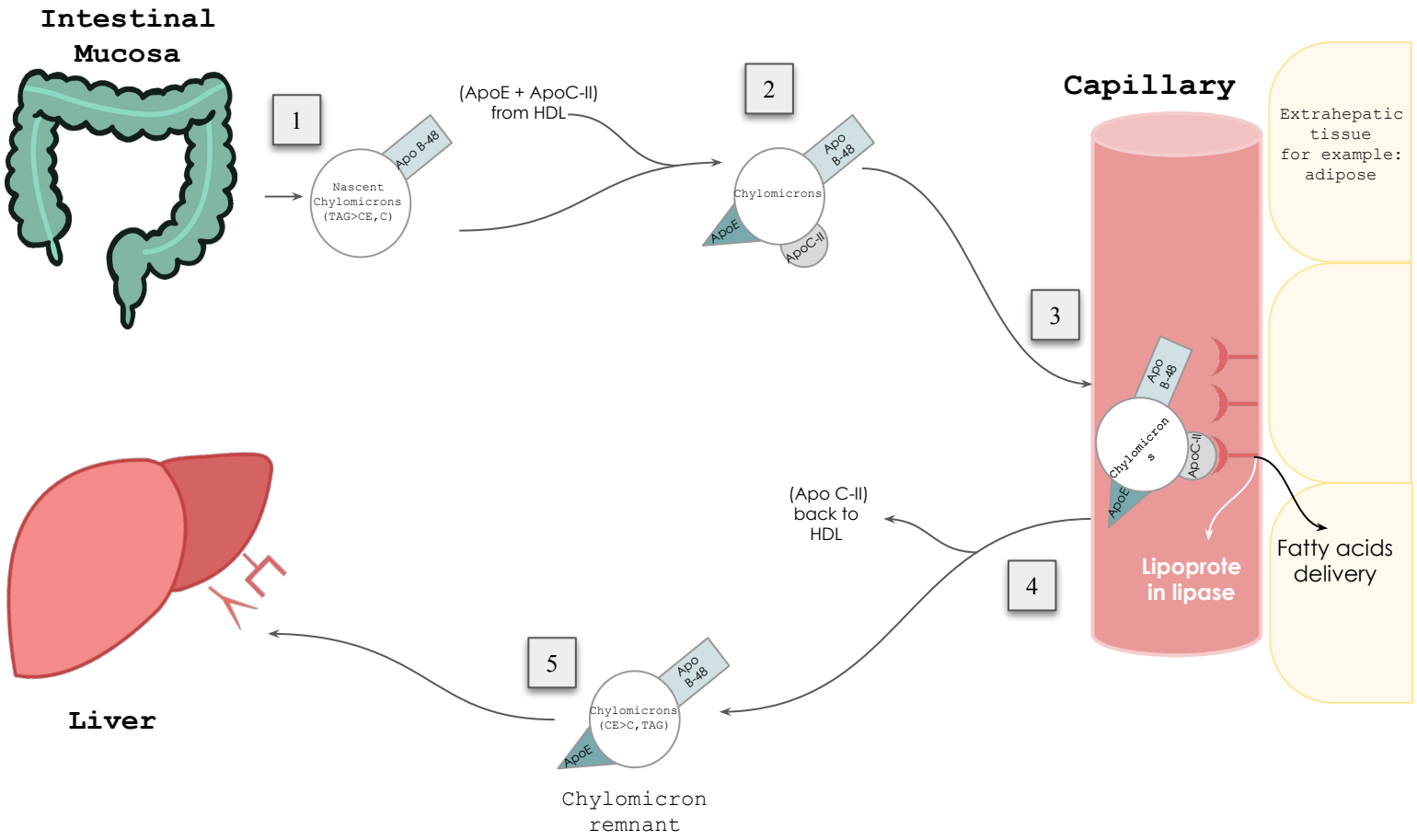
- Lipoproteins are classified depending on the composition: how much cholesterol/ triglycerides it contains, what type of apoprotein, and the clinical approach of the lipoprotein

Lipoprotein	Density	Size (nm)	Major Lipids	Major Apoproteins
Chylomicron	<0.930	75-1200	Triglycerides	Apo B-48, Apo C, Apo E, Apo A-I, A-II, A-IV
Chylomicron Remnants	0930-1.006	30-80	Triglycerides Cholesterol	Apo B-48, Apo E
VLDL	0.930-1.006	30-80	Triglycerides	Apo B-100, Apo E, Apo C
IDL	1.006-1.019	25-35	Triglycerides Cholesterol	Apo B-100, Apo E, Apo C
LDL	1.019-1.063	18-25	Cholesterol	Apo B-100
HDL	1.063-1.210	5-12	Cholesterol Phospholipids	Apo A-I, Apo A-II, Apo C, Apo E
Lp (a)	1.055-1.085	~ 30	Cholesterol	Apo B-100, Apo (α)

◀ Lipoprotein Exogenous Pathway (Post-prandial):

IMP to know the enzymes and their functions

original pic



- **Chylomicrons** transport fats **from the intestinal mucosa** to the **liver** through the portal vein:

1. Intestinal mucosal cells secrete nascent TAG (triacylglycerol) -rich chylomicrons which produced from dietary (exogenous) lipids. And they only have **Apo B-48** on them.

2. Chylomicrons acquire apoproteins C-II and E from HDL particles in the bloodstream. Now, it has all three apolipoproteins: **Apo B-48**, **Apo C-II**, and **Apo E**.

3. Apoprotein C-II binds to specific receptors in adipose tissue and skeletal muscle and the liver, where the endothelial enzyme, **intestinal lipoprotein lipase gets** activated by Apo C-II and it hydrolyses chylomicron to form chylomicron remnants and free fatty acid (Energy source that we store it and use it) into blood stream.

4. **Apo C-II** is returned back to HDL, however **Apo E** and **Apo B-48** are still there.

5. Chylomicron remnant particle delivered to the liver via the portal circulation then taken up by the liver through LDLRs (Low-Density Lipoprotein receptors) which recognizes Apoprotein E then they are endocytosed.

◀ Lipoprotein Endogenous Pathway:

IMP to know the enzymes and their functions

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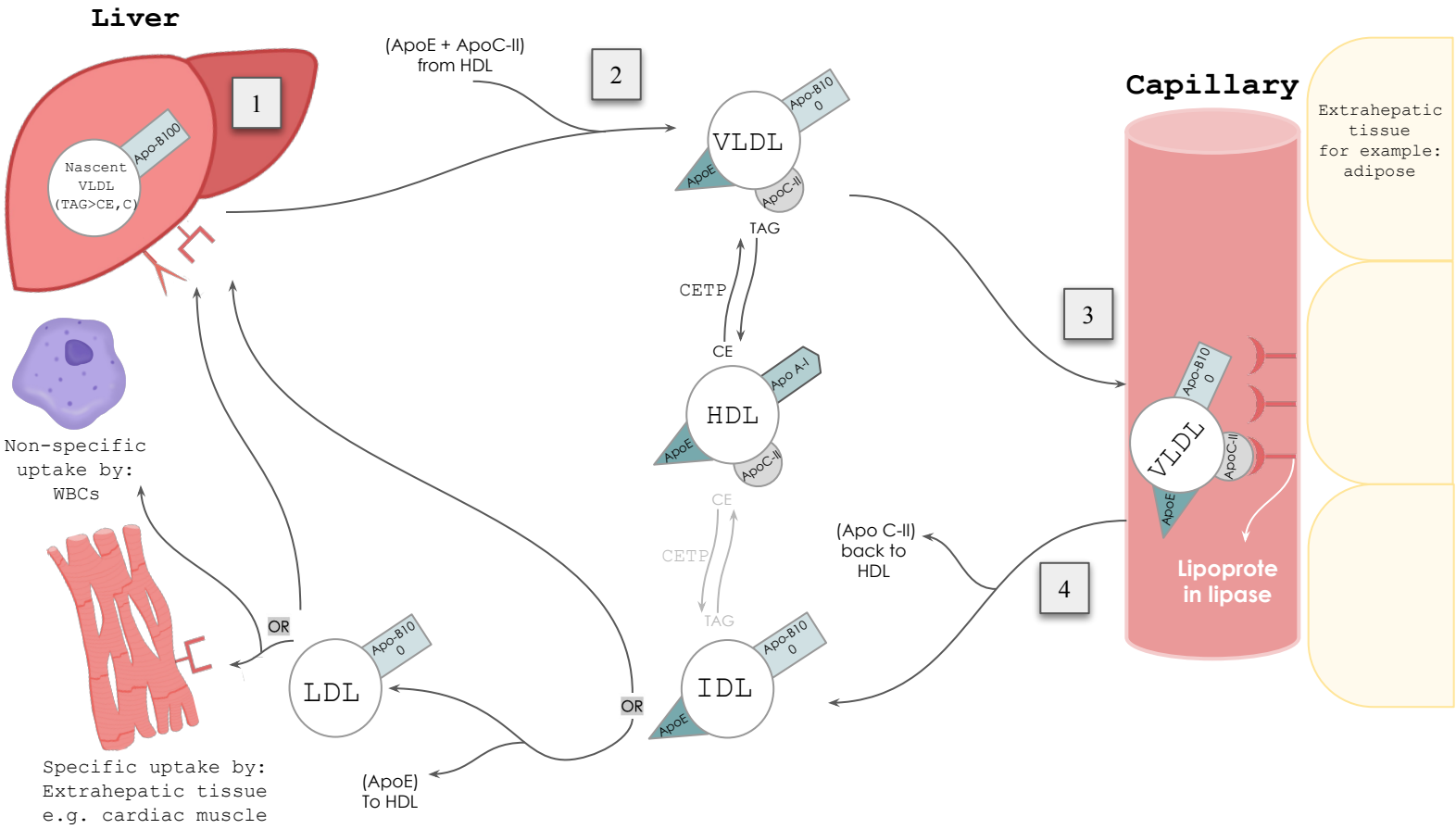


1 In the **liver**, **VLDL** released **to blood stream** to form LDL, IDL and LDL, How? VLDL is produced in the liver and it is called nascent / immature VLDL. because they are the first form that is produced, and it contains TAGs (triacylglycerol), cholesterol, and **Apo B-100 only**. Then it is released to the bloodstream.

2 Once the nascent VLDLs are released in the blood, they obtain **Apo C-II** and **Apo E** from circulating HDL particles (Apo C-II is required for activation of enzyme **Endothelial Lipoprotein Lipase**).

- After the acquisition of these two apolipoprotein, it is now considered as mature VLDL which has all of the three apolipoproteins (Apo B-100, Apo C-II, and Apo E).
- Meanwhile, some VLDL transfer TAGs (triacylglycerol) to HDL in exchange for cholesteryl esters(CE) . This exchange is catalyzed by cholesteryl ester transfer protein (**CETP**).

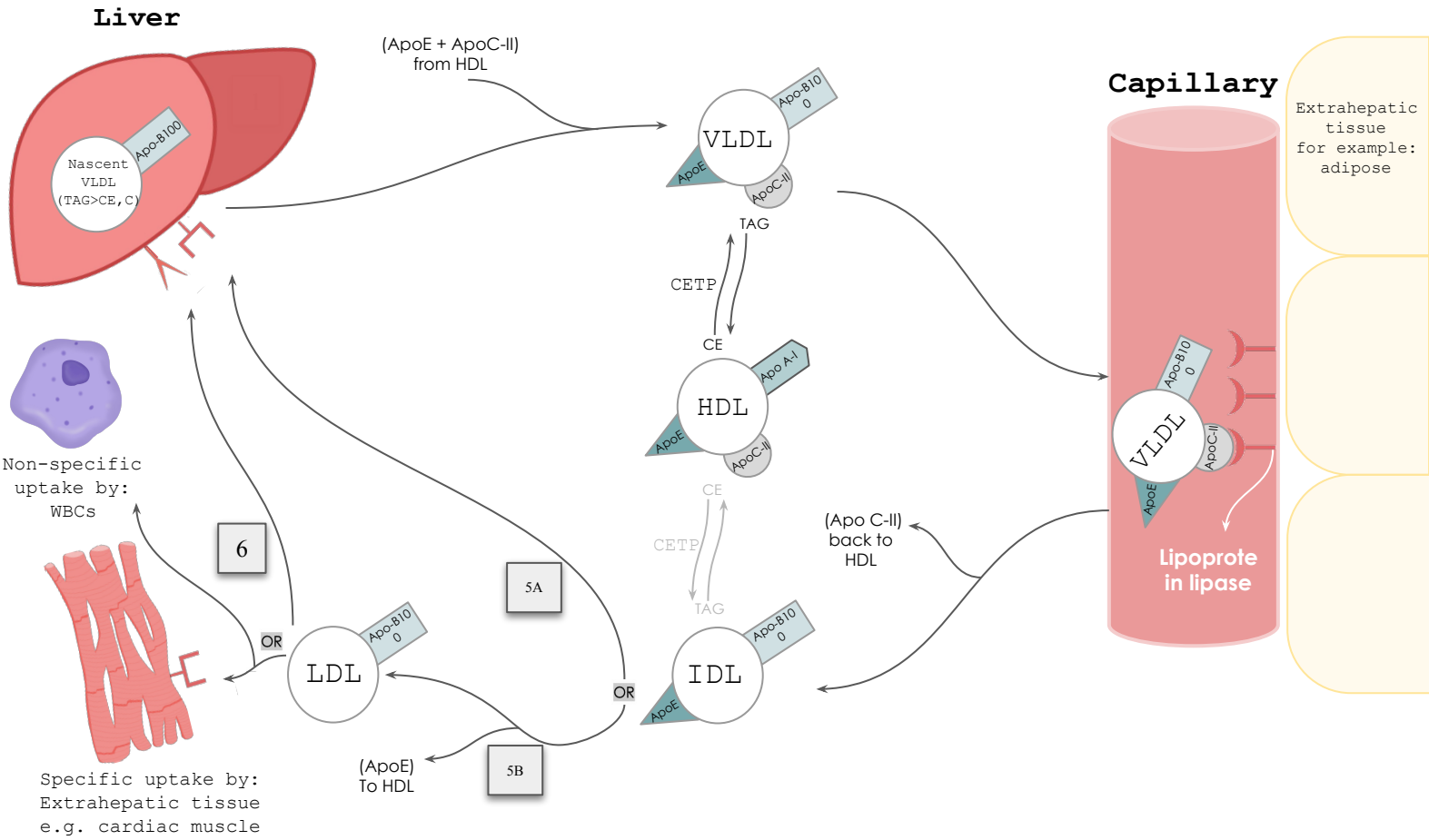
3 Now our mature VLDL can start distributing TAGs to extrahepatic tissues (e.g. adipocytes). The enzyme **Endothelial Lipoprotein lipase** (**LPL**) which is found on the wall of capillaries will be **activated by Apo C-II** and it will start the degradation of TAGs into three fatty acids (to enter the liver as an energy source)+ glycerol. As a result, VLDL molecule will become smaller (IDL).

4 Denser Surface components such as **Apo C-II is released** and returned back to HDL. (the original place it came from).

◀ Lipoprotein Endogenous Pathway *(cont.)*:

IMP to know the enzymes and their functions

original pic



- Now, the molecule is called **IDL** (intermediate density lipoprotein) also called **VLDL remnant**, with **Apo B-100** and **Apo E** only. In Chylomicron remnant we have Apo **B-48** and Apo E

- **However there are two fates of IDL now:**

  5A Some of these IDLs will go to to the liver, and **Apo E** will interact with the remanent receptors to induce **endocytosis** of the molecule. **The end for this path!**

  OR

  5B The left majority will remain in circulation, where they will get rid of **Apo E** and give it back to HDL, After that, they will continue and undergo further triglyceride hydrolysis by enzyme called **hepatic lipase** to become LDL. (hepatic lipase will cleave TAGs so it will lose some density and become low density lipoprotein) and **then proceed to step 6!**

- **Lastly:**

6 **After step 5B:** LDL will use its **Apo B-100** to bind to specific receptors either on extrahepatic tissue "peripheral tissue" (main way) by two means: specific receptor uptake (by muscles such as the cardiac muscle (drawn by the amazing Manal Altwaim♡)) and non-specific uptake (by WBCs) OR on the liver to be finally endocytosed.

- Remember that metabolism of chylomicrons is the same, except that it is produced by intestinal mucosal cells, and that chylomicrons has Apo B-48 instead of Apo B-100 in case of VLDL.
- Note that cardiac muscle prefers fatty acids and ketones as a fuel, and that is due to the fact that unlike skeletal muscle, it does not store glucose as glycogen, So it's glucose consumption is way less than skeletal muscle

Introduction *(cont.)*

◀ Reverse cholesterol transport (HDL):

IMP to know the enzymes and their functions

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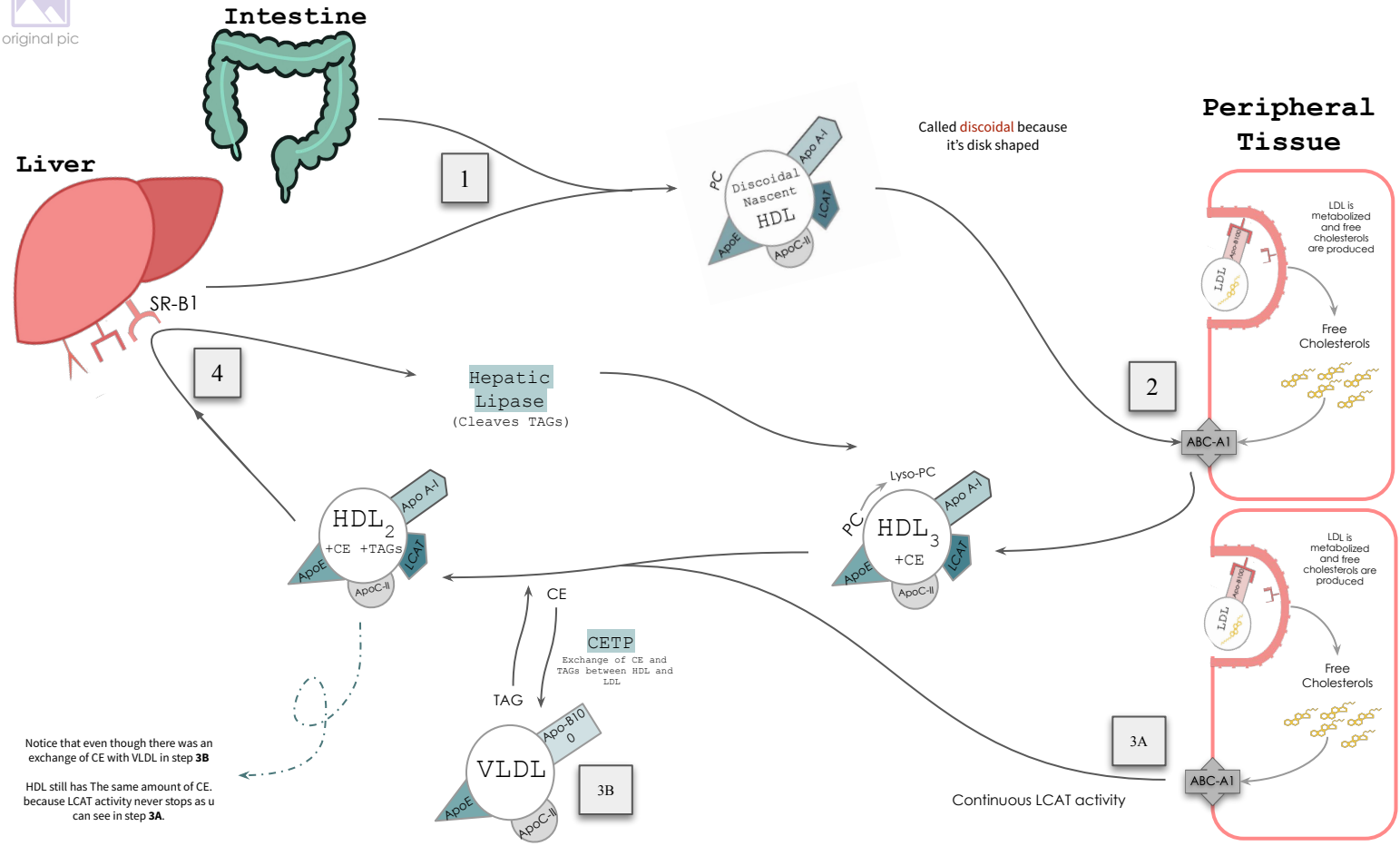


1 Nascent HDL is synthesized in the liver and intestine, then it goes through the circulation to the peripheral tissues to **carry fat and cholesterol from blood vessels (Periphery) to the liver**. with a disk shape (that's why it's called discoidal).

2 Cholesteryl esters are obtained from peripheral tissues and the nascent HDL will become → HDL_3

- The **Cholesterol is released** from the tissue to circulation via a transporter enzyme called **ABC-A1**.
- Because Nascent HDL shell contains too many phospholipids, it will grab this free cholesterol and it will stick to the shell
- In order for us to get this cholesterol in the core of the HDL molecule, we need to convert it to cholesteryl esters first.
- **PC** (Phosphatidylcholine, [Aka. lecithin], which is the phospholipid present in the shell of HDL) will be converted into **Lyso-PC** (Lyso-Phosphatidylcholine, [Aka. lyso-lecithin]) How? **by losing a fatty acid**. (we will need this fatty acid in the next step).
- **Now, Apo A1** will activate **LCAT** enzyme (Lecithin–cholesterol acyltransferase), which will then catalyze the addition of the fatty acid (that was taken from PC) to the free cholesterol on the shell and **transform it into → Cholesteryl ester (CE)** and get it inside the HDL! Now, **nascent HDL became HDL_3.** This mechanism allows more cholesterol intake by keeping a sufficient gradient.

3 HDL_3 (with only CE) will become → HDL_2 (more CE + some TAGs) by:

3A Further addition of cholesteryl esters by **LCAT**. (just as in step 2)

3B Addition of TAGs from VLDL will convert it to HDL_2.

(as we discussed in previous page, there is exchange of TAGs and CEs between VLDL and HDL. This exchange is mediated by CETP enzyme).

4 Finally, HDL_2 goes to the liver and binds there via the **SR-B1 receptor** (scavenger receptor) to unload the cholesterol it collected.

Then, **Hepatic lipase** will act on it, cleaving the TAGs that it got from the VLDL, and converting it back to HDL_3.

- Reversed cholesterol will be converted into colic acid in the liver which will be utilized to form bile acids.

(HDL_3 will then take up free cholesterols in the same way again, take TAGs from VLDL, and unload again via SR-B1 and Hepatic lipase. **The cycle continues over and over again…**)

★ There are two forms of HDL: **Mature HDL** (Already contains cholesterol) and **Nascent HDL** (Empty of cholesterol, carries nothing). So, if you want to inject HDL, **you inject nascent HDL NOT** mature HDL because mature HDL is already saturated with cholesterol)

- In the blood vessels there are crazy macrophages that when they meat **Nascent HDL,** macrophages will give the cholesterol to the **Nascent HDL**

Hyperlipidemia

◀ Dietary sources of cholesterol

Type of fat	Main source	Effect on cholesterol levels
Monounsaturated (the best type)	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 (the worst type)	Most margarines; vegetable shortening; partially hydrogenated vegetable oil; deep-fried chips; many fast foods; most commercial baked goods	Raises LDL

◀ Frederickson classification of inherited hyperlipoproteinemias:

Skipped by the dr " i hated it when i was young so i won't give it to you"

Type		Lipoprotein(s) elevated	Plasma Cholesterol	Plasma TAGs	Relative Frequency
Type I: Familial hyperchylomicronemia		Chylomicron	Normal to mildly ↑	Massively ↑↑↑↑ can be > 2000 mg/dl	<1%
Type II	**IIa:** Familial hypercholesterolemia	LDL	- Homozygotes: >600 mg/dl - Heterozygotes: > 250 mg/dl	Normal	10%
	IIb: Familial combined hyperlipidemia	LDL and VLDL	Massively ↑↑	↑↑	40%
Type III: Familial dysbetalipoproteinemia (remnant hyperlipoproteinemia)		IDL	↑↑	↑↑↑	<1%
Type IV: Familial hypertriglyceridemia		VLDL	Normal to mildly ↑	Massively ↑↑	45%
Type V: Mixed hyperlipidemia		VLDL and Chylomicron	↑ to ↑↑	Massively ↑↑↑↑	5%

◀ Frederickson classification of inherited hyperlipoproteinemias *(cont.)*:

Type		Pathogenesis	Atherogenicity	Treatment
Type I: Familial hyperchylomicronemia		- Deficiency of lipoprotein lipase or apolipoprotein C-II	- Pancreatitis	Diet control
Type II	**IIa:** Familial hypercholesterolemia	- Defective LDL receptors or ApoB-100, missing LDL receptors	+++	Bile acid sequestrants, Statins, Niacin
	IIb: Familial combined hyperlipidemia		+++	Statins, Niacin, Fibrates
Type III: Familial dysbetalipoproteinemia (remnant hyperlipoproteinemia)		- Defective ApoE	+++	Fibrates
Type IV: Familial hypertriglyceridemia		- Hepatic overproduction of VLDL or defective ApoA-V	+	Niacin, Fibrates
Type V: Mixed hyperlipidemia		- Defective ApoA5	+	Niacin, Fibrates

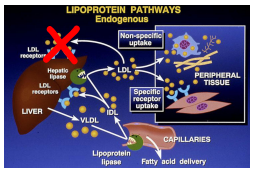
◀ Hyperlipidemia:

	Conditions/Causes
Primary Hyperlipidemia (Hereditary)	• Hypertriglyceridemia (Disorders of VLDL and Chylomicrons) • Hypercholesterolemia (Disorders of LDL) • Disorders of HDL • Combined hyperlipidemia (Hypercholesterolemia and Hypertriglyceridemia
Secondary Hyperlipidemia (Acquired)	• Diet (most common) • Hypothyroidism • Nephrotic syndrome • Anorexia nervosa • Obstructive liver disease • Obesity • Diabetes mellitus • Pregnancy • Acute hepatitis • Systemic lupus erythematosus • AIDS (protease inhibitors)

Hyperlipidemia *(cont.)*

◀ Hereditary causes of hyperlipidemia :

Type IIa: Familial Hypercholesterolemia



- **Pathogenesis: Mutation in LDL receptor** (normally take up LDL from blood stream),resulting in elevated levels of LDL at birth and throughout life (LDL Level > 190 mg/dl)

1. **Heterozygous:**
   - Co-dominant genetic disorder, cooccurs in heterozygous form. needs only one allele
   - It's common, occurs in 1 in 500 individuals
2. **Homozygous:**
   - **Total absence** of LDL receptors
   - Death from ischaemic heart disease in late childhood or adolescence.
   - Repeated plasmapheresis has been used to remove LDL cholesterol. But Liver transplantation is the 'cure'.
   - Very rare 1%

- **Clinical manifestations:**
  - High risk for atherosclerosis (Premature atherosclerosis)
  - Tendon xanthomas (75% of patients) especially in the extensors of the fingers + achilles tendon and Tuberous xanthomas  
  - Xanthelasmas of eyes 
  - Arcus senilis (Corneal arcus): deposits of lipids around the corneal margin (In younger ppl, it's called arcus juvenilis) 
- **Diagnosis:** By finding **raised cholesterol** (Homozygotes: >600 mg/dl, Heterozygotes: > 250 mg/dl)
- **Treatment:**
  - Individuals often require treatment with **diet** and more than one cholesterol-lowering drug (statins are the first line).
  - The cholesterol absorption inhibitor **ezetimibe** is a logical addition to a statin (if treatment goals are not met).
  - Bile acid sequestrants (Colesevelam) are an alternative to ezetimibe (If goals are still not reached), but there are problems with tolerability.
  - Concurrent therapy with **statins and fibrates**, particularly **fenofibrate**, can be used in severe cases.

Type IIb: Familial Combined Hyperlipidemia

- **About:** it's autosomal dominant, its prevalence: 1/50 – 1/100 dominant (15% of MIs <60)
- **Diagnosis**: by finding **raised cholesterol AND triglyceride** concentrations in association with a typical family history. There are no typical physical signs. and there is increased secretions of VLDLs
- **Pathogenesis:** Genetic defect is unknown ⟶ high Apo B-100
- **Clinical manifestations:**
  - Premature CAD
  - TC: 6.5 -13 mM
  - TAG: 2.8 – 8.5 mM.
- **Treatment:** is the same for all varieties of combined hyperlipidaemia.
  - For any given cholesterol concentration the hypertriglyceridemia found in the combined hyperlipidemia **increases the cardiovascular risk considerably**.
  - **Treatment aim:** reducing serum cholesterol below 4.0 mmol/L and triglycerides below 2.0 mmol/L.
  - Therapy is with **diet**
  - Add drugs if an adequate response has not occurred:
    - **Fibrates** are the treatment of choice since these reduce both cholesterol and triglyceride concentrations, and also have the benefit of raising cardioprotective HDL concentrations. Combination with other agents is often needed

Hyperlipidemia *(cont.)*

◀ Hereditary causes of hyperlipidemia *(cont.)*:

Type III: Dysbetalipoproteinemia

- **About:** Rare cause of combined hyperlipidemia and it's autosomal recessive but rarely can be dominant, affects 1 in 10,000 (1/5000)
- **Pathogenesis:** Almost always due to the inheritance of a variant of the apoprotein E allele. Results in apo E2, a binding-defective form of ApoE (which usually plays important role in metabolism of chylomicron and VLDL ⟶ High VLDL and chylomicrons)
    - It is due to accumulation of LDL remnant particles
- Increased risk for atherosclerosis, peripheral vascular disease
- **Clinical manifestations:**
    - Increased risk for atherosclerosis (Premature CAD or Premature atherosclerosis)
    - Increased risk for peripheral vascular disease
    - TC: 6.5 -13 mM
    - TAG: 2.8 – 5.6 mM
    - Tuberous xanthomas: typically over the knees and elbows
    - Xanthomas in the palmar creases (diagnostic)
    - Striae palmaris

◀ other causes of hyperlipidemia :

Disorders of HDL

Very low HDL, low total cholesterol.
Tangier disease:

- **About:** autosomal recessive disorder characterized by a low HDL cholesterol concentration.
- **Pathogenesis:** due to mutation in ABC1 which normally promotes cholesterol uptake from cells by HDL particles.
- **Clinical manifestations:**
    - Cholesterol accumulates in reticuloendothelial tissue and arteries causing enlarged orange-coloured tonsils and hepatosplenomegaly.
    - Cardiovascular disease
    - Corneal opacities
    - Polyneuropathy.

Hyperlipidemia *(cont.)*

◀ Primary hypercholesterolemia :

High **TGs** causes **pancreatitis**
High **Cholesterol** causes **atherosclerosis**

Disorder	Genetic defect	inheritance	Prevalence	Clinical features
★ **Familial hypercholesterolemia** **Dr: Most common in MCQ**	**LDL receptor**	**Dominant**	**heterozygous:** 1/500 (5% of MIs<60 yr) **homozygous:** 1/1 million[1]	• **Heterozygous:** Premature CAD (ages 30-50) TC:7-13 mM • **Homozygous:** CAD (before age 18) TC>13 mM
Familial defective apo B-100 (Combined hyperlipidemia)	apo B-100[2]	dominant	1/700	(same as heterozygous familial hypercholesterolemia) • Premature CAD • TC: 7-13 mM
Familial alphalipoproteinemia	unknown	Variable	common (10% of MIs<60yrs)	• Abdominal cramps • Pancreatitis • Retinal vein thrombosis • TAG: 2.3-6 mM
Familial hyperalphalipoproteinemia	unknown	Variable	Rare	• Less CHD • longer life • Elevated HDL

◀ Primary hypertriglyceridemia :

Disorder	Genetic defect	inheritance	Prevalence	Clinical features
LPL (lipoprotein lipase) deficiency[3]	**Endothelial LPL**	**Recessive**	Rare (1/1 million)	• Hepatosplenomegaly • Abdominal cramps • **Pancreatitis at young age** • TAG: > 8.5 mM
Apo C-II deficiency[4]	**Apo C-II** (the only cofactor that helps LPL to work)			• Abdominal cramps • Pancreatitis • TAG: > 8.5 mM
Familial hypertriglyceridemia	Unknown enhanced hepatic TAG-production	Dominant	1/100	• Abdominal cramps • Pancreatitis • Retinal vein thrombosis • TAG: 2.3-6 mM

1: No LDL receptor, cause massive MI, scenario is usually a young (30s) family member who died of MI.
2: Mutations in the apoprotein B-100 gene: LDL particles bind to their receptor in the liver through apoprotein B-100, defect in it results in high LDL concentration, its clinical picture resembles heterozygous familial hypercholesterolaemia. Treatment approach is the same.
3: Result in very high level of chylomicron and VLDL= ↑**TAGs**
4: Lipoprotein lipase deficiency and apoprotein C-II deficiency: rare diseases produce greatly elevated triglyceride concentrations due to the persistence of chylomicrons (not VLDL particles). Patients present in childhood with eruptive xanthomas, lipaemia retinalis and retinal vein thrombosis, pancreatitis and hepatosplenomegaly.
5- This occurs because when the pancreas cells counter the high concentration of triglycerides, they release the enzyme lipase. Lipase breaks triglycerides into free fatty acids. Too many free fatty acids can be toxic to the pancreatic cells, leading to acute pancreatitis

Hyperlipidemia *(cont.)*

◀ Secondary hyperlipidemias

Disorder	VLDL	LDL	HDL	Mechanism
Secondary hypercholesterolemia "TC: >150 mg/dl"				
Hypothyroidism[3]	↑	↑↑↑	↓	LDL-rec.↓, LPL ↓
Anorexia nervosa	-	↑↑	-	bile secretion ↓, LDL catab. ↓
Nephrotic syndrome	↑↑	↑↑↑	↓	Apo B-100 ↑ LPL ↓ LDL-rec. ↓
Pregnancy **Everything** will increase	↑↑	↑↑	↑	oestrogen ↑ VLDL production ↑, LPL ↓
Biliary obstruction PBC	-	-	↓	Lp-X ↑↑ no CAD; xanthomas
Other causes	• **Drugs:** Diuretics,Ciclosporin, Glucocorticoids, Androgens, ART agents (protease inhibitors).			
Secondary hypertriglyceridaemia "TAG: >150 mg/dl"				
Diabetes mellitus[1]	↑↑↑	↑	↓	VLDL production ↑, LPL ↓, altered LDL[2]
Obesity	↑↑	↑	↓	VLDL production ↑
Uremia, dialysis	↑↑↑	-	↓	LPL ↓, HTGL ↓ (inhibitors ↑)
Alcohol	↑↑↑ **chylomicron.** Risk of pancreatitis	-	↑	dep. on dose, diet, genetics
Other causes	• Hepatocellular disease (Acute hepatitis), SLE and diet. • **Drugs:** B-blockers, Retinoids, Glucocorticoids, ART agents (protease inhibitors).			

◀ When to check lipid panel?

Different Recommendations:

1. **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
2. **United state preventive services task force:**

- **Women ≥ 45** years
- **Men ≥ 35** years

undergo screening with a **total** and **HDL** cholesterol **every 5 years.**

If total **cholesterol > 200** or **HDL< 40** → a fasting panel should be obtained

Cholesterol screening should begin **at 20 years in patients with a history** of:

- Multiple cardiovascular risk factors
- Diabetes
- Family history of:
  - Elevated cholesterol levels
  - Premature cardiovascular disease.

1: most important and most common
2: very bad combination.
3: affect hepatic lipase

◀ Treatment of hyperlipidemia

Click here for a drugs summary table

1. Lifestyle modification, Low-cholesterol diet, Exercise, Alcohol and Smoking cessation
2. Medication

➔ **Goal of treatment[1]:**

LDL: To **prevent coronary heart disease outcomes** (myocardial infarction and coronary death)

Non LDL (Total Cholesterol/HDL)[2]: To prevent coronary heart disease outcomes (myocardial infarction and coronary death)

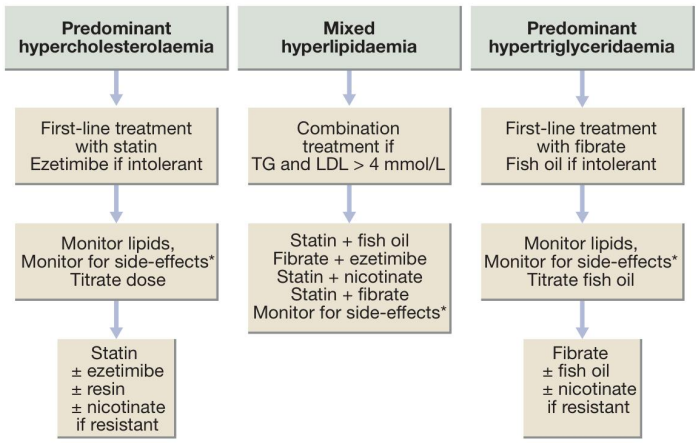
Triglyceride: To **prevent pancreatitis** and may be coronary heart disease outcomes (myocardial infarction and coronary death)

Drug class	Agents[3]	Effects (% change)	Side Effects
HMG CoA reductase inhibitors*	**Statins**	**↓LDL (18-55), ↑HDL (5-15) Triglycerides (7-30)**	• **Myopathy (High CK level)** • **increased liver enzymes**
Fibric Acids[4]	**Gemfibrozil Fenofibrate**	**↓LDL (5-20), ↑HDL (10-20) ↓Triglyceride (20-50)**	• **Dyspepsia** • **Gallstones** • **Myopathy**
Cholesterol absorption inhibitor	**Ezetimibe[5]**	**↓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**
Bile Acid sequestrants	**Cholestyramine**	**↓LDL, ↑HDL No change in triglycerides**	• **GI distress** • **Constipation** • **Decreased absorption of other drugs**
PCSK9 inhibitors[6]	**Evolocumab Alirocumab**	**↓LDL (50-60%)**	• **Injection-site reactions** • **Muscle pain** • **Neurocognitive adverse events → include memory impairment and confusion**

1: normal range of lipoproteins depend on pt plus his medical condition.
2: all lipoproteins except HDL
3: most used classes are: statins, ezetimibe and PCSK9
4: stimulate peroxisome proliferator-activated receptor (PPAR) alpha, which controls the expression of gene products that mediate the metabolism of TAG and HDL (work mainly on TAGs). As a result, it will decrease synthesis of fatty acids, TAG and VLDL, while increase lipoprotein lipase, which catabolises TAG. In addition, production of Apo A1 and ABC A1 is up-regulated, leading to increased HDL. usually well tolerated but share a similar side-effect profile to statins (discussed in the next slide). In addition, they may increase the risk of cholelithiasis and prolong the action of anticoagulants.
5. If statin doesn't work or the patient can't tolerate it we can use it. The problem is that there's no tablet form. Ezetimibe + statins for synergistic effect
6: Monoclonal antibodies that neutralise PCSK9, an enzyme that degrades the LDLR. This causes levels of LDLR to increase, which markedly reduces LDL-C. administered by subcutaneous injection every 2–4 weeks, well tolerated and highly effective. **Treats Hypercholesterolemia**

Hyperlipidemia: treatment *(cont.)*

◀ Flow chart for the drug treatment of hyperlipidemia



◀ Statin therapy

- **MOA:** Reduce cholesterol synthesis by **inhibiting the HMG CoA reductase enzyme** leading to decreased concentration of cholesterol within the cell**. Low** levels of intracellular cholesterol → **up-regulates** production of the **LDL receptor** on the cell → increases the number of LDL receptors promotes the clearance of LDL from the blood and its precursor.
  - Inhibition of cholesterol synthesis → Low intracellular cholesterol → decrease the secretion of VLDL to the bloodstream
- Generally well tolerated and serious side-effects are rare.
  - Liver function test abnormalities and muscle problems, such as myalgia, asymptomatic increase in creatine kinase (CK), myositis and, infrequently, rhabdomyolysis, are the most common.
- **Atorvastatin** and particularly **rosuvastatin** have the **most potent cholesterol-lowering effects**
- There is clear evidence of **protection against total and coronary mortality**, stroke and cardiovascular events across the spectrum of cardiovascular disease risk.
- The same drug can be low, moderate and high density depending on the does

Low intercity statin therapy	Moderate intensity statin therapy	High intercity statin therapy
Daily dose lowers LDL-C, on average **by <30%** - Simvastatin 10 mg - Pravastatin 10–20 mg - Lovastatin 20 mg - Fluvastatin 20–40 mg - Pitavastatin 1 mg	Daily dose lowers LDL-C, on average, by approximately **30% to <50%** - 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	Daily dose lowers LDL-C, on average by approximately **≥50%** - Atorvastatin (40†)–80 mg - Rosuvastatin 20 (40) mg

Hyperlipidemia: treatment *(cont.)*

◀ ASCVD prevention ★ Very Important

Dr: I like to put questions on this part and the numbers will be clear

Stepwise approach:

1) The first question you ask yourself: **does the patient have clinical cardiovascular disease?** (= always treat)

- **if Yes**, what is his age?
  - **Age ≤75 = HIGH-Intensity statins.**
  - **Age >75 = Moderate-Intensity statins.**

2) If the patient has **NO** clinical cardiovascular disease, **is the level of LDL ≥ 190?** (High even for healthy individuals)

- Yes? Give **HIGH-Intensity statins**. Regardless of the age.

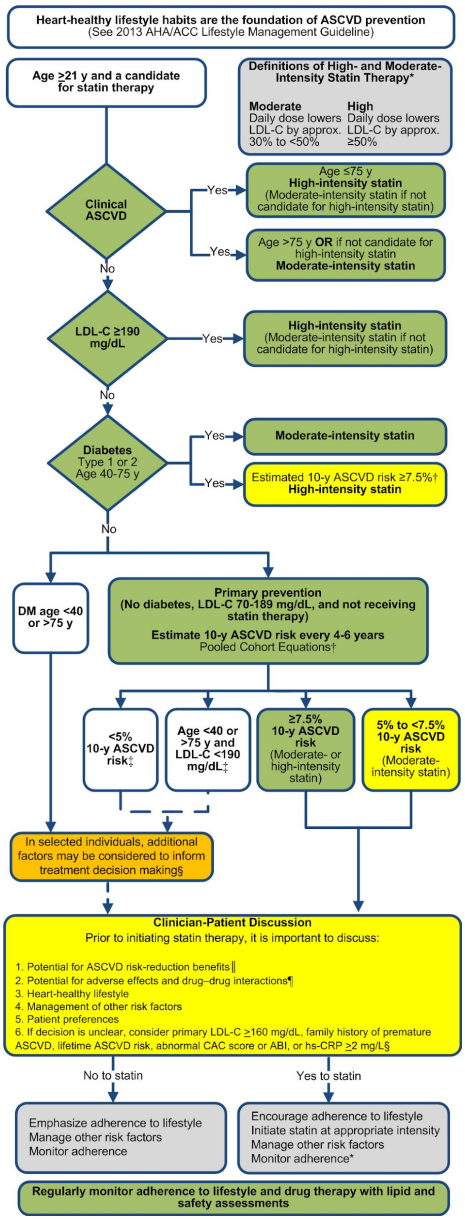
3) If the patient has **NO** clinical cardiovascular disease and the LDL level is **NOT ≥ 190,** the next question is: **does this patient have diabetes?** "Any type of diabetes whether it's type 1 or type 2"

- **if yes,** what is his age <40 or >40?
  - **if the Age is <40** and has **no** IHD **nor** its risk factors = **NO NEED** for treatment
  - **if the Age is <40** and has **no** IHD **but has** its risk factors = **Moderate or high intensity statins**
  - **if the Age is <40** and **has IHD** = **HIGH-Intensity statins.**
  - **if the Age is >40** = Start statins.

4) If the patient has **NO** clinical cardiovascular disease and the LDL level is **NOT ≥ 190 and has NO** diabetes. you calculate the 10-y ASCVD risk.

- **<5% =** No need for treatment
- **5% to <7.5% =** Moderate-intensity statins
- **≥ 7.5 =** Moderate or high intensity statins

- Depending on the risk factors the patient will receive the treatment. E.g. Patient A: has a family history of hyperlipidemia, hypertension and is a smoker. His LDL = 100. Patient B: Doesn't have any risk factors and his LDL = 180. Patient A will take statin and patient B won't (even though he has higher LDL)



◀ Parameters used to estimate 10-year risk for ASCVD:

1. **Age**
2. **SBP/DBP**
3. **Total cholesterol**
4. **HDL**
5. **LDL**
6. **Diabete malitus**
7. **Smoking**
8. **On Anti HTN**
9. **On Statin**
10. **On Aspirin**

scan me

Hyperlipidemia: treatment *(cont.)*

◀ Guideline of therapy

Patient	Risk Factors	Statin Intensity*
>29 Age	ASCVD[1]	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[2]	None
	ASCVD risk factor(s)	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ACS and LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS and LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe

1: any pt with cvd risk it's recommended to use high intensity statin
2: the only condition where diabetic pt won't take statin is if the pt is <40 years old and has no risk factors

Hyperlipidemia: treatment *(cont.)*

◀ Treating Hypertriglyceridemia: ★

- **TAG = <2 mmol/L (<36 mg/dl):**
  - No risk for anything, no treatment required.
    - Just advice lifestyle modification and reassess lipid profile regularly, to ensure that (LDL-C) is at target
- **TAG = ≥2 to <5 mmol/L (≥36 to <90 mg/dl):**
  - At this level, the goal is to **prevent CVS complications**. "CVS protection".
    - Consider pharmacological treatments (**Use statins, You can add omega-3 also** and you can use niacin)
    - lifestyle modifications, control and manage other risk factors.
- **TAG = ≥5 to <10 mmol/L (≥90 to 180 mg/dl):**
  - At this level, the goal is **to prevent pancreatitis**, need something stronger than statins.
    - **Use fibrate therapy** (Bezafibrate, Fenofibrate or Gemfibrozil). in this case fibrate is enough unless the patient has CVD risk we use both.
    - (LDL-C) can't be estimated when TAGs > 5 mmol/L (> 90 mg/dl) so Apo B determination maybe helpful in this case
- **TAG = ≥10 mmol/L (≥180 mg/dl):**
  - **Use fibrate therapy** and monitor serum creatinine
  - Presented with acute pancreatitis:
    - Very low fat diet (10%-15% of energy intake)
    - Cessation of alcohol
    - Insulin, if indicated for glycemic control
    - Admit the patient to the hospital
  - Consider specialist referral

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	

Note: [] = concentration, LDL = low-density lipoprotein, LDL-C = low-density lipoprotein-cholesterol, IV = intravenous.
*For re-evaluation of lipid profile.

Summary

Primary hyperlipidemia	
Primary hypercholesterolemia	- Familial hypercholesterolemia : LDL receptor mutation -> Elevated LDL + Family history of premature CVD death
	- High risk for atherosclerosis, tendon xanthomas, tuberous xanthomas and xanthelasmas of eyes.
Primary hypertriglyceridemia	• LPL deficiency • Familial hypertriglyceridemia: enhanced hepatic TAG-production • Apo-CII deficiency (**All can lead to pancreatitis**)
Secondary hyperlipidemia	
Diabetes Mellitus	VLDL increased production
Obesity	VLDL increased production
Hypothyroidism	Mainly LDL increased production
Anorexia	Increased LDL ONLY
Aims of dyslipidemia treatment (first, life style modification)	
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- Life style 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.

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

Lecture Quiz

Q1: 40 year old gentleman presented to you after doing lipid profile after an advice by his cardiologist. His brother died 3 months ago after a massive myocardial infarction (MI) at age of 32. His BP: 118/72, BMI: 27, LDL-Cholesterol: 305 mg/dl (8mmol/l), HDL-Cholesterol: 45 mg/dl (1.2mmol/l), Triglyceride: 144 mg/dl (1.63mmol/l). Which is the most likely cause of this disorder?

A. Lipoprotein lipase (LPL) deficiency
B. Apo C-11 coenzyme deficiency
C. Familial hypercholesterolemia
D. Nascent HDL deficiency

Q2: 25 years old male, not hypertensive and does not have DM and not a smoker. his brother dies from a cardiovascular disease at age 32.His lipid profile is: LDL: 6.1 mmol/L (=~196), HDL 0.1 and a 10 y risk of AVCAD .0,1%. What is the best management for him?

A. high sustained statin therapy.
B. low sustained statin therapy.
C. moderate sustained statin therapy.
D. don't give him anything.

Q3: 32 years old female presented to you after a routine blood work done for the new employment application. Her BP: 118/72, BMI: 27, LDL-Cholesterol:105 mg/dl (2.7mmol/l), Triglyceride:1444 mg/dl (16.3mmol/l). Which one of the following is your best treatment option to prevent pancreatitis?

A. Nicotinic acid
B. High intensity statin therapy
C. Low intensity statin therapy
D. Fenofibrate

Q4: Which one of the following found to be an important protective factor against coronary artery disease?

A. Low triglyceride level
B. High LDL-Cholesterol
C. High HDL-Cholesterol
D. Low VLDL-Cholesterol

Q5: Which of the following is the most common adverse effect of statin medications?

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

Answers: Q1:C | Q2:A | Q3:D | Q4:C | Q5:A

GOOD LUCK !

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