Hyperlipidemia

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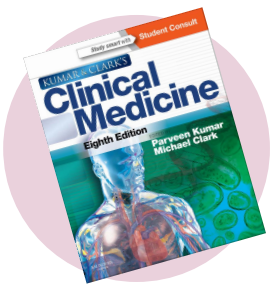
Objectives:

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

References:
Slides - Black
Doctor's notes - Red
Step up / davidson - Blue
Extra explanation - Grey

Optional:

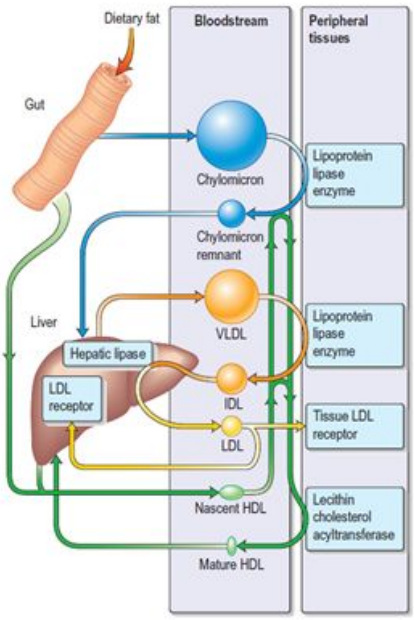


From p1032 to p1038

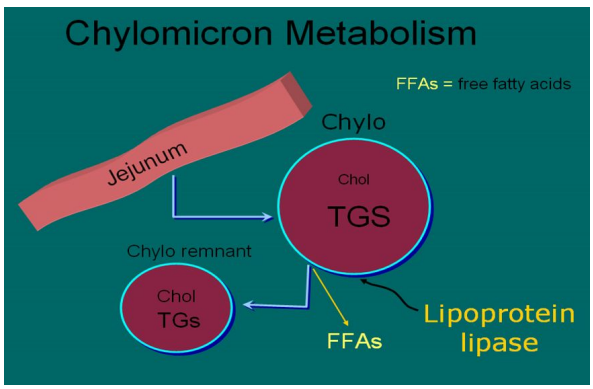
Editing file

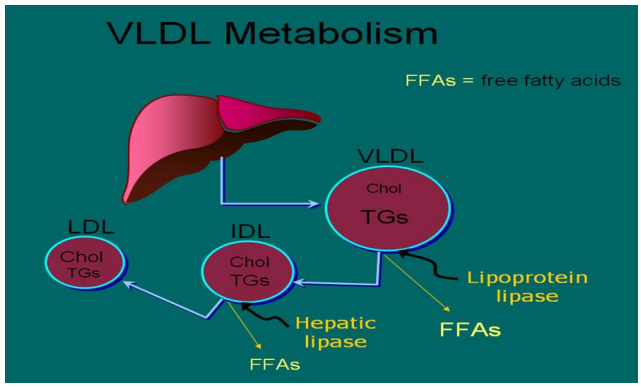
❖ Lipid physiology:

Lipids are insoluble in water, and are transported in the bloodstream as macromolecular complexes. In these complexes, lipids (principally triglyceride, cholesterol and cholesterol esters) are surrounded by a stabilizing coat of phospholipid. Proteins (called apoproteins) embedded into the surface of these 'lipoprotein' particles exert a stabilizing function and allow the particles to be recognized by receptors in the liver and the peripheral tissues.



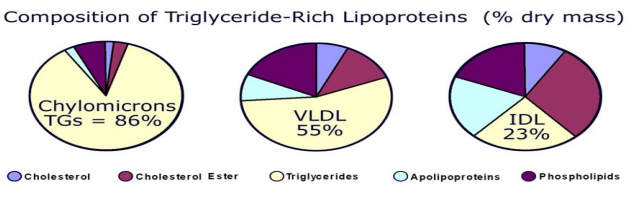
- **Chylomicrons transport fats from the intestinal mucosa to the liver**
- **In the liver, the chylomicrons release triglycerides and some cholesterol and become low-density lipoproteins (LDL).**
- **LDL then carries fat and cholesterol to the body's cells.**
- **High-density lipoproteins (HDL) carry 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 .**

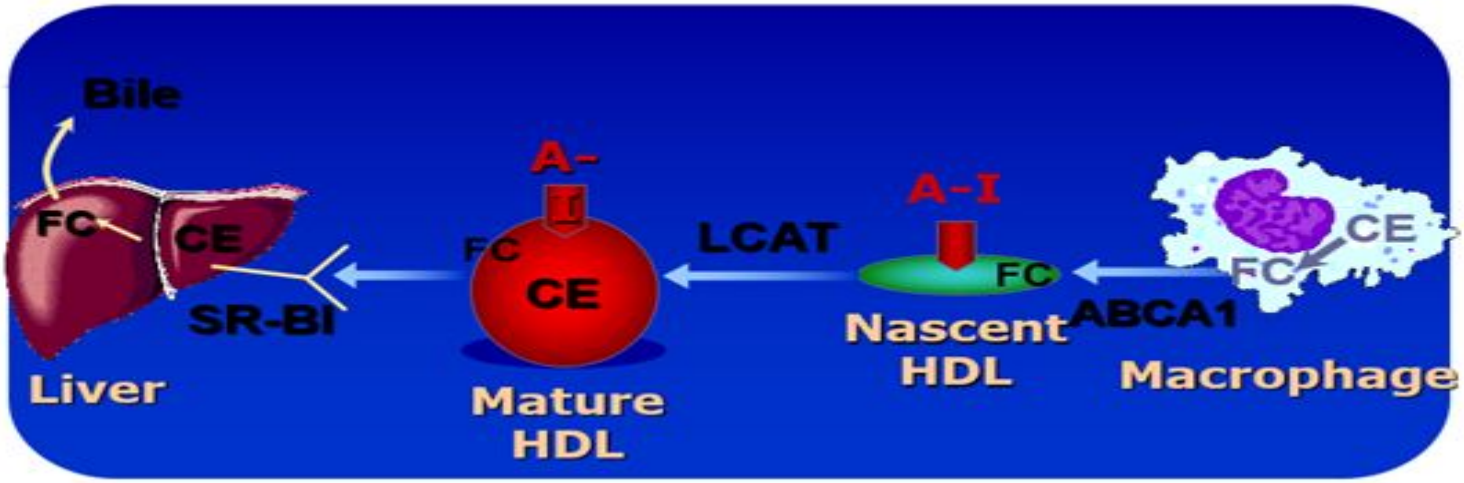




Chylomicrons are synthesized in the small intestine postprandially, passing initially into the intestinal lymphatic drainage, then along the thoracic duct into the bloodstream. They contain triglyceride and a small amount of cholesterol and its ester, and provide the main mechanism for transporting the digestion products of dietary fat to the liver and peripheral tissues.

These are synthesized continuously in the liver and contain most of the body's endogenously synthesized triglyceride and a smaller quantity of cholesterol. They are the body's main source of energy during prolonged fasting. Apoprotein B-100 is an essential component of VLDL.





Nascent HDL particles are produced in both the liver and intestine. They are disc shaped, seemingly inert and contain apoprotein A-I. They are transmuted into mature particles by the acquisition of phospholipids, and the E and C apoproteins from chylomicrons and VLDL particles in the circulation. The more mature HDL particles take up cholesterol from cells in the peripheral tissues aided by cholesterol efflux regulatory protein – a product of the ATP-binding cassette transporter 1 gene (ABC1 gene). As it is taken up , the enzyme lecithin cholesterol acyltransferase (LCAT), activated by the apoprotein A on the particle's surface, esterified the sequestered cholesterol. The HDL particle transports cholesterol away from the periphery and may transfer it indirectly to other particles such as VLDL in the circulation or deliver its cholesterol directly to the liver (reverse cholesterol transport) and steroid-synthetic tissues (ovaries, testes, adrenal cortex).

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	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

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 the worst dietary source	Most margarines; vegetable shortening; partially hydrogenated vegetable oil; deep-fried chips; many fast foods; most commercial baked goods	Raises LDL

Hyperlipidemia

Primary Hyperlipidemia

- Disorders of VLDL and chylomicrons – hypertriglyceridemia alone .
- Disorders of LDL– hypercholesterolaemia alone .
- Disorders of HDL .
- Combined hyperlipidaemia.

Secondary Hyperlipidemia:

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

DM: regulation of the lipoprotein lipase because of the insulin resistance

In anorexia nervosa: there will be a downregulation the LDL receptors because of high LDL

Disorders of VLDL and chylomicrons – hypertriglyceridemia alone:

The majority of cases appear to be due to multiple genes acting together to produce a modest excess of circulating concentration of VLDL particles, such cases being termed polygenic hypertriglyceridemia. In a proportion of cases, there will be a family history of a lipid disorder or its effects (e.g. pancreatitis). Such cases are often classified as familial hypertriglyceridemia. The main clinical feature is a history of attacks of pancreatitis or retinal vein thrombosis in some individuals. The main two types are Lipoprotein lipase deficiency and apoprotein C-II deficiency.

❖ Disorders of LDL – hypercholesterolaemia alone;

Most of the diseases you have to screen for them because it's silent diseases

1. **Heterozygous familial hypercholesterolaemia : is an autosomal dominant monogenic disorder present in 1 in 500 of the normal population.Mutation in LDL receptor, resulting in elevated levels of LDL at birth and throughout life .The genetic defect is the underproduction or malproduction of the LDL cholesterol clearance receptor in the liver. So, liver can not uptake the circulated LDL . approximately 50% of men with the disease will die by the age of 60, most from coronary artery disease, if untreated. affects 30 y/o patients**

2. **Homozygous familial hypercholesterolaemia (severe): is very rare indeed. Affected children have no LDL receptors in the liver. They have a hugely elevated LDL cholesterol concentration , and massive deposition of lipid in arterial walls, the aorta and the skin. The natural history is for death from ischaemic heart disease in late childhood or adolescence. Repeated plasmapheresis has been used to remove LDL cholesterol with some success. Liver transplantation is a 'cure'. affects <18 y/o patients**

the patient will present with massive MI in young age

3. **Mutations in the apoprotein B-100 gene : cause another relatively common single gene disorder. Since LDL particles bind to their clearance receptor in the liver through apoprotein B-100, this defect also results in high LDL concentrations in the blood, and a clinical picture which closely resembles classical heterozygous familial hypercholesterolaemia.The two disorders can be distinguished clearly only by genetic tests.**

4. **Polygenic hypercholesterolaemia is a term used to lump together patients with raised serum cholesterol concentrations, but without one of the monogenic disorders above.**

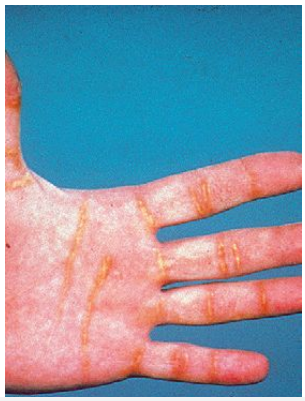
❖ Disorders of HDL (very low HDL, low total cholesterol):

Tangier disease is an autosomal recessive disorder characterized by a low HDL cholesterol concentration. Cholesterol accumulates in reticuloendothelial tissue and arteries causing enlarged orange-coloured tonsils and hepatosplenomegaly. Cardiovascular disease, corneal opacities and a polyneuropathy also occur. It is due to a gene mutation ABC1 gene .

❖ Combined hyperlipidaemia (hypercholesterolaemia and hypertriglyceridemia):

1. **Familial combined hyperlipidaemia: This is relatively common autosomal dominant disease , affecting 1 in 200 of the general population. The genetic basis for the disorder has not yet been characterized. It is diagnosed by finding raised cholesterol and triglyceride mainly VLDLs concentrations in association with a typical family history.t**

2. **Dysbetalipoproteinemia (Remnant hyperlipidaemia) : This is a rare (1 in 5000) cause of combined hyperlipidaemia. It is due to accumulation of LDL remnant particles and is associated with an extremely high risk of cardiovascular disease .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 . It may be suspected in a patient with raised total cholesterol and triglyceride concentrations by finding xanthomas in the palmar creases (diagnostic) and the presence of tuberous xanthomas .**



❖ 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)

Remember:
- **HIgh LDL most likely associated with CVS diseases**
- **High TGA associated with pancreatitis (RISK IF TGA IS more than 5)**

❖ When to check lipid panel:

- **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 a history of multiple cardiovascular risk factors, diabetes, or family history of either elevated cholesterol 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).**

❖ Treatment of Hyperlipidemia:

- Life Style modification:

  Low-cholesterol diet

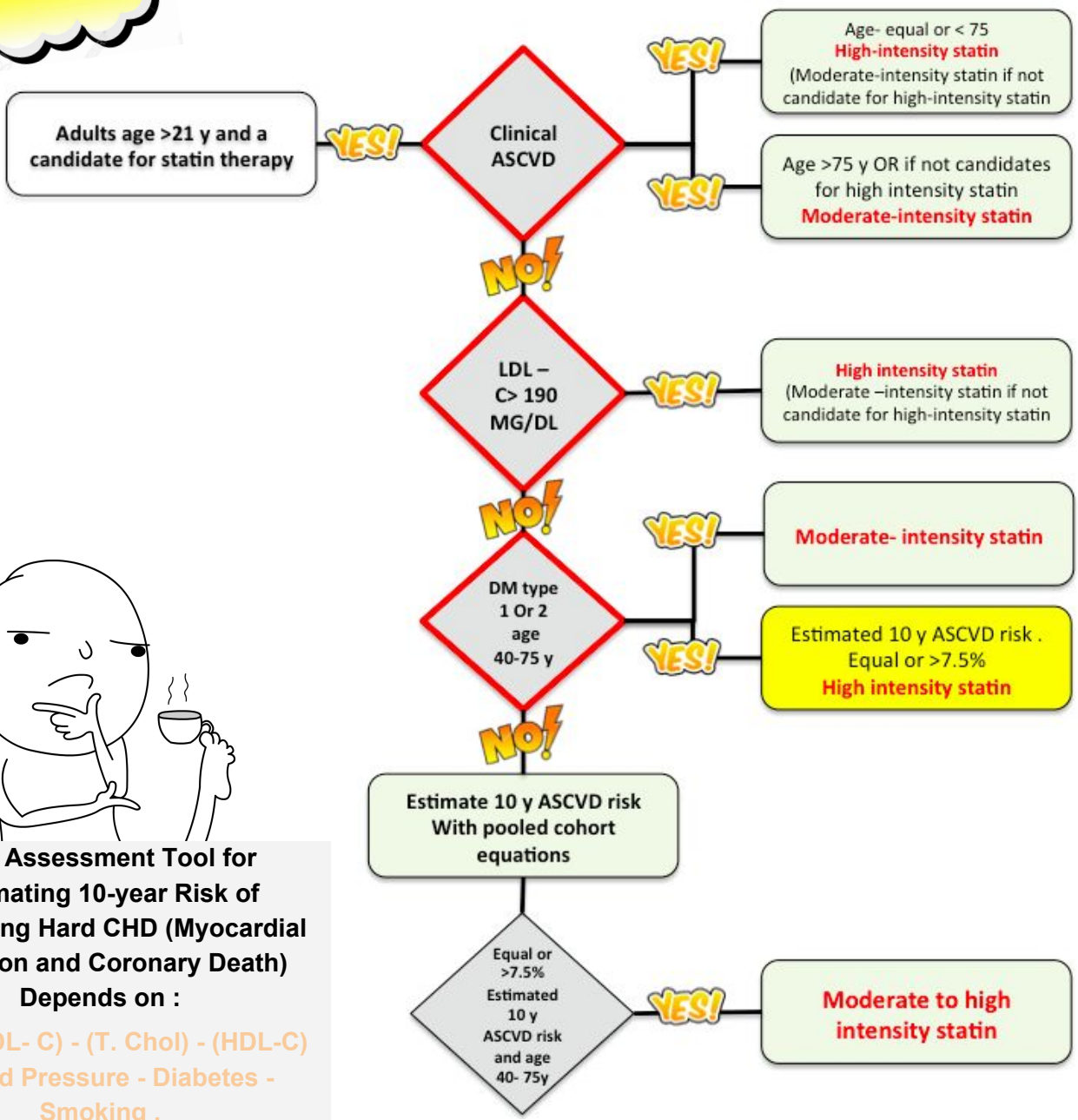
  Exercise
- Medications.

TGA 0-2 = No treatment
TGA 2-5 = Statin - cardiovascular
TGA >5 = fibrate - pancreatitis
TGA >10 = consider him in management as if he has a pancreatitis

❖ Medications for Hyperlipidemia:

Drug Class	Agents	Effects (% change)	Side Effects
HMG CoA reductase inhibitors	Statins	-More in 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	Unclear Probably inhibit lipid synthesis in the liver	-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) -Mainly on Triglyceride (20-50)	Dyspepsia, gallstones, myopathy
Bile Acid sequestrants	Cholestyramine	- LDL - HDL No change in triglycerides	GI distress, constipation, decreased absorption of other drugs

in management remember that the lower the LDL level = the bitter for the patient



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

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

High-Intensity statin therapy	Moderate Intensity statin therapy	Low Intensity statin therapy
Lowers LDL by equal or > 50%	Lowers LDL by 30% to < 50%	Lowers LDL by < 30%
Atrovastatin **Rosuvastatin**	**Atrovastatin** **Rosuvastatin** **Simvastatin** **Pravastatin** **Lovastatin** Fluvastatin **Fluvastatin** Pitovastatin	Simvastatin **Pravastatin** **Lovastatin** Fluvastatin Pitovastatin

❖ STATIN Safety recommendations:

Conditions that could predispose pts to statin side effect:

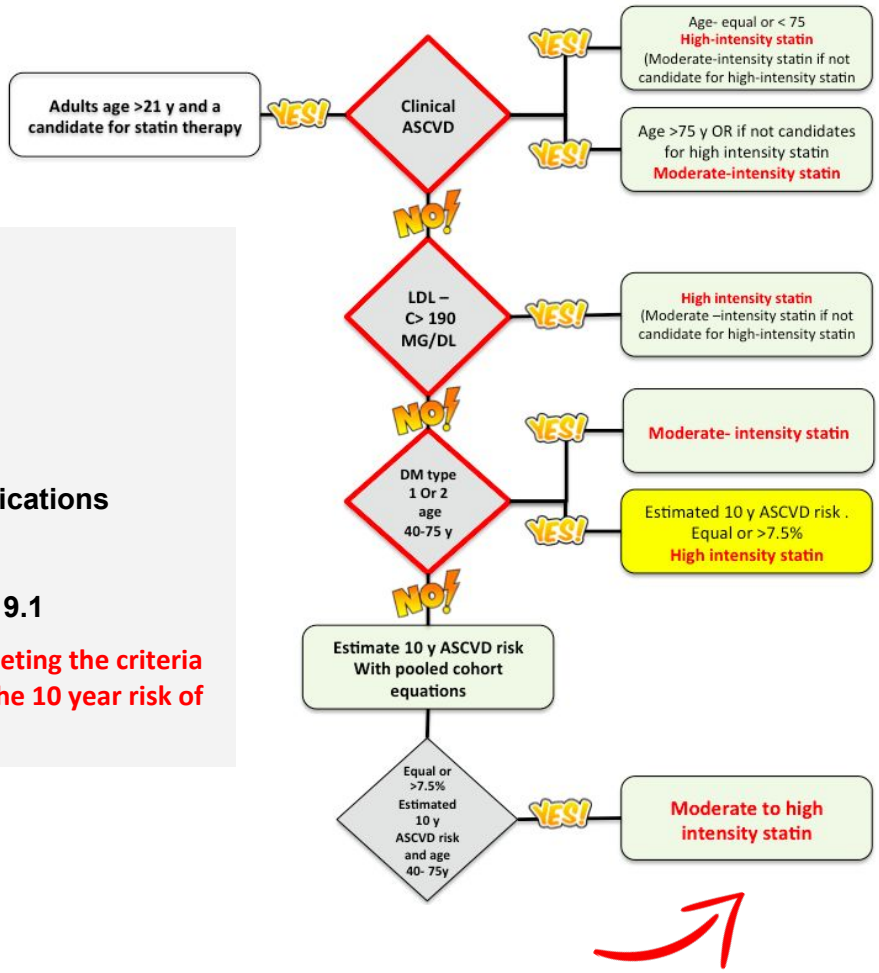
- **Impaired renal or hepatic function**
- **History of previous statin intolerance or muscle disorder**
- **Age >75y**
- **Unexplained ALT elevation > 3x ULN**
- **History of hemorrhagic stroke**
- **Asian ancestry**
- **Check baseline ALT prior initiating the statin (Grade B) .**
- **Check LFTs if patient develops Symptoms of hepatic dysfunction (Grade E) .**
- **If 2 consecutive LDL <40, Consider decreasing the statin dose (Grade C, weak recommendation) .**
- **It may be harmful to initiate simvastatin 80 mg, or increase the dose of simvastatin to 80 mg (Grade B) .**

Case 1

62 year old AA male

- **Total cholesterol: 140**
- **Low HDL: 35**
- **SBP: 130 mmHg**
- **Not taking antihypertensive medications**
- **Non-diabetic**
- **Non-smoker**
- **Calculated 10 yr risk of ASCVD : 9.1**

The patient belongs to the fourth group meeting the criteria for moderate to high intensity statin given the 10 year risk of ASCVD is greater than 7.5%



Moderate Intensity statin therapy
Lowers LDL by 30% to < 50%
Atrovastatin **Rosuvastatin** **Simvastatin** **Pravastatin** **Lovastatin** Fluvastatin **Fluvastatin** Pitovastatin

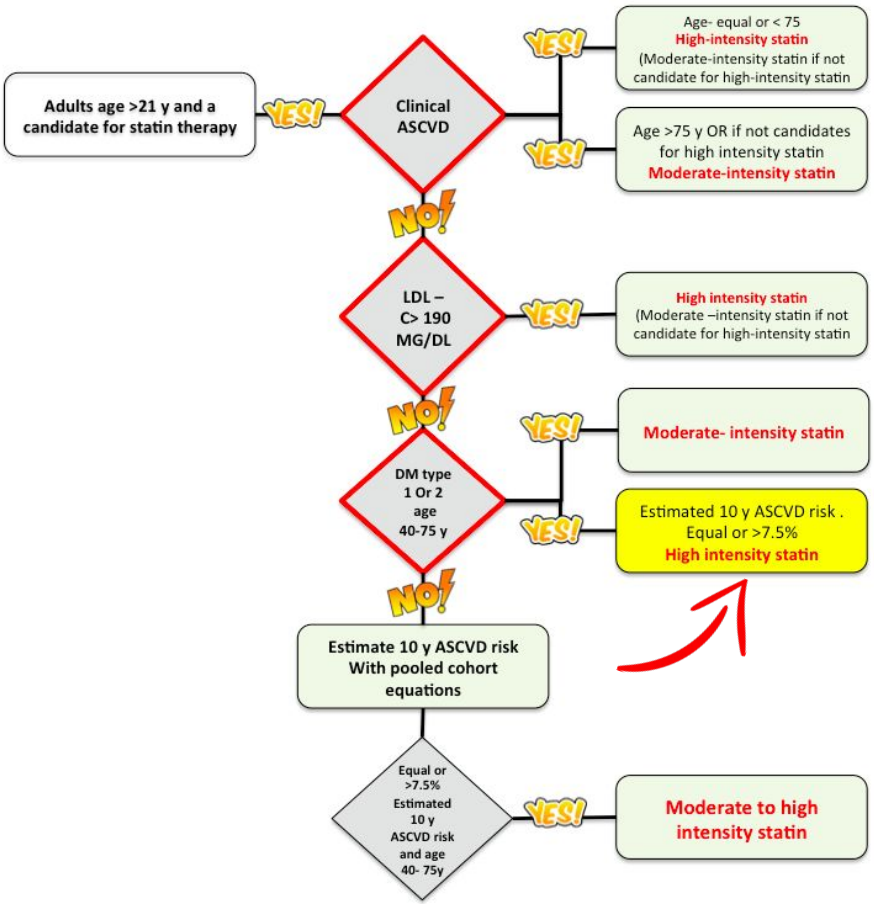
Case 2

50 year old white female

- Total cholesterol 180
- HDL: 50
- SBP: 130
- taking anti-hTN meds
- +diabetic
- +smoker
- Calculated 10 yr ASCVD: 9.8%

The patient is a diabetic with 10 yr risk is greater than 7.5% so he or she is candidate for high intensity statin

High-Intensity statin therapy
Lowers LDL by equal or > 50%
Atrovastatin Rosuvastatin



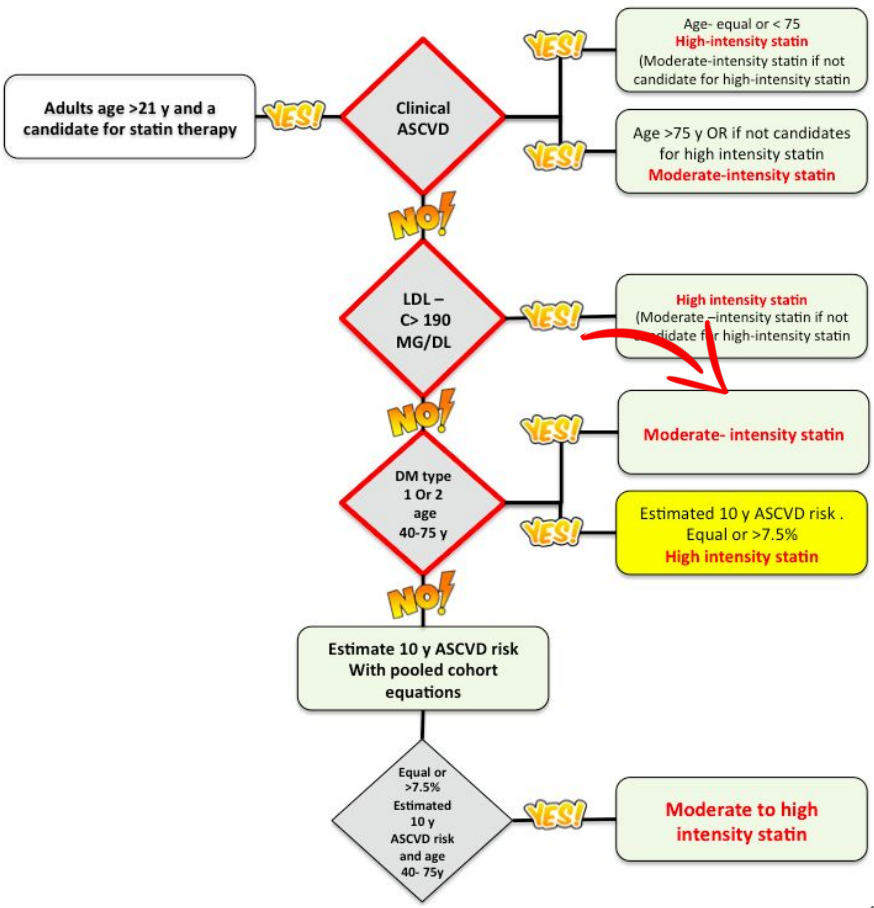
Case 3

48 yo white female

- Total cholesterol 180
- HDL: 55
- SBP: 130
- Not taking anti-hTN meds
- +diabetic
- Non-smoker
- Calculated 10 yr risk ASCVD : 1.8%

The patient is a diabetic but since his or her ASCVD is less than 7.5%, he or she is a candidate for moderate intensity statin

Moderate Intensity statin therapy schedule- Slide 8



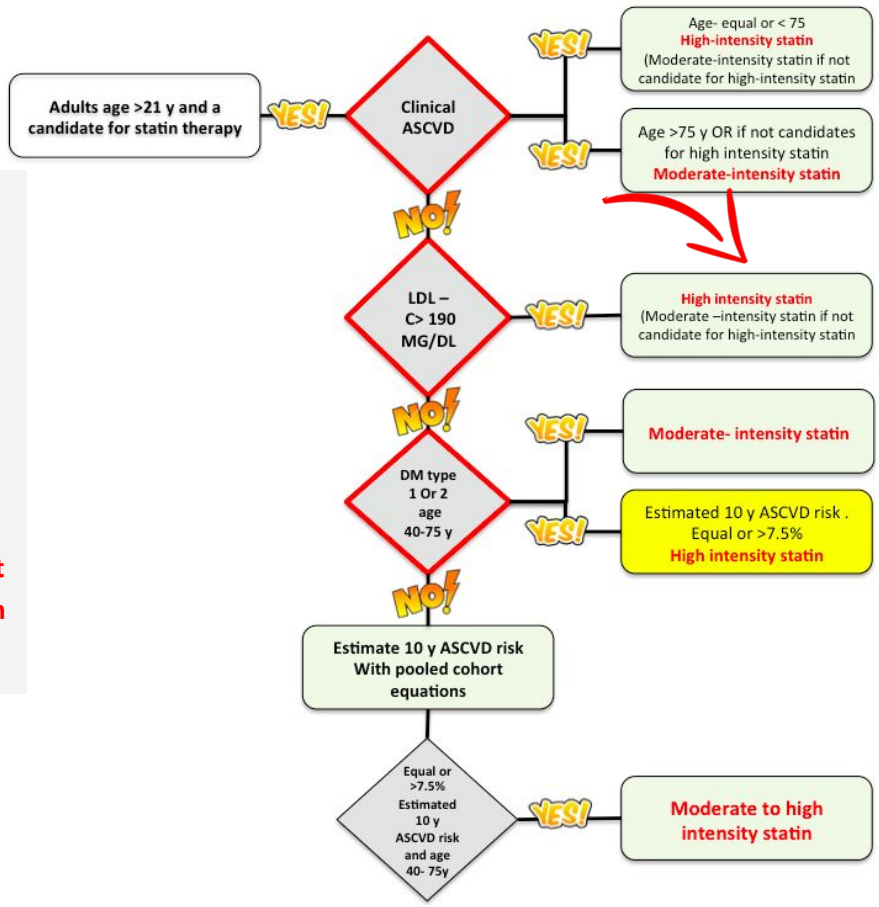
Case 4

22 yo white male

- **LDL: 195**
- **SBP: 120**
- **Not taking anti-HTN meds**
- **Non-diabetic**
- **Non-smoker**

This patient belongs to the second statin benefit group and is a candidate for high intensity Statin regardless of 10 year risk

High Intensity statin therapy schedule- Slide 8



Case 5

66 yo white female

High Total cholesterol: 230

HDL: 55

SBP: 150

taking anti-hTN meds

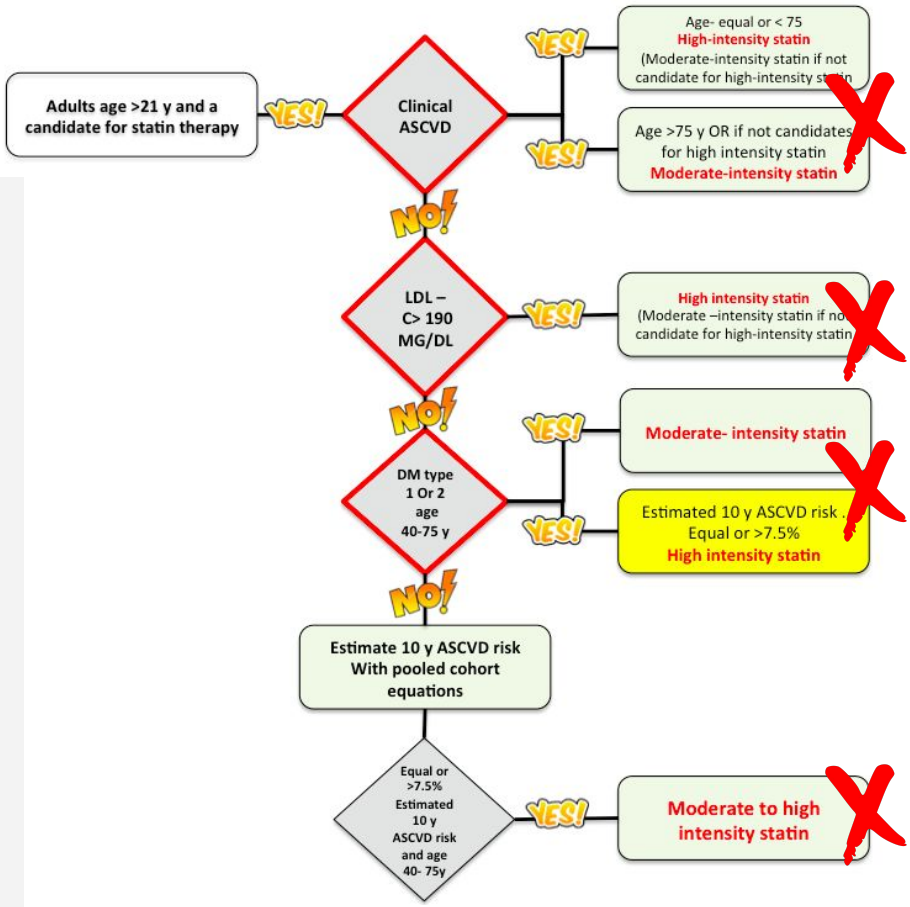
Non-diabetic

Non-smoker

Calculated 10 yr risk of ASCVD : 2.0 %

Statin therapy NOT recommended ..

despite the fact that the total cholesterol is high, since the LDL is less than 195, and patient doesn't meet any other statin benefit group, there is no indication for statin therapy



Summary: Primary hyperlipidemia

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
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
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

Summary: Secondary hyperlipidemia:

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	↑↑	↑↑	↑	estrogen ↑ VLDL production ↑, LPL ↓
Biliary obstruction PBC	-	-	↓	Lipo-protein-X ↑↑ no CAD; xanthomas
Alcohol	↑↑ chylomicron. ↑	-	↑	depend on dose, diet, genetics

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

Rec = Receptor

MCQ's Important!

Q1: A 29 y old man who is not known to have any medical illness has a lipid profile which was done b/c a family history of premature ischemic heart disease. the results are:
HDL: 35
LDL: 199
SBP: 130
he isn't taking any antihypertensive medication, what's your advice regarding Statin therapy?
A) Low intense statin therapy
B) High intense statin therapy
C) Moderate to high statin therapy
D) Not need a statin therapy

Q2: A 21 y man old presented after routine blood work, his lipid profile:
HDL: 35
LDL: 105
SBP: 118/72
BMI: 29
TAG: 1444 = 16.3 m/mol
Which one of the following is the best option to treat?
A) Low intense statin therapy
B) High intense statin therapy
C) Fenofibrate
D) Niacin

Q3: A young man presented after doing his lipid profile, his brother died 3 months ago after a massive MI at age of 32:
HDL: 45
LDL: 305
SBP: 118/72
BMI: 27
TAG: 144
what is the most likely cause of his familial disorder?
A) Lipoprotein lipase deficiency
B) Apo-c deficiency
C) Nascent HDL deficiency
D) Familial hypercholesterolemia

Q4: Which one of the following found to be important protective factor against coronary artery disease?
A) No TAG
B) High HDL
C) High LDL
D) Low VLDL

Answers: 1.B, 2.C, 3.D, 4.B

Thank you

If you have any question please contact with us at:
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