HYPOLIPIDAEMIC DRUGS

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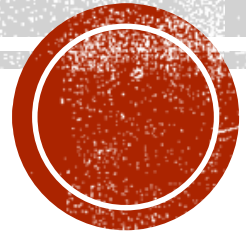


HYPOLIPIDAEMIC DRUGS

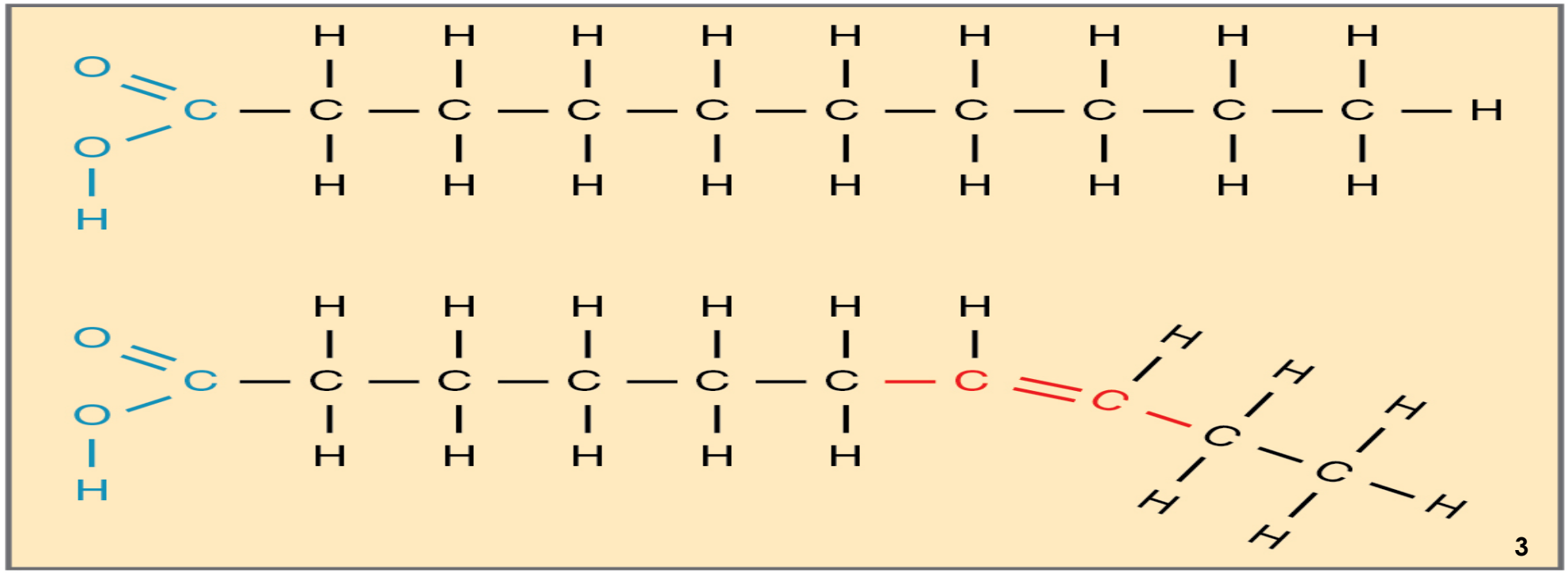
- These are drugs which lower the levels of lipids and lipoproteins in blood.
- They have potential to prevent cardiovascular disease by retarding the accelerated atherosclerosis in hyperlipidaemic individuals.

Fattyacids:

- Saturated fatty acids.

- Monounsaturated fatty acids(MUFAs).

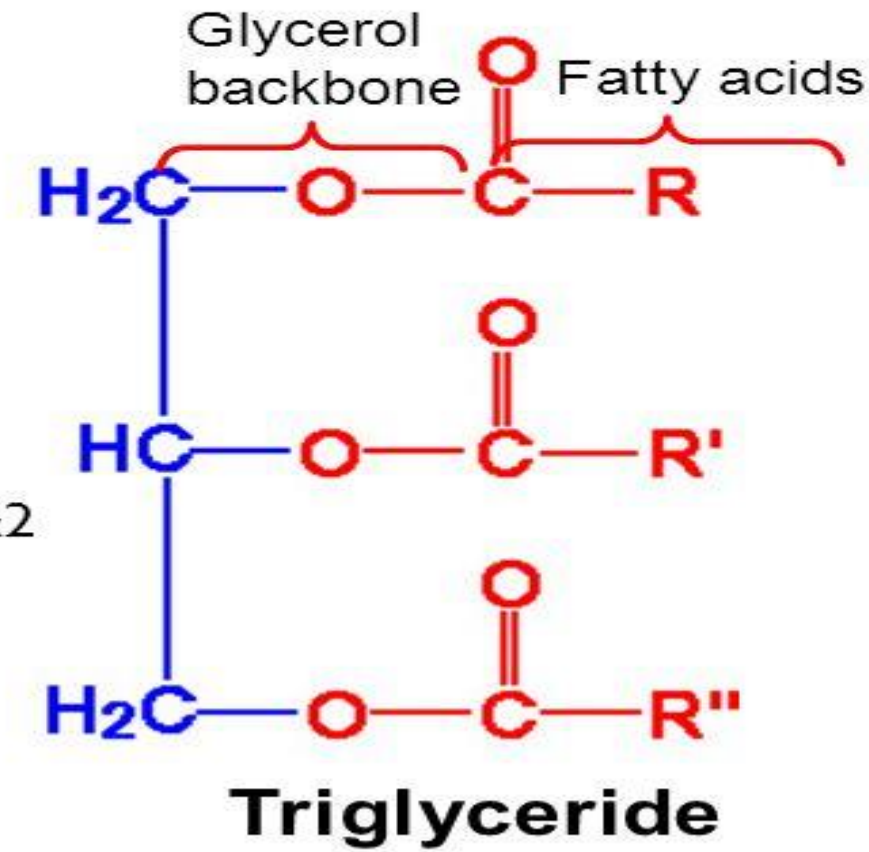
- Polyunsaturated fatty acids (PUFAs).



Lipids : are esters of fatty acids

Classification of lipids (structure)

1) Simple lipids
   - Mono, Di, and Triacylglycerols
     - Account for 98 % lipids in foods
   - Waxes
2) Compound lipids - some polarity
   - Phospholipids
   - Glycolipids
3) Derived lipids – often hydrolyzed 1&2
   - Free fatty acids
   - Sterol esters
   - Tocopherol (Vit-E)
   - β-carotene



Triglyceride

LIPID TRANSPORT

- Most of the fat in the human diet is in the form of triacylglycerol (TAG), which consists of three fatty acids linked to glycerol.

- Chylomicrons are **lipoproteins**, special particles that are designed for the transport of lipids in the circulation.

- Chylomicrons deliver absorbed TAG to the body's cell

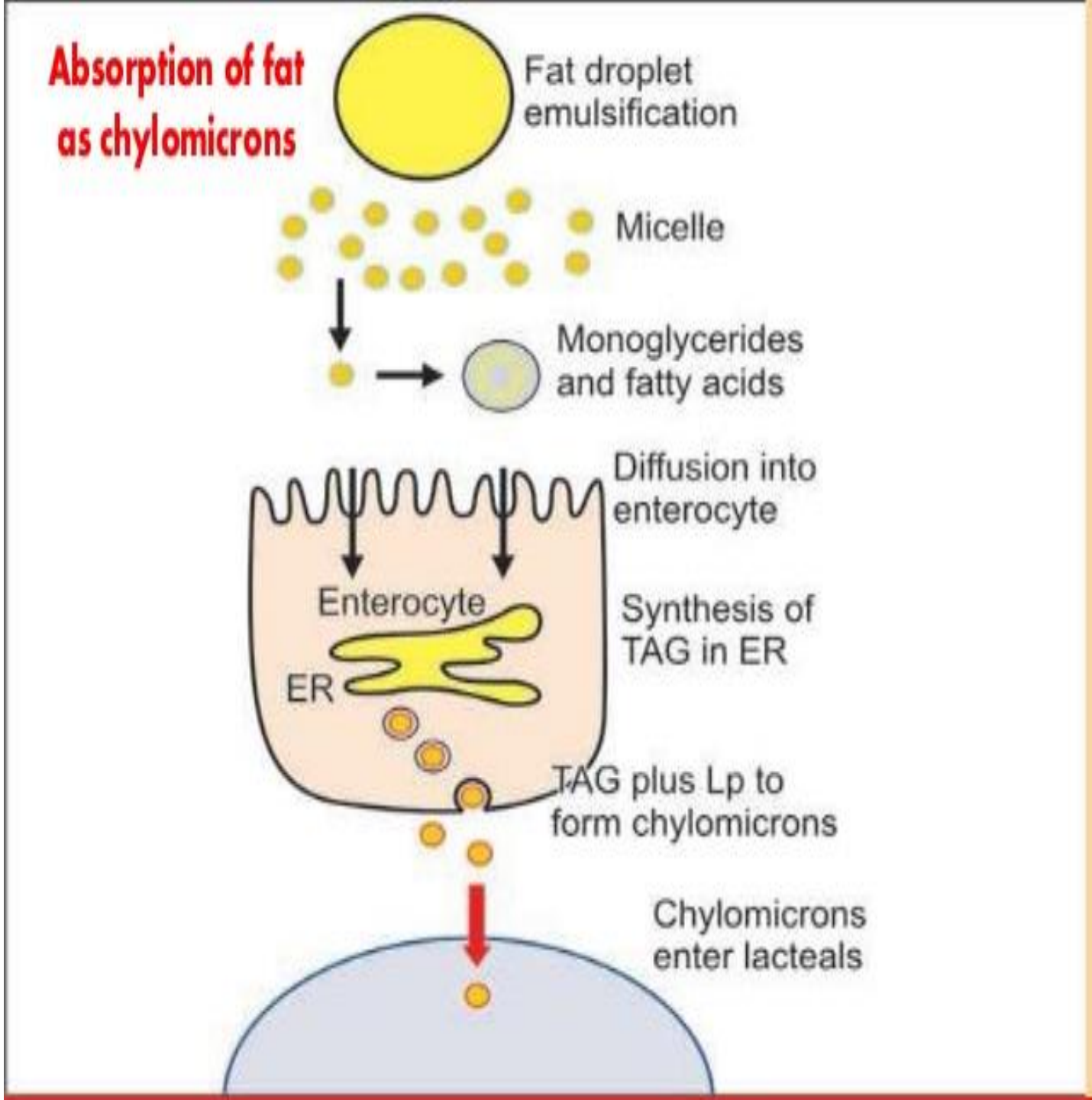
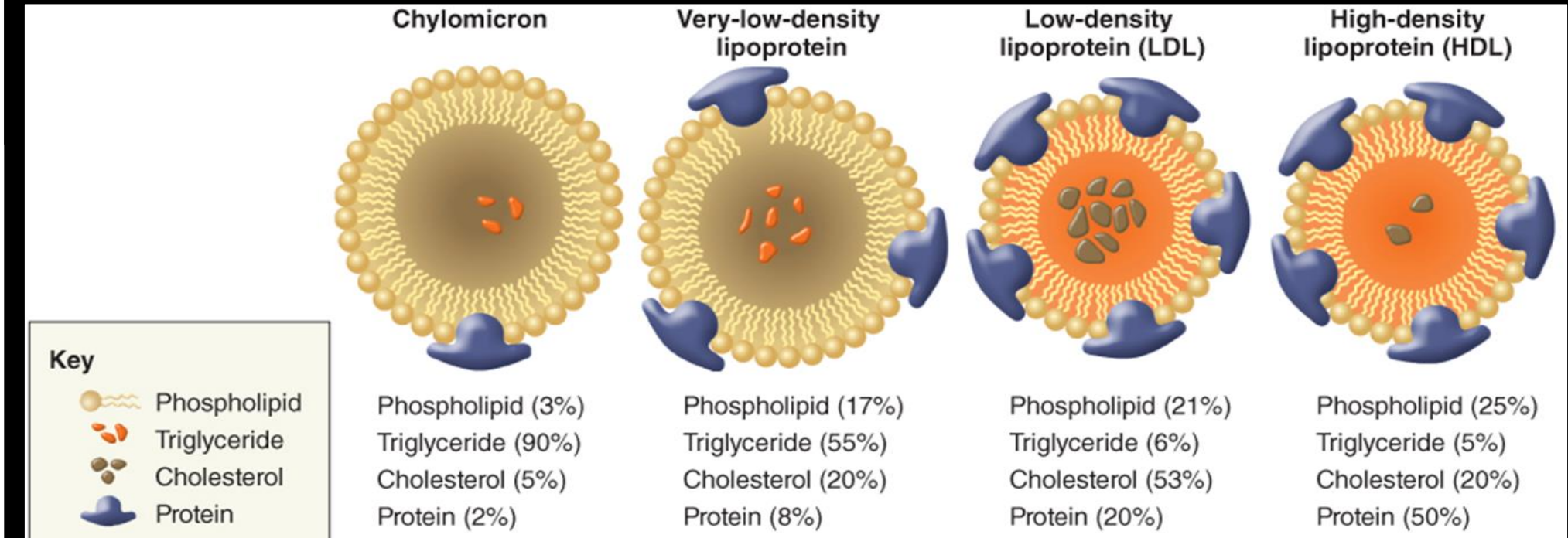
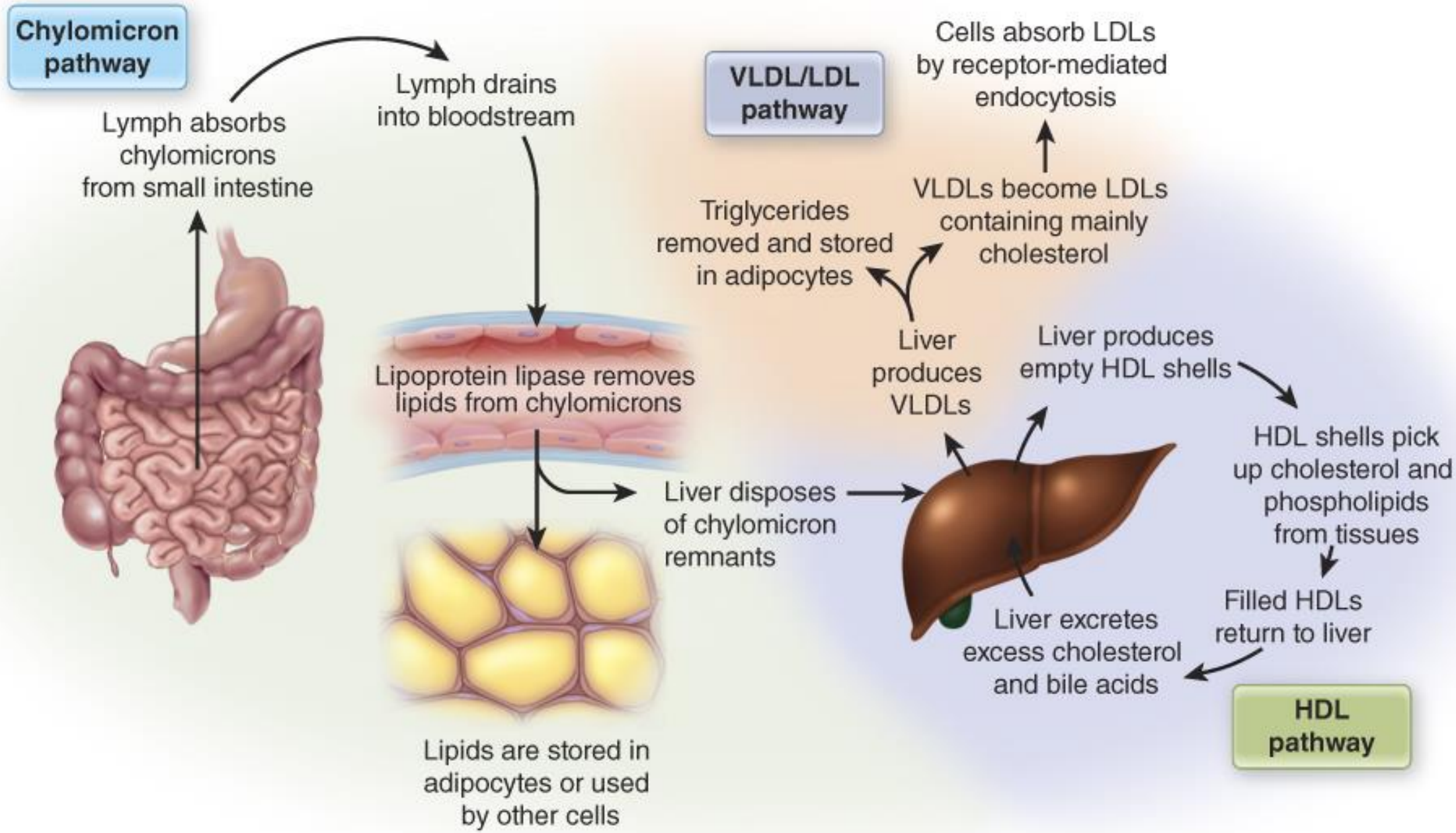


TABLE 45.1 Characteristics and function of plasma lipoproteins

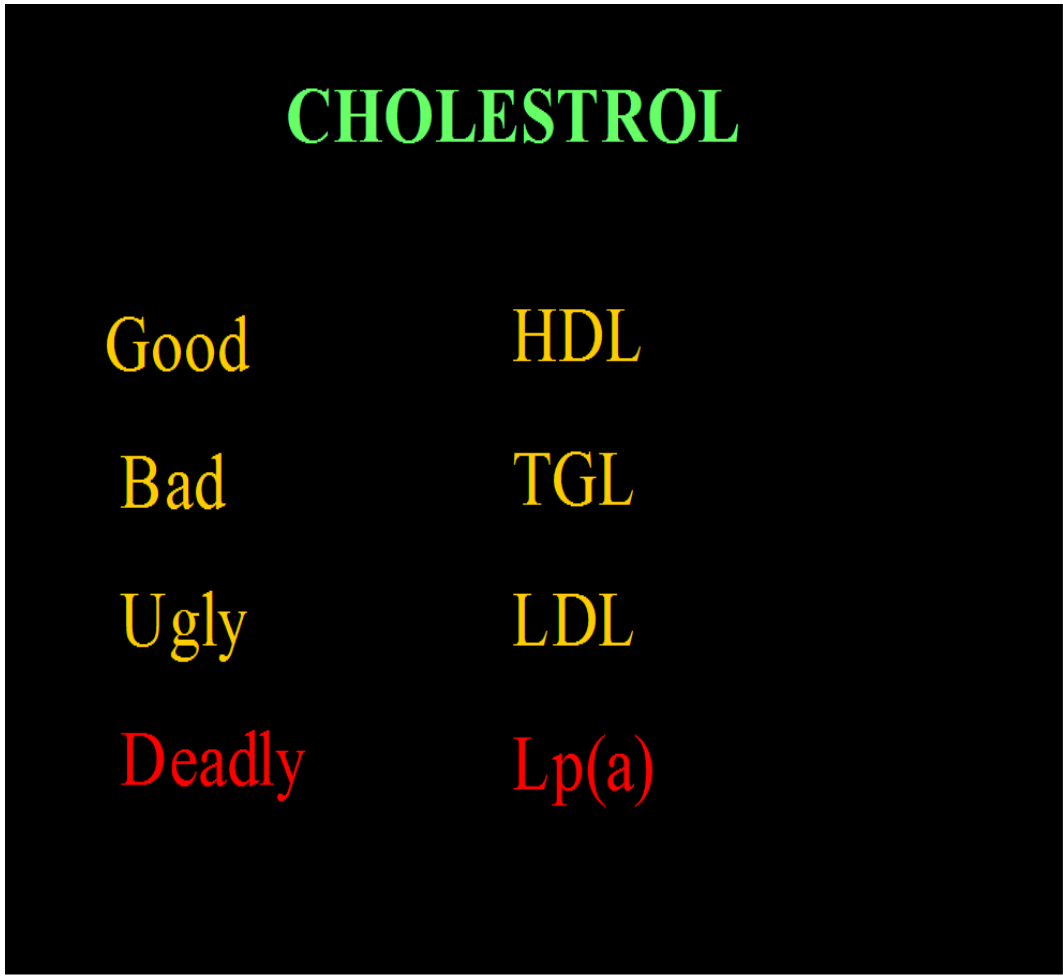
	Lipoprotein class	Diameter (nm)	Lipid contained	Source of lipid	Function
1.	Chy.	100–500	TG >> CHE	Diet	Dietary TG transport
2.	Chy. rem.	30–50	CHE >> TG	Diet, Chy.	Dietary CH transport
3.	VLDL	40–80	TG >> CHE	Liver	Endogenous TG transport
4.	IDL	30–35	CHE ≥ TG	VLDL	Transport CHE & TG to liver, source of LDL
5.	LDL	20–25	CHE	IDL	Transport CH to tissues and liver
6.	HDL	5–10	Phospholipid, CHE	Tissues, cell memb.	Removal of CH from tissues




Chylomicron pathway
Lymph absorbs chylomicrons from small intestine
Lymph drains into bloodstream
Lipoprotein lipase removes lipids from chylomicrons
Liver disposes of chylomicron remnants
Lipids are stored in adipocytes or used by other cells
VLDL/LDL pathway
Cells absorb LDLs by receptor-mediated endocytosis
VLDLs become LDLs containing mainly cholesterol
Triglycerides removed and stored in adipocytes
Liver produces VLDLs
Liver produces empty HDL shells
HDL shells pick up cholesterol and phospholipids from tissues
Filled HDLs return to liver
Liver excretes excess cholesterol and bile acids
HDL pathway

CHOLESTEROL

- Critical substrate for the body:
  - Fundamental building block of steroid hormones
  - Essential for building cell membranes, the myelin sheath, and the brain
  - Core component of bile salts, which helps in digest dietary fats



- **Dyslipidaemias** : means abnormalities of plasma lipid and lipoprotein concentration.

- Dyslipidaemias are the major cause of atherosclerosis and associated conditions.

- These may be. . .

  - Elevated total cholesterol levels.
  - Elevated LDL levels.
  - Elevated TGL levels.
  - Decreased HDL levels.

TABLE 45.4 **Interpretation of plasma lipid levels***

	Plasma lipid levels (mg/dl)			
	Total CH	*LDL-CH*	*HDL-CH*	*TGs*
1. Optimal/desirable	< 200	< 100 (< 70 for CAD pts)	> 40 (men) > 50 (women)	< 150
2. Borderline high	200–239	130–159	—	150–199
3. High	≥ 240	160–189	> 60	200–499
4. Very high	—	≥190	—	≥ 500

* Adopted from NCEP (2001)

Causes of Hyperlipidemia

- Lifestyle
- Diabetes Mellitus
- Kidney disease
- Pregnancy
- Hypothyroidism
- Genetic
- Alcohol
- Drugs- Thiazides, Cyclosporin, Glucocorticoids, Beta Blockers.

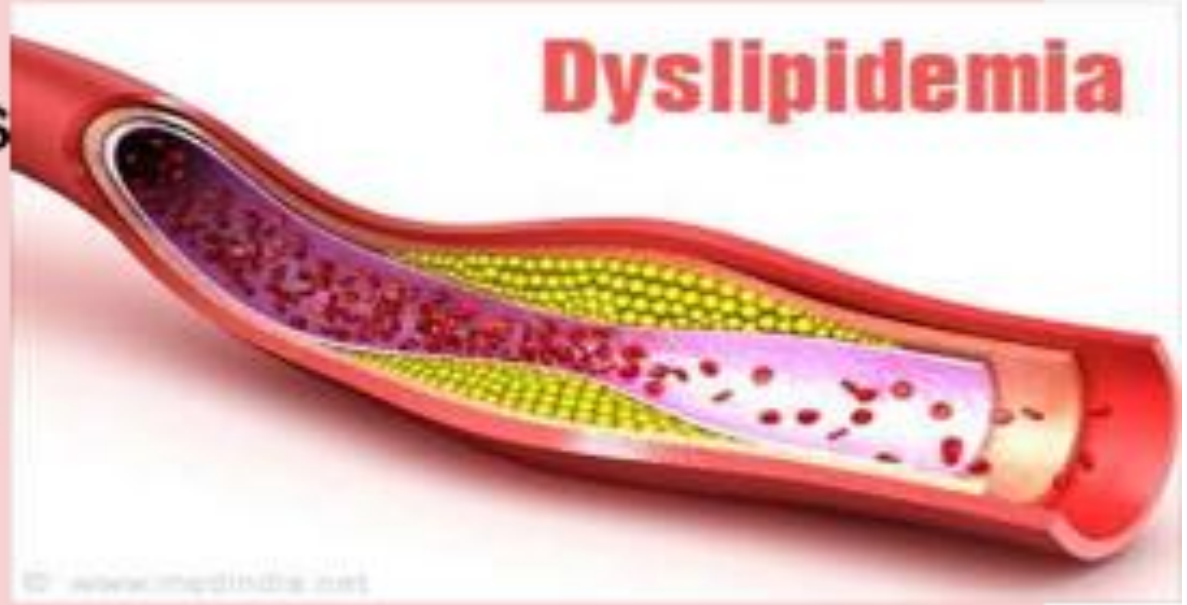


TABLE 45.2 Types of primary hyperlipoproteinaemias

Type	*Disorder*	*Cause*	*Occurrence*	*Elevated plasma lipoprotein*	*Plasma lipids*	
					CH	*TG*
I	Familial lipoprotein lipase deficiency	G	Very rare	Chylomicron	↑↑	↑↑↑
IIa	Familial hypercholesterolaemia	G	Less common	LDL	↑↑	N
IIb	Polygenic hypercholesterolaemia	MF	Commonest	LDL	↑	N
III	Familial dysbetalipoproteinaemia	G	Rare	IDL, Chy. rem.	↑	↑
IV	Hypertriglyceridaemia	MF, G	Common	VLDL	N	↑↑
V	Familial combined hyperlipidaemia	G	Less common	VLDL, LDL	↑	↑

CH—Cholesterol; TG—Triglycerides; G—Genetic; MF—Multifactorial; Chy. rem.—Chylomicron remnants; VLDL—Very low density lipoprotein; IDL—Intermediate density lipoprotein; LDL—Low density lipoprotein.

The genetic defect in some of the monogenic disorders is:

Type I : absence of lipoprotein lipase—TG in Chy cannot be utilized.

Type IIa : deficiency of LDL receptor—LDL and IDL are taken up very slowly by liver and tissues.

Type III : the apoprotein in IDL and Chy. rem. (apoE) is abnormal, these particles are cleared at a lower rate.

Type IV : this type of hypertriglyceridaemia is both multifactorial and monogenic, the former is more prevalent than the latter.

Treatment strategies

- Life style modification.
- Diet.
- Restrict intake of saturated fat.
- Regular exercise.
- Obesity reduction.
- Fish intake-oily sea fish.
- Eg-Tuna & Mackarel.
- Plenty of fruits & vegetebles.
- Stop smoking & alcoholism.
- TREAT THE UNDERLYING CAUSE.

CLASSIFICATION

HMG-COA reductase inhibitors (Statins) :

- Lovastatin. - Simvastatin. - Pravastatin.
- Atorvastatin. -Rosuvastatin.

Activators of lipoprotein lipase(Fibrates) :

- Bezafibrate. - Ciprofibrate.
- - Fenofibrate. - Gemfibrozil.

Bile Acid-Binding Resins : Cholestyramine , Colestipol

Inhibitors of lipolysis & TGL synthesis : Nicotinic acid (Niacin).

Inhibitors of Intestinal Absorption of Cholesterol: - Ezetimibe.

HMG-COA reductase inhibitors:

Lovastatin , Simvastatin, Pravastatin, Atorvastatin, Rosuvastatin

- These are most efficacious & best tolerated drugs.
- A dose dependent effect is seen with statins.
- Produce peak LDL-CH lowering after 1-2 weeks.

MOA: Inhibits the conversion of HMG-COA to Mevalonate.

↓

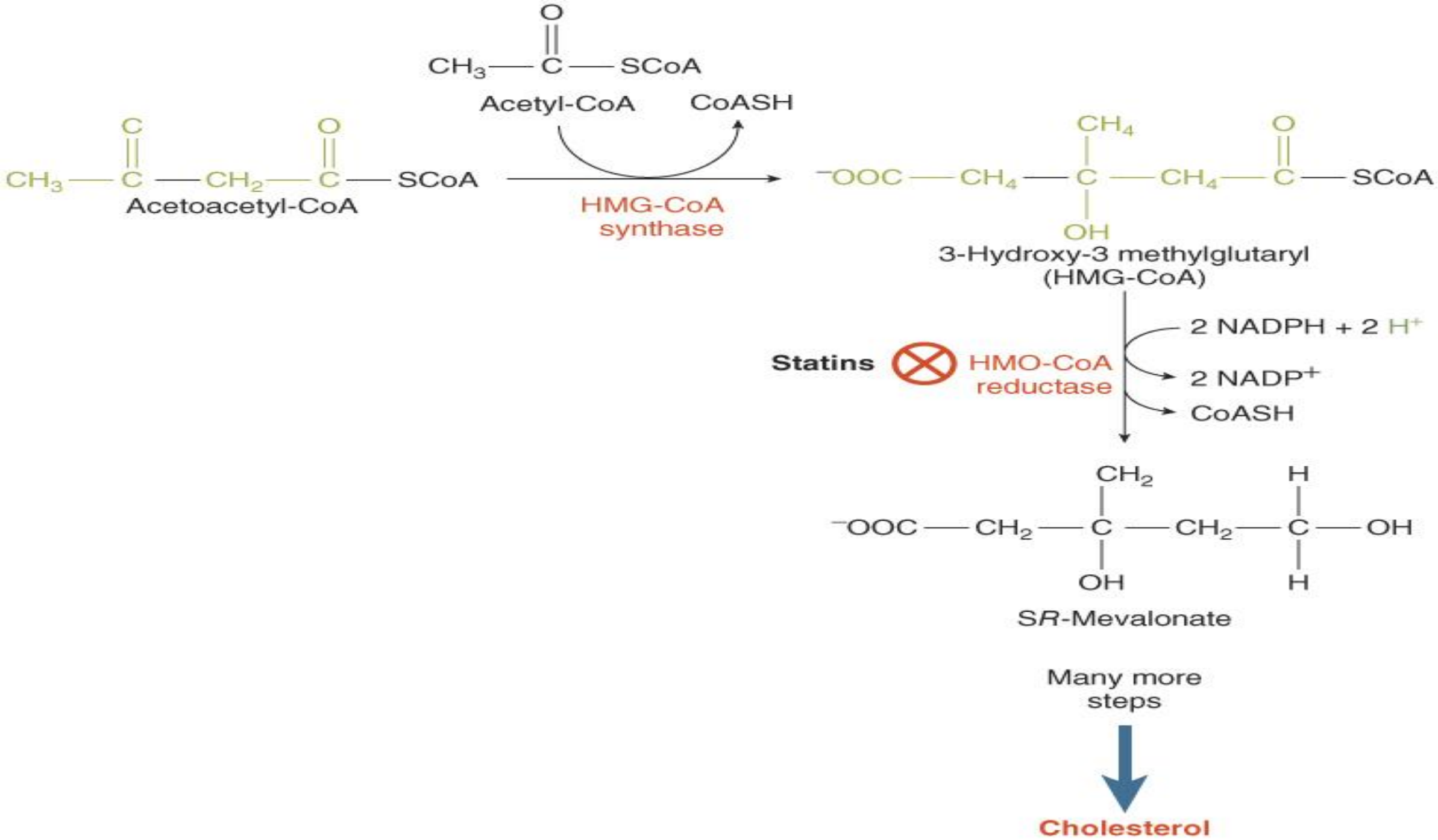
Decreased cholesterol biosynthesis.

↓

Compensatory increase in LDL receptors on liver cells.

↓

Increased receptor mediated uptake & catabolism of IDL &LDL


CH3—C(=O)—SCoA
Acetyl-CoA
CoASH
CH3—C(=O)—CH2—C(=O)—SCoA
Acetoacetyl-CoA
HMG-CoA synthase
⁻OOC—CH4—C(CH4)(OH)—CH4—C(=O)—SCoA
3-Hydroxy-3 methylglutaryl (HMG-CoA)
Statins
HMO-CoA reductase
2 NADPH + 2 H+
2 NADP+
CoASH
⁻OOC—CH2—C(CH2)(OH)—CH2—C(H)(H)—OH
SR-Mevalonate
Many more steps
Cholesterol

Actions

- Also decrease 10-30 % TGL level.
- A rise in 5-15% HDL.
- Simultaneouse use of Resins/Nicotinic acid may boost the effect to 70%.
- Prolonged use may decrease the effect.

Daily Dose: - Lovastatin 40 mg.

- Pravastatin 40 mg.
- Simvastatin 20 mg.
- Atorvastatin 10 mg.
- Rosuvastatin 5 mg.

- Administered at HS for max. effect.
- Given orally.

Adverse effects of Statins

- Headache,
- Sleep disturbance,
- Raise serum transaminase,
- Muscle tenderness & rise in CPK levels.
- Myopathy (<1/1000) is the only serious A/E, it is more when given along with nicotinic acid / gemfibrozil/ CYP3A4 inhibitors e.g ketoconazole.
- Fenofibrate is safe for combining with statins.
- Statins should be avoided in pregnant women.

Uses Of Statins

- ✓ 1st choice in primary (↑LDL, TCH-IIa, IIb, V) & secondary hyper lipidaemias.
- ✓ It decreases CVS mortality by decreasing raised LDL level.
- ✓ Improved coronary compliance and atheromatous plague stabilization.
- ✓ Improvement in endothelial function & increased NO production.
- ✓ They are the 1st choice drugs for dyslipidaemia in diabetics.

Pleotropic effects of Statins:

- ↓ in platelet aggression
- Improvement in endothelial function & ↑ in local NO production.
- ↓ in macrophage infiltration into vessel wall.
- ↓ in arterial muscle proliferation.
- Retardation of progression of the hypertrophy of vessel wall.
- ↓ LDL oxidation in the vessel wall.

FIBRATES: Activators of lipoprotein lipase :

Bezafibrate, Ciprofibrate, Fenofibrate. Gemfibrozil.

- These are isobutyric acid derivatives.

MOA: Activation of **paroxisome proliferator-activated receptor α(PPARα).**

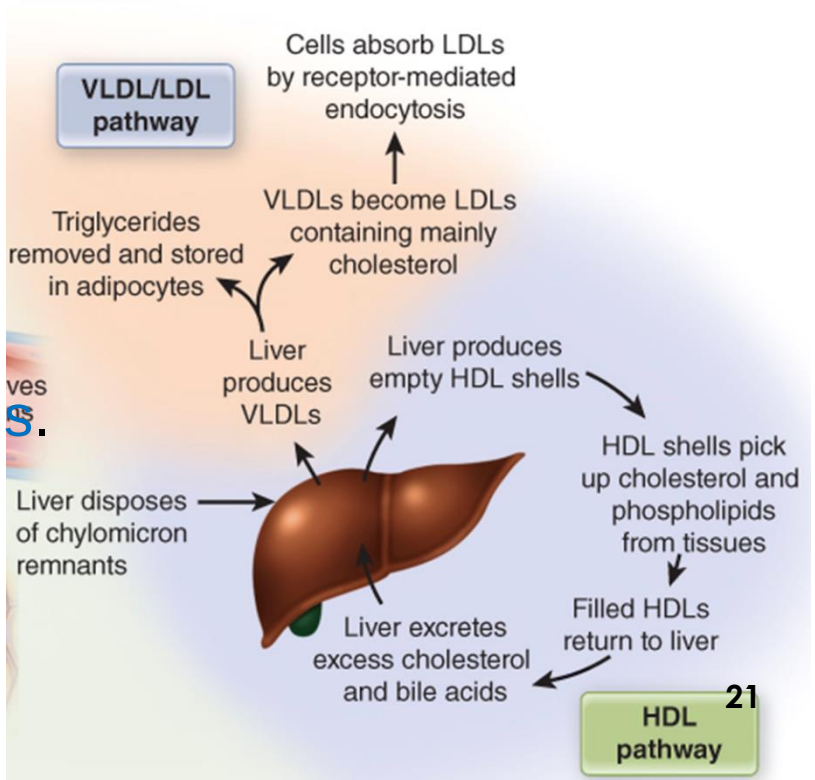
↓

Enhanced lipoprotein lipase synthesis.

↓

Degradation of VLDL & ↓ circulating TGL.

- PPARα also increases LDL receptors on liver cells.
- Decreases TG synthesis in liver.
- Also decreases circulating FFA.



Gemfibrozil:

It is a fibric acid derivative.

- **Actions:**

  - Lowers plasma TG level.
  - Decrease the level of clotting factor VII-phospholipid complex.
  - Promotes fibrinolysis.

- **PK:**

  - Well absorbed orally.
  - Metabolized by glucuronidation.
  - Undergoes enterohepatic circulation.
  - Excreted in urine.

USES: First line drug for patients with markedly raised TG levels, whether or not CH levels are also raised.

ADR:- Epigastic destress.

- Loose motions.
- Skin rashes,body ache,eosinophilia.
- Headache & blurred vision.
- Gemfibrozil+Statin→myopathy.

Uses:- DOC in Pt's with marked rise in TG levels.

- Episodes of acute pancreatitis are prevented.
- Most effective in type III hyperlipoproteinaemia.
- 1st line drug in type IV & type V disease.
- Used as adjuvant drug in type IIb patients.

Contraindicated in pregnancy.

Bezafibrate :

2nd generation fibric acid derivative & alterative to gemfibrozil in (type III, IV & V).

- Has greater LDL lowering action than gemfibrozil.
- A/E are less (G.I upset, rashes etc). Action of anticoagulant is increased.
- Combination with statin not found to increase risk of rhabdomyolysis.

Resins: Cholestyramine, colestipol

- These are insoluble, nonabsorbable anion exchange resins.

MOA: Resins forms complex with neg.charged bile acids & bile salts in the small intestine.

↓

This complex is non-absorbable & get excreted.

↓

preventing the bile acid returning to the liver by enterohepatic circulation.

↓

Biosynthesis of bile acids from CH increases.

↓

Results in up-regulation of LDL receptors.

↓

Fall in circulating levels of LDL.

Actions: - Resins cause an increase in TG levels.

- A small rise in HDL-C (5%).

- Lower LDL-C by 20-30%.

Uses:- DOC in type IIa.

- Pruritis.

- Digitalis toxicity.

ADR:- Constipation.

- GIT distress.

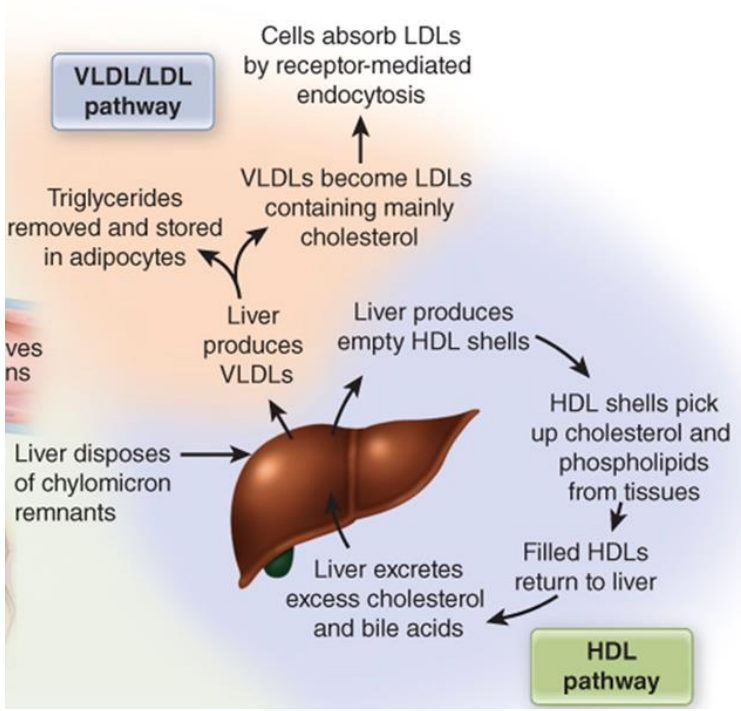
Drug Interactions:

- Fat soluble vitamins.

- Digoxin,tetracycline,statins,diuretics.

Lipolysis & TG synthesis inhibitors: NIACIN

- It is a B group vitamin.
- In higher doses reduces plasma lipids.
- Rapidly decreases TGs & VLDL.
- It is the **most effective drug to raise HDL-CH**.
- Reduces Lp(a) which is more atherogenic



MOA: It strongly **inhibits the lipolysis** in adipose tissues and increases **LIPOPROTEIN LIPASE** activity

↓

reduces the levels of circulating FFAs.

↓

Decrease in liver TG synthesis→VLDL indirectly IDL and LDL.

Uses:

- Useful in type III, IV and V hypertriglyceridaemia

- To control pancreatils associated with hypertriglyceridaemia

- Useful in pt’s at risk of CHD.

Dose: Start with 100 mg TDS, gradually increase to 2–4 g per day in divided doses. It should be taken just after food to minimize flushing and itching

ADR: large doses are poorly tolerated

- Cutaneouse flush & pruritis-first 14days, Rx-Aspirin
- GIT discomfort : Dyspepsia, nausea, vomiting, diarrhoea
- Dryness of skin, Hyperpigmentation

Long term effects :

- Cholestatis.
- Hyperglycaemia.
- Hyperuricaemia.
- Liver dysfunction and jaundice

- It is CI in - pregnancy & in children.
  - Diabetes,Gout,Peptic ulcer.

Sterol absorption inhibitor : Ezetimibe

- MOA: It interferes with specific CH transport protein

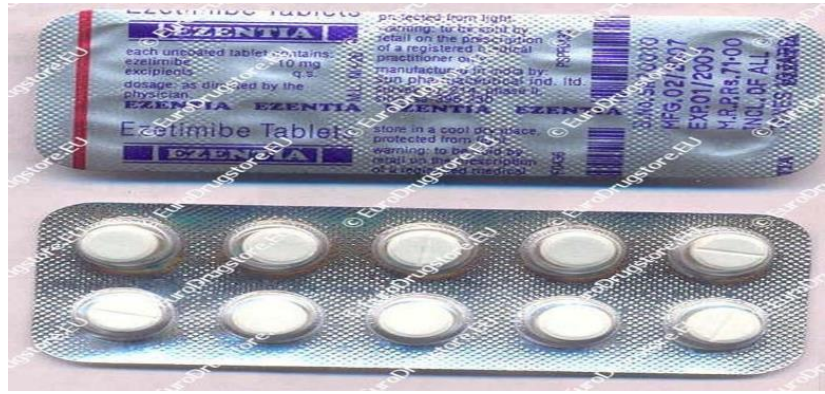
NPC1L1

↓

reduces the intestinal absorption of CH.

↓

LDL-CH level is lowered by 15-20%.



- It may be used alone in mild hypercholesterolemia.
- Used to supplement statins(synergestic)

- Adverse drug effects- GIT discomfort.
  - Reversible hepatic dysfunction
  - rarely Myositis

Fish oil derivatives (Omega-3 fatty acids)

- Contains poly unsaturated fatty acids (PUFA).
- Eicosa-pentanoic & docosa-hexanoic acids.
- Used for prophylaxis in high risk pt. of CAD with hyperlipidaemia.
- Membrane stabilizing & antioxidant action.
- Usually formulated with Vit-E.

Combination Drug Therapy.

- The combination of two lipid lowering drugs is very useful in the treatment of severe hyperlipoproteinemia.
- Commonly used drug combinations includes …..
  - Resins + fibrates.
  - Resins + niacin .
  - Resins + statins.
  - Resins + statins + niacin.
  - Statins + ezetimibe.
  - Niacin + statins.

SUMMARY GUIDELINES ON THE USE OF HYPOLIPIDAEMIC DRUGS:

- ✓Prophylactic use of a statin in CAD/hypertensive patients even with average or lower than average CH levels decreases coronary and stroke events.
- ✓Standard practice : prescribe statin therapy after an acute coronary event irrespective of lipid levels.

Primary approach : Lifestyle modification, such as low fat, low cholesterol diet, limitation of saturated and trans-fats, regular exercise, body weight control, smoking cessation, restriction of alcohol

- All patients who are at risk of CAD or thrombotic stroke : low dose aspirin prophylaxis unless it is contraindicated.
- Prescribe hypolipidemic drugs depends not only on the LDL-CH level and the type of lipid abnormality, but also on associated CAD risk factor(s) or existing CAD or its

Risk factors for coronary artery disease*

- Men > 45 years, women > 55 years
- Family history of MI/sudden cardiac death before 55 year (men), 65 year (women) age in first degree relative
- Smoking
- Hypertension (BP > 140/90 or use of anti-hypertensive medication)
- Diabetes mellitus£
- Low HDL-CH (< 40 mg/dl in men, < 50 mg/dl in women)
- High LDL-CH (≥ 160 mg/dl) or total CH ≥ 240 mg/dl
- Obesity (BMI > 25 Kg/m²)† or waist > 40″ (men), > 35″ (women)

* Adopted from the NCEP-ATP III (2001)
£ Diabetes is considered equivalent to existing CAD
† Not included in NCEP guideline (2001)

- Current American (ACC/AHA -20 I 3)* and British (NICE-20 I4) guidelines recommend that
  - all subjects who require LDL-CH lowering therapy should be treated with a statin.
- The current guidelines divide statin therapy into 3 categories, viz.
  - ' high intensity',
  - 'moderate intensity' and
  - ' low intensity'

Table 46.6: Daily doses of statins for high, medium and low intensity statin therapy

Statin therapy	*High intensity*		*Moderate intensity*		*Low intensity*	
Guideline source	ACC/AHA[1]	NICE[2]	ACC/AHA	NICE	ACC/AHA	NICE
LDL-CH reduction	≥ 50%	>40%	30–50%	31–40%	<30%	20–30%
1. Atorvastatin	40–80 mg	20–80 mg	10–20 mg	10 mg	–	–
2. Rosuvastatin	20–40 mg	10–40 mg	5–10 mg	5 mg	–	–
3. Simvastatin	–	80 mg*	20–40 mg	20–40 mg	10 mg	10 mg
4. Pravastatin	–	–	40–80 mg	–	10–20 mg	10–40 mg
5. Lovastatin	–	–	40 mg	–	20 mg	–
6. Pitavastatin	–	–	2–4 mg	–	1 mg	–

* Increased risk of myopathy; to be used only when benefits outweigh risks.

1. ACC/AHA: American College of Cardiology/American Heart Association guidelines (2013).
2. NICE: National Institute of Health Care Excellence (UK) guideline. cg181 (2014).

Indications for high intensity and moderate intensity statin therapy*

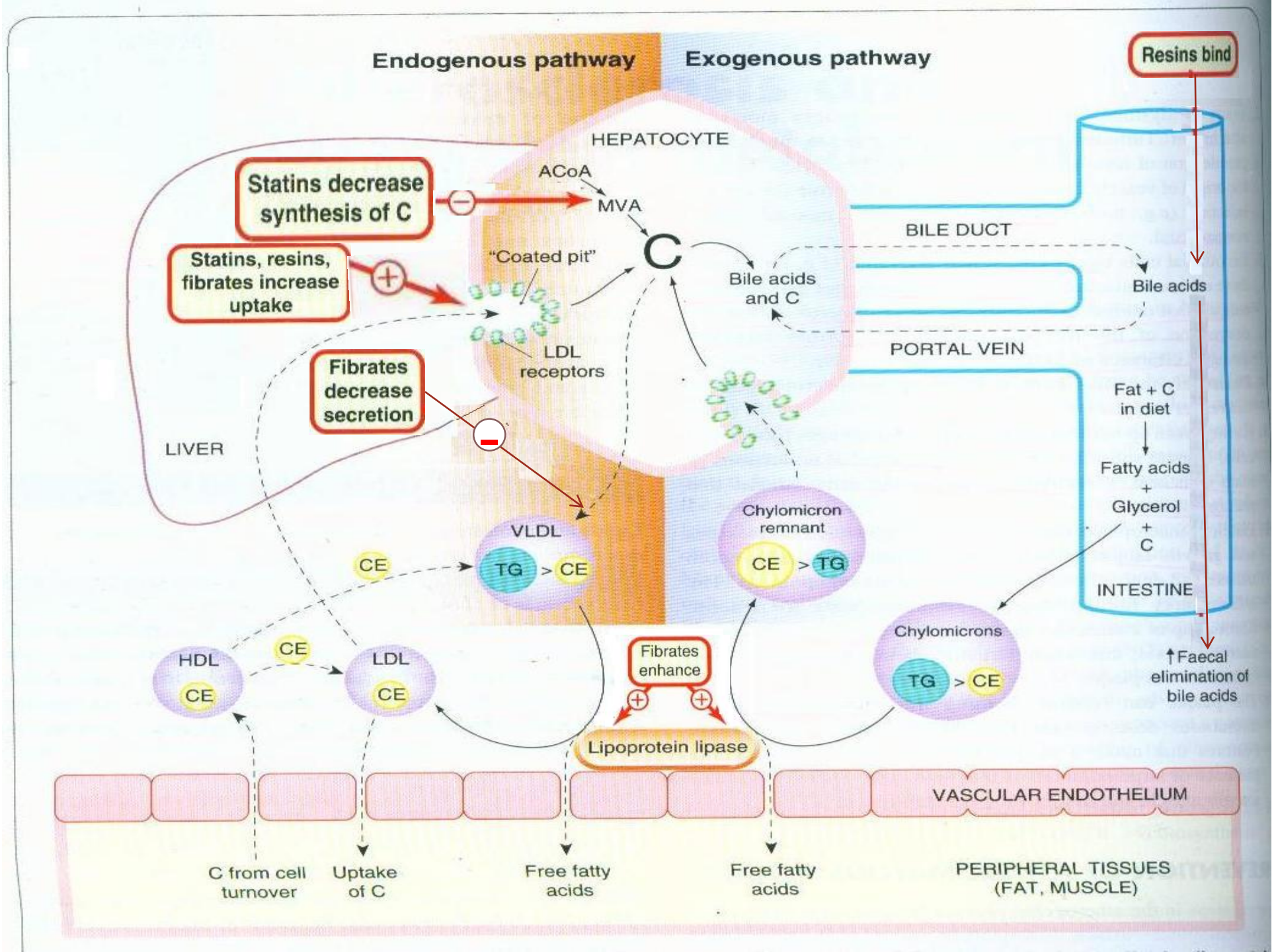
Statin benefit group	*Recommended treatment*
1. Clinical ASCVD present	• Age ≤ 75 yr: High intensity statin (moderate intensity statin if high intensity statin not tolerated or C/I) • Age > 75 yr: Moderate intensity statin
2. No clinical ASCVD, but plasma LDL-CH ≥ 190 mg/dL (primary hypercholesterolemia)	• High intensity statin (moderate intensity statin if high intensity statin not tolerated or C/I)
3. Diabetics aged 40–75 yr with LDL-CH 70–189 mg/dL and no clinical ASCVD	• Moderate intensity statin or • High intensity statin if estimated 10 yr ASCVD risk ≥ 7.5%
4. Non-diabetics aged 40–75 yr without clinical ASCVD, with LDL-CH 70–189 mg/dL and estimated 10 yr ASCVD risk ≥ 7.5%	• Moderate-to-high intensity statin therapy

* Based on ACC/AHA guidelines 2013

ASCVD—Atherosclerotic cardiovascular disease; C/I—contraindicated

- In summary, current indications for statin therapy are:
  - I. All subjects with ASCVD irrespective of plasma CH level.
  - 2. All subjects with LDL-CH above 190 mg/dL.
  - 3. All diabetics aged 40 years or more.
  - 4. Subjects aged 40 years or more with estimated 10 yr ASCVD risk more than 7 .5%, irrespective of plasma CH level.
- The NICE (2014) guidelines advise against routine addition of fibrates or nicotinic acid to a statin for preventing CVD. Extra vigilance is required to guard against risk of myopathy when niacin or fibrate is added to a statin.

Drug	MOA	Uses	Adverse effects
Statins	HMG CoA reductase Inhibition. *Pleomorphic effects* Of statins???	Hyperlipidemias-all types.	↑↑↑ liver enzymes. C/I-Pregnancy, lactation, Children.
Niacin	Lipolysis inhibition in adipose tissue.↓ FFA,↓TGL& ↓ LDL.↑ HDL.↑ tPA ↓ pl.fibrinogen. Reverse ET dysfn.	Most potent antihyperlipidemic drug to elevate HDL.FamilialHyperlipidemias.	Cutaneous flush,pruritus&warmth.IGT.Liver toxicity,nausea,abdominal pain.Gout.
Fibrates	PPAR agonists.↑Genes coding expression of LPL.↓apo CII.↑HDL by ↑ apo AI and apo AII.	Hyper TGL emias. Types III, IV & V.	CI-Severe liver,GB & renal disease.
Bile-acid binding resins	Bind bile acids(-vely) in SI. ↑↑Excretion in feces.>>Cholesterol-bile acids. LDL-receptor upregulation.	Types IIa/ IIb Hyp.lip.Along with Niacin.	GI effects are more common
Ezetimibe T ½ 22 hrs.	SI-absorption inhibitor. molecular target as the Niemann-Pick C1-like	Hypercholesterolemia	CI-Hepatic insufficiency.


Endogenous pathway
Exogenous pathway
Resins bind
HEPATOCYTE
ACoA
MVA
C
Statins decrease synthesis of C
Statins, resins, fibrates increase uptake
"Coated pit"
LDL receptors
Fibrates decrease secretion
LIVER
BILE DUCT
Bile acids and C
Bile acids
PORTAL VEIN
Fat + C in diet
Fatty acids + Glycerol + C
INTESTINE
VLDL
TG > CE
CE
Chylomicron remnant
CE > TG
Chylomicrons
TG > CE
HDL
CE
LDL
CE
Fibrates enhance
Lipoprotein lipase
VASCULAR ENDOTHELIUM
Faecal elimination of bile acids
C from cell turnover
Uptake of C
Free fatty acids
Free fatty acids
PERIPHERAL TISSUES (FAT, MUSCLE)

THANK YOU