DRUGS USED IN DYSLIPIDEMIA

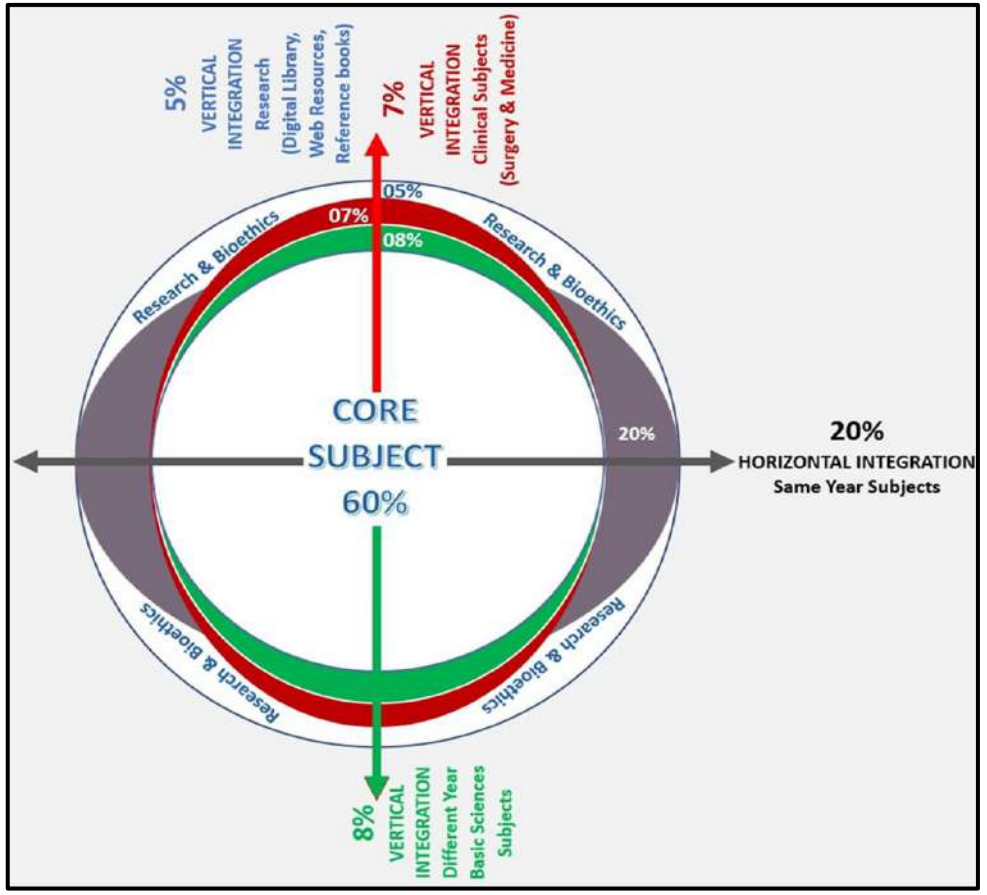
Dr. Zunera Hakim

Sources:

- **Bertram G. katzung Basic & Clinical Pharmacology 16th Edition**
- **Goodman and Gilman's**
  The Pharmacological Basis of Therapeutics 14th edition

UMAR'S MODEL OF INTEGRATION

3rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Pathology (10%)
Vertical Integration – 10%	
Clinical Subjects	• Medicine (10%)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Vertical Integration – 05%	
Research & Bioethics	



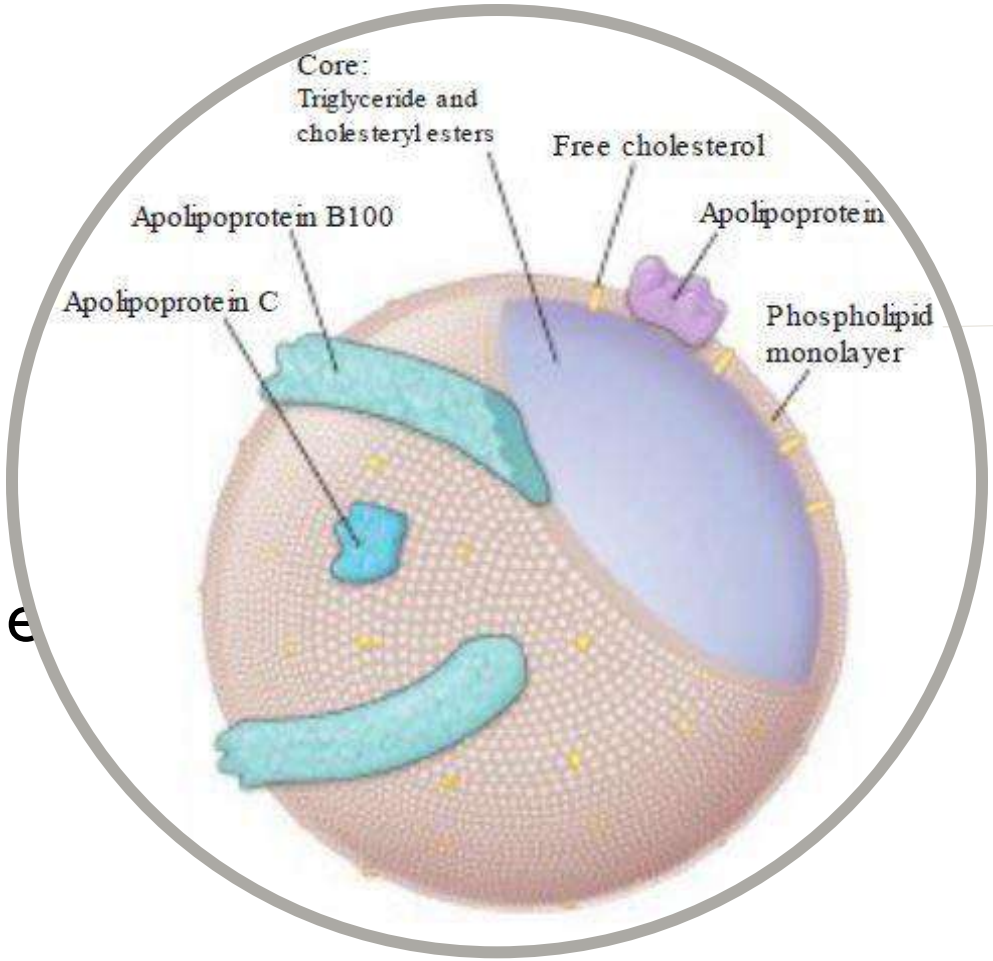
Drug used in Dyslipidemia

LEARNING OBJECTIVES

At the end of this lecture, students of 3rd Year MBBS will be able to;

- Recall salient features of lipid metabolism
- Recognize the relationship between hyperlipoproteinemia and atherosclerosis
- Classify drugs used in dyslipidemia
- Describe the mechanism of action, pharmacokinetics, clinical indications and adverse effects of major classes

Drugs used in Dyslipidemia



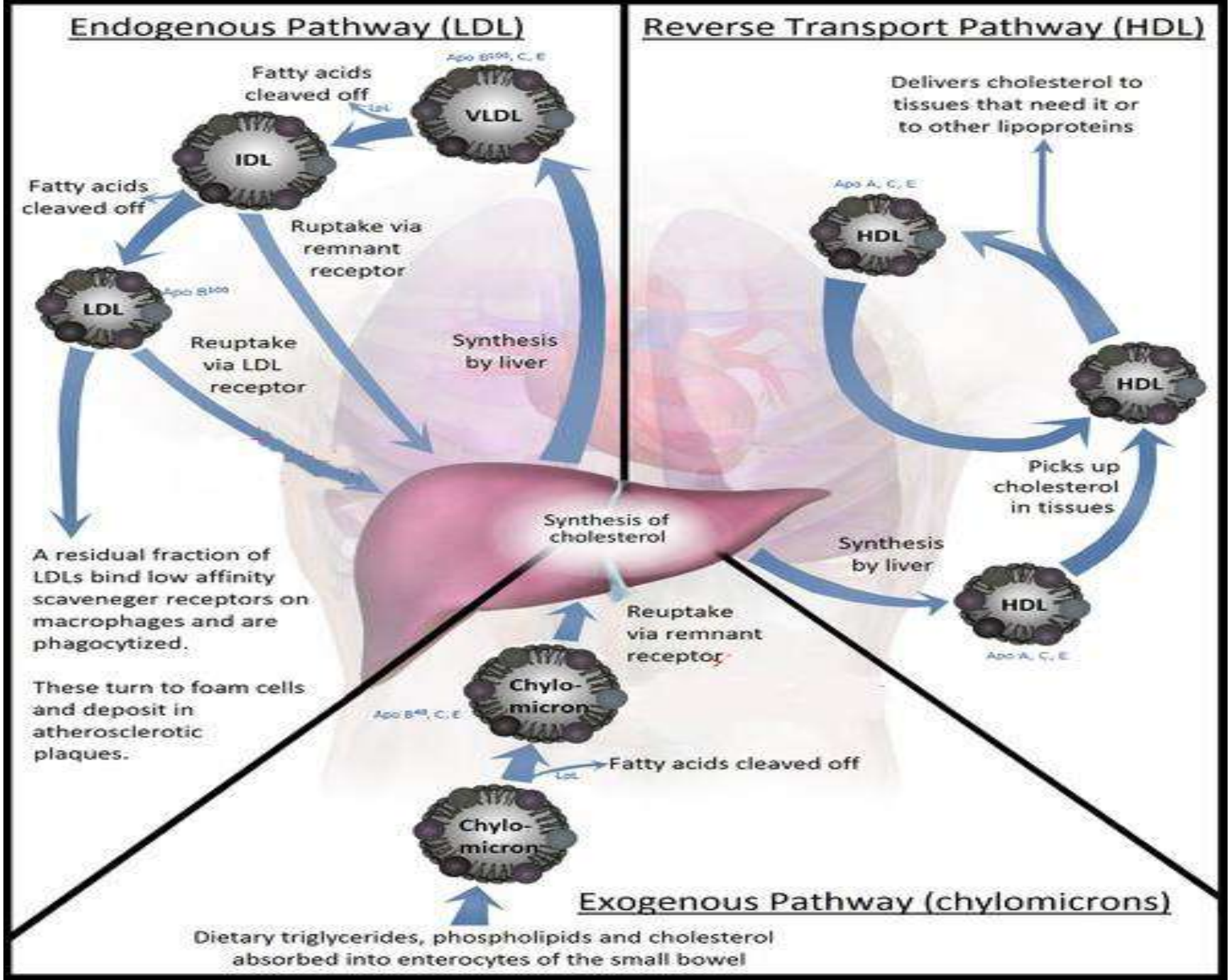
Lipoprotein

TYPES OF LIPOPROTEIN

Lipoprotein	Component	Function	Diameter	Density
Chylomicron Apo B-48 Apo A-I Apo C-II	Triglyceride	Dietary TG transport		
VLDL Apo B-100 Apo C-II	Triglyceride	Endogenous TG transport		
IDL	Cholesteryl esters	Transport CHE and TG to liver, source of LDL		
LDL Apo B-100	Cholesterol/ Cholesteryl esters	Transport CH to tissues and liver		
HDL Apo A-I Apo A-II	Protein Phospholipid	Removal of CH from tissues		

Lipoprotein a (Lp a)

METABOLISM OF LIPOPROTEIN



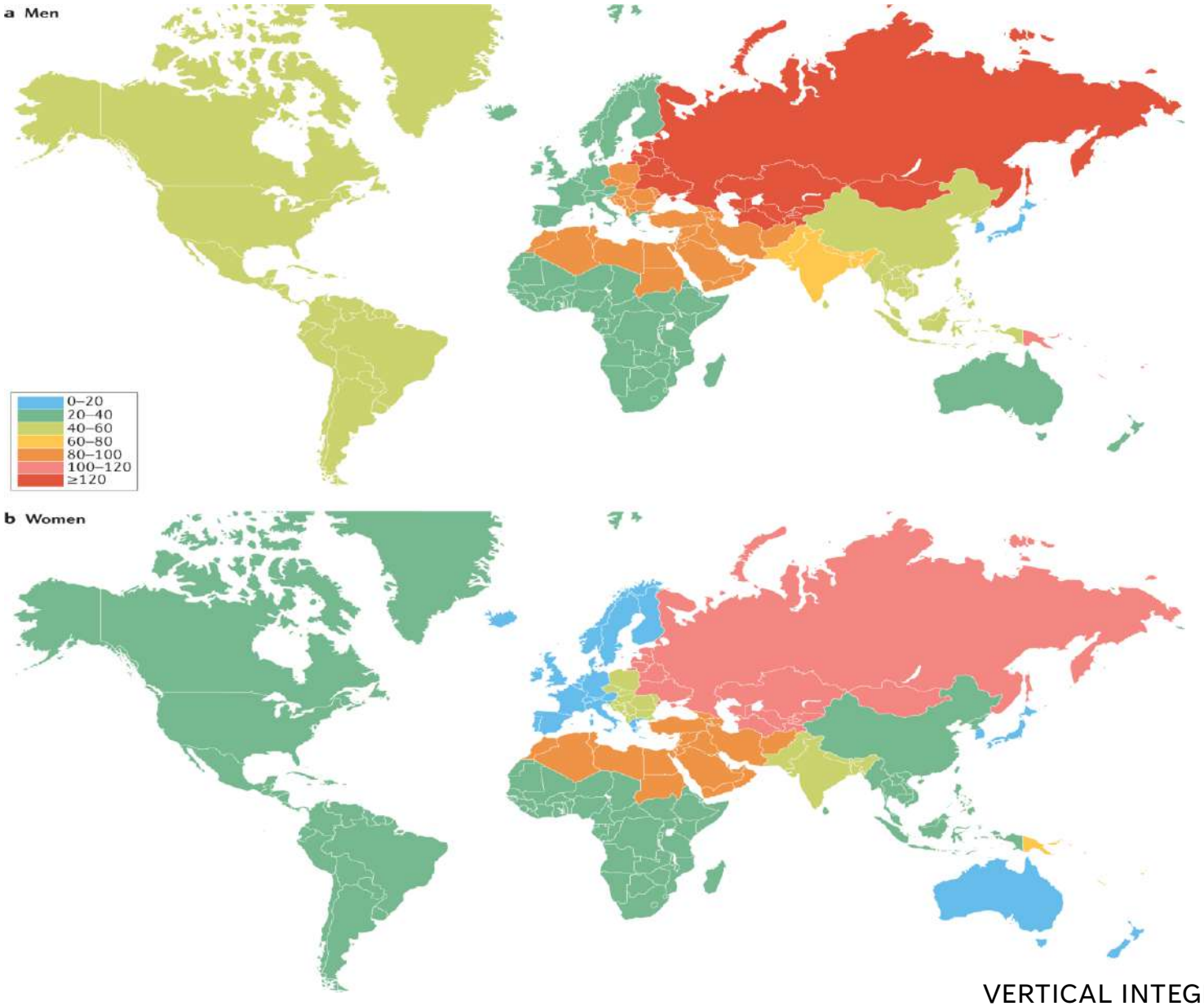
SPIRAL INTEGRATION WITH BIOCHEMISTRY

Drugs used in Dyslipidemia

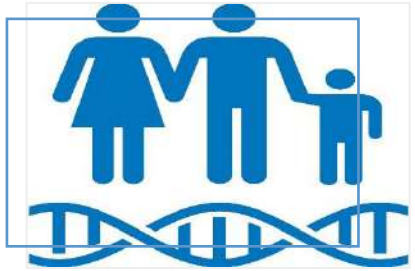
DYSLIPIDEMIA

Dyslipidemia is a general term used to describe high levels of LDL cholesterol (LDL-C) or triglycerides or both, or low levels of HDL cholesterol (HDL-C)

GLOBAL EPIDEMIOLOGY OF HYPERLIPIDEMIA

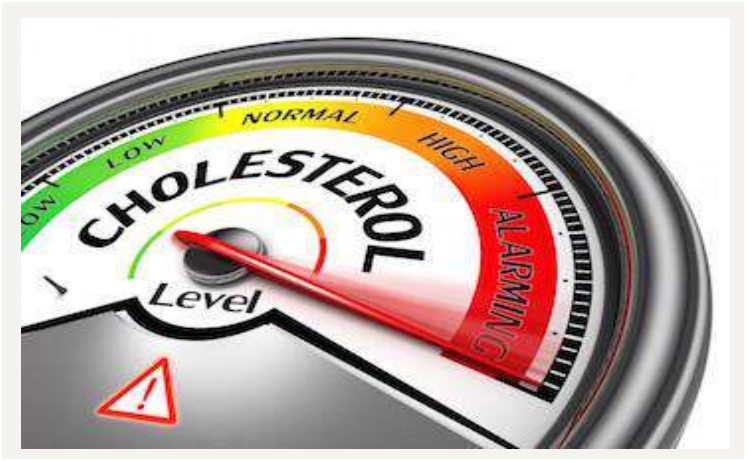


CAUSES OF DYSLIPIDEMIA



Genetic

Diet



Alcohol

Drugs

Smoking

Diseases

CLASSIFICATION OF PRIMARY HYPERLIPIDEMIA

Disorder	Manifestations	Diet + Single Drug[1]	Drug Combination
Primary chylomicronemia (familial lipoprotein lipase, cofactor deficiency; others)	Chylomicrons, VLDL increased	Dietary management; Omega-3 fatty acids, fibrate, or niacin (Apo C-III antisense)	Fibrate plus niacin
Familial hypertriglyceridemia	VLDL increased; chylomicrons may be increased	Dietary management; Omega-3 fatty acids, fibrate, niacin, or reductase inhibitor	Fibrate plus niacin
Familial combined hyperlipoproteinemia	VLDL predominantly increased	Omega-3 fatty acids, fibrate, niacin	Two or three of the single agents[2]
	LDL predominantly increased	Reductase inhibitor or ezetimibe	Reductase inhibitor plus ezetimibe
	VLDL, LDL increased	Omega-3 fatty acids, niacin, reductase inhibitor, or fibrate	Niacin or fibrate plus reductase inhibitor[2]
Familial dysbetalipoproteinemia	VLDL remnants, chylomicron remnants increased	Fibrate, reductase inhibitor, niacin, Omega-3 fatty acids	Reductase inhibitor plus fibrate or niacin
Familial hypercholesterolemia			
Heterozygous	LDL increased	Reductase inhibitor, ezetimibe, resin, niacin, or PCSK9 MAB	Two or three of the individual drugs
Homozygous	LDL increased	Atorvastatin, rosuvastatin, ezetimibe, lomitapide or PCSK9 MAB	Combinations of some of the single agents
Familial ligand-defective apo B-100	LDL increased	Reductase inhibitor, niacin, or ezetimibe	Two or three of the single agents
Lp(a) hyperlipoproteinemia	Lp(a) increased	Niacin, PCSK9 MAB (off label)	

NCEP-ATP-III CLASSIFICATION

VALUE (mg/dL)	CLASSIFICATION
LDL Cholesterol	
<100	Optimal
100-129	Near or above optimal
130-159	Borderline high
160-189	High
≥190	Very High
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High
Triglycerides	
<150	Normal
150-199	Borderline high
200-499	High
≥500	Very high

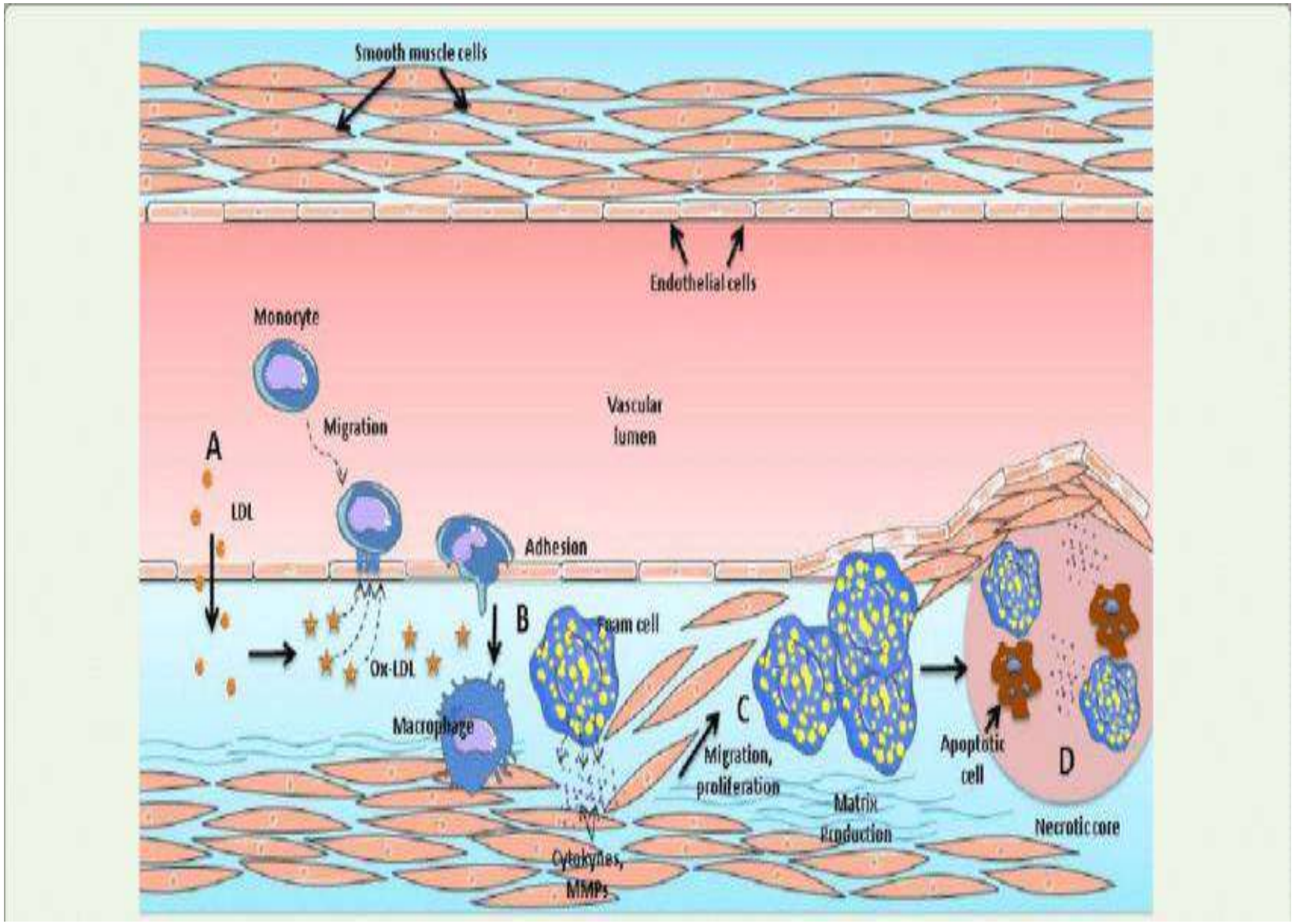
COMPLICATIONS OF HYPERLIPIDEMIA

- Atherosclerosis
- Atherosclerosis associated. conditions
  - CHD
  - Ischemic cerebrovascular disease
  - Peripheral vascular disease
- Acute pancreatitis (hyperlipemia)

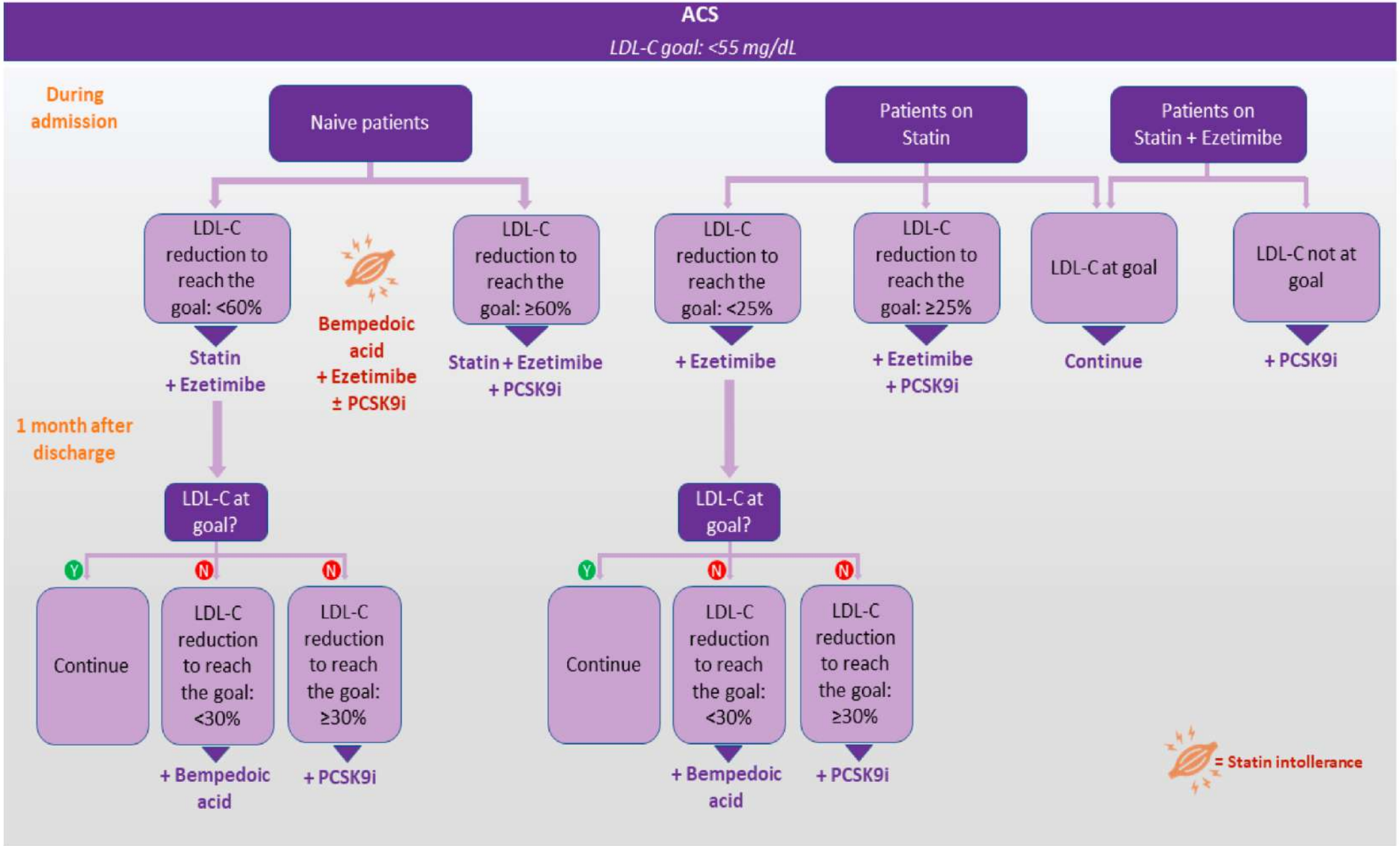
Risk factors

1. Age
2. Family history
3. **Raised LDL**
4. **Reduced HDL**
5. Hypertension
6. Diabetes
7. Cigarette smoking
8. Obesity
9. Physical inactivity
10. Raised C reactive protein
11. Raised coagulation factors
12. Raised homocysteine

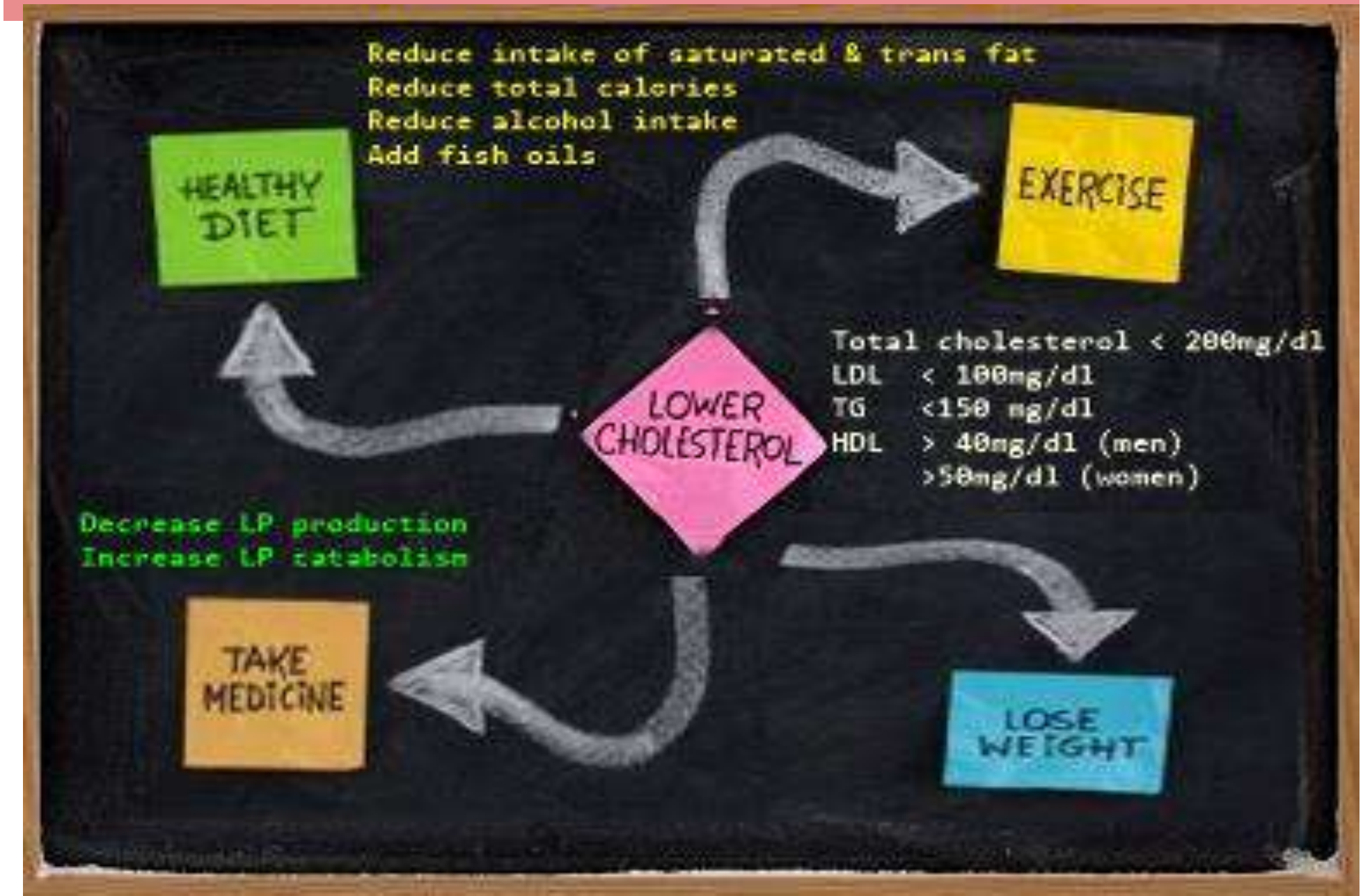
DEVELOPMENT OF ATHEROSCLEROSIS



HORIZONTAL INTEGRATION WITH PATHOLOGY


ACS
LDL-C goal: <55 mg/dL
During admission
Naive patients
Patients on Statin
Patients on Statin + Ezetimibe
LDL-C reduction to reach the goal: <60%
Statin + Ezetimibe
Bempedoic acid + Ezetimibe ± PCSK9i
LDL-C reduction to reach the goal: ≥60%
Statin + Ezetimibe + PCSK9i
LDL-C reduction to reach the goal: <25%
+ Ezetimibe
LDL-C reduction to reach the goal: ≥25%
+ Ezetimibe + PCSK9i
LDL-C at goal
Continue
LDL-C not at goal
+ PCSK9i
1 month after discharge
LDL-C at goal?
Y
N
N
Continue
LDL-C reduction to reach the goal: <30%
+ Bempedoic acid
LDL-C reduction to reach the goal: ≥30%
+ PCSK9i
LDL-C at goal?
Y
N
N
Continue
LDL-C reduction to reach the goal: <30%
+ Bempedoic acid
LDL-C reduction to reach the goal: ≥30%
+ PCSK9i
= Statin intollerance

MANAGEMENT GUIDELINES

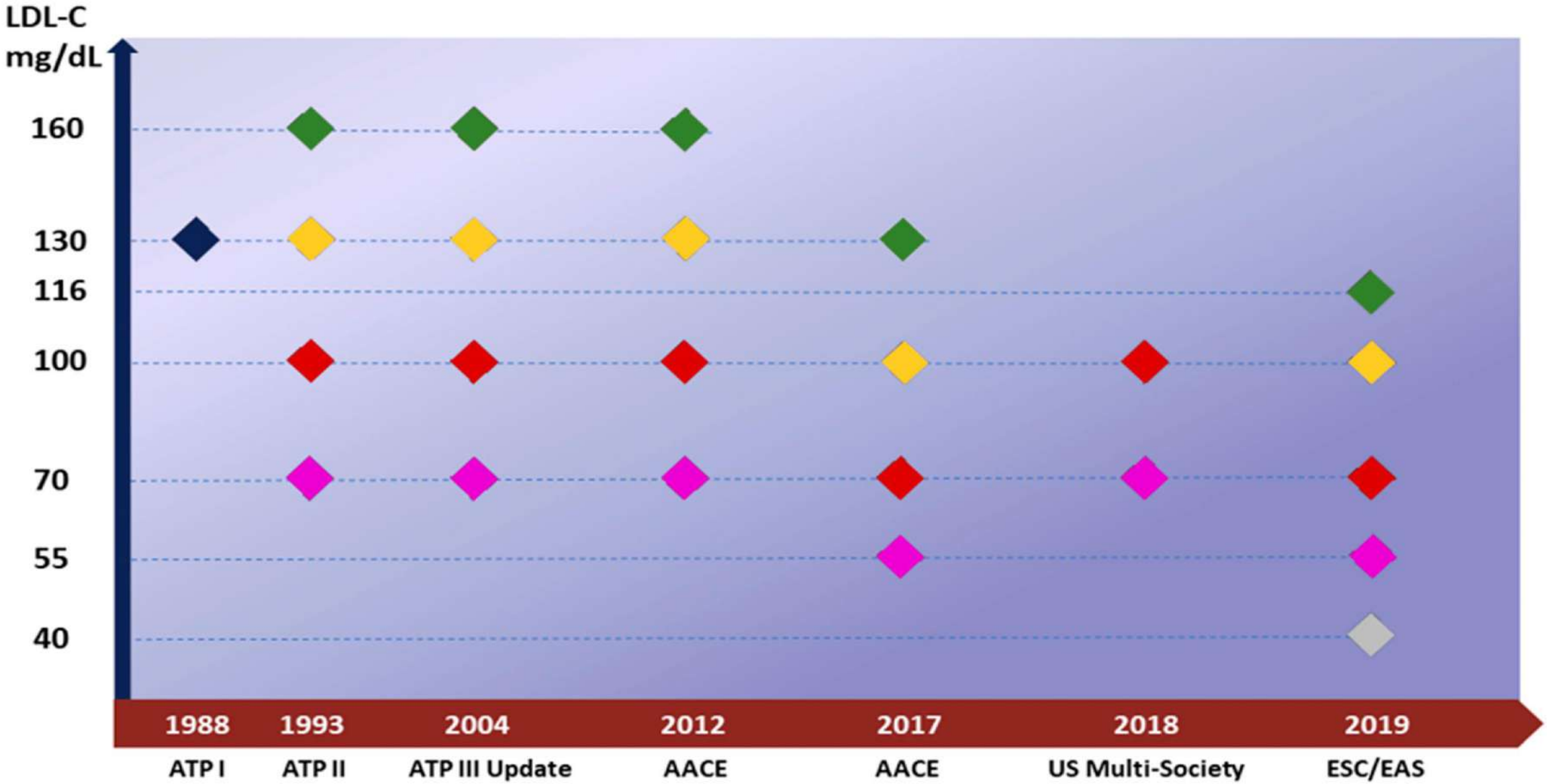


VERTICAL INTEGRATION WITH MEDICINE

MANAGEMENT GUIDELINES

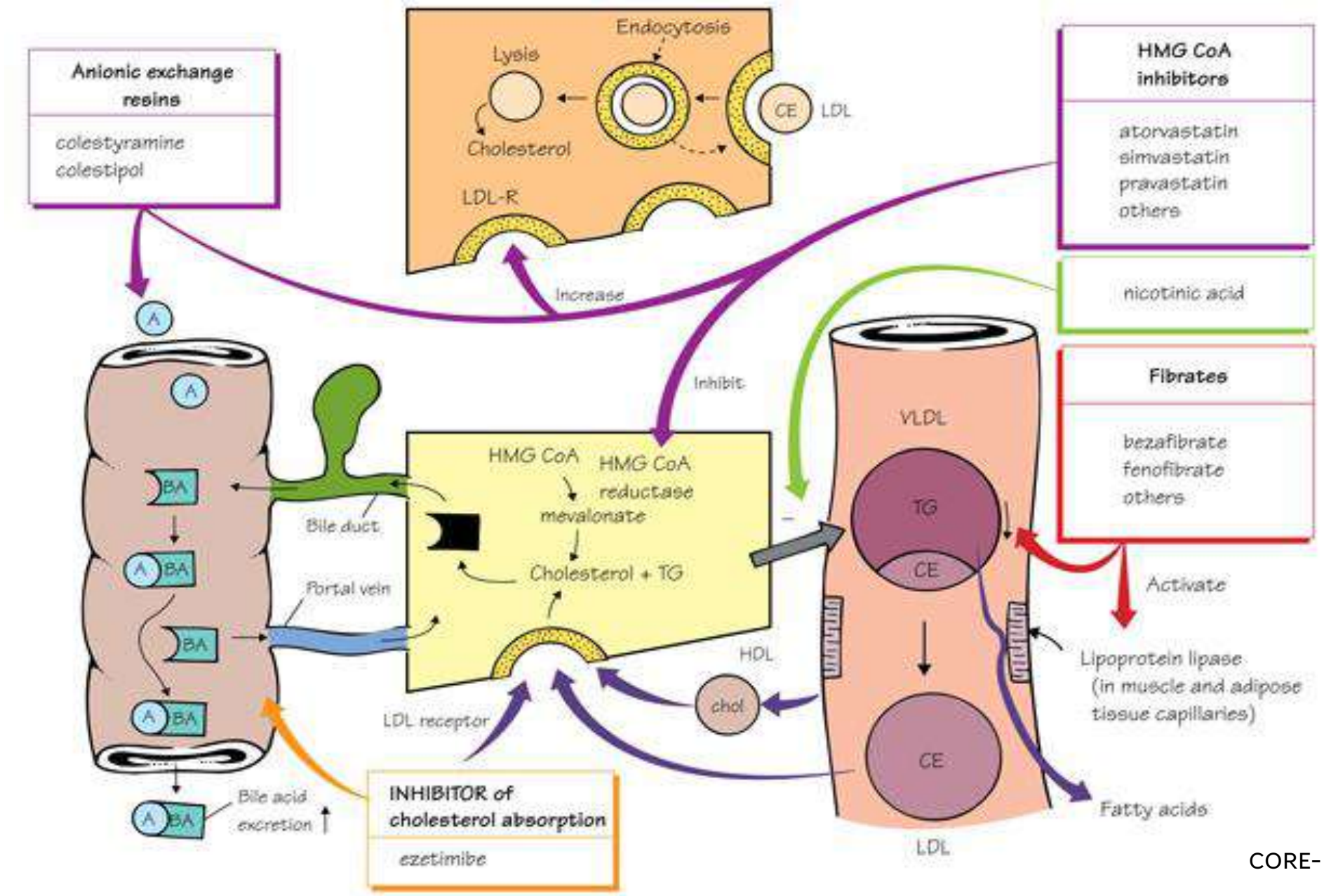
TABLE 15.2 Risk Categories and LDL-C Levels for Initiating Lifestyle Changes and Drug Therapy in Adults*

RISK CATEGORY	LDL-C GOAL (MG/DL)	LDL-C FOR LIVESTYLE CHANGES (MG/DL)	LDL-C FOR DRUG THERAPY (MG/DL)
HIGH RISK (CHD or equivalents†; 10-year risk >20%)	<100 (optional: <70)	≥100 (optional: >70)	≥100–130 (optional: >70)
MEDIUM RISK (≥2 risk factors§;10-year risk 10%–20%)	<130	≥130	≥130–160
LOW RISK (≤1 risk factor§; 10-year risk <10%)	<160	≥160	≥160–190

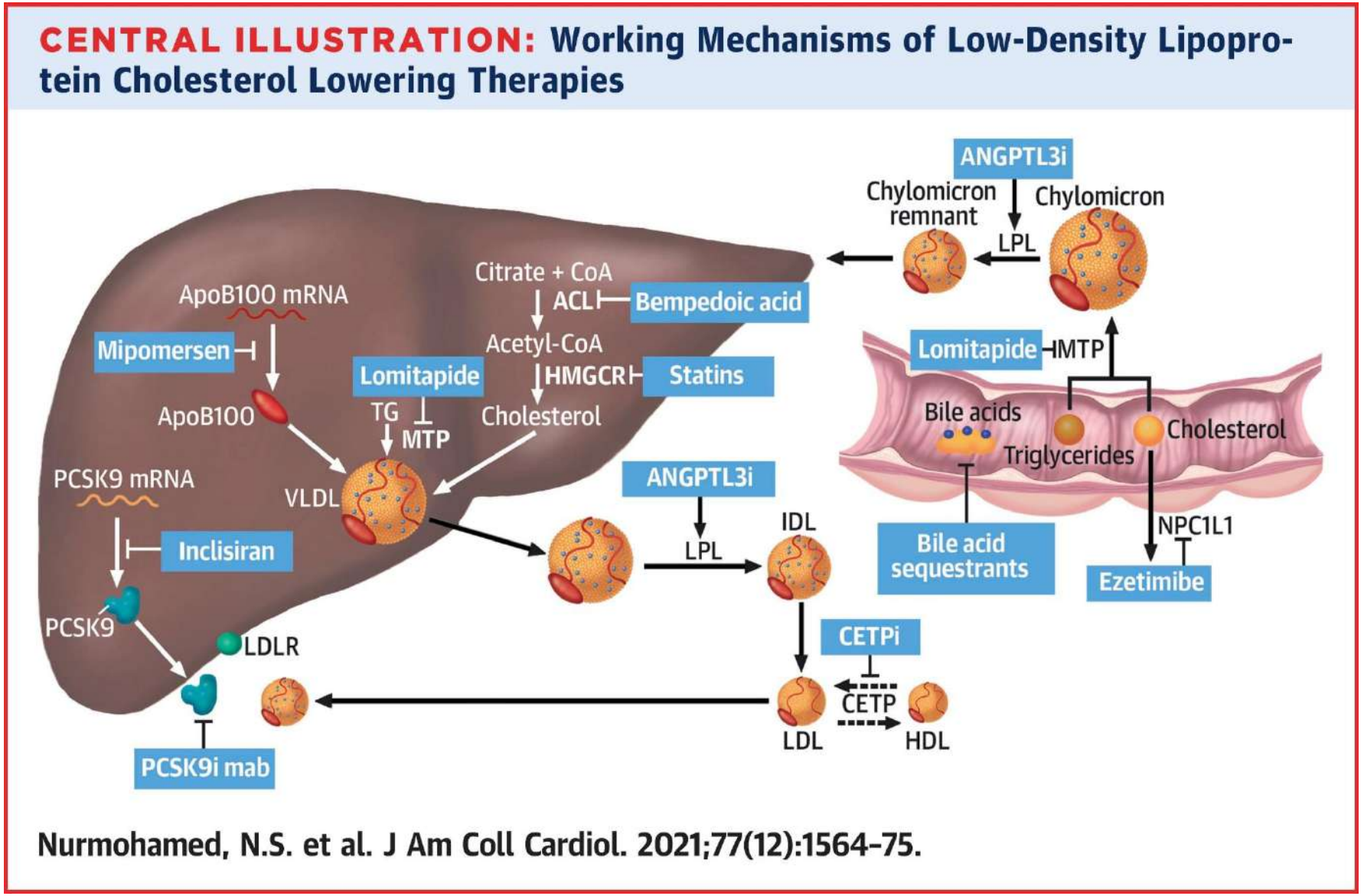

LDL-C
mg/dL
160
130
116
100
70
55
40
1988
1993
2004
2012
2017
2018
2019
ATP I
ATP II
ATP III Update
AACE
AACE
US Multi-Society
ESC/EAS

RESEARCH

CLASSIFICATION



NEWER DRUGS



RESEARCH

CLASSIFICATION

HMG-CoA inhibitors STATINS	• Atorvastatin • Simvastatin • Lovastatin • Fluvastatin • Rosuvastatin • Pravastatin • Pitavastatin
Fibric acid derivatives	• Clofibrate • Fenofibrate • Gemfibrozil • Bezafibrate • Ciprofibrate
Nicotinic acid & derivatives	• Niacin • Acipimox

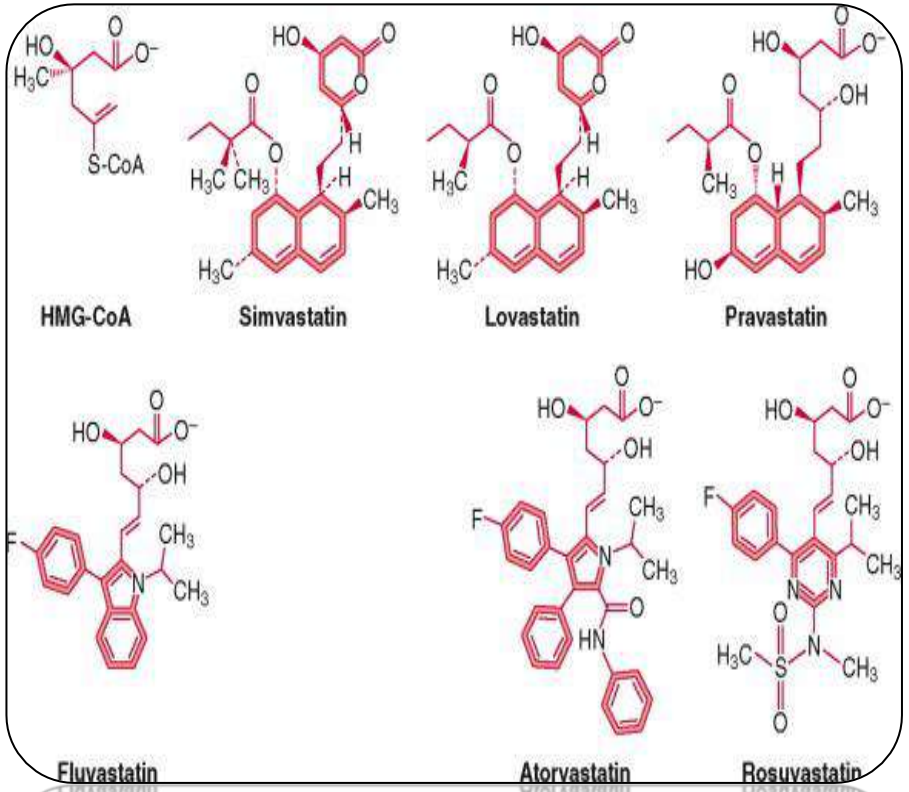
Bile acid sequestrants	• Cholestyramine • Colestipol • Colevesalam
Inhibitor of cholesterol absorption	• Ezetimibe
Inhibitor of microsomal transfer protein (MTP)	• Lomitapide
Inhibitor of Apo-B 100 synthesis	• Mipomersen
PCSK9 inhibitors	• Evolocumab, Alirocumab
Omega 3 fatty acids	

HMG-CoA inhibitors (Statins)

STATINS
(HMG-COA INHIBITORS)

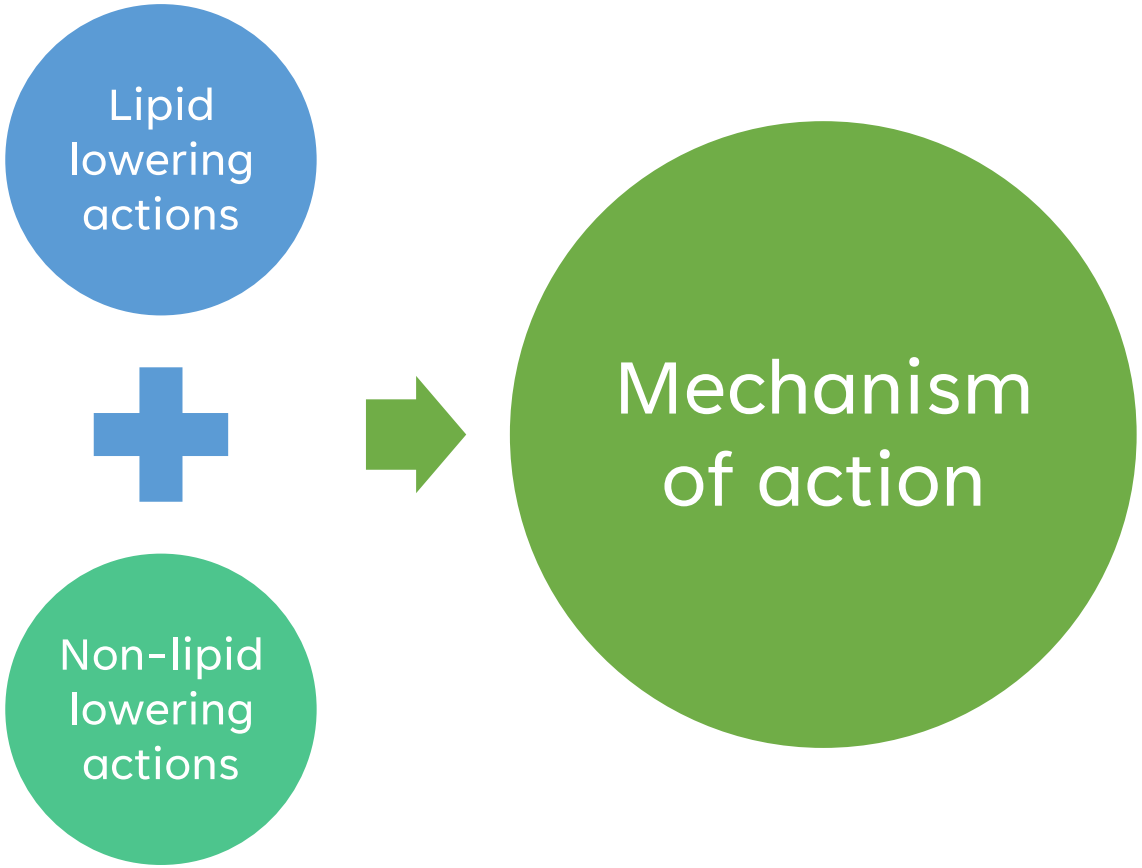
CHEMISTRY

- Structurally similarity to 3-hydroxy-3-methylglutaryl coenzyme A
- Lovastatin & Simvastatin are inactive prodrugs
- Pravastatin....open active lactone ring
- Atrovastatin, fluvastatin & rosuvastatin are fluorine containing congeners that are active

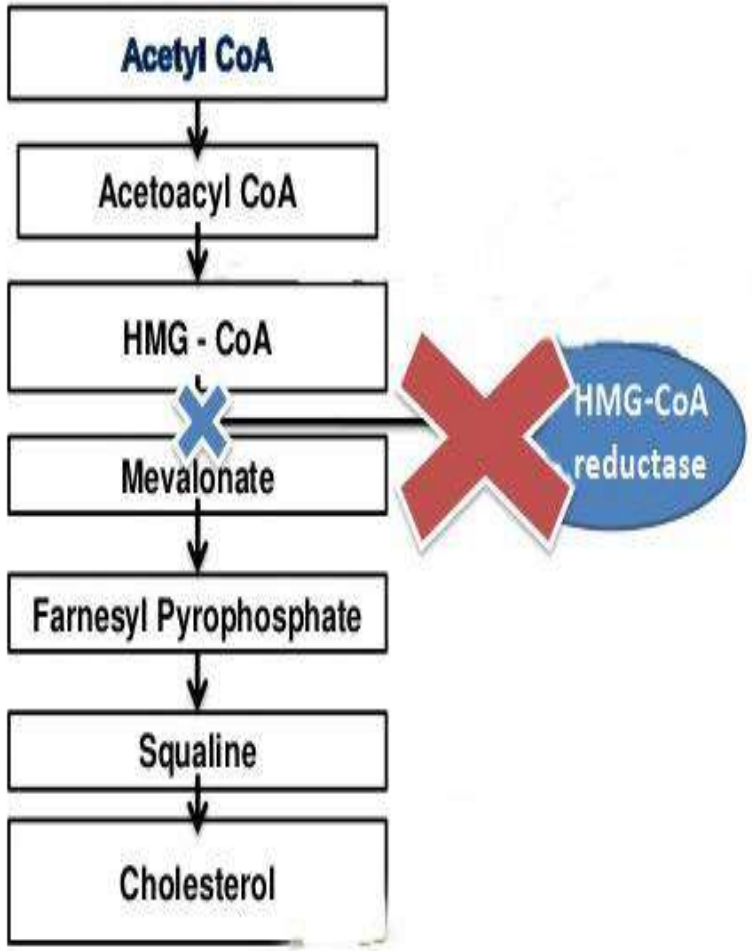


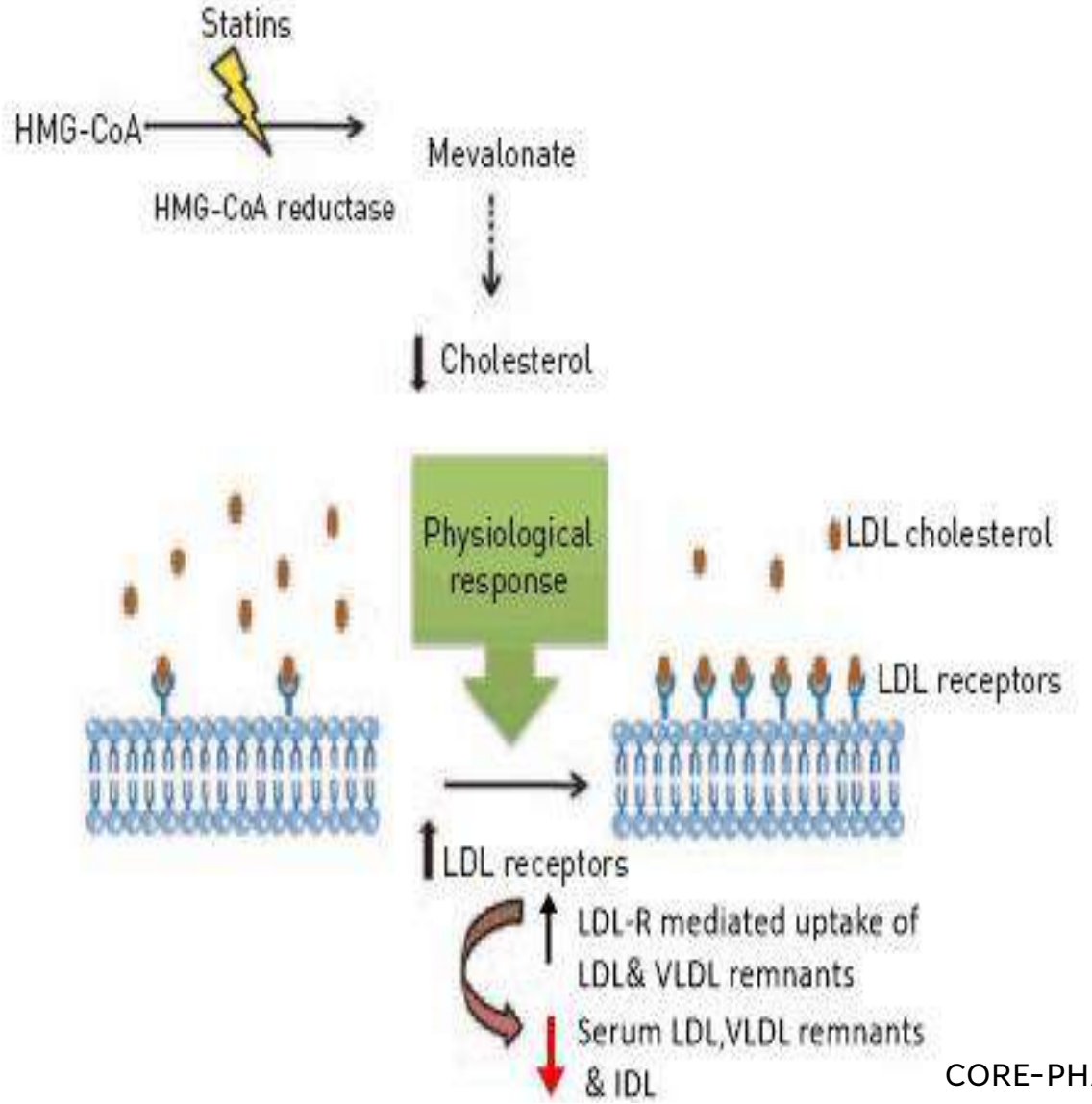
STATINS

MECHANISM OF ACTION



LIPID LOWERING MECHANISM





STATINS
(HMG-COA INHIBITORS)

POTENCY & DOSE

Table 1 High-, Moderate-, and Low-Intensity Statin Therapy

High-Intensity	Moderate-Intensity	Low-Intensity
LDL-C reduction ≥50% with daily dosing	LDL-C reduction 30%-<50% with daily dosing	LDL-C reduction <30% with daily dosing
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 80 mg XL 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

LDL-C: LDL-cholesterol; XL: extended-release. Source: Reference 7.

MECHANISM OF ACTION (STATINS)

NON-LIPID LOWERING EFFECTS

Protein prenylation — Reduce availability of isoprenoids

- Disrupt cell signaling pathways(Rho and Rab)

Anti-inflammatory — Decrease protein C

- Plaque stabilization

Anti-thrombotic — Decrease prothrombin activation

- Enhance fibrinolysis

Anti-oxidant — Decrease oxidation of LDL

- Inhibit vascular smooth muscle proliferation

Anti-platelet — Reduce platelet aggregation

- Enhance endothelial response to NO

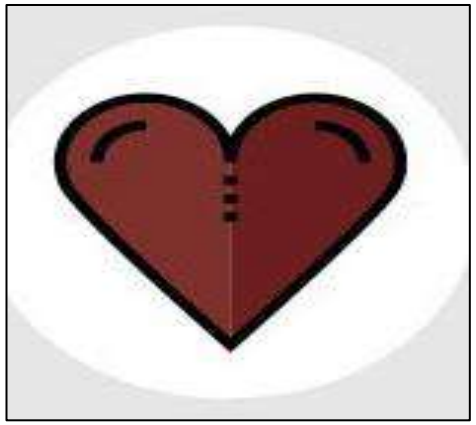
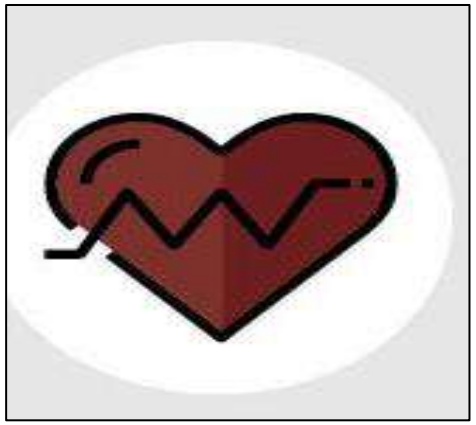
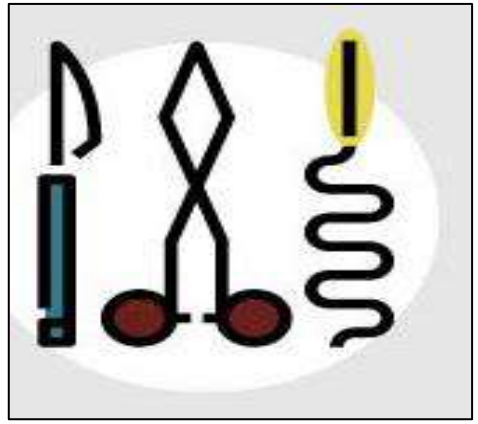
STATINS

PHARMACOKINETICS

- Oral admin. before going to bed as cholesterol synthesis occurs predominantly at night
- Prodrugs are hydrolyzed in GIT to active forms
- Absorption....40-75% except fluvastatin...100% and is affected differently by food
- Lovastatin and simvastatin cross the blood brain barrier
- Extensive first pass metabolism (60% approximately)
- Metabolized by CYP3A4(simvastatin, lovastatin ,atorvastatin) and CYP2C9 (fluvastatin,rosuvastatin,pitavastatin)
- Short half lives of less than 4 hours except atorvastatin (14hrs) & rosuvastatin (20 hrs)
- Excretion mainly in bile only 5-20% in urine

STATINS

THERAPEUTIC USES

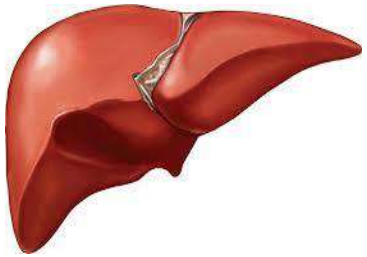





- Reduce LDL in all types of hyperlipidemia (alone or combination with other drugs)
  Familial hypercholesterolemia (with resins/ezetimibe)
  Familial combined hyperlipoproteinemia (with niacin,fibrates & resins)
- Secondary prevention of MI or stroke in patients with evidence of CHD
- Primary prevention of arterial disease

ADVERSE EFFECTS OF STATIN

Muscular damage

Hepatotoxicity



Neurological effects

GIT

Skin

Impaired glucose level

STATINS

DRUG INTERACTIONS

- **Increase plasma conc. of statins**
  - **CYP3A4** - macrolide antibiotics, azole antifungals, fibrates, cyclosporine, HIV protease inhibitors, paroxetine, venlafaxine
  - **CYP2C9 –** Ketoconazole, metronidazole, sulfinpyrazone, amiodarone, cimetidine

- **Decrease plasma conc. of statins**
  - Phenytoin, griseofulvin, barbiturates, rifampin

- Increase plasma levels of certain drugs by inhibiting CYP(warfarin)

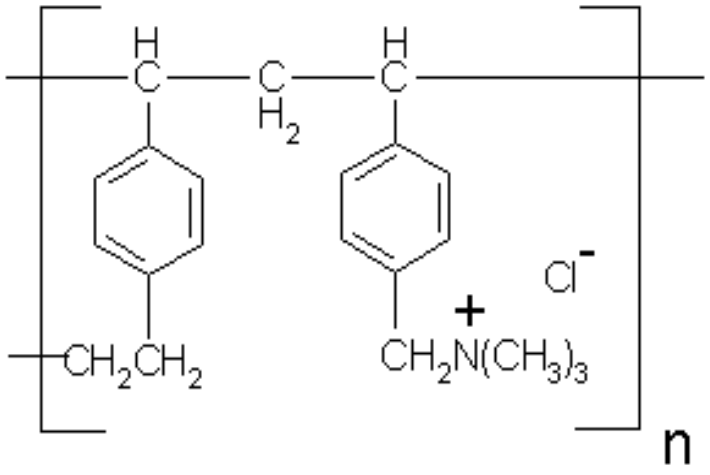
- Increase risk of myopathy with niacin, fibric acid derivatives, verapamil & amiodarone

Increase Cholesterol (bile acid) excretion
(Bile- acid sequestrants)

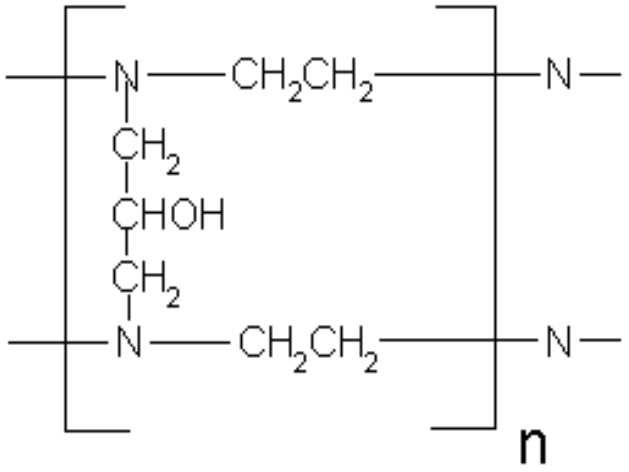
BILE ACID SEQUESTRANT

CHEMISTRY

High molecular weight polymers with a chloride ion



Cholestyramine Resin



Colestipol hydrochloride

BILE ACID SEQUESTRANT

MECHANISM OF ACTION

Bind negatively charged bile acids and salts in intestine

- Non-absorbable complexes excreted in feces

Decrease return of bile acids to liver

- Stimulate conversion of cholesterol to bile acids by increasing 7α hydroxylase

Decrease hepatic cholesterol

- ↑ LDL receptors
- ↑ Clearance of LDL

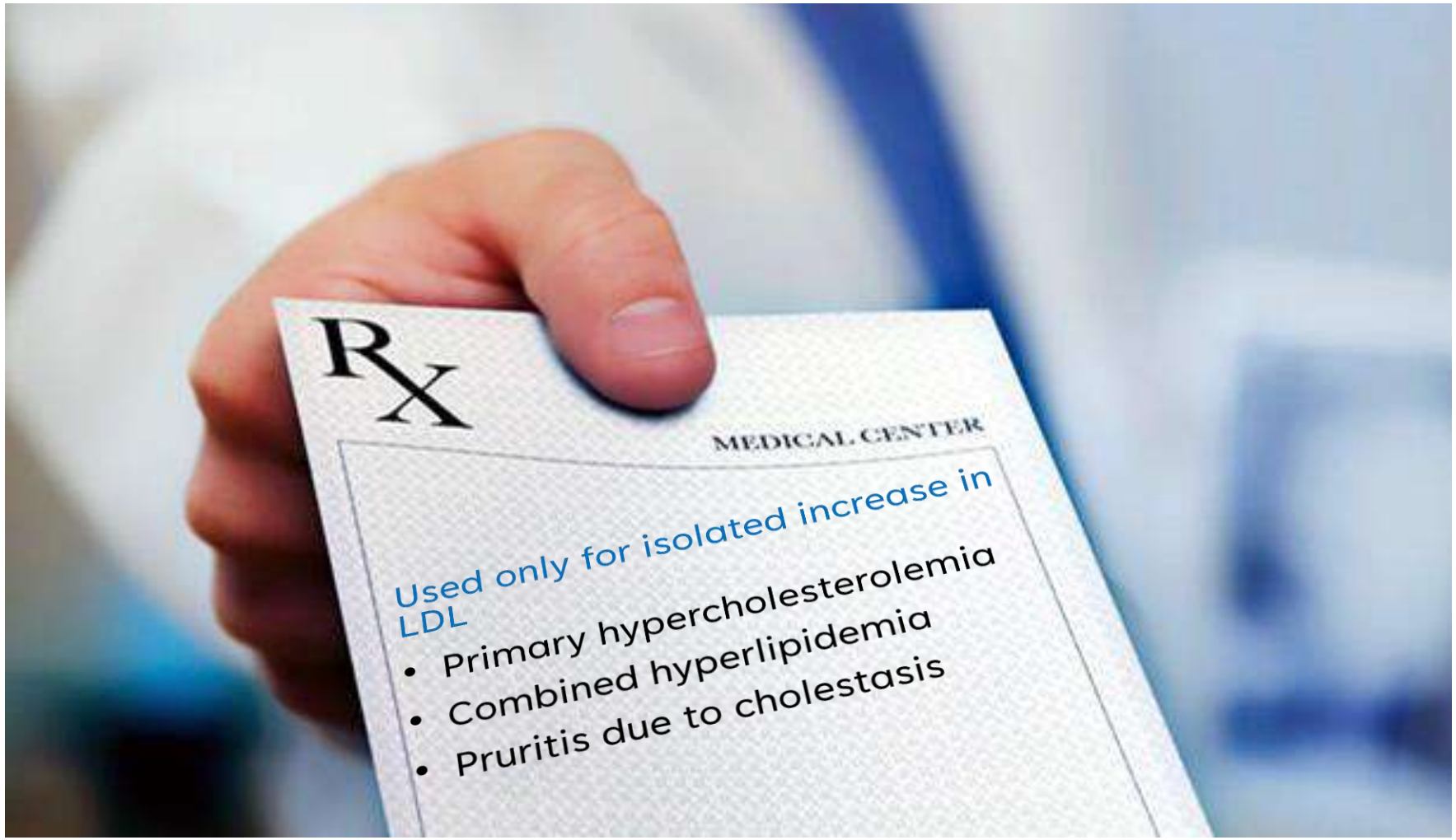
BILE ACID SEQUESTRANT

PHARMACOKINETICS

- Not reabsorbed from GIT
- Action begins within 1-4 days
- Peak in 1-2 weeks
- Resins should never be taken in dry form (mix with juice or water)

Cholestyramine available as granular powder
Colestipol is available as dry powder & tablet
Colevesalam is available as tablet and suspension

BILE ACID SEQUESTRANT



BILE ACID SEQUESTRANT

Gastrointestinal

- Abdominal bloating, flatulence, dyspepsia
- Constipation, steatorrhea

Vitamin malabsorption

- Bleeding due to Vitamin K deficiency
- Fat soluble vitamins

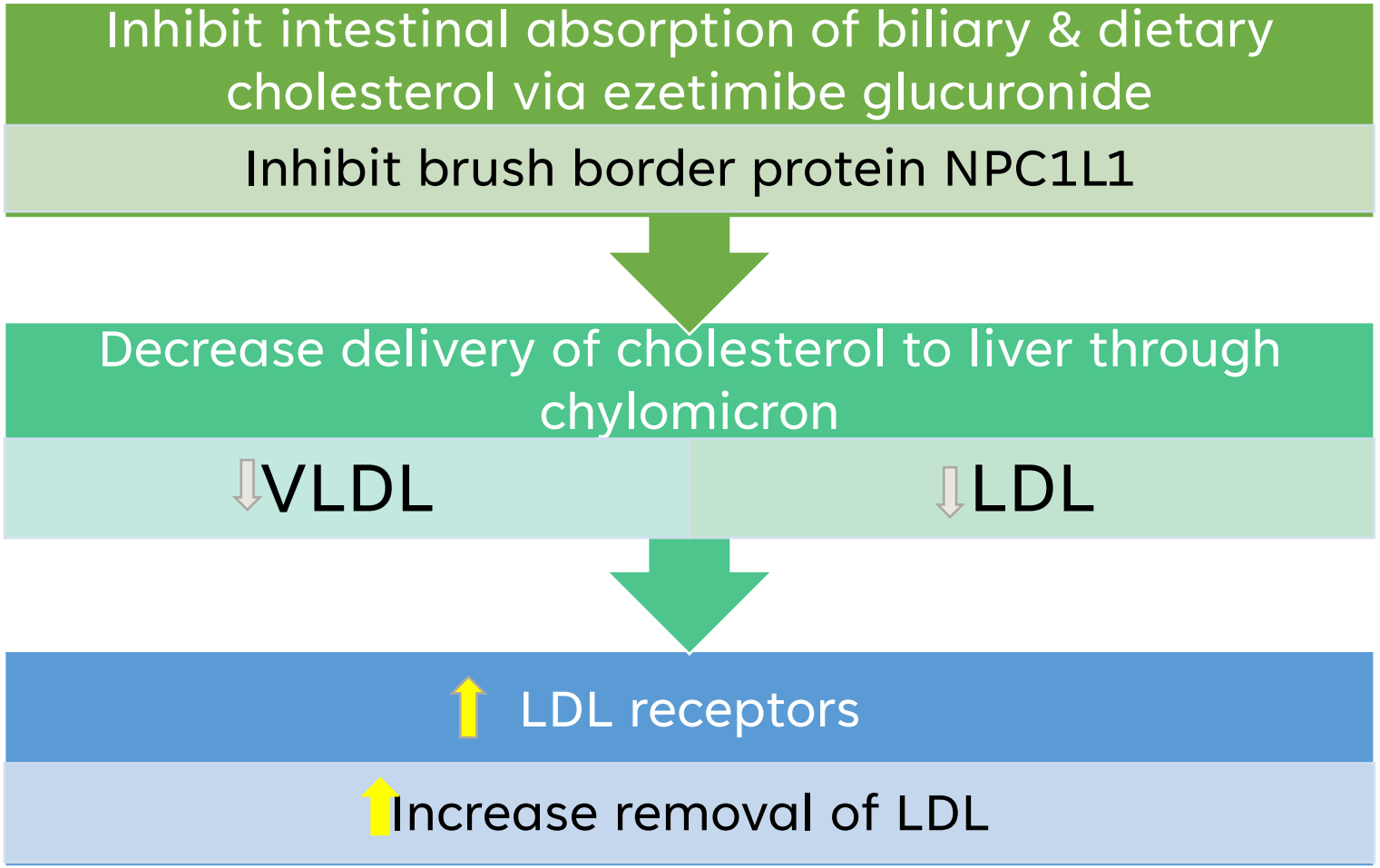
Drug interactions

- Impaired absorption of drugs (digoxin, thiazide, warfarin, tetracycline etc)
- Colesevelam doesn't interfere with absorption of co administered

Inhibition of intestinal sterol absorption (Ezetimibe)

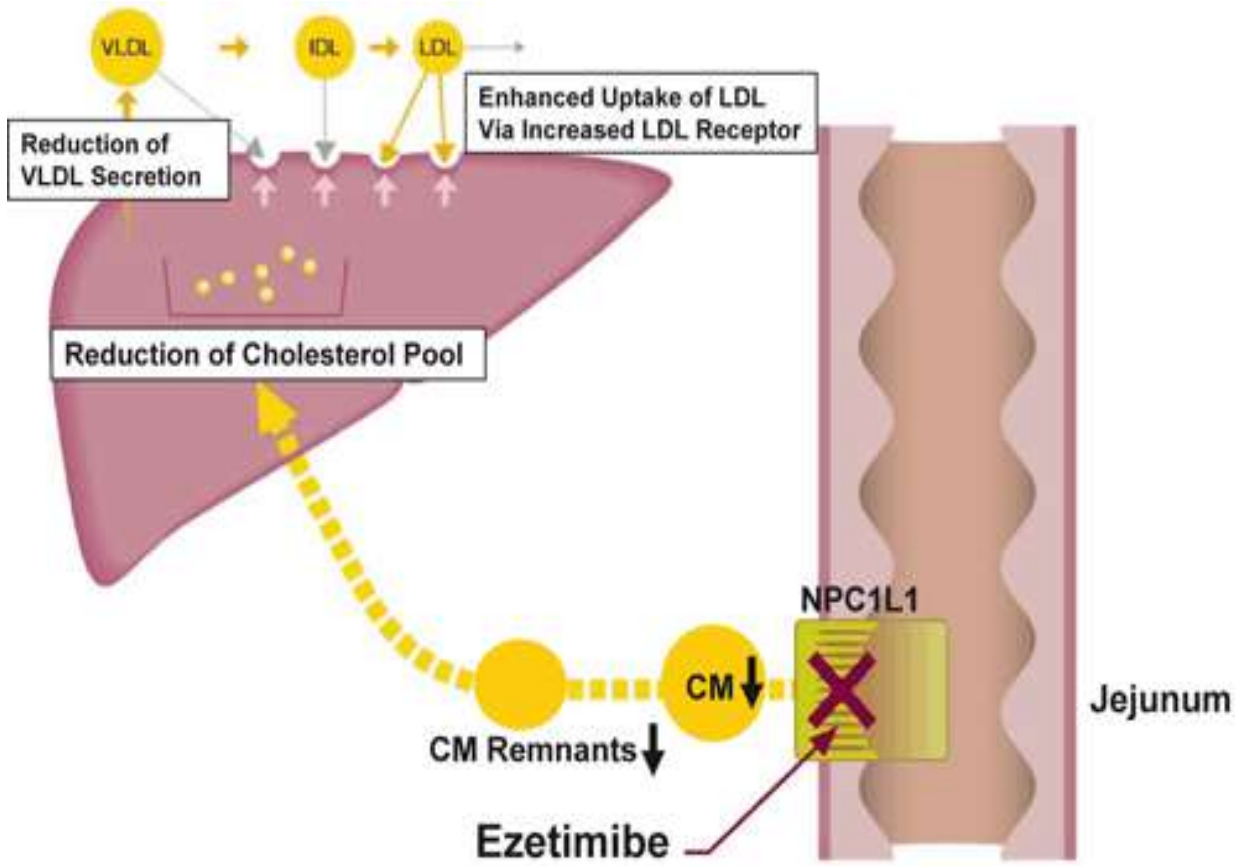
EZETIMIBE

MECHANISM OF ACTION



EZETIMIBE

MECHANISM OF ACTION



LDL

18% (alone)

LDL

25% (with statin)

EZETIMIBE

PHARMACOKINETICS

- Readily absorbed & conjugated in intestine to active glucuronide
- Reaches peak plasma concentration in 12-14 hours
- Half life is 22 hours
- Metabolized in intestine and liver
- Excreted in feces (80%) and urine

EZETIMIBE

THERAPEUTIC USES

- Primary hypercholesterolemia
- Phytosterolemia

ADVERSE EFFECTS

- Impaired hepatic function

1. Myositis

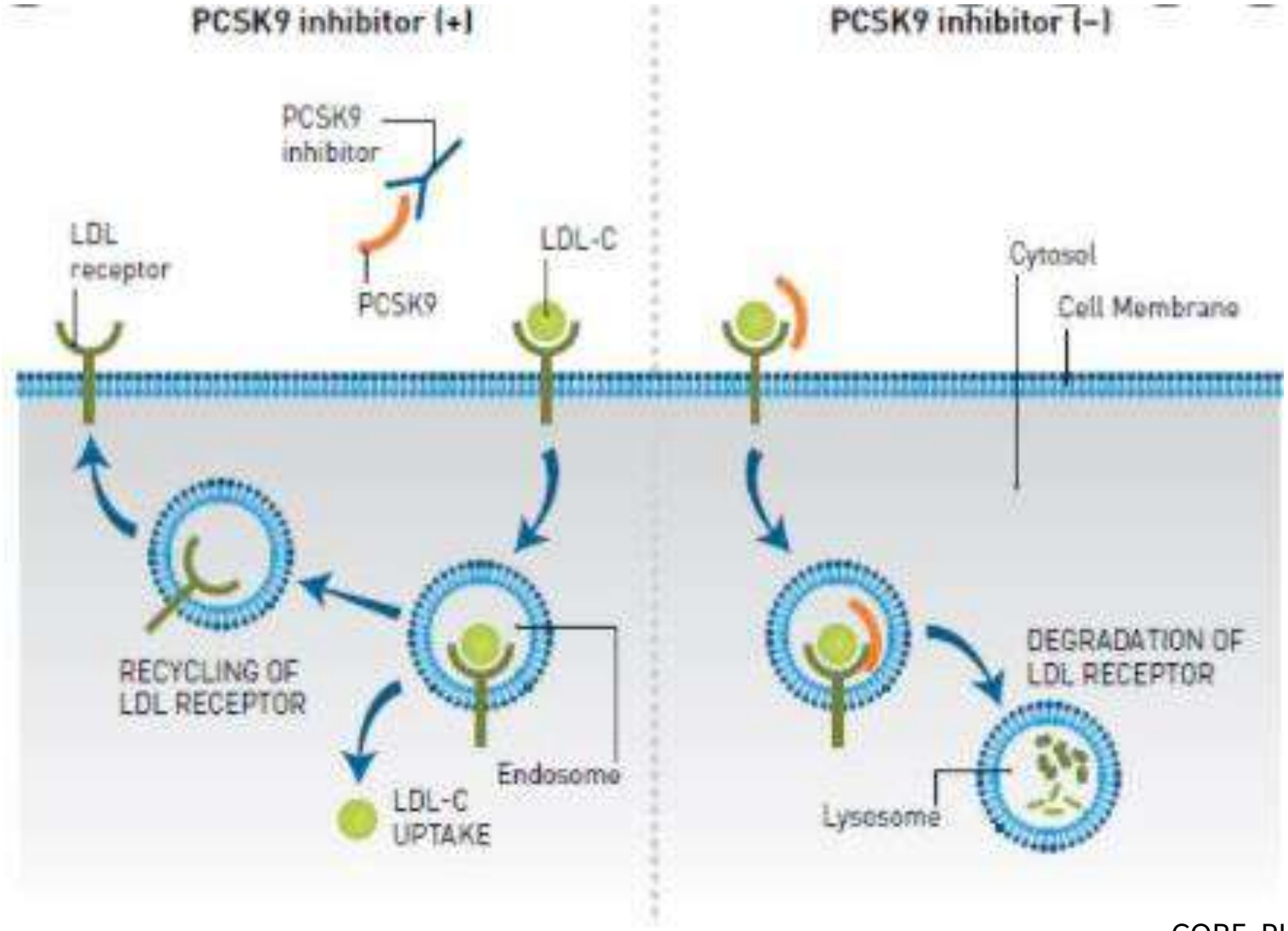
Drugs preventing LDL receptor degradation

(Proprotein convertase subtilisin kexin type -9 inhibitors)

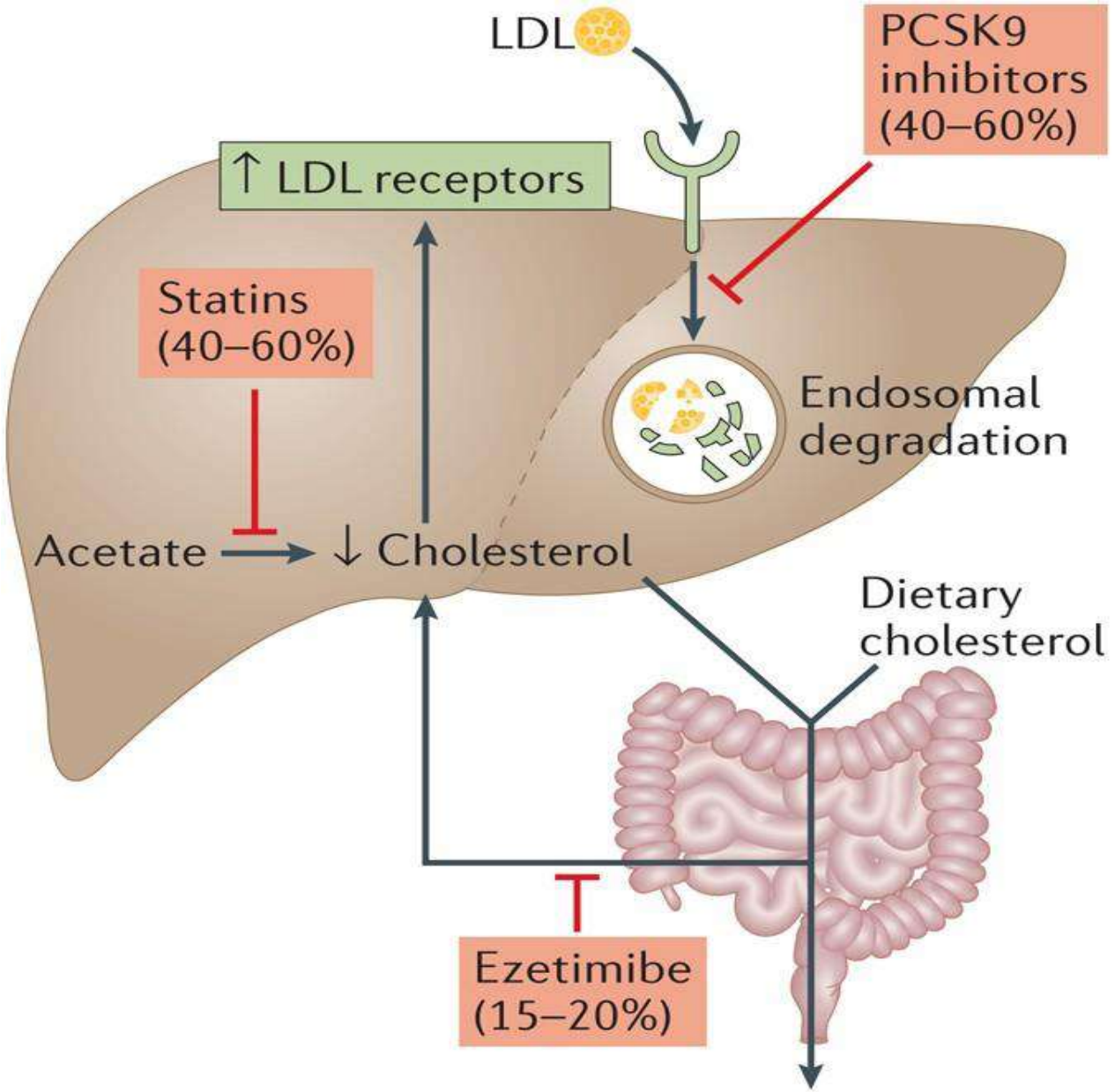
PCSK9 INHIBITORS

- Monoclonal antibodies that prevent PCSK9 mediated degradation of LDL receptors
- Administered subcutaneously every 2 weeks/ once monthly
- Indicated for patients with familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional reduction of LDL
- Adverse effects include injection site reactions and risk of infections

PCSK9 INHIBITORS



VERTICAL INTEGRATION WITH FAMILY MEDICINE



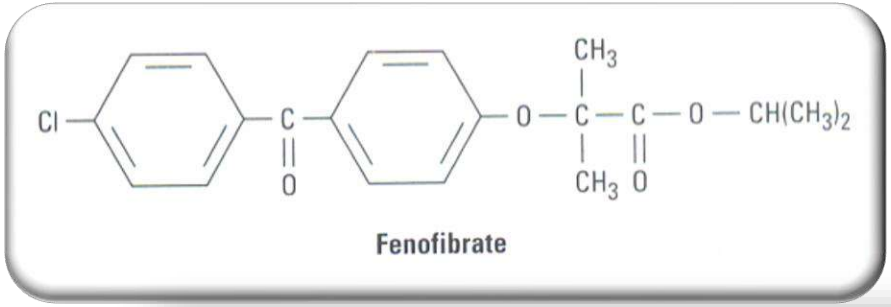
REDUCE THE RISK OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASES

Drugs altering lipoprotein production (Fibric acid derivatives)

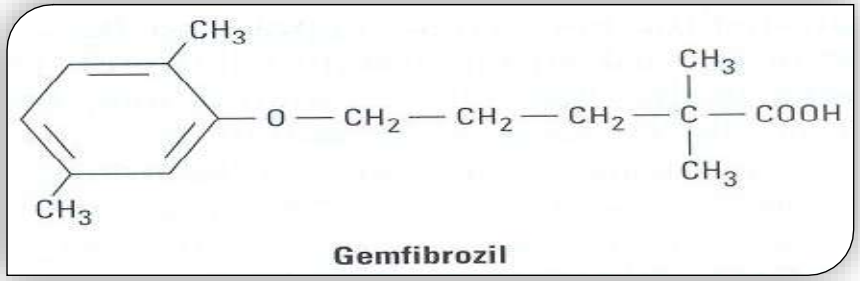
FIBRIC ACID DERIVATIVES (FIBRATES)

CHEMISTRY

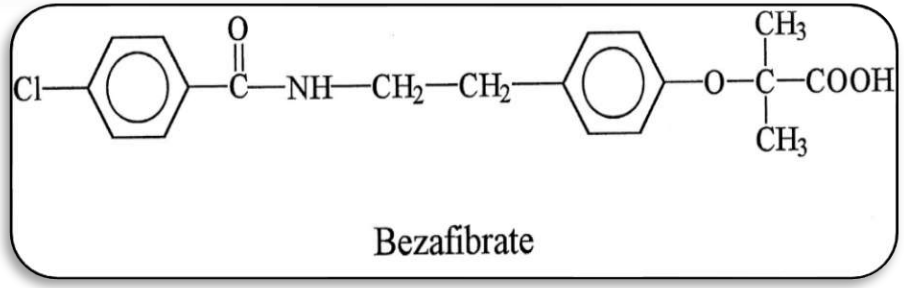
Derivatives of branch chained carboxylic acid known as fibric acid



Fenofibrate

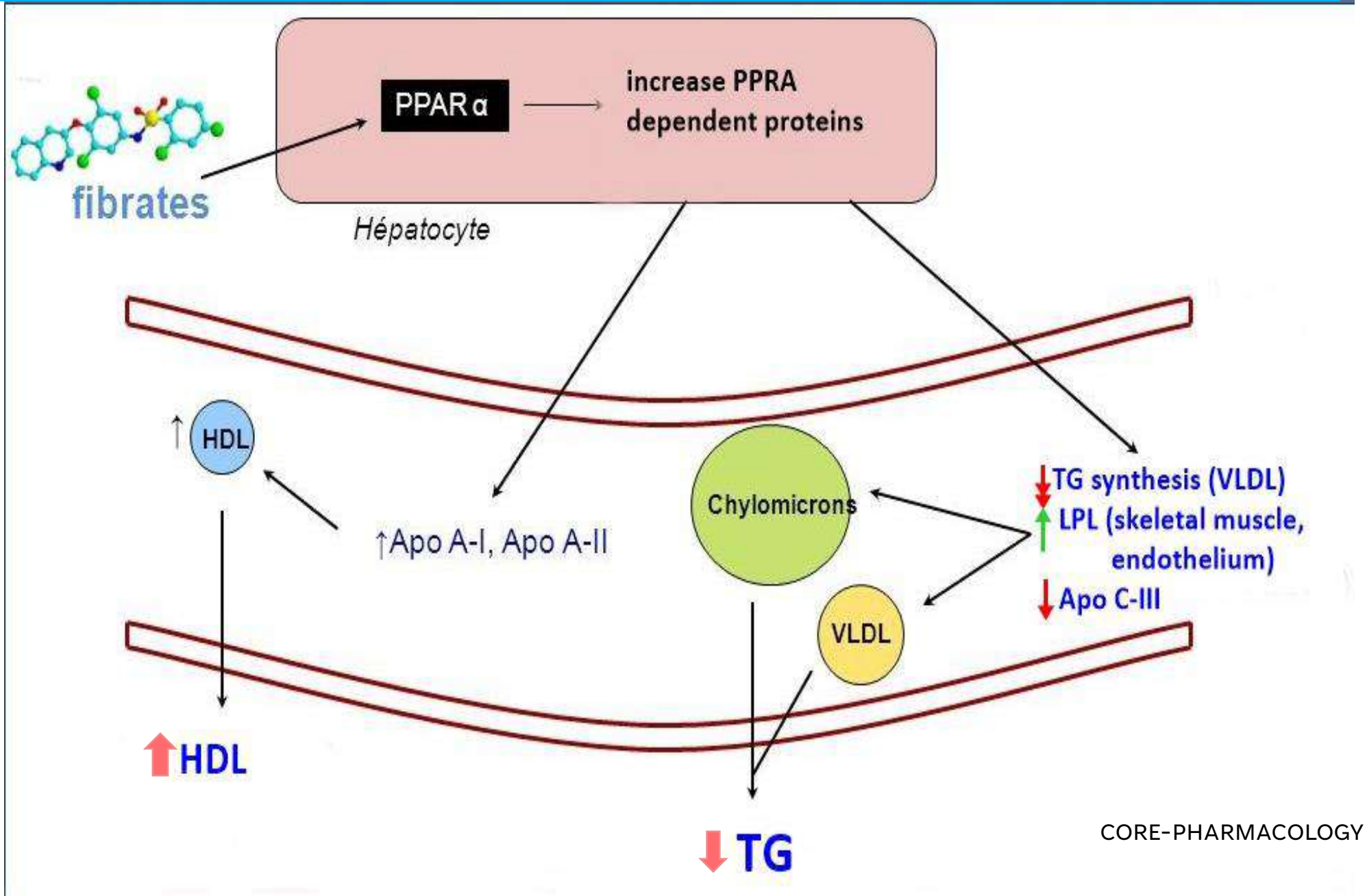


Gemfibrozil



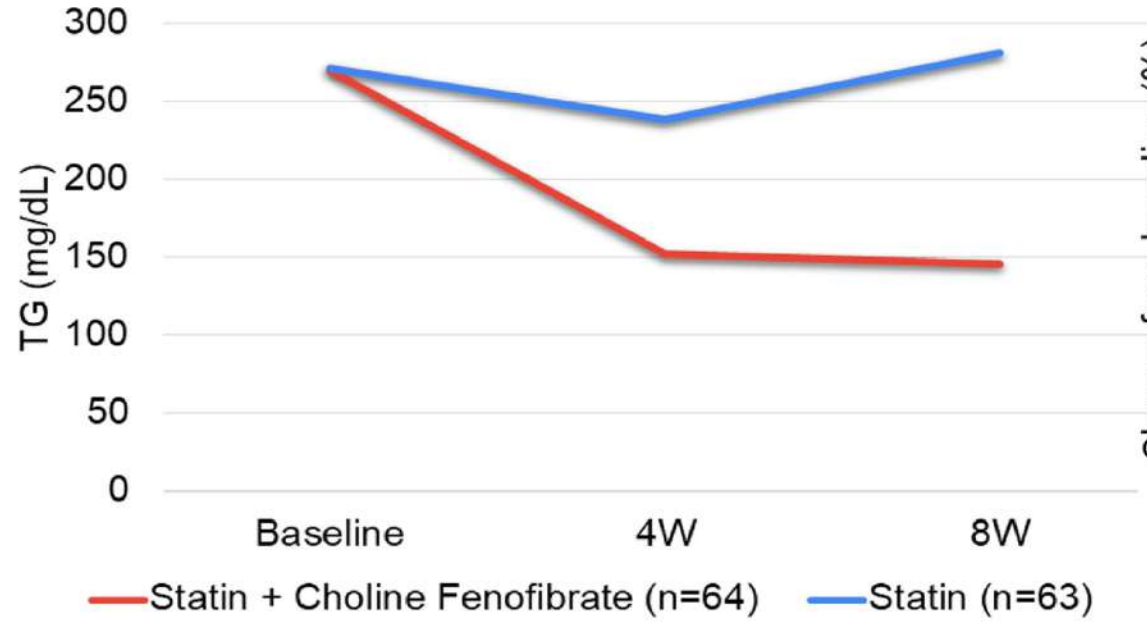
Bezafibrate

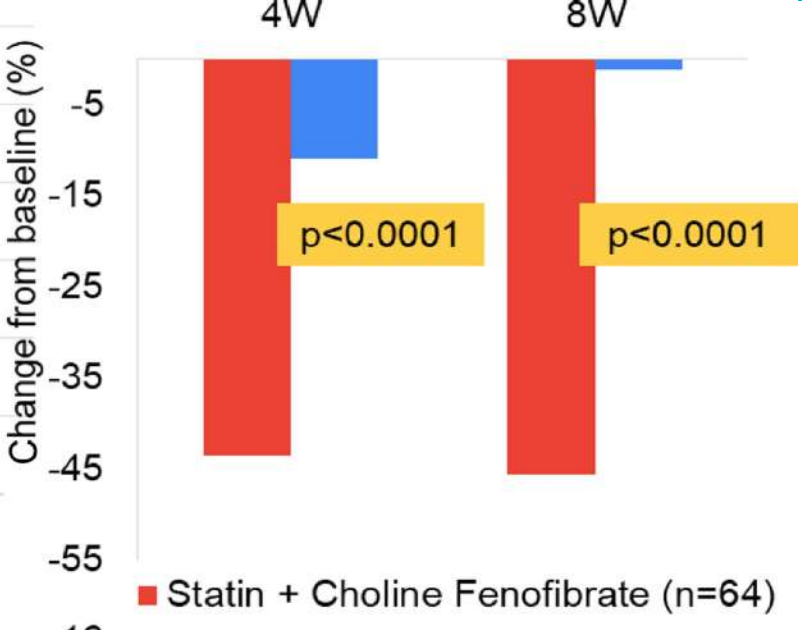
FIBRIC ACID DERIVATIVES (FIBRATES)

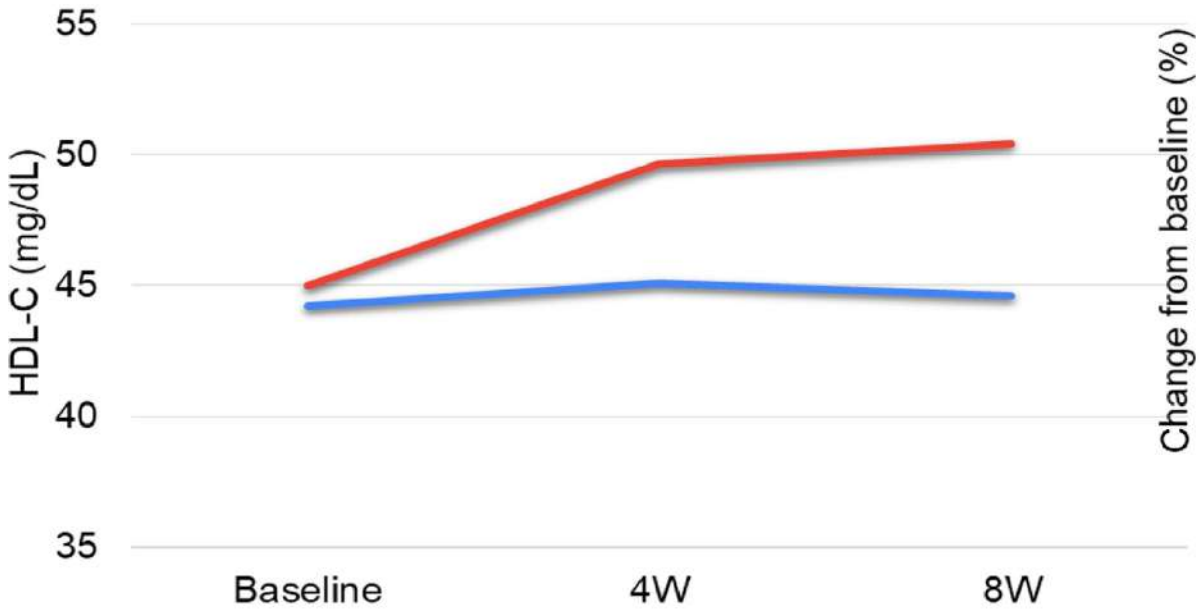


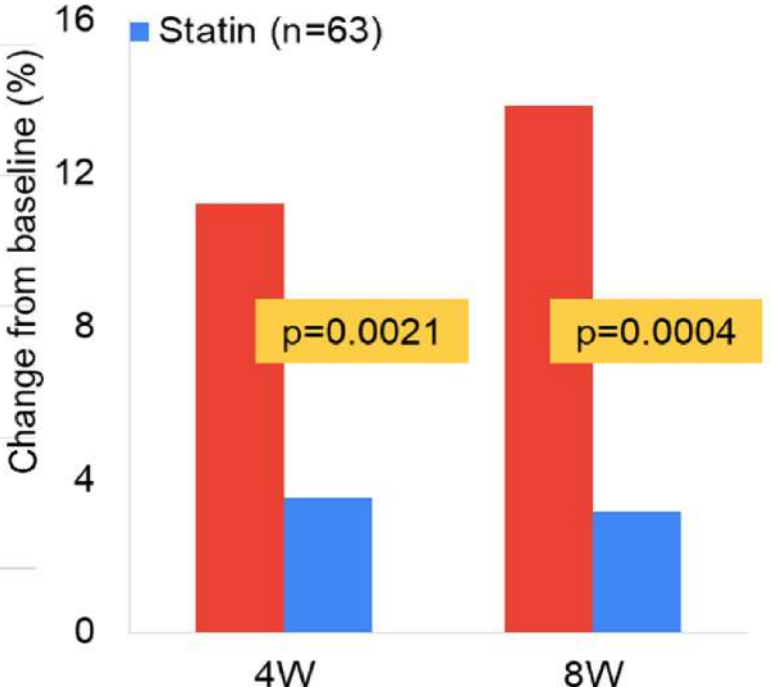
FIBRIC ACID DERIVATIVES (FIBRATES)

RESEARCH









FIBRIC ACID DERIVATIVES (FIBRATES)

PHARMACOKINETICS

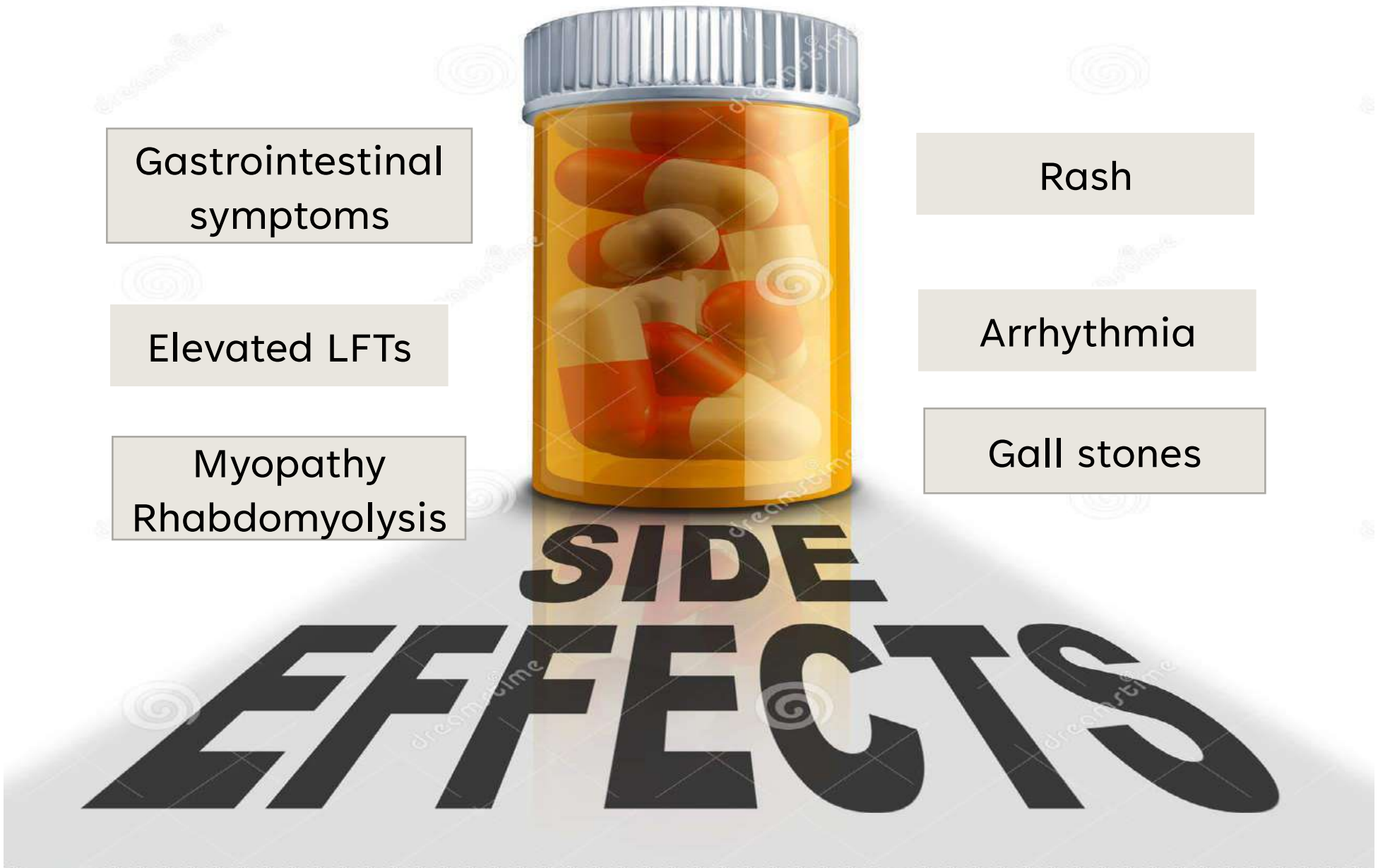
- Well absorbed from GIT after oral administration
- More than 95% of the drug is plasma protein bound
- Gemfibrozil crosses placenta
- *t*1/2 ranges from 1.1 hr (gemfibrozil) to 20 hr (fenofibrate)
- Excretion mainly in urine as glucuronide conjugates (60-90%) with smaller amounts in feces.

FIBRIC ACID DERIVATIVES (FIBRATES)

THERAPEUTIC USES

- Hypertriglyceridemic patients with predominantly raised VLDL
- Dysbetalipoproteinemias
- Hypertriglyceridemia due to viral protease inhibitors

FIBRIC ACID DERIVATIVES (FIBRATES)



- Gastrointestinal symptoms
- Elevated LFTs
- Myopathy
  Rhabdomyolysis
- Rash
- Arrhythmia
- Gall stones

FIBRIC ACID DERIVATIVES (FIBRATES)

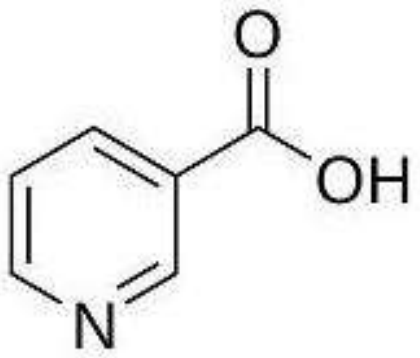
Contraindications	• Pregnancy & lactation • Renal & hepatic impairment • Gall bladder disease(preexisting)
Drug interactions	• Oral anticoagulant

Drugs altering lipoprotein production (Nicotinic acid derivatives)

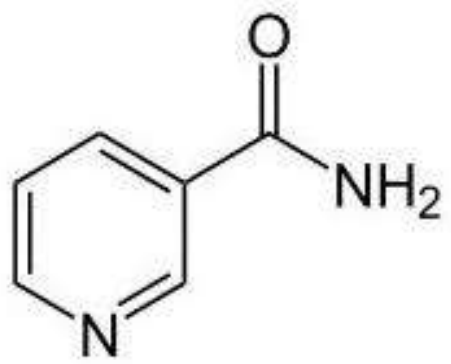
NIACIN

CHEMISTRY

- Niacin(nicotinic acid) is also known as vitamin B3
- Converted in the body to enzyme cofactors (NAD & NADP)required for oxidative reactions in the metabolism of energy substrates and other substances

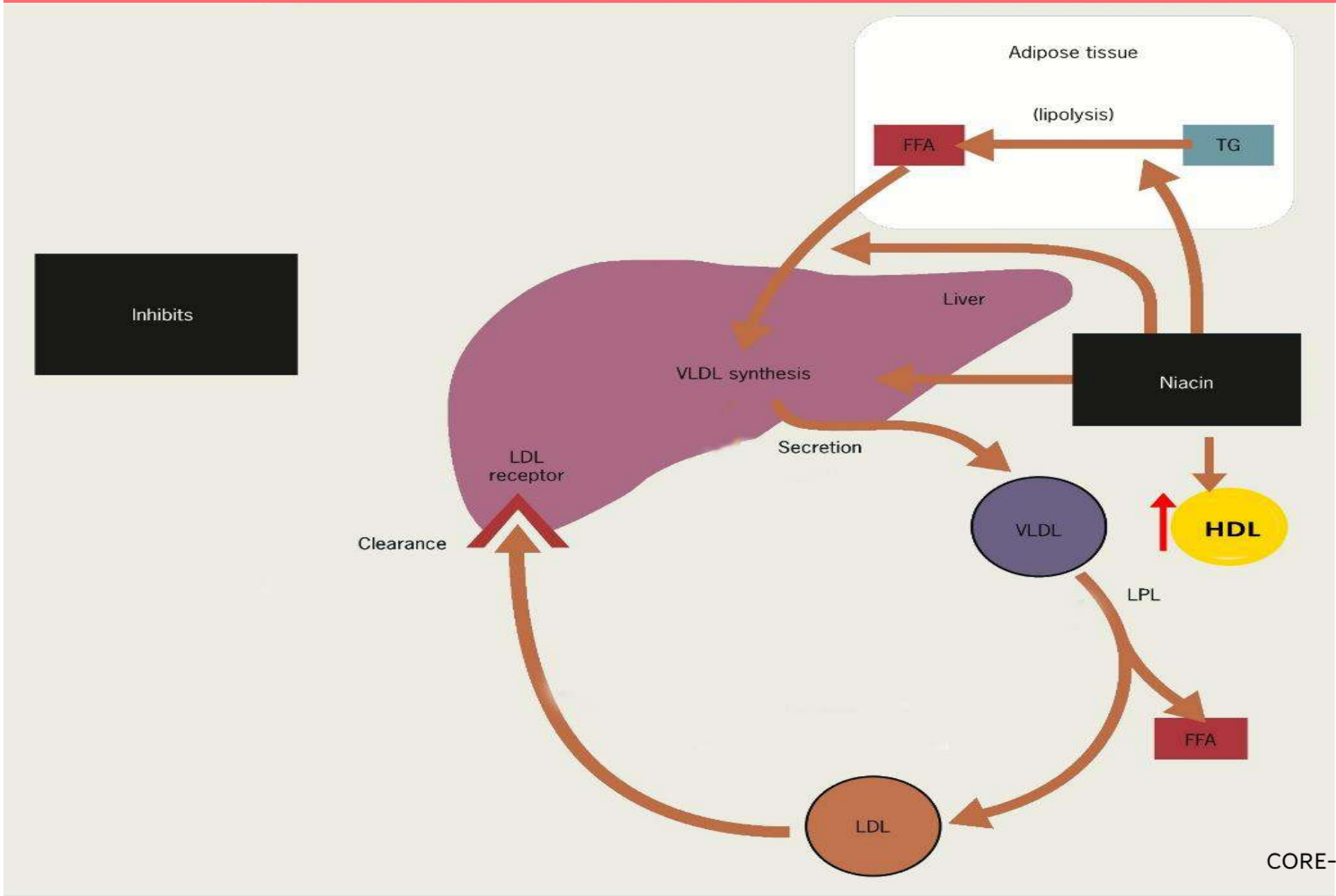


Niacin



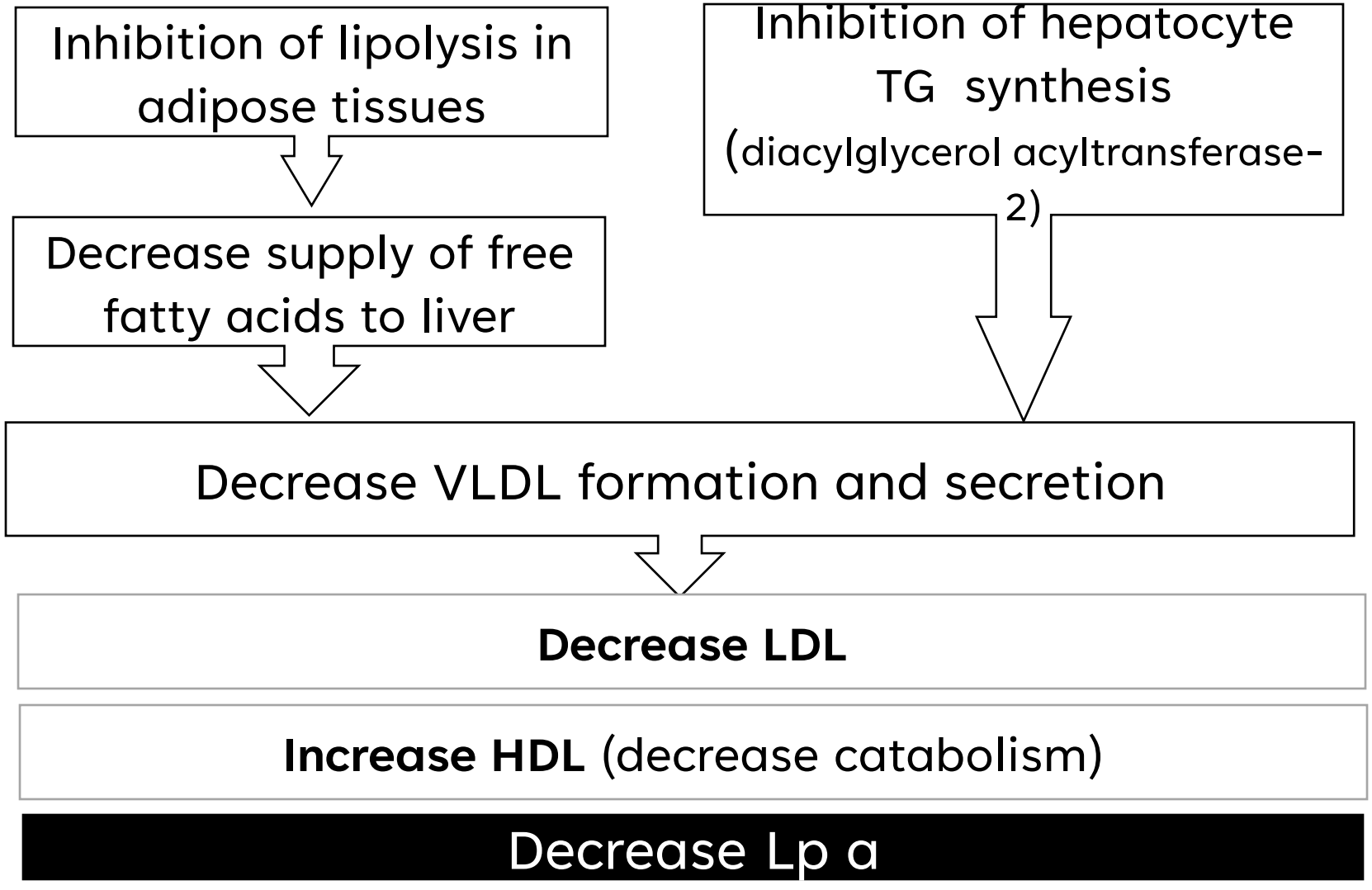
Nicotinamide

NIACIN


Adipose tissue
(lipolysis)
FFA
TG
Inhibits
Liver
VLDL synthesis
Niacin
Secretion
LDL
receptor
Clearance
VLDL
HDL
LPL
FFA
LDL

NIACIN

MECHANISM OF ACTION



NIACIN

TABLE 25–3 Pleiotropic Effects of Niacin

Lipoprotein	Vascular	Thrombosis	Other
Increases HDL ↑ HDL-C ↑ ApoA-I ↓ ApoA-II ↑ large HDL_2	Stabilizes plaque and new lesion formation ↓ lipid core by reverse cholesterol transport	Inhibits thrombosis ↑ fibrinolysis ↓ coagulation factors	Limits ischemia and reperfusion injury, possibly by preservation of glycolysis
Reduces LDL ↓ LDL-C ↓ Small LDL ↓ LDL oxidation	↓ Vascular inflammation	↓ Platelet adhesion and aggregation ↓ fibrinogen ↓ blood viscosity	
VLDL ↓ VLDL-C ↓ VLDL triglycerides Reduces Lp(a)	Improves endothelial function ↑ NO synthase activity ↑ Vasodilation		

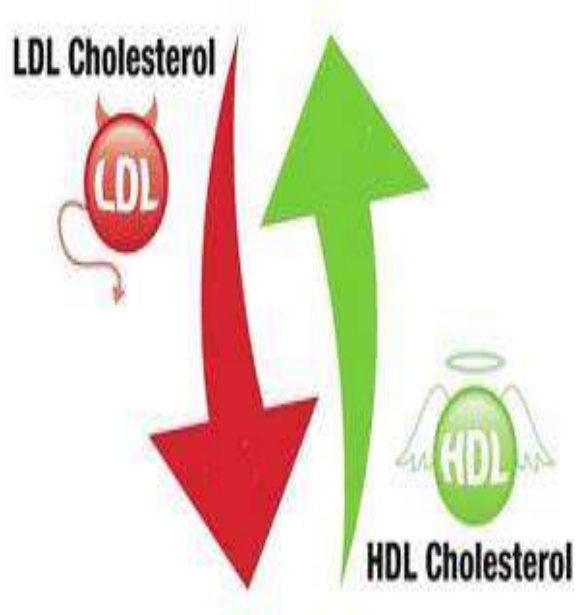
NIACIN

PHARMACOKINETICS

- Well absorbed
- t1/2 60 mins - TDS dosing
- Metabolized by the liver
- Metabolite nicotinuric acid found in urine

NIACIN

THERAPEUTIC USES



- Familial hypercholesterolemia
- Combined hyperlipidemia
- Dysbetalipoproteinemia
- Mixed lipemia

VITAMIN B3/NIACIN side effects

Intense cutaneous flush & feeling of warmth	Impaired glucose control
Skin reactions	Arrhythmia
Nausea, abdominal pain	Blurring of vision
Impairment of LFTs	Terratogenicity in animals
Hyperurcemia	

NIACIN

Contraindications

- Pregnancy
- Lactation
- Peptic ulcer
- Gout
- Diabetes
- Liver impairment

TABLE 15.3 Effects of Diet and Drug Therapy on Serum Lipid Concentrations

THERAPY	LDL-C % CHANGE	HDL-C % CHANGE	TRIGLYCERIDES % CHANGE	OTHER EFFECTS
Dietary modifications	↓ 10–25	Typically ↑	↓ 10–25	Decreased weight and blood pressure
Statins	↓ 20–60	↑ 5–10	↓ 10–30	Increase in hepatic LDL receptors
Bile acid sequestrants	↓ 15–30	↑ 3–5	No change	Increase in hepatic LDL receptors
Fibric acid derivatives	↓ 5–20	↑ 5–20	↓ 30–50	Activation of lipoprotein lipase
Ezetimibe	↓ 20	No change	↓ 8	—
Niacin	↓ 10–25	↑ 15–35	↓ 25–30	Decrease in lipolysis and lipoprotein (a)

HDL-C, High-density–lipoprotein cholesterol; *LDL-C*, low-density–lipoprotein cholesterol.

NEWER DRUGS

Drugs used in Dyslipidemia

Lomitapide	• Reduce production of VLDL • Inhibit microsomal triglyceride transfer protein (MTTP)
Mipomersen	• Prevent synthesis of apo B for VLDL production
Evolocumab Alirocumab	• Prevent destruction of LDL receptors
Metreleptin	• Leptin analogue

Drugs used in Dyslipidemia

Probucol	• Decrease LDL • Antioxidant
Inclisiran	• RNAi inhibitor of PCSK 9
Bempedoic acid	• ATP-Citrate Lyase Inhibitor
Volanesoren	• Antisense Oligonucleotide Inhibitor of Apo C-III
Evacinumab	• Angiopoeitin Like -3 inhibition
CETP inhibitors	• Inhibit CETP
	• Decrease Lp(a)
Adjuvants	• Omega 3 fatty acids • Orlistat • α tocopherol

RESEARCH

Agnello F, Ingala S, Laterra G, Scalia L, Barbanti M. Novel and Emerging LDL-C Lowering Strategies: A New Era of Dyslipidemia Management. *Journal of Clinical Medicine*. 2024; 13(5):1251. https://doi.org/10.3390/jcm13051251

ARTIFICIAL INTELLIGENCE

Krentz AJ, Haddon-Hill G, Zou X, Pankova N, Jaun A. Machine Learning Applied to Cholesterol-Lowering Pharmacotherapy: Proof-of-Concept in High-Risk Patients Treated in Primary Care. Metab Syndr Relat Disord. 2023 Oct;21(8):453-459. doi: 10.1089/met.2023.0009. Epub 2023 Aug 30. PMID: 37646719.

Machine learning can be of value in
(a) quantifying suboptimal lipid-lowering prescribing patterns,
(b) identifying high-risk patients who could benefit from more intensive therapy, and
(c) suggesting evidence-based therapeutic options.

BIOETHICS

Krentz AJ, Haddon-Hill G, Zou X, Pankova N, Jaun A. Machine Learning Applied to Cholesterol-Lowering Pharmacotherapy: Proof-of-Concept in High-Risk Patients Treated in Primary Care. Metab Syndr Relat Disord. 2023 Oct;21(8):453-459. doi: 10.1089/met.2023.0009. Epub 2023 Aug 30. PMID: 37646719.

BIOETHICS

AMA Journal of Ethics®

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CASE AND COMMENTARY

Should a Physician Offer Recommendations Based on Experience but Contrary to Current Practice Guidelines?

Beth A. Lown, MD and Karen E. Victor, MD

END OF LECTURE ASSESSMENT

Mr S is a 50-year-old man who presents to his primary care physician in rural Pennsylvania. He is here to see Dr O for his annual physical examination

Mr S and Dr O begin with some social conversation, then discuss his current health and concerns and proceed to the physical exam, which suggests no abnormalities. Dr O reviews Mr S's recent bloodwork. Despite 6 months of lifestyle modifications, Mr S continues to have elevated low-density lipoprotein (LDL) and total cholesterol levels, and lower than normal high-density lipoprotein (HDL) cholesterol. Dr O thinks that Mr S should continue with the current plan and recheck his lipid panel in 6 months. However, Mr S is concerned that his high cholesterol will not significantly improve in another 6 months and asks Dr O, "Shouldn't I be taking statins or some kind of medication for my high cholesterol at this point, Doc?" Dr O answers as follows: "I don't prescribe statins, which are a class of cholesterol-lowering medications recommended by the American Heart Association. I have taken them myself and experienced terrible muscle pain, whichis a well-documented side effect, to the point where it affected my ability to walk.

Given my personal experiences with statins, I've stopped prescribing them altogether. My role as a good physician is to help improve your quality of life, not worsen it. Statins negatively affected my quality of life and I think they will negatively affect yours, too. Rather than statins, I recommend that you continue with lifestyle changes including increased exercise and a low-fat diet."