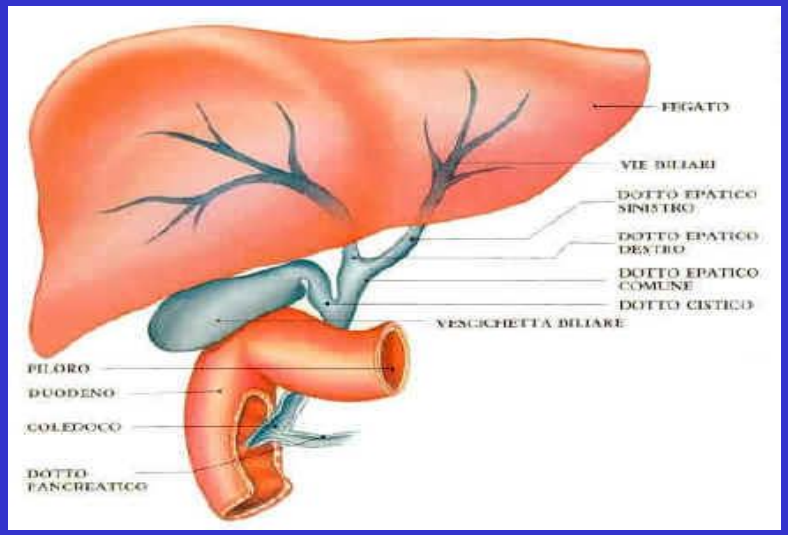
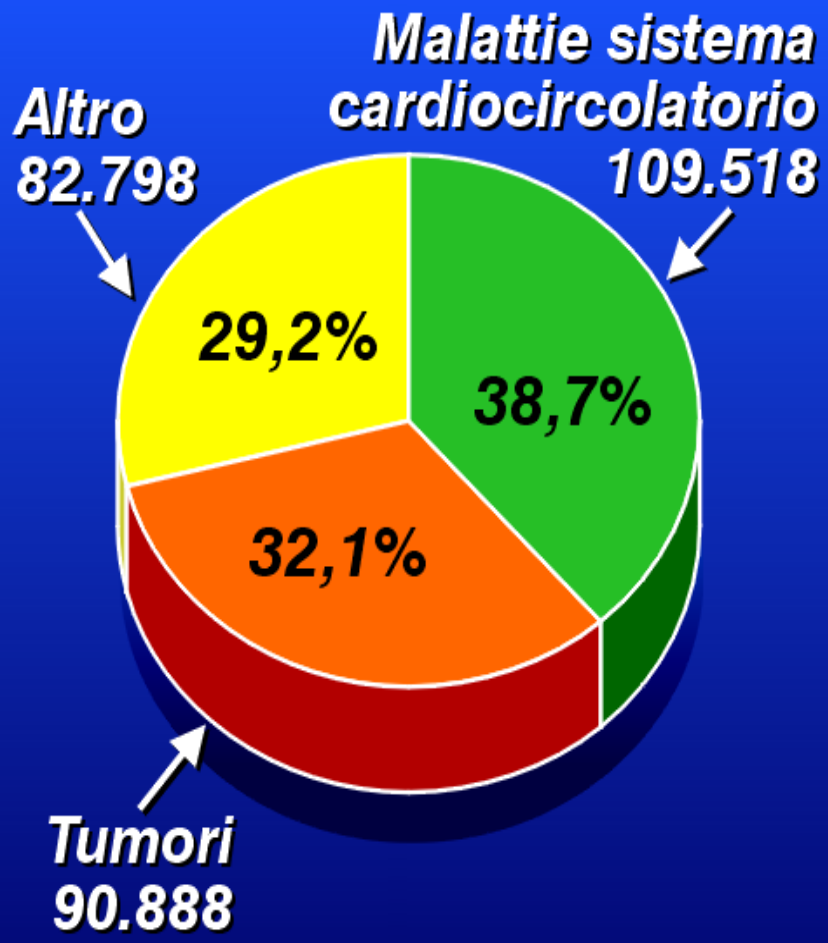
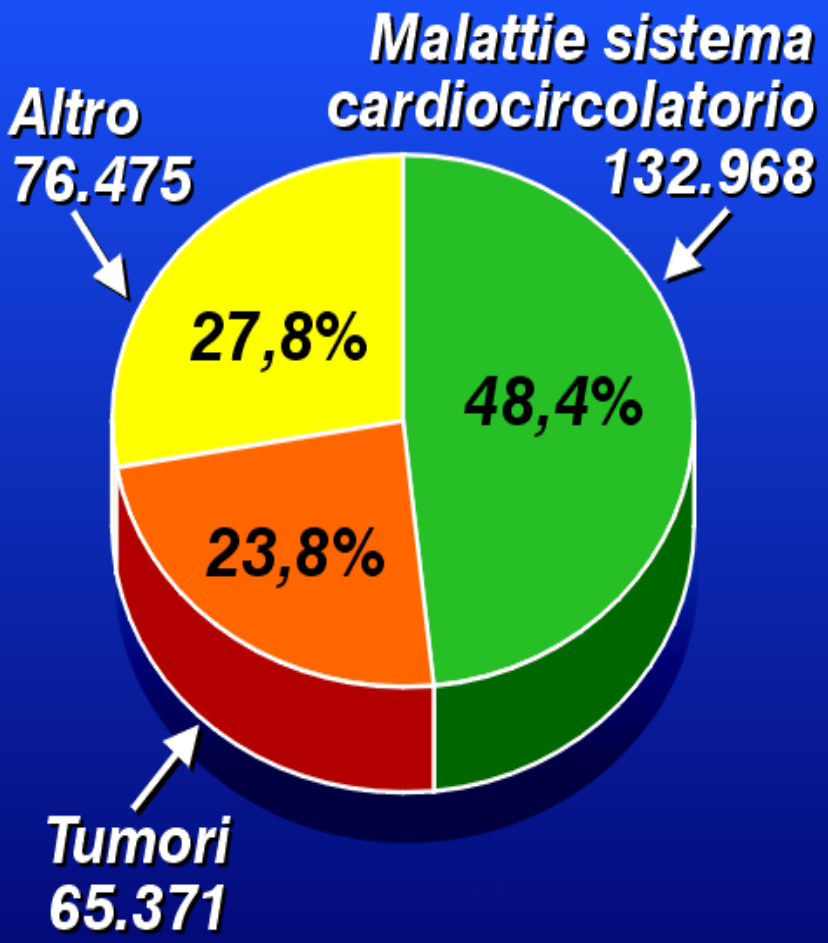
Anti-hyperlipidemic drugs



Principali cause di morte in Italia





Rapporti ISTISAN. 2001

CARDIOVASCULAR DISEASE (CVD) RISK FACTORS

Non-modifiable

- Personal history of CVD
- Family history of CVD
- Age
- Gender

Modifiable

- Dyslipidemia
- Obesity
- Diabetes mellitus
- Raised blood pressure
- Smoking
- Thrombogenic factors

Lipids present in the blood

- **Cholesterol**
- **Triglycerides**
- Phospholipids
- Free fatty acids

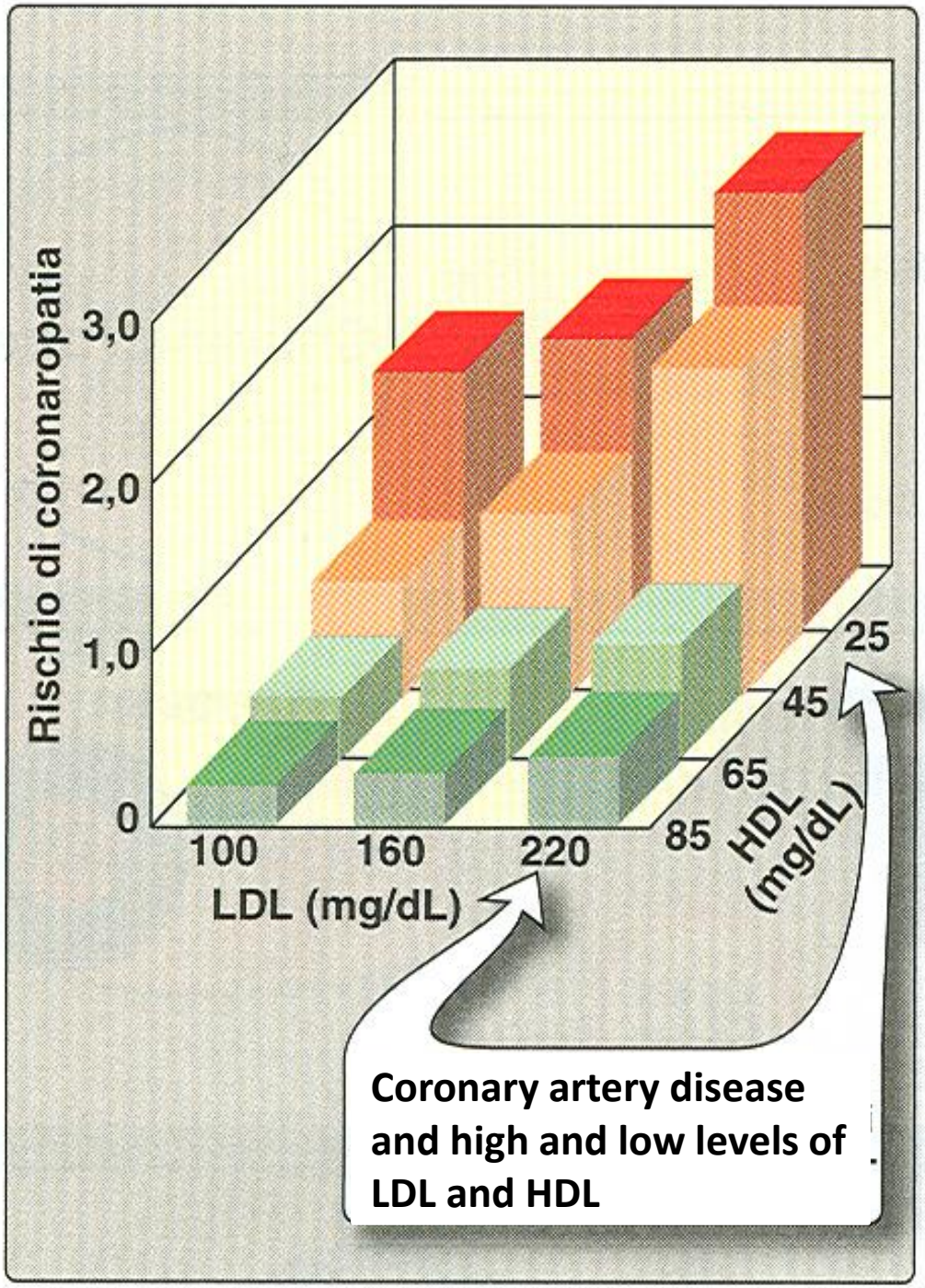
Desirable levels of lipoproteins for the prevention of coronaropathy

Colesterolo totale
<200 mg/dl → Desiderabile
200-239 mg/dl → Elevato bordeline
≥ 240 mg/dl → Alto

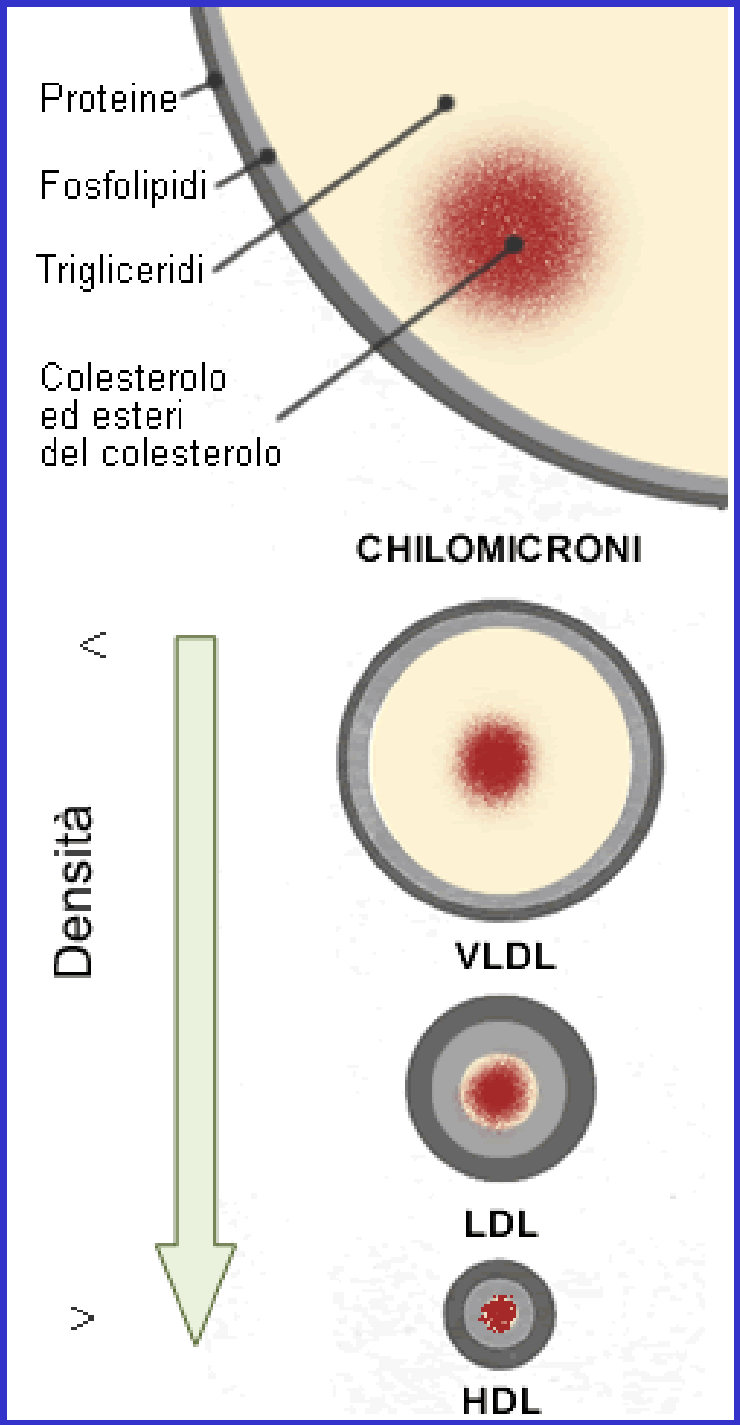
Colesterolo HDL
<40 mg/dl → Basso (considerare < 50 mg/dl come basso nelle donne)
>60 mg/dl → Alto

Colesterolo LDL
<70 mg/dl → Ottimale
100-129 mg/dl → Quasi ottimale
130-159 mg/dl → Elevato borderline
160-189 mg/dl → Elevato
≥ 190 mg/dl → Molto elevato

Trigliceridi
<150 mg/dl → Normale
150-199 mg/dl → Elevato borderline
200-499 mg/dl → Elevato
≥ 500 mg/dl → Molto elevato



Circulating LDL and HDL effect on the risk of cardiopathy



The lipoproteins maintain the lipids in solution in the plasma and carry them from one tissue to another. Hydrophobic interior (triglycerides and cholesterol esters) external hydrophilic
Chylomicrons are formed in enterocytes and convey to the peripheral tissues the products of lipid digestion (triglycerides, cholesterol, cholesterol esters, fat-soluble vitamins) of food origin first in the lymph and then in the blood

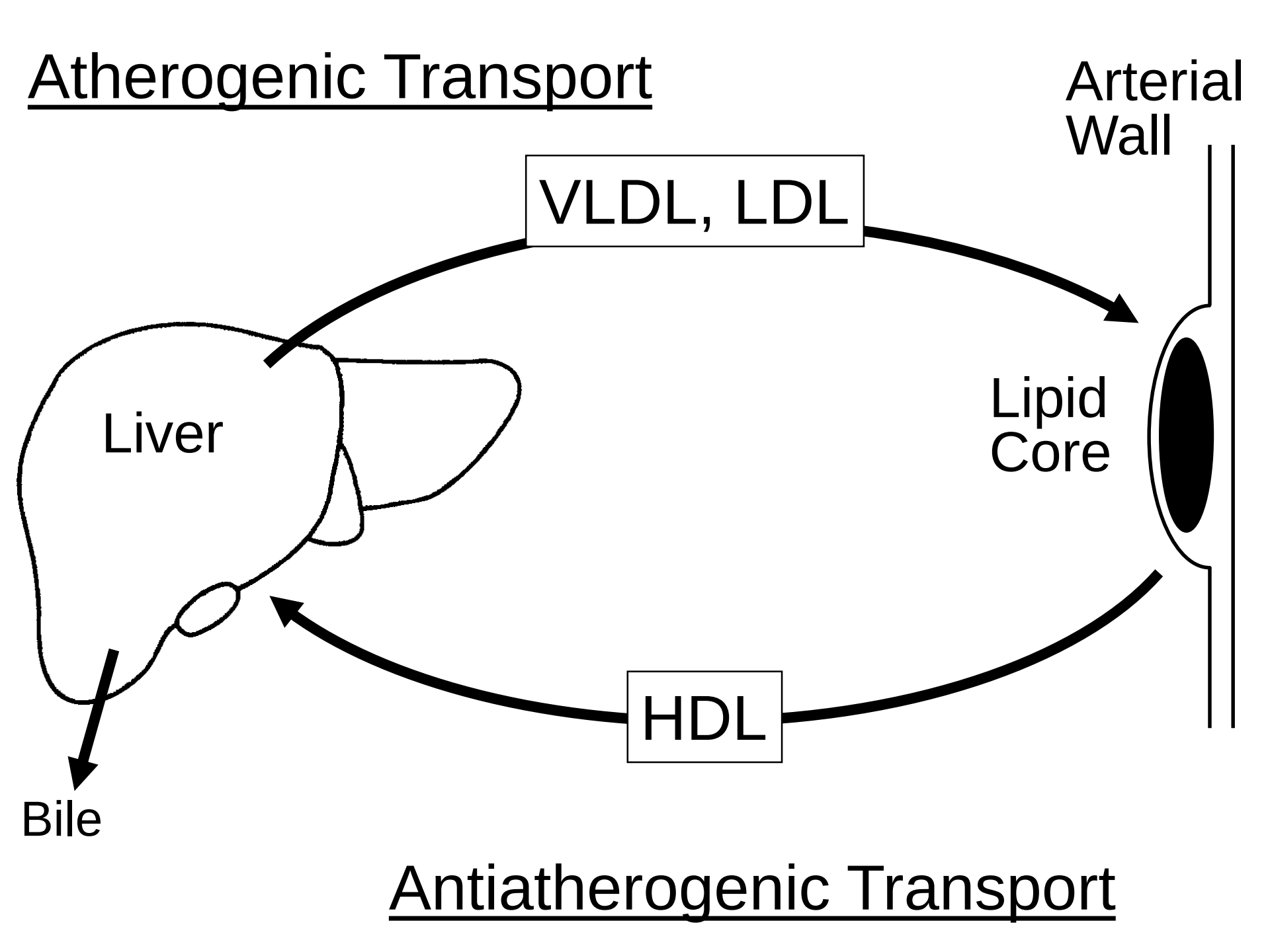
VLDL synthesized by hepatocytes. They transport triglycerides from the liver (where they are synthesized) to other tissues (fat and muscle)

LDLs derive from VLDL, due to the progressive depletion of their triglyceride content. They are loaded with cholesterol that they carry to the peripheral tissues

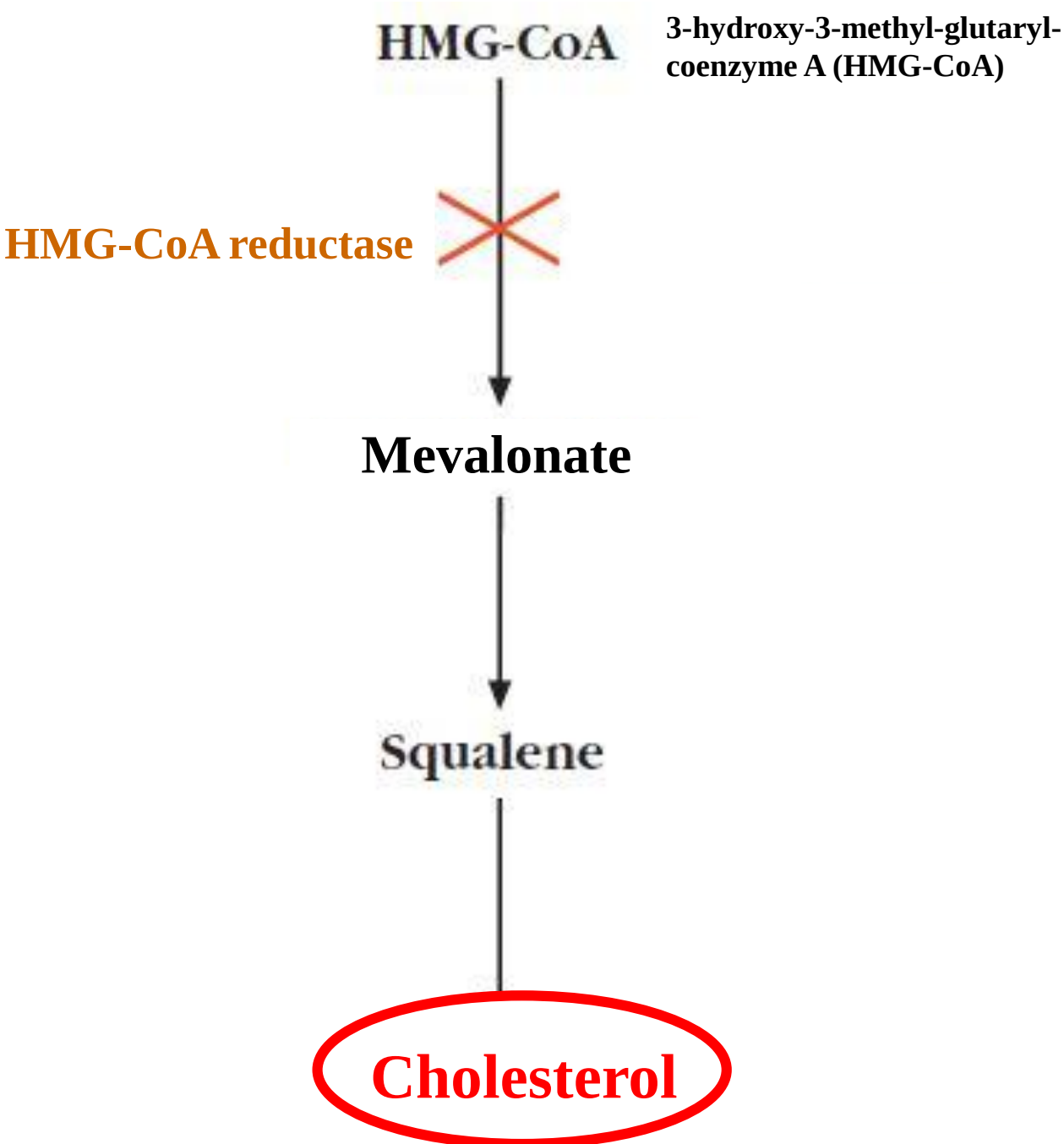
HDLs, secreted in the blood from the liver and intestine, transports cholesterol from peripheral tissues to the liver (reverse cholesterol transport)

Different classes of plasma lipoproteins

Classi di Lipoproteine	Densità	Principali costituenti lipidici	Luogo della sintesi
Chilomicroni e remnants	<<1.006	Trigliceridi della dieta e colesterolo	Intestino
VLDL	<1.006	Trigliceridi endogeni	Fegato
IDL	1.006-1.019	Esteri del colesterolo e trigliceridi endogeni	Prodotti di degradazione delle VLDL
LDL	1.019-1.063	Esteri del colesterolo	Prodotti di degradazione delle VLDL
HDL	1.063-1.210	Fosfolipidi ed esteri del colesterolo	Intestino, fegato, plasma

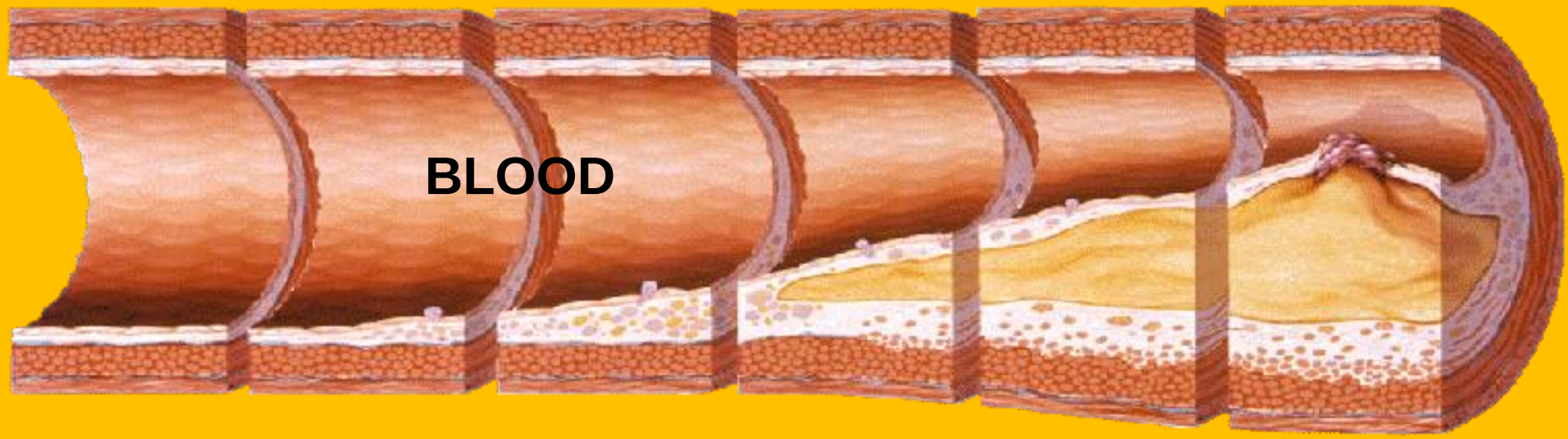

Atherogenic Transport
Arterial Wall
VLDL, LDL
Liver
Lipid Core
HDL
Bile
Antiatherogenic Transport

Synthesis of Cholesterol


HMG-CoA
3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA)
HMG-CoA reductase
Mevalonate
Squalene
Cholesterol

ATHEROSCLEROSIS TIMELINE

Foam Cells | Fatty Streak | Intermediate Lesion | Atheroma | Fibrous Plaque | Complicated Lesion/Rupture

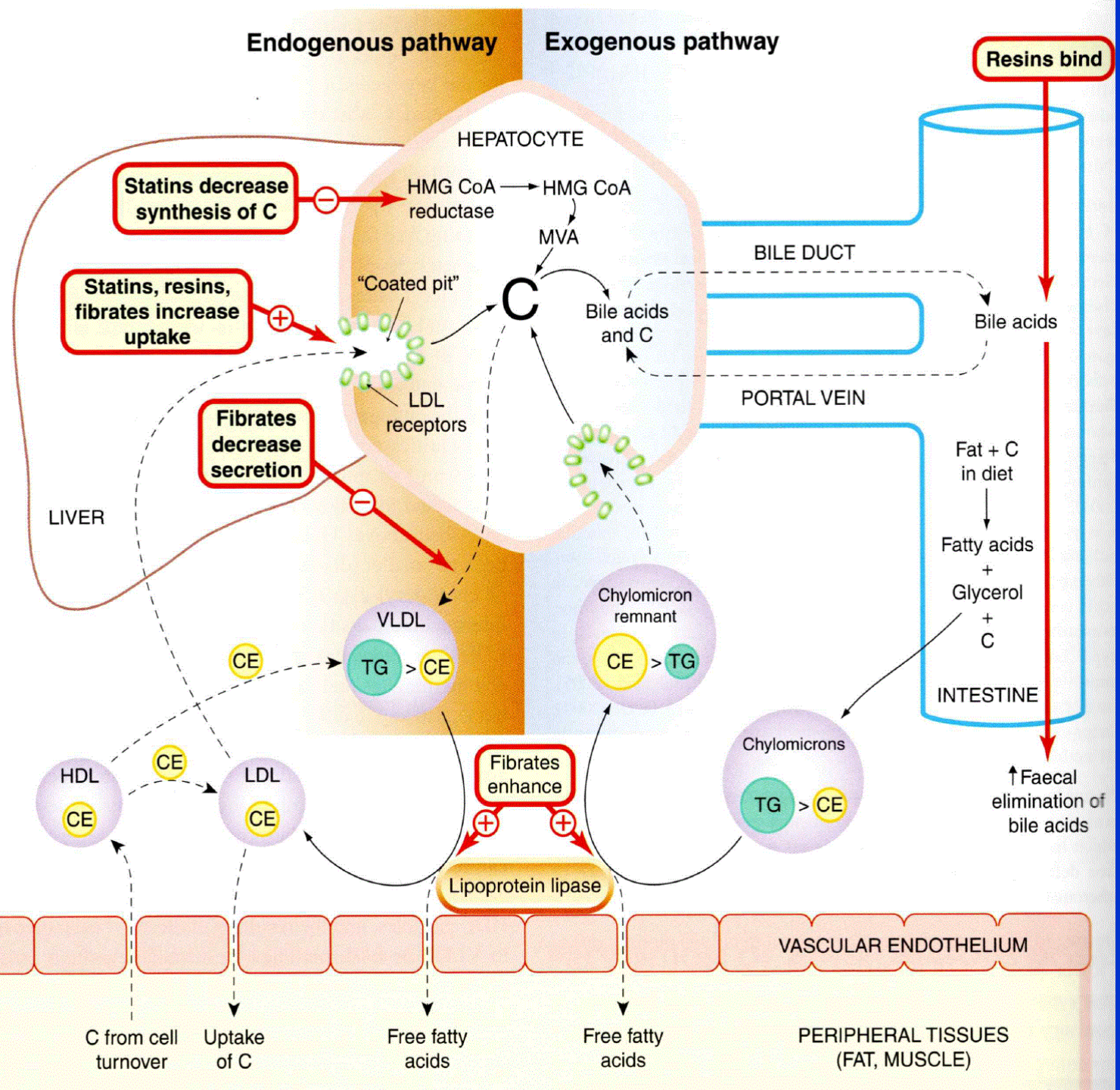


Normal

Asymptomatic Atherosclerosis

Symptomatic Atherosclerosis:
Acute Coronary Syndrome-ACS
Stable Angina
Stroke

Endogenous and exogenous pathway



Cholesterol transport

Lipoproteins:

HDL-C

LDL-C

VLDL

chylomicrons

C = cholesterol

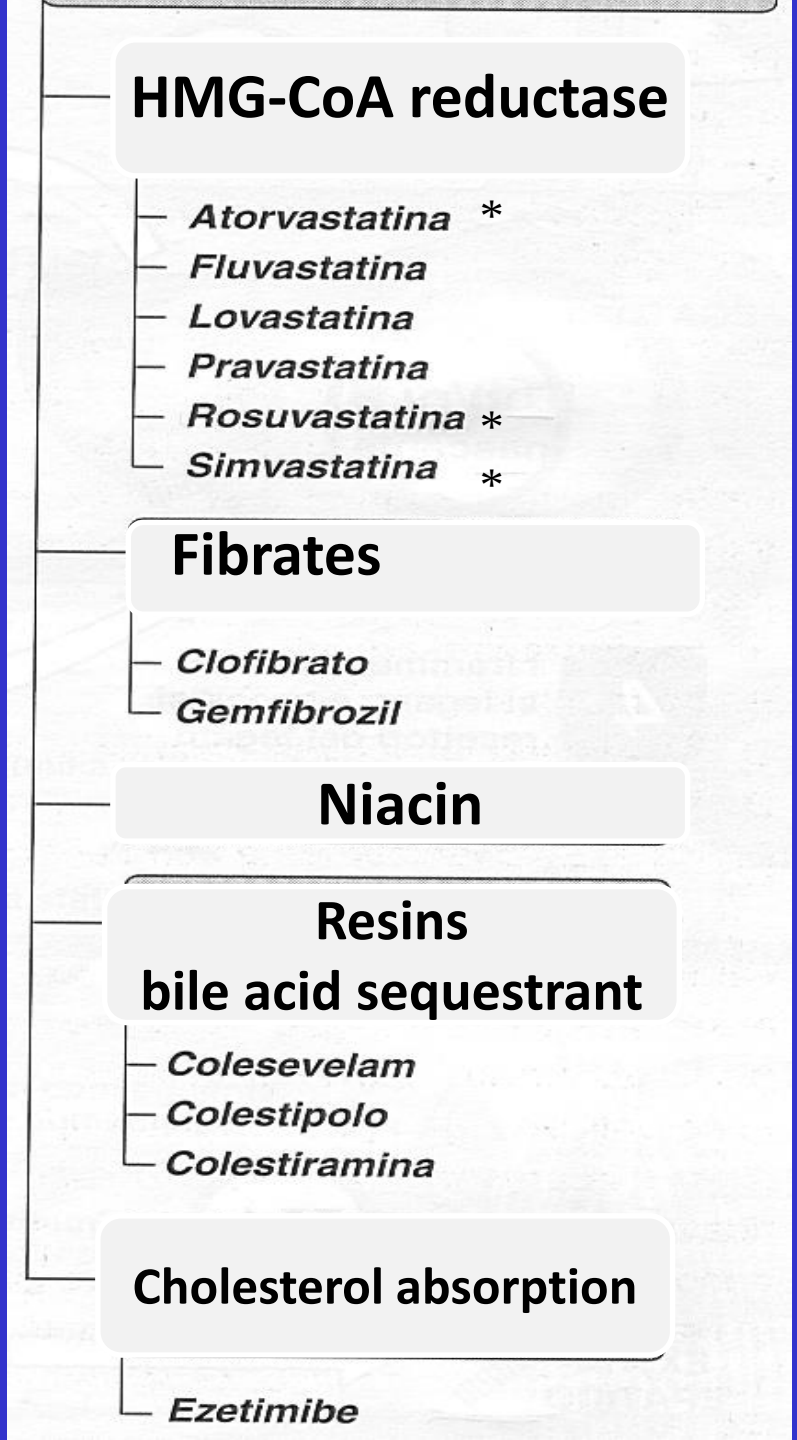
EC = cholesterol esters

HMG = 3-hydroxy-3-methylglutaryl

MVA = mevalonate

TG = triglycerides

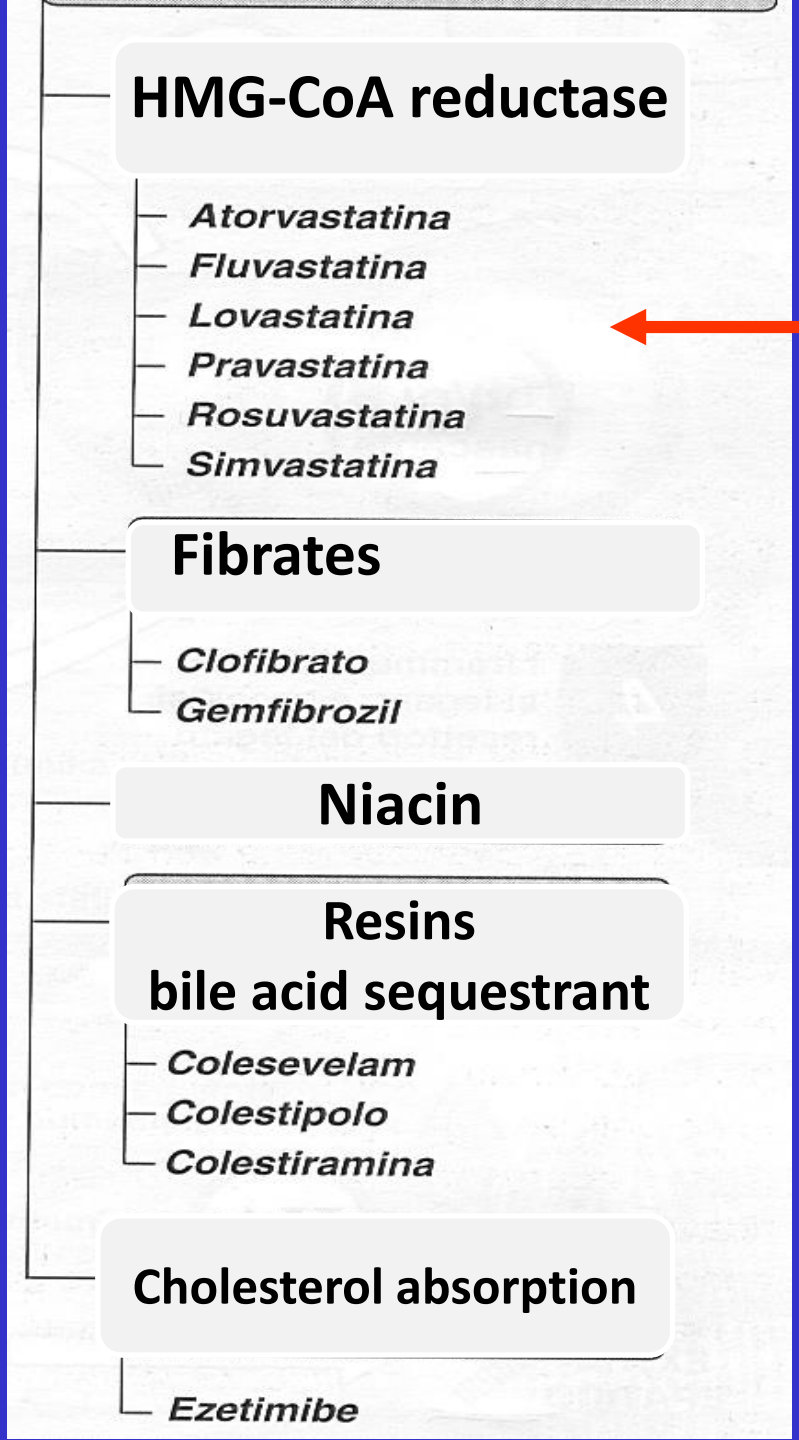
Anti-cholesterol Drugs



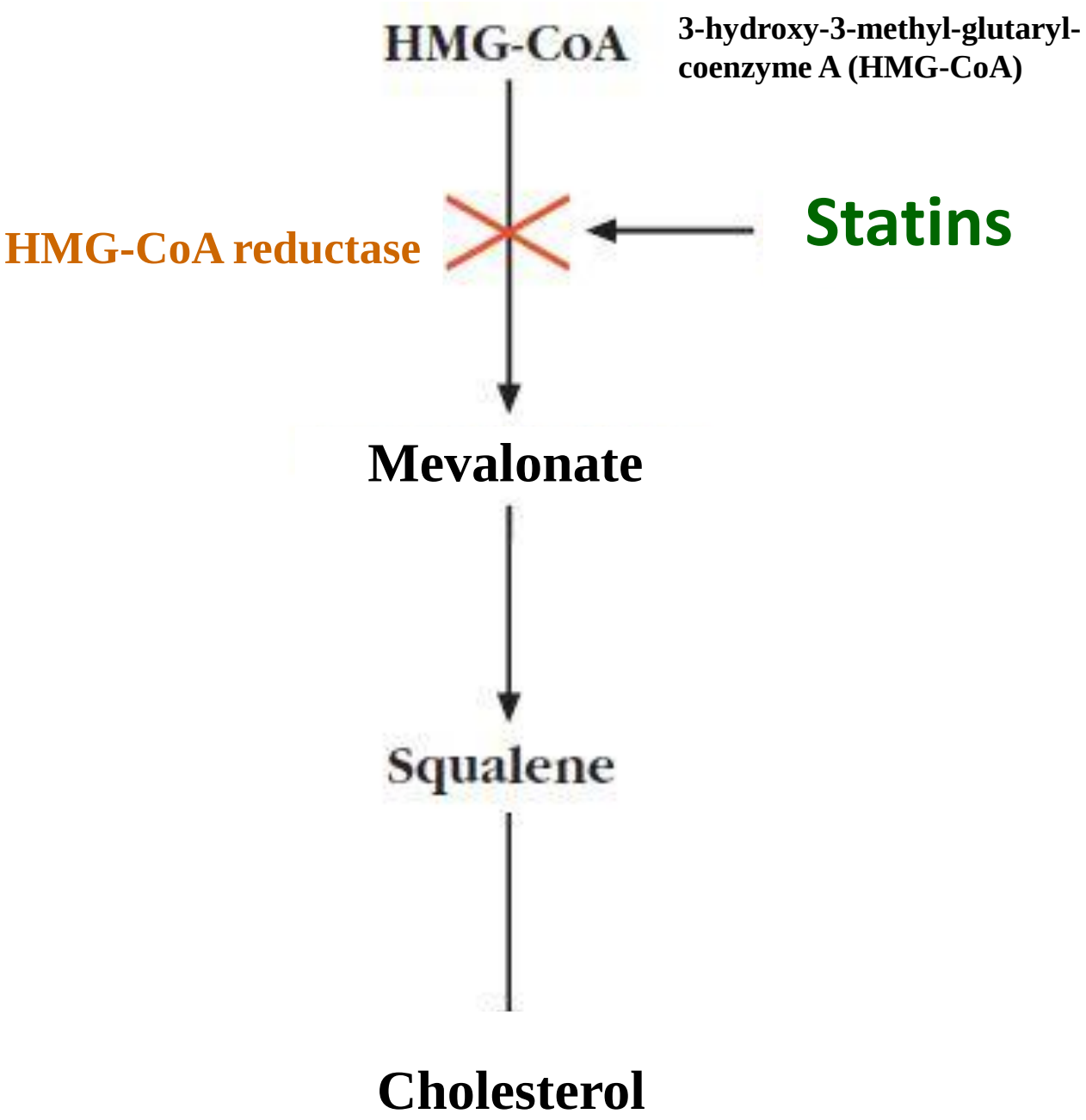
Drugs in dyslipidaemia

The main drugs used in patients with dyslipidaemias are:

- HMG-CoA reductase inhibitors (statins, e.g. **simvastatin**): inhibit synthesis of cholesterol, increasing expression of low-density lipoprotein (LDL) receptors on hepatocytes and hence LDL cholesterol (LDL-C) uptake. Adverse effects include myalgias (rarely, severe muscle damage) and raised liver enzymes.
- Fibrates (e.g. **gemfibrozil**): activate PPARα receptors, increase activity of lipoprotein lipase, decrease hepatic very low-density lipoprotein production, and enhance clearance of LDL-C by the liver. They markedly lower serum triglycerides, and modestly increase high-density lipoprotein cholesterol. Adverse effects include muscle damage.
- Agents that interfere with cholesterol absorption, usually as an adjunct to diet plus statin:
  - ezetimibe
  - stanol-enriched foods
  - bile acid–binding resins (e.g. **colestyramine**).
- Modified-release nicotinic acid. Flushing is the main adverse effect.
- Fish oil derivatives—omega-3-acid ethyl esters.



Statins: analogues of 3-hydroxy -3-methyl-glutaryl-coenzyme A (HMG-CoA)


HMG-CoA
3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA)
HMG-CoA reductase
Statins
Mevalonate
Squalene
Cholesterol

Clinical uses of HMG-CoA reductase inhibitors (statins, e.g. simvastatin. atorvastatin)

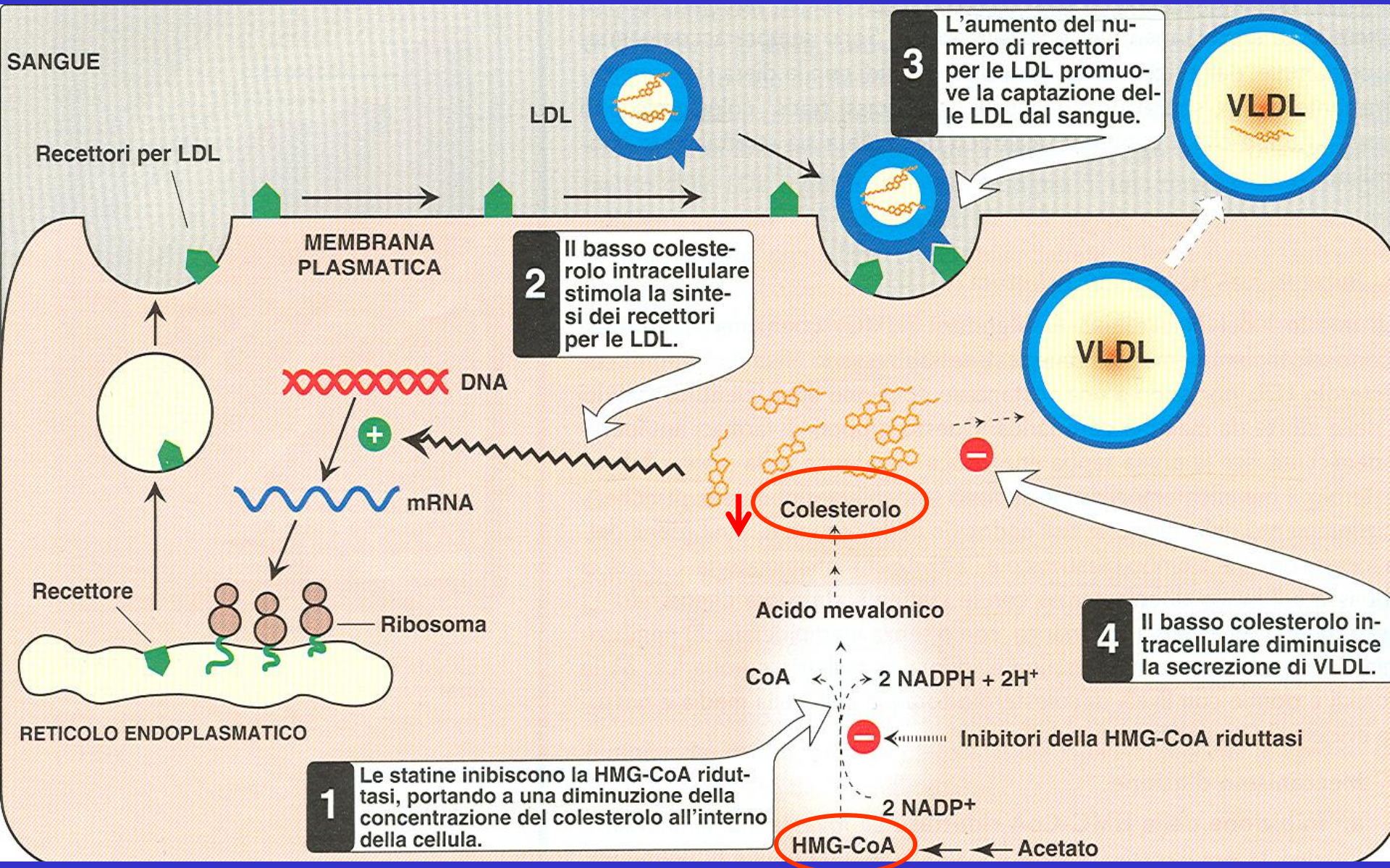
- *Secondary prevention* of myocardial infarction and stroke in patients who have symptomatic atherosclerotic disease (e.g. *angina, transient ischaemic attacks,* or following *myocardial infarction* or *stroke*).
- *Primary prevention* of arterial disease in patients who are at high risk because of elevated serum cholesterol concentration, especially if there are other risk factors for atherosclerosis.

- **Atorvastatin** lowers serum cholesterol in patients with homozygous familial hypercholesterolaemia.
- In severe drug-resistant dyslipidaemia (e.g. heterozygous familial hypercholesterolaemia), **ezetimibe** is combined with statin treatment.

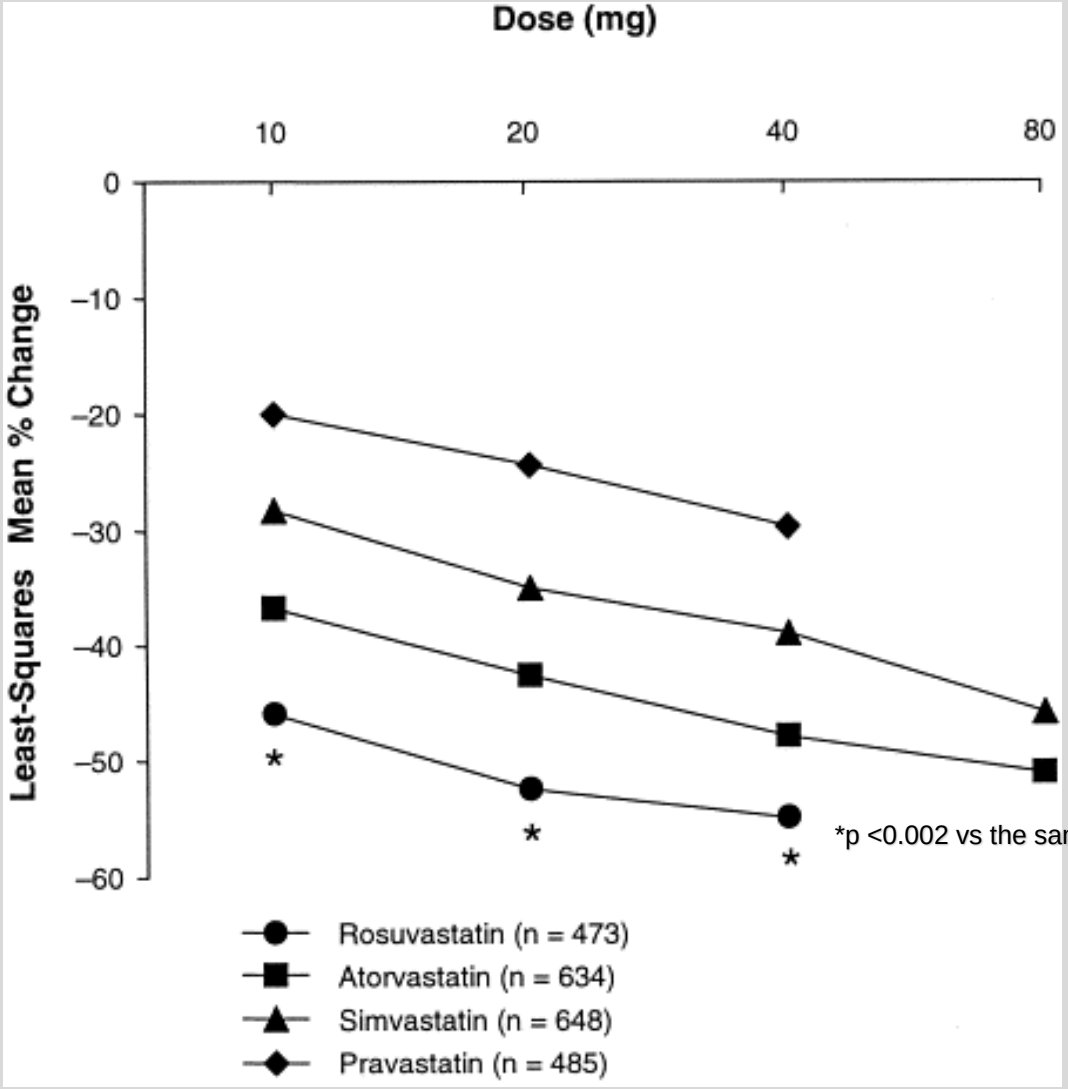
STATIN Mechanisms

1) Enhance NO
2) Stabilize plaque
3) Reduce vascular wall cell proliferation
4) Reduce c-reactive protein concentration
5) Reduce lipoprotein oxidation
6) Reduce platelet aggregation, fibrinogen, thrombosis

Inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase by statins



Mean percent changes in LDL cholesterol from baseline to week 6 *for rosuvastatin, atorvastatin, simvastatin*, and *pravastatin* across the dose ranges from the STELLAR trial



*p <0.002 vs the same dose of the 3 comparators

STELLAR = Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin

Dosage

ATORVASTATINA	FLUVASTATINA	LOVASTATINA	PRAVASTATINA	ROSUVASTATINA	SIMVASTATINA
	40 mg	20 mg	20 mg		10 mg
10 mg	80 mg	40 o 80 mg	40 mg		20 mg
20 mg		80 mg	80 mg	5 o 10 mg	40 mg
40 mg				20 mg	80 mg
80 mg				40 mg	

Therapeutic indications

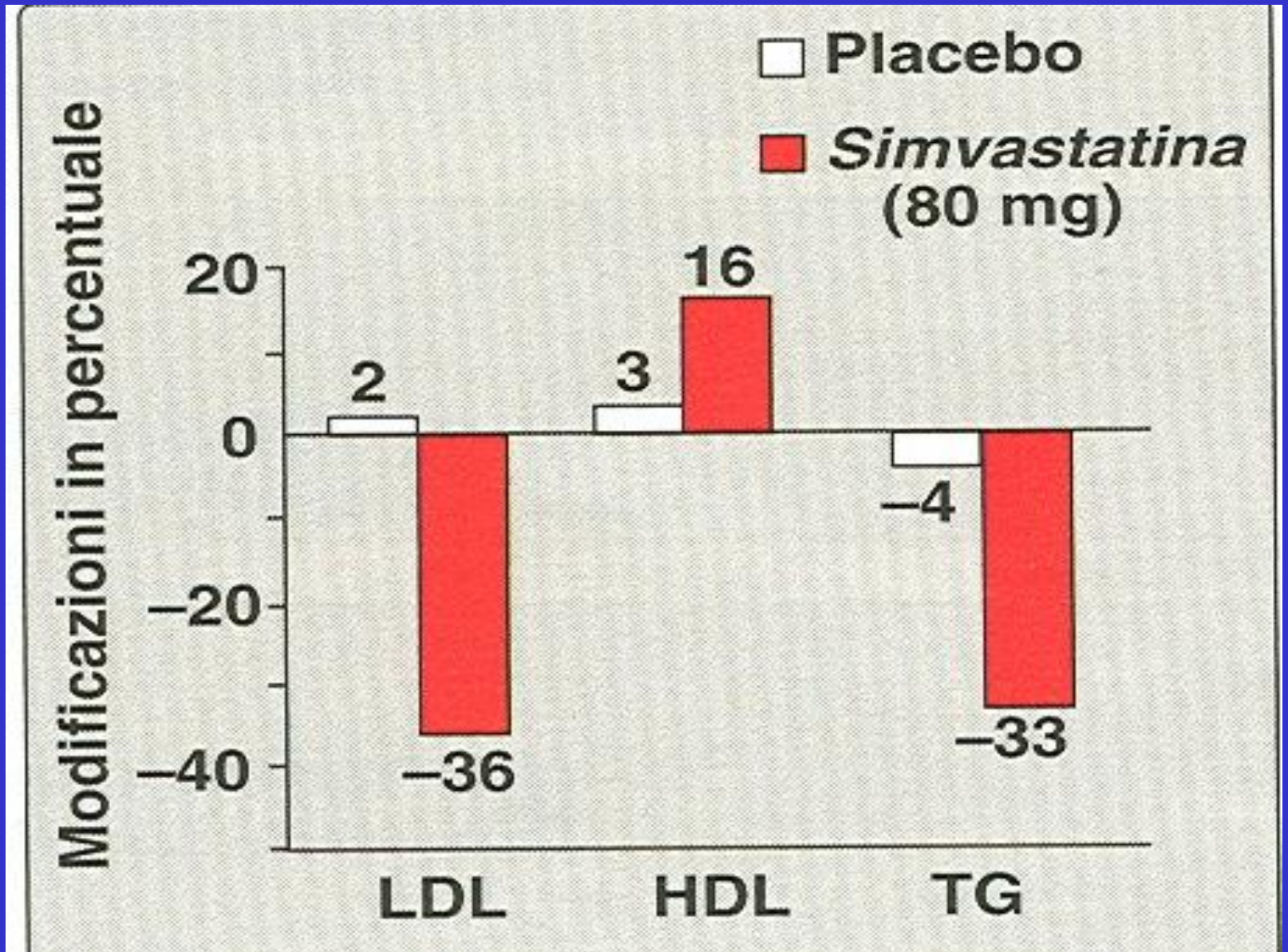
	SIMVASTATINA	PRAVASTATINA	ATORVASTATINA	ROSUVASTATINA	FLUVASTATINA	LOVASTATINA
Ipercolesterolemia primaria e iperlipidemia mista • In aggiunta alla dieta che non ha corretto l'ipercolesterolemia; • In aggiunta a trattamenti non farmacologici; • In aggiunta ad esercizio fisico	✓	✓	✓	✓	✓	✓
Dislipidemia familiare mista • In aggiunta alla dieta • In aggiunta a trattamenti farmacologici di cui:	✓	✓	✓	✓	✓	✓
Tipo eterozigote			✓	✓		✓
Tipo omozigote	✓		✓	✓		
Riduzione della mortalità e morbilità cardiovascolare in pazienti con ipercolesterolemia da moderata a grave e con alto rischio di un primo evento cardiovascolare, in aggiunta alla dieta		✓	✓			✓
PREVENZIONE SECONDARIA						
Riduzione della mortalità e morbilità cardiovascolare in pazienti con livelli normali o elevati di colesterolo e con malattia aterosclerotica	✓					
Riduzione della mortalità e morbilità cardiovascolare in pazienti con livelli normali o elevati di colesterolo e/o con diabete	✓					
Riduzione del rischio di mortalità in pazienti con cardiopatia coronarica o ischemica con storia di infarto miocardico o di eventi cerebrovascolari e con livelli normali o elevati di colesterolo		✓				✓

3-hydroxy-3-methyl-glutaryl-coenzyme A inhibitors (HMG-CoA) reductase

Caratteristica	Atorvastatina	Fluvastatina	Lovastatina	Pravastatina	Rosuvastatina	Simvastatina
Riduzione del colesterolo-LDL sierico ottenuta (%)	50	24	34	34	50	41
Riduzione del triacilglicerolo sierico ottenuta (%)	29	10	16	24	18	18
Aumento del colesterolo-HDL sierico ottenuto (%)	6	8	9	12	8	12
Emivita plasmatica (h)	14	1–2	2	1–2	19	1–2
Penetrazione nel sistema nervoso centrale	No	No	Sì	No	No	Sì
Escrezione renale della dose assorbita (%)	2	<6	10	20	10	13

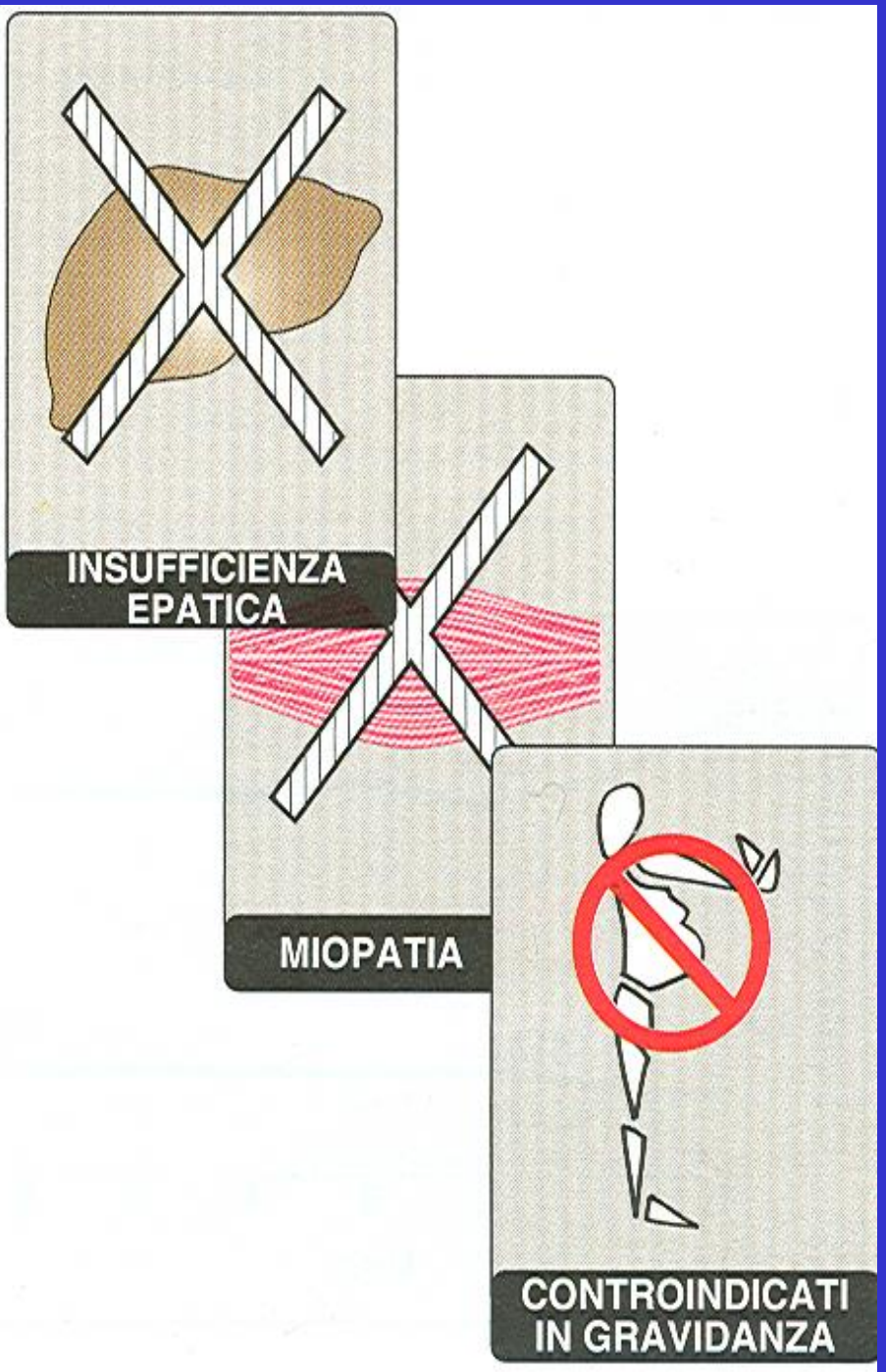
Simvastatine e lovastatine (biotransformation)

Effect of simvastatin on serum lipids in patients with type 2 diabetes (6 weeks treatment)



Characteristics of anti-hyperlipidemic drugs

TIPO DI FARMACO	EFFETTO SUL COLESTEROLO-LDL	EFFETTO SUL COLESTEROLO-HDL	EFFETTO SUI TRIACILGLICEROLI
Inibitori della HMG-CoA riduttasi (statine)	↓↓↓↓	↑↑	↓↓
Fibrati	↓	↑↑↑	↓↓↓↓
Niacina	↓↓	↑↑↑↑	↓↓↓
Sequestranti degli acidi biliari	↓↓↓	↑	Minimo
Inibitori dell'assorbimento del colesterolo	↓	↑	↓



Side effects of inhibitors of the (HMG-CoA) reductase

Hepatotoxicity

Myopathy; Rhabdomyolysis (rare)
(synthesis of sterols)

Mainly metabolized by CYP3A4
kidney failure
(statin concentrations increase)

Predisposing factors for statin-induced myopathy

- Renal impairment
- Hypothyroidism
- Personal or family history of hereditary muscle disorders
- Previous history of muscular toxicity with another statin or fibrate
- Alcohol abuse
- Age > 70 years
- Situations where an increase in plasma levels may occur
- Concomitant use of other drugs

Selected drugs that may increase risk of myopathy and rhabdomyolysis when used concomitantly with statins

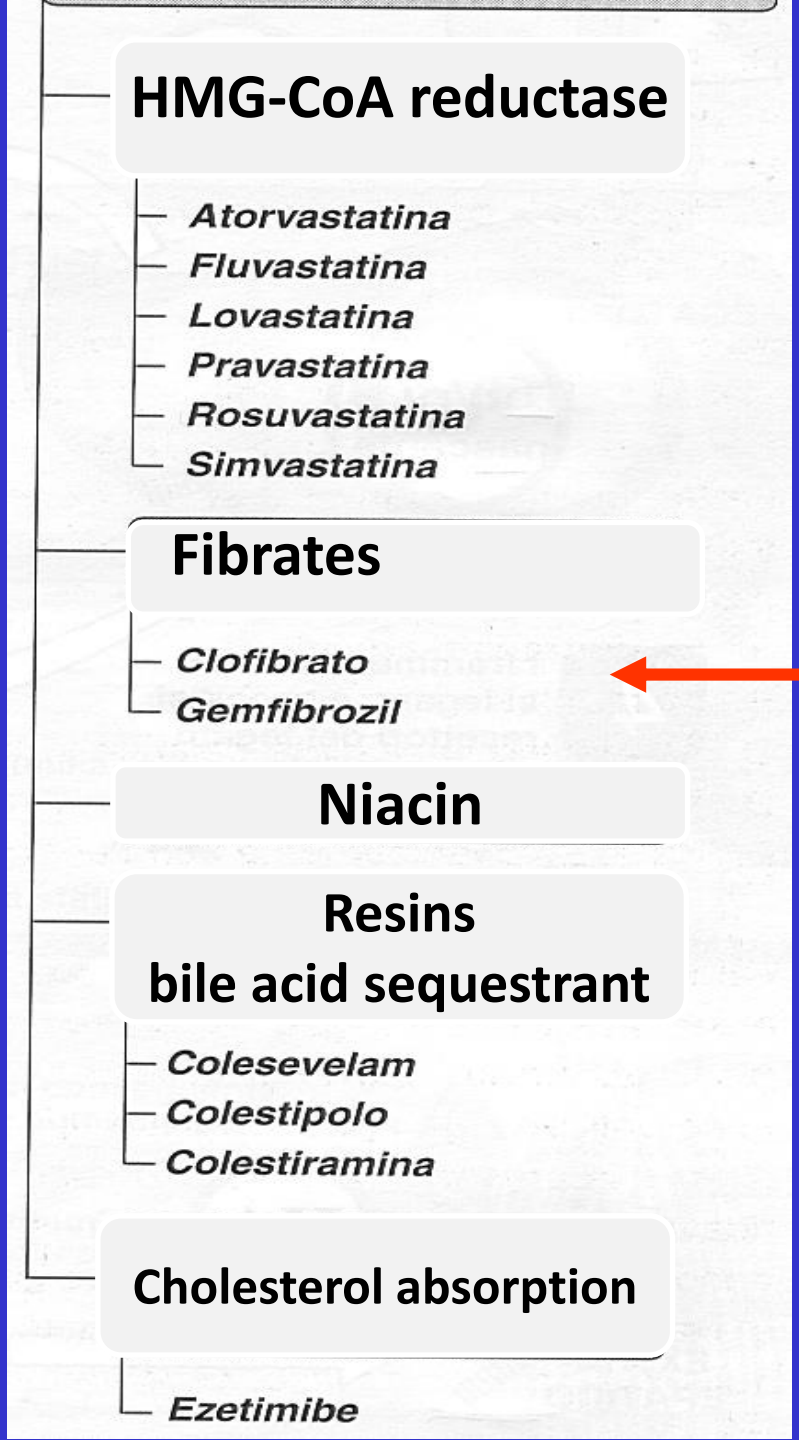
CYP3A4 Inhibitors/Substrates	Others
Cyclosporine, tacrolimus	Digoxin
Macrolides (azithromycin, clarithromycin, erythromycin)	Fibrates (gemfibrozil)
Azole antifungals (itraconazole, ketoconazole)	Niacin
Calcium antagonists (mibefradil, diltiazem, verapamil)	
Nefazodone	
Protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir)	
Sildenafil	
Warfarin	

Adapted from Corsini A, et al. *Pharmacol Ther.* 1999;84:413–428.

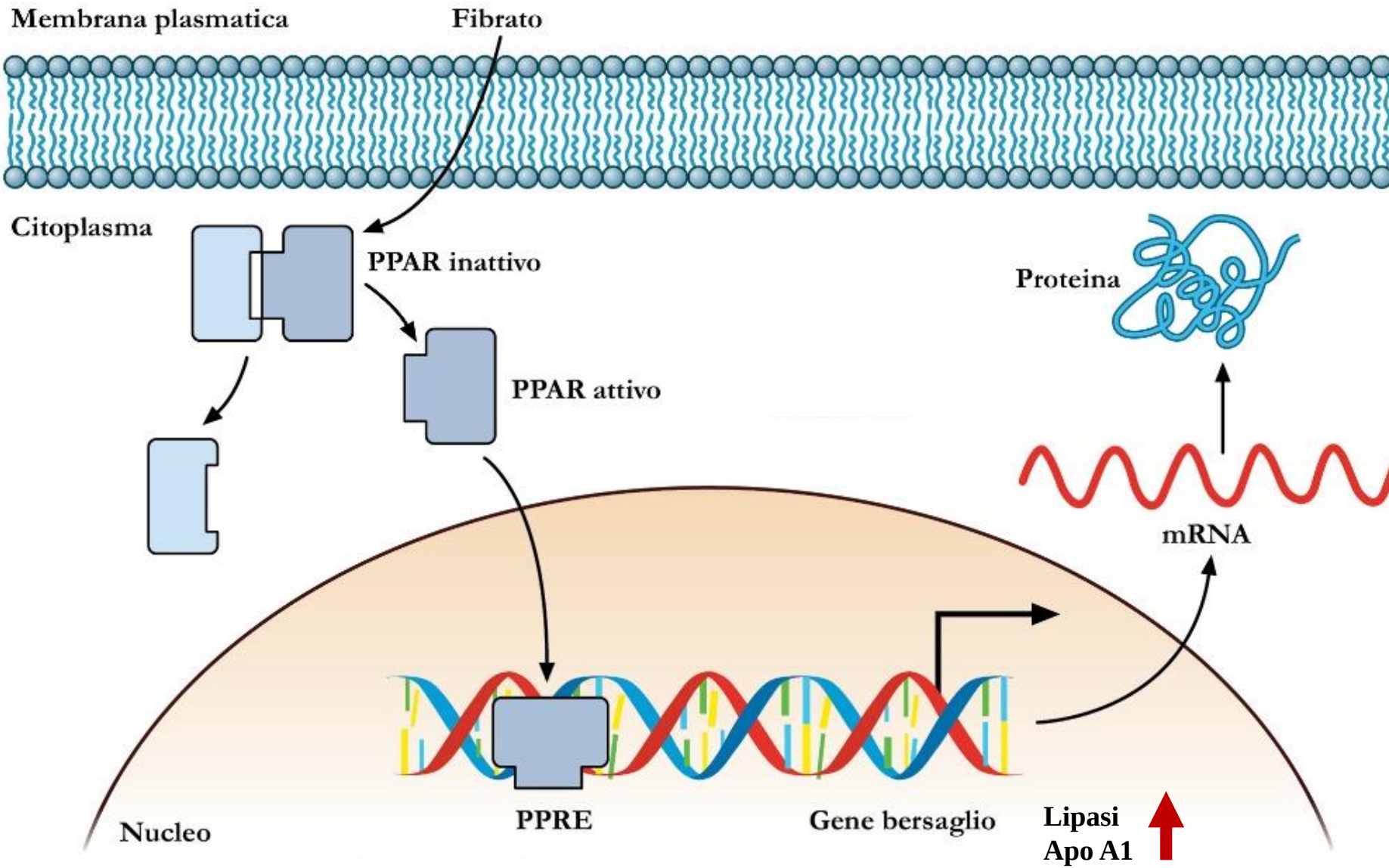
Metabolic interaction with statins and other drugs

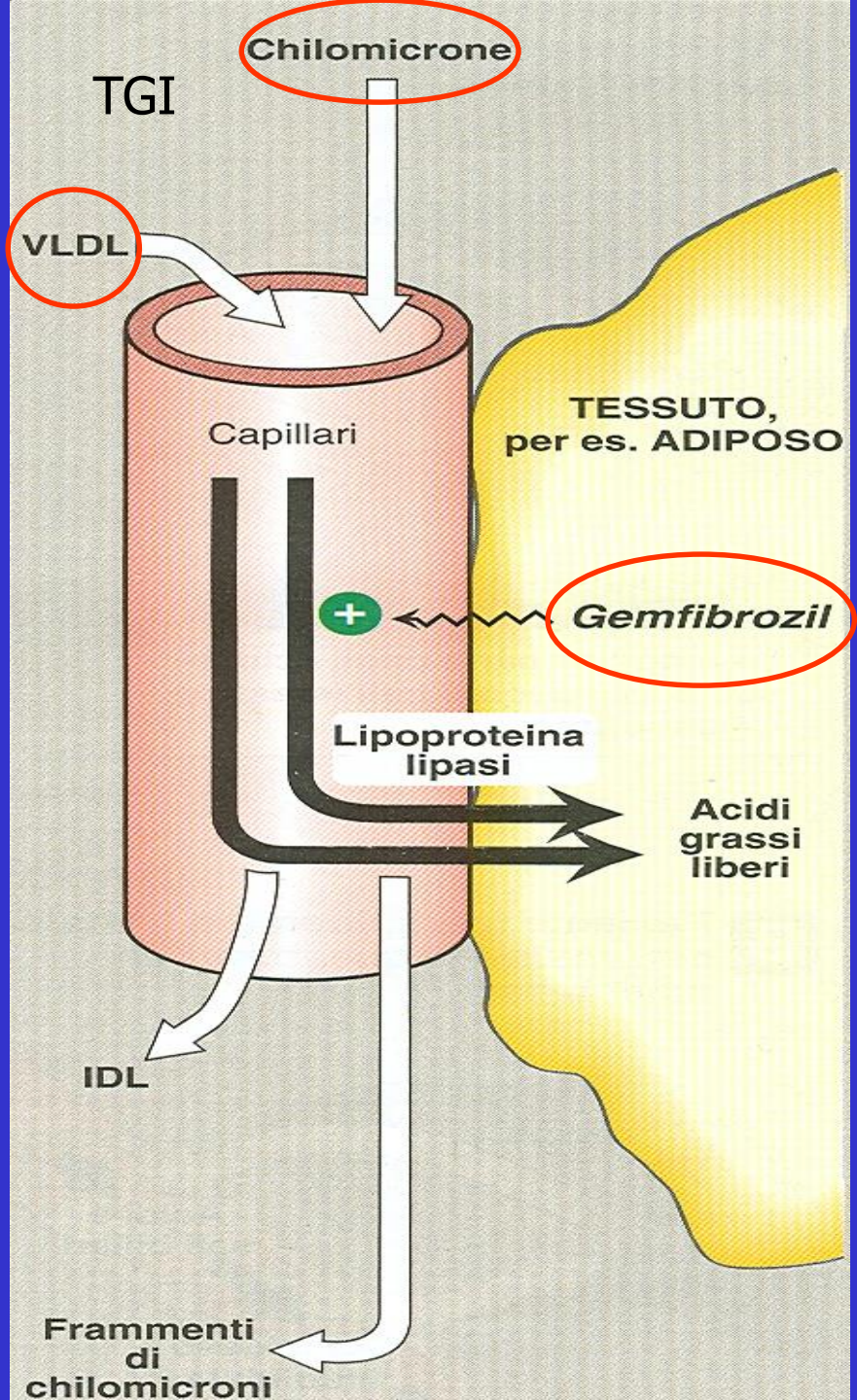
SIMVASTATINA	FLUVASTATINA	ATORVASTATINA	ROSUVASTATINA	LOVASTATINA
CYP3A4	CYP2C9	CYP3A4	2C9-CYP2C19	CYP3A4
Amiodarone	Warfarin	Amiodarone	Warfarin	Amiodarone
Chinidina	Fenitoina	Chinidina	Fenitoina	Chinidina
Verapamil	Diclofenac	Verapamil	Diclofenac	Verapamil
Diltiazem		Diltiazem	Fenobarbitale	Diltiazem
Claritromicina		Claritromicina	Diazepam	Claritromicina
Eritromicina		Eritromicina	Ibuprofene	Eritromicina
Ketoconazolo		Ketoconazolo	Omeprazolo	Ketoconazolo
Itraconazolo		Itraconazolo		Itraconazolo
Warfarin		Warfarin		Warfarin
Clopidrogel		Clopidrogel		Clopidrogel
Lacidipina		Lacidipina		Lacidipina
Nifedipina		Nifedipina		Nifedipina
Felodipina		Felodipina		Felodipina
Misazolam		Misazolam		Misazolam
Triazolam		Triazolam		Triazolam
Ciclosporina A		Ciclosporina A		Ciclosporina A
Inibitori Proteasi		In. Proteasi		In. Proteasi
Niacina		Niacina		Niacina

Fibrates

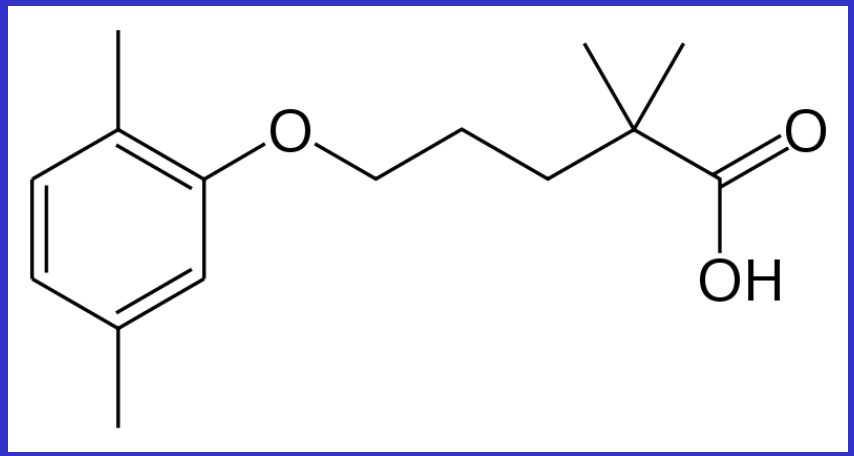


Clofibrate> gemfibrozil
(Hypertriglyceridemia)


Membrana plasmatica
Fibrato
Citoplasma
PPAR inattivo
PPAR attivo
Proteina
mRNA
Nucleo
PPRE
Gene bersaglio
Lipasi
Apo A1



Activation of lipase from *gemfibrozil*



↑HDL ↑ Apo A1

PPAR activation produces:

- increased β-oxidation in the liver
- decreased secretion of triglycerides into plasma by the liver
- increased lipase gene expression and its activity
- increase in clearance of VLDL and reduction of triglyceride
- increase in HDL
- increase in the expression of Apo A1 (that form HDL)
- Apo A1 forms the hydrophilic shell around the cholesterol esters, are capable of binding lipids, are constituents of plasma lipoproteins, are responsible for the transport of cholesterol and triglycerides through the circulation to the various tissues and organs

Characteristics of anti-hyperlipidemic drugs

TIPO DI FARMACO	EFFETTO SUL COLESTEROLO-LDL	EFFETTO SUL COLESTEROLO-HDL	EFFETTO SUI TRIACILGLICEROLI
Inibitori della HMG-CoA riduttasi (statine)	↓↓↓↓	↑↑	↓↓
Fibrati	↓	↑↑↑	↓↓↓↓
Niacina	↓↓	↑↑↑↑	↓↓↓
Sequestranti degli acidi biliari	↓↓↓	↑	Minimo
Inibitori dell'assorbimento del colesterolo	↓	↑	↓

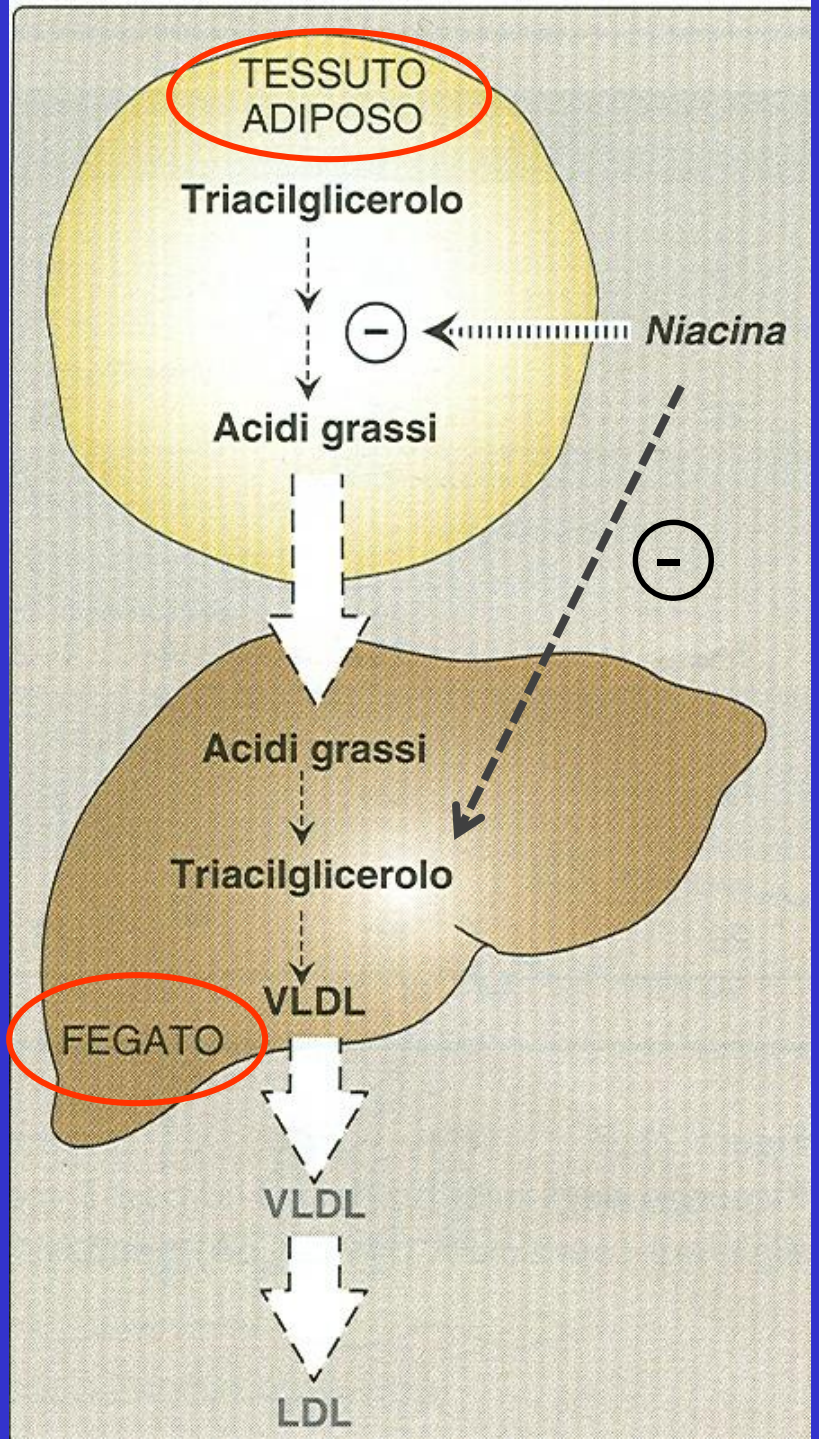
E.C .: Gastrointestinal disorders, gallstones (of excretion cholesterol through bile) myopathy, Rhabdomyolysis. No pregnancy and breastfeeding

Clinical uses of fibrates (e.g. gemfibrozil, fenofibrate)

- *Mixed dyslipidaemia* (i.e. raised serum triglyceride as well as cholesterol), provided this is not caused by excessive alcohol consumption. Fenofibrate is uricosuric, which may be useful where hyperuricaemia coexists with mixed dyslipidaemia.
- In patients with *low high-density lipoprotein* and *high risk of atheromatous disease* (often type 2 diabetic patients; see Ch. 26).
- Combined with other lipid-lowering drugs in patients with severe treatment-resistant dyslipidaemia. This may, however, increase the risk of rhabdomyolysis.

Niacin
(nicotinic acid)

- **HMG-CoA reductase**
  - *Atorvastatina*
  - *Fluvastatina*
  - *Lovastatina*
  - *Pravastatina*
  - *Rosuvastatina*
  - *Simvastatina*
- **Fibrates**
  - *Clofibrato*
  - *Gemfibrozil*
- **Niacin**
- **Bile acid sequestrant**
  - *Colesevelam*
  - *Colestipolo*
  - *Colestiramina*
- **Cholesterol absorption**
  - *Ezetimibe*



Inhibition by niacin
(nicotinic acid)
lipolysis (adipose tissue)
triglyceride synthesis (liver tissue)

Reduce production of VLDL and LDL

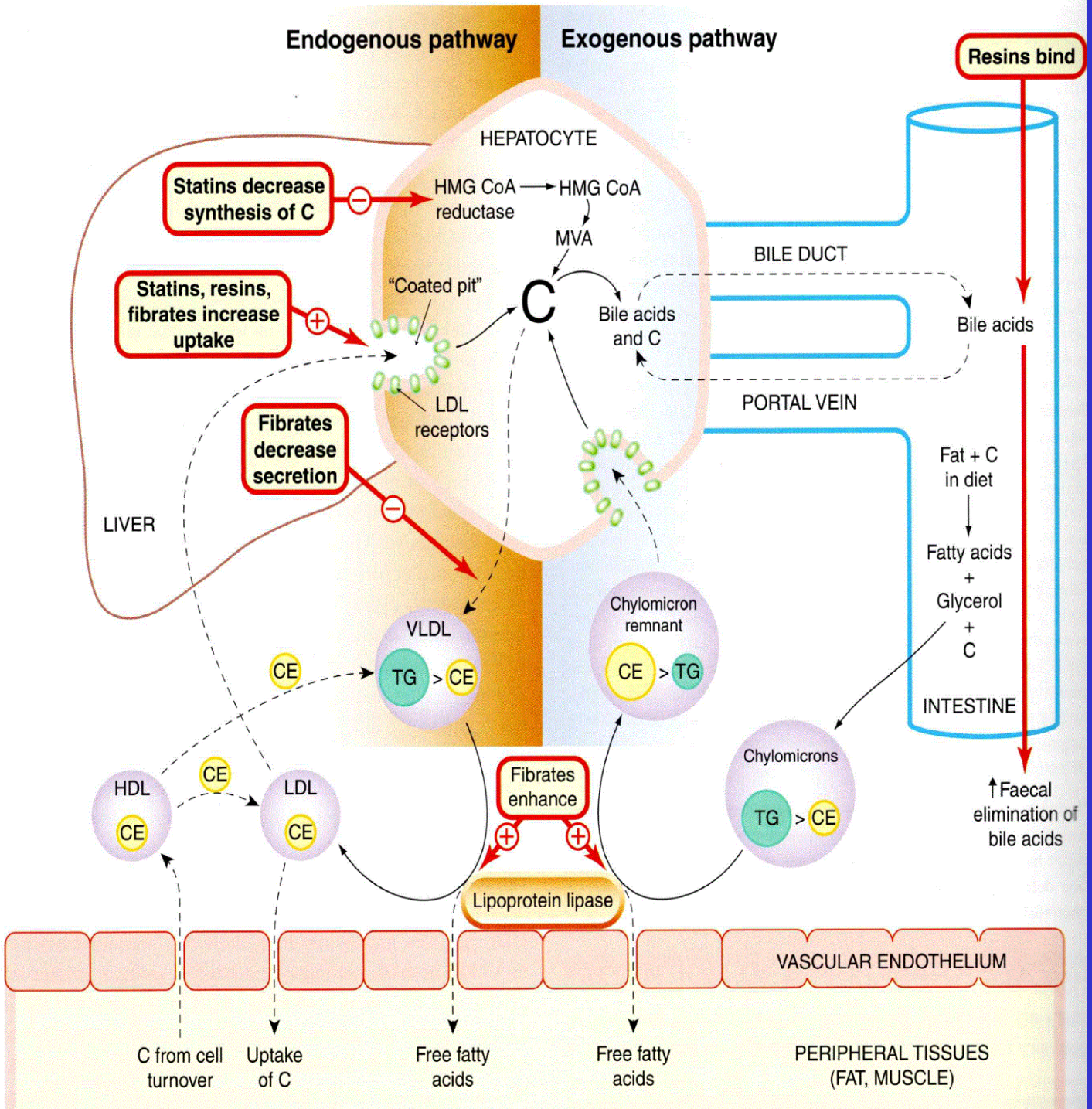
Uses:
When statins contraindicated
In addition to statins

Characteristics of anti-hyperlipidemic drugs

TIPO DI FARMACO	EFFETTO SUL COLESTEROLO-LDL	EFFETTO SUL COLESTEROLO-HDL	EFFETTO SUI TRIACILGLICEROLI
Inibitori della HMG-CoA riduttasi (statine)	↓↓↓↓	↑↑	↓↓
Fibrati	↓	↑↑↑	↓↓↓↓
Niacina	↓↓	↑↑↑↑	↓↓↓
Sequestranti degli acidi biliari	↓↓↓	↑	Minimo
Inibitori dell'assorbimento del colesterolo	↓	↑	↓

It inhibits tubular excretion of uric acid, predisposes to gout

Resins sequestering bile acids

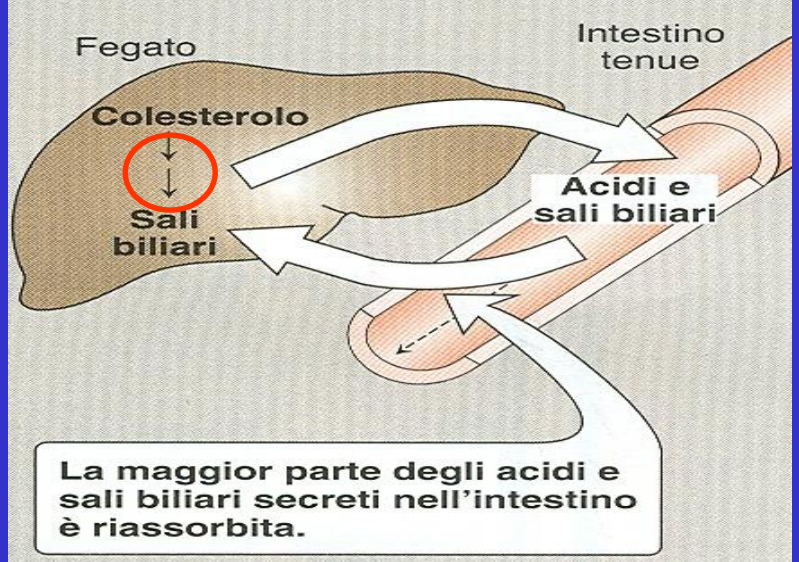


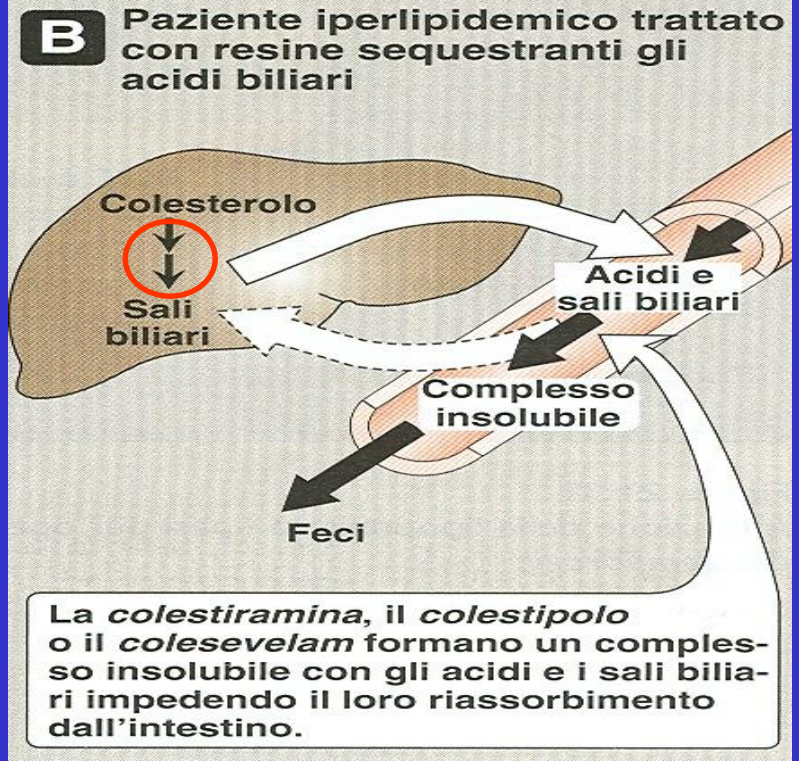
Cholesterol transport

Lipoproteins:
HDL-C
LDL-C
VLDL
chylomicrons

C = cholesterol
EC = cholesterol esters
HMG = 3-hydroxy-3-methylglutaryl
MVA = mevalonate
TG = triglycerides

- **HMG-CoA reductase**
  - *Atorvastatina*
  - *Fluvastatina*
  - *Lovastatina*
  - *Pravastatina*
  - *Rosuvastatina*
  - *Simvastatina*
- **Fibrates**
  - *Clofibrato*
  - *Gemfibrozil*
- **Niacin**
- **Resins**
  bile acid sequestrant
  - *Colesevelam*
  - *Colestipolo*
  - *Colestiramina*
- **Cholesterol absorption**
  - *Ezetimibe*



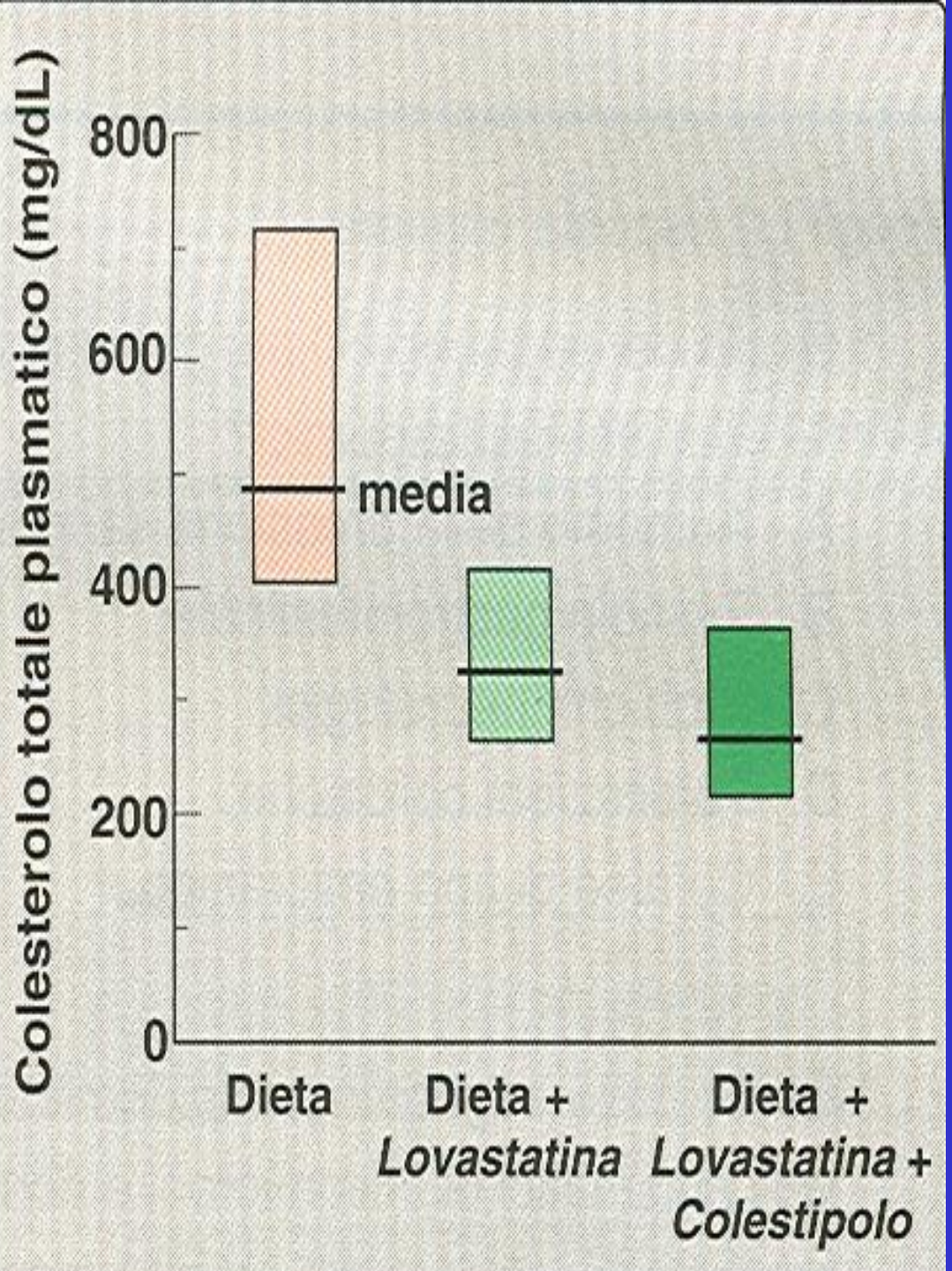


Mechanism of action of resins sequestering bile acid

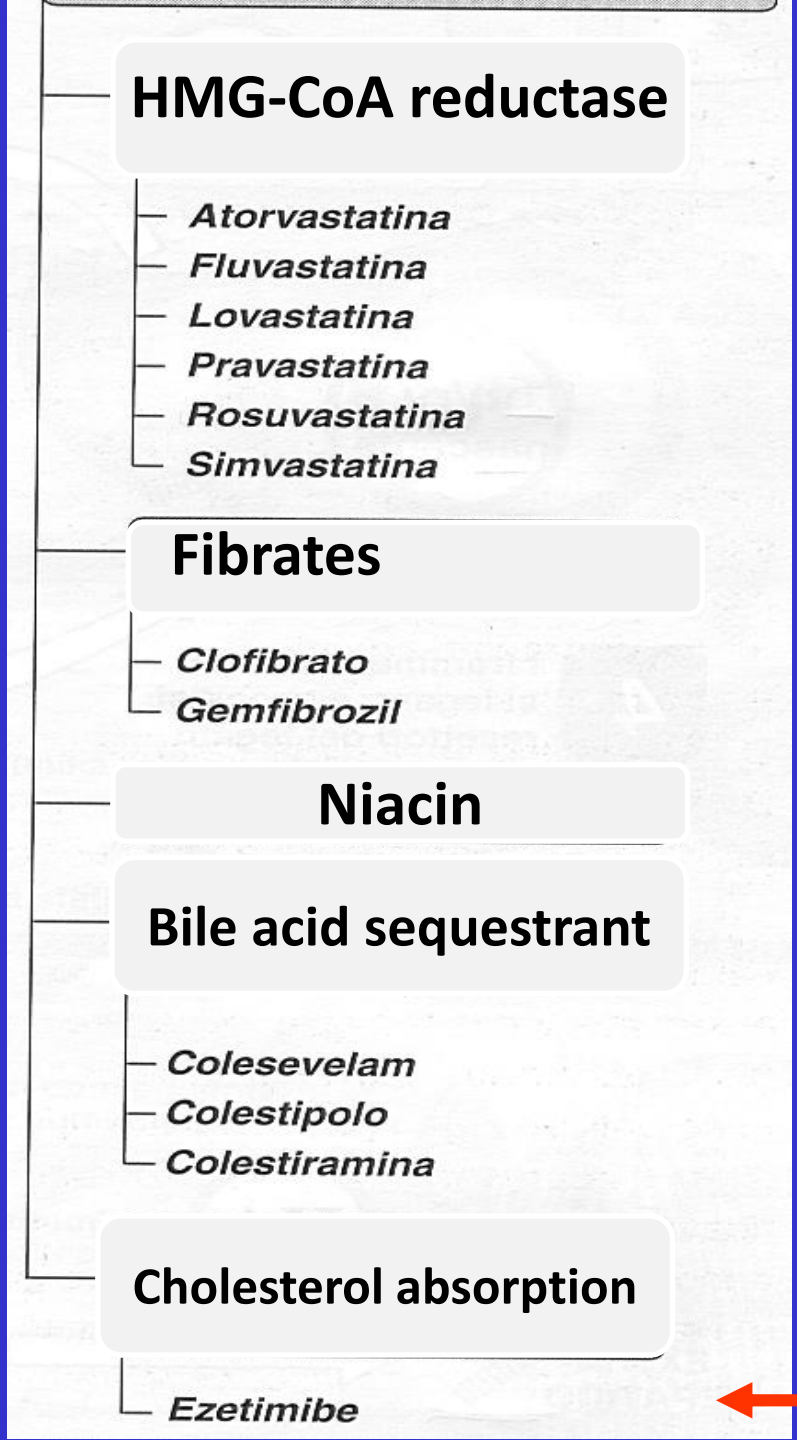
Association with statins

Characteristics of anti-hyperlipidemic drugs

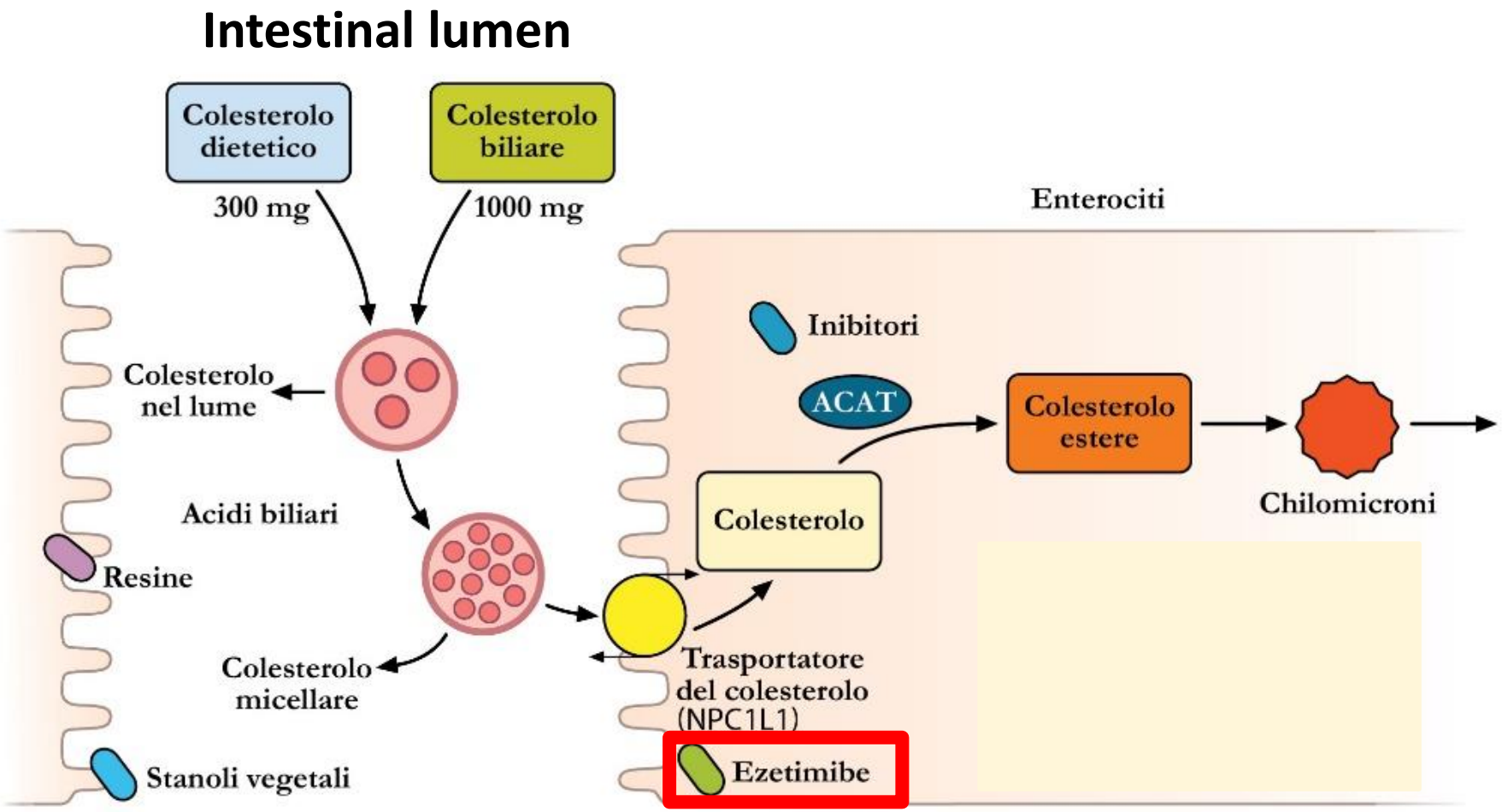
TIPO DI FARMACO	EFFETTO SUL COLESTEROLO-LDL	EFFETTO SUL COLESTEROLO-HDL	EFFETTO SUI TRIACILGLICEROLI
Inibitori della HMG-CoA riduttasi (statine)	↓↓↓↓	↑↑	↓↓
Fibrati	↓	↑↑↑	↓↓↓↓
Niacina	↓↓	↑↑↑↑	↓↓↓
Sequestranti degli acidi biliari	↓↓↓	↑	Minimo
Inibitori dell'assorbimento del colesterolo	↓	↑	↓



Response of total plasma cholesterol to diet and drugs in patients with familial hypercholesterolemia

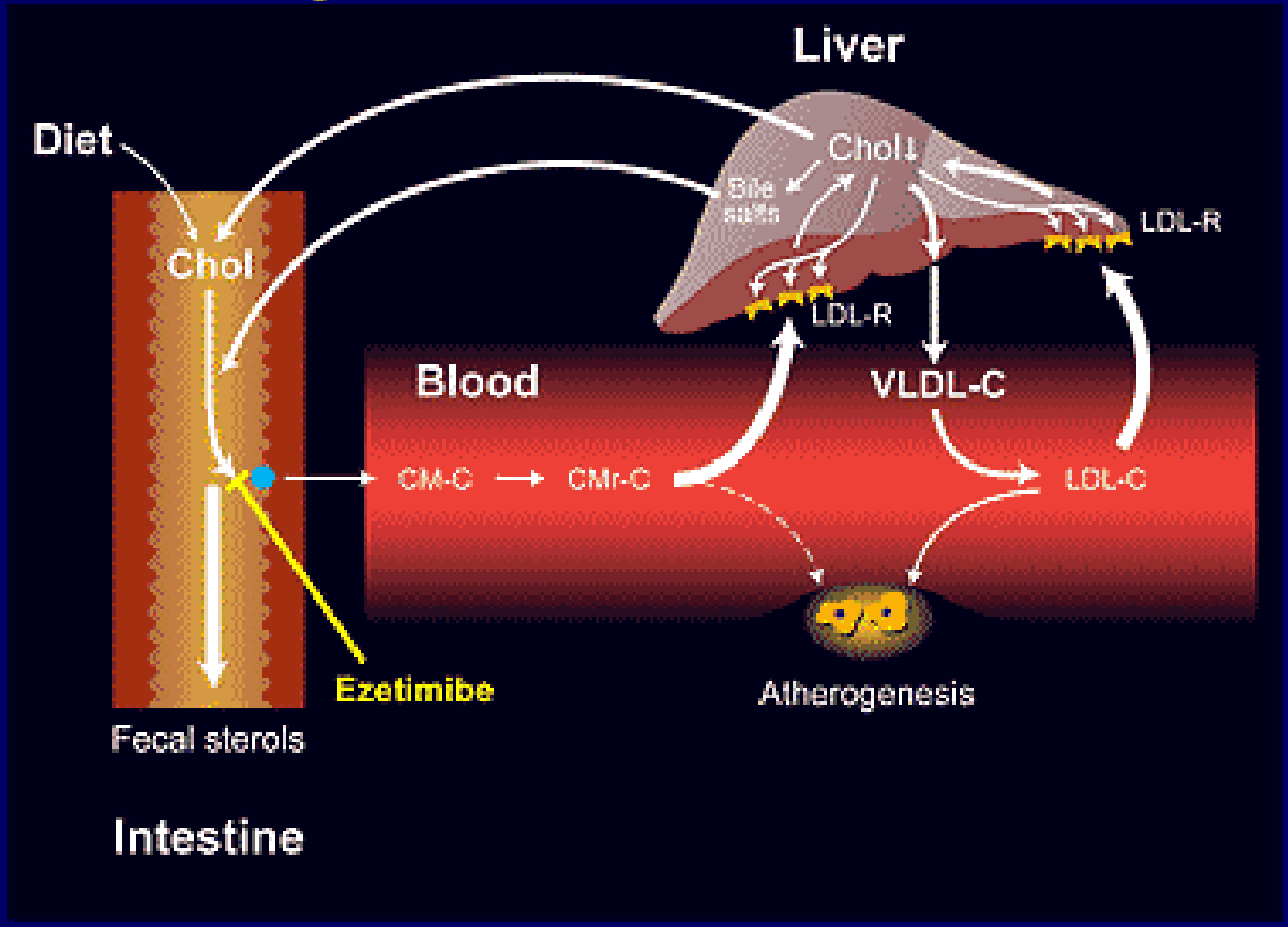

HMG-CoA reductase
Atorvastatina
Fluvastatina
Lovastatina
Pravastatina
Rosuvastatina
Simvastatina
Fibrates
Clofibrato
Gemfibrozil
Niacin
Bile acid sequestrant
Colesevelam
Colestipolo
Colestiramina
Cholesterol absorption
Ezetimibe

Ezetimibe



NPC1L1 : acetylcoenzyme A cholesterol acyltransferase

Reduction of Cholesterol Absorption Results in Less LDL



Characteristics of anti-hyperlipidemic drugs

TIPO DI FARMACO	EFFETTO SUL COLESTEROLO-LDL	EFFETTO SUL COLESTEROLO-HDL	EFFETTO SUI TRIACILGLICEROLI
Inibitori della HMG-CoA riduttasi (statine)	↓↓↓↓	↑↑	↓↓
Fibrati	↓	↑↑↑	↓↓↓↓
Niacina	↓↓	↑↑↑↑	↓↓↓
Sequestranti degli acidi biliari	↓↓↓	↑	Minimo
Inibitori dell'assorbimento del colesterolo *	↓	↑	↓

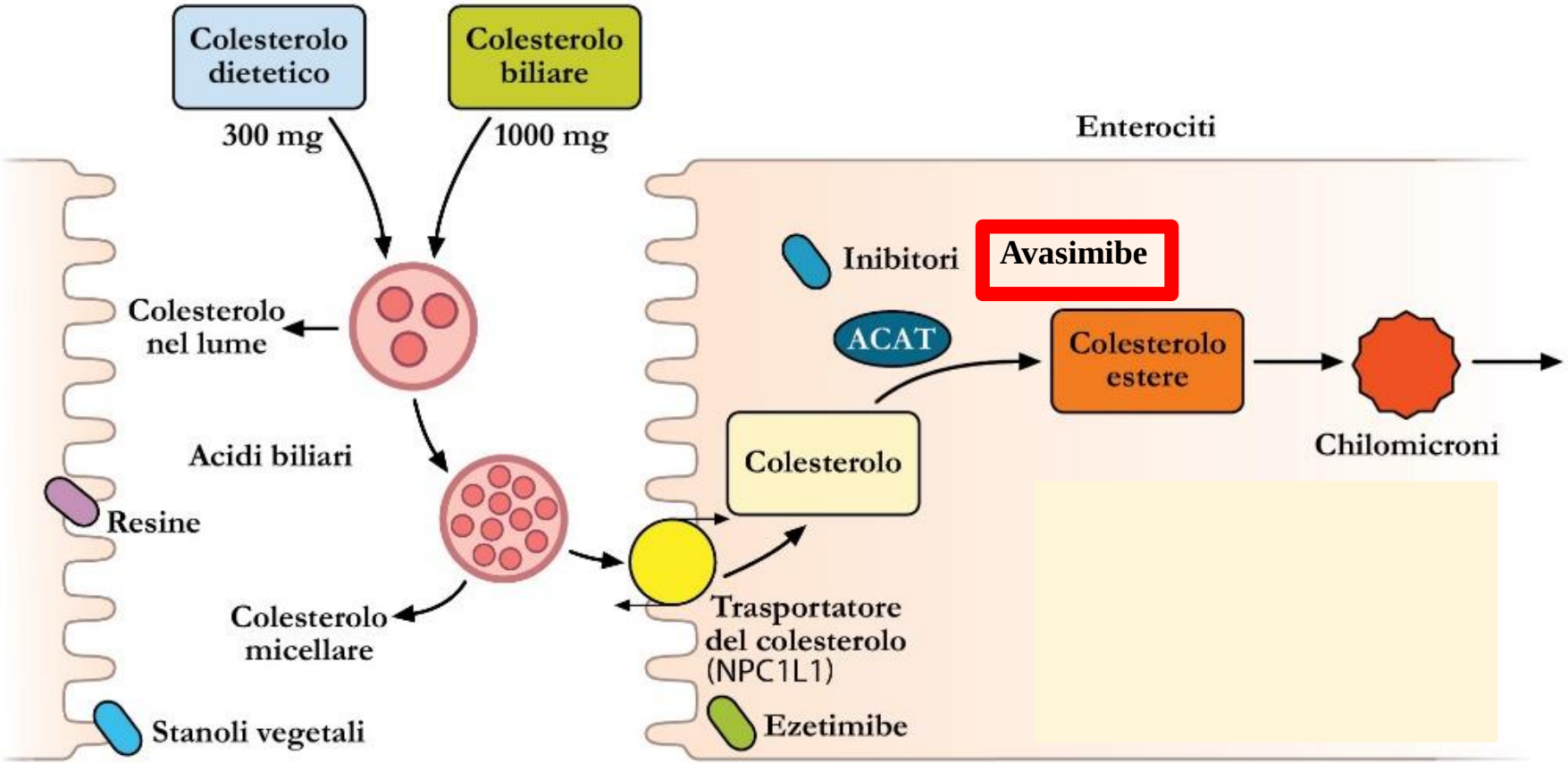
* ezetimibe

Clinical use of drugs that reduce cholesterol absorption: ezetimibe or bile acid–binding resins (e.g. colestyramine)

- As an addition to a statin when response has been inadequate (**ezetimibe**).
- For hypercholesterolaemia when a statin is contraindicated.
- Uses unrelated to atherosclerosis, including:
  - pruritus in patients with partial biliary obstruction (bile acid–binding resin)
  - bile acid diarrhoea, for example caused by diabetic neuropathy (bile acid–binding resin).

New Drugs

Avasimibe

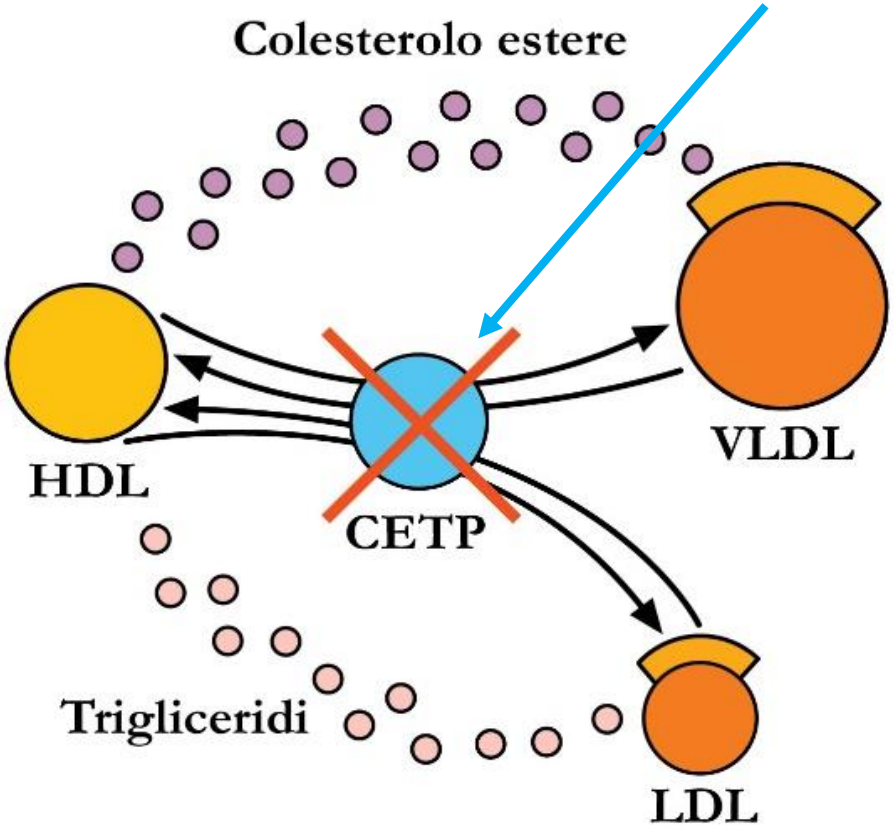


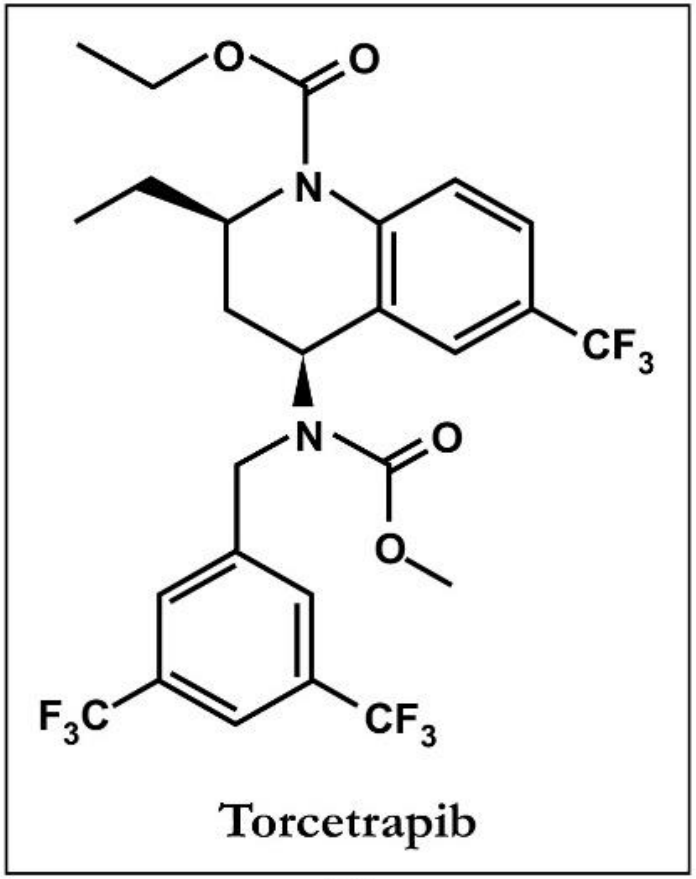
ACAT : acetylcoenzyme A cholesterol acyltransferase
NPC1L1 : acetylcoenzyme A cholesterol acyltransferase

Avasimibe:

- antinflammatory effects, reduces TNFalfa
- improve resistence in vessels function
- inhibits acetilcoenzimaA colesterolo aciltransferasi (ACAT)
- inhibits formation of Foam cells

Torcetrapib





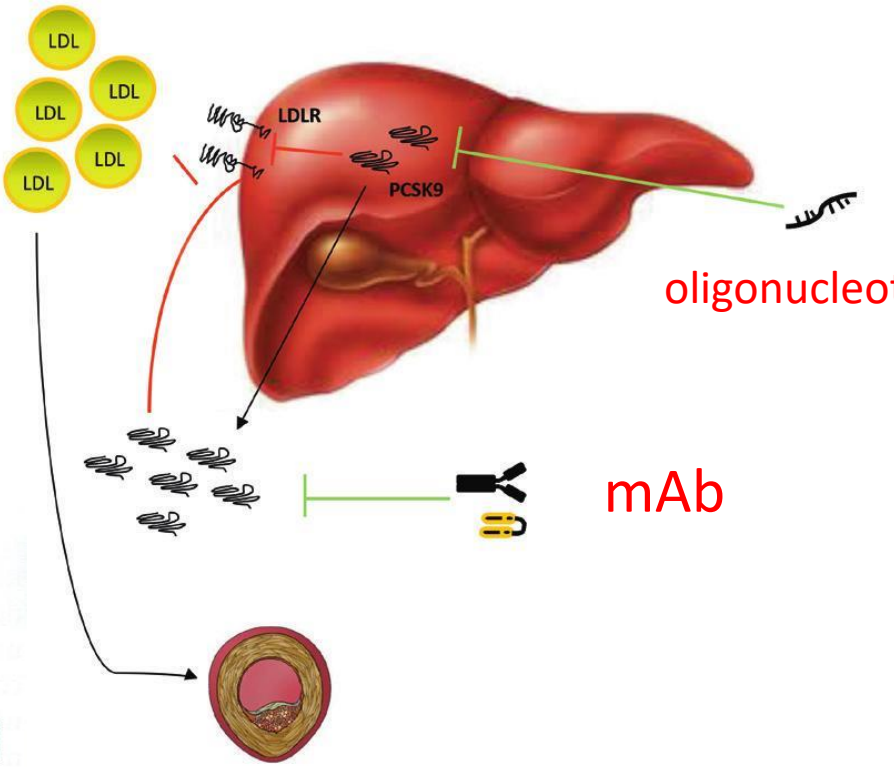
HDL (40%)

LDL (17%)

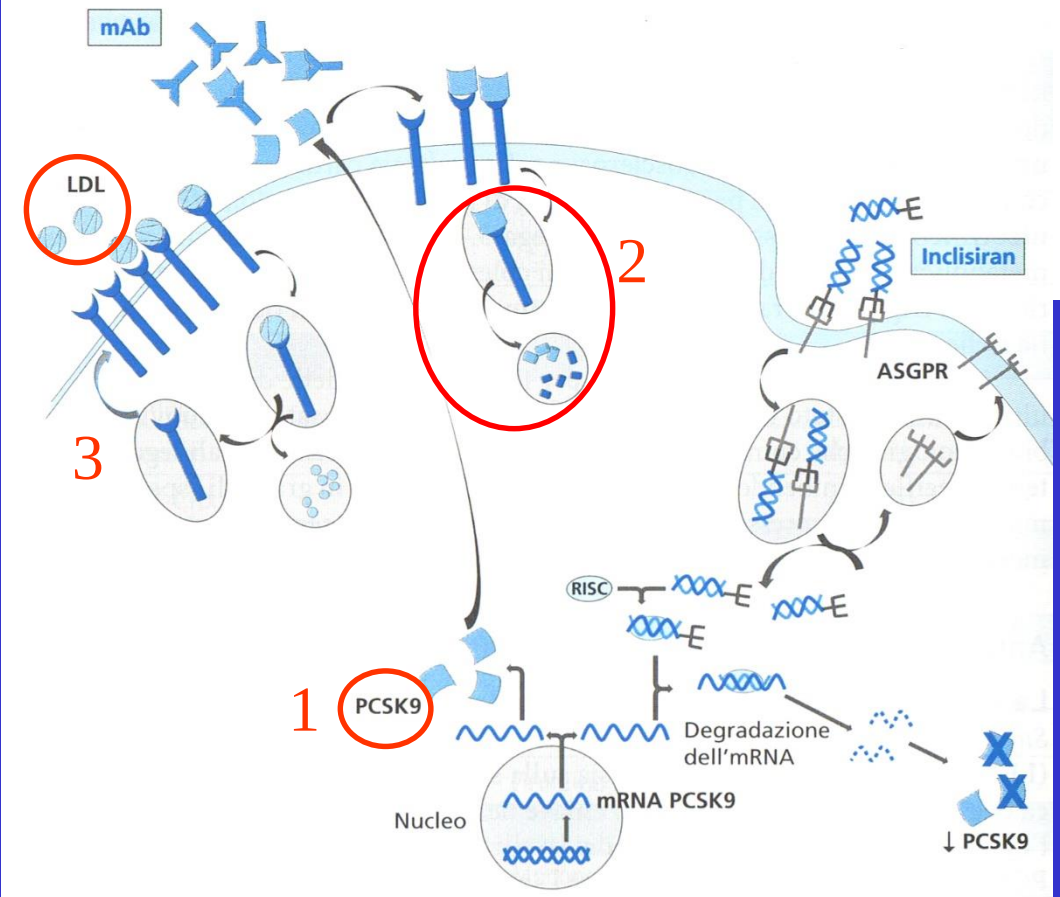
CEPT: cholesterol ester transfer protein

PCSK9 Inhibitors

Proprotein Convertase Subtilisin/Kexin type 9



evolocumab, alirocumab



PCSK9 inhibits recycling of LDLR

- PCSK9 + LDLR - circulating LDL

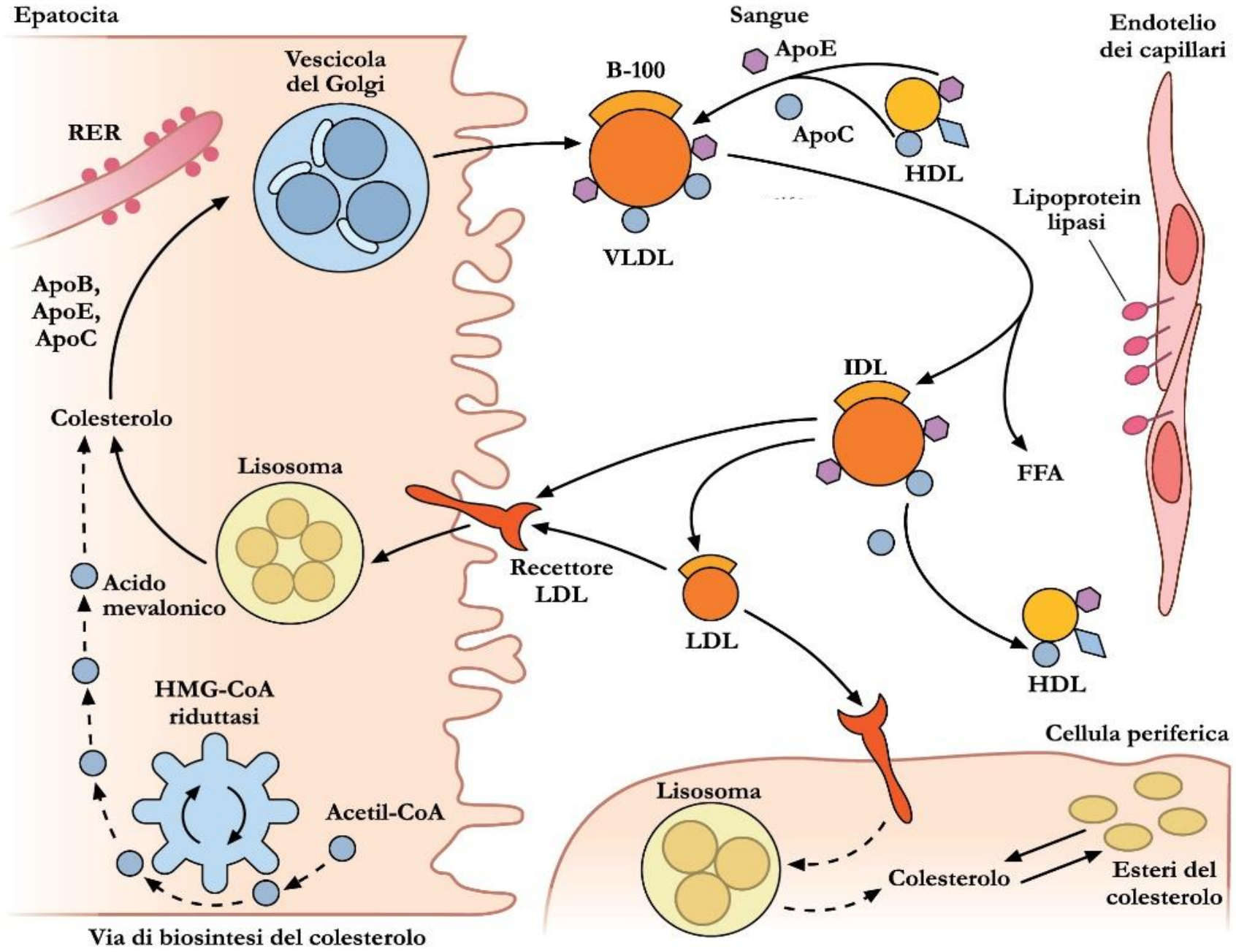


Figura 40.1. Metabolismo delle lipoproteine di origine epatica.

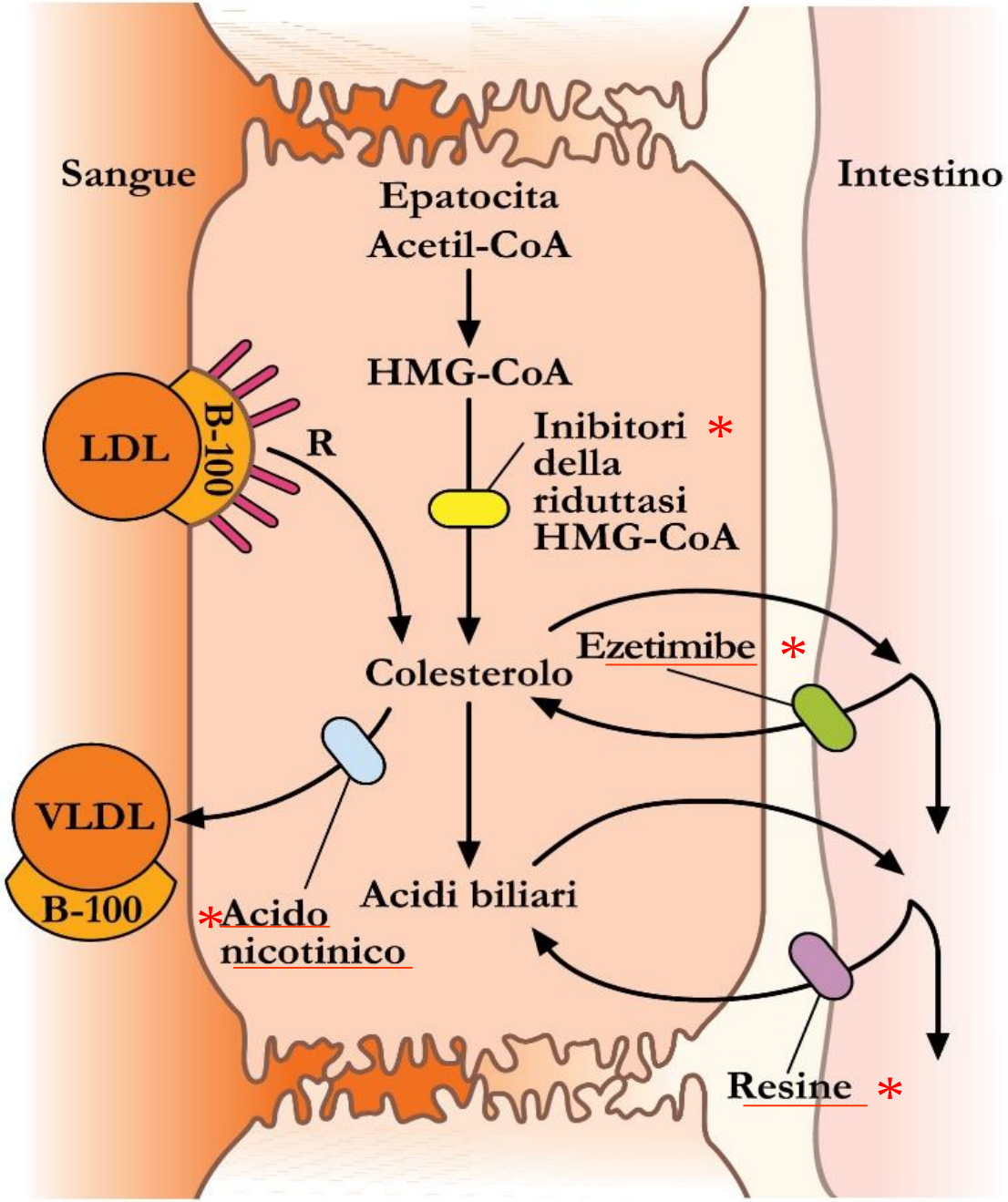


Figura 40.2. Siti d'azione delle principali classi di farmaci antidislipidemici.