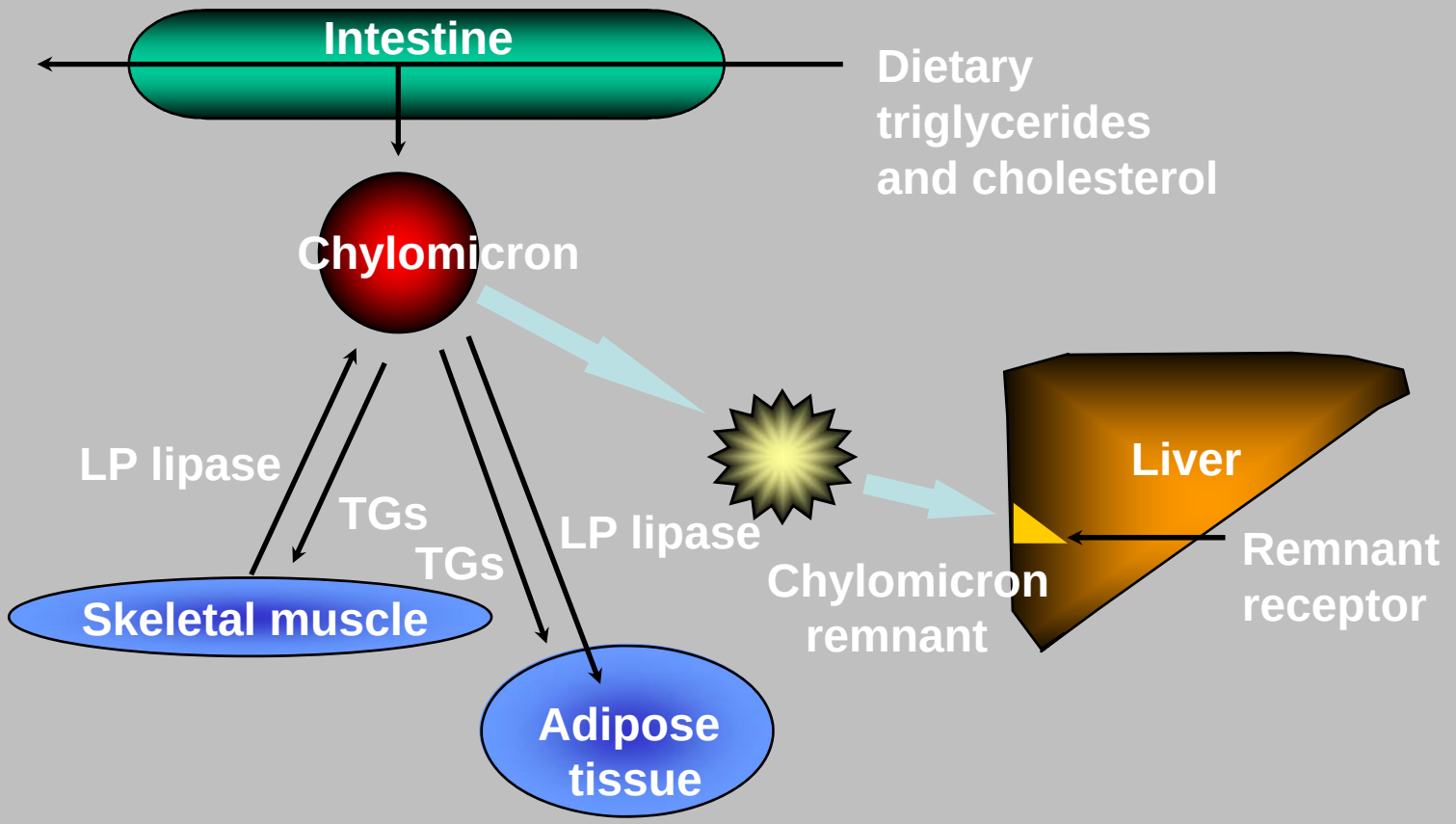
Treatment of hypercholesterolaemia

Classification of Lipoproteins

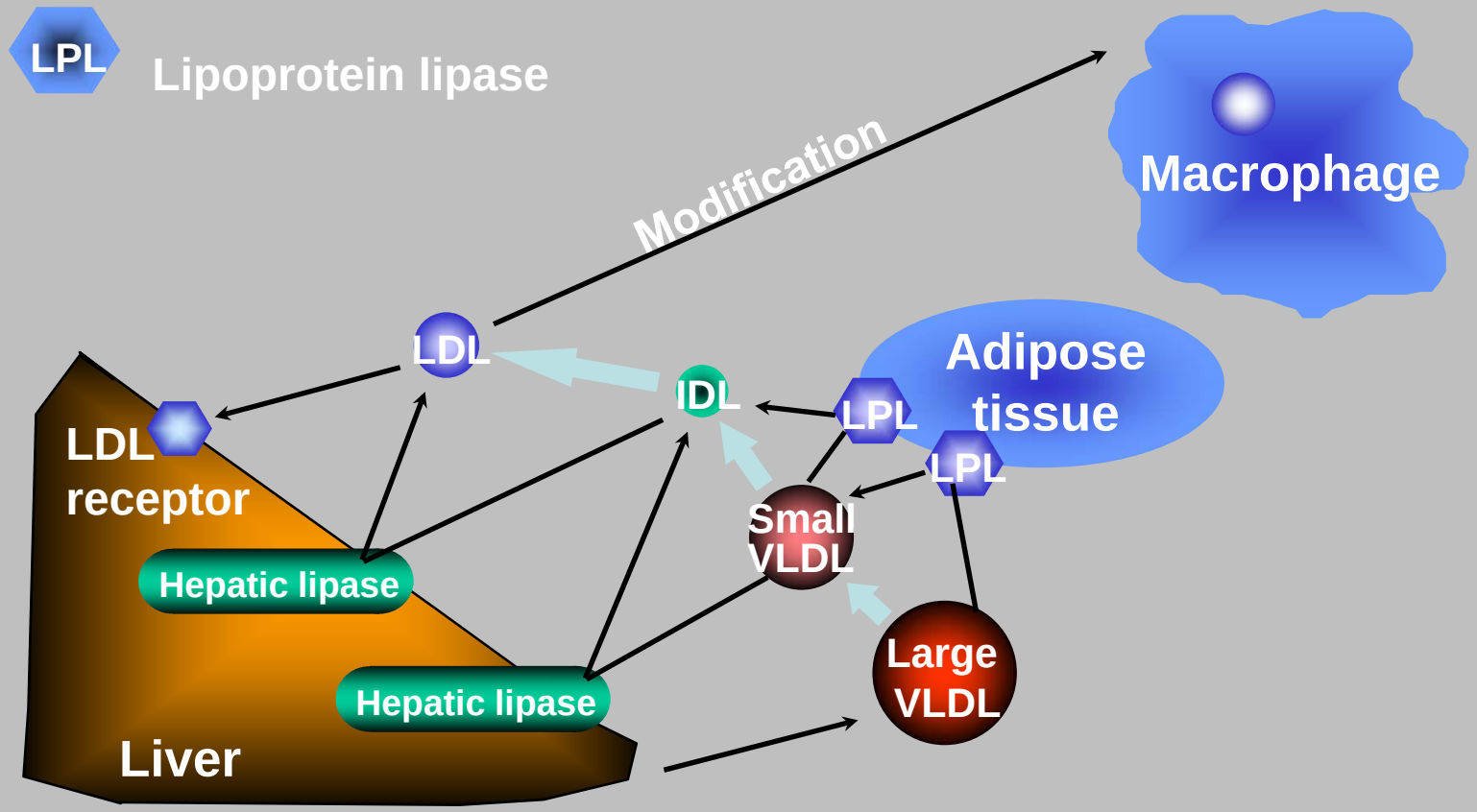
Based on density:

- Chylomicrons
- Very low-density lipoprotein (VLDL)
- Intermediate-density lipoprotein (IDL)
- Low-density lipoprotein (LDL)
- High-density lipoprotein (HDL)

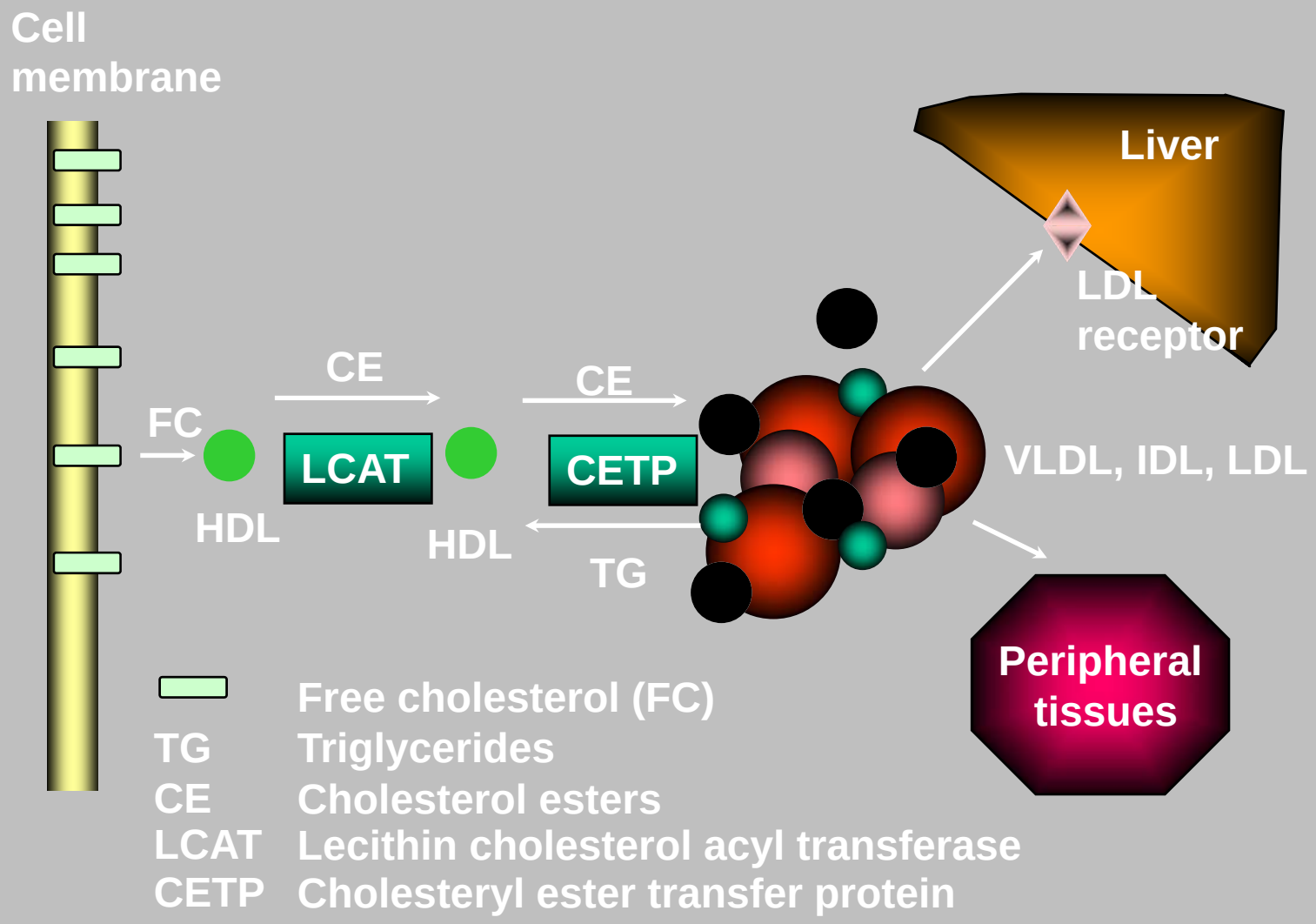
Exogenous Pathway of Lipid Metabolism



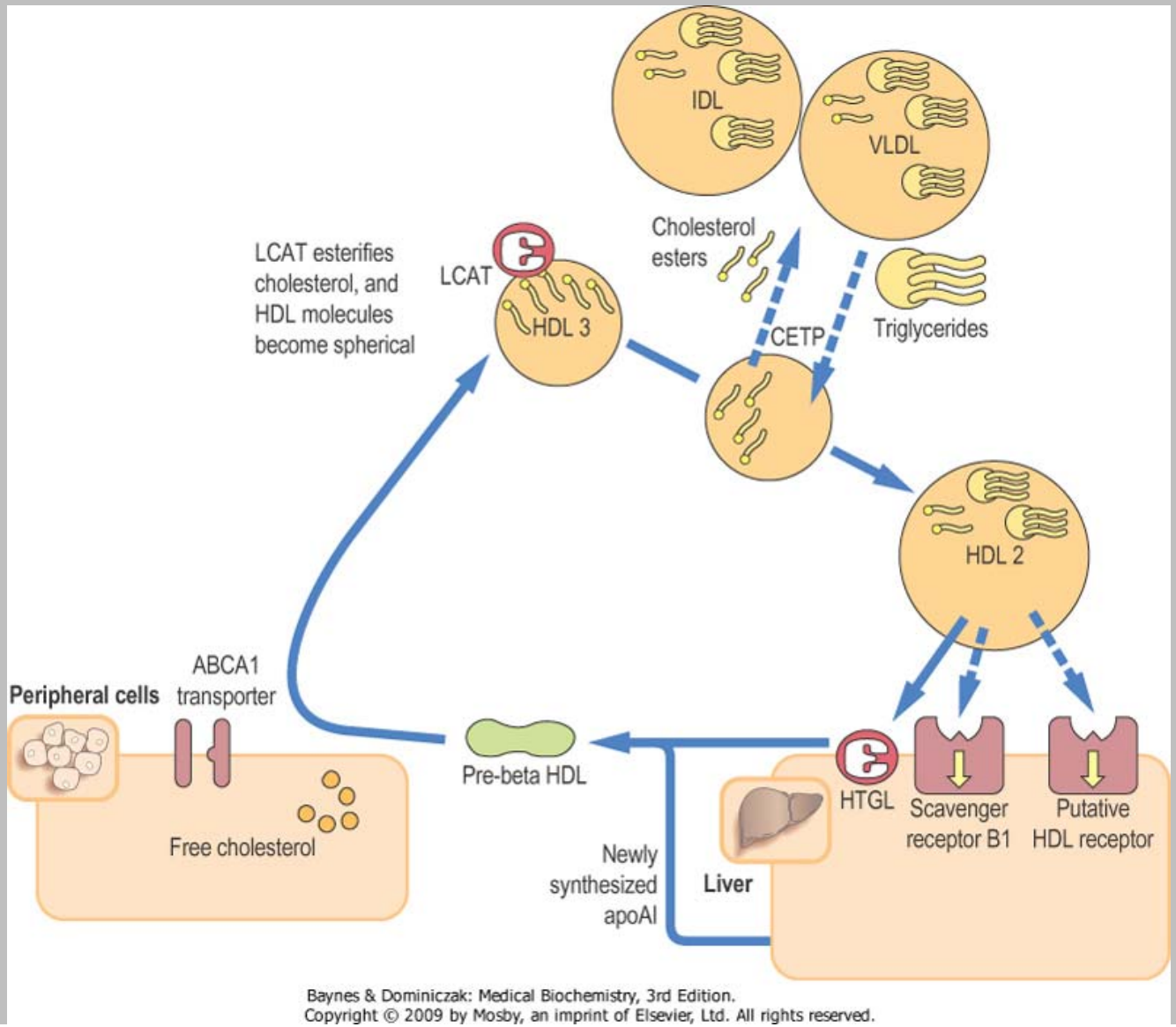
Endogenous Pathway of Lipid Metabolism



Reverse Cholesterol Transport



Reverse cholesterol transport



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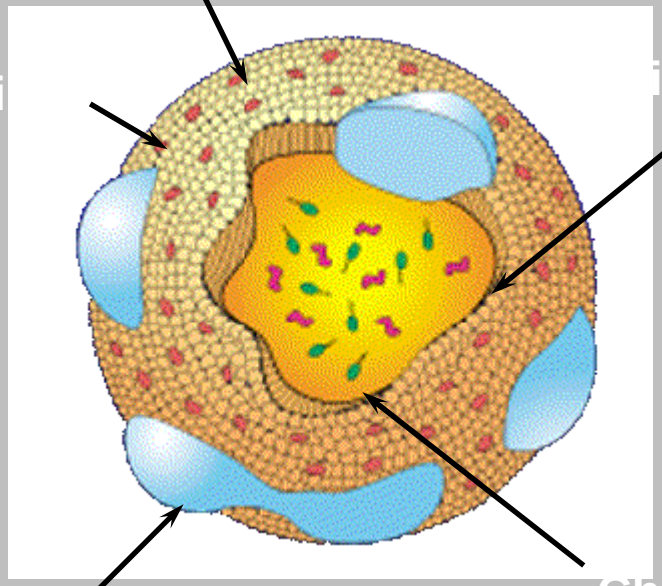
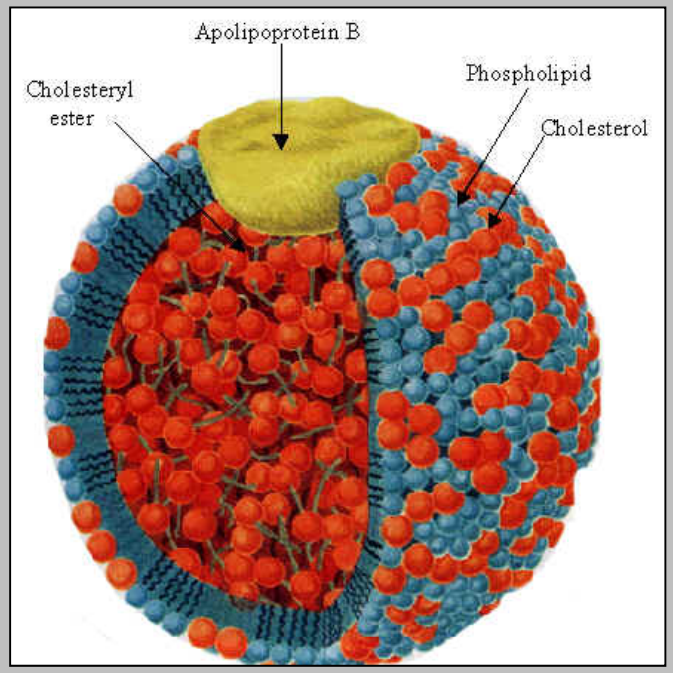
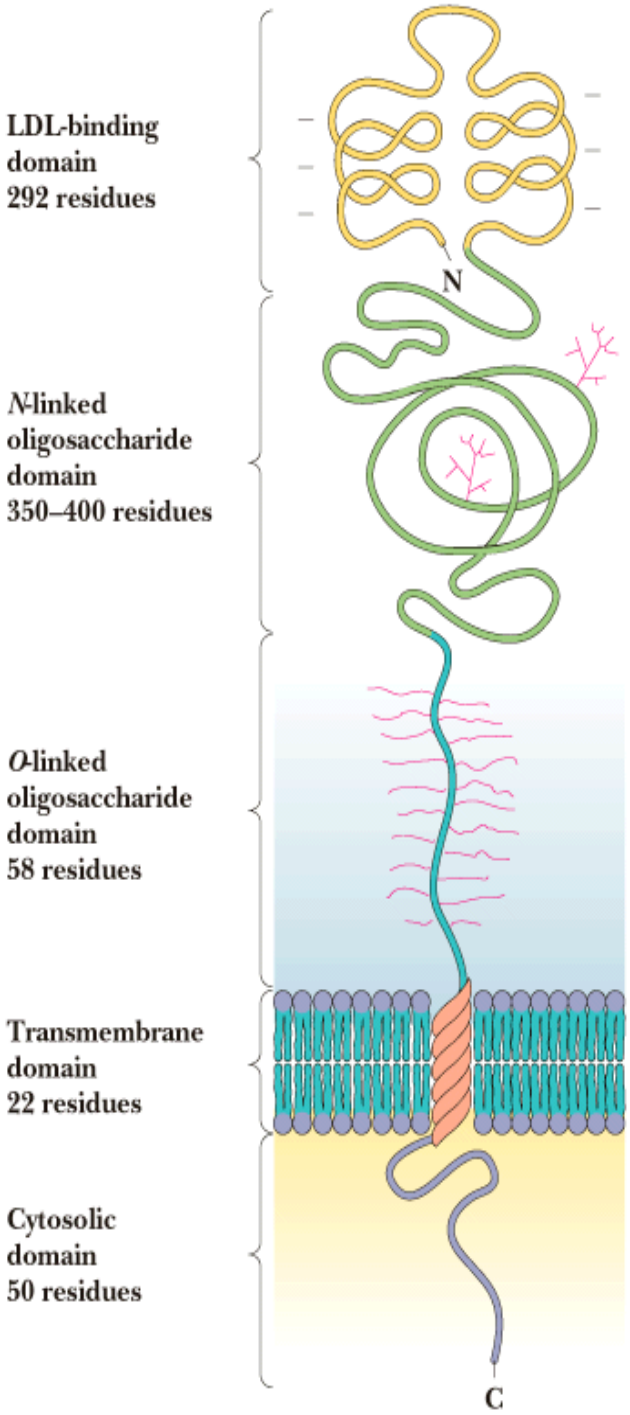
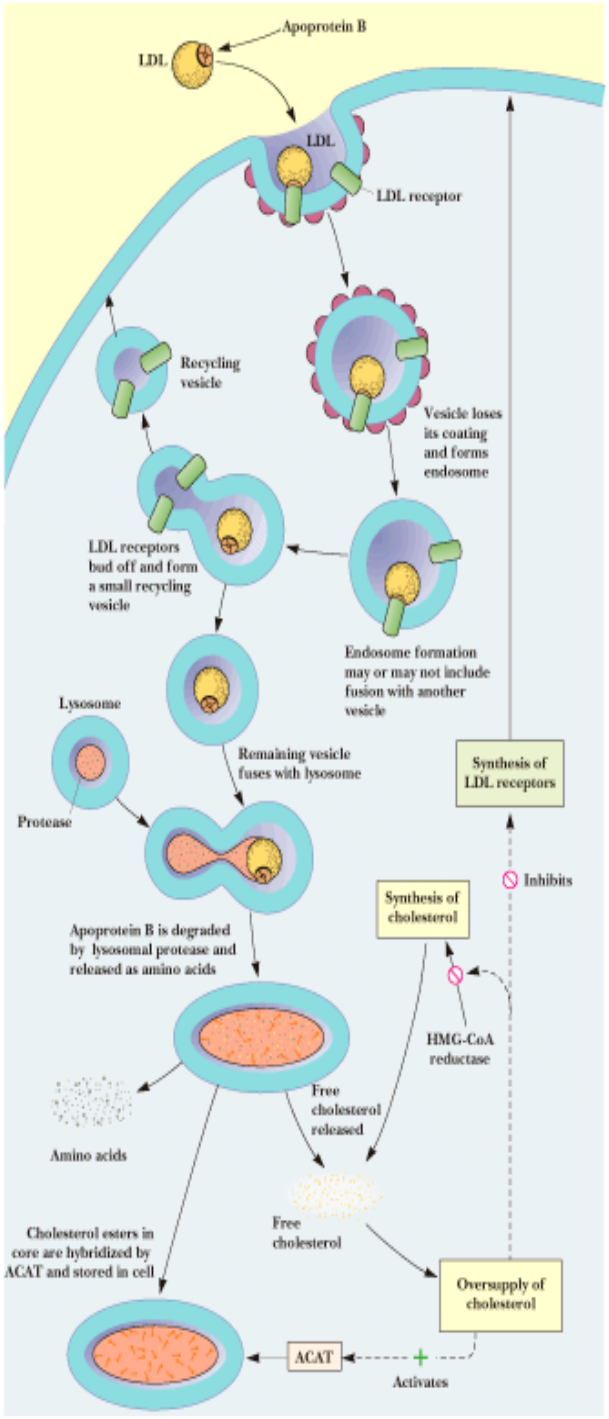
Structure of Lipoproteins






LDL-binding
domain
292 residues
N
N-linked
oligosaccharide
domain
350–400 residues
O-linked
oligosaccharide
domain
58 residues
Transmembrane
domain
22 residues
Cytosolic
domain
50 residues
C


Apoprotein B
LDL
LDL
LDL receptor
Recycling vesicle
Vesicle loses its coating and forms endosome
LDL receptors bud off and form a small recycling vesicle
Endosome formation may or may not include fusion with another vesicle
Lysosome
Remaining vesicle fuses with lysosome
Protease
Synthesis of LDL receptors
Inhibits
Synthesis of cholesterol
Apoprotein B is degraded by lysosomal protease and released as amino acids
HMG-CoA reductase
Free cholesterol released
Amino acids
Free cholesterol
Cholesterol esters in core are hybridized by ACAT and stored in cell
Oversupply of cholesterol
ACAT
Activates

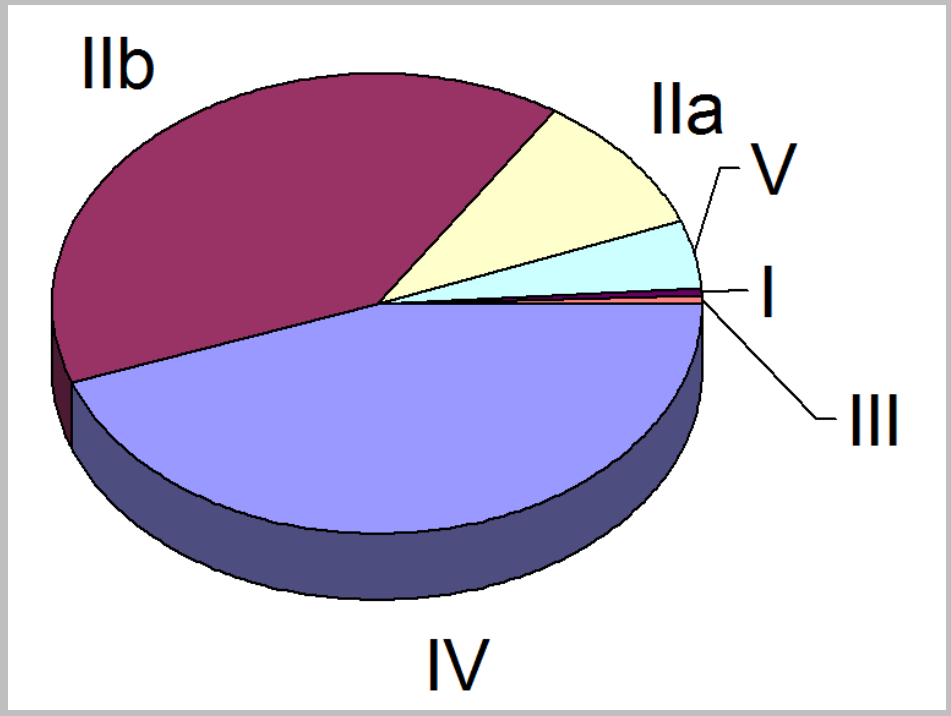
Classification of Dyslipidaemias
Fredrickson (WHO) Classification

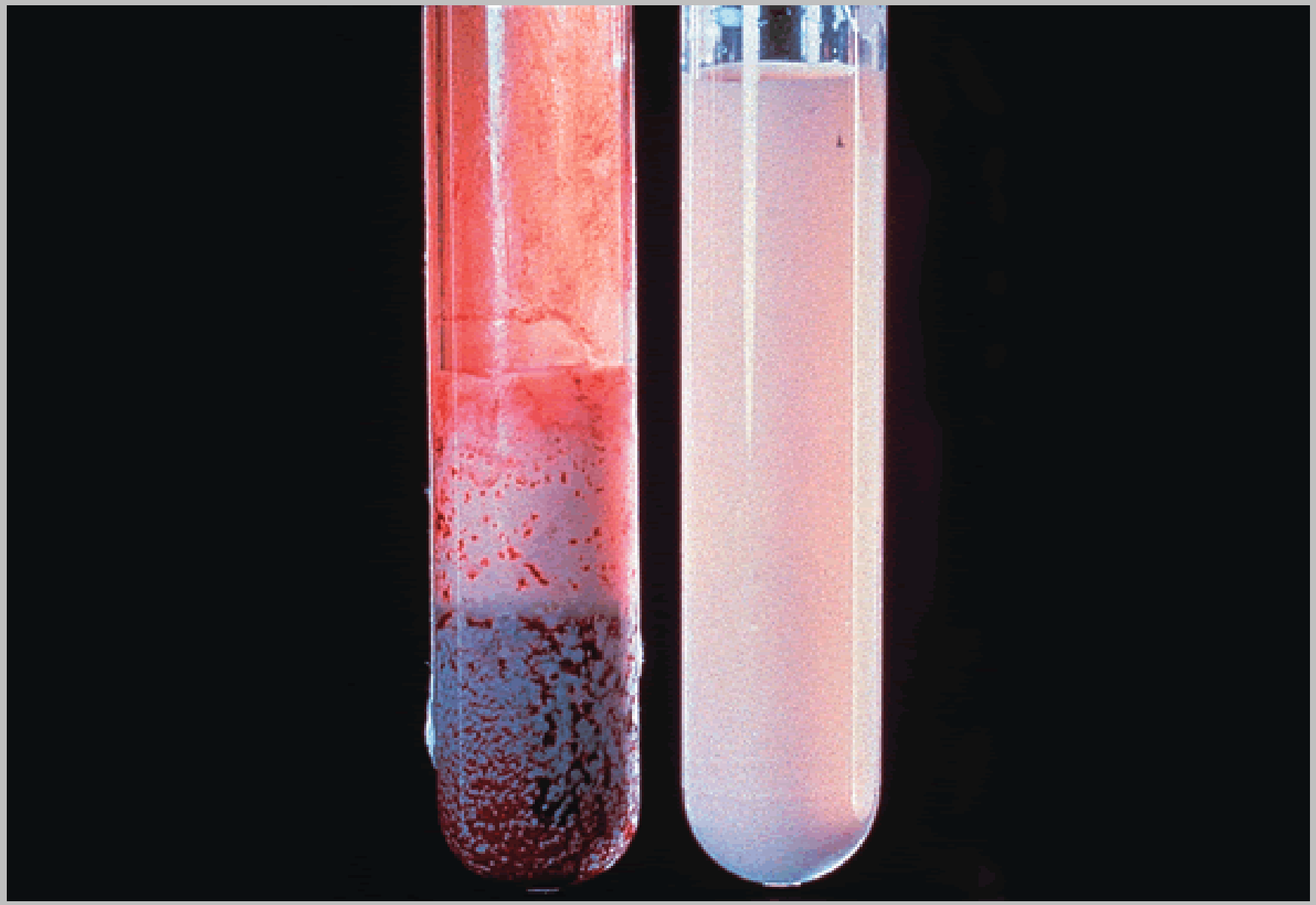
Phenotype	Lipoprotein elevated	Serum cholesterol	Serum triglyceride	Atherogenicity	Prevalence
I	Chylomicrons	Normal to ↑	↑↑↑↑	None seen	Rare
IIa	LDL	↑↑	Normal	+++	Common
IIb	LDL and VLDL	↑↑	↑↑	+++	Common
III	IDL	↑↑	↑↑↑	+++	Intermediate
IV	VLDL	Normal to ↑	↑↑	+	Common
V	VLDL and chylomicrons	Normal to ↑	↑↑↑↑	+	Rare

LDL – low-density lipoprotein; IDL – intermediate-density lipoprotein; VLDL – very low-density lipoprotein. (High-density lipoprotein (HDL) cholesterol levels are not considered in the Fredrickson classification.)

(Adapted from Yeshurun *et al.*, 1995)

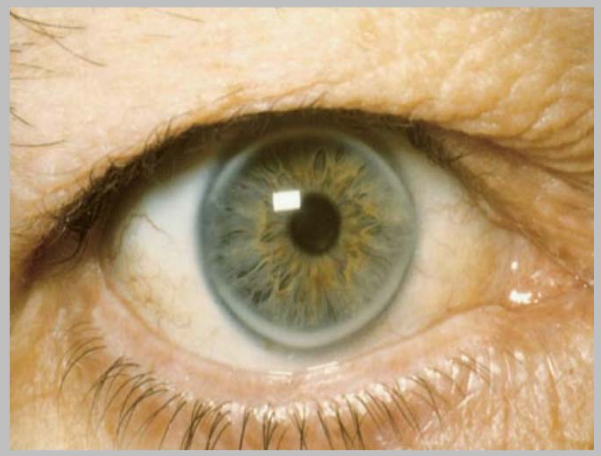
Relative prevalence of familiar hyperlipoproteinemias





Stigmata of Familial Hypercholesterolaemia

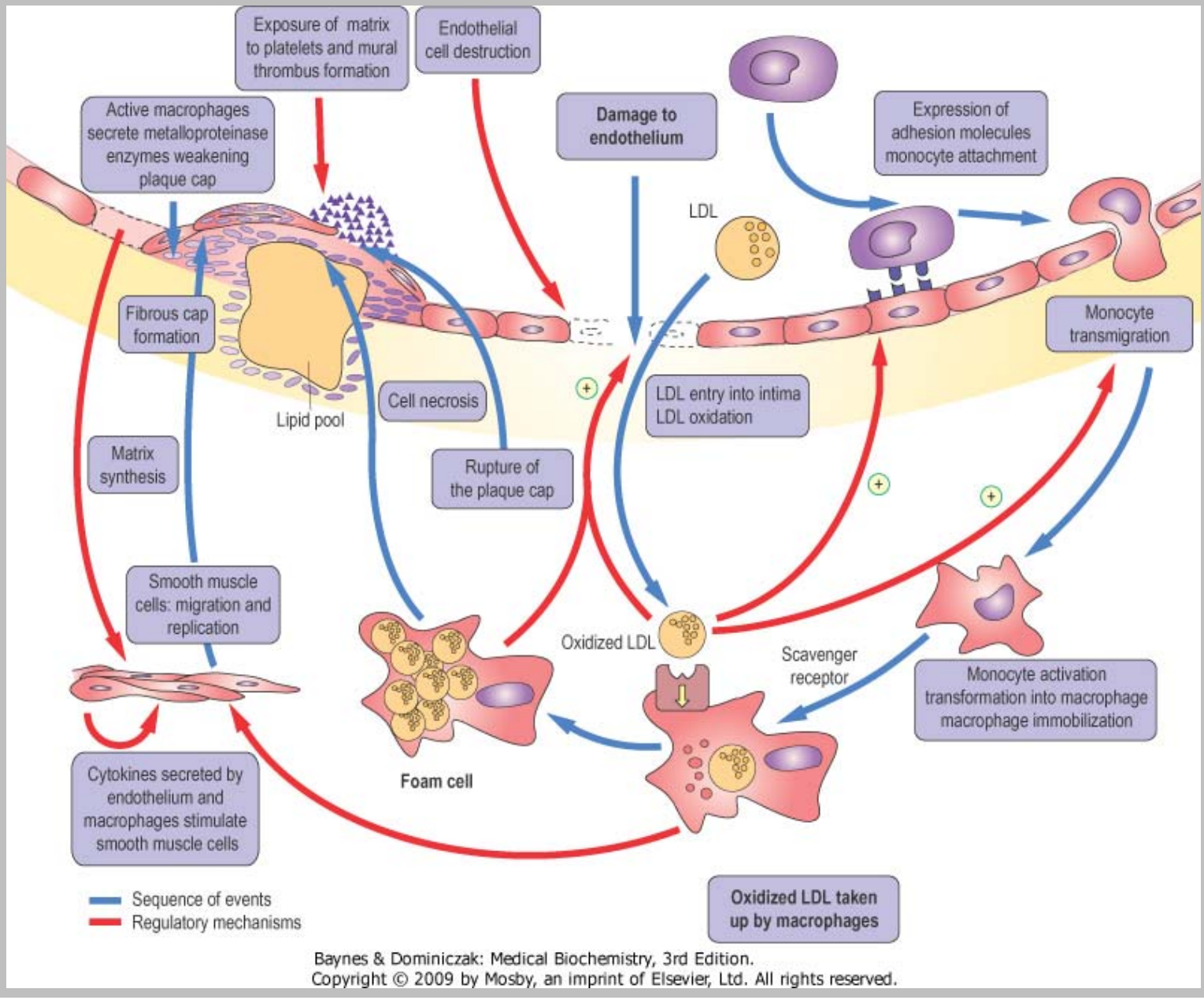
Corneal Arcus



Xanthelasma

Tendon Xanthoma

Definite FH



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Pathogenesis of Atherosclerotic Plaques

Endothelial damage

↓

Protective response results in production of cellular adhesion molecules

↓

Monocytes and T lymphocytes attached to 'sticky' surface of endothelial cells

↓

Migrate through arterial wall to subendothelial space

↓

Macrophages take up oxidised LDL cholesterol

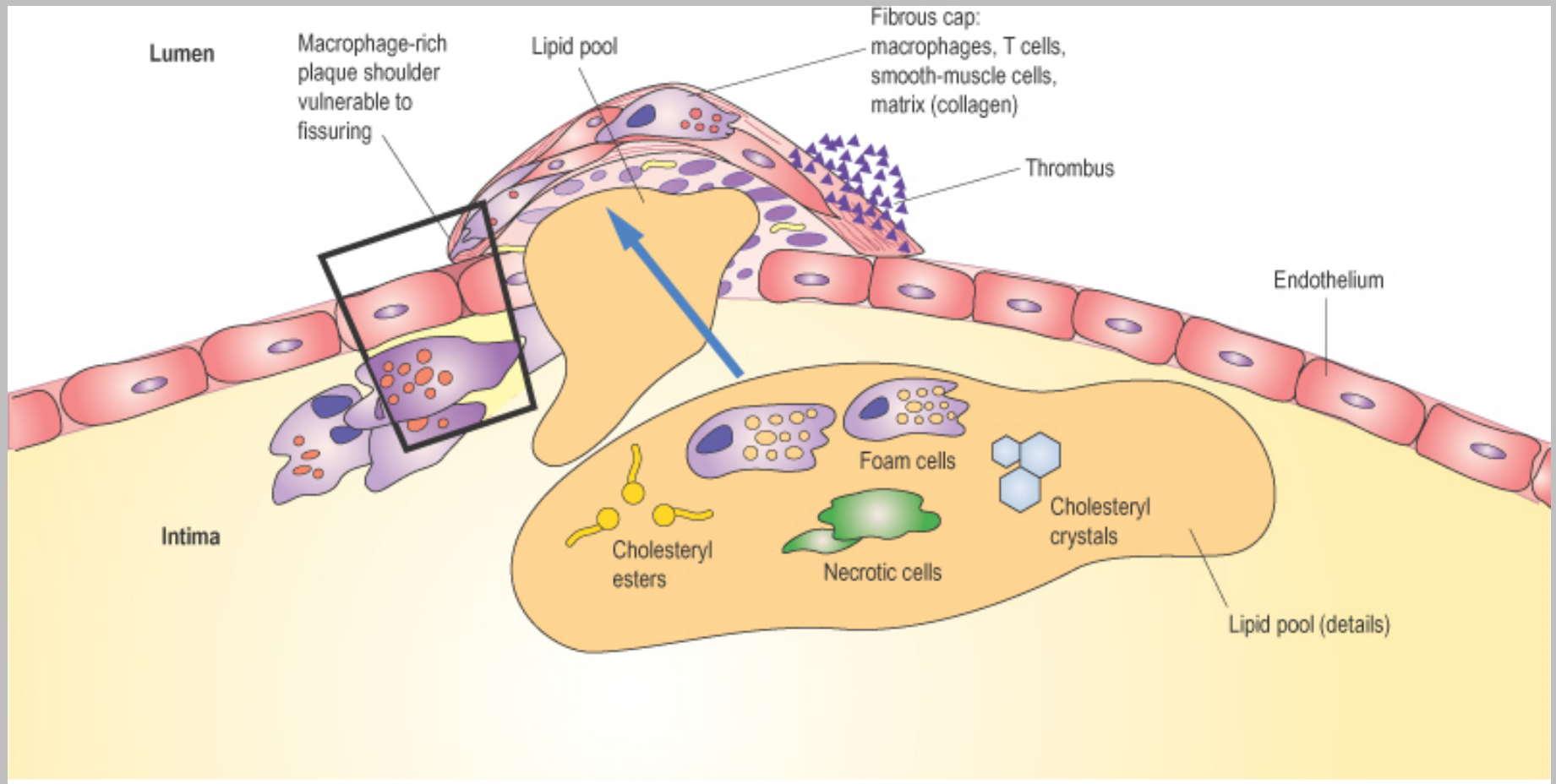
↓

Lipid-rich foam cells

↓

Fatty streak and plaque

Atherosclerosis and cholesterol



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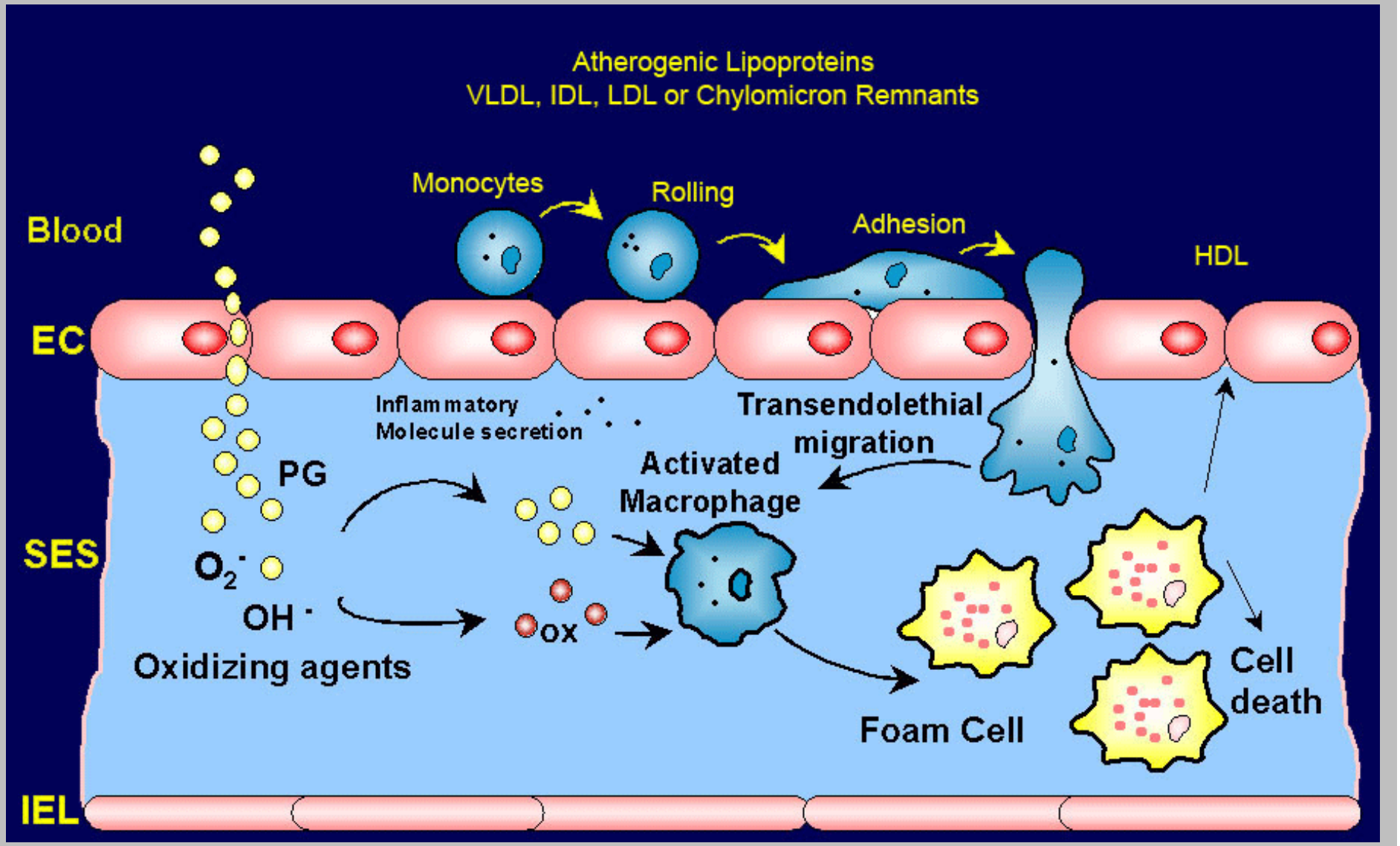
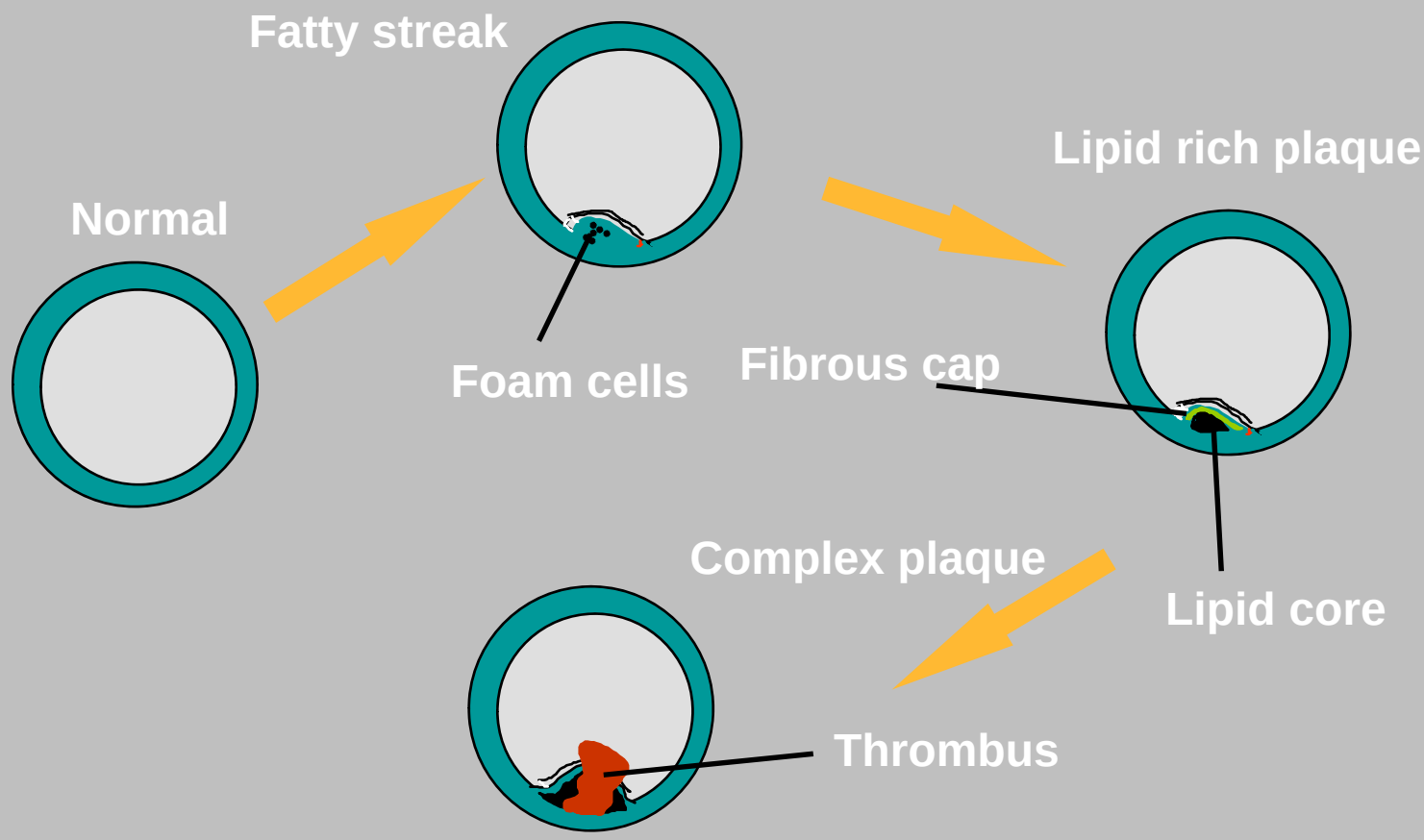
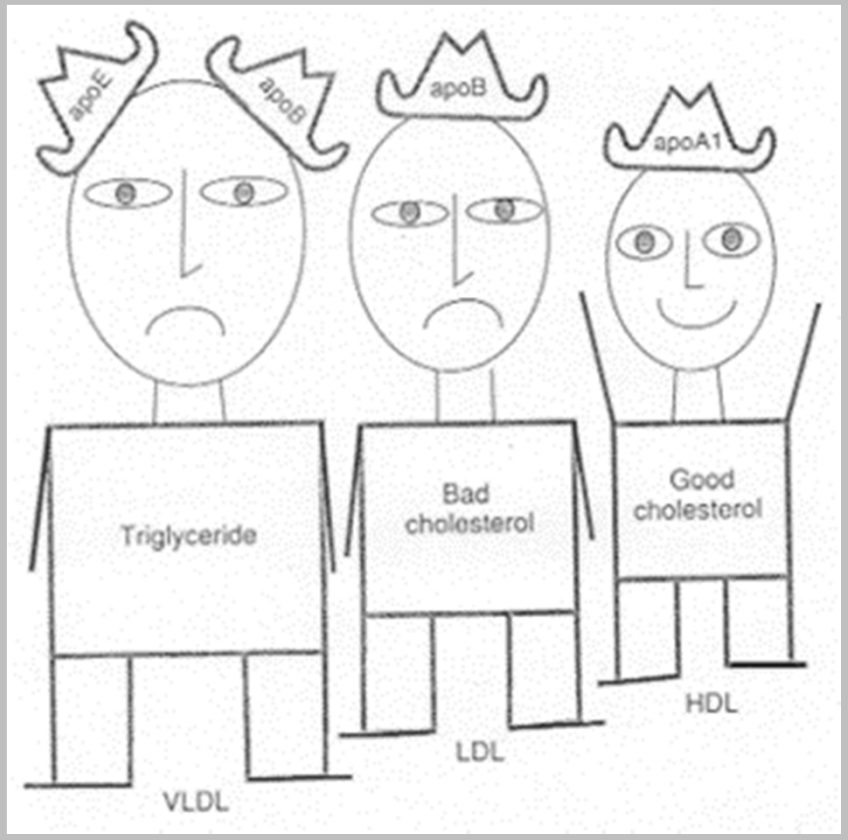

Atherogenic Lipoproteins
VLDL, IDL, LDL or Chylomicron Remnants
Blood
Monocytes
Rolling
Adhesion
HDL
EC
Inflammatory
Molecule secretion
Transendolethial
migration
Activated
Macrophage
PG
SES
$O_2^{\cdot}$
$OH^{\cdot}$
Oxidizing agents
ox
Foam Cell
Cell
death
IEL

Development of Atherosclerotic Plaques



Atherosclerosis and cholesterol

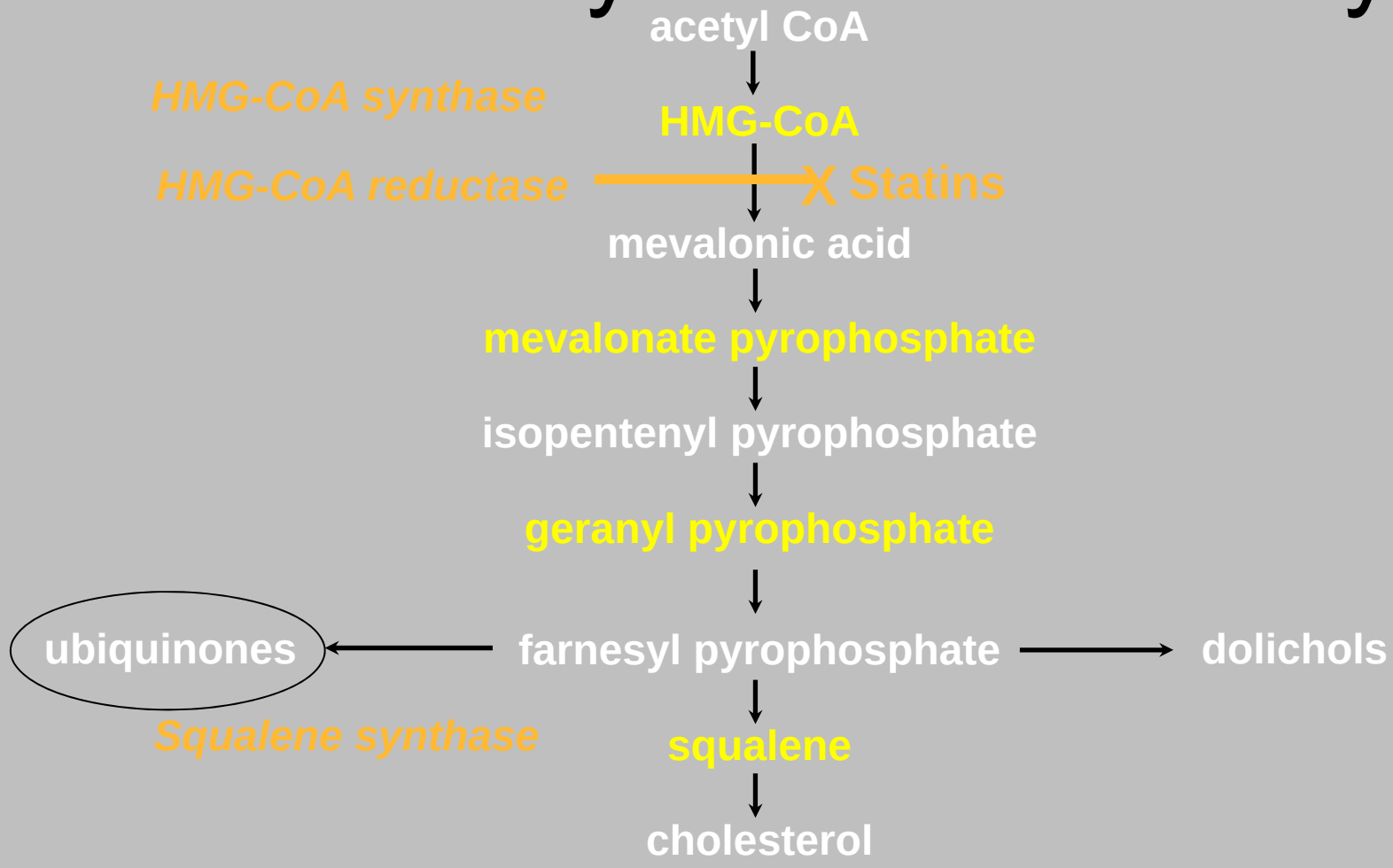


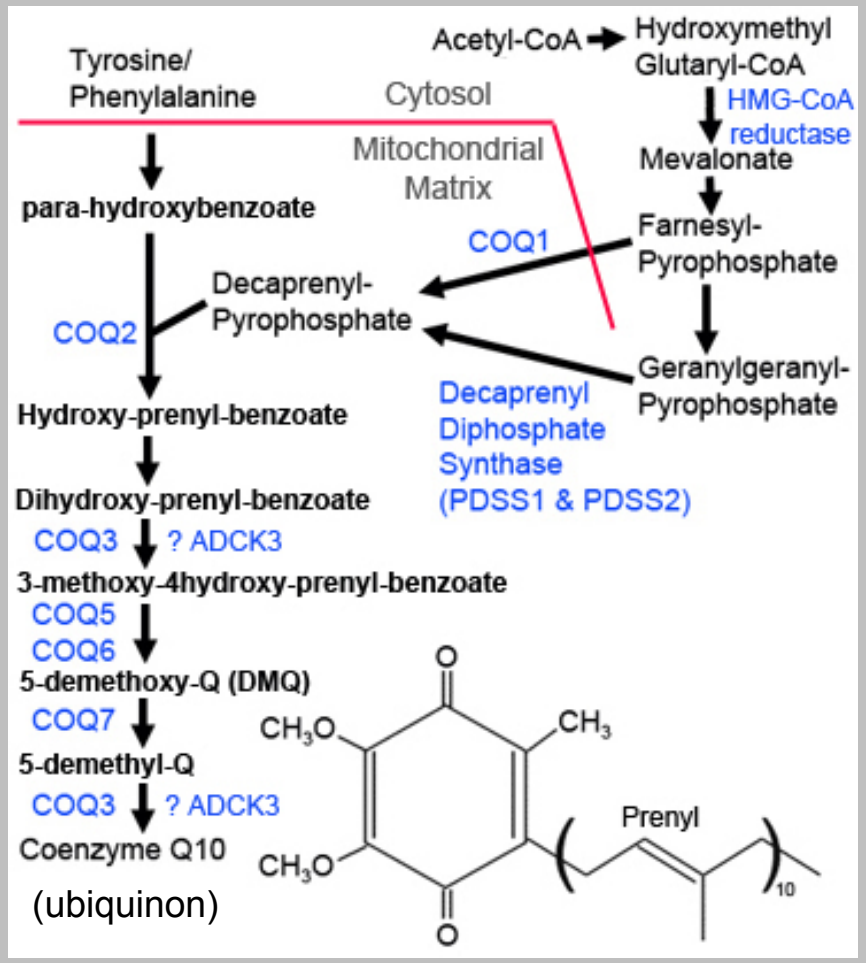
Drugs that may elevate LDL-C or TG cc.

Drugs that elevate LDL-C	Drugs that elevate triglycerides
• Some progestins • Anabolic steroids • Danazol • Isotretinoin • Immunosuppressive drugs (cyclosporine) • Amiodarone • Thiazide diuretics • Glucocorticoids • Thiazolidinediones • Fibric acids (in severe hypertriglyceridemia) • Long chain omega-3 fatty acids (in severe hypertriglyceridemia, if containing docosahexaenoic acid)	• Oral estrogens • Tamoxifen • Raloxifene • Retinoids • Immunosuppressive drugs (cyclosporine, sirolimus) • Interferon • Beta-blockers (especially non-beta 1 selective) • Atypical antipsychotic drugs (fluperlapine, clozapine, olanzapine) • Protease inhibitors • Thiazide diuretics • Glucocorticoids • Rosiglitazone • Bile acid sequestrants • L-asparaginase • Cyclophosphamide

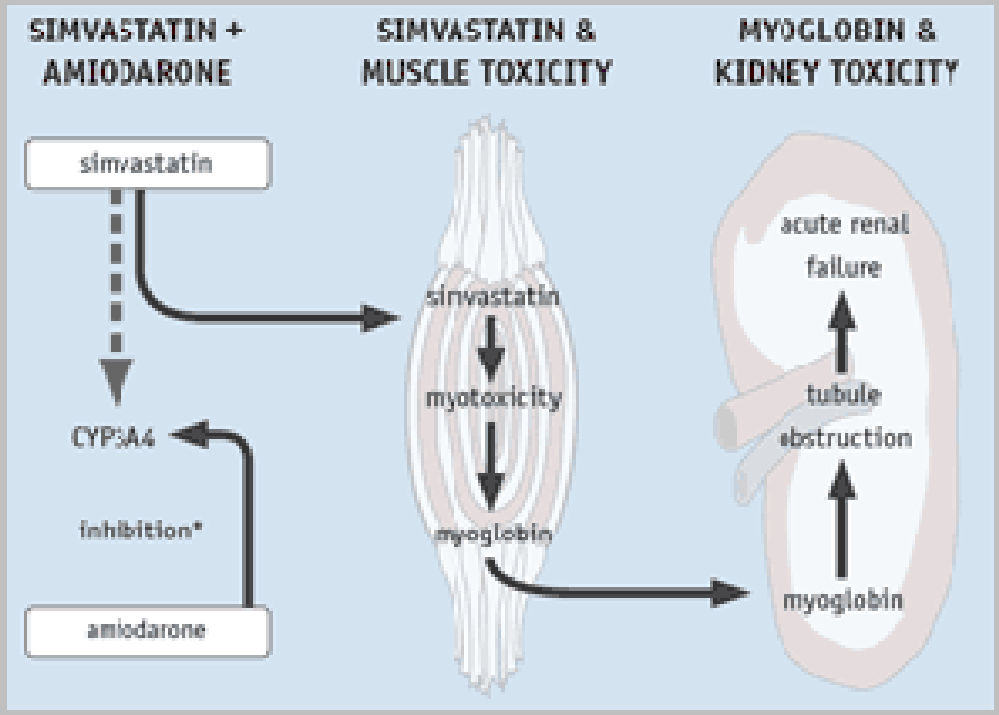
LDL-C, low-density lipoprotein cholesterol.

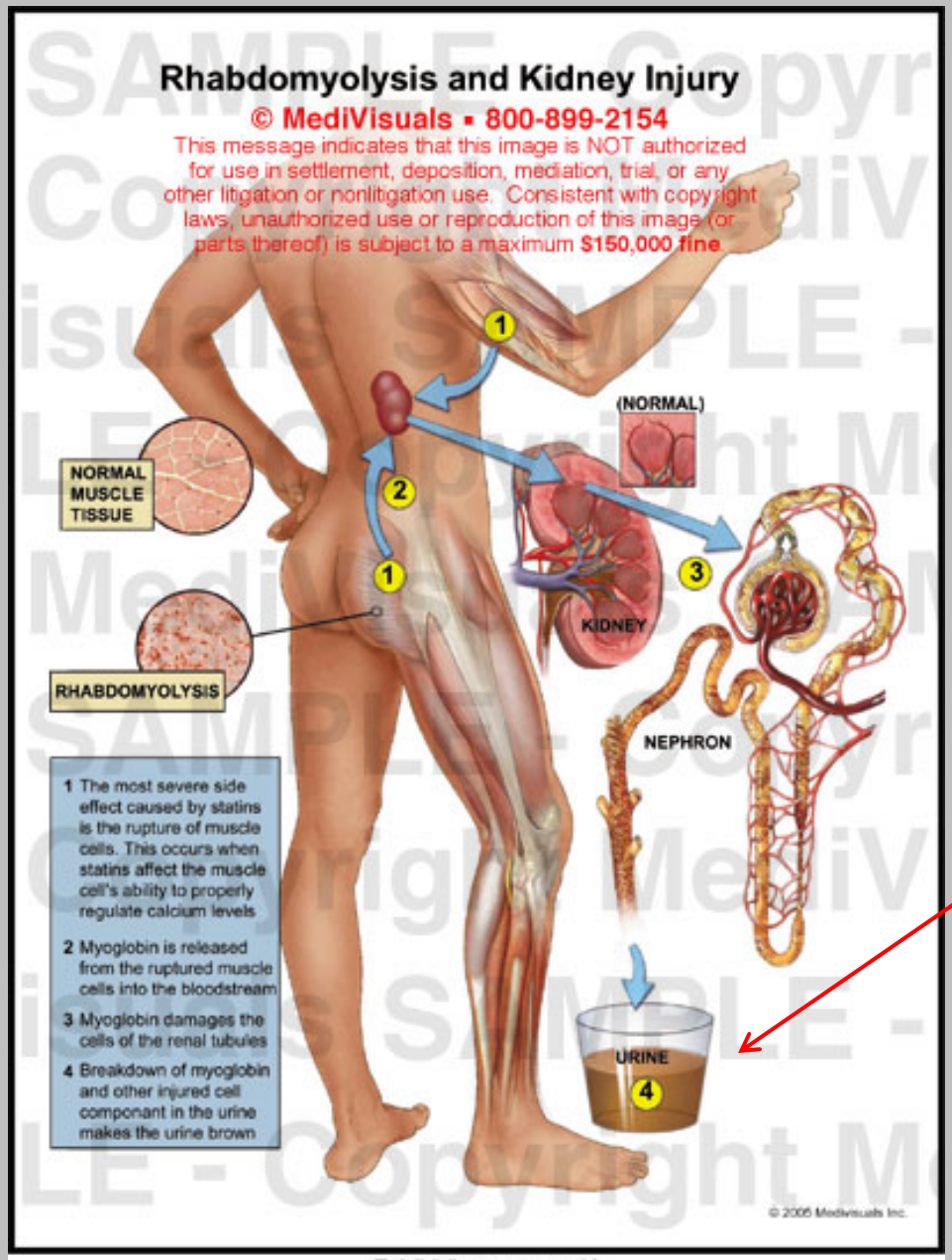
Mechanism of Action of Statins
Cholesterol Synthesis Pathway




Acetyl-CoA
Hydroxymethyl Glutaryl-CoA
Tyrosine/ Phenylalanine
Cytosol
HMG-CoA reductase
Mevalonate
Mitochondrial Matrix
para-hydroxybenzoate
COQ1
Farnesyl-Pyrophosphate
Decaprenyl-Pyrophosphate
COQ2
Geranylgeranyl-Pyrophosphate
Decaprenyl Diphosphate Synthase (PDSS1 & PDSS2)
Hydroxy-prenyl-benzoate
Dihydroxy-prenyl-benzoate
COQ3 ? ADCK3
3-methoxy-4hydroxy-prenyl-benzoate
COQ5
COQ6
5-demethoxy-Q (DMQ)
COQ7
5-demethyl-Q
COQ3 ? ADCK3
Coenzyme Q10
(ubiquinon)
CH3O
CH3
CH3O
Prenyl
10

Rhabdomyolysis





Exhibit# 402252-01X

’ Coca Cola’ urine

Reported Rates of Fatal Rhabdomyolysis per Statin

Medscape® www.medscape.com

Statin	Number of fatal rhabdomyolysis cases	Number of prescriptions (10^6)	Number of cases/10^6 prescriptions
Cerivastatin	31	9.8	3.16
Lovastatin	19	99	0.19
Simvastatin	14	116	0.12
Atorvastatin	6	140	0.04
Pravastatin	3	81	0.04
Fluvastatin	0	37	-
TOTAL	73	484	3.55

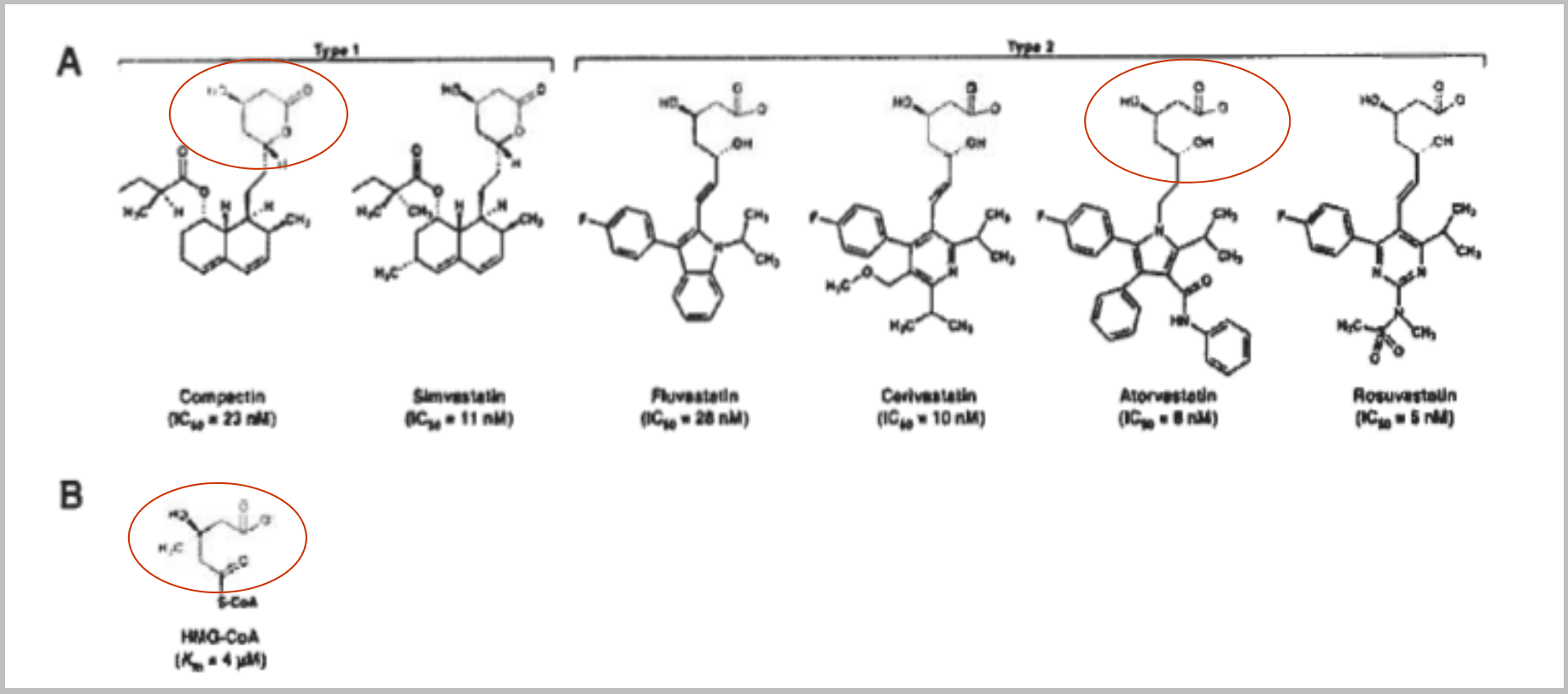
Note: Rosuvastatin had in excess of 10 million prescriptions with no cases of fatal rhabdomyolysis at the time of this publication

Source: Br J Cardiol © 2004 Sherbourne Gibbs, Ltd.

Making the synthetic statins

Lovastatin and compactin can be made in the lab in multistep syntheses.

This allowed scientists to study the structural-activity relationship of statins. The lactone was found to be the business end of the drugs.[4]



HMGCoA-reductase inhibitors (statins)

- Simvastatin (ZOCOR, SICOR VASILIP)
- Atorvastatin (SORTIS, ATORVOX, ATORIS)
- Fluvastatin (LESCOL, STIPATIN)
- Lovastatin
- Mevastatin
- Pitavastatin
- Pravastatin
- Rosuvastatin (CRESTOR, DELIPID, XETER)

Effects of Statins on Lipids

	LDL-C % change	HDL-C % change	Triglycerides % change
atorvastatin	-50	+6	-29
simvastatin	-41	+12	-18
pravastatin	-34	+12	-24
lovastatin	-34	+8.6	-16
cerivastatin	-28	+10	-13
fluvastatin	-24	+8	-10

Daily dose of 40mg of each drug (cerivastatin 0.3mg)

(Adapted from Knopp 1999)

Pharmacokinetics of Statins

Statin	Metabolised by CYP450	Protein binding (%)	Lipophilic	Half-life (h)
lovastatin	Yes	>95%	Yes	~2
pravastatin	No	~50%	No	~2
simvastatin	Yes	95–8%	Yes	~3
atorvastatin	Yes	>98%	Yes	~15
cerivastatin	Yes	>99%	Yes	~3
fluvastatin	Yes	>98%	No	~3

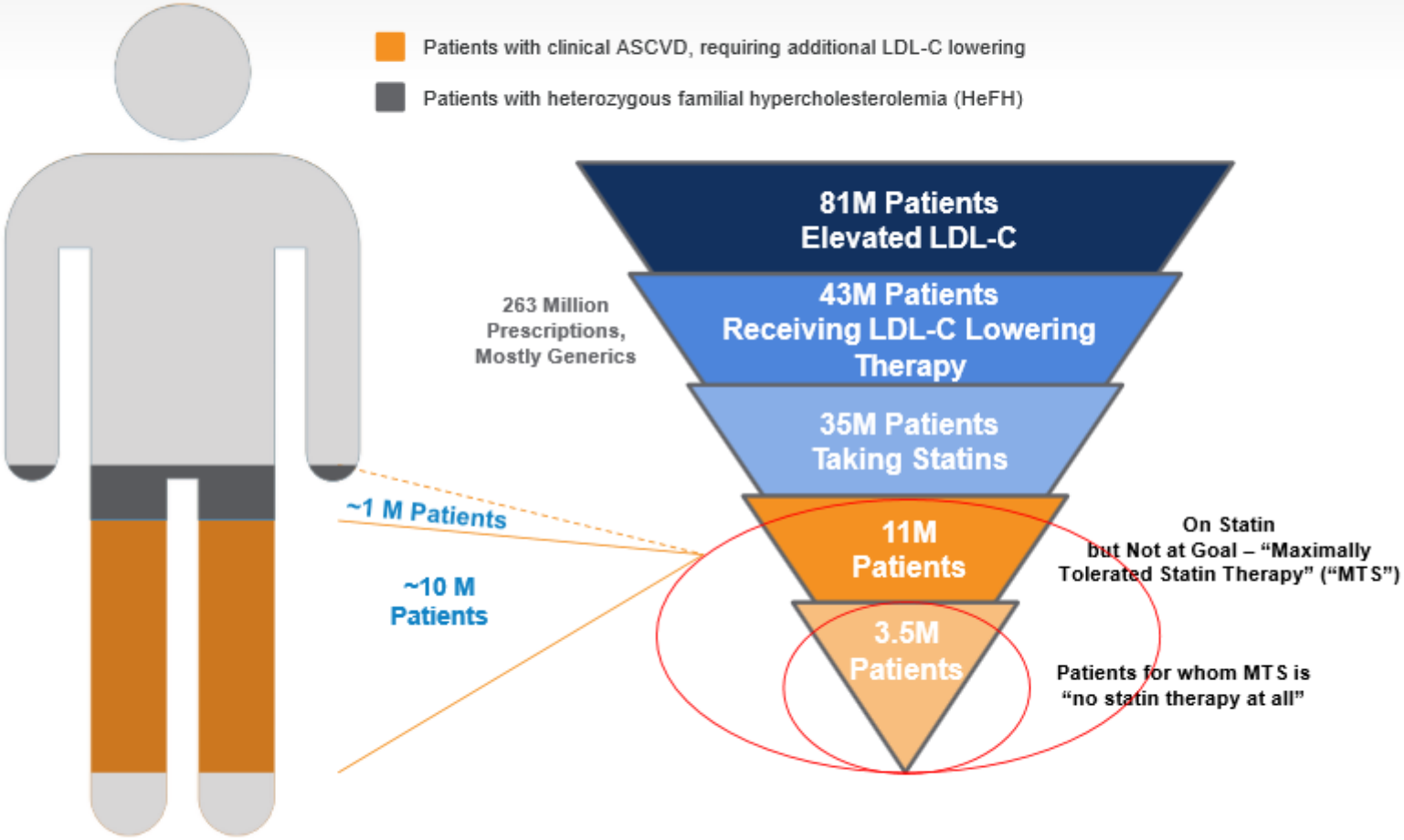
CYP3A4 inhibitors: cyclosporine A, mibefradil, nefazodone, erythromycin, nicotinic acid, fibrates increase toxicity.

Statin dose equivalents

Statin Dose Equivalents by Drug							Target Goal	
Pitavastatin (Livalo®)	Atorvastatin (Lipitor®)	Simvastatin (Zocor®)	Pravastatin (Pravachol®)	Lovastatin (Mevacor®)	Fluvastatin (Lescol®)	Rosuvastatin (Crestor®)	Total Cholesterol Reduction	LDL-C Reduction
1 mg	—	10 mg	20 mg	20 mg	40 mg	—	22%	27%
2 mg	10 mg	20 mg	40 mg	40 mg	80 mg	—	27%	36%
4 mg	20 mg	40 mg	80 mg	80 mg		5 mg	32%	42%
	40 mg	80 mg				10 mg	37%	48% to 52%
	80 mg					20 mg	42%	54%
						40 mg	48%	63%

UNMET NEEDS IN LDL-C LOWERING

STATIN INTOLERANT AND ASCVD/HEFH PATIENTS



Initial market opportunities are highly attractive

Esperion Therapeutics

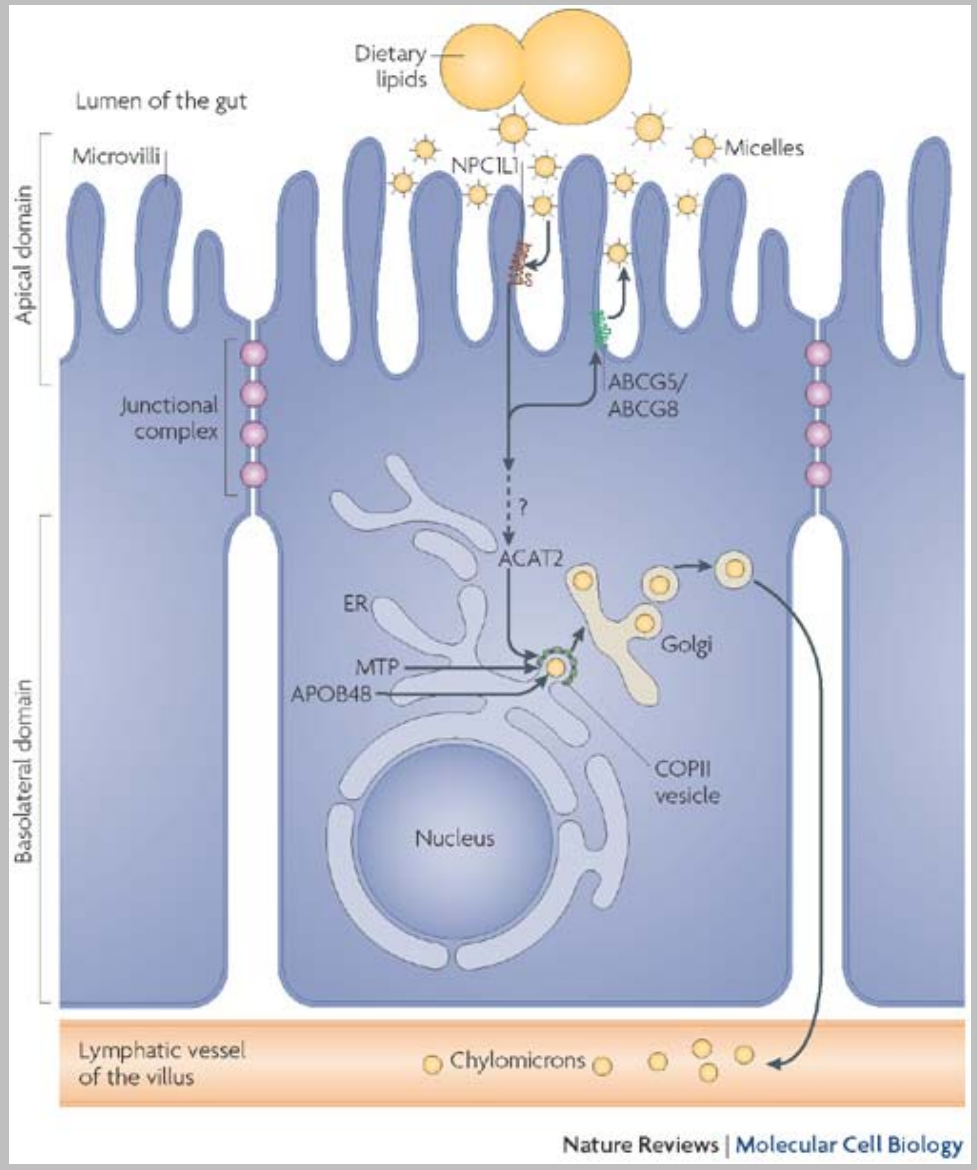
Sources: NHANES, Source Health Analytics, NCEP ATP III guidelines, Esperion analysis

http://tools.acc.org/ASCVD-Risk-Estimator/

Bile acid binding resins

- Cholestyramine, Colestipol, Colestilan, Colextran, Colesevelam
- Cholestiramine resin formed from trimethylbenzylammonium groups in a large copolymer of styrene and divinylbenzene. Water insoluble.
- Cholestipol HCl: copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane. Water soluble. Hygroscopic
- Mechanism of action: stop the enterohepatic recirculation of bile acids, increses the LDLR number and induction of HMG CoA reductase enzyme (with HMG CoA reductase inhibitor a further depletion of IC cholesterol level can be achieved).
- Side effects: bloating, abdominal discomfort, constipation. Resins decrease the absorption of thyroxine, digitalis, anticoagulants, thiazides, propranolol, tetracycline, furosemide, gemfibrosil, pravastatin, fluvastatin. The resins never should be swalloved in dry form, mix it with some kind of fluid and are drunk as a slurry.
- Only indication: Primer biliary cirrhosis!

Instead of resins?



Instead of resins?

Ezetimibe (EZETROL) (annexin-2, caveolin-1 heterocomplex formation is blocked thus inhibits the NPC1L1-dependent (Niemann-Pick C1 Like1) cholesterol uptake route)

- Safety profile is good. Possible side effects: myalgia, rhabdomyolysis, hepatitis, pancreatitis, thrombocytopenia
- Dosing: once-daily dose (10 mg)
- Therapeutic value is questionable:
  - ENHANCE trial of Vytorin (ezetimibe and simvastatin): No change in fatty plaques!
  - ARBITER 6–HALTS trial: Ezetimibe increased (!) arterial wall thickness. (Niacin reduced)
  - SHARP: simvastatin+ezetimibe better than placebo
  - IMPROVE-IT: Simvastatin+ezetimibe vs. Simvastatin alone

Nicotinic acid (niacin)

- Acipimox (OLBETAM) 250 mg caps
- Is beeing converted to NAD and NADP. The hypolipidemic property is unrelated to its vitamin role.
- Mechanism of action: 1. inhibitory effect of lipolysis. 2. decreased delivery of FFA to the liver. 3. decrease in TG synthesis and VLDL-TG transport. - decreased production of VLDL. Niacin increases the HDL level (mech. unknown). Dose 3-6 g/day
- ADME: absorbs readily, plasma peak: 30-60 min. Half life under 1 h. Renal clearance in unchanged form.
- Side effects (a lot): intense facial flushing (Laropiprant (PGD2 antagonist) can reduce it in combination), pruritus (PG mediated, aspirin can alleviate), dyspepsia, vomiting, diarrhoea, peptic ulcer, dry skin, acanthosis nigricans, hyperpigmentation. Abnormalities in hepatic function: serum transaminase level is increased (AST, ALT) occuring in patient taking 2g or more niacin/day. Combination with statins increase the risk of myositis and rhabdomyolysis. Elevated fasting plasma glucose and decreased glucose tolerance occur frequently (diabetes is a relative contraindication), may elevate uric acid - precipitates gout (gout is strong contraindication), optic maculopathy, toxic amblyopia, cardiac arrhythmias, orthostatic hypotension.

Fibric acid derivatives

- Bezafibrat (BEZALIP), Gemfibrosil (INNOGEM), Fenofibrate (LIPANTHYL), Ciprofibrate (LIPANOR)
- Clofibrate (p-chlorophenoxyisobutirate ethylester) 2 g/day
- Mechanism of action: lowers VLDL, raise HDL, variable effects on LDL (mechanism is unclear), decrease hepatic production of apoC-III (inhibitor of lipoprotein lipase), alter the composition of VLDL (increased hydrolysis of VLDL)
- Gemfibriosil treatment (600 mg bid): palmar xanthomas may regress completely, improvement in angina and intermittent claudication also occures. Fenofibrate (300 mg/day) (has a uricosuric effects), bezafibrate, ciprofibrate lowers VLDL and LDL as well.
- ADME: Rapid and effective absorption (>90%). Peak plasma cc. 2-4 h. More than 95% is protein bound. Half life of gemfibrosil: 1.1 h. Half life of fenofibrate: 20 h. Cc in liver, kidney and intestine is higher than in the plasma. Glucuronidation in the liver and 60-90 % is excreted in the urine.
- Side effects: 5-10 %. GI, rash, urticaria, hair loss, myalgias, fatigue, haedache, impotence, anaemia. Potentiate the action of anticoagulants (displacing them from their binding sites on albumin. Myositis-flulike syndrome. Fibrates increase the lithogenicity of bile (gallstone formation).

Probucol

- Designed to be a potent lipophilic antioxidant for manufacturing of tires, but it has hypolipidemic activity. It lowers the HDL cholesterol level - third-line therapeutic agent. Main use: homozygous familial hypercholesterolaemia (tendon and planar xanthomas are decreased)
- Chemically consists of two tertiary butylated hydroxytoluene and the structure resembles to BHT, a commonly used food additive. Extremely hydrophobic - full effect develops after 2-3 months and after discontinuation it takes 6 months to get rid of.
- Mechanism of action: Promotes clearance of LDL via LDLR-independent mechanisms and increases the activity and the amount of cholesterol ester transfer protein (CETP). The antioxidant activity is responsible for the beneficial effect in atherosclerosis.
- ADME: Absorbs poorly and erratically, transported in the hydrophobic core of LDL. Peak plasma level after 4 months. Excreted by the liver.
- Side effects: GI (diarrhae, flatulance, nausea), headache dizziness, combination with cholestyramine is better tolerated than either alone. Prolongs the QTc interval. Contraindicated to give patients, who have prolonged QTc interval, taking Class I and III antiarrythmic agents (amiodarone, sotalol), tricyclic antidepressants, phenothiazines, astemizole, terfenadine (they can precipitate torsades de pointes).
- Dose: 2x500 mg/day.

Effect of Lipid-lowering Therapies on Lipids

Therapy	TC	LDL	HDL	TG	Patient tolerability
Bile acid sequestrants	Down 20%	Down 15–30%	Up 3–5%	Neutral or up	Poor
Nicotinic acid	Down 25%	Down 25%	Up 15–30%	Down 20–50%	Poor to reasonable
Fibrates (gemfibrozil)	Down 15%	Down 5–15%	Up 20%	Down 20–50%	Good
Probucol	Down 25%	Down 10–15%	Down 20–30%	Neutral	Reasonable
Statins*	Down 15–30%	Down 24–50%	Up 6–12%	Down 10–29%	Good

TC–total cholesterol, LDL–low density lipoprotein, HDL–high density lipoprotein, TG–triglyceride. * Daily dose of 40mg of each drug (cerivastatin 0.3mg)

(Adapted from Yeshurun 1995, Knopp 1999)

adma.pdf - Adobe Reader
Fájl Szerkesztés Nézet Dokumentum Eszközök Ablak Súgó
1 / 6 107% Keresés

Clinical Investigation and Reports

Asymmetric Dimethylarginine (ADMA): A Novel Risk Factor for Endothelial Dysfunction

Its Role in Hypercholesterolemia

Rainer H. Böger, MD; Stefanie M. Bode-Böger, MD; Andrzej Szuba, MD; Philip S. Tsao, PhD; Jason R. Chan, BS; Oranee Tangphao, MD; Terrence F. Blaschke, MD; John P. Cooke, MD, PhD

Background—Asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of nitric oxide (NO) synthase. Because endothelial NO elaboration is impaired in hypercholesterolemia, we investigated whether plasma concentrations of ADMA are elevated in young, clinically asymptomatic hypercholesterolemic adults. We further studied whether such elevation of ADMA levels was correlated with impaired endothelium-dependent, NO-mediated vasodilation and urinary nitrate excretion. In a randomized, double-blind, placebo-controlled study, we investigated whether these changes could be reversed with exogenous L-arginine.

Methods and Results—We measured plasma levels of L-arginine, ADMA, and symmetrical dimethylarginine (SDMA) by high-performance liquid chromatography in 49 hypercholesterolemic (HC) and 31 normocholesterolemic (NC) humans. In 8 HC subjects, endothelium-dependent forearm vasodilation was assessed before and after an intravenous infusion of L-arginine or placebo and compared with 8 NC control subjects. ADMA levels were significantly elevated by >100% (2.17 ± 0.15 versus 1.03 ± 0.09 μmol/L; $P<0.05$) in HC subjects compared with NC adults. L-Arginine levels were similar, resulting in a significantly decreased L-arginine/ADMA ratio in HC subjects (27.7 ± 2.4 versus 55.7 ± 5.4; $P<0.05$). In 8 HC subjects, intravenous infusion of L-arginine significantly increased the L-arginine/ADMA ratio and normalized endothelium-dependent vasodilation and urinary nitrate excretion. ADMA levels were inversely correlated with endothelium-mediated vasodilation ($R=0.762$, $P<0.01$) and urinary nitrate excretion rates ($R=0.534$, $P<0.01$).

Conclusions—We find that ADMA is elevated in young HC individuals. Elevation of ADMA is associated with impaired endothelium-dependent vasodilation and reduced urinary nitrate excretion. This abnormality is reversed by adminis-

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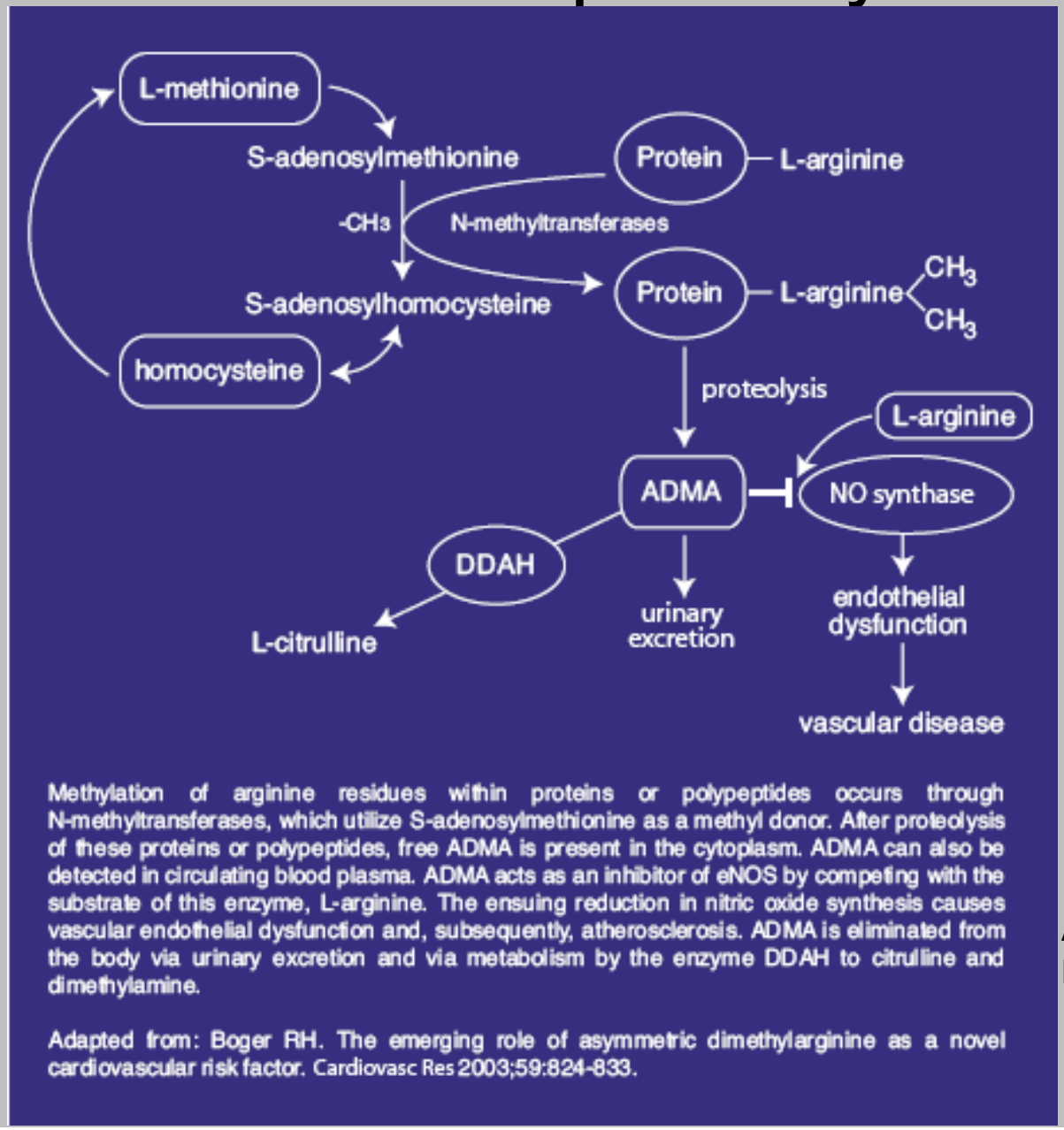
Biochemical pathways related to ADMA



Methylation of arginine residues within proteins or polypeptides occurs through N-methyltransferases, which utilize S-adenosylmethionine as a methyl donor. After proteolysis of these proteins or polypeptides, free ADMA is present in the cytoplasm. ADMA can also be detected in circulating blood plasma. ADMA acts as an inhibitor of eNOS by competing with the substrate of this enzyme, L-arginine. The ensuing reduction in nitric oxide synthesis causes vascular endothelial dysfunction and, subsequently, atherosclerosis. ADMA is eliminated from the body via urinary excretion and via metabolism by the enzyme DDAH to citrulline and dimethylamine.

Adapted from: Boger RH. The emerging role of asymmetric dimethylarginine as a novel cardiovascular risk factor. Cardiovasc Res 2003;59:824-833.

ADMA: asymmetric dimethylarginine
DDAH: dimethylarginine dimethylaminohydrolase

Clinical conditions with elevated ADMA

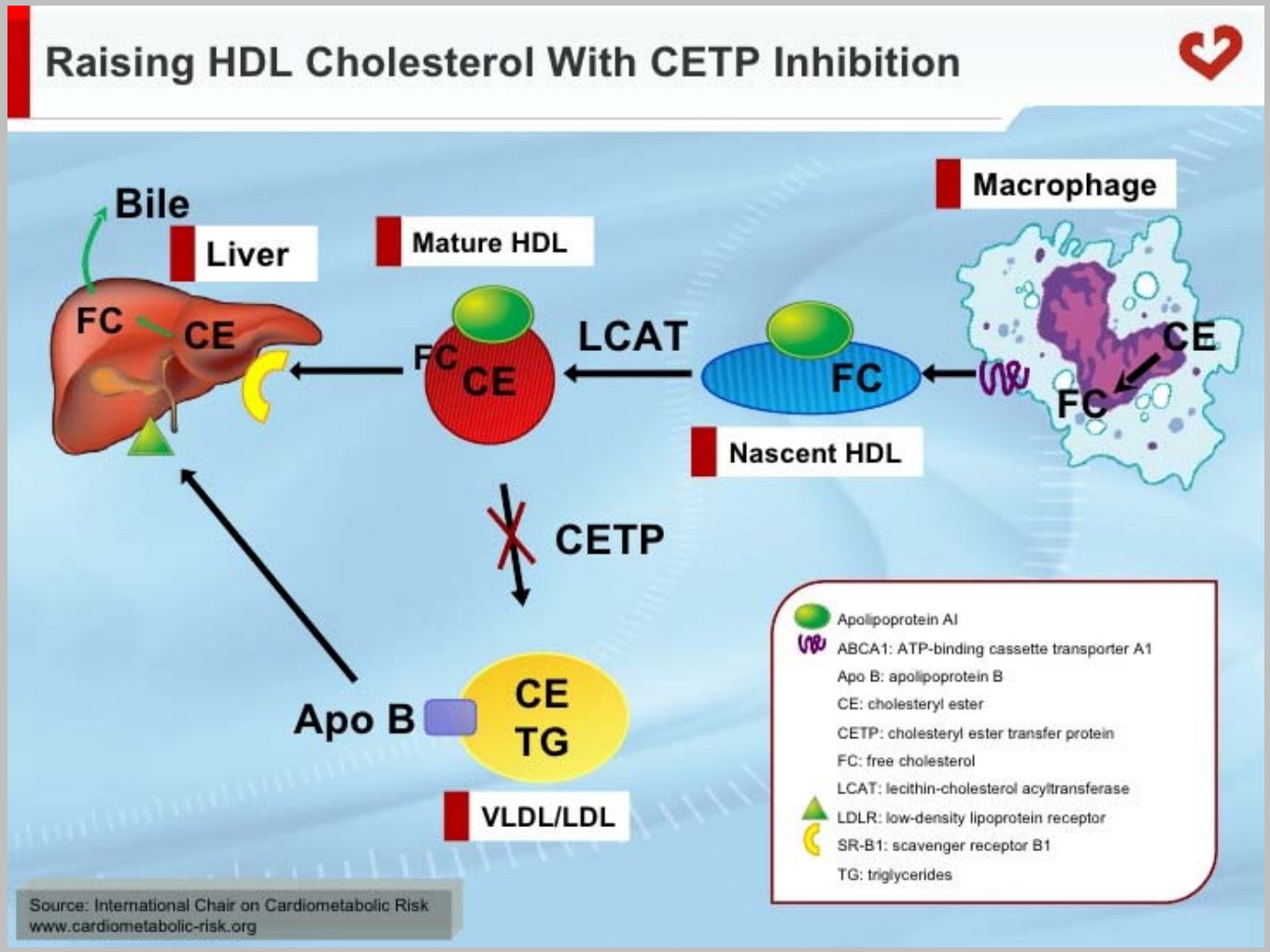
Condition	Fold increase vs. controls
Hypercholesterolemia	2-3
Hypertriglyceridemia	2
Hypertension	2
Pulmonary Hypertension	2-3
Peripheral Arterial Disease	2-4
Chronic Renal Failure	2-12
Congestive Heart Failure	2-3
Type 2 Diabetes	2
Preeclampsia	2

ADMA and statins

- ADMA may block eNOS despite its up-regulated gene expression after statin treatment, and that this blockade may be overcome by L-arginine supplementation.
- Sustained-release L-arginine administration with statins improves the effectiveness of statins.

New directions in the treatment of hypercholesterolemia

- CETP (Cholesteryl ester transfer protein) inhibition: Anacetrapib, Evacetrapib
- MTTP (microsomal triglyceride transfer proteinin) hibitors: Lomitapid, Mitratapid
- PCSK9 (Proprotein convertase subtilisin/kexin type 9) inhibitors: alirocumab, evolocumab,
- Bempedoic acid (ETC-1002)
- Gemcabene
- Selective PPAR modulators
- DGAT-1 inhibitors
- EPA + DHA

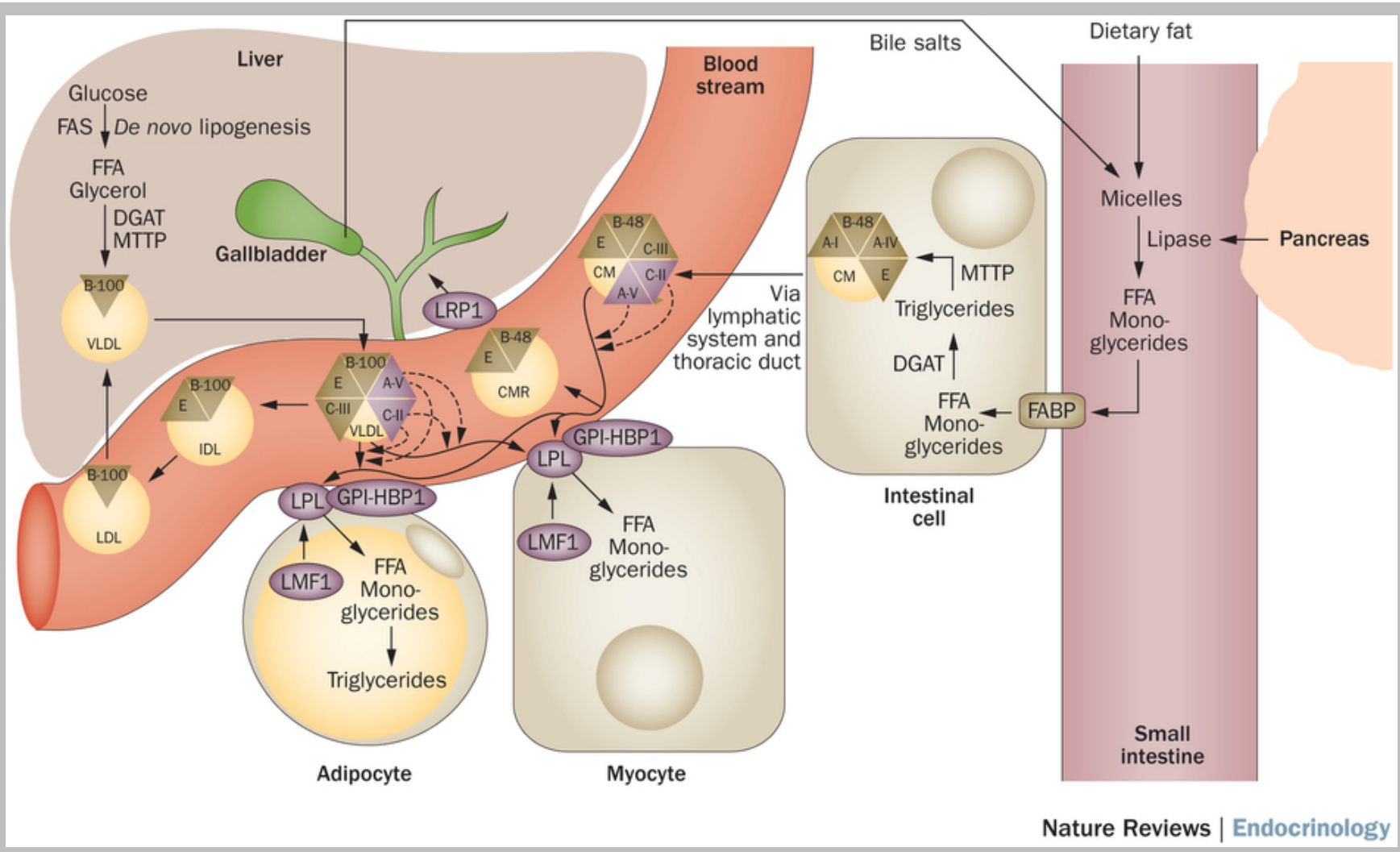


CETP inhibition reduces the atherosclerosis formation. Among Japanese CETP defect is common: no atherosclerosis development.

Rodents naturally deficient in CETP and resistant to development of atherosclerosis.

Cholesteryl ester transfer protein (CETP) inhibitors (HDL)

- Torcetrapib (halted in Phase 3)(2006) Increased BP
- Dalcetrapib (did not raise blood pressure, but no effect on HDL)
- Anacetrapib
  - DEFINE (Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib)
  - REVEAL (Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification)
- Evacetrapib



Shaded molecules (purple) are implicated in monogenic chylomicronaemia. Dashed lines indicate a key functional role of the apolipoprotein in lipolysis. In healthy individuals, dietary fat is hydrolysed by pancreatic lipase and requires emulsification with bile salts, which are produced by the gallbladder. FFA enter intestinal cells via FABP. Triglyceride-rich lipoproteins of intestinal origin are assembled in a multistep process requiring DGAT and MTTP (also known as MTP), and enter the circulation (through the lymphatics) as chylomicrons, which are composed of ~90% triglycerides with a small amount (1–3%) of cholesterol ester and are surrounded by a phospholipid envelope containing several apolipoprotein molecules, including the chylomicron-specific apoB-48 as well as apoA-I, apoA-V, apoC-II, apoC-III and apoE.6 By contrast, endogenously derived triglyceride-rich lipoproteins of hepatic origin are assembled de novo in a process requiring MTTP and DGAT; these lipoproteins circulate in plasma within apoB-100-containing VLDL particles. Chylomicrons are usually cleared from the circulation within minutes by LPL-mediated hydrolysis, which is assisted by the essential cofactor apoC-II and enhanced and stabilized by apoA-V.6, 88 Kinetic studies indicate that chylomicrons compete with VLDL for saturable catabolism by LPL. GPI-HBP1 directs the transendothelial transport of LPL, helps anchor chylomicrons to the endothelial surface and enhances lipolysis.6 FFA generated by lipolysis are taken up by peripheral cells, where they can be oxidized for energy or stored as triglycerides. After lipolysis, chylomicron remnants are removed by the liver, probably via LRP1 receptor, which contrasts with postlipolytic VLDL remnants (or IDL), most of which undergo further processing, ultimately resulting in LDL. Abbreviations: A-I, apolipoprotein A-I (apoA-I); A-IV, apolipoprotein A-IV (apoA-IV); A-V, apolipoprotein A-V (apoA-V); B-48, apolipoprotein B-48 (apoB-48); B-100, apolipoprotein B-100 (apoB-100); C-II, apolipoprotein C-II (apoC-II); C-III, apolipoprotein C-III (apoC-III); CM, chylomicron; CMR, chylomicron remnant; DGAT, diacylglycerol O-acyltransferase; E, apolipoprotein E (apoE); FABP, fatty acid-binding protein; FAS, fatty acid synthase; FFA, free fatty acid; GPI-HBP1, glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1; IDL, intermediate density lipoprotein; LRP1, LDL receptor-related protein 1; LMF1, lipase maturation factor 1; LPL, lipoprotein lipase; MTTP, microsomal triglyceride transfer protein.

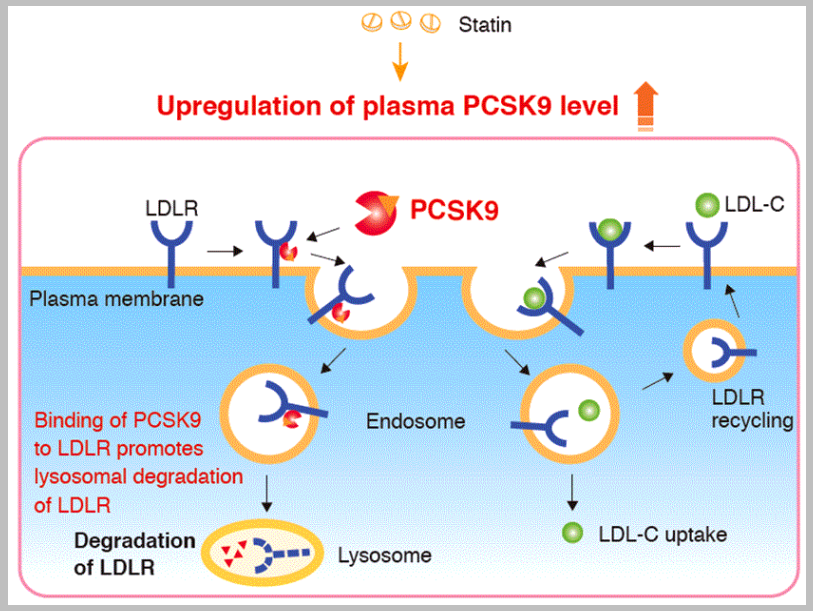
MTTP (microsomal triglyceride transfer protein) inhibitors (VLDL)

- MT(T)P is necessary for VLDL assembly and secretion from the liver.
- Dirlotapide to treat obesity in dogs!
- Lomitapide (JUXTAPID, LOJUXTA) used in homozygous familiar hypercholesterolemia: orphan drug to reduce LDL cholesterol, total cholesterol, apolipoprotein B, and non-high-density lipoprotein (non-HDL) cholesterol
- Mitratapid (YARVITAN) for obese dogs!

PCSK9 function

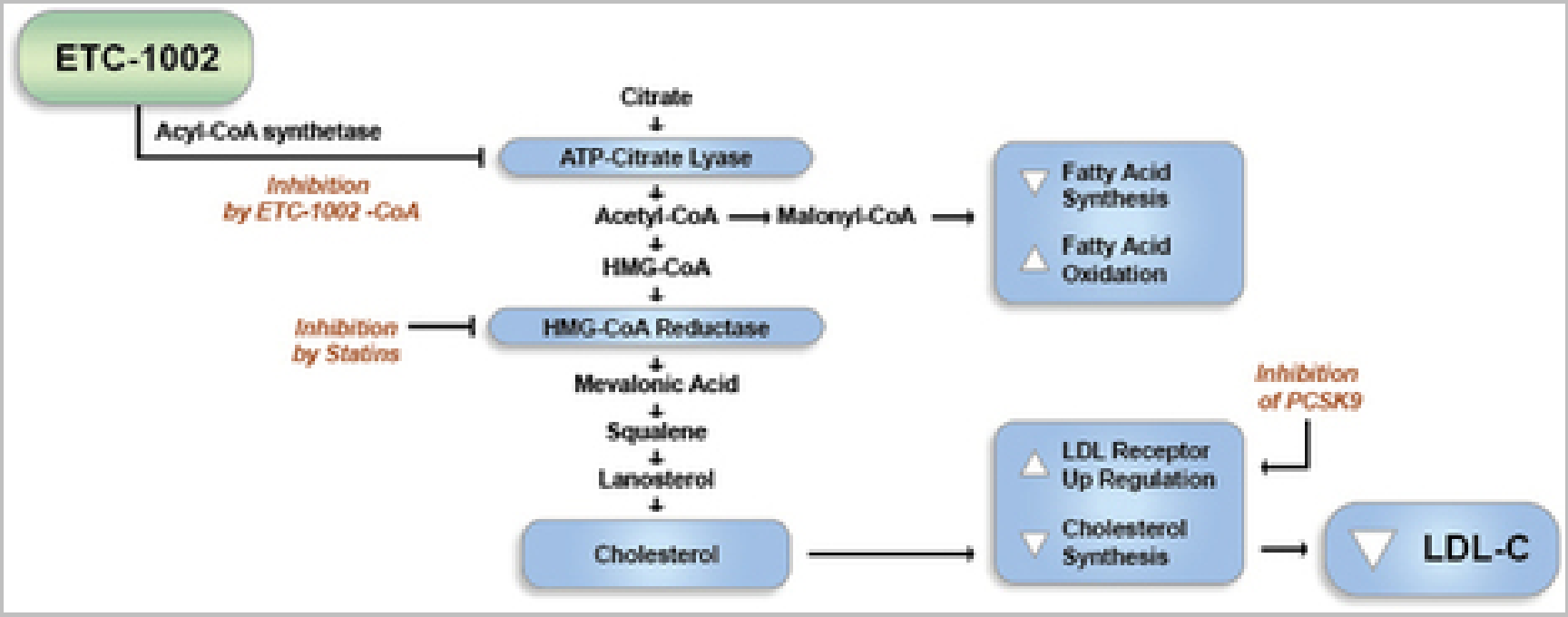
- PCSK9 binds to the receptor for low-density lipoprotein (LDL) cholesterol (LDL-C). In the liver, the LDL receptor (LDLR) removes LDL-C from the blood. When PCSK9 binds to the LDLR, the receptor is broken down and can no longer remove LDL-C from the blood.

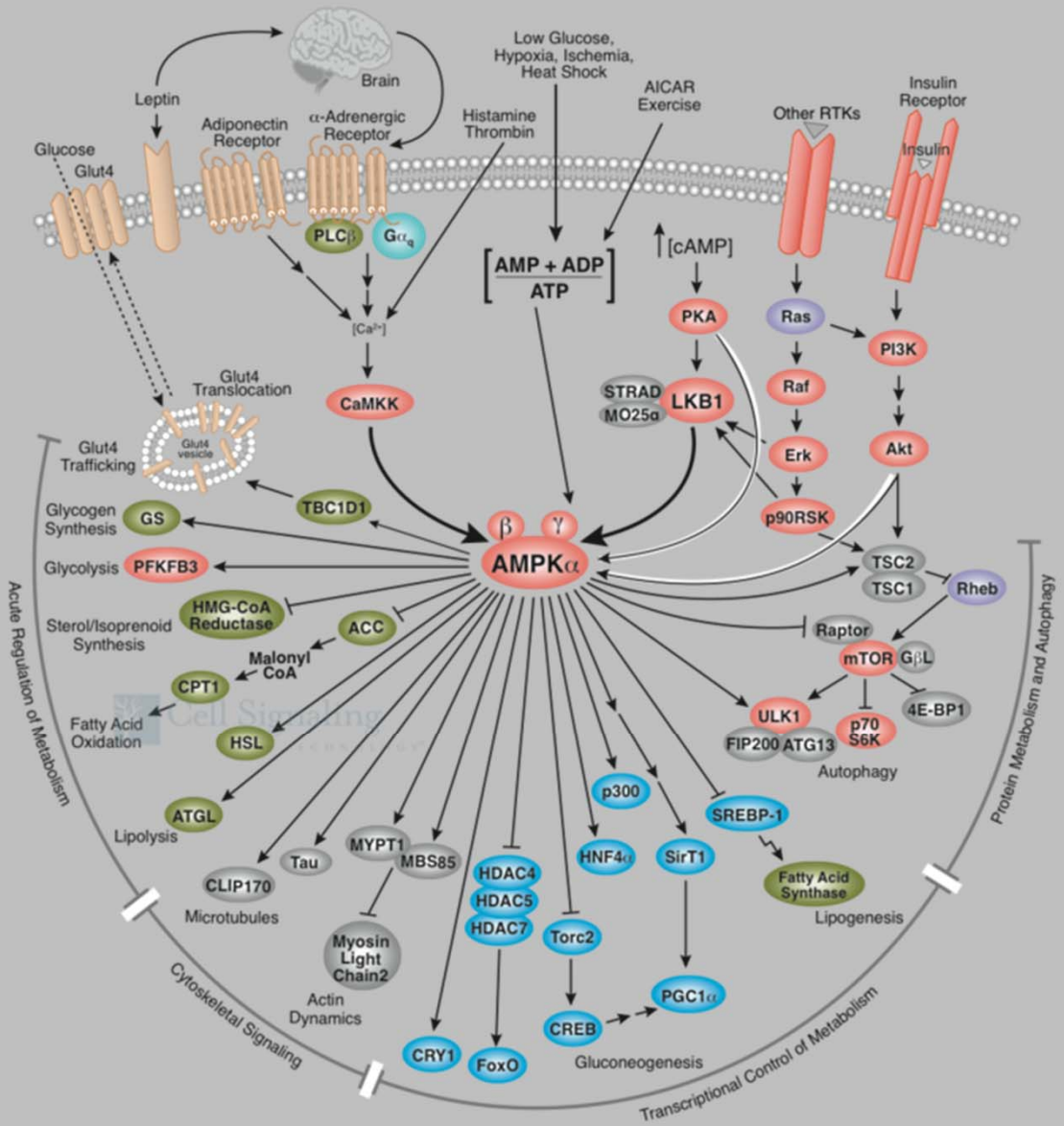
PCSK9 inhibitors: monoclonal antibodies: alirocumab and evolocumab, 1D05-IgG2 (Merck), RG-7652 and LY3015014, as well as the RNAi therapeutic ALN-PCS02



Bempedoic acid (ETC-1002)

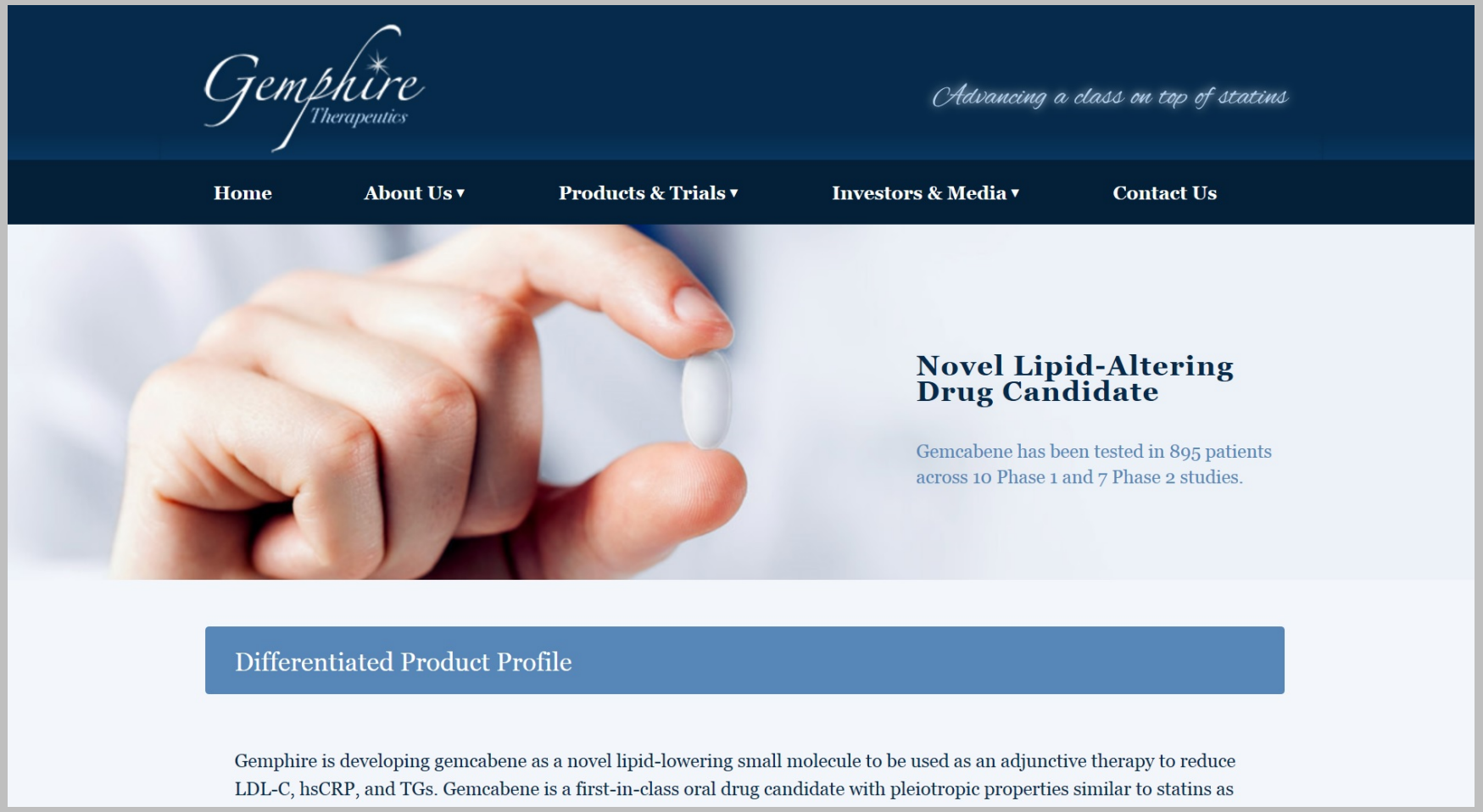
Has two mode of action:
1. ACI inhibition





- 5' adenosine monophosphate-activated protein kinase (AMPK) activation

Gemcabene



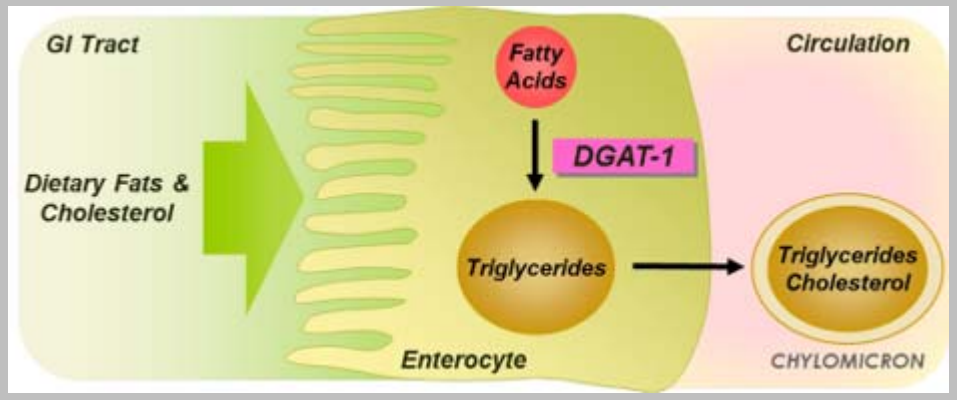
Mode of action is unknown…

Dual PPARα/γ modulators

- PPAR-alpha is a transcription factor and a major regulator of lipid metabolism in the liver. Activation of PPAR-alpha promotes uptake, utilization, and catabolism of fatty acids by upregulation of genes involved in fatty acid transport.
- PPAR-gamma regulates fatty acid storage and glucose metabolism.
- Aleglitazar
- Saroglitazar
- Sodelglitazar
- Tesaglitazar

DGAT-1 (diacylglycerol acyltransferase) inhibitors

- Pradigastat (LCQ908)
- AZD7687



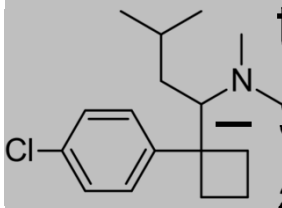
DGAT-1 is an intestinal enzyme involved in fat absorption and triglyceride synthesis. Inhibition of DGAT-1 in the enterocyte reduces post-prandial fat deposition; increases nutrient sensing, satiety.

Table 1. Summary of novel lipid lowering agents and their current state of development

Mechanism of action	Example	State of development
CETP inhibitor	Anacetrapib	Phase 3
ACL inhibitor/AMPK activation	Bempedoic acid (ETC-1002)	Phase 3
Unclear	Gemcabene	Phase 2
PPAR-α agonist	Pemafibrate (K-877)	Phase 2
	LY518674	Phase 2
PPAR-α/γ modulator	Aleglitazar	Phase 3 (halted)
DGAT inhibitor	Pradigastat (LCQ908)	Phase 3
	AZD7687	Phase 1 (unlikely to proceed)
Complex effects on TG-rich lipoproteins	Eicosapentaenoic acid ethyl ester	Phase 3/4
	Omega-3 FFA (EPA + DHA)	Phase 3/4

Others

- Fish oil
- Antiobesity agents:
  - orlistat [tetrahydrolipstatin] (ALLI, BEACITA, XENICAL): Irreversible inhibitor of serine lipases in the gut
  - Sibutramine (SNRI? withdrawn), pramlintide (peptide analogue of amylin)



- Mipomersen (KYNAMRO) It is an antisense therapeutic that targets the messenger RNA for apolipoprotein B. It is administered as a weekly injection.
- Alipogene tiparvovec (GLYBERA) gene therapy: compensates for lipoprotein lipase deficiency (LPLD), which can cause severe pancreatitis. The adeno-associated virus serotype 1 (AAV1) viral vector delivers an intact copy of the human lipoprotein lipase (LPL) gene.

Methods for measuring insulin action

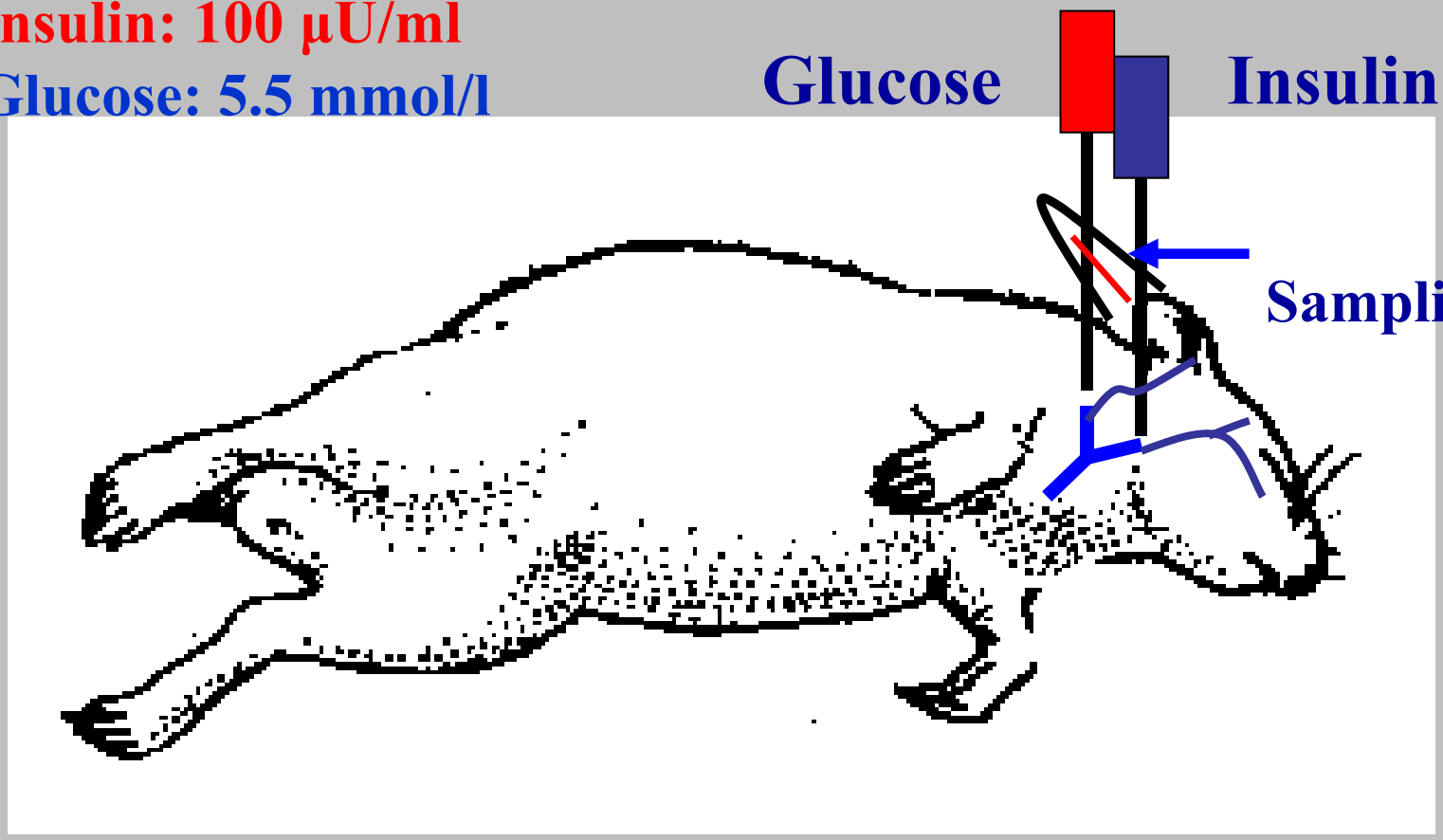
Insulin Tolerance Test
(ITT)

Hyperinsulinaemic Euglycemic
Glucose Clamp
(HEGC)

Rapid Insulin Sensitivity Test
(RIST)

Determination of Insulin Sensitivity: Hyperinsulinaemic Euglycaemic Glucose Clamping (HEGC)

Insulin: 100 µU/ml
Glucose: 5.5 mmol/l



Rapid Insulin Sensitivity Test