ZDRAVILA, KI VPLIVAJO NA METABOLIZEM LIPIDOV

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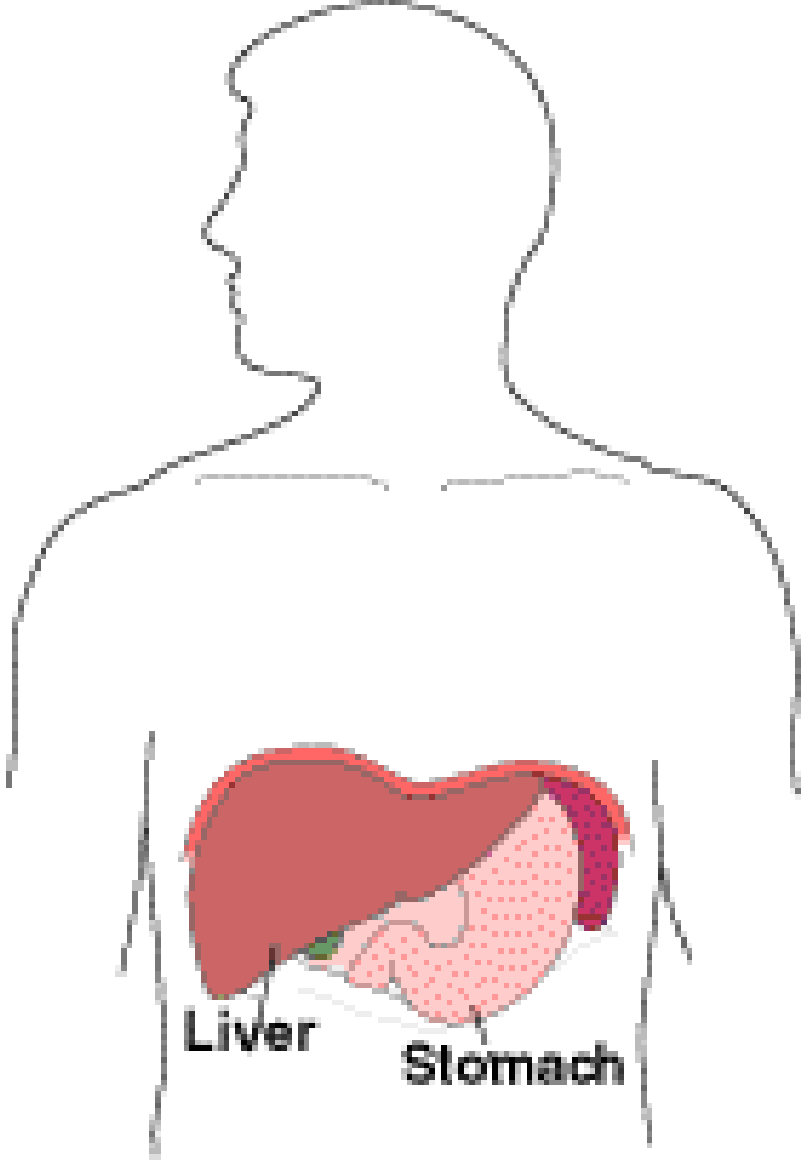
Kratek povzetek zgodbe



Pregled

- Nastanek aterosklerotičnega plaka
- Metabolizem lipidov v plazmi (lipoproteinov)
- Zdravila, s katerimi lahko vplivamo na te procese

Nastanek aterosklerotičnega plaka

vdor lipidov skozi endotel

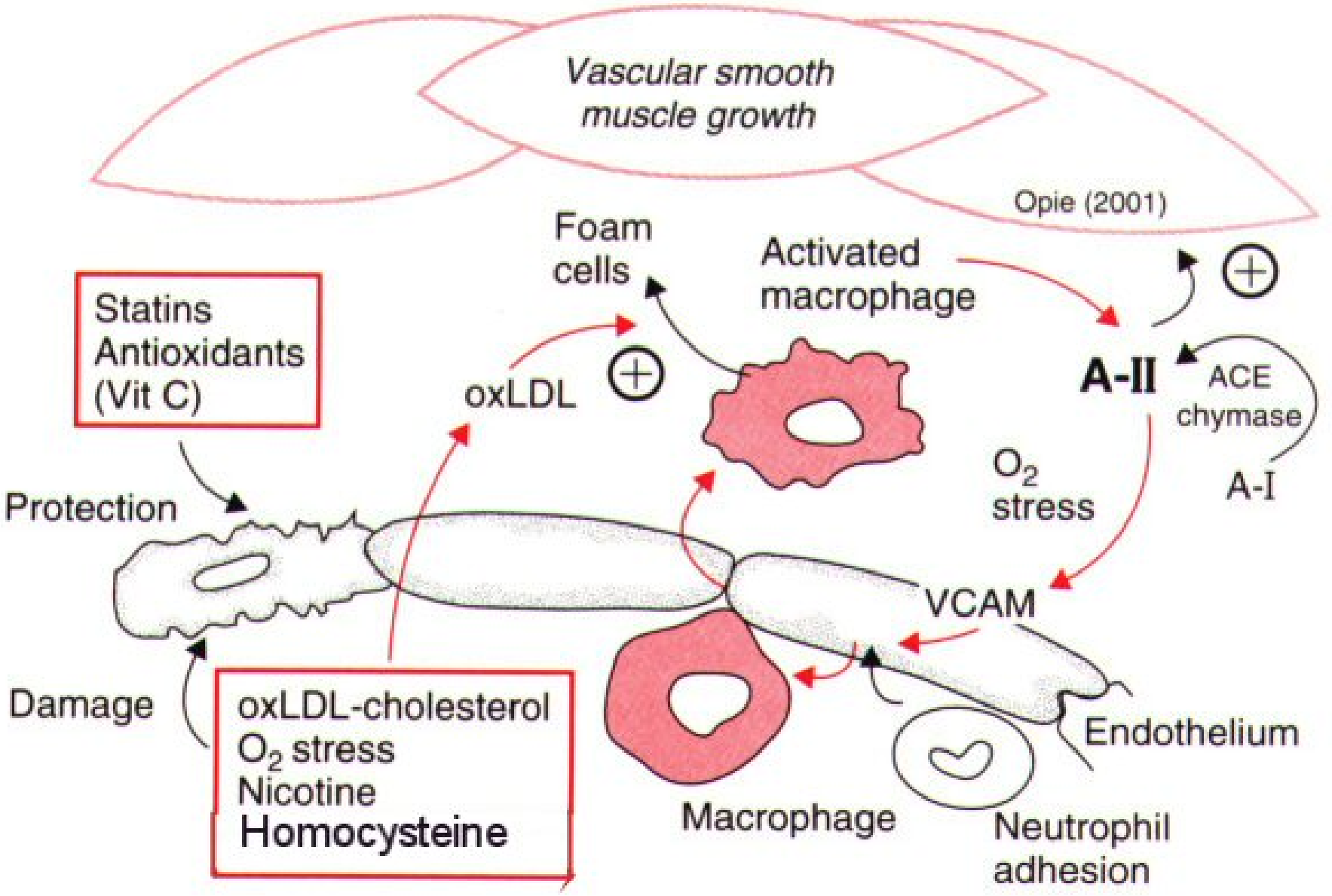
oksidacija lipidov

fagocitoza (makrofagi)

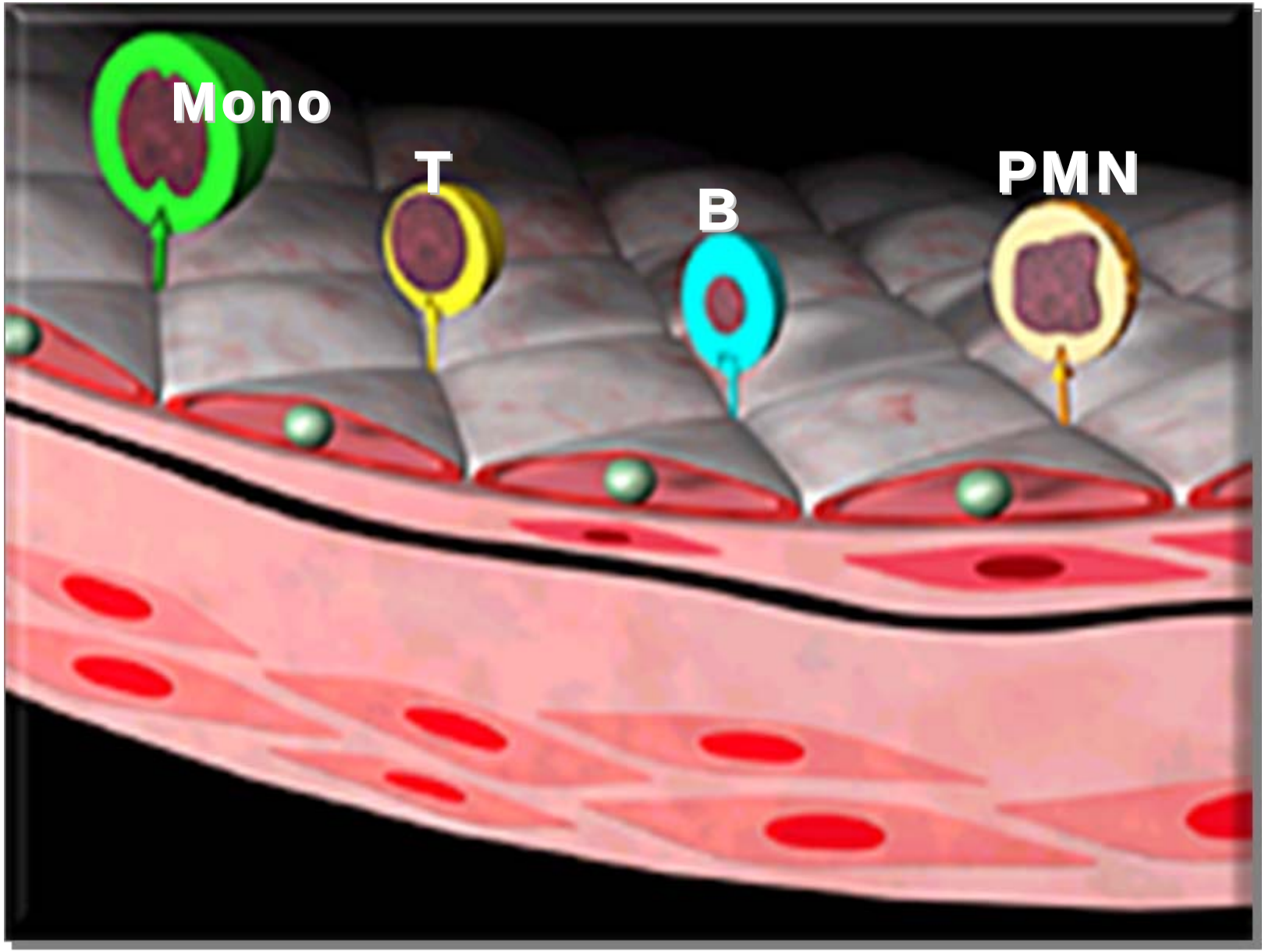
penaste celice
(foam cells)

adhezija trombocitov

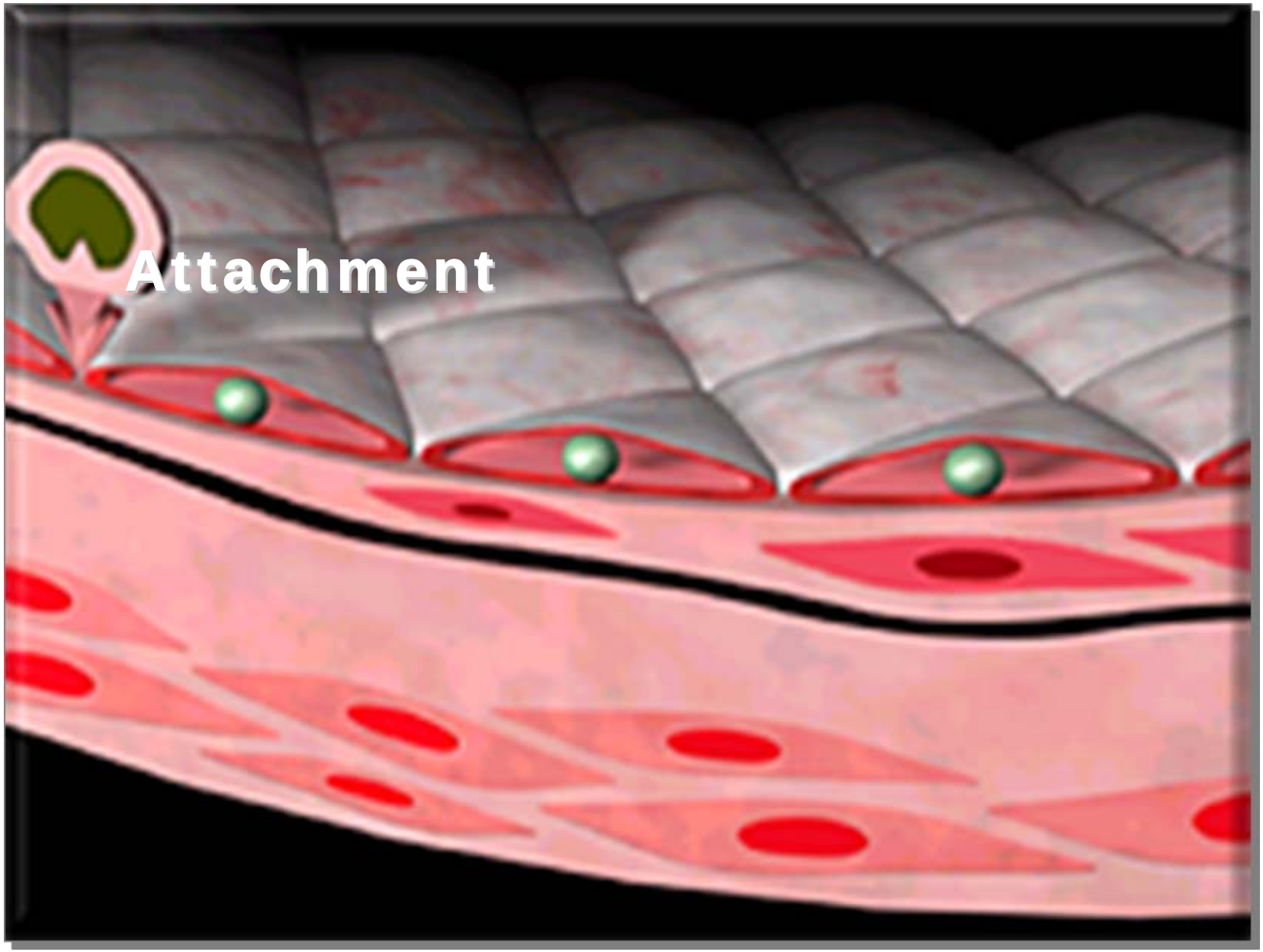
ENDOTHELIUM AND VASCULAR DISEASE



Leukocyte–Endothelial Adhesion Molecules



Macrophage Functions in Atherogenesis



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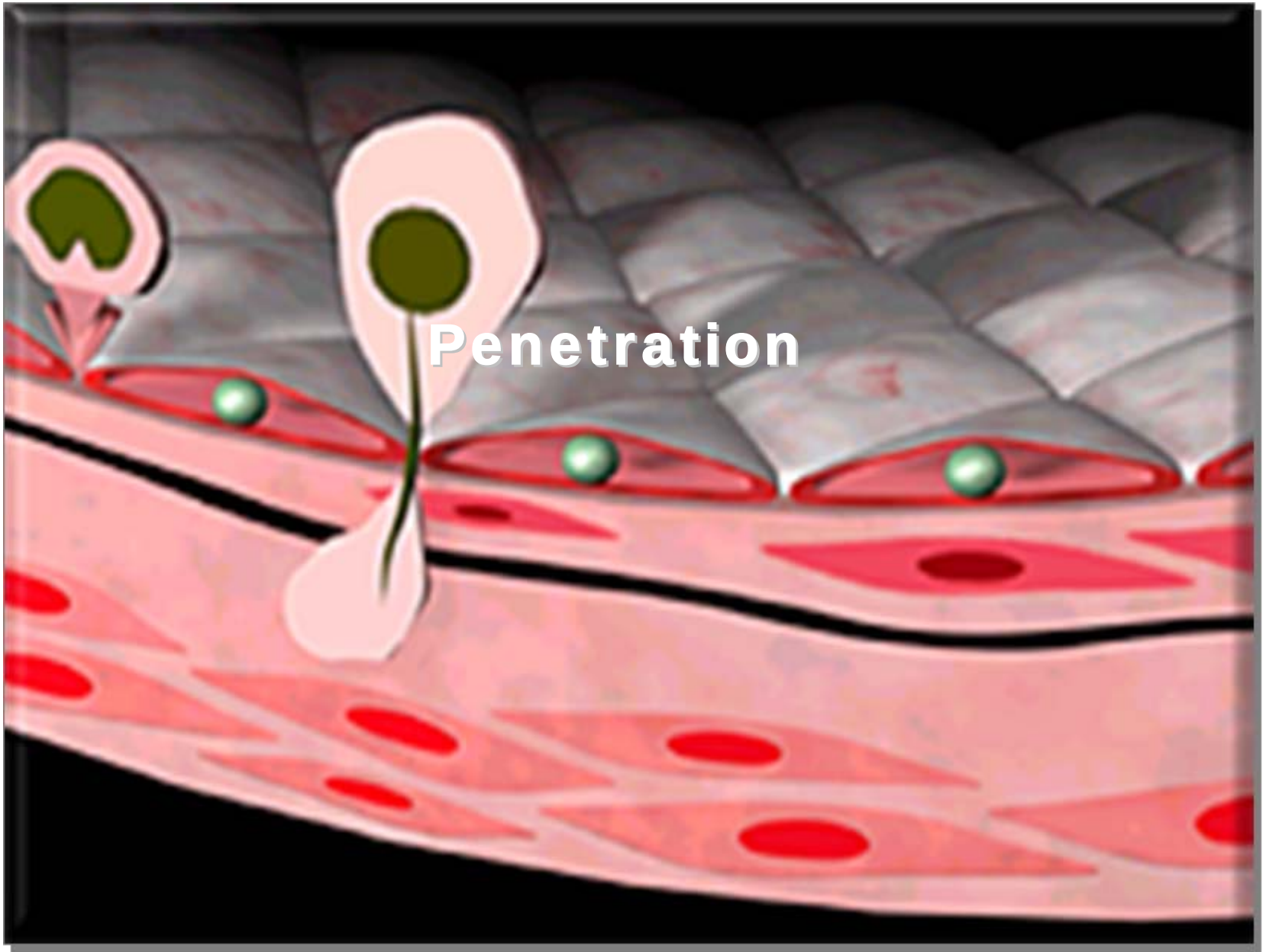

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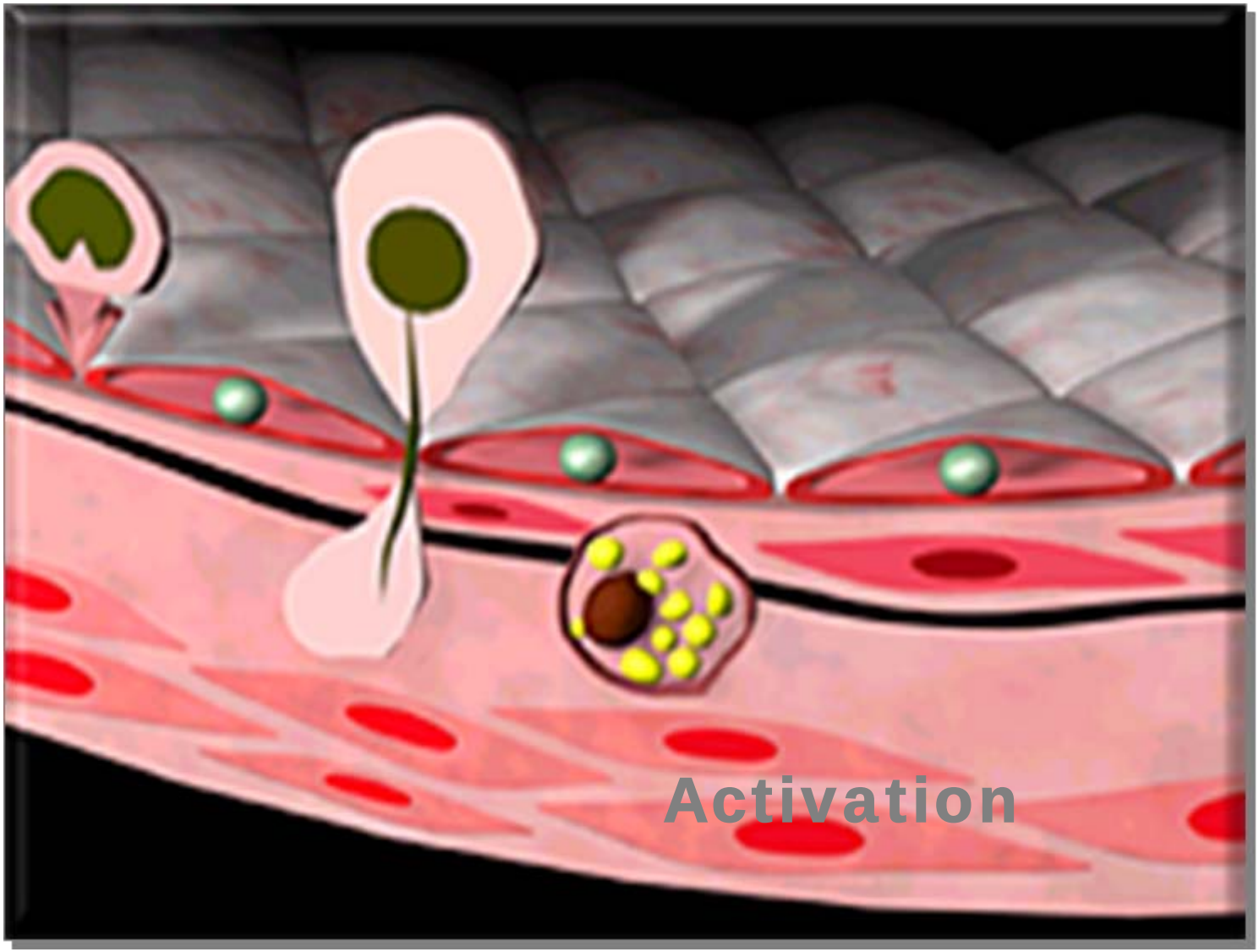

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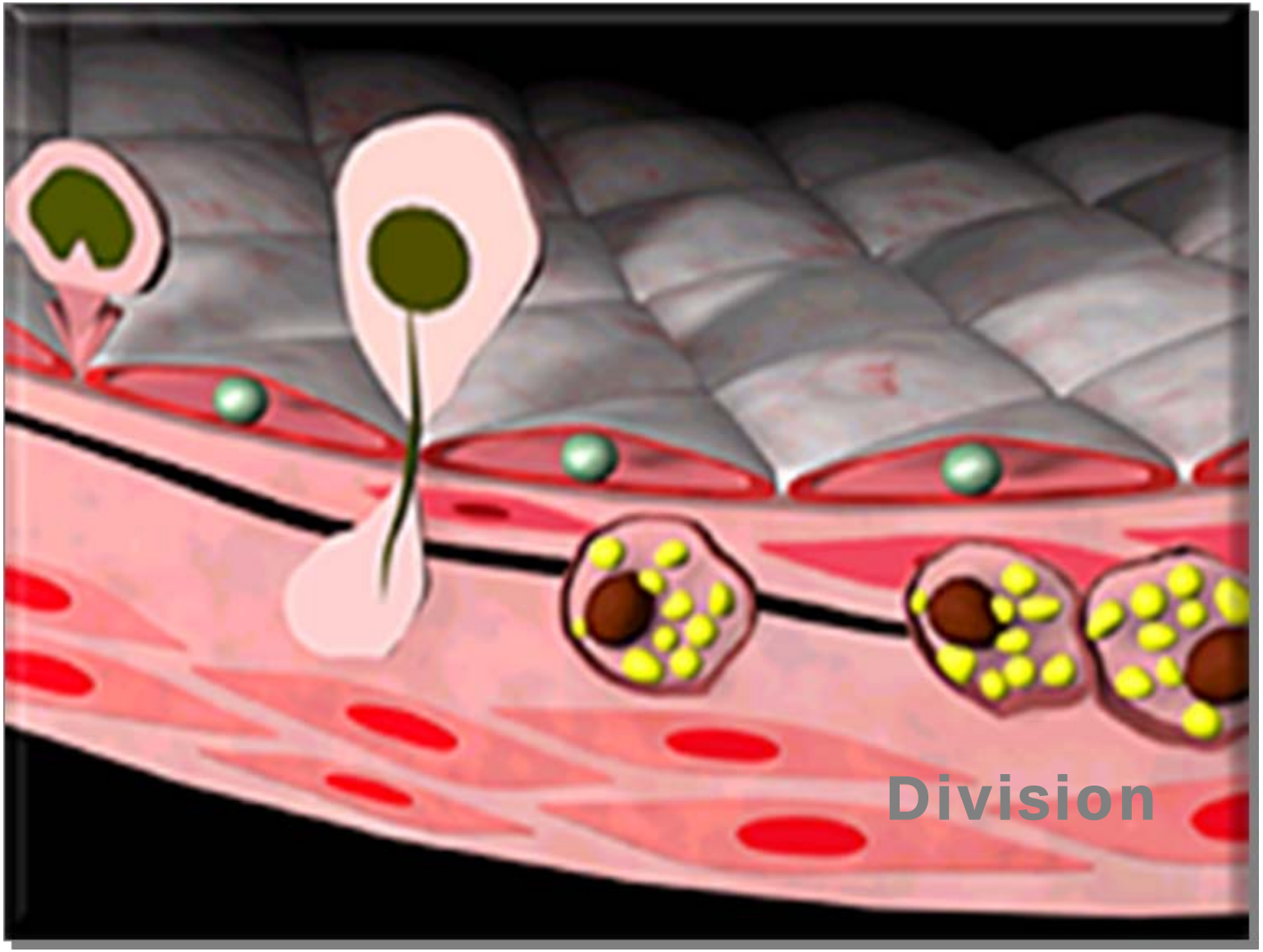
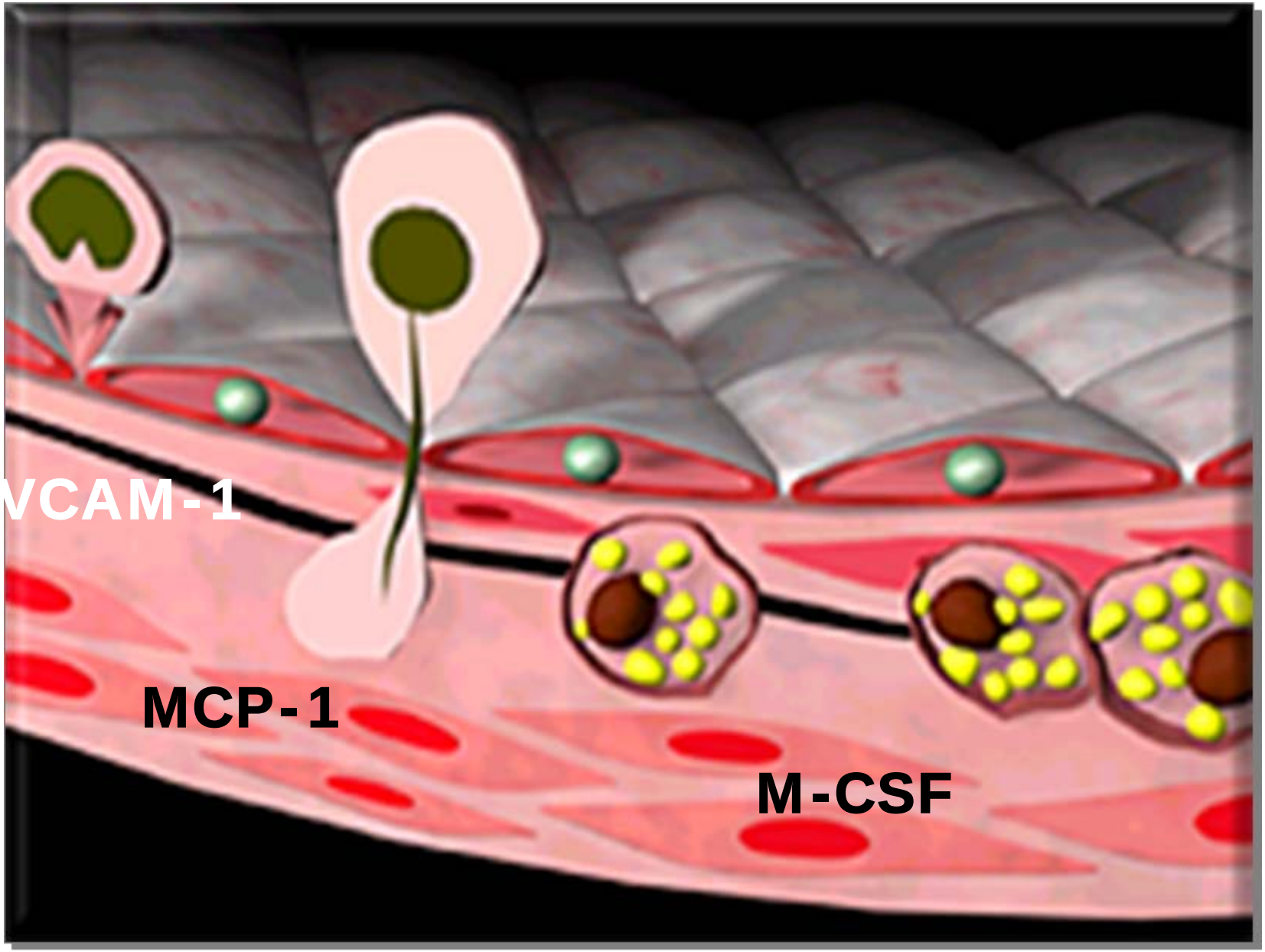


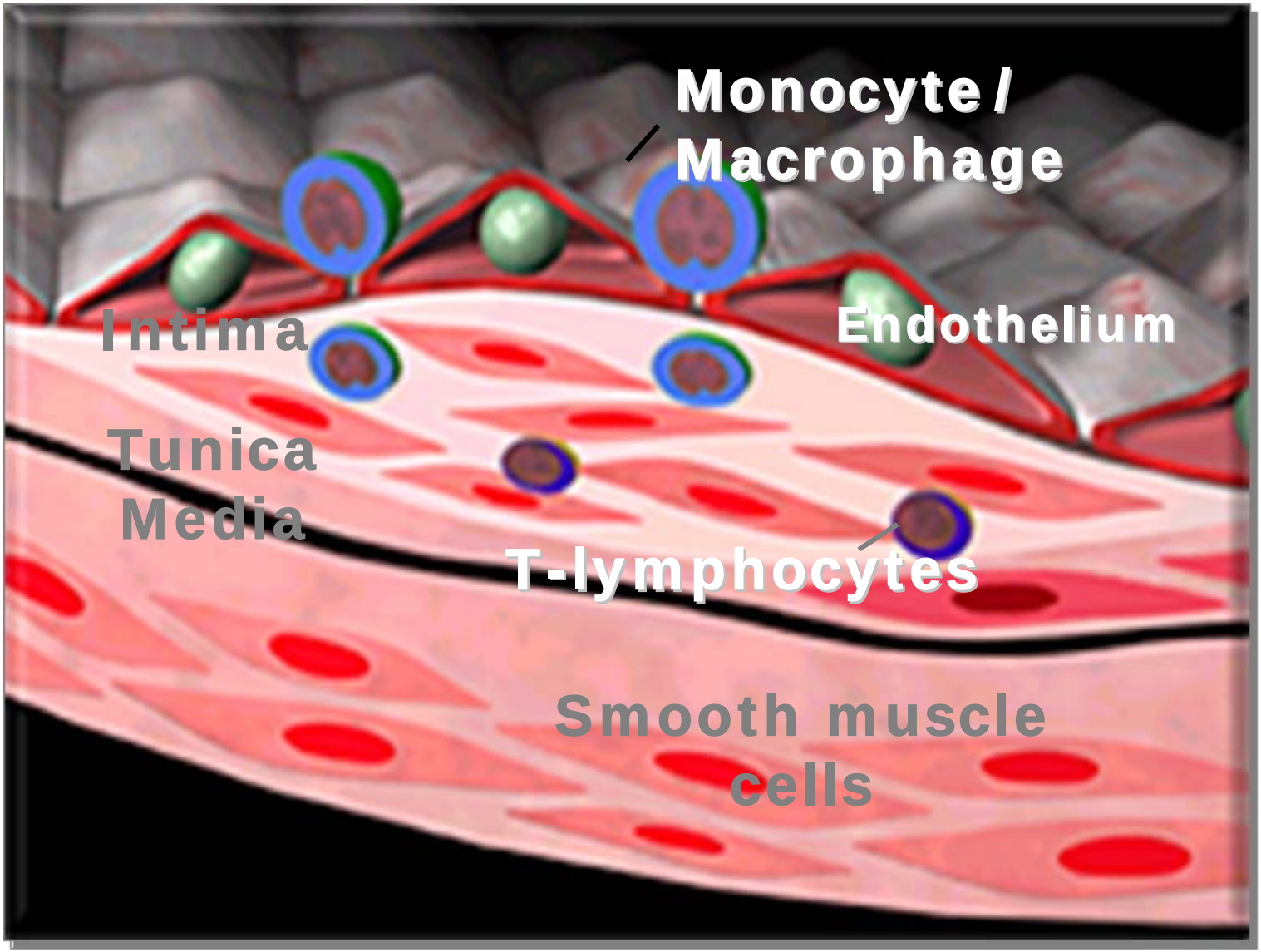
Faktorji, ki sodelujejo v vnetnih dogajanjih v ateromu

- Vascular Cell Adhesion Molecule 1 (VCAM-1)
- Monocyte Chemoattractant Protein 1 (MCP-1)
- Scavenger receptors
- Macrophage Colony-Stimulating Factor (M-CSF)
- Tumor necrosis factor receptor (TNFR = CD40)

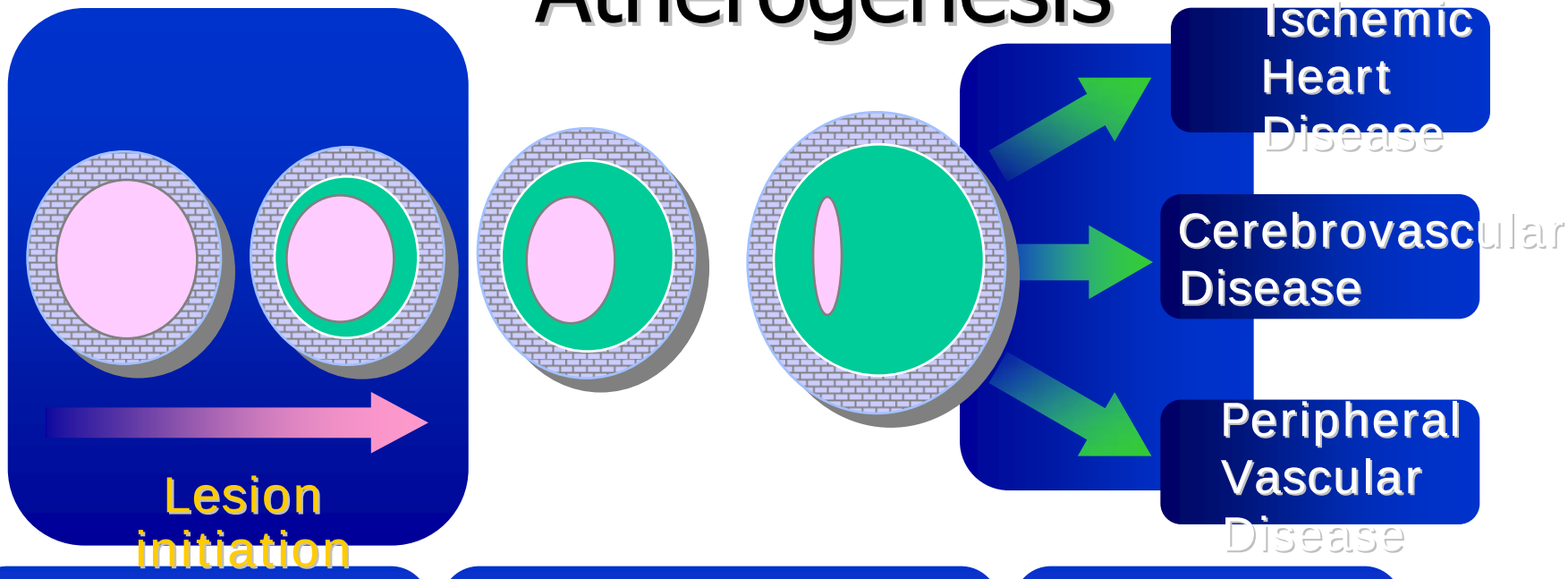
Molecular Mediators of Atherogenesis



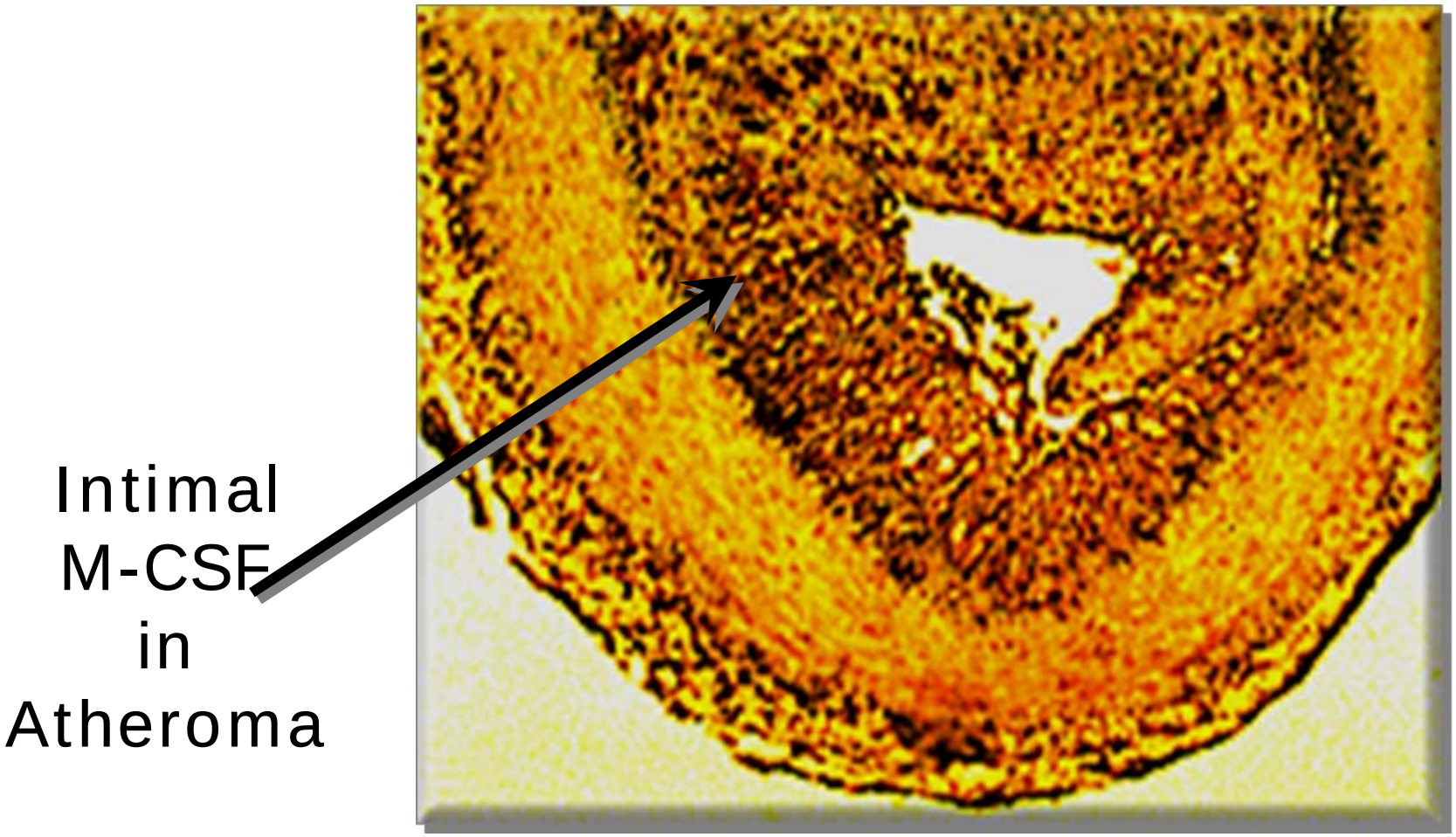
Cell Types in the Human Atheroma



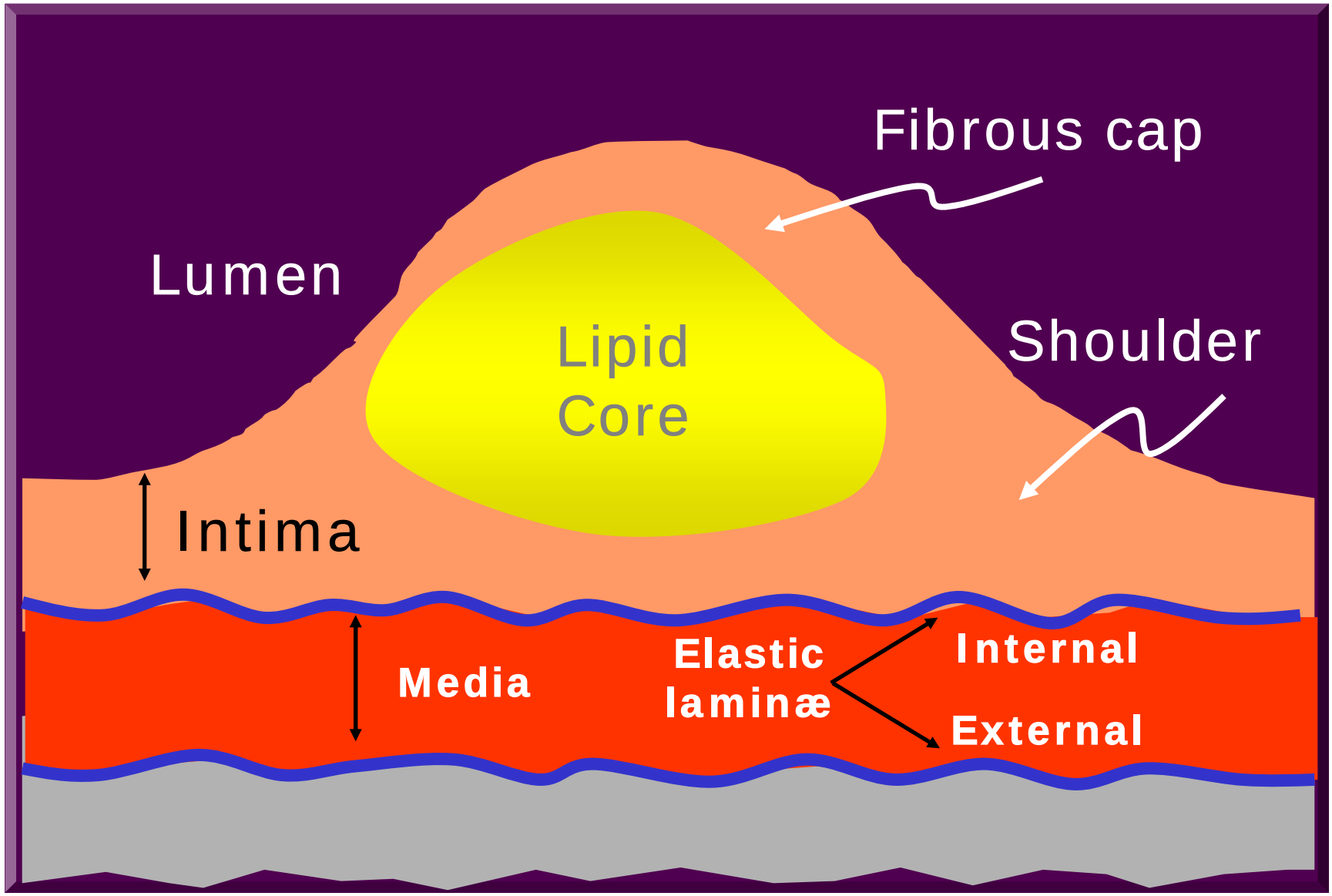
Schematic Time Course of Human Atherogenesis



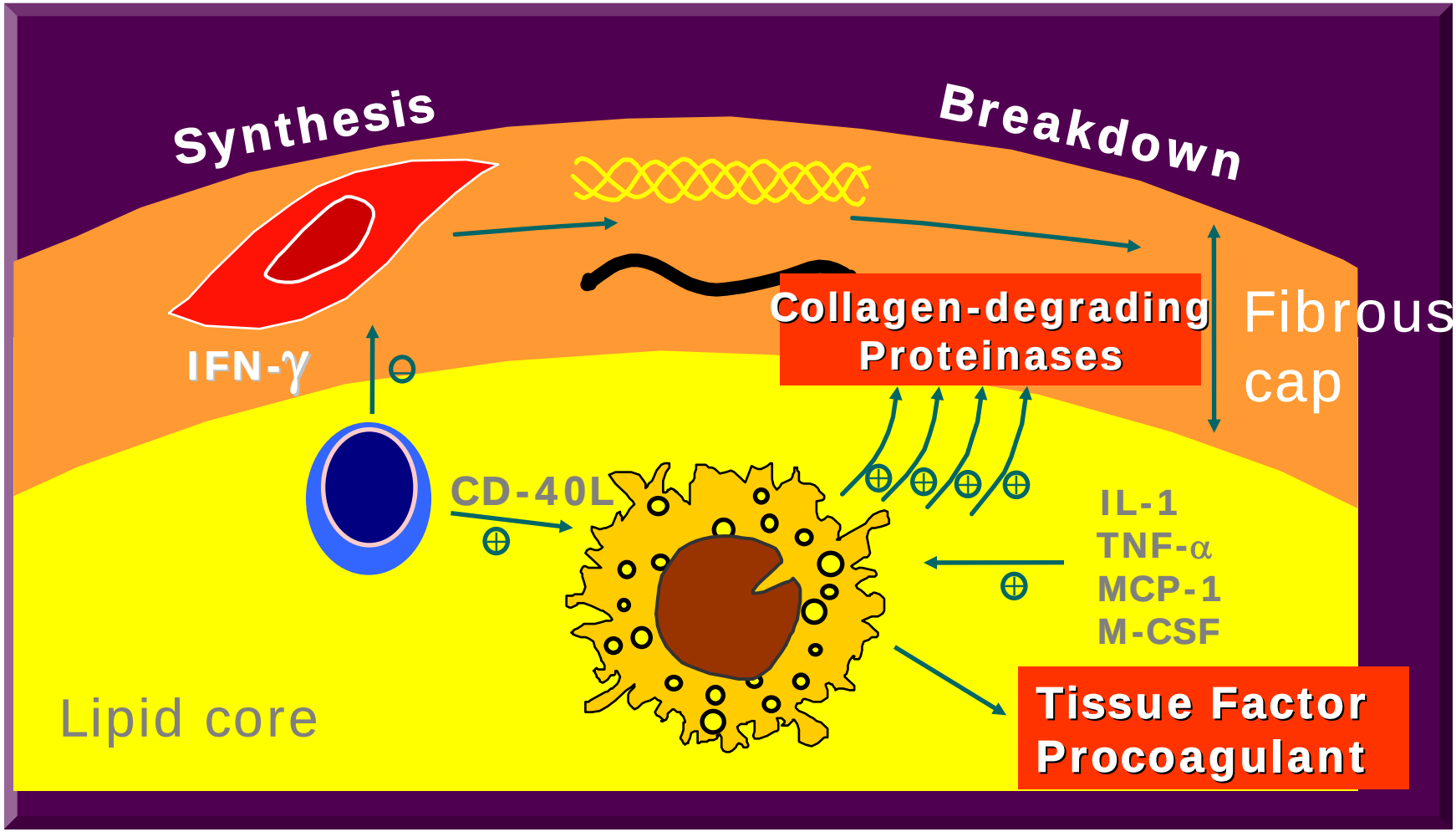
M-CSF Expression in Atheroma



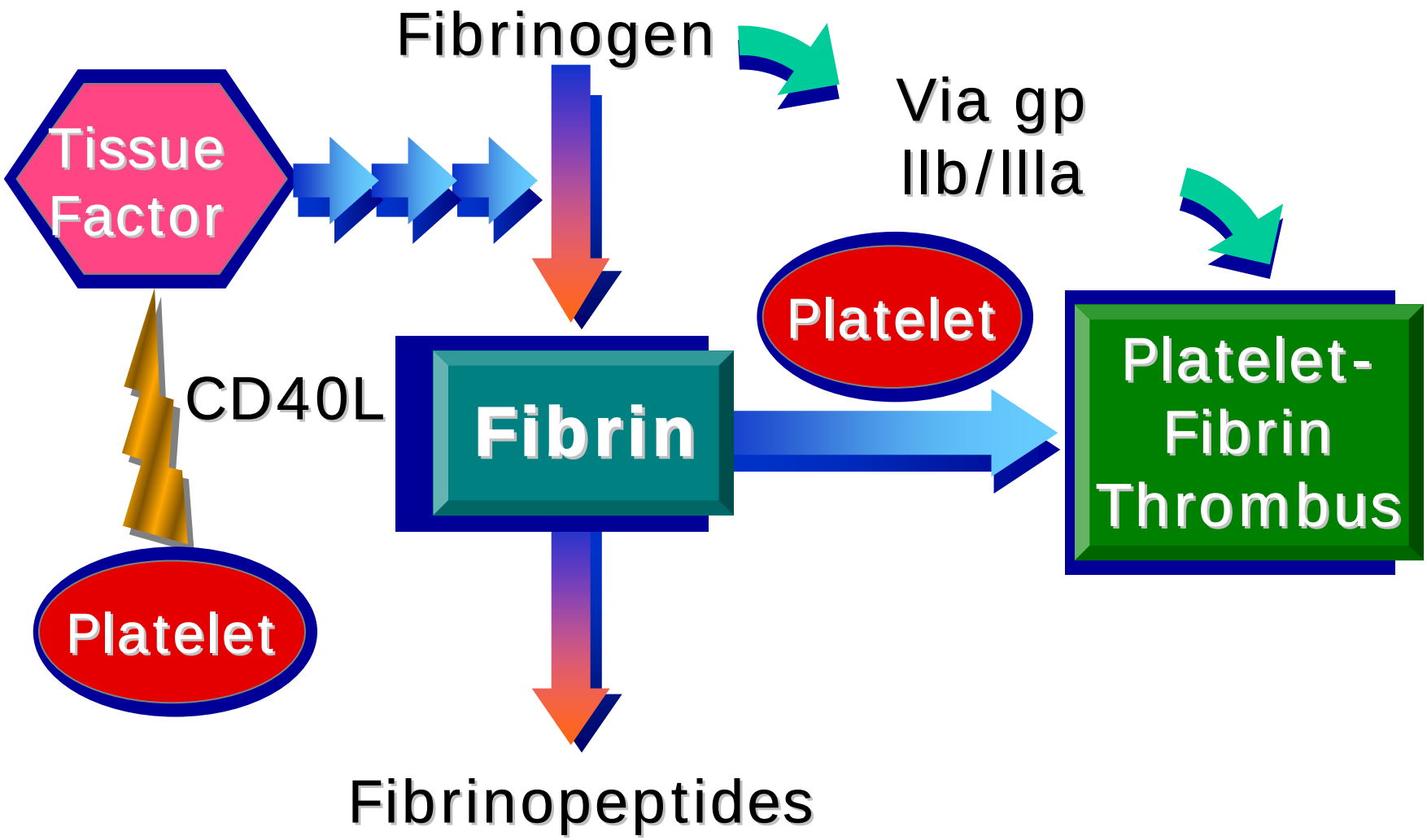
Anatomy of the Atherosclerotic Plaque



Matrix Metabolism and Integrity of the Plaque's Fibrous Cap



Inflammation Can Promote Thrombosis



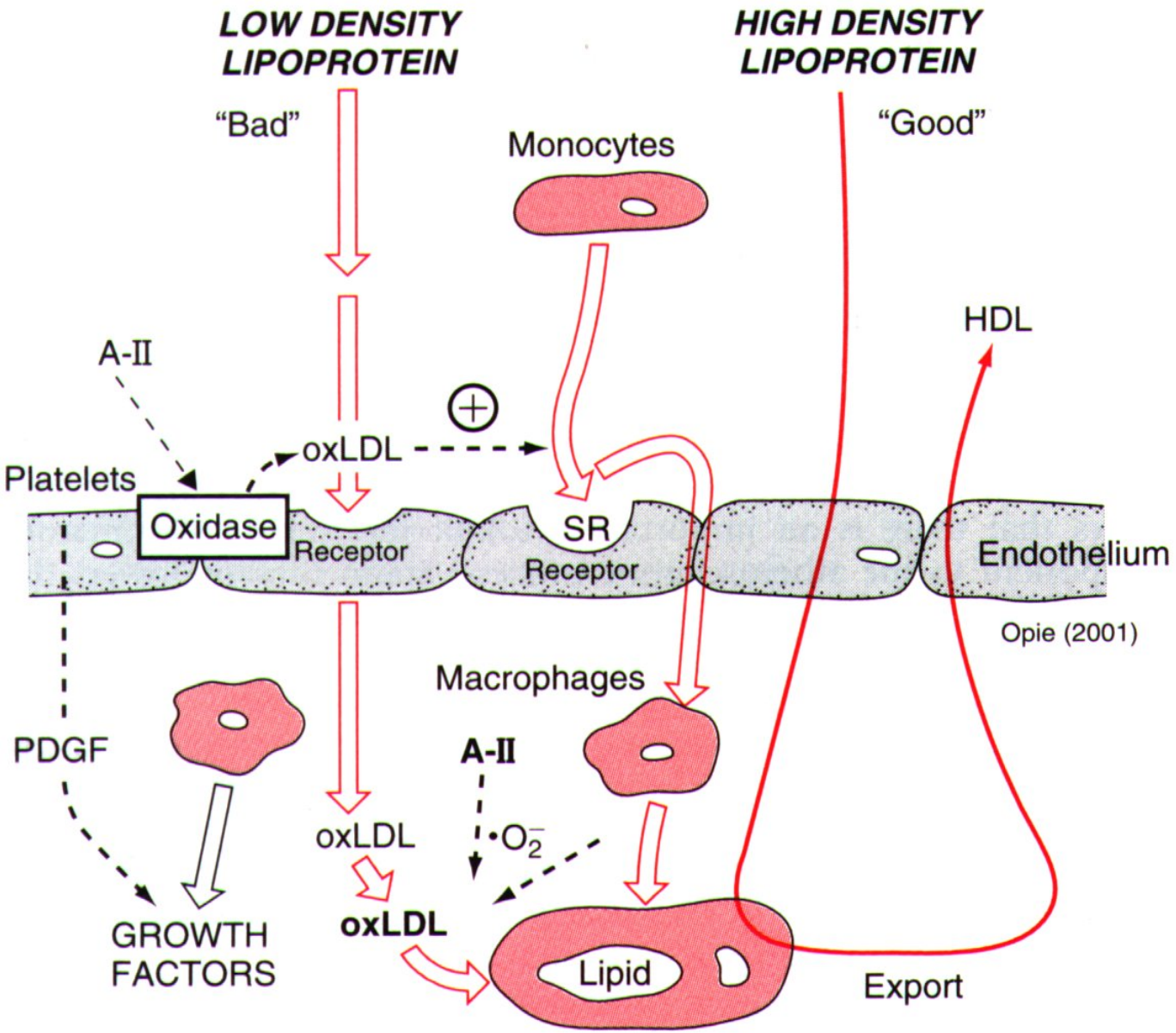
CRP and CV Risk

- CRP is an excellent marker of inflammation
- Elevated CRP correlates with increased risk of cardiac events and mortality
- Proven therapies (ASA, clopidogrel, statins)
  - Greater benefit among patients with elevated CRP
  - In some cases also reduce CRP levels (statins)
- PROVE IT–TIMI 22 and REVERSAL provide evidence that targeting inflammation (CRP) may lead to decreased atherosclerosis and optimized outcomes
- ? Need randomized trial of CRP-based intervention vs. standard cardiac rehab/risk factor modification

Pregled

- Nastanek aterosklerotičnega plaka
- **Metabolizem lipidov v plazmi (lipoproteinov)**
- Zdravila, s katerimi lahko vplivamo na te procese

CHOLESTEROL ROUND-TRIPS

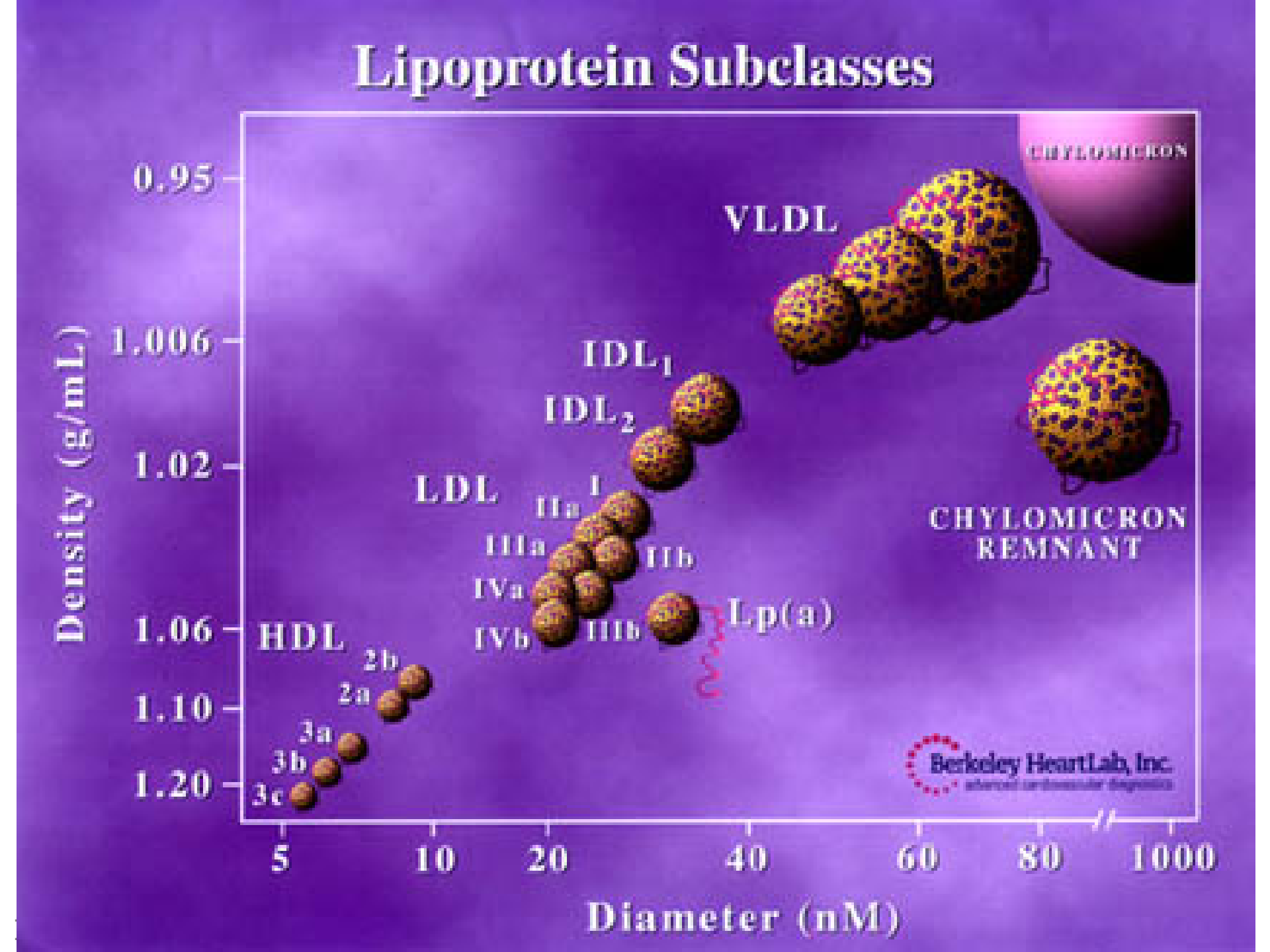


Metabolizem lipidov

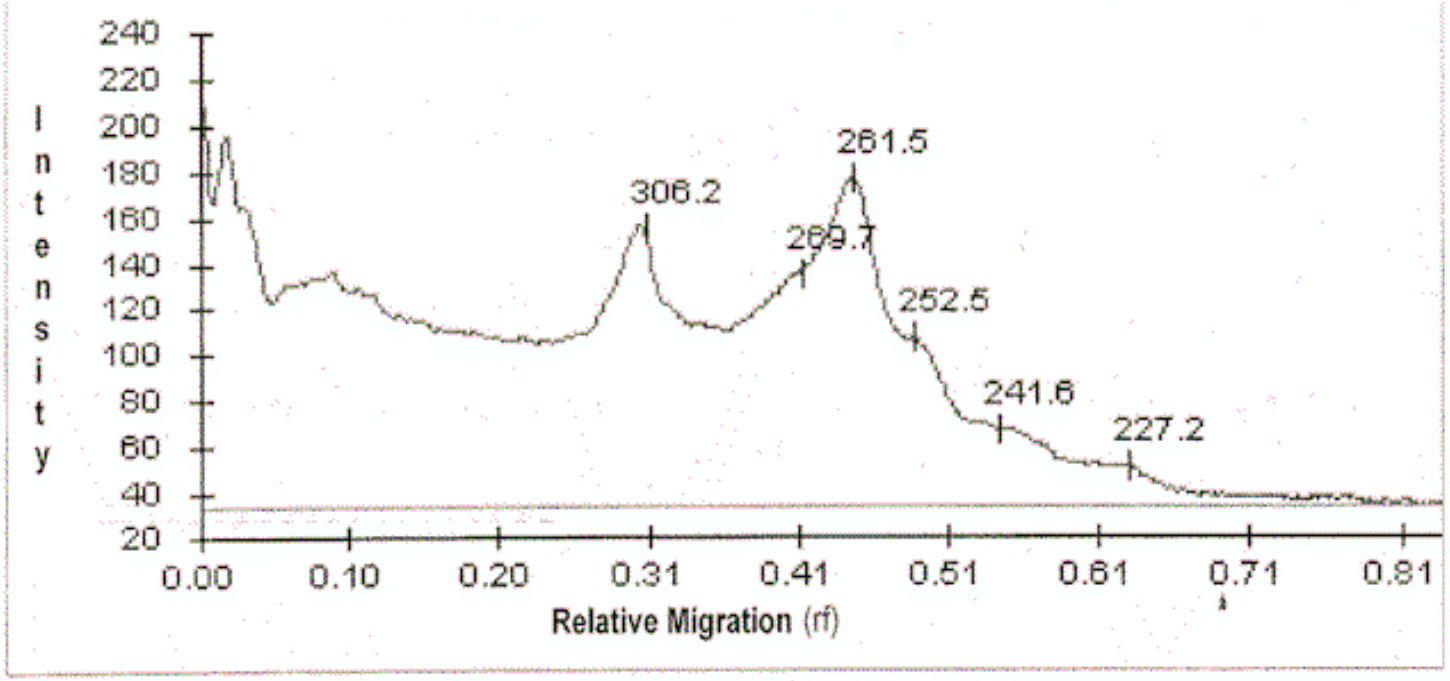
- Transport lipidov po telesu
- Lipoproteini
  - CE (estri holesterola)
  - TG (triliceridi)
  - proteini (apolipoproteini) – ligandi za receptorje, kofaktorji encimov

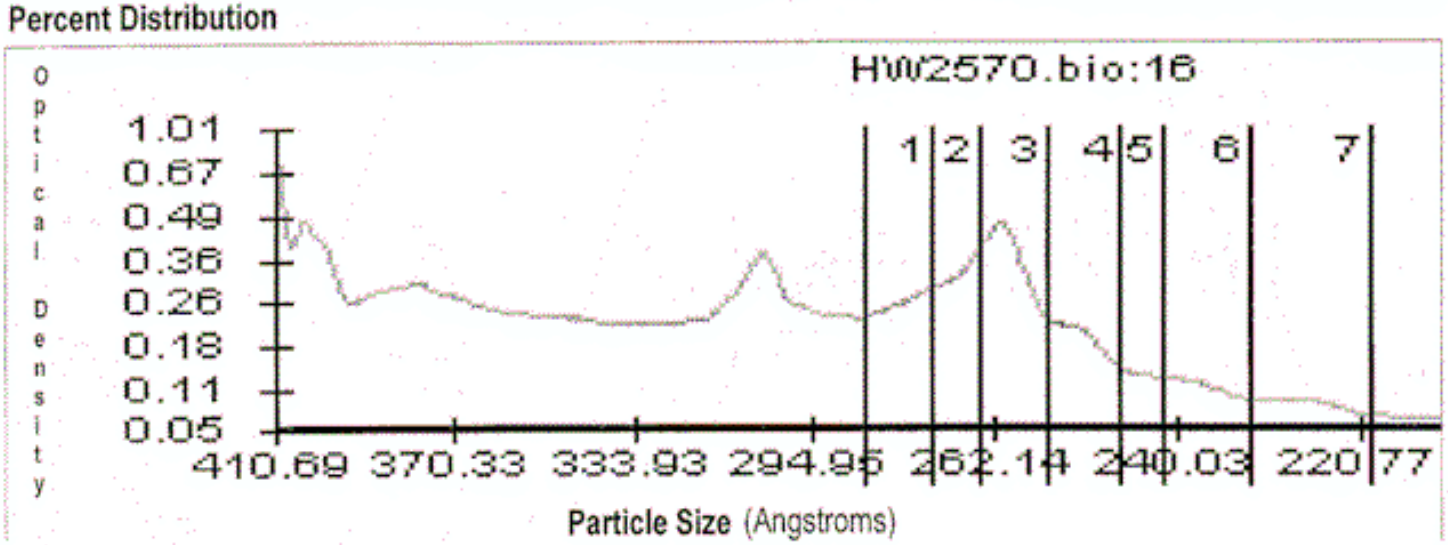
Lipoproteini (LP)

- Več vrst glede na sestavo in gostoto (centrifugiranje na osmotskem gradientu):
  - hilomikroni
  - VLDL – LP zelo majhne gostote
  - IDL – LP srednje gostote
  - LDL – LP majhne gostote
  - HDL – LP velike gostote
- Razlike v vsebnosti in vrsti lipidov in v vrstah apolipoproteinov (ApoA, ApoB, ApoC, ApoE, Apo(a)


Lipoprotein Subclasses
CHYLOMICRON
VLDL
IDL1
IDL2
LDL
I
IIa
IIIa
IIb
IVa
IVb
IIIb
Lp(a)
HDL
2b
2a
3a
3b
3c
CHYLOMICRON REMNANT
Berkeley HeartLab, Inc.
advanced cardiovascular diagnostics
0.95
1.006
1.02
1.06
1.10
1.20
Density (g/mL)
5
10
20
40
60
80
1000
Diameter (nM)

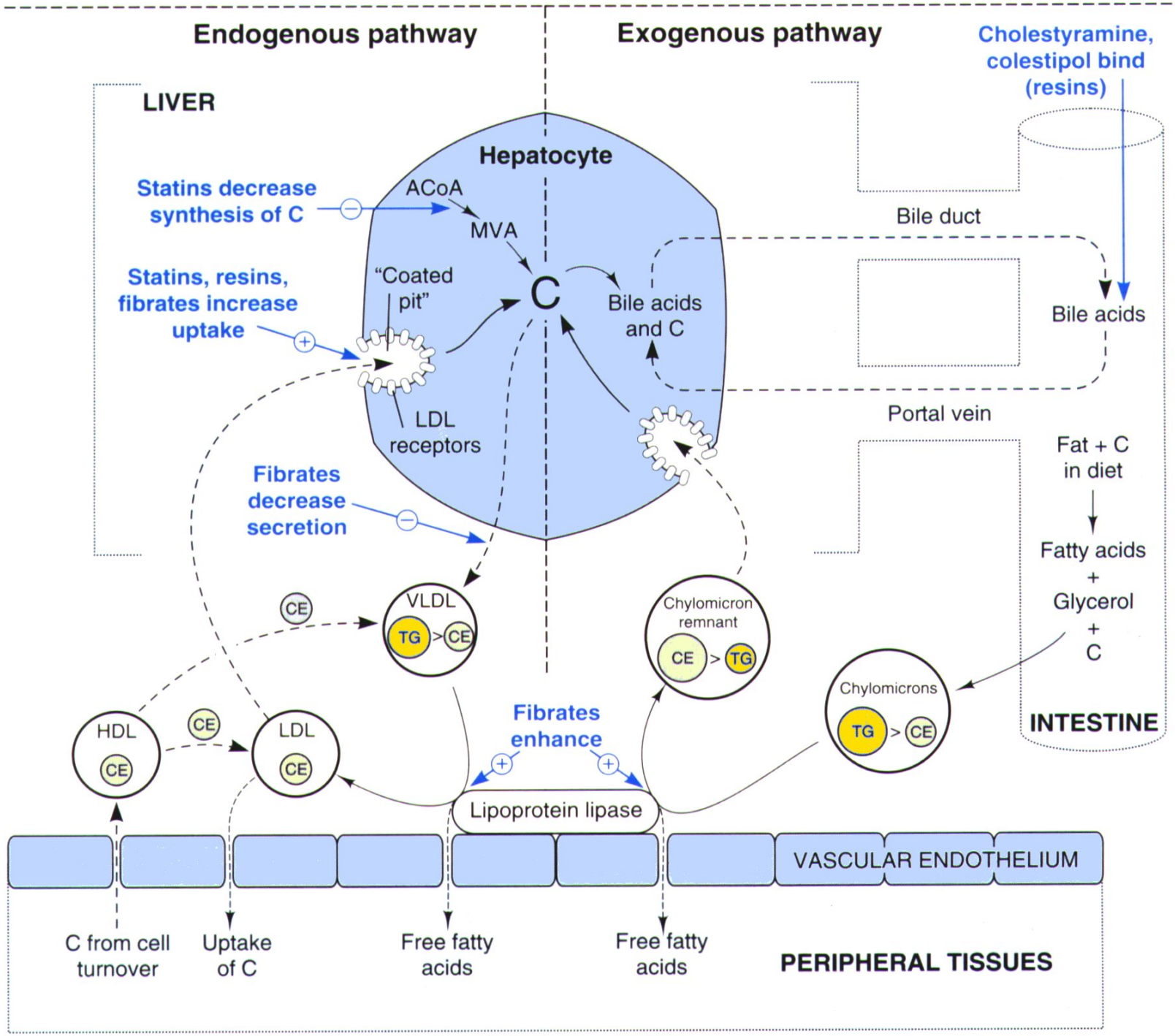
Gelna elektroforeza različnih LP



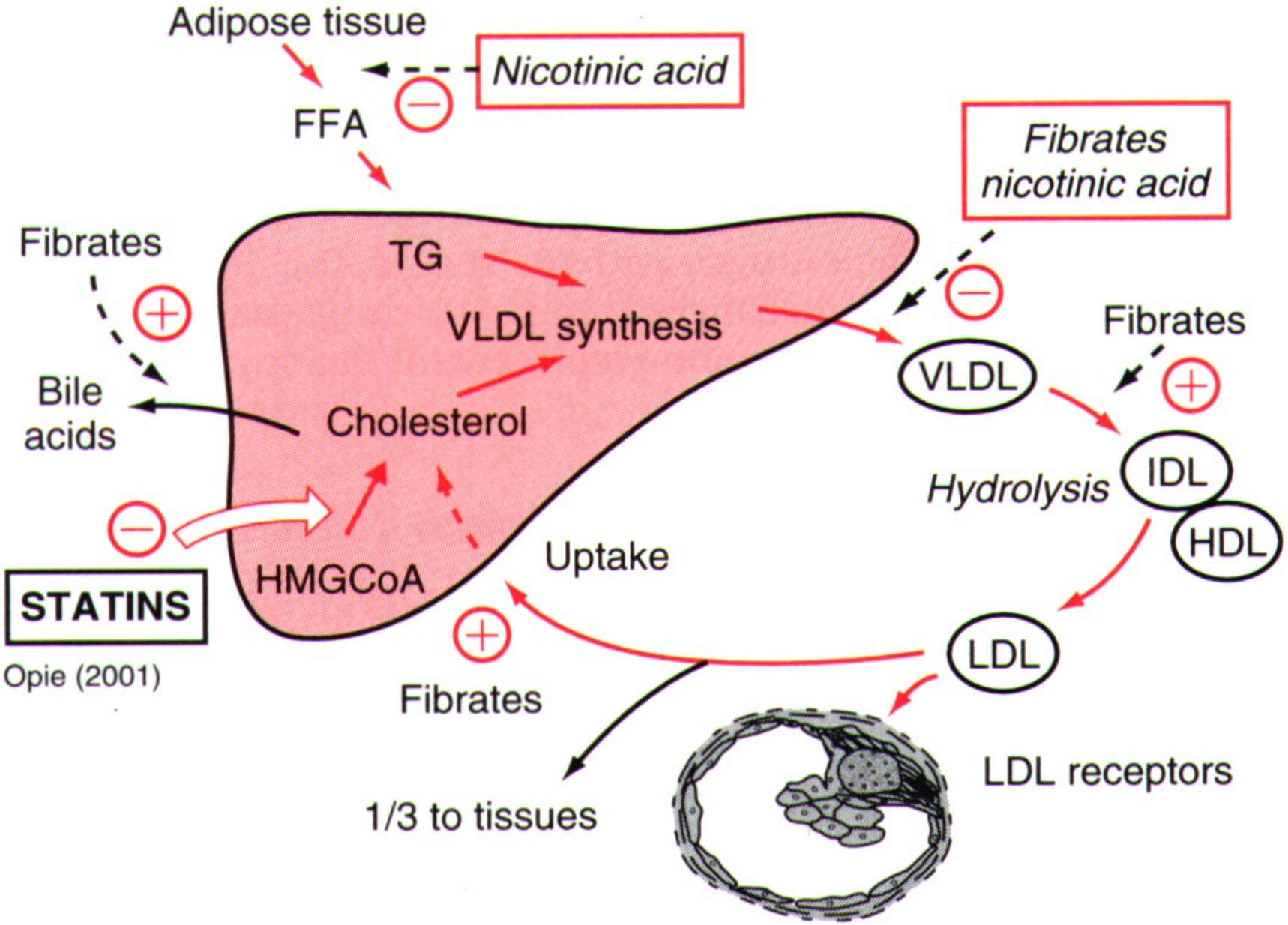


Transport in metabolizem lipidov

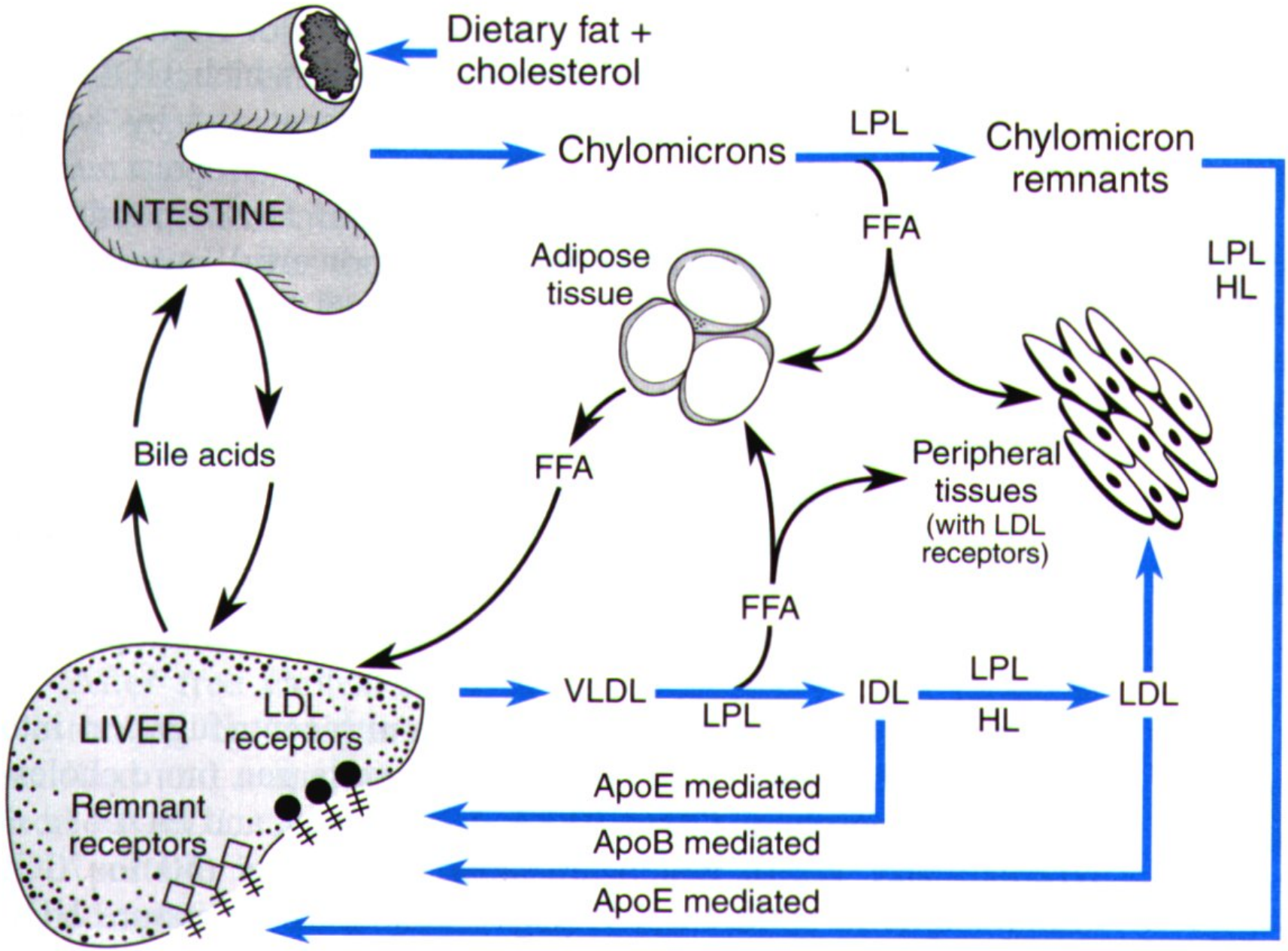
- Pot za endogene lipide
- Pot za eksogene lipide



HEPATIC EXPORT AND IMPORT OF LIPIDS



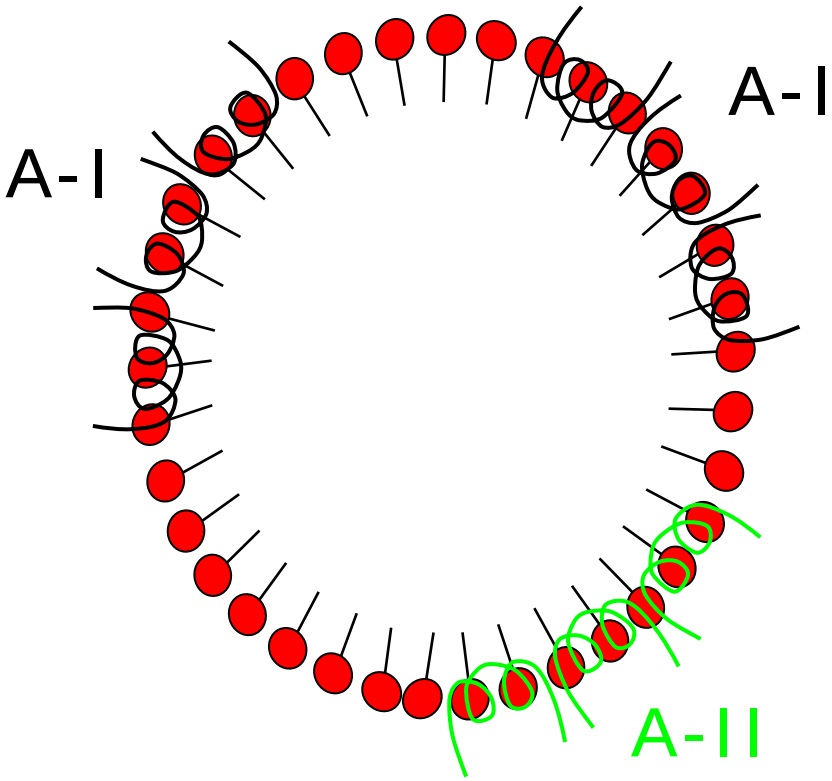
Opie (2001)


Dietary fat +
cholesterol
INTESTINE
Chylomicrons
LPL
Chylomicron
remnants
FFA
LPL
HL
Adipose
tissue
Bile acids
FFA
Peripheral
tissues
(with LDL
receptors)
FFA
LIVER
LDL
receptors
Remnant
receptors
VLDL
LPL
IDL
LPL
HL
LDL
ApoE mediated
ApoB mediated
ApoE mediated

VLOGA HDL

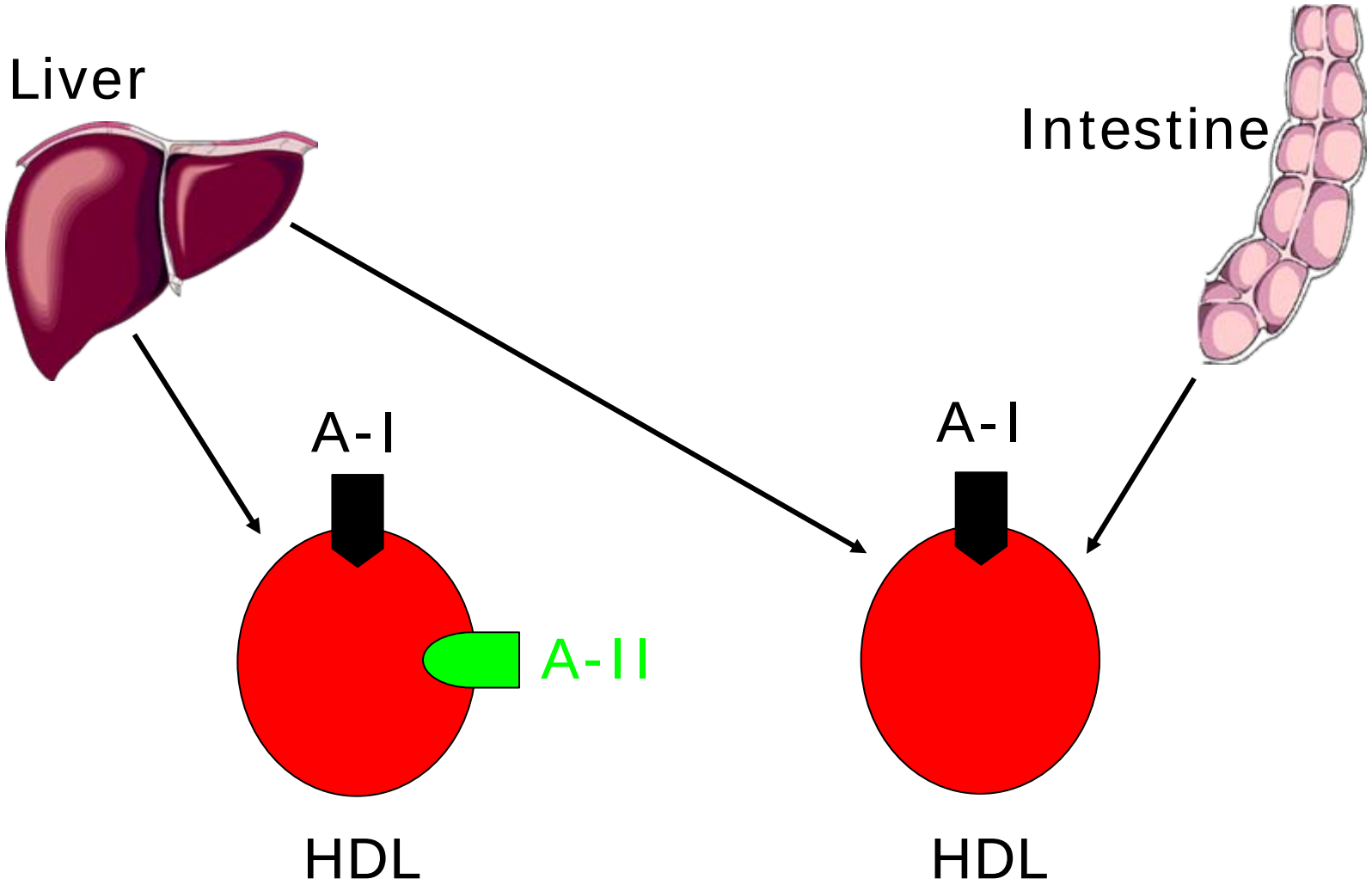
- Transport CE in TG med različnimi lipoproteini in jetri
- Prenos apolipoproteinov CII, CIII, apo E
- Povratni transport holesterola
- Antiaterogeno delovanje

Structure of HDL Particle

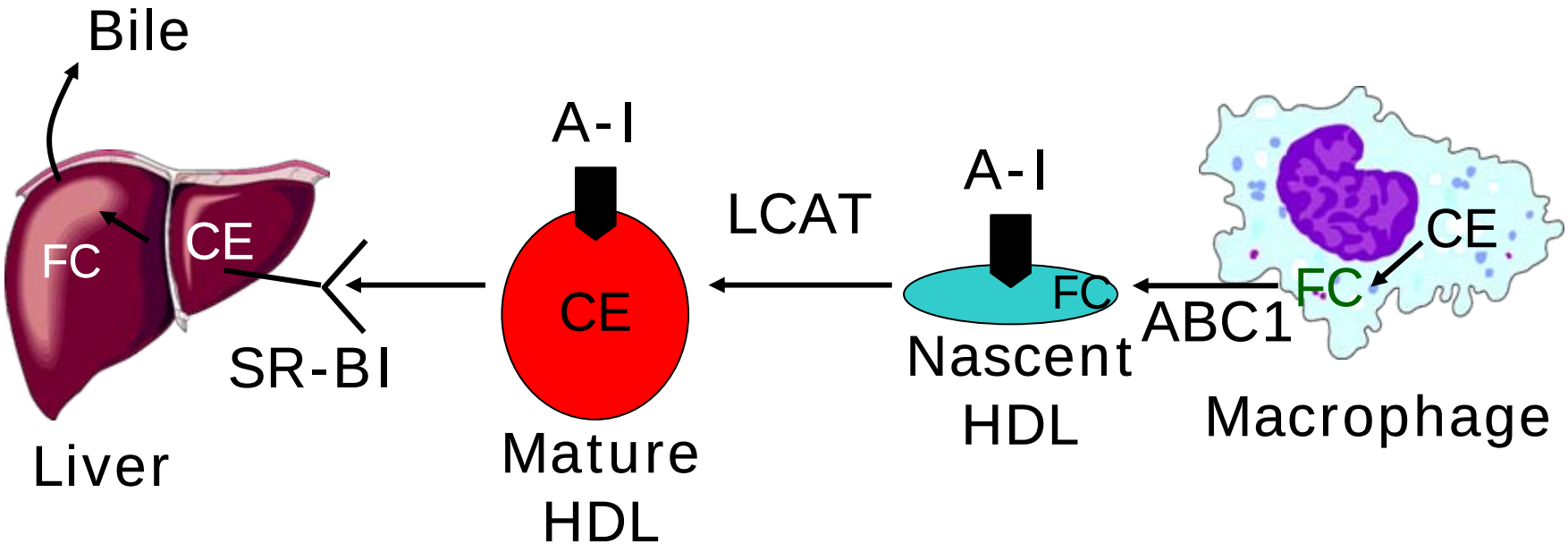


A-I, A-II = apolipoprotein A-I, A-II;
CE = cholesteryl ester; TG = triglycerides

Production of HDL by Liver and Intestine

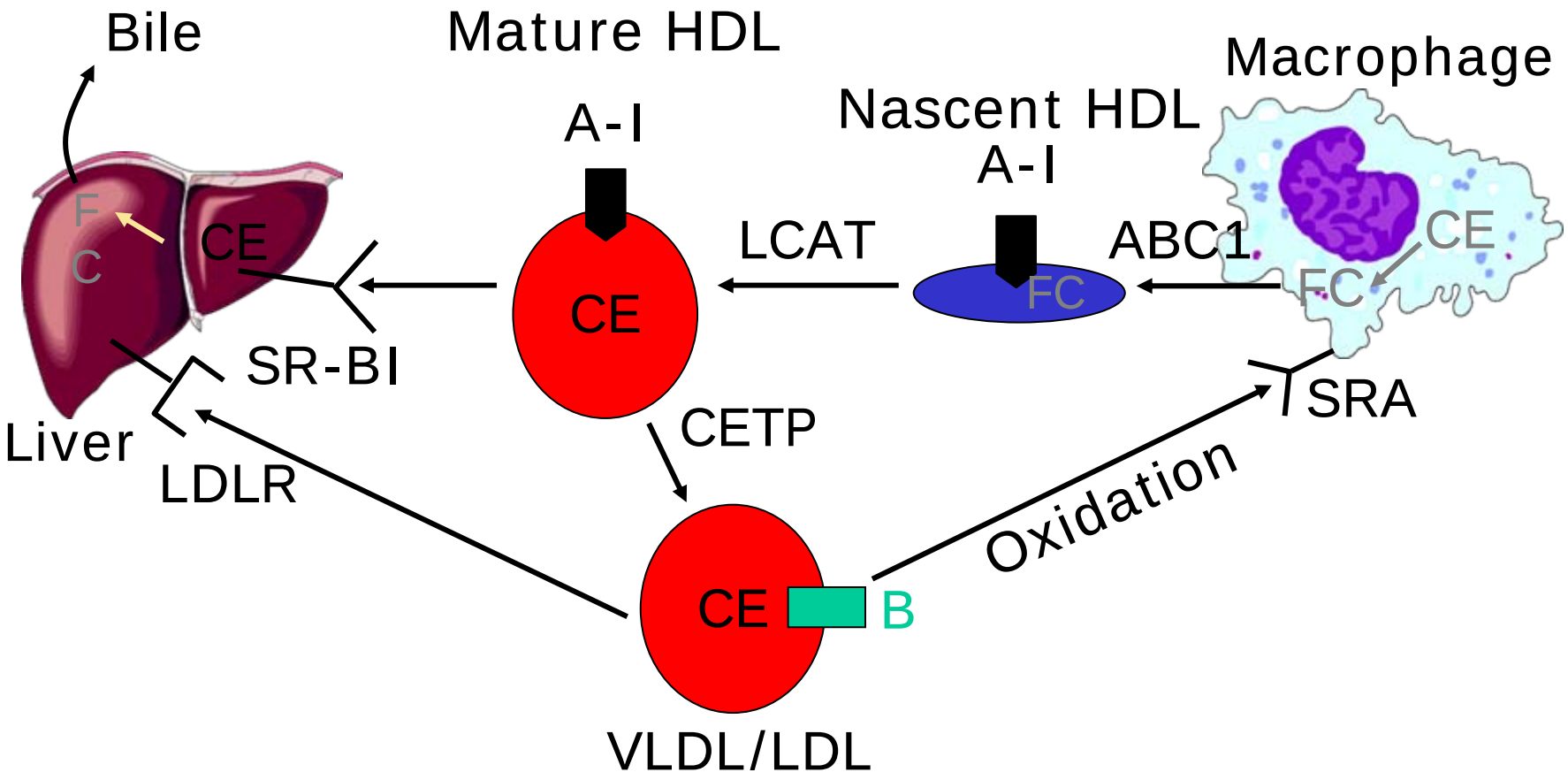


HDL Metabolism and Reverse Cholesterol Transport



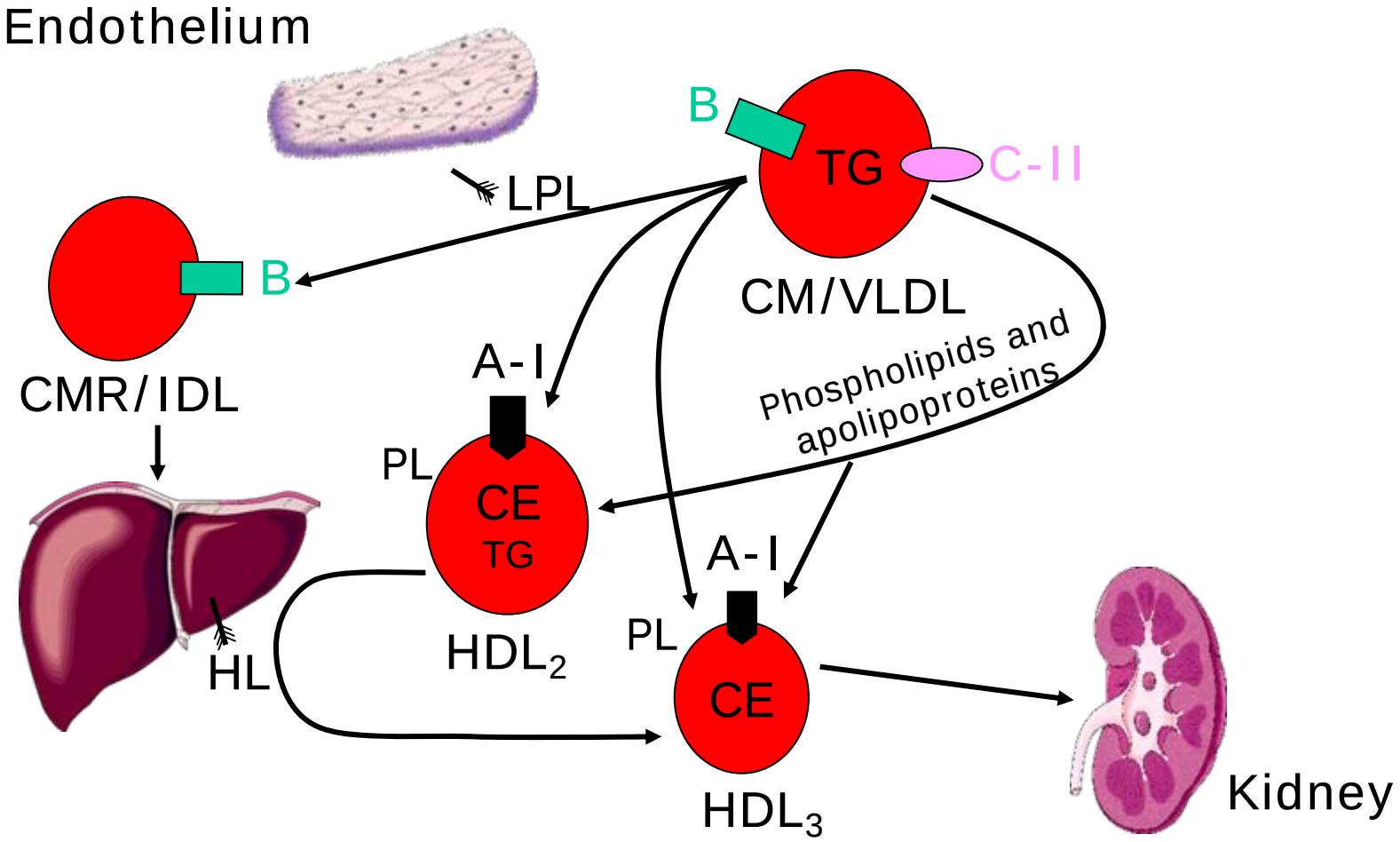
ABC1 = ATP-binding cassette protein 1; A-I = apolipoprotein A-I;
CE = cholesteryl ester; FC = free cholesterol;
LCAT = lecithin:cholesterol acyltransferase;
SR-BI = scavenger receptor class BI

Role of CETP in HDL Metabolism



CETP = cholesteryl ester transfer protein
LDL = low-density lipoprotein
LDLR = low-density lipoprotein receptor
VLDL = very-low-density lipoprotein

Role of Hepatic Lipase and Lipoprotein Lipase in HDL Metabolism



CM = chylomicron; CMR = chylomicron remnant; HDL = high-density lipoprotein; HL = hepatic lipase; IDL = intermediate-density lipoprotein; LPL = lipoprotein lipase; PL = phospholipase; TG = triglyceride

Pregled lipoproteinov (LP)

VRSTA LP	GLAVNE SESTAVINE	APOPROT.	MESTO SINTEZE	POTI KATABOLIZMA
Hilomikroni (CH) in ostanki CH)	Trigliceridi (TG) in holesterol (C) v hrani, 10:1	B-48, E, A-I, A-IV, C-I, C-II, C-III	Črevo	Hidroliza TG z LPL. Privzem ostankov CH v jetrih preko ApoE
VLDL	'Endogeni' ali jetrni TG, 5:1	B-100, E, C-I, C-II, C-III	Jetra	Hidroliza TG z LPL
IDL	Holesterilni estri (CE) in 'endogeni' TG	B-100, E, C-II, C-III	Katabolni produkt VLDL	50% v LDL, posredovana z jetrno lipazo (HL), 50% privzem v jetra z ApoE

Pregled LP

VRSTA LP	GLAVNE SESTAVINE	APOPROTEINI	MESTO SINTEZE	POTI KATABOLIZMA
LDL	CE	B-100	Katabolni produkt VLDL	Privzem z LDL-R (~75% v jetrih), posredovan z ApoB-100
HDL	Fosfolipidi, CE	A-I, A-II, E, C-I, C-II, C-III	Črevo, jetra, plazma	Prenos CE v VLDL in LDL. Privzem HDL C v hepatocite
Lp(a)	CE	B-100, apo(a)	Jetra	Neznano

LASTNOSTI APOLIPOPROTEINOV I

APOLIPOPROTEIN	MESTO SINT.	VLOGA
ApoA-I	Jetra, črevo	Sestavina HDL, kofaktor LCAT, ligand za HDL-R, reverzni transport C
ApoA-II	Jetra	Tvori -S-S- kompleks z apoE-2 in E-3, kar prepreči vezavo apoE-2 in apoE-3 na LP-R
ApoB-100	Jetra	Strukturni protein VLDL, IDL, LDL, ligand LDL-R
ApoB-48	Črevo	Strukturni protein hilomikronov (CM)

LASTNOSTI APOLIPOPROTEINOV II

APOLIPOPROTEIN	MESTO SINT.	VLOGA
ApoC-I	Jetra	Aktivator LCAT. Modulira vezavo ostankov CM na R
ApoC-II	Jetra	Kofaktor LPL
ApoC-III	Jetra	Modulira vezavo ostankov CM na R
ApoE	Jetra, možgani, koža, gonade, vranica	Ligand za LDL-R in za ostanke CM, reverzni transport C (HDL z apoE)
Apo(a)	Jetra	Modulator fibrinolize

Frederickson/WHO classification of hyperlipoproteinaemia

Type	Lipoprotein elevated	Chol	TG	Atherosc l risk	Drug treatment
I	Chylomicrons	+	+++	NE	None
IIa	LDL	++	NE	High	HMG-CoA reductase ± resins
IIb	LDL + VLDL	++	++	High	Fibrates, HMG-CoA reductase inhibitor, nicotinic acid
III	βVLDL	++	++	Moderate	Fibrates
IV	VLDL	+	++	Moderate	Fibrates (± fish oil)
V	Chylomicrons + VLDL	+	++	NE	None (± fish oil)

Chol = cholesterol; TG = triglycerides; LDL = low density lipoprotein;
VLDL = very low density lipoprotein;
βVDL = a qualitatively abnormal form of VLDL identified by its pattern on electrophoresis;
+ = increased concentration; NE = not elevated

Pregled

- Nastanek aterosklerotičnega plaka
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Risk Factors for Coronary Heart Disease* (CHD)

Age

Male > 45 years or female > 55 years

Family history of premature CHD

A first-degree relative (male below 55 years or female below 65 years when the first CHD clinical event occurs)

Current cigarette smoking

Hypertension

Blood pressure ≥ 140/90 or use of antihypertensive medication, irrespective of blood pressure

Low HDL-C

< 40 mg/dl (consider < 50 mg/dl as "low" for women)

Obesity†

Body mass index > 25 kg/m^2 and waist circumference above 40 inches (men) or 35 inches (women)

Lipid Treatment Thresholds for Diet and for Drugs
Units: mg/dl (mmol/L)

	Threshold for Initiation of Dietary Therapy		Threshold for Initiation of Drug Therapy		Treatment Goal (Diet or Drugs)
Category	**TC**	**LDL-C**	**TC**	**LDL-C**	**LDL-C**
0 or 1 Other risk factor without cardiovascular disease	240 (6.2)	160 (4.1)	275 (7.1)	190 (4.9)	<160 (4.1)
<2 other risk factors without cardiovascular disease	200 (5.2)	130 (3.4)	240 (6.2)	160 (4.1)	<130 (3.4)
With cardiovascular disease	160 (4.1)	100 (2.6)	200 (5.2)	130 (3.4)	≤100 (2.6)

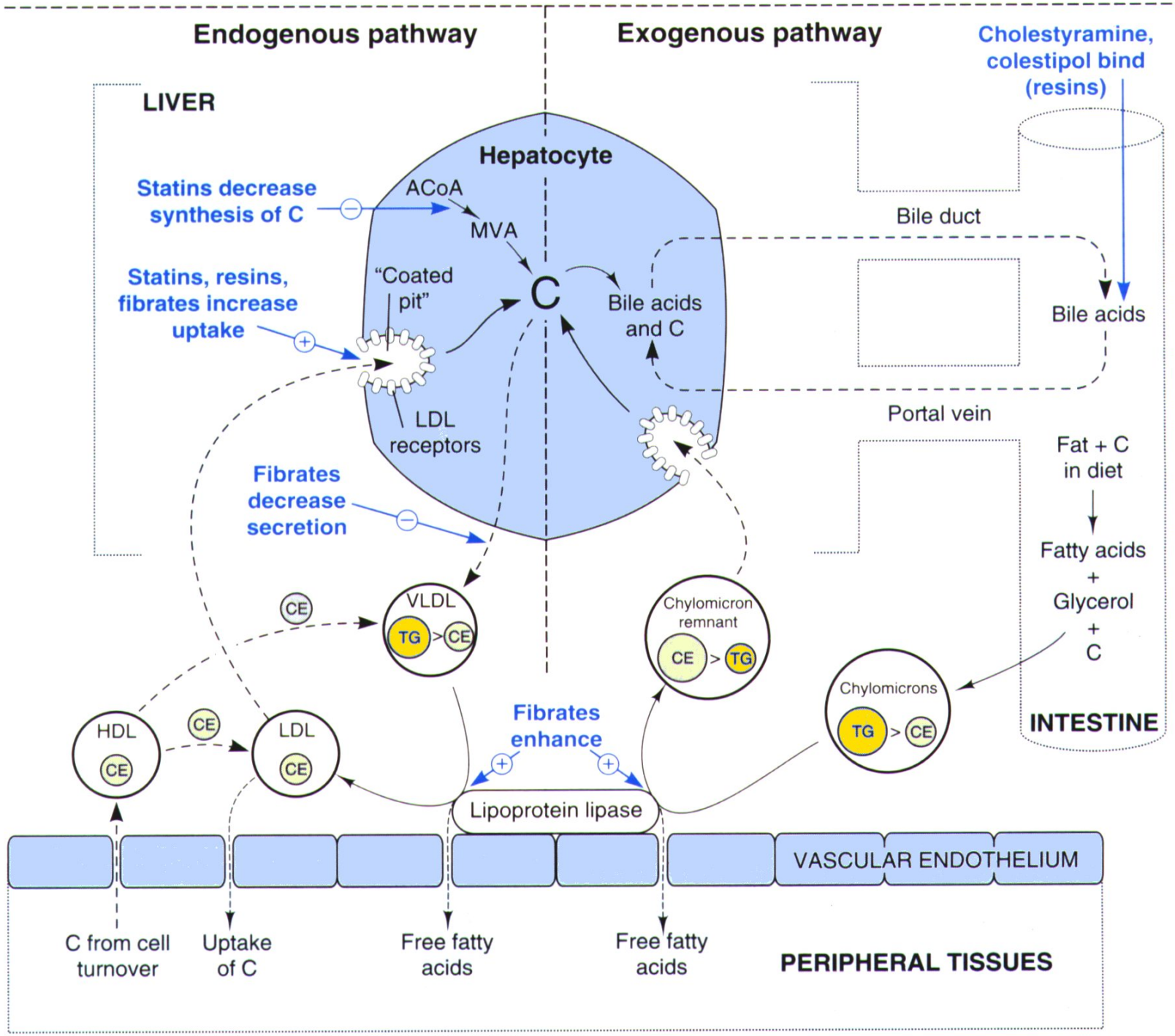
From NCEP[41] HDL treatment goals: Total cholesterol to HDL ratio of <5.0[47]; LDL to HDL ratio of <2.0.[45]
TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol.

Pregled zdravil za zdravljenje hiperlipidemij

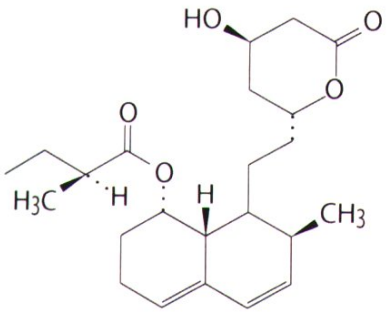
- Inhibitorji HMG-CoA reduktaze
- Smole, ki vežejo žolčne kisline
- Ezetimib
- Derivati fibrične kisline (fibrati)
- Nikotinska kislina (niacin)
- Probukol
- Kombinacije zdravil
- Druga zdravila

HMG-CoA reduktazni inhibitorji

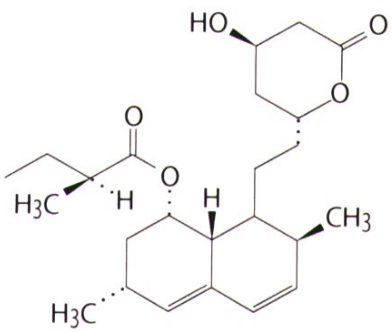
- Hidroksi-metil-glutaril-CoA reduktaza – ključni (rate limiting) encim pri sintezi holesterola
- HMG-CoA $\Rightarrow$ mevalonska kislina
- Posledica: $\Downarrow$ koncentracija holesterola
- Povečana ekspresija gena za HMG-CoA reduktazo
- Povečana ekspresija gena za LDL-R
- Povečano odstranjevanje LDL
- $\Downarrow$ koncentracija LDL



MEVASTATIN



LOVASTATIN



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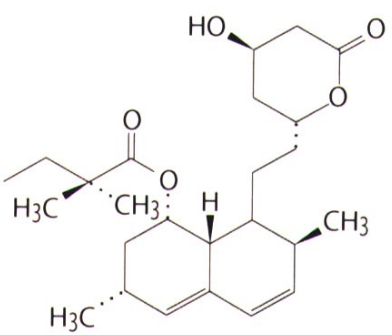

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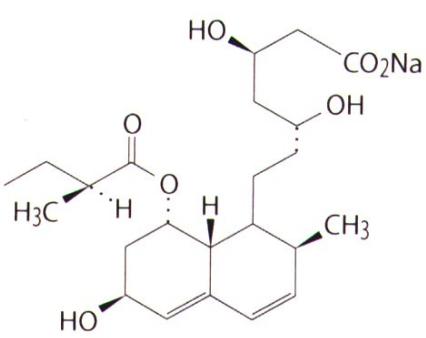
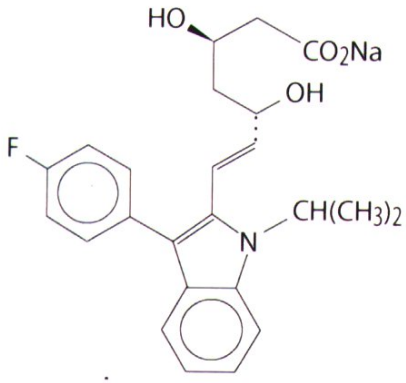


FLUVASTATIN *



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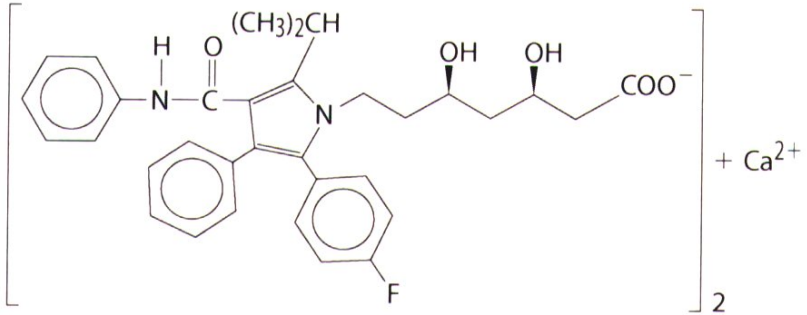
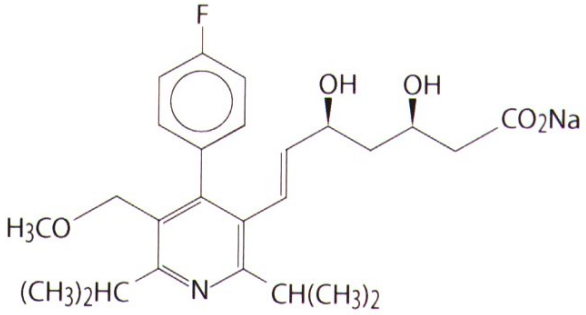
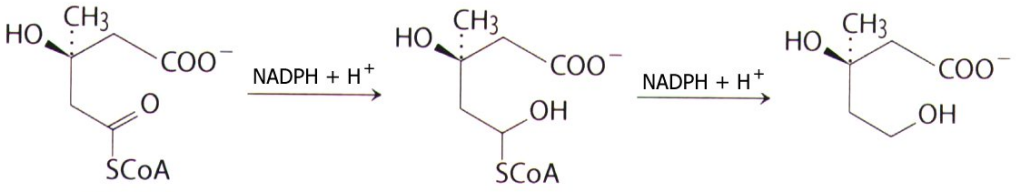


CERIVASTATIN



Reakcija, ki jo katalizira HMGCoA reduktaza



HMG-CoA — vmesni produkt — mevalonat

Farmakokinetika

- Dobra obsorpcija iz prebavil
- Ekstrakcija v jetrih (mesto delovanja)
- Izločanje preko jeter (metabolizem)
- Vezava na plaz. belj. (> 90%)

Klinična uporabnost

- Zmanjšajo morbiditeto in mortaliteto pri izbranih bolnikih
- Indicirani pri bolnikih z manifestno aterosklerozo in tistih z večjim tveganjem za koronarno bolezen
- Neučinkoviti (razen atorvastatina) pri homozigotni družinski hiperholesterolemiji

Stranski učinki

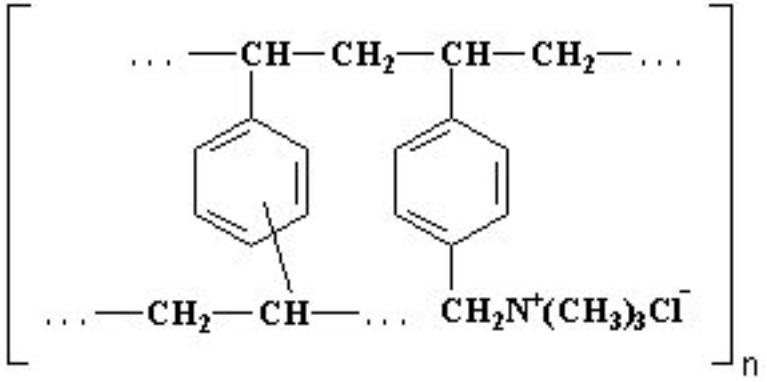
- Relativno skromni
- ⇑ jetrne transaminaze – previdnost pri jetrnih boleznih
- Miopatija ($\Rightarrow$ rabdomioliza)
  - kontrola kreatin fosfokinaze (CPK)
  - 0,1% pacientov z blažjim miozitisom
  - verjetnost večja pri sočasni uporabi fibratov in nikotinske kisline

Smole, ki vežejo žolčne kisline

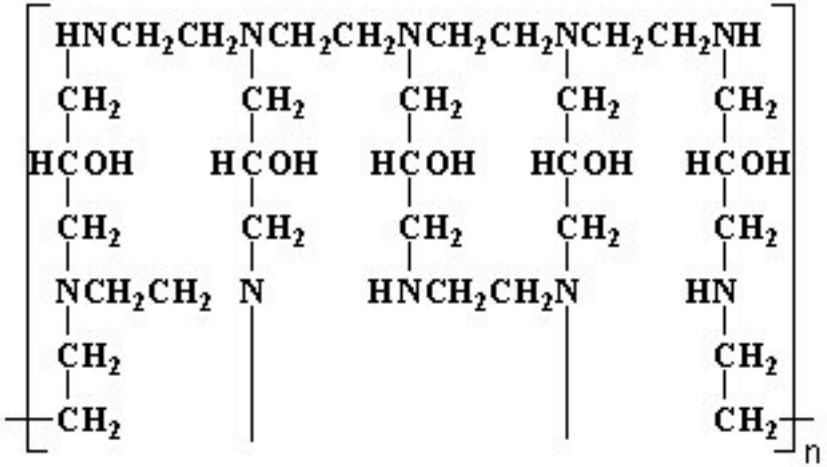
- Delovanje v črevesu – ni sistemskih učinkov
- Preprečevanje enterohepatične cirkulacije žolčnih kislin (97 %)
- ⇑ izločanje iz telesa
- Holesterol ⇒ žolčne kisline
- ⇓ konc. Holesterola
  - ⇑ koncentracija HMG-CoA reduktaze
  - ⇑ sinteza LDL-R
  - ⇑ sinteza cholesterola in TG

Predstavnika

- Holestiramin



- Kolestipol



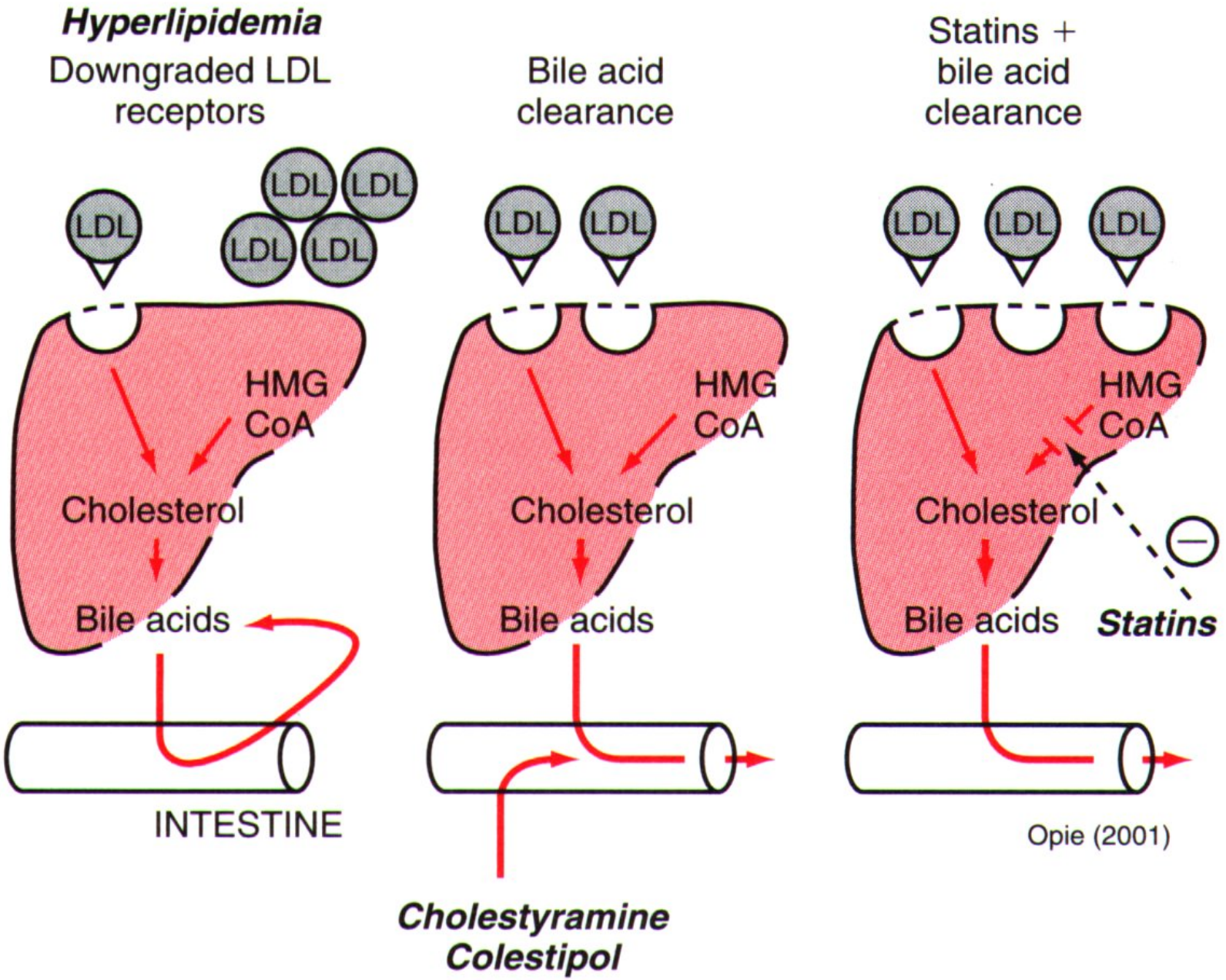
Klinična uporabnost

- Uporabne v kombinaciji s statini (ob nezadostnem učinku)
- Kot monoterapija pri bolnikih s povečanim holesterolom in normalnimi trigliceridi, če so statini kontraindicirani

Stranski učinki

- Napihnjenost v trebuhu
- Zaprtje
- ⇑ alkalne fosfataze (jetra) - zmerno
- Hipertrigliceridemija
- Interakcije s številnimi zdravili na nivoju absorpcije:
  - tiroksin
  - kardiotonični glikozidi
  - antikoagulansi
  - nekateri tiazidi
  - nekatera antilipemična zdravila:
    - nekateri statini
    - gemfibrozil

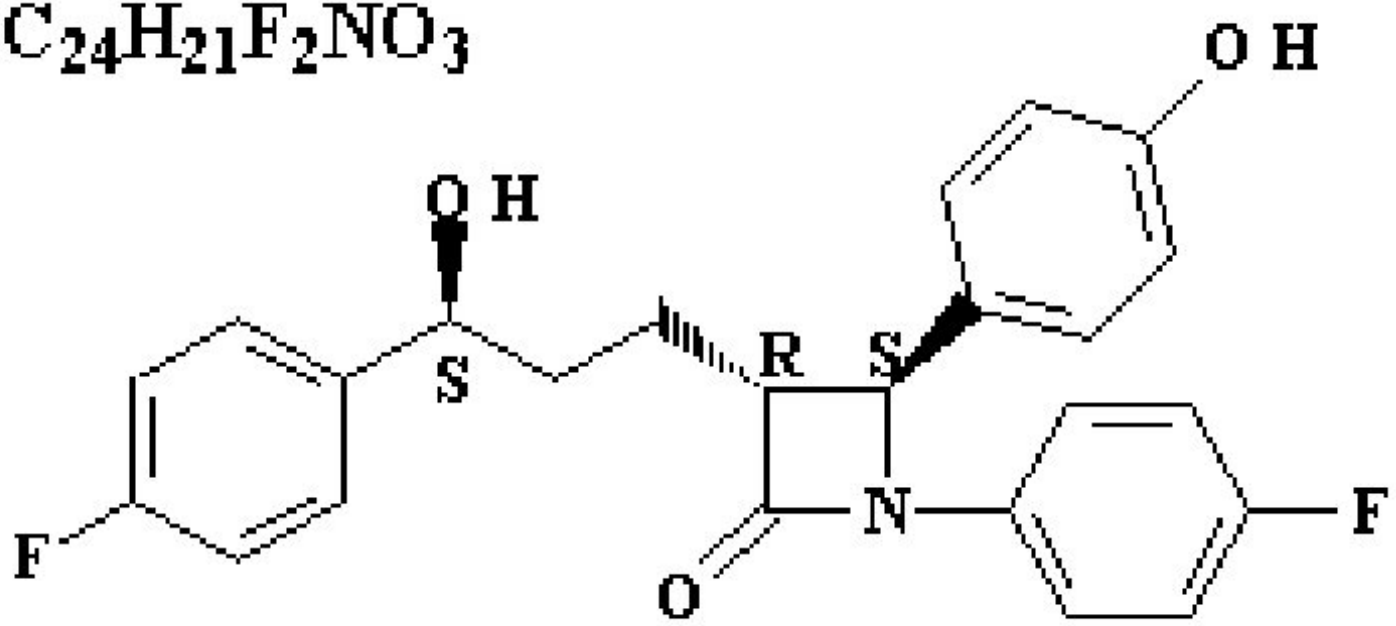
LDL RECEPTORS AND CHOLESTEROL



EZETIMIB

- Relativno novo zdravilo (ZDA – 2002, SLO – 2005)
- Selektivna inhibicija absorpcije holesterola in fitosterolov v črevesu.
- Ezetimib se veže v luminalni membrani epitelnih celic (brush border) v črevesu.
- Molekularna tarča ezetimiba je prenašalec za sterole (sterol transporter).

$C_{24}H_{21}F_2NO_3$



Ezetimib - učinki

- Znižanje LDL – mehanizem podoben kot pri smolah
- Povečan nivo HDL

Farmakokinetika

- Biološka uporabnost variabilna
- Razpolovni čas okrog 22 ur
- Metabolizem: ezetimib-glukuronid

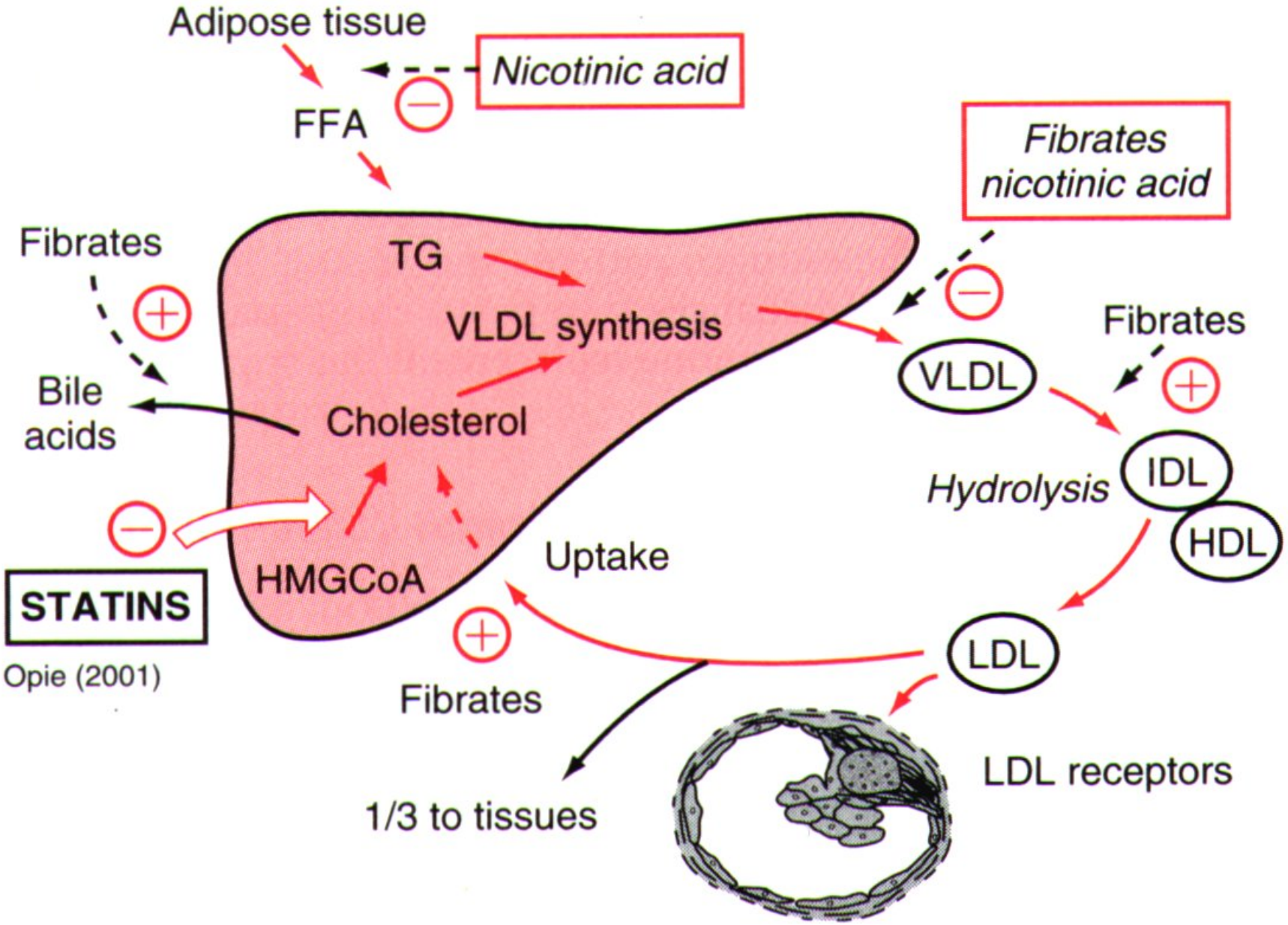
Ezetimib – stranski učinki

- Relativno skromni
- Bolečine v trebuhu
- Mialgija (pogostejša ob kombinaciji s statini)

Derivati fibrične kisline (fibrati)

- Delovanje preko PPARs (peroxisome proliferator activated receptors) (jedrni receptorji – regulacija transkripcije različnih genov – LPL, ApoA, …)
- ⇓ VLDL
- ⇑ HDL
- ⇑ aktivnost LPL ⇒ ⇓ VLDL ⇒ ⇓ IDL
- ⇓ sintezo ApoC-III (ki je inhibitor LPL)
- ⇓ sintezo VLDL v jetrih
- ⇓ aktivnost in agregacijo trombocitov
- ⇓ CRP
- Fenofibrat ⇒ urikozurično delovanje

HEPATIC EXPORT AND IMPORT OF LIPIDS

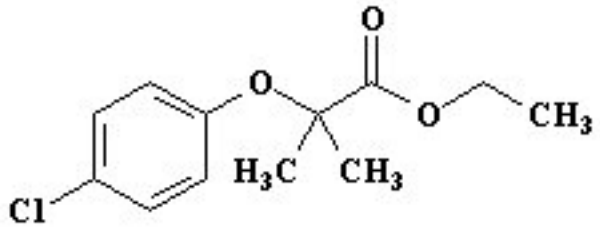


Opie (2001)

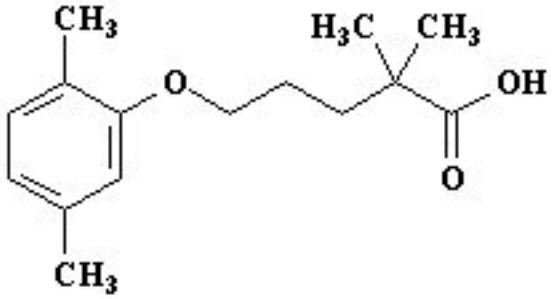
Predstavniki:

- Klofibrat
- Gemfibrozil
- Fenofibrat
- Bezafibrat

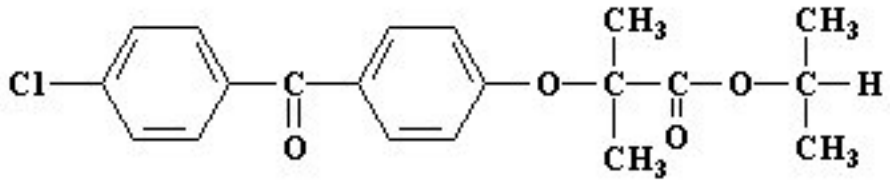
Clofibrate



Gemfibrozil



Fenofibrat



Farmakoinetika:

- Hitra in skoraj popolna absorpcija
- $t_{1/2}$ različen pri različnih predstavnikih:
  - gemfibrozil 1 h
  - fenofibrat 20 h
- Izločajo se kot glukuronidi

Stranski učinki:

- Od strani GIT
- Redko:
  - alergični pojavi
  - spremenjeni jetrni encimi
- Miozitis
- Nagnjenost k holelitiazi
- Interakcije:
  - antikoagulansi (⇑ učinek)
  - inhibitorji HMG-CoA reduktaze (miozitis)

Nikotinska kislina (niacin)

- Vitamin
- ⇓ produkcija VLDL
  - ⇓ sinteza TG
  - ⇓ dotok FFA do jeter
- ⇑ HDL (? mehanizem)

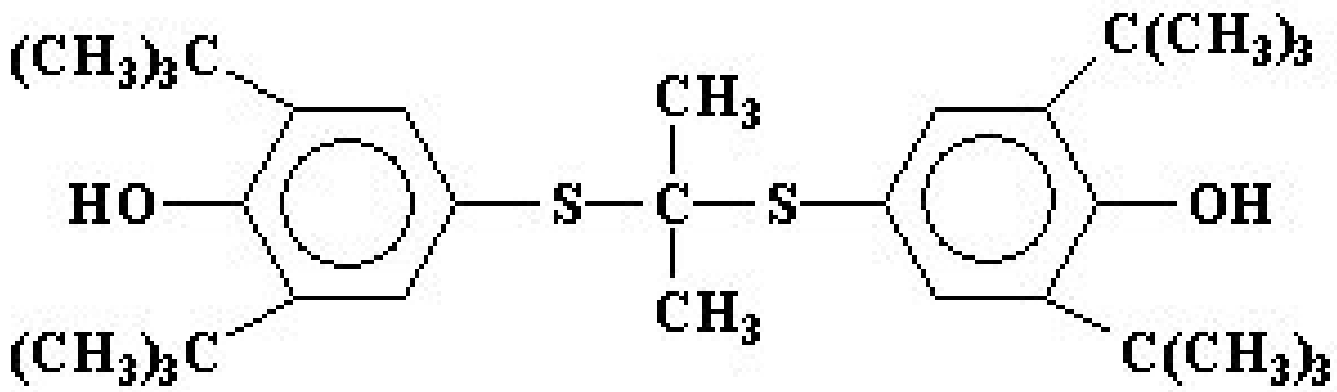
Farmakokinetika in stranski učinki

- Dobra absorpcija
- Kratek $t_{1/2}$ ($\cong$ 1 ura)

- Naval krvi v zgornji del telesa (flushing)
  - udeleženost PG (NSAID zmanjšajo ta učinek)
- Pruritus (povezan s prejšnjim)
- Motena funkcija jeter
  - $\Uparrow$ transaminaze
- $\Downarrow$ toleranca glukoze
- Palpitacije (pogosto spremljajo navale krvi)

Probukol

- Antioksidant
- Zelo lipofilna snov



Učinki probukola

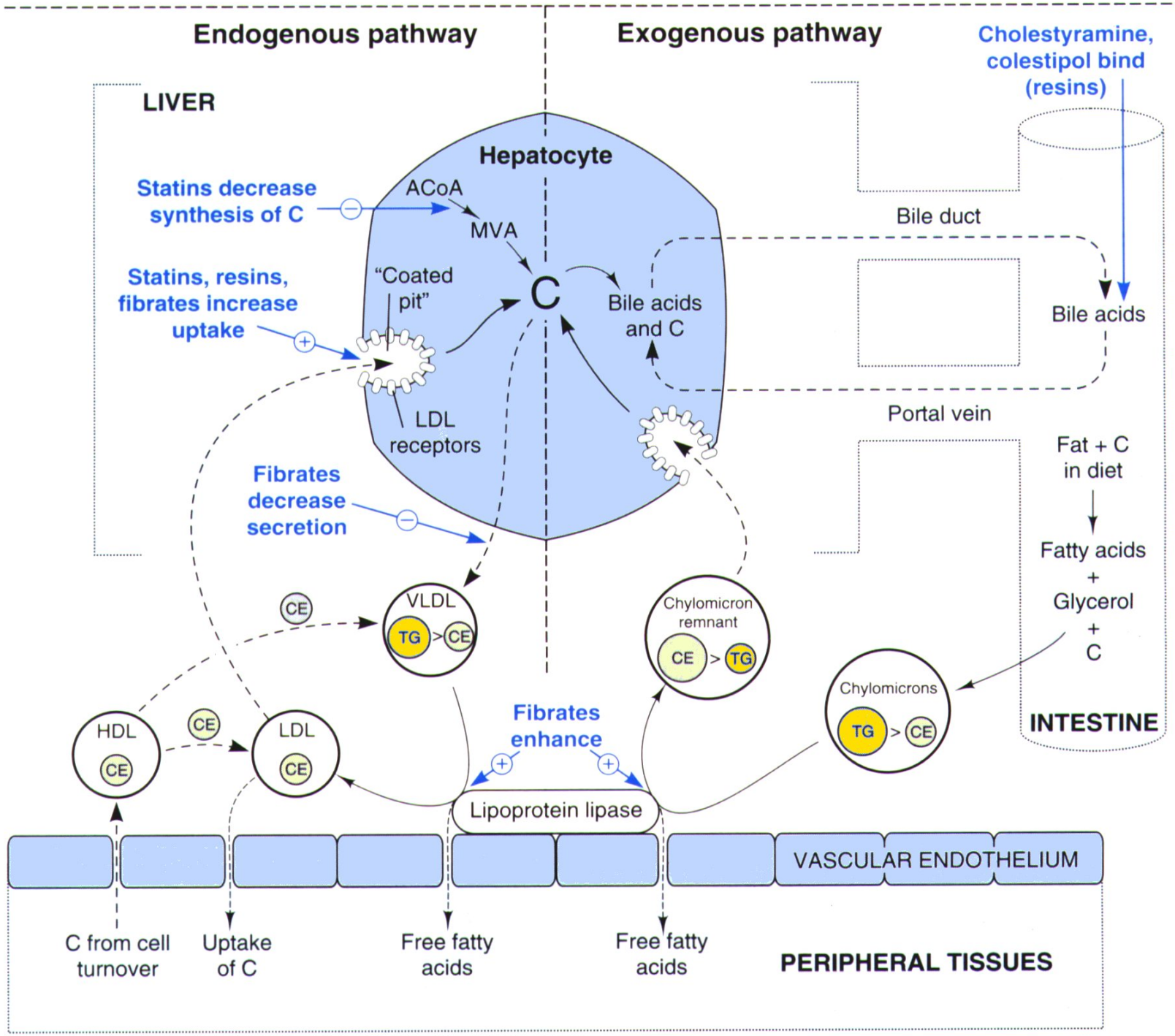
- ⇓ LDL (spremenjena sestava)
- Učinkovit tudi pri homozigotni družinski hiperholesterolemiji
- ⇓ HDL (mehanizem ni jasen)
- ⇑ CETP
- ⇓ Apo A-I
- Inhibicija transporta holesterola skozi črevesno steno
- Motenje sinteze holesterola v zelo začetni stopnji

Farmakokinetika

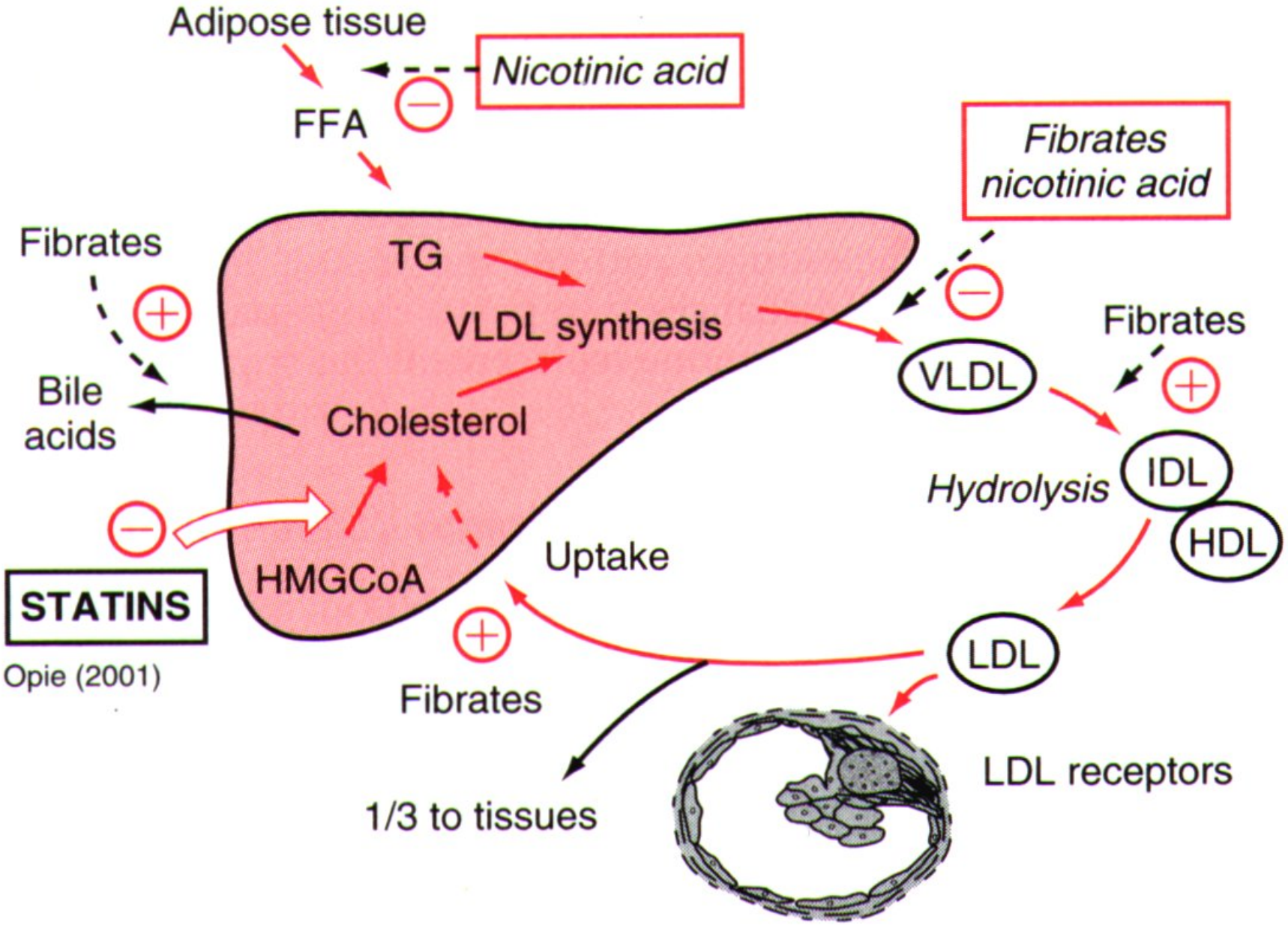
- Slaba in nepredvidljiva absorpcija (boljša ob jemanju s hrano)
- Kopičenje v maščevju
  - vrh koncentracije v plazmi dosežen po 4 mesecih
- Dokazljiv v plazmi še 6 mesecev po prenehanju jemanja

Stranski učinki

- GIT (diareja , navzea)
- Glavobol, omotičnost
- Podaljšanje Q-T intervala
  - kontraindiciran pri uporabi antiaritmikov, TCA, fenotiazinov
- Kontraindiciran pri bolnikih, ki niso na dieti z malo maščobe



HEPATIC EXPORT AND IMPORT OF LIPIDS



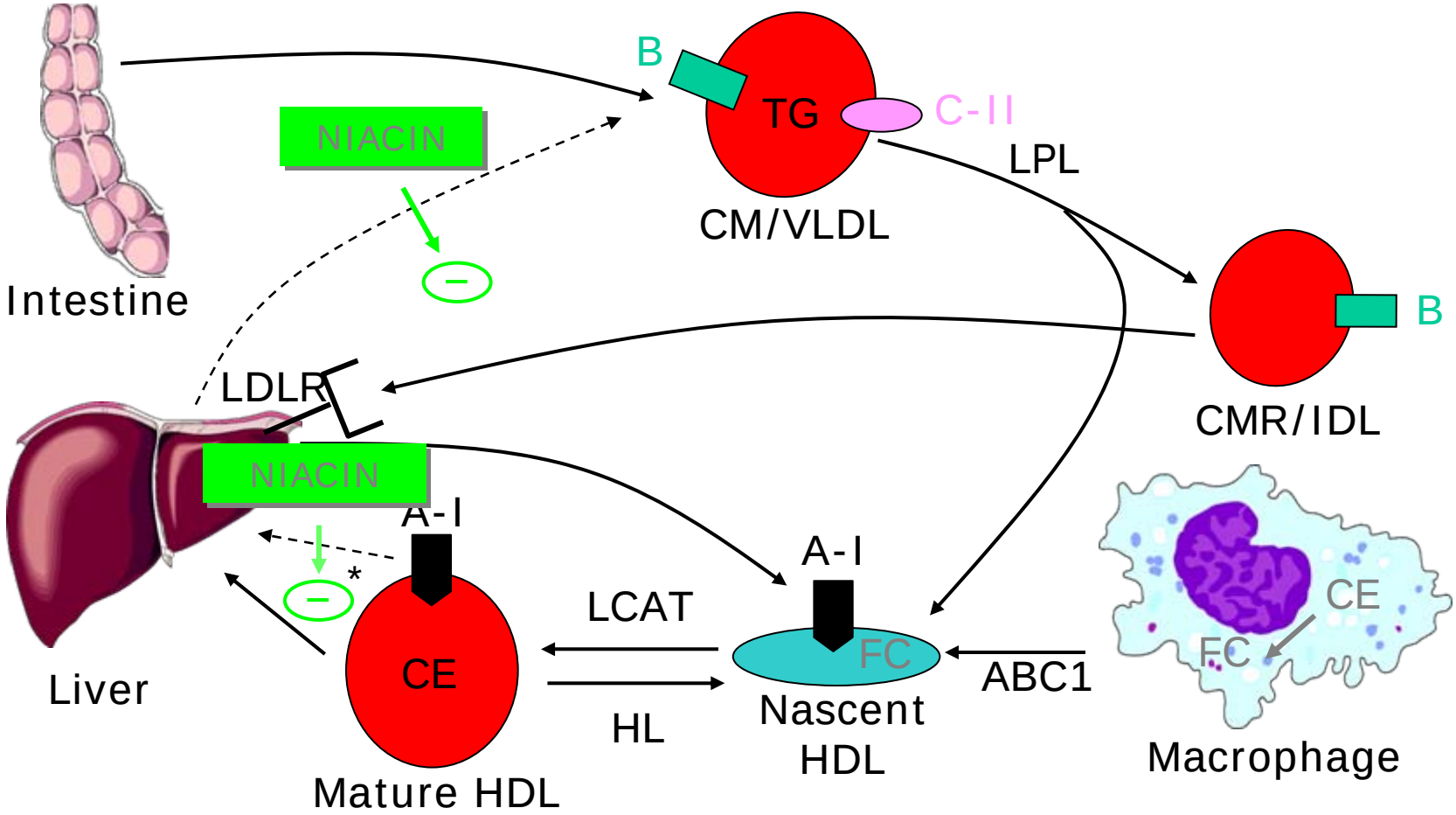
Opie (2001)

Effects of Lipid-Modifying Drugs on HDL-C Levels

Niacin	↑ 15–35%
Fibrates	↑ 10–15%
Estrogens	↑ 10–15%
Statins	↑ 5–10%

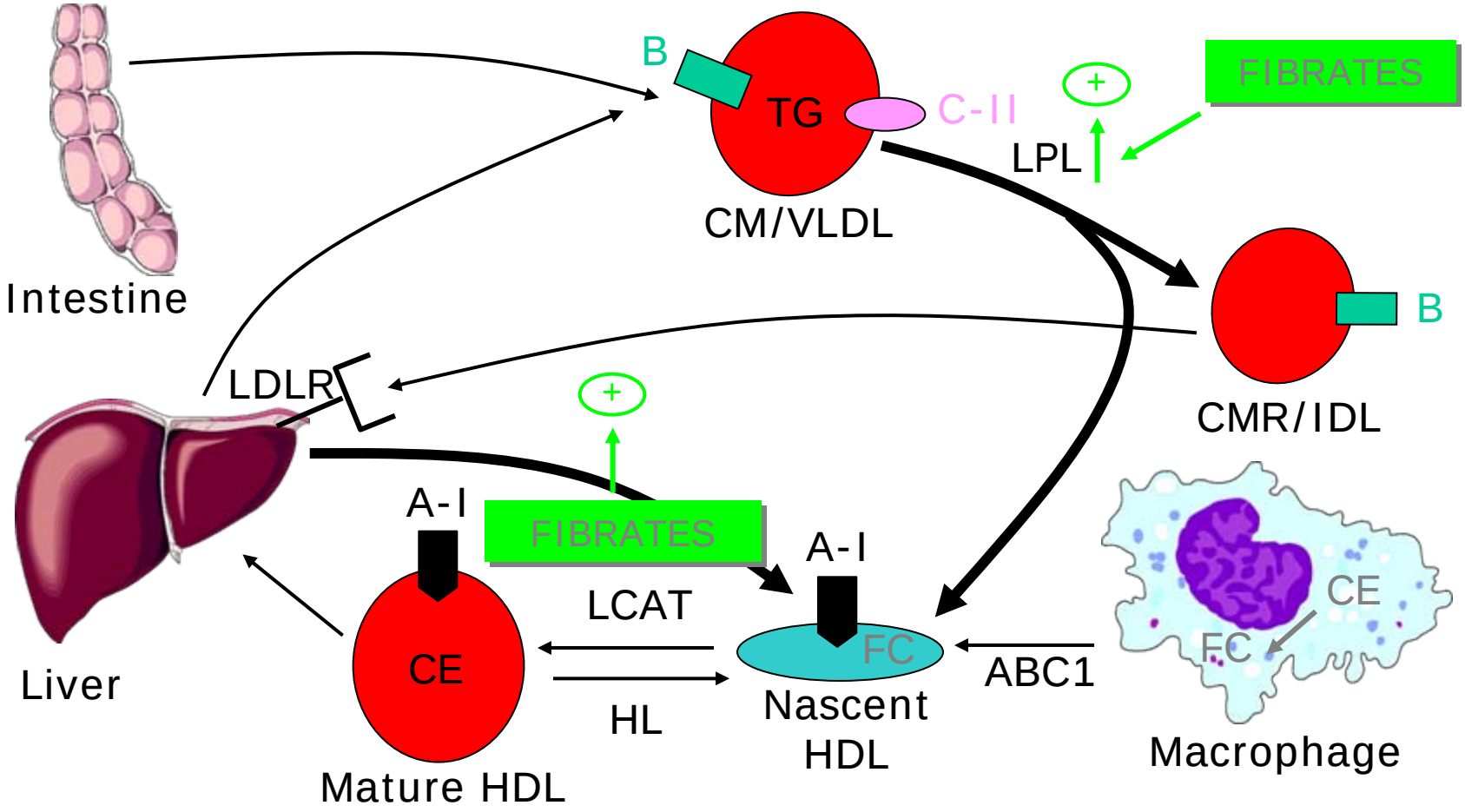
Belalcazar LM et al. *Progr Cardiovasc Dis* 1998;41:151–174

Drug Effects on HDL: Niacin

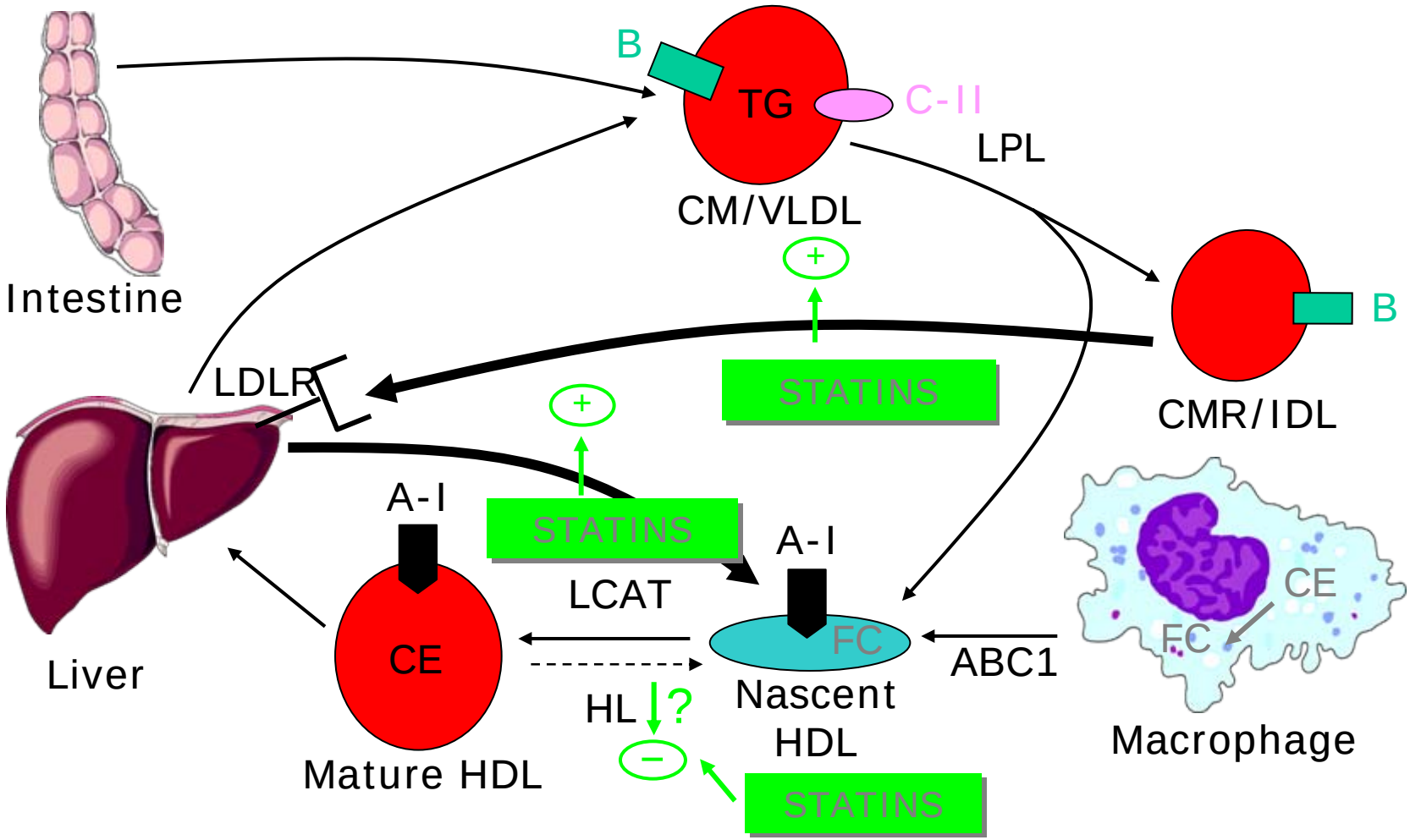


*Inhibits uptake of apoA-I but not CE

Drug Effects on HDL: Fibrates



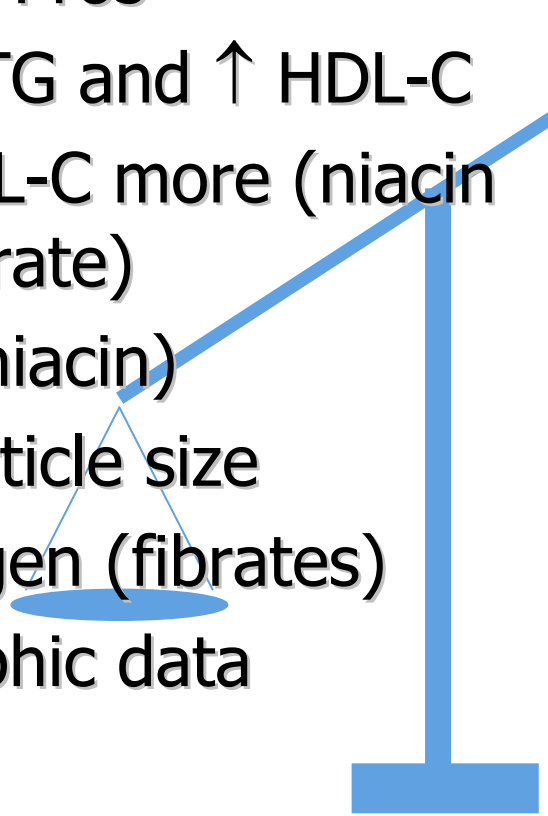
Drug Effects on HDL: Statins



Combination Therapy
Adding Niacin or a Fibrate to a Statin

Pros

- Better ↓ TG and ↑ HDL-C
- May ↓ LDL-C more (niacin or fenofibrate)
- ↓ Lp(a) (niacin)
- ↑ LDL particle size
- ↓ Fibrinogen (fibrates)
- Angiographic data



Cons

- Increased cost and complexity
- Increased myositis risk
- Increased hepatitis risk (niacin)
- Potential for other drug interactions
- Lack of outcome data

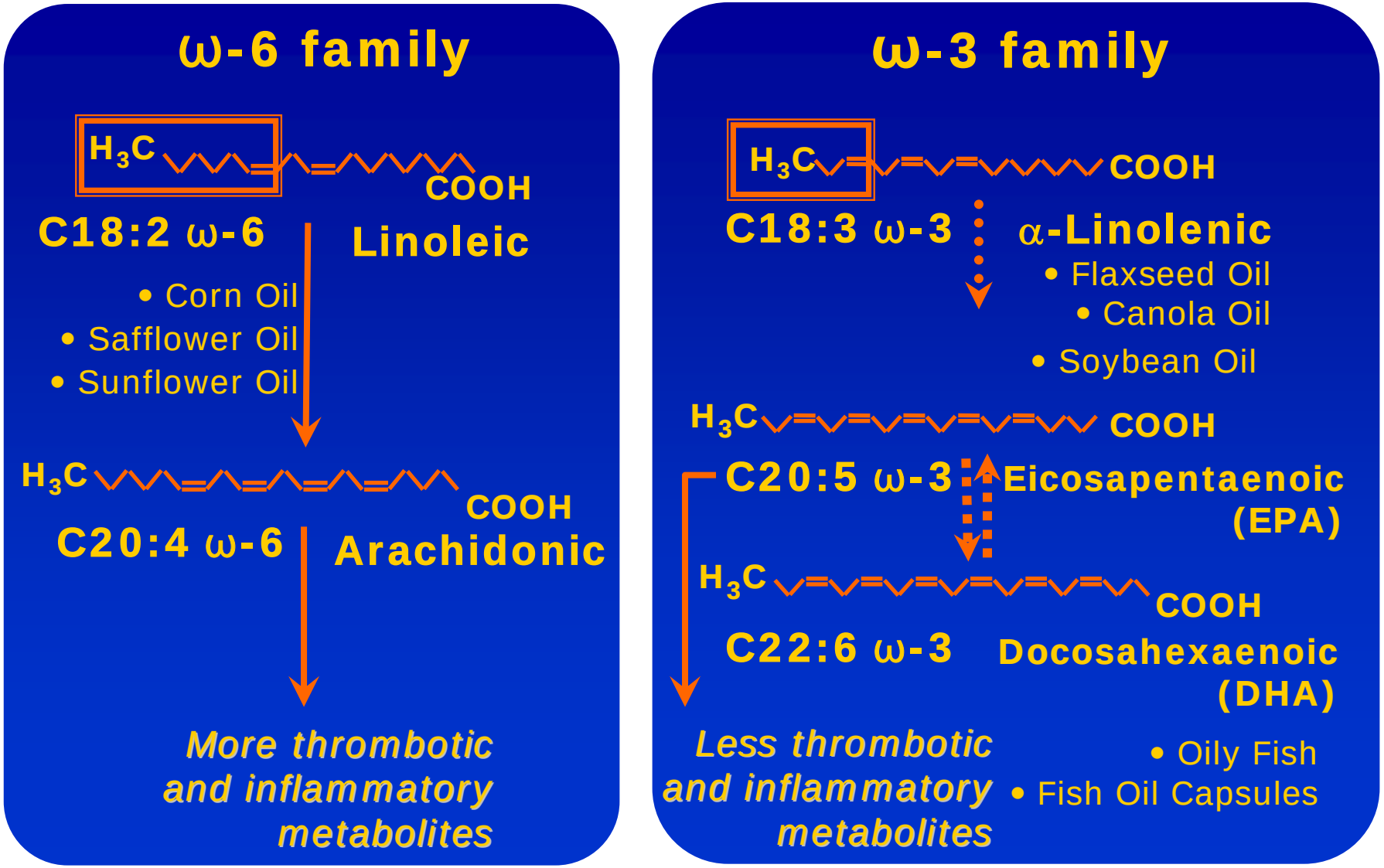
Drugi faktorji z vplivom na lipide oz. na tveganje za CVI

- Ribje olje
- Homocistein
- Antioksidanti
  - Vitamin E
  - Vitamin C
  - Koencim Q10
  - Česen (alicin)
  - Karotenoidi
    - Beta karoten
    - Licopen

Ribje olje

- Vsebuje ω-3 trigliceride
- $\Downarrow$ TG
- $\Uparrow$ holesterol (LDL)
- Mehanizem ni znan
- Zmanjša obolevnost za koronarno boleznijo
  - Vpliv na hemostazo:
    - eikozipentaenoična kislina $\Rightarrow$ zamenja arahidonsko kislino $\Rightarrow$ manj učinkoviti eikozanoidi (TXA_2)

Essential Fatty Acid Families



Zdravila v fazi preizkušanja

- Inhibitorji acil-koencim A holesterol aciltransferaze (ACAT) – paktimib
- Preprečevanje kopičenja holesterola v makrofagih
- Inhibicija nastajanja penastih celic
- Živalski modeli in vivo – zmanjšanje volumna of intravaskularnega ateroma
- Klinične študije – ni bilo pričakovanega učinka

Dodatni viri

- http://www.lipidsonline.org/
- http://www.heartpoint.com/