Dyslipidemia

(Med-341)

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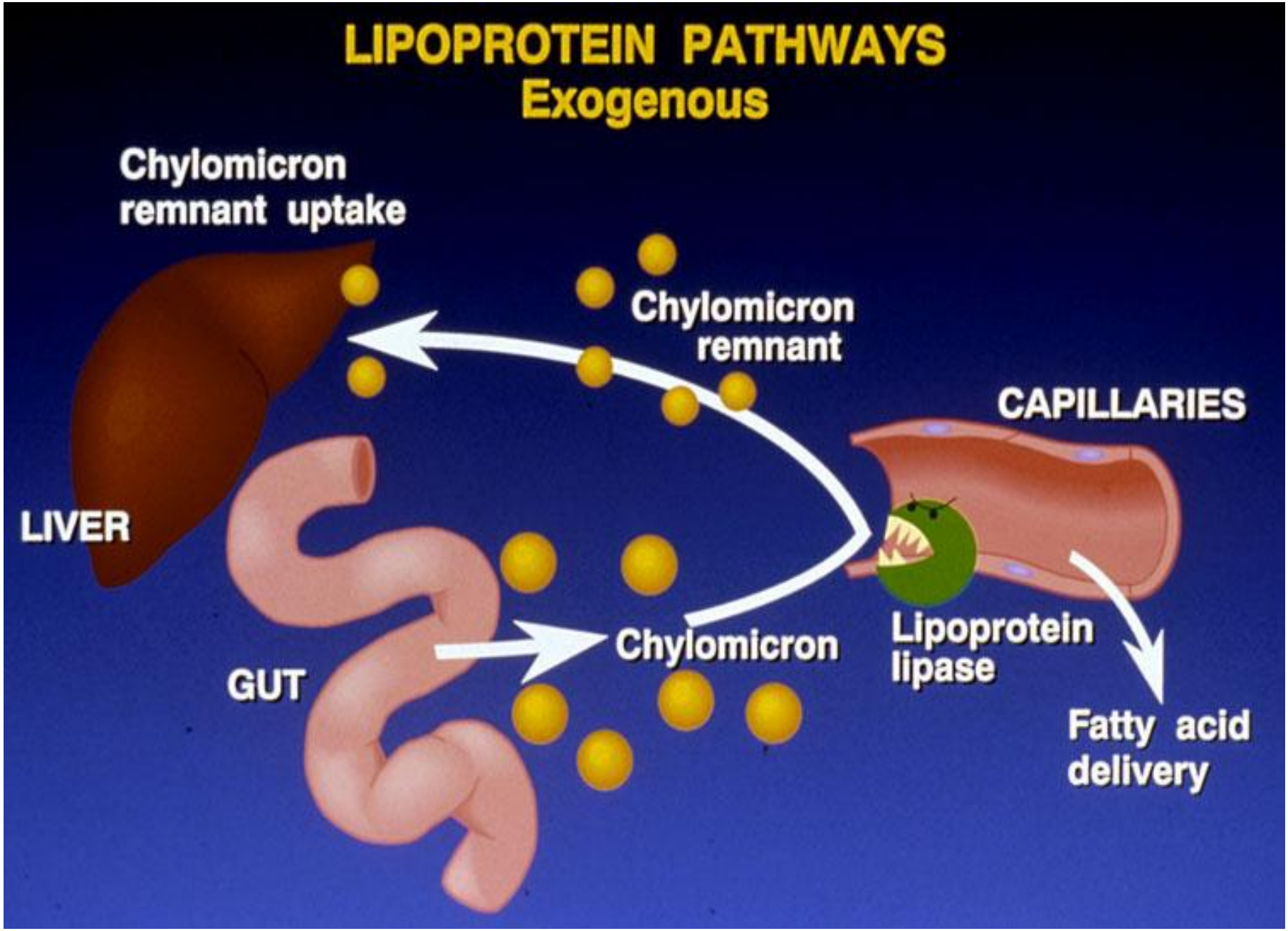
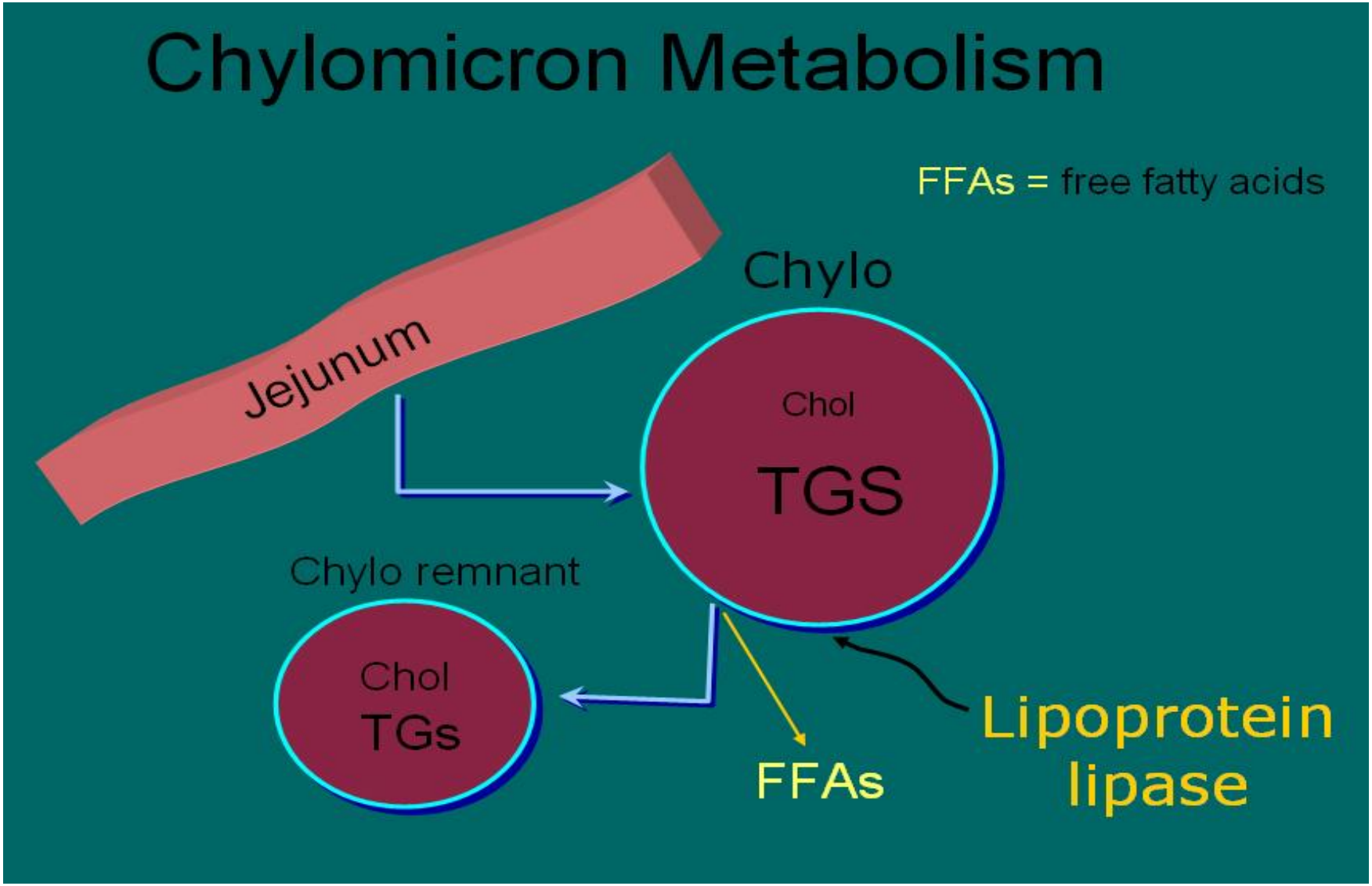
The story of lipids

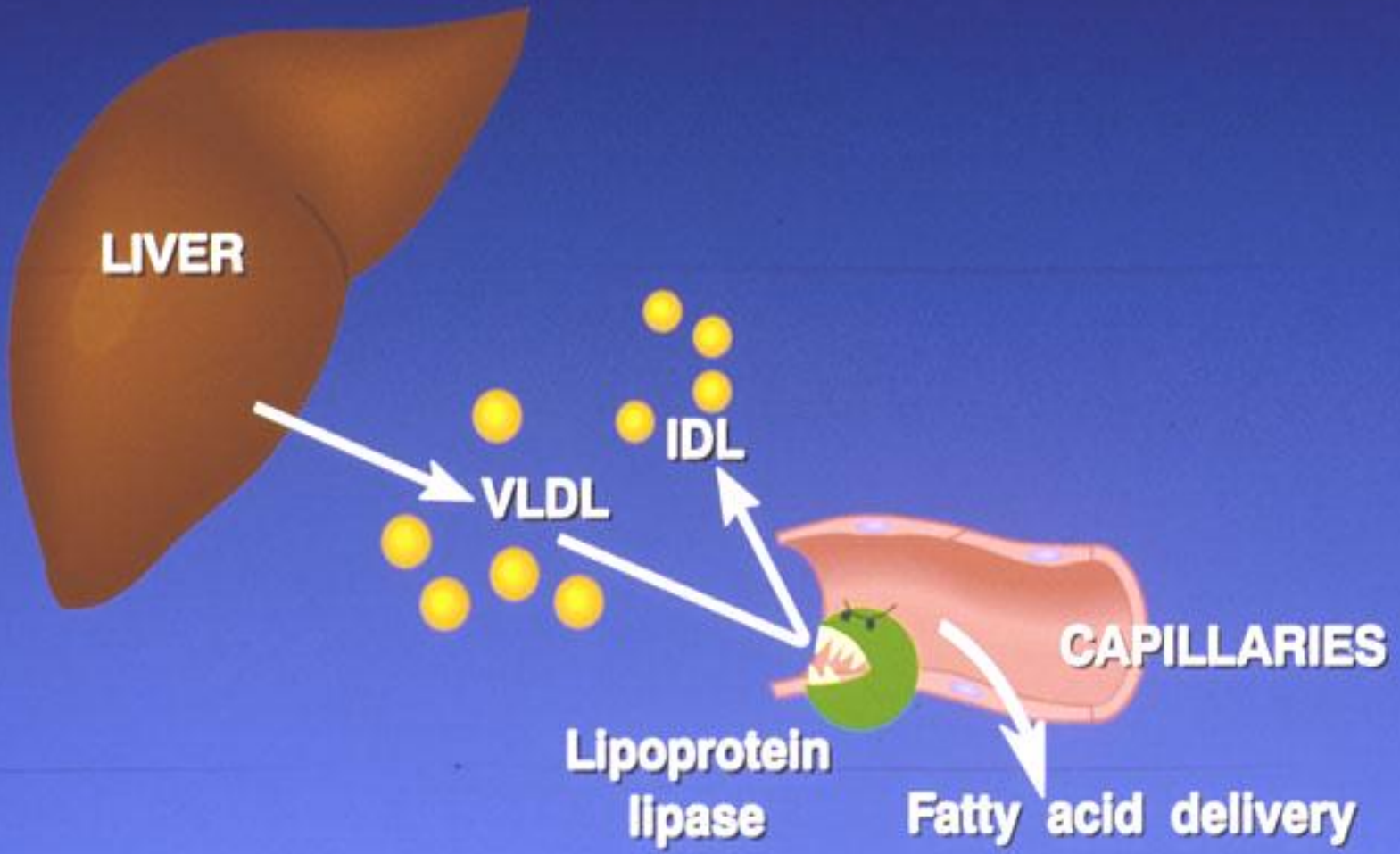
- Chylomicrons transport fats from the intestinal mucosa to the liver
- In the liver, VLDL released to blood stream to form LDL, IDL and LDL.
- LDL then carries fat and cholesterol to the body's cells. LDL receptors in Liver take the LDL to Liver.
- High-density lipoproteins (HDL) released from intestine and liver and carry fat and cholesterol from blood vessels to the liver.


LIPOPROTEIN PATHWAYS
Exogenous
Chylomicron
remnant uptake
Chylomicron
remnant
CAPILLARIES
LIVER
GUT
Chylomicron
Lipoprotein
lipase
Fatty acid
delivery

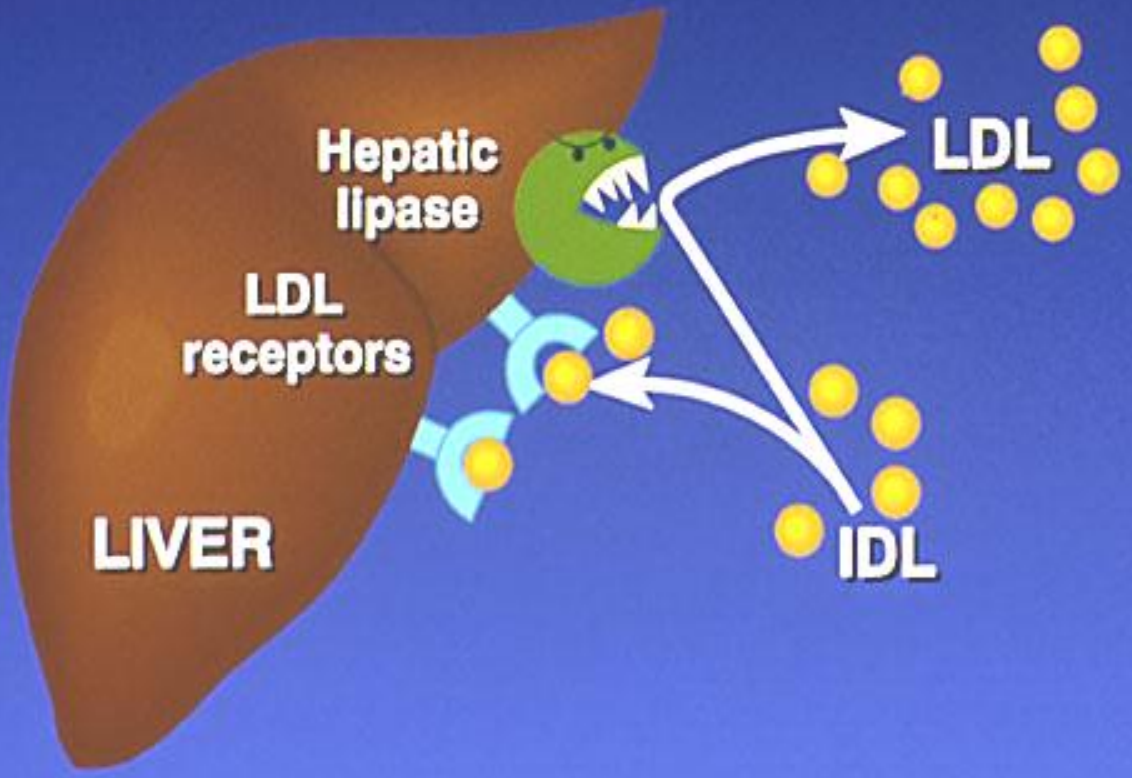
Chylomicron Metabolism



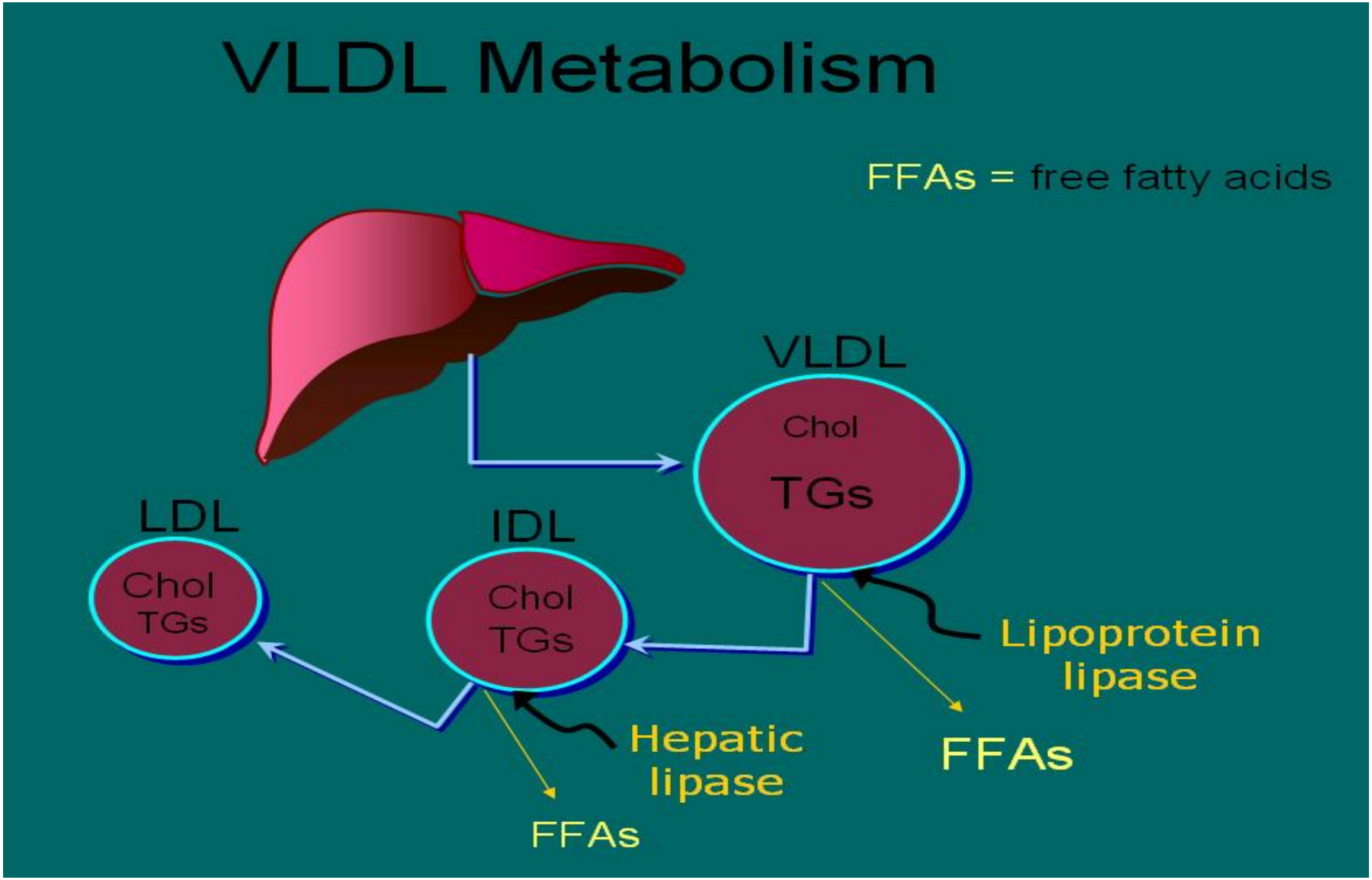
LIPOPROTEIN PATHWAYS
Endogenous
(VLDL-IDL)

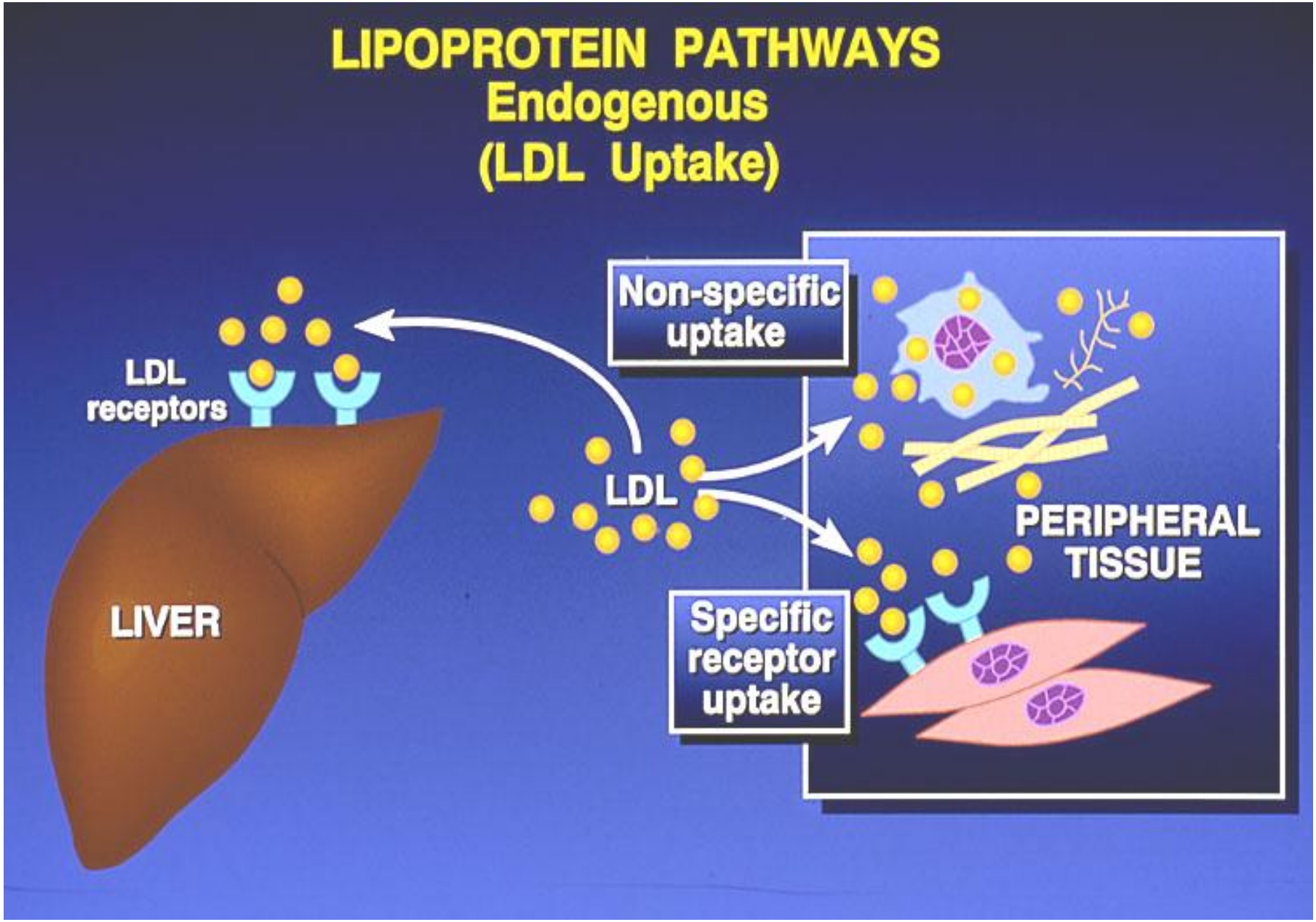


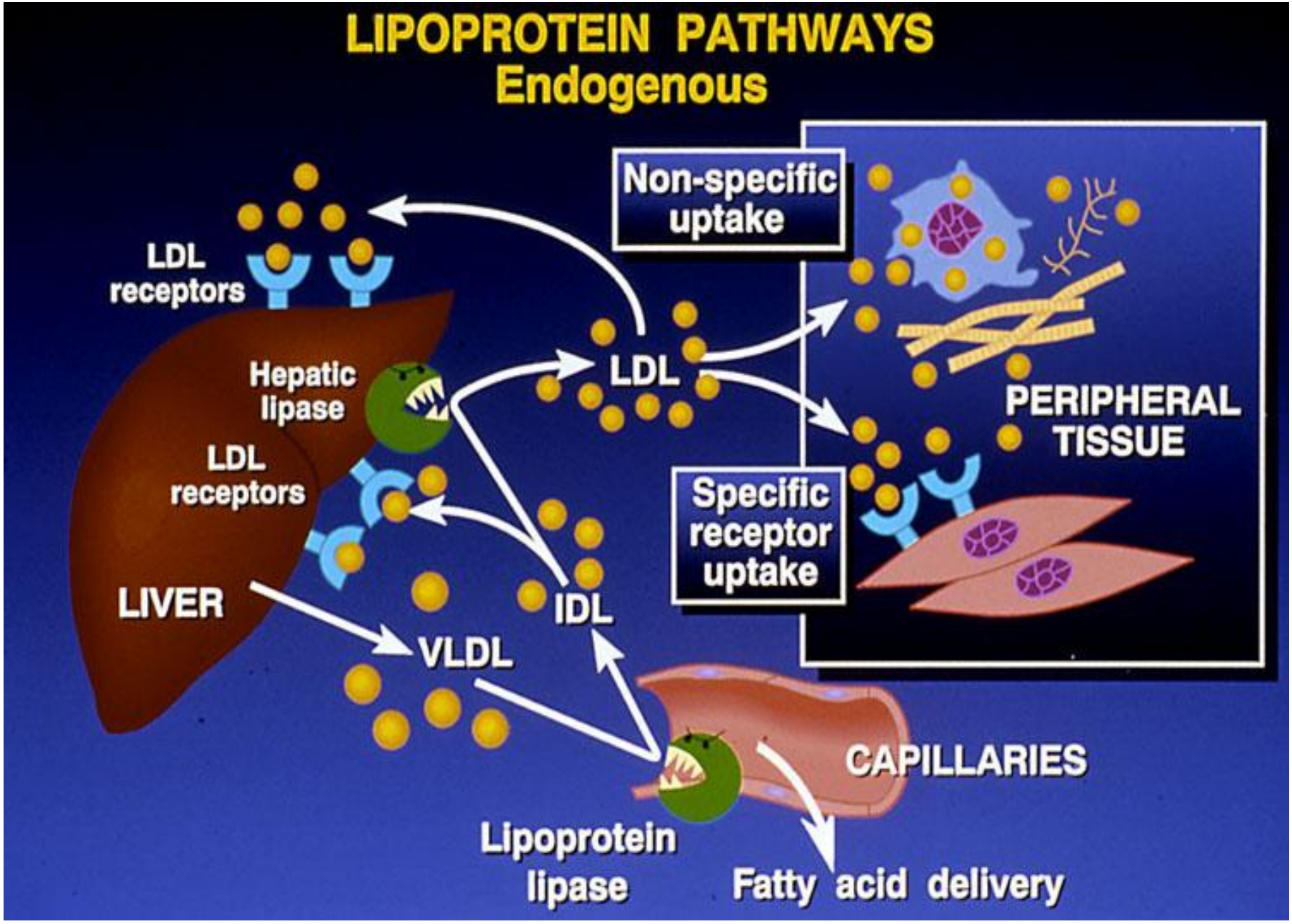
LIPOPROTEIN PATHWAYS
Endogenous
(IDL-LDL)



VLDL Metabolism




LIPOPROTEIN PATHWAYS
Endogenous
(LDL Uptake)
Non-specific uptake
LDL receptors
LDL
PERIPHERAL TISSUE
LIVER
Specific receptor uptake


LIPOPROTEIN PATHWAYS
Endogenous
Non-specific uptake
LDL receptors
Hepatic lipase
LDL receptors
LIVER
LDL
PERIPHERAL TISSUE
Specific receptor uptake
IDL
VLDL
CAPILLARIES
Lipoprotein lipase
Fatty acid delivery

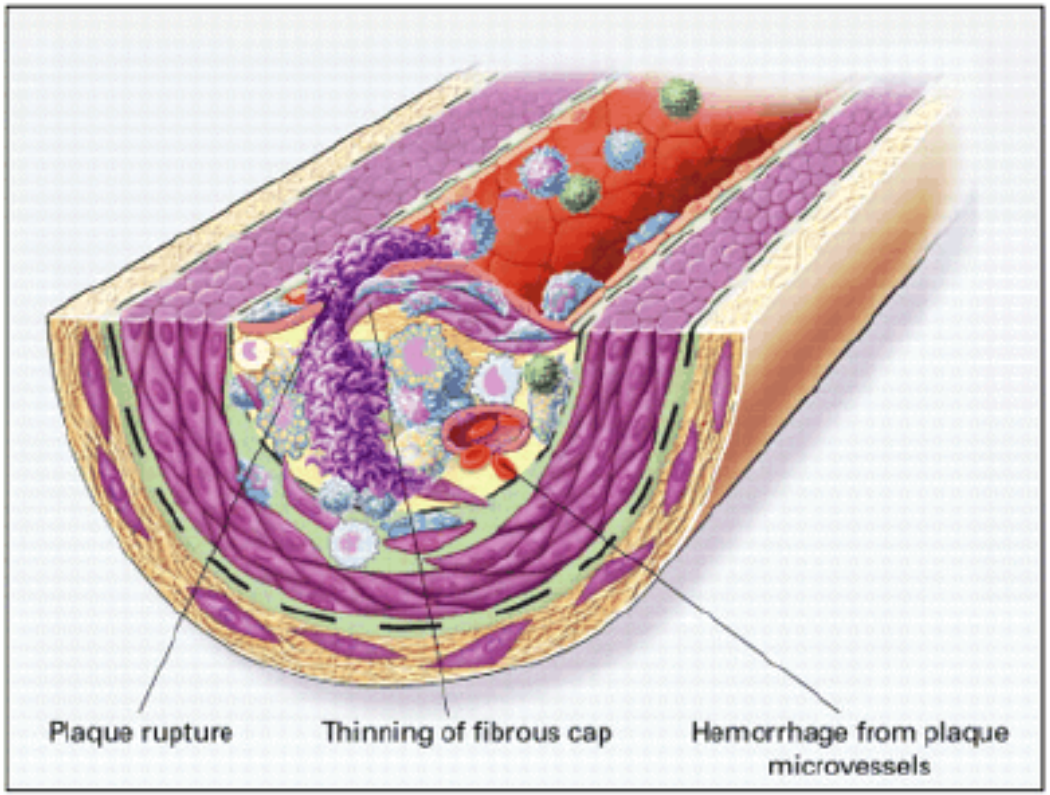
The story of lipids (cont.)

- When oxidized LDL cholesterol gets high, atheroma formation in the walls of arteries occurs, which causes atherosclerosis.

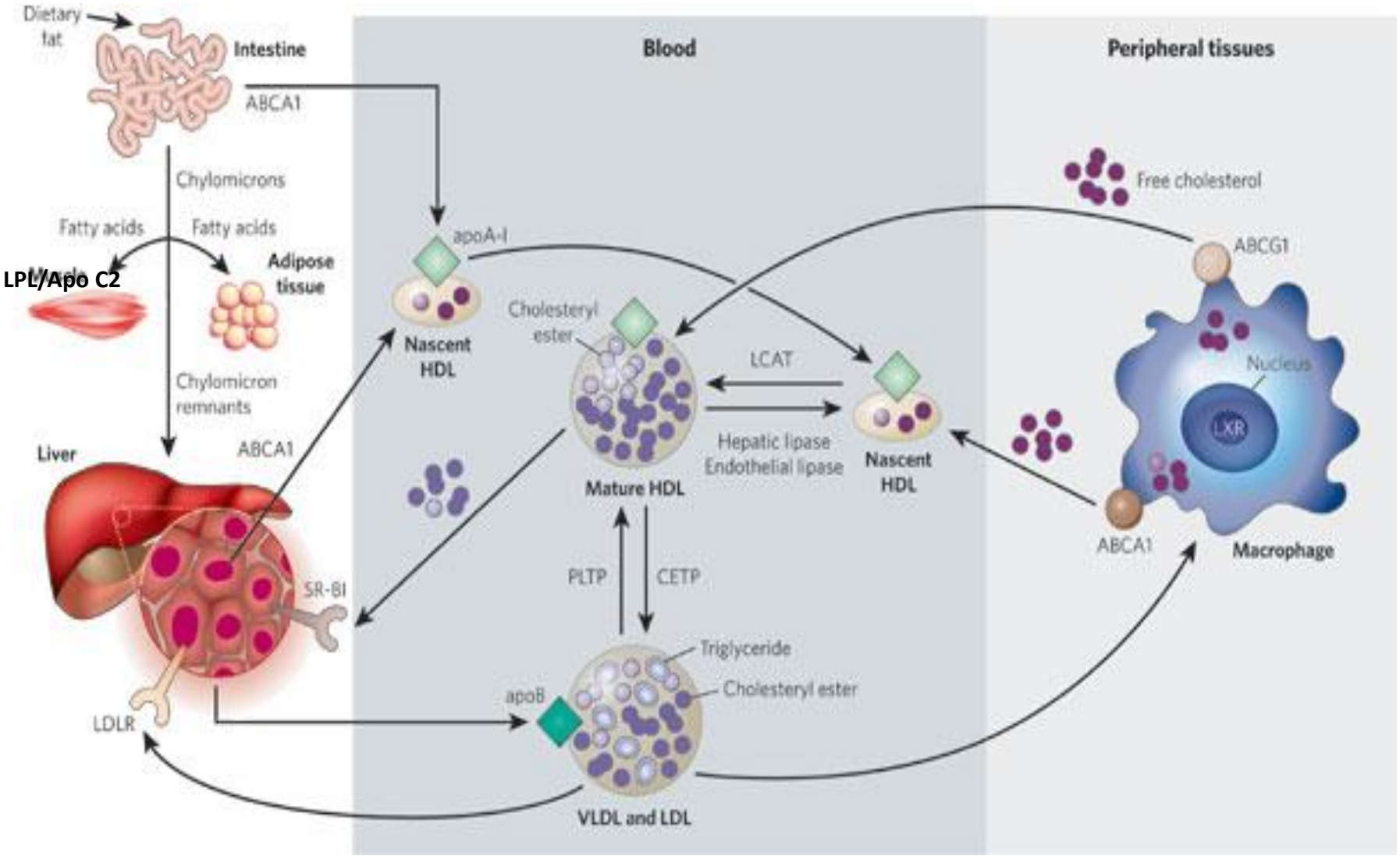
- HDL cholesterol is able to go and remove cholesterol from the atheroma.

- Atherogenic cholesterol → LDL, VLDL, IDL

Atherosclerosis



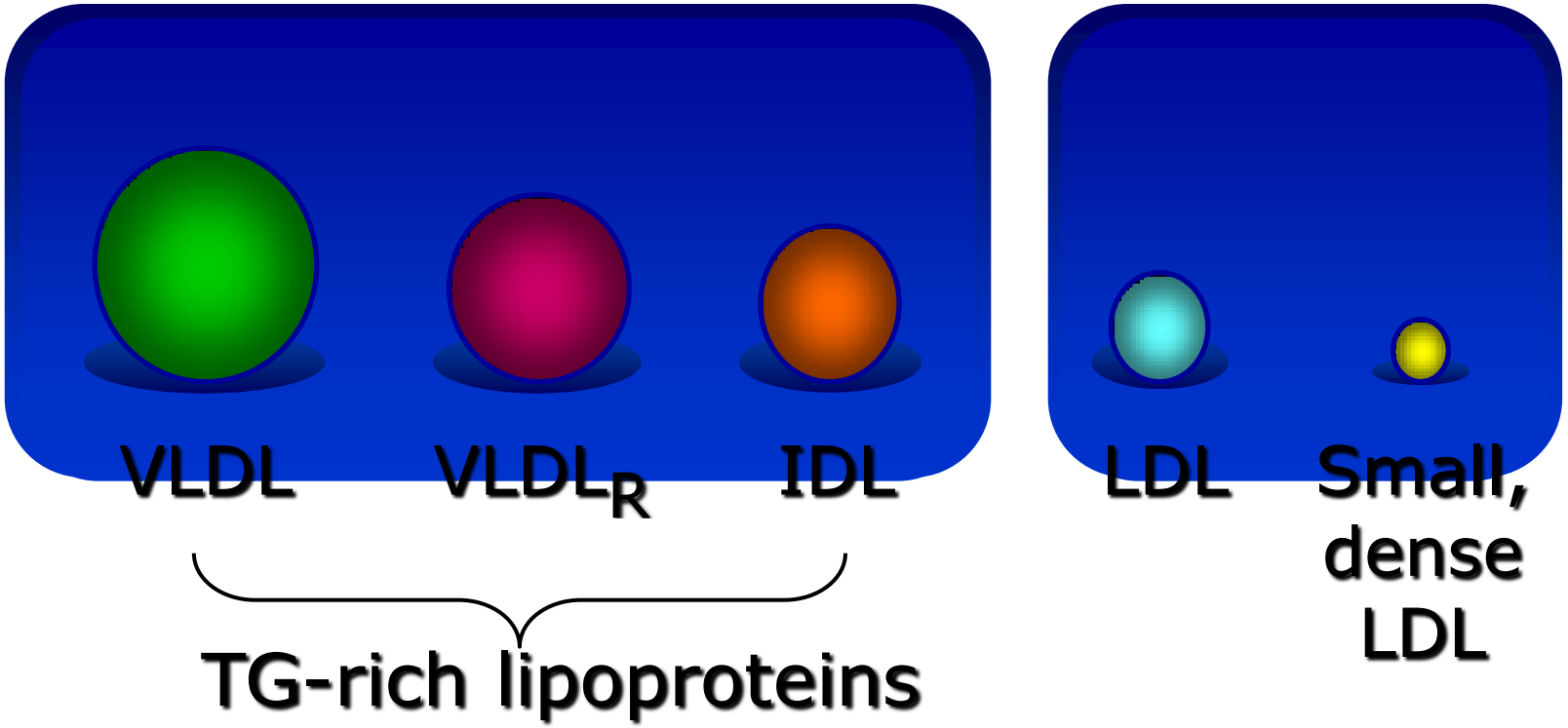
Lipid Transport



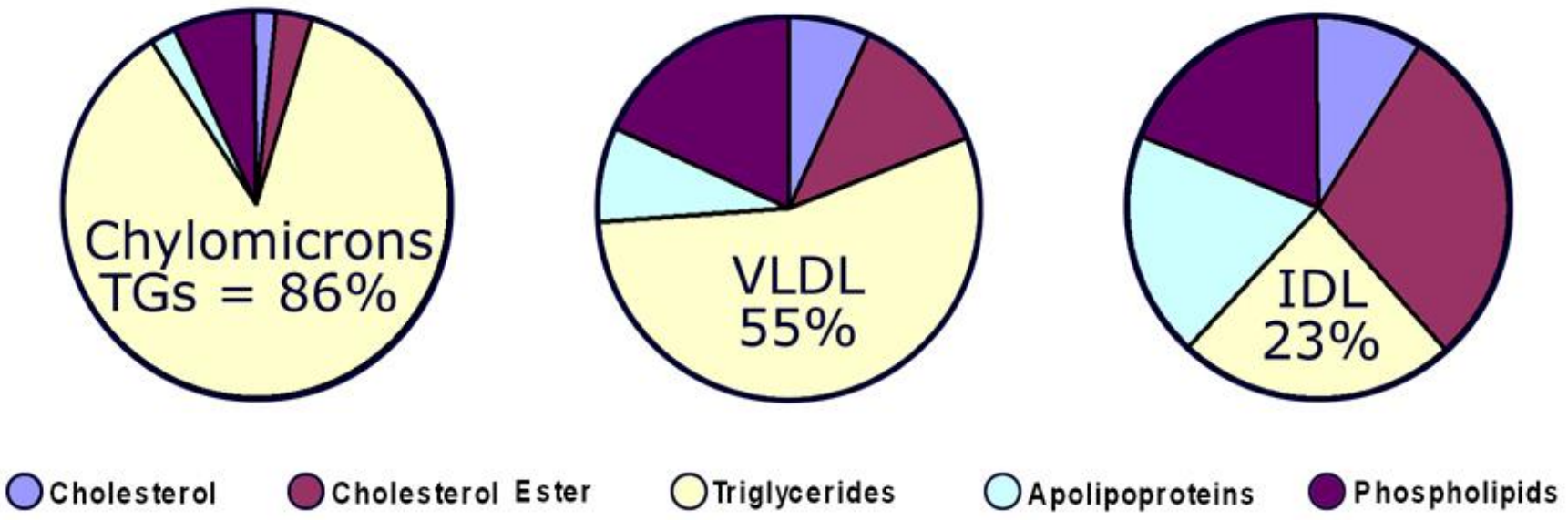
Rader DJ, Daugherty, A Nature 2008; 451:904-913

Atherogenic Particles

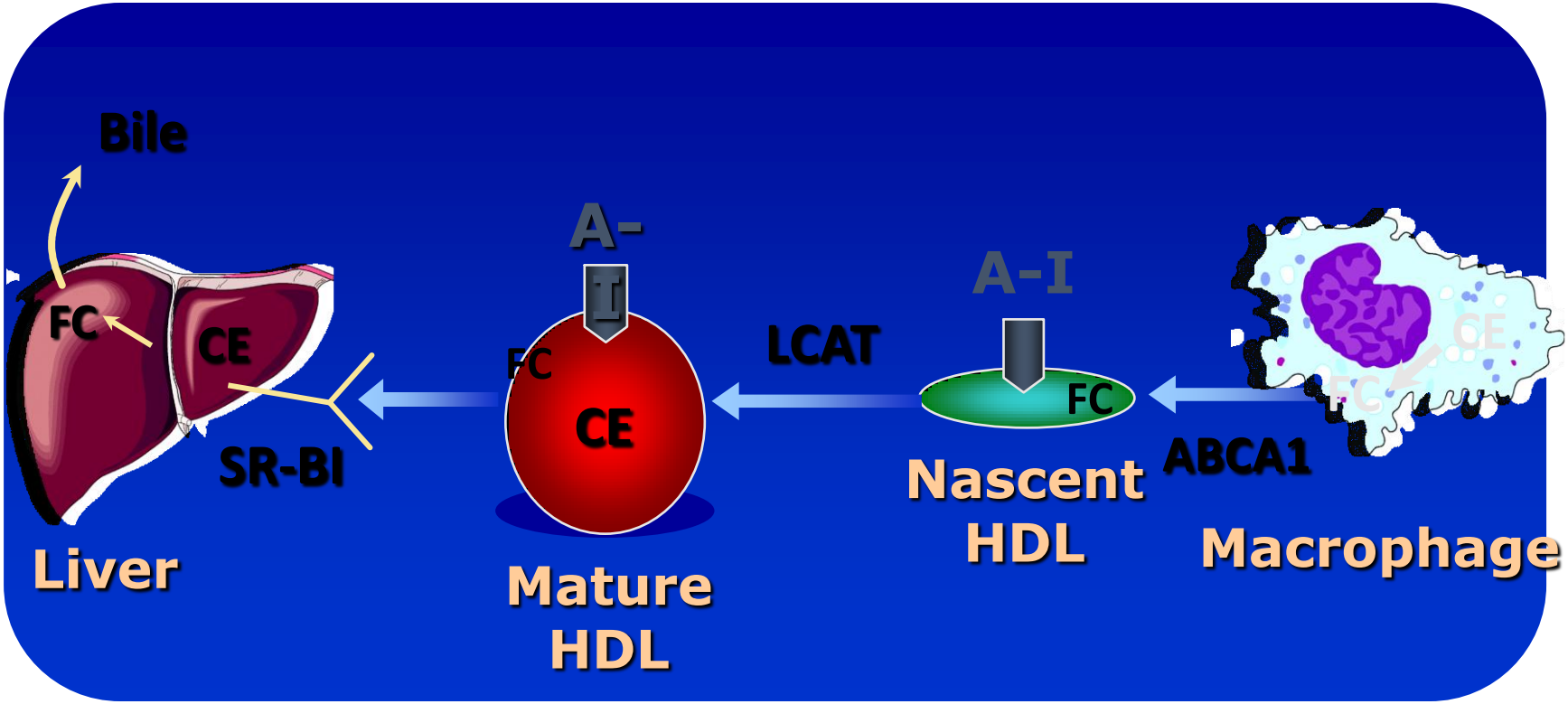
MEASUREMENTS:



Composition of Triglyceride-Rich Lipoproteins (% dry mass)



HDL and Reverse Cholesterol Transport



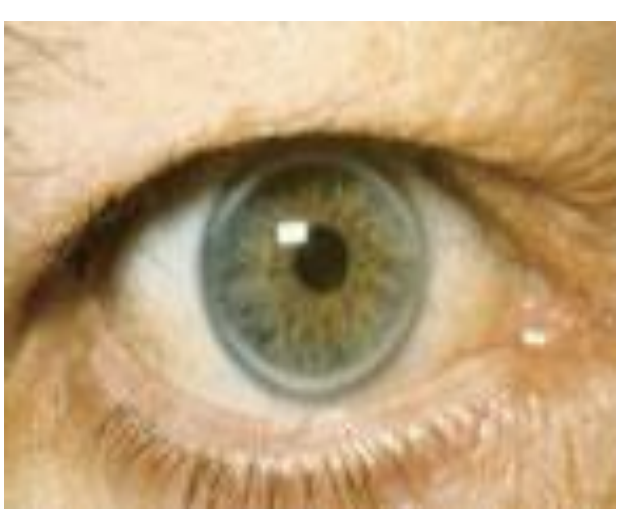
Plasma lipoproteins

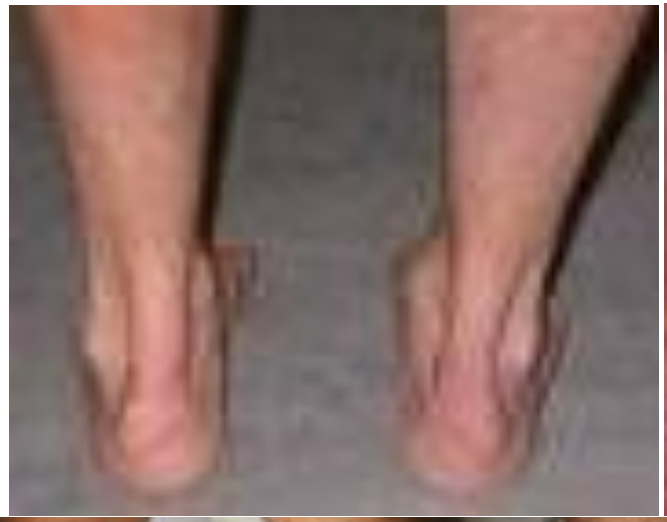
Type	Source	Major lipid	Apoproteins	ELFO	Athero-genicity
Chylomicrons	Gut	Dietary TGs	A-I, B-48, C-I, C-III, E	no mobility	– (pancreatitis)
VLDL	Liver	Endogenous TGs	B-100, E, C-II, C-III,	Pre-β	+
IDL	VLDL remnant	Ch esters, TGs	B-100, C-III, E	Slow pre- β	+
LDL	VLDL, IDL	Ch esters	B-100	β	+++
HDL	Gut, liver	Ch esters, PLs	A-I, A-II, C-II, C-III, D, E	α	anti-atherogenic

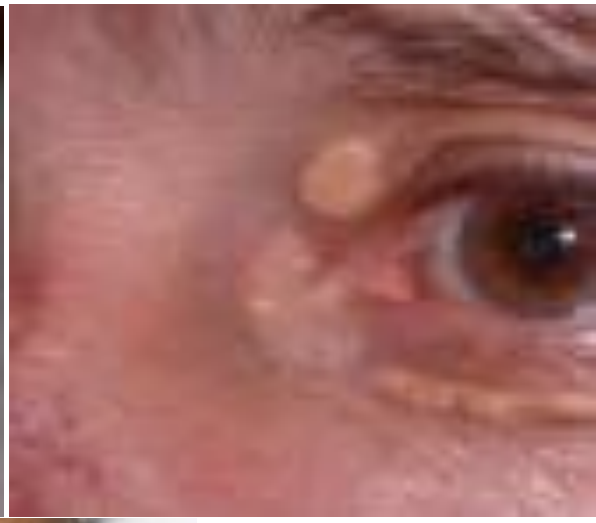
Hereditary Causes of Hyperlipidemia

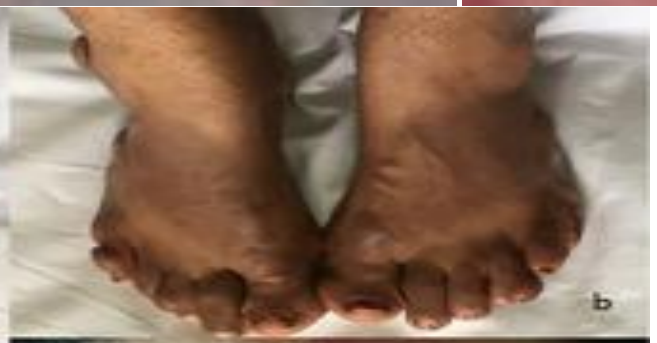
- Familial Hypercholesterolemia
  - Codominant genetic disorder, coccurs in heterozygous form
  - Occurs in 1 in 500 individuals
  - Mutation in LDL receptor, resulting in elevated levels of LDL at birth and throughout life
  - High risk for atherosclerosis, tendon xanthomas (75% of patients), tuberous xanthomas and xanthelasmas of eyes.
- Familial Combined Hyperlipidemia
  - Autosomal dominant
  - Increased secretions of VLDLs
- Dysbetalipoproteinemia
  - Affects 1 in 10,000
  - Results in apo E2, a binding-defective form of apoE (which usually plays important role in catabolism of chylomicron and VLDL)
  - Increased risk for atherosclerosis, peripheral vascular disease
  - Tuberous xanthomas, striae palmaris

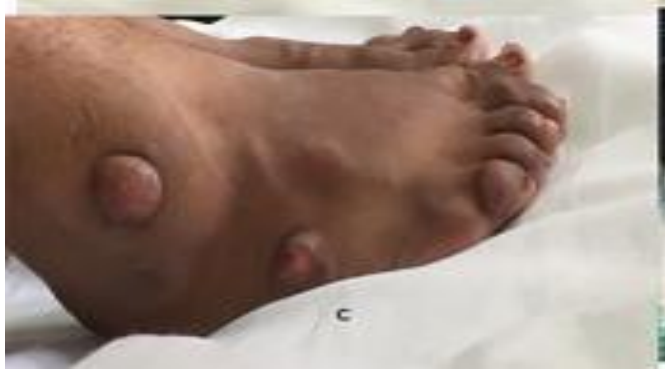
Physical findings











Fredrickson classification of hyperlipidemias

Phenotype	Lipoprotein(s) elevated	Plasma cholesterol	Plasma TGs	Athero-genicity	Rel. freq.	Treatment
I	Chylomicrons	Norm. to ↑	↑↑↑↑	– pancreatitis	<1%	Diet control
IIa	LDL	↑↑	Norm.	+++	10%	Bile acid sequestrants, statins, niacin
IIb	LDL and VLDL	↑↑	↑↑	+++	40%	Statins, niacin, fibrates
III	IDL	↑↑	↑↑↑	+++	<1%	Fibrates
IV	VLDL	Norm. to ↑	↑↑	+	45%	Niacin, fibrates
V	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	+ pancreatitis	5%	Niacin, fibrates

Primary hypercholesterolemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial hyper-cholesterolemia	LDL receptor	dominant	heteroz.:1/500 5% of MIs <60 yr homoz.: 1/1 million	premature CAD (ages 30–50) TC: 7-13 mM CAD before age 18 TC > 13 mM
Familial defective apo B-100	apo B-100	dominant	1/700	premature CAD TC: 7-13 mM
Polygenic hypercholestero lemia	multiple defects and mechanisms	variable	common 10% of MIs <60 yr	premature CAD TC: 6.5-9 mM
Familial hyper-alphalipoprotein emia	unknown	variable	rare	less CHD, longer life elevated HDL

Primary hypertriglyceridemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
LPL deficiency	endothelial LPL	recessive	rare 1/1 million	hepatosplenomegaly abd. cramps, pancreatitis TG: > 8.5 mM
Apo C-II deficiency	Apo C-II	recessive	rare 1/1 million	abd. cramps, pancreatitis TG: > 8.5 mM
Familial hyper-triglyceridemia	unknown enhanced hepatic TG-production	dominant	1/100	abd. cramps, pancreatitis TG: 2.3-6 mM

Primary mixed hyperlipidemias

Disorder	Genetic defect	Inheritance	Prevalence	Clinical features
Familial dysbeta-lipoproteinemia	Apo E high VLDL, chylo.	recessive rarely dominant	1/5000	premature CAD TC: 6.5 -13 mM TG: 2.8 – 5.6 mM
Familial combined	unknown high Apo B-100	dominant	1/50 – 1/100 15% of MIs <60 yr	premature CAD TC: 6.5 -13 mM TG: 2.8 – 8.5 mM

Causes of Hyperlipidemia

- Diet
- Hypothyroidism
- Nephrotic syndrome
- Anorexia nervosa
- Obstructive liver disease
- Obesity
- Diabetes mellitus
- Pregnancy
- Obstructive liver disease
- Acute heaptitis
- Systemic lupus erythematousus
- AIDS (protease inhibitors)

Dietary sources of Cholesterol

Type of Fat	Main Source	Effect on Cholesterol levels
Monounsaturated	Olives, olive oil, canola oil, peanut oil, cashews, almonds, peanuts and most other nuts; avocados	Lowers LDL, Raises HDL
Polyunsaturated	Corn, soybean, safflower and cottonseed oil; fish	Lowers LDL, Raises HDL
Saturated	Whole milk, butter, cheese, and ice cream; red meat; chocolate; coconuts, coconut milk, coconut oil , egg yolks, chicken skin	Raises both LDL and HDL
Trans	Most margarines; vegetable shortening; partially hydrogenated vegetable oil; deep-fried chips; many fast foods; most commercial baked goods	Raises LDL

Secondary hyperlipidemias

Disorder	VLDL	LDL	HDL	Mechanism
Diabetes mellitus	↑ ↑ ↑	↑	↓	**VLDL production ↑, LPL ↓, altered LDL**
Hypothyroidism	↑	↑ ↑ ↑	↓	**LDL-rec.↓, LPL ↓**
Obesity	↑ ↑	↑	↓	**VLDL production ↑**
Anorexia	-	↑ ↑	-	**bile secretion ↓, LDL catab. ↓**
Nephrotic sy	↑ ↑	↑ ↑ ↑	↓	**Apo B-100 ↑ LPL ↓ LDL-rec. ↓**
Uremia, dialysis	↑ ↑ ↑	-	↓	**LPL ↓, HTGL ↓ (inhibitors ↑)**
Pregnancy	↑ ↑	↑ ↑	↑	**oestrogen ↑ VLDL production ↑, LPL ↓**
Biliary obstruction PBC	-	-	↓	**Lp-X ↑ ↑ no CAD; xanthomas**
Alcohol	↑ ↑ **chylomicr. ↑**	-	↑	**dep. on dose, diet, genetics**

When to check lipid panel

- Different Recommendations
  - Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP)
    - Beginning at age 20: obtain a fasting (9 to 12 hour) serum lipid profile consisting of total cholesterol, LDL, HDL and triglycerides
    - Repeat testing every 5 years for acceptable values

United States Preventative Services Task Force

- Women > 45 years and men > 35 years undergo screening with a total and HDL cholesterol every 5 years.
  - If total cholesterol > 200 or HDL <40, then a fasting panel should be obtained
  - Cholesterol screening should begin at 20 years in patients with history of:
    - Diabetes
    - Multiple cardiovascular risk factors
    - Family history elevated cholesteral or premature cardiovascular disease.

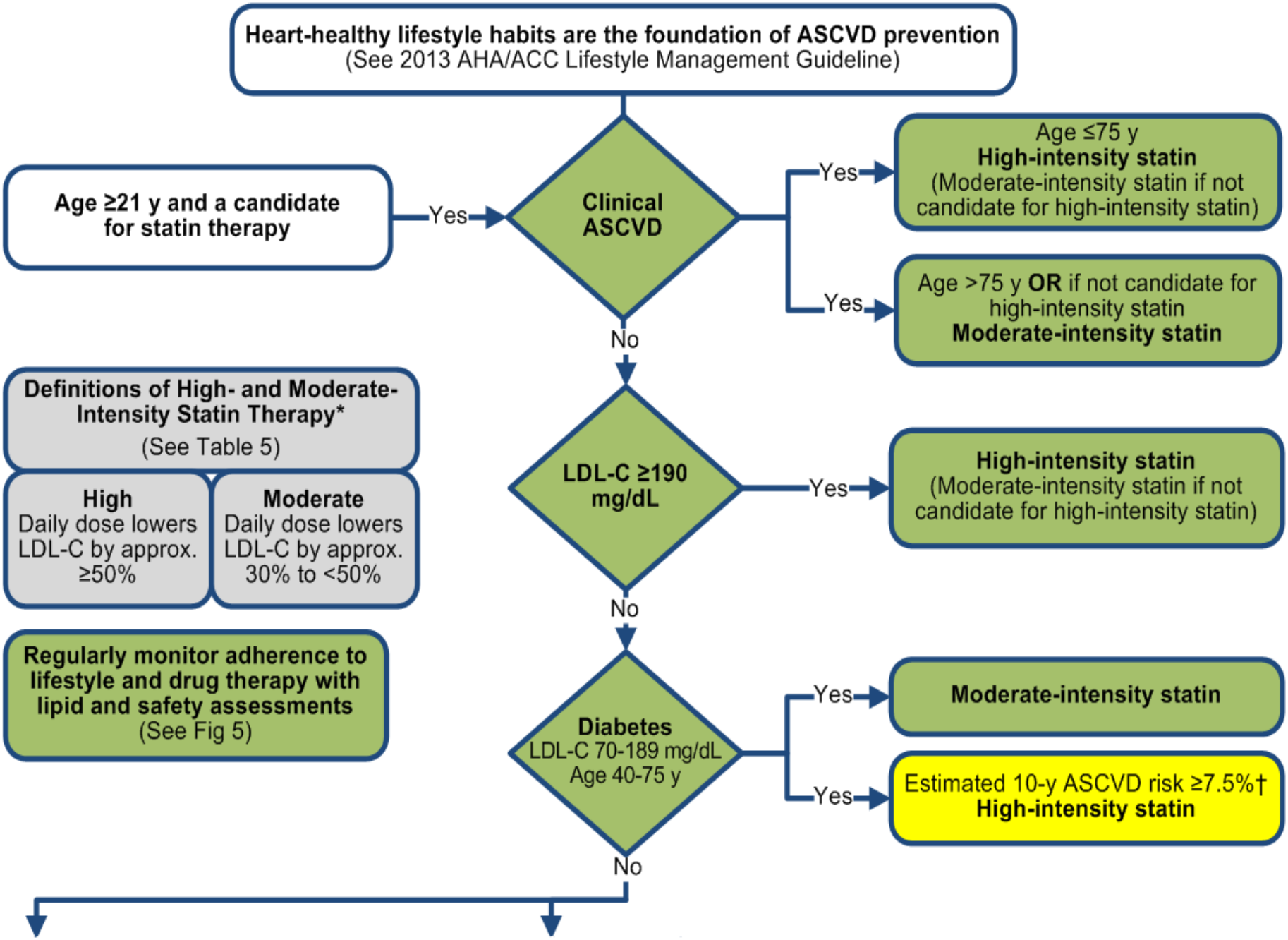
Treatment

Targets

- LDL: To prevent coronary heart disease outcomes (myocardial infarction and coronary death)

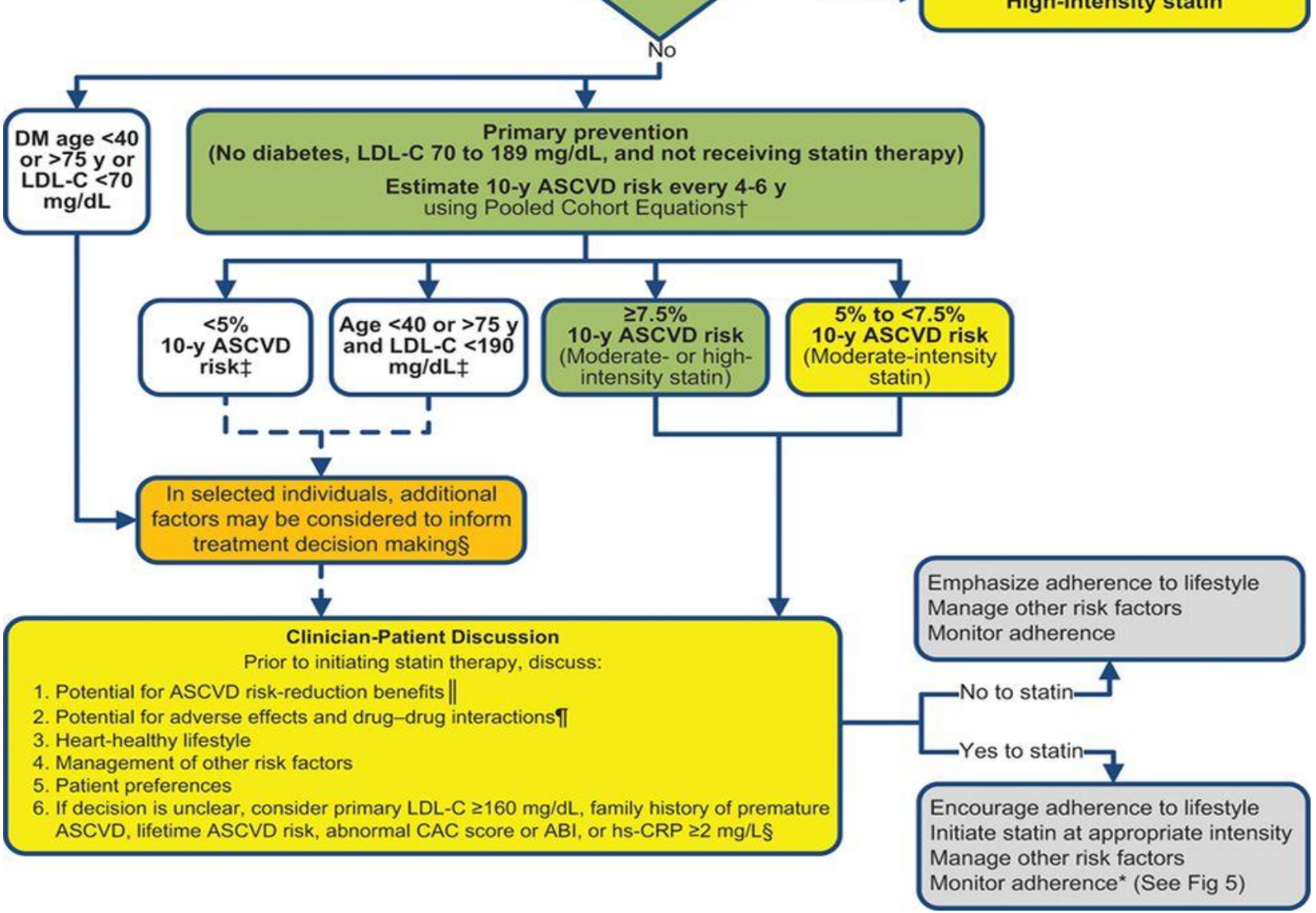
- Non LDL(TC/HDL): To prevent coronary heart disease outcomes (myocardial infarction and coronary death)

- Triglyceride: To prevent **pancreatitis** and may be coronary heart disease outcomes (myocardial infarction and coronary death)


Heart-healthy lifestyle habits are the foundation of ASCVD prevention
(See 2013 AHA/ACC Lifestyle Management Guideline)
Age ≥21 y and a candidate for statin therapy
Yes
Clinical ASCVD
Yes
Age ≤75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
Yes
Age >75 y OR if not candidate for high-intensity statin
Moderate-intensity statin
No
Definitions of High- and Moderate-Intensity Statin Therapy*
(See Table 5)
High
Daily dose lowers LDL-C by approx. ≥50%
Moderate
Daily dose lowers LDL-C by approx. 30% to <50%
LDL-C ≥190 mg/dL
Yes
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
No
Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments
(See Fig 5)
Diabetes
LDL-C 70-189 mg/dL
Age 40-75 y
Yes
Moderate-intensity statin
Yes
Estimated 10-y ASCVD risk ≥7.5%†
High-intensity statin
No

Recommendations in DM

Age	Risk Factors	Statin Intensity*
<40 years	None	None
	ASCVD risk factor(s)	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe



Stone N J et al. Circulation. 2014;129:S1-S45

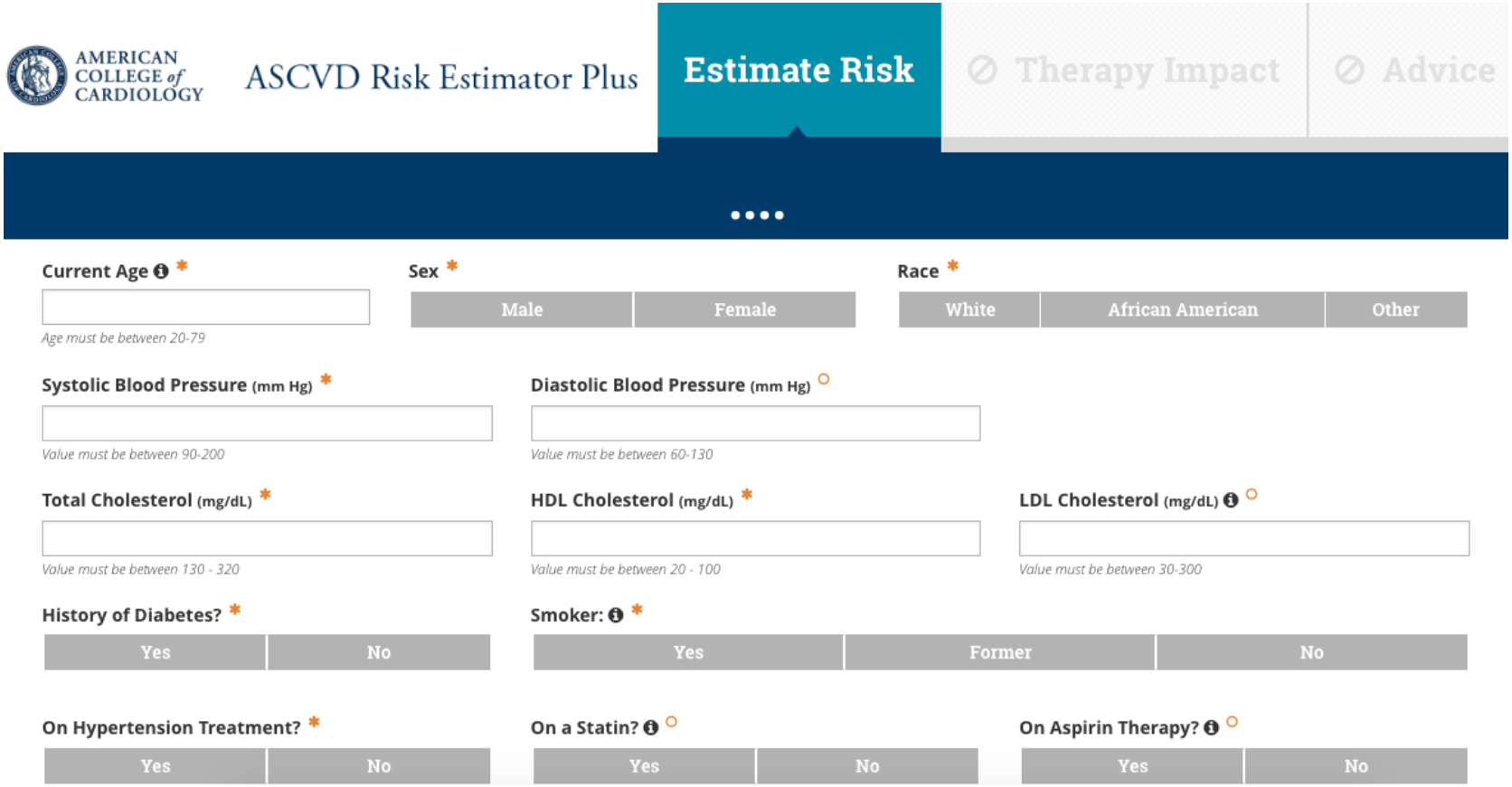
American Heart Association.

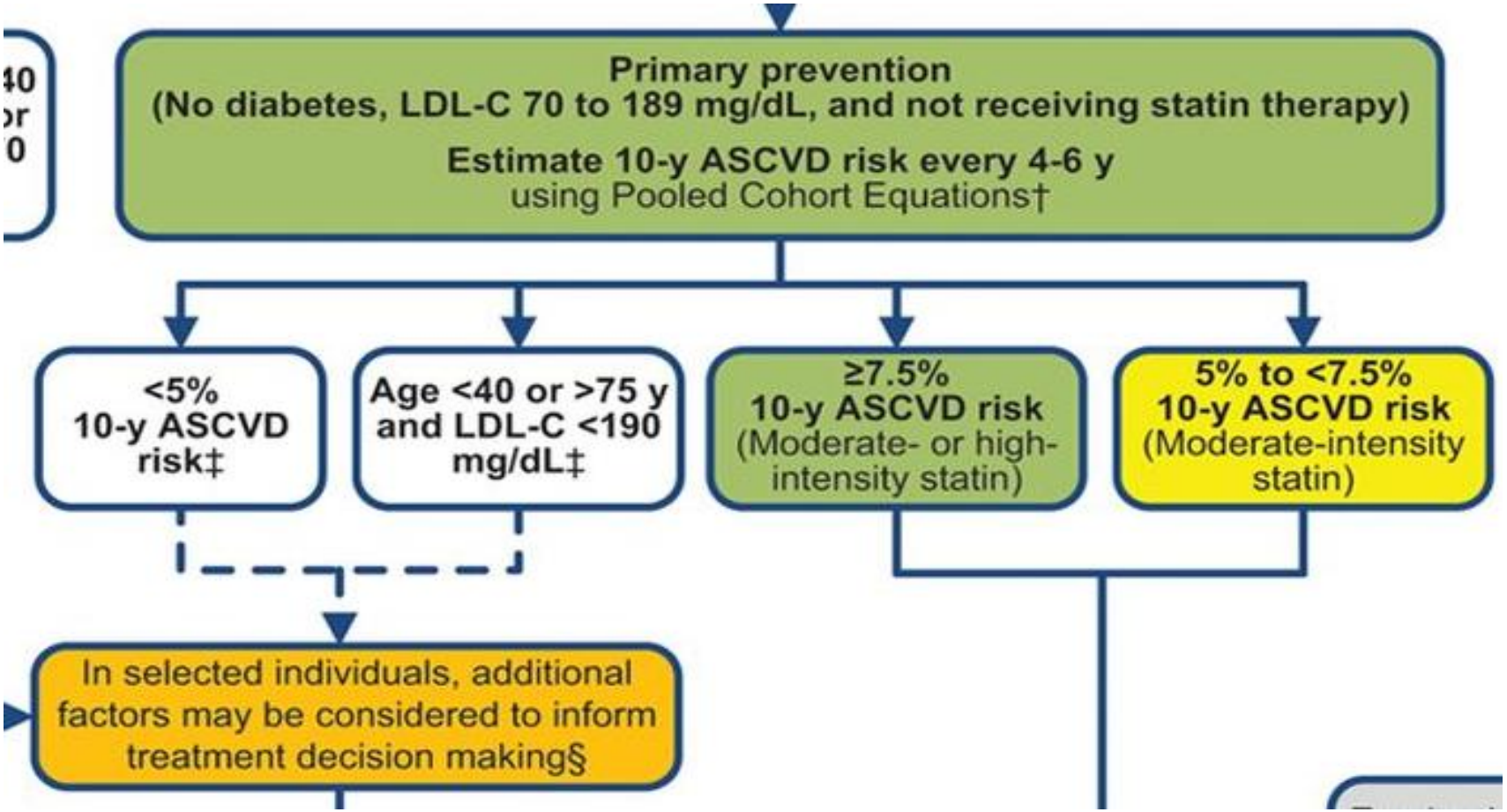
Estimate 10-year risk for ASCVD

http://tools.acc.org/ASCVD-Risk-Estimator-Plus/#!/calculate/estimate/

AGE
SBP/DBP
T cholesterol
HDL
LDL
DM
Smoking
On Anti HTN
On statin
On asprin

Estimate 10-year risk for ASCVD





Stone N J et al. Circulation. 2014;129:S1-S45

Guideline of therapy

Age	Risk Factors	Statin Intensity*
>29 Age	ASCVD	High
>29 years	LDL >190 mg/dl (4.9 mmol/l)	High
NO DM LDL <190	estimate 10-year risk for ASCVD <5%	No
	estimate 10-year risk for ASCVD 5-7.5%	Moderate
	estimate 10-year risk for ASCVD >7.5%	High

Recommendations in DM

Age	Risk Factors	Statin Intensity*
<40 years	None	None
	ASCVD risk factor(s)	Moderate or high
	ASCVD	High
40–75 years	None	Moderate
	ASCVD risk factors	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe
>75 years	None	Moderate
	ASCVD risk factors	Moderate or high
	ASCVD	High
	ACS & LDL ≥50 or in patients with history of ASCVD who can't tolerate high dose statin	Moderate + ezetimibe

Statin Treatment

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50% Atorvastatin (40†)–80 mg Rosuvastatin 20 (40) mg	Daily dose lowers LDL-C, on average, by approximately 30% to <50% Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg‡ Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2–4 mg	Daily dose lowers LDL-C, on average, by <30% Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

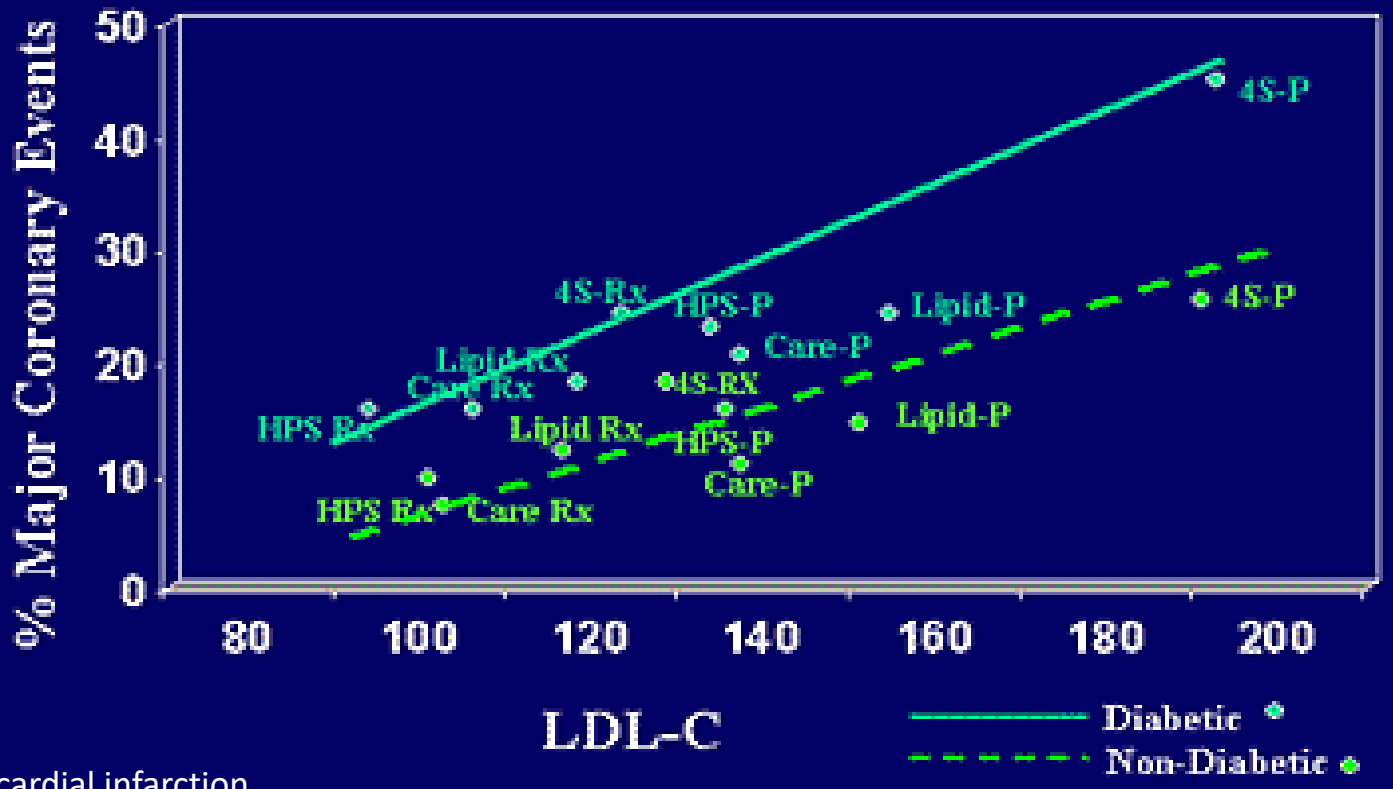
Treatment of Hyperlipidemia

- Lifestyle modification
  - Low-cholesterol diet
  - Exercise
  - Smoking
  - Alcohol

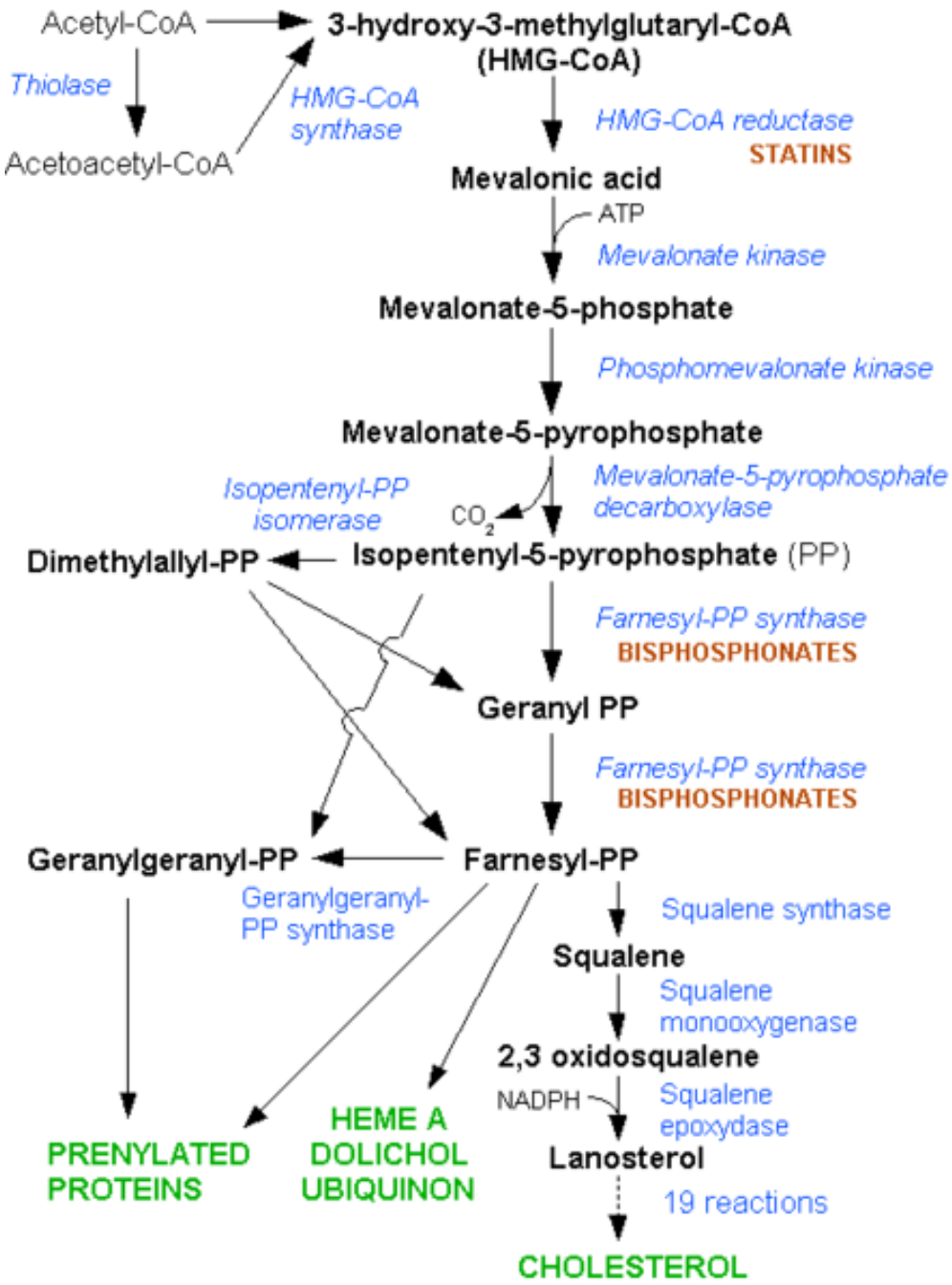
Medications for Hyperlipidemia

Drug Class	***Agents***	***Effects (% change)***	***Side Effects***
HMG CoA reductase inhibitors	**Statins**	**↓LDL (18-55),↑ HDL (5-15) ↓ Triglycerides (7-30)**	**Myopathy, increased liver enzymes**
Cholesterol absorption inhibitor	**Ezetimibe**	**↓ LDL(14-18), ↑ HDL (1-3) ↓Triglyceride (2)**	**Headache, GI distress**
Nicotinic Acid		**↓LDL (15-30), ↑ HDL (15-35) ↓ Triglyceride (20-50)**	**Flushing, Hyperglycemia, Hyperuricemia, GI distress, hepatotoxicity**
Fibric Acids	**Gemfibrozil Fenofibrate**	**↓LDL (5-20), ↑HDL (10-20) ↓Triglyceride (20-50)**	**Dyspepsia, gallstones, myopathy**
Bile Acid sequestrants	**Cholestyramine**	**↓ LDL↑ HDL No change in triglycerides**	**GI distress, constipation, decreased absorption of other drugs**
PCSK9	**Evolocumab Alirocumab**	**↓ LDL (50-60%)**	**injection-site reactions, muscle pain, neurocognitive adverse events. These included memory impairment and confusion**

Statin Risk Reduction in Diabetic Patients and Non-Diabetic Patients



MI = myocardial infarction.


Acetyl-CoA
3-hydroxy-3-methylglutaryl-CoA
(HMG-CoA)
Thiolase
HMG-CoA
synthase
Acetoacetyl-CoA
HMG-CoA reductase
STATINS
Mevalonic acid
ATP
Mevalonate kinase
Mevalonate-5-phosphate
Phosphomevalonate kinase
Mevalonate-5-pyrophosphate
Isopentenyl-PP
isomerase
CO2
Mevalonate-5-pyrophosphate
decarboxylase
Dimethylallyl-PP
Isopentenyl-5-pyrophosphate (PP)
Farnesyl-PP synthase
BISPHOSPHONATES
Geranyl PP
Farnesyl-PP synthase
BISPHOSPHONATES
Geranylgeranyl-PP
Farnesyl-PP
Geranylgeranyl-
PP synthase
Squalene synthase
Squalene
Squalene
monooxygenase
2,3 oxidosqualene
NADPH
Squalene
epoxydase
Lanosterol
19 reactions
PRENYLATED
PROTEINS
HEME A
DOLICHOL
UBIQUINON
CHOLESTEROL

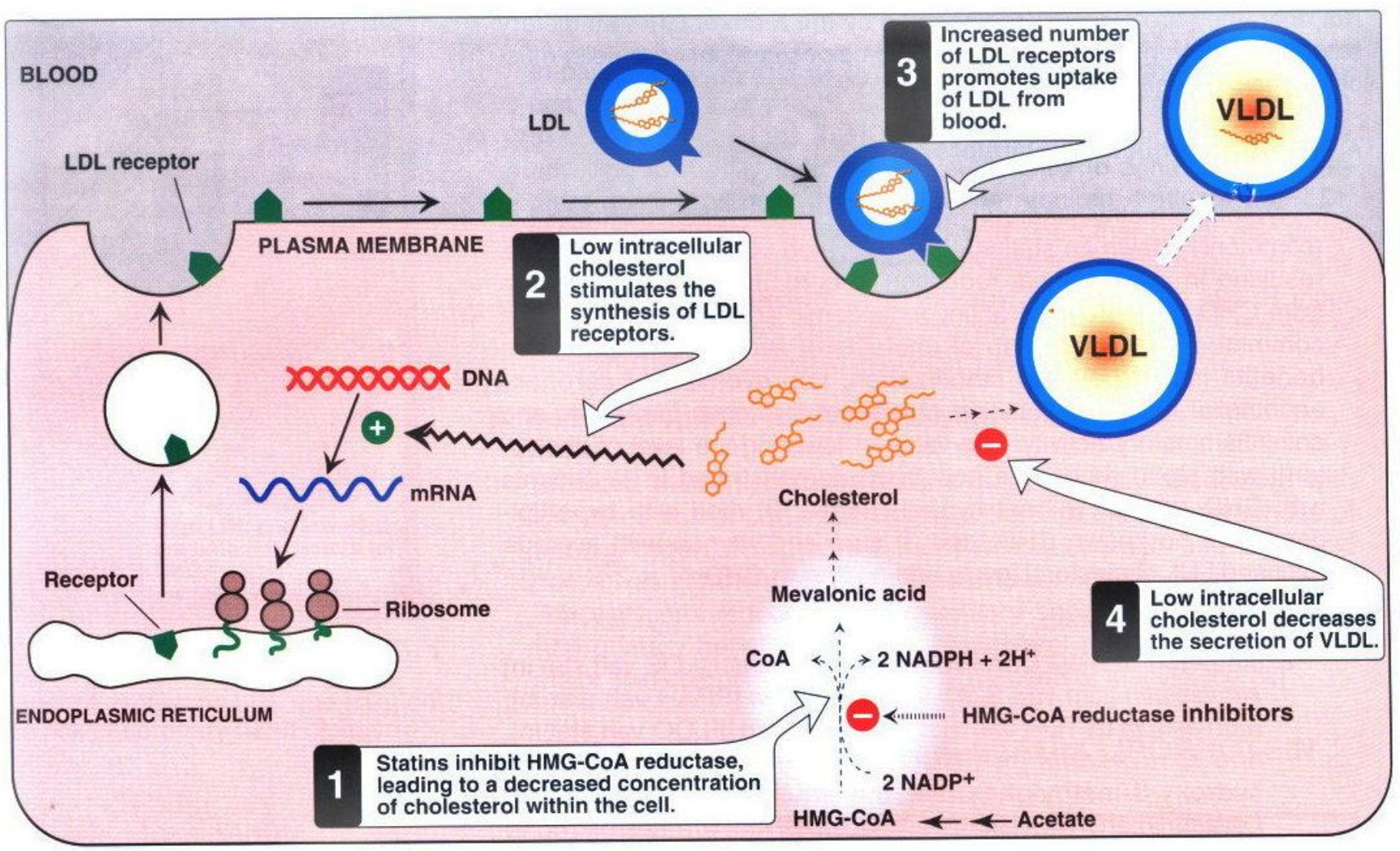


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.

Table 1: Assessment and action strategies for elevated plasma triglyceride concentrations [TG]

[TG], mmol/L	Step	Action and comments	Retest interval, mo*
< 2		Continue current management • Reassess lipid profile regularly, to ensure that [LDL-C] is at target	6-12
≥ 2, < 5	1.	Therapeutic lifestyle measures • Weight control • Reduce dietary fat, simple sugars • Reduce alcohol intake • Increase physical activity Reassess lipid profile regularly, to ensure that [LDL-C] is at target	3-6
	2.	Manage other secondary factors • Control glycemia, if diabetic • Reassess medications; consider lipid-neutral alternatives	
	3.	Consider pharmacologic treatment • Intensify LDL-lowering (e.g., statin therapy) • Fish oil (omega-3 fatty acid) • Niacin (e.g., extended release)	

Table 1: Assessment and action strategies for elevated plasma triglyceride concentrations [TG]

≥ 5, < 10	4. Intensify steps 1-3, above • [LDL-C] cannot be estimated when [triglycerides] > 5 mmol/L • Apolipoprotein B determination might be helpful	2-3
	5. Consider fibrate therapy, e.g., • Bezafibrate (Bezalip) 400 mg/d • Fenofibrate — Lipidil micro 200 mg/d — Lipidil supra 160 mg/d — Lipidil EZ 145 mg/d • Gemfibrozil (Lopid) 600-1200 mg/d	
≥ 10	6. Further intensify steps 1-3 With acute pancreatitis: • Very-low-fat diet (10%-15% of energy intake) • Cessation of alcohol • Insulin, if indicated for glycemic control • Admit patient to hospital — Nothing by mouth: IV fluid replacement — Plasma exchange is unhelpful	1-2
	7. Initiate fibrate therapy • Monitor serum [creatinine]	
	8. Consider specialist referral	

George Yuan, Khalid Z. Al-Shali, Robert A. Hegele
CMAJ • April 10, 2007 • 176(8)

THANK YOU

drjammah@gmail.com

See you in 5th year MED-441 Course