



Dyslipidemia

(Med-341)

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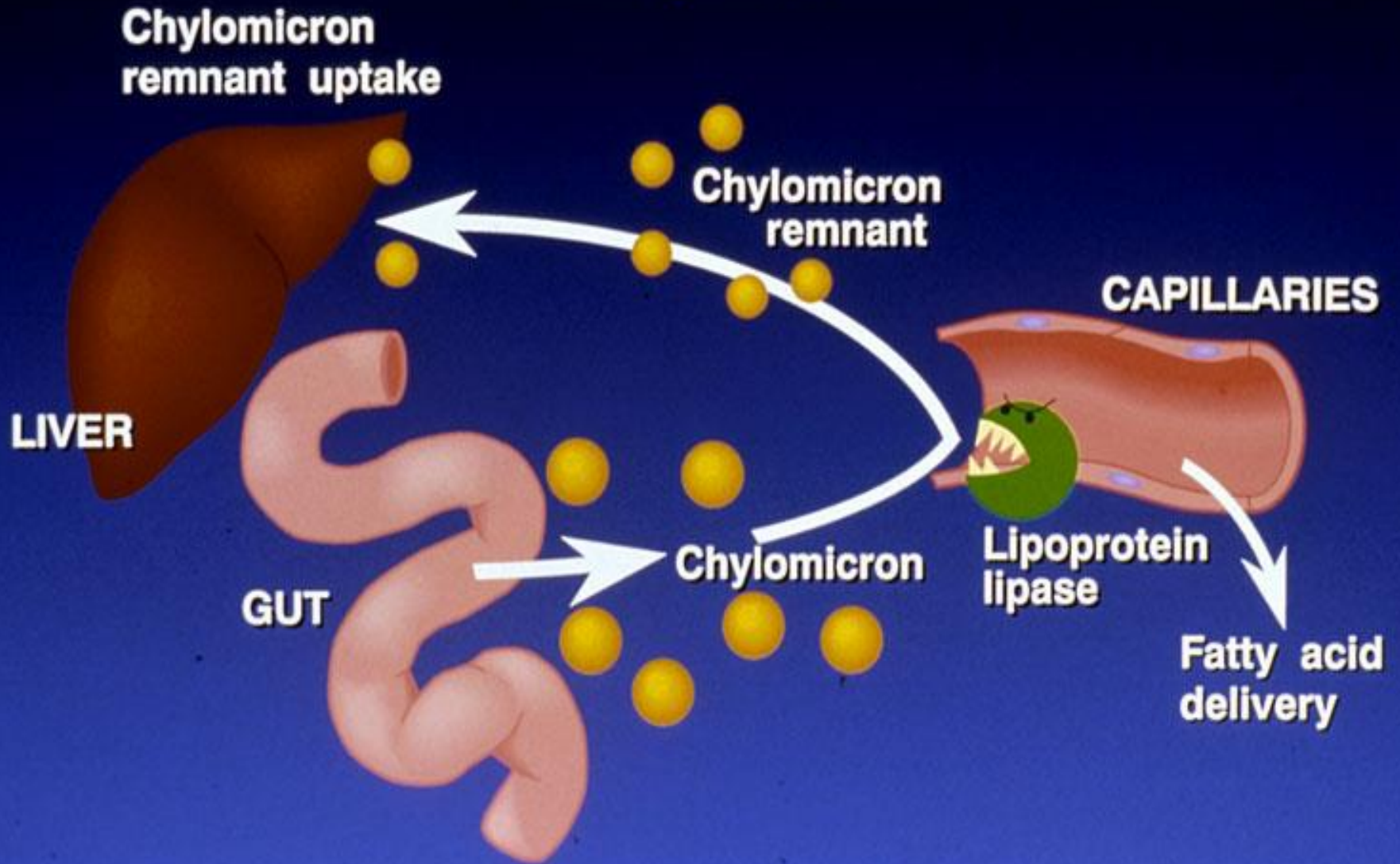
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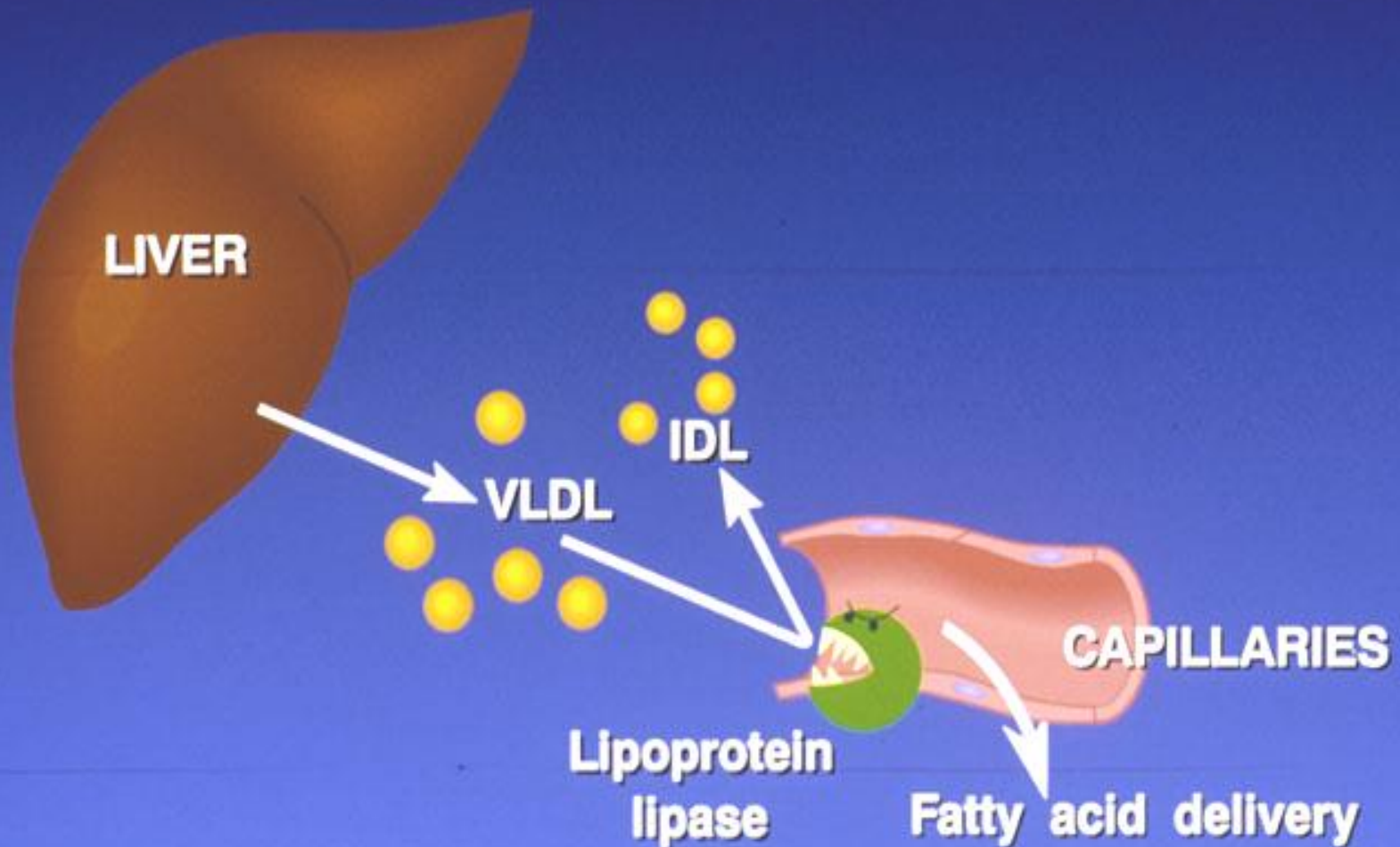
LIPOPROTEIN PATHWAYS

Exogenous



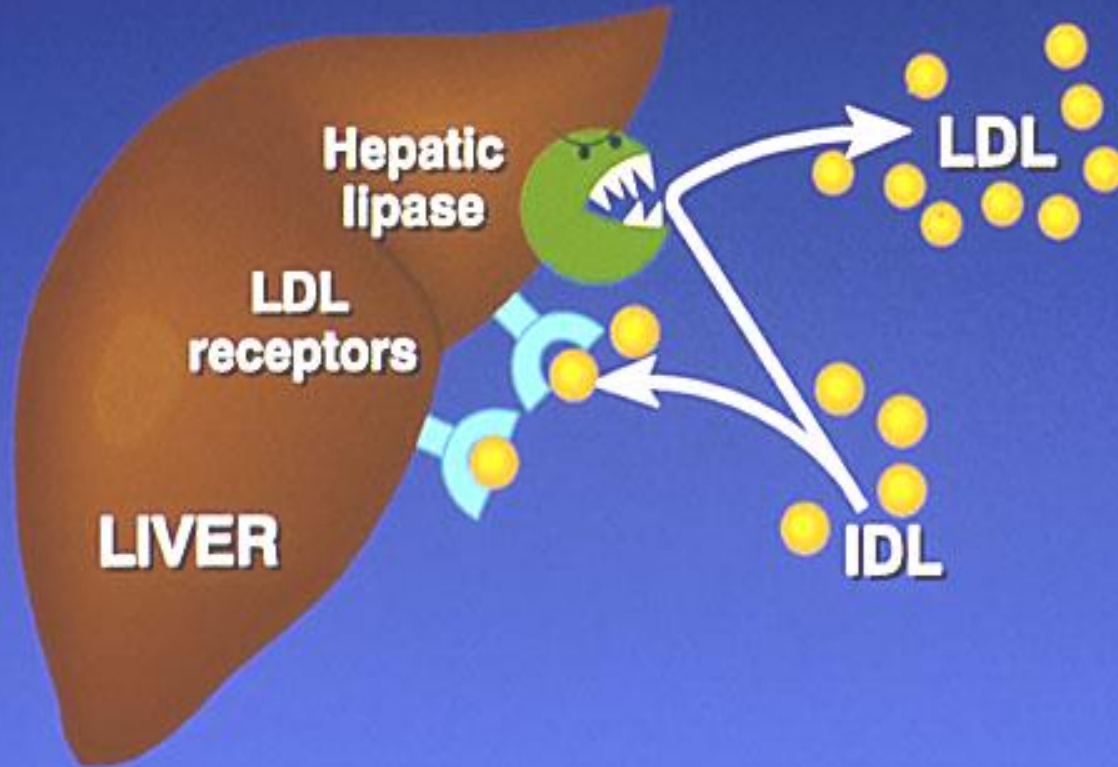
LIPOPROTEIN PATHWAYS

Endogenous (VLDL-IDL)



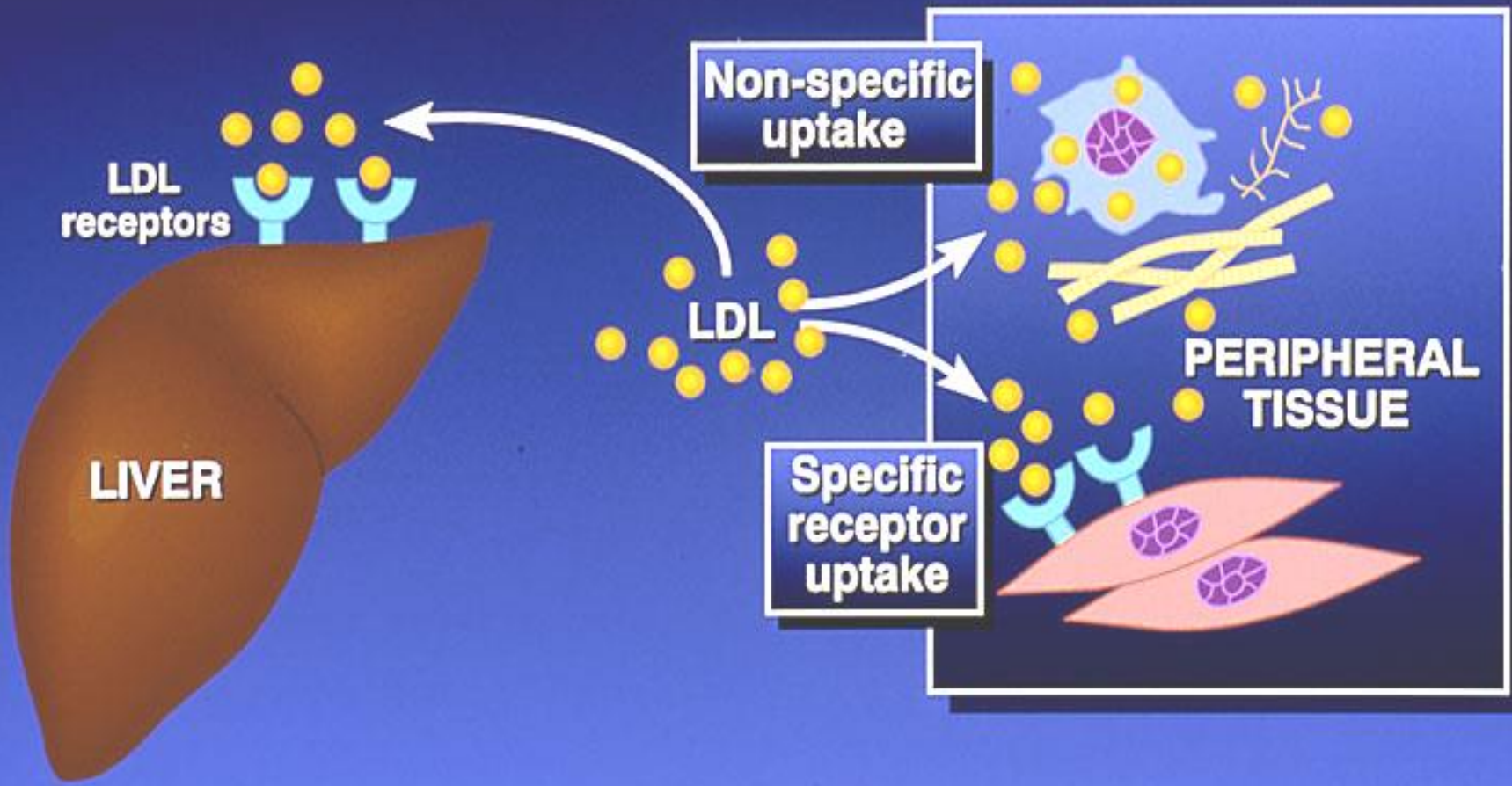
LIPOPROTEIN PATHWAYS

Endogenous (IDL-LDL)



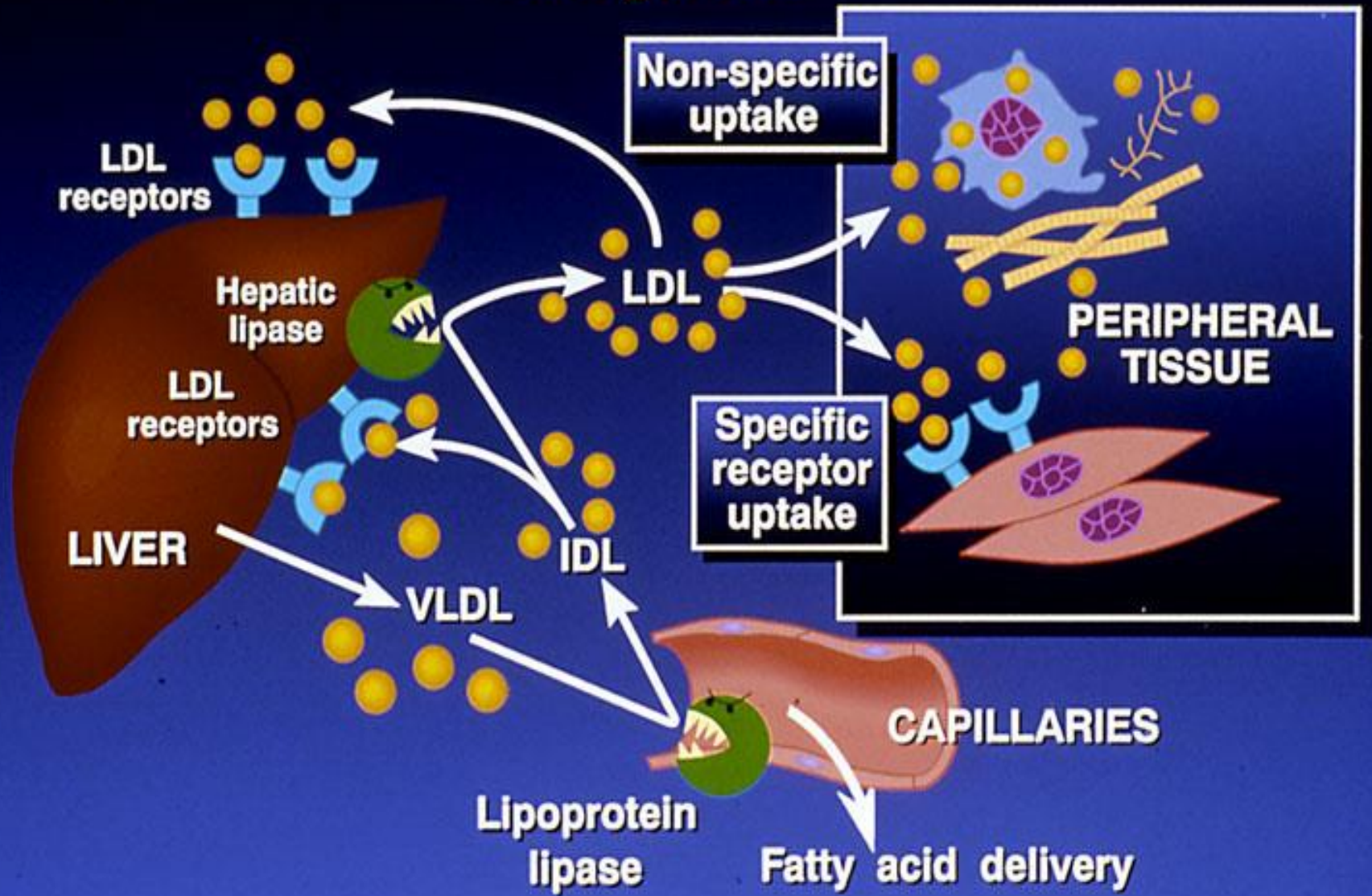
LIPOPROTEIN PATHWAYS

Endogenous (LDL Uptake)



LIPOPROTEIN PATHWAYS

Endogenous



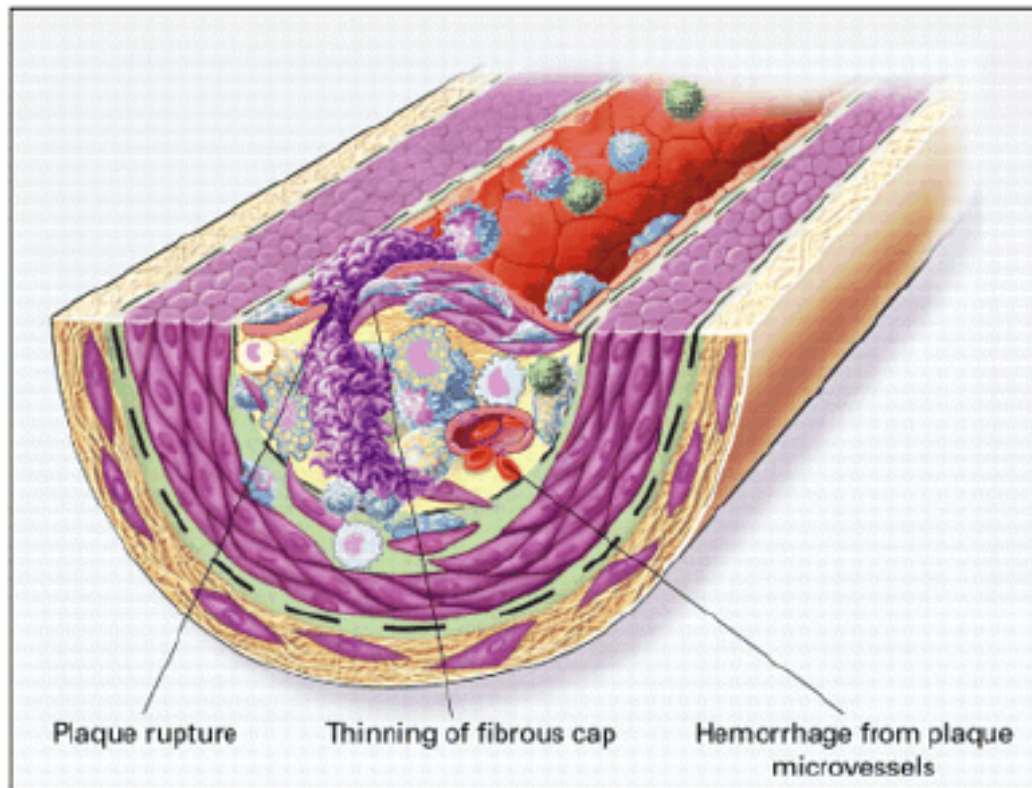
The story of lipids

- ❑ 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.

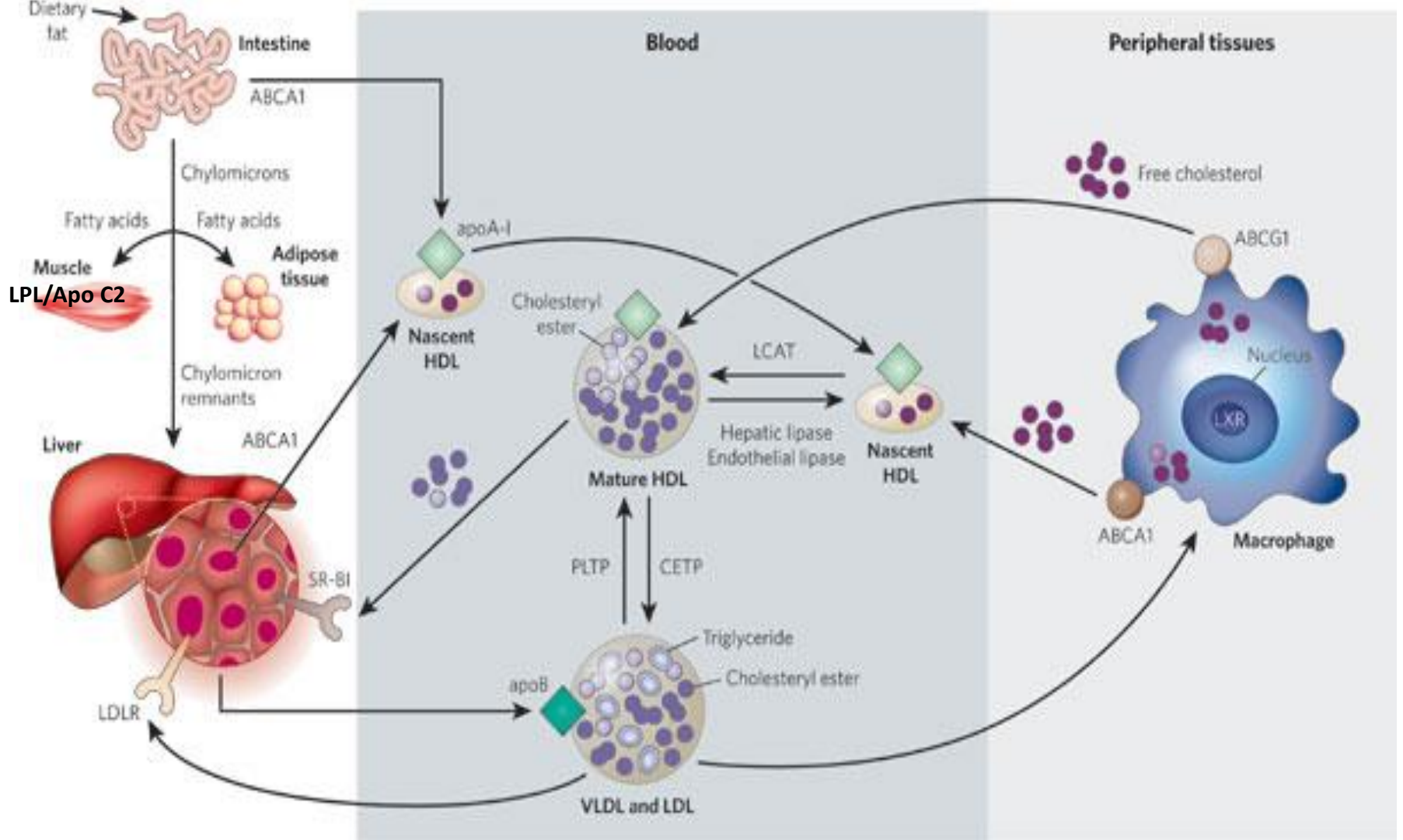
The story of lipids (cont.)

- ❑ 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

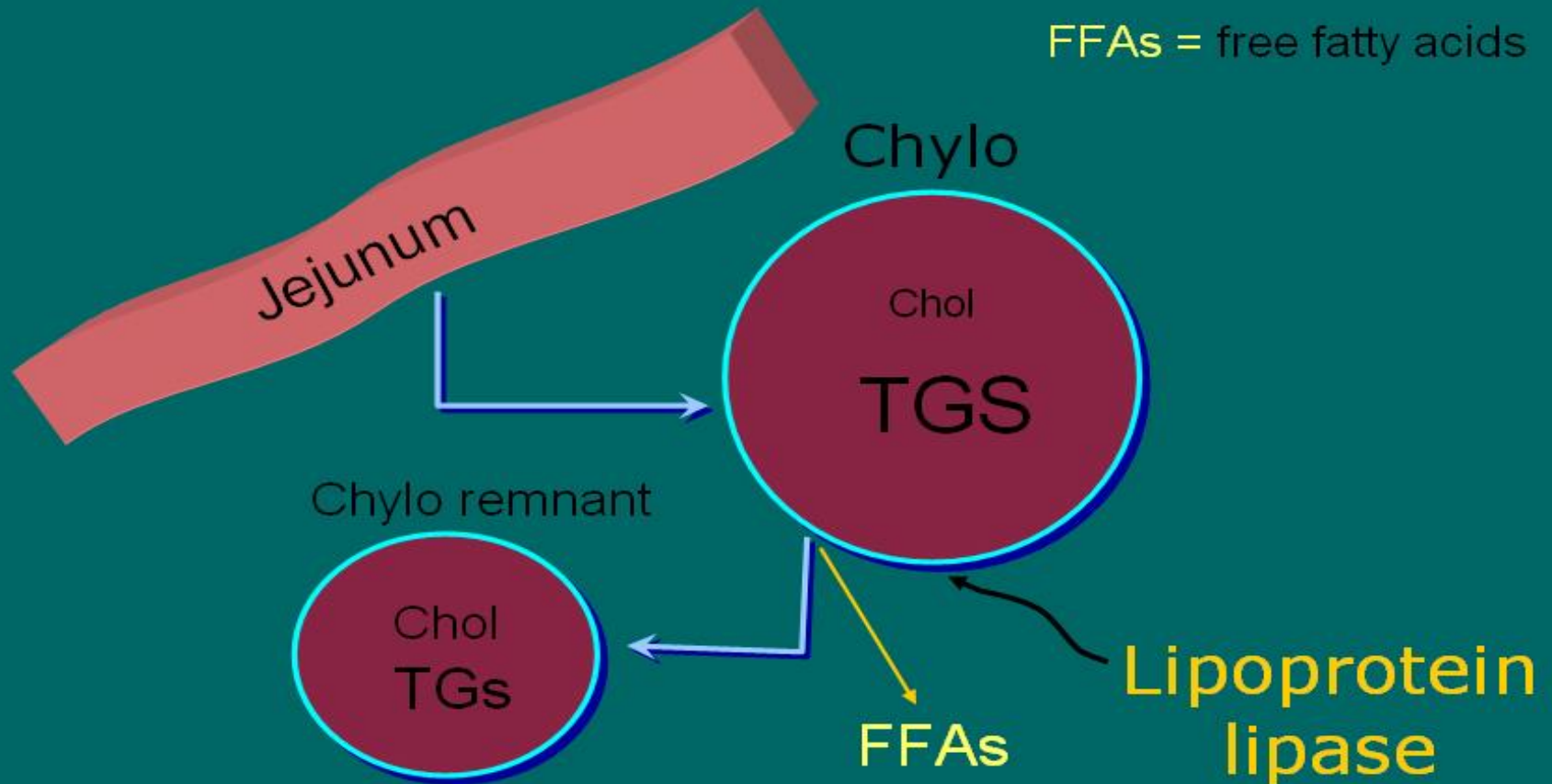


Lipid Transport



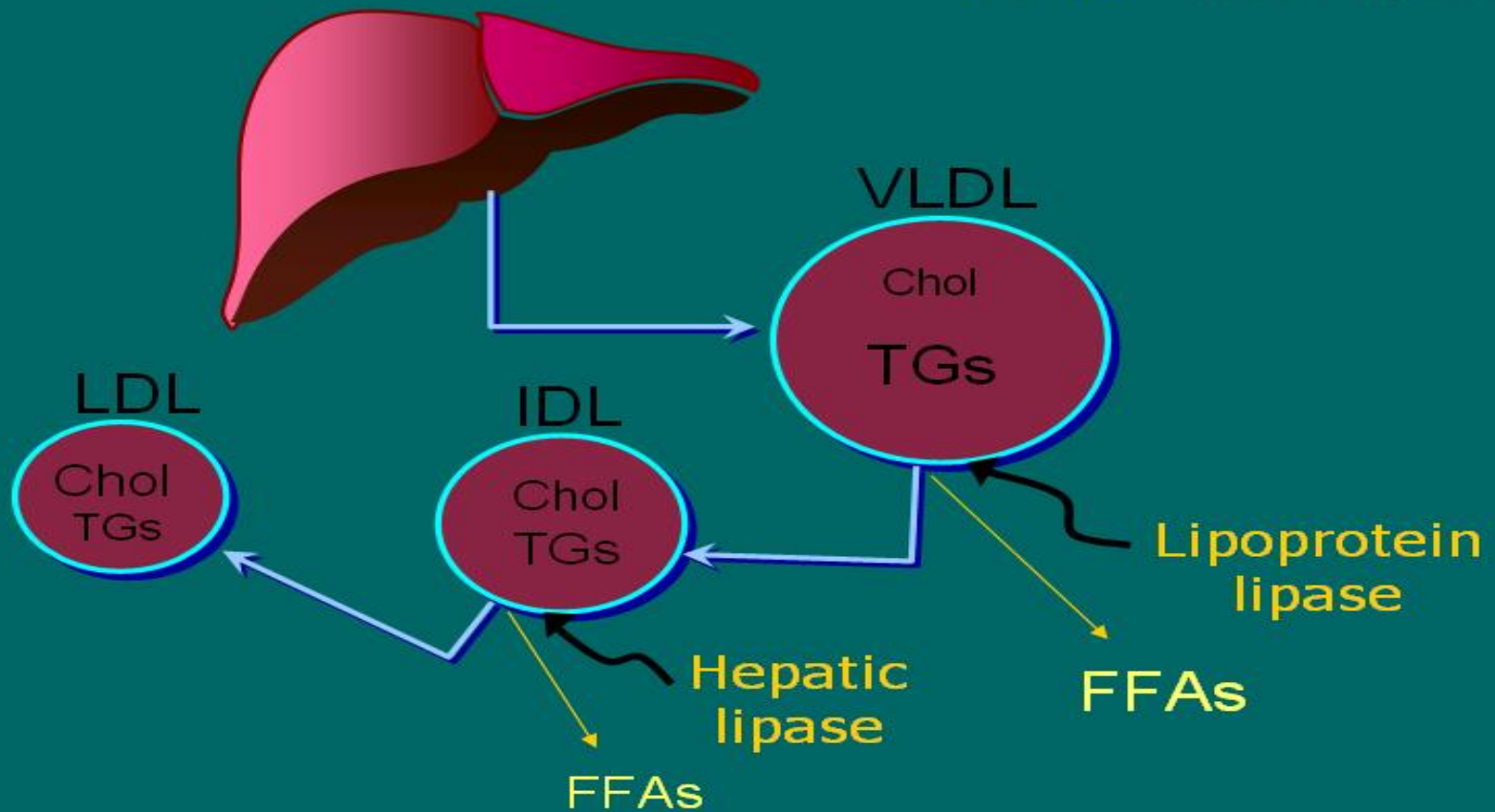
Chylomicron Metabolism

FFAs = free fatty acids



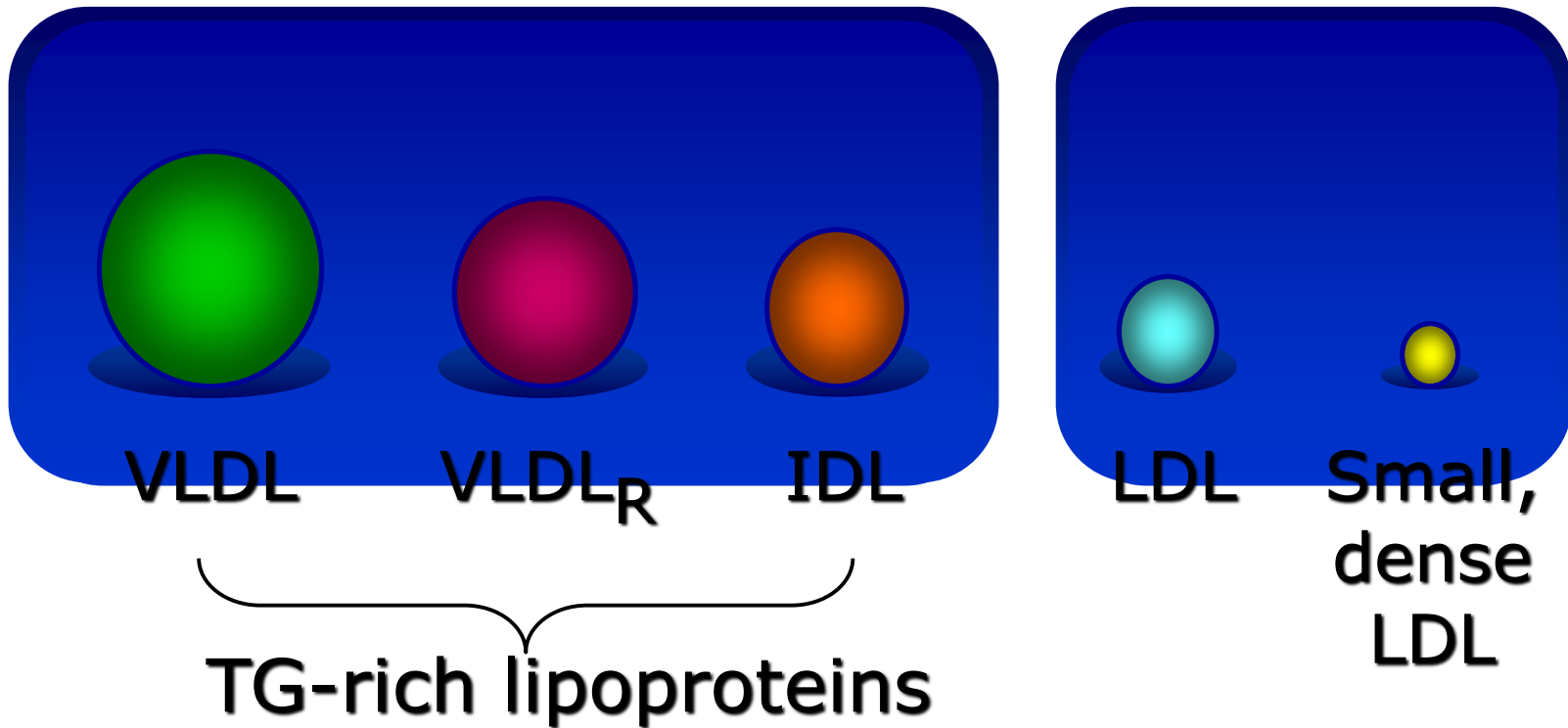
VLDL Metabolism

FFAs = free fatty acids

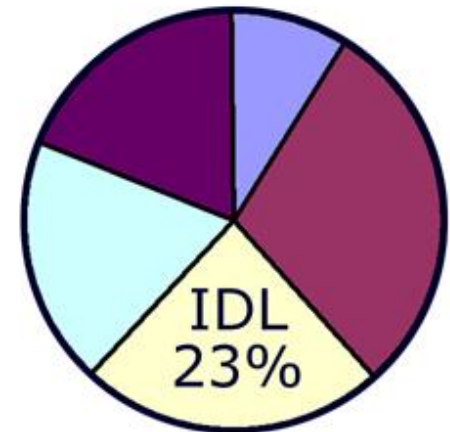
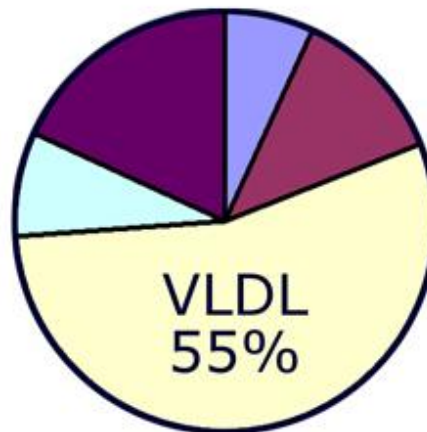
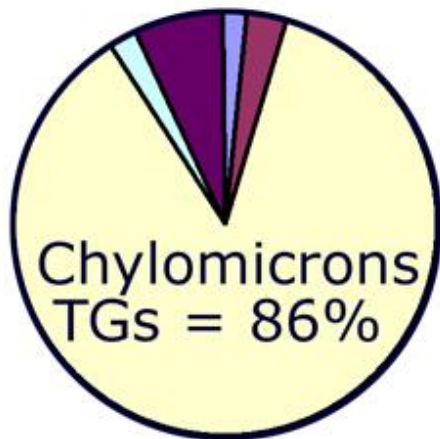


Atherogenic Particles

MEASUREMENTS:

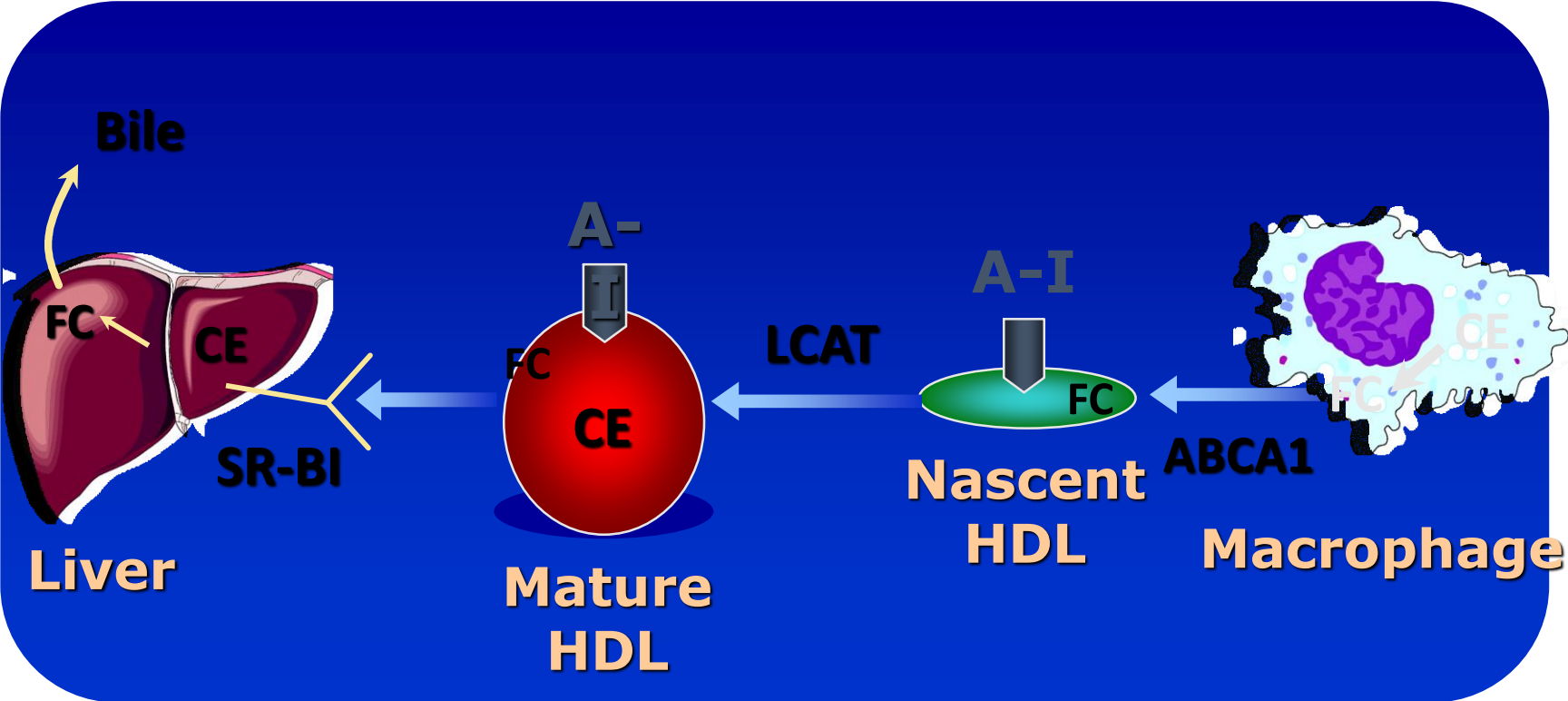


Composition of Triglyceride-Rich Lipoproteins (% dry mass)



● Cholesterol ● Cholesterol Ester ● Triglycerides ● Apolipoproteins ● Phospholipids

HDL and Reverse Cholesterol Transport



Plasma lipoproteins

Type	Source	Major lipid	Apoproteins	ELFO	Atherogenicity
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, occurs 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	Atherogenicity	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 hypercholesterolemia	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 hypercholesterolemia	multiple defects and mechanisms	variable	common 10% of MIs <60 yr	premature CAD TC: 6.5-9 mM
Familial hyperalphalipoproteinemia	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 hypertriglyceridemia	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

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

Causes of Hyperlipidemia

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

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 aged 45 years and older, and men ages 35 years and older 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 a history of multiple cardiovascular risk factors, diabetes, or family history of either elevated cholesterol levels 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

Clinical ASCVD

Age ≤ 75 y
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

Age > 75 y **OR** if not candidate for high-intensity statin
Moderate-intensity statin

Definitions of High- and Moderate-Intensity Statin Therapy*
(See Table 5)

High
Daily dose lowers LDL-C by approx. $\geq 50\%$

Moderate
Daily dose lowers LDL-C by approx. 30% to $< 50\%$

LDL-C ≥ 190 mg/dL

High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)

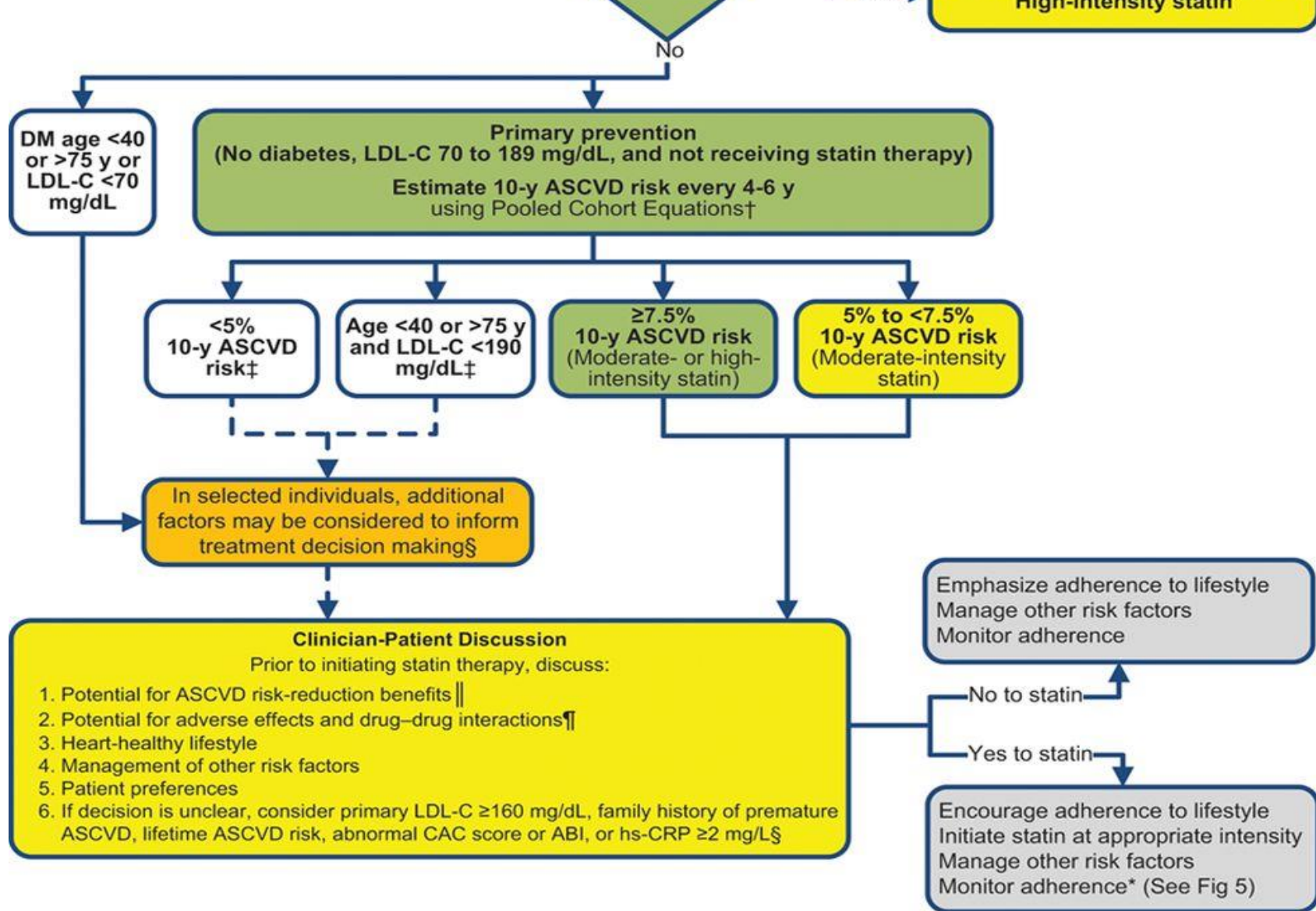
Regularly monitor adherence to lifestyle and drug therapy with lipid and safety assessments
(See Fig 5)

Diabetes
LDL-C 70-189 mg/dL
Age 40-75 y

Moderate-intensity statin

Estimated 10-y ASCVD risk $\geq 7.5\%$ †
High-intensity statin





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

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 aspirin

Estimate 10-year risk for ASCVD



ASCVD Risk Estimator Plus

Estimate Risk

Therapy Impact

Advice



Current Age ⓘ *

Age must be between 20-79

Sex *

Male	Female
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Race *

White	African American	Other
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Systolic Blood Pressure (mm Hg) *

Value must be between 90-200

Diastolic Blood Pressure (mm Hg) ○

Value must be between 60-130

Total Cholesterol (mg/dL) *

Value must be between 130 - 320

HDL Cholesterol (mg/dL) *

Value must be between 20 - 100

LDL Cholesterol (mg/dL) ⓘ ○

Value must be between 30-300

History of Diabetes? *

Yes	No
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Smoker: ⓘ *

Yes	Former	No
-----	--------	----

On Hypertension Treatment? *

Yes	No
-----	----

On a Statin? ⓘ ○

Yes	No
-----	----

On Aspirin Therapy? ⓘ ○

Yes	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 \geq 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 \geq 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
<p>Daily dose lowers LDL-C, on average, by approximately $\geq 50\%$</p> <p>Atorvastatin (40†)-80 mg Rosuvastatin 20 (40) mg</p>	<p>Daily dose lowers LDL-C, on average, by approximately 30% to $< 50\%$</p> <p>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</p>	<p>Daily dose lowers LDL-C, on average, by $< 30\%$</p> <p>Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg</p>

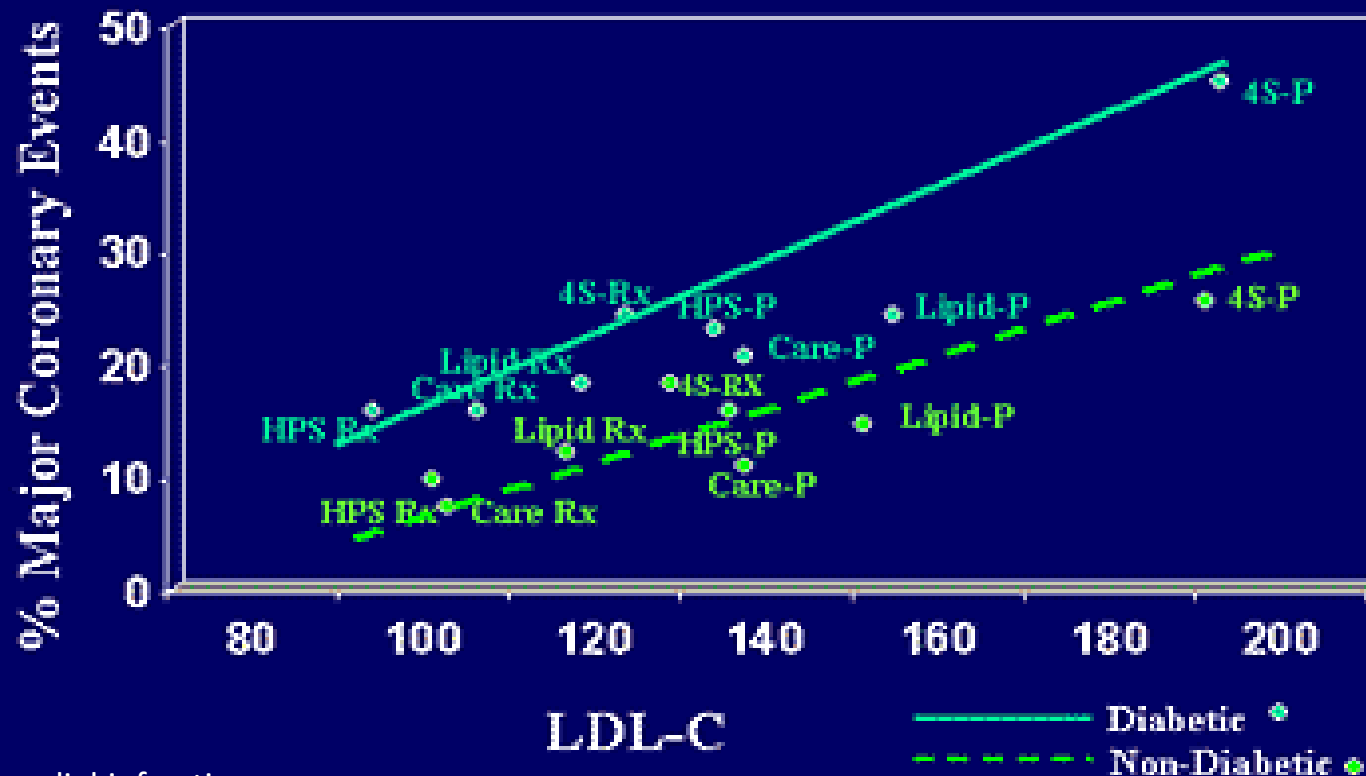
Treatment of Hyperlipidemia

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

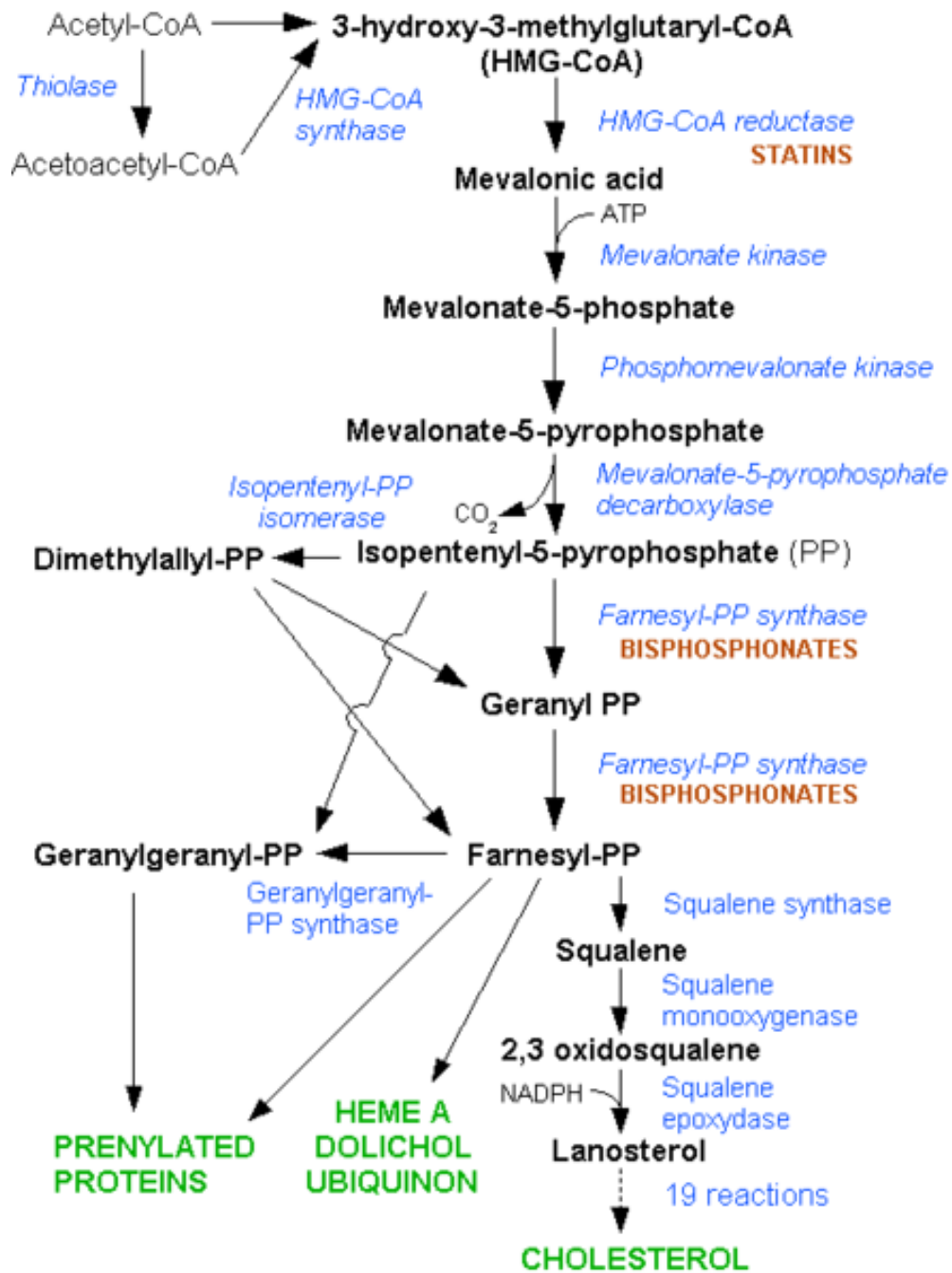
Medications for Hyperlipidemia

<u>Drug Class</u>	<u>Agents</u>	<u>Effects (% change)</u>	<u>Side Effects</u>
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.



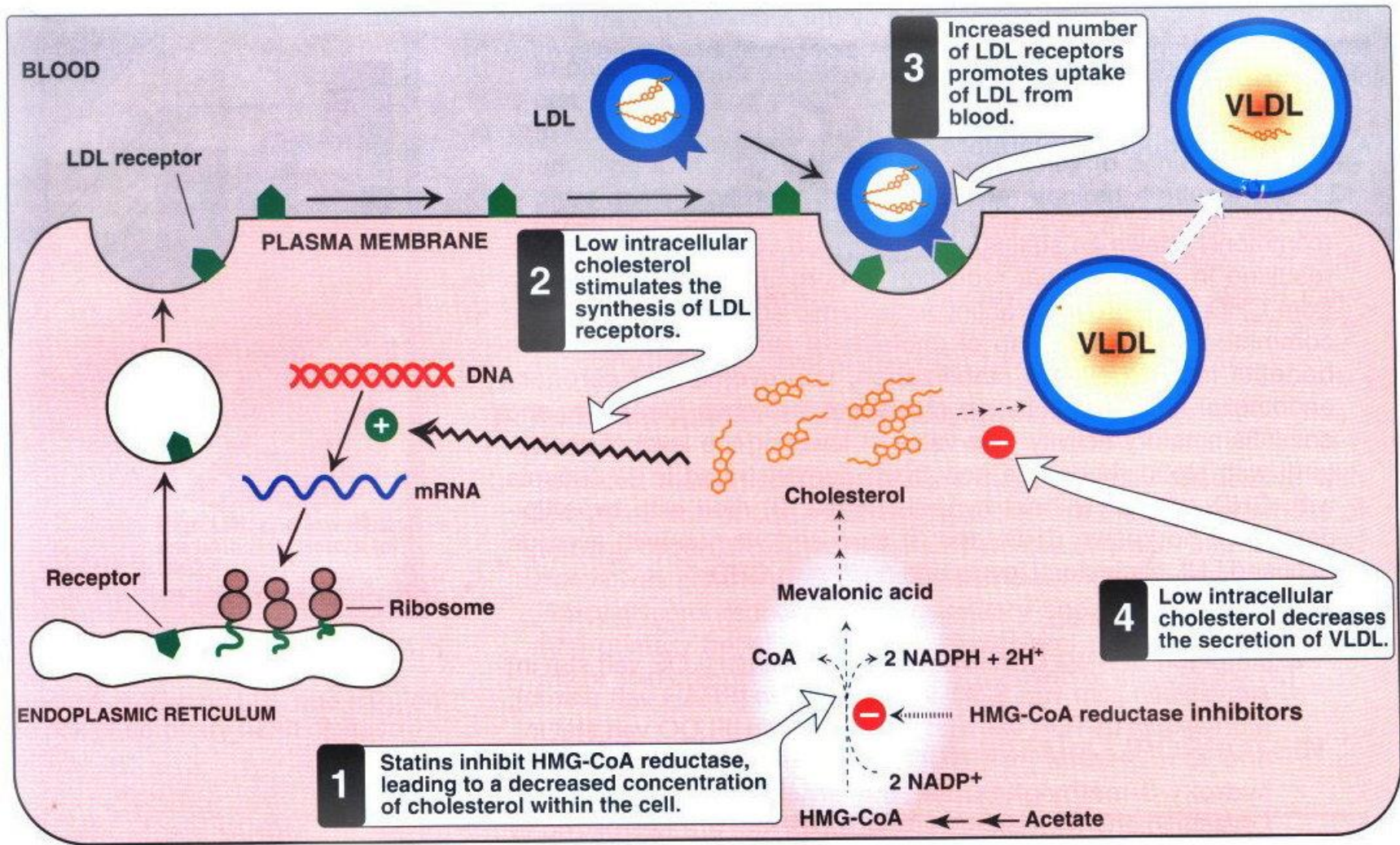


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.

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 <ul style="list-style-type: none"> • Reassess lipid profile regularly, to ensure that [LDL-C] is at target 	6-12
≥ 2, < 5	1.	Therapeutic lifestyle measures <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • Control glycemia, if diabetic • Reassess medications; consider lipid-neutral alternatives 	
	3.	Consider pharmacologic treatment <ul style="list-style-type: none"> • 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	<p>4. Intensify steps 1-3, above</p> <ul style="list-style-type: none"> • [LDL-C] cannot be estimated when [triglycerides] > 5 mmol/L • Apolipoprotein B determination might be helpful 	2-3
	<p>5. Consider fibrate therapy, e.g.,</p> <ul style="list-style-type: none"> • Bezafibrate (Bezalip) 400 mg/d • Fenofibrate <ul style="list-style-type: none"> – Lipidil micro 200 mg/d – Lipidil supra 160 mg/d – Lipidil EZ 145 mg/d • Gemfibrozil (Lopid) 600-1200 mg/d 	
≥ 10	<p>6. Further intensify steps 1-3</p> <p>With acute pancreatitis:</p> <ul style="list-style-type: none"> • Very-low-fat diet (10%-15% of energy intake) • Cessation of alcohol • Insulin, if indicated for glycemic control • Admit patient to hospital <ul style="list-style-type: none"> – Nothing by mouth: IV fluid replacement – Plasma exchange is unhelpful 	1-2
	<p>7. Initiate fibrate therapy</p> <ul style="list-style-type: none"> • Monitor serum [creatinine] 	
	<p>8. Consider specialist referral</p>	

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THANK YOU

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See you in 5th year MED-441 Course