Dyslipidemia

(Med-3)

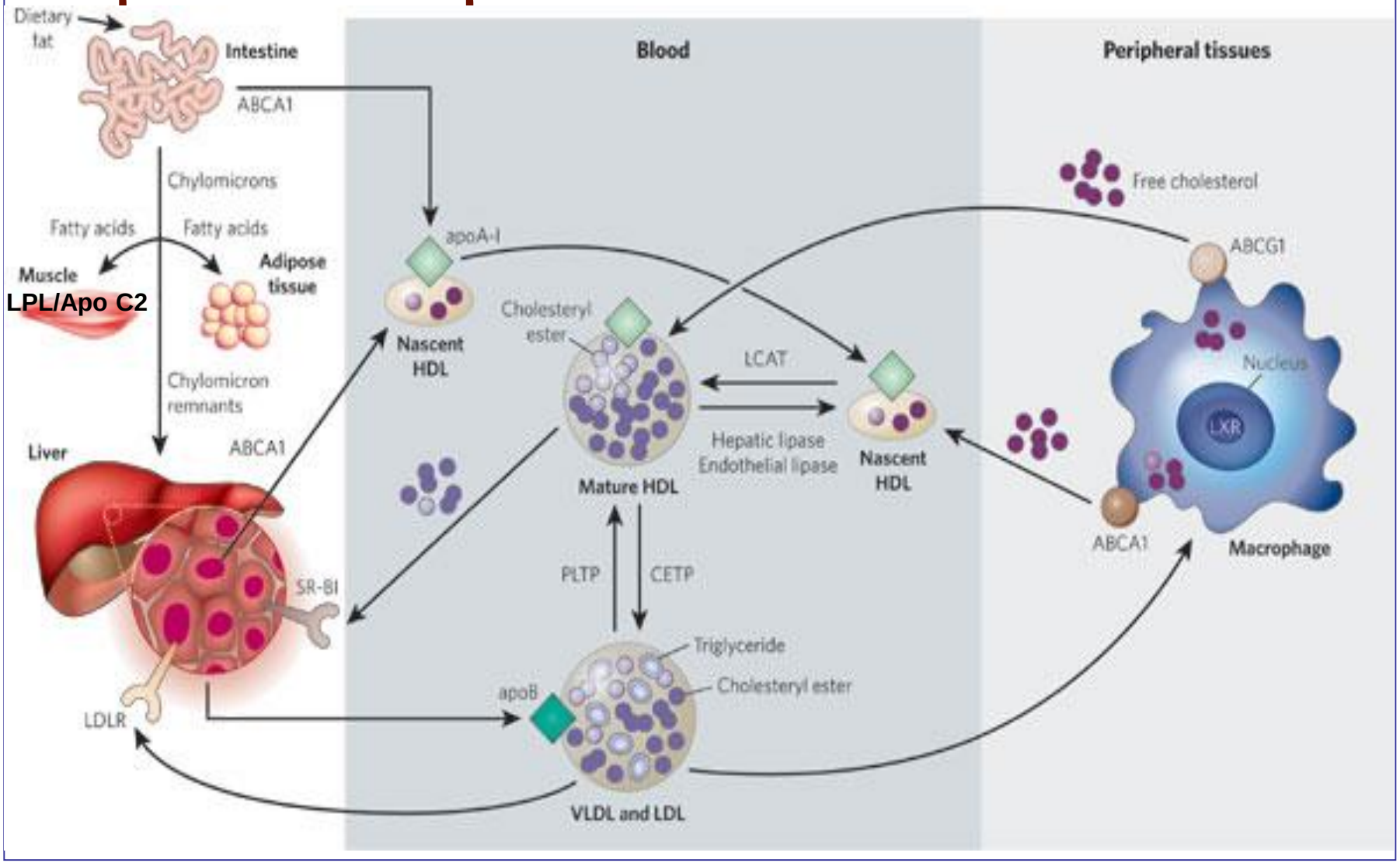
Dr Anwar A Jammah, MD, FRCPC, FACP, CCD, ECNU.

Asst. Professor and Consultant

Medicine, Endocrinology

Department of Medicine, King Saud University

Lipid Transport



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

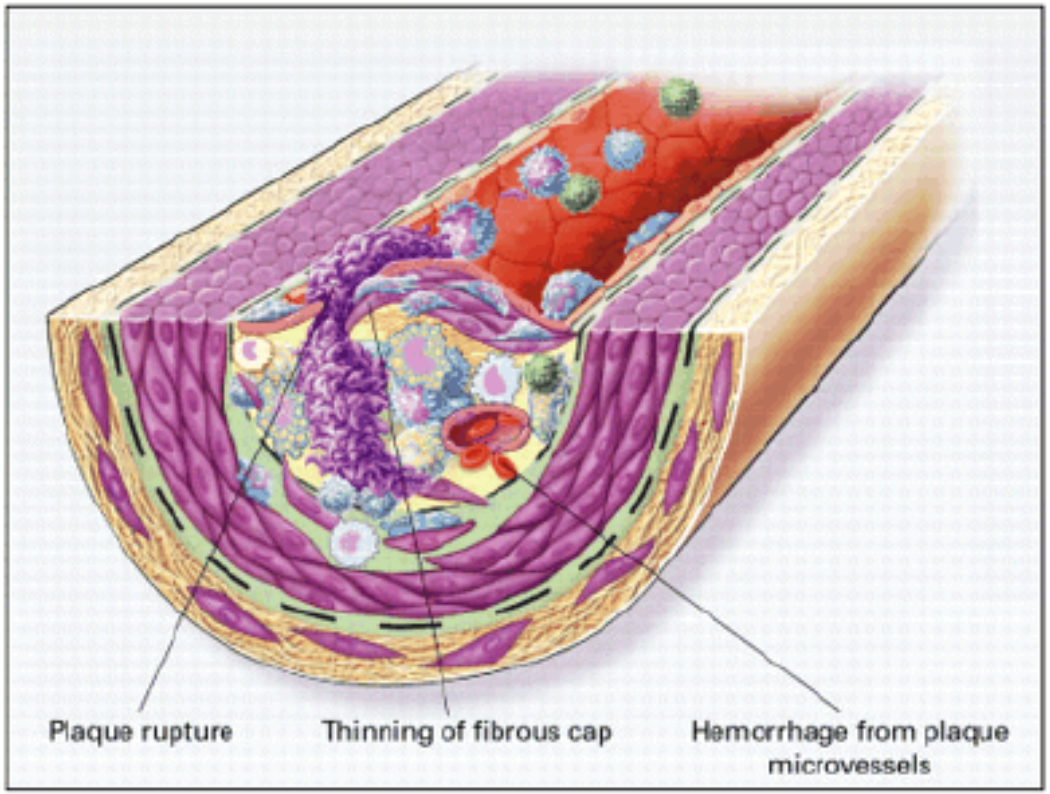
The story of lipids

- Chylomicrons transport fats from the intestinal mucosa to the liver
- In the liver, the chylomicrons release triglycerides and some cholesterol and become low-density lipoproteins (LDL).
- LDL then carries fat and cholesterol to the body's cells.
- High-density lipoproteins (HDL) carry fat and cholesterol back to the liver for excretion.

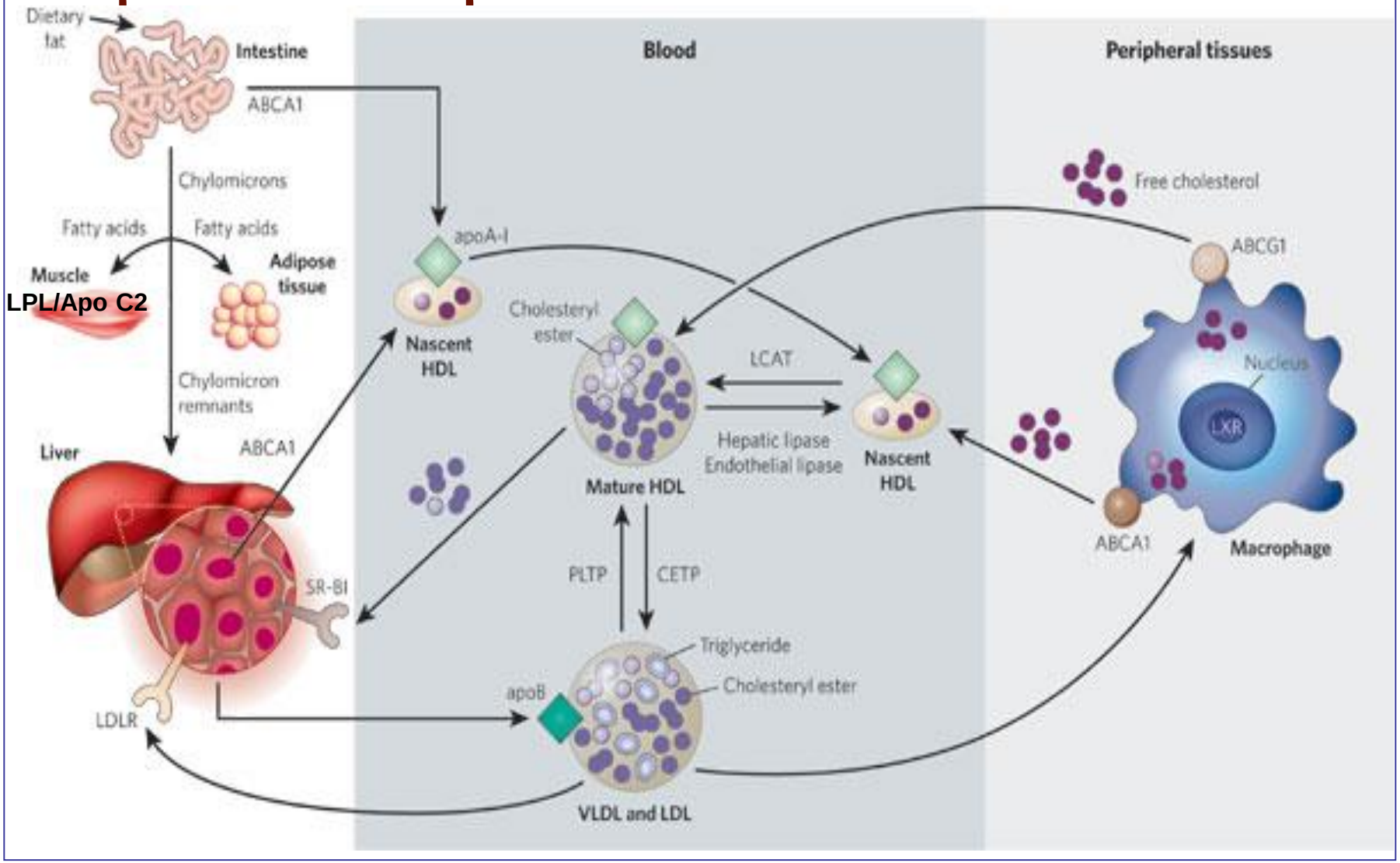
The story of lipids (cont.)

- 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



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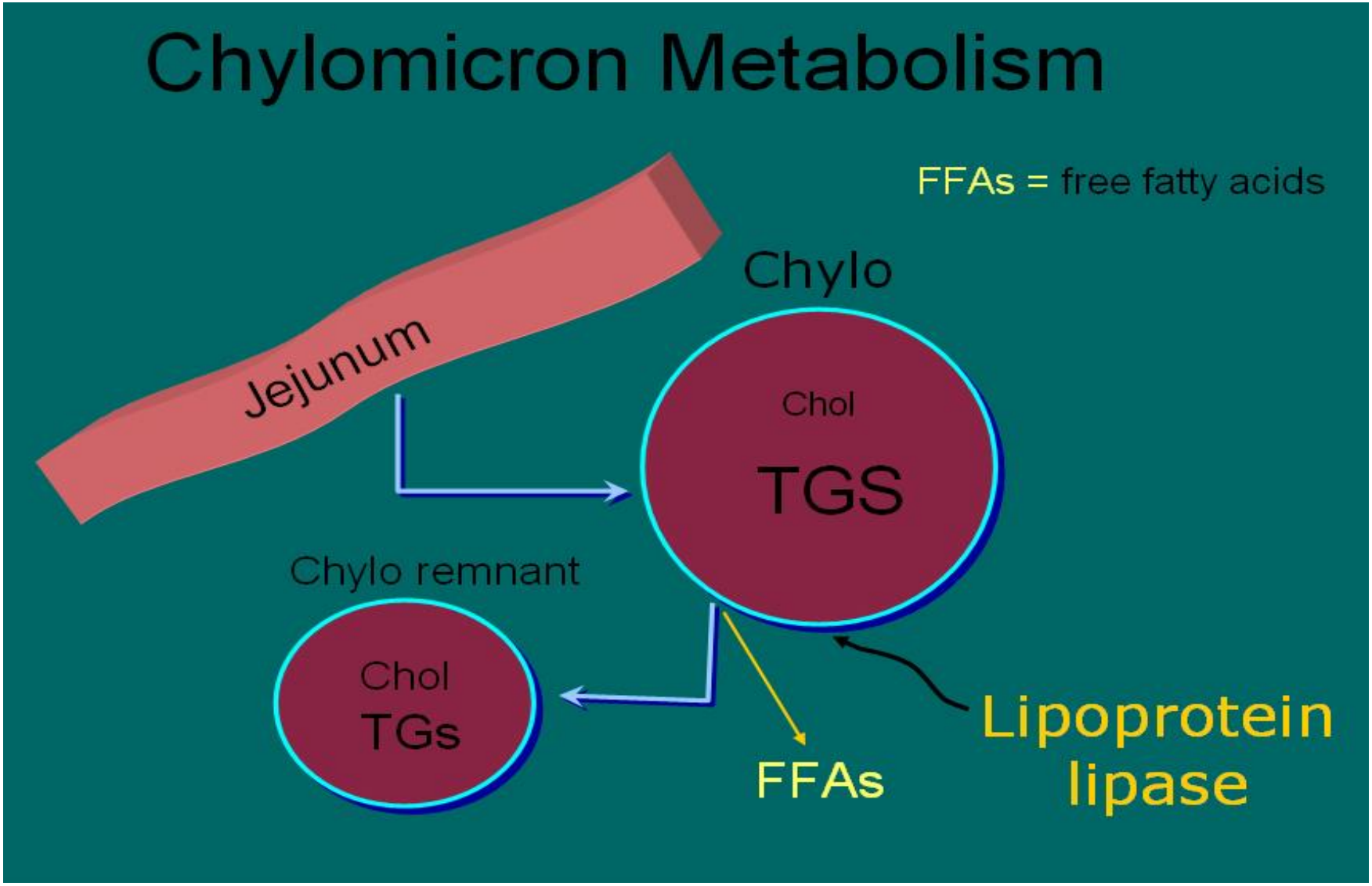
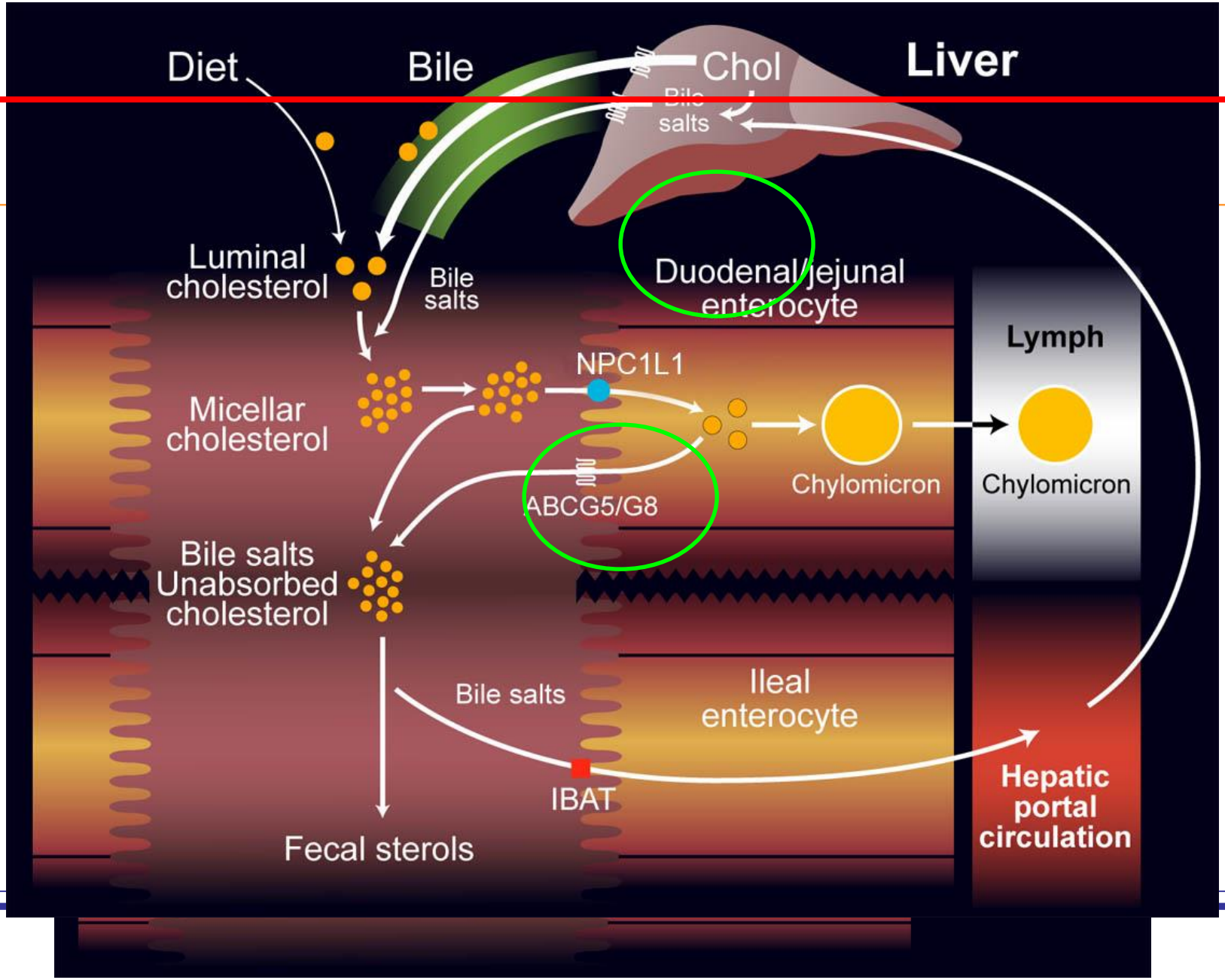
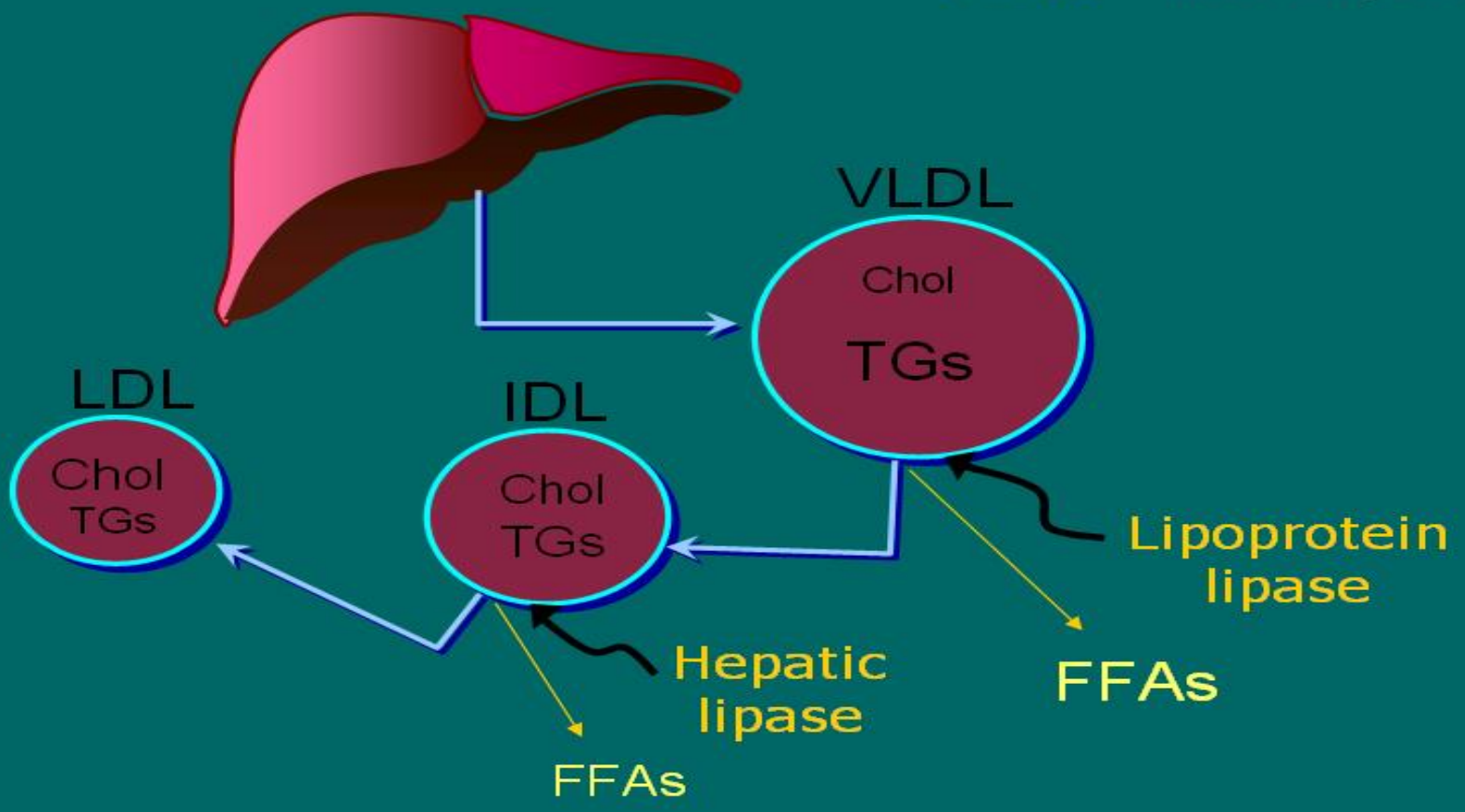

Chylomicron Metabolism
FFAs = free fatty acids
Jejunum
Chylo
Chol
TGS
Chylo remnant
Chol
TGs
FFAs
Lipoprotein
lipase

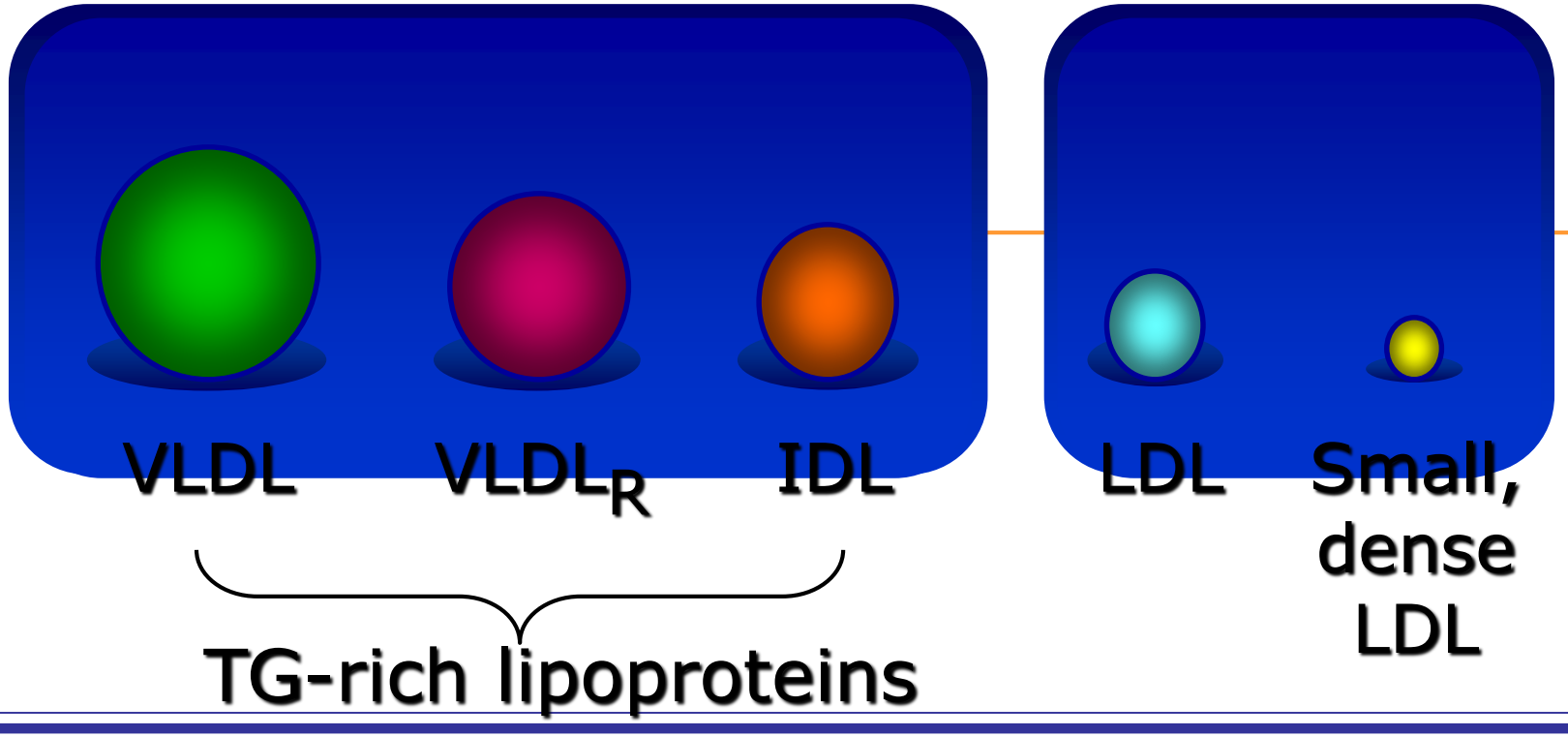

Diet
Bile
Chol
Liver
Bile salts
Luminal cholesterol
Bile salts
Duodenal/jejunal enterocyte
Lymph
NPC1L1
Micellar cholesterol
Chylomicron
Chylomicron
ABCG5/G8
Bile salts Unabsorbed cholesterol
Bile salts
Ileal enterocyte
IBAT
Hepatic portal circulation
Fecal sterols

VLDL Metabolism

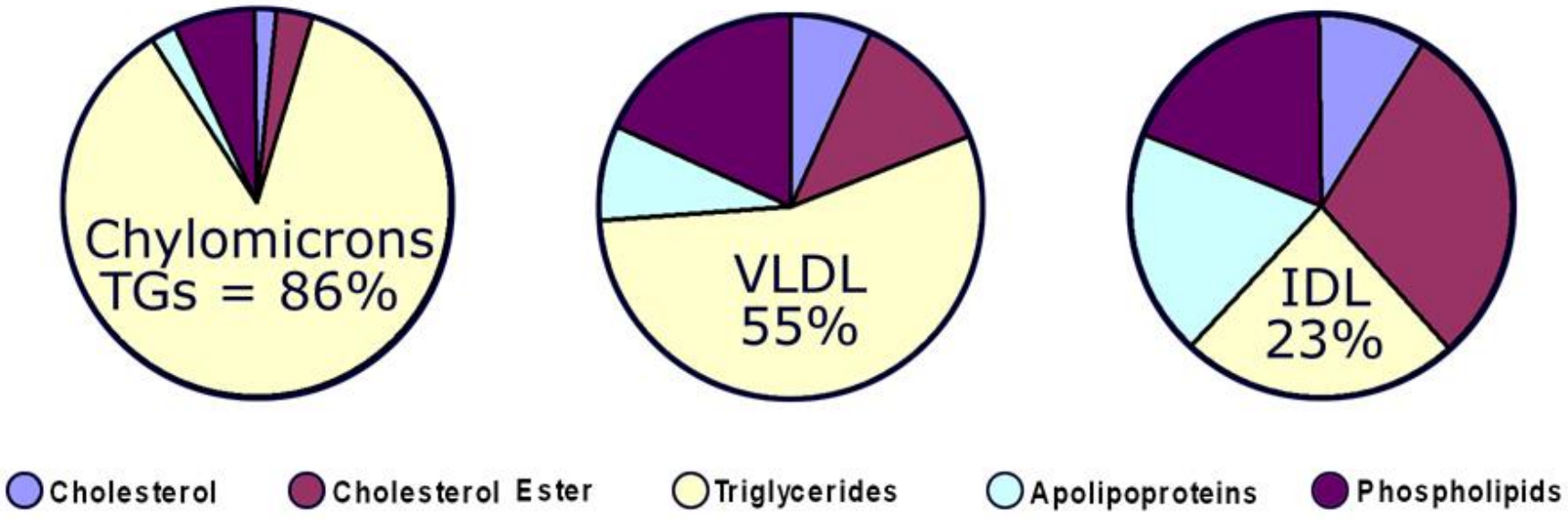


Atherogenic Particles

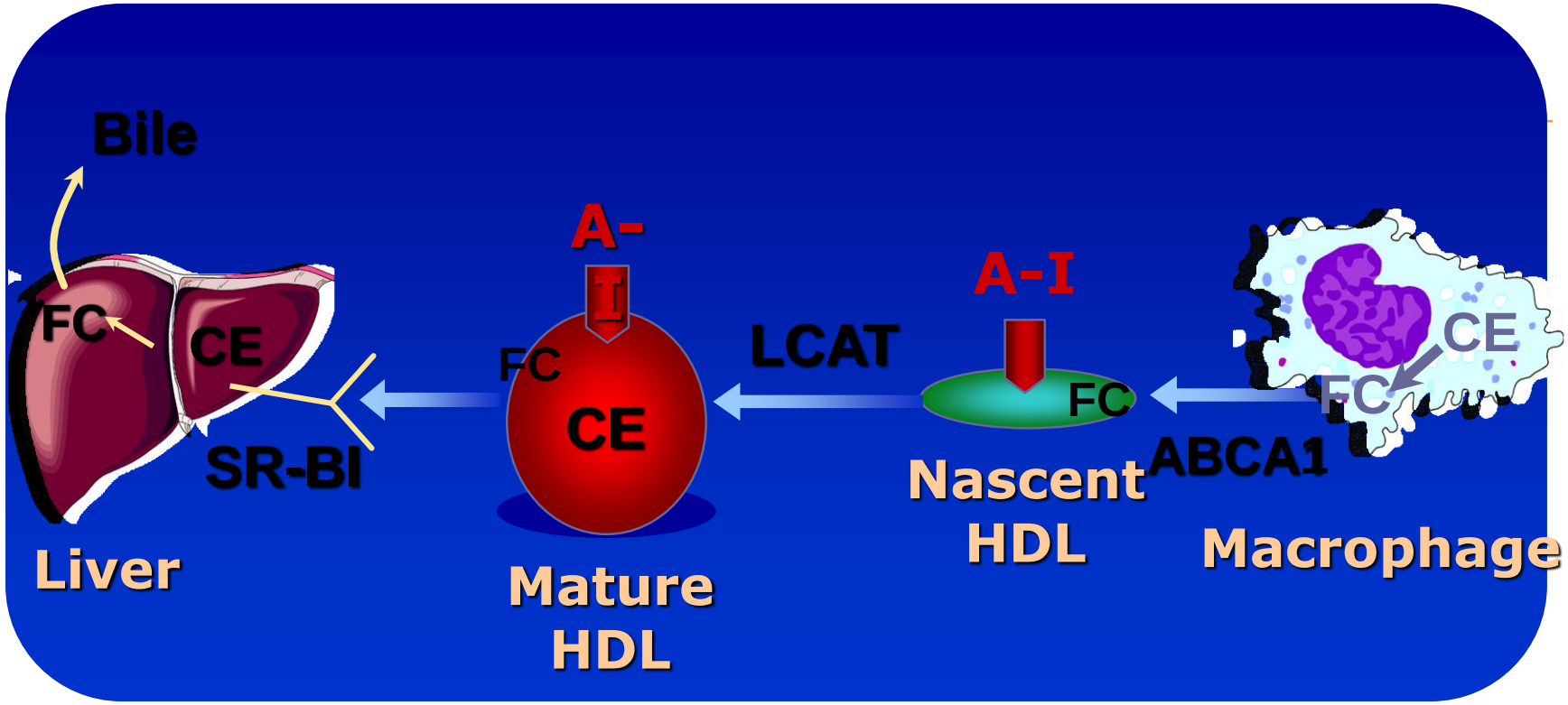
MEASUREMENTS:



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

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

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 heaptitis
- Systemic lupus erythematousus
- 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

Checking lipids

- Nonfasting lipid panel
  - measures HDL and total cholesterol
- Fasting lipid panel
  - Measures HDL, total cholesterol and triglycerides
  - LDL cholesterol is calculated:
    - LDL cholesterol = total cholesterol – (HDL + triglycerides/5)

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 cholesteral 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)

LDL and Non-LDL(HDL/TC)

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

Framingham Heart Study to estimate 10-year risk for coronary heart disease outcomes

http://hp2010.nhlbihin.net/atpiii/CALCULATOR.asp?usertype=prof

- **Age**
- **LDL-C**
- **T. Chol**
- **HDL-C**
- **Blood Pressure**
- **Diabetes**
- **Smoking**

Adult Treatment Panel III Guidelines for Treatment of Hyperlipidemia

Risk Category	***Begin Lifestyle Changes If:***	***Consider Drug Therapy If:***	***LDL Goal***
High: CAD or CAD equivalents (10-yr risk > 20%)	**LDL ≥ 2.58 mM**	**LDL ≥ 2.58 mM (drug optional if < 2.58 mM)**	**< 2.58 mM; < 1.8 mM optional**
Moderate high: ≥ 2 risk factors with 10-yr risk 10 to 20%*	**LDL ≥ 3.36 mM**	**LDL ≥ 3.36 mM**	**< 3.36 mM; < 2.58 mM optional**
Moderate: ≥ 2 risk factors with 10-yr risk < 10%*	**LDL ≥ 3.36 mM**	**LDL ≥ 4.13 mM**	**< 3.36 mM; < 2.58 mM optional**
Lower: 0–1 risk factor	**LDL ≥ 4.13 mM**	**LDL ≥ 4.91 mM (drug optional if 4.13–4.88 mM)**	**< 4.13 mM**

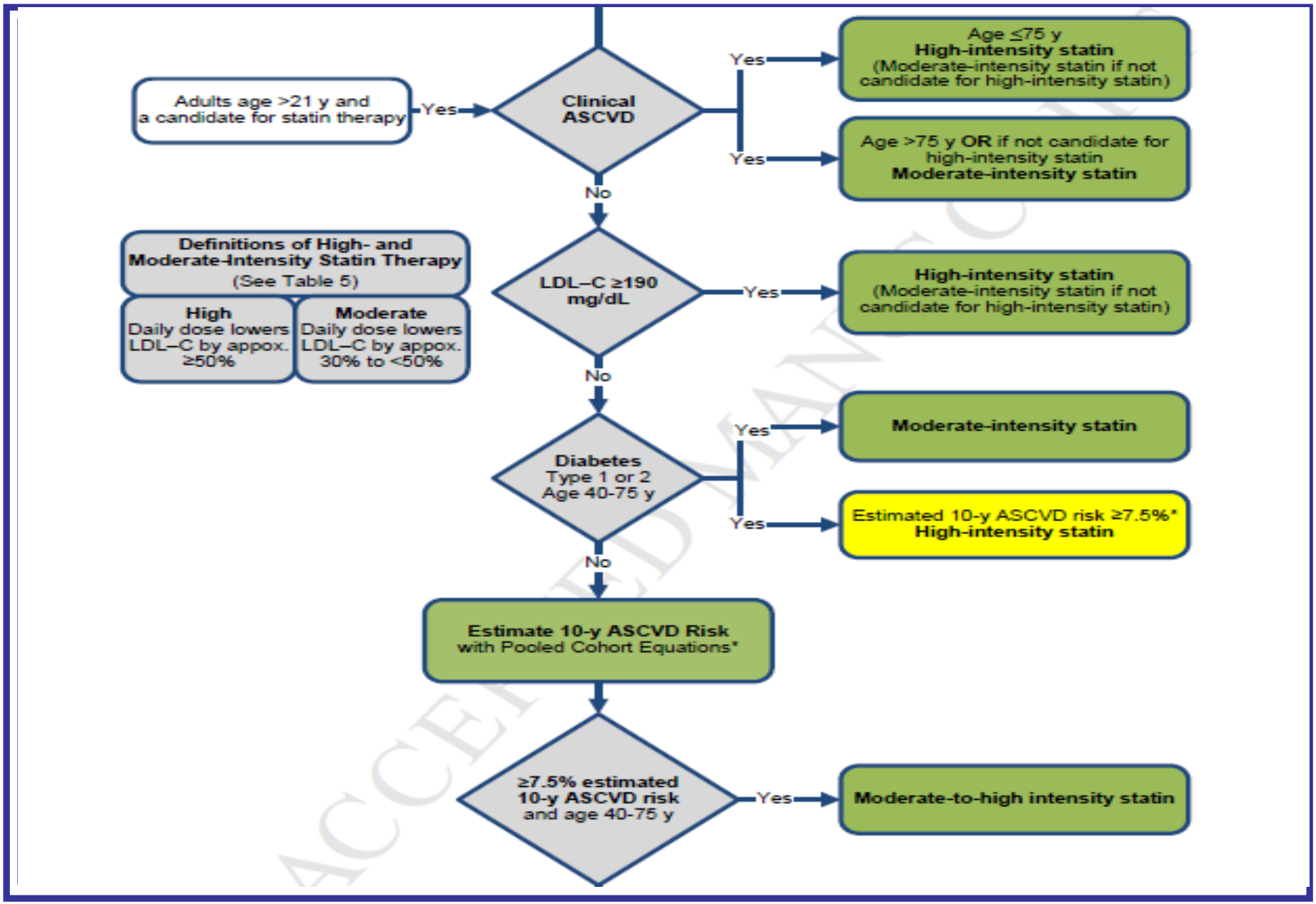
*For 10-yr risk, see Framingham risk tables

Canadian New Guideline

Risk categories

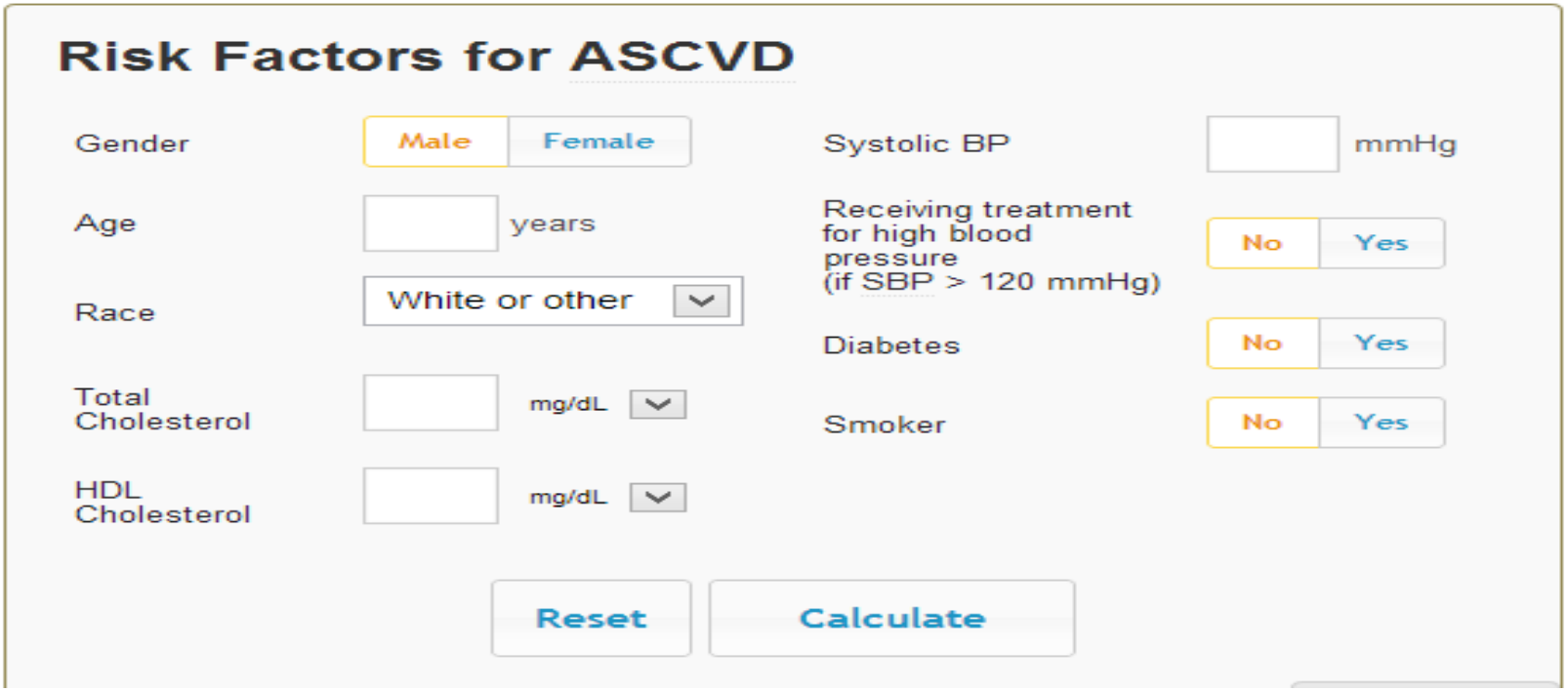
Risk level	10-year CAD risk	Recommendations
High	≥20%	*Treatment targets:* Primary target: LDL-C <2.0 mmol/L Secondary target: TC/HDL-C <4.0
Moderate	10% - 19%	*Treat when:* LDL-C ≥3.5 mmol/L *or* TC/HDL-C ≥5.0
Low	<10%	*Treat when:* LDL-C ≥5.0 mmol/L *or* TC/HDL-C ≥6.0

High risk includes coronary artery disease (CAD), peripheral artery disease, cerebrovascular disease and most patients with diabetes.


Adults 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 appox. ≥50%
Moderate
Daily dose lowers LDL–C by appox. 30% to <50%
LDL–C ≥190 mg/dL
Yes
High-intensity statin
(Moderate-intensity statin if not candidate for high-intensity statin)
No
Diabetes
Type 1 or 2
Age 40-75 y
Yes
Moderate-intensity statin
Yes
Estimated 10-y ASCVD risk ≥7.5%*
High-intensity statin
No
Estimate 10-y ASCVD Risk
with Pooled Cohort Equations*
≥7.5% estimated 10-y ASCVD risk
and age 40-75 y
Yes
Moderate-to-high intensity statin

Pooled Cohort Risk Assessment Equations

Predicts 10-year risk for a first atherosclerotic cardiovascular disease (ASCVD) event



http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx

Intensity of Statin Therapy in primary and secondary prevention

Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

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

Table 8.1—Recommendations for statin treatment in people with diabetes

Age	Risk factors	Recommended statin dose*	Monitoring with lipid panel
<40 years	None	None	Annually or as needed to monitor for adherence
	CVD risk factor(s)**	Moderate or high	
	Overt CVD***	High	
40–75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	High	
	Overt CVD	High	
>75 years	None	Moderate	As needed to monitor adherence
	CVD risk factors	Moderate or high	
	Overt CVD	High	

*In addition to lifestyle therapy.
**CVD risk factors include LDL cholesterol ≥100 mg/dL (2.6 mmol/L), high blood pressure, smoking, and overweight and obesity.
***Overt CVD includes those with previous cardiovascular events or acute coronary syndromes.

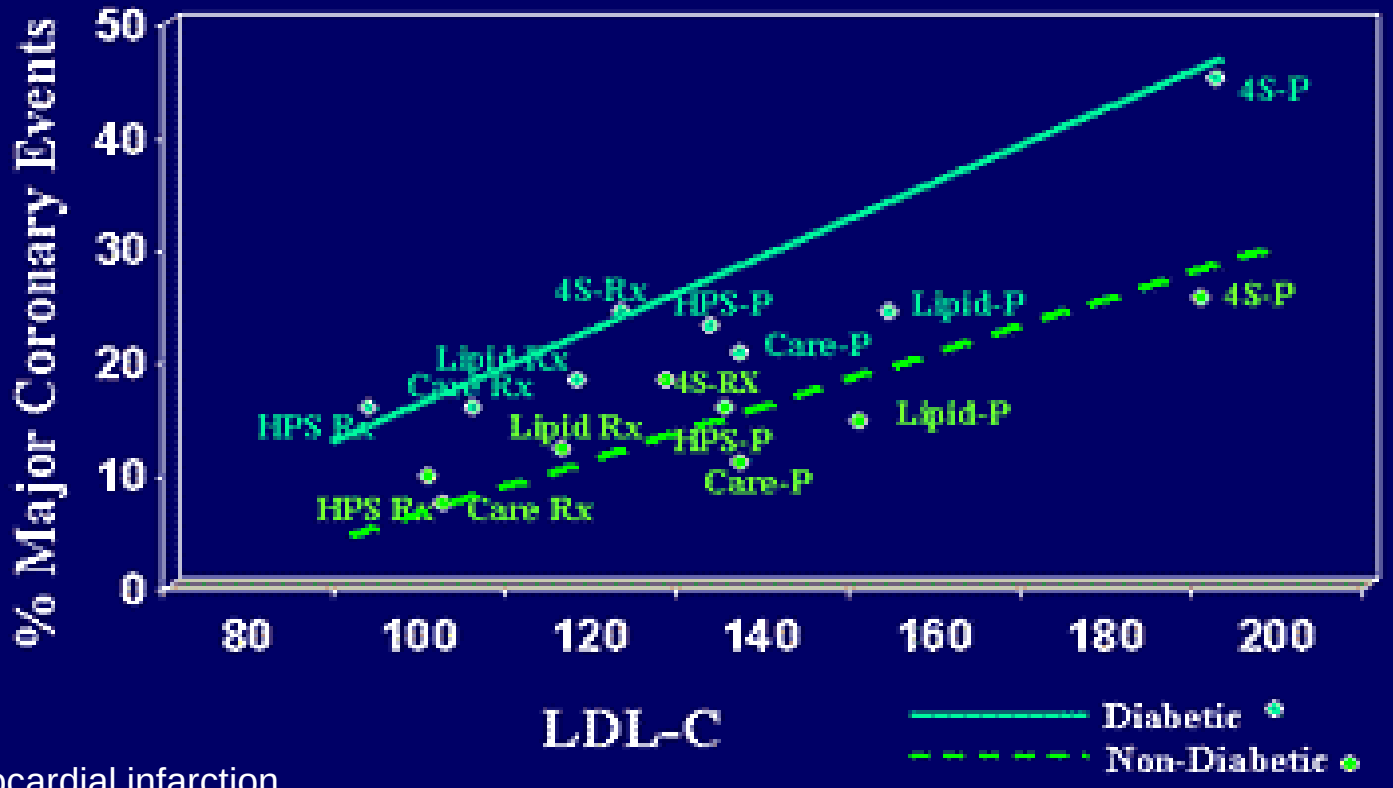
Treatment of Hyperlipidemia

- Lifestyle modification
  - Low-cholesterol diet
  - Exercise

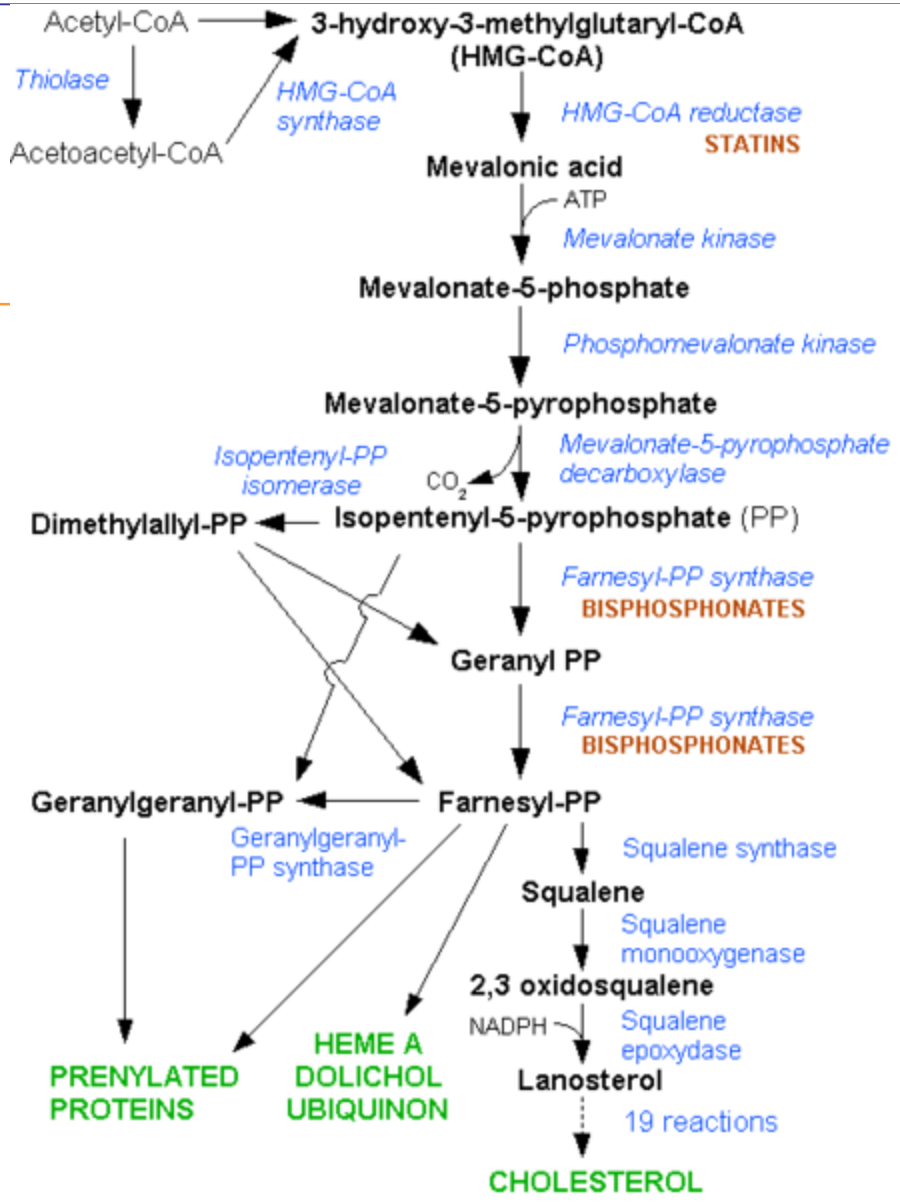
Medications for Hyperlipidemia

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**

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
CO_2
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
CHOLESTEROL
PRENYLATED PROTEINS
HEME A
DOLICHOL
UBIQUINON

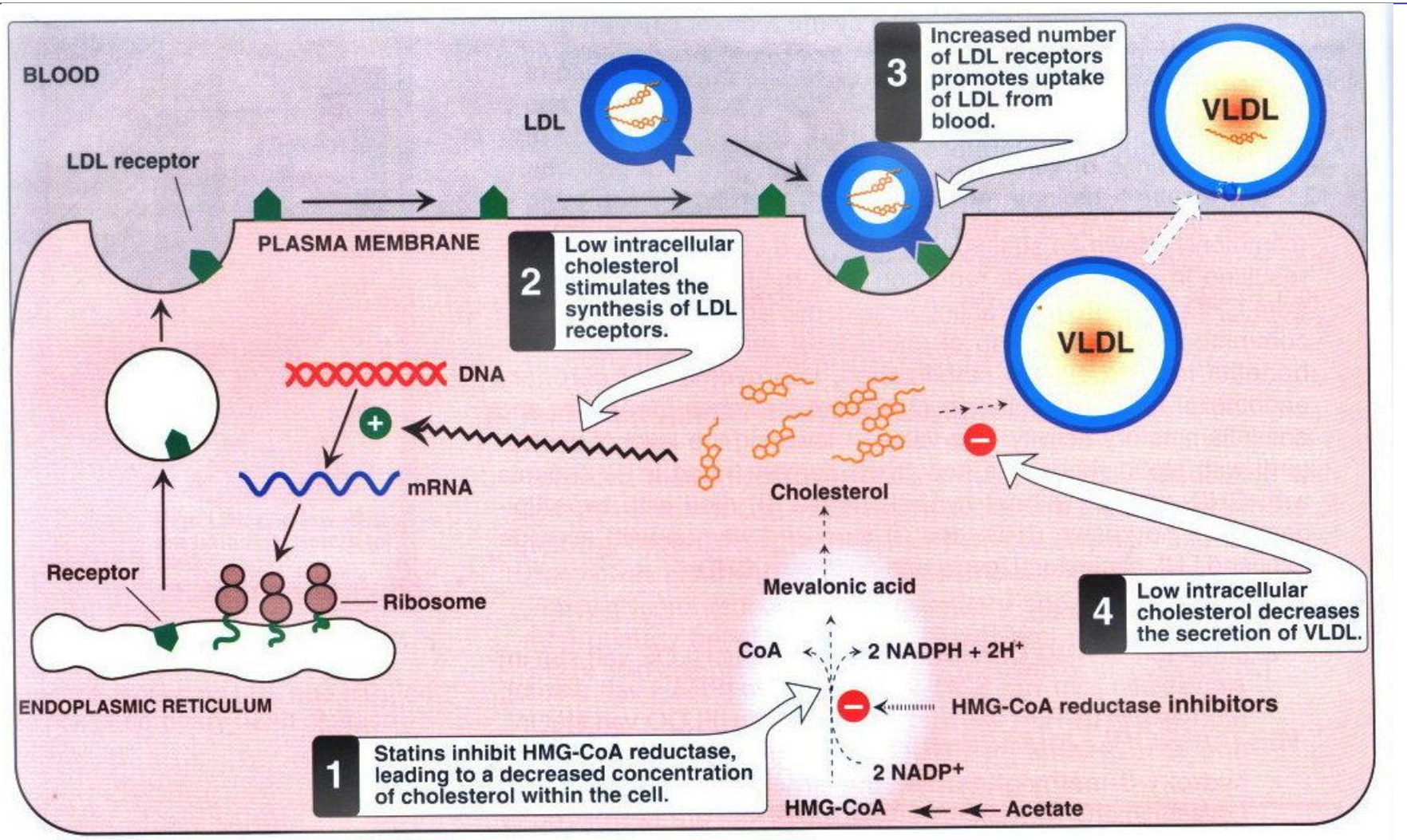


Figure 21.5
Inhibition of HMG-CoA reductase by the statin drugs.

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)

STATIN Safety recommendations

Conditions that could predispose pts to statin side effect:

- Impaired renal or hepatic function
- History of previous statin intolerance or muscle disorder
- Age >75y
- Unexplained ALT elevation > 3x ULN
- History of hemorrhagic stroke
- Asian ancestry

STATIN Safety recommendations

- Check baseline ALT prior initiating the statin (Grade B)
- Check LFTs if patient develops Symptoms of hepatic dysfunction (Grade E)
- If 2 consecutive LDL <40, Consider decreasing the statin dose (Grade C, weak recommendation)
- It may be harmful to initiate simvastatin 80mg, or increase the dose of simvastatin to 80mg (Grade B)