Hypertriglyceridemia: Why, When, and How to Treat

Gregory Cohn, MD, FNLA, FASPC

DISCLOSURES

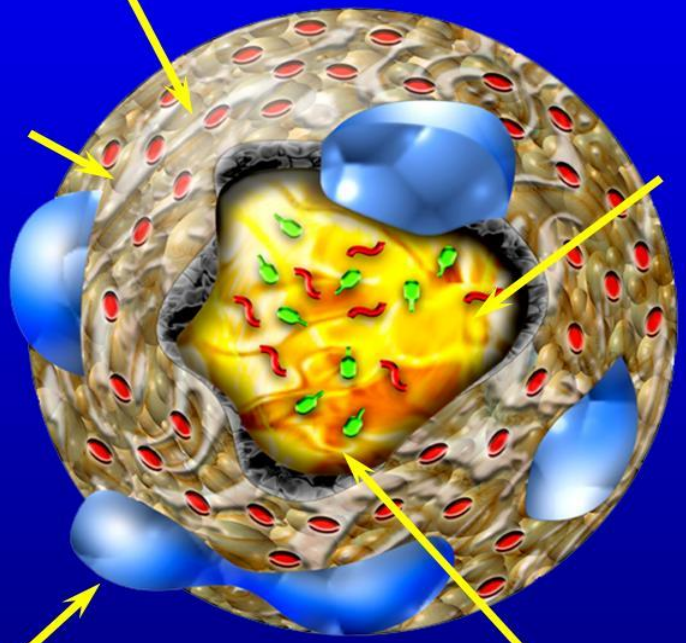
- Consultant to Akcea Therapeutics (in the past 12 months).

OUTLINE

I. Lipoproteins
II. Non-HDL-C
III. Causes and Consequences
IV. Treatment


No Respect

Structure of a Typical Lipoprotein



Free cholesterol
(surface and core)

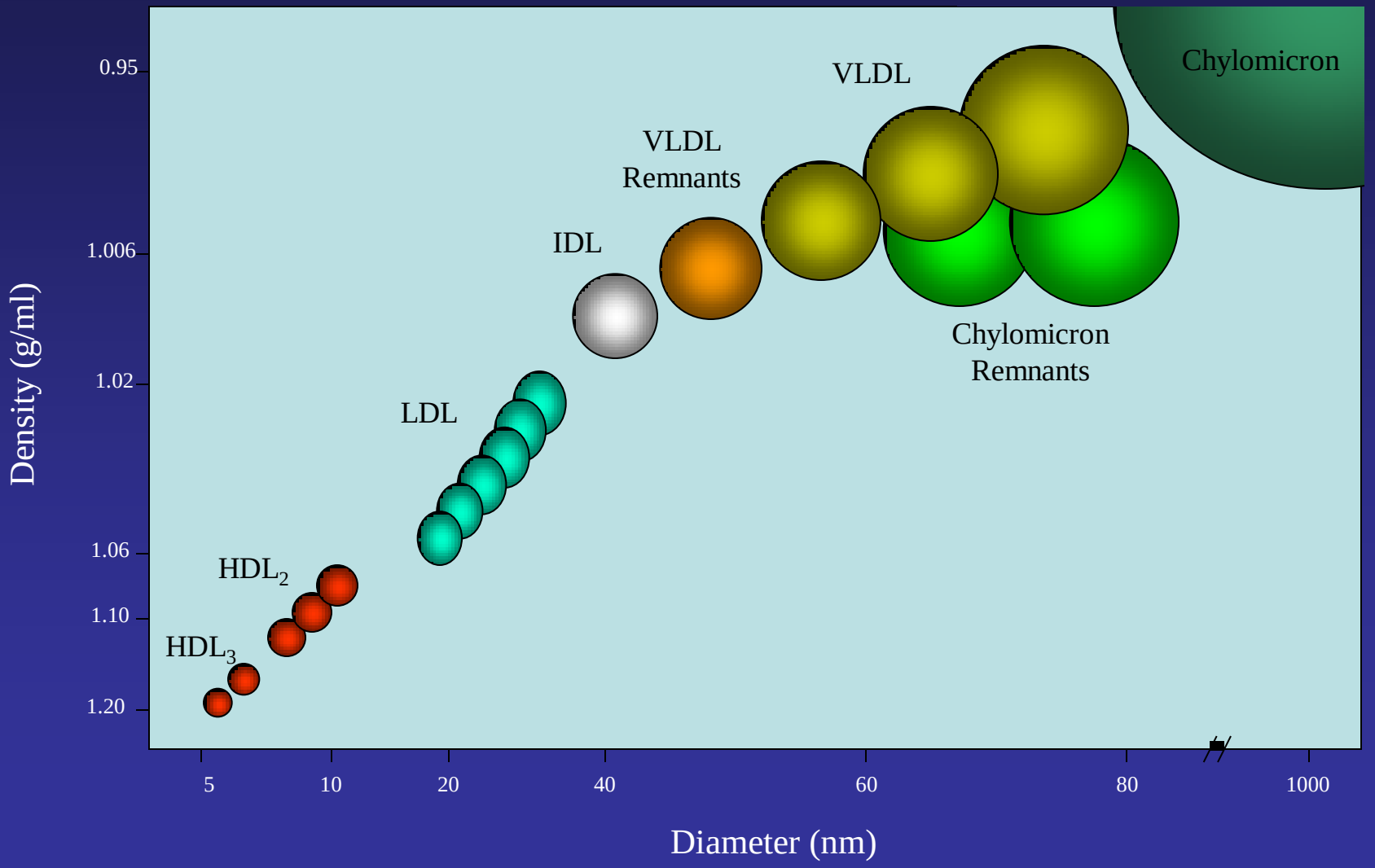
Phospholipid
(amphipath at surface only)

Triglyceride
(core only)

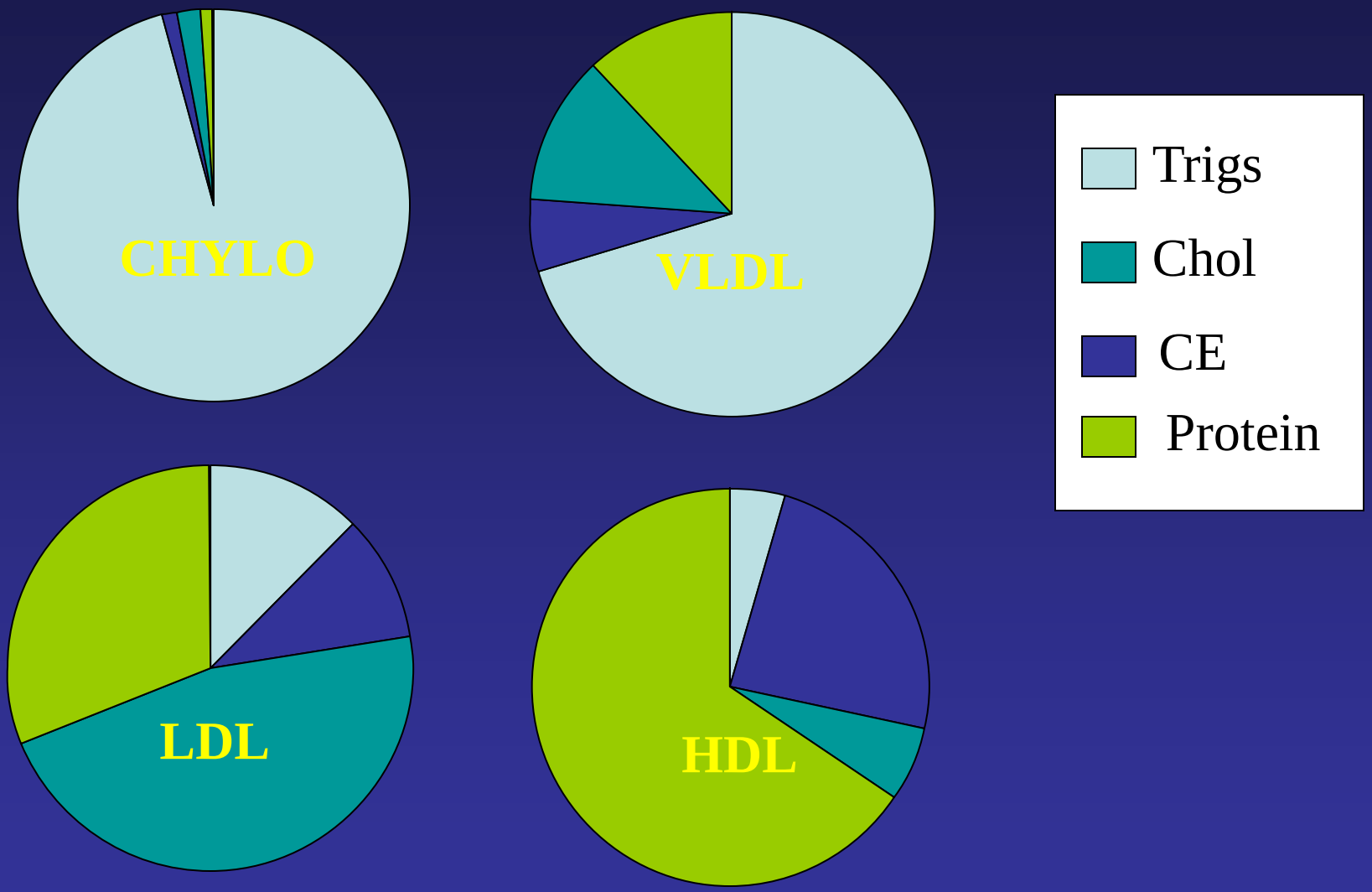
Apolipoprotein
(amphipath at surface only)

Cholesteryl ester
(core only)

Lipoprotein Classes



Lipoprotein Overview

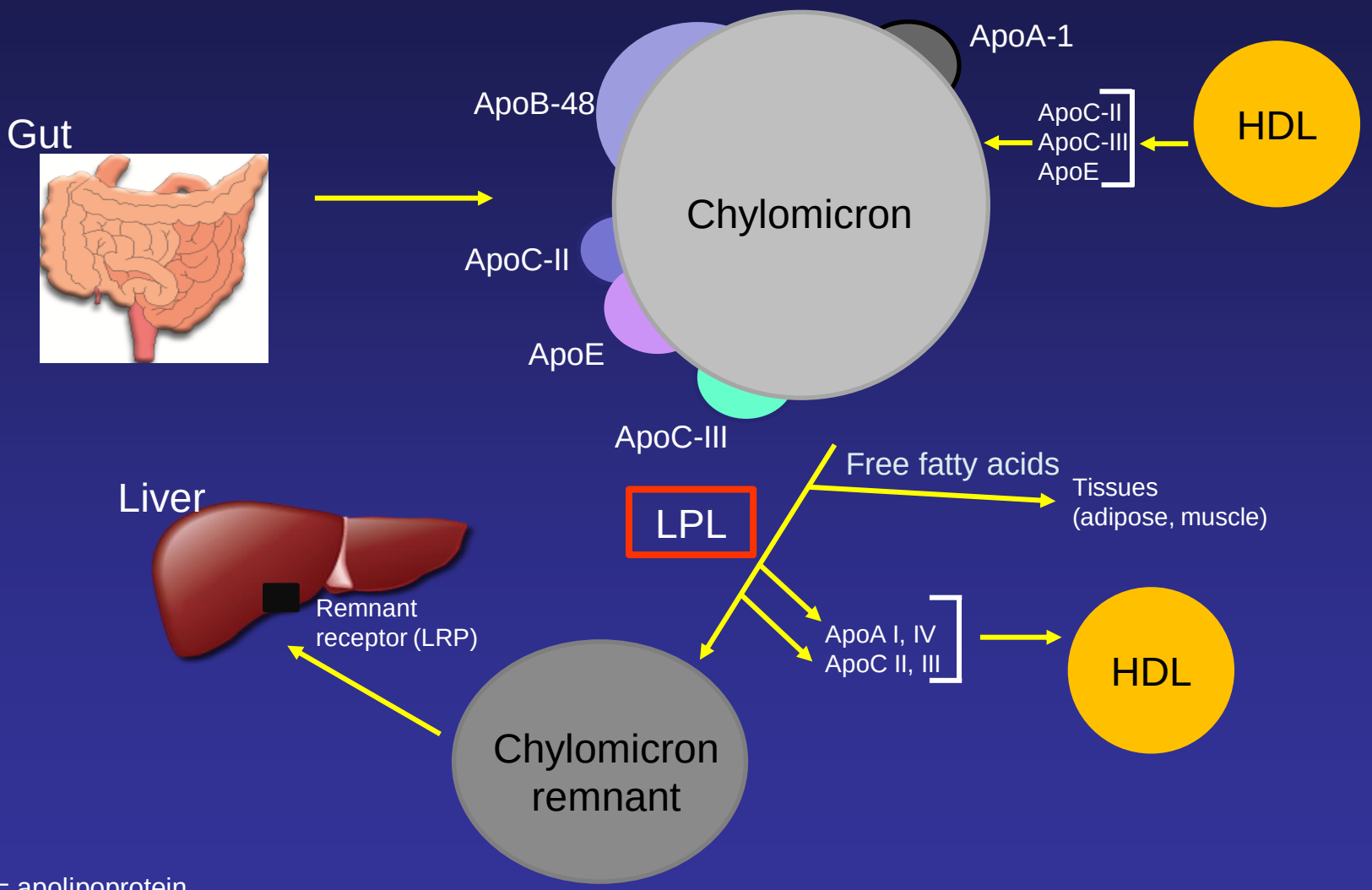


Major Apolipoproteins

Apo	Location	Function	Prevalence	Athero
A-I	HDL (Chyl)	Multi	Common	↓ ↓ ↓
A-II	HDL	??	Common	↓ ?
B-48	Chyl	Exog. TG & Ch transp	Rare (mainly postprandial)	?
B-100	VLDL, LDL	Deliver endog. cholesterol	Common	↑ ↑ ↑
C-II	VLDL, HDL	↑ LPL activity	*Un*common	↓
C-III	VLDL, HDL	↓ LPL activity	*Un*common	↑
E	VLDL, HDL	Remn Lp Catab, Chol Efflux?	*Un*common	↓ ?
(a)	Lp(a)	??	*Un*common	↑ ↑ ↑

Apo B-100 and apo A-I are most important clinically, but all are ~important.

Chylomicron Metabolism



Apo = apolipoprotein.

Adapted from: http://www.myhealthywaist.org/the-concept-of-cmr/intra-abdominal-adipose-tissue-the-culprit/complications-of-intra-abdominal-obesity/atherogenic-dyslipidemia/print.html.

What is Lipoprotein Lipase?

Lipoprotein lipase (LPL):

- Rate-limiting catalytic enzyme involved in the hydrolysis of:
  - Circulating chylomicrons
  - VLDL
- Functions to internalize free fatty acid into:
  - Muscle (cardiac, skeletal)
  - Adipose tissue

Stroes E, et al. *Atheroscler Suppl.* 2017;23:1-7.
Benlian P, et al. *N Engl J Med.* 1996;335:848-854.

Classification of Triglyceride Levels

- Normal: <150 mg/dl
- Borderline: 150 mg/dl – 199 mg/dl
- High: 200 mg/dl - 499 mg/dl
- Very High (Severe): >500 mg/dl
- Optimal levels are < 100 mg/dl

Why do we treat elevated levels of Triglycerides?

When TGs = 151 – 499 mg/dl:

- To prevent and treat atherosclerosis

When TGs ≥ 500 mg/dl

- To prevent and treat acute pancreatitis

A Medical School Refresher:

- Total Cholesterol = LDL-C + HDL-C + VLDL-C.
- Rearranging the above: LDL-C = Total Cholesterol – (HDL-C + VLDL-C)
- But…it is difficult to measure VLDL-C, so we **ESTIMATE** its value.
- The Friedewald Equation: LDL-C = Total Cholesterol – (HDL-C + Triglycerides/5)

TGs and Atherosclerosis

- TGs in plasma are carried by Apo-B containing, TG-rich lipoproteins (TRLs), mainly in VLDLs, but to a lesser extent in IDLs.
- TG concentrations reliably indicate the cholesterol content of TRLs (remnant cholesterol), which are atherogenic.

NCEP ATP III: Triglyceride-Rich Remnant Lipoproteins Are Atherogenic

- Elevated triglyceride levels are a marker for elevated levels of atherogenic remnant lipoproteins
- VLDL-C is the most readily available measure of atherogenic remnant lipoproteins for clinical practice
- When triglyceride levels are elevated, non–HDL-C (LDL-C + VLDL-C) better represents the concentrations of all atherogenic lipoproteins than LDL-C alone
- Non–HDL-C should be a secondary target of therapy when triglyceride levels are ≥200 mg/dL

Third Report of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III). *Circulation*. 2002;106:3143-3421.

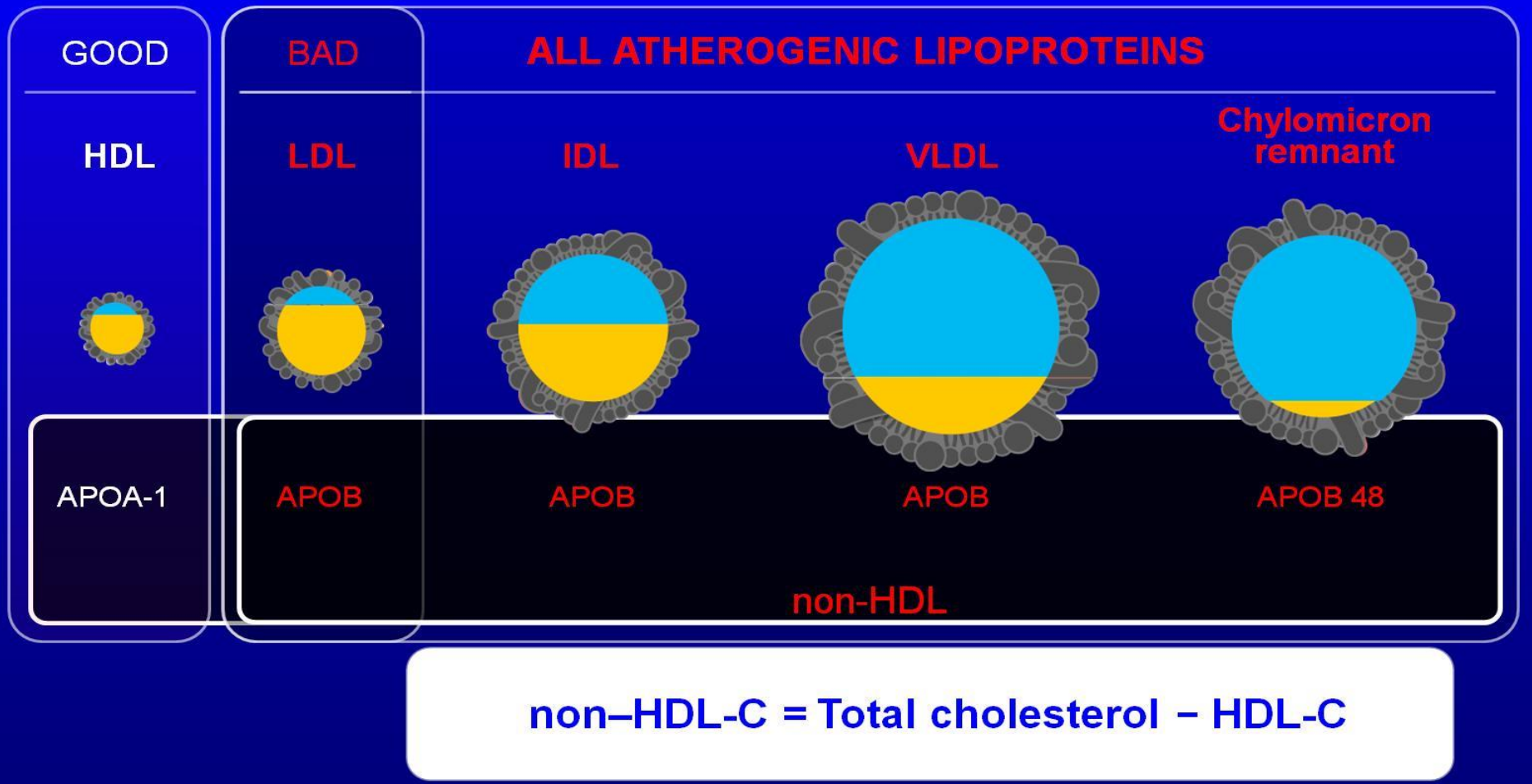
How Can Hypertriglyceridemia (HTG) Be Atherogenic?

- TGRL carry cholesterol and promote atherosclerosis*
- VLDL is precursor to LDL (pro-atherogenic)
- HTG drives:
  - CE enrichment of VLDL (*more* atherogenic)
  - ↓ LDL size (small, dense LDL are *more* atherogenic)*
  - ↓ LDL-C (small, dense LDL carry less cholesterol)*
  - ↓ HDL size (small, dense HDL are unstable and *less* anti-atherogenic)
- HTG is linked to other pro-atherogenic states*
  - Insulin resistance
  - Pro-inflammatory state
  - Prothrombotic state
  - Pro-oxidative state
  - Endothelial dysfunction

*Reasons why *non-HDL-C* is *stronger than LDL-C* as CVD factor.

CE=cholesteryl ester; TGRL=triglyceride-rich lipoproteins; VLDL=very low-density-lipoprotein.

What Is Non–HDL-C?



non–HDL-C = Total cholesterol − HDL-C

1. NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Third Report Executive Summary*. 2001; NIH Publication No. 01-3670.

Non-HDL-C: A Neglected CVD Risk Factor/Rx Goal

- Use whenever TGs ≥ 200 mg/dl
- Normal VLDL-C is ≤ 30 mg/dl (estimated as 150/5 from the Friedewald Equation).
- Thus, the Non-HDL-C goal for any patient is their LDL-C goal + 30 (i.e. if LDL-C goal is < 100 mg/dl, then Non-HDL-C goal is < 130 mg/dl).

Non-HDL-C: A Neglected CVD Risk Factor/Rx Goal

***Whenever* TG > 200 mg/dL:**

1. **Non-HDL-C = Total C – HDL-C (*all* atherogenic lip)**
2. **Non-HDL-C goal = LDL-C goal + 30:**

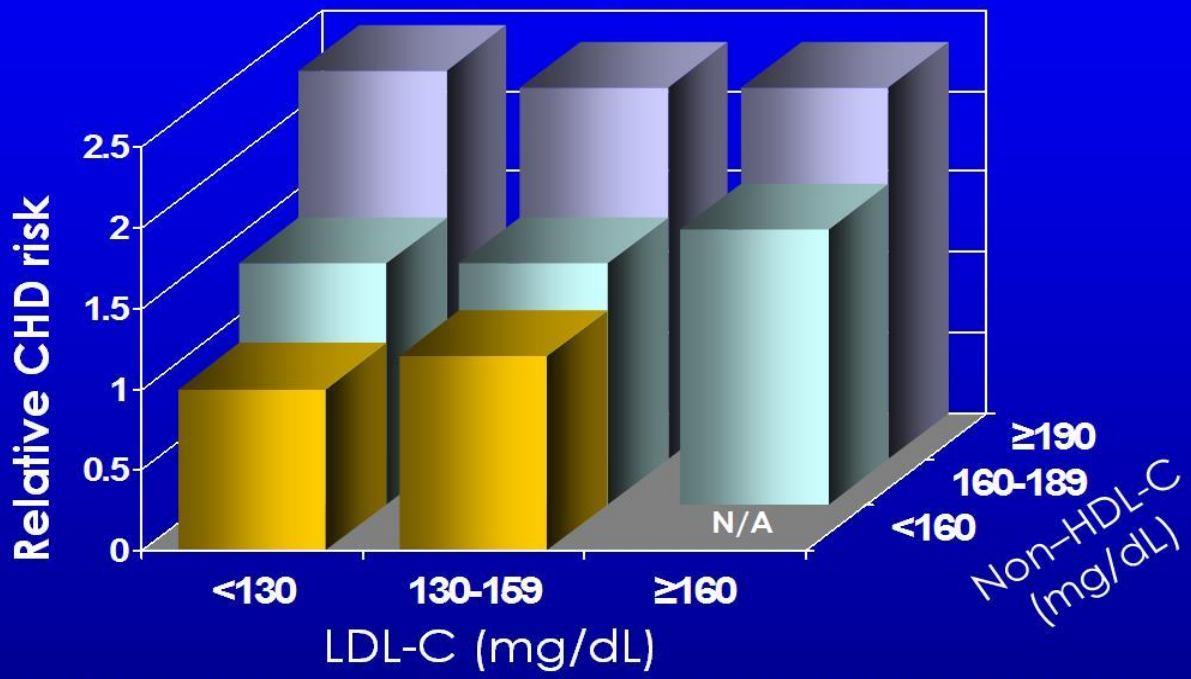
Patient Category	LDL-C Goal (mg/dL)	Non–HDL-C Goal (mg/dL)
CVD, DM+MRF	<70	<100
CHD/CHD risk equivalent	<100	<130
No CHD, 2+ risk factors	<130	<160
No CHD, 0-1 risk factors	<160	<190

Rx to lower Non–HDL-C:

- TG >500: Fibr, P-Om3, NA, statin, ezet?
- TG 200-500: Statin, ezet, Fibr, P-Om3, NA, BAS

ACS = acute coronary syndrome; MS = metabolic syndrome; HTG = hypertriglyceridemia.
Adapted from Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA*. 2001;285:2486-2497; Grundy SM et al. *Circulation*. 2004;110:227-239.

Non–HDL-C Is Superior to LDL-C in Predicting CHD Risk



- Within non–HDL-C levels, no association was found between LDL-C and the risk for CHD
- A strong, positive and graded association between non–HDL-C and risk for CHD occurred within every level of LDL-C

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol.
Liu J et al. *Am J Cardiol*. 2006;98:1363-1368.

Causes of Hypertriglyceridemia

Secondary Causes of HTG
(Screen/Treat in All Cases)

Diseases/States

- Central/visceral adiposity
  - Insulin resistance/metabolic syndrome
  - DM-2 (esp. if poor control)
- Sedentary Lifestyle
- Endocrine disorders/states
  - Hypothyroidism
  - Hypercortisolism
  - Pregnancy
- Renal disorders
  - Nephrotic syndrome
  - End-stage renal disease
- Systemic Inflammation/Infection
  - Arthritis
  - HIV
  - Other?
- Psychiatric disorders

Drugs/Diet

- Recreational
  - Ethanol
  - Marijuana
- Diet
  - ↑ Sucrose/fructose/starch?
  - High fat (TG >~700)
  - High calories?
- Hormones
  - Oral estrogen (BCP & ERT)
  - Systemic glucocorticoids (*not* nasal or topical)
- BP/Lipid Rx
  - Beta blockers (most)
  - Thiazide diuretics
  - Bile-acid sequestrants
- Miscellaneous
  - Cyclosporine
  - Retinoic-acid derivatives
  - HAART (PI and others)
  - Atypical anti-psychotics

HAART = highly active antiretroviral therapy;

PI=protease inhibitors.

Modified from Pejic, R. et al., J Am Board Fam Med 2006;19:310-6.

Genetic Causes of Hypertriglyceridemia

- Familial Combined Hyperlipidemia (Fredrickson Type IIb)
  - Most common (1 in 100)
  - Insulin Resistance, ↑ TRL production, ↓ TRL clearance
  - ↑ TGs, ↓ HDL-C, ↑ LDL-C (small, dense LDL particles)
  - Significant ↑ risk of CVD

Genetic Causes of Hypertriglyceridemia

- Familial Dysbetalipoproteinemia (Fredrickson Type III)
  - Relatively rare (1 in 10,000)
  - ↓ TRL clearance
  - ↑ VLDL/IDL
  - Apo E2/E2 and characteristic physical findings
  - Significant ↑↑ in risk of CVD

Genetic Causes of Hypertriglyceridemia

- Familial Hypertriglyceridemia (Fredrickson Types IV/V)
  - Genetically heterogeneous
  - Production of enlarged VLDL-P and ↓ TRL clearance
  - ↑↑ TGs (typically 200 – 1000 mg/dl), ↓ HDL-C
  - Acute pancreatitis and increased risk of CVD

Genetic Causes of Hypertriglyceridemia

- Familial Hyperchylomicronemia (Fredrickson Type I)
  - Extremely rare (1 in 1 million)
  - Lipoprotein Lipase and/or Apo CII deficiency
  - TGs typically = 2,000 – 10,000 mg/dl
  - Recurrent pancreatitis often starting in early childhood, and some forms have increased risk of CVD

Hypertriglyceridemia and Pancreatitis

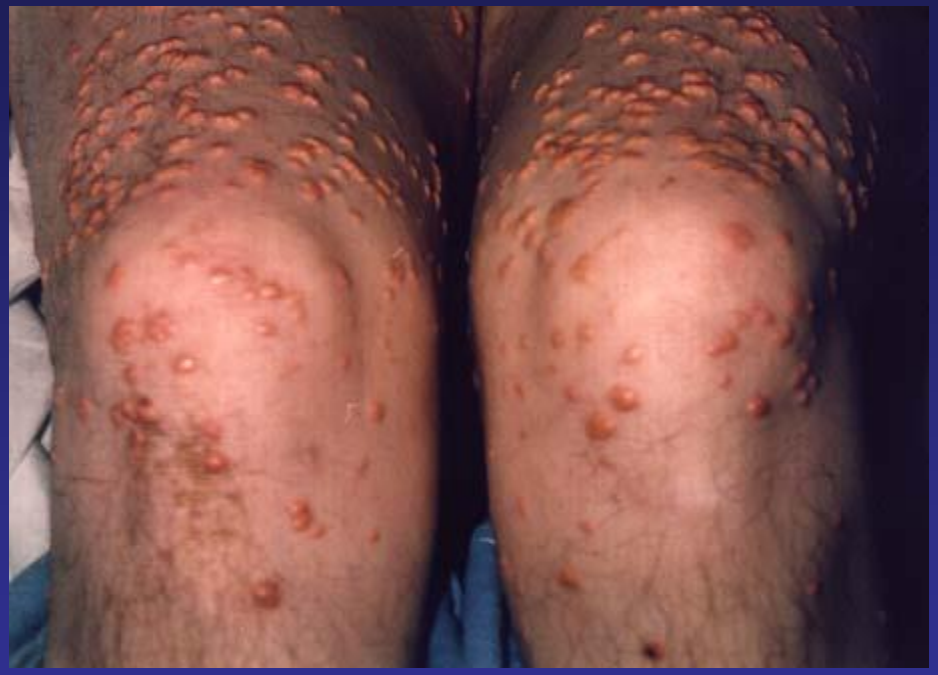
- After gallstones and excessive alcohol consumption, significantly elevated serum triglycerides can precipitate acute pancreatitis.
- TG are typically > 1000 mg/dl, often times much higher.
- Characterized by recurrent abdominal pain, nausea, vomiting

What TG Level is Associated with an Increased Risk of Pancreatitis?

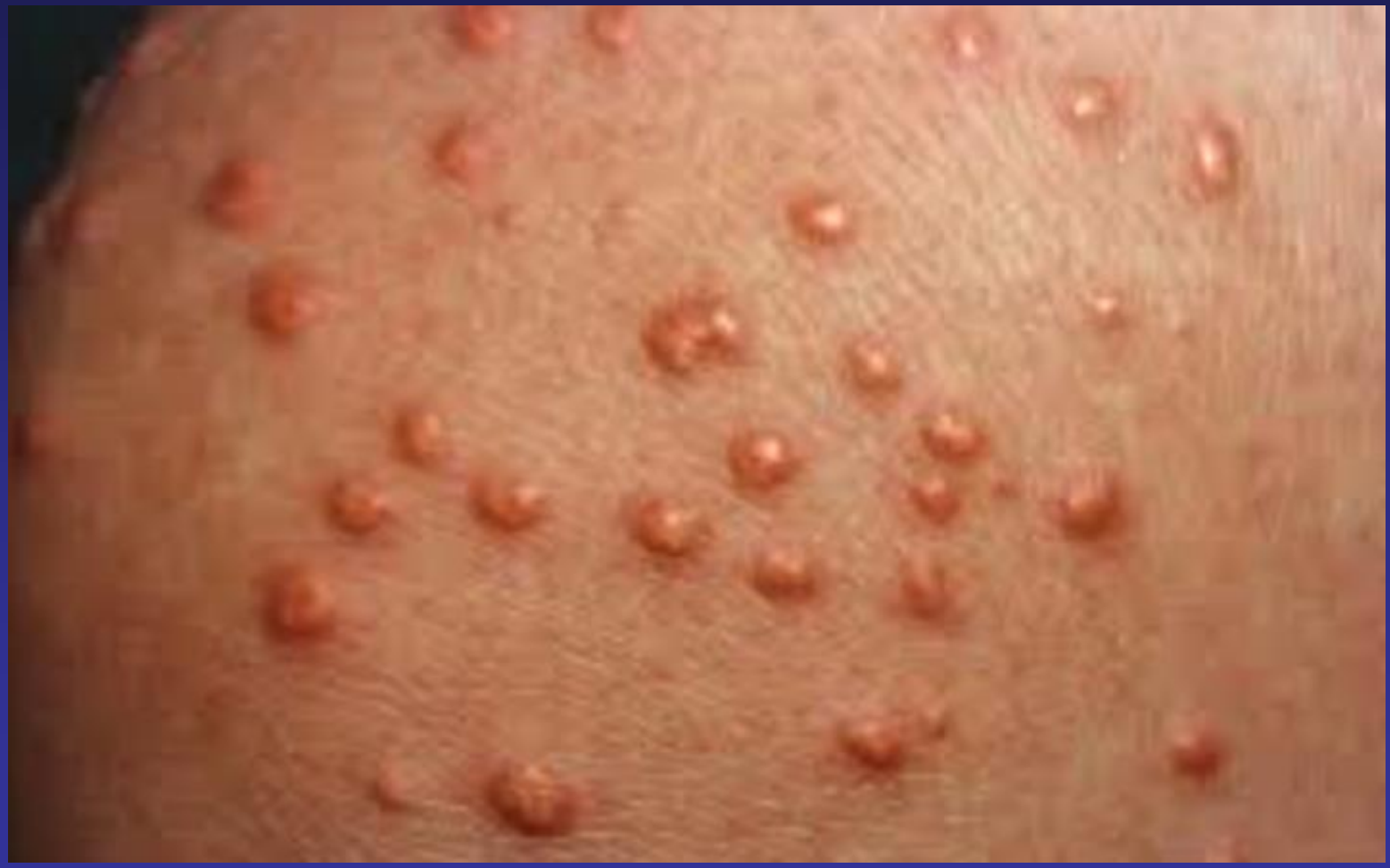
- Fasting TGs > 880 mg/dl
- Why the cut-off at 500 mg/dl then?
  - Significant variation in postprandial TGs, which can range in the hundreds-thousands
  - Patients with this level of TGs have problems with excessive production, slow metabolism, or both

1. Brahm, et al. *Nat Rev Endocrinol.* 2015;11:352–362; 2. Molhuizen H, et al. *Cardiovascular Rev & Rep.* 1999;20(11):607-619; 3. *NORDPhysician'sGuide*.2015.www.nordphysicianguides.org/lipoprotein-lipase-deficiency-lpld/; 4. Tremblay K, et al. *J Clin Lipidol.* 2011;5(1):37-44; 5. Gaudet D, et al. *N Engl J Med.* 2014;371(23):2200-6.

Clinical Manifestations of Primary Hypertriglyceridemia

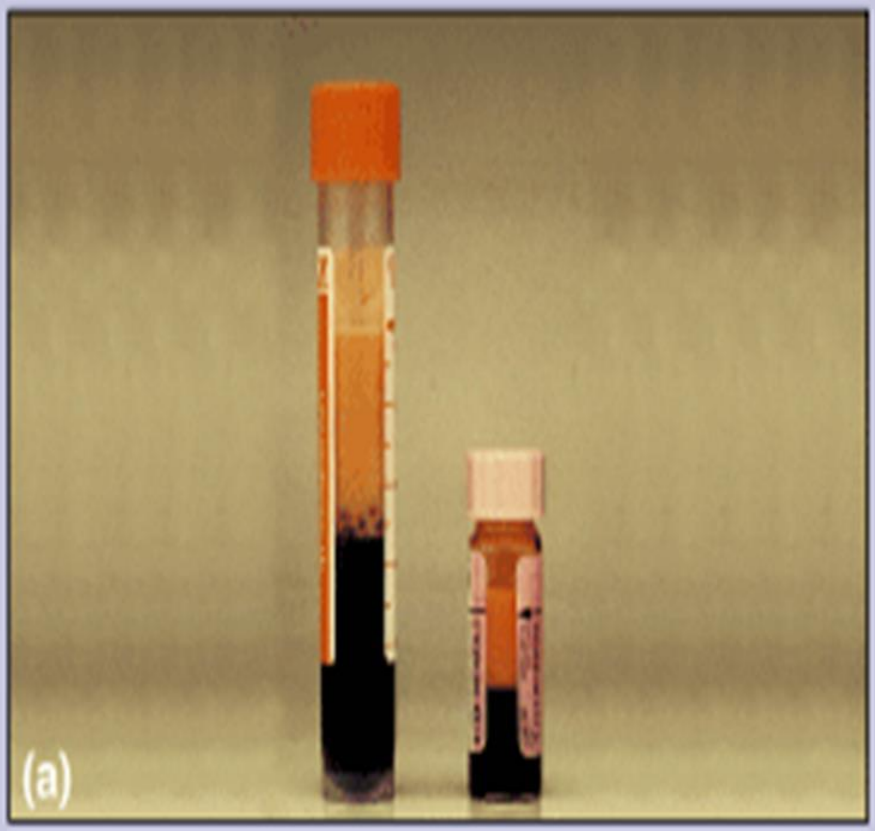


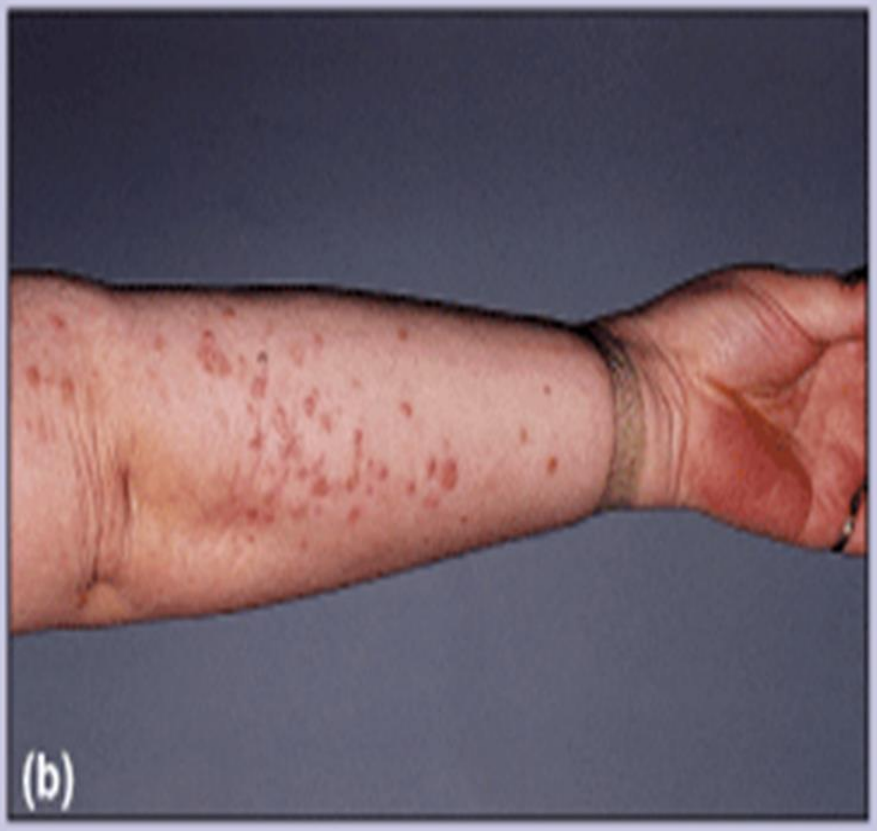
Clinical Manifestations of FCS: Eruptive Xanthomas



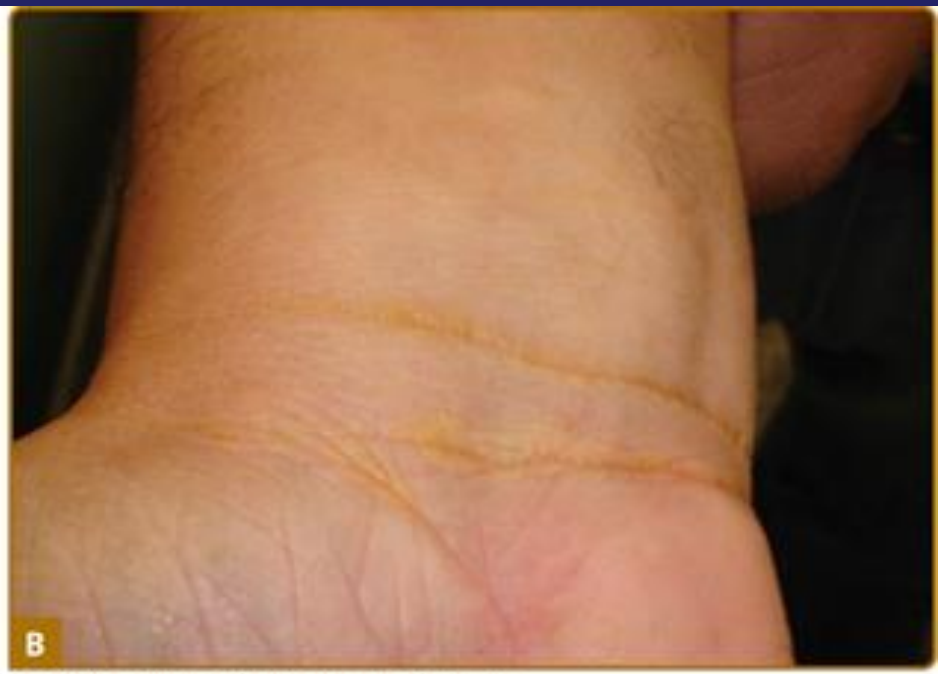
Clinical Manifestations of FCS: Lipemia Retinalis

Manifestations of severe hypertriglyceridaemia





Dermatologic Findings In Severe Hypertriglyceridemia and Familial Dysbetalipoproteinemia



Source: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

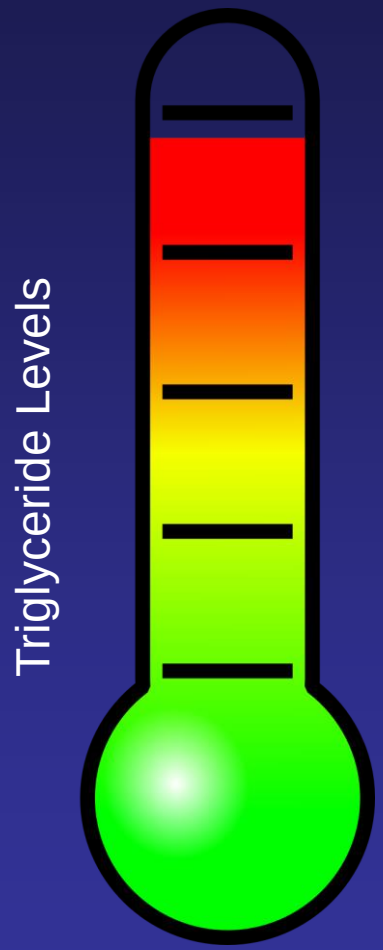
Treatment for Hypertriglyceridemia

Challenges of Treating FCS

- Standard triglyceride-lowering agents (niacin, fish oils, fibrates) are generally not effective.
- Currently, there is a lack of FDA-approved agents to lower TGs in FCS patients.
- Severe dietary restriction is currently the most effective form of therapy but is difficult to maintain.
- Alcohol intake and certain medications that increase TGs should be avoided.

Al Azkawi H, et al. *Case Rep Med.* 2010;2010:807434; Williams L, et al. *J Clin Lipidol.* 2016;10:462-465; Leaf DA. *Am J Med.* 2008;121:10-12.

What is the Goal of Therapy for FCS Patients?



4000 mg/dL – Increased risk of lipemia retinalis, hepatomegaly, splenomegaly

2000 mg/dL – Appearance of eruptive xanthomas

Pancreatitis can occur at any of these levels

<500 mg/dL – Goal of therapy

Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017. Jacobson TA, et al. *J Clin Lipidol.* 2014;8:473-488.

Treatment Options

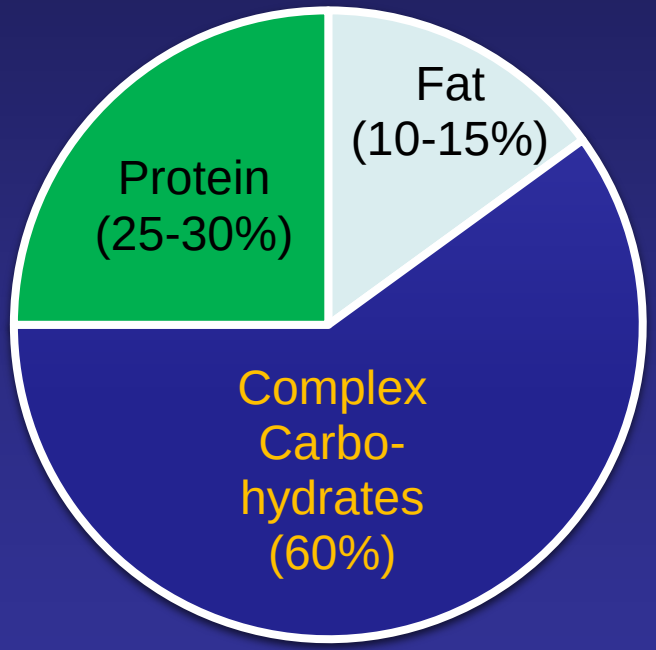
- Diet and lifestyle
- Medications
- Plasmapheresis

Dietary Approaches

- The patient must work closely with a dietician
  - focus on low fat diet to cut off the production of chylomicrons
  - usually < 20 g/d and sometimes as low as 10g/d
  - medium-chain TG-rich foods, such as coconut oil, can be used for cooking, as they are absorbed directly into the portal vein without becoming incorporated chylomicron TG

How Should Patients Manage Fat Intake?

Recommended dietary composition for patients with FCS



Total fat intake should comprise from 10% to 15% of daily caloric needs.

Williams L, et al. *J Clin Lipidol.* 2016;10:462-465.
Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2017.

Physical Activity and Hypertriglyceridemia

- Aerobic activity enhances lipid oxidation, thereby facilitating the hydrolysis and utilization of TG in skeletal muscle.
- Overall, exercise is most effective in lowering TG (~ 20% to 30%) when baseline levels are elevated (i.e., >150 mg/dl), activity is moderate to intensive, and total caloric intake is reduced.

Medications to Lower TGs

- Fibrates
  - Fenofibrate (once daily) or Gemfibrozil (BID)
- Niacin
  - Immediate release (TID), sustained release (Slo-Niacin QD-BID), or programmed release (Niaspan once nightly)

Medications to Lower TGs

- Omega-3 Fish Oil
  - OTC or prescription (Lovaza or Vascepa)
  - FDA approved for TGs > 500 mg/dl at a dose of 4000 mg/d
- Statins
  - All statins lower TGs modestly if they are elevated
  - Most potent statins have the strongest effect (i.e. Atorvastatin and Rosuvastatin)

How to Read a Fish Oil Label

Other Medications to Lower TGs

- Heparin
  - Directly stimulates the release of Lipoprotein Lipase (LPL) from endothelial cells
  - Levels of LPL peak in approximately 1 hour, but the effect rapidly declines
  - No official dosing guidelines and both SQ and IV regimens have been used
- Insulin

Plasmapheresis

- Used for treatment of acute, severe hypertriglyceridemia associated with:
  - acute pancreatitis
  - gestational hypertriglyceridemia
  - iatrogenic hypertriglyceridema
    - corticosteroids, HAART, Accutane

Plasmapheresis

- Indicated for pancreatitis due to severe hypertriglyceridemia.
- Reduces TG levels and circulating activating enzymes, proteases, and inflammatory mediators by physically filtering out these toxic substances from the blood.
- No RCT exist to support the use of plasmapheresis only case reports.

NCEP Guidelines: Treatment Objectives for Elevated Triglycerides

	Primary Objective	Secondary Objective
"Very High" TG ≥500 mg/dL	↓ TG	(↓ LDL-C &) ↓ non–HDL-C
"High" TG 200-499 mg/dL	↓ LDL-C	↓ non–HDL-C

HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; NCEP=National Cholesterol Education Program; TG=triglyceride; VLDL-C=very–low-density lipoprotein cholesterol.

NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *Third Report Executive Summary*. 2001; NIH Publication No. 01-3670.