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Overcoming Obstacles: Expert Perspectives on the Diagnosis and Management of Familial Chylomicronemia Syndrome

This activity is supported by an educational grant from Ionis Pharmaceuticals, Inc.

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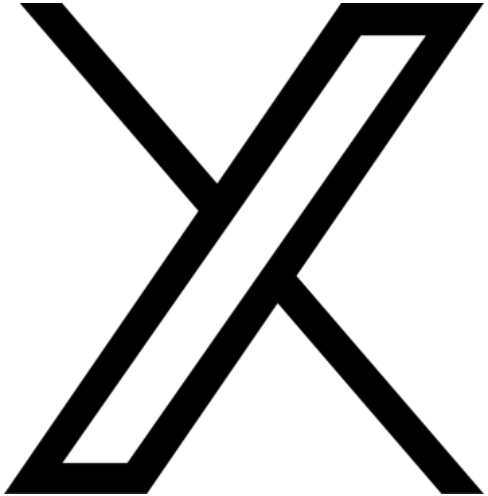

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Learning Objective 1

Identify key diagnostic elements of FCS

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Learning Objective 2

Integrate multidisciplinary approaches that may facilitate adherence to FCS dietary guidelines

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Learning Objective 3

Assess recent study data evaluating current and emerging FCS pharmacologic therapies

Hypertriglyceridemia

- Hypertriglyceridemia is associated with
  - Increasing age
  - Elevated blood glucose levels
  - Higher body mass index
  - Elevated total cholesterol
  - Reduced HDL cholesterol
- Of adults in the US with hypertriglyceridemia
  - 18% of patients had levels ≥ 200 mg/dL
  - 0.4% of patients had levels ≥ 1,000 mg/dL
- Common causes include
  - Obesity/metabolic syndrome
  - Diabetes
  - Chronic liver or kidney disease
  - Hormones/drugs

HDL = high-density lipoprotein

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Audience Response

When should you suspect familial chylomicronemia syndrome in your patient?

A. When extreme triglyceride levels cannot be explained by other causes

B. When a patient has very high LDL-cholesterol and normal HDL-cholesterol

C. When an overweight patient has high triglyceride levels and atherosclerosis

D. When an older patient experiences pancreatitis

E. I don't know

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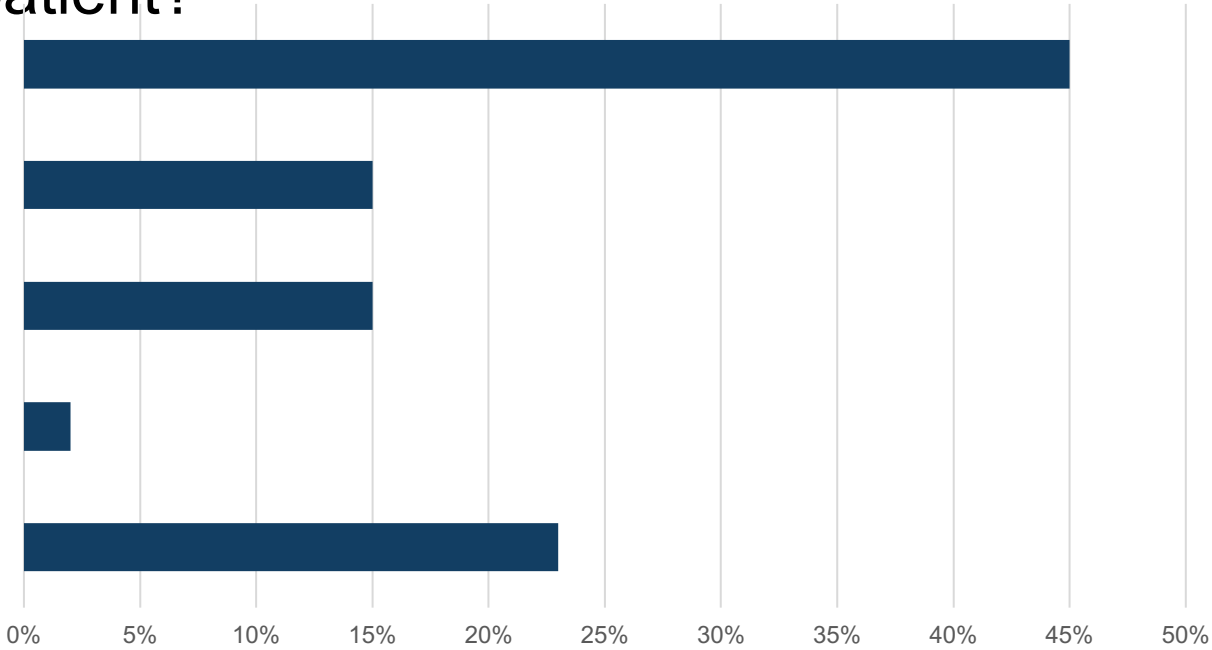

Results recorded on November 15, 2023.

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Patient Case: Richard

- Richard, a 19 yr old male, presents to ER with considerable abdominal discomfort
- History:
  - Intermittent abdominal pain for many years, most commonly after parties
  - Now at college, episodes of abdominal pain have increased
  - Family history is negative for pancreatitis and cardiovascular disease
  - Evening prior to current visit: attended season opener basketball game with friends and enjoyed hotdogs, snack food, and beer

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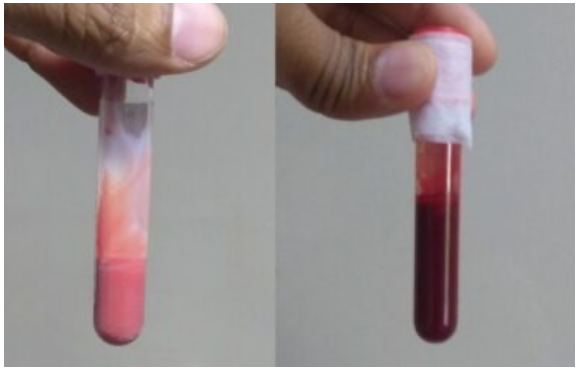
Patient Case: Richard

- Richard, a 19 yr old male, presents to ER with considerable abdominal discomfort
- Physical examination:
  - Height 5’7””; weight 120 lbs; BMI 18.8
  - Temp 99.1; Pulse 132; BP 124/83
  - General: appears to be in considerable discomfort
  - Abdominal examination: marked tenderness in upper abdomen
- Relevant labs:
  - Plasma triglycerides 6378 mg/dL
  - Plasma cholesterol 686 mg/dL
  - Na 125 mg/dL; K 4.0 mg/dL; blood glucose 91 mg/dL
  - Serum amylase 520 U/L (normal = 19-86)



Extreme TG levels + lack of other common causes suggests a genetic component

BMI = body mass index; BP = blood pressure; TG = triglyceride

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Comparison of FCS and MCS

Features	Monogenic FCS	Polygenic MCS
Former designation	Familial chylomicronemia (type 1)	Mixed dyslipidemia (type 5)
Main disturbances	CM only	CM, VLDL, and remnants
Associated disturbances	Reduced VLDL, LDL, HDL	Reduced HDL (LDL variable)
Typical onset	Pediatric; adolescent	Adulthood
Prevalence	$1:10^6$	1:400-500
Inheritance	AR	Familial clustering
Clinical features	Abdominal pain, nausea, vomiting, eruptive xanthomas, lipemia retinalis, pancreatitis, HSM, FTT	Abdominal pain, nausea, vomiting, eruptive xanthomas, lipemia retinalis, pancreatitis, HSM
Associated with CVD	Minimal	Some evidence for risk
Role of 2° factors	Minimal	Major
Genetic causes	*LPL, APOC2, GPIHBP1, APOA5, LMF1:* 2 mutant alleles	Heterozygous rare variants plus high polygenic risk score
Treatment	Fat restriction; minimal effect of current drugs; anti-APOC3	Fat restriction; control 2° factors; omega-3, fibrates, anti-APOC3

CM = chylomicronemia; FCS = familial chylomicronemia syndrome; FTT = failure to thrive; LDL = low-density lipoprotein; MCS = multifactorial chylomicronemia syndrome; VLDL = very-low-density lipoprotein

Brahm AJ, Hegele RA. *Nat Rev Endocrinol.* 2015;11(6):352-62.

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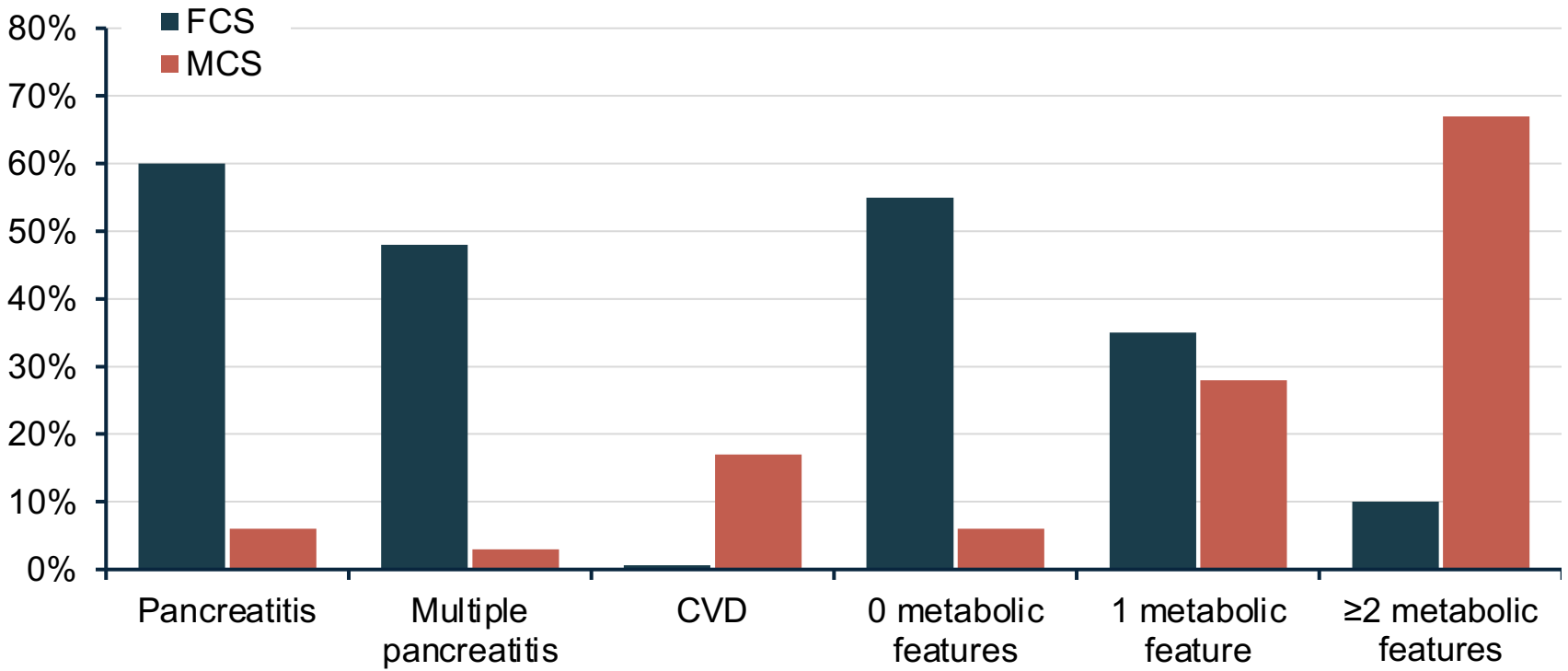
Differentiating FCS from MCS



FCS = familial chylomicronemia syndrome; MCS = multifactorial chylomicronemia syndrome

Paquette M, et al. *Atherosclerosis.* 2019;283:137-142.

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Differentiating FCS from other Chylomicronemias

Triglyceride above 1000 mg/dl hyperchylomicronemia

↓

Screening tool

↓

Additional characteristics which may help identify FCS

↓

Genetic diagnosis

FCS score:
≥ 10: FCS very likely
≤ 9: FCS unlikely
≤ 8: FCS very unlikely

1. Fasting TG > 10 mmol/L for 3 consecutive blood analyses (+5)[a]
Fasting TGs > 20 mmol/L at least once (+1)
2. Previous TG < 2 mmol/L (-5)
3. No secondary factor[b] (except pregnancy and ethinyl oestradiol) (+2)
4. History of pancreatitis (+1)
5. Unexplained recurrent abdominal pain (+1)
6. No family history of FCH (+1)
7. No response to hypolipidemic treatment (+1)
8. Onset of symptoms: age < 40 years (+1), < 20 years (+2) < 10 years (+3)

1. Low BMI (< 26 kg/m2)**
2. Low LDL-c (below 40 mg/dl)**

FCH = familial combined hyperlipidemia; [a]Eruptive xanthoma may be used as a surrogate for high TG levels (rare); [b]Secondary factors include alcohol, uncontrolled diabetes, metabolic syndrome, hypothyroidism, corticotherapy; [c]If diagnosis is made during pregnancy, a second assessment is necessary to confirm diagnosis post-partum; [**]values have been rounded off.

Gallo A, et al. *Curr Atheroscler Rep*. 2020;22(11):63.

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Genetic Basis of Familial Chylomicronemia Syndrome

Gene	Homozygote prevalence	Gene product function	Age of onset
LPL	1 in 1 million (95% cases)	Hydrolysis of TG, peripheral uptake of FFA	Infancy or childhood
APOC2	20 families	Required cofactor of LPL	Childhood or adolescence
LMF1	2 families	Chaperone molecule required for proper LPL folding and/or expression	Late adulthood
APOA5	5 families	Enhancer of LPL activity	Late adulthood
GPIHBP1	15 families	Anchors LPL on capillary endothelium. Stabilizes binding of chylomicrons near LPL, supports lipolysis	Infancy or childhood

Patni N, Ahmad Z, Wilson DP. Genetics and Dyslipidemia. In: Feingold KR, Anawalt B, Blackman MR, et al., eds. Endotext. South Dartmouth (MA): MDText.com, Inc.; 2023.

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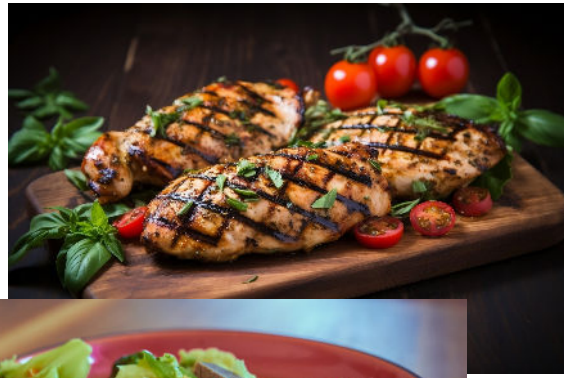
Patient Case, cont'

- Richard receives a clinical diagnosis of FCS
- He receives counselling on lifestyle modifications:
  - Restrict dietary fat to ≤ 10% - 15% of total calories; preferably < 5%
  - Restrict high-glycemic and high-fructose foods and beverages
  - Eliminate alcohol
  - Review medications known to cause hypertriglyceridemia



FCS is commonly misdiagnosed (mean 5 visits to clinic before correct diagnosis; range 1-30)

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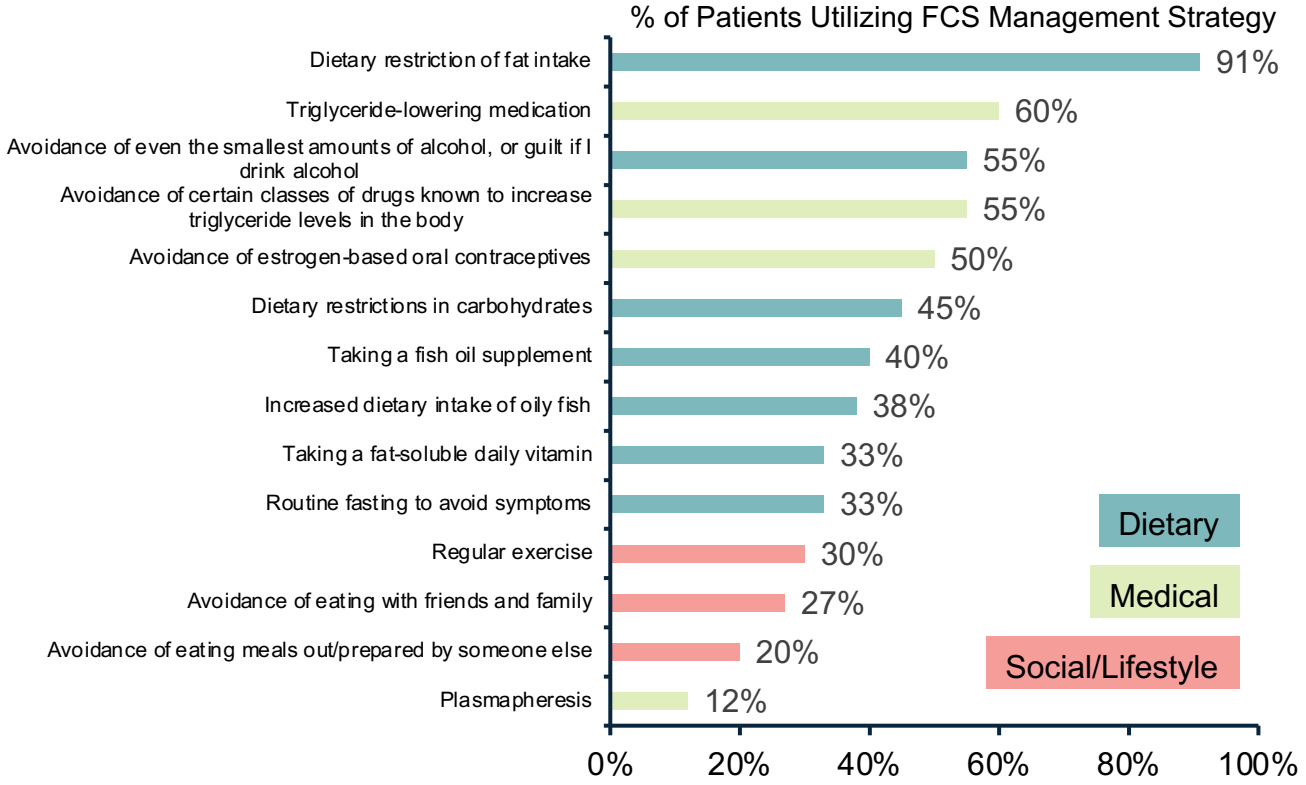
Challenges Pursuing a Low-fat Diet

- Strict dietary adherence is critical for patients with FCS, but is difficult to maintain long term
  - Even when patients adhere to the very-low-fat diet and are monitored, TG levels may remain dangerously high
  - Patients are at high risk of fat-soluble vitamin deficiencies



Davidson M, et al. *J Clin Lipidol*. 2018;12(4):898-907.e892.

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Challenges Pursuing a Low-fat Diet

- Patient frustration
- Increased financial stress
- From IN-FOCUS survey:
  - > 90% of patients found managing fat intake to be difficult.
  - 53% experienced symptoms, despite adherence to their diets.
  - FCS impacted:
    - 94% Employment status
    - 58%-66% Emotional/mental well-being
    - 68%-82% Social relationships

Davidson M, et al. *J Clin Lipidol*. 2018;12(4):898-907.e892.

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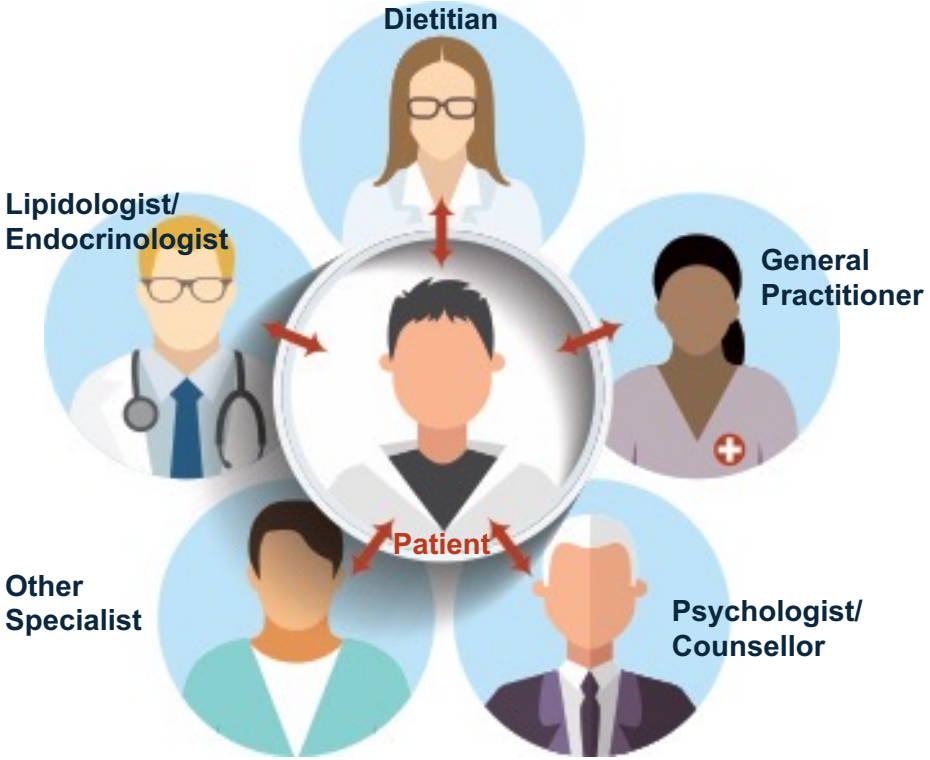
Importance of Multidisciplinary Approach for the Management of FCS

- Long-term feasibility of dietary management
  - Multidisciplinary approach
  - Tools to enhance dietary management

Up to a third of patients with FCS have an eating disorder



Williams L, et al. *J Clin Lipidol*. 2018;12(4):908-919.
Davidson M, et al. *J Clin Lipidol.* 2018;12(4):898-907.e892.

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Living with FCS

- There is no one-size-fits all FCS food plan.
- Establish a cross-functional, collaborative health care team to manage FCS and develop an individualized treatment plan with a registered dietitian nutritionist
- To promote a healthy weight, avoid excessive caloric intake, and engage in physical activity that is enjoyable, sustainable, and as prescribed by the health care provider
- Focus on what can be eaten
  - Create a list of favorite foods, cuisines, and flavors
  - Get to the root of what fuels food cravings
  - Create FCS-friendly versions of the foods
  - Stock FCS-friendly foods at home

People with FCS who feel empowered to control and individualize their diet to their own tastes and needs may increase their adherence to the very-low-fat diet

FCSfocus. https://fcsfocus.com. Accessed November 2, 2023.
Williams L, et al. *J Clin Lipidol*. 2018;12(4):908-919.

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Lifestyle Recommendations

- Eat a very-low-fat diet (< 15–20 g fat per day or <10%–15% daily caloric intake)
  - Space out fat intake and reduce TG excursions by eating small, frequent meals and snacks
  - Medium-chain triglyceride (MCT) is metabolized through a chylomicron-independent pathway, increases overall caloric intake, and adjust the macronutrient distribution of the diet, helping to prevent excessive percentage of overall caloric intake from carbohydrate sources
- Avoid alcohol
  - Alcohol interferes with normal TG metabolism and promotes the accumulation of fat in the liver, increases blood chylomicron levels, and hypertriglyceridemia; may cause TG excursions and exacerbate acute pancreatitis episodes
- Avoid simple sugar (sweets, desserts, fruit juices)
  - Excess sugar is converted to fat
- Achieve adequate water intake and maintain electrolyte balance to promote pancreas function

Williams L, et al. *J Clin Lipidol*. 2018;12(4):908-919.

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General Dietary Recommendations for Adults

- Eat nutrient-dense foods, including vegetables, fruits in limited quantities, whole grains, legumes, lean proteins, and fat-free milk products without added sugars
- Meet EFA requirements of 2%–4% of daily calories; supplement diet with essential fats, as needed; incorporate MCT; supplement with vitamins A, D, E, K, and minerals, as needed
- Review medications known to cause hypertriglyceridemia
- Eat fat-free or low-fat protein foods
- Limit simple and refined carbohydrate foods, and limit total carbohydrate intake to no greater than 60% daily caloric intake; avoid foods with added sugars

Williams L, et al. *J Clin Lipidol*. 2018;12(4):908-919.

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Patient Case, cont'

- Richard is having trouble adhering to dietary restrictions
- Relevant labs:
  - Plasma triglycerides 2461 mg/dL
  - Plasma cholesterol 292 mg/dL
- Pharmacotherapy considerations:
  - Generally, not useful for TG > 1000 mg/dL
  - Drug interactions
  - Cardiovascular risk reduction
- Possible pharmacotherapy:
  - Fibrates
  - Statins
  - Niacin
  - Emerging therapies

Therapies for non-familial hypertriglyceridemia are not usually effective in patients with FCS

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Audience Response

What was a major finding from the volanesorsen open label extension study?

A. Volanesorsen-mediated clinical benefit in TG reduction was rapid and maximal by the 4th weekly infusion, but ceased by month 8

B. Anemia was the most common cause for volanesorsen treatment discontinuation and occurred in approximately a third of patients

C. Occurrence of ocular injury associated with volanesorsen was limited to the first 3 months, with no new cases after this time

D. Volanesorsen induced a dose-dependent and prolonged reduction in plasma APOC3 levels with concomitant lowering of plasma TG levels

E. I don't know

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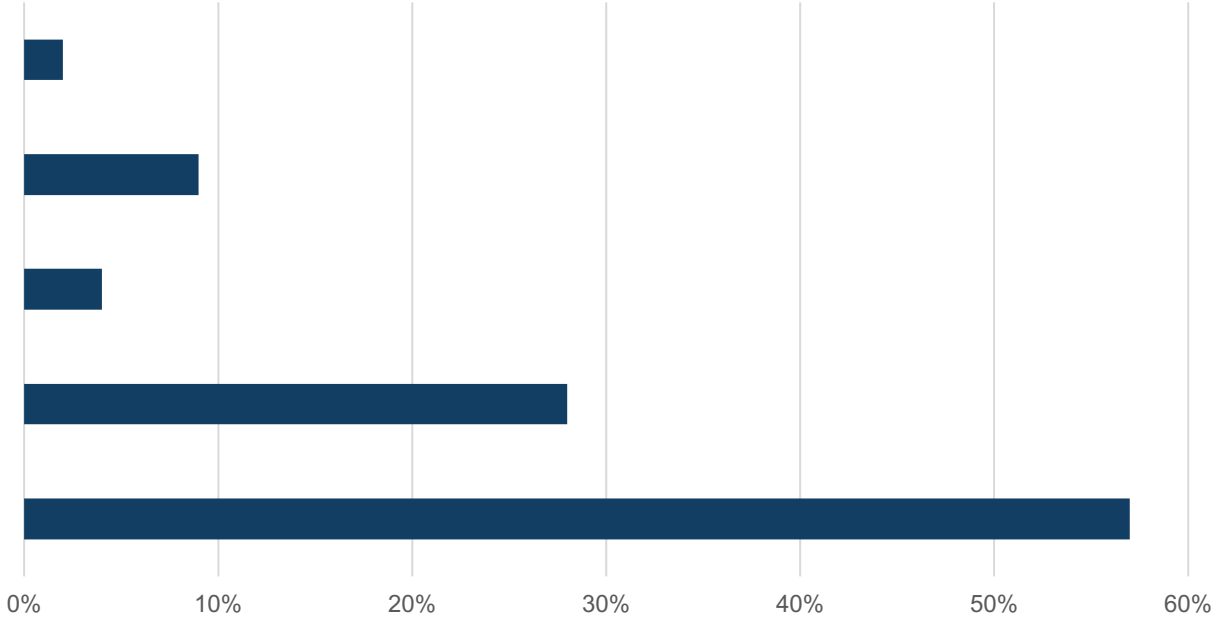

Results recorded on November 15, 2023.

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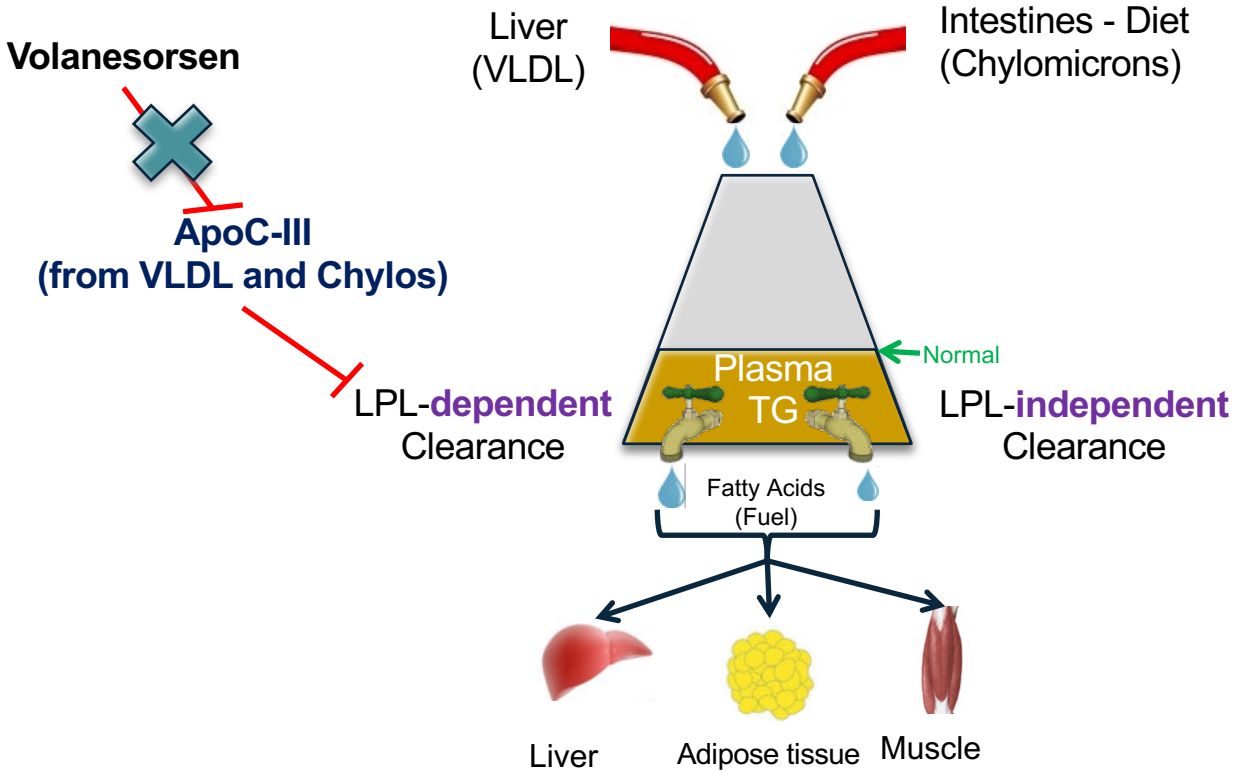
Triglyceride Entry and Clearance from Plasma
Prior Postulated Role of ApoC-III



Gordts PL, et al. *J Clin Invest*. 2016;126(8):2855-2866. Gaudet D, et al. *N Engl J Med*. 2014;371(23):2200-2206.

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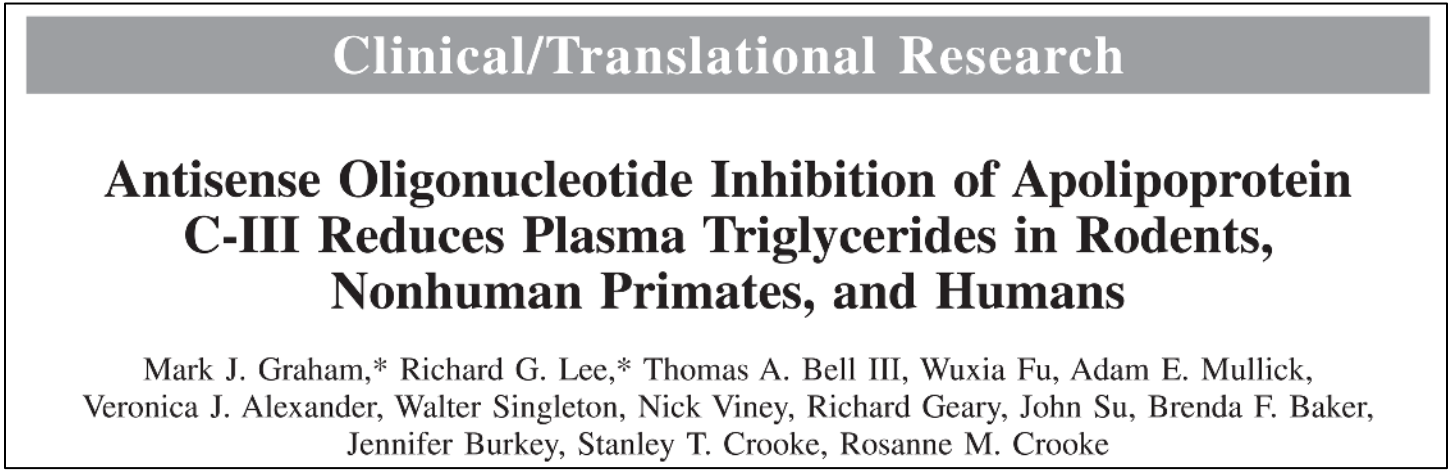


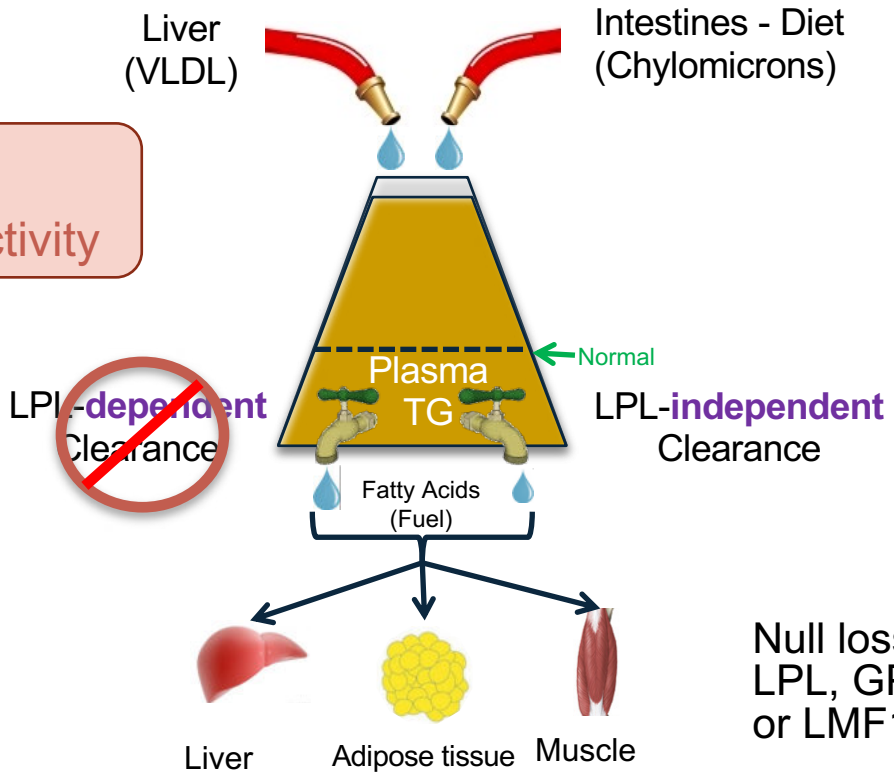
- Antisense inhibition of APOC3 mRNA in a variety of animal models led to dose-dependent reductions of plasma apoC-III and TG levels.
- ApoC-III inhibition did not decrease hepatic VLDL-TG secretion or intestinal TG secretion, but did increase plasma TG clearance
- Inhibition of apoC-III was not associated with hepatic TG accumulation or toxicity
- A phase-I study in healthy subjects demonstrated dose-dependent decreases in plasma apoC-III and concomitant lowering of TG and no safety signals

Graham MJ, et al. *Circ Res*. 2013;112(11):1479-1490.

CME

Plasma Triglyceride Entry and Clearance in FCS

FCS
absence of LPL activity



Null loss-of-function mutations in LPL, GPIHPB1, APOC2, APOA5, or LMF1 genes

Gordts PL, et al. *J Clin Invest*. 2016;126(8):2855-2866. Gaudet D, et al. *N Engl J Med*. 2014;371(23):2200-2206.

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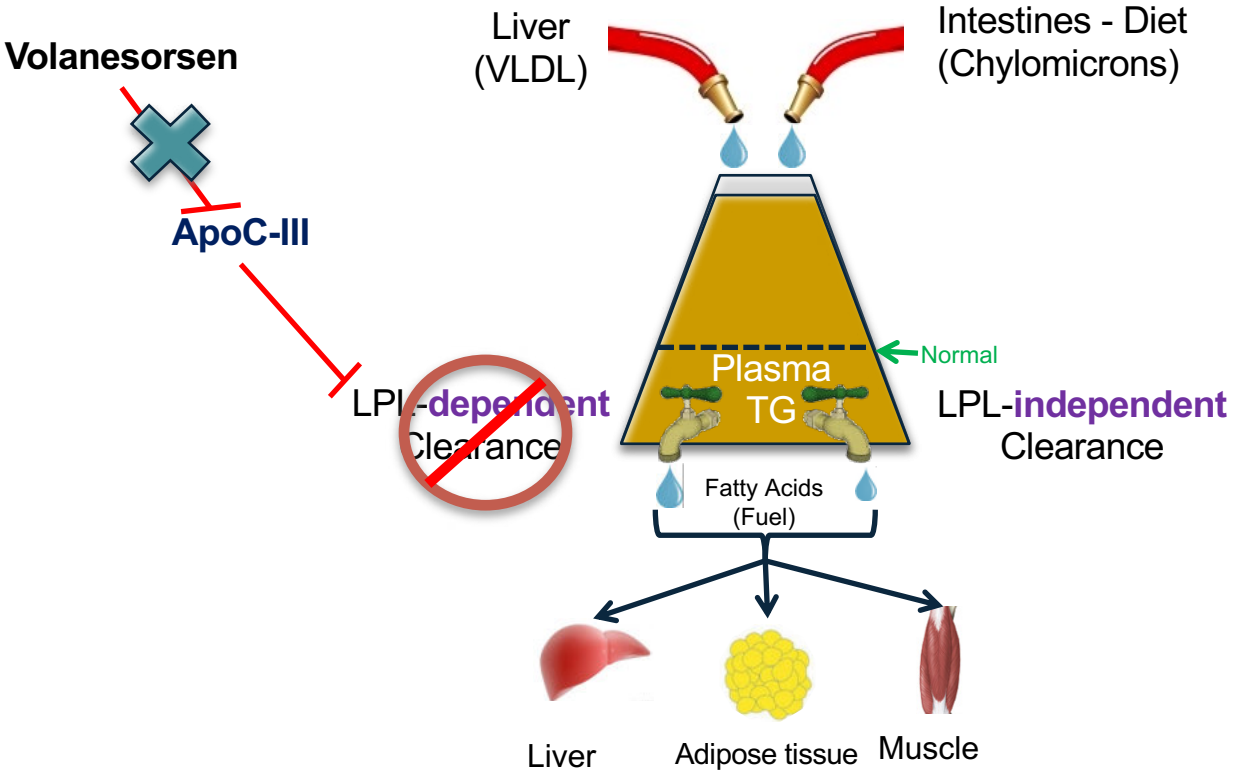
Plasma Triglyceride Entry and Clearance in FCS



Gordts PL, et al. *J Clin Invest*. 2016;126(8):2855-2866. Gaudet D, et al. *N Engl J Med*. 2014;371(23):2200-2206.

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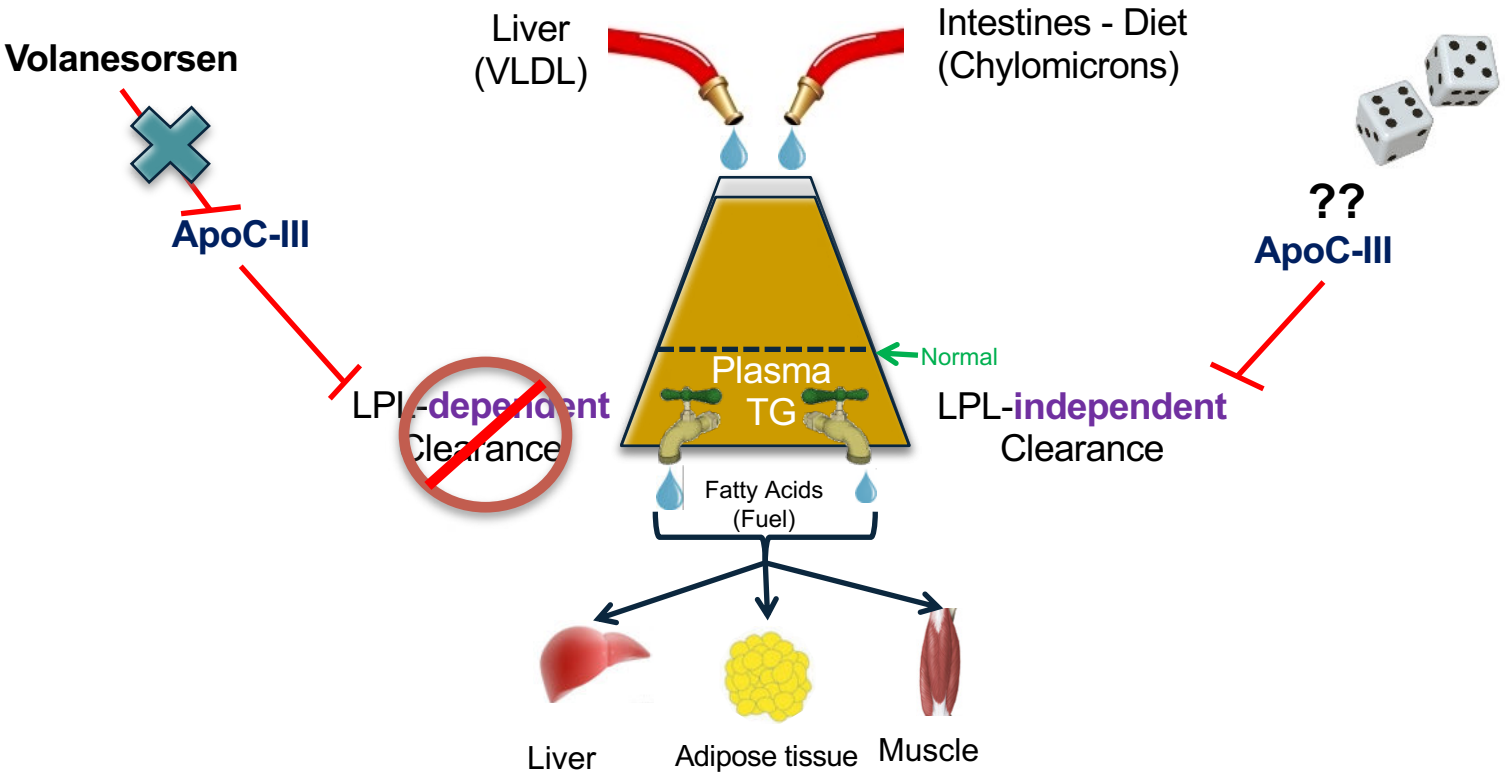
ASO To Lower ApoC-III in FCS: Therapeutic Gamble



Gordts PL, et al. *J Clin Invest*. 2016;126(8):2855-2866. Gaudet D, et al. *N Engl J Med*. 2014;371(23):2200-2206.

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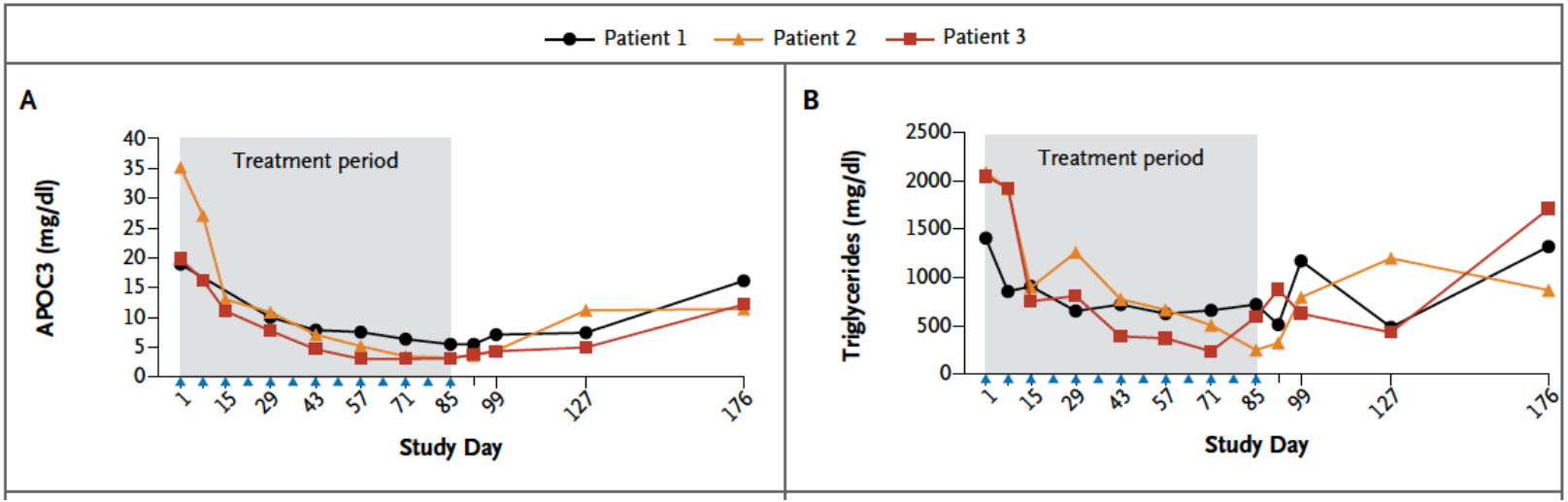
BRIEF REPORT

Targeting APOC3 in the Familial Chylomicronemia Syndrome

N = 3

Daniel Gaudet, M.D., Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D., Veronica J. Alexander, Ph.D., Walter Singleton, M.D., Steven G. Hughes, M.B., B.S., Richard S. Geary, Ph.D., Brenda F. Baker, Ph.D., Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D., and Joseph L. Witztum, M.D.



Gaudet D. et al. *N Enal J Med*. 2014;371(23):2200-2206.

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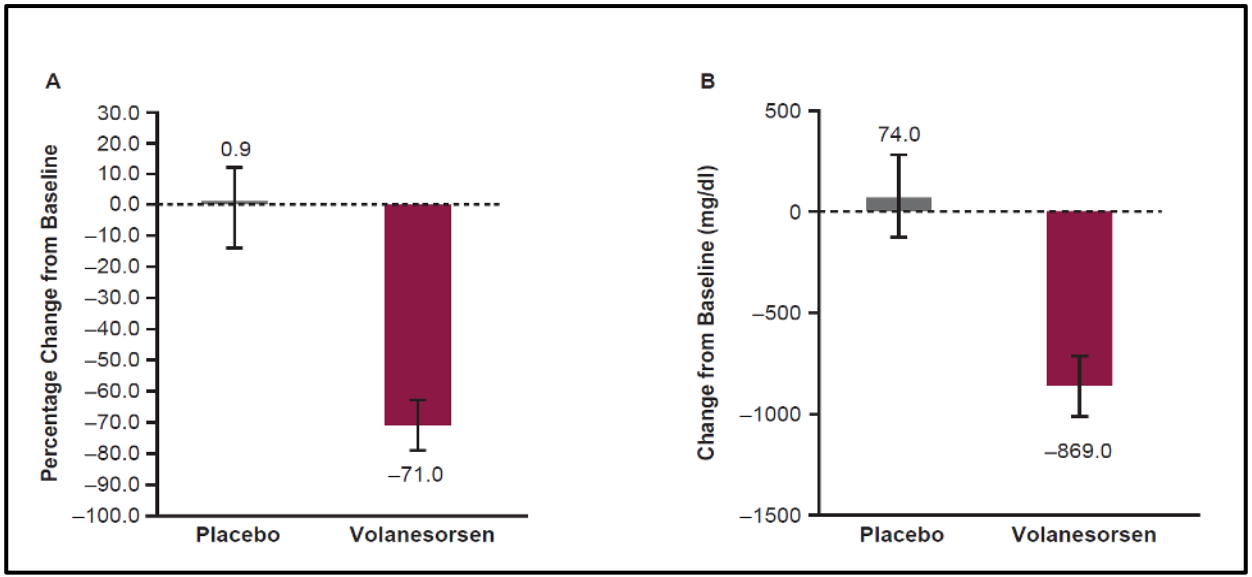
ORIGINAL ARTICLE

Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome

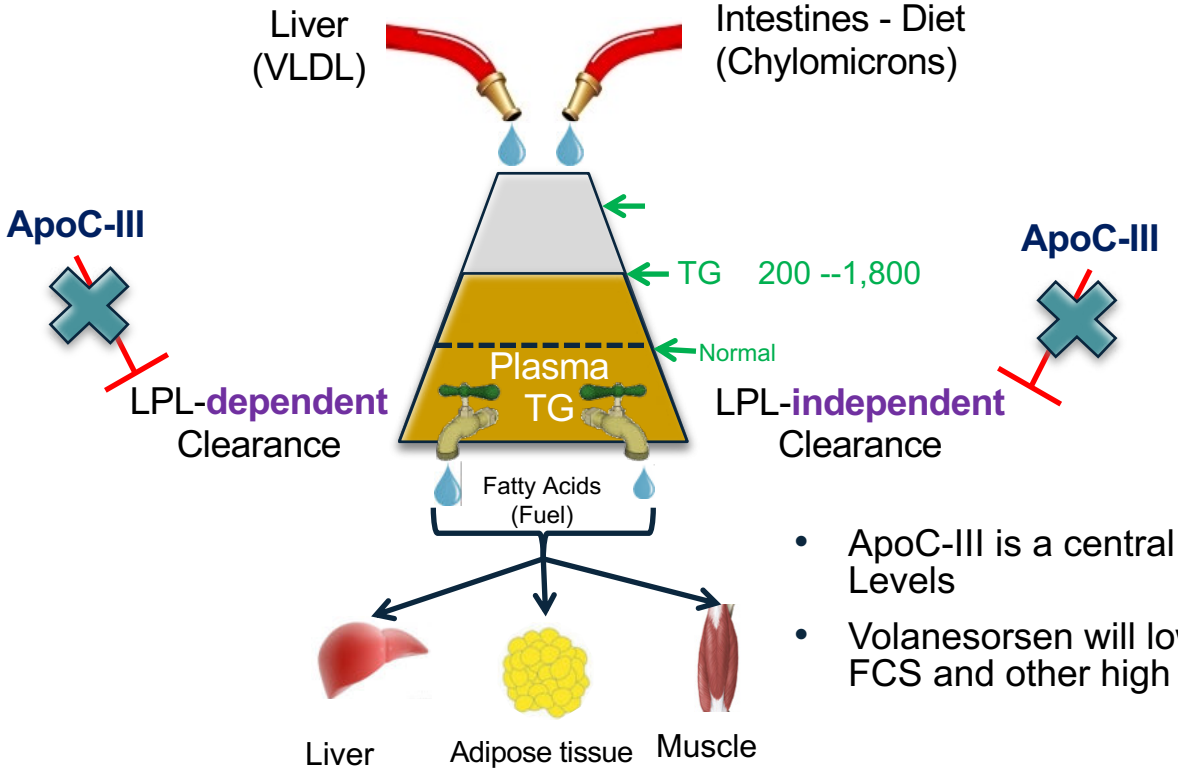
J.L. Witztum, D. Gaudet, S.D. Freedman, V.J. Alexander, A. Digenio, K.R. Williams, Q. Yang, S.G. Hughes, R.S. Geary, M. Arca, E.S.G. Stroes, J. Bergeron, H. Soran, F. Civeira, L. Hemphill, S. Tsimikas, D.J. Blom, L. O'Dea, and E. Bruckert

N = 66



Witztum JL. et al. *N Enal J Med*. 2019:381(6):531-542.

ApoC-III Raises TG by Both LPL-Dependent and LPL-Independent Pathway



- ApoC-III is a central regulator of TG Levels
- Volanesorsen will lower TG in both FCS and other high TG states

Gordts PL, et al. *J Clin Invest*. 2016;126(8):2855-2866.
Gaudet D, et al. *N Engl J Med*. 2014;371(23):2200-2206.

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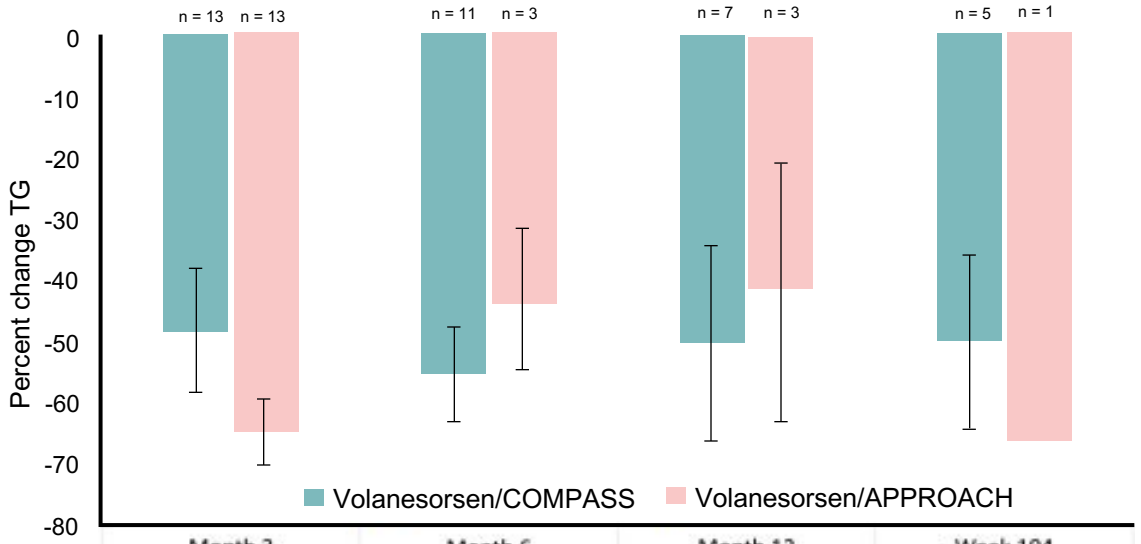
Volanesorsen Open Label Extension

Dose-dependent and prolonged reductions in plasma APOC3 levels with concomitant lowering of plasma TG levels



	Month 3	Month 6	Month 12	Week 104
Volanesorsen/APPROACH, mean % change from baseline	−48.1	−55.3	−50.0	−50.2
Mean change from baseline (mg/dL)	−1320	−1513	−1427	−1325
Volanesorsen/COMPASS, mean % change from baseline	−64.9	−43	−41.6	−65.9
Mean change from baseline (mg/dL)	−1432	−1073	−937	−708

Witztum JL, et al. *J Clin Lipidol*. 2023;17(3):342-355.

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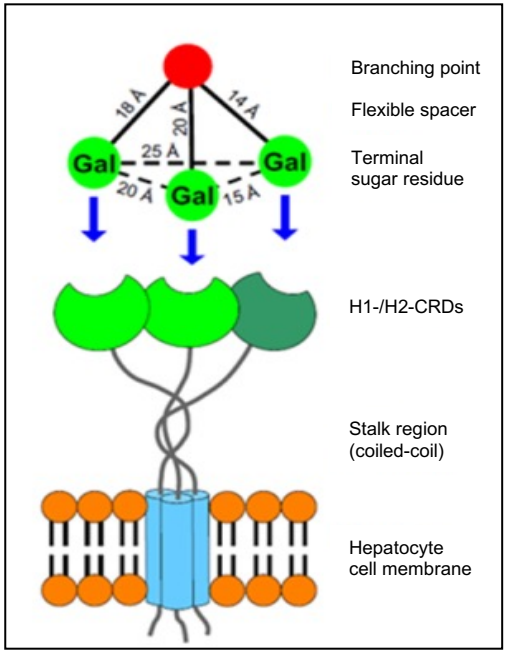
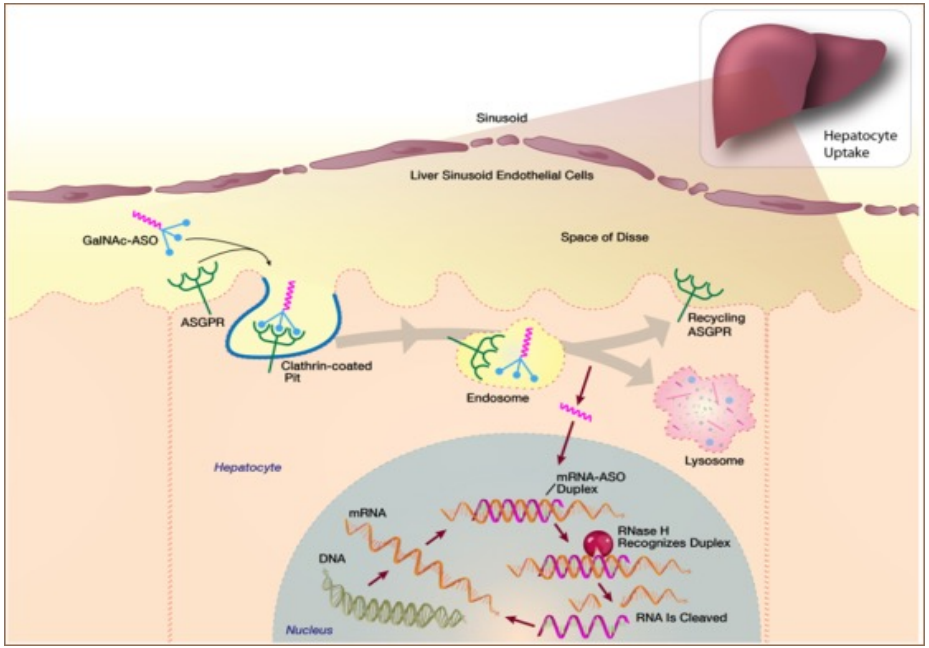
Hepatocyte Targeting Antisense via Asialoglycoprotein Receptor (ASGPR)

- LICA - ligand conjugated antisense





Prakash TP, et al. *Nucleic Acids Res*. 2014;42(13):8796-8807.

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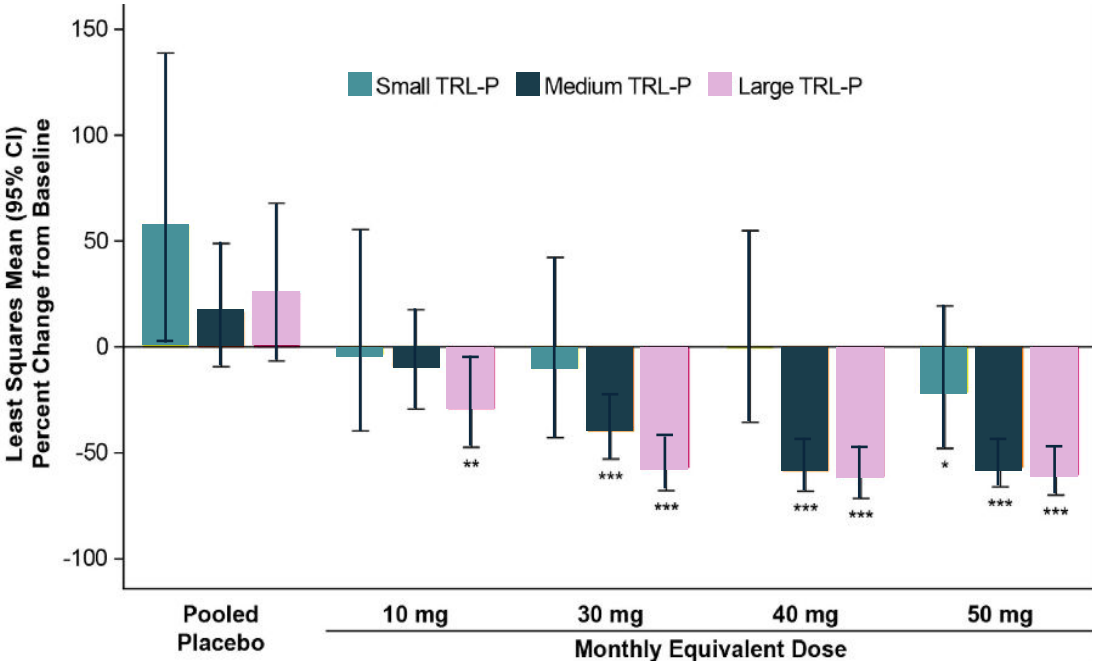
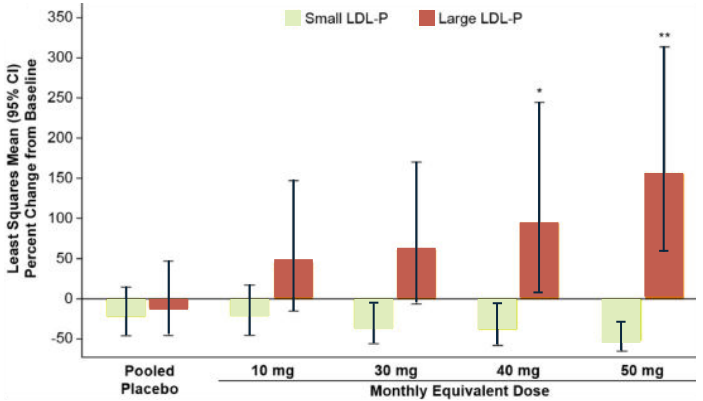
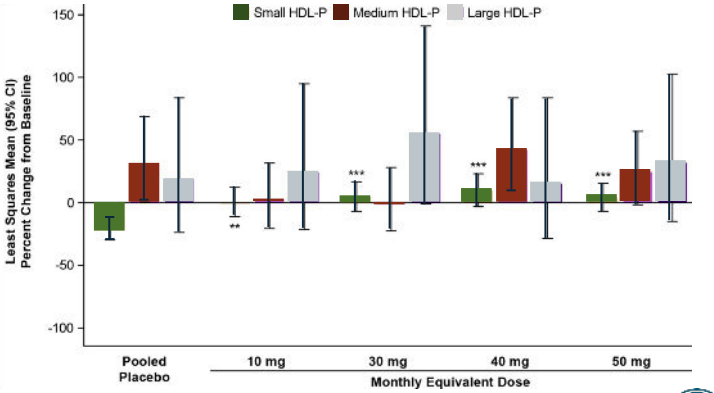
Olezarsen







TRL-P = triglyceride-rich lipoprotein particle

Karwatowska-Prokopczuk E, et al. *J Clin Lipidol*. 2022;16(5):617-625.

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Emerging Agents to Lower Elevated Triglycerides

Agent	Dose	MOA	Main indication	Comments
Apo-CIII inhibitors				
AROAPOC3	50 mg s.c. every 12 wks	siRNA inhibiting *APOC3*	TG reduction	↓ TG up to 90% in phase 1 trials; GalNAc-linked siRNA; Phase 3 trials ongoing
ANGPTL3 inhibitors				
AROANG3	Unspecified (range 100–300 mg), s.c. every 12 wks	ASO inhibiting *ANGPTL3*	LDL-C and TG reduction	TG ↓ up to 65%, LDL-C ↓ up to 55% in phase 1 trials; GalNAc-linked siRNA; Phase 2 trials ongoing
LY3475766	Unspecified, s.c.	mAb targeting ANGPTL3/8 complex	LDL-C and TG reduction	↓ TG up to 70%, LDL-C ↓ up to 37% in phase 1 trials; further development unclear

Gouni-Berthold I, et al. *Curr Atheroscler Rep*. 2023;25(10):701-709.

CME OUTFITTERS

Summary

- Diet and life-style modifications remain the mainstay of FCS management
- It is important to confirm a genetic cause of severe hypertriglyceridemia
- Current therapy options are not sufficient for FCS
- Antisense oligonucleotides provide dose-dependent and prolonged reductions in plasma triglyceride levels

CME OUTFITTERS

Patient Case, cont'

- Richard received volanesorsen
  - 300 mg per 2 weeks, subcutaneous
- Relevant labs:
  - Plasma triglycerides 1184 mg/dL
  - Plasma cholesterol 163 mg/dL
- Ongoing challenges:
  - Fatigue
  - Occasional GI disturbances
  - Social

CME OUTFITTERS

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- See that patients with severe hypertriglyceridemia receive genetic screening
- Support patients with FCS by providing resources to connect with other patients
- Engage the full multidisciplinary team in the management of patients with FCS
- Educate patients on emerging therapies and opportunities to participate in clinical trials

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AFTER THE SHOW

Questions & Answers

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