Today's Rare Disease Challenge: A Wolf in Sheep's Clothing

James A. Underberg, MS, MD, FACPM, FACP, FASH, FNLA

NYU School of Medicine & NYU Center for Prevention of Cardiovascular Disease

Director, Bellevue Hospital Lipid Clinic

New York, NY

Outline

- Case Study
- Lysosomal Acid Lipase Deficiency (LAL-D)
- Familial Chylomicronemia Syndrome (FCS)
- Lipodystrophy

The eye cannot see what the mind does not know.

--Anonymous

Case Study

- 40-year-old male with history of overweight, BMI 26 and mild dyslipidemia. Treated with atorvastatin 20 mg daily, and aggressive diet and lifestyle interventions.
- Total chol 210 mg/dL, HDLc 38 mg/dL, TG 200 mg/dL, LDLc 132 mg/dL
- Mild fatty liver on abdominal sono, ALT 47, AST 52
- Lost to follow-up for 7 years. Returns at age 47. Off statin (told to stop due to increasing liver function tests).
- Total chol 250 mg/dL, HDLc 25 mg/dL, TG 180 mg/dL, LDLc 189 mg/dL
- Repeat AST 110, ALT 100, GGT 280, Bilirubin normal
- BMI 27, repeat sono shows progressive fatty liver with hepato-splenomegaly
- Liver biopsy, mixed macro and microvesicular pattern with some steatohepatitis

Common Causes of Hypertriglyceridemia

High-carbohydrate diet
Excessive alcohol consumption, especially when combined with high saturated fat diet
Hypothyroidism
Renal disease
Poorly controlled insulinopenic T2DM
Physical inactivity, sedentary lifestyle
Pregnancy
Polycystic ovary syndrome
Excess visceral fat, abdominal adiposity
Hepatic steatosis or steatohepatitis
Autoimmune diseases (eg, SLE with anti-LPL antibodies)
Genetic defects involving apo AV, apo CII, LPL, GPIHBP1, and others
Familial combined hyperlipidemia (FCHL): apo B excess (VLDL and LDL excess), polygeneic
Familial hypertriglyceridemia (FHTG): VLDL excess, polygenic
Type III dyslipidemia or dysbetalipoproteinemia:– excess VLDL and IDL remnants, apo E $\varepsilon_2/\varepsilon_2$ genotype

Apo, apolipoprotein; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein binding protein; IDL, intermediate-density lipoprotein; LPL, lipoprotein lipase; T2DM, type 2 diabetes mellitus; SLE, systemic lupus erythematosus; VLDL, very-low-density lipoprotein.

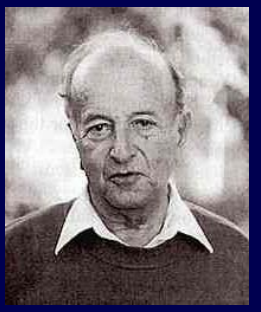
Bays et al. *J Clin Lipid*. 2013;7:304-383.

Drugs Associated with Hypertriglyceridemia

Thiazides	Beta blockers without alpha antagonist activity
Tamoxifen	Atypical antipsychotics
Glucocorticoids	Sirolimus
Raloxifene	Retinoic acid drugs
Protease inhibitors	Oral estrogens (not transcutaneous)
λ-Aspariginase	α-Interferon
Bile acid sequestrants	

Bays et al. *J Clin Lipid*. 2013;7:304-383.

Lysosomal Acid Lipase Deficiency (LAL-D)



- Historical terms to describe the disease
  - "Wolman disease"
    - 1956 by Dr. Moshe Wolman
    - Described an infant who died at the age of 3 months: poor weight gain, GI symptoms, hepatosplenomegaly, and adrenal calcifications
  - "Cholesteryl Ester Storage Disease or CESD"
    - 1963 by Dr. Donald S. Fredrickson
    - Described 12-year-old with hypercholesterolemia + hepatomegaly
- Underlying cause is the same[1-4]
  - Autosomal recessive disease affecting lipid metabolism
  - Results in lysosomal accumulation of lipids (cholesteryl esters and triglycerides) and multi-organ system damage (liver, GI tract, and blood vessel walls)

1. Patrick AD, Lake BD. *Nature*. 1969:222:1067-8.
2. Burke JA, Schubert WK. *Science.* 1972:176:309-10.
3. Cortner JA, et al. *Pediatr Res*. 1976;10:927-32.
4. Goldstein JL, et al. *J Biol Chem*. 1975 ;250:8487-95.

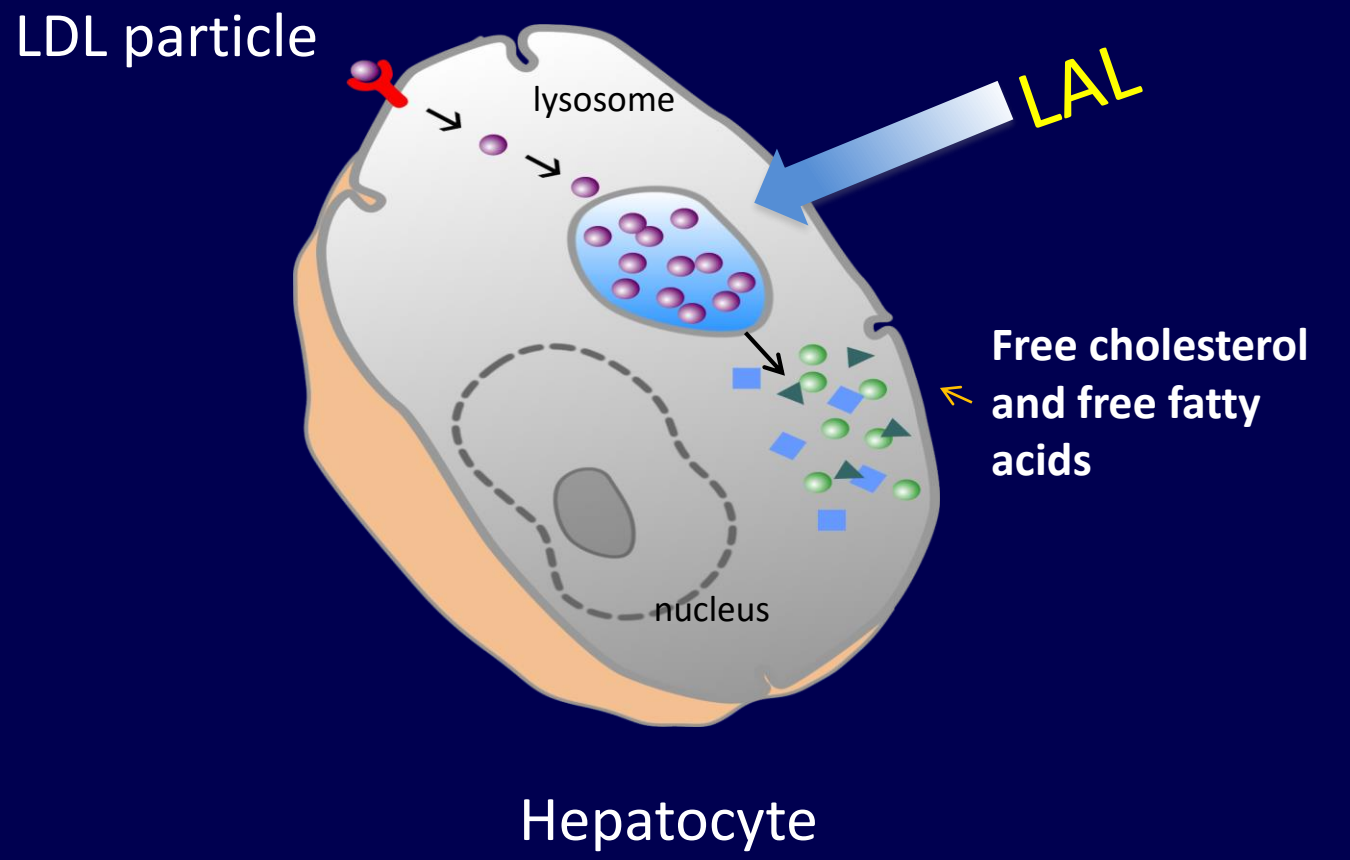
LAL-D Presentation in Children and Adults

- Common presenting abnormalities[1-3]
  - Unexplained persistent elevated ALT/AST
  - High/very high LDL-c and low HDL-c
- Diagnosis requires high index of clinical suspicion[1]
  - Many patients diagnosed in childhood
  - Others present with symptoms but are not diagnosed until adulthood
- High potential for mis- or delayed diagnosis; many patients remain undiagnosed[3]

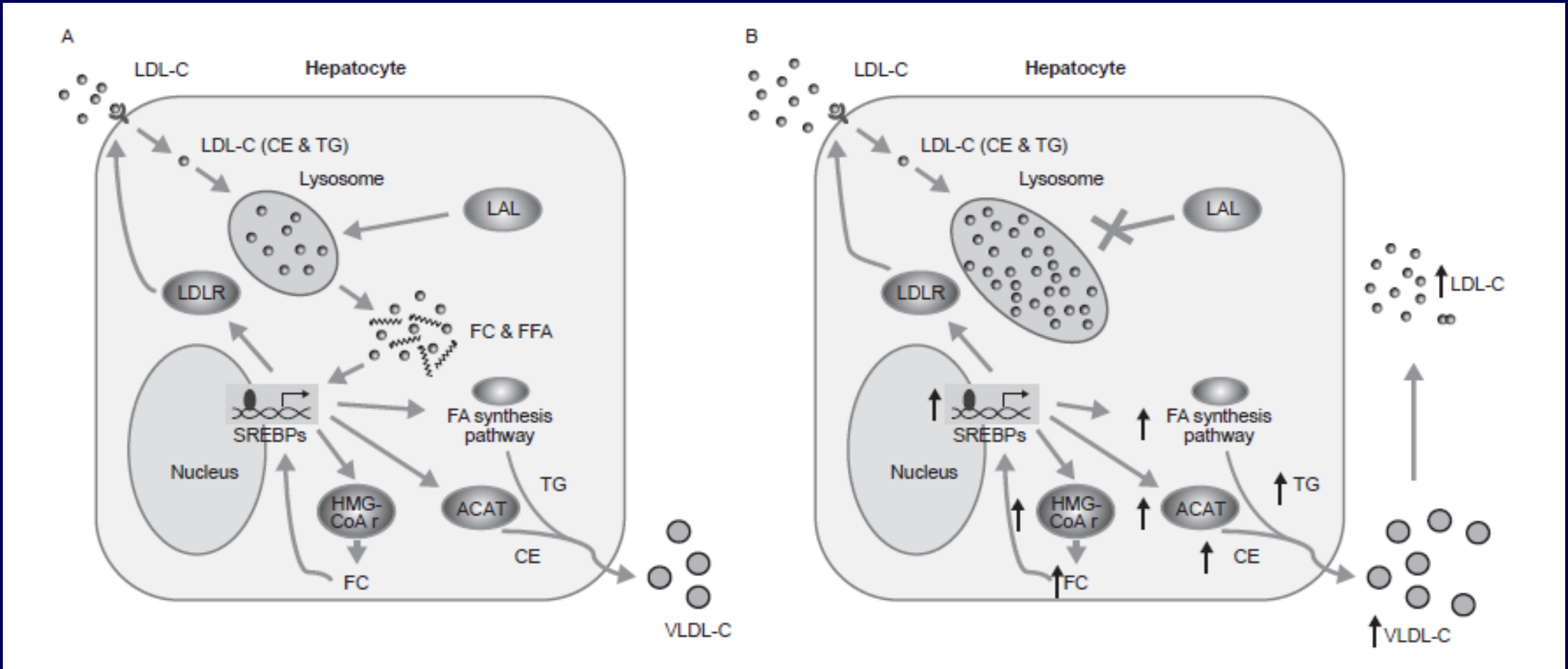
ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL-c: high-density lipoprotein cholesterol

1. Reiner Ž, et al. *Atherosclerosis*. 2014;235:21-30.
2. Bernstein DL, et al. *J Hepatol.* 2013;58(6):1230-1243.
3. Grabowski GA, et al. In: Valle D, et al (eds). OMMBID: The Online Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill. Ch. 142; updated March 2012.

Biology of Lysosomal Acid Lipase



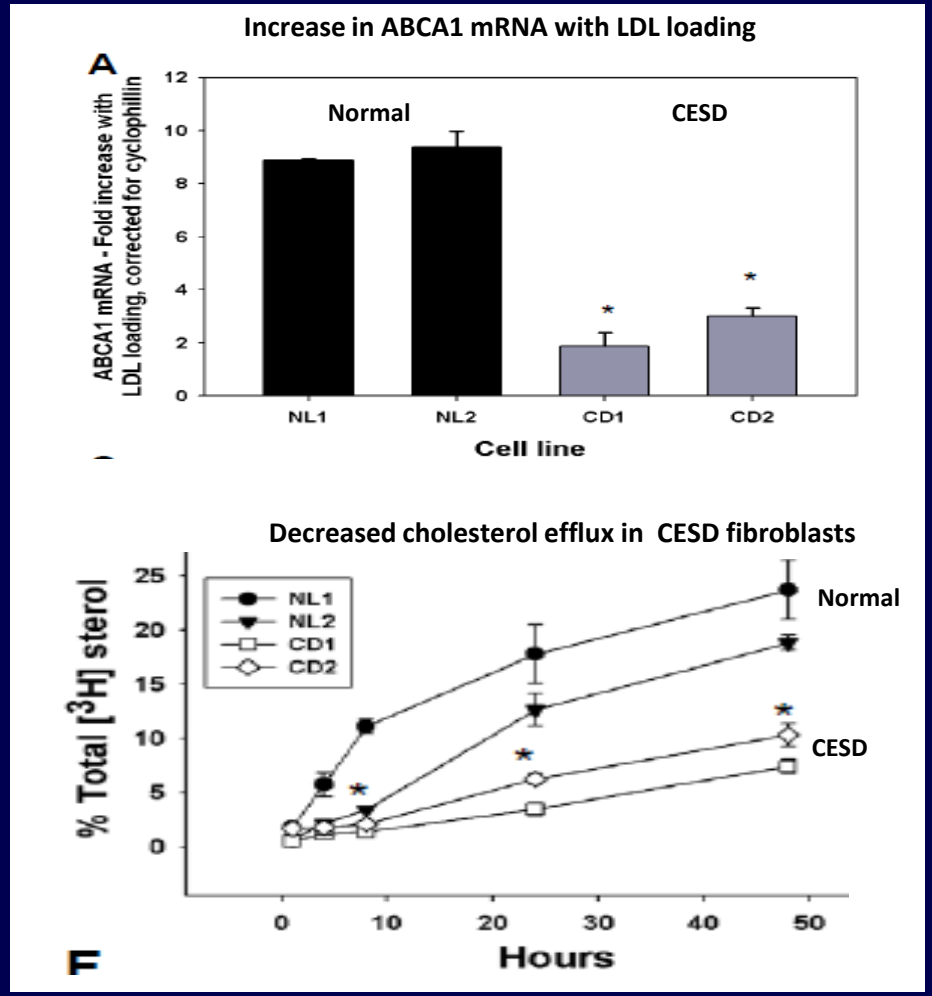
Pathophysiology of LAL-D



Reiner Z, et al.. *Atherosclerosis*. 2014;235:211-30.

Low HDL-C in LAL Deficiency Is Mechanistically Linked to ABCA1

- Recent data indicates that cholesterol flux out of lysosomes is a key regulator of ABCA1 expression (Bowden KL et al, 2011)
- Fibroblasts from LAL deficient patients
  - Decreased basal and LDL stimulated ABCA1 and ABCG1 expression
  - Decreased apoA-I mediated efflux of phosphatidylcholine, sphingomyelin and unesterified cholesterol (UC)
  - LXR agonists correct ABCA1 expression but not efflux
  - Decreased generation endogenous oxysterols including 27 hydrocholesterol



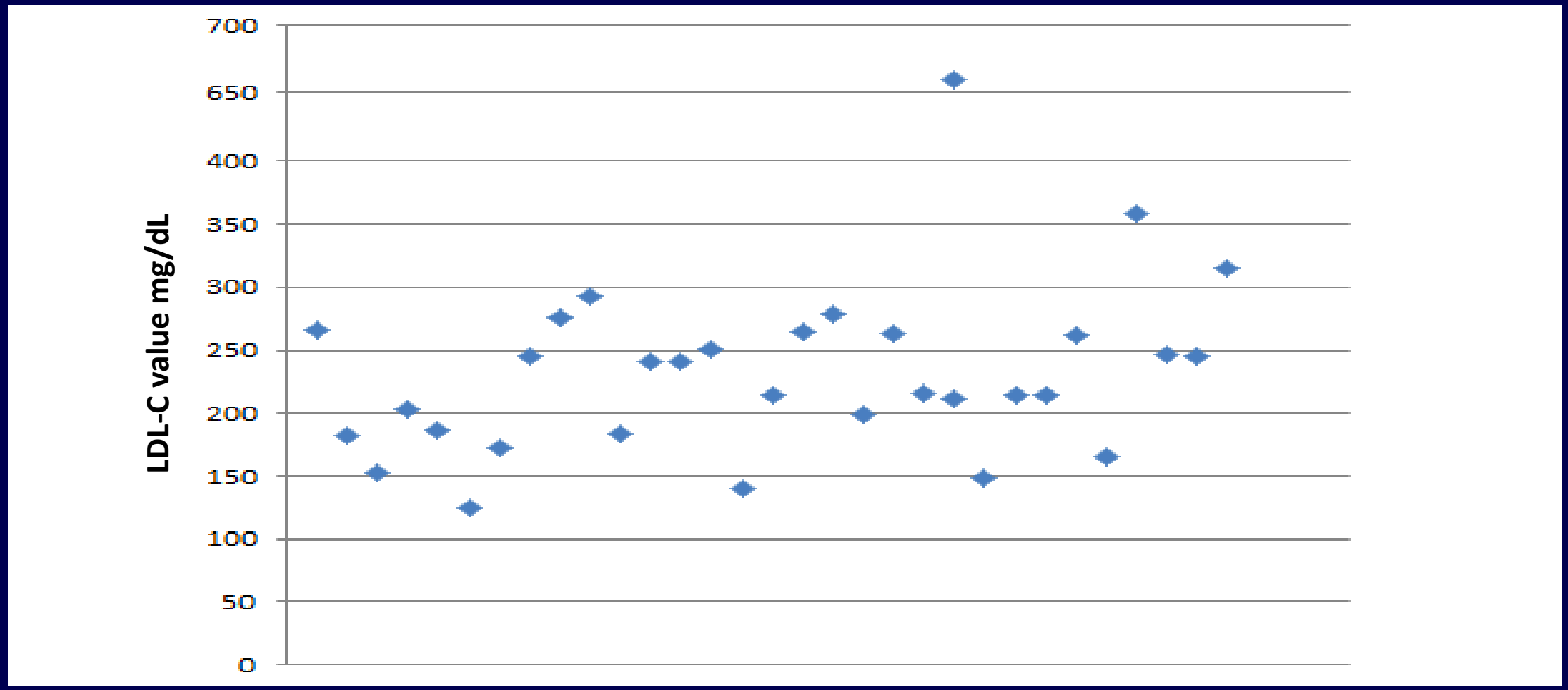
Bowden KL et al. *J Biol Chem.* 2011;286:30624-35.

LAL Deficiency: Genetic Epidemiology

Author	Journal	Carriers of E8SJM/ Sample Size	Estimated Prevalence*
Muntoni et al	Arterioscler Thromb Vasc Biol; 2007;27:1866-8.	10/2023 (German population)	1:43,000 to 1:78,000
Grabowski et al	Scriver's OMMBID; 2012	9/7011 (European Americans)	1:159,000 to 1:294,000
Scott et al	Hepatology; 2013;58:958-65.	14/4569 (Caucasian + Hispanic)	1:111,000 to 1:204,000
Stitziel et al	Arterioscler Thromb Vasc Biol; 2013;33:2909-14.	88/27,472 (European ancestry)	1:102,000 to 1:189,000

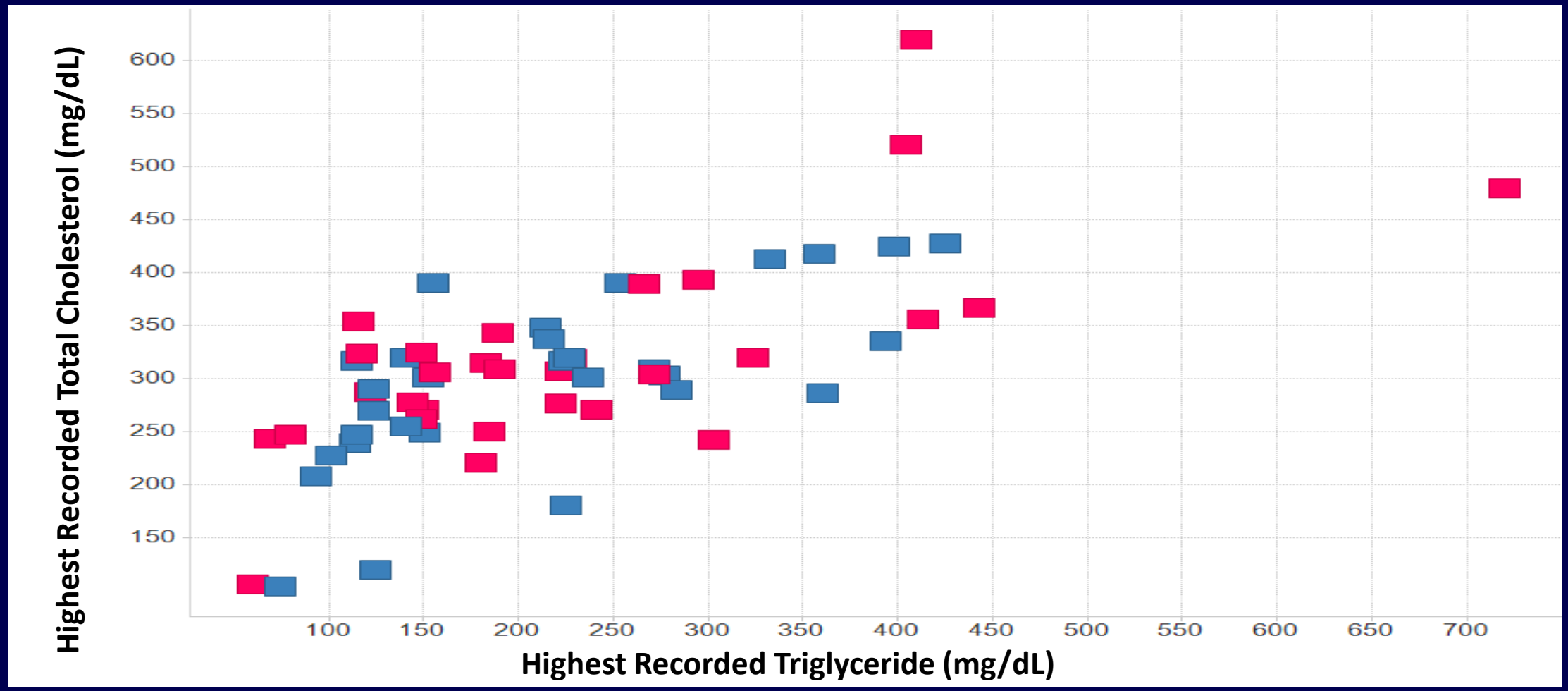
*Range based upon assumption of the "common" E8SJM representing 51 to 69% of all disease causing mutations

Elevated LDL-C Is Common in Patients with Documented LAL Deficiency



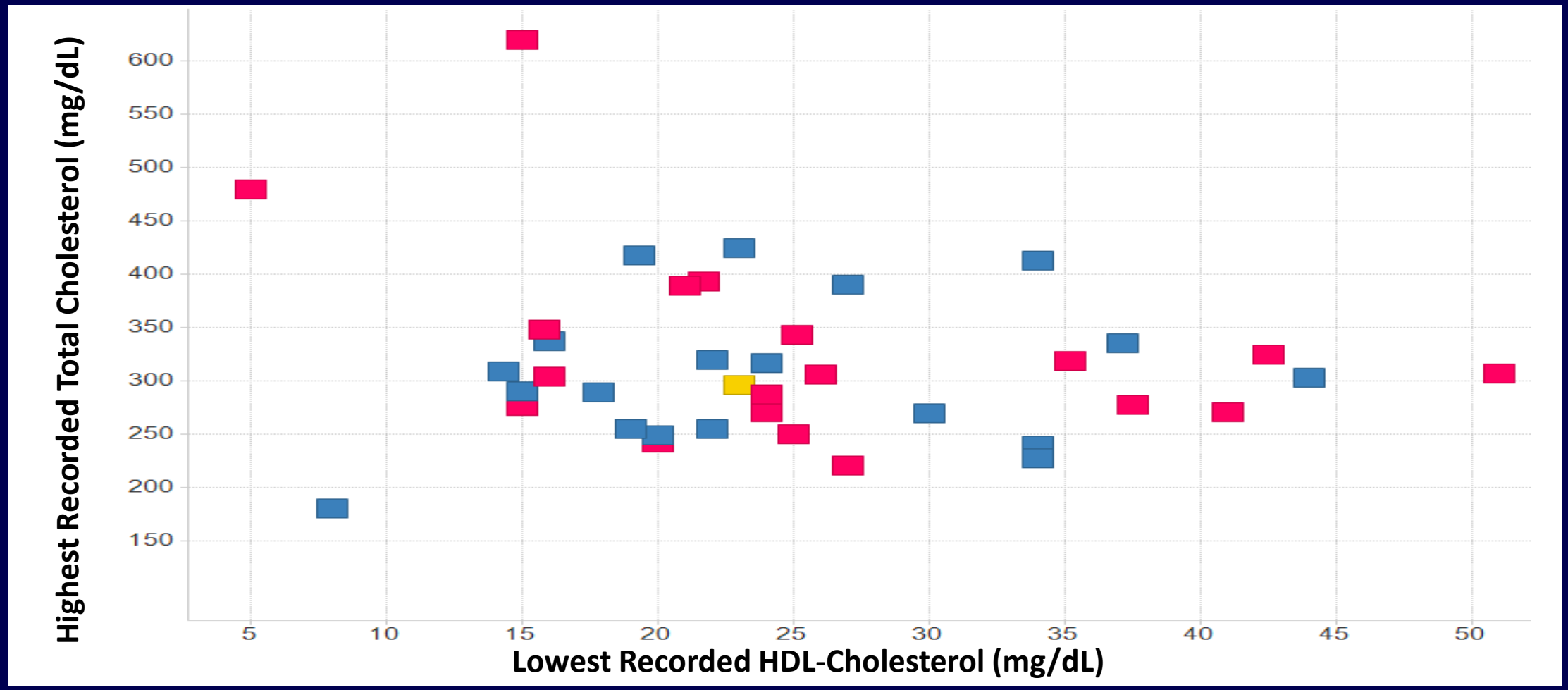
Tripuraneni R et al. *J Clin Lipidology*. 2013; 7:251. Poster presented NLA 2013.

Combined Hyperlipidemia Is a Common Feature of LAL Deficiency



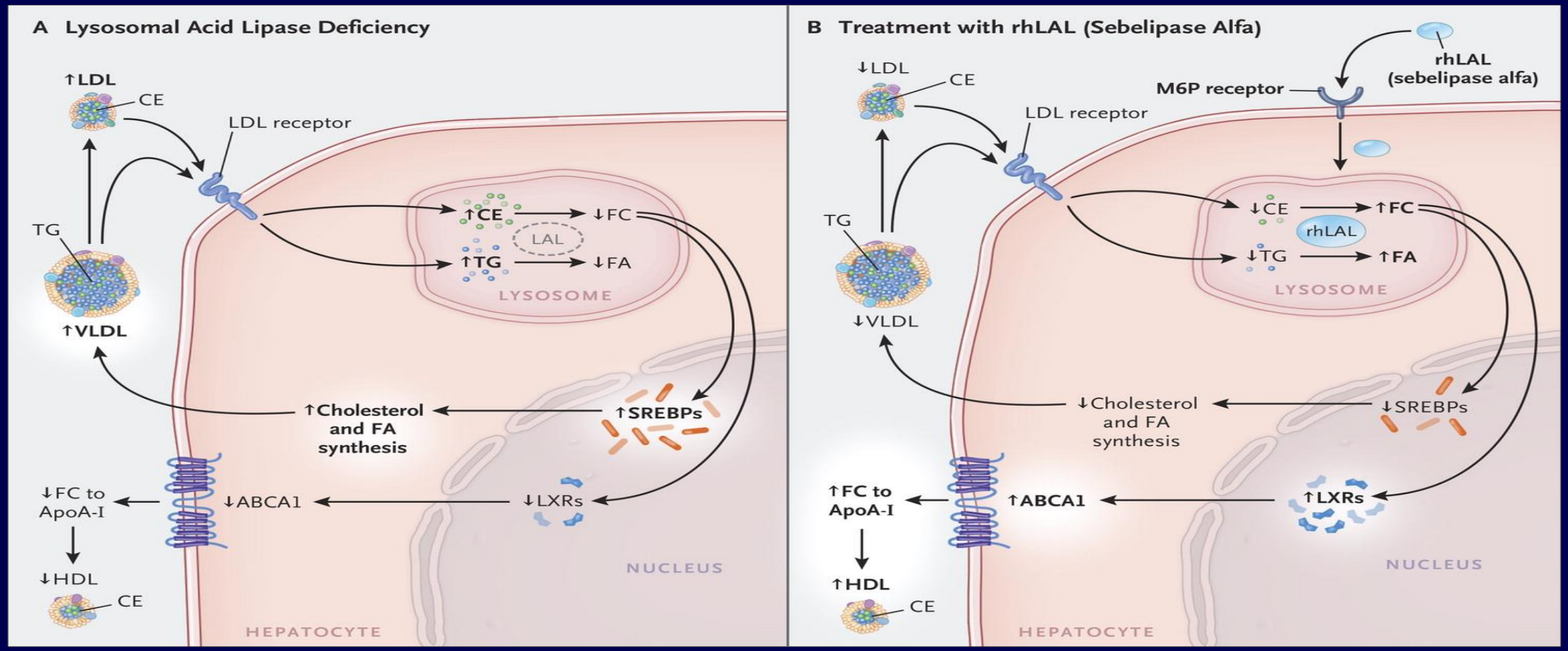
Tripuraneni R et al. *J Clin Lipidology*. 2013; 7:251. Poster presented NLA 2013.

Low HDL-C Is a Characteristic Feature of LAL Deficiency



Tripuraneni R et al. *J Clin Lipidology*. 2013; 7:251. Poster presented NLA 2013.

Effects of Lysosomal Acid Lipase Deficiency on Hepatic and Plasma Lipid Metabolism and Effects of Sebelipase Alfa Infusion

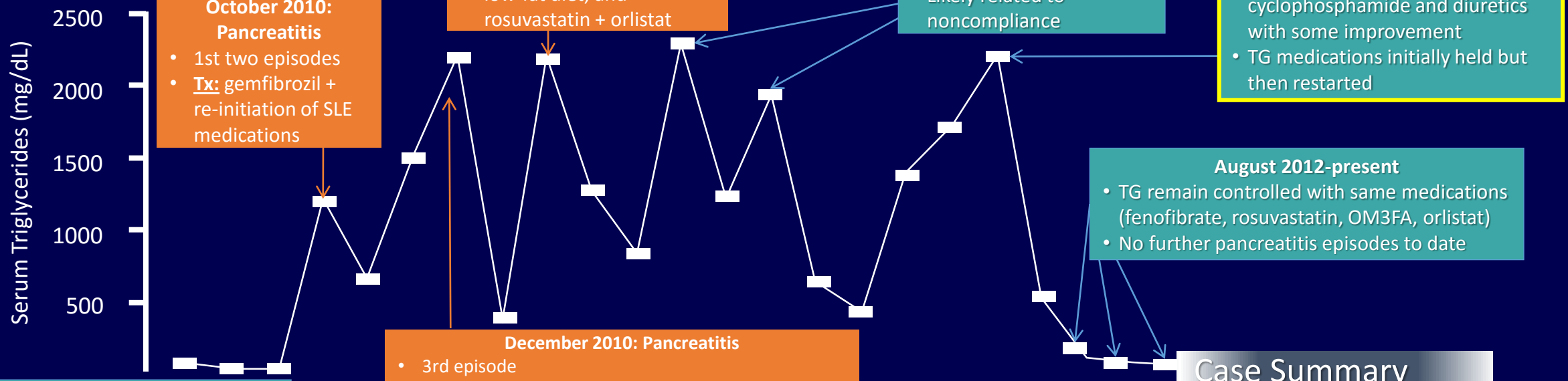


Rader DJ. *N Engl J Med* 2015;373:1071-1073.

Severe Hypertriglyceridemia and Chylomicronemia

Case Study: Severe Hypertriglyceridemia with Multifactorial Etiology

First diagnosed with SLE at age 12



2007-2010
- Stable SLE disease with mycophenolate mofetil
- One mild SLE flare in May 2010

October 2010: Pancreatitis
- 1st two episodes
- **Tx:** gemfibrozil + re-initiation of SLE medications

December 2010: Pancreatitis
- 3rd episode
- No improvement with steroids (initially for SLE related pancreatitis)
- **Tx:** fenofibrate + high-dose OM3FA, low-fat diet

January 2011: Pancreatitis
- 4th episode
- **Tx:** fenofibrate, OM3FA, low-fat diet, and rosuvastatin + orlistat

April-December 2011
- Periodic TG elevation (asymptomatic)
- Likely related to noncompliance

July 2012: Lupus Flare
- Admitted for SLE (Cr) ↑
- **Tx:** pulse dose steroids, IV cyclophosphamide and diuretics with some improvement
- TG medications initially held but then restarted

August 2012-present
- TG remain controlled with same medications (fenofibrate, rosuvastatin, OM3FA, orlistat)
- No further pancreatitis episodes to date

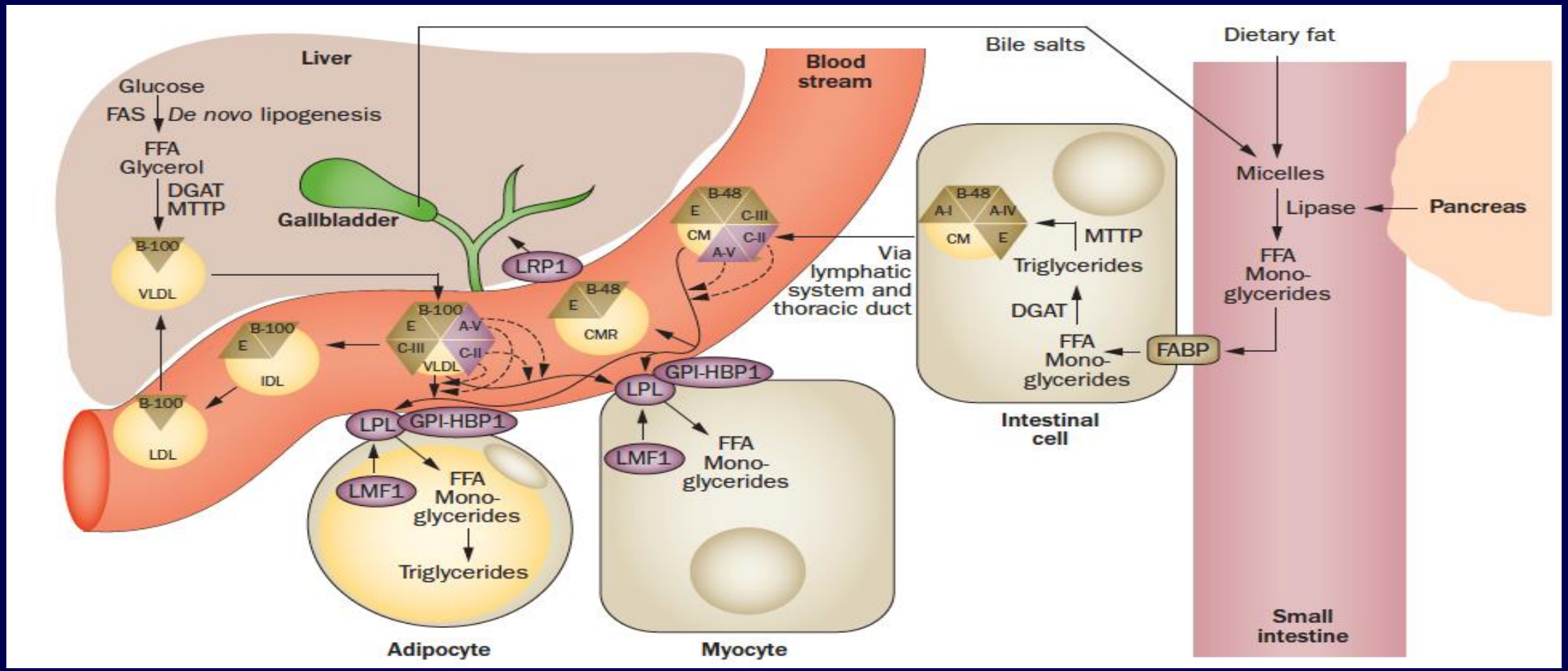
Case Summary

- Patient with recurrent pancreatitis despite treatment
- Genotyping revealed a novel **heterozygous missense mutation of LMF-1**
- Indicated primary cause of symptoms as **severe hypertriglyceridemia**
- Current status after treatment with multiple TG-lowering therapies:
  - Stabilized TG levels (<150mg/dL) for the last six months
  - Stable SLE
  - Patient is doing well

Abbreviations: SLE, systemic lupus erythematous; Tx, treatment; OM3FA, omega-3 fatty acids; TG, triglycerides; LMF-1, Lipase Maturation Factor-1.

Reference: Singh A et al. J Clin Lipidol. 2013;7:249-50.

Triglyceride-rich Lipoprotein Metabolism



Brahm & Hegele. Nat. Rev. *Endocrinol.* advance online publication 3 March 2015; doi:10.1038/nrendo.2015.26

Etiology of Severe Hypertriglyceridemia (Important to make a diagnosis)

- Primary Causes (monogenetic)
- Secondary Causes
- Primary (Less severe phenotype) + Secondary Insult

Primary Chylomicronemia: Monogenic and Polygenic Forms

Features	Monogenic chylomicronaemia	Polygenic chylomicronaemia
Former designations	Familial chylomicronaemia Type 1 hyperlipoproteinaemia (WHO)[2]	Mixed dyslipidaemia Type 5 hyperlipoproteinaemia[2] (WHO)
Main lipoprotein disturbances	Increased number of chylomicron particles only[5,11]	Transient increase in levels of triglyceride-rich lipoproteins Increased number of chylomicron particles Increased levels of VLDL Increased number of chylomicron remnants Increased number of VLDL remnants[4]
Associated lipoprotein disturbances	Reduced levels of VLDL, LDL and HDL	Usually reduced levels of HDL, sometimes reduced levels of LDL
Typical onset	Paediatric or adolescent	Adulthood
Clinical features	Failure to thrive Abdominal pain Nausea Vomiting Eruptive xanthomas Lipaemia retinalis Pancreatitis Hepatosplenomegaly[5]	Abdominal pain Nausea Vomiting Eruptive xanthomas (rare) Lipaemia retinalis (rare) Pancreatitis (~1% risk per year)[4]
Association with CVD	Minimal	Some evidence of increased risk[25,63]
Prevalence	~1:100,000 to ~1:1,000,000[4]	~1:600[6]
Contribution of secondary factors	Minimal	Major
Inheritence pattern	Autosomal recessive	Familial clustering, but no discrete classical pattern
Genetic causes	Mutations in *LPL*,[4] *APOC2*,[4] *APOA5*,[43] *GPIHBP1*[51] and *LMF1*[55]	Genetic pool of affected individuals has increased prevalence of: ▪ Heterozygous rare variants in *LPL*, *APOC2*, *APOB*, *GCKR*, *APOA5*, *LMF1*, *GPIHBP1* and *CREBH* with large effects[60,61] ▪ Common variants (SNP) with small effects in ~40 genes identified in genome-wide association studies[60]
Current treatment	Dietary control: restriction of fat intake ± increased consumption of MCTG Pharmacologic control: minimal effect of fibrates, niacin, ω-3 fatty acids and statins	Dietary control: reduced intake of calories, fats, simple sugars and alcohol Control of secondary factors Pharmacologic control: ω-3 fatty acids and niacin (both have variable efficacy)

Brahm & Hegele. Nat. Rev. *Endocrinol.* advance online publication 3 March 2015; doi:10.1038/nrendo.2015.26

Genetic Causes of Primary Monogenic Chylomicronemia

Gene (gene product)	Homozygote prevalence	Gene product function	Clinical features	Molecular features	% of monogenic mutations	References
LPL (LPL)	~1 per million individuals[4]	Hydrolysis of triglycerides and peripheral uptake of FFA	Severe chylomicronaemia in infancy or childhood	Severely reduced or absent LPL enzyme activity	95.0	4,28,32,36
APOC2 (apoC-II)	10 families reported	Required cofactor of LPL	Severe chylomicronaemia in childhood or adolescence	Absent or non-functional apoC-II	2.0	4,37
GPIHBP1 (GPI-HBP1)	10 families reported	Stabilizes binding of chylomicrons near LPL Supports lipolysis	Chylomicronaemia in late adulthood	Absent or defective GPI-HBP1	2.0	47,51
APOA5 (apoA-V)	Three families reported	Enhancer of LPL activity	Chylomicronaemia in late adulthood	Absent or defective apoA-V	0.6	40,41
LMF1 (LMF1)	Two families reported	Chaperone molecule required for proper LPL folding and/or expression	Chylomicronaemia in late adulthood	Absent or defective LMF1	0.4	55

Abbreviations: apoA-V, apolipoprotein A-V; apoC-II, apolipoprotein C-II; FFA, free fatty acid; GPI-HBP1, glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1; LMF1, lipase maturation factor 1; LPL, lipoprotein lipase.

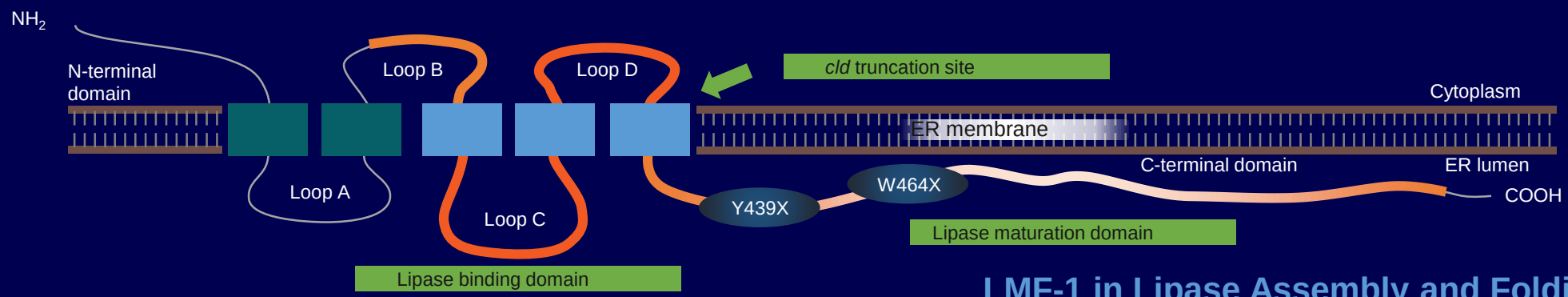
Brahm & Hegele. Nat. Rev. *Endocrinol.* advance online publication 3 March 2015; doi:10.1038/nrendo.2015.26

Emerging Therapies for Chylomicronemia

Drug class (example)	Mechanism of action	Advantages	Disadvantages	References
MTTP inhibition (lomitapide)	Prevents triglyceride transfer to apoB-containing particles during their formation	Small molecule that can be administered orally Reduces triglyceride levels by 30–40%	Common gastrointestinal adverse effects: nausea and diarrhoea Increased levels of liver enzymes and hepatosteatosis Cost	101,104–107
LPL gene therapy (alipogene tiparvovec)	Introduces a normal *LPL* gene into tissues of LPL-deficient patients	One time intramuscular injection Possible improvement in chylomicron kinetics	No enduring triglyceride effect after 12 weeks Indicated only for patients with autosomal recessive *LPL* gene deficiency	108–110,112
DGAT1 inhibition (AZD7687, PF0460110, ABT-046 and LCQ908)	Prevents triglyceride synthesis and re-synthesis	Small molecule that can be administered orally Reduces triglyceride levels by up to 80%	Gastrointestinal adverse effects Limited long-term data and safety data available Possible cross-reactivity with DGAT2	113–119
APOB mRNA interference (mipomersen)	Prevents synthesis and secretion of apoB-containing lipoproteins	Subcutaneous administration of antisense RNA Theoretical efficacy by reducing both apoB-48 and apoC-III production	Limited efficacy data in chylomicronaemia Uncertain delivery of agent to primary site of action (intestine) Common injection site reactions and flu-like symptoms	101,121
APOC3 mRNA interference (ISIS 304801)	Increases LPL activity and reduces triglyceride-rich lipoprotein production	Genetically validated target Subcutaneous administration Reduces triglyceride levels by up to 70%	Limited long-term data and safety data available	120,122,124
ANGPTL3 mRNA interference (ISIS-ANGPTL3Rx)	Promotes LPL activity by reducing ANGPTL3-mediated inhibition	Genetically validated target Subcutaneous administration Efficacy in reducing triglyceride and cholesterol levels	Limited long-term data and safety data available	126–128

Brahm & Hegele. Nat. Rev. *Endocrinol.* advance online publication 3 March 2015; doi:10.1038/nrendo.2015.26

The Role of Lipase Maturation Factor-1 (LMF-1)



LMF-1 in Lipase Assembly and Folding

- LMF-1 is a protein that spans the ER membrane
- Involved in post-translational folding, maturation, and therefore active expression of enzymatic lipases (LPL and HL)
- A conserved C-terminal domain (DUF1222) makes up about ~70% of the gene sequence
- Previously identified human LMF-1 mutations were **homozygous nonsense mutations**
  - Involved truncation of the C-terminal domain
  - A greater level of truncation was associated with increased severity of pancreatitis

In this case study, our patient had a novel
heterozygous missense mutation (D491N) not yet described in the literature

Abbreviations: NH_2, amino terminal; cld, combined lipase deficiency; COOH, carboxy terminal; ER, endoplasmic reticulum; LPL; lipoprotein lipase; HL, hepatic lipase.

Reference: Singh A et al. J Clin Lipidol. 2013;7:249-50.

Conclusions

- Our patient's complex medical history and course point towards the complexity and multifactorial causes which lead to hypertriglyceridemia.
- Description of LMF-1 mutations in animal and human phenotypes has allowed for a more nuanced understanding of the shared pathway which promotes biochemical maturation of LPL, HL, and EL.
- Though the most commonly encountered mutations in primary hypertriglyceridemia remain related to LPL and ApoC-II, LMF-1 mutations are an important addition to the list of possible causes.
- **Clinical Significance**

  Although rare, LMF-1 deficiency should be considered in patients with possible primary hypertriglyceridemia

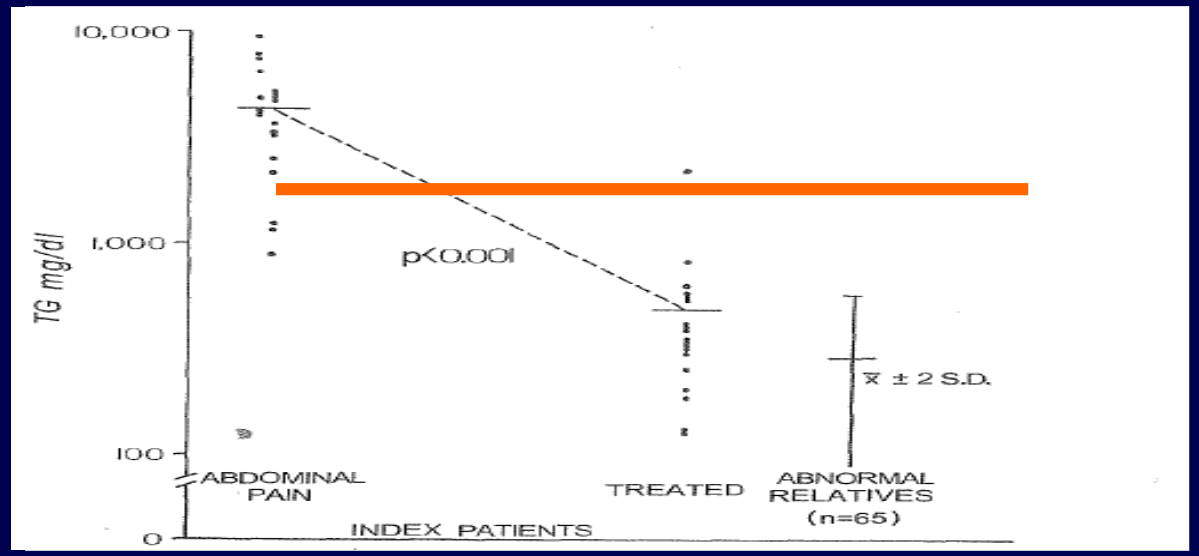
Abbreviations: LMF-1, Lipase Maturation Factor-1, LPL; lipoprotein lipase; HL, hepatic lipase; EL, endothelial lipase; ApoC-II, apolipoprotein C2

Reference: Singh A et al. *J Clin Lipidol*. 2013;7:249-50.

Treatment of Hypertriglyceridemia Results in Fewer Hospital Admissions

- Treatment of familial hypertriglyceridemia may not decrease plasma triglyceride levels
- Additional treatment of the secondary causes of hypertriglyceridemia may be needed to further reduce plasma triglyceride levels

Comparison of plasma TG levels in patients with pancreatitis (index patients) before and after treatment of secondary causes of hypertriglyceridemia



Treatment of secondary causes of high TG levels reduces hospitalization rates due to pancreatitis

Before Treatment:
- 105 admissions per 100 patient years

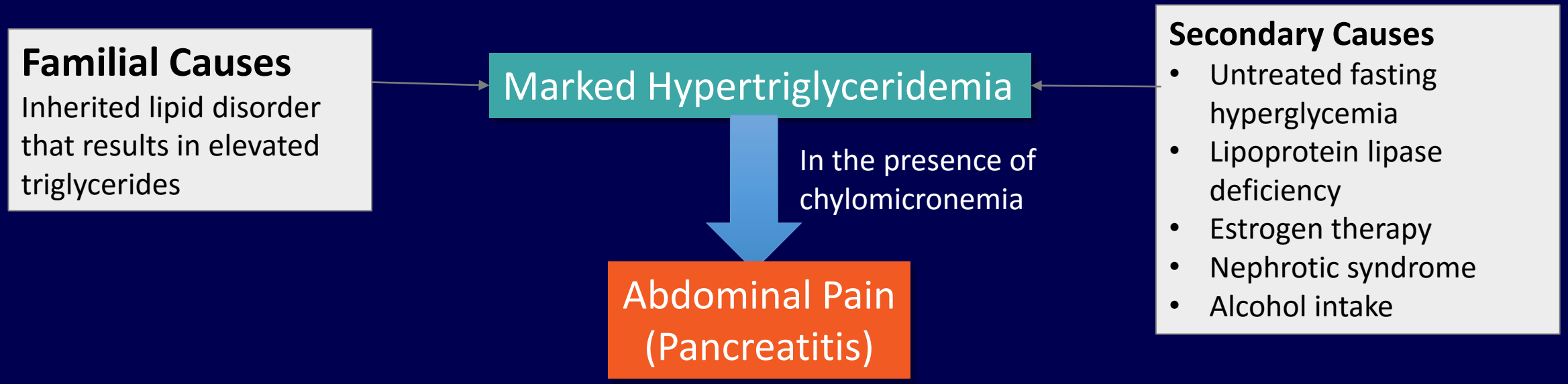
After Treatment:
- 1.8 admissions per 100 patient years

Abbreviations: TG, triglycerides

Reference: Brunzell JD and Schrott HG. *J Clin Lipidology*. 2012;6:409-412.

Proposed Relationship Between Hypertriglyceridemia and Pancreatitis

- Marked hypertriglyceridemia is possibly the result of an interaction between familial lipid disorders and secondary causes of hypertriglyceridemia

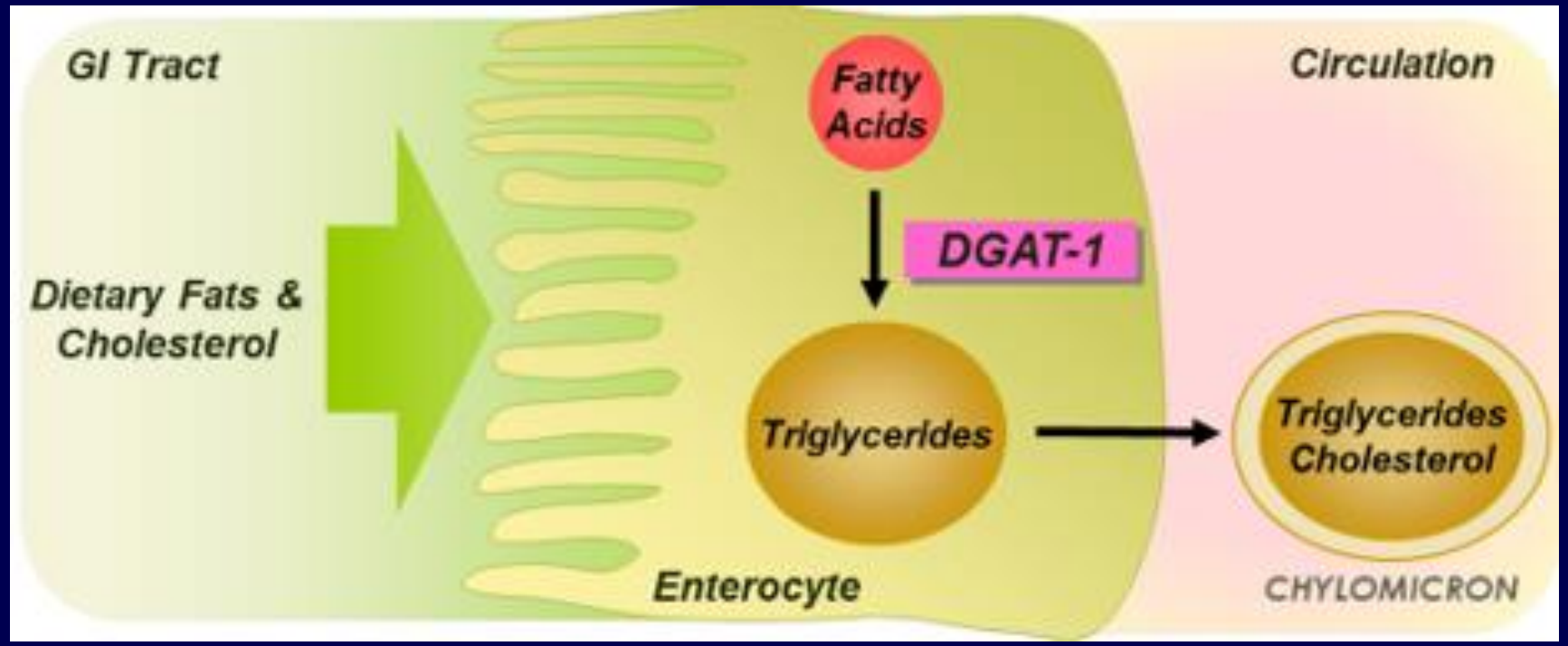


Brunzell JD and Schrott HG. *J Clin Lipidology.* 2012;6:409-412.

Emerging Therapies for Hypertriglyceridemia

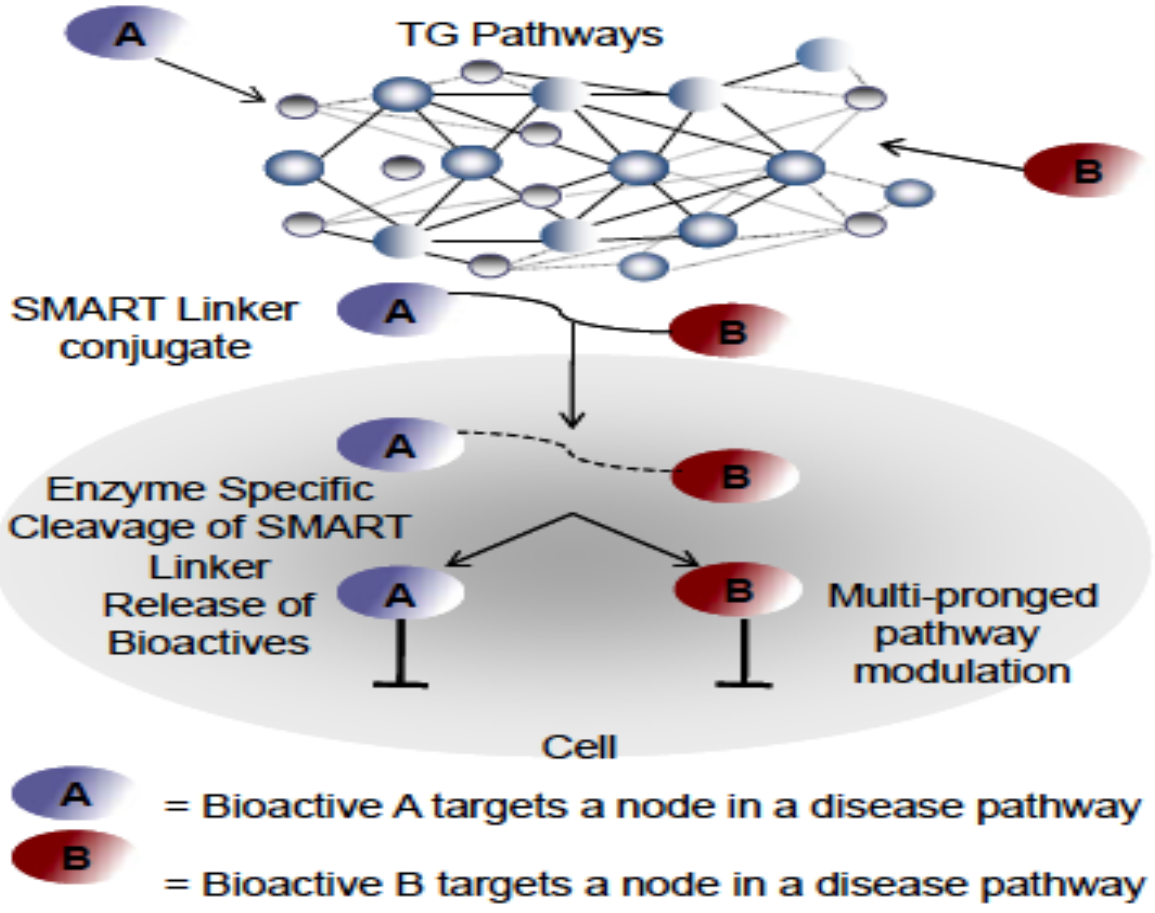
- Omega 3 Ethyl Ester
- DGAT 1 inhibitors
- ApoCIII Inhibitors
- Lomitapide
- Linkage Technology

DGAT 1 Inhibition



http://www.vikingtherapeutics.com/pipeline/dgat-1/

Peptide Linker Technology CAT-2003



SMART Linker Conjugates

- Proprietary linker technology used to construct bifunctional compounds that target a disease pathway at multiple points

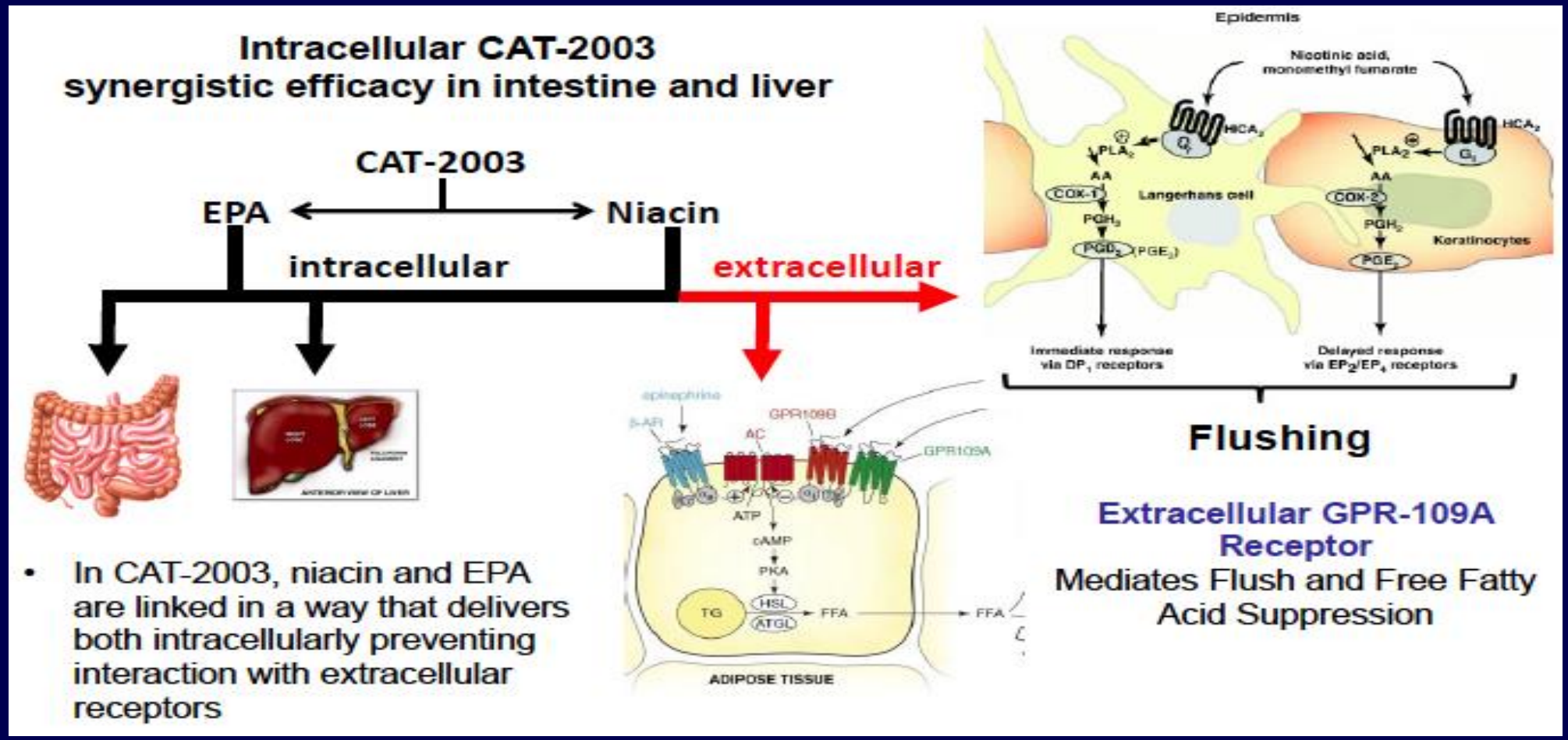
Efficacy

- Focus on key disease targets
- Match PK of bioactives
- Produce mechanistic synergy
- Increase intracellular omega 3 concentration

Tolerability and Safety

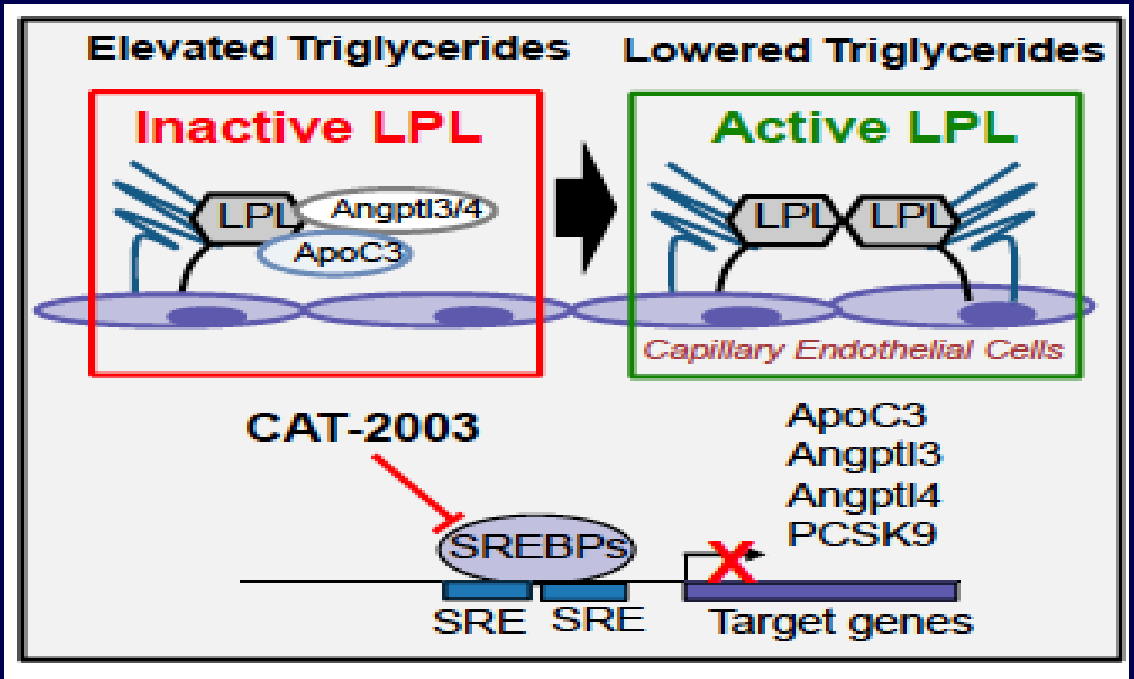
- Pathway targeted compound is inactive until released inside the targeted cell

CAT-2003: Inactive Until Entering the Target Cell



- In CAT-2003, niacin and EPA are linked in a way that delivers both intracellularly preventing interaction with extracellular receptors

CAT-2003 Activates Lipoprotein Lipase (LPL) to Accelerate Triglyceride Clearance



CAT-2003 inhibits the production of the negative regulators of LPL through activated SREBP and reductions in PCSK9

Angptl3/4, angiopoeitin-like protein 3/4

CAT-2003 Clinical Status

Phase 1:

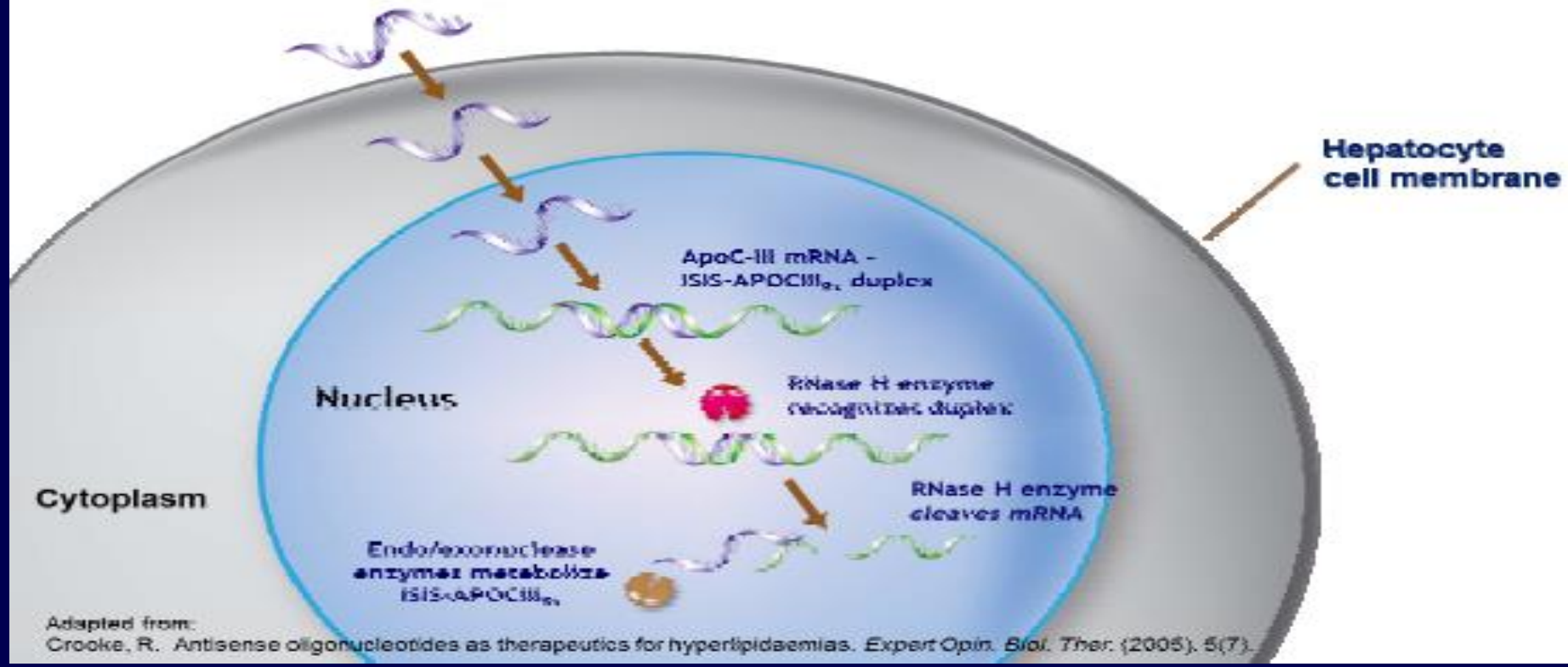
- Established safety and tolerability of single and multiple doses
  - No safety issues
  - No flushing
  - Tolerability acceptable in range where pharmacology demonstrated
- Established clinical exposure
- Proof of concept pharmacological effects
  - Reductions in apo B-containing lipoproteins and PCSK9
  - Profound reductions in post-prandial triglycerides
  - Reductions in fasting triglycerides in hypertriglyceridemic subjects

Phase 2: in progress

http://www.catabasis.com/

ISIS-APOCIIIRx Anti-Sense Therapy

- Structure: 20-nucleotide (20-mer) antisense oligonucleotide (ASO)
- Complementary, specific ASO sequence that crosses the hepatocyte cell membrane and binds in coding region of mRNA for ApoC-III



Adapted from:
Crooke, R. Antisense oligonucleotides as therapeutics for hyperlipidaemias. *Expert Opin. Biol. Ther.* (2005). 5(7).

Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Antisense Oligonucleotide Inhibition of Apolipoprotein C-III Reduces Plasma Triglycerides in Rodents, Nonhuman Primates, and Humans

Mark J. Graham, Richard G. Lee, Thomas A. Bell III, Wuxia Fu, Adam Emile Mullick, Veronica J Alexander, Walter Singleton, Nick Viney, Richard Geary, John Q Su, Brenda F. Baker, Jennifer Burkey, Stanley T. Crooke and Rosanne M. Crooke

Circ Res. published online March 29, 2013;
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7330. Online ISSN: 1524-4571

The NEW ENGLAND JOURNAL of MEDICINE

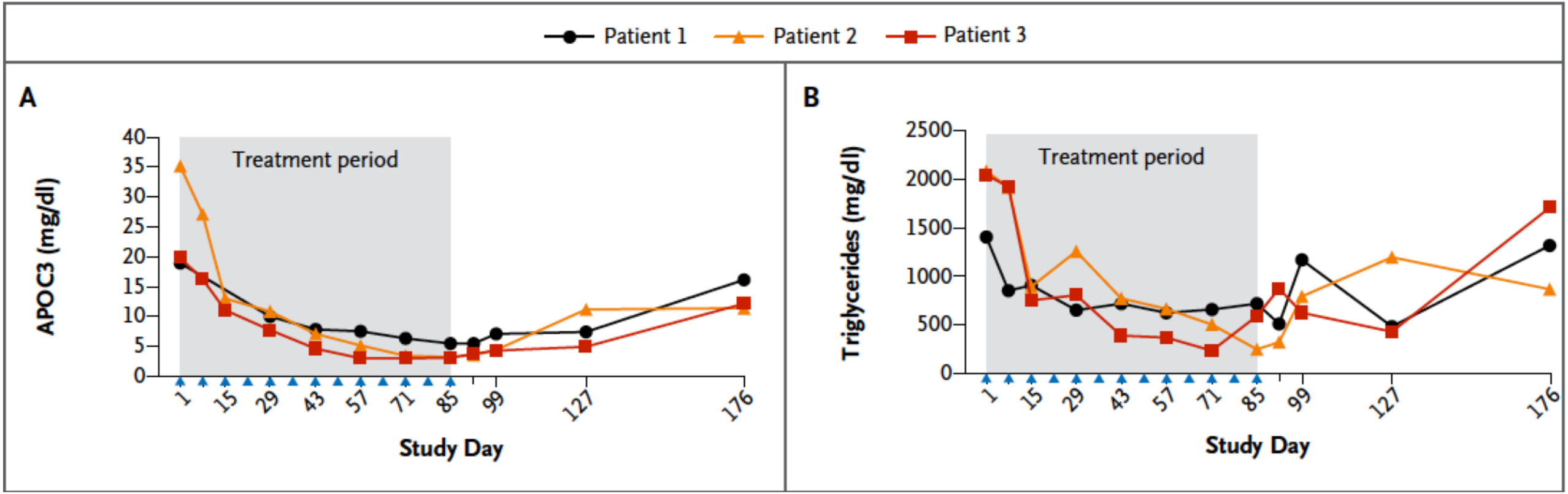
BRIEF REPORT

Targeting APOC3 in the Familial Chylomicronemia Syndrome

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.

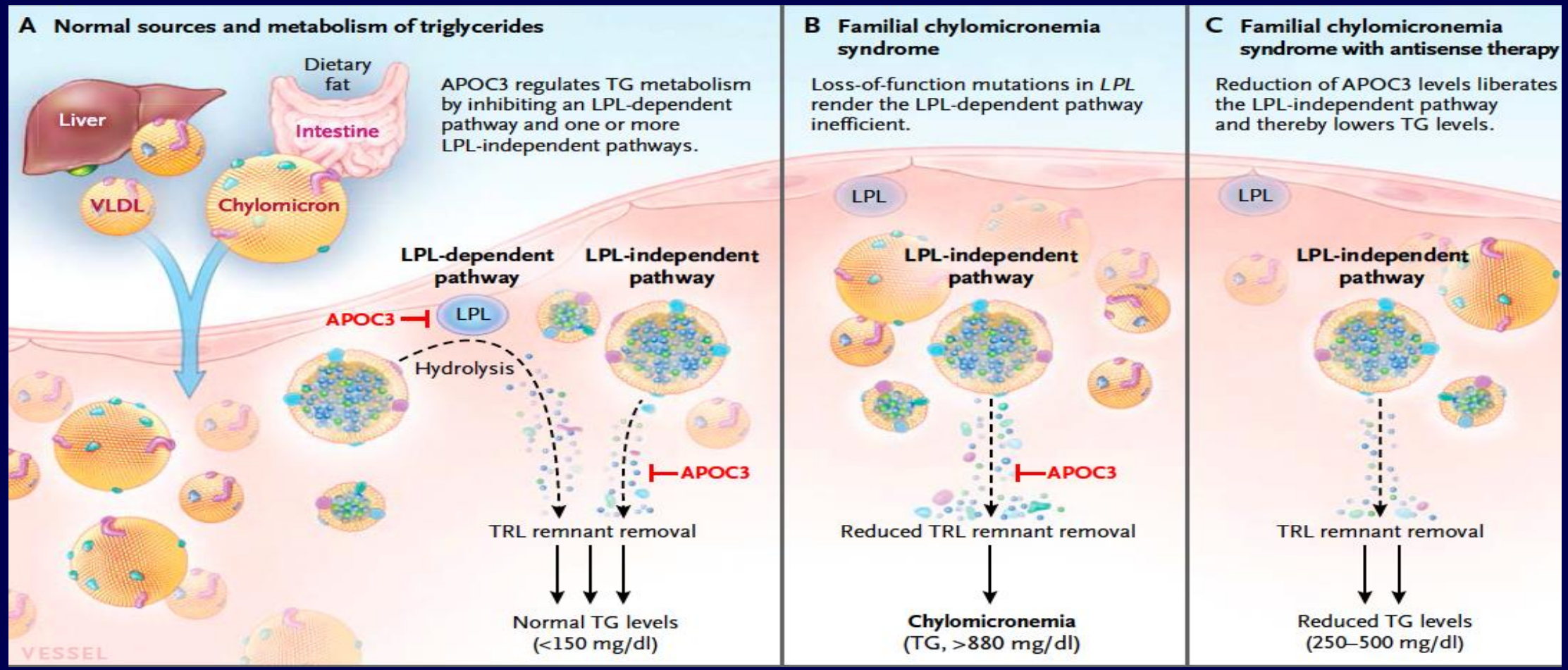
N Engl J Med 2014;371:2200-6.

Change in APOC3 and TG Levels in 3 Patients with Chylomicronemia



Gaudet et al. *N Engl J Med* 2014;371:2200-6.

Plasma Triglyceride Metabolism and the Role of APOC3



Gaudet et al. *N Engl J Med* 2014;371:2200-6.

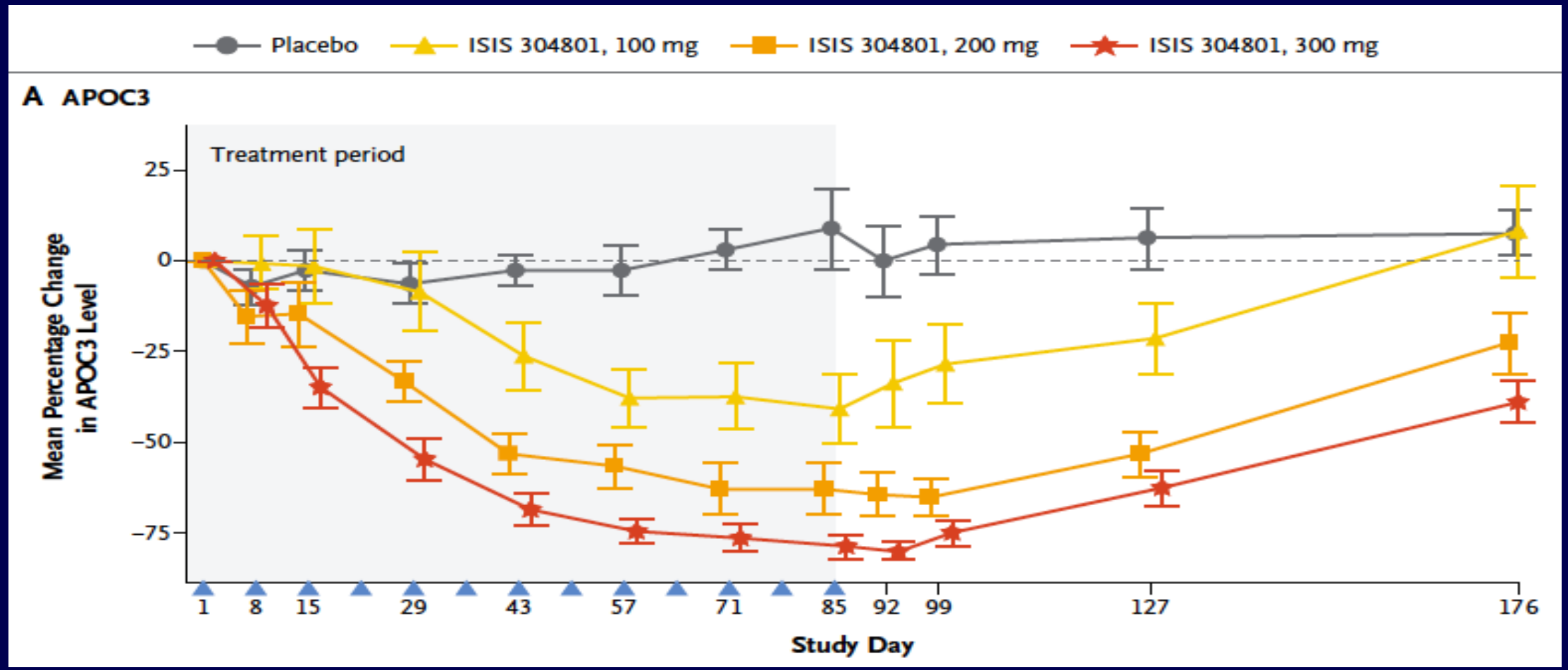
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

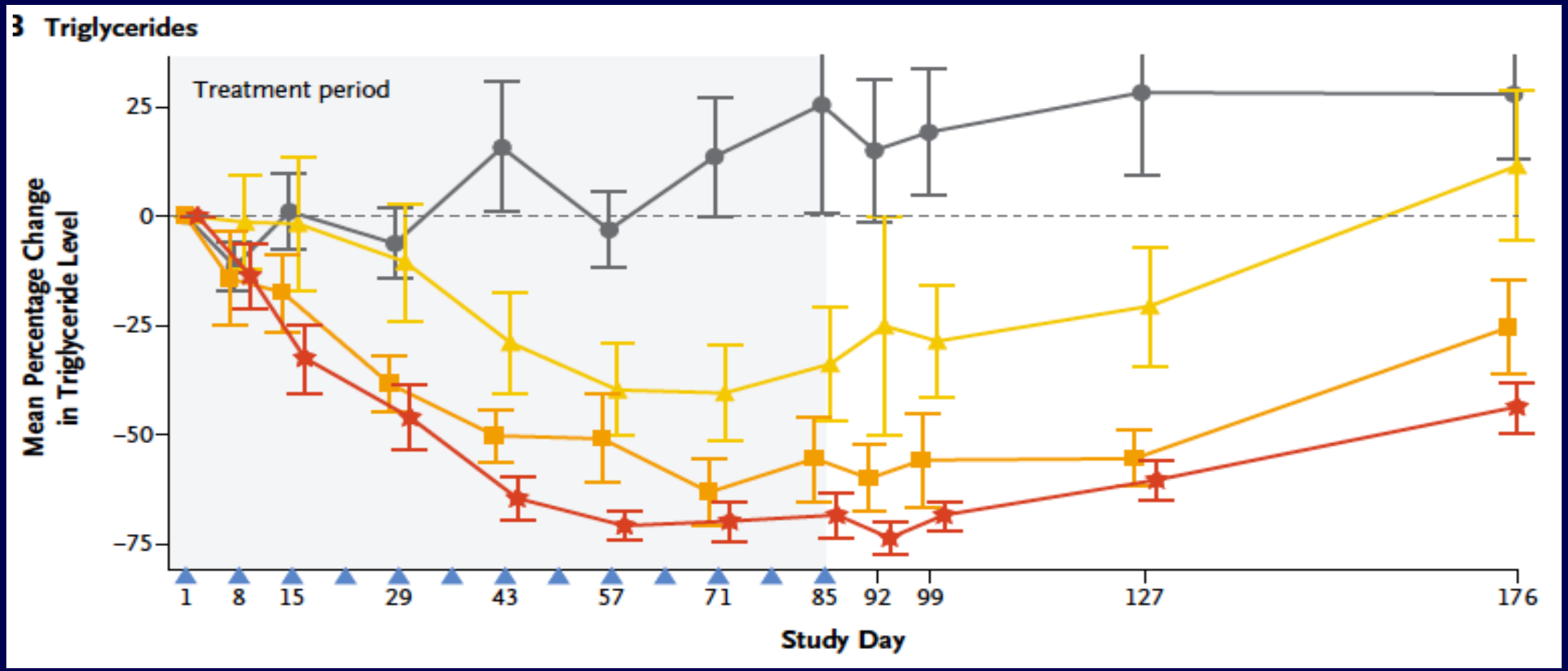
Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia

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

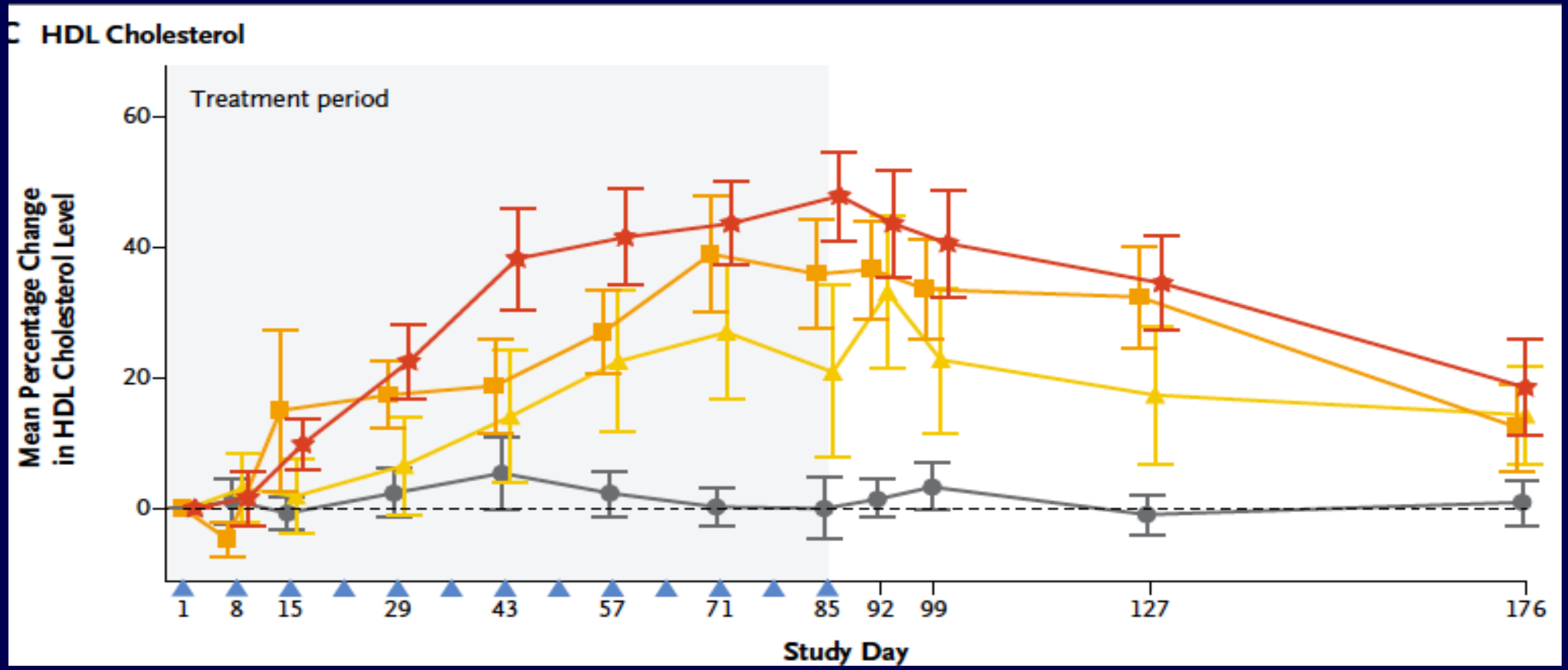
N Engl J Med 2015;373:438-47.



Gaudet et al. *N Engl J Med* 2015;373:438-47.



Gaudet et al. *N Engl J Med* 2015;373:438-47.



Gaudet et al. *N Engl J Med* 2015;373:438-47.

Lipodystrophy, Congenital, Acquired, General, and Partial

- Lipodystrophy is a rare, heterogeneous group of syndromes characterized by the complete or partial loss or absence of subcutaneous adipose tissue
- Often seen with metabolic derangements, including insulin resistance, diabetes mellitus, hepatic steatosis or steatohepatitis, and dyslipidemia
- Can lead to acute pancreatitis (due to severe hypertriglyceridemia), hepatic cirrhosis, and premature cardiovascular disease
- Additional manifestations include polycystic ovarian syndrome (PCOS), acanthosis nigricans (due to severe insulin resistance), and eruptive xanthomas, NAFLD, and progressive liver disease

Handelsman et al. *Endocr Pract.* 2013 Jan-Feb; 19(1): 107–116.

Endocrine Abnormalities

- The key characteristic of lipodystrophy is the selective absence of adipose tissue (primarily subcutaneous), the levels of adipocyte hormones can be altered
- Reduced leptin levels
- Reduced adiponectin levels

Congenital Lipodystrophy: General and Partial

Gene/protein	Specific clinical features	Main role of the affected protein
Congenital generalized lipodystrophies[a]		
AGPAT2/AGPAT2	Bone lesions	Acylation of lysophosphatic acid to form phosphatidic acid in TG and phospholipid biosynthetic pathway
BSCL2/seipin	Extreme lack of body fat, mild mental retardation, cardiomyopathy	Required for lipid droplet formation and for adipogenesis
CAV1/caveolin 1	Short stature, vitamin D deficiency (single case)	Integral protein of caveolae which binds fatty acids and translocates them to lipid droplets
PTRF/cavin 1	Muscular dystrophy, pyloric stenosis	Integral protein of caveolae which regulates the expression of caveolin 1 and caveolin 3
FOS/c-FOS	Growth retardation, hypercholesterolemia (single case)	Transcription factor involved in adipocyte differentiation
Partial lipodystrophies[b]		
LMNA/lamin A/C	Dunnigan syndrome—preserved or excess facial and neck fat at puberty	Protein of the nuclear envelope
PPARG/PPARγ	Preserved abdominal fat, hypertension	Transcription factor for adipocyte differentiation
PLIN1/perilipin 1	Small white adipocytes and increased fibrosis	Integral component of the adipocyte lipid droplet involved in lipid storage and lipolysis regulation
CIDEC/CIDEC	White adipocytes with multilocular lipid droplets (single case)	Regulation of lipid droplet size, thereby favoring lipid storage and inhibiting lipolysis
AKT2/AKT2	Single family	Serine/threonine kinase involved in insulin receptor signaling and adipocyte differentiation

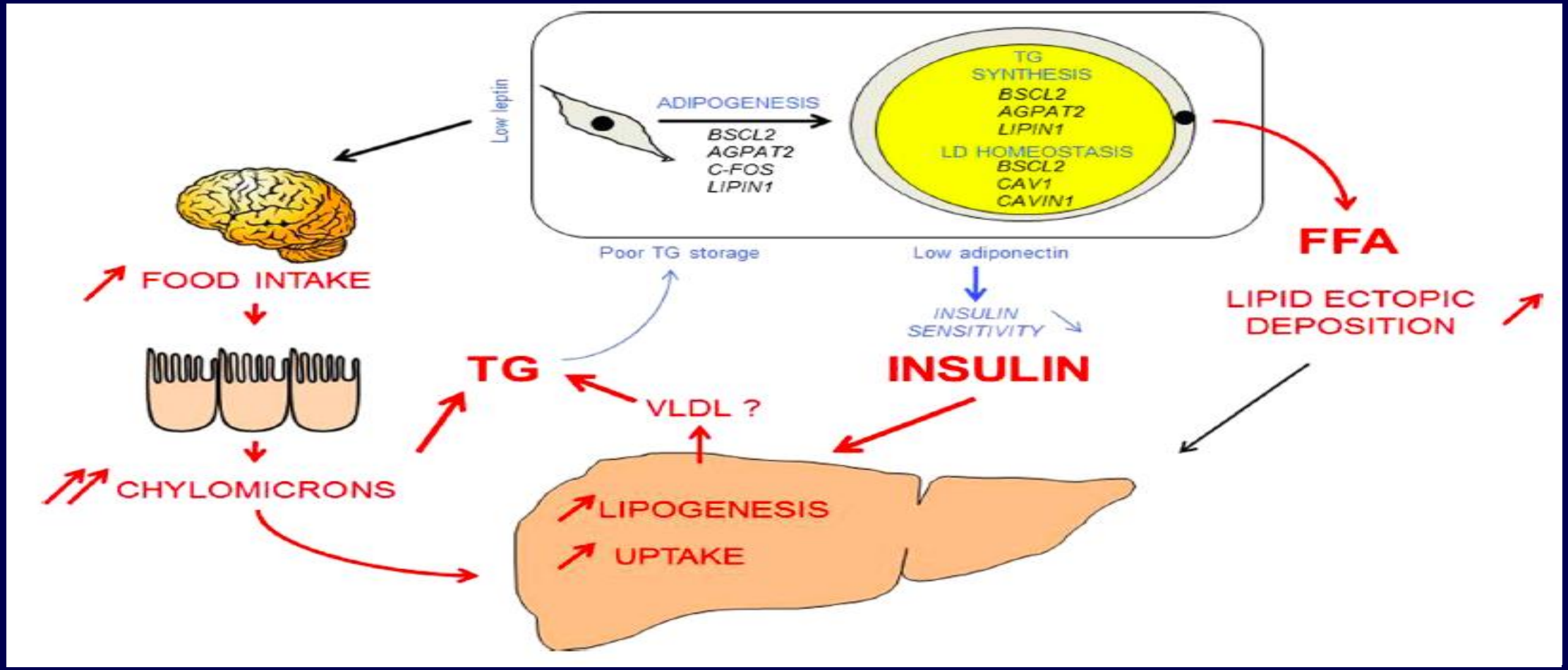
Prieur et al. *Curr Atheroscler* Rep. 2014;16:437

Classification, Clinical Features, and Pathogenetic Basis of Acquired Lipodystrophies

Type	Subtype	Clinical features	Pathogenetic basis/other comments
Lipodystrophy in HIV-infected patients	PI-induced NRTI-induced	Loss of sc fat from the face and extremities and excess fat deposition in the neck and abdomen	PI may inhibit ZMPSTE24 and/or cause dysregulation of transcription factors involved in adipogenesis. NRTI may inhibit mitochondrial polymerase-γ and cause mitochondrial toxicity.
Acquired partial lipodystrophy	Autoimmune MPGN-associated Idiopathic	Loss of sc fat from the face, neck, upper limbs, and trunk, sparing the lower abdomen and lower limbs	Low serum complement 3 levels and presence of an autoantibody, complement 3 nephritic factor, in most of the patients suggest autoimmune-mediated loss of adipose tissue.
Acquired generalized lipodystrophy	Autoimmune Panniculitis-associated Idiopathic	Generalized loss of fat associated with tender sc nodules, autoimmune or other diseases	Panniculitis preceding the loss of sc fat and association of autoimmune diseases suggest immune-mediated loss of adipose tissue. Other mechanisms may also be involved.
Localized lipodystrophy	Drug-induced Panniculitis-induced Pressure-induced Centrifugal Idiopathic	Loss of sc fat from small areas of the body	Multiple mechanisms including local drug-induced, immune-mediated, or pressure-induced atrophy of adipose tissue. Other unknown mechanisms may also be involved.

Garg. *J Clin Endocrinol Metab*, November 2011, 96(11):3313–3325.

Metabolic Impact of Lipodystrophy



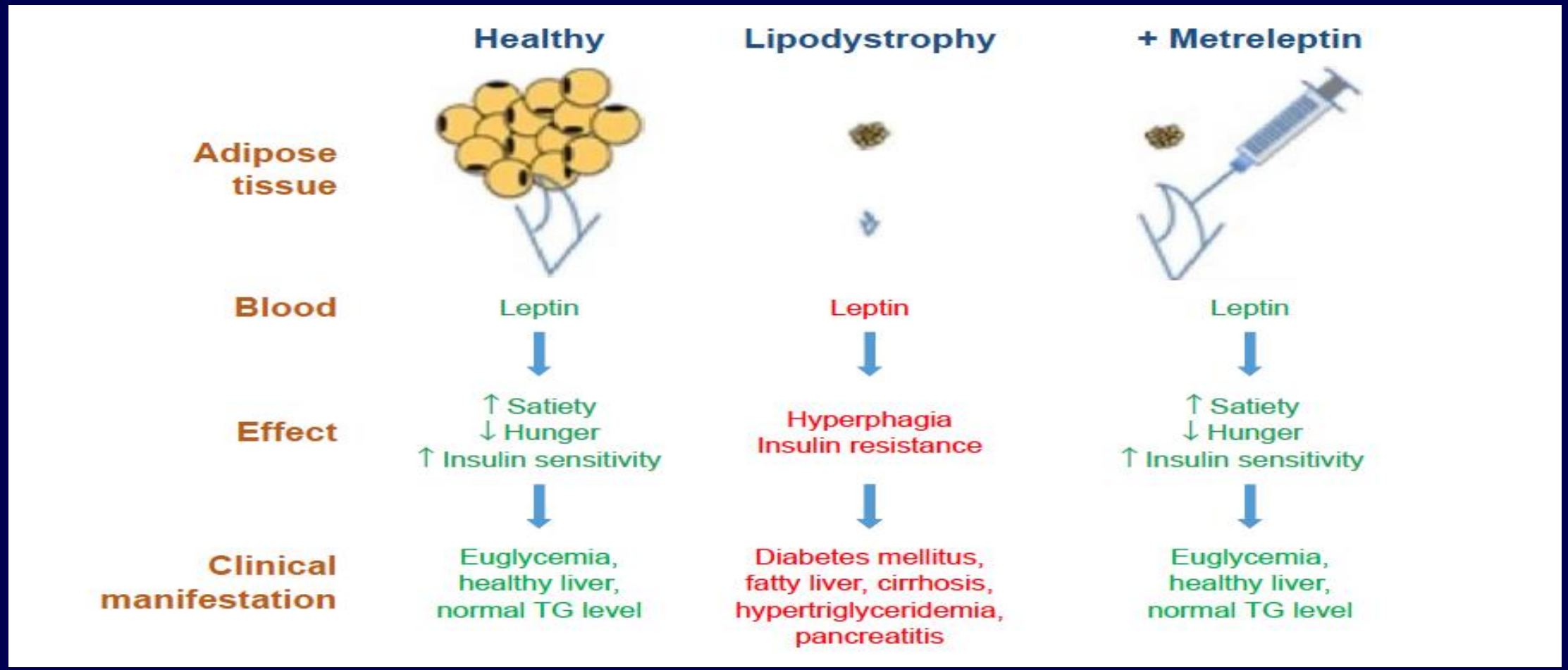
Prieur et al. *Curr Atheroscler Rep*. 2014;16:437

Lipodystrophy Treatment Issues & Options

- Reduce Triglycerides and Cardiovascular Risk
- Insulin Resistance/Diabetes
- Fatty Liver and Progression to Liver Disease
- Treatment
  - TLC: Restriction of total fat intake to between 20 and 30% of total dietary energy
  - N-3 Fatty Acids
  - Fibrates
  - Statins
  - Insulin Sensitizers: metformin and thiazolidinediones
  - Recombinant Leptin Replacement Therapy (Generalized Lipodystrophy): metreleptin

Curr Atheroscler Rep (2014) 16:437

Clinical Action of Metreleptin Treatment in Adipose-deficient Lipodystrophic Patients



Rodriguez et al. Ther Clin Risk Manag. 2015;11:1391-400.

CLINICAL EFFECTS OF LONG-TERM METRELEPTIN TREATMENT IN PATIENTS WITH LIPODYSTROPHY

Jean L. Chan, MD[1]; Karen Lutz, PhD[1*]; Elaine Cochran, MSN, CRNP[2]; Wenying Huang, PhD[1]; Yvette Peters, PhD[1]; Christian Weyer, MD[1]; Phillip Gorden, MD[2]*

Evaluate the long-term clinical effect of treatment with metreleptin (an analogue of human leptin) on glycemic and lipid abnormalities and markers of hepatic steatosis in patients with inherited or acquired lipodystrophy:

- Fifty-five patients (36 with generalized lipodystrophy and 19 with partial lipodystrophy)
- Metreleptin treatment substantially reduced glycemic variables, triglycerides, and liver enzymes (ALT and AST) and demonstrated durability of response throughout a 3-year treatment period.

Endocr Pract. 2011;17:922-932.

Metreleptin

- Approved for treatment of complications related to leptin deficiency in patients with general or acquired generalized lipodystrophy
- No established data for partial lipodystrophy, HIV-associated lipodystrophy, liver disease
- Not to be used for diabetes, hypertriglyceridemia without generalized lipodystrophy
- Safety issues: possibility of anti-drug and anti-neutralizing antibodies and risk of lymphoma

Summary

- The presentation of elevated triglycerides with or without pancreatitis, fatty liver, and other cardiometabolic risk factors is a common presentation in clinical practice.
- Patients can have underlying inherited disorders not with atypical clinical phenotypes.
- Secondary causes can often exacerbate less severe genetic abnormalities, whether monogenic or polygenic.
- Several less common disorders with common presentation can now be treated with new therapeutic interventions. Awareness leads to diagnosis and better management.


CMHC
WEST
CARDIOMETABOLIC HEALTH CONGRESS
March 4-5, 2016 • San Francisco, CA