Management of Hypertriglyceridemia Should we treat?

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May 25, 2019

ag THYROID and ENDOCRINE CLINIC

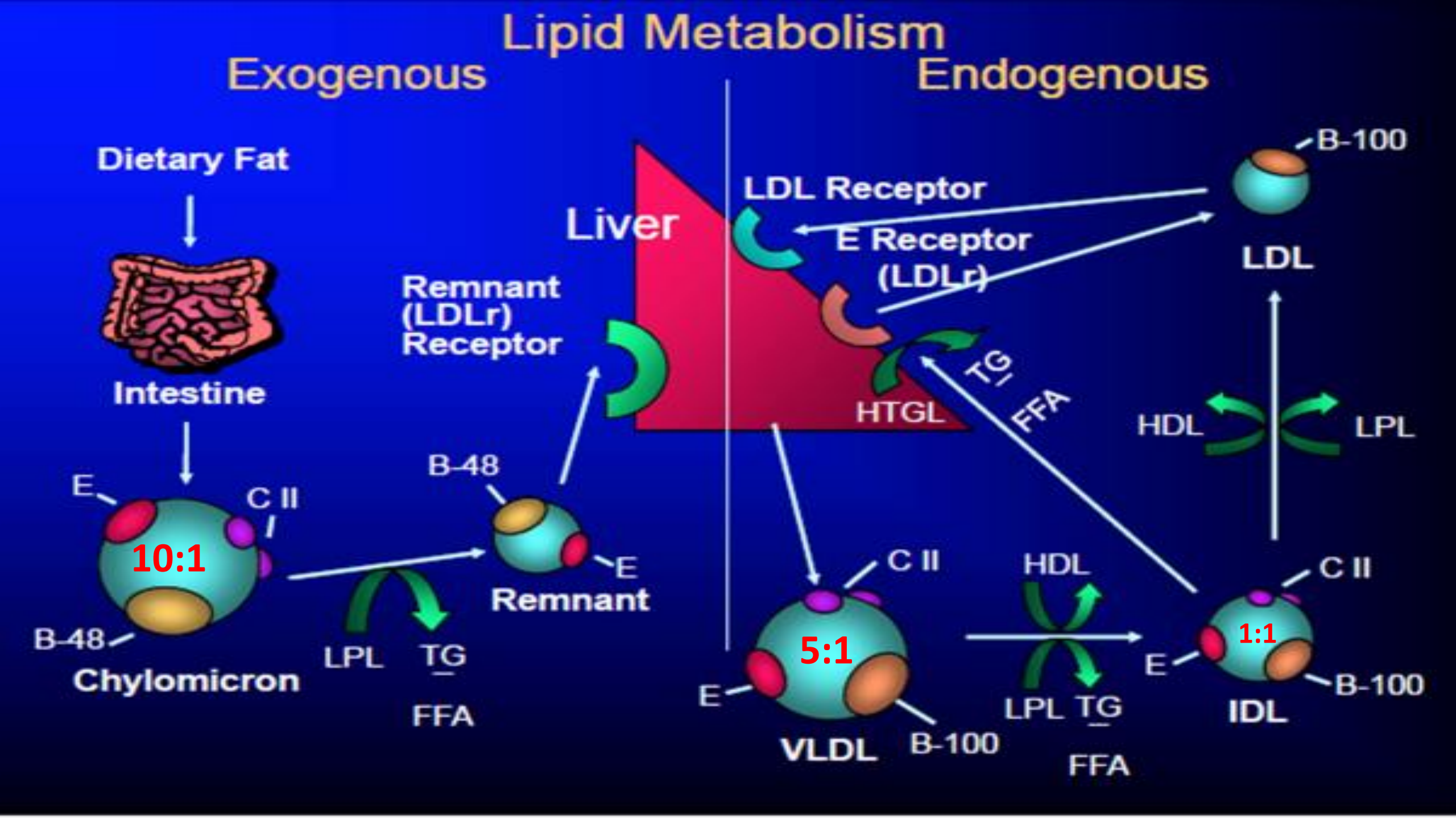
San Juan City Hospital
Endocrinology, Diabetes & Metabolism

Disclosure

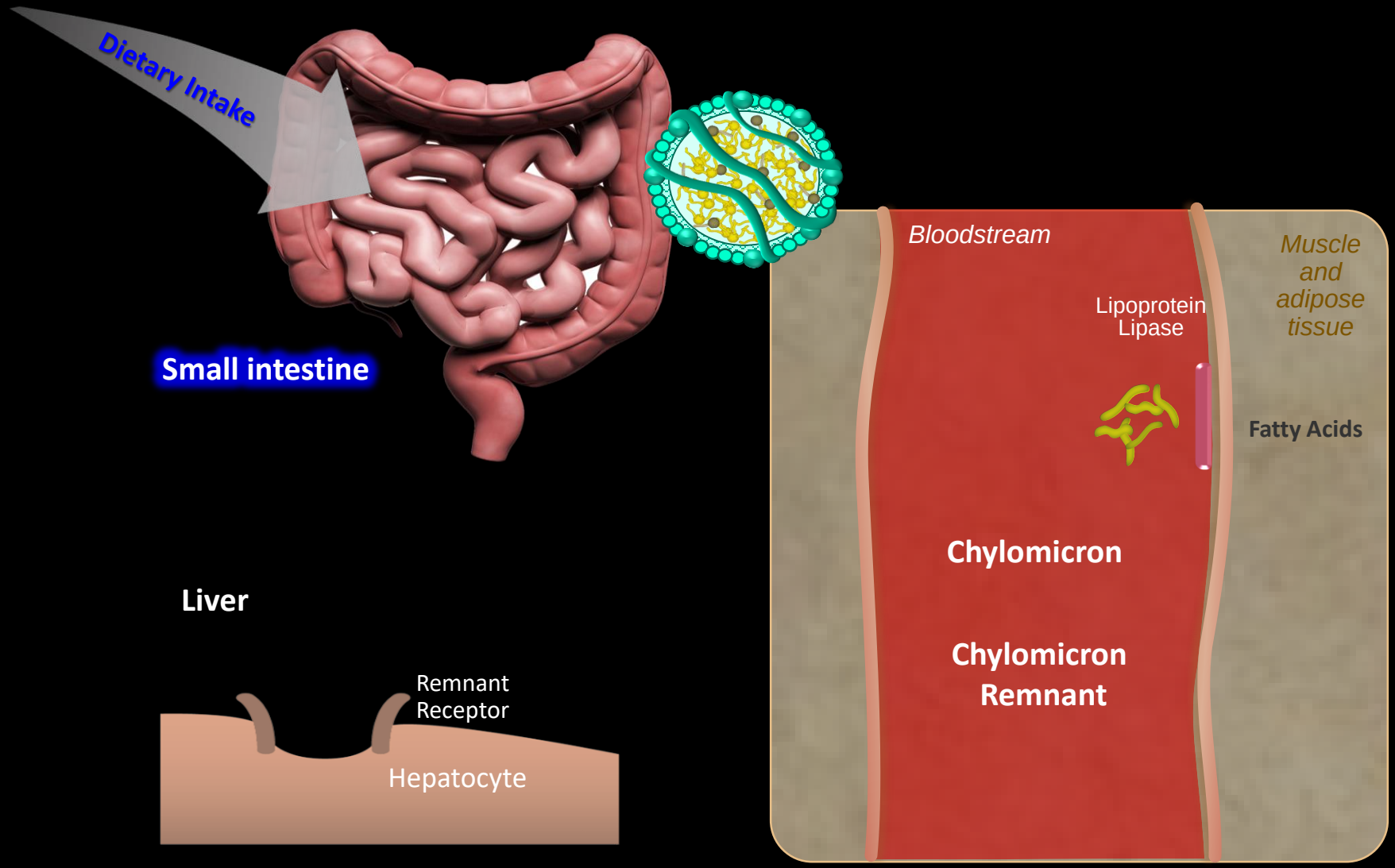
No conflicts of interests to disclose.

Learning Objectives

- At the end of this lectures, participants will be able to:
  - Recognize the Lipid Metabolism.
  - Understand the pathogenesis of hypertriglyceridemia on Pancreatitis and CVD risk.
  - Recognize the primary and secondary causes of hypertriglyceridemia.
  - Understand the treatment for hypertriglyceridemia-based pancreatitis or cardiovascular risk.
  - Recognize and understand the use of Omega 3 on hypertriglyceridemia.

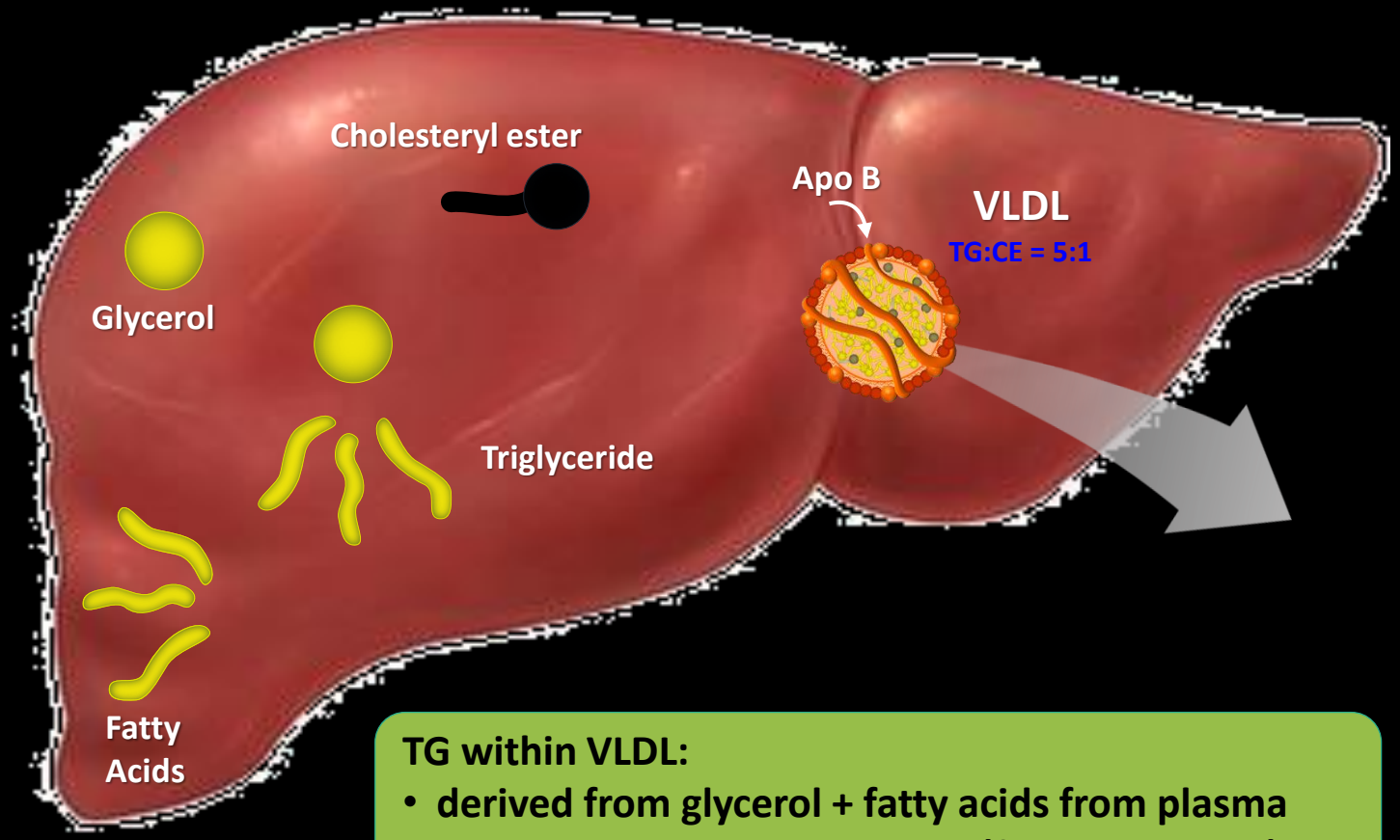

Lipid Metabolism
Exogenous
Endogenous
Dietary Fat
Intestine
Liver
Remnant
(LDLr)
Receptor
LDL Receptor
E Receptor
(LDLr)
B-100
LDL
HTGL
TG
FFA
HDL
LPL
E
C II
10:1
B-48
Chylomicron
LPL
TG
FFA
B-48
E
Remnant
C II
5:1
E
VLDL
B-100
HDL
LPL
TG
FFA
C II
1:1
E
IDL
B-100

Normal Metabolism of TGRLp: Exogenous (Dietary Origin)



1. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. *Circulation*. 2011;123(20):2292-2333. 2. Grundy SM. Atlas of atherosclerosis and metabolic syndrome. Chapters 4 and 5. 4th edition. Current Medicine LLC. 2005.

Normal Metabolism of TGRLp: Endogenous (Hepatic Origin)

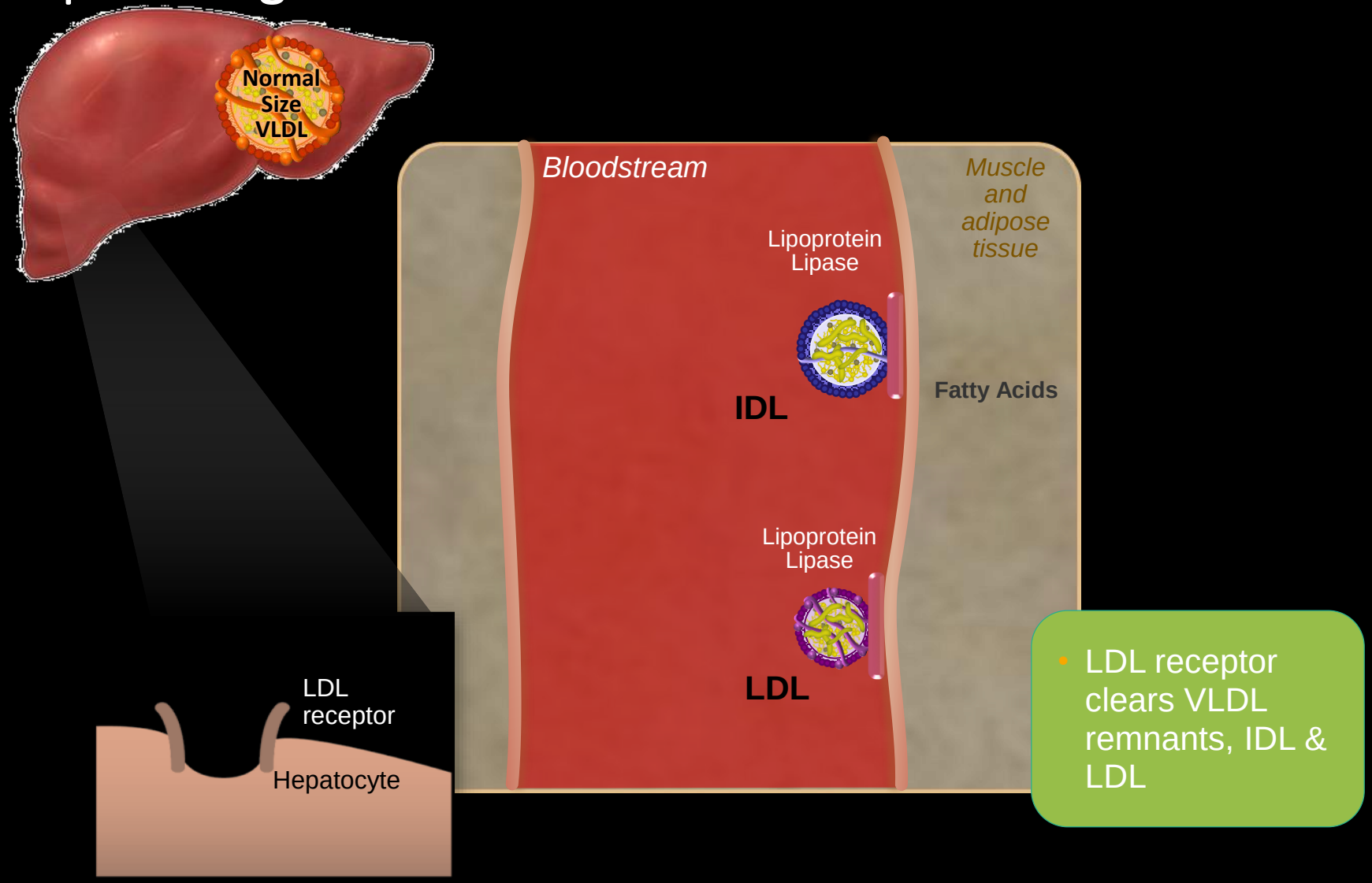


TG within VLDL:
- **derived from glycerol + fatty acids from plasma**
- **newly synthesized in the liver (fructose driven)**

Apo, apolipoprotein; VLDL, very low-density lipoprotein; CE, cholesteryl ester

Kwiterovich PO. Johns Hopkins Textbook of Dyslipidemia. 2009.; Miller M, et al. *Circulation*. 2011;123:2292-2333.; Grundy SM. Atlas of atherosclerosis and metabolic syndrome. 2005.

Normal Plasma Metabolism of TGRLp: Hepatic Origin



- LDL receptor clears VLDL remnants, IDL & LDL

IDL, intermediate-density lipoproteins; LDL, low-density lipoprotein

Kwiterovich PO. Johns Hopkins Textbook of Dyslipidemia. 2009. Miller M, et al. *Circulation*. 2011;123:2292-2333. Grundy SM. Atlas of atherosclerosis and metabolic syndrome. 2005.

HTG by Age, Sex and Ethicity

(US National Health & Nutrition Examination Survey—NHANES, 1999-2008)

Demographic	Triglyceride Cut Points, mg/dL ≥150	≥200	≥500
Overall (age ≥20 y)	31.0	16.2	1.1
Age, y			
20–29	20.7	9.5	0.8
30–39	25.8	14.1	0.7
40–49	32.8	16.7	1.6
50–59	36.7	20.1	1.8
60–69	41.6	22.6	1.0
≥70	34.5	17.2	0.5
Sex			
Men	35.4	19.8	1.8
Women*	26.8	12.7	0.5
Ethnicity			
Mexican American	34.9	19.5	1.4
Non-Hispanic, black	15.6	7.6	0.4
Non-Hispanic, white	33.0	17.6	1.1

%HTG ↑ w/ ↑ Age

Miller M, et al. *Circulation*. 2011;123:2292-333.

Table 1 Classification of fasting triglyceride concentration (mg/dL) by guideline[2,5–7]

NCEP ATP III	Normal <150	Borderline 150–199	High 200–499	Very high ≥500	
AHA 2011	Normal <150	Borderline 150–199	High 200–499	Very high ≥500	
Endocrine Society 2012	Normal <150	Mild HTG 150–199	Moderate HTG 200–999	Severe HTG 1000–1999	Very severe HTG ≥2000
NLA 2014	Normal <150	Borderline 150–199	High 200–499	Very high ≥500	

AHA, American Heart Association; HTG, hypertriglyceridemia; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; NLA, National Lipid Association.

NATIONAL LIPID ASSOCIATION

TABLE 1. Criteria proposed for clinical diagnosis of elevated triglyceride levels under fasting conditions

	NCEP ATP III (3)		The Endocrine Society 2010[a]		
Normal	<150 mg/dl	<1.7 mmol/liter	Normal	<150 mg/dl	<1.7 mmol/liter
Borderline-high triglycerides	150–199 mg/dl	1.7–2.3 mmol/liter	Mild hypertriglyceridemia	150–199 mg/dl	1.7–2.3 mmol/liter
High triglycerides	200–499 mg/dl	2.3–5.6 mmol/liter	Moderate hypertriglyceridemia	200–999 mg/dl	2.3–11.2 mmol/liter
Very high triglycerides	≥500 mg/dl	≥5.6 mmol/liter	Severe hypertriglyceridemia	1000–1999 mg/dl	11.2–22.4 mmol/liter
			Very severe hypertriglyceridemia	≥2000 mg/dl	≥22.4 mmol/liter

[a] The criteria developed for the present guidelines focus on the ability to assess risk for premature CVD *vs.* risk for pancreatitis. The designations of *mild* and *moderate* hypertriglyceridemia correspond to the range of levels predominant in risk assessment for premature CVD, and this range includes the vast majority of subjects with hypertriglyceridemia. Severe hypertriglyceridemia carries a susceptibility for intermittent increases in levels above 2000 mg/dl and subsequent risk of pancreatitis; very severe hypertriglyceridemia is indicative of risk for pancreatitis. In addition, these levels suggest different etiologies. Presence of mild or moderate hypertriglyceridemia is commonly due to a dominant underlying cause in each patient, whereas severe or very severe hypertriglyceridemia is more likely due to several contributing factors.

American Heart Association®

ENDOCRINE SOCIETY

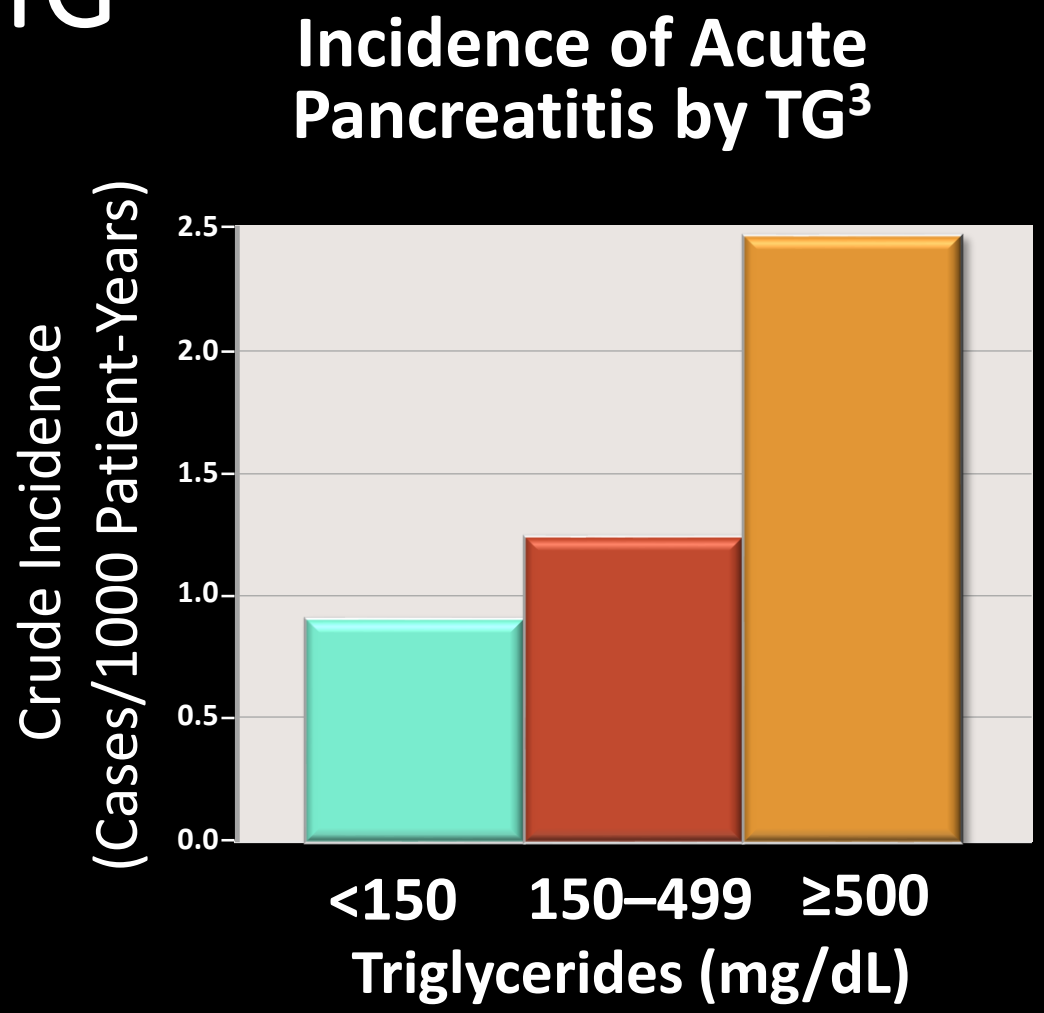
Journal of Clinical Lipidology (2015) 1933-2874

EUROPEAN ATHEROSCLEROSIS SOCIETY

J Clin Endocrinol Metab, September 2012, 97(9):2969–2989

Pancreatitis vs HTG

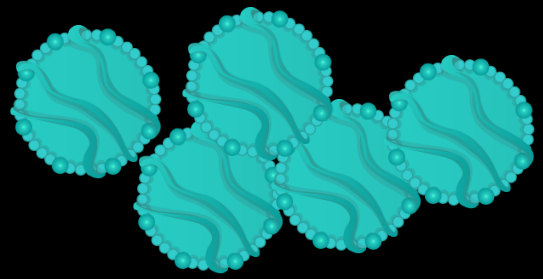
- HTG is the 3rd biggest cause of acute pancreatitis (~10%) after alcohol & gallstones[1,2]
- Acute pancreatitis risk ↑4%/100 mg/dL ↑ TG* (HR, 1.04)[3]



*After adjustment for covariates and removal of patients hospitalized for gallstones, chronic pancreatitis, alcohol-related morbidities, renal failure, and other biliary disease.

1. Cybulska B, Klosiewicz-Latoszek L. *Kardiol Pol.* 2013;71(10):1007-1012; 2. Miller M et al. *Circulation*. 2011;123(20):2292-2333; 3. Murphy M et al. *JAMA Intern Med*. 2013;173(2):162-164. N=n=31,740, 31,887 and 3,642 for 3 TG strata w/ cutpoints 150 and 500 mg/dL

Mechanisms of Chylomicron-Induced Acute Pancreatitis*



Excess Large, TG-Rich Chylomicrons

Genetic predisposition

Impaired pancreatic capillary blood flow

Leak of pancreatic lipase causes ↑ production of FFA

Ischemia

Inflammation

Pancreatic acinar cell injury

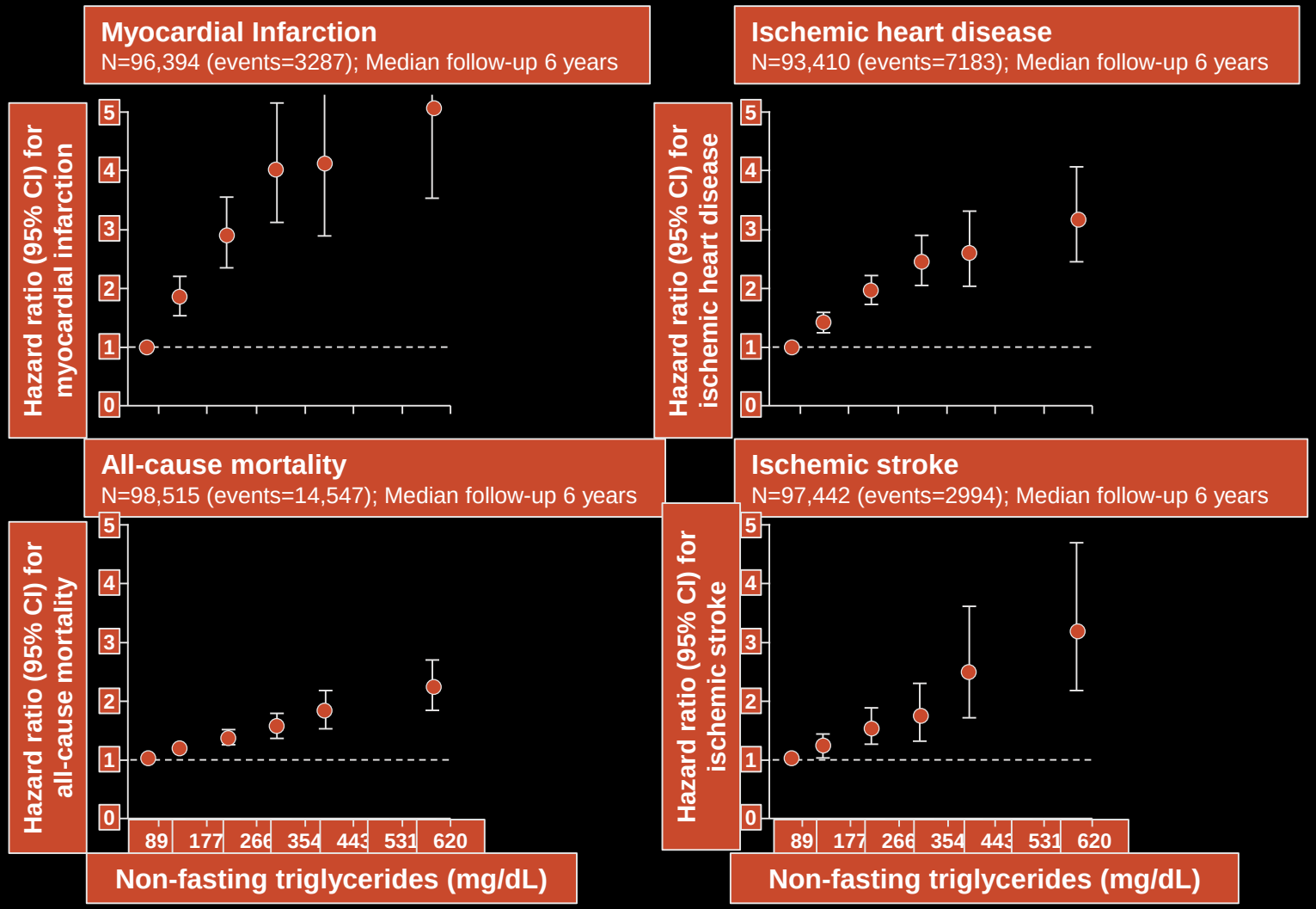
Acute Pancreatitis

* Proposed mechanisms. LPL, lipoprotein lipase; FFA = free fatty acids.

After Gan SI, et al. *World J Gastroenterol.* 2006;12:7197-7202.

Increasing TG Levels Increases CVD and All-cause Mortality

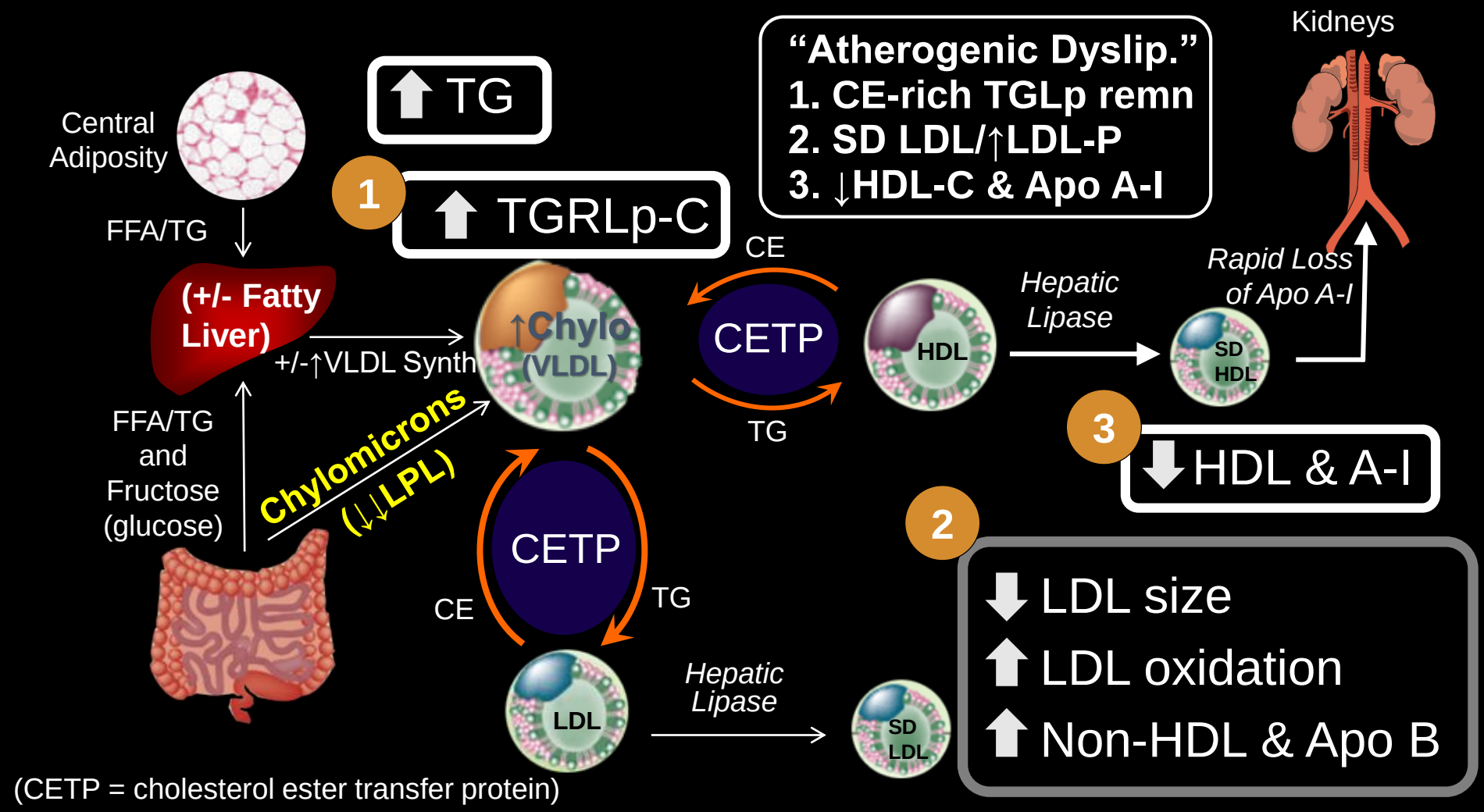
Copenhagen City Heart Study and Copenhagen General Population Study



Hazard ratios were estimated by Cox proportional hazard regression models, and were adjusted for age, sex, and trial group.

Nordestgaard BG et al. *Lancet.* 2014;384:626-35.

Causes and Atherogenic Consequences of Severe HTG/Chylomicronemia

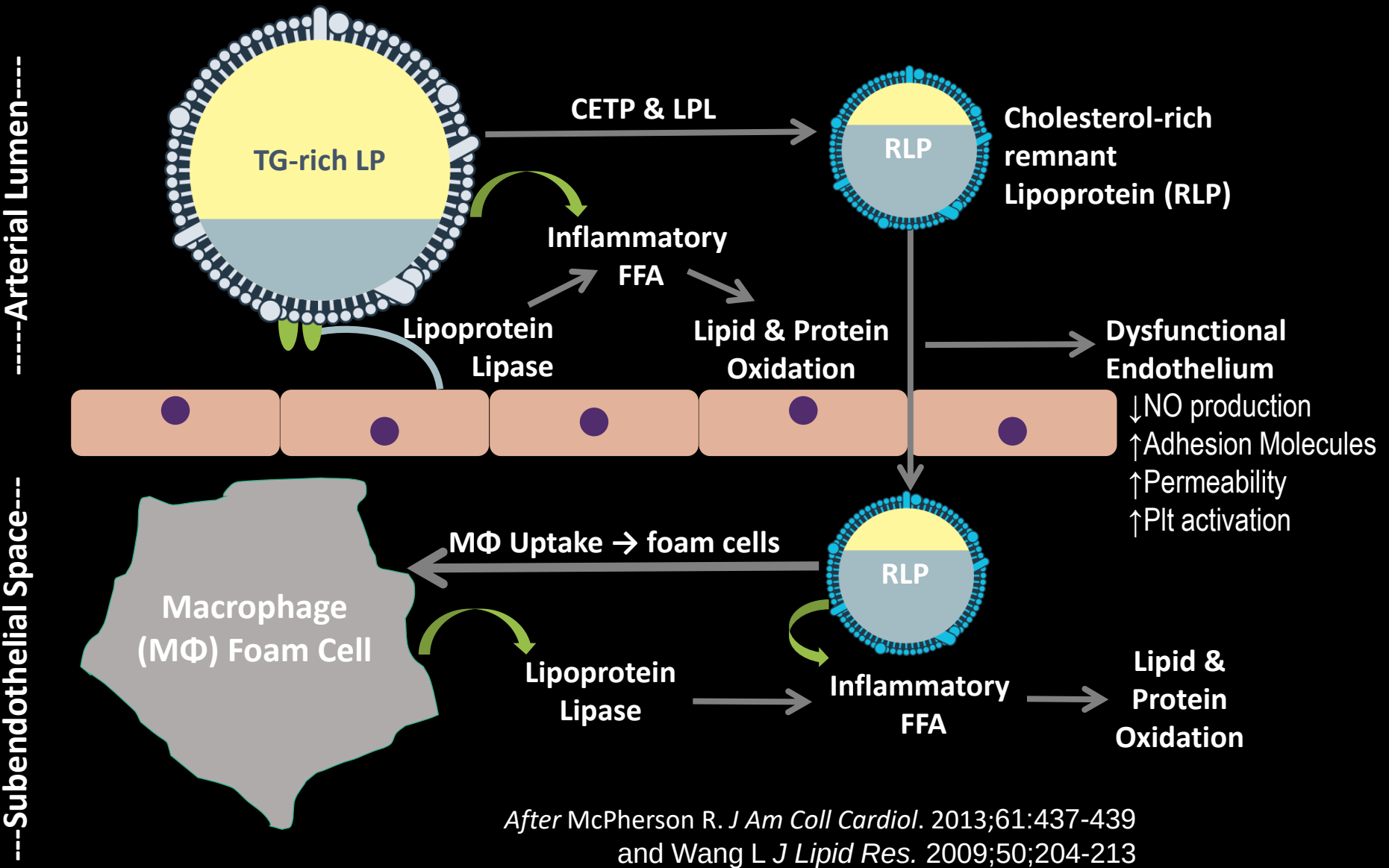


(CETP = cholesterol ester transfer protein)

Moderate LPL deficiency causes ↑↑ chylo (& VLDL) remnant cholesterol leading to ↑↑atherogenicity (even w/ normal VLDL synth & normal fat intake)

Retrieved from: Brinton Eliot, Cream of Tomato Soup" Blood: What's the Skinny on FCS and Other Chylomicronemic States, NLA;Feb/25/2017

Mechanisms of Remnant Lipoprotein Atherogenicity



After McPherson R. *J Am Coll Cardiol*. 2013;61:437-439 and Wang L *J Lipid Res.* 2009;50;204-213

Retrieved from: Brinton Eliot, Cream of Tomato Soup" Blood: What's the Skinny on FCS and Other Chylomicronemic States, NLA;Feb/25/2017

MANAGEMENT

PATIENT # 1

[redacted]

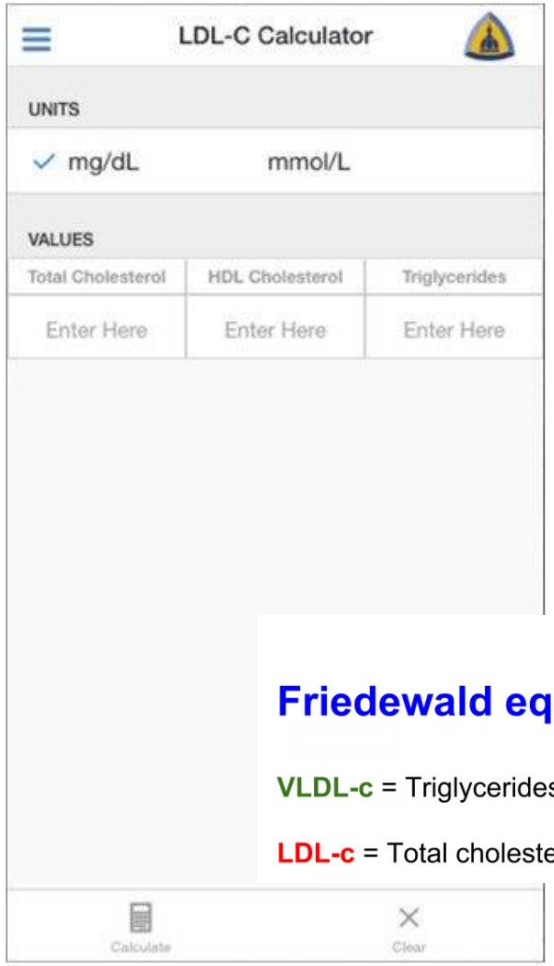
San Juan, PR

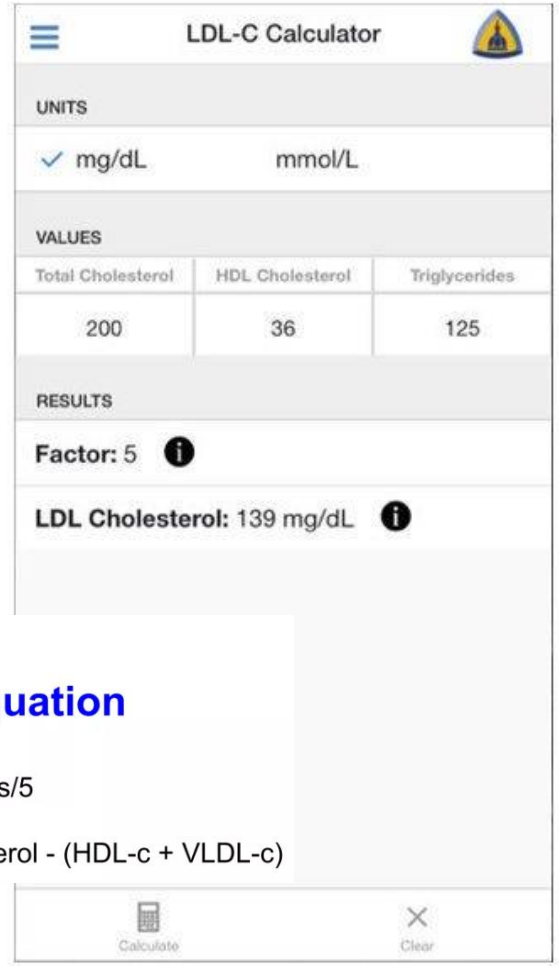
Lipid Profile flowshee[redacted]
Lipid Profile
Cholesterol (Total)
Triglycerides
HDL Cholesterol
LDL Cholesterol (Calculated)
LDL Cholesterol (Direct)
VLDL (Calculated)
Cholesterol non HDL

LDL Cholesterol Calculator

Johns Hopkins Digital

OPEN





Friedewald equation

VLDL-c = Triglycerides/5

LDL-c = Total cholesterol - (HDL-c + VLDL-c)

practicefusion

[redacted]

[redacted]n, PR 00909

AGE AT DOS 37 yrs

Electronically signed by Alex Gonzalez Bossolo MD at 12/21/2018 10:43 am

[redacted]	12/21/18 8:07 AM
	140 mg/dL
	564 mg/dL
	20.0 mg/dL
	64 mg/dL
	56 mg/dL
	140 mg/dL

practicefusion

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Recommendations for Measurements of LDL-C and Non–HDL-C

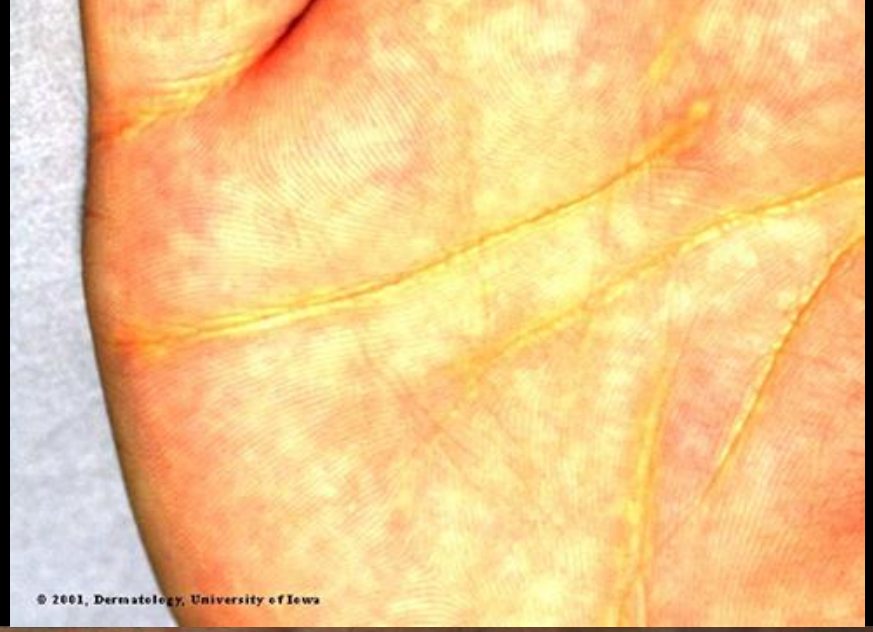
Referenced studies that support recommendations are summarized in Online Data Supplement 1.

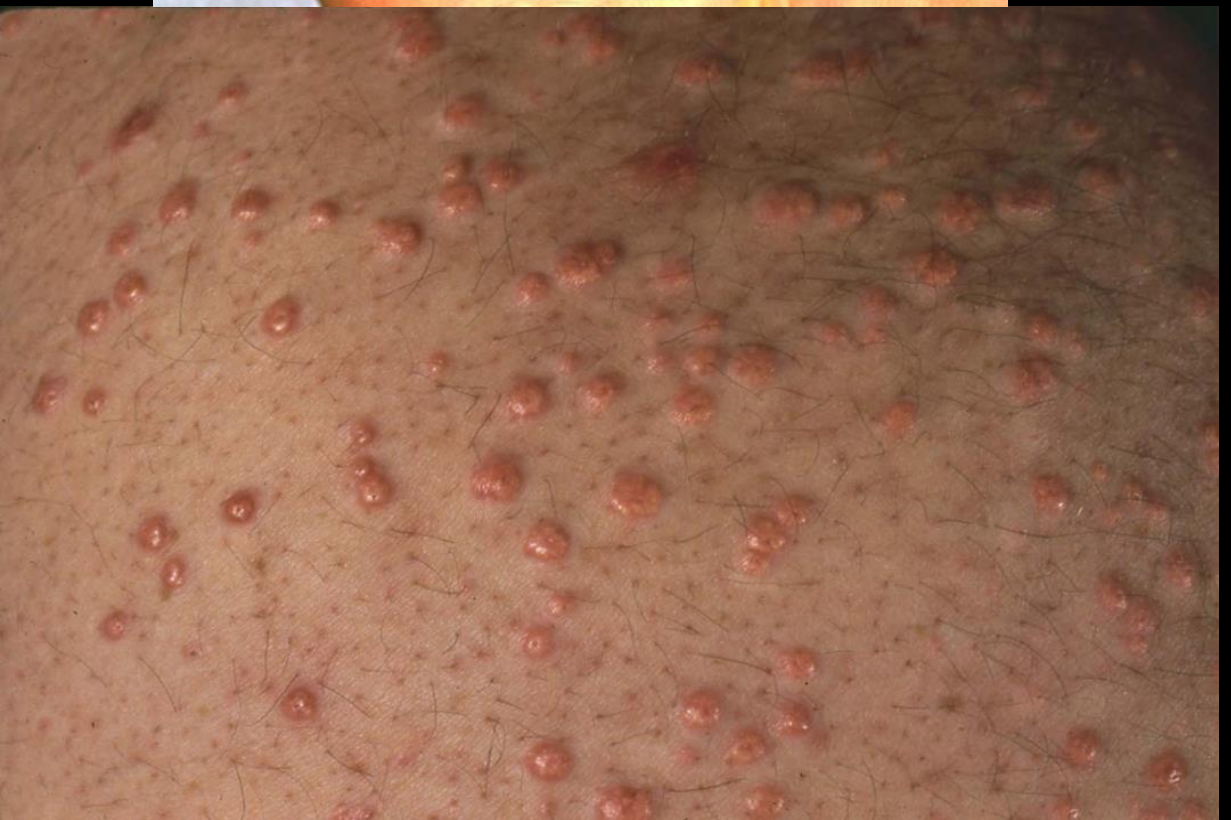
COR	LOE	Recommendations
I	B-NR	1. In adults who are 20 years of age or older and not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL-C (S2.2-1–S2.2-6).
I	B-NR	2. In adults who are 20 years of age or older and in whom an initial nonfasting lipid profile reveals a triglycerides level of 400 mg/dL (≥4.5 mmol/L) or higher, a repeat lipid profile in the fasting state should be performed for assessment of fasting triglyceride levels and baseline LDL-C (S2.2-1–S2.2-4).

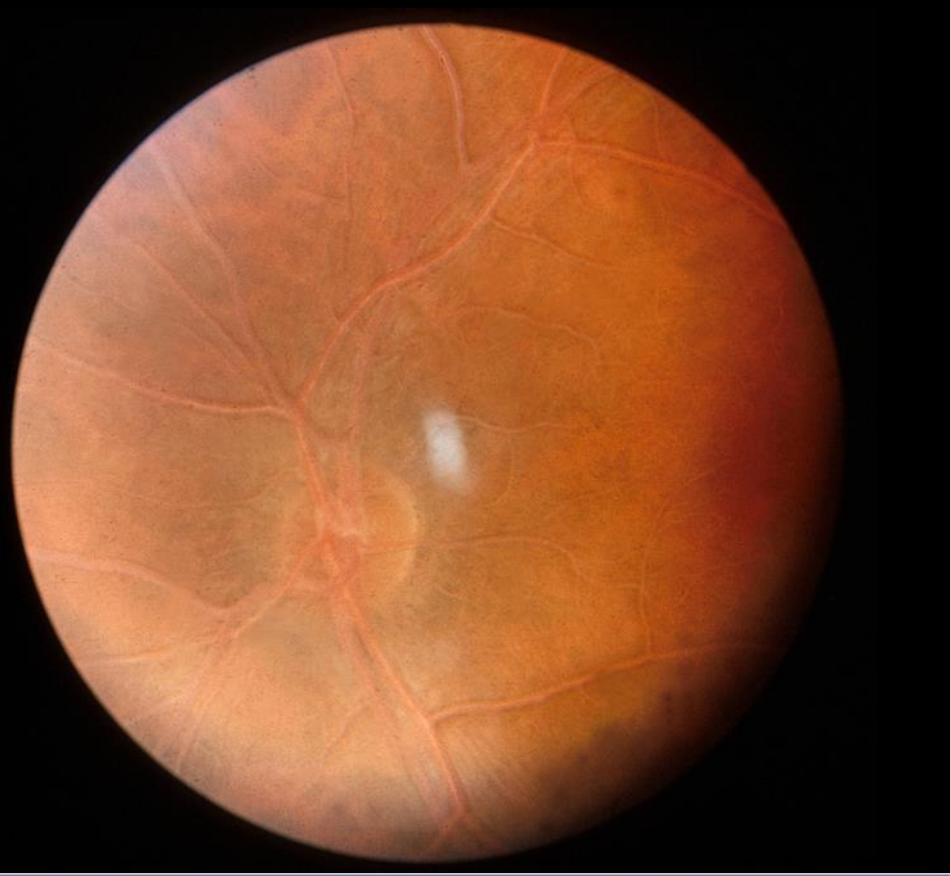
Cause	Clinically useful details
Diet	↑**Fat**, ↓dietary fiber, ↑glycem index?, **ethanol***
	↑Simple sugars, esp. **fructose** (sucrose, etc.)
Adiposopathy	Especially if with ↑**visceral adiposity**
Diabetes mellitus	Especially if **insulin resistant** and/or **hyperglycemic**
Hypothyroidism	Only if inadequately controlled
Renal disease	**Nephrotic syndrome, ESRD**, glomerulonephritis
Systemic Inflammation	Lupus, rheumatoid arthritis, paraproteinemias, etc.
Other conditions	Pregnancy** (especially 3rd trimester)
Medications	**Antiretroviral agents** (for HIV), asparaginase (for leukemia) **2nd-generation anti-Ψ**, phenothiazines, anti-seizure meds Nonselective beta-blockers & thiazide diuretics Bile-acid sequestrants **Oral contraceptives**, oral hormone replacemt.**, tamoxifen **Glucocorticoids, isotretinoin**
Recreational drugs	**Ethanol***, marijuana (↑ApoC-III)

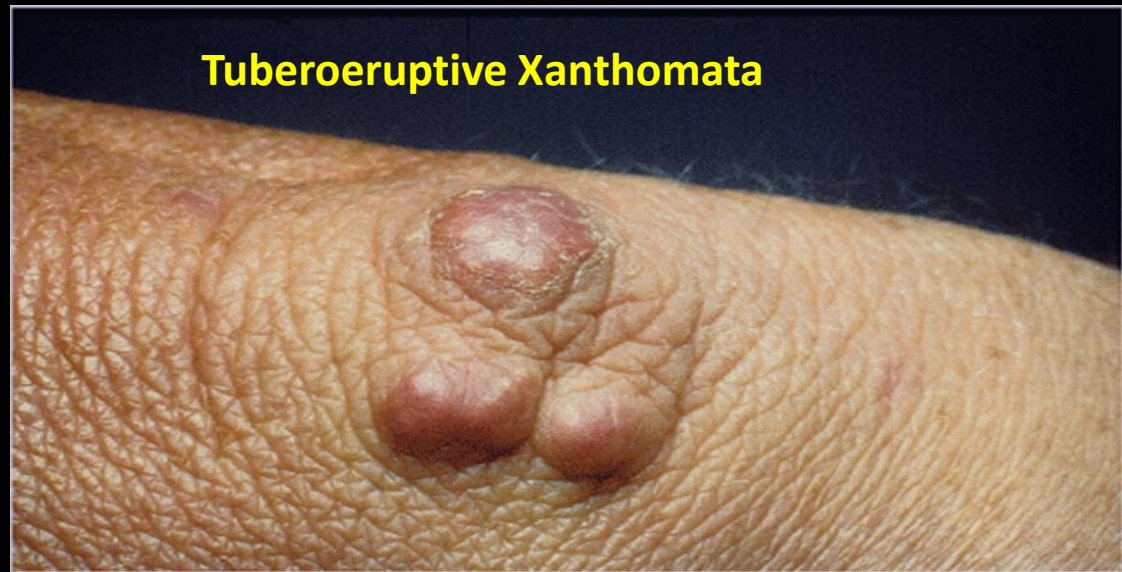
HEREDITARY CAUSES OF HYPERTRIGLYCERIDEMIA

- Primary hypertriglyceridemia
  - Familial Combined Hyperlipidemia (FCHL)
  - Familial Hypertriglyceridemia (FHTG)
  - Familial Dysbetalipoproteinemia (Type III)
  - Familial Chylomicronemia (Type I)
  - Familial Hypoalphalipoproteinemia (FHA)


© 2001, Dermatology, University of Iowa





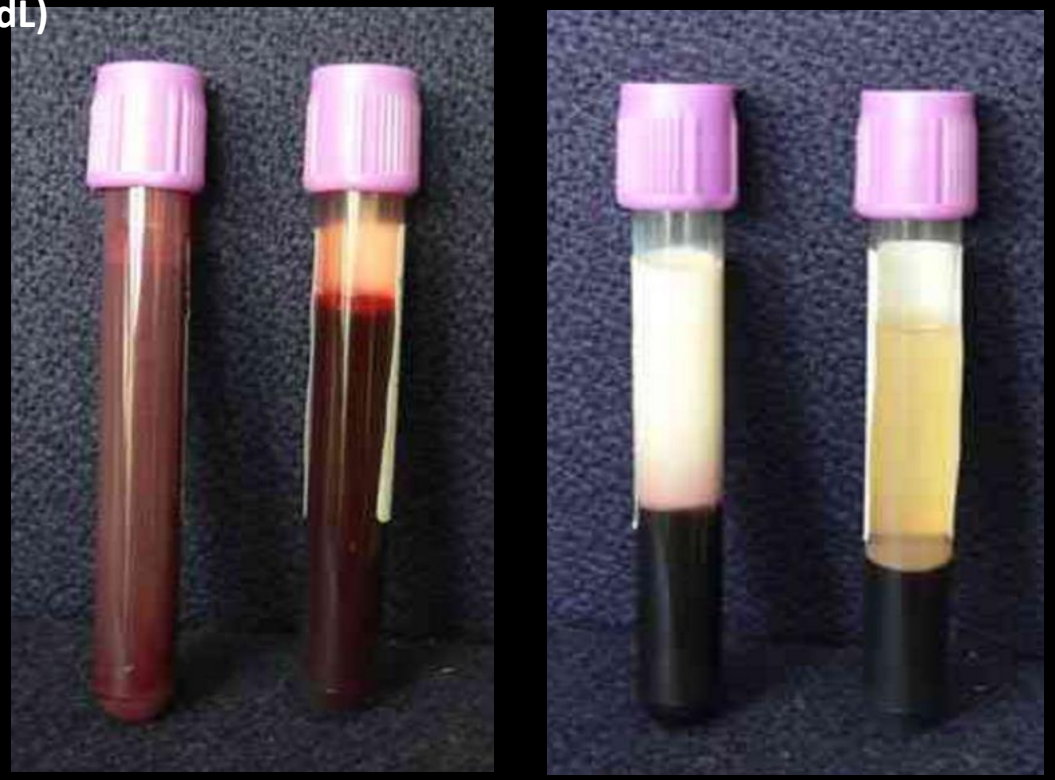

Tuberoeruptive Xanthomata

Lactescent Blood and Plasma in Hyperchylomicronemia

----------Whole blood----------

-----Unspun------ --------Spun-------

TG (mg/dL) 16,713 385 16,713 385



Bastick, AN. Intl J Clinical Med, 2012, 3, 225-228.

MANAGEMENT

- Lifestyle modifications is mandatory!!!
- Diet
  - Reduction of carbohydrates, especially high glycemic and high fructose foods.
  - Hypocaloric diet with a goal of weight loss
  - The diet should restrict consumption of high glycemic index/load foods as well as refined sugars, fruit juices, and high fructose beverages
  - Alcohol
    - No more than 2 drinks per day: men
    - No more than 1 drink per day: women

1) Address non-dietary secondary causes of hypertriglyceridemia including medications and conditions such as uncontrolled diabetes, renal disease and hypothyroidism.
2) Refer to a Registered Dietitian/Nutritionist.

General Dietary Pattern

Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, non-tropical vegetable oils, nuts, seeds; and limits intakes of sweets, sugar–sweetened beverages and high fat meats.

	Borderline 150–199 mg/dL	**High** 200–499 mg/dL	**Very High** 500–999 mg/dL	**Very High** ≥1000 mg/dL with chylomicronemia[a]
Weight Loss	← 5–10% →			
Added Sugars[b]	<10%	<10%	<5%	Near 0%
Total Fat	25–35%	30–35%	20–35%	10–15%
SFA	<7%	<7%	<7%	<3%
EPA+DHA	0.25–2 g/day	1–2 g/day	2-4 g/day	3-4 g/day
Alcohol	Moderate or Less	Moderate or Less	Eliminate	Eliminate
Aerobic Activity	← ≥5x per week →			
		Pharmacologic therapy if needed to attain LDL-C and non-HDL-C goals	*Pharmacologic therapy to lower TG for pancreatitis prevention as the primary objective*	

Monitor to determine response to intervention

Continue intervention or adjust as indicated

Journal of Clinical Lipidology, Vol 9, No 6S, December 2015

Dietary glycemic indices and glycemic load for the top 20 carbohydrate-contributing foods in the Nurses' Health Study in 1984

Foods	Glycemic index*, percent	Carbohydrate per serving, g	Glycemic load per serving
1. Cooked potatoes (mashed or baked)	102	37	38
2. White bread	100	13	13
3. Cold breakfast cereal	Varies by cereal	Varies by cereal	Varies by cereal
4. Dark bread	102	12	12
5. Orange juice	75	20	15
6. Banana	88	27	24
7. White rice	102	45	46
8. Pizza	86	78	68
9. Pasta	71	40	28
10. English muffins	84	26	22
11. Fruit punch	95	44	42
12. Cola	90	39	35
13. Apple	55	21	12
14. Skim milk	46	11	5
15. Pancake	119	56	67
16. Table sugar	84	4	3
17. Jam	91	13	12
18. Cranberry juice	105	19	20
19. French fries	95	35	33
20. Candy	99	28	28

* Standard reference is white bread, which has a glycemic index of 100 percent. All other glycemic index values are relative to white bread.
Adapted from: Liu S, Willett WC. Dietary glycemic load and atherothrombotic risk. Curr Atheroscler Rep 2002; 4:454.

Weekly servings of fish to achieve 250 mg/day of EPA + DHA

Fish name	Number of 3.5 ounce (100 gram) servings*
Oily fish	
Anchovy, canned	1
Herring, Atlantic	1
Salmon, Atlantic	1
Tuna, bluefin	2
Mackerel, Atlantic	2
Bluefish	2
Trout, rainbow	2
Sardines, Atlantic canned	2
Striped bass	2
Tilefish¶	2
Swordfish¶	2
Tuna, albacore canned	3
Salmon, sockeye	3
Carp	4
Salmon, smoked (lox)	4
King mackerel¶	5
White fish	
Sea Bass	3
Pollock, Atlantic	4
Snapper	6
Flounder and sole	6
Tuna, light canned	7
Grouper	8
Catfish, wild	8
Halibut	8
Haddock	12
Cod, Atlantic	12
Shellfish	
Mussels	3
Crab, Alaska king	5
Oysters, eastern raw	6
Clams	7
Shrimp	7
Lobster, northern	10
Scallops	11
Crab, Blue	11

EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid.
* Servings rounded up to a whole number of servings.
¶ High in mercury. Pregnant women should avoid consuming these fish, as well as marlin, orange roughy, shark, and bigeye tuna. See UpToDate topic on fish consumption in pregnancy.
Data from: United States Department of Agriculture (USDA) National Nutrient Database for Standard Reference. USDA website 2012. Available at: http://ndb.nal.usda.gov/. (Accessed June 10, 2013.)

UpToDate®

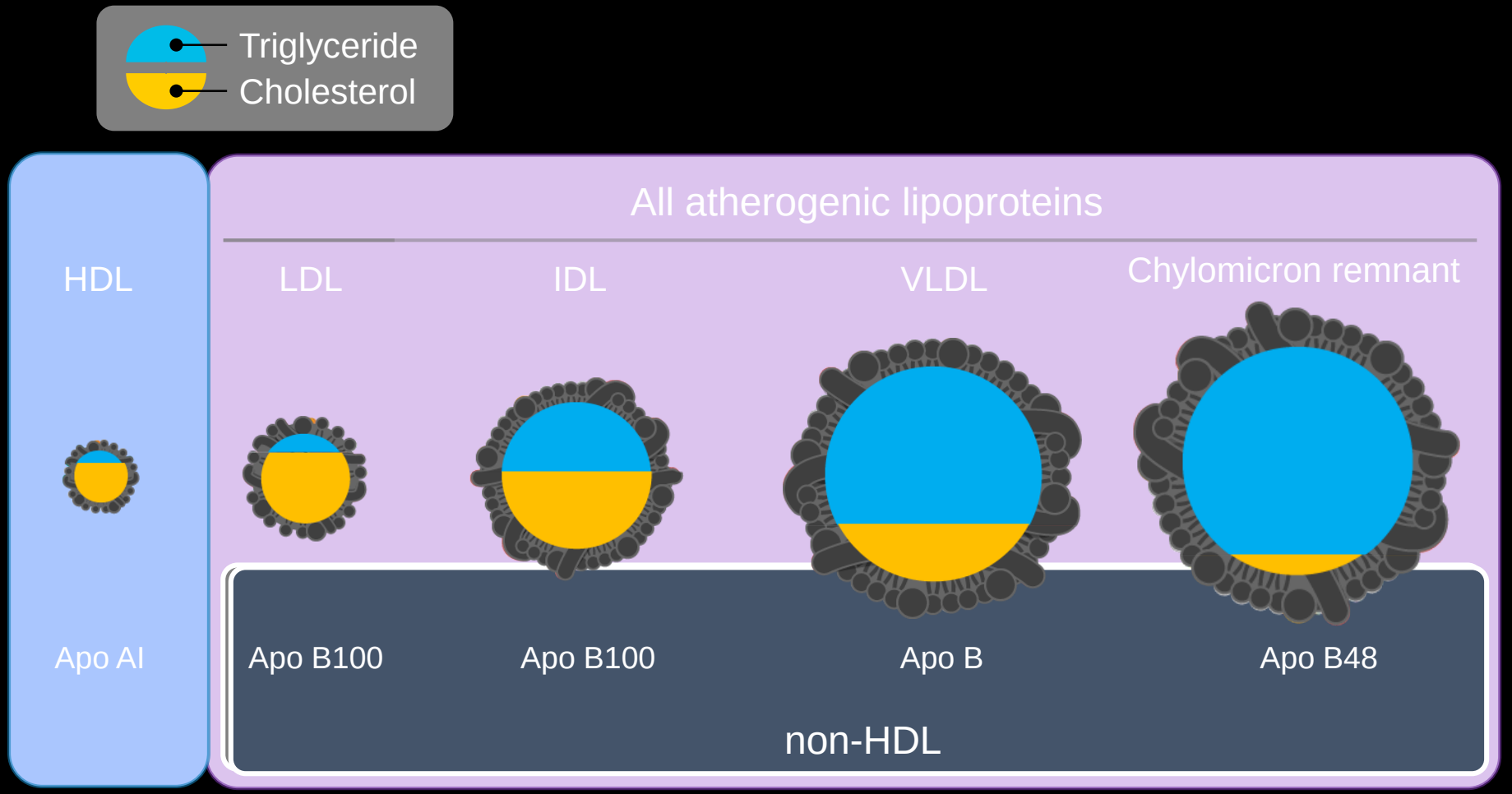
Moderate Hypertriglyceridemia

MODERATE HYPERTRIGLYCERIDEMIA 200-999 ng/dL

- 3.3.”We recommend that the treatment goal for patients with moderate hypertriglyceridemia be a non-HDL cholesterol level in agreement with NCEP ATP guidelines”

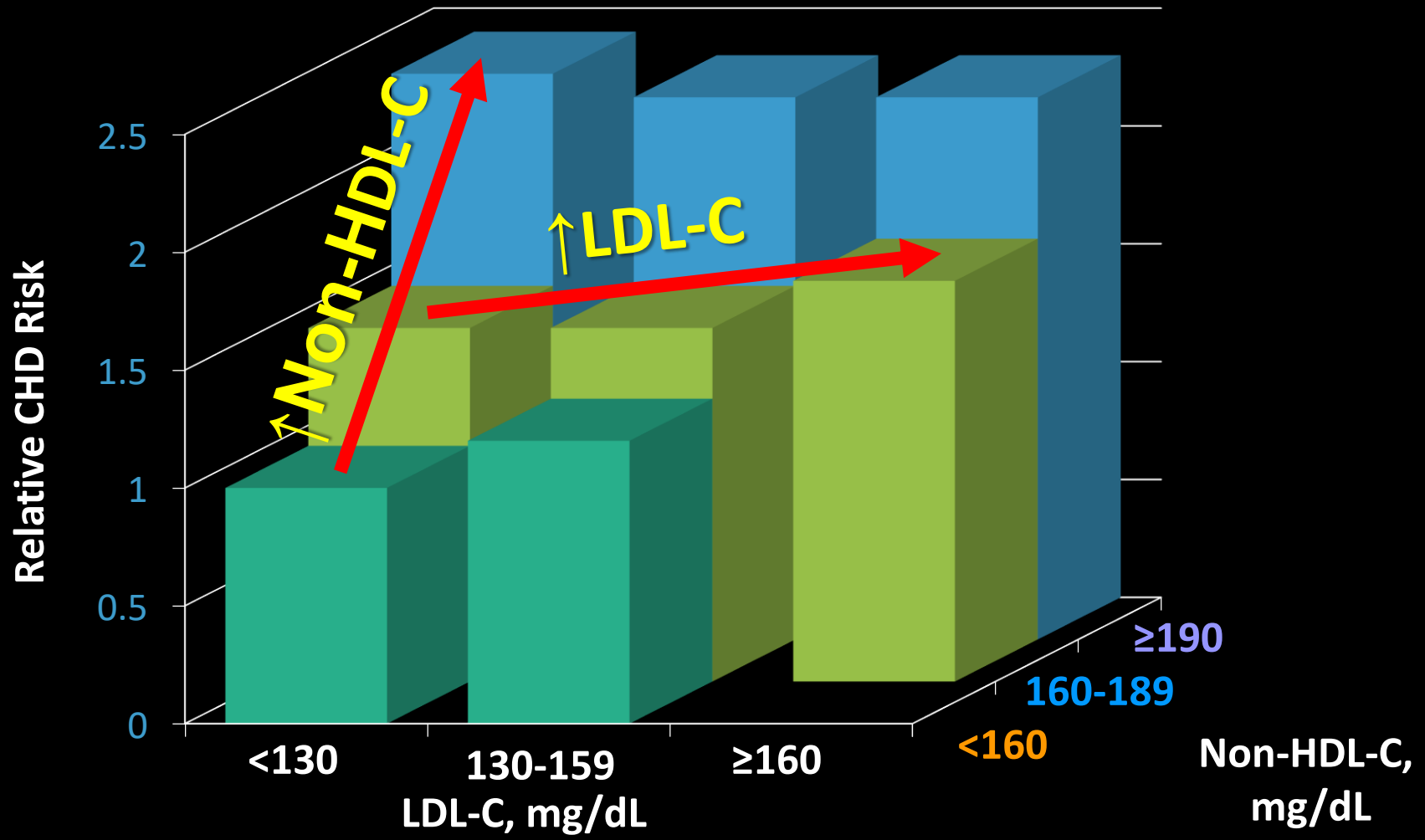
J Clin Endocrinol Metab, September 2012, 97(9):2969–2989

What is Non-HDL-C?



Non-HDL-C = Total cholesterol – HDL-C

Non–HDL-C Is Much Stronger than LDL-C in Predicting CHD Risk



Liu J, et al. *Am J Cardiol.* 2006;98:1363-1368. (Framingham Study)

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
FRS >20%, CHD-RE	<100	<130
FRS 5-20%, 2+ RFs	<130	<160
No CHD, 0-1 RFs	<160	<190

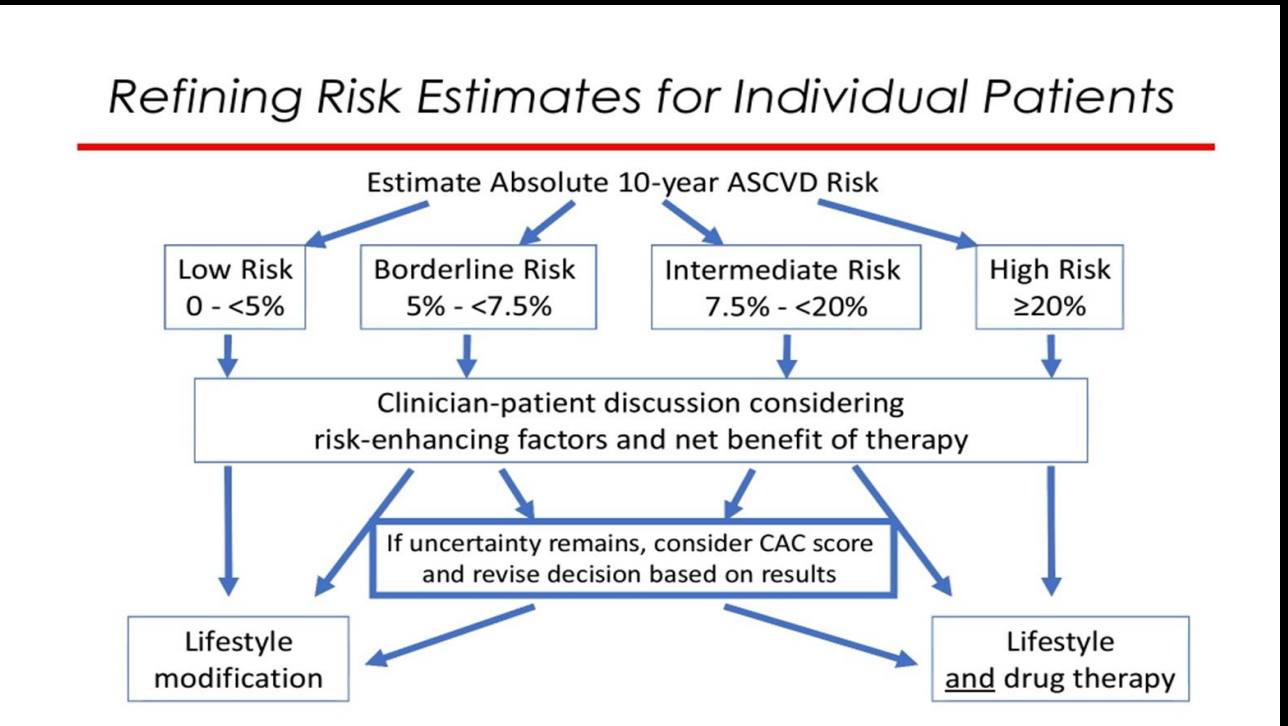
RF= CVD risk factors.

Adapted from ATP-III. *JAMA*. 2001;285:2486-2497; Grundy SM et al. *Circulation*. 2004;110:227-239.

The National Lipid Association reaffirmed similar lipid goals. Jacobson, T. *J Clin Lipid.* 2014;8:473–488.

Moderate Hypertriglyceridemia 200-500 ng/dL

- Therefore, if an adult patient with moderate hypertriglyceridemia has poorly controlled major risk factors for ASCVD and a 10-year risk of ASCVD ≥7.5% by the PCE, it is reasonable to either initiate or intensify statin therapy



Grundy SM, et al.
2018 Cholesterol Clinical Practice Guidelines

Moderate Hypertriglyceridemia 175-499 ng/dL

- 10.27 “ In adults with moderate hypertriglyceridemia (fasting or non-fasting triglycerides 175–499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides”

American Diabetes Association®

Diabetes Care Volume 42, Supplement 1, January 2019

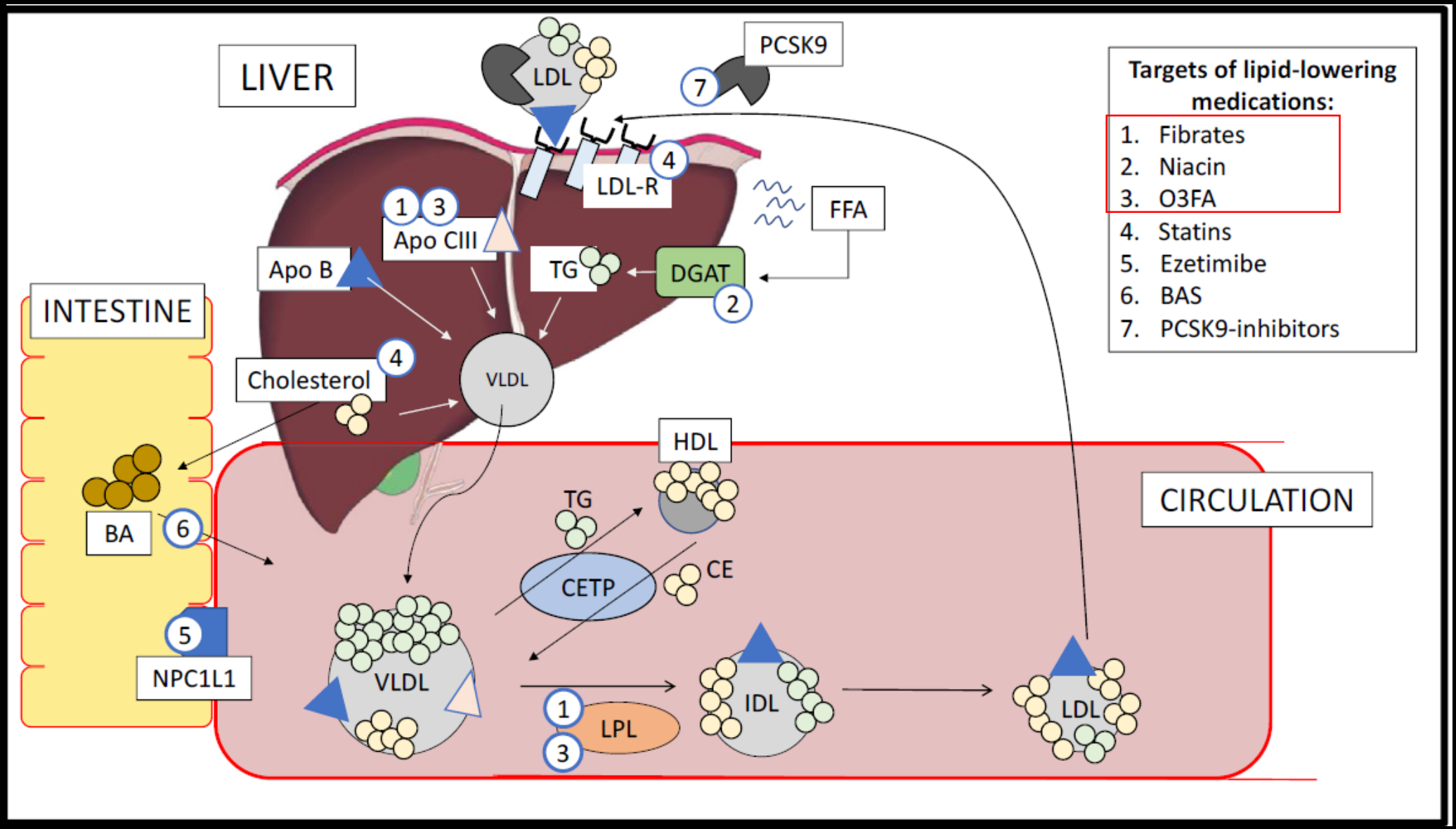
TG Lowering Medications: When? Which?

TG-Lowering Effect by Drug Class

Drug	TG Reduction
Fibrates	30% – 50%
Omega-3	20% – 50%
Immediate-release niacin	20% – 50%
Extended-release niacin	10% – 30%
Statins	10% – 30%
Ezetimibe	5% – 10%

TG reduction values are not always corrected for baseline TG levels. Given that the greatest reduction in TG levels occur in those with the highest TG levels at baseline, this may not be a fair assessment of the TG-lowering effect of lipid-altering drugs in HTG patients.

Miller M et al. *Circulation*. 2011;123:2292-333.



Journal of Clinical Lipidology (2017) 11, 872–879

Fenofibrate Formulations:
Available Fenofibrate Doses (mg/day)

Regular dose	Reduced dose*	Brand Name
200	67**	Lofibra®
160	54/50	Lofibra®/Triglide®
120	40	Fenoglide®
90	30	Antara®

8 Brand Names,
8 Degrees of micronization/bioavailability
16 separate dosages!

Bottom line: pick the one that works best for your patient's payer

*primarily for renal or geriatric patients
** also available at 134 mg
***fenofibric acid
(See FDA-approved prescribing information for further details)

Fibrates Mechanism of Action

Decrease VLDL synthesis

- PPAR alpha activation for stimulation of beta oxidation of fatty acids

Increasing clearance TGs rich lipoproteins

- PPAR alpha activation of the peripheral lipoprotein lipase
- Also PPAR alpha activation promotes apo-CIII inhibition.

Fibrate Trials Summary

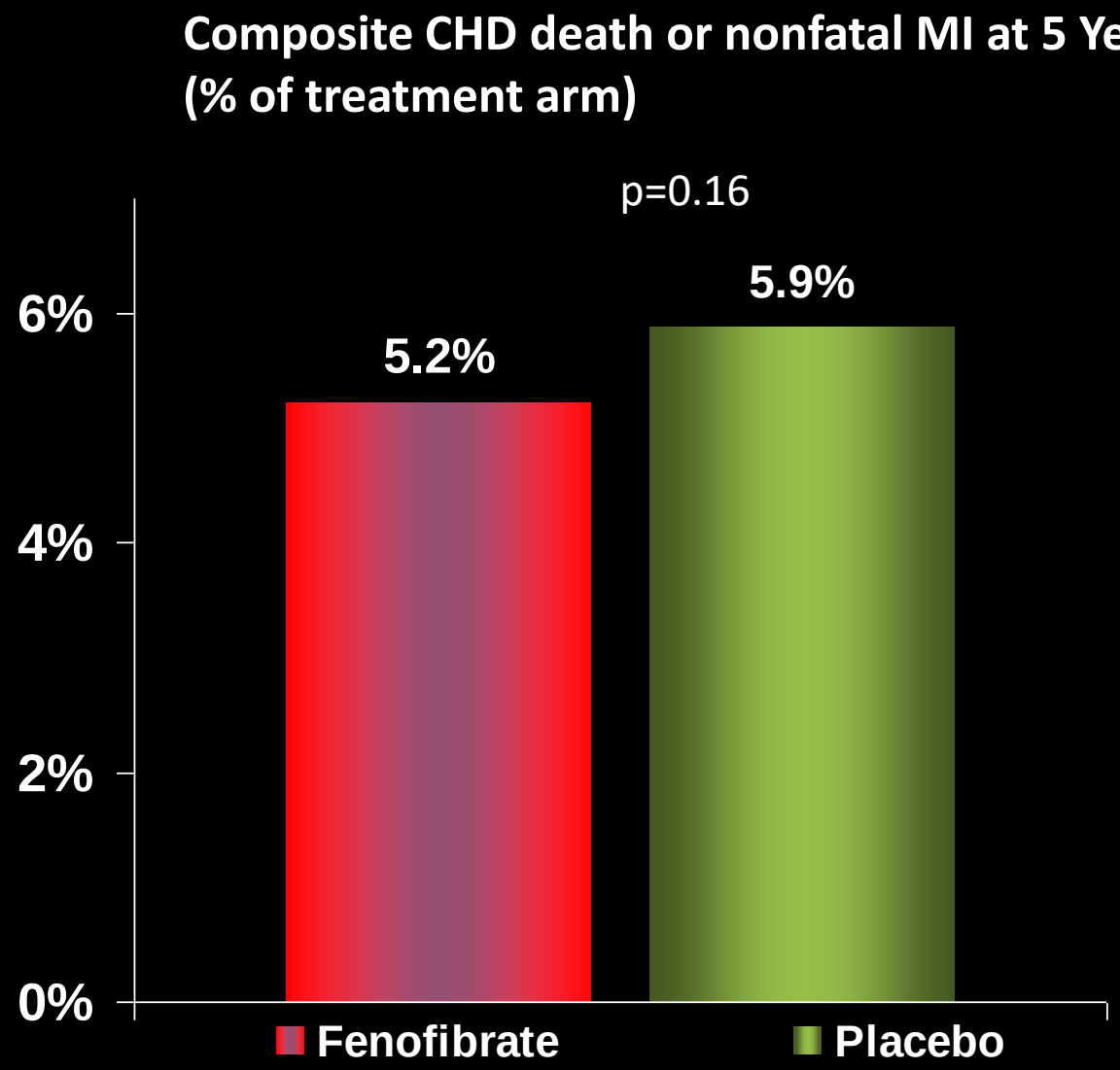
Trial	N	Therapy	Primary Endpoint
ACCORD Lipid[a]	5518	Fenofibrate vs placebo (simvastatin background)	Non-fatal MI or stroke, death from CV cause
FIELD[b]	9795	Fenofibrate vs placebo	CVD event rates
BIP[c]	3090	Bezafibrate vs placebo	Mortality
HHS[d]	6126	Gemfibrozil vs placebo	CHD risk
VA-HIT[e]	2531	Gemfibrozil vs placebo	CHD events

Dyslipidemia: TG ≥ 204mg/dL, HDL-C ≤ 34 mg/dL
Complementary subgroups: TG < 204 mg/dL, HDL-C > 34 mg/dL

Odds ratio ↓ 35% in dyslipidemia[f]

a.ACCORD Study Group, et al. *N Engl J Med*. 2010;362:1563-1574[19]; b. Scott R, et al. *Diabetes Care*. 2010;363:692-694[17]; c. BIP Study Group. *Circulation*. 2000;102:21-27[15]; d. Manninen V, et al. *Circulation*. 1992;85:37-45[14]; e. Robins SJ, et al. *JAMA*. 2001;285:1585-1591[16]; Sacks FM, et al. *N Engl J Med*. 2010;363:692-694.[18]

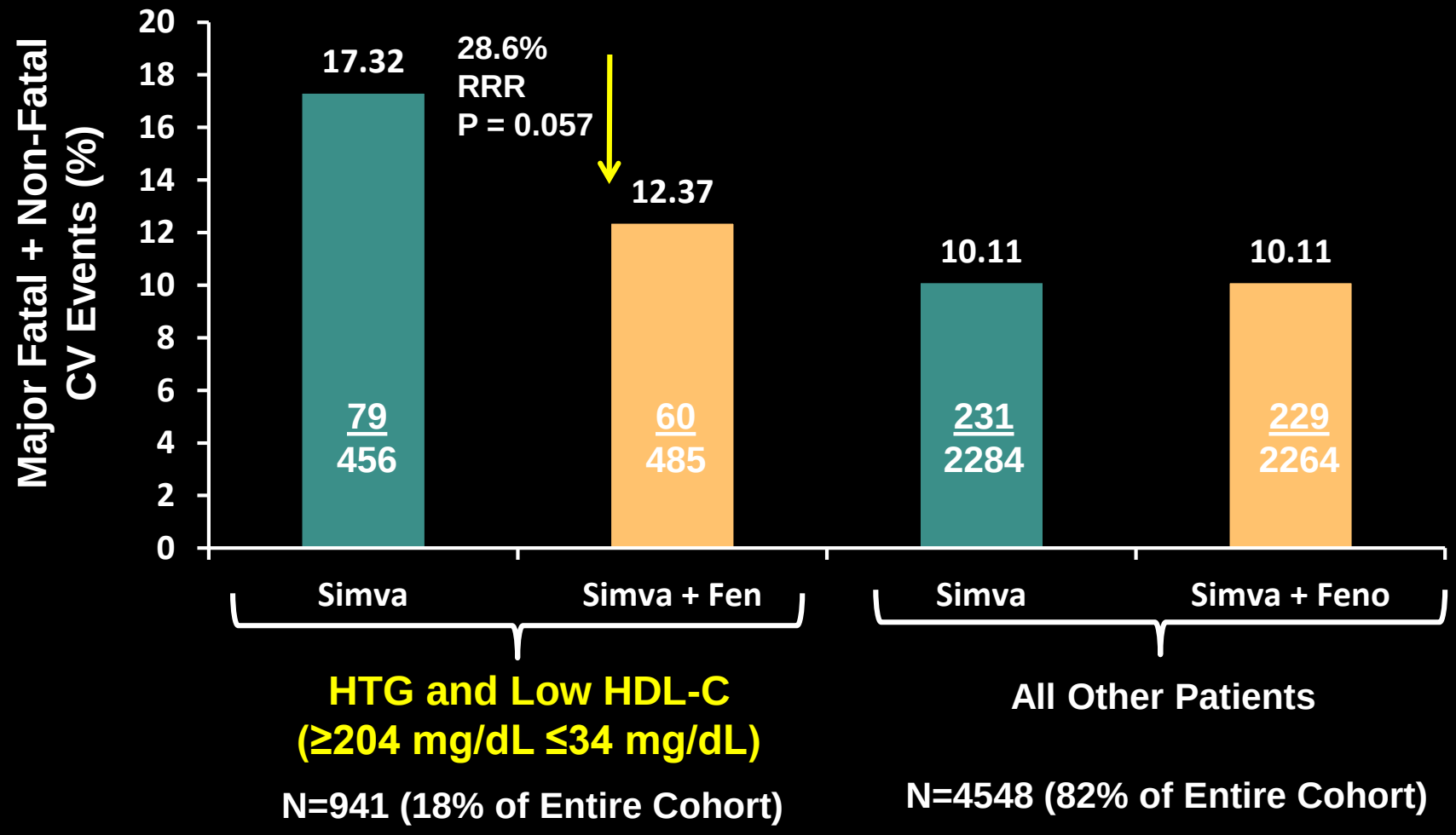
FIELD: Primary Endpoint



- The primary composite endpoint of CHD death or non-fatal MI was not significantly lower in the fenofibrate group compared to the placebo group.

The FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet. 2005.366:1849-1861

ACCORD-Lipid: *Entire* ASCVD Benefit w/ Fenofibrate in HTG/Low HDL-C

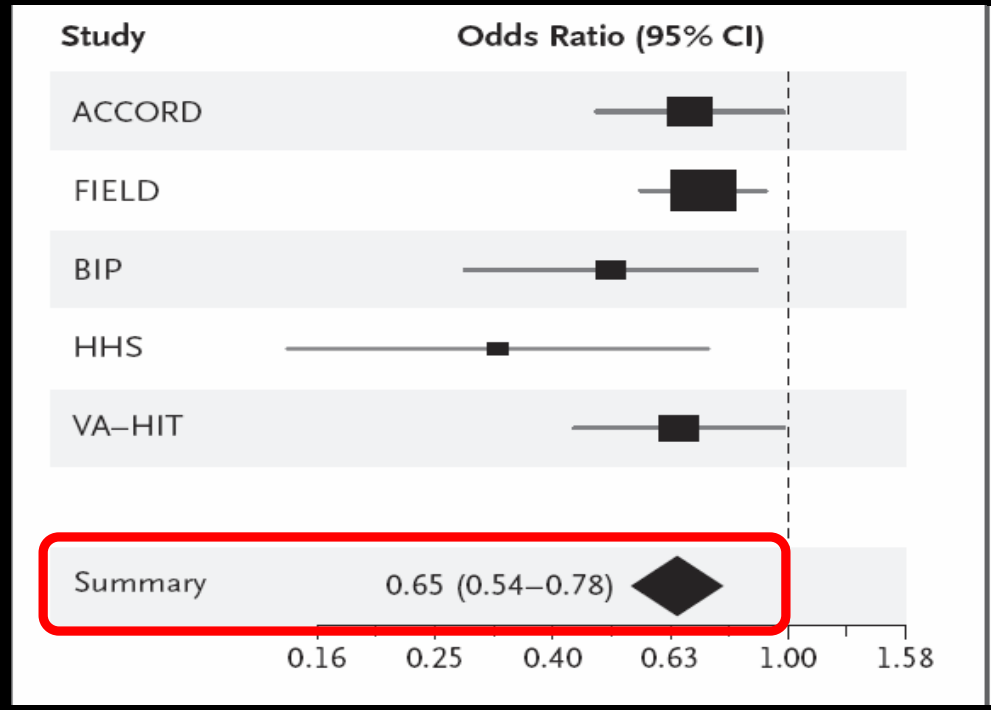


Ginsberg HN for the ACCORD Study Group. *N Engl J Med*. 2010;362:1563-74. Prespecified analysis.

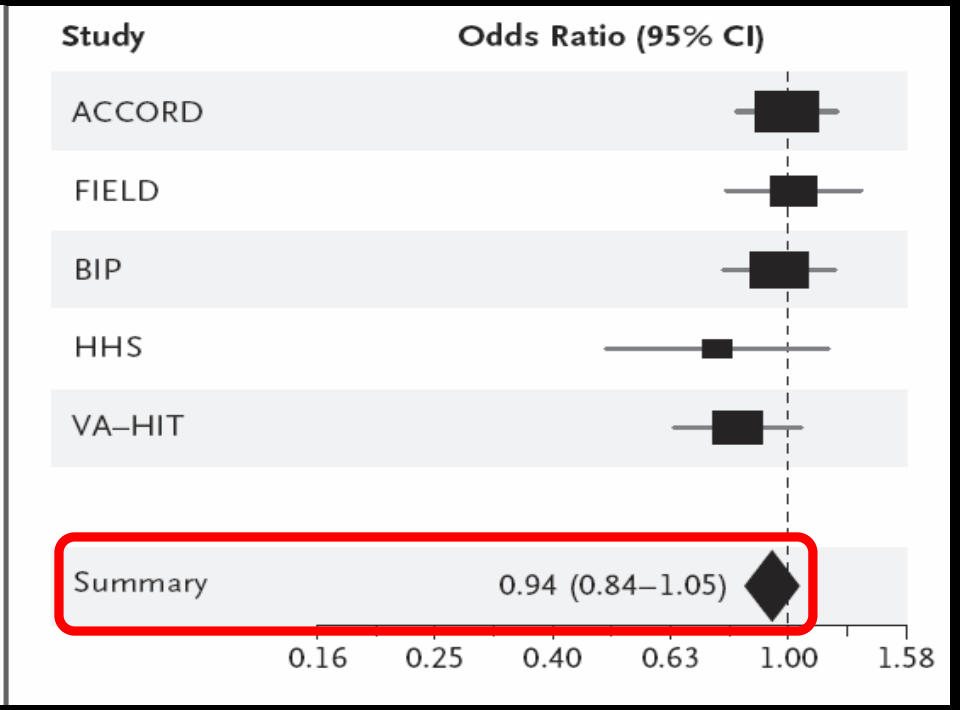
Fibrates Reduce CHD Risk ~35% in Patients with High TG and Low HDL-C

A meta-analysis of randomized fibrate trials

A **Subjects *with* Dyslipidemia**



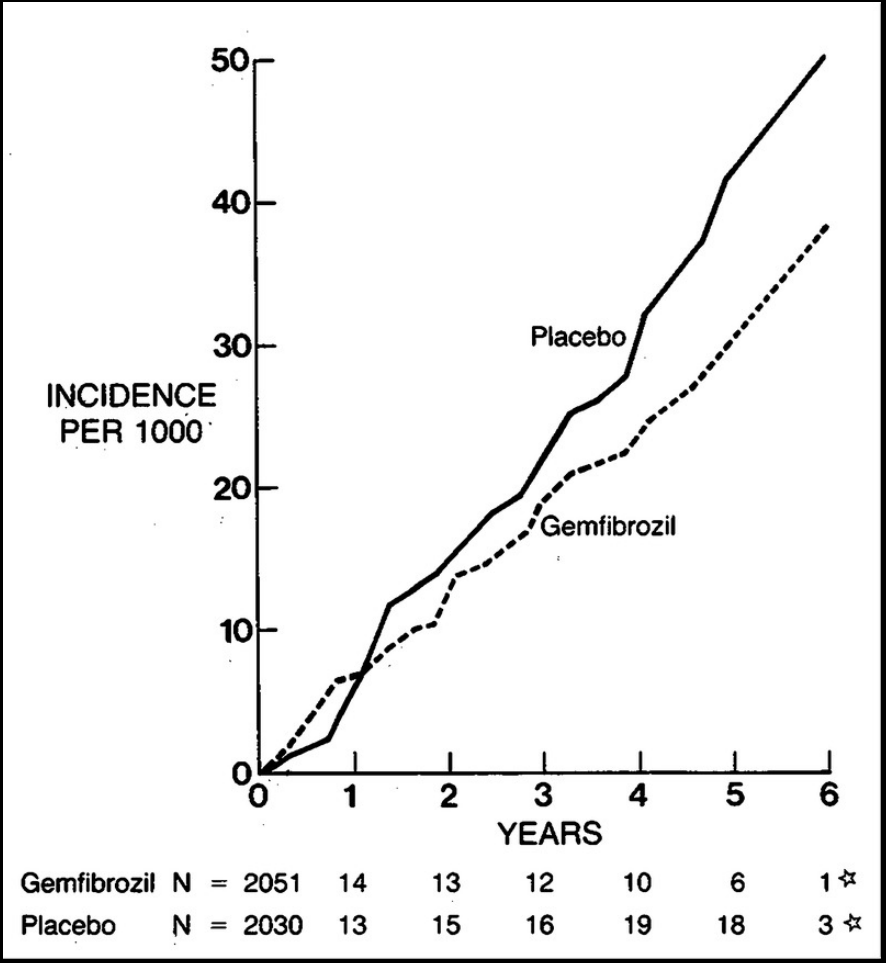
B **Subjects *without* Dyslipidemia**



"With Dyslipidemia"= TG ≥ 204mg/dL and HDL-C ≤ 34mg/dL

After Sacks FM, Carey VJ, Fruchart JC. *N Engl J Med.* 2010;363(7):692-694.

HELSINSKY HEART STUDY

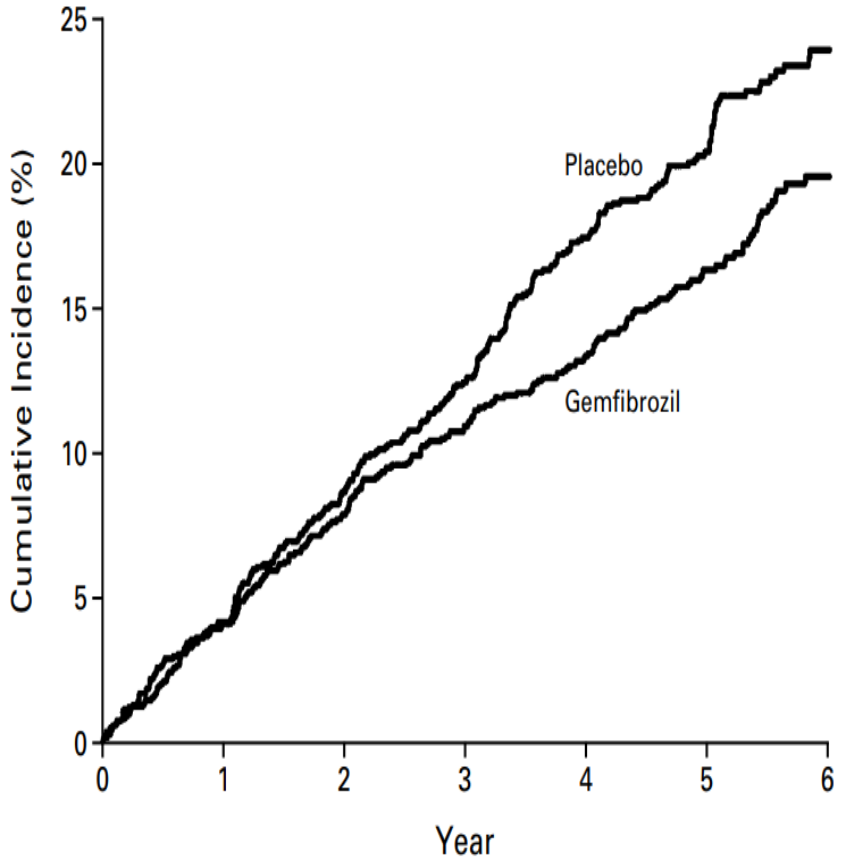


5 year trial that tested efficacy of gemfibrozil for decreasing the risk of coronary artery disease in hypercholesterolemia men without coronary artery disease

The study involved men (40 to 55 years of age) with a non-HDL level > 200 mg/dL (242)

Gemfibrozil was associated with a 34% reduction in coronary artery events

Frick et al. N Engl J Med 1987; 317:1237-1245



No. at Risk

Placebo	1267	1200	1118	1040	962	666	466
Gemfibrozil	1264	1201	1128	1067	1005	706	498

Figure 2. Kaplan–Meier Estimates of the Incidence of Death from Coronary Heart Disease and Nonfatal Myocardial Infarction in the Gemfibrozil and Placebo Groups.

The relative risk reduction was 22 percent (P=0.006), as derived from a Cox model.

Table 2. Major Cardiovascular Events According to Treatment Group.*

Event	Placebo (N=1267)	Gemfibrozil (N=1264)	Risk Reduction (95% CI)	P Value
	no. (%)		%	
Nonfatal myocardial infarction or death due to CHD	275 (21.7)	219 (17.3)	22 (7 to 35)	0.006
Nonfatal myocardial infarction or death due to CHD (excluding silent myocardial infarction)	241 (19)	195 (15.4)	21 (4 to 34)	0.02
Nonfatal myocardial infarction, death due to CHD, or confirmed stroke†	330 (26)	258 (20.4)	24 (11 to 36)	<0.001
Nonfatal myocardial infarction	184 (14.5)	146 (11.6)	23 (4 to 38)	0.02
Death due to CHD	118 (9.3)	93 (7.4)	22 (−2 to 41)	0.07
Death from any cause	220 (17.4)	198 (15.7)	11 (−8 to 27)	0.23
Investigator-designated stroke	88 (6.9)	64 (5.1)	29 (2 to 48)	0.04
Confirmed stroke	76 (6.0)	58 (4.6)	25 (−6 to 47)	0.10
Transient ischemic attack	53 (4.2)	22 (1.7)	59 (33 to 75)	<0.001
CABG	173 (13.7)	164 (13.0)	6 (−17 to 24)	0.60
PTCA	147 (11.6)	120 (9.5)	21 (−1 to 38)	0.06
CABG or PTCA	287 (22.7)	266 (21.0)	9 (−8 to 23)	0.29
Peripheral vascular surgery	28 (2.2)	19 (1.5)	33 (−20 to 63)	0.18
Carotid endarterectomy	44 (3.5)	16 (1.3)	65 (37 to 80)	<0.001
Hospitalization for unstable angina	453 (35.8)	457 (36.2)	−0.4 (−14 to 12)	0.95
Hospitalization for congestive heart failure	168 (13.3)	134 (10.6)	22 (2 to 38)	0.04

*CI denotes confidence interval, CHD coronary heart disease, CABG coronary-artery bypass graft, and PTCA percutaneous transluminal coronary angioplasty. Relative risk reductions, 95 percent confidence intervals, and P values are derived from Cox models. For risk reductions, negative numbers indicate an increase in risk.

†Confirmed stroke was judged by a blinded adjudication panel of three neurologists.

Gemfibrozil Safety

Class III Recommendation: Harm	Level of Evidence
• Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis	B

- Fenofibrate resulted in a 15 times lower rhabdomyolysis rate than did gemfibrozil

Circulation. 2014;129[suppl2]:S1:S45.
J Clin Lipid. 2014;(3 Suppl):S30-46

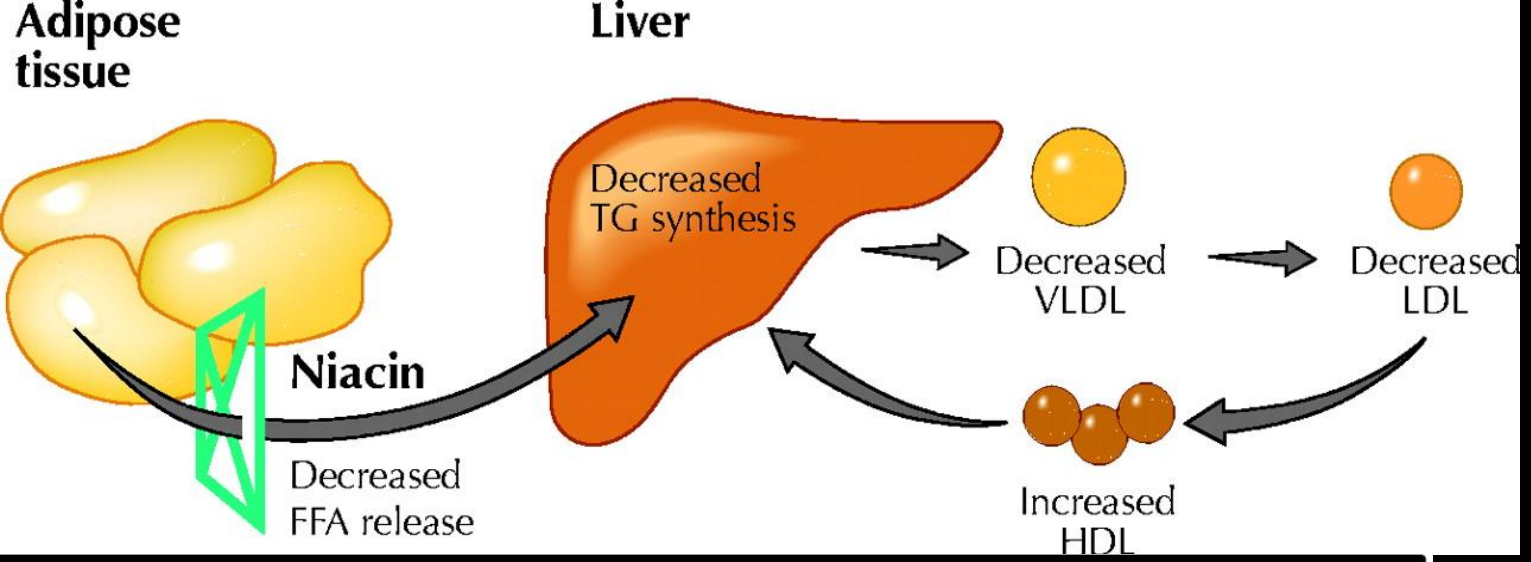
Concomitant medication	Cautions
HMG-CoA Reductase Inhibitors	risk of myopathy and rhabdomyolysis
Anticoagulants	warfarin dosage should be reduced
CYP2C8 Substrates	drugs metabolized CYP2C8 (e.g., dabrafenib, loperamide, montelukast, paclitaxel, pioglitazone, rosiglitazone) may be required to reduce
OATP1B1 substrates	substrates of OATP1B1 (e.g., atrasentan, atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, SN-38 [active metabolite of irinotecan], rosuvastatin, pitavastatin, pravastatin, rifampin, valsartan, olmesartan) may be required to reduce
Bile Acid-Binding Resins	resin-granule drugs such as colestipol (5 g) are recommended at 2 or more hours apart
Colchicine	myopathy, including rhabdomyolysis in chronic administration of colchicine

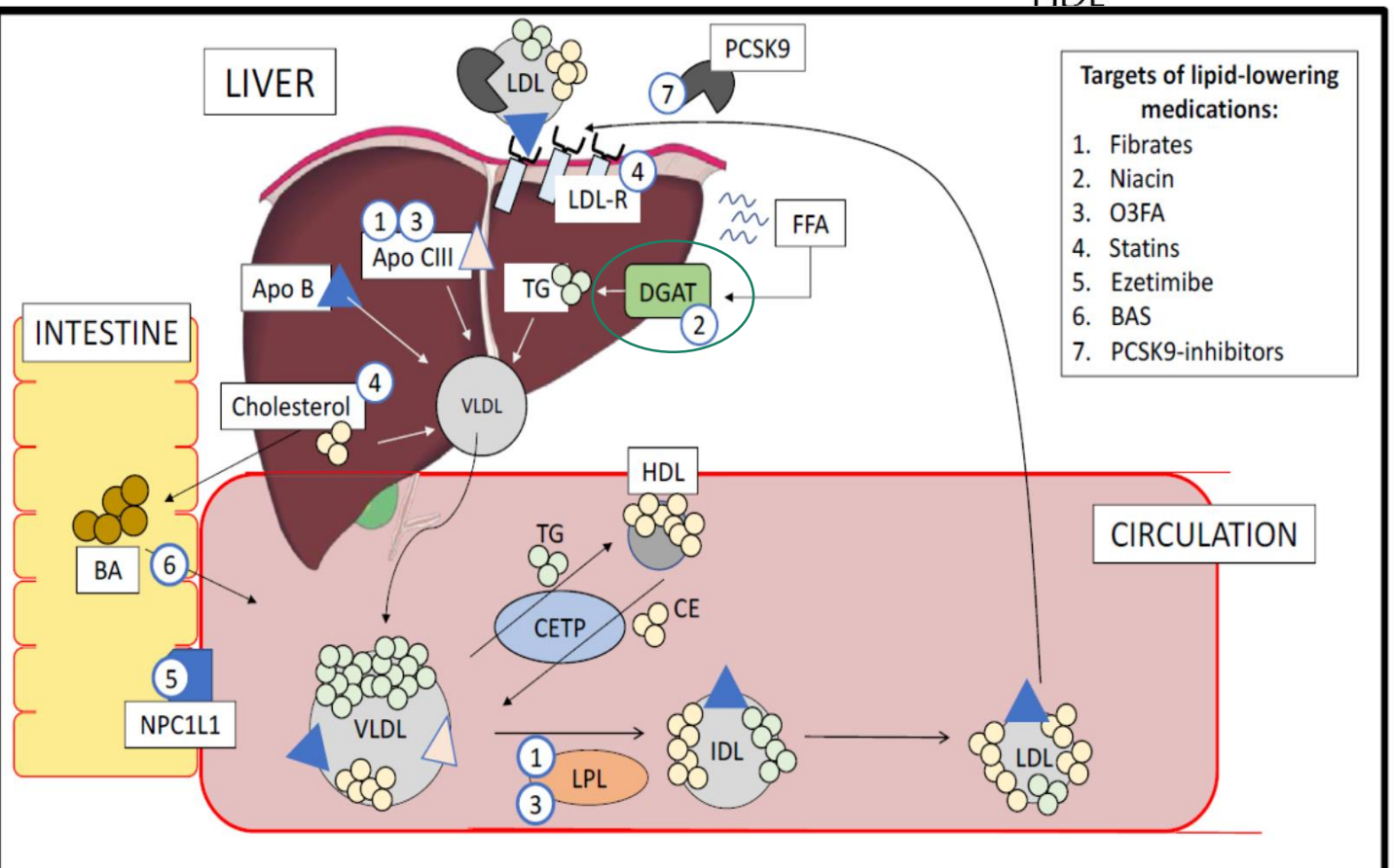
SPC of LOPID issued March.2016

Statin	In combination with gemfibrozil
Atorvastatin	• No dose restriction cited. • Due to increased risk of myopathy/rhabdomyolysis, combination should be avoided.
Fluvastatin	• No dose restriction cited. • Due to increased risk of myopathy/rhabdomyolysis, combination should be avoided.
Lovastatin	• No dose restriction cited. • Due to increased risk of myopathy/rhabdomyolysis, combination should be avoided.
Pitavastatin	• No dose restriction cited. • Due to increased risk of myopathy/rhabdomyolysis, combination should be avoided.
Pravastatin	• No dose restriction cited. • Due to increased risk of myopathy/rhabdomyolysis, combination should be avoided.
Rosuvastatin	• Initiate therapy with 5 mg once daily; the dose should not exceed 10 mg once daily. • Due to increased risk of myopathy/rhabdomyolysis, combination should be avoided.
Simvastatin	• Combination is contraindicated.

Gemfibrozil

Fibrate	Dose based on GFR (mL/min/1.73 m^2)			
	>90	60-90	15-59	<15
Fenofibrate*	High Dose (ex. 200 mg)	Medium Dose (ex. 167 mg)	Low Dose (ex. 67 mg)	AVOID
Gemfibrozil	600 mg Twice daily	600 mg Twice daily	600 mg daily	





NIACIN

- Niacin decreases TG by inhibiting diacylglycerol acyltransferase 2.
- An enzyme that catalyzes the formation of TG from diacylglycerol and acyl-CoA.
- Also inhibits the lipolysis and subsequent release of TG into the circulation.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 15, 2011 VOL. 365 NO. 24

Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy

The AIM-HIGH Investigators*

N Engl J Med 2011;365:2255-67.

Table 4. Primary, Secondary, and Tertiary End Points.

End Point			Hazard Ratio with Niacin (95% CI)	P Value*
Primary end point: deatl myocardial infar for acute corona nary or cerebral			1.02 (0.87–1.21)	0.80
Individual primary-end-				
Death from coronar				
Nonfatal myocardial				
Ischemic stroke				
Hospitalization for a				
Symptom-driven cor				
Secondary end points				
Death from coronar infarction, high- ischemic stroke			1.08 (0.87–1.34)	0.49
Death from coronary heart disease, nonfatal myocardial infarction, or ischemic stroke	138 (8.1)	156 (9.1)	1.13 (0.90–1.42)	0.30
All deaths from cardiovascular causes	38 (2.2)	45 (2.6)	1.17 (0.76–1.80)	0.47

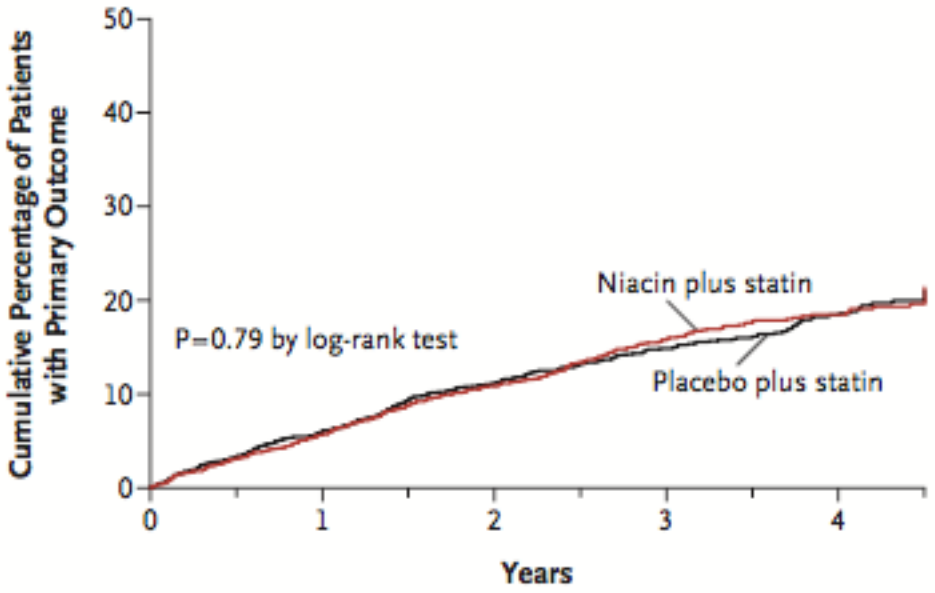
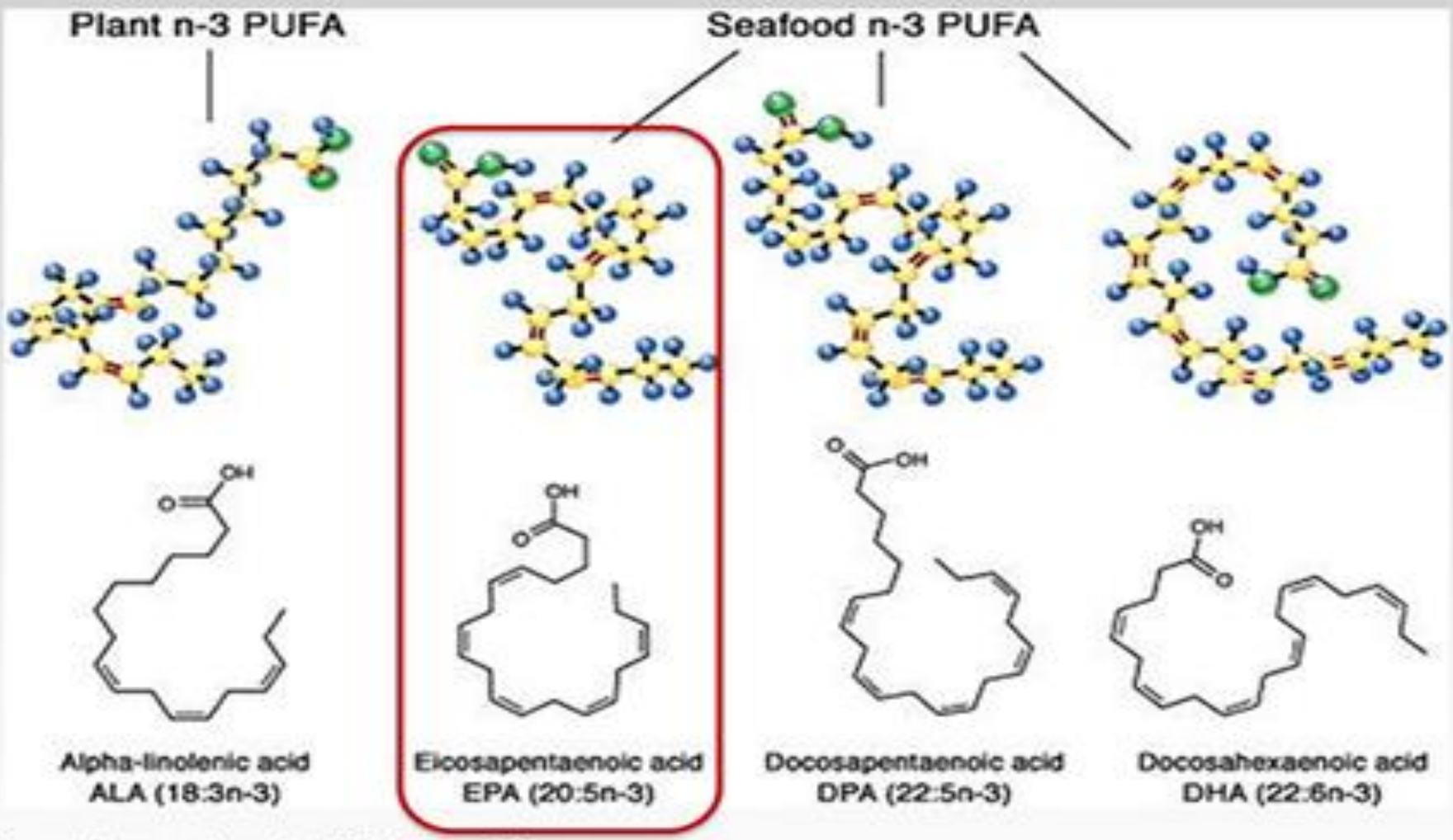


Figure 1. Kaplan–Meier Curve for the Primary End Point.

N Engl J Med 2011;365:2255-67.

OMEGA-3 FATTY ACIDS

ω-3 Fatty Acids

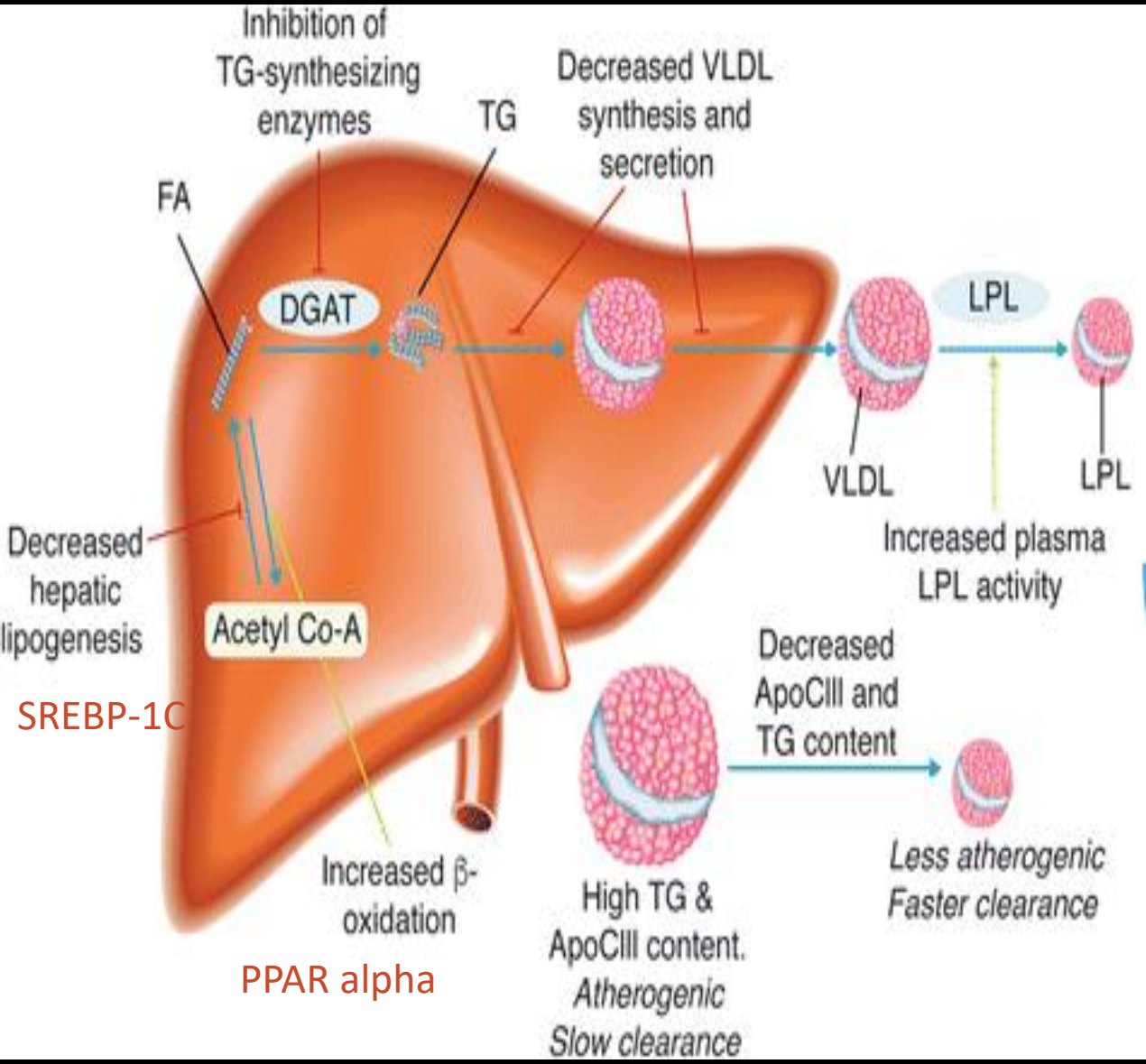


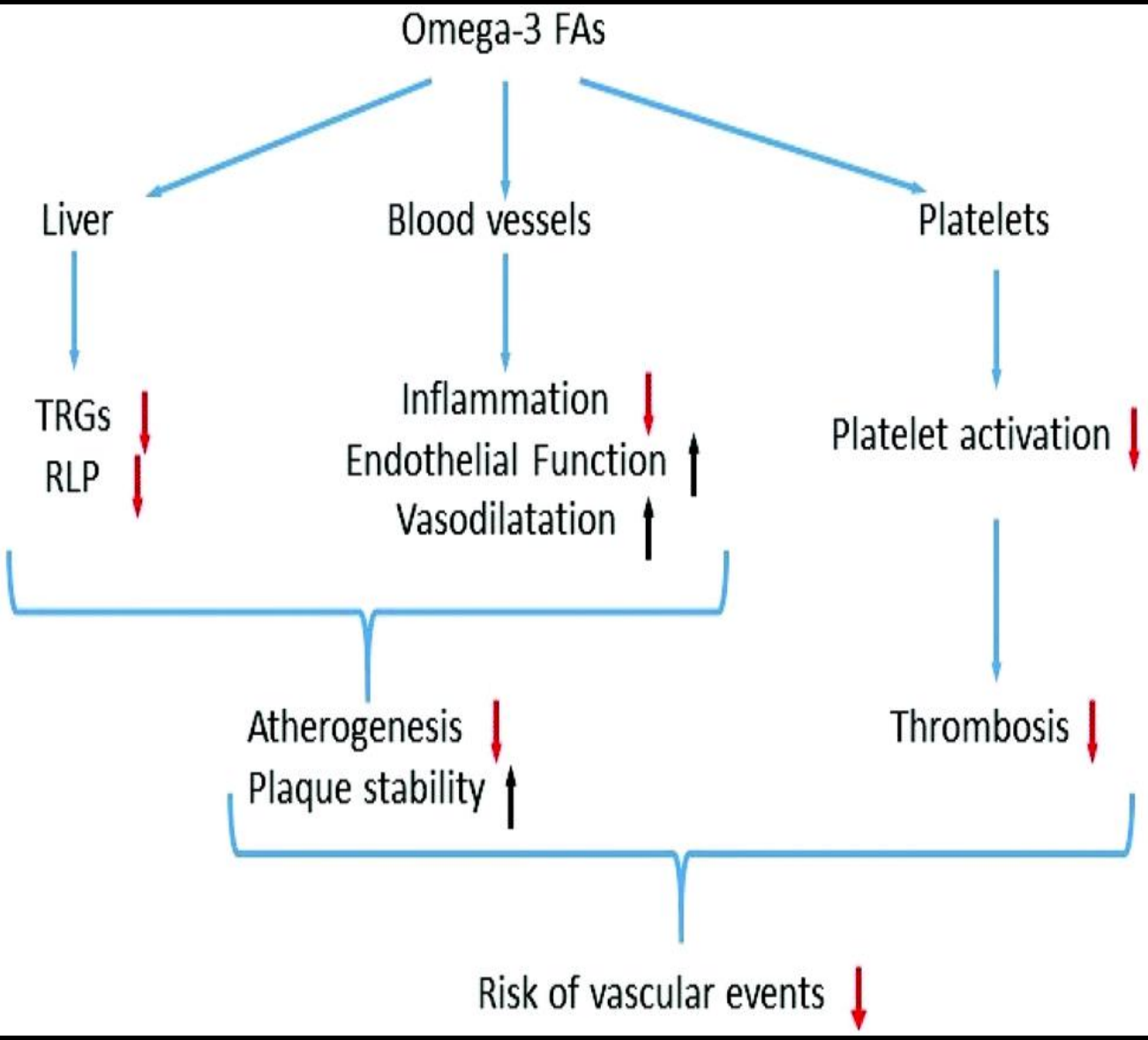
PUFA = polyunsaturated fatty acid.

Adapted from Mozafarian D, Wu JH. *J Am Coll Cardiol.* 2011;58:2047-2067.[2]

Omega 3

Generic Name	Omega-3-ethyl-esters	Icosapent ethyl
Brand Name	Lovaza or Omacor	Vascepa
EPA/capsule	0.465 g	1 g
DHA/capusle	0.375 g	none
Daily Dose	4 capsules/day	4 capsules/day





Backes et. Al *Lipids in Health and Disease*201615:118

Selected Om-3 CVD Outcome Studies

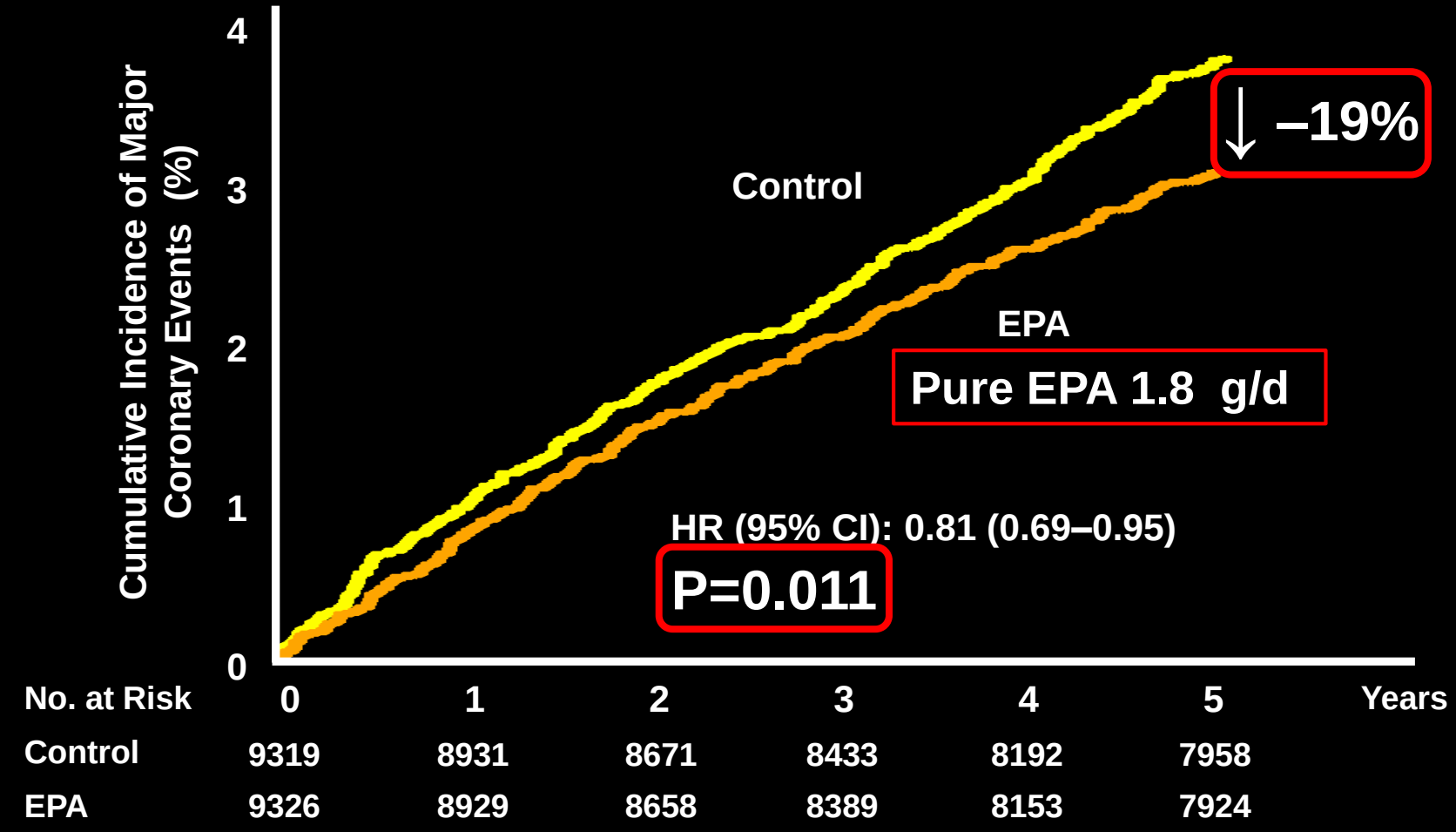
	GISSI-P[1-2]	ORIGIN[3]	JELIS[4]
Om-3 Type/dose	**EPA/DHA 1 g/day[2]**	**EPA/DHA 1 g/day**	**EPA 1.8 g/day**
Population	Italian	International	Japanese
N	11,324	12,536	18,645
Gender	85% male	65% male	31% male
Risk Profile	Recent MI (≤3 mos; median 16 days)	High CV risk, and IFG, IGT, or T2DM	80% 1° prev; TC ≥6.5 mM; excl MI ≤6 mos prior
Follow-up	3.5 years	6.2 years (median)	4.6 years (mean)
Statin Use	**Minimal**	53% in n-3 FA arm, 55% in pbo arm	All on statins (simva or pravastatin)
Primary End Point	All-cause death, non-fatal MI, NF stroke	Death from CV causes	MACE
Result	**RRR 10% (P=0.048)/ 15% (P=0.023)**	**HR=0.98 P=0.72**	**RRR 19% (no minimum TG level) P=0.011**
LDL-C	↑2%–3% >control groups	↓12% both arms	↓25% in both groups (w/ statin)

Low-dose Om-3 doesn't ↓CVD in statin-era. Mid-dose Om-3 does ↓CVD

excl=excluded; GISSI= Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; MACE=major adverse cardiac event; mos=months; ORIGIN=Outcome Reduction with an Initial Glargine Intervention; pbo=placebo; prev=prevention; REDUCE-IT=Reduction of Cardiovascular Events with EPA-Intervention Trial; RR=relative risk; RRR=relative risk reduction.

1. GISSI-Prevenzione Investigators. *Lancet*. 1999;354:447-55. 2. www.trialresultscenter.org/study4440-GISSI-P.htm.
3. ORIGIN Investigators. *N Engl J Med*. 2012;367:309-18. 4. Yokoyama M et al. *Lancet.* 2007;369:1090-8.
5. http://www.clinicaltrials.gov.

↓Major Coronary Events with Pure EPA Added to Statins (JELIS: similar benefit in 1° and 2° Prevention)



N=18,645. EPA=eicosapentaenoic acid; JELIS=Japan EPA Lipid Intervention Study.

Yokoyama M et al. *Lancet.* 2007;369:1090-8.

Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Deepak L Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD,

Eliot A. Brinton, MD, Terry A. Jacobson, MD, Steven B. Ketchum, PhD,

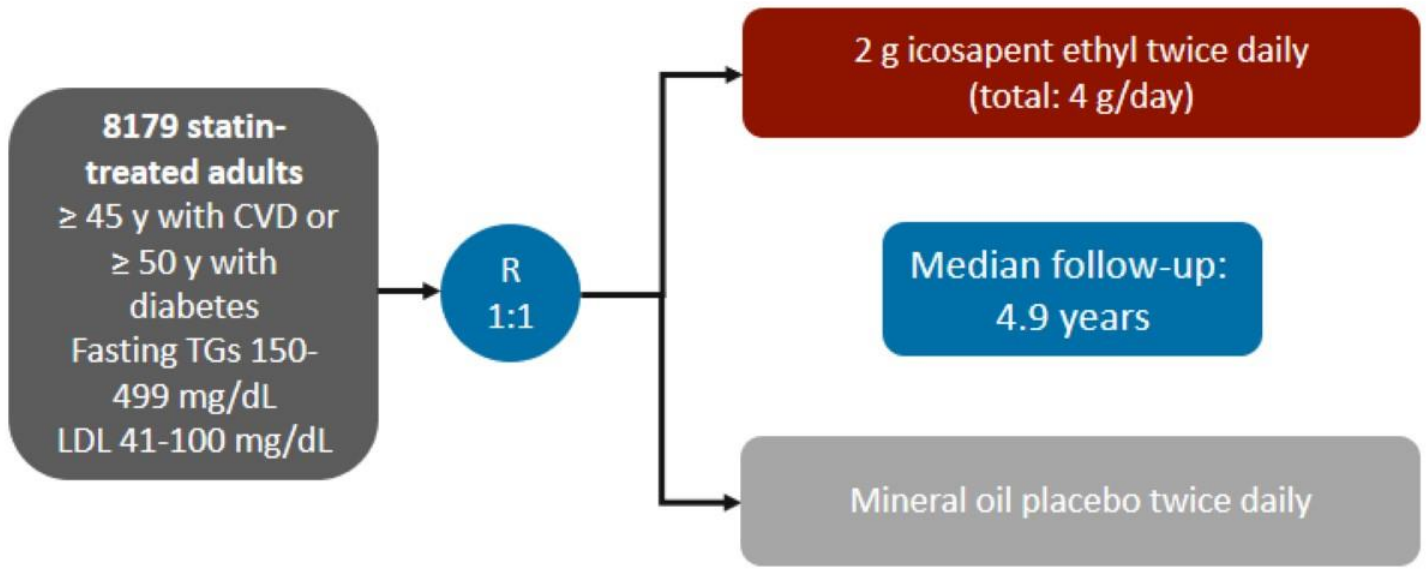
Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD,

Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, Christie M. Ballantyne, MD,

on Behalf of the REDUCE-IT Investigators

REDUCE-IT
Study Design

Phase 3b, double-blind, multicenter, randomized, placebo-controlled trial in statin-treated patients with established CVD or with diabetes



- Primary efficacy endpoint: composite of CV death, nonfatal MI,* nonfatal stroke, coronary revascularization, UA
- Key secondary endpoint: composite of CV death, nonfatal MI,* or nonfatal stroke

*Including silent MI.

Bhatt DL, et al. *N Engl J Med.* 2019;380:11-22.

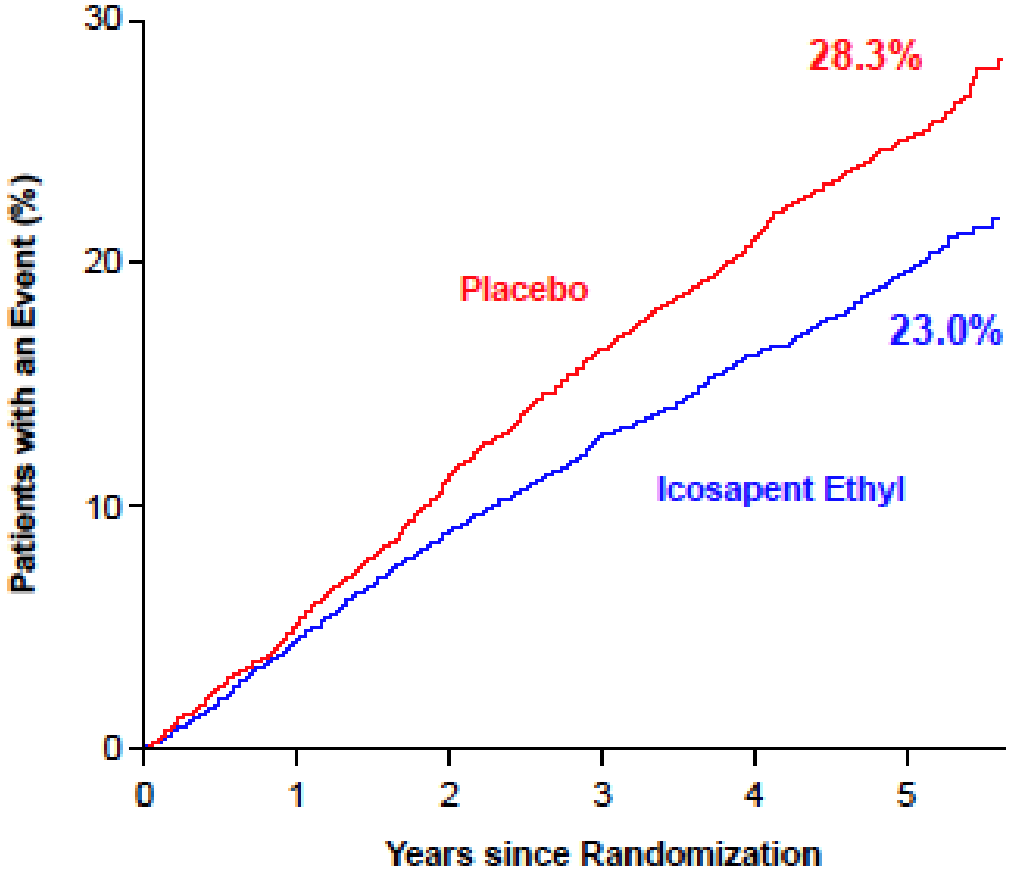
Key Baseline Characteristics

	Icosapent Ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, n (%)	1162 (28.4%)	1195 (29.2%)
Non-White, n (%)	398 (9.7%)	401 (9.8%)
Westernized Region, n (%)	2906 (71.1%)	2905 (71.0%)
CV Risk Category, n (%)		
Secondary Prevention Cohort	2892 (70.7%)	2893 (70.7%)
Primary Prevention Cohort	1197 (29.3%)	1197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2533 (61.9%)	2575 (63.0%)
High	1290 (31.5%)	1226 (30.0%)
Type 2 Diabetes, n (%)	2367 (57.9%)	2363 (57.8%)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)
150 to <200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥200 mg/dL	2481 (60.7%)	2469 (60.4%)

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2018.

Primary End Point:

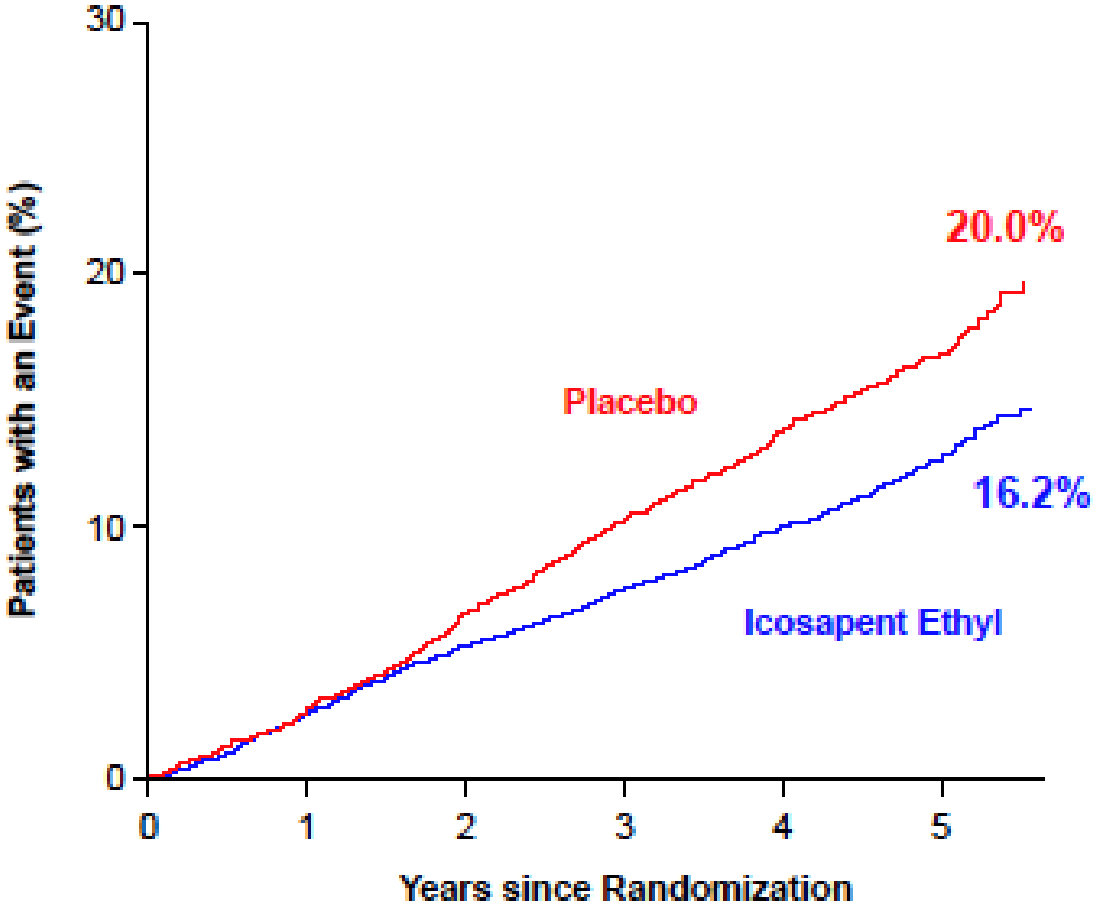
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018. Bhatt DL. AHA 2018, Chicago.

Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

RRR = 26.5%

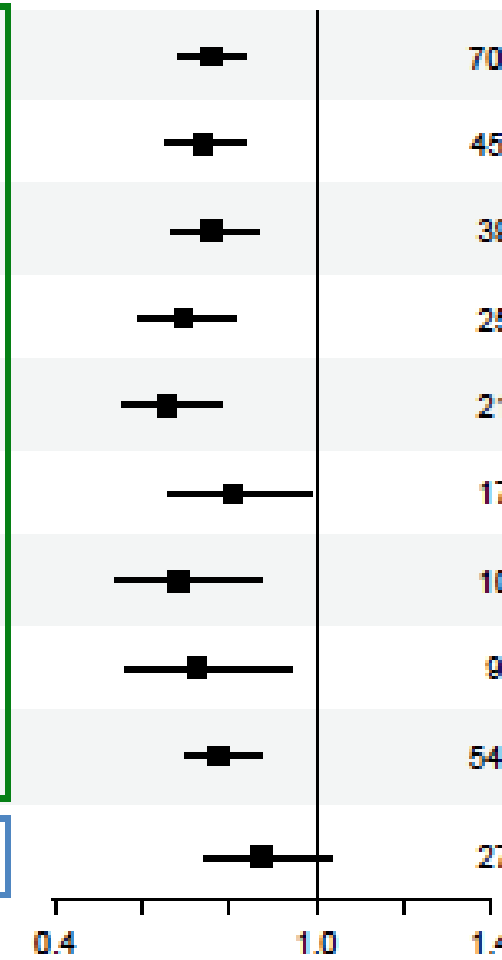
ARR = 3.6%

NNT = 28 (95% CI, 20–47)

P=0.0000006

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018. Bhatt DL. AHA 2018, Chicago.

Prespecified Hierarchical Testing



Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction	392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization	216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke	549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality	274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09

RRR denotes relative risk reduction

Bhatt DL. AHA 2018, Chicago.

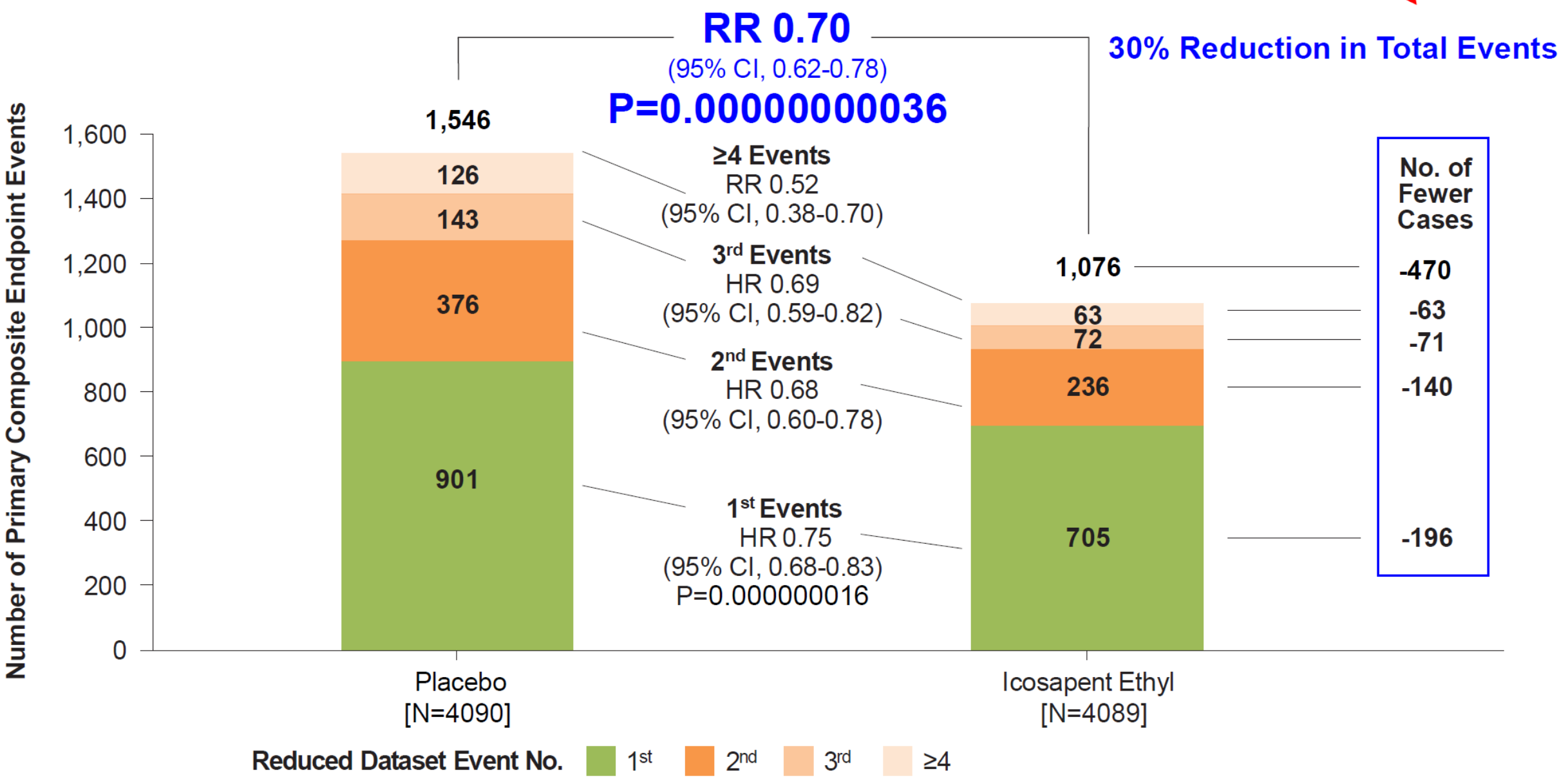
Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med*. 2018.

reduce-it

Reduction in Total Ischemic Events in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Deepak L. Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD, Eliot A. Brinton, MD, Terry A. Jacobson, MD, Steven B. Ketchum, PhD, Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD, Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, John Gregson, PhD, Stuart J. Pocock, PhD, Christie M. Ballantyne, MD, on Behalf of the **REDUCE-IT** Investigators

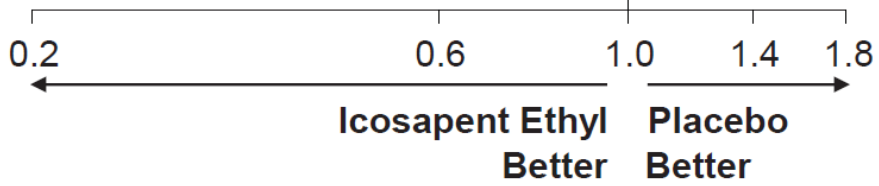
First and Subsequent Events



Note: WLW method for the 1st events, 2nd events, and 3rd events categories; Negative binomial model for ≥4th events and overall treatment comparison.

Primary Composite Endpoint: Total Endpoint Events by Baseline TG Tertiles

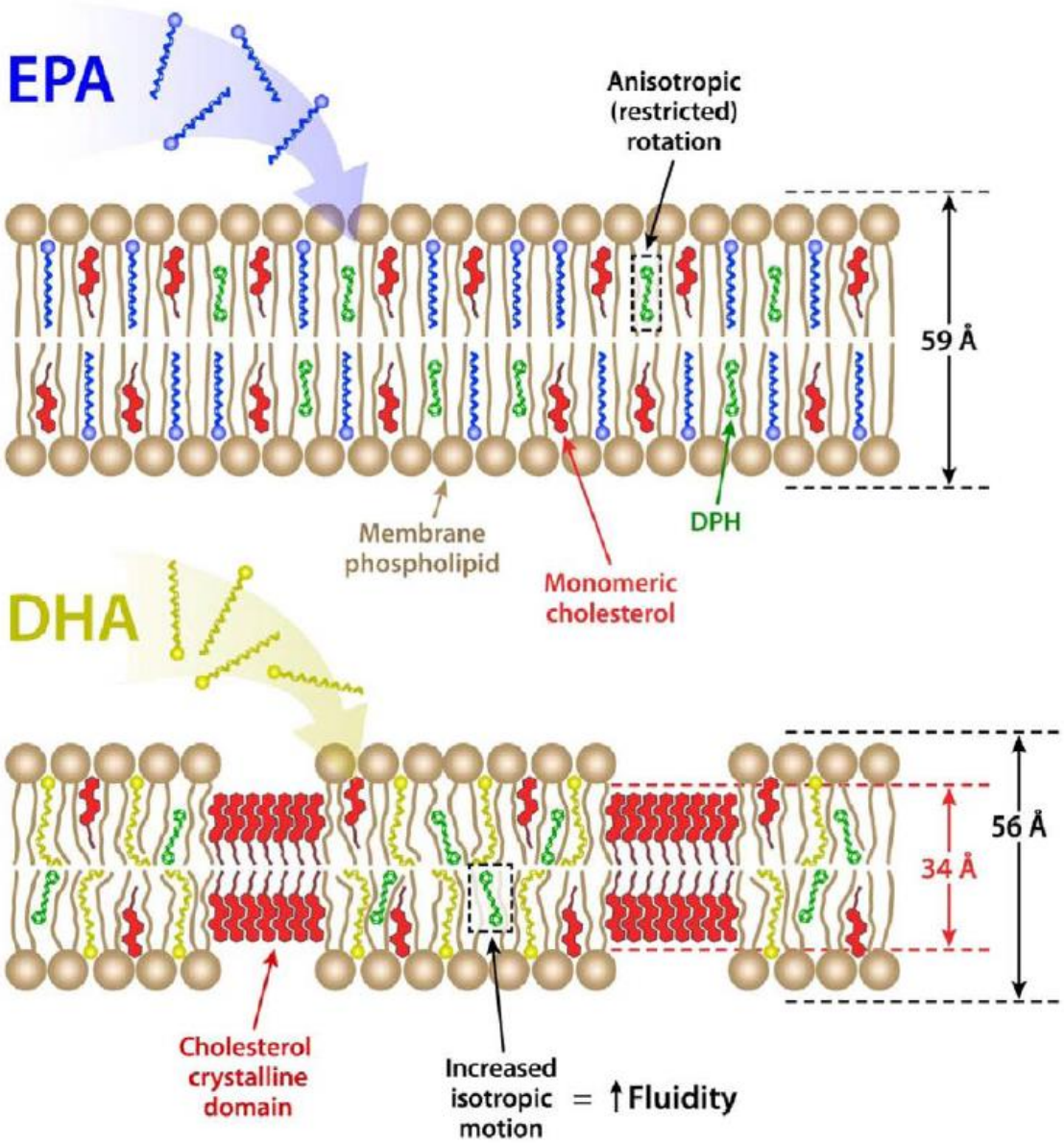
TOTAL EVENTS – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	RR (95% CI)	P-value
	Rate per 1000 Patient Years	Rate per 1000 Patient Years		
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62–0.78)	<0.0001
Baseline Triglycerides by Tertiles*				
≥81 to ≤190 mg/dL	56.4	74.5	0.74 (0.61–0.90)	0.0025
>190 to ≤250 mg/dL	63.2	86.8	0.77 (0.63–0.95)	0.0120
>250 to ≤1401 mg/dL	64.4	107.4	0.60 (0.50–0.73)	<0.0001



***P (interaction) = 0.17**

EPA vs DHA: Membrane Interactions

- Both EPA and DHA integrate into membranes
- EPA lies parallel to surrounding acyl chains
  - Reduces membrane fluidity
  - Reduces formation of cholesterol micro-domains
  - Normalizes bilayer width
- DHA interacts more with the phospholipid head groups
  - Increases membrane fluidity
  - Facilitates formation of cholesterol micro-domains
  - Reduces bilayer width



Sherratt and Mason. Chemistry and Physics of Lipids 2018;212:73-79; Mason et al. Biochimica et Biophysica Acta 2016;1858:3131-3140

Choice of Prescription Om-3

	EE EPA+DHA*	EE EPA only**
Available?	**Yes (generic)**	Yes (branded only)
EPA/DHA (total)	55/45 (84%)	100/0 (98%)
Bioavailability (short-term)	Good	Good
Regimen	2 g bid w/ meals	2 g bid w/ meals
Tolerability issues	Fishy taste & eruct, dyspepsia	**Arthralgia only**
TG-lowering	+++	+++
LDL-C effects	↑↑ (~45%)	**± (no ↑)**
HDL-C effects	↑ (5-10%)	± (no ↑)
↓CVD?	Not at 1g/d, no ongoing trials	**Probably (JELIS) + REDUCE IT**

Caveat: none of these comparisons are based on head-to-head data!

*Lovaza PI. Davidson MH et al Clin Ther 2007;29:1354–1367. ORIGIN Investigators. N Engl J Med. 2012;367:309-18. 4. Risk & Prevention Investigators N Engl J Med 2013;358:1800-8.
**Vascepa PI. Yokoyama M et al. *Lancet.* 2007;369:1090-8. Bays HE, et al. Am J Cardiol. 2011;108:682-90. Ballantyne CM et al Am J Cardiol 2012;110:984-992.
***Epanova PI. Davidson MH, J Clin Lipidology, 2012, 6:573. Offman E, Vasc Health Risk Manag. 2013; 9; 563–573. Kastelein, JJP; J Clin Lip 2013 epub 10 Oct. . Maki KC et al Clin Ther 2013;35:1400–1411.

Over-the-counter “Fish Oil”

Fish Oil 1200 mg
Liquid Softgels

Supplement Facts

Serving Size 2 Softgels
Servings Per Container 30

Amount Per Serving	% Daily Value
Calories 20	
Calories from Fat 20	
Total Fat 2 g	3%**
Saturated Fat 0.5 g	3%**
Polyunsaturated Fat 1 g	
Cholesterol 25 mg	8%**
Total Carbohydrate less than 1 g	less than 1%**
Protein Less than 1 g	
Fish Oil Concentrate 2400 mg	*
Total Omega-3 Fatty Acids 720 mg	*
Omega-3 EPA (Eicosapentaenoic Acid) 360 mg	
Omega-3 DHA (Docosahexaenoic Acid) 240 mg	
Omega-3 Other 120 mg	

Fish Oil One Per
Liquid Softgels

Ultra Omega-3 Mini Fish Oil 500 mg, Burp-Less
Liquid Softgels

Ultra Omega-3 Fish Oil 1400 mg
Liquid Softgels

Fish Oil 1200 mg Lemon Essence
Liquid Softgels

Supplement Facts

Serving Size 2 gummies
Servings Per Container 45

Amount Per Serving	% Daily Value
Calories 20	
Total Carbohydrate 4 g	1%**
Sugars 3 g	*
Sodium 5 mg	<1%
Fish Oil 227 mg	*
Total Omega-3 57 mg	*
Omega-3 DHA 47.5 mg (Docosahexaenoic Acid)	
Omega-3 EPA 9.5 mg (Eicosapentaenoic Acid)	

Fish Oil 1200 mg
Liquid Softgels

Fish Oil 1200 mg, Burp-Less
Liquid Softgels

Fish Oil
ult Gummies

000 mg, Burp-Less
quid Softgels

Fish Oil 1200 mg Plus Vitami
D 1000 IU
Liquid Softgels

TG Lowering Medications: When? Which?

If TG > 500: treat to prevent pancreatitis (& ASCVD)
If TG 200-500: *consider* treating to prevent ASCVD

"TG-Lowering"
1º for >500
2º for 200-500

1º for 200-500
2º for >500

Drug/class	↓Triglycerides
Fibrates	20-50%
Niacin	20-50%
Omega-3 oil (EPA +/- DHA (FFA or EE) *(pharmacologic doses)*	10-45%
Statins	7-30%
Ezetimibe	1-9%

After:

Expert Panel of Detection, Evaluation & Treatment of High Blood Cholesterol in Adults. *JAMA* 2001: 285: 2486-97.
Robinson JG, Stone NJ. *Am J Cardiol* 2006; 98(suppl):39i-49i.
Robinson JG, Davidson MH. *Expert Rev Cardiovasc Ther* 2006; 4: 461-76.
Briel M, et al. BMJ 2009: 338:b92

Severe Hypertriglyceridemia

Chylomicronemia Management
(FCS>>MFSHTG)

Lifelong Dietary Restrictions

Extremely low-fat diet (≤15-20% of energy)

Very-low added-sugar (<100/150 calories, or ~≤7% of energy)

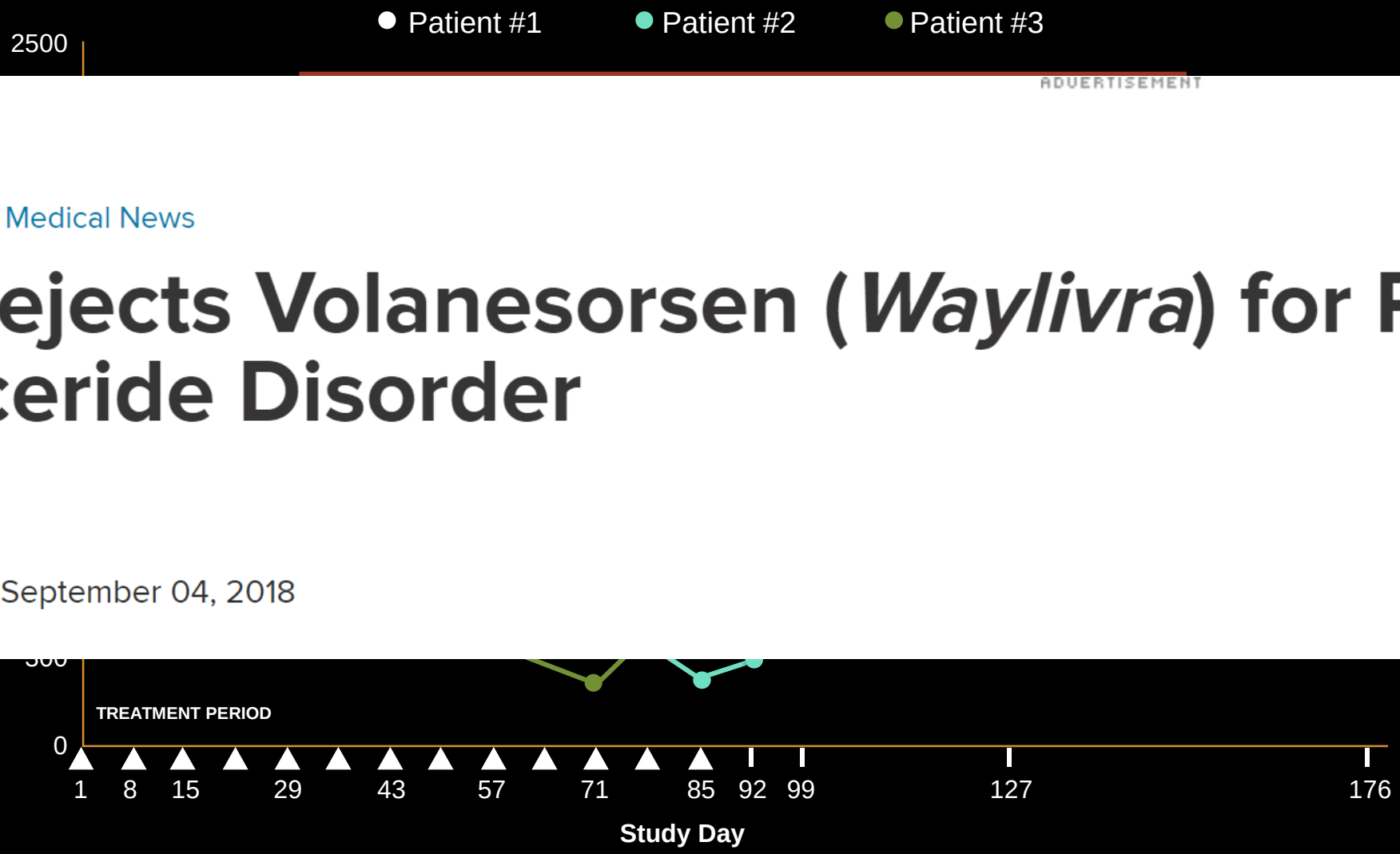
Complete Avoidance of Alcohol

Although difficult, these dietary therapies will ↓TG and can ↓clinical manifestations[1-6]

- ↓Frequency of eruptive xanthomas
- ↓Risk of acute & chronic pancreatitis[1-5]
- ↓Other abdominal pain
- ↓Hepatosplenomegaly
- ↓Peripheral neuropathy, CNS abnormalities

Adapted from: 1. Brahm AJ, Hegele RA. Chylomicronaemia—current diagnosis and future therapies. *Nat Rev Endocrinol.* 2015;11:352-362. doi:10.1038/nrendo.2015.26; 2. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1—full report. *J Clin Lipidol.* 2015;9(2):129-169. doi:10.1016/j.jacl.2015.02.003; 3. The physician's guide to lipoprotein lipase deficiency (LPLD). National Organization for Rare Disorders Physician Guides website. http://nordphysicianguides.org/wp-content/uploads/2015/04/NORD_Physician%E2%80%99s-Guide-to-Lipoprotein-Lipase-Deficiency.pdf. Published 2015. Accessed May 5, 2016; 4. Rahalkar AR, Hegele RA. Monogenic pediatric dyslipidemias: classification, genetics and clinical spectrum. *Mol Genet Metab.* 2008;93(3):282-294. doi:10.1016/j.ymgme.2007.10.007;

Apo C-III Anti-sense RNA (Volanesorsen) Ph-2 in FCS: 300 mg Reduced Fasting Plasma TG Levels



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

Take on message

1. Always address for secondary causes

2. Lifestyle modifications for everyone

3. Choose medication according to the patient risk factors.

Summary

TG >1000

- Primary goal: Reduce pancreatitis first
- Medications : Fibrates > Omega 3> Niacin

TG 500-999 ng/dL

- Primary goal: Reduce pancreatitis first
- Statin is “OK” if no history of pancreatitis
- Medications: Fibrates >Omega 3 > Niacin

Summary

TG > 200-499

- Primary goal: Reduce ASCVD risk by reducing atherogenic lipoprotein burden
- Statins are preferred as initial therapy
- If non-HDL goals are not met, consider adding Omega-3 FA or fibrate to statin therapy.

Questions?

Leonardo da Vinci

He who loves practice without theory is like the sailor who boards ship without a rudder and compass and never knows where he may cast.

AZ QUOTES