Learning Objectives

- Discuss the etiology, diagnosis, and risk assessment of hypertriglyceridemia (HTG)
- Relate the clinical and genetic evidence for the association between elevated triglycerides (TG) / remnant lipoproteins and atherosclerosis
- Describe the anti-atherosclerotic/anti-inflammatory properties of TG-lowering agents, with a focus on prescription omega-3 fatty acids (FA)
- Apply evidence-based guidelines to lifestyle and therapeutic approaches for managing patients with HTG

Association Between Triglycerides and Atherosclerosis/Pancreatitis

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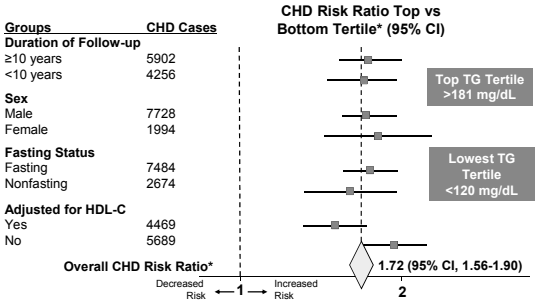
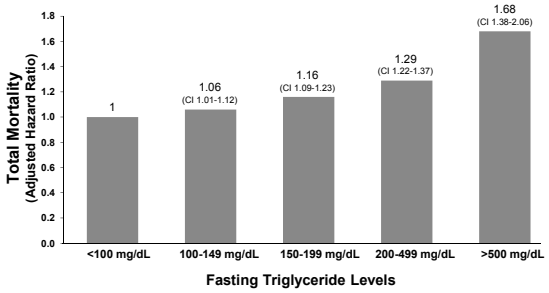
TG Predicts CHD
(Meta-Analysis of 29 Studies, N=262,525)



*Individuals in top vs bottom third of usual log-TG values, adjusted for at least age, sex, smoking status, lipid concentrations, and (in most studies) blood pressure.
HDL-C=high-density lipoprotein cholesterol. Sarwar N et al. *Circulation*. 2007;115:450-8.

All-cause Mortality Risk Increases as TG Levels Increase

15,355 patients who were screened for the Bezafibrate Infarction Prevention (BIP) trial. Twenty-two–year mortality data were obtained from the national registry.



CI=confidence interval. Klempfner R et al. *Circ Cardiovasc Qual Outcomes*. 2016;9:100-8.

Plasma TG Predicts CVD Death & Total Mortality
(Meta-analysis with >1 Million Subjects)

33 studies on CVD mortality (17,018 CVD deaths among 726,030 subjects) and
38 studies on all-cause mortality (58,419 all-cause deaths among 330,566 subjects)

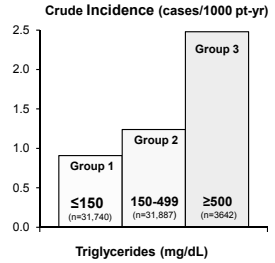
	CVD mortality		All-cause mortality	
TG quartile/mg/dL	RR	P	RR	P
I. **<90**	**0.83**	0.001	**0.94**	0.15
II. **90-149** (referent)	**1.00**		**1.00**	
III. **150-199**	**1.15**	0.015	**1.09**	0.011
IV. **≥200**	**1.25**	0.013	**1.20**	0.011

Median duration of study follow-up was 12.0 years.
Studies in subjects with diabetes, CVD, dyslipidemia or cancer were excluded.

Liu J et al. *Lipids Health Dis*. 2013;12:159.

Increasing TG Levels Increase Risk of Pancreatitis

Pancreatitis risk *further* increases 4% for every 100 mg/dL TG increase above 500 mg/dL*



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

Murphy MJ et al. *JAMA Intern Med*. 2013;173:162-4.

Most Forms of HTG Are of Secondary Origin

Cause	Clinically useful details
Positive energy balance	↓**Exercise,** ↑Saturated fat, ↑glycemic index
↑Carbohydrate intake	↑Simple sugars (**fructose**>>glucose, etc.) & ↓dietary fiber
Adiposopathy	Especially ↑**visceral adiposity**
Diabetes mellitus	Especially **if glycemia is poorly controlled**
Hypothyroidism	If not adequately controlled with thyroid replacement therapy
Nephrotic syndrome	
Medications	**Antiretroviral regimens (for HIV)** Some phenothiazines and 2nd-generation antipsychotics Nonselective beta-blockers Thiazide diuretics **Oral estrogen**, tamoxifen **Glucocorticoids, isotretinoin**
Recreational drugs	**Ethanol**; Marijuana (↑Apo C-III)

Apo=apolipoprotein; HIV=human immunodeficiency virus; HTG=hypertriglyceridemia.
Bays HE. In: Kwiterovich PO Jr, ed. *The Johns Hopkins Textbook of Dyslipidemia*. 1st ed. Lippincott Williams & Wilkins;2010:245-57.

Management of HTG

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Medical Director / President
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NLA: Targets of Therapy – Triglycerides

- An elevated TG level is not a target of therapy per se, except when very high (≥500 mg/dL)
- When TG levels are between 200–499 mg/dL, the targets of therapy are non-HDL-C and LDL-C
- When the TG concentration is very high (≥500 mg/dL, and especially if ≥1000 mg/dL), reducing the concentration to <500 mg/dL to prevent pancreatitis becomes the primary goal of therapy

Jacobson TA et al. *J Clin Lipidol*. 2014;8:473-88.

How are high triglyceride levels treated?

High TG levels are often associated with other heart disease risk factors

- Obesity
- Physical inactivity
- Diabetes mellitus
- High blood pressure
- Elevated cholesterol levels
- Low HDL-C levels

Treating Underlying Factors of HTG

- History of nutrition (calories, fat, sugar, alcohol, body weight trends) and physical activity (frequency, type, intensity)
- Measure BMI and waist, TSH, A1c, urinary protein
- Prescribe low-calorie, low-sugar, low-to-no alcohol, and low-fat plan. Recommend patient-appropriate physical activity plan.
- Treat underlying diseases
- Discontinue TG-raising medications or supplements

Bays HE. In: Kwiterovich PO Jr, ed. *The Johns Hopkins Textbook of Dyslipidemia*.
1st ed. Lippincott Williams & Wilkins;2010:245-57.

Lifestyle and Diet Can Have Big Effects on Hypertriglyceridemia

Diet / Lifestyle Change	Lipid Profile Change
Weight loss in overweight or obese individuals (5–10%)	20% - 50% Reduction in TG possible with Lifestyle Interventions
Diet ↑ Fruits, vegetables & low-fat dairy ↓ Total carb, added sugars ↓ Saturated fats	
Exercise Brisk 30-min walk, 3x/wk	

Miller M et al. *J Am Coll Cardiol.* 2008;51:724-30.
Sampson UK et al. *Curr Atheroscler Rep.* 2012;14:1-10.

Physical Activity and Lipid Levels in Patients with Overweight or Obesity

- TG reduction is the first and most notable effect of increased physical activity on the lipid profile
  - Sustained 3%–5% weight loss is likely to result in clinically meaningful TG decreases
  - Degree of effect is proportional to baseline TG
- HDL-C increases require extensive activity
  - ~700–2000 kcal/week (~30 min/day, moderate intensity)
- LDL-C usually does not change
  - However, weight loss via exercise may decrease levels

Bays HE et al. *J Clin Lipidol*. 2013;7:304-83.
Couillard C et al. *Arterioscler Thromb Vasc Biol*. 2001;21:1226-32.
Jensen MD et al. *J Am Coll Cardiol*. 2014;63:3029-30.

Table X: Approximate levels of eicosapentaenoic acid and docosahexaenoic acid in dry-heat cooked fish (2, 109, 142).*

Fish	EPA plus DHA (mg/100 g eaten)
Salmon Atlantic wild	1,840
Salmon Atlantic farmed	2,150
Salmon Chinook	1,740
Salmon Coho wild	1,060
Salmon Coho farmed	1,280
Herring Atlantic	2,000
Herring Pacific	2,130
Mackerel Pacific and jack	1,950
Mackerel Atlantic	1,200
Mackerel king	400
Halibt Atlantic and Pacific	470
Halibut Greenland	1,180
Tuna bluefin	1,500
Tuna yellowfin	280
Tuna skipjack	300
Bluefish	990
Pollock Alaskan	120***
Cod Atlantic	160
Cod Pacific	280
Sablefish (black cod)**	1,790
Bass sea	760
Bass freshwater	760
Whitefish	1,610
Trout rainbow wild	990
Trout rainbow farmed	1,150

DHA = docosahexaenoic acid (22:6 n-3); EPA = eicosapentaenoic acid (20:5 n-3). *Cooked fish (dry heat) often has less omega-3 fatty acid content than raw fish: 100 g of fish would be approximately 4 ozs, which would be a bit larger than a deck of playing cards or cassette tape. The amount of omega-3 fatty acids varies considerably in the same type of fish, depending on the environment and location. **Sablefish or "black cod" is not part of the codfish family. ***Alaskan Pollock is the fish used in many fast-food restaurants, where it is usually battered and fried.

Since 2008, the amount of omega-3 fatty acids in farmed salmon may have decreased as much as 50%, due to reduced quantity of forage fish (eg, anchovy, sardines, or menhaden) in fishmeal feed. Omega-3 fatty acids originate in fish from algae and phytoplankton.

Bays HE. *Drugs Today (Barc)*. 2008,44:205-46.

FDA-approved Pharmacologic Therapy for Very High TG Levels and Fredrickson Types

Drug Class	Very High TG Indications*			Notable Adverse Effects
	TG >500 mg/dL	Type III Hyper-lipidemia	Type IV Hyper-lipidemia	
Omega-3 FA (EPA/DHA)[a]	√			**Eructation, dyspepsia, diarrhea, nausea, abdominal pain or discomfort**
Omega-3 FA (EPA only)[a]	√			**Arthralgia**
Fenofibrate[b]	√			**Dyspepsia, nausea, cholesterol gallstones**
Extended-release Niacin[c]	√			**Flushing, pruritus, diarrhea, vomiting, hyperglycemia, hyperuricemia/gout, dyspepsia/peptic ulcer exacerbation, hepatotoxicity**
Statins[d,e]	√	√	√	**Myopathy, LFT elevations, hyperglycemia**

*Data from individual product labeling for each drug in patients with very high TG. [a]4 g per day. [b]145 mg per day. [c]2 g per day. [d]Atorvastatin, rosuvastatin, and simvastatin. [e]Atorvastatin and simvastatin. Miller M et al. *Circulation*. 2011;123:2292-333. Fredrickson DS, Lees RS. *Circulation*. 1965;31:321-7. Lewis B. *Proc R Soc Med*. 1971;64:905-8.

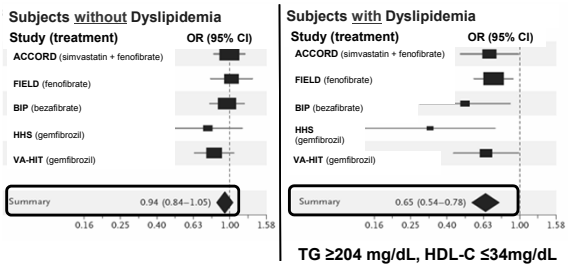
Statins Reduce CVD Events in HTG Patients (HTG Subgroup Data)

Trial (Subgroup, mg/dL) (Drug)	Risk difference vs placebo (P-value)	
	All subjects	HTG subgroup
WOSCOPS (TG ≥148) (Pravastatin)	**–31% (<0.001)**	**–32% (0.003)**
CARE (TG ≥144) (Pravastatin)	**–24% (0.003)**	**–15% (0.07)**
PPP Project (TG ≥200) (Pravastatin)	**–23% (<0.001)**	**–15% (0.029)**
4S (TG >159, HDL-C <39) (Simvastatin)	**–34% (<0.001)**	**–52% (<0.001)**
JUPITER (TG ≥150) (Rosuvastatin)	**–44% (<0.001)**	**–21% (NS)**
CTT (TG >177) (Various)	**–21% (<0.001)**	**–24% (<0.001)**

Median follow-up: ≥5 yrs.
CARE=Cholesterol and Recurrent Events Trial; CTT=Cholesterol Treatment Trialists; JUPITER=Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; NS=not significant; PPP=Prospective Pravastatin Pooling; 4S=Scandinavian Simvastatin Survival Study; WOSCOPS=West of Scotland Coronary Prevention Study. Ballantyne CM et al. *Circulation*. 2001;104:3056-51. CTT Collaborators. *Lancet*. 2005;366:1267-78. Maki KC et al. *J Clin Lipidol*. 2012;6:413-26.

Fibrates Reduce CHD Risk in Patients with HTG and Low HDL-C

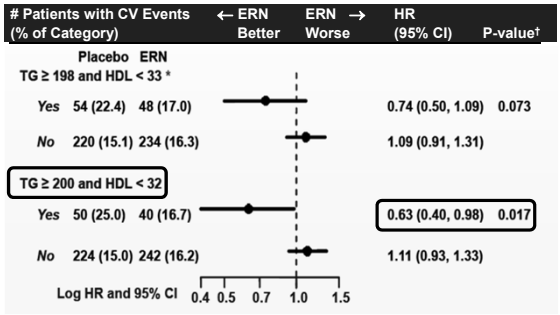
A meta-analysis of randomized fibrate trials



TG ≥204 mg/dL, HDL-C ≤34mg/dL

Sacks FM et al. *N Engl J Med.* 2010;363:692-4.

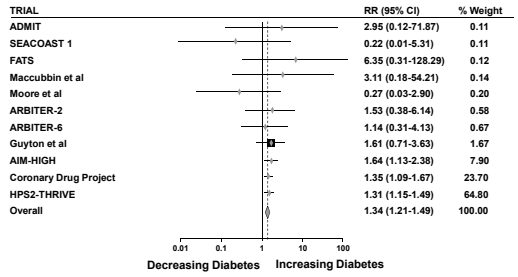
Post-hoc Analysis of AIM-HIGH: Niacin ER in Patients with HTG & Low HDL-C



*Highest tertile of TG and lowest tertile of HDL-C. †Heterogeneity by treatment.
All measurements in mg/dL. ER=extended release; ERN=ER niacin.
Guyton JR et al. *J Am Coll Cardiol*. 2013;62:1580-4. Guyton JR et al. Paper presented at: AHA SS; Nov. 6, 2012; Los Angeles, CA.

Niacin Increases New-onset Diabetes

- Meta-analysis regarding new-onset diabetes from 11 trials of niacin, involving 26,340 patients
- Niacin therapy led to a 34% higher risk of developing diabetes
- Not influenced by the presence or absence of statin therapy or by co-administration with laropiprant



NOTE: Weights are from random effects analysis. Goldie C et al. *Heart*. 2016;102:198-203.

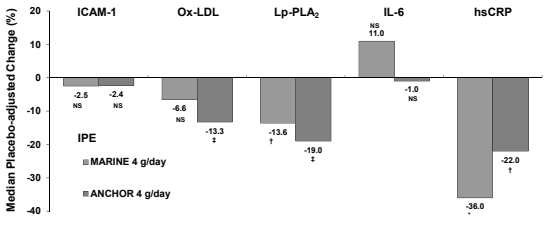
Available Prescription Omega-3 Fatty Acid Formulations

	EPA+DHA EE[1,2]	EPA only EE[3]	EPA+DHA FFA[4]
Brand Name	Lovaza	Vascepa	Epanova
Generic Available?	Yes	No	No
Indication	Indicated as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia		
Omega-3 Content	EPA: 0.465 g DHA: 0.375 g EPA/DHA: 55%/45%	EPA: 1 g EPA/DHA: 100%/0%	EPA: 0.55 g DHA: 0.2 g EPA/DHA: 73%/27%
Regimen, Capsules	2 BID w/ meals or 4 QD w/ meals[2]	2 BID w/ meals	2 or 4 QD, meal independent

1. Lovaza prescribing information, generics available. 2. Omtryg prescribing information.
3. Vascepa prescribing information. 4. Epanova prescribing information.
EE=ethyl ester; FA=fatty acid(s); FFA=free FA.
Sperling LS, Nelson JR. *Curr Med Res Opin*. 2016;32:301-11.

What about omega-3 fatty acids and inflammation?

Effect of EPA on Inflammatory Markers
(Baseline to week 12, intent-to-treat population)

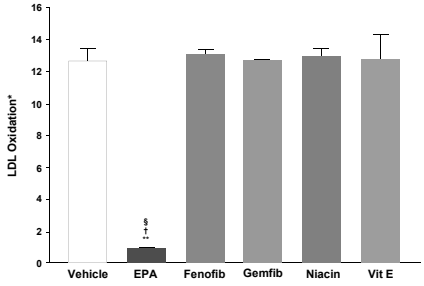


*P<0.01; †P<0.001; ‡P<0.0001 (vs placebo). P values for Lp-PLA2 were adjusted for multiple comparisons.

hsCRP=high-sensitivity C-reactive protein; ICAM-1=intercellular adhesion molecule-1; IL-6=interleukin-6; IPE=icosapent ethyl; Lp-PLA2=lipoprotein-associated phospholipase A2; NS=not significant; Ox-LDL=oxidized low-density lipoprotein.

Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-46.

Comparative Effects of EPA, Fenofibrate, Niacin, Gemfibrozil, and Vitamin E on *in vitro* Human LDL Oxidation



*LDL oxidation as measured by MDA Equivalents (mM). **P<0.001 vs vehicle-treated control. †P<0.01 vs Fenofib, Niacin, or Gemfib. §P<0.001 vs Vit E. (Student-Newman-Keuls multiple comparisons test; overall ANOVA: P<0.0001, F=132.37). Values are mean ± SD. (N = 3).
Mason RP, Jacob RF. *Biochim Biophys Acta*. 2015;1848:502-9.

Potential Cardiovascular Benefits of Fish Oils Rich in Omega-3 Fatty Acids

Antidysrhythmic
- Reduced sudden death
- Possible prevention of atrial fibrillation
- Possible protection against pathologic ventricular arrhythmias
- Improvement in heart rate variability

Anti-atherogenic
- Reduction in non-HDL-C levels
- Reduction in TG and VLDL-C levels
- Reduction in chylomicrons
- Reduction in VLDL and chylomicron remnants
- Increase in HDL-C levels
- "Improvement" (increase) in LDL and HDL particle size
- Plaque stabilization

Antithrombotic
- Decreased platelet aggregation
- Improved blood rheologic flow

Anti-inflammatory and endothelial protective effects
- Reduced endothelial adhesion molecules and decreased leukocyte adhesion receptor expression
- Reduction in proinflammatory eicosanoids and leukotrienes
- Vasodilation

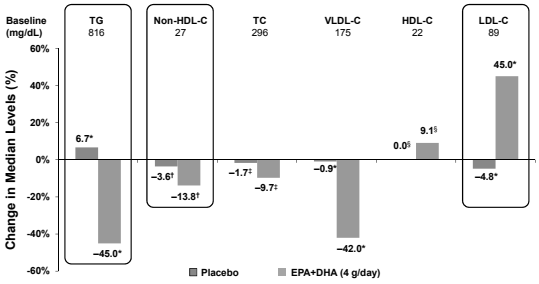
Decreased systolic and diastolic blood pressure

Bays HE. Chapter 21. The John Hopkins Textbook of Dyslipidemia, by Peter O Kwiterovich, Copyright 2010; 245-257.

What have the omega-3 fatty acid clinical trials shown?

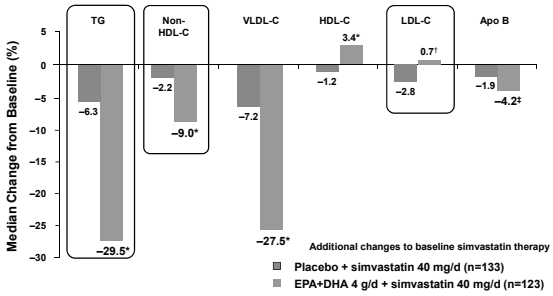
EPA+DHA Lipid Efficacy in Non-Statin Treated Patients

TG >500 mg/dL



*P<0.0001; †P=0.0015; ‡P=0.0059; §P=0.0002 between groups. Pooled analysis (N=82).
Harris WS et al. *J Cardiovasc Risk* 1997;4:385-91. Pownall HJ et al. *Atherosclerosis* 1999;143:285-97.

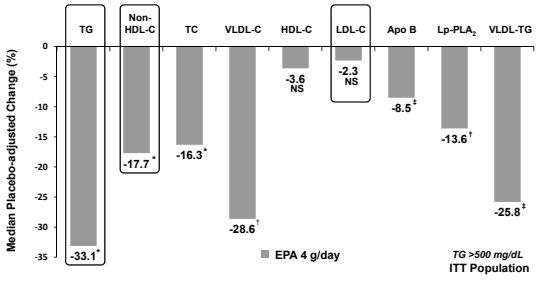
Statin + EPA/DHA: COMBOS Trial Lipid Efficacy



*P<0.0001. †P=0.0522. ‡P=0.0232 between groups. COMBOS=Combination of Prescription Omega-3 with Simvastatin.
Davidson MH et al. *Clin Ther*. 2007;29:1354-67.

EPA: MARINE Trial Lipid Efficacy

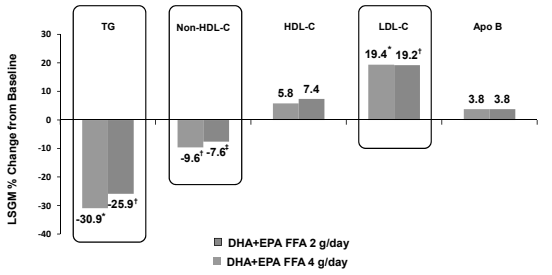
TG ≥500 mg/dL and ≤2000 mg/dL (with or without background statin therapy)



*P<0.0001. †P<0.001. ‡P<0.01. NS = P≥0.05. P-values reflect differences between EPA vs placebo.
ITT=intention to treat; Lp-PLA=lipoprotein-associated phospholipase A; MARINE=Multi-center, Placebo-controlled, Randomized, Double-blind, 12-week Study with an Open-label Extension. Bays HE et al. *Am J Cardiol*. 2011;108:682-90.

EVOLVE: DHA+EPA Free Fatty Acid and Lipid Efficacy

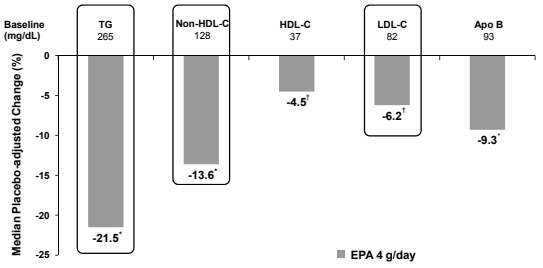
n=99, *TG ≥500 but <2000 mg/dL*



*P<0.001. †P<0.01. ‡P<0.05. P-values reflect differences between DHA+EPA free fatty acid (FFA) vs statin+ olive oil.
LSGM=least-squares geometric mean. Kastelein JJP et al. *J Clin Lipidol*. 2014;8:94-106.

ANCHOR Study: EPA and Lipid Efficacy

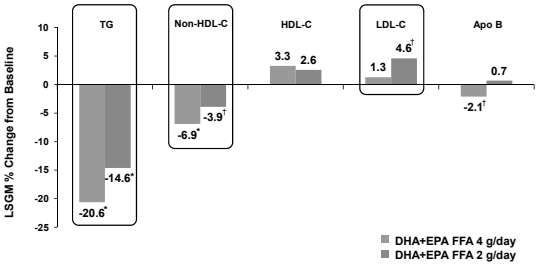
N=702, TG ≥200 and <500 mg/dL



*P<0.0001. †P<0.01. P-values reflect differences between EPA vs placebo.
12-week trial in high-risk statin-treated patients (N=702) with residually ↑TG levels (≥200 and <500 mg/dL) despite LDL-C control (≥40 and <100 mg/dL). ANCHOR=Effect of AMR101 (Ethyl Icosapentate) on Triglyceride (Tg) Levels in Patients on Statins With High Tg Levels (≥200 and <500 mg/dL). Ballantyne CM et al. *Am J Cardiol*. 2012;110:984-92.

ESPRIT: DHA+EPA Free Fatty Acid and Lipid Efficacy

n=207, *TG ≥200 and <500 mg/dL*

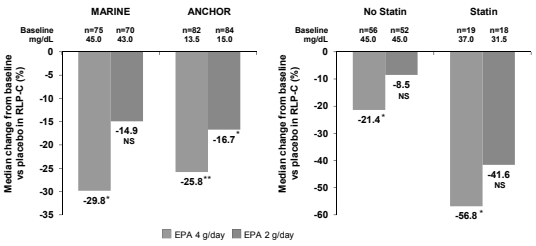


*P<0.001. †P<0.05. P-values reflect differences between DHA+EPA free fatty acid (FFA) vs statin+ olive oil.
LSGM=least-squares geometric mean. Maki KC et al. *Clin Ther* 2013;35:1400-11.

Effects on Remnant-like Particle Cholesterol from the MARINE and ANCHOR Studies

Median percent change from baseline to week 12 vs placebo in RLP-C in patients from the MARINE and ANCHOR studies†

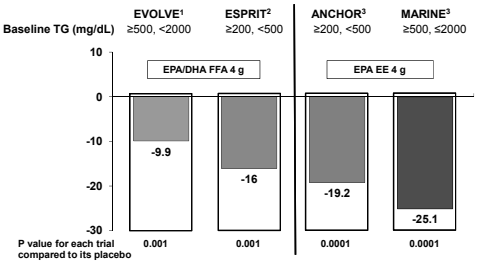
Median percent change from baseline to week 12 vs placebo in RLP-C by statin use in patients from the MARINE study†



*P<0.05. **P<0.01. †Median differences in percent changes vs placebo are Hodges-Lehmann medians.
NS=not significant; RLP-C=remnant-like particle cholesterol.
Ballantyne CM et al. *J Clin Lipidol*. 2015;9:463-4(Abstract 172).

Prescription Omega-3s Significantly Reduce Apo C-III Concentration

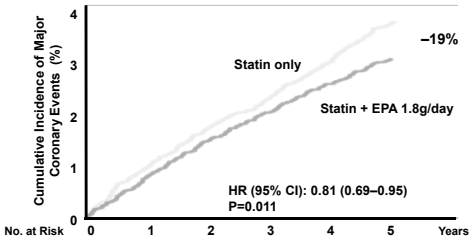
Apo C-III concentration change from baseline, vs placebo (%)



Note: No head-to-head comparisons are represented or implied.

EE=ethyl ester; FFA=free fatty acid.
1. Kastelein JJ et al. *J Clin Lipidol*. 2014;8:94-106. 2. Dunbar RL et al. *Lipids Health Dis*. 2015;14:98.
3. Ballantyne CM et al. *J Clin Lipidol*. 2016;10:635-45.

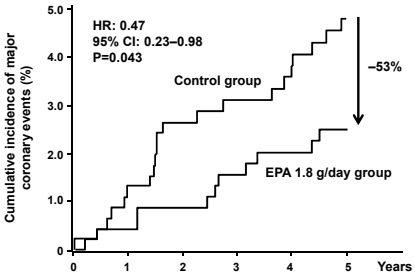
JELIS: EPA Reduced Major Coronary Events* in Hypercholesterolemic Patients on Statins



N=18,645 Japanese pts with TC ≥251 mg/dL prior to baseline statin Rx. Baseline TG=153 mg/dL.
Statin up-titrated to 20 mg pravastatin or 10 mg simvastatin for LDL-C control.
*Primary endpoint: Sudden cardiac death, fatal and non-fatal MI, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass graft.

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

JELIS: Larger Decrease in MACE in those with TG >150 mg/dL & HDL-C <40 mg/dL*



HR and P-value adjusted for age, gender, smoking, diabetes, and HTN

*Pre-specified. MACE=major adverse CV event. Saito Y et al. *Atherosclerosis*. 2008;200:135-40.

What about fish oil supplements?

Background: Dietary Supplement Omega-3

- Fish oil is among the most commonly used dietary supplement by US adults[1]
  - Global sales may reach $3.3 billion by 2020[2]
- ~7.8% of US adults (19 million) have taken a fish oil supplement in the previous 30 days[3]
- Omega-3 dietary supplements are widely available, but their content, integrity and efficacy remain unverified[4]
- Non-marine omega-3 (flaxseed and walnut) do not lower TG
- There are **no OTC** omega-3 products in US (just Rx & DS)!

1. Barnes PM et al. National Health Statistics Reports. 2008;12:1-24.
2. http://globenewswire.com/news-release/2014/10/28/677161/10104781/en/Global-Fish-Oil-Market-By-Application-Aquaculture-Direct-Human-Consumption-Is-Expected-to-Reach-USD-3-300-0-Million-by-2020-New-Report-By-Grand-View-Research-Inc.html?parent=676724#sthash.GIGle3SR.dpuf
3. NIH NCCIH. Available at: https://nccih.nih.gov/health/omega3/introduction.htm
4. Mason RP et al. Poster presented at the AMCP 2015 Nexus. Orlando, FL.

Prescription vs Dietary Supplement Omega-3

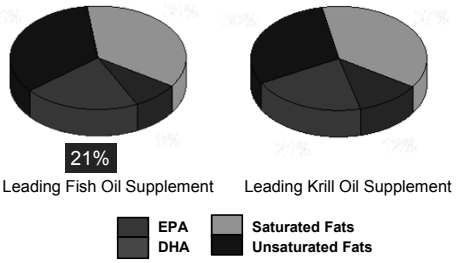
	Prescriptions		Dietary Supplements
	EPA	EPA +DHA	
FDA classification	Drug	Drug	Food
FDA approval	Yes	Yes	No
Ingredients	EPA	EPA + DHA	Variable EPA + DHA (none pure EPA) + other PUFAs and saturated FA
Omega-3 per capsule	0.98 g	0.84 g	Usually 0.2–0.4 g EPA; 0.1–0.3 g DHA
Capsules/day to provide 4 g omega-3	4	~4	Usually 10–20
Recommended dose	4 g/day	4 g/day	· General: Eat oily fish or 1 g/day · Prior CHD: 1–2 g/day (>2 g/day directed by HCP) · For ↓TG: 2–4 g/day directed by HCP
Purity/efficacy & safety tested	Yes	Yes	Not required (usually not done)

FA=fatty acid; HCP=health care provider.

Krill Oil

- Krill are oceanic, shrimplike, planktonic crustaceans. Krill feed on phytoplankton, and thereby accumulate omega-3 fatty acids.
- Marketing claims suggest krill oil may be a better source of omega-3 fatty acids
  - Reduced fishy aftertaste
  - Improved bioavailability (administered as a phospholipid instead of an ethyl ester)
  - Incorporation of an antioxidant (astaxanthin)
  - Low levels of metallic and other toxins
- Most of the published data regarding krill oil evaluated less than (and often substantially less than) 4 g of omega-3 fatty acids (FA) per day
  - Phospholipids sometimes compose 50% of the capsule content
  - 4 g of omega-3 FA per day via a 1-g krill oil supplement containing 300 mg of total omega-3 FA per capsule = 13 krill oil capsules per day
  - 4 g of omega-3 FA per day via a 0.5-g krill oil supplement containing 90 mg of total omega-3 FA per capsule = 44 krill oil capsules per day

Fatty Acid Content of Leading Fish-Oil and Krill-Oil Supplements



These chromatography findings have been noted by R. Preston Mason, PhD (unpublished data, 2015).

Summary

- **HTG is an important public health burden**
  - Optimal TG level is <100 mg/dL
  - HTG is common in central obesity and T2DM
  - Causal factor for ASCVD events, ***even when LDL-C is optimal***
- **Guidelines and recommendations**
  - Appropriate nutrition and physical activity in all
  - Medical Rx for very high TG (>500 mg/dL) to help prevent pancreatitis
  - Medical Rx for HTG 200–500 mg/dL, *consider* in high-risk pt on statin (see below)
- **Recommended medical Rx**
  - Statins (for all high risk w/ TG 200-500, unless statin-intolerant)
  - Fenofibrate (HTG subgroups positive in T2DM)
  - Omega-3 (JELIS, HTG subgroup especially positive)
  - Niacin (AIM-HIGH HTG subgroup positive, but difficult to use)

ASCVD=atherosclerotic CVD; T2DM=type 2 diabetes mellitus.

"Another factor contributing to the uncertainty is that no prospective CHD outcome drug trial conducted in hypertriglyceridemic patients has ever shown as a primary endpoint that lowering TG levels (and only TG levels) reduces CHD events."

Bays HE. *Drugs Today (Barc).* 2008,44:205-46.

Ongoing EPA+DHA and EPA-only: CVD Outcome Studies

	REDUCE-IT[1] (Ongoing)	STRENGTH[2] (Ongoing)
Omega-3 type Dose	EPA 4 g/day	EPA+DHA (FFA) 4 g/day
Population	International	International
N	~8000	Estimated 13,000
Gender	Men and non-pregnant or sterile women ages 45 or older	Men or women, ≥18 years of age
Risk Profile	TG >150 mg/dL +CHD or ↑CHD risk	High CV risk (50%), prior ASCVD (50%)
Follow-up	4–6 years (planned)	3-5 years (planned)
Statin Use	100% (at LDL-C goal)	100% (at LDL-C goal)
Primary End Point	Expanded major adverse cardiac event	Expanded Major adverse cardiac event
Result	Powered for 15% RRR	Powered for 15% RRR
Baseline TG	>200 mg/dL	≥200 mg/dL, <500 mg/dL

1,2. http://www.clinicaltrials.gov. RRR=relative risk reduction.

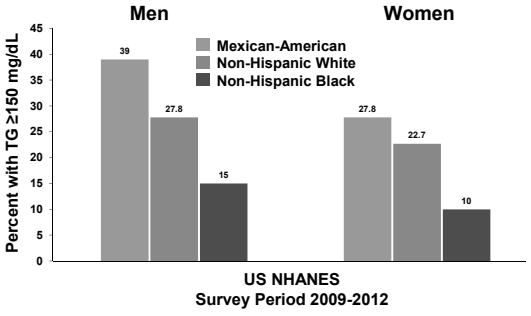
Role and Importance of HTG in CVD Risk Assessment

Prevalence of Elevated TG NHANES 1999-2008

20+ Years	Triglyceride Cut Points, mg/dL		
	>150	>200	>500
Overall	31%	16%	1.1%
Men	35%	20%	1.8%
Women	27%	13%	0.5%
Heritage			
Mexican	35%	20%	1.4%
African	16%	8%	0.4%
European	33%	18%	1.1%

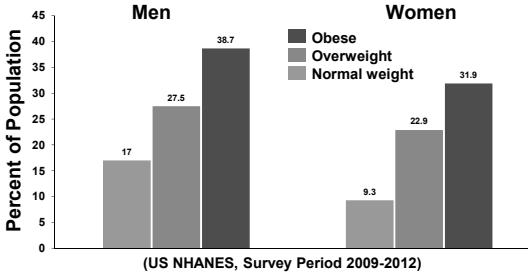
Miller M et al. *Circulation.* 2011;123:2292-333.

Elevated TG (≥150 mg/dL) More Common in Mexican Americans, Less Common in Blacks



Carroll MD et al. NCHS Data Brief, No 198. National Center for Health Statistics. 2015.

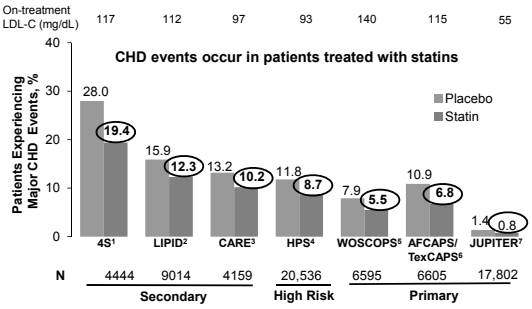
Increasing Obesity Strongly Predicts Fasting TG ≥150 mg/dL



Normal weight: BMI 18.5-24.9 kg/m²;
Overweight: BMI 25-29.9 kg/m²; Obese: BMI ≥30kg/m²

Carroll MD et al. NCHS Data Brief, No 198. National Center for Health Statistics. 2015.

Major Statin Trials: Despite Benefit, Substantial Residual CV Risk Remains

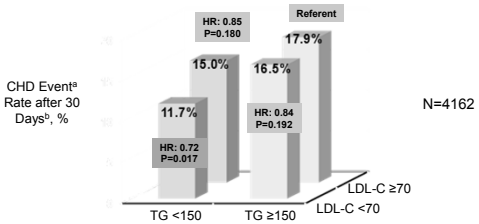


[1]4S Group. *Lancet.* 1994;344:1383-9.
[2]LIPID Study Group. *N Engl J Med.* 1998;339:1349-57.
[3]Sacks FM et al. *N Engl J Med.* 1996;335:1001-9.
[4]HPS Collaborative Group. *Lancet.* 2002;360:7-22.
[5]Shepherd J et al. *N Engl J Med.* 1995;333:1301-7.
[6]Downs JR et al. *JAMA.* 1998;279:1615-22.
[7]Ridker PM et al. *N Engl J Med.* 2008;359:2195-207.

CHD Risk: Does High LDL/Low TG = Low LDL/High TG?

PROVE IT-TIMI 22 Trial: High LDL/Low TG = Low LDL/High TG

ACS patients on atorvastatin 80 mg or pravastatin 40 mg

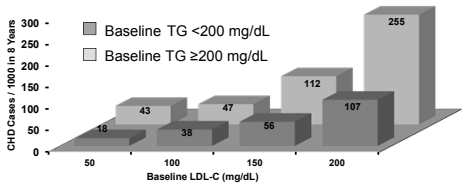


[a]Death, MI, and recurrent ACS.
[b]Adjusted for age, gender, low HDL-C, smoking, hypertension, obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment.
Lipid values are in mg/dL.

Miller M et al. *J Am Coll Cardiol.* 2008. 51;724-30.

PROCAM: High LDL/Low TG = Low LDL/High TG

Incidence of CHD Events According to Serum LDL-C and TG Concentration*

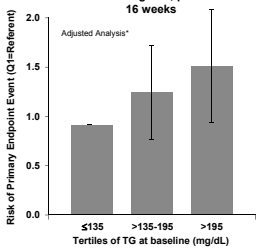


*Lipids from 4849 middle-aged men who were followed for 8 years to record incidence of CHD. Study demonstrated that TG fasting levels were an independent risk factor for CHD events, irrespective of serum levels of LDL-C.
The effect of prescription omega-3 (ω-3) on the risk of pancreatitis in patients with very high TG levels has not been evaluated. The effect of prescription ω-3 on cardiovascular mortality and morbidity in patients with very high TG levels has not been determined.

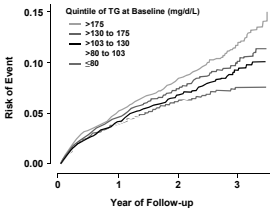
Adapted from Assmann G et al. *Eur Heart J.* 1998;19(Suppl M):M8-M14.

On Statin Rx, TG Levels Associate with Short- and Long-Term CV Risk

N=1501 MIRACL
Atorva 80 mg arm; post-ACS
16 weeks



N=15,817 Dal-OUTCOMES
97% statin-treated; post-ACS
Median follow-up 31 months



Fasting TG levels are strongly linked to both short-term and long-term major CV event risk on background statin therapy, independent of LDL-C

*P for trend=0.03.
ACS=acute coronary syndrome. Schwartz GG et al. *J Am Coll Cardiol*. 2015;65:2267-75.

2014 National Lipid Association Classification of TG Levels

Fasting Triglycerides (mg/dL)	
<150	Normal
150–199	Borderline high
200–499	High
≥500	Very high

These are the same as the AHA Scientific Statement of 2011, which also included "Optimal" for fasting TG <100 mg/dL.

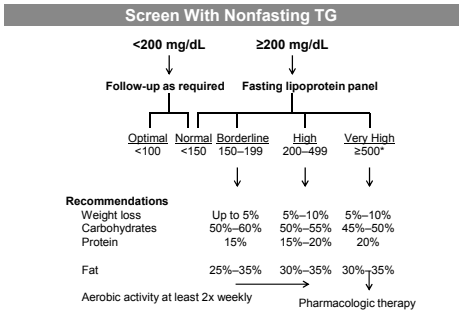
Jacobson TA et al. *J Clin Lipidol*. 2014;8:473-88.
American Heart Association (AHA) Scientific Statement. Miller M et al. *Circulation*. 2011;123:2292-333.

Fasting vs Nonfasting Measurements of TG and Non-HDL-C

- Fasting TG is used to categorize TG elevation
- Studies have supported nonfasting TG as a superior predictor of incident CVD vs fasting TG
- Nonfasting TG is **similar** to fasting after a low-fat meal (eg, <15 g fat)
- If nonfasting TG is ≥200 mg/dL, a fasting lipid panel is recommended soon (eg, 2-4 wks later)
- Non-HDL-C is accurate fasting ***or*** nonfasting**,** and is the best predictor of CVD risk in patients with HTG*

*National Lipid Association (NLA) Recommendations. Jacobson TA et al. *J Clin Lipid*ol. 2014;8:473-88.
AHA Scientific Statement. Miller M et al. *Circulation*. 2011;123:2292-333.

Practical Algorithm for Screening and Managing Elevated TG

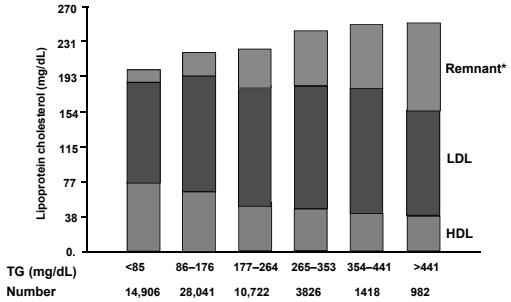


AHA Scientific Statement. Miller M et al. *Circulation*. 2011;123:2292-333.

Mechanisms of Increased ASCVD in Patients with HTG

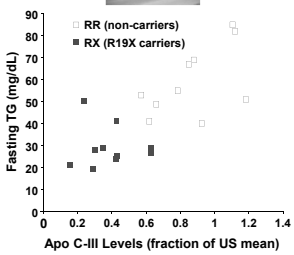
"Remnant Cholesterol"* Increases with Increasing Non-Fasting TG

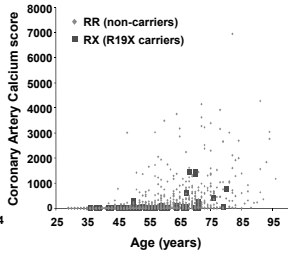
Lipoprotein cholesterol as a function of increasing levels of non-fasting TG among 72,000 Danish participants not on lipid-lowering therapy



*"Remnant cholesterol" is actually just TG/5. Varbo A et al. *J Am Coll Cardiol*. 2013;61:427-36.

An ApoC-III Loss-of-Function Mutation Causes Very Low TG Levels and Lower Coronary Calcium Scores

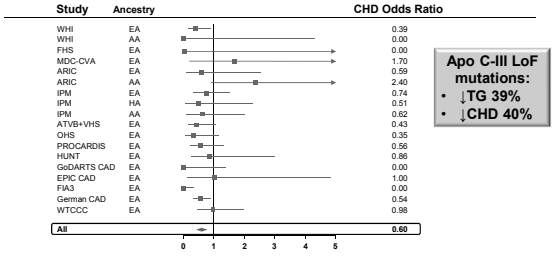




Apo C-III=gene encoding apolipoprotein (apo) C-III.
Data for R19x mutation in Amish population. Pollin TI et al. *Science*. 2008;322:1702-5.

Apo C-III Loss-of-function Mutations Reduce Apo C-III Levels *and* CHD Risk

Odds ratio of CHD of subjects with any of 4 Apo C-III LoF mutations
14 Studies; N= 110,970 participants (34,002 w/ CHD, 76,968 controls)



Apo C-III LoF mutations:
- **↓TG 39%**
- **↓CHD 40%**

AA=African ancestry; EA=European ancestry; HA=Hispanic ancestry; LoF=loss of function.
The TG and HDL Working Group of the Exome Sequencing Project, NHLBI. *New Eng J Med*. 2014;371:22-31.

Summary

- TG-rich particles promote atherogenesis through several mechanisms
- High LDL/low TG = Low LDL/high TG
- The LDL hypothesis is not challenged by the knowledge that other Apo B-containing lipoproteins also participate in atherogenesis

Case: 56-yo African American Woman with HTG and T2DM, No Prior CHD Events

Meds:

Atorvastatin 40 mg/d, metformin 500 mg BID, HCTZ 50 mg/d

Exam:

BMI=33 kg/m^2, BP=138/92 mm Hg, Waist=36", Non-smoker

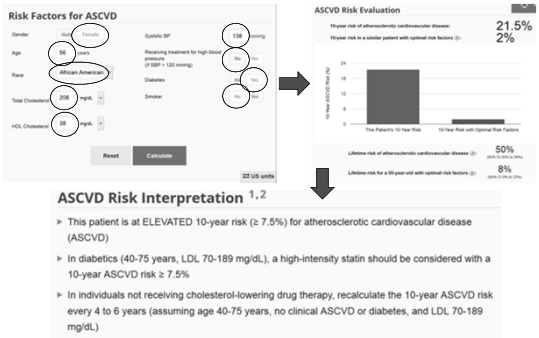
Labs:

Fasting glucose	115 mg/dL
A1c	6.2%
TC	208 mg/dL
TG	559 mg/dL
HDL-C	38 mg/dL
LDL-C	108 mg/dL
Non-HDL-C	170 mg/dL

How high is her CVD risk? ?

1. Low
2. Moderate
3. High
4. Very high

Case 1: ASCVD 10-Year Risk Evaluation



ACC/AHA 2013 Prevention Guidelines CV Risk Calculator. http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx.
1. Goff DC Jr et al. *Circulation*. 2014;129(25 Suppl 2):S49-S73. 2. Stone NJ et al. *Circulation*. 2014;129(25 Suppl 2):S1-45.

Which result is most concerning to you? ?

1.	BP	138/92 mm Hg
2.	BMI	33 kg/m^2
3.	Fasting glucose	115 mg/dL
4.	A1c	6.2%
5.	TC	208 mg/dL
6.	TG	559 mg/dL
7.	HDL-C	38 mg/dL
8.	LDL-C	108 mg/dL
9.	Non-HDL-C	170 mg/dL

Current Guidelines/Recommendations for Treatment of Moderate Hypertriglyceridemia

Guideline	Classification (mg/dL)	Recommendation
ACC/AHA 2013	Not addressed	Refer to AHA 2011
AHA 2011[1]	<100 (optimal)[1] <150 (normal)	• Emphasized lifestyle modification • No recommendations for pharmacotherapy in TG <500 mg/dL
NLA 2014[2]	150–199 (borderline) 200–499 (high) ≥500 (very high)	• Elevated TG not a primary target of therapy unless very high (>500 mg/dL) • For TG 200-499, statin 1st-line therapy. When non-HDL-C goals* not achieved: Fibrates, high-dose (2-4 g/d) omega-3 FA or niacin.

1. Miller M et al. *Circulation*. 2011;123:2292-333. 2. Jacobson TA et al. *J Clin Lipidol*. 2014;8:473-88.
*Non-HDL-C goals: <130 mg/dL in most patients; <100 mg/dL in very high risk patients.

ACC=American College of Cardiology; AHA= American Heart Association; FA=fatty acid(s); NLA=National Lipid Association.