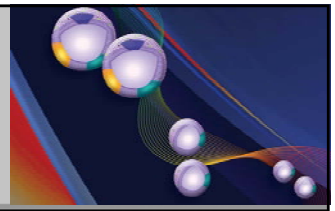
Learning Objectives

- Discuss the etiology, diagnosis (including non-HDL-C), and risk assessment of hypertriglyceridemia (HTG), and the impact of residual CVD risk that remains beyond statin therapy, including patients with HTG
- Summarize the clinical and genetic evidence for the observational and causal association between elevated triglycerides (TG) / TG-rich lipoproteins (TRL) and atherosclerosis
- Apply evidence-based guidelines to lifestyle and therapeutic approaches for managing patients with elevated non-HDL-C and HTG
- Describe the anti-atherosclerotic / anti-inflammatory properties of TG-lowering agents, with a focus on prescription omega-3 fatty acids (FA), and biologic/clinical characteristics of EPA and DHA
- Relate the current status and recommendations on omega-3 FA dietary supplementation
- Increase competency to formulate an action plan for managing elevated non-HDL-C and HTG, taking into account overall therapeutic value to achieve individualized patient goals

Atherogenic Lipids and Cardiovascular Disease



Peter Libby, MD
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Brigham and Women's Hospital
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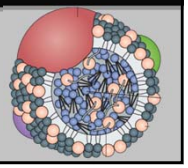
Boston, MA

Introduction to Triglyceride-rich Lipoproteins



56-yo Hispanic Woman with T2DM but No Prior CVD Events

Meds: Atorvastatin 40 mg/d, metformin 1000 mg BID, HCTZ 50 mg/d
Exam: BMI=34 kg/m^2, BP=128/82 mm Hg, Waist=36", Non-smoker
Labs:

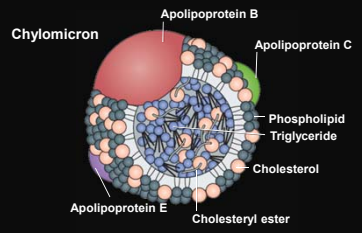
Fasting glucose	115 mg/dL
A1c	6.2%
TC	208 mg/dL
TG	559 mg/dL
HDL-C	36 mg/dL
LDL-C	88 mg/dL
Non-HDL-C	172 mg/dL

These are all "pro-atherogenic" levels

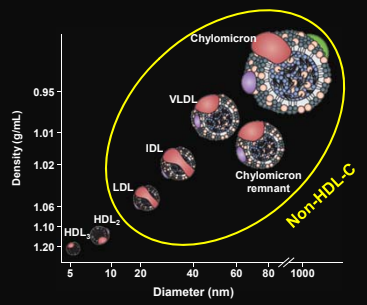
A1c=glycosylated hemoglobin; BMI=body mass index; BP=blood pressure; CHD=coronary heart disease; HTG=hypertriglyceridemia; T2DM=type 2 diabetes mellitus; TC=total cholesterol.

Human Serum Lipoproteins

Structural components of lipoproteins

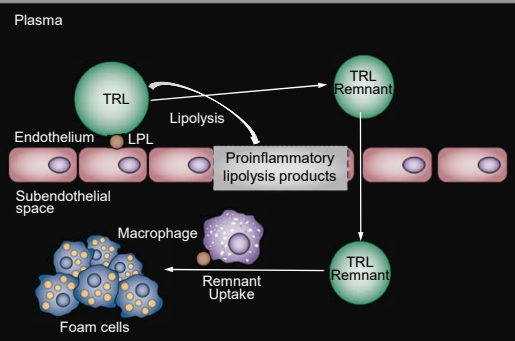


Relation of diameter to density



Genest J, Libby P. Lipoprotein Disorders and Cardiovascular Disease. Braunwald's Heart Disease: A textbook of cardiovascular medicine, 10th edition. Elsevier 2014.

Proposed Mechanisms for the Atherogenicity of TG-rich Lipoproteins[1-4]

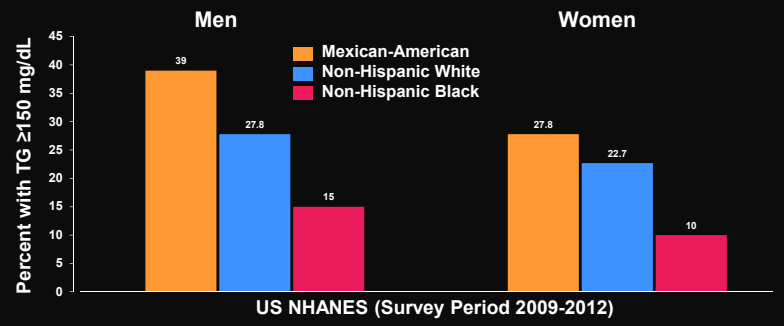


Atherogenic actions

- ↑Adhesion molecules
- Inflammation
- Oxidative stress
- Thrombosis
- Coagulation
- Endothelial dysfunction
- ↑Endothelial permeability

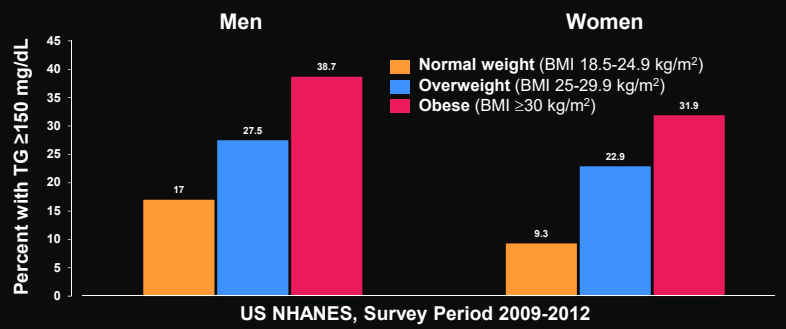
1. Watts GF et al. *Nat Rev Cardiol*. 2013;10:648-61. 2. Wang L et al. *J Lipid Res*. 2009;50:204-13.
3. Takahashi M et al. *J Lipid Res*. 2013;54:1124-34. 4. Miller M et al. *Circulation*. 2011;123:2292-333.
LPL=lipoprotein lipase; TRL=TG-rich lipoprotein. Adapted from Watts GF et al. *Nat Rev Cardiol*. 2013;10:648-61.

Elevated TG (≥150 mg/dL) Is More Common in Men and Mexican-Americans and 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

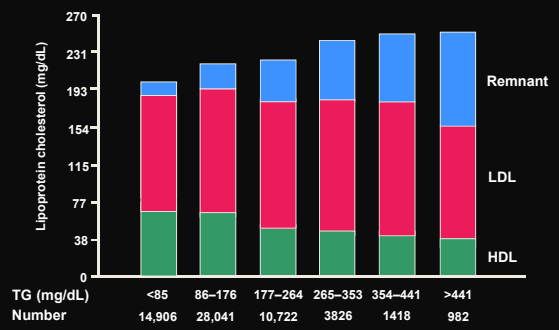


Carroll MD et al. NCHS Data Brief, No 198. National Center for Health Statistics. 2015.

Syllabi/slides for this program are a supplement to the live CME session and are not intended for other purposes.

The Higher the TG Level, the Greater the Amount of Cholesterol Is Due to Remnants

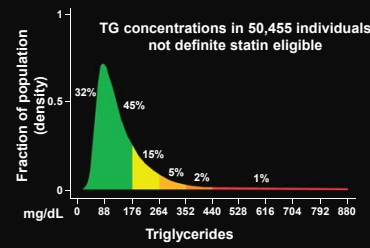
Lipoprotein cholesterol levels of nonfasting TG among 72,000 Danish participants not on lipid-lowering therapy



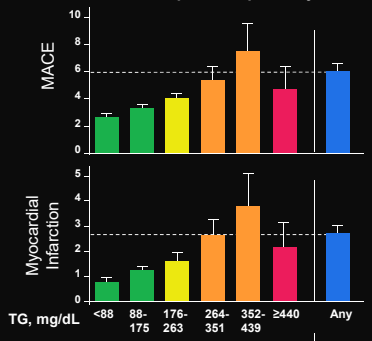
Varbo A et al. *J Am Coll Cardiol.* 2013;61:427-36.

Elevated TG Concentrations in Non-statin-treated Patients Associated with MACE and Myocardial Infarction

Copenhagen General Population Study



Incidence rate per 1000 person-years

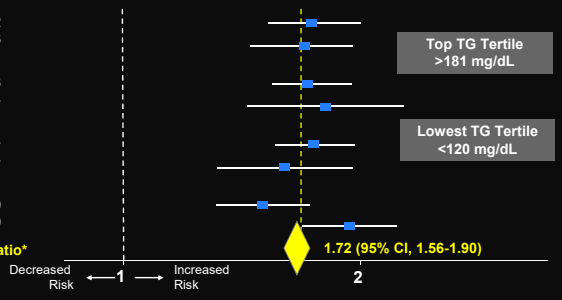


MACE=major adverse CV event (CV death, non-fatal MI, unstable angina pectoris, & stroke). Madsen CM et al. *Eur Heart J.* 2017;Nov 22 [Epub ahead of print].

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

Groups	CHD Cases
Duration of Follow-up	
≥10 years	5902
<10 years	4256
Sex	
Male	7728
Female	1994
Fasting Status	
Fasting	7484
Nonfasting	2674
Adjusted for HDL-C	
Yes	4469
No	5689
Overall CHD Risk Ratio*	

CHD Risk Ratio: Top vs Bottom Tertile* (95% CI)

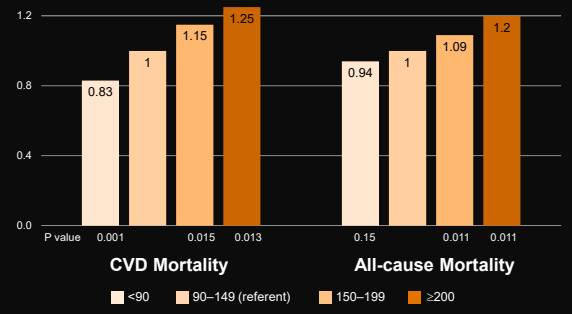


*Individuals in top vs bottom third of usual log-TG values, adjusted for at least age, sex, smoking status, lipid concentrations, and (in most studies) blood pressure. CI=confidence interval. Sarwar N et al. *Circulation.* 2007;115:450-8.

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

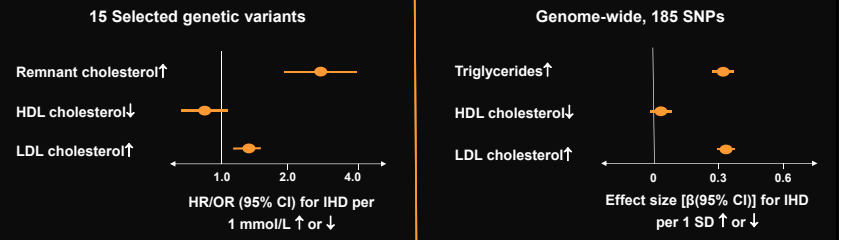
- 33 studies on CVD mortality
  - 17,018 CVD deaths among 726,030 subjects
- 38 studies on all-cause mortality
  - 58,419 all-cause deaths among 330,566 subjects

Relative Risk by TG quartile (mg/dL)



Median duration of study follow-up was 12.0 years. Liu J et al. *Lipids Health Dis.* 2013;12:159-69.

Mendelian Randomization Studies Show Elevated LDL-C and TG, but *not* HDL-C, Are Causally Associated with ASCVD



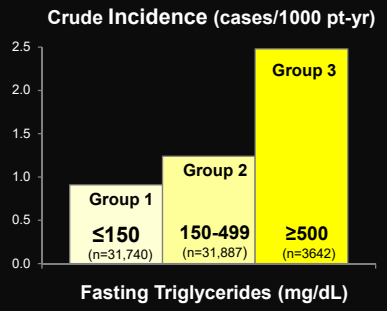
N=66,000 (12,000 IHD)
Varbo A et al. *J Am Coll Cardiol.* 2013;61:427-36.

N=87,000 (22,000 IHD)
Do R et al. *Nat Genet.* 2013;45:1345-52.

ASCVD=atherosclerotic CV disease; HR=hazard ratio; IHD=ischemic heart disease; OR=odds ratio; SD=standard deviation; SNP=single nucleotide polymorphism.
Nordestgaard BG. *Circ Res*. 2016;118:547-63.

TG ≥500 mg/dL Is Associated with Greatly Increased Pancreatitis Risk

Risk of incident pancreatitis ↑ by 4% for every 100-mg/dL ↑ in TG concentration*



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

High TG Levels Are Often Associated with Other Heart Disease Risk Factors

Besides iatrogenic causes and co-morbidities, common risk factors include

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

The "Atherogenic Triad" in diabetes:
- ↑ Triglyceride-rich lipoproteins (TRLs)
- ↑ Small dense LDL-C
- ↓ HDL-C

Be more aggressive as the risk level increases

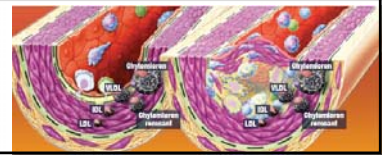
American Heart Association (AHA) Scientific Statement. Miller M et al. *Circulation*. 2011;123:2292-333.

2014 National Lipid Association (2011 AHA) Classification of TG Levels

Fasting Triglycerides (mg/dL)	
<100	Optimal
<150	Normal
150–199	Borderline high
200–499	High
≥500	Very high

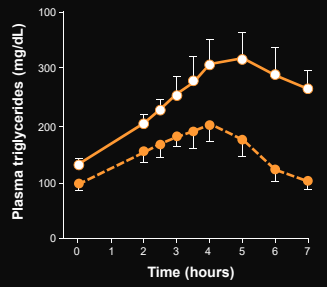
Jacobson TA et al. *J Clin Lipidol*. 2014;8:473-88. Miller M et al. *Circulation*. 2011;123:2292-333.

Fasting and Non-Fasting TG



Fasting Levels of Triglycerides Do Not Reflect True Exposure

Serial changes and plasma triglycerides following an oral fat load



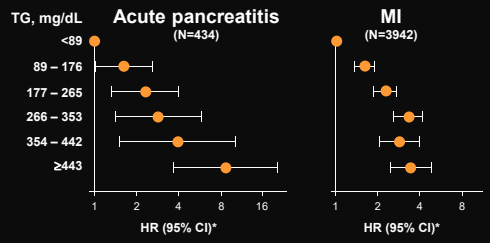
Following an oral fat load, TG levels change dramatically over a 7-hour period in normal subjects and those with hyperapobetalipoproteinemia

- Patients with hyperapobetalipoproteinemia
- Normal patients

Genest J et al. *Arteriosclerosis*. 1986;6:297-304.

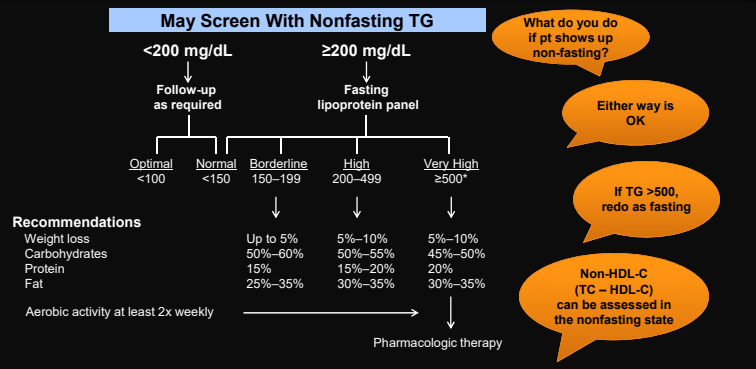
Nonfasting Mild-to-moderate HTG and Risk of Acute Pancreatitis and MI

N=116,550 Individuals from the general population



*Multivariable adjusted for age, sex, education, smoking, hypertension, statin use, birth year, and study cohort.
HTG=hypertriglyceridemia; MI=myocardial infarction; TG=triglyceride(s). Pederson SB et al. *JAMA Intern Med*. 2016;176:1834-42.

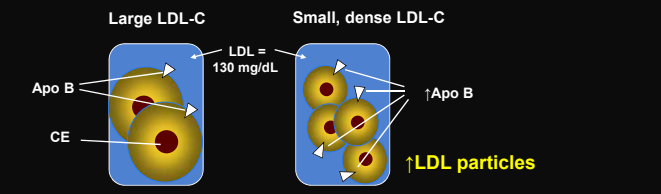
No Fasting Required: Practical Algorithm for Screening and Managing Elevated TG



Miller M et al. *Circulation*. 2011;123:2292-333. Nordestgaard BG et al. *Eur Heart J*. 2016;37:1944-58.

About Non-HDL-C

In HTG Subjects, LDL-C Measurements Underestimate CVD Risk

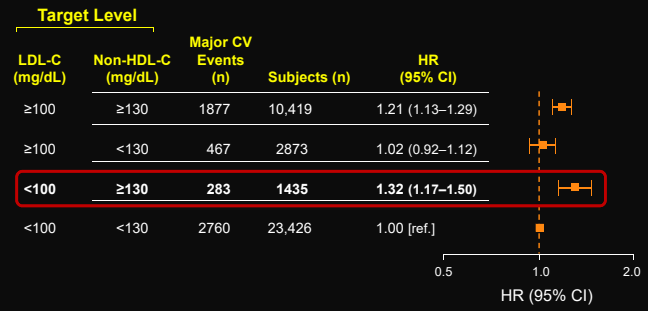


Fasting Lipid Panel:		Fasting Lipid Panel:		
TC	198 mg/dL	TC	210 mg/dL	
LDL-C	130 mg/dL ↔	LDL-C	130 mg/dL	
TG	90 mg/dL	TG	250 mg/dL	
HDL-C	50 mg/dL	HDL-C	30 mg/dL	↓HDL-C
Non-HDL-C	148 mg/dL	Non-HDL-C	180 mg/dL	↑Non-HDL-C

Otvos JD et al. *Am J Cardiol*. 2002;90:22i-29i.

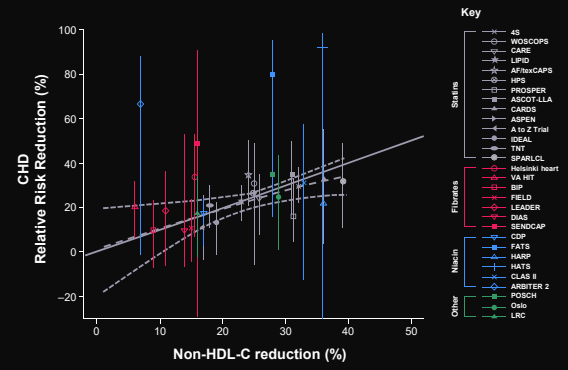
Non-HDL-C ≥130 mg/dL Is a Better ASCVD Risk Predictor than LDL-C >100 mg/dL

N=62,154



Meta-analysis data at baseline and at 1-year follow-up; 8 randomized controlled statin trials published 1994-2008. Boekholdt M et al. *JAMA*. 2012;307:1302-9.

Direct, Consistent Relationship between Magnitude of Non-HDL-C Lowering and CV Risk Reduction

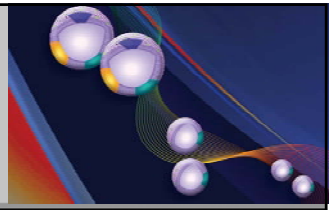


Robinson JG et al. *J Am Coll Cardiol.* 2009;53:316-22.

Summary

- Elevated TG levels are common in US population, especially in obese, male, Mexican-American, and those with diabetes
- Remnants of TG-rich lipoproteins (chylomicron remnants, smaller VLDL, IDL) promote atherogenesis
- Non-HDL-C is a better predictor of CVD than LDL-C, especially in patients with HTG
- Very high TGs are associated with increased risk for pancreatitis

Practical Approach to the Management of Atherogenic Lipids



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Professor of Medicine
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AACE 2017 Lipid Treatment Goals

Atherosclerotic CVD Risk Categories and LDL-C Treatment Goals

		Treatment goals		
Risk category	**Risk factors/10-year risk**	**LDL-C (mg/dL)**	**Non-HDL-C (mg/dL)**	**Apo B (mg/dL)**
Extreme risk	• Progressive ASCVD, including unstable angina in patients after achieving an LDL-C <70 mg/dL • Established clinical CVD in patients with DM, CKD 3/4, or HeFH • History of premature ASCVD (<55 male, <65 female)	<55	<80	<70
Very high risk	• Established or recent hospitalization for ACS, coronary, carotid or peripheral vascular disease, 10-year risk >20% • Diabetes or CKD 3/4 with ≥1 risk factor(s) • HeFH	<70	<100	<80
High risk	• ≥2 risk factors and 10-year risk 10%-20% • Diabetes or CKD 3/4 with no other risk factors	<100	<130	<90
Moderate risk	• ≤2 risk factors and 10-year risk <10%	<100	<130	<90
Low risk	• 0 risk factors	<130	<160	NR

NR=not recommended. Garber AJ et al. *Endocr Pract.* 2017;23:207-38.

Treating Underlying Factors of HTG

- History of nutrition (calories, fat, sugar, alcohol, body weight and weight changes) and physical activity (frequency, type, intensity)
- Measure BMI & waist, TSH, fasting glucose A1c, urinary protein
- Prescribe low-calorie, low-sugar, low-to-no alcohol, and low-fat diet. Recommend patient-appropriate physical activity plan.
- Treat underlying diseases causing HTG (eg, hypothyroidism)
- Determine whether changes of TG-raising medications or supplements are needed

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

NLA: Targets of Therapy – Triglycerides

Elevated TG level: Not a target of therapy, except when very high (≥500 mg/dL)

- TG 200–499 mg/dL: Targets of therapy:
  - Non-HDL-C
  - LDL-C
- TG ≥500 mg/dL (especially ≥1000 mg/dL): Primary goal of therapy (to prevent pancreatitis): ↓ TG concentration to <500 mg/dL

NLA=National Lipid Association. Jacobson TA et al. *J Clin Lipidol*. 2014;8:473-88.

Lifestyle Approaches to the Management of HTG

Lifestyle and Diet Can Have Big Effects on Hypertriglyceridemia

Diet / Lifestyle Change	
Weight loss in overweight or obese individuals (5–10%)	**20% - 50% reduction in TG is 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: 1st & most notable effect of ↑physical activity on lipid profile**
  Exercise may ↓TG even without weight loss
  - Sustained 3%–5% weight ↓ may cause clinically meaningful ↓TG
  - Degree of TG-lowering is proportional to baseline TG
- **↑HDL-C: Requires stable weight loss ± extensive physical activity**
  - ~700–2000 kcal/week (~30 min/day, moderate intensity)
- **LDL-C usually does not change**
  - But ↓weight ± ↑exercise should ↑ particle size and may ↓LDL-C levels

Adapted from 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(25 Pt B):2985-3023.

Diets Rich in Marine Sources of EPA and DHA Have Less Coronary Disease

	EPA+DHA (mg/100 g)
Anchovy	2055
Herring, Atlantic	2014
Salmon, farmed	1966
Salmon, wild	1840
Mackerel, Atlantic	1203
Bluefish	988
Sardines, Atlantic	982
Trout	936
Goldenbass (tilefish)	905
Swordfish	899
Tuna, white (albacore)	862
Mussels	782
Striped bass	754
Shark	689
Pollock, Atlantic	542

Nurses' Health Study
- 1,086,261 person-years of follow-up
- 574 incident strokes documented

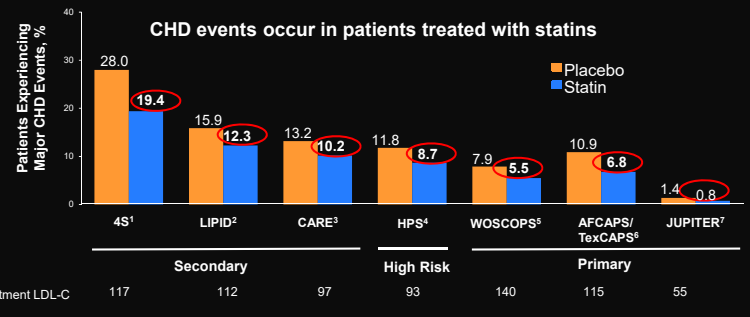
# Marine-based Meals	Stroke Reduced Risk
1–3 per month	7%
1 per week	22%
2–4 per week	27%
>5 per week	52%

Iso H et al. *JAMA*. 2001:285:304-12.

Mozaffarian D, Wu JHY. *J Nutr*. 2012;142:614S-625S. Data from the USDA National Nutrition Database for Standard Reference Release 23, 2010.

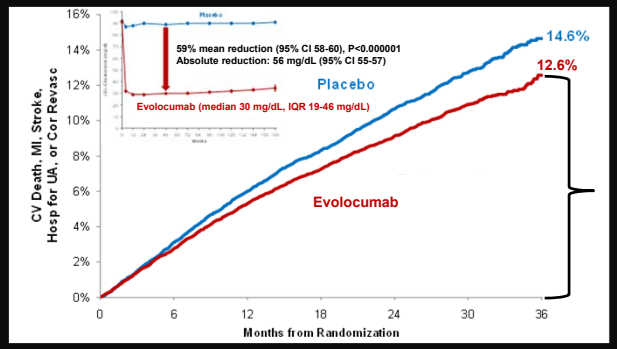
Managing Residual CV Risk

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.

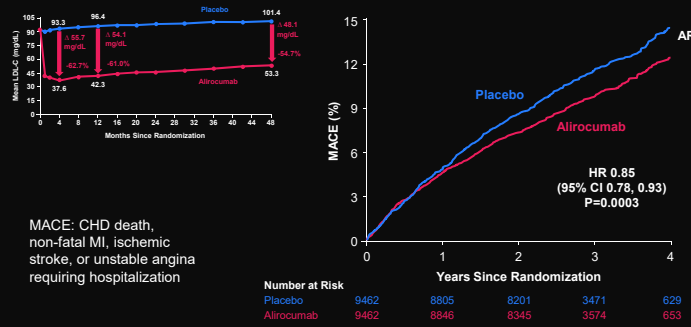
FOURIER: Significant Reduction in CV Events, but Even More Significant Risk Remains



Residual risk despite statin and PCSK9 therapy

Sabatine MS et al. *N Engl J Med*. 2017;376:1713-22.

ODYSSEY OUTCOMES Also Shows Significant Reduction in CV Events, But Significant Risk Remains



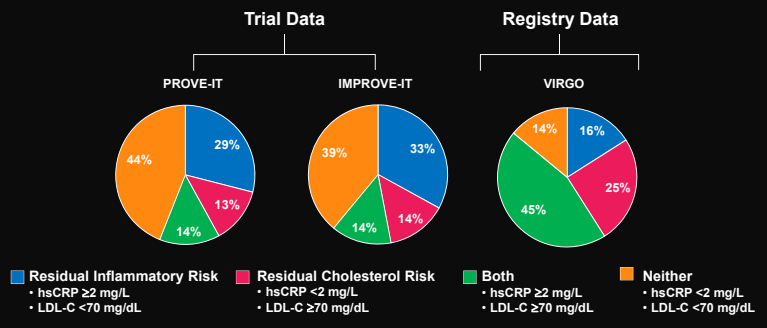
MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

Residual risk despite statin and PCSK9 therapy

*Based on cumulative incidence

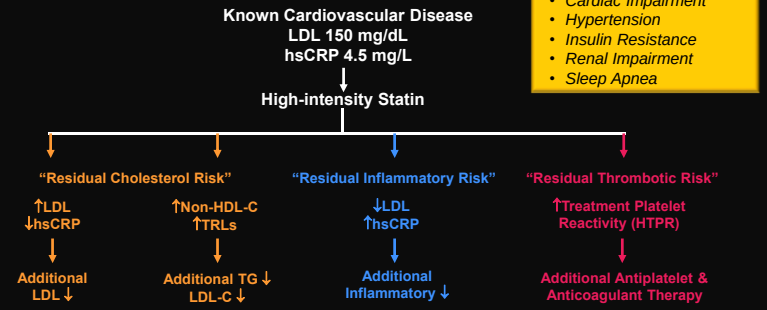
Steg G et al. American College of Cardiology 67th Scientific Sessions March 10, 2018.

Proportion of CAD Patients Taking Statin Therapy Who Have Residual Cholesterol or Inflammatory Risk



hsCRP=high-sensitivity C-reactive protein. IMPROVE-IT=Improved Reduction of Outcomes: Vytorin Efficacy International; PROVE-IT=Pravastatin or Atorvastatin Evaluation and Infection Therapy; US VIRGO Registry=Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients. Ridker PM. *Circ Res*. 2017;120:617-9.

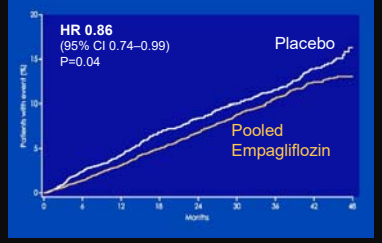
Current Treatment Hypothesis: Tailored Therapy in CAD



Lowering HbA1c Reduces CV Events

EMPA-REG OUTCOME Trial

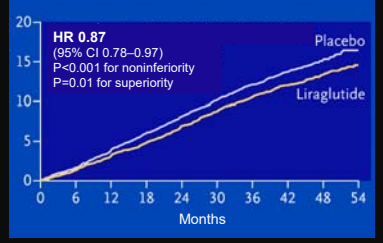
Empagliflozin Trial: Death, Stroke, and MI



Zinman B et al. *N Engl J Med.* 2015;373:2117-28.

LEADER Trial

Liraglutide Trial: Death, Stroke, and MI



Marso SP et al. *N Engl J Med.* 2016;375:311-22.

Working Towards a Pragmatic Approach to Reduce Residual CVD Risk

Causes	Threshold	Rx Value	Rx Representative
LDL-C	≥70 mg/dL	*Balance of* • Efficacy • Safety • QoL • Cost	Atorvastatin
HbA1c	≥6.5 mg/dL		Empagliflozin, liraglutide
HsCRP	>2 mg/L		Canakinumab?
Residual thrombotic risk	ACS		Single, dual antiplatelet, rivaroxaban
TG	>150 mg/dL		Statin + EPA

Courtesy of BEAT-HTG Curriculum Planning Meeting. Oct. 4, 2017.

Pharmacologic Management of HTG

Therapy for Very High TG: Current FDA-approved

Drug Class	TG >500 mg/dL*	Notable Adverse Effects (AEs)†
Statins[a]	√	Myalgia, new-onset DM, hyperglycemia
Omega-3 FA (EPA/DHA)[b]	√	Eructation, dyspepsia, taste perversion
Omega-3 FA (EPA only)[b]	√	Arthralgia
Fenofibrate[c]	√	Abnormal liver function test, myalgia, increased creatinine, nausea
Extended-release niacin[d]	√	Flushing, nausea, diarrhea, vomiting, cough

New FDA retraction

New FDA retraction

*Data from individual product labeling for each drug in patients with very high TG. †AEs: Incidence >Placebo and: ≥3% for omega-3/EPA/DHA; ≥2% for omega-3/EPA, Fenofibrate, Statins; ≥5% for Niacin. [a]Atorvastatin, rosuvastatin, simvastatin. [b]4 g per day. [c]145 mg per day. [d]2 g per day.
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;104:3046-51. CTT Collaborators. *Lancet*. 2005;366:1267-78. Maki KC et al. *J Clin Lipidol*. 2012;6:413-26.

Fibrate Outcome Studies with Statin Use

Study	CV Risk Profile	N	Daily Intervention	Statin Use	Baseline TG Level	Effect on TG Level	Primary Outcome	Primary Outcome Results
ACCORD	• T2DM • 40-79 yrs + CVD or • 55-79 yrs + ≥2 CV risk factors	5518	Fenofibrate	Open-label simvastatin (mean dose: 22 mg)	162 mg/dL (median)	–26%	• Nonfatal MI or Stroke or • CV death • Mean f/u: 4.7 yrs	• HR=0.92 • P=0.32 • ARR=NC
FIELD	50-75 yrs + T2DM	9795	Micronized fenofibrate 200 mg QD	Added during study in 2547 pts	154 mg/dL (median)	–30% at 1 year	• Nonfatal MI or • CHD death • Median f/u: 5 yrs	• HR=0.89 • P=0.16 • ARR=1.4%

Total Trial Population

Subjects without Dyslipidemia

Study (treatment)	OR (95% CI)
ACCORD (simvastatin + fenofibrate)	
FIELD (fenofibrate)	

Post hoc: TG≥204 mg/dL; HDL-C ≤34 md/dL

Subjects with Dyslipidemia

Study (treatment)	OR (95% CI)
ACCORD (simvastatin + fenofibrate)	
FIELD (fenofibrate)	

ARR=absolute risk reduction; NC=not calculated. Adapted from Handelsman Y, Shapiro MD. *Endocr Pract*. 2017;23:100-12. Sacks FM et al. *N Engl J Med*. 2010;363:692-4.

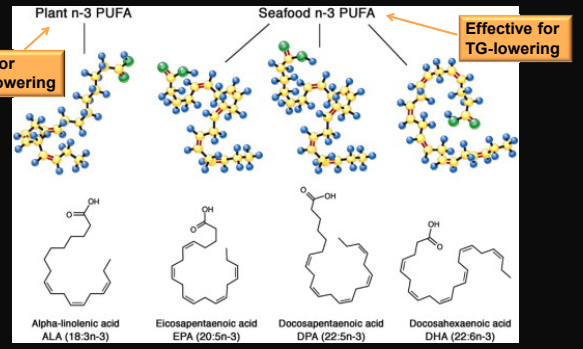
FDA withdraws Approval of Niaspan ER and Fenofibric Acid DR in Combination with Statins

On April 18th 2016, the FDA announced retraction of prior approvals related to combinations of statins with niacin extended release (ER) and statins with fenofibric acid delayed release (DR).[1]

Besides being difficult to use, niacin causes a moderate increase in new-onset diabetes, making its use less desirable.[2]

1. http://www.pbm.va.gov/PBM/linksotherresources/ezminutes/docs/Statins_Niacin_or_Fibrates_EZ_Minutes_submission_5_2016.pdf
2. Goldie C et al. *Heart*. 2016;102:198-203.

Omega-3 Fatty Acid Molecular Structure



ALA has poor conversion to EPA (0.3-8% and DHA <1%) in humans[1]

1. Arterburn LM et al. *Am J Clin Nutr*. 2006;83:1467S-76S. Graphic from Mozaffarian D, Wu JH. *J Am Coll Cardiol*. 2011;58:2047-67.

Reported Clinical and Biologic CV Benefits of Omega-3 FA

Anti-arrhythmic
- ↓Sudden death (GISSI-P *only*)
- ↓AF
- ↓Protection against ventricular arrhythmias (vs ↑)
- Heart rate variability improvement

Anti-atherogenic
- ↓Non-HDL-C
- ↓TG and ↓VLDL-C
- ↓Chylomicrons
- ↓VLDL and ↓Chylomicron remnants
- ↑HDL-C levels (vs ↓ w/ EPA-only)
- ↑LDL and HDL particle size
- Plaque stabilization

Antithrombotic
- ↓Platelet aggregation
- ↑Blood rheologic flow

Anti-inflammatory and endothelial protective effects
- ↓Endothelial adhesion molecules
- ↓Leukocyte adhesion receptor expression
- ↓Proinflammatory eicosanoids
- ↓Proinflammatory leukotrienes
- Vasodilation

↓Systolic and diastolic BP

AF=atrial fibrillation; CV=cardiovascular; FA=fatty acid(s).
After Nelson JR et al. *Vascul Pharmacol.* 2017;91:1-9. *After* Bays HE. Chapter 21. *The John Hopkins Textbook of Dyslipidemia*, by Peter O Kwiterovich, 2010; 245-57.

Prescription Omega-3 Fatty Acid Formulations

	EPA+DHA EE[1,2]	EPA only EE[3]	EPA+DHA FFA[4]
Brand Name	*Lovaza*	*Vascepa*	*Epanova (not yet available)*
Generic Available?	Yes[5]	No	No
Indication	Adjunct to diet to ↓TG levels in adult patients with severe HTG (≥500 mg/dL)		
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/ food or • 4 QD w/ food[2]	• 2 BID w/ food	• 2 or 4 QD, meal independent

1. Lovaza PI, generics available. 2. Omtryg PI. 3. Vascepa PI. 4. Epanova PI. 5. Generic and Lovaza cost the same. EE=ethyl ester; FFA=free FA; PI=prescribing information. Sperling LS, Nelson JR. *Curr Med Res Opin*. 2016;32:301-11.

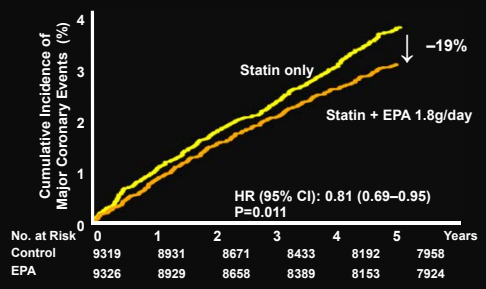
Similarities and Differences of Prescription Omega-3 Fatty Acid Formulations

	EPA+DHA EE[1,2]	EPA only EE[3]	EPA+DHA FFA[4]
Brand Name	Lovaza	Vascepa	Epanova
Lowers TG	Yes	Yes	Yes
Lowers non-HDL-C	**Yes**	**Yes**	**Yes**
Raises LDL-C	Yes	No	Yes

Not available now

1. Lovaza prescribing information, generics available. 2. Omtryg prescribing information. 3. Vascepa prescribing information. 4. Epanova prescribing information. Sperling LS, Nelson JR. *Curr Med Res Opin*. 2016;32:301-11.

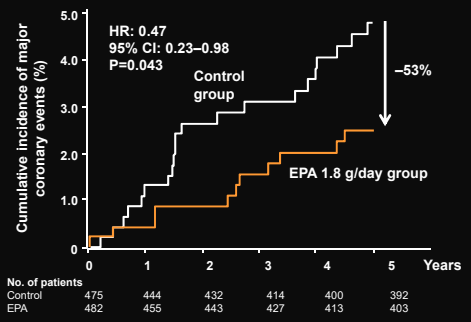
JELIS: EPA Reduced Major Coronary Events* in Hypercholesterolemic Patients on Statins



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*

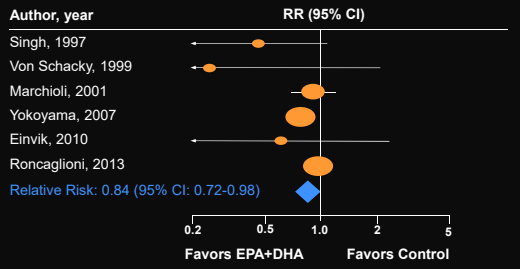


HR and P-value adjusted for age, gender, smoking, diabetes, and HTN

*Pre-specified. Saito Y et al. *Atherosclerosis*. 2008;200:135-40.

Randomized Controlled Trials and Prospective Cohort Studies of EPA+DHA and CHD Risk

Subjects with baseline TG levels >150 mg/dL

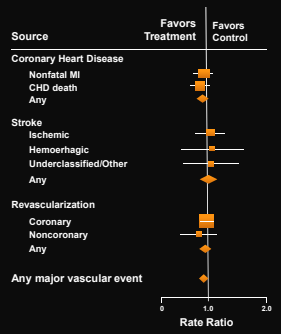


Alexander DD et al. *Mayo Clin Proc*. 2017;92:15-29.

Confusing Meta-analysis Data on OM-3 Benefit Could Be Due to Dosing and Dietary Supplement Use

"… omega-3 fatty acids had no significant association with fatal or nonfatal coronary heart disease or any major vascular events."

Study (Year)	EPA/DHA Dose (mg/d)	EPA / DHA Source
DOIT (2010)	1150 / 800	Dietary supplement
AREDS-2 (2014)	650 / 350	Dietary supplement
SU.FOL.OM3 (2010)	400 / 200	Dietary supplement
JELIS (2007)	1800 / NA	Pure EPA Rx
Alpha Omega (2010)	226 / 150	Margarine with dietary supplement
OMEGA (2010)	460 / 380	Rx EPA/DHA
R&P (2013)	500 / 500	Rx EPA/DHA
GISSI-HF (2008)	850 / 950	Rx EPA/DHA
ORIGIN (2012)	465 / 375	Rx EPA/DHA
GISSI-P (1999)	850 / 1700	Rx EPA/DHA



Aung T et al. *JAMA Cardiol*. 2018;3:225-34.

CV Outcomes Trials in Patients with HTG

	REDUCE-IT*	STRENGTH*	PROMINENT*
Agent Dose	EPA (EE) 4 g/d	EPA+DHA (FFA) 4 g/d	SPPARMα – Pemafibrate 0.2 mg bid
N	~8000	Estimated 13,000	Estimated 10,000
Age	≥45 years	≥18 years	≥18 years
Risk Profile	CVD (70%) or ↑CVD risk (30%)	CVD (50%) or ↑CVD risk (50%)	T2DM only CVD (2/3) or ↑CVD risk (1/3)
Follow-up	4–6 years (planned)	3–5 years (planned)	5 years (planned)
Statin Use	100% (at LDL-C goal)	100% (at LDL-C goal)	Moderate- / high-intensity or LDL <70 mg/dL
Primary Endpoint	Expanded MACE	Expanded MACE	Expanded MACE
Entry TG Entry HDL-C	200–499 mg/dL N/A	200–499 mg/dL <40 mg/dL M, <45 mg/dL W	200–499 mg/dL ≤40 mg/dL

*Locations: International sites; Statistics: Powered for 15% RRR.

http://www.clinicaltrials.gov; REDUCE-IT: NCT01492361; STRENGTH: NCT02104817; PROMINENT: NCT03071692.

Low-Moderate Dose Omega-3 FA CV Outcomes Trials

	VITAL Q2 2018	ASCEND Q2 2018	RESPECT-EPA Q4 2019
Funding	NIH funding	British Heart Foundation	Japan Heart Foundation
Study	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled	Randomized, open-label
Patient Population	US adults (no elevated cancer or CVD risk)	Patients with diabetes, no initial CV event	Statin-treated patients with CAD
Treatments	Vitamin D 2000 IU/d Omacor (Lovaza) 1 g/d	Aspirin 100 mg/d Omacor (Lovaza) 1 g/d	EPA 1800 mg/d + statin Statin alone
N	25,875	15,480	3900
Primary Endpoint	Risk reduction of total cancer and major CVD events (composite endpoint)	Risk reduction for CV events (composite endpoint)	Risk reduction (secondary prevention) for CV events (composite endpoint)

ASCEND: NCT00135226; RESPECT-EPA: UMIN000012069 (https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000002496); VITAL: NCT01169259.

Non-Prescription Omega-3 Fatty Acids

Peter Libby, MD

Dietary Supplement Omega-3 FA Are Popular

- Fish oil: Among the most commonly used dietary supplements by US adults[1]
  - Global sales may reach $3.3 billion by 2020
  - 19 million (8%) took fish oil dietary supplement in previous 30 days[2]
- ***No OTC omega-3*** FA products in US (just Rx & dietary supplements)
- Dietary supplements are unregulated. Their content, integrity and efficacy often remain unverified.[3]

Saturated fatty acid following isolation

1. Barnes PM et al. National Health Statistics Reports. 2008;12:1-24.
2. NIH NCCIH. Available at: https://nccih.nih.gov/health/omega3/introduction.htm
3. Mason RP, Sherratt SC. *Biochem Biophys Res Commun*. 2017;483:425-9.

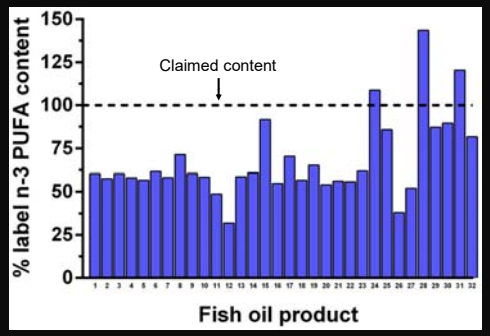
Prescription vs Dietary Supplement Omega-3 FA

	Prescriptions		Dietary Supplements
	EPA	EPA +DHA	
FDA classification	Drug	Drug	Food
FDA approval	Yes	Yes	No
Ingredients	EPA	EPA + DHA	Variable EPA + DHA (vs few 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 (or >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)

AHA recommendation before Rx available

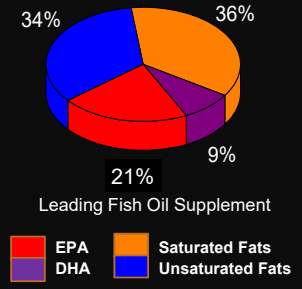
HCP=health care provider.

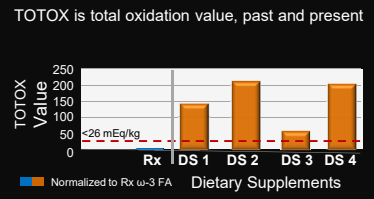
Fish Oil Supplement Claims are Inaccurate and Overstate Actual Content



Albert BB et al. *Sci Rep*. 2015;5:7928

Fatty Acid Content and TOTOX of Leading Fish Supplements





Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483 :425-429. Mason RP et al. Poster presented at the AMCP 2015 Nexus. Orlando, FL.

Summary of Fish Oil Dietary Supplements: Right for CV Patients?

FDA Product Classification[1] → Food

Clinical Trials/FDA Pre-Approval[1] → Not Required

Content & Purity[2-9]
- Difficult to achieve AHA recommended OM3 levels
- Contain high levels of saturated fats linked to dyslipidemia
- Advertised omega-3 content overstated
- Contain oxidized lipids leading to dyslipidemia and increased CV risk
- Contain PCBs and dioxins at levels known to be harmful for humans

1. US Food and Drug Administration. www.fda.gov/Food/DietarySupplements/default.htm. Updated April 4, 2016. Accessed May 23, 2016; 2. Hilleman D, Smer A. *Manag Care*. 2016;25(1):46-54. 3. Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483 :425-429 .4. Albert BB et al. *Sci Rep*. 2015;5:7928. 5. Albert BB et al. *Sci Rep*. 2015;5:7928. 6. Kleiner AC et al. *J Sci Food Agric*. 2015;95:1260. 7. J.C. Ritter JC et al. *J Sci Food Agric*. 2013:93:1935. 8. Jackowski SA et al. *J Nutr Sci*. 2015;4:30. 9. Rundblad A et al. *British Journal of Nutrition*. 2017; 10.1017:1.

Dietary Supplement Omega-3 not Recommended to Treat Serious Medical Conditions

APhA

"While omega-3 dietary supplements can be an important part of consumer wellness, unlike regulated prescription and OTC drugs, dietary supplements are not required to meet strict FDA drug standards for safety, efficacy, and manufacturing and are not intended to treat serious medical conditions like VHTG. Patients should consult with their doctor about appropriate FDA-approved drug therapy."[1]

ADA Standards of Medical Care in Diabetes – 2017

"Randomized controlled trials also do not support recommending omega-3 supplements for primary or secondary prevention of CVD."[2]

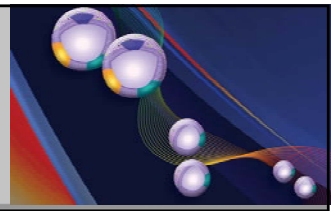
1. Agarwal P. American Pharmacists Association Web site. https://www.pharmacist.com/apha-convenes-stakeholders-appropriate-omega-3-fish-oil-use-vht. Published April 21, 2015.
2. ADA Standards of Medical Care - 2017. *Diabetes Care*. 2017;40(Suppl 1):S1-S135.

Summary

- **Guidelines and Recommendations**
  - Optimal TG level is <100 mg/dL
  - Appropriate nutrition and physical activity in all
  - Medical Rx for very high TG (>500 mg/dL) to help prevent pancreatitis
  - Medical Rx for TG 200–500 mg/dL, consider in high-risk patient on statin (see below)
- **Recommended Medical Rx**
  - Statins (for all high risk with TG 200–500 mg/dL, unless statin-intolerant)
  - Fenofibrate*
  - Omega-3† (no dietary supplements for therapy)
  - Niacin difficult to use and no longer recommended

*HTG/low HDL-C subgroups had ↓CVD—T2DM cohort. †JELIS showed ↓CVD, HTG/low HDL-C subgroup especially positive.

Case Study and Q&A



Christie Ballantyne, MD
Peter Libby, MD

Case: 69-yo Hispanic Woman on Medicare with Insulin Resistance, CHD, HTN, and Moderate HTG

S/P: MI 4 yrs, started on atorvastatin 40 mg/d. Repeat PCI 3 months ago, started on ezetimibe.

Meds: Enalapril 10 mg/d, HCTZ 25 mg/d, atorvastatin 40 mg/d, ASA 81 mg/d, clopidogrel 75 mg/d, ezetimibe 10 mg/d

Exam: BMI=29 kg/m^2, BP=149/86 mm Hg, Waist=41", non-smoker

Labs:

A1c	6.4%	LDL-C	65 mg/dL
Glucose	123 mg/dL	HDL-C	50 mg/dL
TC	168 mg/dL	Non-HDL-C	118 mg/dL
TG	265 mg/dL		

ASA=aspirin; MI=myocardial infarction; PCI=percutaneous coronary intervention.

She now comes to visit you for a F/U, asking:

"What else should I do?"

"Am I still at risk of having heart problems?"

"What about my triglycerides?"