10:00 - 11:15 AM

## Practical Guide to the Management of Atherogenic Lipids

**SPEAKERS**

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## Disclosures

This session is supported by an independent educational grant from **Amarin Pharma Inc.**

**The following relationships exist related to this presentation:**

- Michael Miller, MD: Advisory Board for Akcea Therapeutics, Inc. Consultant for Amarin Pharma Inc.
- James A. Underberg, MS, MD, FACP, FNLA: Advisory Board for Akcea Therapeutics, Inc.; Alexion Pharmaceuticals, Inc.; Amgen Inc.; Invitae Corporation; Regeneron Pharmaceuticals, Inc.; and Sanofi US. Consultant for Amarin Pharma Inc. and Amgen Inc. Contracted Research for Aegerion Pharmaceuticals and Pfizer Inc. Speaker's Bureau for Alexion Pharmaceuticals, Inc.; Amarin Pharma Inc.; Amgen Inc.; Regeneron Pharmaceuticals, Inc.; Sanofi US; and True Health Diagnostics.

**Off-Label/Investigational Discussion**

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Boston, MA
December 6, 2018

## *Practical Guide to the Management of Atherogenic Lipids*

## Atherogenic Lipids and Cardiovascular Disease

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University of Maryland Medical Center
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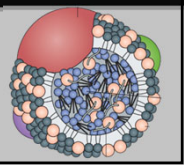
# Introduction to Triglyceride-rich Lipoproteins



## 56-yo Hispanic Woman with T2DM and No CVD

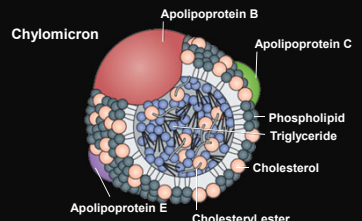
**Meds:** Atorvastatin 40 mg/d, metformin 1000 mg BID, HCTZ 50 mg/d
**Exam:** BMI=34 kg/m$^2$, BP=128/82 mm Hg, Waist=36", Non-smoker
**Labs:**

| | |
|---|---|
| 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 |

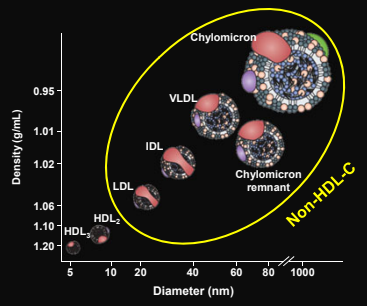
A1c=glycosylated hemoglobin; BMI=body mass index; BP=blood pressure; CHD=coronary heart disease; HTG=hypertriglyceridemia; T2DM=type 2 diabetes mellitus; TC=total cholesterol.

## Human Serum Lipoproteins

### Structural components of lipoproteins

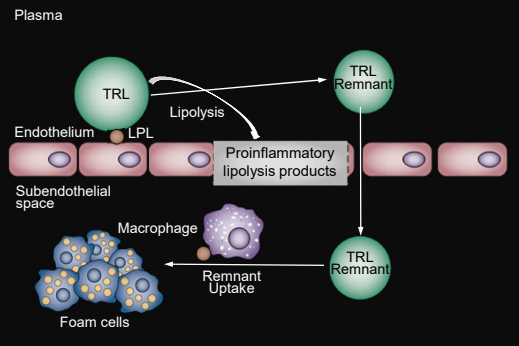



### Relation of diameter to density




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

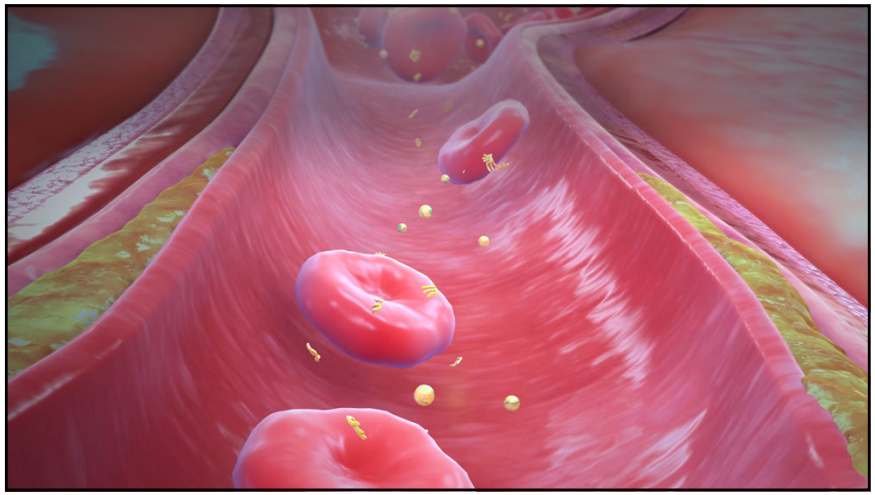
## Proposed Mechanisms for the Atherogenicity of TG-rich Lipoproteins[1-4]

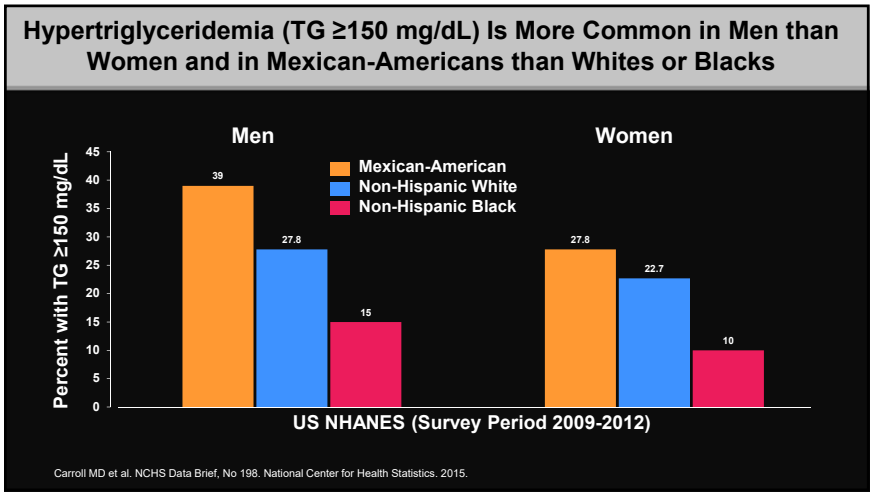


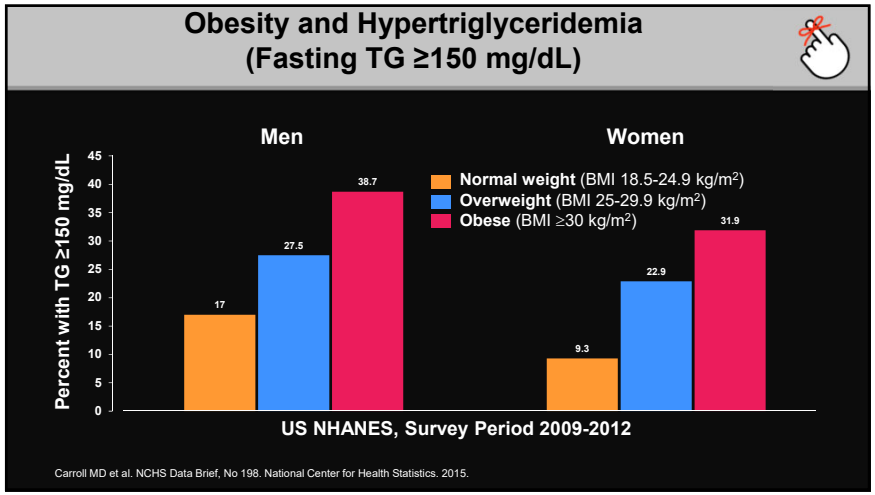

**Atherogenic actions**

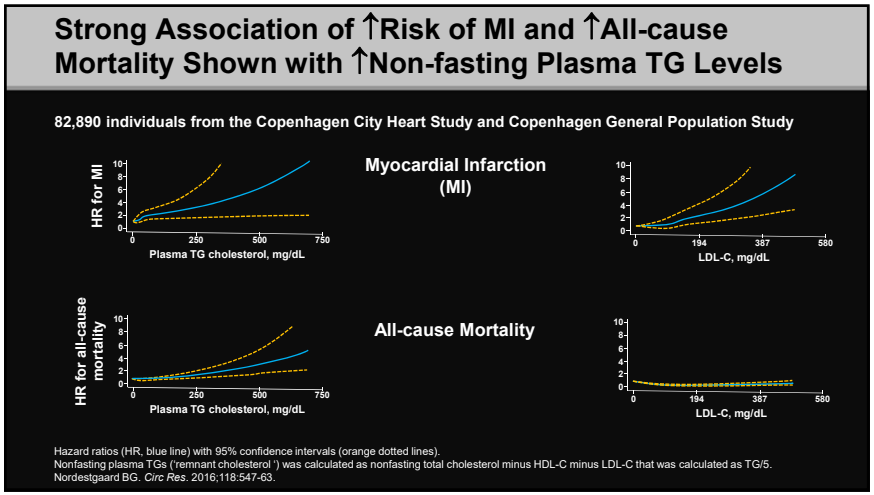
- ↑Adhesion molecules
- Inflammation
- Oxidative stress
- Thrombosis
- Coagulation
- Endothelial dysfunction
- ↑Endothelial permeability

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.



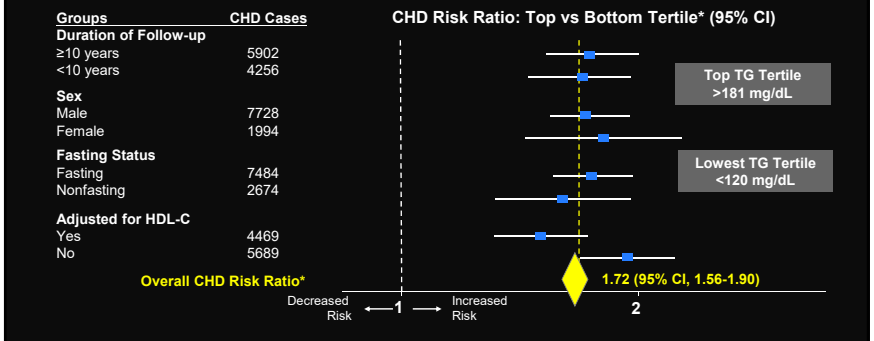



Syllabi/Slides for this program are a supplement to the live CME session and are not intended for other purposes.

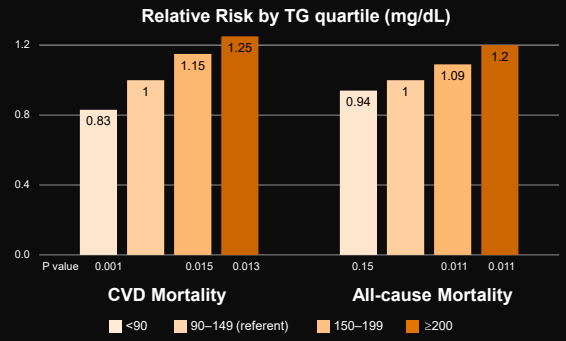
## TG Predicts CHD
### (Meta-Analysis of 29 Studies; N=262,525)




*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. CI=confidence interval. Sarwar N et al. *Circulation*. 2007;115:450-8.

## Plasma TG Levels Predict CVD and Total Mortality
### (Meta-analysis of studies including >1 million subjects)

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



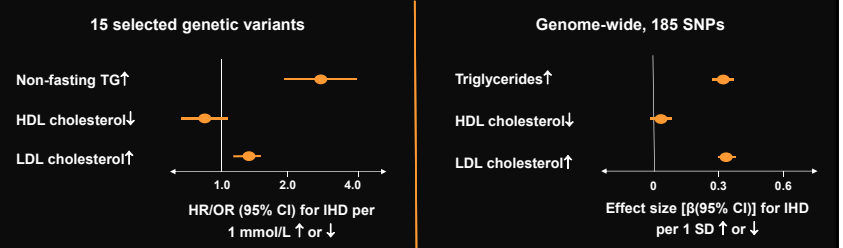

Median duration of study follow-up was 12.0 years. Liu J et al. *Lipids Health Dis*. 2013;12:159-69.

## Genetic Studies Examined TG-rich Lipoprotein Causality for Atherosclerotic Cardiovascular Disease (ASCVD)

- Causality directly connects one process (the cause, eg, remnant) with another (the effect, eg, ASCVD)
  - Several different types of evidence are necessary to determine whether elevated TG-rich lipoproteins are a cause of ASCVD
- Besides epidemiology, this includes evidence from
  - Randomized trials
  - Mendelian randomization studies of human genetics
    - Double-blind and randomized because of nature's own method of distributing alleles
    - Capture a life-long effect
    - Genotypes do not change on repeated measurement
  - Biological insight on potential mechanisms from elevated TG-rich lipoproteins to atherosclerosis and ASCVD

Nordestgaard BG. *Circ Res*. 2016;118:547-63.

## Mendelian Randomization Studies Showed That Elevated LDL-C and TG Are Causally Associated with ASCVD. HDL-C is not.



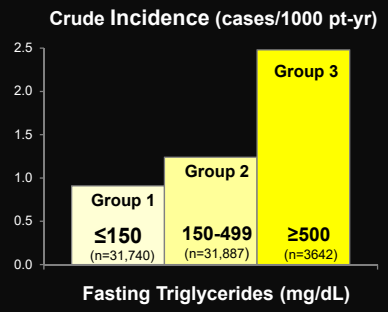

**N=66,000 (12,000 IHD)**
Varbo A et al. *J Am Coll Cardiol*. 2013;61:427-36.

**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. Nonfasting plasma TGs ('remnant cholesterol') was calculated as nonfasting total cholesterol minus HDL-C minus LDL-C that was calculated as TG/5. 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.

## Important Secondary Causes of HTG

| Cause | Clinically useful details |
|---|---|
| Caloric imbalance | ↓**Exercise**, ↑Saturated fat, ↑Glycemic index, Excess alcohol intake |
| ↑Carbohydrate intake | ↑Simple sugars (**fructose**>>glucose, etc.) and ↓Dietary fiber |
| Adiposity | Especially **↑visceral adiposity** |
| Diabetes mellitus | Especially **if poorly controlled** |
| Hypothyroidism | If not adequately controlled |
| Nephrotic syndrome | |
| Medications | **Antiretroviral regimens (for HIV)**; **Oral estrogen**; **Glucocorticoids**; **Isotretinoin**; Some phenothiazines and 2nd-generation antipsychotics; Nonselective beta-blockers; Thiazide diuretics; Tamoxifen; Bile-acid seq. |
| Recreational drugs | Alcohol, heavy marijuana use (↑Apo C-III) |

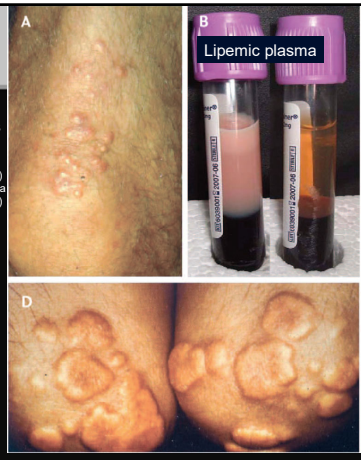
Apo=apolipoprotein; HIV=human immunodeficiency virus. Bays HE. In: Kwiterovich PO Jr, ed. *The Johns Hopkins Textbook of Dyslipidemia*. 1st ed. Lippincott Williams & Wilkins;2010:245-57.

## High TG Levels Are Often Associated with Other Cardio-Metabolic Risk Factors

- 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

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




Eruptive cutaneous xanthomas
Familial chylomicronemia (hyperlipoproteinemia type 1) or primary mixed dyslipidemia (hyperlipoproteinemia type 5)

Tuberous xanthomas on elbows
Usually appear on extensor surfaces in familial dysbetalipoproteinemia (hyperlipoproteinemia type 3)

Lipemia retinalis
Milky appearance of the retinal vessels and pink retina can be seen when TG concentration >3000 mg/dL

Palmar crease xanthomas
familial dysbetalipoproteinemia (hyperlipoproteinemia type 3)

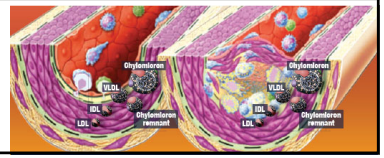
Yuan G et al. *CMAJ*. 2007;176:1113-20.

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

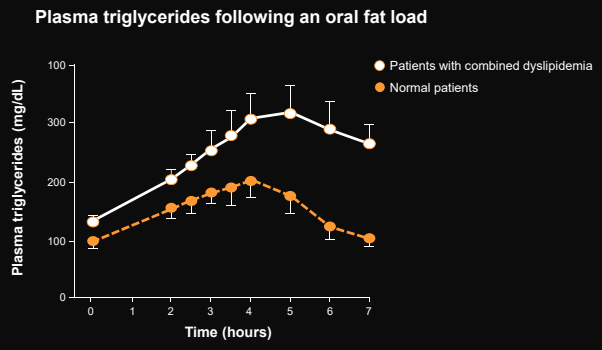
| Fasting Triglycerides (mg/dL) | |
|---|---|
| <100 | Optimal |
| <150 | Normal |
| 150–199 | Borderline high |
| 200–499 | High |
| ≥500 | Very high |

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

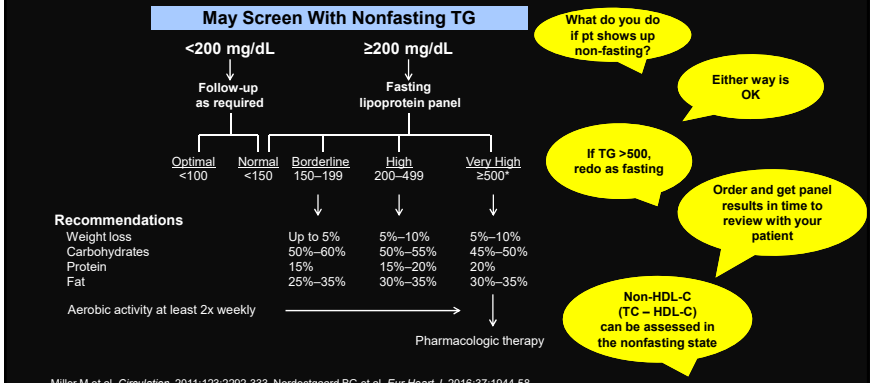



## Fasting TG Levels are Proportional to Post-Prandial Levels, And Less Noisy




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

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



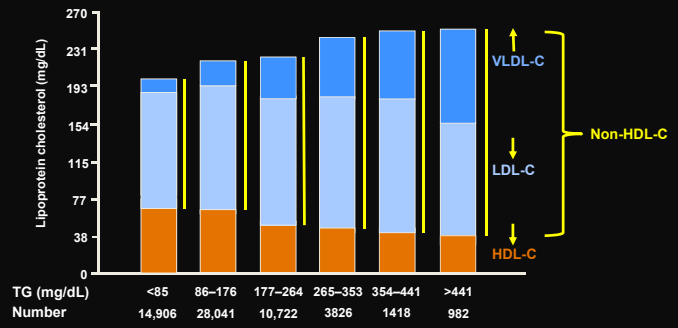

Miller M et al. *Circulation*. 2011;123:2292-333. Nordestgaard BG et al. *Eur Heart J*. 2016;37:1944-58.

## Non-HDL-C vs LDL-C

- The Framingham Heart Study, Women's Health Study, Health Professionals Follow-up Study, and others showed the superiority of non-HDL-C vs LDL-C as an independent CV risk factor
- Unless measured directly, LDL-C is usually calculated from total cholesterol, HDL-C, and TG (Friedewald equation)
- Friedewald-calculated LDL-C tends to be artifactually depressed in/if:
  - Non-fasting blood sample
  - TG > ~200 (fasting or not)
  - TG < ~50
  - LDL-C <50
- Non-HDL-C remains accurate in all of the above situations

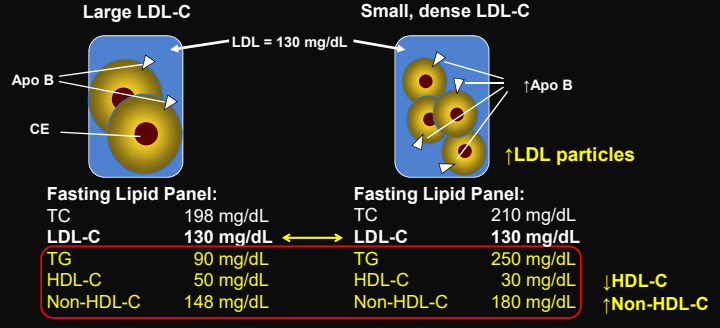
## With Increasing HTG, VLDL-C Increases as LDL-C Decreases, Making non-HDL-C a Better CVD Lipid Marker Than LDL-C

Lipoprotein cholesterol distribution among 72,000 Danish individuals off lipid-lowering therapy



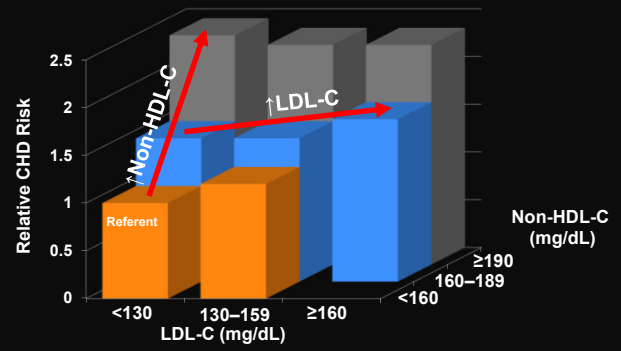

Varbo A et al. *J Am Coll Cardiol.* 2013;61:427-36.

## In HTG Subjects, LDL-C Measurements Underestimate CVD Risk




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

## Framingham Heart Study: Non-HDL-C Is a Stronger Predictor of ASCVD Risk than LDL-C



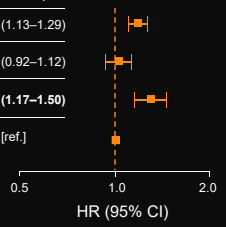

Liu J et al. *Am J Cardiol.* 2006;98:1363-8. (Framingham Study)

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

## Non-HDL-C >130 mg/dL Is a Better ASCVD Risk Predictor Compared With LDL-C >100 mg/dL

Meta-analysis data at baseline and at 1-year follow-up from 62,154 patients enrolled in 8 randomized controlled statin trials published 1994–2008

| Target Level | | Major CV Events (n) | Subjects (n) | HR (95% CI) |
|---|---|---|---|---|
| LDL-C (mg/dL) | Non-HDL-C (mg/dL) | | | |
| ≥100 | ≥130 | 1877 | 10,419 | 1.21 (1.13–1.29) |
| ≥100 | <130 | 467 | 2873 | 1.02 (0.92–1.12) |
| **<100** | **≥130** | **283** | **1435** | **1.32 (1.17–1.50)** |
| <100 | <130 | 2760 | 23,426 | 1.00 [ref.] |

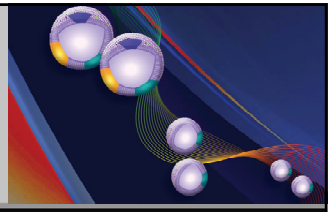



Boekholdt SM et al. *JAMA*. 2012;307:1302-9.

## Summary

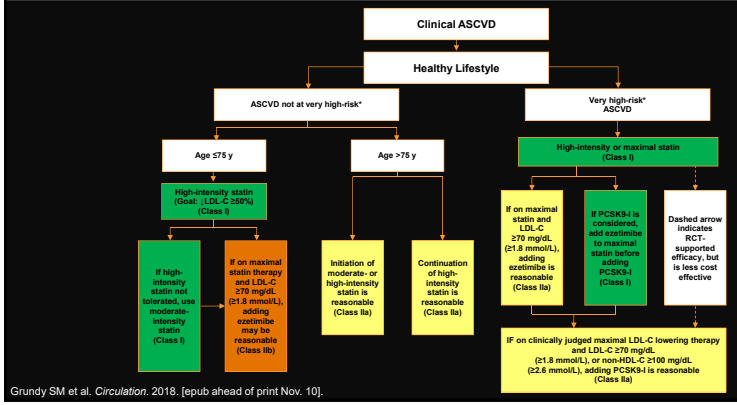
- Elevated TG levels are common, especially among the overweight, obese, and diabetics
- Remnants of TG-rich lipoproteins (chylomicron remnants, VLDL remnants, IDL) promote atherogenesis
- Non-HDL-C is a better CVD predictor than LDL-C, especially in patients with HTG
- Very high TGs are associated with increased risk for pancreatitis

## Practical Approach to the Management of Atherogenic Lipids



**James A. Underberg, MD, MS**
Clinical Lipidology
Clinical Assistant Professor of Medicine
NYU School of Medicine & NYU Center for Prevention of Cardiovascular Disease
Director, Bellevue Hospital Lipid Clinic
President, National Lipid Association
New York, NY

## Secondary Prevention



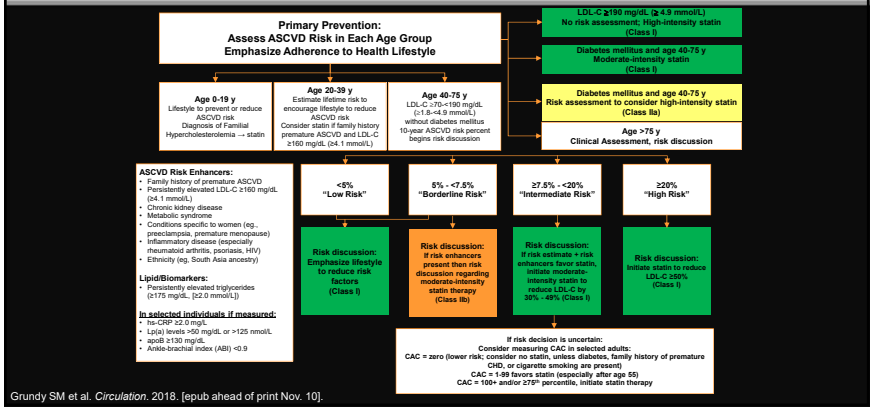

Grundy SM et al. *Circulation*. 2018. [epub ahead of print Nov. 10].

## Very High Risk of Future CVD Events

| Major ASCVD Events |
|---|
| Recent ACS (within the past 12 mo) |
| History of MI (other than recent ACS event listed above) |
| History of ischemic stroke |
| Symptomatic peripheral arterial disease (history of claudication with ABD <0.85, or previous revascularization or amputation) |
| **High-Risk Conditions** |
| Age ≥65 y |
| Heterozygous familial hypercholesterolemia |
| History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s) |
| Diabetes mellitus |
| Hypertension |
| CKD (eGFR 15-59 mL/min/1.73 m$^2$) |
| Current smoking |
| Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe |
| History of congestive HF |

Grundy SM et al. *Circulation*. 2018. [epub ahead of print Nov. 10].

## Primary Prevention




Grundy SM et al. *Circulation*. 2018. [epub ahead of print Nov. 10].

## Diagnosing and Treating Secondary Causes of HTG

- Take a Hx of diet (calories, fat, sugar, alcohol, body weight and weight changes) and physical activity (frequency, type, intensity)
- Measure BMI & waist, TSH, fasting glucose, A1c, urinary protein
- Recommend low-calorie, low-sugar, low-to-no alcohol, low-fat but high-fiber diet
- Recommend patient-appropriate physical activity plan
- Treat underlying diseases causing HTG (eg, ↑A1c, ↓thyroid function)
- Consider possible changes away from TG-*raising* medications

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** (at least 5–10%) |
| **Diet**<br>↑ Fruits, veggies & low/non-fat dairy<br>↓ Total carb, added sugars<br>↓ Total fat (if fasting TG >~800)<br>↑ Dietary fiber |
| **Exercise**<br>Any type is helpful, the more the better (e.g. brisk 30-min walk, 3x/wk) |

**20% - 50% reduction in TG may be possible with lifestyle interventions!**

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

## Lipid Effects of ↑Physical Activity and ↓Weight in Patients with Overweight/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 often does not change**
  - But ↓weight ± ↑exercise should ↑ particle size and/or 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 Are Associated with Decreased Stroke Risk

| | 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% |

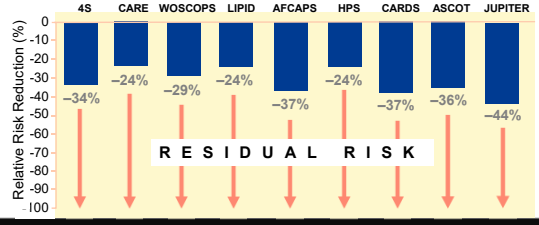
Iso H et al. *JAMA*. 2001:285:304-12.

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


## Considerable ASCVD Risk Remains Despite Statin Monotherapy

*Statin-based LDL-C lowering to reduce CAD risk*[2-10]

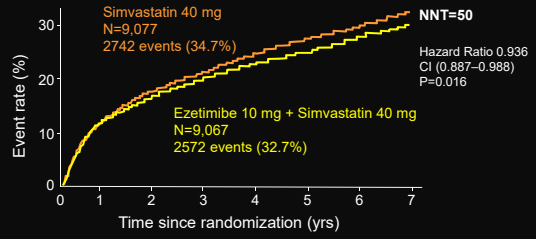



*Statins reduce CAD/CVD risk by ~24%-44% but 56% to 76% residual risk remains*[1-10]

1. Adapted from Rader DJ et al. www.medscape.org/viewarticle/569095.
2. Shepherd J et al. *N Engl J Med*. 1995;333:1301-1307.
3. Scandinavian Simvastatin Survival Study Group. *Lancet*. 1994;344:1383-1389.
4. Ballantyne CM. *Am J Cardiol*. 1998;82:3Q-12Q.
5. Sacks FM et al. *N Engl J Med*. 1996;335:1001-1009.
6. Downs JR et al. *JAMA*. 1998;279:1615-1622.
7. LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357.
8. Brown BG. *Eur Heart J Suppl*. 2005;7:F34-F40.
9. Grundy SM et al. *Circulation*. 2004; 110:227-239.
10. Ridker PM et al. *N Engl J Med*. 2008;359:2195-2207.

## IMPROVE-IT: Add-on Ezetimibe to Statin Beneficial; Lower LDL-C Is Better

**Primary Endpoint – ITT:** CV death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



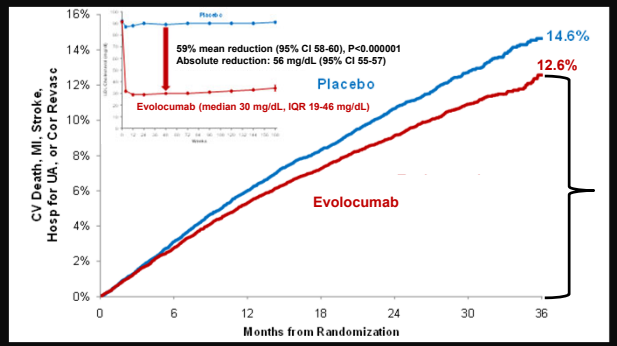

**NNT=50**

Hazard Ratio 0.936
CI (0.887–0.988)
P=0.016

| 1-Yr Mean (mg/dL) | LDL-C | TC | TG | HDL-C | hsCRP |
|---|---|---|---|---|---|
| Simvastatin 40 mg | 69.9 | 145.1 | 137.1 | 48.1 | 3.8 |
| Ezetimibe 10 mg + Simvastatin 40 mg | 53.2 | 125.8 | 120.4 | 48.7 | 3.3 |
| Change | -16.7 | -19.3 | -16.7 | +0.6 | -0.5 |

hsCRP=high-sensitivity C-reactive protein (CRP); IMPROVE-IT=Improved Reduction of Outcomes: Vytorin Efficacy International.
Cannon CP. AHA Late-Breaking Clinical Trials Session, Nov. 2014.

## FOURIER: Significant Reduction in CV Events, but Significant Risk Remains

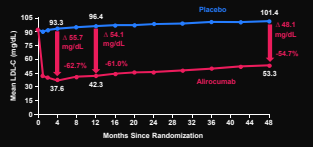


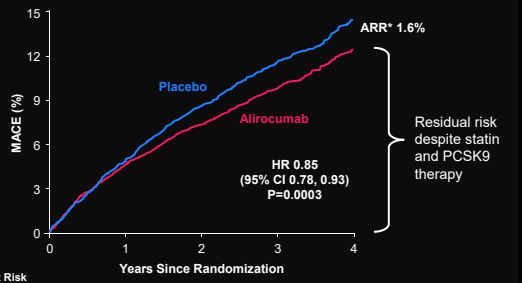

Residual risk despite statin and PCSK9 therapy

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

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

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



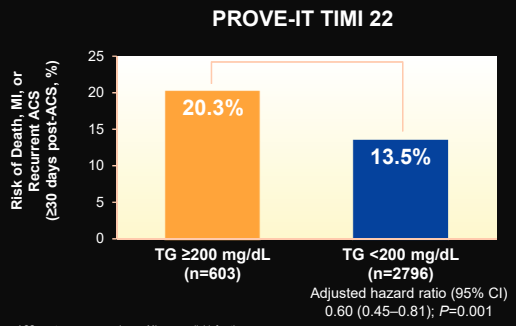

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

| Number at Risk | | | | | |
|---|---|---|---|---|---|
| Placebo | 9462 | 8805 | 8201 | 3471 | 629 |
| Alirocumab | 9462 | 8846 | 8345 | 3574 | 653 |

*Based on cumulative incidence

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

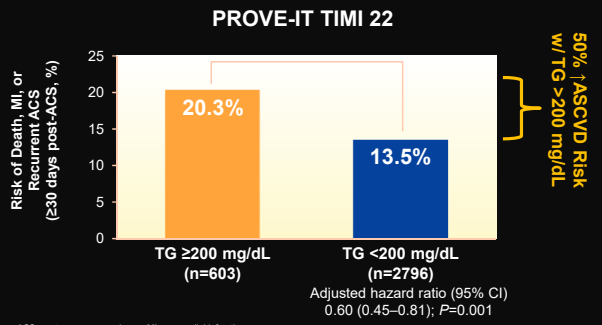
## HTG Is Associated With Residual Risk Despite LDL-C <70 mg/dL on Statin




ACS=acute coronary syndrome; MI=myocardial infarction.

Miller M et al. *J Am Coll Cardiol.* 2008;51(7):724-730.

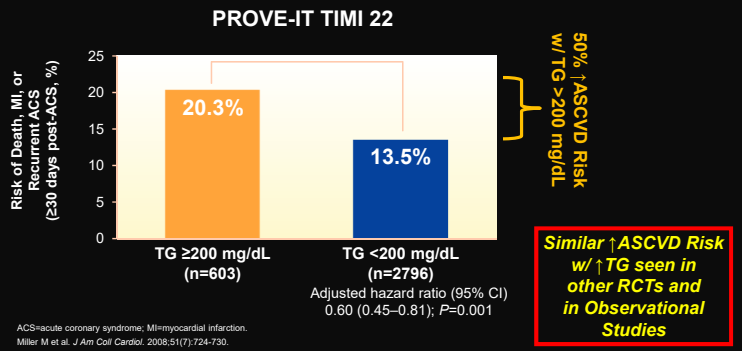
## HTG Is Associated With Residual Risk Despite LDL-C <70 mg/dL on Statin




ACS=acute coronary syndrome; MI=myocardial infarction.

Miller M et al. *J Am Coll Cardiol.* 2008;51(7):724-730.

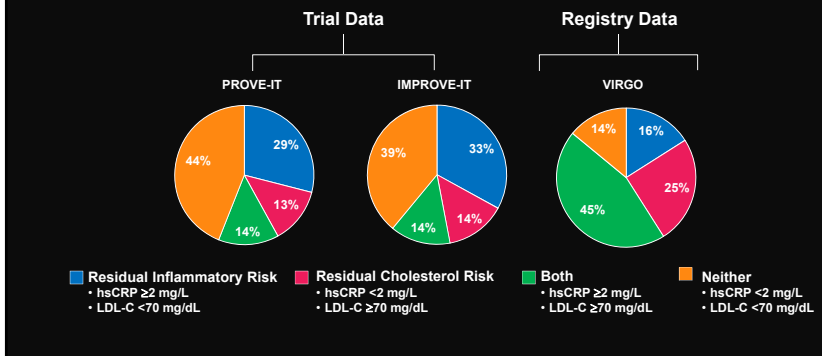
## HTG Is Associated With Residual Risk Despite LDL-C <70 mg/dL on Statin




ACS=acute coronary syndrome; MI=myocardial infarction.

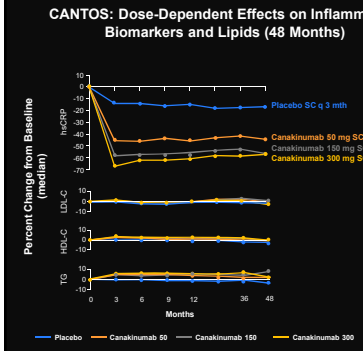
Miller M et al. *J Am Coll Cardiol.* 2008;51(7):724-730.

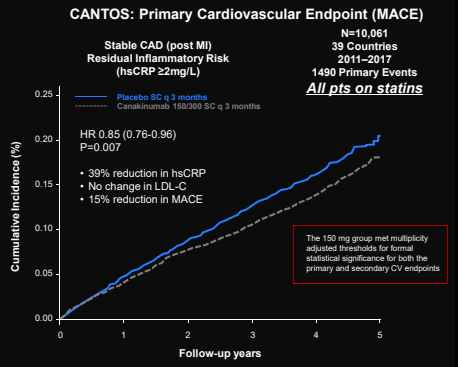
## Proportion of CAD Patients Taking Statin Therapy Who Have Residual *Cholesterol* or *Inflammatory* Risk




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.

## CANTOS: Reducing Inflammation "Alone" (Anti IL1-beta mAb, marker hsCRP) Reduces CV Events

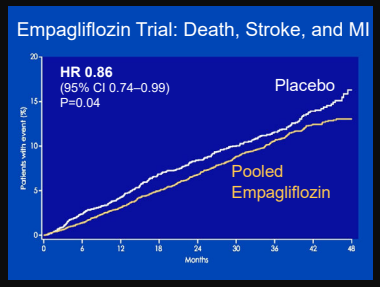



Ridker PM et al. *N Engl J Med*. 2017;377:1119-31.

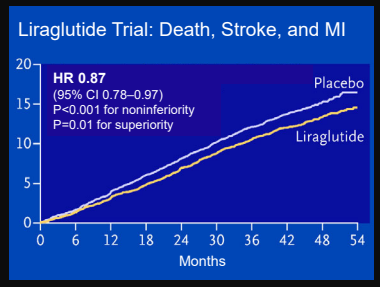
## SGLT2i and GLP1-RA Lower CV risk in DM2

EMPA-REG OUTCOME Trial




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

LEADER Trial




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

## COMPASS: NOAC Rivaroxaban Heralds a Change in CAD or PAD Management

Objective: Efficacy and safety of rivaroxaban, low-dose rivaroxaban plus ASA or ASA alone for reducing risk of MI, stroke or CV death in CAD or PAD

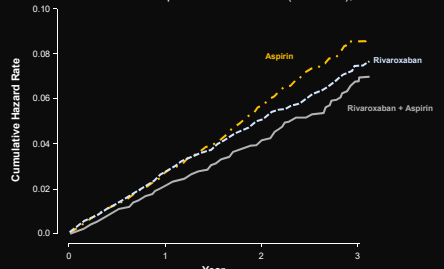
Population:
N=27,400 patients with documented CAD or PAD (***statin use unknown***)

Rivaroxaban 2.5 mg bid + ASA 100 mg od
± pantoprazole 40 mg od

Rivaroxaban 5.0 mg bid
± pantoprazole 40 mg od

ASA 100 mg od
± pantoprazole 40 mg od

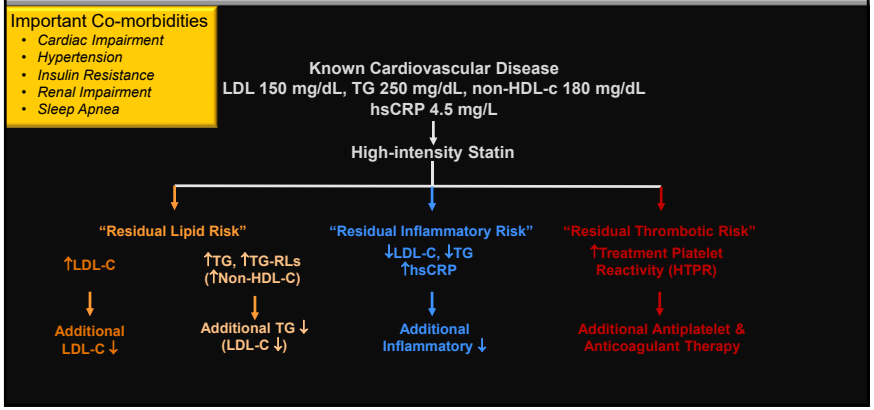
Rivaroxaban + Aspirin vs Aspirin: HR 0.76 (0.66-0.86); P≤0.0001
Rivaroxaban vs Aspirin: HR 0.90 (0.79-1.03); P=0.12




| No. at Risk | | | | |
|---|---|---|---|---|
| Rivaroxaban + Aspirin | 9152 | 7904 | 3912 | 658 |
| Rivaroxaban | 9117 | 7824 | 3862 | 670 |
| Aspirin | 9126 | 7808 | 3860 | 669 |

Eikelboom JW et al. *N Engl J Med*. 2017;377:1319-30.

## Personalized Treatment Hypothesis in CAD




## Working Towards a Pragmatic, Personalized Approach to Reduce Residual CVD Risk

| Causes | Setting (Threshold) | Rx Value | Rx Choices |
|---|---|---|---|
| LDL-C | ≥70 mg/dL | *Balance of* • Efficacy • Safety • QoL • Cost | Statin, Ezetimibe, PCSK9i |
| HbA1c | ≥6.5 mg/dL | | SGLT-2i, GLP-1 agonist |
| HsCRP | >2 mg/L | | Canakinumab or methotrexate? |
| Residual thrombotic risk | ACS | | Single, dual antiplatelet, rivaroxaban? |
| TG | >150 mg/dL | | Statin + Omega 3 (vs fibrate??) |

## 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.

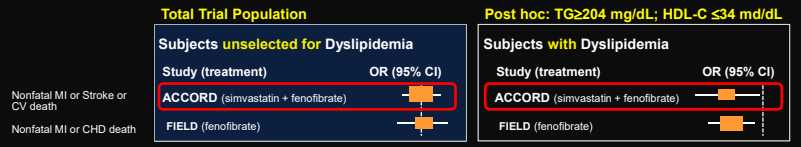
## Lipid Effects of Drug Classes in Mixed Dyslipidemia and HTG

| Medication | TG | LDL-C | HDL-C | Non-HDL-C |
|---|---|---|---|---|
| | Range, % | | | |
| **Mixed dyslipidemia** | | | | |
| • Statins | –10 to –37 | –26 to –63 | +5 to +16 | –44 to –60 |
| • Omega-3 fatty acids | –19 to –44 | –6 to +25 | –5 to +7 | –1 to –7 |
| • Fibrates | –24 to –36 | –5 to –31 | +10 to +16 | –17 |
| • Niacin | –5 to –38 | –3 to –17 | +10 to +26 | NR |
| **Isolated HTG** | | | | |
| • Statins | –21 to –52 | –27 to –45 | +3 to +22 | –29 to –52 |
| • Omega-3 fatty acids | –26 to –52 | –6 to +49 | +9 to +14 | –10 to –14 |
| • Fibrates | –46 to –62 | +3 to +47 | +18 to +23 | NR |

NR=not reported. Maki KC, Bays HE, Dicklin MR. *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 | Follow-up (mean) |
|---|---|---|---|---|---|---|---|
| ACCORD | • T2DM<br>• 40-79 yrs + CVD or<br>• 55-79 yrs + ≥2 CV risk factors | 5518 | Fenofibrate | Open-label simvastatin (mean dose: 22 mg) | 162 mg/dL (median) | –26% | 4.7 yrs |
| 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 | 5 yrs |




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.

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

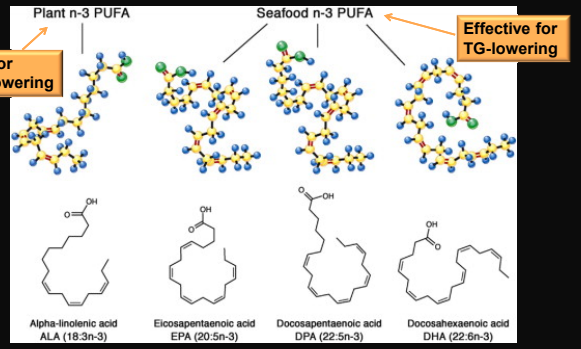
| Trial (Subgroup, mg/dL) (Drug) | Risk difference vs placebo (P-value) | |
|---|---|---|
| | All subjects | HTG subgroup |
| WOSCOPS (TG ≥148) (Pravastatin) | –31% (<0.001) | –32% (0.003) |
| CARE (TG ≥144) (Pravastatin) | –24% (0.003) | –15% (0.07) |
| PPP Project (TG ≥200) (Pravastatin) | –23% (<0.001) | –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.

## OM-3s are Highly Polyunsaturated Fatty Acids (PUFAs)

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.

## 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<br>• DHA: 0.375 g<br>• EPA/DHA: 55%/45%<br>• ~16% mon EPA/DHA | • EPA: 1 g<br>• EPA/DHA: 100%/0%<br>• ~4% non-EPA | • EPA: 0.55 g<br>• DHA: 0.2 g<br>• EPA/DHA: 73%/27%<br>• ~15% non-EPA/DHA |
| **Regimen, Capsules** | • 2 BID w/ food or<br>• 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.

## Proposed Mechanisms of Potential CV Benefits of Omega-3 FA

**Anti-arrhythmic**
- ↓Sudden death (GISSI-P *only*)
- ↓Atrial Fibrillation? (EPA+DHA might ↑)
- ↓Protection against ventricular arrhythmias (vs ↑)
- Heart rate variability improvement

**Anti-atherogenic**
- ↓Non-HDL-C
- ↓TG and ↓VLDL-C
- ↓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
- ↑NO production/vasodilation
- ↑Resolvins/protectins/maresins

**↓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.

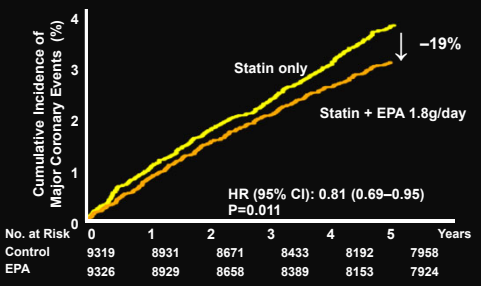
## Endothelial and Anti-inflammatory Biology of EPA Improves Plaque Properties

**Effects of EPA on Plaque Progression**

| | Endothelial Dysfunction / Oxidative Stress | Inflammation / Plaque Growth | Unstable Plaque |
|---|---|---|---|
| Increase | Endothelial function<br>Nitric oxide bioavailability | EPA/AA ratio | Fibrous cap thickness<br>Lumen diameter<br>Plaque stability |
| Decrease | Cholesterol crystalline domains<br>Ox-LDL<br>RLP-C<br>Adhesion of monocytes<br>Macrophages<br>Foam cells | IL-6<br>ICAM-1<br>IL-10<br>hsCRP<br>Lp-$PLA_2$<br>MMPs | Plaque volume<br>Arterial stiffness<br>Plaque vulnerability<br>Thrombosis<br>Platelet activation |

Ganda OP et al. *J Am Coll Cardiol*. 2018;72:330-43.

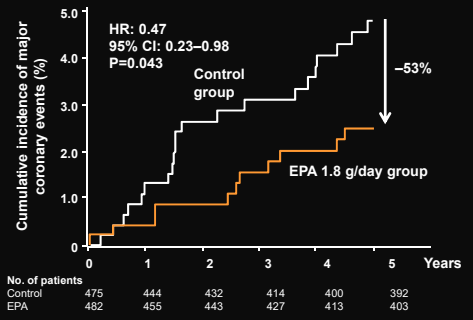
## JELIS: EPA Reduced Major Coronary Events* in Hypercholesterolemic Patients on Statins




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*

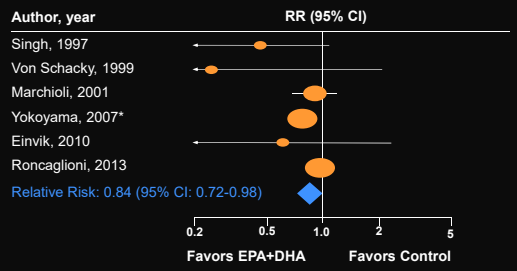



HR and P-value adjusted for age, gender, smoking, diabetes, and HTN

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

## Randomized Controlled Trials and Prospective Cohort Studies of EPA+DHA or EPA-Only vs CHD Risk

### Subjects with baseline TG levels >150 mg/dL

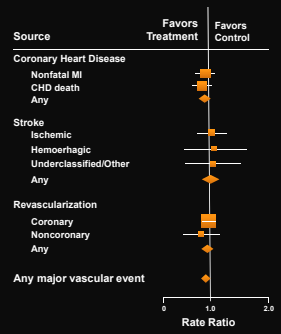



Alexander DD et al. *Mayo Clin Proc*. 2017;92:15-29. *EPA-only.

## Lack of Apparent Effect of OM-3 on ASCVD May be Due to Low-Doses, Use of Dietary Supplements, or Lack of HTG Subjects

"… 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.

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

## Low-Moderate Dose Omega-3 FA CV Outcomes Trials

| | VITAL<br>AHA Nov 2018 | ASCEND<br>ESC Aug 2018 | RESPECT-EPA<br>Q4 2019 |
|---|---|---|---|
| **Funding** | NIH | British Heart Foundation | Japan Heart Foundation |
| **Design** | RDBPC | RDBPC | PROBE |
| **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<br>Omacor (Lovaza) 1 g/d (2X2) | Aspirin 100 mg/d<br>Omacor (Lovaza) 1 g/d (2X2) | EPA 1800 mg/d + statin<br>vs Statin alone |
| **N** | 25,875 | 15,480 | 3900 |
| **Primary Endpoint** | Cancer and major CVD events (composite) | CV events (composite)<br>***FAILED to show benefit*** | CV events (composite) |

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

## CV Outcomes Trials in Patients with HTG

| | REDUCE-IT* | STRENGTH* | PROMINENT* |
|---|---|---|---|
| **Agent<br>Dose** | EPA (EE)<br>4 g/d | EPA+DHA (FFA)<br>4 g/d | SPPARMα – Pemafibrate<br>0.2 mg bid |
| **N** | ~8000 | Estimated 13,000 | Estimated 10,000 |
| **Age** | ≥45 y/o | ≥18 y/o | ≥18 y/o |
| **Risk Profile** | CVD (70%) or<br>↑CVD risk (30%) | CVD (50%) or<br>↑CVD risk (50%) | T2DM only<br>CVD (2/3) or<br>↑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<br>Entry HDL-C** | 200–499 mg/dL<br>N/A | 200–499 mg/dL<br><40 mg/dL M, <45 mg/dL W | 200–499 mg/dL<br>≤40 mg/dL |

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

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

## REDUCE-IT: Reduction of CV Events with Icosapent Ethyl – Intervention Trial

- Men and women ≥45 years of age
- Established CHD or at high risk for CHD (diabetes + ≥1 risk factor)
- Atherogenic dyslipidemia
  - All patients required to be on stable statin therapy for at least 4 weeks
  - LDL-C >40 mg/dL and ≤100 mg/dL prior to randomization into the study
  - TG ≥200 mg/dL

N≈8000

reduce-it

Omega-3 + Stable Statin Therapy

Placebo + Stable Statin Therapy

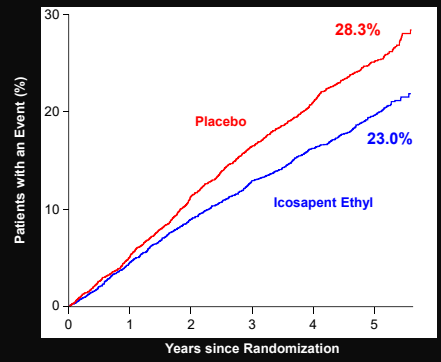
Study duration ≈ 4–6 years

**Primary Endpoint**
Prevention of 1st major CV event (MACE); defined as:
- CV death
- Nonfatal MI
- Nonfatal stroke
- Coronary revascularization
- Unstable angina requiring hospitalization

- Randomized, double-blind, parallel-group design
- Secondary outcome measures: incidence of additional CV events, lipid and lipoprotein levels, subgroup analyses such as patients with diabetes, etc.
- International trial; first patient dosed in December 2011
- All potential endpoint events adjudicated by blinded Clinical Endpoint Committee

Bhatt DL, Steg PG, Brinton E, et al. *Clin Cardiol*. 2017; 40:138-48. http://www.clinicaltrials.gov/ct2/show/NCT01492361

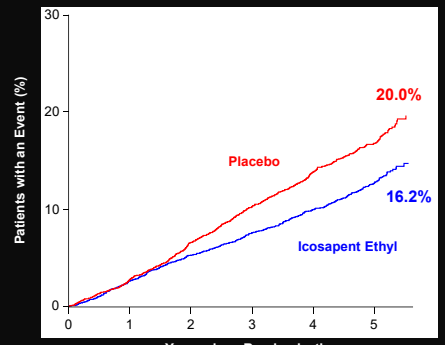
## Primary Endpoint:
### CV Death, MI, Stroke, Coronary Revasc, Unstable Angina




**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.

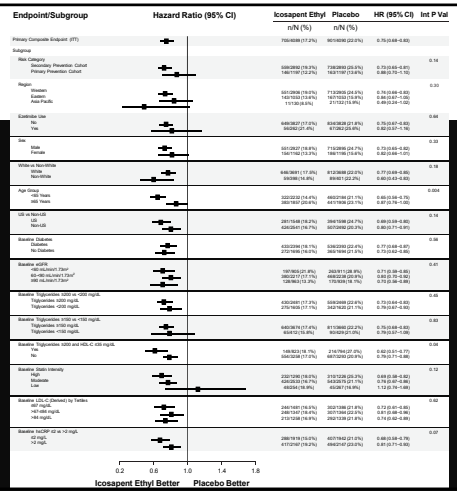
## Key Secondary Endpoint:
### CV Death, MI, Stroke




**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.

## Primary Endpoint in Subgroups




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

## Prespecified Hierarchical Testing

| Endpoint | Hazard Ratio (95% CI) | 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 |

0.4 1.0 1.4
Icosapent Ethyl Better Placebo Better
RRR denotes relative risk reduction

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

## Treatment-Emergent Adverse Events

| | Icosapent Ethyl (N=4089) | Placebo (N=4090) | P-value |
|---|---|---|---|
| Subjects with at Least One TEAE, n (%) | 3343 (81.8%) | 3326 (81.3%) | 0.63 |
| Serious TEAE | 1252 (30.6%) | 1254 (30.7%) | 0.98 |
| TEAE Leading to Withdrawal of Study Drug | 321 (7.9%) | 335 (8.2%) | 0.60 |
| Serious TEAE Leading to Withdrawal of Study Drug | 88 (2.2%) | 88 (2.2%) | 1.00 |
| Serious TEAE Leading to Death | 94 (2.3%) | 102 (2.5%) | 0.61 |

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

## Treatment-Emergent Adverse Event of Interest: Serious Bleeding

| | Icosapent Ethyl (N=4089) | Placebo (N=4090) | P-value |
|---|---|---|---|
| Bleeding related disorders | 111 (2.7%) | 85 (2.1%) | 0.06 |
| Gastrointestinal bleeding | 62 (1.5%) | 47 (1.1%) | 0.15 |
| Central nervous system bleeding | 14 (0.3%) | 10 (0.2%) | 0.42 |
| Other bleeding | 41 (1.0%) | 30 (0.7%) | 0.19 |

- No fatal bleeding events in either group
- Adjudicated hemorrhagic stroke - no significant difference between treatments (13 icosapent ethyl vs 10 placebo; P=0.55)

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

## Most Frequent Treatment-Emergent Adverse Events: ≥5% in Either Treatment Group and Significantly Different

| Preferred Term | Icosapent Ethyl (N=4089) | Placebo (N=4090) | P-value |
|---|---|---|---|
| Diarrhea | 367 (9.0%) | 453 (11.1%) | 0.002 |
| Peripheral edema | 267 (6.5%) | 203 (5.0%) | 0.002 |
| Constipation | 221 (5.4%) | 149 (3.6%) | <0.001 |
| Atrial fibrillation | 215 (5.3%) | 159 (3.9%) | 0.003 |
| Anemia | 191 (4.7%) | 236 (5.8%) | 0.03 |

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

## Conclusions

Compared with placebo, icosapent ethyl 4 g/day significantly reduced important CV events by **25%**, including:

- **20%** reduction in death due to cardiovascular causes
- **31%** reduction in heart attack
- **28%** reduction in stroke

Low rate of adverse effects, including:

- Small but significant increase in atrial fibrillation/flutter
- Non-statistically significant increase in serious bleeding

Consistent efficacy across multiple subgroups

- Including baseline triglycerides from 135-500 mg/dL
- Including secondary and primary prevention cohorts

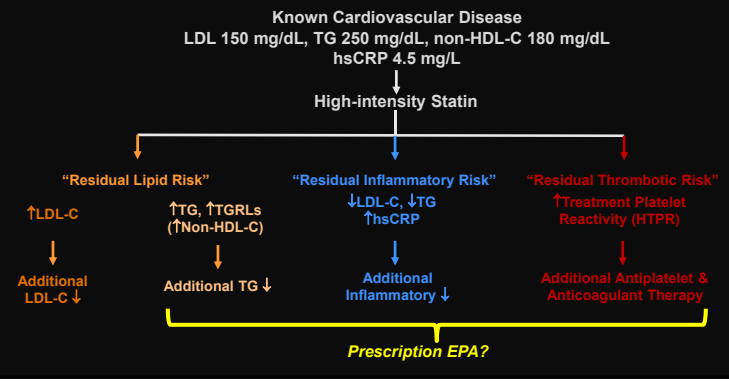
## Relative Risk Reductions (RRR) of Primary Endpoint in Recent CV Trials of Lipid or Inflammation Targeted Therapies

| Cardiovascular Outcomes Trial<br>All patients on statin treatment | Active Treatment | Population | RRR (%) | NNT |
|---|---|---|---|---|
| Cholesterol absorption inhibitor<br>**IMPROVE-IT (2015)** | Ezetimibe | 18,144 ACS patients | 6 | 50 |
| PCSK9 inhibitor<br>**FOURIER (2017)**<br>**ODYSSEY OUTCOMES (2018)** | Evolocumab<br>Alirocumab | 27,564 pts with ASCVD+LDL-C>70 mg/dL<br>18,924 ACS patients | 15<br>15 | 67<br>62.5 |
| IL1-beta inhibitor<br>**CANTOS (2017)** | Canakinumab | 10,061 stable ACS pts + hsCRP ≥2 mg/L | 15 | 56 |
| CETP inhibitor<br>**REVEAL (2017)** | Anacetrapib | 30,449 pts w/ ASCVD on intensive atorvastatin RX | 9 | 100 |
| Omega-3 fatty acid<br>**REDUCE-IT (2018)** | EPA, 4 g/d | 8179 Pts; 71% ASCVD, 29% high CVD risk + T2DM | 25 | 21 |

*Note: these cross-trial **comparisons** are **very rough**, at best, due to differences in subject populations, primary outcome differences, and other trial design aspects.*

Cannon CP et al. *N Engl J Med* 2015;372:2387-97. Sabatine MS et al. *N Engl J Med*. 2017;376:1713-22. Schwarz GG et al *N Engl J Med*. 2018. [epub ahead of print Nov. 7]. Ridker PM et al. *N Engl J Med*. 2017;377:1119-31. The HPS3/TIMI55–REVEAL Collaborative Group. *N Engl J Med*. 2017; 377:1217-27. Bhatt DL et al. *N Engl J Med*. 2018. [epub ahead of print Nov. 10].

## Personalized Treatment Hypothesis in CAD




## Non-Prescription Omega-3 Fatty Acids

Michael Miller, MD

## Dietary Supplement Omega-3 FA Are Popular But Are ***Not*** FDA-Regulated *(only Rx forms are regulated)*

- 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]
- There are ***no omega-3 OTC products*** in US (just prescription ***or*** dietary supplements)
- Dietary supplements are ***not*** FDA regulated. Content and efficacy often remain unverified.[3]

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. *Biochem Biophys Res Commun*. 2017;483 :425-429.

## 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 |
| Purity/efficacy & safety tested | Yes | Yes | Not required (usually not done) |

**Recommended dose** (AHA recommendation *before* Rx available)
- General: Eat oily fish or 1 g/day
- Prior CHD: 1–2 g/day (or >2 g/day directed by health care provider)
- For ↓TG: 2–4 g/day directed by health care provider

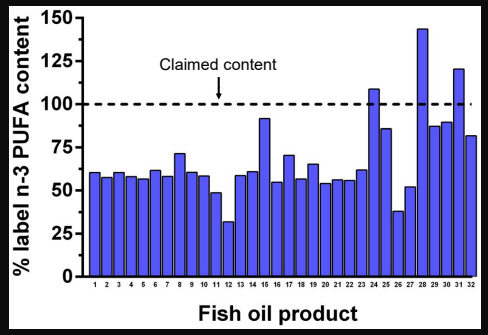
## Achieving a Recommended 4 g Daily Dose of Omega-3 with Common Fish Oil Supplements

Leading fish oil dietary supplement

Leading krill oil dietary supplement

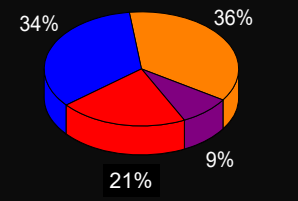
Courtesy of P. Mason, AHA-2017 presentation.

## Fish-Oil Supplements Often Have *Less* Omega-3 Than Stated on the Label



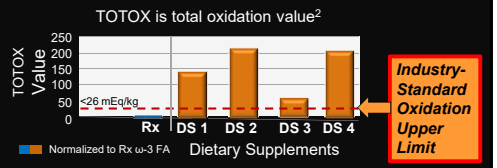

Albert BB et al. *Sci Rep.* 2015;5:7928

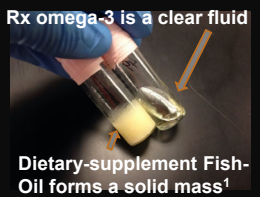
## Leading Dietary Supplement Fish Oils Have *Highly Saturated* and *Oxidized* Fatty-Acid Content




Leading Fish Oil Supplement[1]

EPA
DHA
Saturated Fats
Unsaturated Fats




***High saturated-fat content shown by solidity of FFA at room temperature***

1. Mason RP. *Biochem Biophys Res Commun.* 2017;483:425-429.
2. 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[2-8]
- Difficult to achieve AHA recommended OM-3 dosing
- May contain high saturated fat content
- Advertised omega-3 content may be overstated
- Often contain oxidized fatty acids which may increase CV risk
- Might contain PCBs and dioxins at harmful concentrations

1. US Food and Drug Administration. www.fda.gov/Food/DietarySupplements/default.htm. Updated April 4, 2016. Accessed Nov. 4, 2018. 2. Hilleman D and Smer A. *Manag Care.* 2016;25:46-52. 3. Mason RP and Sherratt SCR. *Biochem Biophys Res Commun.* 2017;483:425-9. 4. Albert BB et al. *Sci Rep.* 2015;5:7928. 5. Kleiner AC et al. *J Sci Food Agric.* 2015;95:1260-7. 6. Ritter JC et al. *J Sci Food Agric.* 2013;93:1935-9. 7. Jackowski SA et al. *J Nutr Sci.* 2015;4:e30. 8. Rundblad A et al. *Br J Nutr.* 2017;117:1291-8.

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

## 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]

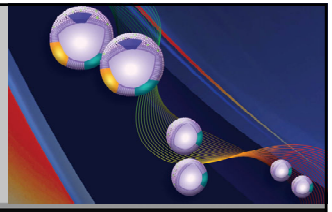
1. Agarwal P. American Pharmacists Association Web site. https://www.pharmacist.com/apha-convenes-stakeholders-appropriate-omega-3-fish-oil-use-vht. Published April 21, 2015.
2. ADA Standards of Medical Care - 2017. *Diabetes Care*. 2017;40(Suppl 1):S1-S135.

## 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



**Michael Miller, MD**
**James A. Underberg, MD, MS**

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

**S/P:** MI 4 yrs prior, 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?"