Evaluating the Latest Evidence in ASCVD Risk Reduction: Experts Tell All

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Welcome, Introductions, and Program Overview

Christie Ballantyne, MD
Chief, Sections of Cardiology and Cardiovascular Research
Professor and Vice Chair of Research
J.S. Abercrombie Chair, Atherosclerosis & Lipoprotein Research
Department of Medicine
Director, Center for Cardiometabolic Disease Prevention
Baylor College of Medicine
Houston, Texas

Agenda

- TG, TG-rich Lipoproteins, and Association with ASCVD
- Clinical Perspective On Reducing CV Events in the Patient with High TGs. Where We Stand After REDUCE-IT and STRENGTH
- Clinical Update: Using Statins and the Newly Recommended Statin Adjunct IPE (pure EPA) for CV Event Reduction
- Case Presentation on Primary and Secondary Prevention
- Q&A

Learning Assessment 1

All of the following are reasons why TG-rich lipoproteins and their remnants are causally related to ASCVD ***EXCEPT*****?**

A. Observational studies indicate that mild-moderate HTG is a strong and independent predictor of ASCVD and all-cause mortality

B. Mendelian randomization (genetic) studies indicate that factors related to TG metabolism support causality in ↑CV risk

C. TG-rich lipoproteins promote inflammation much less than does LDL

D. Remnant lipoproteins accumulate in arterial intima macrophage foam cells more readily than does LDL

Learning Assessment 2

Which of the following statements about the REDUCE-IT and STRENGTH omega-3 fatty acid trials is true?

A. Both REDUCE-IT and STRENGTH testing icosapent ethyl (IPE, Vascepa) and omega-3-carboxylic acids (Epanova), respectively, failed to show CVD benefit.

B. The REDUCE-IT trial showed CVD benefit with the study drug vs placebo, but the STRENGTH trial was neutral

C. The REDUCE-IT trial showed CVD benefit and STRENGTH also showed benefit in subjects with the highest on-study EPA levels

D. Both REDUCE-IT and STRENGTH showed CVD benefit in their whole study populations

Learning Assessment 3

According to the ACC Expert Consensus to Reduce ASCVD Risk, what treatment should be considered for an adult with ASCVD, fasting HTG 150-499 mg/dL and LDL-C <70 mg/dL after optimizing lifestyle and ruling out secondary causes?

A. Ezetimibe

B. Niacin

C. Fibrates

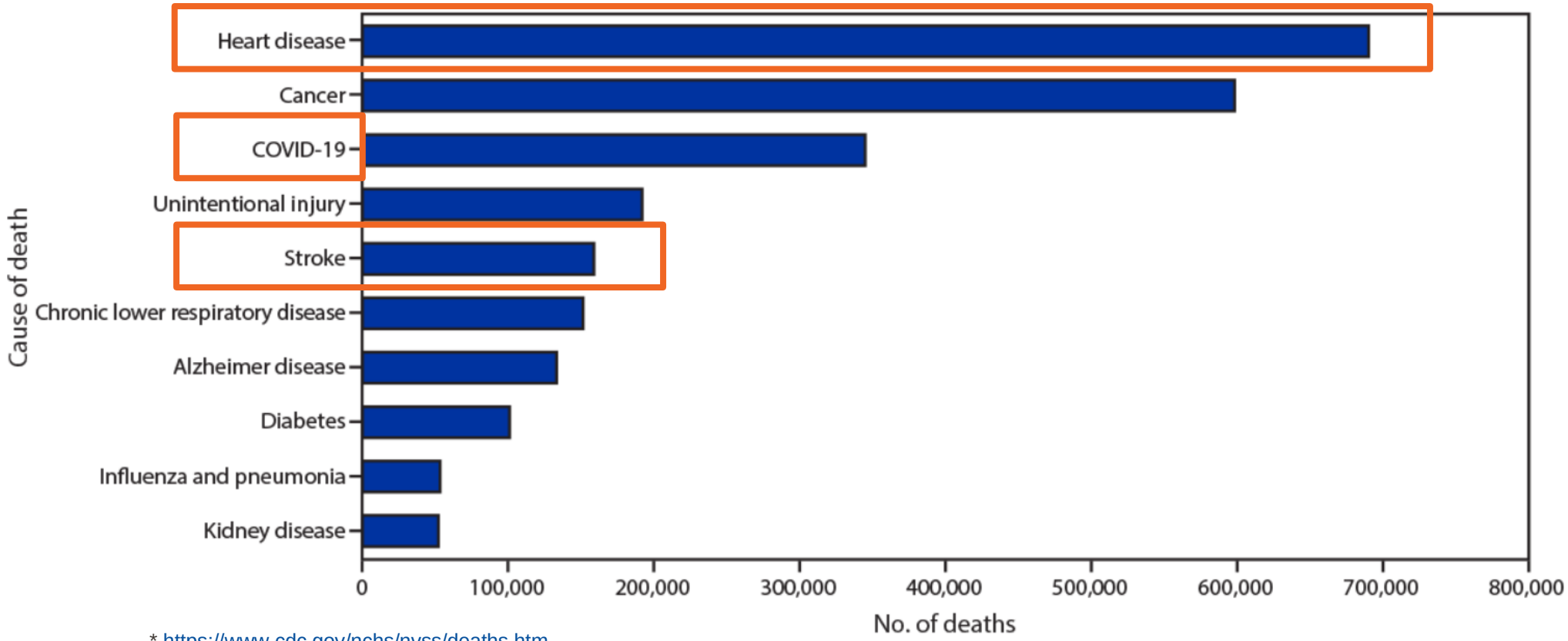
D. Icosapent Ethyl

TG, TG-rich Lipoproteins, and Association with ASCVD

Christie Ballantyne, MD

Despite COVID-19, Heart Disease Remains the #1 Cause of Death

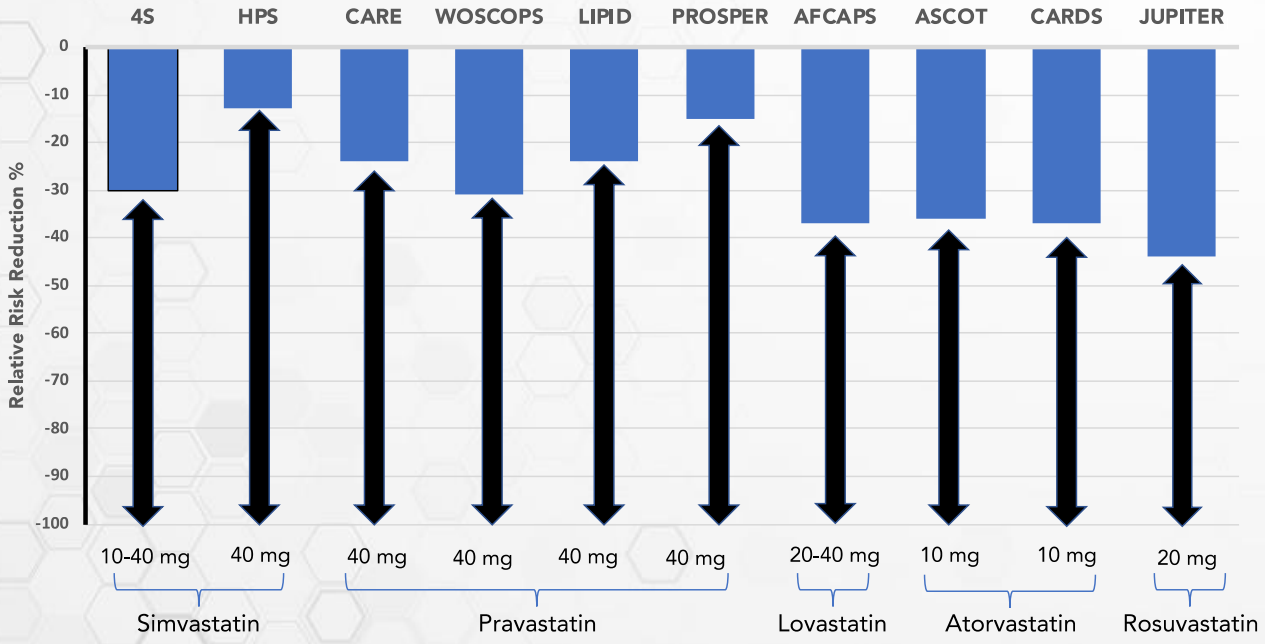
FIGURE 2. Provisional* number of leading underlying causes of death† — National Vital Statistics System, United States, 2020



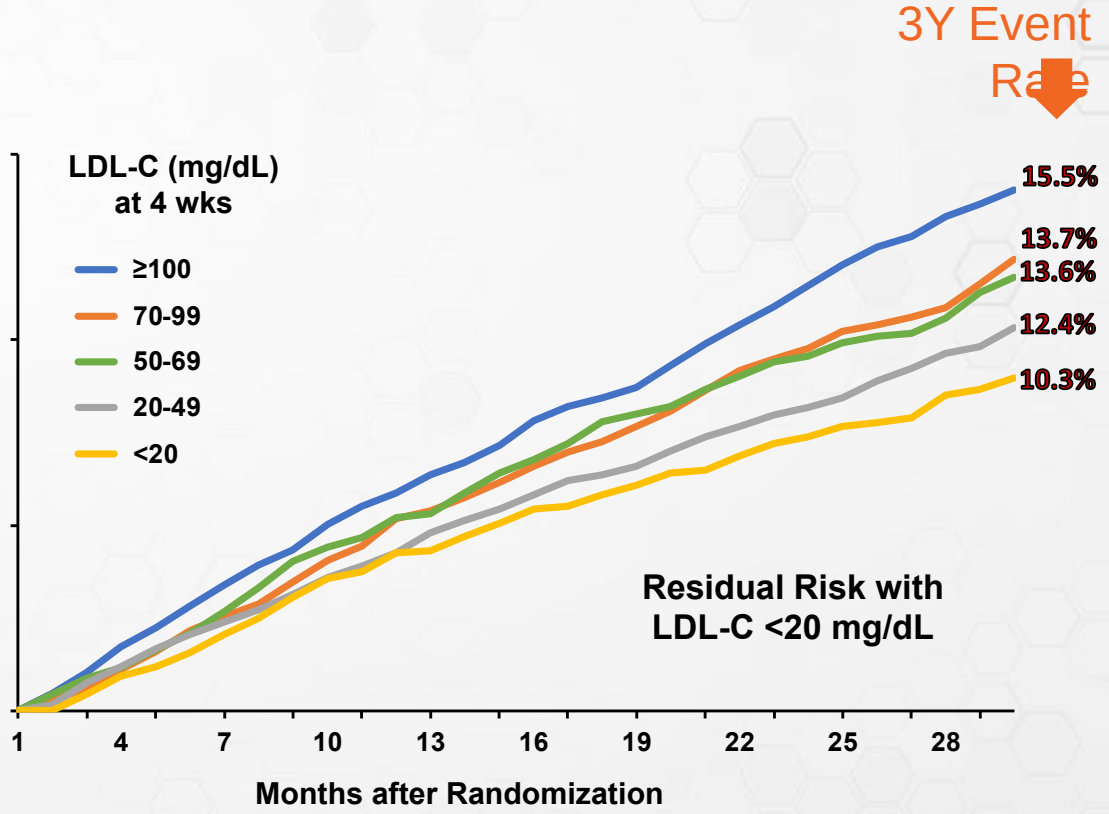
* https://www.cdc.gov/nchs/nvss/deaths.htm

† Based on death records received and processed as of March 21, 2021, for deaths occurring in the United States among US residents. Data included in this analysis include >99% of deaths that occurred in 2020. Ahmad FB, et al. *MMWR Morb Mortal Wkly Rep*. 2021;70(14):519-522.

Despite ↓ASCVD with Statin Monotherapy or in Combination with PCSK9i, Substantial CV Risk Remains

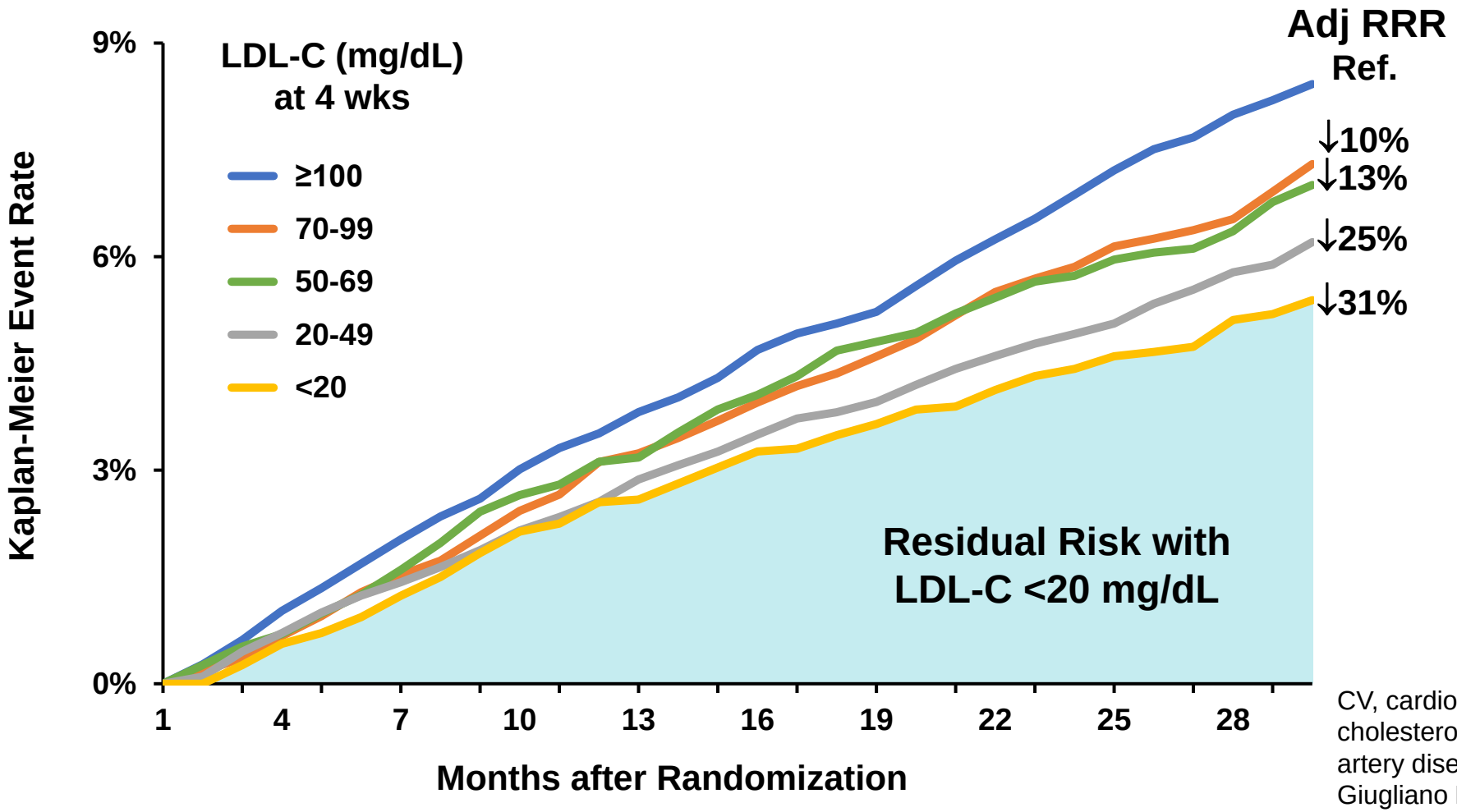


Adapted from MJ Chapman et al. *Pharm & Therapeutics* 2010; 314-45.



Giugliano RP et al. *Lancet.* 2017;390:1962-71.

Despite Low Achieved LDL-C at 1 Month, Risk of CV Death, MI, or Stroke Remains Substantial



FOURIER

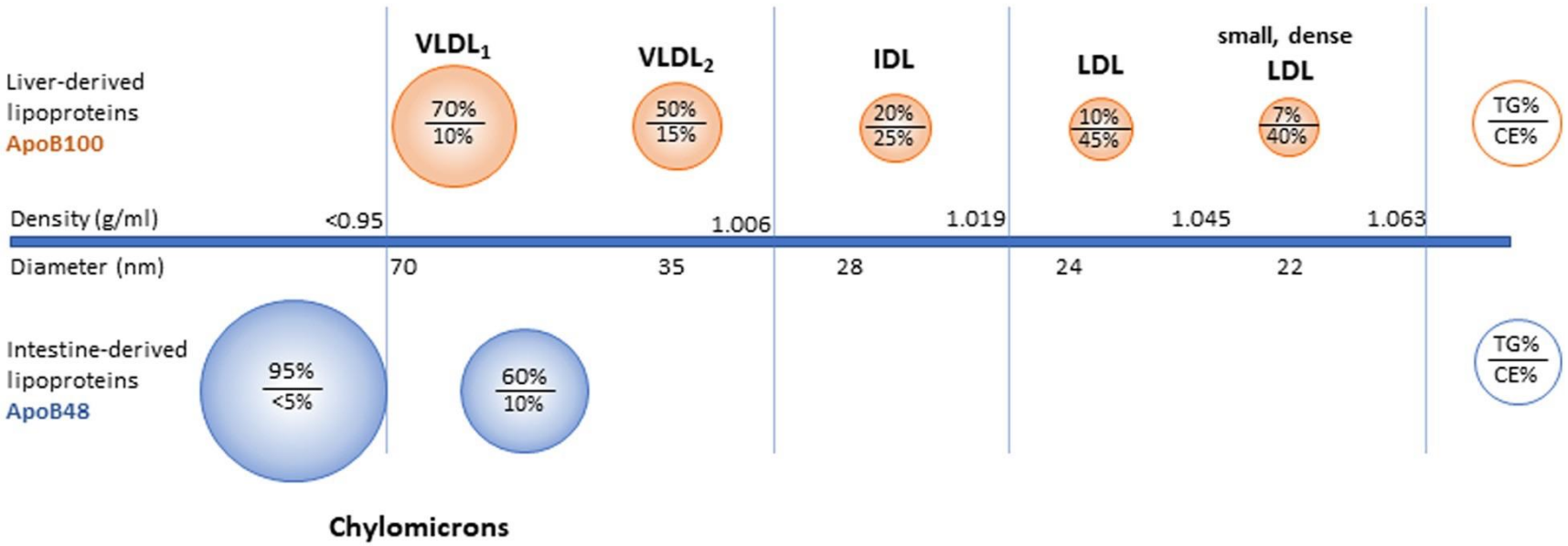
25,982 high-risk, stable patients with established CV disease (prior MI or stroke, or symptomatic PAD) randomized to evolocumab or placebo

CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; RRR, relative risk ratio.

Giugliano RP, et al. *Lancet.* 2017;390(10106):1962-1971.

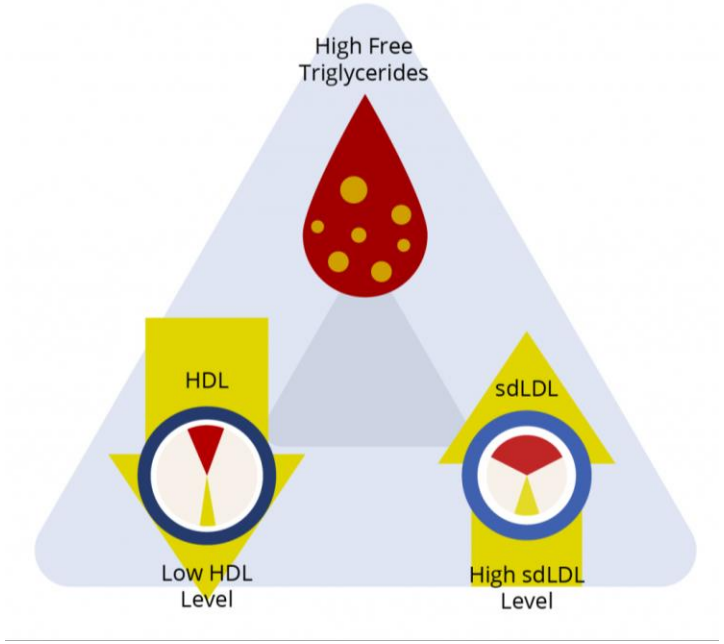
Management Strategies that Focus Exclusively on LDL Ignore Other Atherogenic Lipids

Atherogenic lipids (apo B containing lipid particles) include a range of particles



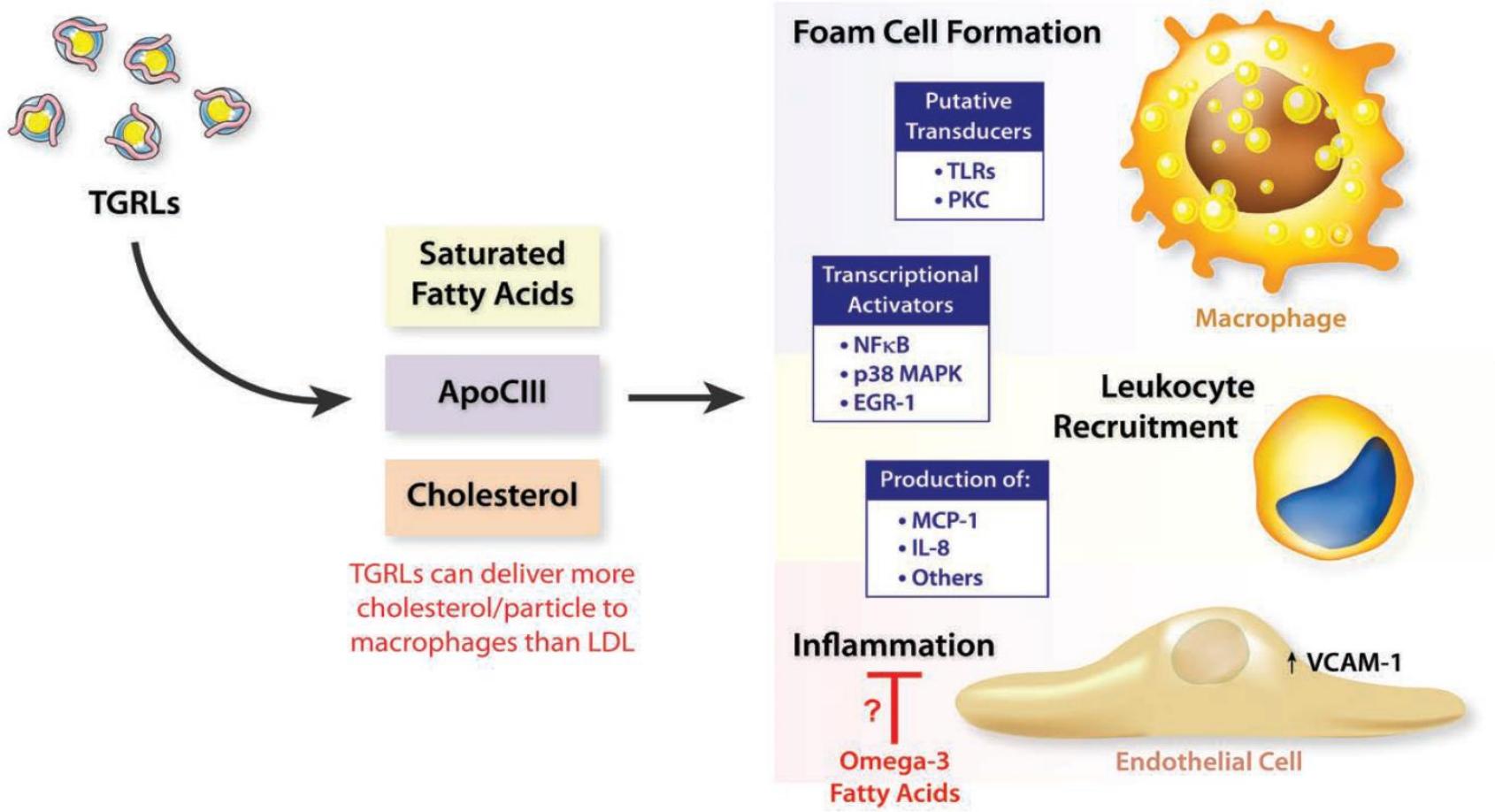
Atherogenic Dyslipidemia Triad

Clinical Markers



Ginsberg H et al. European Heart Journal 2021;(42):47:4791–4806,

Atherogenic Pathways for Triglyceride-Rich Lipoproteins (TGRLs)



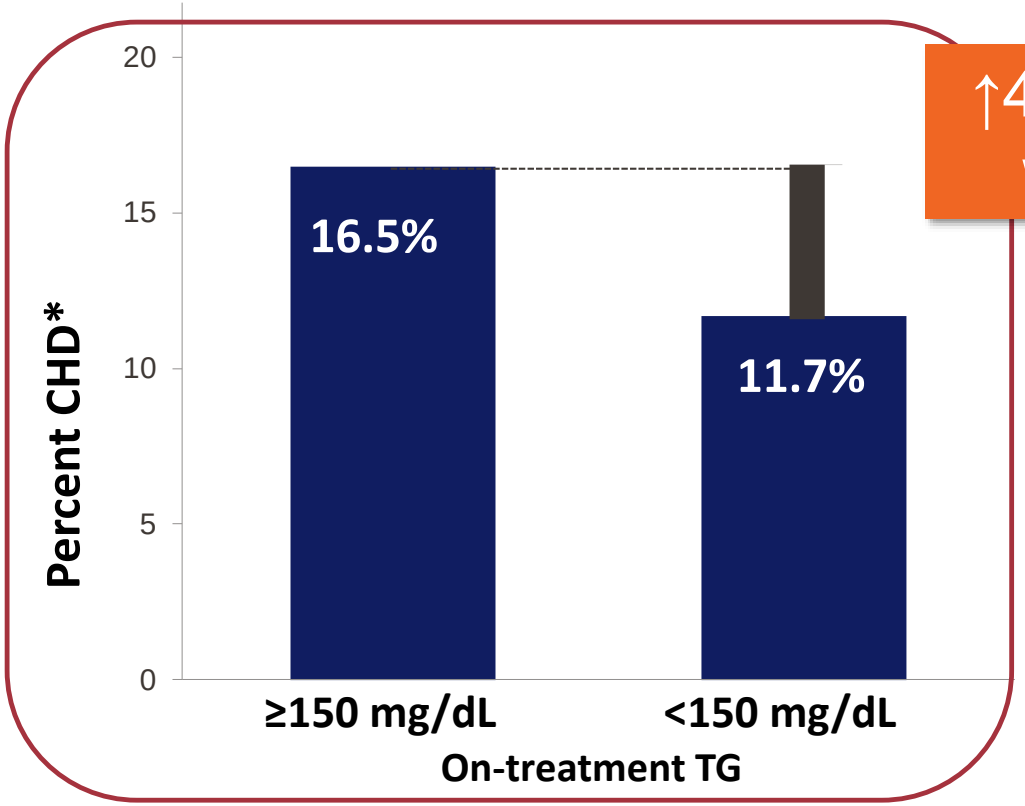
EGR-1, early growth response protein 1; LDL, low-density lipoprotein; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor-κB; PKC, protein kinase C; TLR, toll-like receptors; VCAM-1, vascular cell adhesion molecule 1.

Why Triglyceride-Rich Lipoproteins and Their Remnants Are *Causally* Related to ASCVD

- Observational studies: mild-moderate HTG is a strong and independent predictor of ASCVD and all-cause mortality[1]
- Mendelian randomization (genetic) studies: factors related to TG metabolism support *causality* in ↑CV risk[2]
  - Apo A-5
  - Apo C-3
  - ANGPTL4
  - ANGPTL3
  - Lipoprotein lipase
- TG-rich lipoproteins promote inflammation much *more* than does LDL[3]
- Remnant lipoproteins accumulate in arterial intima macrophage foam cells *more readily* than does LDL[1]

[1]*Nordestgaard B. Circ Res. 2016;118(4):547-563.* [2]*Rip J, et al. Arterioscler Thromb Vasc Biol. 2006;26(6):1236-1245;* [3]*Hansen SEJ, et al. Clin Chem. 2019;65(2):321-332. Plutzky PNAS 2006. Johansen, et al. J Lipid Res. 2011;52(2):189-206. Voight BF, et al. Lancet. 2012;380(9841):572-580. Nordestgaard BG, Varbo A. Lancet. 2014;384(9943):626-635. TG and HDL Working Group of the Exome Sequencing Project, National Heart, Lung, and Blood Institute. N Engl J Med. 2014;371(1):22-31. Wang J, et al. Nat Clin Pract Cardiovasc Med 2008;5(11):730-737.*

Residual HTG Predicted Residual ASCVD Risk Despite *LDL-C at Goal* on High-Intensity Statin Monotherapy

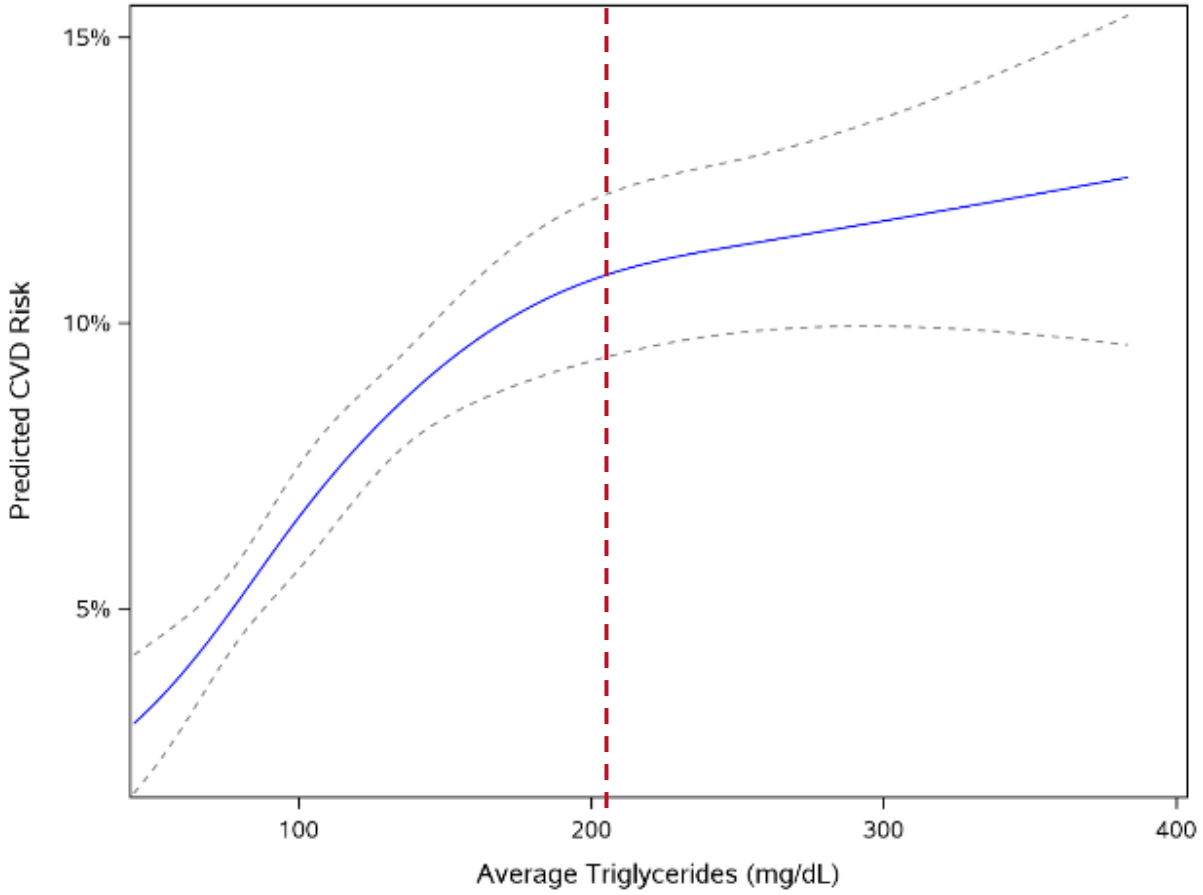


↑41% CVD Risk w/ mild HTG

Despite LDL-C <70 mg/dL on high-dose statin,
patients with TG ≥150 have a 41% higher risk of coronary events*

*Death, myocardial infarction, or recurrent acute coronary syndrome. PROVE-IT-TIMI 22, Miller M, et al. *J Am Coll Cardiol*. 2008;51(7):724-730.

Lower Triglycerides Are Better: Direct Association Between Average Triglyceride Level and CVD



95% confidence intervals shown as dotted lines.

Aberra T, et al. J Clin Lipidol. 2020; 14(4):438-447.e3.

- Data from 8,068 primary prevention patients in Atherosclerosis Risk in Communities Study (ARIC) and Framingham Offspring Study
- Baseline characteristics:
  - 40 to 65 years old
  - No CVD
- ≥2 TG measurements on record
- Endpoint: Time to MI, stroke, or CV death
- Follow-up for up to 10 years to first event

CVD events steeply increase across the entire range of TG levels to ~200 mg/dL, above which the relationship is less graded.

Summary

- Elevations in TG demonstrate increased risk in ASCVD events beyond monotherapy with statins **(residual TG-associated risk)**
- TGs and their remnants, TGRLs, are atherogenic **(biology)**
- Elevated TG levels are pervasive in the U.S. **(burden)**
- Guidelines are evolving to reflect these shifts **(treatment)**

Clinical Perspective on Reducing CV Events in the Patient with High TGs. Where We Stand After REDUCE-IT and STRENGTH

Peter Toth, MD, PhD

Director of Preventative Cardiology

CGH Medical Center

Sterling, IL

Professor of Clinical Family and Community Medicine

University of Illinois College of Medicine

Peoria, IL

A Revolution in Omega-3 Fatty Acid Research

Sources

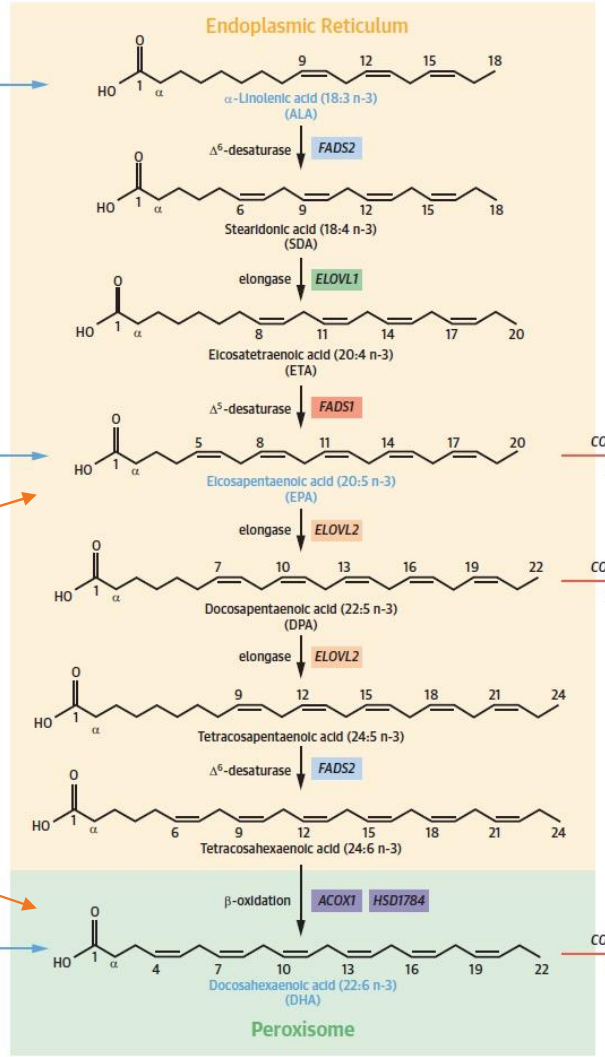
Chia seeds,
Flax seeds,
Walnuts

Marine fish
only

Prescription omega-3 fatty acid

Prescription omega-3 fatty acid

Marine fish
only



Metabolites

COX, LOX
CYP

Eicosanoids
F3 Isoprostanes
SPMs

COX, LOX
CYP

Docosanoids
SPMs

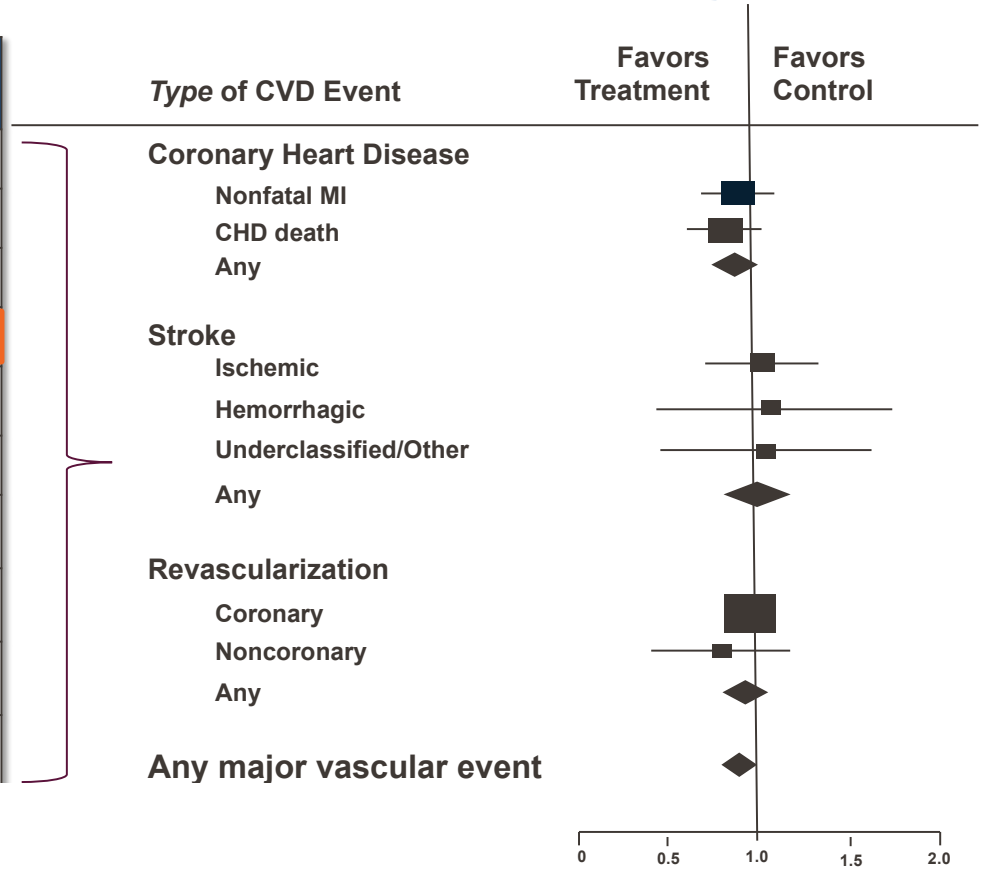
COX, LOX
CYP

Docosanoids
F4 Isoprostanes

Reproduced with permission. Bhatt DL, Budoff MJ, Mason RP. J Am Coll Cardiol. 2020;76(18):2098-2101.

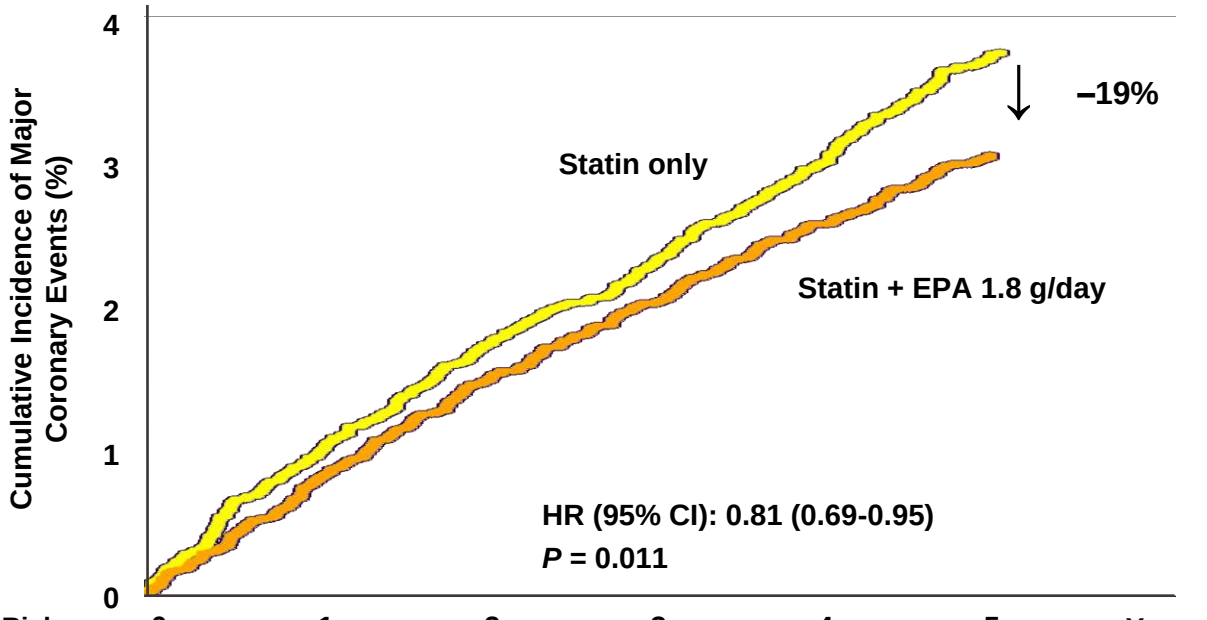
Lack of ↓CVD with Omega-3 FA: Due to Low Doses, Use of Dietary Supplements, Presence of DHA and/or Lack of Focus on HTG Subjects?

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 / 0	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

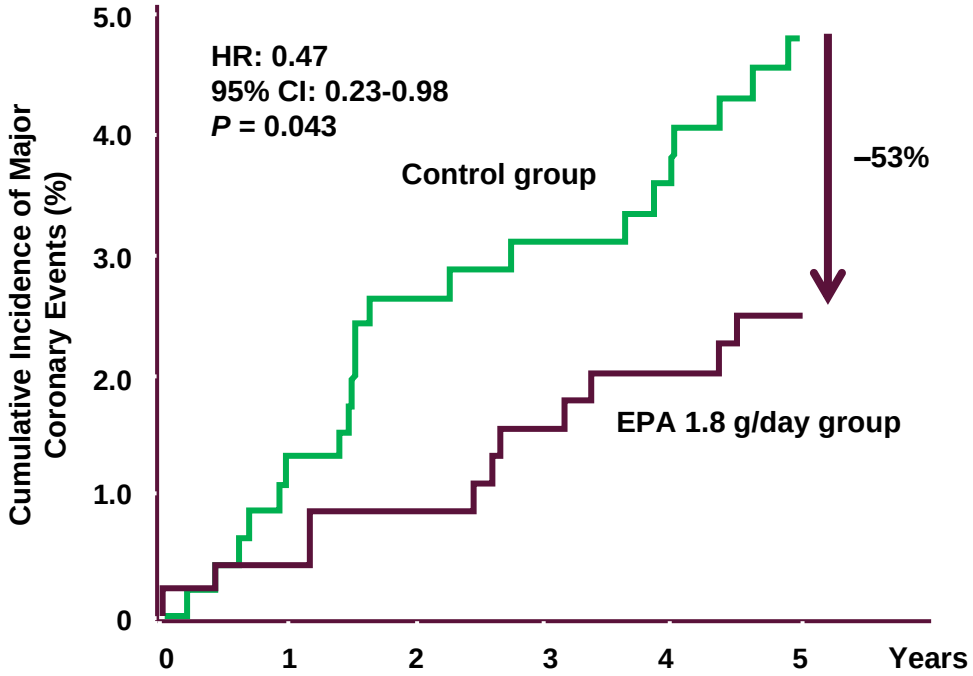


Aung T, et al. JAMA Cardiol. 2018;3(3):225-234.
Manson JE, et al. N Engl J Med. 2019;380(1):23-32.
man L, et al. N Engl J Med. 2018;379(16):1540-1550.
Bhatt DL, et al. N Engl J Med. 2019;380(1):11-22.

JELIS: Rx Pure EPA + Statins Led to ↓Major Coronary Events* in Hypercholesterolemic Patients on Statins and in HTG Subgroup†



No. at Risk	0	1	2	3	4	5	Years
Control	9319	8931	8671	8433	8192	7958	
EPA	9326	8929	8658	8389	8153	7924	



No. of patients						
Control	475	444	432	414	400	392
EPA	482	455	443	427	413	403

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 nonfatal MI, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass graft.

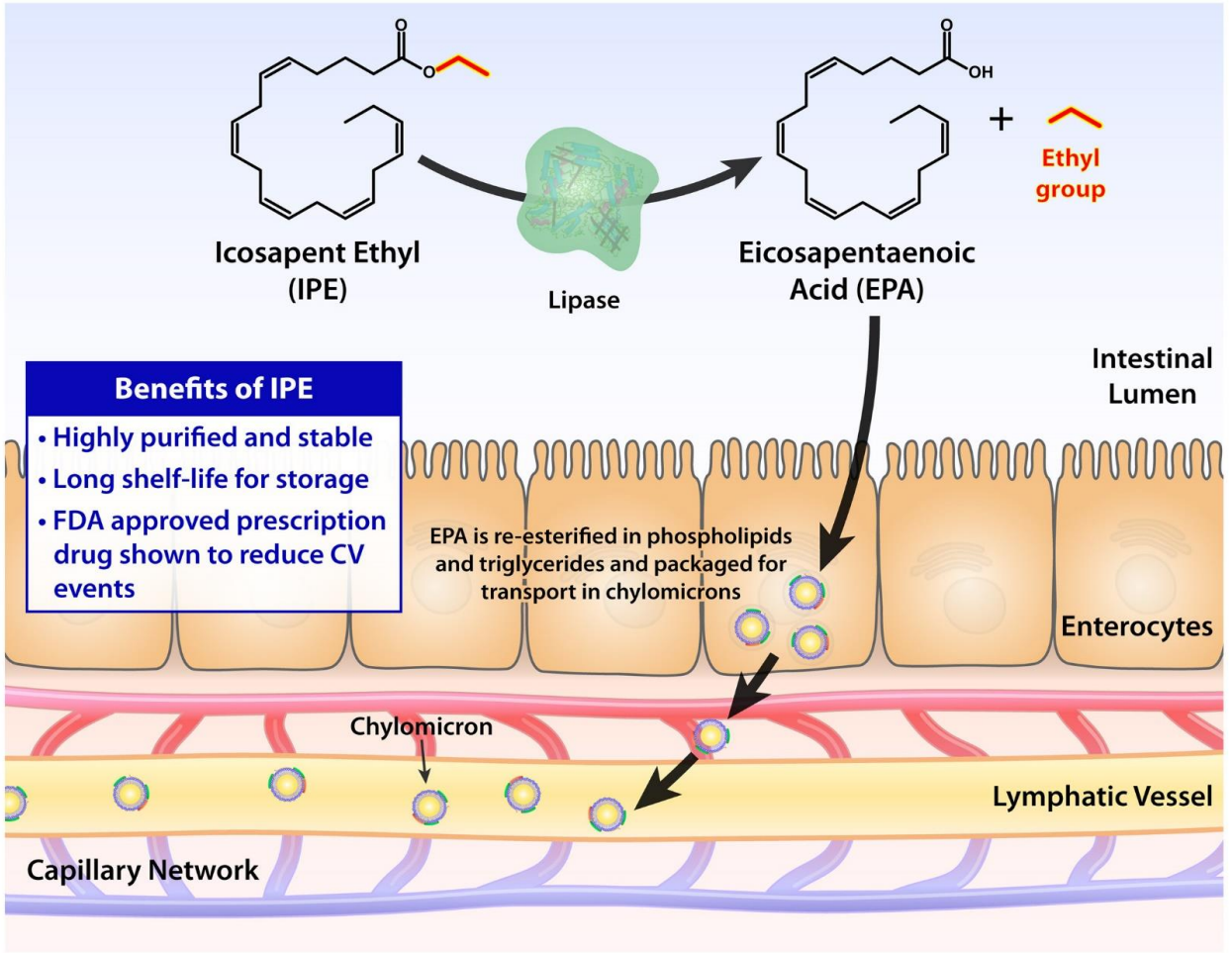
HR and *P* value adjusted for age, gender, smoking, diabetes, and HTN.

† Prespecified.

Yokoyama M, et al. *Lancet.* 2007;369(9567):1090-1098.

Saito Y, et al. *Atherosclerosis*. 2008;200(1):135-140.

Intestinal Processing and Absorption of Icosapent Ethyl (IPE)

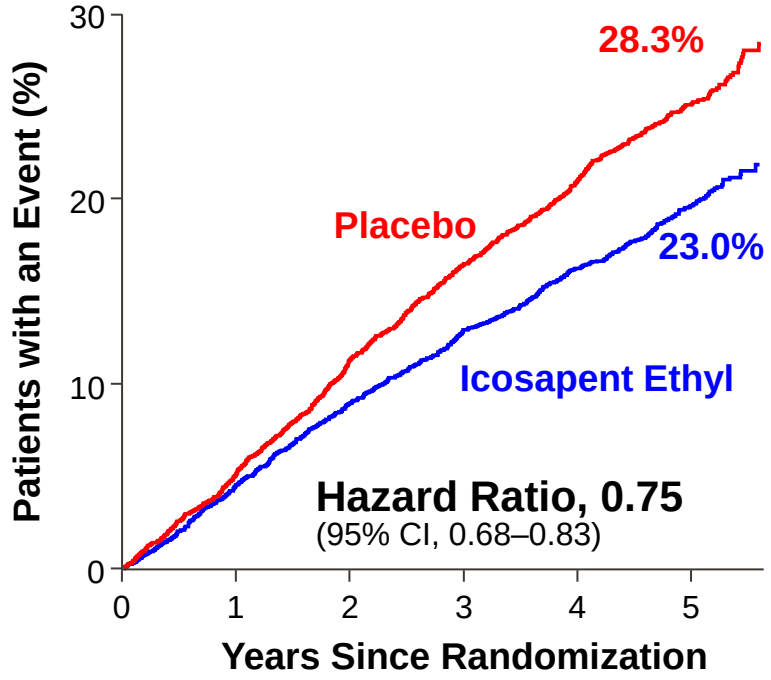


Wang X, Verma S, Mason RP, Bhatt DL. *Curr Diab Rep*. 2020;20(11):65.

REDUCE-IT Primary and Secondary Endpoints

Primary Composite Endpoint:

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



RRR = 24.8%

ARR = 4.8%

NNT = 21 (95% CI, 15–33)

***P* = 0.00000001**

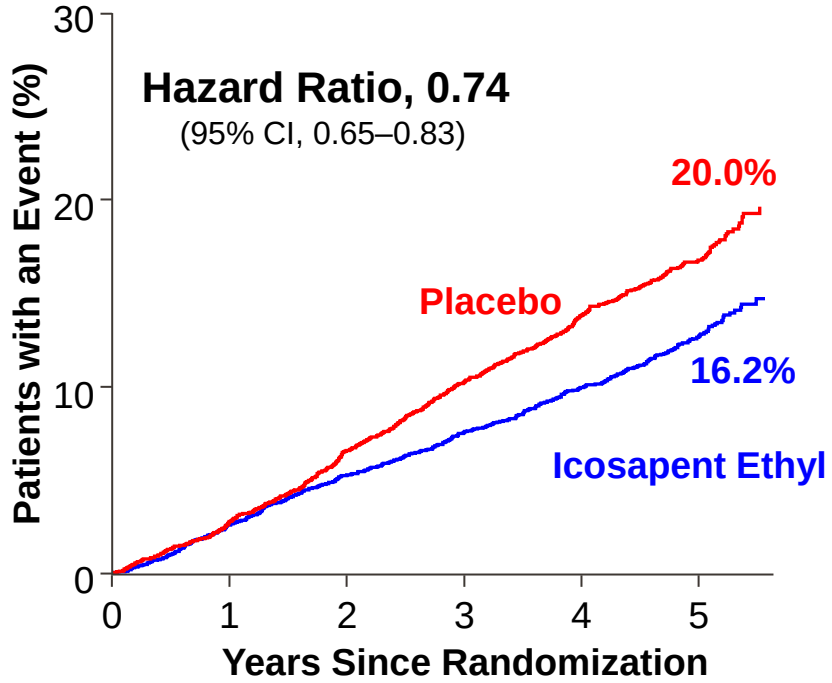
Bhatt DL, et al. *N Engl J Med*. 2019;380(1):11-22.

Key Inclusion Criteria

- Statin-treated men and women ≥45 yrs
- Established CVD (~70% of patients) or DM + ≥1 risk factor
- TG ≥ 150 mg/dL and <500 mg/dL
- LDL-C >40 mg/dL and ≤100 mg/dL

Key Secondary Composite Endpoint:

CV Death, MI, Stroke



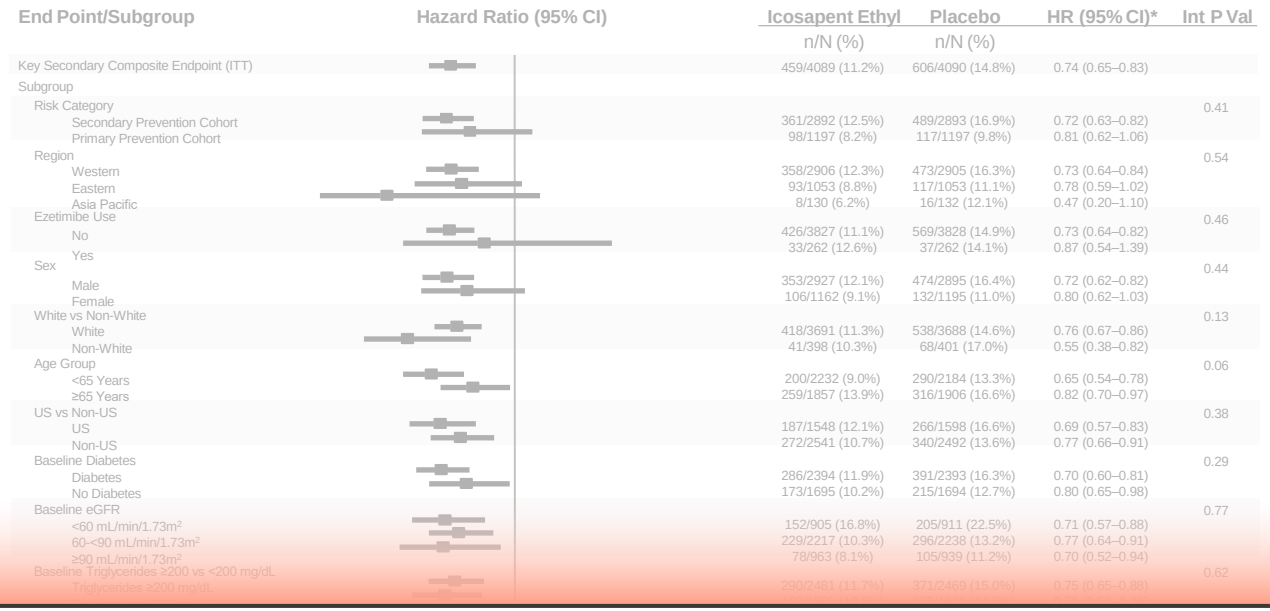
RRR = 26.5%

ARR = 3.6%

NNT = 28 (95% CI, 20–47)

***P* = 0.0000006**

↓CVD with IPE Did *NOT* Vary by *Baseline* TG *(similar HR if TG ≥ or < 150 mg/dL)*



Subgroup	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	Int P Val
Baseline Triglycerides ≥150 vs <150 mg/dL					0.68
Triglycerides ≥150 mg/dL		421/3674 (11.5%)	546/3660 (14.9%)	0.74 (0.65–0.84)	
Triglycerides <150 mg/dL		38/412 (9.2%)	60/429 (14.0%)	0.66 (0.44–0.99)	

Bhatt DL, et al. *N Engl J Med.* 2019;380(1):11-22.

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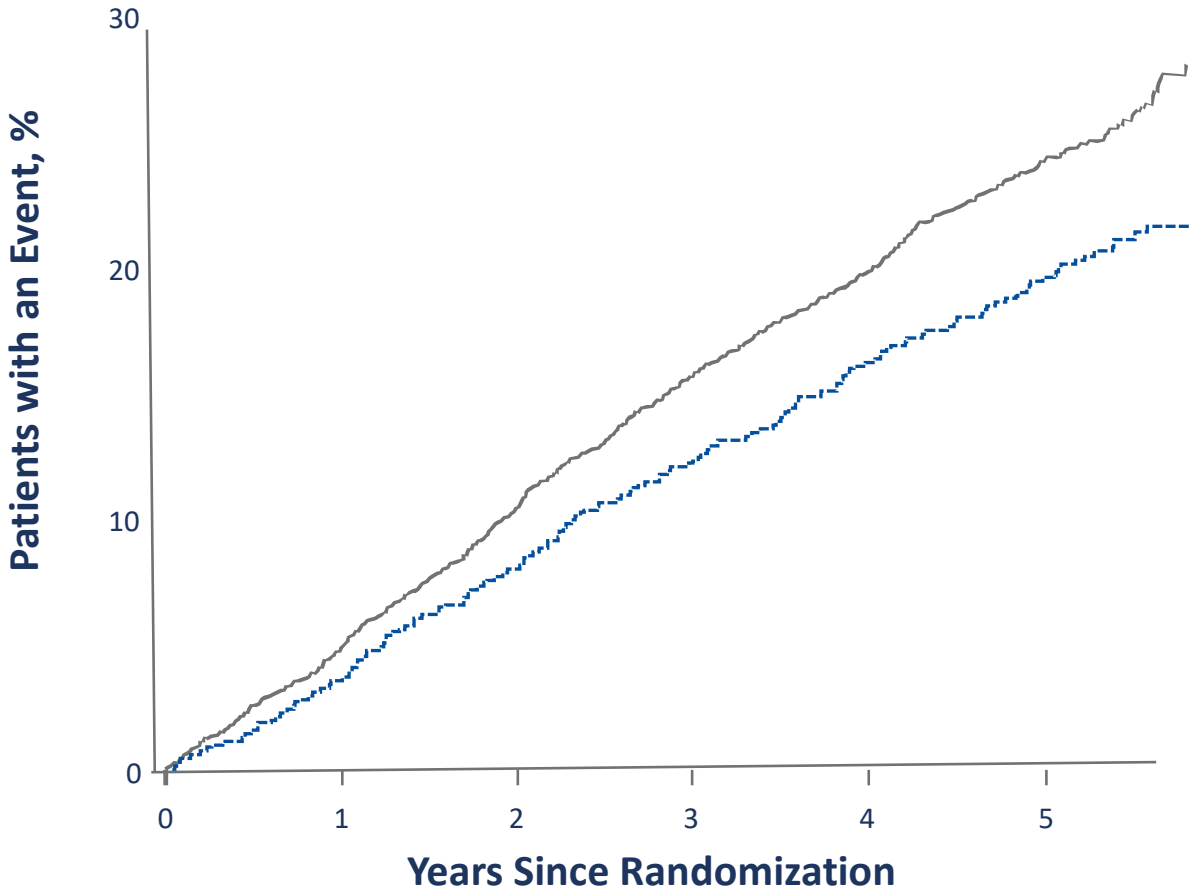
REDUCE-IT: On-Treatment TG (< or ≥ 150) Did Not Alter CVD Risk



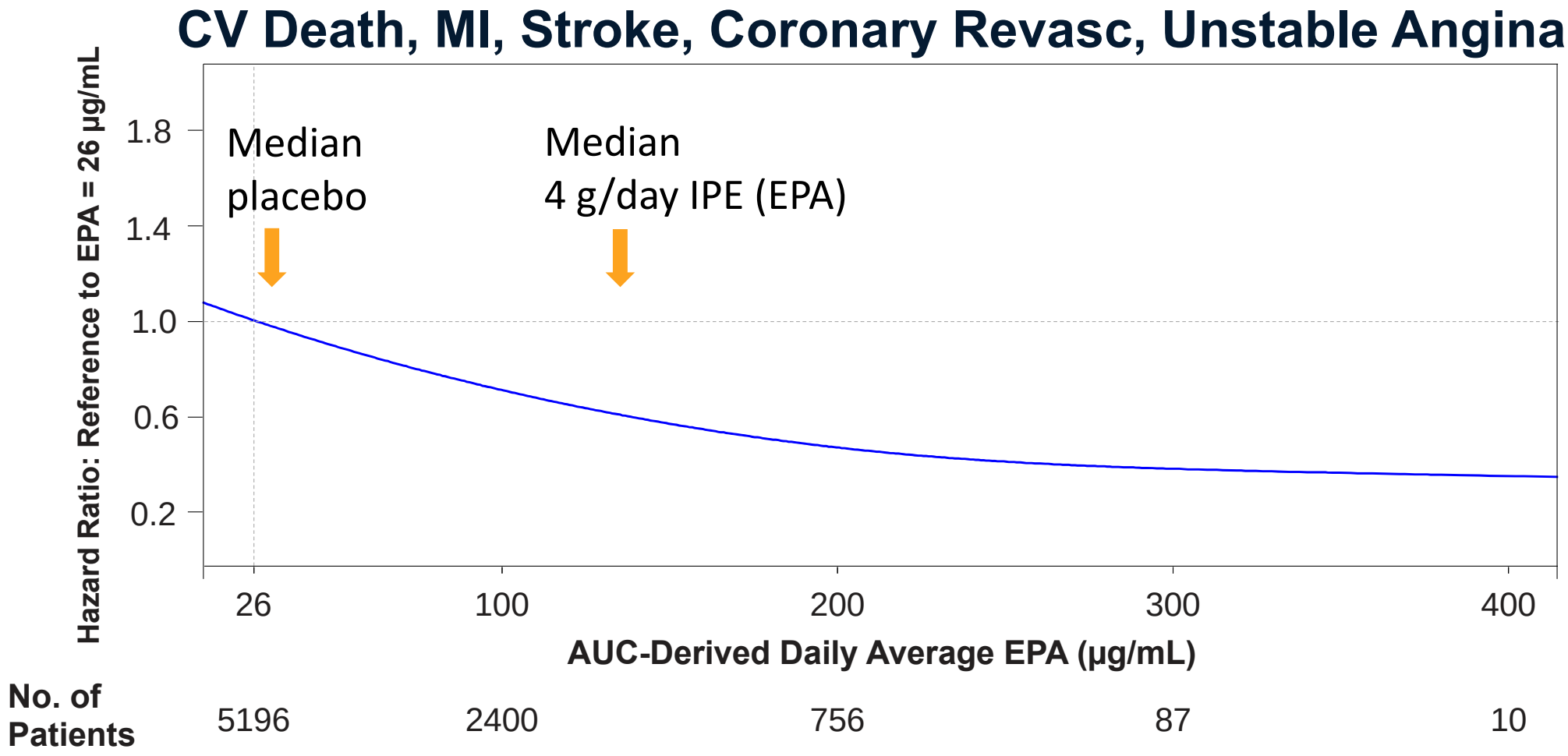
Statin + Placebo (Reference)

Statin + IPE *TG ≥150 mg/dL*, HR 0.71 (0.63-0.79)

Statin + IPE *TG <150 mg/dL*, HR 0.71 (0.60-0.81)

First event composite: CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, hospitalization for unstable angina.
Bhatt DL, et al. *N Engl J Med.* 2019;380(1):11-22.

Primary Endpoint by On-Treatment Serum EPA

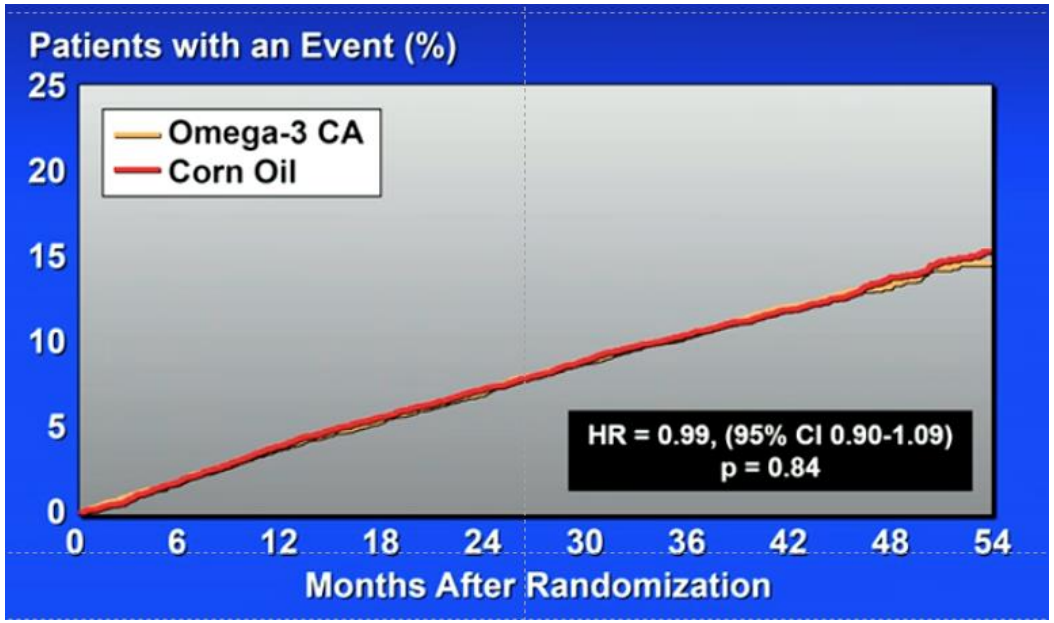


Adapted from Bhatt DL. Abstract presented at: ACC.20/WCC Virtual Meeting; March 30, 2020.

STRENGTH Trial Design, Details, and Primary Endpoint

- Randomized 13,078 patients Oct. 2014 – June 2017
- Trial stopped by Data Monitoring Board for “futility” January 8, 2020, after review of 1,384 MACE outcomes
- 1,580 MACE endpoints accrued by last patient visit May 14, 2020
- Median follow-up time 42.0 months, and study drug 38.4 months

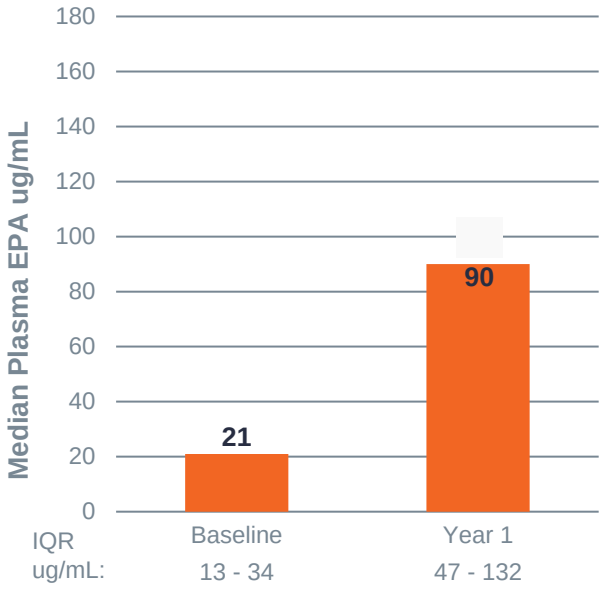
Primary Endpoint: MACE (CV death, MI, stroke, coronary revascularization, or hospitalization for unstable angina)



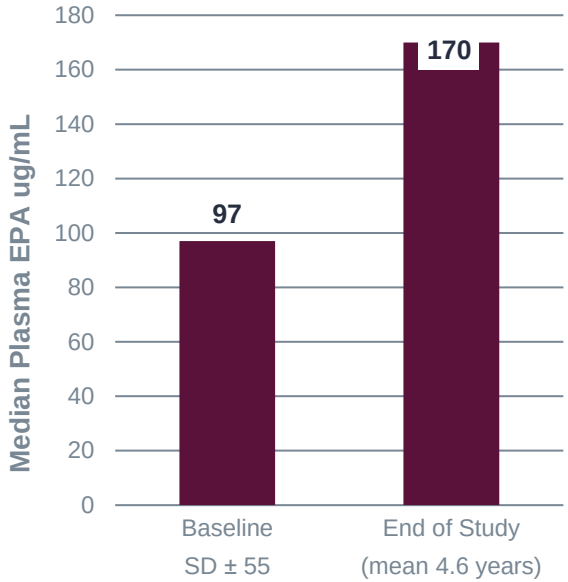
Lincoff AM. American Heart Association Virtual Scientific Sessions; November 15, 2020. Nicholls SJ, et al. *JAMA*. 2020;324(22):2268-2280.

Baseline and Achieved EPA Levels in Omega-3 CVOTs: Cross-Study Comparison

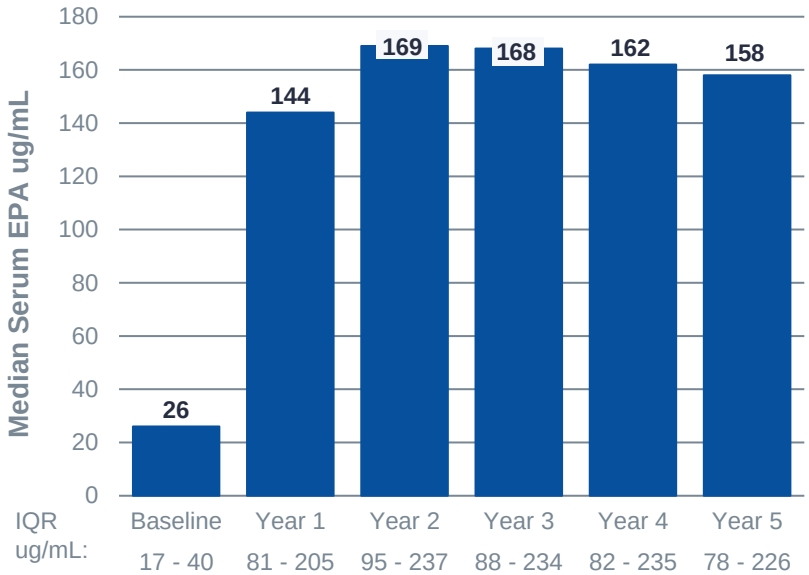
STRENGTH[1]
Plasma EPA



JELIS[2]
Plasma EPA



REDUCE-IT[3]
Serum EPA



Drug:	850 mg EPA/DHA carboxylic acid/ 1-g capsule	300 mg capsules of >98% EPA ethyl esters	1g icosapent ethyl (EPA ethyl ester)/ 1-g capsule
Dose:	4 g/d as 2 capsules 2x daily	1.8 g/d as 2 capsules 3x daily	4 g/d as 2 capsules 2x daily
Population:	International	Japanese	International

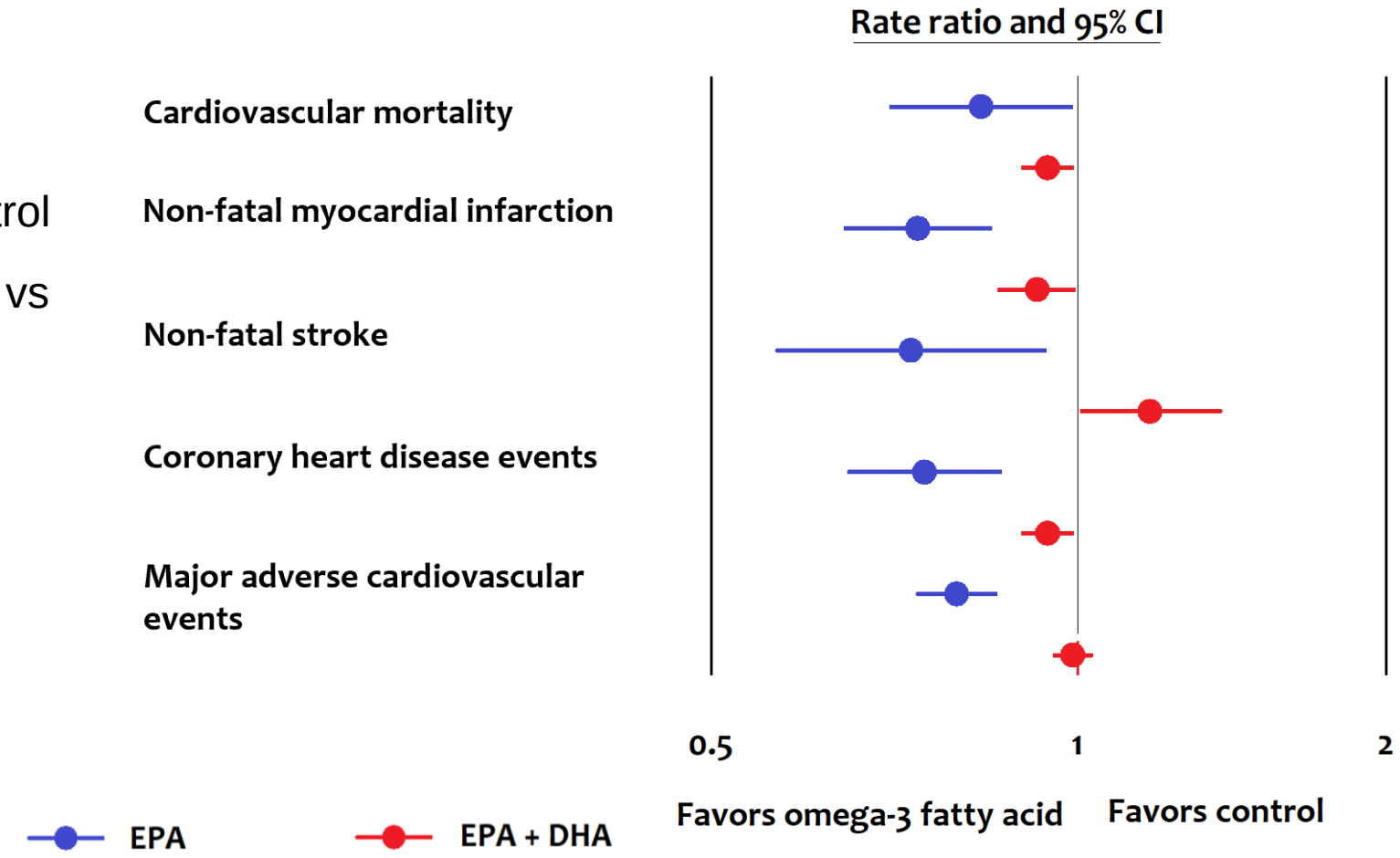
Plasma and serum EPA levels have been strongly correlated, with plasma levels being slightly higher than serum levels[4,5]

1. Nicholls SJ, et al. *JAMA*. 2020;324(22):2268-2280. 2. Itakura H, et al. *J Atheroscler Thromb*. 2011;18(2):99-107. 3. Bhatt DL, et al. ACC 2020 Scientific Session (ACC.20)/World Congress of Cardiology (WCC); March 30, 2020. Abstract 20-LB-20501-ACC. 4. Dunbar RL, et al. Poster presented at the Gordon Conference on Atherosclerosis; Newry, Maine; June 16-21, 2019. 5. Dunbar RL, et al. Poster presented at NLA Scientific Sessions; December 9-12, 2020.

Effect of Omega-3 Fatty Acids on CV Outcomes

Meta-Analysis of OM3 Trials

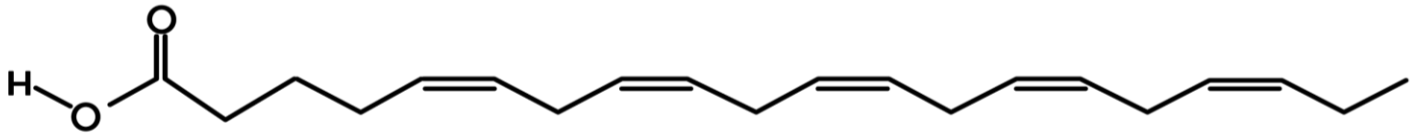
- 38 trials
  - 4 compared EPA vs control
  - 34 compared EPA+DHA vs control
  - 22 studied primary prevention

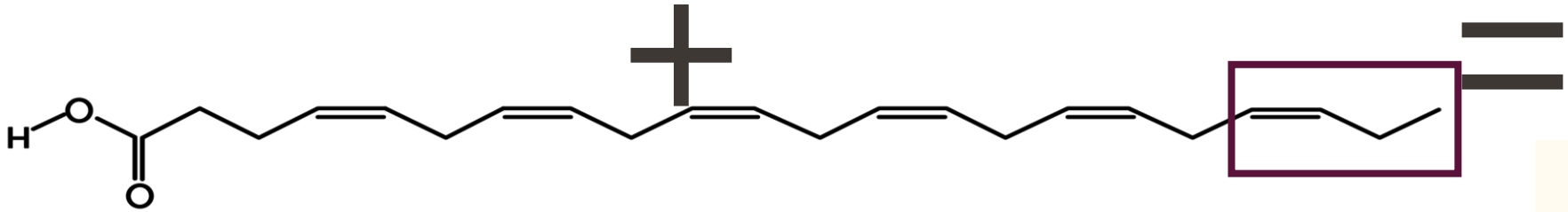


Khan SU, et al. EClinicalMedicine. 2021;38:100997.

EPA Versus DHA: They Look Similar but Are Very Different!

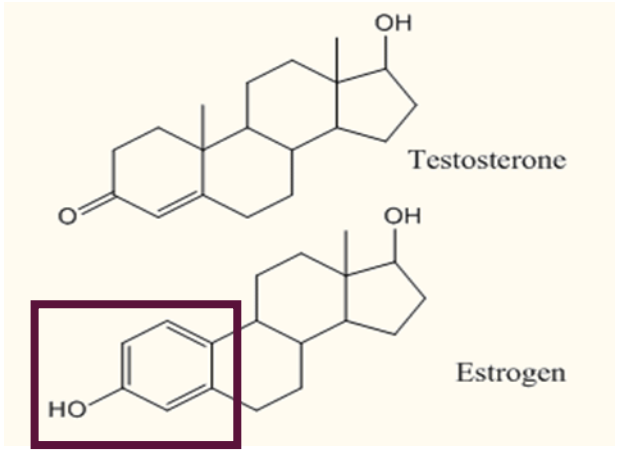
Eicosapentaenoic acid (EPA) 20:5





Docosahexaenoic acid (DHA) 22:6

Omega-3 PUFA

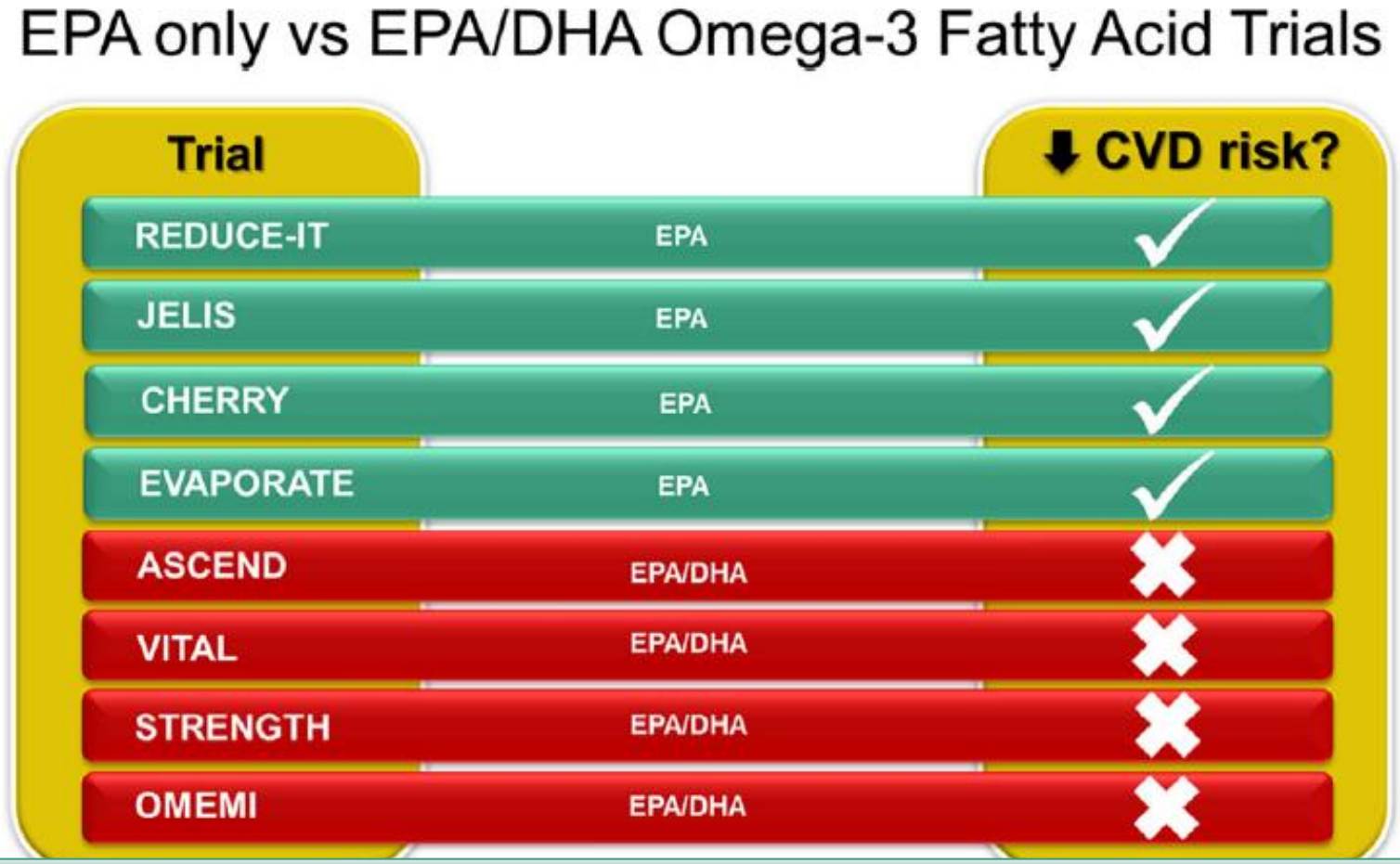


Comparative Effects of Omega-3 Fatty Acids and TG-Lowering Agents on Plaque Development

Mechanism of Action	EPA	DHA	Fibrates/Niacin
Does not raise LDL in pts with very high TGs[1,2,3]	+	–	–
Reduces hsCRP in patients with elevated TGs[4,5,6]	+	–	+
Maintains membrane cholesterol distribution[7]	+	–	–
Preserves membrane stability[7,8]	+	–	–
Inhibits cholesterol domains[9,10]	+	–	–
Enhances endothelial function with statin[11]	+	–	–
Inhibits sdLDL, LDL, VLDL, HDL oxidation[9,10,12,13]	+	–	–
Enhances ABCA-1 Cholesterol Efflux[14]	+	–	N/A

[1]Bays HE et al. *Am J Cardiol.* 2011; 108:682-690; [2]Jacobson T A et al. *J Clin Lipidol*. 2012; 6:5-18; [3]Goldberg AC et al. *Clin Ther.* 1989;11(1):69-83; [4]Bays HE et al. *Am J Cardiol.* 2013; 13:37-46; [5]Dunbar RL et al. *Lipids in Health and Disease*. 2015; 14:98; [6]Belfort R et al. *J Clin Endocrin Metabol.* 2010; 95:829-836; [7]Mason RP et al. *Biochimica et Biophysica Acta*. 2016; 1858:3131-3140; [8]Sherratt SC and RP Mason. *Chem Phys Lipid*. 2018; 212:73-79; [9]Sherratt SC et al. *Biochimica et Biophysica Acta.* 2020; 1862(7); [10]Mason RP and RF Jacob. *Biochimica et Biophysica Acta.* 2015; 1848:502-509;; Sherratt SCR, Juliano R and Mason RP, *Biochim Biophys Acta* doi.org/10.1016/j.bbamem.2020.183254; [11]Mason RP et al. *Biomed Pharmacother*. 2018; 103:1231-1237; [12]Mason RP et al. *J Cardiovasc Pharmacol.* 2016; 68:33-40; [13]Sherratt SC and RP Mason. *Biochem Biophys Res Comm.* 2018; 496:335-338.[14]Dakroub H et al. *Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids*. 2021;1866:159016.

What Have We Learned From the Recent Marine Omega-3 Fatty Acid Clinical Trials?



Studies demonstrate that EPA (without DHA) on top of standard of care consistently demonstrate greater reduction in atheromatous volume or CVD events than standard-of-care therapies alone.

Iqbal T, Miller M. *Curr Cardiol Rep*. 2021;23(8):111.

Distinct Differences Exist Between Marine Omega-3 Fatty Acids EPA and DHA

- Membrane stabilization and fluidity are very different
- Different resolvins are engaged
- Activity on oxidized LDL-C is different
- Different effects of anti-inflammatory biomarkers such as hsCRP

Mason RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol*. 2020;40(5):1135-1147. Sherratt SCR, Mason RP. *Chem Phys Lipids*. 2018;212:73-79. Mason RP, et al. *J Cardiovasc Pharmacol*. 2016;68(1):33-40. Kohli P, Levy BD. *Br J Pharmacol*. 2009;158(4):960-971.

Summary

- There remains substantial ASCVD risk despite low levels of LDL-C; elevated triglycerides and their remnants account for a portion of this residual risk
- Combination therapy of statins with fibrates or niacin have not shown effectiveness and are generally not recommended to reduce ASCVD event risk
- REDUCE-IT was a landmark trial showing that icosapent ethyl 4 g/day in addition to maximally tolerated statin therapy could reduce ASCVD events significantly, though its impact on triglycerides appears not to account for all of the substantial benefits of this therapy

Clinical Update: Using Statins and the Newly Recommended Statin Adjunct IPE (pure EPA) for CV Event Reduction

Christie Ballantyne, MD

Classification of Fasting TG Levels (2011 AHA/2014 NLA)

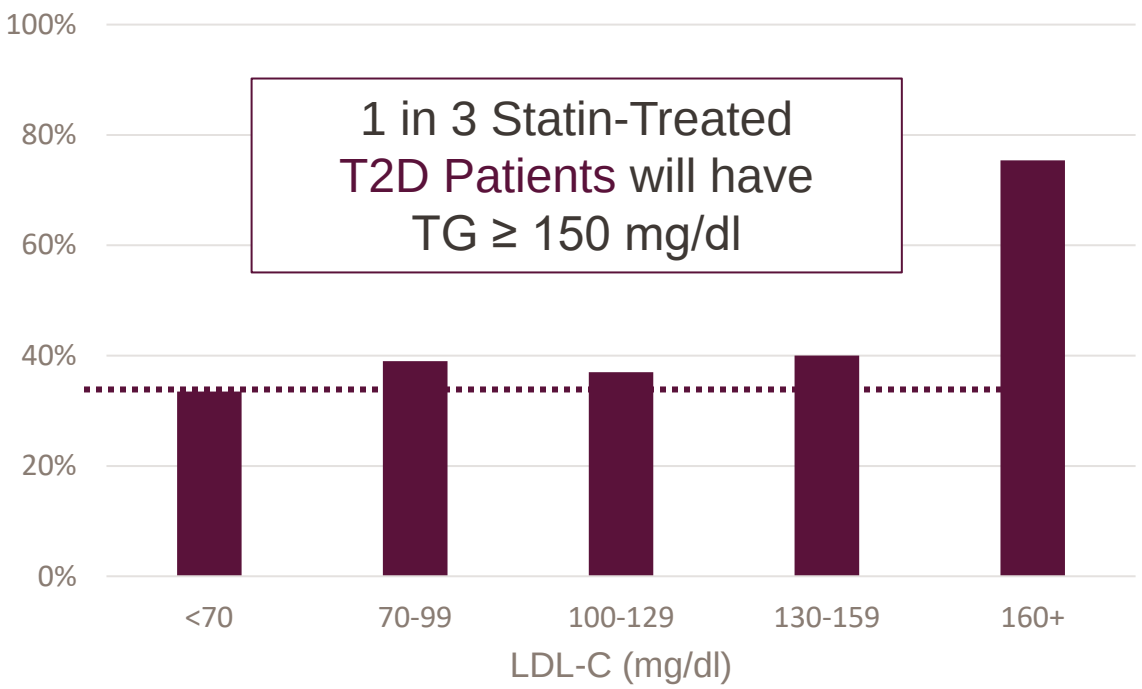
Fasting Triglycerides (mg/dL)	
<100	Optimal
<150	Normal
150–199	Borderline high
200–499	High
≥500	Very high

AHA=American Heart Association; NLA=National Lipid Association.

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

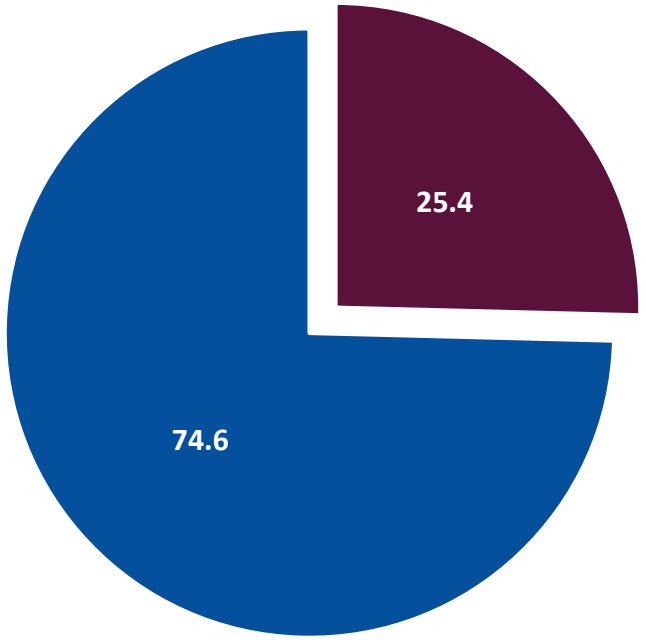
Contemporary Rates of HTG in Statin Treated T2D or CVD

NHANES 2007-2014



W Fan et al, Diabetes Care 2019;42:2307-14.

Ontario CVD Cohort (n=196,717)



1 in 4 CVD Patients
LDL < 100 mg/dl
TG ≥ 135 mg/dl

Lawler P et al, Eur Heart J 2020;41:86-94.

First, Rule Out Major Secondary Causes of Hypertriglyceridemia

Conditions

- Diabetes mellitus, insulin resistance
- Obesity
- Alcohol
- Chronic kidney disease
- Nephrotic syndrome
- Hypothyroidism
- HIV
- Hepatocellular disease
- Inflammatory diseases

Medications

- Oral estrogens
- Bile acid sequestrants
- Antiretroviral regimens
  - especially for HIV disease
- Phenothiazines – 2nd generation
- Nonselective beta-blockers
- Diuretics
- Glucocorticoids
- Immunosuppressants
- Tamoxifen
- Isotretinoin

Bays HE. In: Kwiterovich PO Jr, ed. *The Johns Hopkins Textbook of Dyslipidemia*. 1st ed. Lippincott Williams & Wilkins;2010:245-257.

Second, Optimize Diet and Exercise

- Most important is what the patient can do, and do lifelong
- Need consistent, relentless messaging from medical professionals

Lifestyle Intervention	Reduction in Triglycerides (%)	Qualifier
Weight loss (54-56)	Up to 70%	Although most patients will likely experience reductions in triglyceride levels of 10%-20% with weight loss, evidence suggests that in some patients, a reduction in triglyceride levels of up to 70% may be achieved
Dietary modifications (including alcohol—restrict or abstain completely) (57)	>70%	Response may vary depending on the baseline triglyceride level and how strictly dietary recommendations are followed
Physical activity and exercise (58-62)	Up to 30%	Response may vary depending on the type, duration, and intensity of activity

- Access and ability to pay for fresh fruits, vegetables, lean meat
- Processed foods require no preparation time
- In many places, unhealthy calories are simply most affordable option.
- But with extheercise (cheap), a good rule of thumb is every 5 to 10% decrease in weight gets about 20% lower triglycerides.

Virani S. 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients with Persistent Hypertriglyceridemia. JACC 2021;28(9)960-993

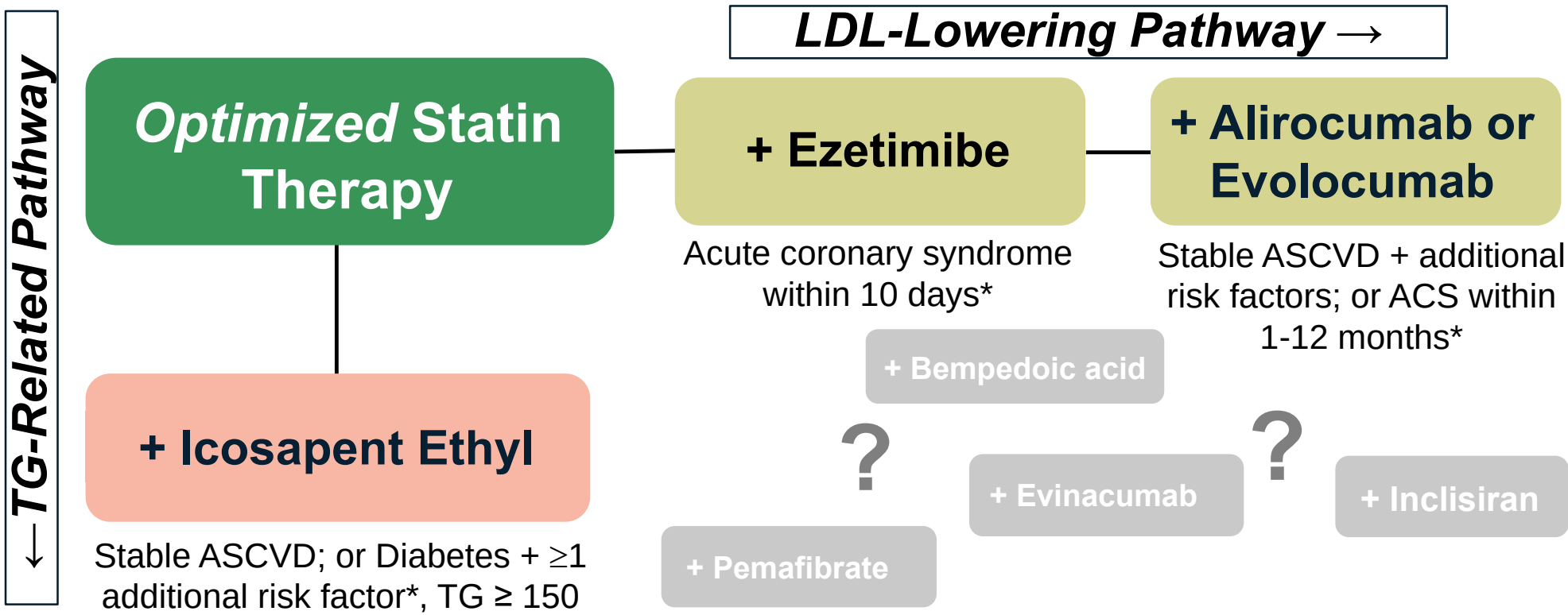
Key Prompts and Messaging Regarding Diet and Exercise

Component	Ask Your Patients	Clinical Message
Sugar-Sweetened Beverages	• How often do you drink sugar-sweetened beverages (soft drinks, fruit drinks, or sports/energy drinks)?	• Instead, try no-calorie sparkling water with lemon slice
Sweets	• How often do you eat sweets (pastries, desserts, or candy)?	• Instead, try fresh fruit or a small piece of dark chocolate
Alcohol	• How often do you drink alcoholic beverages (beer, wine, or spirits)?	• If you drink alcohol, have 1 beer or glass of wine instead of a mixed drink (high in alcohol, sugar, and calories)
Saturated Fats	• How often do you eat foods that are deep fried or high in saturated fats (butter, coconut oil, full-fat dairy, fatty red meat)?	• Try lean meats (chicken). Switch to liquid oils (canola or olive) instead of butter or tropical oils. Try switching to low-fat dairy.
Weight	• Have you gained any weight in the past year?	• If you are ready to lose weight, follow a healthy weight loss diet that achieves slow, steady (and sustained) weight loss instead of a fad diet
Exercise	• What do you do for physical activity? How often?	• Incorporate walks with small weights • Park farther away, take stairs, stand more

Be Specific
Be Numeric

Virani S, et al. *J Am Coll Cardiol*. 2021;78(9):960-993

Third, Medical Therapy



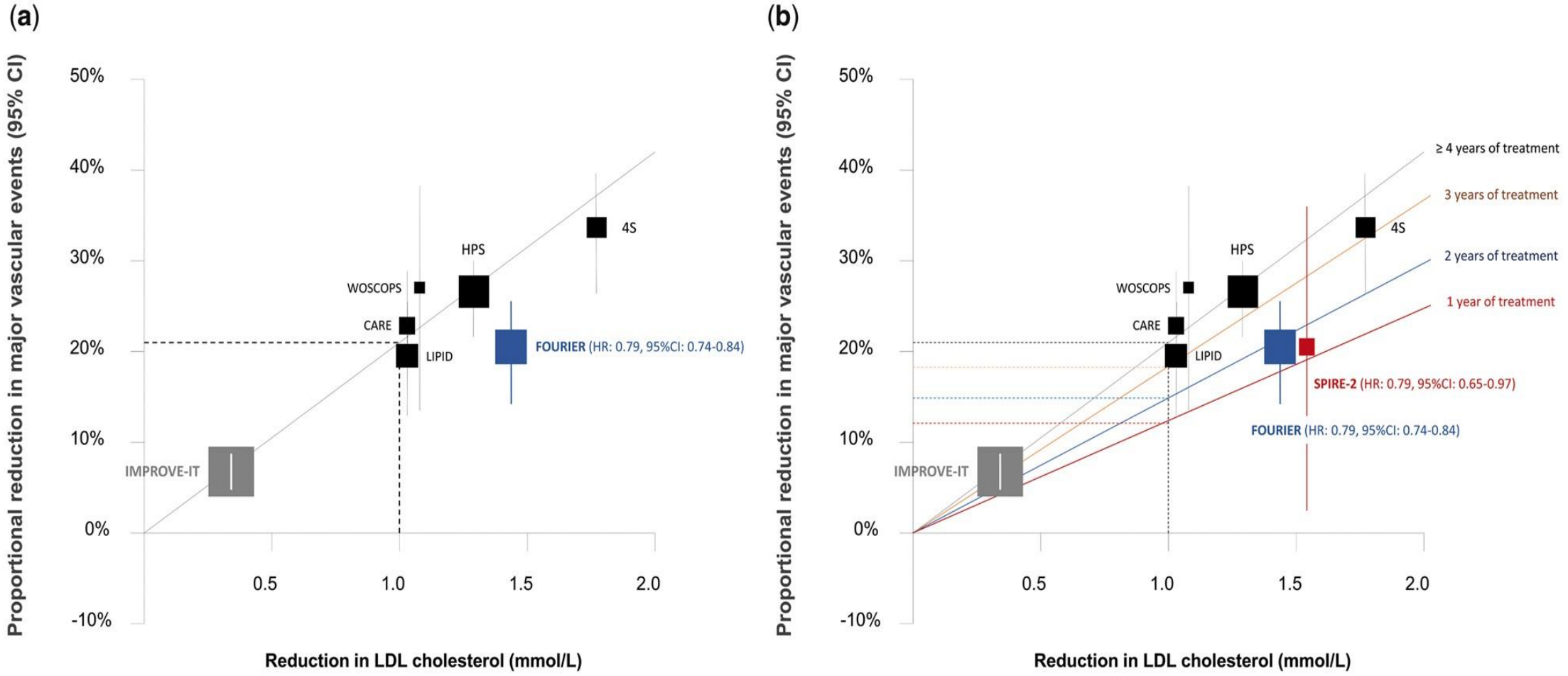
*Major inclusion criteria for respective CVOTs.
ACS=acute coronary syndrome; ASCVD=atherosclerotic cardiovascular disease. HeFH=Heterozygous familial hypercholesterolemia
After Orringer CE. *Trends in Cardiovasc Med*. 2019. Apr;30(3):151-157.

Intensity of Statin Therapy

HIGH RISK PATIENT	MODERATE RISK PATIENT	LOW RISK PATIENT
High Intensity Statin	**Moderate Intensity Statin**	**Low Intensity Statin**
Daily dose lowers LDL-c ~50%	Daily dose lowers LDL-c ~30% -50%	Daily dose lowers LDL-c <30%
Atorvastatin (40†)-80 mg **Rosuvasatin 20** *(40)* **mg**	Atorvastatin 10 (*20*) mg Rosuvastatin *(5)* 10 mg Simvastatin 20-40 mg‡ Pravstatin 40 *(80)* mg Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* Pravastatin 10-20 mg Lovastatin 20 mg *Fluvastatin 20-40 mg* *Pitavastatin 1 mg*

Stone NJ, et al. *Circulation*. 2014;129(25 Suppl 2):S1-S45.

Every 40 mg/dL Reduction in LDL ≈ 25% Reduction in Hard MACE (CV Death, MI, Stroke)



Ference, BA, et al. *Eur Heart J*. 2018;39(27):2540-2545.

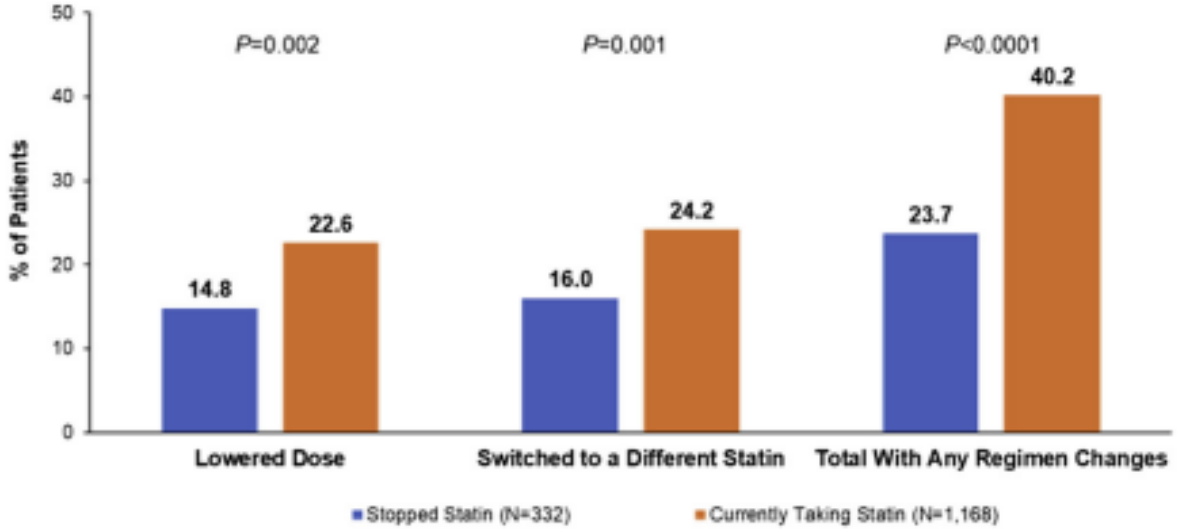
Adherence to Statin Therapy Is *Important*

- Statins are generally well tolerated
  - >Three-quarters of the general population tolerate statin therapy, but
  - 10%-20% of patients prescribed a statin report statin intolerance
- Very effective in preventing 1st/recurrent ASCVD across all LDL-C levels
- Rates of serious adverse events are very low
  - The risk of statin-induced serious muscle injury, including rhabdomyolysis, is <0.1%
  - The risk of serious hepatotoxicity is ≈0.001%
  - The risk of statin-induced newly diagnosed diabetes mellitus is ≈0.2% per year of treatment

Toth PP, et al. *Am J Cardiovasc Drugs.* 2018;18(3):157-173.
Newman CB, et al. *Arterioscler Thromb Vasc Biol*. 2019;39(2):e38-e81.

Adherence to Statin Therapy Is *Difficult*

- Large proportion (40%-70%) of patients *discontinue* statin therapy within 1-2 years, with resulting large *increase* in CVD events
- Perceived vs real effect may play a role as multiple studies show *nocebo* effect
  - **Many patients *can* tolerate statins on *rechallenge* after reported statin *intolerance***



Results from STATE survey

Toth PP, et al. *Am J Cardiovasc Drugs.* 2018;18(3):157-173.
Newman CB, et al. *Arterioscler Thromb Vasc Biol*. 2019;39(2):e38-e81.
Jacobson TA, et al. *J Clin Lipidol*. 2019;13(3):415-424.

Large Clinical Trials of Statin Adjuncts: Ezetimibe, PCSK9 Inhibitors, Fibrates, and Niacin

Positive Studies		Neutral Studies	
IMPROVE-IT Ezetimibe	HR = 0.936 (95% CI, 0.89-0.99) *P* = 0.016	ACCORD Fenofibrate	HR = 0.92 (95% CI, 0.79-1.08) *P* = 0.32
FOURIER Evolocumab	HR = 0.85 (95% CI, 0.79-0.92) *P* = 0.0001	FIELD Fenofibrate	HR = 0.89 (95% CI, 0.75-1.05) *P* = 0.16
ODYSSEY OUTCOMES Alirocumab	HR = 0.85 (95% CI, 0.78-0.93) *P* = 0.0001	AIM-HIGH Extended-release niacin	HR = 1.02 (95% CI, 0.87-1.21) Log-rank *P* = 0.79
		HPS2-THRIVE Extended-release niacin/laropiprant	HR = 0.96 (95% CI, 0.90-1.03) Log-rank *P* = 0.29

Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-2397. Sabatine MS, et al. *N Engl J Med.* 2017;376(18):1713-1722. Schwartz GG, et al. *N Engl J Med*. 2018;379(22):2097-2107.

ACCORD Study Group, et al. *N Engl J Med*. 2010;362(17):1563-1574. Keech A, et al. *Lancet*. 2005;366(9500):1849-1861. AIM-HIGH Investigators, et al. *N Engl J Med.* 2011;365(24):2255-2267. HPS2-THRIVE Collaborative Group, et al. *N Engl J Med*. 2014;371(3):203-212.

Current Guidance Regarding Available Statin Adjuncts: Fibrates, Niacin, Ezetimibe, or PCSK9i

- Combination therapy (**statin/fibrate**) has *not* been shown to improve ASCVD outcomes and is generally not recommended. (A)
- Combination therapy (**statin/niacin**) has *not* been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended. (A)
- For patients with **diabetes and ASCVD, if LDL cholesterol is ≥70 mg/dL on high-intensity statin dose, consider adding additional LDL-lowering therapy** (such as ezetimibe or PCSK9 inhibitor). (A)
  - Ezetimibe may be preferred due to lower cost.

(A), high quality evidence.
Grundy SM, et al. *Circulation*. 2019;139(25):e1082-e1143.

Icosapent Ethyl (IPE) Indicated by the FDA for CVD Event Reduction

New December 2019

- As an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥150 mg/dL) and
  - Established cardiovascular disease or
  - Diabetes mellitus and 2 or more additional risk factors for cardiovascular disease.

Original July 2012 (still indicated)

- As an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia
- Limitations of use: The effect of IPE on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined
- The daily dose is 4 g per day

Released December 13, 2019. After https://www.vascepa.com/assets/pdf/Vascepa_PI.pdf

Icosapent Ethyl Is Now Included in the Treatment Guidelines or Recommended for Use by 26 Medical Associations Worldwide

American College of Cardiology

European Society of Cardiology

American Association of Clinical Endocrinology

European Atherosclerosis Society

American Diabetes Association

Chinese Society of Cardiology

American Heart Association

Japan Circulation Society

National Lipid Association

Brazilian Society of Cardiology

Endocrine Society

Thrombosis Canada

Virani SS, et al. *J Am Coll Cardiol.* 2021;78(9):960-993. Handelsman Y, et al. *Endocr Pract*. 2020;26(10):1196-1224. American Diabetes Association http://main.diabetes.org/dorg/bod/2019-2020/ADA-Strategic-Architecture.pdf. Kimura K, et al. *Circ J*. 2019;83(5):1085-1196. American Heart Association https://www.heart.org. European Society of Cardiology https://www.escardio.org/The-ESC/Who-we-are. European Atherosclerosis Society https://www.eas-society.org/page/about_eas. National Lipid Association https://www.lipid.org/about. American Association of Clinical Endocrinology https://www.aace.com/about/about-aace. Brazilian Society of Cardiology Cardiovascular Prevention Guideline Update http://publicacoes.cardiol.br/portal/abc/ingles/aop/2019/aop-diretriz-prevencao-cardiovascular-ingles.pdf. The Thrombosis Canada Clinical Guides. https://thrombosiscanada.ca/clinicalguides/#. Vargas-Uricoechea H, et al. *Revista ACE*. 2020;7(1):4-36, http://revistaendocrino.org/index.php/rcedm/article/view/573. Arnold SV, et al. *Circulation*. 2020; 141(19):e779-e806. Collet JP, et al. *Eur Heart J*. 2021;42(14):1289-1367. Newman C, et al. *J Clin Endocrinol Metab*. 2020; 105(12):dgaa674. Cardiology Committee of the National Medical Association, et al. *Chinese Journal of Cardiovascular Diseases*. 2020;48(12):1000-1038.

Icosapent Ethyl (IPE) Warnings and Precautions

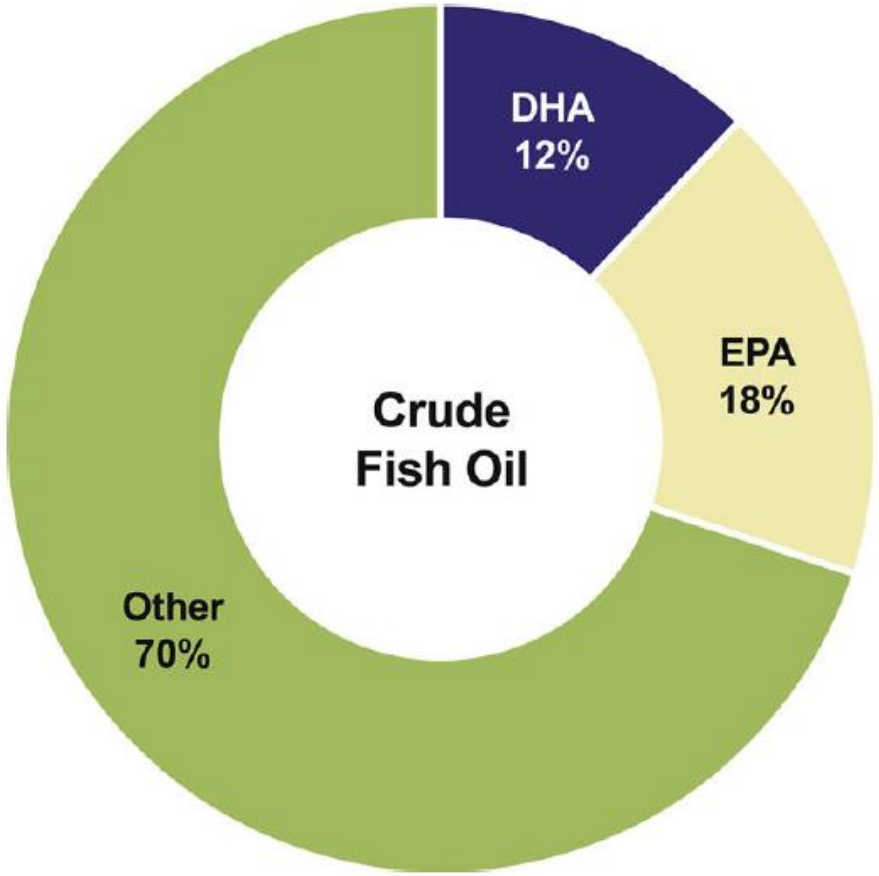
- **Atrial Fibrillation/Flutter:** IPE was associated with an increased risk of atrial fibrillation or atrial flutter requiring hospitalization (REDUCE-IT). The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or atrial flutter.

- **Potential for Allergic Reactions** *in Patients with Fish Allergy:* IPE contains ethyl esters of the omega-3 fatty acid eicosapentaenoic acid (EPA) obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to IPE.

- **Bleeding:** IPE was associated with an increased risk of bleeding (REDUCE-IT). The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin.

https://www.vascepa.com/assets/pdf/Vascepa_PI.pdf

EPA and DHA Are Available in Several Forms



Fish Oil Dietary Supplement

~20% DHA
~30% EPA
~50% Other undisclosed fatty acids

Combination OM-3 Prescription Product

42% DHA
52% EPA
6% Other OM-3 fatty acids

EPA-only Prescription Product

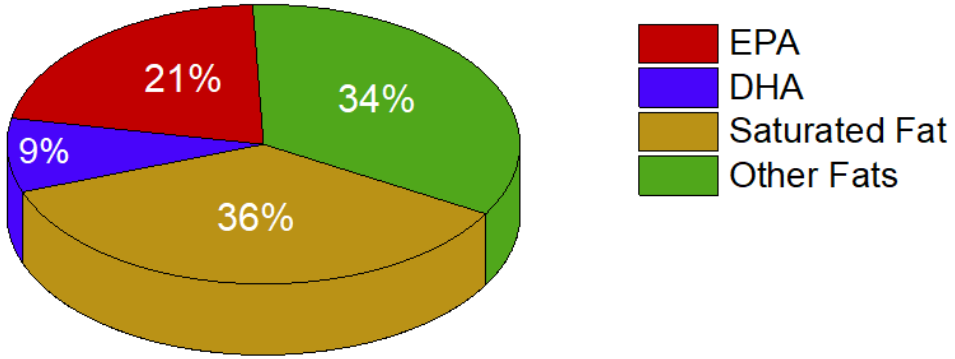
100% icosapent ethyl
(ethyl ester of EPA)

Hilleman DE, et al. Adv Ther. 2020;37(2):656-670.

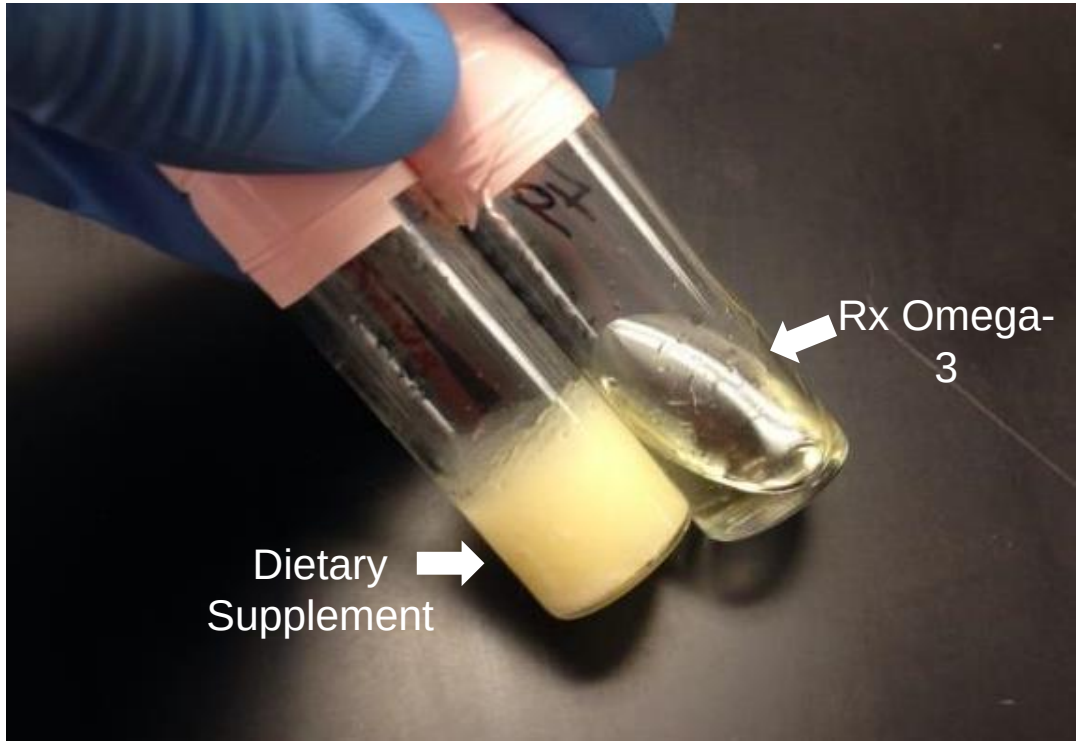
Fish Oil *Dietary Supplements*: Poorly Regulated but Widely Used

- There are *NO* over-the-counter omega-3 products (that would be FDA-regulated but non-prescription); *ONLY* dietary supplements (with minimal FDA oversight)
- Dietary supplements are *NOT* recommended to treat diseases, ***but***
- Benefits are claimed for heart, brain, weight, vision, inflammation, skin, liver fat, depression, age-related cognitive decline, allergies, bones, pregnancy/neonatal health, childhood behavior…
- Approximately 8% of US adults (19 million) take fish oil dietary supplements

Dubious Content of *Leading* US Fish Oil Dietary Supplements



- Up to 36% of content may be saturated fat
- Omega-3 FA content often overstated
- Oxidation of omega-3 FA content can be high
  - even those meeting industry standards are more oxidized than Rx meds
- Contamination risk (pesticides, PCBs, etc.)
- Difficult to achieve EPA+DHA doses similar to Rx meds



High saturated fatty acid content of common fish oil dietary supplement makes it ***solid at room temperature*** (post-isolation)

Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483(1):425-429. Hilleman D, Smer A. *Manag Care*. 2016;25(1):46-52. Albert BB, et al. *Sci Rep*. 2015;5:7928. Kleiner AC, et al. *J Sci Food Agric*. 2015;95(6):1260-1267. Ritter JC, et al. *J Sci Food Agric*. 2013:93(8):1935-1939. Jackowski SA, et al. *J Nutr Sci*. 2015;4:e30. Rundblad A, et al. *Br J Nutr*. 2017;117(9):1291-1298. European Medicines Agency, 2018: 712678.

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EXPERT CONSENSUS DECISION PATHWAY

2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia

A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the National Lipid Association

What Does Expert Consensus Tell Us About Managing Triglycerides?

EXPERT CONSENSUS DECISION PATHWAY

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Fasting TG ≥150 or Non-fasting ≥175 and <500 mg/dL

ASCVD

Age ≥ 40 with DM but no ASCVD

Age ≥ 20 without ASCVD or DM

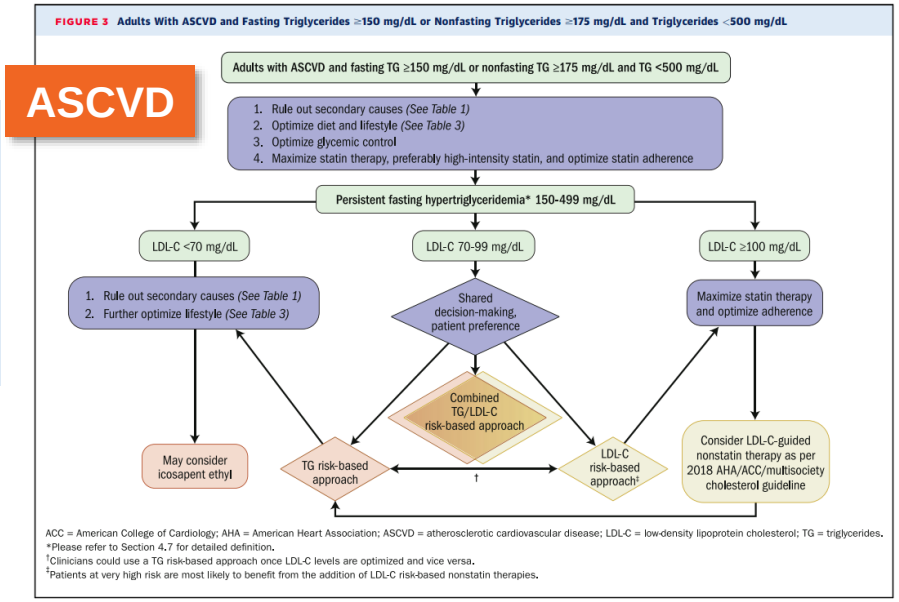
TG ≥ 500, "especially" ≥ 1000mg/dL

Medical Therapy

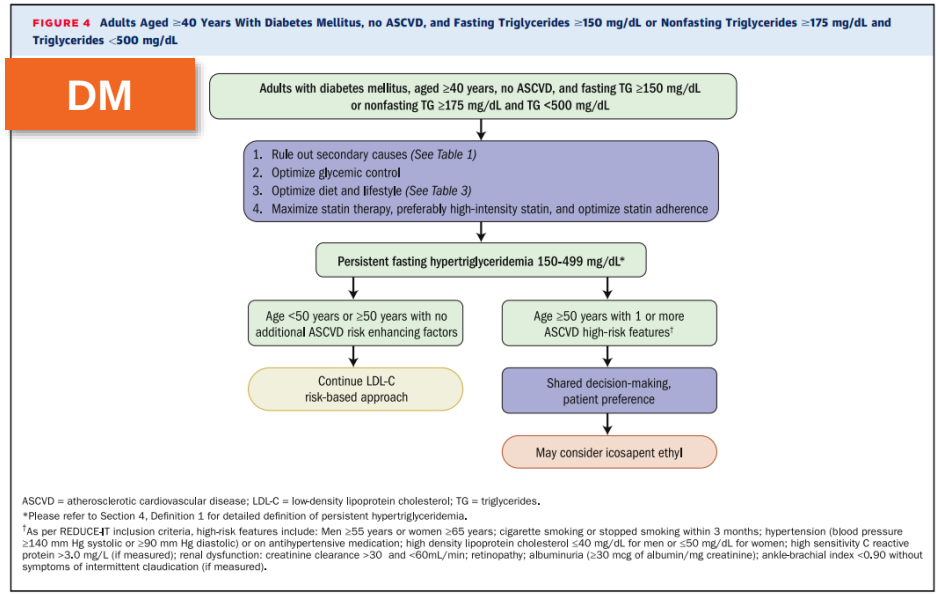
LDL-Lowering Pathway

TG-Lowering Pathway

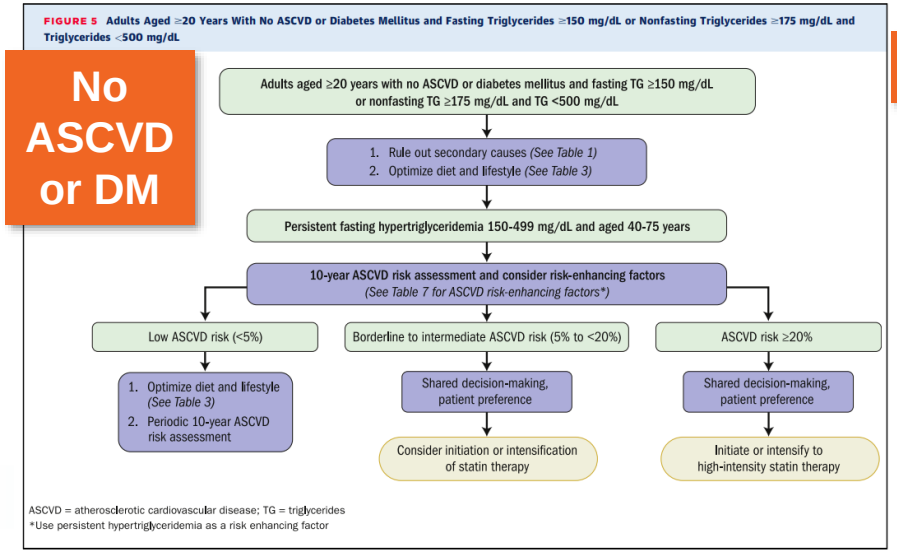
ASCVD



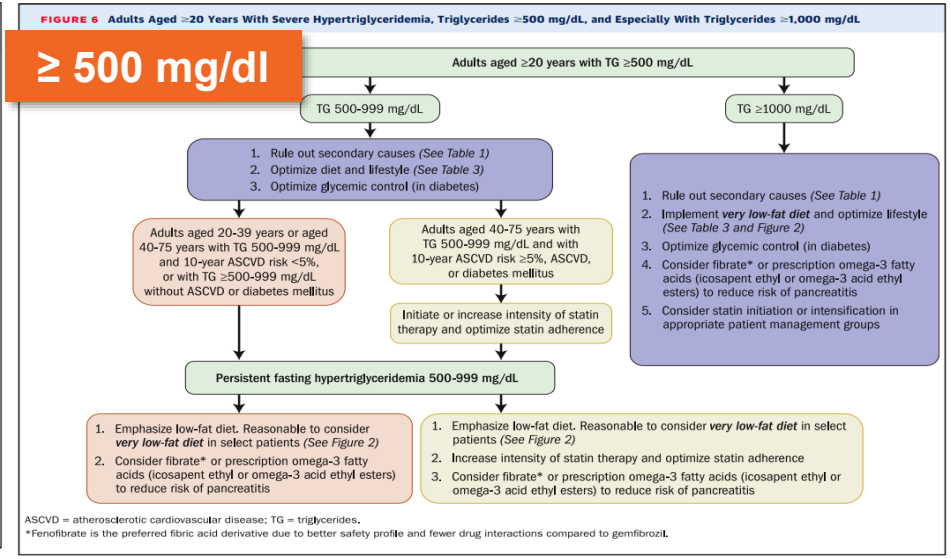
DM



No ASCVD or DM



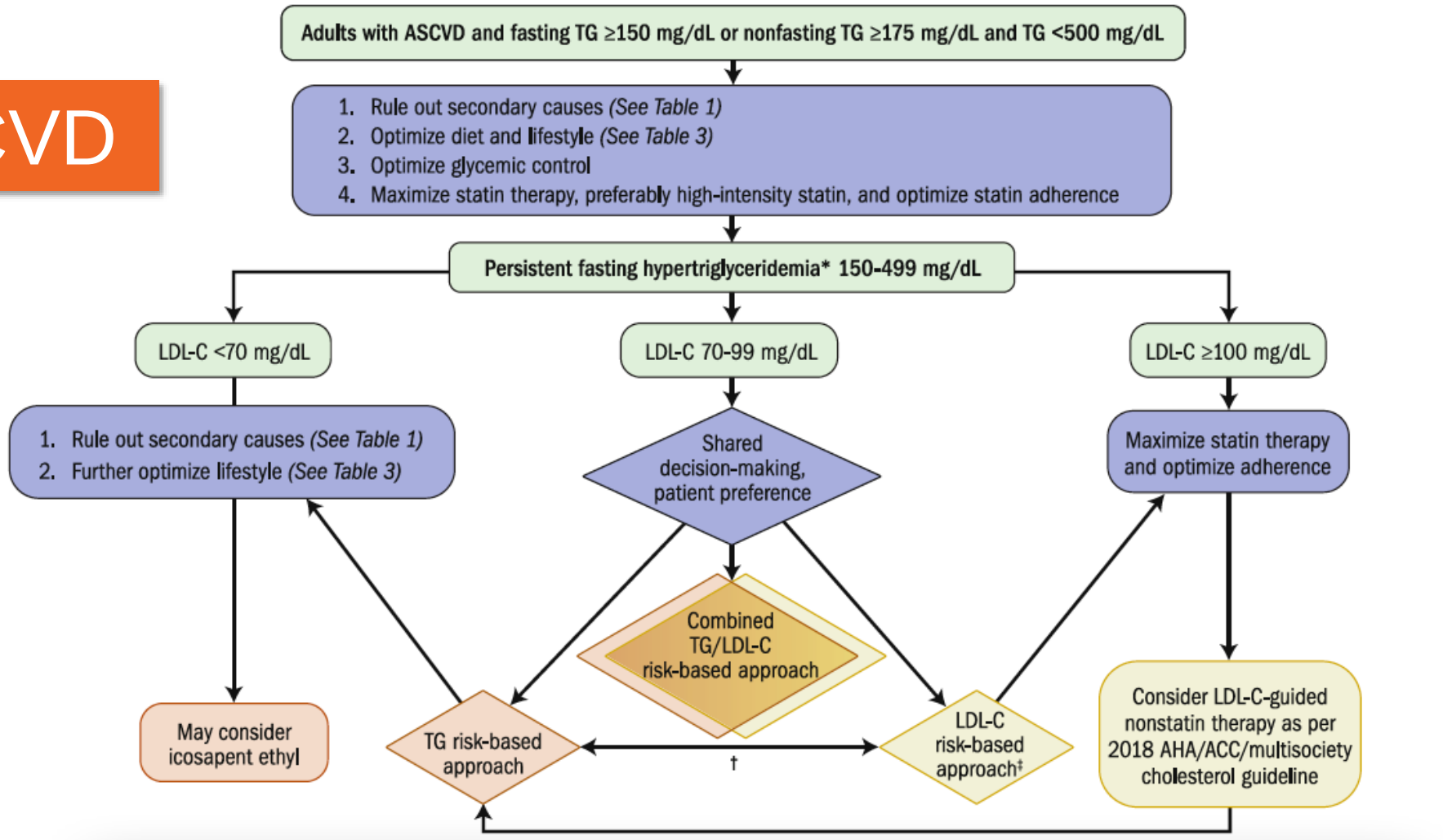
≥ 500 mg/dl



medtelligence℠

ASCVD

FIGURE 3 Adults With ASCVD and Fasting Triglycerides ≥150 mg/dL or Nonfasting Triglycerides ≥175 mg/dL and Triglycerides <500 mg/dL



Virani SS, Morris PB, Agarwala A, et al. *J Am Coll Cardiol.* 2021;78(9):960-993.

Counseling Tips

- Dietary supplements ARE NOT EQUAL to prescription omega-3

Dietary supplements ≠ Rx

- All Rx are not equal (omega-3-acid ethyl esters are DHA/EPA while icosapent ethyl is EPA only)
- MUST take 2 g BID
- Talk about safety concerns with the patient

Share the exciting changes with your patients!!!

Monitoring Response to Drug Therapy

- Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes and
  - Repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment
  - Repeat every 3 to 12 months as needed
- Responses to lifestyle and statin therapy are defined by percentage reductions in LDL-C levels compared with baseline
- Remind your patients how important it is for them to take their medications
  - Long-term benefits for them, their families, and community

Grundy SM, et al. *J Am Coll Cardiol.* 2019.25;73(24):e285-e350.

Getting Insurance Approval for ASCVD Medications

- Typically, at least 1 drug per class is on formulary
- Some hurdles for approval
- 2 key actions:
  - Make sure your patient information regarding indication criteria is clearly described
  - Include guidelines recommendations and FDA indications citations and/or copies
- Don’t take NO! for an answer; try again until it gets approved
- Once you get the process down, it will be easier the next time

Case Presentation on Primary and Secondary Prevention

Peter Toth, MD, PhD

Our Patient #1: First Visit

- 60-year-old man
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, treated
- BMI 29 kg/m2
- Smoker
- **What is his yearly risk of ‘hard’ cardiovascular endpoints (heart attack, stroke, or death from cardiovascular disease)?**

CVD Risk Scores in Secondary Prevention

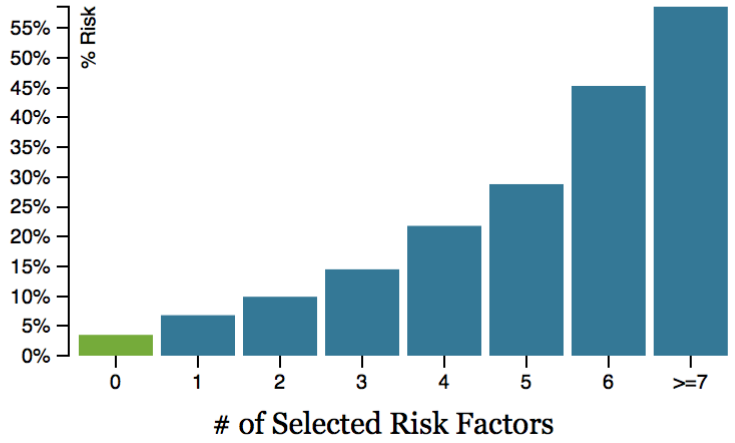
TIMI Risk Score for Secondary Prevention (TRS 2°P)

Risk in Patients with Known Atherosclerotic Vascular Disease

CHF
HTN
Age >= 75
DM
Prior Stroke
Prior CABG
PAD
eGFR < 60
Current Smoking

0 Risk Indicators Selected

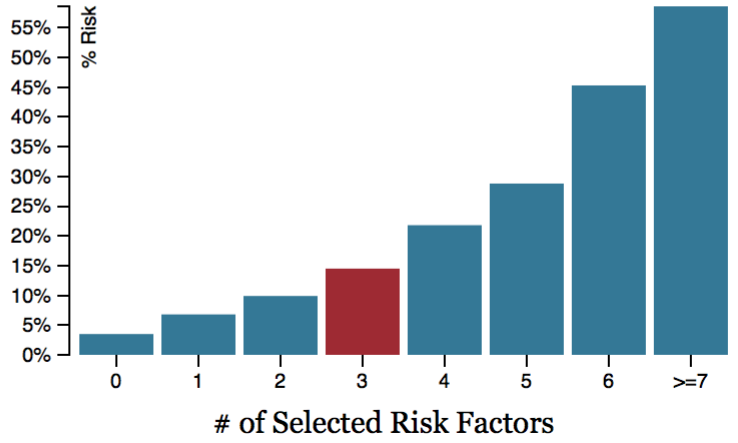
3.5% risk at 3 years of CV death, MI or Ischemic Stroke.



CHF
HTN
Age >= 75
DM
Prior Stroke
Prior CABG
PAD
eGFR < 60
Current Smoking

3 Risk Indicators Selected

14.5% risk at 3 years of CV death, MI or Ischemic Stroke.



Bohula EA, et al. *Circulation* 2016;134(4):304-313.

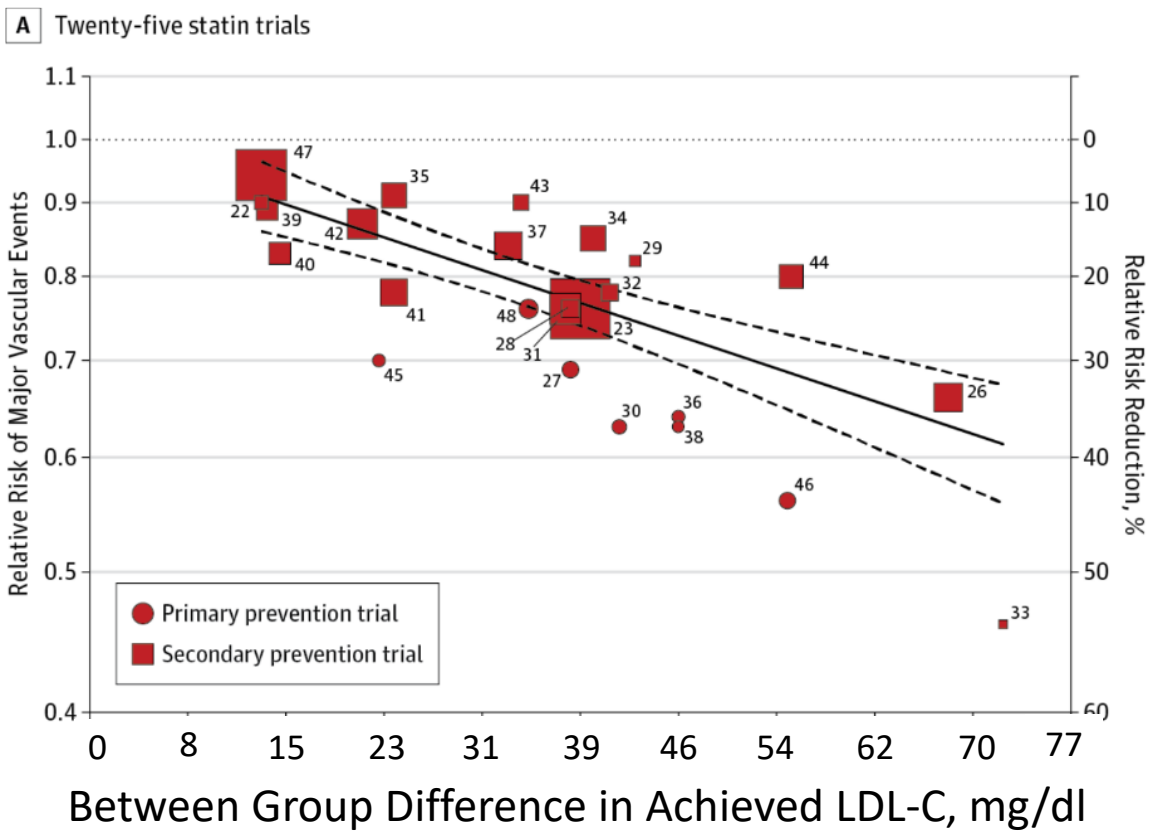
Validated in both trial and non-trial settings: www.timi.org

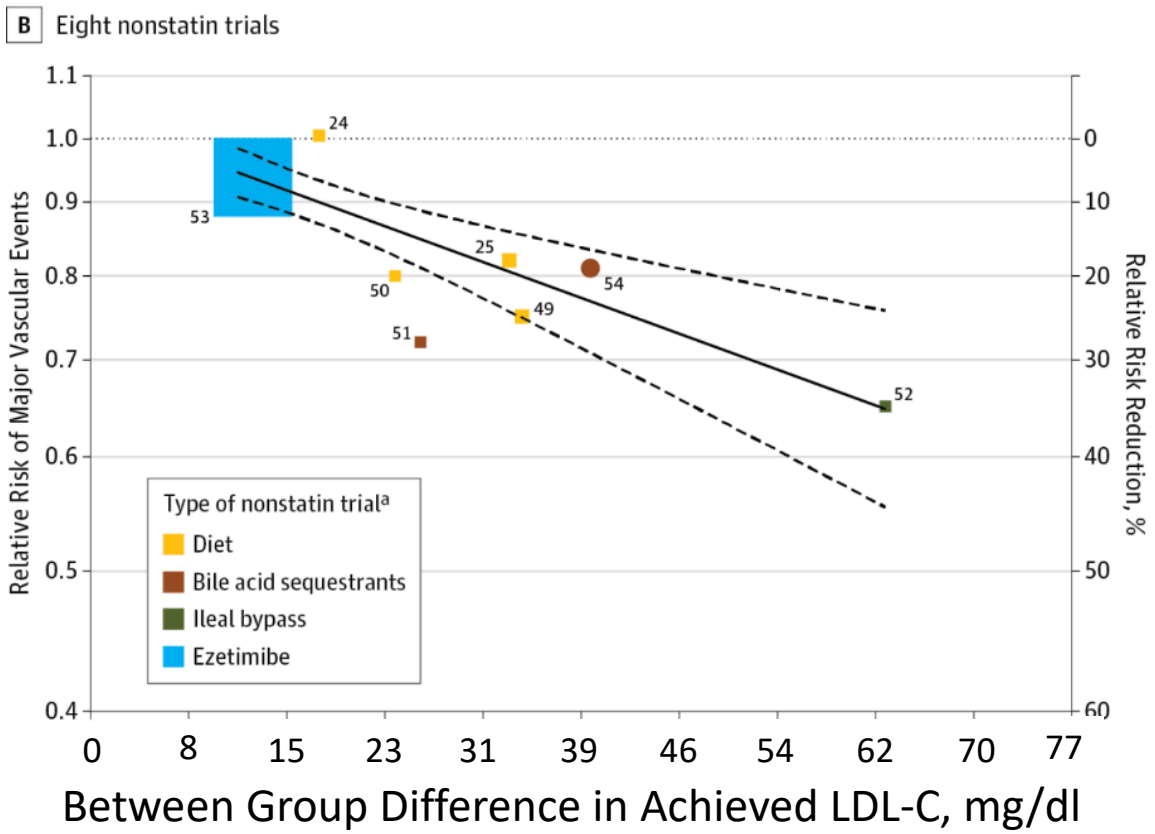
Our Patient #1: First Visit
Annual Risk of 3-Point MACE ~5% (TRS 2ºP)

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension
- BMI 29 kg/m2

	Pre-Treatment
TC	260 mg/dL
LDL-C	170 mg/dL
TG	280 mg/dL
HDL-C	34 mg/dL
Non-HDL-C	226 mg/dL

Every 40 mg/dL Reduction in LDL ≈ 25% Reduction in Hard MACE





Silverman MG et al, JAMA. 2016;316(12):1289-1297. Association Between LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-Analysis

Intensity of Statin Therapy

HIGH RISK PATIENT	MODERATE RISK PATIENT	LOW RISK PATIENT
High Intensity Statin	**Moderate Intensity Statin**	**Low Intensity Statin**
Daily dose lowers LDL-c ~50%	Daily dose lowers LDL-c ~30% -50%	Daily dose lowers LDL-c <30%
Atorvastatin (40†)-80 mg **Rosuvasatin 20 *(40)* mg**	Atorvastatin 10 *(20)* mg Rosuvastatin *(5)* 10 mg Simvastatin 20-40 mg‡ Pravstatin 40 *(80)* mg Lovastatin 40 mg *Fluvastatin XL 80 mg* Fluvastatin 40 mg bid *Pitavastatin 2-4 mg*	*Simvastatin 10 mg* Pravastatin 10-20 mg Lovastatin 20 mg *Fluvastatin 20-40 mg* *Pitavastatin 1 mg*

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL.
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.
Stone NJ, et al. *Circulation*. 2014;129(25 Suppl 2):S1-S45.

Our Patient #1: After High-Intensity (HI) Statin
Annual Risk of 3-Point MACE ~3%

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, treated
- BMI 29 kg/m2

	Pre-Treatment	Post-Treatment
TC	260 mg/dL	168 mg/dL
LDL-C	170 mg/dL	85 mg/dL
TG	280 mg/dL	238 mg/dL
HDL-C	34 mg/dL	36 mg/dL
Non-HDL-C	226 mg/dL	133 mg/dL

- 85 mg/dl ~ -40% MACE
(7-30% ⇊ TG)

Do we need more LDL lowering?

Our Patient #1: After HI Statin + Ezetimibe

Annual Risk of 3-Point MACE ~2.8%

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, treated
- BMI 29 kg/m2

	Pre-Treatment	Post-Treatment
TC	168 mg/dL	152 mg/dL
LDL-C	85 mg/dL	72 mg/dL
TG	238 mg/dL	214 mg/dL
HDL-C	36 mg/dL	37 mg/dL
Non-HDL-C	133 mg/dL	115 mg/dL

-98 mg/dl ~ -43% MACE
(10-15% ⇊ TG)

Do we need more LDL lowering?

Our Patient #1: HI Statin + Ezetimibe + PCSK9i

Annual Risk of 3-Point MACE ~2.3%

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, treated
- BMI 29 kg/m2

	Pre-Treatment	Post-Treatment
TC	152 mg/dL	104 mg/dL
LDL-C	72 mg/dL	29 mg/dL
TG	214 mg/dL	184 mg/dL
HDL-C	37 mg/dL	38 mg/dL
Non-HDL-C	115 mg/dL	66 mg/dL

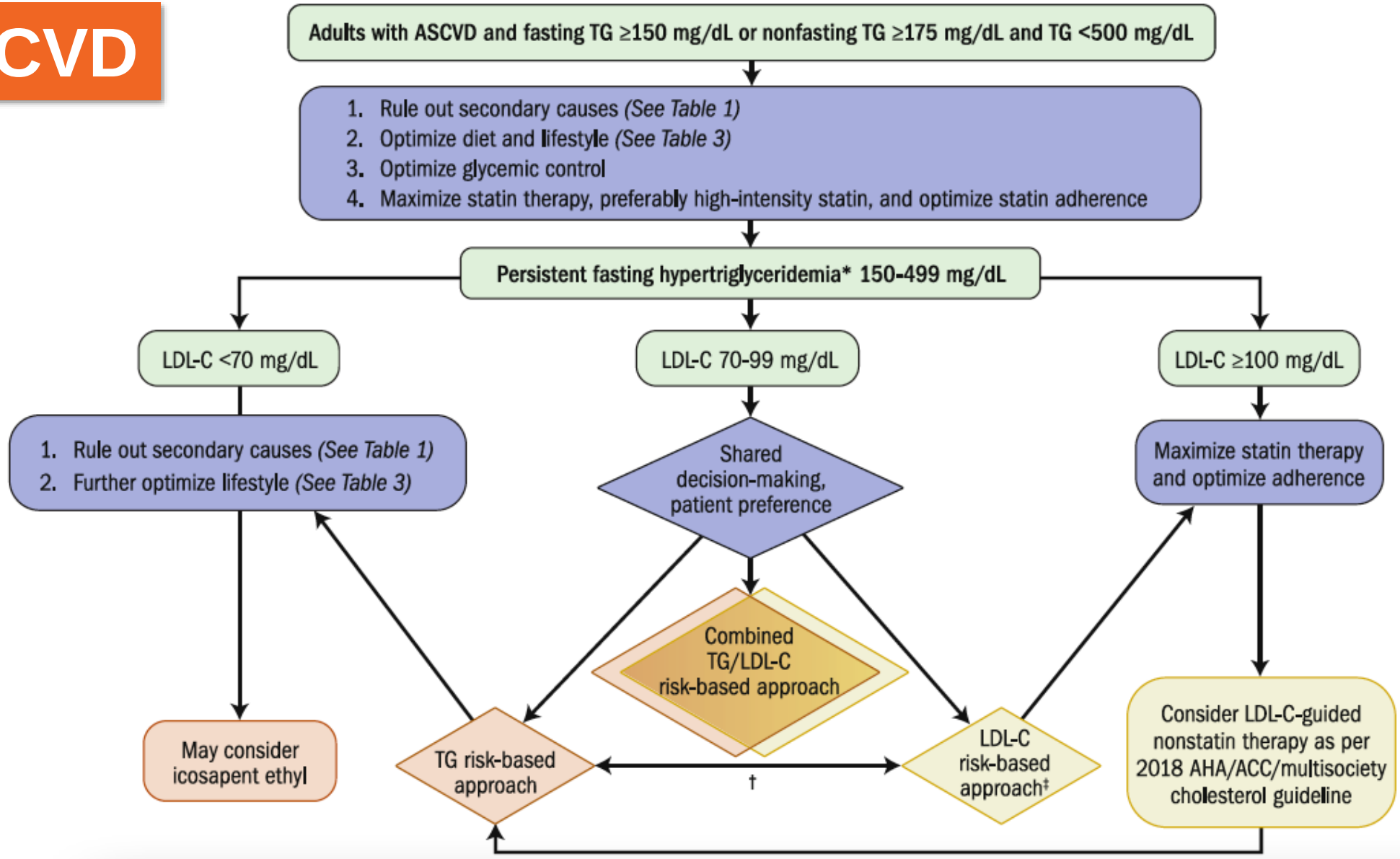
-141 mg/dl ~ -54% MACE

(5-25% ⇊ TG)

Other Choices?

FIGURE 3 Adults With ASCVD and Fasting Triglycerides ≥150 mg/dL or Nonfasting Triglycerides ≥175 mg/dL and Triglycerides <500 mg/dL

ASCVD



medtelligence℠

Virani SS, Morris PB, Agarwala A, et al. *J Am Coll Cardiol.* 2021;78(9):960-993.

In Patients with Hypertriglyceridemia, We Have Another Option

- Prior to REDUCE-IT, no randomized clinical trials have demonstrated benefit in patients specifically enrolled based on hypertriglyceridemia
- Because of the data we've shown you, icosapent ethyl is another option in this high-risk patient

Our Patient #1: HI Statin + Ezetimibe + EPA (IPE)

Annual Risk of 3-Point MACE ~2.1% (Versus 2.3% with PCSK9i)

- 60-year-old man, smoker
- Post-MI; h/o PAD, s/p R fem-pop bypass
- Hypertension, treated
- BMI 29 kg/m2

	Pre-Treatment	Post-Treatment
TC	152 mg/dL	145 mg/dL
LDL-C	72 mg/dL	72 mg/dL
TG	214 mg/dL	176 mg/dL
HDL-C	37 mg/dL	38 mg/dL
Non-HDL-C	115 mg/dL	107 mg/dL

- 26% in 3-pt MACE with enhanced efficacy in Patients with Mixed Dyslipidemia

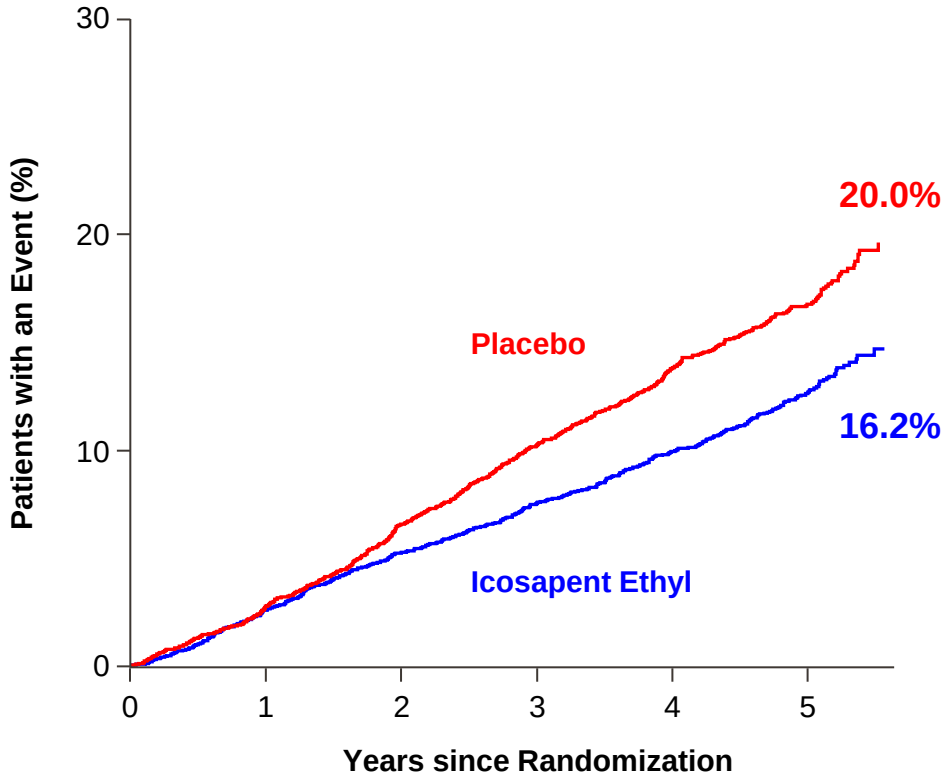
Addition of EPA (IPE)

When to Add Icosapent Ethyl in Secondary Prevention

- The bifurcation is at near goal LDL in the patient with residual hypertriglyceridemia
- Achieve similar risk reduction from baseline versus addition of PCSK9i
- Possibly add earlier in treatment plan when LDL-C <100 mg/dL (CV mortality benefit), but many statin and non-statin LDL-lowering therapies will have some (modest) effects on TGs

Remember That the Treatment Benefit Emerges After 1.5 Years

Composite: CV death, nonfatal MI, nonfatal 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, et al. *N Engl J Med*. 2019;380(1):11-22.

Learning Assessment 1

All of the following are reasons why TG-rich lipoproteins and their remnants are causally related to ASCVD ***EXCEPT*****?**

A. Observational studies indicate that mild-moderate HTG is a strong and independent predictor of ASCVD and all-cause mortality

B. Mendelian randomization (genetic) studies indicate that factors related to TG metabolism support causality in ↑CV risk

C. TG-rich lipoproteins promote inflammation much less than does LDL

D. Remnant lipoproteins accumulate in arterial intima macrophage foam cells more readily than does LDL

Learning Assessment 2

Which of the following statements about the REDUCE-IT and STRENGTH omega-3 fatty acid trials is true?

A. Both REDUCE-IT and STRENGTH testing icosapent ethyl (IPE, Vascepa) and omega-3-carboxylic acids (Epanova), respectively, failed to show CVD benefit.

B. The REDUCE-IT trial showed CVD benefit with the study drug vs placebo, but the STRENGTH trial was neutral

C. The REDUCE-IT trial showed CVD benefit and STRENGTH also showed benefit in subjects with the highest on-study EPA levels

D. Both REDUCE-IT and STRENGTH showed CVD benefit in their whole study populations

Learning Assessment 3

According to the ACC Expert Consensus to Reduce ASCVD Risk, what treatment should be considered for an adult with ASCVD, fasting HTG 150-499 mg/dL and LDL-C <70 mg/dL after optimizing lifestyle and ruling out secondary causes?

A. Ezetimibe

B. Niacin

C. Fibrates

D. Icosapent Ethyl

Q&A

Christie Ballantyne, MD and Peter Toth, MD PhD