Going Beyond LDL in Assessing and Managing Residual Risk: Lp(a) and Triglycerides

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Disclosure

Consultant: Amgen; Bayer; Boehringer Ingelheim; Eli Lilly; Jazz Pharma; Medtronic; Novartis; Novo Nordisk; Roche

Ownership Interest (Founder & Shareholder): Epirium Bio

Research Grant: Dysautonomia International Grant; Hillblom Network Grant; National Institutes of Health (NIH)

Steering Committee: Amgen; Boehringer Ingelheim; Cleerly; Medtronic; Merck; Novartis

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Learning Objectives

- Review of Lp(a) and its role in the pathogenesis of atherosclerosis and aortic stenosis.
- Review of agents currently available and in development for Lp(a) lowering.
- Overview of the role of triglycerides in CV disease and agents to lower them.

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A 45-year-old male is very anxious about his risk of heart attack as his father died from heart attack at age 47.

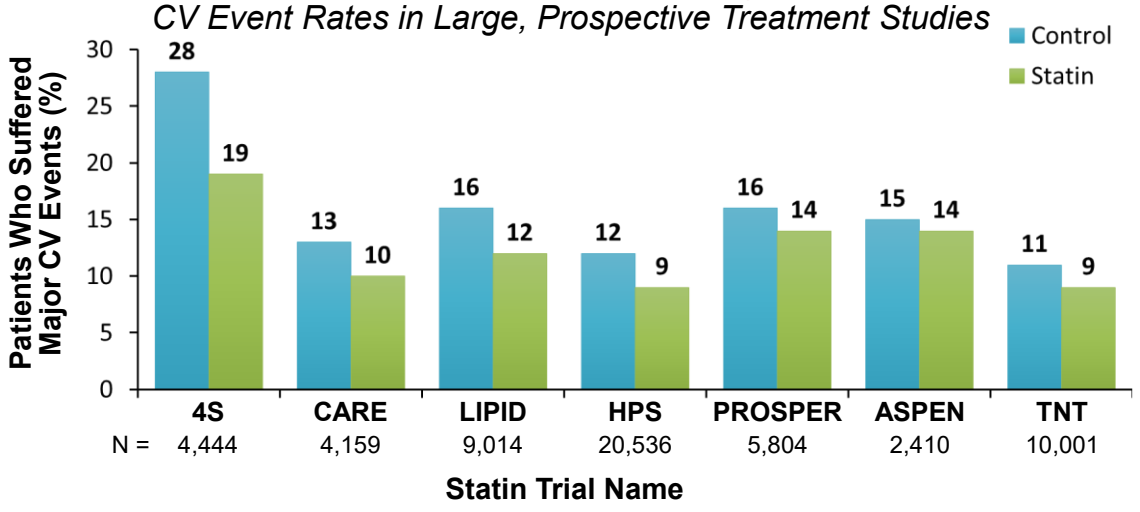
- He is very active and maintains a Mediterranean diet.
- He has no medical issues and has normal BMI, blood pressure, A1c.
- His LDL cholesterol is 70.

What Do You Recommend?

A. Reassure him and tell him no further testing is needed
B. Check myeloperoxidase
C. Check Lipoprotein-associated phospholipase A_2 (Lp-PLA_2)
D. Check lipoprotein A

Residual CV Risk Persists Despite LDL-C Lowering

CV Event Rates in Large, Prospective Treatment Studies



Sampson UK, et al. *Curr Atheroscler Rep*. 2012;14:1-10.

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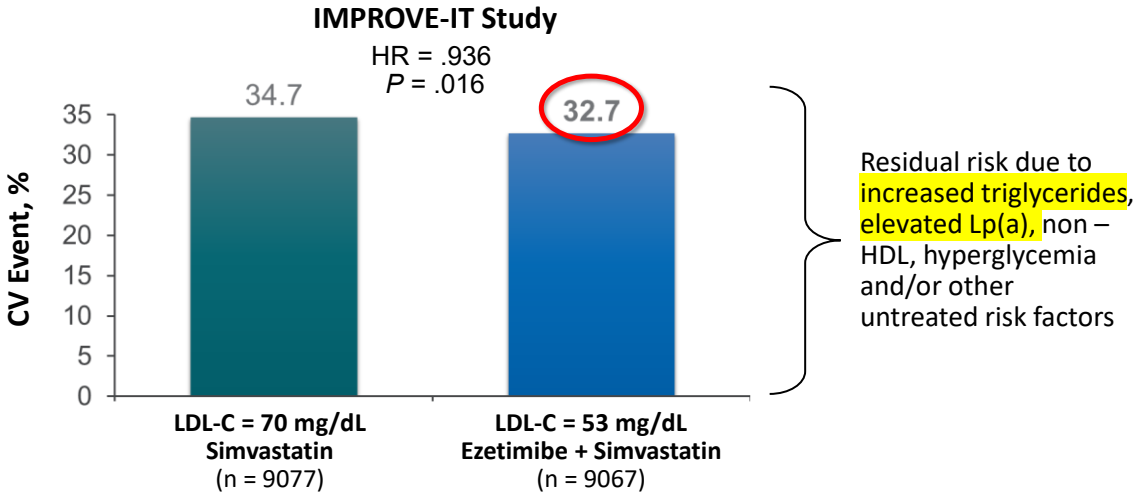
Aggressive LDL-C Lowering Does Not Eliminate ASCVD Risk Significant Residual Risk Remains Untreated



Cannon CP, et al. *NEJM*. 2015;372(25)2387-97.

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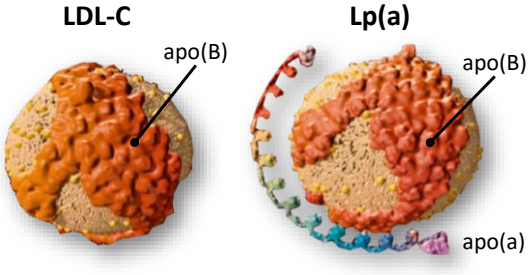
Lipoprotein(a)

- Elevated Lp(a) occurs in 1 in 5 people worldwide
  - 63 million people in the US have elevated Lp(a)
- Elevated Lp(a) is currently the strongest, single, inherited risk factor for early CAD and aortic stenosis
- Elevations in Lp(a) (typically > 50 mg/dL) result in 2-4x higher risk of CV events
- High Lp(a) occurs more commonly among African Americans and South Asians



J Am Coll Cardiol. 2018;71:177–192; *J Am Coll Cardiol*. 2017;69:692–711.

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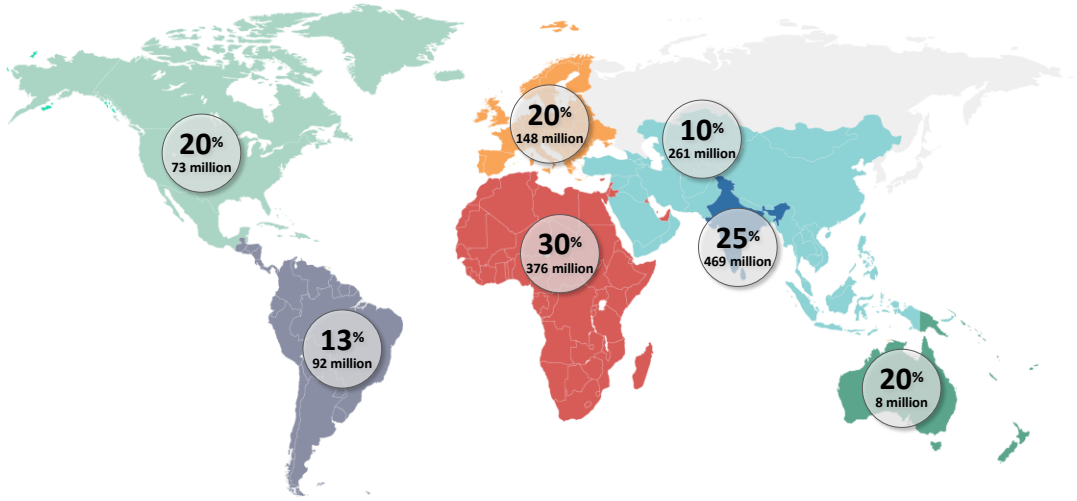
Estimated Prevalence of Elevated Lp(a) Globally

10%-30% 1.43 Billion – Prevalence Roughly Equal Between Females and Males



J Am Coll Cardiol. 2018;71:177–192.

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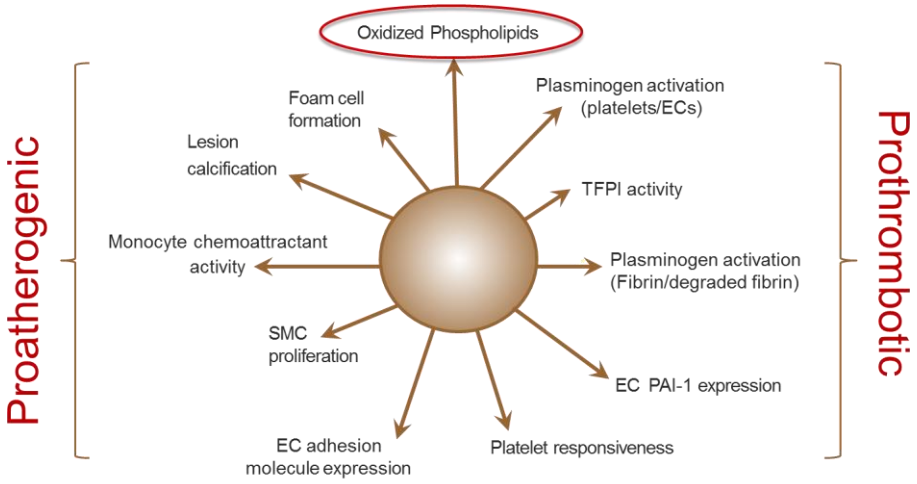
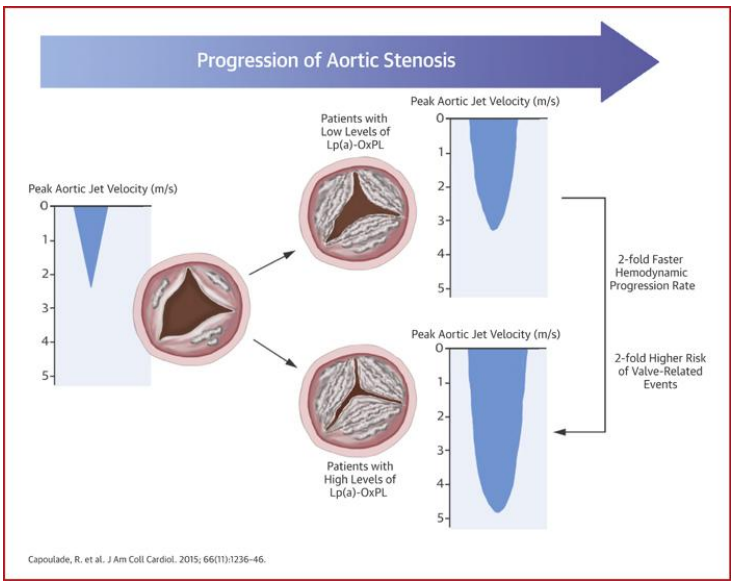
Proposed Pathogenic Mechanisms for Lp(a)



Spence and Koschinsky (2012) ATVB 32:1550-1551; Koschinsky & Marcovina (2004) Curr. Opin. Lipidol. 15: 167-74

9

Lipoprotein A Is an Evolving Biomarker for Assessing Progression of Aortic Stenosis



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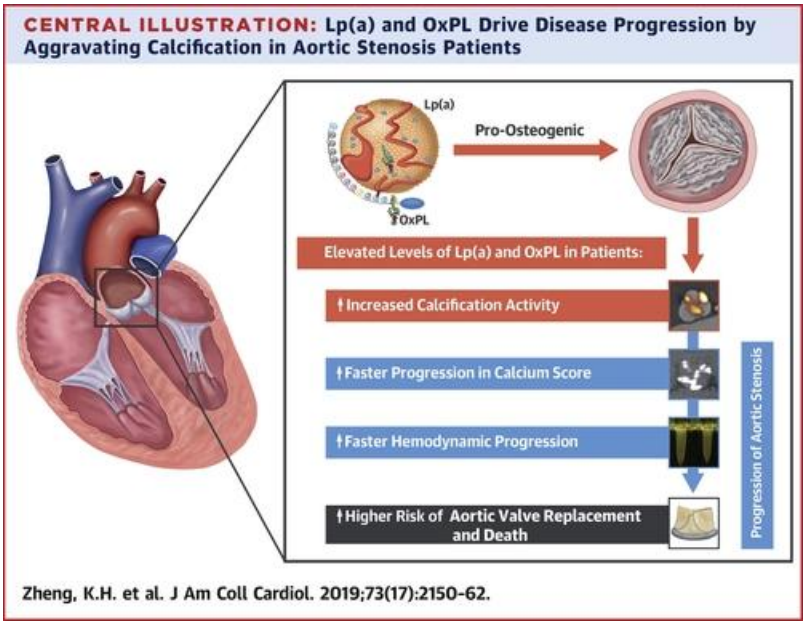

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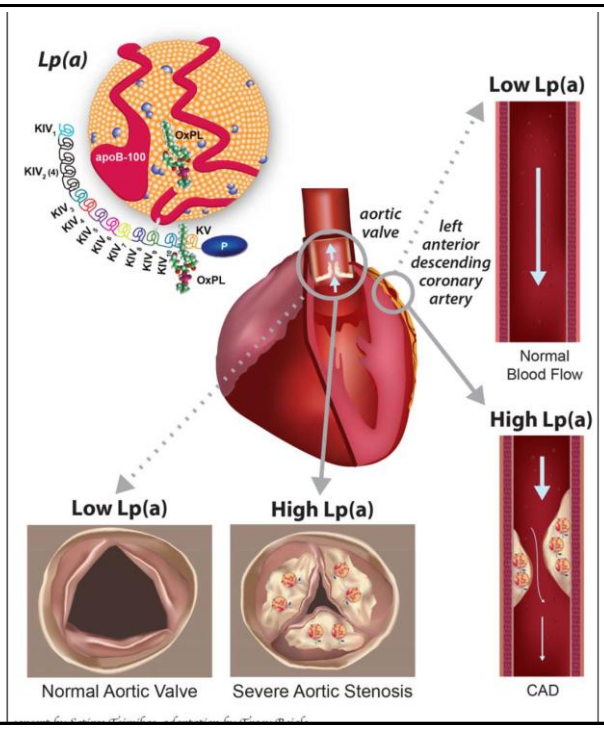

Journal Of Lipid Research Cover March 2016

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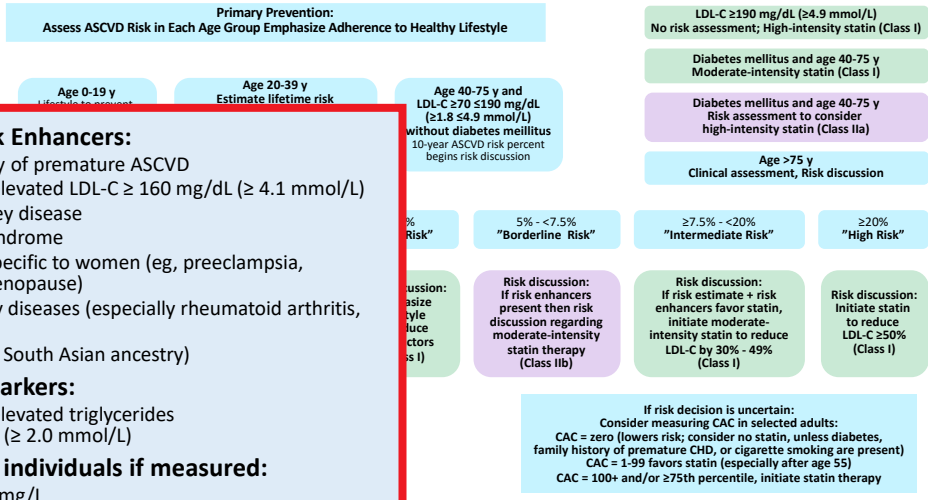
2018 Blood Cholesterol Guideline

ASCVD Risk Enhancers



ASCVD Risk Enhancers:

- Family history of premature ASCVD
- Persistently elevated LDL-C ≥ 160 mg/dL (≥ 4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (eg, preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (eg, South Asian ancestry)

Lipid/Biomarkers:

- Persistently elevated triglycerides (≥ 175 mg/dL, (≥ 2.0 mmol/L)

In selected individuals if measured:

- hs-CRP ≥ 2.0 mg/L
- Lp(a) levels > 50 mg/dL or > 125 mmol/L
- apoB ≥ 130 mg/dL
- Ankle-branchial index (ABI) < 0.9

Grundy SM, et al. *J Am Coll Cardiol.* 2018; S0735-1097(18)39034-X

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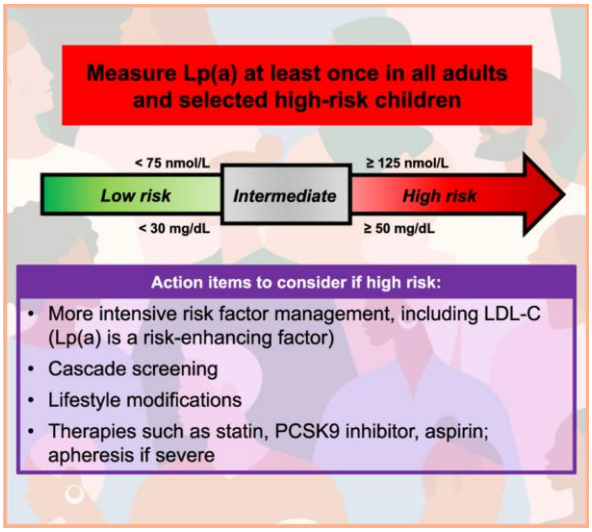

A focused update to the 2019 NLA scientific statement on use of lipoprotein(a) in clinical practice
Marlys L. Koschinsky, PhD, Archna Bajaj, MD, MSCE, Michael B. Boffa, PhD, Dave L. Dixon, PharmD, Keith C. Ferdinand, MD, Samuel S. Gidding, MD, Edward A. Gill, MD, Terry A. Jacobson, MD, Erin D. Michos, MD, MHS, Maya S. Safarova, MD, PhD, Daniel E. Soffer, MD, Pam R. Taub, MD, Michael J. Wilkinson, MD, Don P. Wilson, MD, Christie M. Ballantyne, MD
Journal of Clinical Lipidology **;DOI: 10.1016/j.jacl.2024.03.001**

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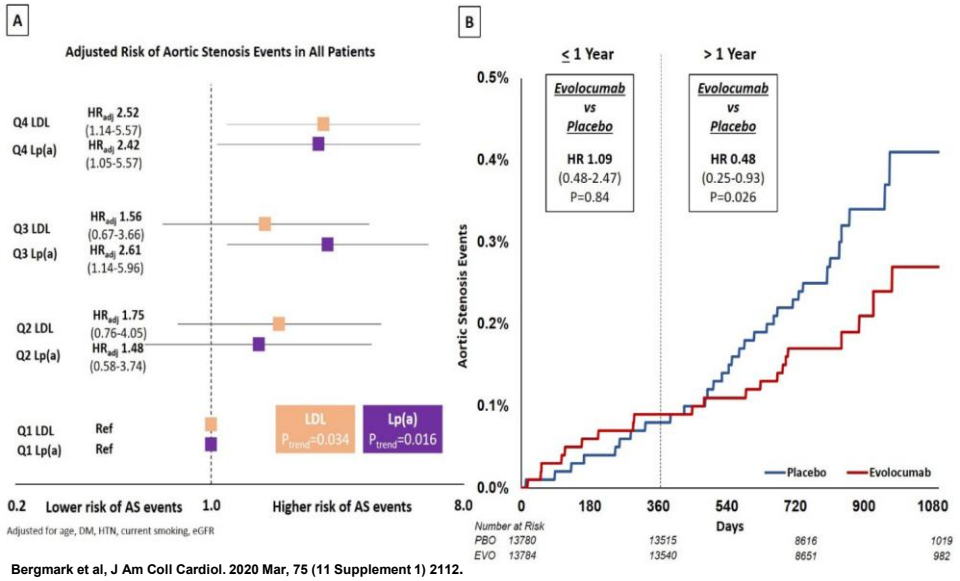
Decrease in Aortic Stenosis Events with PCSK9 Inhibitor



Bergmark et al, J Am Coll Cardiol. 2020 Mar, 75 (11 Supplement 1) 2112.

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CENTRAL ILLUSTRATION: Aspirin, Lipoprotein(a) Genotypes, and Primary Prevention of Cardiovascular Disease Events

ASPREE RCT

19,114 healthy older individuals with no history of CVD events

Randomization to 100 mg Aspirin vs Placebo

Median 4.7 years follow-up
Adjudicated endpoints

- Major adverse cardiovascular events (MACE)
- Clinically significant bleeding (BLEEDS)

Genotyping

No stratification by genotype

All genotyped participants N = 12,815
MACE 1.7 reduced per 1,000 person-years
BLEEDS 1.7 increased per 1,000 person-years
→ ±0 events = No net benefit of aspirin (parity)

rs3798220-C Carriers N = 406
MACE 11.4
BLEEDS 3.3
+8.1 events per 1,000 person-years =Net benefit of aspirin
$P_{interaction}$ rs37982220-C * Aspirin = 0.049

Genotypes associated with elevated Lp(a) levels

High LPA-GRS Quintile N = 2,556
MACE 3.3
BLEEDS 1.6
+1.7 events per 1,000 person-years =Net benefit of aspirin
$P_{interaction}$ High LPA-GRS * Aspirin = 0.550

Lacaze P, et al. J Am Coll Cardiol. 2022;80(14):1287-1298.

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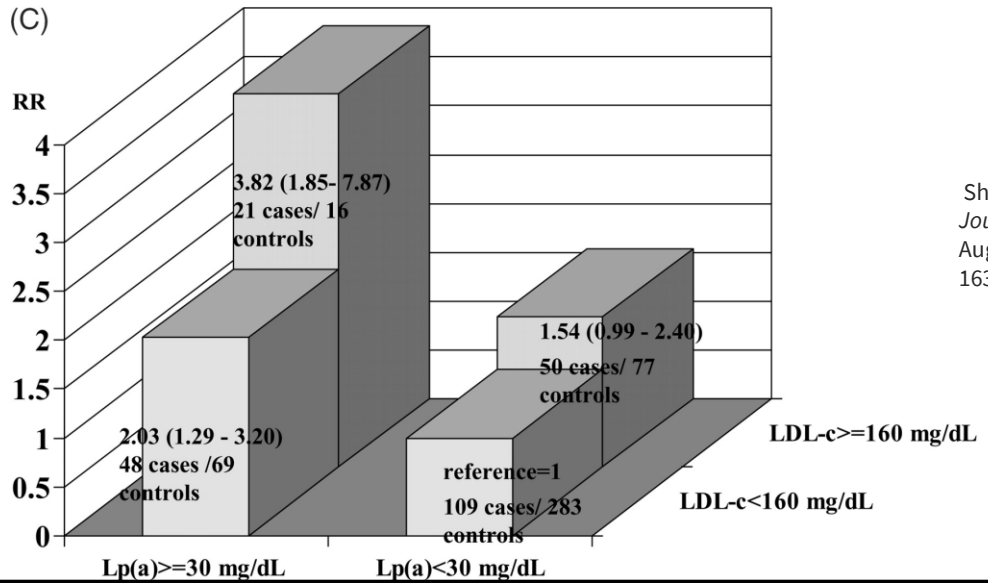
Interaction of Lp(a) and LDL from the Nurses Health Study: When LDL Is Elevated CV Risk Is Higher



Shai I et al., *European Heart Journal*, Volume 26, Issue 16, August 2005, Pages 1633–1639,

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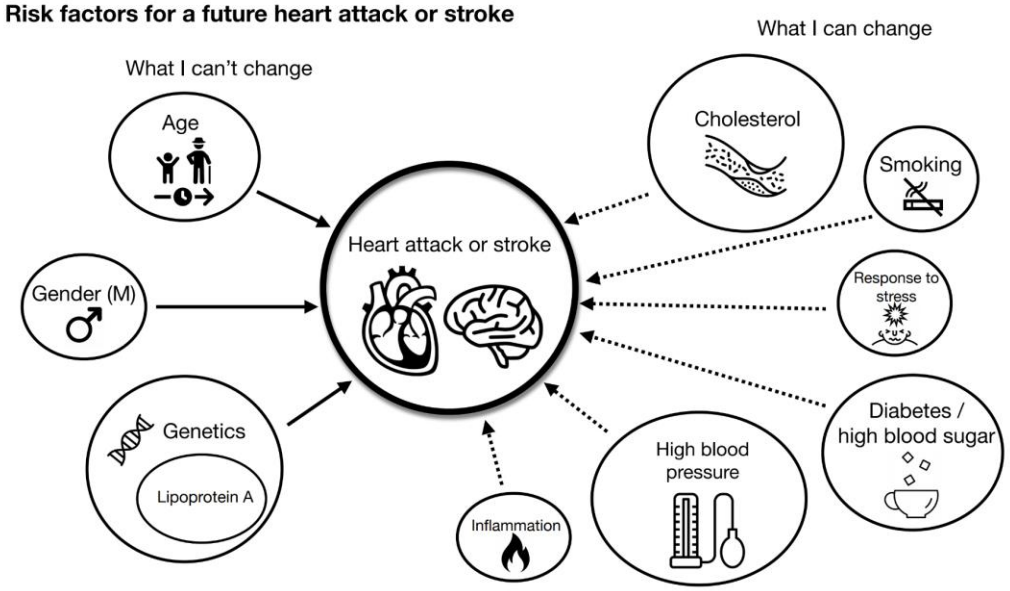
Need to Incorporate Lp(a) Into Clinical Risk Assessment



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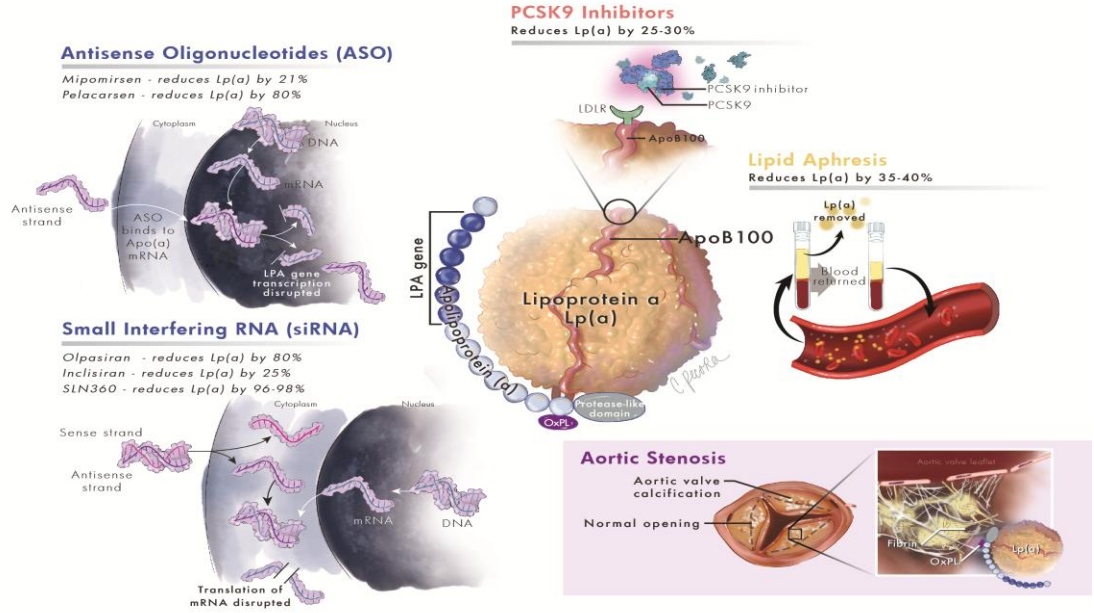
Lipoprotein A Lowering Drugs



Patel N, Taub PR. *Current Cardiovascular Risk Reports*. 2022;16:111-120.

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Effect of Lipid Lowering Drugs on Lp(a) Levels

Statins	No Effect or slight increase
Ezetimibe	No Effect or slight increase
Fibrates	No Effect
Niacin	Decrease 15-25%. Greatest decrease in patients with highest Lp(a) levels
PCSK9 Inhibitors	Decrease 20-30%
Estrogen	Decrease 20-35%
Mipomersen*	Decrease 25-30%
Lomitapide*	Decrease 15-20%
CETP Inhibitors**	Decrease ~ 25%
Apo (a) antisense**	Decrease > 75%

Only PCSK9 Inhibitors Have Become Shown to Improve CV Outcomes

McNeal CJ, Peterson AL. Lipoprotein (a) in Youth. [Updated 2020 Feb 9]. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.;

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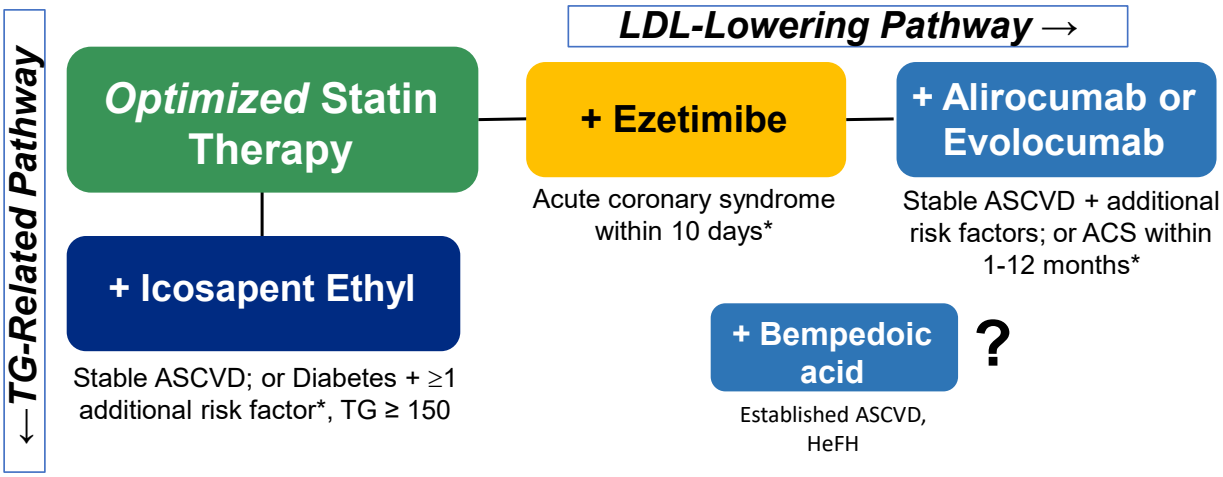
According to ACC/AHA Guidelines, Which of the Following Is the Threshold for Lp(a) Is Considered an ASCVD Risk Enhancer?

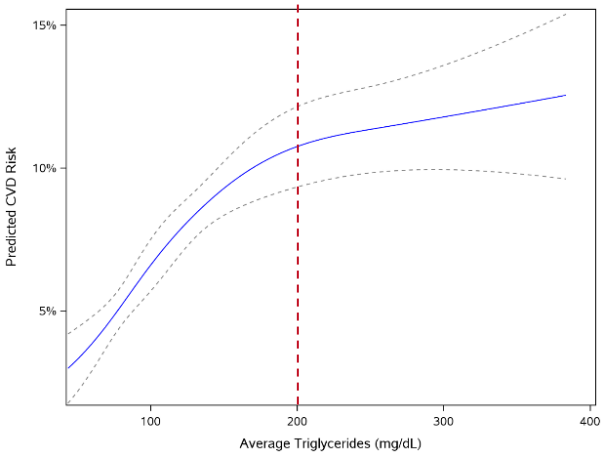
A. > 1 mg/dL or 10 nmol/L
B. > 10 mg/dL or 18 nmol/L
C. > 50 mg/dL or 125 nmol/L
D. > 300 mg/dL or 650 nmol/L

Statin Therapy Adjuncts *Proven* to Reduce ASCVD



*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.

CVD Increases Dramatically w/ TG Increases Even Just "Normal" to "Upper Normal" Range



- 8,068 primary prevention patients in Atherosclerosis Risk in Communities Study (ARIC) and Framingham Offspring Study
  - 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.

95% confidence intervals shown as dotted lines.
Aberra T, et al. *J Clin Lipidol*. 2020;14(4):438-447.e3.

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REDUCE-IT Population

Double-blind parallel group trial; median follow-up 4.9 years

- Statin treated men and women (aged ≥45 years)
- Well controlled LDL-C (41-100 mg/dL) (median baseline 75mg/dL)

8179 Patients

At High Risk for CV Events Due To:
- TG 150-499 mg/dL (median baseline 216 mg/dL), and
- Established CVD

OR

- Diabetes mellitus + aged ≥50 years + ≥1 risk factor for CVD

Randomization 1:1

Stable Statin + icosapent ethyl 4g/d

Stable Statin + Placebo

PRIMARY COMPOSITE (MACE) ENDPOINT

CV Death
Nonfatal MI
Coronary Revascularization
Nonfatal Stroke
Unstable Angina requiring hospitalization

Bhatt DL et al. *Circulation*. 2020;141:367–375.

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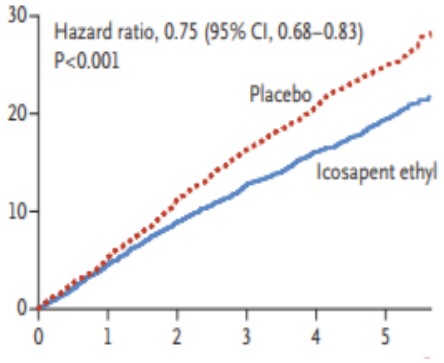
REDUCE-IT: Icosapent Ethyl Reduces ASCVD Risk

Pleotropic Benefits Beyond Triglyceride Lowering



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

25% RRR
NNT=21

In patients with well-controlled LDL on stable statin therapy with elevated triglycerides, addition of Icosapent ethyl resulted in a 4.8% absolute risk reduction and 25% relative risk reduction (*P* < 0.001) in the composite endpoint of:

- CV
- nonfatal MI
- nonfatal stroke
- coronary revascularization
- unstable angina requiring hospitalization

Bhatt DL et al. *Circulation*. 2020;141:367–375.

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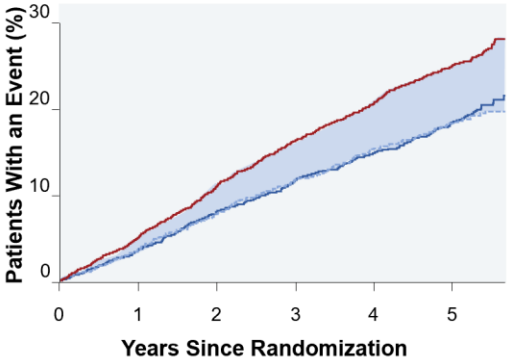
CV Risk Reduction Is Independent of Triglyceride Level Achieved

Primary Endpoint Stratified by Achieved TG Level at 1 Year



Statin +
Placebo

VASCEPA TG ≥150 mg/dL 0.71 (0.63–0.79)
VASCEPA TG <150 mg/dL 0.71 (0.60–0.81)

Similar results were observed for the key secondary endpoint

Results suggest pleiotropic effects and opportunity to treat the patient rather than a lab score

From New England Journal of Medicine; Bhatt DL et al; for the REDUCE-IT Investigators, Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia, Supplementary Appendix 380(1), 48. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Copyright © 2019 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

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

Vascepa

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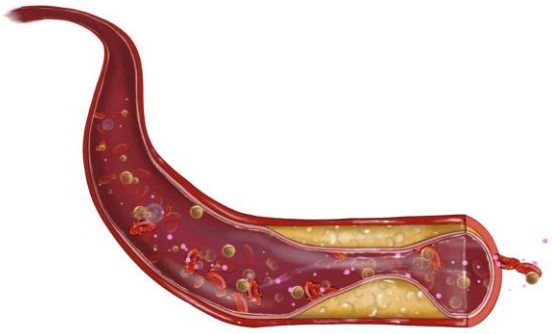
Triglycerides are a Reflection of the Bad Company they Keep



- "It is what is flowing with it."
- Capturing an atherogenic phenotype

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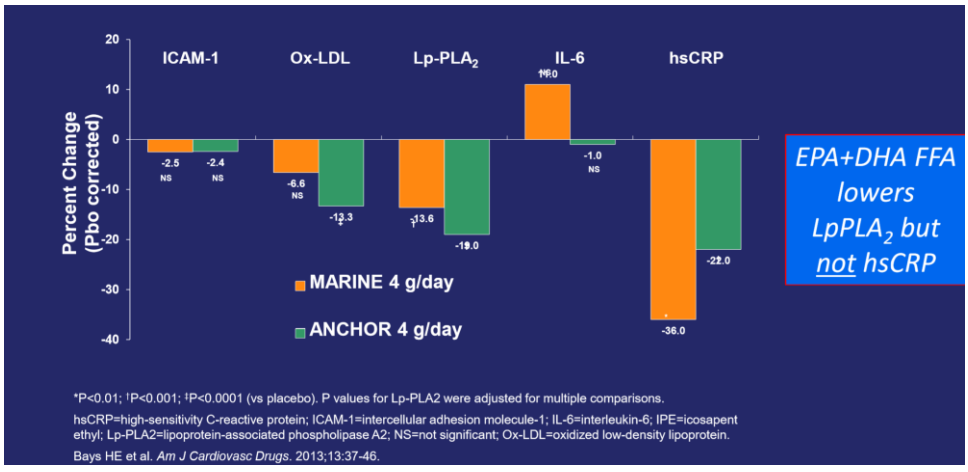
Icosapent Ethyl Lowers Inflammatory Biomarkers



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

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

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

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REDUCE-IT

Effects on Biomarkers from Baseline to Year 1

	Icosapent Ethyl (n = 4089) Median		Placebo (n = 4090) Median		Median Between Group Difference at Year 1		
Biomarker*	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change *P*-value
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	< 0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	< 0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	< 0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	< 0.0001
Apo B (mg/dL)	82.0	800	83.0	89.0	-8.0	-9.7	< 0.0001
hsCRP (mg/L)	**2.2**	**1.8**	**2.1**	**2.8**	**-0.9**	**-39.9**	**< 0.0001**
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	< 0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	**+358.8**	< 0.0001

Bhatt DL, et al. *NEJM*. 2019;380(1):11-22.

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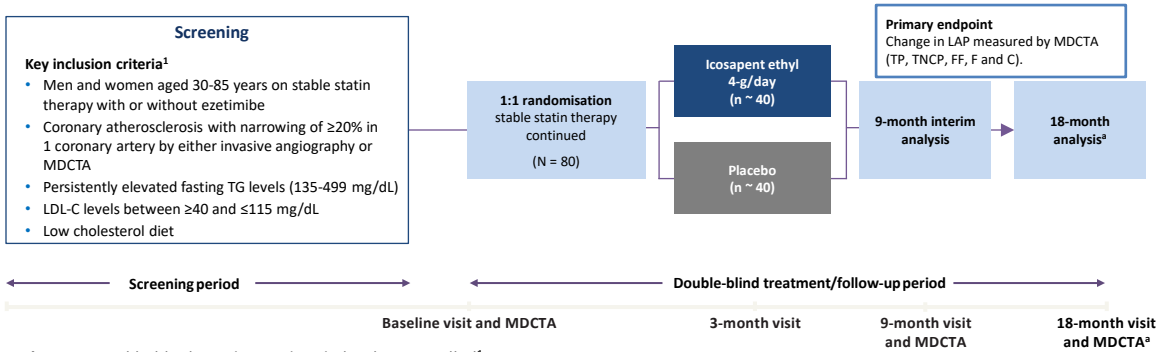
EVAPORATE

Study Design[1,2]

A double-blind, randomised and placebo-controlled trial (NCT02926027)



Study type: Double-blind, randomised and placebo-controlled[1]

Study aim: The objective the of EVAPORATE study was to evaluate the effects of 4 g of icosapent ethyl per day as an adjunct to diet and statin therapy, in patients with elevated fasting TG levels on coronary computed tomographic angiography plaque volumes over 18 months of therapy.[1]

[a]If efficacy is not achieved at 9 months as determined by the Data Safety and Monitoring Board and a statistician, then the patients will be followed for an additional 9 months to check the progression of low-attenuation plaque volume by MDCTA. At 9 months if the *P*-value of ≤0.006 is achieved, then the study will terminate as the efficacy boundary will have been achieved

C, calcified plaque; F, fibrous plaque; FF, fibrofatty plaque; LAP, low-attenuation plaque; LDL-C, low-density lipoprotein cholesterol; MDCTA, multidetector computed tomographic angiography; TNCP, total non-calcified plaque; TP, total plaque

1. Budoff M, et al *Eur Heart J*. 2020;41(40):3925-3932 2. Budoff M, et al. *Clin Cardiol*. 2018;41(1):13-19.

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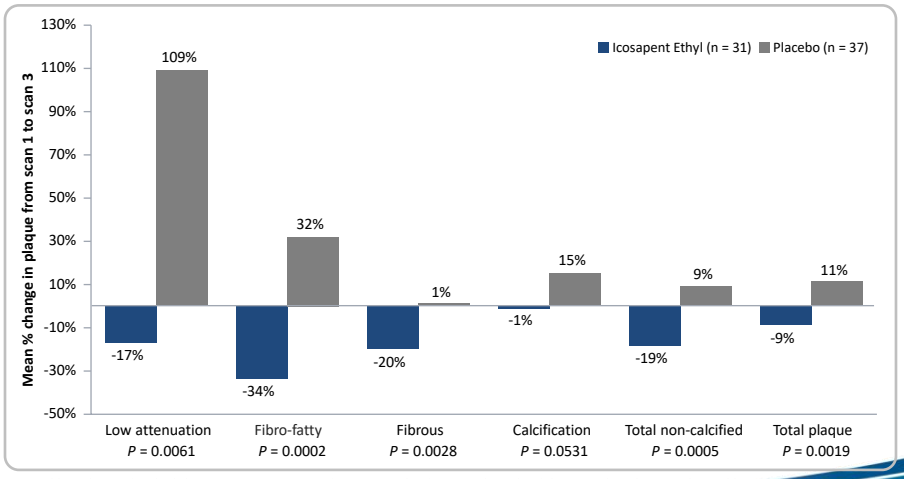
EVAPORATE

Mean Plaque Progression Measured on Cardiovascular CT



Dense calcium showed a significant difference in univariable analysis ($P = 0.046$) versus placebo. It did not show any significant difference between groups in multivariable modelling ($P = 0.053$).

Univariable analysis and multiple linear regression were used to examine the change in plaque levels between the cohorts. Multivariable models were adjusted by age, sex, diabetes status, hypertension and baseline TG levels. All statistical analyses report 2-sided *P*-values for the outcomes. A *P-value* <0.048 was considered significant for the outcomes.

CT, computerised tomography; TG, triglyceride.

Budoff M, et al. *Eur Heart J.* 2020;41(40):3925-3932.

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EVAPORATE

Conclusions

- The EVAPORATE study is the first study to assess IPE as an additional therapy to statins in CV population with high TGs by evaluating coronary plaque characteristics by MDCTA.
- A significant reduction in the primary endpoint was noted as IPE reduced LAP plaque volume by 17%, and in the placebo group the LAP plaque volume increased by +109% ($P = 0.0061$).
- The plaque volumes for other types regressed in the IPE group and progressed in the placebo group ($P<0.01$ for all).
- Despite reducing atherosclerotic plaque, statin therapy increases coronary calcification. In this study, there was no increase in the coronary artery calcium volume on IPE therapy, and a trend of decreasing calcification was noted when compared with placebo ($P = 0.053$).
- IPE has been shown to have anti-arrhythmic, anti-oxidant, anti-inflammatory and pro-resolving effects. This could have a favourable effect on multiple steps of the atherosclerotic pathway.
- In patients with significant atherosclerosis, IPE could be added to the existing statin therapy given the robust CV event reduction in clinical trials of IPE and reduction in plaque volume.

CV, cardiovascular; IPE, Icosapent ethyl; LAP, low-attenuation plaque; MDCTA, multidetector computed tomographic angiography; TG, triglyceride.

Budoff M, et al. *Eur Heart J.* 2020;41(40):3925-3932.

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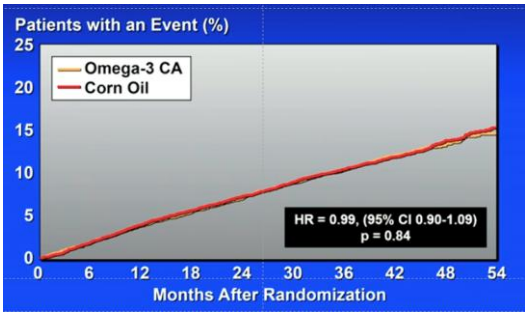
STRENGTH Trial Design, Details, and Primary Endpoint

- Randomized 13,078 patients Oct. 2014 – June 2017 (686 sites, 22 countries)
- Trial stopped by Data Monitoring Board for "futility" Jan. 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)



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

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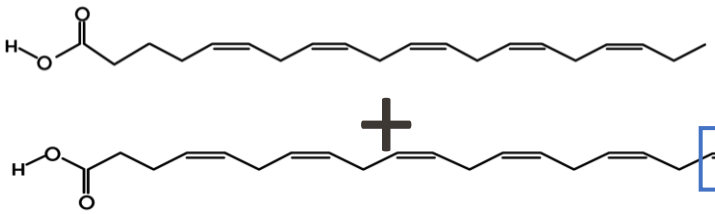
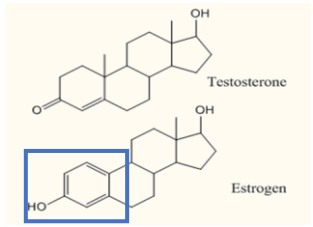
Basic Biochemistry: The Molecule Matters! Why Do We Struggle with This When It Comes to EPA versus DHA?

Eicosapentaenoic acid (EPA) 20:5



Docosahexaenoic acid (DHA) 22:6

Omega-3 PUFA



Even ***small*** ***structural differences*** can have ***large*** ***biological differences***

Slide adapted from R. Preston Mason, PhD, Elucida Research and Harvard/Brigham & Women's Hospital.

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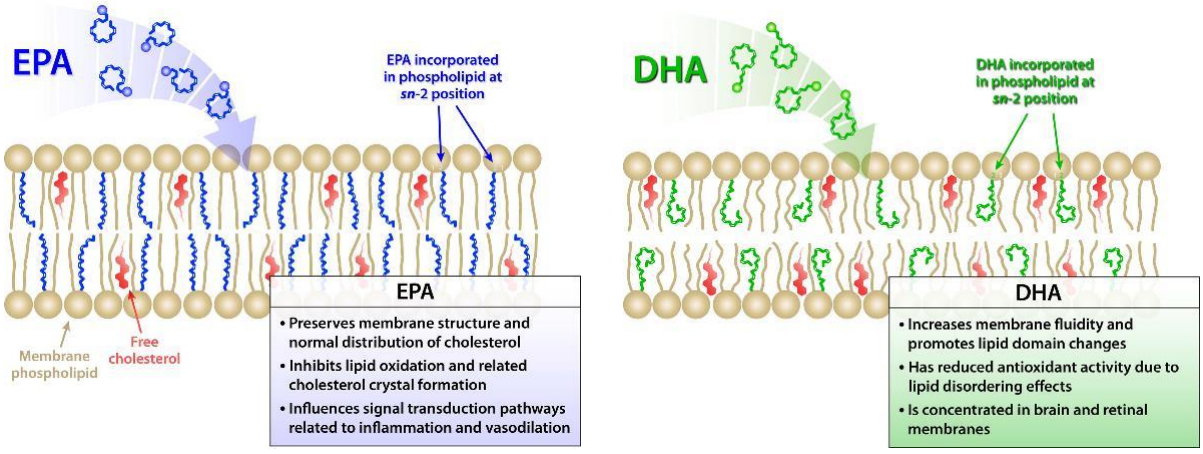
Contrasting Effects of EPA and DHA



Reproduced with permission. Mason RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol*. 2020;40:1135–1147.

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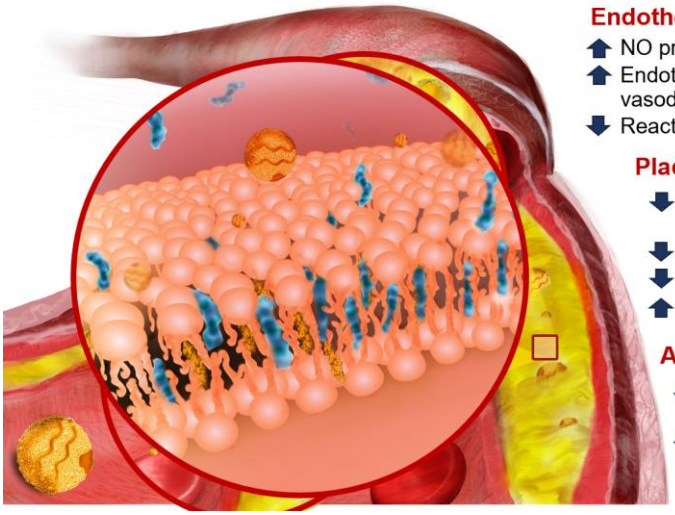
Pleotropic Effects of Icosapent Ethyl



Endothelial function
- ↑ NO production
- ↑ Endothelium-dependent vasodilation
- ↓ Reactive oxygen species

Plaque stability
- ↓ Plaque formation, progression, and rupture
- ↓ Thrombosis
- ↓ Platelet activation
- ↑ Fibrous cap thickness

Anti-inflammatory effects
- ↓ Proinflammatory eicosanoids and cytokines
- Inflammatory cell recruitment

Mason RP Current Atheroscler Rep 2019; 21(1):2

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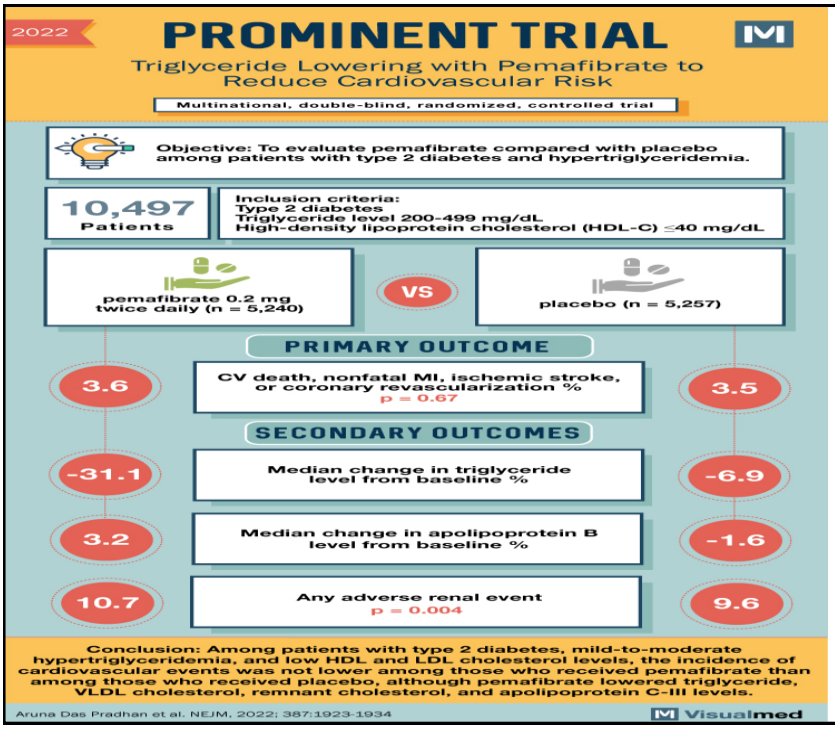

Fibrates: No Role in CVD Risk Reduction

In PROMIENT triglycerides were lowered by 26.2% and HDL increased by 5.1%.
No decrease in ApoB.
No change in non-HDL.

In REDUCE-IT ApoB was lowered by 9.7% whereas in STRENGTH no change in ApoB.

Studies highlight the net lowering of atherogenic lipoprotein levels rather than lowering of triglyceride levels alone.

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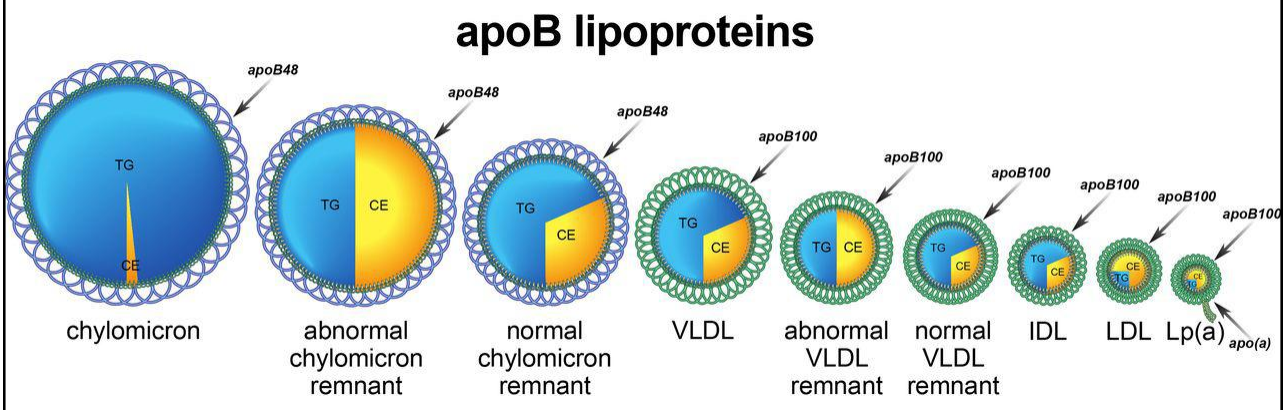
Apo B Is the Structural Backbone of All Atherogenic Lipids



apoB is a better predictor of cardiovascular events than LDL-C

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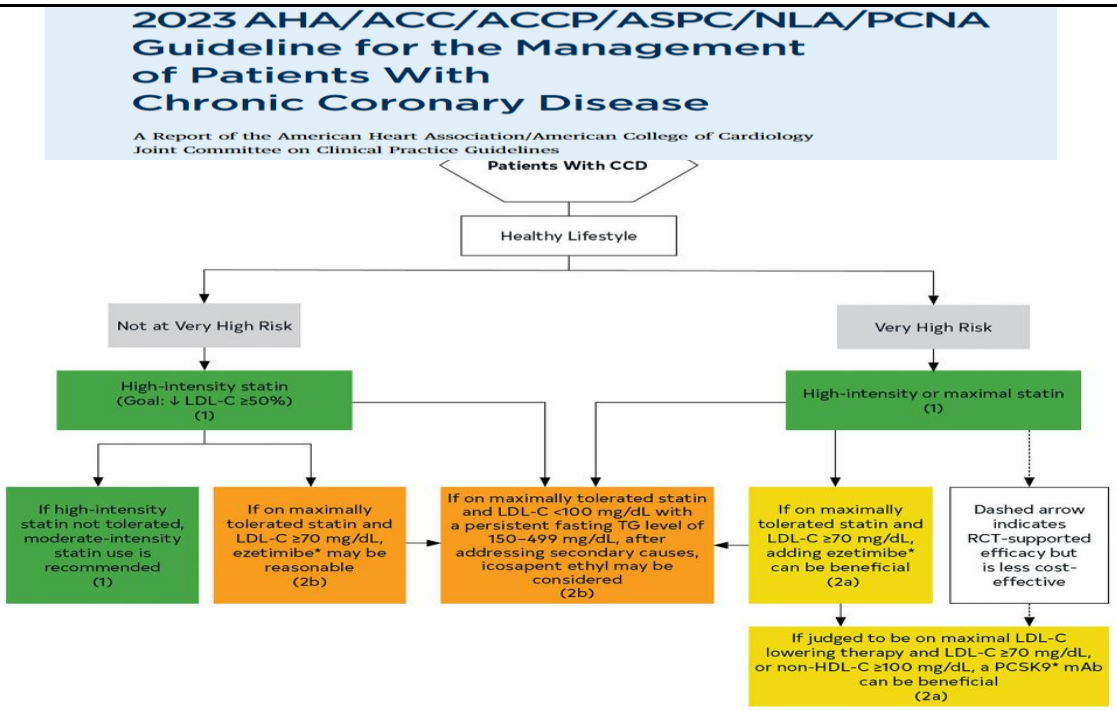

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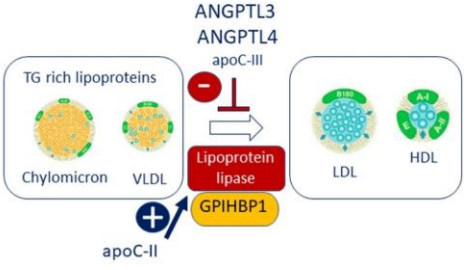
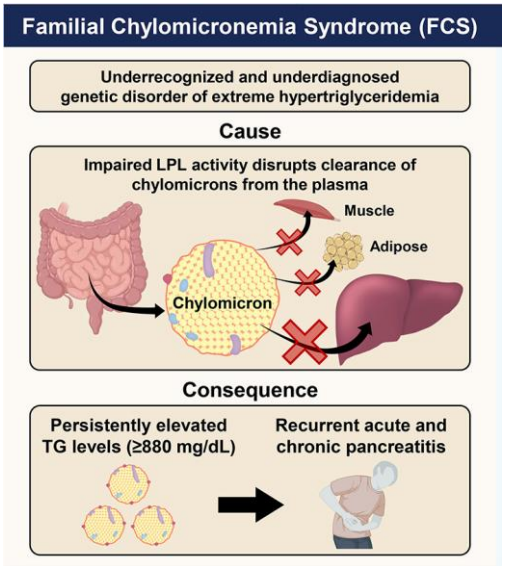
Plozasiran vs Olezarsen

- Plozasiran (siRNA) received FDA approval November 18, 2025 to treat Familial Chylomicronemia Syndrome (FCS)
- Olezarsen (ASO) approved to treat FCS in 2024
- apoCIII inhibitors (siRNA, ASO)





Figures modified from: A. Bajaj, et al., AJPC 2025 and Ruscica, M. Pharmacological Research 2020, 153:104653

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Definition of Severe Hypertriglyceridemia sHTG

- sHTG has been traditionally defined as TG ≥500mg/dL
- sHTG is associated with increased risk of acute pancreatitis and cardiovascular disease.
- sHTG is commonly associated with obesity, metabolic syndrome, insulin resistance, type 2 diabetes mellitus and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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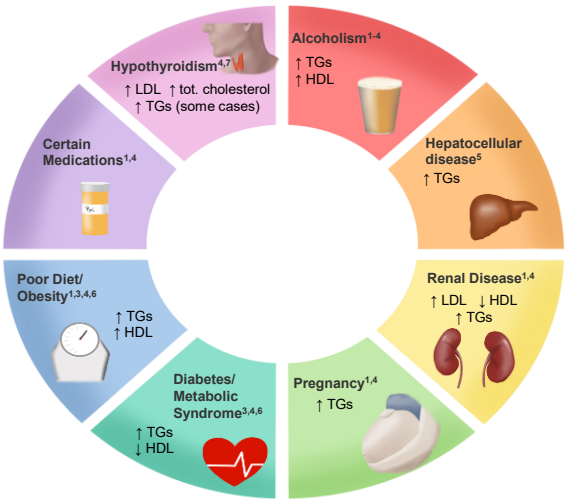
Identifying Secondary Causes of HTG



1. Yuan G, et al. *CMAJ*. 2007;176:1113-1120. 2. Van de Wiel A. *Int J Vasc Med*. 2011;2012:1-4. 3. O'Keefe JH, et al. *J Am Coll Cardiol*. 2008;51:249-255. 4. Chait A, Eckel RH. *Ann Intern Med*. 2019;170:626-634. 5. Alves-Bezerra M, Cohen DE. *Compr Physiol*. 2017;8:1-8. 6. Alberti K, et al. *Lancet*. 2005;366;1059-1062. 7. Rizos C, et al. *Open Cardiovasc Med J*. 2011;5:76-84.

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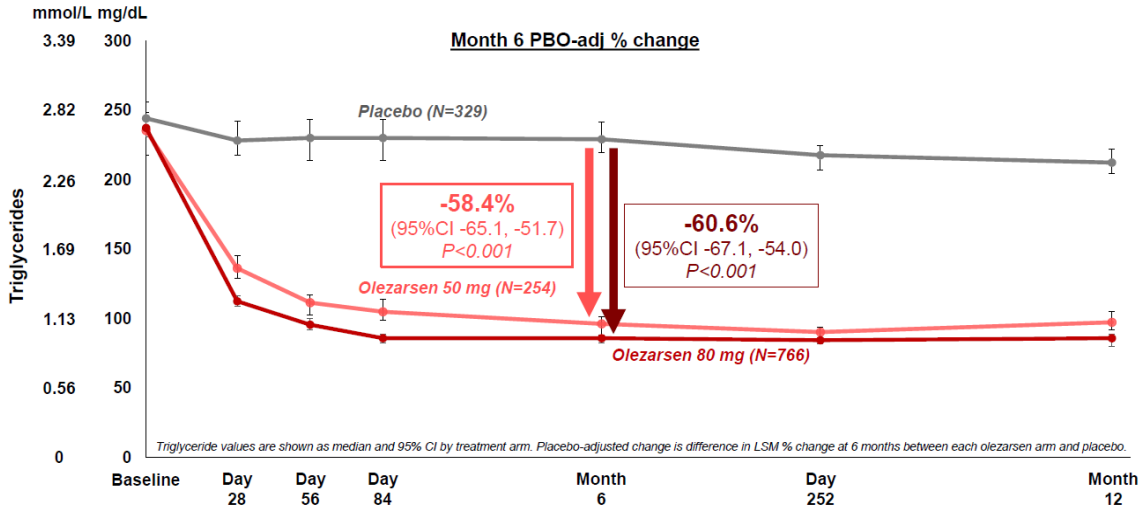
Essence: Olezarsen in Patients with mHTG (TG 150-499 mg/dL) and High CV Risk or with sHTG (≥500 mg/dL



Bergmark BA et.al N Engl J Med. 2025;393:1279-1291.

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Case Presentation

- 66-year-old female with a history of CAD, PCI of LAD 8 months ago, HTN, T2DM, atrial fibrillation, and hypothyroidism.
- Current medications: atorvastatin 40 mg, amlodipine 10 mg, aspirin 81 mg, clopidogrel 75 mg, levothyroxine 75 mcg, apixaban 5 mg bid, metformin 1000 mg bid, empagliflozin 10 mg qd
- Exam: Blood Pressure: 130/85 HR 70; BMI 30 kg/m^2
- Laboratory Data:

Total Cholesterol: 140 mg/dL

HDL: 30 mg/dL

Calculated LDL: 53 mg/dL

Triglycerides: 287 mg/dL

Non-HDL: 110 mg/dL

HbA1c: 7.6

Creatinine 1.4 mg/dL; eGFR 55 mL/min

44

Management of This Patient

- Optimize Lifestyle Strategies
  - Discuss lifestyle management including: aerobic exercise, Mediterranean diet avoidance of concentrated sugars/alcohol and improved glycemic control
- Get the LDL-C/non HDL-C "as low as you can go" with a minimum goal of less than 55 mg/dL in this very high-risk patient
  - Optimize statin therapy and utilize non-statin agents
- Concomitantly add Icosapent Ethyl for Global CV Risk Reduction
  - In addition to triglyceride lowering icosapent ethyl will have an impact on multiple aspects of residual risk.

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Summary

- Check Lp(a) in everyone
- For those with elevated Lp(a) maximize statin and consider aspirin based on risk/benefit discussion
- Test family members of patients with elevated Lp(a)
- Triglycerides are markers for increased CV risk and risk increases with even with mild elevation >100 mg/dL.
- In clinical trials where triglycerides were lowered concomitantly with ApoB (such as REDUCE IT with icosapent ethyl), improvement in CV outcomes was seen.
- Will have FDA approved therapies for sHTG

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