Lipoprotein (a), Triglycerides, and Cardiovascular Risk

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Disclosure

Consultant: Amgen; Arrowhead Pharmaceutical; Astra Zeneca; Boehringer Ingelheim; Edwards Lifesciences; Eli Lilly; Esperion; Ionis Pharmaceuticals; Medtronic; Merck; New Amsterdam; Novartis; Novo Nordisk; Pfizer

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Learning Objectives

Part 1: Lipoprotein (a)

- To review the genetic and observational data linking lipoprotein (a) as a causal risk factor for atherosclerotic cardiovascular disease (ASCVD) and aortic stenosis
- Review actionable strategies that can be undertaken now in 2024 to reduce CV-risk associated with elevated lipoprotein (a)
- To summarize emerging therapies currently under investigation that may be options for patients with elevated Lp(a) in near future

Part 2: Triglyceride risk lipoproteins (TRLs)

- Review genetic and observational data of TRLs suggesting their causal role for ASCVD
- Discuss lifestyle and pharmacological approaches to managing hypertriglyceridemia (HTG)
- Discuss the trials, successes and failures, investigating fibrate therapy and omega-3 fatty acid therapy for ASCVD prevention in persons with HTG
- Summarize emerging therapies currently under investigation targeting apoC3 and ANGTL3 that may be future options for patients with severe HTG

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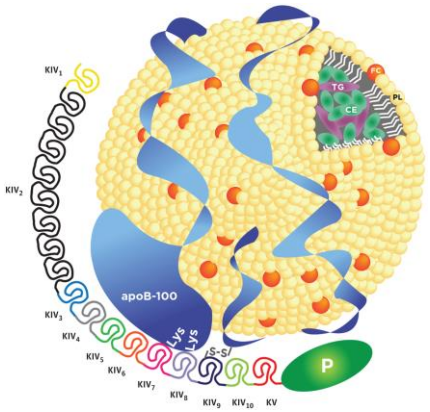
Lipoprotein (a)



CE, cholesterol ester; FC, free cholesterol; Lys, lysine; KIV, Kringle IV; KV, Kringle V; P, protease-like domain; PL, phospholipid. Image from *JAMA Cardiol.* 2022;7(7):760-769.

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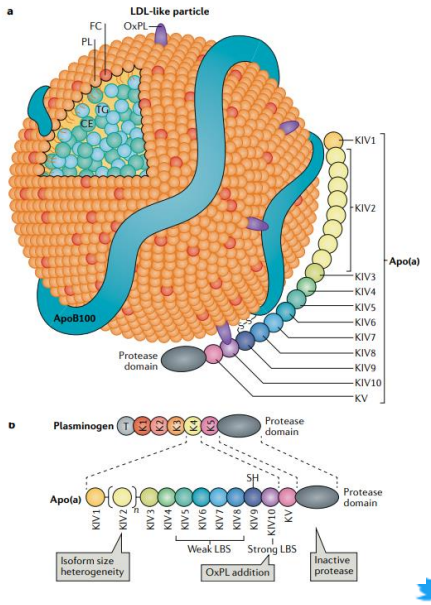
Structure of Lp(a)

- Lp(a) is a LDL-like particle with an apoB100 bound to apo(a)
- Major lipoprotein carrier of pro-inflammatory and pro-calcific oxidized phospholipids (OxPL)
- Apo(a) is highly homologous to plasminogen
- The apo(a) part consists of 10 subtypes of kringle domain IV (KIV_{1-10}), a kringle domain V (KV) and an inactive protease domain.



Boffa and Koschinsky, Nat Rev Cardiol 2019;16:305-318

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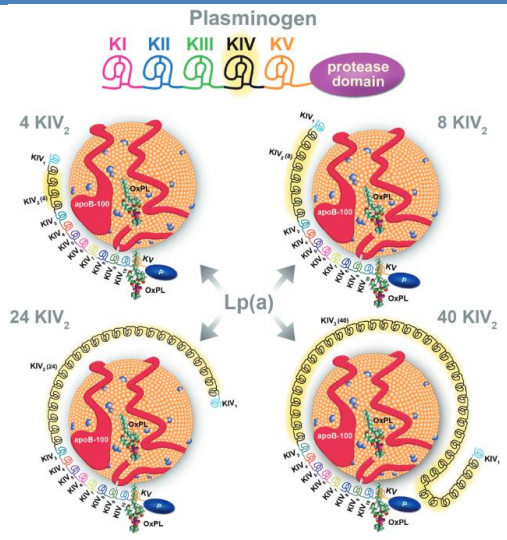
Structure of Lipoprotein (a)



Duarte Lau F, et al. *JAMA Cardiol*. 2022;7(7):760-769.

Tsimikas S. *J Am Coll Cardiol*. 2017;69:692-711.

- ≥ 90% of plasma Lp(a) levels are genetically determined
- KIV_2 can expand into more than 40 identically repeated copies.
- Within a population, significant heterogeneity in apo(a) size and thus different Lp(a) size
- Direct conversion between Lp(a) mass (mg/dL) and concentration (nmol/L) is an imprecise approximation since all conversion factors are inherently isoform dependent
- Should be measured by isoform insensitive assay and reported in nmol/L

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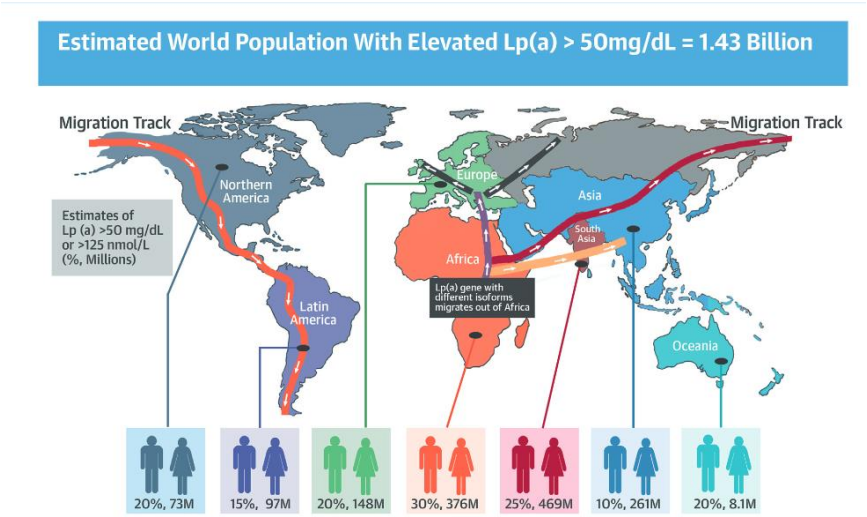
An Estimated 20% to 25% of the Global Population Have Lp(a) Levels of ≥50 mg/dL (~125 nmol/L)



Tsimikas S. et al. *J Am Coll Cardiol.* 2018;71:177-192.

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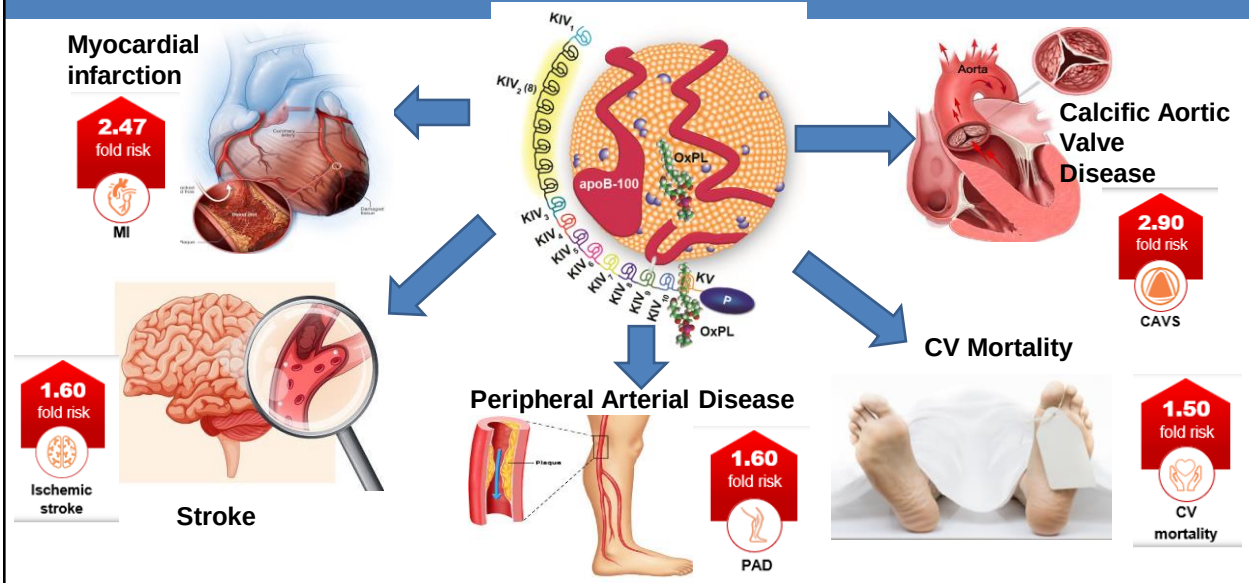
Lp(a) and Cardiovascular Disease (CVD) Risk



Reyes-Soffer G…**Michos ED**…Ballantyne CM. AJPC 2024

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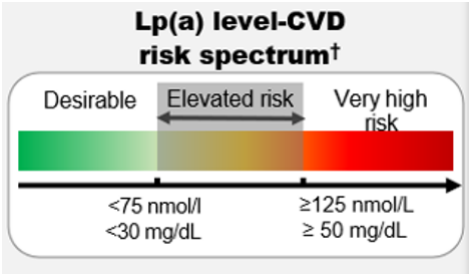
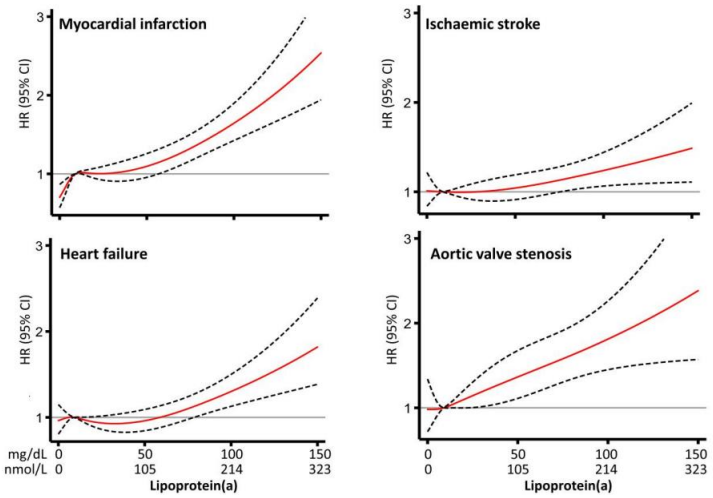
Risk of Clinical Outcomes with Lp(a) Concentration

Risk is continuous



Reyes-Soffer G…**Michos ED** …Ballantyne CM. AJPC 2024



Based on data from 70 286 White individuals in the Copenhagen General Population Study with a median 7.4 years of follow-up.

Kronenberg F et al. Eur Heart J. 2022; 43(39):3925–3946.

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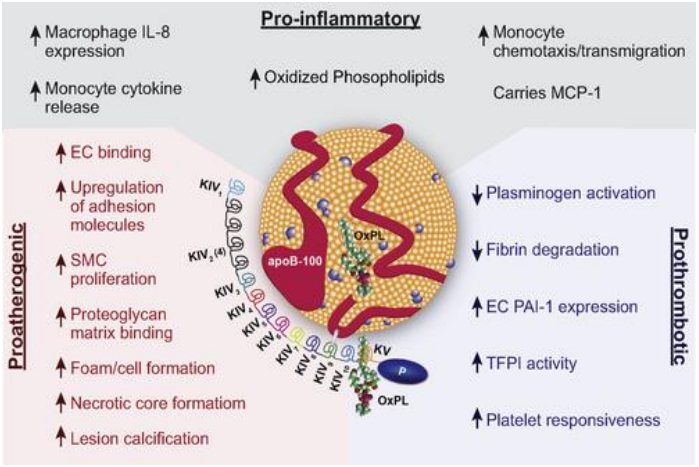
Pathogenic Mechanisms of Lp(a)



- Promotes CVD through 4 mechanisms:
  - Vascular inflammation
  - Atherogenesis
  - Calcification
  - Thrombosis.

Tsimikas S et al. *J Am Coll Cardiol.* 2017;69:692-711.

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Lp(a) Measurement: When, Who, Why?

Reyes-Soffer G…**Michos ED**…Ballantyne CM. AJPC 2024: 100651

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Who to Screen for Lp(a)?

A Focused Update to the 2019 NLA Scientific Statement on Use of Lipoprotein(a) in Clinical Practice

nla

Measure Lp(a) at least Once in all Adults and Selected High-risk Children

Candidates for Lp(a) Screening

1. The adult population
2. The pediatric population (specifically, high-risk children and youth)
   - Clinically suspected or genetically confirmed familial hypercholesterolemia
   - First-degree relatives with a history of premature ASCVD
   - Ischemic stroke or unknown cause
   - First-degree relatives with elevated Lp(a)

National Lipid Association
Koschinsky ML….**Michos ED**….Ballantyne CM. J Clin Lipidol. 2024: S1933-2874(24)00033-3.

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Why Screen for Lp(a)?

Action Items to Consider if High Risk:

- More intensive risk factor management, including LDL-C (Lp(a) is a risk-enhancing factor)
- Cascade screening
- Lifestyle modifications
- Therapies such as statin, PCSK9 inhibitor, aspirin; apheresis if severe

Recommendations to Consider Offering to Patients

1. Lifestyle modification
2. Statins
3. Ezetimibe
4. PCSK9-directed therapies
5. Aspirin
6. Lipoprotein apheresis

Koschinsky ML….**Michos ED**….Ballantyne CM. J Clin Lipidol. 2024: S1933-2874(24)00033-3.

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EAS Recommendations: Intervention Strategies as a Function of Total CV Risk and Untreated Lp(a) Concentration

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	Total CV risk (SCORE) %	Untreated Lp(a) concentrations < 10 mg/dL < 25 nmol/L	10 to <30 mg/dL 25 to <75 nmol/L	30 to <50 mg/dL 75 to <125 nmol/L	50 to <75 mg/dL 125 to <188 nmol/L	75 to <100 mg/dL 188 to <250 nmol/L	≥100 mg/dL ≥250 nmol/L
Primary Prevention	< 1 low-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Primary Prevention	≥1 to <5, or moderate-risk	Lifestyle advice	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Primary Prevention	≥5 to <10, or high- risk	Lifestyle advice	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Primary Prevention	≥10, or at very-high risk due to a risk condition	Lifestyle advice	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)
Secondary Prevention	Very-high-risk	Lifestyle intervention, consider drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)	Lifestyle and drug intervention (e.g. LDL-C, BP, glucose)

Kronenberg F et al. Eur Heart J. 2022; 43(39):3925–3946.

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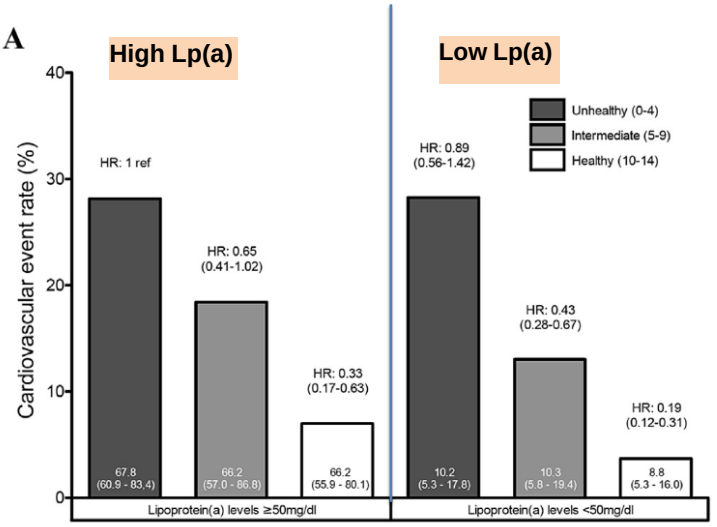
Ideal Cardiovascular Health Influences CVD Risk Associated with High Lp(a) Levels

14,051 participants of the EPIC-Norfolk study followed for 11.5 years

CVD Events



Perrot N et al. Atherosclerosis 2017; 256: 47-52.

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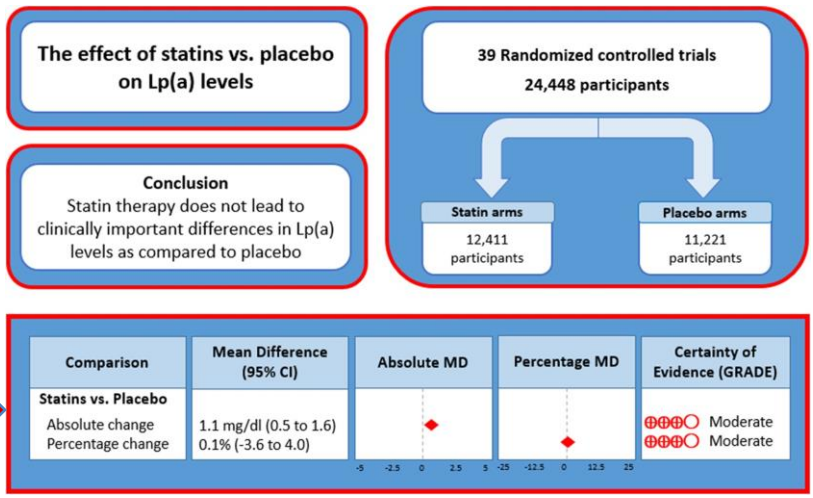
Effect of Statins on Lp(a) Level: Meta-Analysis of 39 Studies (24 ,448 Participants)

- Increase in Lp(a) with statins is modest.
- Not a reason not to use statins in pts with high Lp(a)



DeBoer LM et al. *Eur J Prev Cardiol* 2022;29:779-792.

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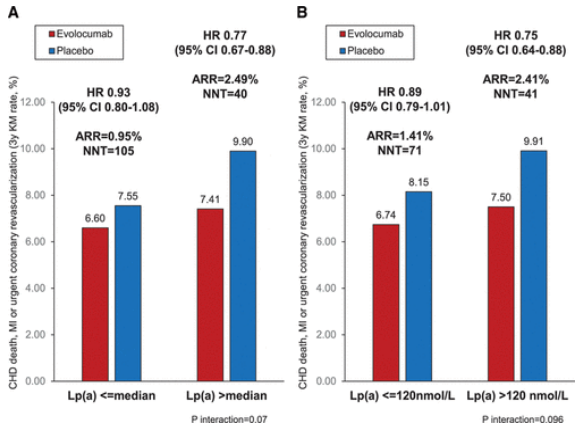
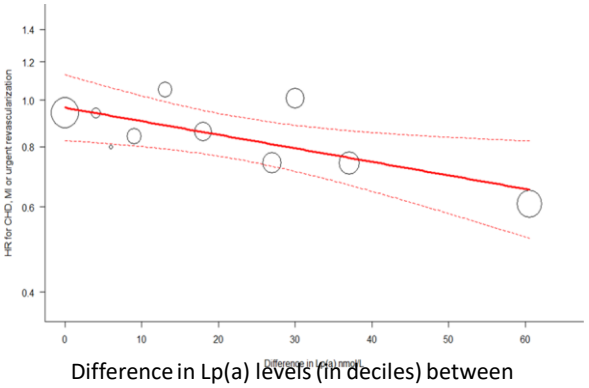
Efficacy of Evolocumab (a PCSK9i) in MACE Reduction by Lp(a) Concentration

At 48 weeks, evolocumab significantly reduced Lp(a) by a median (IQR) of 26.9% (6.2%–46.7%).



120 nmol/L (~50 mg/dL)



Difference in Lp(a) levels (in deciles) between evolocumab and placebo and risk for MACE

O'Donoghue ML et al. Circulation 2019; 139 (12);1483-1492, DOI: (10.1161/CIRCULATIONAHA

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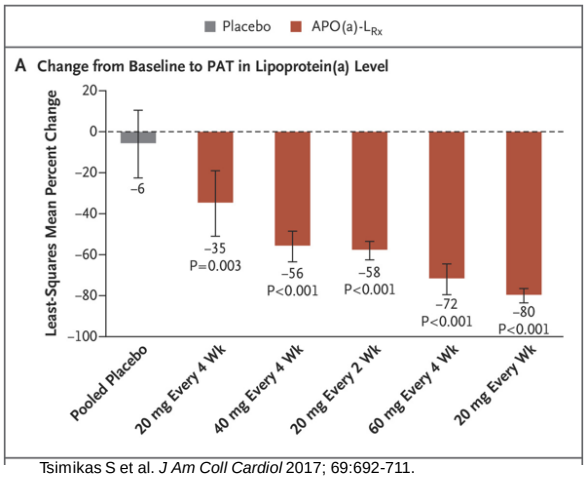
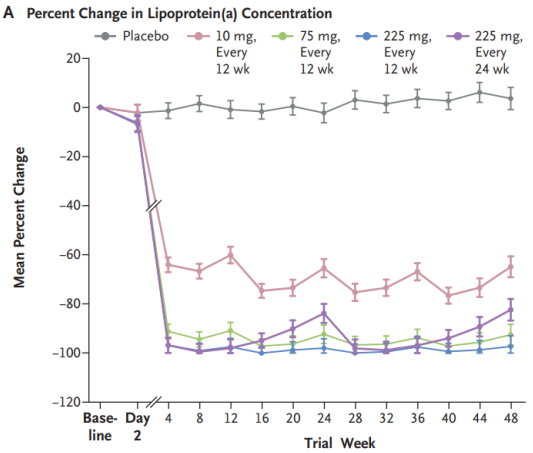
New Strategies to Targeting Lp(a) Under Investigation. Results from Phase II Trials

Pelacarsen - an ASO



Tsimikas S et al. *J Am Coll Cardiol* 2017; 69:692-711.

Olpasiran: an siRNA



O'Donoghue ML et al. N Engl J Med 2022;387:1855-1864

***The agents on this slide are investigational; not commercially available**

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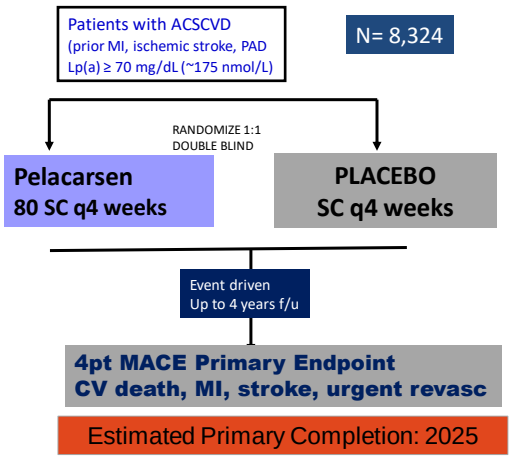
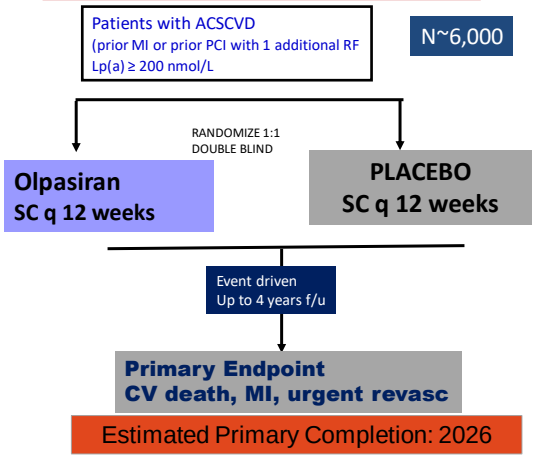
CVOT Trials for Lp(a) Therapeutics (Secondary Prevention Populations)

Lp(a) HORIZON



OCEAN Outcomes



*The agents on this slide are investigational; not commercially available

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Other Lp(a) Lowering Agents Under Study

- **Lepodisiran***: long-acting siRNA targeting Lp(a)
  - **Phase 3 CVOT in progress [ACCLAIM- Lp(a), NCT06292013]**
- **Zerlasiran***: another siRNA targeting Lp(a)
- **Muvalaplin***: small oral inhibitor of Lp(a) (disrupter of apo(a) X apo(B) interaction
- **Obicetrapib***: oral next generation CETP inhibitor developed for potent LDL-C lowering (~60%), also lowers Lp(a) by ~60%.
  - **Phase 3 CVOT in progress [PREVAIL, NCT05202509]**

apo(a), apolipoprotein A; apo(B), apolipoprotein B

*The agents on this slide are investigational; not commercially available

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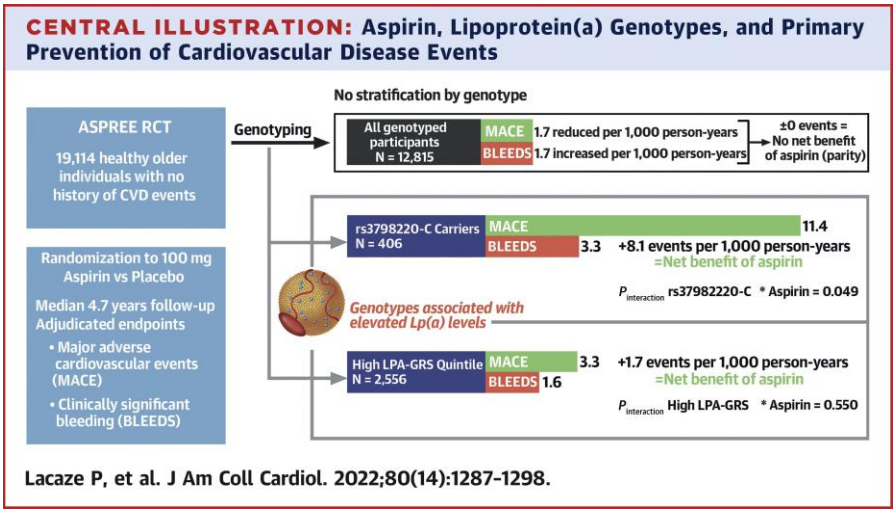
Aspirin May Benefit Older Individuals with Elevated LP(a) Genotypes in Primary Prevention



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

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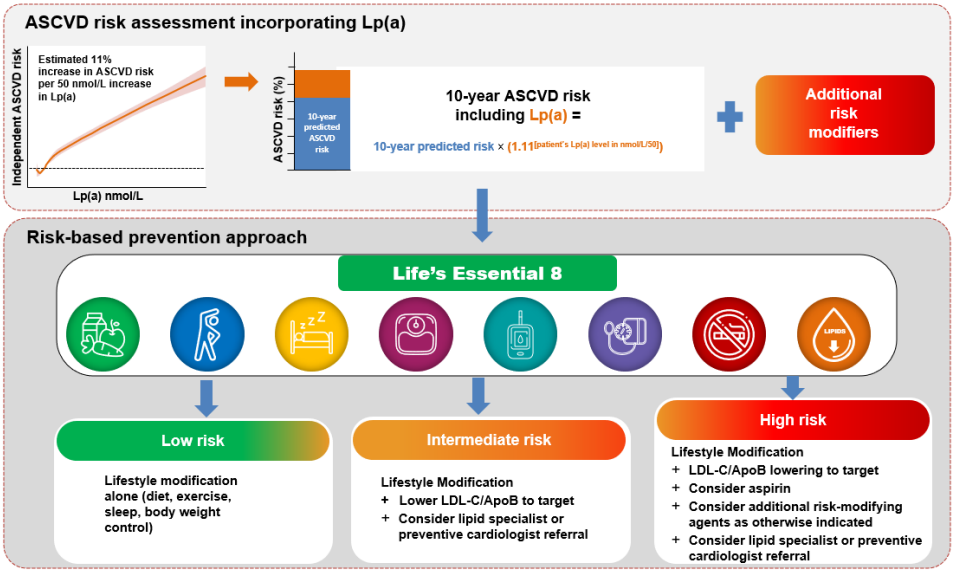
Risk-based Strategies for Managing High Lp(a)



Reyes-Soffer G...**Michos ED**...Ballantyne CM. AJPC 2024

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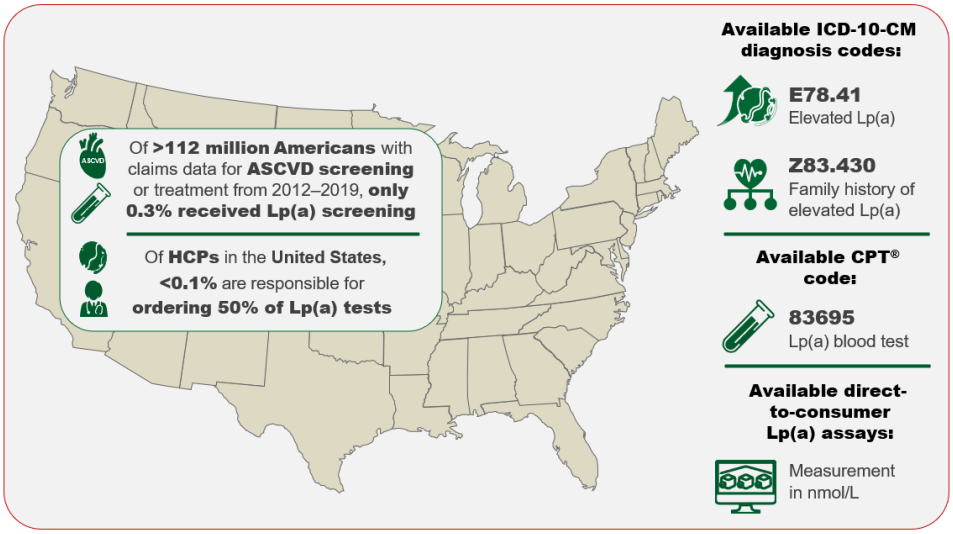
Current Landscape of Measurement of Lp(a) in U.S.



Reyes-Soffer G…**Michos ED**…Ballantyne CM. AJPC 2024

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Why Measure Lipoprotein (a)?

- Identify individuals with very high Lp(a)
- Reclassify borderline, intermediate, and high risk individuals
- Optimize management and treatment of other CVD risk factors
- Identify familial risk, cascade testing

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Conclusions: Lp(a)

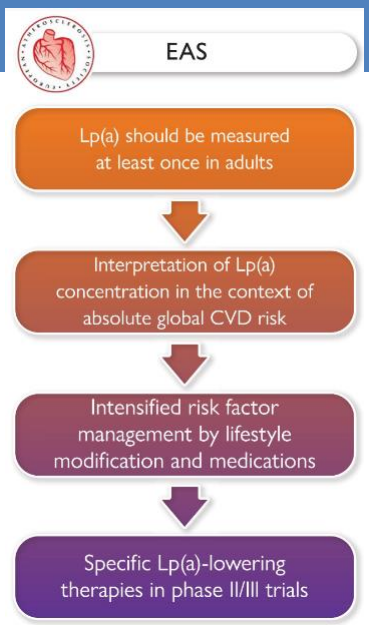
•Elevation of Lp(a) is a common risk factor responsible for considerable cardiovascular morbidity and mortality

•No pharmacological therapies are currently approved by regulatory authorities specific for Lp(a) management.

•In the absence of specific Lp(a)-lowering therapies, early risk factor management is recommended for individuals with elevated Lp(a), taking into account their absolute global cardiovascular risk and Lp(a) level.

•Thus, a high Lp(a) is ACTIONABLE now.

•Nucleic acid therapeutics offer a highly promising approach to treat this previously untreatable disorder. Cardiovascular outcomes trials will determine whether these therapies can reduce the incidence of MACE. Stay tuned.



Kronenberg F et al. Eur Heart J. 2022; 43(39):3925–3946.

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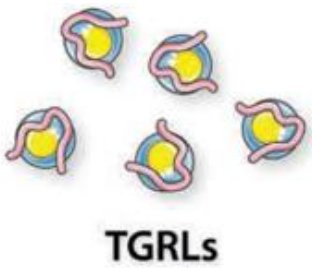
Triglycerides (TG) and Triglyceride Rich Lipoproteins (TRLs)



TGRL, triglyceride rich lipoprotein

Figure from Mason, RP, Libby P, Bhatt DL. *Arterioscler Thromb Vasc Biol*. 2020;40(5):1135–1147.

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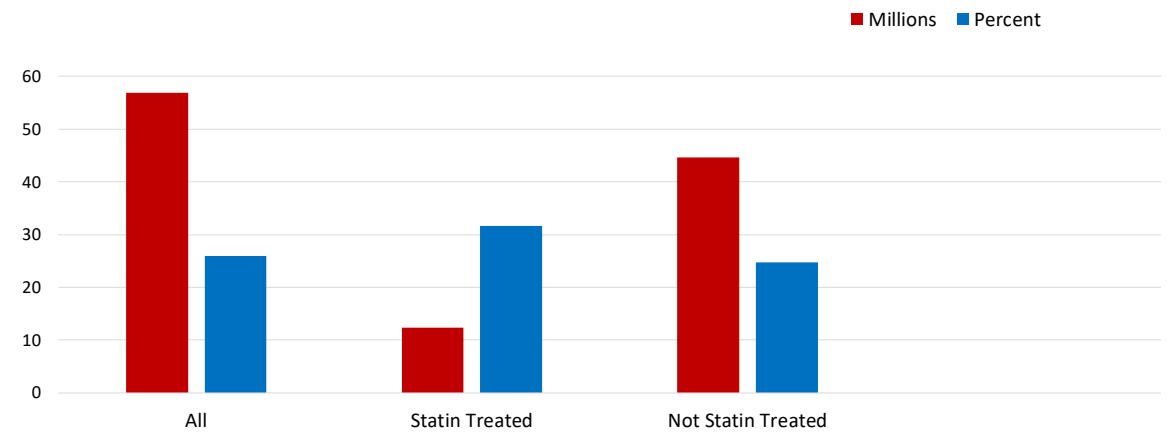
US Prevalence of Triglycerides (TG) ≥150 mg/dL



9,593 US adults aged >20 years (219.9 million projected) in the US National Health and Nutrition Examination Surveys 2007-2014 were studied.
Fan W, et al. *J Clin Lipidol*. 2019;13(1):100-108.

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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

Moderate HTG

Severe HTG

Risk of pancreatitis markedly increases at levels >1000 mg/dl

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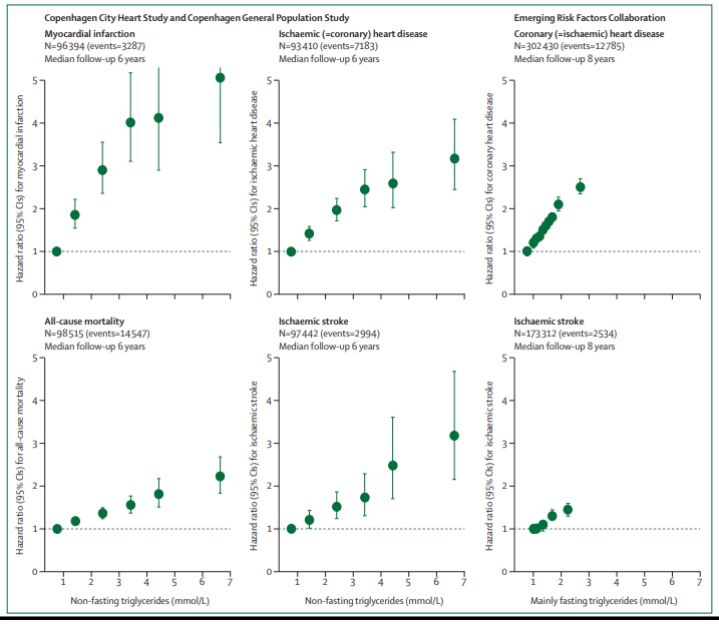
Observational associations between elevated triglycerides, CVD and all-cause mortality in several population studies



Nordestgaard BG, Varbo A. Lancet 2014; 384: 626–635

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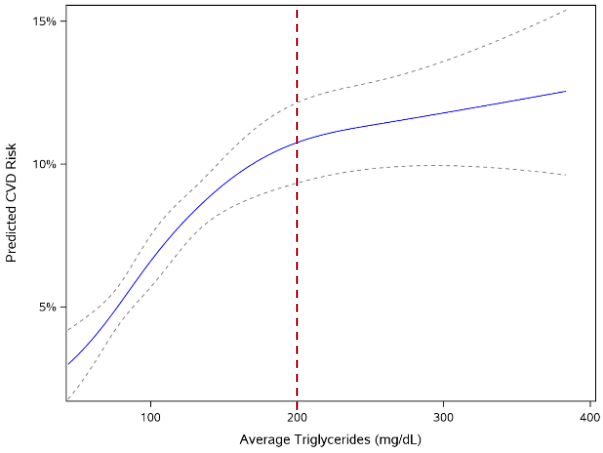
CVD Increases Dramatically w/ TG Increases Even Just "Normal" to "Upper Normal" Range



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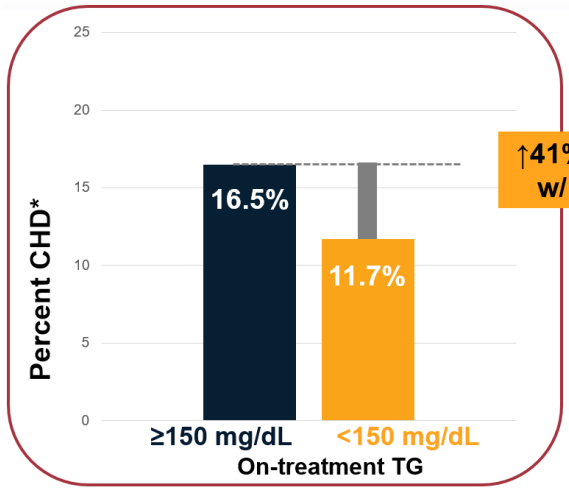
Residual HTG Predicted Residual ASCVD Risk Despite *LDL-C at Goal* on Statin Monotherapy



↑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.

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Evaluate for Secondary Causes of High Triglycerides

- Lifestyle/Medical Conditions
  - High fructose, sucrose, simple carbs intake
  - Alcohol intake
  - Low fiber intake
  - Sedentary
  - T2D (if poor glycemic control)
  - Hypothyroidism
  - Nephrotic syndrome
- Drugs that elevated TGs
  - Oral estrogens
  - Tamoxifen
  - Raloxifene
  - Retinoids
  - Immunosuppressive drugs (cyclosporine, sirolimus)
  - Atypical antipsychotic drugs (clozapine, olanzapine)
  - Protease Inhibitors
  - Thiazide Diuretics
  - Glucocorticoids
  - Rosiglitazone
  - Bile Acid Sequestrants
  - Cyclophosphamide

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Lifestyle Measures to Reduce Triglycerides

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Quispe R...**Michos ED**. Curr Atheroscler Rep 2022:24(10):767-778.

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2019 ACC/AHA Primary Prevention Guideline: Risk Enhancing Factors

Risk-enhancing Factors

- **History of premature menopause (before age 40) and history of adverse-associated conditions that increase later ASCVD risk, such as preeclampsia.**
- **Family history of premature ASCVD (men, age <55 years; women, <65 years)**
- **Primary hypercholesterolemia** (LDL-C 160–189 mg/dL [4.1–4.8 mmol/L]; non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])
- **Metabolic syndrome (increased waist circumference** [by ethnically appropriate cutpoints], **elevated triglycerides [>150 mg/dL, nonfasting]**, **elevated blood pressure, elevated glucose**, and low HDL-C [<40 mg/dL in men; <50 mg/dL in women] are factors; a tally of 3 makes the diagnosis)
- **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation)
- **Chronic inflammatory conditions,** such as psoriasis, RA, lupus, or HIV/AIDS
- **High-risk race/ethnicity** (eg, South Asian ancestry)
- **Lipids/biomarkers**: associated with increased ASCVD risk
- Persistently **elevated hypertriglycerides** (≥175 mg/dL, nonfasting);
- **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
- **Elevated Lp(a):** An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).
- **Elevated apoB** (≥130 mg/dL): A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor.
- **ABI** (<0.9)

Arnett DK, Blumenthal RS,….**Michos ED**…et al. Circulation 2019

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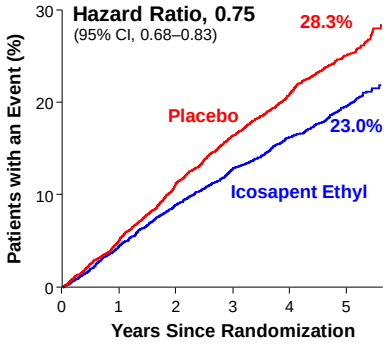
REDUCE-IT CVOT with Icosapent Ethyl Primary and Secondary Endpoints

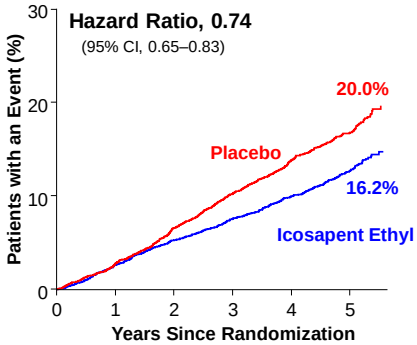
Primary Composite Endpoint:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P = 0.00000001

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

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

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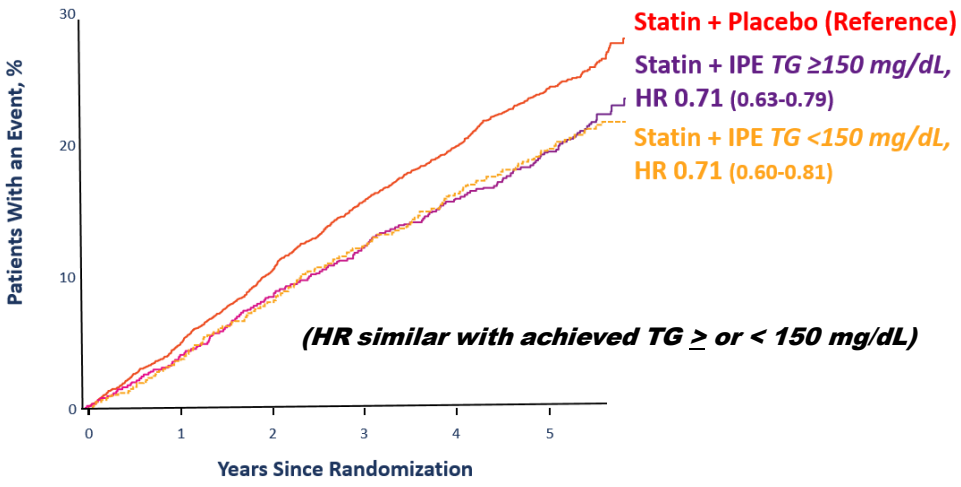
↓CVD with Icosapent Ethyl Did *NOT* Vary by Achieved TG Level



Primary Endpoint by Achieved TG at 1 year

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

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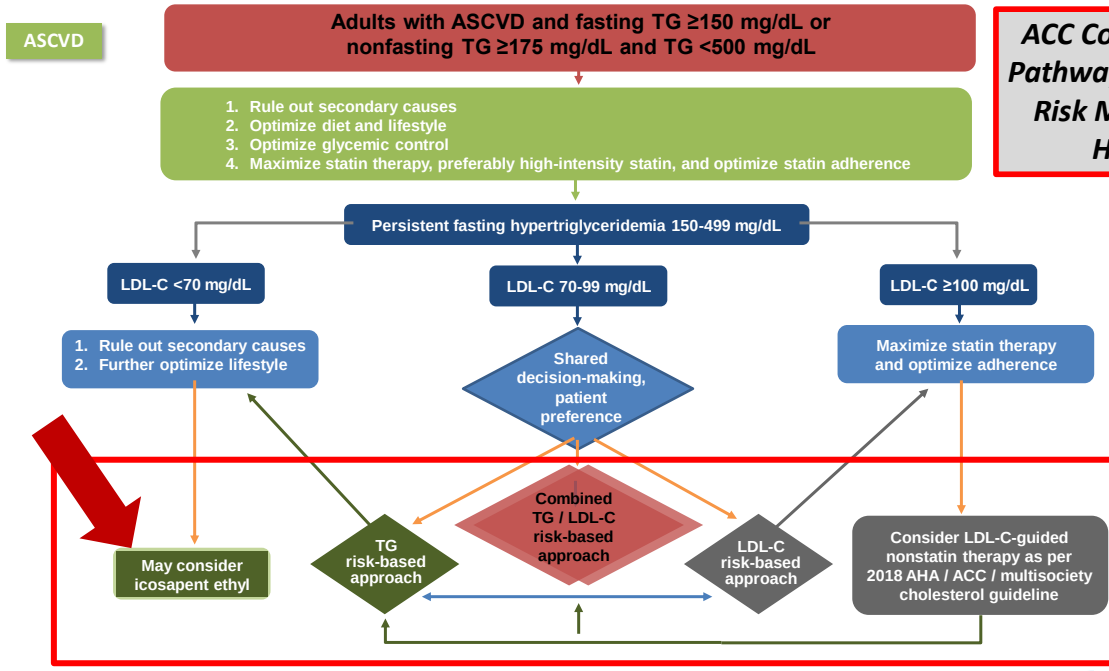

ACC Consensus Pathway for CVD Risk Mgmt in HTG

AHA, American Heart Association; HTG, hypertriglyceridemia

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

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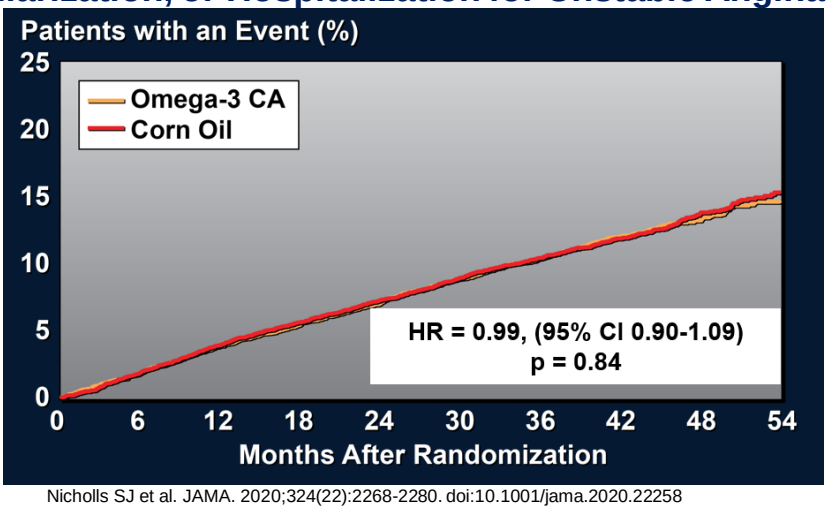
STRENGTH – Primary Endpoint

1º Endpoint – CV Death, MI, Stroke, Coronary Revascularization, or Hospitalization for Unstable Angina



Nicholls SJ et al. JAMA. 2020;324(22):2268-2280. doi:10.1001/jama.2020.22258

AHA 2020

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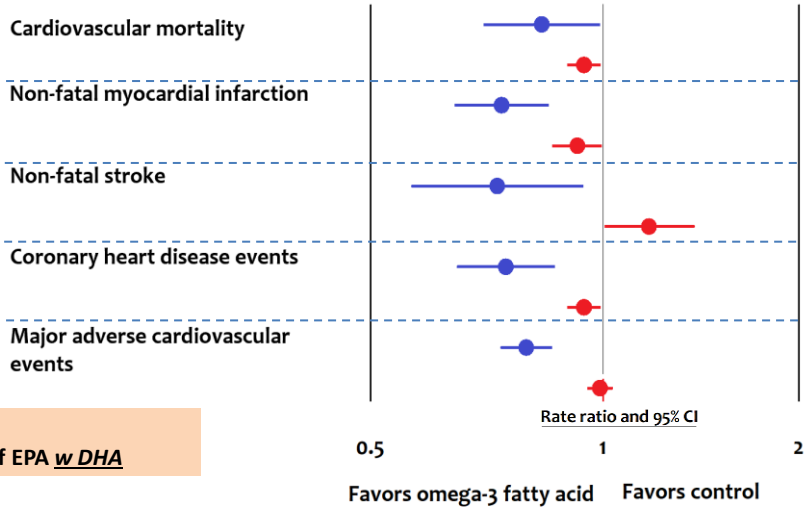
Meta-analysis Effect of Omega-3 Fatty Acids on CV Outcomes

Recent meta-analysis of 4 trials of EPA alone vs 34 trials of EPA + DHA



EPA-Only ↓CVD
vs ***Neutral*** Effect of EPA ***w DHA***

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

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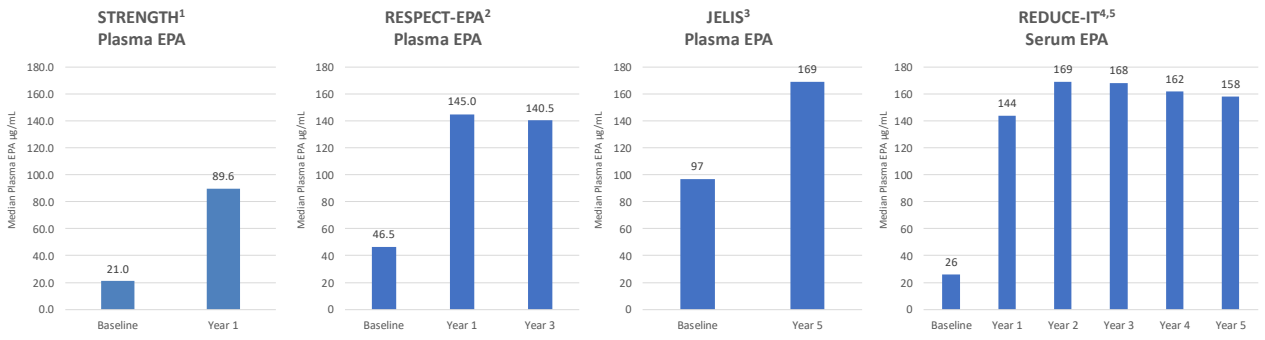
Baseline and Achieved EPA Levels in Omega-3 CVOTs: An Indirect Cross-Study Comparison



Drug:	850 mg mixed omega-3 carboxylic acid / 1 g capsule	>980 mg EPA ethyl ester / 1 g capsule	>980 mg EPA ethyl ester / 1 g capsule	1 g icosapent ethyl (EPA ethyl ester) / 1 g capsule
Dose:	4 g/d	1.8 g/d	1.8 g/d	4 g/d
Population:	International	Japanese	Japanese	International

Note: Clinical trials are conducted under widely varying conditions. In the absence of head-to-head clinical trials, the clinical trials of a drug cannot be directly compared to the clinical trials of another drug. Plasma and serum EPA levels have been strongly correlated, with plasma levels being slightly higher than serum levels.[6]

1. Nicholls SJ, et al. *JAMA*. 2020;324(22):2268-2280; 2. Daida H, et al. Presented at: American Heart Association Scientific Sessions; Chicago, IL; November 5-7, 2022; 3. Yokoyama M, et al. *Lancet*. 2007;369:1090-1098; 4. Bhatt DL, et al; for REDUCE-IT Investigators. *N Engl J Med*. 2019;380(1):11-22; 5. Bhatt DL, et al. Presented virtually at: ACC/WCC; Chicago, IL; March 28-30, 2020; 6. Dunbar R, et al. Presented virtually at: National Lipid Association Scientific Sessions; December 10-12, 2020. https://els-jbs-prod-cdn.jbs.elsevierhealth.com/pb/assets/raw/Health%20Advance/journals/jacl/jacl1584.pdf.

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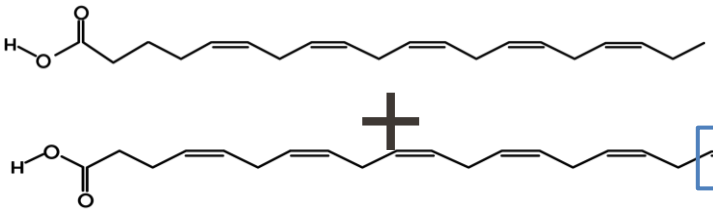
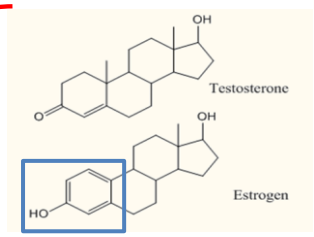
EPA Versus DHA: Structurally Similar but Functionally Different!

Eicosapentaenoic acid (EPA) 20:5



Docosahexaenoic acid (DHA) 22:6

Omega-3 PUFA



Note that 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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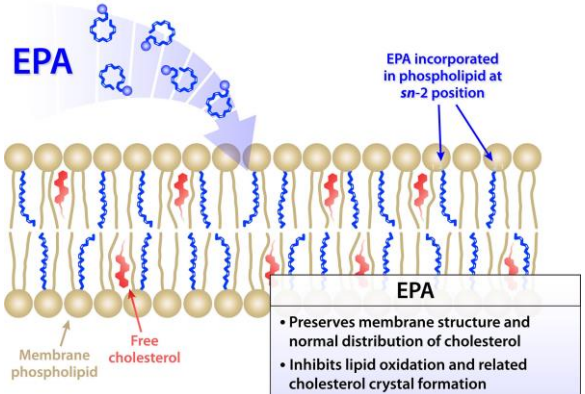
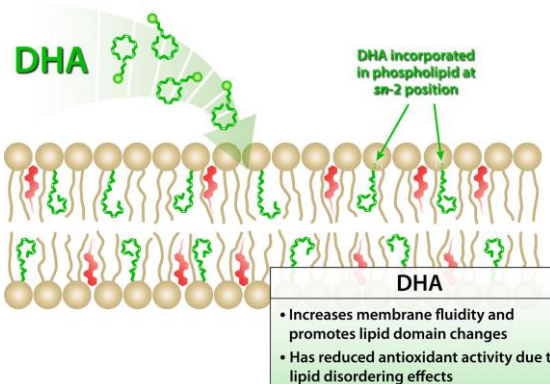
EPA Promotes More Membrane Stabilization



EPA

- Preserves membrane structure and normal distribution of cholesterol
- Inhibits lipid oxidation and related cholesterol crystal formation
- Influences signal transduction pathways related to inflammation and vasodilation



DHA

- Increases membrane fluidity and promotes lipid domain changes
- Has reduced antioxidant activity due to lipid disordering effects
- Is concentrated in brain and retinal membranes

Mason RP, et al. *Artherioscler Thromb Vasc Biol.* 2020;40(5):1135-1147. Open Access

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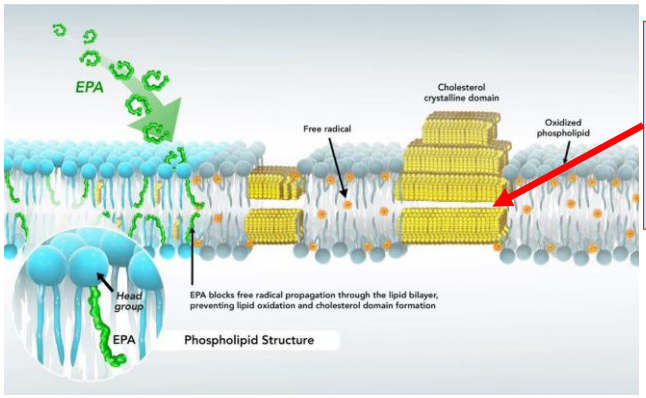
DHA Increases Membrane Fluidity and Is a Less-Effective Antioxidant, Leading to ↑Cholesterol Crystalline Domains & ↑Cholesterol Crystals

EPA incorporates into phospholipids of membrane bilayers and interrupts the propagation of oxygen free radicals and **prevents cholesterol domain formation**



DHA ***promotes*** formation of ***cholesterol crystalline domains*** which may lead to ***cholesterol crystals***

- Sherratt SCR, et al. *Curr Atheroscler Rep*. Published online December 29, 2022. doi:10.1007/s11883-022-01075-x

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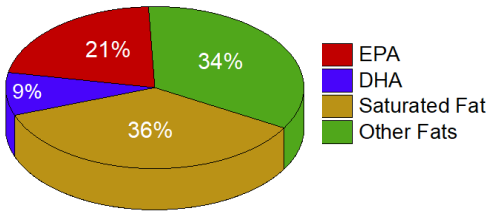
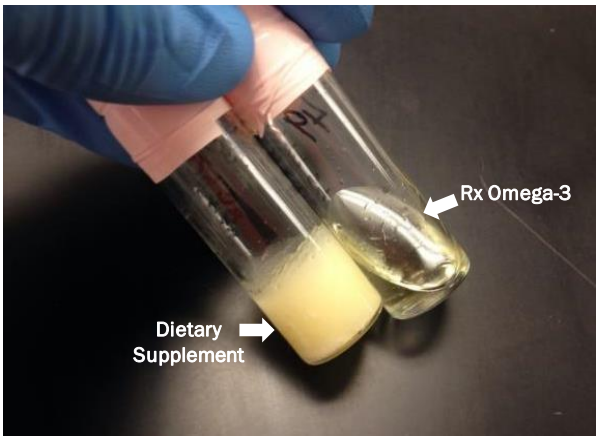
Problems w/ Content of *Leading* US Fish Oil Dietary Supplements



- Up to 36% of content may be saturated fat
- Omega-3 FA content often overstated
- Oxidation of omega-3 FA content tends to 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 DS* makes it ***solid at room temperature*** (post-isolation)

*DS=dietary supplement. Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483:425-429. Hilleman D and Smer A. *Manag Care*. 2016;25:46-52. Albert BB et al. *Sci Rep*. 2015;5:7928. Kleiner AC et al. *J Sci Food Agric*. 2015;95:1260-7. Ritter JC et al. *J Sci Food Agric*. 2013:93:1935-9. Jackowski SA et al. *J Nutr Sci*. 2015;4:e30. Rundblad A et al. *Br J Nutr*. 2017;117:1291-8. European Medicines Agency, 2018: 712678.

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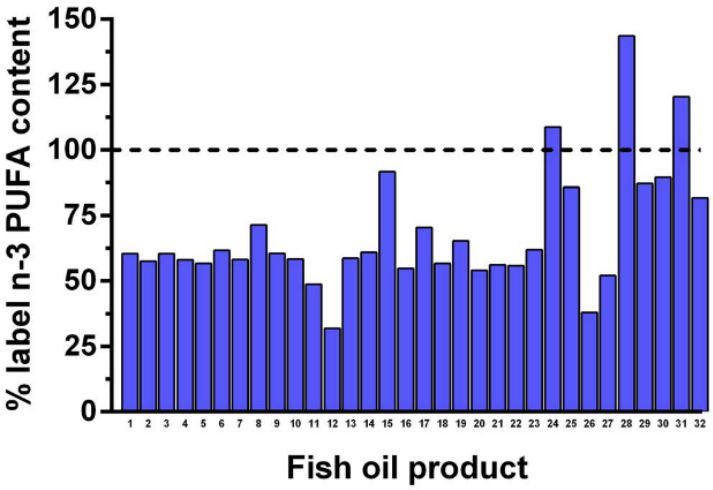
Fish Oil Supplement Claims are Inaccurate



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

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Omega 3 Fatty Acid Summary

PUFAs – not all the same

- **Type matters**
- **Dose matters**
- **Achieved level of EPA matters**
- **Mineral oil comparator unlikely to explain away the entire IPE benefit**
- **This is why EPA is the preferred for the patient with high TG**

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TG Reduction Alone with Fibrates & Niacin Has Shown No CV Benefit

Neutral Studies	
ACCORD Fenofibrate	HR = 0.92 (95% CI, 0.79-1.08) *P* = 0.32
FIELD Fenofibrate	HR = 0.89 (95% CI, 0.75-1.05) *P* = 0.16
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

HPS2-THRIVE Collaborative Group, et al. *N Engl J Med*. 2014;371(3):203-212. Kowa Research Institute. https://www.prnewswire.com/news-releases/kowa-to-discontinue-k-877-pemafibrate-prominent-cardiovascular-outcomes-study-301520956.html. Published April 8, 2022. Accessed April 14, 2022.

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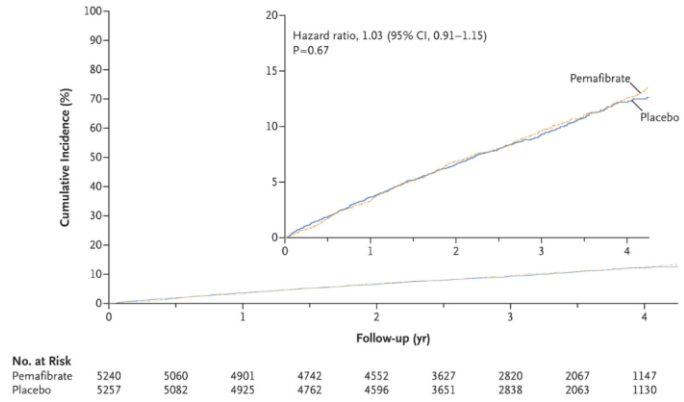
Prominent Trial of Pemafibrate in Patients with T2D with mHTG and Low HDL-

Type 2 Diabetes with Mixed Dyslipidemia on Background Guideline Directed LDL-C Lowering
One-third Primary Prevention, two-thirds Secondary Prevention

HR 1.03, 95% CI 0.91-1.15



Effect of Pemafibrate	% Change vs PBO	Absolute Difference
Triglycerides	- 26.6%	56 mg/dL
Remnant cholesterol	- 25.6%	14 mg/dL
LDL-C	+ 12.3%	11.1 mg/dL
ApoB	+ 4.8%	6 mg/dL

Pradhan AD, et al. *N Engl J Med*. 2022;387(21):1923-1934.

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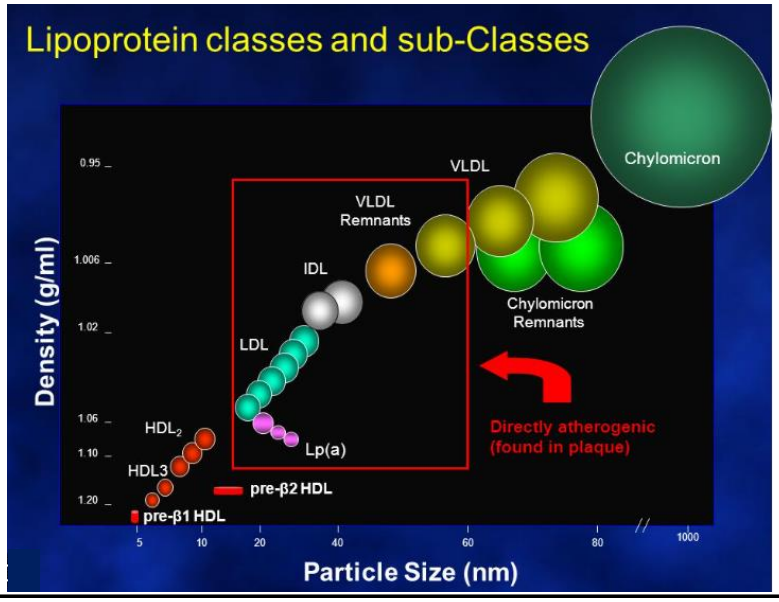
TGRLs Can Deliver More Cholesterol Per Particle to Macrophages than LDL



Feingold KR. Introduction to Lipids and Lipoproteins. [Updated 2024 Jan 14]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK305896/

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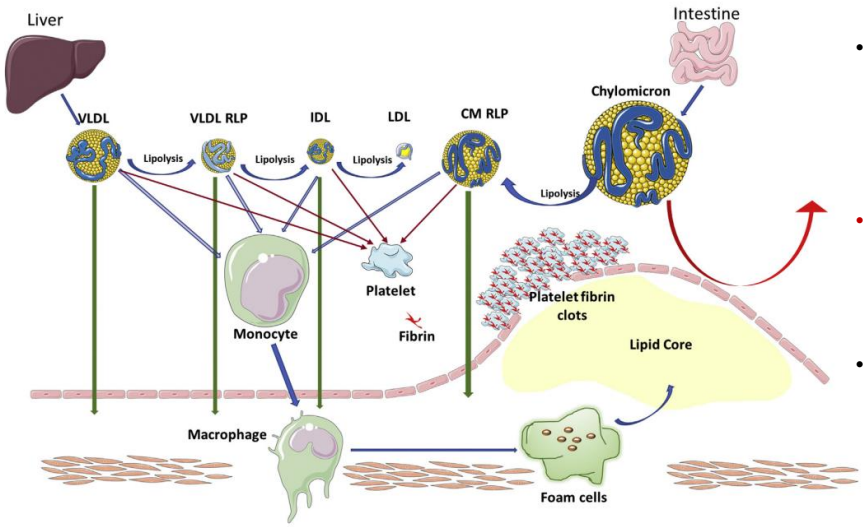
Triglyceride Remnant Lipoproteins and Mechanisms of Atherogenicity



- Remnant cholesterol is defined as the cholesterol content of triglyceride-rich lipoproteins, including chylomicron remnants, VLDL cholesterol, and IDL
- **Triglyceride-rich remnant lipoproteins are more atherogenic than LDL per particle**
- Remnant lipoproteins accumulate in arterial intima macrophage foam cells *more readily* than does LDL

Rosenson RS et al J Am Coll Cardiol. 2021; 78(18): 1817-1830

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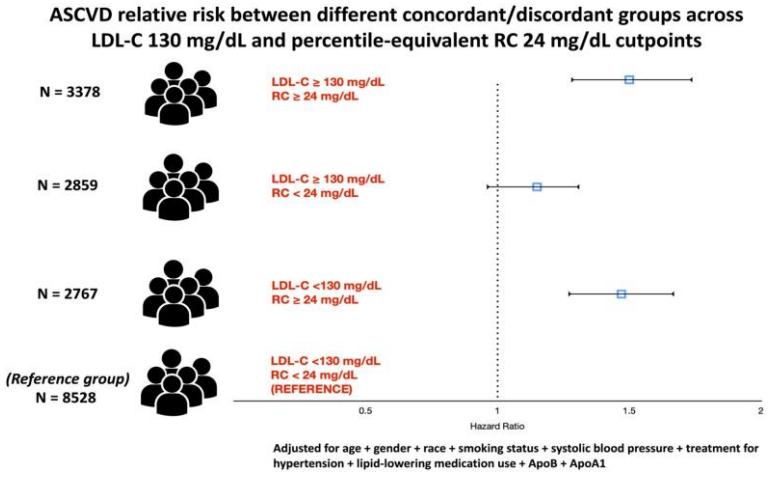
Remnant Cholesterol Predicts ASCVD Risk Independent of LDL-C and ApoB



Quispe R….**Michos ED**…Elshazly MB. Eur Heart J 2021

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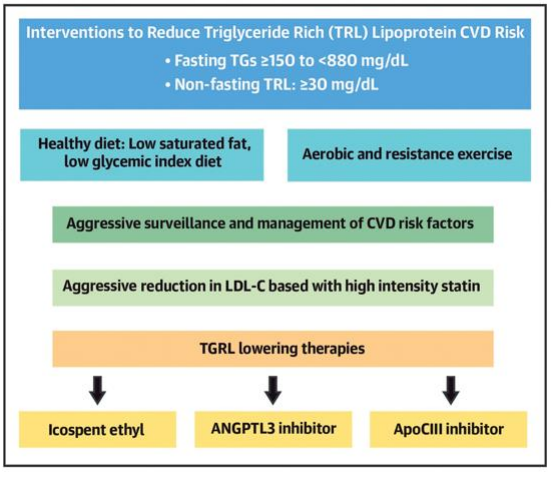
Approach to Treatment of High Triglycerides

- MARKER of RISK
  - Elevated triglycerides
- GOALS: To reduce
  - **Remnant cholesterol**
  - **Non-HDL cholesterol** (this includes LDL-C)
  - **ApoB** (this includes LDL-C)



ApoCIII, apolipoprotein C-III
Rosenson RS et al J Am Coll Cardiol. 2021; 78(18): 1817-1830

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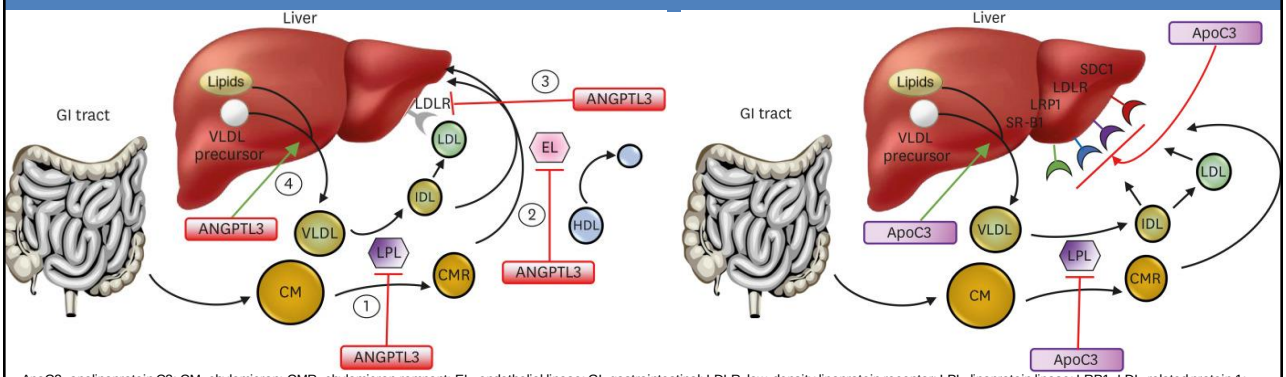
Mechanisms of ANGLTL3 and ApoC3 Inhibition



ApoC3, apolipoprotein C3; CM, chylomicron; CMR, chylomicron remnant; EL, endothelial lipase; GI, gastrointestinal; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; LRP1, LDL-related protein 1; SDC1, sydecan-1; SR-B, scavenger receptor B1

Action of ANGPTL3 in lipoprotein metabolism. ANGPTL3 inhibits 1) lipoprotein lipase and 2) endothelial lipase. It may also 3) inhibit the liver uptake of LDL particles and 4) stimulate release of VLDL particles from the liver. Inhibition of ANGPTL3 reduces triglycerides from chylomicron and VLDL remnants, reduces HDL-C, and in the absence of functioning LDL receptors, remnant particles and LDL can be taken up by the liver via an endothelial lipase-dependent mechanism.

Action of apoC3 in lipoprotein metabolism. ApoC3 inhibits lipoprotein lipase and inhibits the liver uptake of remnants and LDL particles by the LDLR or LRP1, and possibly SDC1 and SRB1, by interfering with the binding of apoE to those receptors. It may also stimulate release of VLDL particles from the liver. When LPL activity is absent, inhibition of apoC3 facilitates hepatic uptake of particles by the LDLR and LRP1.

Tomlinson B et al. J Lipid Atheroscler. 2024 Jan;13(1):2-20.

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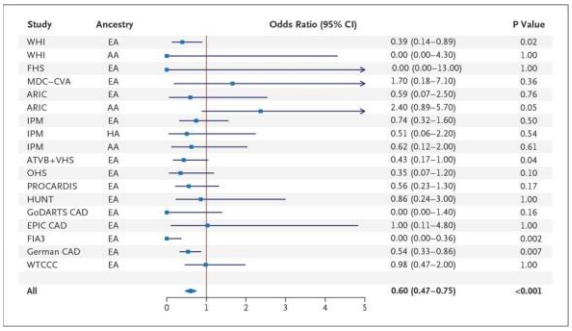
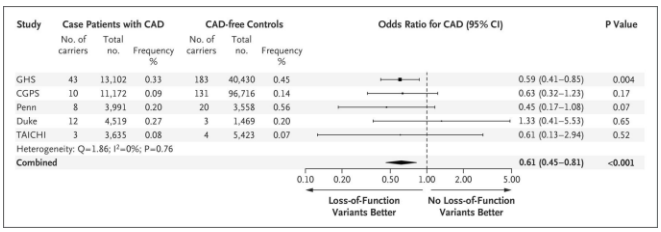
Genetic Studies Suggest That Silencing ApoC3 and ANGLTL3 May Decrease CAD Risk

***APOC3* LoF Variants and CAD**



Exome Sequencing Project, n= 3734
•Mutations in *APOC3* gene associated with **39% lower triglyceride levels** and **46% lower APOC3**
•Risk of coronary heart disease with *APOC3* mutations **40% lower (OR, 0.60**; 95% CI, 0.47 to 0.75)

***ANGPTL3* LoF Variants and CAD**



DiscovEHR human genetics study, n= 58,335
•Mutations in *ANGPTL3* gene associated with **28% lower triglyceride levels** and **7% lower LDL**
•Risk of coronary heart disease with *APOC3* mutations **41% lower (OR, 0.59**; 95% CI, 0.41 to 0.85)

LoF, loss of function; OR, odds ratio

N Engl J Med 2014;371:22-31.
Dewey FE, et al. N Engl J Med 2017; 377:211-221

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Emerging Therapies for Hypertriglyceridemia

- Olezarsen*
  - an ASO inhibitor of ApoC3.
  - Orphan drug indication by Food and Drug Administration (FDA) for Familial Chylomicronemia Syndrome (FCS) (awaiting regulatory approval).
  - Being studied for severe HTG and mixed dyslipidemia
- Investigational
  - Plozasiran* (an siRNA inhibitor of ApoC3)
- Evinacumab
  - A monoclonal Ab targeting ANGPTL3
  - FDA approved for homozygous familial hypercholesterolemia (HoFH)
- Investigational
  - Zodasiran* (an siRNA inhibitor of ANGPTL3)
  - Solbinsiran* (an siRNA inhibitor of ANGPTL3)

- There is currently an unmet need for management of severe hypertriglyceridemia which can lead to life-threatening bouts of recurrent acute pancreatitis. These drugs have potential to fill that gap.
- Whether the ANGPTL3i (which also reduce LDL-C) can reduce CV events in patients with moderate HTG remains to be seen with future trials.

*Olezarsen, Plozasiran, Zodasiran, Solbinsiran are investigational agents.
**Evinacumab is only FDA approved for HoFH, any other use would be off-label

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Which of the Following Statements Is FALSE?

A. Risk associated with Lp(a) is continuous
B. Lp(a) is associated with CV risk independent of LDL-C
C. Statins should be avoided as they raise Lp(a)
D. PCSK9i reduce Lp(a) by 20-25%
E. Aspirin may decrease risk in patients with Lp(a)

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Which Statement About Triglycerides (TG) Is TRUE?

A. TG-rich lipoproteins are more atherogenic per particle than LDL
B. Fibrates reduce ASCVD proportional to their degree of TG lowering
C. Elevated TGs are no longer associated with ASCVD risk after statin treatment
D. Dietary Omega 3 supplements are recommended for ASCVD risk reduction in persons with HTG

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