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# What's New in Cholesterol Lowering Therapy?: A Case Based Review

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Minneapolis Heart Institute

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## Cases

1: Non-Statin Therapy

2: Elevated Lpa

3: Severe Hypertriglyceridemia

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## Disclosures:

- Site Principal Investigator for Clinical Trials with MHIF
- Lpa lowering Trials : HORIZON, OCEAN a
- PCSK9i Trials: VESALIUS (Repatha)-use in Primary Prevention
- Incliseran: VICTORIAN INCEPTION-use in ACS patients

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## CASE #1: 55 male with ASCVD, prior CABG, prior PCIs, longstanding h/o hyperlipidemia referred for “statin intolerance”

- Dad had CABG at 45 yo, very high cholesterol
- h/o gout
- Did not tolerate atorvastatin due to myalgias
- Having myalgias from statin doses above 20 mg rosuvastatin
- On zetia 10 mg daily
- Fear of ”needles”
- Baseline LDL 195 mg/dl prior to RX

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## Case #1

Total Cholesterol: 191 mg/dl
HDL: 50 mg/dl
TG: 105 mg/dl
LDL: 120 mg/dl (41 % reduction from baseline)

Next best step?

1. Add bempedoic acid
2. Add Repatha/Praluent
3. Add Incliseran

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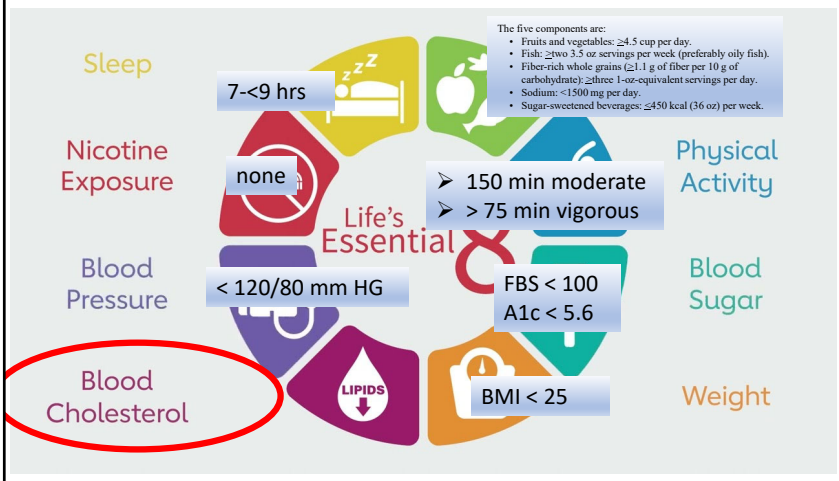
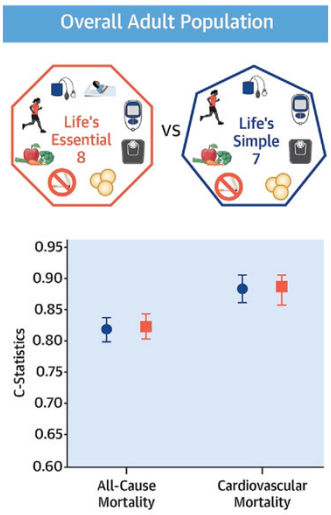
# Simple 7 and Essential 8

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Association of Life's Essential 8 and Simple 7 Scores With Mortality: JACC Adv. 2024 Jun, 3 (6) 100945

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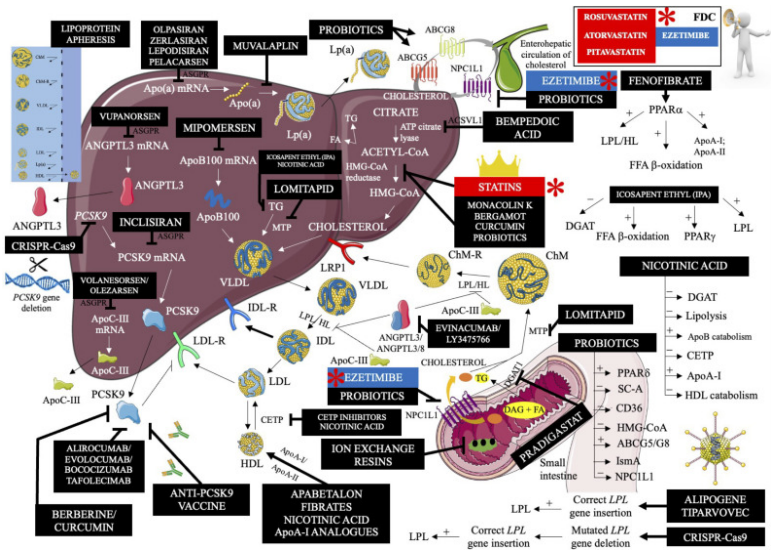


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Banach, Surma, Toth 2023 Nov 2;19(6):1602–1615. doi: 10.5114/aoms/174743

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## What's the guidance for LDL targets in patients with ASCVD?

- "Not at very high risk" = LDL <70
- "Very high risk" = LDL <55
- What is "very high risk?"
  - >1 major cardiovascular event
  - 1 major cardiovascular event and multiple high-risk conditions

Major ASCVD events:
- MI < 12 months
- prior MI/stroke
- symptomatic PAD with ABI <0.85 or prior procedure

High-risk conditions:
- Age >65 years
- Heterozygous familial hypercholesterolemia
- History of prior CABG/PCI
- Diabetes
- Hypertension
- CKD (eGFR 15-59 mL/min/1.73 m2)
- Current smoking
- LDL >100 mg/dL on maximally tolerated statin + ezetimibe
- History of heart failure

Lloyd-Jones DM et al. JACC 2022

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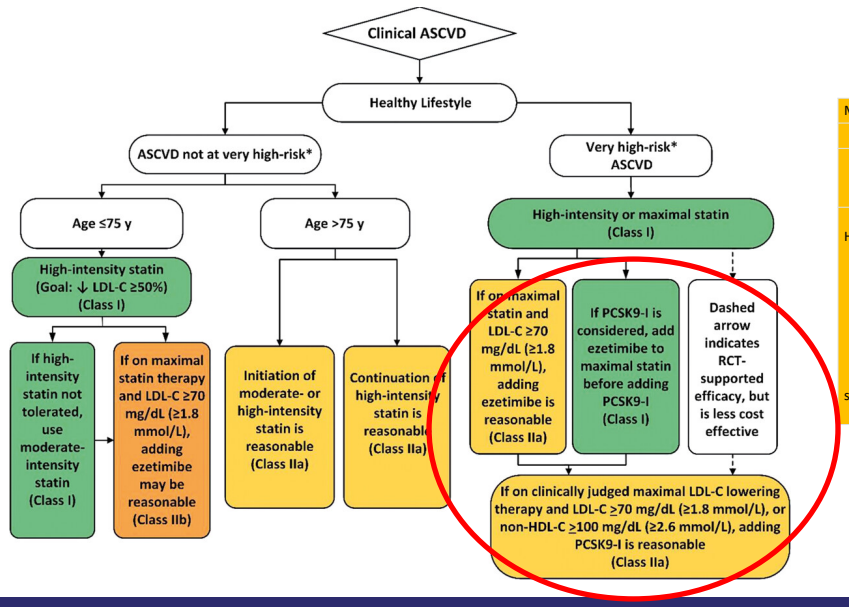


Major ASCVD Events
- Recent ACS (within the past 12 mo)
- History of MI (other than recent ACS event listed above)
- History of ischemic stroke
- Symptomatic peripheral arterial disease

High-Risk Conditions
- Age > 65 yo
- Heterozygous FH
- H/O prior CABG/PCI
- Diabetes
- HTN
- CKD (GFR < 59 mL/min)
- Current smoker
- Persistent elevated LDL > 100 despite maximally tolerated statin and zetia
- H/O CHF

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*Very high-risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.

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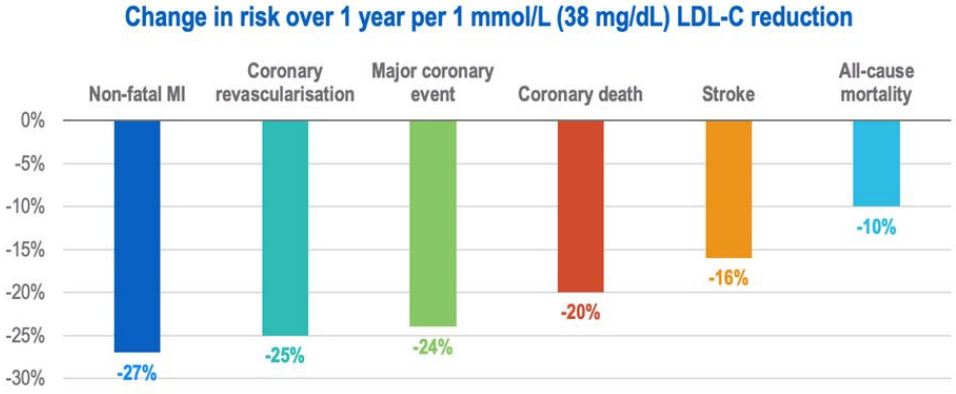
# Statins

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Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials
Cholesterol Treatment Trialists' (CTT) Collaboration

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# Statin therapy and expected LDL reduction

| | High Intensity | Moderate Intensity | Low Intensity |
|---|---|---|---|
| LDL-C lowering† | ≥50% | 30%–49% | <30% |
| Statins | **Atorvastatin (40 mg‡) 80 mg**<br>**Rosuvastatin 20 mg (40 mg)** | **Atorvastatin 10 mg** (20 mg)<br>**Rosuvastatin** (5 mg) **10 mg**<br>**Simvastatin 20–40 mg**§ | Simvastatin 10 mg |
| | ... | **Pravastatin 40 mg** (80 mg)<br>**Lovastatin 40 mg** (80 mg)<br>Fluvastatin XL 80 mg<br>**Fluvastatin 40 mg BID**<br>Pitavastatin 1–4 mg | **Pravastatin 10–20 mg**<br>**Lovastatin 20 mg**<br>Fluvastatin 20–40 mg |

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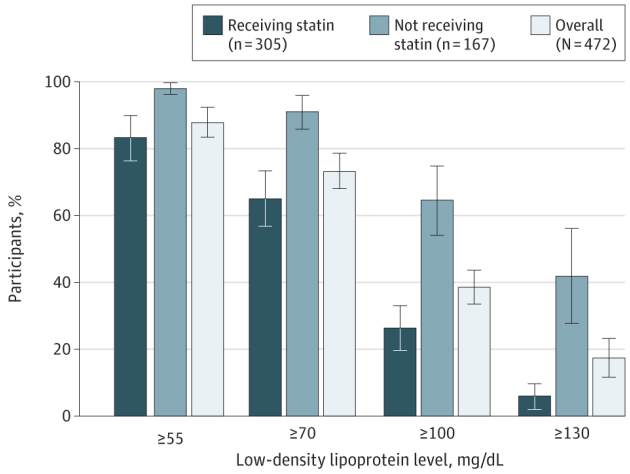
**Low-Density Lipoprotein Cholesterol Levels in Adults With Coronary Artery Disease in the US, January 2015 to March 2020: NHANES (National Health and Nutrition Survey)**




Zetia use: 6-10%

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*"Factors contributing to low rates of attaining guideline goals may include inadequate statin treatment intensification, insufficient add-on therapy use (eg, ezetimibe), and low use of novel therapies (monoclonal antibody PCSK-9 inhibitors, inclisiran, and bempedoic acid).*

*Low rates of statin use and intensification may relate to prescriber or patient hesitation".*

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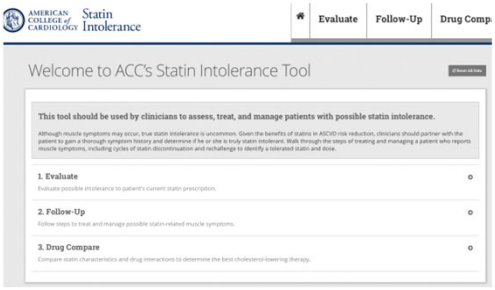
# Statin Intolerance

- Reported incidence of 5 - 25 % (clinical trials lowest)
- Intolerance may be <u>partial or complete</u>
- May be <u>real or perceived</u>
- Intolerance to <u>at least two statins</u> (hydrophilic statin)
- Check for modifiable factors
    - TSH
    - ETOH
    - Vitamin D deficiency
    - Strenuous exercise without hydration
    - Drug to drug interactions (e.g., gemfibrozil, protease inhibitors, amiodarone, calcium channel blockers, azole antifungals, macrolides, immunosuppressants, colchicine)

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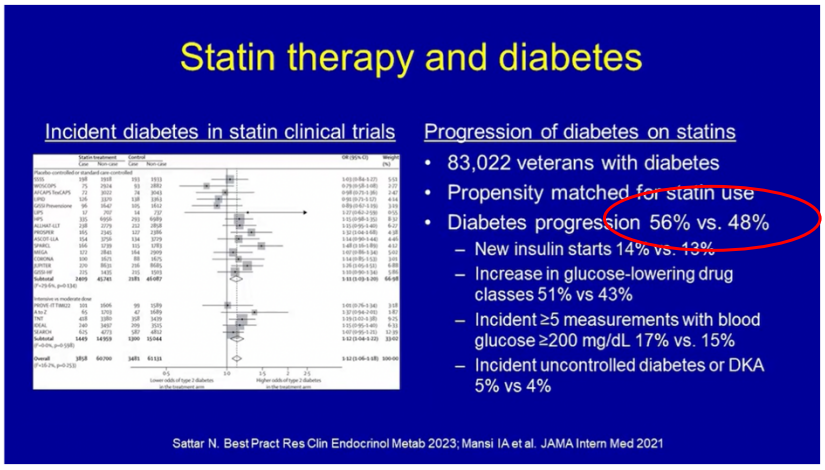
# Statins and Diabetes

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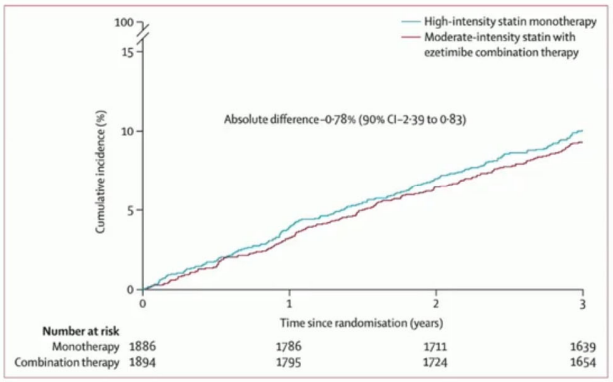
## Statins are first line; time for combination therapy up front?




Event rate: 9.1% vs. 9.9%
LDL-C <70 mg/dL at 3 years: 72% vs. 58%
Median LDL-C at 3 years: 58 vs. 66 mg/dL
Drug discontinuation / reduction: 4.8% vs. 8.2%

[4] Kim et al, Lancet 2022

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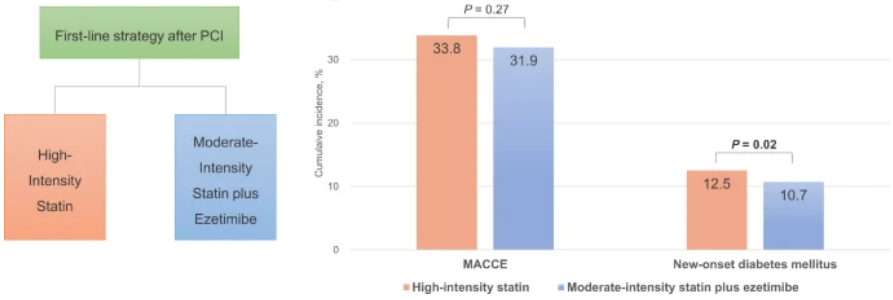
## New strategies: Moderate Intensity Statin + zetia

- 45,000 pts
- 16% Less DM
- Similar MACE

Cumulative incidence according to the first-line lipid-lowering strategy in patient undergoing percutaneous coronary intervention

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Efficacy and diabetes risk of moderate-intensity statin plus ezetimibe versus high-intensity statin after percutaneous coronary intervention Nov 2024, Choo et al Card Diabetology

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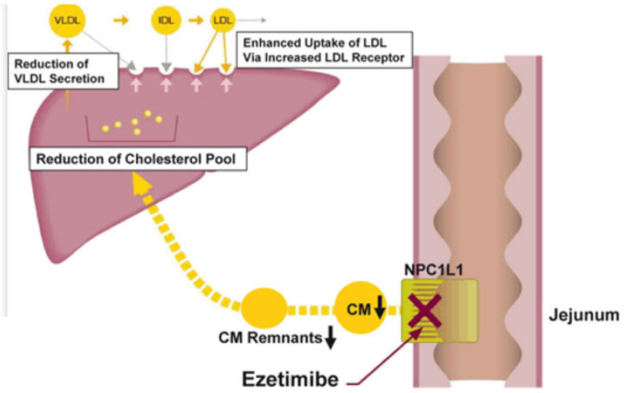
## First Line Add On Therapy: Zetia

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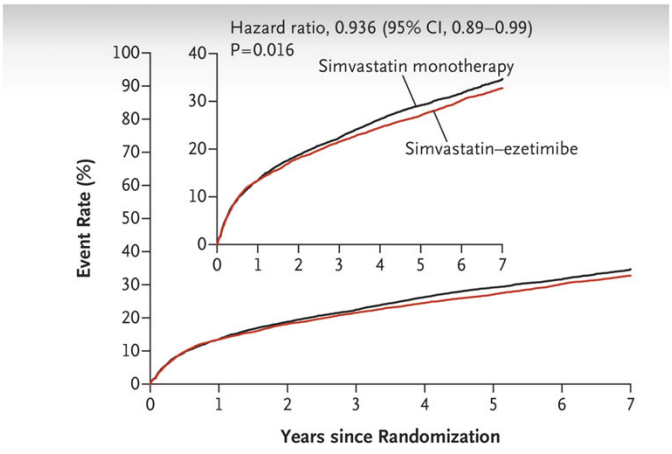
## IMPROVE– IT Trial

18,144 pts with ACS
Simva 40 vs Simva 40/zetia 10
Simva LDL 69mg/dl
Simva + Zetia LDL 54 mg/dl (-22%)

6 % lower MACE at 7 years

Supports “lower is better”

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# PCSK9 INHIBITORS

Proprotein convertase subtilisin kexin type 9 inhibitors

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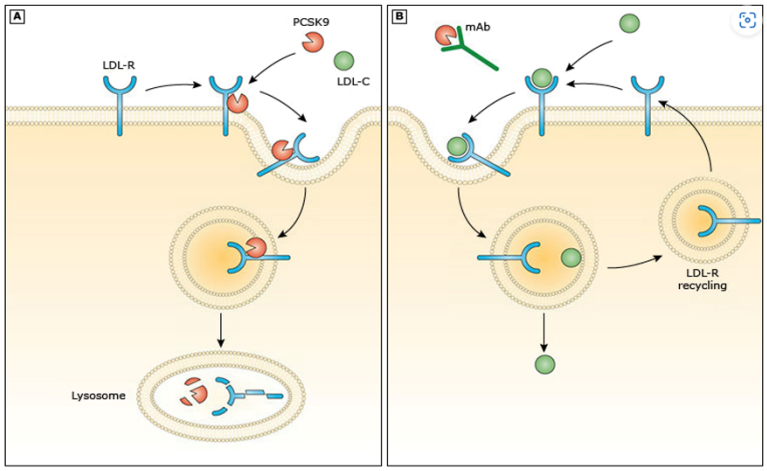
## PCSK9 INHIBITION BY MONOCLONAL ANTIBODIES




LDL-R: low density lipoprotein cholesterol receptor.

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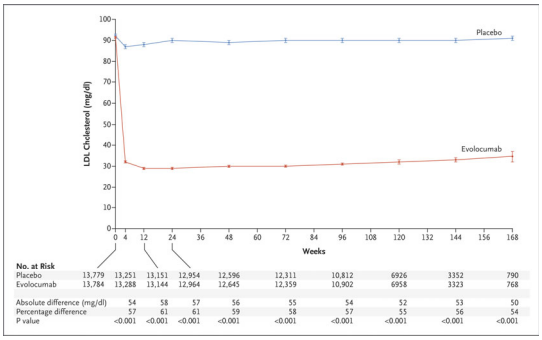
## Evolocumab (Repatha)

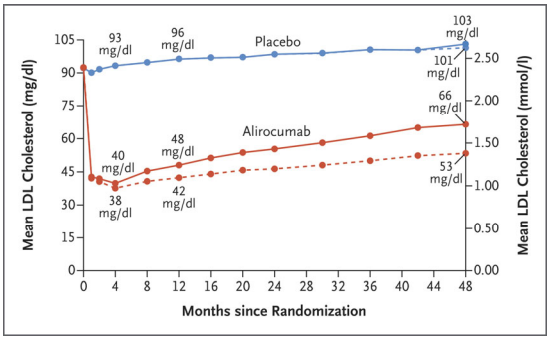
FOURIER Trial
27,564 pts with ASCVD
On maximally tolerated statin




LDL – 59%

## Alirocumab (Praluent)

ODYSSEY OUTCOMES
18,924 pts with ACS < 1 year
On maximally tolerated statin




LDL – 55%

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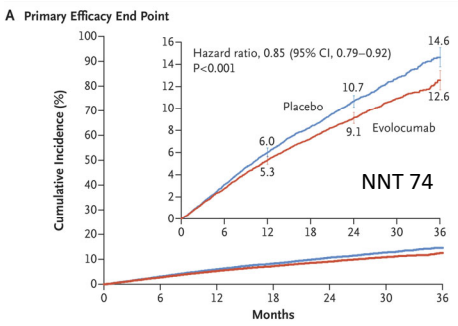
## Evolocumab (Repatha)

FOURIER Trial
27,564 pt with ASCVD
On maximally tolerated statin




composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization

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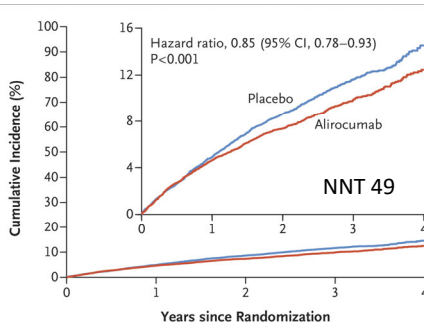


a composite of death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization)

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Only significant side effect was small increase in injection site reactions 1-1.5 %

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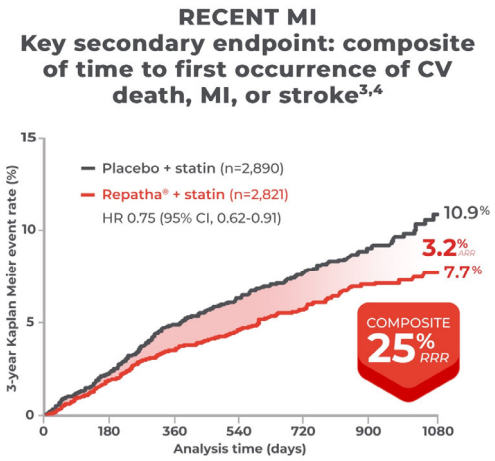
FOURIER SUB -analysis




- Recent MI patients within 1 year of a heart attack have a higher CV risk[3,5]

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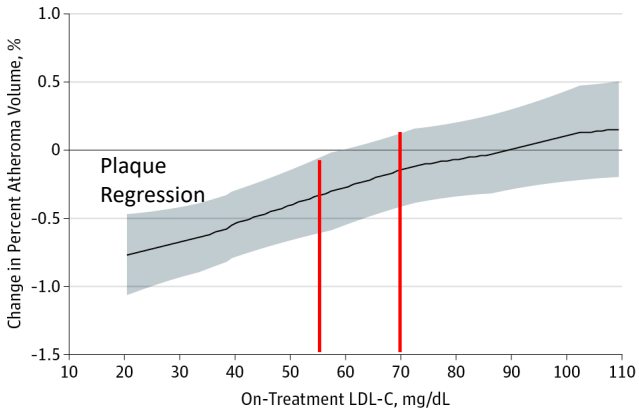
JAMA Network

From: **Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial** JAMA. 2016;316(22):2373-2384. doi:10.1001/jama.2016.16951

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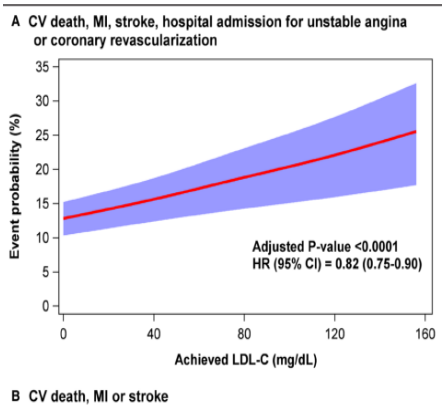
Association Between Achieved Low-Density Lipoprotein Cholesterol Levels and Long-Term Cardiovascular and Safety Outcomes: An Analysis of **FOURIER-OLE: 2022**

8.6 years follow up/LDL down to <20 mg/dl

No increased AE's in low LDL group

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# Repatha / Praluent Highlights

- Removed by proteolysis
  - No adjustment for kidney or liver disease
  - No increased myalgias
  - No neurocognitive effects
  - Adverse events reported similar to placebo up to 8 years
- Self injection well tolerated with occasional site reactions
- No association with increased glucose/A1c
- Lower Lpa - 27%

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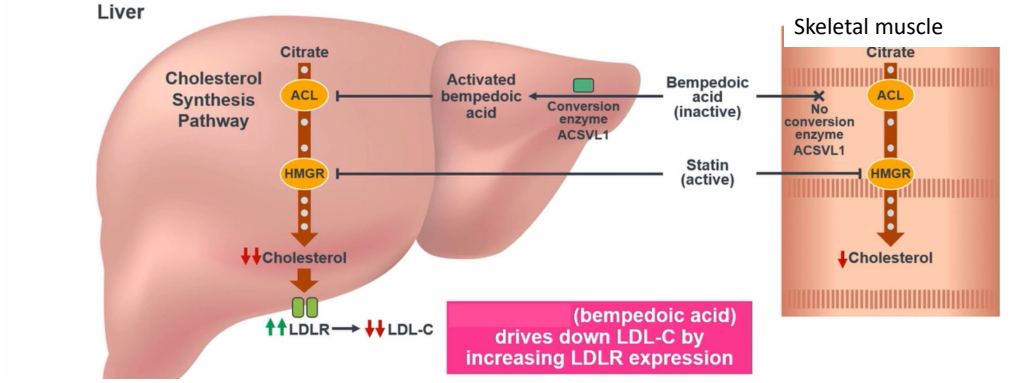
## BEMPADOIC ACID

Lowers cholesterol in the blood by inhibiting the enzyme adenosine triphosphate-citrate lyase (ACL) in the liver




(bempedoic acid) drives down LDL-C by increasing LDLR expression

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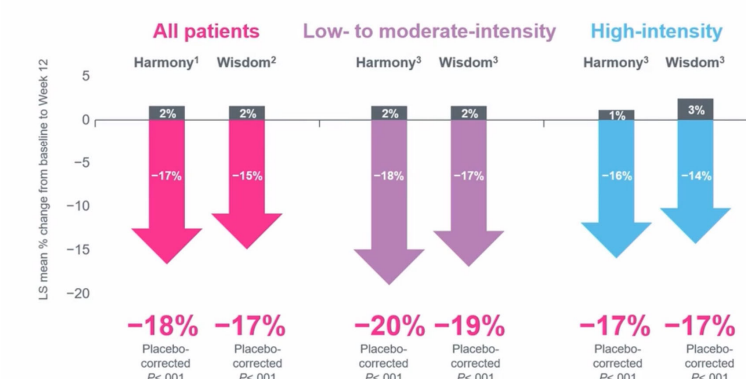
## Pts with ASCVD or HeFH on maximally tolerated statin therapy

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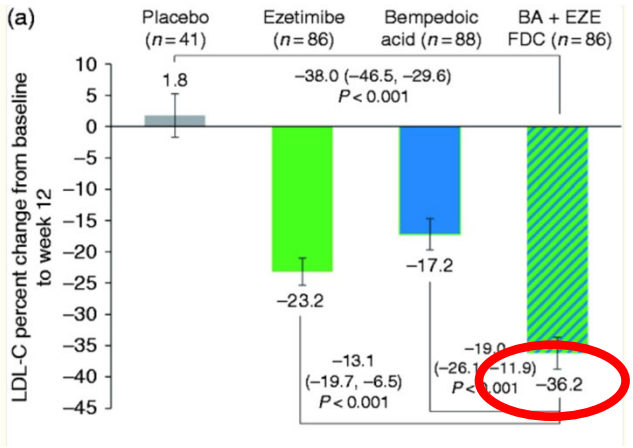
Nexlizet: Bempedoic acid + zetia
324 pts with ASCVD, HeFH on max tolerated statin

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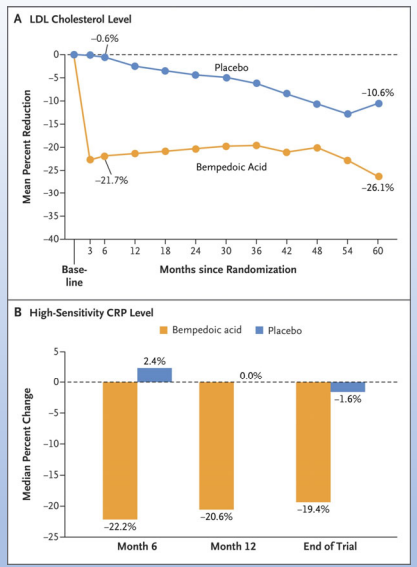


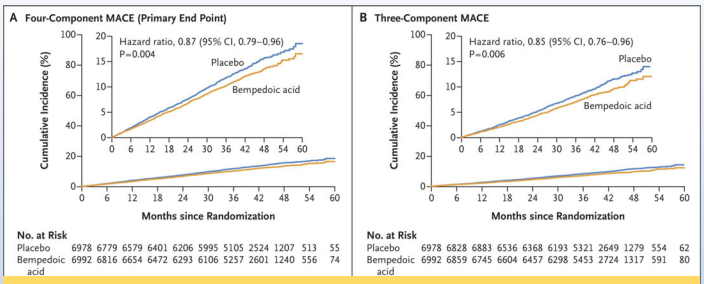


CLEAR OUTCOMES Trial

N Engl J Med 2023;388:1353-1364

Bempedoic Acid: 180 mg
21 % reduction in LDL
22 % reduction in hs CRP
13% reduction in MACE

Nissen SE et al. N Engl J Med2023;388:1353-1364

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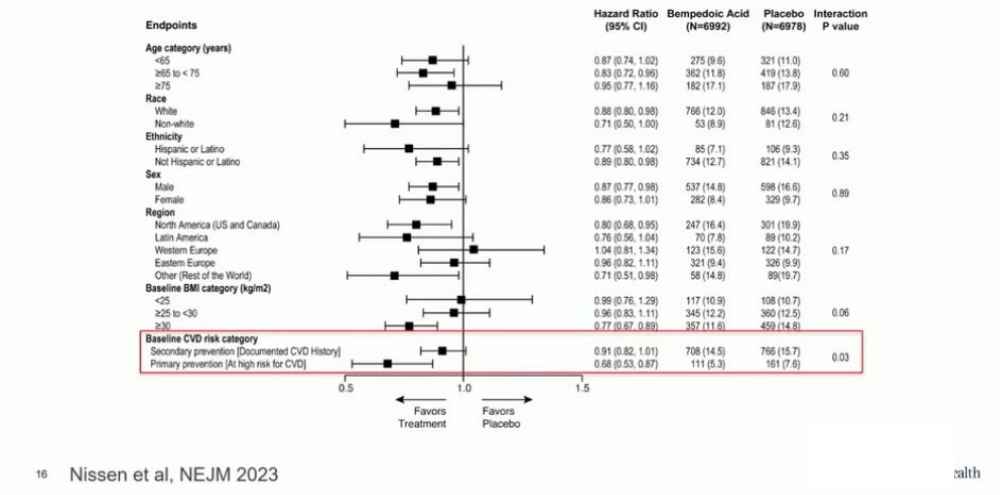
## Bempedoic acid




16 Nissen et al, NEJM 2023



## Bempedoic Acid: Adverse effects

Table 3. Investigator-Reported Adverse Events and Laboratory Safety-Related Findings in the Safety Population.[a]

| Event | Bempedoic Acid (N = 7001) | Placebo (N = 6964) |
|---|---|---|
| Any adverse event that started or worsened after the first dose of a trial agent — no. (%) | 6040 (86.3) | 5919 (85.0) |
| Serious adverse event that started or worsened after the first dose of a trial agent — no. (%) | 1767 (25.2) | 1733 (24.9) |
| Adverse event leading to discontinuation of the trial regimen — no. (%) | 759 (10.8) | 722 (10.4) |
| Prespecified adverse events of special interest | | |
| Myalgia — no. (%) | 393 (5.6) | 471 (6.8) |
| Discontinuation of the trial regimen because of myalgia — no. (%) | 124 (1.8) | 129 (1.9) |
| New-onset diabetes in patients without diabetes at baseline — no./total no. (%) | 621/3856 (16.1) | 640/3740 (17.1) |
| New-onset diabetes in patients with prediabetes at baseline — no./total no. (%)† | 569/2918 (19.5) | 586/2877 (20.4) |
| New-onset diabetes in patients with normoglycemia at baseline — no./total no. (%)† | 52/938 (5.5) | 54/863 (6.3) |
| Worsening hyperglycemia — no./total no. (%)‡ | 713/3145 (22.7) | 746/3224 (23.1) |
| Hypoglycemia — no. (%) | 304 (4.3) | 267 (3.8) |
| Metabolic acidosis — no. (%) | 13 (0.2) | 11 (0.2) |
| Elevated hepatic-enzyme level — no. (%) | 317 (4.5) | 209 (3.0) |
| Renal impairment — no. (%) | 802 (11.5) | 599 (8.6) |
| Neurocognitive disorders — no. (%) | 58 (0.8) | 69 (1.0) |
| Atrial fibrillation — no. (%) | 229 (3.3) | 246 (3.5) |
| Adjudicated tendon rupture — no. (%) | 86 (1.2) | 66 (0.9) |
| Tendinopathies — no. (%) | 118 (1.7) | 128 (1.8) |
| Malignant conditions — no. (%) | 321 (4.6) | 344 (4.9) |
| Other adverse events — no. (%) | | |
| Hyperuricemia | 763 (10.9) | 393 (5.6) |
| Gout | 215 (3.1) | 143 (2.1) |
| Cholelithiasis | 152 (2.2) | 81 (1.2) |
| Laboratory results after 6 mo — mg/dl | | |
| Change from baseline in uric acid level | 0.70±1.2 | -0.03±1.0 |
| Change from baseline in creatinine level | 0.05±0.2 | 0.01±0.2 |
| Laboratory results after 12 mo | | |
| Change from baseline in glycated hemoglobin level — %‖ | 0.04±0.74 | 0.06±0.70 |
| Abnormal enzyme level at any visit — no. (%) | | |
| Creatine kinase level >5× ULN, single occurrence | 45 (0.6) | 40 (0.6) |
| Creatine kinase level >5× ULN, repeated and confirmed | 8 (0.1) | 8 (0.1) |
| Creatine kinase level >10× ULN, single occurrence | 18 (0.3) | 15 (0.2) |
| Creatine kinase level >10× ULN, repeated and confirmed | 2 (<0.1) | 4 (0.1) |
| Alanine aminotransferase level >3× ULN¶ | 83 (1.2) | 53 (0.8) |
| Aspartate aminotransferase level >3× ULN¶ | 80 (1.1) | 43 (0.6) |

## CASE #1: 55 male with ASCVD, prior CABG, prior PCIs, longstanding h/o hyperlipidemia referred for “statin intolerance”

- Did not add bempedoic acid
  - H/O gout
  - Magnitude of LDL reduction needed
- Added Repatha 140 mg q 2 weeks sub Q
- After 6 months therapy
  - **LDL 48 mg/dl**
- Called office after 9 months having “injection reactions”

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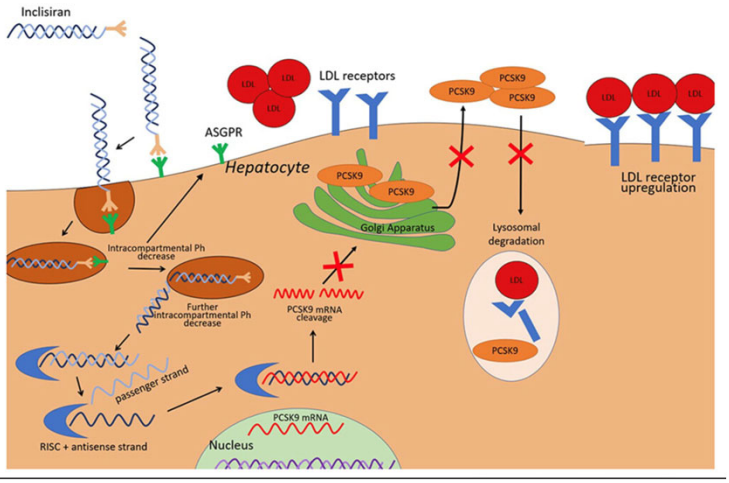
## Incliseran: siRNA “small interfering RNA”




RNA-induced silencing complex (RISC)

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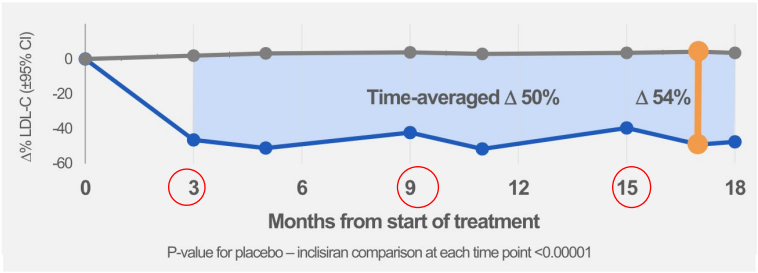
# Incliseran LDL lowering: 2 DOSES PER YEAR

284 mg subcutaneously, as a single injection initially, again at 3 months and then every 6 months

## ORION-11: Efficacy
## Durable, potent and consistent effect over 18 months

Percent change in LDL-C over time – observed values ITT patients




1. All 95% confidence intervals are less than ±2% and therefore are not visible outside data points

## ORION-11: Exploratory endpoint
## Adverse cardiovascular events

| Cardiovascular TEAEs | Placebo N = 804 | Inclisiran N = 811 |
|---|---|---|
| Pre-specified exploratory CV endpoint[3] | 83 (10.3%) | 63 (7.8%) |
| Cardiovascular death | 10 (1.2%) | 9 (1.1%) |
| Fatal or non-fatal MI and stroke[4] | 30 (3.7%) | 12 (1.5%) |
| Fatal or non-fatal MI | 22 (2.7%) | 10 (1.2%) |
| Fatal or non-fatal stroke | 8 (1.0%) | 2 (0.2%) |

## ORION-11: Safety and tolerability
## Adverse event profile similar to placebo

| Treatment emergent adverse event (TEAE) | Placebo N = 807 | Inclisiran N = 810 |
|---|---|---|
| Patients with at least one TEAE | 655 (82%) | 671 (83%) |
| Diabetes mellitus adverse events | 94 (12%) | 88 (11%) |
| Nasopharyngitis | 90 (11%) | 91 (11%) |
| Hypertension | 54 (7%) | 53 (7%) |
| Upper respiratory tract infection | 49 (6%) | 52 (6%) |
| Arthralgia | 32 (4%) | 47 (6%) |
| Osteoarthritis | 40 (5%) | 32 (4%) |

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1617 pts with ASCVD (LDL > 70 or ASCVD RISK EQUIVALENT (LDL > 100 MG/DL)

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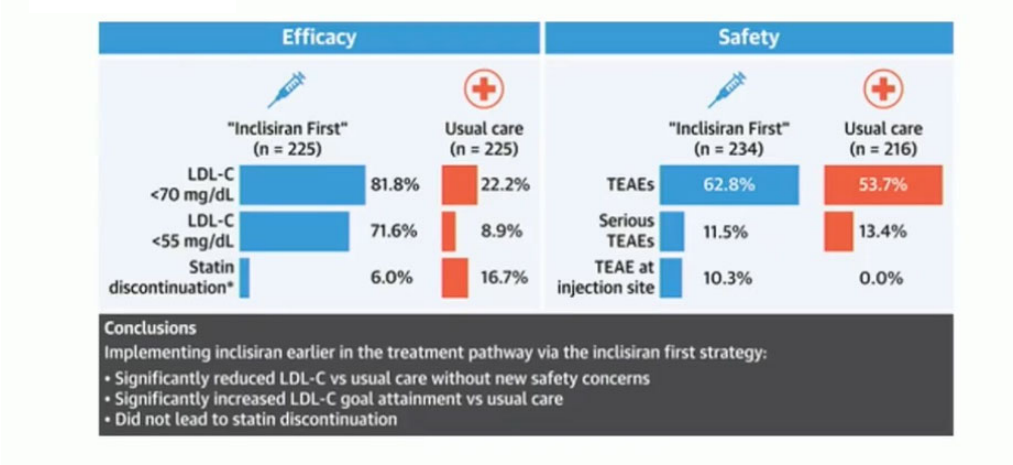
# Incliseran First




Koren eta IJACC. 2024 May, 83 (20) 1939–1952 VICTORIAN INITIATE TRIAL

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# INCLISERAN OUTCOME TRIALS

**VICTORIAN -1- PREVENT**: A Randomized, Double-blind, Placebo-controlled Multicenter Study to Evaluate the Effect of Inclisiran on Preventing Major Adverse Cardiovascular Events in High-risk Primary Prevention Patients

**VICTORIAN – 2 – PREVENT**; Established ASCVD assess Adverse Cardiovascular Events (3P-MACE) defined as a composite of CV death, non-fatal myocardial infarction (MI) and non-fatal ischemic stroke.

ORION-4: A Double-blind Randomized Placebo-controlled Trial Assessing the Effects of Inclisiran on Clinical Outcomes Among People With Atherosclerotic Cardiovascular Disease

**VICTORIAN – INCEPTION** trail: A Randomized Study to Compare LDL-C-Lowering Effects of Inclisiran with Usual Care vs Usual Care Alone in Patients with Recent Hospitalization for an Acute Coronary Syndrome

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# Incliseran advantages/disadvantage

- Advantages
  - 6 month dosing
  - Improved adherence
  - Lowers Lpa 26%
  - No effect on A1c, muscles

- Disadvantages
  - Administered at clinic/hospital
  - Await outcome data
  - Exploratory endpoints favorable

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## Summary: Non statin therapy

- Ezetimibe:
  - First line add on RX pts on statins (22% with statin combination)
  - 6 % relative event reduction at 7 years
- Bempedoic acid:
  - Good alternate for statin intolerant patients that need moderate LDL lowering
  - Lowers crp/inflammation
  - Avoid with gout
  - Monotherapy (-21%), Combination with Zetia (NEXLEZET) (-38%)
  - Outcomes: 13 % event reduction at 5 years
- PCSK9i:
  - Mab's : Evolocumab (Repatha), Alirocumab (Praluent) (-57%)
  - siRNA: Incliseran (Leqvio) (-50%)

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## Other LDL lowering medications

- Bile Acid Sequestrants: Welchol (Colesevelam), Colestipol (Colestid), Cholestyramine (Questran)
  - Avoid when TG above 150 mg/dl
  - Limited outcome data (only cholestyramine)
  - GI side effects
  - Safe in pregnancy
- Drugs for Homozygous FH (LDL > 400 mg/dl)
  - Mipomersen (Kynamro): ASO to Apo B
  - Lomitipide: MTP inhibitor: Juxtapid REMS program
  - Evinacumab (Evkeeza): ANGPTL3 Inhibitor

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# Case 2: Asymptomatic 65 yo Female

- Mother had MI in her 60's
- Found to have high Lpa
- Very active, eats well, exercises regularly, never smoked
- "Hesitant" to take meds but concerned about risk

- TC: 210 mg/dl
- HDL: 47 mg/dl
- TG: 130 mg/dl
- LDL: 137 mg/dl

- Lpa: 270 nmol/L (high risk > 120 nmol/L)

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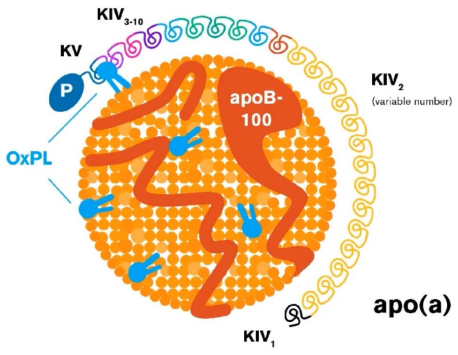
## What Is Lipoprotein(a)?




- LDL-like particle in which apoB is covalently attached to apo(a)
- ApoB is a central determinant of atherogenesis in CVD
- Apo(a) is characterized by a variable number of repeated kringle IV type 2 ($KIV_2$) sequences
- $KIV_2$ repeat polymorphism of the *LPA* gene that codes for apo(a) leads to variable Lp(a) size

Lp(a) = Lipoprotein(a)

Reyes-Soffer G, et al. *Am J Preven Cardiol*.2024;18:100651; Reyes-Soffer G, et al. *Arterioscler Thromb Vasc Biol*. 2022;42:e48-e60.

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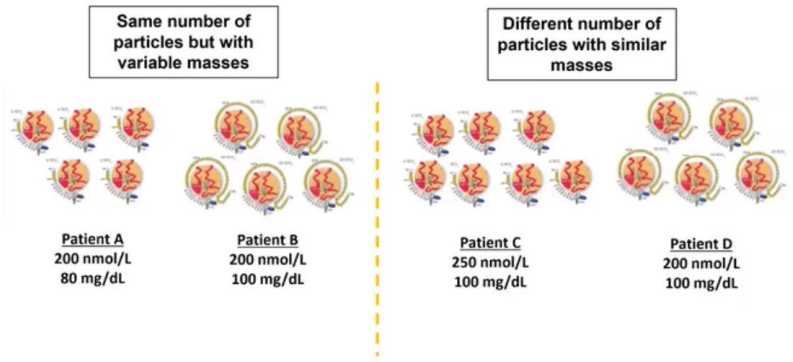
## Particle Concentration vs Mass Concentration




**Risk is likely better captured by # of particles (measured with nmol/L).**

Wilson DP, et al. *J Clin Lipidol* 2019; 13: 374-392

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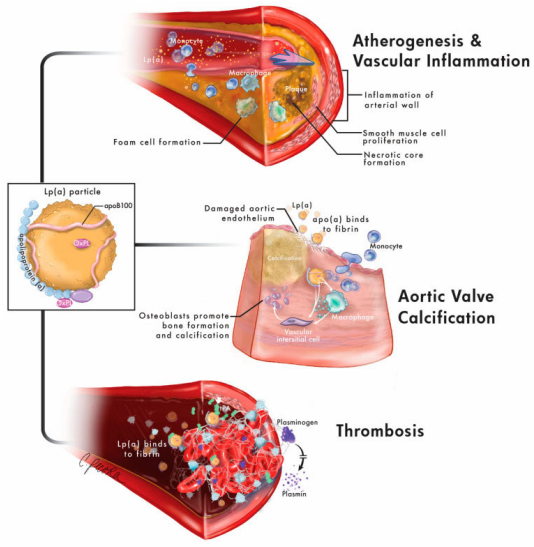


- **Autosomal Dominant**
- **20-30% world population (1 in 5) elevated**
- **1.6 billion people affected with high levels**
- **Associated with aortic stenosis progression**
- **lifestyle factors such as diet and physical exercise have limited impact** on Lpa levels

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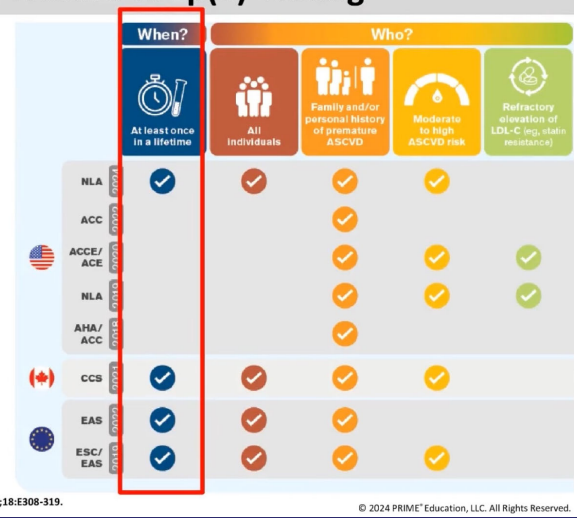
## Guideline and Consensus Statement Recommendations: The Who's and When's of Lp(a) Testing

NLA scientific statement recommends checking Lp(a) at least once in a lifetime




Reyes-Soffer G, et al. *Am J Preven Cardiol*.2024;18:100651; Koschinsky ML, et al. *J Clin Lipid*. 2024;18:E308-319.



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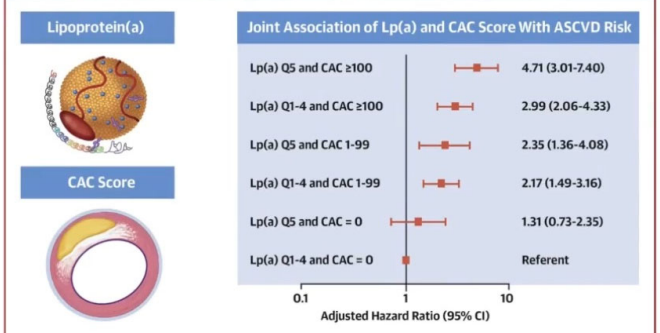
## Who to test for Lpa ?

**CENTRAL ILLUSTRATION: Joint Association of Lipoprotein(a) and CAC Score With Atherosclerotic Cardiovascular Disease Risk**




Mehta, A. et al. J Am Coll Cardiol. 2022;79(8):757-768.

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# Most Likely to benefit from Lpa Testing

- Some subclinical atherosclerosis (e.g. CAC)
- Calcific aortic valve disease (detected on TTE or CT)
- Prevalent ASCVD
- Family history of premature ASCVD, hypercholesterolemia, or aortic stenosis

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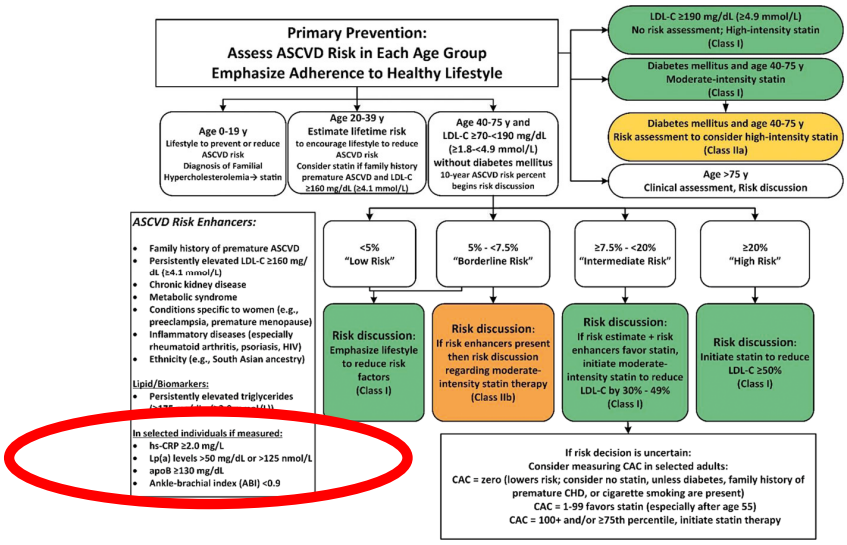


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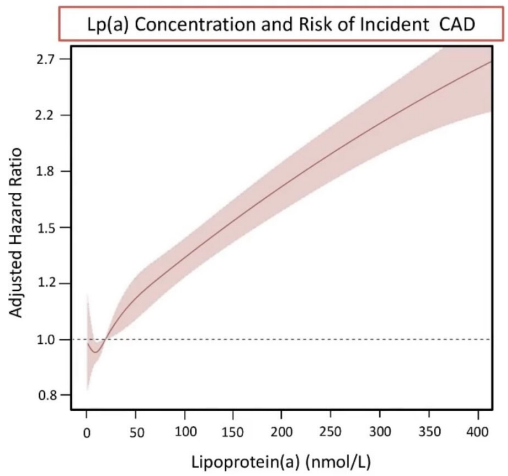
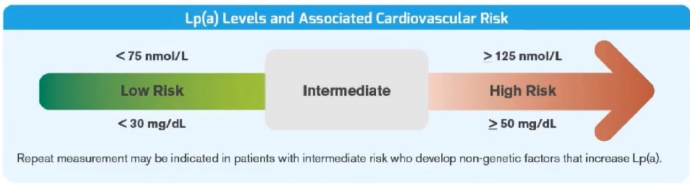
## Risk for ASCVD increases 11% for each increment of 50 nmol/L of Lp(a)

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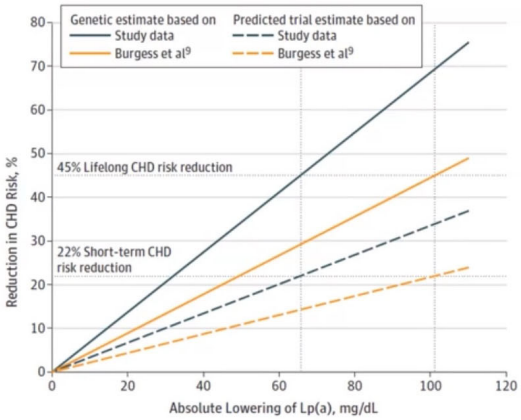
## Predicted Magnitude of Risk Reduction with Lp(a) Lowering




Variety of genetic estimates, ranging from 66 to 101.5 mg/dl (or 140 to 217 nmol/L) ↓ in Lp(a) needed to see comparable effects on MACE reduction as 1 mM ↓ in LDL-C (ie, ~22% RRR) over median of 4.8 years

Lamina et al., *JAMA Cardiol* 2019;4:575-579

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# Effects of Established Therapies

| Therapy | Effects on Lp(a) |
|---|---|
| Nicotinic acid | ↓ 20-30% |
| Mipomersen | ↓ 20-40% |
| Lomitapide | ↓ 17% |
| Statins | ↑ 8-24% |
| Ezetimibe/fibrates/bile acid sequestrants | ? neutral |
| PCSK9 inhibitors | ↓ 20-30% |
| Lipid apheresis | ↓ 70% acute, 35% time-averaged |

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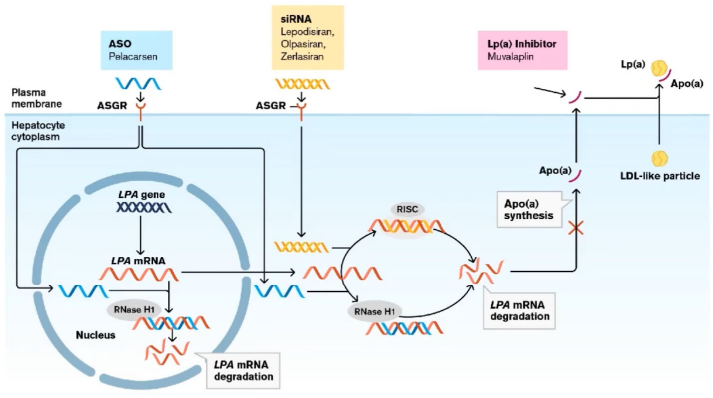
# Mechanisms of Emerging Lp(a)-Lowering Therapies

**ASO** and **siRNA** therapies prevent translation of *LPA* mRNA, therefore blocking production of apo(a)

**Lp(a) inhibitors** bind to apo(a) preventing it from binding to apoB100, therefore blocking production of Lp(a)




ASO = Antisense Oligonucleotide ; siRNA = small interfering Ribonucleic Acid
Brandts J, et al. *Nature Rev Cardio*. 2023;20:600-616.



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## Investigational Therapies for Elevated Lp(a)

| | | Clinical Trial Phase | Dose Frequency | Route of Administration | |
|---|---|---|---|---|---|
| | | | | Oral | SubQ |
| **RNA-Based Therapies** | | | | | |
| ASO | Pelacarsen | III | Monthly | | ✓ |
| siRNA | Lepodisiran | III | Every 6-12 months* | | ✓ |
| | Olpasiran | III | Every 3 months | | ✓ |
| | Zerlasiran | II | Every 4-6 months* | | ✓ |
| **Small Molecule Inhibitor Therapy** | | | | | |
| Lp(a) Inhibitor | Muvalaplin | II | Daily | ✓ | |

osing interval still being determined.



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## AKCEA-APO(a)-$L_{Rx}$ Study: Lp(a) Levels Were Significantly Reduced With Pelacarsen

N = 286 patients with ASCVD and Lp(a) ≥ 150 nmol/L

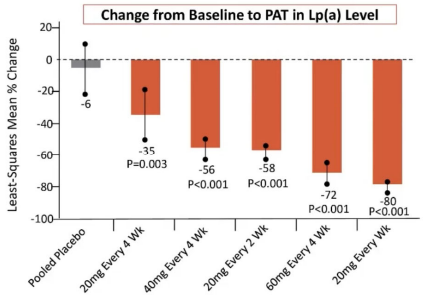
Pelacarsen vs. placebo (variable dosing intervals)

Median baseline Lp(a) levels: 205-247 nmol/L

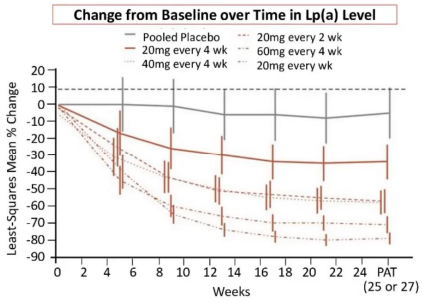
Baseline therapies: PCSK9i: 20% Statins: 80%

In the highest dose group, 98% of patients achieved Lp(a) levels ≤125 nmol/L

**Change from Baseline to PAT in Lp(a) Level**




**Change from Baseline over Time in Lp(a) Level**




PAT = Primary Analysis Time Point

No difference in platelet count or hepatic and renal safety measures compared to placebo

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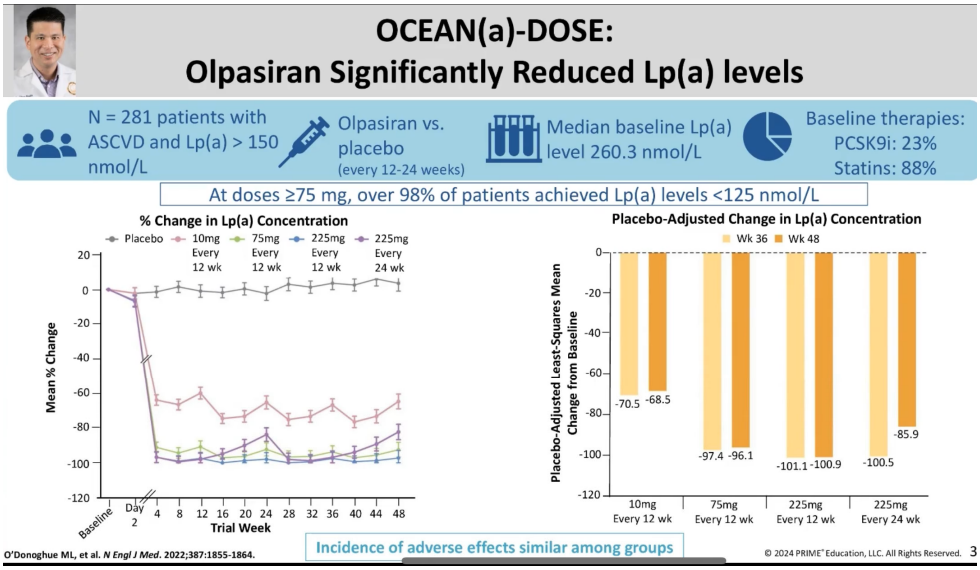


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# Current Phase III trials Lpa: Outcomes

- **Lp(a) HORIZON**: Pelecarsen monthly in patients with ASCVD, elevated Lpa (> 70 mg/dl). Completed patient enrollment. Topline data from the study are expected in 2025
- **OCEAN(a)**: Olpasirin every 3 months in patients with ASCVD elevated Lpa ( > 200 nmol/L) Results are expected in 2027

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## Key Takeaways

- Elevated Lp(a) is an independent causal risk factor of ASCVD
- Lp(a) is recommended to be checked at least once in a lifetime and cascade screening should occur in 1st-degree relatives of those with elevated Lp(a)
- Lifestyle modifications, intensive risk factor modification, and LDL-C targeting therapies are recommended if Lp(a) levels are elevated
- Emerging therapies in late-stage clinical trials have proven to lower Lp(a)



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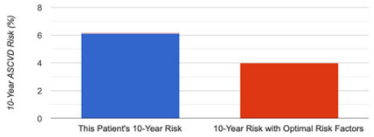
## Case 2: Asymptomatic 65 yo Female

- TC: 210 mg/dl
- HDL: 47 mg/dl
- TG: 130 mg/dl
- LDL: 137 mg/dl

- Lpa: 210 nmol/L

**ASCVD Risk Evaluation**

| | |
|---|---|
| 10-year risk of atherosclerotic cardiovascular disease: | 6.1% |
| 10-year risk in a similar patient with optimal risk factors: | 4% |




**ASCVD Risk Interpretation** [1,2]

Statin recommendations based on ASCVD risk is intended for patients age 40-75 years with LDL-C 70 to < 190 mg/dL (1.8 to < 4.9 mmol/L) without diabetes mellitus

| Low Risk (< 5%) | Borderline Risk (5% to < 7.5%) | Intermediate Risk (≥ 7.5% to < 20%) | High Risk (≥ 20%) |
|---|---|---|---|
| Emphasize healthy lifestyle factors to reduce risk factors (class I) | Consider moderate-intensity statin if risk-enhancing factors† are present (class IIb) | Consider moderate-intensity statin if risk-enhancing factors† are present (class I) | Consider high-intensity statin (class I) |

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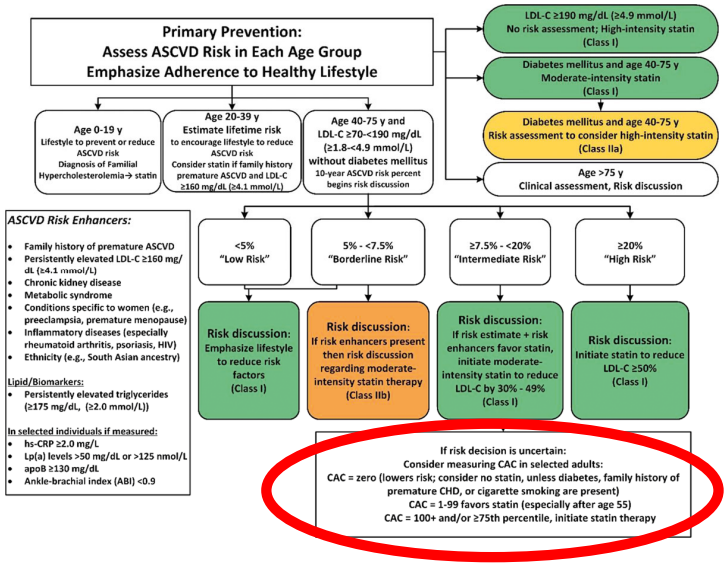


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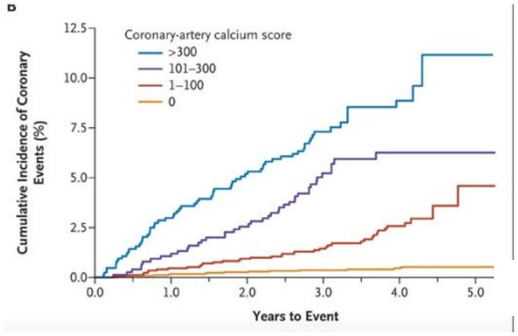
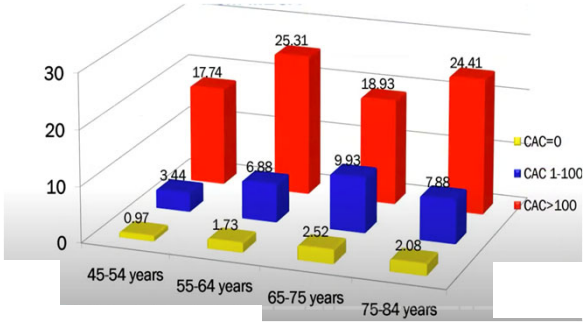
# Coronary Calcium Risk

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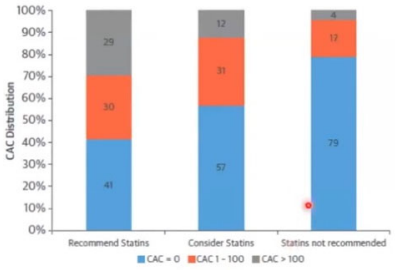
## The Lipid Guidelines Don't Perform Well

- MESA analysis
  - CAC and prognosis by ACC Lipid Guideline Recommendations

- CAC = 0 in ~ 50% of patient for whom statins are suggested
- CAC >0 in 1 in 5 NOT recommended statins

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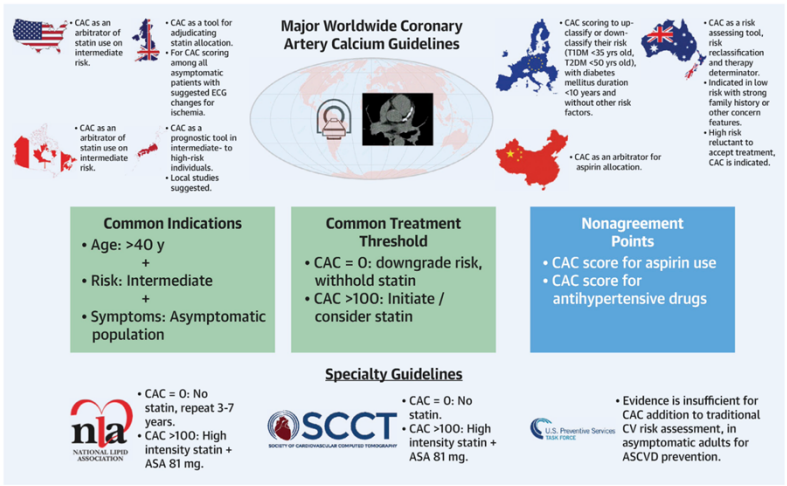
## CENTRAL ILLUSTRATION: Summary of Major Global CAC Guidelines




Golub IS, et al. J Am Coll Cardiol Img. 2023;16(1):98-117.

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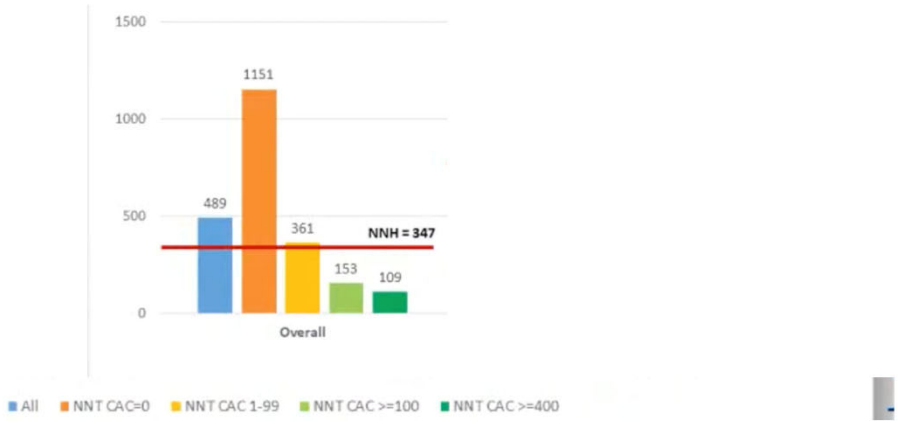
# Aspirin: CAC > 100, BENEFIT > RISK

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| CAC Score | Lifestyle | Statin and Statin Intensity | Non-Statin Add-on* | Aspirin |
|---|---|---|---|---|
| 0 | ✓ | | | |
| 1-99<br>< 75th %<br>≥ 75th % | <br>✓<br>✓ | <br>*Consider Mod*<br>Moderate | | |
| 100-299 | ✓ | Moderate to High | | ✓ |
| ≥ 90th % | ✓✓ | High | Consider | ✓ |
| > 300 | ✓ | High | Consider | ✓ |
| >1000 | *SECONDARY PREVENTION!!* | | | |

GOAL LDL

30-50% reduction

< 70 mg/dl

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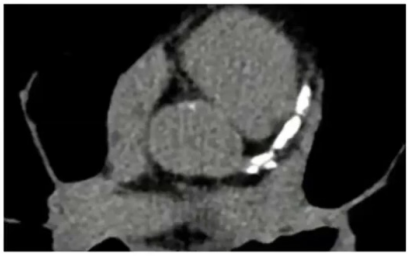
# Case 2: Asymptomatic 65 yo Female



\+ CAC 310
92 nd % for age/sex

= Crestor 20 mg qHS
Goal LDL < 70 mg/dl
ASA 81 mg added

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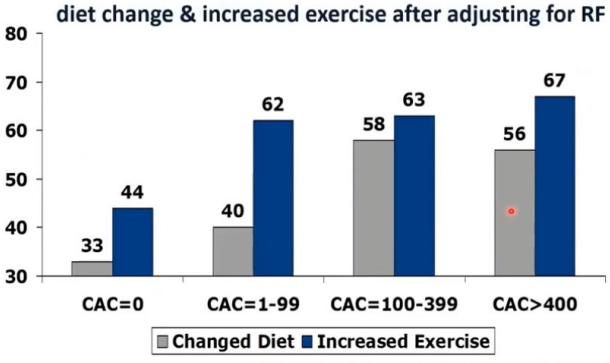
## Changes in Diet & Exercise after CAC Screening

Those with increasing CACS had 1.3-3.3 (P<0.05)-fold increase in diet change & increased exercise after adjusting for RF




Orakzai R, Nasir K, Blumenthal RS, Budoff MJ (Am J Cardiol 2008 & ACC 2008)

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# Case 3: RK

- 48 yo male with recent hospitalization for 2nd pancreatitis
- PMH: PCI
- H/O severely elevated TG
- Statin intolerance: Repatha, Fenofibrate, Vascepa 2 bid, zetia
- BMI 25.2.  No DM. No ETOH
- Total cholesterol 642
- TG 4334
- LDL 17

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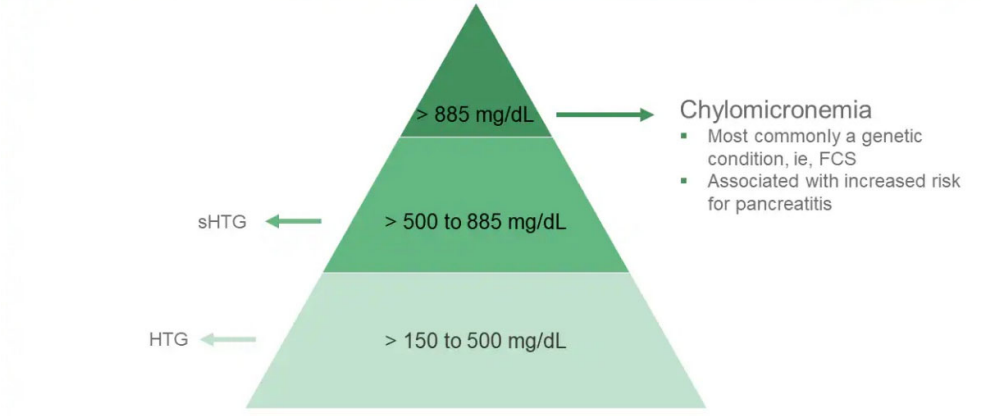
## Spectrum of sHTG




FCS, familial chylomicronemia syndrome; HTG, hypertriglyceridemia; MCS, multifactorial chylomicronemia syndrome; sHTG, severe hypertriglyceridemia.
Figure adapted from Gallo A, et al. Curr Atheroscler Rep. 2020;22:63; Ginsberg HN, et al. Eur Heart J. 2021;42:4791-4806; Grundy SM, et al. Circulation. 2019;139:31082-31143.

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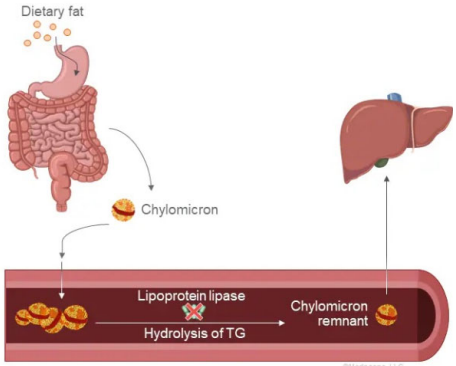
## Familial Chylomicronemia Syndrome (FCS)
### Key Characteristics

- Very high TGs, typically > 1000 mg/dL
- Does not respond to currently available treatments
- No associated conditions; typically not overweight
- Cholesterol to TG ratio of 1:10 or 1:20
- Genetic testing remains the cornerstone of diagnosis

LPL, lipoprotein lipase.

**In FCS, LPL Dysfunction Causes Chylomicronemia**

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# Severe Hypertriglyceridemia TG > 885 mg/dl

**Multifactorial Chylomicronemia Syndrome MCS Type V**

Common
Secondary risk factors present:
- Uncontrolled DM
- Obesity; high BMI
- Excessive ETOH
- High carbohydrate diet

Risk of Pancreatitis
Rx: Fibrates helpful

**Familial Chylomicronemia Syndrome (FCS) Type I**

Rare
Secondary risk factors absent
Very high risk pancreatitis
Normal BMI
**Gene mutation LPL**
Fibrates not helpful

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# Low Fat Diet Critical

## Lifestyle Modifications in Patients With Hypertriglyceridemia

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

| Implement shared decision-making intervention | TG < 500 mg/dL | TG 500-999 mg/dL | TG ≥ 1,000 mg/dL |
|---|---|---|---|
| Added Sugars (% Calories) | < 6% | < 5% | Eliminate |
| Total Fat (% Calories) | 30-35% | 20-25% | 10-15% |
| Alcohol | Restrict | Abstain completely | Abstain completely |
| Aerobic Activity | At least 150 min/week of moderate intensity or 75 min/week of vigorous aerobic physical activity | | |
| Weight Loss (% Body weight) | Goal is 5-10% of body weight for all patients with elevated TG | | |

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

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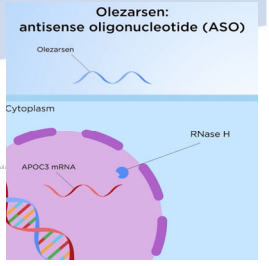
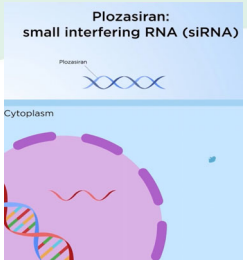
## Emerging Therapies for sHTG and FCS
### ApoC-III Inhibitors

**Olezarsen (BALANCE trial)**
ASO targeting *APOC3* mRNA in the liver




**Plozasiran (PALISADE trial)**
siRNA targeting *APOC3* mRNA in the liver

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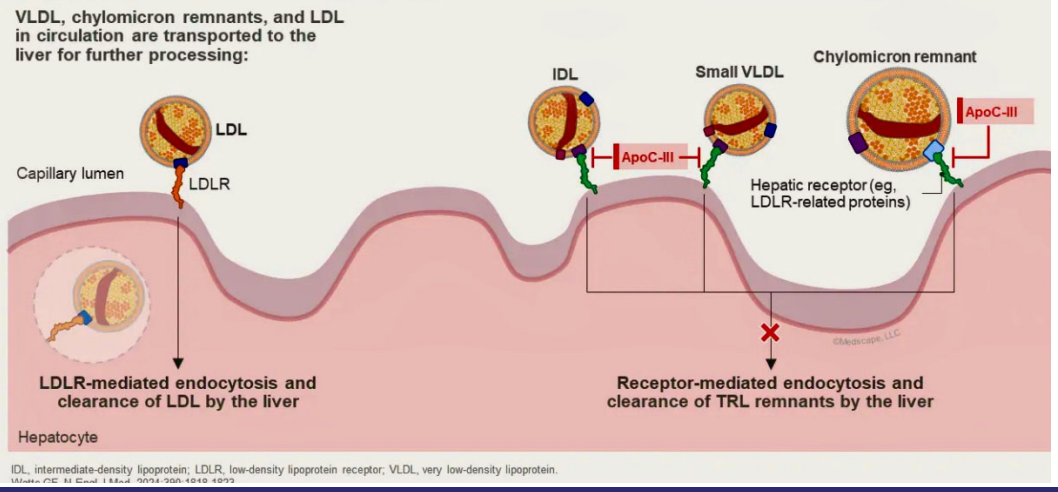
## LPL-Independent Pathways of Lipoprotein Metabolism
### ApoC-III Inhibition




IDL, intermediate-density lipoprotein; LDLR, low-density lipoprotein receptor; VLDL, very low-density lipoprotein.

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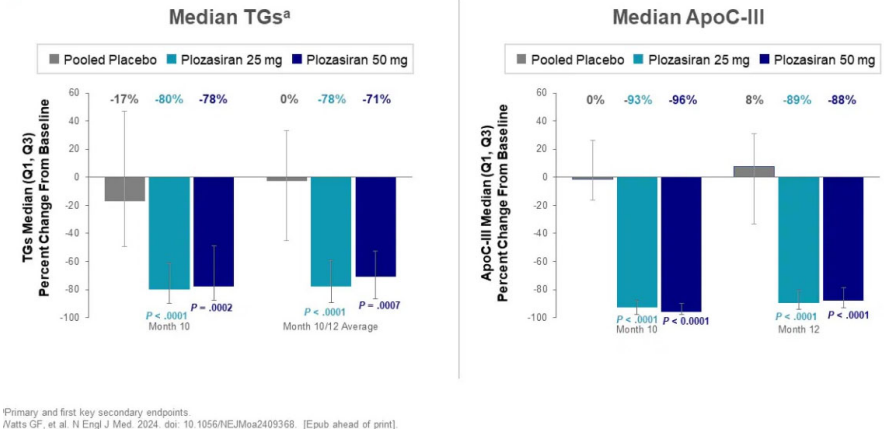
## Plozasiran Reduced Plasma TGs and ApoC-III Relative to Placebo in Persistent Chylomicronemia




[a]Primary and first key secondary endpoints.
Watts GF, et al. N Engl J Med. 2024. doi: 10.1056/NEJMoa2409368. [Epub ahead of print].

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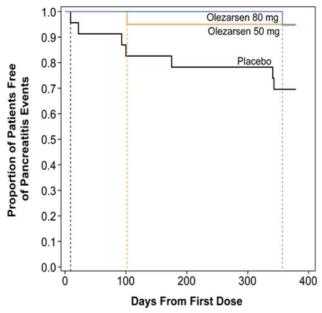
# Reduced Pancreatitis

## Reduced Incidence of Pancreatitis Events in Olezarsen-Treated Patients

Time to first pancreatitis event per patient




Patients with pancreatitis events

| | Placebo (n = 23) | Olezarsen 50 mg (n = 21) | Olezarsen 80 mg (n = 22) |
|---|---|---|---|
| Patients with events, n | 7 | 1 | 1 |
| Pancreatitis events, n | 11 | 1 | 1 |
| First pancreatitis event, study day | 9 | 102 | 357 |

Selected prespecified secondary endpoints

| Adjudicated Acute Pancreatitis Endpoint (Week 1 to 53) | Event Rate per 100 PY (95% CI) | | Mean Rate Ratio[a] (95% CI) |
|---|---|---|---|
| | Placebo | Pooled Olezarsen | |
| All patients | 36.3 (14.7, 89.7) | 4.37 (0.942, 20.3) | 0.12 (0.022, 0.656) |
| Patients with history within last 10 years | 66.2 (30.5, 144) | 6.73 (1.61, 28.1) | 0.10 (0.020, 0.506) |
| Patients with ≥ 2 events within last 5 years | 119 (61.2, 230) | 16.6 (4.05, 67.9) | 0.14 (0.029, 0.669) |

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"Based on current information, both olezarsen (developed by Ionis Pharmaceuticals) and plozasiran (developed by Arrowhead Pharmaceuticals) are expected to receive FDA approval for the treatment of familial chylomicronemia syndrome (FCS) in the near future, with potential regulatory filings anticipated in 2024, both drugs have received Fast Track designation from the FDA for this indication, highlighting a high priority for review"

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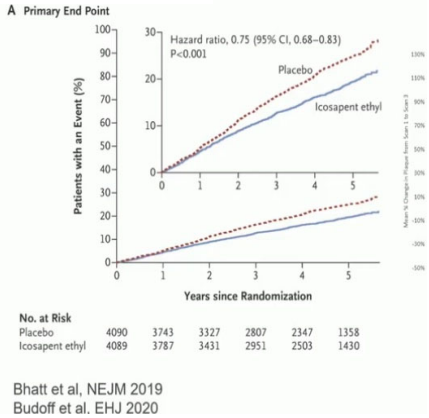
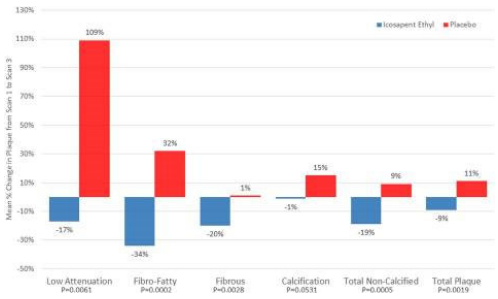
## ICOSAPENT ETHYL (VASCEPA): EPA only OMEGA 3 FAs




Bhatt et al, NEJM 2019
Budoff et al. EHJ 2020

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## Approach to Hypertriglyceridemia

| TG > 150 < 500 mg/dl | TG > 500 <1000 mg/dl | TG > 1000 mg/dl |
|---|---|---|
| • CV risk "risk enhancer"<br>• Consider LDL goal/statin therapy<br>• Check secondary causes:<br>TSH, A1c, CKD<br>Drugs: thiazides, steroids, HIV drugs, retinoids, estrogen<br>• < 35 % calories from fat<br>• < 6% added sugars<br>• Reduce ETOH<br>• 150/75 minutes mod/vigorous exercise<br>• Add Icosapent ethyl (Vascepa ) if ASCVD based on REDUCE-IT trial | • Prior treatment plus:<br>Risk of pancreatitis<br>• Add fibrate (do not combine gemfibrozil and statin)<br>• Fenofibrate (tricor) | • Marked increased risk for pancreatitis<br>• Consider FCS genetic testing<br>• < 15% calories from fat<br>• No ETOH<br>• Consider Apo CIII agents and referral to lipid specialist |

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

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# Summary

- Statins remain the mainstay of LDL lowering
  - Statin intolerance / DM issues lead to suboptimal LDL lowering
  - Under achievement of LDL goals
  - Moderate dose statins/plus non statin therapy is a new strategy
- There is <u>underutilization</u> of non statin therapies
- Pipeline of “pharmacogenetics” is rapid and prolific

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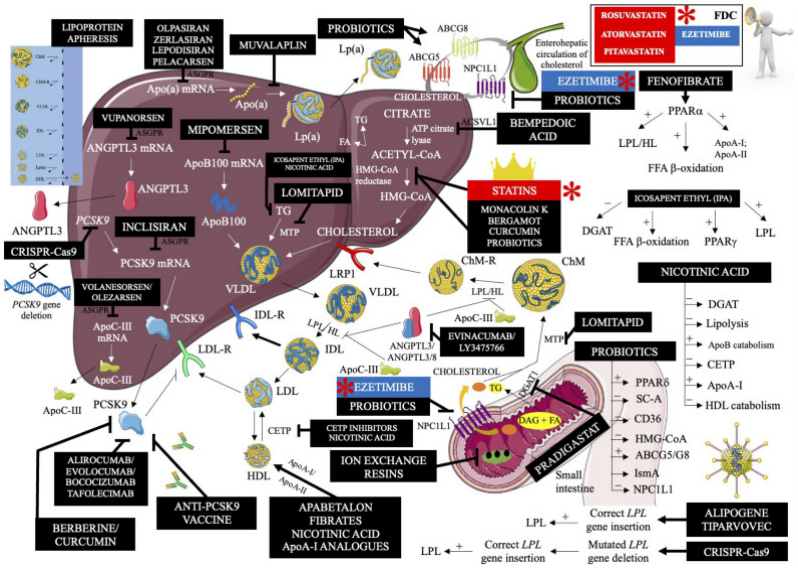


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Banach, Surma, Toth 2023 Nov 2;19(6):1602–1615. doi: 10.5114/aoms/174743

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## Prior Authorization Questions?

- Alyson.Ryan @allina.com (PCSK9i, bempedoic acid)
- Kieth.Behrend@allina.com (Incliseran)

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## Key factors: Lipid Lowering Meds

- Provider establishes patient specific goals
- Pt understands importance of risk reduction
- Provider has tools/knowledge to achieve goal
  - What % LDL lowering is desired/ which add on or substitute Rx
  - What are the associated lipid abnormalities: High TG's, Low HDL, Lpa
  - Provider has assistance in the PA process
  - Patient understand associated costs
- Plan is implemented to maximize efficacy and adherence

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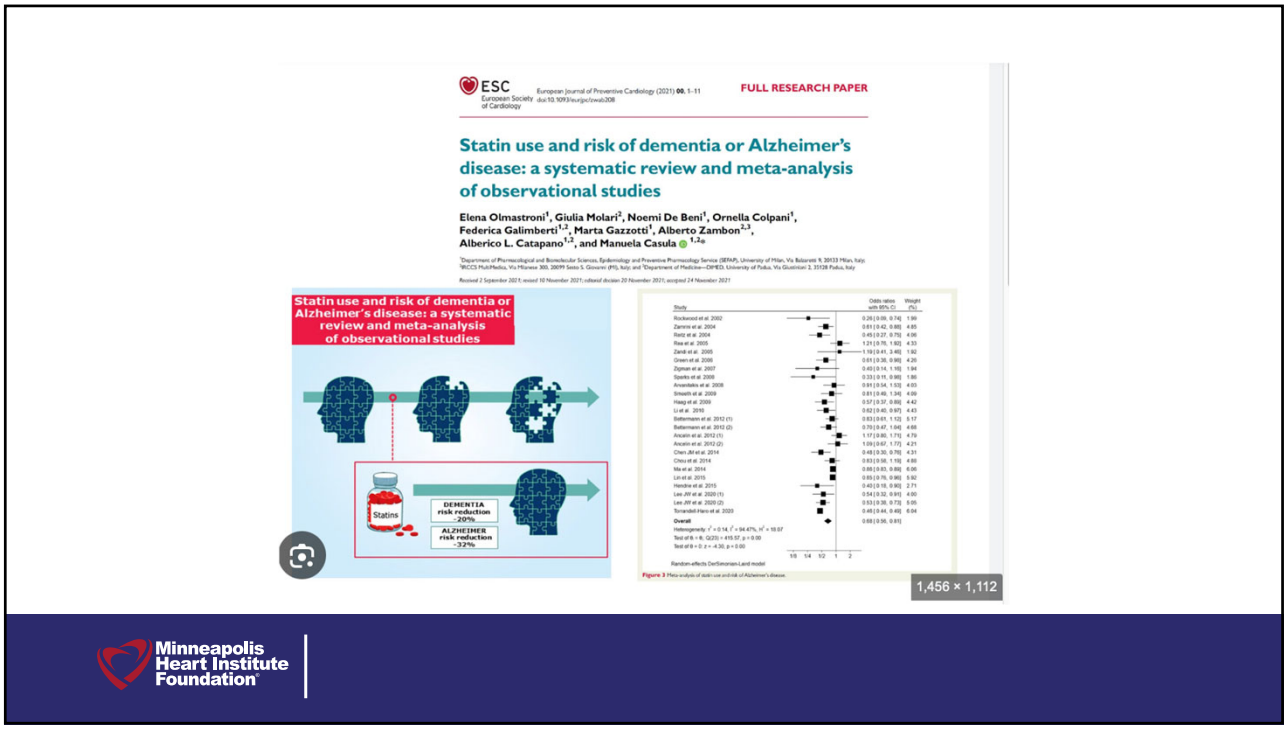
ESC
European Journal of Preventive Cardiology (2021) 00, 1–11
European Society of Cardiology
FULL RESEARCH PAPER
Statin use and risk of dementia or Alzheimer's disease: a systematic review and meta-analysis of observational studies
Elena Olmastroni, Giulia Molari, Noemi De Beni, Ornella Colpani, Federica Galimberti, Marta Gazzotti, Alberto Zambon, Alberico L. Catapano, and Manuela Casula
Statin use and risk of dementia or Alzheimer's disease: a systematic review and meta-analysis of observational studies
Statins
DEMENTIA risk reduction -20%
ALZHEIMER risk reduction -32%
Odds ratio with 95% CI
Weight (%)
Random-effects DerSimonian-Laird model
1,456 × 1,112
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