Managing LDL-C and Lp(a): An Update

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Disclosure

Consultant: Alnylam (Hypertension); Blue Earth Diagnostics; Corcept; Eli Lilly (SURPASS-CVOT); Idorsia; Medtronic; Mineralys; Novo Nordisk; ReCor (Renal Denervation); ReCor-PI (Renal Denervation); UpToDate (Hypertension Section)

Research Grant: Ablative Solutions (Target BP I); Corcept; Eli Lilly (TRIUMPH); ReCor (Radiance I and II); Sonivie – THRIVE Study

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Objectives

1) **Review the most recent cholesterol updated guideline on LDL-C thresholds for treatment including the "newest" 2022 LDL-C target for the very-high risk patient.**

2) **Review currently available "newer" non-statin cholesterol-lowering therapies and their roles for LDL-C Reduction.**

3) **Learn When and Why You Should Measure Lp(a) understanding its relationship to CV Disease.**

4) **Review what you can currently do for Lp(a) elevation and the Clinical Trials Currently in Progress.**

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ARS Question 1

- 62-year-old female with a hx of CAD and a stent placed 1 year ago is referred for lipid management.
- She has a hx of Type II Diabetes, Hypertension, and Obesity.
- Current medications include simvastatin 20 mg, benazepril 20 mg/amlodipine 5 mg qam (fixed-dose combination pill), aspirin 81 mg, metformin 1000 mg bid, and semaglutide 2.4 mg sq weekly.
- Her current BMI is down to 30 and her BP is 118/68 mm Hg.
- Recent labs: Total Chol 150, HDL 40, TG 140, Calculated LDL-82, non-HDL-C 110, and A1C 6.2%.

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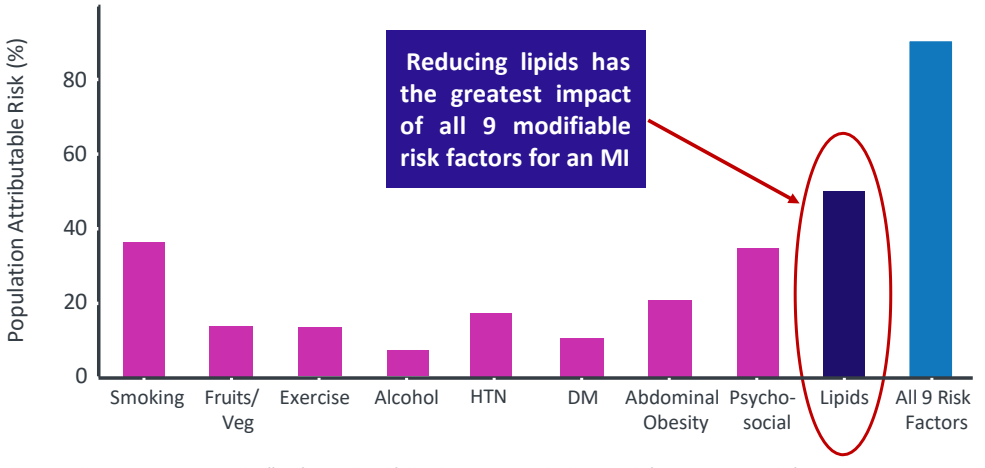
ARS Question 1
Being on Simvastatin 20 mg, the Best Choice to Manage Her LDL-C is:

A. Add Niacin 500 mg tid
B. Add fenofibrate 160 mg qd
C. Add ezetimibe 10 mg qd
D. Add evolocumab 420 mg sq monthly
E. Change simvastatin 20 mg to Atorvastatin 40 mg qd

Total Chol 150, HDL 40, TG 140, Calculated LDL-82, non-HDL-C 110, and A1C 6.2%.

Abnormal Lipids Increase Risk of Myocardial Infarction

Case-control study of 15,152 patients with acute myocardial infarction and 14,820 controls from 52 countries (INTERHEART study)

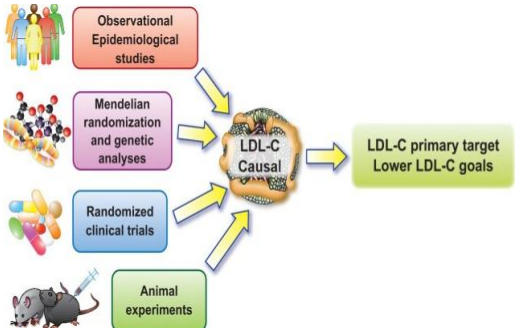


DM = diabetes mellitus; HTN = hypertension; INTERHEART = The Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction; MI = myocardial infarction

Yusuf S. *Lancet*. 2004; 364(9438):937-952.

Support for LDL Causality in ASCVD

- Observational Epi Data
- Genetic Studies
- Randomized Trials
- Animal Experimental



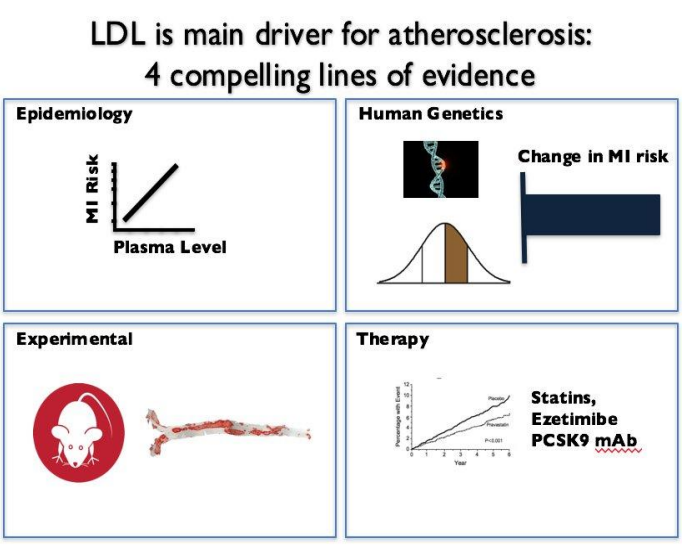


Figure 2. Tokgozoglu L., Libby P. Eur Heart Junl 2022;43(34):3198-3206.

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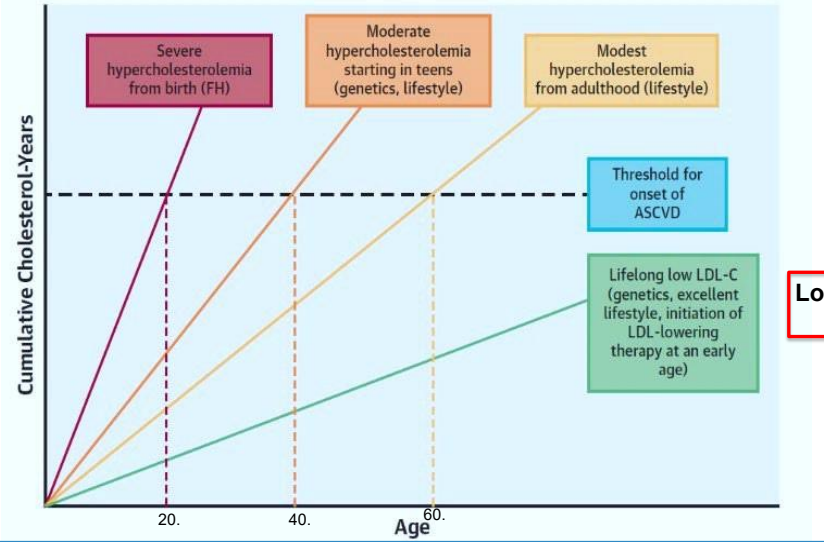
Assessing Cholesterol-Years for ASCVD Risk Prediction



Lower for Longer is Better

Cumulative prior exposure to elevated LDL-C is a critical driver of ASCVD Risk

Shapiro MD, Bhatt DL. *J Am Coll Cardiol*. 2020;76(13):1517-1520.

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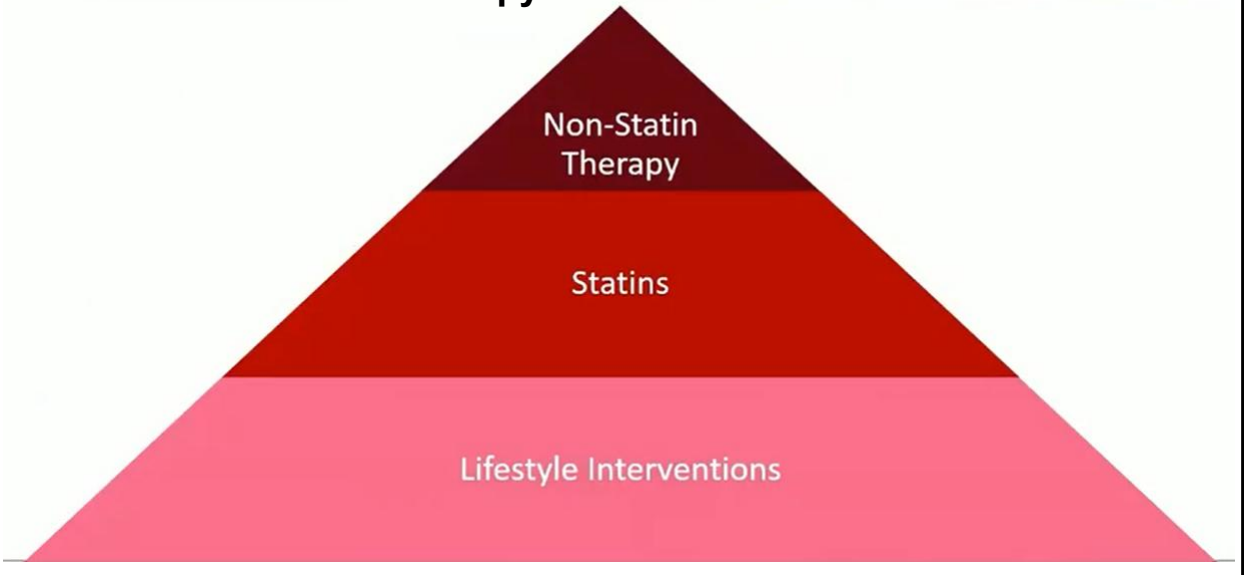
It Starts with Statins When Reducing LDL-Cholesterol After Lifestyle Modification

9

Statins: First-Line Pharmacotherapy for the Treatment of LDL-C Excess



Grundy S.M. et al. *J Am Coll Cardiol.* 2019;73:e285-e350.

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CTT Collaborators Meta-analysis Results of 90,056 Participants in 14 Randomized Trials of Statins per mmol/L Reduction in LDL-C

- 12 % reduction in all-cause mortality (p<0.0001)
- 19% reduction in coronary mortality (p<0.0001)
- 23% reduction in MI or coronary death (p<0.0001)
- 24% reduction in coronary revascularization (p<0.0001)
- 17% reduction in fatal/nonfatal stroke (p<0.0001)
- 21% reduction in combination of above vascular events (p<0.0001)
- No change in non-CVD mortality or cancer incidence
- Benefit of statins related to absolute reductions in LDL-C
- Statins safely reduce MACE 21% per every 1 mmol/L reduction in LDL-C (39mg/dL), regardless of baseline lipids, risk, age, gender

Lancet 2005;366:1267-78.

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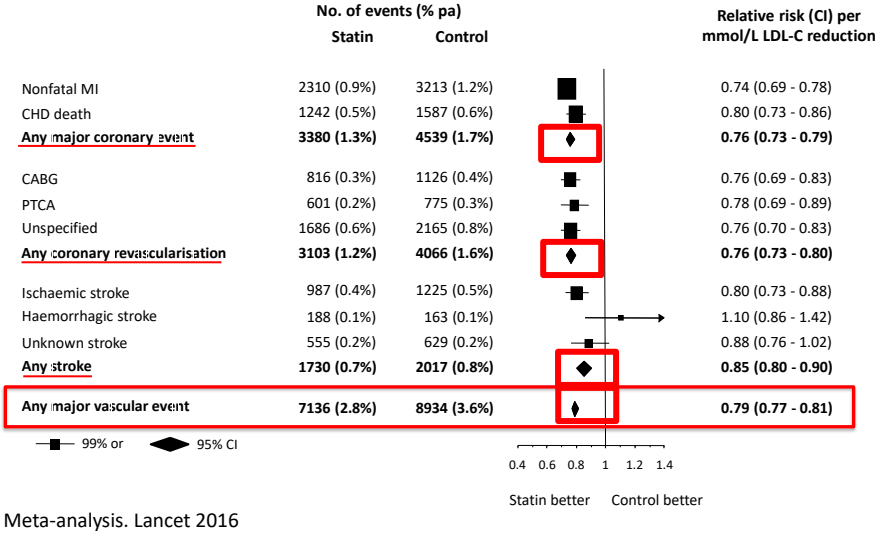
Reducing LDL-C Reduces CV Events Statin v. Control



CTT Meta-analysis. Lancet 2016

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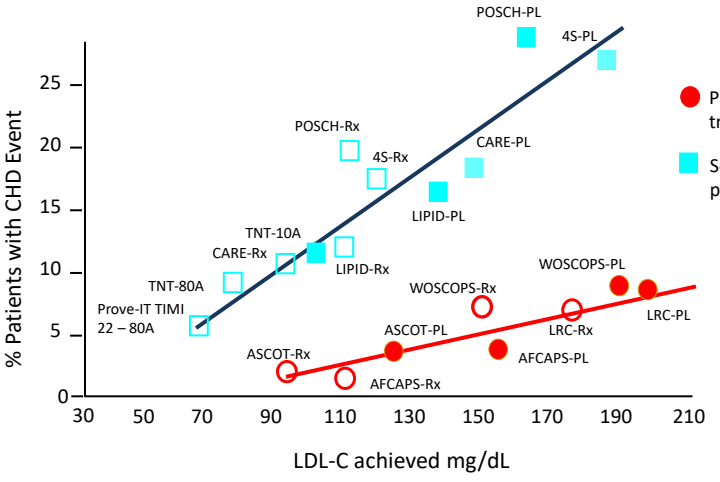
Reducing LDL-C Reduces CV Events



The Slope is Much Steeper for Secondary Prevention Showing Greater Benefit For The Same Reduction In LDL-C as the Risk is Greater for Sec. Prevention

PL = placebo (Circles or Boxes Full)
Rx = active Rx (Circles or Boxes open)

Ballantyne CM. *Am J Cardiol*. 1998;82:737-743.
O'Keefe JH, et al, *J Am Coll Cardiol*. 2004;43:2142-2146.

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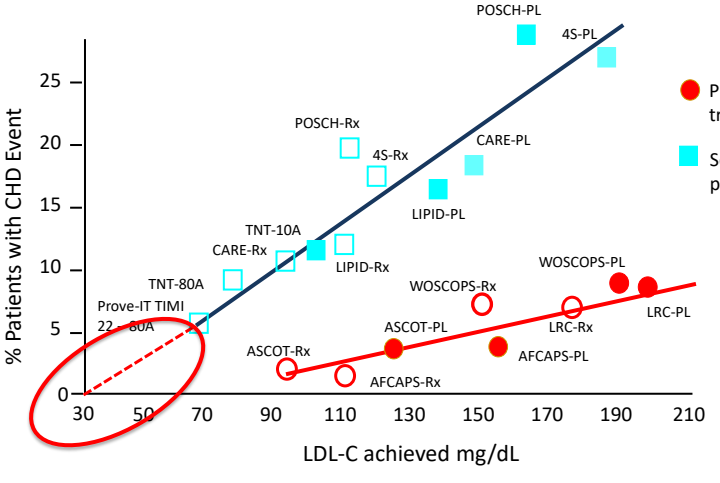
The Big Question…How Low a Reduction in LDL-C Is Enough?



Lower LDL-C is Better

PL = placebo (Full)
Rx = active treatment (open)

Ballantyne CM. *Am J Cardiol*. 1998;82:737-743.
O'Keefe JH, et al, *J Am Coll Cardiol*. 2004;43:2142-2146.

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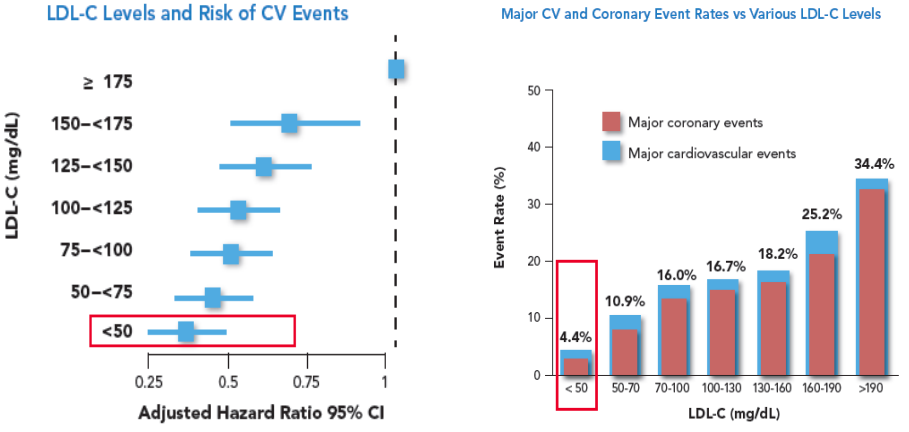
Very Low Levels of Atherogenic Lipoproteins and the Risk of Cardiovascular Events

A Meta-Analysis of Statin Trials



Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64:485–94.

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Monitoring of Therapeutic Response Is Critical And Often Not Done

- After therapy initiation
- With dose titration

} Recheck lipids in 4-12 weeks

- During long-term therapy
  - Are intensity of therapy and LDL-C concentration still appropriate for patient's ASCVD risk?
  - Is patient adherent to therapy?
  - If so, recheck every 3-12 months as needed

Grundy SM, et al. *J Am Coll Cardiol*. 2018 Nov 8. pii: S0735-1097(18)39034-X.; Grundy SM et al. *Circulation*. 2018

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With Using Statins, Recognize the Importance of:

1) Intensity of Statin Used
2) Amount and Length of LDL-C Reduction Achieved
3) Use and Adherence to Statin Achieved

   Less adherence even on a high-intensity statin is associated with increased mortality!

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With Using Statins, Recognize the Importance of:

1) Intensity of Statin Used

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Statin Intensity

- Statins
  - Intensity defined by % LDL-C lowering
  - Aim for ≥50% LDL-C lowering in high-risk patients and very-high risk individuals
  - Aim for 30 to <50% LDL-C lowering in moderate-risk patients
  - Notice I have not included low intensity statins as they are no longer recommended

High Intensity	Moderate Intensity
Lowers LDL-C on average by ≥50%	Lowers LDL-C on average by 30% to <50%
Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg

Grundy et al. Circ 2019;139:e1082-e1143

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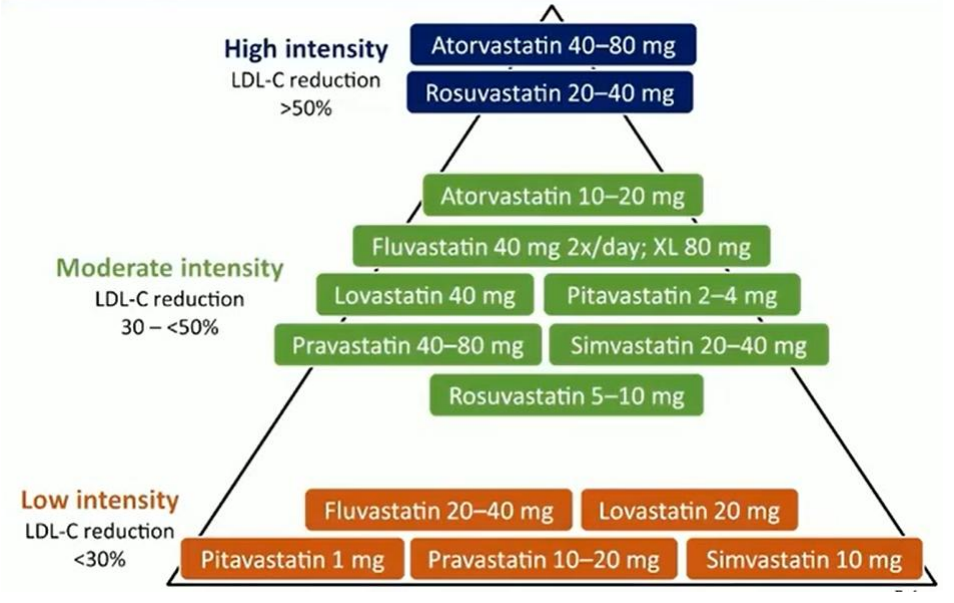
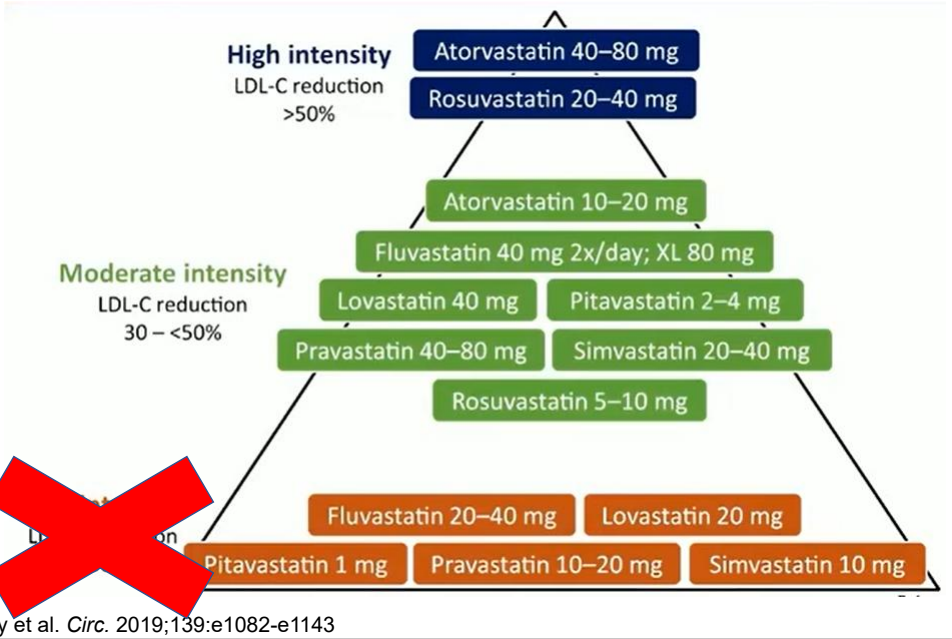
Statin Intensity



Grundy et al. *Circ.* 2019;139:e1082-e1143

20

Statin Intensity



Grundy et al. *Circ.* 2019;139:e1082-e1143

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With Using Statins, Recognize the Importance of:

1) Intensity of Statin Used
2) **Amount and Length of LDL-C Reduction Achieved**

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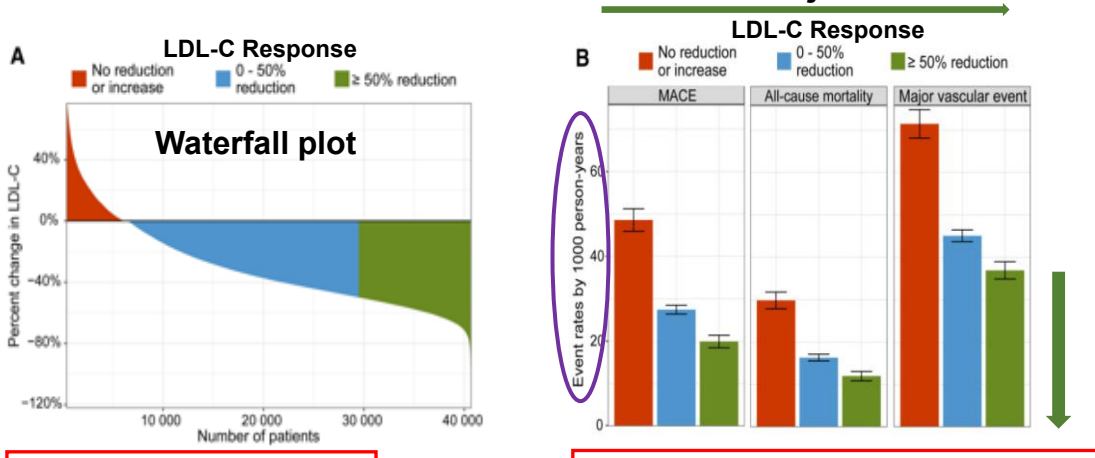
SWEDEHEART MI Registry:
Statin Intensity and LDL-C Reduction Matters:
More LDL-C Reduction Post MI Reduces More Major Vascular Events



- N=40,607
  Median F/U 3.8 years

LDL-C: BL and F/U visit p 6-10 weeks
Median Δ: - 1.2 mmol/L (50 mg/dl)

Schubert et al. *Eur Heart Jnl* 2021;Vol 42:Issue 3, Jan 14, 2021, pages 243-252.

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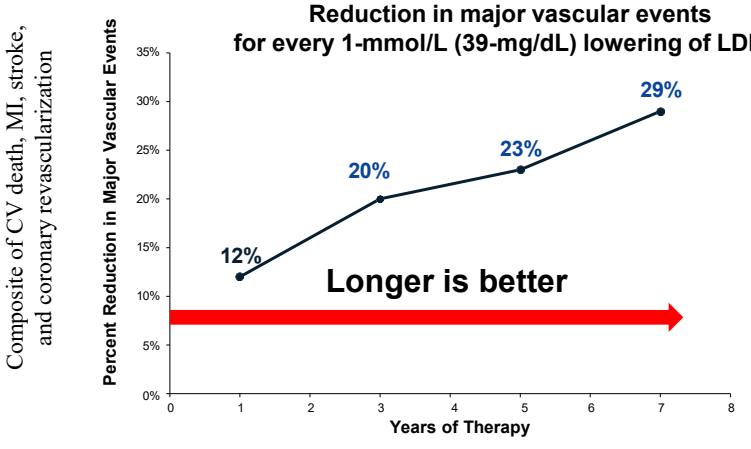
Duration of LDL-C Lowering Is Also Important

Meta-analysis of 21 trials with statins, ezetimibe, and PCSK9i's in 184,012 patients with ave mean f/up of 4.4 trs



. Wang N, et al. *Circ Cardiovasc Qual Outcomes.* 2022;15(6):416-424.

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With Using Statins, Recognize the Importance of:

3) Use and Adherence to Statin Achieved

Less use and adherence even on a high-intensity statin is associated with increased mortality!

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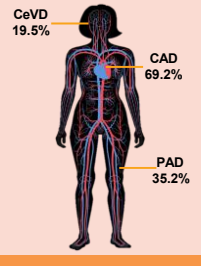
Up to One-Half of Patients with Underlying ASCVD Are Not Taking a Statin

Study Population

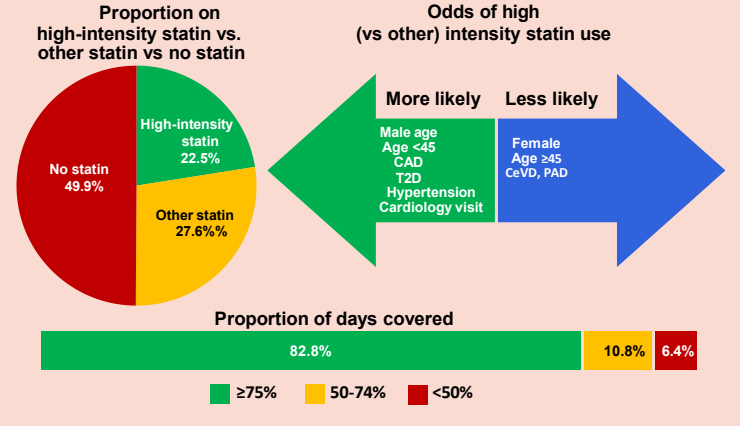
601,934 patients with ASCVD
Mean age: 67.5 ± 13.3 years



Outcomes

Statin usage on
January 31, 2019 ± 30 days
Proportion of days covered

Results



Abbreviations: CAD=coronary artery disease; CeVD=cerebrovascular disease; PAD=peripheral artery disease; T2DM=type 2 diabetes mellitus

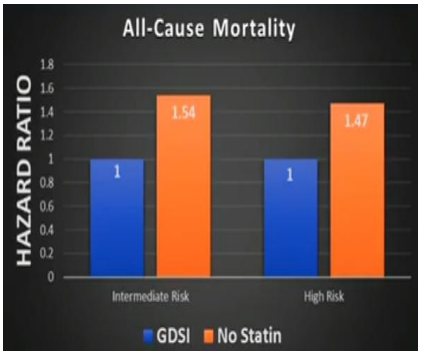
Nelson AJ, et al. *J Am Coll Cardiol*. May 2022;79 (18):1802-

26

Up to 1/3 of Those in Primary Prevention from a Large HealthCare Network with a ≥ 20% PCE Risk Are On No Statin

Table 2. Statin Therapy Utilization per the 10-y ASCVD Risk Category

	ASCVD risk category (n)			
Statin therapy/intensity	<5% Low (163 178)	5% - <7.5% Borderline (29 134)	≥7.5% - <20% Intermediate (63 299)	≥20% High (26 687)
No statin	135 025 (82.8%)	16 326 (56.0%)	27 58 (43.2%)	8300 (31.1%)
Low intensity	1434 (0.9%)	576 (2.0%)	1663 (2.6%)	868 (3.3%)
Moderate intensity	20 536 (12.6%)	8868 (30.4%)	23 544* (37.2%)	11 305* (42.4%)
High intensity	6183 (3.8%)	3364 (11.6%)	10 734* (17.0%)	6214* (23.3%)



GDSI-Guideline Directed Statin-Intensity

Saeed A., Zhu J. Thoma F., et al. Circ. Cardiovasc. Outcomes. Vol 14, Issue 9, Sept 2021; Page e00748.

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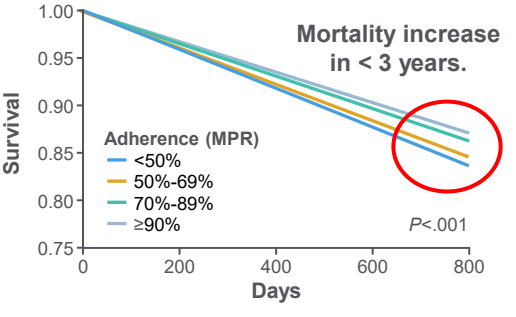
Association of Statin Adherence & Mortality in Veteran Patients with ASCVD

	Adherence level (MPR), No. (%)			
Variable	<50%	50%-69%	70%-89%	≥90%
Total No.	19,757 (6%)	30,606 (9%)	76,083 (22%)	220,658 (63%)
MPR vs. MPR ≥ 90%, aHR (95% CI)				
Statin intensity				
High	1.35 (1.27-1.43)	1.23 (1.17-1.30)	1.10 (1.06-1.14)	-

35% increased mortality when adherence < 50%

Survival Curves by Statin Adherence Level as Defined by Medication Possession Ratios (MPRs)



No. at risk: 347,104 325,772 304,209 229,681

MPR, medication possession ratio

Rodriguez F. et al. JAMA Cardiol. 2019; 4(3):206-213.

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So Intensity and Use (Adherence) of Statins Makes a Difference

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What About Statin Side Effects

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Reported Patient Complaints with Statin Therapy

Most Common: Myalgias (5-30% of patients but only 5-10% in clinical trials)
- Skeletal muscle-related symptoms that can be characterized by soreness, aches, cramps, fatigue, and/or weakness, usually bilateral without creatine kinase elevation

Less Common: Myopathy (~1 in 10,000 patients per year)
- Characterized by Unexplained muscle pain or weakness, accompanied by creatine kinase concentration > 10 times the upper limit of normal."

Rare: Rhabdomyolysis (~1 in 100,000 patients per year)
- Characterized by "creatine kinase concentration typically >40 times the upper limit of normal, which can cause myoglobinuria and acute renal failure.

Other Signs or Symptoms
- Transaminase elevation (very rare) and worsening glycemia (more likely with high-potency statins).
- There is no evidence that statins affect cognition.

Journal of Clinical Lipidology (2022) 16, 361–375

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2018 AHA/ACC Cholesterol Guidelines:
No Routine CPK Monitoring; But Check in Those with Suspected Myositis

III: No Benefit / C-LD	In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.
I / C-LD	In patients treated with statins, it is recommended to measure creatine kinase levels in individuals with severe statin-associated muscle symptoms, objective muscle weakness, and to measure live transaminases (aspartate aminotransferase, alanine aminotransferase) as well as total bilirubin and alkaline phosphatase (hepatic panel) if there are symptoms suggesting hepatotoxicity.

Adapted from Grundy SM, Stone NJ et al. 2018 AHA-ACC-Multi-Society Cholesterol Guidelines

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Statin Intolerance Definition

Statin intolerance
- ≥1 adverse effect associated with statin use
- Resolves with dose reduction or discontinuation
- Minimum of 2 statins tried, at least 1 at lowest approved daily dose

Nocebo effect
Perceived negative symptoms experienced by patients when anticipating a treatment to be harmful

Complete intolerance
Inability to take statin at any lipid-lowering dose

Partial intolerance
Maximally tolerated statin dose fails to reach therapeutic target

Consider non-statin therapies

Alternative statin type

Intermittent dosing

Adjunctive non-statin therapies

Cheeley MK et al. *J Clin Lipidol.* 2022;16(4):361-375.

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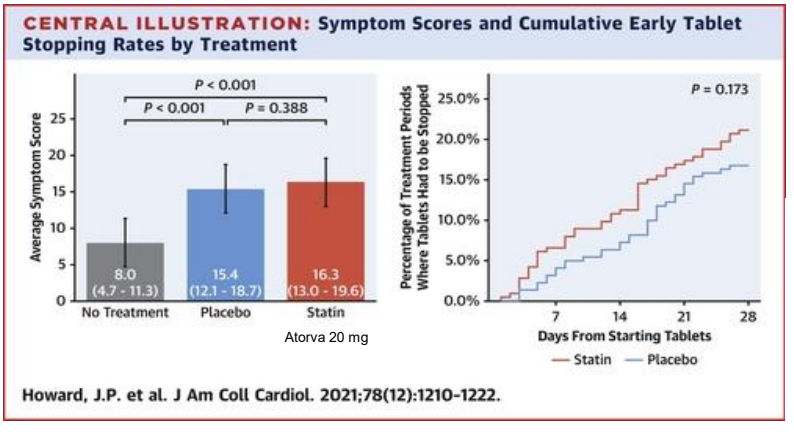
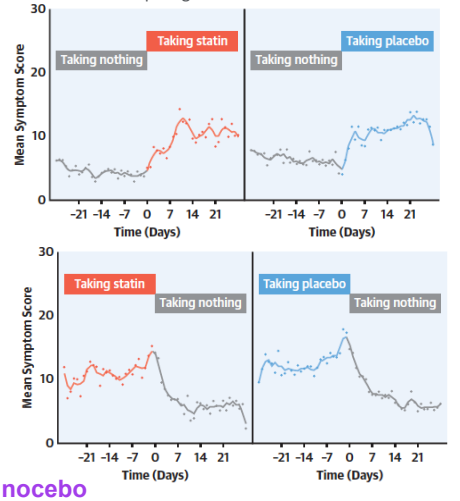
The SAMSON Trial=n=60 (49 Finished the Study)
(Self-Assessment Method for Statin Side-effects Or Nocebo)

-49 subjects got #12 1-month medication bottles
-49 subjects got #4 Atorva 20 mg, #4 placebo, #4 empty
-49 subject with an app had Daily symptom intensity measured and **nocebo ratio measured-**
ratio of sxs induced by statin that was also induced by placebo
Overall ratio 0.9

Nocebo – Perceived negative symptoms experienced by patients when anticipating a treatment to be harmful





Conclusion: The majority of symptoms caused by statin tablets were nocebo

Howard JP et al. *J Am Coll Cardiol.* 2021;78:1210-1222.

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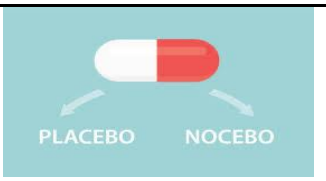

"Nocebo" Effect"

- For patients with statin-intolerance, it is reasonable to consider some proportion of statin-associated symptoms to the nocebo effect; however, this does not make such symptoms less clinically relevant.
- Regardless of the reason that patients will not take statins, continued ASCVD risk related to elevated atherogenic lipoproteins should be addressed with other therapies.

Cheeley MK et al. *Journal of Clinical Lipidology.* 2022;16, 361–375.

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Statin Roulette

Consider a Different Statin That Differs in Pharmacokinetics

CYP450 Drug Interactions
Remember 3A4 ones

-3A4: *lovastatin*, *simvastatin*, *atorvastatin* — **Lipophilic**

-2C9: fluvastatin (less so, rosuvastatin) — **Hydrophilic**

-Neutral:
pravastatin (sulfated)
pitavastatin (minimally)

Adapted from Grundy SM, Stone NJ et al. 2018 AHA-ACC-Multi-Society Cholesterol Guidelines

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How to Treat Statin Intolerance

- **Non-statin drug treatment:**
  Ezetimibe, bile acid resins, PCSK9 inhibitors, bempedoic acid
- **Alternative day dosing:**
  Once a week (rosuvastatin)
  Three times a week (rosuvastatin, atorvastatin)
  Every other day
  Try all available statins, including pravastatin, fluvastatin, pitavastatin
- **CoQ10 not found to be beneficial in clinical trials**
- **Vitamin D replacement (if < 15 ng/mL), may be helpful**

Lloyd-Jones DM, et al. *JACC.* 2016;68:92-125.

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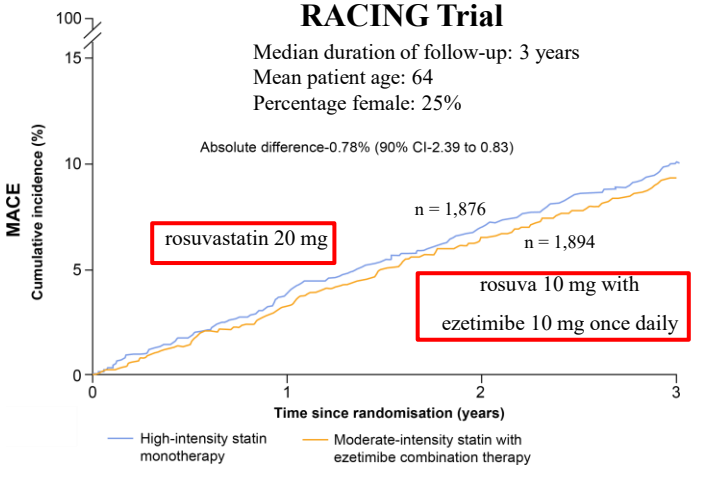
RACING Trial: Moderate Intensity Statin + Ezetimibe (Rosuvastatin 10 + Ezetimibe 10) vs High Intensity Statin (Rosuvastatin 20 mg) in Patients with ASCVD



- Among patients with ASCVD, moderate-intensity statin with ezetimibe combination therapy was non-inferior to high-intensity statin monotherapy for the 3-year composite outcomes
- LDL-C <70 mg/dL at 1, 2, and 3 years were observed in 73%, 75%, and 72% of patients in the combination therapy group, and 55%, 60%, and 58% of patients in the high-intensity statin monotherapy group (all p<0·0001).
- Discontinuation or dose reduction of the study drug by intolerance was observed in 4.8% in combination therapy group and 8.2% with high-intensity statin (p<0.0001).

Adapted from Kim B-K et al. Lancet 2022; 400: 380–90

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Take Home Points – Statin Therapy

- Statins remain underutilized
- Poor adherence is associated with poor outcomes
- Statin intensity matters
- Monitoring of statin therapy is important
- Statin intolerance may not be what you think it is

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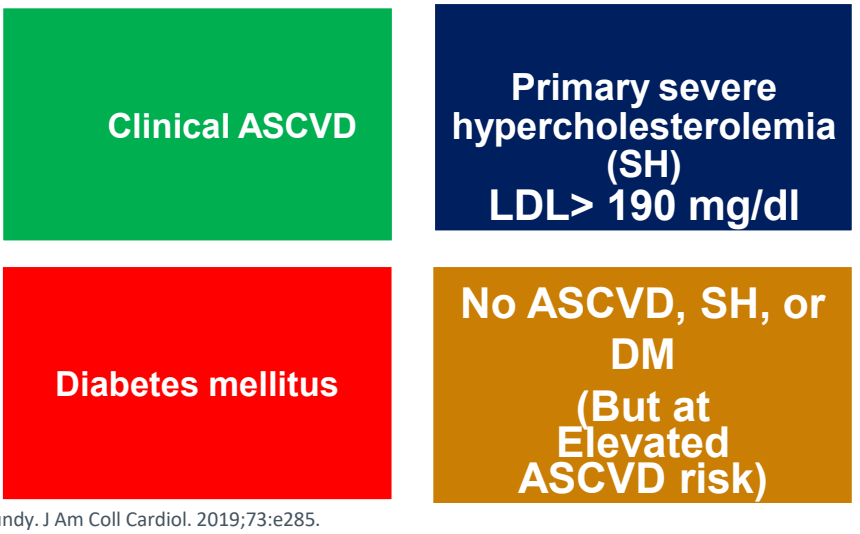
4 Key Groups Warranting LDL-C Lowering Therapy

Across all guidelines, statins remain 1st line pharmacological therapy for LDL-C lowering



Adapted from Grundy. J Am Coll Cardiol. 2019;73:e285.

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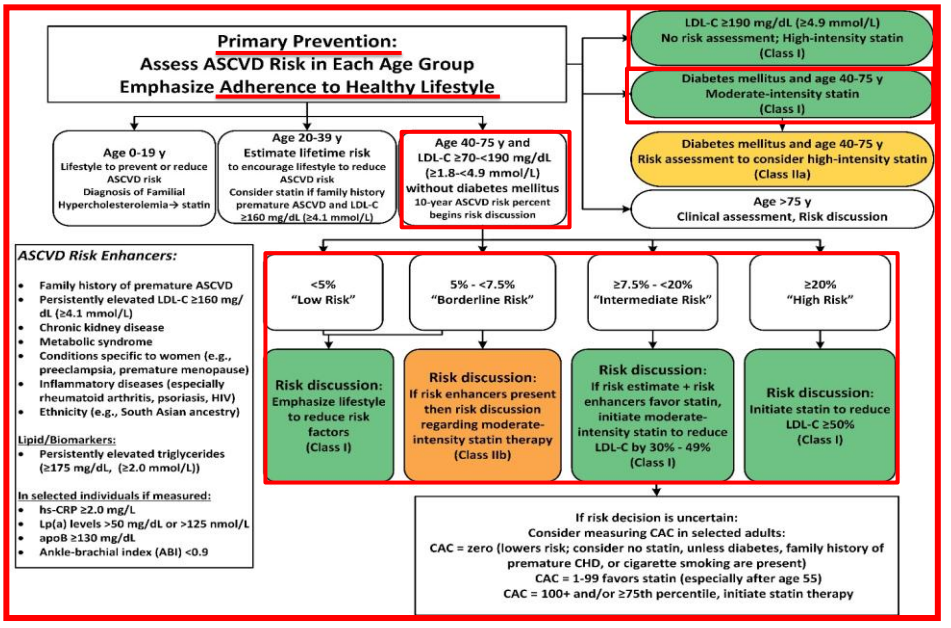
2018 Cholesterol Guidelines: Primary Prevention



Grundy SM, et al. *J Am Coll Cardiol*. 2018 Nov 8. pii: S0735-1097(18)39034-X.; Grundy SM et al. *Circulation*. 2018 Nov 10:CIR0000000000000625.

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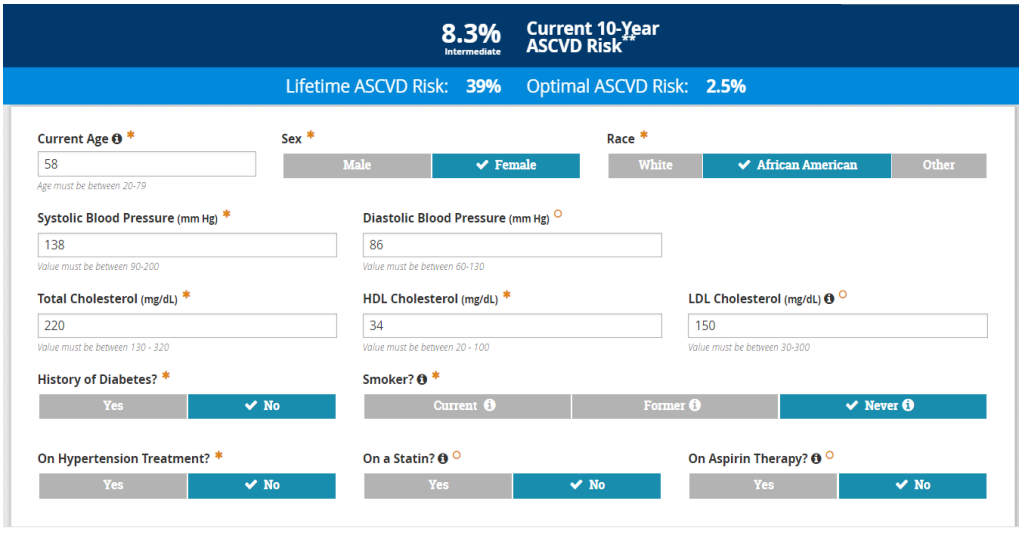
ASCVD Risk Estimator-2013 Pooled Cohort Equation



http://tools.acc.org/ASCVD-Risk-Estimator/

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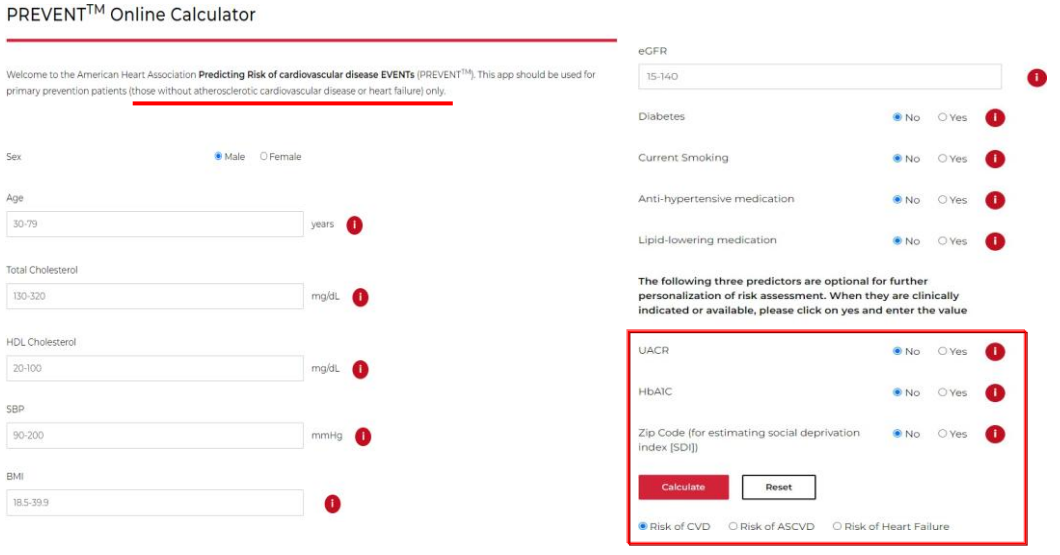
NEW PARADIGM FOR CVD RISK: PREVENT™

https://professional.heart.org/prevent

Predicting Risk of CVD EVENTs Calculator



Khan SS et. al. *Circulation* 2023

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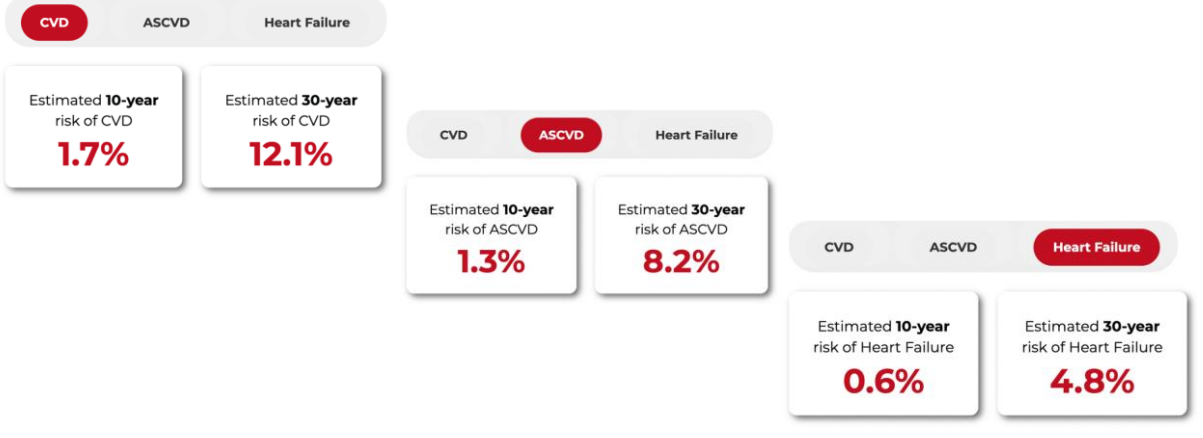
Predicting Risk of CVD EVENTs Calculator

PREVENT RISK CALCULATOR

The American Heart Association PREVENT™ Online Calculator



Khan SS et. al. *Circulation* 2023

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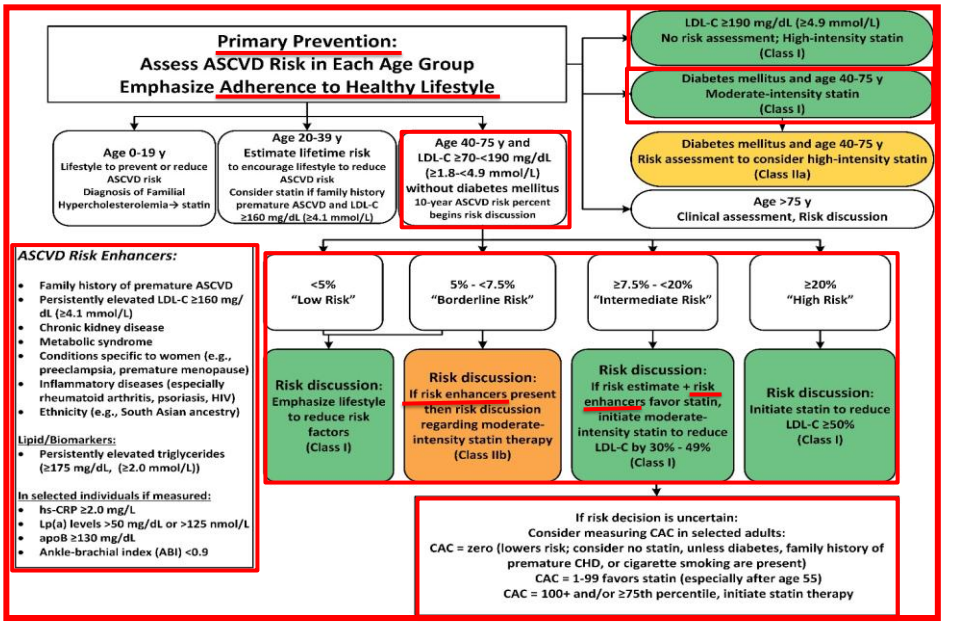
2018 Cholesterol Guidelines: Primary Prevention



Grundy SM, et al. *J Am Coll Cardiol.* 2018 Nov 8. pii: S0735-1097(18)39034-X.; Grundy SM et al. *Circulation.* 2018 Nov 10:CIR0000000000000625.

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Role of Coronary Calcium Score (CAC) in Lipidology

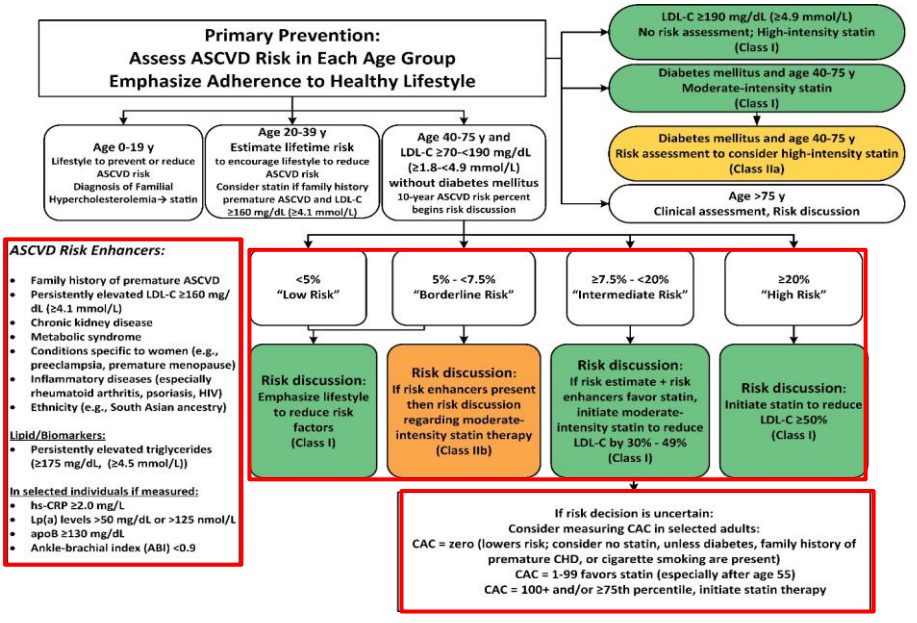
When on the fence use ASCVD Risk Estimate + CAC Score →

Using 10-year ASCVD risk estimate plus coronary artery calcium (CAC) score to guide statin therapy				
Patient's 10-year atherosclerotic cardiovascular disease (ASCVD) risk estimate:	<5%	5-7.5%	>7.5-20%	>20%
Consulting ASCVD risk estimate alone	Statin not recommended	Consider for statin	Recommend statin	Recommend statin
Consulting ASCVD risk estimate + CAC				
If CAC score =0	Statin not recommended	Statin not recommended	Statin not recommended	Recommend statin
If CAC score >0	Statin not recommended	Consider for statin	Recommend statin	Recommend statin
Does CAC score modify treatment plan?	✗ CAC not effective for this population	✓ CAC can reclassify risk up or down	✓ CAC can reclassify risk up or down	✗ CAC not effective for this population

Greenland, P. et al. *J am Coll Cardiol.* 2018;72(4):434-447.

46

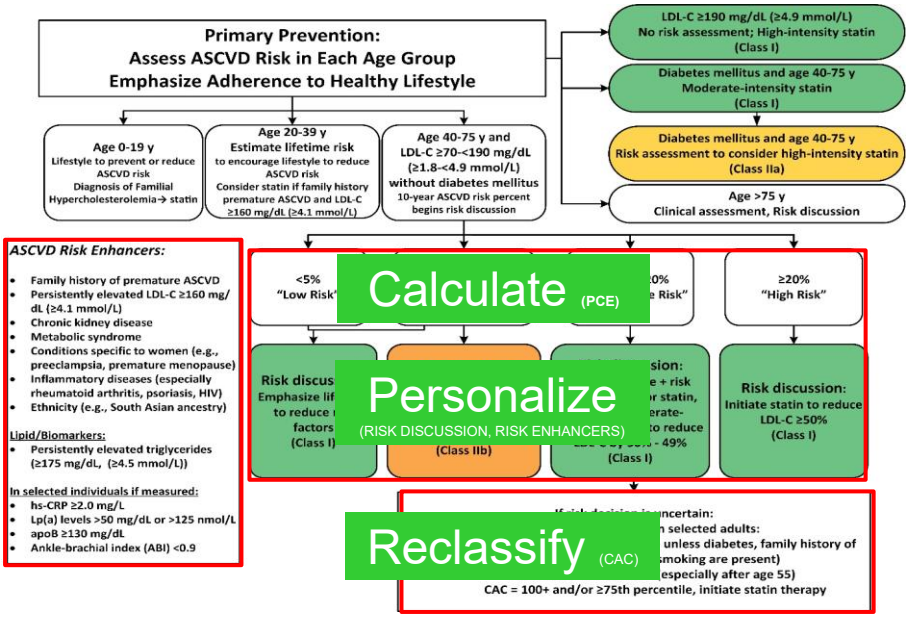
2018 Cholesterol Guidelines: Putting It All Together-CPR



Grundy SM, et al. *J Am Coll Cardiol*. 2018 Nov 8. pii: S0735-1097(18)39034-X.; Grundy SM et al. *Circulation*. 2018 Nov 10:CIR0000000000000625.

47

2018 Cholesterol Guidelines: Putting It All Together-CPR



Grundy SM, et al. *J Am Coll Cardiol*. 2018 Nov 8. pii: S0735-1097(18)39034-X.; Grundy SM et al. *Circulation*. 2018 Nov 10:CIR0000000000000625.

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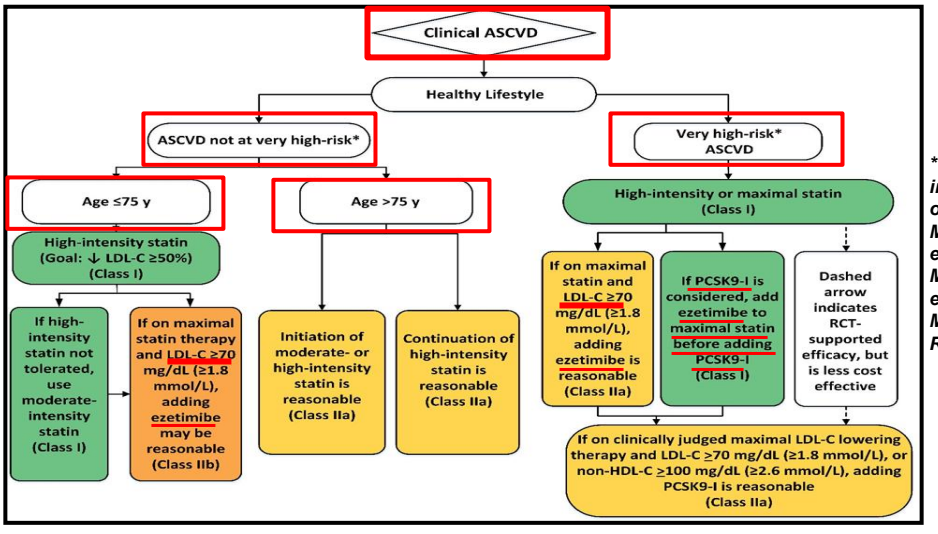
Secondary Prevention of ASCVD



**Very high risk includes a history of 2 or more MAJOR ASCVD events or 1 MAJOR ASCVD event and MULTIPLE HIGH-RISK conditions.*

Grundy SM, et al. *J Am Coll Cardiol*. 2018 Nov 8. pii: S0735-1097(18)39034-X.; Grundy SM et al. *Circulation*. 2018 Nov 10:CIR0000000000000625.

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Very High-Risk ASCVD Patients*

** ≥2 MAJOR ASCVD Events*

** 1 MAJOR and MULTIPLE HIGH-RISK CONDITIONS*

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

Very high risk includes a history of 2 or more MAJOR ASCVD events or 1 MAJOR ASCVD event and MULTIPLE HIGH-RISK conditions.

Grundy SM, et al. J Am Coll Cardiol. 2018 Nov 8. pii: S0735-1097(18)39034-X.; Grundy SM et al. Circulation. 2018 Nov 10:CIR0000000000000625.

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Differences Between US Cholesterol Guidelines and European Dyslipidemia Guidelines[1,2]

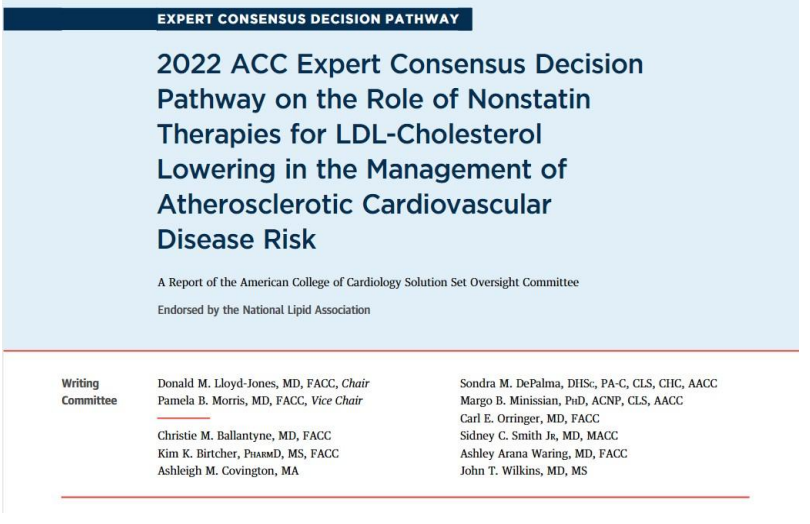
Characteristic	2018 AHA/ACC Guidelines	2019 ESC/EAS Guidelines
Risk scoring	10-year risk of CV event	10-year risk of fatal CVD
LDL-C goals		
Moderate risk	30%-50% reduction from baseline	LDL-C <100 mg/dL
→ High risk	≥50% reduction from baseline	LDL-C <70 mg/dL and ≥50% reduction from baseline
→ Very high risk	LDL-C <70 mg/dL and non-HDL-C <100 mg/dL	LDL-C <55 mg/dL and ≥50% reduction from baseline
Therapies included	Statins, ezetimibe, PCSK9is	Statins, ezetimibe, PCSK9is
Therapies not discussed	Bempedoic acid, inclisiran, lomitapide, evinacumab	Bempedoic acid and inclisiran are "future therapies"

1. Grundy SM et al. *J Am Coll Cardiol.* 2019;73:e285-e350.
2. Mach F et al. *Eur Heart J.* 2020;41:111-188.

51

Updated Recommendations for LDL-C Lowering

August 26th, 2022 →


EXPERT CONSENSUS DECISION PATHWAY

2022 ACC Expert Consensus Decision Pathway on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk

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

Endorsed by the National Lipid Association

Writing Committee

Donald M. Lloyd-Jones, MD, FACC, *Chair*
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Carl E. Orringer, MD, FACC
Sidney C. Smith Jr, MD, MACC
Ashley Arana Waring, MD, FACC
John T. Wilkins, MD, MS

Lloyd-Jones D. et al. *J Am Coll Cardiol* 2022; 80:1366-1418.

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Secondary Prevention
% LDL-C Reduction vs LDL-C Target

CV Risk	Example	Target LDL Reduction
Very High	Multiple CV events **OR** Prior CV event + multiple risks (diabetes, smoking, etc.)	≥ 50% **AND** < 55 mg/dL
High	Prior CV event, but not very high risk **OR** 10-year CV risk ≥ 20%	≥ 50% **AND** < 70 mg/dL

Lloyd-Jones DM et al.J Am Coll Cardiol. 2022;80:1366–1418.

53

Secondary Prevention
% LDL-C Reduction vs LDL-C Target

CV Risk	Example	Target LDL Reduction
Very High	Multiple CV events **OR** Prior CV event + multiple risks (diabetes, smoking, etc.)	≥ 50% **AND** < 55 mg/dL
High	Prior CV event, but not very high risk **OR** 10-year CV risk ≥ 20%	≥ 50% **AND** < 70 mg/dL
Intermediate	10-year CV risk 7.5% to < 20%	≥ 30% **AND** < 100 mg/dL

J Am Coll Cardiol. 2022;80:1366–1418

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ASCVD at Very High Risk for Secondary Prevention

- In view of evidence demonstrating CV outcomes benefits of LDL-C to lower levels, new lower LDL-C threshold of 55 mg/dL for addition of non-statin therapies.
  - IMPROVE-IT treatment group: 54 mg/dL
  - FOURIER/ODYSSEY Outcomes: 30 mg/dL

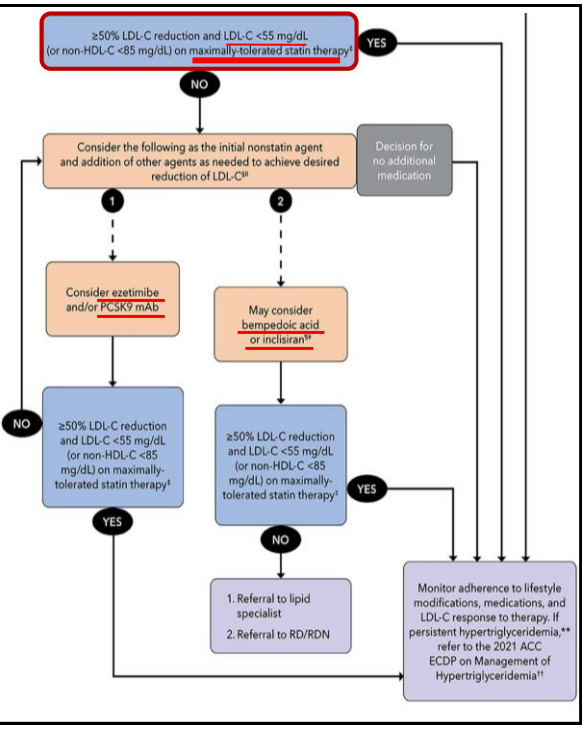

Fig 2a. Jones D.L. et al. *J Am Coll Cardiol* 2022; 80:1366-1418.

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Objectives

1) Review the most recent cholesterol updated guideline on LDL-C thresholds for treatment including the newer 2022 LDL-C target for the very-high risk patient.

2) **Review currently available "newer" non-statin cholesterol-lowering therapies and their roles for LDL-C Reduction.**

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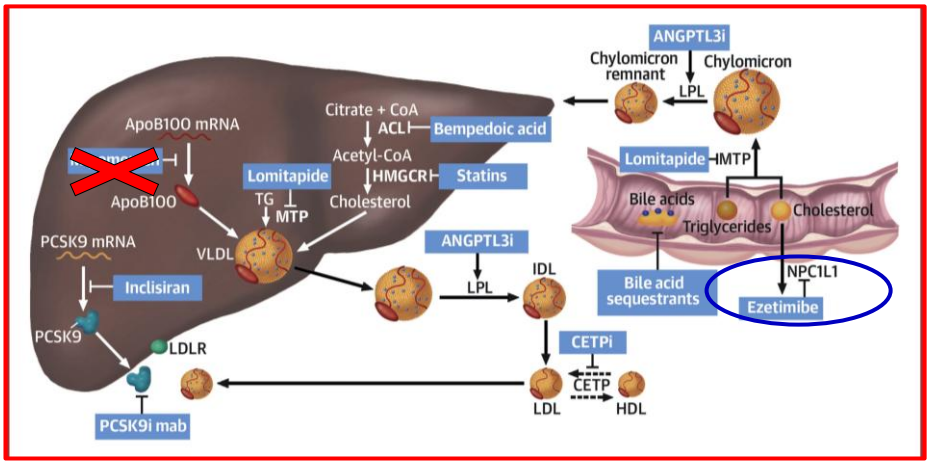
Ezetimibe



Nurmohamed, *et al. JACC*. 77:1564-75, 2021

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Ezetimibe (*Zetia*)

- Cholesterol absorption inhibitor
  - Blocks the Nieman Pick C1 like 1 (NPC1L1) protein in the jejunal brush border
  - Reducing cholesterol absorption which leads to reduced delivery of cholesterol to the liver and subsequent upregulation of LDL receptors
- Indicated as an adjunctive therapy in patients with hypercholesterolemia
- Lowers LDL-C by 18-25%
- Small reductions in CV outcomes, better outcomes in those w diabetes?
- Side Effects: clinically almost unheard of!
- Dosing: 10mg daily, available as combination pills with other agents (statins, bempedoic acid)
- Cost Conscious (Good Rx $31.85 for 90-10 mg)-9/13/25

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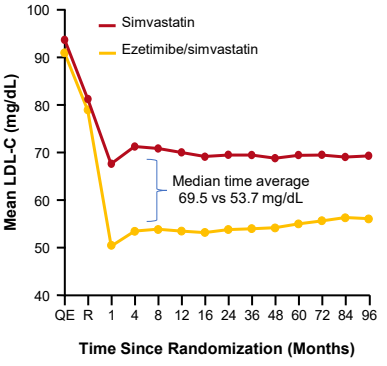
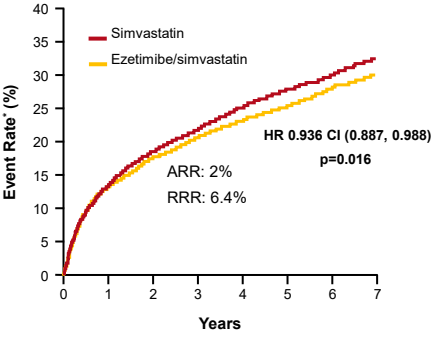
Impact of Ezetimibe in ASCVD: IMPROVE-IT

18,144 ACS patients randomized to simvastatin (40 mg QHS) or simvastatin/ezetimibe (40 mg/10 mg QHS) for 7 years





*Composite of CV death, MI, unstable angina, coronary revascularization, or stroke

Cannon CP, et al. NEJM 2015;372:2387-2397

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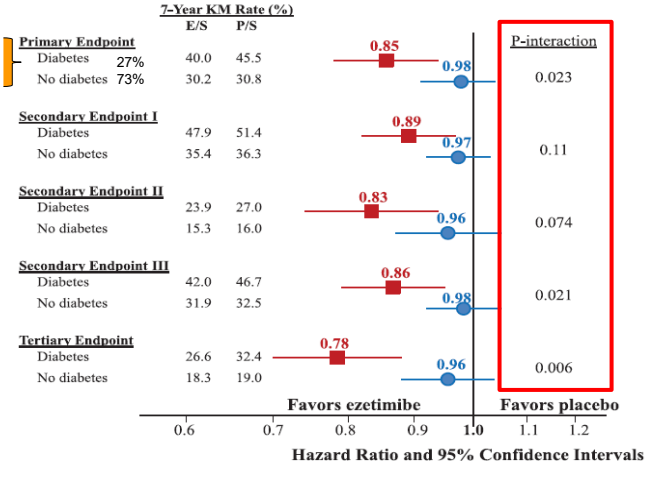
IMPROVE-IT: Composite Efficacy Outcomes Stratified by Treatment and Pre-Specified Diabetes Status

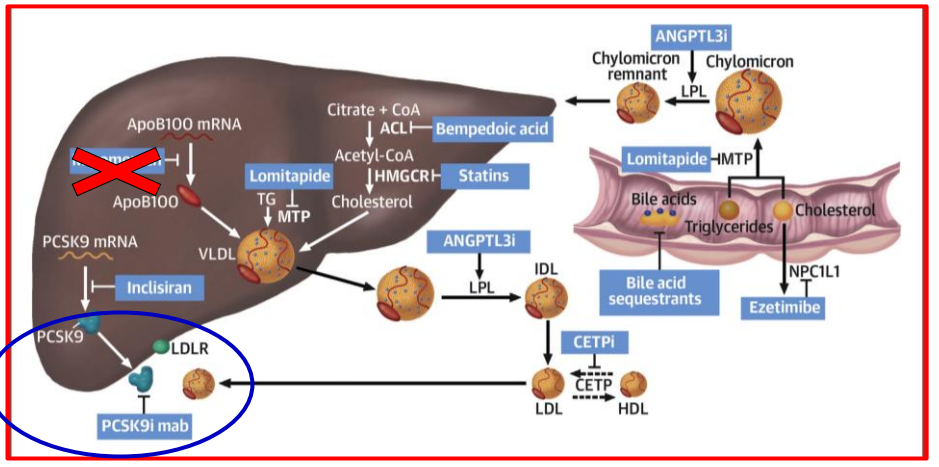
CV death, Major coronary event Stroke



Giugliano RP et al, *Circulation* 137:1571, 2018

60

PCSK9 Inhibitors



Nurmohamed, *et al. JACC*. 77:1564-75, 2021

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PCSK9 Inhibitors

- Are Monoclonal antibodies that inhibit PCSK9, a protein which normally helps degrade LDL-C receptors on the surface of the liver. With more LDL-C receptors, there is an increased clearance of LDL-C.
- ↓ LDL-C by 40-70%: when used in addition to maximally tolerated statin therapy and in statin-intolerant patients.
- Reduces ASCVD events.
- Indicated as an adjunctive therapy in patients with hypercholesterolemia and ASCVD or FH
- Well tolerated and safe even with very low LDL-C levels
  - Side effects: injection site reactions, rhinitis
- Dosing:
  - Alirocumab (*Praluent*): 75-150 mg SC every 2 weeks
    300 mg SC every 4 weeks
  - Evolocumab (*Repatha*): 140 mg SC every 2 weeks
    420 mg SC every 4 weeks

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PCSK9 Monoclonal Antibody Trials: Outcome Trial Characteristics

Design Feature	FOURIER	ODYSSEY Outcomes
Patient Population	Stable ASCVD: MI, stroke, PAD; median 3 years since index event	Post ACS; median 2.6 months since index event
N (% women)	27,564 (25)	18,294 (25)
Mean age (years)	63	58
LDL-C entry criterion	≥ 70 mg/dL	≥ 70 mg/dL
Baseline LDL-C	92 mg/dL	87 mg/dL
High intensity statin	69%	89%
Ezetimibe	5%	3%
PCSK9 dosing	Evolocumab 140 mg Q 2 weeks or 420 mg Q 4 weeks	Alirocumab 75 mg or 150 mg Q 2 weeks; titrated to target LDL-C 25-50 mg/dL
Follow-up	2.2 years	2.8 years (44% ≥3 years)
Primary Endpoint	MACE: CV death, MI, stroke, UA, coronary revasc	MACE: CHD death, MI, ischemic stroke, UA
	Sabatine M, et al. NEJM 2017	Schwartz G, et al. NEJM 2018

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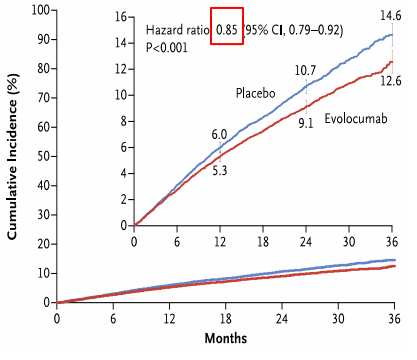
PCSK9 Inhibitors – CV Outcome Trials

FOURIER:

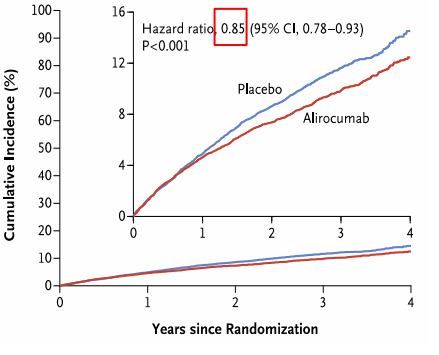
- 27,564 patients with h/o Stable ASCVD and LDL-C ≥70
- LDL-C 92 vs 30 mg/dl with Evolocumab



Sabatine et al. *NEJM*, 2017.

ODYSSEY OUTCOME:

- 18,924 patients with h/o ACS and LDL-C ≥70
- LDL-C 103 vs 66 mg/dl with Alirocumab

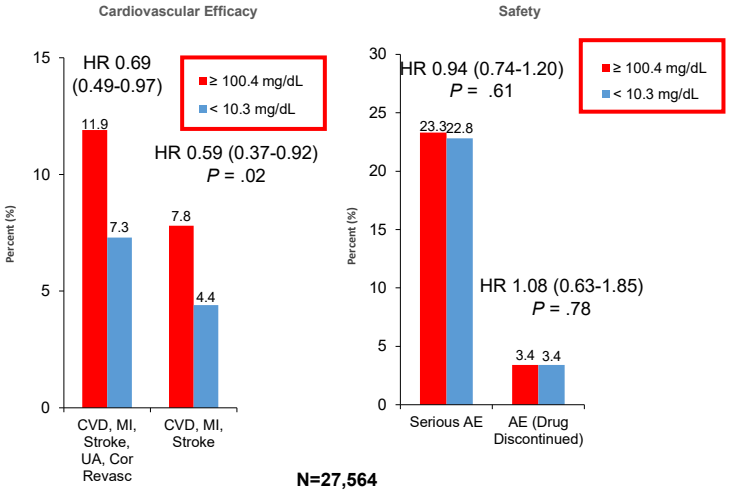


Schwartz et al. *NEJM*, 2018.

64

FOURIER Trial:

Efficacy and Safety in Patients Achieving an LDL-C <10 mg/dL



N=504 patients achieved LDL-C <10 mg/dL

Giugliano RP, et al. Lancet 2017;390:1962-1971

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PCSK9 Inhibitors: Where Do They Fit In?

- Severe or difficult to treat hypercholesterolemia
- Statin intolerant patients
- Secondary prevention
- Patients with elevated lipoprotein(a)?
- What about cost?-more cost conscious with recent reduction in price, has savings card, still $$ without insurance

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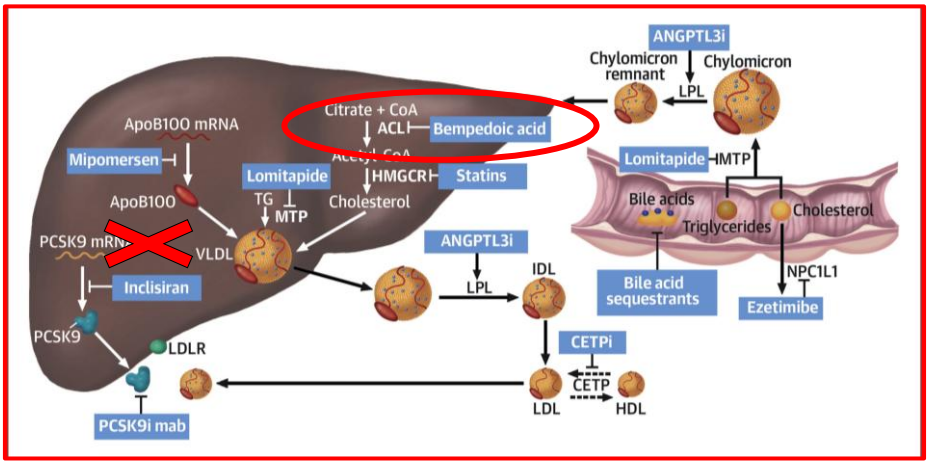
Bempedoic Acid



Nurmohamed, *et al. JACC*. 77:1564-75, 2021

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Bempedoic Acid (BA) (*Nexletol*)

- Inhibits the Adenosine Citrate Lyase (ACL) enzyme 1-step upstream from HMG-CoA reductase in the cholesterol biosynthesis pathway.
- Not the rate-limiting step in cholesterol synthesis so effects are < statins.
- Indicated as an adjunctive therapy in patients with hypercholesterolemia and ASCVD or FH, both primary and secondary prevention.
- Lowers LDL-C by 16% w statin up to 24% w/o statin and 35% with ezetimibe.
- CV outcome data (CLEAR Outcomes) met its primary endpoint in patients who were statin-intolerant.
- Side effects: ↑ uric acid/gout, tendon rupture (achilles), inc LFTs.
- The specific isozyme (ACSVL1), which converts BA into an active drug, is not present in skeletal muscle, so it should not be associated with myalgia.
- Lowers hs-CRP, but has no effect on glucose (unlike statins).
- Dosing: 180 mg po daily
  - Also available in combination with ezetimibe (Nexlizet 180mg/10 mg)
  - Has savings card but Good Rx price $231 per month (Publix 9/13/25)

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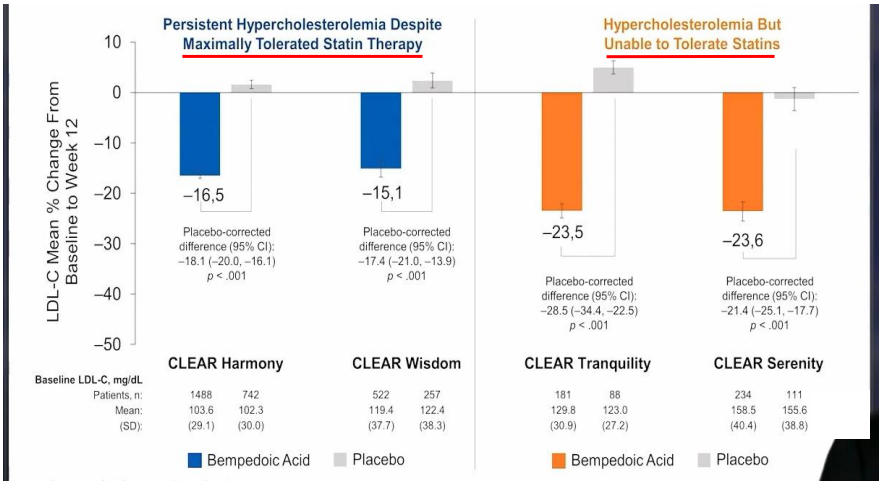
LDL-Lowering with Bempedoic Acid



Ray et al, *NEJM*, 2017
Goldberg et al, *JAMA*, 2019
Ballantyne et al, *Atherosclerosis*, 2018
Banach et al, *J Am Heart Assoc*, 2019

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

S.E. Nissen, A.M. Lincoff, D. Brennan, K.K. Ray, D. Mason, J.J.P. Kastelein, P.D. Thompson, P. Libby, L. Cho, J. Plutzky, H.E. Bays, P.M. Moriarty, V. Menon, D.E. Grobbee, M.J. Louie, C.-F. Chen, N. Li, L.A. Bloedon, P. Robinson, M. Horner, W.J. Sasiela, J. McCluskey, D. Davey, P. Fajardo-Campos, P. Petrovic, J. Fedacko, W. Zmuda, Y. Lukyanov, and S.J. Nicholls, for the CLEAR Outcomes Investigators*

ABSTRACT

BACKGROUND

Bempedoic acid, an ATP citrate lyase inhibitor, reduces low-density lipoprotein (LDL) cholesterol levels and is associated with a low incidence of muscle-related adverse events: its effects on cardiovascular outcomes remain uncertain.

SE Nissen et al. April 13, 2023 N Engl J Med 2023; 388:1353-1364

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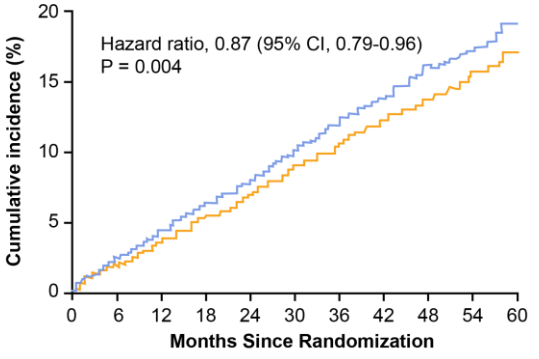
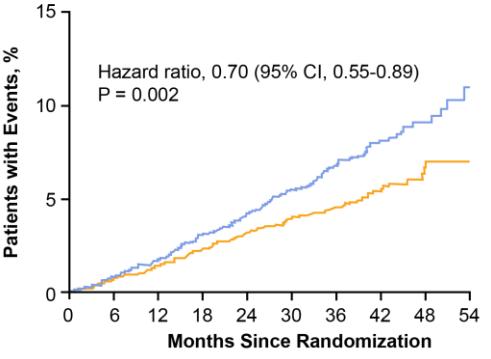
CLEAR Outcomes: Bempedoic Acid Reduced MACE

Inclusion criteria: Established ASCVD (2◦ prevention) or at high risk of developing ASCVD (1◦ prevention)
Documented statin intolerance: LDL-C ≥100 mg/dL on maximally tolerated lipid-lowering therapy



Main Analysis
N=13,970
Median follow-up 40.6 months

Nissen SE, et al. *N Engl J Med.* 2023;388(15):1353-1364.



Primary Prevention Analysis
N=4206
Median follow-up 39.9 months

Nissen SE, et al. *JAMA.* 2023;330(2):131-140.

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CLEAR Outcomes: Select Adverse Events in Total Trial Population

AE, %	Bempedoic Acid (n = 7001)	Placebo (n = 6964)
Serious treatment-emergent AE	25.2	20.8
AE leading to discontinuation	9.9	9.9
Any muscle disorder	12.8	13.9
New-onset diabetes	6.4	6.9
Elevated hepatic enzymes	4.5	2.6
Prespecified renal events	10.3	8.1
Gout	2.6	2.0
Cholelithiasis	2.5	2.0

Nissen SE. et al. JAMA. July 11, 2023; 330(2): 131-140.

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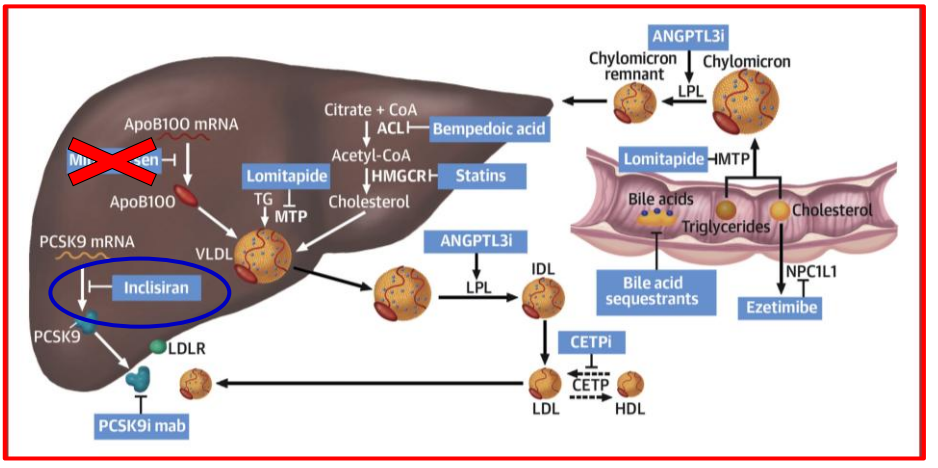
Inclisiran



Nurmohamed, *et al. JACC*. 77:1564-75, 2021

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Inclisiran (Leqvio)

- Mechanism of Action:
  - Synthetic, small interfering RNA (siRNA) that inhibits translation of PCSK9. Binds to mRNA precursor of PCSK9 which undergoes degradation not allowing PCSK9 to be formed.
  - Leads to upregulation of LDL-receptors and increased clearance of LDL-C
- Lowers LDL-C by ~50-55%
- Indicated on July 2021 as an adjunctive therapy in patients with hypercholesterolemia and ASCVD or HeFH
- Recently updated 7/10/23 for primary prevention as adjunct to diet and statin Rx for patient's w/o CV events but at increased risk of heart disease.
- Updated on 7/31/25 as a first-line monotherapy to reduce LDL-C in adults with hypercholesterolemia in addition to diet and exercise (w/o statin therapy).
- Side Effects: injection site reaction, arthralgia, UTI, diarrhea, bronchitis, extremity pain, dyspnea.
- Dosing: 284 mg SC injection administered by a HCP at an initial dose, at 3 months, and then twice a year dosing.
- Pharmacodynamics: no dose adjustment for renal/hepatic impairment.

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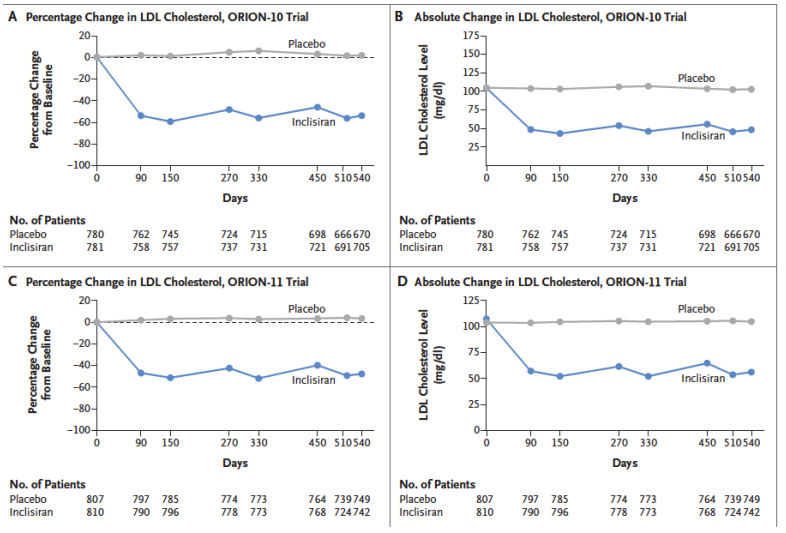
Inclisiran-Favorable Reductions in LDL-C



Ray et al. *NEJM* 2020

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Where Does Inclisiran Fit In?

- Similar indications to PCSK9 inhibitors
- Well tolerated
- Every 6-month dosing, after initial 2 doses separated by 3 months, but by HCP (“buy and bill”)
- Awaiting ORION-4 Outcome data in late 2026/2027
- Consider:
  - instead of PCSK9i?
  - for patient's intolerant to PCSK9i?
  - For Medicare patients (under Medicare B)?

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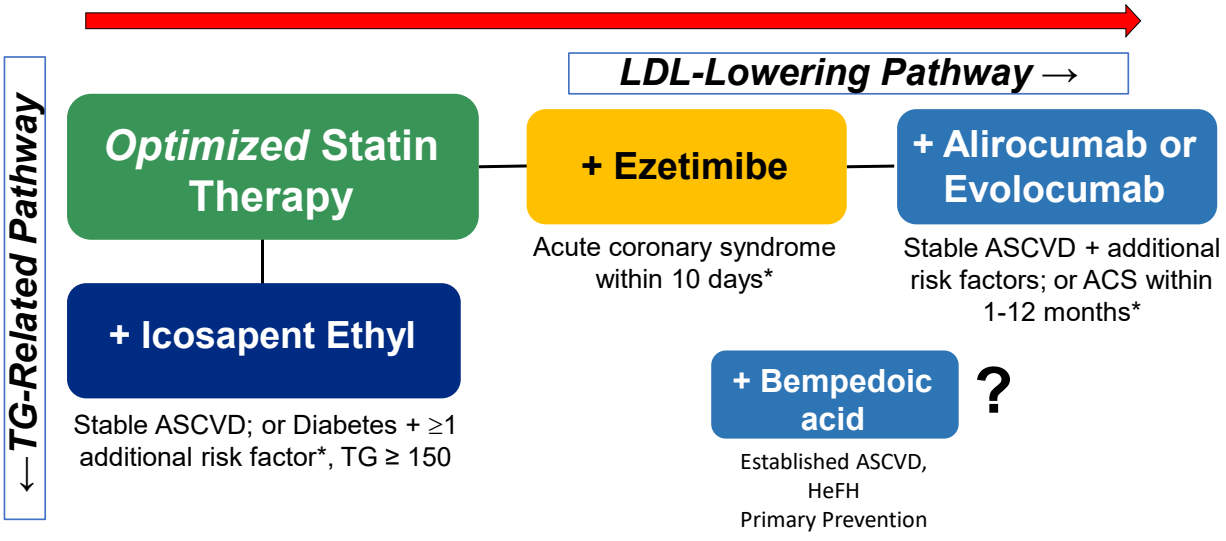
Statin Therapy Adjuncts *Proven* to Reduce ASCVD



*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.

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Take Home Points

- **For LDL-C, Lower for longer is better for CV Outcomes.**
- **Management of patients unable or unwilling to take statins is challenging and regardless of a nocebo effect, high-risk patients need alternative Rxs.**
- **Very High Risk ASCVD patients require aggressive LDL-C lowering to < 55 mg/dL and often require multiple classes of lipid-lowering Rx.**
- **PCSK9 monoclonal antibodies when added to statins and ezetimibe reduce ASCVD events and may reduce mortality in very high-risk patients.**
- **Bempedoic acid reduces LDL-C and may provide an oral alternative to statins in statin-intolerant patients for primary and secondary prevention.**
- **The data supports the incremental benefit of LDL-C lowering with ezetimibe, bempedoic acid, and PCSK9 inhibition in high and very high-risk patients, including those with statin intolerance.**
- **New Lipid Guidelines should be coming out in 2026.**

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And What About Lp(a)

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Objectives

1) Review the most recent cholesterol updated guideline on LDL-C thresholds for treatment including the newer 2022 LDL-C target for the very-high risk patient.

2) Review currently available "newer" non-statin cholesterol-lowering therapies and their roles for LDL-C Reduction.

3) **Learn When and Why You Should Measure Lp(a) understanding its relationship to CV Disease.**

4) **Review what you can currently do for Lp(a) elevation and the Clinical Trials Currently in Progress.**

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ARS Question 2

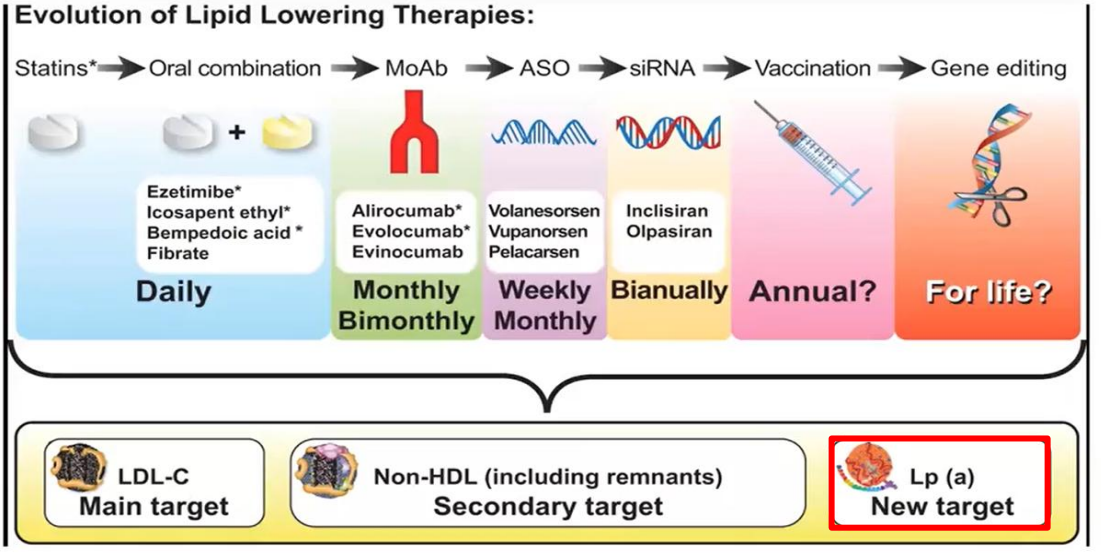
- A 41-year-old male is very concerned of his own personal risk as his father died of a heart attack at age 47 and his father's brother, his uncle, had a stroke at age 36.
- He exercises 5 days a week and gets in 7500 steps a day, maintains a vegan diet, and has no significant medical issues.
- He has a BMI of 26, a BP of 126/72, an A1C of 4.8, and normal renal function and u/a.
- Recent labs: Total Chol 140, HDL 45, TG 130, Calculated LDL-69, non-HDL-C 95.
- He is on no medications.

ARS Question 2

What Would You Recommend?

A. Reassurance and no further testing
B. Draw Genetic testing for Familial
C. Hypercholesterolemia
D. Draw hs-CRP
E. Order a Coronary Calcium Score
F. Check Lp(a)

A New Era Of Lipid-Lowering Therapies

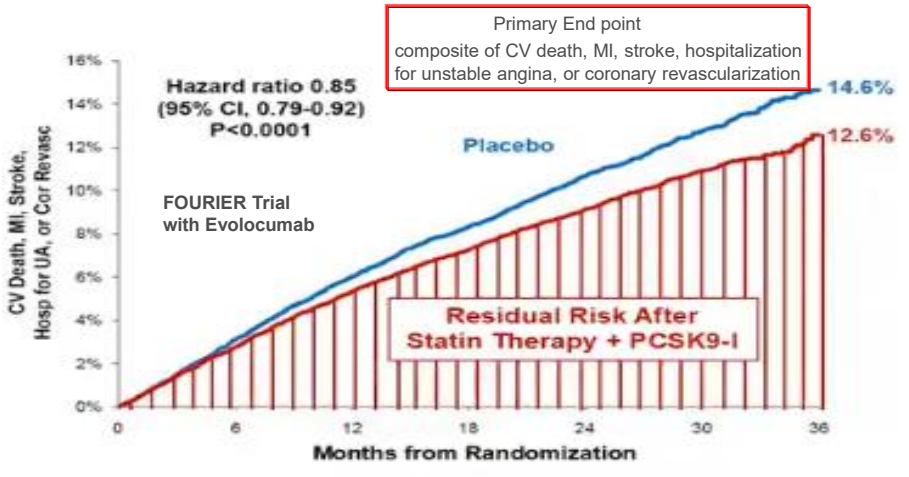


*Therapies Shown to decrease CV events

Tokgozoglu L., Libby P. Eur Heart Journal 2022;43(34):3198-3206.

83

Despite Significant ASCVD Risk Reduction with Statin + PCSK9 Use, Residual Risk Remains



Sabatine M. et al. N Engl J Med 2017; 376:1713-1722

84

The Multiple Facets of Residual Risk

Despite available treatments, residual risk for CV events persists in people with or at high risk for ASCVD

Type of residual risk	Inflammatory	Cholesterol	Thrombotic	Triglyceride	Lp(a)	Diabetes
Biomarker	hsCRP ≥ 2 mg/L	LDL-C ≥ 100 mg/dL	No simple biomarker	TG ≥ 150 mg/dL	Lp(a) ≥ 125 nmol/L	A1C Fasting glucose
Intervention	Targeted inflammation reduction	Targeted LDL-C/Apo B reduction	Targeted antithrombotic reduction	Targeted triglyceride reduction	Targeted Lp(a) reduction	SGLT2 inhibitors GLP-1 RAs
Trial evidence	CANTOS COLCOT LoDoCo2	IMPROVE-IT FOURIER SPIRE ODYSSEY	PEGASUS COMPASS THEMIS	REDUCE-IT	Ongoing	EMPA-REG CANVAS DECLARE CREDENCE LEADER SUSTAIN-6 REWIND

A1C = glycated hemoglobin; Apo B = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; GLP-1 RA = glucagon-like peptide-1 receptor agonist; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein a; SGLT2 = sodium glucose cotransporter 2; TG = triglyceride.

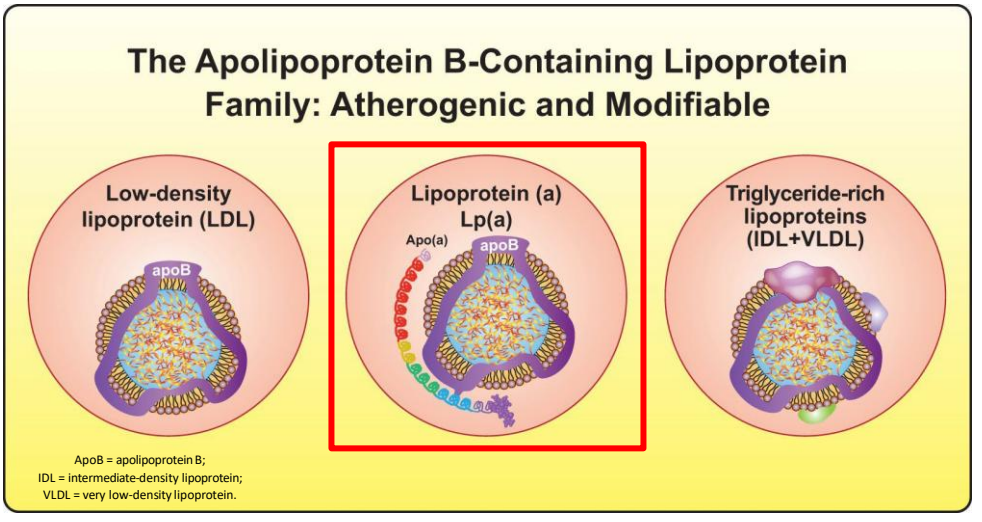
Adapted from Lawler PR et al. *Eur Heart J.* 2021;42(1):113-131.

85

What Is Lp(a)

86

Atherogenic ApoB-containing Lipoproteins

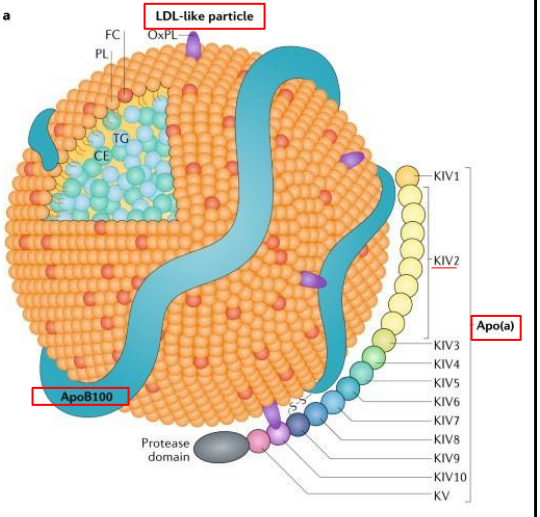


Tokgözoğlu L et al. *Eur Heart J*. 2022;43(34):3198-3208.

87

Lipoprotein(a) Structure

- Lp(a) is an LDL-like particle with apoprotein (a) on its surface covalently bound to apo B100
- Major lipoprotein carrier of pro-inflammatory and pro-calcific oxidized phospholipids (OxPL)
- Apo(a) is highly homologous to plasminogen interfering with the fibrinolytic system which normally breaks down clots
- The apo(a) part consists of 10 subtypes of kringle domain IV (KIV1-10), a kringle domain V (KV) and an inactive protease domain. KIV-2 repeats is inversely correlated with CV risk.



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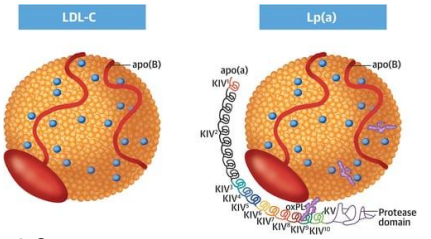
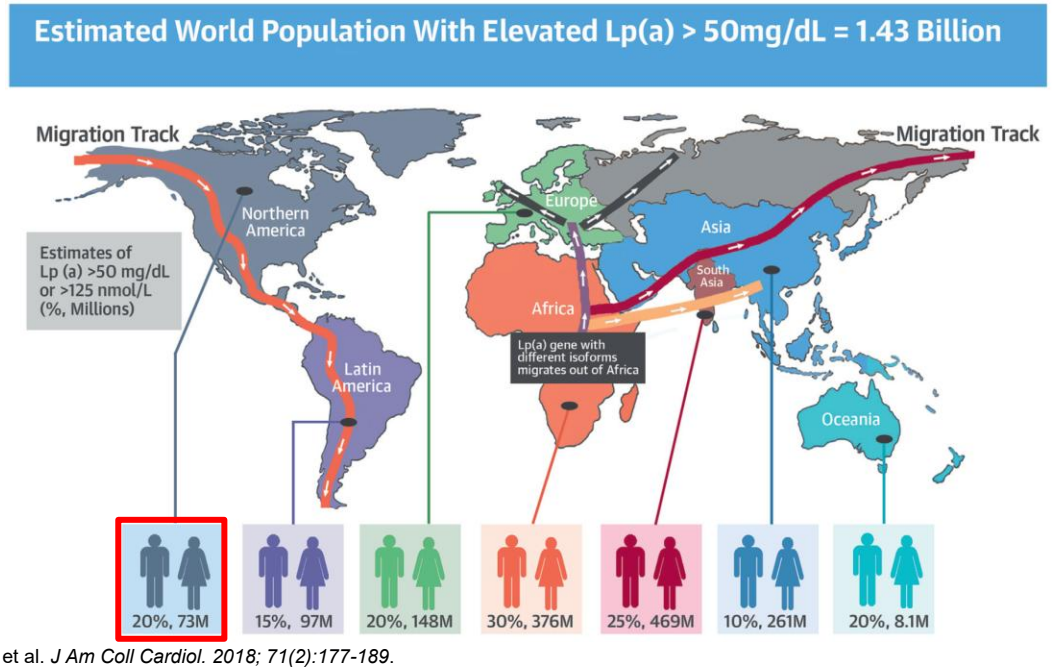
Lipoprotein A – Lp(a)



- 80-90% of Lp(a) is genetically determined and fully expressed by age 5 and then remains stable over one's lifetime
- Elevated Lp(a) occurs in 1 in 5 people globally (about 20%)[1]
- Elevated Lp(a) is currently the strongest single inherited risk factor for early CAD and aortic stenosis[1]
- Elevations in Lp(a) result in 2 to 4 times higher risk of CV events[1]
- High Lp(a) occurs in all ethnic groups
  - More common among African Americans and South Asians[2]
- Major landmark RCTs have shown that elevated Lp(a) is associated with less benefit from statin therapy and elevated Lp(a) is associated with higher residual CV risk

1. Wilson DP, et al. *J Clin Lipidol* 2019;13(3):374-392,
2. Grundy SM et al. *J Am Coll Cardiol* 2019;73(24):3234-3237

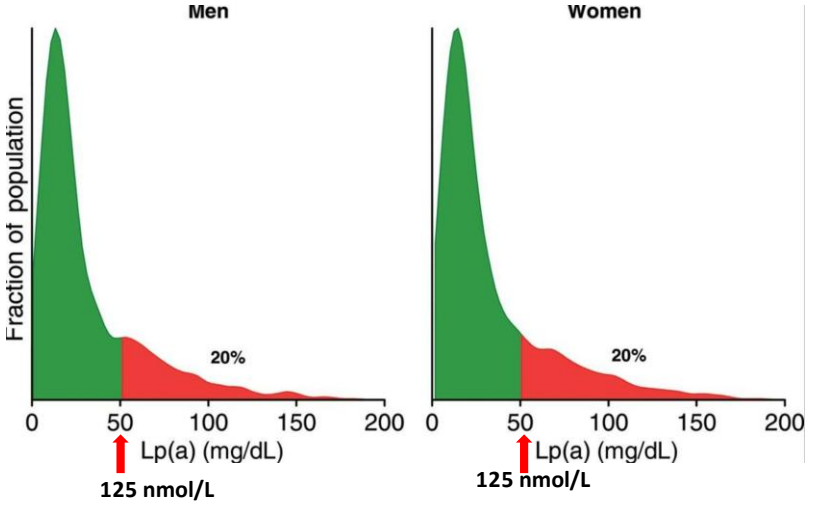
89



Tsimikas S. et al. *J Am Coll Cardiol. 2018; 71(2):177-189.*

90

Distribution of Lp(a) Levels in the General Danish Population



- Graphs are based on non-fasting fresh serum samples from ~3000 men and 3000 women from the Copenhagen General Population Study
- **Green**= levels <80th percentile
- **Red** = levels >80th percentile

Perhaps 1 in 5 in the Danish High Risk

Nordestgaard BG, et al.European Atherosclerosis Society Consensus Panel. Lipoprotein(a) as a cardiovascular risk factor: current status. *Eur Heart J*. 2010 Dec;31(23):2844-53.

91

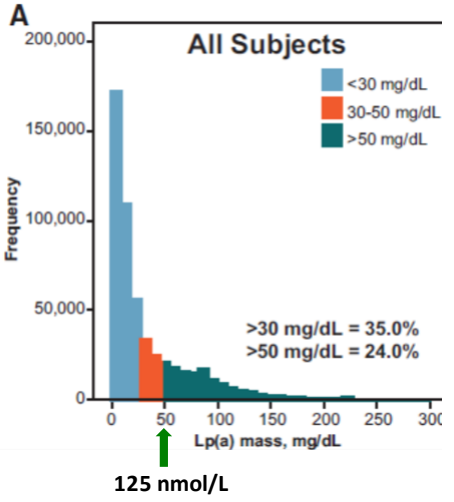
How Common Is Lp(a) Levels in a US Population

Particle conc >> Mass units

Lipoprotein(a) Cutoffs	nmol/L	mg/dL
-Normal(desirable):	<70	<30
-Intermediate Risk:	70-125	30-50
-High Risk:	>125	>50-125

N=531,144

M=255,542
F=265,601

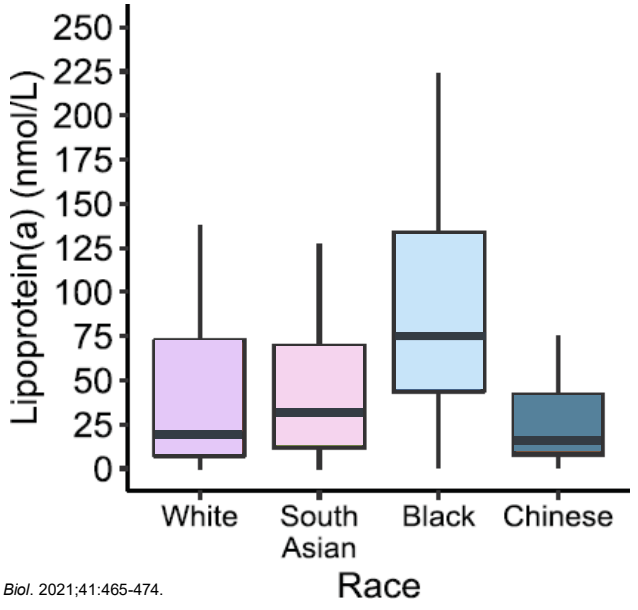


Perhaps 1 in 4 in the US High Risk

Varvel S. et al. Arteriosclerosis, Thrombosis, and Vascular Biology . Sept 2016 Vol 36, No. 11.pg 2239.

92

Ethnic Differences in Lp(a) Concentrations in the UK Biobank



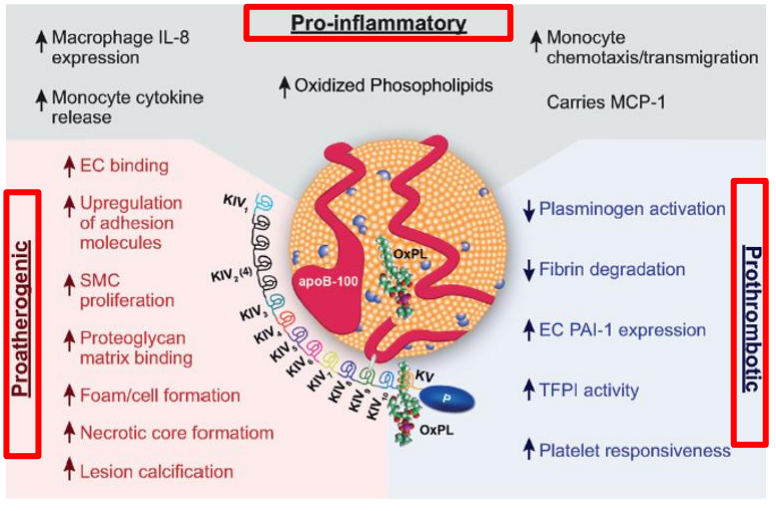
Patel AP et al. *Arterioscler Thromb Vasc Biol*. 2021;41:465-474.

93

Potential Mechanisms by Which Lp(a) Mediates ASCVD & Calcific Aortic Stenosis

Promotes CVD via 4 mechanisms:

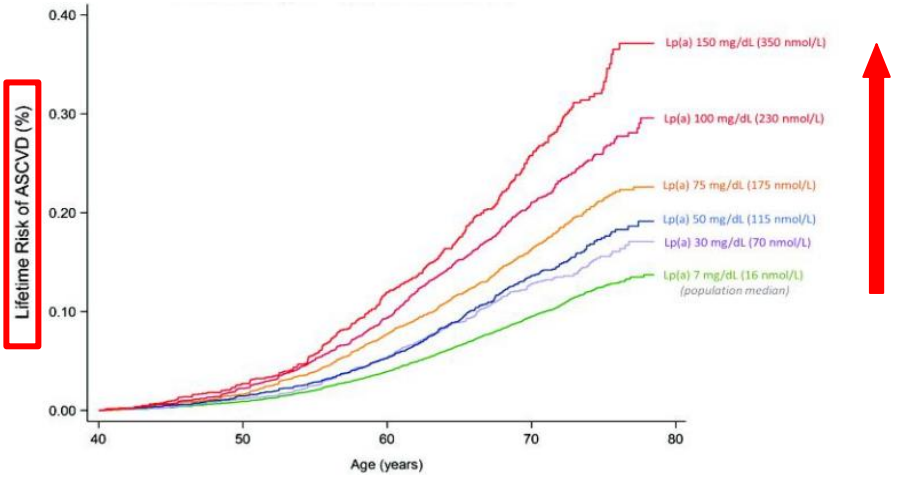
1. Vascular inflammation
2. Atherogenesis
3. Calcification
4. Thrombosis



Tsimikas S, *J Am Coll Cardiol* 2017;69:692–711

94

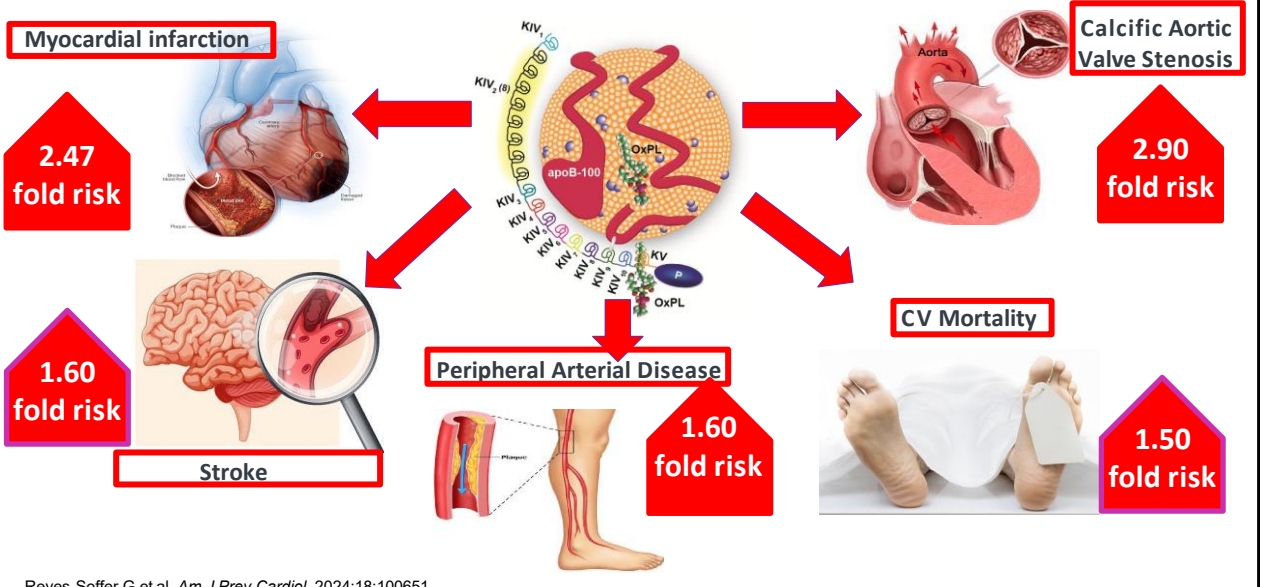
Lifetime Risk for Major CV Events Increases with Increasing Lp(a) Concentrations from UK Biobank



Kronenberg F. et al. Eur Heart Jnl (2022) 43; 3925-3946..

95

Lp(a) and Cardiovascular Disease (CVD) Risk



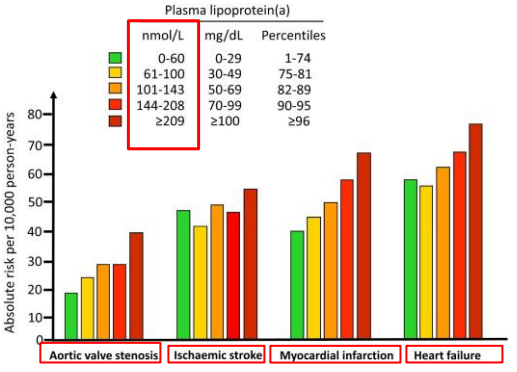
Reyes-Soffer G et al. *Am J Prev Cardiol*. 2024;18:100651.

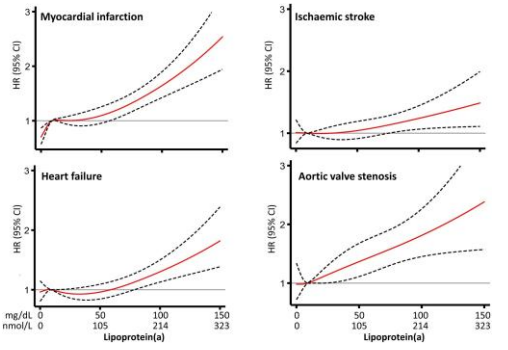
96

Risk of Clinical Outcomes by Lp(a) Concentration

- Increasing levels of Lp(a) concentration and absolute/relative risk:
  - Aortic valve stenosis
  - Ischemic stroke
  - Myocardial infarction
  - Heart failure

- MACE higher at Lp(a) >50 mg/dL, even when LDL-C levels were <70mg/dL.





Kronenberg F, et al. Eur Heart J. 2022 Oct 14;43(39):3925-3946.

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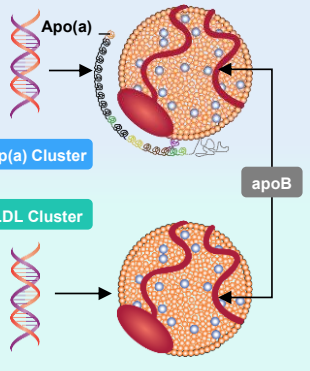
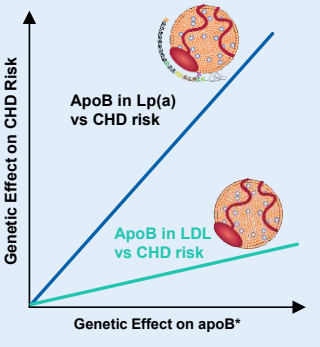
Lp(a) Is Approximately 6-fold More Atherogenic* Than LDL on a Per-particle Basis

Genetic variants that raise apoB by raising Lp(a)



Genetic variants that raise apoB by raising LDL

Mendelian Randomisation



*apoB attached to either an LDL or Lp(a) particle

- Both Lp(a) and LDL contain **one apoB molecule per particle**
- A study of UK Biobank data† identified genetic cluster variants (SNPs) associated with LDL or Lp(a) particles in plasma to determine their **relationship with CHD risk**
- Per 50 nmol/L increase in apoB in **Lp(a)** the **OR of increased CHD risk** was **1.28** (95% CI:1.24–1.33)
- Per 50 nmol/L increase in apoB in **LDL**, the **OR** was **1.04** (95% CI:1.03–1.05)

*Atherogenicity was defined as the difference in CHD risk per unit difference in Lp(a) or LDL particle number (molar concentration); †This study was principally based on the UK Biobank population (>502,000 UK residents of mainly European ancestry); a replication cohort, the CARDIoGRAMplusC4D (Coronary ARtery Disease Genome wide Replication and Meta-analysis [CARDIoGRAM] plus The Coronary Artery Disease Genetics] data set tested the generalizability of these findings.

Björnson E, et al. *J Am Coll Cardiol.* 2024;83:385–395.

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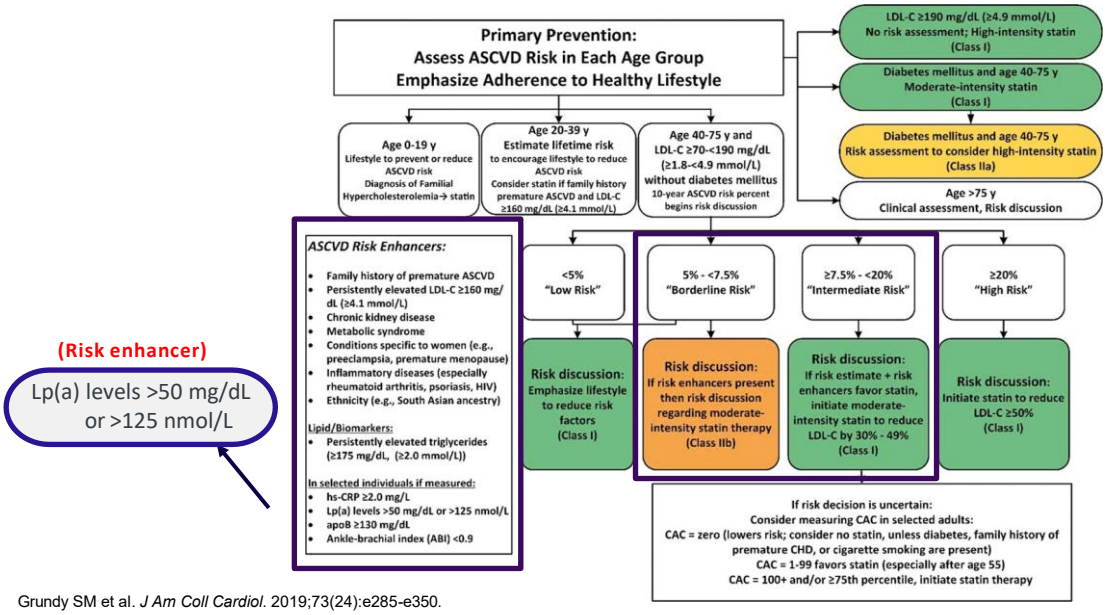
Lp(a) in Refinement of Risk Assessment



Grundy SM et al. *J Am Coll Cardiol*. 2019;73(24):e285-e350.

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Guideline and Consensus Recommendations for Lp(a) Measurement

In Whom Should Lp(a) Be Measured?

2024 NLA Scientific Statement	2022 EAS Lp(a) Consensus	2021 Canadian CV Society Dyslipidemia Guidelines	*2018 AHA/ACC Cholesterol Guidelines*	2019 ESC/EAS Dyslipidemia Guidelines
• **All adults** • **High-risk children** • **Cascade testing**	• **All adults** • In youth with hx ischemic stroke or family hx premature ASCVD or high Lp(a) and no other risk factors • **Cascade testing**	• **All individuals**, with initial screening	• If decision is made to measure Lp(a), an Lp(a) ≥50 mg/dL or ≥125 nmol/L **may be considered a risk-enhancing factor**	• **All adults**

In the absence of therapies substantially altering lipoprotein(a), a single accurate measurement of lipoprotein(a) molar concentration is an efficient method to inform CAD risk.

Adapted from Kronenberg F et al. *Curr Opin Lipidol.* 2022;33(6):342-352.
Kronenberg F et al. *Eur Heart J.* 2022;43(39):3925-3946.
Pearson GJ et al. *Can J Cardiol.* 2021; 37:1129-1150.
Grundy SM et al. *J Am Coll Cardiol.* 2019;73(24):e285-e350.
Mach F et al. *Eur Heart J.* 2020;41(1):111-188.

100

Impact of LDL-C Lowering Therapies on Lp(a)

There are currently no approved pharmacologic therapies for lowering Lp(a).

No/minimal impact

- Diet[1] (saturated fat may lower slightly)[2]
- Bempedoic acid[3]
- Ezetimibe[3]
  - Possible reduction, 0–5%

Reduction

- Niacin[3]
  - ~20% (no benefit RCT + statin)
- **PCSK9 inhibitors (mAb/siRNA)[3]**
  - **20–25% (benefit RCT + statin)**
- Lipoprotein apheresis[3]
  - 70–80% (benefit in observational data)
- Lomitapide[4] (HoFH only)
  - ~13% (no outcomes data)

Possible increase

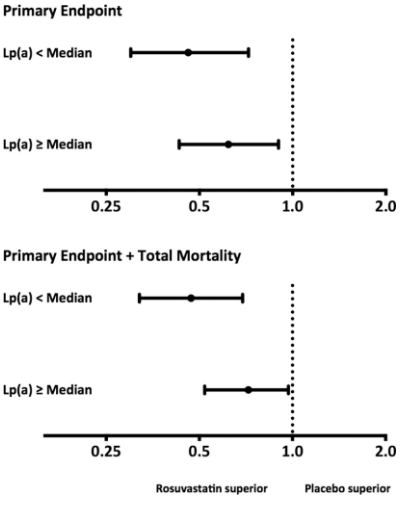
- Statins[3]
  - Possible increase, 0–10% but still felt indicated for LDL-C excess

1. Enkhmaa B et al. Nutrients. 2020;12(7):2024;
2. Ginsberg HN et al. Arterioscler Thromb Vasc Biol. 1998;18(3):441-449;
3. Schwartz GG, Ballantyne CM. Atherosclerosis. 2022;349:110-122;
4. Rader DJ, Kastelein JJP. Circulation 2014;129(9):1022-1032.

101

Statins in the Jupiter Trial and LP(a)

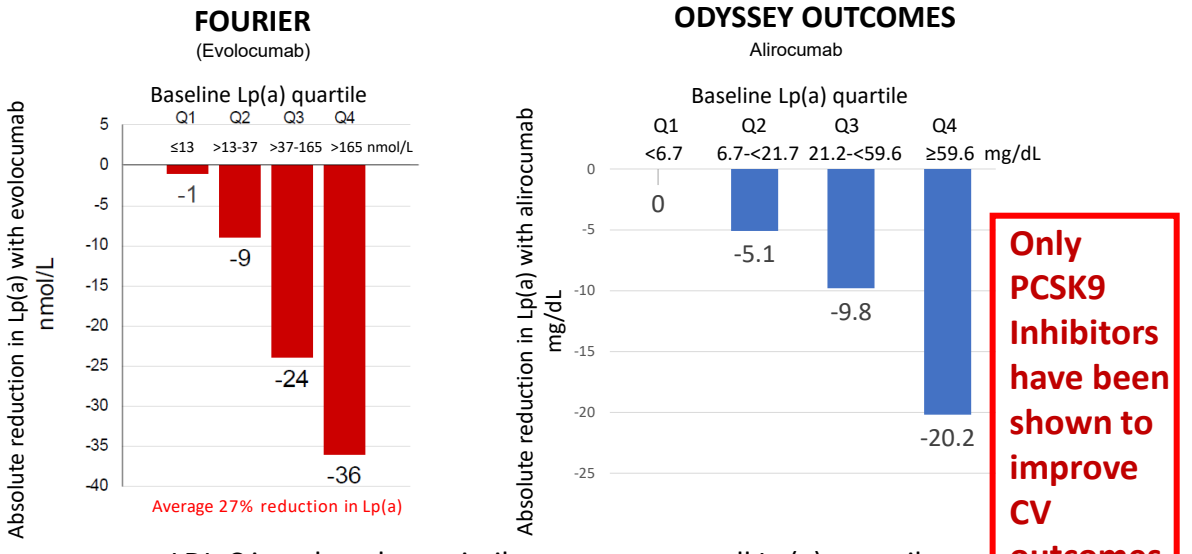
- Increase Lp(a) levels
- Significantly reduced incident of cardiovascular disease in participants with elevated Lp(a)



Khera AV, et al.Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial Circulation. 2014 Feb 11;129(6):635-42.

102

Lp(a) Reduction with PCSK9i Varies by Baseline Lp(a)



Only PCSK9 Inhibitors have been shown to improve CV outcomes

LDL-C is reduced to a similar extent across all Lp(a) quantiles

O'Donoghue et al. Circulation 2019;39:1483-1492

Bittner et al. JACC 2020;74:133-144

103

Lipoprotein Apheresis

Only FDA Approved Therapy for Secondary Prevention in Those with High Lp(a)

- Reduces Lp(a) levels by 50-80% with each treatment
- Reduce risk 75-95% based on studies in Germany
- Targeted and available
- Done Weekly to biweekly

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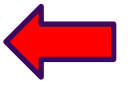
FDA-approved Indications for Lipoprotein Apheresis (Updated as of January 2025)

Patient Group	Criteria for Treatment
Group A	Functional hypercholesterolemic homozygotes (HoFH) with LDL-C >500 mg/dL
Group B	Functional hypercholesterolemic heterozygotes (HeFH) with LDL-C ≥300 mg/dL
Group C	Functional hypercholesterolemic heterozygotes (HeFH) with LDL-C ≥70 mg/dL and either documented coronary artery disease or peripheral artery disease
Group D	Lp(a) >60 mg/dL (>130 nmol/L) with either documented coronary artery disease or documented peripheral artery disease



www.aspconline.org/news/httpsliposorbercompostsexpanded-indication-for-kanekas-liposorber-la-15-system.

105

Clinical Trials in Progress

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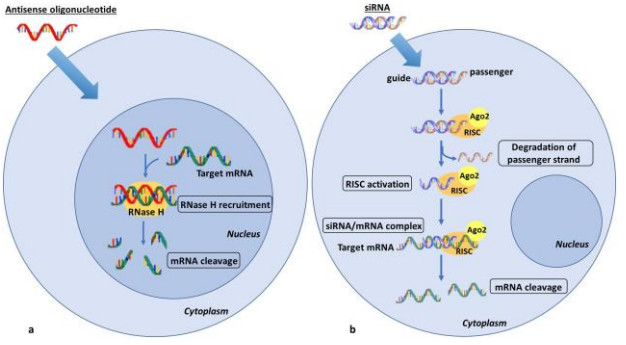
Nucleic Acid Therapies for Lp(a)

ASO
Pelacarsen



siRNA

- Olpasiran
- Lepodisiran
- Zerlasiran

- Small molecule inhibitor

Muvalaplin

ASO-Anti-Sense Oligonucleotide
SiRNA-Small Interfering RNA

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Drugs in Development Targeting Lp(a)

Drug	Company	Mechanism	Drug administration	Trial	CV Outcomes Completed
Pelacarsen	Novartis	ASO	Subcutaneous injection Q4weeks	HORIZON: Phase 3	~~May 2025~~ Early 2026
Olpasiran	Amgen	siRNA	Subcutaneous injection Q12 weeks	OCEAN (a): Phase 3	December 2026
Lepodisiran	Eli Lilly	siRNA	Subcutaneous injection Q6 months?	ALPACA: Phase 2 ACCLAIM-Lp(a): Phase 3	March 2029
Zerlasiran (SLN360)	Silence Therapeutics	siRNA	Subcutaneous injection	APOLLO: Phase 2	No phase 3 as of yet
Muvalaplin	Eli Lilly	Oral small molecule	Oral medication once daily	MOVE-Lp(a): Phase 3	March 2031

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NLA Treatments Recommendations for Elevated Lp(a)

- **Diet and lifestyle changes**
- Control all **other CV risk factors**
- Maximize LDL-C lowering with **statins**
  - Although statins may slightly increase Lp(a), the overall benefits on ASCVD risk reduction suggest that this therapy should remain the standard of care.
- **In high-risk or very-high-risk patients** taking a maximally tolerated statin, **adding ezetimibe** is reasonable in those with on-treatment LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL)
- **PCSK9-directed therapies**: for whom?
  - Linked to 20%-30% decrease in Lp(a) levels and an associated reduction in MACE
  - May be a good choice in high-risk patients who also have not reached LDL-C goals on maximally tolerated statin therapy

  Lp(a) apheresis – only FDA-approved treatment for high Lp(a) in secondary prevention
- **Aspirin** for risk lowering?
  - Risk-benefit discussion may be warranted for primary prevention of ASCVD
- Refer to a lipid specialist and/or a clinical trial.
- Secondary prevention patients: waiting results of HORIZON, OCEAN(a), ACCLAIM, MOVE-Lp(a).
- High risk primary prevention: waiting results of the ACCLAIM trial

Koschinsky ML et al. *J Clin Lipidol.* 2024;18(3):e308-e319.

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CONCLUSIONS

- **Now Know When and Why You Should Measure Lp(a) understanding its relationship to CV Disease.**
- **Now Know what you can currently do for Lp(a) elevation and anxiously await the Clinical Trials Currently in Progress.**

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