Hyperlipidemia: Latest Concepts

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- Spousal employment: Vertex

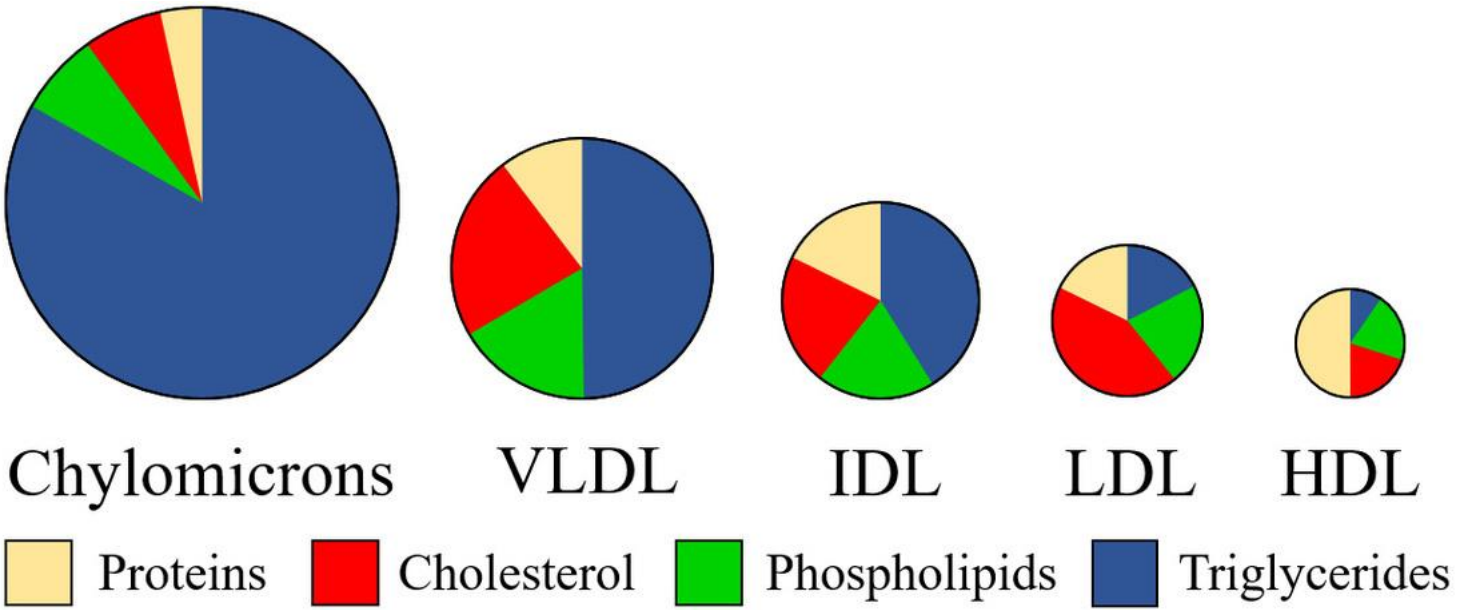
Learning Objectives

- Recognize that LDL-C-lowering represents a key strategy in primary and secondary prevention of atherosclerotic cardiovascular disease.
- Identify available and emerging therapies for lipid modulation and improving atherosclerotic cardiovascular disease risk.
- Understand the role of novel lipid-related biomarkers in atherosclerotic cardiovascular disease risk stratification.

Outline

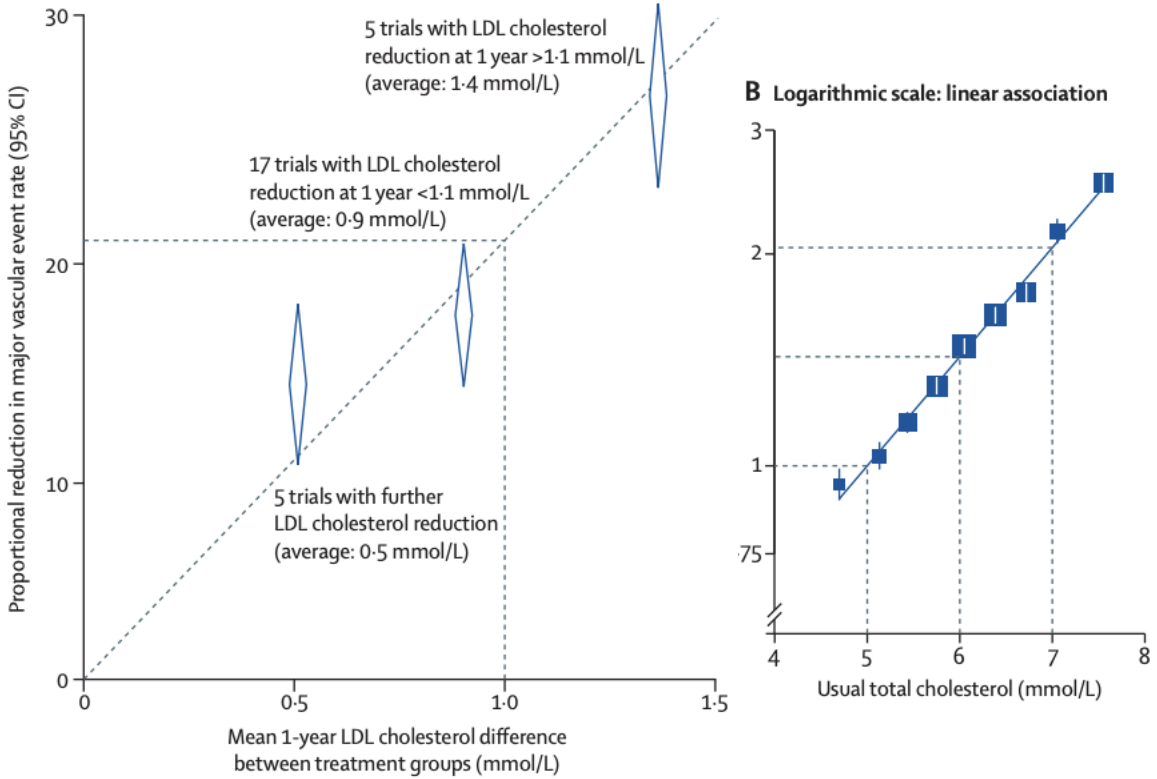
- Solid evidence
  - LDL cholesterol
- Unsupportive evidence
  - HDL cholesterol
- Emerging, promising evidence
  - Triglycerides
  - Lipoprotein(a)
  - Apolipoprotein B

Lipoproteins allow transport of water-insoluble lipids (cholesterol, triglycerides)



LDL CHOLESTEROL

Statin-mediated LDL-C-lowering translates into CVD risk reduction

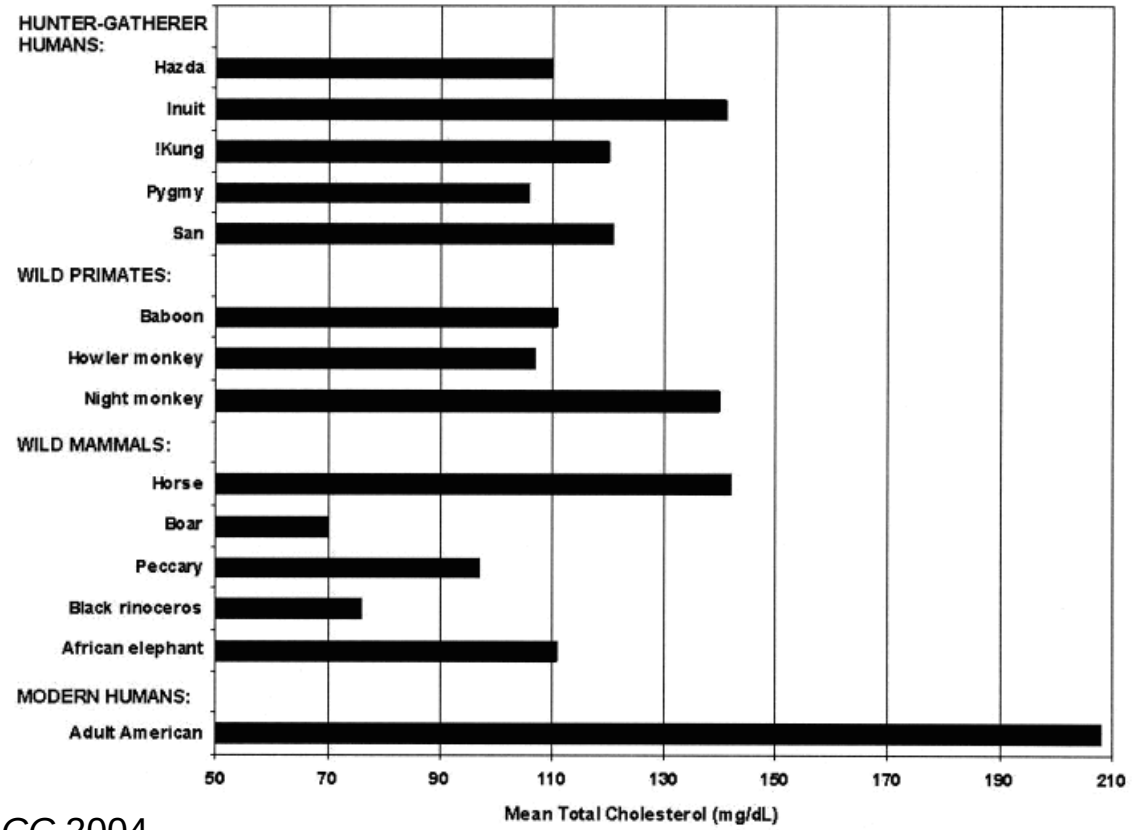


Collins R et al. *Lancet* 2016

For every 40 mg/dl (1mmol/L) LDL-C reduced:

- MACE reduced by 25%
- All-cause death reduced by 10%

Physiologic TC is 70-140 mg/dl (and LDL-C is 35-70 mg/dl)



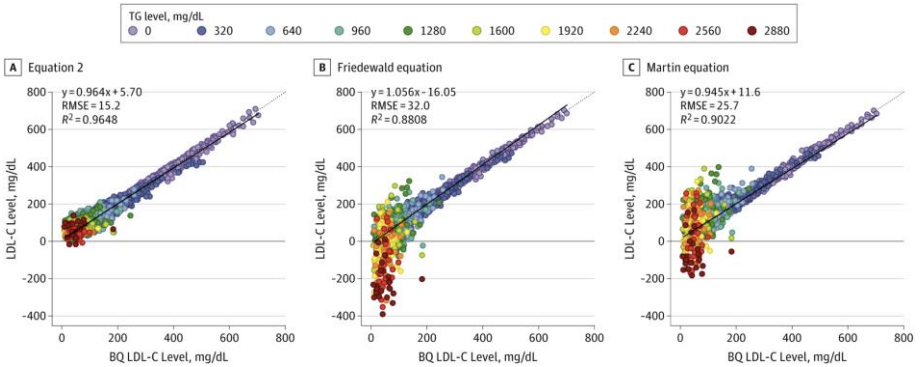
O'Keefe JH et al. *JACC* 2004

Measurement

- Screen adults ≥ 20 years (fasting or non-fasting)
  - If triglycerides > 400 mg/dl, check fasting

$$\text{LDL-C} = \frac{\text{TC}}{0.948} - \frac{\text{HDL-C}}{0.971} - \left(\frac{\text{TG}}{8.56} + \frac{\text{TG} \times \text{Non-HDL-C}}{2140} - \frac{\text{TG}^2}{16100}\right) - 9.44.$$

- If LDL-C < 70 mg/dl, consider alternate estimations of LDL-C
  - Martin-Hopkins (*JAMA* 2013)
  - Sampson-NHLBI (*JAMA Cardiology* 2020)
  - Excel file to calculate: https://nih.figshare.com/ndownloader/files/22694093

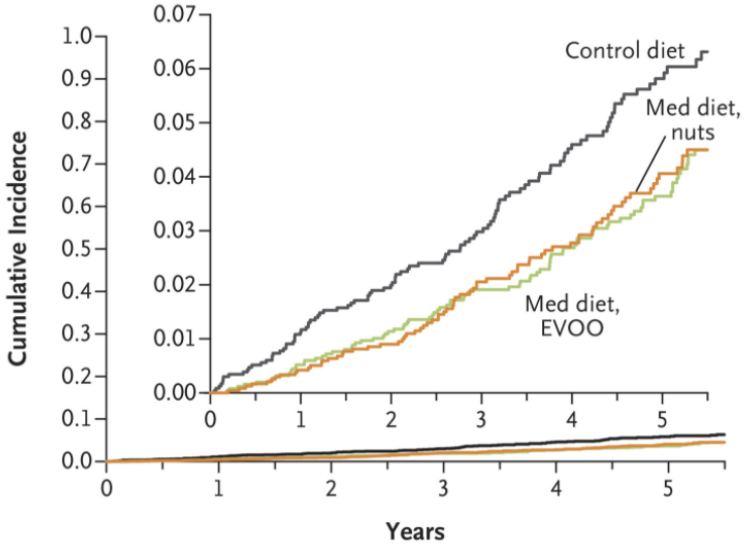


Sampson M et al. *JAMA Cardiology* 2020

PREDIMED

A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)

Med diet, EVOO: hazard ratio, 0.69 (95% CI, 0.53–0.91)
Med diet, nuts: hazard ratio, 0.72 (95% CI, 0.54–0.95)



No. at Risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

Estruch R et al. *NEJM* 2018

Saturated Fats

- Recommendations: <10% of total calories
- Relationship to CVD is complicated, particularly if restriction is at the expense of increased refined carbohydrates (Astrup A et al *JACC* 2020)
- If cholesterol is elevated, identify sources of saturated fat and replace with polyunsaturated fats

Dietary priorities to improve lipids and overall CV health

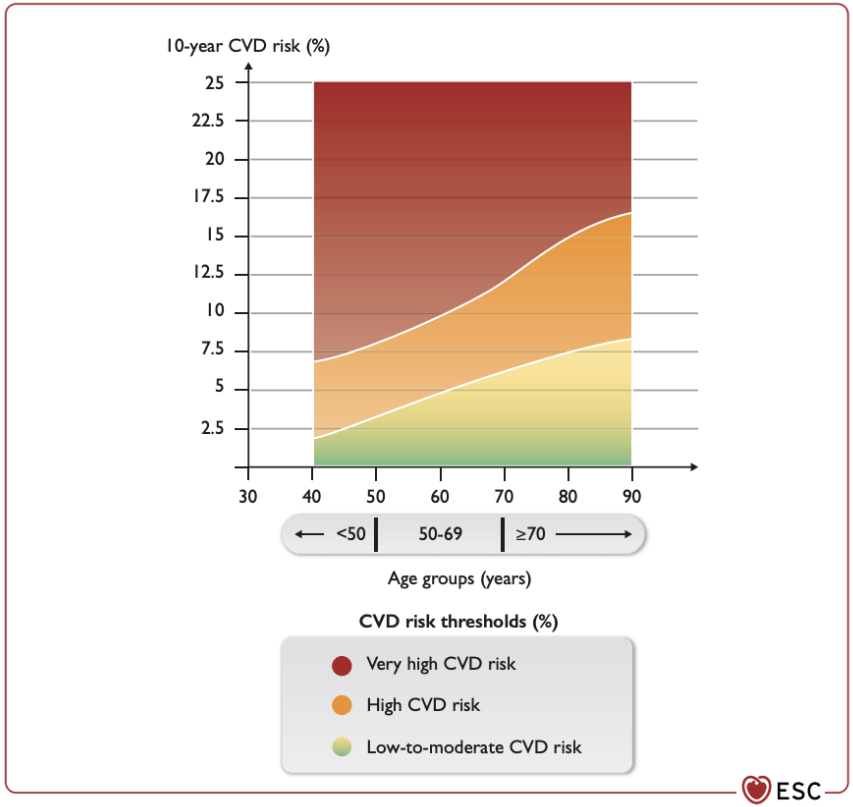
Healthy diet characteristics	
↑ plant-based, ↓ animal-based	>200g/d (>2-3 servings/d) vegetables
Sat FA <10% total energy	<350-500g/w red meat, minimize processed meat
Minimize Trans FA	1-2 servings/w fish, particularly fatty fish
<5g/d Na	30g/d
30-45g/d fiber	<100g/w alcohol
>200g/d (>2-3 servings/d) fruits	Discourage sugar-sweetened beverages

Visseren FLJ et al. *Eur Heart J*. 2021

LDL-C Treatment Targets
Primary Prevention

	ACC/AHA	**ESC**
Severe hypercholesterolemia (LDL-C > 190 mg/dl)	>50% lower AND <100 mg/dl	>50% lower AND <70 mg/dl
Diabetes mellitus	30-49% lower (>50% lower)	>50% lower AND <100 mg/dl (>50% lower AND <70 mg/dl)
High risk (non-diabetic, LDL-C < 190 mg/dl)	>50% lower	<55 mg/dl
Borderline/Intermediate 10-year ASCVD risk (non-diabetic, LDL-C < 190 mg/dl)	30-49% lower	<70 mg/dl

2021 ESC: Adjustment of primary prevention risk categories by age



“Risk-enhancing factors” to evaluate statin suitability

- Evaluate among those at intermediate (7.5-20%) risk
- Consider among those at borderline (5-7.5%) risk

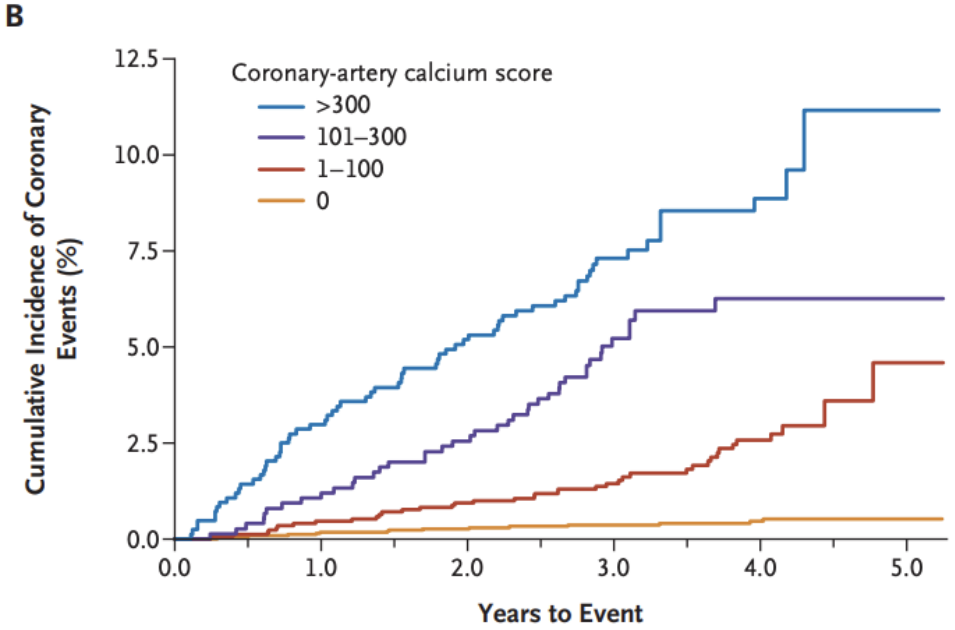
Family h/o premature ASCVD
LDL-C 160-189 or non-HDL-C 190-219 mg/dL
Metabolic syndrome
CKD (eGFR 15-59)
Chronic inflammatory conditions
h/o premature menopause, h/o preeclampsia
South Asian ancestry
Triglycerides ≥ 175 mg/dL, non-fasting
If measured: hsCRP ≥ 2.0 Lp(a) ≥ 50 ApoB ≥ 130 ABI < 0.9

Consider CAC if statin Rx equipoise persist for primary prevention

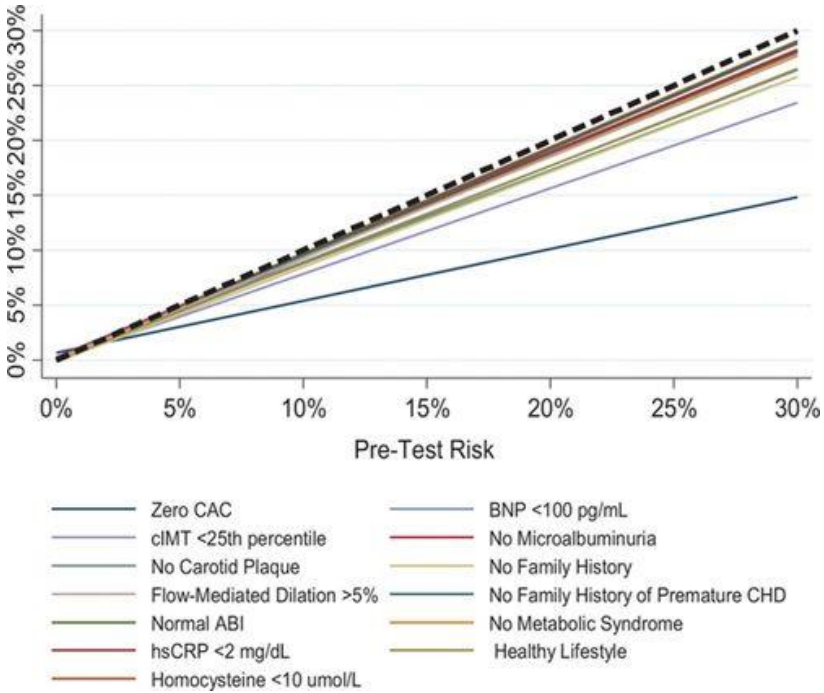
- Consider if statin Rx equipoise for intermediate (7.5-20%) risk and selected borderline (5-7.5%) risk

- Low yield in low risk or <40 years

CAC strongly predicts future CAD events



Detrano R et al. *NEJM*. 2008



Blaha M et al. *Circulation*. 2016

If CAC scoring performed and 0 for borderline/ intermediate risk, consider deferring statin

IIa	B-NR	7. In intermediate-risk adults or selected borderline-risk adults in whom a CAC score is measured for the purpose of making a treatment decision, AND • If the coronary calcium score is zero, it is reasonable to withhold statin therapy and reassess in 5 to 10 years, as long as higher risk conditions are absent (diabetes mellitus, family history of premature CHD, cigarette smoking); • If CAC score is 1 to 99, it is reasonable to initiate statin therapy for patients ≥55 years of age; • If CAC score is 100 or higher or in the 75th percentile or higher, it is reasonable to initiate statin therapy (S4.4.2-17, S4.4.2-23).

Is CAC>0 primary or secondary prevention?

- In the primary prevention algorithm, and classification is not covered in major guidelines
- Many payers do recognize as secondary prevention
- My impression: any CAC in <70yo (particularly in <50yo) merits pharmacologic LDL-C-reduction (Khetarpal S, et al. *JAMA Cardio*. 2021)

LDL-C Treatment Targets
Secondary Prevention

	ACC/AHA	**ESC**
ASCVD AND not very high risk	>50% lower	<55 mg/dl
ASCVD AND very high risk	>50% lower AND <70 mg/dl	<55 mg/dl
ASCVD AND recurrent event within 2y on max tolerated statin		<40 mg/dl

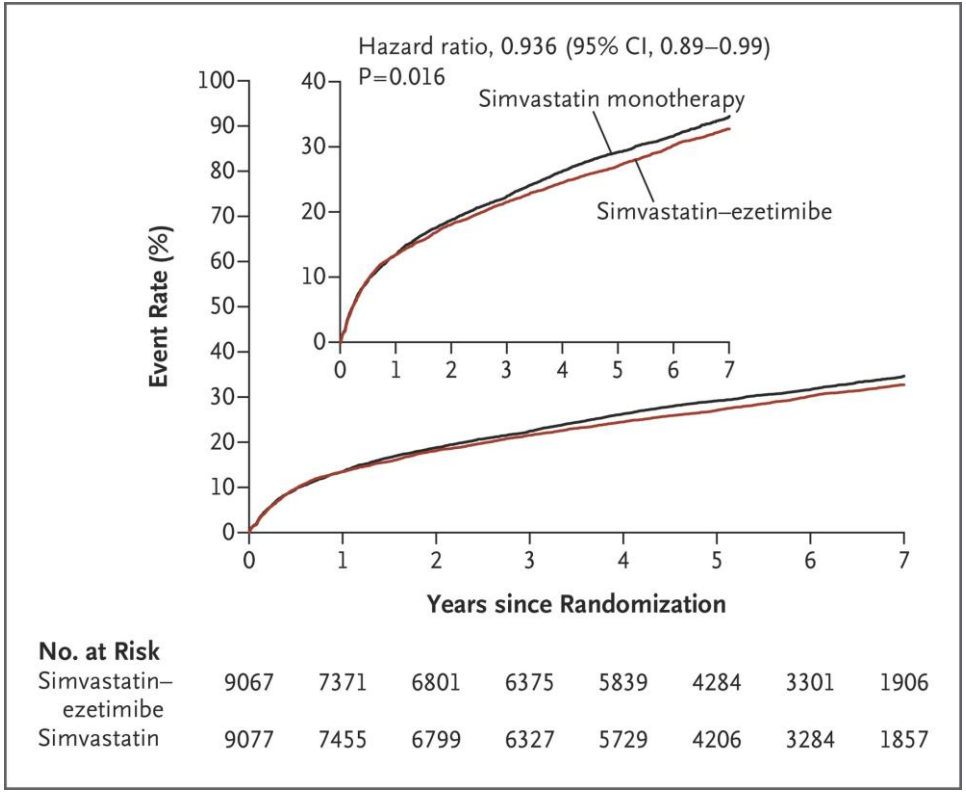
Statin-associated side effects in RCTs

Symptom/Condition	Fold risk compared to placebo	Citations
Medication discontinuation	Null	Kashani A, et al. *Circulation*. 2006; Riaz H, et al. *Am J Cardiol*. 2017
Myalgias	Null	Gupta A, et al. *Lancet*. 2017
ALT/AST elevation	4.2	Kashani A, et al. *Circulation*. 2006; Bjornsson E, et al. J Hepatol. 2012
Diabetes mellitus	1.1	Swerdlow DI, et al. *Lancet*. 2015

Minimizing statin-associated side effects

- To minimize risks of:
  - Muscle symptoms: Avoid drug interactions, check/address TSH first
  - Liver toxicity: Avoid drug interactions, consider checking LFTs at baseline
  - Diabetes mellitus: Minimize prescriptions in low CVD risk groups

Ezetimibe (Zetia)

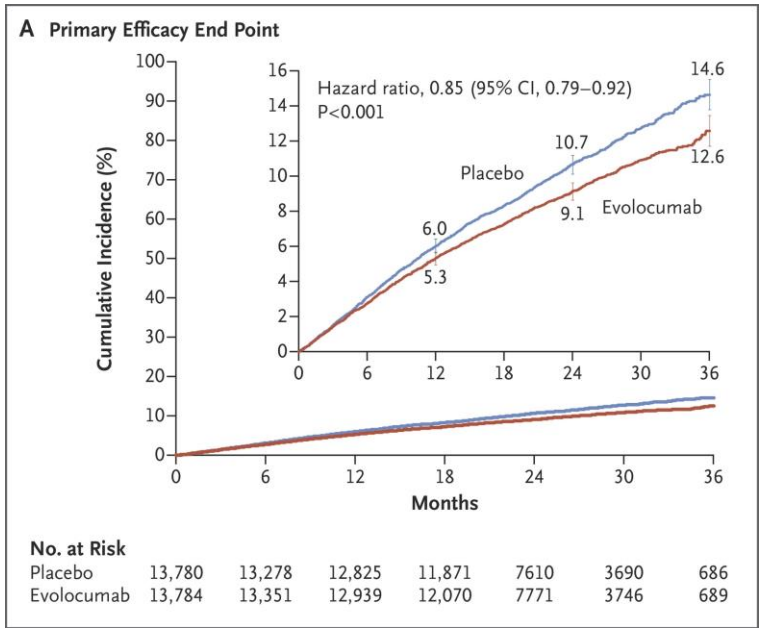


Cannon CP et al. *NEJM*. 2015

PCSK9 monoclonal antibodies

FOURIER

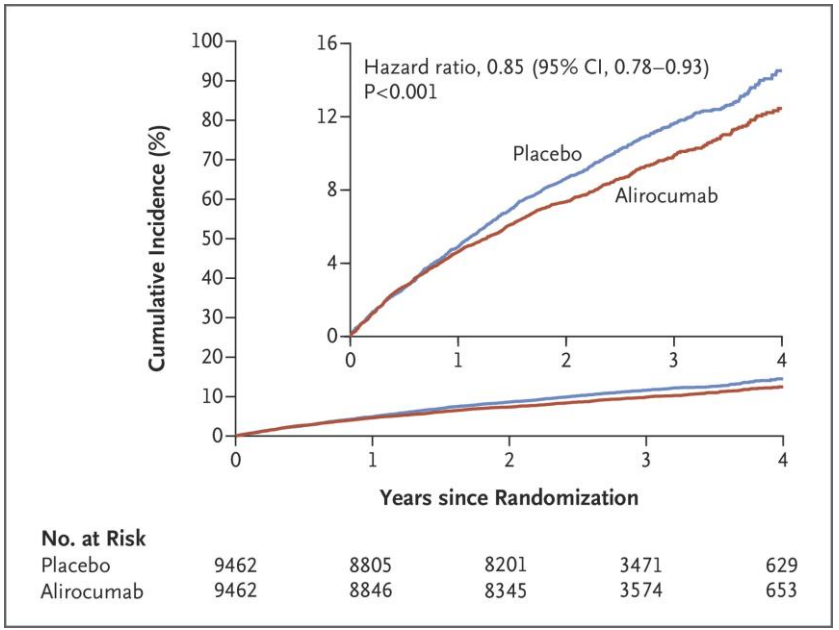
Evolocumab (Repatha)



Sabatine MS et al. *NEJM*. 2017

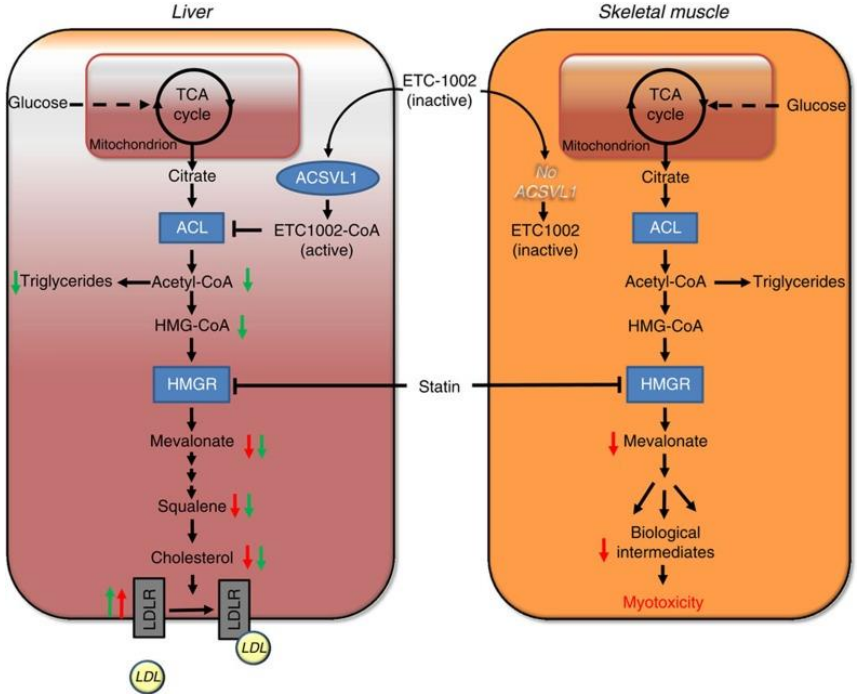
ODYSSEY OUTCOMES

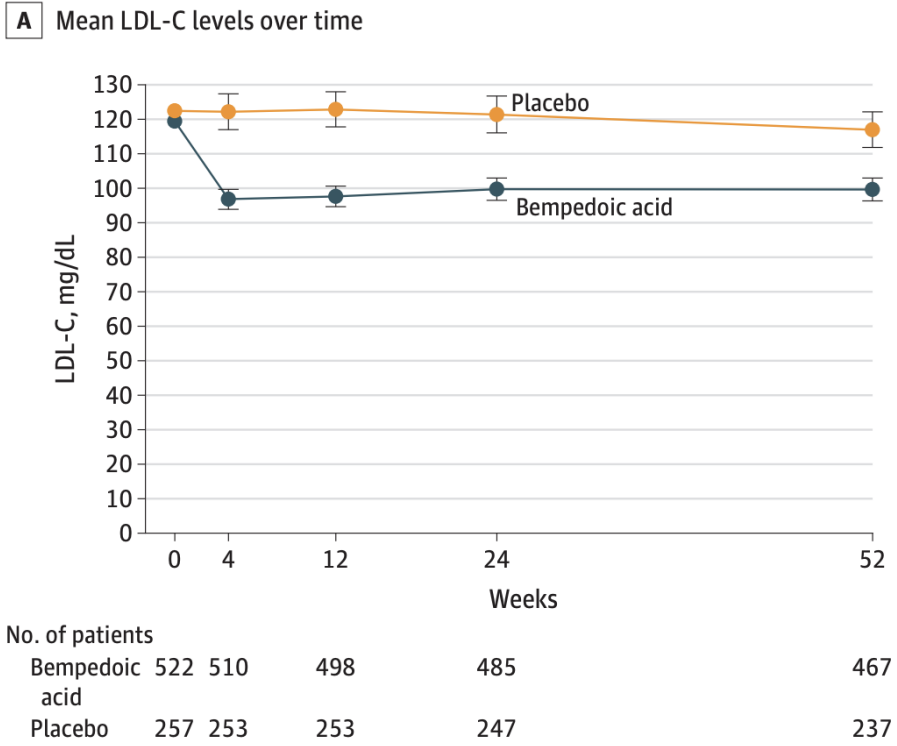
Alirocumab (Praluent)



Schwartz G et al. *NEJM*. 2018

Bempedoic acid (Nexletol): ACL inhibitor





Pinkosky SL et al. *Nat Commun* 2016

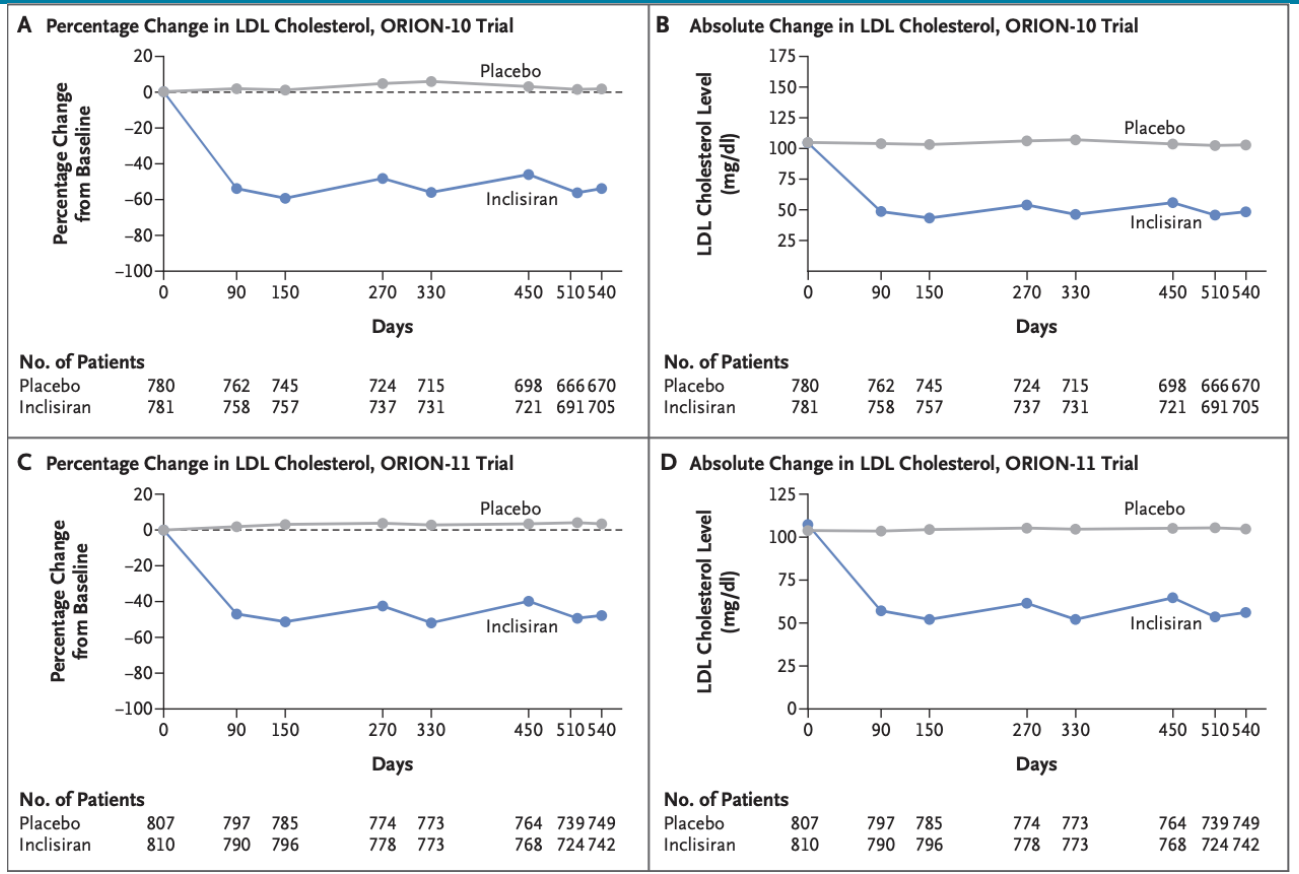
Goldberg A et al. *JAMA* 2019

+1-2% risk of gout with bempedoic acid

- CLEAR Wisdom (Goldberg A et al JAMA 2019):
  - Of N=11 experiencing gout
    - 5 had a prior history of gout
    - 10 had hyperuricemia before starting the medication

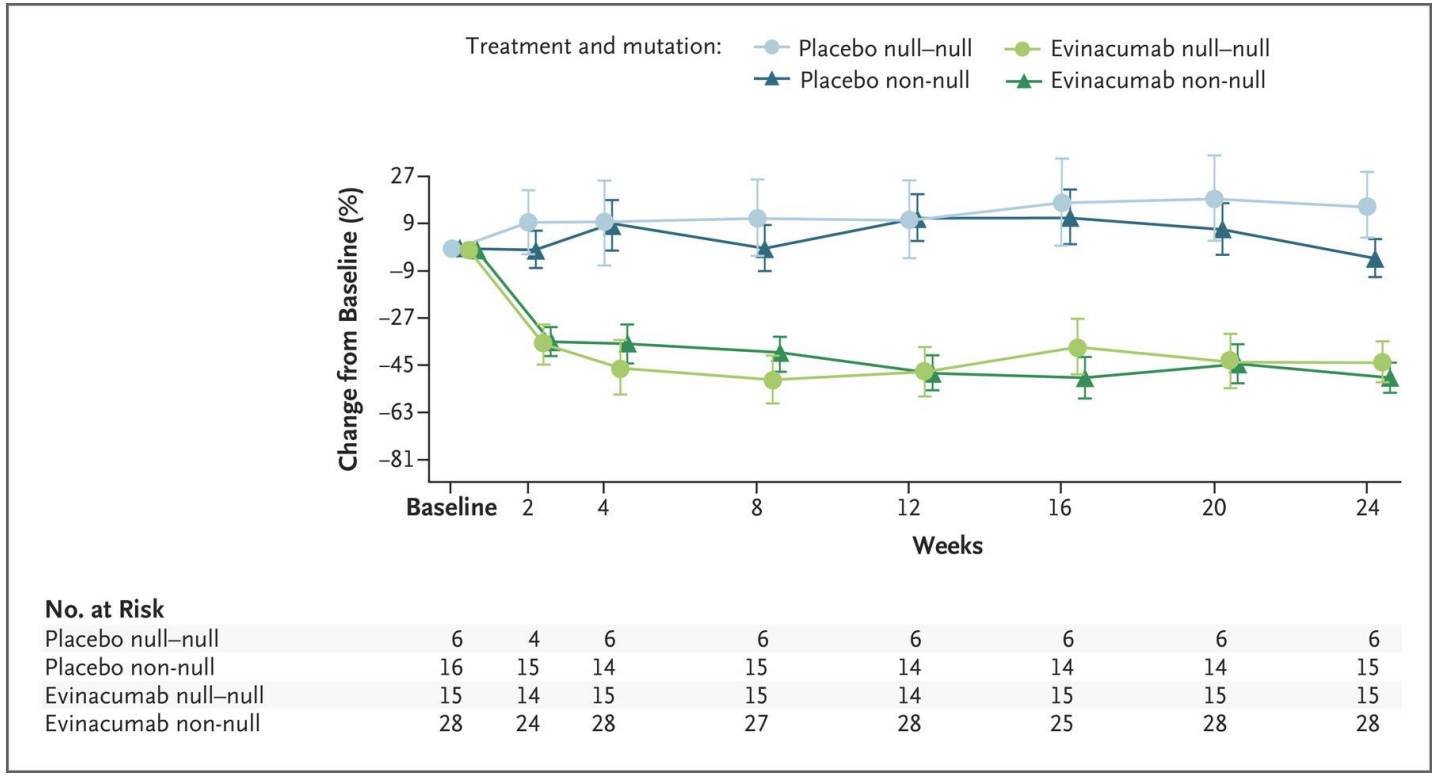
- Key Messages:
  - Avoid bempedoic acid among patients with a prior history of gout
  - If no history of gout, check uric acid – avoid bempedoic acid if uric acid is elevated
  - Note: combo pill with ezetimibe has same co-pay as without

Inclisiran: PCSK9 sq siRNA q6mo



Ray KK et al. *NEJM 2020*

Evinacumab (Evkeeza): ANGPTL3 iv q4w for HoFH



No. at Risk

Placebo null–null	6	4	6	6	6	6	6	6
Placebo non-null	16	15	14	15	14	14	14	15
Evinacumab null–null	15	14	15	15	14	15	15	15
Evinacumab non-null	28	24	28	27	28	25	28	28

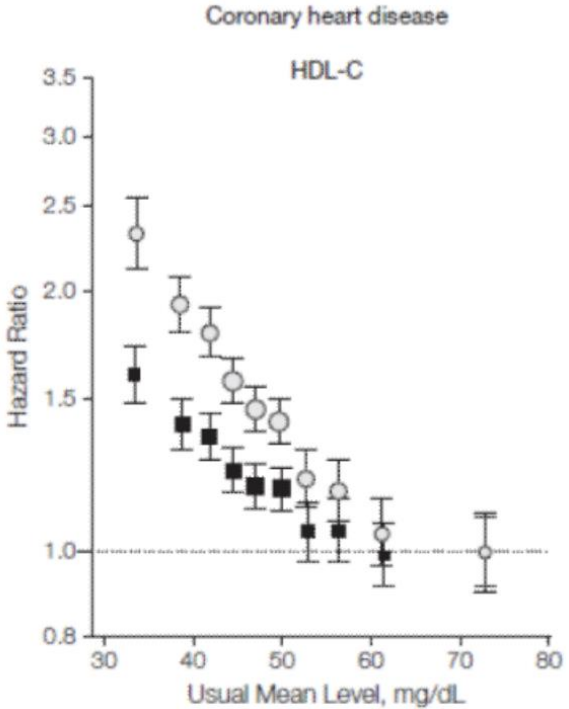
Raal FJet al. *NEJM 2020*

LDL-C Key Points

- Statins for clinical ASCVD, diabetes mellitus, severe hypercholesterolemia, high/intermediate/borderline ASCVD risk
- Consider more aggressive LDL-C targets for eligible patients with: ezetimibe, bempedoic acid, PCKS9 mAbs, inclisiran

HDL CHOLESTEROL

HDL-C concentration is inversely correlated with ASCVD risk



Emerging Risk Factors Collaboration. *JAMA*. 2009

In contemporary RCTs (high statin Rx prevalence), no benefit of HDL-C-raising medicines

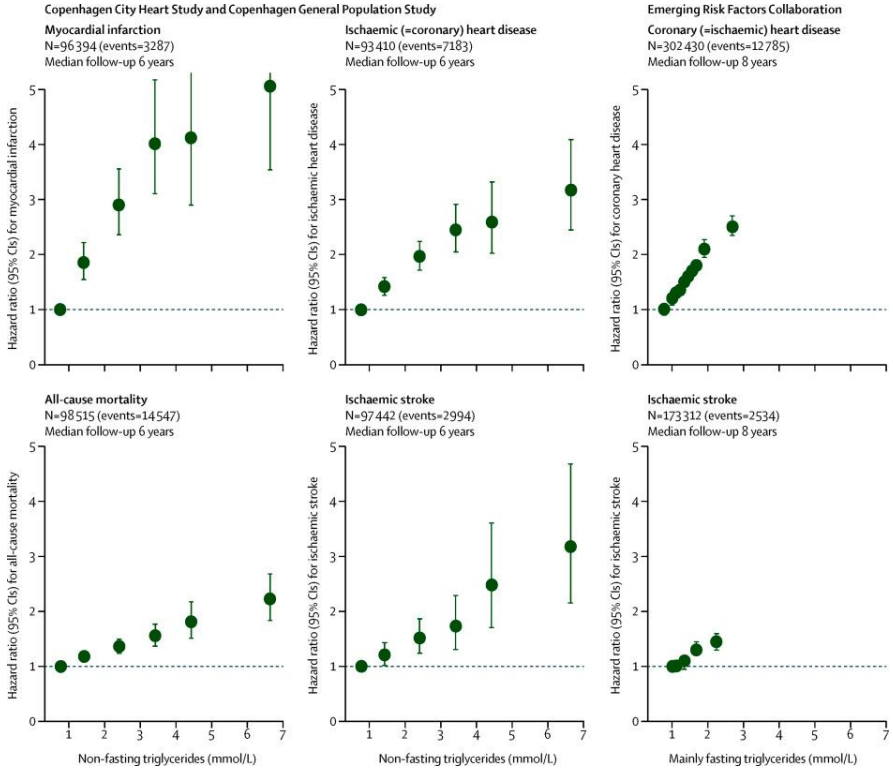
Trial	HDL-C Effect	LDL-C Effect	CVD Effect
Niacin			
HPS2-THRIVE	+6 mg/dl	-10 mg/dl	Null
AIM HIGH	+9 mg/dl	-9 mg/dl	Null
CETP Inhibitors			
ILLUMINATE (torcetrapib)	+34 mg/dl	-22 mg/dl	**Detrimental**
dal-OUTCOMES (dalcetrapib)	+10 mg/dl	0 mg/dl	Null
REVEAL (anacetrapib)	+43 mg/dl	-26 mg/dl	**Protective**
ACCELERATE (evacetrapib)	+59 mg/dl	-27 mg/dl	Null

HDL-C Key Points

- HDL-C is still a very good CVD risk predictor
- Avoid using the term “good cholesterol” since it implies causality
- Other factors correlated with increased HDL-C may explain the relationship with CVD – lack of diabetes mellitus, lack of obesity, healthful diet, lower triglyceride-rich lipoproteins

TRIGLYCERIDES

Preferred: “Triglyceride-rich lipoproteins”



Nordestgaard B et al. *Lancet*. 2015

Icosapent ethyl 2g bid

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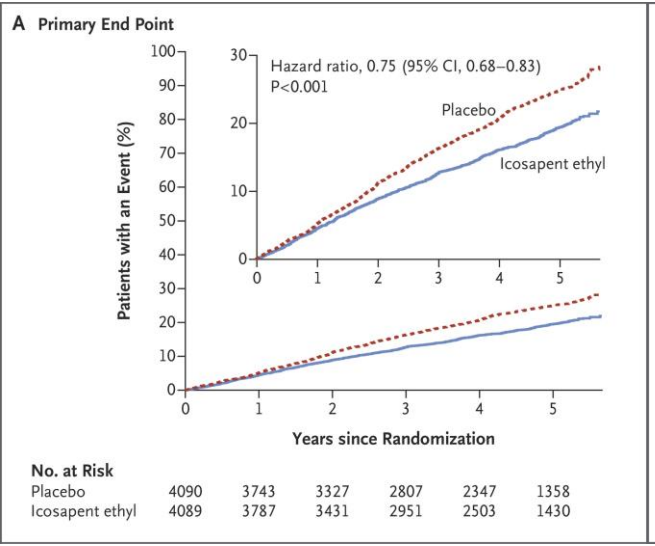
REDUCE-IT



End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—

- ASCVD, or DM + risk factors
- LDL-C 40-100 mg/dl AND TG 135-499 mg/dl

Bhatt DL et al. *NEJM*. 2019

PROMINENT phase 3 study terminated

- Pemafibrate: selective PPAR-alpha modulator
- CV outcomes trial among high-risk patients with type 2 diabetes, mild-moderate hypertriglyceridemia, and low HDL-C on statins
- Terminated 4/2022 after interim analysis indicated endpoint was unlikely to be met

Confusion

- All other omega-3 fatty acid CV trials are null
- Non-inert mineral oil placebo in REDUCE-IT?
- STRENGTH (Nicholls SJ et al *JAMA* 2020) testing EPA/DHA 4g/d vs corn oil was null

Triglycerides Key Points

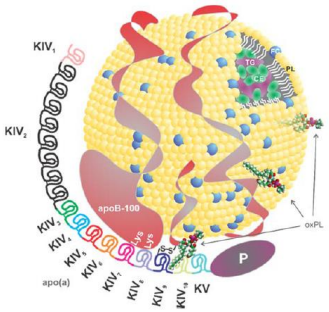
- For triglycerides > 500 mg/dl, triglycerides should be lowered with diet +/- medicines to reduce the risk of pancreatitis

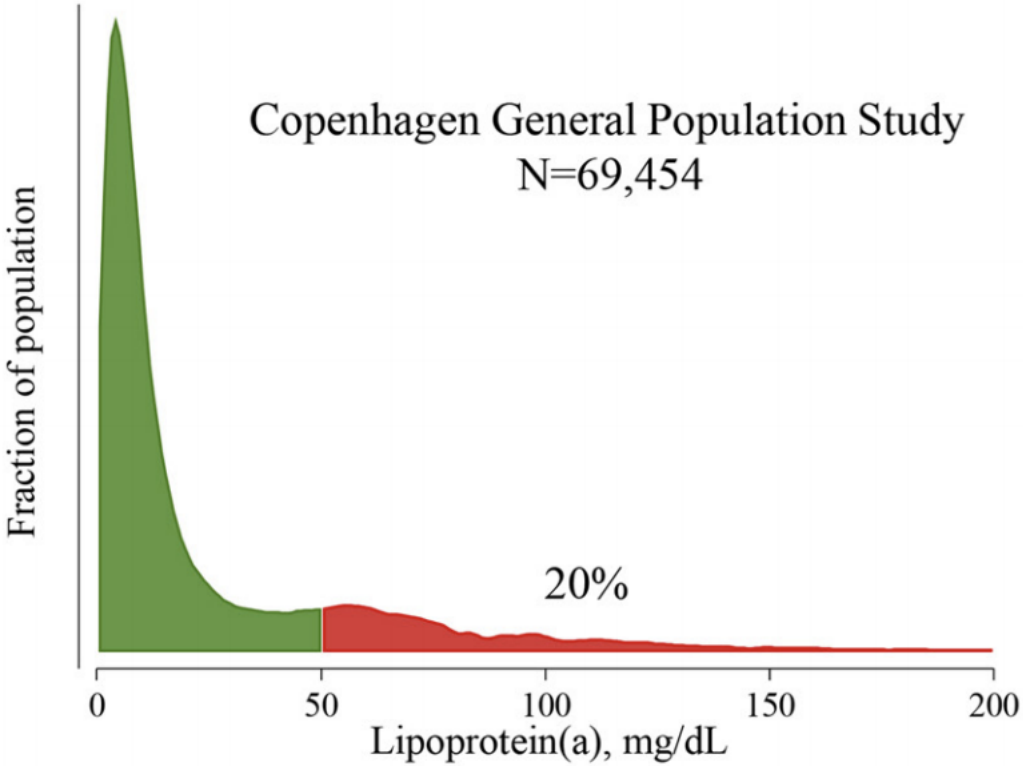
- For triglycerides > 135 mg/dl + ASCVD or DM, icosapent ethyl may be considered for CVD risk reduction

- REDUCE-IT is not a pure test of the triglyceride hypothesis and several questions still remain

LIPOPROTEIN(a)

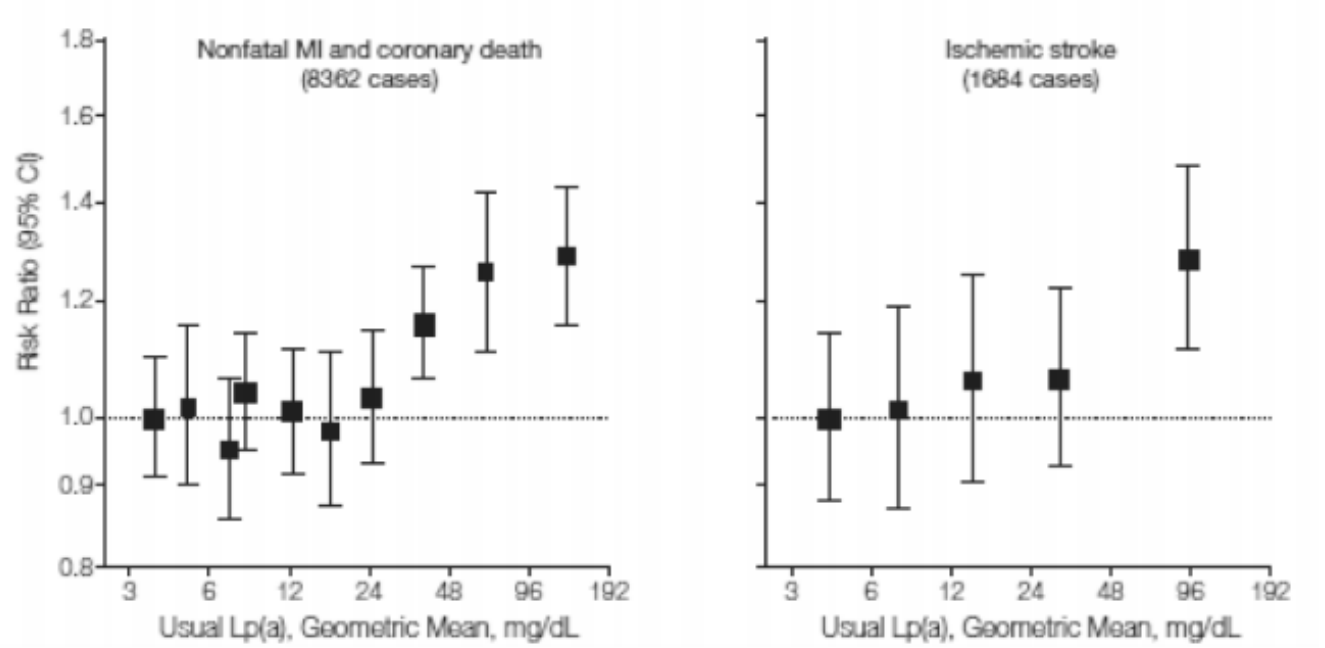
LDL-like particle elevated in 1 in 5





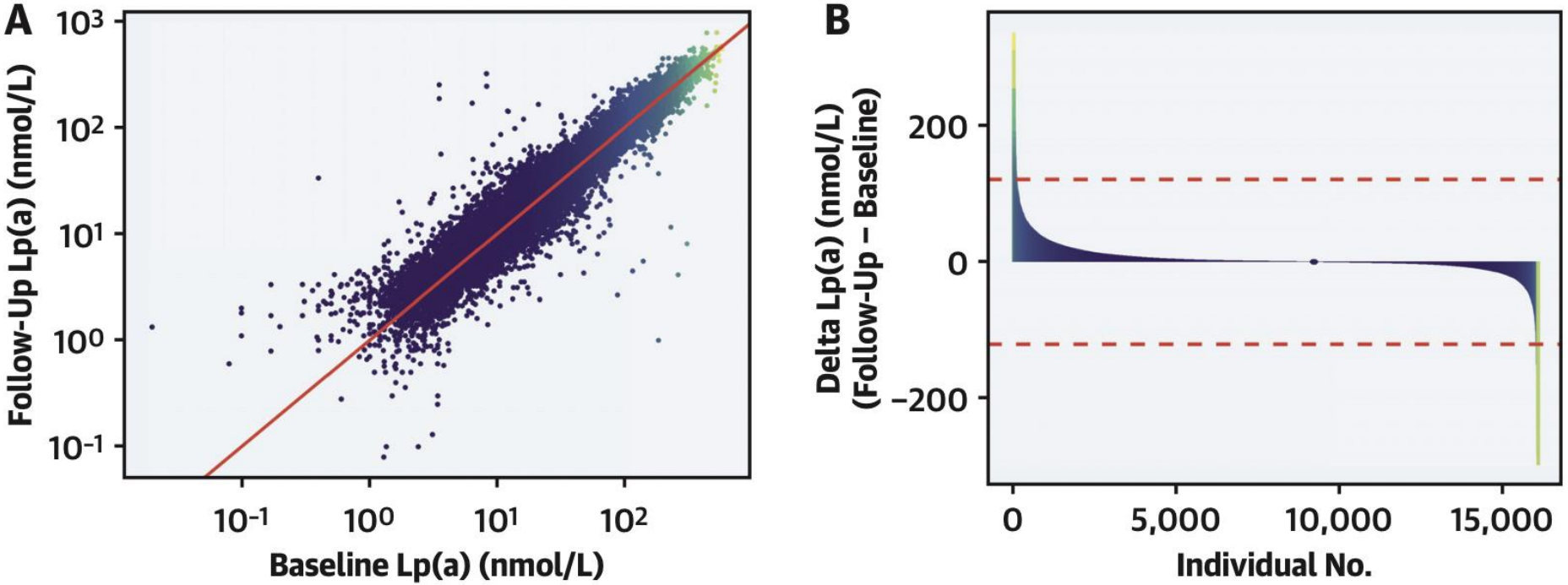
Nordestgaard B et al. *JLR*. 2016

Elevated Lp(a) associated with 1.3-1.5-fold CVD risk



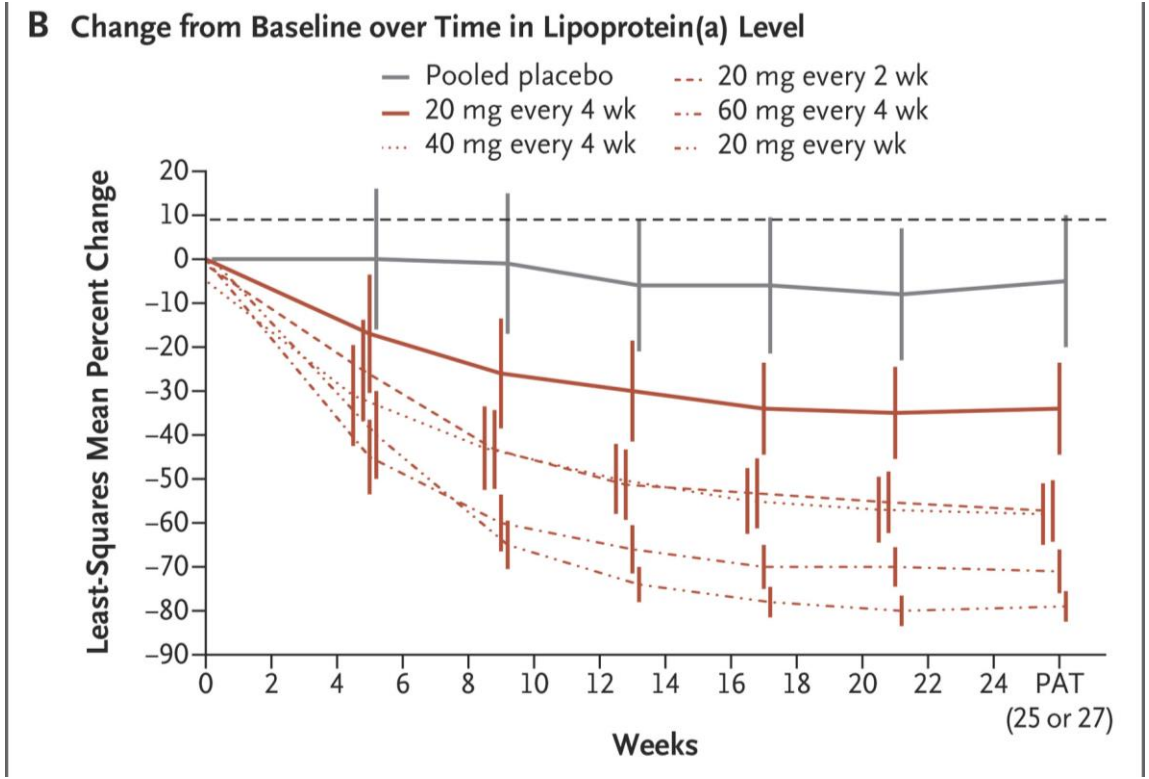
Emerging Risk Factors Collaboration. *JAMA*. 2009

Lp(a) is largely stable in adulthood



Trinder M et al. *JACC*. 2022

Lp(a)-lowering medicines are in clinical development



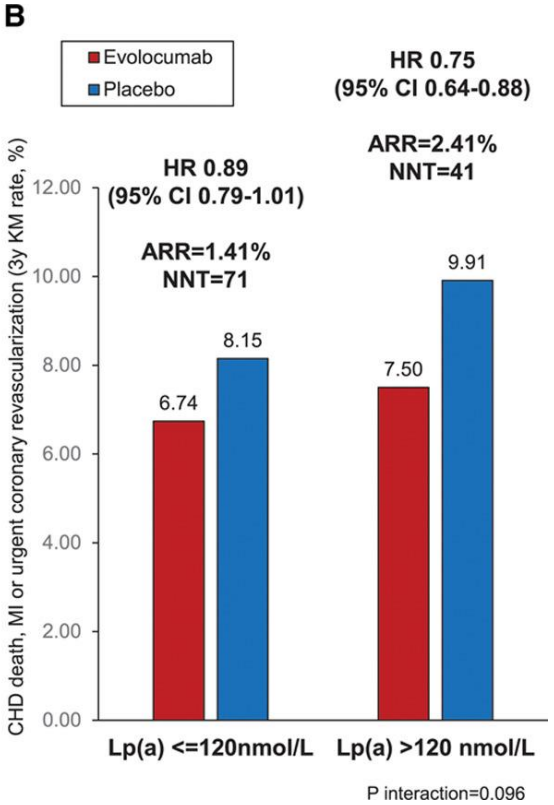
Tsimikas S et al. *N Eng J Med*. 2020

Who should have lipoprotein(a) assessed?

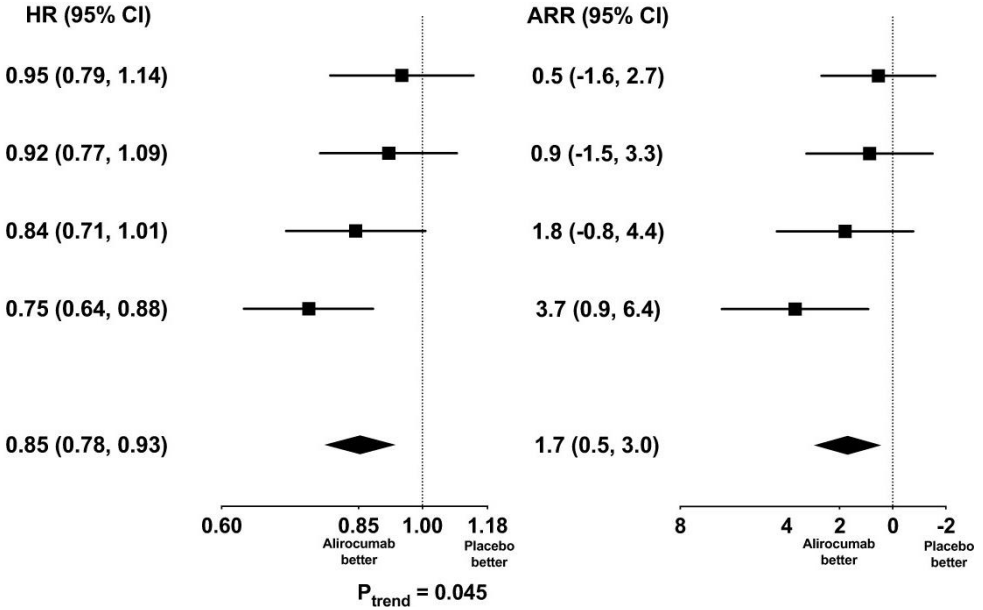
- Highest yield:
  - family history of premature ASCVD
  - personal history of premature ASCVD
  - recurrent ASCVD events despite guidelines appropriate therapy
  - Non-HDL-C > 190 mg/dl

- ESC/EAS: one-time measurement for all adults
- ACC/AHA: consider in borderline/intermediate risk primary prevention

PCSK9 mAbs are particularly beneficial among patients with high Lp(a)



O'Donoghue M et al. *Circulation*. 2019



Szarek M et al. *Eur Heart J*. 2020

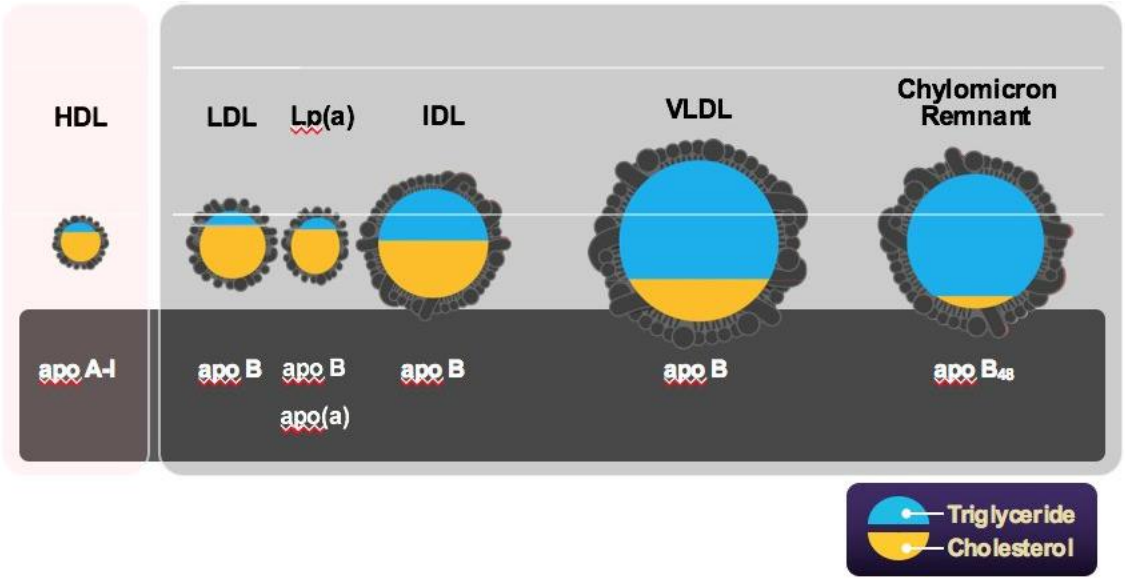
Management

- Pay attention to units and reference ranges
- 2018 ACC/AHA Cholesterol guidelines: use as a risk-enhancing factor to support statin Rx
- Niacin and PCSK9 mAbs reduce Lp(a) but are not FDA-approved for this indication
  - Niacin is poorly tolerated and generally not recommended
  - If consider PCSK9i, definitely go for it if high Lp(a)
- Ongoing CV outcomes RCTs are evaluating the CVD risk reducing efficacy of apo(a) antisense oligonucleotides

Miksenas H, et al. *JAMA*. 2021

APOLIPOPROTEIN B

ApoB is a common feature of atherogenic lipoproteins



ApoB, LDL-C, and non-HDL-C predict CVD risk similarly

	Adjusted HR per 1 SD Increase	*P* Value
ApoB	1.23 (1.20–1.26)	<0.001
Direct LDL-C,	1.20 (1.17–1.23)	<0.001
Friedewald LDL-C	1.17 (1.14–1.20)	<0.001
Martin/Hopkins LDL-C	1.19 (1.16–1.22)	<0.001
Non–HDL-C	1.21 (1.18–1.24)	<0.001
HDL-C	0.81 (0.79–0.84)	<0.001
ApoA1	0.81 (0.78–0.83)	<0.001

Expectation: LDL-C/ApoB = 1.1

Welsh C, et al. *Circulation*. 2019

Guidelines

- 2018 ACC/AHA: Use apoB > 130 mg/dl as a ‘risk-enhancing factor’ among those with borderline/intermediate risk

- 2019 ESC/EAS: ApoB is recommended for risk assessment among those with hypertriglyceridemia, diabetes mellitus, obesity, metabolic syndrome, or very low LDL-C levels.

ApoB analysis is recommended for risk assessment, particularly in people with high TG levels, DM, obesity, metabolic syndrome, or very low LDL-C levels. It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-HDL-C in people with high TG levels, DM, obesity, or very low LDL-C levels.	I	C

Key Points re: Apolipoprotein B

- LDL-C and non-HDL-C are generally sufficient
- In 2018 ACC/AHA Cholesterol guidelines, apoB is a risk-enhancing factor
- May have a role in higher risk patients to verify suitable lowering of atherogenic lipoproteins (apoB target would be similar as LDL-C target)

Take-Home Points

- Virtually no modern human has an optimal LDL-C
- Dietary modification should be included in any approach addressing CVD risk
- Reducing the concentration of cholesterol in atherogenic lipoproteins is the hallmark of primary and secondary prevention
- Among individuals with elevated triglycerides and ASCVD or DM, consider icosapent ethyl
- Elevated Lp(a) may support aggressive LDL-C-lowering (particularly with PCSK9i) and ongoing RCTs are evaluating Lp(a)-lowering strategies
- ApoB has a limited role in addition to conventional lipids but may be useful in select patients