Lipid Management

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Disclosures

Honoraria/Consulting Fees – Amgen, AstraZeneca, Boston Scientific, Abbott

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Objectives

- Review the relationship of dyslipidemia, atherosclerosis and risk of cardiovascular events
- Identify lipid treatment goals for various populations
- Compare and differentiate therapeutic treatment options: efficacy, MOA and AEs

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Case

- SB is a 68 year-old woman with a history of prior MI and hypertension who is referred for CV assessment
- Current meds include aspirin; losartan; atorvastatin 20 mg
- BP 125/70 mm Hg; TC 200 mg/dL; HDL-C 35 mg/dL; LDL-C 90 mg/dL

- **What is her level of CV risk**: low; borderline; intermediate; high; very high
- **What is her LDL-C goal**: < 70 mg/dL; < 55 mg/dL; already at goal
- **What is best next step for her lipid lowering therapy**: continue atorva 20; increase to 40 or 80; add ezetimibe; add PCSK9i

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Outline

- Framework for atherosclerosis
- Pharmacologic interventions: Statins; PCSK9i; Ezetimibe; Bempedoic acid
- Risk Assessment; Guidelines; Risk Enhancers

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- **Framework for atherosclerosis**

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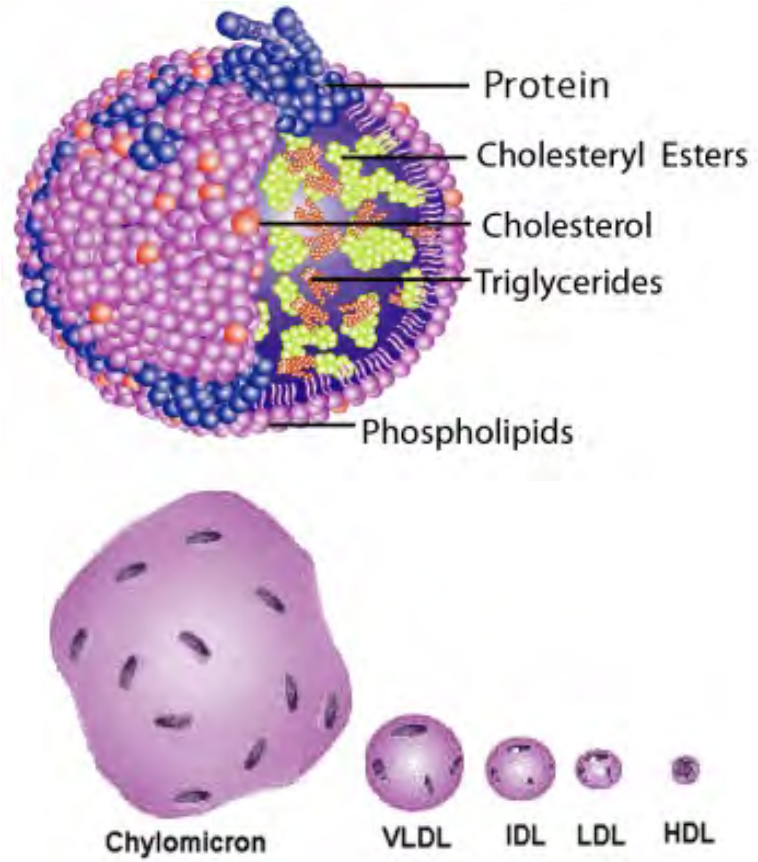
Lipids - Definition

- Organic compounds insoluble in water
- Comprise sterols (cholesterol), fatty acids, phospholipids
- Transport requires lipoproteins
  - LDL: liver - > peripheral tissues
  - HDL: peripheral tissues -> liver
- Critical components of cell membranes, energy storage and precursor for steroid hormones
- Atherogenic lipoproteins contain ApoB



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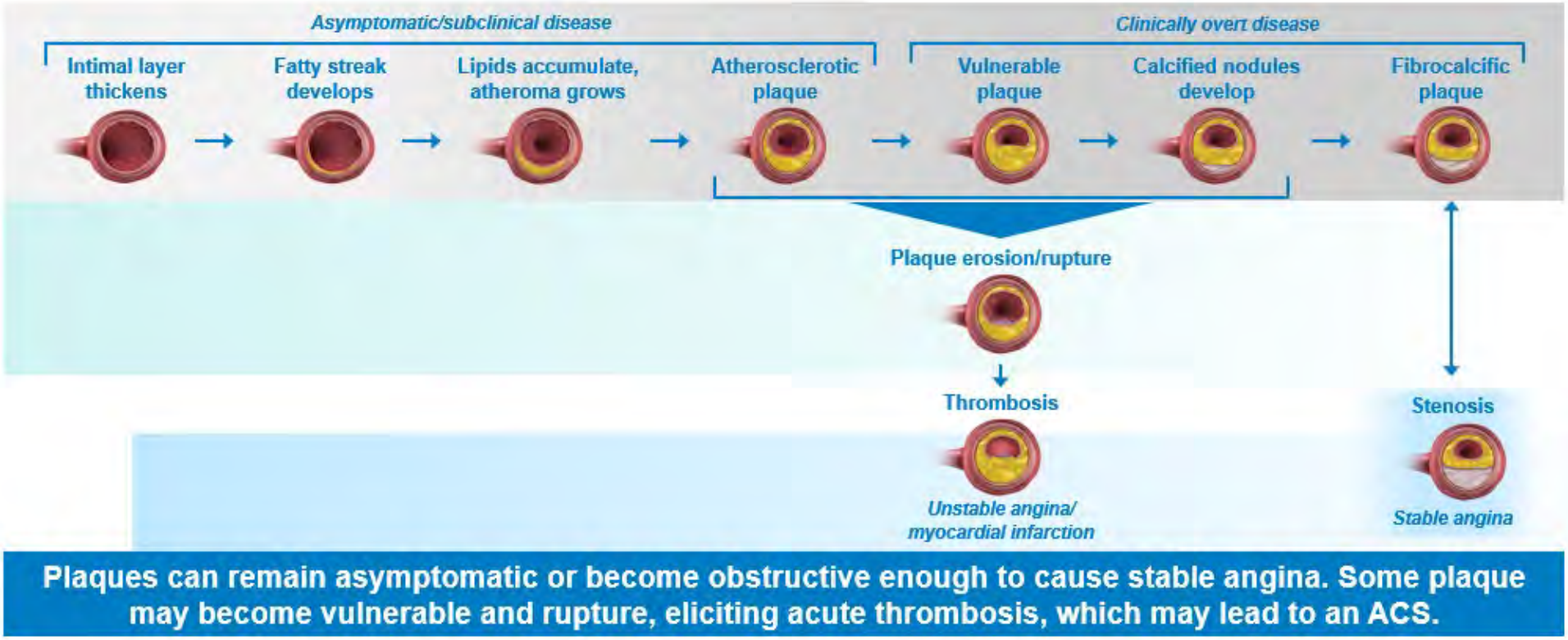
Atherosclerotic Paradigm



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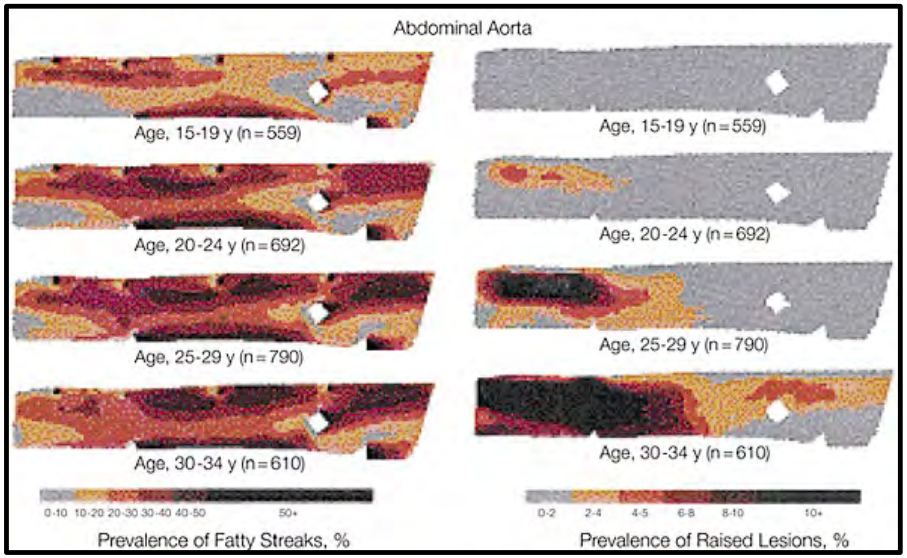
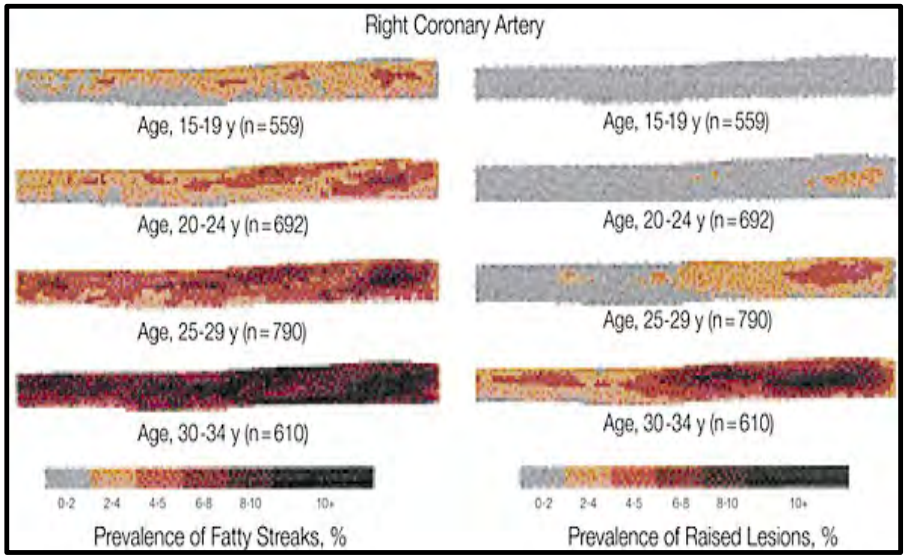
Atherosclerosis in Youth

Pathobiological Determinants of Atherosclerosis in Youth (PDAY)

Autopsy study of atherosclerosis among individuals between ages 15 – 34 who died of external causes (n=2876)





Strong et al., JAMA 1999

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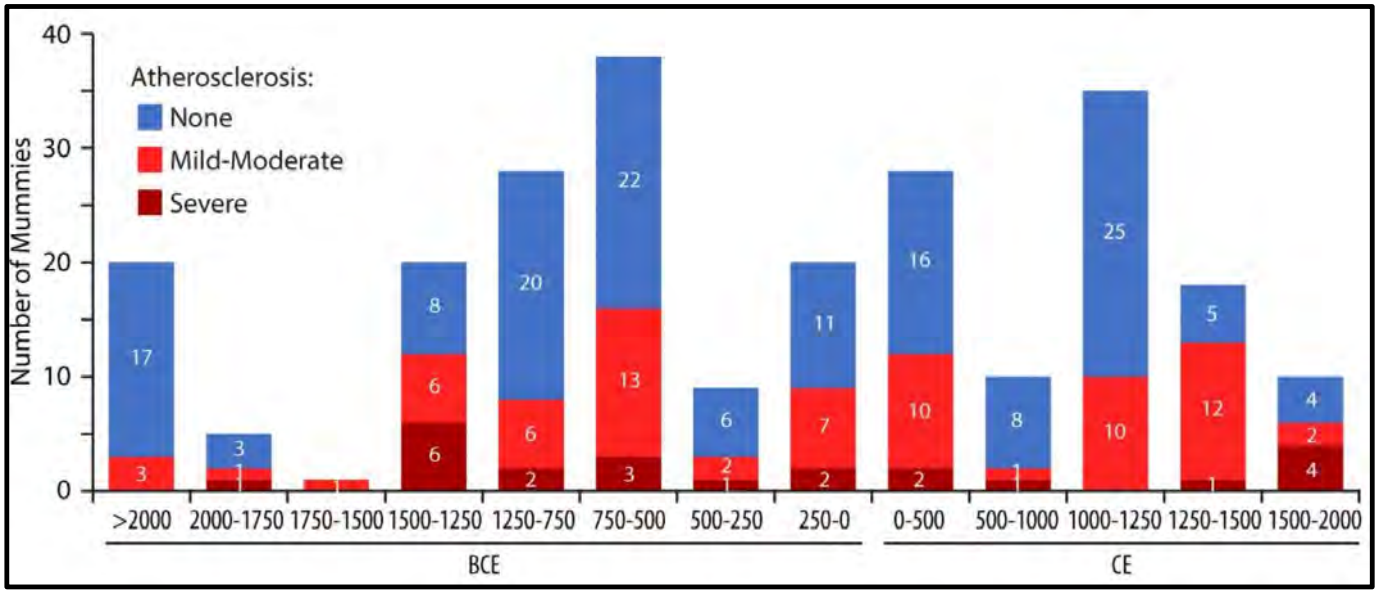
Atherosclerosis in Ancient Humans



Thompson et al., EHJ 2024

HORUS

Study of atherosclerosis in mummies using whole body CT

Overall prevalence atherosclerosis ~ 37% and consistent across cultures and time periods

"These findings support the existence of an innate human predisposition to atherosclerosis. Modern cardiovascular risk factors….may drive the extent and impact…."

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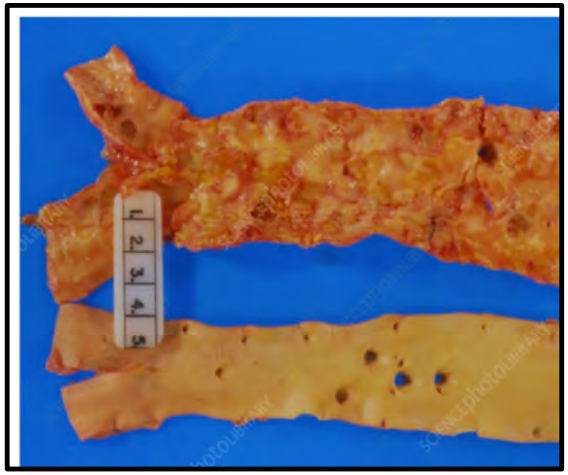
Serum Cholesterol and Atherosclerosis

1910

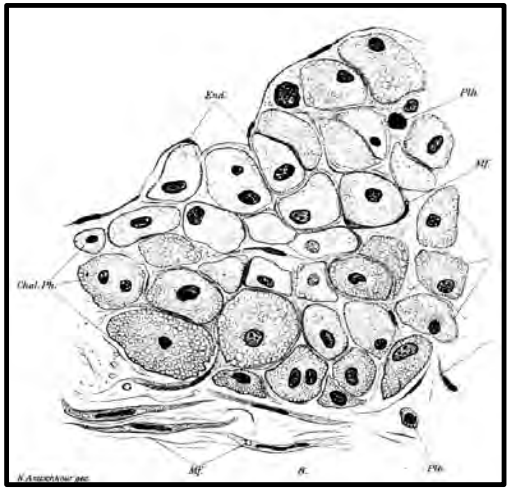


https://www.sciencephoto.com/media/258277/view/aorta-affected-by-atherosclerosis-normal-one

Atherosclerotic lesions in aorta contain 25X more cholesterol than normal

A. Windaus

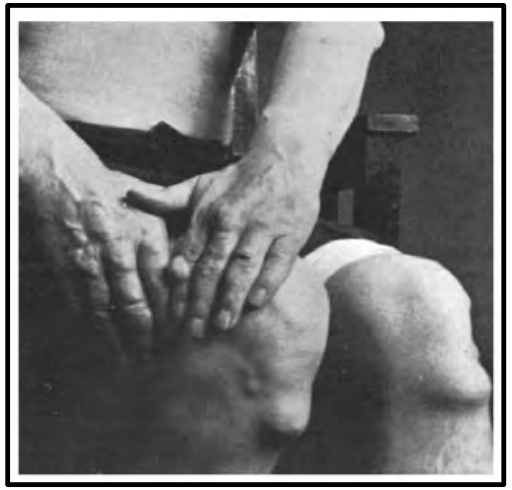
1913



Atheroslcerotic lesions in rabbits fed cholesterol illustrating foam cells

A. Anitschkov

1939



Monogenic diseases links elevated cholesterol with xanthomas and coronary heart disease (FH)

C. Muller

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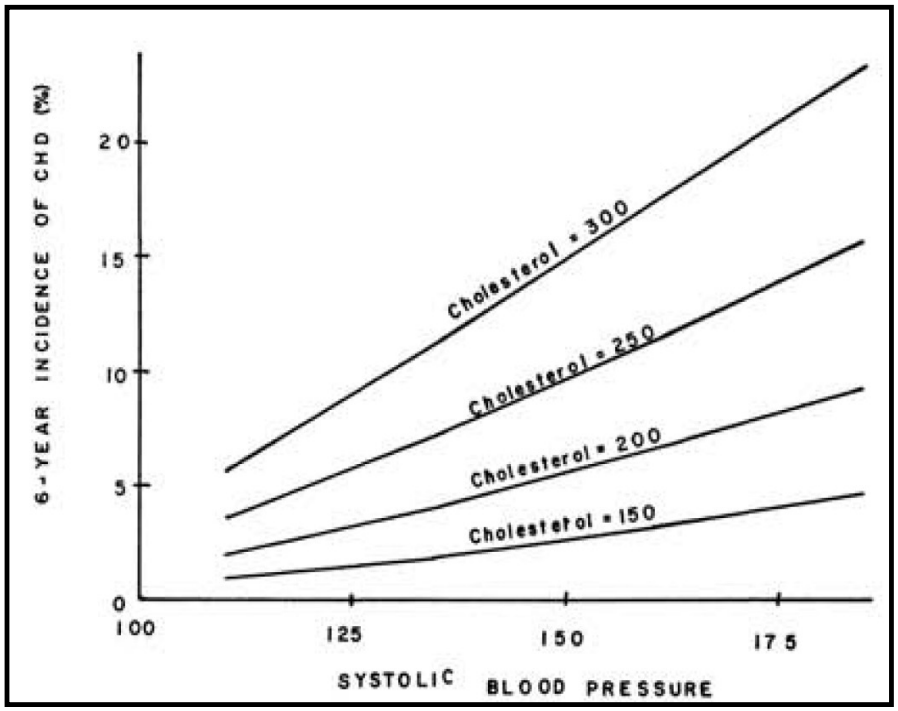
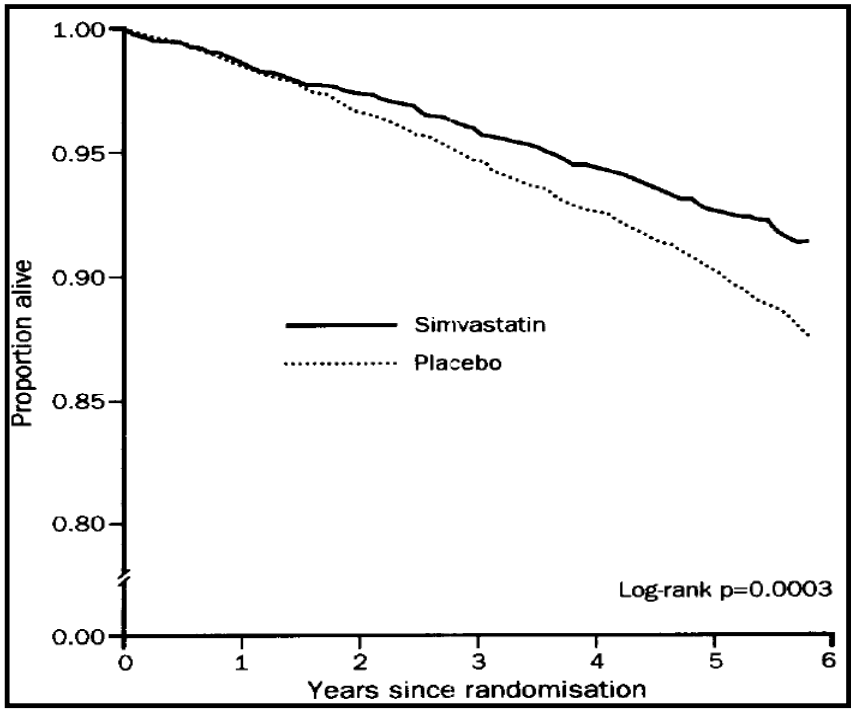
Serum Cholesterol and Atherosclerosis



Framingham Study, Annals of Internal Medicine, 1961



4S study, Lancet, 1994

Outline

- Framework for atherosclerosis

- **Pharmacologic interventions: Statins; PCSK9i; Ezetimibe; Bempedoic acid**

- Risk Assessment; Guidelines; Risk Enhancers

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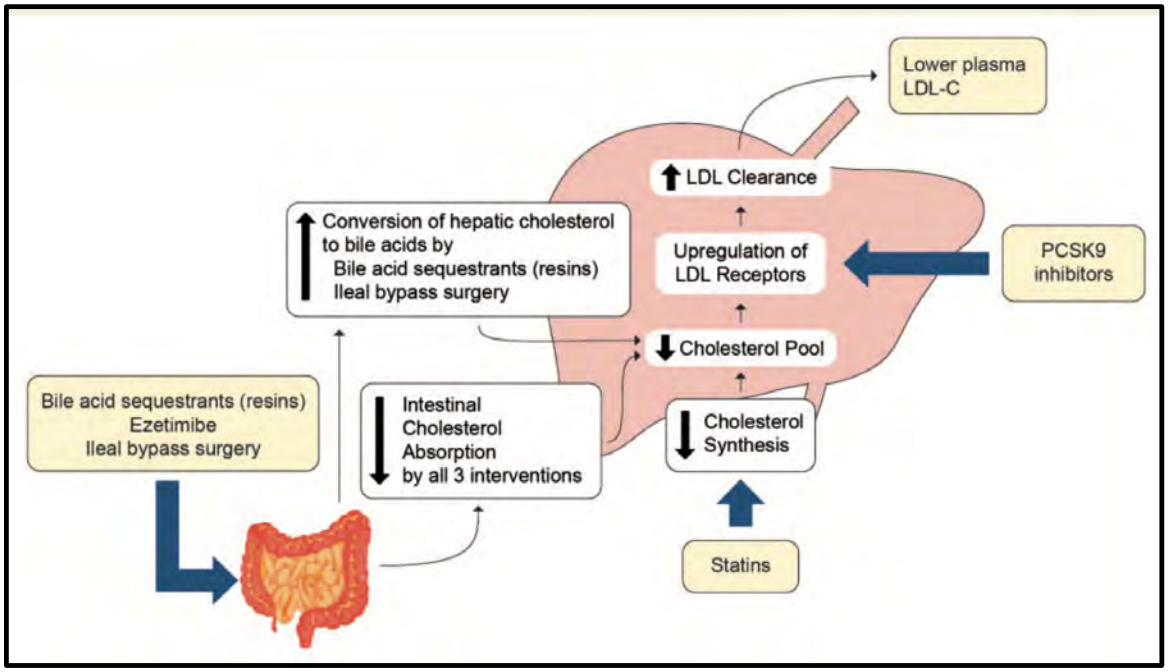
Pharmacologic Lowering of LDL-C: Mechanisms



Ference et al., EHJ 2017

Liver is principal regulator of cholesterol homeostasis

Liver synthesizes, clears and absorbs cholesterol

Key pharmacologic targets
- Enzymatic synthesis (statins; bempedoic acid)
- Intestinal absoroption (ezetimibe)
- LDL-C receptor (PSCK9i)

All pharmacologic approaches to lower LDL-C involve upregulation of LDL-C receptors

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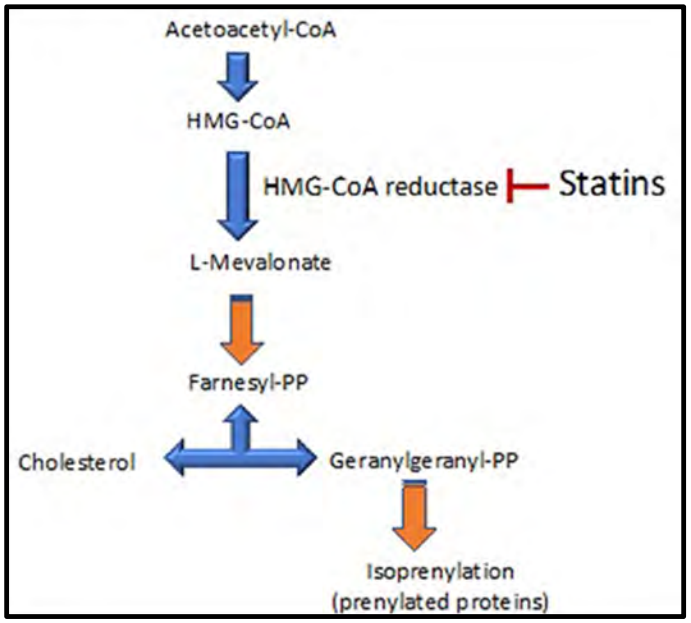
Statins: Mechanism



Bravo et al., JACC 2020

- Statins are structural analogs of HMG-CoA and thereby competitively inhibit the rate-limiting enzyme in cholesterol biosynthesis: HMG-CoA reductase
- By reducing hepatic production of cholesterol -> LDL-C receptor upregulated -> Increased clearance of serum LDL-C
- Secondary effects on improving endothelial function; lowering inflammation and plaque stabilization
- Modest effects on lowering triglycerides and raising HDL-C

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Statins: Intensity

TABLE 2 Examples of High-, Moderate-, and Low-Intensity Statin Therapy (Adapted From 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults)

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately ≥50%.	Daily dose lowers LDL-C, on average, by approximately 30% to <50%.	Daily dose lowers LDL-C, on average, by <30%.
Atorvastatin 40-80 mg	**Atorvastatin 10-20 mg**	Fluvastatin 20-40 mg
Rosuvastatin 20-40 mg	**Fluvastatin 40 mg twice daily**	**Lovastatin 20 mg**
	Fluvastatin XL 80 mg	Pitavastatin 1 mg
	Lovastatin 40 mg	Pravastatin 10-20 mg
	Pitavastatin 2-4 mg	Simvastatin 10 mg
	Pravastatin 40-80 mg	
	Rosuvastatin 5-10 mg	
	Simvastatin 20-40 mg	

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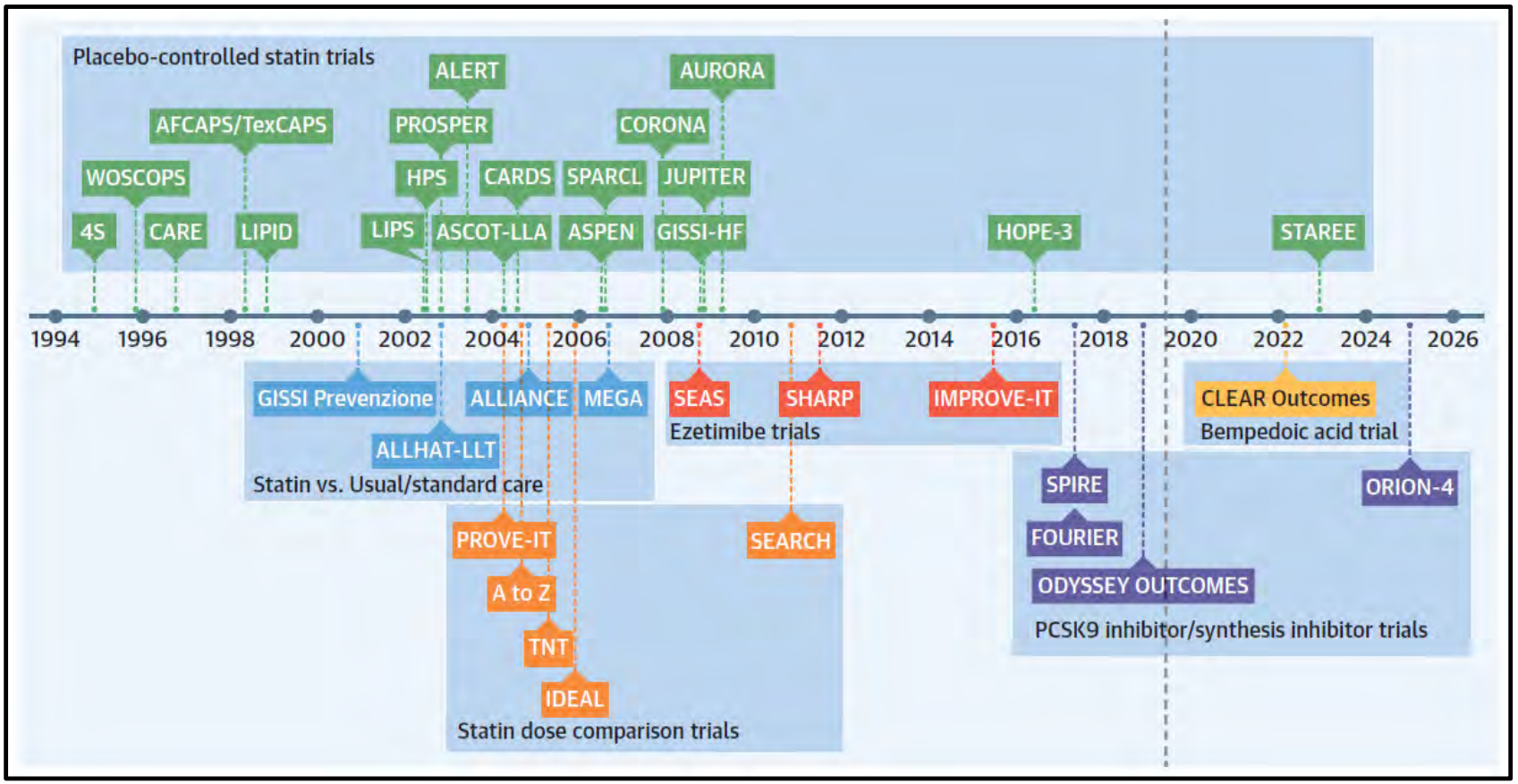
Statins: Evidence Base



Preiss et al., JACC 2020

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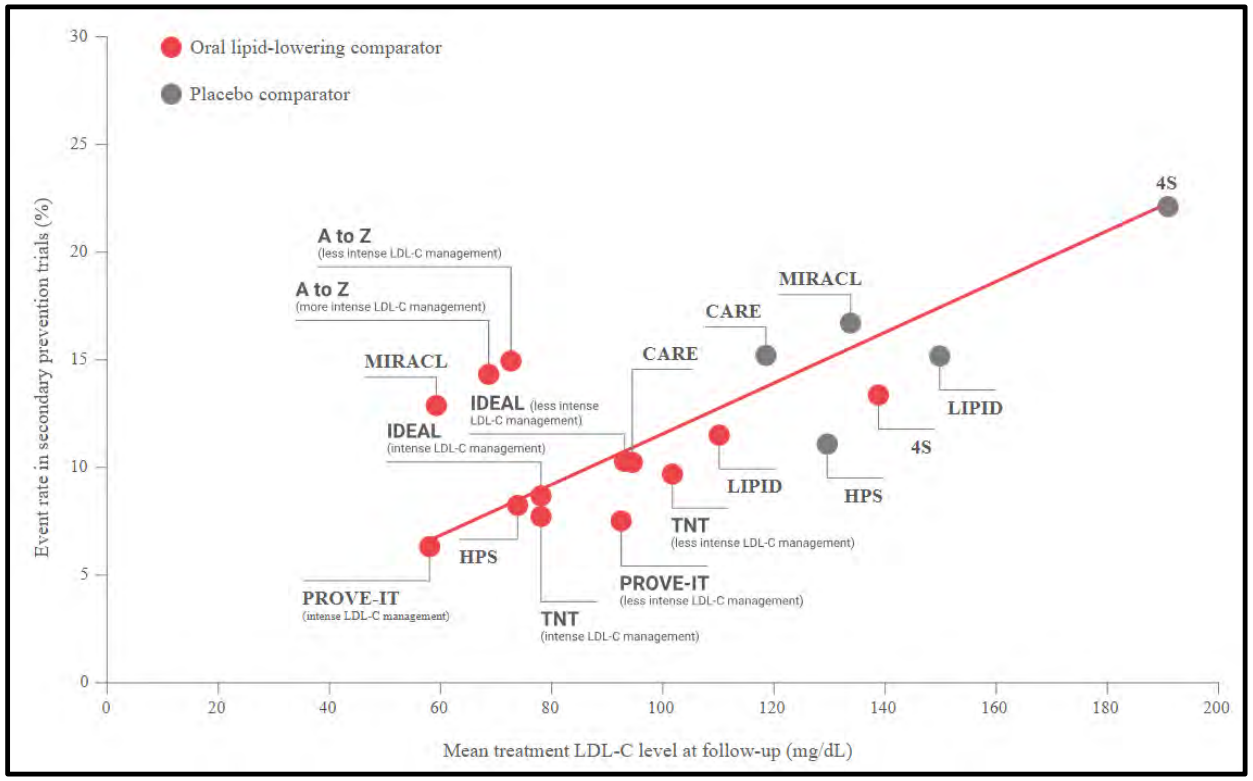
Linear Reduction in CHD with LDL-C Lowering With Statins



For each ~ 40 mg/dl reduction in LDL-C with statin therapy there is an ~ 23% relative reduction in cardiovascular events

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Statin Adverse Events: Statin Associated Muscle Symptoms (SAMS)

- Any muscle symptom temporally related to statin use without implying causality

- Most common reason for statin discontinuation

- Higher in observational studies (10% - 25%) vs. RCT (~5%/year)

- Myalgia (no CK elevation) -> myopathy (CK > 10 ULN) -> rhabdomyolysis (CK > 40 ULN)

Warden et al. , 2023; Newman et al., 2019

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Statin Adverse Events: Muscle Symptoms

Myopathy/Rhabdomyolysis

- Very rare; myopathy (1/1,000); rhabdo (1/10,000)
- Risk factors: hypothyroidism; prior muscle disease; CKD
- Risk is highest in first year of Rx; after dose increase or addition of interacting drug
- May be genetic susceptibility

Warden et al. , 2023; Newman et al., 2019

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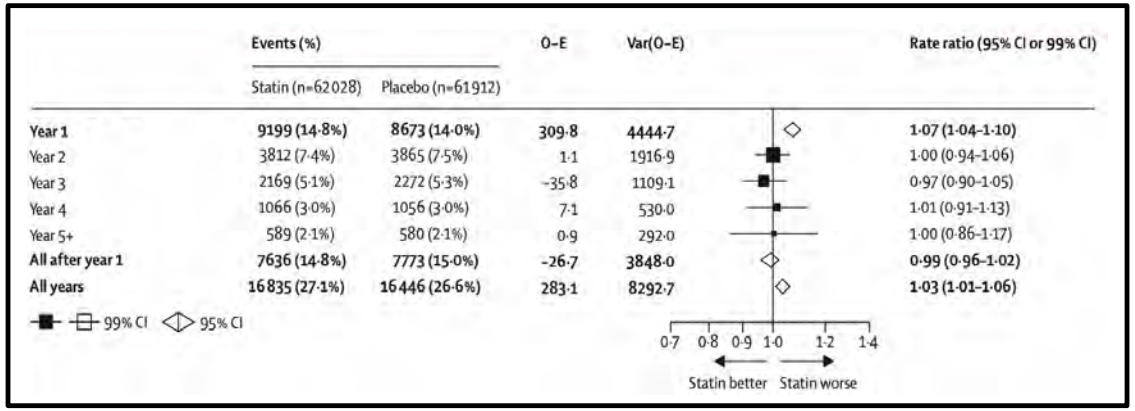
SAMS: Causal Link?



Warden et al. , 2023; Newman et al., 2019

Patient-level meta-analysis; 19 trials

Follow-up 4.3 years

Muscle pain/weakness 27.1% vs. 26.6% (RR 1.03)

Risk highest in year 1 with no difference after

"Most (>90%) of all reports of muscle symptoms …. were not due to the statin. The small risks of muscle symptoms are much lower than the known cardiovascular benefits."

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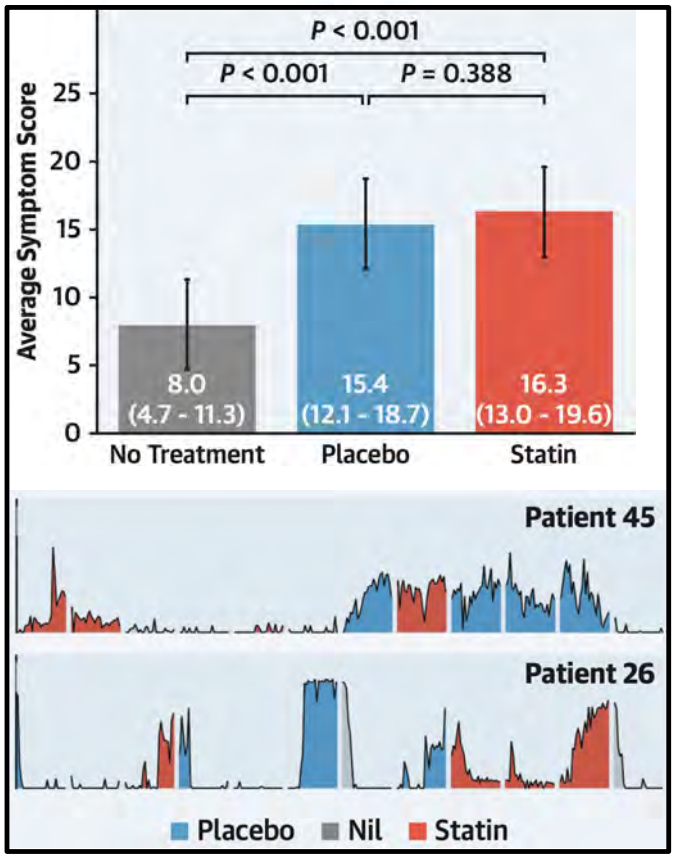
SAMSON Trial: Nocebo Effect



Howard et al., JACC 2020

Nocebo refers to patient expectation of harm with intervention

Included statin-intolerant patients (n=60)

Randomly allocated to receiving 1 month bottles that contained: atorva 20; placebo; nothing

Daily symptoms recorded using an app (scale 1 – 100)

No differences in mean symptom score between placebo and statin

Nocebo ratio 0.90

"The majority of symptoms caused by statin tablets were nocebo. Clinicians should not interpret symptom intensity or timing of symptom onset or offset … as indicating pharmacological causation, because the pattern is identical for placebo."

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Statins and Muscle Adverse Events: Mitigation

- Rechallenge at same or lower dose after temporary discontinuation
- Consider drug/drug interactions (avoid gemfibrozil; caution with antifungals; immunosuppressive agents; macrolide antibiotic; antiarrhythmics)
- Decrease dosing frequency. Consider statin with long half-life (rosuvastatin)
- Switch to different (less potent) statin – Fluvastatin or pravastatin
- Non-statin lipid lowering agents

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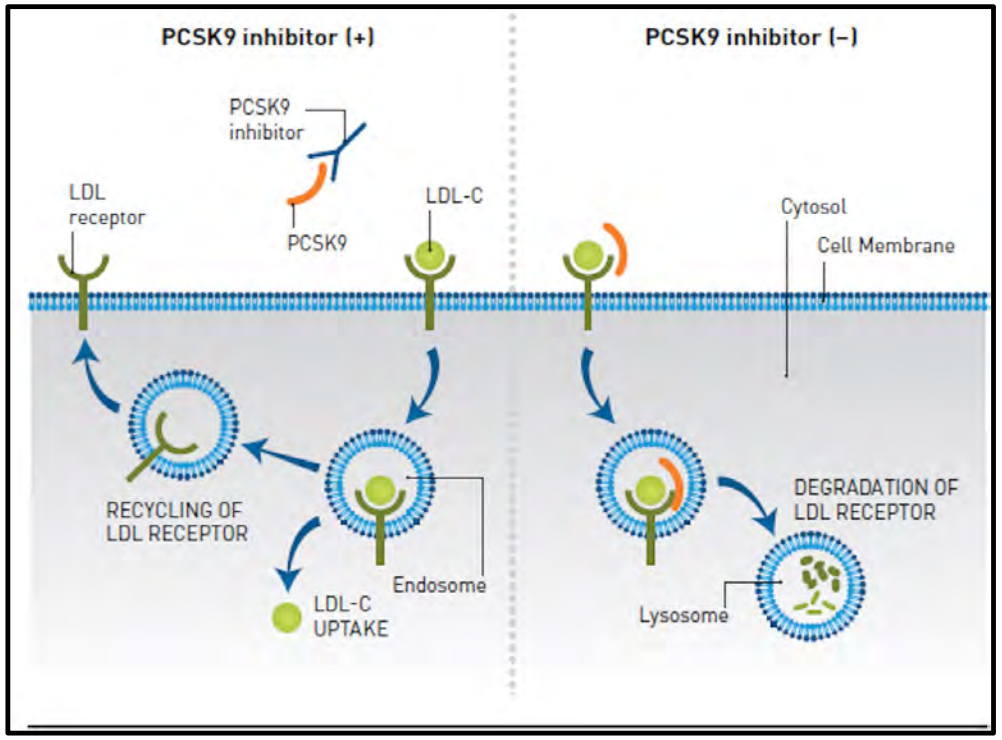
PCSK9 inhibition: Mechanism



Ahn et al., 2015

PCSK9 is an enzyme involved in regulation of LDL-C receptor

The enzyme “tags” the receptor for lysosomal degradation

PCSK9 may be inhibited by monoclonal antibodies injected subcutaneously (alirocumab or evolocumab)

PCSK9 expression can be inhibited using silencing RNA (inclisiran)

With inhibition of PCSK9, the LDL-C receptor is recycled to cell surface thereby increasing clearance of serum LDL-C

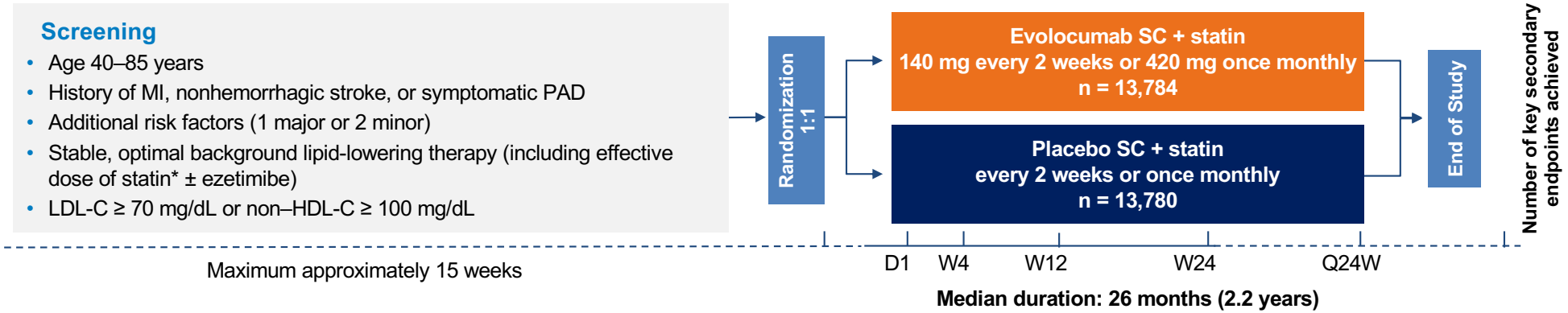
PCSK9i results in ~ 60% lowering of LDL-C

FOURIER: Study Design

Objective: Evaluate the benefit of LDL-C reduction with evolocumab in patients with established CVD

Screening

- Age 40–85 years
- History of MI, nonhemorrhagic stroke, or symptomatic PAD
- Additional risk factors (1 major or 2 minor)
- Stable, optimal background lipid-lowering therapy (including effective dose of statin* ± ezetimibe)
- LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL



Key Baseline Characteristics

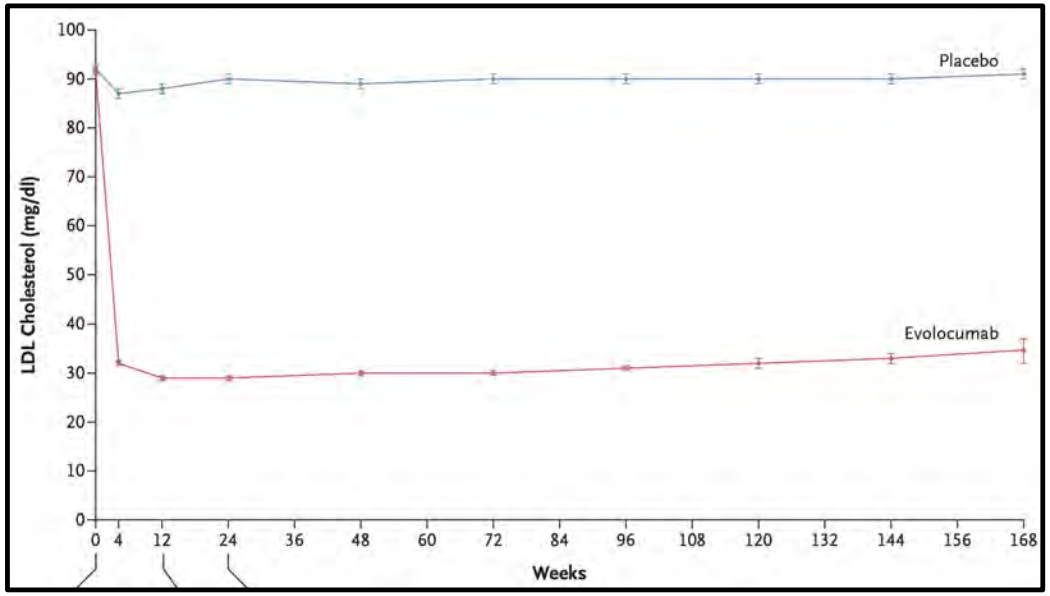
- **Mean age:** 63 years; 75% male
- **History of CV disease:** 81% MI; 19% stroke; 13% PAD
- **Additional CV risk factors:** 80% HTN; 37% DM; 28% smokers
- Background statin use (69% high intensity; 30% moderate intensity); background ezetimibe use (5%)
- Background CV medications included 93% antiplatelet agents; 76% beta-blockers; 56% ACEi; or 23% ARB

*Ideally a high-intensity statin, but at least atorvastatin 20 mg daily or equivalent. Data shown are median values with 95% CIs in the two arms. ITT analysis.

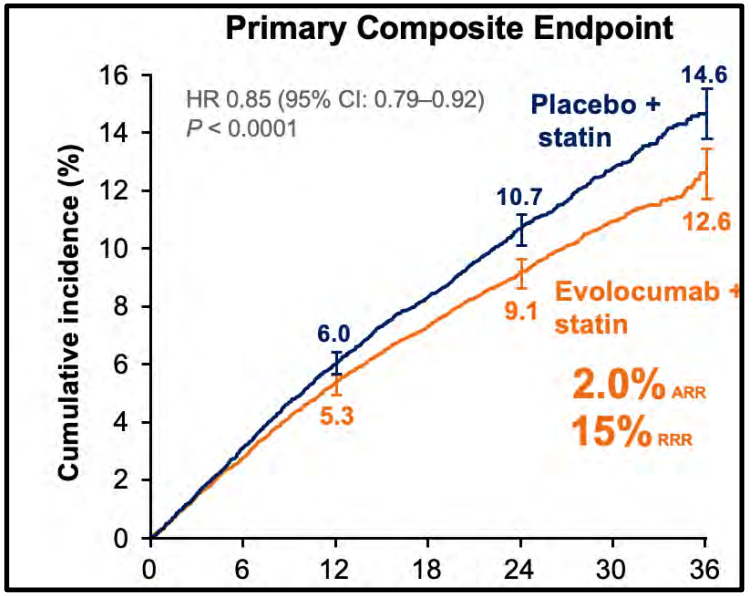
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAD, peripheral artery disease; Q24W, every 24 weeks; SC, subcutaneous.

1. Repatha® (evolocumab) prescribing information, Amgen. 2. Sabatine MS, et al. *Am Heart J*. 2016;173:94-101. 3. Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-1722.

FOURIER: Efficacy



Median LDL-C in evolocumab group 30 mg/dL
By trial end 42% of patients had LDL-C < 25 mg/dL



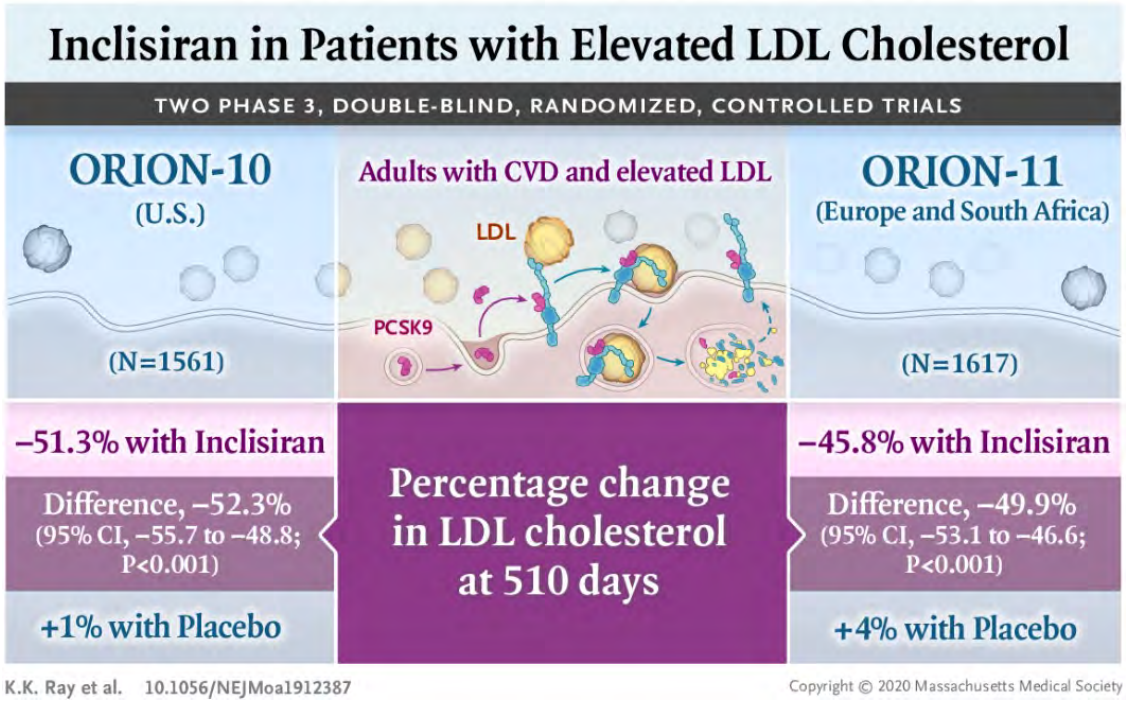
Efficacy consistent in subgroups, including those with LDL-C < 80 mg/dL at baseline

FOURIER: Safety

Safety Profile[1,3]	Evolocumab + statin (N = 13,769)	Placebo + statin (N = 13,756)
Adverse events, %		
Diabetes	8.8	8.2
Adjudicated case of new-onset diabetes	8.1	7.7
Nasopharyngitis	7.8	7.4
Upper respiratory tract infection	5.1	4.8
Muscle-related event	5.0	4.8
Allergic reaction	3.1	2.9
Injection-site reaction	2.1	1.6
Cataract	1.7	1.8
Neurocognitive event	1.6	1.5
Rhabdomyolysis	0.1	0.1

1. Repatha® (evolocumab) prescribing information, Amgen. 2. Sabatine MS, et al. Am Heart J. 2016;173:94-101. 3. Sabatine MS, et al. N Engl J Med. 2017;376:1713-1722.

PCSK9i using siRNA



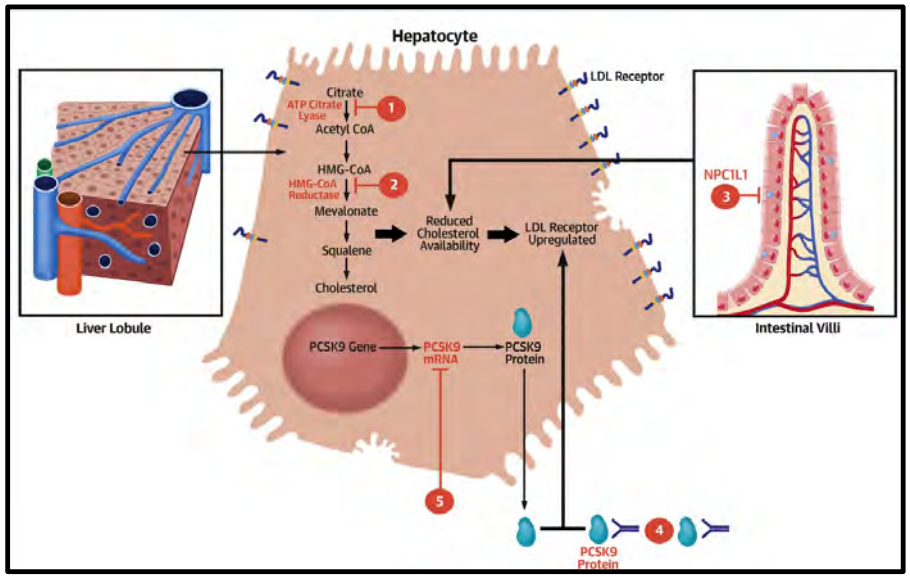
Small interfering RNA (siRNA) that cleaves the mRNA for PCSK9

Reduces synthesis of PCSK9

Administered as subcutaneous injection twice a year

Highly effective in lowering LDL-C with minimal side effects

Ezetimibe: Mechanism



Preiss et al., JACC 2020

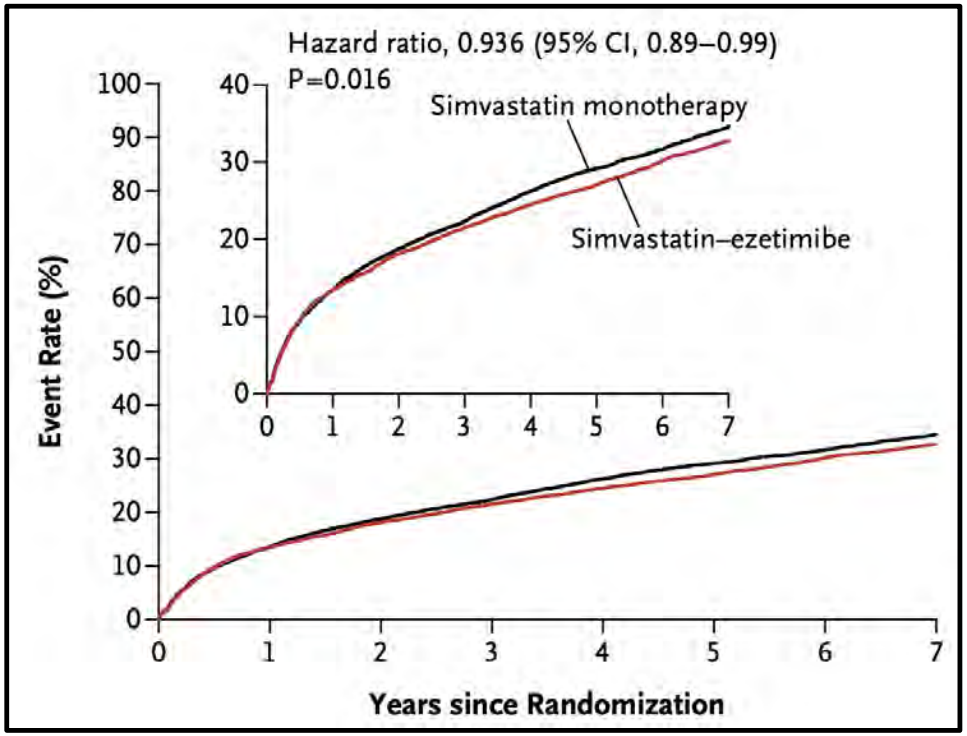
Ezetimibe decreases intestinal absorption of cholesterol by ~ 50% by inhibiting the NPC1L1 enzyme

Orally administered, once daily dosing

Decrease in hepatic cholesterol -> upregulation of LDLR

Ezetimibe reduces LDL-C ~ 20%

Ezetimibe: IMPROVE-IT RCT



Cannon et al., NEJM 2015

n=18,144

Simvastatin 40 mg + ezetimibe 10 mg versus simvastatin 40 mg + placebo

Included patients with recent ACS

Follow-up ~ 6 years

LDL-C lowered by ~ 24% in treatment group (53 vs. 69 mg/dL)

Primary composite EP favored combination Rx

Significant reductions in non-fatal MI and ischemic stroke

Long-term efficacy and safety of moderate-intensity statin with ezetimibe combination therapy versus high-intensity statin monotherapy in patients with atherosclerotic cardiovascular disease (RACING): a randomised, open-label, non-inferiority trial

High-intensity statin (rosuvastatin 20 mg) versus combination of moderate intensity statin (rosuvastatin 10 mg) + ezetimibe

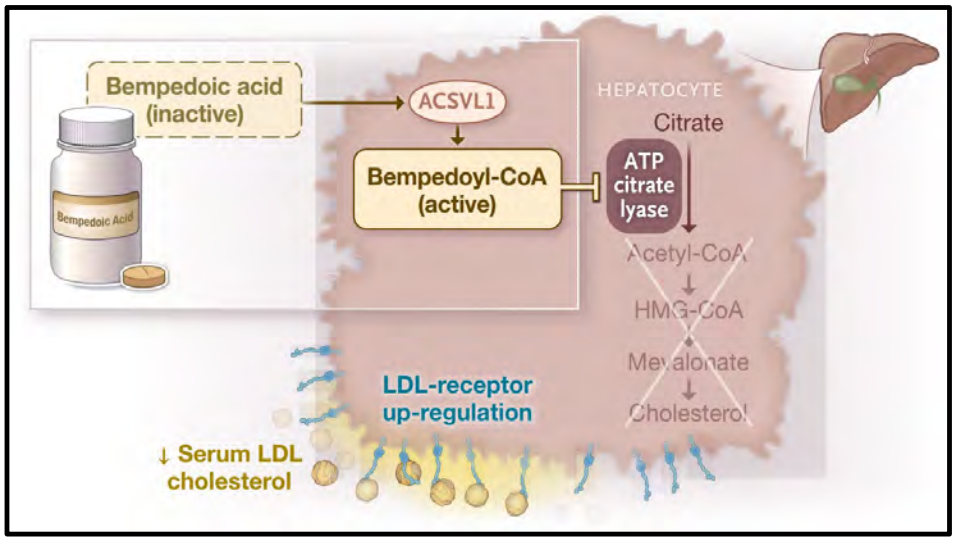
Patients (n=3780) with ASCVD included; conducted in S. Korea

Better LDL-C reduction with combination group (LDL-C < 70 observed 72% vs. 58%)

Less discontinuation with combination therapy (4.8% vs. 8.2%)

Combination therapy with moderate intensity statin + ezetimibe may enable patients unable to tolerate high-intensity statin to achieve greater LDL-C reduction with better adherence

Bempedoic Acid: Mechanism



Inhibits enzyme ATP citrate lyase

Targets cholesterol synthesis upstream of statins

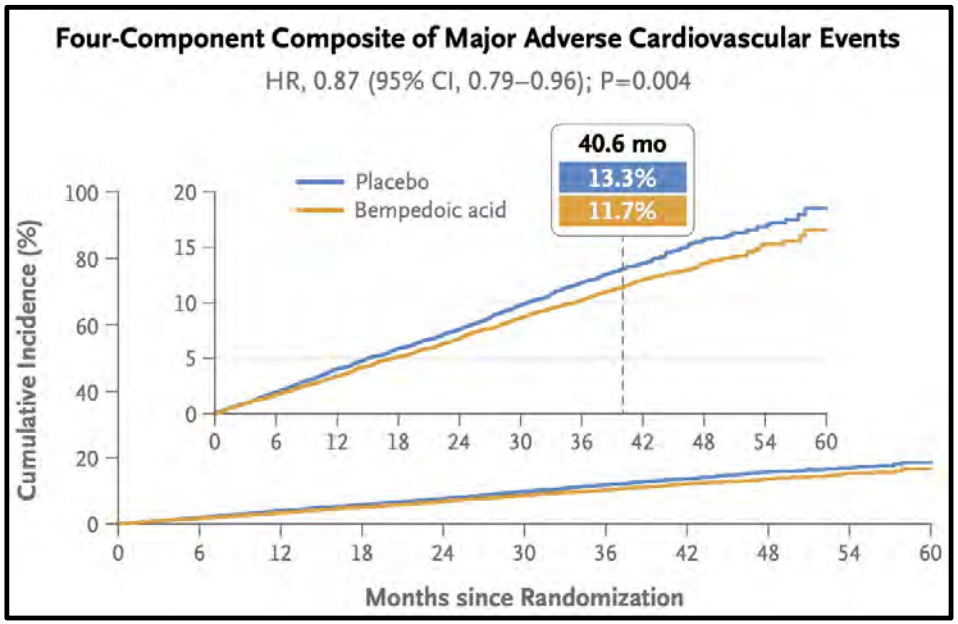
Reduces hepatic cholesterol -> LDLR upregulation

Prodrug that is activated in the liver and not in skeletal muscle that may reduce potential for muscle AE

Inhibits renal transporter involved in uric acid excretion

Bempedoic Acid: CLEAR Outcomes

13,970 patients at elevated cardiovascular risk unable or unwilling to take recommended statin dose



Adverse Events

	Bempedoic acid (N=7001)	Placebo (N=6964)
	no. of patients (%)	
Any adverse event	6040 (86.3)	5919 (85.0)
Elevated hepatic enzymes	317 (4.5)	209 (3.0)
Renal impairment	802 (11.5)	599 (8.6)
Hyperuricemia	763 (10.9)	393 (5.6)
Gout	215 (3.1)	143 (2.1)
Cholelithiasis	152 (2.2)	81 (1.2)

Risk of gout highest in patients with elevated levels of uric acid at baseline and with prior history

Myalgias numerically lower with Bempedoic acid (5.6% vs. 6.8%)

Outline

- Framework for atherosclerosis
- Pharmacologic interventions: Statins; PCSK9i; Ezetimibe; Bempedoic acid
- **Risk Assessment; Guidelines; Risk Enhancers**

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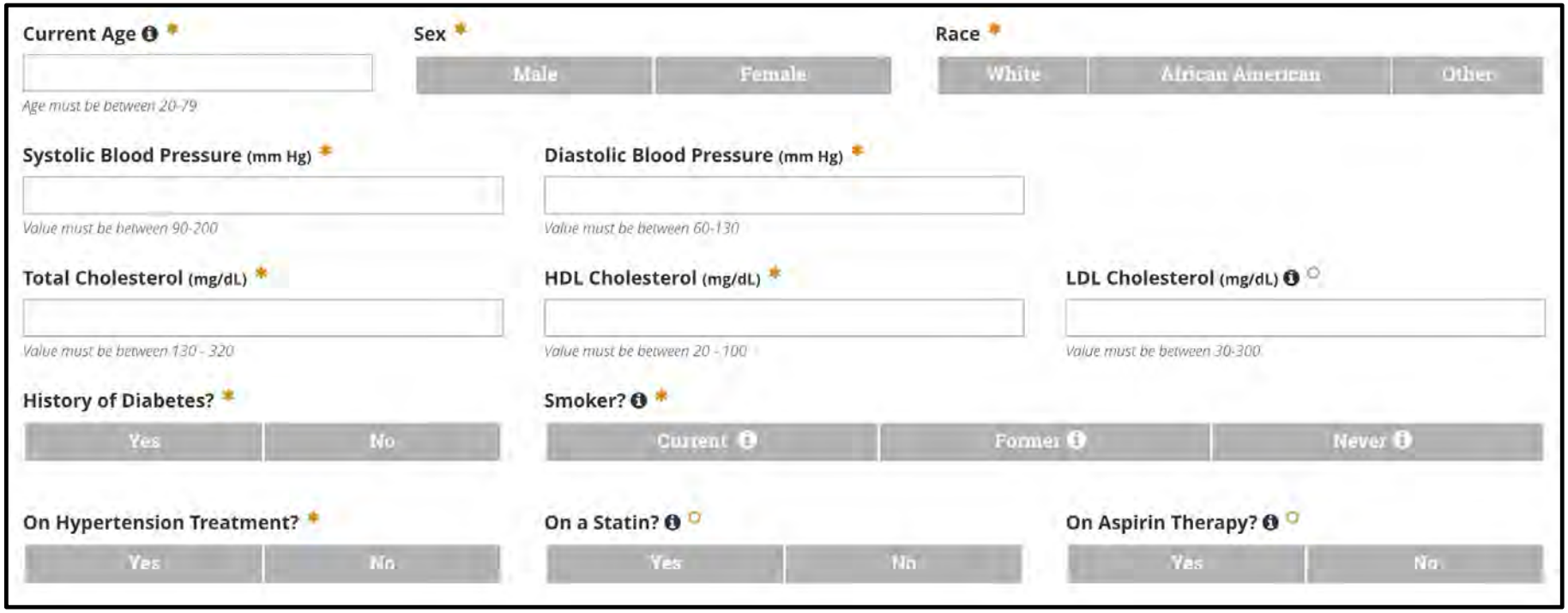
Risk Assessment: Pooled Cohort Equations



10-year risk estimates: low (<5%); Borderline (5-7.5%); Intermediate (7.5%-20%); High (> 20%)

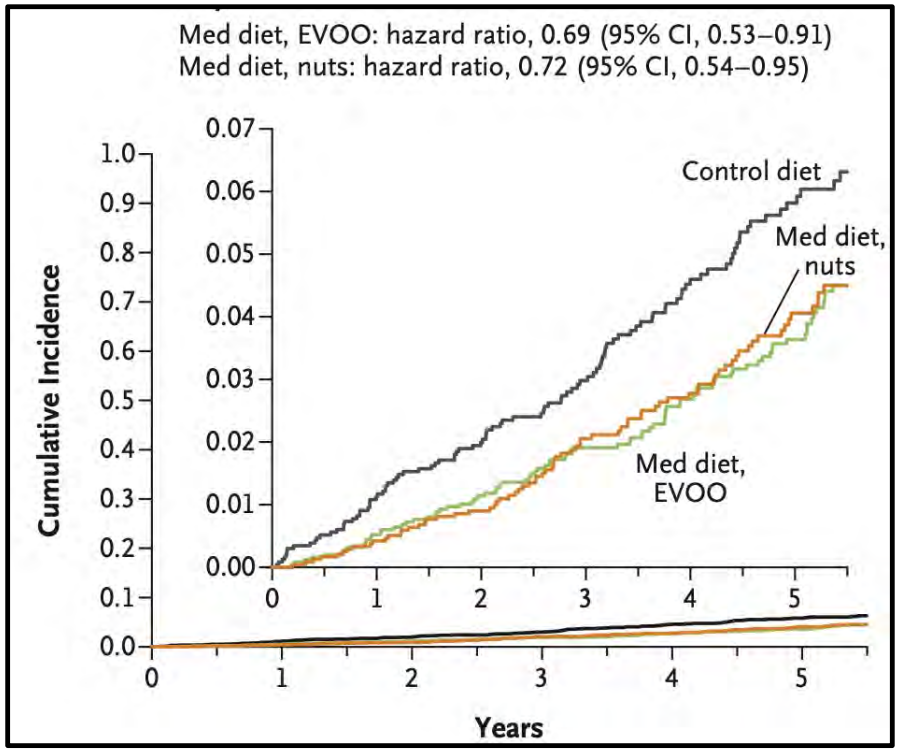
ACC/AHA Primary Prevention Guidelines: Nutrition and Diet

COR	LOE	Recommendations
I	B-R	1. A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended to decrease ASCVD risk factors.[S3.1-1–S3.1-11]
IIa	B-NR	2. Replacement of saturated fat with dietary monounsaturated and polyunsaturated fats can be beneficial to reduce ASCVD risk.[S3.1-12,S3.1-13]
IIa	B-NR	3. A diet containing reduced amounts of cholesterol and sodium can be beneficial to decrease ASCVD risk.[S3.1-9,S3.1-14–S3.1-16]
IIa	B-NR	4. As a part of a healthy diet, it is reasonable to minimize the intake of processed meats, refined carbohydrates, and sweetened beverages to reduce ASCVD risk.[S3.1-17–S3.1-24]
III: Harm	B-NR	5. As a part of a healthy diet, the intake of *trans* fats should be avoided to reduce ASCVD risk.[S3.1-12,S3.1-17,S3.1-25–S3.1-27]

Arnett et al., Circulation 2019

Food	Goal
Mediterranean diet	
Recommended	
Olive oil*	≥4 tbsp/day
Tree nuts and peanuts†	≥3 servings/wk
Fresh fruits	≥3 servings/day
Vegetables	≥2 servings/day
Fish (especially fatty fish), seafood	≥3 servings/wk
Legumes	≥3 servings/wk
Sofrito‡	≥2 servings/wk
White meat	Instead of red meat
Wine with meals (optionally, only for habitual drinkers)	≥7 glasses/wk
Discouraged	
Soda drinks	<1 drink/day
Commercial bakery goods, sweets, and pastries§	<2 servings/wk
Spread fats	<1 serving/day
Red and processed meats	<1 serving/day

Mediterranean Diet Randomized Evidence: PREDIMED Trial



Estruch et al., NEJM 2018

n = 7447

High risk for CVD

Mediterranean diet with extra-virgin olive oil; mixed nuts or control diet

Follow-up 4.8 years

~ 30% reduction in cardiovascular events with either Meditteranean diet

ACC/AHA Primary Prevention Guidelines: Exercise and Physical Activity

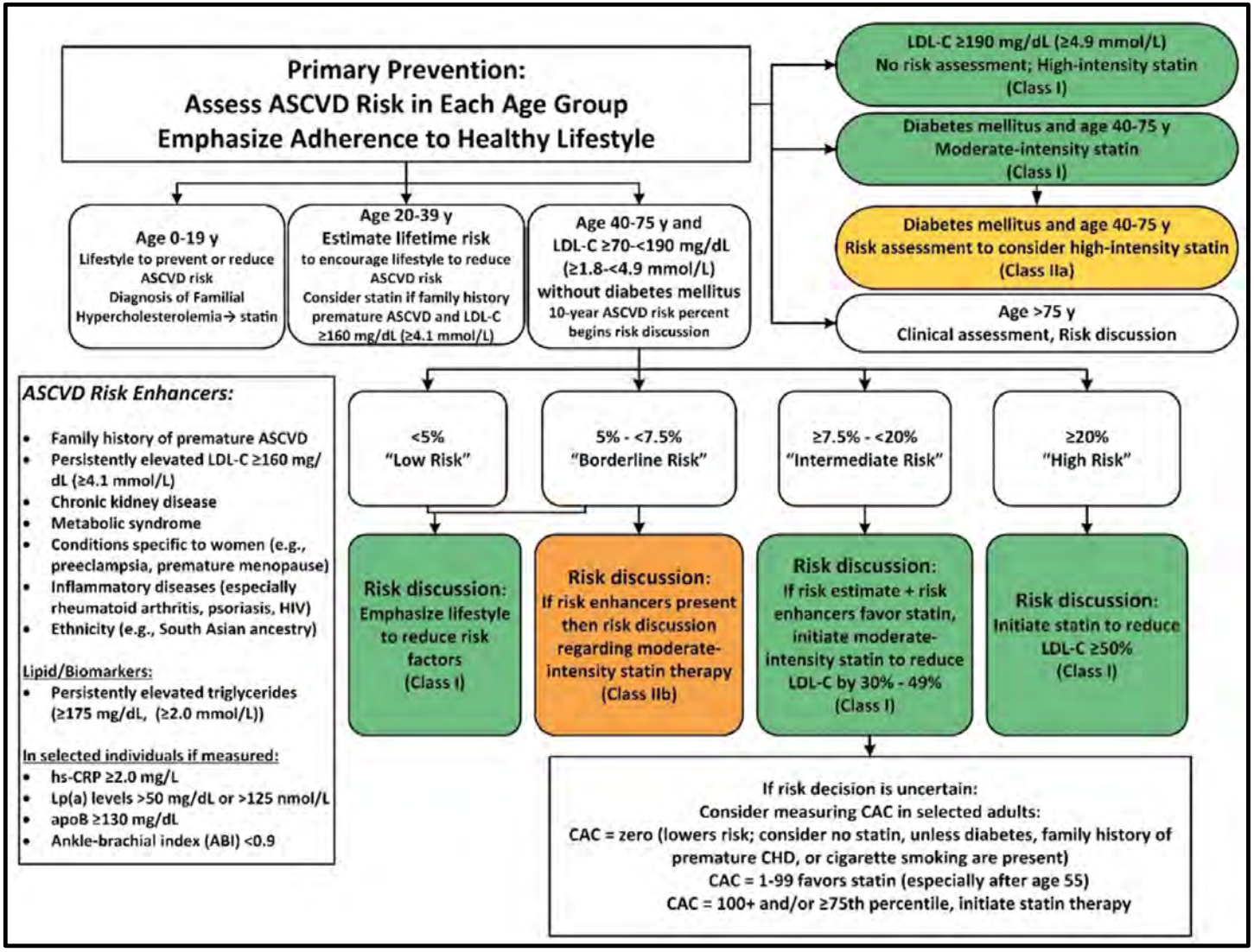
COR	LOE	Recommendations
I	B-R	1. Adults should be routinely counseled in healthcare visits to optimize a physically active lifestyle.[S3.2-1,S3.2-2]
I	B-NR	2. Adults should engage in at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity (or an equivalent combination of moderate and vigorous activity) to reduce ASCVD risk.[S3.2-3–S3.2-8]

Arnett et al., Circulation 2019

Intensity	METs	Examples
Sedentary behavior*	1–1.5	Sitting, reclining, or lying; watching television
Light	1.6–2.9	Walking slowly, cooking, light housework
Moderate	3.0–5.9	Brisk walking (2.4–4 mph), biking (5–9 mph), ballroom dancing, active yoga, recreational swimming
Vigorous	≥6	Jogging/running, biking (≥10 mph), singles tennis, swimming laps

2018 ACC/AHA Blood Cholesterol Guideline

Grundy et al., Circulation 2018



Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease

METHODS

In one comparison from a 2-by-2 factorial trial, we randomly assigned 12,705 participants in 21 countries who did not have cardiovascular disease and were at intermediate risk to receive rosuvastatin at a dose of 10 mg per day or placebo. The first coprimary outcome was the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, and the second coprimary outcome additionally included revascularization, heart failure, and resuscitated cardiac arrest. The median follow-up was 5.6 years.

RESULTS

The overall mean low-density lipoprotein cholesterol level was 26.5% lower in the rosuvastatin group than in the placebo group. The first coprimary outcome occurred in 235 participants (3.7%) in the rosuvastatin group and in 304 participants (4.8%) in the placebo group (hazard ratio, 0.76; 95% confidence interval [CI], 0.64 to 0.91; P=0.002). The results for the second coprimary outcome were consistent with the results for the first (occurring in 277 participants [4.4%] in the rosuvastatin group and in 363 participants [5.7%] in the placebo group; hazard ratio, 0.75; 95% CI, 0.64 to 0.88; P<0.001). The results were also consistent in subgroups defined according to cardiovascular risk at baseline, lipid level, C-reactive protein level, blood pressure, and race or ethnic group. In the rosuvastatin group, there was no excess of diabetes or cancers, but there was an excess of cataract surgery (in 3.8% of the participants, vs. 3.1% in the placebo group; P=0.02) and muscle symptoms (in 5.8% of the participants, vs. 4.7% in the placebo group; P=0.005).

CONCLUSIONS

Treatment with rosuvastatin at a dose of 10 mg per day resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; HOPE-3 ClinicalTrials.gov number, NCT00468923.)

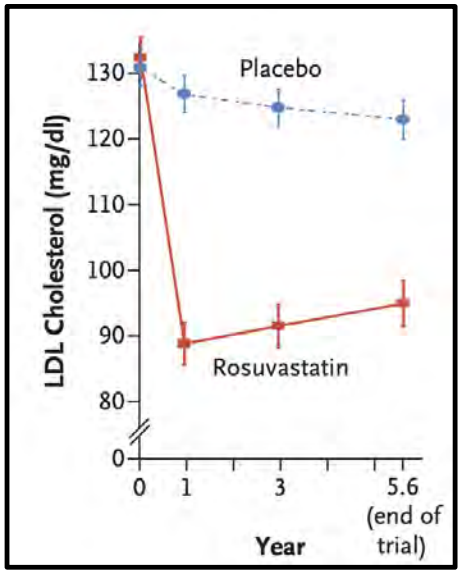
Yusuf et al., NEJM 2016

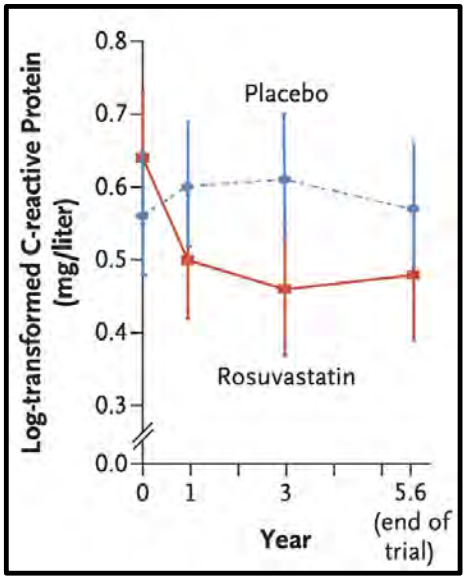
HOPE-3 Clinical Trial

Intermediate Risk Patients randomized to rosuvastatin 10 mg versus placebo

Significant reductions in LDL-C

Significant reductions in hard cardiovascular endpoints





Risk Enhancer: CRP

Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

METHODS

We randomly assigned 17,802 apparently healthy men and women with low-density lipoprotein (LDL) cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) and high-sensitivity C-reactive protein levels of 2.0 mg per liter or higher to rosuvastatin, 20 mg daily, or placebo and followed them for the occurrence of the combined primary end point of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

RESULTS

The trial was stopped after a median follow-up of 1.9 years (maximum, 5.0). Rosuvastatin reduced LDL cholesterol levels by 50% and high-sensitivity C-reactive protein levels by 37%. The rates of the primary end point were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (hazard ratio for rosuvastatin, 0.56; 95% confidence interval [CI], 0.46 to 0.69; P<0.00001), with corresponding rates of 0.17 and 0.37 for myocardial infarction (hazard ratio, 0.46; 95% CI, 0.30 to 0.70; P=0.0002), 0.18 and 0.34 for stroke (hazard ratio, 0.52; 95% CI, 0.34 to 0.79; P=0.002), 0.41 and 0.77 for revascularization or unstable angina (hazard ratio, 0.53; 95% CI, 0.40 to 0.70; P<0.00001), 0.45 and 0.85 for the combined end point of myocardial infarction, stroke, or death from cardiovascular causes (hazard ratio, 0.53; 95% CI, 0.40 to 0.69; P<0.00001), and 1.00 and 1.25 for death from any cause (hazard ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02). Consistent effects were observed in all subgroups evaluated. The rosuvastatin group did not have a significant increase in myopathy or cancer but did have a higher incidence of physician-reported diabetes.

CONCLUSIONS

In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. (ClinicalTrials.gov number, NCT00239681.)

Ridker et al., NEJM 2008

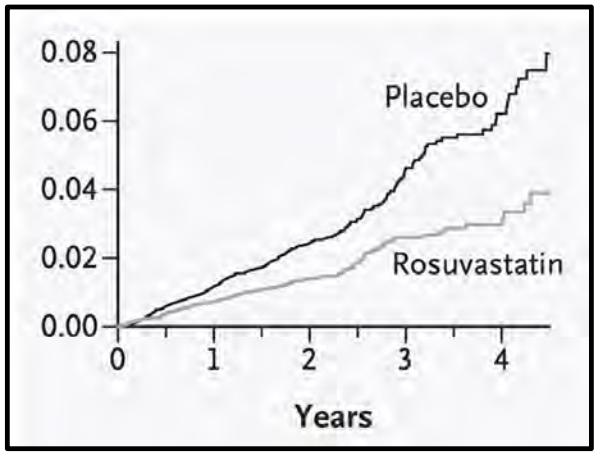
JUPITER

n = 17,802

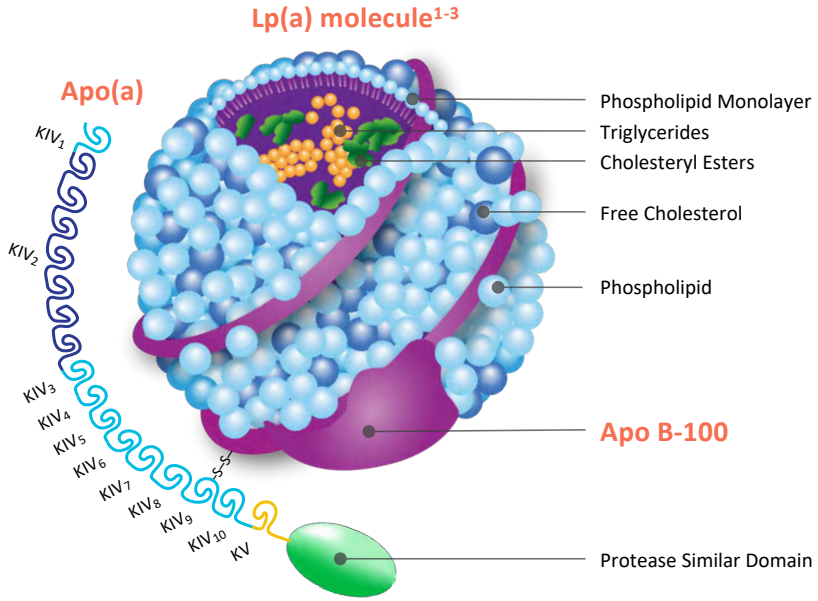
LDL-C < 130 mg/dL and CRP > 2.0 mg/L

Rosuvastatin 20 mg versus placebo

LDL-C reduced by 50% and CRP by 37% - > 44% reduction in CVD



Lp(a) is Atherogenic, Prothrombotic and Proinflammatory



- Lp(a) is produced in the liver and has two main components joined by a covalent disulfide bond[1,2]
  - A lipid core moiety that is an LDL-like particle containing apolipoprotein B-100, which is proatherosclerotic[1,2]

    and
  - A single molecule of apolipoprotein(a)[1-3]

Lp(a) differs from LDL in that Lp(a) contains a molecule of apo(a)[1,2]

apo, apoprotein; KI, kringle type I; KII, kringle type II; KIII, kringle type III; KIV, kringle type IV; KV, kringle type V; Lp(a), lipoprotein (a).

1. Cai A, et al. *Dis Markers*. 2013;35(5):551-559. 2. Tsimikas S. *J Am Coll Cardiol*. 2017;69:692-711. 3. Jawi MM, et al. *J Lipids*.2020:1-26. doi.org /10.1155/2020/3491764.

Lp(a) Concentration Primarily Controlled by Genetics

Major influence

Genetics predominantly control Lp(a) concentrations: (70% to >90%)[1]

Lesser influence

Some non-genetic factors may influence Lp(a) levels[1]

- Chronic kidney disease: ↑Lp(a) with ↓GFR (nephrotic syndrome)[1]
- Liver disease: ↓Lp(a)[1]
- Hypothyroidism: ↑Lp(a)[1]
- Menopausal women: ↑Lp(a)[2]
- Acute inflammatory processes (acute phase reactant): transient ↑Lp(a)[3]

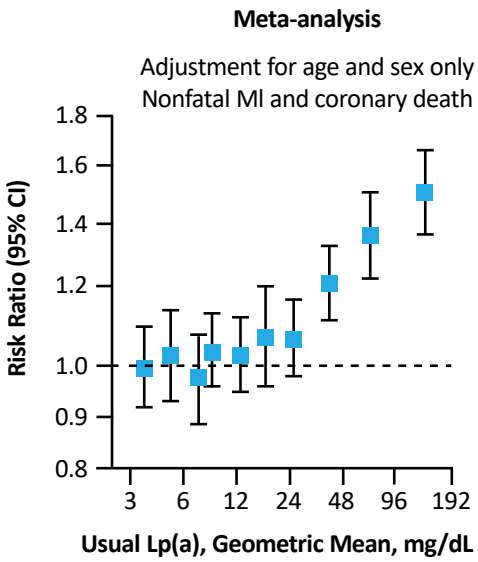
No effect

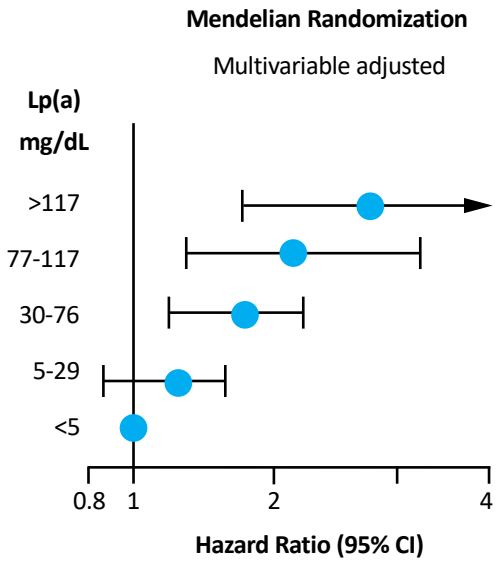
Lifestyle changes such as diet and physical exercise have **NO** significant impact on Lp(a) plasma concentrations[4]

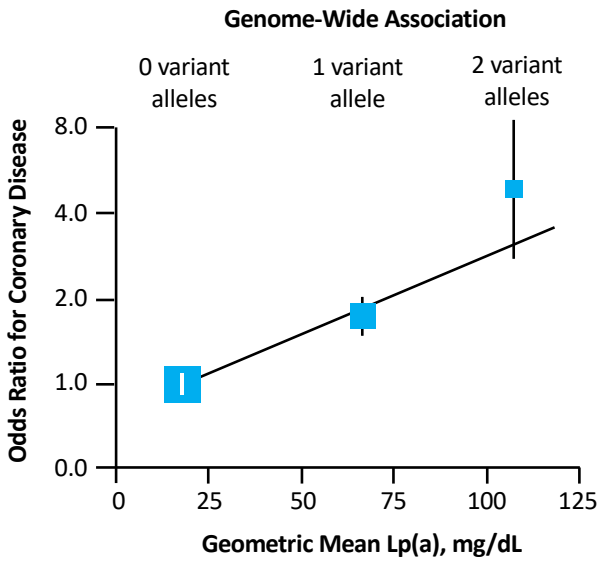
GFR, glomerular filtration rate; Lp(a), lipoprotein(a)

1. Cegla J, et al. *Atherosclerosis*. 2019;291:62-70. 2. Newman CB, et al. *J Clin Endocrinol Metab*. 2020;105:3613-3682. 3. Pirro M, et al. *Pharmacol Res.* 2017;119:178-187.
4. Wilson DP, et al. *J Clin Lipidology*. 2019;63:374-392.

Lp(a) is an Independent Risk Factor for CVD







Elevated Lp(a) is associated with a higher risk for CVD, particularly MI, as shown by epidemiological studies, meta-analyses, Mendelian randomization, & genome-wide association studies

CI, confidence interval; CVD, cardiovascular disease; Lp(a), lipoprotein(a); MI, myocardial infarction

As summarized in Tsimikas S. *J Am Coll Cardiol*. 2017;69(6):692-711.

Coronary Artery Calcium (CAC) scoring

IIa	B-NR	6. In intermediate-risk or selected borderline-risk adults, if the decision about statin use remains uncertain, it is reasonable to use a CAC score in the decision to withhold, postpone or initiate statin therapy.[S4.4.2-15,S4.4.2-17,S4.4.2-23]
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]

Grundy et al., Circulation 2018

Readily available

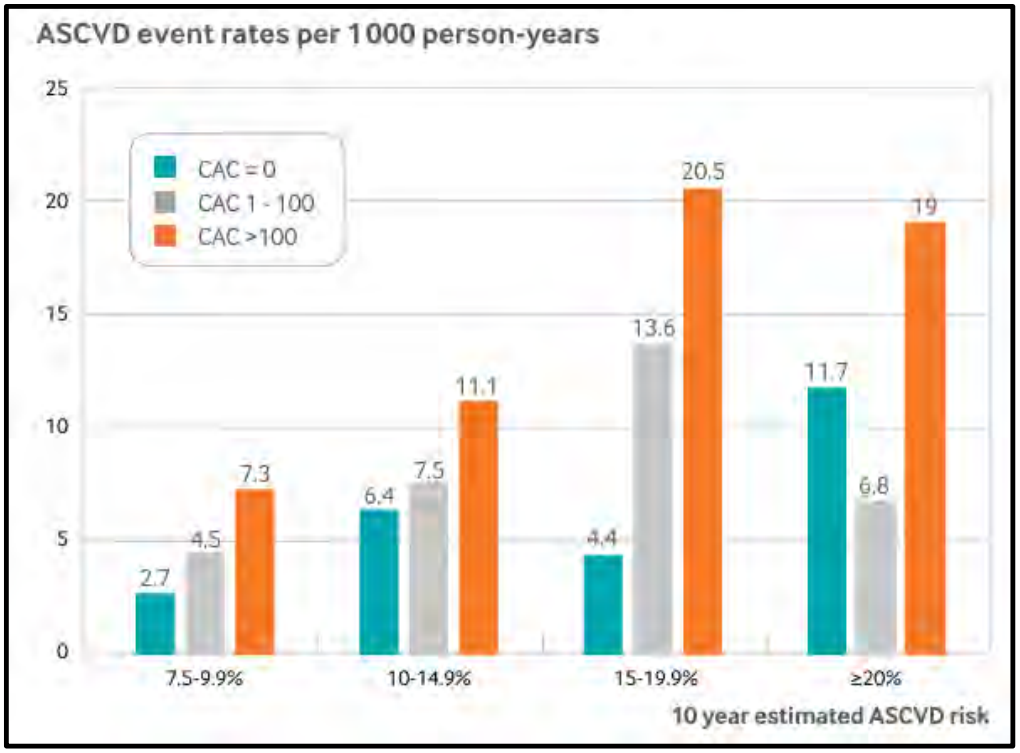
Minimal risk and low cost

Lack of calcium (zero) associated with very low risk in absence of high-risk conditions (DM, active smoking, family history)

Elevated CAC scores identify intermediate risk patients who may benefit from lipid lowering Rx

No utility in patients already treated with statins

Coronary Artery Calcium (CAC) scoring



Nasir et al., BMJ 2021

"power of zero"

"… the absence of CAC confers a sufficiently low risk of future cardiovascular events …. Allowing for more flexible treatment goals including deferring specific pharmacotherapies and focusing on lifestyle interventions."

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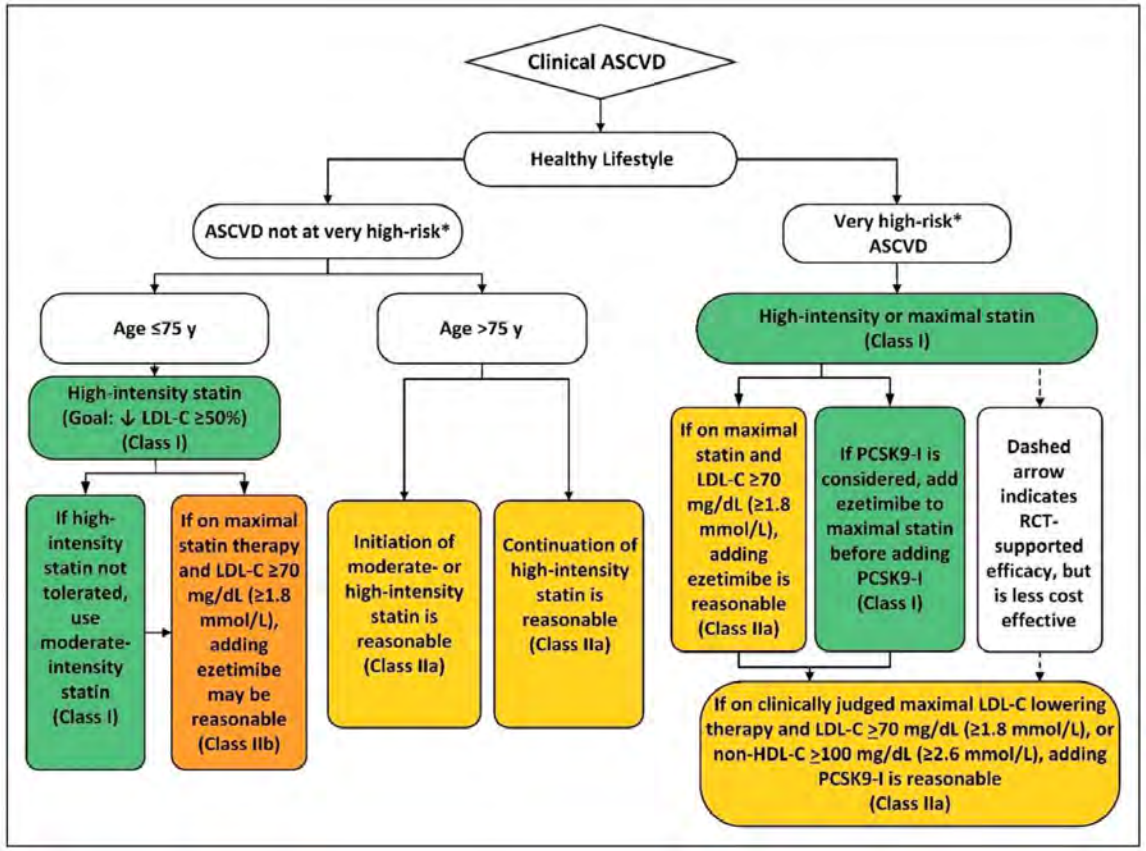
Secondary Prevention



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[S4.1-40])
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)[S4.1-15,S4.1-17]
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 multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.

Grundy et al., Circulation 2018

Most Patients with ASCVD Met Guideline Definition of Very High Risk

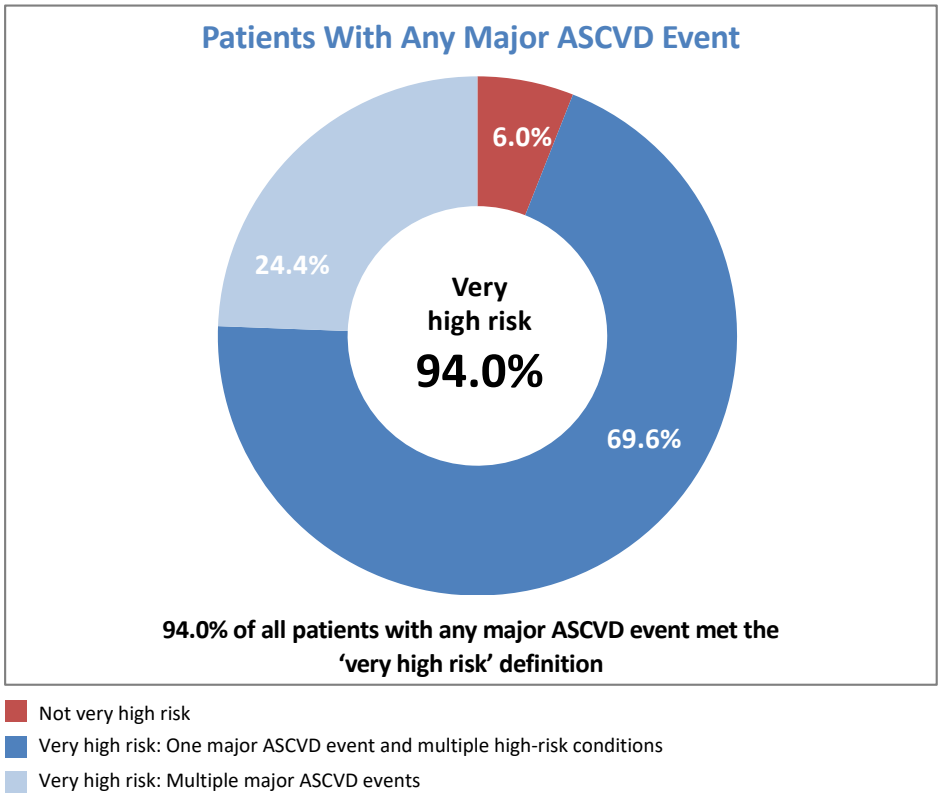
Patients:

US adults with a history of a major ASCVD event in the MarketScan database (N = 16,344)

→ Experienced an ACS in the past year (n = 3,626)

→ Followed from Jan 1, 2016, to December 31, 2017, for recurrent ASCVD events

- A majority of patients were ≥ 65 years of age (54.5%) and had a prior PCI or CABG (51.2%) and DM (51.9%)
- HTN was the most common high-risk condition, present among 93.2% of patients
- 66.8% had an LDL-C ≥ 70 mg/dL



ACC, American College of Cardiology; AHA, American Heart Association; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; DM, diabetes mellitus; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; US, United States; VHR, very high risk.

Muntner P, et al. *Cardiovasc Drugs Ther.* 2022;36:475-481.

2022 ACC Expert Consensus Decision Pathway (ECDP)

The 2022 ACC Consensus Pathway provided updated recommendations for adults with clinical ASCVD on maximally tolerated statin therapy for secondary prevention and for adults without ASCVD on a statin for LDL-C lowering based on the following patient characteristics:

ASCVD at VHR* Threshold: LDL-C **< 55 mg/dL and/or ≥ 50%** LDL-C reduction	**ASCVD Not at VHR** Threshold: LDL-C **< 70 mg/dL and/or ≥ 50%** LDL-C reduction
If optimal reduction isn't achieved:	**If optimal reduction isn't achieved:**
• **1st** Consider **PCSK9 mAbs,** like evolocumab, and/or ezetimibe.[†,‡] If still not achieved:	• **1st** Consider ezetimibe. If still not achieved:
• **2nd** May consider bempedoic acid or inclisiran[§]	• **2nd** May consider adding or replacing with **PCSK9 mAbs**, like evolocumab.[‡] If still not achieved:
	• **3rd** May consider bempedoic acid or inclisiran[§]

Adults in the Above Categories With Possible Statin-Associated Side Effects

Consider **1st PCSK9 mAbs** and/or ezetimibe; if still not achieved, **2nd** bempedoic acid or inclisiran; if still not achieved, **3rd** consider evinacumab for HoFH**

Some adults in above categories who require greater LDL-C reduction than any therapy alone can expect to achieve, may consider simultaneous addition of 2 agents to reduce the risk of recurrent events more rapidly. Consider maximally tolerated statin therapy with or without ezetimibe AND PCSK9 mAb, OR maximally tolerated statin therapy and ezetimibe

*Defined as having a history of major ASCVD events or having 1 major ASCVD event and multiple high-risk conditions (eg, aged ≥ 65 years, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD events[s]).

[†]PCSK9 mAbs may be preferred as the initial non-statin agent in patients who require > 25% additional lowering of LDL-C or based on clinician-patient decision-making. Potential considerations in use of PCSK9 mAbs compared to ezetimibe include net risk reduction benefits of a PCSK9 mAb, subcutaneous injection administration, biweekly or monthly dosing schedule, storage requirements, and cost.

[‡]Strongly consider PCSK9 mAbs if fully statin intolerant and attempts to lower LDL-C with ezetimibe or BAS result in persistent < 50% LDL-C reduction (or may consider if LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL). Consider PCSK9 mAbs only if on maximally tolerated statin therapy and persistent < 50% LDL-C reduction (or may consider if LDL-C ≥ 70 mg/dL or non-HDL ≥ 100 mg/dL).

[§]For adults with ASCVD at VHR with confirmation of FH or adults without ASCVD may consider evinacumab, lomitapide, and/or LDL apheresis for HoFH under care of a lipid specialist for adults with ASCVD without confirmation of FH, may consider LDL apheresis for HoFH under care of a lipid specialist.

**Evinacumab considered third line for adults with possible statin-associated side effects and very high-risk clinical ASCVD or baseline LDL-C ≥ 190 mg/dL, or without ASCVD or with LDL-C ≥ 190 mg/dL.

ACC, American College of Cardiology; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; BAS, bile acid sequestrants; HDL, high-density lipoprotein; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; mAb, monoclonal antibody; PCSK9, proprotein convertase subtilisin/kexin type 9; VHR, very high risk.

Lloyd-Jones D, et al. *J Am Coll Cardiol.* 2022. In press. doi:10.1016/j.jacc.2022.07.006.

GOULD: Less than One Third of ASCVD Patients had LDL-C < 70 mg/dL Over 2 years

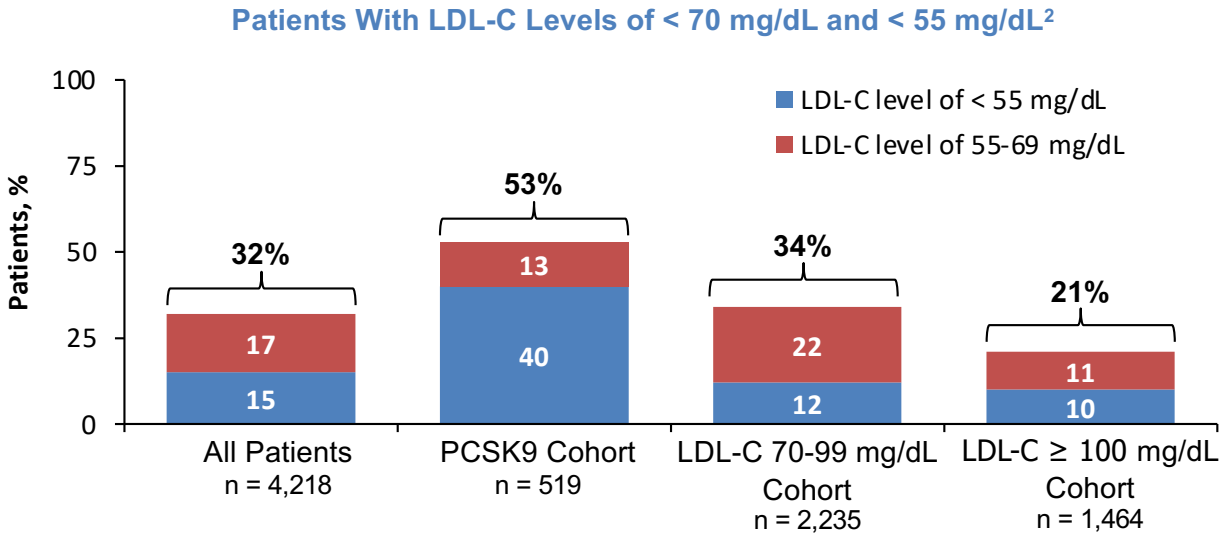
Prospective observational registry study: Getting to an Improved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia Management (GOULD): Patients from 119 sites in the US[1,2]

Patients:

N = 5,006*
Adult patients with ASCVD† who have received stable LLT for at least 4 weeks prior to enrollment

Mean Age (SD):

67.8 (9.9) years



- Only **17%** patients had some type of LLT intensification
- Lipid panels were measured at least once in 89% of patients - **11%** of patients did not have any lipid testing, and **21%** had only one lipid testing

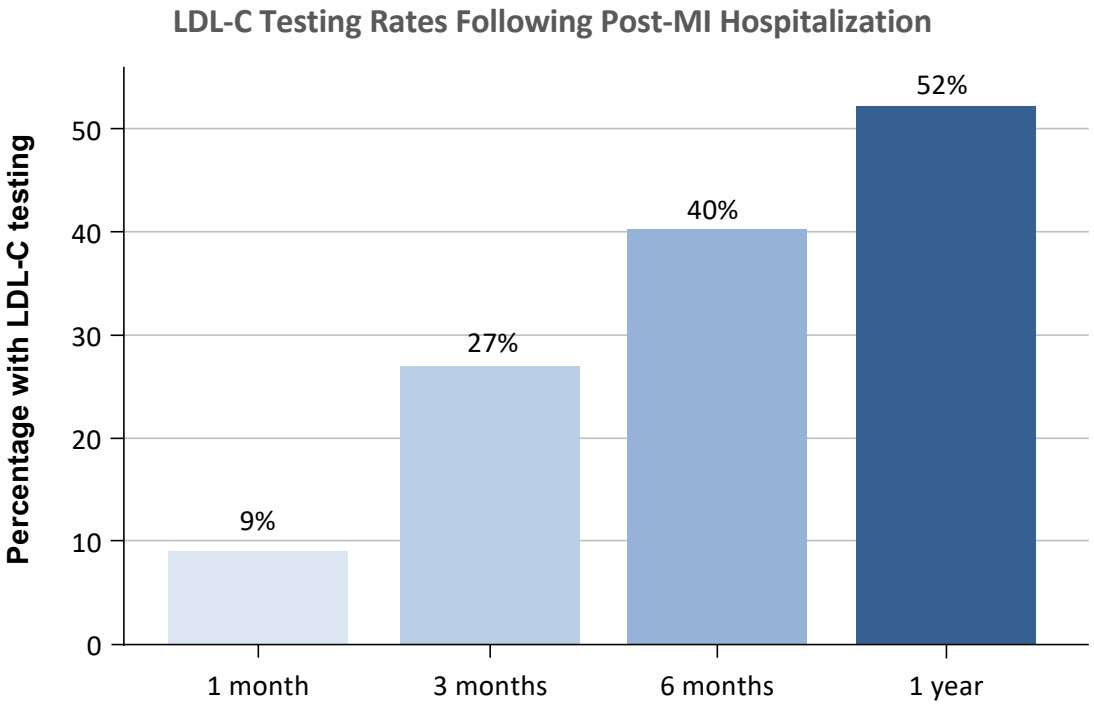
32% of all patients had an LDL-C < 70 mg/dL and only 15% had an LDL-C < 55 mg/dL[1,2]

*5,006 patients were enrolled between December 2016 and July 2018. Analysis was done on data collected as of October 5, 2020, when 4,257 patients (85.0%) had completed 2 years of follow-up: 3,745 (84.1%) patients in the LDL-C cohorts and 512 (92.4%) patients in the PCSK9i cohort. †Defined as having any one of the following clinical conditions: a history of MI, coronary artery disease, coronary or other arterial revascularization, ischemic stroke or transient ischemic attack, carotid artery stenosis, or documented peripheral arterial disease secondary to atherosclerosis.

ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; SD, standard deviation; US, United States.

1. Cannon CP, et al. *JAMA Cardiol*. 2021;6:1060-1068. 2. Cannon CP, et al. Oral presentation presented at: AHA Scientific Sessions 2020.

LDL-C Testing Rates in Patients After MI Suboptimal



- 27% received an LDL-C test by 3 months
- 52% received any LDL-C testing in the year following MI

In the study cohort, 389, 367 patients were hospitalized for their first MI during the study. 60% aged < 65 years, 64%, and in the year leading up to MI, 36% had statin use and 40% received any LDL-C testing.

LDL-C, low-density lipoprotein C; MI, myocardial infarction.

Levintow SN, et al. *Clin Epidemiol*. 2022;14:737-748.

Case

- SB is a 68 year-old woman with a history of prior MI and hypertension who is referred for CV assessment
- Current meds include aspirin; losartan; atorvastatin 20 mg
- BP 125/70 mm Hg; TC 200 mg/dL; HDL-C 35 mg/dL; LDL-C 90 mg/dL

- **What is her level of CV risk**: low; borderline; intermediate; high; very high
- **What is her LDL-C goal**: < 70 mg/dL; < 55 mg/dL; already at goal
- **What is best next step for her lipid lowering therapy**: continue atorva 20; increase to 40 or 80; add ezetimibe; add PCSK9i

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THANK YOU!!