UT Southwestern Medical Center

Lipid Management

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01/08/2026

Outline

- Questions
- Basics in Lipids
- Secondary Causes
- Therapeutic Modalities
  - Statin
  - Non-statin therapies
- Tx for Clinical ASCVD – AKA Secondary Prevention
- Tx for High-Risk Groups
- Tx for Primary Prevention
- Take Home Points

Question 1

A 60-year-old man presents for the routine follow-up of intermittent claudication. He feels well. His medical history includes iliofemoral arterial disease status/post percutaneous revascularization, hypertension, hypercholesterolemia, and type 2 diabetes mellitus. He quit smoking a few months earlier. His medications include aspirin 81 mg, rosuvastatin 40 mg, lisinopril 20 mg, metformin 1000 mg twice daily, chlorthalidone 25 mg, and varenicline 0.5 mg.

His vital signs are pulse rate 70 bpm, blood pressure 139/81 mm Hg, and respiratory rate 14 breaths/min. His examination findings are remarkable only for decreased pedal and posterior tibial pulses. Laboratory evaluation findings include total cholesterol level 170 mg/dL, high-density lipoprotein cholesterol (HDL-C) level 34 mg/dL, low-density lipoprotein cholesterol (LDL-C) level 98 mg/dL, and triglyceride (TG) levels 190 mg/dL. His calculated 10-year atherosclerotic cardiovascular disease (ASCVD) risk is 24% using the Pooled Cohort Equation.

The addition of which one of the following is most appropriate for this patient?

A. Niacin
B. Clopidogrel
C. Fish Oil
D. Ezetemibe
E. Vitamin E

Question 2

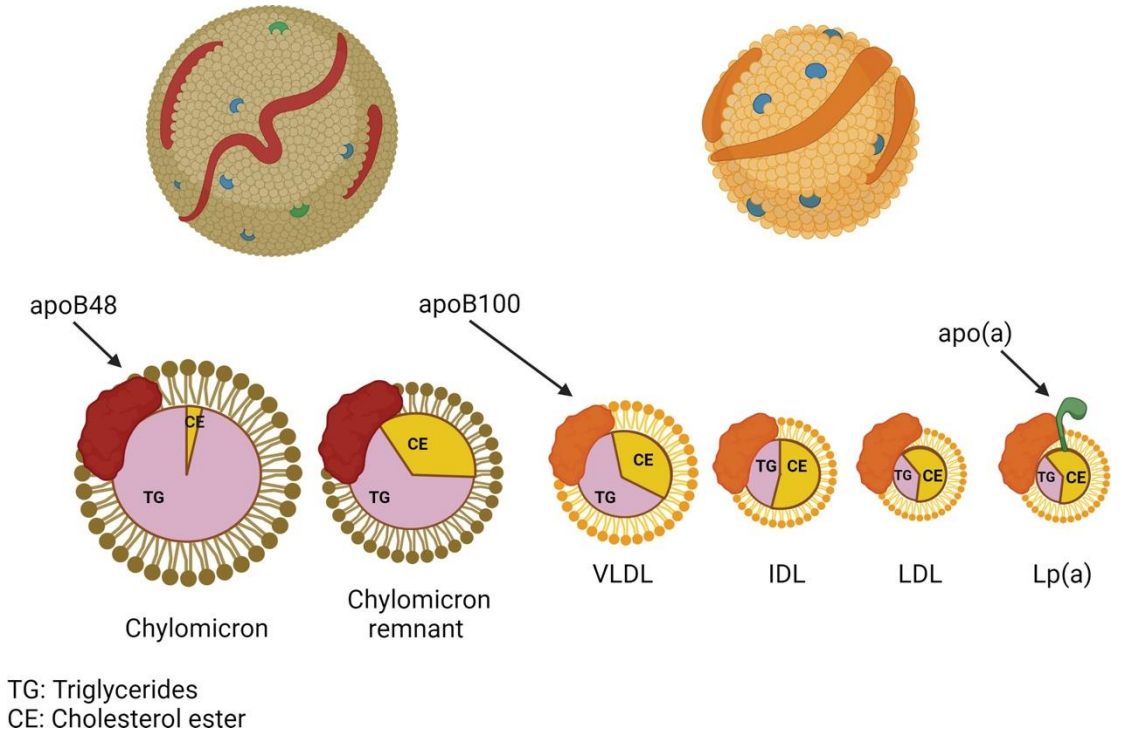
A 54-year-old man with hypertension and myocardial infarction 11 months prior treated with stenting of the posterior descending artery is seen in clinic for routine follow-up. He denies any chest discomfort or dyspnea with activity. He would like to reduce his medications if possible. Since his previous visit 6 months prior, he has been diagnosed with diabetes mellitus, and he asks whether the statin is responsible. His daily medications include aspirin 81 mg, metoprolol succinate 25 mg, lisinopril 10 mg, and atorvastatin 40 mg. On examination, his heart rate is 62 bpm and blood pressure is 112/65 mm Hg. The remainder of his examination is normal. An echocardiogram reveals normal left ventricular ejection fraction (LVEF). Creatinine is 0.9 mg/dL and low-density lipoprotein is 68 mg/dL.

What would you advise regarding his medication regimen?

A. Discontinue Aspirin
B. Continue current therapy
C. Discontinue Metoprolol
D. Increase Lisinopril
E. Substitute Ezetimibe for Atorvastatin

Lipid Basics

- LDL-C is the dominant form of atherogenic cholesterol.
- VLDL is the also atherogenic
- HDL-C is not atherogenic.
- Chylomicrons transport dietary fat; chylomicron atherogenicity is uncertain.
- ApoB 100 is the major apolipoprotein embedded in all atherogenic particles



Friedewald Equation for Estimating LDL-C

- The standard calculation method for LDL-C is the Friedewald formula
- *Total Cholesterol = LDL-C + VLDL-C + HDL-C*
  - LDL-C = Total Cholesterol – HDL-C - VLDL-C
    - VLDL-C ~ Triglycerides/5 (only for Trig <400)
  - **LDL-C = Total Cholesterol – HDL-C – Trig/5**

I	B-NR	1. In adults who are 20 years of age or older and not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating ASCVD risk and documenting baseline LDL-C.[S2.2-1–S2.2-6]
I	B-NR	2. In adults who are 20 years of age or older and in whom an initial nonfasting lipid profile reveals a triglycerides level of 400 mg/dL or higher (≥4.5 mmol/L), a repeat lipid profile in the fasting state should be performed for assessment of fasting triglyceride levels and baseline LDL-C.[S2.2-1–S2.2-4]

Martin Equation for Low Density Lipoprotein (LDL-C)

Non-HDL =
Total Cholesterol – HDL

LDL =
Non-HDL - (Triglycerides / Novel Factor)

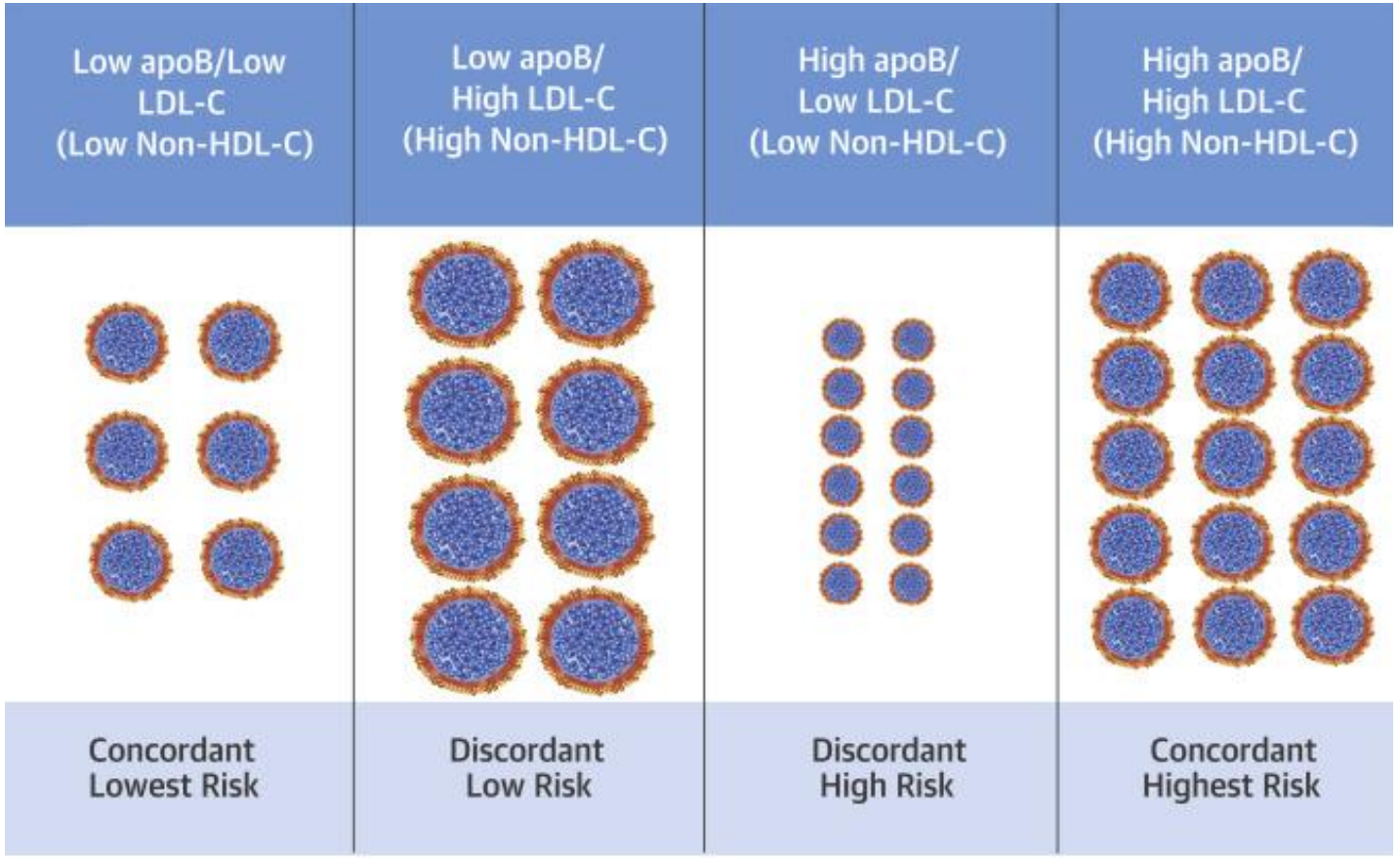
LDL =
TC – HDL - (TG/Novel Factor)

Triglycerides [mg/dL]	NOVEL FACTOR Non-HDL Cholesterol [mg/dL] <100	100-129	130-159	160-189	190-219	≥220
7-49	3.5	3.4	3.3	3.3	3.2	3.1
50-56	4.0	3.9	3.7	3.6	3.6	3.4
57-61	4.3	4.1	4.0	3.9	3.8	3.6
62-66	4.5	4.3	4.1	4.0	3.9	3.9
67-71	4.7	4.4	4.3	4.2	4.1	3.9
72-75	4.8	4.6	4.4	4.2	4.2	4.1
76-79	4.9	4.6	4.5	4.3	4.3	4.2
80-83	5.0	4.8	4.6	4.4	4.3	4.2
84-87	5.1	4.8	4.6	4.5	4.4	4.3
88-92	5.2	4.9	4.7	4.6	4.4	4.3
93-96	5.3	5.0	4.8	4.7	4.5	4.4

AND THE TABLE GOES ON…

ApoB 100

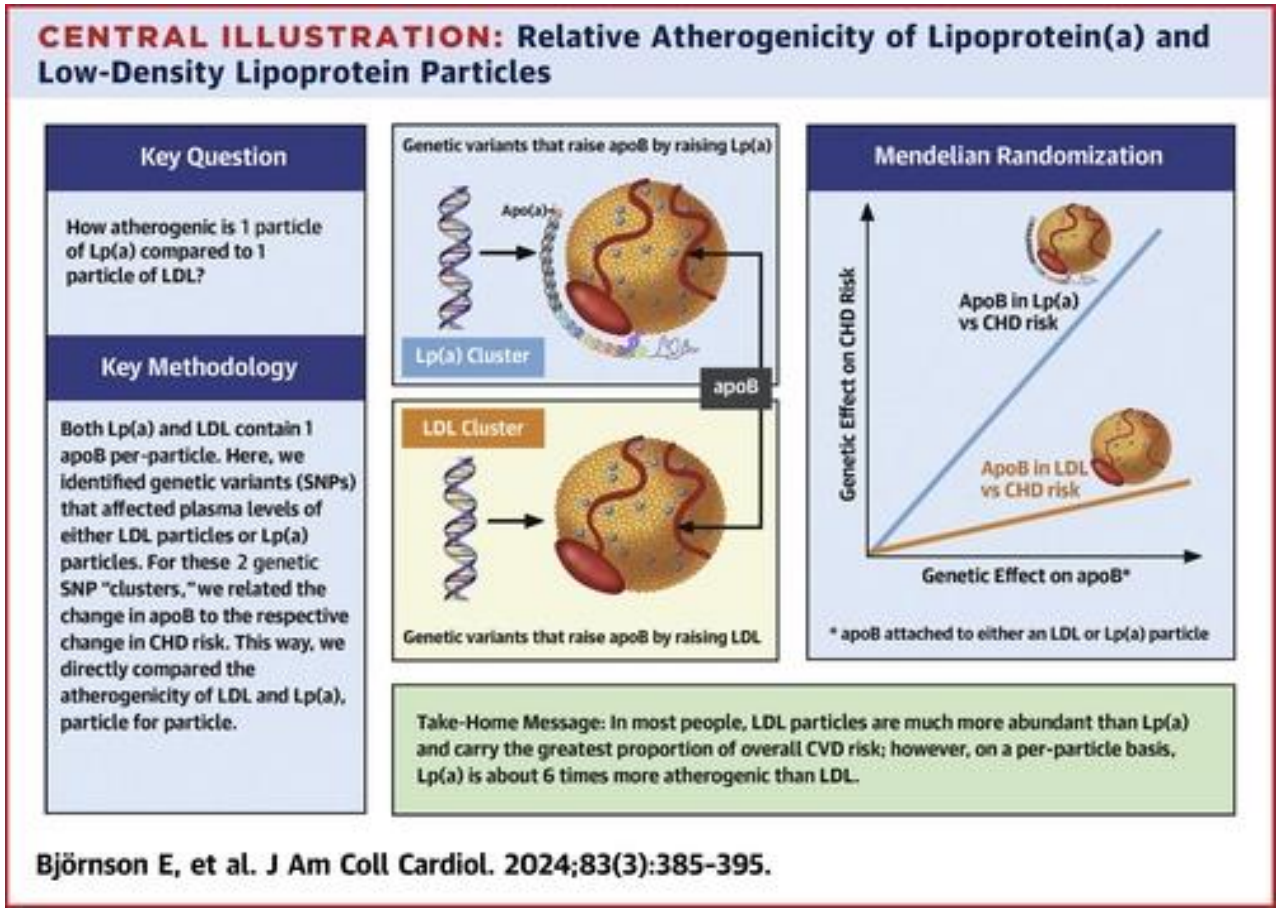
- High correlation between ApoB 100 and Non-HDL-C
- Relative indication for its measurement would be triglyceride ≥200 mg/dL
- A level >130 mg/dL corresponds to an LDL-C level ≥160 mg/dL and constitutes a risk-enhancing factor.



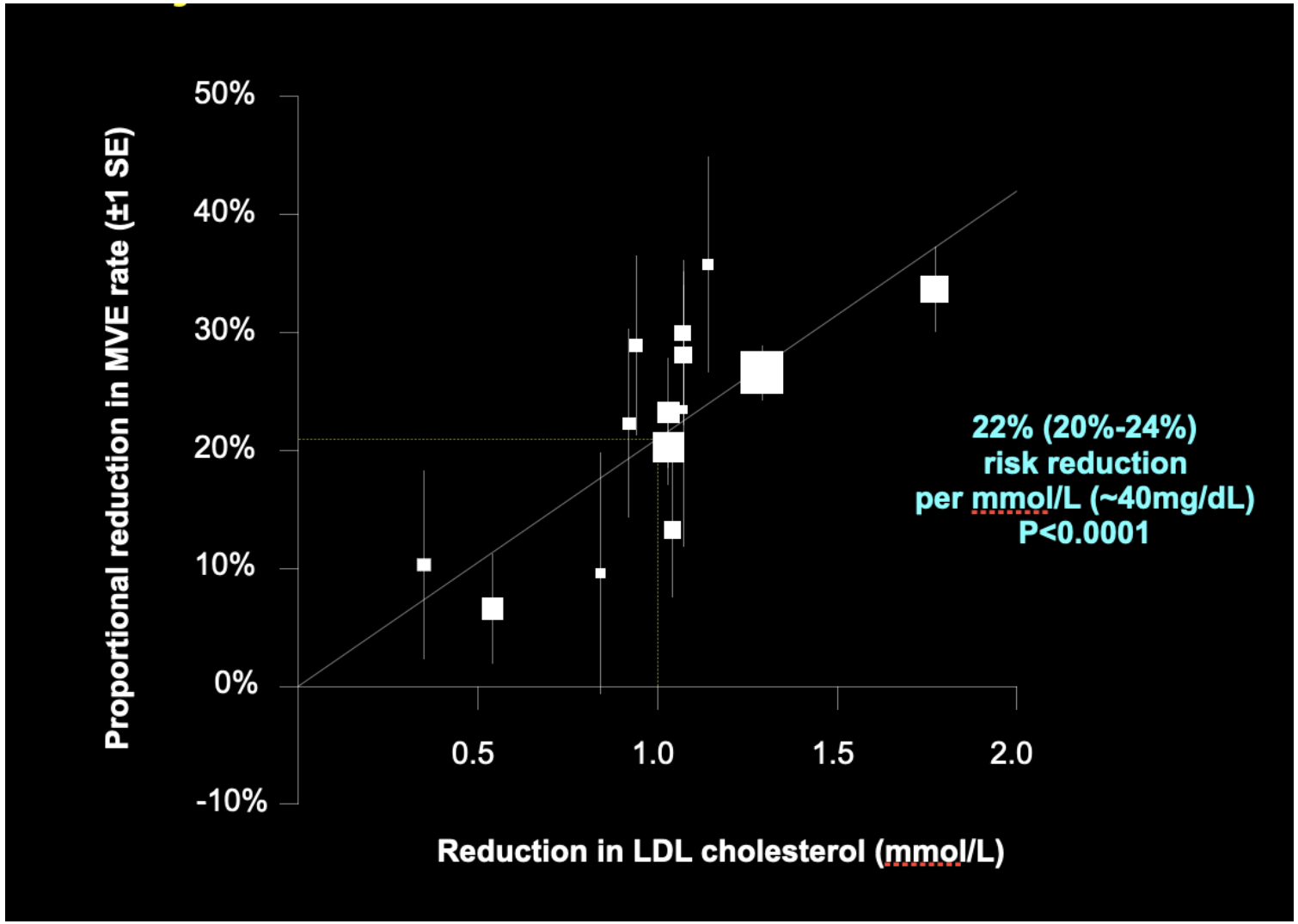
Wilkins, J.T. et al. J Am Coll Cardiol. 2016; 67(2):193-201.

Lipoprotein A

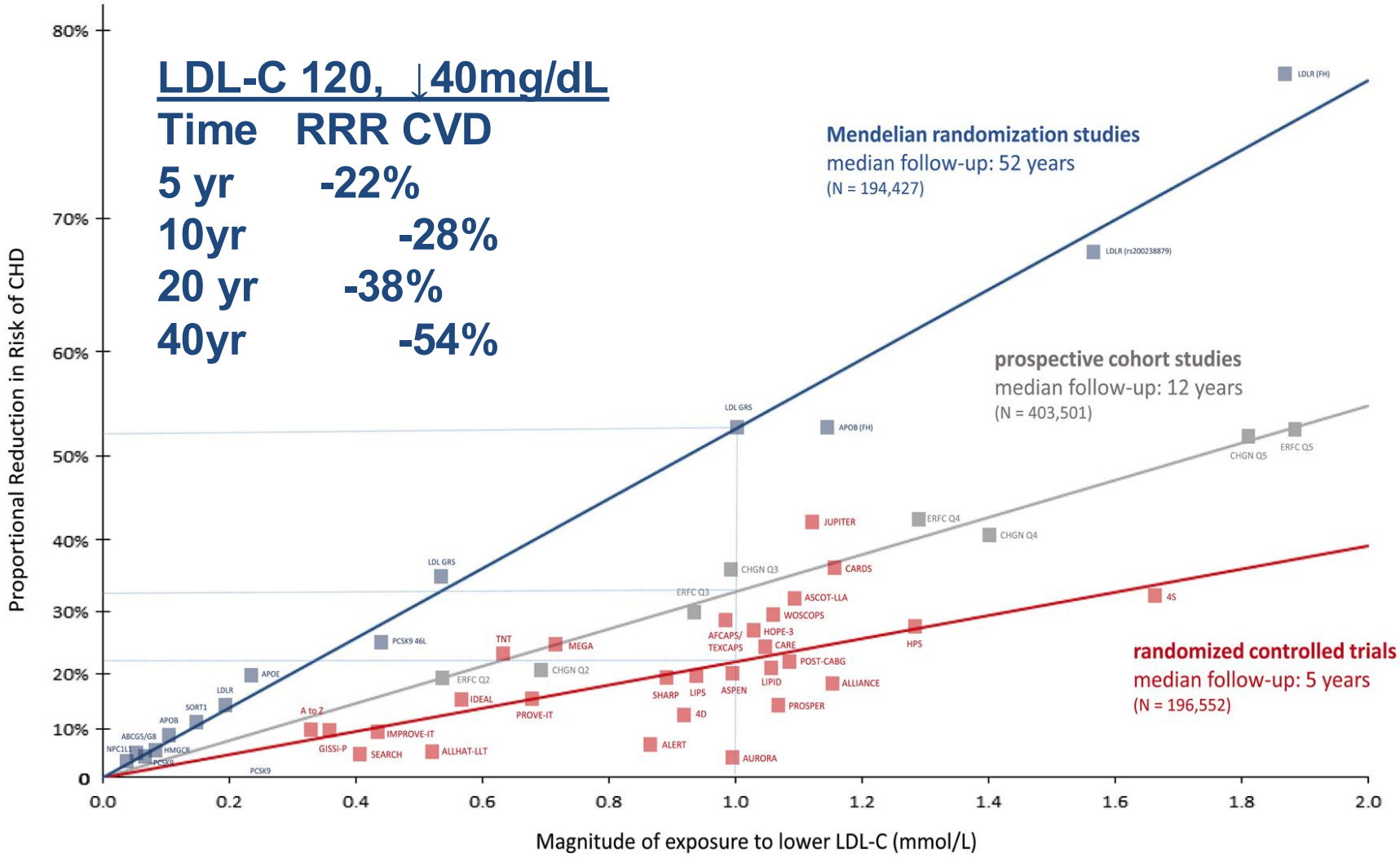
- Lp(a) is a modified form of LDL that appears to possess atherogenic potential
- Consider for family history of premature ASCVD or personal history of ASCVD not explained by major risk factors
- NLA 2024 focused update recommends checking once in all adults
- Lp(a) ≥50 mg/dL or ≥125 nmol/L, Lp(a) is considered a risk-enhancing factor



CTT Metanalysis: Relation between LDL-C Reduction and Major Vascular Events in 14 statin trials



LDL-C Lowering-Not Just How Low, But How Long



Ference B et al. *Eur Heart Journal 2017;38:2459–2472.*

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Greater benefit of statin at higher baseline LDL-C levels

10-year risk of ASCVD 1%
<u>35% reduction with statin</u>
= 0.7% risk of CHD
0.3% absolute reduction minus harms

10-year risk of ASCVD 18%
<u>35% reduction with statin</u>
= 12% risk of CHD
6% absolute reduction minus harms

Secondary Causes of Dyslipidemia

High LDL

- Nephrotic Syndrome
- Hypothyroidism
- Obstructive liver disease
- Keto Diet
- CKD
- Uncontrolled DM
- Accutane

High Triglycerides

- Diabetes
- Alcohol
- Glucocorticoids
- Thiazide diuretics
- Beta Blockers

TREATMENT MODALITIES

Approach to Treatment

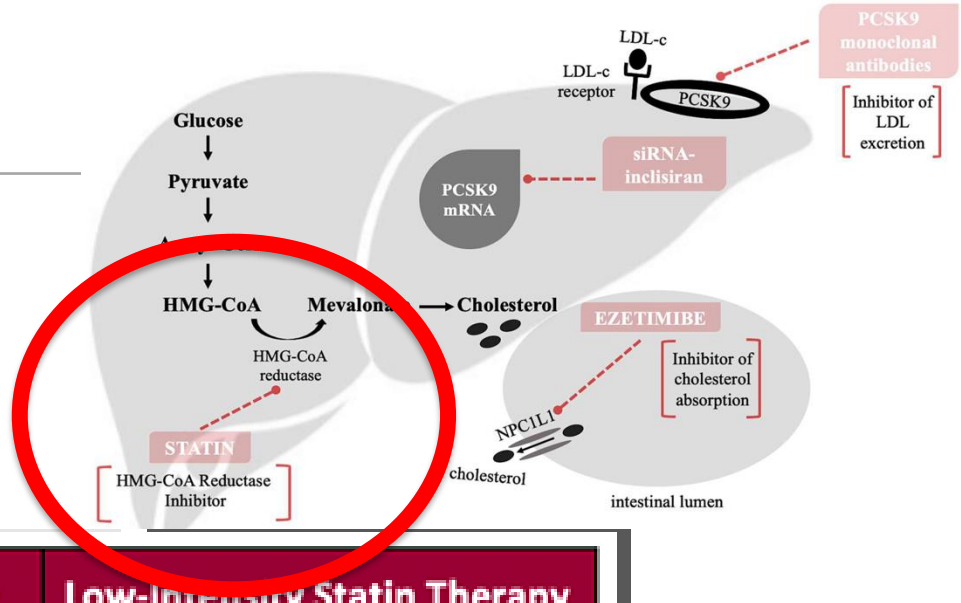
1. *Rule out secondary causes*
2. *Initiate Therapeutic Lifestyle Changes*
3. *Determine the patient's risk level*
    - *Baseline LDL-C, Coronary calcium, Hs-CRP, etc.*
4. *Start lipid lowering therapy if necessary*
    - *Check baseline LDL-C*
    - *LDL-C at 4-12 weeks to assess response*
    - *Annually to ensure compliance*

Lifestyle Therapies

- Emphasizes intake of vegetables, fruits, whole grains, legumes, healthy protein sources (low-fat dairy products, low-fat poultry (without the skin), fish/seafood, and nuts), and nontropical vegetable oils
- Limit intake of sweets, sugar-sweetened beverages, and red meats
- Engage in moderate aerobic physical activity 3-4 sessions per week, lasting on average 40 minutes per session
- Good adherence to various LDL-lowering diets will reduce LDL-C levels by 10% to >15%

Statin Therapy

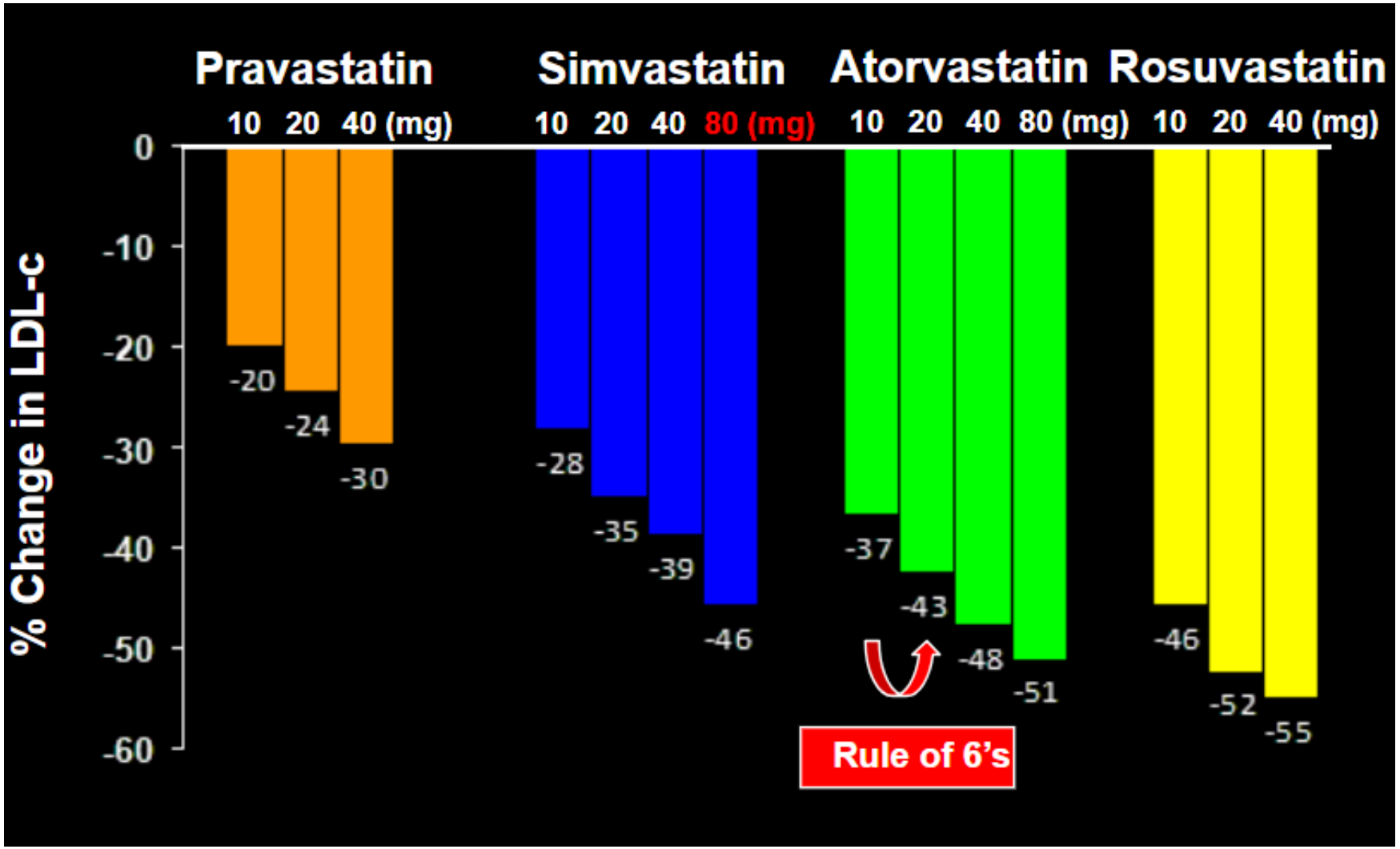
- Statins inhibit HMG-CoA reductase thereby lowering the amount of cholesterol the liver produces



High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL on average by ≥50%	Daily dose lowers LDL on average by approximately 30-49%	Daily dose lowers LDL on average by <30%
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	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg

UND Center for Rural Health. *Statin use—statin intensity table*. 2017.

Change in LDL Values with Different Statin Doses



Jones PH, *Am J Cardio*. 2003;92:152-160

Statin Safety and Associated Side Effects

- **Muscle aches – 1-10%**
- **Rhabdomyolysis- 1:10,000**
- **Elevated LFT's- inconsequential <3x ULN**
  - **No need for routine monitoring**
- **Diabetes**
  - Slightly increases risk of DM, about 1–2 extra cases per 1,000 patients per year
  - For every 1 case of diabetes, statins prevent about 5 major cardiovascular events
- **Cognitive issues- case reports, no evidence in large RCTs**

What to do if patient experiences side effects

- If muscle pain is severe stop statin and check Creatinine Kinase level to evaluate for rhabdomyolysis.

- If concern for liver injury check LFTs, Total Bilirubin, Alk Phos

- If okay to restart - Re-challenge with:
  - Different statin
  - Lower dose of statin
  - Alternate-day dosing of statin

Statin Safety Recommendations

I	B-R	5. In patients with increased diabetes mellitus risk or new-onset diabetes mellitus, it is recommended to continue statin therapy, with added emphasis on adherence, net clinical benefit, and the core principles of regular moderate-intensity physical activity, maintaining a healthy dietary pattern, and sustaining modest weight loss.[S5-8–S5-12]
I	C-LD	6. 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 liver transaminases (aspartate aminotransferase, alanine aminotransferase) as well as total bilirubin and alkaline phosphatase (hepatic panel) if there are symptoms suggesting hepatotoxicity.[S5-13–S5-15]
III: No Benefit	B-R	9. Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS.[S5-20,S5-21]
III: No Benefit	C-LD	10. In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.[S5-13–S5-15]

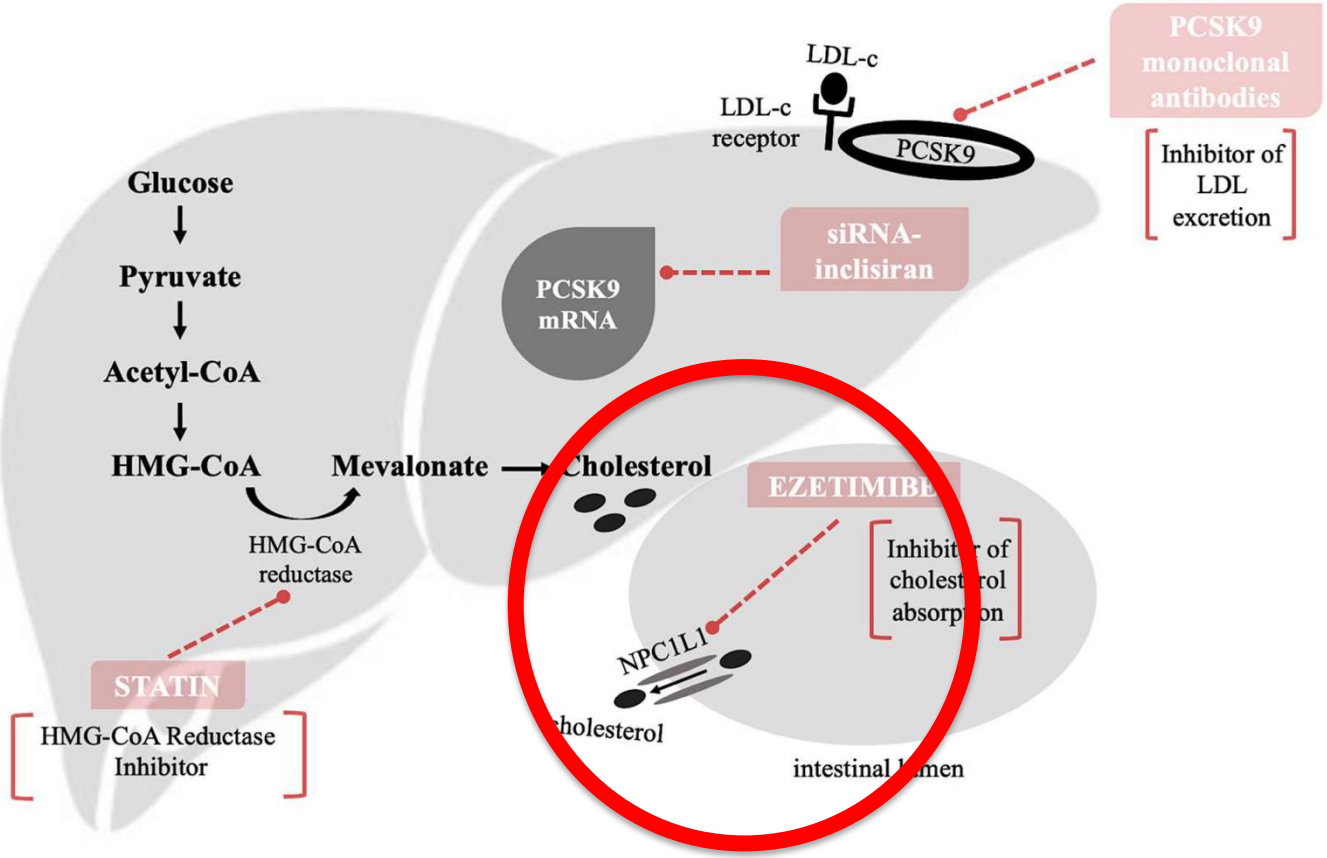
Statins in Pregnancy

- 2021 FDA removed overt contraindication for statins in pregnancy
- Statins should still be discontinued in MOST patients
  - Only used for those at very high risk
    - Homozygous Familial Hypercholesterolemia
    - Prior history of stroke or heart attack
- Statins are safe to prescribe in patients who are not pregnant but may become pregnant.
  - Reassure patients who have an unintended exposure to statins in early pregnancy that it is unlikely to cause harm to the developing fetus
- Statins should <u>not</u> be continued while breastfeeding

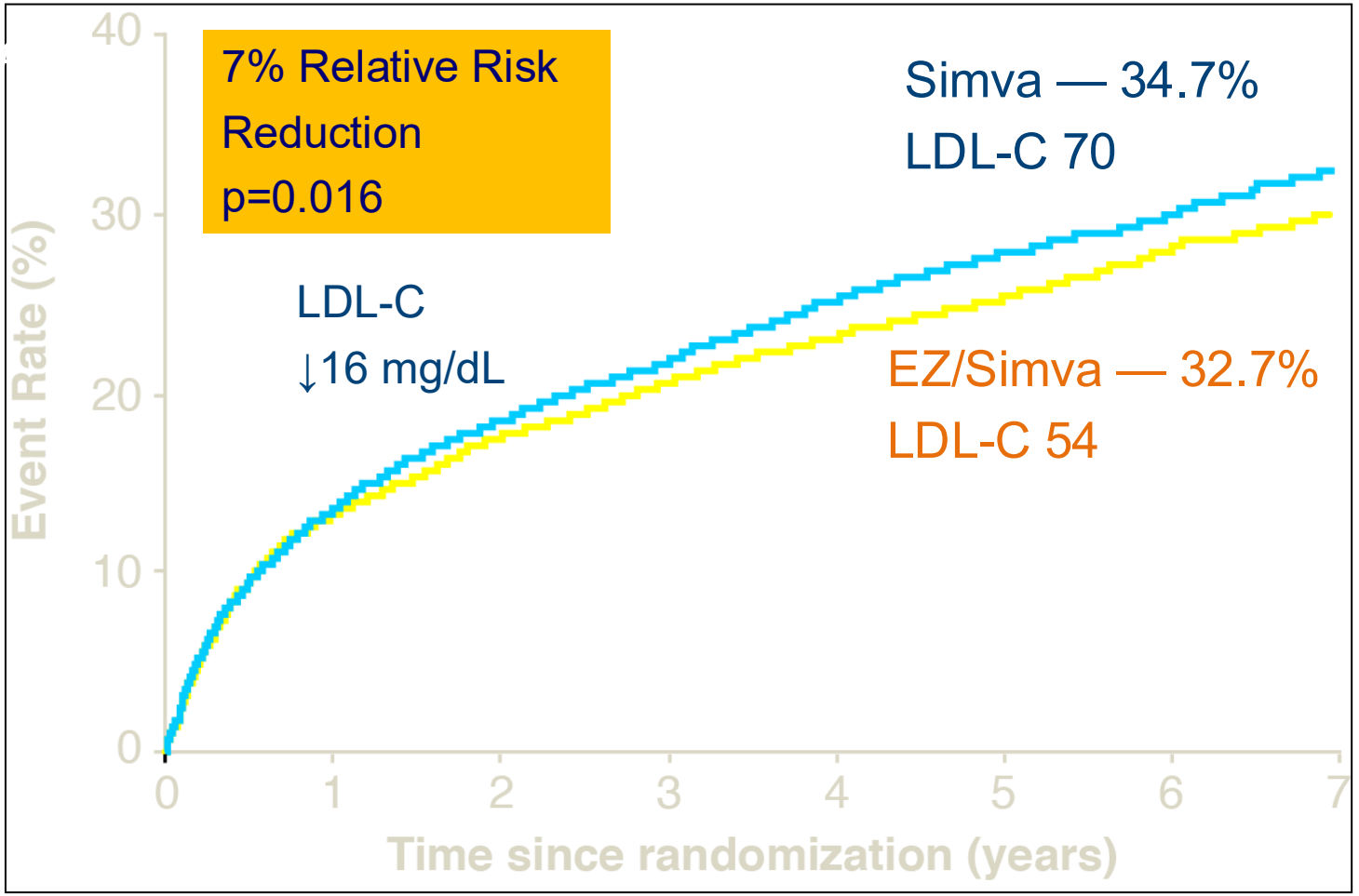
Ezetimibe

- Ezetimibe inhibits absorption of cholesterol in the small intestine by blocking NPC1L1 protein.

- Lowers LDL-C levels by 13% to 20%.



IMPROVE IT: Effect of Ezetimibe in Patients with Recent Heart Attack



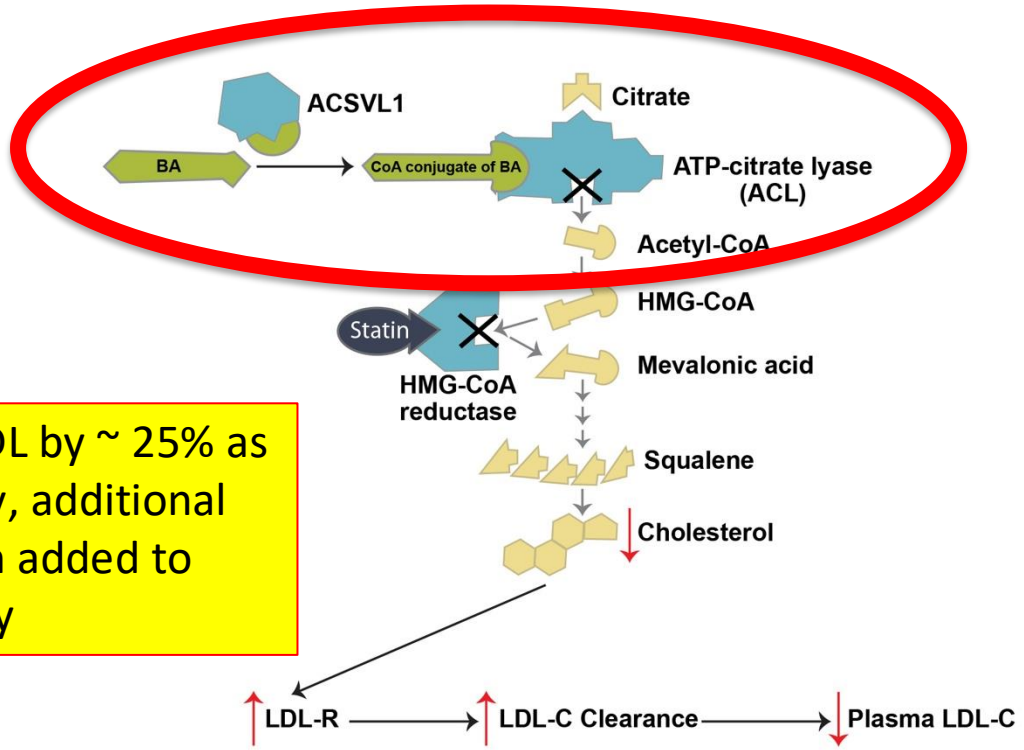
7-year event rates

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

Cannon CP, et al. *NEJM 2015*

Bempedoic Acid Mechanism of Action

Converted to the CoA Conjugate of Bempedoic Acid, the Active Form, Only in Liver



Decreased LDL by ~ 25% as monotherapy, additional 15-18% when added to statin therapy

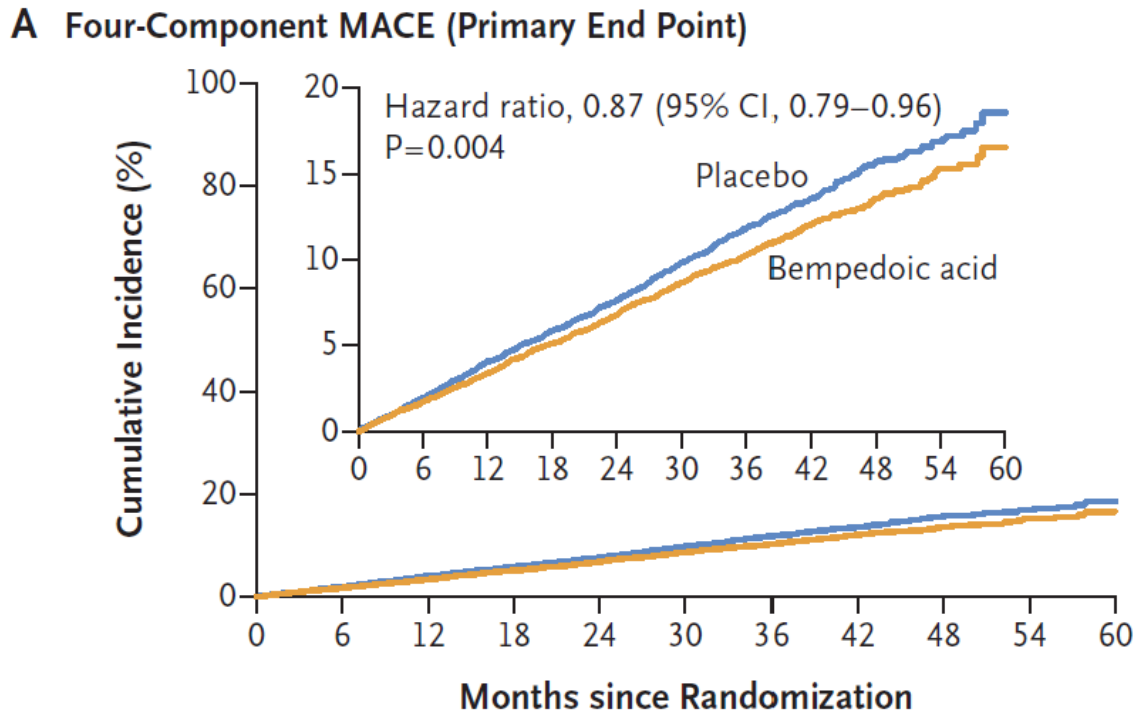
- Bempedoic acid (BA) acts in the same cholesterol biosynthesis pathway as statins
- BA targets ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Upregulates LDL receptors and lowers LDL-C
- Specific isozyme (ACSVL1) that converts BA into an active drug is not present in skeletal muscle

ACSVL1, very long-chain acyl-CoA synthetase-1;
CoA, coenzyme A; LDL-C, low-density lipoprotein cholesterol.

Ray KK et al. Presented at ESC, Munich, 2018.

Bempedoic Acid: and CV Outcomes

CLEAR OUTCOMES Trial



Clinical Considerations

- ***Oral***
- ***No ↑ glucose/DM***
- ***No ↑ myalgia***

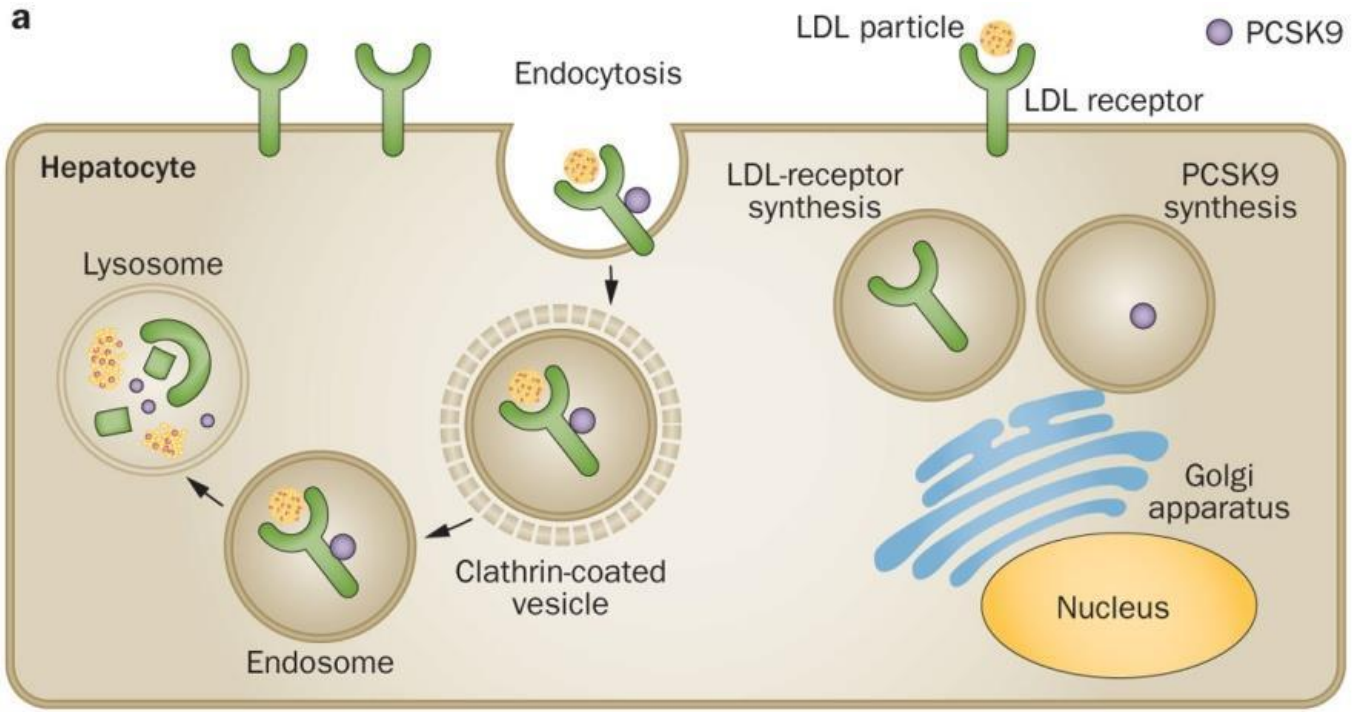
- ***↑ Hyperuricemia/Gout***
- ***0.5% Tendon rupture***
- ***Modest LDL-C lowering but combo with ezetimibe***

Nissen S et al NEJM 2023

PCSK9 (proprotein convertase subtilisin/kexin type 9): Physiology

Alirocumab (Praluent) - 45-58% reduction in LDL

Evolocumab (Repatha) - 58–64% reduction in LDL

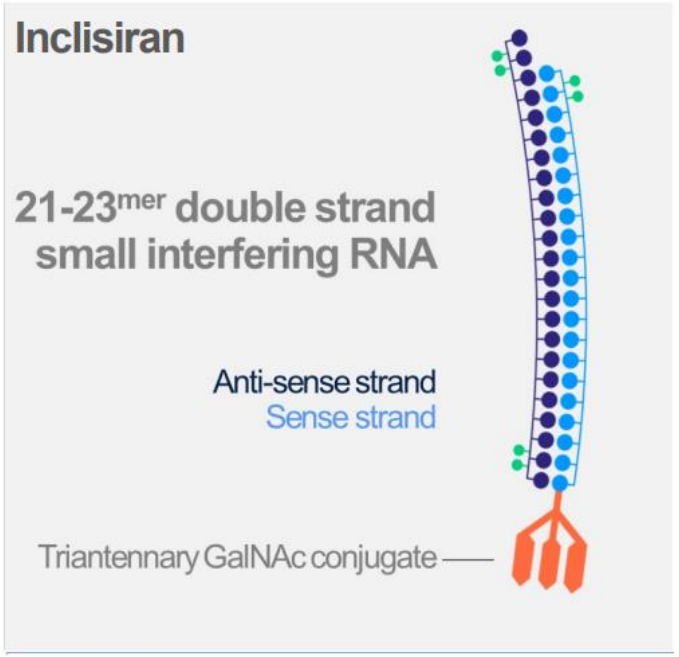


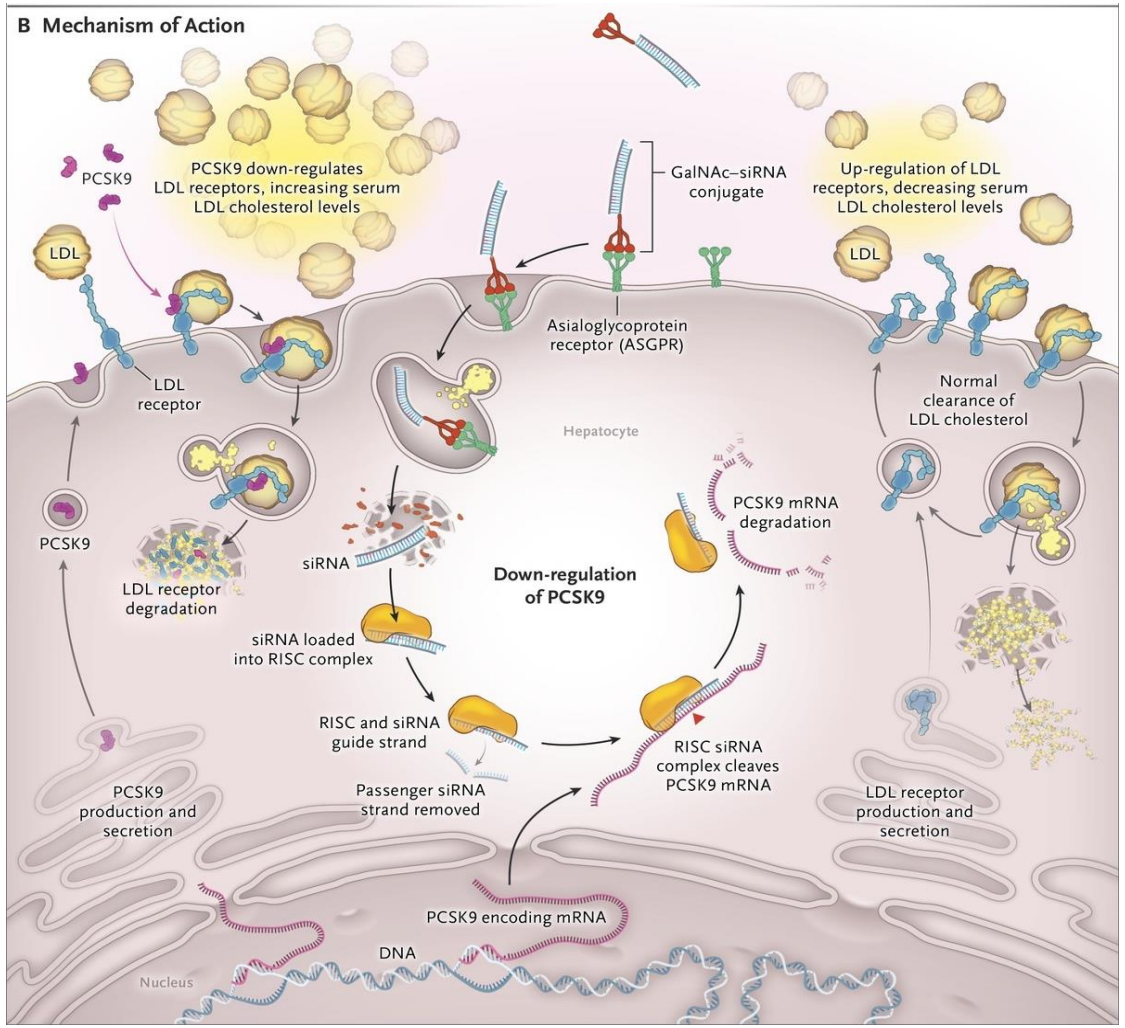
↑ PCSK9*
(↓LDL receptors)
↑ LDL-C

↓ PCSK9
(↑LDL receptors)
↓ LDL-C

*Abifadel M. *Nat Genet* 2003;34(2):154-6
Ballantyne. *Nat. Rev. Cardiol.* 2014.84
Jay D. Horton et al. *J. Lipid Res*. 2009;50:S172-S177

Inclisiran: Chemical Configuration and Mechanism of Action





Dosed SQ baseline, 3 mo, Q6 months

~ 50% LDL reduction

Khvorova A. N Engl J Med 2017;376:4-7.

Bile Acid Sequestrants

- Cholestyramine, colestipol, and colesevelam are a few examples
- Bile acid sequestrants can bind other drugs, other medications should be given > 4 hours prior.
- May increase TG and cause acute pancreatitis. Monitor TG, discontinue if signs/symptoms of acute pancreatitis.
- Safe in pregnancy/breast feeding.
- 15-30% reduction in LDL

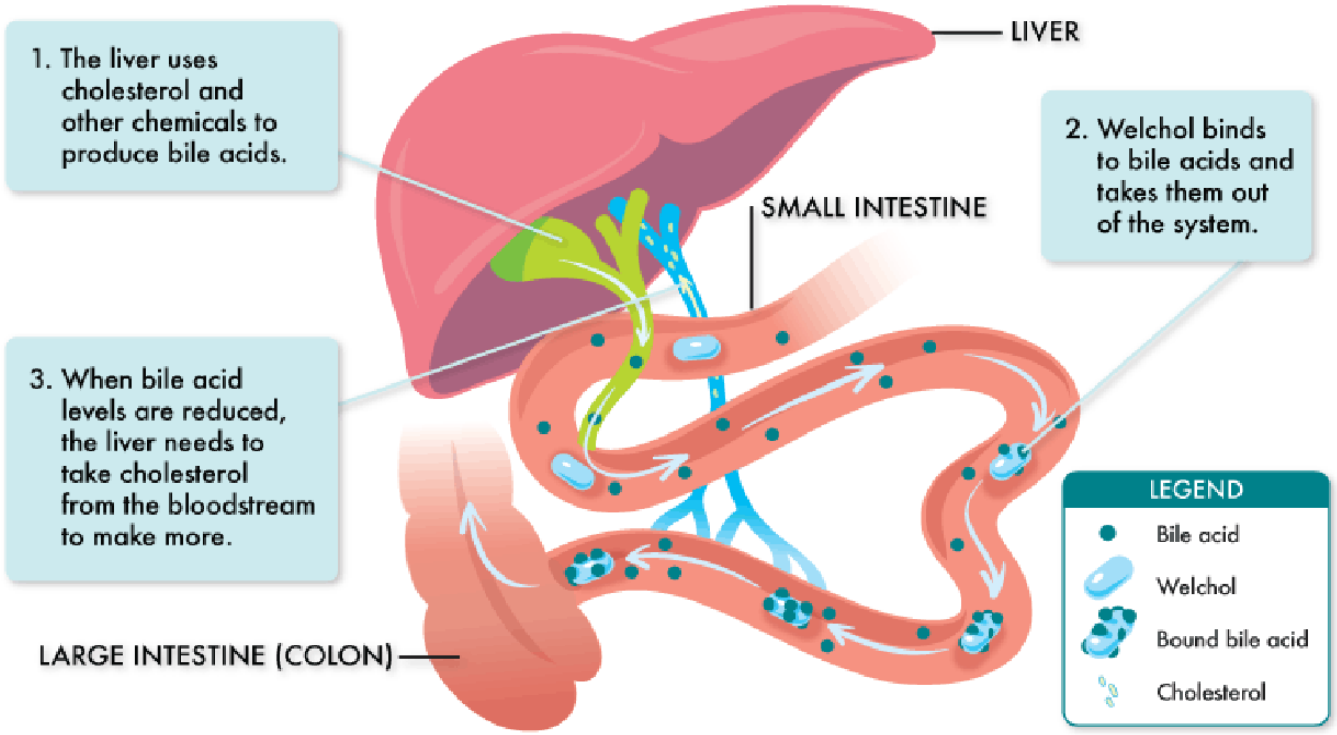
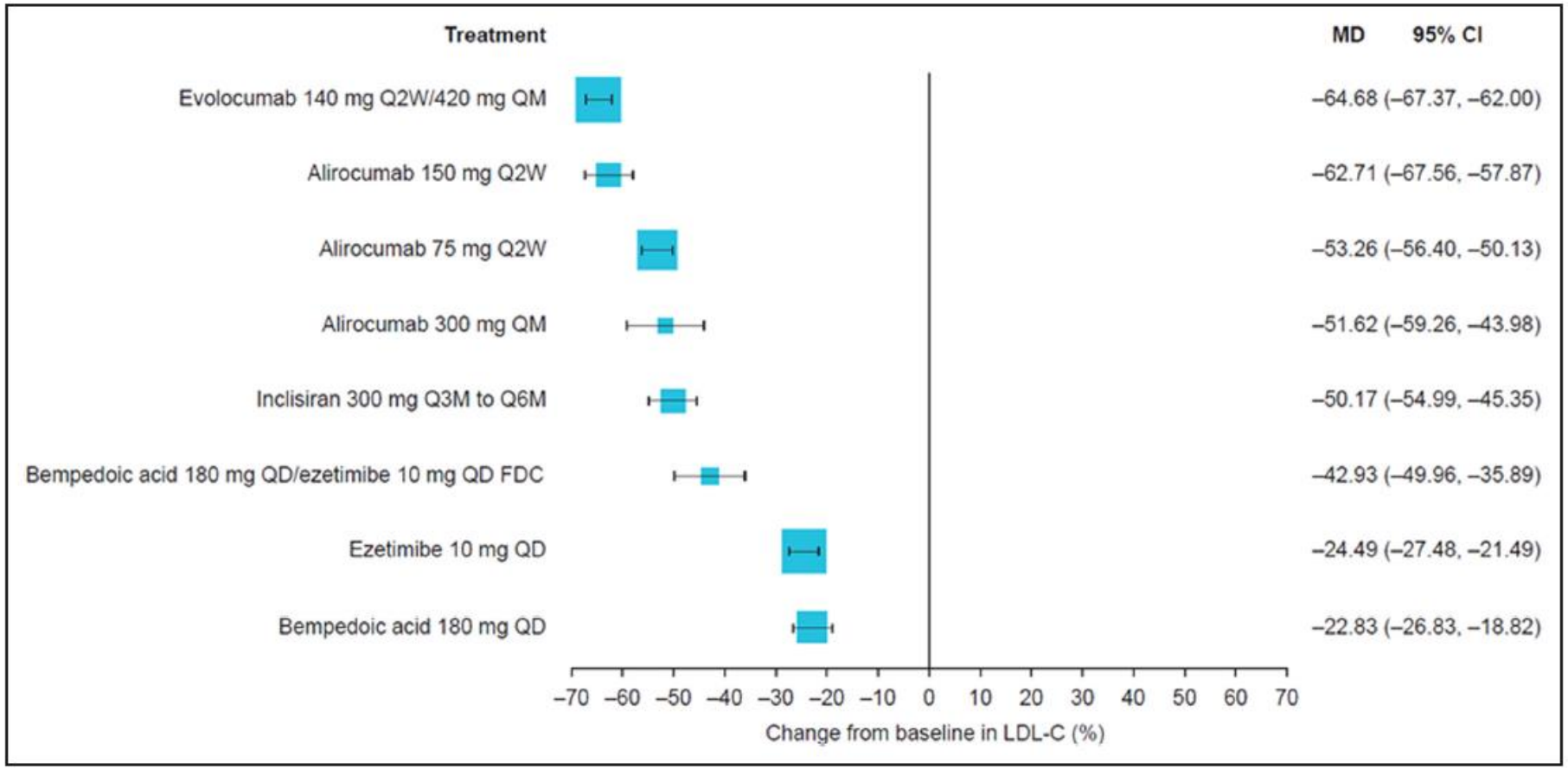


Figure 1.6 – Bile acid sequestrant (Welchol) effect on the enterohepatic

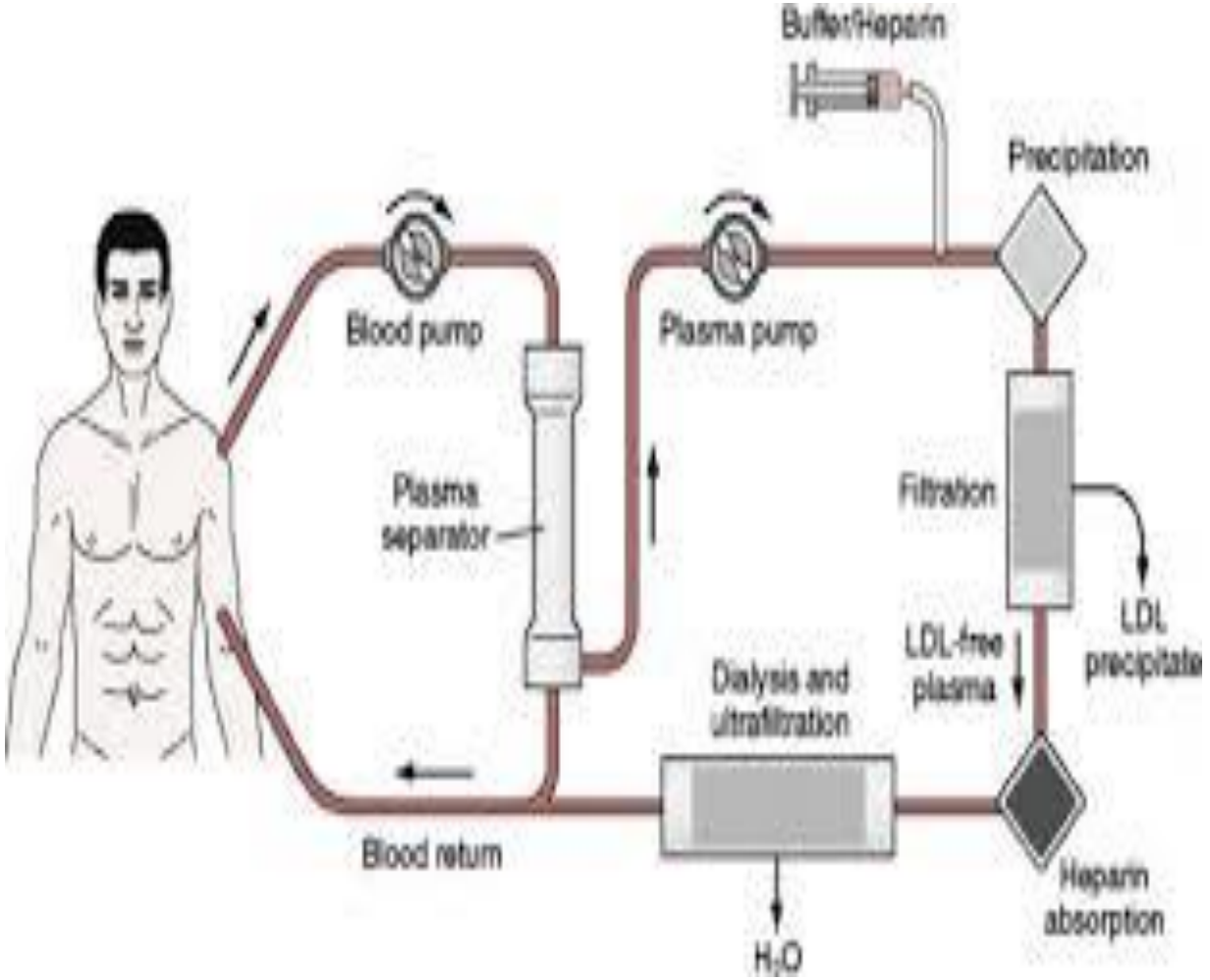
LDL-C Reduction of Non-Statin Therapies



Toth P et al. JAHA 2022;11:e025551. DOI: 10.1161/JAHA.122.025551

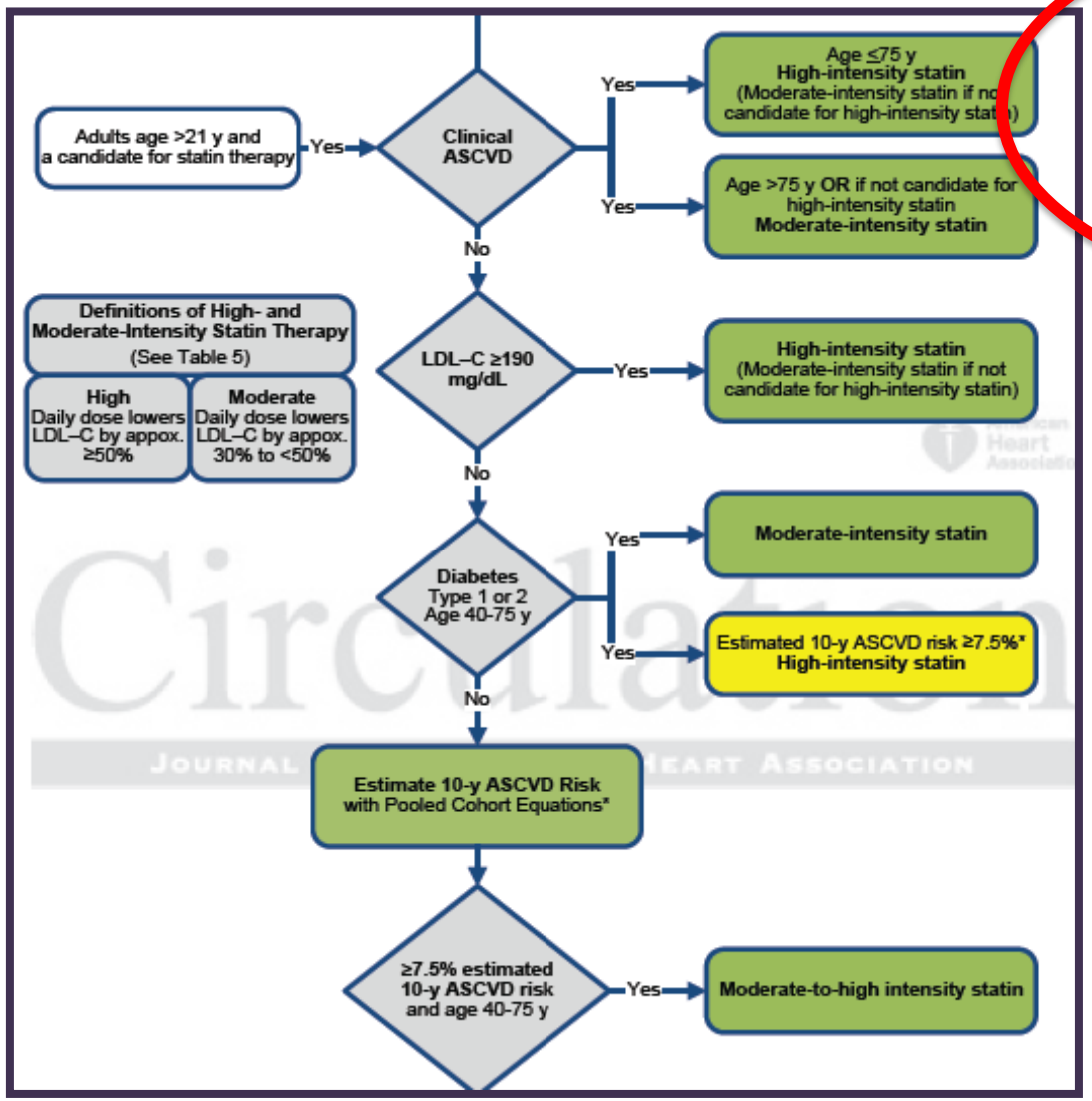
LDL Apheresis

- Selectively removes apo B-containing lipoproteins, producing an acute reduction in LDL-C.
- FDA approved indication:
  - Patients with FH unresponsive to pharmacologic and dietary management who are either functional homozygotes with an LDL-C >500 mg/dL
  - Functional heterozygotes with no known CV disease but anLDL-C >300 mg/dL
  - Functional heterozygotes with known cardiovascular disease and LDL-C >200 mg/d



WHO TO TREAT

Statin Therapy Recommendations- 4 Groups



Clinical ASCVD
-High

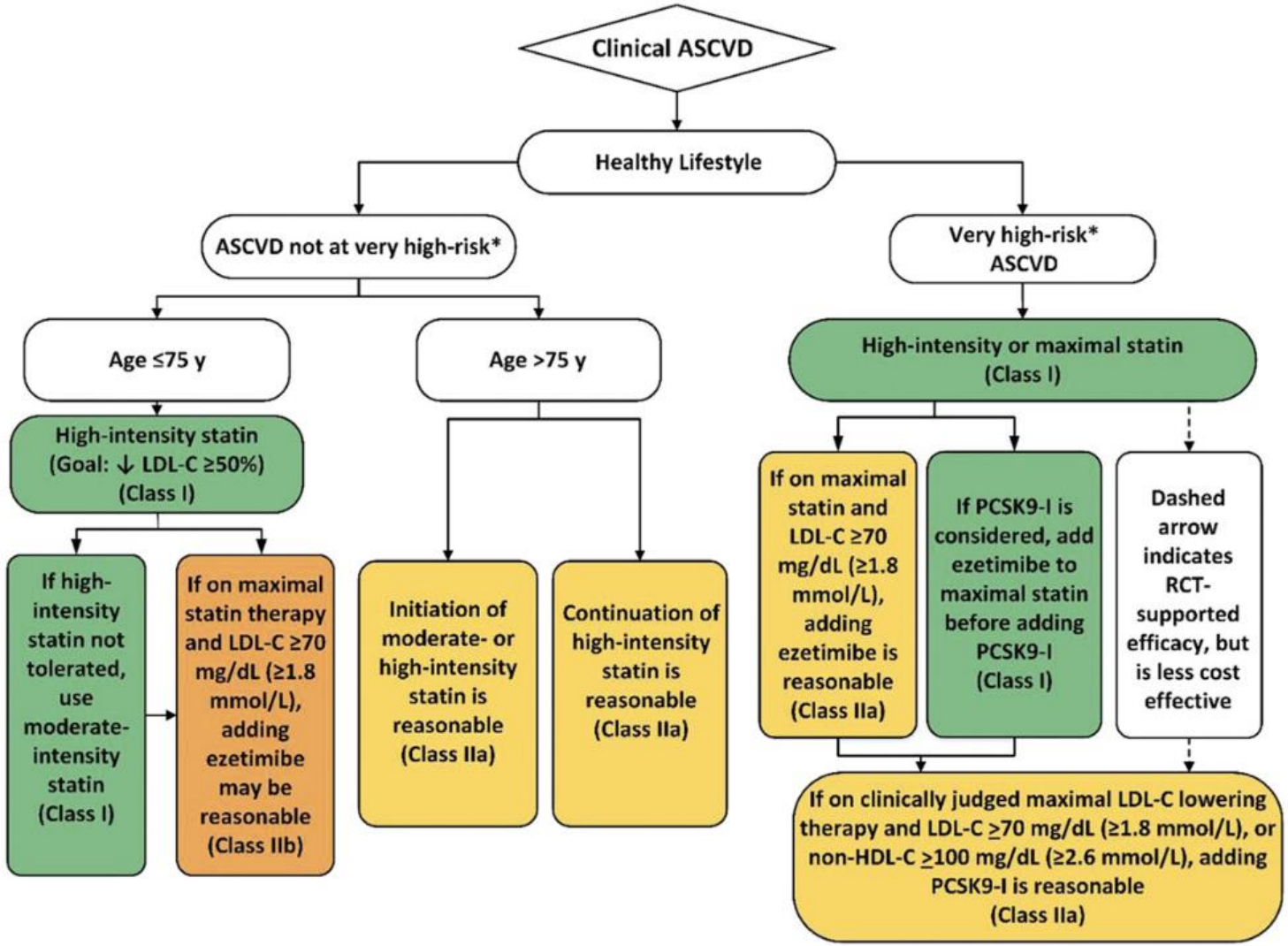
LDL-C ≥ 190
-High

Diabetes
(Age 40-75)
-Mod (High)

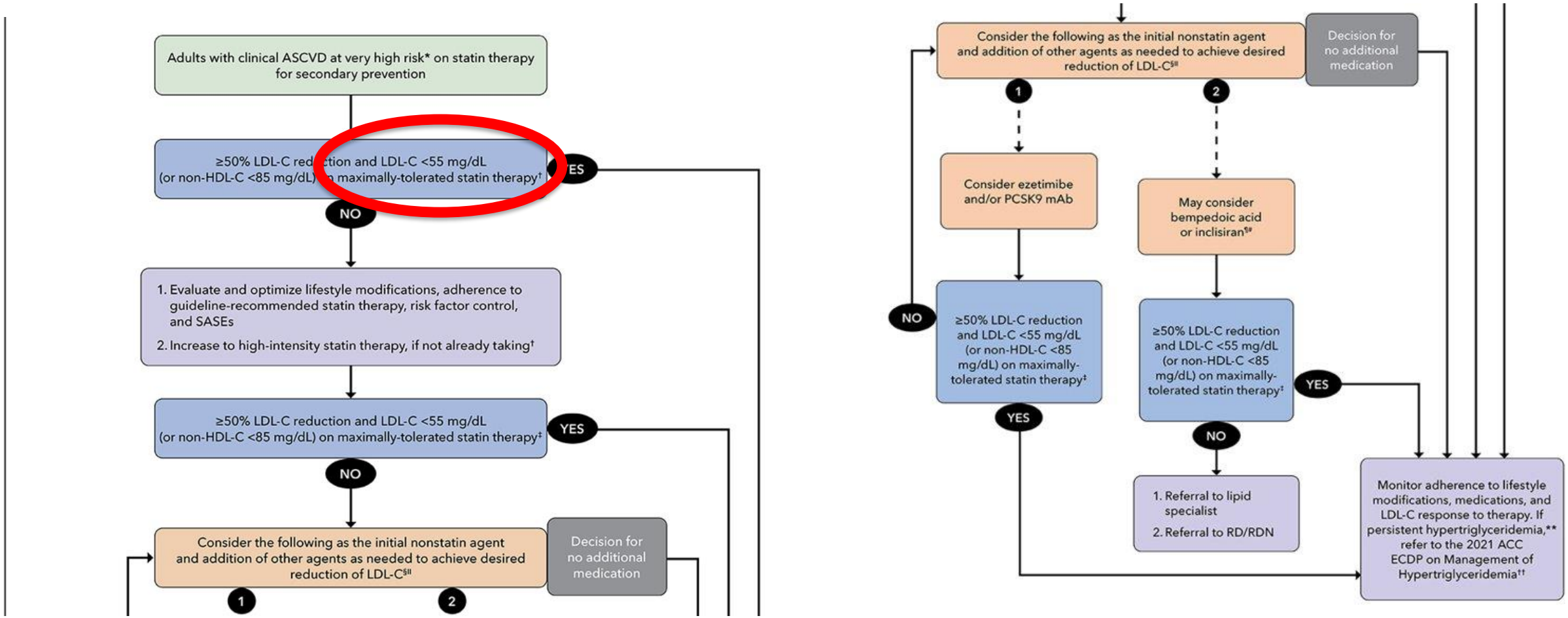
Risk ASCVD≥ 7.5%
(Age 40-75)
-Mod (High)

-statin intensity

Clinical ASCVD – AKA Secondary Prevention



Secondary Prevention – Very High Risk ACC



Lloyd-Jones DM, *JACC*, 2022

Clinical ASCVD - Very High-Risk Features

Table 4. Very High-Risk* of Future ASCVD Events (Table view)

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

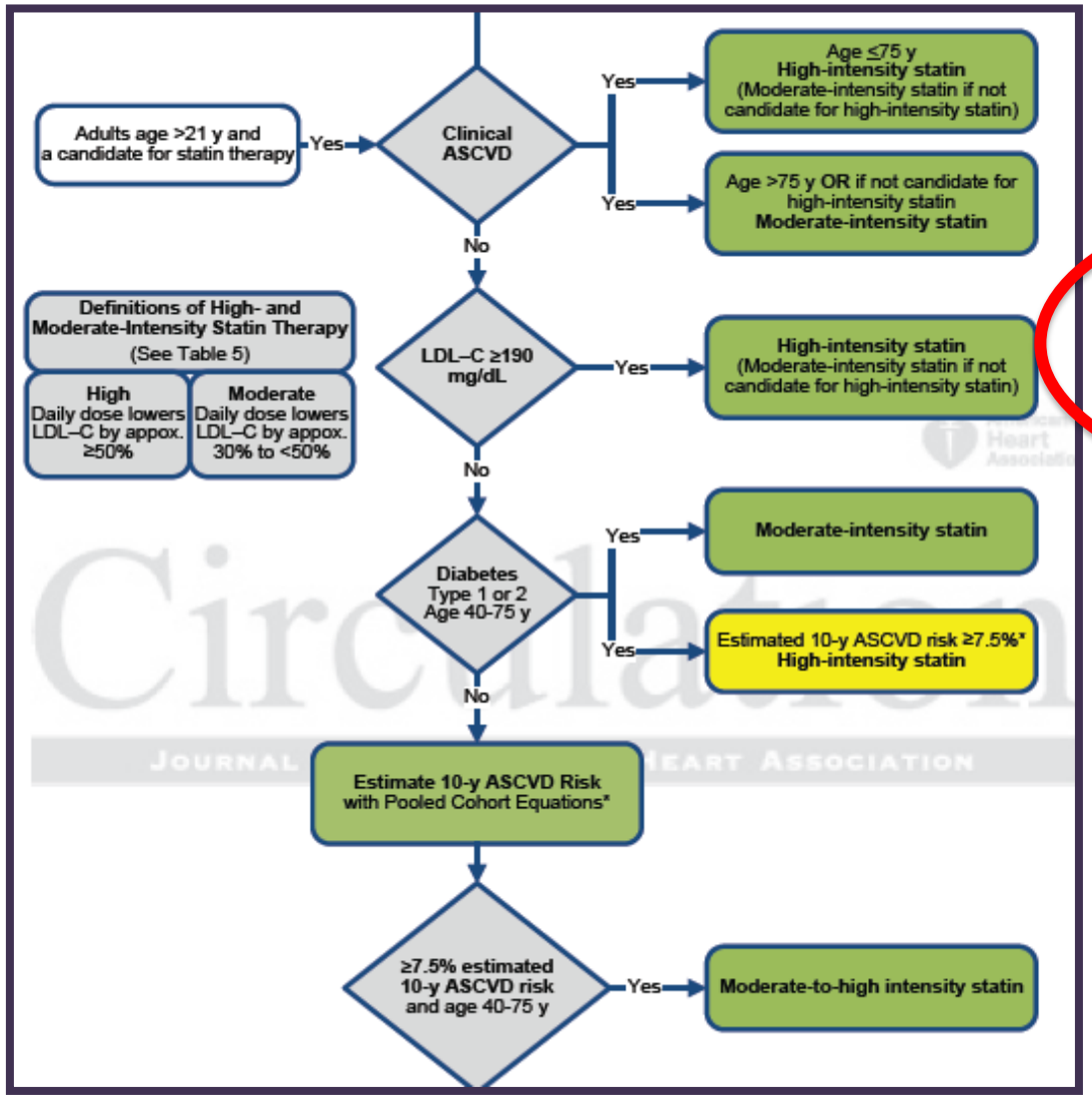
LDL-C Goal for Secondary Prevention in Current Cholesterol Guidelines

Guideline	LDL-C Goal
2018 US ACC/AHA Cholesterol	<70mg/dL*
2019 ESC Guidelines	<55mg/dL**
2022 ACC Consensus Statement	<55mg/dL*

* for "Very High Risk"
**Optional <40mg/dL

Consider combination therapy at index hospitalization for high-risk patients.

Statin Therapy Recommendations- 4 Groups



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-High

LDL-C ≥ 190
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-Mod (High)

Risk ASCVD≥ 7.5%
(Age 40-75)
-Mod (High)

-statin intensity

Patient Management – Severe Hypercholesterolemia

- ***Defined as LDL-C ≥190 mg/dL***
- ***Small proportion will have Familial Hypercholesterolemia (2-7%)***
- ***Up to 5-fold lifetime risk of CHD***

Khera A.V. et al. *JACC* 2016;67:2758-2789.
Bucholz E et al. Circulation 2018; 137:2218-2230.
Perak A et al Circulation 2016;134:9-19.

Familial Hypercholesterolemia(s)

- Definition: Severe hypercholesterolemia with autosomal dominant inheritance pattern
- *Homozygous (~1:500,000); LDL-C >400mg/dl*
- *Heterozygous (~1:250); LDL-C 200-400mg/dl*
- Simon Broome Criteria or Dutch Lipid Criteria

Total cholesterol >290 or LDL >190 mg/dl in adult,
or total cholesterol >260 or LDL>160mg/dl in child

AND

Definite: Tendon xanthoma or + gene in patient or relative

Probable: Family history of premature heart attack, OR
Hypercholesterolemia in 1st or 2nd degree relative

Goldberg AC et al. J Clin Lipid 2011;5:S1-S8

FH Diagnostic Categories

ICD-10 Category	Clinical Criteria	With Genetic Testing Performed
Heterozygous FH	LDL-C ≥160 mg/dL (4 mmol/L) for children and ≥190 mg/dL (5 mmol/L) for adults and with 1 first-degree relative similarly affected or with premature CAD or with positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9)	Presence of 1 abnormal LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9) Diagnosed as heterozygous FH if LDL-C–raising defect positive and LDL-C <160 mg/dL (4 mmol/L) Occasionally, heterozygotes will have LDL-C >400 mg/dL (10 mmol/L); they should be treated similarly to homozygotes Presence of both abnormal LDL-C–raising gene defects (LDL receptor, apoB, or PCSK9) and LDL-C–lowering gene variant(s) with LDL-C <160 mg/dL (4 mmol/L)
Homozygous FH	LDL-C ≥400 mg/dL (10 mmol/L) and 1 or both parents having clinically diagnosed FH, positive genetic testing for an LDL-C–raising gene defect (LDL receptor, apoB, or PCSK9) or autosomal-recessive FH If LDL-C >560 mg/dL (14 mmol/L) or LDL-C >400 mg/dL (10 mmol/L) with aortic valve disease or xanthomata at <20 years of age, homozygous FH highly likely	Presence of 2 identical (true homozygous FH) or nonidentical (compound heterozygous FH) abnormal LDL-raising gene defects (LDL receptor, apoB, or PCSK9); includes the rare autosomal-recessive type Occasionally, homozygotes will have LDL-C <400 mg/dL (10 mmol/L)
Family history of FH	LDL-C level not a criterion; presence of a first-degree relative with confirmed FH	Genetic testing not performed

Physical Exam Findings in FH

Tendinous Xanthomas (any age)

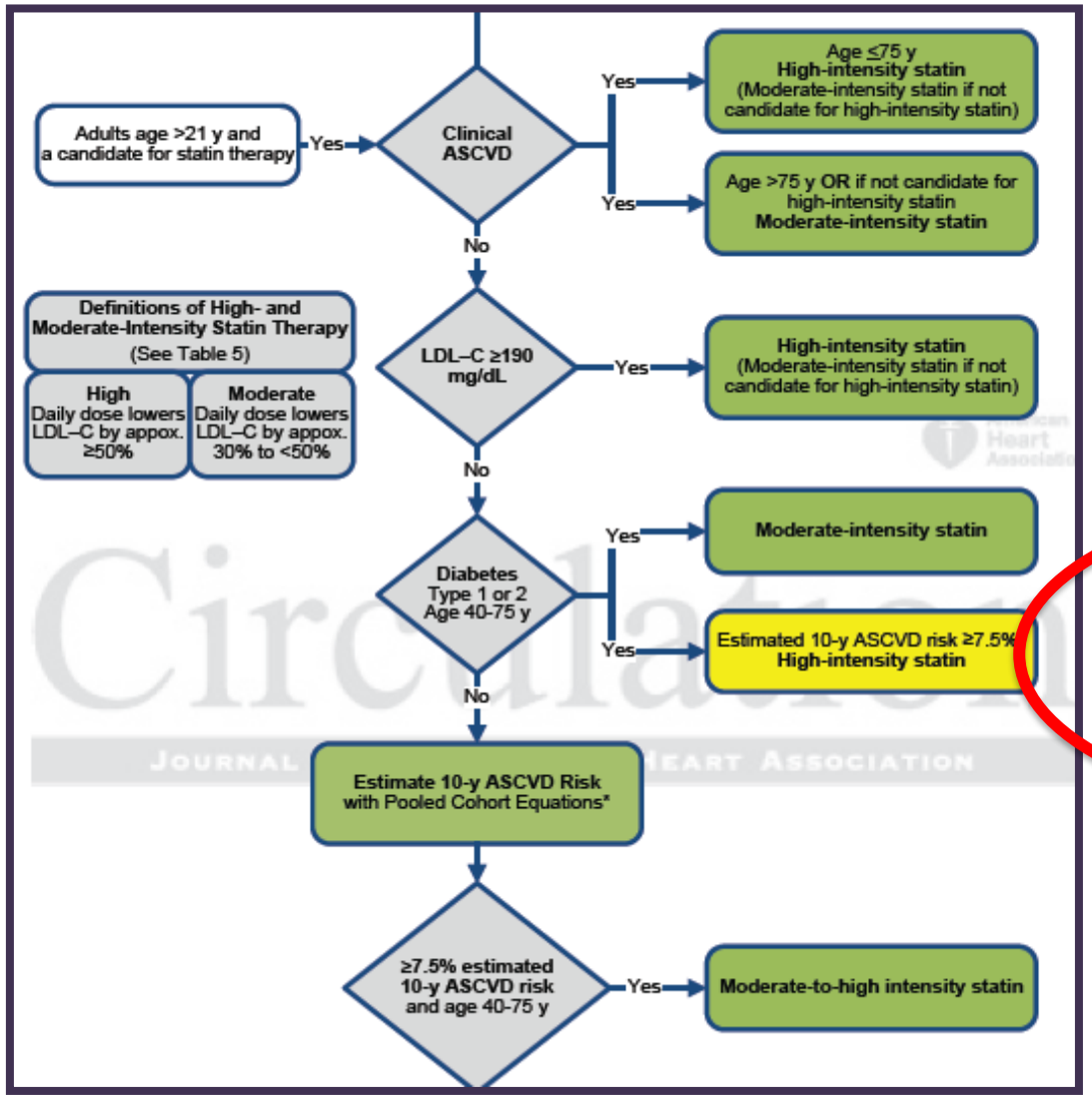
Corneal Acus (<45yo)

Xanthelasma (<25yo)

ACC/AHA Guidelines – Severe Hypercholesterolemia

I	B-R	1. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (≥4.9 mmol/L), maximally tolerated statin therapy is recommended.[S4.2-1–S4.2-7]
IIa	B-R	2. In patients 20 to 75 years of age with an LDL-C level of 190 mg/dL or higher (≥4.9 mmol/L) who achieve less than a 50% reduction in LDL-C while receiving maximally tolerated statin therapy and/or have an LDL-C level of 100 mg/dL or higher (≥2.6 mmol/L), ezetimibe therapy is reasonable.[S4.2-8–S4.2-10]
IIb	B-R	3. In patients 20 to 75 years of age with a baseline LDL-C level of 190 mg/dL or higher (≥4.9 mmol/L), who achieve less than a 50% reduction in LDL-C levels and have fasting triglycerides 300 mg/dL or lower (≤3.4 mmol/L), while taking maximally tolerated statin and ezetimibe therapy, the addition of a bile acid sequestrant may be considered.[S4.2-11,S4.2-12]

Statin Therapy Recommendations- 4 Groups



Clinical ASCVD
-High

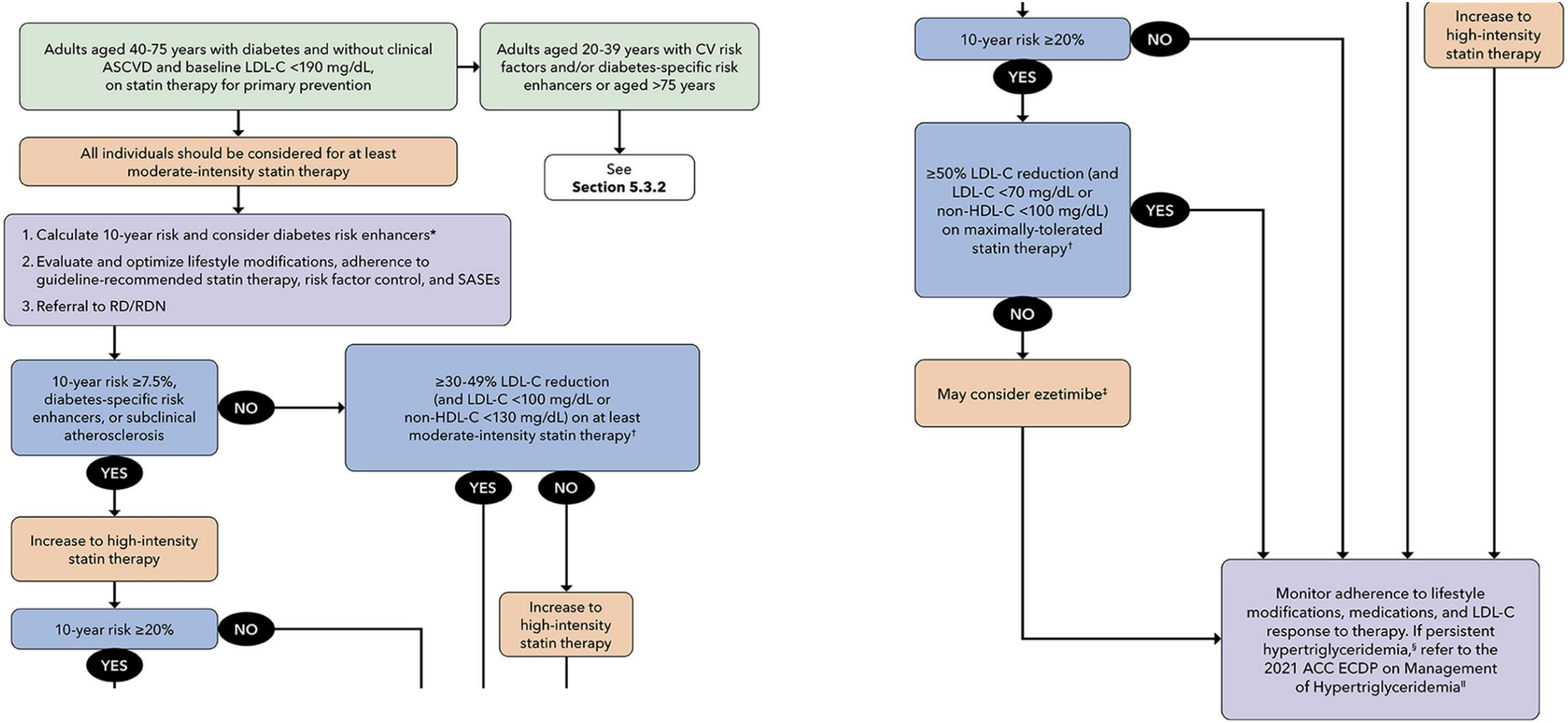
LDL-C ≥ 190
-High

Diabetes
(Age 40-75)
-Mod (High)

Risk ASCVD≥ 7.5%
(Age 40-75)
-Mod (High)

-statin intensity

Adults with Diabetes 40-75 Years Old

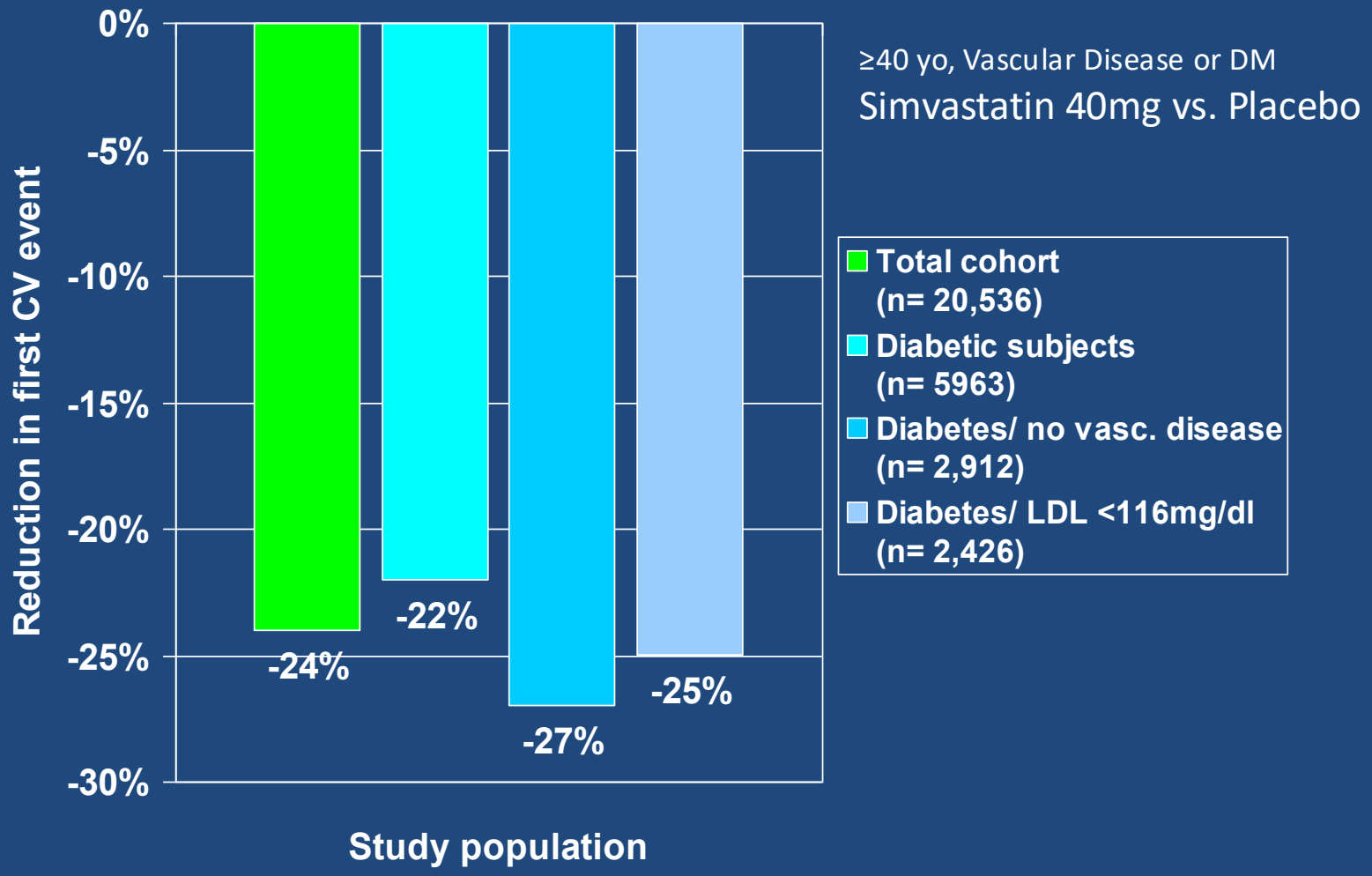


Lloyd-Jones DM, *JACC*, 2022

Adults with Diabetes 20-39 Years Old

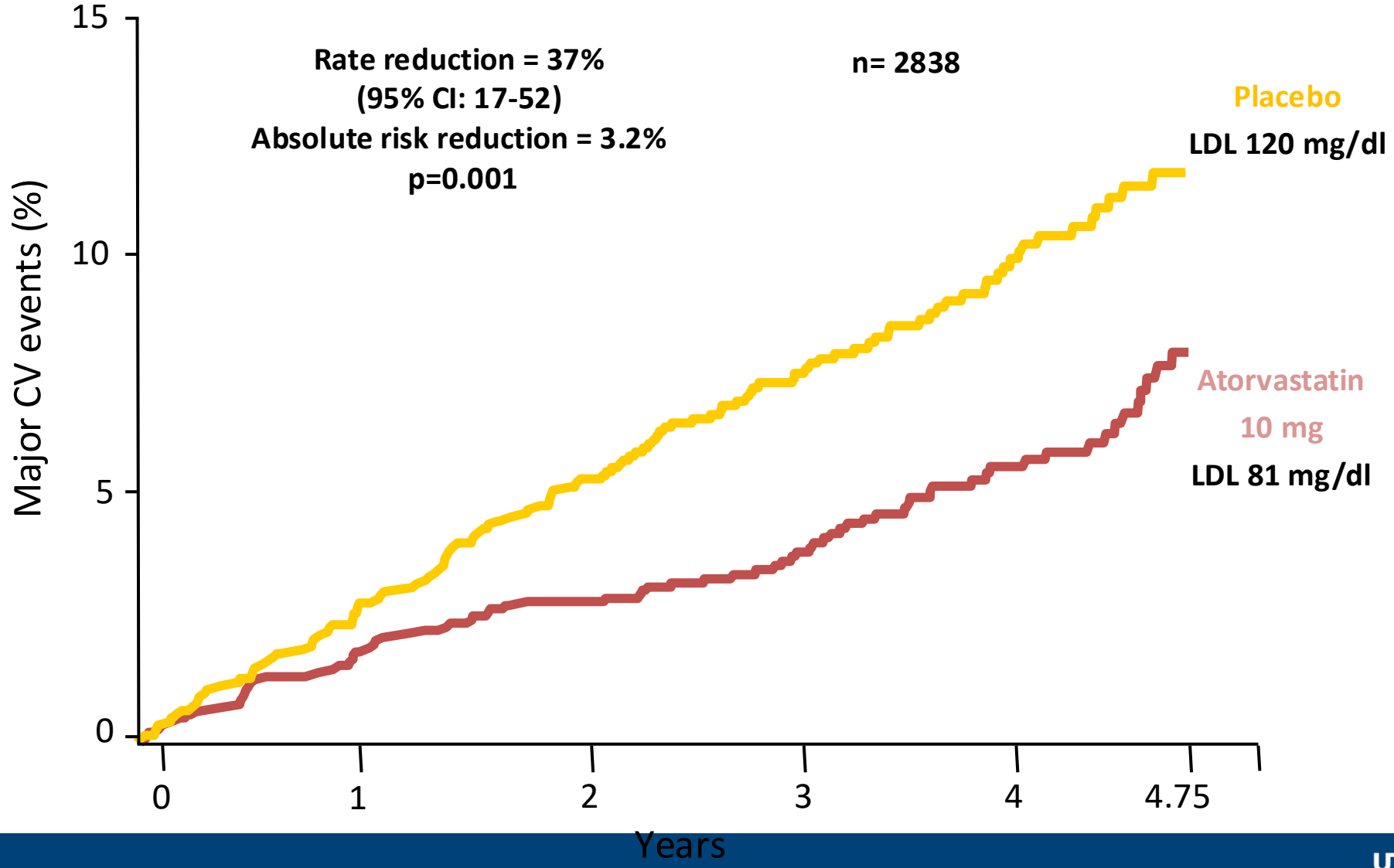
IIb	C-LD	7. In adults 20 to 39 years of age with diabetes mellitus that is either of long duration (≥10 years of type 2 diabetes mellitus, ≥20 years of type 1 diabetes mellitus), albuminuria (≥30 mcg of albumin/mg creatinine), estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2, retinopathy, neuropathy, or ankle-brachial index (ABI; <0.9), it may be reasonable to initiate statin therapy.[S4.3-5,S4.3-6,S4.3-8,S4.3-16–S4.3-25]

Effect of Simvastatin in Diabetic Subgroup: Heart Protection Study



HPS. *Lancet.* 2002;360:7-22.

CARDS: Statins Lower CV Risk in Diabetic Patients



Colhoun HM, et al. *Lancet*. 2004;364:685-696.

Patient Management – Diabetes Mellitus

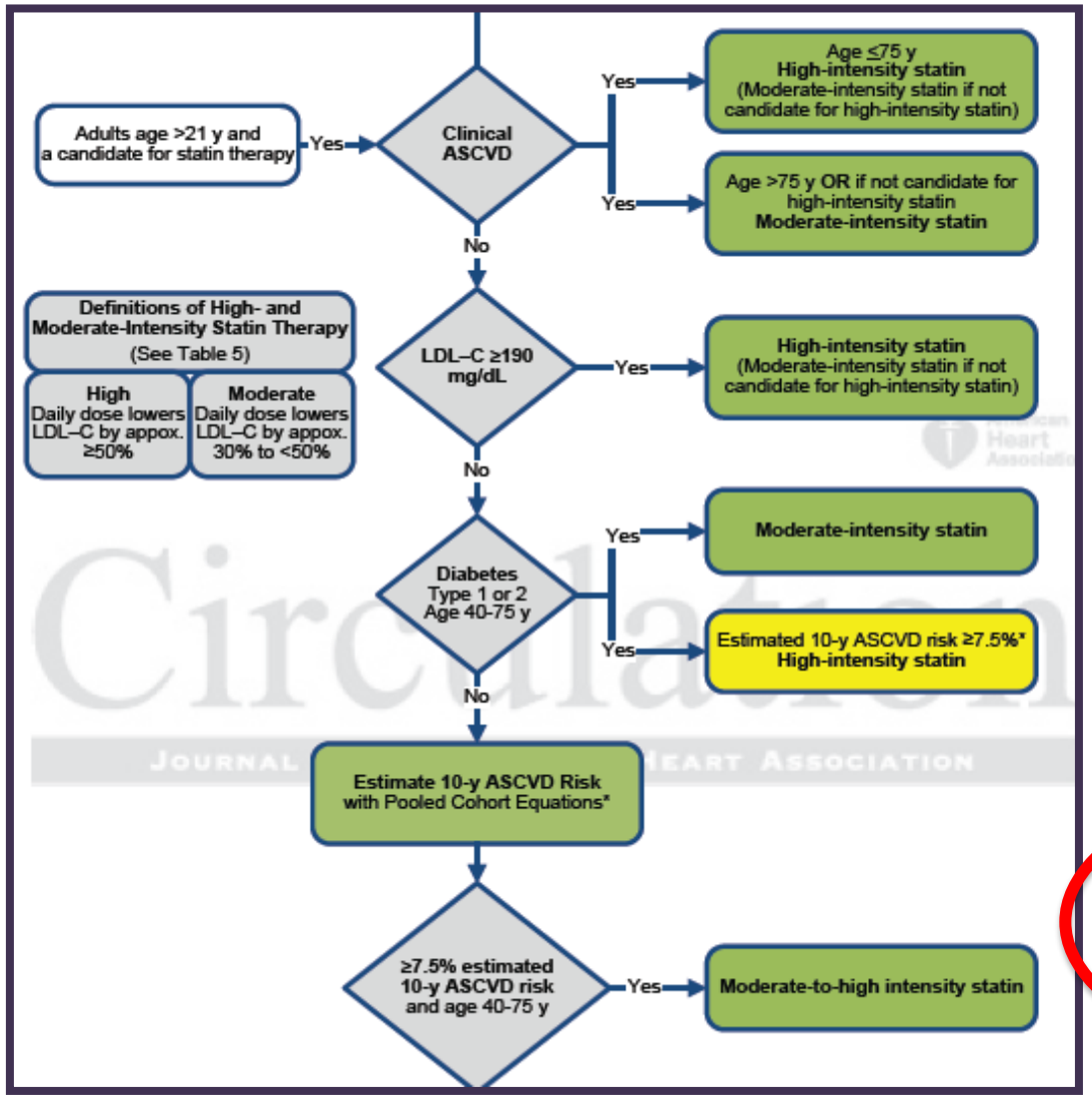
COR	LOE	Recommendations
I	A	1. In adults 40 to 75 years of age with diabetes mellitus, regardless of estimated 10-year ASCVD risk, moderate-intensity statin therapy is indicated.[S4.3-1–S4.3-9]
IIa	B-R	3. In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.[S4.3-12,S4.3-13]

Table 5. Diabetes-Specific Risk Enhancers That Are Independent of Other Risk Factors in Diabetes Mellitus

Risk Enhancers
Long duration (≥10 years for type 2 diabetes mellitus[S4.3-20] or ≥20 years for type 1 diabetes mellitus[S4.3-6]
Albuminuria ≥30 mcg of albumin/mg creatinine[S4.3-25]
eGFR <60 mL/min/1.73 m^2[S4.3-25]
Retinopathy[S4.3-19]
Neuropathy[S4.3-16]
ABI <0.9[S4.3-22,S4.3-24]

ABI indicates ankle-brachial index; and eGFR, estimated glomerular filtration rate.

Statin Therapy Recommendations- 4 Groups



Clinical ASCVD
-High

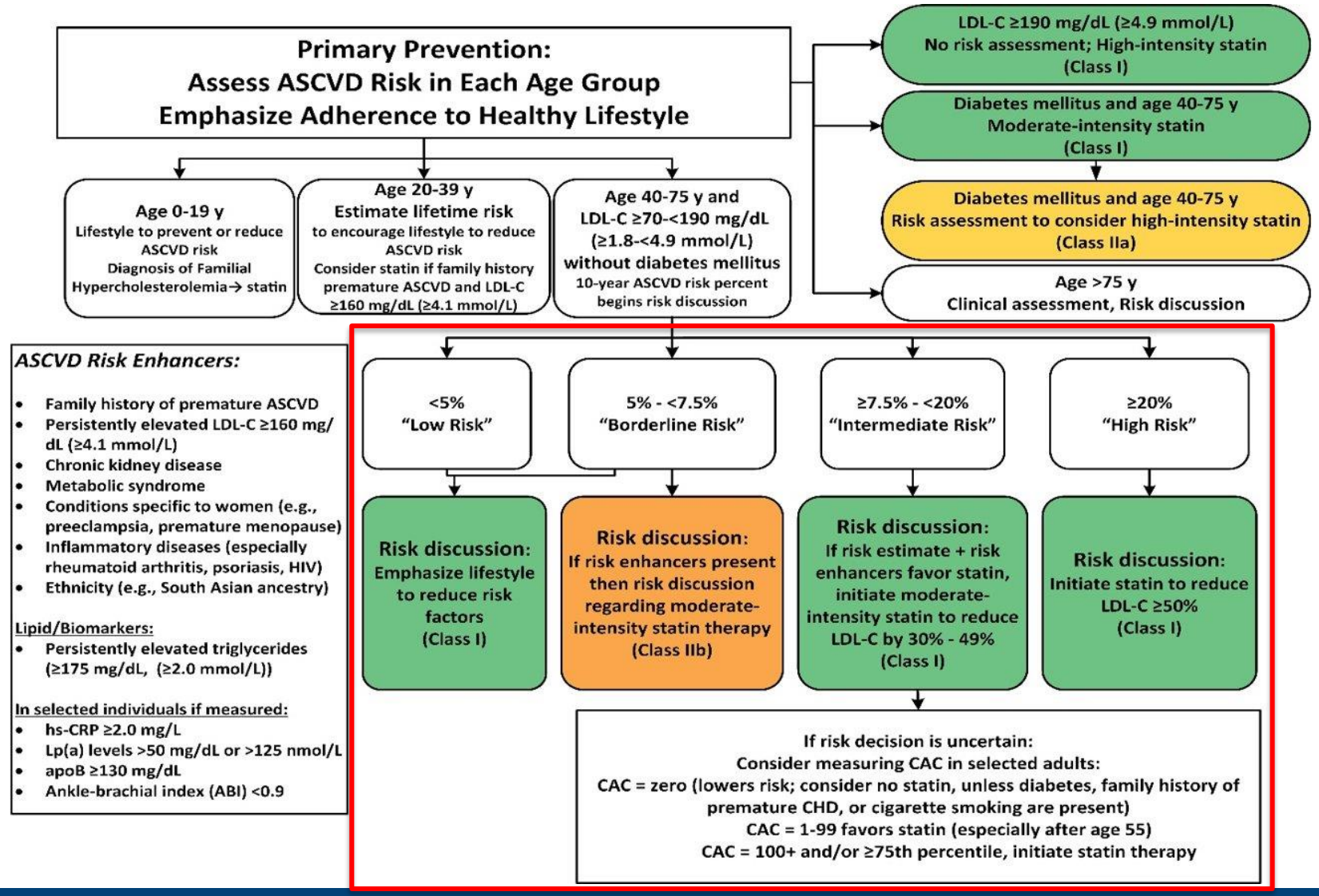
LDL-C ≥ 190
-High

Diabetes
(Age 40-75)
-Mod (High)

Risk ASCVD≥ 7.5%
(Age 40-75)
-Mod (High)

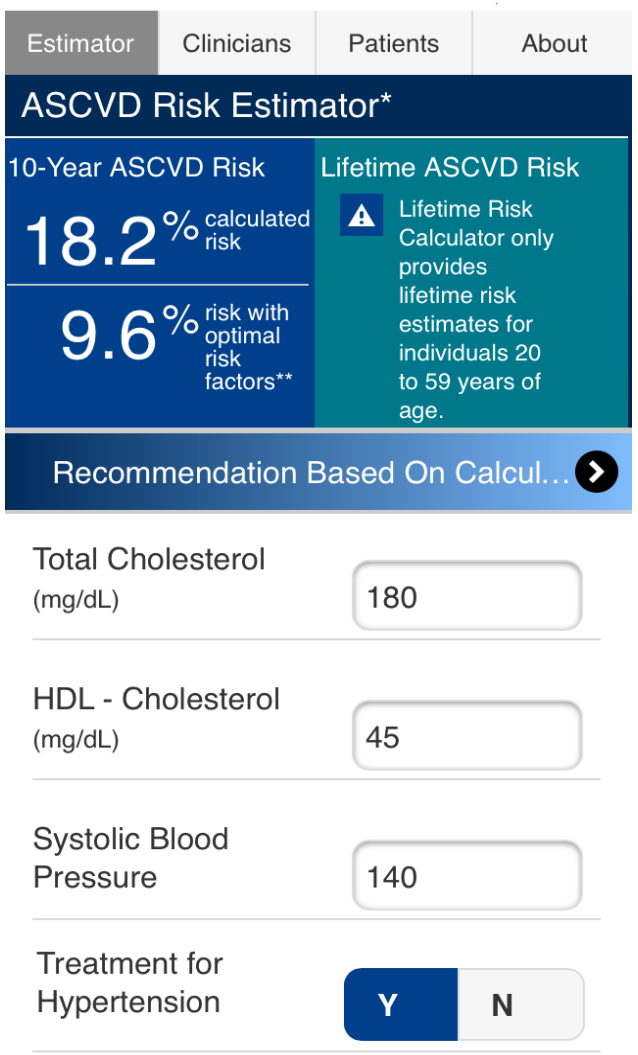
-statin intensity

Patient Management – Primary Prevention



Pooled Cohort Equation

- Developed 2013 (ACC/AHA) to estimate **10-year ASCVD risk** (MI, stroke, CV death).
- Age, sex, race (Black/White/Other), total cholesterol, HDL, systolic BP, HTN, diabetes, smoking
- Limitations: based on older cohorts, may **over/underestimate risk** in contemporary, diverse populations.



PREVENT Equation

- Predicting Risk of cardiovascular disease EVENTs (PREVENT) equation
- Developed in 2023 by AHA
- Estimates 10-year and 30-year risk for total cardiovascular disease (CVD), including atherosclerotic CVD (ASCVD) and heart failure (HF)

https://professional.heart.org/en/guidelines-and-statements/prevent-risk-calculator/prevent-calculator

	American Heart Association PREVENT™ Equations	PCEs
Demographic factors		
Age	√	√
Sex	Sex-specific equations	Sex-specific equations
Race	Do not include race or ethnicity	Race-specific (Black race or White race only) coefficients
Clinical predictors		
Systolic blood pressure	√	√
Total cholesterol		√
HDL cholesterol	√	√
Non-HDL cholesterol	√	
BMI	√	
Diabetes	√	√
Tobacco use	√	√
Lipid-lowering drug treatment	√	
Antihypertensive drug treatment	√	√
eGFR	√	
UACR*	√	
HbA1c*	√	
Social drivers of health		
SDI*	√	
Outcomes†		
Total CVD (ASCVD and HF)	√	
ASCVD	√	√
CHD	√	
Stroke	√	
HF	√	

ASCVD Risk Enhancers

Risk-Enhancing Factors
• **Family history f premature ASCVD** (males, age <55 y; females, age <65 y) • **Primary hypercholesterolemia** (LDL-C, 160–189 mg/dL [4.1–4.8 mmol/L); non–HDL-C 190–219 mg/dL [4.9–5.6 mmol/L])* • **Metabolic syndrome** (increased waist circumference, elevated triglycerides [>175 mg/dL], elevated blood pressure, elevated glucose, and low HDL-C [<40 mg/dL in men; <50 in women mg/dL] are factors; tally of 3 makes the diagnosis) • **Chronic kidney disease** (eGFR 15–59 mL/min/1.73 m^2 with or without albuminuria; not treated with dialysis or kidney transplantation) • **Chronic inflammatory conditions** such as psoriasis, RA, or HIV/AIDS • **History of premature menopause (before age 40 y) and history of pregnancy-associated conditions that increase later ASCVD risk such as preeclampsia** • **High-risk race/ethnicities** (e.g., South Asian ancestry)

ASCVD Risk Enhancers

Risk-Enhancing Factors

• **Lipid/biomarkers**: Associated with increased ASCVD risk
  • Persistently* elevated, primary hypertriglyceridemia (≥175 mg/dL);
  • If measured:
  • **Elevated high-sensitivity C-reactive protein** (≥2.0 mg/L)
  • **Elevated Lp(a):** A relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor especially at higher levels of Lp(a).
  • **Elevated apoB** ≥130 mg/dL: A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
  • **ABI** <0.9

Role of Coronary Calcium Testing

CAC Testing

0
Lifestyle
(unless smoking, DM, premature fam hx)

1-99,
Mod Statin

≥100 or ≥75th%
High Statin

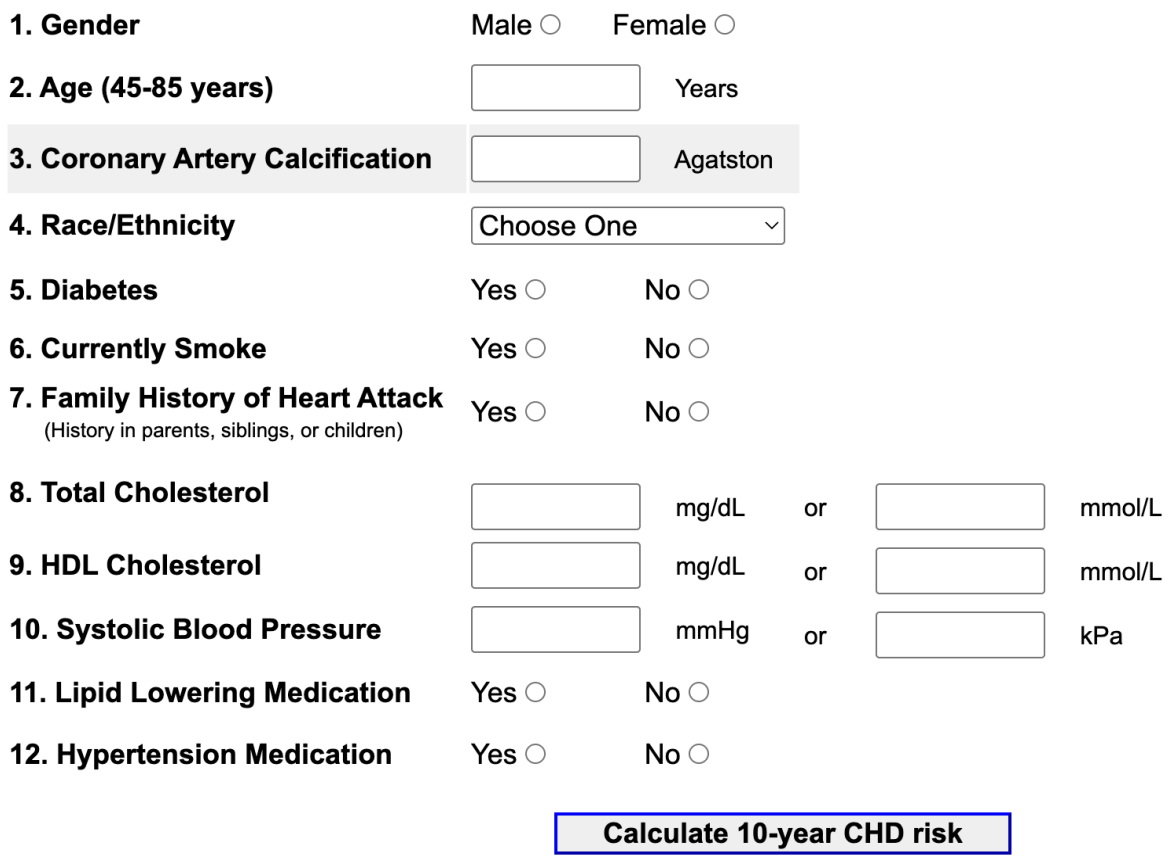
When the CAC score is zero, remeasure after 5 to 10 years.

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]

MESA Calculator

- Derived from the **Multi-Ethnic Study of Atherosclerosis** cohort.
- Estimates **10-year CHD risk** in adults without known CVD.
- Uses traditional risk factors (age, sex, race/ethnicity, cholesterol, BP, diabetes, smoking) **plus coronary artery calcium (CAC) score**.
- Especially helpful for **borderline/intermediate PCE risk** patients—CAC refines risk up or down.
- Validated in **White, Black, Hispanic, and Chinese-American** populations.
- Online tool available: mesariskcalculator.com.



High-Sensitivity C-Reactive Protein (hs-CRP)

- Acute-phase reactant produced by the liver in response to IL-6.
- Marker of vascular inflammation, independent of LDL-C.
- Helps guide statin therapy in borderline / intermediate-risk primary prevention patients.
- Statins and Bempedoic Acid have both been shown to reduce hs-CRP levels.

Hs-CRP Level	CV Risk Category
<1.0	Low risk
1.0 – 3.0	Intermediate risk
3.0 – 10.0	High risk
>10	Consider non-CV inflammatory condition; repeat test

Recommendations for Older Adults

Recommendations for Older Adults

Referenced studies that support recommendations are summarized in Online Data Supplements 18 and 19.

COR	LOE	Recommendations
IIb	B-R	1. In adults older than 75 years of age with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate-intensity statin may be reasonable[S4.4.4.1-1–S4.4.4.1-8]
IIb	B-R	2. In adults older than 75 years of age, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy.[S4.4.4.1-9]
IIb	B-R	3. In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy.[S4.4.4.1-10,S4.4.4.1-11]

2018 AHA Cholesterol Guidelines: LDL-C Testing in Children

IIa	B-R	3. In children and adolescents 10 years of age or older with an LDL-C level persistently 190 mg/dL (≥4.9 mmol/L) or higher or 160 mg/dL (4.1 mmol/L) or higher with a clinical presentation consistent with FH (see Section 4.2.) and who do not respond adequately with 3 to 6 months of lifestyle therapy, it is reasonable to initiate statin therapy (S4.4.4.3-13–S4.4.4.3-16).
IIa	B-NR	4. In children and adolescents with a family history of either early CVD* or significant hypercholesterolemia,† it is reasonable to measure a fasting or nonfasting lipoprotein profile as early as age 2 years to detect FH or rare forms of hypercholesterolemia (S4.4.4.3-17–S4.4.4.3-21).

Statin option
≥ 10yrs

LDL-C testing
≥ 2yrs

	Acceptable, mg/dL	Borderline, mg/dL 75th	Abnormal, mg/dL 95th
TC	<170 (<4.3 mmol)	170-199 (4.3-5.1 mmol)	≥200 (≥5.1 mmol)
Triglycerides (0-9 y)	<75 (<0.8 mmol)	75-99 (0.8-1.1 mmol)	≥100 (≥1.1 mmol)
Triglycerides (10-19 y)	<90 (<1.0 mmol)	90-129 (1.0-1.5 mmol)	≥130 (≥1.4 mmol)
HDL-C	>45 (>1.2 mmol)	40-45 (1.0-1.2 mmol)	<40 (<1.0 mmol)
LDL-C	<110 (<2.8 mmol)	110-129 (2.8-3.3 mmol)	≥130 (≥3.4 mmol)
Non–HDL-C	<120 (<3.1 mmol)	120-144 (3.1-3.7 mmol)	≥145 (≥3.7 mmol)

IIa	B-NR	5. In children and adolescents found to have moderate or severe hypercholesterolemia, it is reasonable to carry out reverse-cascade screening of family members, which includes cholesterol testing for first-, second-, and when possible, third-degree biological relatives, for detection of familial forms of hypercholesterolemia.[S4.4.4.3-22–S4.4.4.3-24]

Hypertriglyceridemia

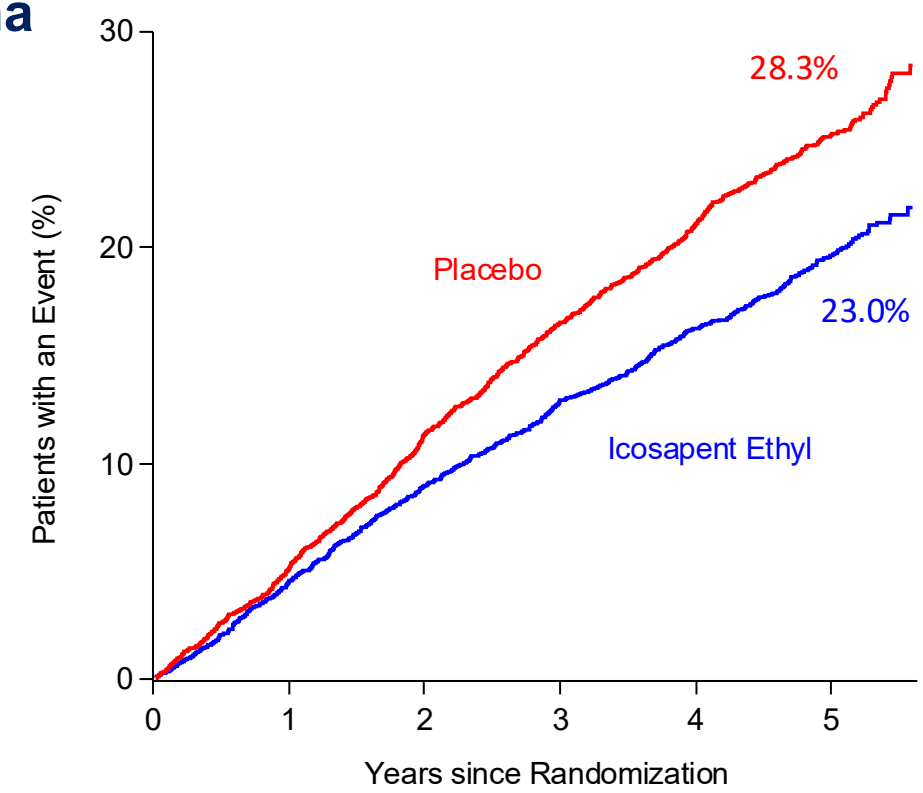
I	B-NR	1. In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [2.0 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides.[S4.5.2-1]
IIa	B-R	2. In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.).[S4.5.2-2–S4.5.2-6]

IIa	B-NR	4. In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L]), and especially fasting triglycerides ≥1000 mg/dL (11.3 mmol/L)), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy.[S4.5.2-7,S4.5.2-9]

Treatment of Hypertriglyceridemia Uncertain

REDUCE-IT:

Primary End Point: CV Death, MI, Stroke, Coronary Revascularization, Unstable Angina



Hazard Ratio, 0.75

(95% CI, 0.68–0.83)

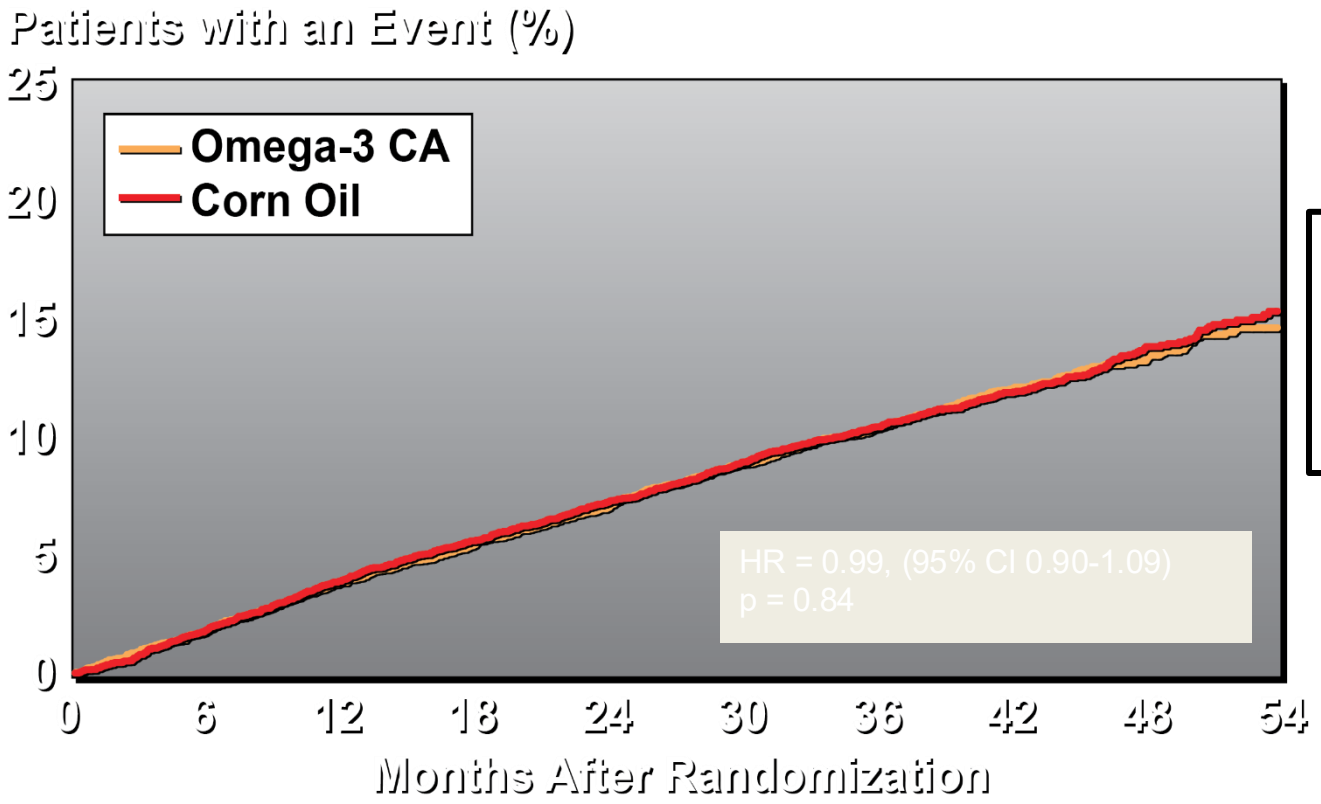
P=0.00000001

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019.

Treatment of Hypertriglyceridemia Uncertain

STRENGTH TRIAL

1° Endpoint Components and All-Cause Death



↑ Afib
2.2 vs 1.3%
HR, 1.69 [95%CI, 1.29-2.21]

No ↑ bleeding

Why the Differences in REDUCE-IT vs. STRENGTH?

1. *EPA alone vs. EPA + DHA*
   - *DHA may raise LDL?*

2. *Effect of placebo – Mineral Oil (REDUCE-IT) vs Corn Oil (STRENGTH)*
   - *Mineral oil may worsen outcome exaggerating benefit?*
   - *Corn oil could have favorable effect minimizing separation?*

Issues Specific To Women

I	B-NR	1. Clinicians should consider conditions specific to women, such as premature menopause (age <40 years) and history of pregnancy-associated disorders (hypertension, preeclampsia, gestational diabetes mellitus, small-for-gestational-age infants, preterm deliveries), when discussing lifestyle intervention and the potential for benefit of statin therapy.[S4.5.3-1–S4.5.3-6]

I	C-LD	2. Women of childbearing age who are treated with statin therapy and are sexually active should be counseled to use a reliable form of contraception.[S4.5.3-7–S4.5.3-12]
I	C-LD	3. Women of childbearing age with hypercholesterolemia who plan to become pregnant should stop the statin 1 to 2 months before pregnancy is attempted, or if they become pregnant while on a statin, should have the statin stopped as soon as the pregnancy is discovered.[S4.5.3-7–S4.5.3-12]

When to refer

- Consider referring any patient with ASCVD and/or baseline LDL-C ≥190 mg/dL, baseline LDL-C ≥190 mg/dL, or intolerance to at least [illegible] approved dose and a trial of an alternative statin t[illegible]
- Referral is recommend[illegible] did not achieve ↓ LDL-C ≥50% and LDL-C <70[illegible] erapy in combination with nonstatin therapy
- May also consider refe[illegible]
- **Considerations in refe[illegible]ng:** Lipid specialists may be available for virtual visits for patients in some rural or remote locations

ANYTIME THERE IS A QUESTION

Top Take Home Points

- Emphasize healthy lifestyle
- Clinical ASCVD = High intensity statin
- Very-high risk patients = goal LDL 55mg/dL
  - Start non-statin medication if needed.
- LDL > 190 = high intensity statin
- DM + Age 40-75 = statin (at least moderate to start, high intensity if high risk)
- Calculate ASCVD risk for primary prevention patients.
  - PREVENT or MESA > Pooled Cohort
- Don't forget risk enhancing factors!
- Consider coronary calcium scan to aid in treatment decisions
- Assess treatment response with repeat lipid measurements and adjust meds as needed
- Don't be afraid to refer

67

Question 1

A 60-year-old man presents for the routine follow-up of intermittent claudication. He feels well. His medical history includes iliofemoral arterial disease status/post percutaneous revascularization, hypertension, hypercholesterolemia, and type 2 diabetes mellitus. He quit smoking a few months earlier. His medications include aspirin 81 mg, rosuvastatin 40 mg, lisinopril 20 mg, metformin 1000 mg twice daily, chlorthalidone 25 mg, and varenicline 0.5 mg.

His vital signs are pulse rate 70 bpm, blood pressure 139/81 mm Hg, and respiratory rate 14 breaths/min. His examination findings are remarkable only for decreased pedal and posterior tibial pulses. Laboratory evaluation findings include total cholesterol level 170 mg/dL, high-density lipoprotein cholesterol (HDL-C) level 34 mg/dL, low-density lipoprotein cholesterol (LDL-C) level 98 mg/dL, and triglyceride (TG) levels 190 mg/dL. His calculated 10-year atherosclerotic cardiovascular disease (ASCVD) risk is 24% using the Pooled Cohort Equation.

The addition of which one of the following is most appropriate for this patient?

A. Niacin
B. Clopidogrel
C. Fish Oil
D. Ezetemibe
E. Vitamin E

Question 2

A 54-year-old man with hypertension and myocardial infarction 11 months prior treated with stenting of the posterior descending artery is seen in clinic for routine follow-up. He denies any chest discomfort or dyspnea with activity. He would like to reduce his medications if possible. Since his previous visit 6 months prior, he has been diagnosed with diabetes mellitus, and he asks whether the statin is responsible. His daily medications include aspirin 81 mg, metoprolol succinate 25 mg, lisinopril 10 mg, and atorvastatin 40 mg. On examination, his heart rate is 62 bpm and blood pressure is 112/65 mm Hg. The remainder of his examination is normal. An echocardiogram reveals normal left ventricular ejection fraction (LVEF). Creatinine is 0.9 mg/dL and low-density lipoprotein is 68 mg/dL.

What would you advise regarding his medication regimen?

A. Discontinue Aspirin
B. Continue current therapy
C. Discontinue Metoprolol
D. Increase Lisinopril
E. Substitute Ezetimibe for Atorvastatin

Thank You

Questions: Reynaldo.sanchez@utsouthwestern.edu