Cholesterol Management: Newer Recommendations and Therapies

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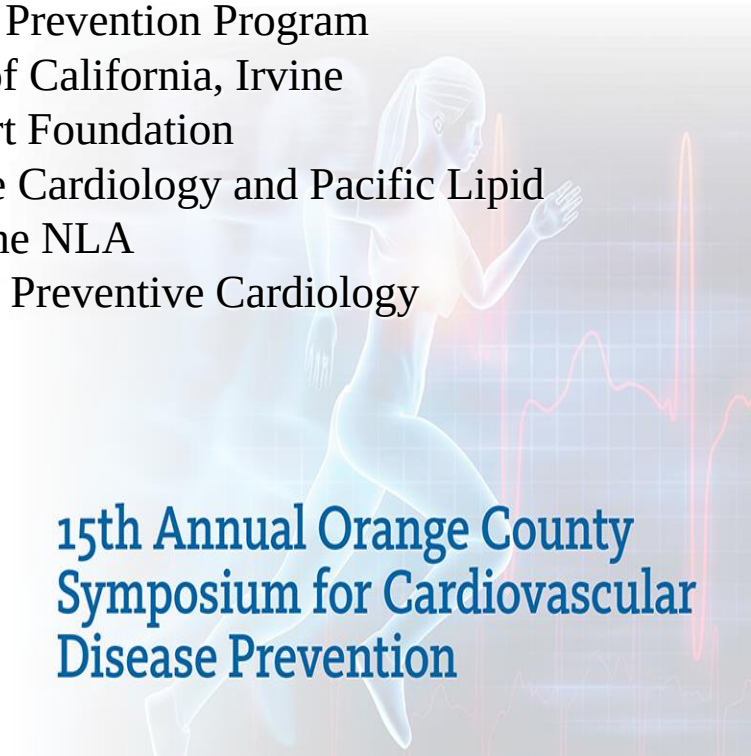
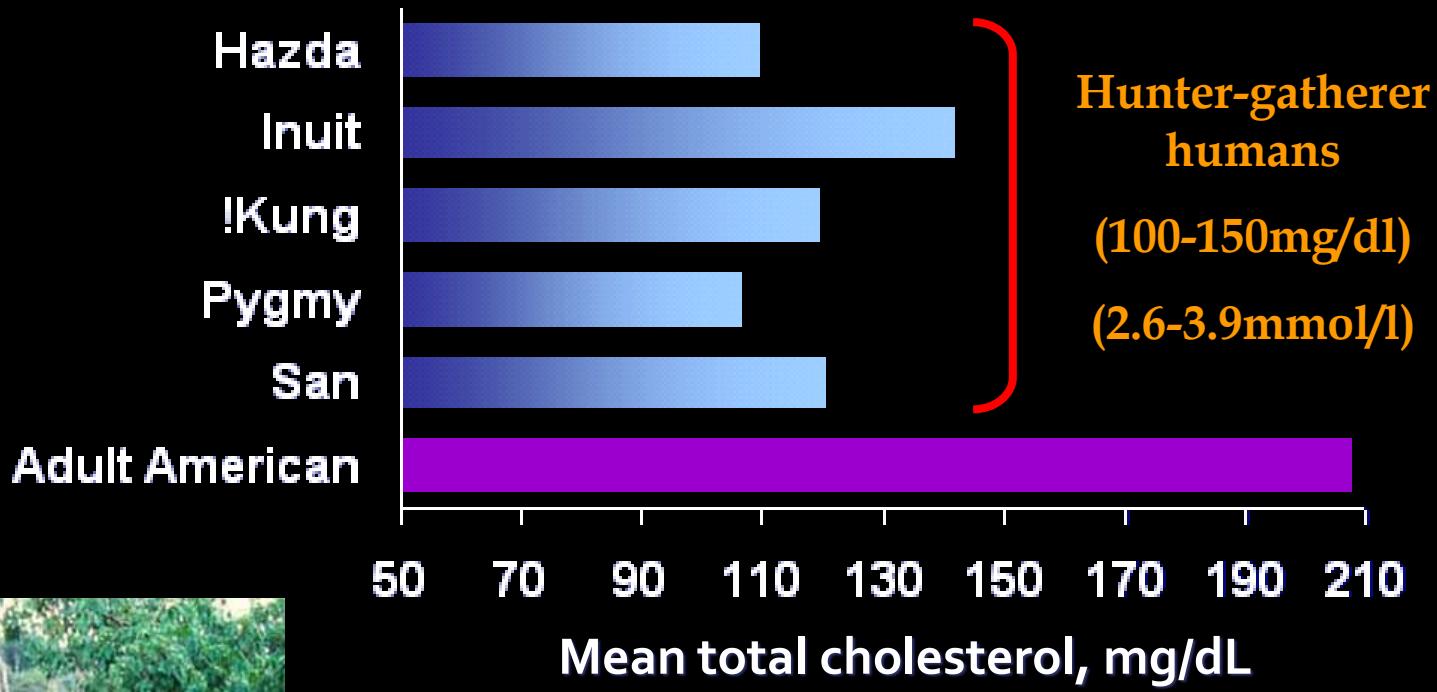


15th Annual Orange County Symposium for Cardiovascular Disease Prevention

Disclosures

Dr. Wong receives research support through his institution from Novartis, Regeneron, Novo Nordisk, and Lilly and is a consultant for Novartis, Agepha, Ionis, and Kaneka

What Is Desirable Cholesterol?



Human neonates:
LDL-C 0.8-1.9mmol/l
(30-75mg/dl)

Adapted from O'Keefe JH Jr et al. J Am Coll Cardiol. 2004;43:2142–2146.

Evolution of LDL-C Targets with Newer Guidelines

- ATP I (1988) LDL< 130mg/dl HRG
- ATP II (1993) LDL< 100mg/dl CAD
- ATP III (2001) LDL< 100mg/dl CAD& CAD EQ
- ATP III (Update 2004) LDL< 70mg/dl VHRG
- ACC/AHA (2006) LDL< 70mg/dl VHRG
- ADA/ ACC 2008 LDL< 70mg/dl CAD
- EAS 2011 LDL< 70mg/dl CAD
- ACC/AHA 2013 No LDL-C Target
- ESC / EAS 2016 LDL<70 mg/dl CAD
- ACC/AHA/Multisociety 2018 LDL>=70 threshold for nonstatins ASCVD
- ESC/ EAS 2019 LDL<55 mg/dl all ASCVD and very high risk
  LDL<40 recurrent CAD
- Lipid Association of India 2020 LDL<30 mg/dl extreme risk ASCVD group

- **ACC Evidenced Based Consensus Document 2022**
  LDL-C threshold of >=55 mg/dL for non-statin therapy in very high risk ASCVD patients

Evidence-Based Cardioprotective Dietary Patterns

DASH and Mediterranean-style dietary patterns

High intake of

- Plant-based foods: vegetables, fruits, and whole grain foods; legumes, nuts, and seeds
- Fish or seafood, lean meats, and non-fat or low-fat (1%) dairy products
- Plant-based oils (non-tropical) in place of animal fats

Limit intake of

- High-fat red meat and high-fat dairy products
- Sweets, sugar-sweetened beverages

2015–2020 Dietary Guidelines for Americans. Available at http://health.gov/dietaryguidelines/2015/guidelines/.
Eckel R. et al. *J Am College Cardiol.* 2014;63(25):2960–84.
Jacobson T et al. *J Clin Lipidol.* 2015;9(6 Suppl):S1-S122.

Exercise and Physical Activity

Recommendations for 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.
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.

Intensity of Statin Therapy

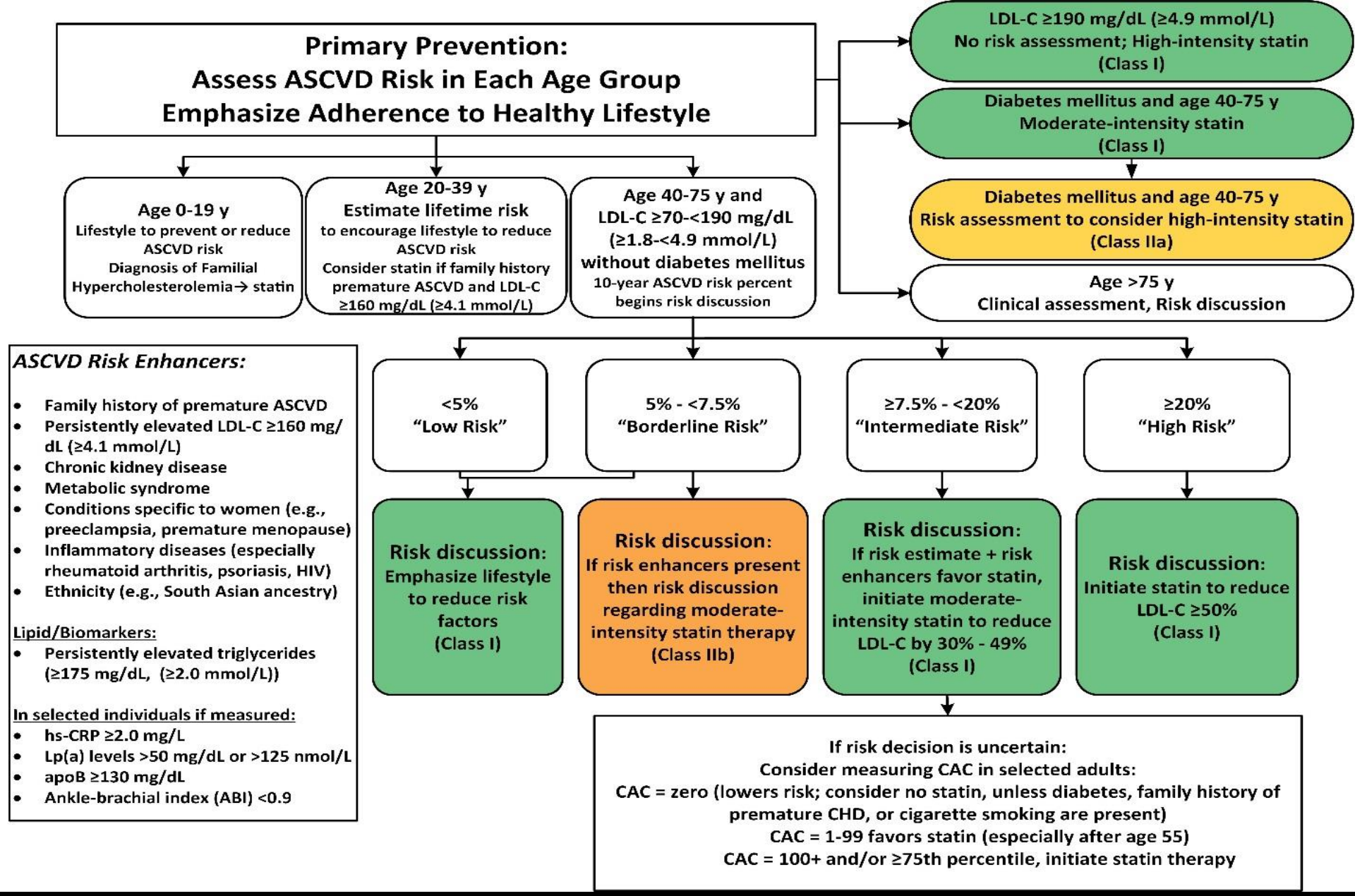
High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)*

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 **Rosuvasatin 20** *(40)* **mg**	**Atorvastatin 10 (***20***) mg** **Rosuvastatin** *(5)* **10 mg** **Simvastatin 20-40 mg‡** **Pravstatin 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* *Pitavastatin 1 mg*

*Individual responses to statin therapy varied in the RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.

†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).

‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA due to the increased risk of myopathy, including rhabdomyolysis.


Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle
LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)
Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)
Age >75 y
Clinical assessment, Risk discussion
Age 0-19 y
Lifestyle to prevent or reduce ASCVD risk
Diagnosis of Familial Hypercholesterolemia→ statin
Age 20-39 y
Estimate lifetime risk
to encourage lifestyle to reduce ASCVD risk
Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Age 40-75 y and
LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L)
without diabetes mellitus
10-year ASCVD risk percent begins risk discussion
ASCVD Risk Enhancers:
Family history of premature ASCVD
Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
Chronic kidney disease
Metabolic syndrome
Conditions specific to women (e.g., preeclampsia, premature menopause)
Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
Ethnicity (e.g., South Asian ancestry)
Lipid/Biomarkers:
Persistently elevated triglycerides (≥175 mg/dL, (≥2.0 mmol/L))
In selected individuals if measured:
hs-CRP ≥2.0 mg/L
Lp(a) levels >50 mg/dL or >125 nmol/L
apoB ≥130 mg/dL
Ankle-brachial index (ABI) <0.9
<5%
"Low Risk"
5% - <7.5%
"Borderline Risk"
≥7.5% - <20%
"Intermediate Risk"
≥20%
"High Risk"
Risk discussion:
Emphasize lifestyle to reduce risk factors
(Class I)
Risk discussion:
If risk enhancers present then risk discussion regarding moderate-intensity statin therapy
(Class IIb)
Risk discussion:
If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%
(Class I)
Risk discussion:
Initiate statin to reduce LDL-C ≥50%
(Class I)
If risk decision is uncertain:
Consider measuring CAC in selected adults:
CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
CAC = 1-99 favors statin (especially after age 55)
CAC = 100+ and/or ≥75th percentile, initiate statin therapy

EXPERT CONSENSUS DECISION PATHWAY

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

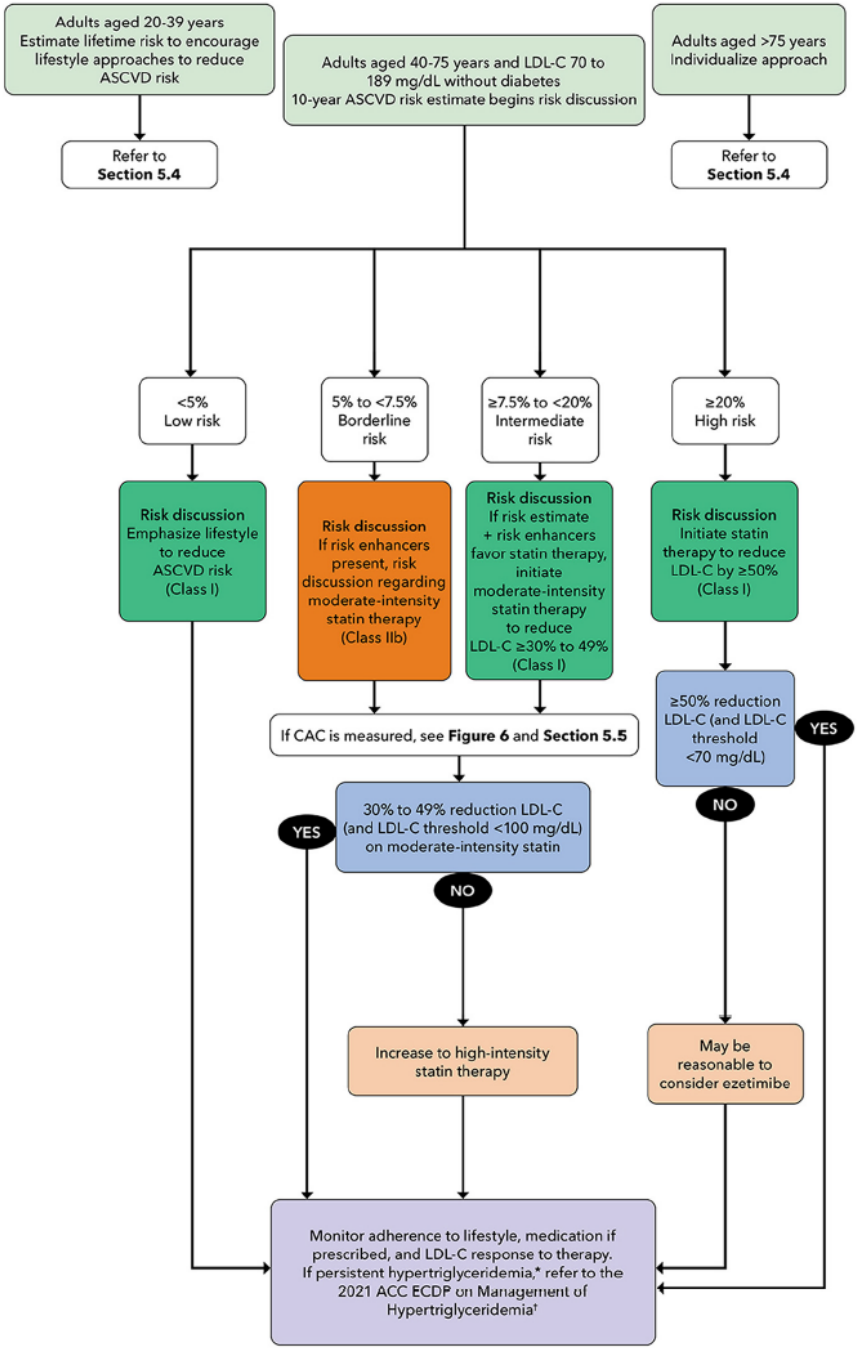
A Report of the American College of Cardiology Solution Set Oversight Committee

Endorsed by the National Lipid Association

Recommendations for Primary Prevention Patients without Diabetes or LDL-C >=190 mg/dL

- Consider moderate intensity statin therapy for those at 5-<20% 10-year ASCVD risk.
- If 30-49% LDL-reduction and LDL-C<100 not reached, consider high intensity statin
- For high risk (>=20%) persons, consider high intensity statin.
- If >=50% LDL-C reduction and LDL-C<70 mg/dL not reached, consider adding ezetimibe
- Address HTG according to 2021 ACC ECDP on HTG

FIGURE 5 Adults Without Clinical ASCVD or Diabetes (LDL 70-189 mg/dL)



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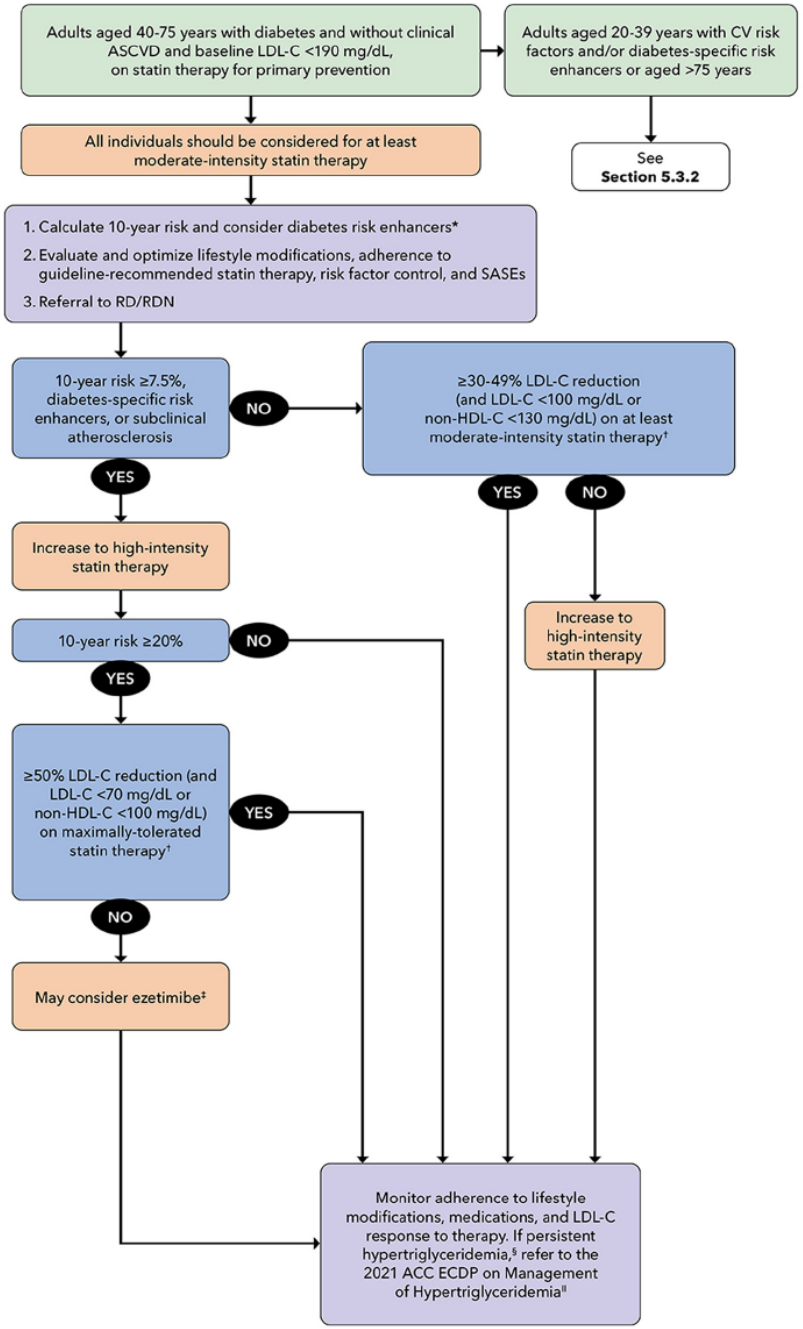
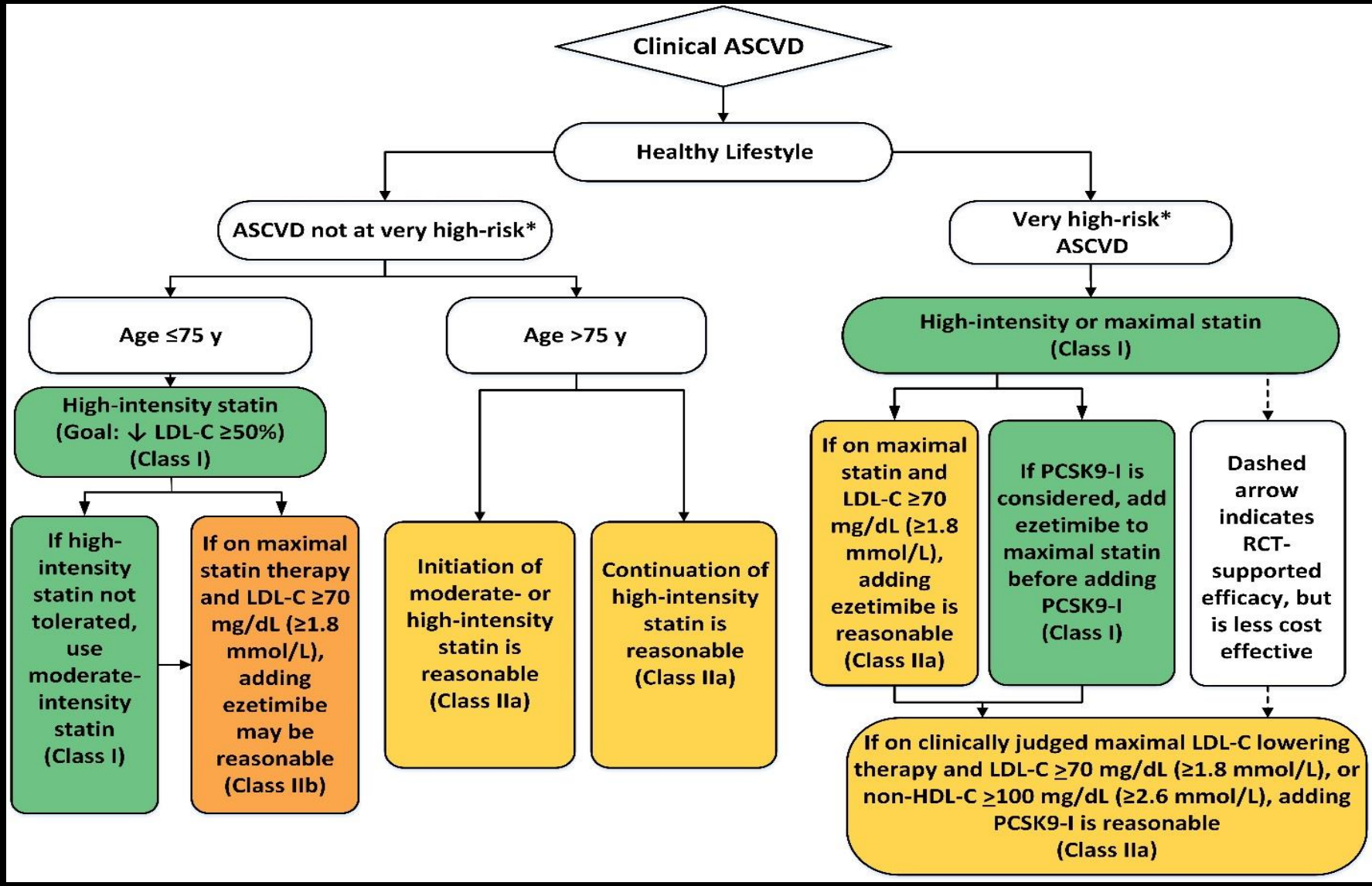
Recommendations for Patients with Diabetes without ASCVD

- All pts at least on moderate intensity statin
- If 10-year risk >=7.5% or DM risk enhancers or subclinical athero present, then give high intensity statin
- For those with >=20% risk, of >=50% LDL-C reduction or LDL-C<70 not reached, consider adding ezetimibe
- Address HTG based on 2021 ACC ECDP on HTG

FIGURE 4 Adults With Diabetes and Without ASCVD and Baseline LDL-C <190 mg/dL on Statin Therapy for Primary Prevention



Secondary Prevention



Very High-Risk* of Future ASCVD Events

Major ASCVD Events

Recent ACS (within the past 12 mo)

History of MI (other than recent ACS event listed above)

History of ischemic stroke

Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

High-Risk Conditions

Age ≥65 y

Heterozygous familial hypercholesterolemia

History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)

Diabetes mellitus

Hypertension

CKD (eGFR 15-59 mL/min/1.73 m^2)

Current smoking

Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe

History of congestive HF

* Very High-Risk is defined as multiple major ASCVD events or one major ASCVD event and multiple high risk conditions

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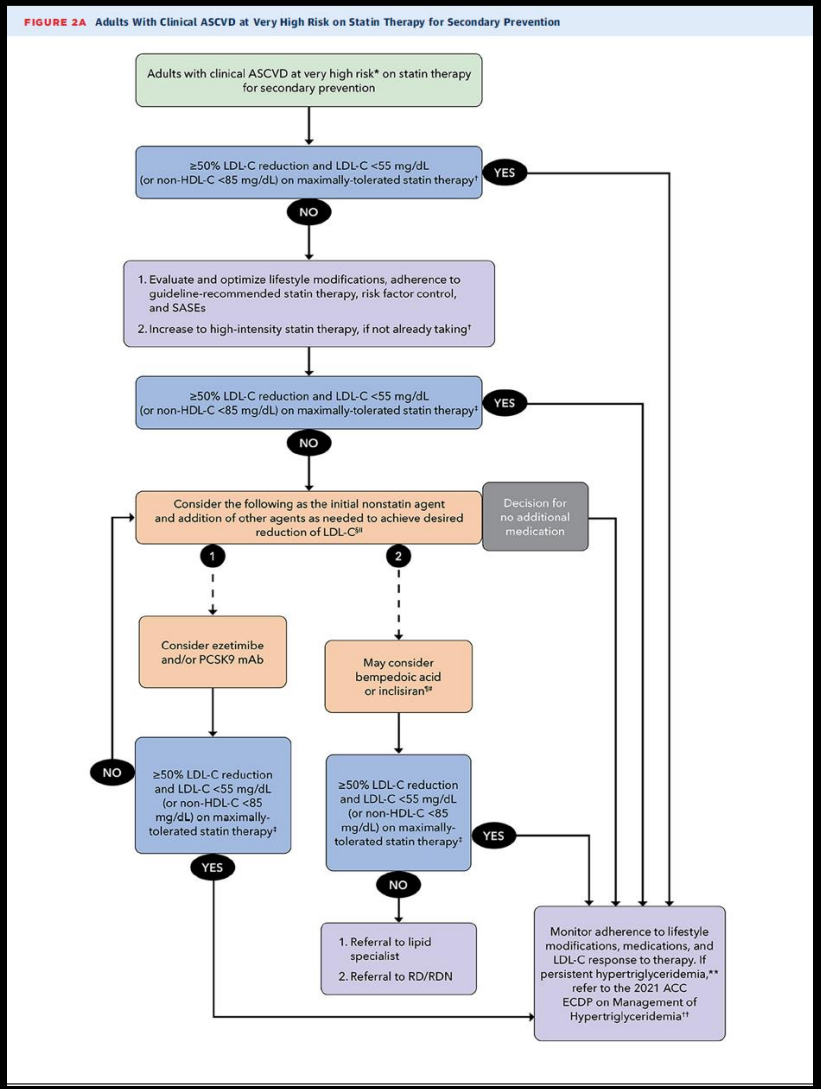
Recommendations for ASCVD Very High Risk Patients

If LDL-C ≥55 mg/dL (or non-HDL-C ≥85 mg/dL) despite high intensity or maximally tolerated statin

- Ezetimibe or a PCSK9 inhibitor are the first choice of non-statins for further LDL-C lowering which have been shown to improve ASCVD outcomes
- Inclisiran or bempedoic are alternative non-statin therapies that may be considered



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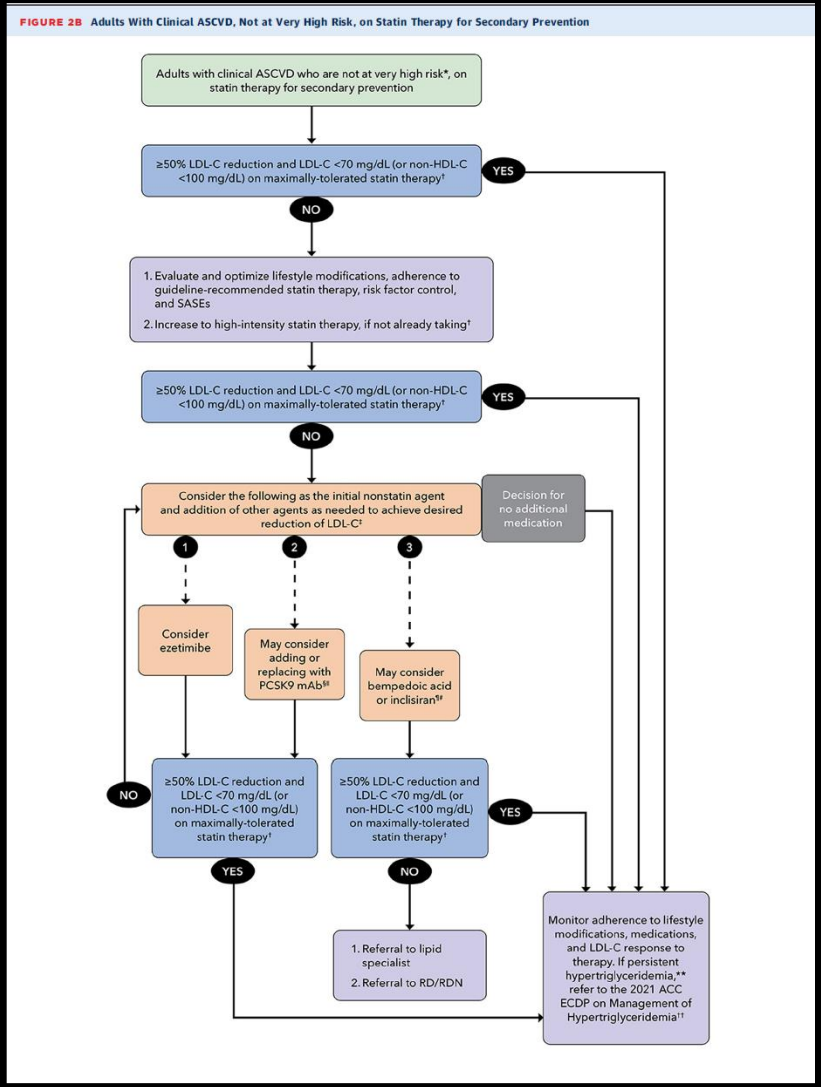
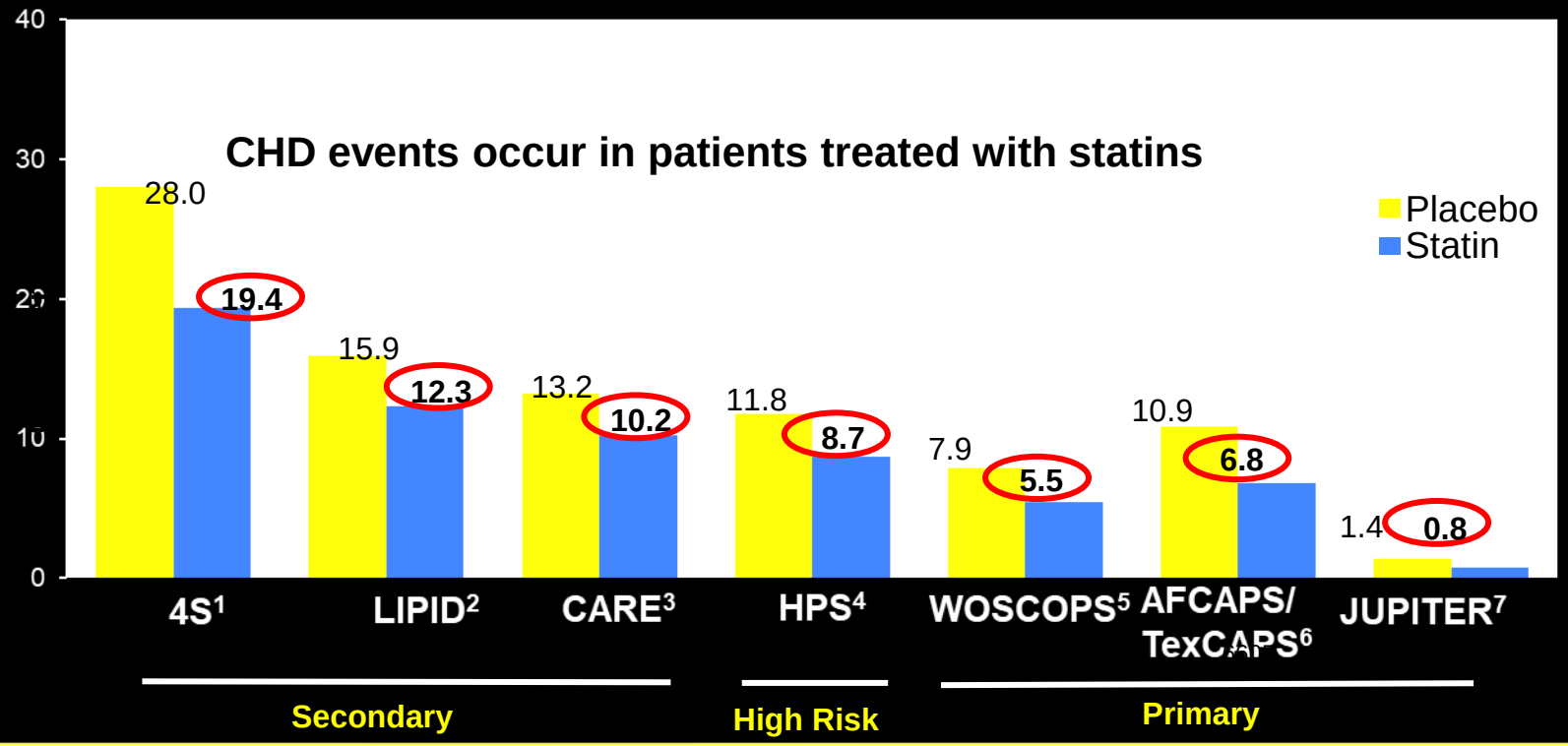
Recommendations for ASCVD Not at Very High Risk Patients

If LDL-C ≥70 mg/dL (or non-HDL-C ≥100 mg/dL) despite high intensity or maximally tolerated statin

- Ezetimibe or a PCSK9 inhibitor are the first choice of non-statins for further LDL-C lowering which have been shown to improve ASCVD outcomes
- Inclisiran or bempedoic are alternative non-statin therapies that may be considered



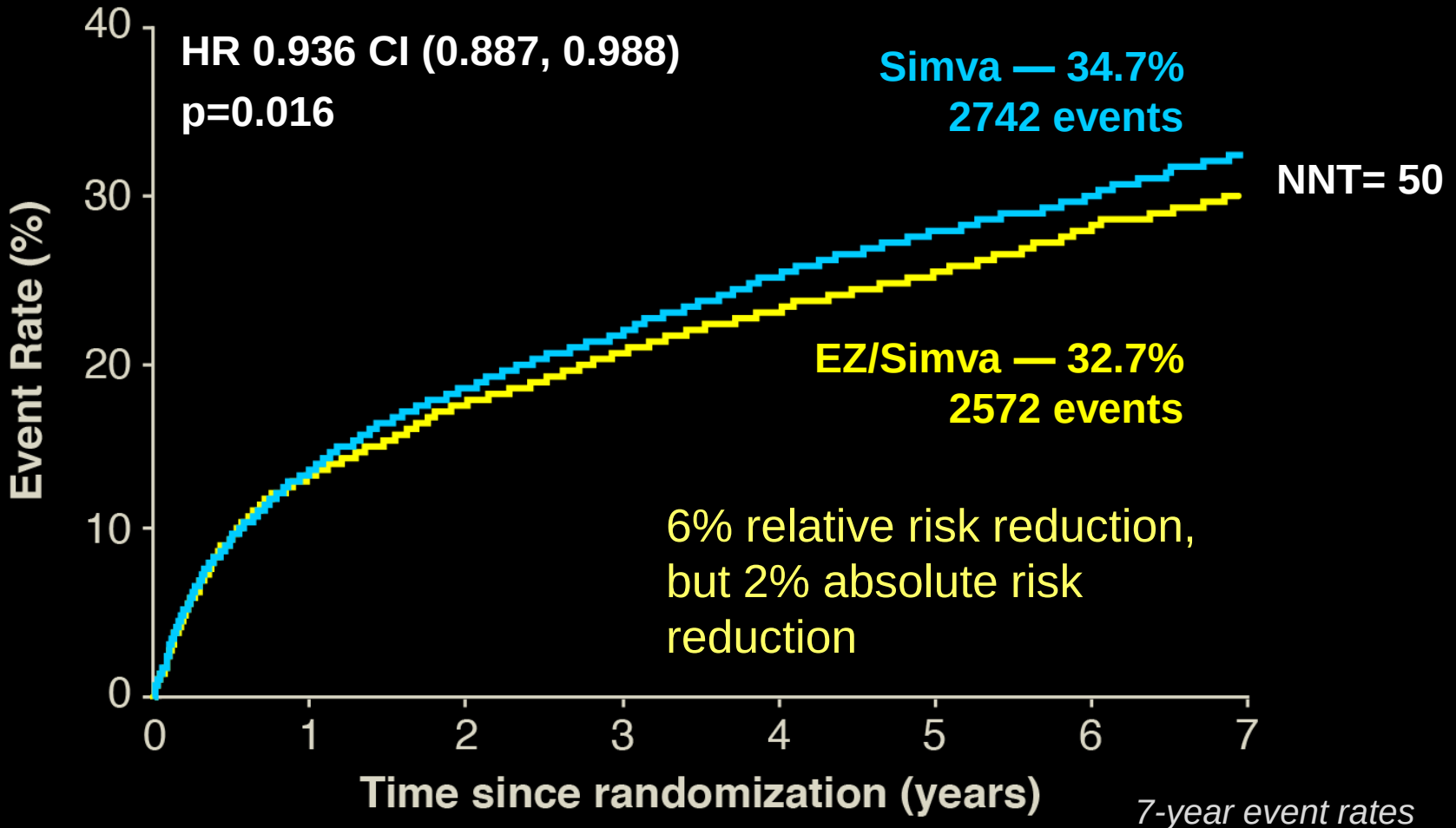
Despite ASCVD Benefit with Statin Monotherapy, Substantial Residual CV Risk Remains



Residual CV risk may be due not only to other lipid measures that may not be controlled, but other risk factors at suboptimal control such as hypertension, diabetes, or smoking.

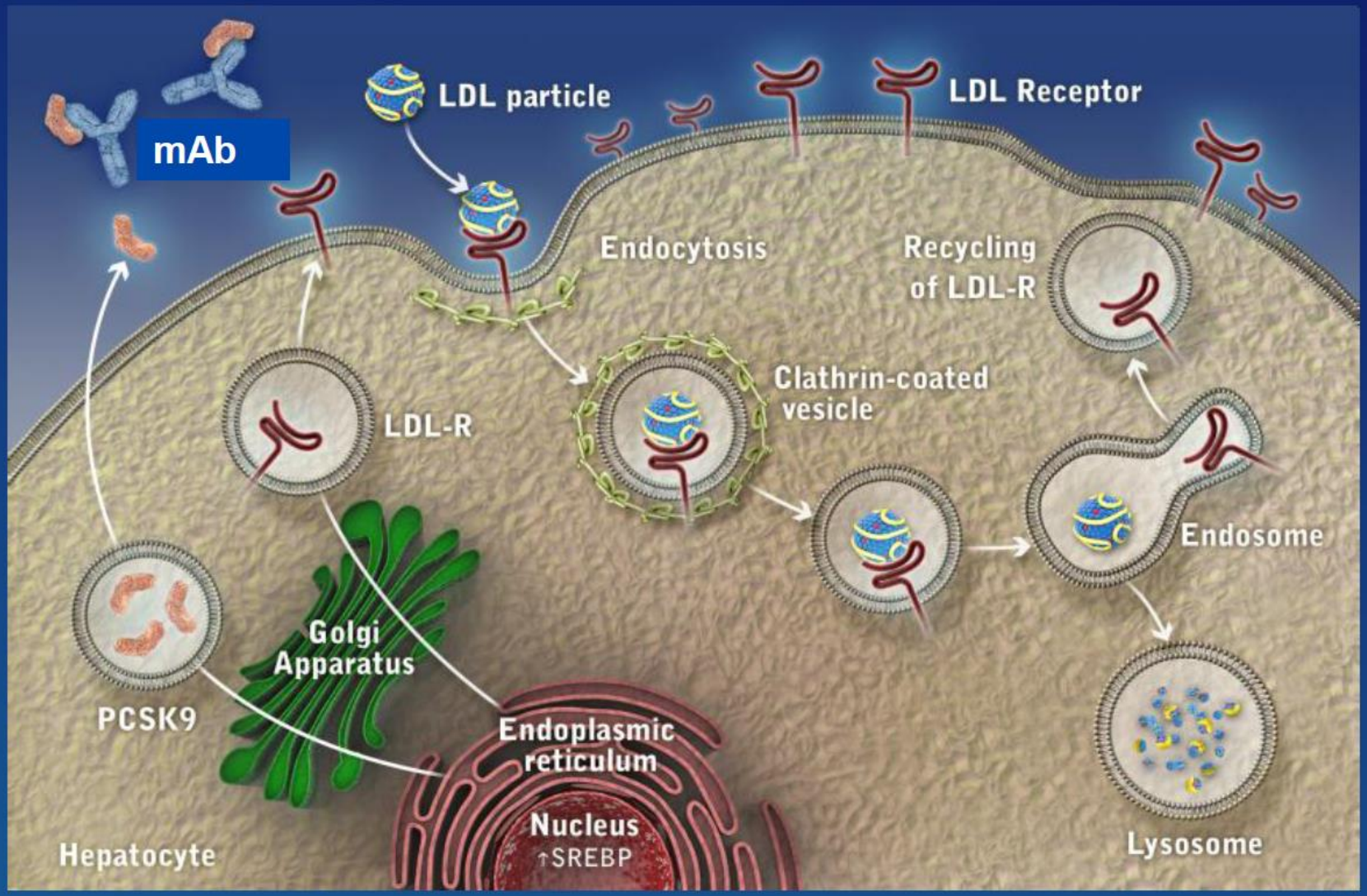
Primary Endpoint — ITT

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



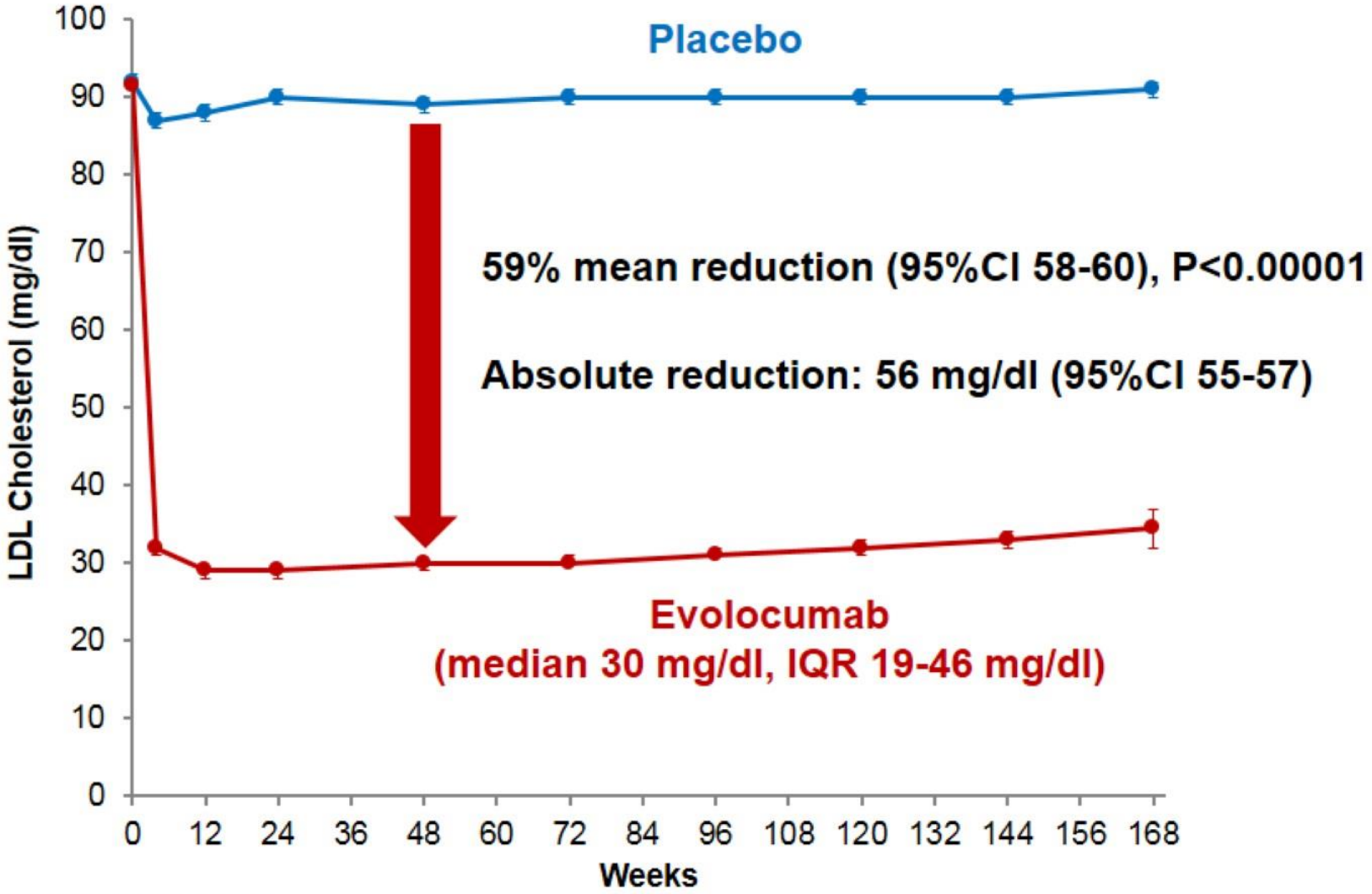
7-year event rates

Impact of an PCSK9 mAb on LDL Receptor Expression



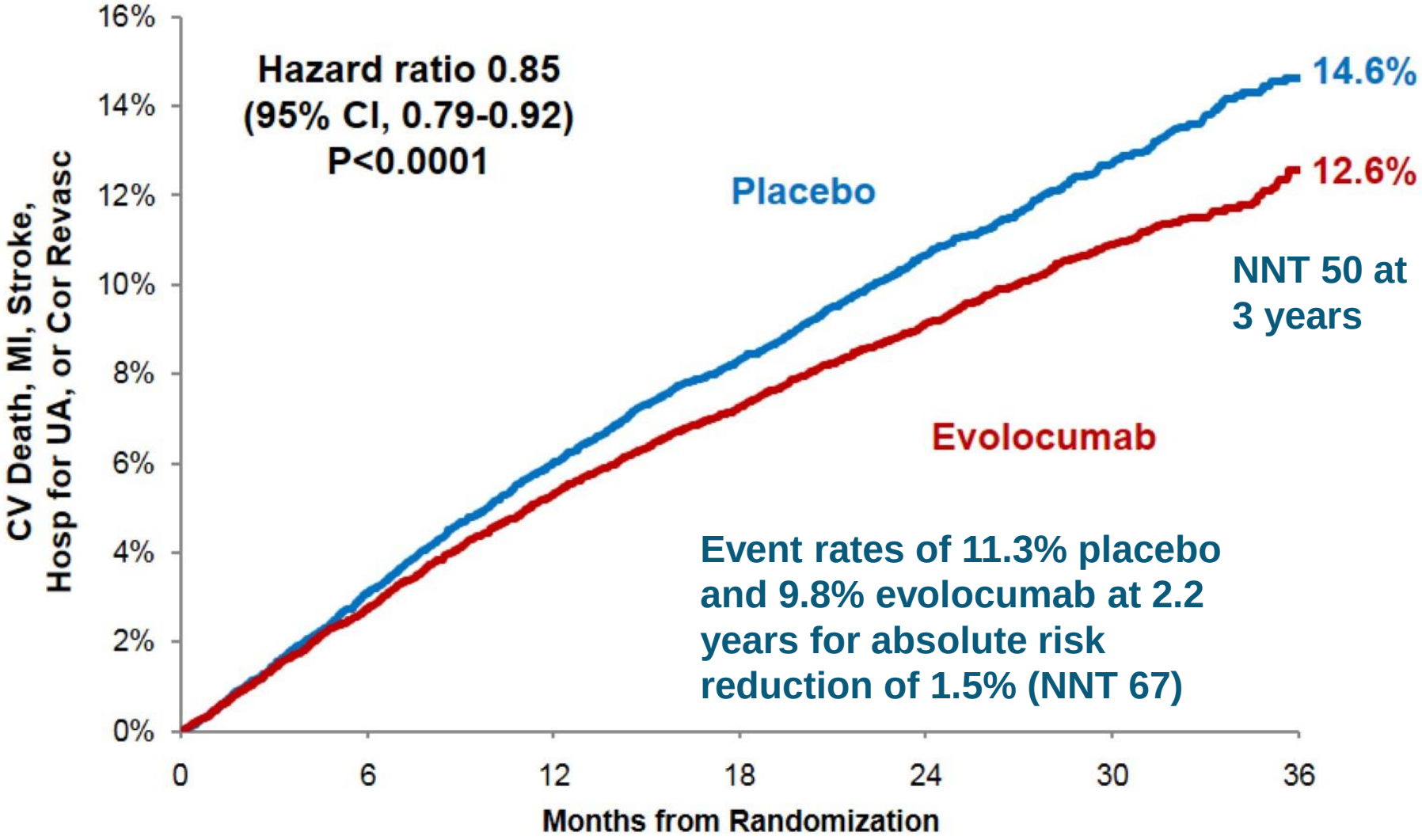
LDL Cholesterol

FOURIER TRIAL



Primary Endpoint

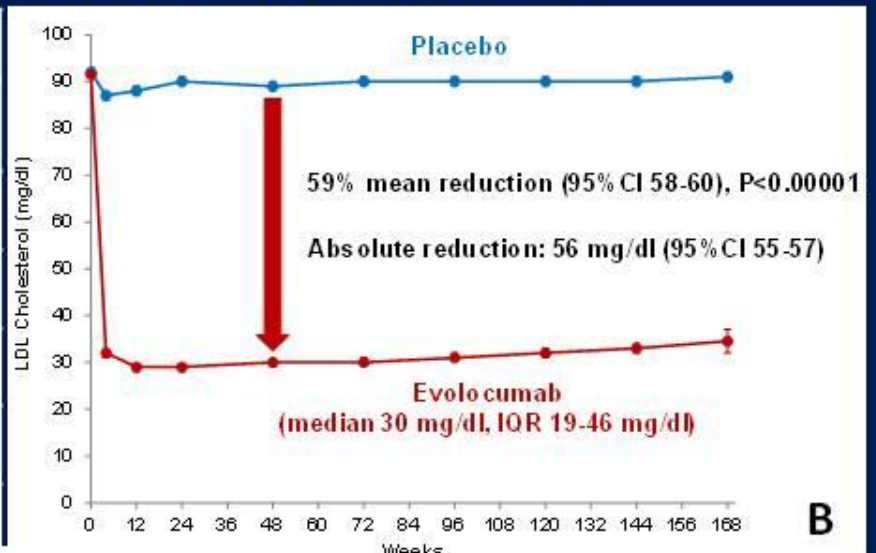
FOURIER TRIAL



Incremental benefit for reduction of primary endpoint according to achieved LDL-C levels at 4 weeks

Achieved LDL -C	Percentage of patients	
	Evolocumab	Placebo
≤ 70 mg/dL	87%	18%
≤ 40 mg/dL	67%	0.5%
≤ 25 mg/dL	42%	< 0.1%
≤ 15 mg/dL	5%	0%
≤ 10 mg/dL	2%	0%

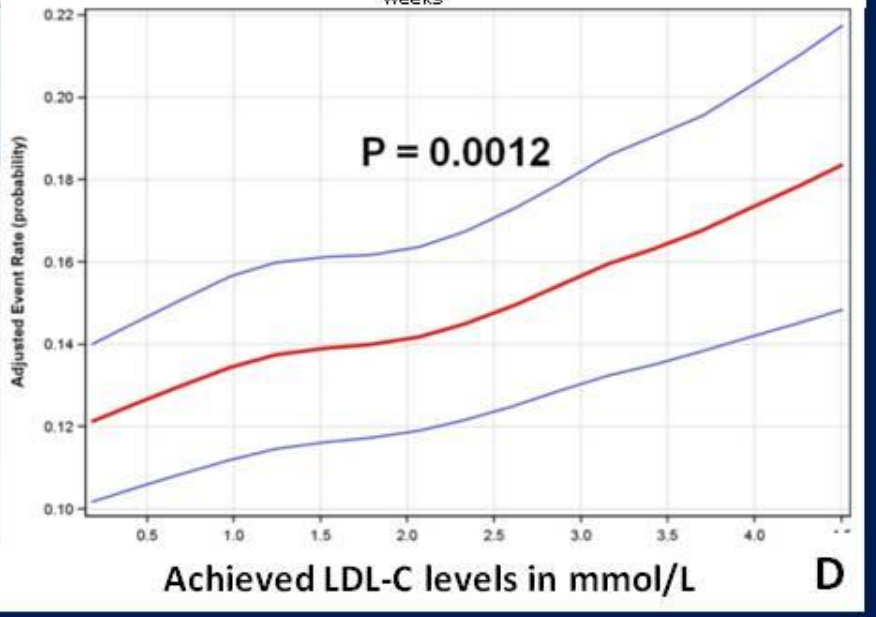
A



B

Achieved LDL-C		Hazard ratio (95% CI)	RRR
mmol/L	mg/dl		
<0.26	<10	0.69 (0.49-0.97)	31%
<0.5	<20	0.76 (0.64-0.90)	24%
0.5-1.3	20-49	0.85 (0.76-0.96)	15%
1.3-1.8	50-69	0.94 (0.82-1.09)	6%
1.8-2.6	70-99	0.97 (0.86-1.09)	3%
≥2.6	≥100	Reference	

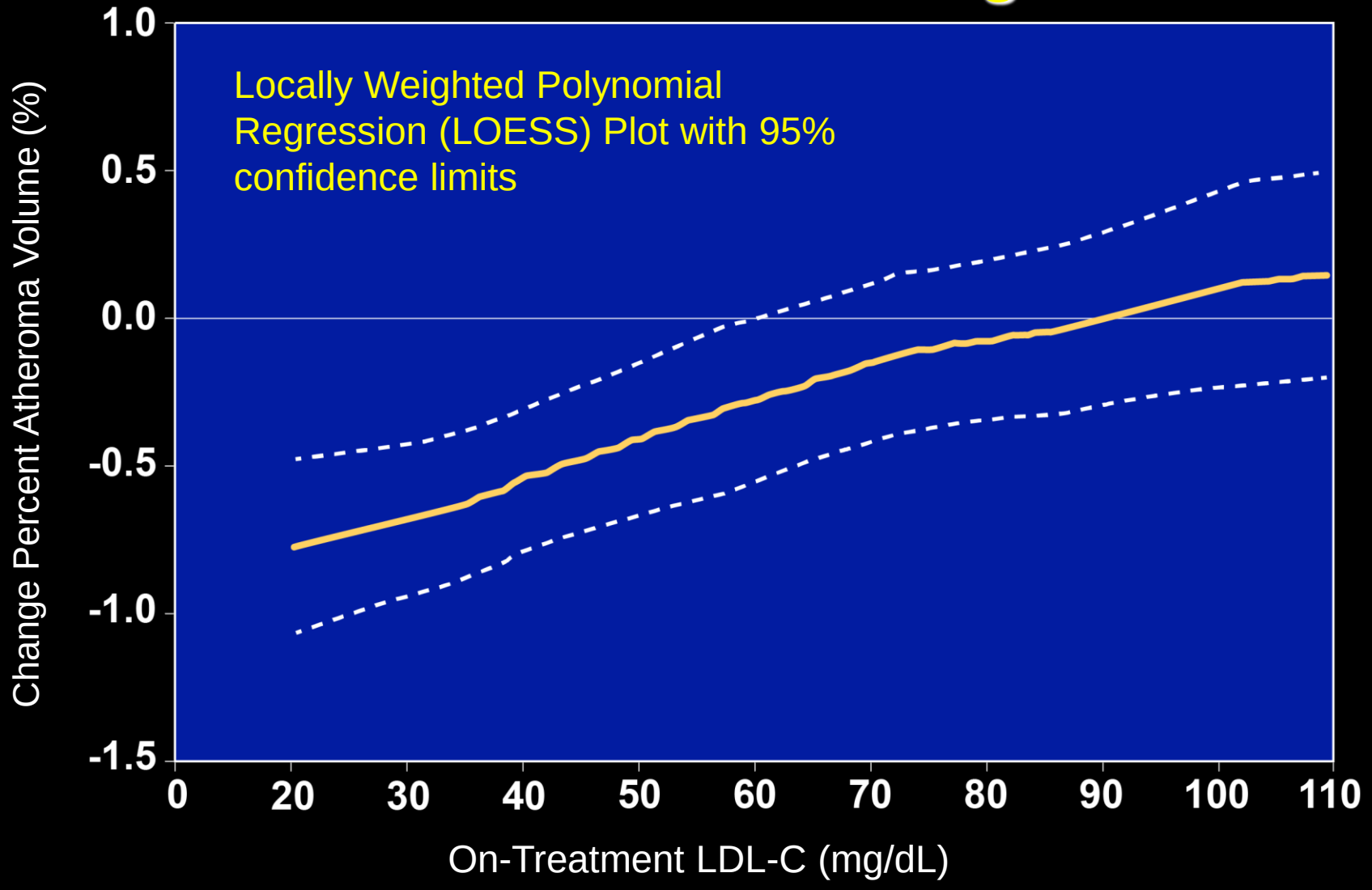
C



D

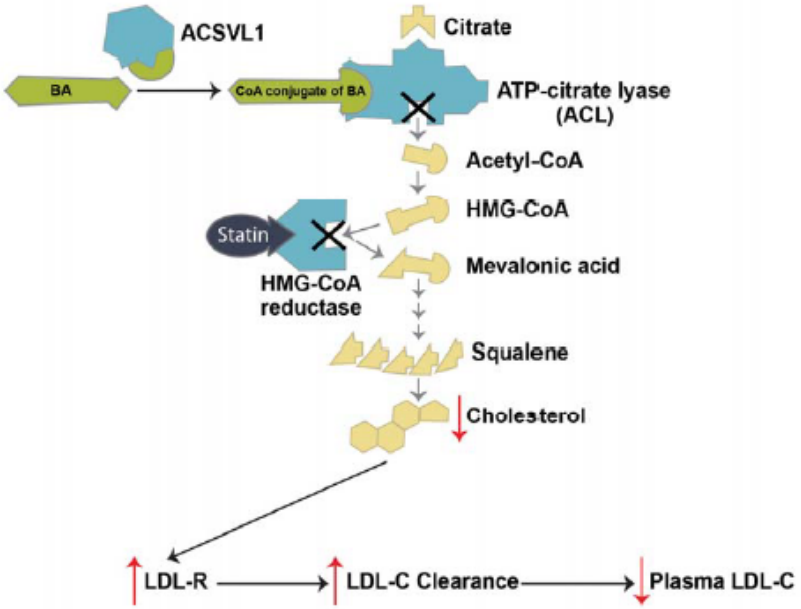
Gugliano Lancet 2017

GLAGOV Study of Evolocumab: Mean On-Treatment LDL-C vs. Change in PAV



Nissen et al., JAMA 2017

Bempedoic Acid Mechanism of Action



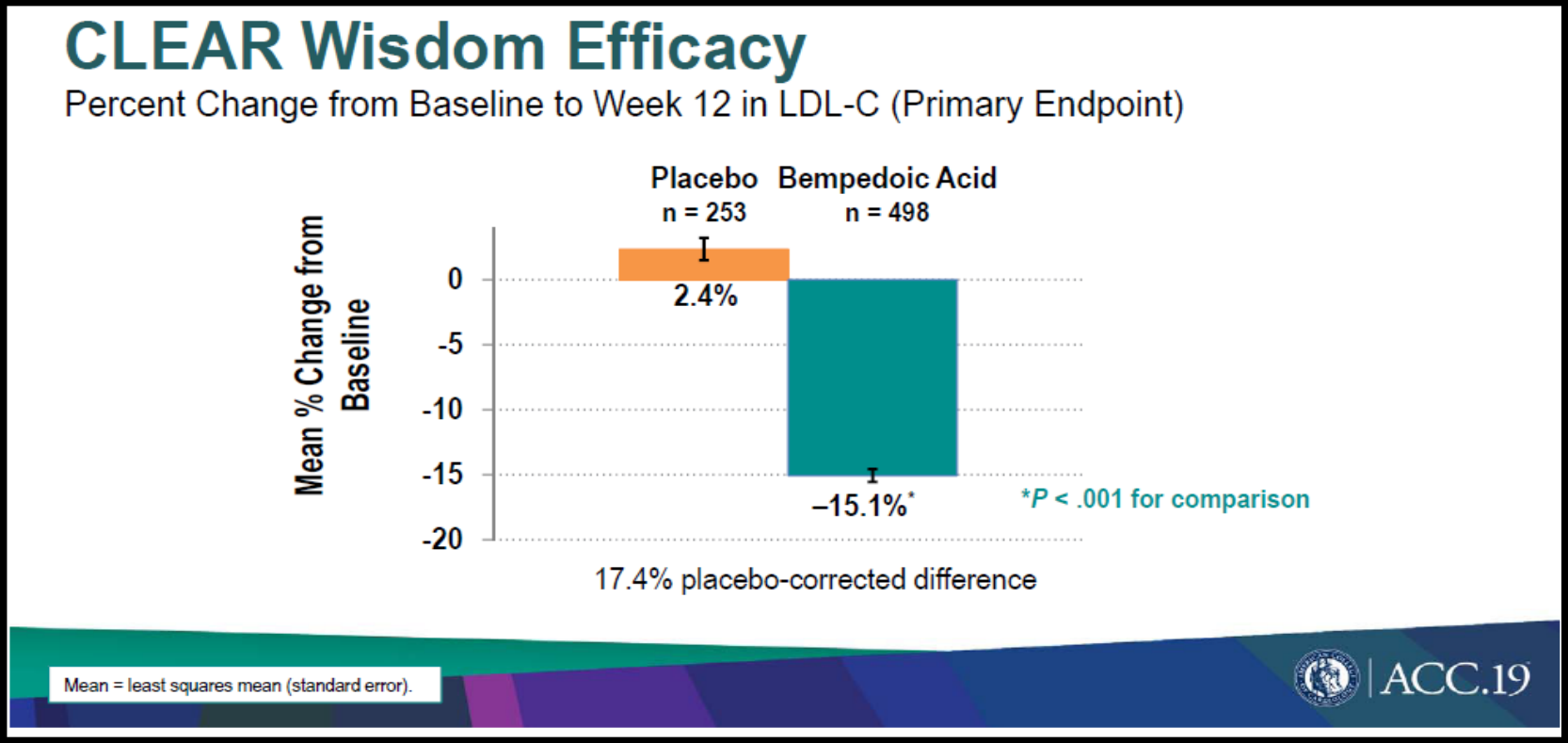
- Bempedoic acid is a prodrug activated in liver by very-long-chain acyl-CoA synthetase-1 (ACSVL1)
- Activated bempedoic acid acts in the same cholesterol synthesis pathway as statins
- Bempedoic acid inhibits ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Bempedoic acid upregulates LDL receptors and lowers LDL-C
- Activated bempedoic acid is not present in skeletal muscle

For review see: Pinkosky SL, et al. *Nat Commun.* 2016:28;7:13457.
BA, bempedoic acid.

ACC.19

Bempedoic Acid and Bempedoic Acid-Ezebimibe FDA-Approved February 2020

Indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established atherosclerotic cardiovascular disease (ASCVD) who require additional lowering of LDL-C. The effect of on cardiovascular morbidity and mortality has not been determined. First oral, once-daily, non-statin LDL-C lowering medicine approved since 2002 for indicated patients.



CLEAR HARMONY trial reported at ESC showed in 2000+ pts on maximially tolerated statin therapy placebo corrected LDL-C reduction of 16.8% in treated group.

Bempedoic Acid – Ezetimibe fixed dose combination provides 36% LDL-C lowering

Bempedoic acid trials showed no safety concerns.

CLEAR Outcomes Trial (N=14,032)

- Age 18 - 85 years
- History of ASCVD (CAD, symptomatic PAD, CVD disease, or at high risk for a CV event
- Statin intolerance (intolerant ≥2 statins, one at low dose)
- LDL ≥ 100 mg/dL

Exclusion criteria:

- Fasting TGs >500 mg/dL
- Major CV events, TIA, or unstable or symptomatic arrhythmia < 90 days
- History of severe HF
- Uncontrolled HTN or DM

Randomized 1:1 Double Blinded

Bempedoic acid 180 mg po QD (N ≈ 7000)

Placebo po QD (N ≈ 7000)

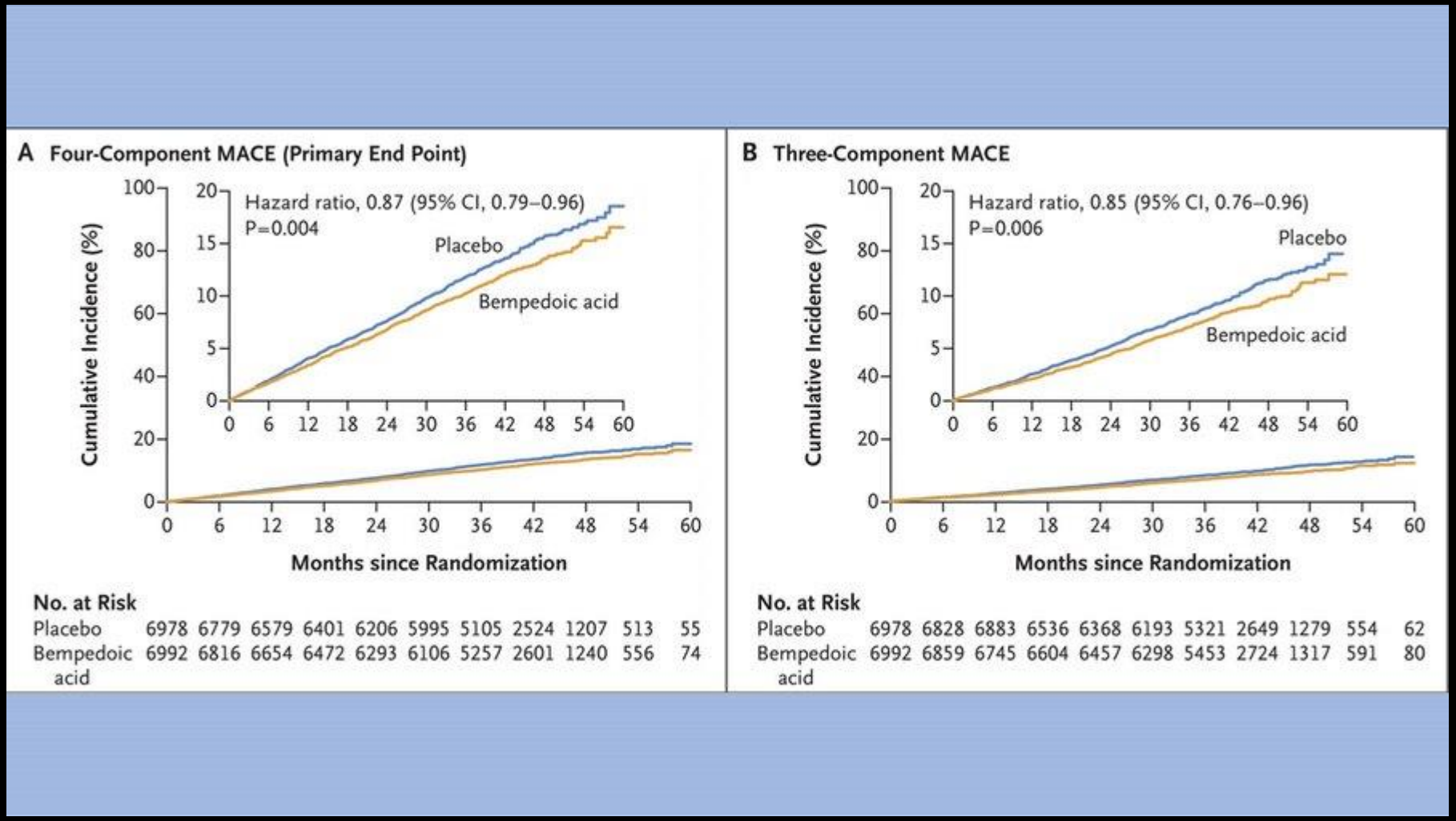
Estimated average treatment duration: 3.75 years

CV death, nonfatal MI, nonfatal stroke, or coronary revascularization.

Start: November 18, 2016
Enrollment end: Sep 5, 2019
Completion: Q4 of 2022

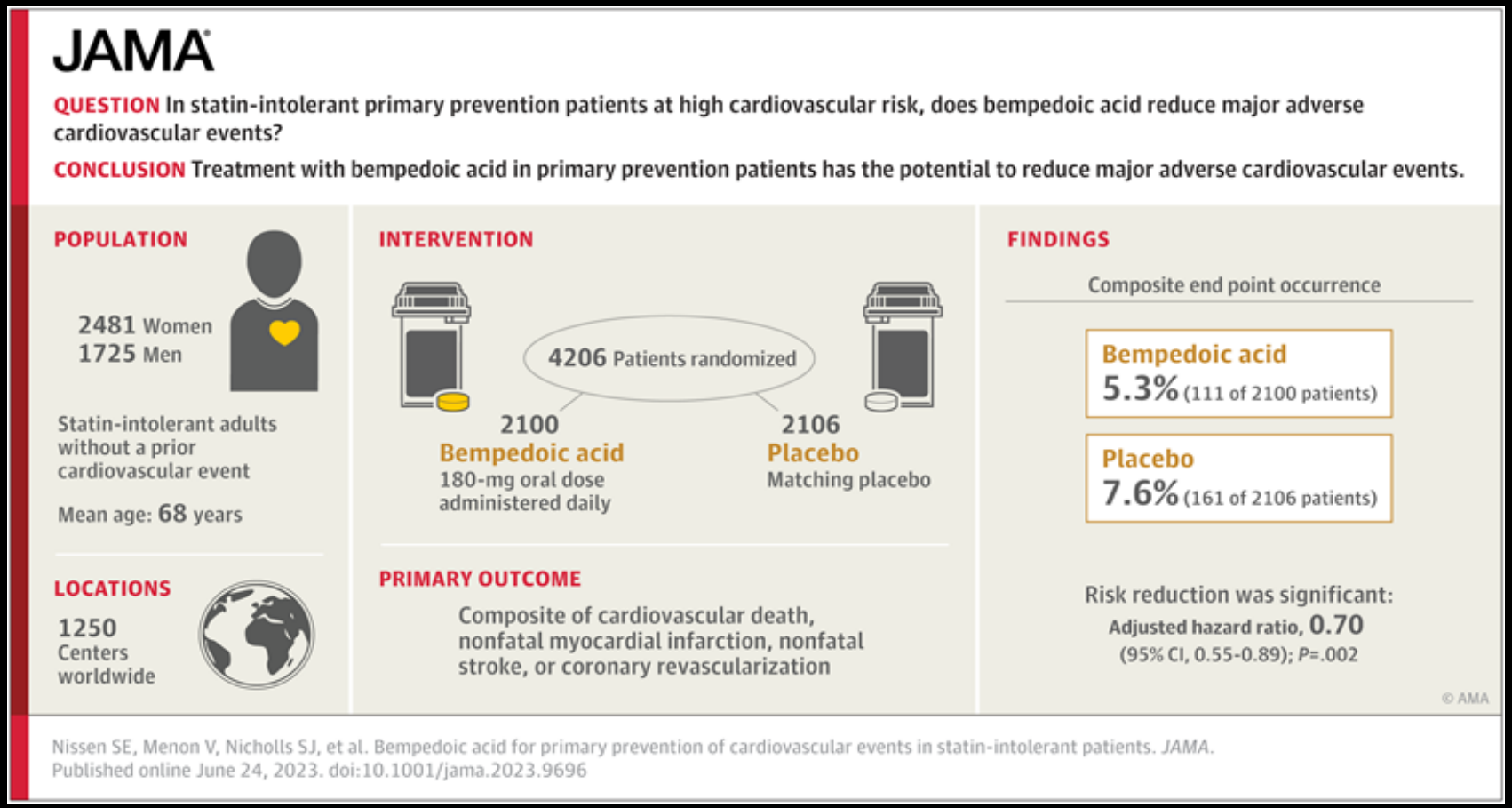
Nissen S et al., NEJM 2022

CLEAR OUTCOMES (RESULTS)



Nissen S et al., NEJM 2022

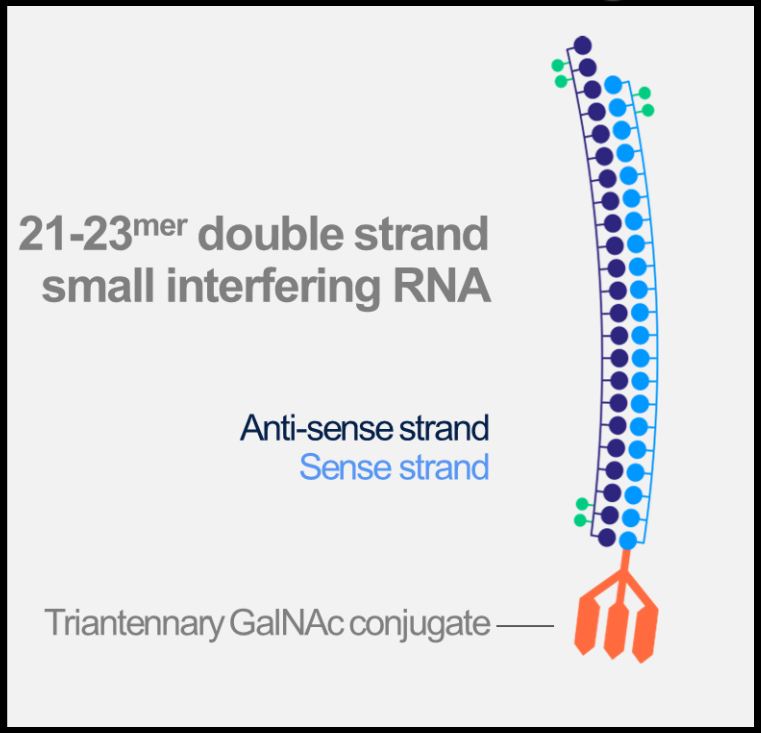
Bempedoic Acid in Primary Prevention



Nissen SE, Menon V, Nicholls SJ, et al. Bempedoic acid for primary prevention of cardiovascular events in statin-intolerant patients. *JAMA*. Published online June 24, 2023. doi:10.1001/jama.2023.9696

INCLISIRAN – FDA Approved Dec. 2021 for ASCVD and HeFH Patients Needing Additional LDL-C Lowering

Background and rationale
Harnessing the natural process of RNAi



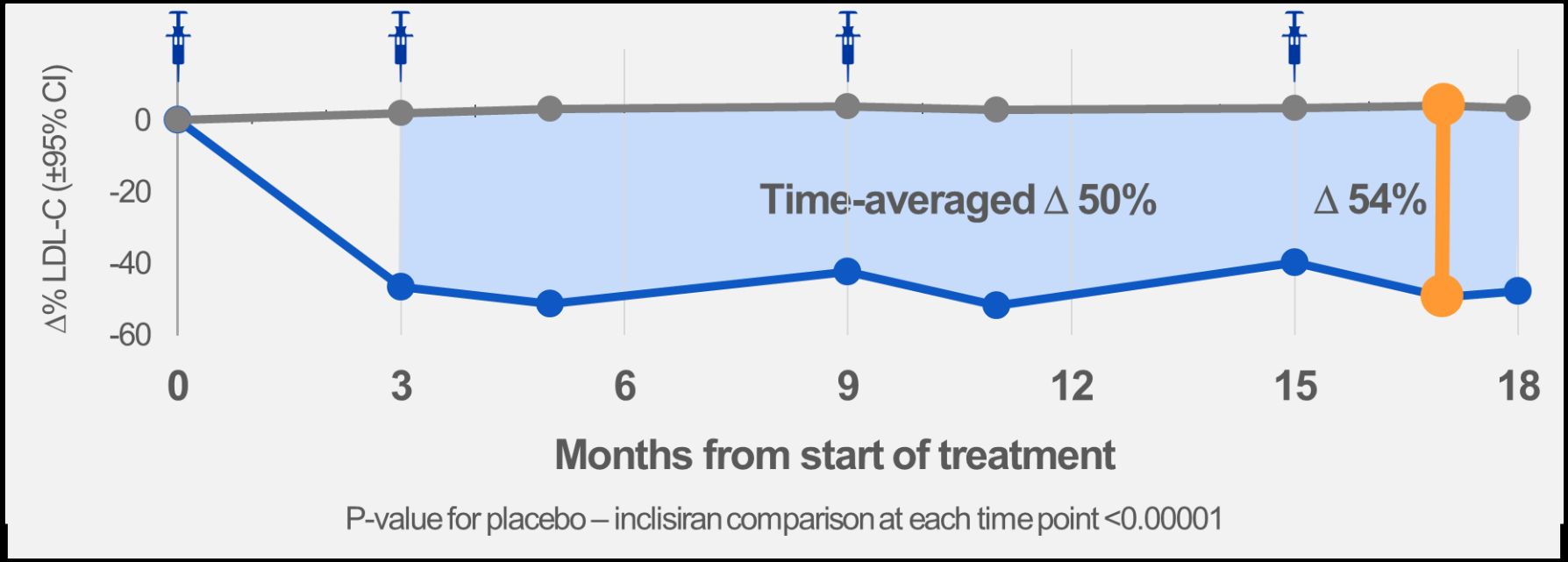
Small interfering double-stranded RNA

- Harnesses the natural process of RNAi
- Nucleotides modified for durability and low immunogenicity
- Distributed to liver due to GalNAc conjugation
- Inhibits production of PCSK9 specifically, durably and potently

ORION-11: Efficacy

Durable, potent and consistent effect over 18 months

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



ESC European Society of Cardiology
European Heart Journal (2022) **00**, 1–10
https://doi.org/10.1093/eurheartj/ehac594

Inclisiran and cardiovascular events: a patient-level analysis of phase III trials

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Gregory G. Schwartz [1
Lorena Garcia Conde[11], **a**
Phase III investigators

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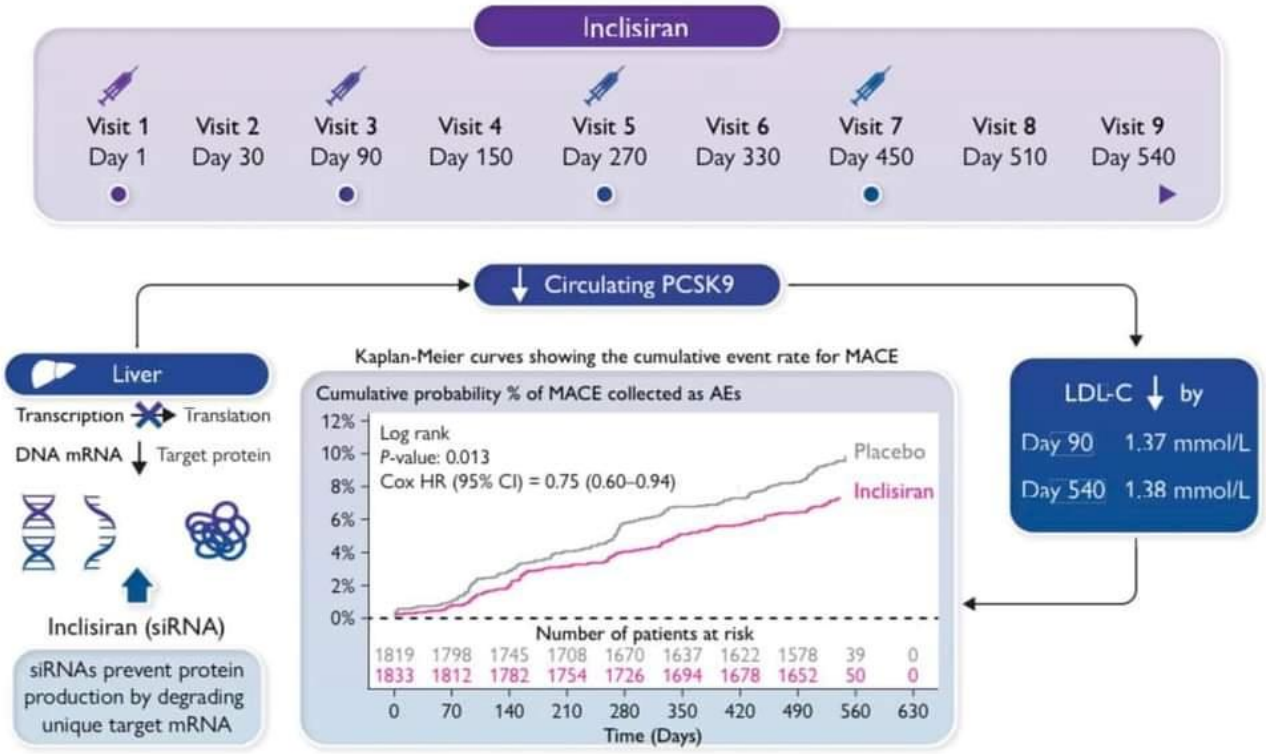
Received 6 September 2022; revised 26 September 2022;

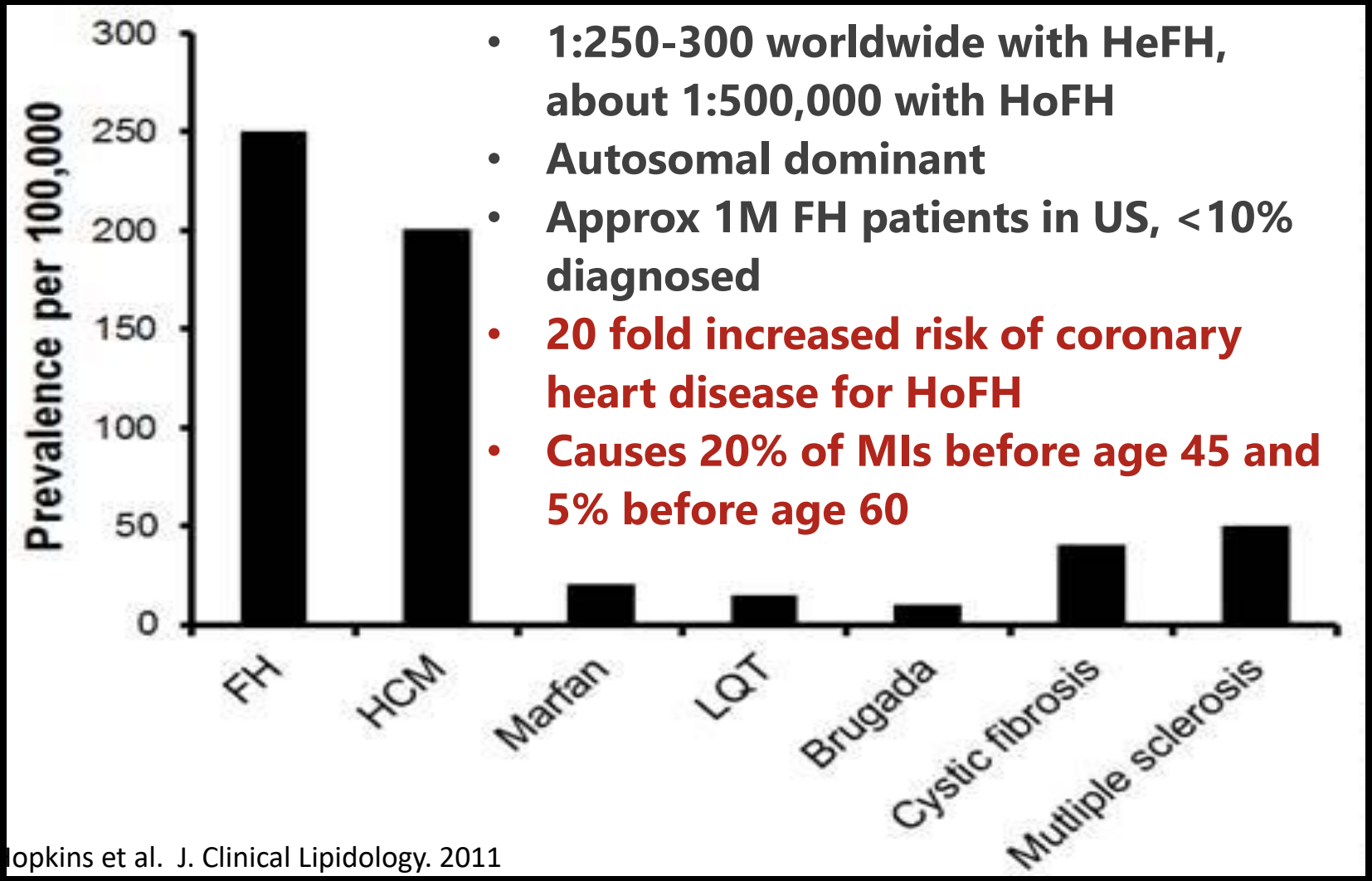


Inclisiran and risk of reported MACE from the patient-level pooled ORION-9, ORION-10 and ORION-11 trials.

AE, adverse event; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; mRNA, messenger ribonucleic acid; OR, odds ratio; PCSK9, pro-protein convertase subtilisin/kexin type 9; siRNA, small interfering ribonucleic acid.

Keywords Inclisiran • LDL-C • Major adverse cardiovascular events • Atherosclerotic cardiovascular disease

FH is more common than many well known genetic diseases but <10% are diagnosed – key challenge is to improve identification



- 1:250-300 worldwide with HeFH, about 1:500,000 with HoFH
- Autosomal dominant
- Approx 1M FH patients in US, <10% diagnosed
- 20 fold increased risk of coronary heart disease for HoFH
- Causes 20% of MIs before age 45 and 5% before age 60

lopkins et al. J. Clinical Lipidology. 2011

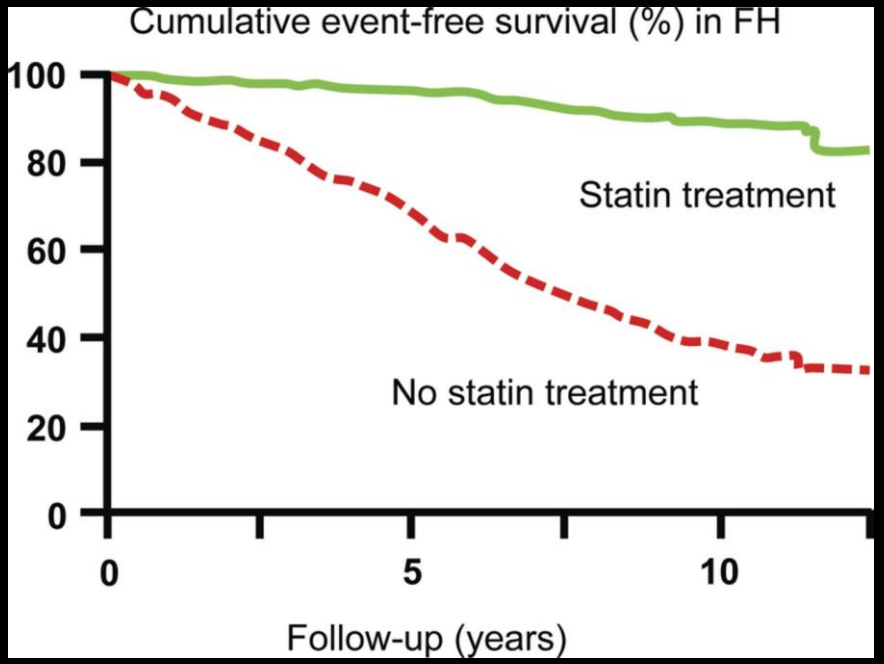
FH is a "Winnable battle": Therapeutic Options

Available Therapies

- High intensity statin
- Ezetimibe
- PCSK9mAb (HeFH)
- Bempedoic Acid (HeFH)
- Mipomersen (HoFH)
- Lomitapide (HoFH)
- Evinacumab (HoFH)
- Inclisiran (HeFH)

Emerging Therapies

- Pelacarsen for Lp(a)

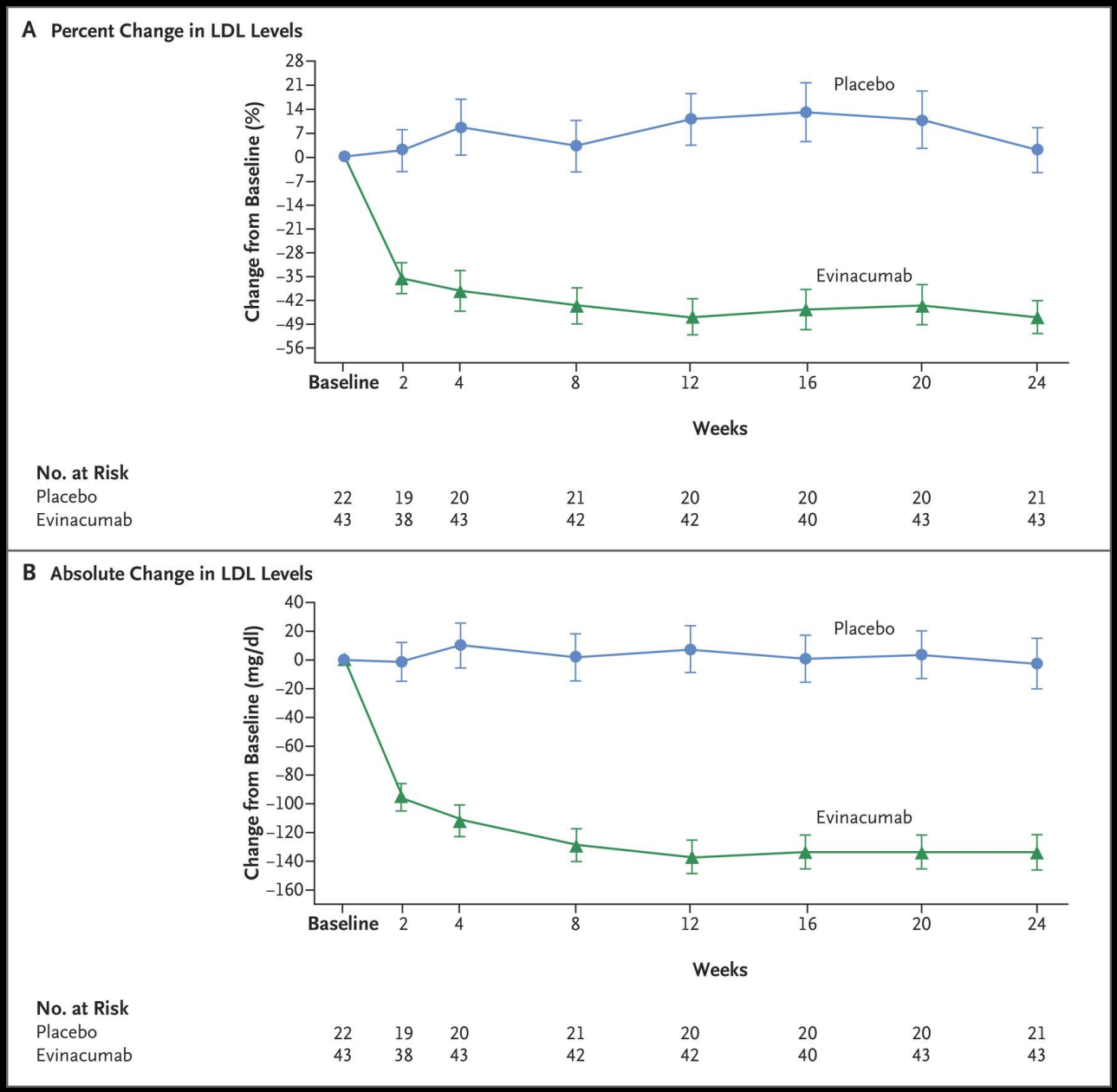


Dutch subjects with HeFH on or off statin treatment (Versmissen et al)

Evinacumab, a fully human monoclonal antibody blocks ANGPTL3, reducing LDL-C production independent of the LDL receptor

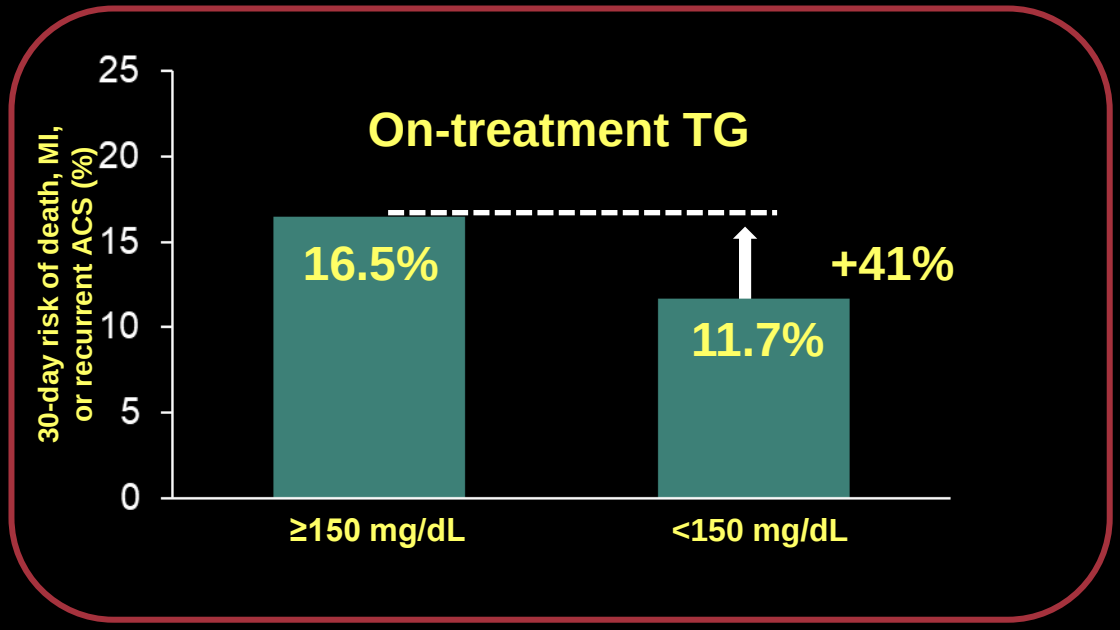
47% relative reduction in LDL-C at 24 weeks

(Raal FJ et al. NEJM 2020)



Residual HTG Predicts Residual ASCVD Risk Despite *LDL-C at Goal* on Statin Monotherapy

Despite achieving LDL-C <70 mg/dL with a high-dose statin,
patients with TG ≥150 mg/dL have a 41% higher risk of coronary events*



*Death, myocardial infarction, or recurrent acute coronary syndrome, PROVE-IT-TIMI 22
Miller M et al. *J Am Coll Cardiol*. 2008;51:724-30.

But prior clinical trials of TG lowering with fibrates (e.g., ACCORD and FIELD) and niacin (e.g., AIM-HIGH, HPS2 Thrive) have not been shown to reduce ASCVD outcomes

PROMINENT: Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes

Purpose: To evaluate if lowering triglyceride levels and improving other lipid levels with pemafibrate would reduce the elevated risk of CVD in patients with type 2 diabetes who were on statins.

Trial Design: Multinational, double blind RCT (N=10,497). All patients (with type 2 diabetes, mild to moderate hypertriglyceridemia, and with HDL ≤ 40 mg/dl) received standard of care management of CV risk factors, including treatment with high-intensity statins. In addition, patients received either pemafibrate (0.2mg twice daily) or placebo.

Primary Endpoints: Composite of nonfatal MI, ischemic stroke, coronary revascularization, or CV death.

Key Takeaways for the Clinician:

- In patients with diabetes, mild to moderate hypertriglyceridemia and low levels of HDL, lowering triglycerides with pemafibrate did not lower rates of cardiovascular disease.
- The study results calls into question whether TG lowering should be used at all in patients with diabetes who are already on statins.

Presented by: **Aruna D Pradhan**, BRIGHAM AND WOMENS HOSPITAL, Boston, MA;

	Placebo (N= 5257)	Pemafibrate (N= 5240)	HR (95%CI)	P value
Primary Composite Endpoint	560	572	1.03 (0.91-1.15)	0.67
Components				
Nonfatal MI	178	205	1.16 (0.95-1.42)	-
Nonfatal Ischemic Stroke	104	95	0.92 (0.69-1.21)	-
Coronary revascularization	344	334	0.98 (0.84-1.13)	-
Death from CV causes	133	133	1.00 (0.79-1.28)	-

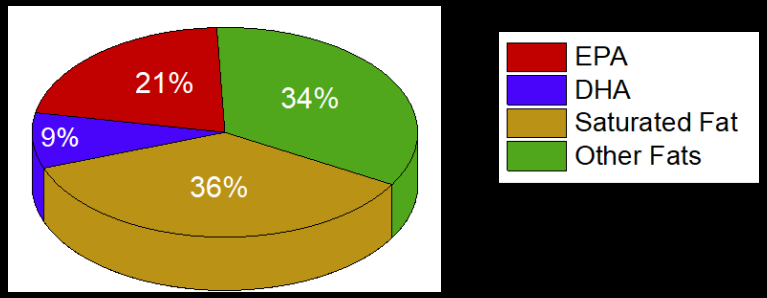
Results:

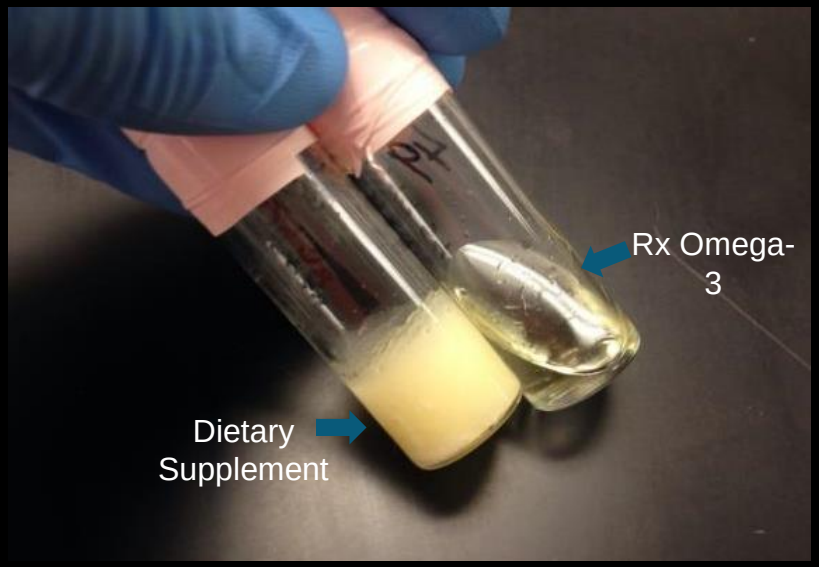
- Although levels of TG, VLDL cholesterol, Apo C-III and remnant cholesterol were 26-28% lower in the pemafibrate group, the incidence of CV events was not lower compared to the placebo group.
- The overall incidence of serious adverse events did not differ significantly between the groups, but pemafibrate was associated with a higher incidence of adverse renal events and VTE and lower incidence of NAFLD.

Results reflect the data available at the time of presentation.

There were approximately 12% increases in LDL-C as well as increases in ApoB in the pemafibrate group, which may have counteracted any benefit from lowering TG levels. Pemafibrate was also associated with increased adverse renal events and VTE.

Dubious Content of *Leading* US Fish Oil Dietary Supplements





- Up to 36% of content may be saturated fat
- Omega-3 FA content often overstated
- Oxidation of omega-3 FA content can be high
  - even those meeting industry standards are more oxidized than Rx meds
- Contamination risk (pesticides, PCBs, etc.)
- Difficult to achieve EPA+DHA doses similar to Rx meds

High saturated fatty acid content of common fish oil dietary supplement makes it ***solid at room temperature*** (post-isolation)

Mason RP, Sherratt SCR. *Biochem Biophys Res Commun*. 2017;483(1):425-429. Hilleman D, Smer A. *Manag Care*. 2016;25(1):46-52. Albert BB, et al. *Sci Rep*. 2015;5:7928. Kleiner AC, et al. *J Sci Food Agric*. 2015;95(6):1260-1267. Ritter JC, et al. *J Sci Food Agric*. 2013:93(8):1935-1939. Jackowski SA, et al. *J Nutr Sci*. 2015;4:e30. Rundblad A, et al. *Br J Nutr*. 2017;117(9):1291-1298. European Medicines Agency, 2018: 712678.

REDUCTION OF CARDIOVASCULAR EVENTS WITH ICOSAPENTYL ETHYL – INTERVENTION TRIAL

REDUCE-IT

(AHA 2018 and Bhatt et al. NEJM November 2018)

Key Inclusion Criteria

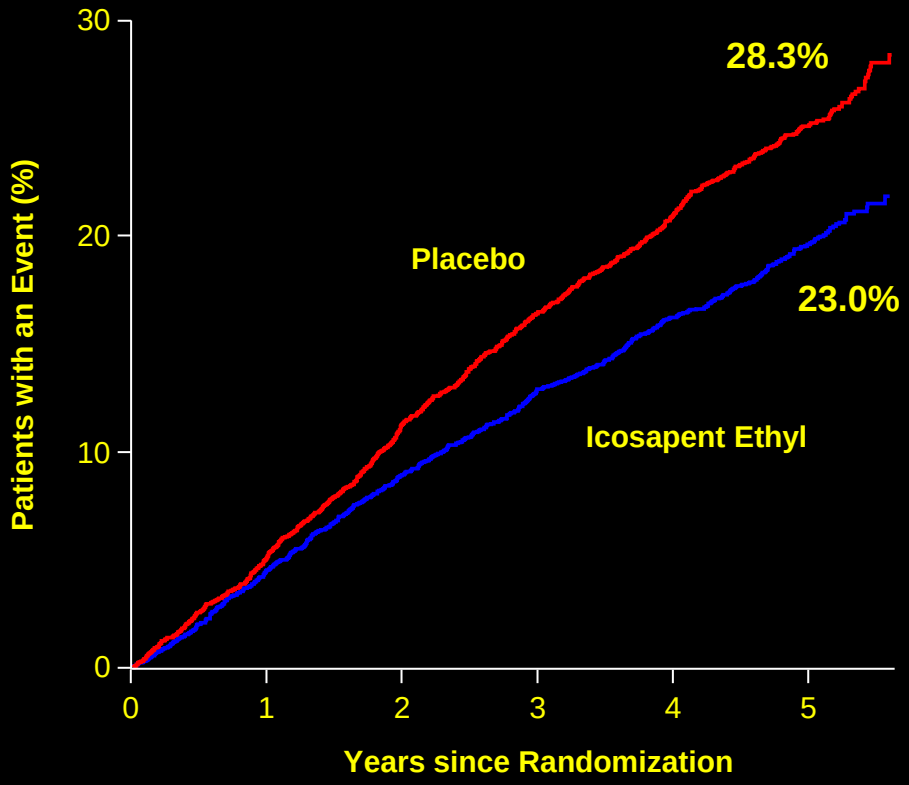
1. Age ≥45 years with established CVD (Secondary Prevention Cohort) *or* ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)

2. Fasting TG levels ≥150 mg/dL and <500 mg/dL*

3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

*Due to the variability of triglycerides, a 10% allowance existing in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.

Primary Endpoint:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio 0.75
(95% CI 0.68–0.83)

RRR=24.8%

ARR=4.8%

NNT=21 (95% CI 15–33)

P=0.00000001

Bhatt DL et al. *N Engl J Med.* 2018. Nov 10 [epub ahead of print]. Bhatt DL. AHA 2018, Chicago.

New Guidelines/Recommendations for Icosapent Ethyl to Prevent ASCVD in Patients with TG 135-499 mg/dL

Scientific Society	Treatment with Statin and Icosapent Ethyl for ASCVD Risk Reduction
American Diabetes Association (ADA)	In patients with ASCVD or other cardiac risk factors with controlled LDL-C, but elevated triglycerides (135-499)
European Society of Cardiology (ESC) / European Atherosclerosis Society (EAS)	In high-risk (or above) patients with TG levels between 135-499 mg/dL, n-3 PUFAs (icosapent ethyl 2x2 g/day) should be considered in combination with a statin
National Lipid Association (NLA)	For patients 45 years of age or older with clinical ASCVD, or 50 years of age or older with diabetes mellitus requiring medication and ≥1 additional risk factor, with fasting TG 135-499 mg/dL
American Heart Association (AHA)	The use of n-3 FA (4 g/d) for improving atherosclerotic cardiovascular disease risk in patients with hypertriglyceridemia is supported by a 25% reduction in major adverse cardiovascular events in REDUCE-IT
American Association of Clinical Endocrinologists (AACE) / American College of Endocrinology (ACE)	If TG 135-499, add icosapent ethyl 4 g/day if high ASCVD risk on maximally tolerated statins

atherosclerotic cardiovascular disease; HTG, hypertriglyceridemia; LDL-C, low-density lipoprotein cholesterol; PUFA, polyunsaturated fatty acids; TG, triglyceride.

Heart J. 2020;41(1):111-188. Orringer CE, et al. *J Clin Lipidol.* 2019;13(6):860-872. Skulas-Ray AC, et al. *Circulation.* 2019;140(12):e673-e691. Arnold SV, et al. *Circulation*. 2020;141(19):e779-e806. Garber AJ, et al. *Endocr Pract*. 2020;26(1):107-139.

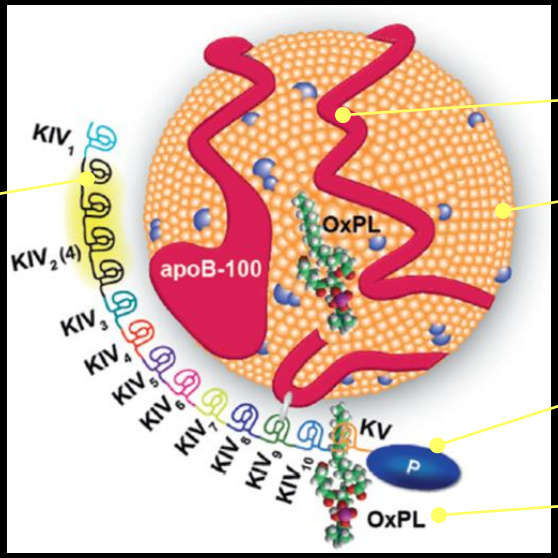
Elevated Lp(a) is a critical risk factor for ASCVD

Lp(a) contains all the proatherogenic components of LDL-C **plus** apo(a)

Elevated Lp(a) is primarily **genetically determined**, without significant dietary or environmental influences

Elevated Lp(a) is an **independent**, **genetic**, and **causal risk factor** for **ASCVD**

The Lp(a) particle is composed of 2 parts:
(1) LDL-like particles with apoB-100, and
(2) apo(a) covalently bound to apoB-100 by disulfide bonds



apoB-100

LDL-like component with apoB-100

apo(a) that contains 10 types of KIV subtypes, an inactive protease-like domain, and oxidized phospholipids

Inactive protease-like domain

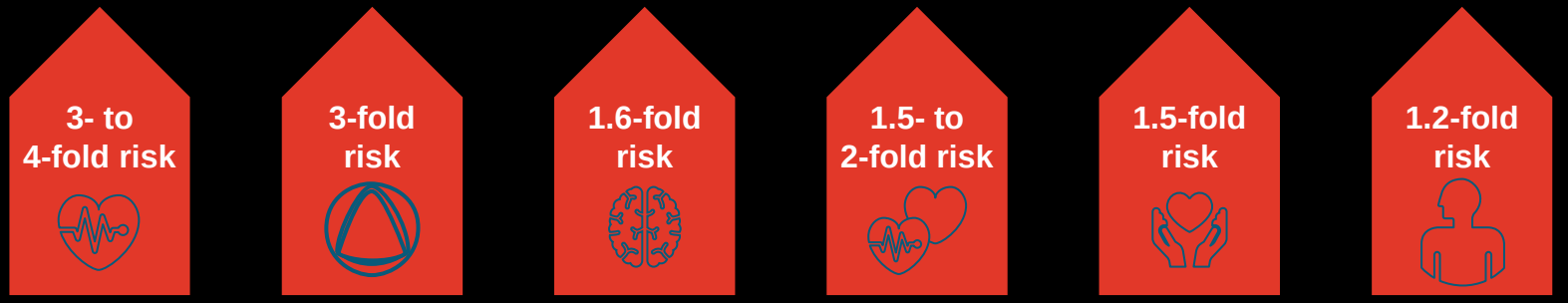
Oxidized phospholipids

apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; KIV, kringle 4; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); OxPL, oxidized phospholipids; P, protease.
Tsimikas S. *J Am Coll Cardiol.* 2017;69(6):692-711.

Elevated Lp(a) is an inherited, independent, and causal risk factor for ASCVD[1,2]

Epidemiological, genome-wide association, and Mendelian randomization studies have demonstrated an association between elevated Lp(a) levels and increased ASCVD risk[1,2]

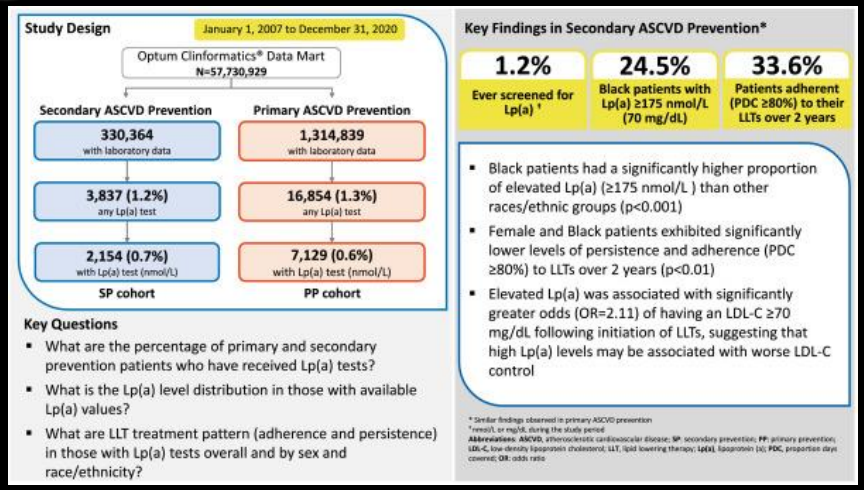
people with elevated Lp(a) levels have increased ASCVD risk[3,*]



Lp(a) Testing: Unmet Need

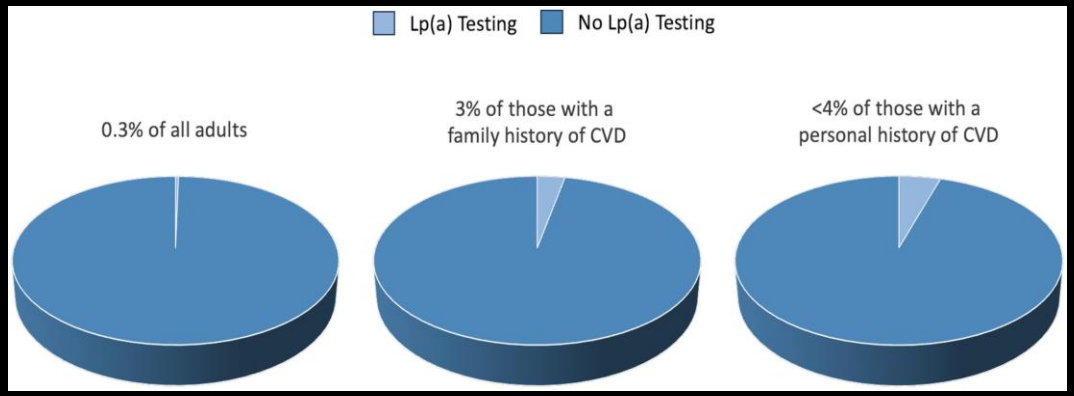
Characteristics and lipid lowering treatment patterns in patients tested for lipoprotein(a): A real-world US study (Hu X et al. Am J Prev Cardio 2023)

- Evaluation of data in 57.7 million persons from Optum Clinformatics Data Mart among 330,364 secondary prevention and 1,314,839 primary prevention patients in 2007-2020.
- Only 1.2% of SP and 1.3% of PP patients had an Lp(a) test done.
- Among SP patients, adherence to lipid lowering therapies was only slightly greater in those with Lp(a) ≥175 nmol/L vs. <175 nmol/L (35% vs. 33%)

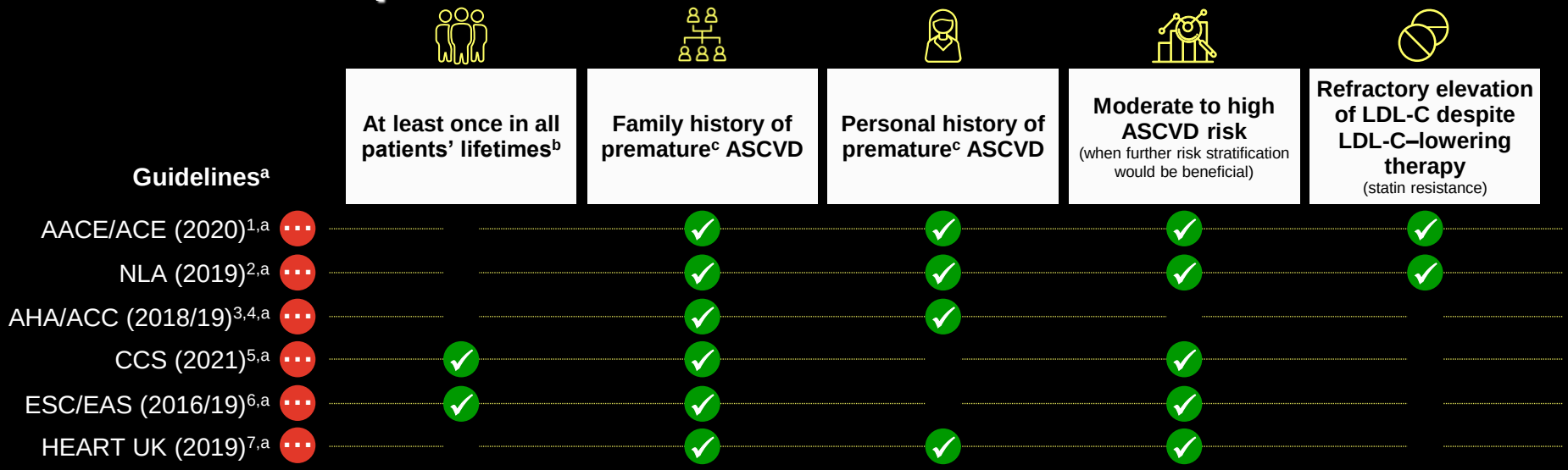


Lipoprotein(a) Testing Trends in a Large Academic Health System in the United States (Bhatia HS et al., JAHA 2023)

- Evaluation of 5.5 million US adults in the Univ. of CA Health data warehouse in 20`1-2021
- Only 18,972 (0.3%) had Lp(a) testing done
- Older persons, men, and those of White race more likely to be tested
- Small increase in testing among those with a CVD diagnosis over recent years



Dyslipidemia management and CVD prevention guidelines recommend considering Lp(a) testing for a variety of patients for ASCVD risk assessment

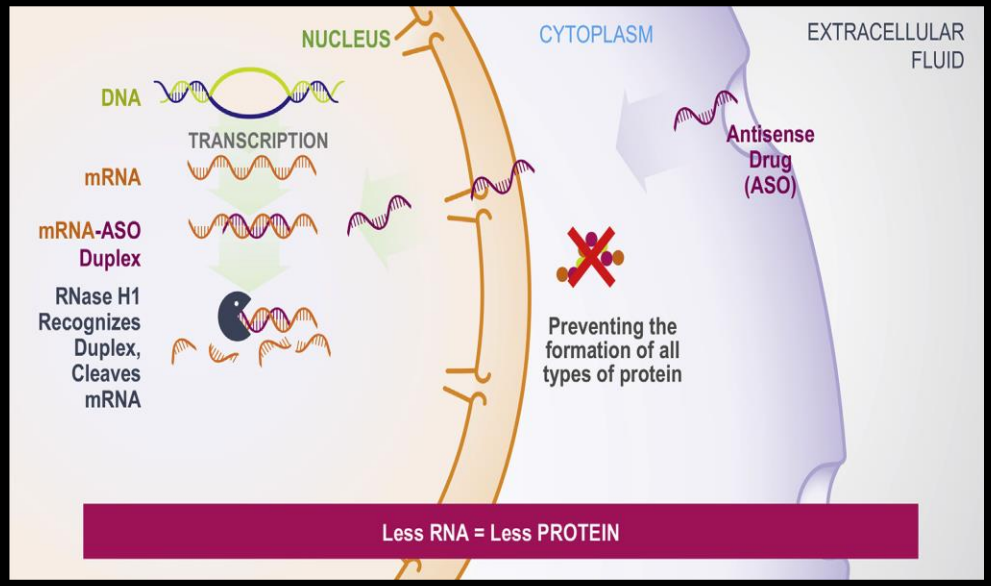


AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CCS, Canadian Cardiovascular Society; CV, cardiovascular; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); NLA, National Lipid Association.
A green check indicates guidelines recommend considering Lp(a) testing in this setting. [a]Synopsis of guideline recommendations. [b]Recommended once in each person's lifetime in 2019 dyslipidemia guidelines[5] but not in 2016 CVD prevention guidelines.[6] [c]"Premature" defined as ASCVD occurring in males aged <55 years or females aged <65 years.[1-6]

1. Handelsman Y et al. *Endocr Pract.* 2020;26(10):1196-1224. **2.** Wilson DP et al. *J Clin Lipidol.* 2019;13(3):374-392. **3.** Grundy SM et al. *Circulation.* 2019;139(25):e1082-e1143. **4.** Arnett DK et al. *Circulation.* 2019;140(11):e596-e646. **5.** Pearson GJ et al. *Can J Cardiol.* Published online March 26, 2021. doi:10.1016/j.cjca.2021.03.016 **6.** Mach F et al. *Eur Heart J.* 2020;41(1):111-188. **7.** Cegla J et al. *Atherosclerosis.* 2019;291:62-70.

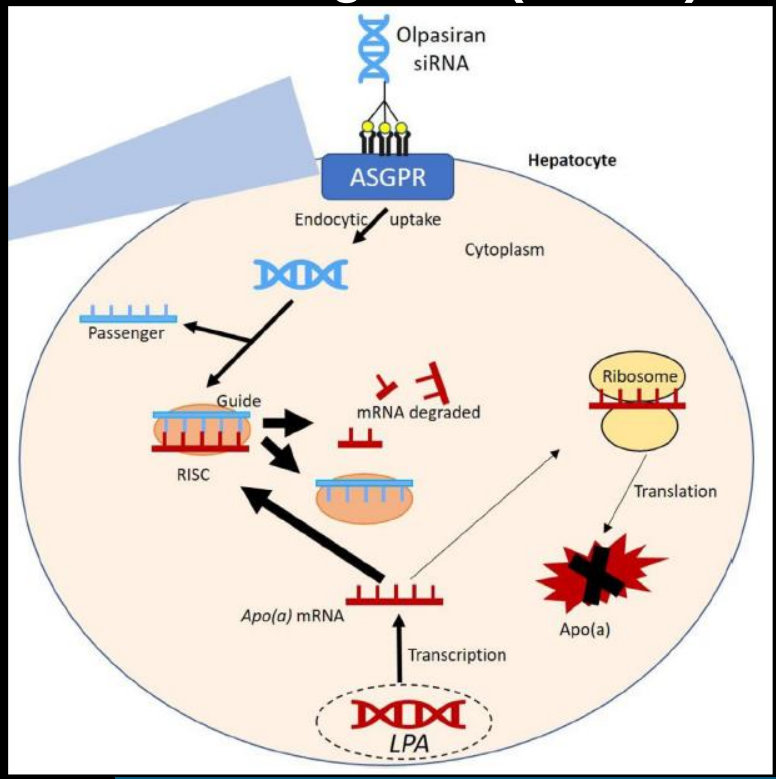
RNA Targeted Therapies for Lipoprotein(a) Lowering

Pelacarsen – antisense oligonucleotide (ASO) therapy



Tsimikas, JACC 2021

Olpasiran – small interfering RNA (siRNA)



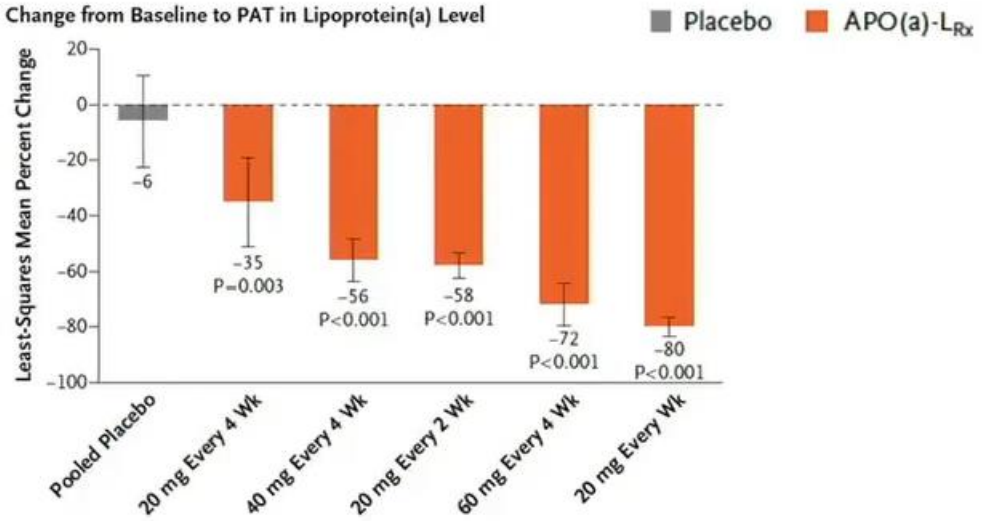
N-acetyl-galactosamine (GalNAc) modifications improve hepatocyte targeting

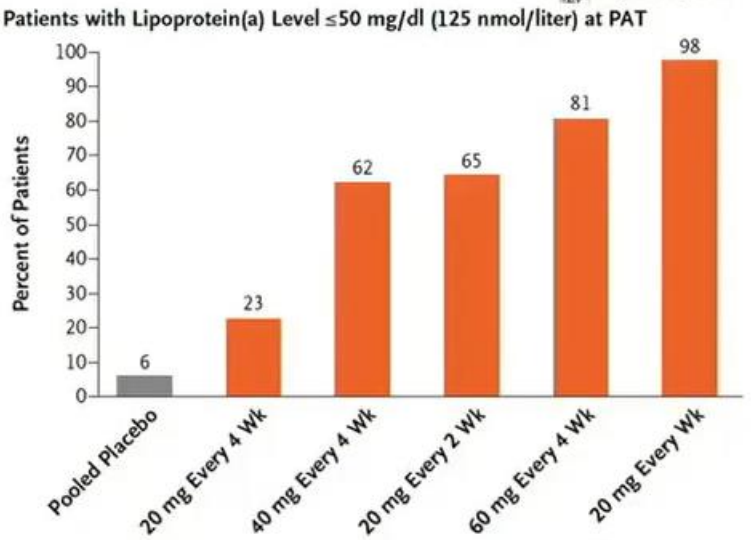
O'Donoghue, Am Heart J 2022

Pelacarsen Phase 2 trial

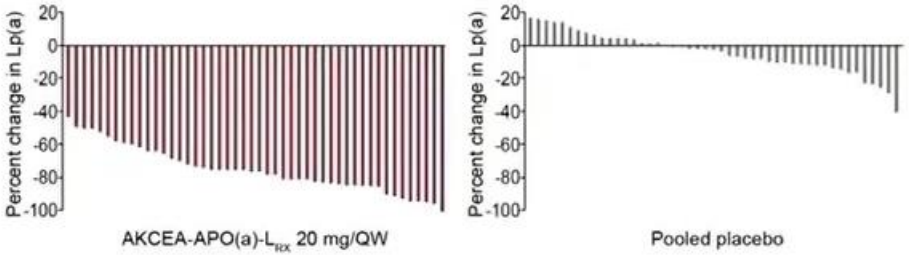
Mean 80% reduction in Lp(a) with pelacarsen 80 mg/monthly equivalent dose
98% of patients reached ideal level of <50 mg/dL (<125 nmol/L)

90TH EAS CONGRESS
MILAN ITALY | May 22-25, 2022





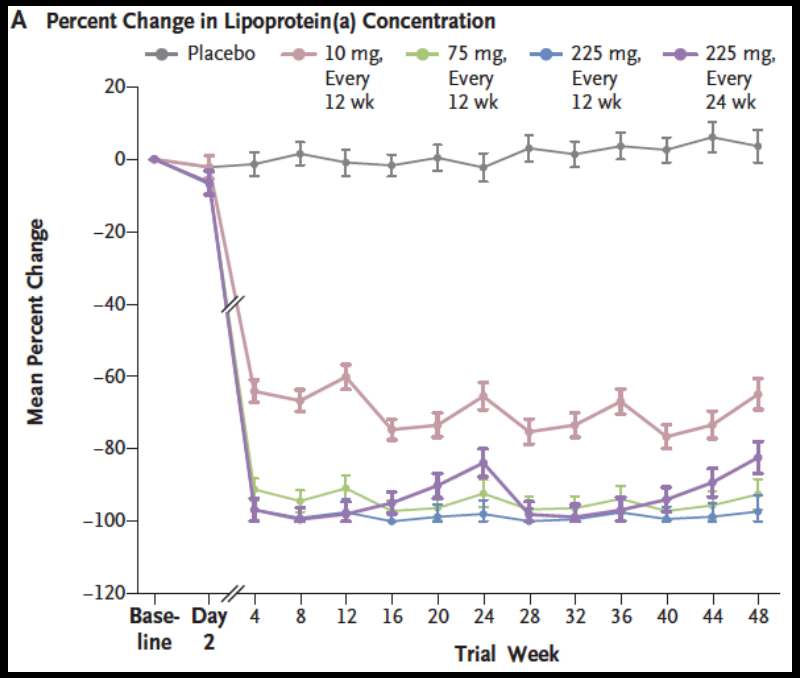
Waterfall Plot – individual Lp(a) decreases ranged from 43-100%

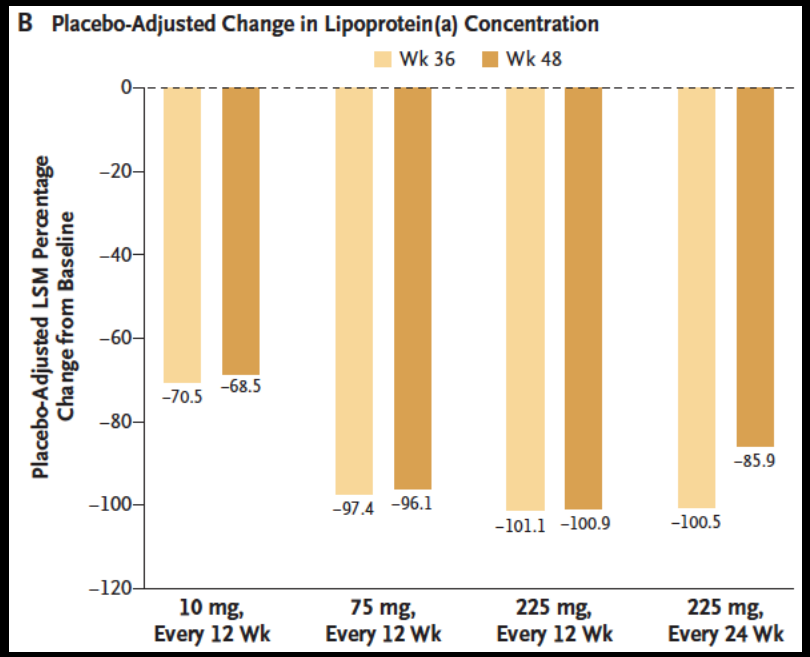


eas-congress.com/2022

Tsimikas et al N Engl J Med 2020;382:244-55

Olpasiran: Phase 2 Study



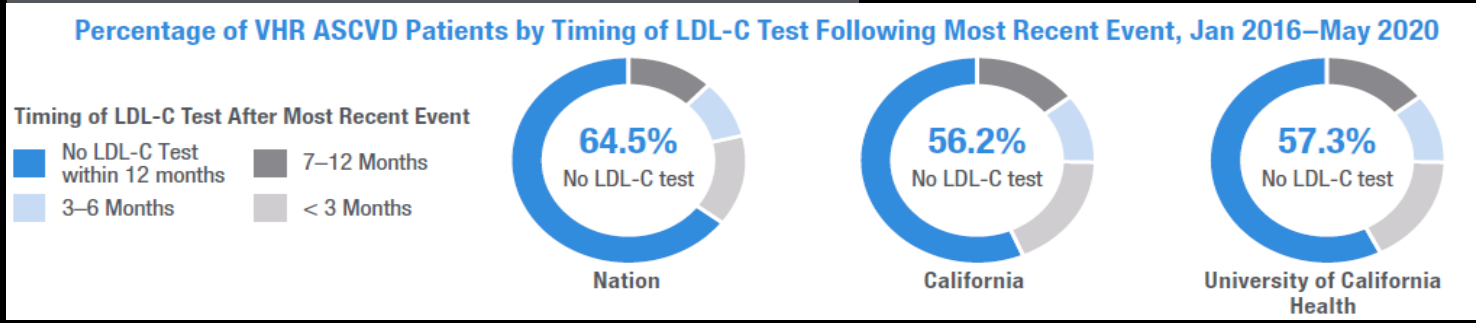


Koren et al Nat Med. 2022;28:96-103

CV Population Health Management Report

University of California Health | 2021

N=213,619 pts with ASCVD
N=116,097 pts with very high risk ASCVD



Percentage of VHR ASCVD Patients, Treated vs. Untreated with LLT, Following Most Recent Event, Jan 2016–May 2020

Population	Treated: Low- to Moderate-Intensity Statin ± Ezetimibe	Treated: High-Intensity Statin ± Ezetimibe	No LLT
Nation	31.2%	38.3%	38.8%
California	30.6%	34.8%	42.9%
University of California Health	**37.1%**	**52.0%**	**23.9%**

Percentage of VHR ASCVD Patients, Treated vs. Untreated with LLT, by LDL-C Level Following Most Recent Event, Jan 2016–May 2020

	Treated: Low- to Moderate-Intensity Statin ± Ezetimibe			Treated: High-Intensity Statin ± Ezetimibe			No LLT		
Population	≥ 70 mg/dL	≥ 100 mg/dL	> 130 mg/dL	≥ 70 mg/dL	≥ 100 mg/dL	> 130 mg/dL	≥ 70 mg/dL	≥ 100 mg/dL	> 130 mg/dL
Nation (N = 809,342)	61.6%	25.8%	9.9%	53.3%	21.2%	8.6%	66.7%	33.8%	13.1%
California (N = 80,116)	58.8%	23.2%	8.7%	50.7%	19.1%	7.6%	66.1%	31.8%	11.8%
University of California Health (N = 7,983)	**60.5%**	**26.9%**	**10.5%**	**52.4%**	**22.2%**	**9.0%**	**66.0%**	**32.3%**	**11.9%**

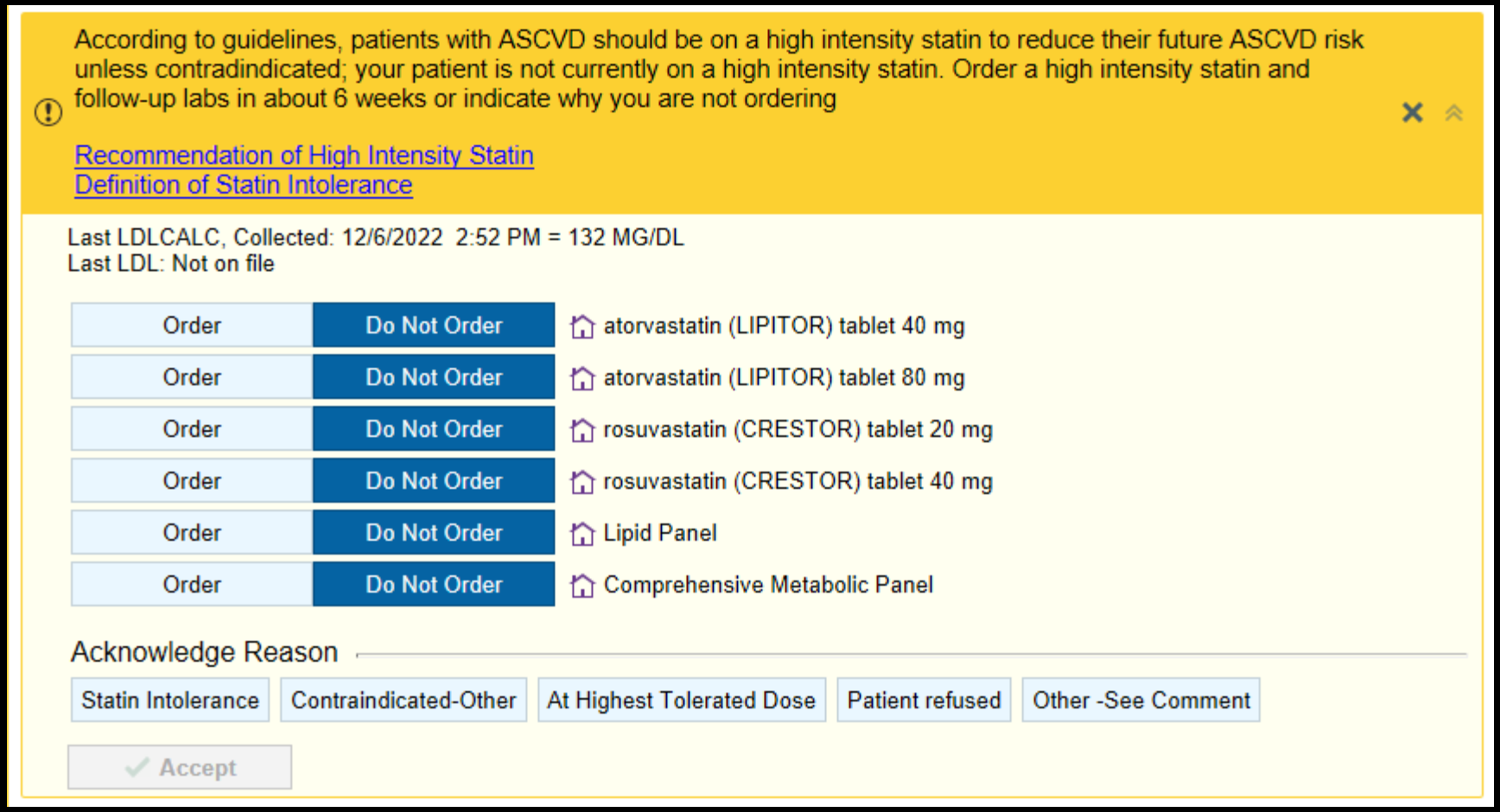
Note: Numbers of patients reflect those for whom documented LDL-C levels were available in lab data.

- 57% had no LDL-C test in past year
- 24% not on lipid therapy
- Among treated, only 52% on high intensity statin
- 52% of those on high intensity statin still with LDL-C ≥70 mg/dL

IMPROVE ASCVD Quality Improvement Program at UCI Health Launched April 2023 for Patients with ASCVD

- Health Maintenance prompt for lipid profile if not done within past 18 months
- Best practice advisory (BPA) for initiation of high intensity statin if not already on one, or requirement to indicate contraindication (eg statin intolerance, refusal)
- BPA / smart set for consideration of non-statin (including ezetimibe, PCSK9 inhibitor, inclisiran, and bempedoic acid) if on maximially tolerated statin therapy and LDL-C $\geq$70 mg/dL (or $\geq$55 mg/dL if very high risk ASCVD)
- Expanded to those with LDL-C $\geq$190 or FH with Lp(a) testing also added in August 2023

UC Irvine ASCVD BPA for High Intensity Statin Therapy



UC Irvine ASCVD Very High Risk BPA for Non-Statin Therapy if LDL-C ≥55 mg/dL despite High Intensity Statin Therapy

Patient is considered ASCVD at very high risk and is on a high intensity or maximally tolerated statin (or statin intolerant), but LDL-C is NOT <55 mg/dL, consider adding ezetimibe or PCSK9 inhibitor

Recommendation for Non-Statin Therapy
2022 ACC Expert Consensus Decision Pathway
2018 Guideline on the Management of Blood Cholesterol

Patient is very high risk for recurrent ASCVD event
(Very high ASCVD risk is defined as two (2) or more major ASCVD events or one (1) major ASCVD event and two or more high risk conditions.)

Major ASCVD Events	High Risk Conditions
• Recent ACS (past 12 months) • Hx of MI • Hx of ischemic stroke	• Age >=65 • Heterozygous familial hypercholesterolemia • Hx of prior CABG or percutaneous coronary intervention • DM • HTN • CKD • Current smoking • Persistent elevated LDL despite high intensity statin or ezetimibe • Hx of CHF

Patient's ASCVD Documented Risk Factors: MI in last 12 months (Major Event), Hypertension (1 pt), CHF (1 pt),
Last LDL: Not on file
Last LDLCALC, Collected: 1/13/2023 = 65

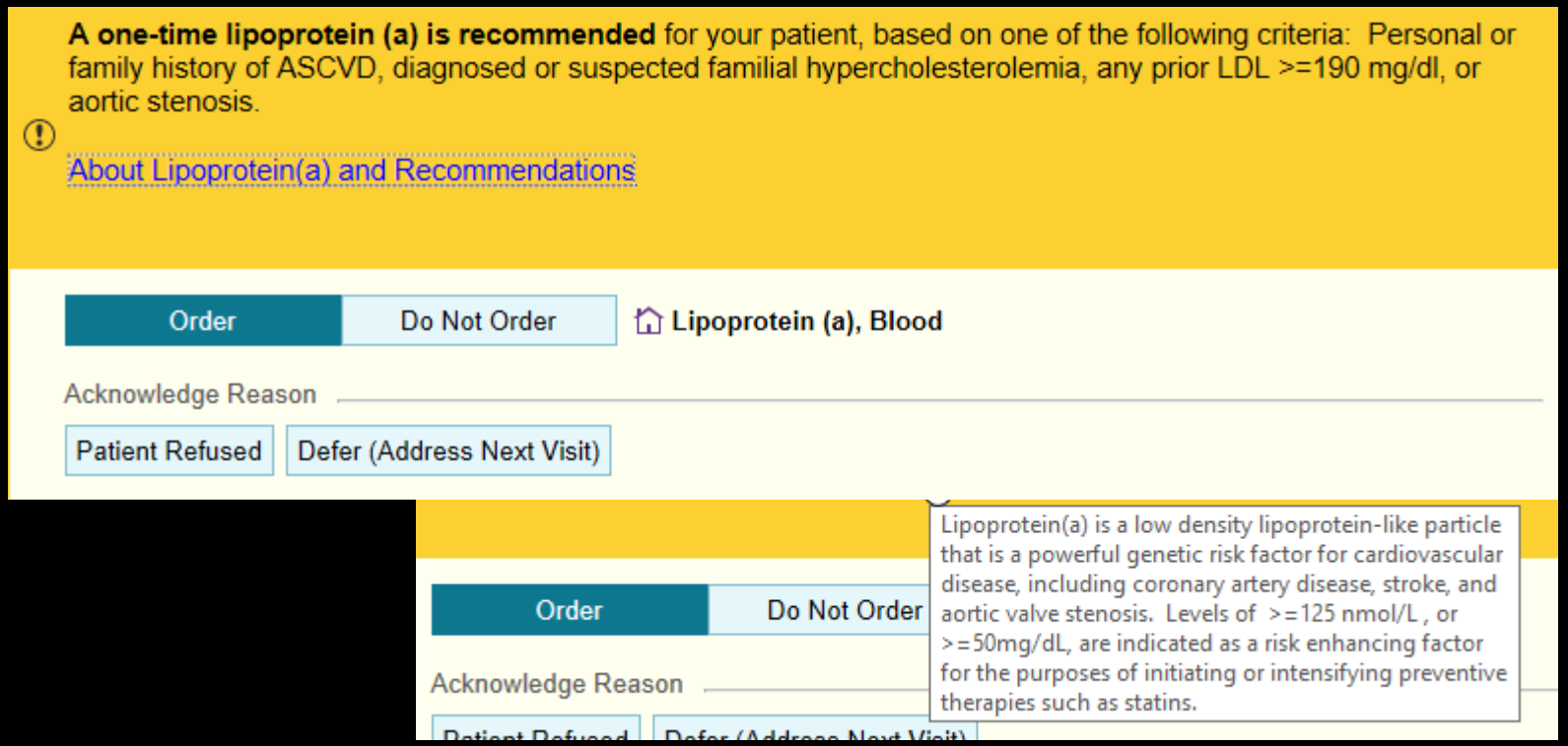
Open SmartSet	Do Not Open	Additional lipid lowering options including PCSK9 inhibitor, labs, Ref to Card and information to support prescribing best practices Preview
Order	Do Not Order	ezetimibe (ZETIA) tablet 10 mg

Acknowledge Reason

Contraindicated | Patient Refused | Other (see comment)

Accept

Lp(a) Testing Best Practice Advisory Implementation at UC Irvine, Aug 2023



Top 10 Take Home Messages

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.
2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy.
3. Assess adherence and percentage response to LDL-C–lowering medications and lifestyle changes with repeat lipid measurement 4 to 12 weeks after statin initiation or dose adjustment, repeated every 3 to 12 months as needed.
4. Use a LDL-C threshold of 70 mg/dL (or non-HDL-C 100 mg/dL) to consider addition of nonstatins to statin therapy. For very high risk ASCVD this LDL-C threshold is 55 mg/dL (non-HDL-C 85 mg/dL)

Top 10

Top 10 Take Home Messages

5. Ezetimibe or a PCSK9i is the first choice for non-statin therapy, followed by inclisiran or bempedoic acid
6. In patients with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL[≥4.9 mmol/L]) without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk.
7. In patients 40 to 75 years of age with diabetes mellitus start moderate intensity statin and if ≥7.5% 10-year risk high intensity statin therapy and for those ≥20% risk consideration for ezetimibe if LDL-C < 70 mg/dL is not achieved.
8. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, have a clinician–patient risk discussion before starting statin therapy.

Top 10

Top 10 Take Home Messages

8. In adults 40 to 75 years of age evaluated for primary ASCVD prevention, for those 10-year ASCVD risk of 5-<20% risk, start a moderate-intensity statin, consider high intensity if 30-49% LDL-C reduction of LDL <100 mg/dl not achieved.

9. In adults 40 to 75 years of age without diabetes mellitus and with >=20% 10-year ASCVD risk consider high intensity statin and if 50% LDL-C reduction or <70 mg/dL not achieved, consider adding ezetimibe.

10. Address hypertriglyceridemia according to 2021 ACC ECDP on hypertriglyceridemia – those with ASCVD or DM and multiple RF maximized on statin therapy, consider icosapent ethyl therapy.

THANK YOU

Preventive Cardiology Program

Take control of your health

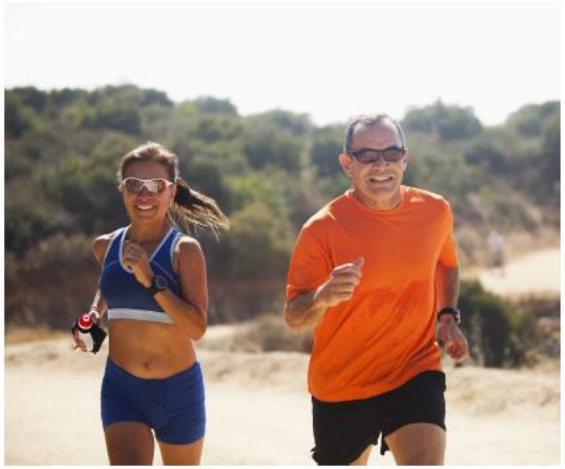
Life-threatening cardiac events often can be prevented through early diagnosis, risk assessment, treatment and lifestyle changes.

The UC Irvine Health Preventive Cardiology Program uses the latest evidence-based guidelines for cardiovascular disease prevention. Services include:

- Initial evaluation by cardiologist, plus follow-up to track progress
- Comprehensive laboratory measures for cardiac risk factors and biomarkers, plus further evaluation with optional imaging tests
- Computerized cardiovascular risk profiles and risk scoring
- Comprehensive dietitian consultation with a specific focus on cardiovascular risk factor management
- Physical activity prescriptions and consultations with an exercise specialist
- A full report sent to the patient's referring physician when the program is finished

Our preventive cardiology program's multidisciplinary team includes:

- Cardiologists
- Registered dietitian
- Exercise physiologist
- Prevention researchers/ specialists



Our program can help you if you have been diagnosed with at least one risk factor for cardiovascular disease, including:

- Hypertension
- Hypercholesterolemia/ dyslipidemia
- Metabolic syndrome
- Diabetes
- Cigarette smoking

Patients with pre-existing cardiovascular disease who need more guidance with risk factor modification to prevent disease progression or recurrence are also ideal candidates.

To learn more, call 714-456-6699.

UC Irvine Health

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15th Annual Orange County Symposium for Cardiovascular Disease Prevention