State of the Art in Cardiometabolic Disease 2025

Deepak Talreja, MD, FACC

Clinical Chief of Cardiology| Sentara Health

Medical Director, Cardiovascular Service Line| Sentara Heart

Associate Professor | Joan Brock Virginia Health Sciences at Old Dominion University

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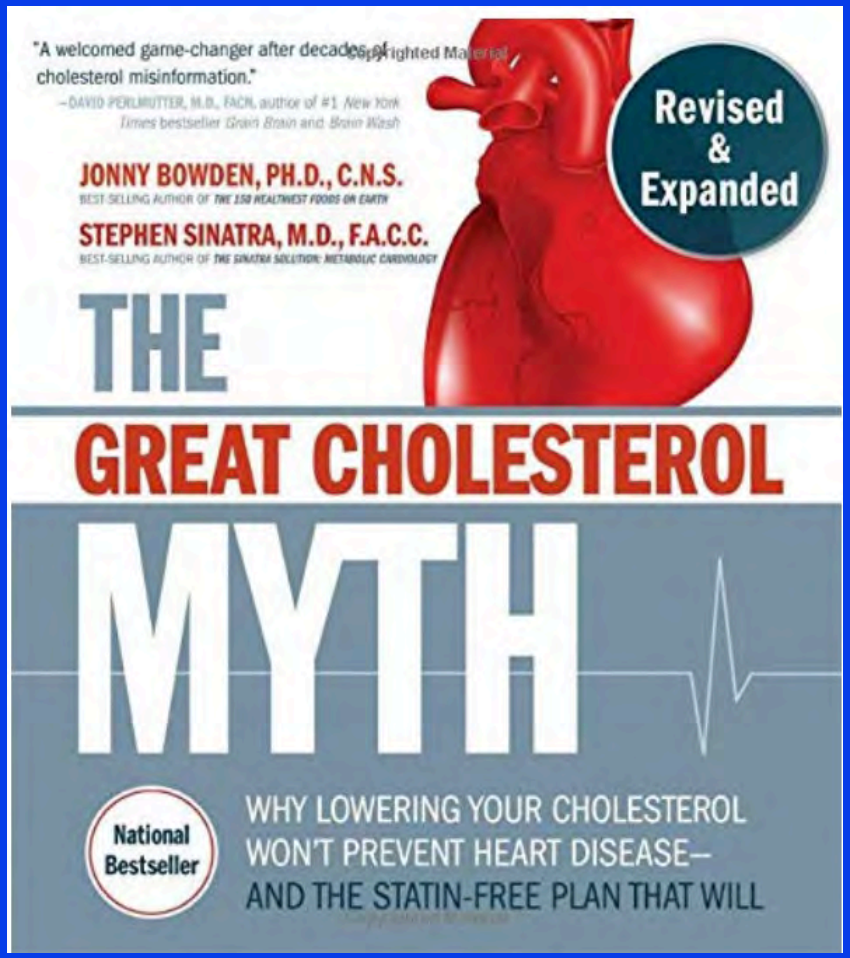
EVMS

Eastern Virginia Medical School

TAVR CLINIC vs LIPID CLINIC



AGENDA

- Epidemiology & Pathophysiology
- Lifestyle Options - Pritikin
- Pharmacotherapy Options
- Guidelines
- Sentara Cardiology Lipid Program

Prevalence of ASCVD in the United States

In the United States, as of 2020, an estimated[1-4]

30.2 million were living with some form of ASCVD

19.03 million were receiving statin therapy for some form of ASCVD

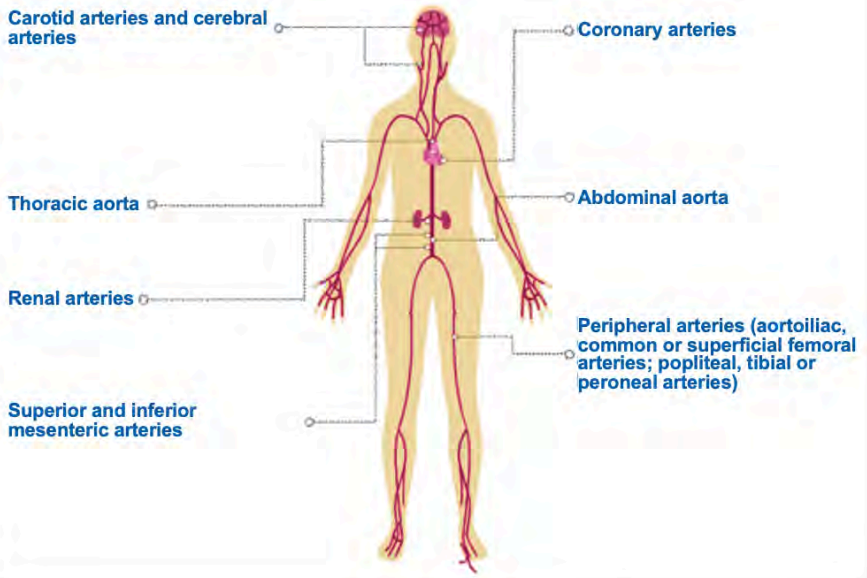
15.17 million receiving statin therapy for some form of ASCVD were not at the ACC/AHA-recommended goal of LDL-C <70 mg/dL

ACC, American College of Cardiology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

1. Wong ND et al. *J Clin Lipidol*. 2016;10(5):1109-1118; **2.** Selvin E, Hirsch AT. *Atherosclerosis*. 2008;201(2):425-433; **3.** Benjamin EJ et al. *Circulation*. 2019;139(10):e56-e528; **4.** Choi CI, Brandt, N (2019). *Dyslipidemia/Atherosclerosis 2021-2030*. 2Q ed. Ser;2021:54-61.

ASCVD Encompasses a Heterogeneous Group of Diseases

Atherosclerosis affects several arterial beds[1]



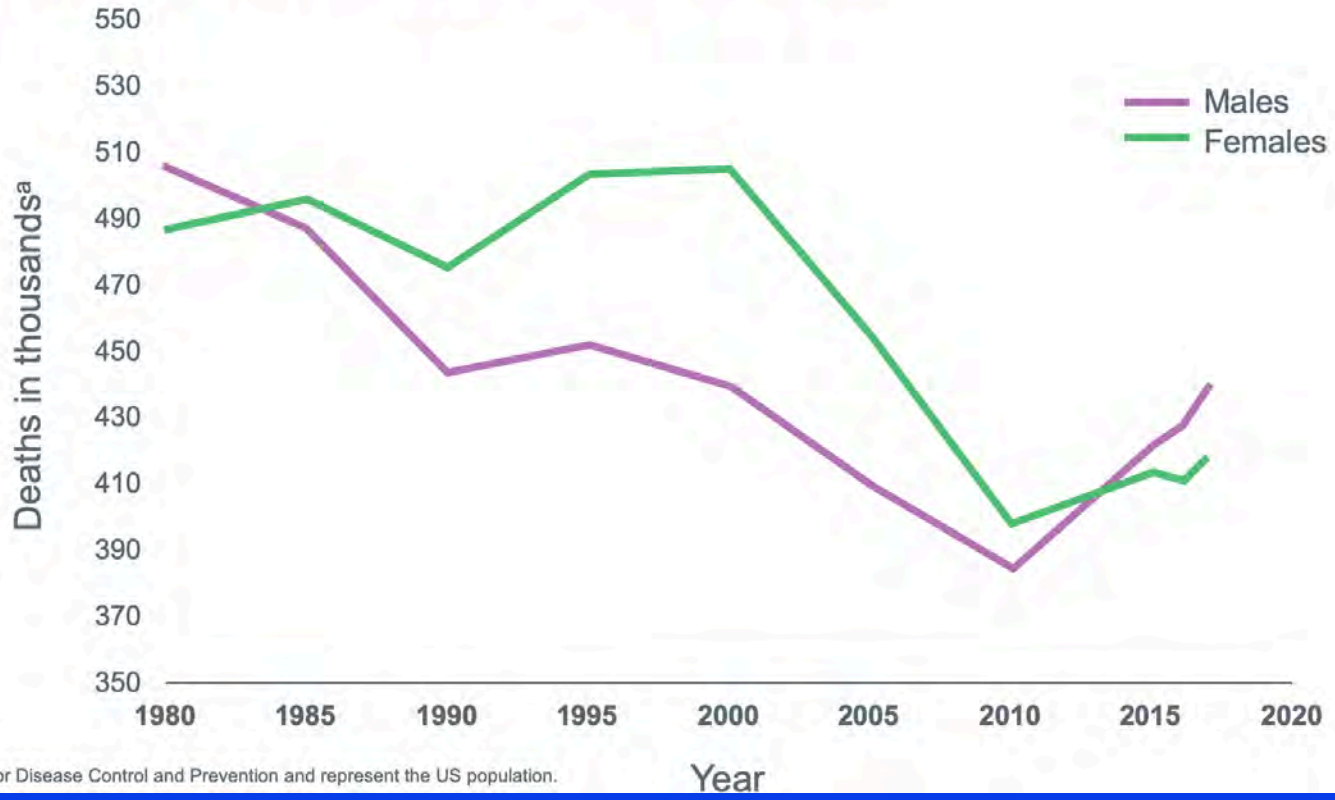
Adapted with permission from Libby P et al.[1]

Clinical ASCVD includes[2]

- History of MI
- Stable angina
- ACS
- Coronary or other arterial revascularization
- Stroke
- Transient ischemic attack
- PAD, including aortic aneurysm

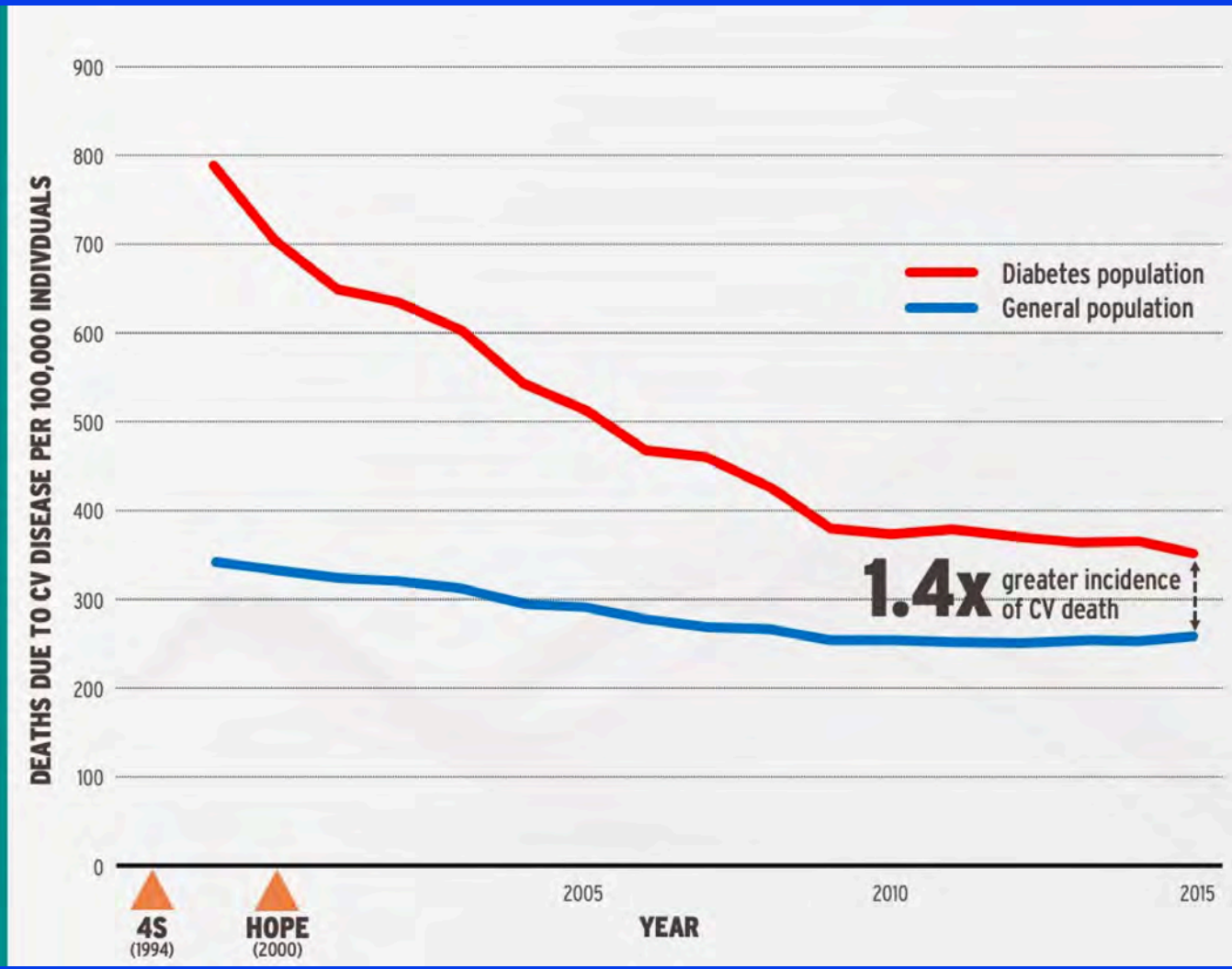
Cardiovascular disease deaths have increased in recent years in the US

DEATHS ATTRIBUTABLE TO CARDIOVASCULAR DISEASE (US, 1980-2017)



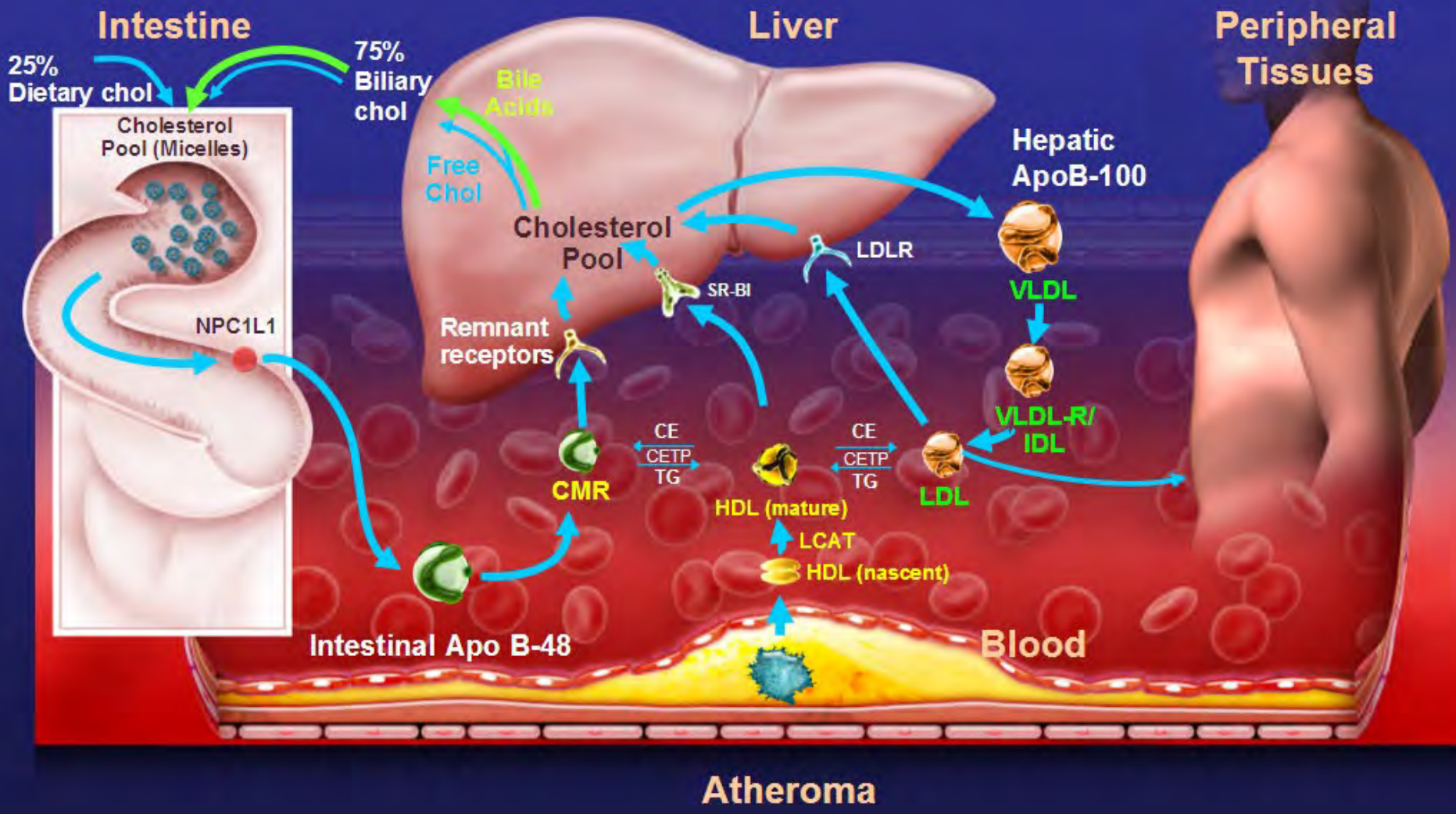
[a]The data are from the US Centers for Disease Control and Prevention and represent the US population.

INCIDENCE OF CV DEATH REMAINS GREATER IN PATIENTS WITH DIABETES DESPITE ADVANCES IN STANDARD OF CARE



1. Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2016 on CDC WONDER Online Database, released December, 2017. Data are from the Multiple Cause of Death Files, 1999-2016, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at http://wonder.cdc.gov/mcd-icd10.html on May 8, 2018;
2. Centers for Disease Control and Prevention. Long-term trends in diabetes. http://www.cdc.gov/diabetes/data. Published April 2017. Accessed on May 10, 2018;
3. 4S Investigators. Lancet. 1994;344:1383-90;
4. HOPE Investigators. N Engl J Med. 2000;342(3):145-53.

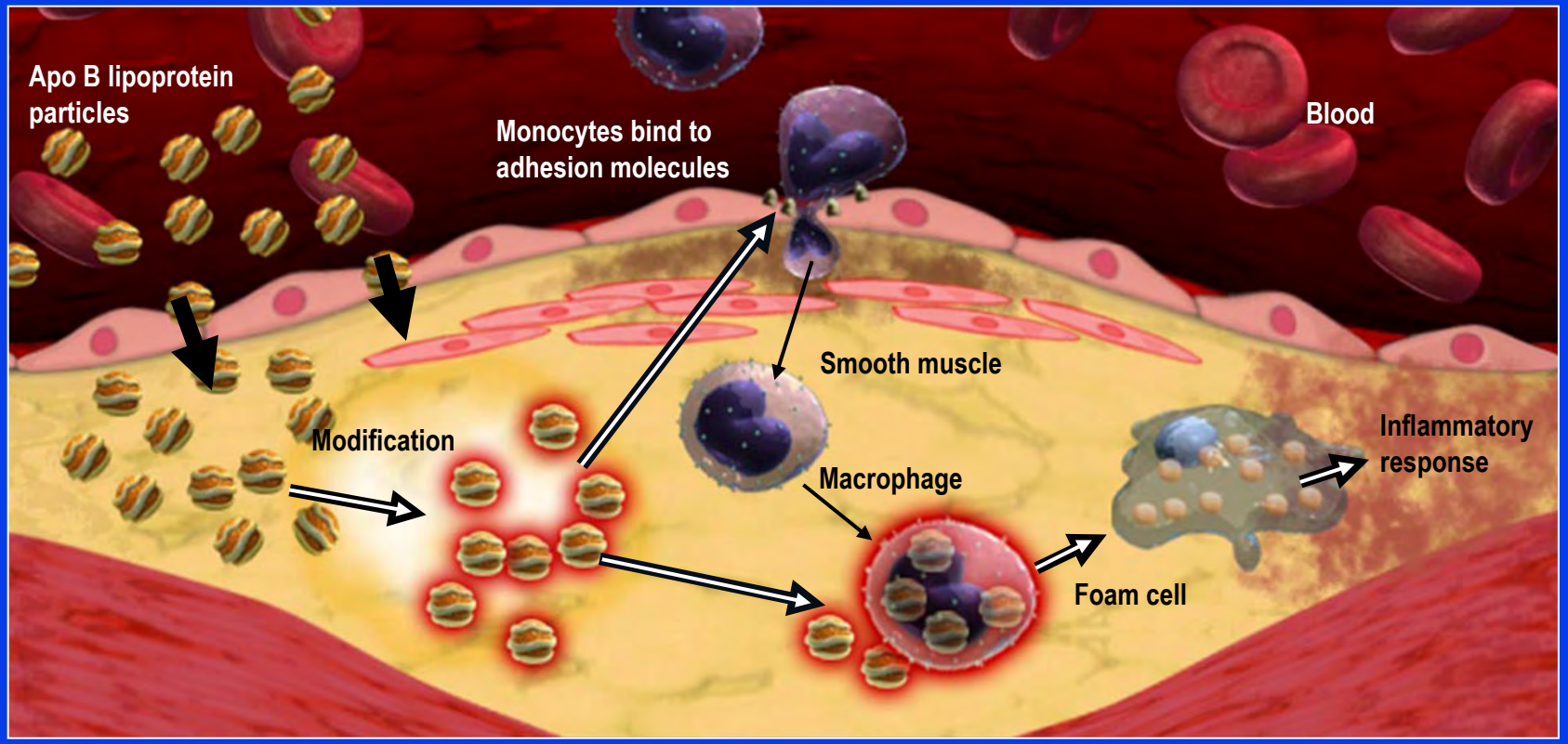
Lipoprotein Metabolism[1–5]



1. Goldstein JL et al. *Science*. 2001;292:1310–1312. **2.** Shepherd J. *Eur Heart J*. 2001;3(suppl E):E2–E5. **3.** Turley SD, et al. *Prev Cardiol*. 2003;6:29–33, 64. **4.** Mudd JO et al. *J Am Coll Cardiol*. 2007;50:1735–1741. **5.** Altmann SW et al. *Science*. 2004;303:1201–1204.

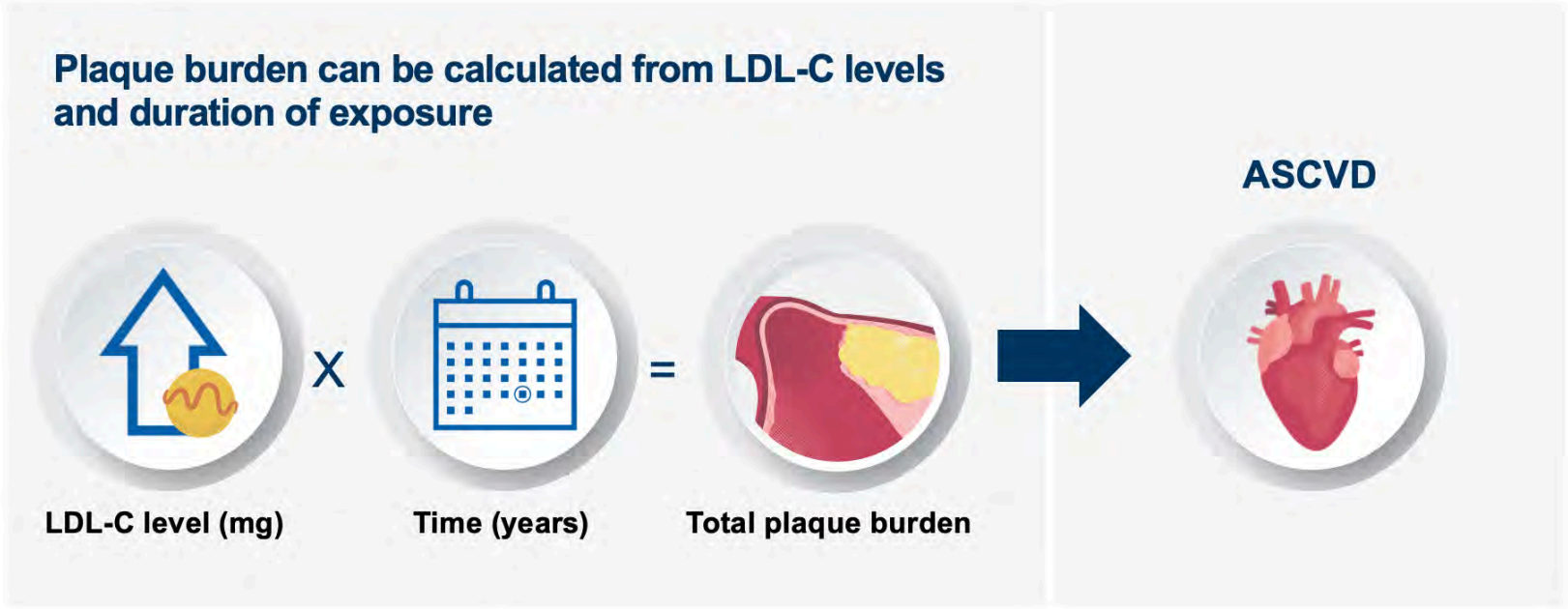
High Plasma Apo B Lipoprotein Levels Promote Atherogenesis

Rationale for therapeutic lowering of Apo B lipoproteins: decrease the probability of inflammatory response to retention



Tabas I et al. *Circulation.* 2007;116:1832-1844.
Williams KJ et al. *Arterioscler Thromb Vasc Biol.* 1995;15:551-561.
Hoshiga M et al. *Circ Res.* 1995;77:1129-1135.
Williams KJ et al. *Arterioscler Thromb Vasc Biol.* 2005;25:1536-1540.
Merrilees MJ et al. *J Vasc Res.* 1993;30:293-302.
Nakata A et al. *Circulation.*1996;94:2778-2786.
Steinberg D et al. *N Engl J Med.* 1989;320:915-924.

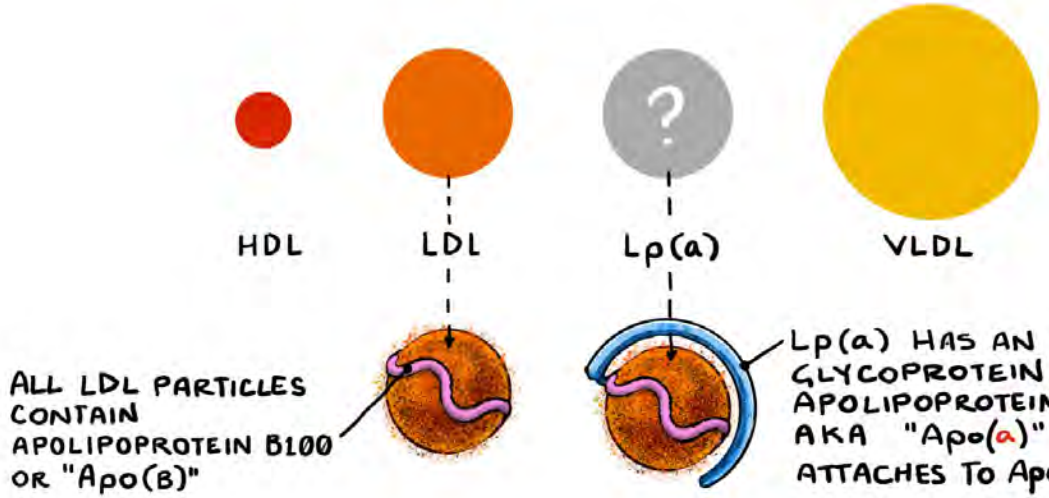
Both Magnitude and Duration of LDL-C Exposure Impact ASCVD



CORE IM

WHAT IS LIPOPROTEIN(a) ?

LIPOPROTEIN(a) OR "Lp(a)" IS A LIPOPROTEIN SIMILAR TO LDL.

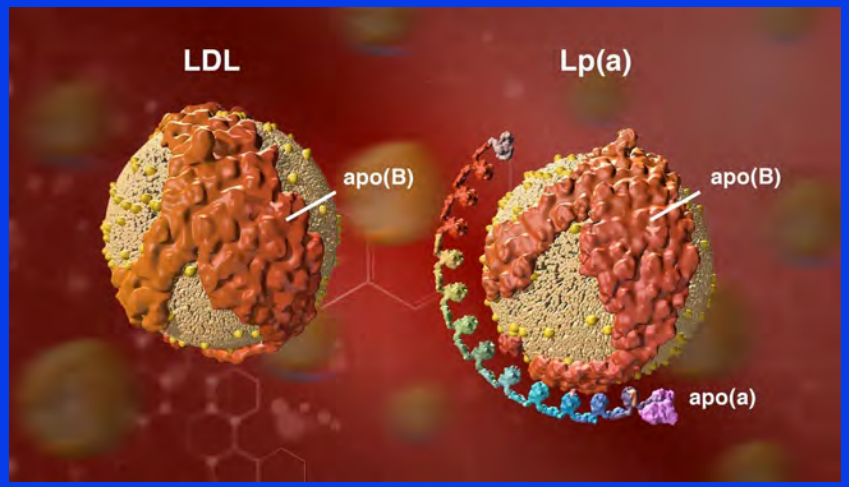


Lp(a) IS NOT SPECIFICALLY MEASURED ON A STANDARD LIPID PANEL.

BUT IT HAS IMPORTANT IMPLICATIONS FOR CV HEALTH.

IT CAN ACCELERATE ATHERO-SCLEROSIS.

IT CAN ACCELERATE CALCIFIC AORTIC STENOSIS.



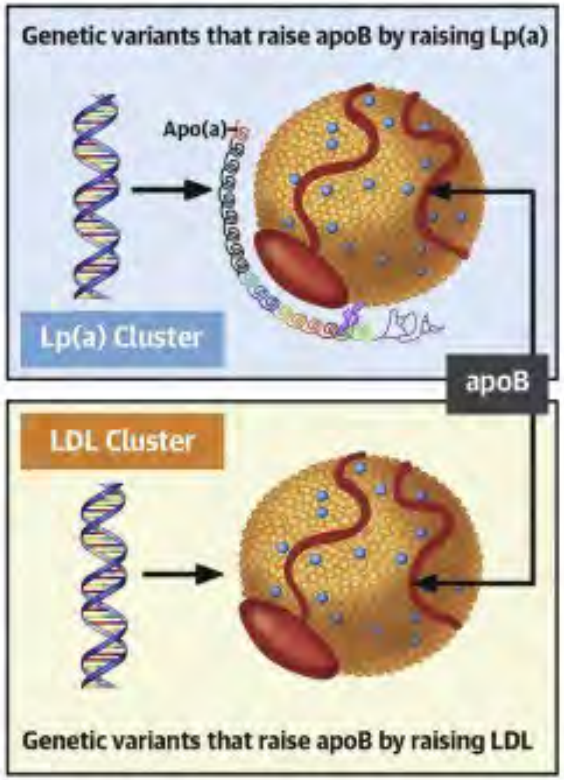
CENTRAL ILLUSTRATION: Relative Atherogenicity of Lipoprotein(a) and Low-Density Lipoprotein Particles

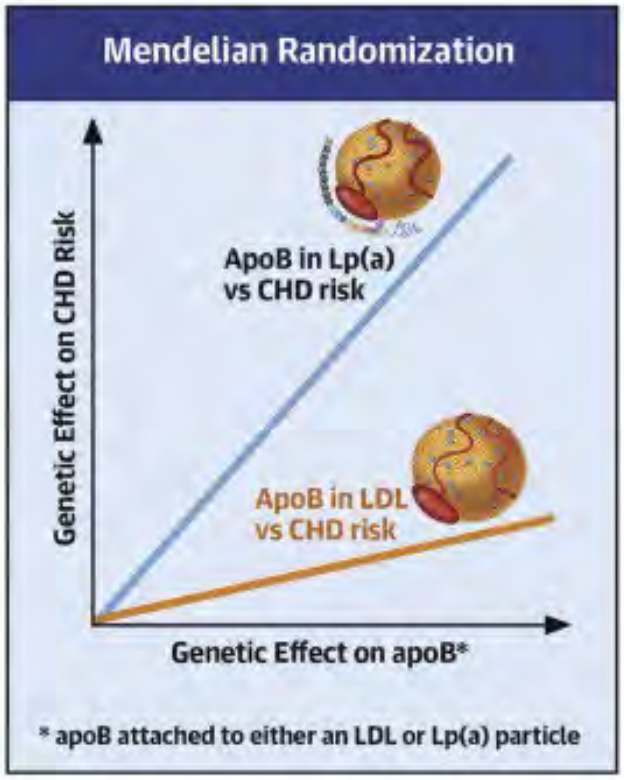
Key Question

How atherogenic is 1 particle of Lp(a) compared to 1 particle of LDL?

Key Methodology

Both Lp(a) and LDL contain 1 apoB per-particle. Here, we identified genetic variants (SNPs) that affected plasma levels of either LDL particles or Lp(a) particles. For these 2 genetic SNP "clusters," we related the change in apoB to the respective change in CHD risk. This way, we directly compared the atherogenicity of LDL and Lp(a), particle for particle.



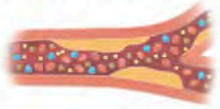


Take-Home Message: In most people, LDL particles are much more abundant than Lp(a) and carry the greatest proportion of overall CVD risk; however, on a per-particle basis, Lp(a) is about 6 times more atherogenic than LDL.

Björnson E, et al. J Am Coll Cardiol. 2024;83(3):385-395.

Lipoproteins and plaque development in PROSPECT II

Increased non-HDL, LDL, and total cholesterol levels



Increased Lp(a) levels

associated with

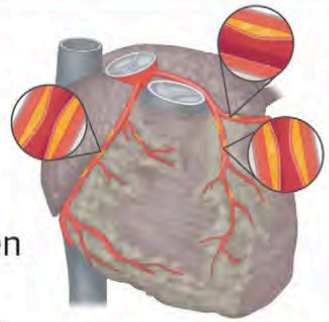
Increased non-HDL, LDL, and total cholesterol were not associated with development of focal vulnerable plaques

Increased Lp(a) was not associated with overall lipid deposition or plaque burden

associated with

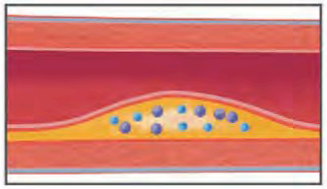
Lipid deposition and plaque burden in the coronary tree

Increase in average lipid core burden index (LCBI) and average plaque burden in the coronary tree



Formation of high-risk vulnerable plaques that cause acute coronary syndromes

Increase in the proportion of focal plaques with $maxLCBI_{4mm}$ ≥324.7 and plaque burden ≥70%



Erlinge D, et al. JACC. 2025;85(21):2011-2024.

The latest clinical guidelines recommend measuring Lp(a) at least once

Reyes-Soffer et al. Am J Prev Cardiol. 2024 in press

Two Lp(a) world views

Belief Driven

Measure Lp(a) in Some

One in Some

- Old guidelines
- Rarely done, even in high risk patients with recurrent or premature ASCVD
- Often measured after the first event
- Missed opportunity to prevent ASCVD is costly to patients and society

Evidence Driven

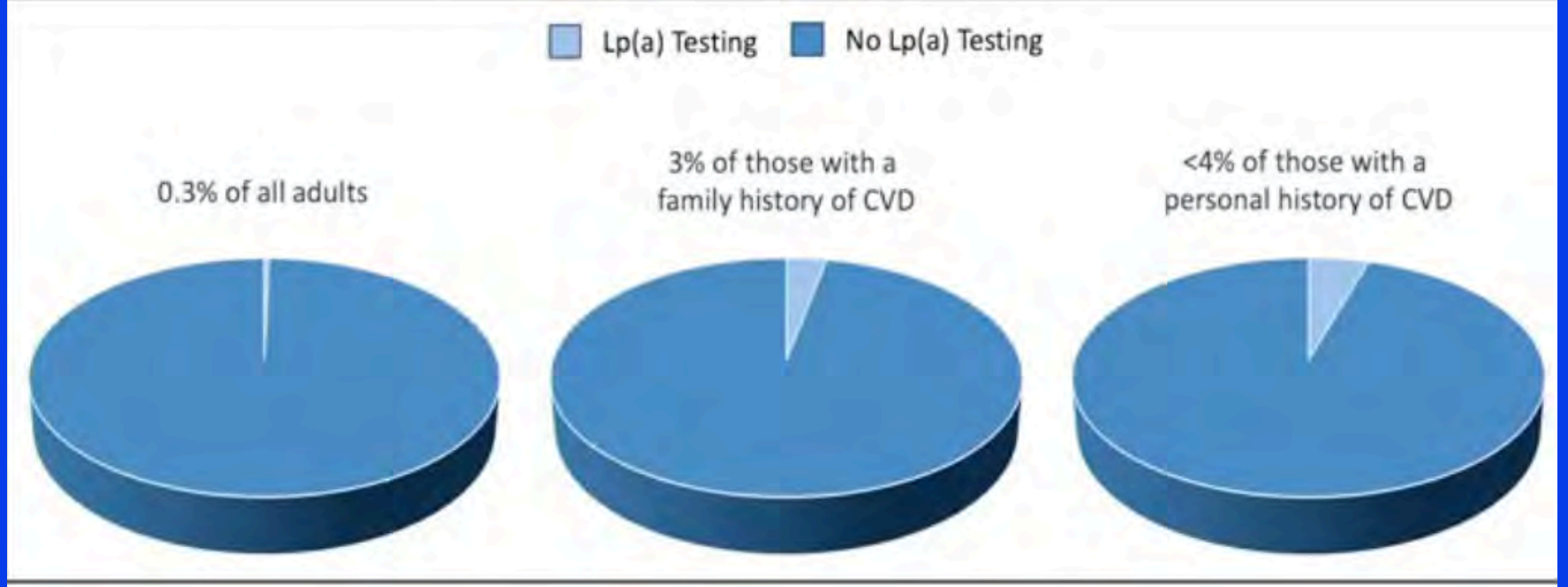
Measure Lp(a) in All

One & Done

- **New** guidelines
- **Causal** lifetime genetic risk factor for ASCVD, AS
- Simple nonfasting test
- Added cost is minimal
- All assays detect high Lp(a) levels
- Patients want to know

What is current clinical practice?

>5.5 million adults, 6 academic health systems in California



Bhatia et al.: J. Am. Heart Assoc. 12:e031255, 2023

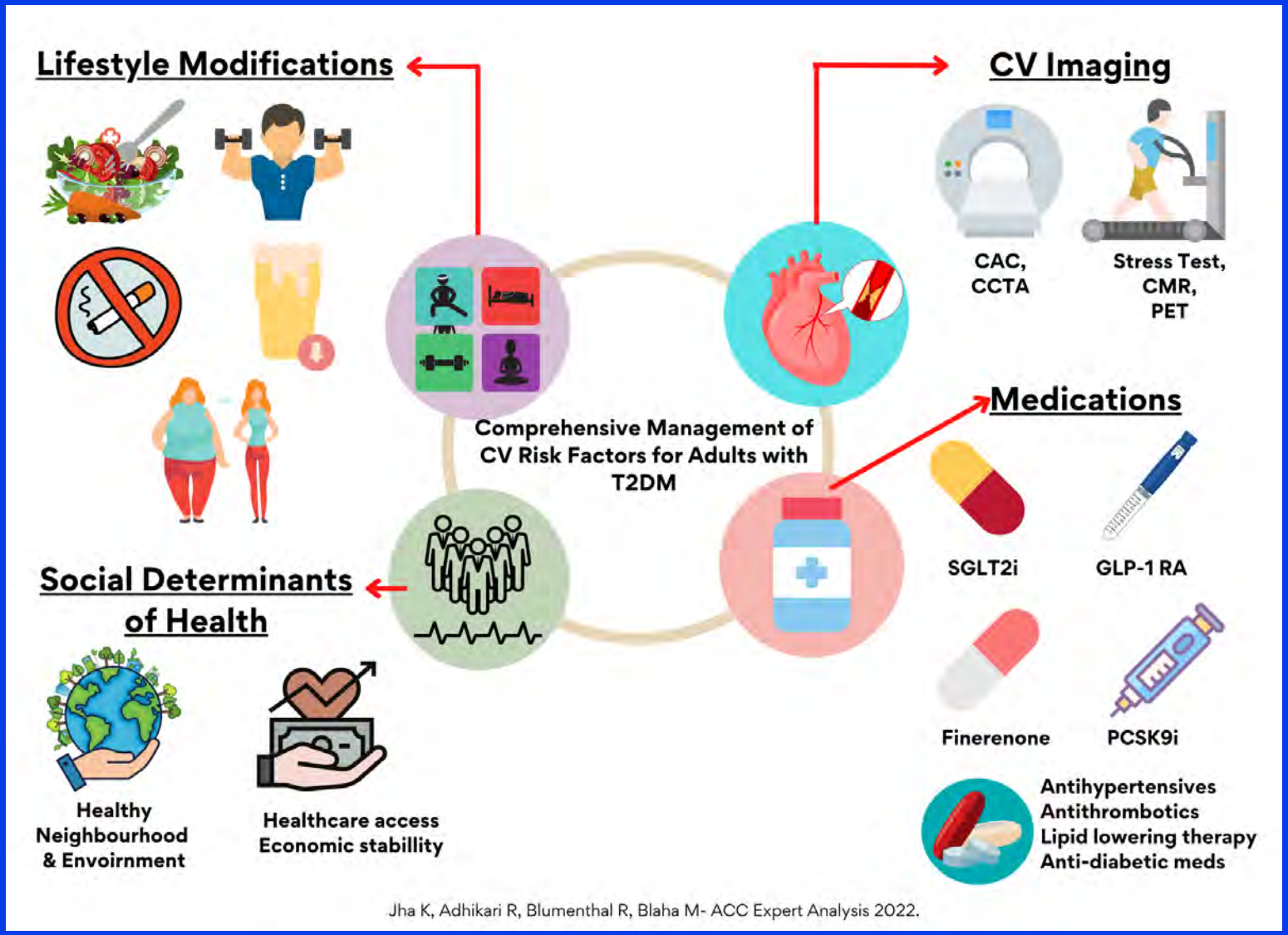
Key Phase 2 and 3 Trials of Novel Therapies Targeting LPA Gene Transcription or Lp(a) Assembly

Study Name	Trial phase	Compound	Mechanism	Status / Results
AKCEA-APO(a)-L_{Rx}	2	Pelacarsen (AKCEA-APO(a)-L_{Rx}; IONIS-APO(a)-L_{Rx})	ASO	Up to 80% Lp(a) reduction at highest dose
HORIZON	3	Pelacarsen (AKCEA-APO(a)-L_{Rx}; IONIS-APO(a)-L_{Rx})	ASO	Expected completion 5/2025
OCEAN(a)-DOSE	2	Olpasiran (AMG 890)	siRNA	>95% reduction at highest doses
OCEAN(a)-Outcomes	3	Olpasiran (AMG 890)	siRNA	Expected completion 12/2026
ALPACAR 360	2	Zerlasiran (SLN360)	siRNA	≥90% reduction. Follow-up is ongoing.
KRAKEN	2	Muvalaplin (LY3473329)	Small molecule inhibitor (oral)	Expected completion 3/2024
LY3819469	2	Lepodisiran (LY3819469)	siRNA	Expected completion 10/2024
ACCLAIM-Lp(a)	3	Lepodisiran (LY3819469)	siRNA	Enrolling. Expected completion 3/2029

Lifestyle Modification

First and Foremost

2022 AHA Statement on the Comprehensive Management of CV Risk Factors For Adults With T2DM



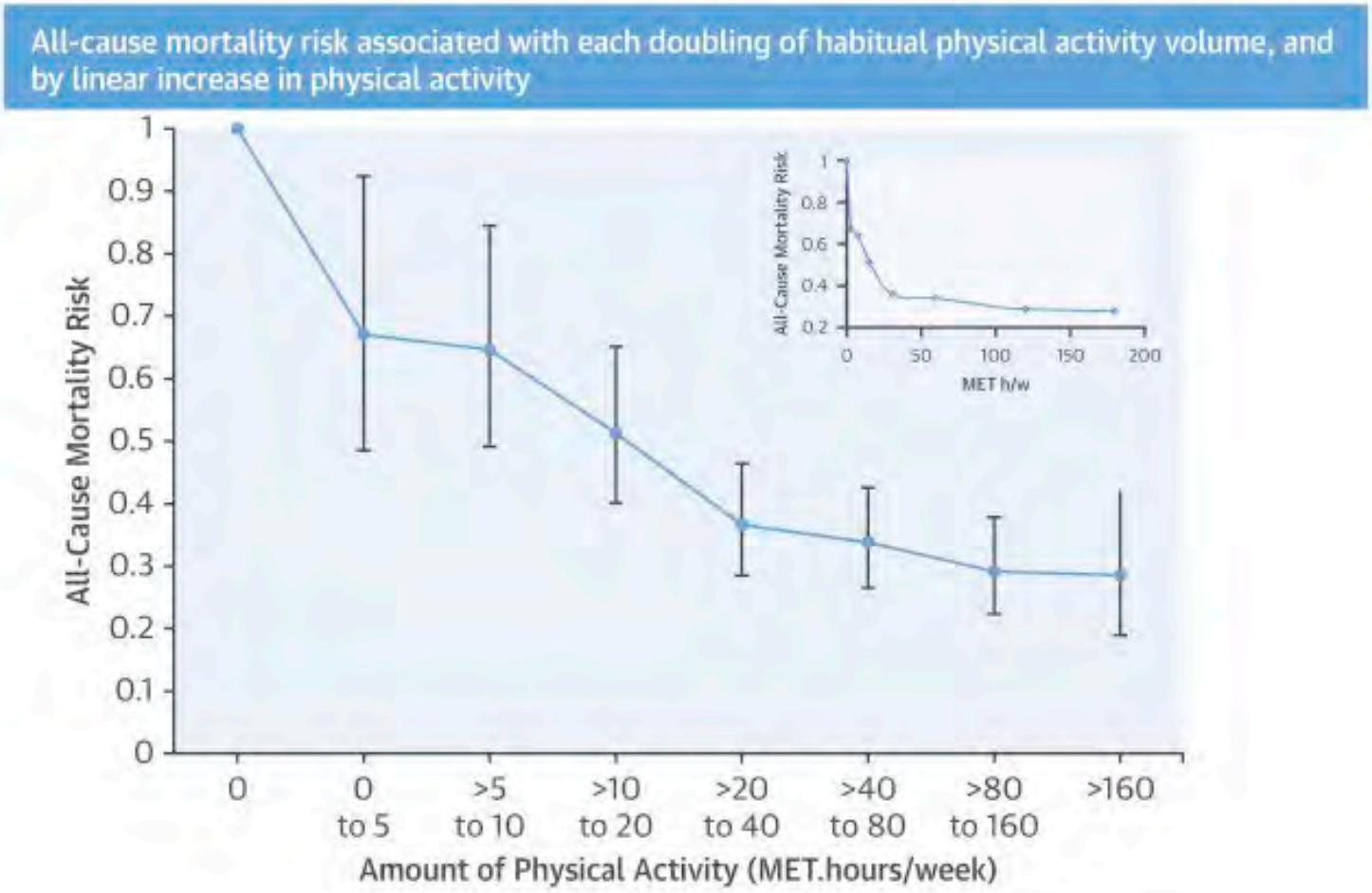
Lifestyle Recommendations

	General recommendations	Initial considerations	Implementation
Nutrition	Whole-food, plant-based, Mediterranean, and DASH diets recommended	Nuts, seeds, and avocado OK if no adiposity. If animal products consumed, order of preference: fish (especially fatty fish); lean meat and skinless poultry; limit processed foods	Focus on whole grains, legumes, vegetables, and fruits Avoid added sugars, salt, and fat Limit low-fiber grains and potatoes ("white starches"), fried foods, fast foods, and alcohol (especially if high triglycerides) Limit calories for 5-10% weight reduction[a] (if overweight/obesity)
Physical activity	Physical activity ≥3 times/week Reduce/break up prolonged sitting	Start with low duration and intensity of activity and increase slowly until activity goals are met	150-300 minutes/week of moderate-intensity or 75-150 minutes/week of high-intensity activity Resistance training ≥2 times/week
Sleep	Sleep duration 6-8 hours/night	Screen for and treat sleep apnea	Lifestyle modification with weight loss as needed Avoid sleeping pills
Mental health	Assess for depression, anxiety, and substance abuse	Lifestyle modification Address substance abuse Refer to mental health professionals as needed	Encourage community involvement (community centers, charitable organizations, schools, houses of worship, etc) and use of support services
Smoking	No tobacco or nicotine related products	Avoid passive exposure to tobacco smoke	Nicotine in any formulation is associated with atherosclerosis

[a] See AACE/ACE Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity and AACE/ACE Treatment Algorithm for the Medical Care of Patients With Obesity.

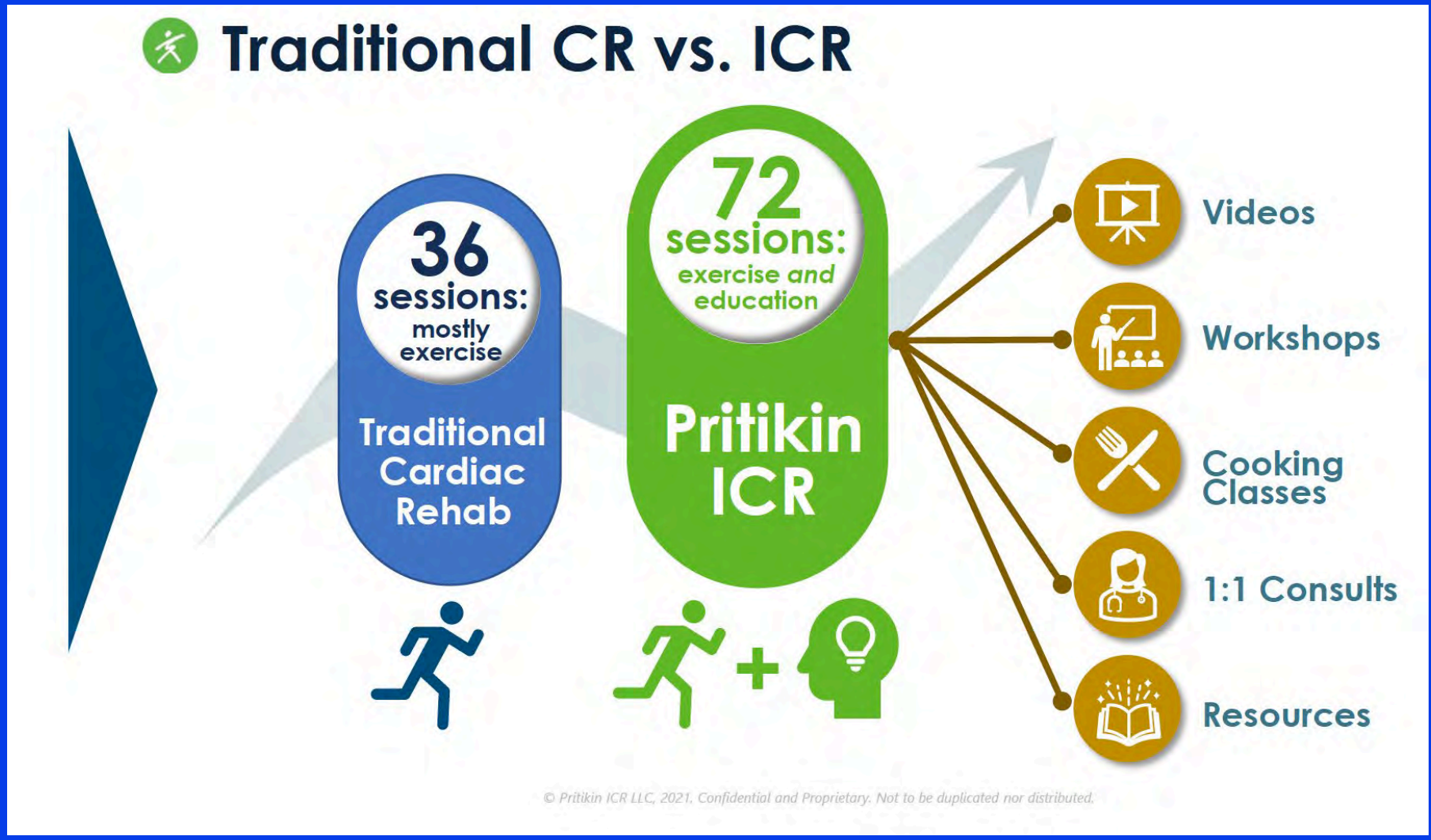
Abbreviations: CV = cardiovascular; DASH = Dietary Approaches to Stop Hypertension.

Physical Activity and Mortality in Patients with Stable CAD

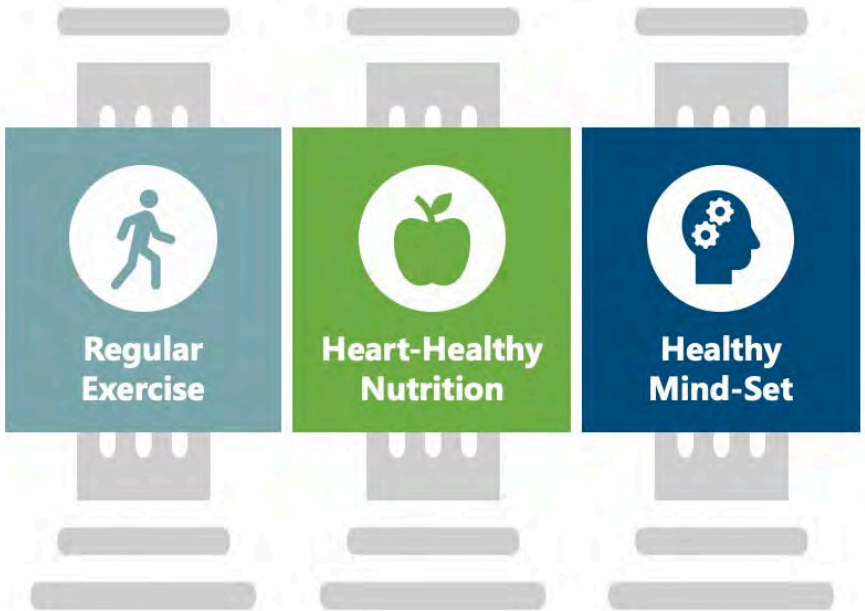


Stewart, R.A.H. et al. J Am Coll Cardiol. 2017;70(14):1689-700.

Pritikin Intensive Cardiac Rehab Program



Pritikin Program Pillars



Video Library

Nutrition

- ***Calorie Density***
- ***Dining Out – Part 1***
- ***Facts on Fats***
- ***Label Reading***
- ***Nutrition Action Plan***
- ***Overview of the Pritikin Eating Plan***
- Cooking School- Becoming a Pritikin Chef
- Cooking School- Breakfast and Snacks
- Cooking School- Healthy Salads and Dressings
- Cooking School- Dinner
- Cooking School- Sides, Soups, and Desserts
- Planning Your Eating Strategy
- Fueling a Healthy Body
- Dining Out – Part 2
- Vitamins & Minerals
- Menu Workshop
- Targeting Your Nutrition Priorities

Healthy Mind-Set / Medical

- ***Diseases of Our Time – Focusing on Diabetes***
- ***Healthy Minds, Bodies, Hearts***
- ***Heart Disease Risk Reduction***
- ***How Our Thoughts Can Heal Our Hearts***
- ***Hypertension & Heart Disease***
- ***Metabolic Syndrome & Belly Fat***
- Introduction to Yoga
- Smoking Cessation
- Diseases of Our Time – Overview
- Biology of Weight Control
- Decoding Your Labs
- Aging- Enhancing Your Quality of Life
- Sleep Disorders

Exercise

- ***Biomechanical Limitations***
- ***Body Composition***
- ***Exercise Action Plan***
- ***Move It***
- Improve Performance

Group Workshops

Nutrition

- Label Reading
- Menus and Dining Out
- Mindful Eating
- Fueling a Healthy Body
- Targeting Your Nutrition Priorities

Healthy Mind-Set / Medical

- Stress and Health
- Taking Charge of Stress
- New Thoughts, New Behaviors
- Managing Moods and Relationships
- Tobacco Cessation

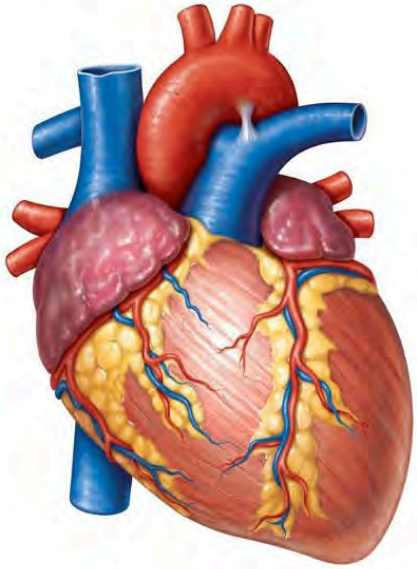
Exercise

- Exercise Basics: Building Your Action Plan
- Exercise Biomechanics
- Balance Training and Fall Prevention
- Heart Disease Risk Reduction

Cooking School Workshops

- Taught by your dietitian or chef
- Attendees learn to prepare meals that are:
  - Quick and Easy
  - Healthy
  - Affordable
  - Tasty
- Class topics:
  - Adding Flavor – Sodium Free
  - Fast and Healthy Breakfasts
  - Satisfying Salads and Dressings
  - Savory Soups
  - Simple Sides and Sauces
  - Tasty Appetizers and Snacks
  - Delicious Desserts
  - Plant-Based Proteins
  - Fast Evening Meals
  - Weekend Breakfasts
  - Efficiency Cooking
  - One-Pot Meals

Qualifying Events: Same as CR



- Acute myocardial infarction
- Coronary artery bypass surgery
- Current stable angina pectoris
- Heart valve repair or replacement
- Percutaneous transluminal coronary angioplasty / stenting
- Heart or heart-lung transplant
- Chronic heart failure with reduced EF

Image courtesy of Pearson Education, Inc.

Therapy Post-ACS / PCI

All Class IA Interventions:

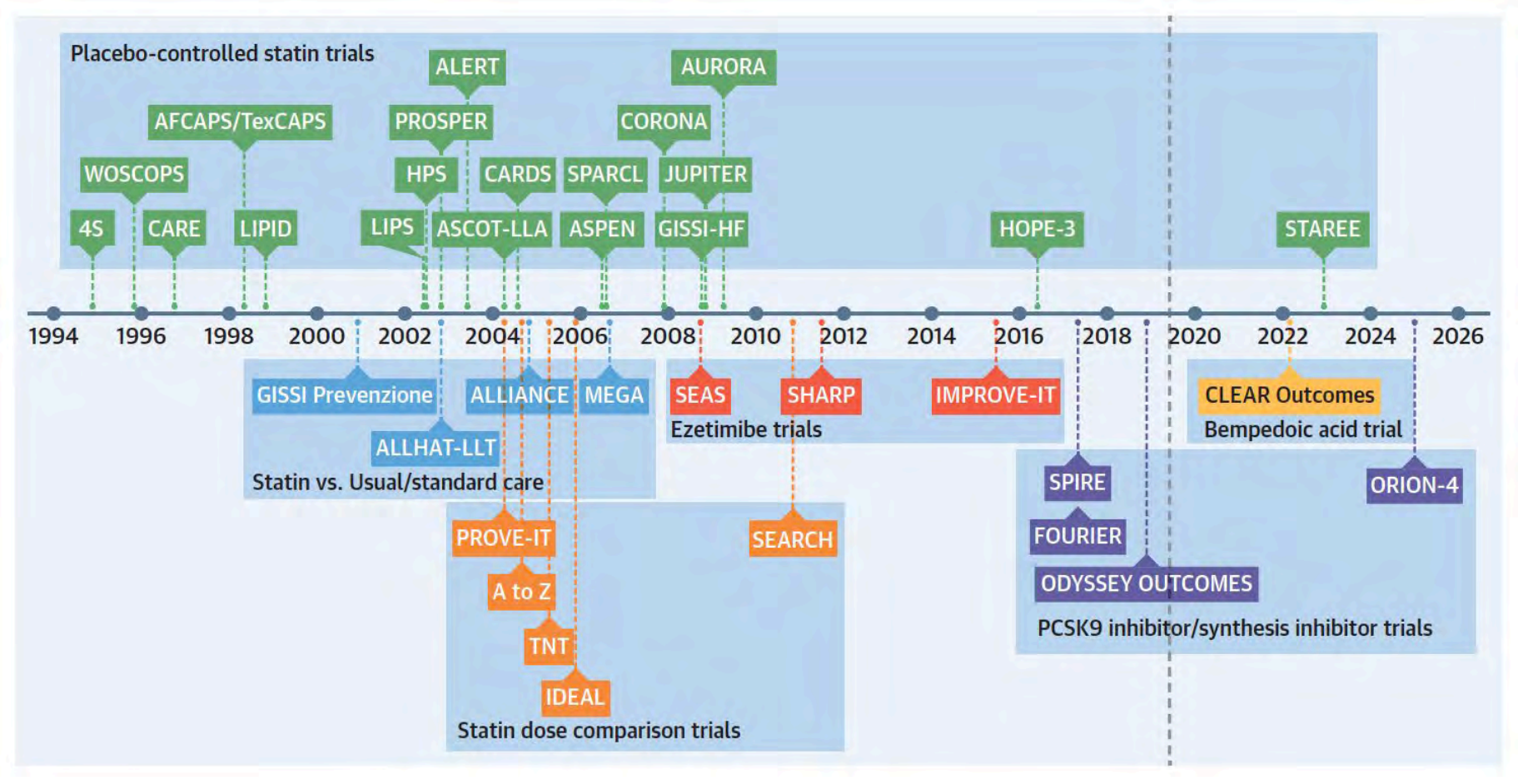
Intervention	Relative Risk Total/CV Mortality	Side Effect %	Discharge Use
ASA	0.71-0.78	17%	95%
Beta Blocker	0.61-0.72	39%	81%
Statin	0.7-0.82	37%	89%
ACEI	0.71-0.80	49%	71%
Cardiac Rehab	**0.53-0.82**	**0%**	**10-20%**

Provided courtesy of Frank Smith, MD, Michigan Heart Hospital

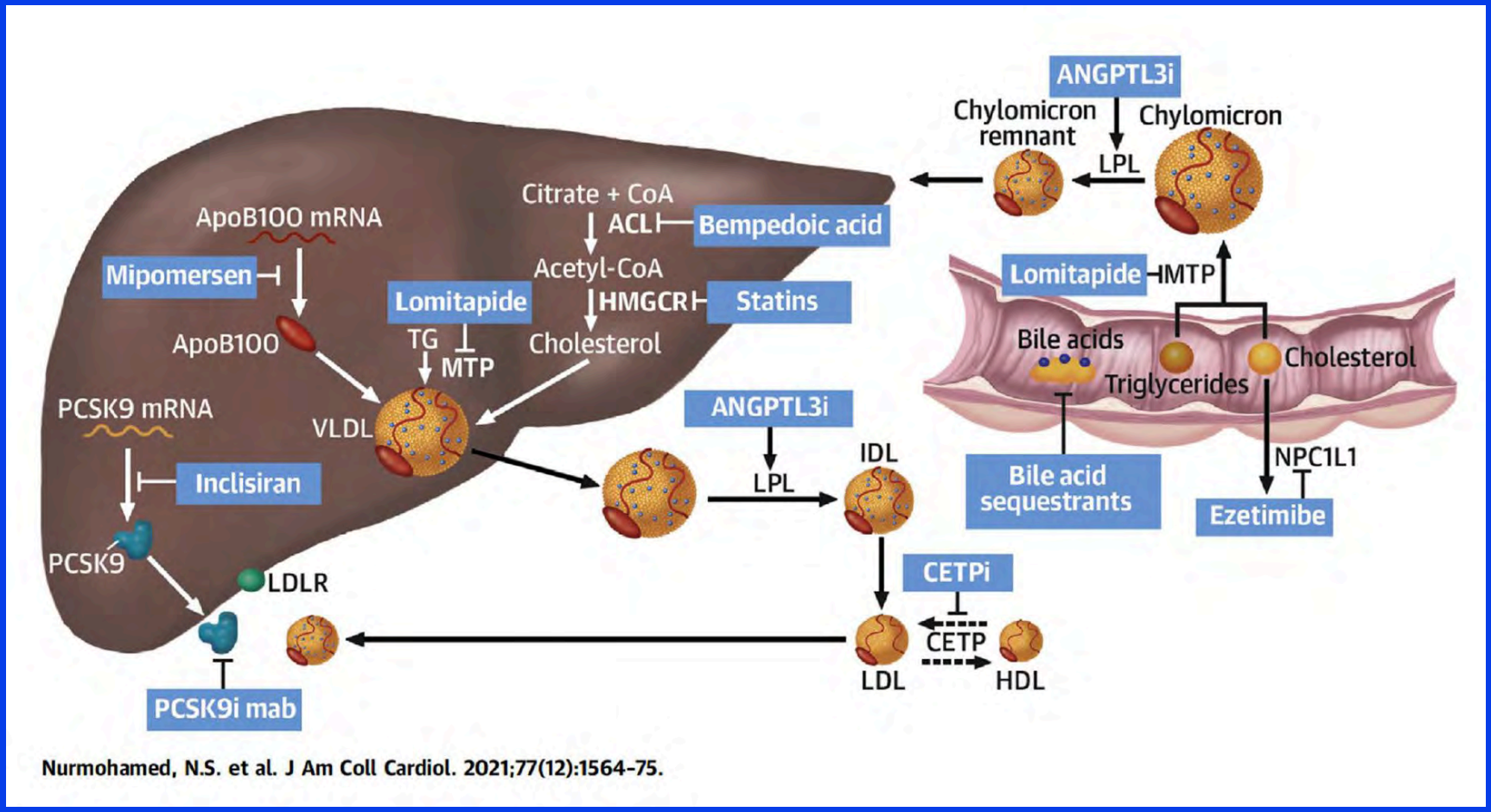
Pharmacotherapy

The Next Step…

Key Trials in the Lipid Space

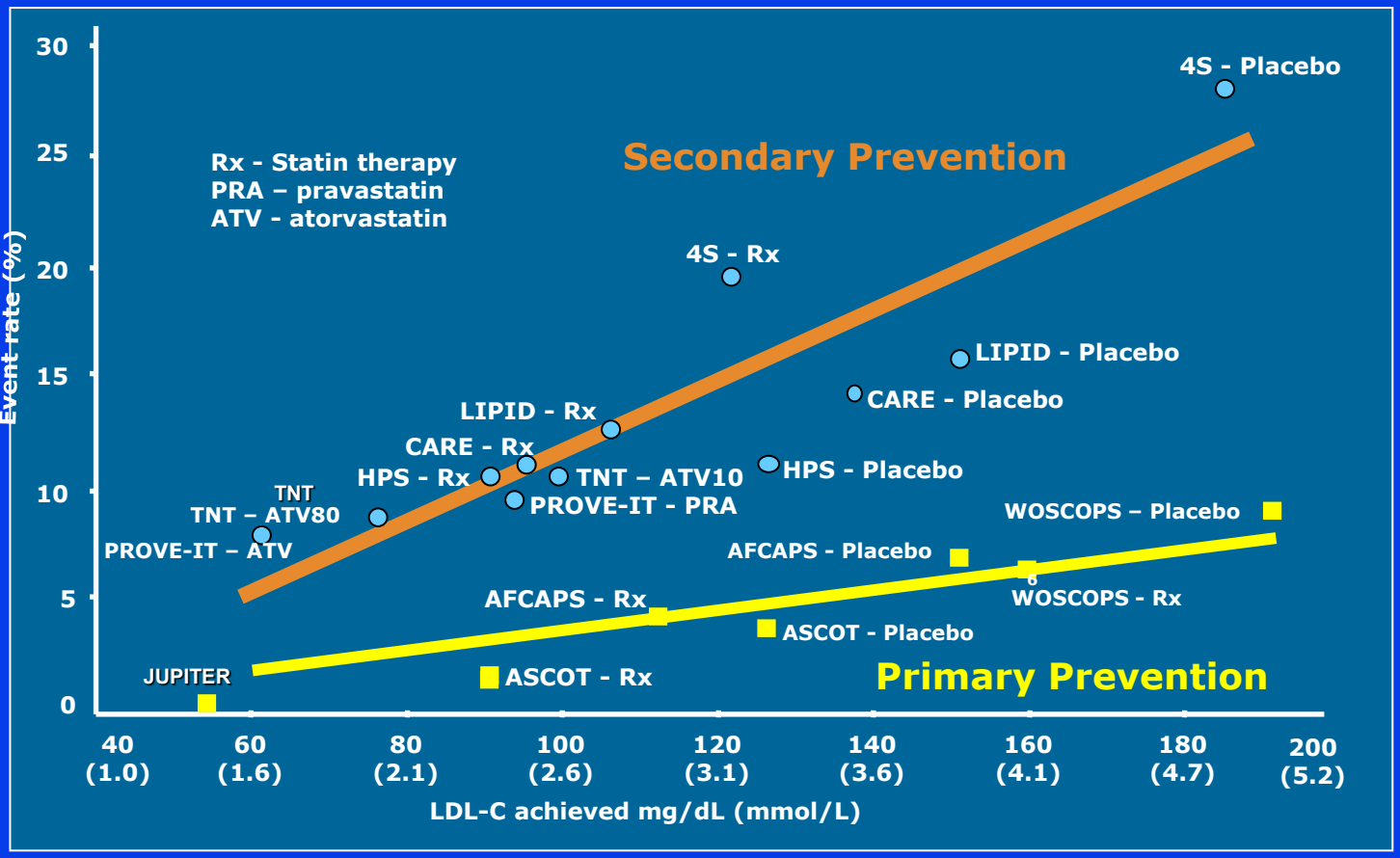


MOA for Lipid Lowering Agents



Nurmohamed, N.S. et al. J Am Coll Cardiol. 2021;77(12):1564-75.

Statins – No Brainer



Adapted from Rosensen RS. *Exp Opin Emerg Drugs* 2004;9(2):269-279

LaRosa JC *et al. N Engl J Med* 2005;352:e-version

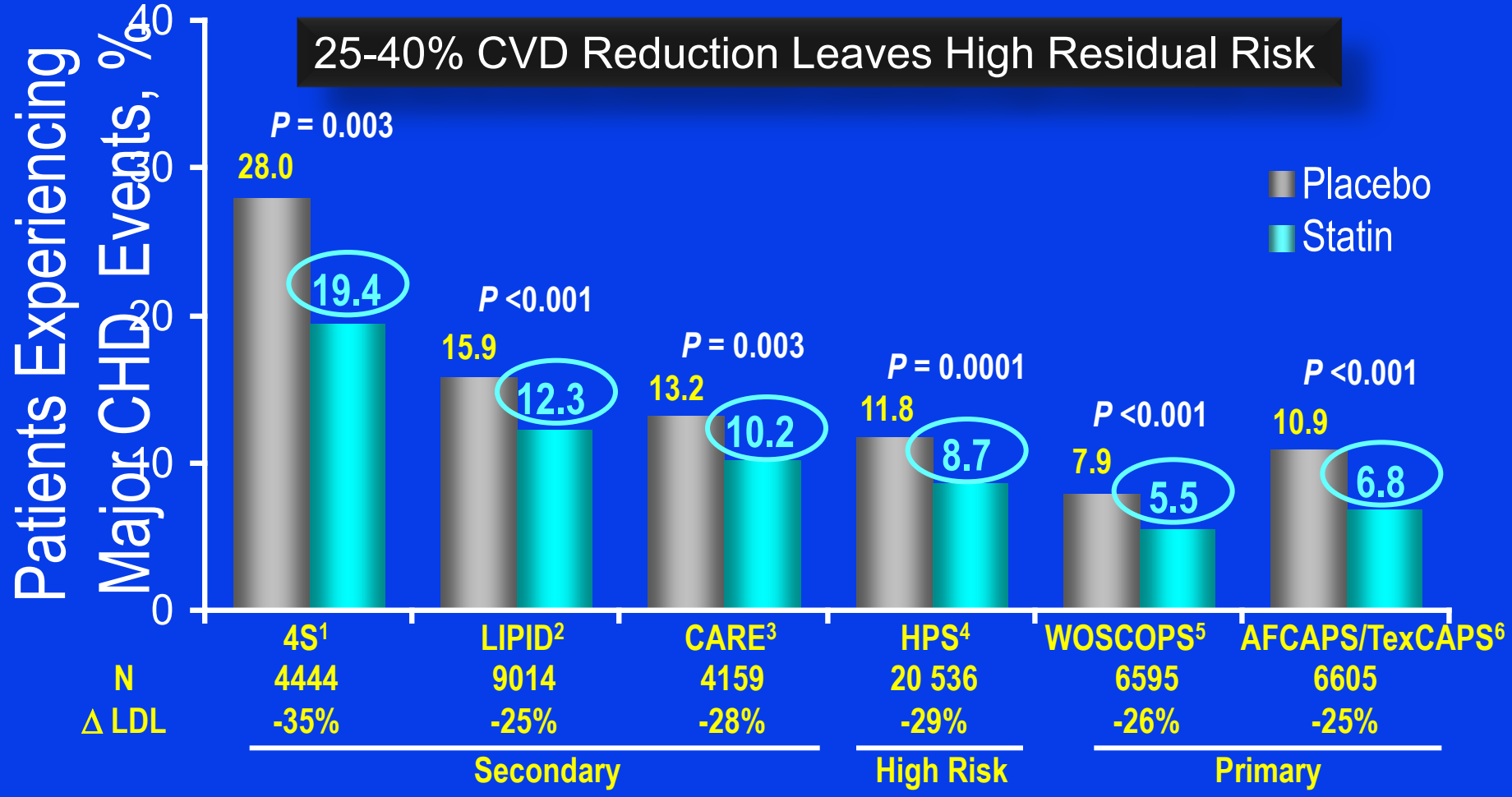
Cholesterol Treatment Trialists' (CCT) Collaboration: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomized trials of statins (The Lancet 9/27/05)

Over 5 year treatment period (average reduction in LDL-C by 40 mg/dl) showed:

- 12% reduction in all-cause mortality
- 19% reduction in coronary mortality
- 23% reduction in MI or CHD death
- 17% reduction in stroke
- 21% reduction in major vascular events

Trials of Statin vs Placebo

Many CHD Events Still Occur in Statin-Treated Patients



[1]4S Group. *Lancet.* 1994;344:1383-1389.
[2]LIPID Study Group. *N Engl J Med.* 1998;339:1349-1357.
[3]Sacks FM et al. *N Engl J Med.* 1996;335:1001-1009.
[4]HPS Collaborative Group. *Lancet.* 2002;360:7-22.
[5]Shepherd J et al. *N Engl J Med.* 1995;333:1301-1307.
[6] Downs JR et al. *JAMA.* 1998;279:1615-1622.

IMPROVE-IT: Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

*3.2mM
**2.6mM

N=18,144

Standard Medical & Interventional Therapy

Simvastatin 40 mg

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

Ezetimibe / Simvastatin 10 / 40 mg

Follow-up Visit Day 30, every 4 months

90% power to detect ~9% difference

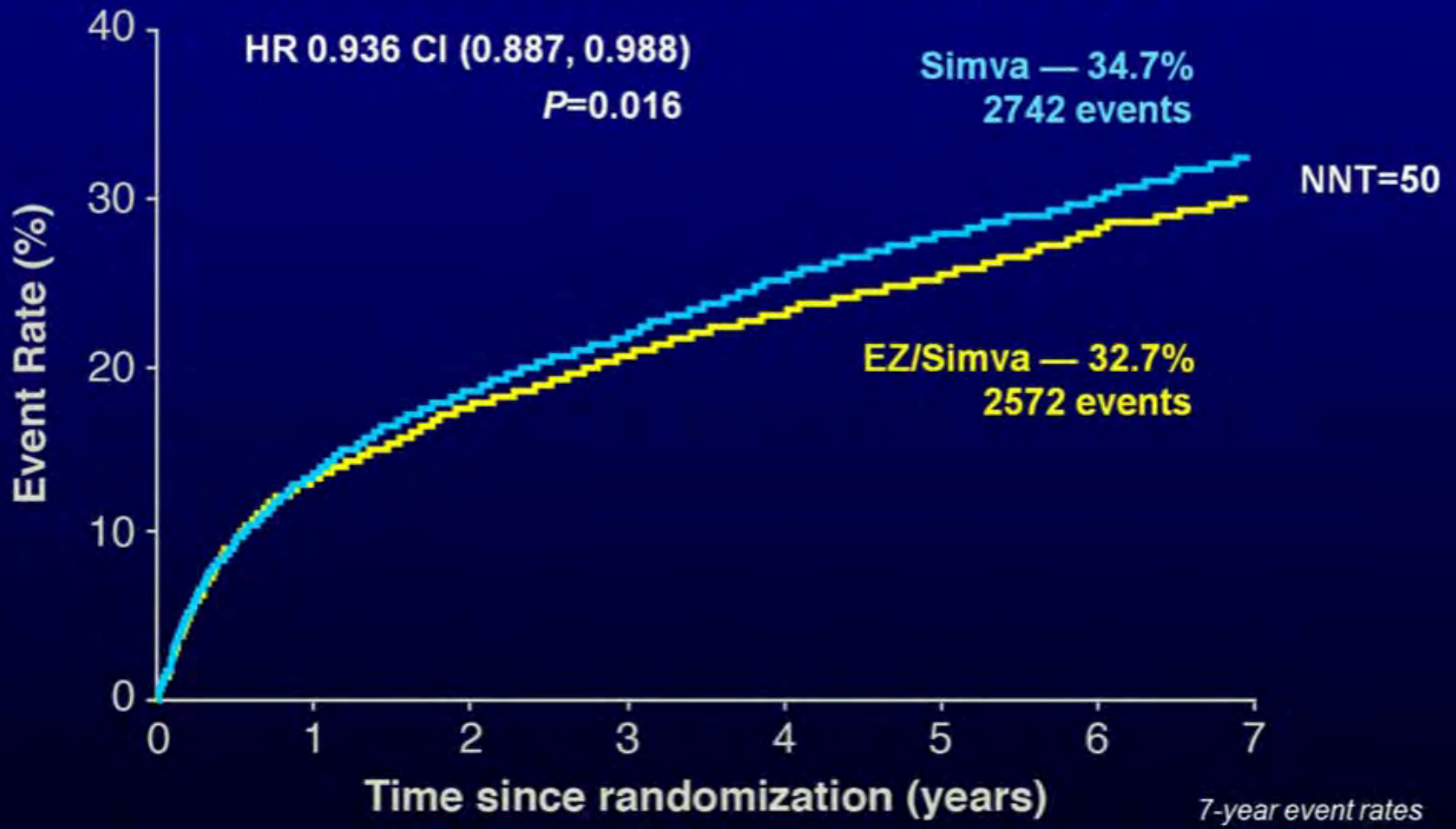
Duration: Minimum 2 ½-year follow-up **(at least 5250 events)**

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Blazing MA, *Am Heart J.* 2014;168:205-212

IMPROVE-IT: Primary Endpoint (ITT)

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



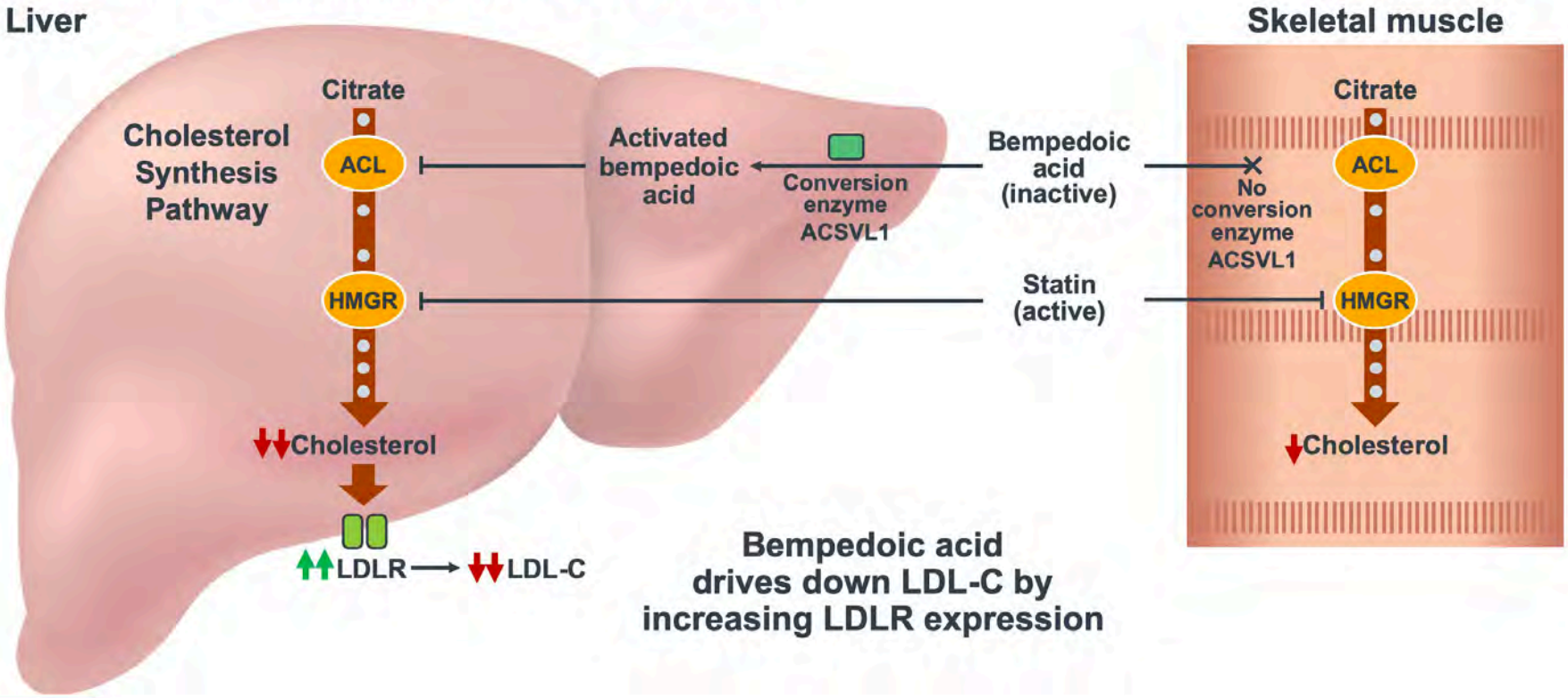
7-year event rates

Adapted from Cannon CP, et al. Presented at: American Heart Association Scientific Sessions 2014; November 17, 2014; Chicago, IL.

Bempedoic Acid

Bempedoic acid reduces cholesterol synthesis by inhibiting ACL 2 steps upstream from HMG-CoA reductase

INHIBITION OF CHOLESTEROL SYNTHESIS BY BEMPEDOIC ACID[1,2]



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

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

ABSTRACT

BACKGROUND

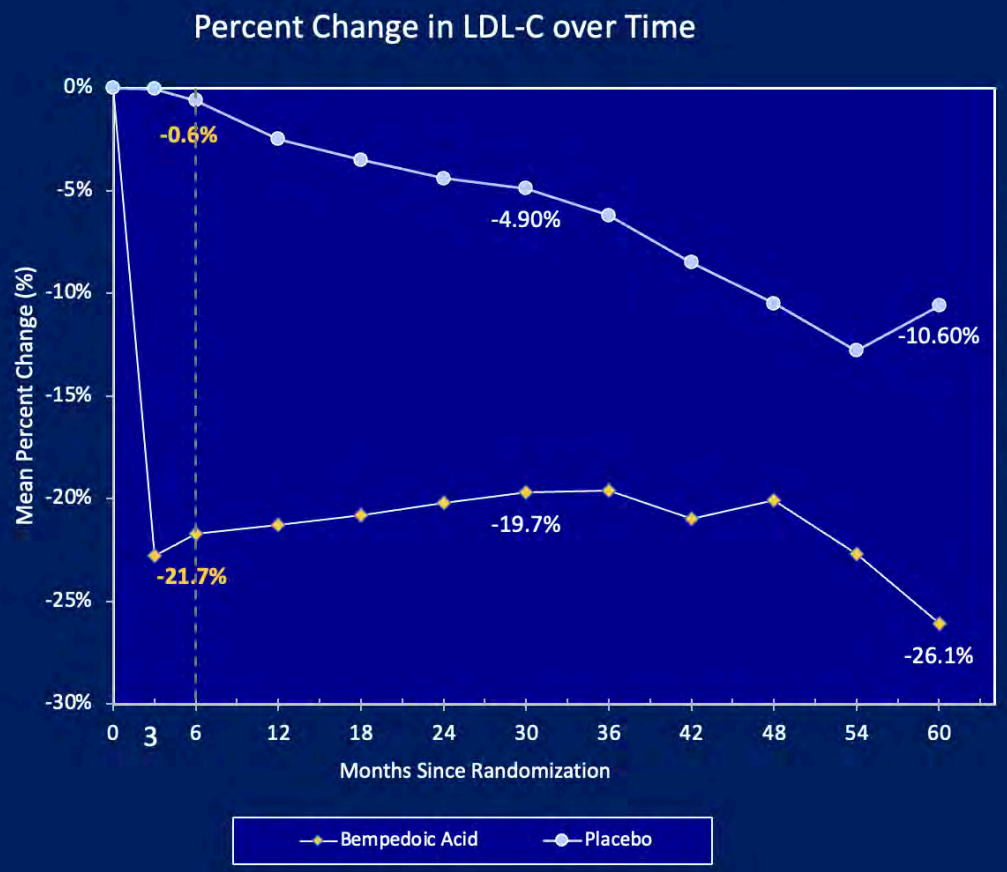
Bempedoic acid, an ATP citrate lyase inhibitor, reduces low-density lipoprotein (LDL) cholesterol levels and is associated with a low incidence of muscle-related adverse events; its effects on cardiovascular outcomes remain uncertain.

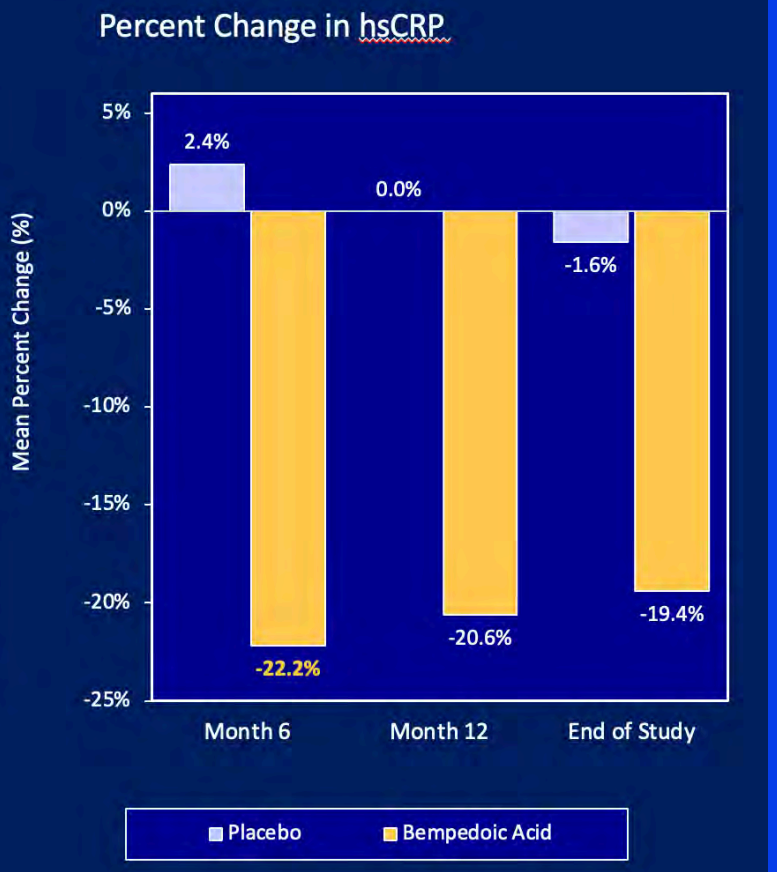
CLEAR Outcomes Trial

Cholesterol Lowering via Bempedoic Acid, an ACL-Inhibiting Regimen

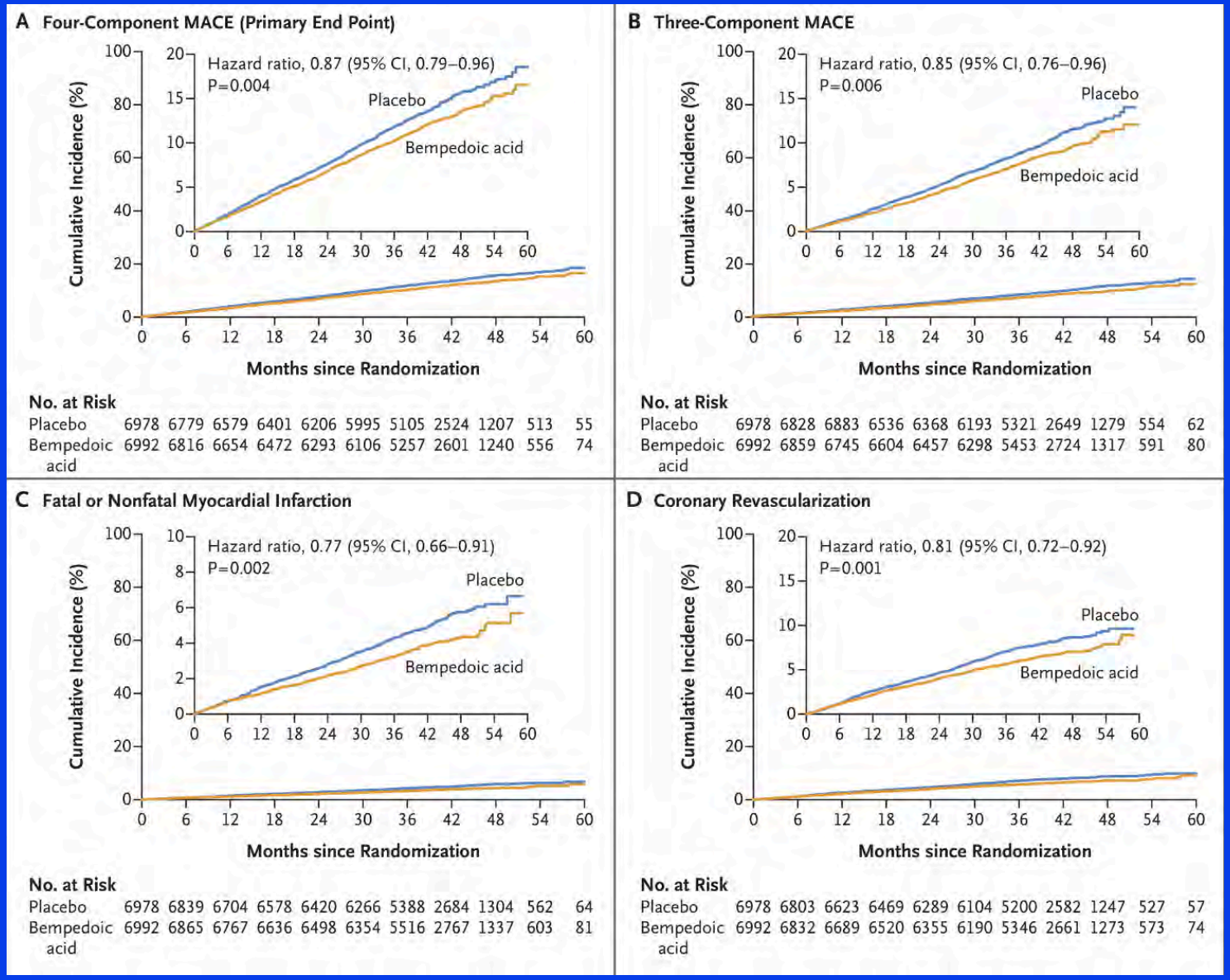
- Statin intolerance: An adverse effect that started or increased during statin therapy and resolved or improved after therapy discontinued.
- Intolerance to 2 or more statins or 1 statin if unwilling to attempt a second statin or advised by physician to not attempt second statin. Very low dose statin therapy permitted (< lowest approved dose).

Effect of Trial Regimens on LDL-C and hsCRP

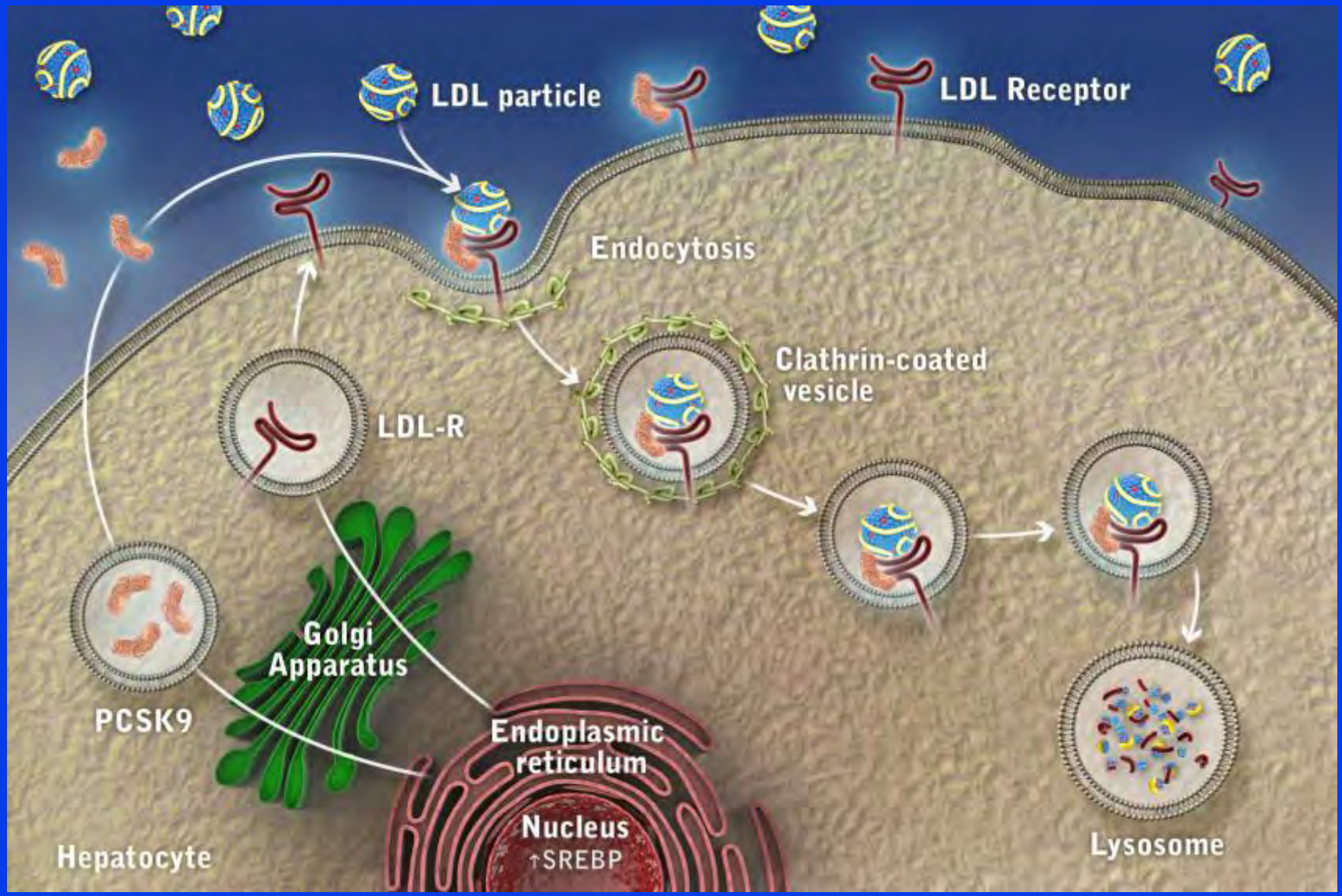




Bempedoic Acid Reduces Events



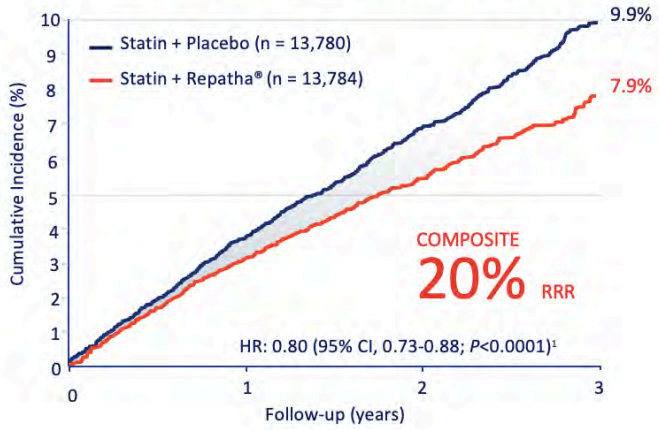
The Role of PCSK9 in the Regulation of LDL Receptor Expression



Fourier Trial

FOR PATIENTS WITH ESTABLISHED CVD, REPATHA® ADDED TO A STATIN **REDUCED THE RISK OF CV EVENTS BY 20%** IN A MEDIAN OF 2.2 YEARS[1,2]

Key secondary endpoint: composite of CV death, MI, or stroke[1,2]



Primary composite endpoint of time to first occurrence of CV death, MI, hospitalization for UA, stroke, or coronary revascularization: HR: 0.85 (95% CI, 0.79-0.92; *P*<0.0001)[1,2]

Key secondary composite endpoint of time to first occurrence of CV death, MI, or stroke: HR 0.80 (95% CI, 0.73-0.88; *P*<0.0001), ARR = 2.0%[1,2]

- **27% RRR** MI[1]
- **22% RRR** Revascularization[1]
- **21% RRR** Stroke[1]

RRRs for the primary and secondary composite endpoints were driven by a reduction in the risk of MI: HR 0.73 (95% CI, 0.65-0.82), stroke: HR 0.79 (95% CI, 0.66-0.95), and coronary revascularization: HR 0.78 (95% CI, 0.71-0.86)[1,

*Not statistically significant.

AMERICAN COLLEGE of CARDIOLOGY®

Oral PCSK9 Inhibitor MK-0616

Efficacy and Safety of the Oral PCSK9 Inhibitor MK-0616

Phase 2b, Multicenter, International, Double-Blind, Randomized, Placebo-Controlled Trial

OBJECTIVE: To evaluate the efficacy and safety of MK-0616 (an oral PCSK9 inhibitor) in participants with hypercholesterolemia.

380
PATIENTS

INCLUSION CRITERIA:

1. Clinical ASCVD plus LDL-C ≥70 mg/dL and ≤160 mg/dL
2. Intermediate or higher risk for ASCVD: No clinical ASCVD with a ≥7.5% 10-year risk of an ASCVD event and/or an ASCVD-risk-equivalent plus LDL-C ≥100 mg/dL and ≤200 mg/dL
3. Borderline risk for ASCVD: No clinical ASCVD with a ≥5.0% and ≤7.5% 10-year risk of an ASCVD event plus LDL-C ≥130 mg/dL and ≤250mg/dL

MK-0616 6 MG (N=77), 12 MG (N=76), 18 MG (N=76) OR 30 MG (N=76) DOSE

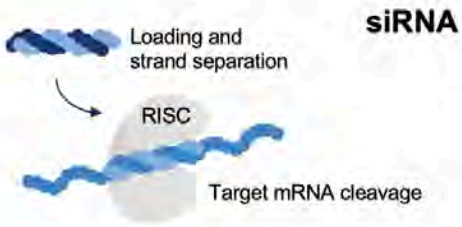
VS.

PLACEBO (N=75)

RNA-based Therapeutics Utilize Different Technologies

Types of RNA therapy[1]

siRNA

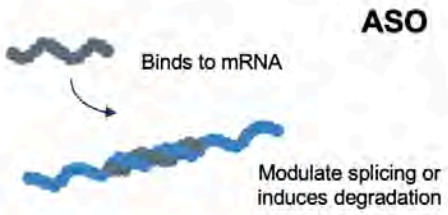


Target: mRNA[2]

Site of action: cytoplasm[2]

Mechanism: double-stranded RISC mechanism[2]

Antisense RNA

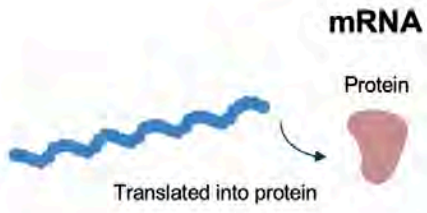


Target: mRNA[2]

Site of action: nucleus and cytoplasm[3]

Mechanism: Single-stranded RNase H mechanism[2]

mRNA

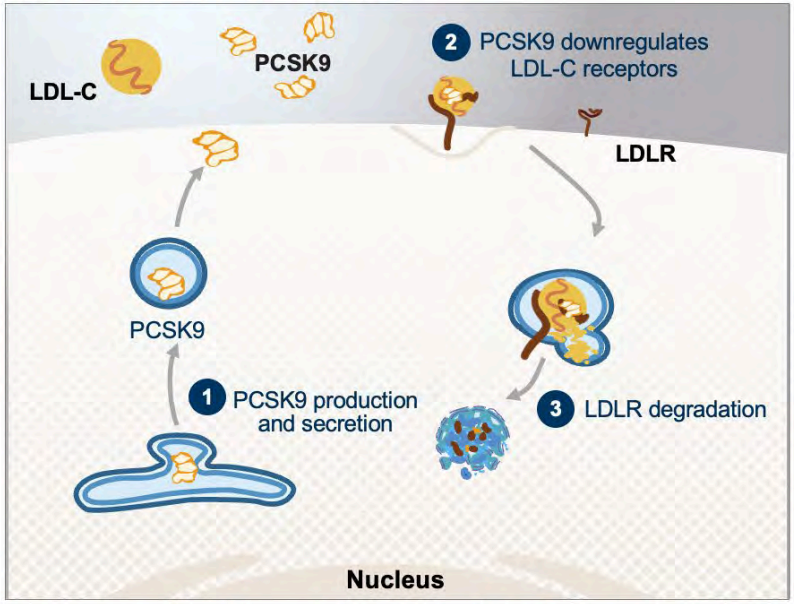


Target: protein manufacturing mechanisms[4]

Site of action: cytoplasm[4]

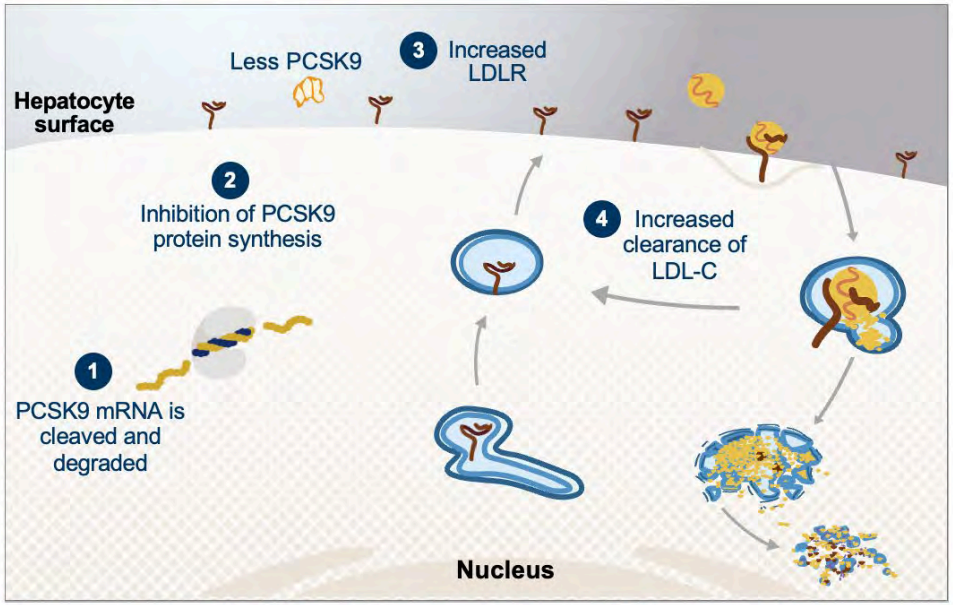
Mechanism: mRNA introduced into the cell is translated into a protein, which functions as either an enzyme or an antigen[1]

How does PCSK9 work?



PCSK9 is produced and secreted from hepatocytes → PCSK9 binds LDLR enhancing their degradation → Reduced LDLR leads to increased serum LDL-C levels

How does inclisiran work?



Inclisiran prevents the production of PCSK9 protein → Less PCSK9 allows for increased LDLR and greater uptake of circulating LDL-C → Increased LDL-C clearance leads to reduced serum LDL-C levels

ORION-10:

Reduction of LDL-C in Patients With ASCVD on Maximally Tolerated Statin Therapy*

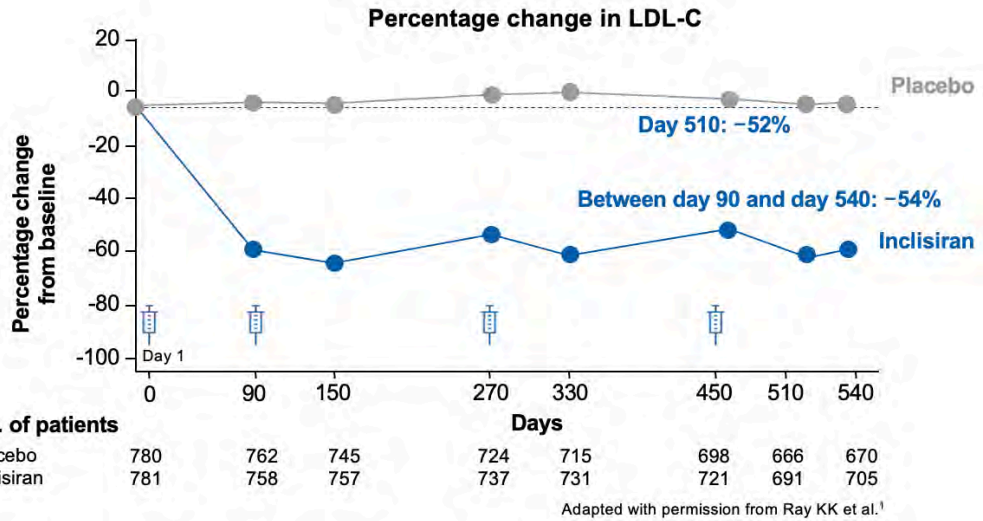
Similar efficacy achieved in ORION-11

52% ▼
effective
LDL-C reduction

difference from placebo at day 510†
(95% CI, −55.7% to −48.8%; *P*<.001)

54% ▼
sustained
LDL-C reduction

between-group difference after day 90 and up to day 540†,‡
(95% CI, −56.2% to −51.3%; *P*<.001)



No. of patients								
Placebo	780	762	745	724	715	698	666	670
Inclisiran	781	758	757	737	731	721	691	705

Adapted with permission from Ray KK et al.[1]

Homozygous Familial Hypercholesterolemia

AHA-recommended diagnostic criteria for HoFH

Clinical

- LDL-C ≥400 mg/dL and 1 or both parents have clinically diagnosed FH, positive genetic testing for an LDL-C raising (LDLR, ApoB, or PCSK9) gene defect, or autosomal-recessive FH[1]*
- LDL-C >560 mg/dL or LDL-C >400 mg/dL with aortic valve disease or xanthomas at <20 years of age[1]*
- **Individuals diagnosed by clinical criteria, regardless of genetic diagnosis, should be eligible for HoFH LLTs[1]**

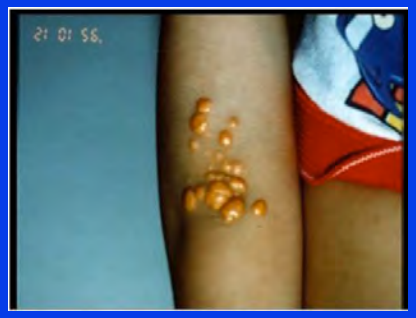
*These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH.[2]

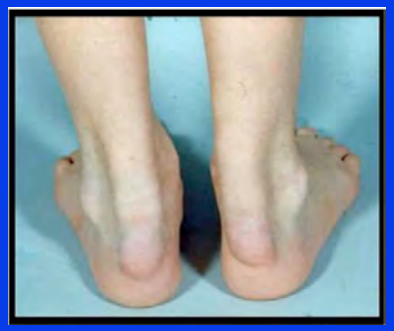
Genetic

- Presence of 2 identical (homozygote) or 2 nonidentical (compound or double heterozygous FH) abnormal LDL-C–raising gene defects (eg, most commonly LDLR, ApoB, PCSK9, or LDLRAP1)[1,2]
- There are additional mutations not yet characterized, and genetics alone may be inconclusive[1,2]

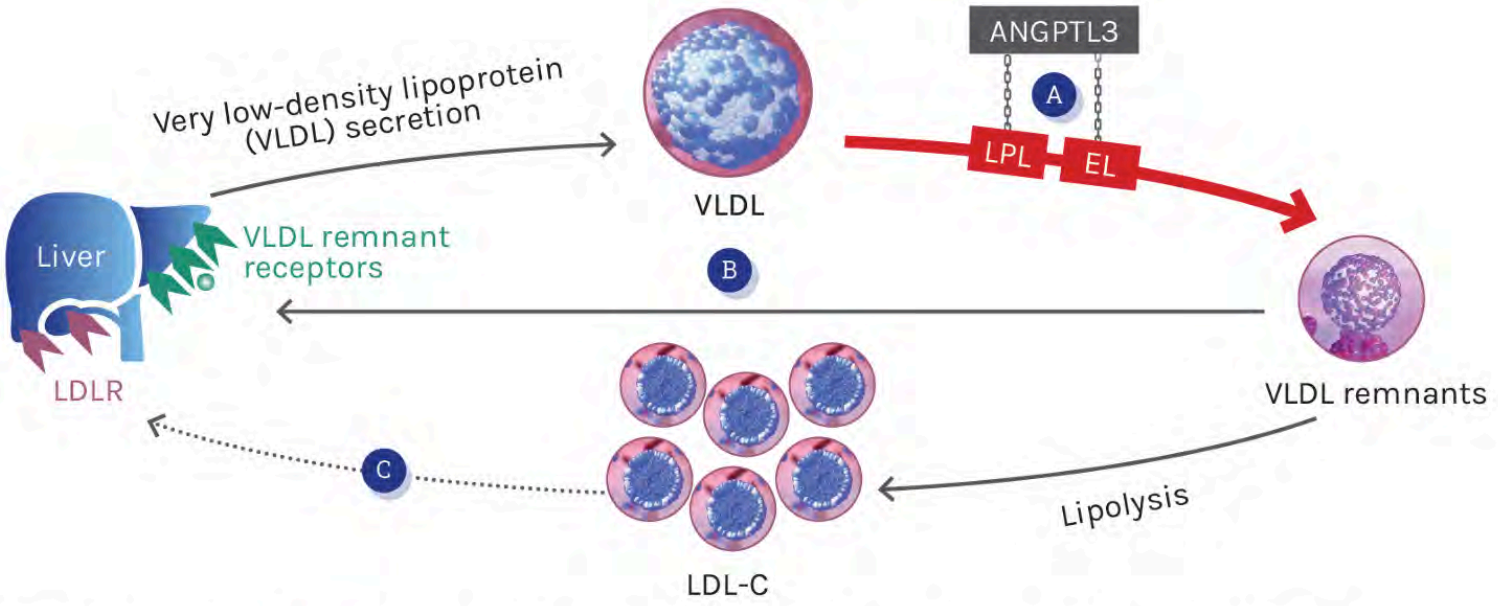
AHA=American Heart Association; ApoB=apolipoprotein B; FH=familial hypercholesterolemia; HoFH=homozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; LDLR=low-density lipoprotein receptor; LDLRAP1=low-density lipoprotein receptor adapter protein 1; LLT=lipid-lowering therapy; PCSK9=proprotein convertase subtilisin/kexin type 9.

References: 1. Gidding SS, et al. *Circulation.* 2015;132:2167-2192. **2.** Cuchel M, et al. *Eur Heart J.* 2014;35(32):2146-2157.





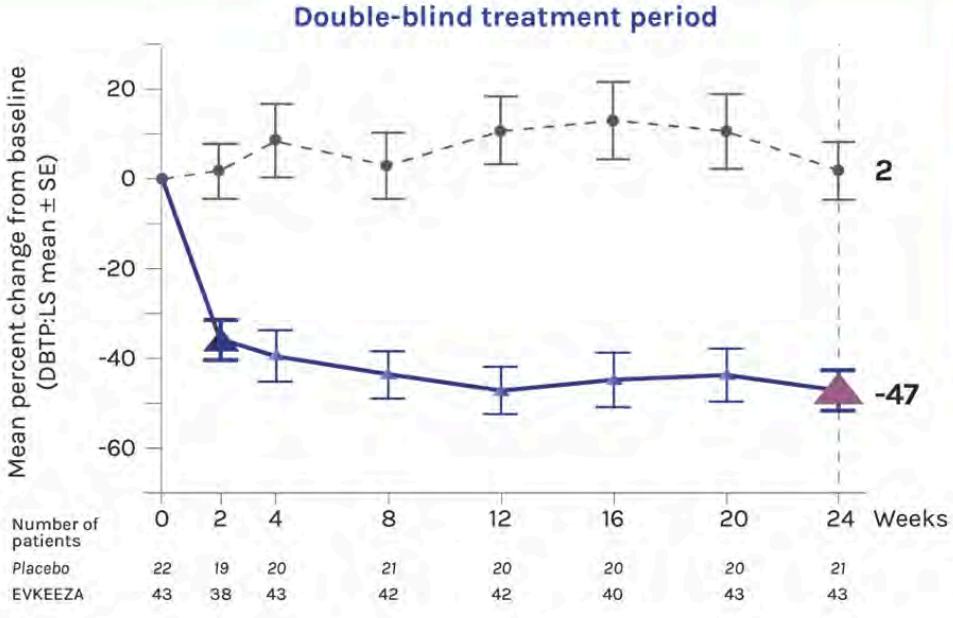
Patients with HoFH have increased LDL-C due to diminished or absent LDL-receptor (LDLR) function[1,2]



ANGPTL3=angiopoietin-like 3; EL=endothelial lipase; HoFH=homozygous familial hypercholesterolemia; LDL-C=low-density lipoprotein cholesterol; LDLR=LDL-receptor; LPL=lipoprotein lipase.

References: 1. EVKEEZA Prescribing Information. Tarrytown, NY: Regeneron Pharmaceuticals; 2021. **2.** Adam RC, et al. *J Lipid Res.* 2020;61(9):1271-1286.

Calculated LDL-C LS mean percent change from baseline over time through week 24[1]



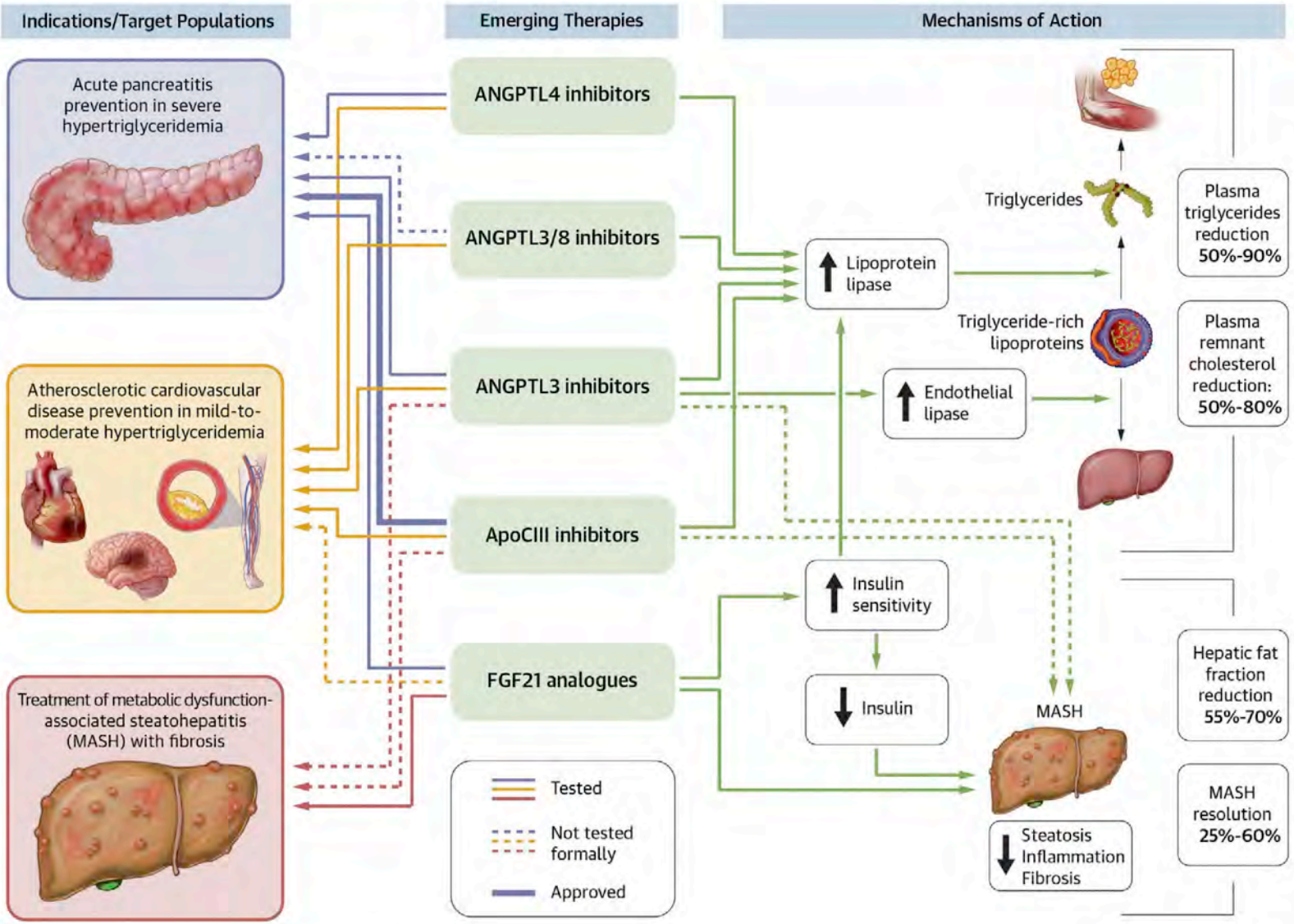
Approximately **50%** **LDL-C reduction**

At week 24, the LS mean treatment difference in LDL-C from baseline between EVKEEZA and placebo was -49% (95% CI: -65% to -33%; $P<0.0001$)[1]

CI=confidence interval;
DBTP=double-blind treatment period;
LDL-C=low-density lipoprotein cholesterol;
LLT=lipid-lowering therapy; LS=least squares;
SE=standard error.

References: 1. EVKEEZA Prescribing information. Tarrytown, NY: Regeneron Pharmaceuticals; 2021.
2. Raal FJ, et al. *N Engl J Med.* 2020;383(8):711-720.

CENTRAL ILLUSTRATION: Target Populations, Mechanisms of Action, and Approved or Potential Indications of ApoCIII Inhibitors, ANGPTL3, ANGPTL3/8, and ANGPTL4 Inhibitors, and FGF-21 Analogues



Nordestgaard AT, et al. JACC. 2025;85(19):1876-1897.

The Guidelines

Lots of ‘em…

Guideline Recommendations Endorse Even Lower LDL-C Goals

2018 AHA/ACC guidelines[1]

Clinical ASCVD

LDL-C reduction

≥50%

Very high-risk ASCVD*

LDL-C reduction to

<70 mg/dL

(**1.8** mmol/L)

2019 ESC/EAS guidelines[2]

LDL-C reduction

≥50%

AND

High CV risk

LDL-C reduction to

<70 mg/dL

(**1.8** mmol/L)

Very high CV risk

LDL-C reduction to

<55 mg/dL

(**1.4** mmol/L)

2019 ADA guidelines[3]

Diabetes and ASCVD

LDL-C reduction to

<70 mg/dL

(**1.8** mmol/L)

2017 AACE/ACE guidelines[4]

Very high CV risk†

LDL-C reduction to

<70 mg/dL

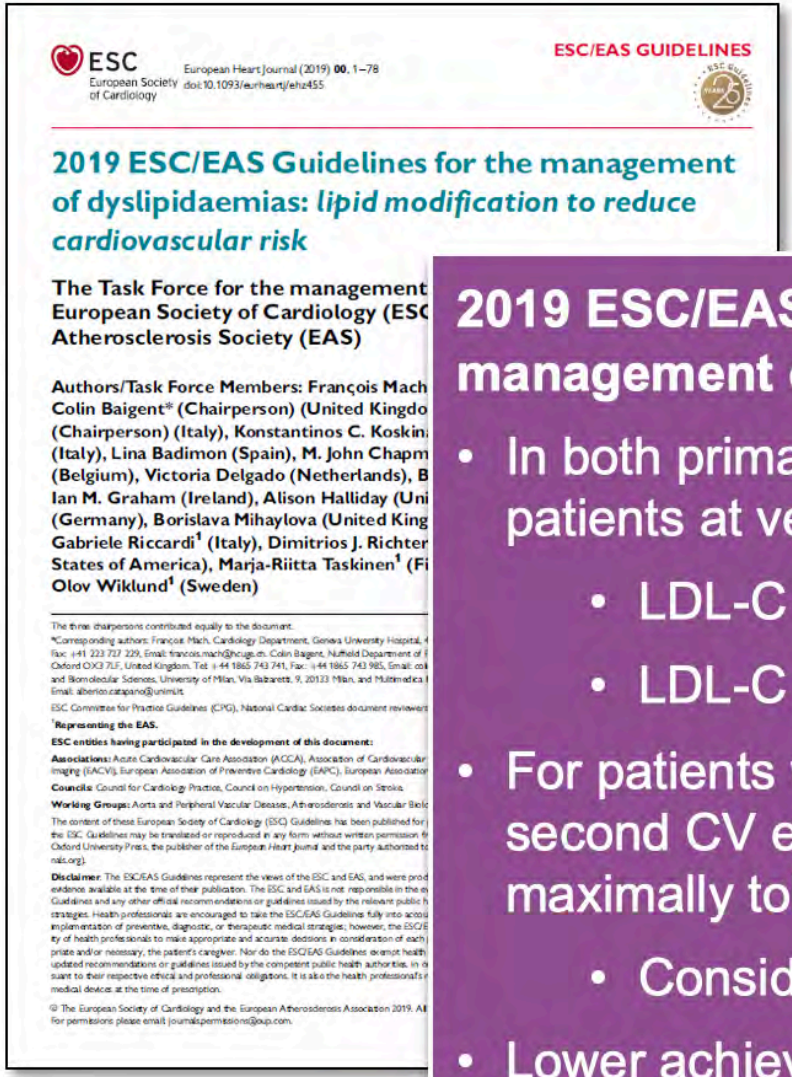
(**1.8** mmol/L)

Extreme CV risk‡

LDL-C reduction to

<55 mg/dL

(**1.4** mmol/L)



ESC European Society of Cardiology

European Heart Journal (2019) 00, 1–78
doi:10.1093/eurheartj/ehz455

ESC/EAS GUIDELINES

2019 ESC/EAS Guidelines for the management of dyslipidaemias: *lipid modification to reduce cardiovascular risk*

The Task Force for the management
European Society of Cardiology (ESC
Atherosclerosis Society (EAS)

Authors/Task Force Members: François Mach
Colin Baigent* (Chairperson) (United Kingdo
(Chairperson) (Italy), Konstantinos C. Koskin
(Italy), Lina Badimon (Spain), M. John Chapm
(Belgium), Victoria Delgado (Netherlands), B
Ian M. Graham (Ireland), Alison Halliday (Uni
(Germany), Borislava Mihaylova (United King
Gabriele Riccardi[1] (Italy), Dimitrios J. Richter
States of America), Marja-Riitta Taskinen[1] (Fi
Olov Wiklund[1] (Sweden)

The three chairpersons contributed equally to the document.

*Corresponding authors: François Mach, Cardiology Department, Geneva University Hospital,
Fax: +41 223 727 229, Email: francois.mach@hcuge.ch. Colin Baigent, Nuffield Department of
Oxford OX3 7LF, United Kingdom. Tel: +44 1865 743 741, Fax: +44 1865 743 985, Email: col
and Biomolecular Sciences, University of Milan, Via Balzaretti, 9, 20133 Milan, and Multimedica
Email: alberico.catapano@unimi.it

ESC Committee for Practice Guidelines (CPG), National Cardiac Societies document reviewers

[1]Representing the EAS.

ESC entities having participated in the development of this document:

Associations: Acute Cardiovascular Care Association (ACCA), Association of Cardiovascular
Imaging (EACVI), European Association of Preventive Cardiology (EAPC), European Associatio

Councils: Council for Cardiology Practice, Council on Hypertension, Council on Stroke.

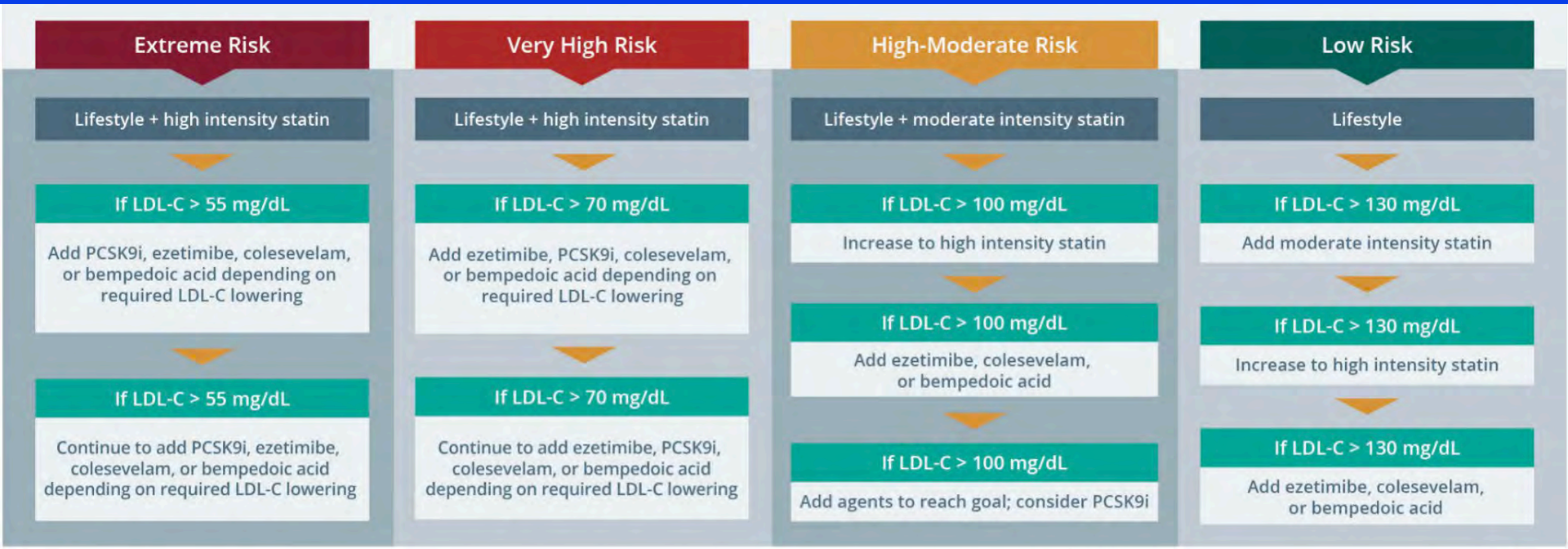
Working Groups: Aorta and Peripheral Vascular Diseases, Atherosclerosis and Vascular Biol

Disclaimer: The ESC/EAS Guidelines represent the views of the ESC and EAS, and were pro
evidence available at the time of their publication. The ESC and EAS is not responsible in the e
Guidelines and any other official recommendations or guidelines issued by the relevant public h
strategies. Health professionals are encouraged to take the ESC/EAS Guidelines fully into accou
implementation of preventive, diagnostic, or therapeutic medical strategies; however, the ESC/E
ty of health professionals to make appropriate and accurate decisions in consideration of each
priate and/or necessary, the patient's caregiver. Nor do the ESC/EAS Guidelines exempt health
updated recommendations or guidelines issued by the competent public health authorities, in
suant to their respective ethical and professional obligations. It is also the health professional's
medical devices at the time of prescription.

2019 ESC/EAS guidelines for the management of dyslipidemias[2]

- In both primary and secondary prevention for patients at very high risk[b]
  - LDL-C reduction of ≥50%
  - LDL-C goal of <55 mg/dL
- For patients with ASCVD who experience a second CV event within 2 years while taking maximally tolerated statin therapy
  - Consider LDL-C goal of <40 mg/dL
- Lower achieved LDL-C levels are associated with lower risk of future cardiovascular events, with no lower limit for LDL-C values[2]

AACE 2020 - Treat LDL to Goal



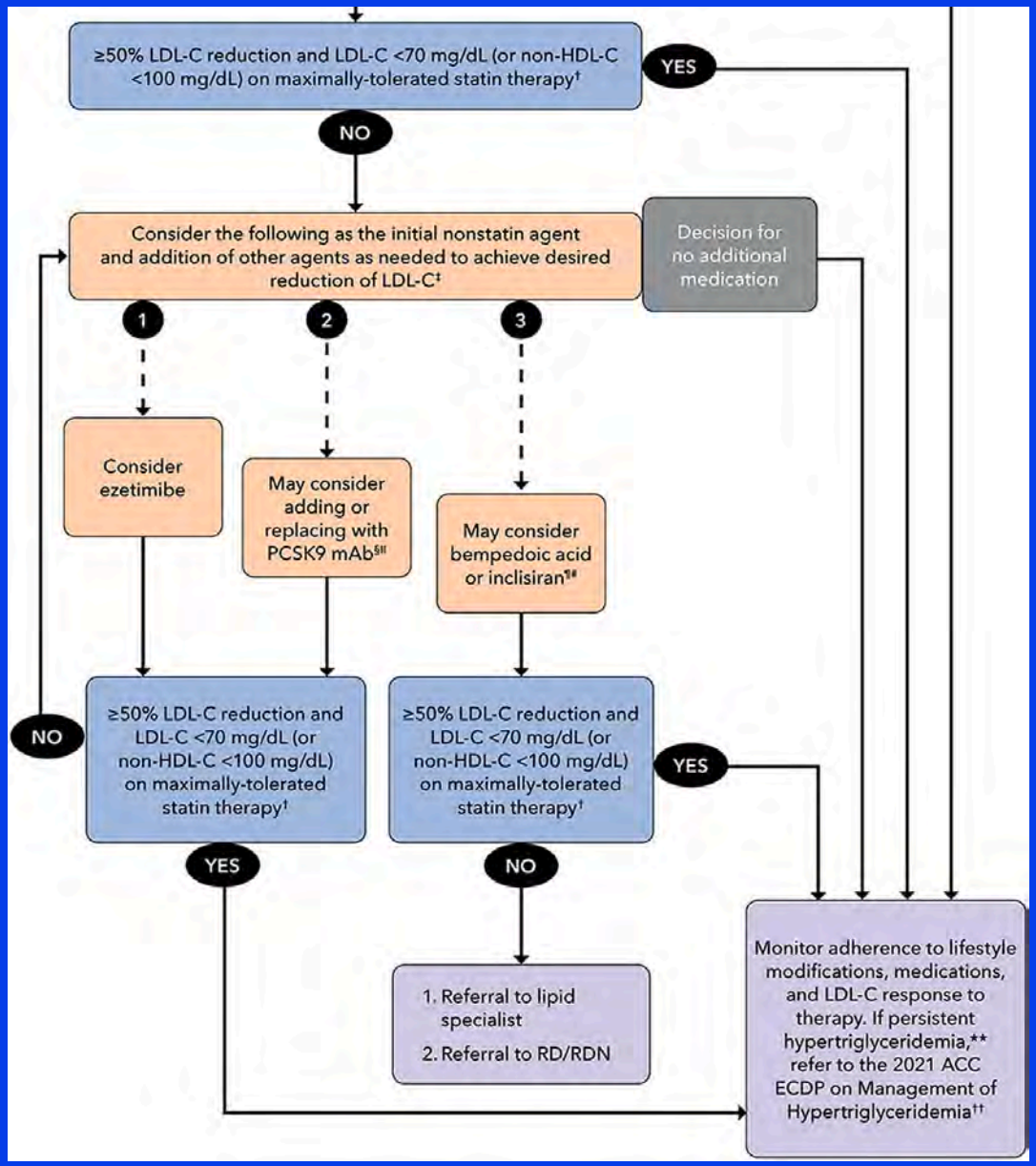
CHECK LIPIDS EVERY 3 MONTHS OR MORE FREQUENTLY WHEN NECESSARY

HIGH-INTENSITY STATIN THERAPY	MODERATE-INTENSITY STATIN THERAPY				EZETIMIBE	PCSK9 INHIBITORS	COLESEVELAM	BEMPEDOIC ACID
Atorvastatin 40–80 mg	Rosuvastatin 5–10 mg	Atorvastatin 10–20 mg	Simvastatin 20–40 mg	Pitavastatin 2–4 mg	Ezetimibe 10 mg	Evolocumab 140 mg Q2W, 420 mg Q4W	Colesevelam 3.75 mg	Bempedoic Acid 180 mg
Rosuvastatin 20–40 mg	Fluvastatin XL 80 mg	Fluvastatin 40 mg BID	Pravastatin 40–80 mg	Lovastatin 40 mg		Alirocumab 75-150 mg Q2W		

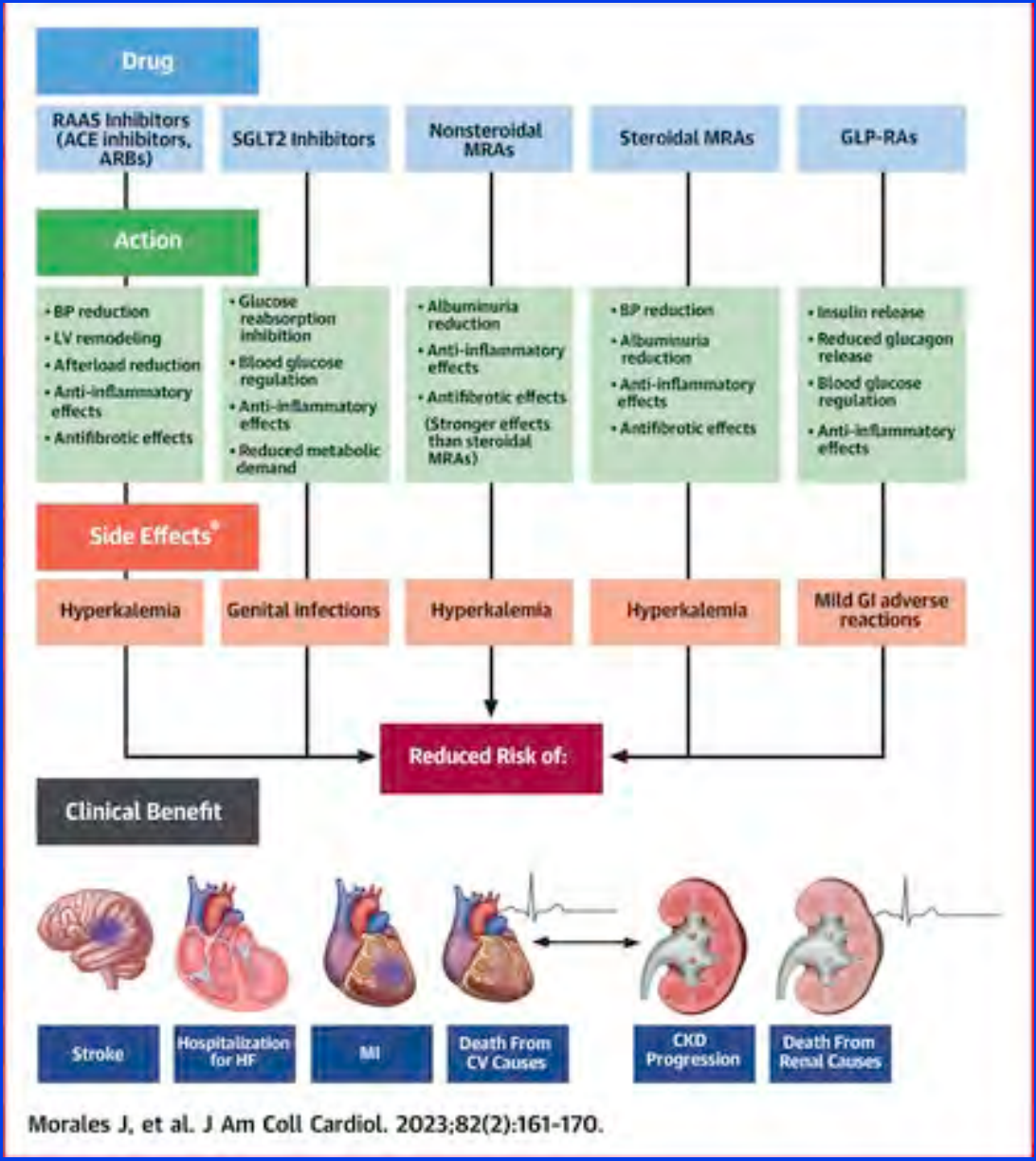
When LDL-C goal is achieved, please refer to TG and Lp(a) slides.

Abbreviations: BID = twice daily; LDL-C = low-density lipoprotein cholesterol; PCSK9i = proprotein convertase subtilisin/kexin type 9 inhibitor; Q2W once every 2 weeks; TG = triglyceride.

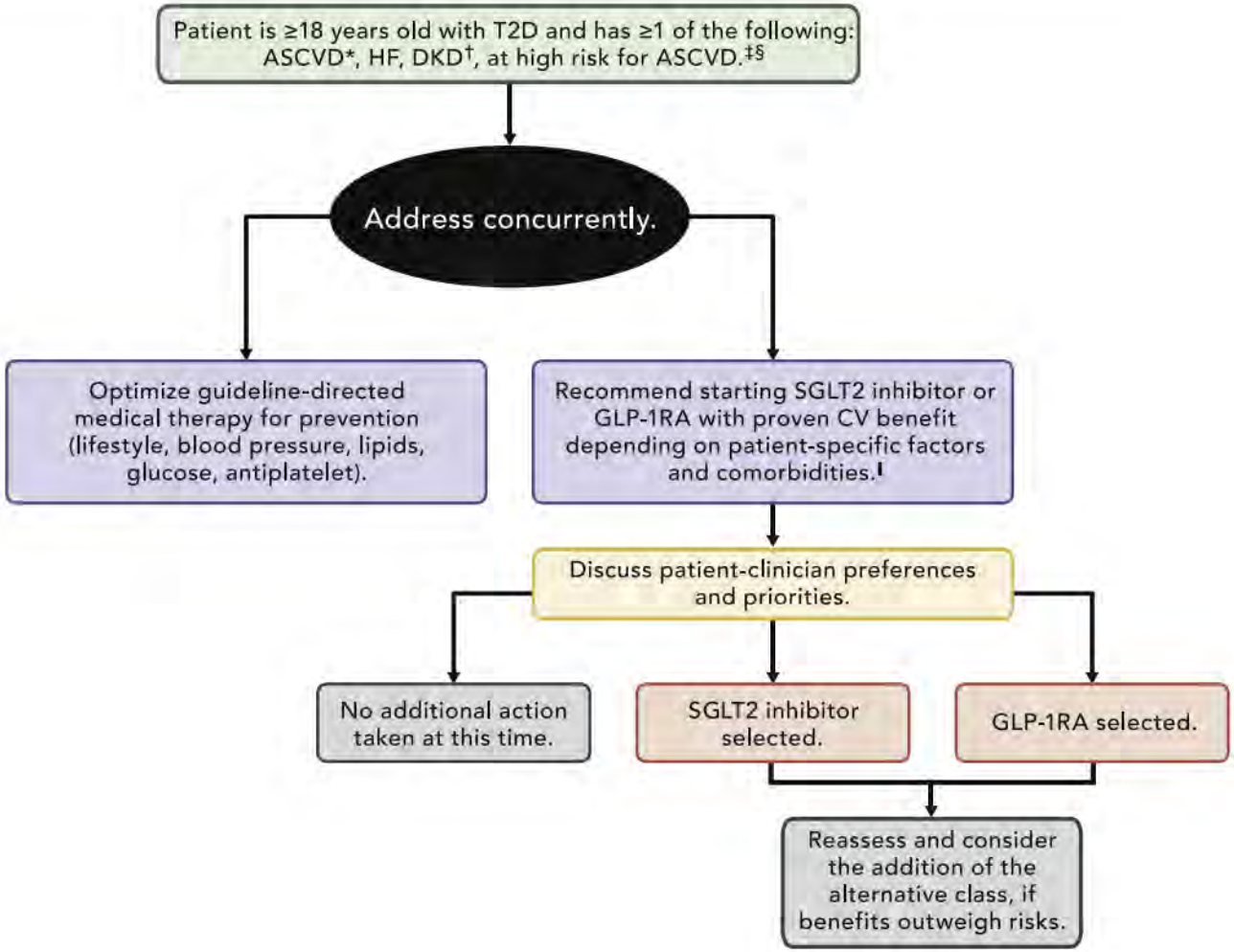
2022 ACC/AHA ECDP Guidelines



Reduction of CV Risk in DM/CKD



Morales J, et al. J Am Coll Cardiol. 2023;82(2):161-170.



*ASCVD is defined as a history of an acute coronary syndrome or MI, stable or unstable angina, coronary heart disease with or without revascularization, other arterial revascularization, stroke, or peripheral artery disease assumed to be atherosclerotic in origin.

†DKD is a clinical diagnosis marked by reduced eGFR, the presence of albuminuria, or both.

‡ Consider an SGLT2 inhibitor when your patient has established ASCVD, HF, DKD or is at high risk for ASCVD. Consider a GLP-1RA when your patient has established ASCVD or is at high risk for ASCVD.

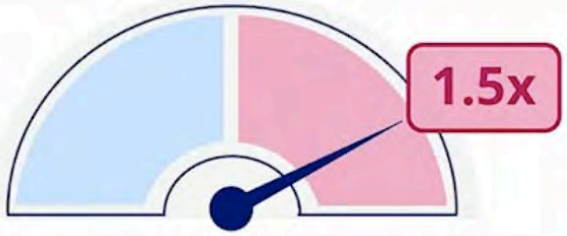
§ Patients at high risk for ASCVD include those with end organ damage such as left ventricular hypertrophy or retinopathy or with multiple CV risk factors (e.g., age, hypertension, smoking, dyslipidemia, obesity).

ǁ Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; DKD = diabetic kidney disease; eGFR = estimated glomerular filtration rate; GLP-1RA = glucagon-like peptide-1 receptor agonist; HF = heart failure; MI = myocardial infarction; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes

Albuminuria Is a CVD Risk Factor[1,2,a]

Increased albuminuria in patients with T2D is associated with[3,4]:

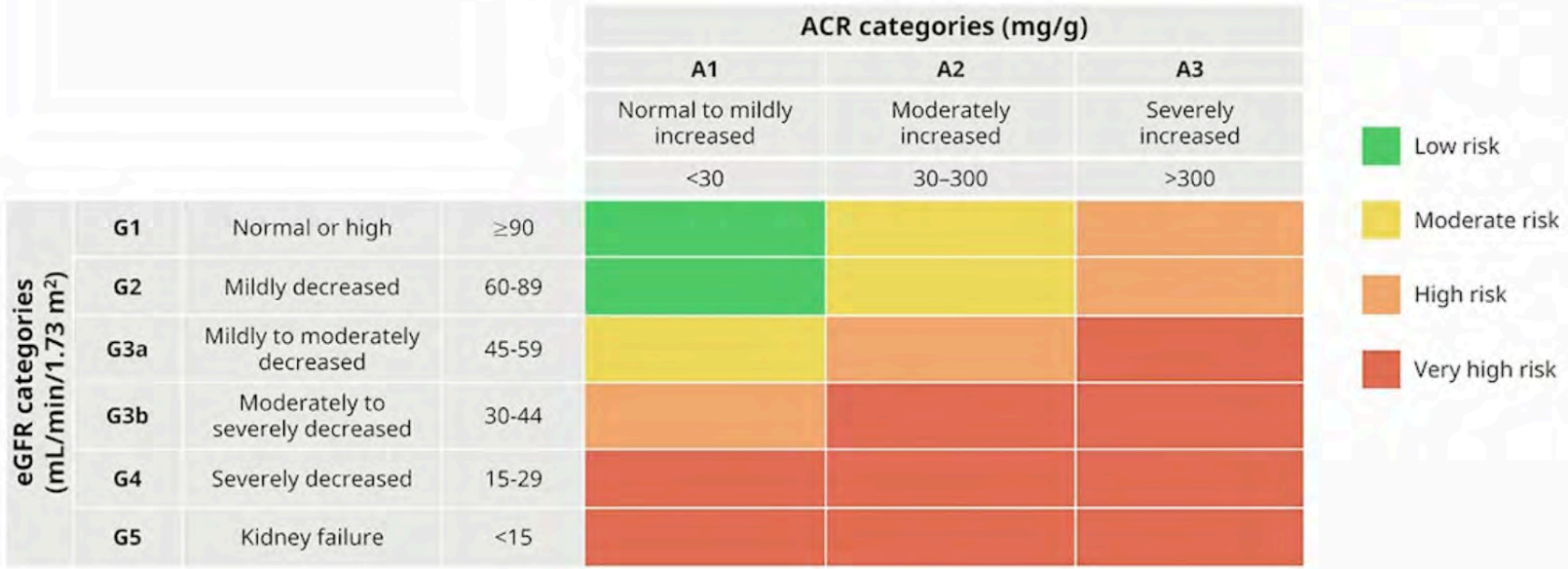


ACR values ≥30 mg/g were associated with a **50% increased risk for a CV event in patients with T2D[2]**

2024 KDIGO Guideline

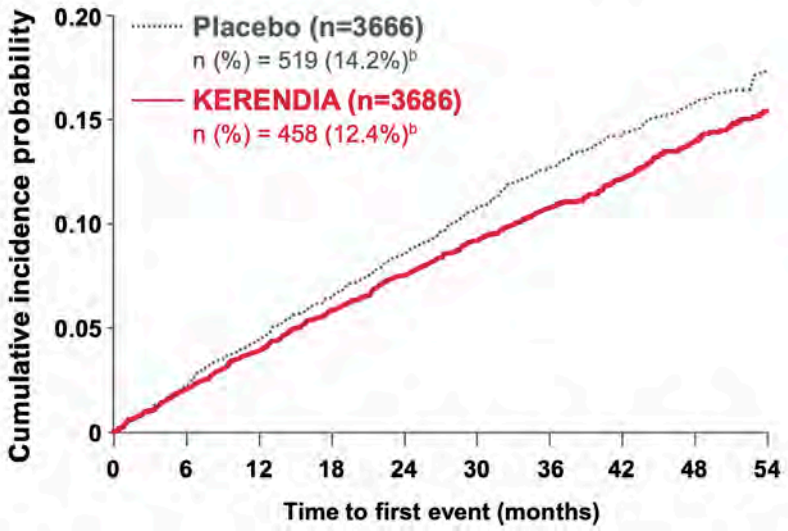
Prognosis of CKD Is Staged by Values of Both eGFR and ACR

Prognosis of CKD by eGFR and albuminuria categories



Finerone Reduced CV endpoints in DM+CKD On top of ACEi/ARB

The treatment effect was mainly driven by an effect on HHF, though CV death also contributed to the treatment effect[1]



13% RRR[1]
HR=0.87
(95% CI, 0.76-0.98)
P=0.026

At 3.5 years

NNT: 47
(95% CI, 26-226)
to prevent a primary composite outcome event[2]

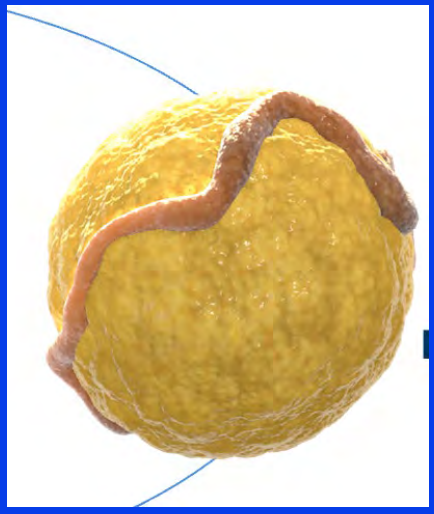
ARR: 2.1%
(95% CI, 0.4-3.8)[2]

The Sentara Cardiology

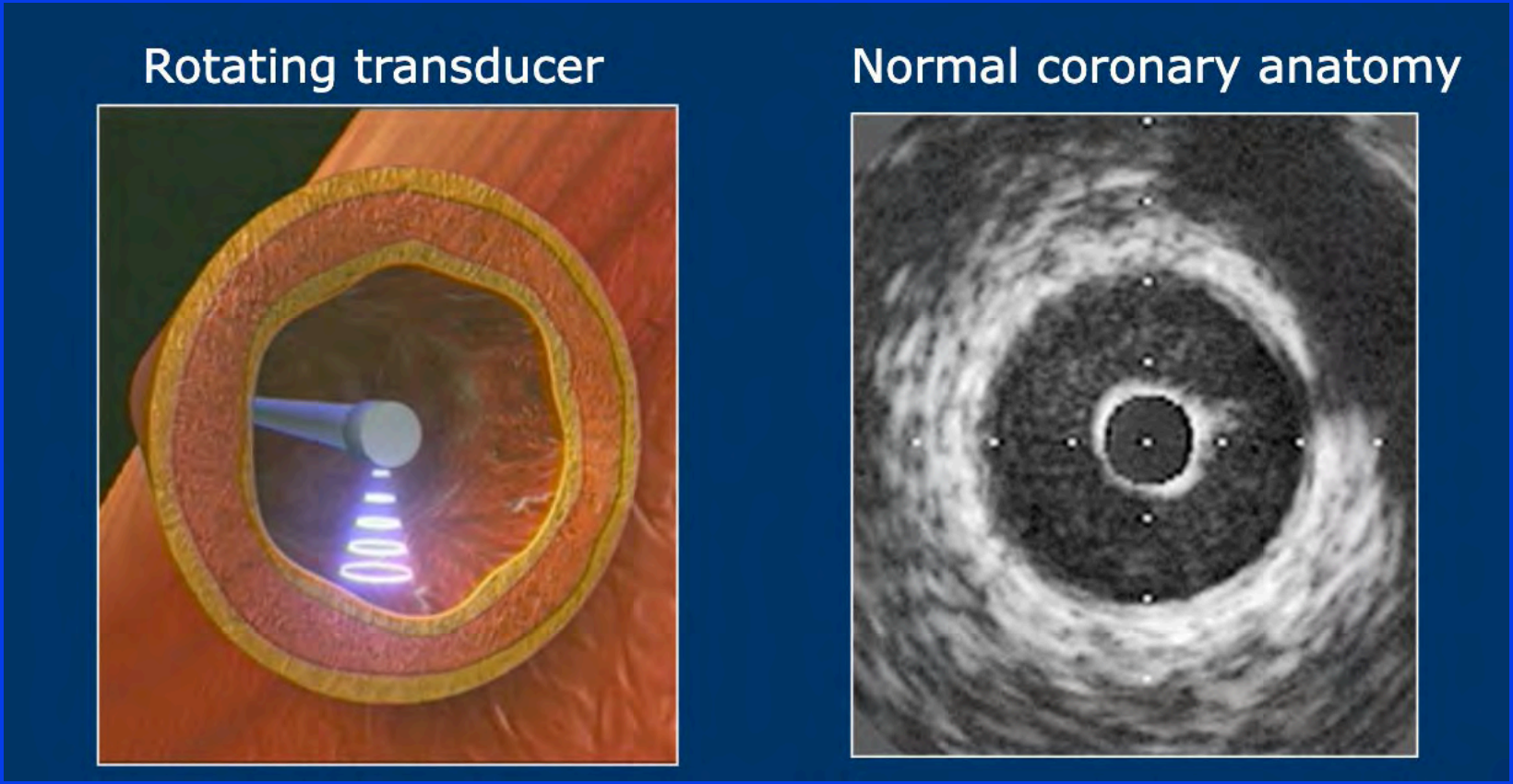
Lipid Program

SENTARA HEART™

Your community, not-for-profit health partner



Why Intensive Lipid Modification? –Some Good News

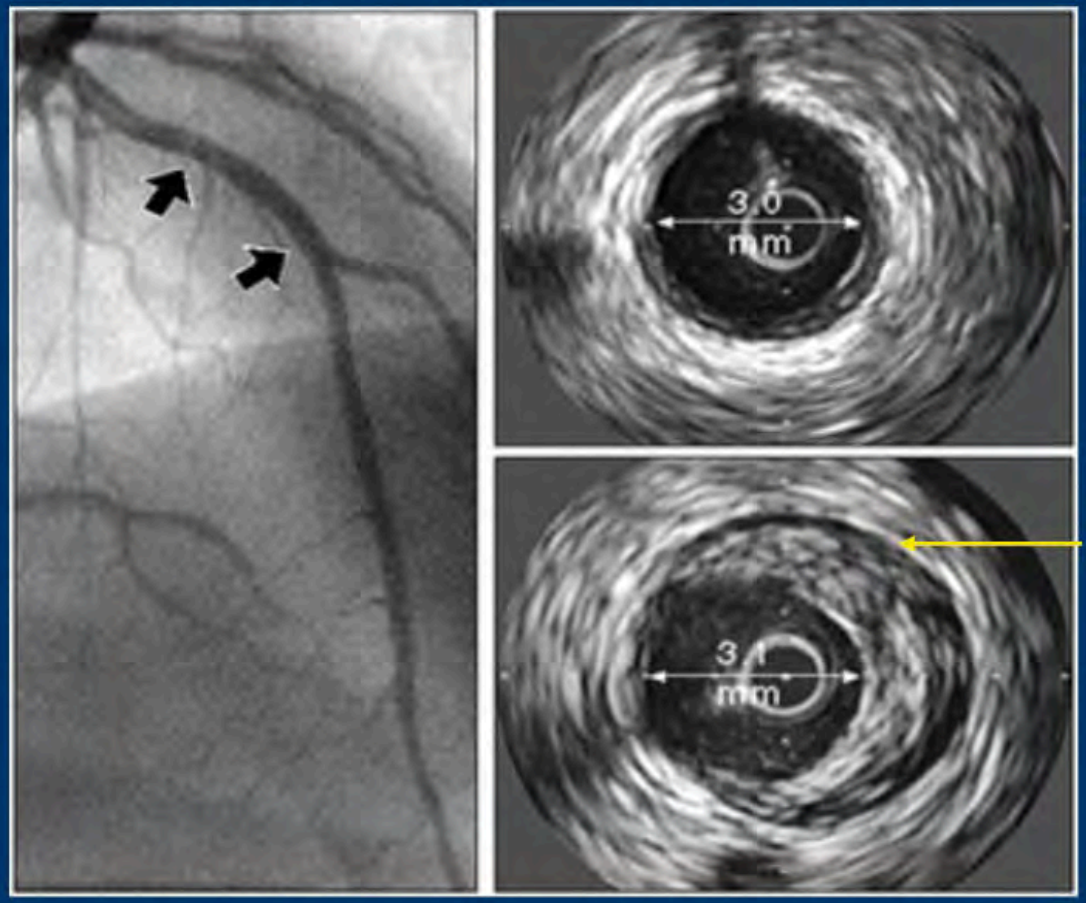


Asteroid Trial, 2006

Angiogram

No evidence of disease

IVUS



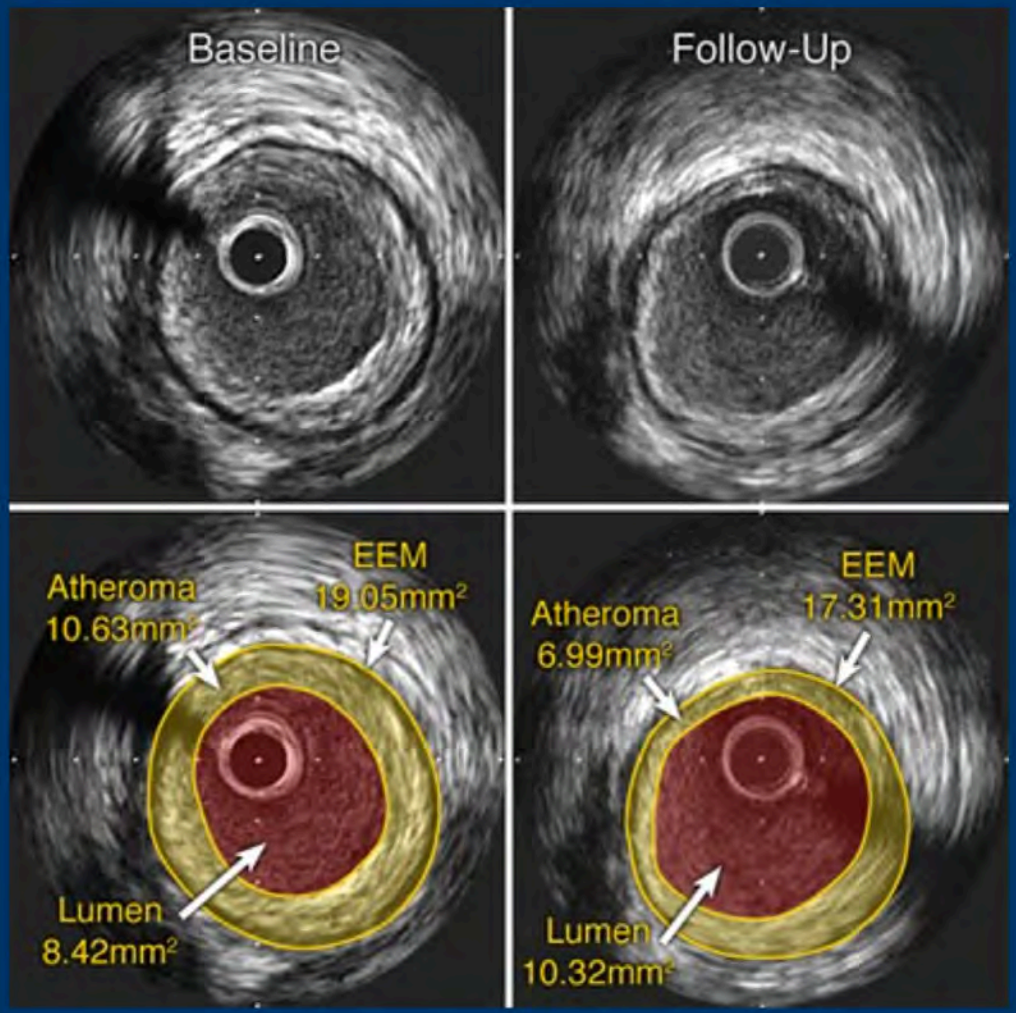
Little evidence of disease

Atheroma

Nissen S, Yock P. *Circulation* 2001;103:604–16.

Asteroid Trial, 2006

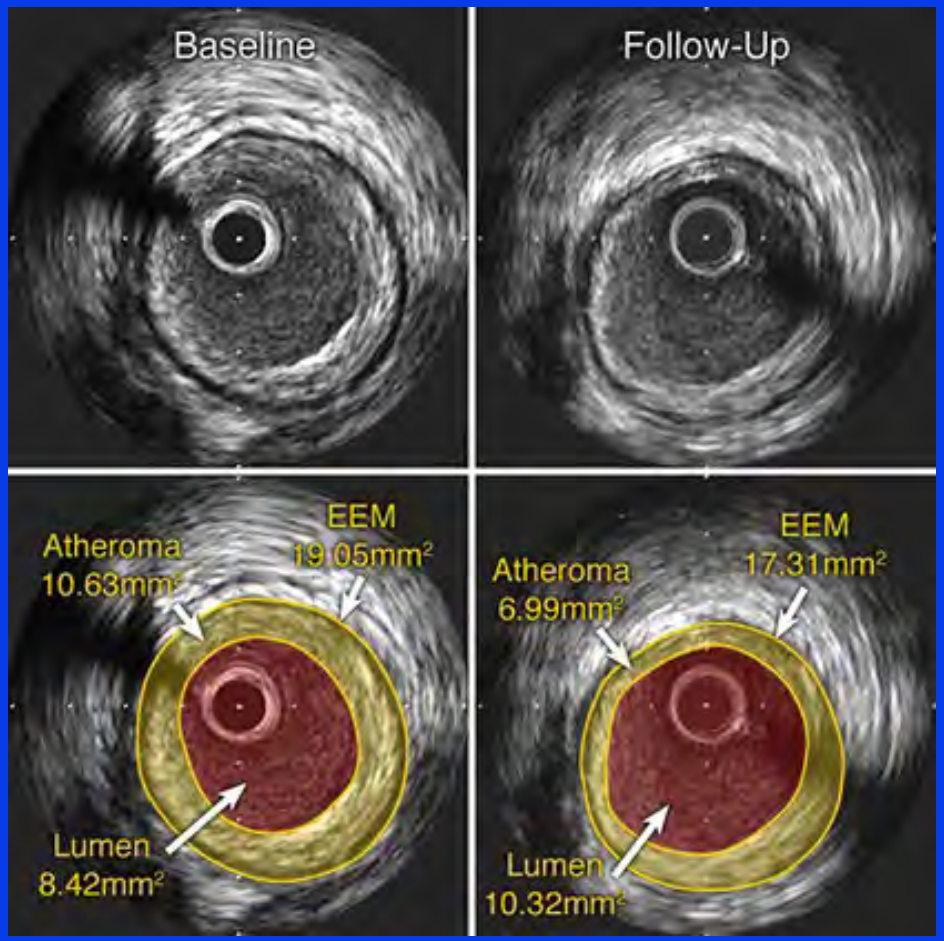
Example of Regression of Atherosclerosis with Rosuvastatin in ASTEROID (measured by IVUS)



Sipahi I, Nicholls S, Tuzcu E, Nissen S. Interpreting the ASTEROID trial: Coronary atherosclerosis can regress with very intensive statin therapy. *Cleve Clin J Med*, 2006; **73**:937-944.

Asteroid Trial, 2006

Why Intensive Lipid Modification?



Regression of Atherosclerosis in patients on Rosuvastatin the the Asteroid trial

Sipahi I, Nicholls S, Tuzcu E, Nissen S. Interpreting the ASTEROID trial: Coronary atherosclerosis can regress with very intensive statin therapy. *Cleve Clin J Med*, 2006; **73**:937-944.

THANK YOU!