Diabetes and Dyslipidemia: Recent Insights and Evolving Treatments

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The Endocrine Society: 8th Annual Dimensions in Diabetes, Mumbai, India; Oct 15-16, 2022

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  Regeneron

- Consultant/ Honoraria:
  Clinical Overview (Elsevier)

- Editorial Board
  Dynamed Plus

No Stocks or Options in any Pharma/Biotech

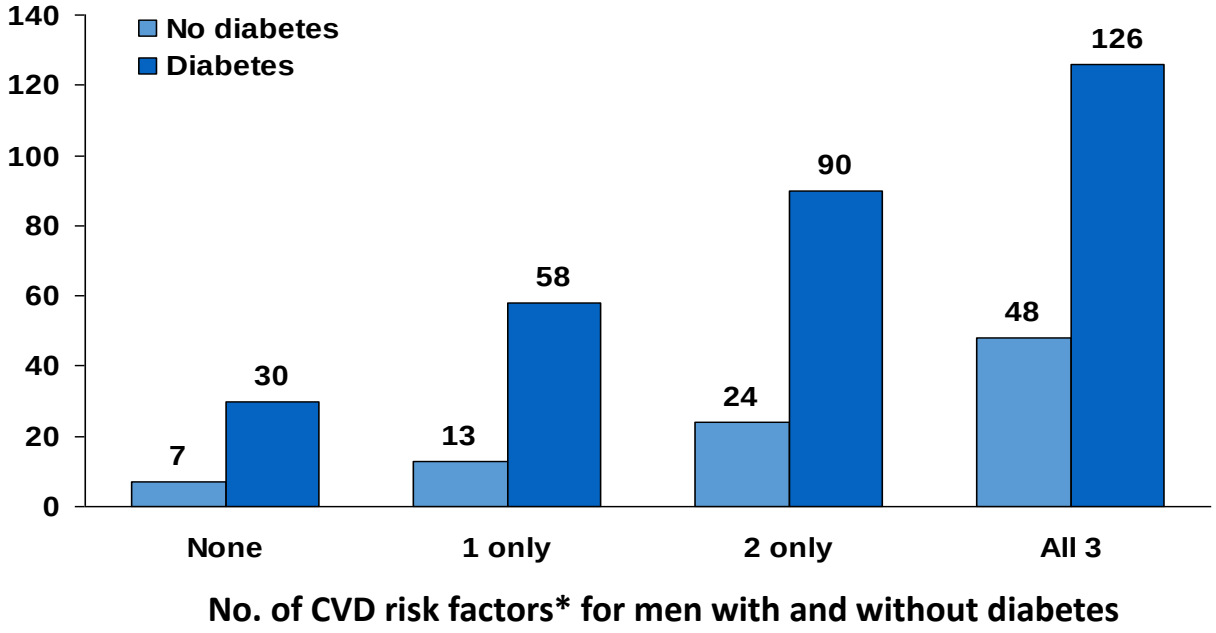
Jeremiah Stamler: Father of "Preventive Cardiology"

1999-2022

MRFIT:

Diabetes Increases CVD Risk, Regardless of Other Risk Factors

n~ 350,000, with ~ 5,500 with DM
Age-adjusted CVD death rate per 10,000 patient-yrs



No. of CVD risk factors* for men with and without diabetes

***serum cholesterol >200 mg/dL, smoking, and SBP >120 mm Hg**

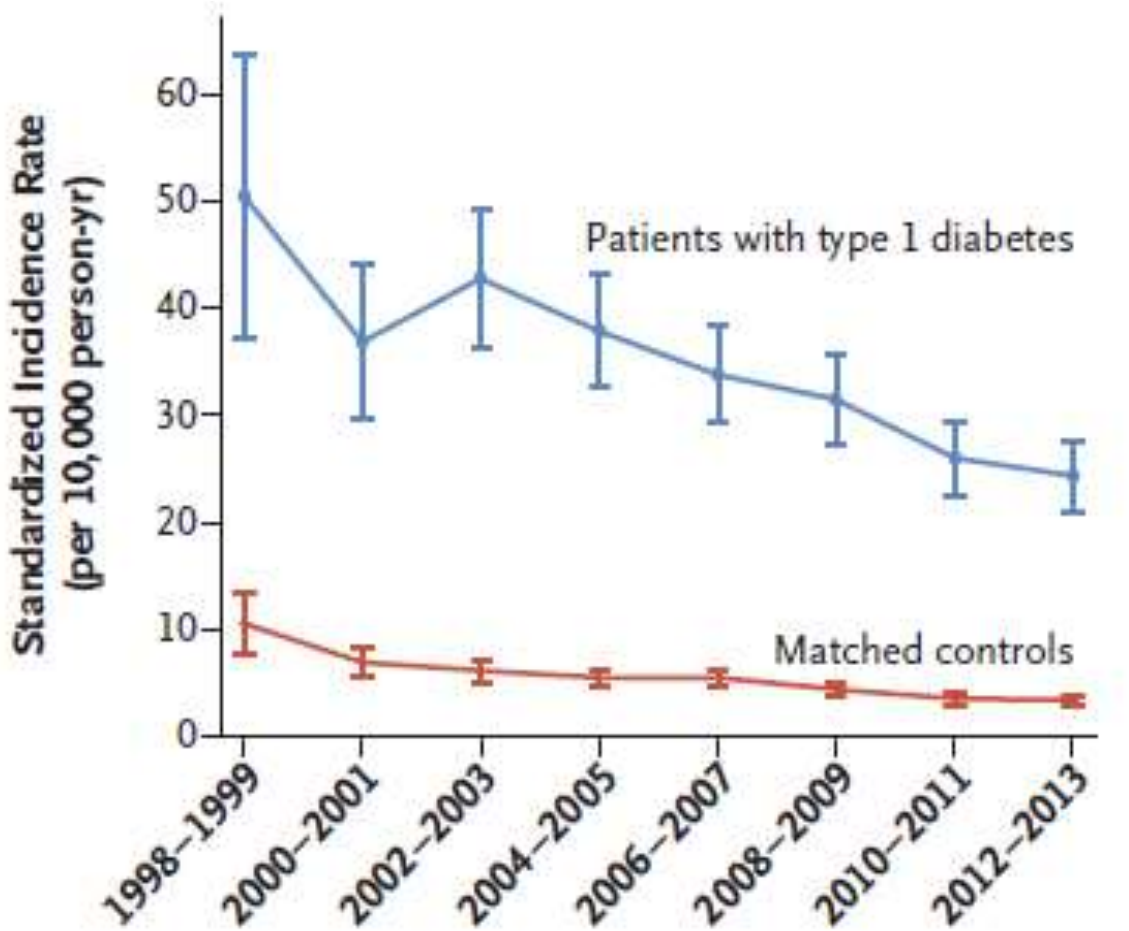
Stamler J, et al. *Diabetes Care*. 1993;16:434-444.

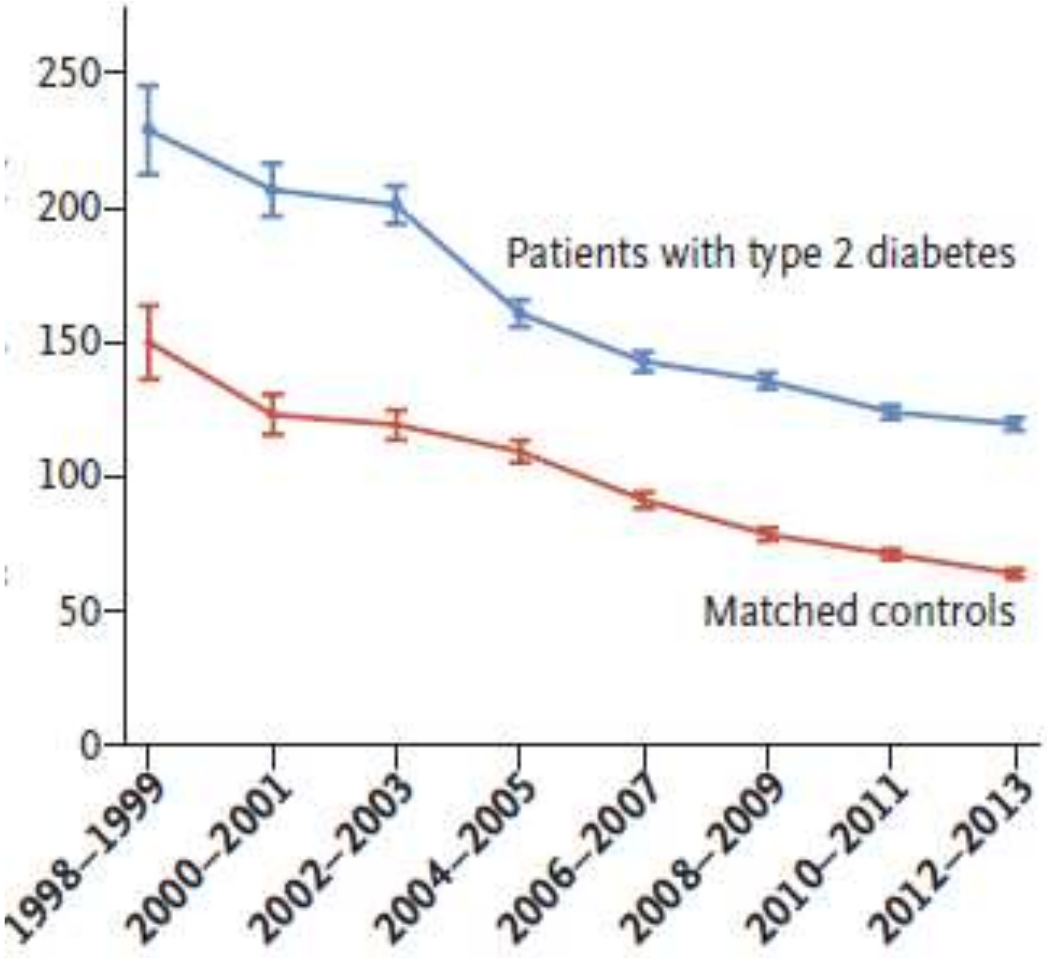
Learning Objectives

- Impact of diabetes on ACVD events
- Current approach to manage LDL-Cholesterol
- Novel and upcoming treatment options to achieve LDL-Cholesterol goals
- Rationale to manage dyslipidemia beyond LDL-Cholesterol, and current evidence-based options

Trends in CV Mortality in Type 1 and Type 2 DM

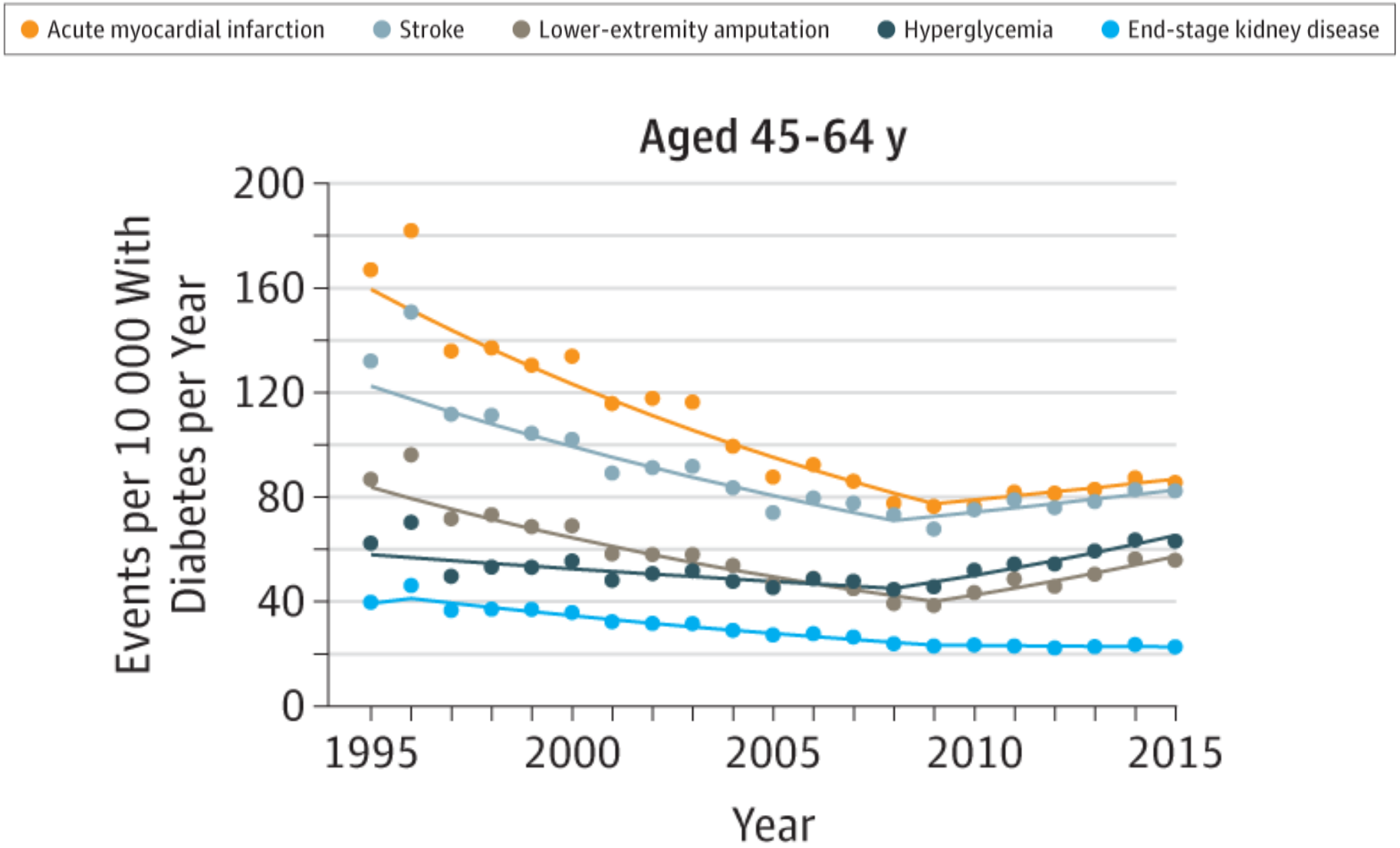
n ~ 37,000 T1, mean f/u 11.2 yr; ~ 457,000, T2DM, mean f/u 6.5 yr; age and –gender matched with controls





Rawshani, A et al NEJM 2017; 376: 1407-18

CVD Complications of Diabetes on the Rise



Gregg EW et al.. *JAMA*. 2019;321(19):1867–1868.

Incidence of ASCVD in South Asians vs Europeans

UK Databank prospective cohort

N=449,349 Europeans vs 8,124 south Asian

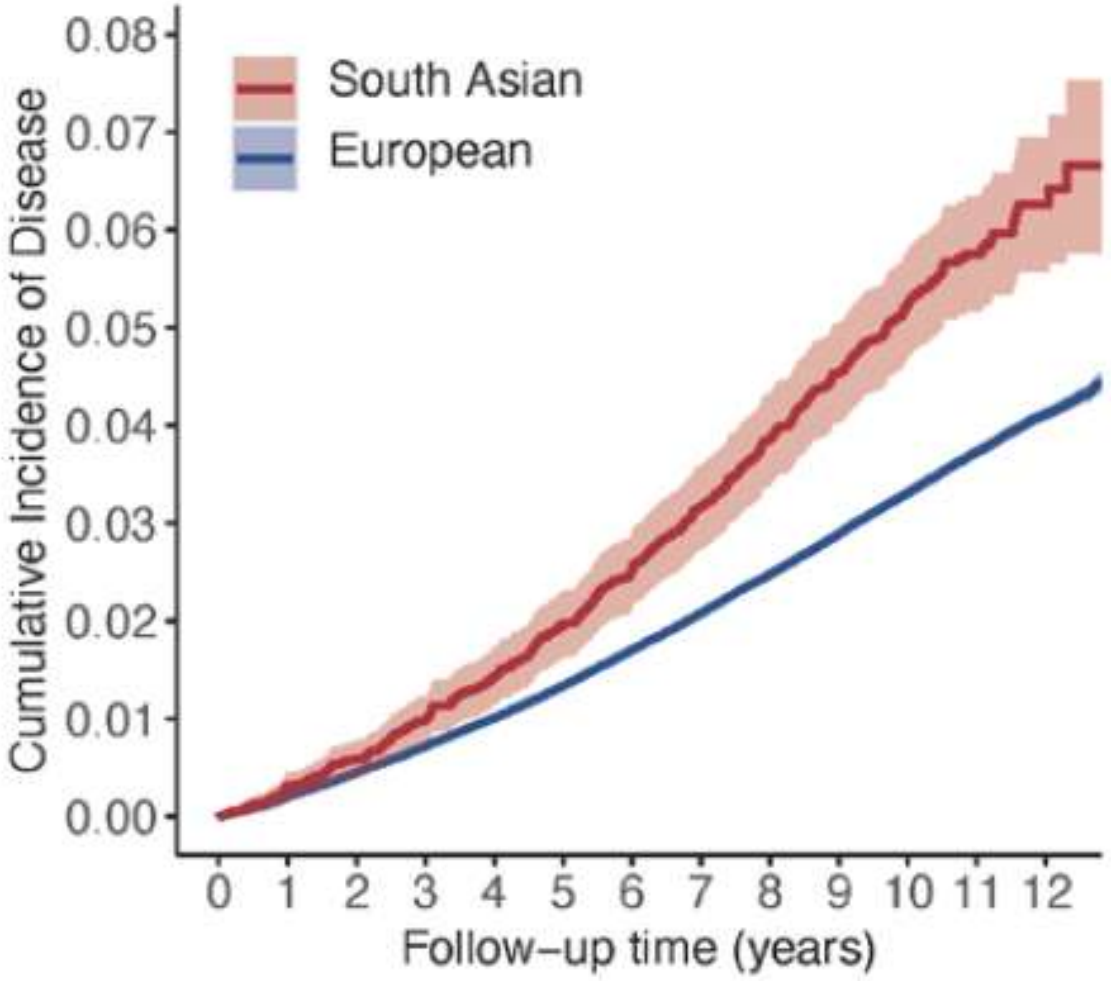
CVE: MI, Coronary revasc, or Ischemic stroke

Mean age, 57 yr; median f/u 11.0 yr

Unadjusted HR 2.03 (CI 1,86-2.22); p< 0.001

Adjusted HR 1.45 (1.28- 1.65); p< 0.011

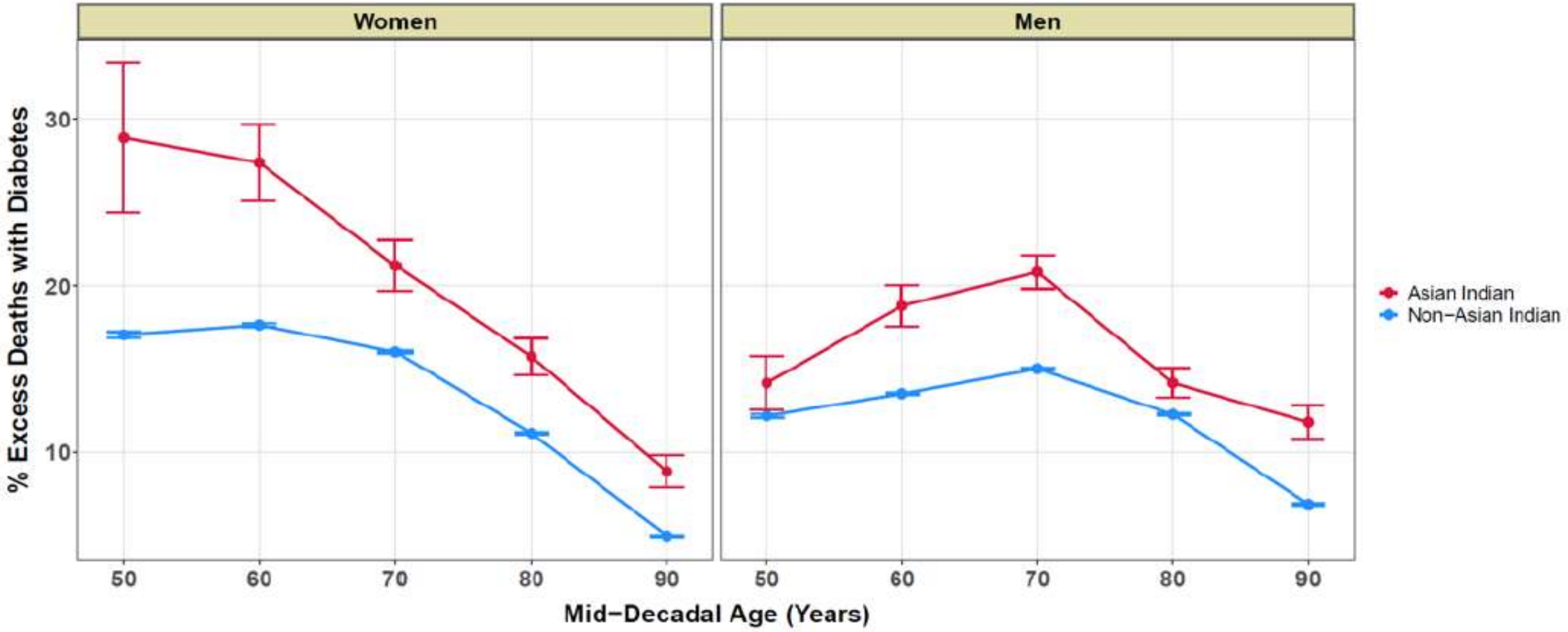
Major determinants: Diabetes, HBP, Central obesity



Patel AP et al Circulation 2021; 144: 410-22

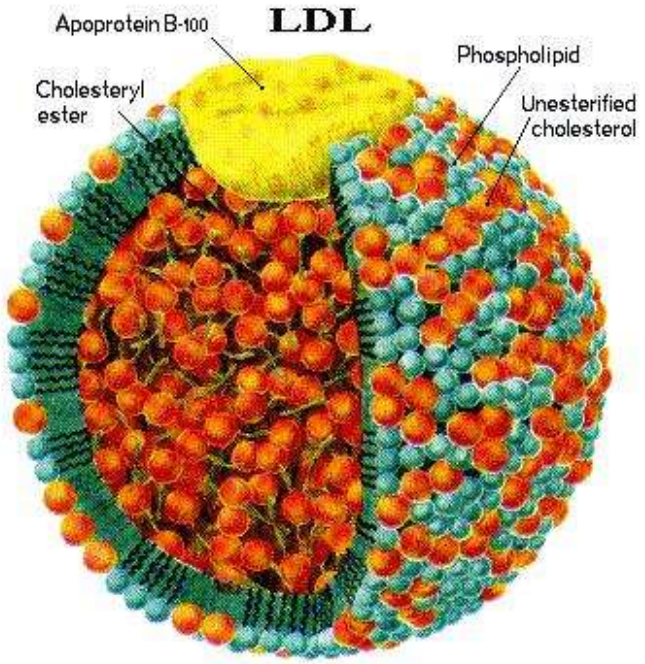
Excess of ASCVD –related Deaths in Asian Indians (AI) vs non- AI in USA (2010-2019)

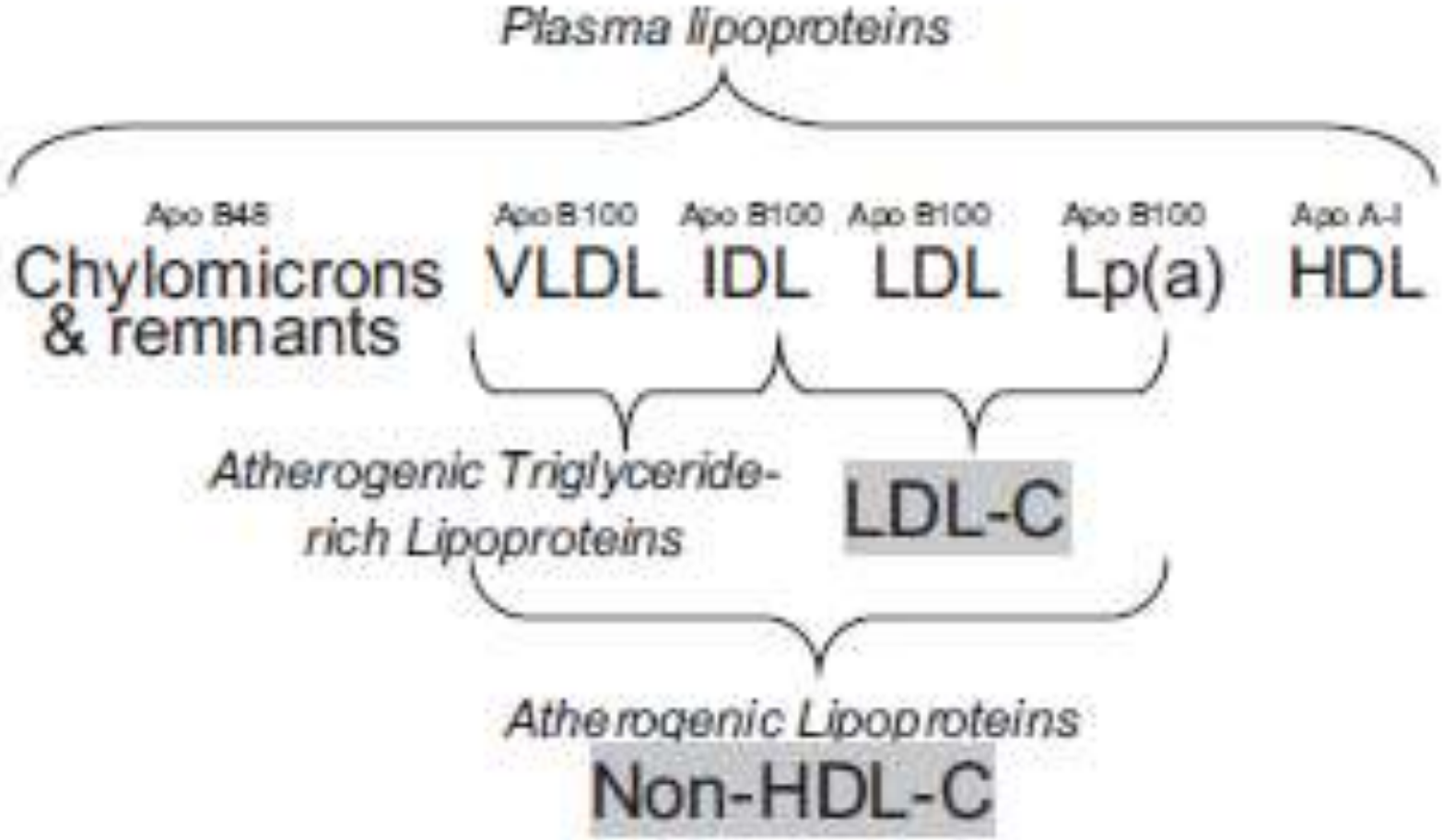
NCHS database; n=20.1 million- non-AI vs 55,461- AI deaths, age ≥ 45 years



Nair, DR et al Research Square- Preliminary Report, Aug 2022

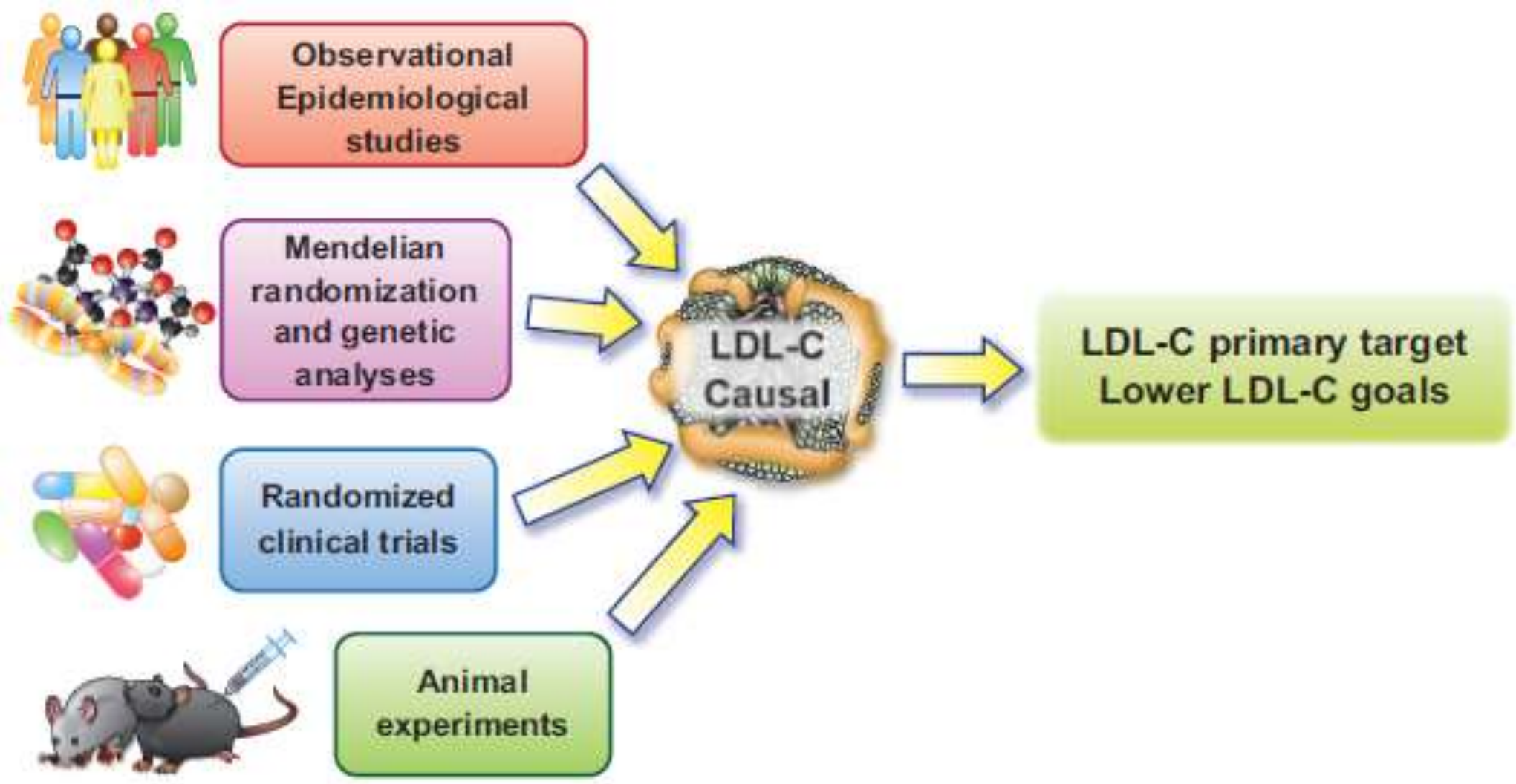
Blood Lipids and Lipoproteins





Robinson, JG, 2010

ASCVD: LDL-C is the Primary Target



Toglozoglu, L et al Eur Heart J 2022

Statins:

There is Incontrovertible Evidence for the Long-term Efficacy and Safety for HMG-CoA Reductase Inhibitors (Statins) to Reduce Cardiovascular Events

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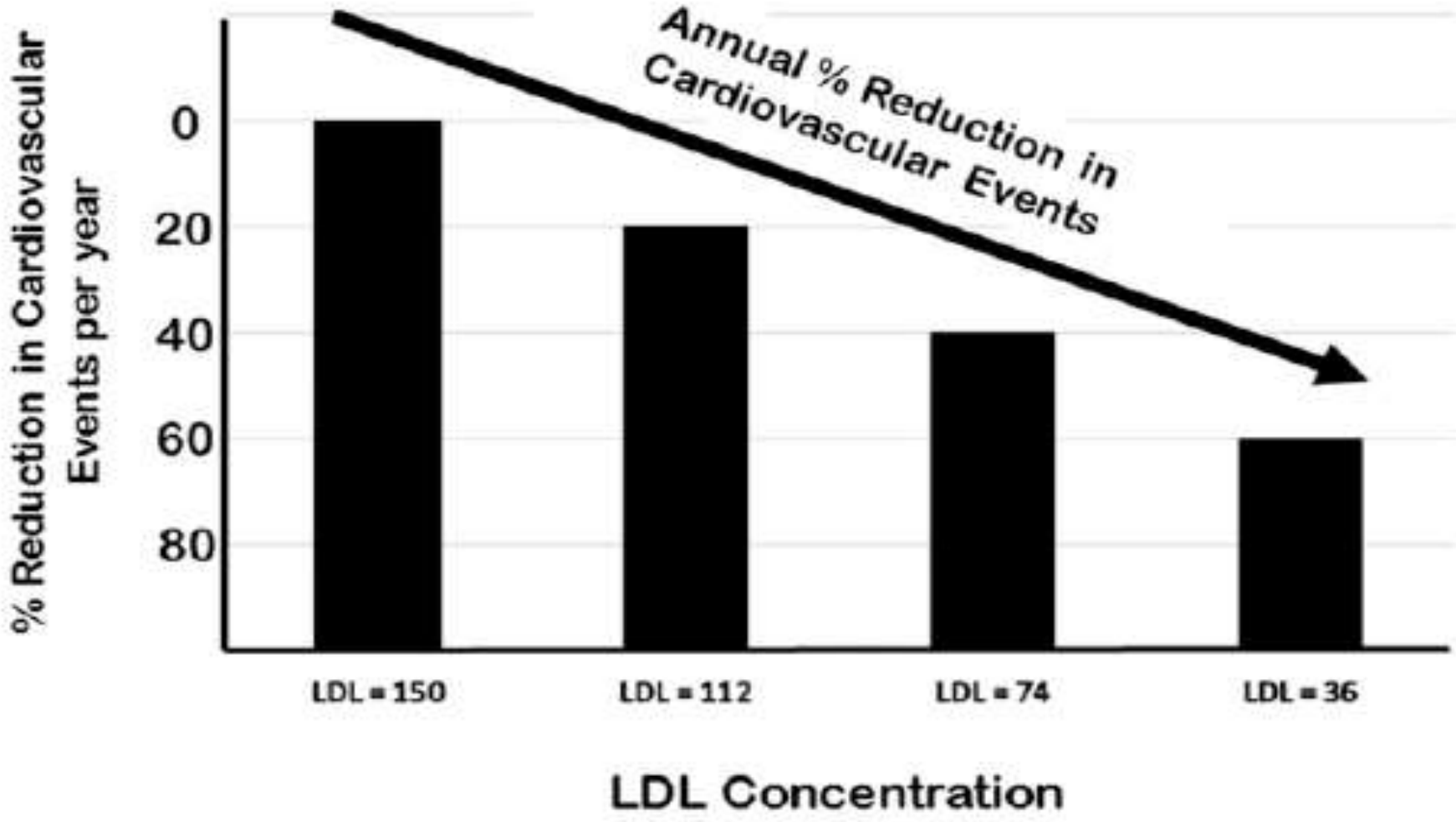
Meta-analysis: CV Event Reduction with Statins by LDL-C reduction in 27 RCTs

n > 170, 000



CV mortality
- 20%

Total mortality
- 10%

Collins, R et al Lancet 2016; 388: 2532-61, Schade and Eaton, 2019

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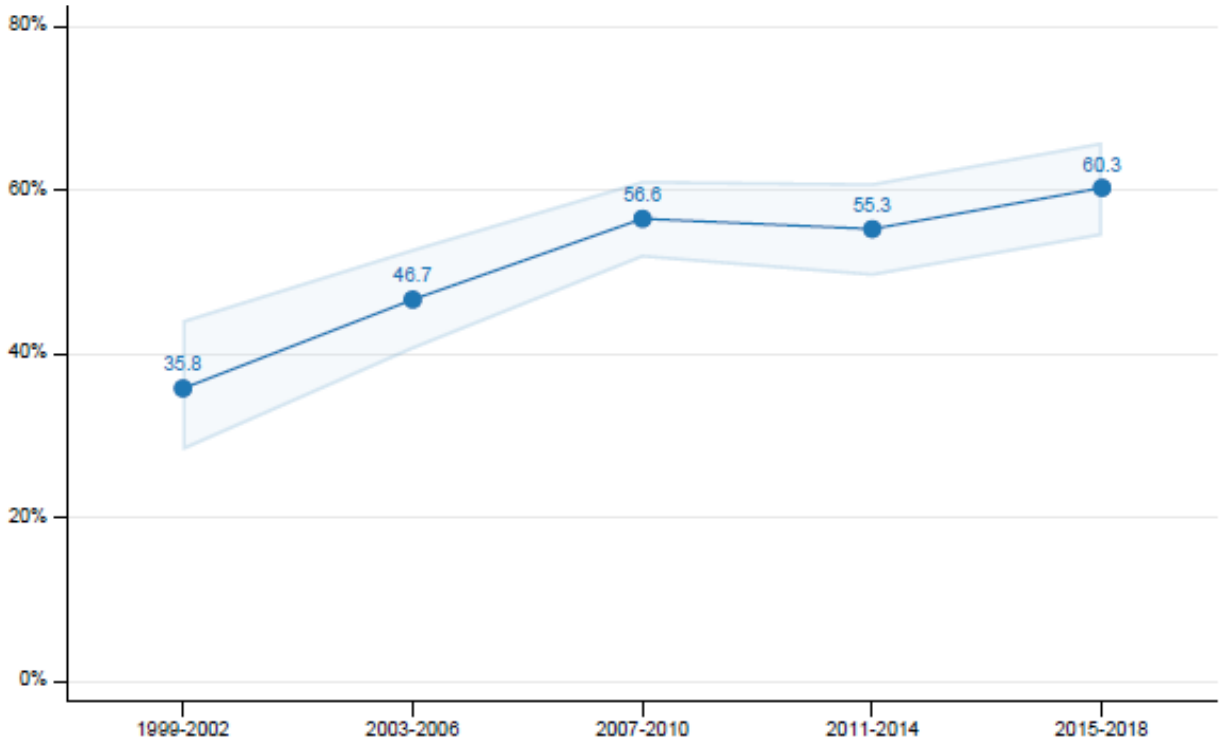
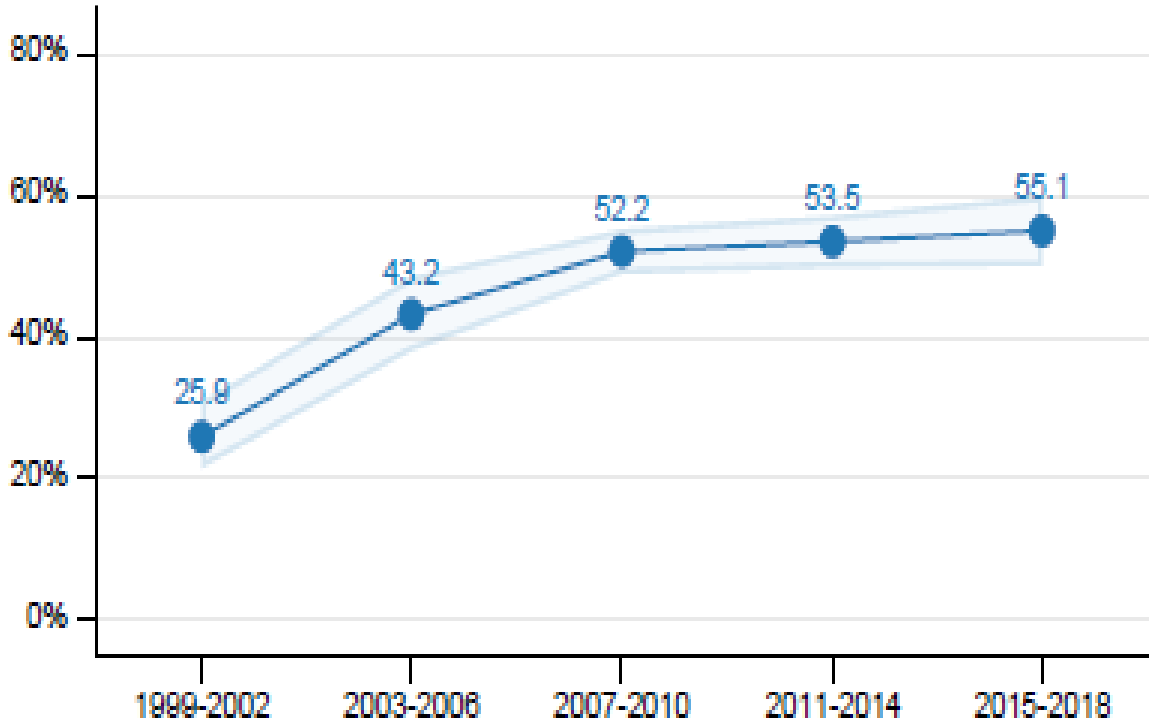
NHANES Survey: Lipid Trends 1999-2018

US Adults with Diabetes , n> 6,600

LDL-C < 100 mg/dl



Non-HDL-C < 130 mg/dl



Fang M et al NEJM 2021, June 10; on line

AHA/ADA: Primary Prevention Goals (Risk- based):

LOE	Recommendation
A	**For patients with diabetes aged 40–75 years without atherosclerotic cardiovascular disease (ASCVD), use moderate-intensity statin therapy in addition to lifestyle therapy**
C	**For patients with diabetes aged 20–39 years with additional ASCVD risk factors, it maybe reasonable to initiate statin therapy in addition to lifestyle therapy**
B	**In patients with diabetes at higher risk, especially those with multiple ASCVD risk factors or aged 50–70 years, it is reasonable to use high-intensity statin therapy**
C	**In adults with diabetes and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL cholesterol levels by 50% or more**

ADA Professional Practice Committee;. Diabetes Care 2022; 45 (Supplement_1): S144–S174.

Primary Prevention: Risk Enhancing Factors

- f/h of premature ASCVD
- Persistently elevated LDL-C ≥ 160 mg/dl
- metabolic syndrome
- CKD (eGFR 15-59, with or without albuminuria)
- h/o preeclampsia or premature menopause, age< 40 years
- Chronic inflammatory states: RA, Psoriasis, HIV
- Hi risk ethnic populations, eg South Asians
- Persistent elevations in TG ≥ 175 mg/dl (non-fasting).
- If measured:

  Apo-B ≥ 130 mg/dl,
  CRP ≥ 2 mg/dl

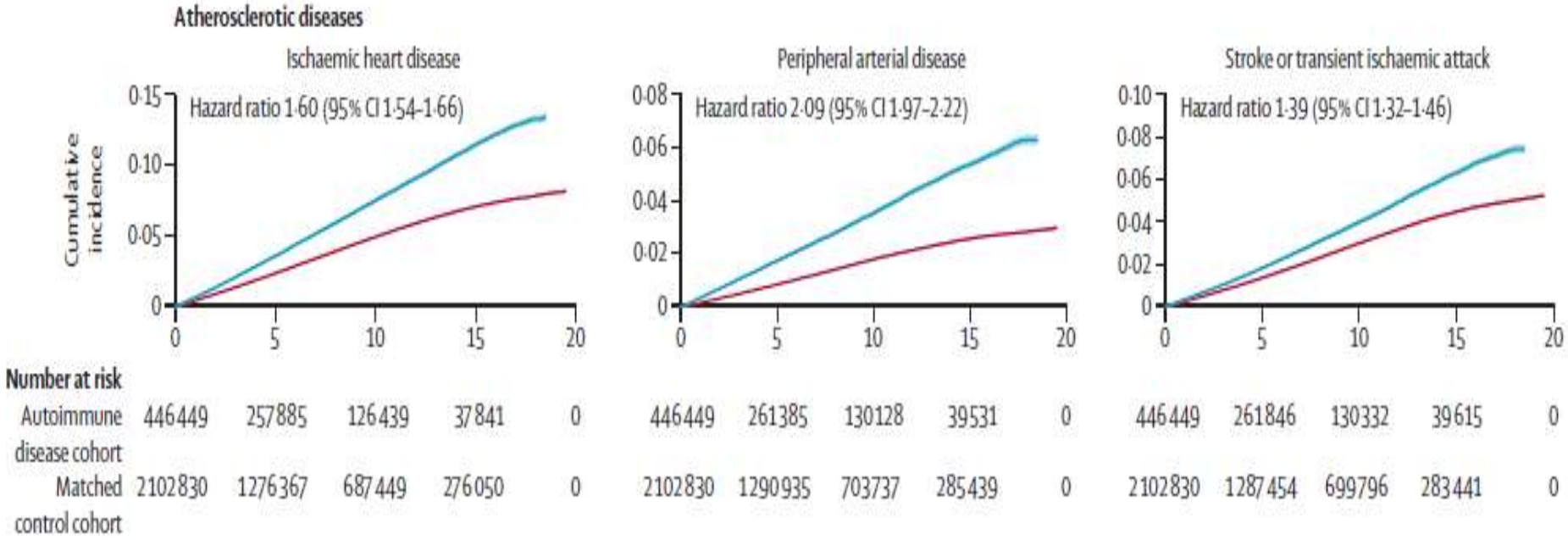
  LP(a) ≥ 50 mg/dl or 125 mmol/L

  ABI < 0.9

AHA/ACC guidelines, 2019

Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK

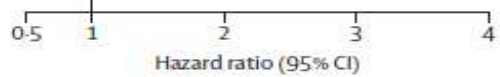
n= 446,449 with auto-immune disorders, matched with 2.1 million controls
Mean age 47.5 yr, median f/u 6.2 yr



Conrad N et al Lancet 2022; 400: 733-43

Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK

	Cohort		Events		Hazard ratio (95% CI)
	Autoimmune disease	Matched controls	Autoimmune disease	Matched controls	
Any autoimmune disease	446449	2102830	68413	231410	1·56 (1·52–1·59)
Number of autoimmune diseases					
1	404547	1902682	55301	198769	1·41 (1·37–1·45)
2	37226	177676	11005	28570	2·63 (2·49–2·78)
≥3	4676	22472	2107	4071	3·79 (3·36–4·27)
Connective tissue diseases	160217	761918	36846	118391	1·68 (1·63–1·74)
Ankylosing spondylitis	9864	46121	1423	3822	1·97 (1·65–2·35)
Polymyalgia rheumatica	48102	231802	15390	55870	1·47 (1·40–1·54)
Rheumatoid arthritis	66796	318456	15520	46594	1·83 (1·74–1·92)
Sjögren's syndrome	9933	47330	2327	6139	2·08 (1·81–2·39)
Systemic lupus erythematosus	10483	49402	2204	4227	2·82 (2·38–3·33)
Systemic sclerosis	2159	10310	752	1320	3·59 (2·81–4·59)
Vasculitis	37940	178494	7839	22658	1·87 (1·73–2·01)
Organ-specific diseases	407078	1909992	53706	175205	1·60 (1·56–1·64)
Addison's disease	2548	12055	604	1218	2·83 (1·96–4·09)
Coeliac disease	24895	115692	2507	8618	1·50 (1·33–1·69)
Type 1 diabetes	50264	235540	9697	23568	2·36 (2·21–2·52)
Inflammatory bowel disease	49214	230236	6470	19532	1·71 (1·59–1·85)
Graves' disease	44001	207508	6409	20535	1·61 (1·49–1·74)
Hashimoto's thyroiditis	7630	35650	822	2364	1·76 (1·41–2·19)
Multiple sclerosis	12006	56523	1356	3876	1·85 (1·56–2·20)
Myasthenia gravis	2171	10319	544	1812	1·61 (1·21–2·15)
Pernicious anaemia	32910	156887	8228	27099	1·61 (1·50–1·73)
Psoriasis	185178	869184	21197	73465	1·47 (1·41–1·53)
Primary biliary cirrhosis	4612	21973	1086	3060	2·00 (1·66–2·41)
Vitiligo	23709	109914	1791	6526	1·38 (1·19–1·60)



Conrad N et al Lancet 2022; 400: 733-43

ACC/AHA Lipid Guidelines: Secondary ASCVD Prevention

Very High Risk for Future ASCVD Events

≥ 2 Major ASCVD Events

- Recent acute coronary syndrome (within the past 12 months)
- History of myocardial infarction (other than recent acute coronary syndrome event listed above)
- History of ischemic stroke
- Symptomatic peripheral arterial disease (history of claudication with ankle-brachial index <0.85 or previous revascularization or amputation)

1 Major and ≥ 2 High-Risk Conditions

- **Age ≥65 years**
- HeFH
- History of prior CABG or PCI outside of the major ASCVD event(s)
- **DM**
- **Hypertension**
- **CKD** (eGFR 15-59 mL/min/1.73 m^2)
- Current smoking
- Persistently elevated LDL-C ≥100 mg/dL despite maximally tolerated statin therapy and ezetimibe
- History of congestive heart failure

Grundy SM et al Circulation 2019

What is the Optimal LDL-C Goal in Patients with *very high Risk* of CV Events?

	LDL-C mg/dl	Non-HDL-C mg/dl	Apo-B mg/dl	Comments
AHA/ACC, 2018 ADA, 2020	**< 70 and ≥ 50%**			
NLA, 2018 Canadian (CCS)	**< 70 and ≥ 50%**	**< 100**	**< 80**	
Endo Soc, 2020	**< 55**			Established ASCVD or multiple RFs
AACE 2017, 2022 ACC, 2022	**< 55**	**< 85**	**< 65**	
EAS/ESC, 2019	**< 40**	**<70**		**If 2nd event in < 2 yr**

AHA/ACC: Additional Considerations for Statin by Age in Patients with Diabetes without pre-existing ASCVD

- **In older adults age > 75 years, already on statin therapy, it is reasonable to continue.**

- **In older adults age > 75 years, it is reasonable to initiate statin therapy, after clinician- patient discussion of potential benefits and risks.**

- **In younger adults (20-39 years old), it is reasonable to start, if either:**
  - Long duration (Type 2 ≥ 10 yr/ Type 1 ≥ 20 yr)
  - Alb/creat raio ≥ 30 mcg/mg, eGFR < 60
  - Retinopathy
  - Neuropathy
  - ABI < 0.9

Grundy SM et al Circulation 2019

Options for LDL-C reduction in high-risk subjects, when…

- Statin therapy inadequate (< 50% reduction, or LDL-C > 70 mg/dl)

- Statin Intolerance

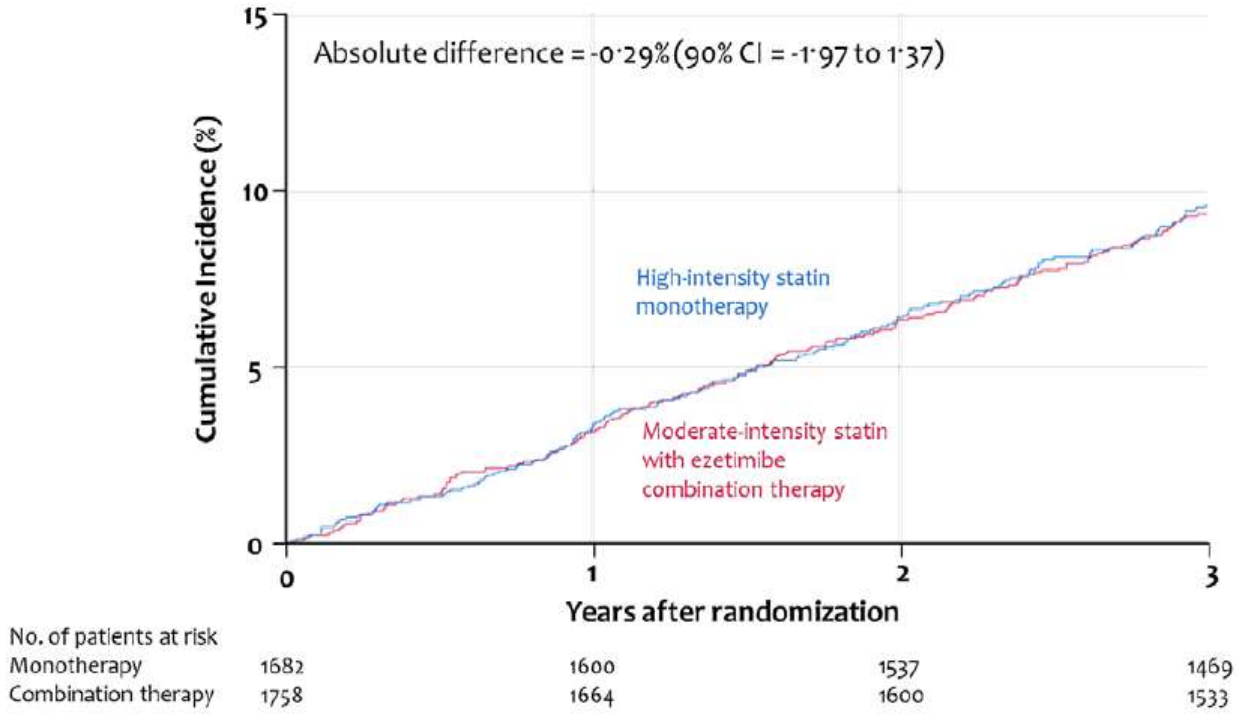
Approach to Patient-Provider Considerations for "Statin intolerance"

- Rule- out secondary causes, e.g. Hypothyroidism, Vitamin D deficiency
- Rule- out drug-drug interactions; dose adjustments
- Consider discontinuing statin> re-challenge after a few weeks.
- Use lowest dose on alternate days, or 1-2 x /week > titrate up
- Use maximally tolerated statin and add other agents: Ezetimibe ± PCSK9 inhibitor or Bempedoic acid

Moderate-Intensity Statin + Ezetimibe vs High Intensity Statin: Efficacy and CV Outcomes

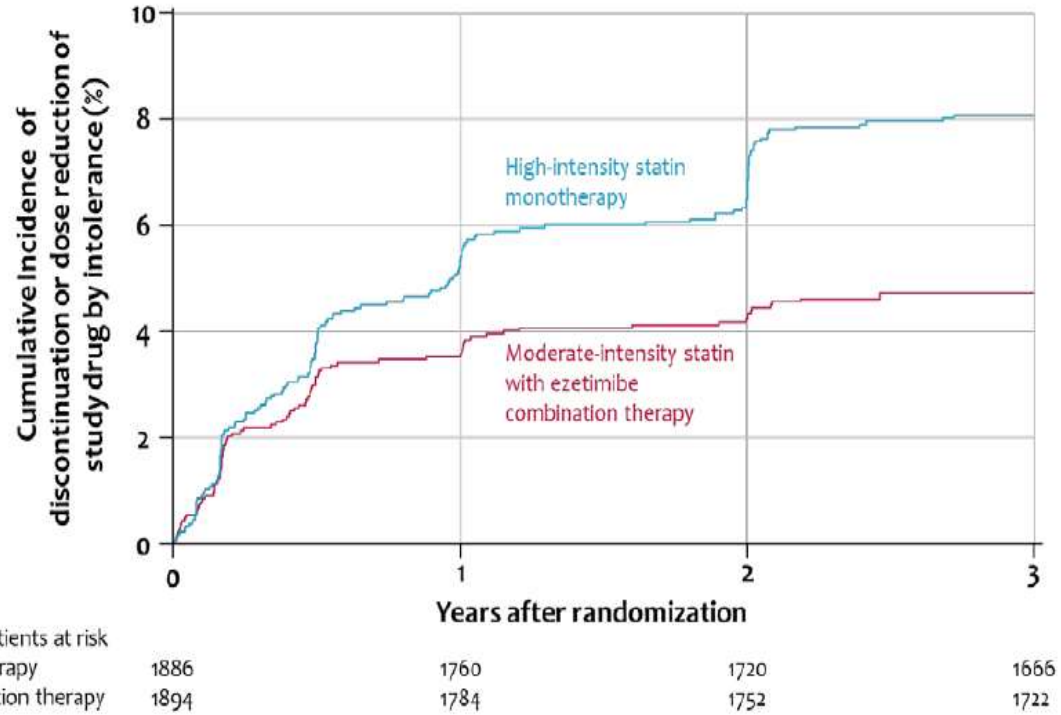
N=3,780, 37 % with DM , ASCVD, median LDL-C, 80 mg/dl

CV Death, Major CV event, or non-fatal stroke



No. of patients at risk				
Monotherapy	1682	1600	1537	1469
Combination therapy	1758	1664	1600	1533

Drug discontinuation or dose reduction



No. of patients at risk				
Monotherapy	1886	1760	1720	1666
Combination therapy	1894	1784	1752	1722

Median LDL-C achieved, 58 vs 66 mg/dl

Kim, B-K et al Lancet 2022; July 18

Novel and Emerging Options for LDL-C

- **PCSK-9 Inhibitors:** Monoclonal Antibodies or si-RNA approach

  -Oral PCSK-9 inhibitor (MK 0616) (in development)

- **Bempedoic Acid**, an oral ATP-Citrate Lyase inhibitor

  (Approved for secondary prevention, or FH, after statin +/- ezetimibe)

- **Evinacumab**, an ANGPTL-3 inhibitor

  (Approved for refractory Ho-FH patients, 2021); i/v infusion q 4 wk

- Thyro-mimetics - THR-β agonists (in development)

- ? CRISPR technology to extinguish potential loci for atherogenesis

PCSK9 Inhibitors:

Mechanism of Action and When to Use?

A serendipitous discovery

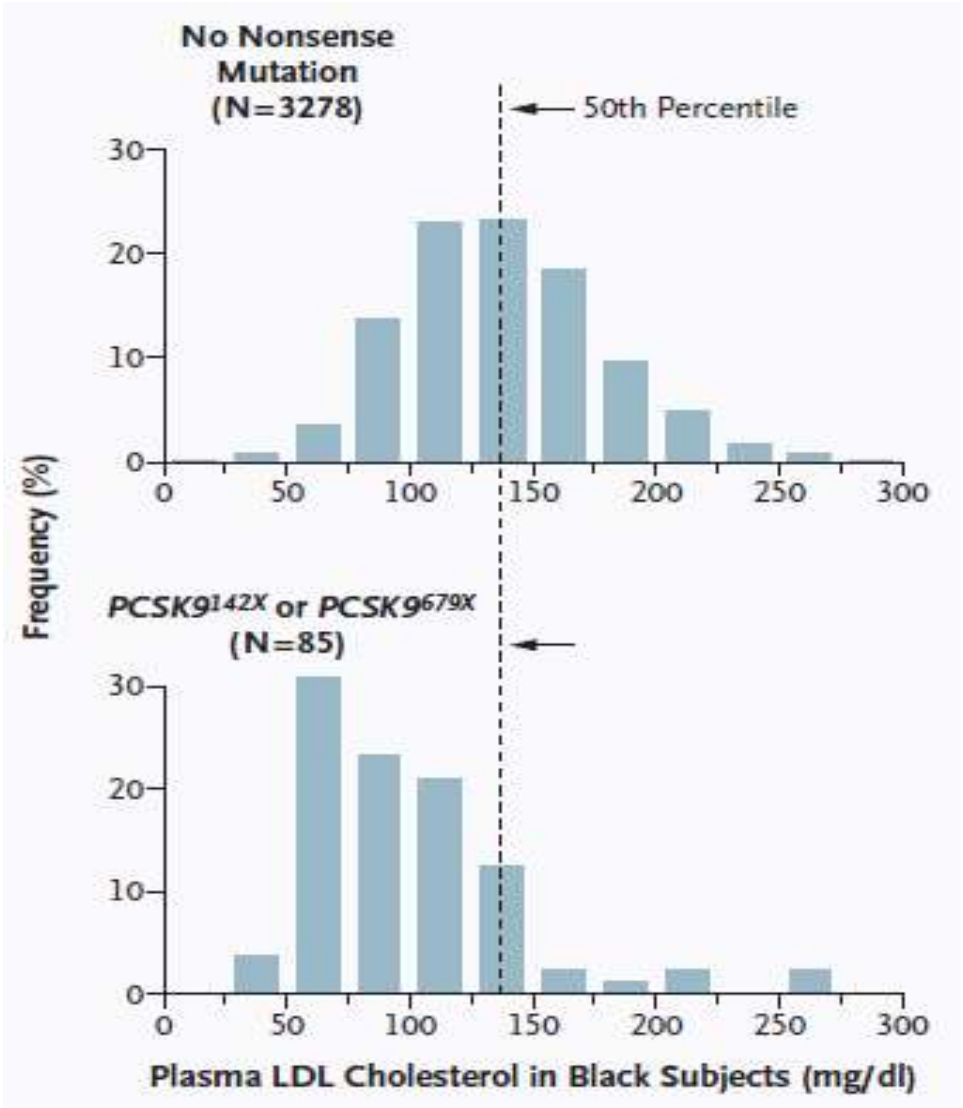
NEJM 2006;
354:1264-1272

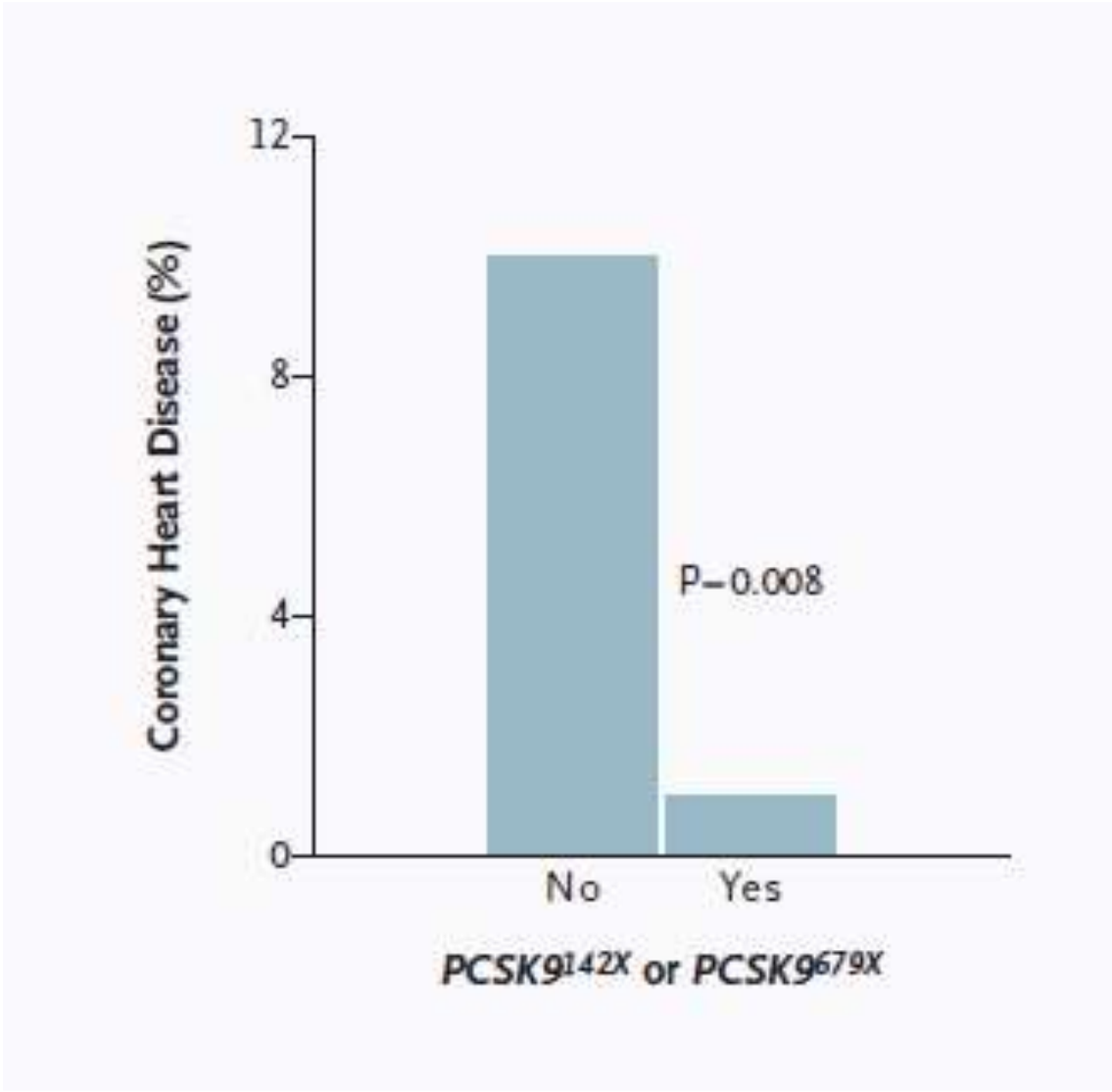
Sequence Variations in *PCSK9*, Low LDL, and Protection against Coronary Heart Disease

Jonathan C. Cohen, Ph.D., Eric Boerwinkle, Ph.D., Thomas H. Mosley, Jr., Ph.D., and Helen H. Hobbs, M.D.

LDL Cholesterol Levels and CHD According to the Presence or Absence of a PCSK9^{142X} or PCSK9^{679X} Allele

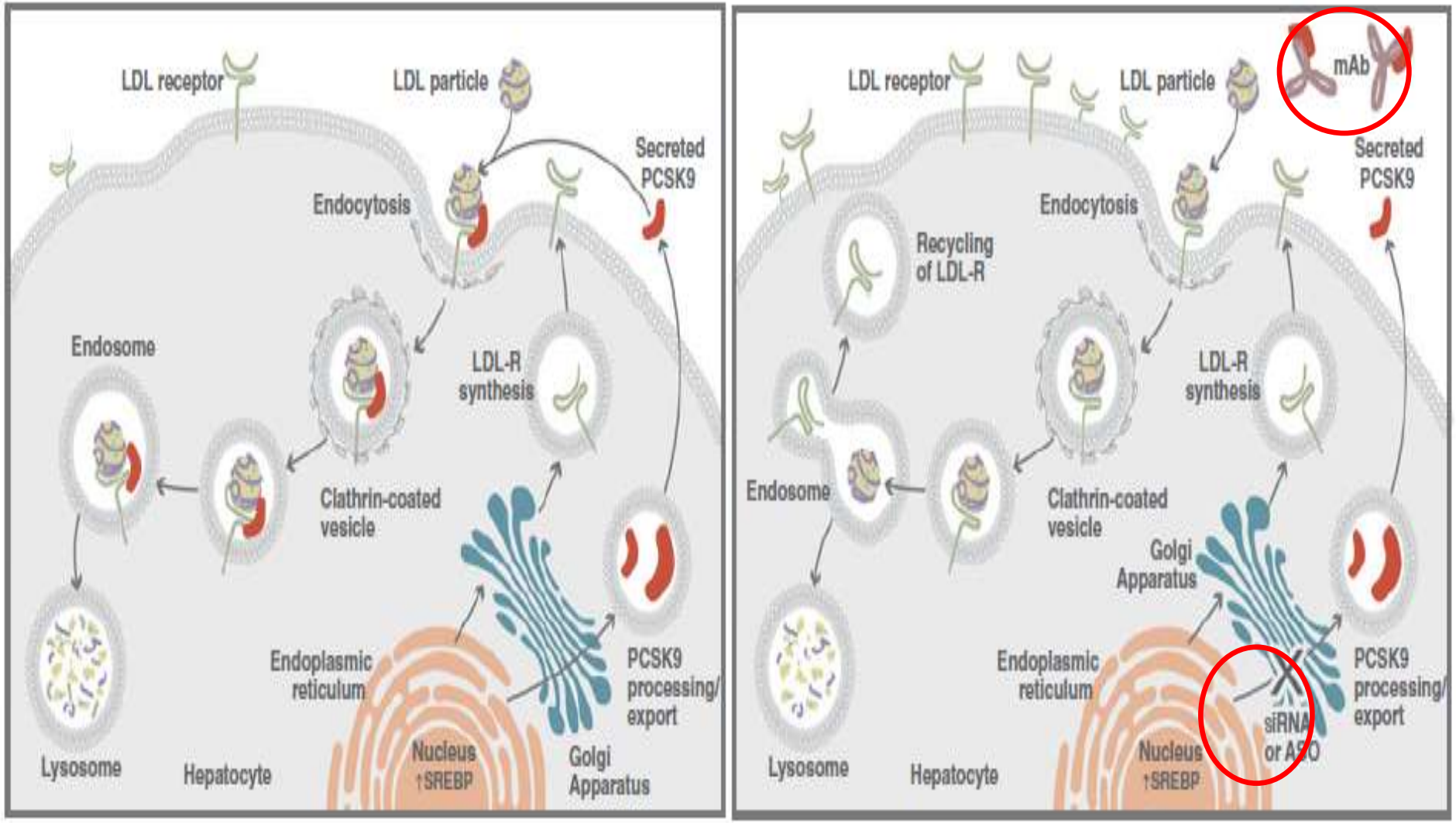
3278 Black subjects without and 85 with mutation; mean LDL- C 138 vs 100 mg/dl; p<0.001





Cohen, J. et al.
NEJM 2006;
354:1264-1272

PCSK-9 and LDL-Receptor Interaction



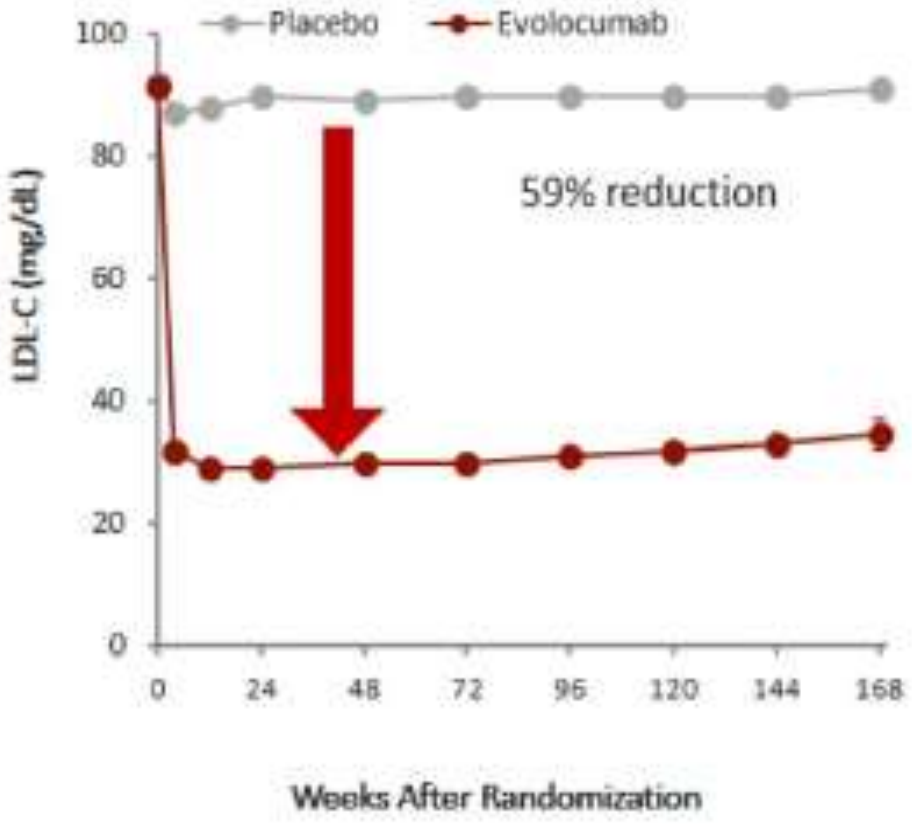
Lambert, G et al J Lipid Res 2012; 53: 2515-24; Stein, EA Curr Athero Rep 2013; 15: 310

PCSK9 Inhibitor CVOTs: LDL-C

(Most participants on high- or moderate intensive statin dose)

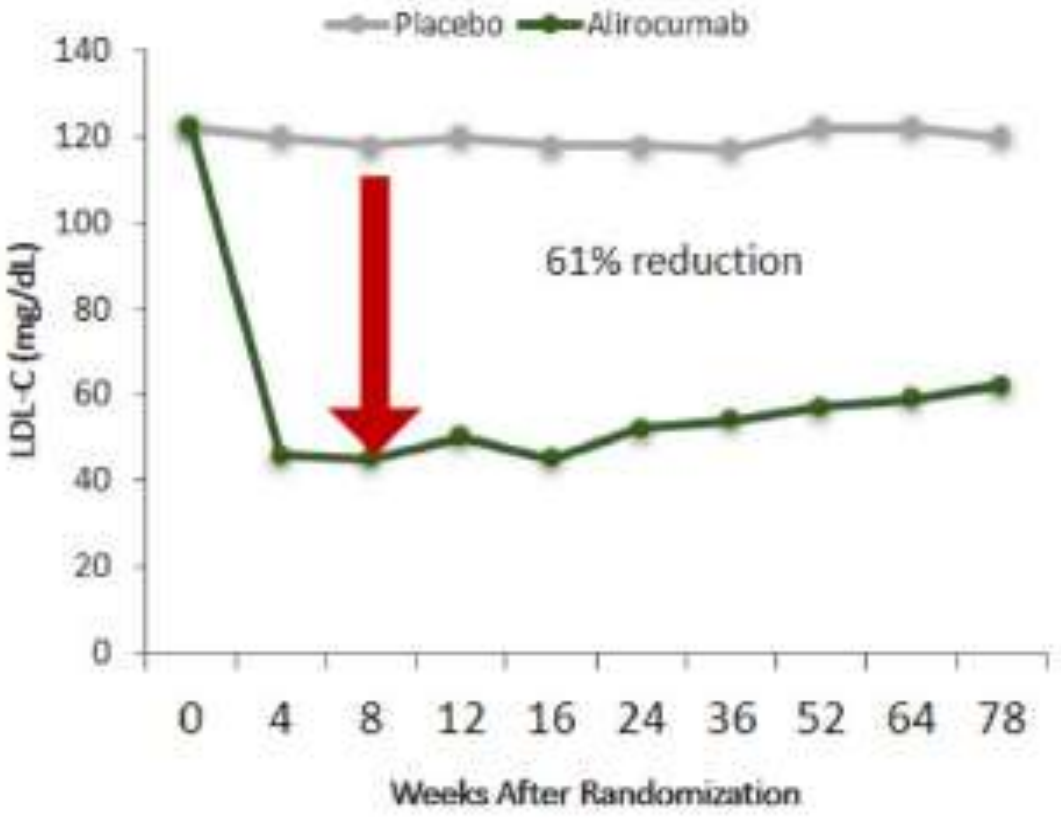
FOURIER [a] **N= 27,564**

Change in LDL-C Over Time



ODYSSEY OUTCOMES[c] **N= 18,924**

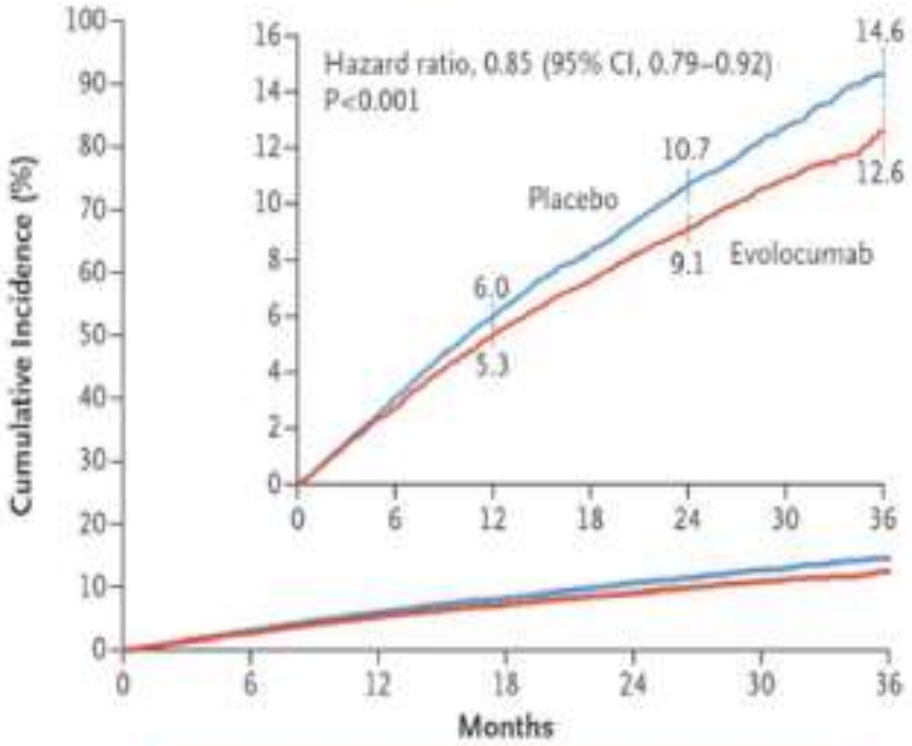
Change in LDL-C Over Time



a. Sabatine M, et al. *N Engl J Med.* 2017;376:1713-1722; b. Steg PG, et al. *N Engl J Med.* 2018;379:2097-2107;
c. Robinson JG, et al. *N Engl J Med.* 2015;372:1489-1499.

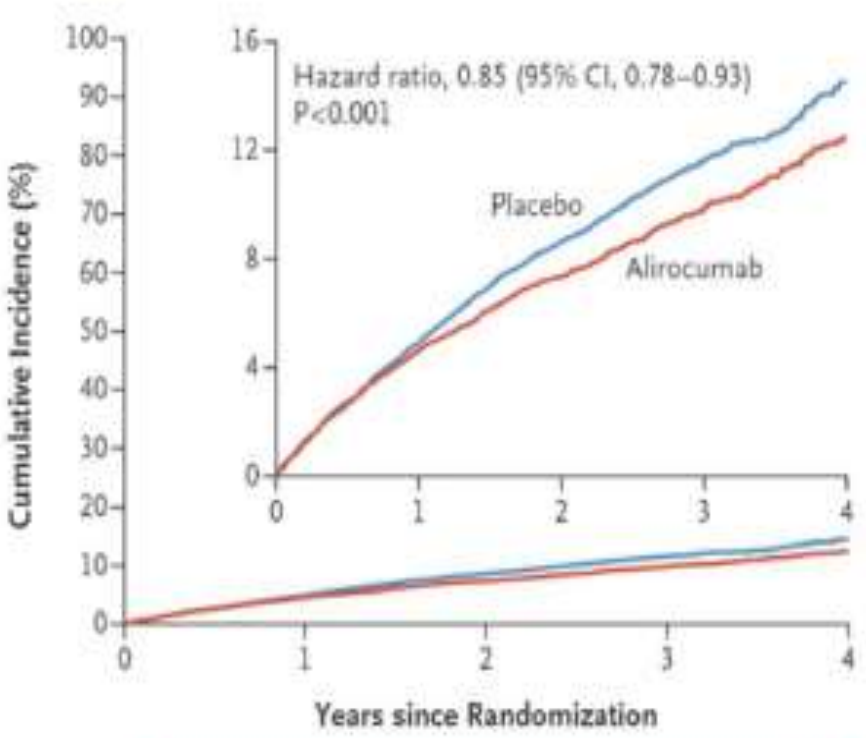
Major CV Outcomes with PCSK9 Inhibitors

FOURIER: Evolocumab[a]



MACE: CV death, MI, stroke, hospitalization for UA, or coronary revascularization

ODYSSEY Outcomes: Alirocumab[b]



MACE: CHD death, nonfatal MI, ischemic stroke, or UA requiring hospitalization

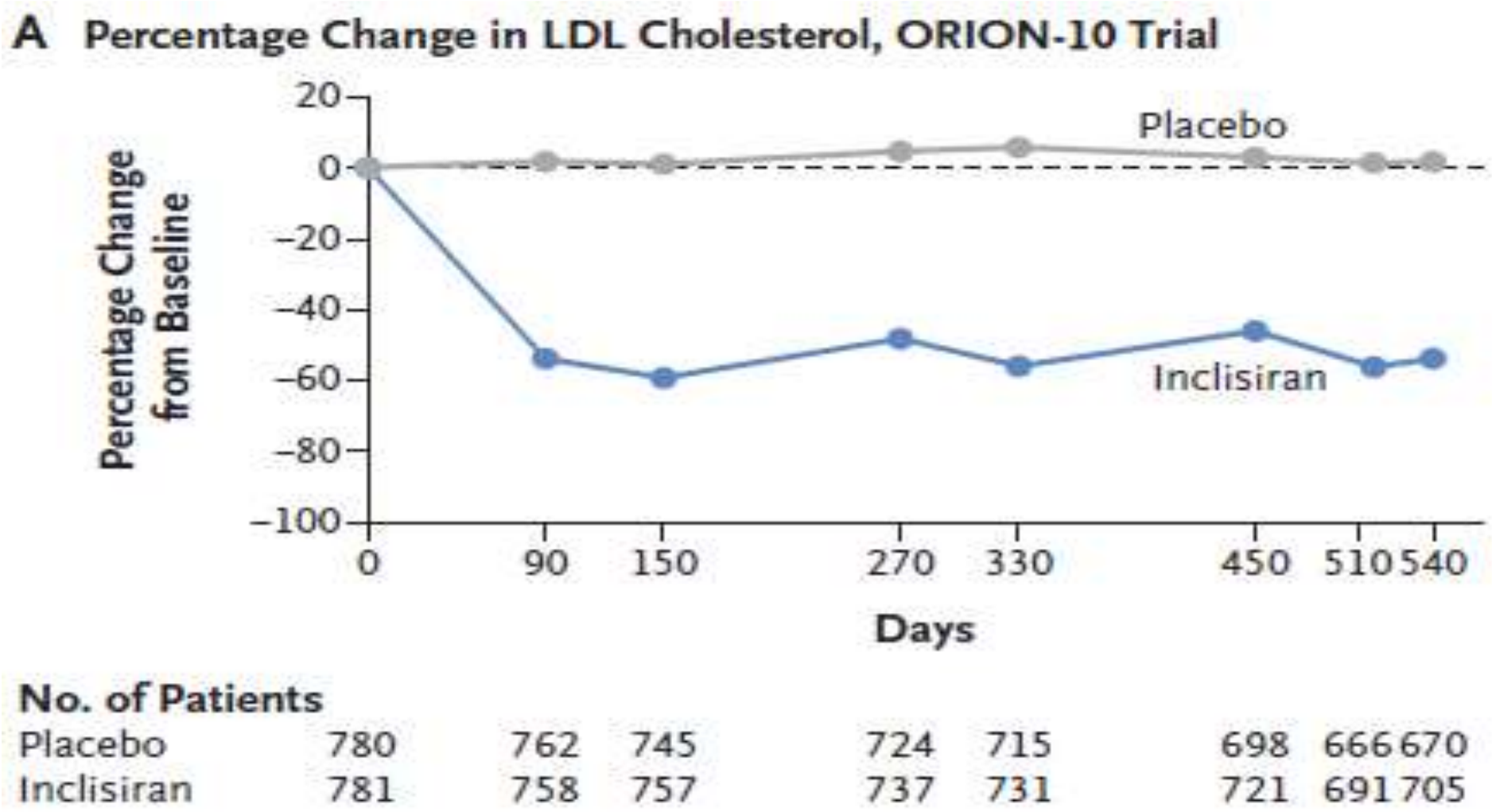
a. Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-1722; b. Schwartz GG, et al. *N Engl J Med*. 2018;379:2097-2107.

FOURIER: Key Adverse Events

Outcome	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results — no. of patients/total no. (%)		
Aminotransferase level >3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level >5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

Inclisiran: A Novel siRNA Approach to Inhibit PCSK9

n=1,561; ASCVD, mean age 66 years, baseline LDL-C 105 mg/dl; on statin.
Inclisiran 284 mg s/c vs placebo at time 0, 90 min, then q 180 days x 2

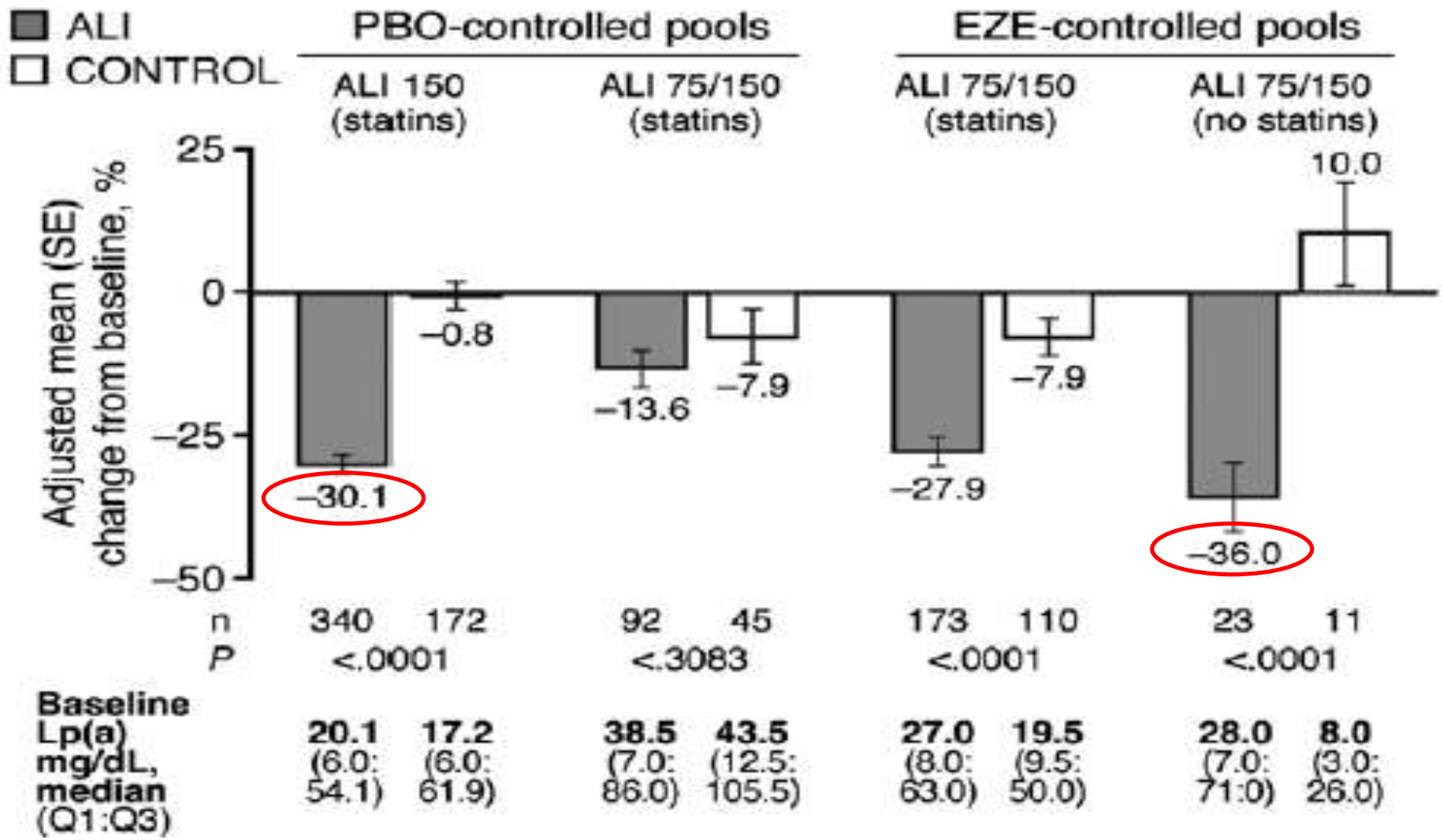


Ray KK et al
NEJM 2020

ORION-4; RCT for CV Events; in progress

Effects of PCSK9i on Lp(a)

Meta-analyses of 9 RCTs in subjects with DM and ASCVD, n= 984

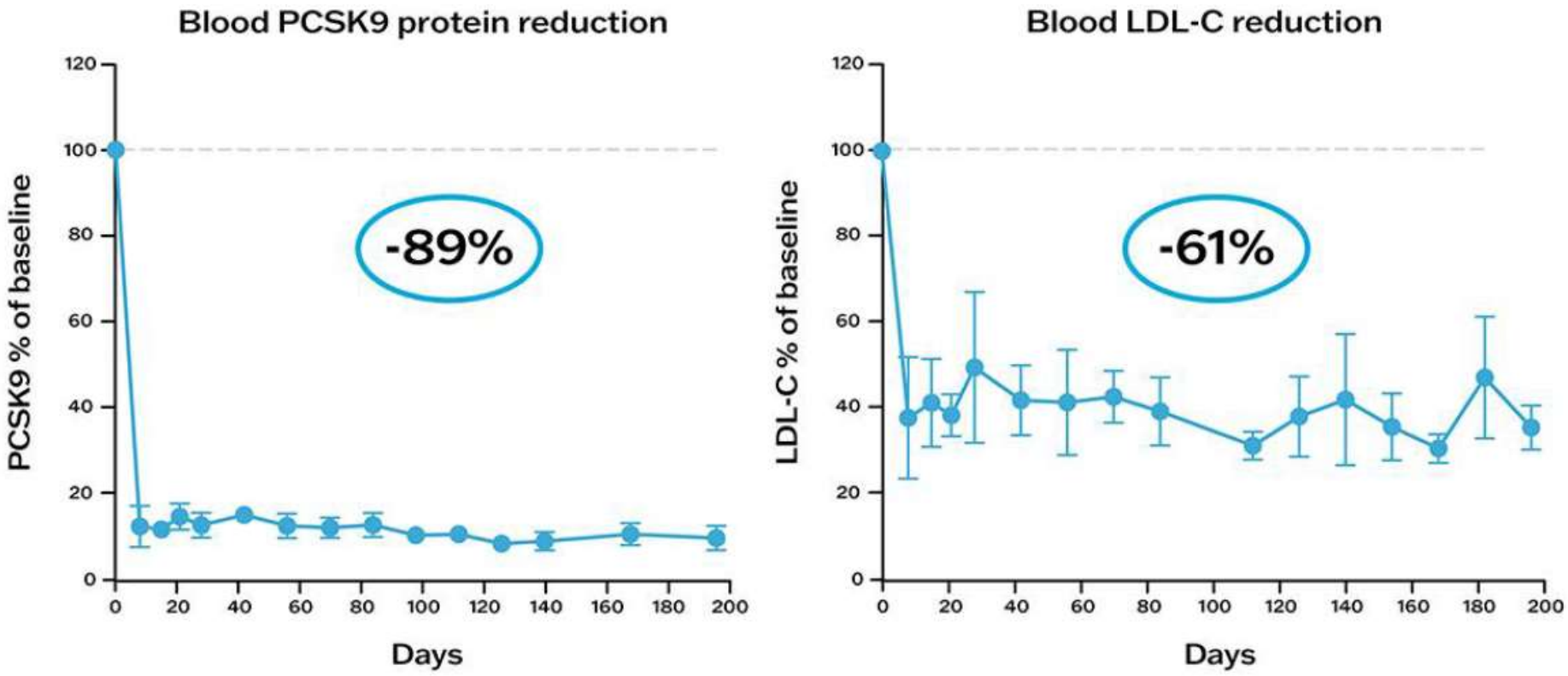


Ganda, OP et al Diab Ob Metab 2018; 20: 2089-98

VERVE-101: A gene-editing Approach to PCSK-9 in FH

HEART-1
NCT 05398029

Goal:
Once in Lifetime!



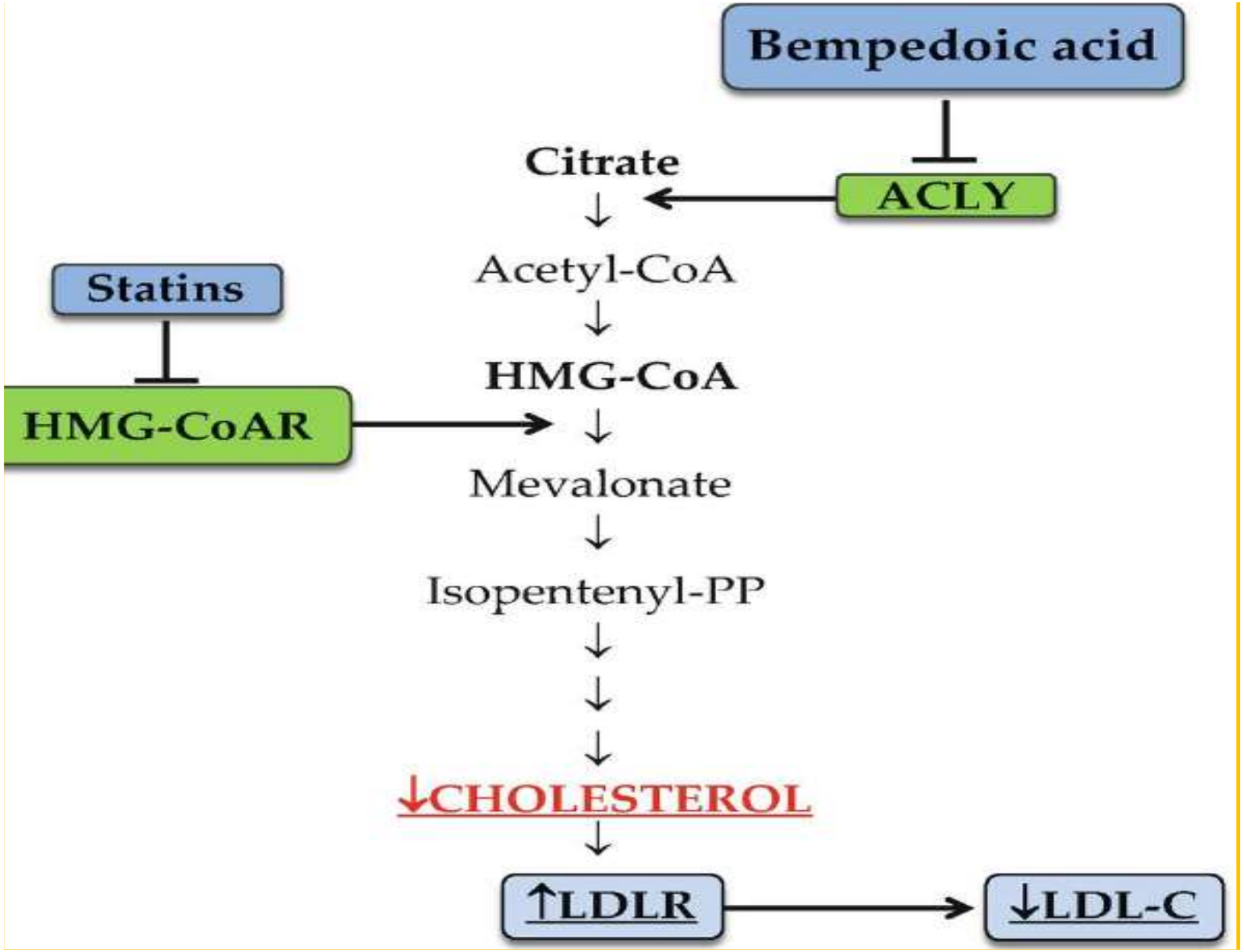
Each data point represents a consecutive measurement from n = 4 cynomolgus monkeys

News Release:
Verve Therapeutics, 2022; July 12

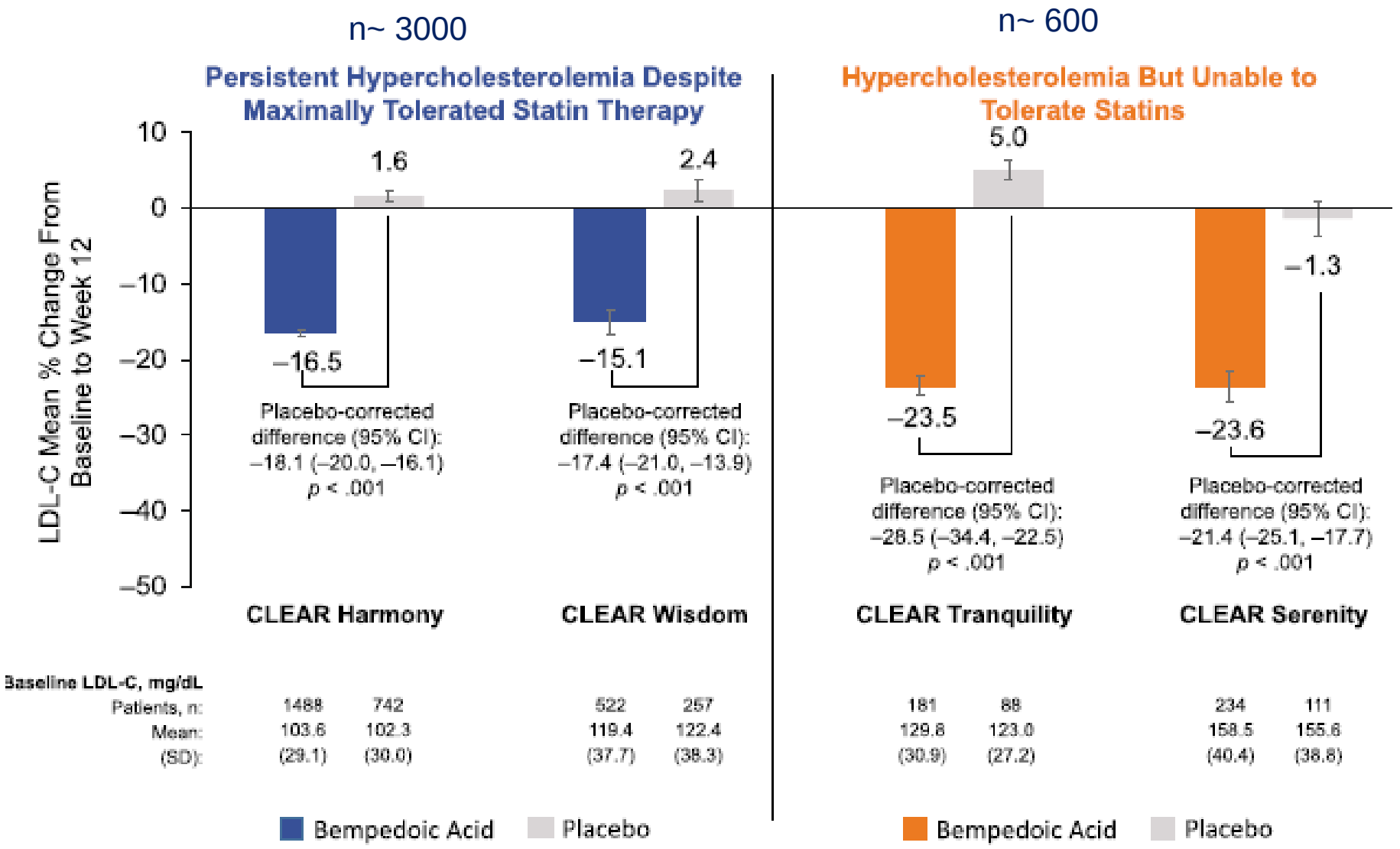
Bempedoic Acid:

How does it work?

A pro-drug, selectively activated in liver by CoA thioester



Bempedoic Acid: Effect on LDL-C at 12 weeks



AEs:
-Hyperuricemia, ~ 0.8 mg/dl
- Mild ↓ GFR
- Mild ↑ ALT/AST
-Tendon rupture (v rare)

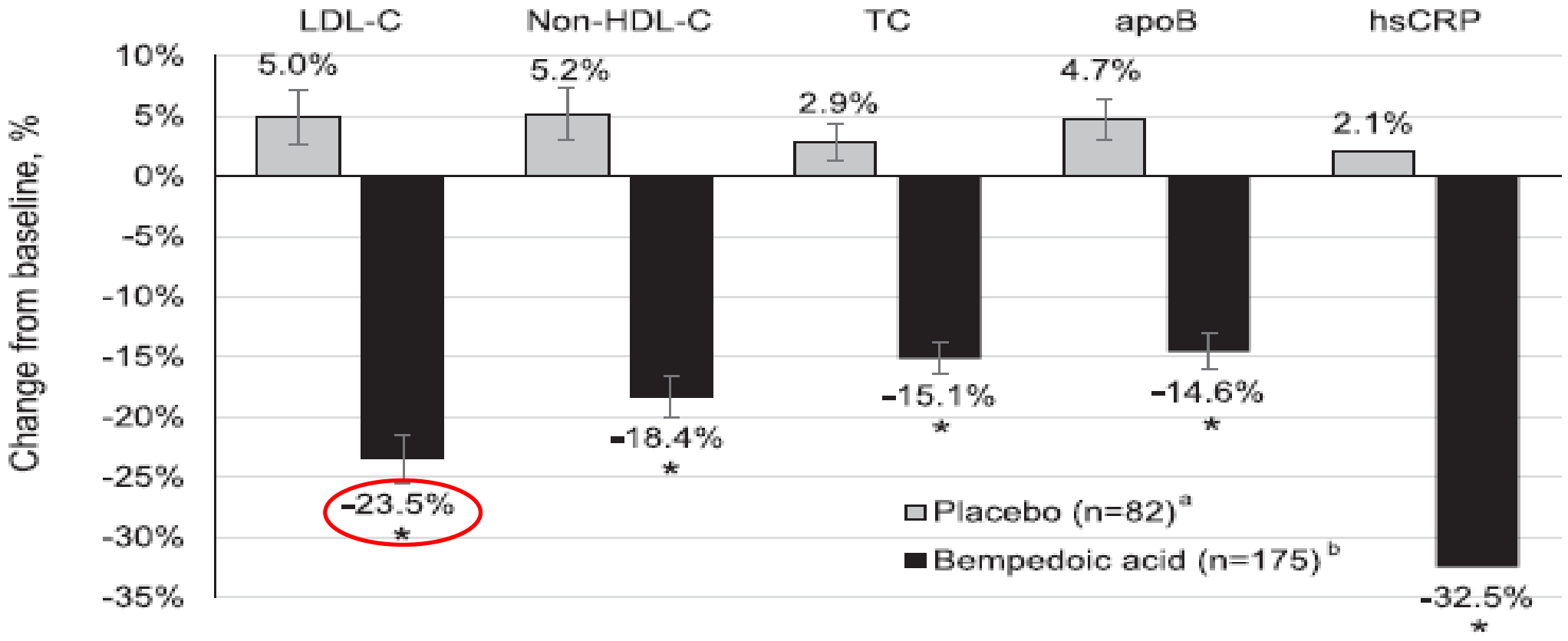
? Lower risk of new DM

CV-RCT -underway (CLEAR Outcomes) ~ 2022

Ballantyne, CB et al 2021; on line; Lin Y et al BMJ Open 2022- on line

Bempedoic Acid add-on to Ezetimibe or Placebo in Statin – Intolerant subjects

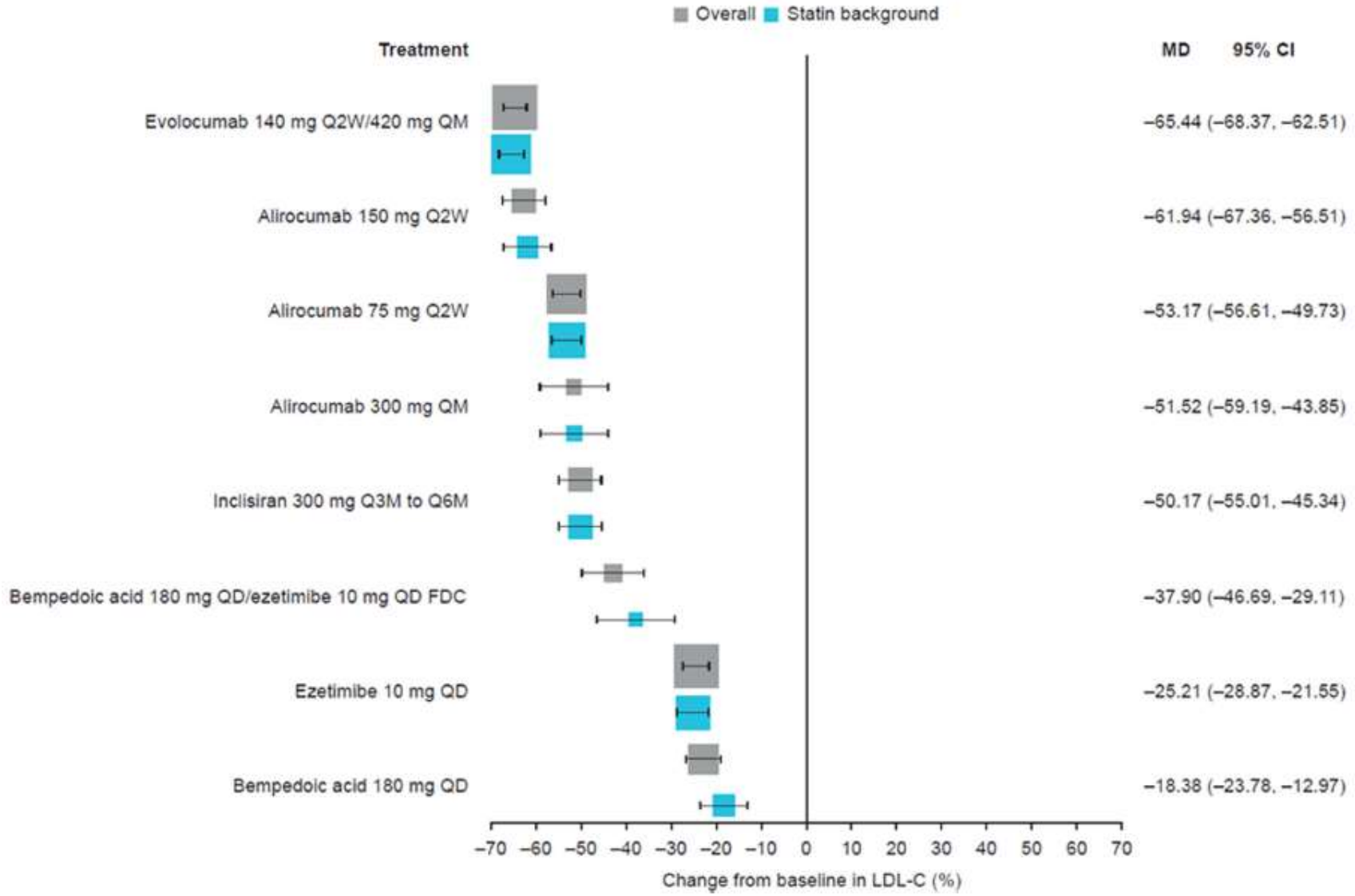
Phase 3, 12 week RCT, n=269; mean LDL-C at baseline, 127.6 mg/dl



Ballantyne, CM et al Atherosclerosis 2018; 277: 195-203

LDL –C Reduction with non-statin Rx vs Placebo

Network Meta-analysis, week 12



Toth PP et al ; J Am Heart Assn sept 2022

Residual Risk of CVD after achieving LDL-C Goal?

~30-40% of recurrent CVD events occur in statin/ezetimibe treated patients

Possible Reasons:

- LDL goal?

- Triglyceride –Rich Lipoproteins (TRL): Remnant cholesterol

- LP(a)

-Others

Clinical Trials Targeting Dyslipidemia after LDL-C in "Optimal" Range

- **ACCORD- LIPID (mean LDL-C, 81 mg/dl)** Ginsberg et al NEJM 2010; 362:1563

  Statin + fibrate vs statin on CVD events in type 2 diabetes (n=5,518)

  HR 0.91 (95% CI 0.87-1.21)

  If TG ≥ 204 and HDL-C ≤ 34 mg/dl, cf others (p= 0.06)

- **AIM-HIGH (mean LDL-C, 64 mg/dl)** Boden, et al NEJM 2011; 365: 2255

  Statin + niacin vs statin in CVD and metabolic syndrome (n =3414, 34 % with DM)

  HR 1.02 (95% CI 0.87-1.21)

- **HPS2-THRIVE (mean LDL-C, 53 mg/dl)** Landray et al NEJM 2014; 371: 203

  Statin + niacin/laropiprant vs statin in pts with CVD (n =25,673, 32 % with DM)
  Risk Ratio 0.96 (95% CI 0.90 – 1.03)

The Unfulfilled Promise of CETP Inhibitors

Drug	HDL-C	LDL-C	Trial Outcome	Status
Torcetrapib	+ 72 %	-25 %	Mortality, HR: 1.58 (1.14-2.19)	Halted in 2006
Dalcetrapib	+31 to +40%	No change	Mortality, HR: 0.99 (0.82-1.19)	Halted in 2012
Evacetrapib	+ 133 %	- 31 %	MCE: 1.01 90.91-1.11)	Halted in Oct 2015
Anacetrapib	**+ 104 %**	**- 17%**	**MCE: 0.91 (0.85-0.97)**	**P< 0.01**
Obecetrapib (TA-8995)	+74 to +177 %	-28 to -69%	Phase-3	In progress

Cannon, CP et al NEJM 2010; 363: 2406-2415; Nichols, SJ et al JAMA 2011; 306: 2099-2109; Schwartz, GG et al NEJM 2012; 367: 2089-2099 ; Hovingh, GK et al Lancet 2015; 386: 452-460; Bowman, L et al; NEJM, 2017; Aug 29

Margaret Albrink: A Pioneer in Triglyceride-CAD Connection

1920-2012

One of the rare women of her generation to pursue career in academic medicine (MD '46-Yale)

LIPOPROTEIN PATTERN AS A FUNCTION OF TOTAL TRIGLYCERIDE CONCENTRATION OF SERUM *

By MARGARET J. ALBRINK

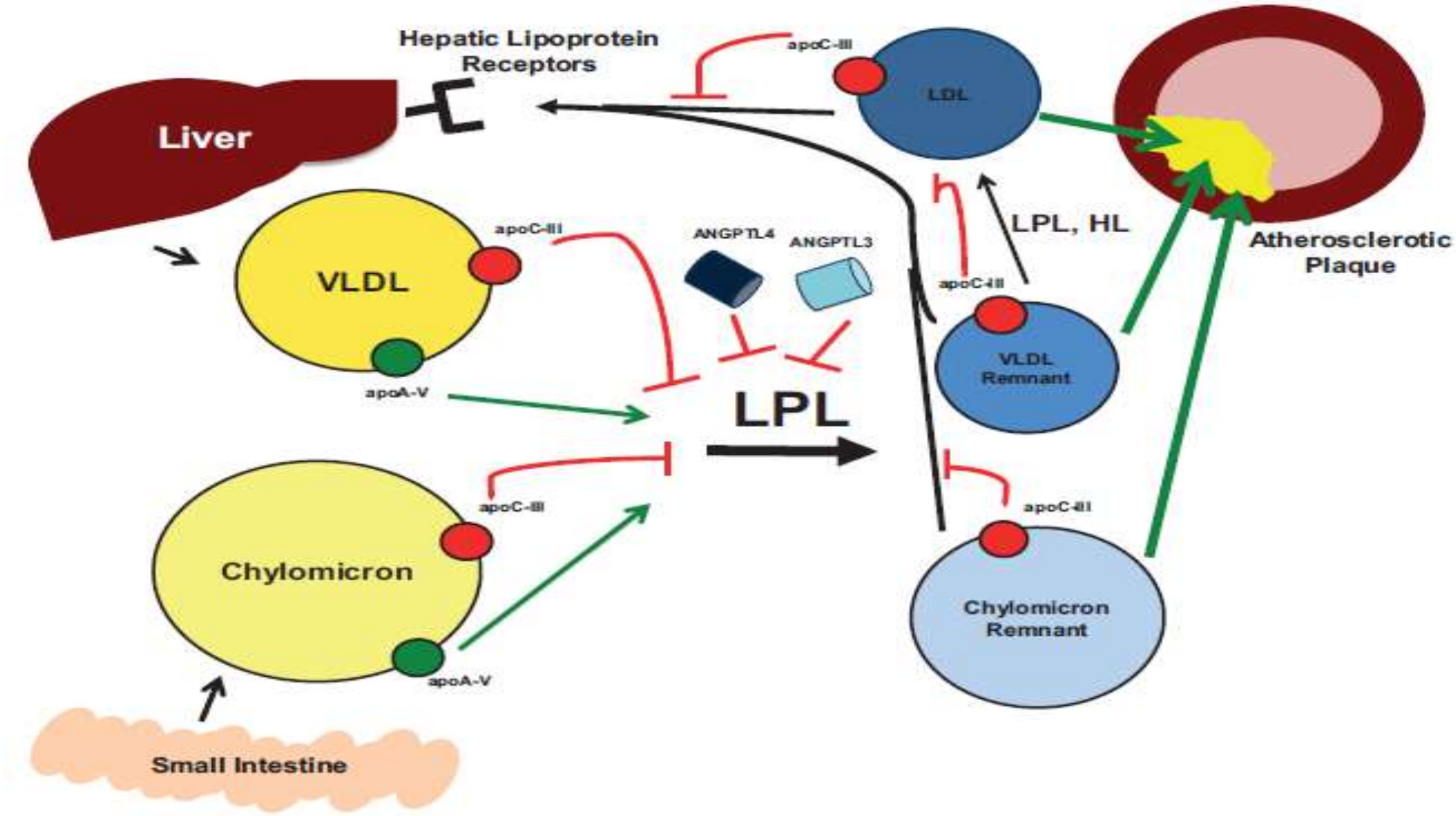
JCI 1961; 40: 536-544

Triglycerides, Lipoproteins, and Coronary Artery Disease

Arch Intern Med 1962; 109: 345-359

Hypertriglyceridemia: New Revelations

Metabolic Fate of Triglyceride-Rich Lipoproteins

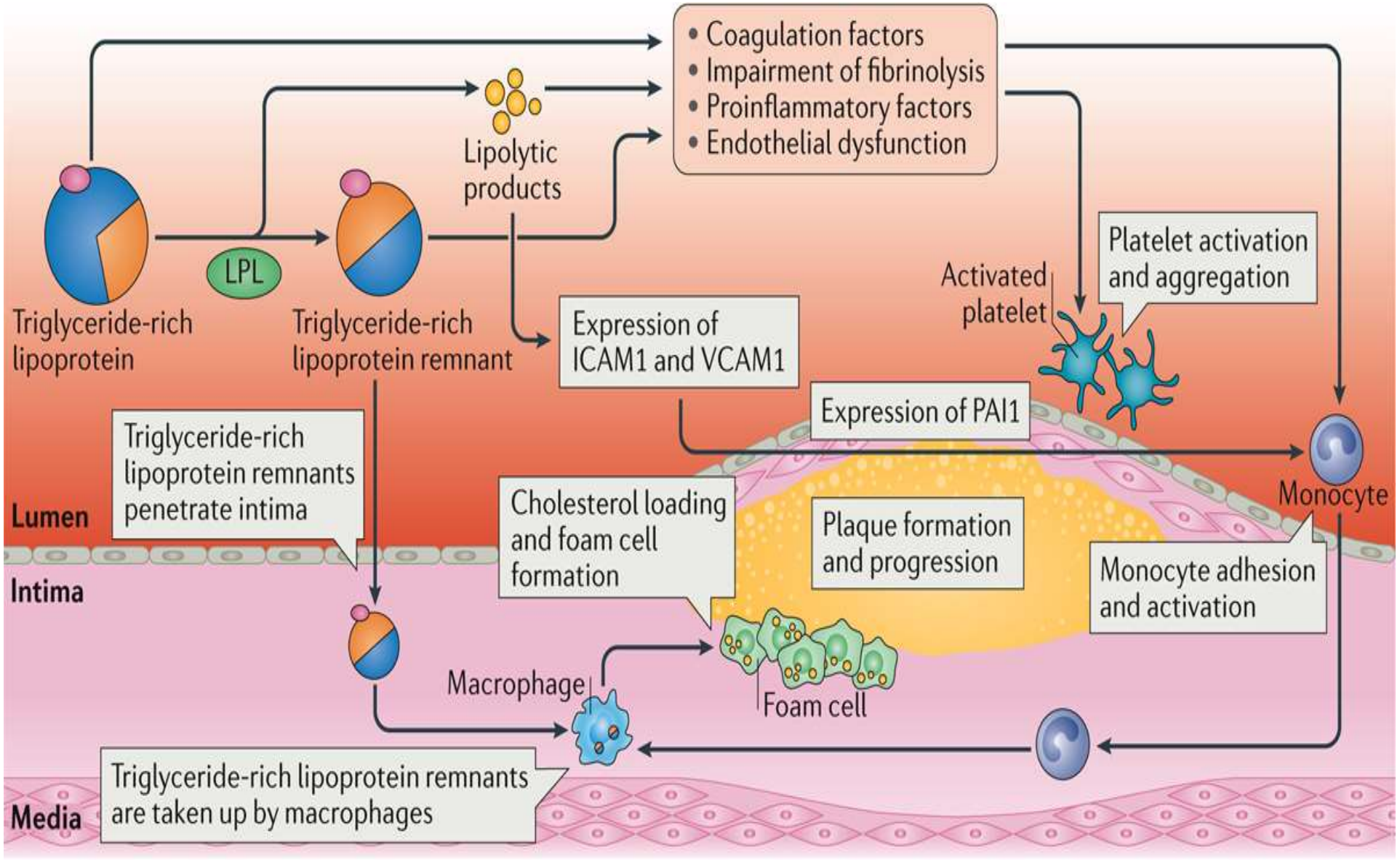


Khetrapal, SA, Rader, DA ATVB 2015; 35: e-3-9

TG-rich Lipoproteins (TRLs): Postulated Mechanisms in Atherogenesis

Direct Toxic Effects

Remnant Cholesterol Entrapment

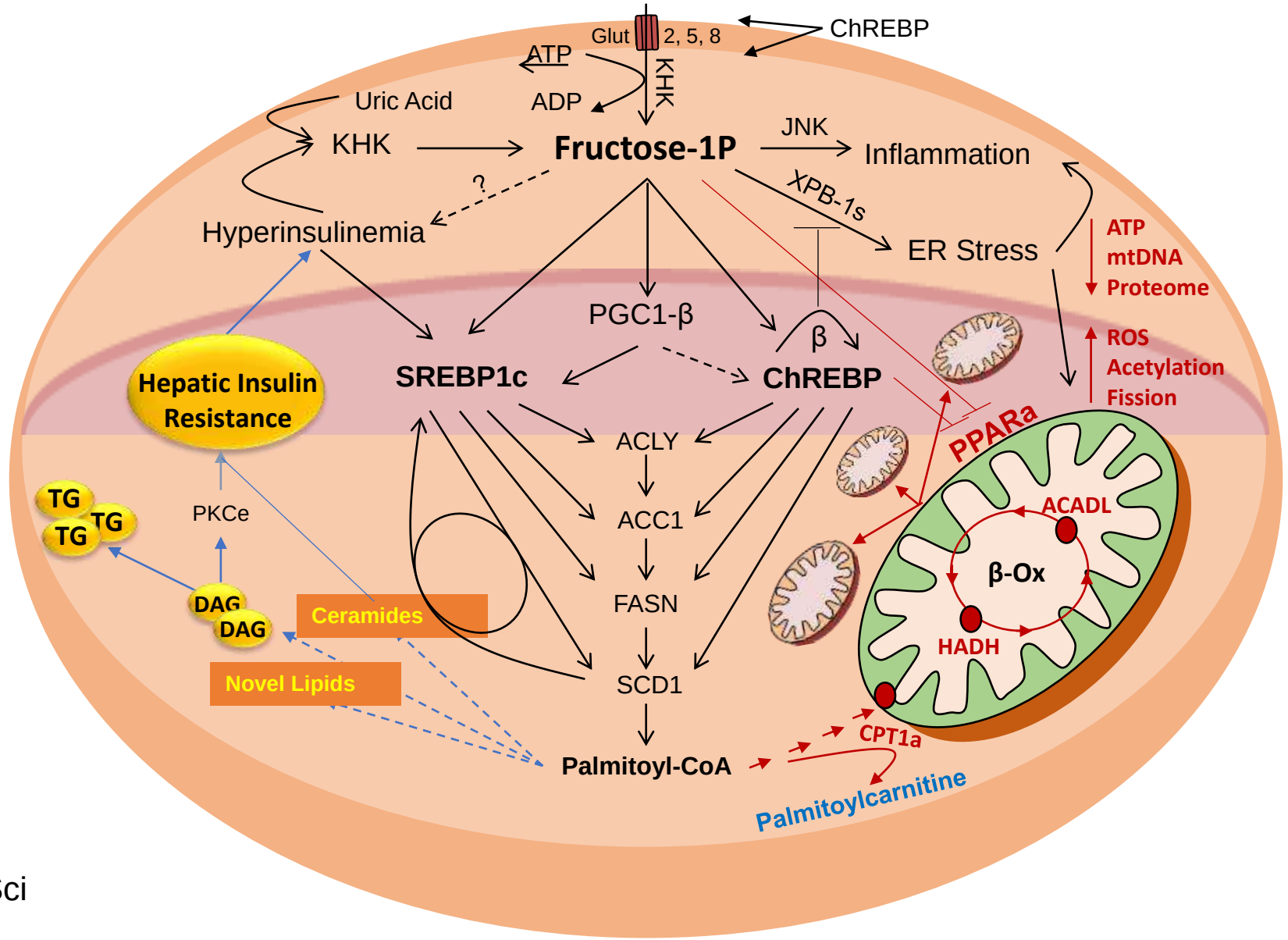


Reiner,Z
Nature Rev Cardiology
2017, 7: 401-411

Initial Approach: Treat Secondary Factors

- Lifestyle factors
- Sucrose/Fructose
- Hyperglycemia
- Co-morbidities (e.g. Hypothyroidism, CKD, GSD, Gammopathy)
- Drugs: corticosteroids, oral estrogen, isotretinoin, HIV- PIs, second generation antipsychotics, immuno-suppressants, etc.

Fructose- induced Pathways to Insulin Resistance



Softic, S et al
Crit Rev Clin Lab Sci
2020, 57: 308-322

Current and Novel Agents for TG-Rich Lipoprotein Management

- Fibrates (gemfibrozil, fenofibrate, others)
- Nicotinic acid (niacin)
- Omega-3 fatty acids (EPA*, EPA with DHA)
- Microsomal transfer Protein (MTP) inhibitor (lomitapide)

Newer agents (in development/trials)

- Pemafibrate (K-877), a novel selective PPARα modulator
- Apolipoprotoein C-3 antagonist (volanesorsen, ISIS 304801)
- Angiopoietin-like Protein 3 (ANGPTL3) inhibitors
- Angiopoietin-like Protein 4 (ANGPTL4) inhibitors
- Lipoprotein Lipase (LPL) gene therapy

*EPA (Eicosapent Ethyl), the only evidence-based omega-3 fatty acid for ASCVD event reduction in combination with statin.

PROMINENT: Study Design

MEN AND WOMEN WITH TYPE 2 DIABETES

10,000 PARTICIPANTS 24 COUNTRIES

TG 200-499 mg/dL (2.26-5.64 mmol/L) and HDL ≤40 mg/dL (1.03 mmol/L)

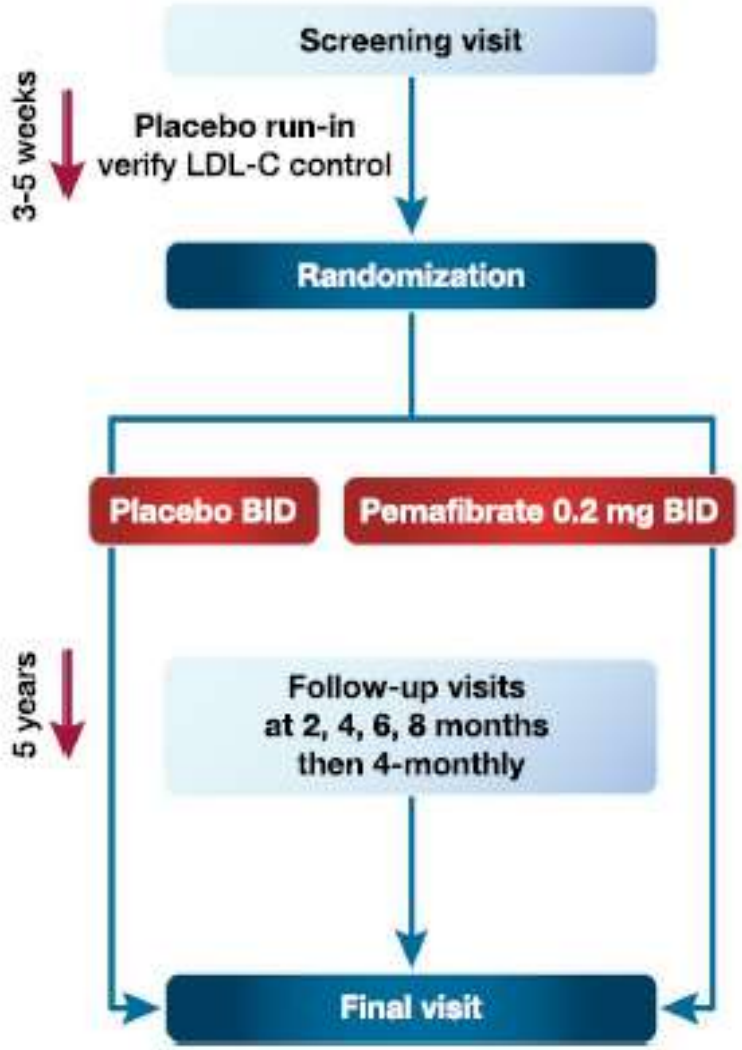
Moderate-High Intensity Statin Therapy or LDL-C Control
(≤70 mg/dL or ≤100 mg/dL if statin intolerant)
1/3 Primary Prevention, 2/3 Secondary Prevention

ENDPOINTS

Event Driven: 1092 Primary Endpoints, 200 in women

PRIMARY ENDPOINT (MACE):
Myocardial infarction, ischemic stroke, or unstable angina requiring unplanned revascularization, cardiovascular death

Secondary/Tertiary Endpoints: all-cause mortality, any coronary revascularization, heart failure, total stroke, retinopathy, nephropathy, glycemic control, PAD, biomarkers, quality of life



Adapted from Pradhan et al 2018

PROMINENT (Pemafibrate) CV Trial: Top-line Results

April 8, 2022

Based on the review of a planned interim analysis, the DSMB concluded that the primary endpoint was unlikely to be met.

Full results
–AHA Meeting Nov 5, 2022

Reduction of Cardiovascular Events with Icosapent Ethyl – Intervention Trial

Baseline Characteristics

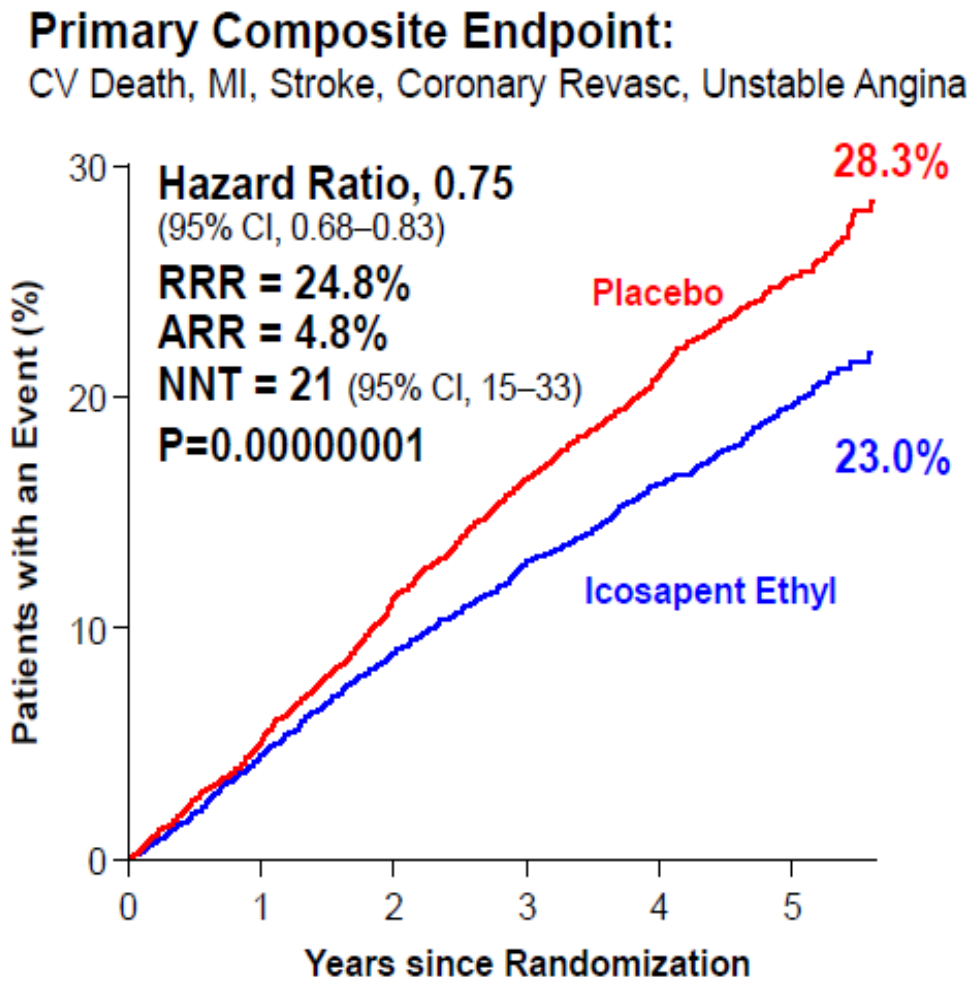
- n= 8,179, Median age, 64 yr, 71 % men,
- All on statin (LDL-C, 40-100; TG 150-499 mg/dl)
  Median Lipids, TG 216, LDL-C 75, HDL-C 40 mg/dl
- CVD, 71 %
- T2DM, 58%
- T2 DM , no prior CVD, 29%

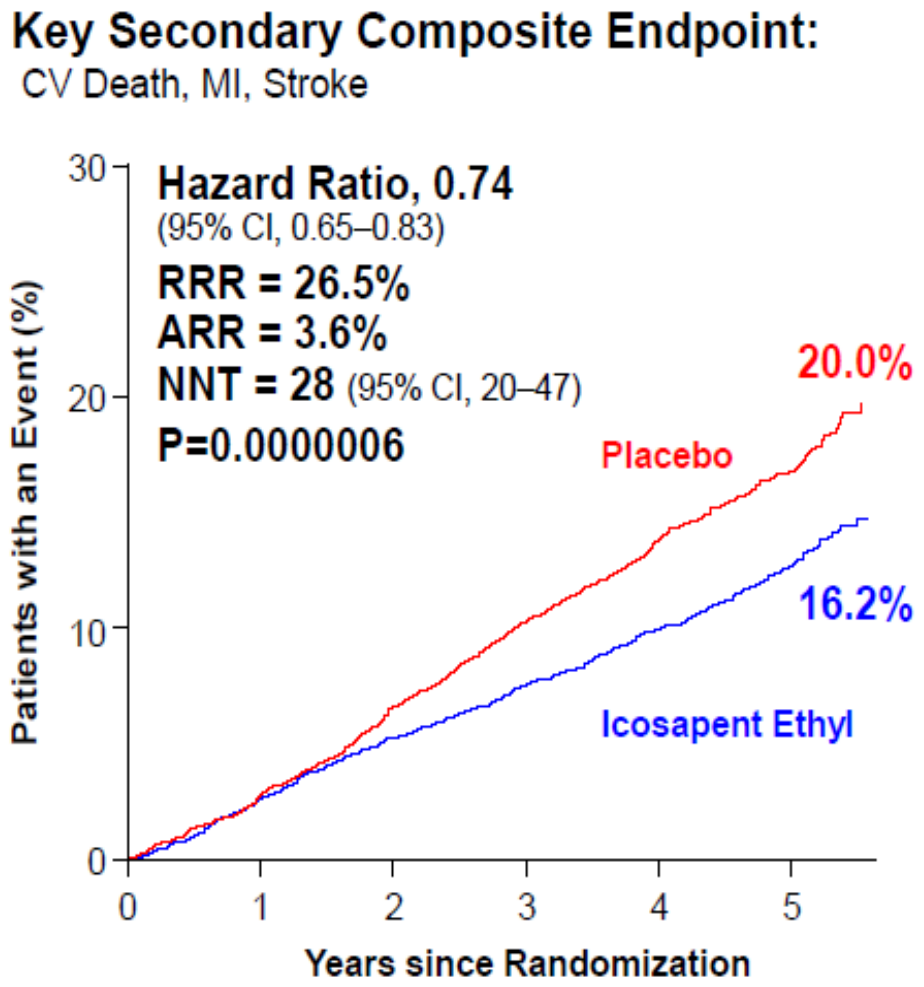
Bhatt, DL et al NEJM 2018; Nov 10; on- line

Effects on Biomarkers from Baseline to Year 1

Biomarker*	Icosapent Ethyl (N=4089) Median		Placebo (N=4090) Median		Median Between Group Difference at Year 1		
	Baseline	Year 1	Baseline	Year 1	Absolute Change from Baseline	% Change from Baseline	% Change P-value
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.0	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
Log hsCRP (mg/L)	0.8	0.6	0.8	1.0	-0.4	-22.5	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	+114.9	+358.8	<0.0001

Primary and Key Secondary Endpoints



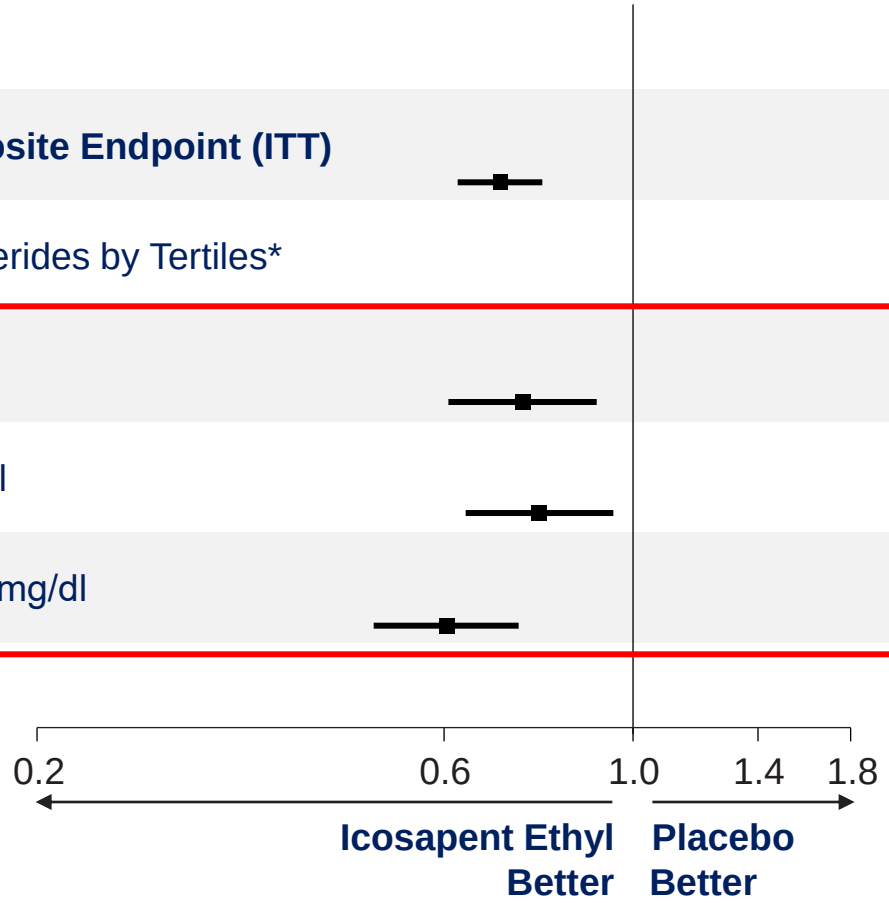


Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

Primary Composite Endpoint:

Total Events by Baseline TG Tertiles

TOTAL EVENTS – Primary Composite Endpoint/Subgroup	Icosapent Ethyl	Placebo	RR (95% CI)	P-value
	Rate per 1000 Patient Years	Rate per 1000 Patient Years		
Primary Composite Endpoint (ITT)	61.1	88.8	0.70 (0.62–0.78)	<0.0001
Baseline Triglycerides by Tertiles*				
80-180 mg/dl	56.4	74.5	0.74 (0.61–0.90)	0.0025
181-250 mg/dl	63.2	86.8	0.77 (0.63–0.95)	0.0120
251 to ≤1400 mg/dl	64.4	107.4	0.60 (0.50–0.73)	<0.0001



***P (interaction) = 0.17**

Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;74:1159-61.

REDUCE-IT: Adverse Events of Interest

Serious Bleeding and AF

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P
Bleeding related disorders	**111 (2.7%)**	**85 (2.1%)**	**0.06**
Gastrointestinal bleeding	**62 (1.5%)**	**47 (1.1%)**	**0.15**
Central nervous system bleeding	**14 (0.3%)**	**10 (0.2%)**	**0.42**
Other bleeding	**41 (1.0%)**	**30 (0.7%)**	**0.19**

- **No fatal bleeding events in either group**
- **Adjudicated hemorrhagic stroke – no significant difference between treatments (13 icosapent ethyl vs 10 placebo; P=0.55)**

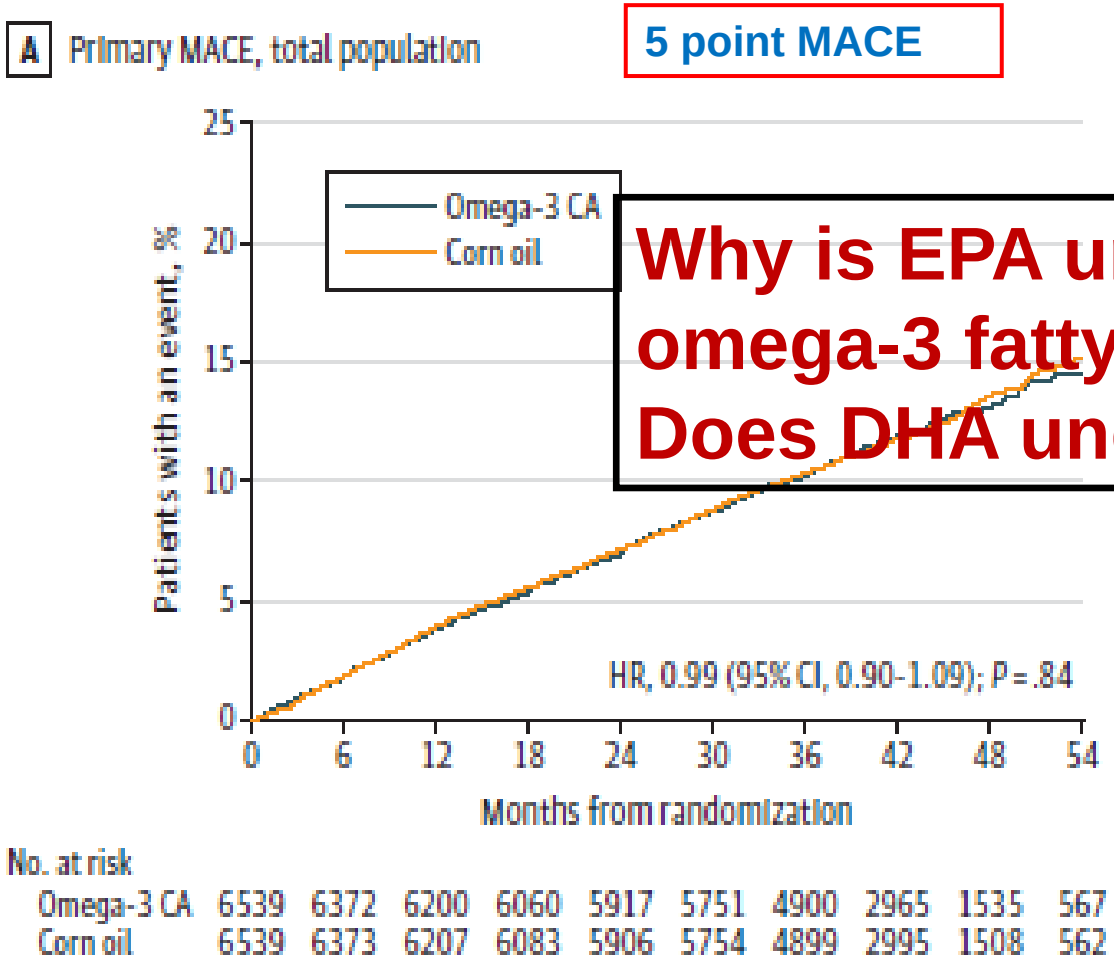
Adjudicated hospitalization for atrial fibrillation/flutter	**127 (3.1%)**	**84 (2.1%)**	**0.004**

Bhatt DL et al. *N Engl J Med.* 2019;380:11-22.

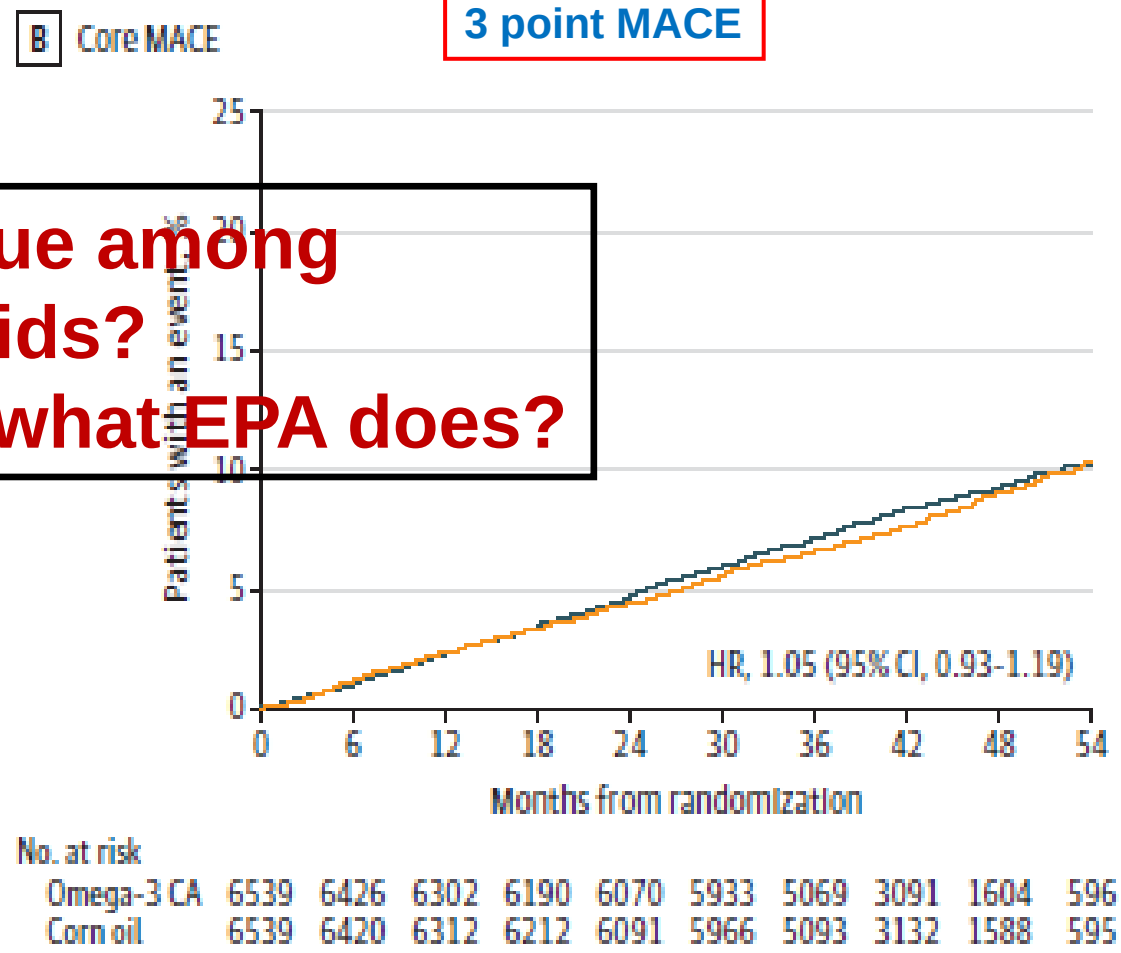
STRENGTH Trial: CV Outcomes with EPA + DHA

Baseline: n, 13078, mean age 63 yr, 35% women, 70% had DM; 56% had ASCVD, on statin
Baseline median Lipids; LDL-C 75, TG 240, HDL-C 36

5 point MACE



3 point MACE

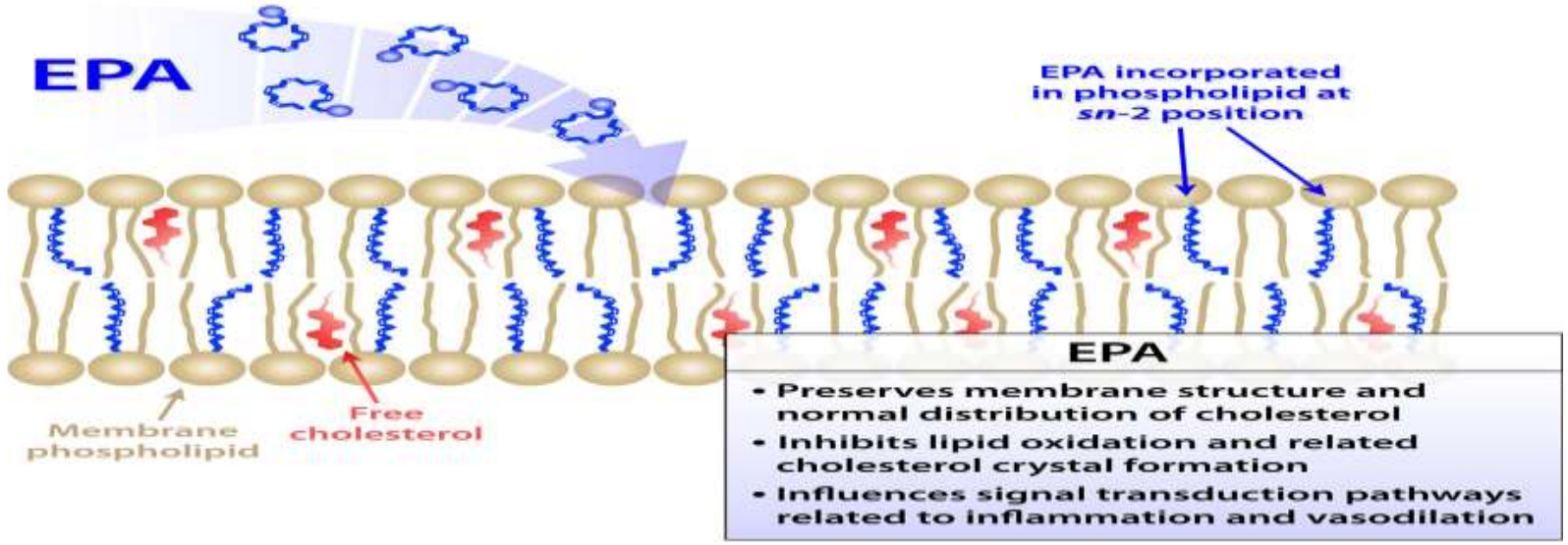


Why is EPA unique among omega-3 fatty acids?
Does DHA undo what EPA does?

Nichols, SJ et al JAMA 2020, Nov 15; on line

Atrial Fib 2.2 vs 1.3 %; P< 0.001

Potential Benefits of EPA in ASCVD

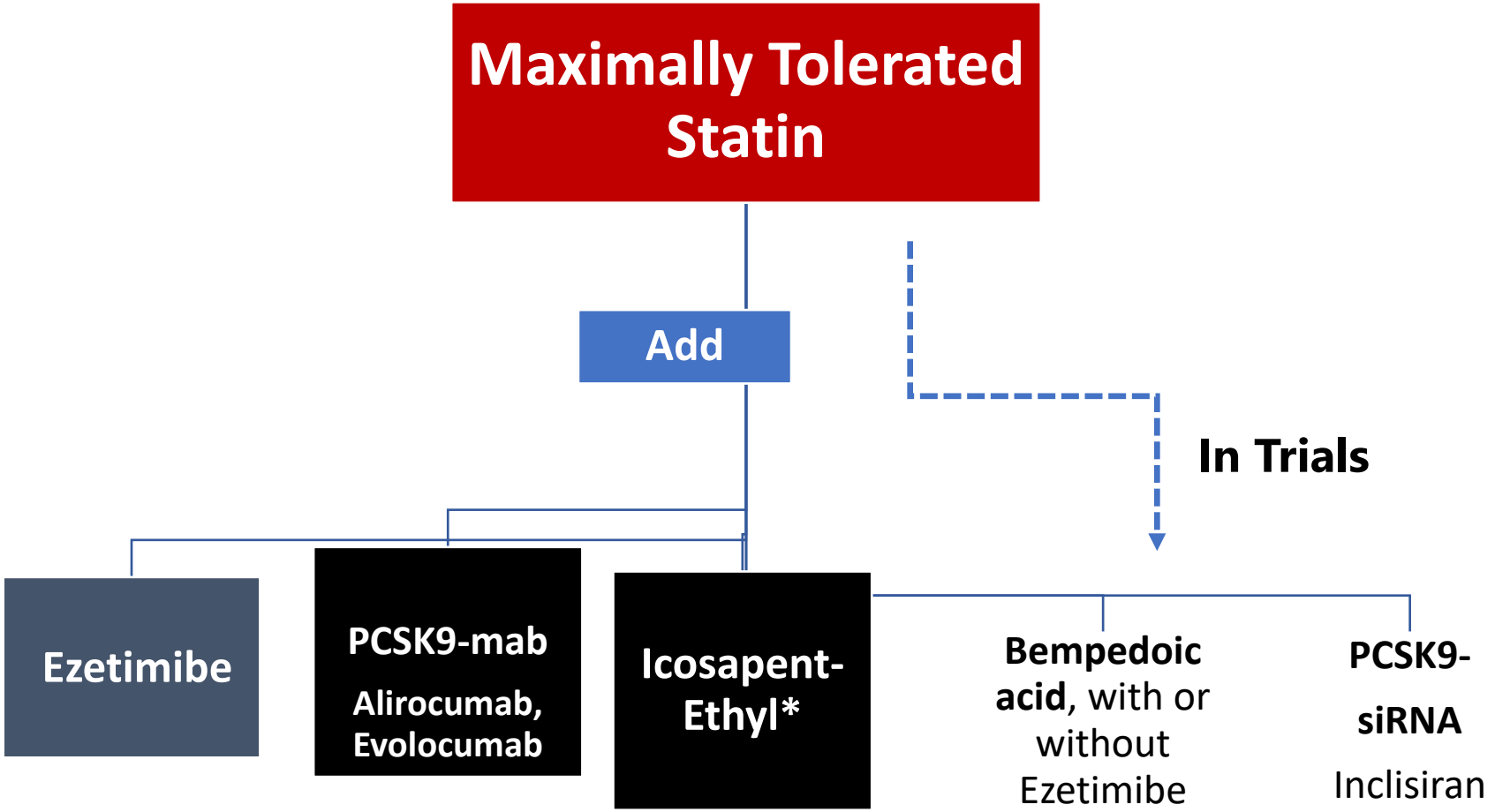


Effects of EPA on Plaque Progression

	Endothelial Dysfunction/ Oxidative Stress	Inflammation/ Plaque Growth	Unstable Plaque
Increase	Endothelial function Nitric oxide bioavailablity	EPA/AA ratio IL-10	Fibrous cap thickness Lumen diameter Plaque stability
Decrease	Cholesterol crystalline domains Ox-LDL RLP-C Adhesion of monocytes Macrophages Foam cells	IL-6 ICAM-1 hsCRP Lp-PLA_2 MMPs	Plaque volume Arterial stiffness Plaque vulnerability Thrombosis Platelet activation

Ganda OP et al. *JACC*. 2018;72:330-343. Mason RP et al. ATVB, 2020

Additional Options for ASCVD Risk Reduction in Statin- Treated Patients with ASCVD, or at High Risk

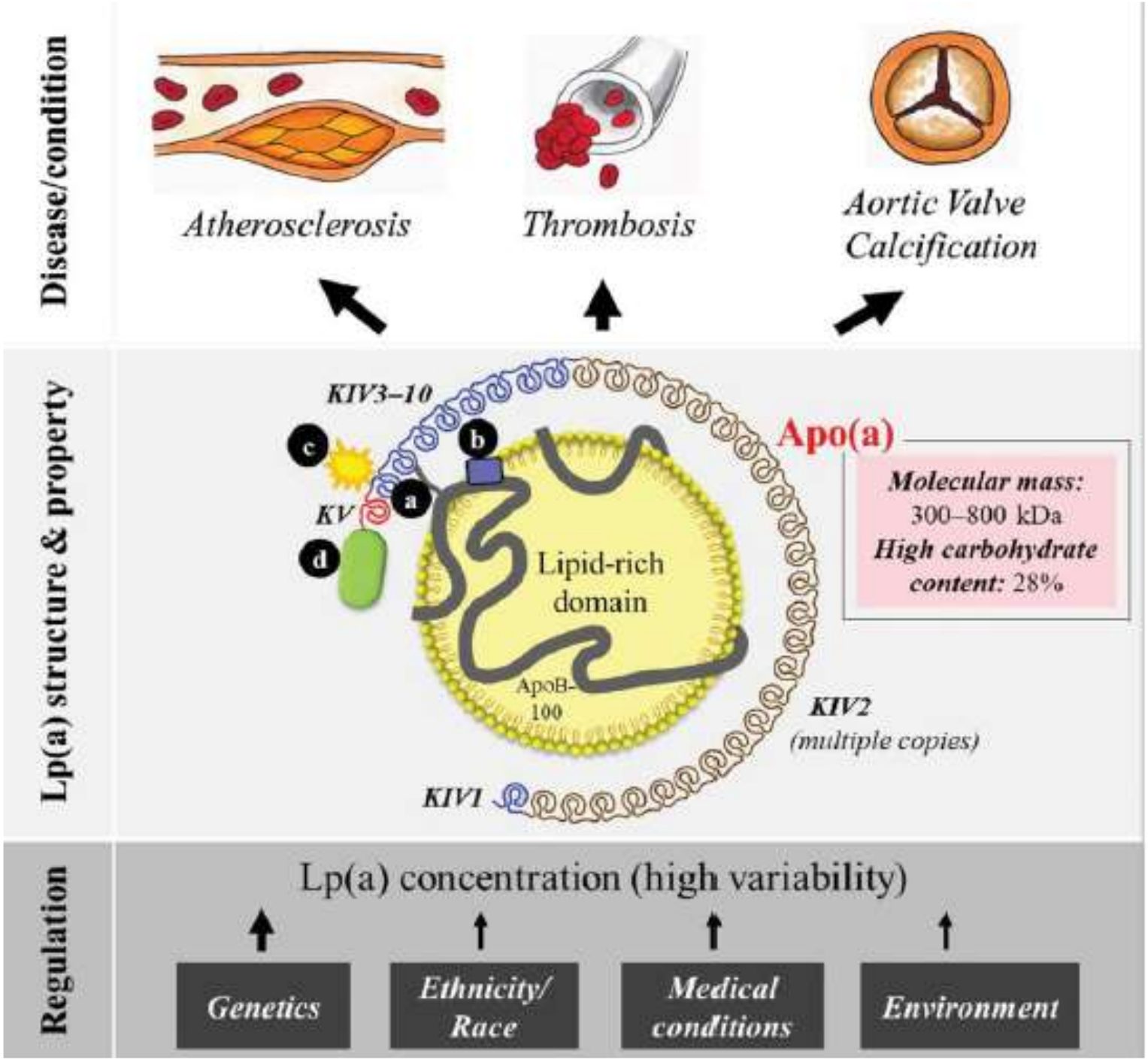


***Stable ASCVD; or Diabetes, age ≥45 years and 2 or more additional risk factors, and TG 135-499 mg/dl**

Adapted from, Ganda, OP Current Opin Lipidol; 2020; 31: 238-245

LP(a):

Postulated Mechanisms of Multiple Actions-



AHA Scientific statement, 2022

LP(a): Emerging Evidence

Lipoprotein(a): the revenant **Gencer B et al Eur Heart Journal, 2017**

National Lipid Association (NLA) Scientific Statement - JCL,2019

Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come.

AHA SCIENTIFIC STATEMENT- ATVB,2022

Lipoprotein(a): A Genetically Determined, Causal, and Prevalent Risk Factor for Atherosclerotic Cardiovascular Disease:

JACC FOCUS SEMINAR- JACC, 2021

Emerging RNA Therapeutics to Lower Blood Levels of Lp(a)

HORIZON –A secondary prevention CVOT with Pelacarsen: an Lp(a) antisense oligonucleotide (in progress)

LP(a): Endocrine Society CPG - 2020

In adult patients with a family history of premature ASCVD, or a personal history of ASCVD, or a family history of high lipoprotein(a), we suggest measuring lipoprotein(a) to inform decision-making about short-term and lifetime ASCVD and the need to intensify LDL-C-lowering therapy. (2⊕⊕OO)

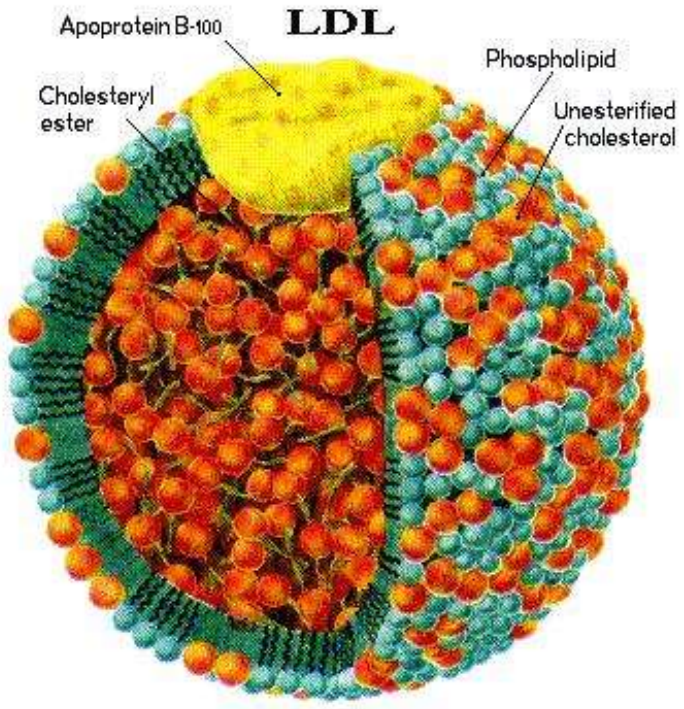
Lipoprotein(a) ≥50 mg/dL (125 nmol/L) enhances the risk of atherosclerotic cardiovascular disease.

Lipoprotein(a) testing does not need to be repeated if it has previously been measured (ie, in childhood or early adulthood).

Newman CB et al J Clin Endocrinol Metab 2020; 105:1-70

Take Home Points

- Major RCTs over the past 25 years have established the predominant role of LDL-C in ASCVD event risk.
- When statin alone is not enough, several novel options are currently available, or in trials, for getting LDL-C to goal
- New evidence from genetic studies and clinical trials have highlighted the importance of TG- rich particles in explaining the residual CV risk after achieving LDL-C targets
- Icosapent Ethyl is the only evidence- based Omega-3FA for CV- event reduction, but the precise mechanism is likely beyond TG- reduction.
- Severe HTG leading to Chylomicronemia syndrome is a treatable cause to prevent hospitalization for acute pancreatitis, but better therapeutic agents are needed
- On- going clinical trials to address LP(a) are addressing its independent role in ASCVD events



Thank You!

VLDL