

Hyperlipidemia

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- University of North Carolina School of Medicine
- Medicine Residency: Brigham and Women's Hospital
- Cardiovascular Medicine Fellowship: BWH
- Research Fellowships: NIH, MIT
- Associate Professor of Medicine, HMS
- Clinical focus:
 - Preventive Cardiology (Director), Lipids, Diabetes, Obesity
- Research focus:
 - Mechanisms of transcriptional regulation of cardio-metabolic issues
 - Translational studies: CV risk in HIV, Rheumatology
 - Health care delivery:
 - Remote management
 - Cardiologist management of diabetes

Disclosures

Consultant

Amgen

Boehringer Ingelheim

Corcept

Merck

New Amsterdam

Novartis

Novo Nordisk

Toku Eyes

Clinical Trials Steering Committee

Esperion, CLEAR, Bempedoic Acid, Secondary Prevention

Novo Nordisk, SELECT, Semaglutide, Secondary Prevention, Obesity, Non-Diabetes

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OBJECTIVES

Within a context of clinical practice as well as board examinations:

Review physiologic pathways and key genetic disorders of lipid metabolism.

Understand contemporary treatment of hypercholesterolemia, including agents, landmark clinical trials as well as recent guideline update.

Discuss hypertriglyceridemia and its management

Review common issues encountered often encountered in clinical situations:

- Statin intolerance, including rhabdomyolysis
- Lipoprotein (a) as an emerging risk factor



MOC REFLECTIVE STATEMENT (BRIEF TAKE HOME NOTES FOR REFERENCE)

Extensive evidence establishes statin therapy as being safe, generally well tolerated and significantly decreases CV risk by lowering LDL-C.

Multiple additional non-statin tools for LDL lowering exist - for patients not achieving optimal LDL levels or who cannot tolerate a statin despite best efforts:

Ezetimibe, PCSK9 inhibitors (alirocumab and evolocumab), bempedoic acid, inclisiran all accessible.

Extensive attention is directed towards lipoprotein (a) as a potential unmet need driving CV risk, with first Lp(a) lowering trial results anticipated in 2026.

Lifestyle still matters, especially with hypertriglyceridemia, along with icosapent ethyl.



Hyperlipidemia

Agenda: Update and Board Review

1. Overview of physiologic pathways of lipid metabolism (context)
2. Genetic disorders of key clinical (and board) relevance
3. Treatment of cholesterol and lipid disorders:
 - Agents
 - Landmark clinical trials
 - Guidelines, including new 2026 AHA/ACC guidelines
4. Common clinical issues
 - Statin intolerance
 - New agents
 - Emerging lipid risk factors

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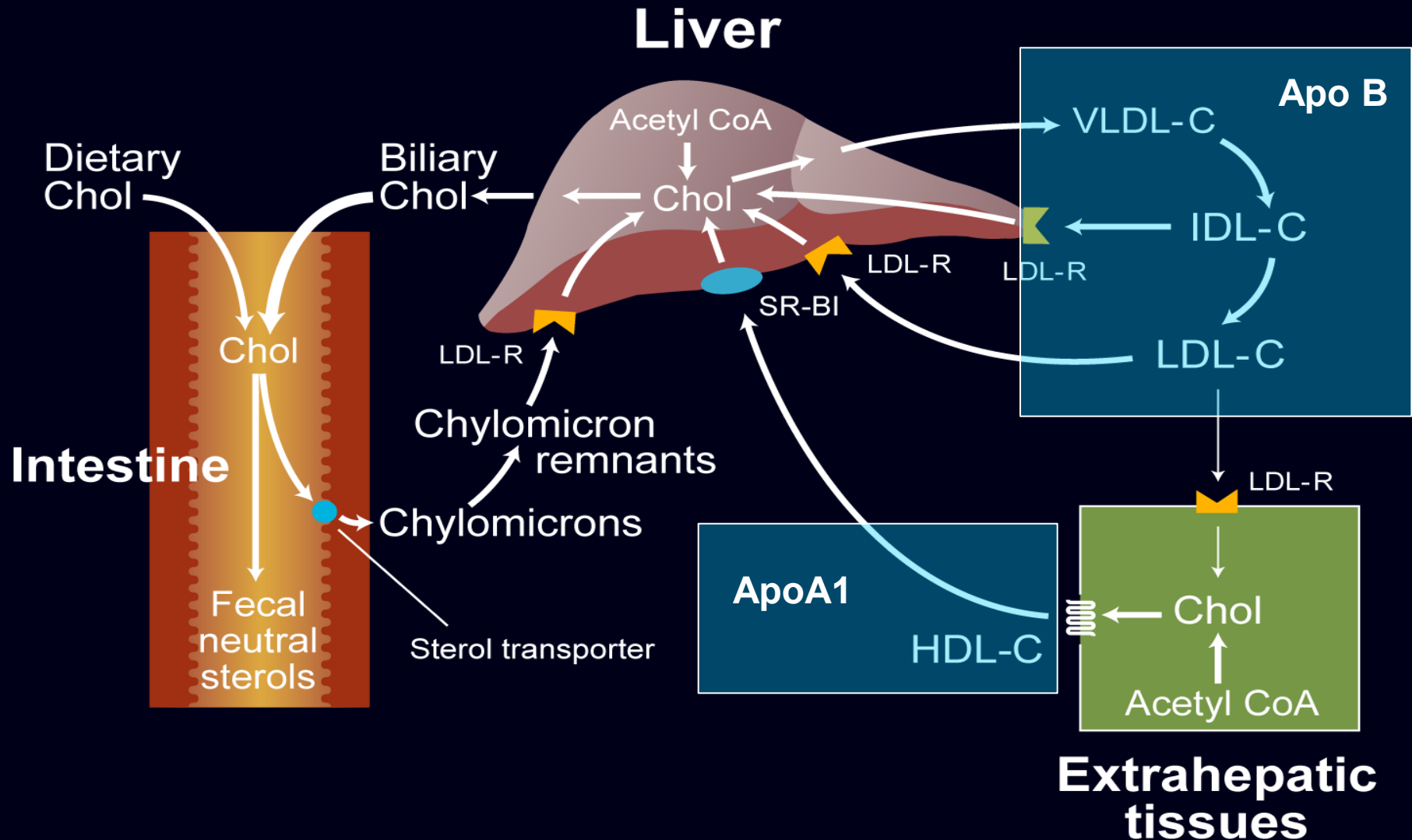
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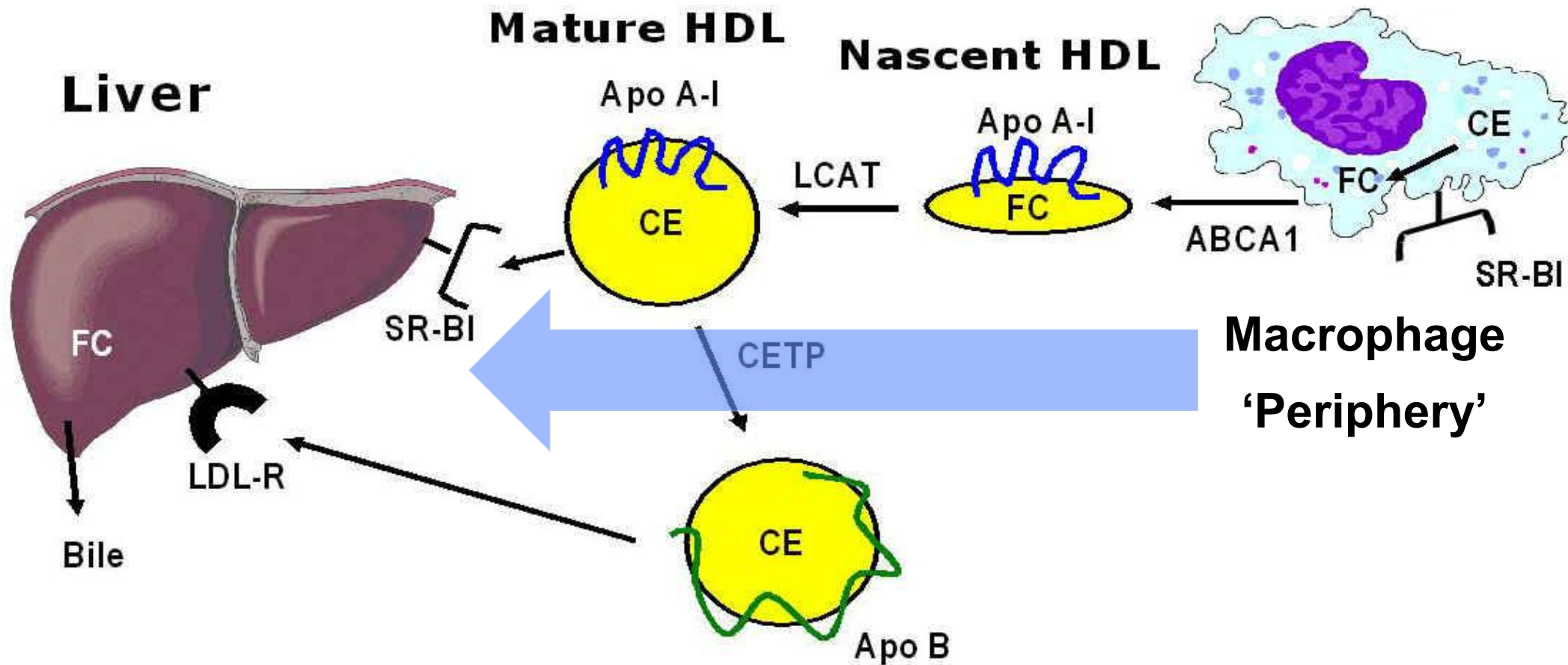
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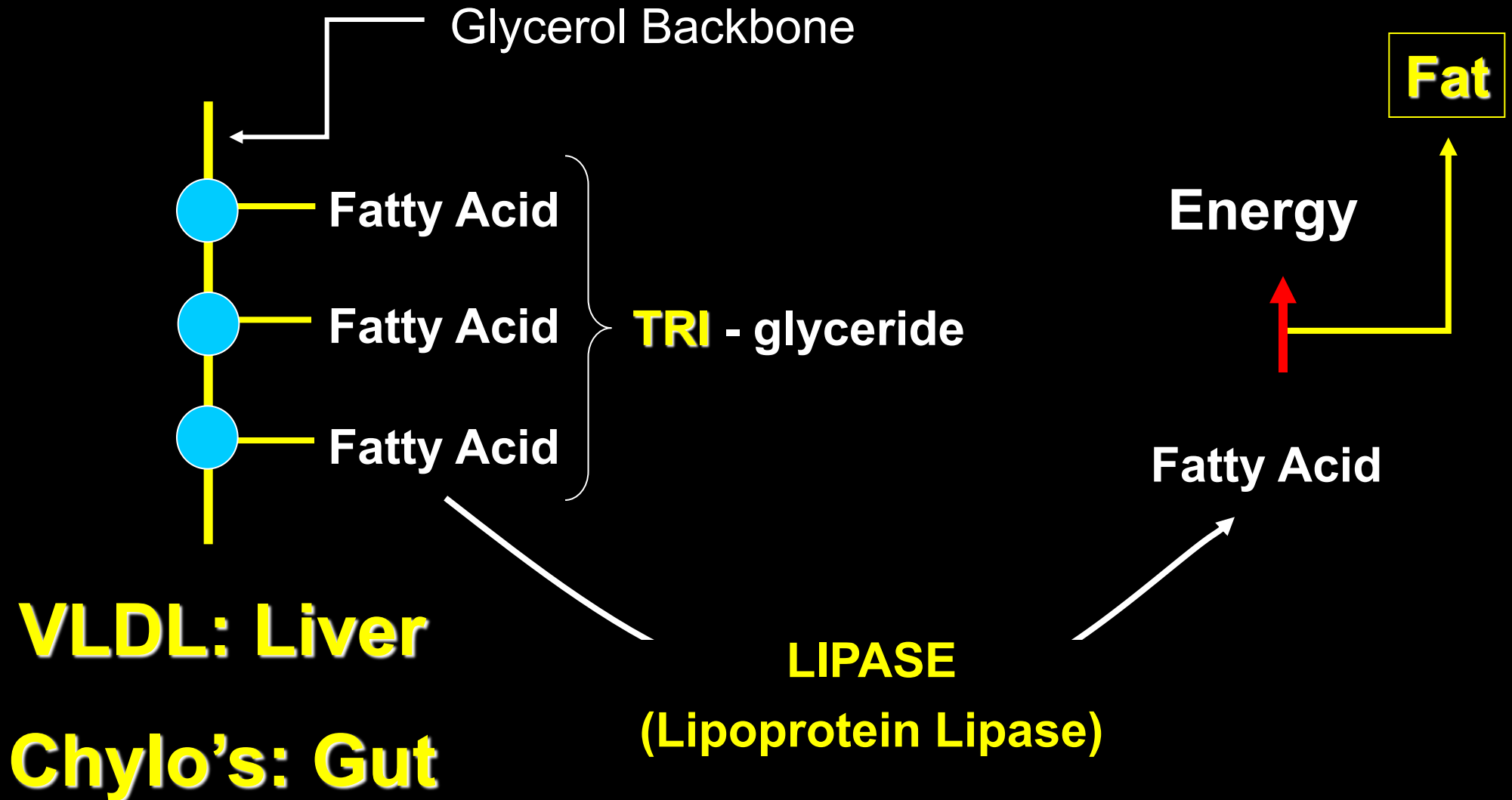
Overview of Cholesterol Transport



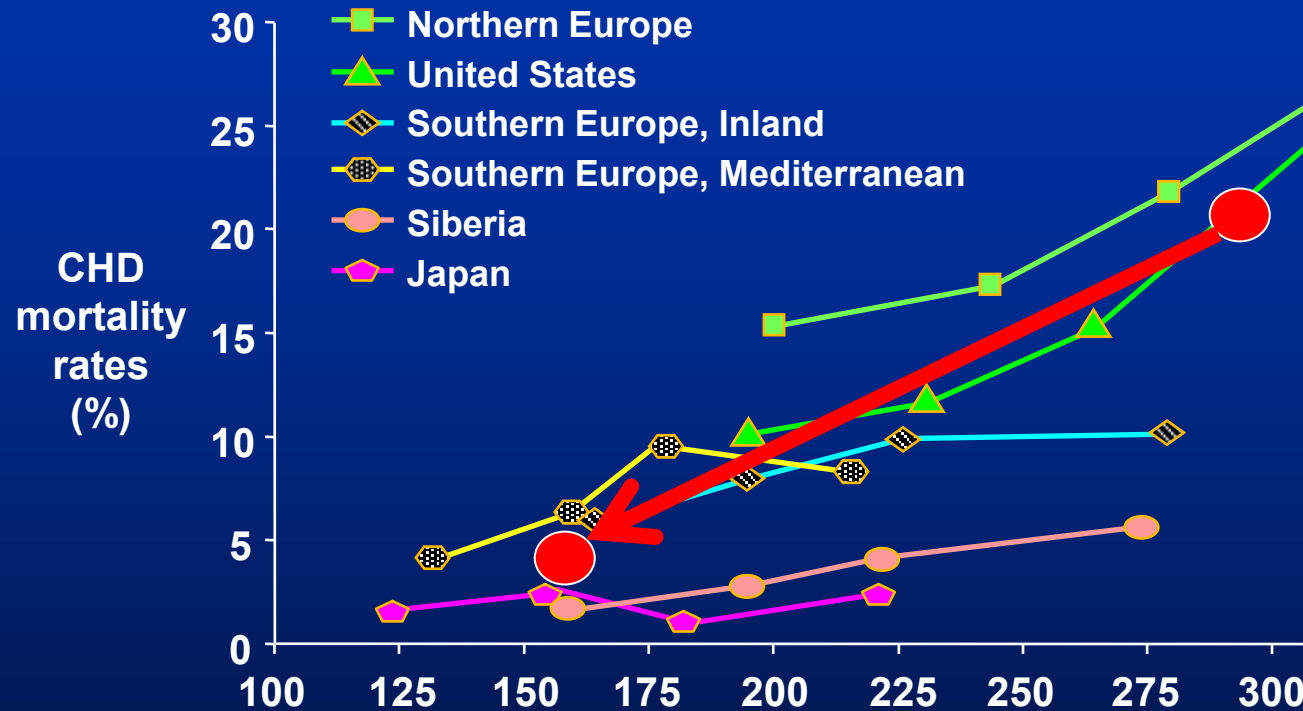
Reverse Cholesterol Transport



Triglycerides: Energy Resource



1957: Seven Countries Study, Ancel Keys "The Cholesterol Hypothesis"



Ancel Keys

Cholesterol predicts CV Mortality around the world

K (Keys) ration, military, Mediterranean style diet



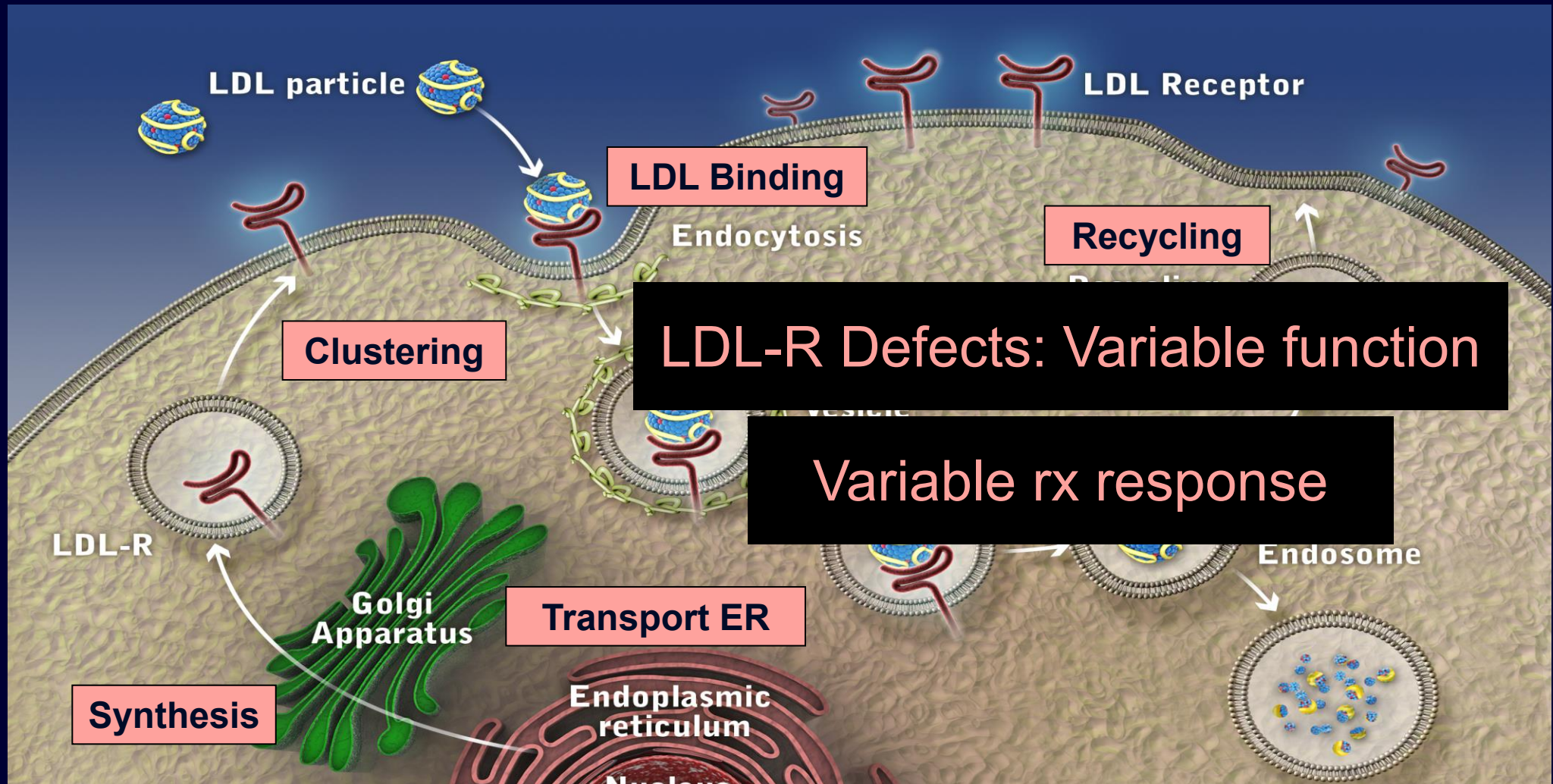
January 1961

Homozygous FH

- Two mutant alleles
- 1: 1 million (debated)
- Characterized:
 - Receptor negative: < 2% LDLR activity - worse prognosis
 - Receptor defective: 2-25% LDLR activity
- Present in childhood:

Cutaneous xanthoma, tendinous xanthomas, corneal arcus
- TC > 500 - 1200 mg/dL (LDL > 300 mg/dL)
- Atherosclerosis: Aortic root. Aortic valve (aortic stenosis). CAD
- Treatment (depends on LDL-R functionality)
 - Statin, PCSK9i, Ezetimibe...
 - Evinacumab (Evkeeza) – antibody to ANGPTL3
 - Ileal bypass, liver transplant, apheresis; gene therapy?

Function and Life Cycle of the LDL Receptor



LDL Receptor Defects: Span biologic function

Heterozygous FH

- 1:500 persons
- Lipids: Elevated TC, LDL, normal Tg
- Fam Hx: hyper-CHO/CAD
- Tendinous xanthoma virtually diagnostic:
 - Achilles tendon, digit extensor MCP
- R/O: hypothyroidism, obstructive liver dz
- Clinical manifestations often greater in men vs women
- Variability of clinical course dictated by mutations, genetics
 - Consistency within a kindred
 - LDL level correlation with onset CAD can vary

FH Diagnosis: Clinical

- **Definitive:**
 - CHO > 260 in children < 16 yo or >290 adults **OR**
 - LDL > 190 adults
 - AND**
 - Tendon xanthoma in patient or 1st, 2nd degree relative
- **Possible:**
 - Elevated LDL plus
 - FHx MI < 50 in 2nd degree, < 60 1st degree
 - FhX CHO > 290
- **NOT xanthelasma**

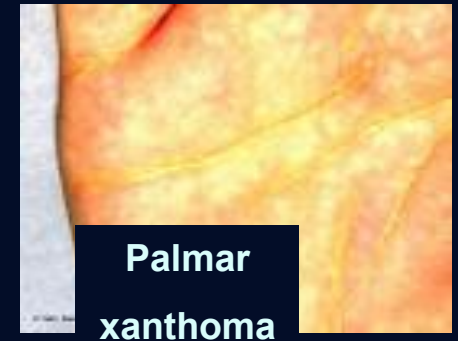


4 Genes Associated with Familial Hypercholesterolemia

Mutant Gene Product	Pattern of Inheritance (chromosome)	Prevalence	Mutation Effect	Aver LDL-C (mg/dL)
LDL receptor	Auto Dom (19p13.2)	HTZs: 1/500 HMZs: 1/10 ⁶	Loss of function	HTZs: 350 HMZs: 700
Apolipoprotein B-100	Auto Dom (2p24)	HTZs: 1/1000* HMZs: 1/10 ⁶ *	Loss of function	HTZs: 270 HMZs: 320
ARH adaptor	Auto Rec (1p36-p35)	Very rare	Loss of function	HMZs: 470
PCSK9 protease	Auto Rec (1p34.1-p32)	Very rare	Gain of function	HTZs: 225

Genetic Dyslipidemic Diseases, that Commonly Present on the Boards

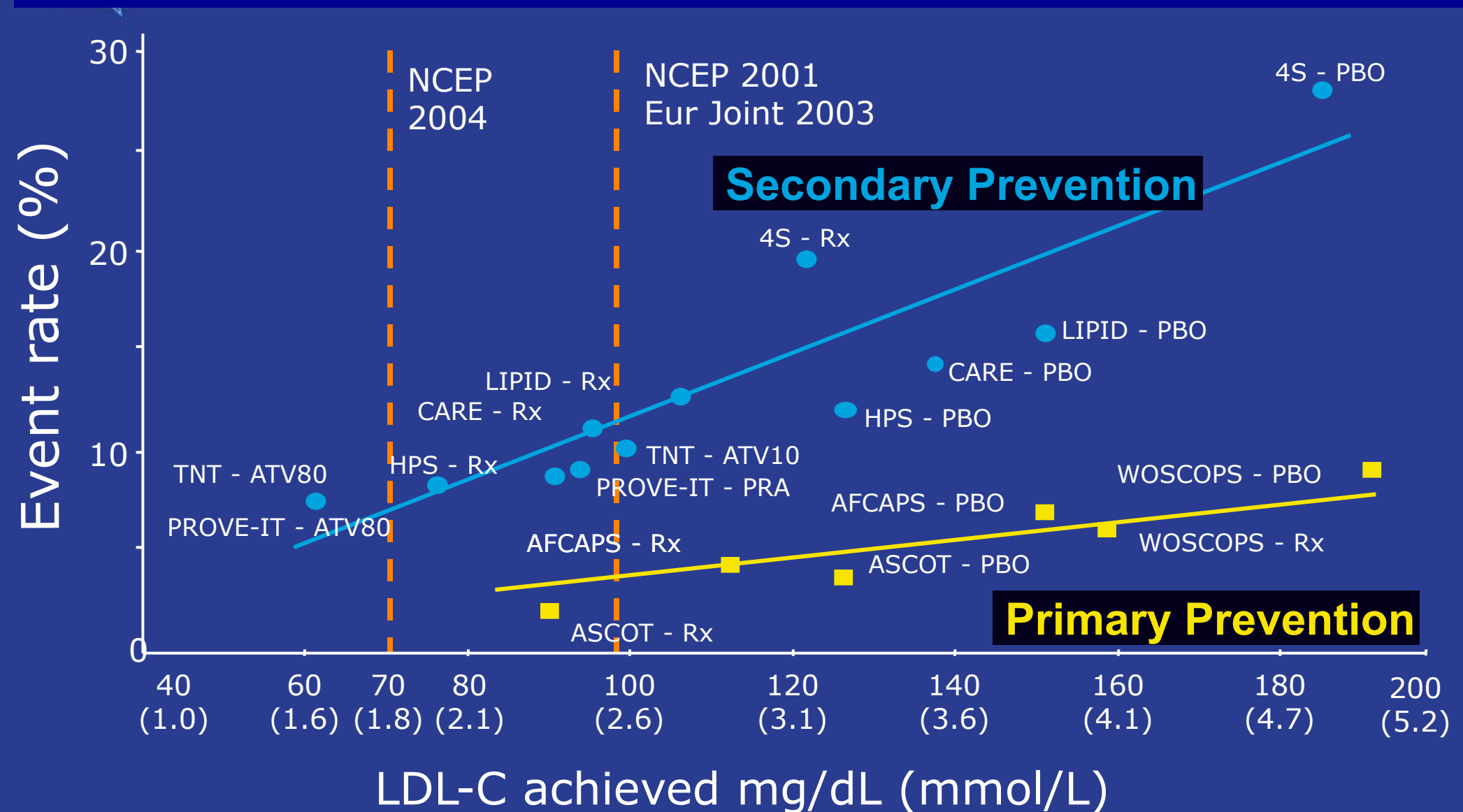
- Triglycerides:
 - Type III Hyperlipidemia
 - LPL defects



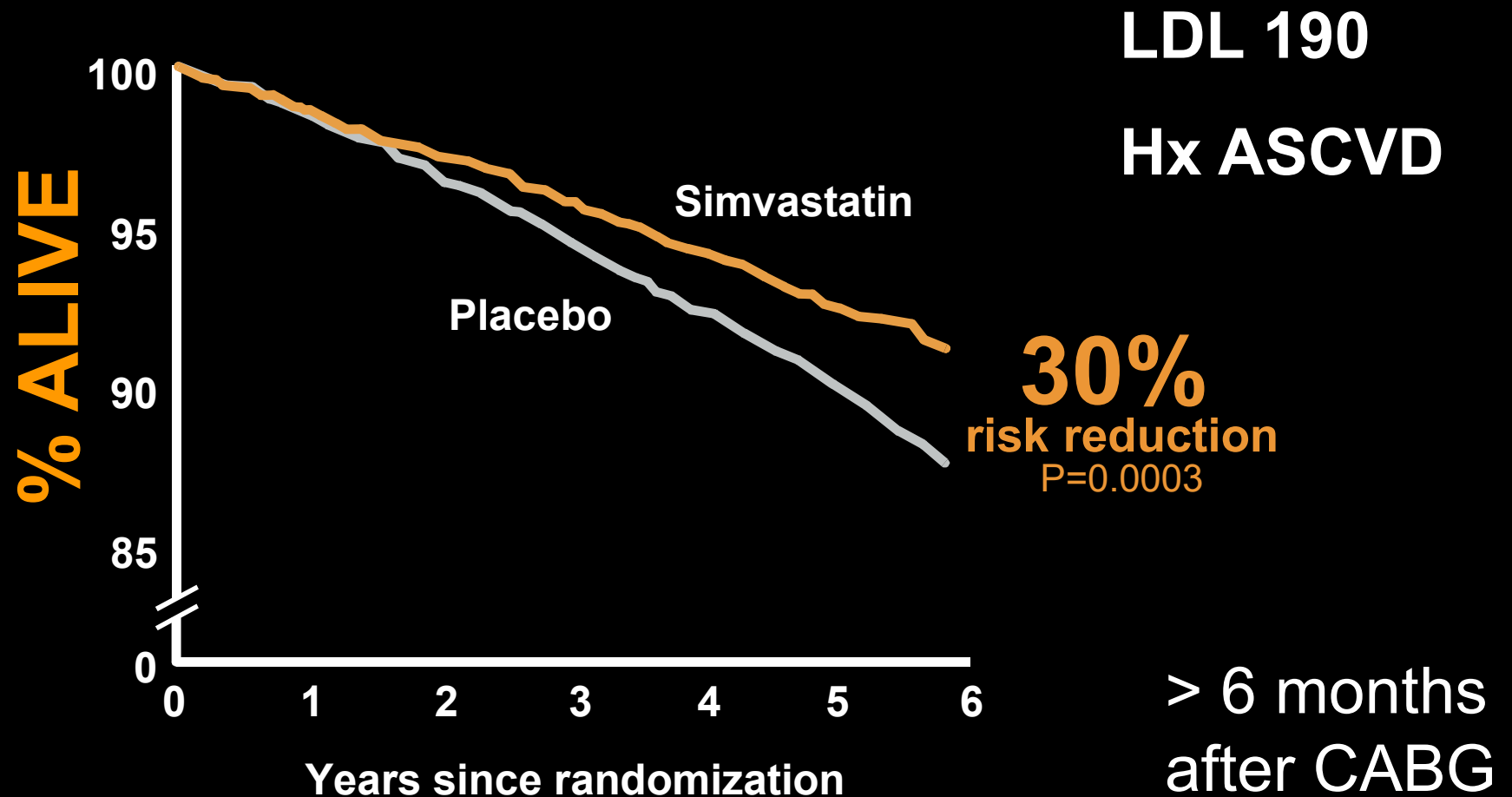
- HDL
 - Tangier's Disease
 - Low HDL
 - Defect in ABCA1
 - Orange tonsils



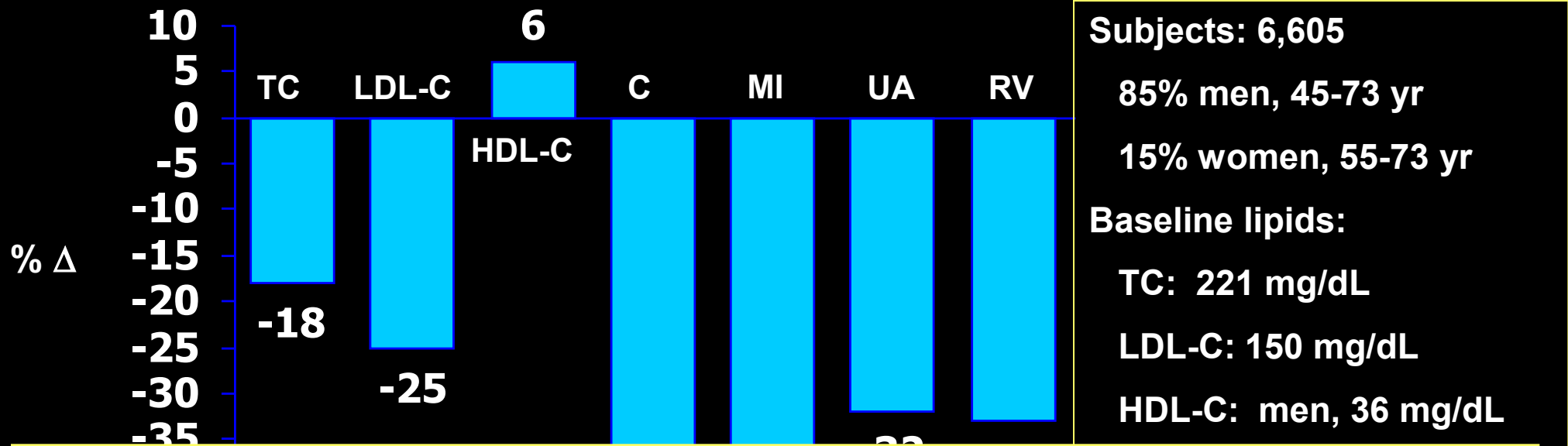
Statins: CV Benefit With LDL-C Lowering Across CV Risk



4S: Total Mortality/Overall Survival



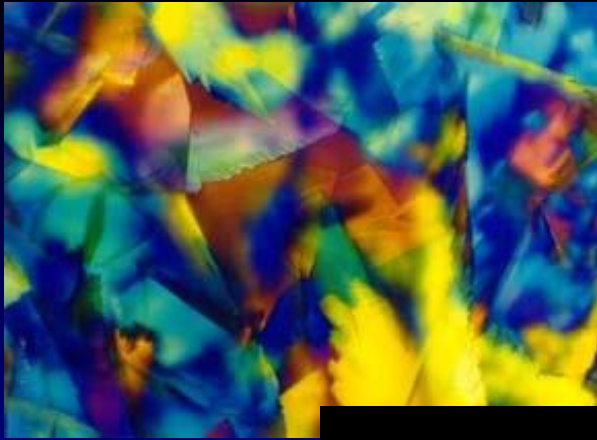
AFCAPS: LDL-Lowering in **PEOPLE** With No HX OF CAD and Average Cholesterol Levels



**70% of AFCAPS subjects
untreated under ATP II**

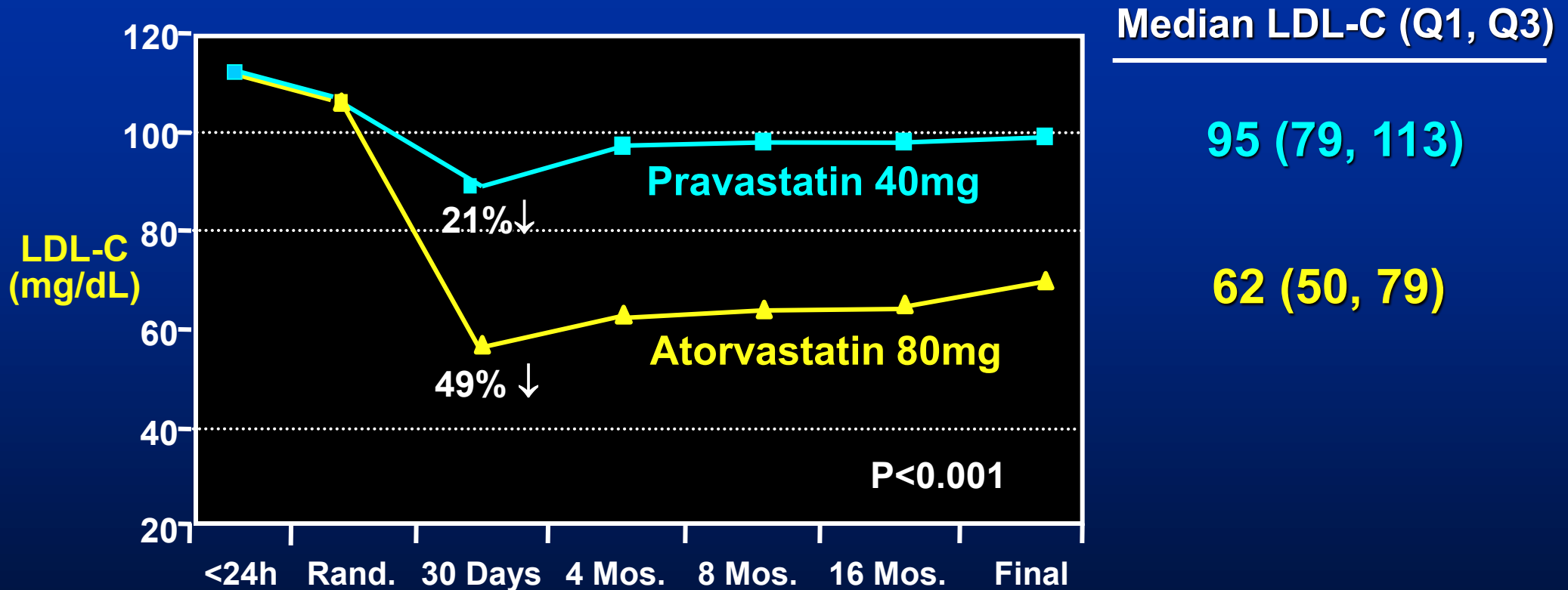
MI=fatal/nonfatal myocardial infarction; UA=unstable angina;
RV=revascularizations.

Downs JR et al. *JAMA*. 1998;279:1615-1622.



Is even lower LDL better
In high risk population:
acute coronary syndrome?
PROVE-IT

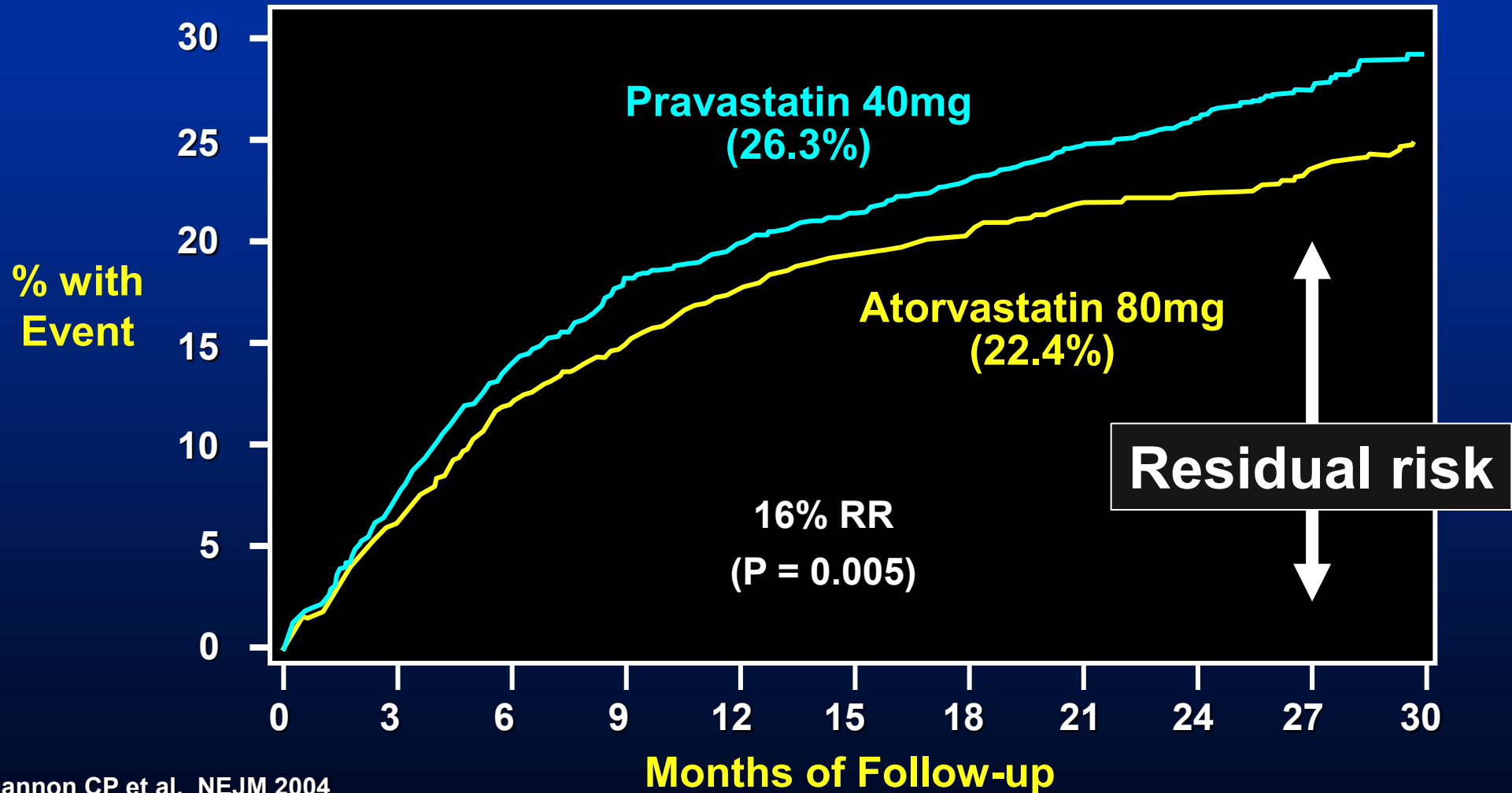
PROVE-IT: Changes from Post-ACS Baseline LDL-C



Note: Changes in LDL-C may differ from prior trials:

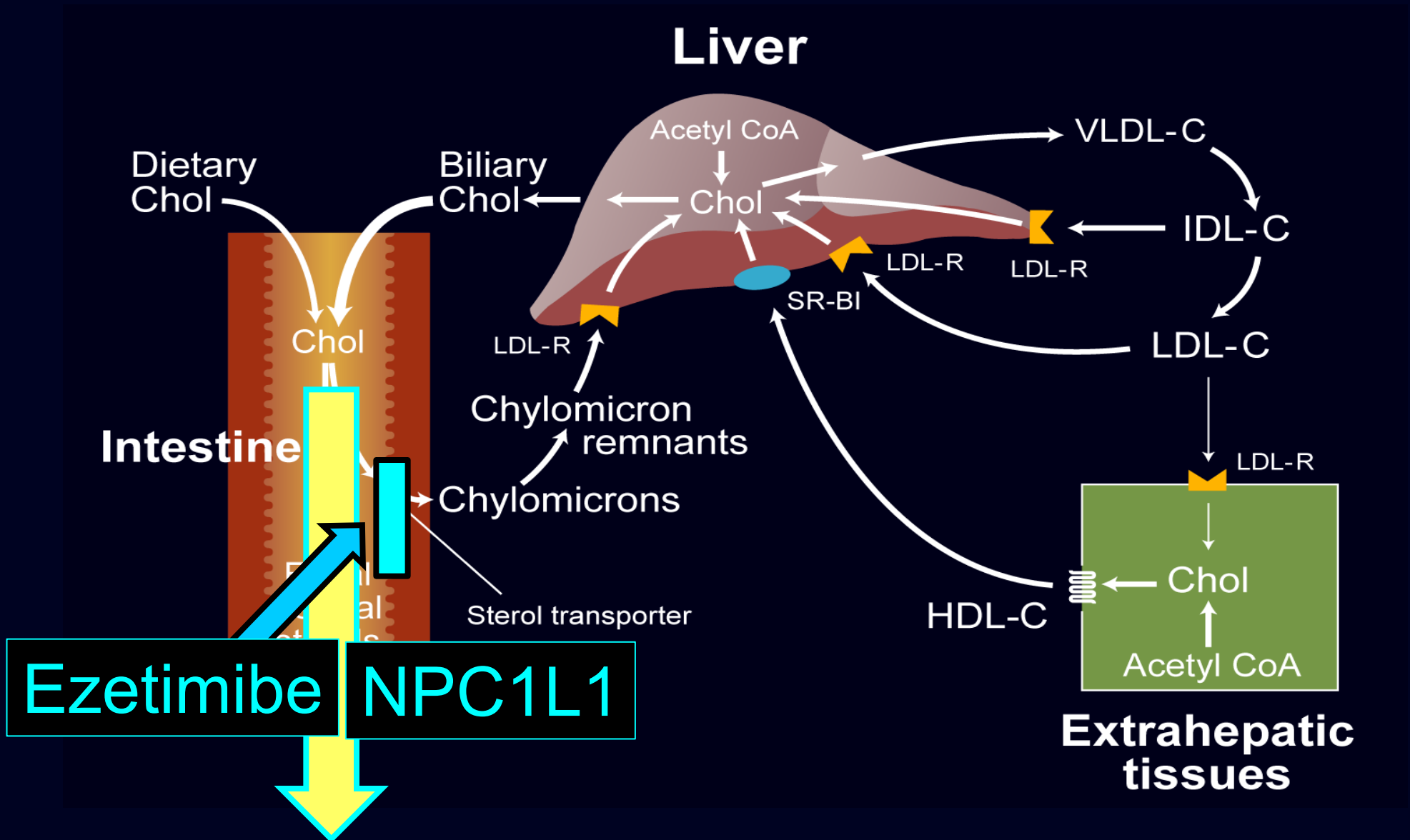
- 25% of patients on statins prior to ACS event
- ACS response lowers LDL-C from true baseline

All-Cause Death or Major CV Events in All Randomized Subjects

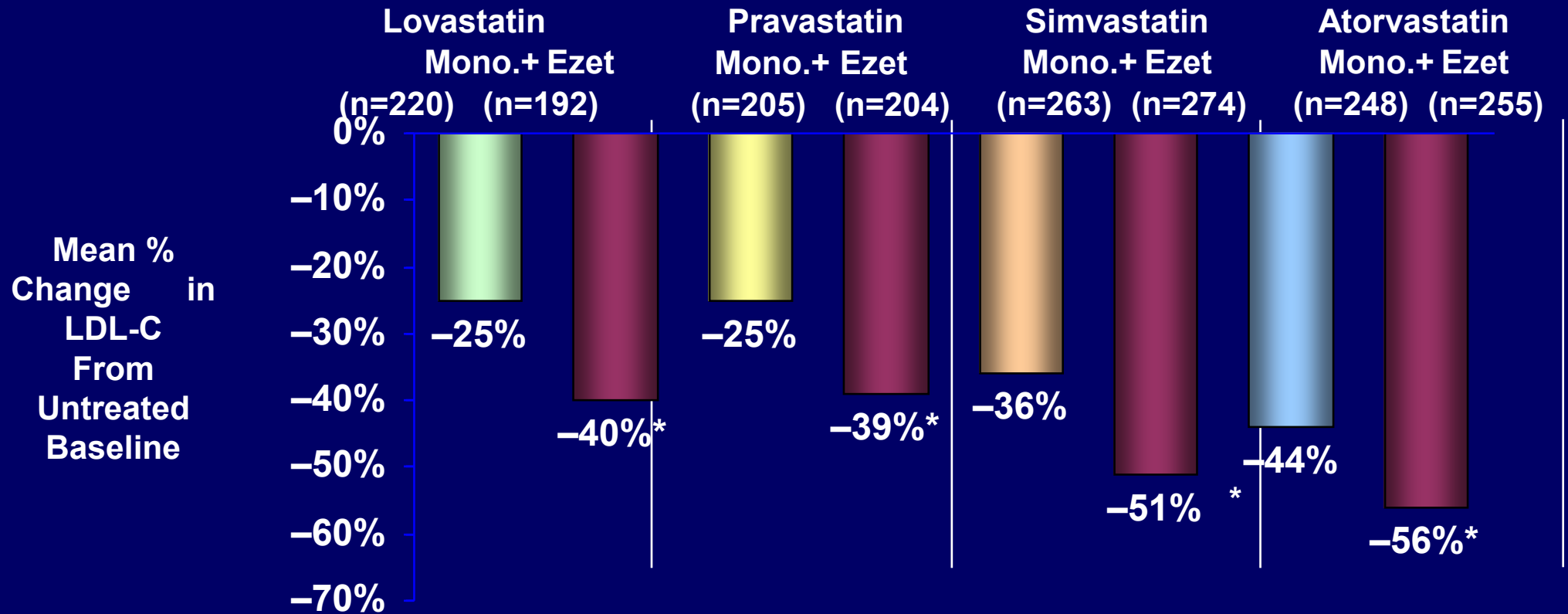


Overview of Cholesterol Transport

Non-statin



Ezetimibe + Statin: ~10-20% LDL Reduction With All Tested Statins



All data are pooled across doses.

* $P < 0.01$ for ZETIA + statin vs statin alone.

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**

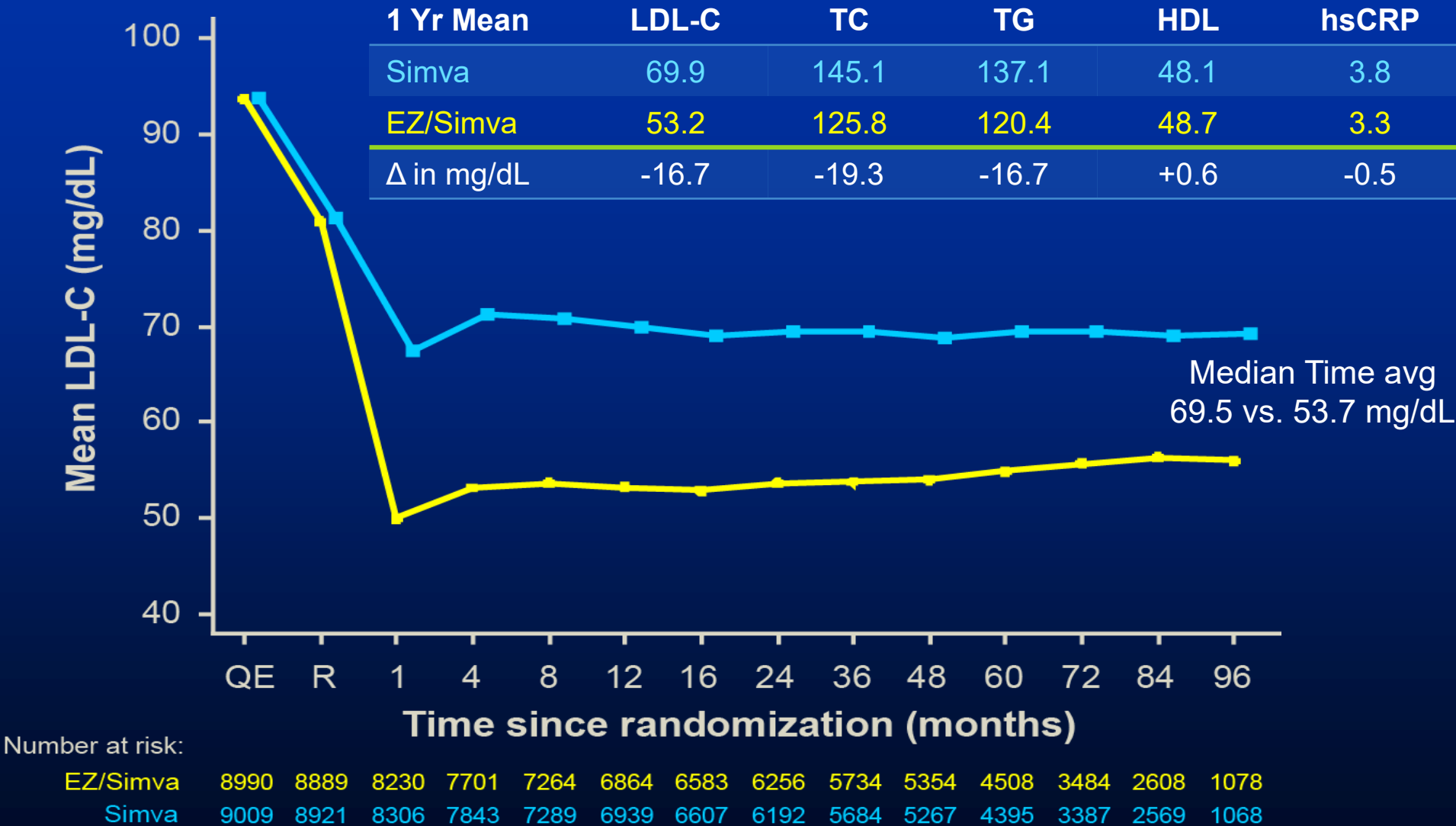
Follow-up Visit Day 30, every 4 months

*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

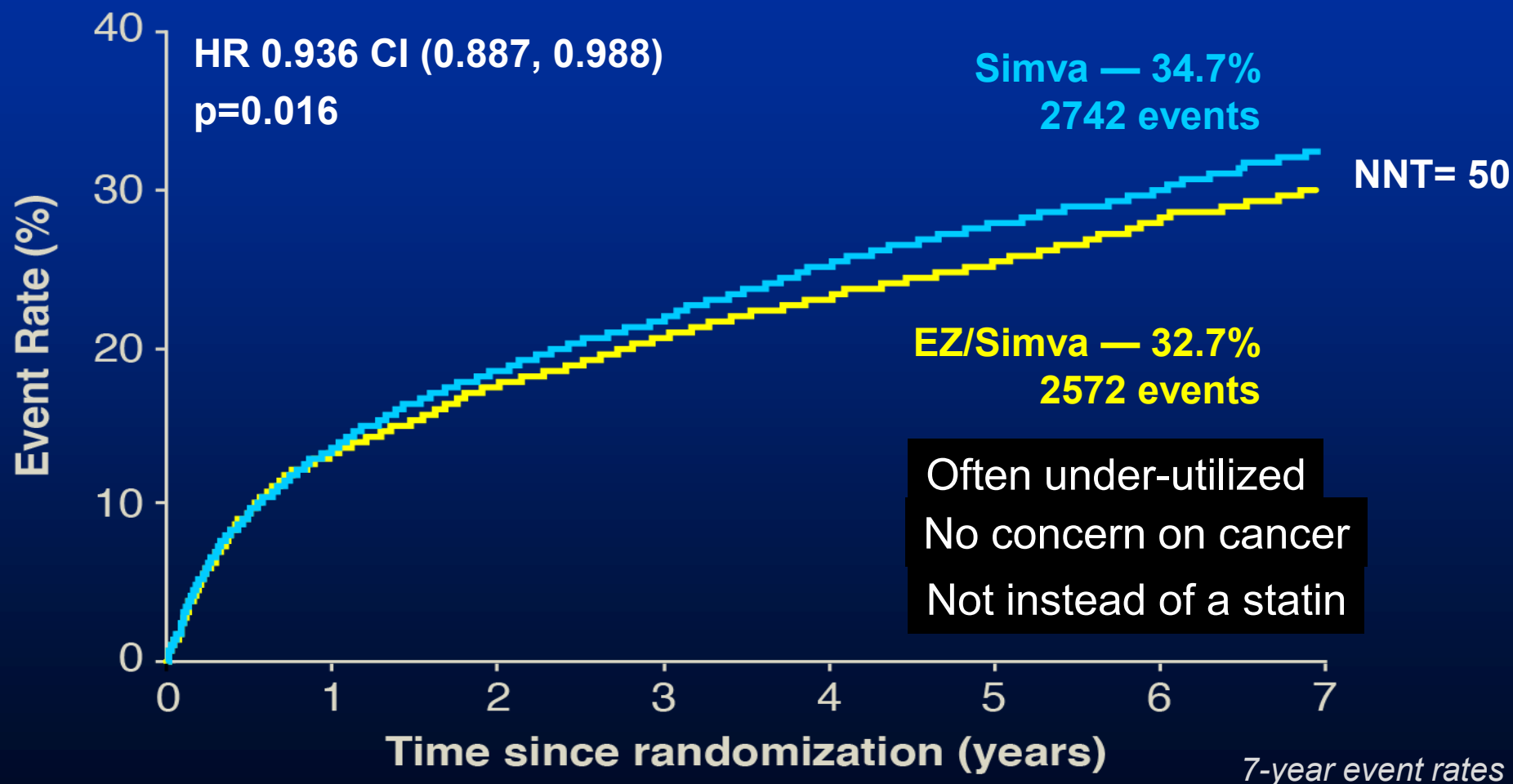
LDL-C and Lipid Changes



Primary Endpoint — ITT



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



RACING: Moderate-dose Statin + EZE vs. high-dose Statin

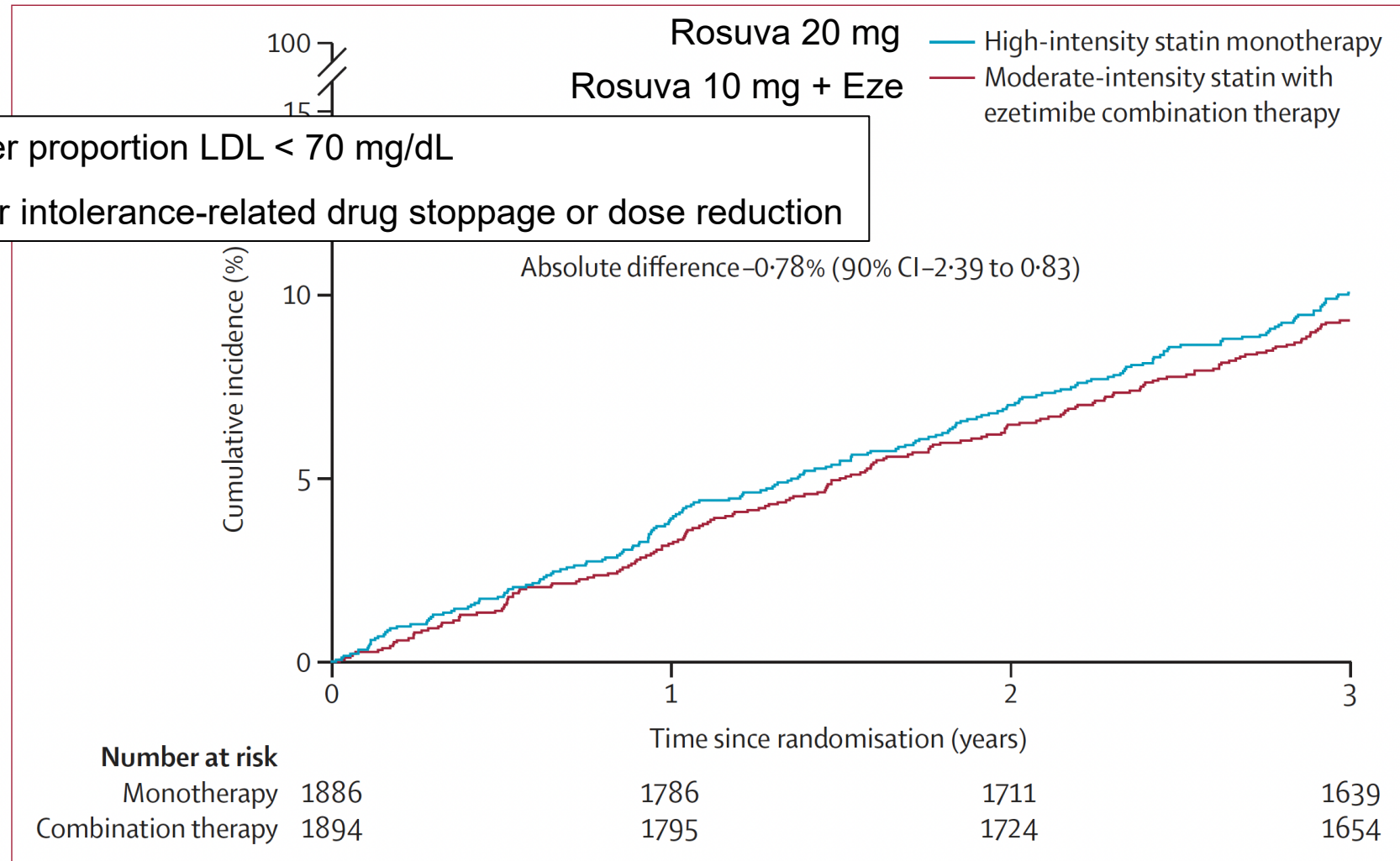
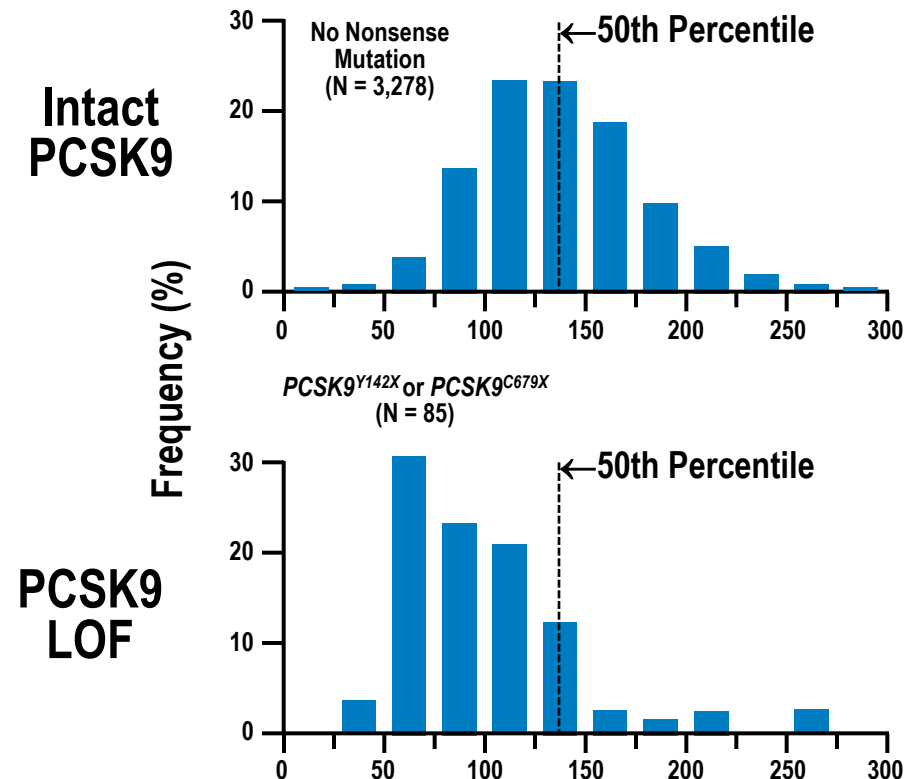


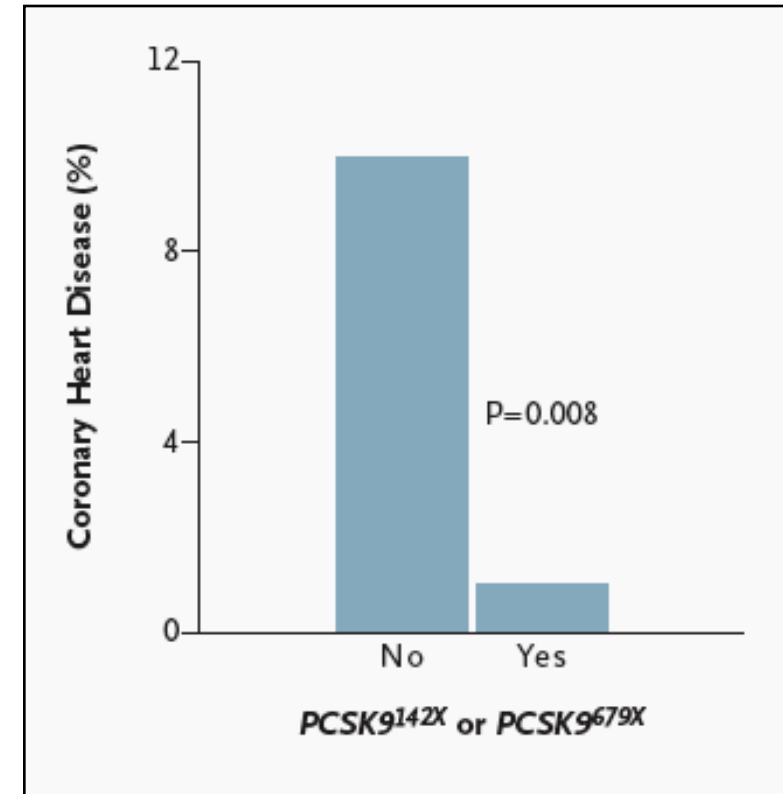
Figure 2: Kaplan-Meier curves of the primary endpoint of the intention-to-treat population

PCSK9 Loss of Function Mutations: Decreased Plasma LDL-C and CHD

Plasma LDL-C Distribution



Coronary Heart Disease

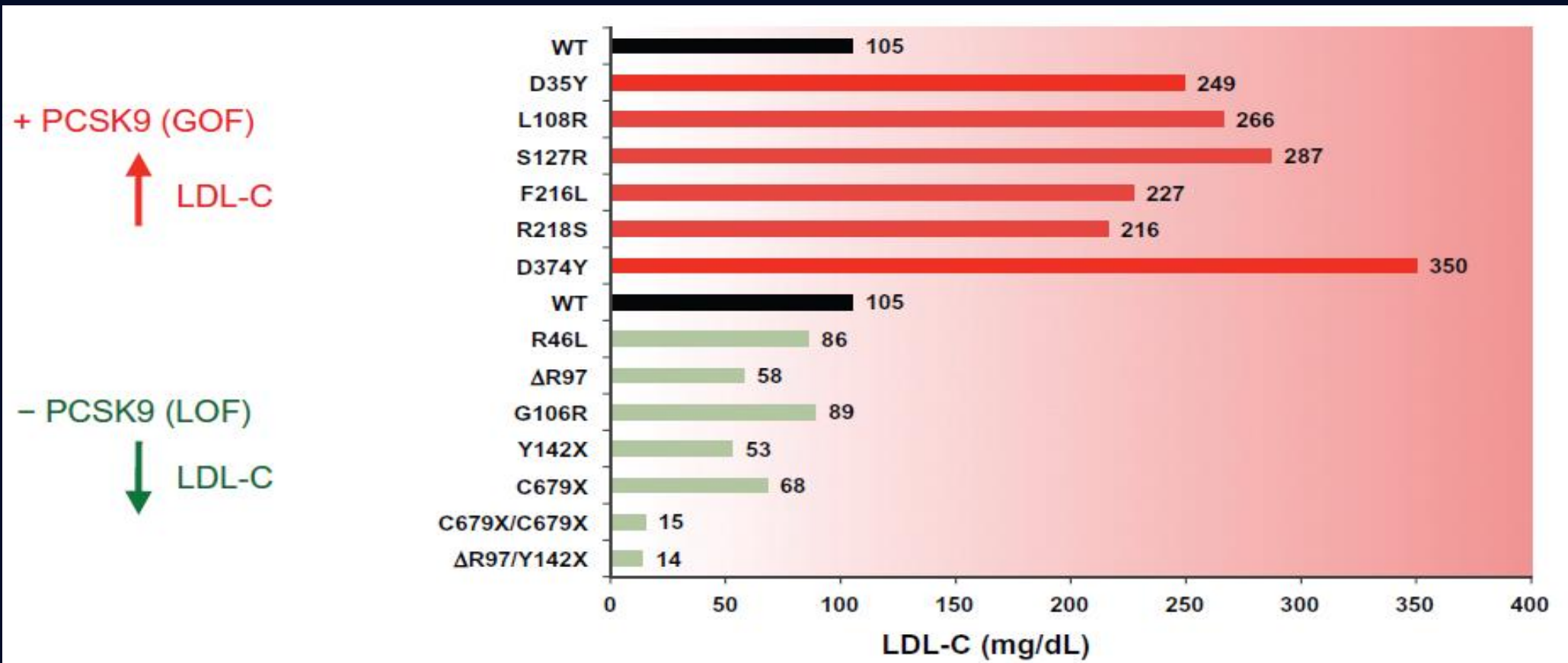


81% of PCSK9^{Y142X} and PCSK9^{C679X} subjects had mean plasma LDL-C below 50th percentile

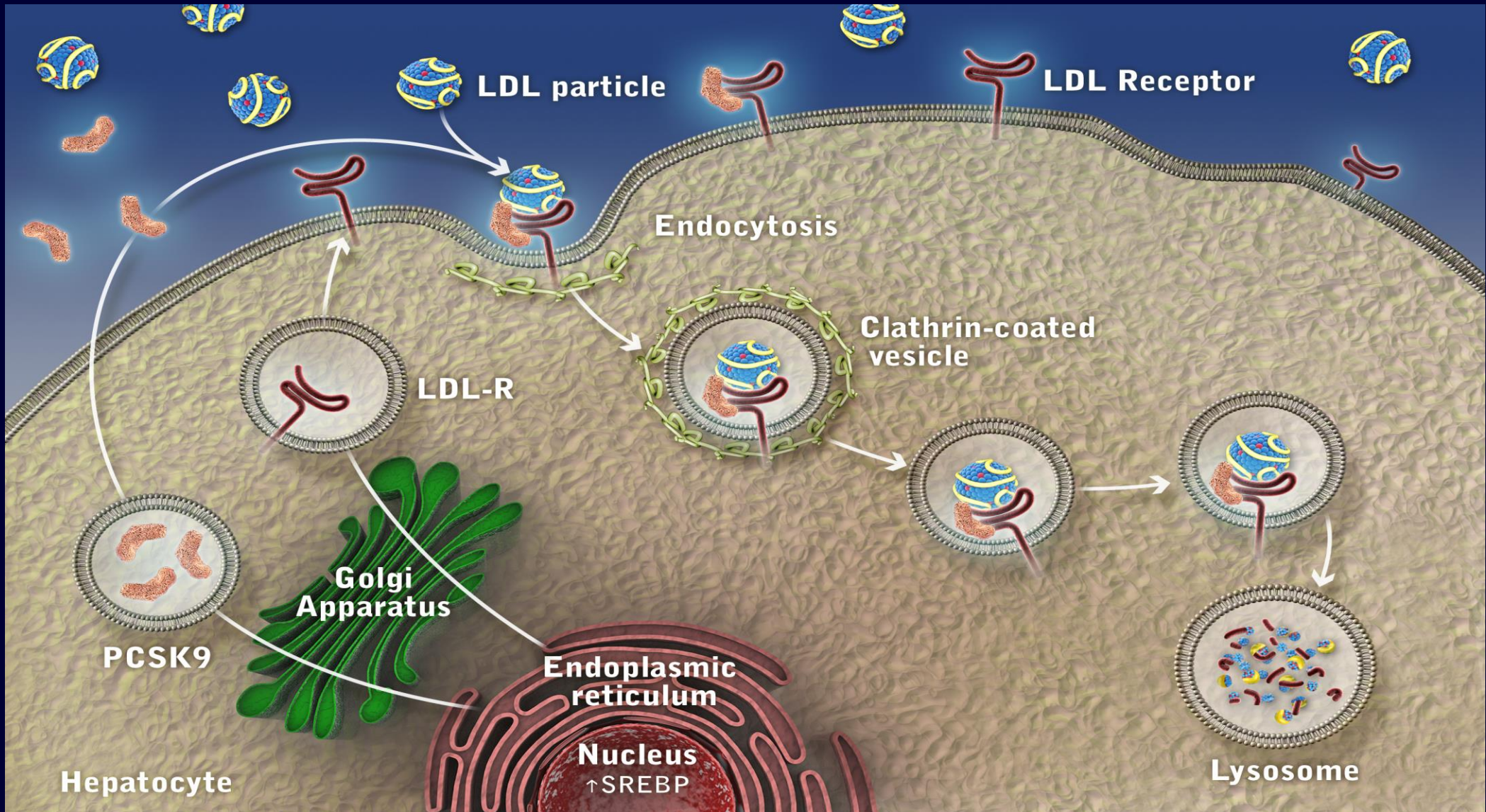
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Effect of Human Mutations in PCSK9 on Plasma LDL-C



PCSK9 in Determining LDL Receptor Levels

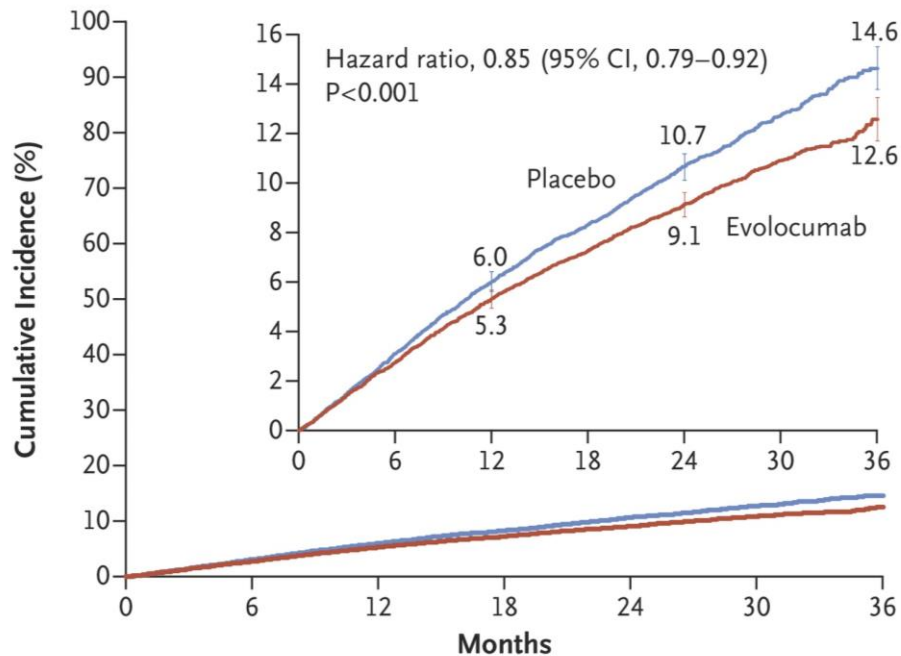


PCSK9 Inhibitors Decrease CV Events

FOURIER (Evolocumab)

15% RRR

CV death, MI, CVA, UA hosp or cor revasc

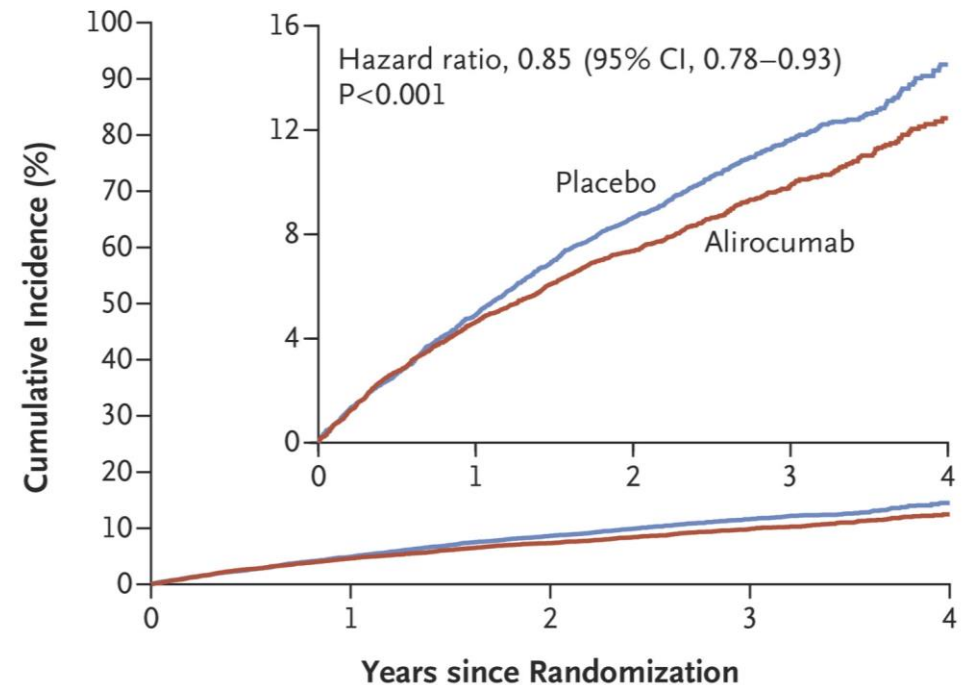


- ~70% high intensity statin use
- ~59% ↓LDL
- 92 mg/dL → 30 mg/dL

ODYSSEY (Alirocumab)

15% RRR

CHD death, MI, CVA, UA hosp



- ~89% high intensity statin use
- ~61% ↓LDL
- 92 mg/dL → 42 mg/dL

PCSK9 Inhibitors – Well Tolerated, Easily Administered

FOURIER - 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)

* The between-group difference was nominally significant ($P<0.001$).

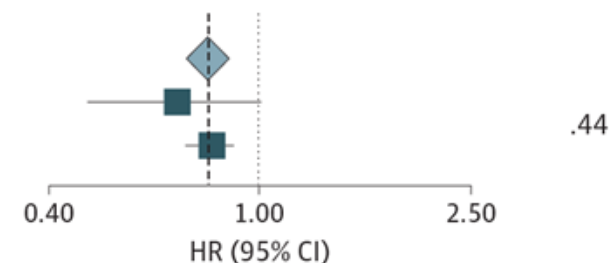
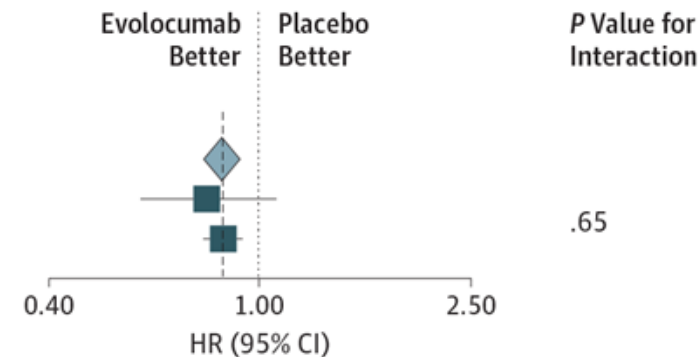
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.

FOURIER (Evolocumab): Benefits evident even in lower baseline LDL

Efficacy by baseline LDL

Primary composite end point	HR (95% CI)
All	0.85 (0.79-0.92)
Baseline LDL-C level, <70 mg/dL	0.80 (0.60-1.07)
Baseline LDL-C level, ≥70 mg/dL	0.86 (0.79-0.92)

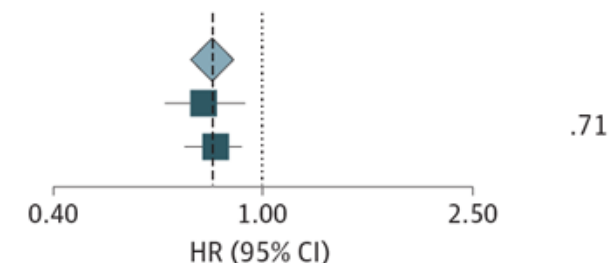
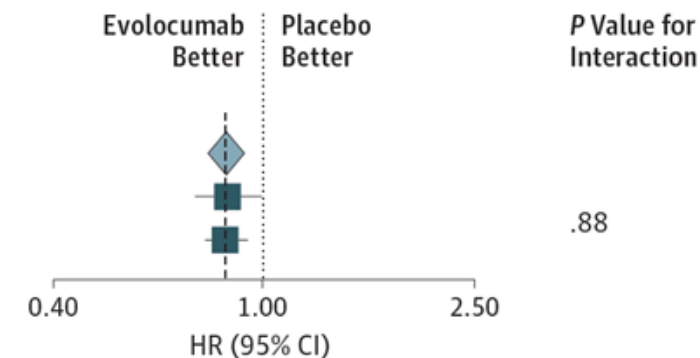
Secondary composite end point	HR (95% CI)
All	0.80 (0.73-0.88)
Baseline LDL-C level, <70 mg/dL	0.70 (0.48-1.01)
Baseline LDL-C level, ≥70 mg/dL	0.81 (0.73-0.89)



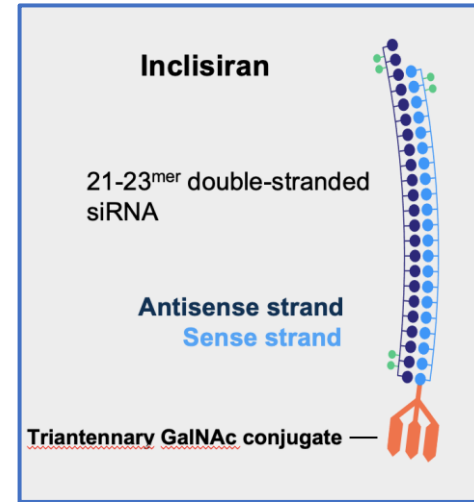
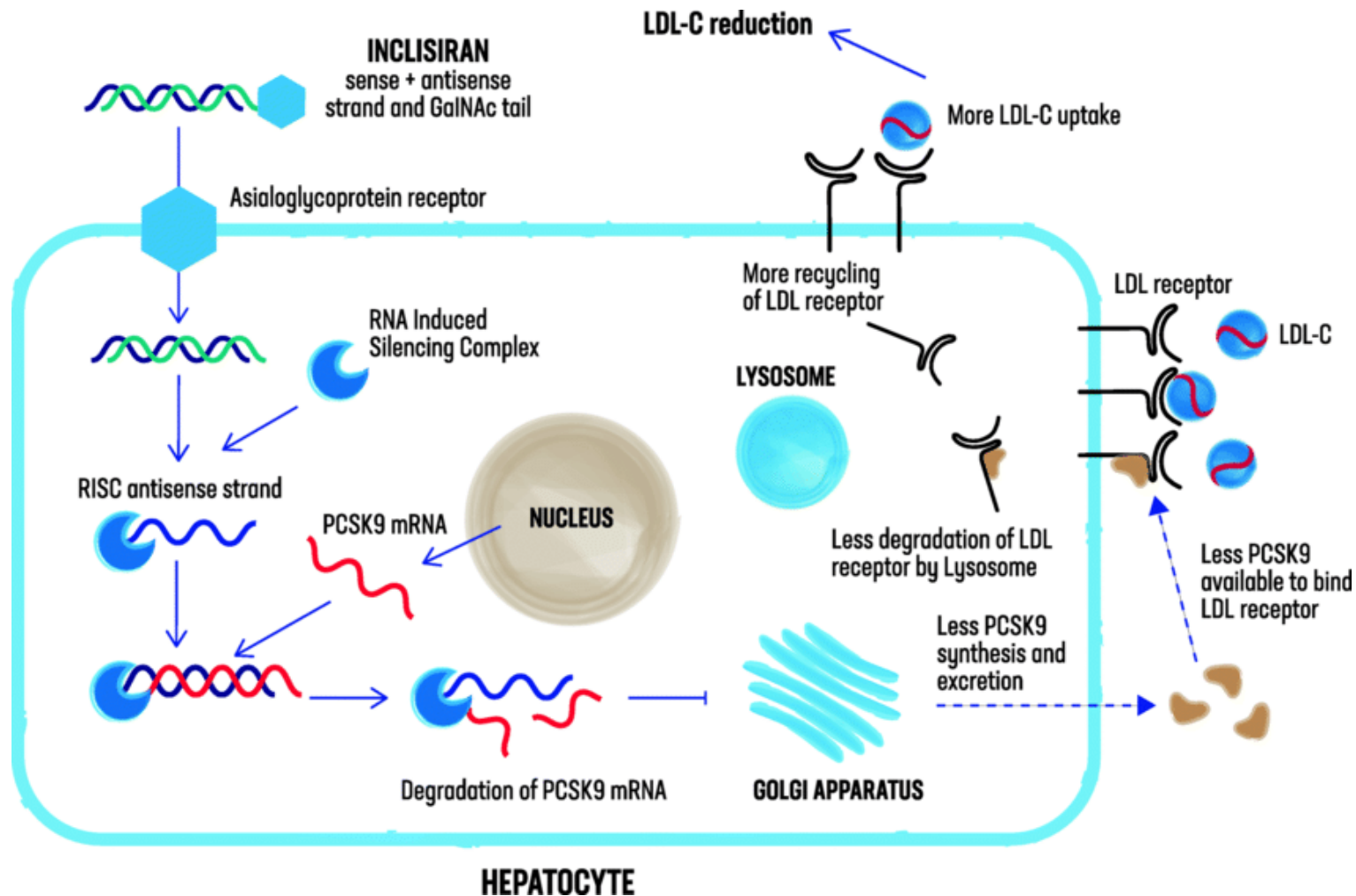
Efficacy by background statin

Primary composite end point	HR (95% CI)
All	0.85 (0.79-0.92)
Maximum intensity statin	0.86 (0.75-0.98)
Less intense statin	0.85 (0.78-0.93)

Secondary composite end point	HR (95% CI)
All	0.80 (0.73-0.88)
Maximum intensity statin	0.78 (0.66-0.92)
Less intense statin	0.81 (0.72-0.90)

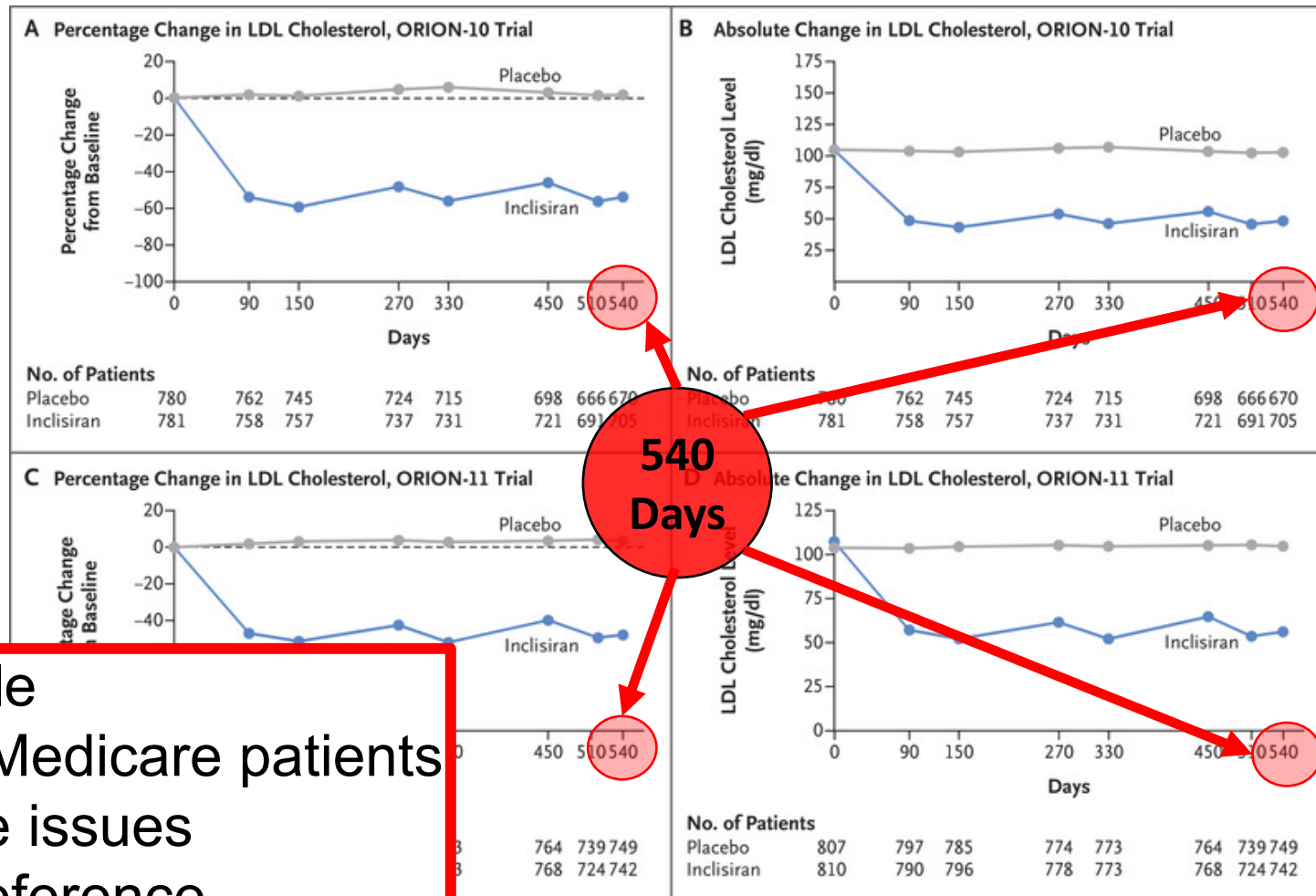


Inclisiran: Targeting PCSK9 Using siRNA



Inclisiran Efficacy in LDL-Lowering in Two Phase 3 Trials

ORION 10



Approvable
 Covered: Medicare patients
 Adherence issues
 Patient preference

REVIEW ARTICLE | Originally Published 13 March 2026 |  Check for updates**2026**

ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/A PhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines



2026 Dyslipidemia Guidelines What Changed?



LDL-C goals
return



PREVENT
risk model



Lp(a) for
all adults



CAC for
reclassification

1

PRACTICE-CHANGING

Treat earlier. Lifestyle counselling from youth. Pharmacotherapy in youth with FH and young adults with LDL-C ≥ 160 mg/dL (4.1 mmol/L) or strong family Hx premature ASCVD.

2

NEW

PREVENT™ replaces PCE for 10- and 30-year risk. Use the **CPR Model**: Calculate → Personalise → Reclassify with CAC.

3

REVISED

Borderline risk starts at 3%. LLT can be considered at PREVENT 3–<5% and should be considered at 5–<10%.

4

PRACTICE-CHANGING

Treatment goals are back. LDL-C and non-HDL-C absolute targets now guide therapy alongside percentage LDL-C reduction.

5

NEW

ApoB for residual risk. Useful once LDL-C/non-HDL-C goals met, especially with elevated TG, diabetes, or achieved LDL-C <70.

6

NEW — COR 1

Lp(a) at least once in all adults. ≥ 125 nmol/L / 50 mg/dL ($\sim 1.4 \times$ risk). ≥ 250 nmol/L / 100 mg/dL ($\geq 2 \times$ risk). If elevated, intensify LDL-C lowering and manage other modifiable risk factors.

7

REVISED — COR 1

CAC for reclassification. Men ≥ 40 , women ≥ 45 . CAC >0 → initiate LLT. CAC ≥ 100 or ≥ 75 th %ile → high-intensity. CAC 0 → may defer.

8

NEW — COR 1

LLT for diabetes, CKD 3–4, HIV regardless of LDL-C in adults 40–75. After 75, consider with shared decision-making.

9

PRACTICE-CHANGING

Very-high-risk ASCVD: LDL-C <55 mg/dL (1.4 mmol/L), non-HDL-C <85 mg/dL (2.2 mmol/L). Ezetimibe no longer required before PCSK9 mAb. Bempedoic acid added.

10

REVISED

Hypertriglyceridemia: Statin first-line for ASCVD risk. TG-lowering for pancreatitis prevention especially TG ≥ 1000 .

Patient Category	% LDL-C ↓	LDL-C Goal mg/dL (mmol/L)	Non-HDL-C Goal mg/dL (mmol/L)	ApoB
ASCVD — Very High Risk	≥50%	<55 (1.4)	<85 (2.2)	<55
ASCVD — Not Very High Risk	≥50%	<70 (1.8)	<100 (2.6)	Consider
Severe Hypercholest. + HeFH / Risk / CAC	≥50%	<70 (1.8)	<100 (2.6)	—
Severe Hypercholest. (no additional risk)	Max tolerated	<100 (2.6)	<130 (3.4)	—
Diabetes + Multiple Risk Factors	≥50%	<70 (1.8)	<100 (2.6)	Consider
Diabetes (40–75 y, no ASCVD)	≥30–49%	<100 (2.6)	<130 (3.4)	—
CAC ≥1000 AU	≥50%	<55 (1.4)	<85 (2.2)	—
CAC 100–999 or ≥75th %ile	≥50%	<70 (1.8)	<100 (2.6)	—
CAC 1–99 and <75th %ile	≥30–49%	<100 (2.6)	<130 (3.4)	—
Primary Prev. — High (≥10%)	≥50%	<70 (1.8)	<100 (2.6)	—
Primary Prev. — Intermediate (5–<10%)	≥30–49%	Individualise	Individualise	—
Primary Prev. — Borderline (3–<5%)	≥30–49%	Individualise	Individualise	—

C

Calculate

Use **PREVENT-ASCVD** for 10-year risk in adults 30–79 y without ASCVD.

Low: <3%

Borderline: 3–<5%

Intermediate: 5–<10%

High: ≥10%

P

Personalise

Consider **risk enhancers** not captured by PREVENT.

Lp(a) ≥125 nmol/L

hsCRP ≥2 mg/L

Family Hx premature ASCVD

South Asian / Filipino ancestry

Reproductive risk markers

Chronic inflammatory disease

R

Reclassify

Use **CAC scoring** when LLT decision uncertain.

CAC 0: Defer, repeat 3–7 y

1–99: Moderate → LDL <100 (2.6)

≥100: High-intensity → LDL <70 (1.8)

≥300: ≥50% ↓ → LDL <70 (1.8)

≥1000: ≥50% ↓ → LDL <55 (1.4)

Biomarkers & Testing

What to measure, when, and what each test adds.

BASELINE TEST

Standard Lipid Profile

TC, LDL-C, HDL-C, TG, non-HDL-C.
Screen from age 19 y. Children 9–11 y.

LDL-C: Martin/Hopkins or Sampson/NIH preferred

Non-HDL-C: Report routinely (TC – HDL-C)

Fasting: Not required unless known hypertriglyceridemia

ADD-ON — COR 2A

ApoB

Atherogenic particle number.
Superior when LDL-C and apoB discordant.

When: ASCVD, CKM, DM, TG >200, LDL <70

Very-high-risk goal: <55 mg/dL

Note: Unaffected by fasting

NEW — COR 1

Lp(a)

Genetically determined. Measure once. Minimally affected by lifestyle/LLT.

≥125 nmol/L (50 mg/dL): ~1.4× ASCVD risk

≥250 nmol/L (100 mg/dL): ≥2× risk

Action: If elevated → risk enhancer → intensify LDL-C lowering and other modifiable risk factors

Lp(a) comprehensive review →

RECLASSIFICATION — COR 1

CAC Score

Men ≥40, women ≥45. Absolute score + percentile both prognostic.

CAC 0: Very low near-term risk

≥100 or ≥75th %ile: High-intensity LLT

Incidental CAC: Non-cardiac CT → trigger LLT

Calcium score explained →

2013 AHA/ACC Cholesterol Guidelines

Four main statin benefit groups

ASCVD

- Age $\leq$ 75 – High-intensity statin[†]
- Age > 75 – Moderate-intensity statin

LDL $\geq$ 190

- High-intensity statin

Age 40-75 with diabetes

LDL 70-189

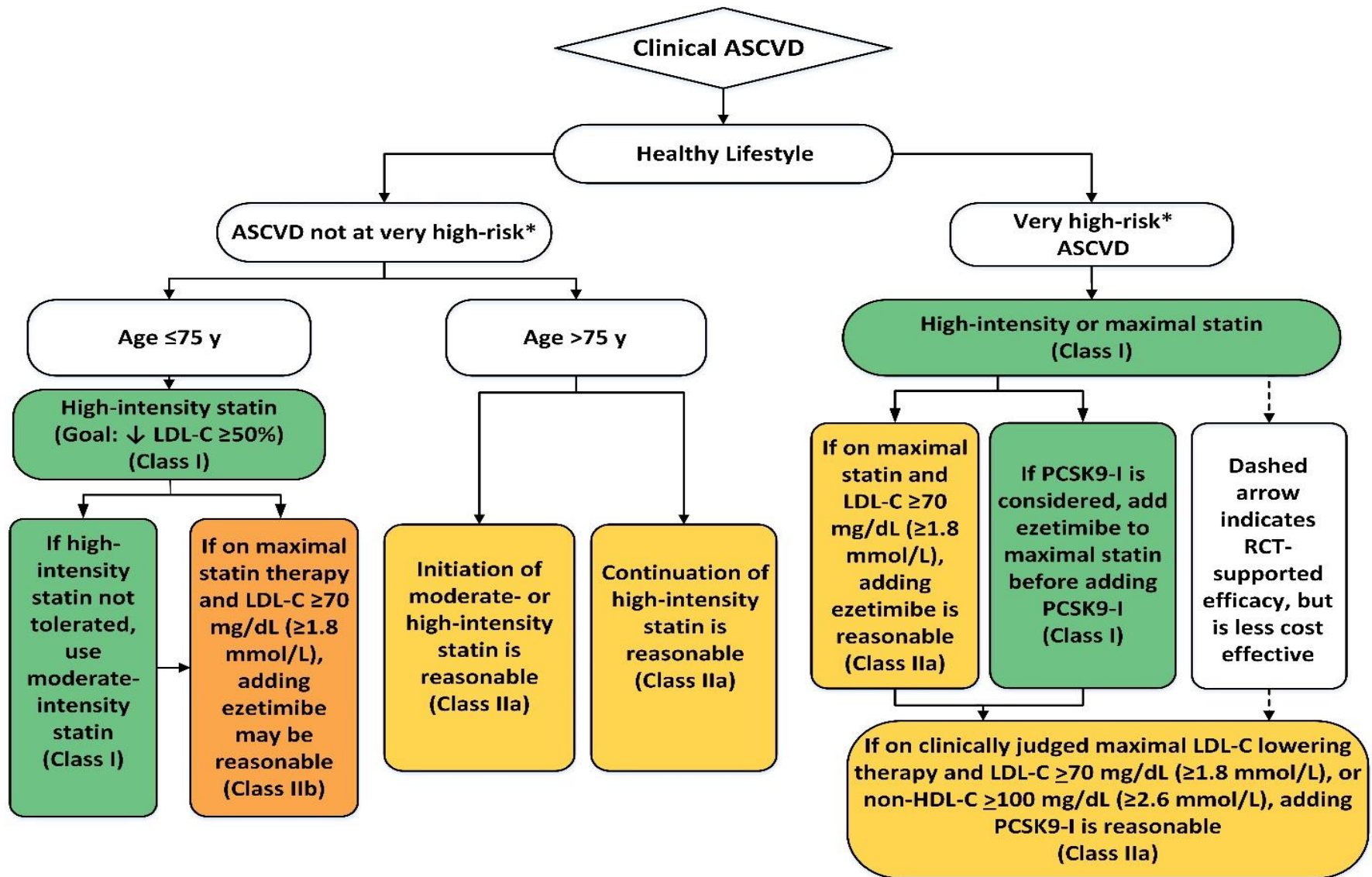
- 10-year risk $\geq$ 7.5% - High-intensity statin
- 10-year risk < 7.5% - Moderate-intensity statin

Age 40-75 without ASCVD or diabetes

10-year risk $\geq$ 7.5%

- Moderate- to high-intensity statin

Secondary Prevention



Very High Risk for Future ASCVD events

Multiple major ASCVD events

One major ASCVD event
+
Multiple high risk conditions

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)
High-Risk Conditions
Age ≥ 65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event(s)
Diabetes Mellitus
Hypertension
Chronic kidney disease (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 heart failure

Statin Intolerance

Increased LFTs → Up to 3x ULN

Increased CKs → Up to 10x ULN

Myalgias → With or without CK changes

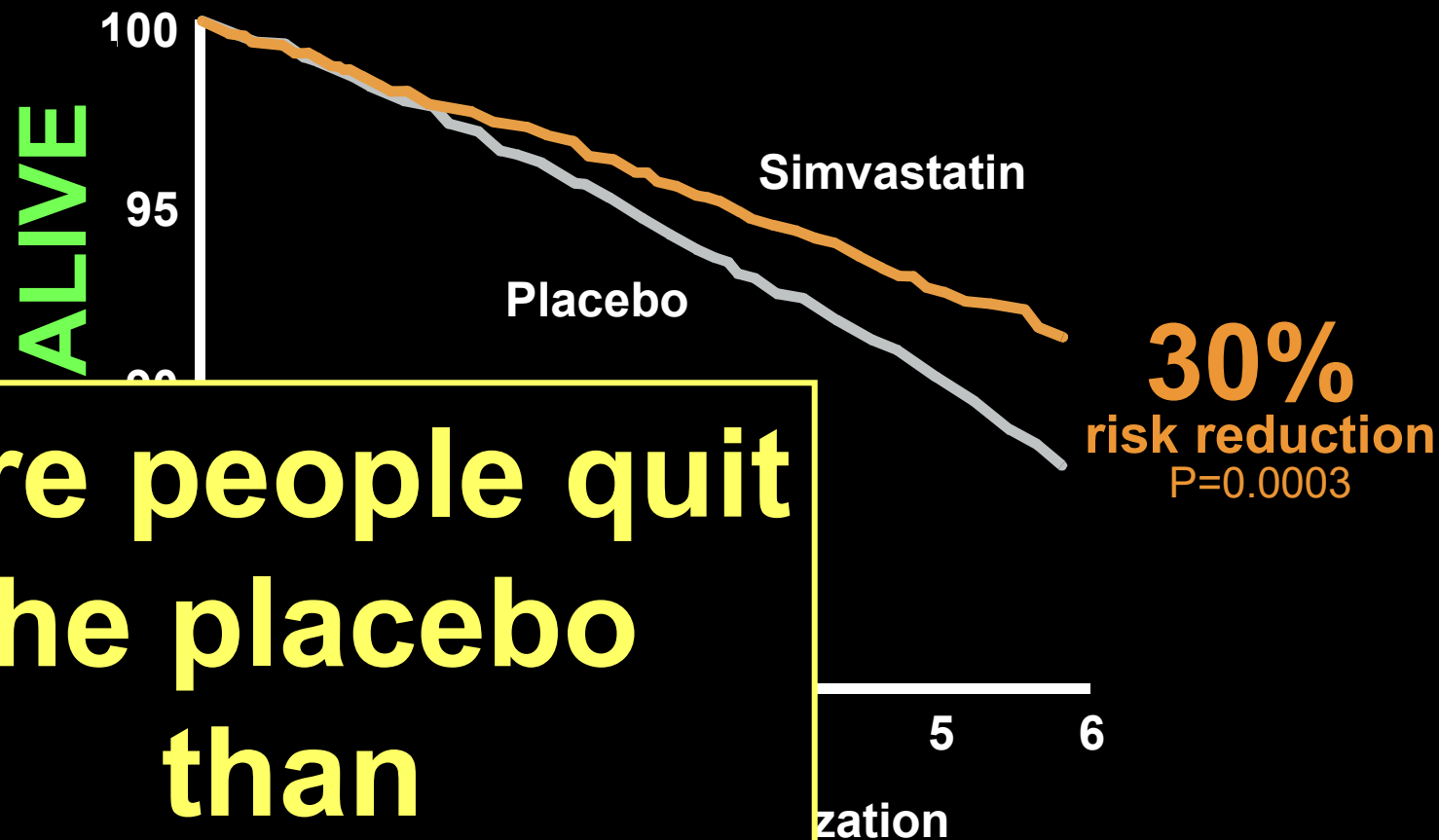
Clinical trials: ~5 % subjects

Clinical experience: Higher? 15-20%?

Serious adverse event: Rare

Rhabdomyolysis 1.5 cases per 1000,000 exposures

4S: Total Mortality/Overall Survival



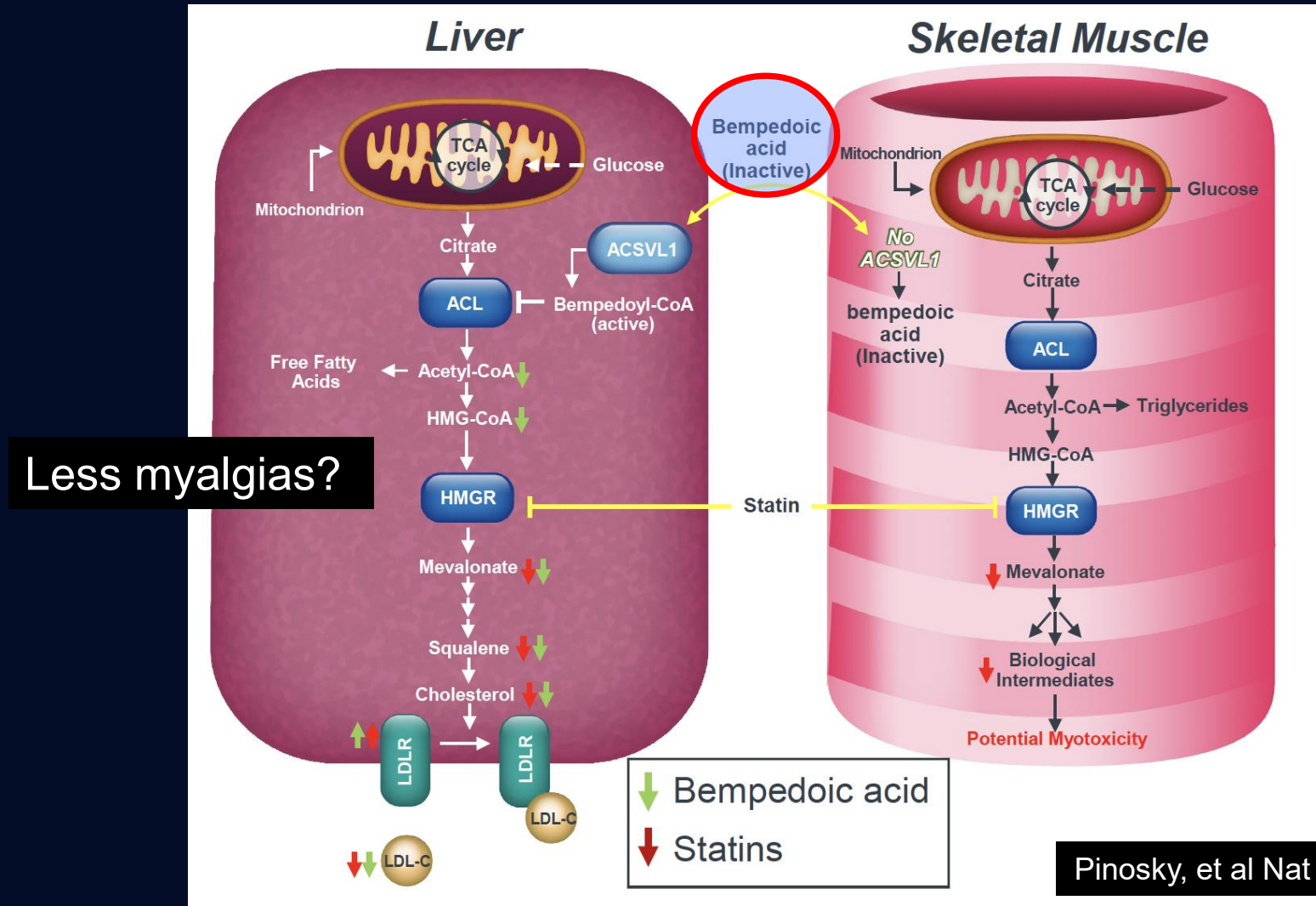
More people quit
the placebo
than
quit the Statin



Statin Intolerance?

- It may not be the statin.
Education.
- It may be dose related. Start lowest possible.
Half lowest dose? Rosuva 2.5 M W F?
- It may be statin specific. Try different one.
Rosuva? Pitavastatin (Livalo)?
- Soft data: CoQ10 200 mg BEFORE statin, correct vitamin D
- Placebo test? Ezetimibe tolerability
- True statin intolerance? Bempedoic Acid, PCSK9 inhibitors

Bempedoic Acid: Hepatic-Restricted Drug Activation by ACSVL1



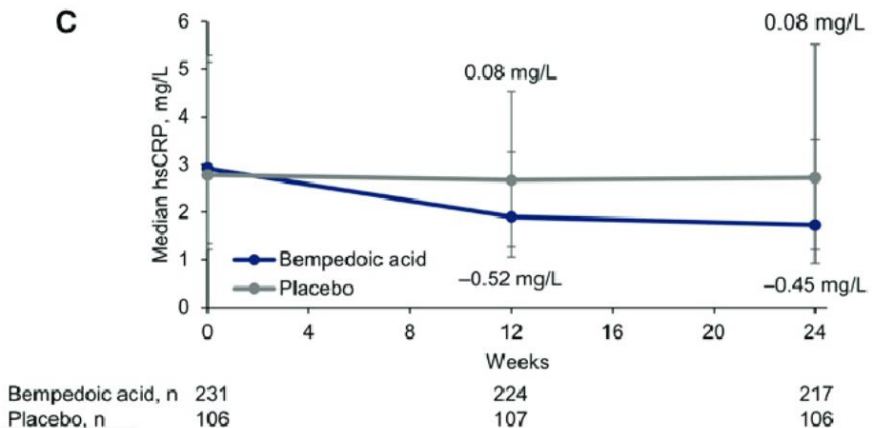
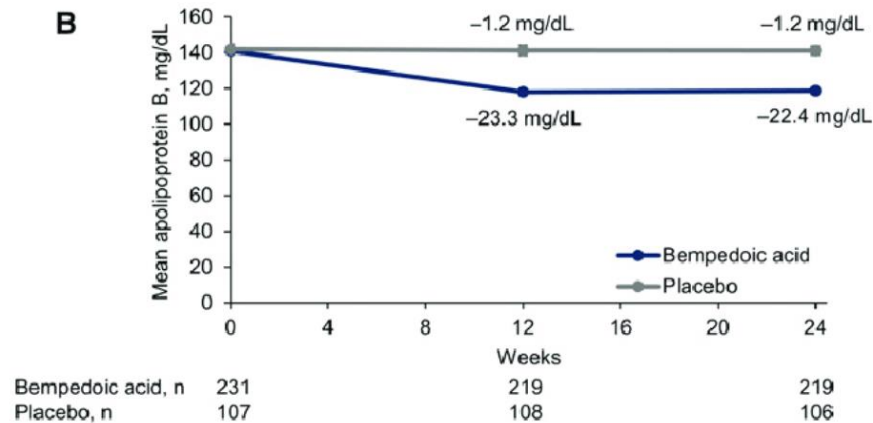
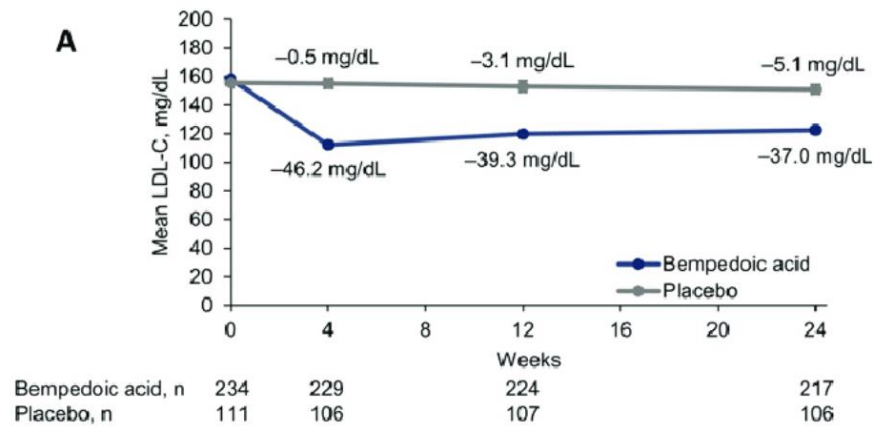
Bempedoic Acid (BA, Nexletol)

LDL reduction:
~20% added to statin
~30% monotherapy

hsCRP reduction:
~20-40%

BA + Ezetimibe (Nexlizet)

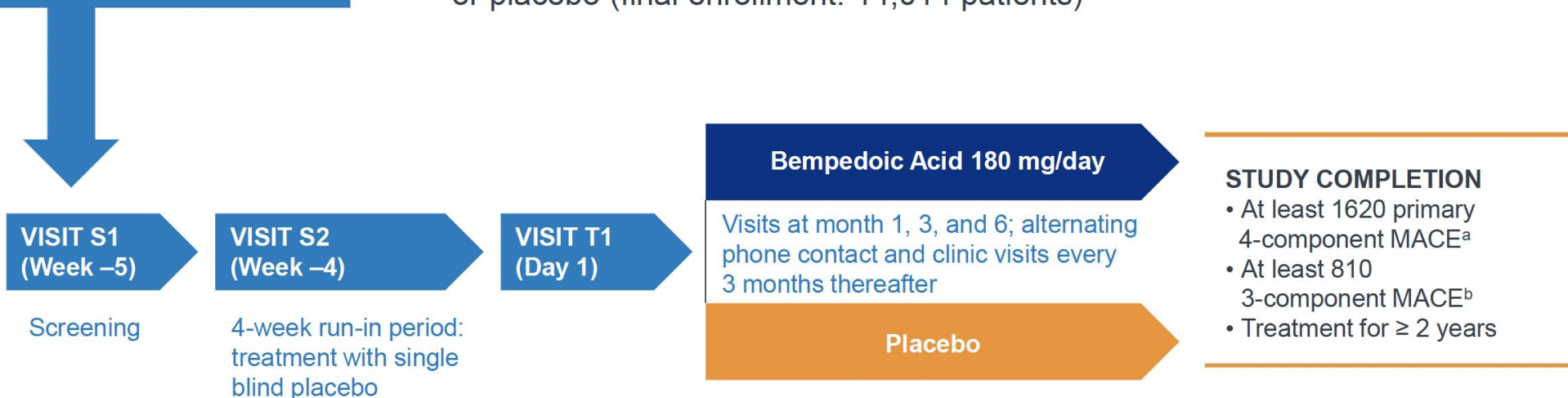
LDL reduction:
~30% added to statin
~45% monotherapy



CLEAR Outcomes

Patients unable to tolerate statin therapy with, or at high-risk for, ASCVD and who had fasting LDL-C ≥ 100 mg/dL

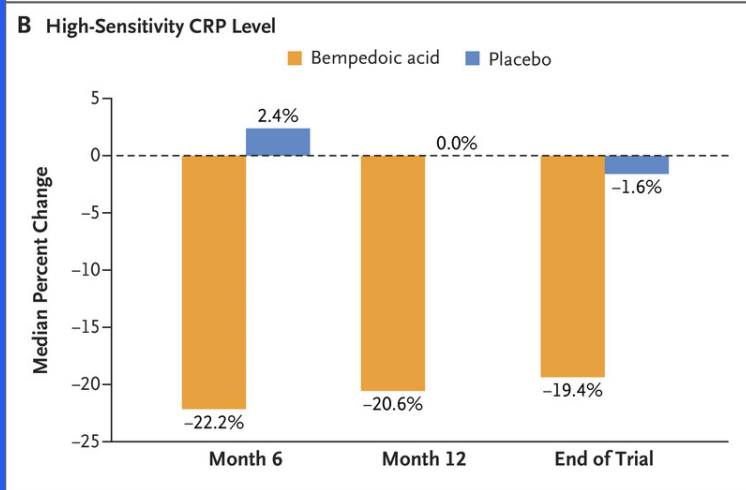
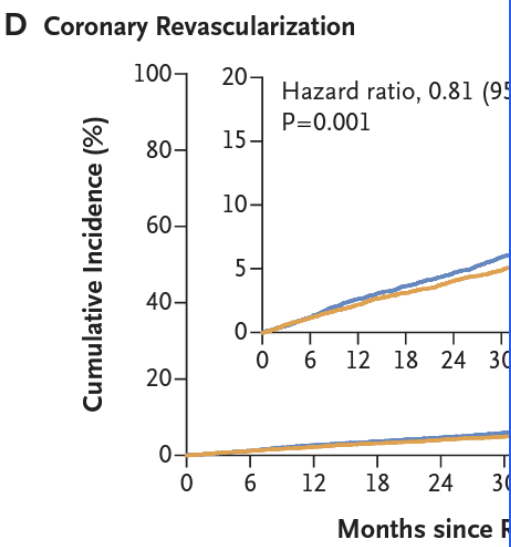
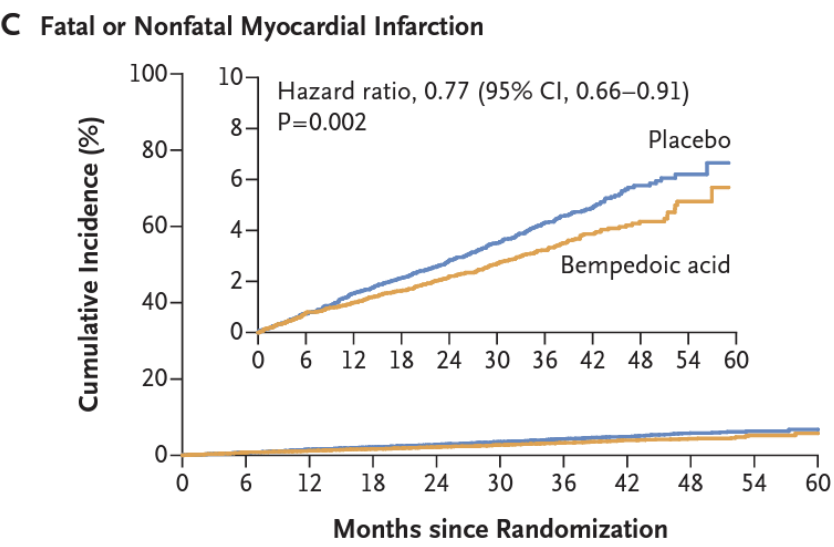
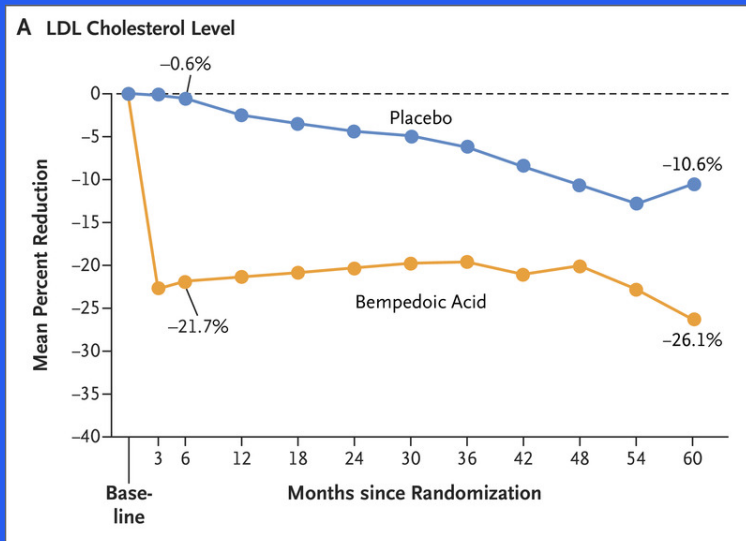
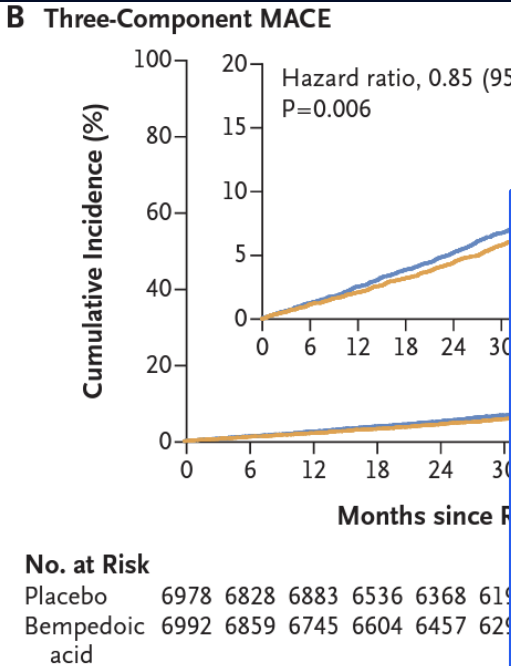
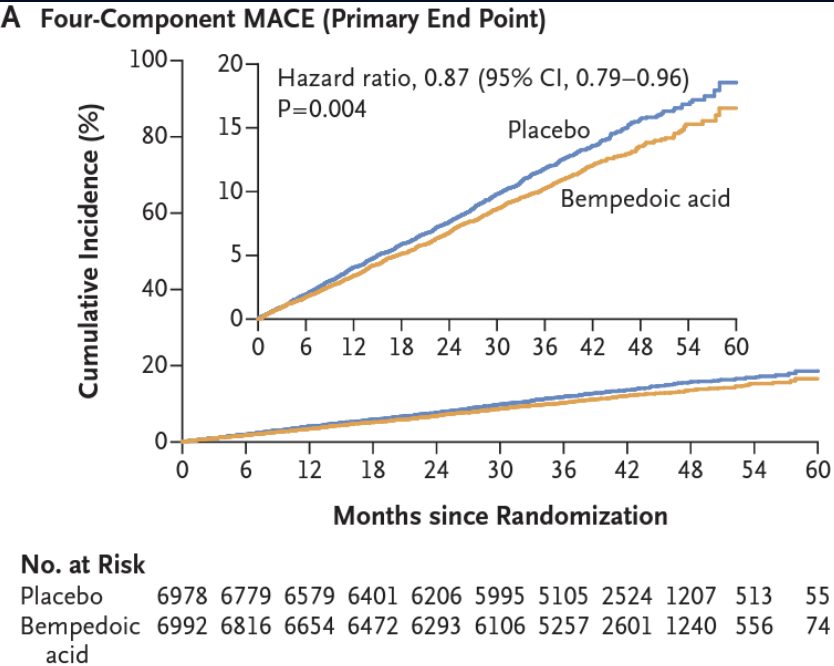
- Phase 3, randomized, double-blind, placebo-controlled, cardiovascular outcomes trial
 - Designed with a sample size of 14,000 patients to provide more than 95% power to detect a 17% reduction in the primary endpoint (time to first occurrence of 4-component MACE^a) in the bempedoic acid treatment group
- Patients were randomized in a 1:1 ratio to treatment with bempedoic acid or placebo (final enrollment: 14,014 patients)



CLEAR Outcomes:

BA Significant Decreased MACE (CV death, nonfatal MI, nonfatal stroke, cor revasc)

April 13, 2023
N Engl J Med 2023; 388:1353-1364

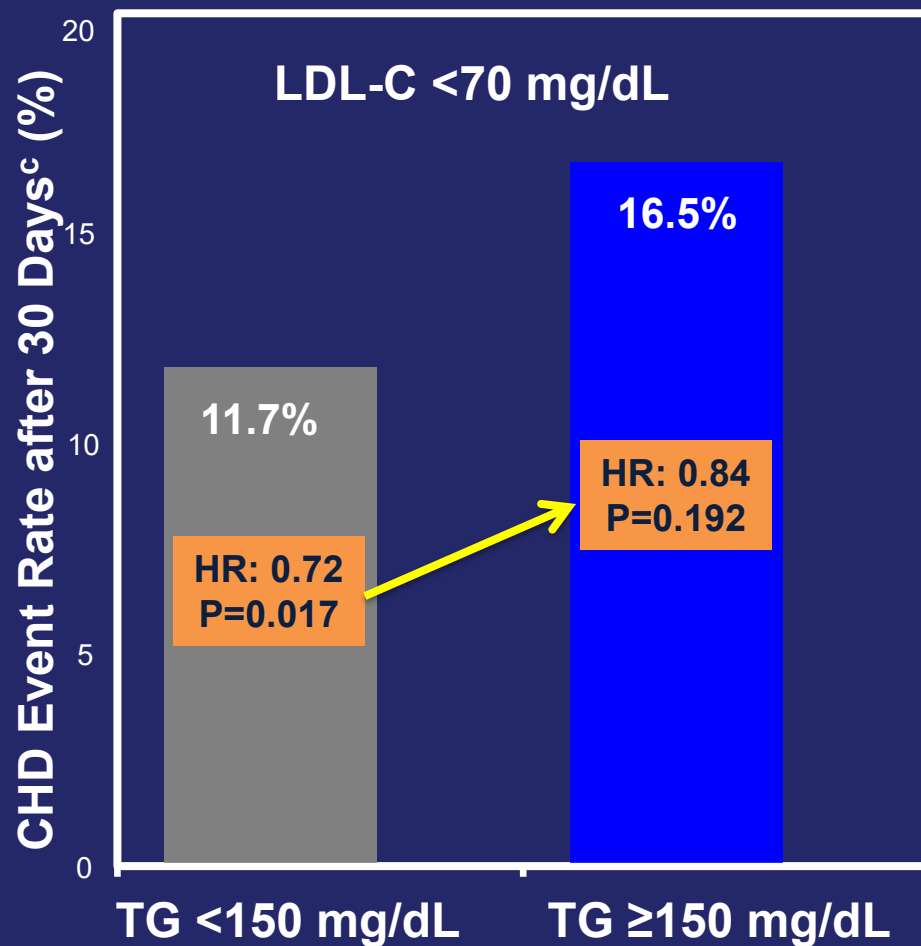


BA + BA/Eze Use

- Statin intolerant patients (myalgias)
 - LDL lowering w/ ezetimibe approaching PCSK9i
- CLEAR: CV risk reduction in primary prevention ~= statins
- Inadequate LDL lowering?
 - On statin + ezetimibe, swap in BA/Eze for Eze.
- PCSK9i alternative?
 - Payer driven? Less expensive
- Elevated hs-CRP?

TG ≥ 150 mg/dL Predicts Higher CHD^a Risk in Statin Takers with LDL-C < 70 mg/dL

**PROVE IT-
TIMI 22 Trial^b**
(N=4162)



Referent
LDL-C ≥ 70 mg/dL
TG ≥ 150 mg/dL
Event Rate=17.9%

^aDeath, MI, and recurrent ACS. ^bACS patients on atorvastatin 80 mg or pravastatin 40 mg. ^cAdjusted for age, gender, low HDL-C, smoking, hypertension (HTN), obesity, diabetes, prior statin therapy, prior ACS, peripheral vascular disease, and treatment. CHD=coronary heart disease; HR=hazard ratio; PROVE IT-TIMI=Pravastatin or Atorvastatin Evaluation and Infection Therapy Thrombolysis In Myocardial Infarction. Miller M et al. *J Am Coll Cardiol*. 2008;51:724-30.

Secondary Causes of Hypertriglyceridemia

- Nephrotic syndrome (Urine analysis)
- Thyroid abnormalities (TSH)
- Drugs (Thiazides, HRT, beta blockers, HIV rx)
- Diet (Excess carbs)
- Diabetes:
 - Inadequate control
 - Undiagnosed
- Alcohol
- Obesity

~50% Reduction
in TG with
Lifestyle
Interventions

TG-Lowering and CV Risk

Fibrate (PPAR α agonists)

- VA-HIT ASCVD Gemfibrozil No statin Positive 1 $^{\circ}$
- FIELD ASCVD + T2D Fenofibrate Statin drop ins Negative 1 $^{\circ}$

Positive 2 $^{\circ}$

Positive subgrps:

Higher TG

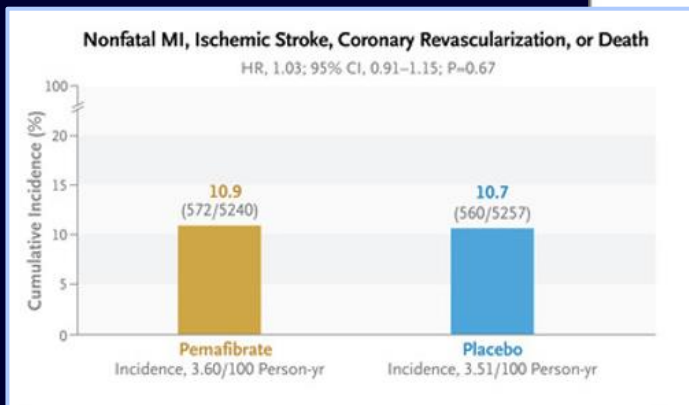
Baseline TGs not high enough?

Agent specific issues

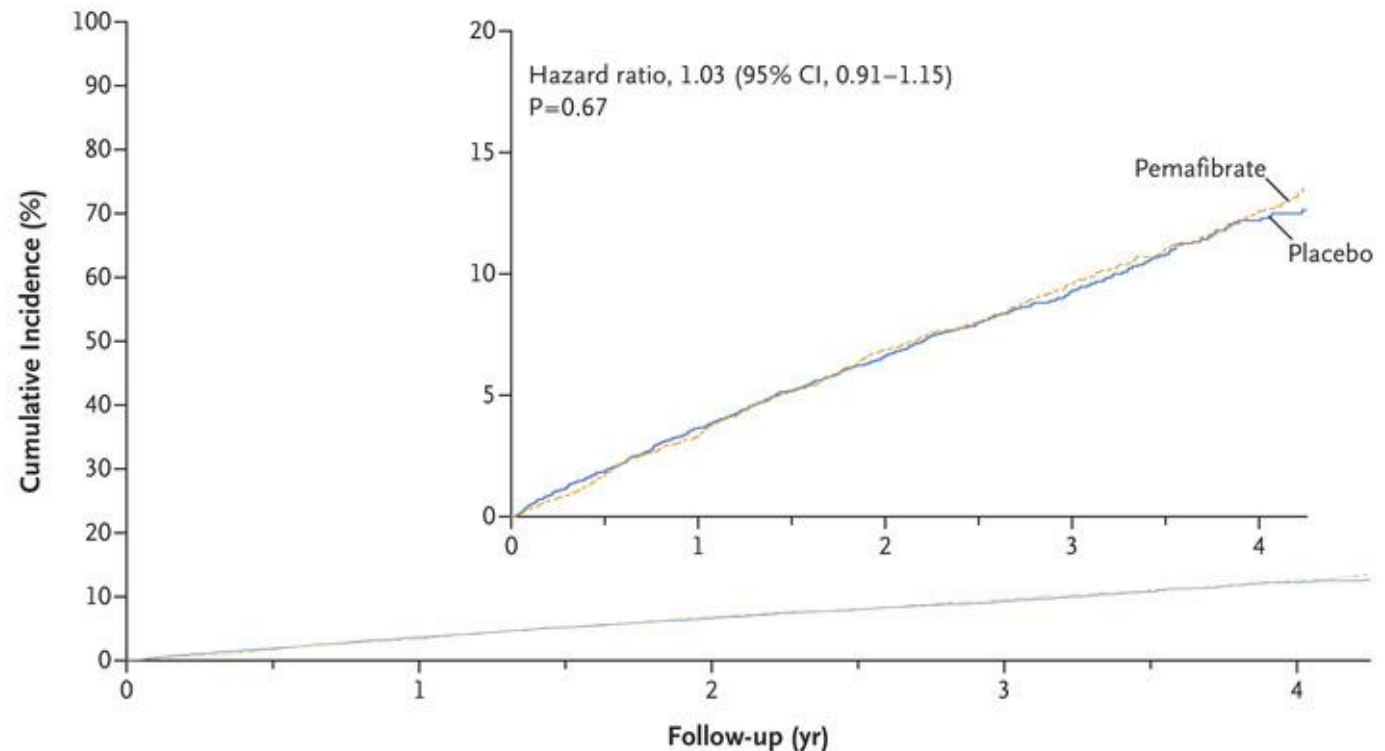
- ACCORD ASCVD, T2D Fenofibrate + Statin vs Statin Negative 1 $^{\circ}$
Positive subgrps
Higher TG

Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk

Aruna Das Pradhan, M.D., M.P.H., Robert J. Glynn, Sc.D., Jean-Charles Fruchart, Ph.D., Jean G. MacFadyen, B.A., Elaine S. Zaharris, B.A., Brendan M. Everett, M.D., M.P.H., Stuart E. Campbell, B.A., Ryu Oshima, M.S., R.Ph., Pierre Amarenco, M.D., Dirk J. Blom, M.D., Ph.D., Eliot A. Brinton, M.D., Robert H. Eckel, M.D., et al., for the PROMINENT Investigators*



CV events: 572 + 560



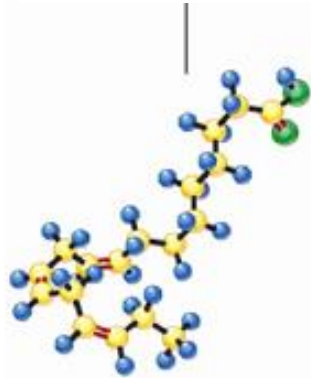
No. at Risk									
Pemafibrate	5240	5060	4901	4742	4552	3627	2820	2067	1147
Placebo	5257	5082	4925	4762	4596	3651	2838	2063	1130

OMEGA-3 FATTY ACIDS

Dietary Sources ALA

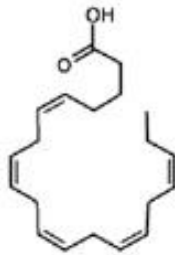
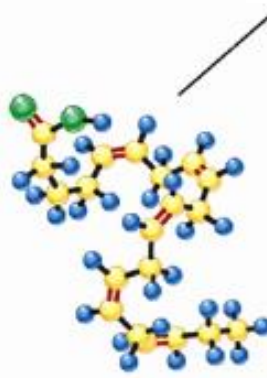
Flaxseed
Canola Oil
Walnuts
Chia
Soybeans

Plant O-3 FA

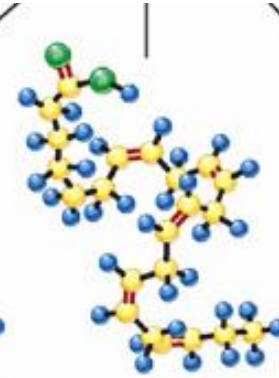


Alpha-Linolenic Acid:
ALA

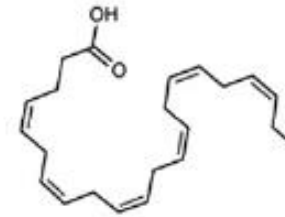
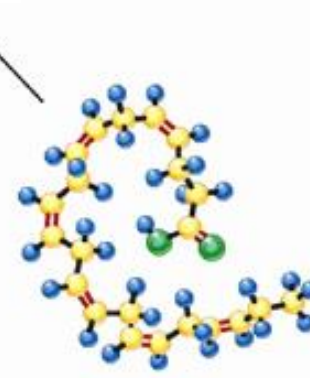
Marine O-3 FA



Eicosapentaenoic Acid:
EPA



Docosapentaenoic Acid:
DPA



Docosahexaenoic Acid:
DHA

- ① Plant-derived O-3's (ALA) do not consistently reduce triglycerides; less evidence for CV benefit and should not be used for TG lowering.
- ② Data for DPA less robust than for EPA and DHA.

ORIGINAL ARTICLE

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia J. Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators

REDUCE-IT

Omega 3 Fatty Acids:

DHA

EPA

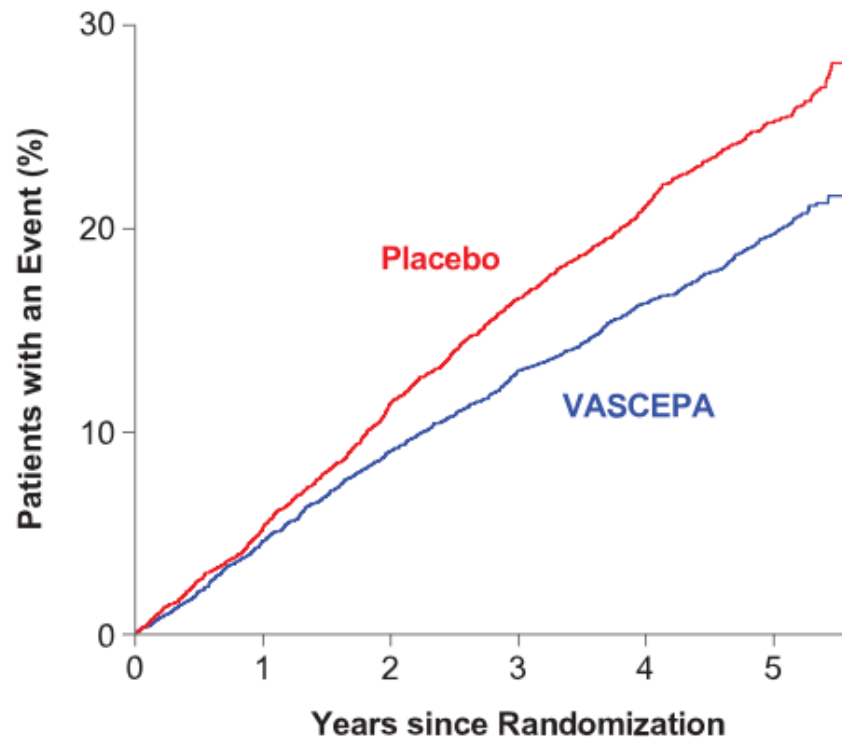
Icosapent ethyl (Vascepa)

- Established ASCVD or Diabetes + other risk factors,
- On statin therapy
- Fasting triglyceride 135 - 499 mg/dL
- LDL-C 41 - 100 mg/dL
- **Icosapent ethyl** vs Mineral Oil
- 8179 patients (70.7% secondary prevention)
- Median 4.9 years.

REDUCE-IT

Icosapent ethyl (EPA) Reduced CV risk in Established CVD or CV Risk

Primary Composite Endpoint



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

‘Newest’

25%_{RRR}
NNT=21

No. at Risk

Placebo	4090	3743	3327	2807	2347	1358
VASCEPA	4089	3787	3431	2951	2503	1430

Bhatt DL, et al. N Engl J Med. 2018

November 15, 2020

Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk
The STRENGTH Randomized Clinical Trial

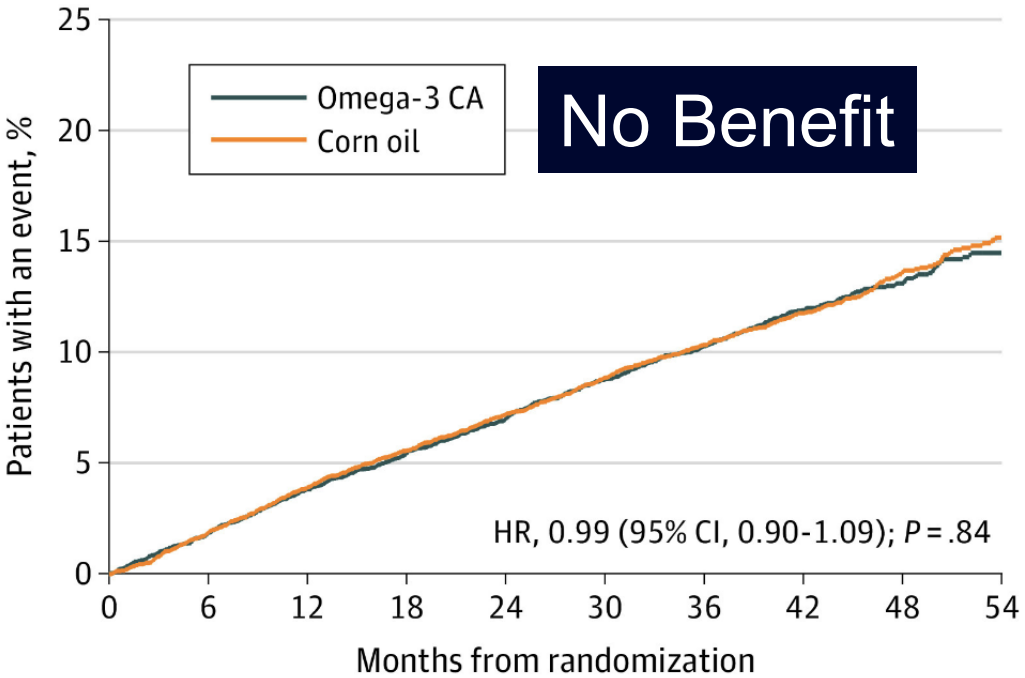
Stephen J. Nicholls, MBBS, PhD¹; A. Michael Lincoff, MD²; Michelle Garcia, RN, BSN, CCRC²; et al

» Author Affiliations | Article Information

JAMA. 2020;324(22):2268-2280. doi:10.1001/jama.2020.22258

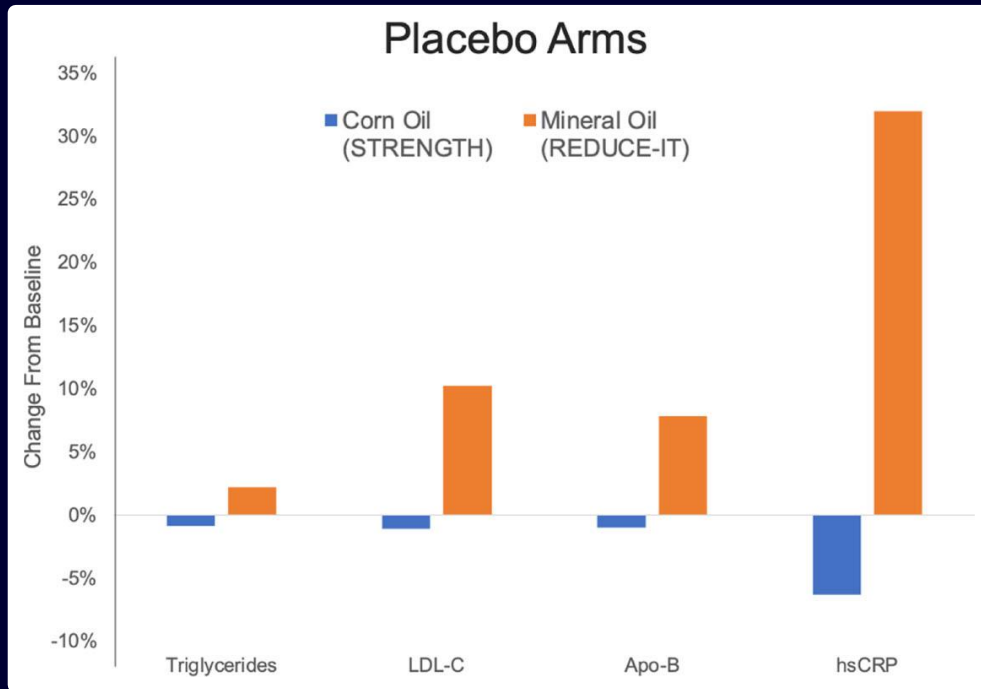
Epanova:
EPA + DHA vs corn oil

A Primary MACE, total population



No. at risk										
Omega-3 CA	6539	6372	6200	6060	5917	5751	4900	2965	1535	567
Corn oil	6539	6373	6207	6083	5906	5754	4899	2995	1508	562

REDUCE-IT vs STRENGTH: Icosapent Ethyl Better bc Control Group Did Worse?



STRENGTH: Corn Oil

REDUCE-IT: Mineral Oil

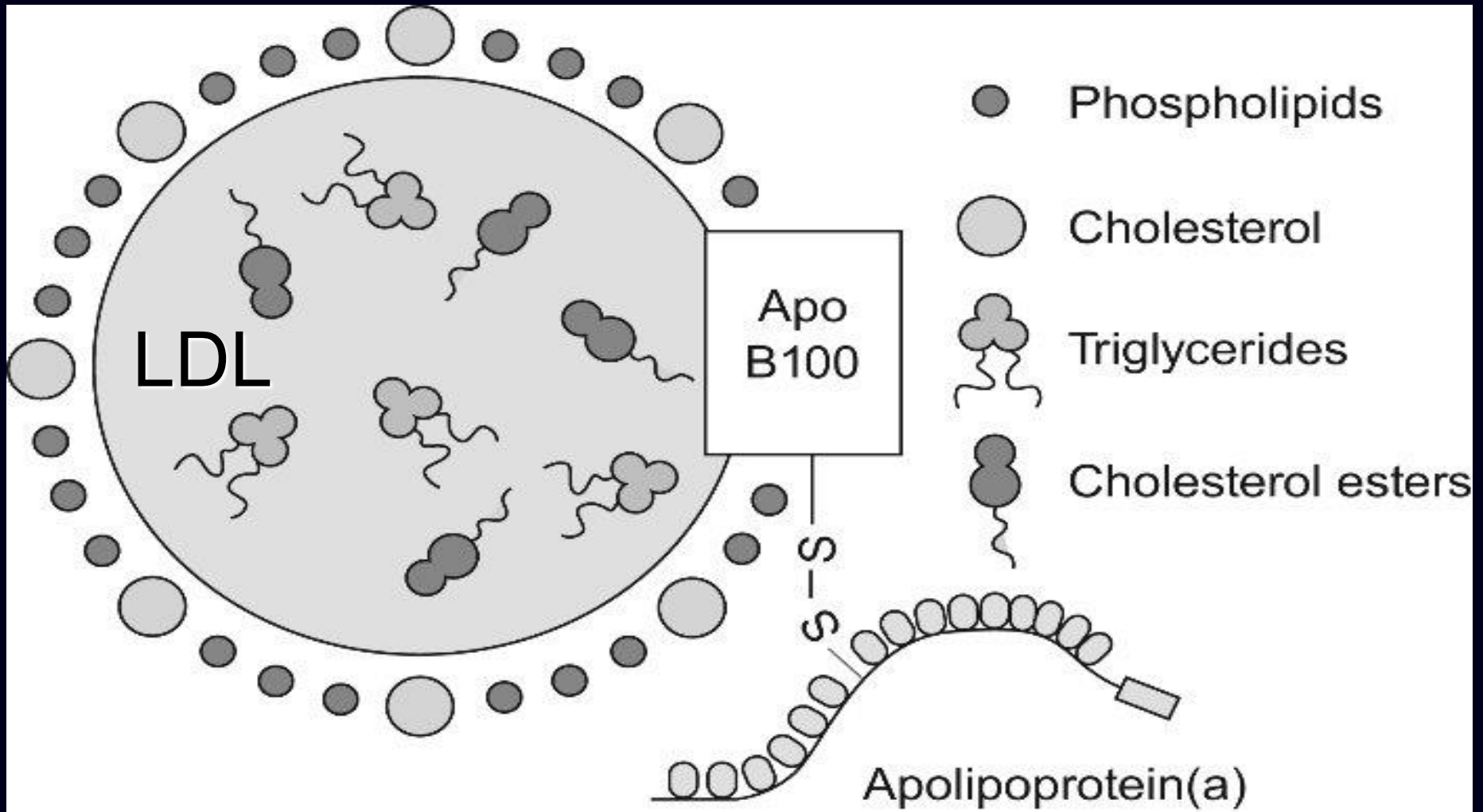
Not enough to explain away benefit?

Summoning STRENGTH to Question the Placebo in REDUCE-IT. Bostrom. 2021;144:407–409

Icosapent Ethyl Use

- Hypertriglyceridemia (> 150 mg/dL? > 200 mg/dL)
- Increased CV risk?
 - Low HDL < 40 mg/dL
 - Recurrent CV events?
 - Residual, unaddressed risk?
- If prohibitively expensive, consider EPA alone?
- Note: Increased bruising – more so with DAPT
- Major HyperTG - pancreatitis:
 - Fenofibrate, statin, icosapent ethyl
 - Olezarsen (Tryngolza): Familial Chylomicronemia Syndrome antisense to ApoC3

Lipoprotein (a)



Lp(a) and CV risk?

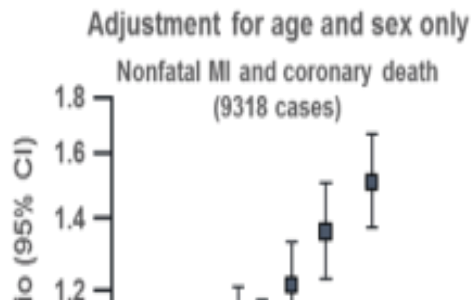
Clinical evaluation Lp (a):

- Check for a reason?:
 - Premature CAD (event, family hx)
 - Unattributable CVD risk
- Prim Prev: Independent of other CV risk?
- Further risk stratify? CRP, CAC

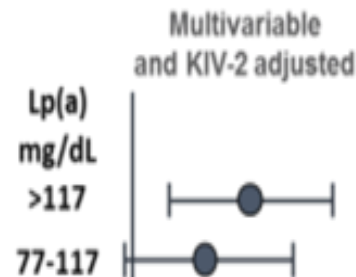
If managing:

- Statin: cornerstone rx
- More aggressive LDL lowering?
- Aspirin rx, even if primary prevention
- PCSK9i?

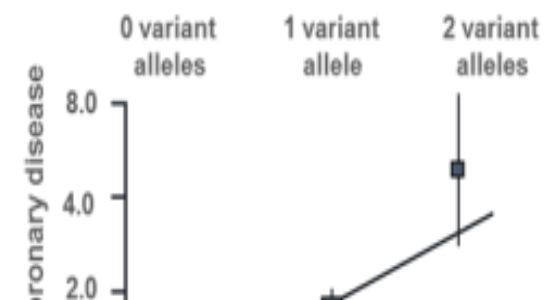
Epi/Meta-analyses



Mendelian Randomization



Genome-wide Association



PCSK9 inhibitors: ~30% Lp(a) decrease

Post-hoc analysis: Lp(a) greater risk, greater benefit

Lp(a) Not a basis for approval

Clinical trials underway for Lp(a) lowering agents

Key Take Aways

Cholesterol and lipid metabolism is a complex, interconnected system for moving lipoprotein particles and their cargo (cholesterol, triglycerides) through the body.

Genetic 'experiments of nature' establish LDL-C as being directly related to CV risk - both with familial hypercholesterolemia, and low (PCSK9 loss of function) LDL-C levels.

Statins decrease CV risk across a range of risk and in multiple trials.

Despite statin's strong record of safety and efficacy in reducing CV risk, statin intolerance is reported, more than in trials. Statin intolerance can be overcome w/ education, different statins or moving on to other non-statin options, including ezetimibe, PCSK9 inhibitors and/or bempedoic acid.

PCSK9 inhibitors are effective, well tolerated, and approvable; inclisiran has arrived as an every 6 month approach to targeting PCSK9 and lowering LDL-C.

Hypertriglyceridemia can be a risk issue for pancreatitis and may also identify increased risk through its relationship with LDL-C properties, with treatment tools that include icosapent ethyl.

Lipoprotein (a) is perhaps the most common unmet need for CV risk reduction, with trials underway.



REFERENCES

2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 153: 17, 2026.

Watts, G.F., Gidding, S.S., Hegele, R.A. *et al.* International Atherosclerosis Society guidance for implementing best practice in the care of familial hypercholesterolaemia. *Nat Rev Cardiol* **20**, 845–869 (2023).

<https://doi.org/10.1038/s41569-023-00892-0>

Bempedoic Acid and Cardiovascular Outcomes in Statin-Intolerant Patients

Nissen, et al. <https://orcid.org/0000-0002-7231-6464>, *N Engl J Med* 2023;388:1353-1364

DOI: 10.1056/NEJMoa2215024

NLA scientific statement on statin intolerance: a new definition and key considerations for ASCVD risk reduction in the statin intolerant patient

Cheeley, et al *Open Access J Clinical Lipidology*, 2022 DOI:<https://doi.org/10.1016/j.jacl.2022.05.068>



Homozygous familial hypercholesterolemia is characterized by

- a) Pancreatitis due to severely elevated triglycerides
- b) Palmar xanthomas
- c) Autosomal dominant pattern of inheritance
- d) Restricted to those with LDL receptor genetic defects
- e) Extensor tendon xanthomas

Answer: e) A thickened, roughened Achilles tendon
(extensor tendon xanthoma)

Treatment of severe hypertriglyceridemia with levels over ~800 mg/dL is warranted given:

- a) Given unequivocal evidence for a reduction in CV risk as seen with omega 3 fatty acids.
- b) The evidence that even with treatment of diabetes, hypothyroidism, weight loss and smoking cessation, all of which increase triglycerides, the CV risk of hypertriglyceridemia will persist.
- c) Concerns over the risk of potential pancreatitis.
- d) Pancreatitis as a complication of GLP1 receptor agonist treatment
- e) Levels like this indicate that there would be little difference between fasting and non-fasting triglycerides.

Answer: c: Potential pancreatitis