# Hypertriglyceridemia: Association or Causative for ASCVD Management?

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# Duality of Interests

— *Consultant/Advisory Boards*

Amgen
Arrowhead
Better Co.
89bio
Lexicon
Novo Nordisk
Precision BioSciences
The Healthy Aging Co.
Tolmar
UpToDate
WW (Weight Watchers)

# Goals

- Discuss problems with the definition, related prevalence and causes of hypertriglyceridemia.
- Provide updates on if/how hypertriglyceridemia relates to atherosclerotic CVD using informative CVOTs.
- Evaluate strategies for triglyceride management:
  - Moderate
  - Severe
- Summarize HDL-C science and management.

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# Challenges with the Definition, Prevalence and Causes of Hypertriglyceridemia

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# Plasma Triglycerides are Inversely Associated with HDL-C
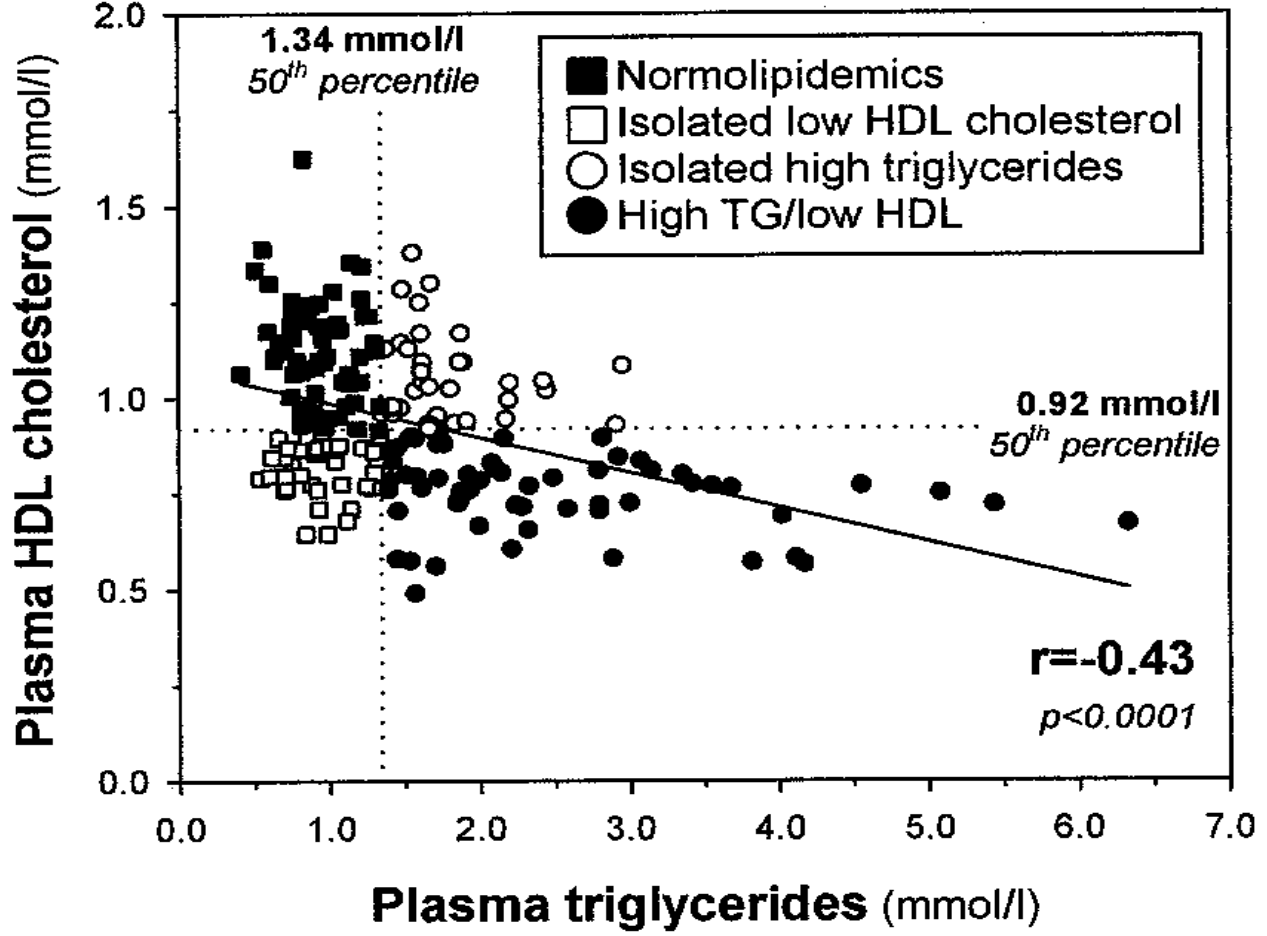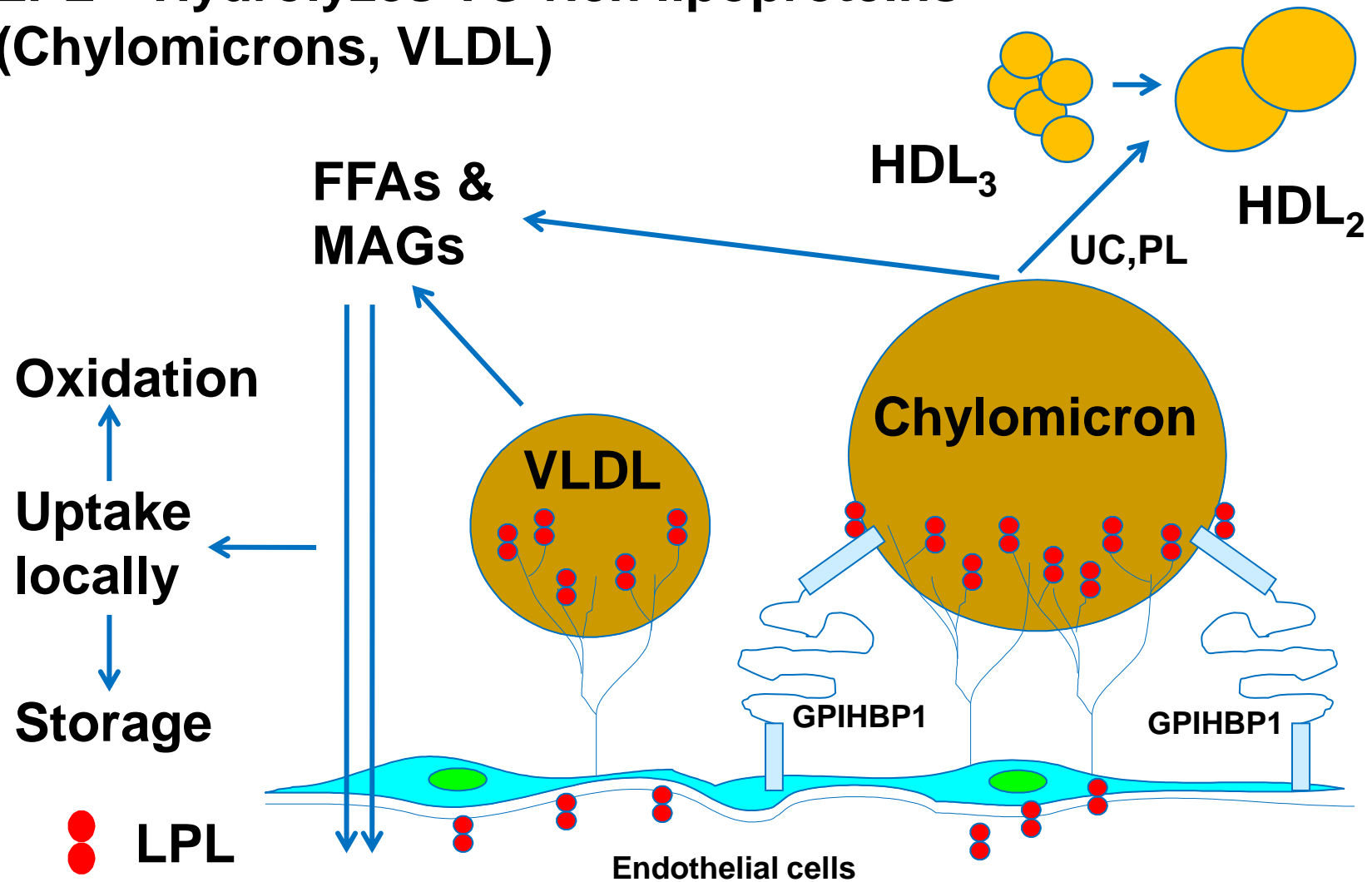


Couillard C et al, *ATVB* 21:1228, 2001

# Why are Levels of HDL-C Inversely Related to Plasma Triglycerides?

- The formation of larger more buoyant cholesterol-enriched HDL is dependent on the hydrolysis of TG-rich lipoproteins by lipoprotein lipase (LPL).

Eisenberg S. Klin Wochenschr 61:119, 1983

# Lipoprotein Lipase

**LPL – Hydrolyzes TG-rich lipoproteins (Chylomicrons, VLDL)**

# Why are Levels of HDL-C Inversely Related to Plasma Triglycerides?

- The formation of larger more buoyant cholesterol-enriched HDL is dependent on the hydrolysis of TG-rich lipoproteins by lipoprotein lipase (LPL).

- When hypertriglyceridemia is present, HDL particles are more TG-enriched, replacing cholesterol ester with TG in the lipoprotein core.

- TG-enriched HDL are more rapidly catabolized.

Eisenberg S. Klin Wochenschr 61:119, 1983
Deckelbaum RJ et al, Arteriosclerosis 4:225, 1984
Goldberg IJ et al, JCI 86:463, 1990

# Hypertriglyceridemia is the Most Difficult Lipid Disorder to Evaluate and Treat – Why?

- The common disorders are not single genes.
- The acquired disorders are numerous.
- The clinical trials with TG lowering drugs have suffered:
  - design
  - number of trials
  - results have been mostly hypothesis-generating
- Is it TG or the TG-rich particles that confer risk for ASCVD and/or the company they keep?

# Problems Defining Hypertriglyceridemia

- Fasting levels are variable.

# Intra-Individual Variability of Lipids and Lipoproteins

| Diurnal Biological Variability (CV) | Monthly Biological Variability (CV) |
|---|---|
| ➤ **TG ⟹ 29.5%** | ➤ **TG ⟹ 20.7%** |
| ➤ Apo B ⟹ 6.5% | ➤ Apo B ⟹ 9.7% |
| ➤ Apo A-1 ⟹ 6.5% | ➤ Apo A-1 ⟹ 9.4% |
| ➤ LDL-C ⟹ 5.1% | ➤ LDL-C ⟹ 5.2% |
| ➤ HDL-C ⟹ 3.5% | ➤ HDL-C ⟹ 4.1% |
| ➤ TC ⟹ 2.4% | ➤ TC ⟹ 4.2% |

# Results: Generalized Additive Model (GAM) Analyses of TG Variability and CHD

**Univariate Analyses**

| Variable | Parameter estimate | P-value |
|---|---|---|
| SD log (TG) [linear] | 0.25 | 0.64 |
| SD log (TG) [non-linear] | --- | 0.02 |

**Multivariate Analyses**

| Variable | Parameter estimate | P-value |
|---|---|---|
| SD log (TG) [linear] | 1.41 | 0.13 |
| SD log (TG) [non-linear] | --- | <0.0001 |

*Other significant CHD predictors include mean LDL-C, baseline age, male gender, and log TG*

# Problems Defining Hypertriglyceridemia

- Fasting levels are variable.

- Population data are skewed.

- Relationships to CHD often fail to relate to extent of elevations.

- What is a normal TG level:

    – Is it a fasting TG of <150 mg/dl?

    – Or should it be based on non-fasting levels?
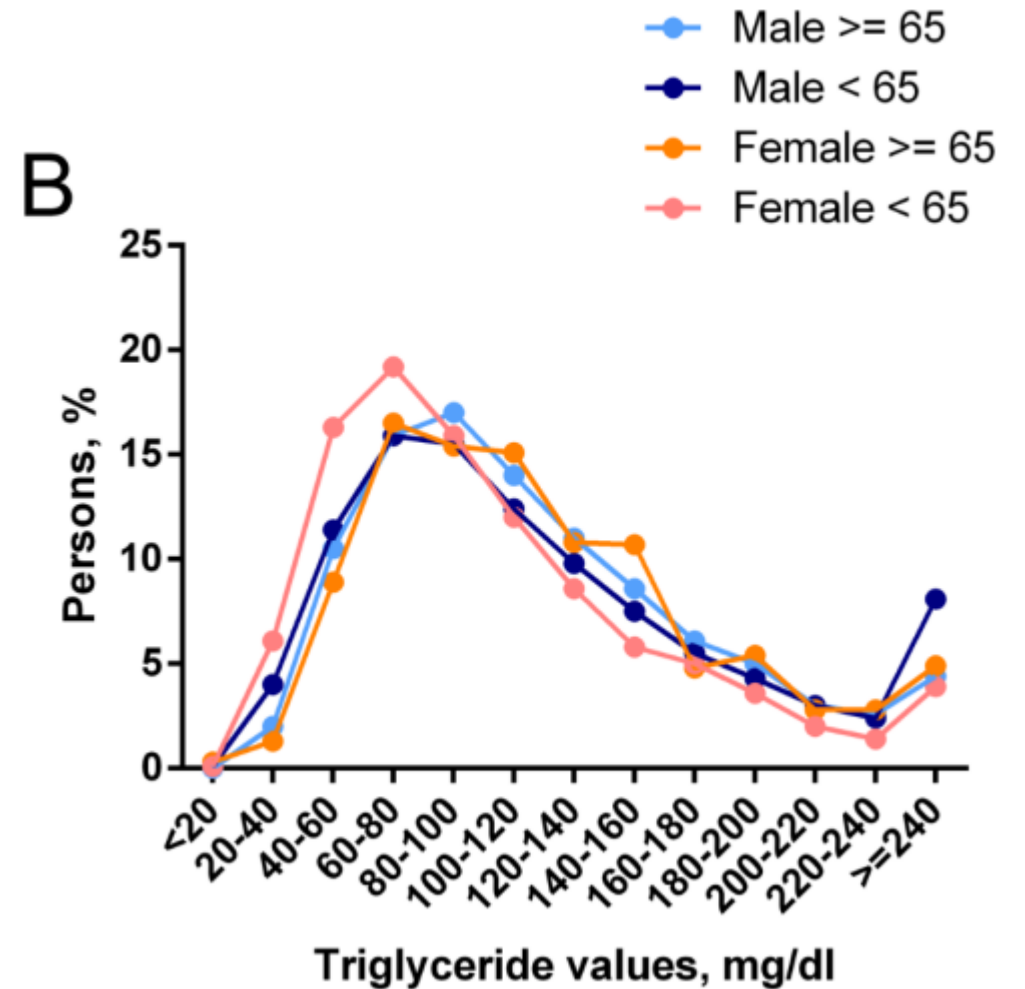
# Definitions of Hypertriglyceridemia

| Society | Category | Serum triglyceride conc. mg/dL (mmol/L) |
|---|---|---|
| AHA/ ACC/ Multisociety | Normal<br>Moderate<br>Severe | ≤ 175 (≤ 2.0)<br>175-499 (2.0-5.6)<br>≥ 500 (≥ 5.7) |
| ESC | Normal<br>Mild- moderate<br>Severe | <150 (< 1.7)<br>150-180 (1.7-9.9)<br>>880 (>10) |
| Endocrine Society | Normal<br>Mild<br>Moderate<br>Severe<br>Very severe | <150 (<1.7)<br>150-199 (1.7 – 2.3)<br>200-999 (2.3-11.2)<br>1000-1999 (11.2-22.4)<br>≥ 2000 (>22.4) |

- **Normal** – <150 mg/dL (<1.7 mmol/L)
- **Moderate hypertriglyceridemia** – 150 to 499 mg/dL (1.7 to 5.6 mmol/L)
- **Moderate to severe hypertriglyceridemia** – 500 to 999 mg/dL (5.65 to 11.3 mmol/L)
- **Severe hypertriglyceridemia** – ≥1000 mg/dL (≥11.3 mmol/L)

Virani, Salim S., et al. Journal of the American College of Cardiology 78.9 (2021): 960-993.

## Overall Prevalence of Hypertriglyceridemia in NHANES 2007-2014 (%)

| Fasting TG ≥150 mg/dL | Prevalence % |
|---|---|
| Overall (age ≥20 y) | 25.9 |
| Statin-treated | 31.6 |
| Statin-treated, LDL-C <100 mg/dL | 27.6 |
| Statin-treated & Diabetes | 39.5 |
| Statin-treated & ASCVD | 30.5 |
| Statin-treated & Diabetes or ASCVD | 34.4 |

## Distribution of Plasma Triglycerides in NHANES 2007-2018 (%)



B — Distribution of Plasma Triglycerides. Legend: Male >= 65, Male < 65, Female >= 65, Female < 65. Y-axis: Persons, %. X-axis: Triglyceride values, mg/dl (<20, 20-40, 40-60, 60-80, 80-100, 100-120, 120-140, 140-160, 160-180, 180-200, 200-220, 220-240, >=240)

Fan W et al Cardiol Ther 9:207, 2020

Li Z et al, Lipids Health Disease 21:111, 2022

# Hypertriglyceridemia & ASCVD Risk

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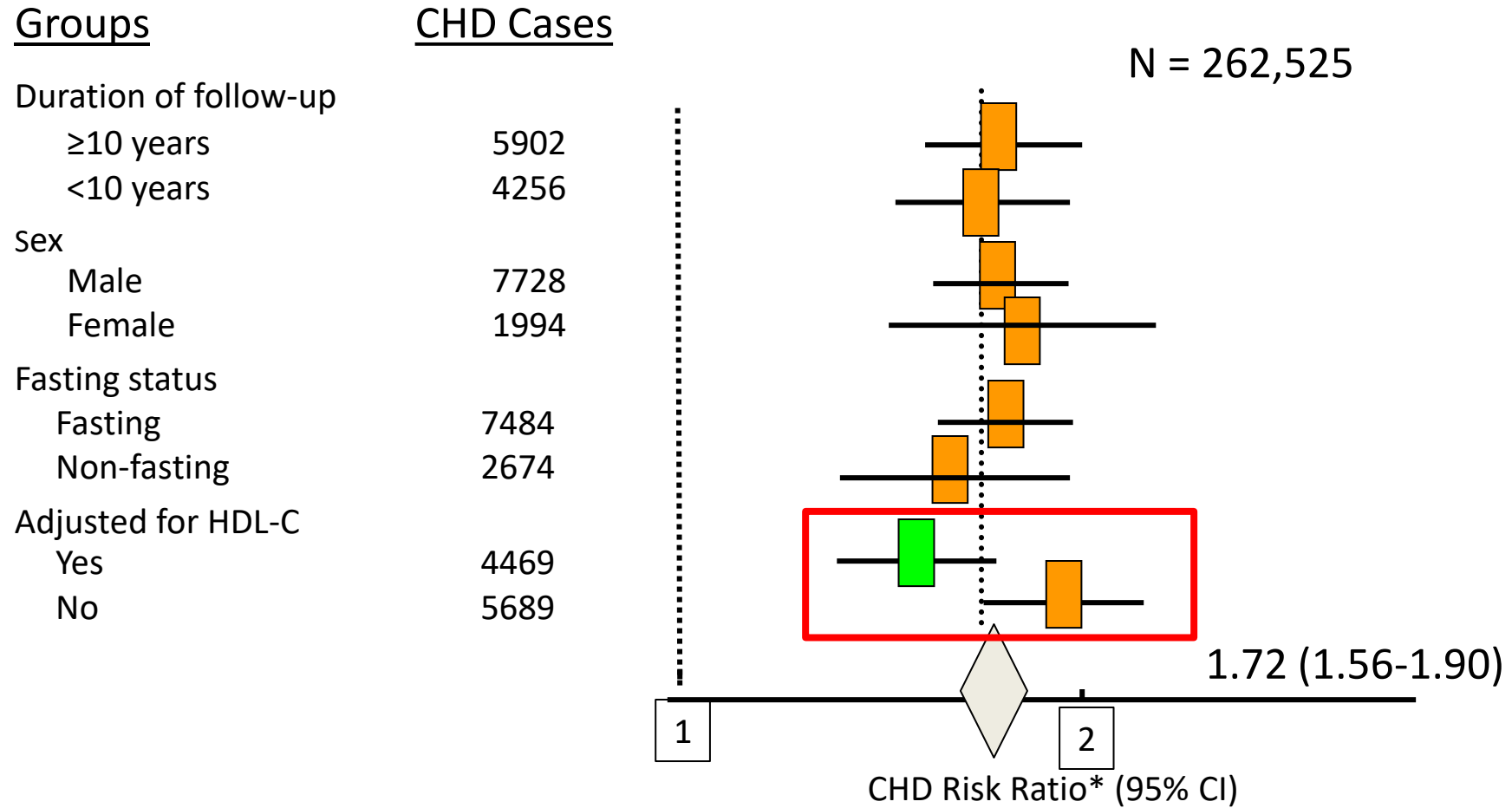**robert.eckel@cuanschutz.edu**

# Goals

- Discuss problems with the definition, related prevalence and causes of hypertriglyceridemia.

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- Evaluate strategies for triglyceride management:
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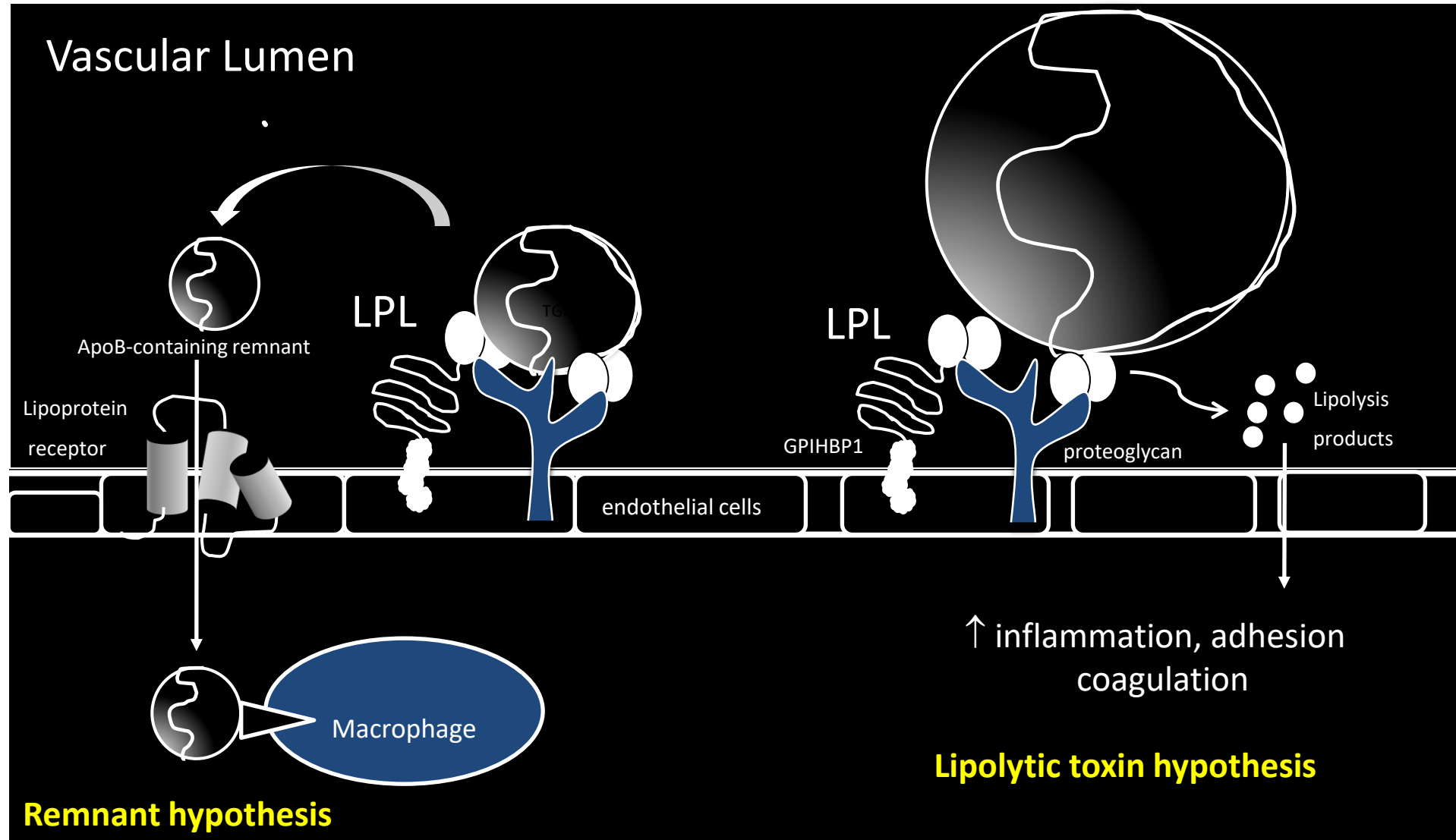
- Summarize HDL-C science and management.

# Plasma Triglycerides and CHD: Meta-Analysis of 29 Studies

| Groups | CHD Cases |
|---|---|
| Duration of follow-up | |
| ≥10 years | 5902 |
| <10 years | 4256 |
| Sex | |
| Male | 7728 |
| Female | 1994 |
| Fasting status | |
| Fasting | 7484 |
| Non-fasting | 2674 |
| Adjusted for HDL-C | |
| Yes | 4469 |
| No | 5689 |

N = 262,525

1.72 (1.56-1.90)

CHD Risk Ratio* (95% CI)

**Sarwar N et al. Circulation.115:450, 2007**

# Atherogenicity of TG-Rich Lipoproteins



**Vascular Lumen**

ApoB-containing remnant

LPL

TG

LPL

Lipoprotein receptor

GPIHBP1

proteoglycan

Lipolysis products

endothelial cells

↑ inflammation, adhesion coagulation

Macrophage

**Remnant hypothesis**

**Lipolytic toxin hypothesis**

**Goldberg IJ, Eckel RH, McPherson R, ATVB, 31:1716, 2011**

# Are Triglycerides Simply Innocent Bystanders?



Basu D & Bornfeldt KE, Front Endocrinol, 11:504, 2020
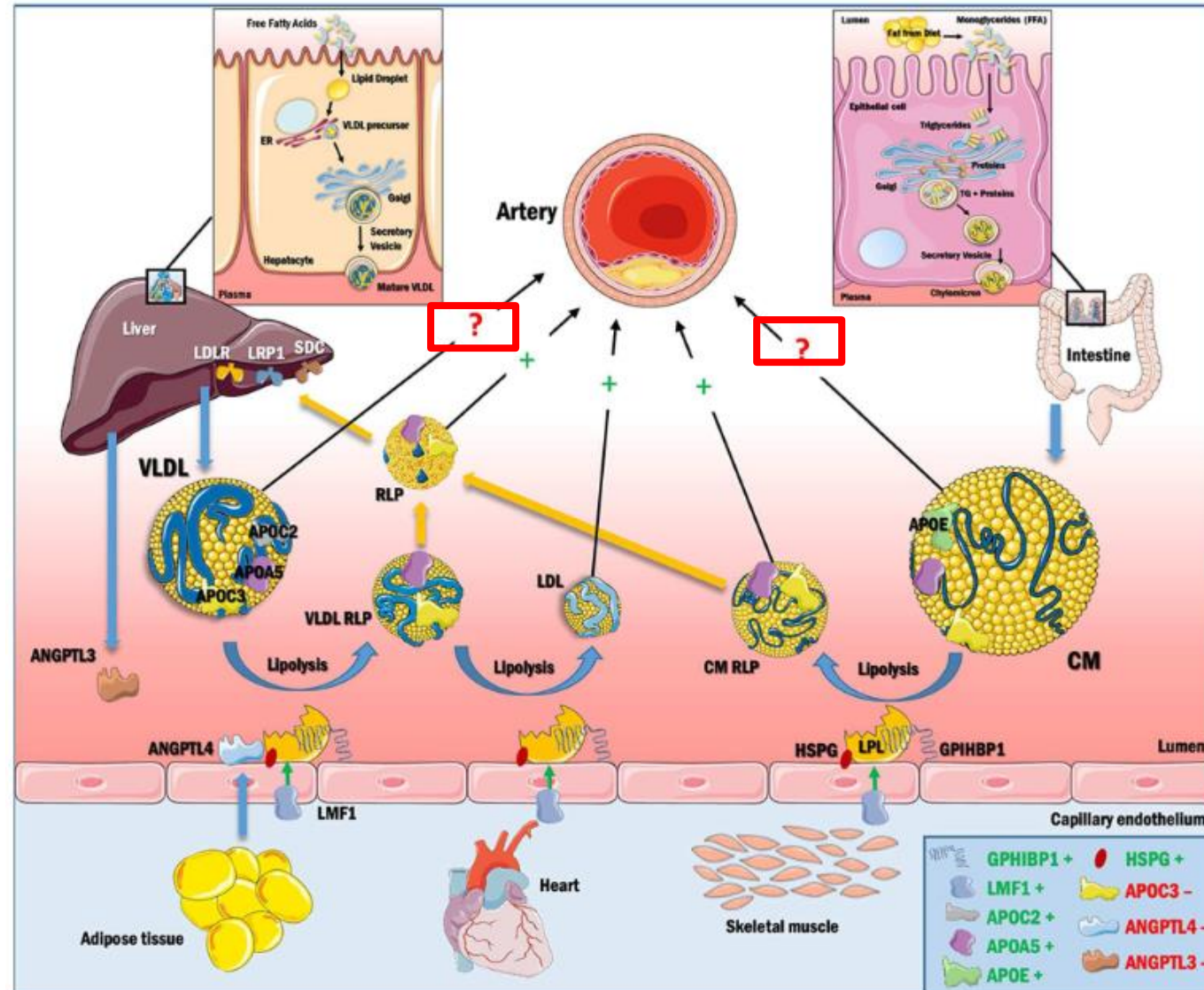
# Mechanistic Insights from REDUCE-IT STRENGTHen the Case Against Triglyceride Lowering as a Strategy for Cardiovascular Disease Risk Reduction

R. Preston Mason, PhD,[a] Robert H. Eckel, MD[b]

[a]Brigham and Women's Hospital and Harvard Medical School, Boston, Mass; [b]University of Colorado Anschutz Medical Campus, Aurora.

**ABSTRACT**

Elevated triglyceride (TG) levels have been linked to residual atherosclerotic cardiovascular risk in patients with controlled low-density lipoprotein cholesterol. However, outcome trials testing TG-lowering agents have failed to demonstrate cardiovascular risk reduction in statin-treated subjects. One such example is the recent STRENGTH trial, which tested mixed omega fatty acids (n3-FAs, 4 g/d) in high-risk patients with elevated TGs. Similar to trials using fibrates and niacin, the STRENGTH trial failed despite effective TG lowering. Results from these studies have contributed to skepticism about the use of TG-lowering therapy for cardiovascular risk. However, new mechanistic insights are provided by the REDUCE-IT

## CLINICAL SIGNIFICANCE

Elevated triglycerides (TGs) are associated with increased cardiovascular risk; however, current TG-lowering therapies are ineffective in reducing such risk

Icosapent ethyl, highly purified eicosapentaenoic acid, was recently shown to reduce cardiovascular events by 25% and was not associated with TG lowering.

Icosapent ethyl appears to have broad pleiotropic effects associated with on-treatment eicosapentaenoic acid levels.

Evidence against TG lowering in reducing cardiovascular risk should guide other therapeutic strategies to lower residual risk.

Mason RP, Eckel RH, Am J Med 134:1085, 2021

# Proposed Location and Contrasting Effects of EPA and DHA on Membrane Structure, Lipid Oxidation and Tissue Distribution
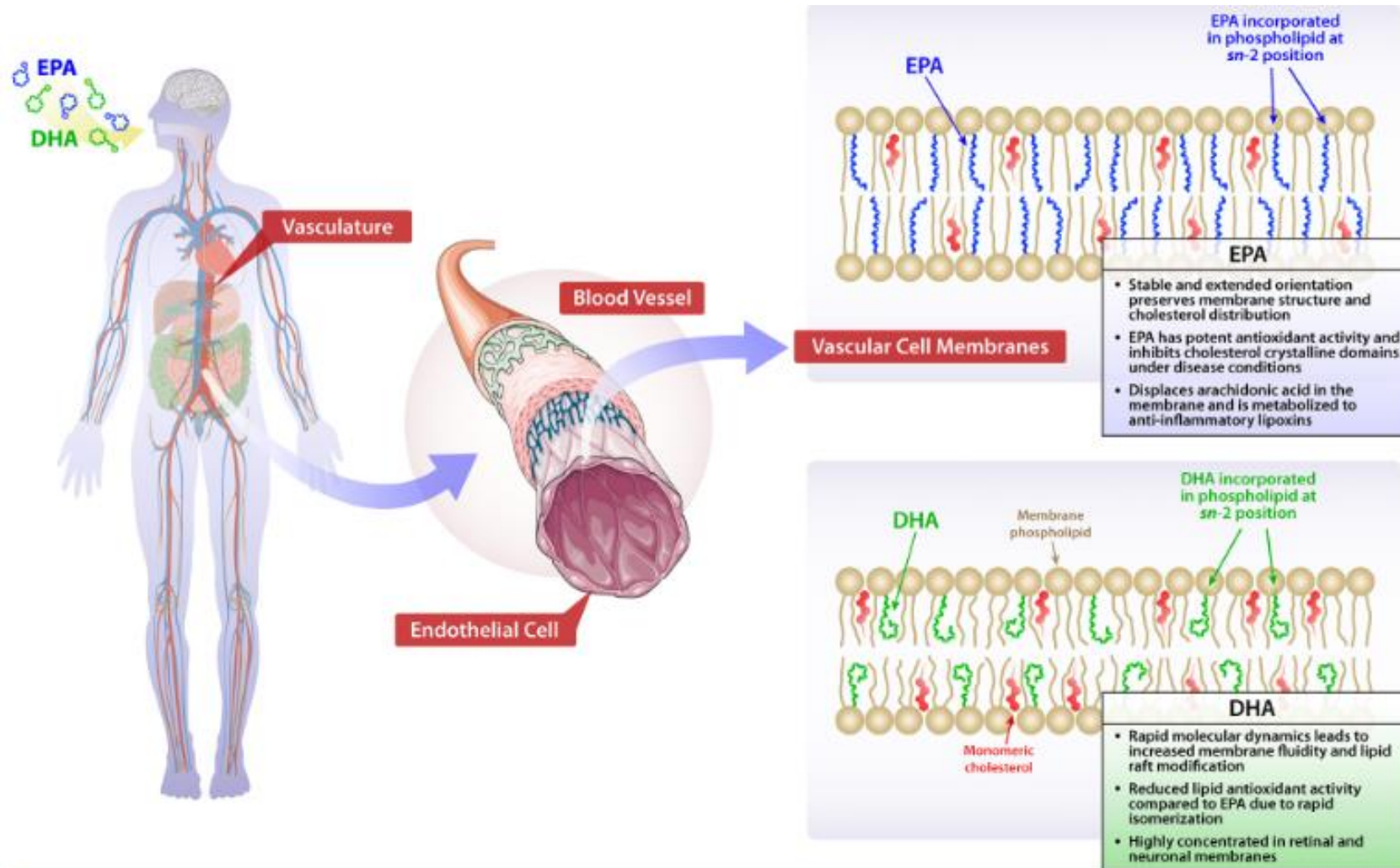
ELSEVIER

Invited critical review
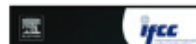
# Postprandial hypertriglyceridemia as a coronary risk factor

Jan Borén [a,*], Niina Matikainen [b,c], Martin Adiels [a], Marja-Riitta Taskinen [b]

[a] Department of Molecular and Clinical Medicine/Wallenberg Laboratory, University of Gothenburg, Gothenburg, Sweden
[b] HUCH Heart and Lung Centre, Research Programs Unit Diabetes and Obesity, Cardiovascular Research Group, Finland
[c] Department of Endocrinology, Helsinki University Central Hospital, Diabetes & Obesity, University of Helsinki, Helsinki, Finland

Lipoprotein cholesterol as a function of increasing levels of non-fasting triglycerides. Red = remnant cholesterol, blue = LDL-cholesterol and green = HDL-cholesterol.

| TG, mmol/L | < 1 | 1–1.99 | 2–2.99 | 3–3.99 | 4–4.99 | 5–5.99 |
|---|---|---|---|---|---|---|
| Number | 14906 | 28,041 | 10,722 | 3,826 | 1,418 | 982 |

## ARTICLE INFO

## ABSTRACT

Postprandial hypertriglyceridemia is now established as an important risk factor for cardiovascular disease (CVD). This metabolic abnormality is principally initiated by overproduction and/or decreased catabolism of triglyceride-rich lipoproteins (TRLs) and is a consequence of predisposing genetic variations and medical conditions such as obesity and insulin resistance. Accumulation of TRLs in the postprandial state promotes the retention of remnant particles in the artery wall. Because of their size, most remnant particles cannot cross the endothelium as efficiently as smaller low-density lipoprotein (LDL) particles. However, since each remnant particle contains approximately 40 times more cholesterol compared with LDL, elevated levels of remnants may lead to accelerated atherosclerosis and CVD. The recognition of postprandial hypertriglyceridemia in the clinical setting has been severely hampered by technical difficulties and the lack of established clinical protocols

# VLDL Defined by Apolipoprotein Content



Lp B

Lp B:E

**Lp B:C-III**
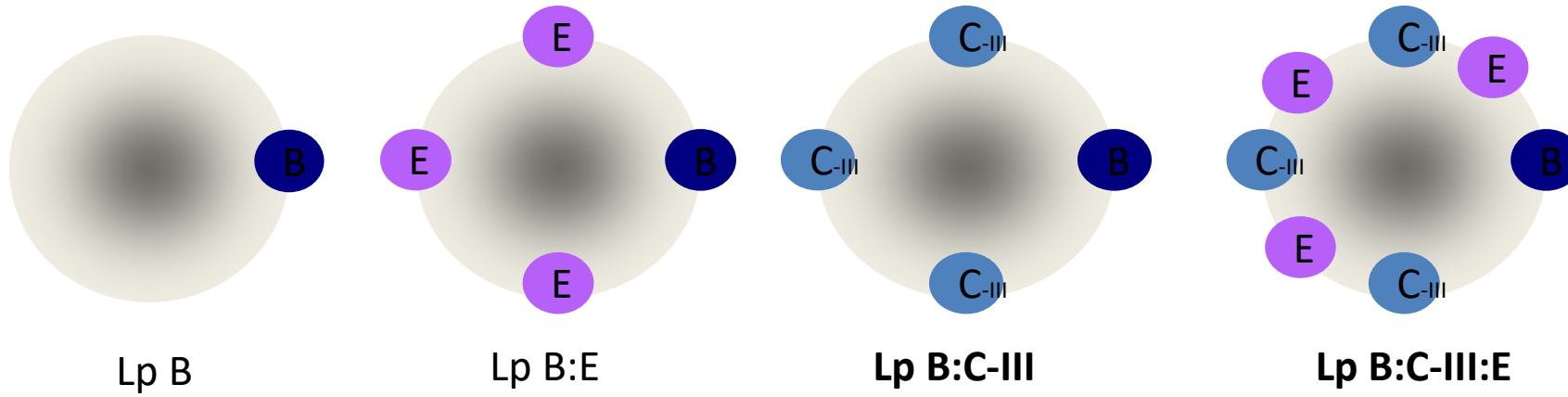
**Lp B:C-III:E**

ORIGINAL ARTICLE

# Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia

Daniel Gaudet, M.D., Ph.D., Veronica J. Alexander, Ph.D., Brenda F. Baker, Ph.D., Diane Brisson, Ph.D., Karine Tremblay, Ph.D., Walter Singleton, M.D., Richard S. Geary, Ph.D., Steven G. Hughes, M.B., B.S., Nicholas J. Viney, B.Sc., Mark J. Graham, M.S., Rosanne M. Crooke, Ph.D., Joseph L. Witztum, M.D., John D. Brunzell, M.D.,* and John J.P. Kastelein, M.D., Ph.D.

## ABSTRACT

### BACKGROUND

Apolipoprotein C-III (APOC3) is a key regulator of plasma triglyceride levels. Elevated triglyceride levels are associated with a risk of adverse cardiovascular events and pancreatitis. ISIS 304801 is a second-generation antisense inhibitor of APOC3 synthesis. [...] glycerides owing to mutations in the gene encoding apolipoprotein C3 (APOC3) are associated with a reduced risk of ischemic cardiovascular disease in the general population is unknown.

### METHODS

We s[...]

From the Department of Medicine, Université de Montréal and Ecogene-21 Clinical Research Centre, Chicoutimi, QC, Canada (D.G., D.B., K.T.); Isis Pharma-[...] sity Hospital and [...] edical Sciences, [...]n (A.B.J., R.F.-S., B.G.N., A.T.-H.), the Department of Clinical Biochemistry, Rigshospitalet (A.B.J., R.F.-S., A.T.-H.), the Department of Clinical Biochemistry (B.G.N.) and the Copenhagen General Population Study (R.F.-S., B.G.N., A.T.-H.), Herlev Hospital, and the Copen-

# Mechanisms of Atherogenicity of Apo CIII Containing TG-Rich Lipoproteins

- $\uparrow$ secretion in insulin resistant states
  - Metabolic syndrome
  - Type 2 diabetes
- Apo CIII itself $\uparrow$ PKC$\beta$ and $\rightarrow$ insulin resistance
- Apo CIII gene expression $\uparrow$ by NF-$\kappa$B
- $\downarrow$ TG-rich lipoprotein catabolism
- $\downarrow$ binding of apo B lipoproteins to hepatic apo B/E receptors
- $\uparrow$ adherence of monocytes to the endothelium
- $\uparrow$ monocyte activation (TLR2)

American Heart Association.

ORIGINAL ARTICLE

# Elevated Triglyceride Level Is Independently Associated With Increased All-Cause Mortality in Patients With Established Coronary Heart Disease

Twenty-Two–Year Follow-Up of the Bezafibrate Infarction Prevention Study and Registry

Editorial, see p 97

Robert Klempfner, MD, Aharon Erez, MD, Ben-Zekry Sagit, MD, Ilan Goldenberg, MD, Enrique Fisman, MD, Eran Kopel, MD, Nir Shlomo, MA, Ariel Israel, MD, and Alexander Tenenbaum, MD, PhD

**BACKGROUND—** The independent association between elevated triglycerides and all-cause mortality among patients with established coronary heart disease is controversial. The aim of this study was to investigate this association in a large cohort of patients with proven coronary heart disease.

**METHODS AND RESULTS—** The study cohort comprised 15 355 patients who were screened for the Bezafibrate Infarction Prevention (BIP) trial. Twenty-two–year mortality data were obtained from the national registry. Patients were divided into 5 groups according to strata of fasting serum triglycerides: (1) low-normal triglycerides (<100 mg/dL); (2) high-normal triglycerides (100–149 mg/dL); (3) borderline hypertriglyceridemia triglycerides (150–199 mg/dL); (4) moderate hypertriglyceridemia triglycerides (200–499 mg/dL); (5) severe hypertriglyceridemia triglycerides (≥500 mg/dL). Age- and sex-adjusted survival was 41% in the low-normal

**Klempfner R et al, Circ Card Qual Outcomes 9:100, 2016**
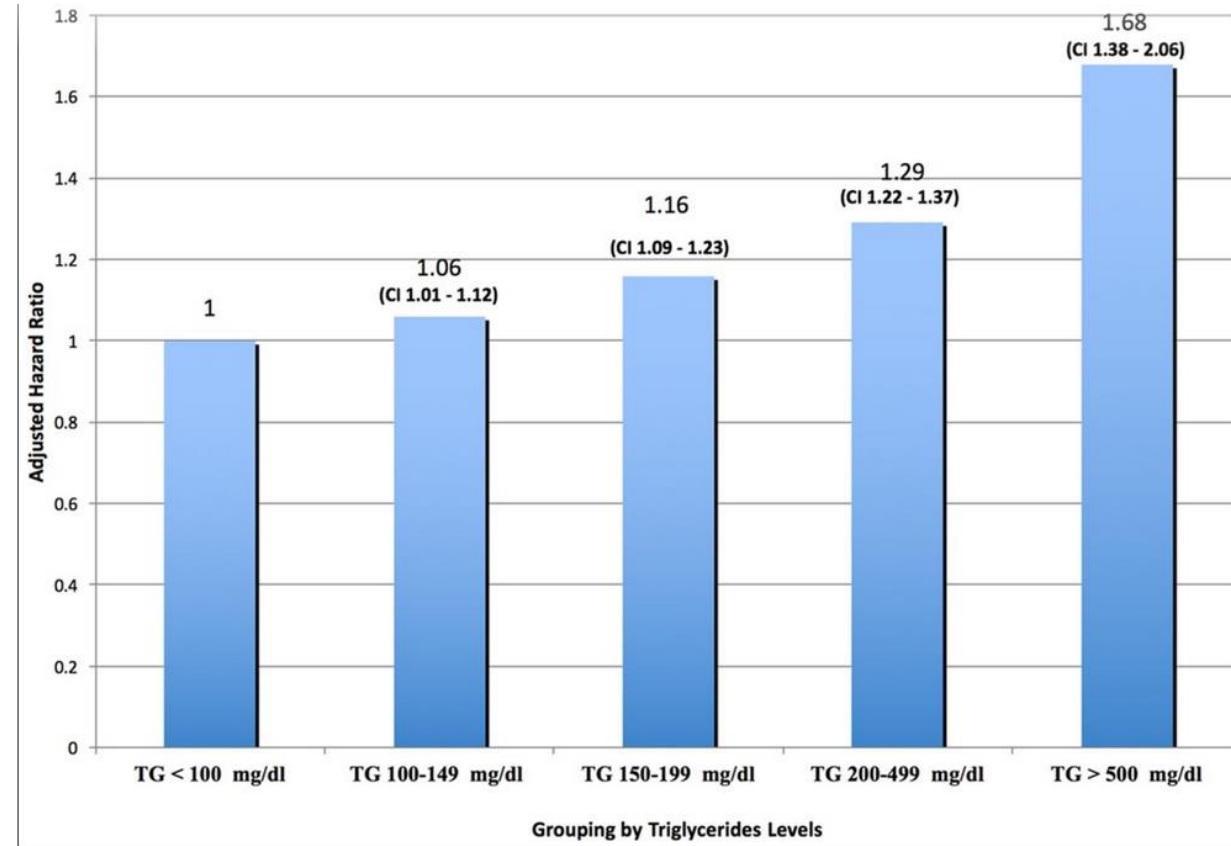
# What are the Genetics of Hypertriglyceridemia?

- FCHL and FHTG are not single genes but polygenic traits.

- A number of SNPs have been identified that relate to hypertriglyceridemia.

# Common DNA Polymorphisms Associated with Hypertriglyceridemia

| CHR | Gene | SNP | Risk allele | OR (95% CI) | *P*-value |
|---|---|---|---|---|---|
| 11 | *APOA5* | rs964184 | G | 3.43 (2.72–4.31) | $1.12 \times 10^{-25}$ |
| 2 | *GCKR* | rs1260326 | T | 1.64 (1.36–1.97) | $1.97 \times 10^{-7}$ |
| 8 | *LPL* | rs12678919 | A | 2.21 (1.52–3.22) | $3.5 \times 10^{-5}$ |
| 8 | *TRIB1* | rs2954029 | A | 1.50 (1.24–1.81) | $3.8 \times 10^{-5}$ |
| 1 | *ANGPTL3* | rs2131925 | T | 1.51 (1.23–1.85) | $1.0 \times 10^{-4}$ |
| 7 | *MLXIPL* | rs7811265 | A | 1.63 (1.25–2.13) | $3.3 \times 10^{-4}$ |
| 4 | *KLHL8* | rs442177 | T | 1.36 (1.13–1.64) | $1.5 \times 10^{-3}$ |
| 10 | *CYP26A1* | rs2068888 | G | 1.29 (1.08–1.55) | $5.9 \times 10^{-3}$ |
| 19 | *CILP2* | rs10401969 | T | 1.72 (1.16–2.54) | $6.8 \times 10^{-3}$ |
| 2 | *APOB* | rs1042034 | T | 1.28 (1.02–1.61) | 0.032 |

# Increased Genetic Burden of TG-Raising Alleles on Fasting Plasma TG: Canadian Heart Health Survey



Johansen CT et al, J. Lipid Res 52:189, 2011
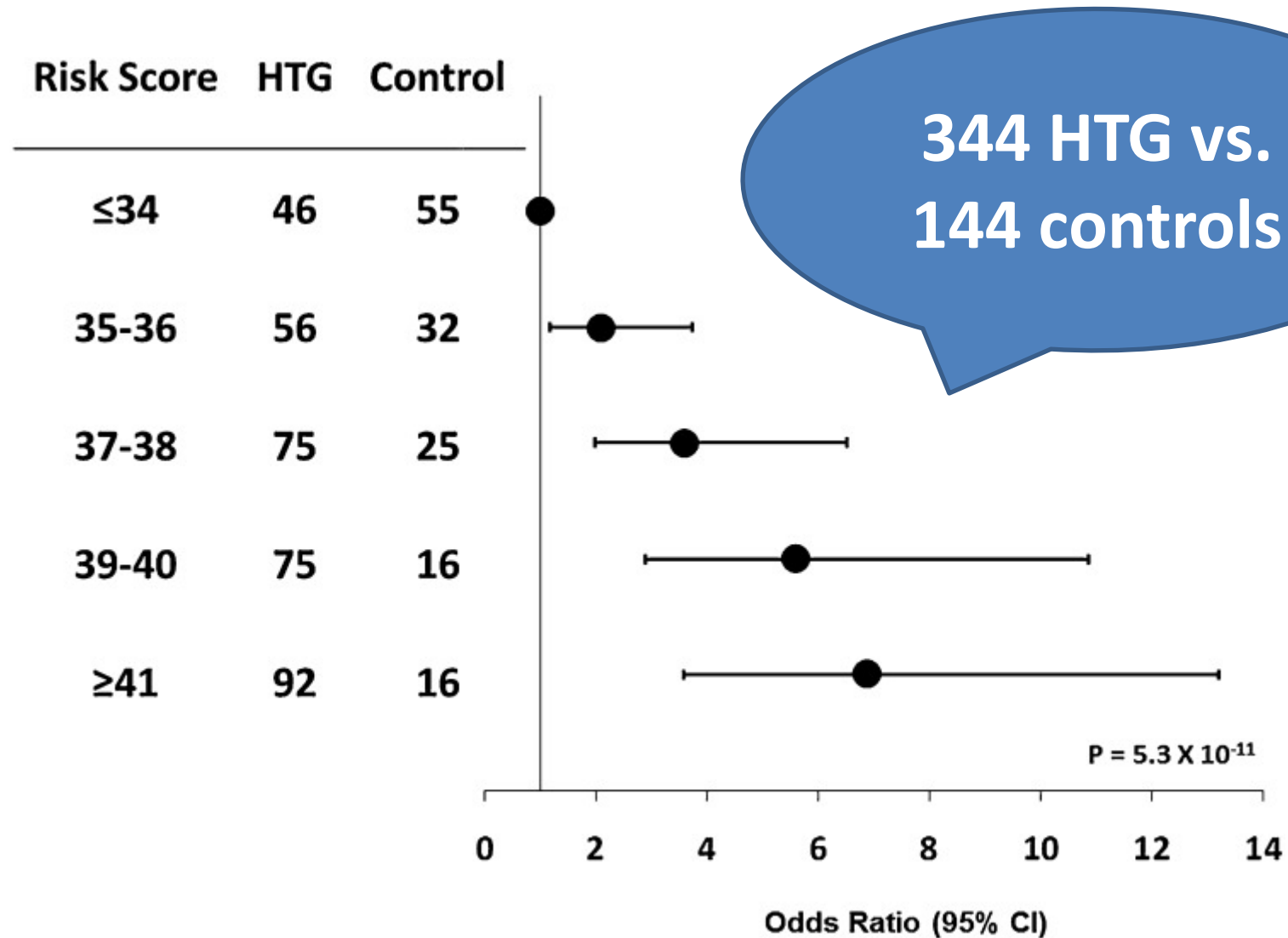
# Genetics, Lipids/Lipoproteins and Risk for Myocardial Infarction
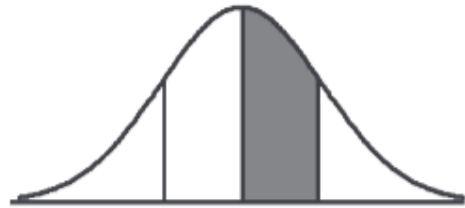


Musunuru K & Kathiresan S, Circ Res 118:579, 2016
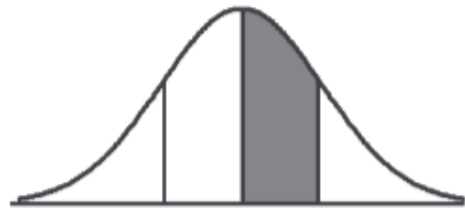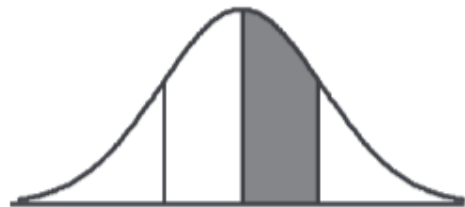
# Major Secondary Causes of Hypertriglyceridemia

## Disease States and Risk Factors

- Diabetes Mellitus, Insulin Resistance
- Obesity
- Alcohol
- Chronic Kidney Disease
- Nephrotic syndrome
- Hypothyroidism
- HIV
- Hepatocellular disease
- Inflammatory diseases

# Major Secondary Causes of Hypertriglyceridemia

## **<u>Drugs</u>**

- Oral estrogens
- Bile-acid sequestrants
- Antiretroviral regimens
  – especially for HIV disease
- Phenothiazines - 2nd-generation
- Nonselective beta-blockers
- Thiazide diuretics
- Loop diuretics
- Glucocorticoids
- Immunosuppressants
- Tamoxifen
- Isotretinoin

# Is apo B useful in predicting CVD risk in patients with hypertriglyceridemia?

One apo B molecule/particle

Assesses potentially atherogenic particle number

Most apo B is in LDL

# Multivariable Mendelian Randomization of ApoB, LDL-C & TG with CHD Risk

| Analysis | Variables | Odds Ratio for CHD (95% CI) | P Value |
|---|---|---|---|
| Association of ApoB with risk of CHD | ApoB | 0.770 (0.760-0.781) | 1.42E-170 |
| Association of LDL-C with risk of CHD | LDL-C | 0.846 (0.833-0.858) | 8.16E-77 |
| Association of triglycerides with risk of CHD | Triglycerides | 0.815 (0.785-0.846) | 1.37E-18 |
| Association of LDL-C and triglycerides with risk of CHD included in same model | LDL-C | 0.862 (0.849-0.875) | 6.92E-65 |
| | Triglycerides | 0.876 (0.850-0.902) | 1.36E-14 |
| Association of LDL-C, triglycerides, and ApoB with risk of CHD included in same model | ApoB | 0.761 (0.723-0.798) | 7.51E-20 |
| | LDL-C | 1.010 (0.967-1.055) | .186 |
| | Triglycerides | 1.014 (0.965-1.065) | .189 |
| Association of LDL-C, ApoB with risk of CHD included in same model | ApoB | 0.762(0.738-0.787) | 1.27E-36 |
| | LDL-C | 1.009(0.977-1.042) | 0.140 |
| Association of triglycerides, and ApoB with risk of CHD included in same model | ApoB | 0.765(0.751-0.779) | 1.20E-105 |
| | Triglycerides | 1.011(0.975-1.048) | 0.161 |

# Correlations Between Apo B, Cholesterol, LDL Cholesterol and Non-HDL Cholesterol

Sniderman AS et al, Am J. Card 91:1173, 2003
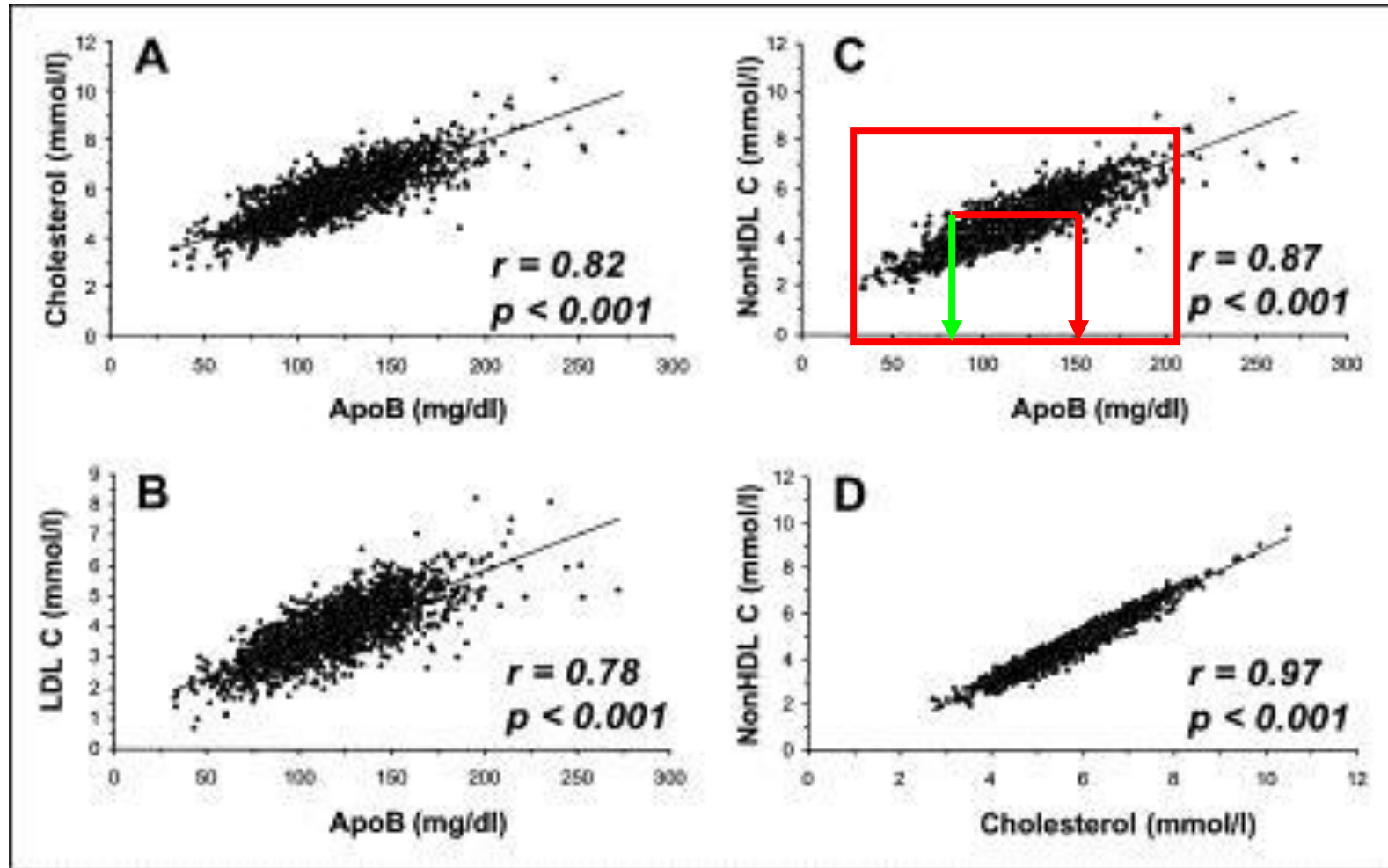
# CVD Risk: Triglycerides vs. Non-HDL-C

- Are studies focused on th
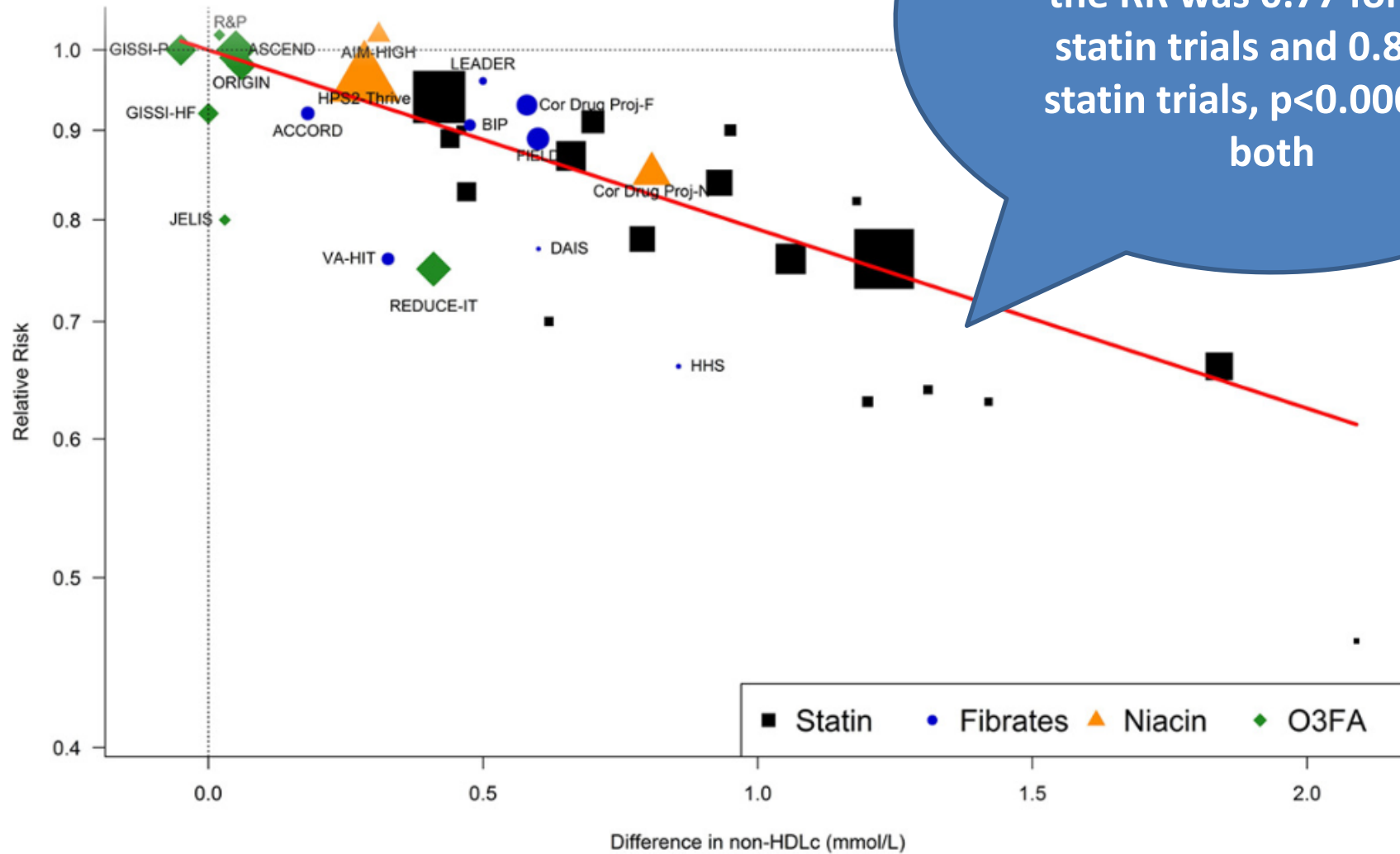
For 1 mmol/L (~39mg/dL) reduction in non-HDL-C, the RR was 0.77 for non-statin trials and 0.80 for statin trials, p<0.0001 for both



Marston NA et al, Circulation 140:1308, 2019

# Goals

- Discuss problems with the definition, related prevalence and causes of hypertriglyceridemia.
- Provide updates on if/how hypertriglyceridemia relates to atherosclerotic CVD using informative CVOTs.
- **Evaluate strategies for triglyceride management:**
  - Moderate
  - Severe
- Summarize HDL-C science and management.

# Lifestyle Recommendations for Patients with Hypertriglyceridemia

- Heart healthy lifestyle
  - Mediterranean-style or DASH diet
    - When implemented, additional simple carbohydrate restriction is not necessary
  - Regular physical activity
    - 3 to 4 sessions a week
    - lasting on average 40 min per session
    - involving moderate-to-vigorous intensity physical activity
  - Weight loss
    - 5-10%

# Range of Triglyceride Lowering with Drugs

- Fibrates                                   20-45%
- Nicotinic acid                        10-30%
- Omega-3 fatty acids            15-35%
- Statins                                      0-35%
  - Low end – minimal or no effect
  - High end – mod to high dose

# Major Fibrate CVD Outcome Trials

| Study (Year) | N | Study drug | Comparator | Primary Outcome | Results | |
|---|---|---|---|---|---|---|
| HHS (1987) | 4081 | Gemfibrozil | Placebo | Fatal or nonfatal MI or cardiac death | 34% reduction | * |
| VA-HIT (1999) | 2531 | Gemfibrozil | Placebo | Nonfatal MI or cardiac death | 22% reduction | * |
| BIP (2000) | 3090 | Bezafibrate | Placebo | Fatal or nonfatal MI or sudden death | 9.4% reduction | NS |
| LEADER (2002) | 1568 | Bezafibrate | Placebo | CHD or stroke | 4% reduction | NS |
| FIELD (2005) | 9795 | Fenofibrate | Placebo | CHD death or nonfatal MI | 11% reduction | NS |
| ACCORD (2010) | 5518 | Simvastatin + Fenofibrate | Simvastatin | Nonfatal MI, nonfatal stroke, CVD death | 8% reduction | NS |
| ACCORDION (2017) | 4644 | Simvastatin + Fenofibrate | Simvastatin | Nonfatal MI, nonfatal stroke. CVD death | 7% reduction | NS |

# Hazard Ratios for the Primary Outcome in Pre-Specified Subgroups: ACCORD, 14 Year Data

| Subgroup | Fenofibrate | Placebo | Hazard ratio (95% CI) | P for interaction |
|---|---|---|---|---|
| | % of events (no. in group) | | | |
| HDL | | | | |
| <35 | 197/956 (20.61) | 224/903 (24.81) | 0.81 (0.67-0.98) | .20 |
| 35-40 | 159/852 (18.66) | 157/858 (18.30) | 1.01 (0.81-1.26) | |
| ≥41 | 150/916 (16.38) | 155/959 (16.16) | 1.02 (0.81-1.27) | |
| Triglycerides | | | | |
| <129 | 146/879 (16.61) | 186/930 (20.00) | 0.83 (0.67-1.03) | .37 |
| 129-203 | 171/918 (18.63) | 160/908 (17.62) | 1.04 (0.84-1.29) | |
| ≥204 | 189/927 (20.39) | 190/882 (21.54) | 0.93 (0.76-1.13) | |
| Dyslipidemia | | | | |
| No | 407/2242 (18.15) | 415/2266 (18.31) | 0.99 (0.86-1.13) | .05 |
| Triglycerides >204 and HDL-C <34 | 99/482 (20.54) | 121/454 (26.65) | 0.73 (0.56-0.95) | |
| Hemoglobia A$_{1c}$ | | | | |
| <8.1 | 236/1313 (17.97) | 250/1322 (18.91) | 0.93 (0.78-1.11) | .975 |
| ≥8.1 | 271/1421 (19.07) | 289/1408 (20.53) | 0.93 (0.79-1.10) | |

0.5    1.0    2.0
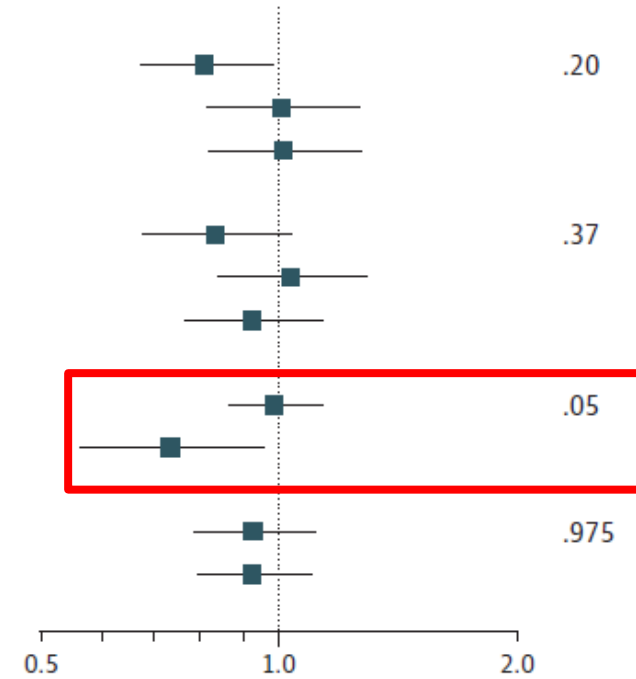
**Fenofibrate better**    **Placebo better**

Elam MB et al. JAMA Card 2:370, 2016

# Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes (PROMINENT)

The primary objective of the study is to determine whether pemafibrate administered twice daily will delay the time to first occurrence of any component of the clinical composite endpoint of:

- Nonfatal Myocardial Infarction
- Nonfatal ischemic stroke
- Hospitalization for unstable angina requiring unplanned coronary revascularization; or
- CVD death

- Condition or disease: T2DM, dyslipidemia

# PROMINENT Study Design

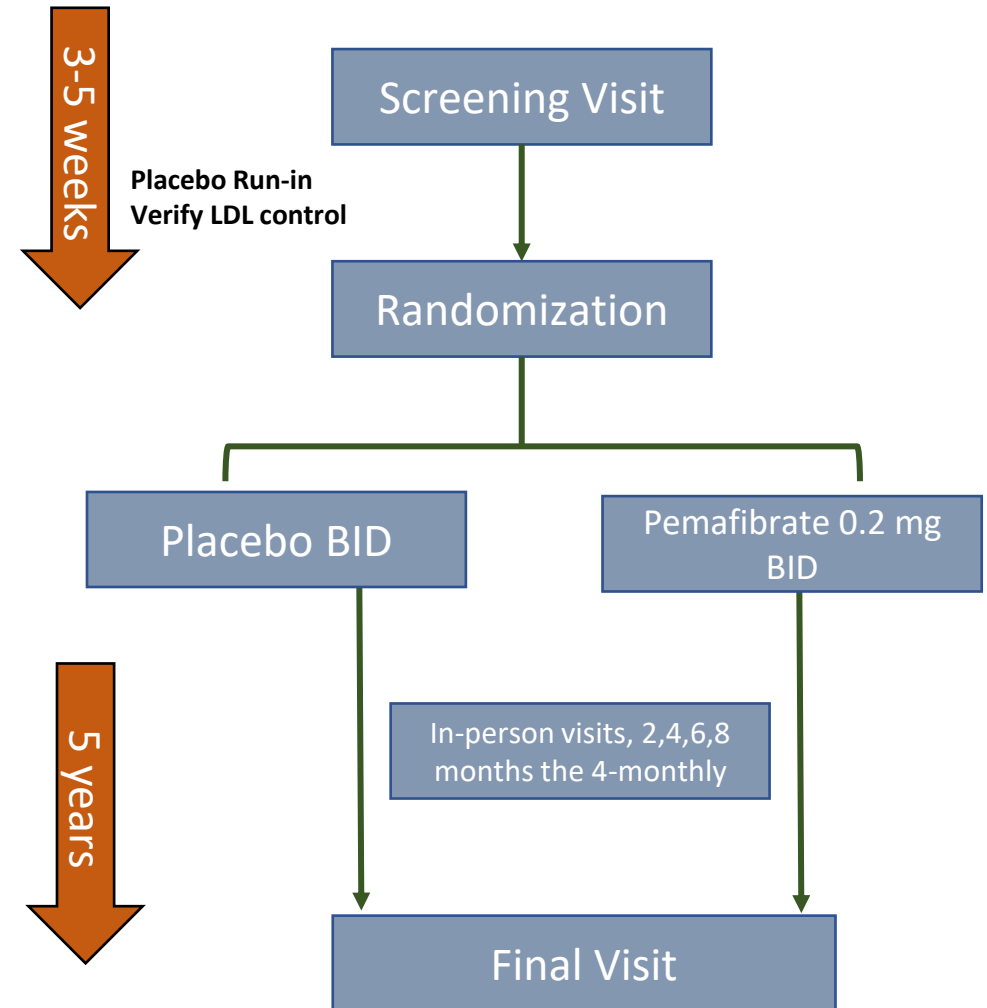**Men and Women with T2D (10,000 participants and 24 countries)**

TG 200-499 mg/dl (2.26-5.64 mM) and HDL ≤ 40mg/dl (1.03mM)
Moderate-high intensity Statin therapy or LDL-C control (≤70mg/dl other therapy or ≤100 mg/dl if statin intolerant)
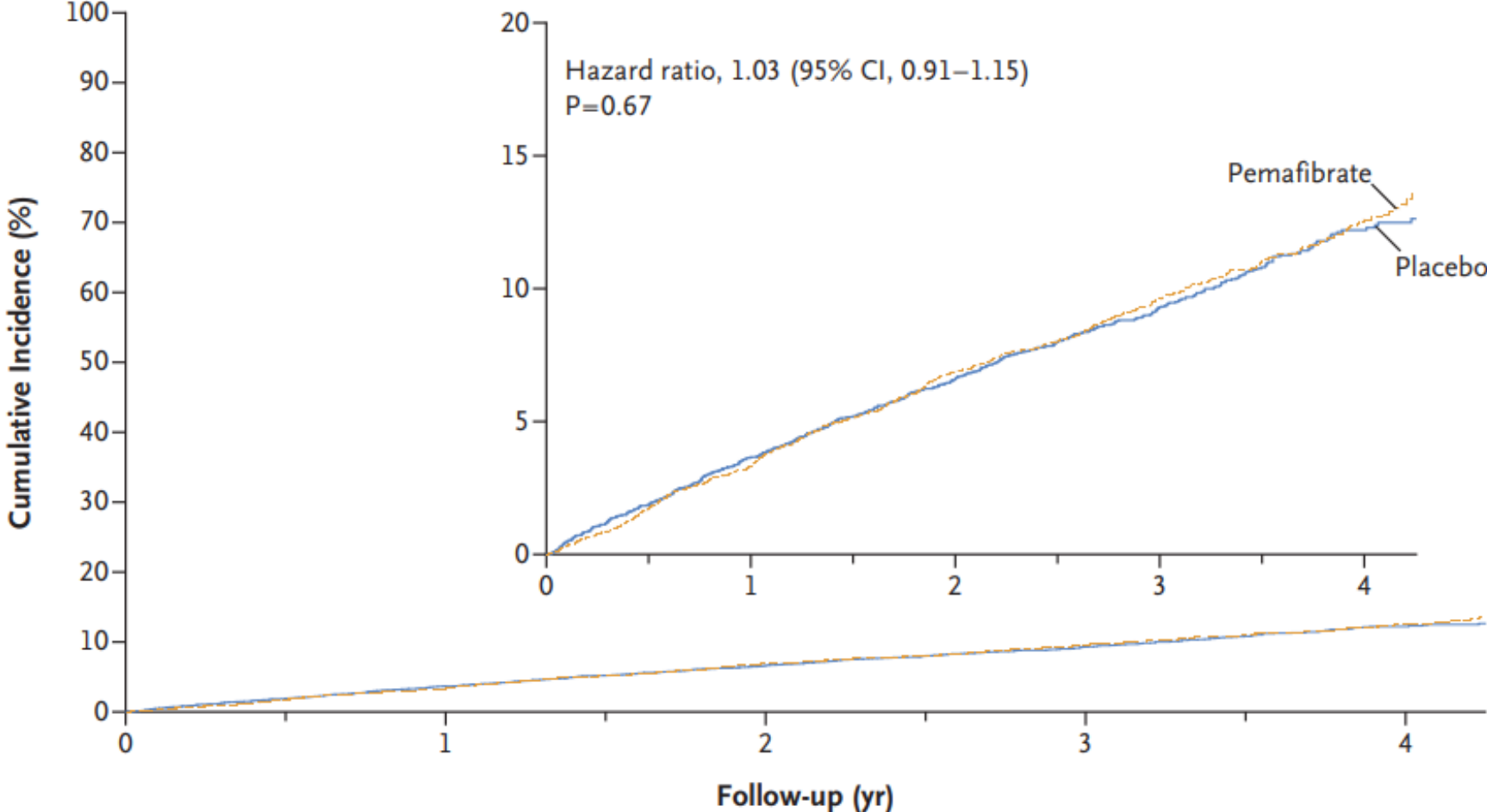1/3 Primary Prevention, 2/3 Secondary Prevention)

## ENDPOINTS

Event Driven: 1092 Primary endpoints, 200 in females

Primary Endpoint (MACE +)
MI, Ischemic stroke or unstable angina requiring unplanned revascularization, CV death

Secondary/ Tertiary Points: all cause mortality, any coronary revascularization, HF, total stroke, retinopathy, nephropathy, glycemic control, PAD, biomarkers, QOL
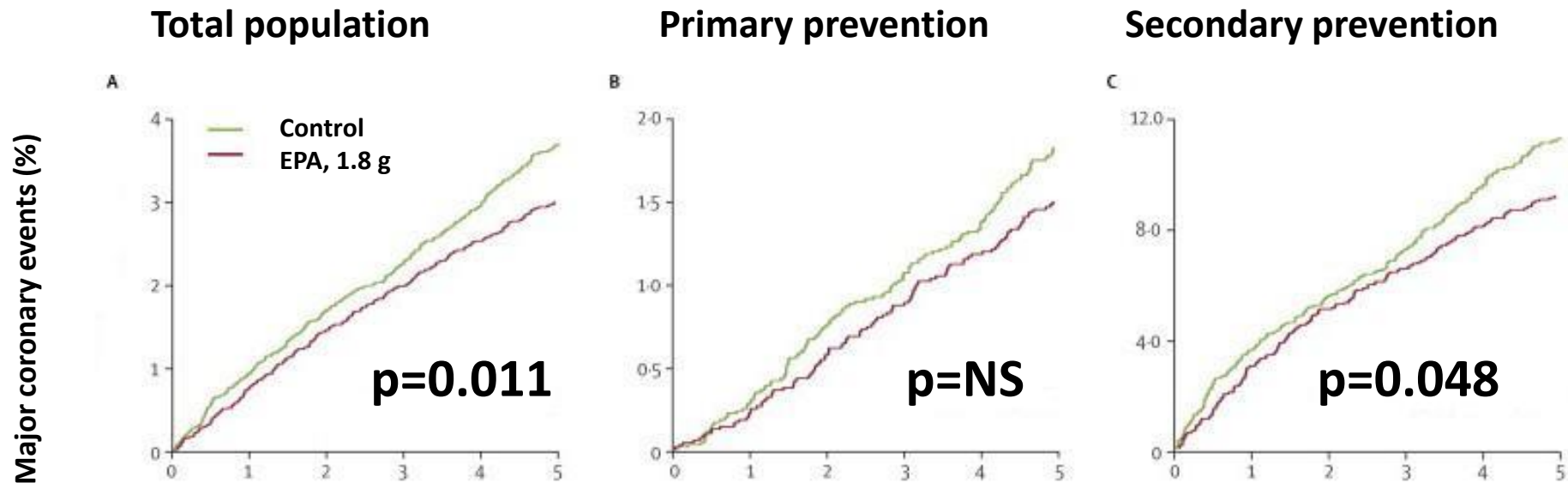
**3-5 weeks**

Placebo Run-in
Verify LDL control

Screening Visit

Randomization

Placebo BID

Pemafibrate 0.2 mg BID

**5 years**

In-person visits, 2,4,6,8 months the 4-monthly

Final Visit

Pradhan AD et al, Am Heart J, 206:80, 2018

# PROMINENT Trial Results



Das Pradham A et al, NEJM 387:1923, 2022

# JELIS Study: Major Coronary Events



**Total population**

**Primary prevention**

**Secondary prevention**

Major coronary events (%)

Control
EPA, 1.8 g

p=0.011

p=NS

p=0.048

**Numbers at risk**

| Control | 9319 | 8931 | 8671 | 8433 | 8192 | 7958 | 7478 | 7204 | 7103 | 6841 | 6678 | 6508 | 1841 | 1727 | 1658 | 1592 | 1514 | 1450 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment | 9326 | 8929 | 8658 | 8389 | 8153 | 7924 | 7503 | 7210 | 7020 | 6823 | 6649 | 6482 | 1823 | 1719 | 1638 | 1566 | 1504 | 1442 |

N= 18,645; baseline total cholesterol >250 mg/dl; statin ±1.8 g of EPA

Yokoyama M, et al. Lancet. 369:1090, 2007

# JELIS Study:

## CVD Risk Reduction of EPA in Patients with ↑ TG and ↓ HDL-C



HR: 0.47
95%CI: 0.23-0.98
$P = 0.043$

- 53%

Control group

EPA group

Number of patients

| | | | | | | |
|---|---|---|---|---|---|---|
| Control | 475 | 444 | 432 | 414 | 400 | 392 |
| EPA | 482 | 455 | 443 | 427 | 413 | 403 |

Saito y, et al. Atherosclerosis 200:135, 2008
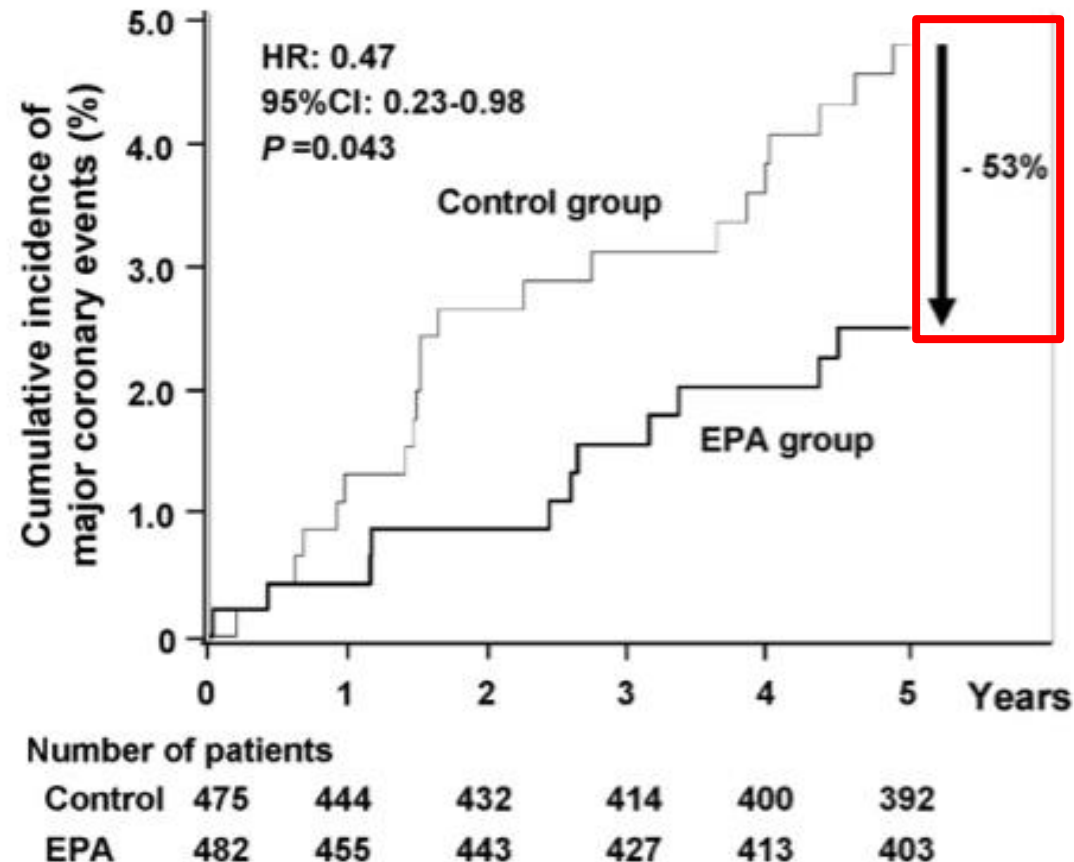
# Primary Prevention of CVD with High Dose Omega-3 Fatty Acids

**REDUCE-IT: Baseline TG 135-500 mg/dL)**
**STRENGTH: Baseline TG 180-500 mg/dL**

| Trial | Drug | Size (n) | Primary Outcome |
|---|---|---|---|
| REDUCE-IT | Icosapent ethyl | 8179 | 5-point MACE |
| STRENGTH | Omega-3 carboxylic acids | 13,086 | 5-Point MACE |

All patients on statins

# 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 Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D.,
for the REDUCE-IT Investigators*

## ABSTRACT

### BACKGROUND

Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

### METHODS

We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary

From Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston (D.L.B.); FACT (French Alliance for Cardiovascular Trials), Département Hospitalo-Universitaire FIRE (Fibrose, Inflammation, and Remodeling), Assistance Publique–Hôpitaux de Paris, Hôpital Bichat, Université Paris-Diderot, INSERM Unité 1148, Paris (P.G.S.); National Heart and Lung Institute, Imperial College, Royal Brompton Hospital, London (P.G.S.); the Department of Medicine, University of Maryland School of

# REDUCE-IT Population

*Double-blind parallel group trial; median follow-up 4.9 years*

> Statin treated men and women (aged ≥45 years)
> Well controlled LDL-C (41-100 mg/dL)
>   (median baseline 75mg/dL)

## 8179 Patients

**At High Risk for CV Events Due To:**
> TG 150-499 mg/dL (median baseline 216 mg/dL), and
> Established CVD
>     OR
> Diabetes mellitus + aged ≥50 years + ≥1 risk factor for CVD
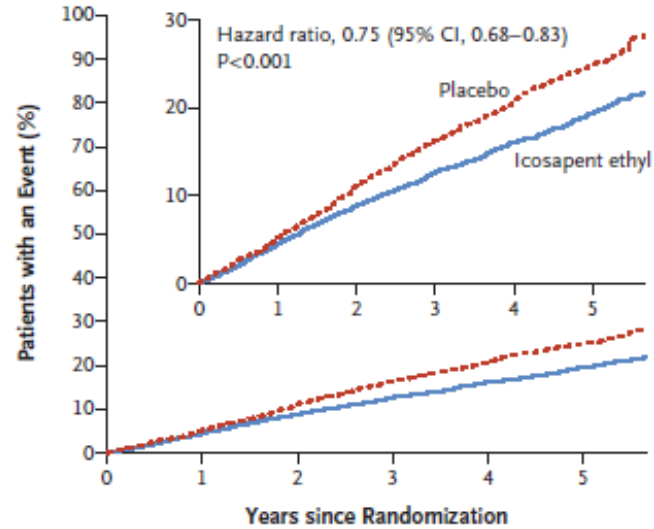
## Randomization 1:1

### Stable Statin + icosapent ethyl (4g/d)

### Stable Statin + Placebo

**PRIMARY COMPOSITE (MACE) ENDPOINT**

| | |
|---|---|
| CV Death | Nonfatal MI |
| Coronary Revascularization | Nonfatal Stroke |
| Unstable Angina requiring hospitalization | |

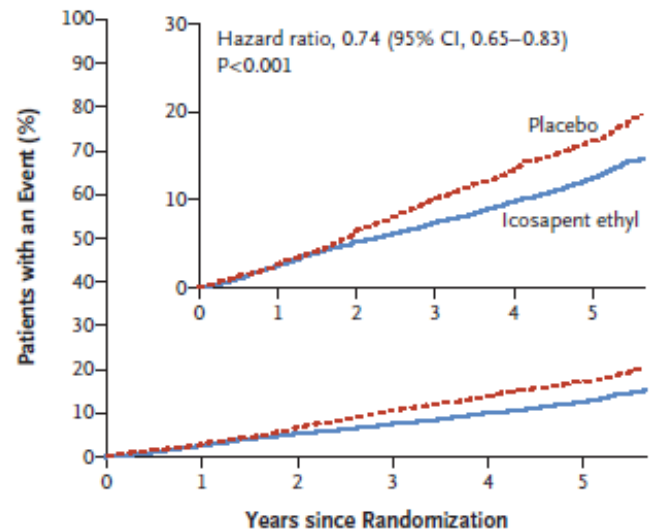**REDUCE-IT:**
**Impact of Icosapent Ethyl on Major CVD Events**

Bhatt DL et al, NEJM 380:11, 2019

# REDUCE-IT:
## Hierarchial Testing of the Impact of Icosapent Ethyl on Major CVD Events

| End Point | Icosapent Ethyl (N=4089) | Placebo (N=4090) | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | *no. of patients with event (%)* | | | |
| Primary composite | 705 (17.2) | 901 (22.0) | 0.75 (0.68–0.83) | <0.001 |
| Key secondary composite | 459 (11.2) | 606 (14.8) | 0.74 (0.65–0.83) | <0.001 |
| Cardiovascular death or nonfatal myocardial infarction | 392 (9.6) | 507 (12.4) | 0.75 (0.66–0.86) | <0.001 |
| Fatal or nonfatal myocardial infarction | 250 (6.1) | 355 (8.7) | 0.69 (0.58–0.81) | <0.001 |
| Urgent or emergency revascularization | 216 (5.3) | 321 (7.8) | 0.65 (0.55–0.78) | <0.001 |
| Cardiovascular death | 174 (4.3) | 213 (5.2) | 0.80 (0.66–0.98) | 0.03 |
| Hospitalization for unstable angina | 108 (2.6) | 157 (3.8) | 0.68 (0.53–0.87) | 0.002 |
| Fatal or nonfatal stroke | 98 (2.4) | 134 (3.3) | 0.72 (0.55–0.93) | 0.01 |
| Death from any cause, nonfatal myocardial infarction, or nonfatal stroke | 549 (13.4) | 690 (16.9) | 0.77 (0.69–0.86) | <0.001 |
| Death from any cause | 274 (6.7) | 310 (7.6) | 0.87 (0.74–1.02) | — |

Icosapent Ethyl Better — Placebo Better

(Hazard Ratio axis: 0.4 0.6 0.8 1.0 1.2 1.4)

Bhatt DL et al, NEJM 380:11, 2019

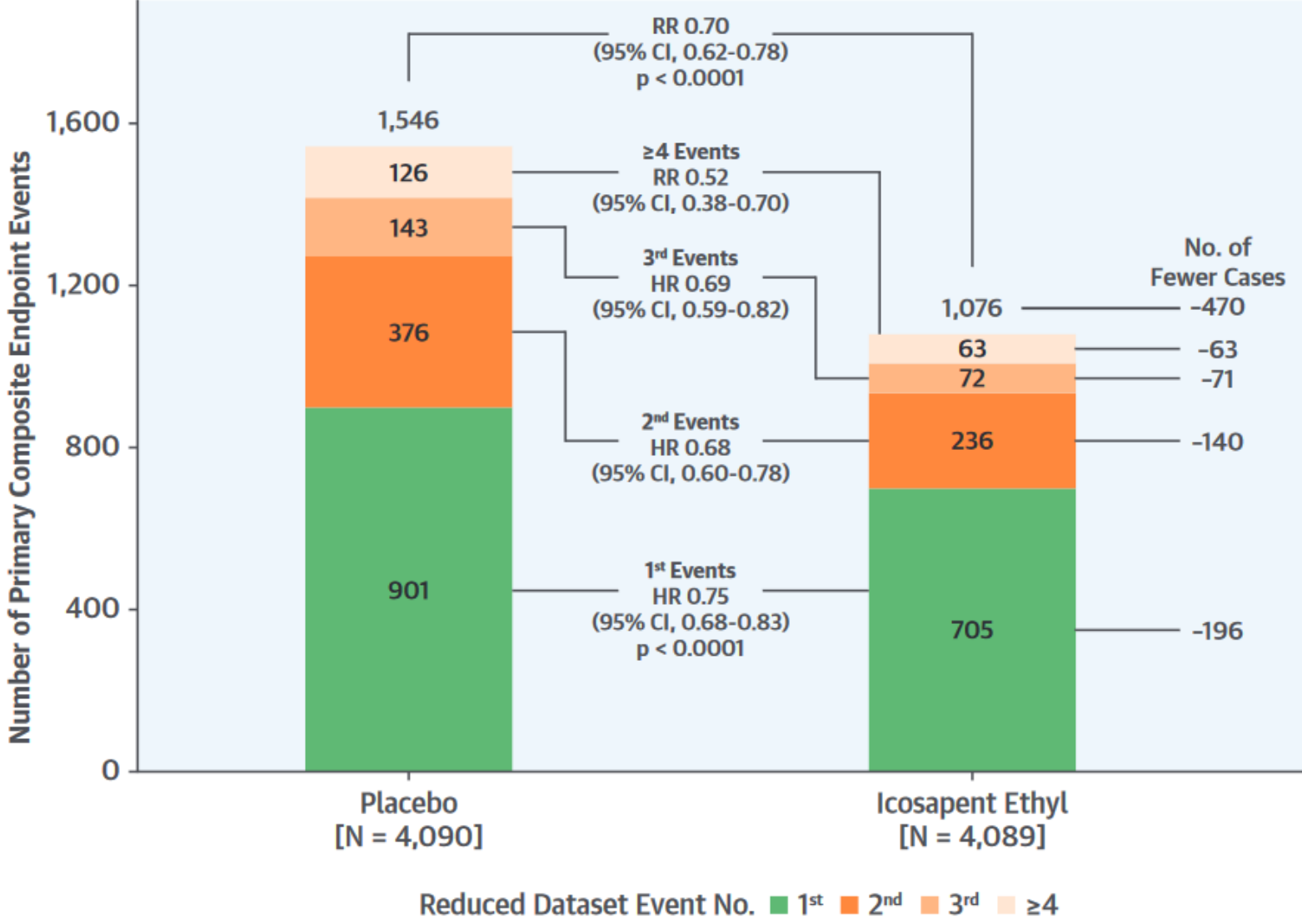# REDUCE-IT:

## Hierarchial Testing of the Impact of Icosapent Eth̶  ̶D Events



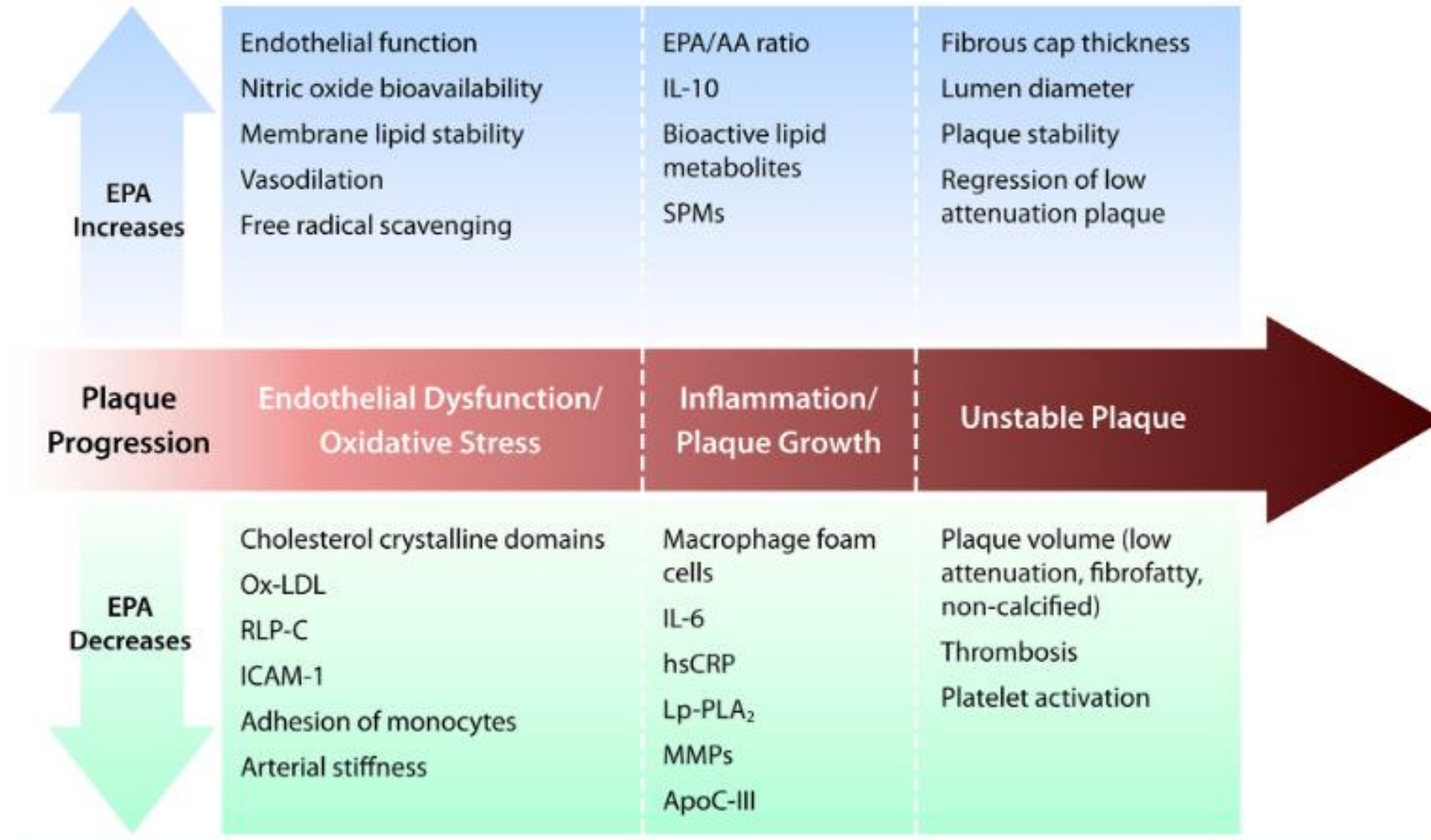Importantly, the CVD benefit did not relate to the amount of TG lowering!

| End Point | Icosapent Ethyl (N=4089) | Placebo (N=4090) | | | Value |
|---|---|---|---|---|---|
| | no. of patients with event (%) | | | | |
| Primary composite | 705 (17.2) | 901 (22.0) | | 0.73 (0.68–0.83) | <0.001 |
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| Cardiovascular death | 174 (4.3) | 213 (5.2) | | 0.80 (0.66–0.98) | 0.03 |
| Hospitalization for unstable angina | 108 (2.6) | 157 (3.8) | | 0.68 (0.53–0.87) | 0.002 |
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| Death from any cause, nonfatal myocardial infarction, or nonfatal stroke | 549 (13.4) | 690 (16.9) | | 0.77 (0.69–0.86) | <0.001 |
| Death from any cause | 274 (6.7) | 310 (7.6) | | 0.87 (0.74–1.02) | — |

0.4    0.6    0.8    1.0    1.2    1.4

Icosapent Ethyl Better        Placebo Better

**Bhatt DL et al, NEJM 380:11, 2019**

# REDUCE-IT: First and Subsequent CVD Events



RR 0.70
(95% CI, 0.62-0.78)
p < 0.0001

≥4 Events
RR 0.52
(95% CI, 0.38-0.70)

3rd Events
HR 0.69
(95% CI, 0.59-0.82)

2nd Events
HR 0.68
(95% CI, 0.60-0.78)

1st Events
HR 0.75
(95% CI, 0.68-0.83)
p < 0.0001

No. of
Fewer Cases

Placebo
[N = 4,090]

Icosapent Ethyl
[N = 4,089]

Reduced Dataset Event No. ■ 1st ■ 2nd ■ 3rd ■ ≥4

Bhatt DL et al, JACC 73:2791, 2019

# Recent Cardiovascular Outcome Trials with Omega-3 Fatty Acids

| | JELIS (18,645) | REDUCE-IT (8179) | STRENGTH (13,078) |
|---|---|---|---|
| Population* | Hypercholesterolemic | High cardiovascular risk, Elevated TG | High cardiovascular risk, Elevated TG, low HDL |
| Formulation | IPE (1.8 g/d EPA) | IPE (4 g/d EPA) | EPA/DHA carboxylic acids (4 g/d) |
| Baseline median TG (mg/dL) | 153 | 216 | 240 |
| Baseline EPA ($\mu$g/mL) | 97 | 26.1 | 21.0 |
| Achieved EPA ($\mu$g/mL) | 169 | 144 | 89.6 |
| Increase in achieved EPA levels (%) | 70 | 394 | 269 |
| TG lowering (%) | 9 | 17 | 19 |
| Primary endpoint | Major coronary events | Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina | Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina |
| HR, 95% CI of primary endpoint | 0.81, 0.69-0.95 ($P = .011$) | 0.75, 0.68-0.83 ($P = .00000001$) | 0.99, 0.90-1.09 ($P = .84$) |

Mason RP, Eckel RH, Am J Med, 134:1085, 2021

# Atheroprotective Effects of EPA

# ESC/EAS Guidelines: Treatment Targets and Goals for CVD Prevention

| | |
|---|---|
| **Non-HDL-C** | Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively. |
| **ApoB** | ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively. |
| **Triglycerides** | No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors. |

Drug treatments of patients with hypertriglyceridaemiaIn high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135 - 499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 2g/day) should be considered in combination with statins.

**Antisense Apo-CIII (volanesorsen) and Plasma Triglycerides**

Kastelein J et al, NEJM 373:438, 2015
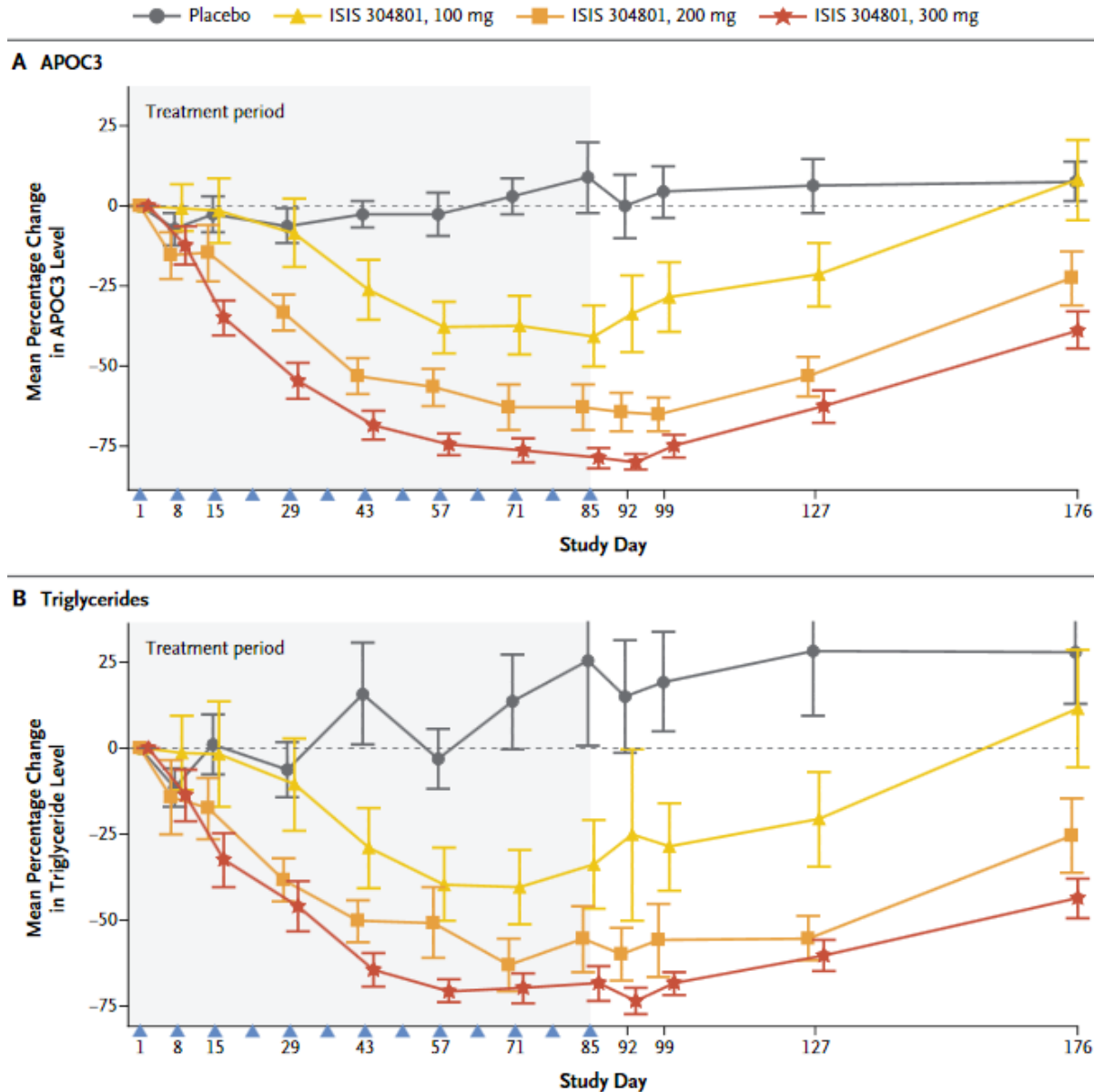
# Angiopoietin-Like Proteins are a Genetically Validated Triglyceride Target

- ANGPTL3, 4, 8 are important modulators of lipid metabolism.

- ANGPTL3 is a circulating protein synthesized in the liver that modulates lipid-lipoprotein metabolism and has pleiotropic functions

- The ANGPTL3 coding gene (*ANGPTL3*) is specifically expressed in the hepatocytes and its expression is regulated by LXR.

- ANGPTL3 undergoes cleavage which is mediated by PCSK3 and PPCSk6 and phosphorylation

- The effect of ANGPTL3 on LPL activity is more pronounced post-prandially due to its interaction with ANGPTL8

# Antisense ANGPTL3 and Plasma Triglycerides



Graham MJ et al, NEJM 377:222, 2017
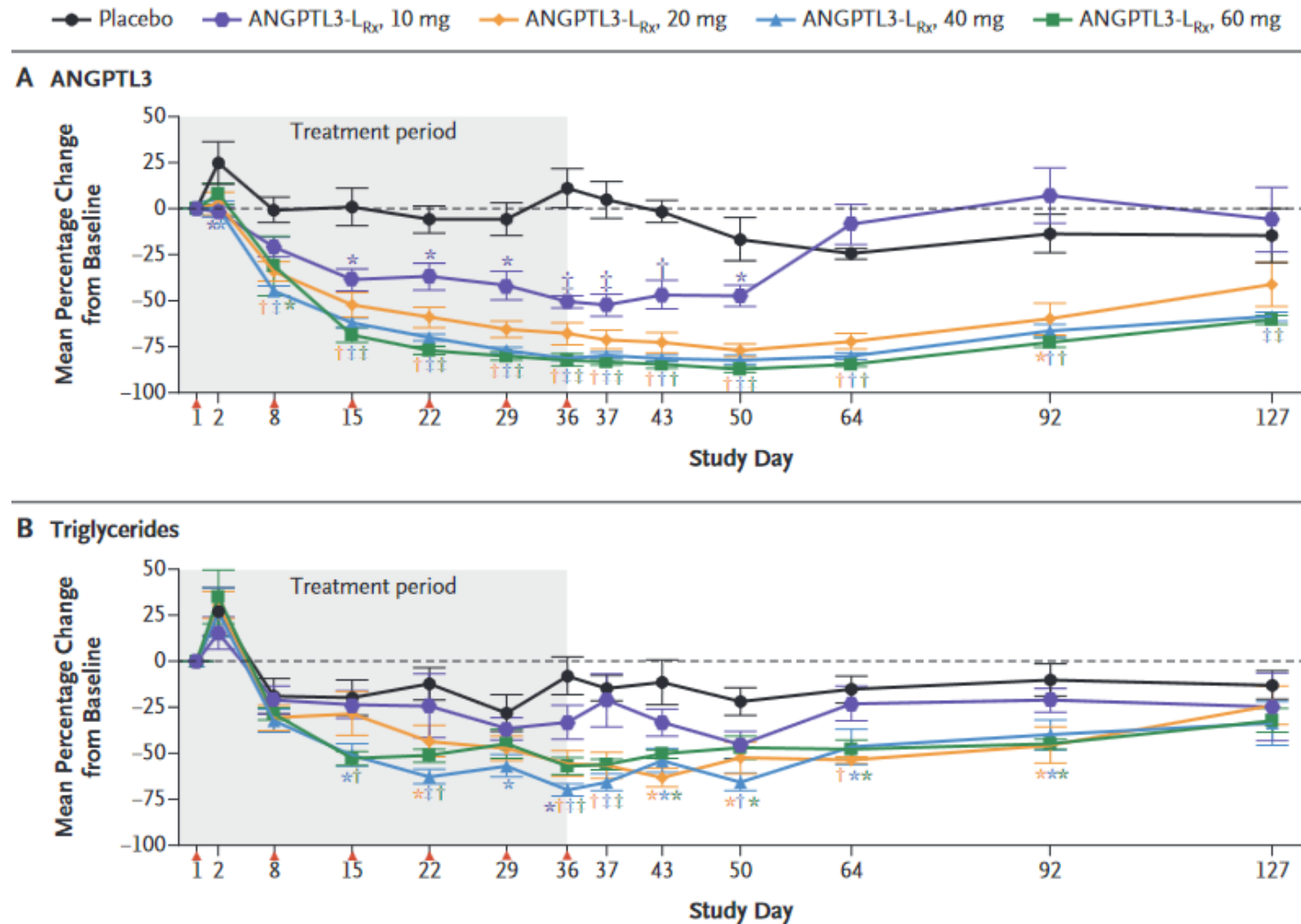
# Evinacumab: Percent Median (Q1–Q3) Change in Plasma Triglycerides
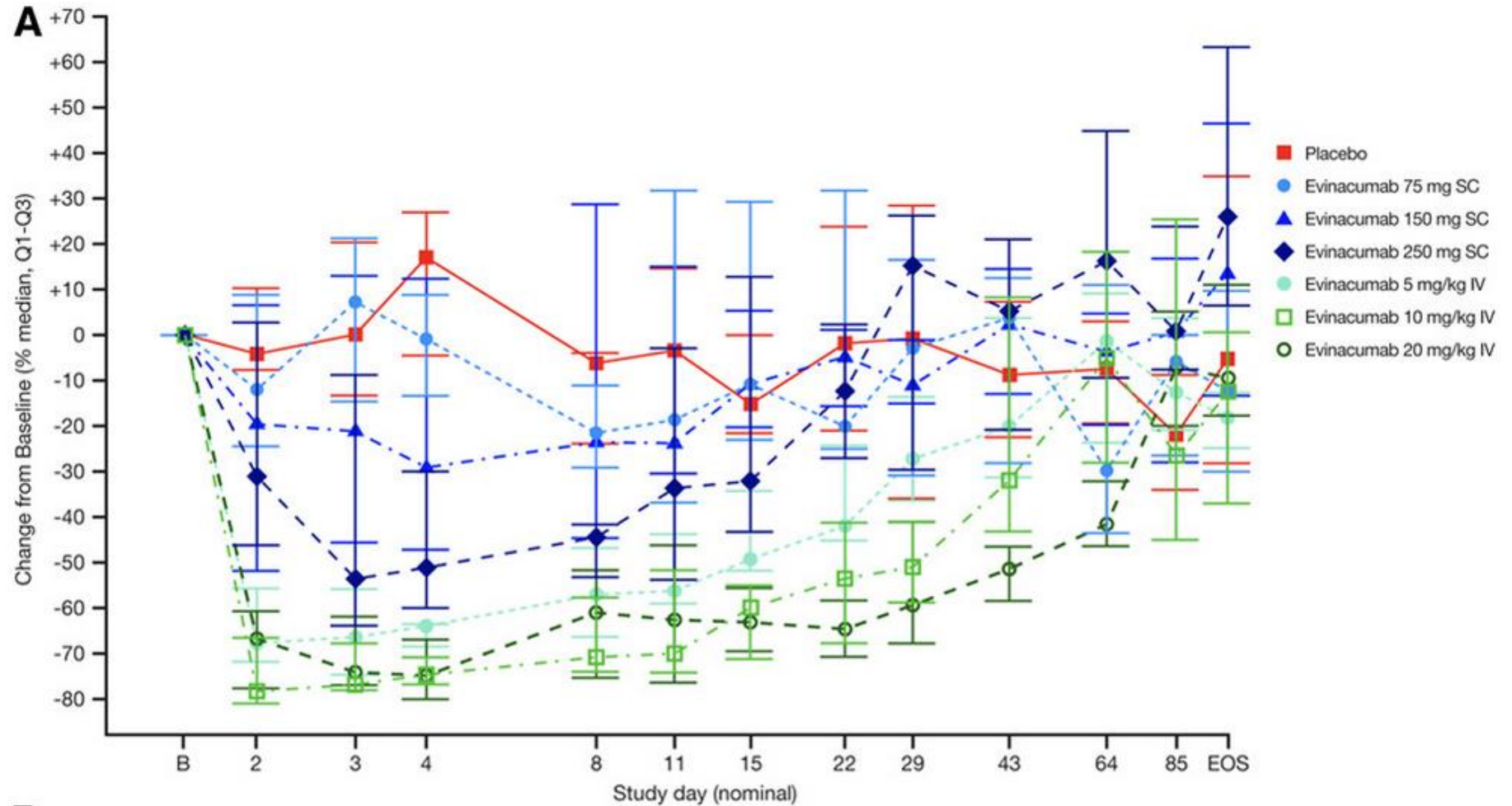
# GalNAc3-conjugated Antisense ANGPTL3 (vupanorsen) and Plasma Triglycerides
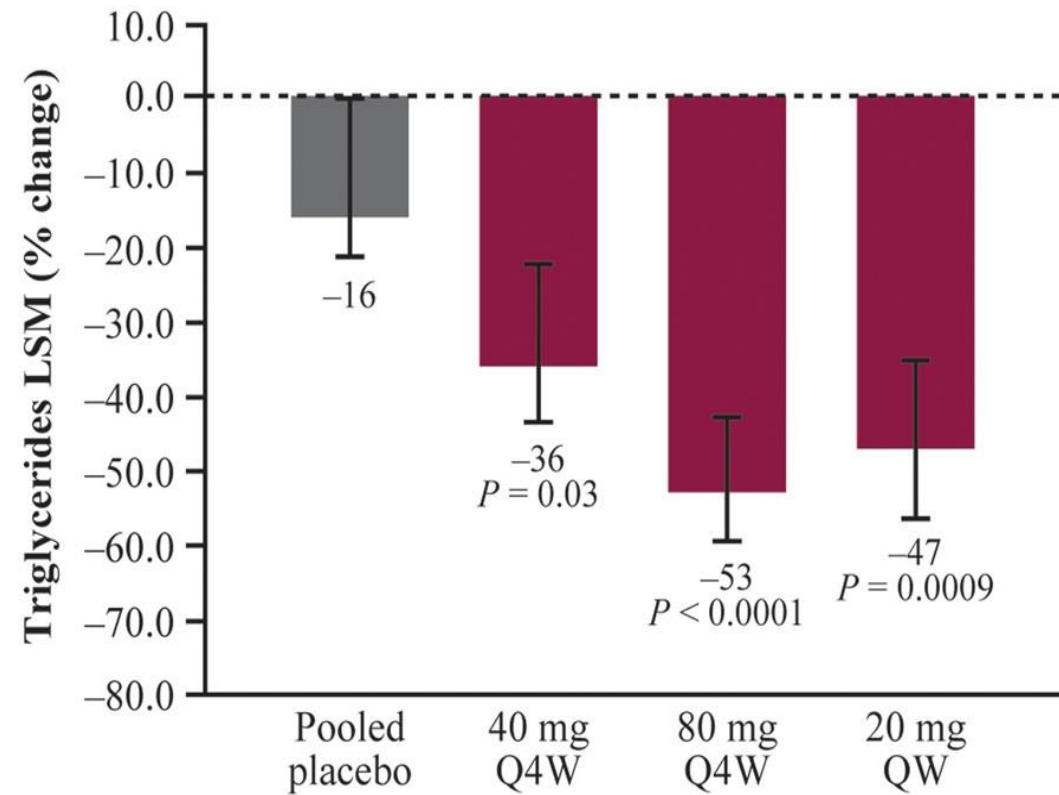
# Management of Severe Hypertriglyceridemia

**Robert H. Eckel, MD, FAHA, FACC**
**Professor of Medicine, Emeritus**
**Division of Endocrinology, Metabolism and Diabetes**
**Division of Cardiology**
**S/P Charles A. Boettcher II Chair in Atherosclerosis**
**University of Colorado Anschutz Medical Campus**
**robert.eckel@cuanschutz.edu**

www.cardiometabolichealth.org

**Foundations of Cardiometabolic Health Certification Course**

**Certified Cardiometabolic Health Professional (CCHP)**
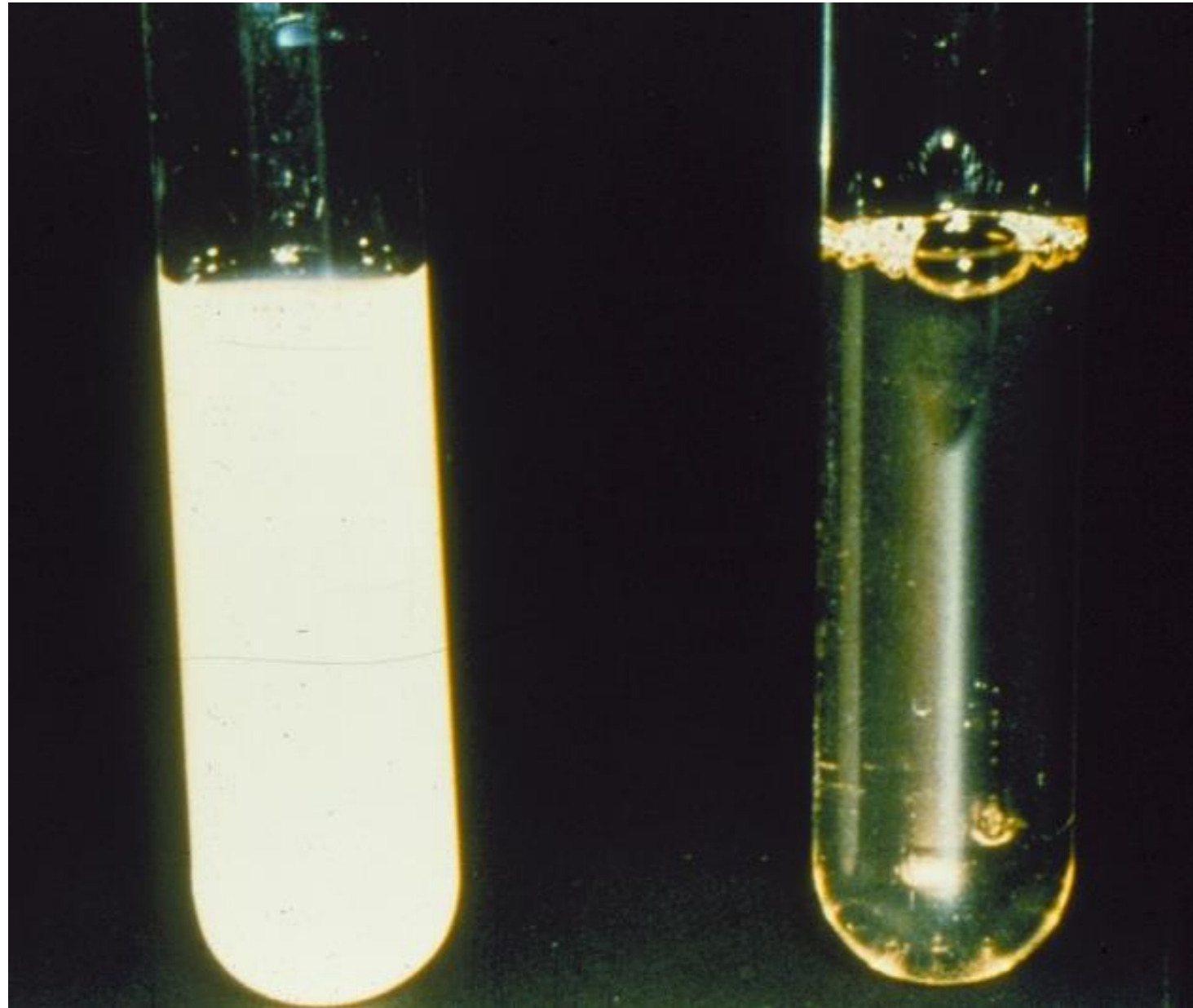
# Genetics of Severe Hypertriglyceridemia

- **Familial Chylomicronemia**
  - All etiologies do not require secondary disorders
  - Pancreatitis risk
  - No premature CHD
  - Eruptive xanthoma
  - Lipemia retinalis
- LPL deficiency
  - Rare: ~1/1,000,000
    - French Canadians: ~1/40,000
    - South Africans: ~1/40,000
- Apo CII deficiency
- LMF-1 deficiency
- GPIHBP1 deficiency
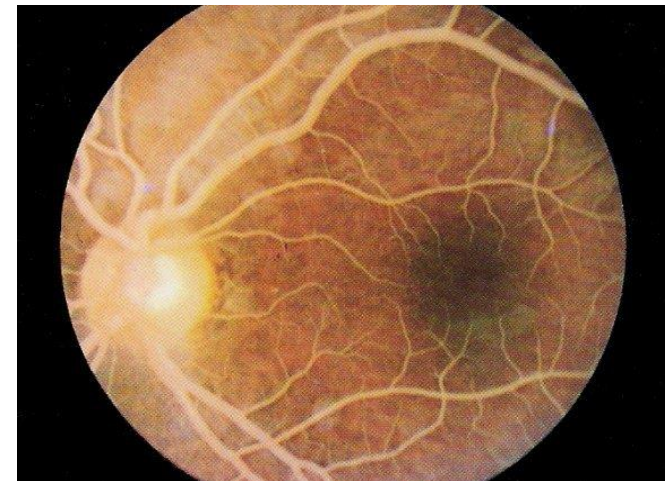
# Most Severe Hypertriglyceridemia

(Type 5 Hyperlipoproteinemia)

Genetic Hypertriglyceridemia

**+**

Acquired Secondary Factor(s)

Chait A, Brunzell JD Metabolism 32:209, 1983

# Triglyceride Clearance is Saturable



LPL kinetics

$K_m$ 90 mg/dL

Dietary fat

(1) TG removal not saturated
(Outflow = Inflow)

(2) TG removal saturated
(Inflow > outflow)

**Chait A, Eckel RH, Ann Int Med, 170:626, 2019**
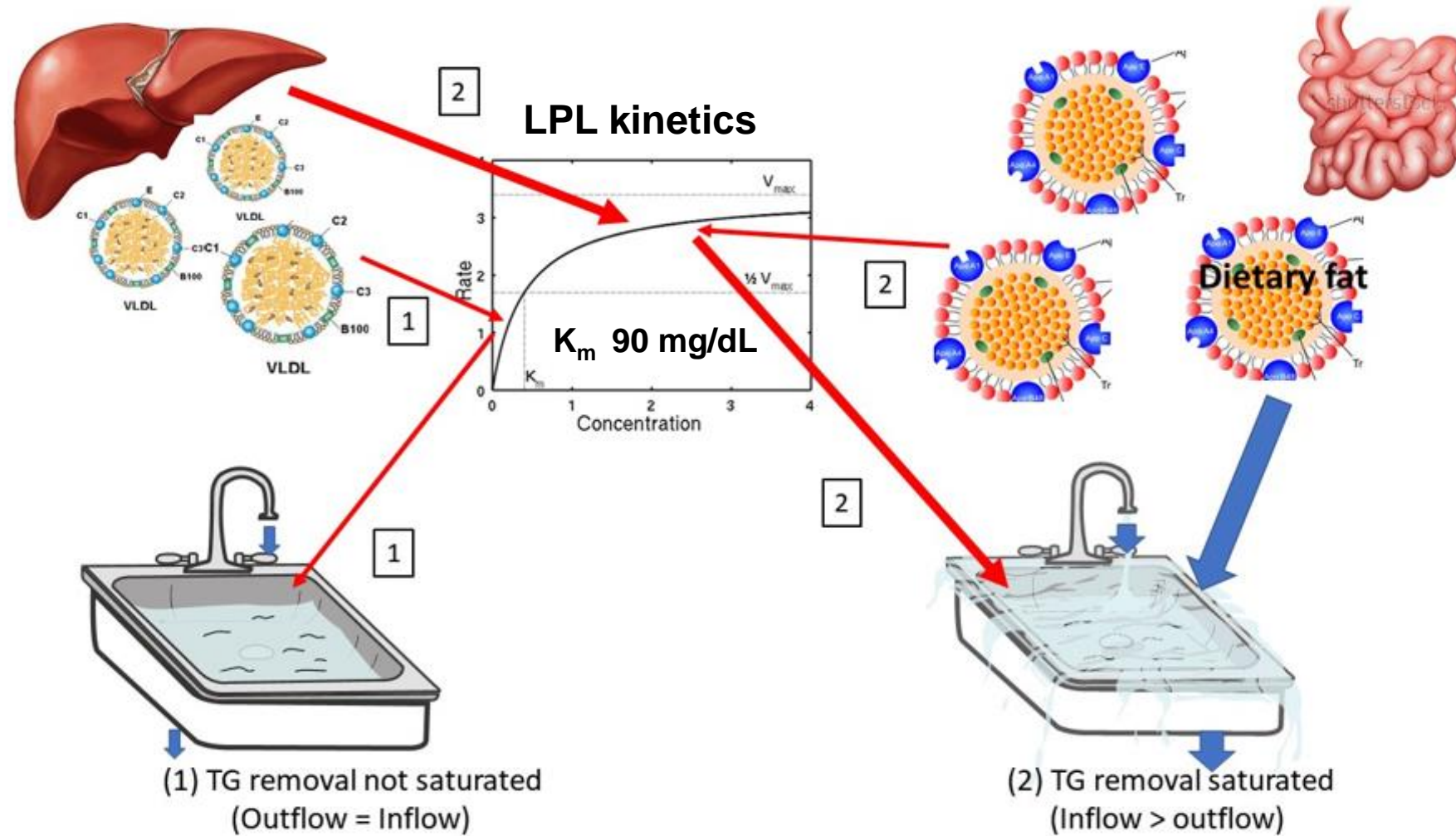
# Dietary Treatment of Severe Hypertriglyceridemia

- **TG >1000 mg/dl:** < 5% fat; no ETOH
  - ? D/C all TG-lowering Rx
    - < 5% fat → ~25% TG ↓ daily in saturation kinetics
    - Fasting TG q 3 days until <1000 mg/dl
    - Restart Rx when TG <1000 mg/dl
    - If TG do not reach <1000 mg/dl, hospitalize & control diet

# Dietary Treatment of Moderate Hypertriglyceridemia

- **TG = 500-1000 mg/dl:**

    - 20-35% fat

        If TG $\uparrow$, $\downarrow$ CHO  and $\uparrow$ PUFA & MUFA

        $\pm$ ETOH when <400 mg/dl

- Fiber:  >25 g daily

- Sucrose in moderation

# Hypertriglyceridemia: What's the Bottom Line?

- Lower fasting TG to <500 mg/dl
  - $\downarrow$ pancreatitis risk
- Use current guidelines to reduce LDL-C
- Consider Apo B as an indicator of CVD risk in patients with LDL-C <100-130 mg/dL
- In patients with fasting TG >200 mg/dl $\pm$ HDL-C <35 mg/dl
  - Consider a fibrate or omega-3 fatty acids
- Icosapent ethyl in most high CVD risk patients?
  - There's now an FDA indication

This 54-year-old woman with strong FHx of T2DM and CVD has new onset T2DM, treated hypertension, dyslipidemia on statin and is referred for evaluation of cardiometabolic risk for CVD. She has known hypothyroidism and obstructive sleep apnea on CPAP.

No tobacco, rare alcohol, on South Beach diet, almost no physical activity, works at a desk job.

Lisinopril 20 mg daily
Levothyroxine 100 µg daily
Atorvastatin 40 mg daily
Metformin, 500 mg bid

This 54-year-old woman with strong FHx of T2DM and CVD has new onset T2DM, treated hypertension, dyslipidemia on statin and is referred for evaluation of cardiometabolic risk for CVD.

**PE:**
Weight 179 lb., WC – 96 cm
BMI 29.5 kg/m$^2$
BP 142/82
No xanthomas
No carotid bruits, cardiac murmurs
Liver 8 cm
Dorsalis pedis pulses 1+ bilaterally

**Labs:**
Cholesterol – 210 mg/dL
TG – 340 mg/dL
HDL-C – 38 mg/dL
LDL-C – 104 mg/dL
AST,ALT - normal
Creatinine 1.0 mg/dL
UAC – 75µg/g
HbA1c – 7.4%
TSH – 1.6 mU/L

# Questions:

- Should TG of 340 mg/dL be treated?

# Range of Triglyceride Lowering with Drugs

- Fibrates                                    20-45%
- Omega-3 fatty acids          15-35%
- Nicotinic acid                      10-30%
- Statins                                       0-35%
  - Low end – minimal or no effect
  - High end – mod to high dose

# Efficacy of TG Lowering Drug Classes on CVD Outcomes in RCTs

| | Active treatment | Placebo | Relative risk | Absolute effects (events/1000) |
|---|---|---|---|---|
| **Fibrate** | | | | |
| CHD mortality | 904/21 886 | 1032/23 536 | 0.92 (0.81–1.04) | −4 (−8 to +2) |
| Nonfatal MI | 1104/21 896 | 1574/23 549 | 0.80 (0.72–0.96) | −14 (−19 to −3) |
| Stroke | 610/20 784 | 672/22 404 | 1.01 (0.90–1.13) | 0 (−3 to +4) |
| **Niacin** | | | | |
| CHD mortality | 565/16 795 | 852/18 034 | 0.93 (0.76–1.12) | −3 (−11 to +6) |
| Nonfatal MI | 645/17 030 | 921/18 271 | 0.85 (0.72–1.01) | −8 (−14 to +1) |
| Stroke | 620/16 788 | 797/18 020 | 0.96 (0.75–1.22) | −2 (−11 to +10) |
| **Omega-3 (low dose)** | | | | |
| CHD mortality | 1570/28 947 | 1631/28 940 | 0.96 (0.90–1.02) | −2 (−5 to +1) |
| Nonfatal MI | 816/31 094 | 807/30 996 | 0.90 (0.78–1.05) | −2 (−6 to +1) |
| Stroke | 707/31 094 | 673/30 996 | 1.08 (0.94–1.24) | +2 (−1 to +5) |
| **Omega-3 (high dose)** | | | | |
| CHD mortality | 513/10 809 | 543/11 007 | 0.96 (0.86–1.08) | −2 (−7 to +4) |
| Nonfatal MI | 451/10 809 | 557/11 007 | 0.84 (0.73–0.93) | −8 (−14 to −4) |
| Stroke | 241/10 659 | 259/10 657 | 0.93 (0.78–1.11) | −2 (−5 to +3) |

# Questions:

- Should TG of 340 mg/dL be treated?
- What about non-HDL-C vs. LDL-C as a better goal for treatment?

# Kaplan–Meier Curve of LDL-C and non–HDL-C and CVD Mortality



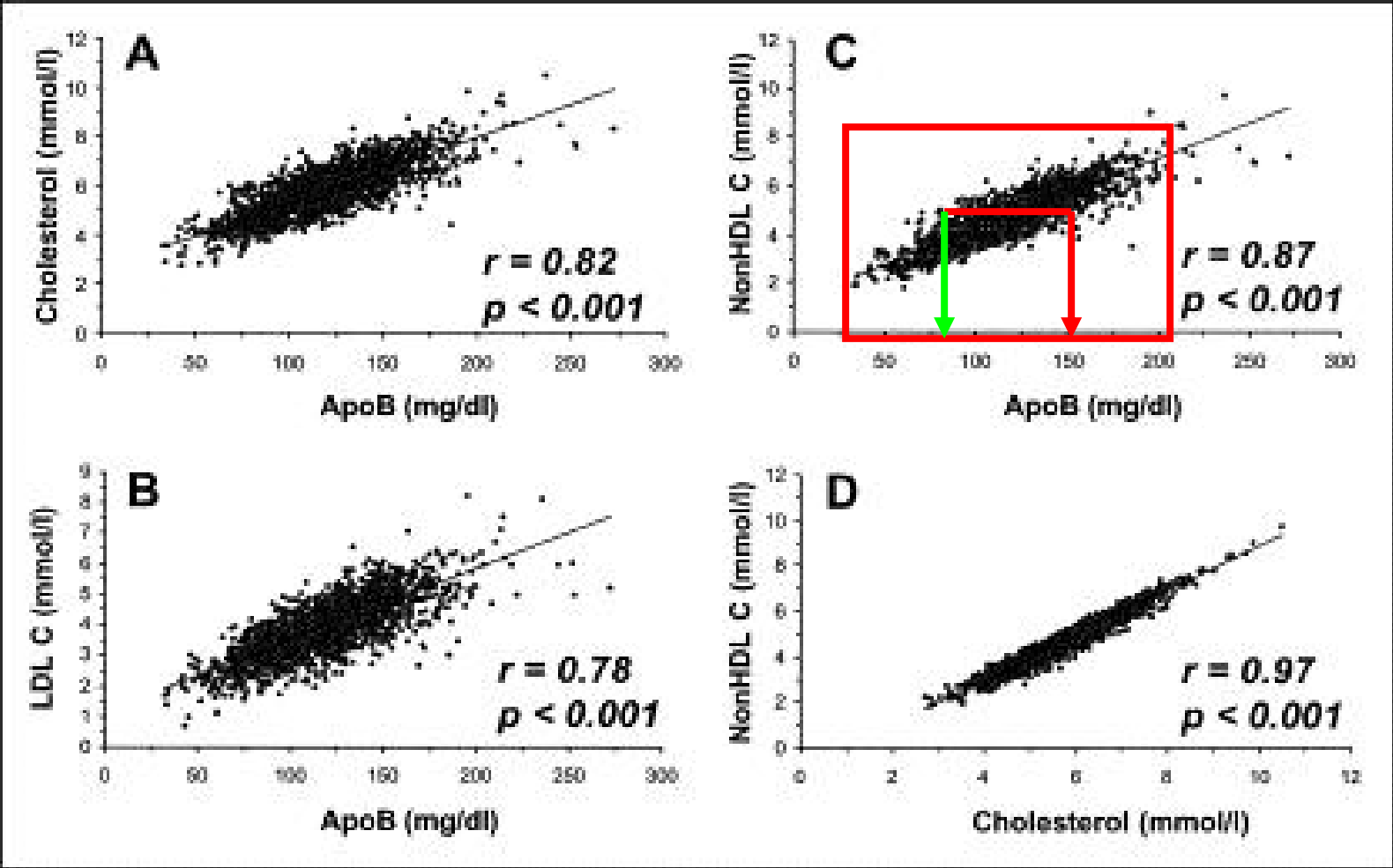Abdullah SM et al, Circulation 138:2315, 2018

# Questions:

- Should TG of 340 mg/dL be treated?
- What about non-HDL-C vs. LDL-C as a better goal for treatment?
- When Is apo B useful and isn't it the same as non-HDL-C?

# Odds Ratios for the Development of CHD: Lipid and Lipoprotein Phenotypes

Odds are adjusted for age, smoking, alcohol, blood pressure, gender, and medications
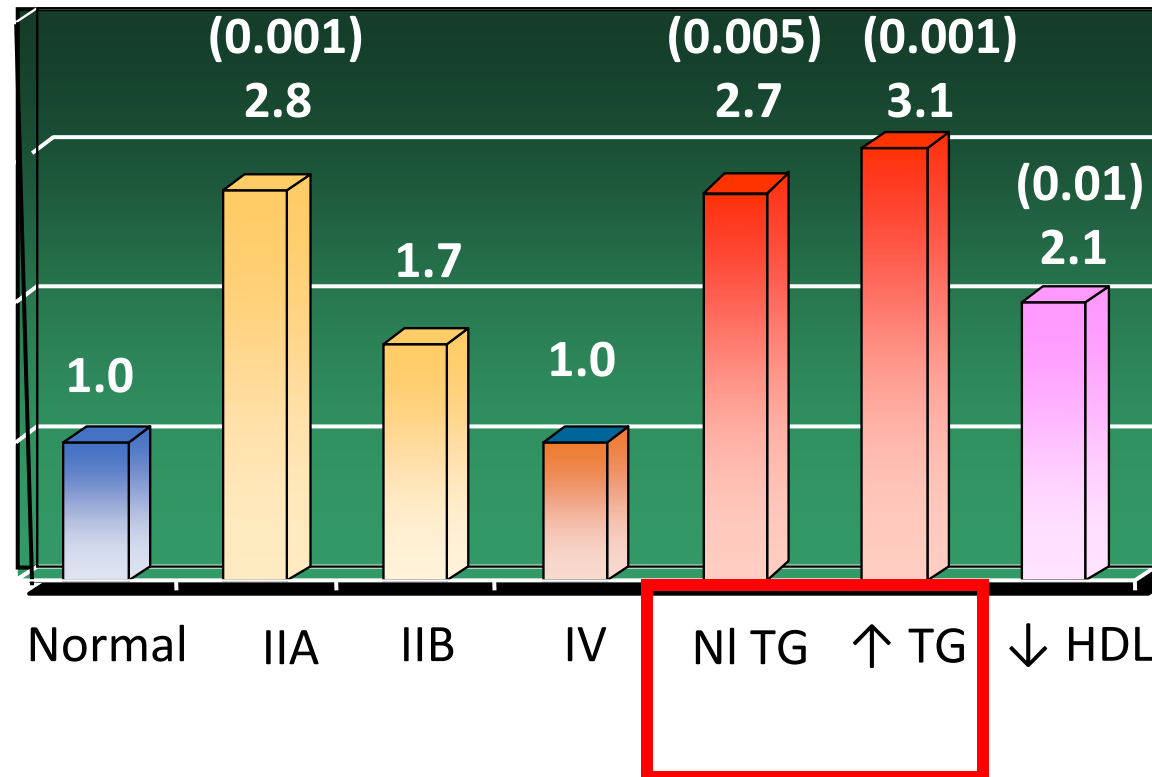


Lamarche B et al, Am J Card 75:1189,1995

# Correlations Between Apo B, Cholesterol, LDL Cholesterol and Non-HDL Cholesterol



Sniderman AS et al, Am J. Card 91:1173, 2003

# Standardized Vascular RRRs Comparison of Non-HDL-C, Apo B and LDL-C from 12 Independent Epidemiological Studies LReporting RRRs for Both Apo B and non-HDL-C
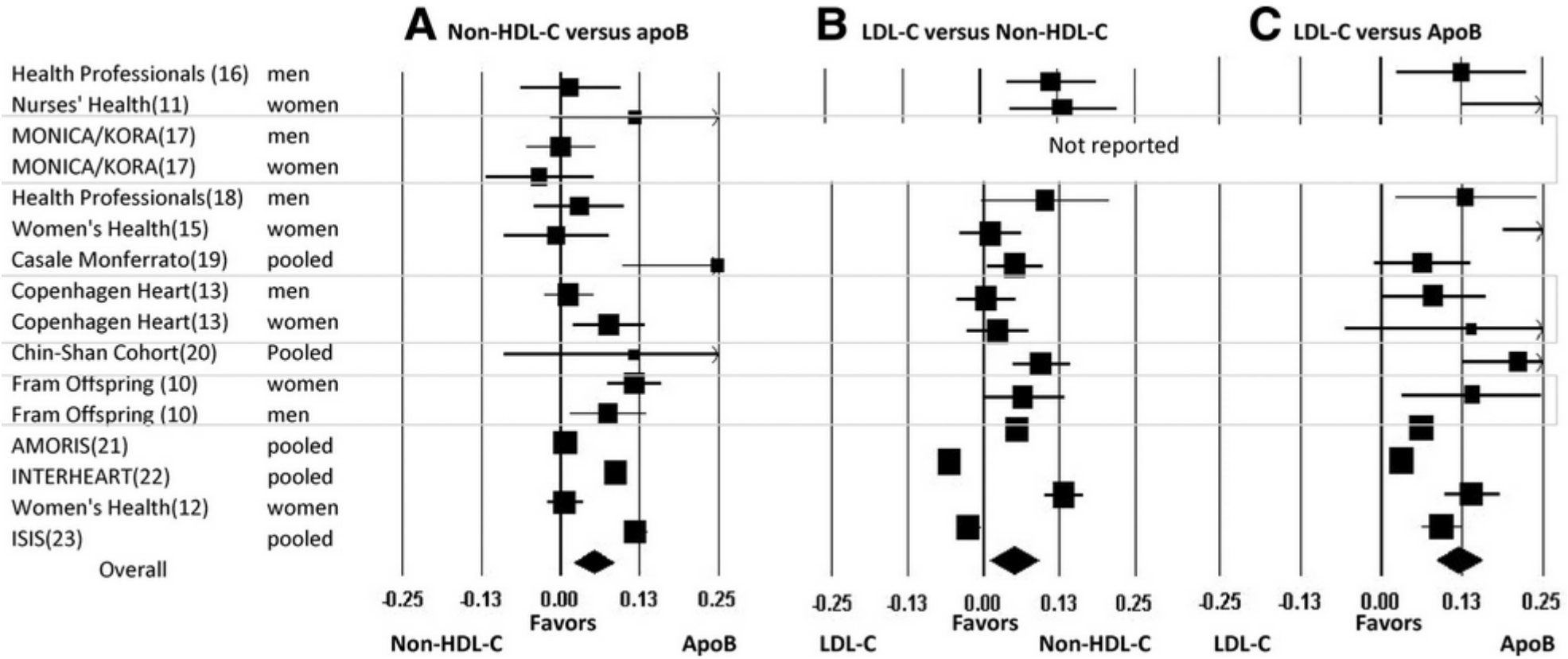
# Questions:

- Should TG of 340 mg/dL be treated?
- What about non-HDL-C vs. LDL-C as a better goal for treatment?
- When Is apo B useful and isn't it the same as non-HDL-C?
- What have the fibrate trials told us?

# Major Fibrate CVD Outcome Trials

| Study (Year) | N | Study drug | Comparator | Primary Outcome | Results | |
|---|---|---|---|---|---|---|
| HHS (1987) | 4081 | Gemfibrozil | Placebo | Fatal or nonfatal MI or cardiac death | 34% reduction | * |
| VA-HIT (1999) | 2531 | Gemfibrozil | Placebo | Nonfatal MI or cardiac death | 22% reduction | * |
| BIP (2000) | 3090 | Bezafibrate | Placebo | Fatal or nonfatal MI or sudden death | 9.4% reduction | NS |
| LEADER (2002) | 1568 | Bezafibrate | Placebo | CHD or stroke | 4% reduction | NS |
| FIELD (2005) | 9795 | Fenofibrate | Placebo | CHD death or nonfatal MI | 11% reduction | NS |
| ACCORD (2010) | 5518 | Simvastatin + Fenofibrate | Simvastatin | Nonfatal MI, nonfatal stroke, CVD death | 8% reduction | NS |
| ACCORDION (2017) | 4644 | Simvastatin + Fenofibrate | Simvastatin | Nonfatal MI, nonfatal stroke. CVD death | 7% reduction | NS |

# Fibrate Outcome Studies in High TG Subgroups

| | Trial (Drug) | Primary Endpoint: Entire Cohort (p-value) | Lipid Subgroup Criterion | Primary Endpoint: HTG Subgroup (p-value) |
|---|---|---|---|---|
| Pre-Statin Era | HHS (Gemfibrozil) | -34% (0.02) | TG > 204 mg/dL LDL-C/HDL-C > 5.0 | -71% (0.005) |
| Some Statin Use | FIELD (Fenofibrate) (no statins at entry) | -11% (0.16) | TG ≥ 204 mg/dL HDL-C < 42 mg/dL | -27% (0.07) |
| Statin Add-On | ACCORD (Fenofibrate/simva) | -8% (0.32) | TG ≥ 204 mg/dL HDL-C ≤ 34 mg/dL | -31% (0.057) |
| | AIM-HIGH Niacin ER/ Simvastatin ± EZE | +2% (0.80) | TG ≥ 198 mg/dL HDL-C ≤ 33 mg/dL | -26% (0.073) |

# PROMINENT Trial Results
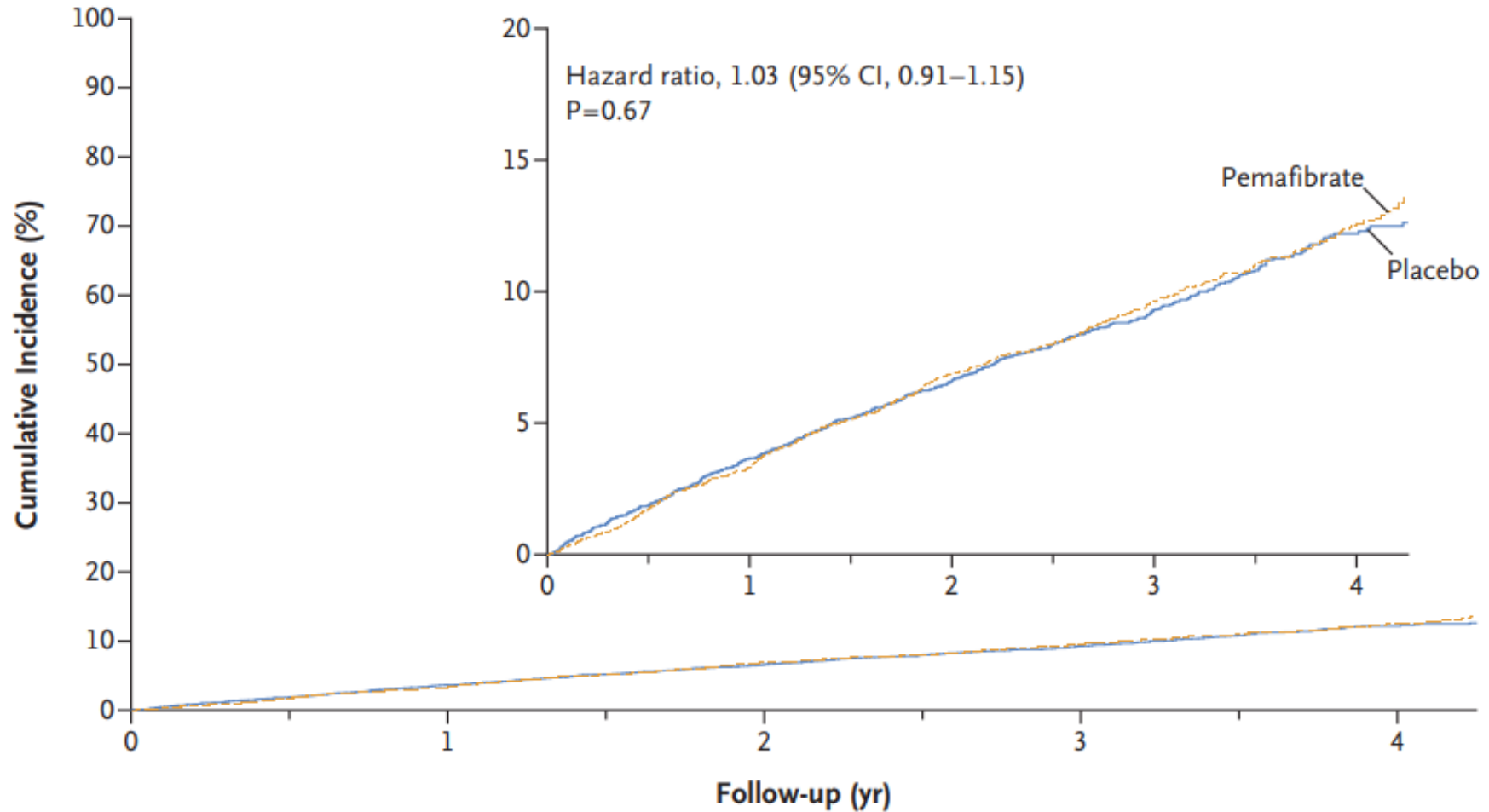


Das Pradham A et al, NEJM 387:1923, 2022

# Questions:

- Should TG of 340 mg/dL be treated?
- What about non-HDL-C vs. LDL-C as a better goal for treatment?
- When is apo B useful and isn't it the same as non-HDL-C?
- What have the fibrate trials told us?
- Are high dose omega-3 fatty acid trials any different?

# Major Omega-3 Fatty Acid CVD Outcome Trials

**Table**   Recent Cardiovascular Outcome Trials with Omega-3 Fatty Acids

|  | JELIS (18,645) | REDUCE-IT (8179) | STRENGTH (13,078) |
|---|---|---|---|
| Population* | Hypercholesterolemic | High cardiovascular risk, Elevated TG | High cardiovascular risk, Elevated TG, low HDL |
| Formulation | IPE (1.8 g/d EPA) | IPE (4 g/d EPA) | EPA/DHA carboxylic acids (4 g/d) |
| Baseline median TG (mg/dL) | 153 | 216 | 240 |
| Baseline EPA ($\mu$g/mL) | 97 | 26.1 | 21.0 |
| Achieved EPA ($\mu$g/mL) | 169 | 144 | 89.6 |
| Increase in achieved EPA levels (%) | 70 | 394 | 269 |
| TG lowering (%) | 9 | 17 | 19 |
| Primary endpoint | Major coronary events | Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina | Composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina |
| HR, 95% CI of primary endpoint | 0.81, 0.69-0.95 ($P = .011$) | 0.75, 0.68-0.83 ($P = .00000001$) | 0.99, 0.90-1.09 ($P = .84$) |

CI = confidence interval; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; HDL = high-density lipoprotein; HR = hazard ratio; IPE = icosapent ethyl; MI = myocardial infarction; TG = triglyceride.
   *Statin use was 100%.

# ESC/EAS Guidelines: Treatment Targets and Goals for CVD Prevention

| | |
|---|---|
| **Non-HDL-C** | Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively. |
| **ApoB** | ApoB secondary goals are <65, 80, and 100 mg/dL for very-high-, high-, and moderate-risk people, respectively. |
| **Triglycerides** | No goal, but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors. |

Drug treatments of patients with hypertriglyceridaemiaIn high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135 - 499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 2g/day) should be considered in combination with statins.

# Questions:

- Should TG of 340 mg/dL be treated?
  - Evidence to indicate that TG lowering is beneficial is not convincing, but for patients who are at high risk or have ASCVD, icosapent ethyl should be considered.
- What about non-HDL-C vs. LDL-C as a better goal for treatment?
  - In patients with high TG/low HDL-C, non-HDL-C may be a better goal for treatment than LDL-C
- When Is apo B useful and isn't it the same as non-HDL-C?
  - No, apo B is related to but not the same as non-HDL-C and may be more useful in individual patients than non-HDL-C in assessing CVD risk.
- What have the fibrate trials told us?
  - The CVD benefit is variable, mostly negative, and not related to TG lowering.
- Are high dose omega-3 fatty acid trials any different?
  - EPA alone relates to CVD benefit in patients who are at high risk or have ASCVD, an effect not related to TG lowering.

**Patient is a 42-year-old woman with a history of hypertriglyceridemia recently found to have very elevated levels of fasting triglycerides and referred for further evaluation.**

Patient has had hypertension for >5 yrs. Maximum wt. 165 lb. Eats one fish serving a week, whole grains ~ 2 servings a day, F&V 4-5 servings a day. Drinks several glasses of wine a day; no tobacco.  Walks ~15 minutes daily. She denies abdominal pain. She works as a desk clerk in a local bank. Family history is relevant for T2DM in her mother and sudden death in an older brother – age 53.  Meds included:

    Fenofibrate 145 mg daily
    Omega-3 fatty acids 1 g daily
    35 µg ethinyl estradiol

**Patient is a 42-year-old woman with a history of hypertriglyceridemia recently found to have very elevated levels of fasting triglycerides and referred for further evaluation.**

## PE:

Weight 172 lb., WC – 32 in.

BMI – 26.9 kg/m$^2$

Eruptive xanthomata – upper trunk

No lipemia retinalis

No carotid bruits, cardiac murmurs

Liver 10 cm; no abdominal tenderness

No lower extremity edema

## Labs:

Cholesterol - 312 mg/dL

TG - 2860 mg/dL

HDL-C - 32 mg/dL

HbA1c – 6.8%

AST, ALT - normal

Creatinine – 0.9  mg/dL

TSH: 1.6 mIU/L

U/A  – negative

# Severe Hypertriglyceridemia

- What is the most likely explanation for this phenotype?

    A. Familial chylomicronemia
    B. Excessive alcohol intake
    C. Oral estrogen
    D. Undiagnosed type 2 diabetes
    E. Genetic form of hypertriglyceridemia + acquired factors

# Severe Hypertriglyceridemia

- The best management strategy is:

    A. Reduce dietary fat intake to 20% and substitute 2 g bid of omega-3 fatty acids for 1 g daily.
    B. Reduce dietary fat intake to 20% and discontinue alcohol and oral estrogen
    C. Reduce dietary fat intake to 20%, substitute 2 g bid of omega-3 fatty acids for 1 g daily, discontinue alcohol and oral estrogen, and add rosuvastatin 40 mg daily.
    D. Reduce dietary fat intake to <5%, discontinue alcohol and oral estrogen and measure fasting triglycerides every 3 days.
    E. Reduce dietary fat intake to <5%, discontinue alcohol and oral estrogen, and instruct her in basal/bolus insulin administration.

Chylomicrons

Chait A and Brunzell JD & Bierman EL, Brunzell JD. *Med Clin NA*. 66:455, 1982 , 1992
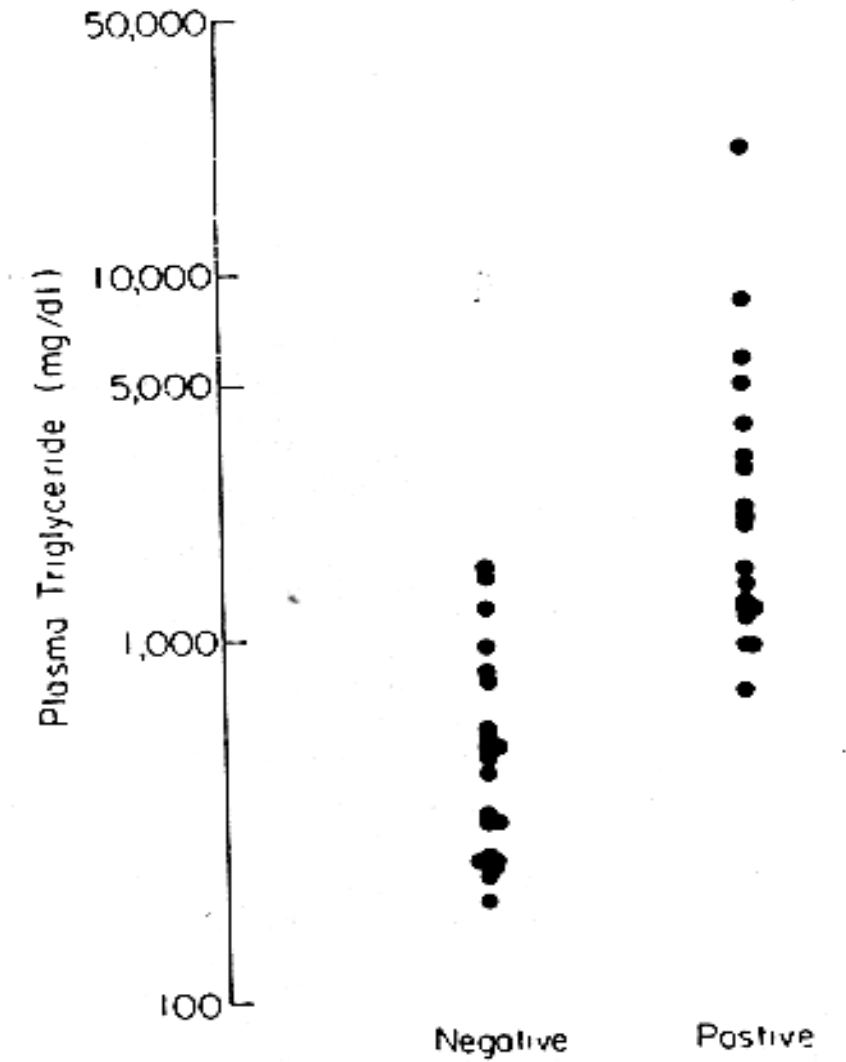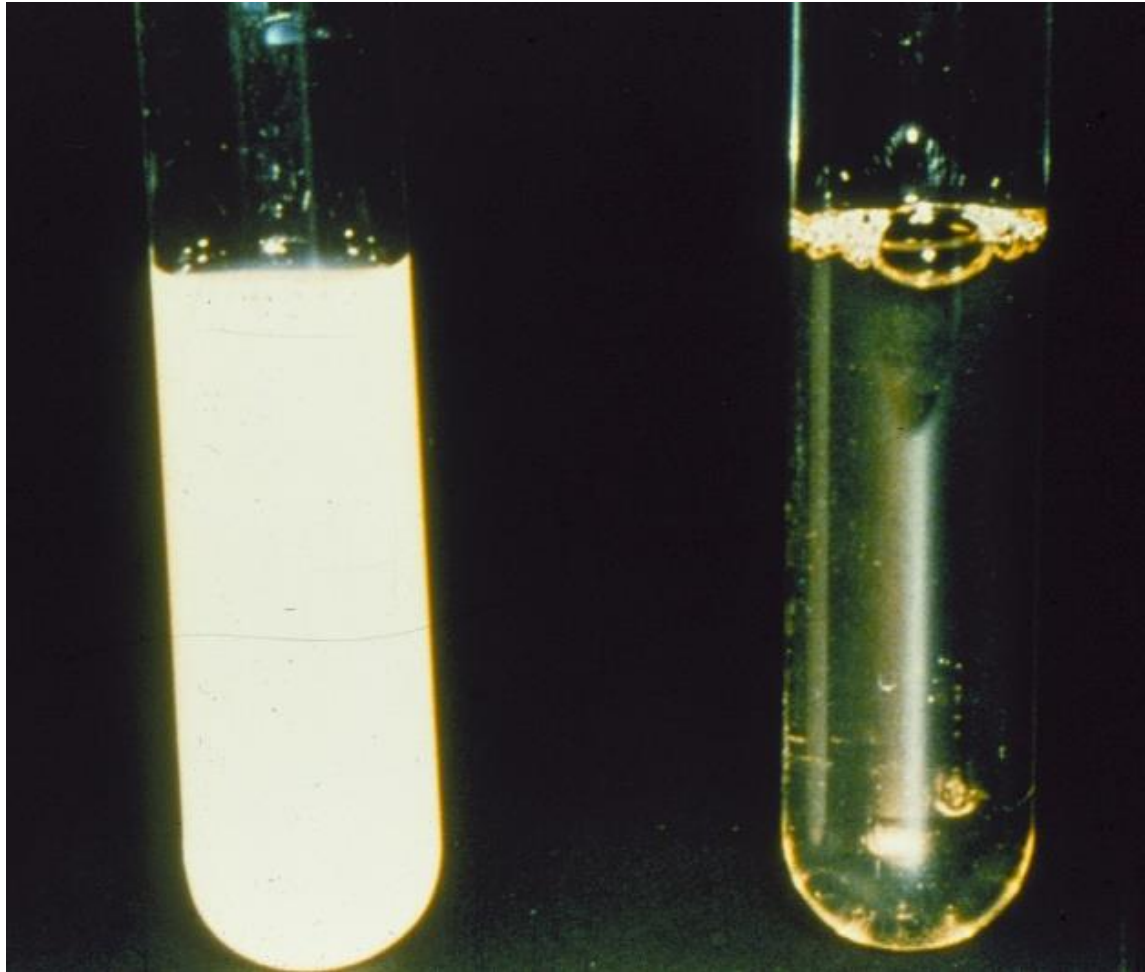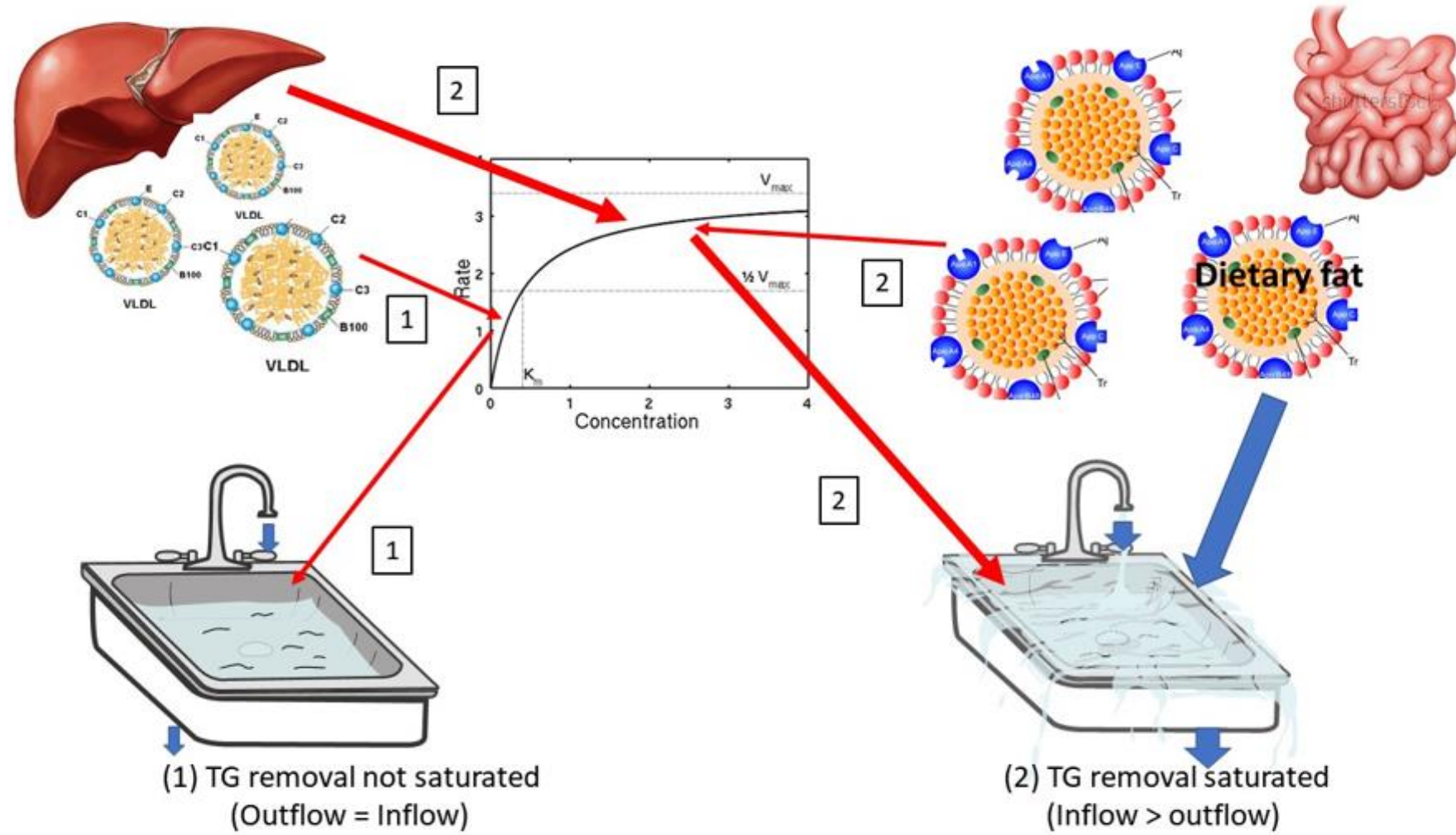
# Most Severe Hypertriglyceridemia
## (Type 5 Hyperlipoproteinemia)

Genetic Etiology of Hypertriglyceridemia

**+**

Acquired Secondary Factor(s)

# Triglyceride Clearance is Saturable



(1) TG removal not saturated
(Outflow = Inflow)

(2) TG removal saturated
(Inflow > outflow)

Chait A and Eckel RH, Ann Int Med, 170:626, 2019

# Severe Hypertriglyceridemia

**Familial Chylomicronemia**
    LPL deficiency
    Apo CII deficiency
    GPIHBP1 deficiency
    Rare: ~1/1,000,000
        French Canadians: ~1/40,000
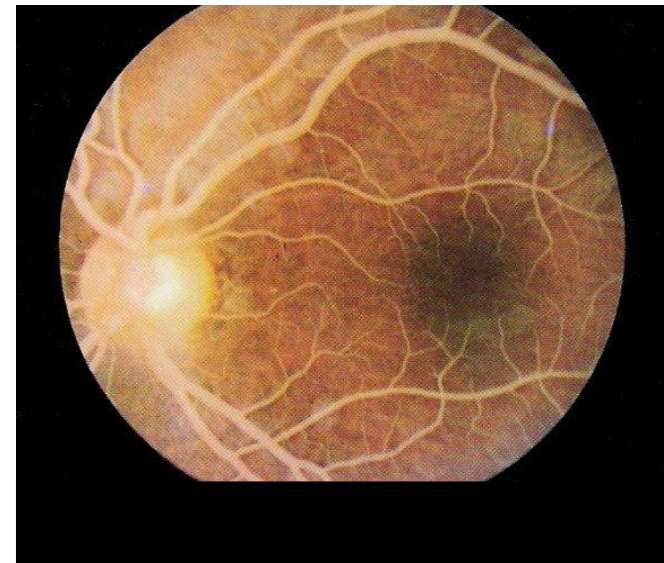        South Africans: ~1/40,000
    Does not require secondary
        disorder
    Pancreatitis risk
    No premature CHD
    Lipemia Retinalis
    Eruptive xanthomata

# Dietary Treatment of Severe Hypertriglyceridemia

## TG >1000 mg/dl:

1. < 5%  fat; no ETOH
2. ? D/C all TG-lowering Rx
3.  < 5% dietary fat → ~25% TG ↓ daily in saturation kinetics
4. Fasting TG every 3 days until <1000 mg/dl
5. Restart Rx when TG <1000 mg/dl
6. If TG do not reach <1000 mg/dl, hospitalize & control diet
7. IV insulin or heparin, or plasmapheresis add little if anything
8. Once TG <1000 mg/dL, liberalize dietary fat and avoid simple sugars
and ETOH based on rate and amount of TG decline.

Chait A and Eckel RH, Ann Int Med, 170:626, 2019

www.cardiometabolichealth.org

**Foundations of Cardiometabolic Health Certification Course**

**Certified Cardiometabolic Health Professional (CCHP)**

# HDL-C Science and Management

**Robert H. Eckel, MD, FAHA, FACC**
**Professor of Medicine, Emeritus**
**Division of Endocrinology, Metabolism and Diabetes**
**Division of Cardiology**
**S/P Charles A. Boettcher II Chair in Atherosclerosis**
**University of Colorado Anschutz Medical Campus**
**robert.eckel@cuanschutz.edu**

# Goals

- Discuss problems with the definition, related prevalence and causes of hypertriglyceridemia.
- Provide updates on if/how hypertriglyceridemia relates to atherosclerotic CVD using informative CVOTs.
- Evaluate strategies for triglyceride management:
  - Moderate
  - Severe
- Summarize HDL-C science and management.

# HDL-C Predictive Value

HDL-C is a strong predictor of CHD in subjects with desirable Total-Cholesterol

## Men and women without CHD history



Castelli W et al JAMA. 256:2835, 1996
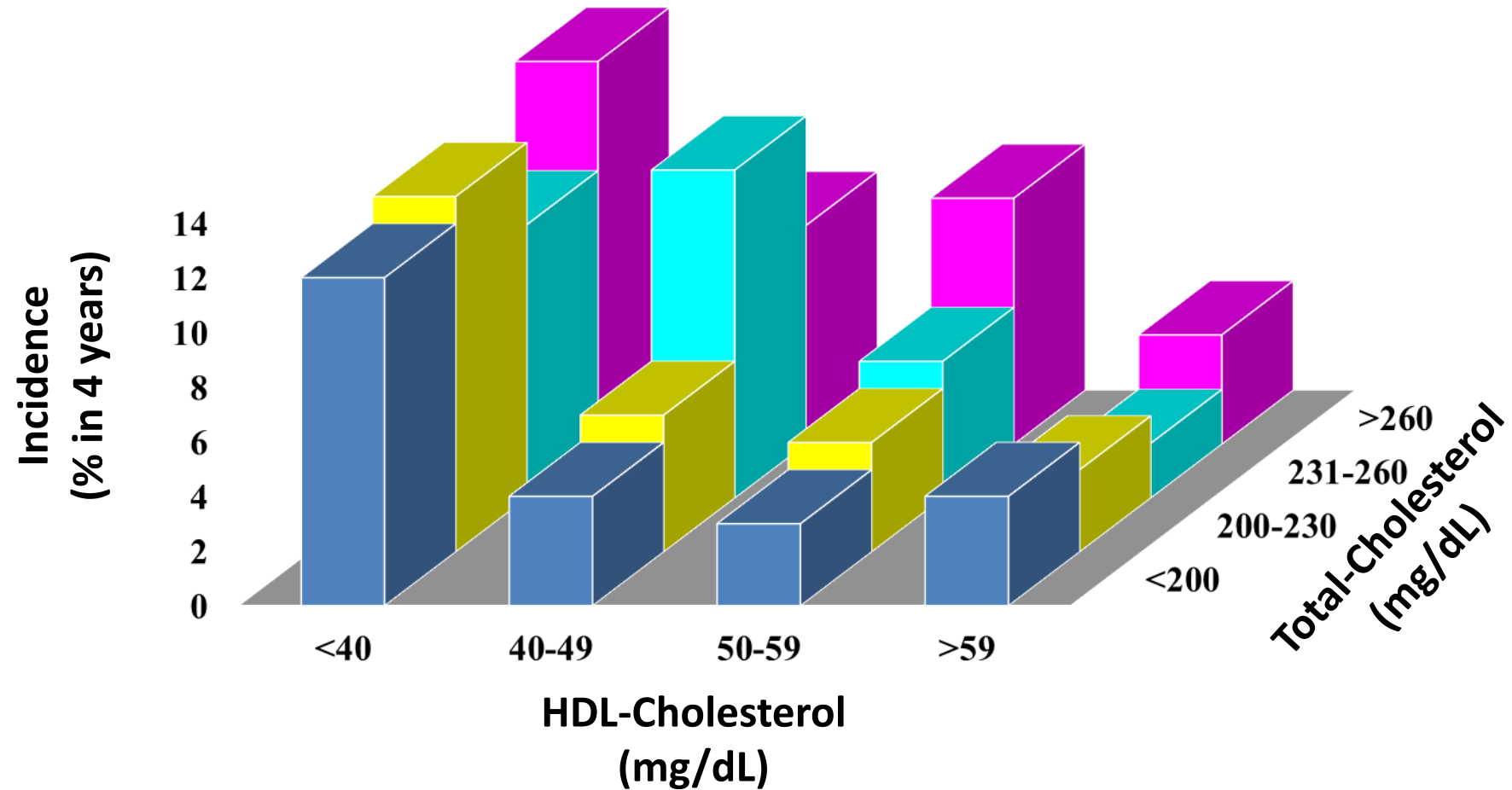
# Acquired Causes of Low HDL-C

- Insulin resistance
  - Hypertriglyceridemia
  - Obesity
- Tobacco
- Anabolic steroids
- Drugs
  - sirolimus, protease inhibitors, β-blockers, IL-2
- Proteinuria
- Critical illness
- Paraproteinemias
- Obstructive liver disease
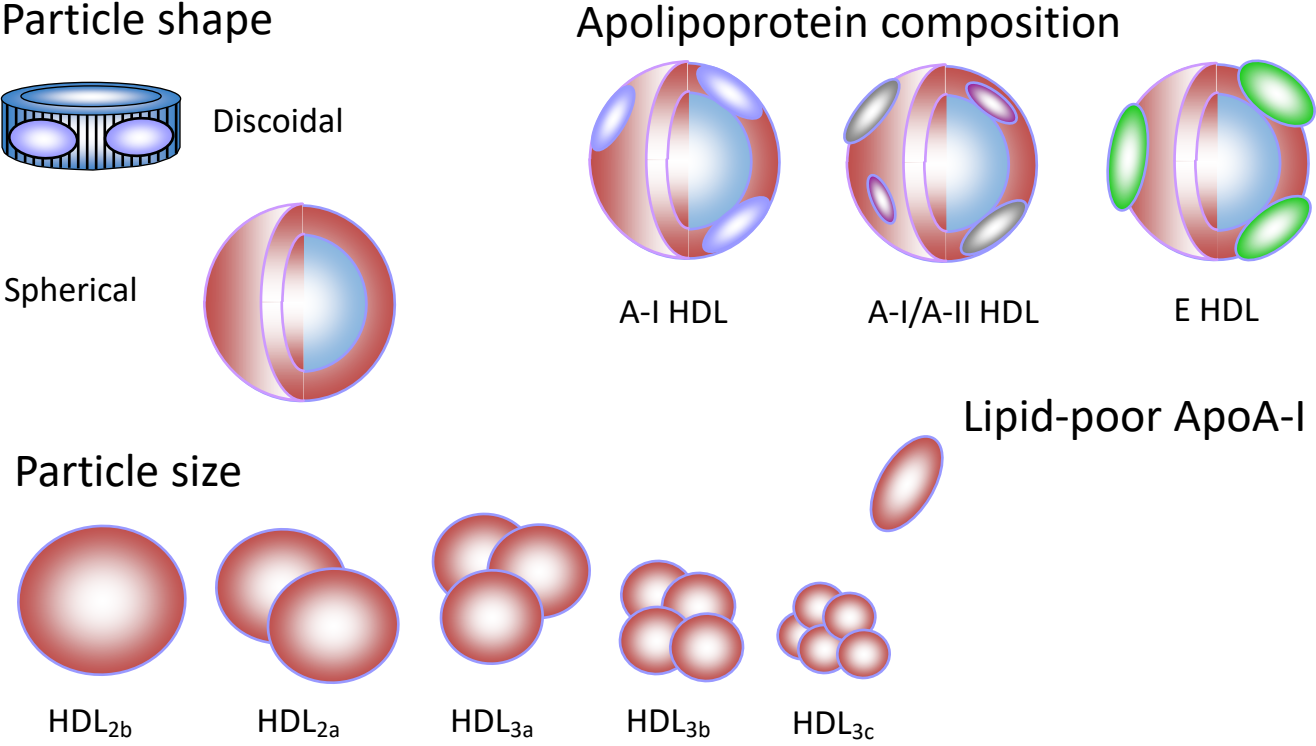- Disappearing HDL syndrome

# HDL- Paradox

- CETP deficient Japanese families with HDL-C levels
  - 80-100 mg/dL or higher in heterozygotes
  - But, possibly an increase in CHD risk
- Apo A1$_{Milano}$
  - Low HDL octogenarians with low CHD risk
- Tangier Disease
  - ABCA1 gene deficiency
- Genetically low HDL-C: Turkey (HTGL gene mutation) and China
  - When relocated to an urban environment, ↑ CHD risk
- Type 1 diabetes
  - HDL-C is increased but so is CHD
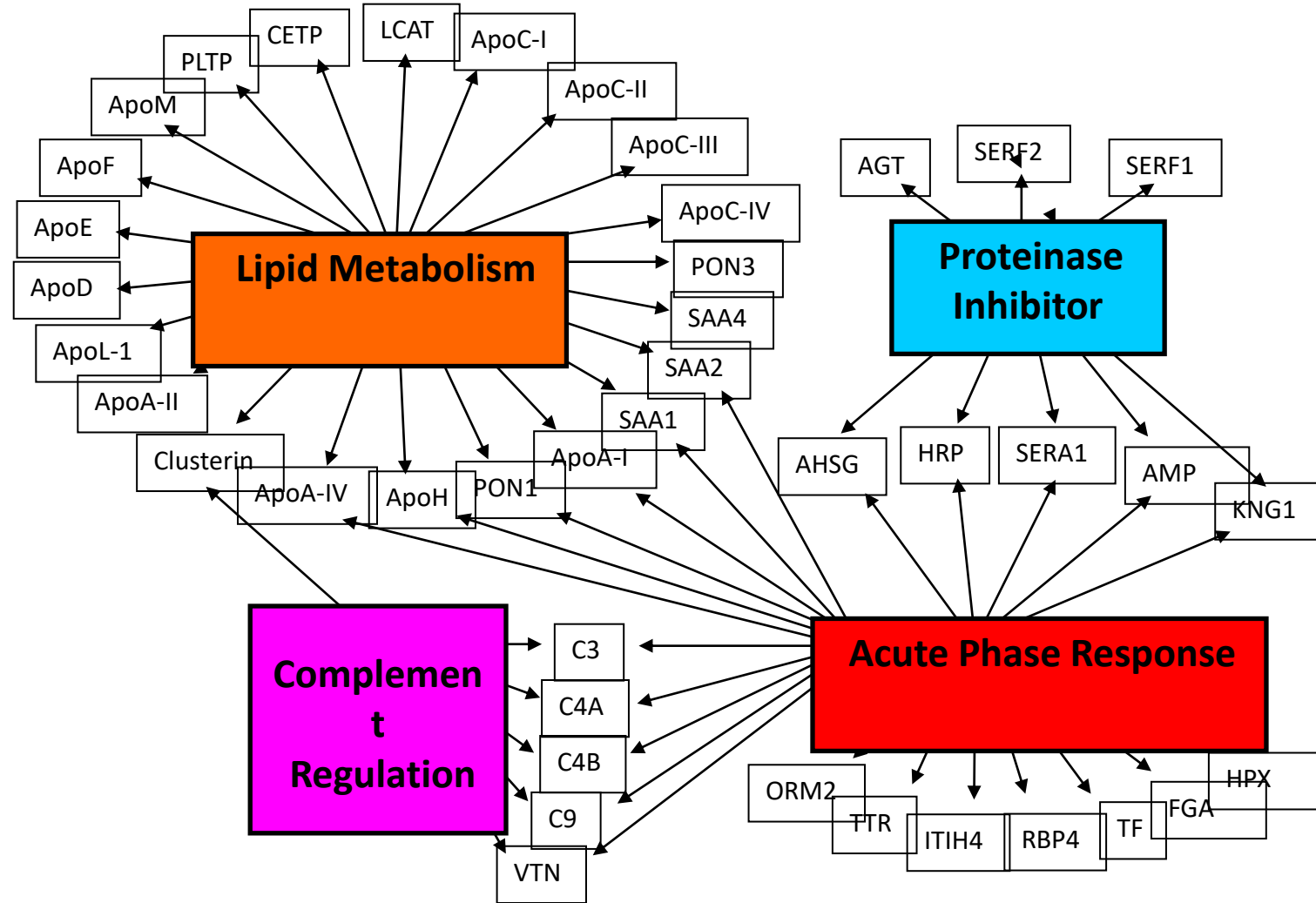- Many patients without low HDL-C have CHD

# Dysfunctional HDL

- Increased levels of circulating HDL-C do not necessarily decrease the risk of CHD events, CHD deaths, or mortality.

- HDL can act as an anti- or a pro-inflammatory molecule, depending on the context and environment.

- Based on a number of recent studies, it appears that the anti- or pro-inflammatory nature of HDL may be a more sensitive indicator of the presence or absence of atherosclerosis than HDL-C levels.
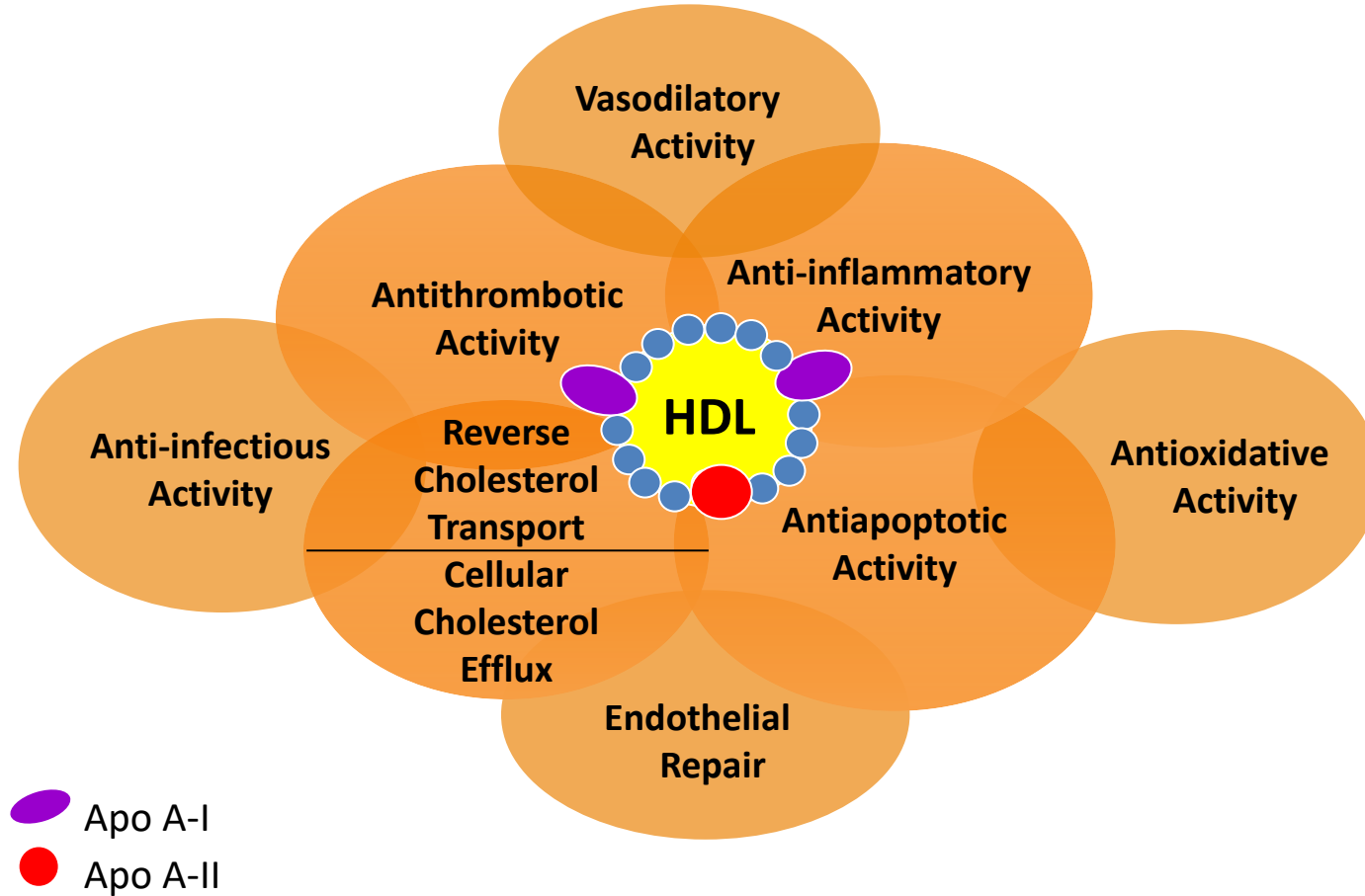
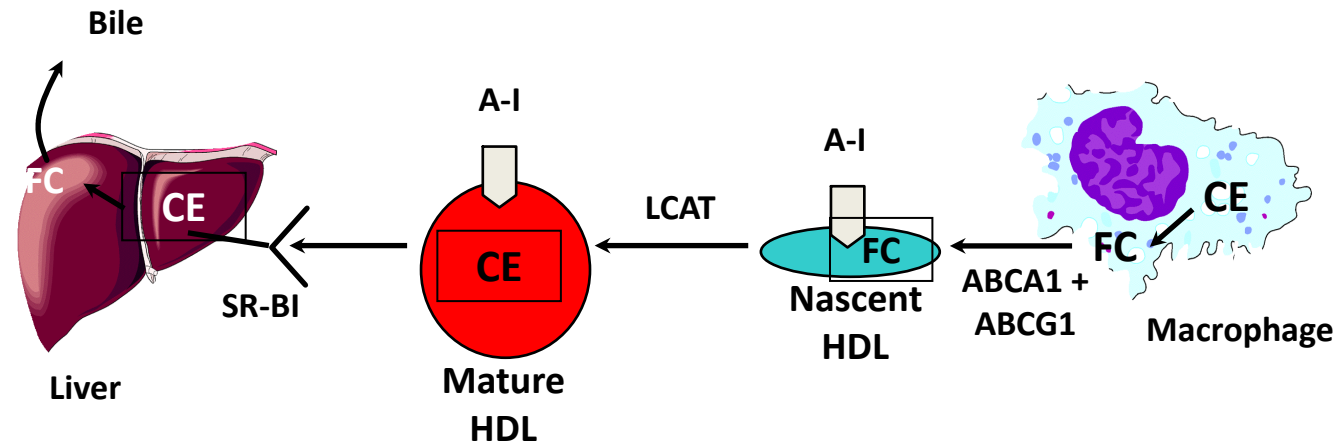# HDL Can be Subdivided into Various Subpopulations

**Particle shape**

Discoidal

Spherical

**Apolipoprotein composition**

A-I HDL

A-I/A-II HDL

E HDL

**Lipid-poor ApoA-I**

**Particle size**

$HDL_{2b}$

$HDL_{2a}$

$HDL_{3a}$

$HDL_{3b}$

$HDL_{3c}$

# The HDL Proteome

# Potential Anti-atherogenic Actions of HDL

Chapman MJ, et al. Curr Med Res Opin. 20:1253, 2004
Assmann G, et al. Annu Rev Med. 53:321, 2003

# HDL Metabolism and Reverse Cholesterol Transport
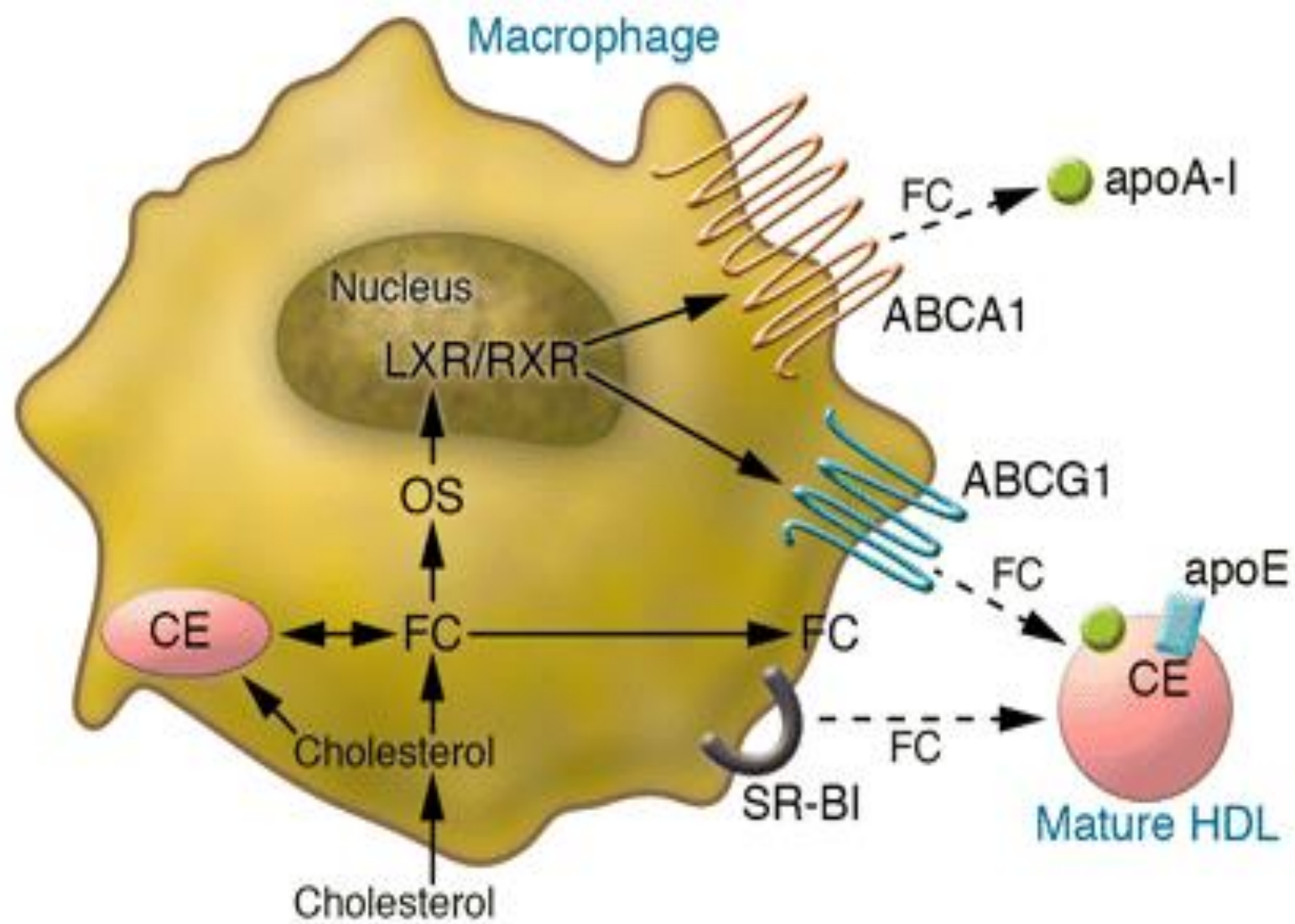
# CETP Inhibitors Markedly Increase HDL-C Levels



Bile

FC

CE

A-I

FC

SR-BI

LCAT

A-I

FC

CE

FC

ABCA1, ABCG1

**Macrophage**

CETP

LDL-R

B

CE
TG

VLDL/LDL
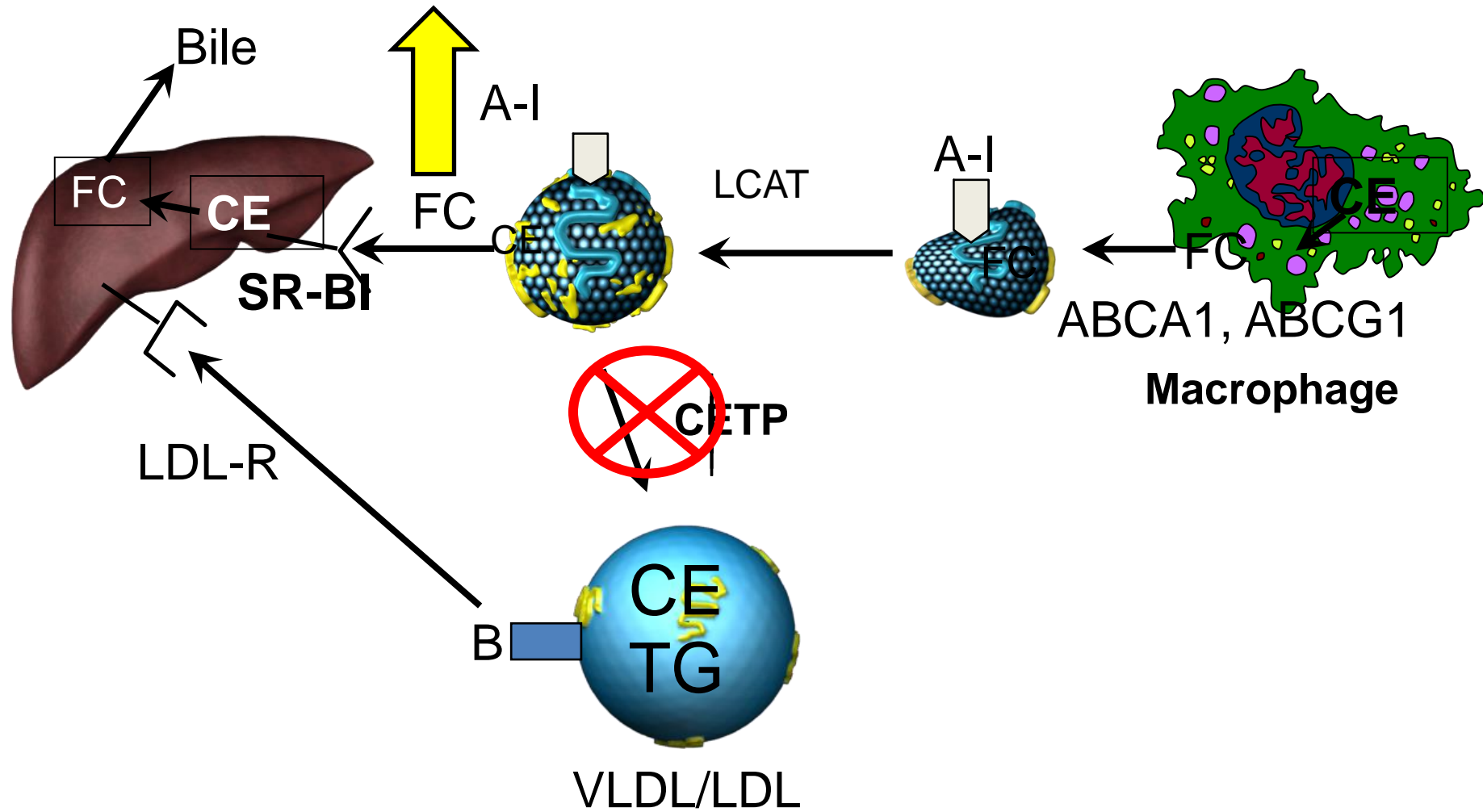
# Cholesterol Efflux Capacity beyond HDL-C Levels in Coronary Artery Disease (CAD) Patients
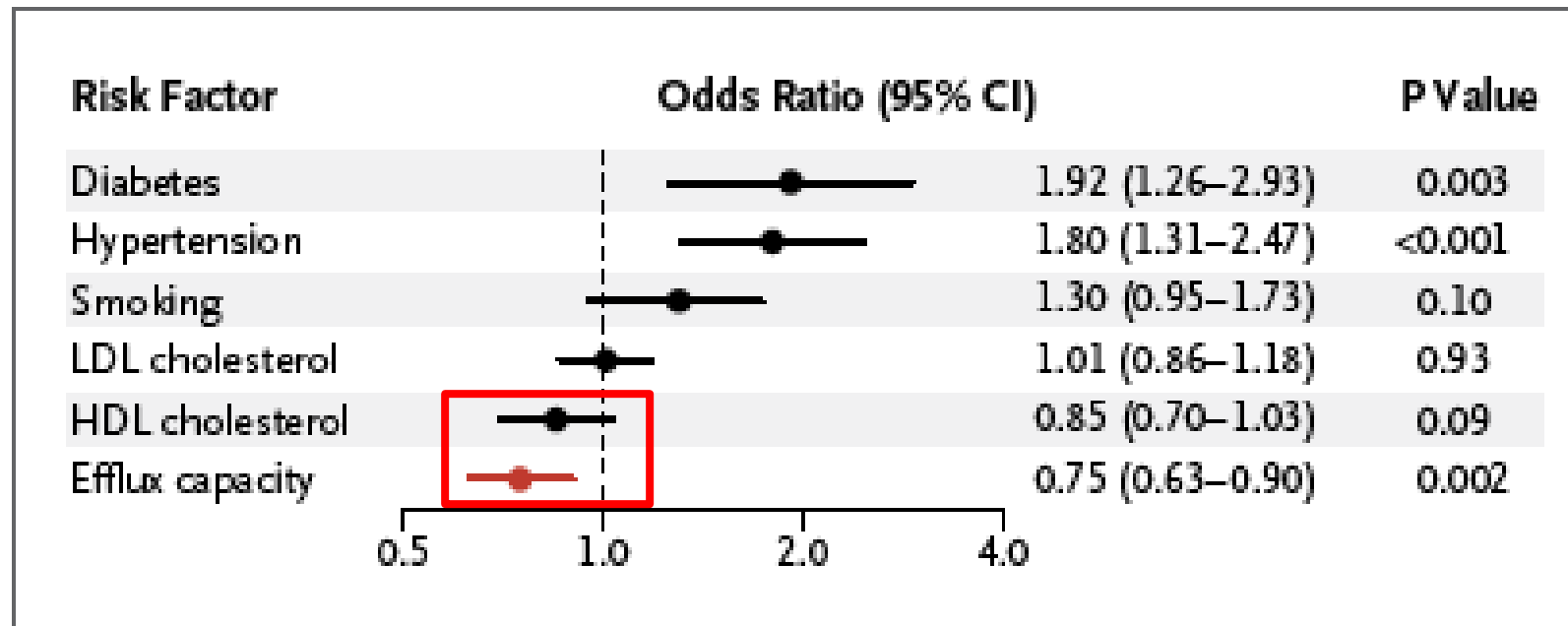


Figure 1. Odds Ratios for Coronary Artery Disease According to Efflux Capacity and Selected Risk Factors.

The logistic-regression model was also adjusted for age and sex. Odds ratios for continuous variables are per 1-SD increase.

| Risk Factor | Odds Ratio (95% CI) | P Value |
|---|---|---|
| Diabetes | 1.92 (1.26–2.93) | 0.003 |
| Hypertension | 1.80 (1.31–2.47) | <0.001 |
| Smoking | 1.30 (0.95–1.73) | 0.10 |
| LDL cholesterol | 1.01 (0.86–1.18) | 0.93 |
| HDL cholesterol | 0.85 (0.70–1.03) | 0.09 |
| Efflux capacity | 0.75 (0.63–0.90) | 0.002 |

Khera AV, et al. N Engl J Med. 364:127, 2011

# Effects of Drugs on HDL-C Levels

| | |
|---|---|
| Niacin | 15-35% |
| Fibrates | 5-15% |
| Statins | 5-10% |
| Resins | 5-10% |
| Estrogens – p.o. | 10-15% |
| PCSK9 inhibitors | 5-10% |

# HPS2-THRIVE Study

- Largest ever randomized trial of effects of ER niacin on safety and CV events in diverse high-risk patients.

- Among those tolerating ERN/LRPT for 8 weeks, 76% remain compliant with active treatment after 3 years (vs 85% allocated placebo).

- ERN/LRPT increases risk of myopathy among patients on statin therapy, particularly in the Chinese

- No clear adverse effects of ERN/LRPT on liver, but known niacin side-effects on skin & GI confirmed

- Effects of 4 years of ERN/LRPT on vascular events in HPS2-THRIVE were published in 2014.

The HPS2-THRIVE Collaborative Group. N Engl J Med. 371:203-212, 2014

# HPS2-THRIVE: First Major Vascular Event During Follow-up
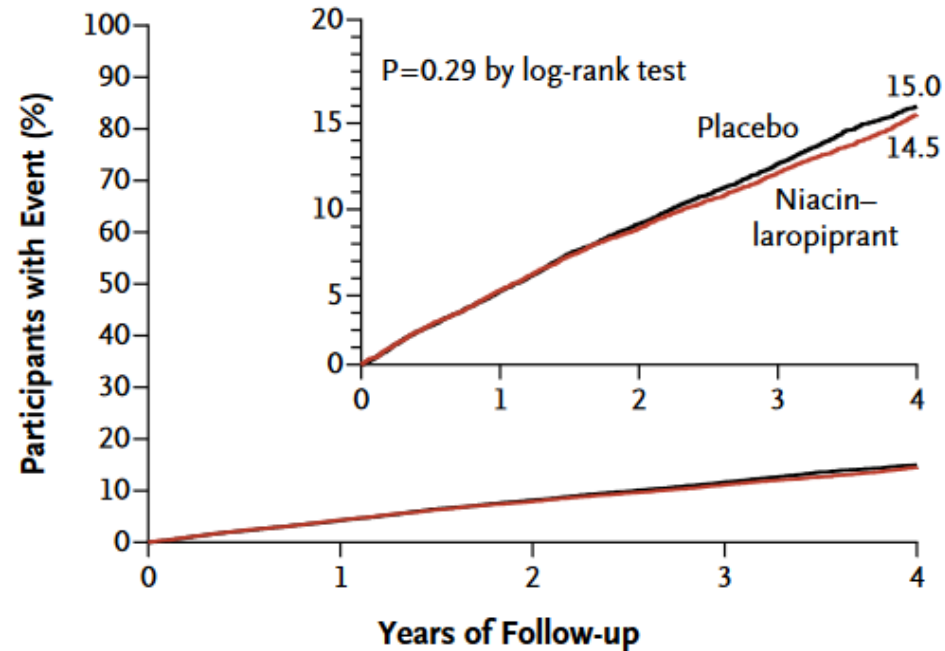


| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Niacin–laropiprant | 12,838 | 12,232 | 11,517 | 7672 | 4978 |
| Placebo | 12,835 | 12,247 | 11,523 | 7643 | 5036 |
| Benefit per 1000 participants assigned to niacin–laropiprant | | 0±3 | 3±3 | 5±5 | 5±7 |

# Effects of Drugs on HDL-C Levels

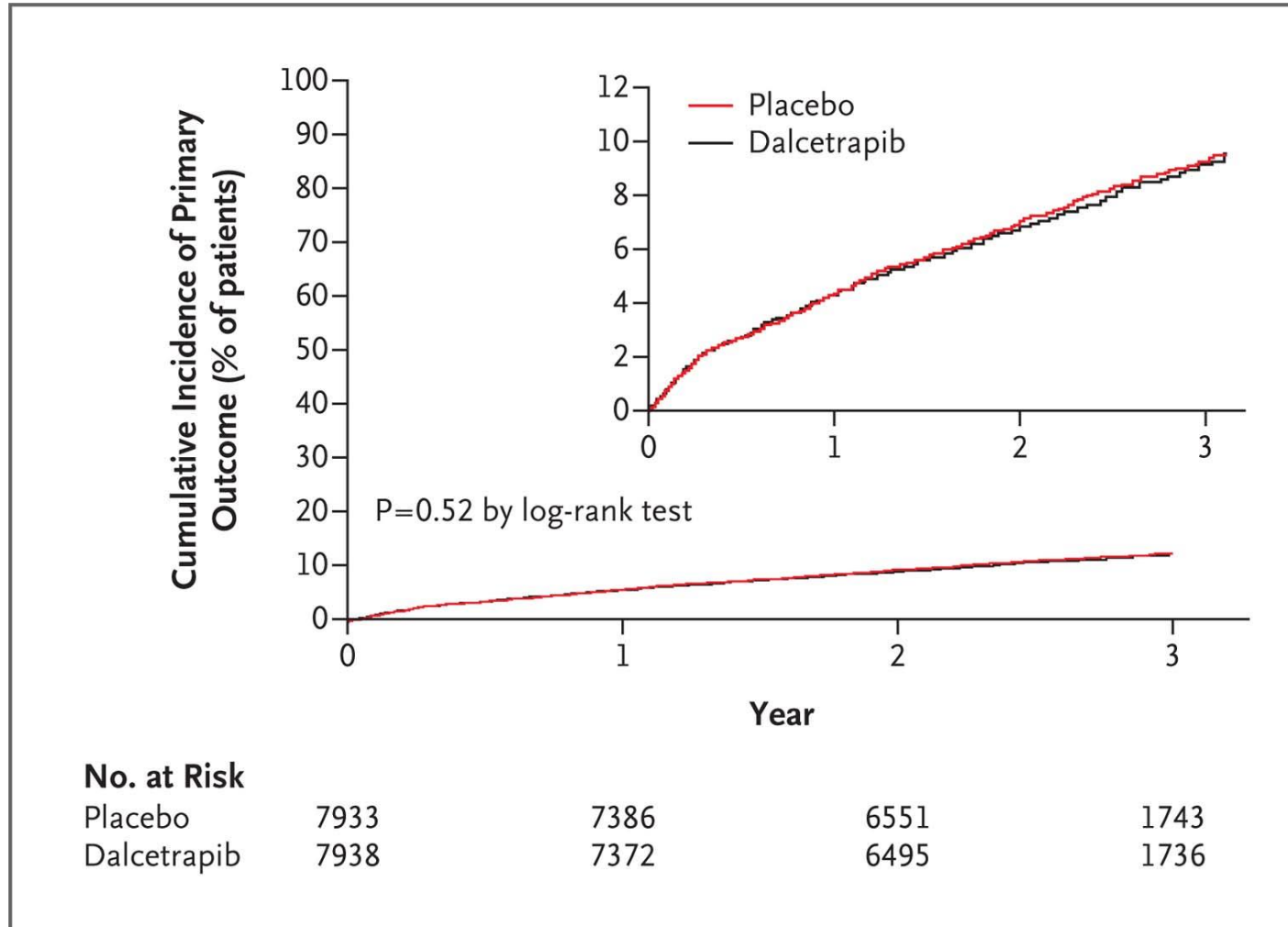| | |
|---|---|
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| Fibrates | 5-15% |
| Statins | 5-10% |
| Resins | 5-10% |
| Estrogens – p.o. | 10-15% |
| PCSK9 inhibitors | 5-10% |
| CETP inhibitors<br>• Torcetrapib - ↑ mortality; abandoned<br>• Dalcetrapib (JTT-705): Phase 3 trial stopped<br>• Anacetrapib (MK-0859): Phase 3 data – study completed<br>• Evacetrapib: Phase 3 stopped | 25-60% |

# Dal-OUTCOMES Study

- 15,600 patients with stable CHD after recent ACS
  - Fully recruited
- Background LDL-lowering with atorvastatin
- Randomized to dalcetrapib 600 mg vs. placebo
- Primary outcome: CVD morbidity and mortality in patients who are clinically stable after recent ACS and long-term safety profile

Schwartz GG, et al. Am Heart J. 158:896, 2009

# Dal-OUTCOMES: Lipid Effects



**A**

HDL-C

**B**

LDL-C

Schwartz GG et al. NEJM 367:208, 2012
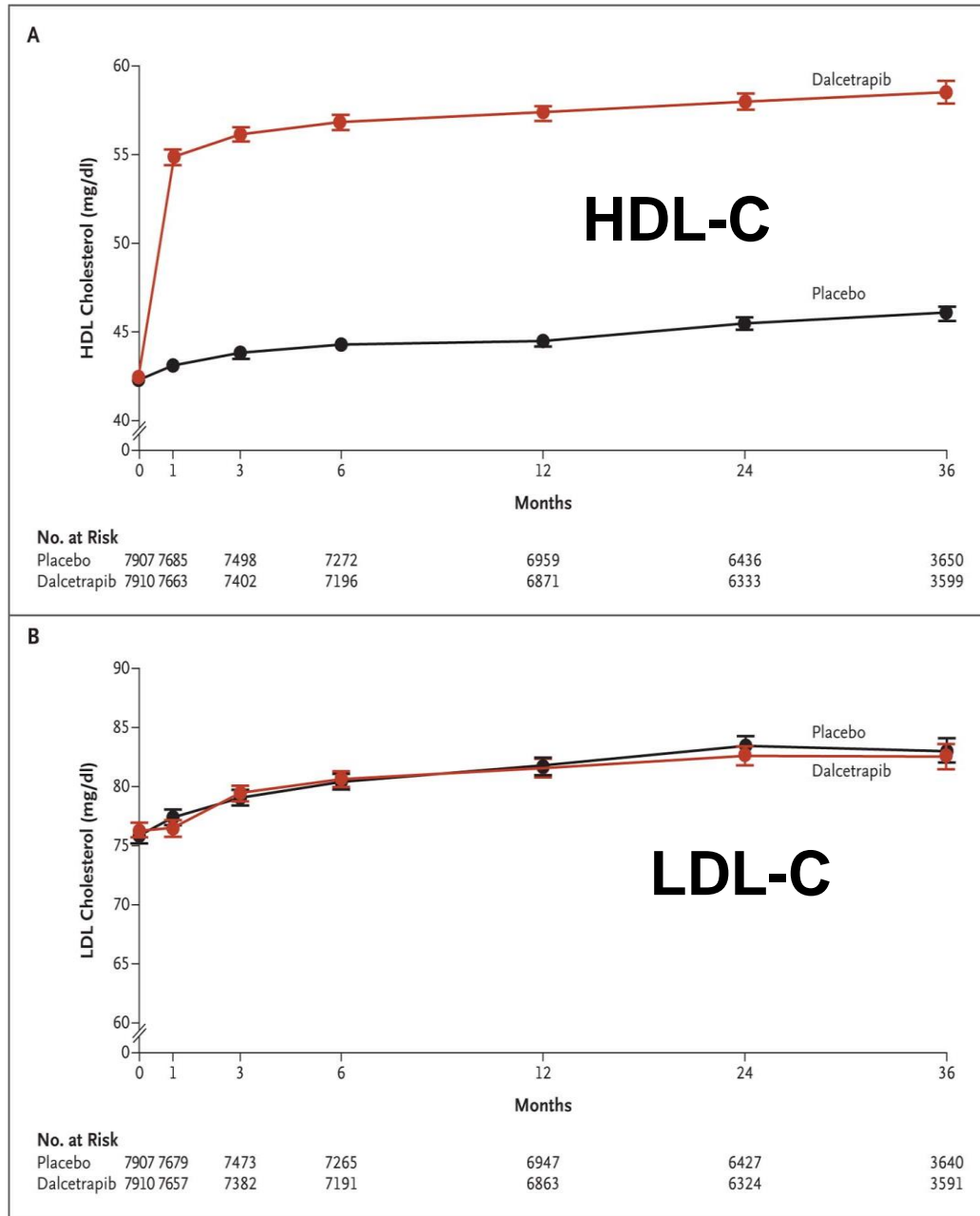
# Dal-OUTCOMES: Incidence of the Primary Efficacy End Point



Schwartz GG et al. NEJM 367:208, 2012

# Novel Therapies for Raising HDL

- Autologous delipidated HDL
- Reconstituted HDL
- Apo A-1 or apo A-1 peptides
- Apo A-1 Milano/Phospholipids
- RVX-208
- Endothelial lipase inhibitors
- Niacin receptor agonists
- LXR receptor agonists
- LCAT activators
- PPAR-$\alpha$/$\delta$ dual agonists
- Apo A-1 mimetic peptides
  - e.g. 4F

**The evidence is now overwhelming that low levels of HDL-C do not cause CHD and drug treatment is not indicated**

Why not then increase HDL in other heart healthy ways?

# Heart Healthy HDL-C Raising Therapies

- Exercise: ≤10% - benefit relates to fat loss
  - Kodama S et al, *Arch Int Med* 167:000, 2007

- Sustained Weight Loss: 3-10%
  - Kelley GA et al, *Int J Obesity* 29:881, 2005
  - Belalcazar LM et al, *JLR* 53:2726, 2012

- Alcohol: 5-15%
  - Gaziano JM et al, *NEJM* 329:1829, 1994

- Smoking cessation: 5-10%
  - Maeda K et al, *Prev Med* 37:283, 2003

University of Colorado
Anschutz Medical Campus

**Thank You!**