Triglycerides, LDL and CVD: What Are the Connections?

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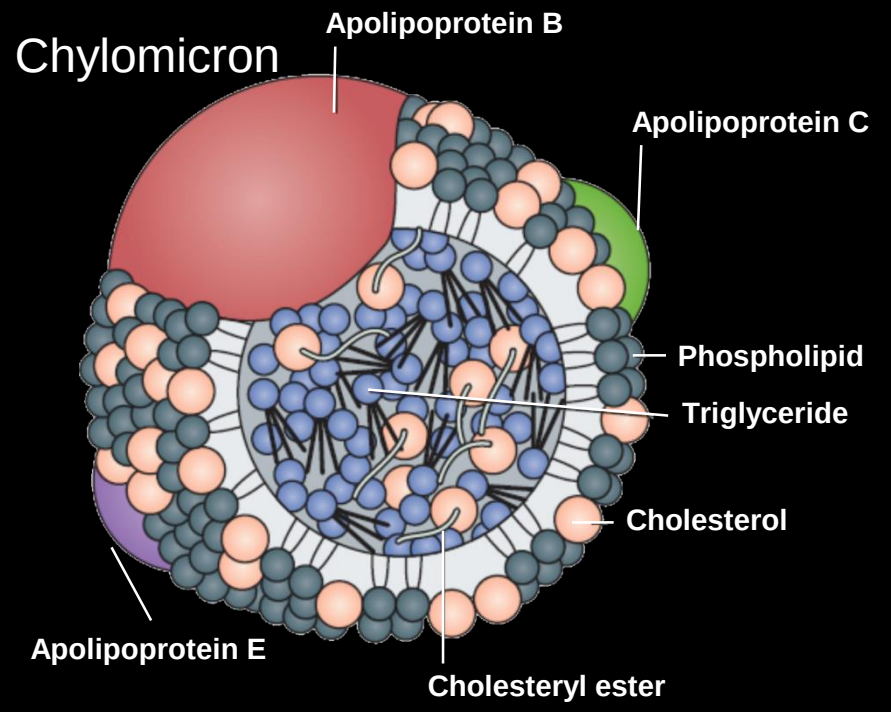
Triglycerides and Lipoproteins

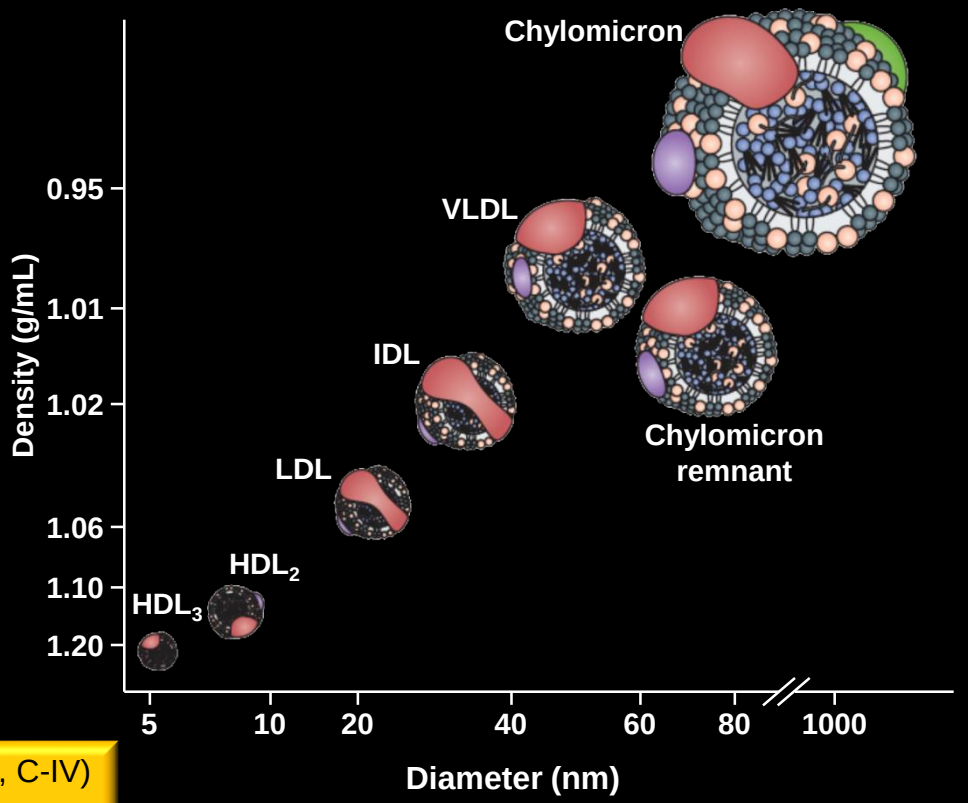
- Triglycerides (TG) are hydrophobic molecules, and do not circulate freely. They are carried in plasma by lipoproteins.
- Fasting hypertriglyceridemia is the result of accumulation of remnant lipoproteins in plasma.
- In the post-prandial state, TG-containing lipoproteins include chylomicrons and their remnants, VLDL remnants, and IDL; in the fasting state, these are mostly IDL.
- Remnants are atherogenic because they carry both cholesterol and triglycerides into the sub-endothelial space. Triglycerides are a source of diacylglycerol and free fatty acid, which participate in the inflammatory response.

Components, Size, and Density of Human Serum Lipoproteins

Structural components of lipoproteins



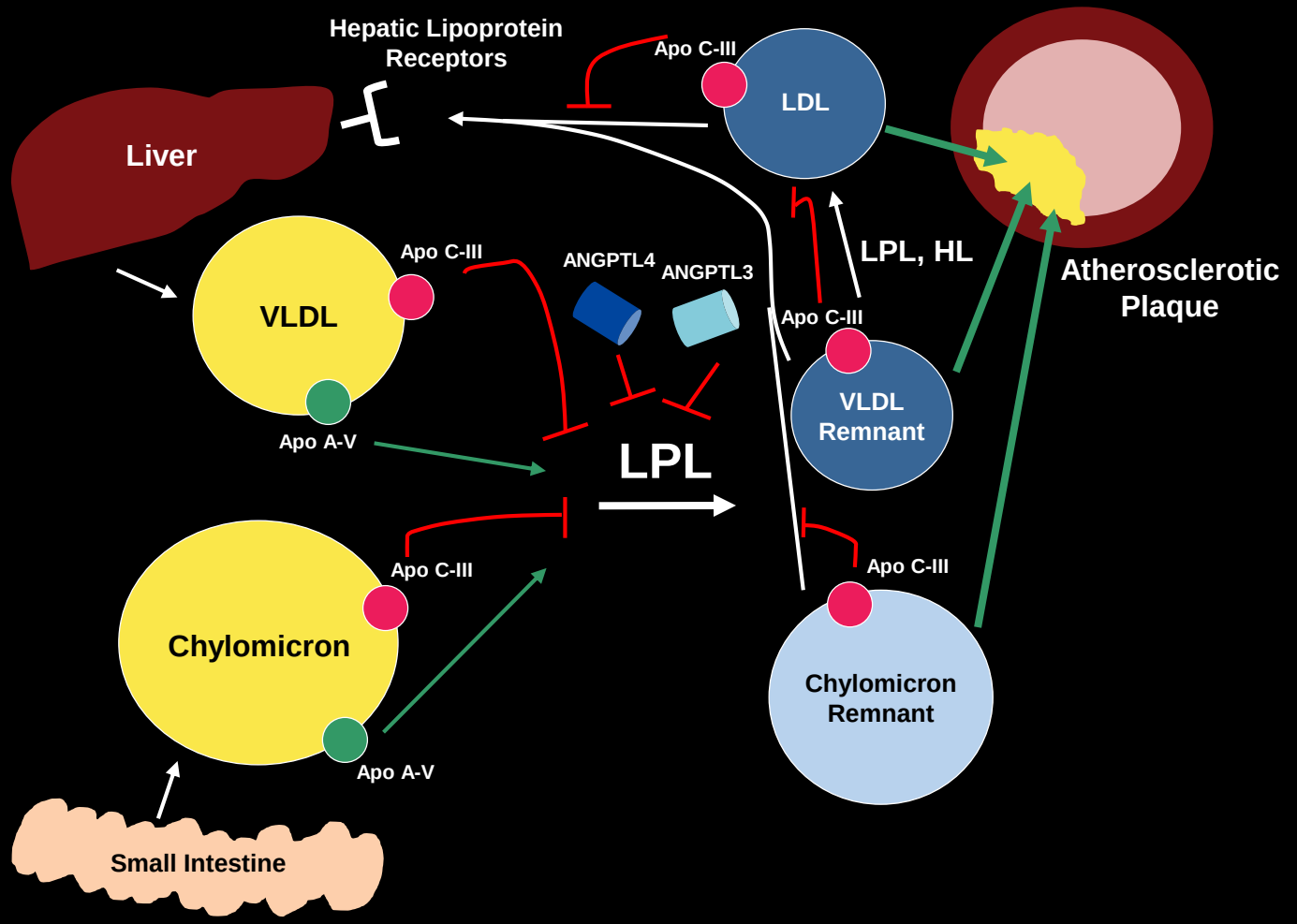
Relation to diameter and density



Apolipoproteins (A-I, A-II, A-IV, A-V, B48, B100, C-I, C-II, C-III, C-IV)
- Assist in structural integrity and solubility
- Serve as co-factors in enzymatic reactions
- Act as ligands

Genest J, Libby P. Lipoprotein Disorders and Cardiovascular Disease. Braunwald's Heart Disease: a textbook of cardiovascular medicine, tenth edition. Elsevier 2014, Chapter 45.

Metabolism of Plasma Triglycerides



ANGPTL=angiopoietin-like protein; HL=hepatic lipase; LPL=lipoprotein lipase.

Khetarpal SA, Radar DJ. Arterioscler Thromb Vasc Biol. 2015;35:e3-9.

Most Forms of HTG Are of Secondary Origin

Cause	Clinically useful details
Positive energy balance	↑Saturated fat, ↑glycemic index content, alcohol
↑Carbohydrate intake	↑Simple sugars (fructose, sucrose, etc.) & dietary fiber
Adiposopathy	Especially ↑ visceral adiposity
Diabetes mellitus	More so if poorly controlled
Hypothyroidism	Only if not adequately controlled with thyroid replacement therapy
Nephrotic syndrome	
Medications	Antiretroviral regimens (for HIV) Some phenothiazines and 2nd-generation antipsychotics Nonselective beta-blockers Thiazide diuretics Oral estrogen, hormone Rx, tamoxifen Glucocorticoids and isotretinoin
Recreational drugs	Marijuana (↑ApoC-III)

HIV=human immunodeficiency virus.

Bays HE. In: Kwiterovich PO Jr, ed. The Johns Hopkins Textbook of Dyslipidemia. 1st ed. Lippincott Williams & Wilkins;2010:245-57.

Genetic Causes of Hypertriglyceridemia (HTG)

Common

- Familial combined hyperlipidemia (FCHL)
  - Variable ↑TG and cholesterol genetic defects in lipoprotein metabolism
- Familial hypertriglyceridemia (FHTG)
  - ↑TG levels only, related to ↑hepatic VLDL production and/or polygenic vs environmental ↓lipoprotein lipase (LPL) activity

Rare

- Familial dysbetalipoproteinemia (Fredrickson Type III)
- LPL deficiency
- ApoC-II deficiency
- GPIHBP1 deficiency
- ApoA-V mutations

While Mendelian randomization studies strongly suggest that genetically determined HTG causes atherosclerosis, genetic testing for causes of HTG is rarely useful clinically and is not recommended as a routine practice.

Bays HE. In: Kwiterovich PO Jr, ed. The Johns Hopkins Textbook of Dyslipidemia. 1st ed. Lippincott Williams & Wilkins;2010:245-57.

National Lipid Association Classification of Cholesterol and TG Levels (mg/dL)

Non-HDL-C	
<130	Desirable
130-159	Above desirable
160-189	Borderline high
190-219	High
≥220	Very high

HDL-C	
<40 (men)	Low
<50 (women)	Low

LDL-C	
<100	Desirable
100-129	Above desirable
130-159	Borderline high
160-189	High
≥190	Very high

Triglycerides	
<150	Normal
150-199	Borderline high
200-499	High
≥500	Very high

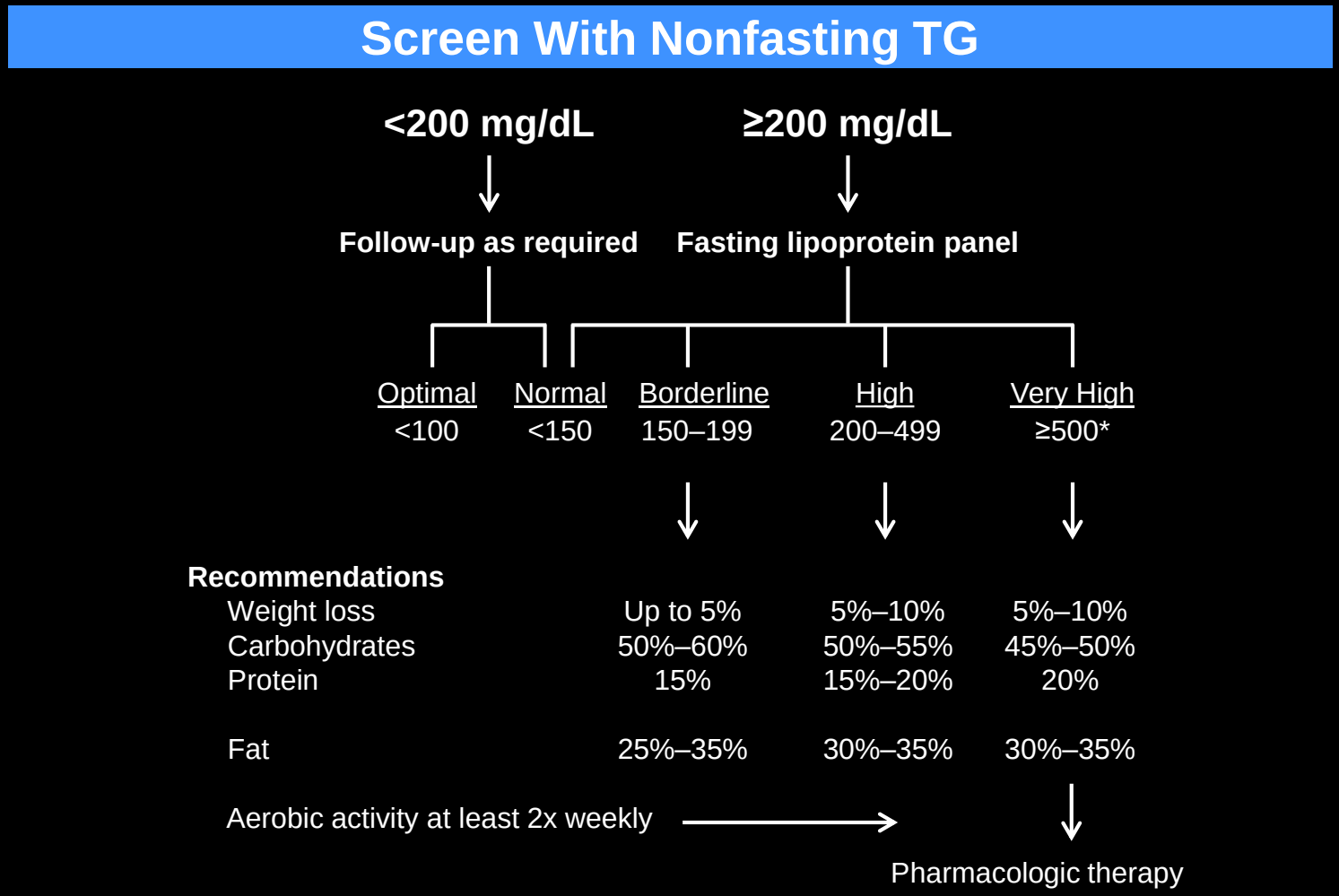
www.lipid.org.

Practical Algorithm for Hypertriglyceridemia Screening

- Fasting samples provide a more accurate estimate of baseline TG levels
- Nonfasting TG levels are a superior predictor of incident CVD compared with fasting levels.
- Nonfasting TG are similar to fasting when meals contain less than 15 g of fat.
- Non-HDL-C can be assessed in the nonfasting state and is more accurately determined because it is not influenced by variation in fasting TG concentrations.

AHA Scientific Statement. Miller M et al. Circulation. 2011;123:2292-333.

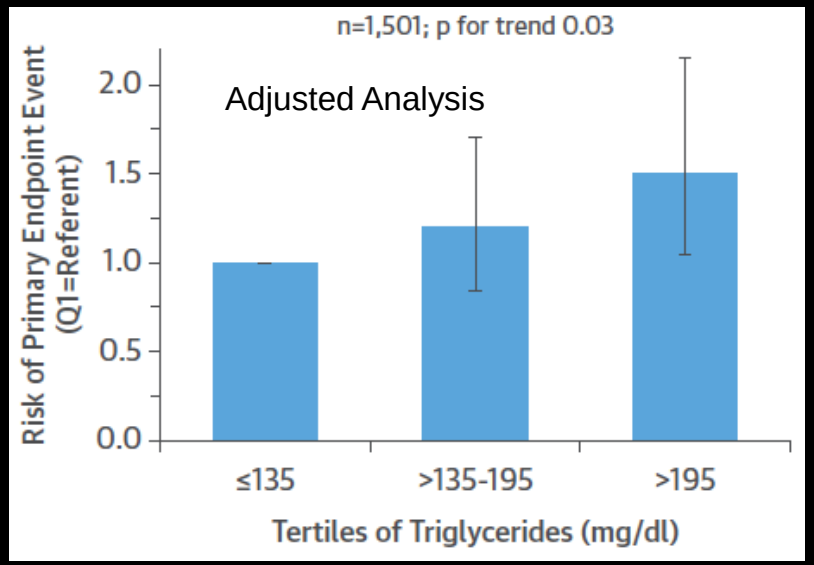
Practical Algorithm for Screening and Managing Elevated TG



AHA Scientific Statement. Miller M et al. Circulation. 2011;123:2292-333.

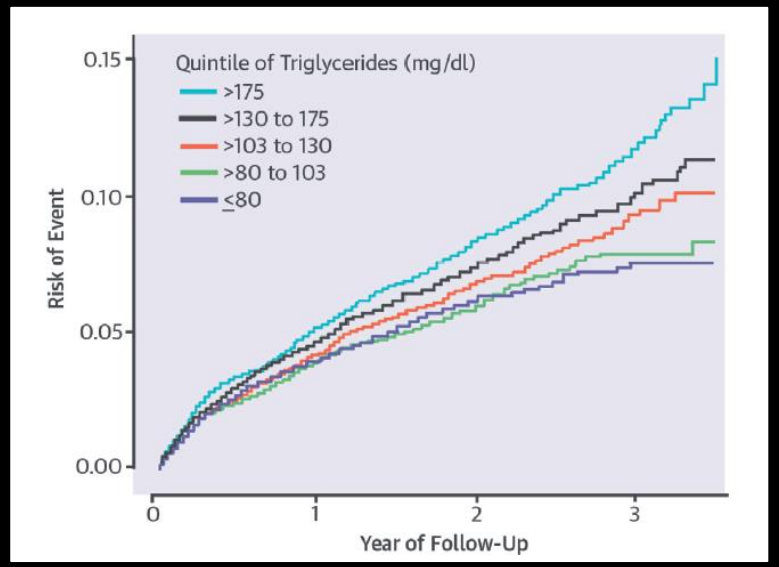
On Statin Rx, TG Levels Associate with Short- and Long-Term CV Risk

N=1501 MIRACL,
80 atorva arm; post-ACS
TG at randomization



16 Weeks

N=15,817 Dal-OUTCOMES;
97% statin-treated; post-ACS
TG at randomization

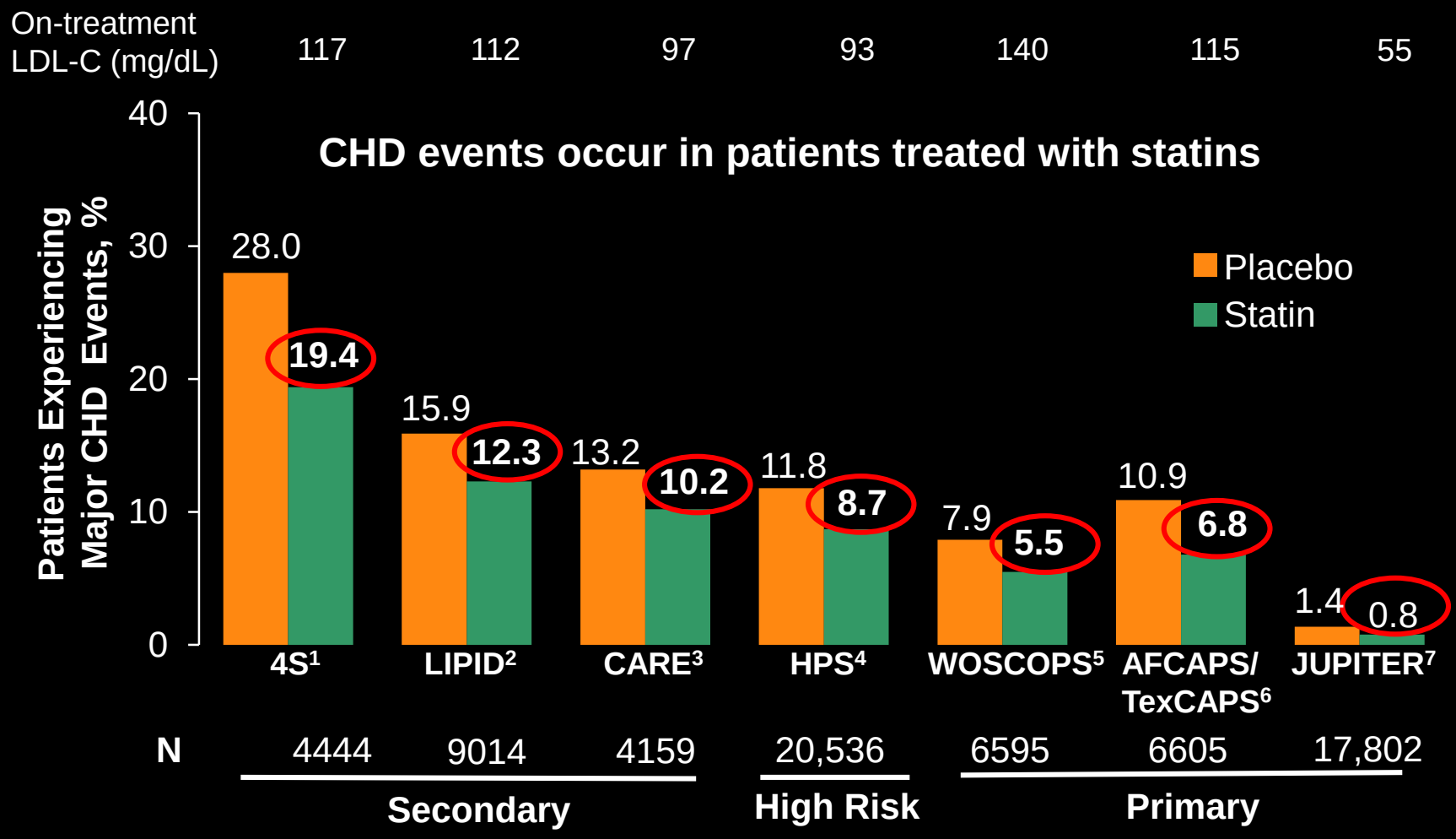


Median follow-up 31 months

Fasting TG levels are strongly linked to both short-term and long-term major CV event risk on background statin therapy, independent of LDL-C.

Schwartz GG et al. JACC. 2015;65;2267-75.

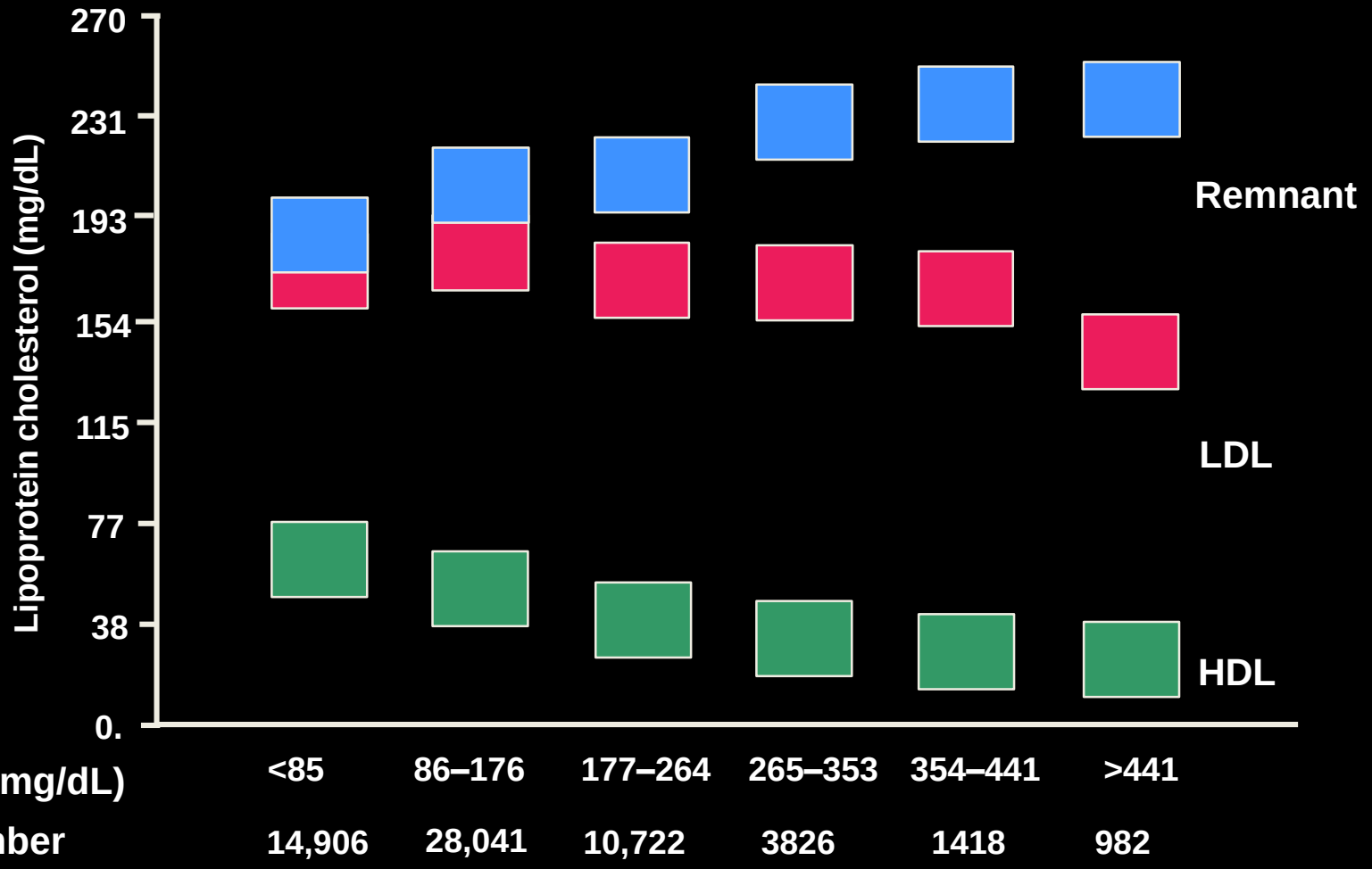
Major Statin Trials: Despite Benefit, Substantial Residual CV Risk Remains



[1]4S Group. Lancet. 1994;344:1383-9.
[2]LIPID Study Group. N Engl J Med. 1998;339:1349-57.
[3]Sacks FM et al. N Engl J Med. 1996;335:1001-9.
[4]HPS Collaborative Group. Lancet. 2002;360:7-22.
[5]Shepherd J et al. N Engl J Med. 1995;333:1301-7.
[6] Downs JR et al. JAMA. 1998;279:1615-22.
[7] Ridker PM et al. N Engl J Med. 2008;359:2195-207.

Remnant Cholesterol as a Causal Risk Factor for Ischemic Heart Disease

Lipoprotein cholesterol as a function of increasing levels of non-fasting TG among 72,000 Danish participants not on LLD



Varbo A et al. J Am Coll Cardiol. 2013;61:427-36.

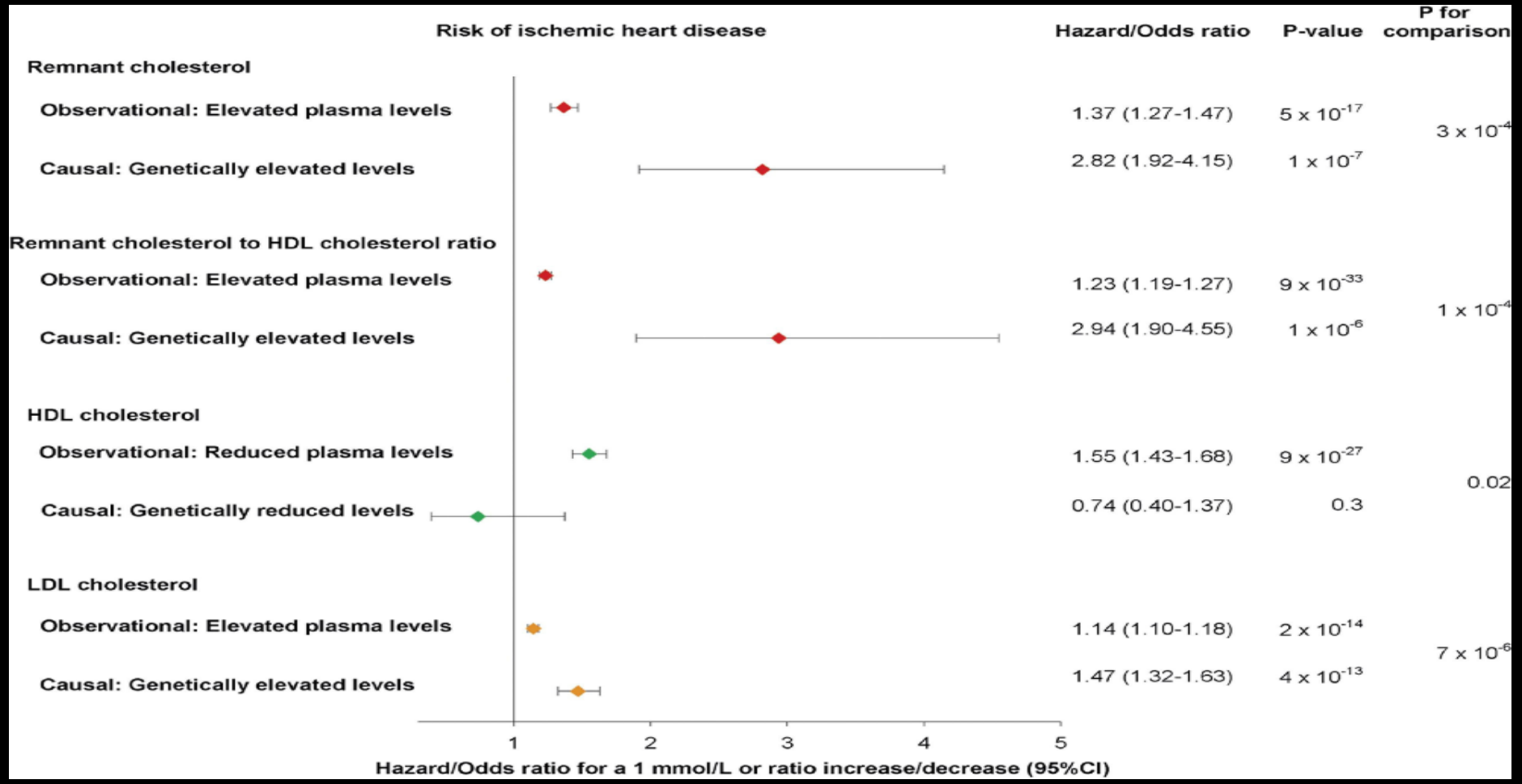
TG, Remnants, and Risk of Ischemic Stroke

Variable	Odds Ratio*	P for trend
TG	**1.56**	**<0.01**
IDL Particle No.	**1.46**	**0.02**
VLDL Size	**1.59**	**0.03**
TC	1.08	0.80
TC/HDL	1.17	0.40
HDL-C	0.82	0.28
HDL particle no.	0.90	0.88
HDL size	0.95	0.95
LDL-C	0.94	0.84
LDL particle no.	1.23	0.28
LDL size	0.96	0.85
VLDL particle no.	1.16	0.41
VLDL TG	1.28	0.09
Lipoprotein (a)	1.16	0.45

*OR for highest vs lowest quartile

Berger JS et al. Stroke. 2012;43958-66.

Risk Estimates for Ischemic Heart Disease: Observational vs. Genetic Data



Observational risk estimates are from the prospective Copenhagen General Population Study, Copenhagen City Heart Study, and Copenhagen Ischemic Heart Disease Study controls combined, adjusted for age, sex, smoking, hypertension, time since last meal, time of day for blood sampling, and lipid-lowering therapy.

Causal risk estimates are from the Copenhagen General Population Study, Copenhagen City Heart Study, and Copenhagen Ischemic Heart Disease Study combined, estimated by instrumental variable analyses.

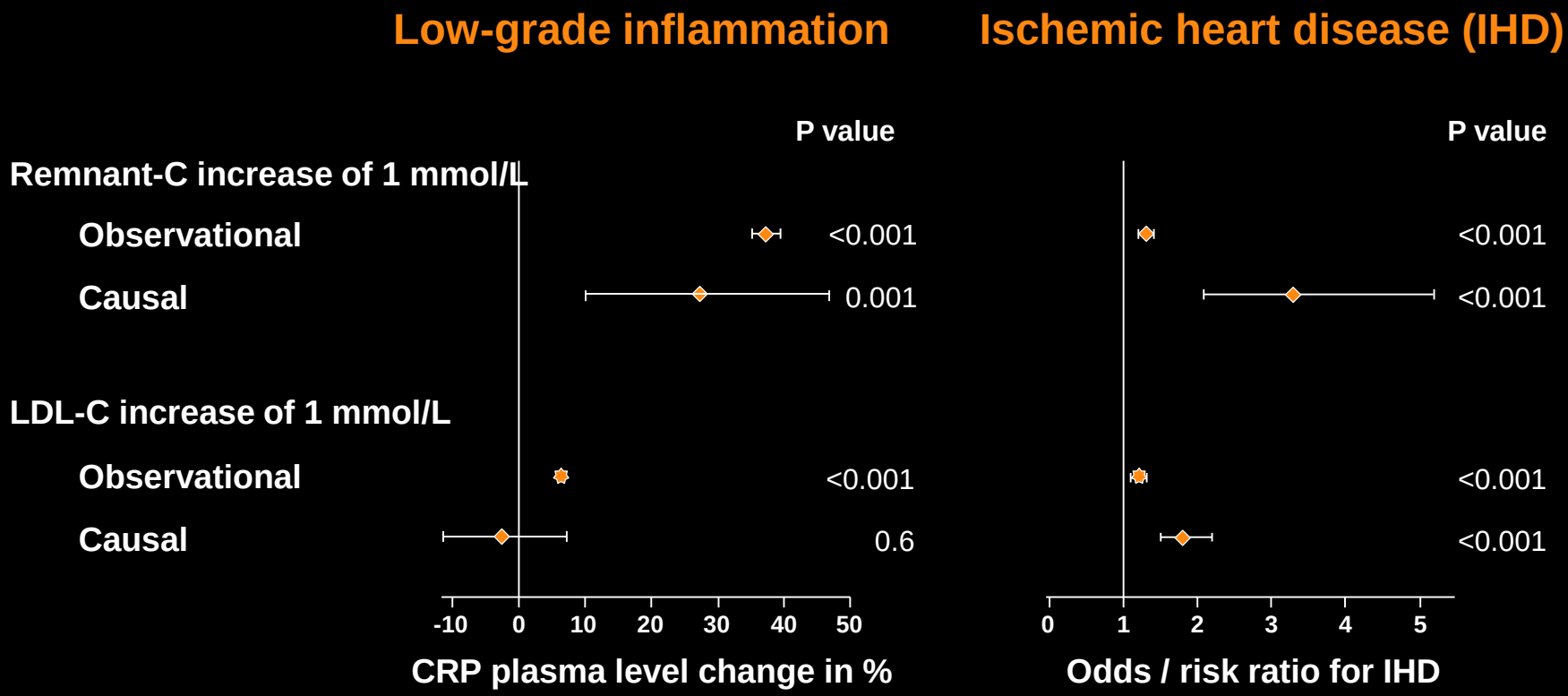
Varbo A et al. J Am Coll Cardiol. 2013;61:427-36.

Remnant Cholesterol and CVD

- Chylomicron remnants, VLDL remnants, and IDL. Rich in both triglycerides and cholesterol.
- Remnant levels correlate with cIMT, carotid plaque macrophage density, ischemic stroke, and with risk for acute CV events in patients with established CAD.
- Remnants can be extracted from the atherosclerotic plaque.
- Remnants up-regulate the expression of pro-inflammatory cytokines, TNFα, IL-6, VCAM-1 and ICAM-1, and MCP-1, and are directly cytotoxic to endothelium.

Kugiyama K et al. Circulation. 1999;99:2858-60. Karpe F et al. J Lipid Res. 2001;42:17-21. Zambon A et al. Atherosclerosis. 2013;230:106-9. Kim JY et al. J Clin Neurol. 2011;7:203-9. Maggi FM et al. J Clin Endocrinol Metab. 2004;89:2946-50. Rapp JH et al. Arterioscler Thromb. 1994;14:1767-74. Takeya M et al. Hum Pathol. 1993;24:534-9. Domoto K et al. Atherosclerosis. 2003;171:193-200. Twickler TB et al. J Clin Endocrinol Metab. 2003;88:1228-33. Doi H et al. Circulation. 2000;102:670-6.

Elevated Remnant Cholesterol vs. Elevated LDL-C: Correlations with CHD and Inflammation



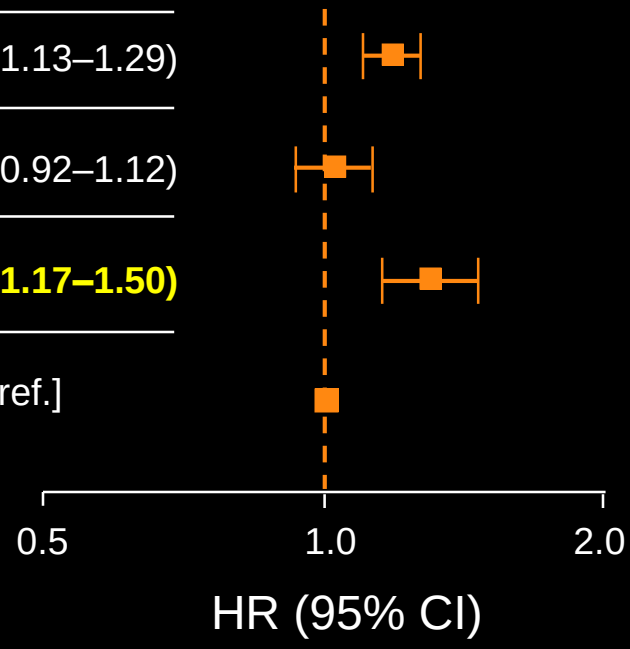
CRP=C-reactive protein.

Varbo A et al. Pharmacol Ther. 2014;141:358-67.

Non-HDL-C >130 mg/dL Is a Better ASCVD Risk Predictor Than LDL-C >100 mg/dL

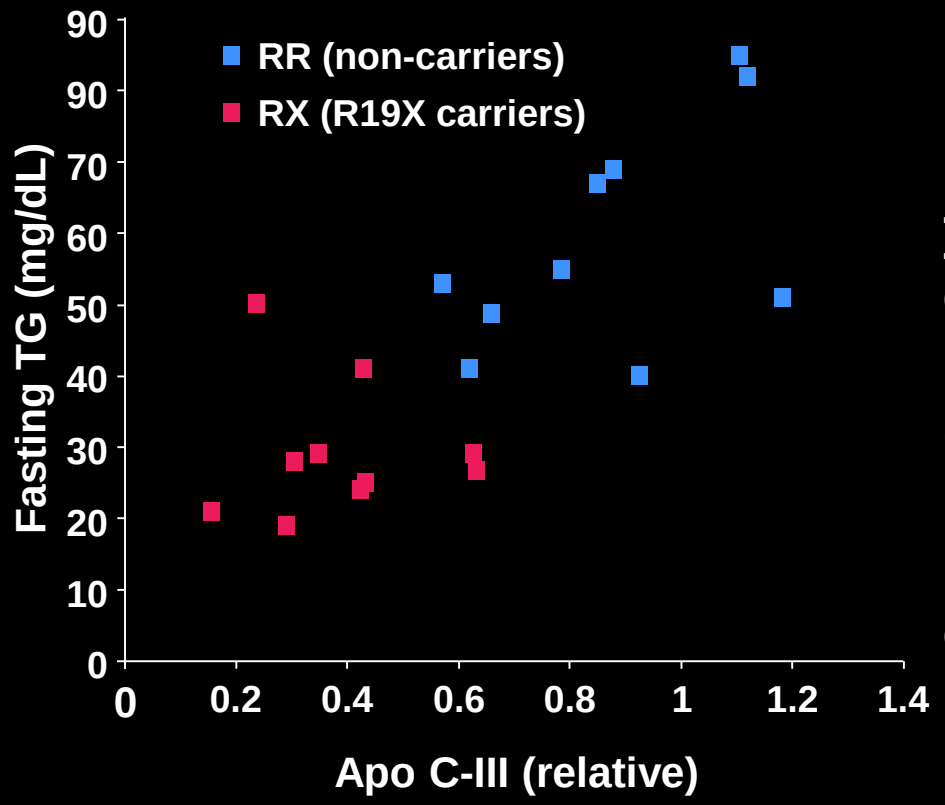
Meta-analysis data at baseline and at 1-year follow-up from 62,154 patients enrolled in 8 randomized controlled statin trials published 1994–2008.

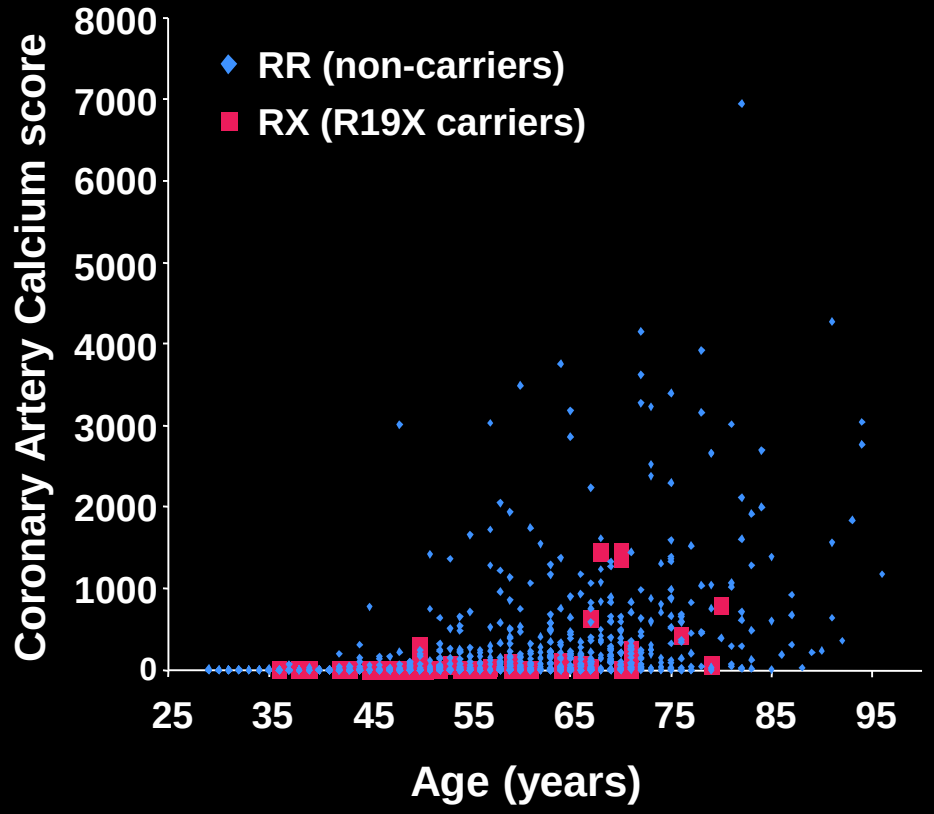
Target Level		Major CV Events (n)	Subjects (n)	HR (95% CI)
LDL-C (mg/dL)	Non-HDL-C (mg/dL)			
≥100	≥130	1877	10,419	1.21 (1.13–1.29)
≥100	<130	467	2873	1.02 (0.92–1.12)
<100	**≥130**	**283**	**1435**	**1.32 (1.17–1.50)**
<100	<130	2760	23,426	1.00 [ref.]



Boekholdt M et al. JAMA. 2012;307:1302-9.

A Mutation in APOC3 Causes Low TG Levels and Predicts Low Coronary Calcium Scores





APOC3=gene encoding apolipoprotein (apo) C-III.

Pollin TI et al. Science. 2008;322:1702-5.

Association of *APOC3* Loss-of-Function Mutation Carrier Status with Blood Lipid Levels and Subclinical Atherosclerosis

	Noncarriers (n=6331)	Carriers (n=64)	Effect Estimate	P value
Blood lipids				
Triglycerides, mg/dL*	166.1 ± 96.2	91.2 ± 44.1	-43.7%	1.83×10^{-21}
HDL cholesterol, mg/dL	55.6 ± 15.2	66.6 ± 15.0	+11.1	3.55×10^{-10}
LDL cholesterol, mg/dL	103.3 ± 36.4	131.6 ± 35.8	+1.5	0.75
Subclinical atherosclerosis				
Coronary arterial calcification, Agatston units†	46.0 (0.0 to 245.0)	29.0 (0.0 to 227.5)	-27.9	0.019
Carotid plaque, mm^2†	183.8 (0.0 to 555.9)	112.8 (0.0 to 367.2)	-8.7	0.79
Carotid intima media thickness, mm*	0.76 ± 0.16	0.74 ± 0.13	-1.7%	0.47

CI=confidence interval; HDL=high-density lipoprotein; LDL=low-density lipoprotein.

Natarajan P et al. J Am Coll Cardiol. 2015;66:2053-4.

Genetic Epidemiology: TG, HDL-C, and ASCVD

- Single nucleotide polymorphisms (SNPs) that alter TG levels are strongly correlated with CVD risk
  - Association maintained after adjusting for LDL-C and HDL-C

- SNPs of HDL-C are non-significant when adjusted for SNPs of LDL-C and TG

In assessing ASCVD risk, recent large-scale genetic studies support a causal effect of TG, but not HDL-C

Do R et al. Nat Genet. 2013;45:1345-52. Holmes MV et al. Eur Heart J. 2014;Jan 27 [Epub ahead of print]. Triglyceride Coronary Disease Genetics Consortium and Emerging Risk Factors Collaboration. Lancet. 2010;375:1634-9. Jorgensen AB et al. N Engl J Med. 2014; 371:32-41. The TG and HDL Working Group of the Exome Sequencing Project, NHLBI. N Engl J Med. 2014;371:22-31.

Statins Reduce CVD Events in HTG Patients

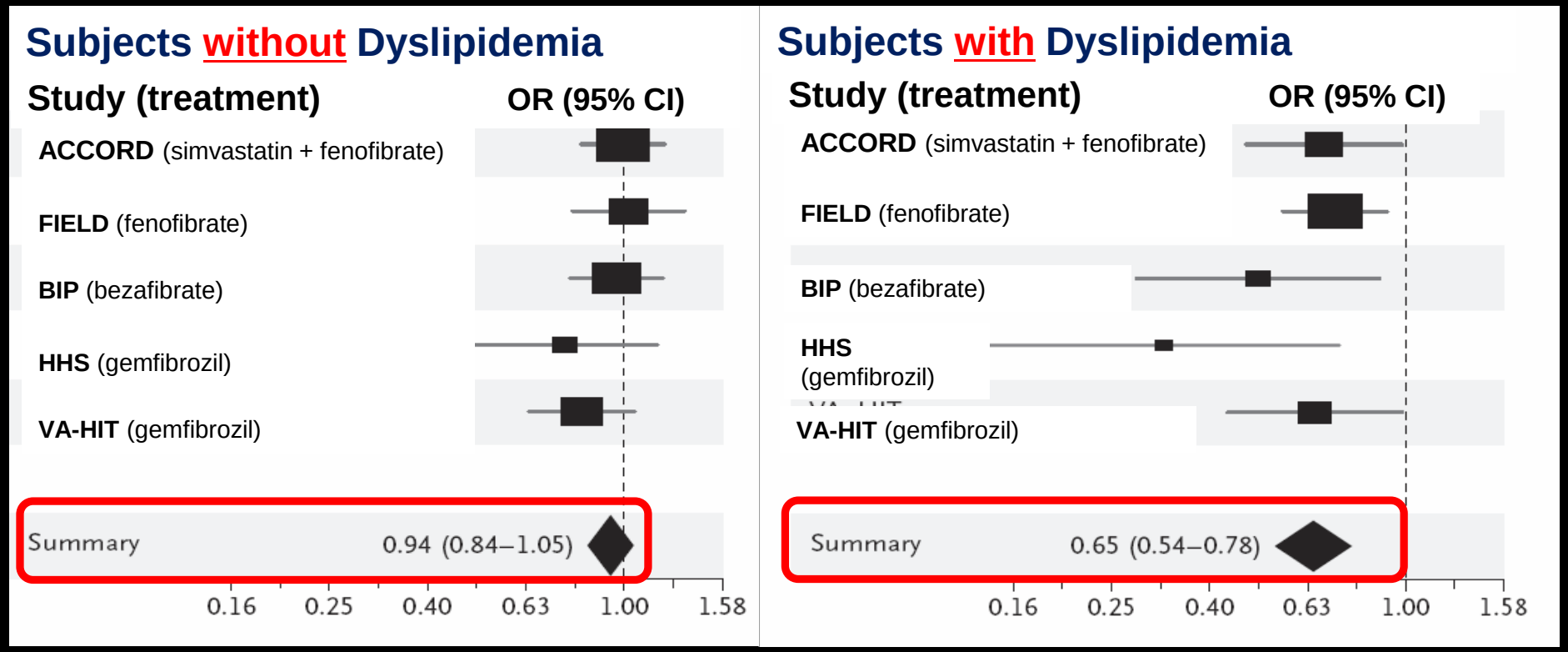
Trial (Subgroup, mg/dL) (Drug)	Risk difference vs placebo (P-value)	
	All subjects	HTG subgroup
WOSCOPS (TG ≥148) (Pravastatin)	**–31% (<0.001)**	**–32% (0.003)**
CARE (TG ≥144) (Pravastatin)	**–24% (0.003)**	**–15% (0.07)**
PPP Project (TG ≥200) (Pravastatin)	**–23% (<0.001)**	**–15% (0.029)**
4S (TG >159, HDL-C <39) (Simvastatin)	**–34% (<0.001)**	**–52% (<0.001)**
JUPITER (TG ≥150) (Rosuvastatin)	**–44% (<0.001)**	**–21% (NS)**
CTT (TG >177) (Various)	**–21% (<0.001)**	**–24% (<0.001)**

Median follow-up: ≥5 yrs.

CARE=Cholesterol and Recurrent Events Trial; CTT=Cholesterol Treatment Trialists; JUPITER=Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; NS=not significant; PPP=Prospective Pravastatin Pooling; 4S=Scandinavian Simvastatin Survival Study; WOSCOPS=West of Scotland Coronary Prevention Study. Ballantyne CM et al. Circulation. 2001;104:3056-51. CTT Collaborators. Lancet. 2005;366:1267-78. Maki KC et al. J Clin Lipidol. 2012;6:413-26.

Fibrates Reduce CHD Risk in Patients with HTG and Low HDL-C

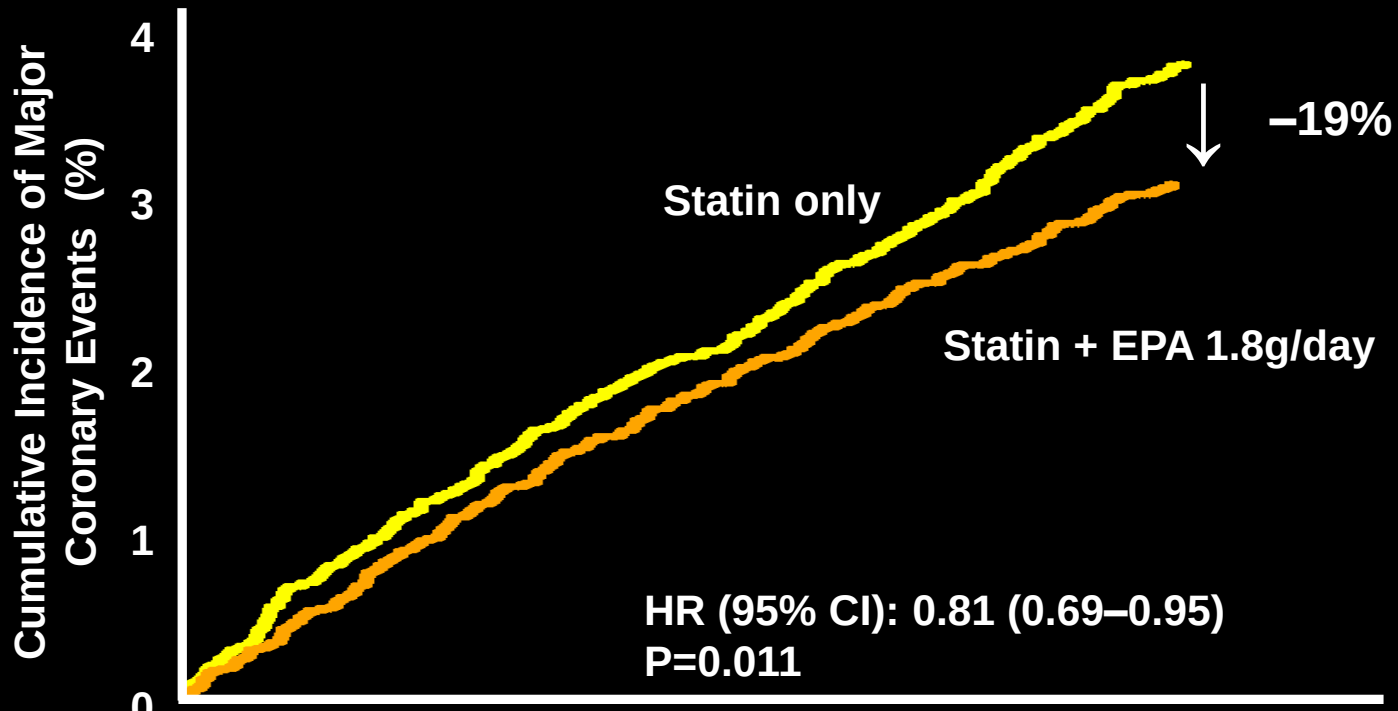
A meta-analysis of randomized fibrate trials



TG ≥204 mg/dL, HDL-C ≤34mg/dL

Sacks FM et al. N Engl J Med. 2010;363:692-4.

JELIS: EPA Reduced Major Coronary Events* in Hypercholesterolemic Patients on Statins



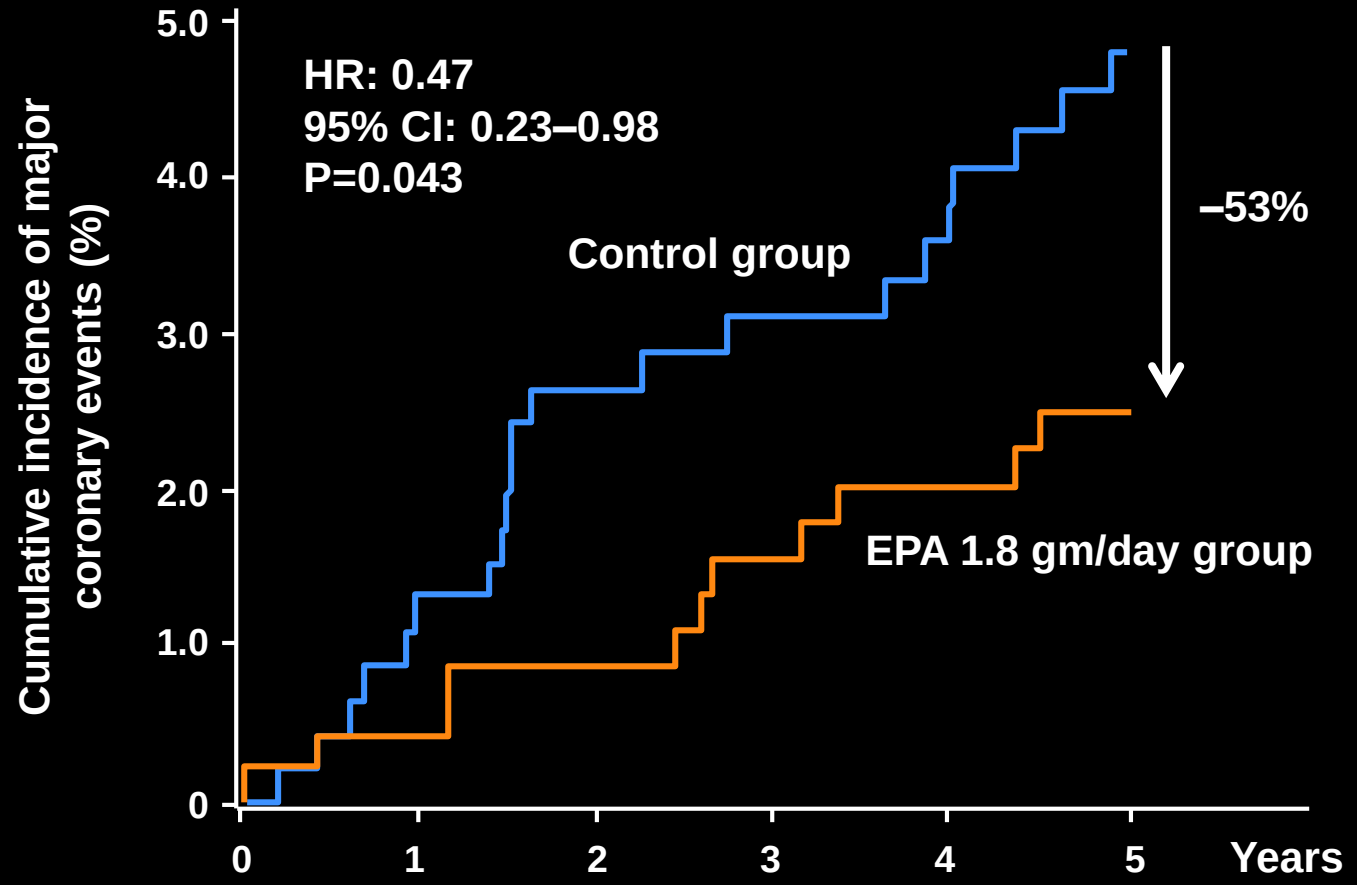
No. at Risk	0	1	2	3	4	5	Years
Control	9319	8931	8671	8433	8192	7958	
EPA	9326	8929	8658	8389	8153	7924	

N=18,645 Japanese pts with TC ≥251 mg/dL prior to baseline statin Rx. Baseline TG=153 mg/dL. Statin up-titrated to 20 mg pravastatin or 10 mg simvastatin for LDL-C control.

*Primary endpoint: sudden cardiac death, fatal and non-fatal MI, unstable angina pectoris, angioplasty, stenting, or coronary artery bypass graft.

Yokoyama M et al. Lancet. 2007;369:1090-8.

JELIS: Larger Decrease in MACE in Those with TG >150 mg/dL & HDL-C <40 mg/dL*



No. of patients						
Control	475	444	432	414	400	392
EPA	482	455	443	427	413	403

HR and P-value adjusted for age, gender, smoking, diabetes, and HTN

*Pre-specified. MACE=major adverse CV event.

Saito Y et al. Atherosclerosis. 2008;200:135-40.

Summary

- **HTG is a growing public health burden**
  - Common in central obesity and T2DM
  - Causal factor for ASCVD events
- **HTG relates to and causes ASCVD**
  - TG-containing lipoproteins have a full load of cholesterol
  - Release of fatty acids triggers local inflammation
  - Genetic epidemiology studies suggest a causal role
  - Intervention studies show residual risk in those with HTG
- **TG lowering and CVD risk**
  - Statins reduce risk less in HTG
  - Fibrates provide suggestion of benefits
  - OM-3 fats provide suggestion of benefits
  - Definitive studies in progress