

XIII CONGRESSO NAZIONALE Milano 25-26 Ottobre 2019

Four Points by Sheraton Milan Center

GIORNATA PRE-CONGRESSUALE

Ricerca clinica e di base nell'ambito dell'aterosclerosi

In collaborazione con SISA Regione Lombardia

Milano 24 Ottobre 2019

Four Points by Sheraton Milan Center

Hot topics

Ipertrigliceridemia, remnant e rischio cardiovascolare

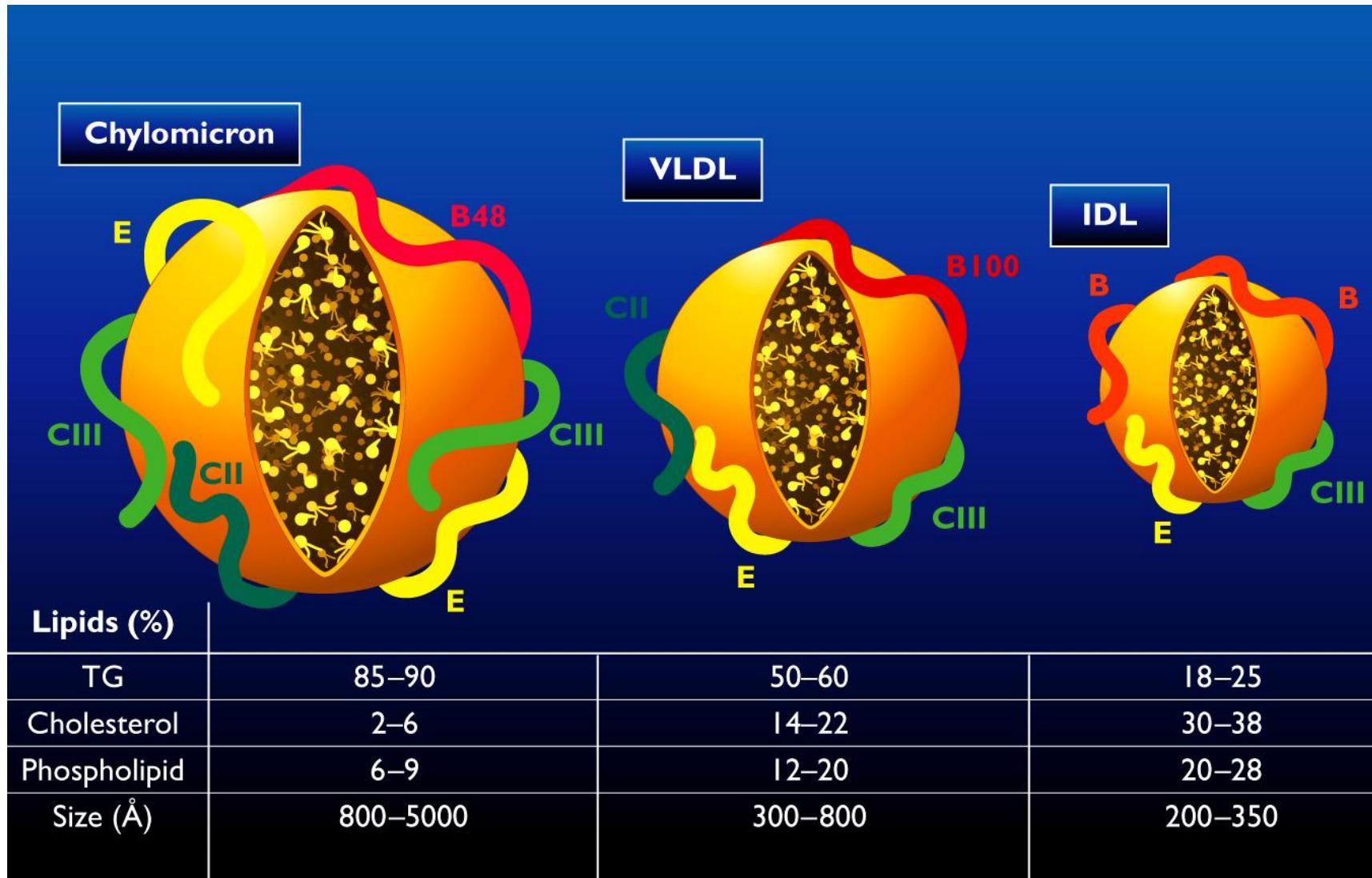
Giuseppe Danilo Norata

Department of Excellence in Pharmacological and Biomolecular Sciences,
University of Milan, Italy

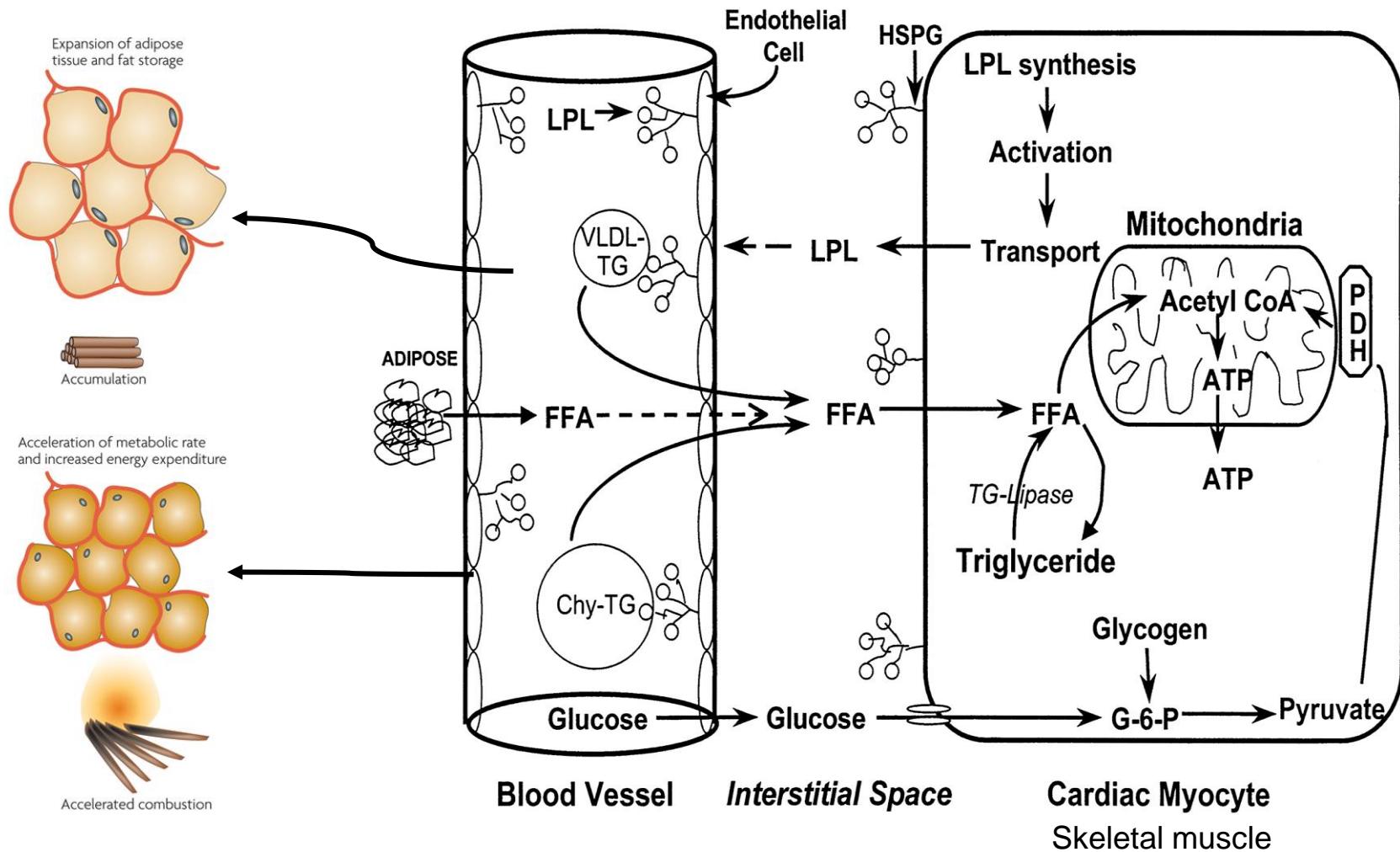


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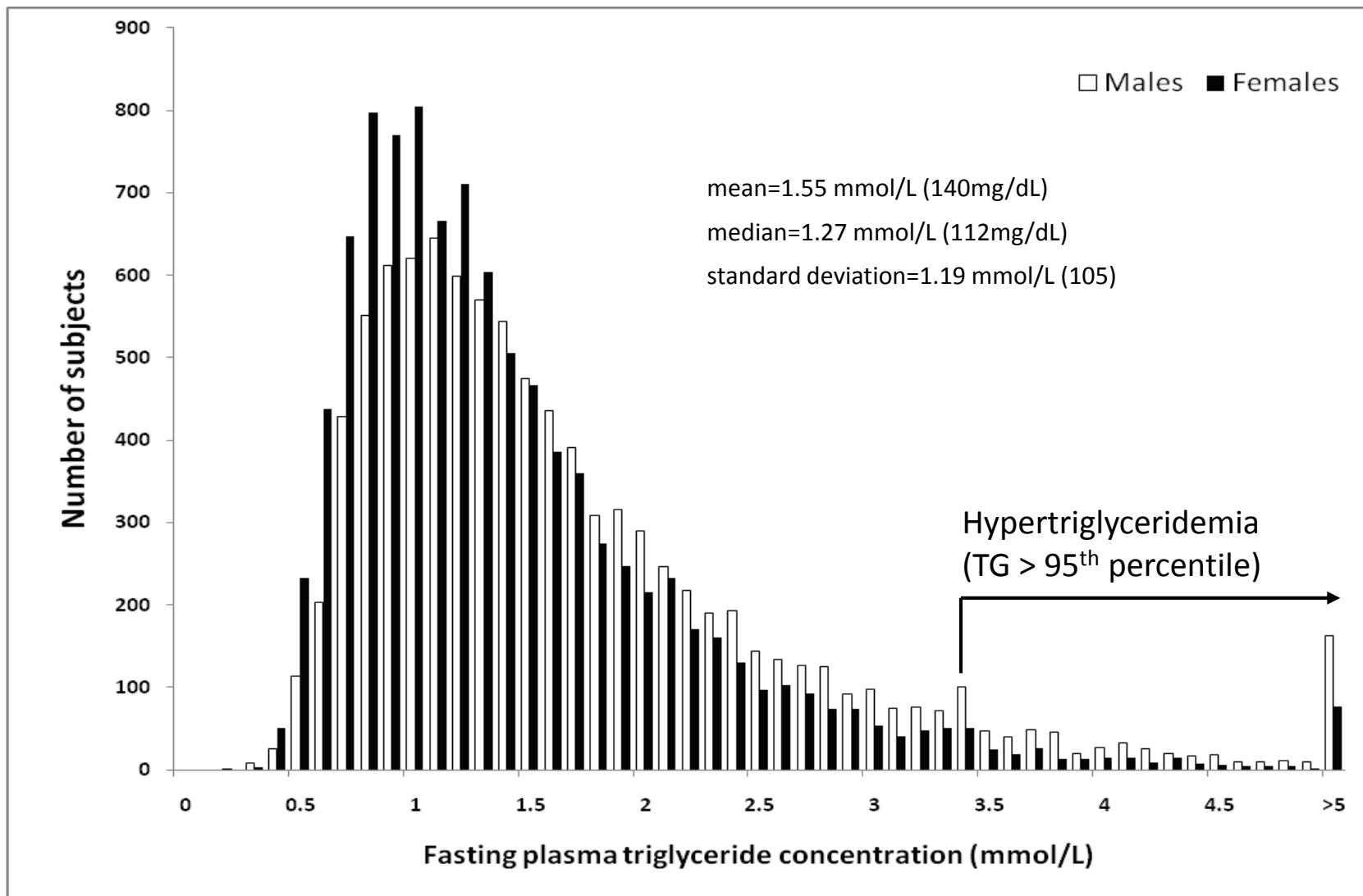
TG-rich lipoproteins in physiology



TG-rich lipoproteins in physiology

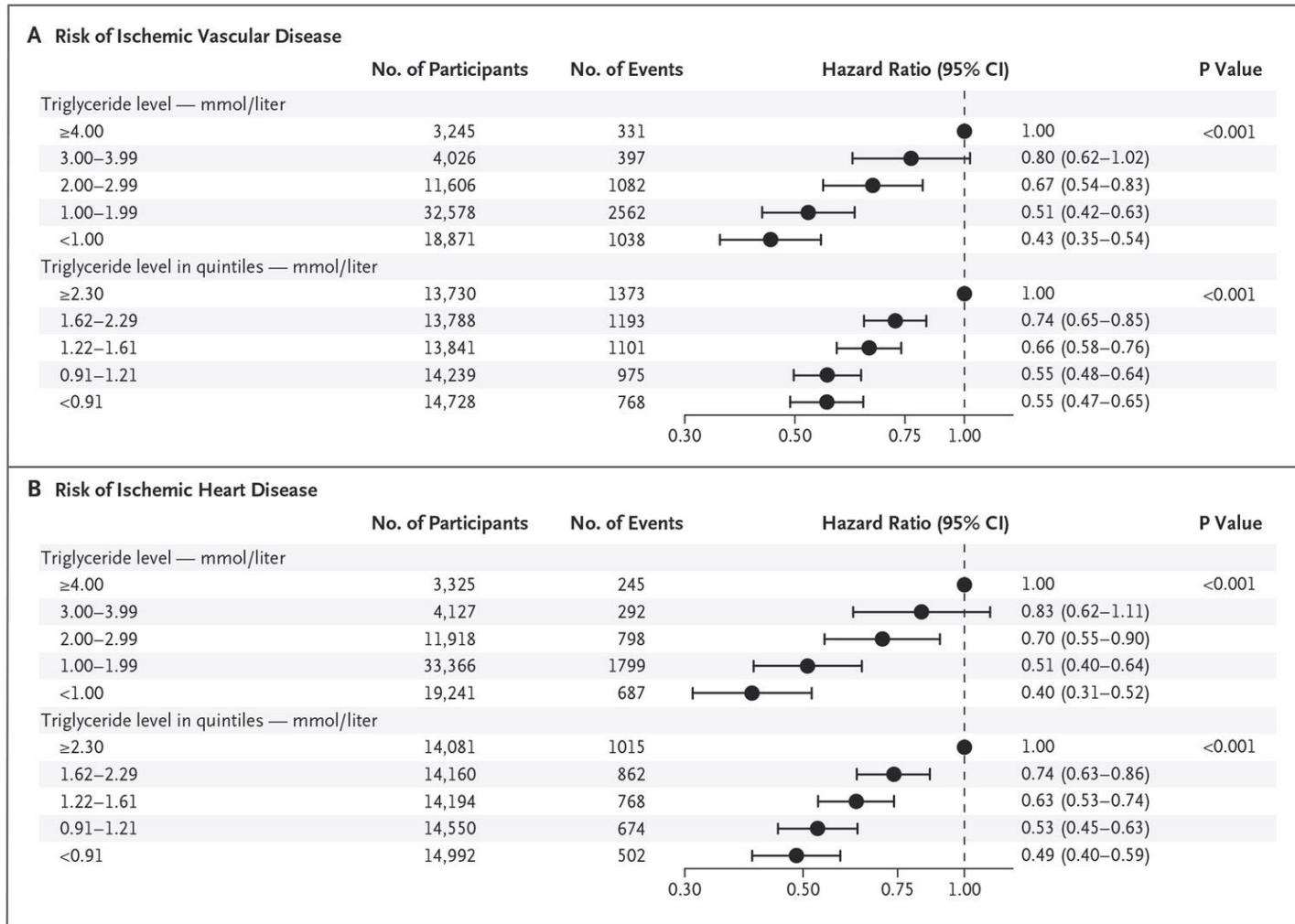


Plasma TG distribution



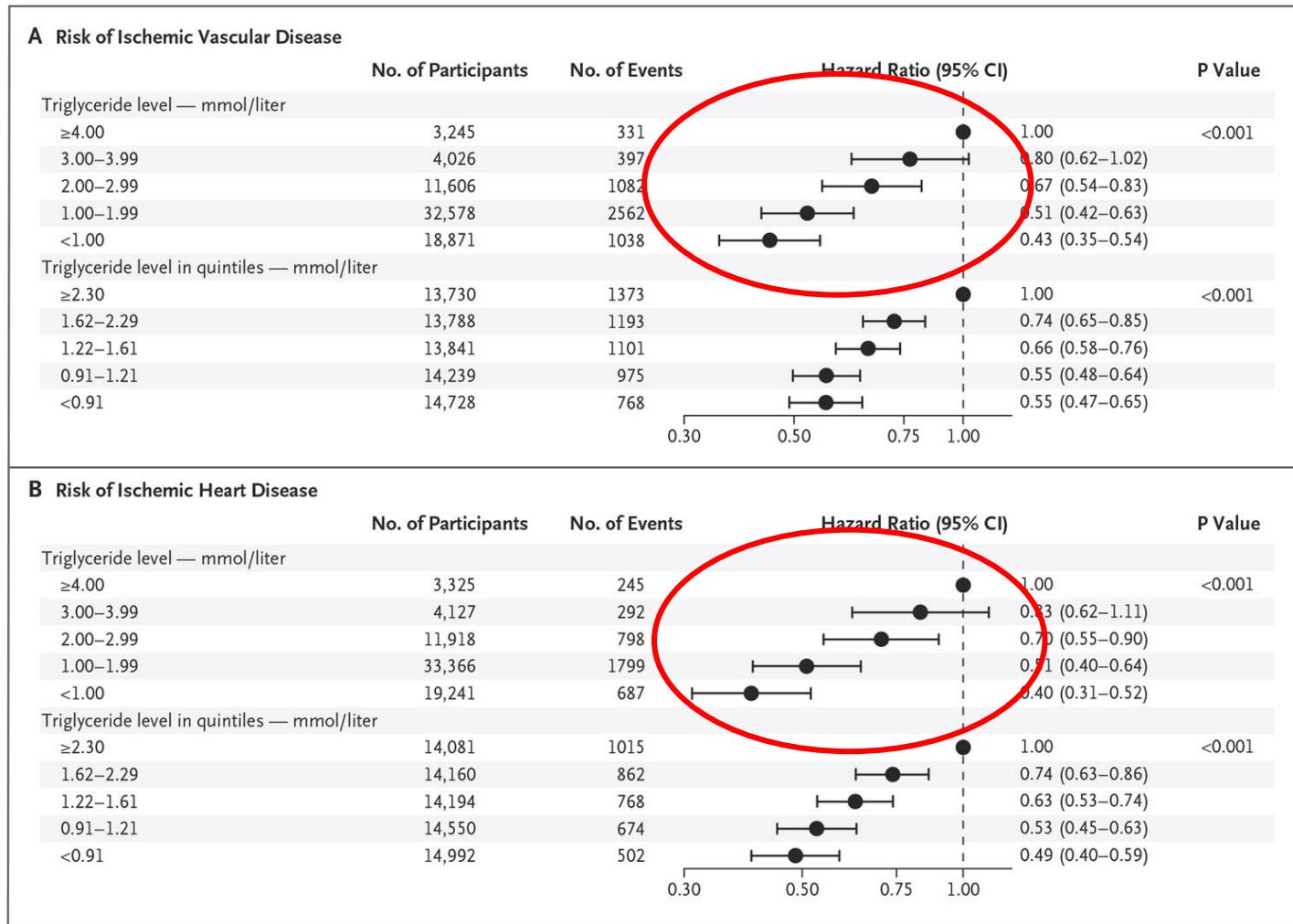
Canadian Heart Health Surveys (N=19390)

Risks of Ischemic Vascular Disease and Ischemic Heart Disease as a Function of Plasma Levels of Triglycerides.



Jørgensen AB et al. N Engl J Med 2014;371:32-41.

Risks of Ischemic Vascular Disease and Ischemic Heart Disease as a Function of Plasma Levels of Triglycerides.



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Clinical measures of atherogenic lipoproteins

Lipo-protein	direct measures	Indirect estimators		
Lp(a)	Lp(a)	nonHDL-cholesterol	apoB	
LDL	LDL-C, LDL-P			
IDL			?	
CMR	remnant-C (measured)			
VLDL				
CM				triglycerides

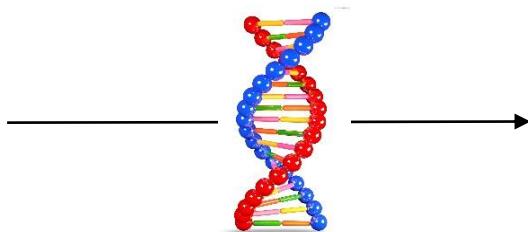
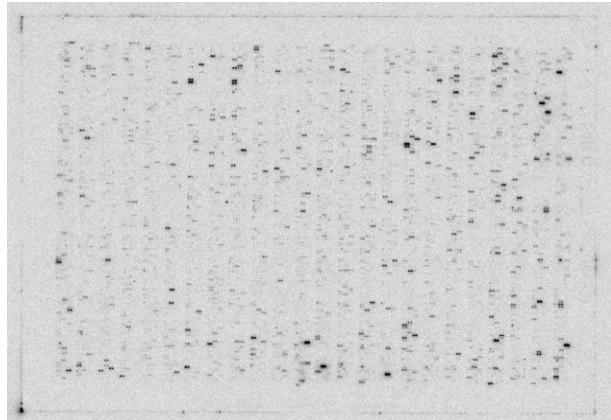
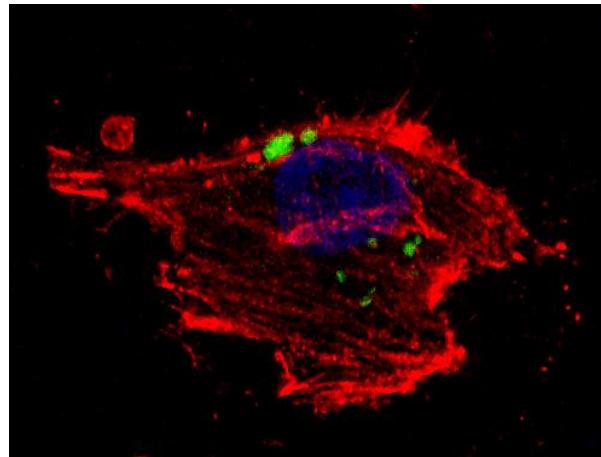
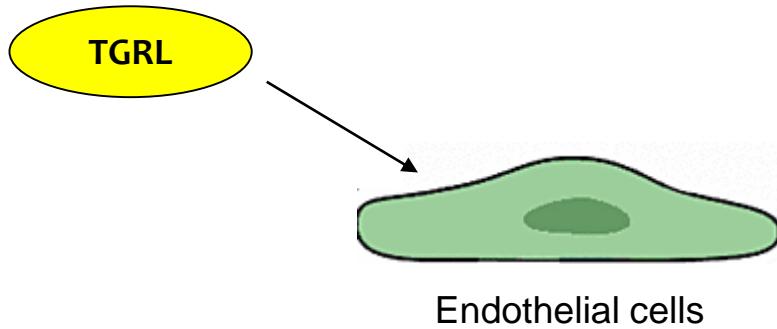
Lp(a) = lipoprotein(a);

LDL = low density lipoprotein, IDL = intermediate density lipoprotein, VLDL = very low density lipoprotein,

CM = chyomicron; CMR = chylomicron remnant

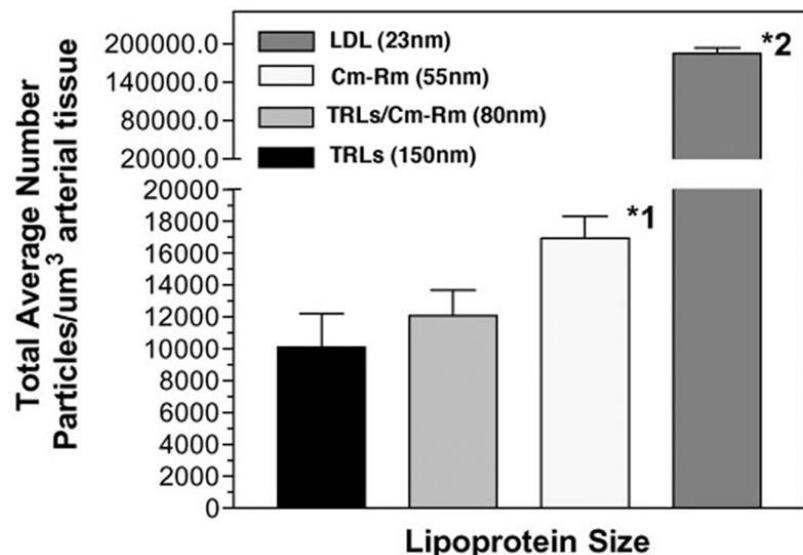
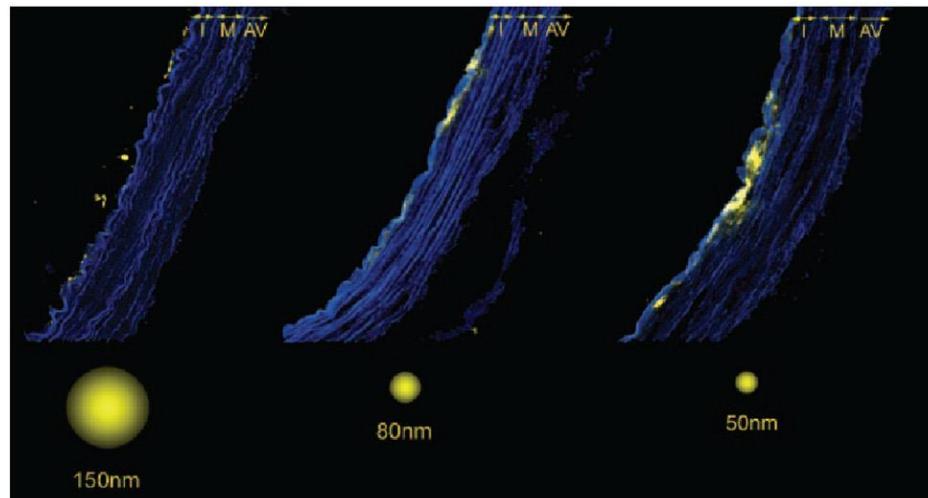
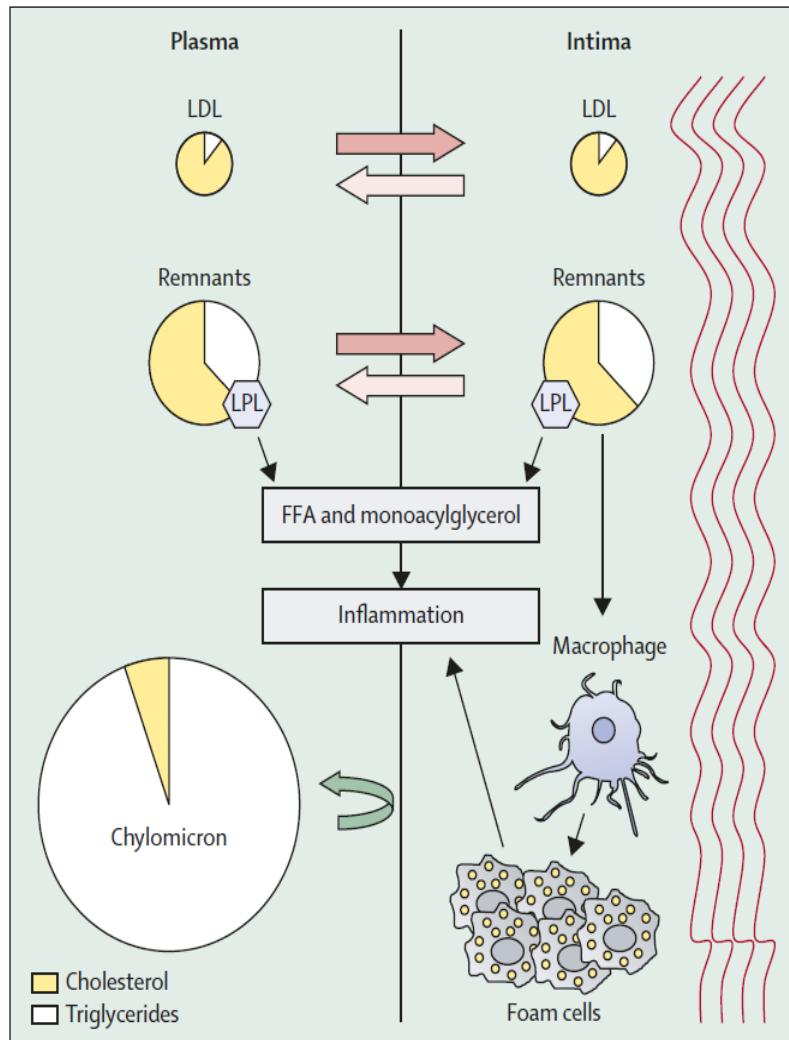
TG plasma levels reflect
the atherogenicity of TG Rich Lipoproteins,
which could be the consequence on their cholesterol content.

TG-rich lipoproteins promote endothelial dysfunction



Increased endothelial cells activation and enhanced pro-inflammatory response (post-prandial phase)

Suggested role of triglyceride-rich lipoproteins and their remnants in atherosclerosis

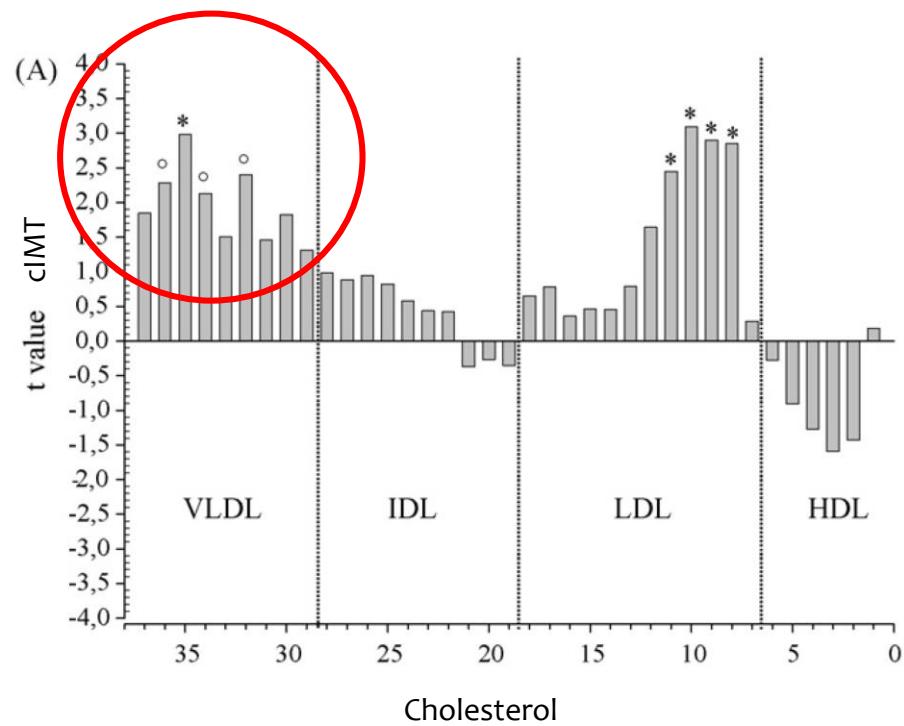
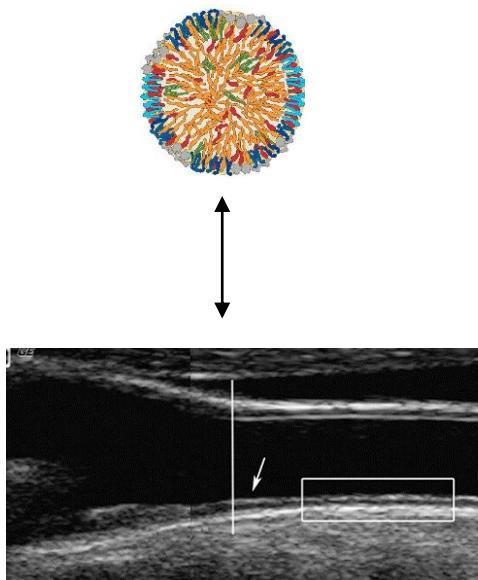


Nordestgaard and Varbo; Lancet 2014; 384: 626–635
Rosensen et al. J Am Coll Cardiol 2014;64:2525–40.

1) Does cholesterol content in TG-rich lipoproteins fractions associate to atherosclerosis?

Small dense LDL and VLDL predict common carotid artery IMT and elicit an inflammatory response in peripheral blood mononuclear and endothelial cells

Giuseppe Danilo Norata ^{a,b,*}, Sara Raselli ^{a,b,1}, Liliana Grigore ^b, Katia Garlaschelli ^b, Daniela Vianello ^c, Sandra Bertocco ^c, Alberto Zambon ^c, Alberico Luigi Catapano ^{a,b}



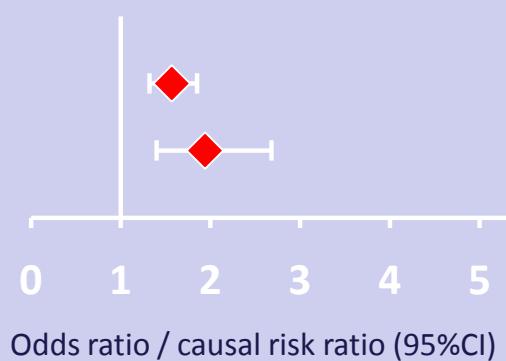
- 1) Does cholesterol content in TG-rich lipoproteins fractions associate to atherosclerosis? 
- 2) Does cholesterol content in TG-rich lipoproteins fractions increase CVD risk?

Triglyceride doubling in levels

	N total	N events	Risk estimate
Observational	10,391	1,098	1.6
Causal using genetics	60,113	5,705	1.9

From Jørgensen Eur Heart J 2013; 34: 1826-33

Myocardial infarction

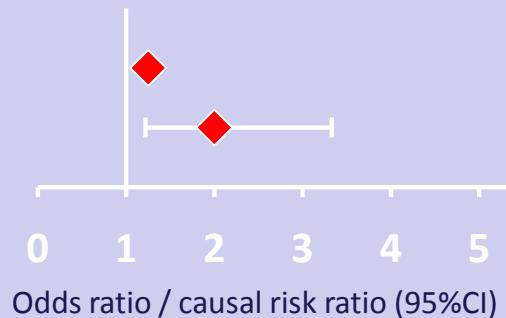


Triglyceride increase of 1 mmol/L

Observational	13,957	9,991	1.2
Causal using genetics	10,208	4,005	2.0

From Thomsen Clin Chem 2014; 60: 737-46

All-cause mortality



Remnant cholesterol
increase of 1 mmol/L

Observational

Causal using genetics

N total

56,667

73,513

N events

2,874

11,984

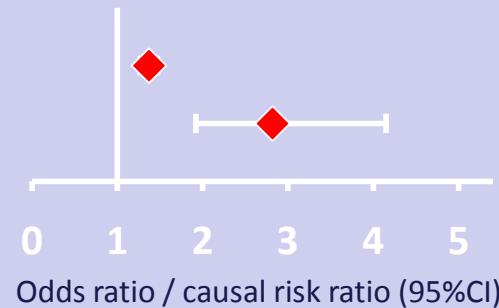
Risk estimate

1.4

2.8

From Varbo JACC 2013; 61: 427-36

Ischemic heart disease



Remnant cholesterol
doubling in levels

Observational

Causal using genetics

10,391

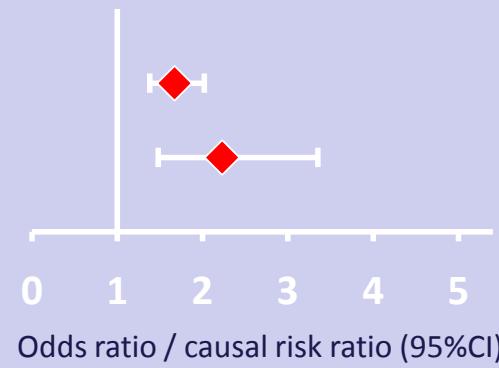
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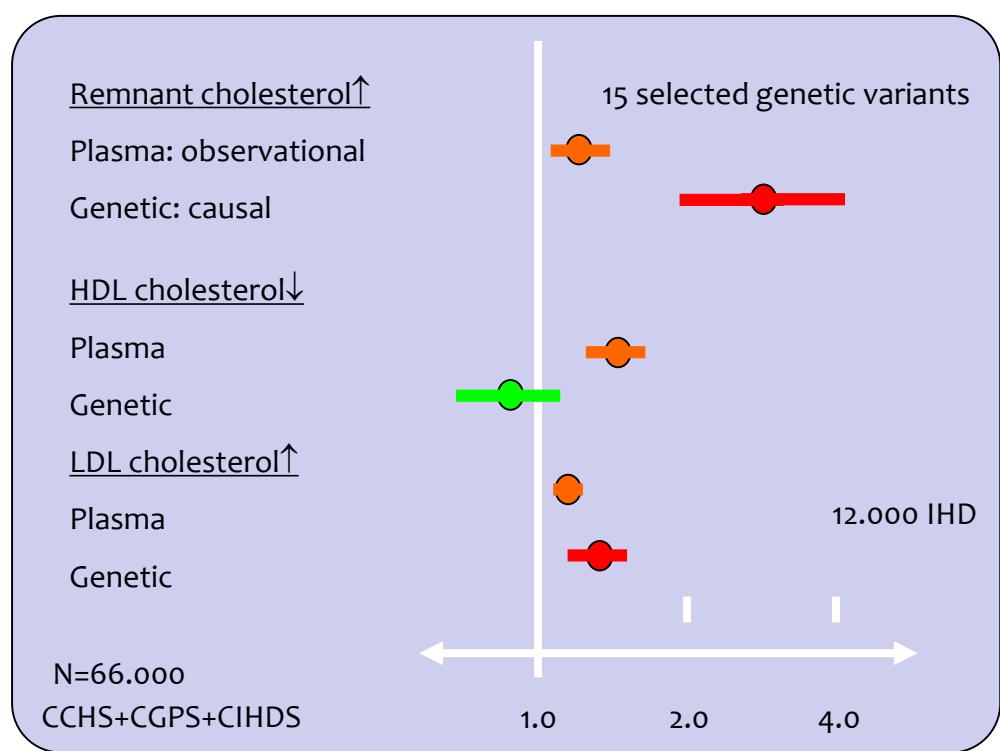
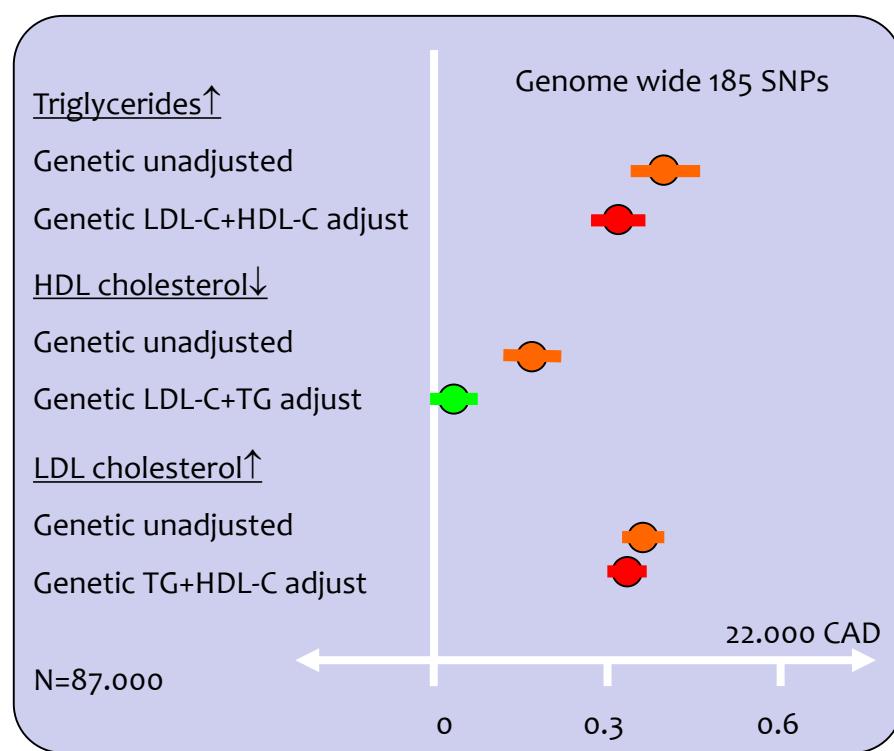
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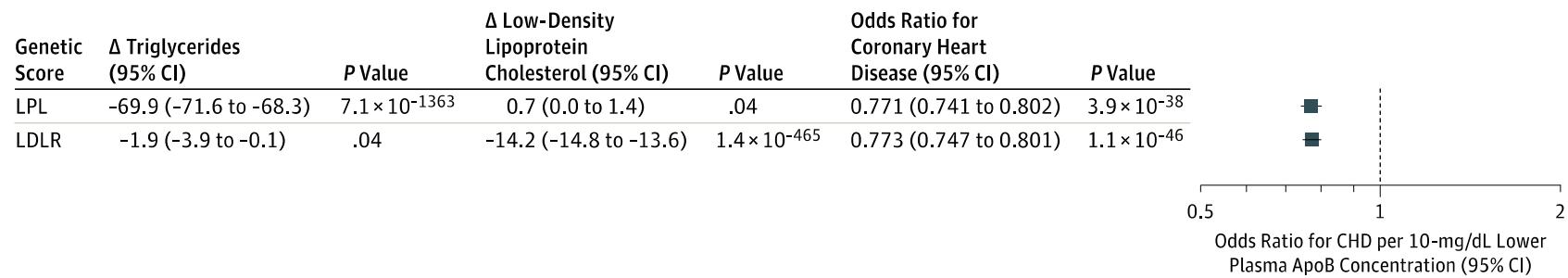
- 1) Does cholesterol content in TG-rich lipoproteins fractions associate to atherosclerosis? 
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- 3) Do genetics variants affecting TGRL metabolism impact remnant chol levels and CVD risk independently of LDL-C?

Genetics variants affecting lipid traits



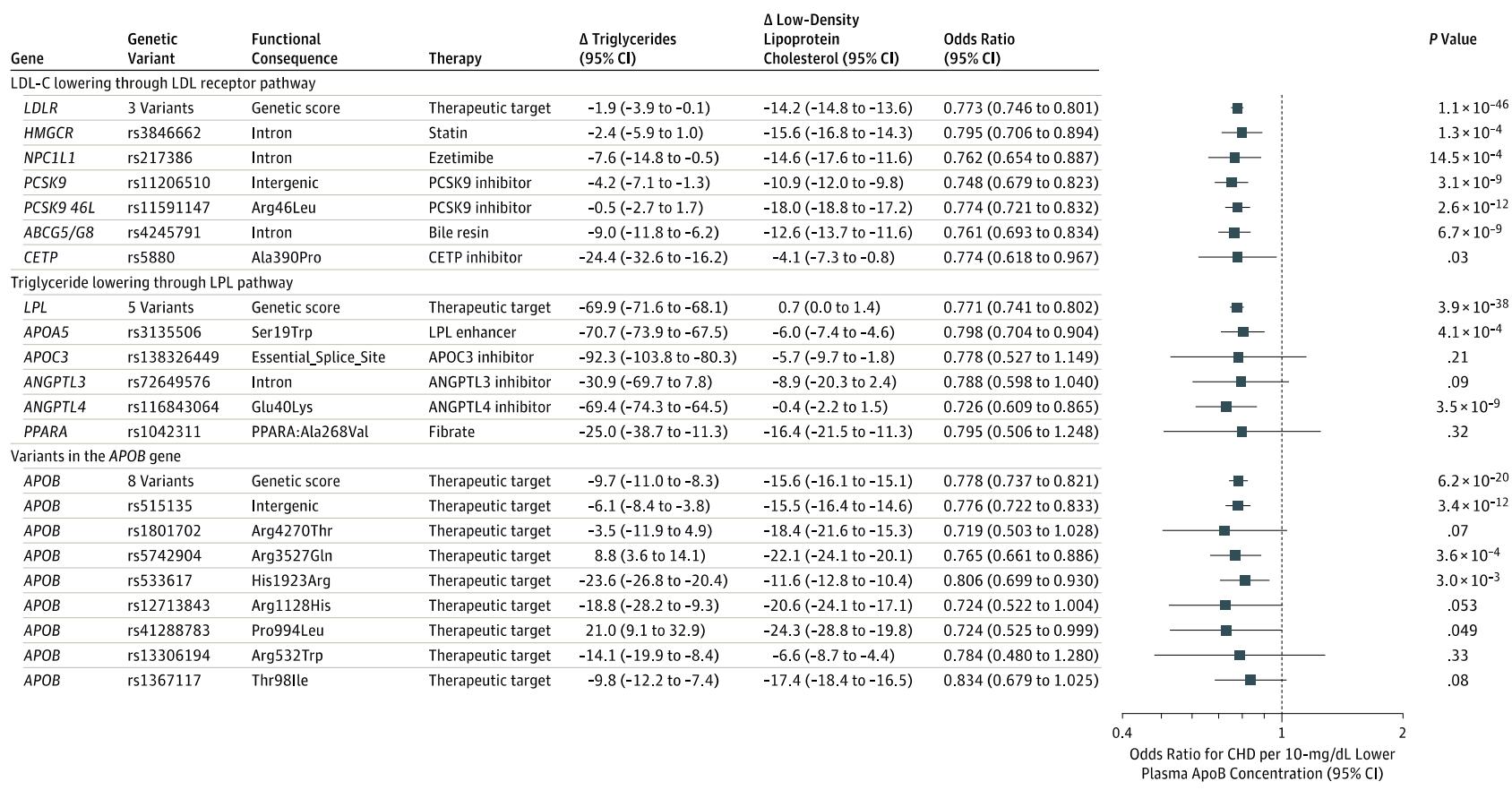
Reduction in Apolipoprotein B (ApoB) and Lower Risk of Coronary Heart Disease is independent of the mechanism of apoB reduction.

Figure 1. Associations Between the Lipoprotein Lipase (*LPL*) and LDL Receptor Gene (*LDLR*) Genetic Scores With Triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Risk of Coronary Heart Disease (CHD) per 10-mg/dL Lower Concentration of Apolipoprotein B (ApoB)-Containing Lipoproteins

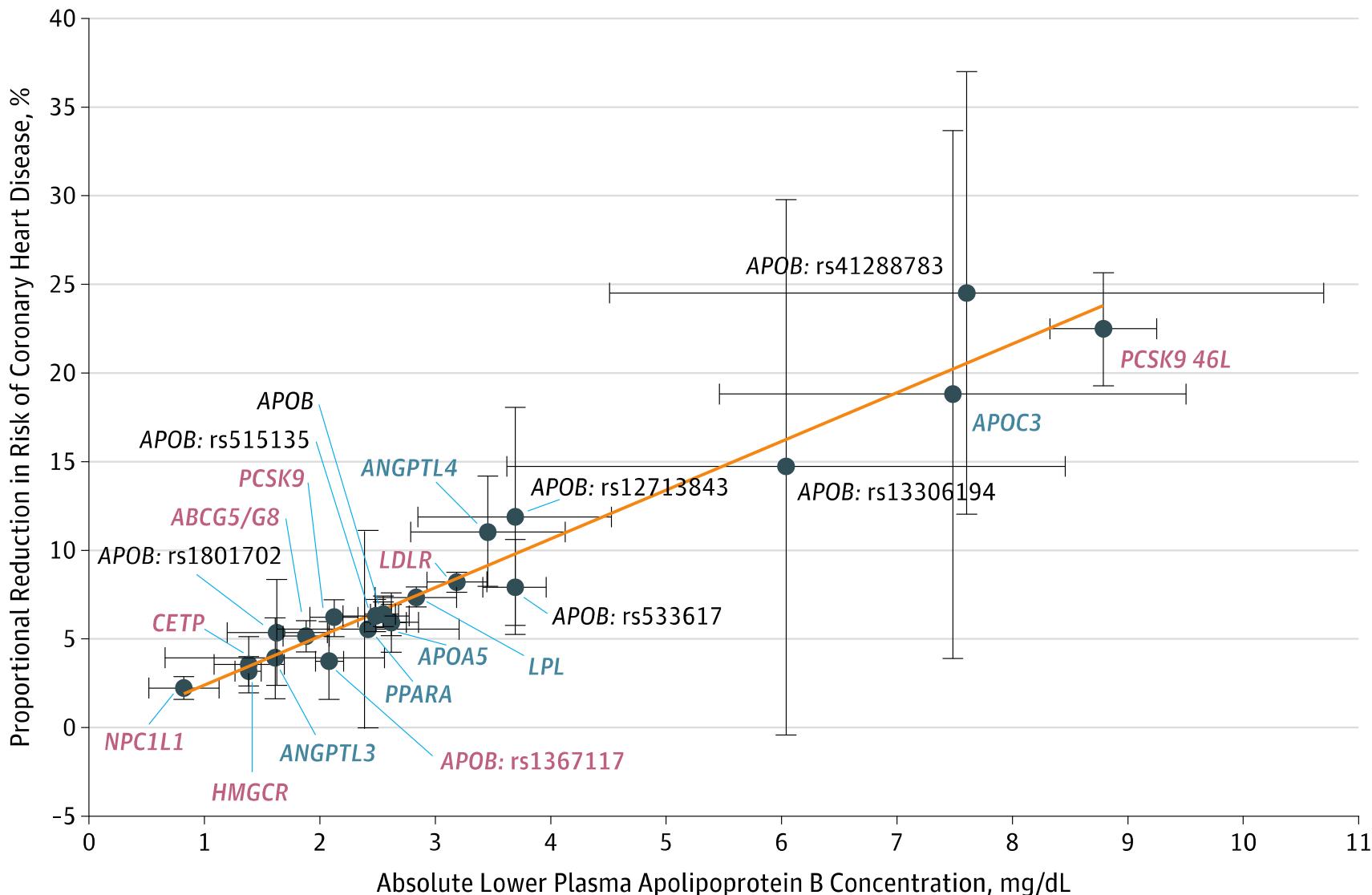


Reduction in Apolipoprotein B (ApoB) and Lower Risk of Coronary Heart Disease is independent of the mechanism of apoB reduction.

Figure 2. Association of Genetic Variants and Genetics Scores With Triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Risk of Coronary Heart Disease (CHD) per 10-mg/dL Lower Concentration of Apolipoprotein B (ApoB)-Containing Lipoproteins



Log-Linear Association Between Absolute Differences in Apolipoprotein B (ApoB) and Lower Risk of Coronary Heart Disease



- 1) Does cholesterol content in TG-rich lipoproteins fractions associate to atherosclerosis? 
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- 3) Do genetics variants affecting TGRL metabolism impact remnant chol levels and CVD risk independently of LDL-C? 
- 4) Do pharmacological approaches aimed at targeting TG metabolism decrease cholesterol content in TG-rich lipoproteins and CVD risk?

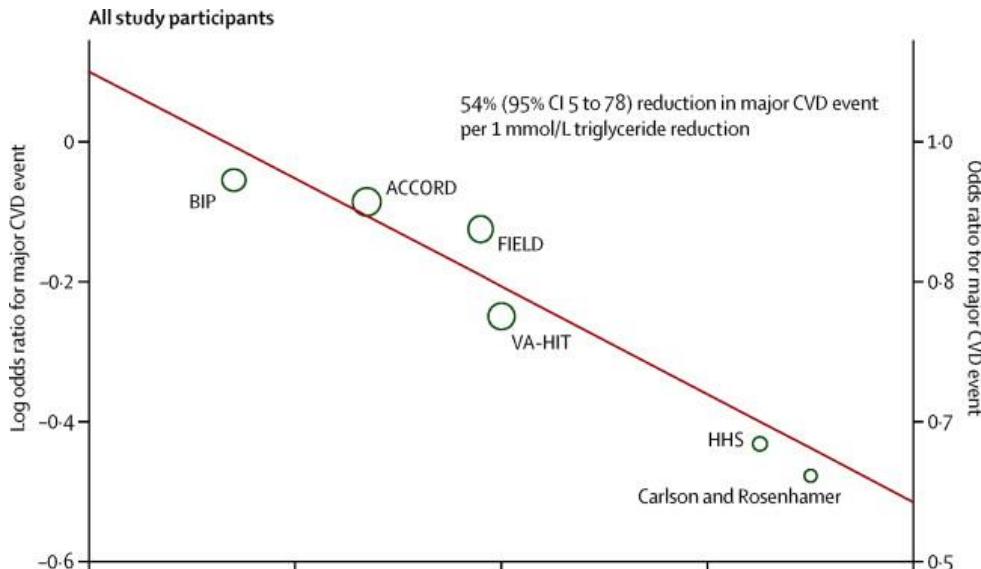
Comparison of ACCORD subgroup results with those from prior fibrate studies

Trial (Drug)	Primary Endpoint: Cohort (P-Value)	
HHS (Gemfibrozil)	-34% (0.02)	
BIP (Bezafibrate)	-7.3% (0.24)	
FIELD (Fenofibrate)	-11% (0.16)	
ACCORD (Fenofibrate)	-8% (0.32)	

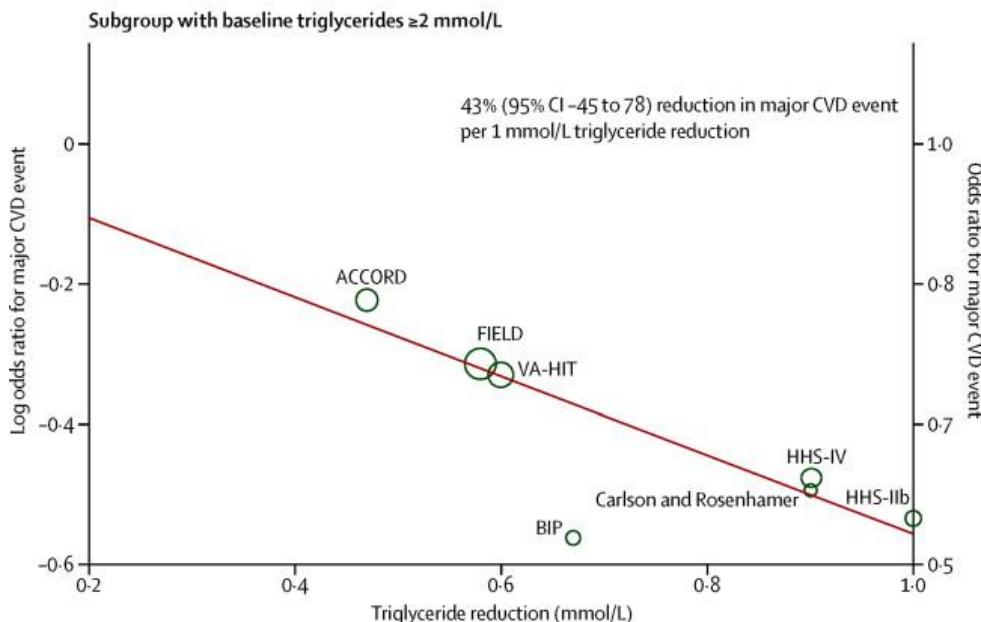
Comparison of ACCORD subgroup results with those from prior fibrate studies

Trial (Drug)	Primary Endpoint: Cohort (P-Value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup
HHS (Gemfibrozil)	-34% (0.02)	TG >200 mg/dl (2.3 mmol/L) LDL-C/HDL-C >5.0	-71% (0.005)
BIP (Bezafibrate)	-7.3% (0.24)	TG ≥200 mg/dl (2.3 mmol/L)	-39.5% (0.02)
FIELD (Fenofibrate)	-11% (0.16)	TG ≥204 mg/dl (2.3 mmol/L) HDL-C <42 mg/dl (1.1 mmol/L)	-27% (0.005)
ACCORD (Fenofibrate)	-8% (0.32)	TG ≥204 mg/dl (2.3 mmol/L) HDL-C ≤34 mg/dl (0.8 mmol/L)	-31% (p<0.01)

Results from Clinical Trials with fibrates



baseline triglycerides
≥2 mmol/L
were included.



- 1) Does cholesterol content in TG-rich lipoproteins fractions associate to atherosclerosis? 
- 2) Does cholesterol content in TG-rich lipoproteins fractions increase CVD risk? 
- 3) Do genetics variants affecting TGRL metabolism impact remnant chol levels and CVD risk independently of LDL-C? 
- 4) Do pharmacological approaches aimed at targeting TG metabolism decrease cholesterol content in TG-rich lipoproteins and CVD risk? 

Conclusions

- TG plasma levels reflect the atherogenicity of TG Rich Lipoproteins, which could be the consequence of their cholesterol content.
- Mendelian randomization studies support the critical role of apoB containing lipoproteins in promoting CHD, with a similar impact of “*per particle*” reduction of LDL or remnants on CHD.
- Reducing TG levels in subjects with high TG , reduces CVD events.
- TG particles play a major role in pancreatitis.