

SNAF Symposium

Metabolic Syndrome and Stroke



Kwang-Yeol Park

Dep. of Neurology, Chung-Ang University, Seoul South Korea

How to treat the following case

- 53/Male
- Lacunar infarction in Lt. CR and Rt. proximal ICA stenosis (35%)
- 170cm / 88 kg (BMI 30.4)
- waist circumference 102cm

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- Total cholesterol 200 mg/dL
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- Fasting glucose 104 mg/dL, HbA1c 5.5%
- Total cholesterol 200 mg/dL
- LDL-cholesterol 98 mg/dL
- HDL-cholesterol 42 mg/dL
- TG 300 mg/dL

Metabolic syndrome

Table – Criteria for clinical diagnosis of the metabolic syndrome.

Measure	Categorical cut points
Elevated waist circumference ^a	≥ 102 cm in males ≥ 88 cm in females
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator ^b)	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator ^b)	< 40 mg/dL (1.0 mmol/L) in males < 50 mg/dL (1.3 mmol/L) in females
Elevated blood pressure (anti-hypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥ 130 and/or diastolic ≥ 85 mmHg
Elevated fasting glucose ^c (drug treatment of elevated glucose is an alternate indicator)	≥ 100 mg/dL

HDL-C indicates high-density lipoprotein cholesterol.

^a Waist circumference cut points used in the USA. Cut points for other populations are listed in the parent document [4].

^b The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking one of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose n-3 fatty acids presume high triglycerides.

^c Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the current criteria [4].

Metabolic syndrome

표 2. NCEP–ATP III 진단기준

Three or more of the following five risk factors:	
Risk factor	Defining level
Central obesity	Waist circumference
Men	>102cm(>40in)
Women	>88cm(>35in)
Triglyceride	≥150mg/dL(1.7mmol/L)
HDL cholesterol	
Men	<40mg/dL(1.03mmol/L)
Women	<50 mg/dL(1.29 mmol/L)
Blood pressure	≥130 / ≥85mmHg
Fasting glucose	≥110mg/dL(6.1mmol/L)

표 5. 인종에 따른 허리둘레값의 기준

Country/Ethnic group	Waist circumference	
Europids	male female	≥ 94cm ≥ 80cm
In the USA, the ATP III values are likely to continue to be used for clinical purpose		
South Asians	male female	≥ 90cm ≥ 80cm
Chinese	male female	≥ 90cm ≥ 80cm
Japanese	male female	≥ 85cm ≥ 90cm
Ethnic South and Central Americans	Use South Asian recommendations until more specific data are available	
Sub-Saharan Africans	Use European data until more specific data are available	
Eastern Mediterranean and Middle East(Arab) populations	Use European data until more specific data are available	

Metabolic syndrome

표 7. AHA / NHLBI 진단기준

Measure (any 3 of 5)	Categorical Cutpoints
Elevated waist circumference	>102cm in men ≥88cm in women
Elevated triglycerides	≥150mg/dL (1.7mmol/L) or on drug treatment
Reduced HDL-C	<40mg/dL (0.9mmol/L) in men <50mg/dL (1.1mmol/L) in women or on drug treatment
Elevated blood pressure	≥130mmHg systolic BP or ≥85mmHg diastolic BP or on antihypertensive drug treatment in a patient with a history of hypertension
Elevated fasting glucose	≥100mg/dL or on drug treatment for elevated glucose

표 5. 인종에 따른 허리둘레값의 기준

Country/Ethnic group	Waist circumference
Europids	
In the USA, the ATP III values are likely to continue to be used for clinical purpose	male ≥ 94cm female ≥ 80cm
South Asians	male ≥ 90cm female ≥ 80cm
Chinese	male ≥ 90cm female ≥ 80cm
Japanese	male ≥ 85cm female ≥ 90cm
Ethnic South and Central Americans	Use South Asian recommenda- tions until more specific data are available
Sub-Saharan Africans	Use European data until more specific data are available
Eastern Mediterranean and Middle East(Arab) populations	Use European data until more specific data are available

Metabolic syndrome

- Energy excess / obesity
- Elevated BP
- Insulin resistance / elevated blood glucose
- Atherogenic dyslipidemia
 - Low HDL-cholesterol
 - High TG

Pathogenesis of metabolic syndrome

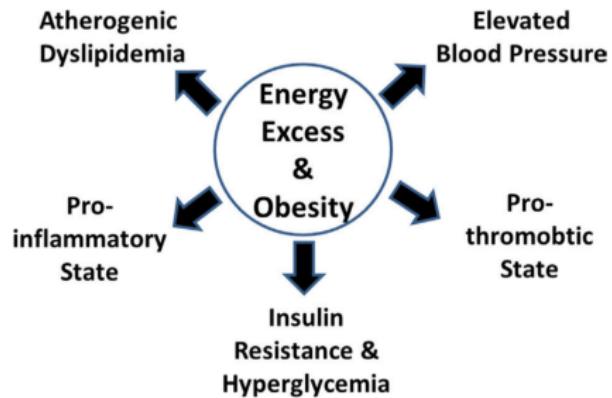


Fig. 1 – Relationships between energy excess/obesity and risk factors of the metabolic syndrome. Available evidence indicates that excess energy intake and concomitant obesity are major causes of all the metabolic risk factors.

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- TG 300 mg/dL

Diet: Caloric restriction

Do not eat anything delicious!

- Reasonable goal might be 10%
- Avoid saturated fat
- Caloric restriction could improve metabolic syndrome
 - Beneficial in weight reduction, lowering BP, and glucose control.
- Weight reduction 10% + 150min/week exercise could cut the rate of conversion of pre-DM to DM in half

How to treat the following case

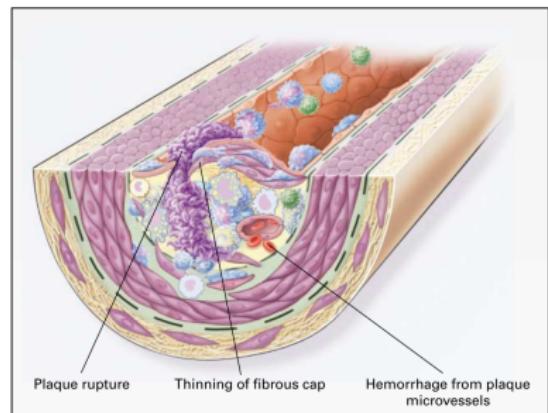
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Good predictor or Cause of Atherosclerosis ?

- ① LDL-cholesterol
- ② HDL-cholesterol
- ③ Triglyceride
- ④ Non-HDL-cholesterol

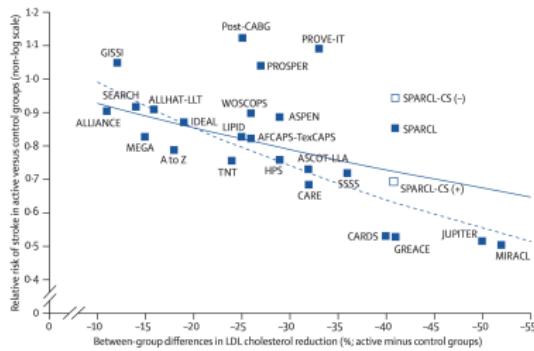
Atherosclerosis: Leading cause of ischemic stroke

- Artery wall thickens as a result of invasion and accumulation of white blood cells with cholesterol fatty substances, calcium and fibrin.
- Intima of medium and large sized systemic arteries are involved.



Ross R. N Engl J Med 1999

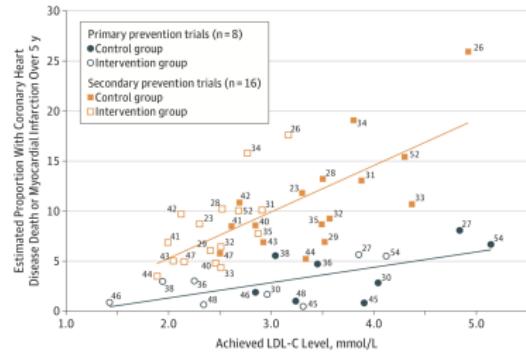
Dose-response relationship in Stroke/IHD and LDL-C



Estimates of relative risk reduction

- 10% LDL reduction: relative risk reduction 7.5% (2.3-12.5) overall
relative risk reduction 13.5% (7.7-18.8) for primary prevention of stroke
- 1 mmol/l (39 mg/dl) LDL reduction: relative risk reduction 21.1% (6.3-33.5) overall
relative risk reduction 35.9% (21.7-47.6) for primary prevention of stroke

Figure 4. Association Between Achieved Low-Density Lipoprotein Cholesterol (LDL-C) and Major Coronary Event Rates From 24 Trials of Established Interventions That Lower LDL-C Predominantly Through Upregulation of LDL Receptor Expression



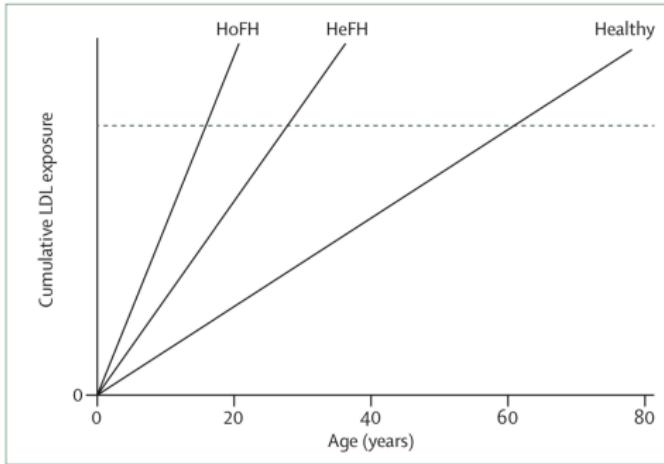
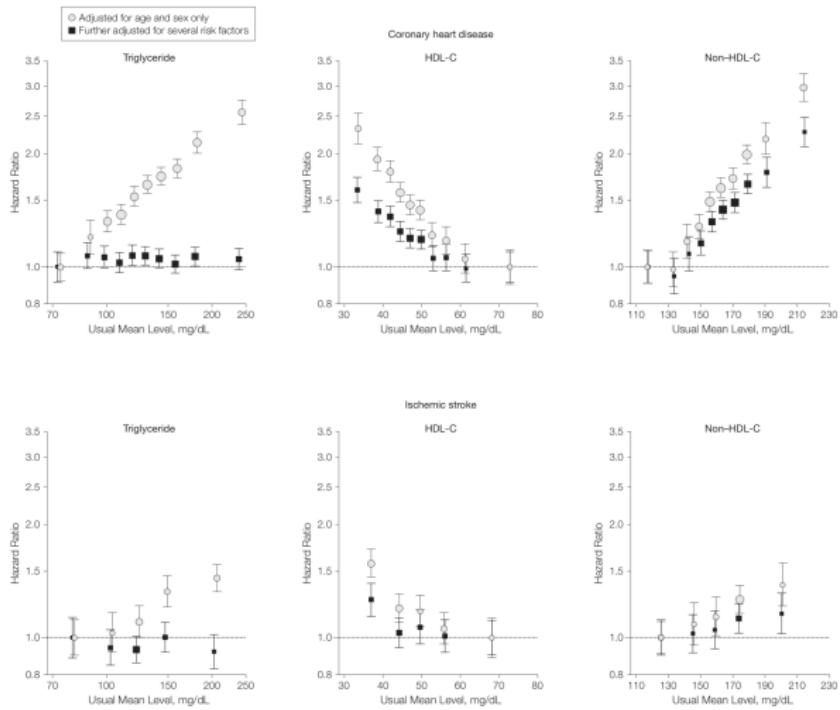


Figure 2: Approximate age of onset of atherosclerotic symptoms for those with homozygous familial hypercholesterolaemia or heterozygous familial hypercholesterolaemia, and those without inherited defects of the LDL-receptor

Adopted from Horton and colleagues.⁶ HoFH=homozygous familial hypercholesterolaemia. HeFH=heterozygous familial hypercholesterolaemia.

Figure 1. Hazard Ratios for Coronary Heart Disease or Ischemic Stroke Across Quantiles of Usual Triglyceride, HDL-C, and Non-HDL-C Levels

Analyses for coronary heart disease were based on 302 430 participants (involving 12 785 cases) from 68 studies. Analyses for ischemic stroke were based on 173 312 participants (involving 2534 cases) from 32 studies. Regression analyses were stratified, where appropriate, by sex and trial group. Values with further adjustments

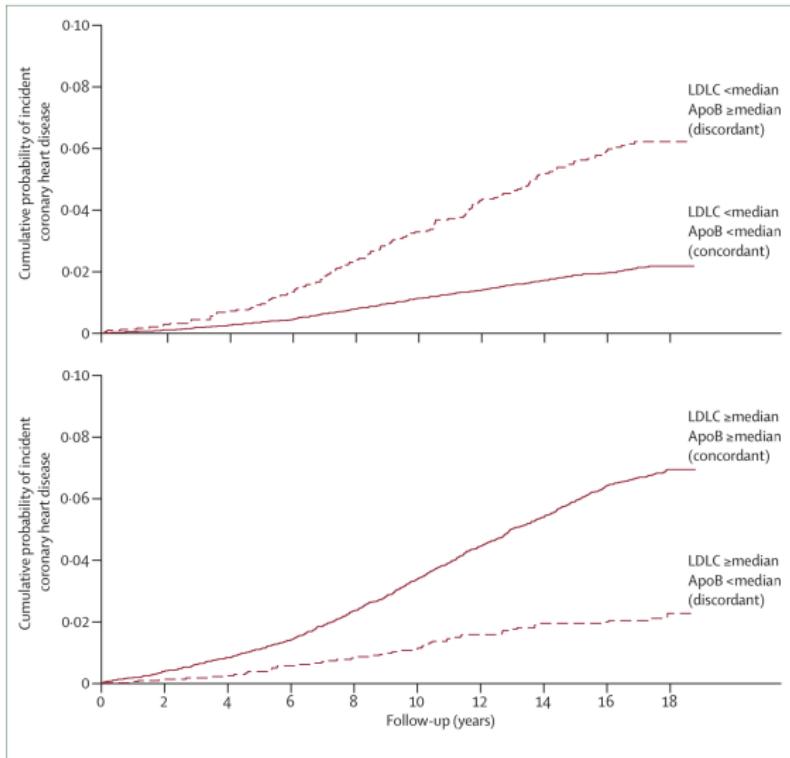


Figure 4: Differential predictive usefulness of the atherogenic lipoproteins LDLC and apolipoprotein B
 Assessed in individuals where there was concordance and discordance between LDLC and apolipoprotein B.
 Adopted from Mora and colleagues.²⁷ LDLC=LDL cholesterol. ApoB=apolipoprotein B.

Ridker PM. Lancet 2014

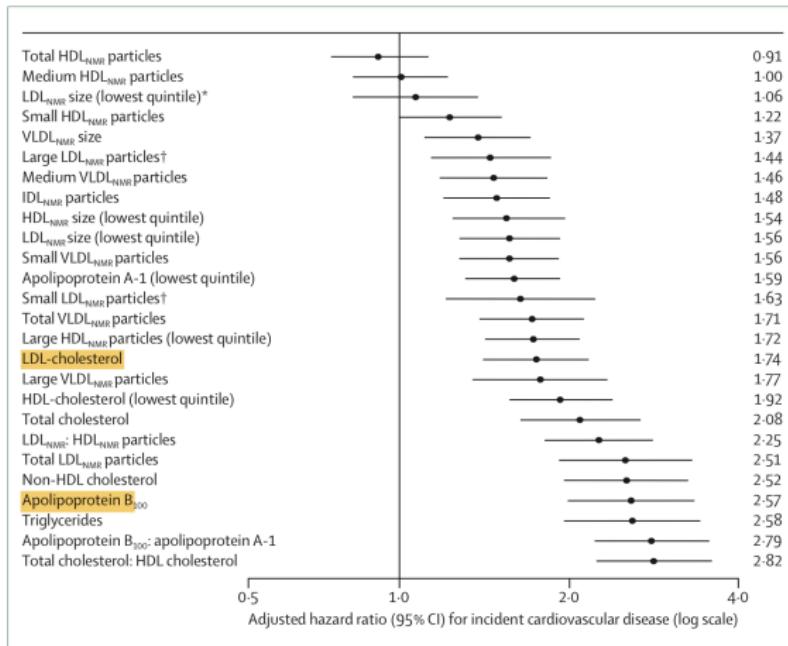
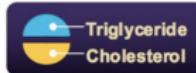
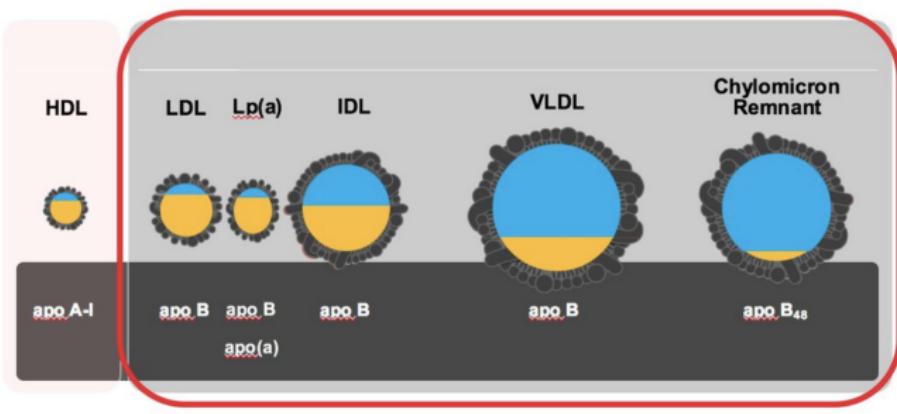


Figure 3: Direct comparison of 26 lipid fractions as predictors of first-ever cardiovascular events in apparently healthy women

Data are shown for the top versus bottom quintile of each lipid fraction, unless otherwise indicated. *Additionally adjusted for total LDL_{NMR} particle concentration. †Additionally adjusted for the other NMR proteins. Adopted from Mora and colleagues.²²

Non-HDL-C captures cholesterol in all atherogenic (apoB-containing) lipoproteins



The statin era

Without background treatment with statins, fibrates were seen to reduce non-fatal myocardial infarction, and niacin to reduce both non-fatal myocardial infarction and stroke. However, in the modern era when treatment with statins is standard, this effect has not been apparent (fig 4). Attempts at risk reduction through these treatments to increase high density lipoprotein levels on top of statin treatment have been unsuccessful so far.

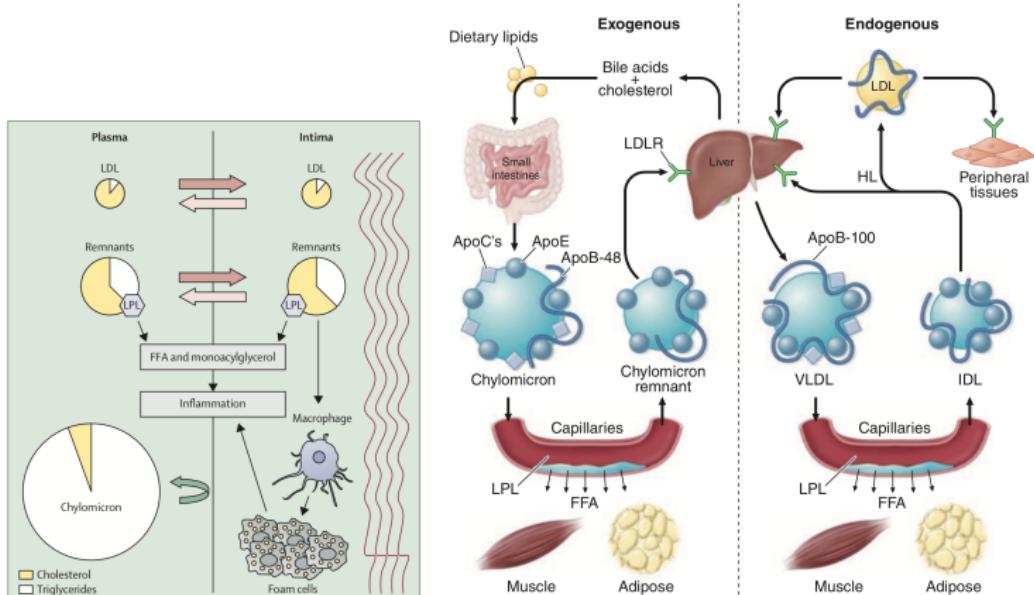


Figure 2: Suggested role of raised plasma triglycerides and remnant cholesterol in intimal low-grade inflammation and development of atherosclerosis
Triglycerides and remnant cholesterol could act through triglyceride hydrolysis and cholesterol accumulation in arterial wall foam cells leading to development of atherosclerosis. FFA=free fatty acids, LPL=lipoprotein lipase.

FIGURE 400-2 The exogenous and endogenous lipoprotein metabolic pathways. The exogenous pathway transports dietary lipids to the periphery and the liver. The endogenous pathway transports hepatic lipids to the periphery. FFA, free fatty acid; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

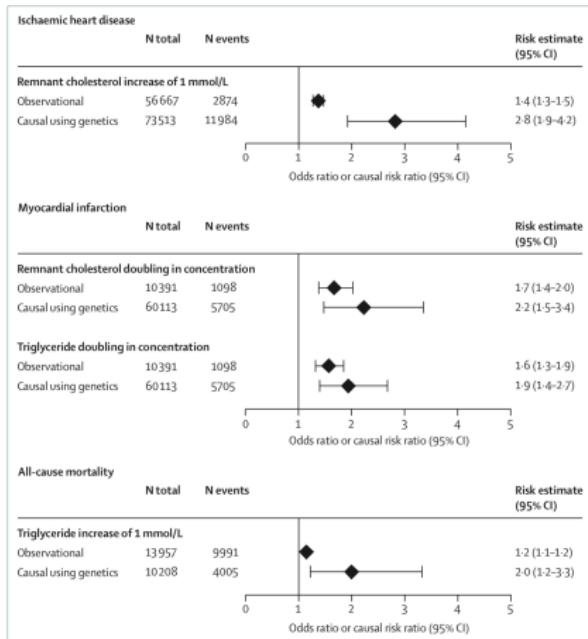


Figure 3: Observational and causal (by use of genetics) associations of raised remnant cholesterol and triglycerides with risk of ischaemic heart disease, myocardial infarction, and all-cause mortality
Top section adapted from Varbo and colleagues.¹⁹ Middle section adapted from Jørgensen and colleagues.¹⁸

OPEN

Role of Blood Lipids in the Development of Ischemic Stroke and its Subtypes A Mendelian Randomization Study

George Hindy, MD, PhD; Gunnar Engström, MD, PhD; Susanna C. Larsson, PhD;
Matthew Traylor, PhD; Hugh S. Markus, DM; Olle Melander, MD, PhD;
Marju Orho-Melander, PhD; on behalf of the Stroke Genetics Network (SiGN)

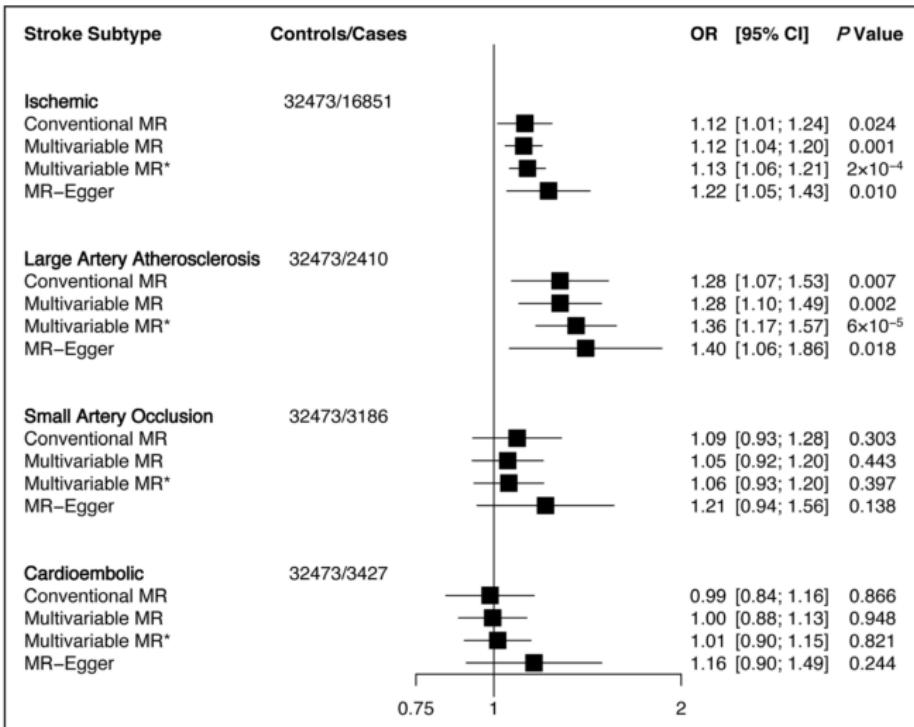


Figure 1. Association of low-density lipoprotein cholesterol with ischemic stroke and subtypes using different Mendelian randomization

Hindry G et al Stroke 2018

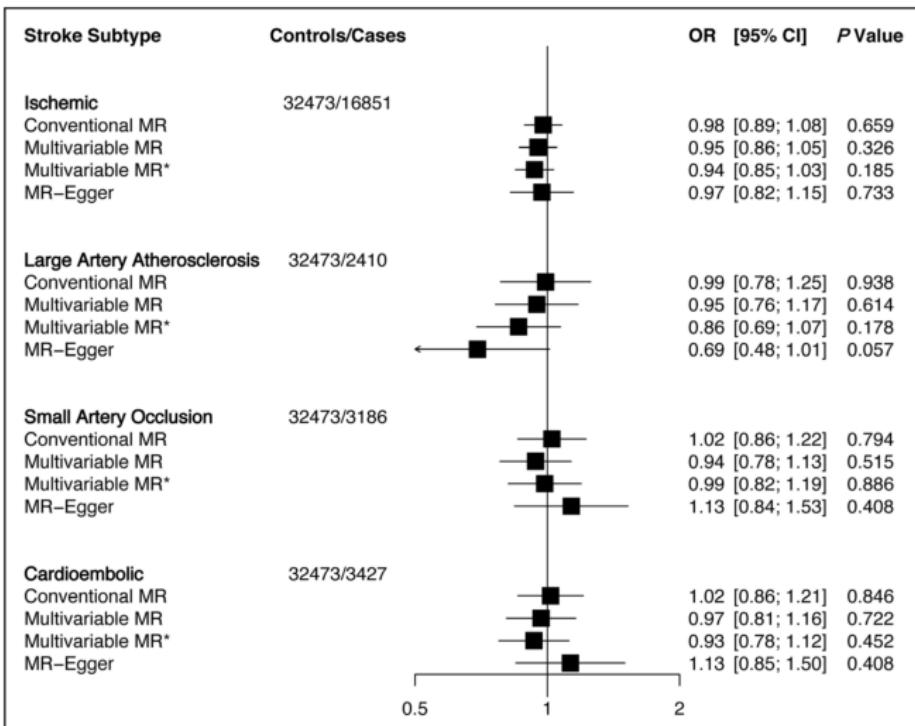


Figure 3. Association of triglycerides with ischemic stroke and subtypes using different Mendelian randomization (MR) analyses. Odds

Hindry G et al Stroke 2018

Published Ahead of Print on February 20, 2019 as 10.1212/WNL.0000000000007091

ARTICLE

OPEN ACCESS

Relative effects of LDL-C on ischemic stroke and coronary disease

A Mendelian randomization study

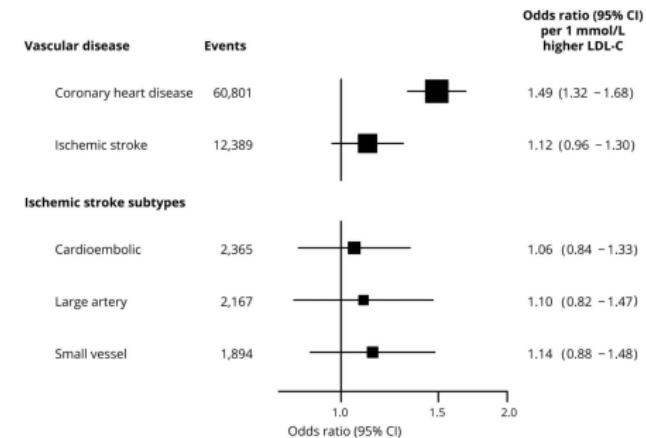
Elsa Valdes-Marquez, PhD, Sarah Parish, DPhil, Robert Clarke, FRCP, Traianu Stari, PhD, and Bradford B. Worrall, MD, METASTROKE Consortium of the ISGC and Jemma C. Hopewell, PhD

Neurology® 2019;92:e1-e12. doi:10.1212/WNL.0000000000007091

Correspondence

Dr. Hopewell
Jemma.Hopewell@ndph.ox.ac.uk

Figure 2 Effects of genetically determined low-density lipoprotein cholesterol (LDL-C) on vascular disease and ischemic stroke subtypes



JAMA | Original Investigation

Association of Triglyceride-Lowering *LPL* Variants and LDL-C-Lowering *LDLR* Variants With Risk of Coronary Heart Disease

Brian A. Ference, MD, MPhil, MSc; John J. P. Kastelein, MD, PhD; Kausik K. Ray, MD, MPhil; Henry N. Ginsberg, MD; M. John Chapman, PhD, DSc; Chris J. Packard, DSc; Ulrich Laufs, MD, PhD; Clare Oliver-Williams, PhD; Angela M. Wood, PhD; Adam S. Butterworth, PhD; Emanuele Di Angelantonio, MD; John Danesh, DPhil; Stephen J. Nicholls, MBBS, PhD; Deepak L. Bhatt, MD, MPH; Marc S. Sabatine, MD, MPH; Alberico L. Catapano, PhD

Ference BA et al JAMA 2019

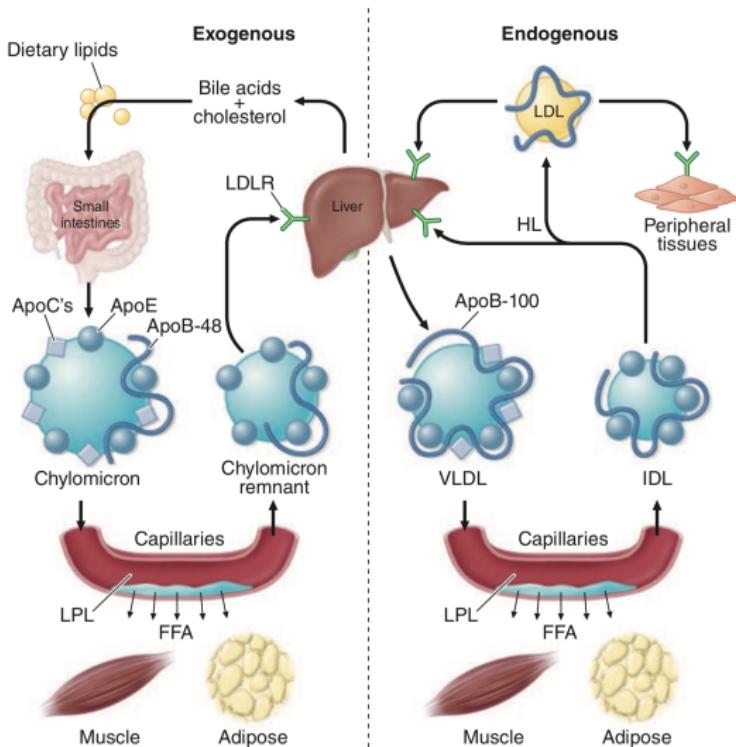
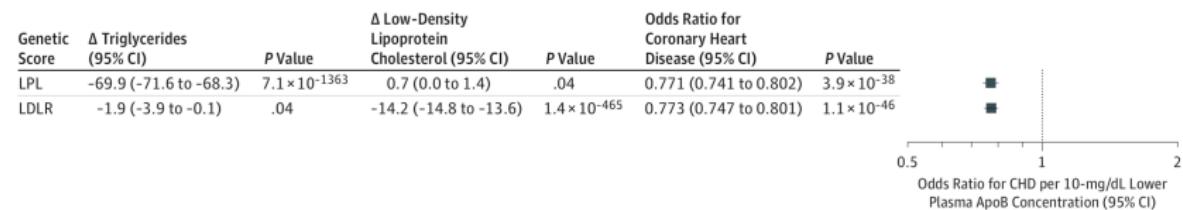


FIGURE 400-2 The exogenous and endogenous lipoprotein metabolic pathways. The exogenous pathway transports dietary lipids to the periphery and the liver. The endogenous pathway transports hepatic lipids to the periphery. FFA, free fatty acid; HL, hepatic lipase; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; LPL, lipoprotein lipase; VLDL, very-low-density lipoprotein.

Methods

- Calculation of genetic score of LPL and LDL-R
- Genetic score - TG/LDL-C/ApoB and CHD (Linear and logistic regression)
- Associations of each score with risk of CHD was scaled for a common 10-mg/dL lower level of ApoB-containing lipoproteins
- The point estimates derived from the individual participant data and the summary data were then combined across studies in a fixed-effect inverse variance-weighted meta-analysis

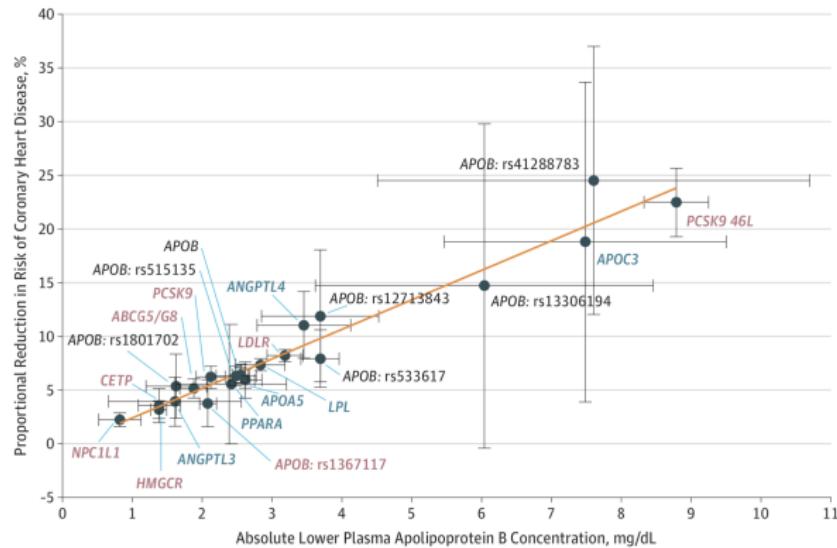
Figure 1. Associations Between the Lipoprotein Lipase (*LPL*) and LDL Receptor Gene (*LDLR*) Genetic Scores With Triglycerides, Low-Density Lipoprotein Cholesterol (LDL-C), and Risk of Coronary Heart Disease (CHD) per 10-mg/dL Lower Concentration of Apolipoprotein B (ApoB)-Containing Lipoproteins



Triglycerides are carried in plasma by ApoB-containing triglyceride-rich lipoproteins while cholesterol is carried predominantly by ApoB-containing low-density lipoproteins. Changes in plasma triglycerides and LDL-C concentration are thus markers of the corresponding changes in the concentration of the ApoB-containing lipoproteins that transport these lipids. Variants in the *LPL* gene that increase *LPL* activity are associated with lower triglycerides and a corresponding lower ApoB concentration, while variants in the *LDLR* gene that increase activity of the LDL receptor are associated with lower LDL-C and a corresponding lower ApoB. The figure shows that for each 10-mg/dL lower plasma ApoB concentration associated with variants in the *LPL* score, there is a corresponding 69.9-mg/dL lower triglyceride level, no change in LDL-C, and a lower risk of CHD (odds ratio, 0.771 [95% CI, 0.741-0.802]). By contrast,

for the same 10-mg/dL lower plasma ApoB concentration associated with variants in the *LDLR* score, there is a corresponding 14.1-mg/dL lower LDL-C level, no change in triglycerides, and a similar lower risk of CHD (odds ratio, 0.773 [95% CI, 0.747-0.801]). Therefore, despite being associated with changes in different lipids, the *LPL* and *LDLR* scores were associated with similar lower risk of CHD for the same lower plasma ApoB concentration. The data presented are for the associations of the *LPL* and *LDLR* genetic scores with risk of CHD per 10-mg/dL decrease in ApoB-containing lipoproteins in all 654 783 participants included in the study. The associations of either score with changes in triglycerides and LDL-C per 10-mg/dL lower level of ApoB-containing lipoproteins are from up to 305 699 participants enrolled in the Global Lipid Genetics Consortium. Boxes represent effect size estimates and lines represent 95% CIs.

Figure 3. Log-Linear Association Between Absolute Differences in Apolipoprotein B (ApoB) and Lower Risk of Coronary Heart Disease (CHD)



The associations of each genetic variant with ApoB concentration is plotted against its unadjusted association with CHD, expressed as a proportional lower risk (calculated as $[1-OR_{CHD}] \times 100$). Variants in the genes that encode the targets of therapies that lower triglycerides through the LPL pathway are marked with blue labels, and variants in the genes that encode the targets of therapies that lower LDL-C through upregulation of the LDL receptor are marked by red labels. Circles represent the associated absolute change in ApoB

and corresponding proportional lower risk of CHD for each variant. The horizontal lines through each circle represent ± 1 standard errors for the associated absolute change in ApoB for each variant; and the vertical line through each circle represents ± 1 standard errors for the associated proportional lower risk of CHD. Associations with CHD were measured in all 654 783 participants included in the study; associations with ApoB were measured in a meta-analysis of 14 studies including up to 84 324 participants.

Table 3. Multivariable Mendelian Randomization Analysis of the Association Between Plasma Triglycerides, LDL-C, and ApoB With the Risk of CHD^a

Analysis	Variables	Odds Ratio for CHD (95% CI)	P Value
Association of 10-mg/dL lower ApoB with risk of CHD	ApoB	0.770 (0.760-0.781)	1.42E-170
Association of 10-mg/dL lower LDL-C with risk of CHD	LDL-C	0.846 (0.833-0.858)	8.16E-77
Association of 50-mg/dL lower triglycerides with risk of CHD	Triglycerides	0.815 (0.785-0.846)	1.37E-18
Association of 10-mg/dL lower LDL-C and 50-mg/dL lower 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 10-mg/dL lower LDL-C, 50-mg/dL lower triglycerides, and 10-mg/dL lower 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)	.19
	Triglycerides	1.014 (0.965-1.065)	.19

Abbreviations: ApoB, apolipoprotein B; CHD, coronary heart disease; LDL-C, low-density lipoprotein cholesterol.

^a Data presented are derived from a multivariable meta-regression analysis of 186 genetic variants, including the 5 variants included in the *LPL* score, 3 variants included in the *LDLR* score, and 178 variants associated with either triglycerides, LDL-C, or both at genome-wide significance as reported by the Global Lipids Genetics Consortium. Effect sizes for the associated risk of CHD are reported per 10-mg/dL lower ApoB concentration, per 10-mg/dL lower LDL-C level, or per 50-mg/dL lower triglyceride level (because dividing triglyceride concentration by 5 estimates the cholesterol content carried by triglyceride-rich ApoB-containing lipoproteins as estimated by the Friedewald formula). In these analyses, the dependent variable was the effect estimate for risk of CHD in all 654 783 participants included in the study for each variant and the independent variables were the effect estimates for the associated changes in plasma triglycerides, LDL-C, and ApoB, measured in up to 305 699 participants in Global Lipids Genetics Consortium for each variant. The analysis

was weighted by the inverse squared standard error of the associated risk of CHD for each variant and forced to pass through the origin. For example, in multivariable mendelian randomization analyses involving these 186 genetic variants, both triglycerides (odds ratio [OR], 0.876 per 50-mg/dL lower triglycerides) and LDL-C (OR, 0.862 per 10-mg/dL lower LDL-C) were independently associated with a lower risk of CHD at genome-wide level of significance. By contrast, when ApoB was included in the multivariable mendelian randomization analyses, the associations with CHD for both triglycerides (OR, 1.014 per 50-mg/dL lower triglycerides) and LDL-C (OR, 1.010 per 10-mg/dL lower LDL-C) became null, but the association per 10-mg/dL lower ApoB remained unchanged (OR, 0.761 per 10-mg/dL lower ApoB). The unadjusted associations with triglycerides, LDL-C, ApoB, and CHD for each variant included in the analysis are provided in eTable 7 in the *Supplement*. Additional multivariable meta-regression analyses for various combinations of these variants is provided in eTable 8 in the *Supplement*.

Key Points

Question What is the clinical benefit of lowering plasma triglyceride levels compared with lowering low-density lipoprotein cholesterol levels?

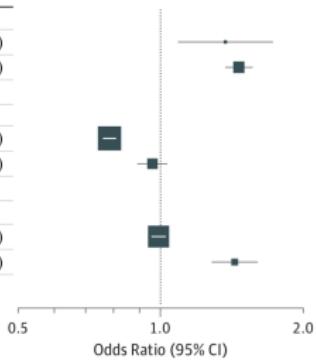
Findings In mendelian randomization analyses involving 654 783 participants, triglyceride-lowering variants in the lipoprotein lipase gene and low-density lipoprotein cholesterol (LDL-C)-lowering variants in the LDL receptor gene were associated with similar lower risk of coronary heart disease per 10-mg/dL lower level of apolipoprotein B (ApoB)-containing lipoproteins (odds ratios of 0.771 and 0.773, respectively).

Meaning The clinical benefit of lower triglyceride levels was similar to the clinical benefit of lower LDL-C levels per unit difference in ApoB and may be related to the absolute reduction in ApoB-containing lipoprotein particles.

Summary

Figure. Comparison of Observational Estimates and Mendelian Randomization Estimates of the Association of Low-Density Lipoprotein (LDL) Cholesterol, High-Density Lipoprotein (HDL) Cholesterol, and Triglycerides With Coronary Heart Disease

Analysis	Source	Odds Ratio (95% CI)
LDL cholesterol		
Observational	ERFC ²	1.37 (1.09-1.73)
Mendelian randomization	Do et al ³	1.46 (1.37-1.56)
Test for heterogeneity: $P = .60$		
HDL cholesterol		
Observational	ERFC ²	0.78 (0.76-0.81)
Mendelian randomization	Do et al ³	0.96 (0.89-1.03)
Test for heterogeneity: $P < .01$		
Triglycerides		
Observational	ERFC ²	0.99 (0.96-1.03)
Mendelian randomization	Do et al ³	1.43 (1.28-1.60)
Test for heterogeneity: $P < .01$		



Observational estimates are derived from the Emerging Risk Factors Collaboration (ERFC).² Mendelian randomization estimates are derived from Do et al³ based on an analysis of 185 genetic variants that alter plasma lipids and mutually adjusted for other lipid fractions (eg HDL cholesterol and triglycerides for LDL cholesterol). A formal test of heterogeneity (Cochran Q test) shows that the observational and mendelian randomization causal estimates are consistent for LDL cholesterol but not so for HDL cholesterol or triglycerides.

lipoprotein = lipid + apolipoprotein

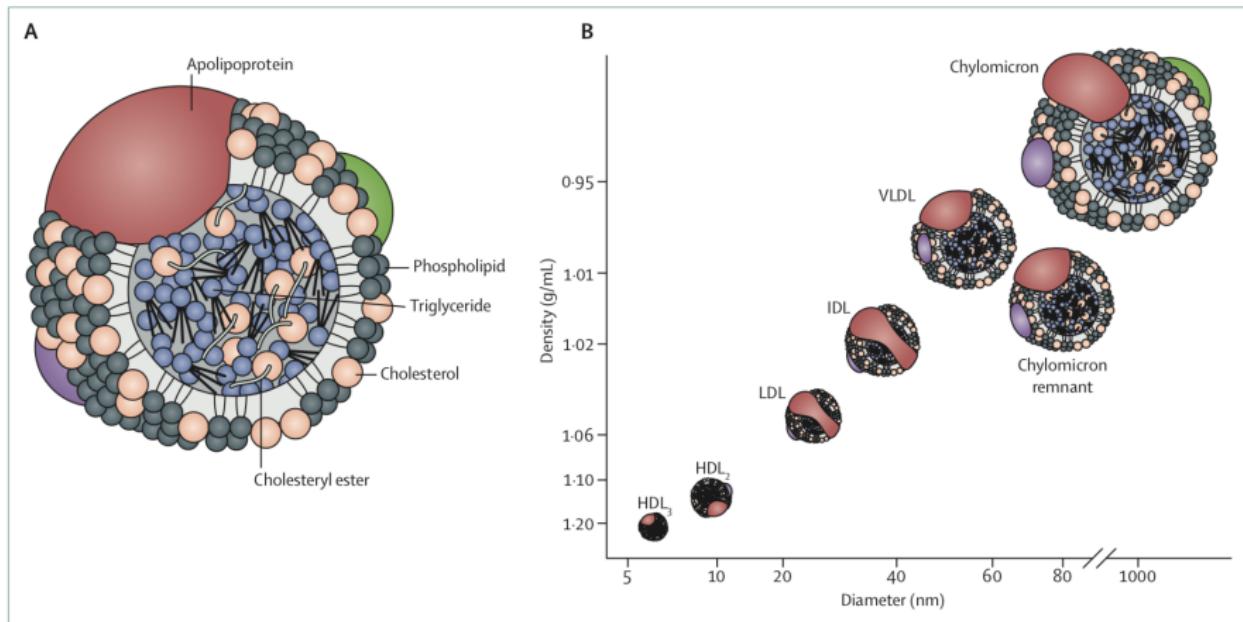


Figure 1: The structural components of lipoproteins (A) and their relation to diameter and density (B)

Adopted from Genest J, Libby P. Lipoprotein Disorders and Cardiovascular Disease. Braunwald's Heart Disease: a textbook of cardiovascular medicine, ninth edition. Elsevier 2012, pp: 975-95. IDL=intermediate-density lipoprotein.

Ridker PM. Lancet 2014

TABLE 400-1 Major Lipoprotein Classes

LIPOPROTEIN	DENSITY, g/mL ^a	SIZE, nm ^b	ELECTROPHORETIC MOBILITY ^c	APOLIPOPROTEINS		OTHER CONSTITUENTS
				MAJOR	OTHER	
Chylomicrons	0.930	75–1200	Origin	ApoB-48	A-I, A-V, C-I, C-II, C-III, E	Retinyl esters
Chylomicron remnants	0.930–1.006	30–80	Slow pre-β	ApoB-48	A-I, A-V, C-I, C-II, C-III, E	Retinyl esters
VLDL	0.930–1.006	30–80	Pre-β	ApoB-100	A-I, A-II, A-V, C-I, C-II, C-III, E	Vitamin E
IDL	1.006–1.019	25–35	Slow pre-β	ApoB-100	C-I, C-II, C-III, E	Vitamin E
LDL	1.019–1.063	18–25	β	ApoB-100		Vitamin E
HDL	1.063–1.210	5–12	α	ApoA-I	A-II, A-IV, A-V, C-III, E	LCAT, CETP, paroxonase
Lp(a)	1.050–1.120	25	Pre-β	ApoB-100	Apo(a)	Oxidized phospholipids

^aThe density of the particle is determined by ultracentrifugation. ^bThe size of the particle is measured using gel electrophoresis. ^cThe electrophoretic mobility of the particle on agarose gel electrophoreses reflects the size and surface charge of the particle, with β being the position of LDL and α being the position of HDL.

Note: All of the lipoprotein classes contain phospholipids, esterified and unesterified cholesterol, and triglycerides to varying degrees.

Abbreviations: CETP, cholesteryl ester transfer protein; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LCAT, lecithin-cholesterol acyltransferase; LDL, low-density lipoprotein; Lp(a), lipoprotein A; VLDL, very-low-density lipoprotein.