Behind LDL: The Metabolism of ApoB, the Essential Apolipoprotein in LDL and VLDL

Sung-Joon Lee, PhD

Division of Food Science

Institute of Biomedical Science and Safety

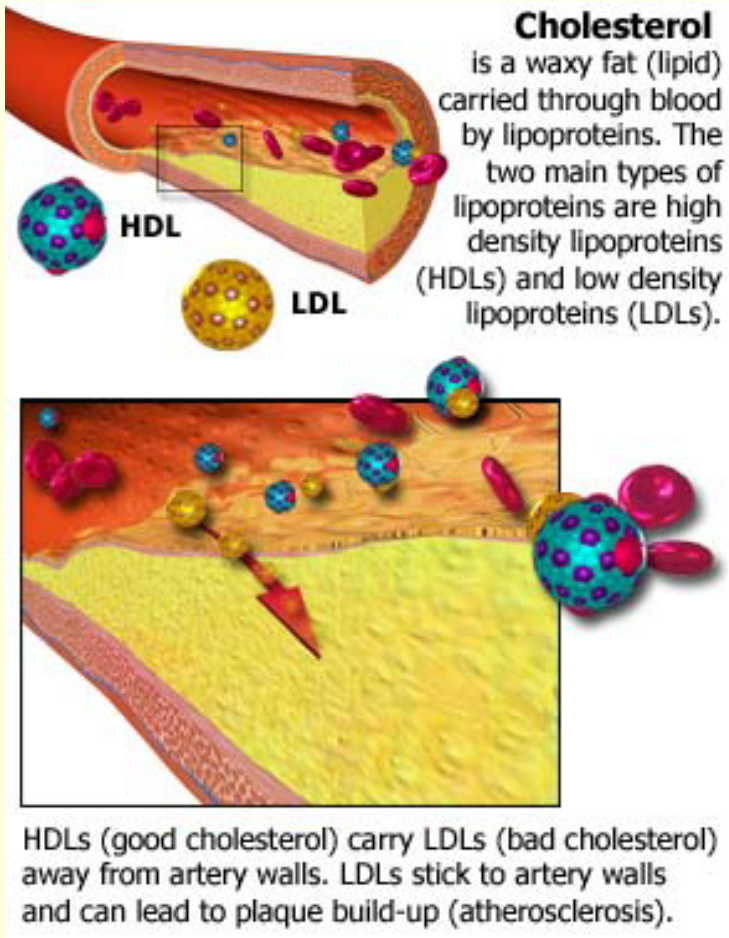
Korea University

Composition of Lipoproteins: cholesterol carrying particles

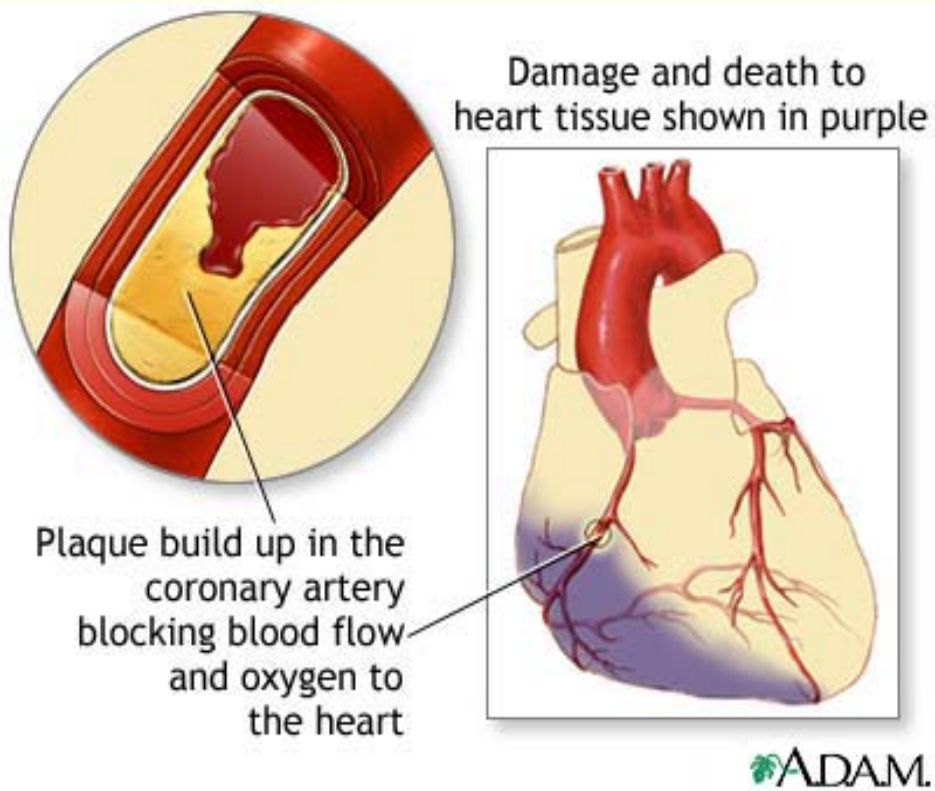
Classification by density

Complex	Source	Density (g/ml)	%Prot	%TG	%PL	%CE	%C	%FFA[e]
Chylomicron	Intestine	<0.95	1-2	85-88	8	3	1	0
VLDL	Liver	0.95-1.006	7-10	50-55	18-20	12-15	8-10	1
IDL	VLDL	1.006-1.019	10-12	25-30	25-27	32-35	8-10	1
LDL	VLDL	1.019-1.063	20-22	10-15	20-28	37-48	8-10	1
*HDL_2	Intestine, liver	1.063-1.125	33-35	5-15	32-43	20-30	5-10	0
*HDL_3	Intestine, liver	1.125-1.21	55-57	3-13	26-46	15-30	2-6	6
Albumin-FFA	Adipose tissue	>1.281	99	0	0	0	0	100

Good and Bad Cholesterol

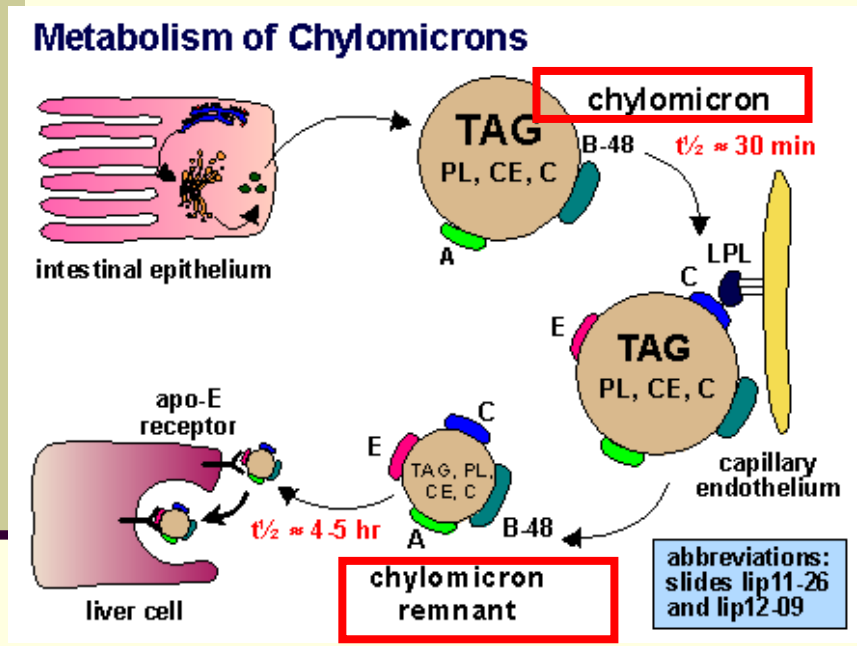


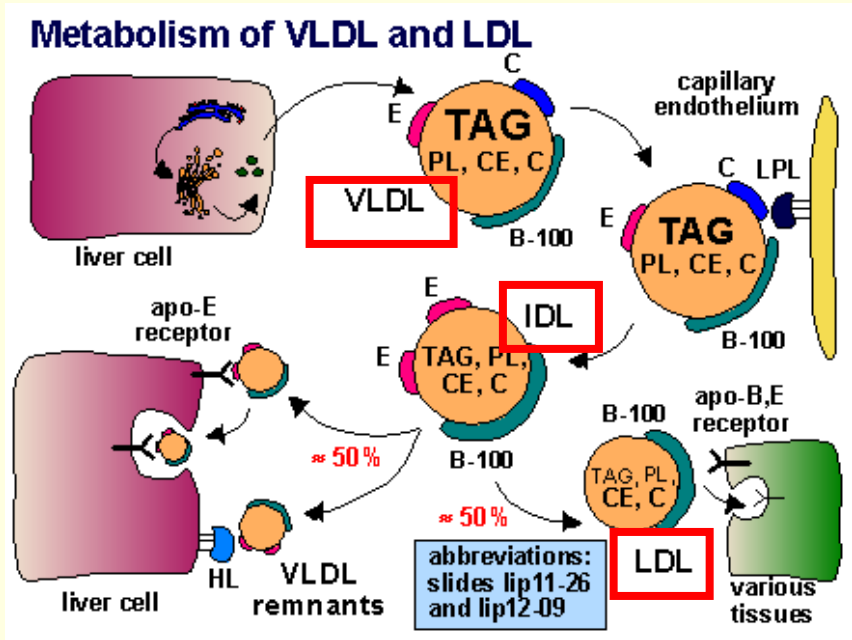
Atherosclerosis



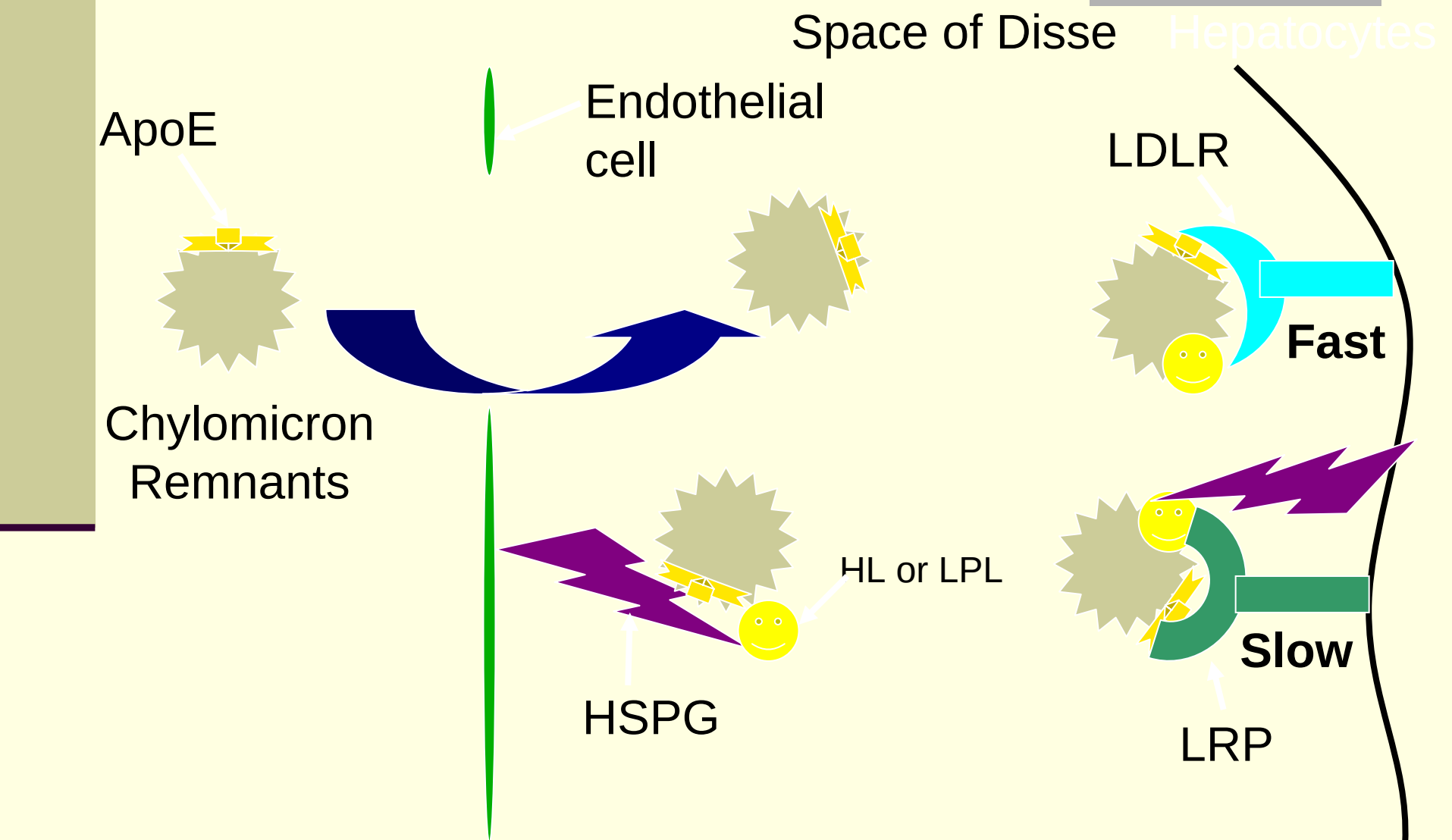
Metabolic Pathways of ApoB-Lipoproteins:

Endogenous vs. Exogenous Pathways





Pathways of Chylomicron Remnants Removal by the Liver



Metabolic Pathways of ApoB-Lipoproteins:

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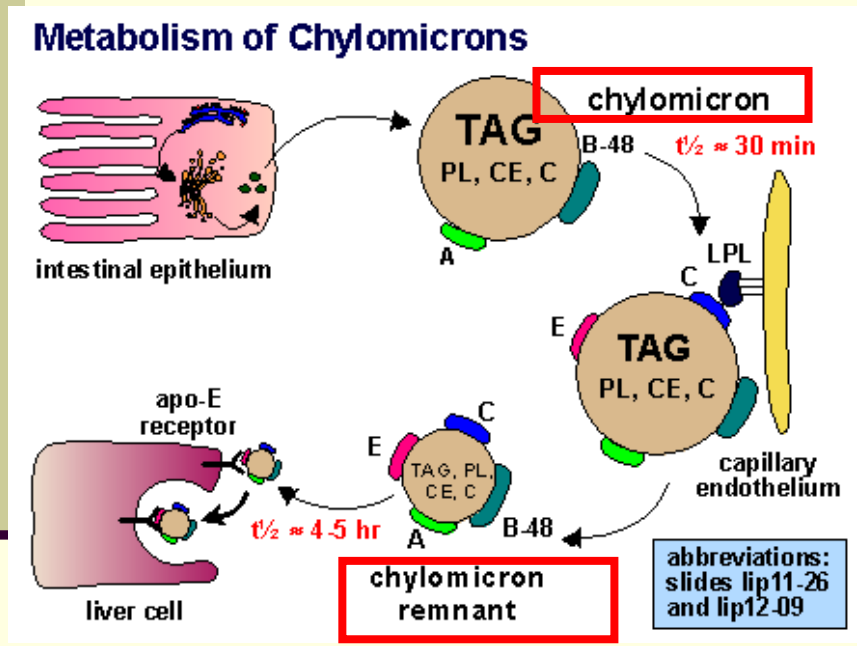
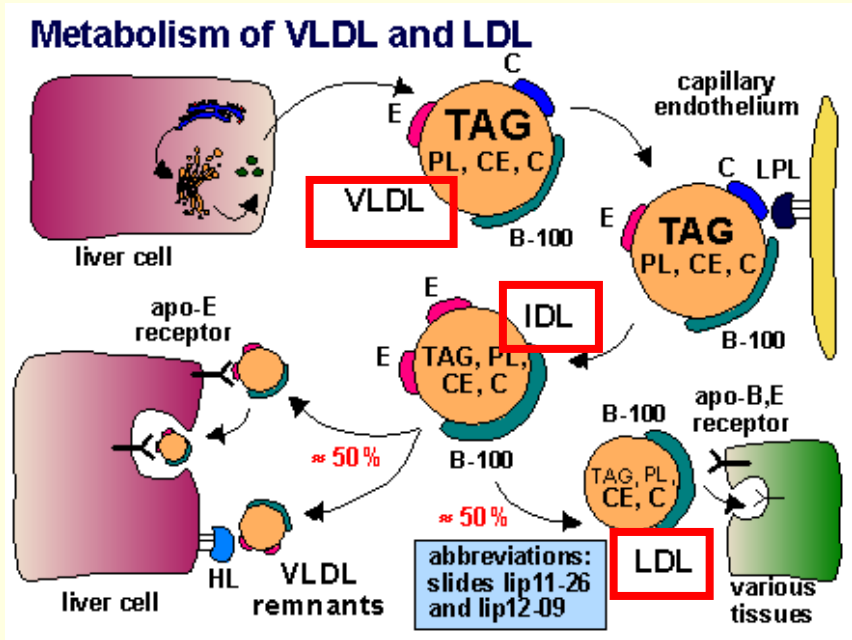
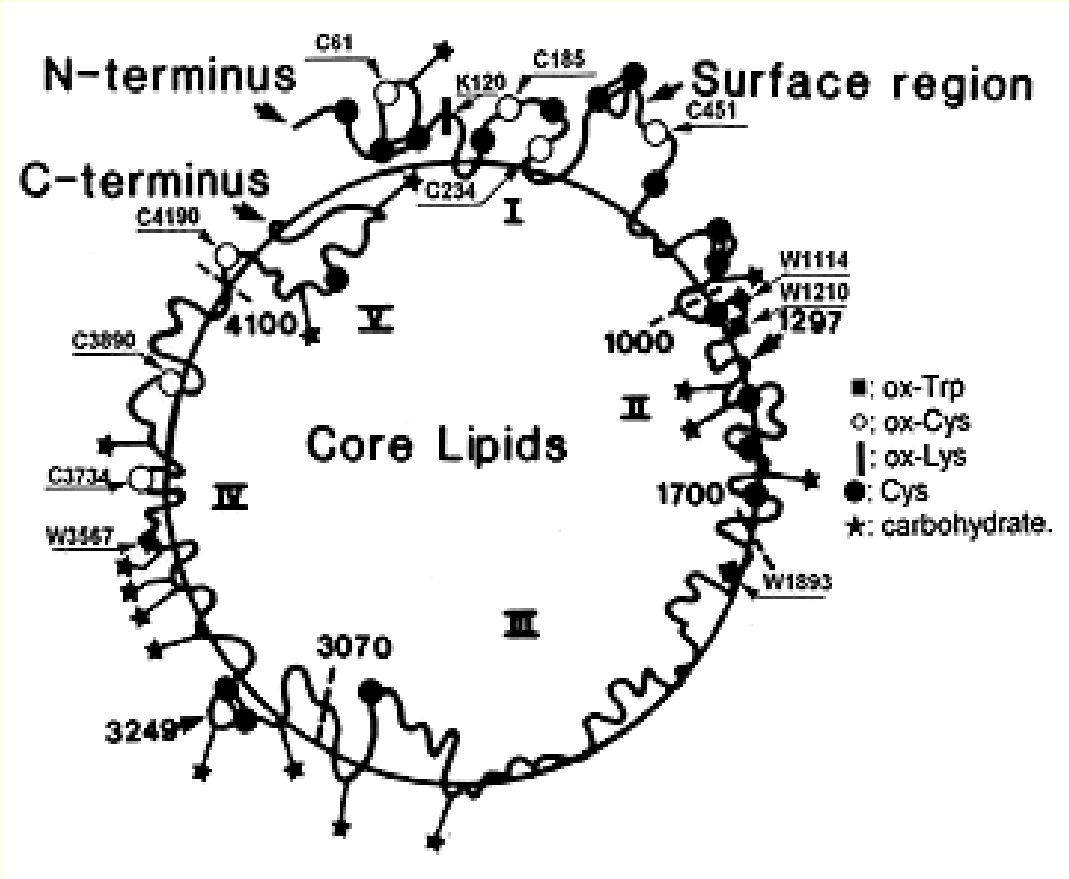




Many apolipoproteins are associated with the risk for CHD

Type	Lipoprotein Association	Function and Comments	Association with CHD
apoA-I	CM, HDL	major protein of HDL, activates lecithin:cholesterol acyltransferase, LCAT	Yes
apoA-II	CM, HDL	primarily in HDL, enhances hepatic lipase activity	Unknown
apoA-IV	CM and HDL	present in triacylglycerol rich lipoproteins	Yes
apoB-48	CM	exclusively found in CM	Yes
apoB-100	VLDL-LDL	major protein of LDL, LDL receptor ligand	Yes
apoC-I	CM, VLDL,HDL	may activate LCAT	Unknown
apoC-II	CM, VLDL, HDL	activates lipoprotein lipase	Unknown
apoC-III	CM, VLDL, HDL	inhibits lipoprotein lipase	In ApoB, Yes
apoD	HDL	closely associated with LCAT	Unknown
CETP	HDL	exclusively associated with HDL, cholesteryl ester transfer	Yes
apoE	CR, VLDL, HDL	LDL receptor ligand	Phenotype, Yes
apo(a)	LDL	disulfide bonded to apoB-100, forms a complex with LDL identified as lipoprotein(a), Lp(a)	Yes

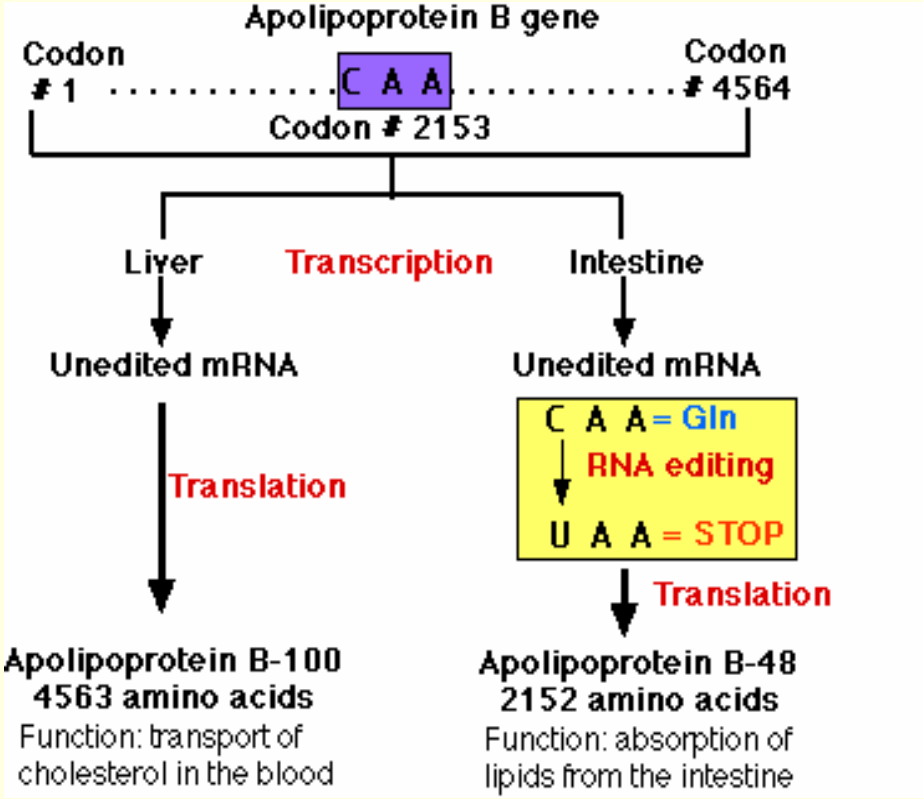
Structure of ApoB-containing Lipoproteins



ApoB is a structural protein for chylomicron, VLDL, IDL, and LDL.

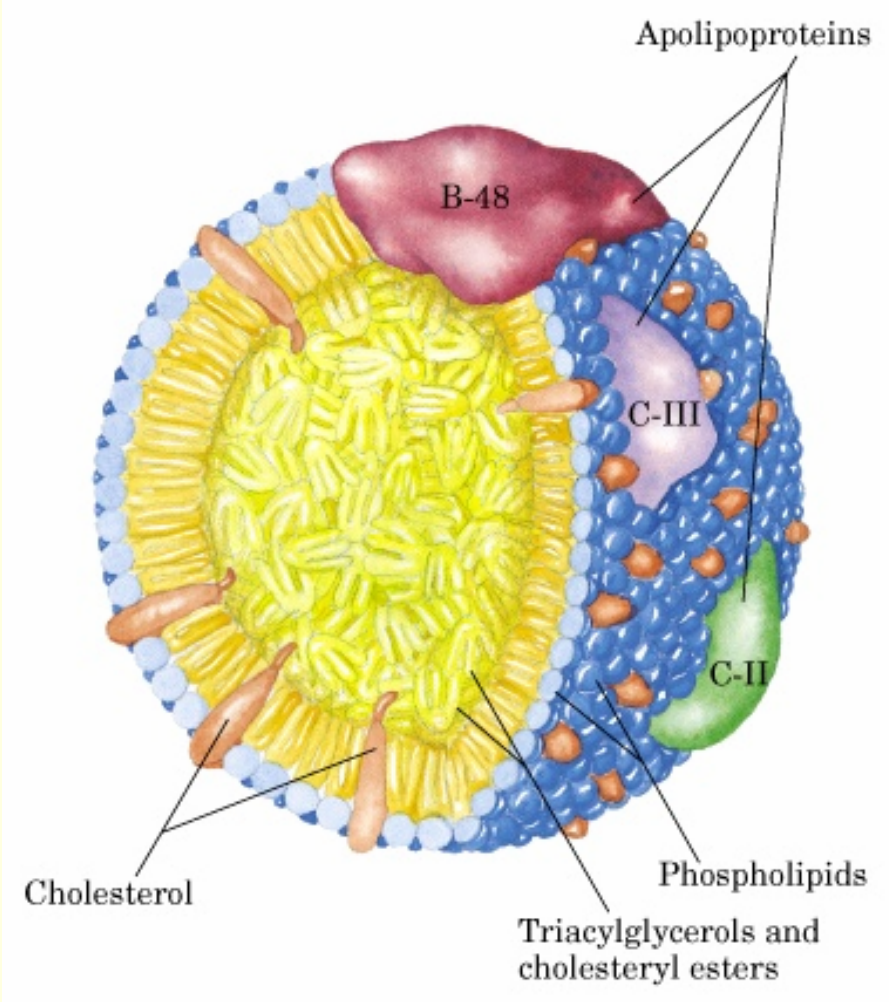
ApoB100 vs. ApoB48

The Role of RNA editing



- 27 N-terminal signal sequence; 4536 aa
- Receptor binding site is terminated

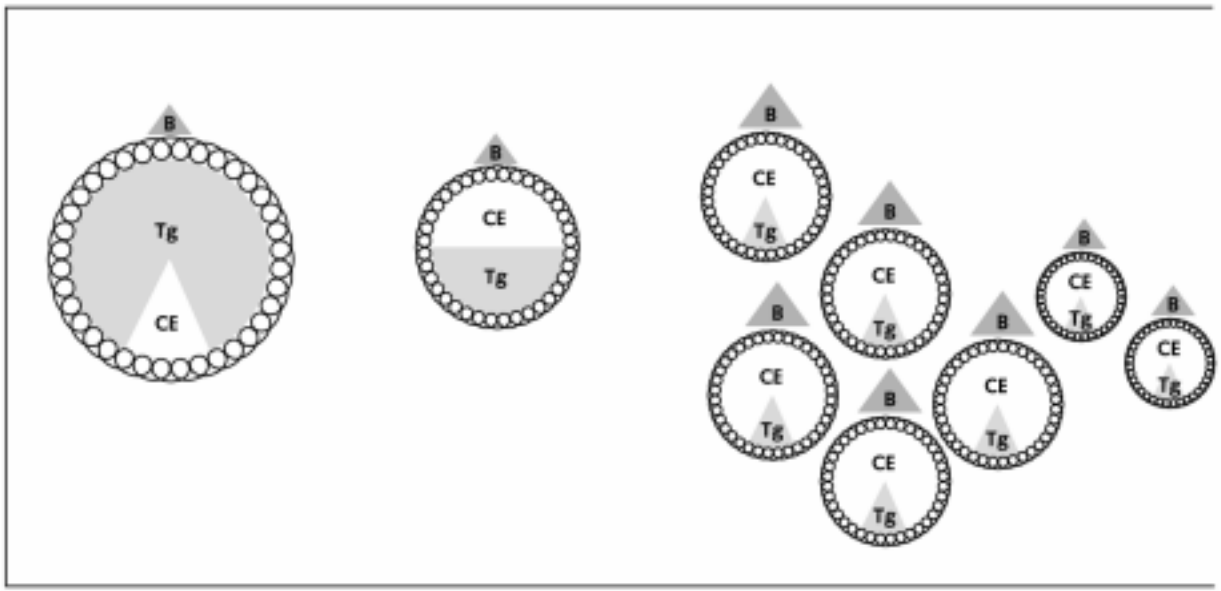
Structure of ApoB containing Lipoproteins



Relative Number of VLDL, IDL, and LDL

Plasma apoB level is correlated with LDL cholesterol.

The relative number of very-low-density lipoprotein (VLDL) (*left*), intermediate-density lipoprotein (*middle*), and low-density lipoprotein (LDL) (*right*) particles.



The LDL particles always greatly outnumber VLDL particles. The LDL particles also differ in composition; in this instance, most LDL particles are LI
A rather than LDL B. B = apoB100; CE = cholesterol ester; Tg = triglyceride.

The half life of LDL is nine times longer compared with VLDL.

In circulation, nine times more LDL particles than VLDL particles.

Is apoB more sensitive indicator for CHD risk than LDL?

- In cross-sectional studies, HTG with normal apoB is not associated with an increased risk for CHD, whereas HTG with increased apoB is

- Sniderman AD et al. Ann Intern Med. 1982:97:833-9
- Brunzell JD et al. Metabolism. 1976:25:313-20
- Durrington PN et al. Br. Heart J. 1986:56:206-12
- Barbir M et al. Br Heart J. 1988:60:397-403
- Kutika H et al. Atherosclerosis. 1985:55:143-9
- Kwiterovich PO et al. Am J Cardiol. 1993:71:631-9

ApoB vs. Cholesterol:
Studies in not on statin treatment

	Type of analysis	Hazard ratio* (95% CI)		p	
		LDL-cholesterol	Apolipoprotein B	LDL-cholesterol	Apolipoprotein B
Not on statin treatment					
Observational studies					
Lamarche et al[3]	Multiple regression (tertile data available)	NA	1·44 (1·22–1·67)	..	<0·001
Moss et al[4]	Q4 : Q1-3	0·60 (0·30–1·18)	2·37 (1·28–4·36)	0·1399	0·057
AMORIS[2]	Multivariate regression				
	Males	1·14 (1·01–1·28)	1·33 (1·17–1·51)	0·0234	<0·0001
	Females	0·85 (0·69–1·05)	1·53 (1·25–1·88)	0·1387	<0·0001
NPHS[5]	Q4 : Q1	2·60 (1·60–4·40)	2·90 (1·82–4·64)	<0·05	<0·005
Placebo group in clinical trials					
AFCAPS/TexCAPS[6]	T3 : T1	1·44† (NA)	1·39† (NA)	NS	NA
LIPID[7]	Regression analysis				
	Unadjusted	1·15 (1·04–1·27)	1·64 (1·21–2·21)	0·008	0·002
	Adjusted	1·28 (1·07–1·31)	2·07 (1·21–2·24)	0·002	0·001

AMORIS age-adjusted hazard ratio for summary atherogenic indices.

	Men		Women	
	HR/SD (95% CI)	p	HR/SD (95% CI)	p
TC/HDL-C	0·96 (0·92–1·02)	0·1657	1·05 (0·99–1·10)	0·1019
vs apoB/A-I	1·59 (1·48–1·72)	0·0001	1·33 (1·19–1·49)	0·0001
LDL-C/HDL-C	0·96 (0·91–1·01)	0·0783	1·03 (0·96–1·10)	0·4003
vs apoB/A-1	1·62 (1·50–1·75)	0·0001	1·36 (1·02–1·40)	0·0001
Non-HDL-C/HDL-C	0·96 (0·92–1·02)	0·1657	1·05 (0·99–1·10)	0·1019
vs apoB/A-1	1·59 (1·48–1·72)	0·0001	1·33 (1·19–1·49)	0·0001

TC=total cholesterol; HDL-C=HDL cholesterol; LDL-C=LDL cholesterol; apoB/A-1=apolipoprotein B/A-1; HR/SD=hazard ratio per standard deviation of that variable. In every case, the lipid ratio is compared with the apolipoprotein ratio by multivariate analysis. NS=p⩾0·05.

ApoB vs. Cholesterol:
Studies in not on statin treatment

- ApoB is a better predictor of risk than LDL cholesterol.
- Ratio of apoB/apoAI is superior to total cholesterol/HDL cholesterol as an overall index of risk.

ApoB vs. Cholesterol:
Studies of On statin treatment

		Hazard Ratio		P value	
		LDL	apoB	LDL	apoB
On statin treatment					
Epidemiological studies					
Roeters van Lennep et al[8]	Regression analysis	1·16 (0·80–1·67)	3·21 (1·10·9·35)	NS	0·033
Treated group in clinical trials					
AFCAPS/TexCAPs[6]	Regression analysis	1·26† (NA)	1·66† (NA)	NS	<0·001
LIPID[7]	Regression analysis				
	Unadjusted	1·08 (0·84–1·23)	1·49 (1·02–2·17)	NS	0·05
	Adjusted	1·20 (1·00–1·45)	2·10 (1·21–3·64)	0·04	0·008

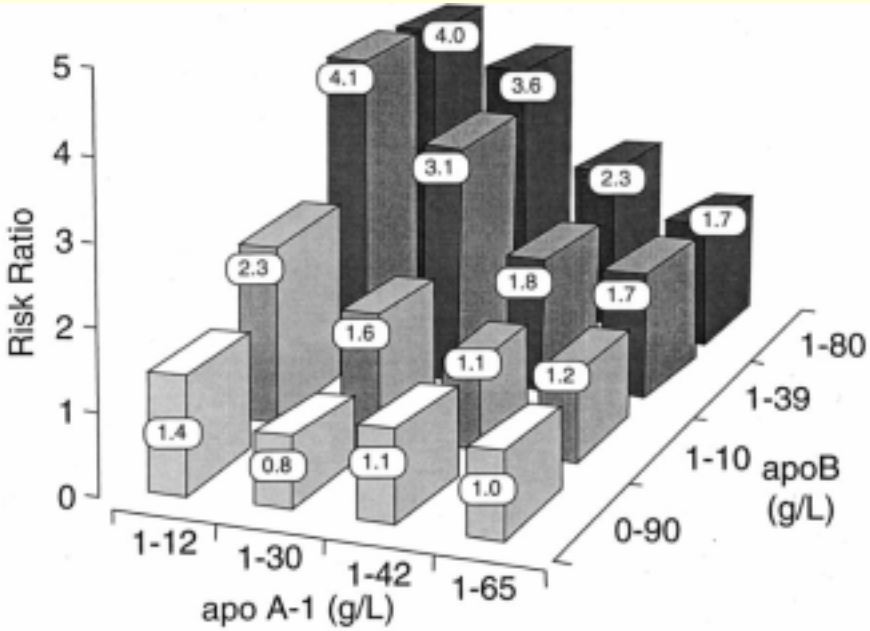
NA=not available; T=tertiles; Q=quartiles; NS=p≥0·05. *Hazard ratios from 4S[9] not yet available. †Estimated from graph.

LDL cholesterol versus apolipoprotein B as predictors of vascular events

ApoB vs. Cholesterol:

- LDL cholesterol is an independent predictor for coronary events in untreated patients.
- The association is weaker in patients in truncated placebo groups of major statin trials than in those in major epidemiology studies.
- ApoB is overall stronger predictor of coronary events than LDL cholesterol.
- ApoB/apoAI is the stronger predictor than total/HDL cholesterol.

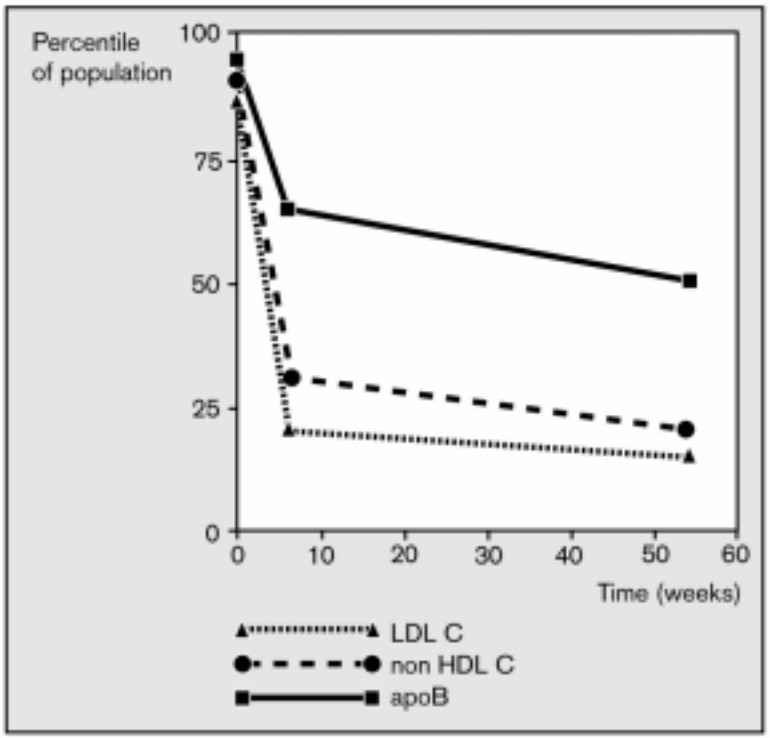
Inter-relationship beteen RR, apoB, and apoAI



Results in men <70 years from the Apoprotein-Related Mortality Risk Study (AMORIS). The risk ratios were calculated after adjustment for cholesterol and triglycerides and age. Apo = apolipoprotein. (Reproduced with permission from *Lancet*.[5])

Statin treatment may need to reduce atherogenic lipoprotein particles *per se*.

Results from a subgroup of 1889 patients from the ACCESS study



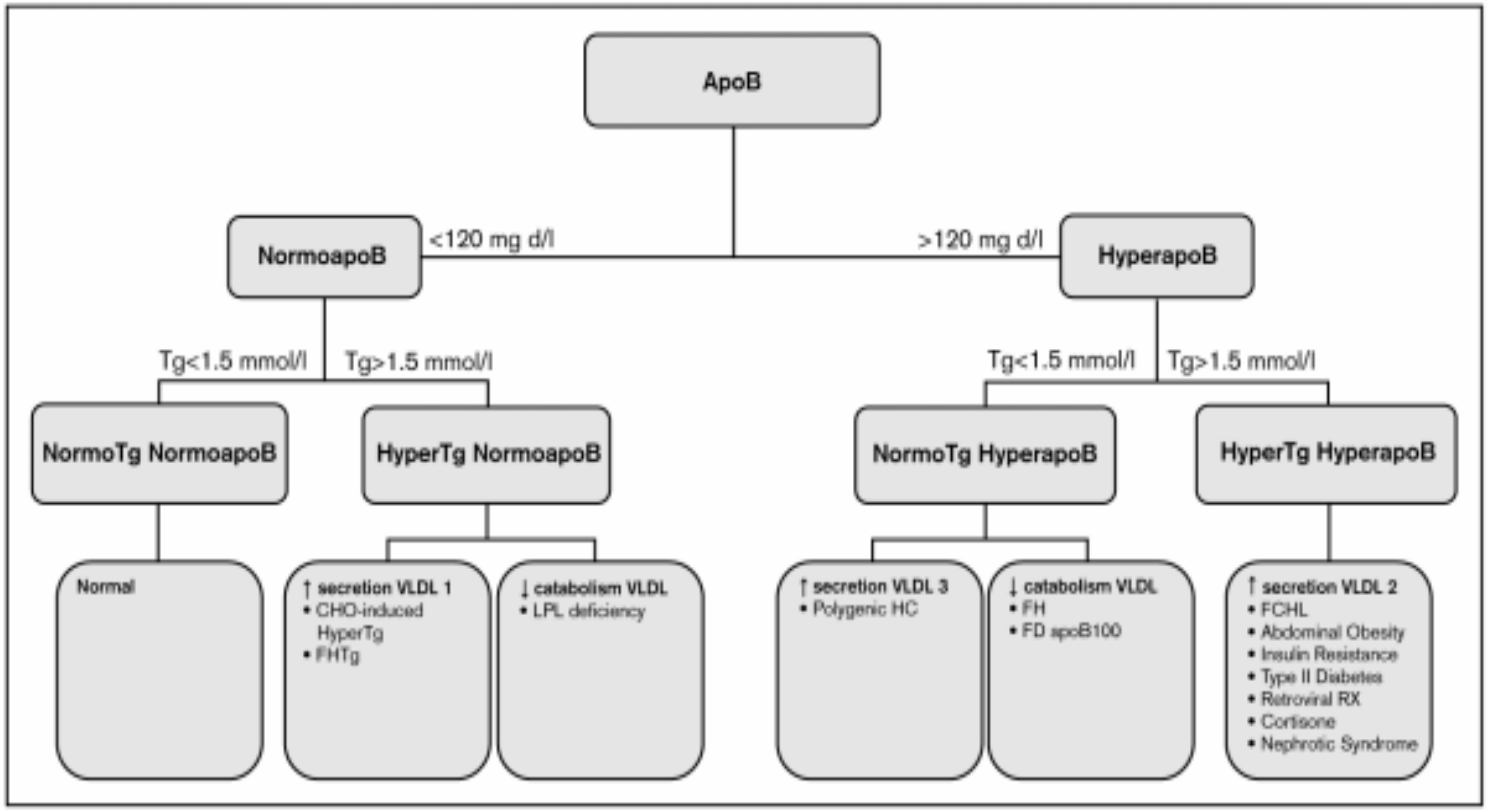
Values for LDL cholesterol (LDL C), non-HDL cholesterol (non-HDL C), and apolipoprotein B (apoB) are presented relative to the population; that is, as percentiles before and after treatment with a statin (from [3••]).

Statin effectively lowers cholesterol levels but does not reduce apoB sufficiently.

Implication for Practice

- Data suggest apoB and the apoB/apoAI ratio are more sensitive indices of risk for CHD than LDL.
- ApoB-guided statin therapy should be substantially more effective in prevention of vascular events than vascular treatment guided by LDL.
- Cutoff for >75% is ~110-140 mg/dl depending on the population characteristics.

An apolipoprotein B/triglycerides diagnostic algorithm



ApoB, apolipoprotein; Tg, triglyceridemia; hyperTg, hypertriglyceridemia; CHO-induced hyperTg, carbohydrate-induced hypertriglyceridemia; FHTg, familial hypertriglyceridemia; HC, hypercholesterolemia; FH, familial hypercholesterolemia; FD apoB100, familial defective apoB100; FCHL, familial combined hyperlipidemia; LDL, low-density lipoprotein; VLDL, very-low-density lipoprotein.

LDL Containing ApoCIII is an Independent Risk Factors for Recurrent Coronary Events in Diabetic Humans.

Sung-Joon Lee 1, Hannia Campos 1, Lemuel Moye 2, Frank M. Sacks 1.

1 Harvard School of Public Health, Department of Nutrition;
2 Texas School of Public Health.

Risk Factors for Atherosclerosis

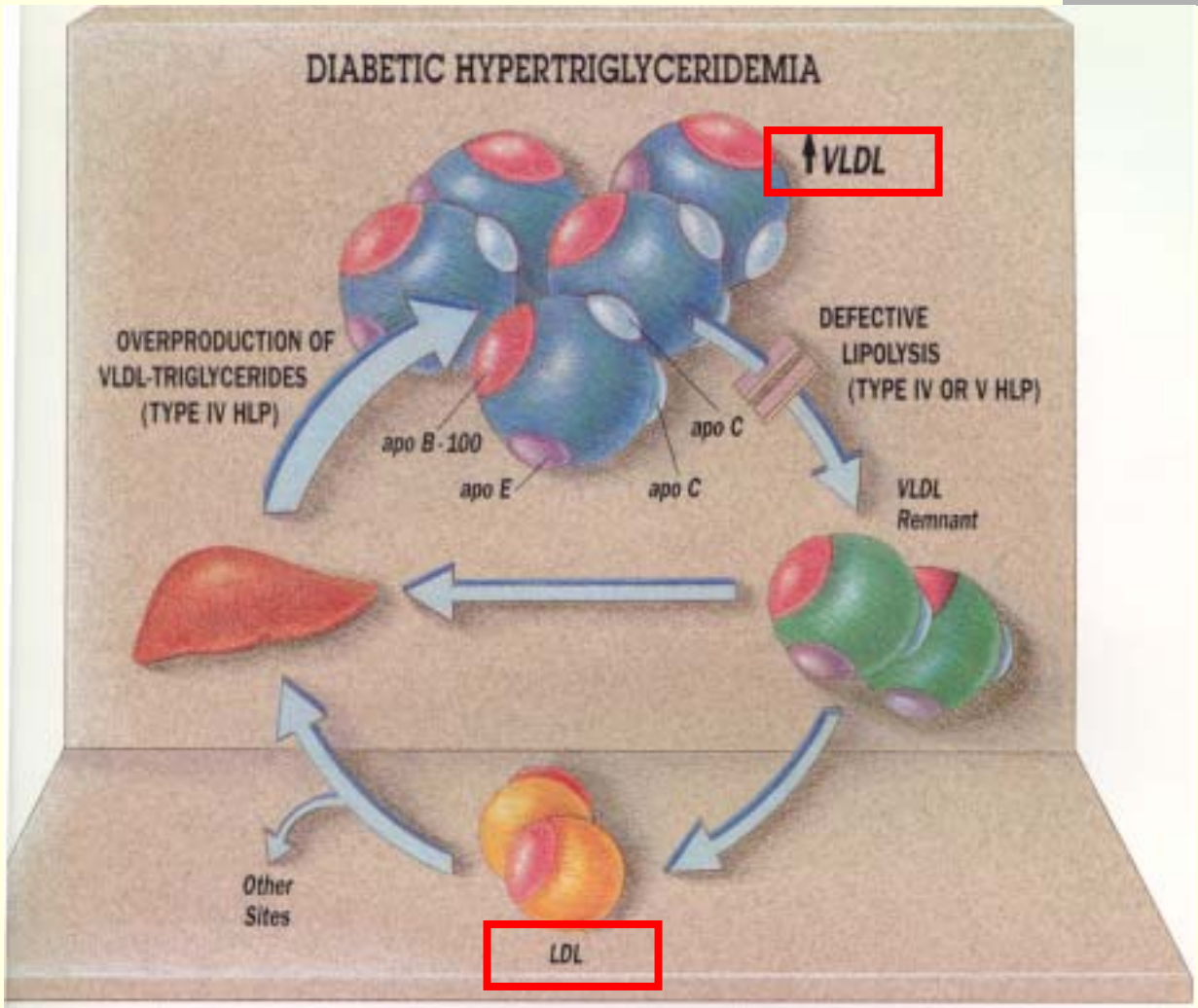
- Modifiable risk factors
  - By life-style
    - Smoking
    - Obesity
    - Physical inactivity
  - By pharmacotherapy and or life-style
    - Lipid disorders
    - Diabetes
    - Hypertension
- Unmodifiable risk factors
  - Age
  - Male gender
  - Genetics

The Risk of Coronary Heart Disease (CHD) in Diabetes Mellitus (DM).

- Patients with diabetes mellitus (DM) have 2-3 times higher age-adjusted risk of CHD than nondiabetic patients.

- Hypertriglyceridemia and the level of LDL cholesterol do not explain the high risk of CHD in patients with diabetes.

Diabetic Dyslipidemia

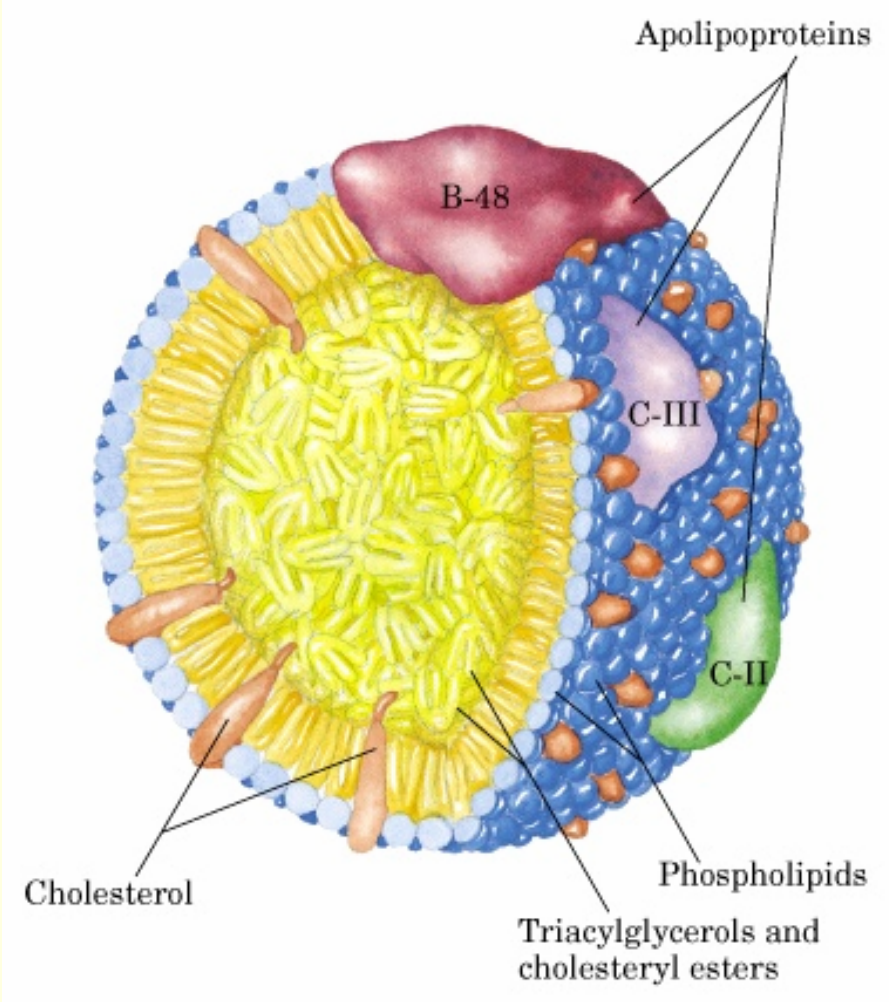


Research Question

- What lipoproteins can explain the high risk of CHD in patients with diabetes?

– Since VLDL and LDL particles are heterogeneous in composition and metabolic pathway, it is possible that certain VLDL or LDL types are more atherogenic than other types and are associated with the risk of heart disease.
– ApoCIII may be associated with risk of CHD in patients with diabetes.

Structure of ApoB containing Lipoproteins



Apolipoprotein CIII

- ApoCIII
  - Inhibitor for lipoprotein lipase.
  - Inhibitor for receptor-mediated particle clearance: both apoB- and apoE-dependent.
  - The gene expression and fasting/postprandial plasma levels of apoCIII are elevated in DM.
  - The apoCIII level in apoB lipoproteins (VLDL+LDL) is a risk factor for CHD in DM.

Apolipoprotein E

- ApoE
  - A ligand for LDL-R and LRP.
  - Anti-oxidant property: both liver- and macrophage-derived apoE.
  - Its level in VLDL+LDL is a risk factor for CHD.
  - Multiple logistic model considering both apoE and apoC3 together: the apoC3 but not apoE was an independent risk factor for coronary events.

Selected Clinical Trials of Statin Therapy for Prevention of Coronary or CHD Events

Trial	Previous MI	Lipids	Before lipid lowering, mmol/L (mg/dL)	Decrease in cholesterol, mmol/L(mg/dL)	CHD event reduction, %
WOSCOPS	-	Total cholesterol LDL	7.0(272) 5.0(192)	0.52(20) 0.67(26)	31
AFCAPS/TexCAPS	-	Total cholesterol LDL	5.7(220) 4.0(156)	0.47(18) 0.65(25)	36
4S	+	Total cholesterol LDL	6.7(261) 4.9(188)	0.65(25) 0.91(35)	34
CARE	+	Total cholesterol LDL	5.4(209) 3.6(139)	0.52(20) 0.72(28)	24
LIPID	+	Total cholesterol LDL	5.7(219) 3.9(150)	0.47(18) 0.65(25)	24

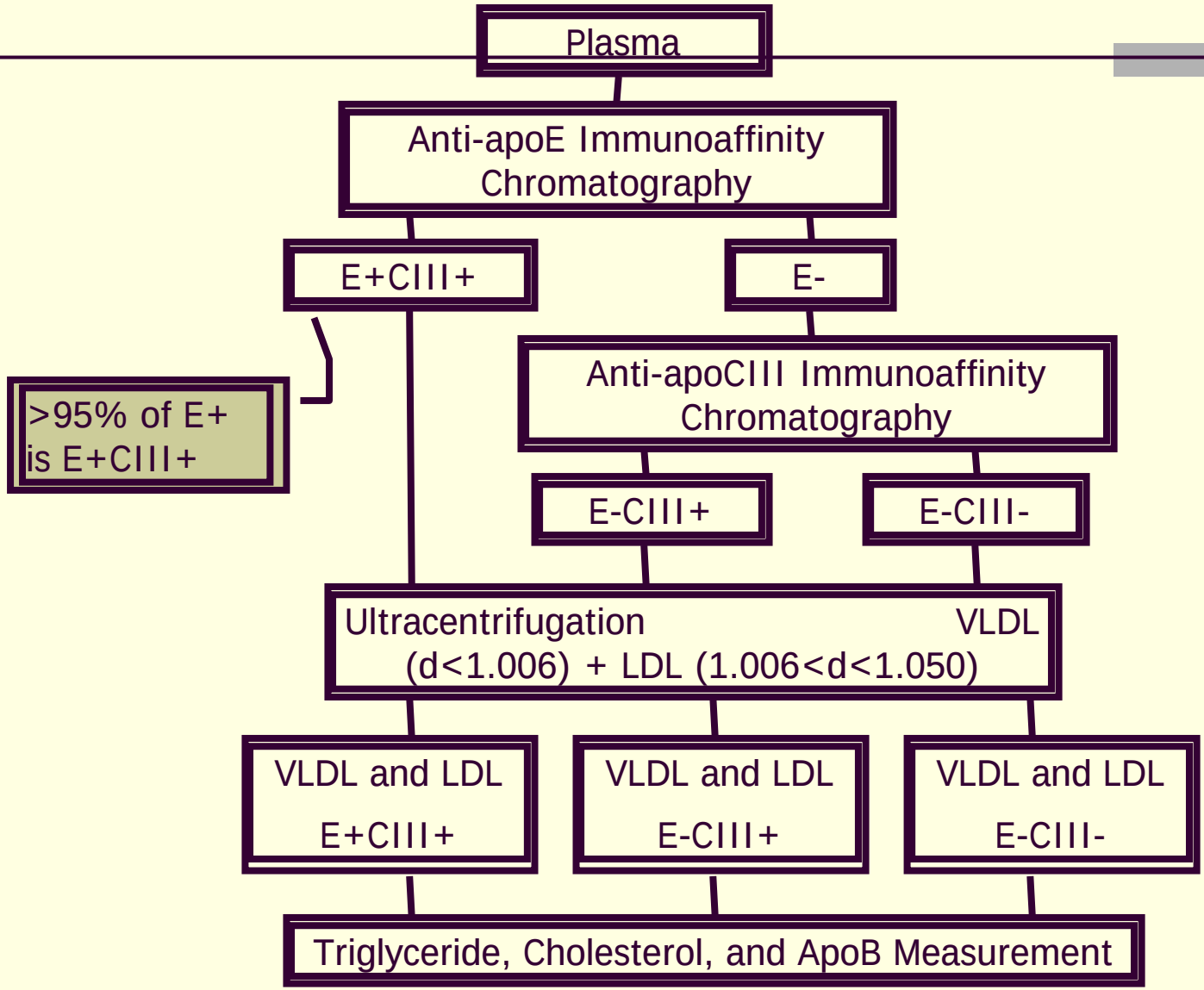
WOSCOPS: J Shepherd et al: West of Scotland Coronary Prevention Study Group. N Engl J Med 333:1301, 1995.AFCAPS/TexCAPS: JR Downs et al: Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 279:1615, 1998.4S: Anonymous: The Scandinavian Simvastin Survival Study. Lancet 344:1383, 1994.CARE: FM Sacks et al: Cholesterol and Recurrent Events Trial (CARE) Investigators. N Engl J Med 335:1001, 1996.LIPID: Anonymous: The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. N Engl J Med 339:1349, 1998.

Study Design

- **We conducted a prospective, nested case-control study among 242 diabetic patients from the CARE trial.**

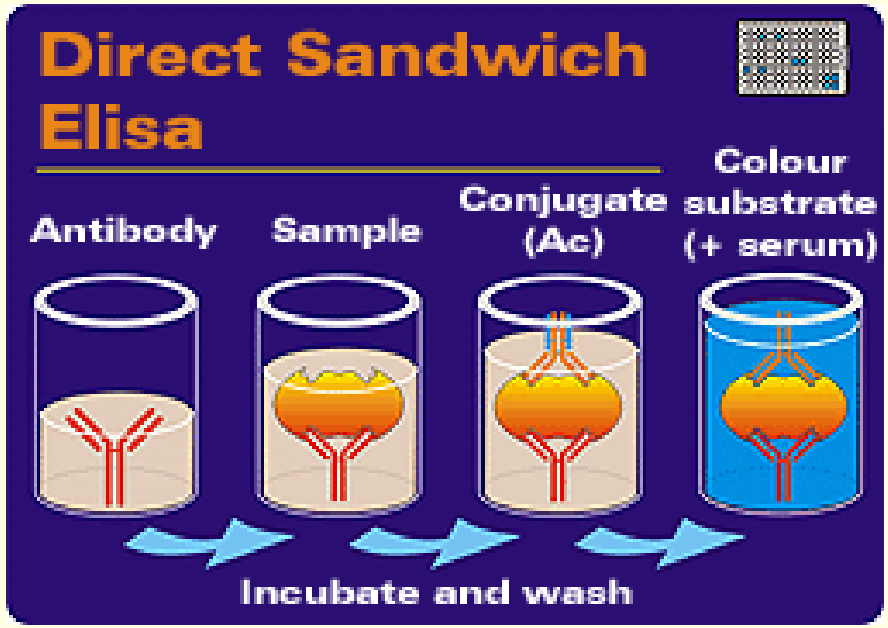
- **The cases were diabetic patients with at least one of the following recurrent coronary event during 5-year follow-up: fatal, or non-fatal myocardial infarction (MI), CABG, or PTCA. The controls were diabetic patients without a recurrent coronary event or a stroke during the follow-up.**

Isolation of Lipoproteins Containing ApoCIII



Apolipoprotein Measurement in Human Plasma

- Sandwich ELISA assay
- Fast and sensitive
- Well-established method
- Inter and intra-CV is ~5-7%



Baseline Characteristics in case and control groups.

	Controls	Cases	*P* Value
n	121	121	
Triglyceride, mg/dL	165±69	164±66	0.88
Cholesterol, mg/dL			
Total	206±17	207±16	0.74
LDL	135±14	136±14	0.66
HDL	38±10	38±9	0.95
non-HDL	168±18	169±16	0.77
Glucose, mg/dL	143±49	149±52	0.35
Age, y	61±8	61±9	0.72
Male sex	83	83	1
White race	86	87	0.71
Alcohol, drinks/wk			0.30
None	76	73	
1–4	17	17	
5–10	5	3	
≥11	2	10	

Baseline Characteristics in case and control groups.

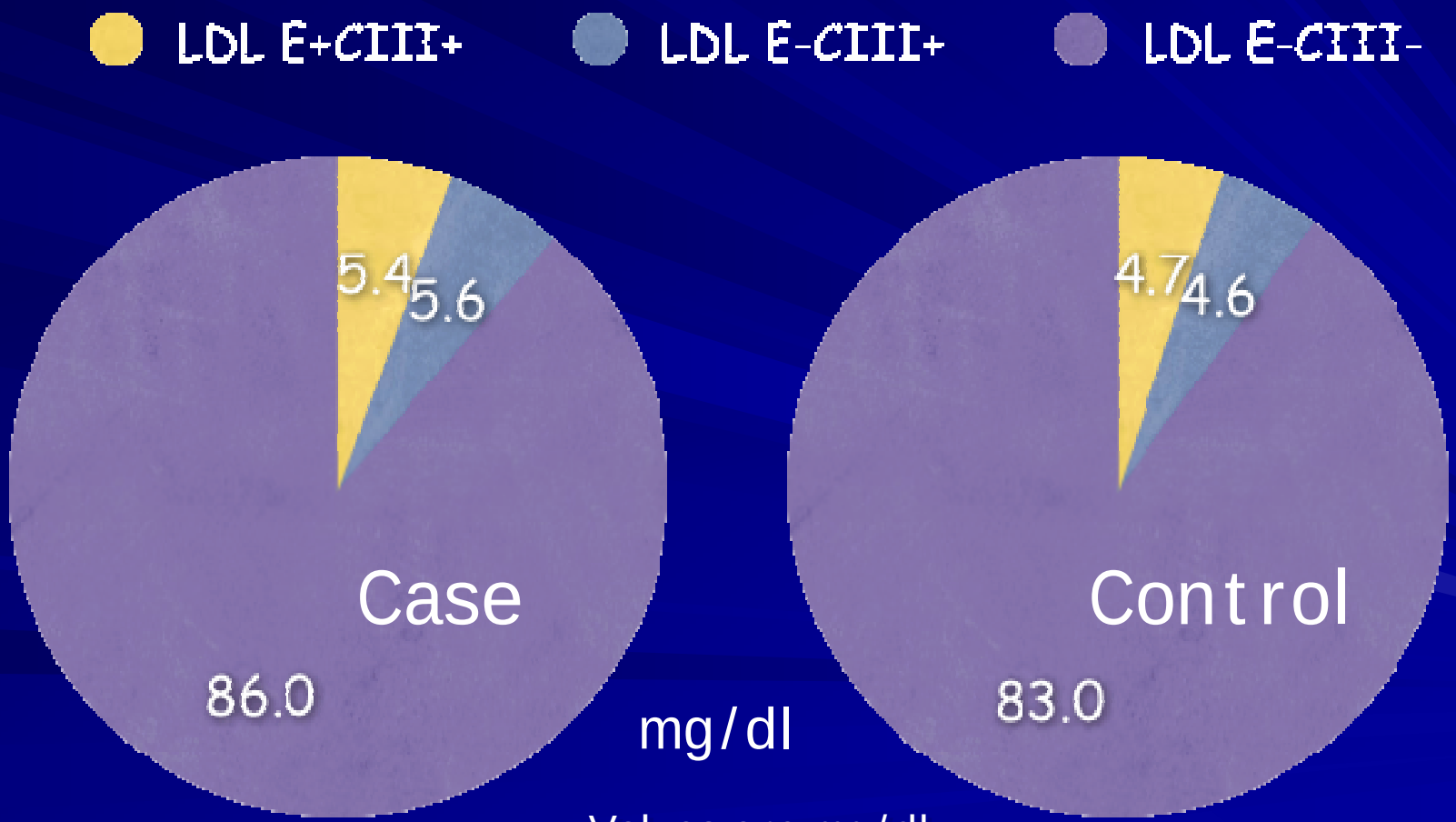
	Controls	Cases	*P* Value
Current smoker	11	16	0.26
Systolic blood pressure	131±20	134±19	0.19
Diastolic blood pressure	77±10	78±11	0.46
Diabetes	100	100	—
Hypertension	49	63	0.61
Angina	21	33	0.04
CABG	35	19	0.006
PTCA	27	26	0.77
LVEF	52±13	51±12	0.65
Body mass index, kg/m^2	29±5	29±5	0.41
Waist circumference, cm	99±12	102±16	0.06
Medication use			
Oral hypoglycemic	40	50	0.09
β-blockers	35	43	0.19
ACE inhibitor	21	24	0.65
Diuretics	21	23	0.76
Insulin	13	20	0.17
Estrogen	2	2	0.65

Particle concentration (ApoB), cholesterol and triglyceride levels in apoB lipoproteins containing apoC3 or apoE

	Control subjects N=121	Cases N=121	P-value*
LDL E+C3+			
ApoB	4.7 ± 1.7	5.4 ± 2.4	0.0001
Cholesterol	19 ± 6.1	20 ± 7.1	0.005
Triglyceride	11 ± 5.2	12 ± 5.7	0.08
LDL E-C3+			
ApoB	4.6 ± 2.4	5.6 ± 3.2	0.0002
Cholesterol	18 ± 9.7	20 ± 11	0.02
Triglyceride	6.8 ± 3.5	7.9 ± 3.9	0.01
LDL E-C3-			
ApoB	83 ± 25	86 ± 27	0.003
Cholesterol	112 ± 29	112 ± 29	0.13
Triglyceride	17 ± 5.2	19 ± 7.7	0.02

N=121/group.
Values are mean±std. *P-values are calculated from paired t-test.

Composition of LDL in case and control groups.



Values are mg/dl.

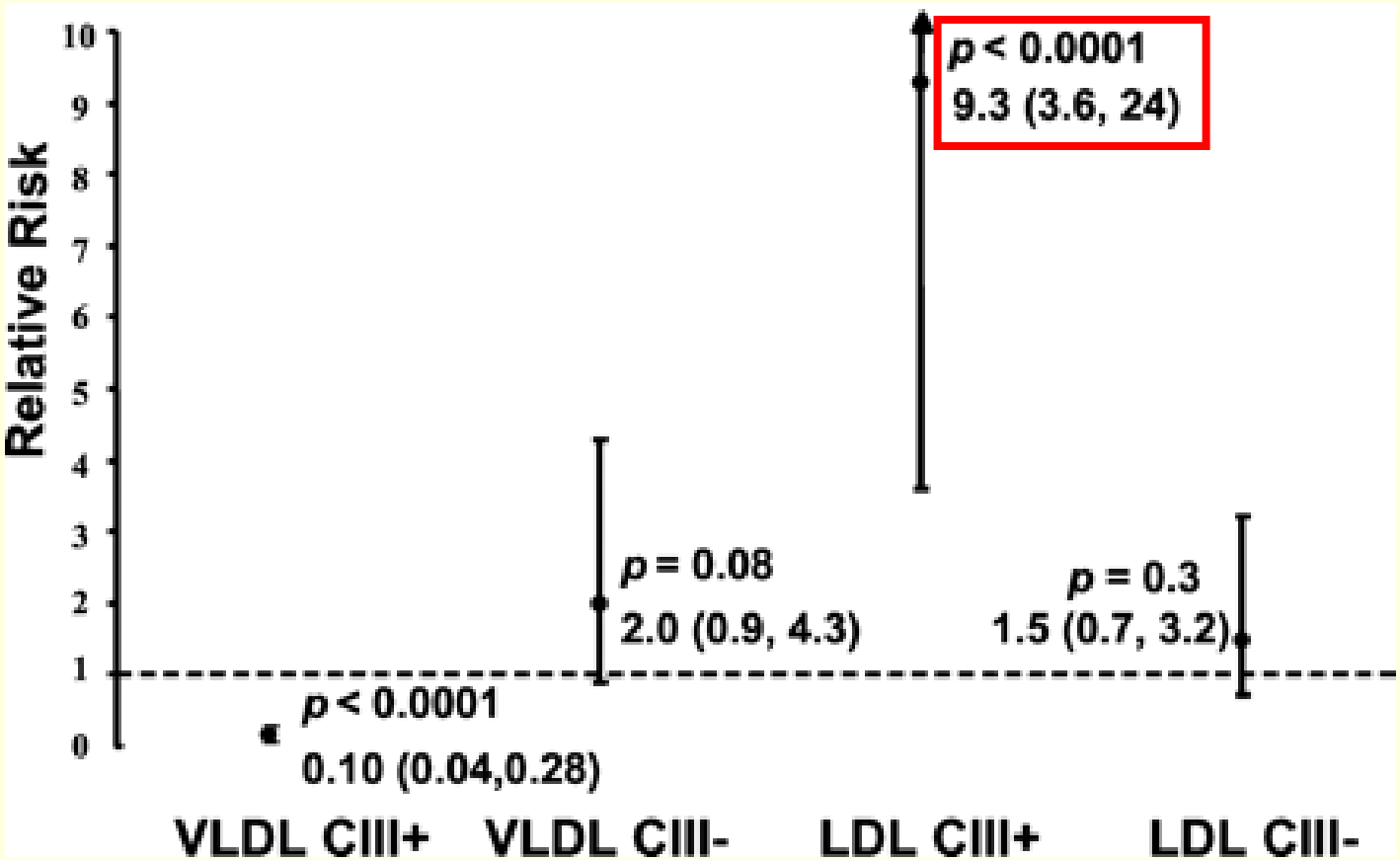
Relative risks and recurrent coronary events for lipoprotein concentration and composition

		Quartiles			
		1	2	3	4
VLDL CIII+	Mean	0.8	1.4	2.3	3.9
adjusted	RR (CI)	1	0.5 (0.2,1.0)	0.6 (0.3,1.3)	0.5 (0.2,1.1)
	p		0.06	0.2	0.07
VLDL CIII-	Mean	0.9	1.9	2.4	3.8
adjusted	RR (CI)	1	1.0 (0.4,2.3)	0.5 (0.2,1.3)	2.3 (1.0,5.3)
	p		1.0	0.2	0.05
LDL CIII+	Mean	4.5	5.9	7.2	10.4
adjusted	RR (CI)	1	3.0 (1.2,7.6)	1.7 (0.6,4.7)	6.6 (2.6,17)
	p		0.02	0.3	<0.0001
LDL CIII-	Mean	42	55	65	86
adjusted	RR (CI)	1	1.0 (0.4,2.2)	1.6 (0.7,3.7)	2.2 (0.9,5.0)
	P		0.9	0.2	0.07

Mean values are apolipoprotein B concentrations (mg/dl). Adjusted: Baseline triglyceride, LDL cholesterol, HDL cholesterol, age, gender, exercise, waist circumference, CABG, angina, glucose, oral hypoglycemic use, and treatment group (placebo or pravastatin) were included. RR= Relative risk, CI=95% confidence interval. "LDL" includes the IDL fraction. In the nomenclature of Alaupovic,9 CIII+ is Lp-B:C and CIII- is Lp-B.

Lee et al. Arterioscler Thromb Vasc Biol. 2003 May 1;23(5):853-8.

Multivariate analysis of VLDL and LDL types as predictors of recurrent coronary events in diabetes. The apoB concentrations of VLDL and LDL particle types were included together. The LDL fraction includes IDL.



Lee et al. Arterioscler Thromb Vasc Biol. 2003 May 1;23(5):853-8.

Conclusion

• ApoCIII+ LDL (E+CIII+, E-CIII+) are independent predictors of recurrent coronary events in diabetic patients beyond standard lipid measurements (LDL, HDL, and triglyceride).

ApoCIII+ LDL may be particularly atherogenic, more so the major LDL particles (the E-CIII- type), since a small increase in concentration is associated with a 6-fold increase in risk.

In multivariate analysis, the LDL particle concentrations of E+CIII+ was not protective (RR=2.40, p=0.04). This finding suggests that apoCIII may have a dominant role in atherogenicity of the lipoprotein particles.

Can pravastatin reduce apoCIII-containing LDL?

- **To test whether pravastatin, an HMG CoA reductase inhibitor, reduces LDL apoCIII+ as well as LDL apoCIII-, which represents conventional LDL particles.**

Study Design

- 45 age- and sex-matched placebo-pravastatin pairs were randomly selected among diabetic patients from the CARE.

- Lipoprotein types were isolated with affinity chromatography, the levels of particle types were measured at both baseline and after 1 year of treatment, and the baseline-1 year differences were compared between the placebo and the pravastatin groups.

Baseline characteristics of the placebo and pravastatin groups with diabetes mellitus

TABLE 1 Baseline Characteristics of the Placebo and Pravastatin Groups With Diabetes Mellitus

Variable	Placebo (n = 45)	Pravastatin (n = 45)	p Value
Age (yrs)	60 ± 9	62 ± 8	0.3
Caucasian	39 (87%)	39 (87%)	1.0
Men	35 (78%)	35 (78%)	1.0
Current smoker	6 (13%)	6 (13%)	1.0
Coronary bypass	11 (24%)	14 (31%)	0.5
Coronary angioplasty	13 (29%)	10 (22%)	0.5
Hypertension	24 (53%)	22 (49%)	0.7
Exercise (>3 times/wk)	23 (51%)	25 (56%)	0.7
Blood pressure (mm Hg)			
Systolic	129 ± 19	134 ± 25	0.4
Diastolic	76 ± 10	79 ± 11	0.3
Blood glucose (mg/dl)	148 ± 44	147 ± 49	0.9
Body mass index (kg/m^2)	29 ± 5	31 ± 6	0.16
Waist circumference (cm)	102 ± 13	104 ± 14	0.5
Oral hypoglycemic	23 (51%)	14 (31%)	0.06
Insulin	12 (27%)	7 (16%)	0.2
β blockers	19 (42%)	15 (33%)	0.4

Data are presented as number of patients (percent) in the population and mean ± SD. p Values were calculated from paired *t* tests.

Plasma lipid concentration at baseline and one year of treatment

TABLE 2 Plasma Lipid Concentrations at Baseline and After One Year of Treatment

	Placebo Group (n = 45)			Pravastatin Group (n = 45)				
	Mean ± SD			Mean ± SD			Pravastatin/Placebo	
Variable	Baseline	1-Yr	p Value	Baseline	1-Yr	p Value	% Change†	p Value
Total cholesterol (mg/dl)	206 ± 18	207 ± 56	0.58	208 ± 18	172 ± 34	0.0002	−18%	0.006
LDL cholesterol (mg/dl)	135 ± 16	134 ± 31	0.70	137 ± 14	93 ± 28	<0.0001	−31%	0.01
HDL cholesterol (mg/dl)	38 ± 9	39 ± 10	0.23	37 ± 9	38 ± 8	0.94	−2%	0.21
Triglyceride* (mg/dl)	148 ± 44	150 ± 54	0.55	159 ± 50	166 ± 55	0.69	−1%	0.62

*Triglyceride values are geometric mean ± SD.

†Percent change means the percentage difference between the 1-year baseline difference in the placebo and the 1-year baseline difference in the pravastatin group.

Particle concentration and cholesterol and triglyceride levels

TABLE 3 Particle (apo-B) Concentration and Cholesterol and Triglyceride Levels in Apo-B Lipoproteins Containing Apo-CIII or Apo-E at Baseline and After One Year of Treatment in Placebo and Pravastatin Groups

	Placebo (n = 45)			Pravastatin (n = 45)			Pravastatin/Placebo	
	Baseline	1 Yr	p Value	Baseline	1 Yr	p Value	% Change*	p Value
VLDL E+CIII+								
Apo-B	1.9 ± 1.4	2.1 ± 1.3	0.3	2.0 ± 1.5	2.3 ± 1.5	0.3	1%	1.0
Cholesterol	12 ± 9	13 ± 10	0.5	13 ± 8	14 ± 12	0.4	3%	0.8
Triglycerides	67 ± 56	79 ± 63	0.3	64 ± 46	79 ± 57	0.09	6%	0.8
VLDL E−CIII+								
Apo-B	0.8 ± 0.6	1.1 ± 0.8	0.002	1.0 ± 1.1	1.4 ± 1.7	0.04	−9%	0.9
Cholesterol	3.6 ± 3.0	4.5 ± 3.4	0.11	4.4 ± 4.2	6.2 ± 8.0	0.09	17%	0.5
Triglycerides	20 ± 17	28 ± 22	0.03	23 ± 22	37 ± 48	0.02	26%	0.3
VLDL E−CIII−								
Apo-B	3.2 ± 1.4	3.4 ± 1.6	0.6	3.6 ± 1.8	3.5 ± 3.8	0.9	−8%	0.7
Cholesterol	6.3 ± 3.2	7.3 ± 4.0	0.09	7.3 ± 3.4	6.9 ± 6.9	0.8	−21%	0.3
Triglycerides	20 ± 10	22 ± 12	0.17	21 ± 11	20 ± 18	0.8	−16%	0.4
IDL+LDL E+CIII+								
Apo-B	4.2 ± 1.6	3.3 ± 1.2	<0.0001	6.5 ± 3.6	2.3 ± 1.2	<0.0001	−42%	0.02
Cholesterol	20 ± 6	14 ± 7	<0.001	25 ± 11	10 ± 7	<0.001	−29%	0.002
Triglycerides	12 ± 7	11 ± 9	0.8	12 ± 7	9 ± 5	0.003	−28%	0.5
IDL+LDL E−CIII+								
Apo-B	5.6 ± 3.2	4.5 ± 3.2	0.01	5.7 ± 3.6	3.6 ± 2.6	0.0001	−17%	0.7
Cholesterol	21 ± 11	16 ± 11	<0.001	23 ± 14	11 ± 7	<0.001	−25%	0.2
Triglycerides	7.9 ± 3.8	10 ± 9	0.12	7 ± 3	7 ± 6	0.9	−24%	0.7
IDL+LDL E−CIII−								
Apo-B	86 ± 29	92 ± 24	0.3	92 ± 29	72 ± 22	0.0002	−29%	0.002
Cholesterol	111 ± 25	114 ± 35	0.7	129 ± 43	85 ± 31	<0.001	−36%	<0.0001
Triglycerides	18 ± 5	19 ± 4	0.07	18 ± 5	16 ± 6	0.02	−22%	0.003

Values (mg/dl) are mean ± SD.

*Percent change means the percentage difference between the 1-year baseline difference in the placebo and the 1-year baseline difference in the pravastatin group.

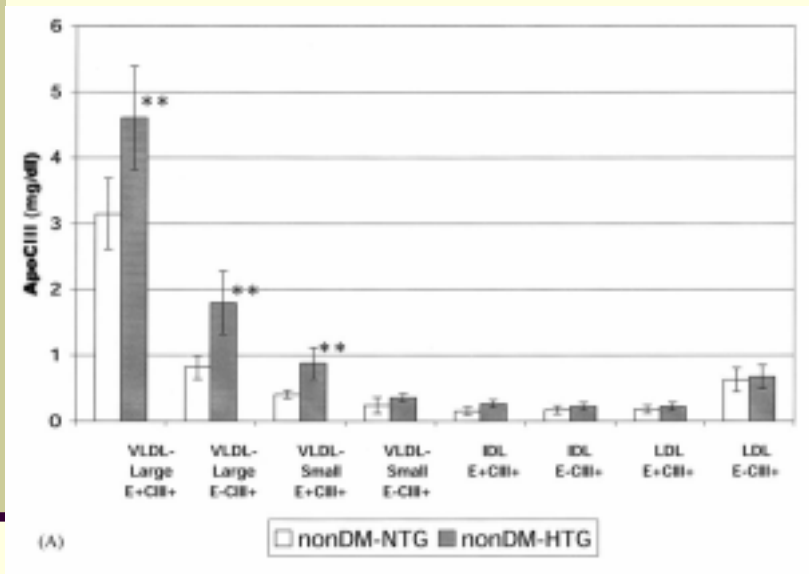
Am. J. Cardiol. 92 121-124 2003.

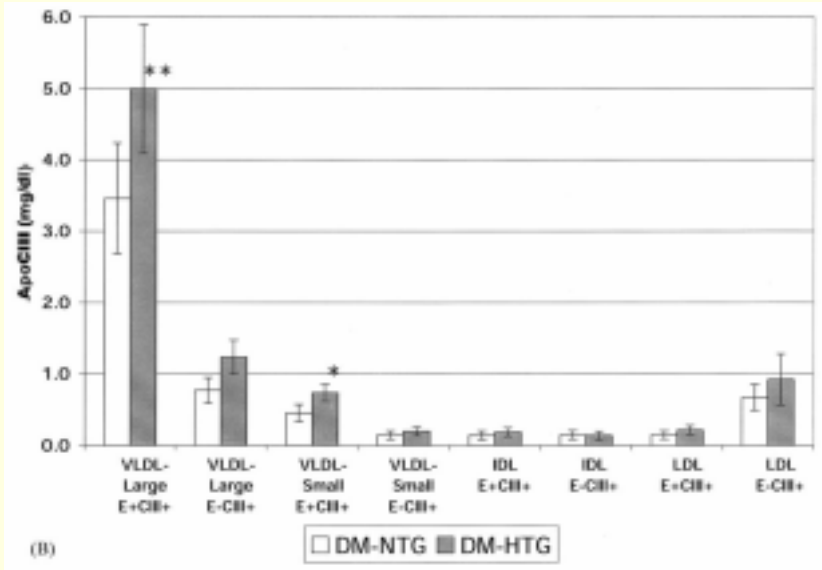
Conclusion

- Our results show that apoCIII+ LDL particles as well as the major type of LDL, the E-CIII- subtype, are reduced by pravastatin therapy.

- Since the percentage reduction in apoCIII+ LDL is similar to the reduction in LDL E-CIII-, the benefit from reducing apoCIII+ LDL could be more important than the lowering of LDL E-CIII.

Apolipoprotein CIII concentrations in HTG and NTG groups





A shows DM groups while B shows non-DM groups.
Lee at al. Atherosclerosis. 2003 167:293-302.

Conclusion

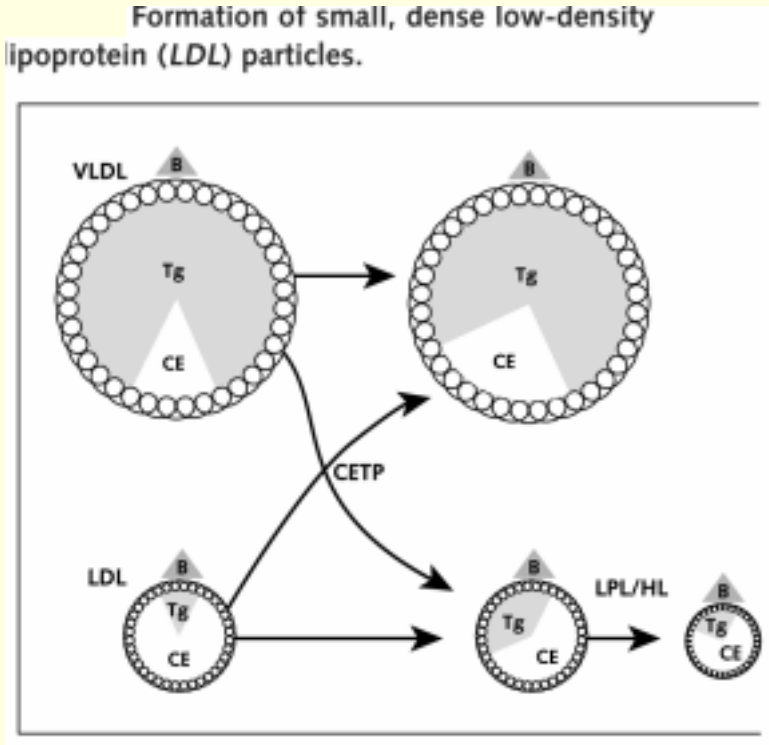
- ApoB is a stronger predictor for CHD risk than cholesterol.
- ApoCIII-LDL is potent atherogenic lipoprotein particles in diabetic patients with previous MI.
- ApoCIII-LDL is reduced by 1-year of pravastatin therapy.
- ApoCIII-LDL exists similar level in both diabetic and non-diabetic patients with previous MI.

Watch out apoB as well as LDL!

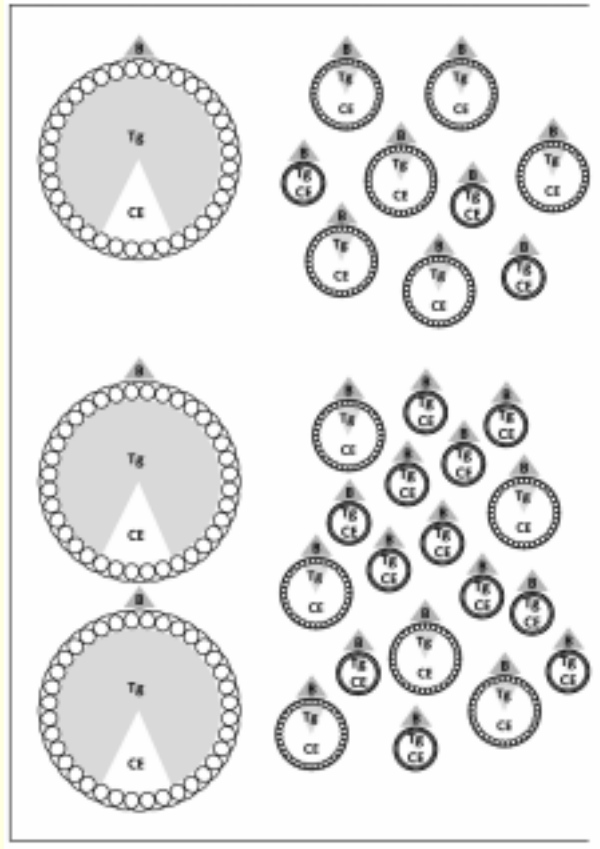
Thank you ☺

Formation of Small Dense LDL

- Transfer of TG from VLDL to LDL results in formation of TG rich LDL.
- TG rich LDL is a good substrate for LPL
- LPL degrades TG component in LDL resulting in the generation of small dense LDL.
- The rate of this pathway depends on hepatic VLDL secretion
- Hypertriglyceridemia is associated with the prevalence of small dense LDL



ApoB lipoprotein particles in healthy persons (*left*) and those with hypertriglyceridemic hyperapoB (*right*).



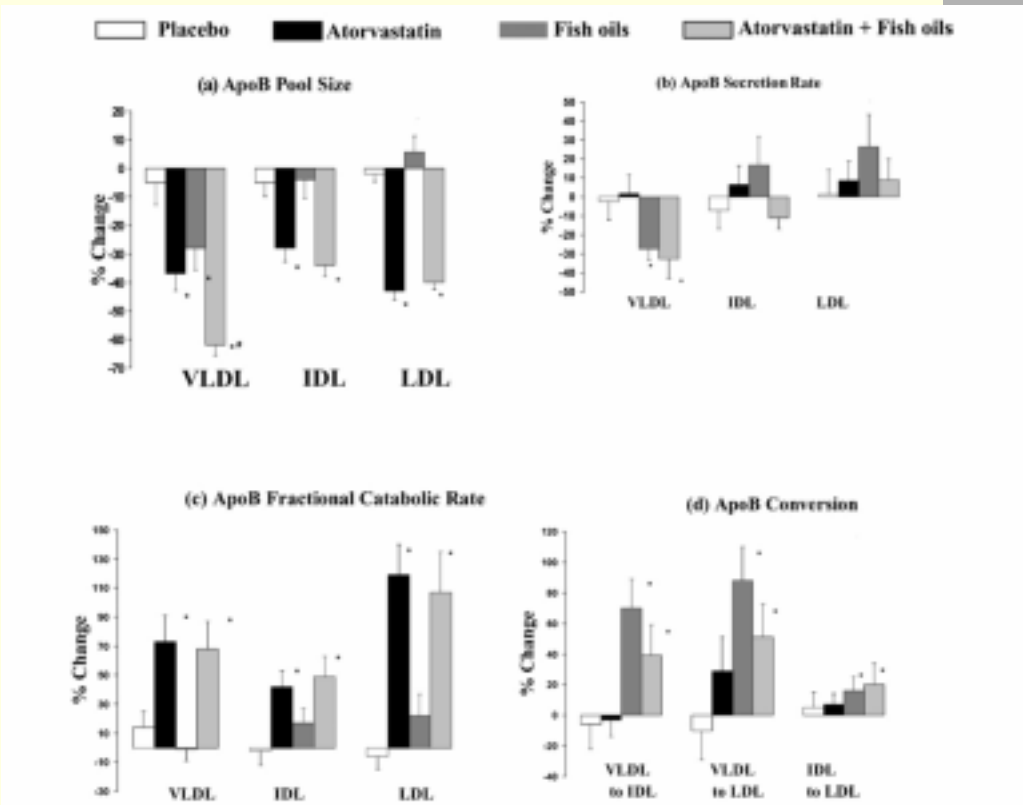


Figure 3 Percentage change in apoB (a) pool sizes, (b) secretion rate, (c) fractional catabolic rate and (d) conversion for VLDL, IDL and LDL on placebo, atorvastatin, fish oils and atorvastatin + fish oils respectively

*$P < 0.01$ compared with the placebo group; **$P < 0.05$ compared with the atorvastatin or fish oil groups.

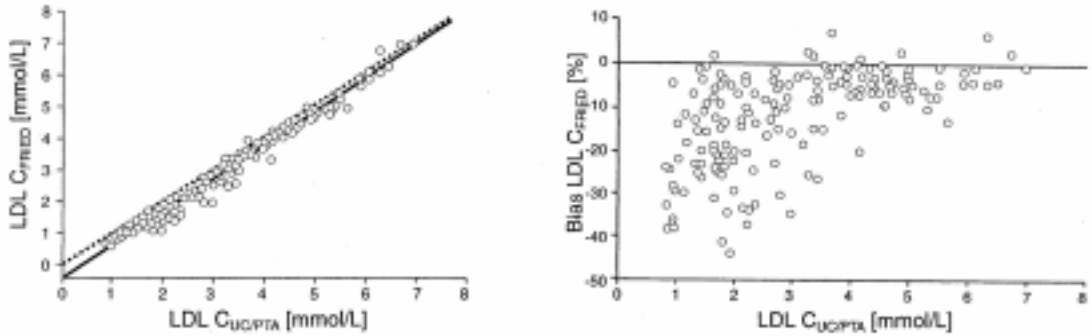


FIGURE 2. (*Left*) Overall relation between low-density lipoprotein (LDL) cholesterol measured by beta quantitation (LDL $C_{UC/PTA}$) and LDL cholesterol calculated by the Friedewald (Fried) formula. Beta quantitation is performed first by removal of very low-density lipoprotein by ultracentrifugation (UC) and then precipitation of LDL with phosphotungstic acid/Mg Cl2 (PTA). (Reproduced with permission from *Clin Chem Lab Med.*[14])

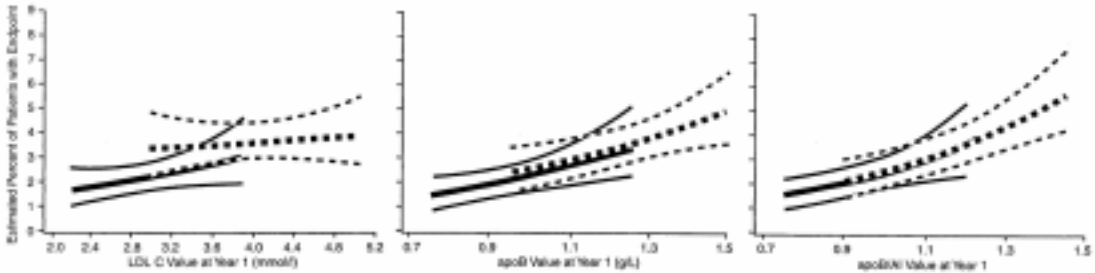


FIGURE 3. (*Left*) Relation between risk in the placebo group (*dashed line*) and the treated group (*solid line*) and the level of low-density lipoprotein cholesterol (LDL-C) at 1 year. (*Center*) The same relations for apolipoprotein (apo) B and apo B/apoAI (*right*). (Adapted from *Circulation.*[10])

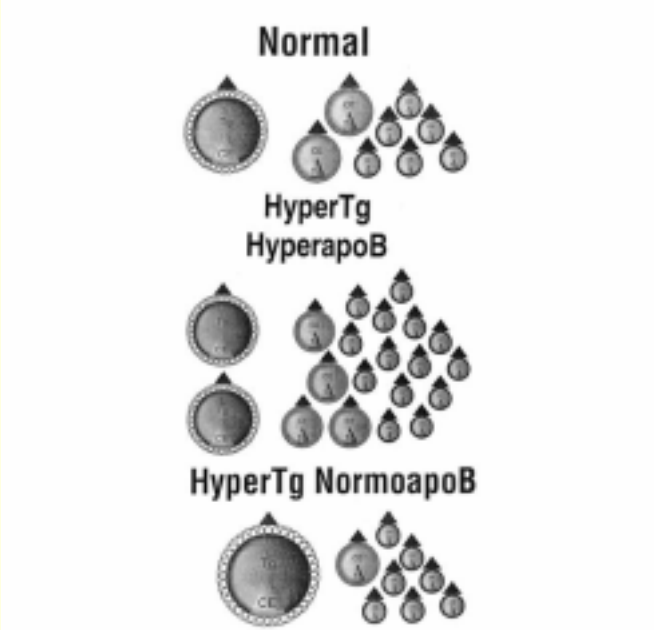


FIGURE 4. (*Top*) Very low-density lipoprotein and low-density lipoprotein particle number and composition in a normal subject. (*Middle*) A patient with hypertriglyceridemic (hyperTg) hyperapo B. (*Bottom*) A patient with hyperTg normoapo B. apo = apolipoprotein.

TABLE 1 Diagnostic Utility of Apolipoprotein B in Hypertriglyceridemia

Case	TG (mg/dL)	TC (mg/dL)	Non–HDL-C (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Apo B (mg/dL)
1	370	197	161	94	36	69
2	266	254	211	157	43	144
3	400	300	265		35	90
4	400	300	265		35	140

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides.

TABLE 2 Diagnostic Utility of Apolipoprotein B in Hypercholesterolemia

Case	TG (mg/dL)	LDL Cholesterol (mg/dL)	Apo B (mg/dL)
1	100	165	110
2	200	165	145
3	100	350	160

Apo = apolipoprotein; LDL = low-density lipoprotien; TG = triglycerides.

TABLE 3 Diagnostic Utility of Apolipoprotein B with Normal Cholesterol and Triglycerides

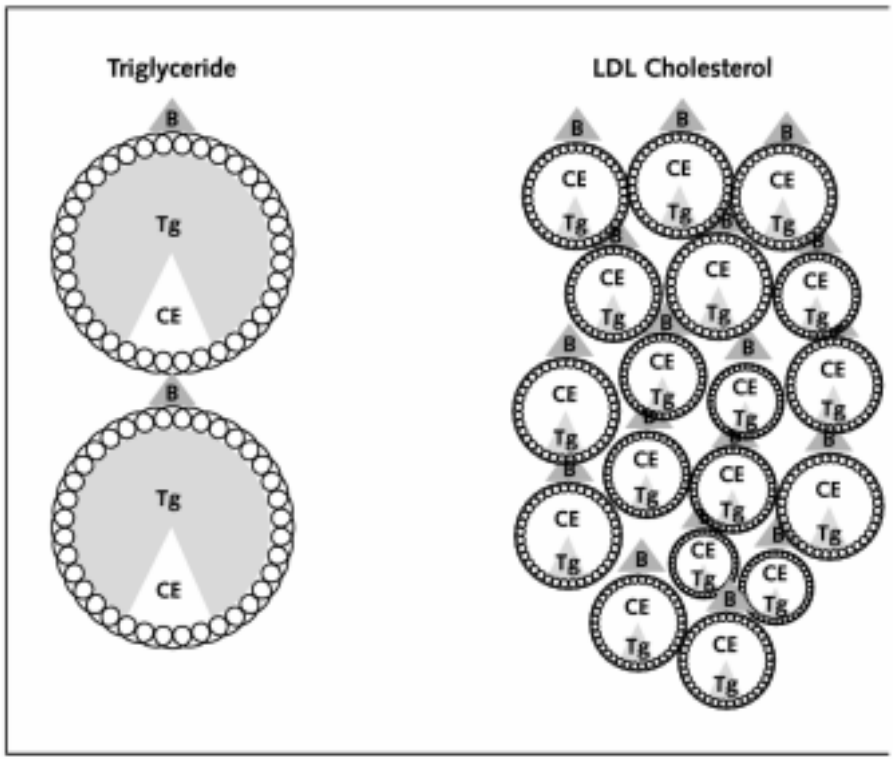
Case	TG (mg/dL)	LDL Cholesterol (mg/dL)	Apo B (mg/dL)	HDL Cholesterol (mg/dL)
1	120*	135	100	45
2	120	135	130	45
3	100	130	90	25
4	100	130	125	25

Apo = apolipoprotein; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglycerides.

Composition of ApoB Lipoproteins:

VLDL vs LDL

Differences between lipoprotein lipids and lipoprotein particles in a patient with a plasma triglyceride level of 3 mmol/L (264 mg/dL) and a low-density lipoprotein (*LDL*) cholesterol level of 3 mmol/L (116 mg/dL).



B = apoB100; CE = cholesterol ester; Tg = triglyceride.