Apolipoprotein B

The surface apolipoprotein on chylomicrons, chylomicron remnants, VLDL particle and remnants, intermediate and low density lipoproteins

Diseases of The Heart and Circulation
Paul Wood MD FRCP
1958

The total serum cholesterol, which is normally around ***150-300*** mg% is certainly related to atherosclerosis, but has found to be only a crude measure of blood lipid disturbance.

In atherosclerosis there is a relative and absolute increase in the **ß lipoproteins,** even when the blood cholesterol is normal.

J B Lippincott Co Philadelphia, PA

The Heart
J. Willis Hurst and R. Bruce Logue

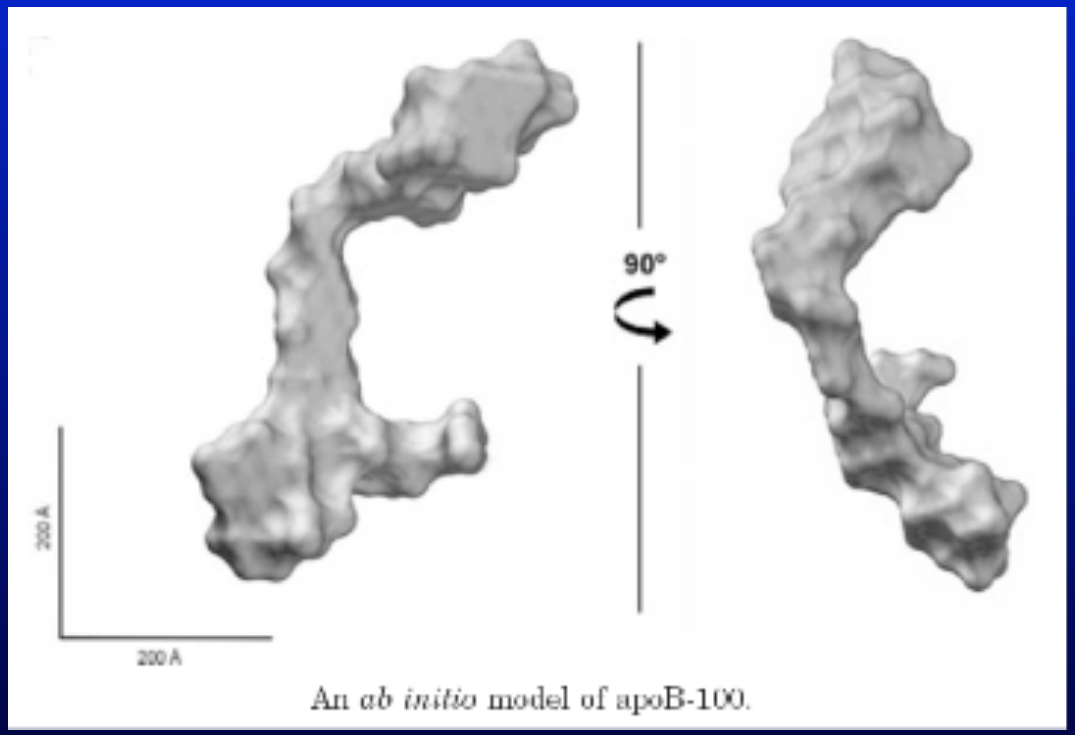
Cholesterol is distributed throughout all of the lipoprotein fractions of the plasma.

The preoccupation of cholesterol as a cause of atheromatosis has probably been attributed to then fact that **it is relatively easy to measure** and does to a certain extent reflect the concentration of  lipoproteins.

The view is the  lipoproteins may be considered the agent for atherosclerosis.

McGraw Hill, New York, NY 1966

Apolipoprotein B



An *ab initio* model of apoB-100.

Low density lipoproteins (LDL) transport cholesterol and triglycerides to various cells and tissues throughout the body. The receptor mediated uptake of LDL is triggered by apolipoprotein B-100, which is the only protein component of LDL.

Human apolipoprotein B-100 is a glycoprotein with a molecular mass of about 550 kDa. It associates with hydrophobic molecules in a noncovalent fashion to facilitate their transport and targeting in a hydrophilic environment.

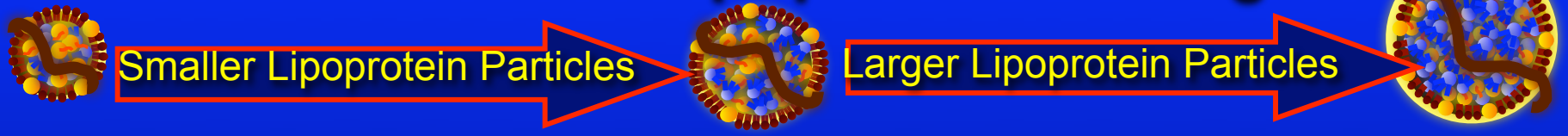
***J. Biol. Chem.* 2006, 281, 19732–19739**

Lipid Transportation

- In vertebrates the predominant means of bulk lipid transport is achieved by apolipoprotein (apo) B containing lipoprotein assembly which is responsible for intestinal chylomicron formation and VLDL assembly in the liver and heart.
- Although apoB-containing lipoproteins are critical for lipid absorption and triglyceride homeostasis, their accumulation plasma induces atherosclerosis

Shelness GS & Ledford AS Curr Opin Lipidol 2005;16:325-332

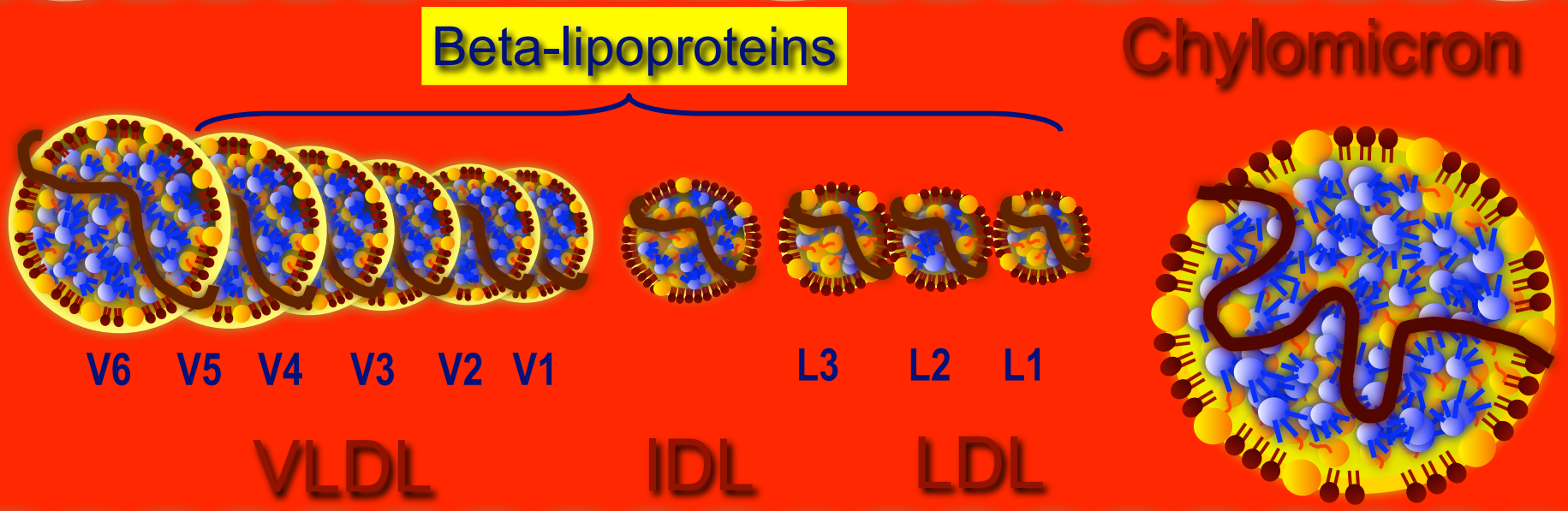
Advanced Lipoprotein Testing



Segmented gradient gel electrophoresis	**Berkeley HeartLab Inc.**									
LDL Particles	Pattern B			Pattern Intermediate			Pattern A			
	IVb	IVa		IIIb	IIIa	IIb	IIa	I		MeasuredApoB value
HDL Particles	3c		3b		3a	2a		2b		
VLDL Particles	VLDL subclass not measured by this commercial method									
Nuclear Magnetic Resonance	**LipoScience**									
LDL Particles	Pattern B							Pattern A		
	L1			L2			L3			LDL-P value
HDL Particles		H1	H2		H3			H4	H5	
VLDL Particles	V1	V2		V3		V4		V5	V6	
Short, single vertical spin density-gradient ultracentrifugation (Vertical Auto Profile/VAP)										
LDL Particles	Pattern B			Pattern A/B			Pattern A			
	LDL 4		LDL3			LDL2		LDL1		In-house calculated apoB value
HDL Particles	HDL3 (d,c,b,a)					HDL2 (a,b,c)				
VLDL Particles	VLDL 3b			VLDL 3a			VLDL 1+2			

Bays et al. Preventive Cardiology 2003 (fall);VI:187

Lipoprotein Class & Subclass



There is one molecule of apoB on each beta-lipoprotein particle. Because of its l2-3 day half-life, over 90% of apoB particles are LDLs

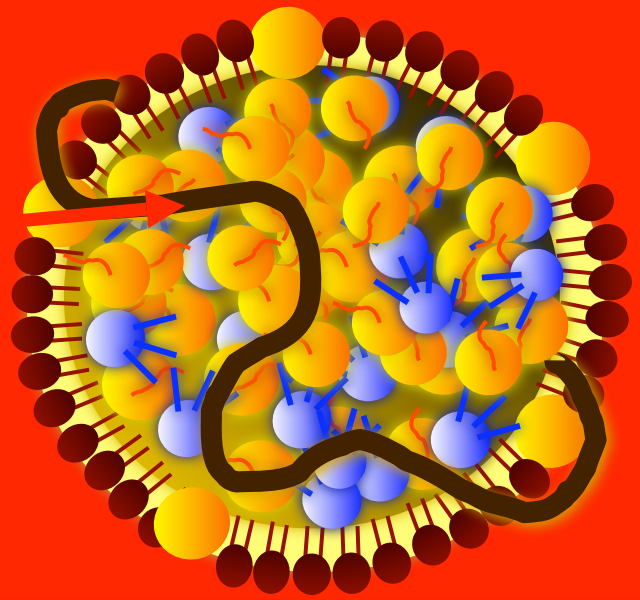
Arterioscler Thromb Vasc Biol 1998;18:1046-1053

Handbook of lipoprotein Testing 2nd Ed 2000 AACC Press Washington DC

LDL Particle Concentration

Estimated by Apo B-100 concentration

Normal is < 90 mg/dl



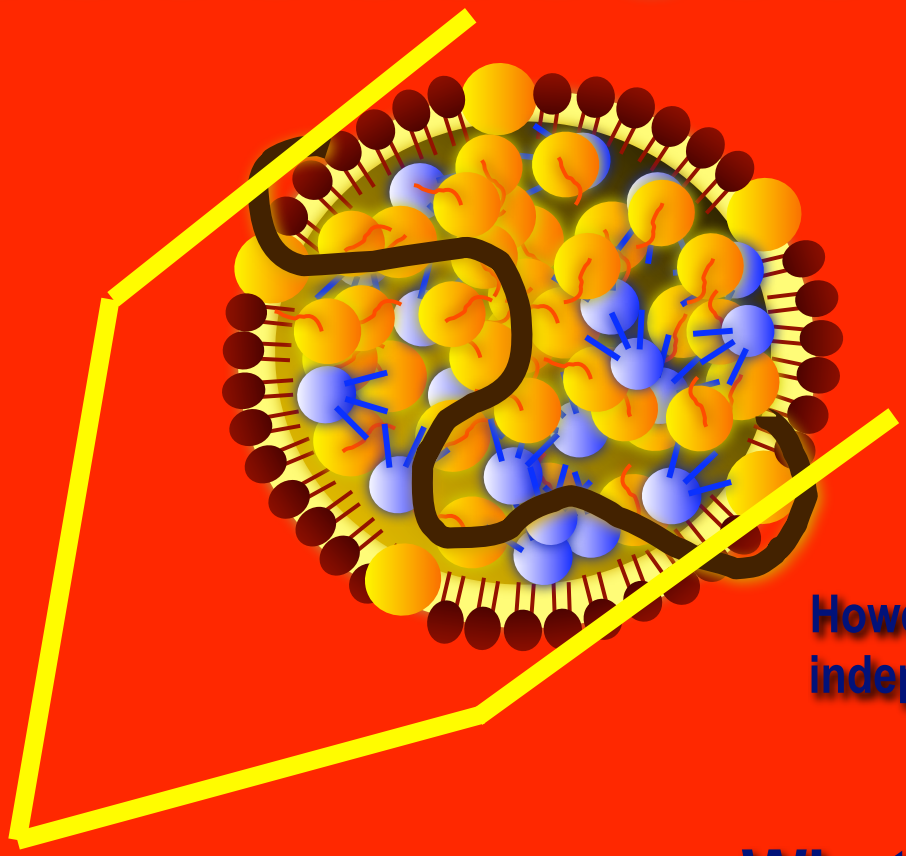
LDL-P is most accurately measured by NMR spectroscopy

Perfect is < 1000 umol/L

Because of their longer half-life, 90% of apoB particles are LDL

LDL particle concentration is the single best independent predictor that we have of CHD risk

Lipoprotein Particle Size



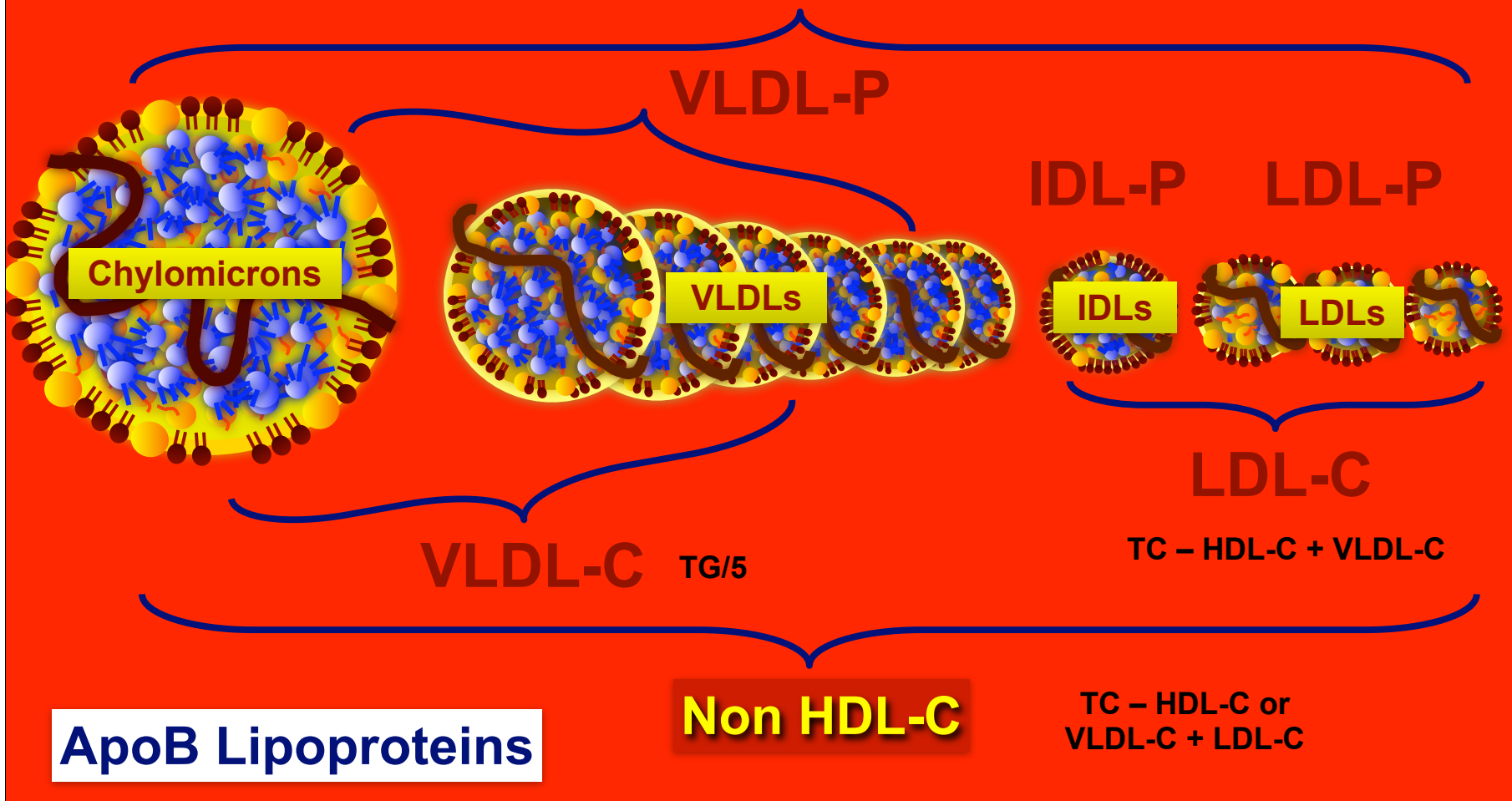
LDL Particle Size

The smaller the size of an apoB particle the easier to enter the arterial intima and the less likely to be cleared by hepatic LDL receptors

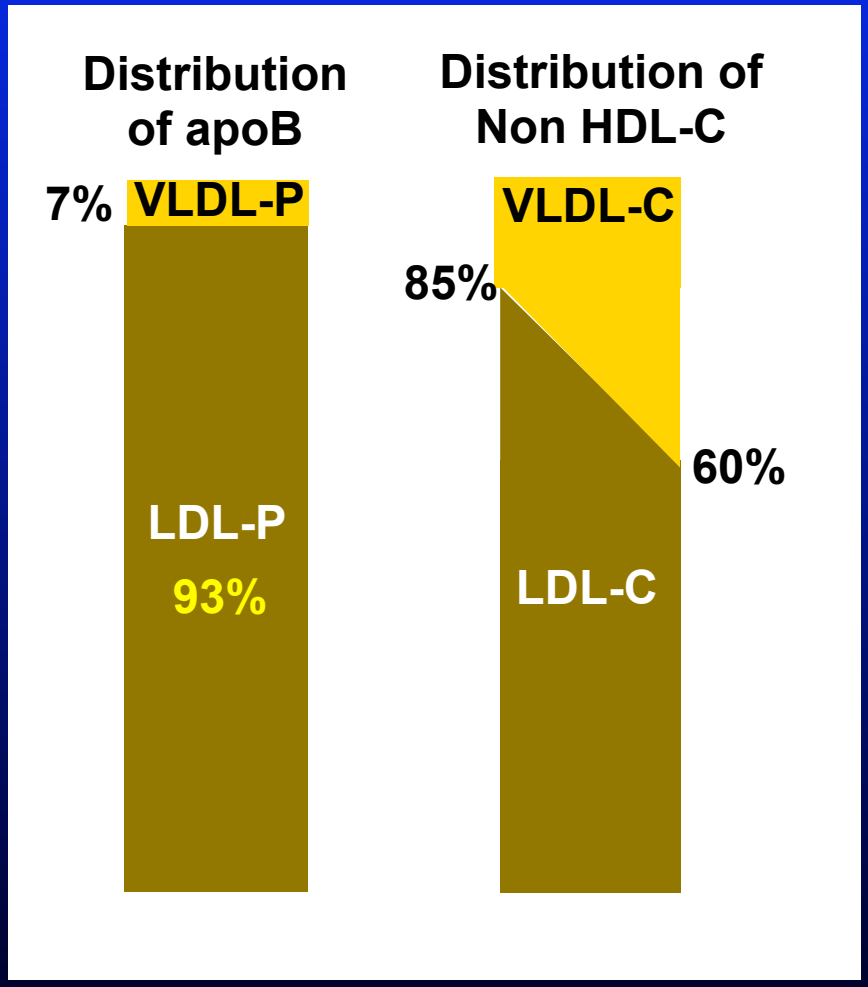
However, particle size has no independent ability to predict CV events

What makes an LDL particle Atherogenic?

Lab Analysis of ApoB Lipoproteins



Non HDL-C and VLDL-C



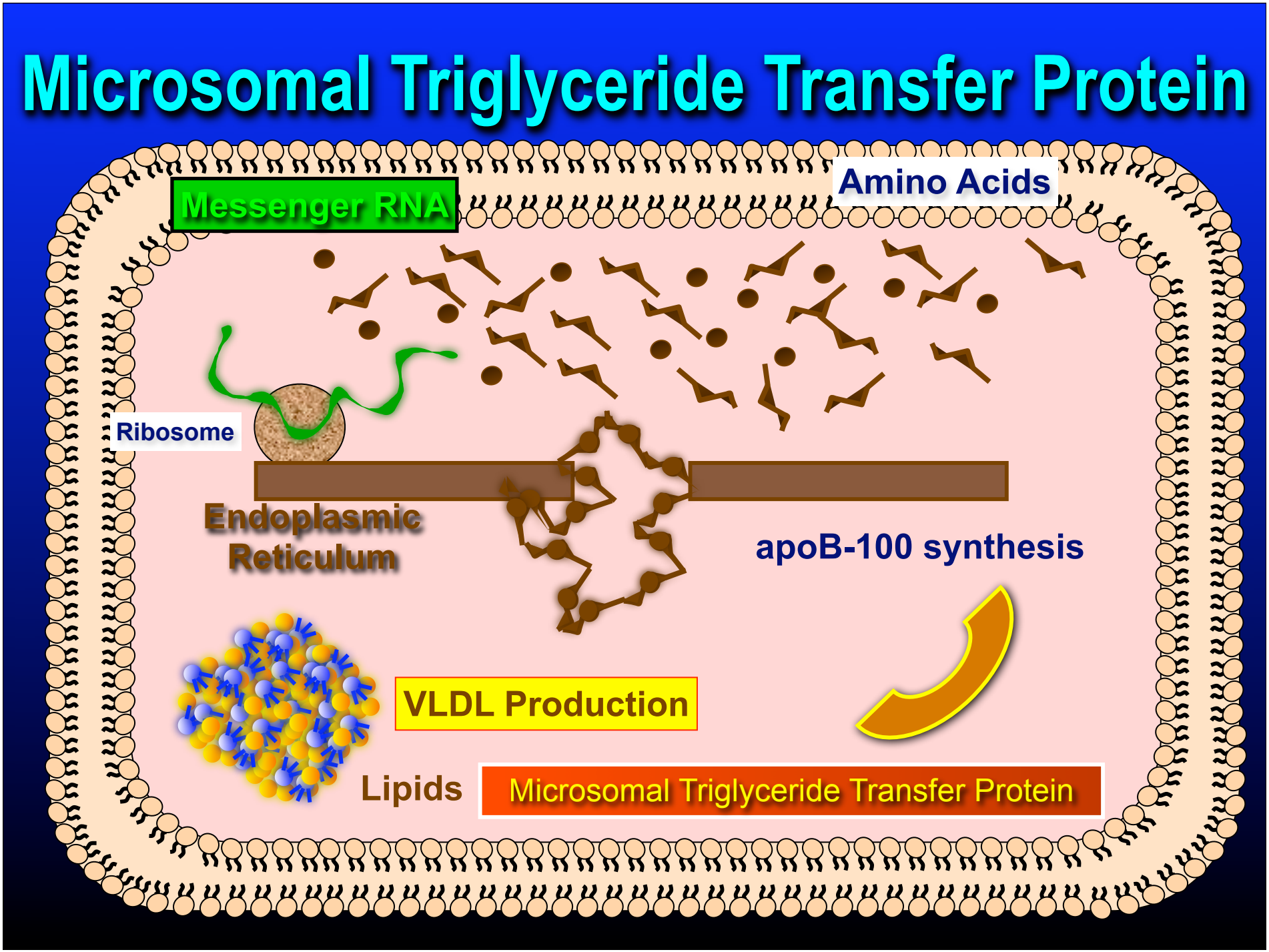
The variable contributions of VLDL and LDL cholesterol to non-HDL cholesterol.

Because the amount of cholesterol in VLDL particles is variable, the proportion that VLDL cholesterol contributes to non-HDL cholesterol varies.

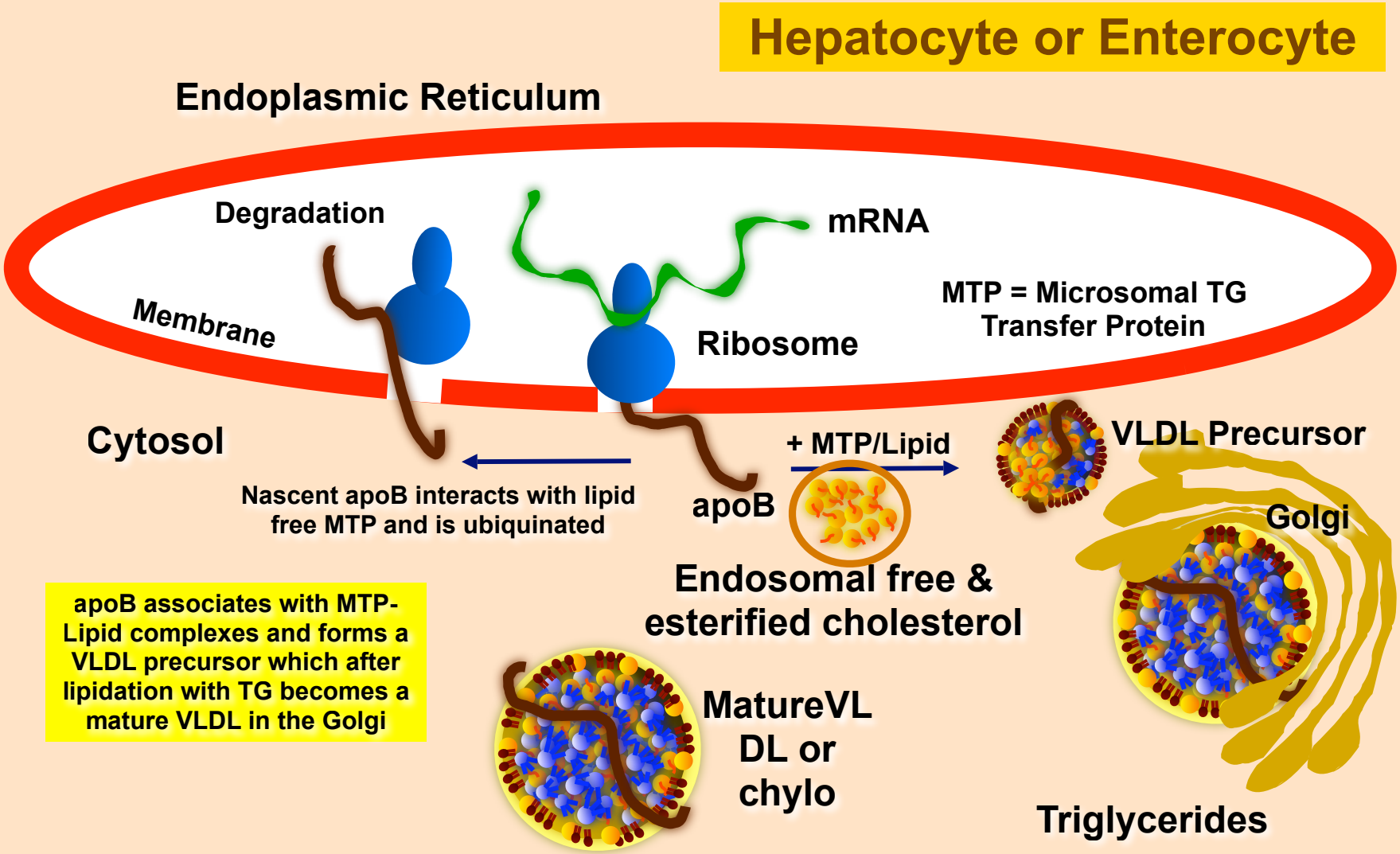
By contrast, the proportion of VLDL apoB to LDL apoB varies little.

Sniderman A D& Marcovina SM. Clin Lab Med 26 (2006) 733–750

Microsomal Triglyceride Transfer Protein

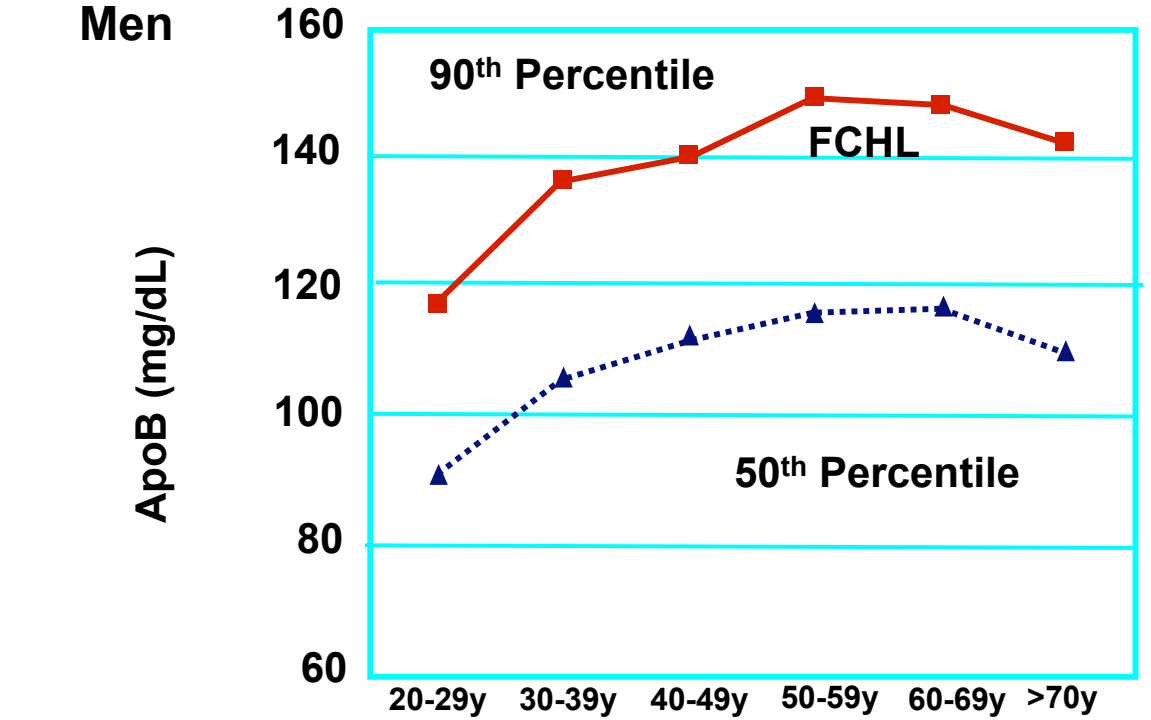


Lipidation of Apolipoprotein B



Whitfield AJ et al. Clin Chem 2004;50:1725-1732

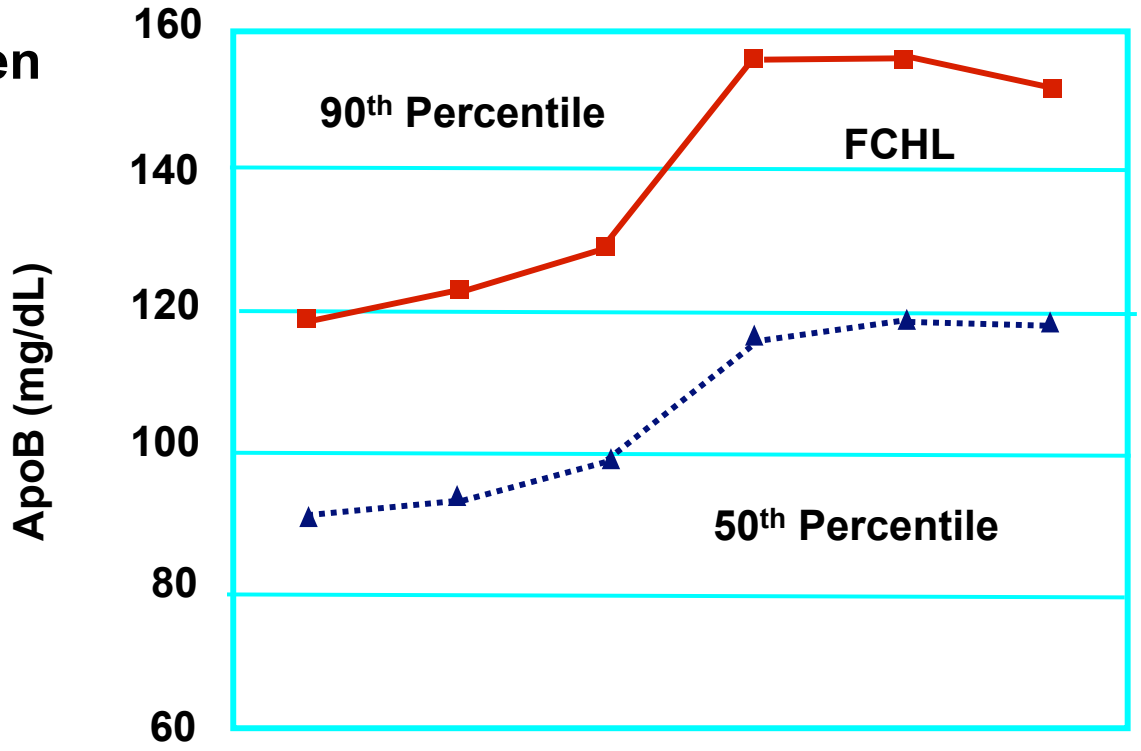
NHANES III: Apolipoprotein B Levels in Men by Age 50th and 90th Percentile



	20-29y	30-39y	40-49y	50-59y	60-69y	>70y
Mean	91	106	112	116	117	110
90th percentile	117	138	140	149	148	142

Carr M & Brunzell J J Clin Endo & Metab 2004;89:2601-2607

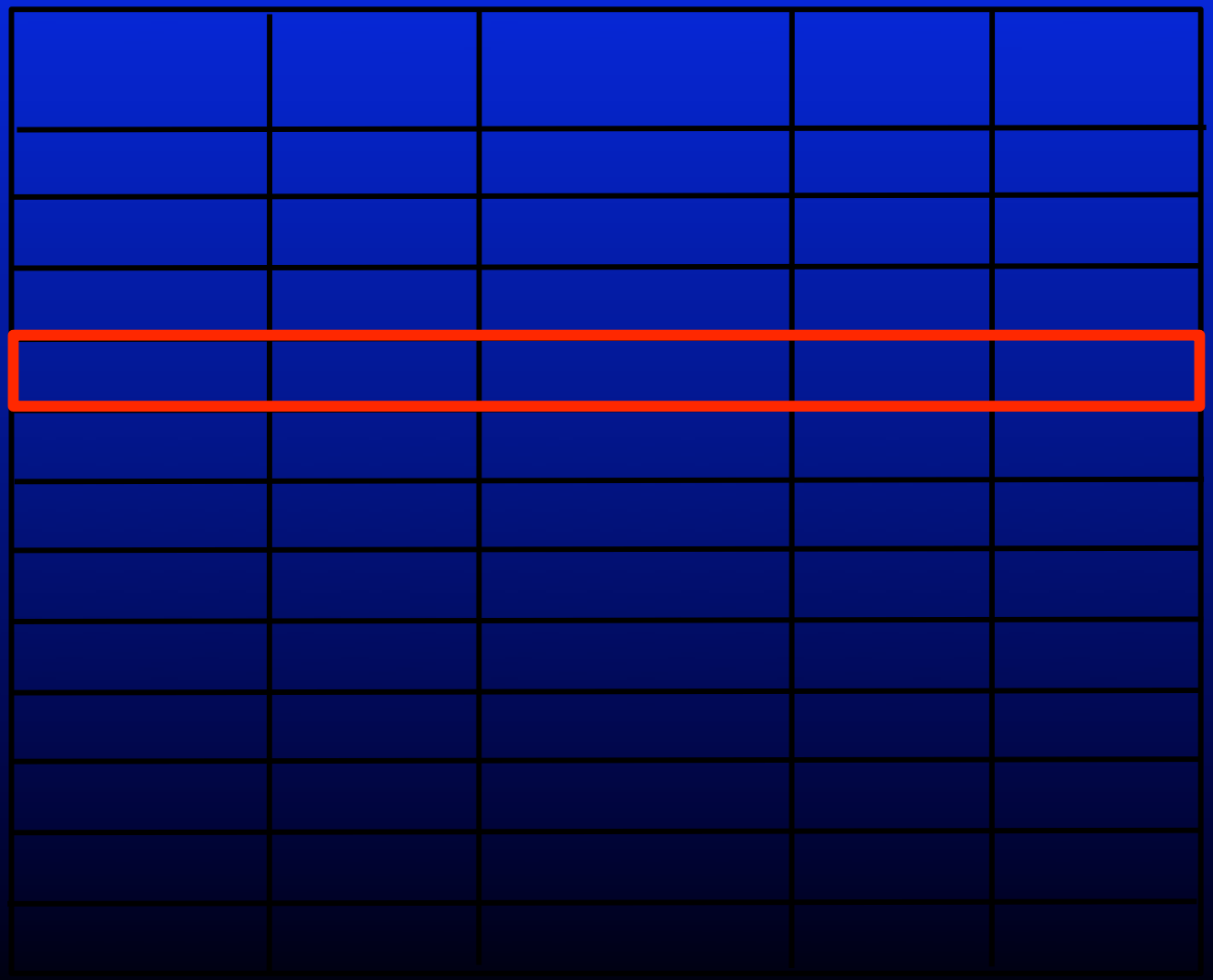
NHANES III: Apolipoprotein B Levels in Women by Age 50th and 90th Percentile



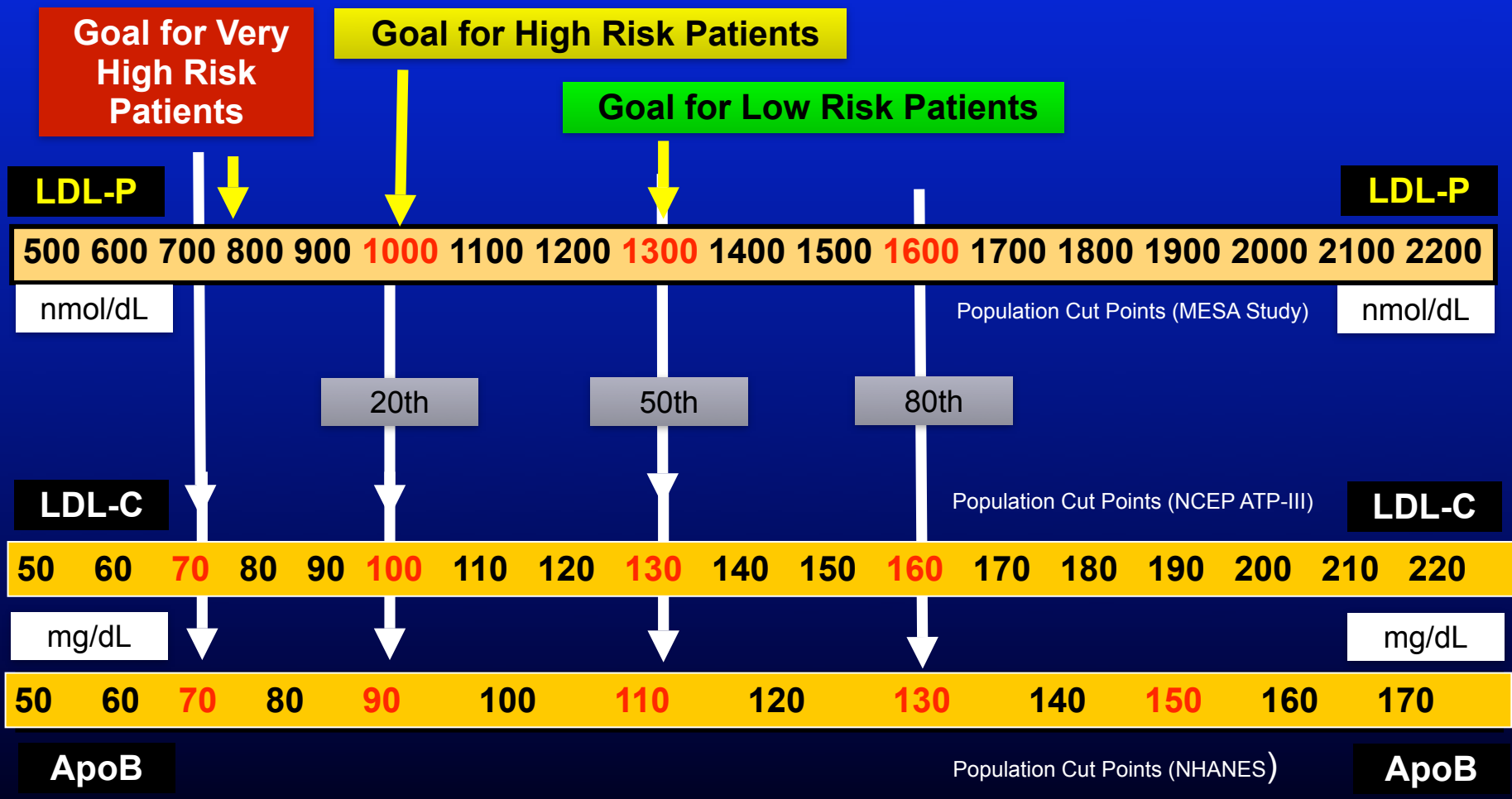
	20-29y	30-39y	40-49y	50-59y	60-69y	>70y
Mean	91	93	99	116	119	118
90th percentile	119	123	129	156	156	152

Carr M & Brunzell J J Clin Endo & Metab 2004;89:2601-2607

Framingham Offspring Study 1988-1991 (exam cycle 4)

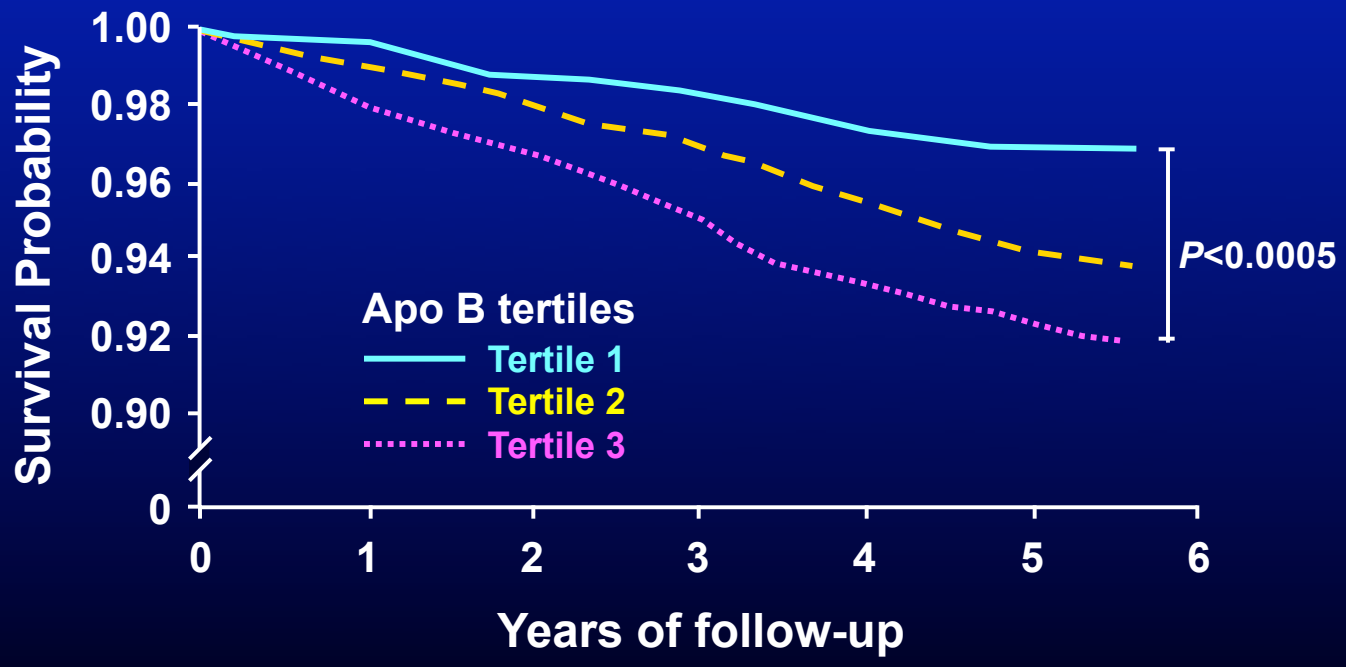


Population Percentile Cut Points & Goals for LDL-P, LDL-C and Apolipoprotein B



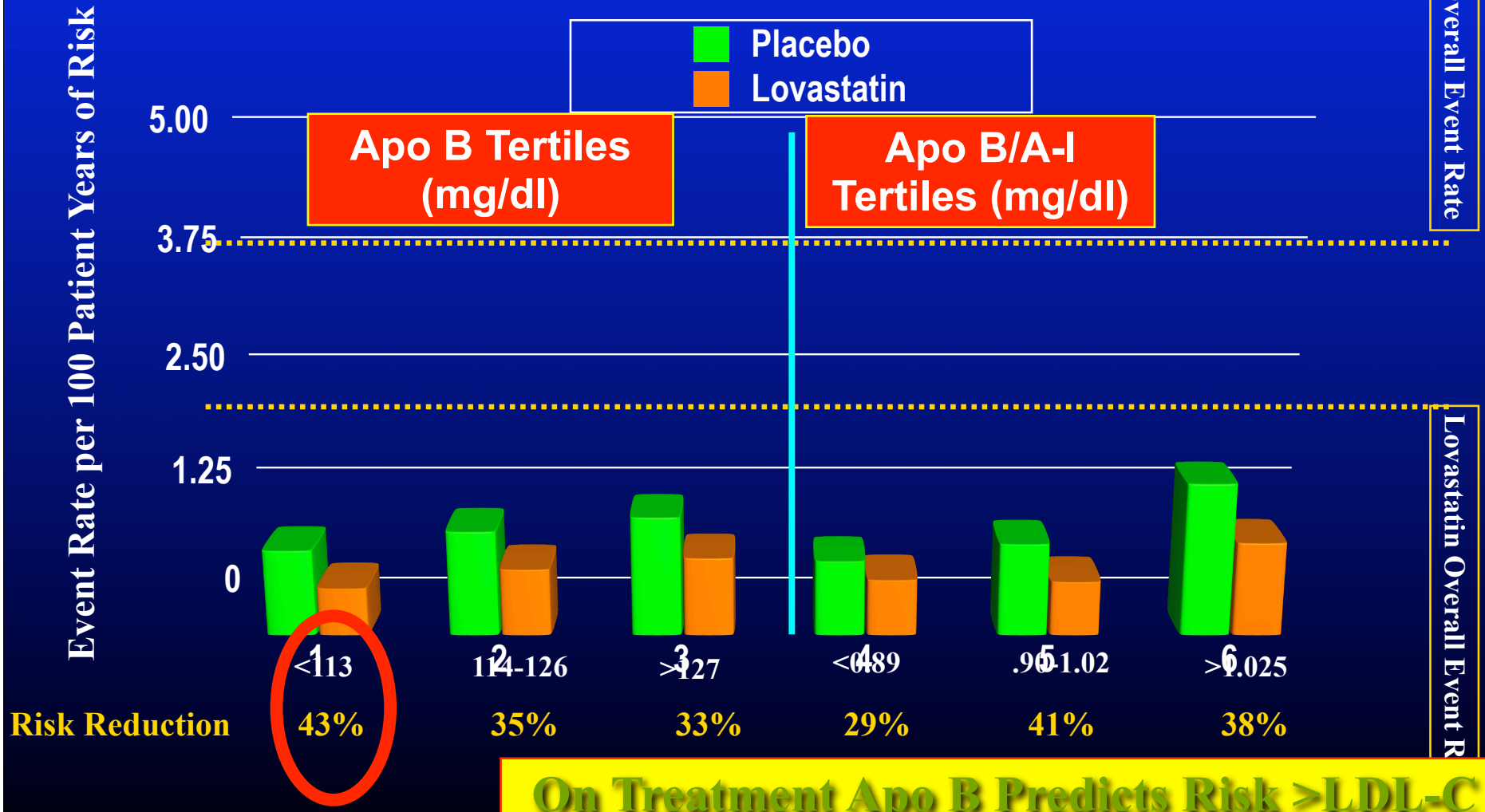
Association of Apo B and Ischemic Heart Disease

- **Analysis is based on a cohort of 2,155 men aged 45–76 years who were free of clinical signs of CHD at entry from the Québec Cardiovascular Study**



Lamarche B et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Québec Cardiovascular Study. *Circulation.* 1996;94:273–278, with permission from Lippincott Williams & Wilkins.

Lipids and Major Coronary Events in AFCAPS/TexCAPS



On Treatment Apo B Predicts Risk >LDL-C

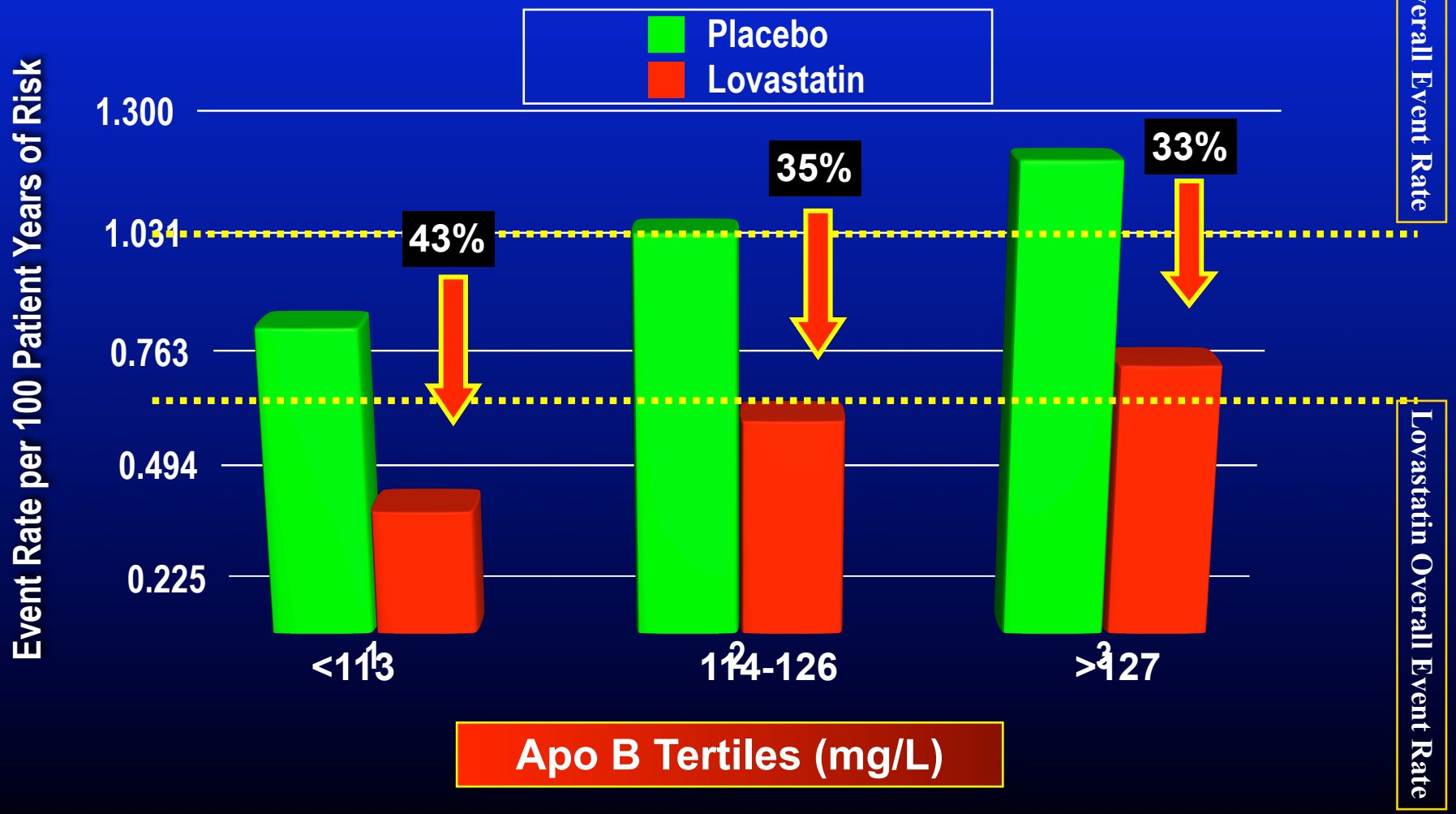
Circulation 2000;101:477-484

Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS): Lipids,

- It is well documented by many observational studies, including the Quebec Cardiovascular Study, that **apoB** is a more powerful independent predictor of CHD than LDL-C.
- Although apoB is associated with known atherogenic lipoprotein species, such as IDL remnants and small, dense LDL (a distinct, highly atherogenic subpopulation), LDL has a variable cholesterol content.
- This variability in the composition of LDL has been hypothesized to explain the clinically observed variation in risk that appears to be independent of LDL-C.
- Our results suggest that it may be more valid to use **apoB** rather than LDL-C to assess the on-treatment effect of reducing the atherogenic burden, especially when LDL-C is not markedly elevated.

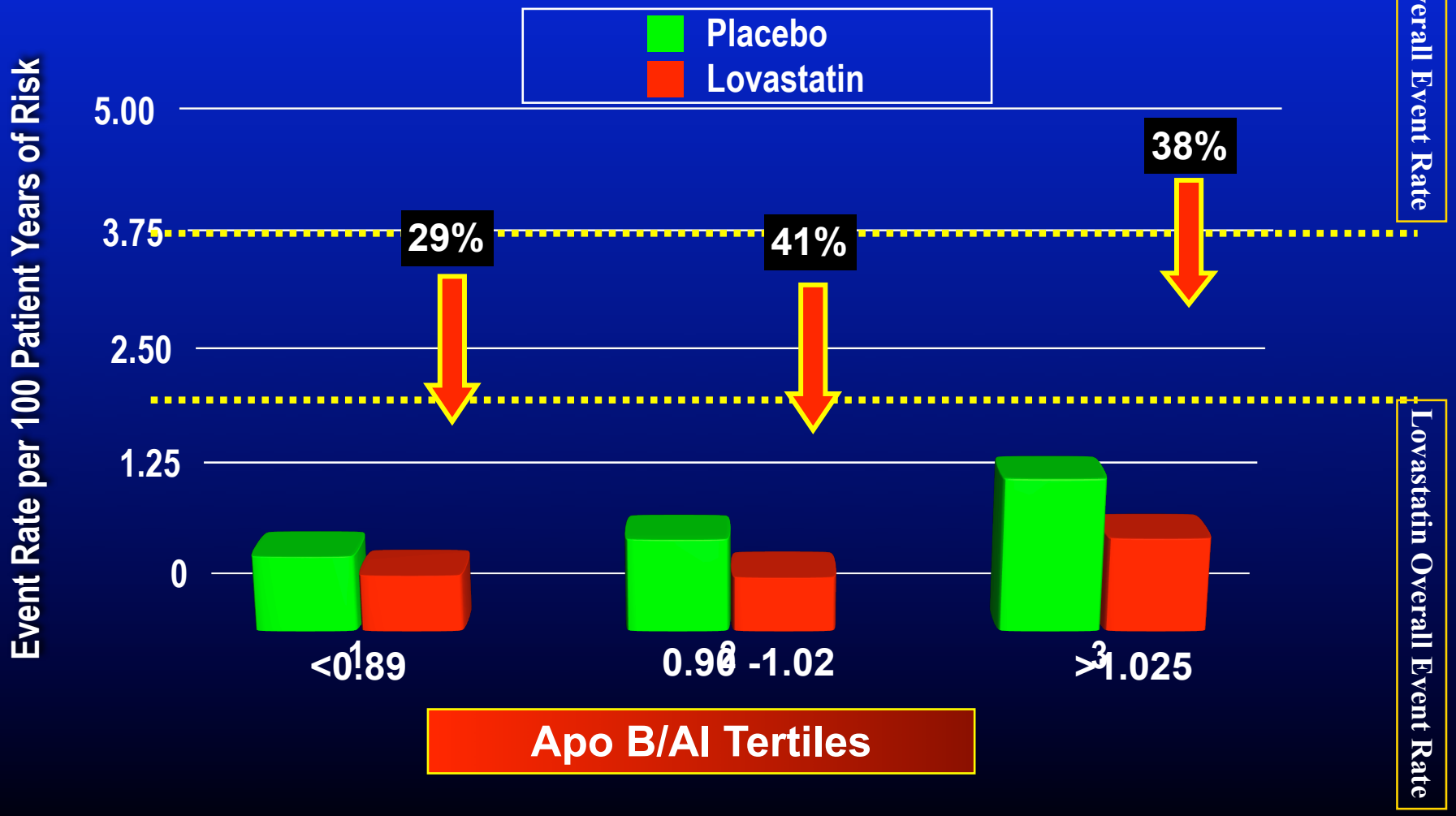
Gotto et al. Circulation 2000;101:477-484

Event Rate by Treatment Group and ApoB Tertile



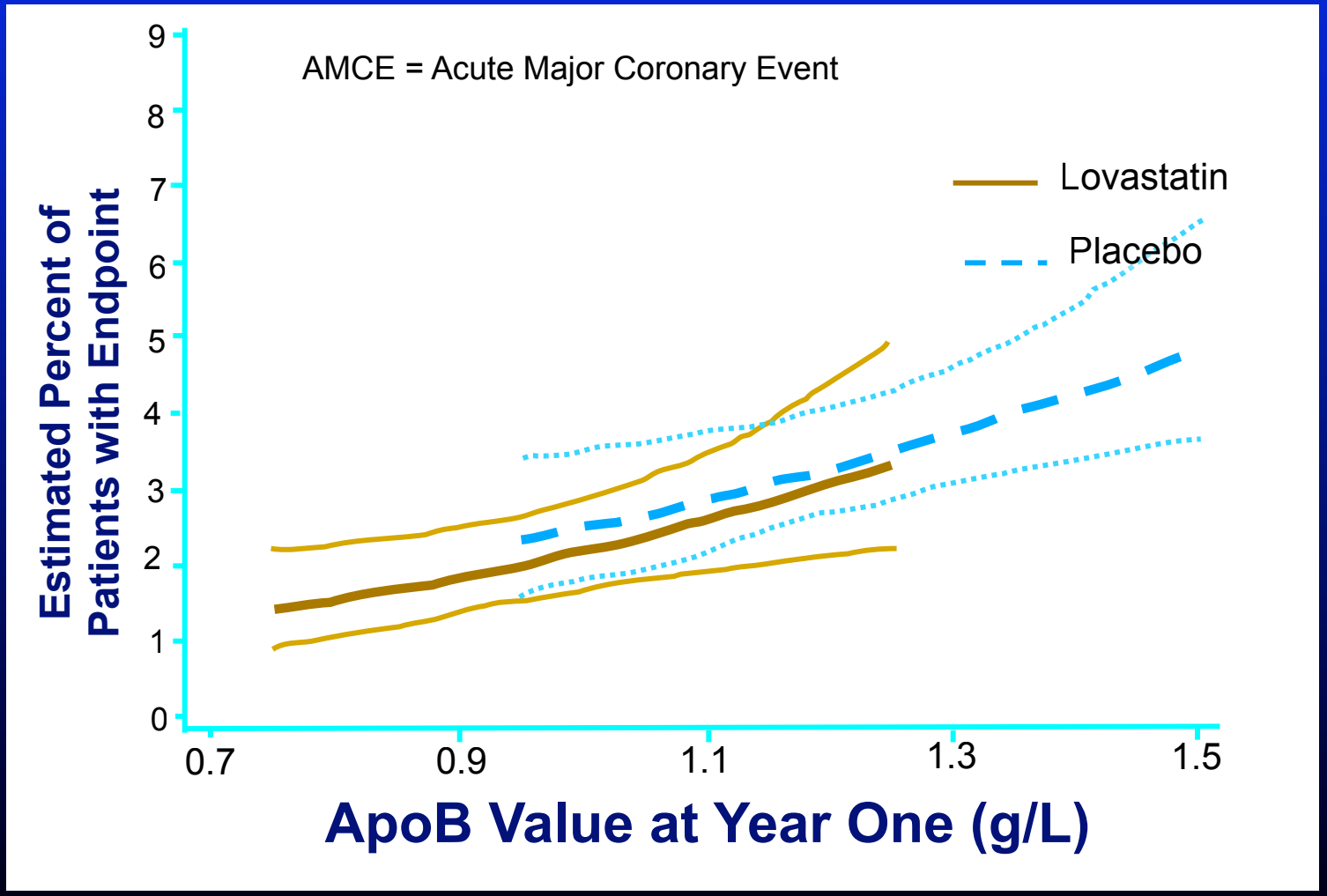
Gotto et al. Circulation 2000;101:477-484

Event Rate by Treatment Group and ApoB/AI Ratio Tertile



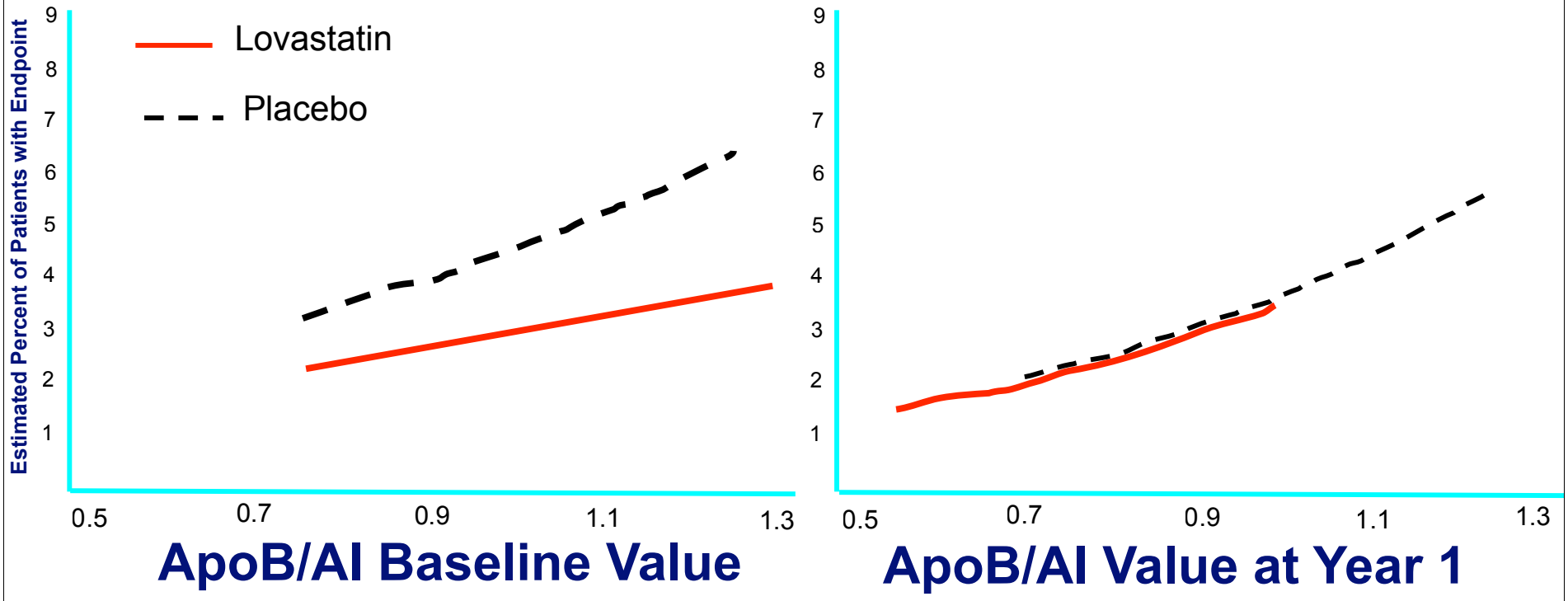
Gotto et al. Circulation 2000:101:477-484

Adjusted Logistic Regression Model Relationship of AMCE and On-treatment ApoB



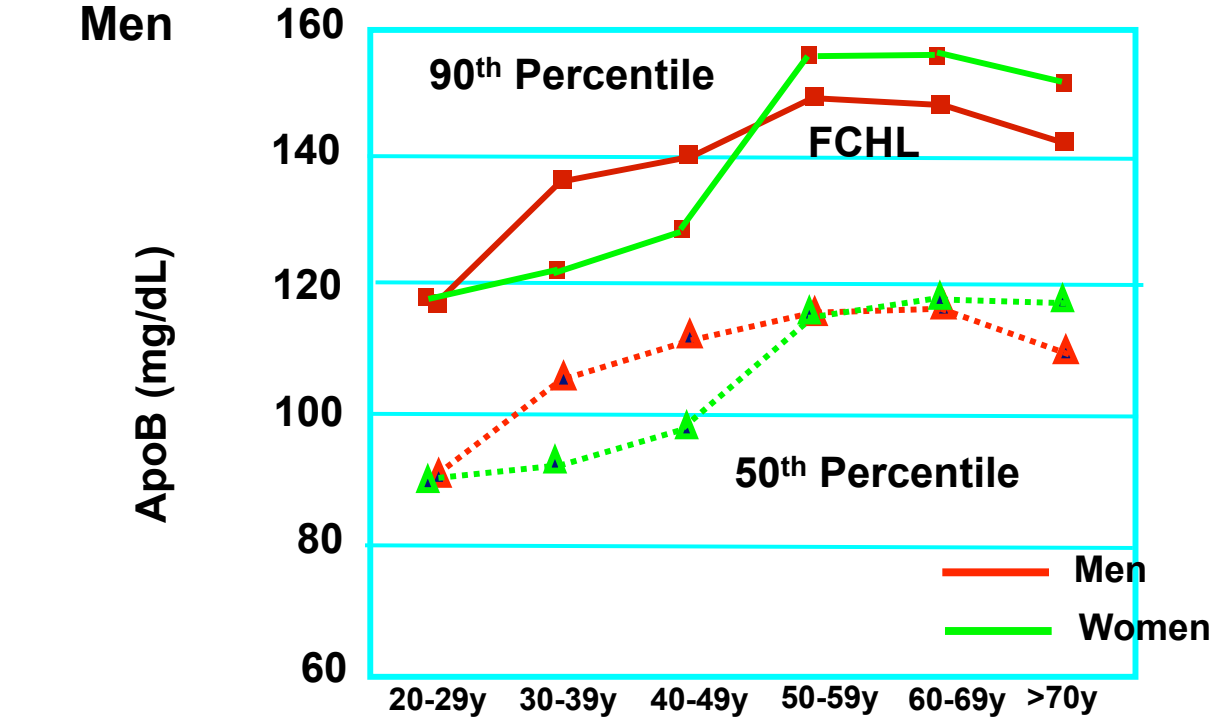
Gotto et al. Circulation 2000;101:477-484

Adjusted Logistic Regression Model Relationship of AMCE and Baseline & On-treatment ApoB/AI Ratio



Gotto et al. Circulation 2000;101:477-484

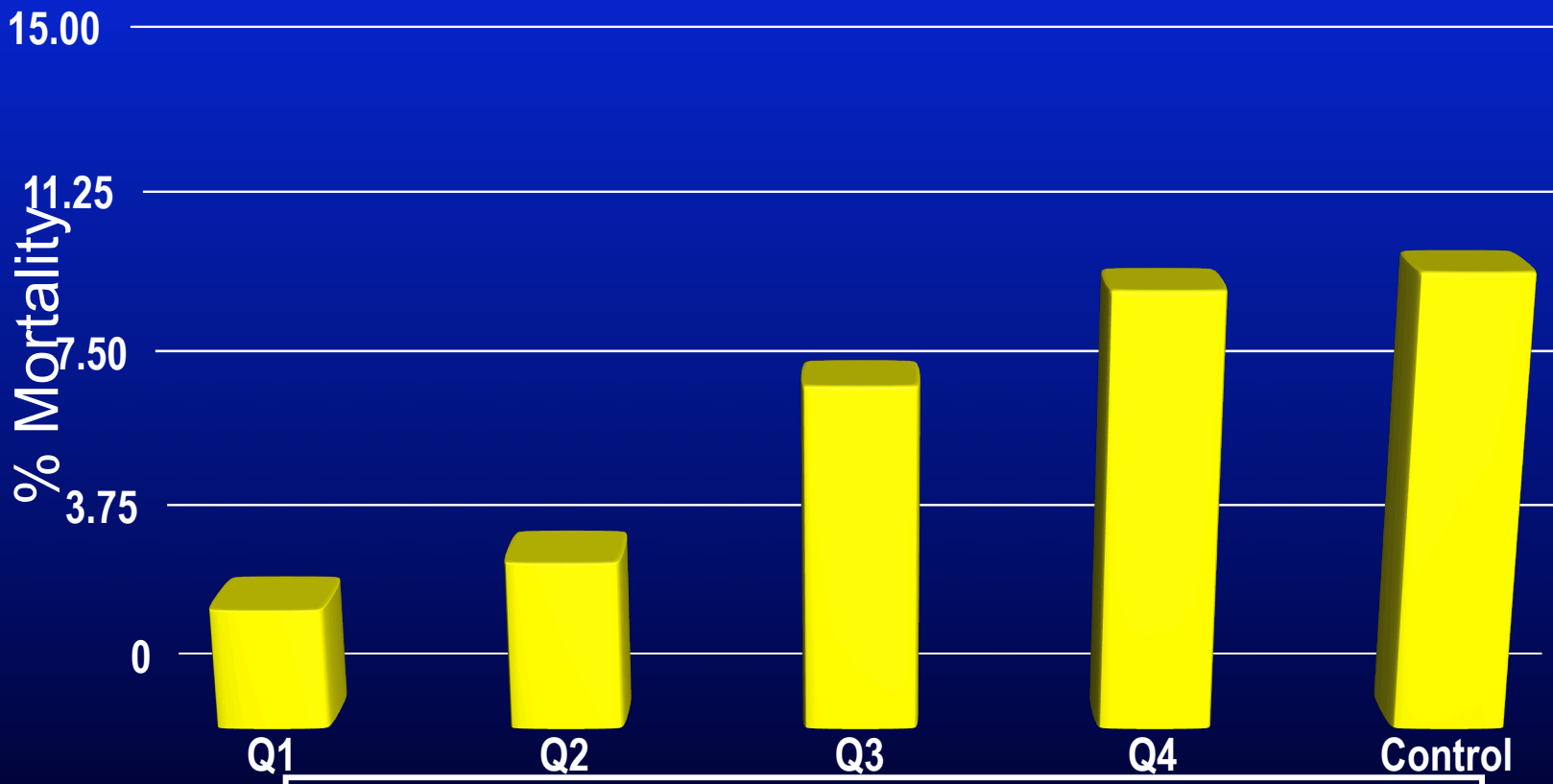
NHANES III: Apolipoprotein B Levels by Age 50th and 90th Percentile



Mean	91	106	112	116	117	110
90th percentile	117	138	140	149	148	142

Carr M & Brunzell J J Clin Endo & Metab 2004;89:2601-2607

Apo B vs Mortality in 4S Trial

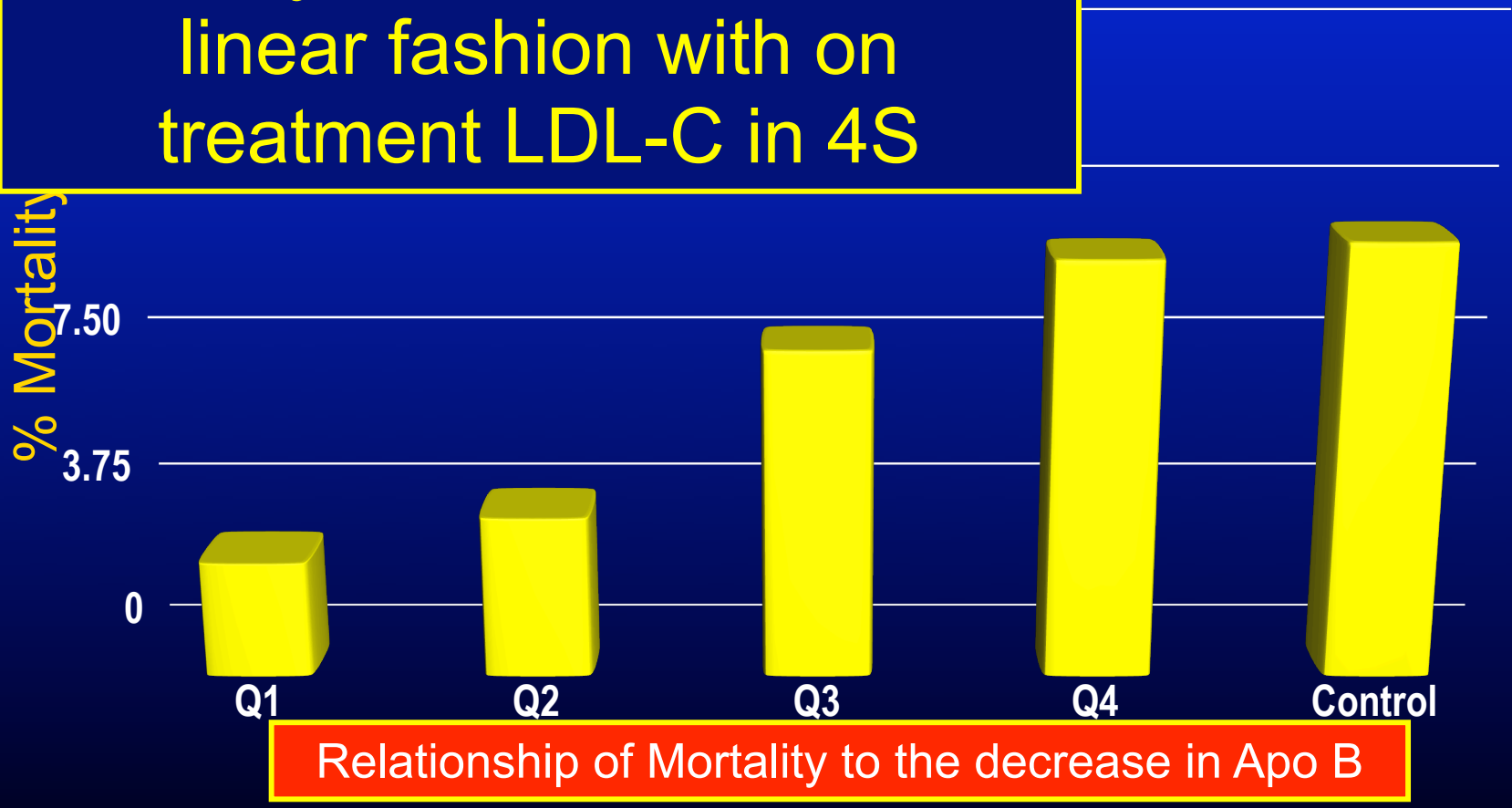


Relationship of Mortality to the decrease in Apo B

Davidson M Amer J Card 2001;87 (suppl):1A-7A

Apo B vs Mortality in Scandinavian Simvastatin Survival Study (4S)

Mortality did not correlate in a linear fashion with on treatment LDL-C in 4S



Relationship of Mortality to the decrease in Apo B

Davidson M Amer J Card 2001;87 (suppl):1A-7A

Apoprotein-related MOrtality RISk
AMORIS Study

- 175,553 patients from screening programs
  - 98,722 men and 76,831 women
- Examined relationship of apoproteins and lipids and prediction of fatal MI
- Mean Follow up 66-68 months

Wallidius G et al Lancet 2001;358:2026-2033

Apoprotein-related MOrtality RISk AMORIS Study

- In multivariate analyses adjusted for age, TC and TG
  - The values for **Apo B** and the **ApoB/ApoA-I** ratio were strongly and positively related to risk of fatal MI in men and women

- **Apo A-I** was protective
- **Apo B** was a stronger predictor of risk than LDL-C in both sexes

Wallidius G et al Lancet 2001;358:2026-2033

Apoprotein-related MOrtality RISk
AMORIS Study

- 175,553 patients from screening programs
  - 98,722 men and 76,831 women
- Examined relationship of apoproteins and lipids and prediction of fatal MI
- Mean Follow up 66-68 months

Wallidius G et al Lancet 2001;358:2026-2033

Apoprotein-related MOrtality RISk
AMORIS Study

- In multivariate analyses adjusted for age, TC and TG
- **Apolipoprotein B** was a stronger predictor of risk than LDL-C in both sexes

Wallidius G et al Lancet 2001;358:2026-2033

Apoprotein-related MOrtality RISk
AMORIS Study

- In multivariate analyses adjusted for age, TC and TG
- ✦ **Apolipoprotein B** was a stronger predictor of risk than LDL-C in both sexes
- ✦ **Apolipoprotein A-I** was protective

Wallidius G et al Lancet 2001;358:2026-2033

Apoprotein-related MOrtality RISk
AMORIS Study

- In multivariate analyses adjusted for age, TC and TG

✦ **Apolipoprotein B** was a stronger predictor of risk than LDL-C in both sexes

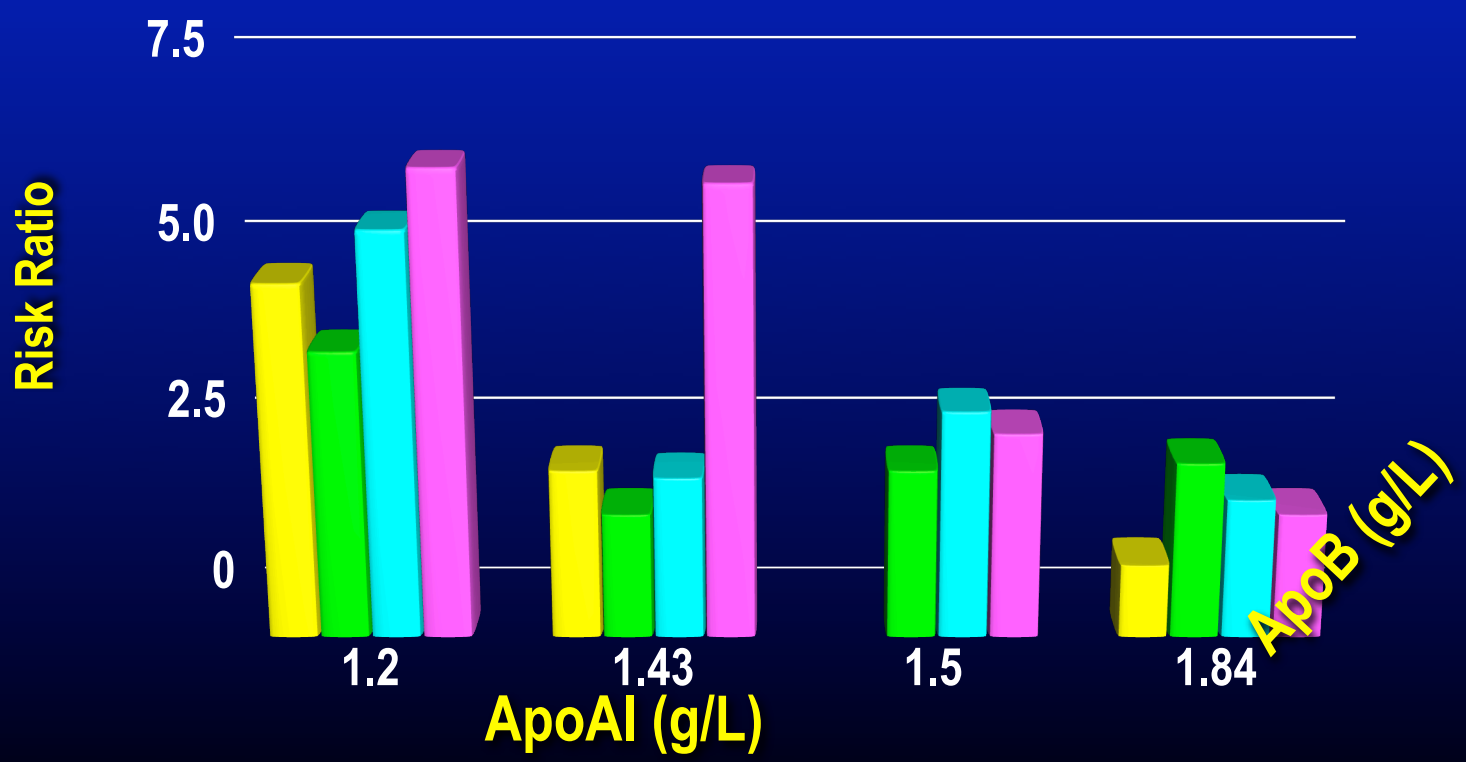
✦ **Apolipoprotein A-I** was protective

  - The values for **ApoB/ApoA-I** ratio were strongly and positively related to risk of fatal MI in men and women

Wallidius G et al Lancet 2001;358:2026-2033

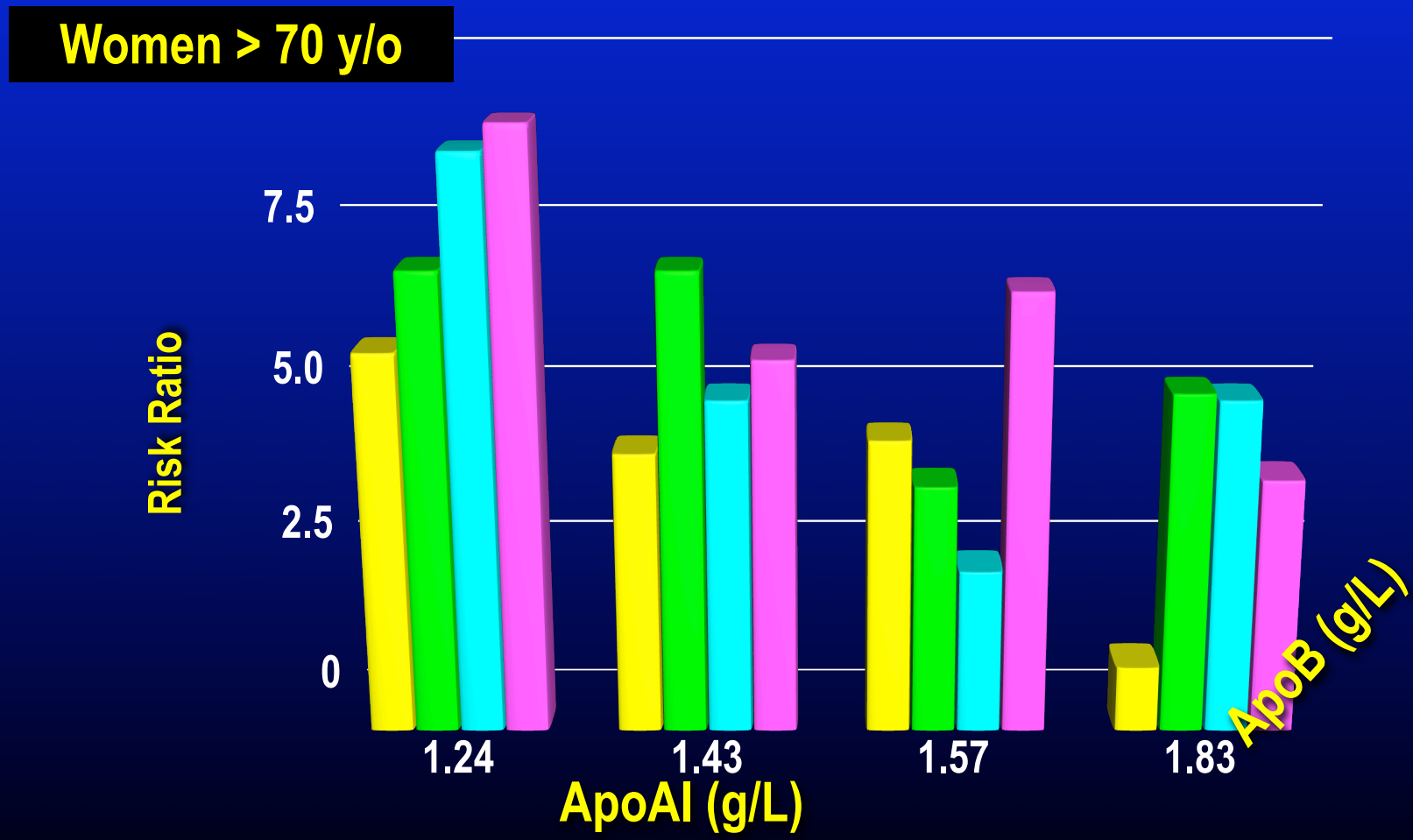
Apoprotein-related MOrtality RISk (AMORIS) Study

Women < 70 y/o



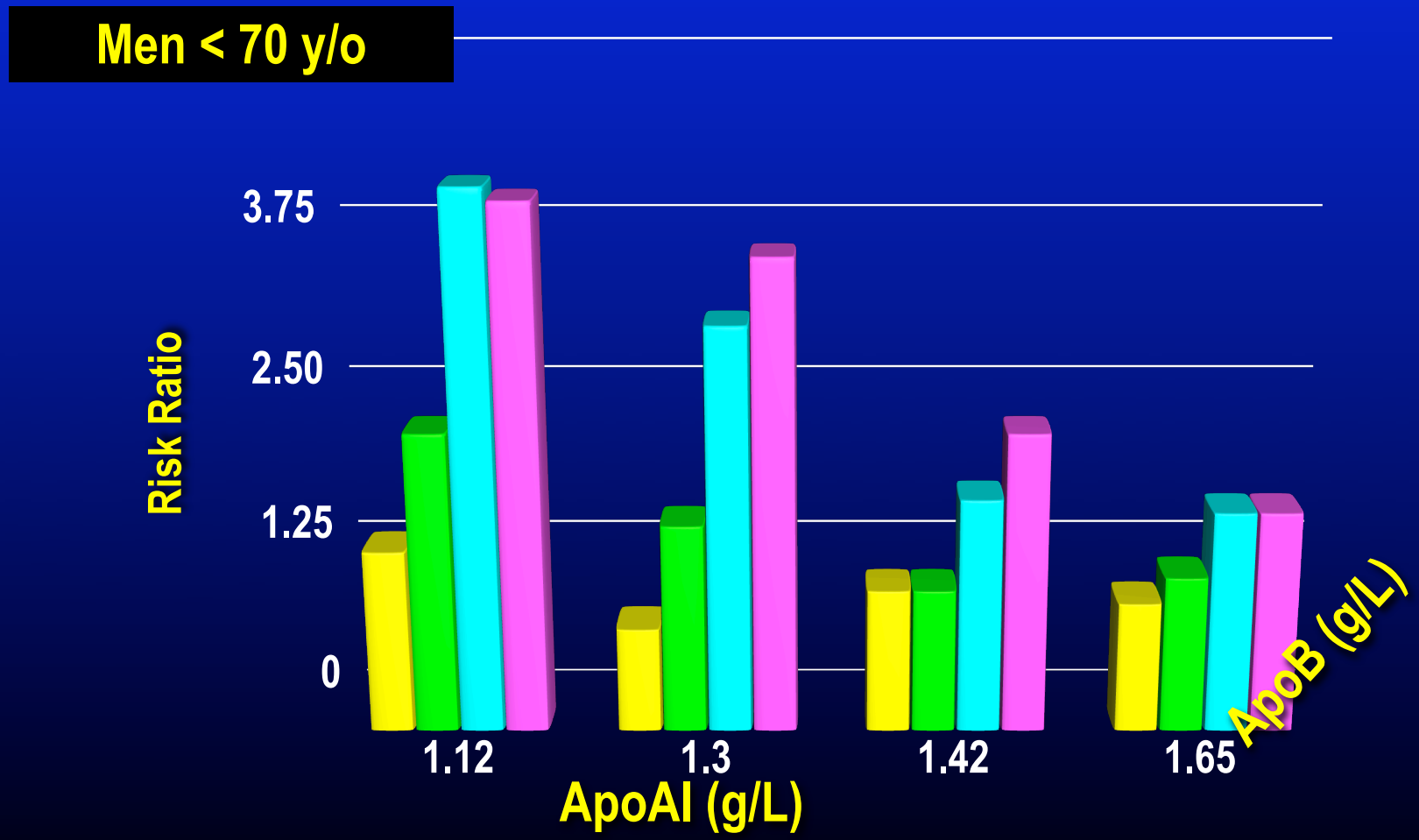
Wallidius G et al Lancet 2001;358:2026-2033

Apoprotein-related MOrtality RISk (AMORIS) Study



Wallidius G et al Lancet 2001;358:2026-2033

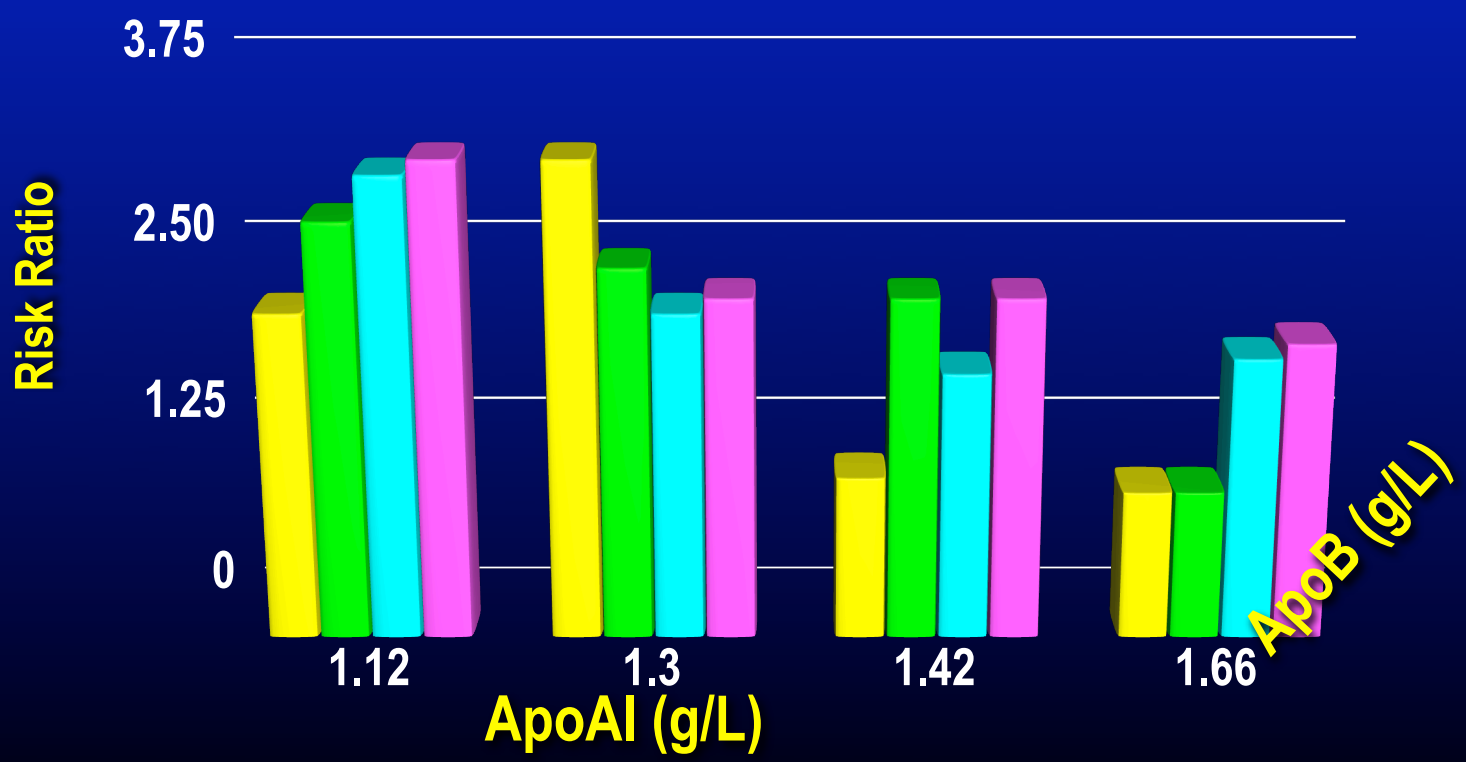
Apoprotein-related MOrtality RISk (AMORIS) Study



Wallidius G et al Lancet 2001;358:2026-2033

Apoprotein-related MOrtality RISk (AMORIS) Study

Men > 70 y/o



Wallidius G et al Lancet 2001;358:2026-2033

Canadian Medical Association Recommendations for Management of Dyslipidemia

- Four prospective studies showed apoB is a better estimate of risk than LDL-C
- Risk is highest in persons with apoB > 120 mg/dL and a TG of 120 mg/dL
  - This is typical of insulin resistance dyslipidemia
- In the statin trials apoB levels during treatment relate more strongly to clinical outcomes than do LDL-C levels
- Fasting is not required

Genest J et al. CMAJ 2003;168:921-924

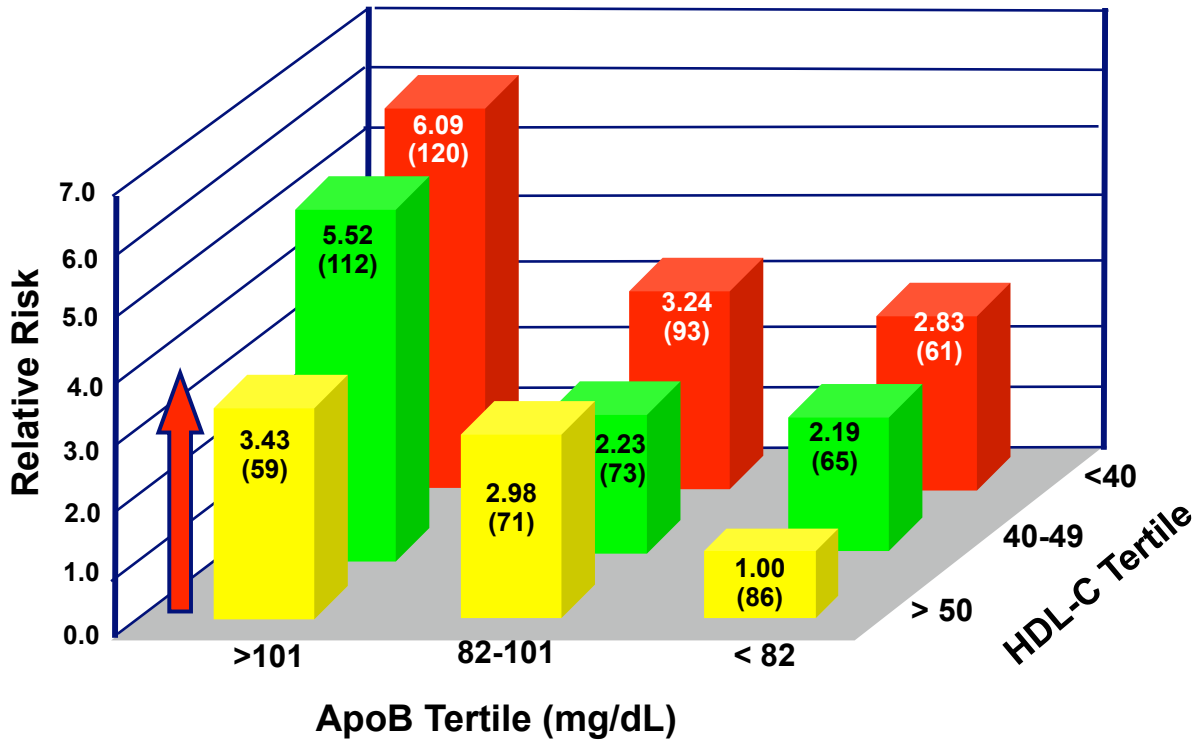
Canadian Medical Association Recommendations for Management of Dyslipidemia

- Apo B has been standardized and most labs have the equipment to measure it
- Population levels (Canadian)
  - 90 mg/dL 20th percentile
  - 105 mg/dL 50th percentile
  - 120 mg/dL 75th percentile

Genest J et al. CMAJ 2003;168:921-924

Physicians Health Study
HDL-C vs apoB in CV Prediction in Men

CHD relative risk over 6 years



Adjusted for age, smoking, BMI, premature family history, diabetes, physical activity, hypertension and alcohol intake

HDL-C is inversely related to apoB

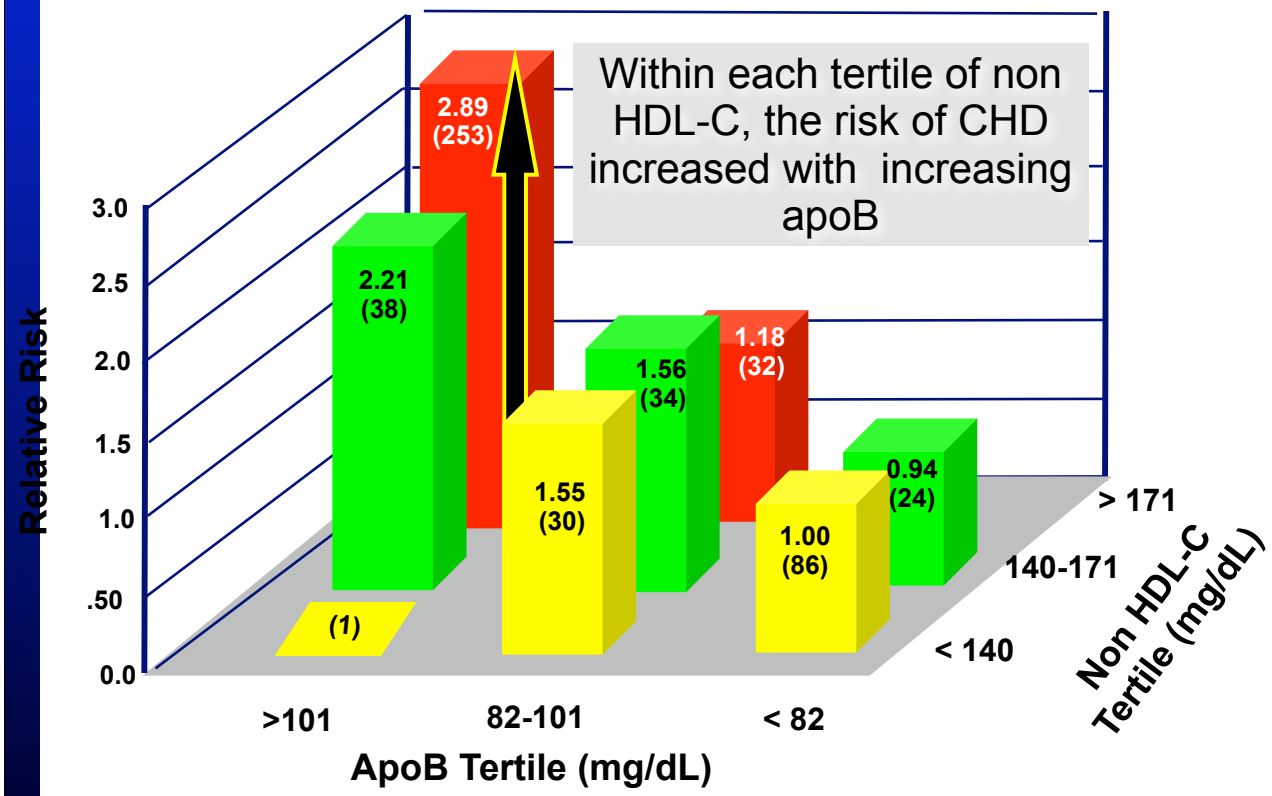
However: apoB adds predictive value at any level of HD-C

Numbers indicate relative risks; numbers in parentheses indicate number of subjects.

Pischon T et al. Circulation. 2005;112:3375-3383

Physicians Health Study Non HDL-C vs apoB in CV Prediction in Men

CHD relative risk over 6 years



Adjusted for age, smoking, BMI, premature family history, diabetes, physical activity, hypertension and alcohol intake

No subject was in the group defined as the lowest tertile of non–HDL-C and highest tertile of apoB.

Only one subject was in the group defined as the highest tertile of non–HDL-C and lowest tertile of apoB.

Numbers indicate relative risks; numbers in parentheses indicate number of subjects.

Pischon T et al. Circulation. 2005;112:3375-3383

Physicians Health Study Non HDL-C vs apoB in CV Prediction in Men

Conclusions—Although non–HDL-C and apoB were both strong predictors of CHD in this male cohort, more so than LDL-C, the findings support the concept that the **plasma concentration of atherogenic lipoprotein particles measured by apoB is more predictive** in development of CHD than the cholesterol carried by these particles, measured by non–HDL-C.

Pischon T et al. Circulation. 2005;112:3375-3383

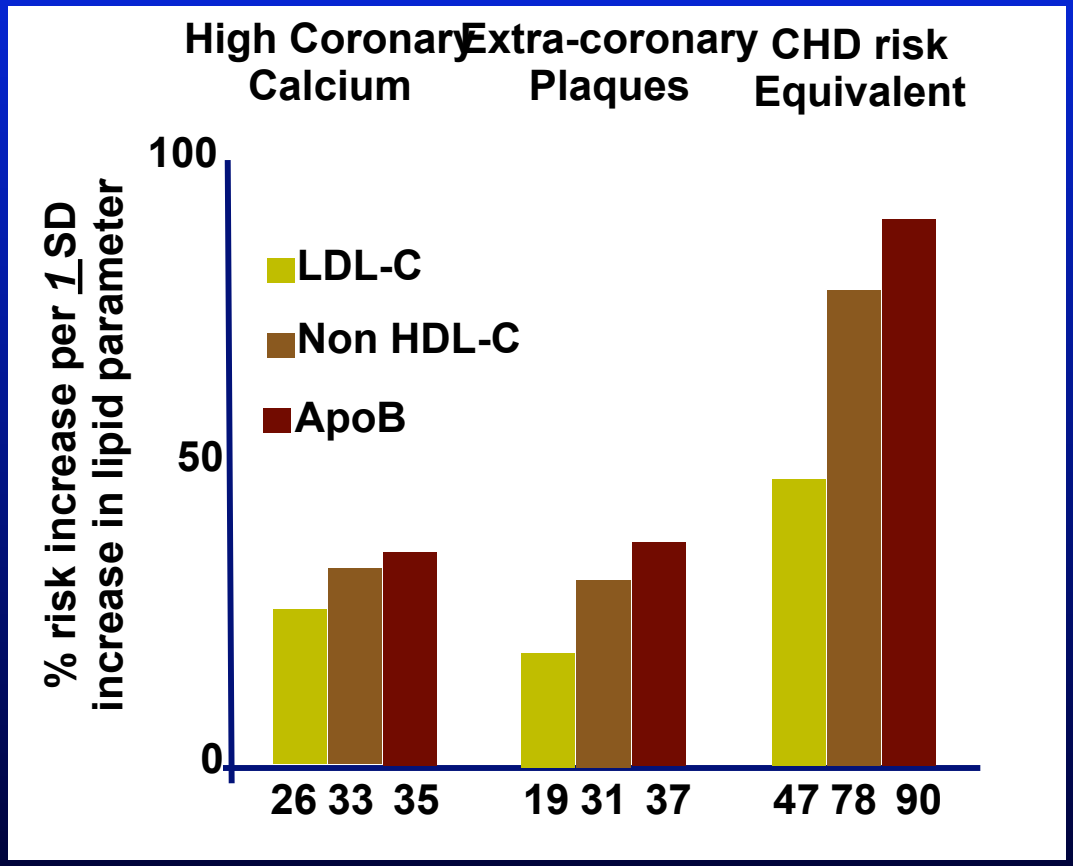
Physicians Health Study Non HDL-C vs apoB in CV Prediction in Men

In conclusion, we found in a generally healthy male population that non–HDL-C is more strongly related to CHD than is LDL-C; however, our study suggests that **apoB** as a direct measurement of the number of atherogenic lipoprotein particles **is more closely related to risk of CHD** than the cholesterol concentration provided by these particles.

Pischon T et al. Circulation. 2005;112:3375-3383

CV Markers and Prediction of Risk

723 asymptomatic men with no history of CVD



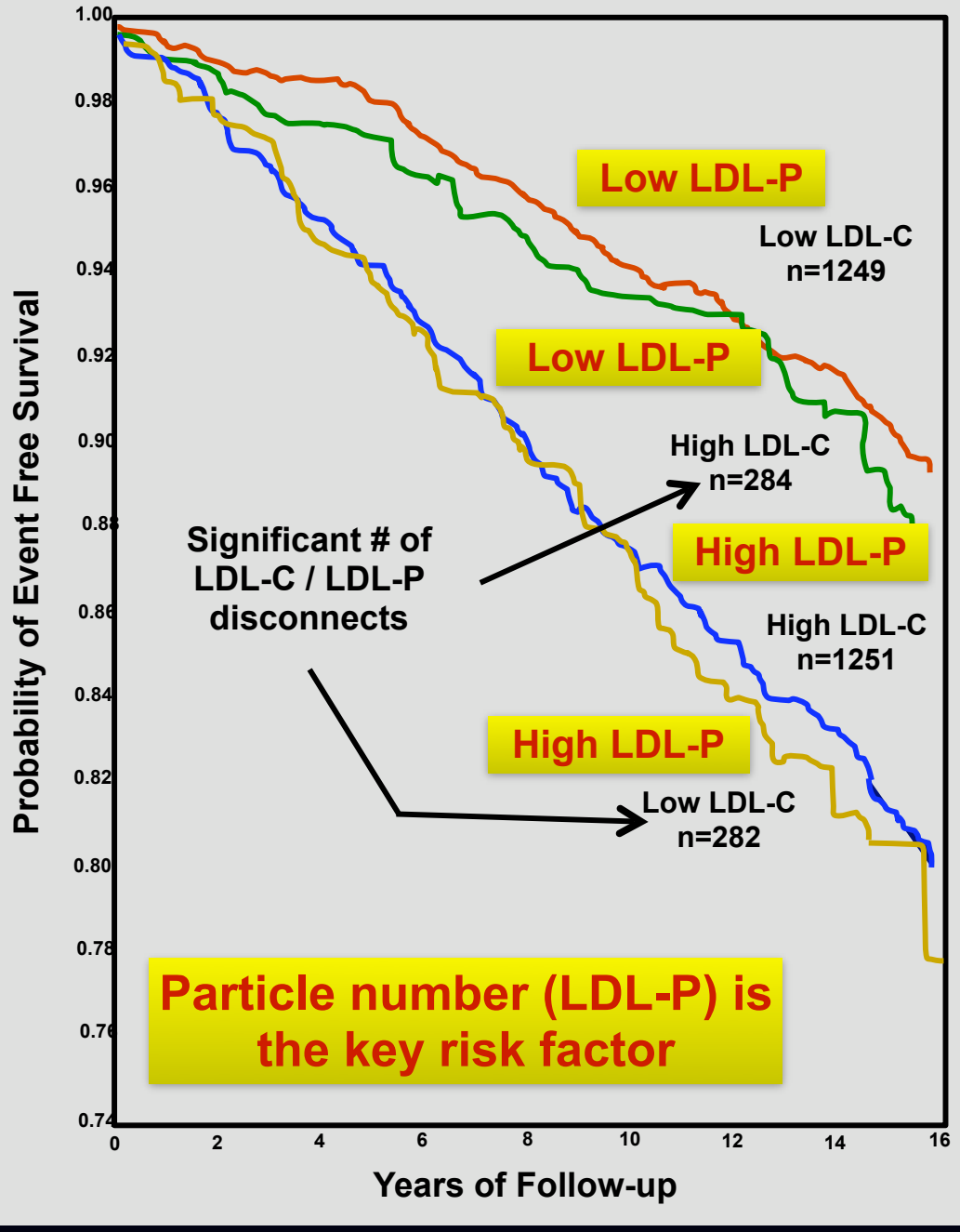
Percent increase in risk of having high coronary calcium deposit, extra-coronary plaques at multiple sites, and CHD risk equivalent per increase in one standard deviation of LDLC, non-HDLC, and apoB.

Conclusions: ApoB was the best predictor, non-HDL-C the second best predictor, and LDL-C the poorest predictor of high cardiovascular risk

Subclinical extra-coronary and coronary atherosclerosis, and triglycerides participated to these differences.

Simon, A. et al. Atherosclerosis 2005;179:339-344

Framingham Heart Study Offspring Cohort



Event-free survival among participants with low-density lipoprotein cholesterol (LDL-C) and LDL particle number (LDL-P) above or below the median.

Median values were 131 mg/dL for LDL-C and 1414 nmol/L for LDL-P.

LDL-P was strongly associated with increased CVD risk in both men and women ($p<0.0001$)

When data for men and women were combined, LDL-P was approximately twice as strongly related to CVD incidence as LDL-C

Cromwell W et al. J Clin Lipidol 2007;1:583-592

Framingham Heart Study: Offspring Cohort

Table 4 Age- and gender-adjusted incidence of cardiovascular disease by quartile of alternative measures of atherogenic lipoprotein concentrations*

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Lowest LDL-C Quartile				
< 111 men < 102 women				
LDL-C				
Median (mg/dL)	92	118	142	170
No. of events	75	100	114	142
CVD event rate per 1000 person-years (95% CI)	81 (57–103)	86 (63–108)	88 (66–110)	119 (92–144)
Non–HDL-C				
Median (mg/dL)	109	140	165	198
No. of events	65	95	115	156
CVD event rate per 1000 person-years (95% CI)	74 (51–96)	79 (57–100)	94 (71–116)	123 (96–149)
LDL-P				
Lowest LDL-P Quartile				
Median (nmol/L)	967	1279	1548	1931
1252 men < 1061 women				
No. of events	55	109	101	166
CVD event rate per 1000 person-years (95% CI)	59 (38–79)	89 (66–112)	81 (60–102)	139 (110–166)

*Quartiles were gender-specific. LDL-C cutpoints were 111, 134, and 156 mg/dL for men; 102, 124, and 150 mg/dL for women. Non–HDL-C cutpoints were 134, 159, and 183 mg/dL for men; 118, 144, and 174 mg/dL for women. LDL-P cutpoints were 1252, 1511, and 1785 nmol/L for men; 1061, 1313, and 1617 nmol/L for women.

Cromwell W et al. J Clin Lipidol 2007;1:583-592

Framingham Heart Study: Offspring Cohort

- The graph makes a very simple point
- When LDL-C and LDL-P are both high there is risk and when the two indices are both low, risk is low
- The issue is what happens when the two indices are discordant:
  - When LDL-P is low, even though LDL-C is high, risk is low. Similarly when LDL-P is high and LDL-C is low, risk is high

Risk follows LDL-P, not LDL-C

Sniderman AD . Future Lipidology 2008;3:257-264

Evidence Supporting Apo B over LDL-C: Prospective Epidemiologic Studies & Placebo Wing of Major Statin Trials

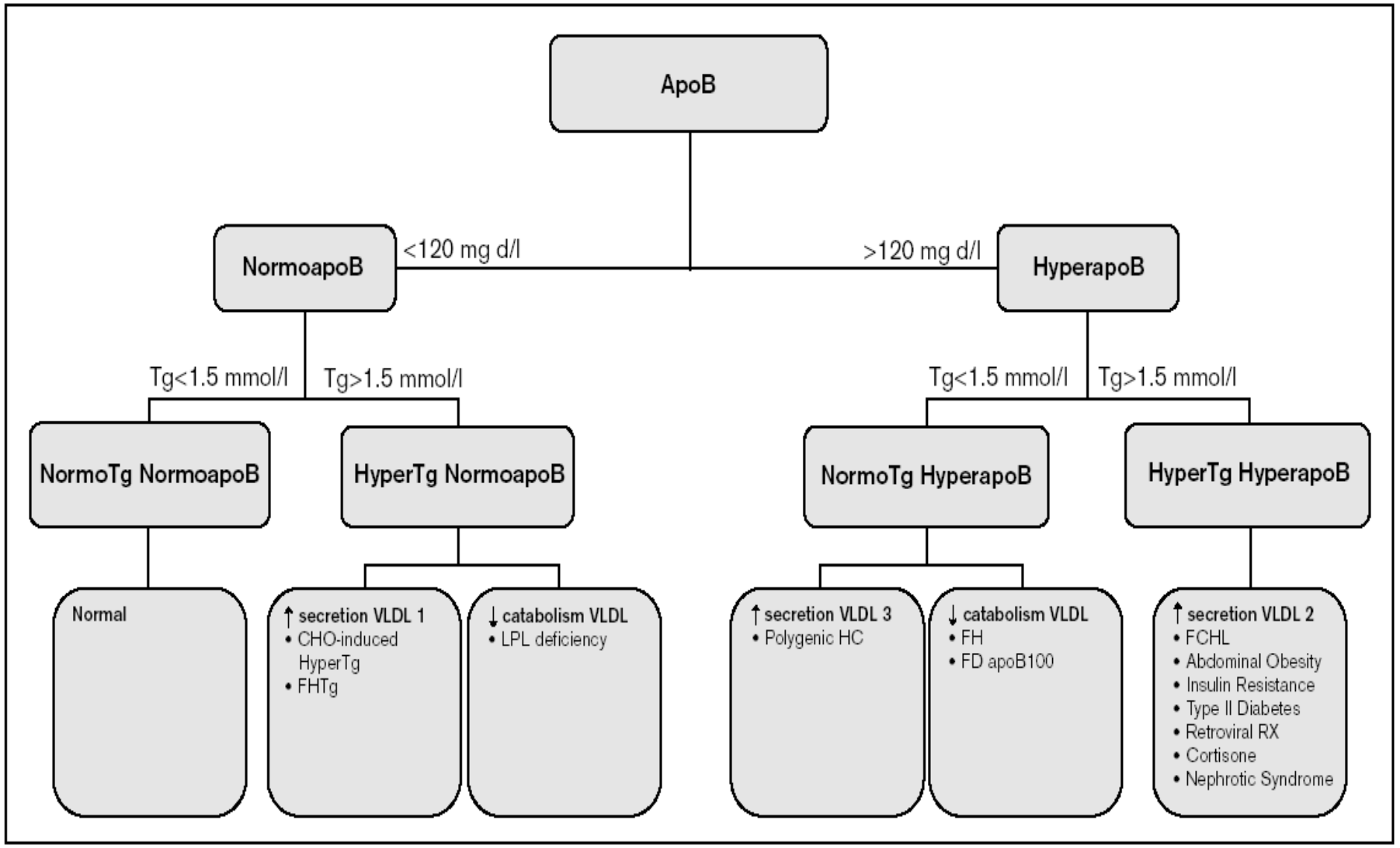
QCVS-13:	Quebec Cardiovascular Study 13 year follow up
THROMBO MS	Thrombogenic Factors & Recurrent Coronary Events Metabolic Synd
LIPID	Long-term Intervention with Pravastatin in Ischemic Disease
AFCAPS/TexCAPS	Air Force Texas Coronary Atherosclerosis Prevention Study
4S	Scandinavian Simvastatin Survival Study
Womens HS	Women's Heart Study
THROMBO	Thrombogenic Factors & Recurrent Coronary Events
NPHS	Northwick Park Heart Study
AMORIS	Apolipoprotein-related Mortality Risk
QCVS-5	Quebec Cardiovascular Study 5 year follow up

Sniderman A D& Marcovina SM. Clin Lab Med 26 (2006) 733–750

Evidence Supporting Apo B over Non HDL-C: Prospective Epidemiologic Studies & Placebo Wing of Major Statin Trials

	ApoB Superior as a Predictor
Carotid IMT	Carotid Intimomedial Thickness Studies (4)
CMS	Casale Monferrator Study
HHMS	Harvard healthy Men Study
AMORIS	Apolipoprotein-related Mortality Risk
	Equal Predictors of Risk
Womens HS	Women's Heart Study
J-DM	Jiang Diabetes Mellitus

Sniderman A D& Marcovina SM. Clin Lab Med 26 (2006) 733–750



Sniderman. *Curr Opin Lipid*. 2004;15:433-438.

REVIEW

Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel

All of the national and transnational screening and therapeutic guidelines are based on total or LDL cholesterol.

This presumes that cholesterol is the most important lipoprotein-related proatherogenic risk variable.

On the contrary, risk appears to be more directly related to the number of circulating atherogenic particles that contact and enter the arterial wall than to the measured concentration of cholesterol in these lipoprotein fractions.

Each of the atherogenic lipoprotein particles contains a single molecule of apolipoprotein (apo) B and therefore the concentration of apo B provides a direct measure of the number of circulating atherogenic lipoproteins.

Evidence from fundamental, epidemiological and clinical trial studies indicates that apo B is superior to any of the cholesterol indices to recognize those at increased risk of vascular disease and to judge the adequacy of lipid-lowering therapy.

Barter PJ et al. J Intern Med 2006;249:247-258


REVIEW

Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel

The evidence also indicates that the **apo B/apo A-I ratio is superior to any of the conventional cholesterol ratios** in patients without symptomatic vascular disease or diabetes to evaluate the lipoprotein-related risk of vascular disease.

Barter PJ et al. J Intern Med 2006;249:247-258


REVIEW

Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty-person/ten-country panel

- apo B measures total atherogenic particle number in plasma and is superior to LDL cholesterol as an index of the lipid-related risk of vascular disease and as a guide to the adequacy of LDL-lowering therapy.
- Measurement of apo B is simple, standardized and does not require fasting plasma.
- **apo B is a better guide** than any of the cholesterol indices for judging the adequacy of LDL-lowering therapy.
- The apo B/apo A-I ratio appears to be superior to any of the cholesterol ratios for quantifying the lipoprotein-related risk of vascular disease.

Barter PJ et al. J Intern Med 2006;249:247-258

Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 50, No. 18, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.07.045

STATE-OF-THE-ART PAPER

Beyond Low-Density Lipoprotein Cholesterol

Defining the Role of Low-Density Lipoprotein Heterogeneity in Coronary Artery Disease

James O. Mudd, MD,* Barry A. Borlaug, MD,* Peter V. Johnston, MD,* Brian G. Kral, MD, MPH,* Rosanne Rouf, MD,* Roger S. Blumenthal, MD,* Peter O. Kwiterovich, JR, MD†

Baltimore, Maryland

Recent clinical trials in patients with coronary artery disease (CAD) provide evidence that low-density lipoprotein cholesterol (LDL-C) levels should be lowered even further to prevent recurrent CAD. However, despite more aggressive interventions for lowering LDL-C levels, the majority of CAD events go undeterred, perhaps related to the fact that intervention was not started earlier in life or that LDL-C levels represent an incomplete picture of atherogenic potential. Nevertheless, LDL-C remains the contemporary standard as the primary goal for aggressive LDL reduction. If triglycerides are >200 mg/dl, the measurement of non–high-density lipoprotein cholesterol (HDL-C) is recommended. Measurement of apolipoprotein (apo)B has been shown in nearly all studies to outperform LDL-C and non–HDL-C as a predictor of CAD events and as an index of residual CAD risk. This is because apoB reflects the total number of atherogenic apoB-containing lipoproteins and is a superior predictor of the number of low-density lipoprotein particles (LDL-P). Estimates of LDL-P and size can also be made by nuclear magnetic resonance spectroscopy, density gradient ultracentrifugation, and gradient gel electrophoresis. Although a number of studies show that such estimates predict CAD, LDL-P, and size often accompany low HDL-C and high triglyceride levels, and therefore such additional lipoprotein testing has not been recommended for routine screening and follow-up. Because apoB is a superior predictor of LDL-P, we recommend that apoB

We recommend that apoB and the apoB/A-I ratio be determined after the measurement of LDL-C, non HDL-C and the ratio of total cholesterol/HDL-cholesterol to better predict CAD and assess its efficacy to treatment

Reviews/Commentaries/ADA Statements

CONSENSUS STATEMENT

Lipoprotein Management in Patients With Cardiometabolic Risk

Consensus statement from the American Diabetes Association and the American College of Cardiology Foundation

John D. Brunzell, MD, FACP[1]
Michael Davidson, MD, FACC[2]
Curt D. Furberg, MD, PHD[3]
Ronald B. Goldberg, MD[4]
Barbara V. Howard, PHD[5]
James H. Stein, MD, FACC, FACP[6]
Joseph L. Witztum, MD[7]

April 2008

Diabetes Care 2008;31:811-822 JACC 2008;51:1513:1512–24

ADA and ACC Consensus Statement on Lipoprotein Management

Particle Quantification

- In particular apoB should be used to guide adjustments to therapy
- LDL-P as measured by NMR appears equally informative as apoB
- The panel recommends that the apoB goal be reached

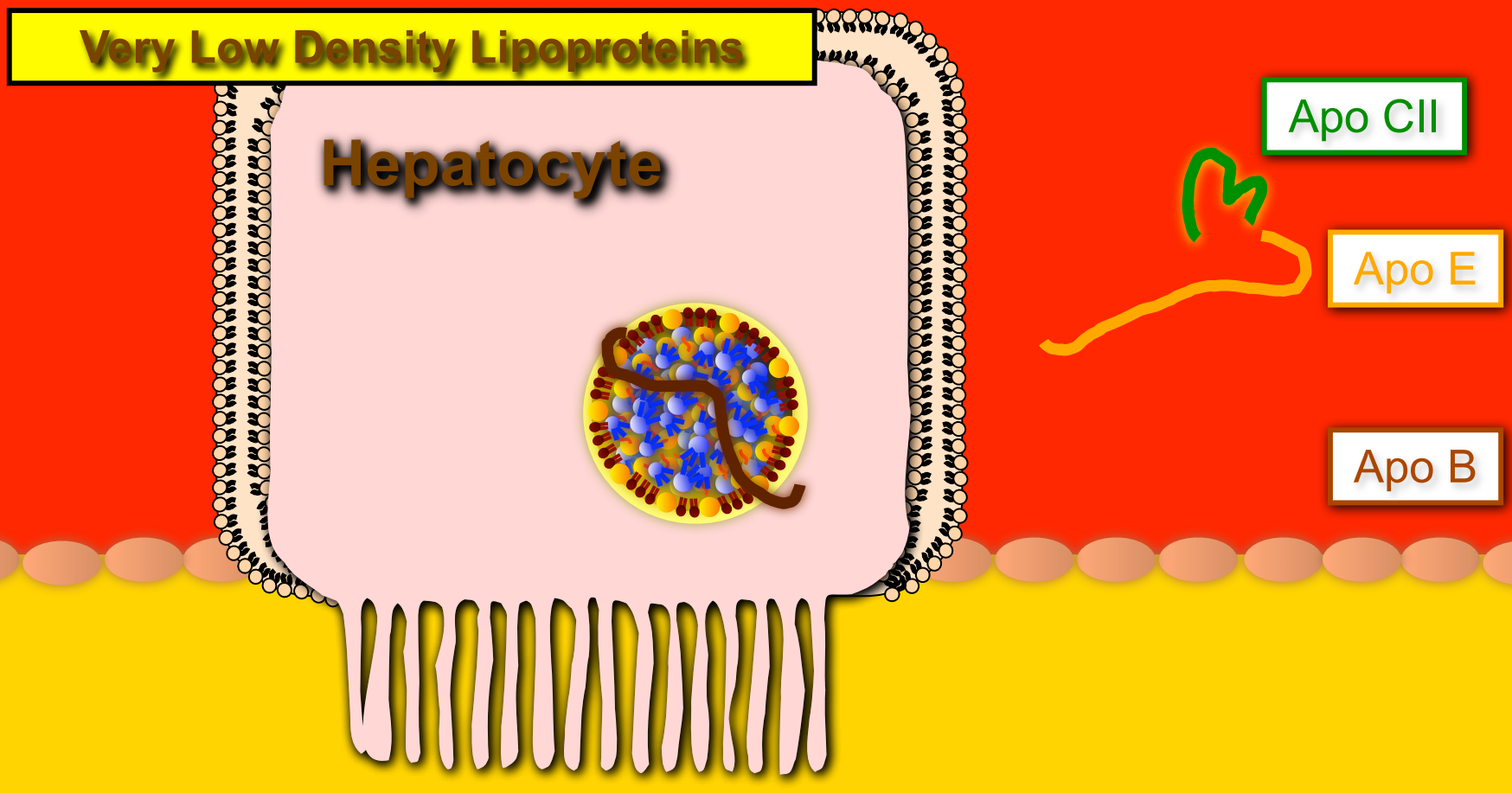
Brunzell JD, Davidson M, Furberg CD et al. Diabetes Care 2008;31:811-822

ADA and ACC Consensus Statement on Lipoprotein Management in Patients with Cardiometabolic Risk

TREATMENT GOALS	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	ApoB (mg/dL)
Highest-risk patients, including those with 1) known CVD or 2) Diabetes plus one or more additional CVD risk factor	< 70	< 100	< 80
High-risk patients, including those with 1) no diabetes or known clinical CVD but 2 or more additional major CVD risk factors or 2) Diabetes but no other CVD risk factors	< 100	< 130	< 90

Brunzell JD, Davidson M, Furberg CD et al. Diabetes Care 2008;31:811-822

Hepatocyte: Lipids & Lipoproteins

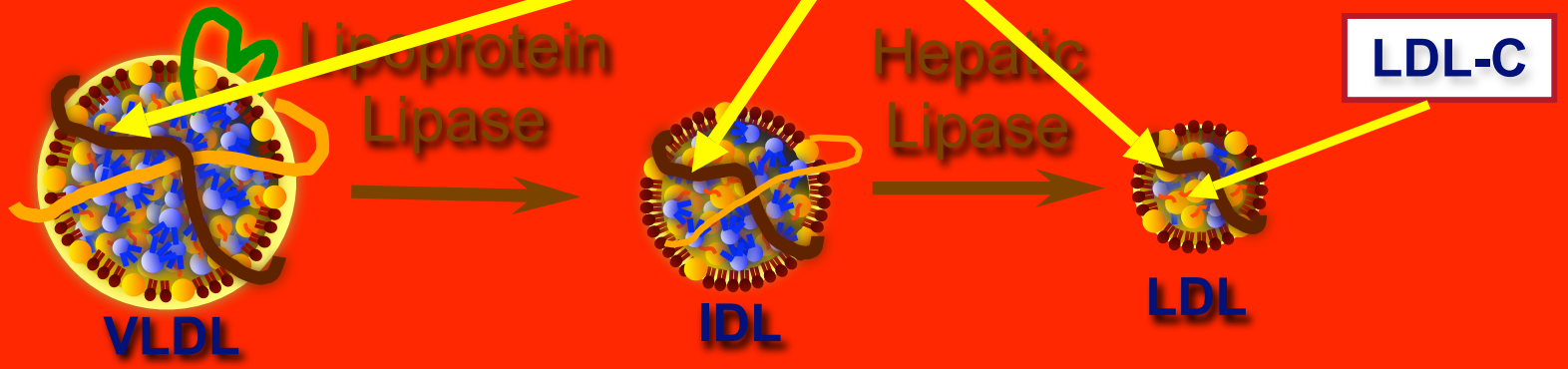


Anything that raises hepatic Triglycerides will increase VLDL production or size

Hepatic VLDL Lipolysis
Normal Lipoprotein Metabolism

Lipolysis or hydrolysis of triglycerides

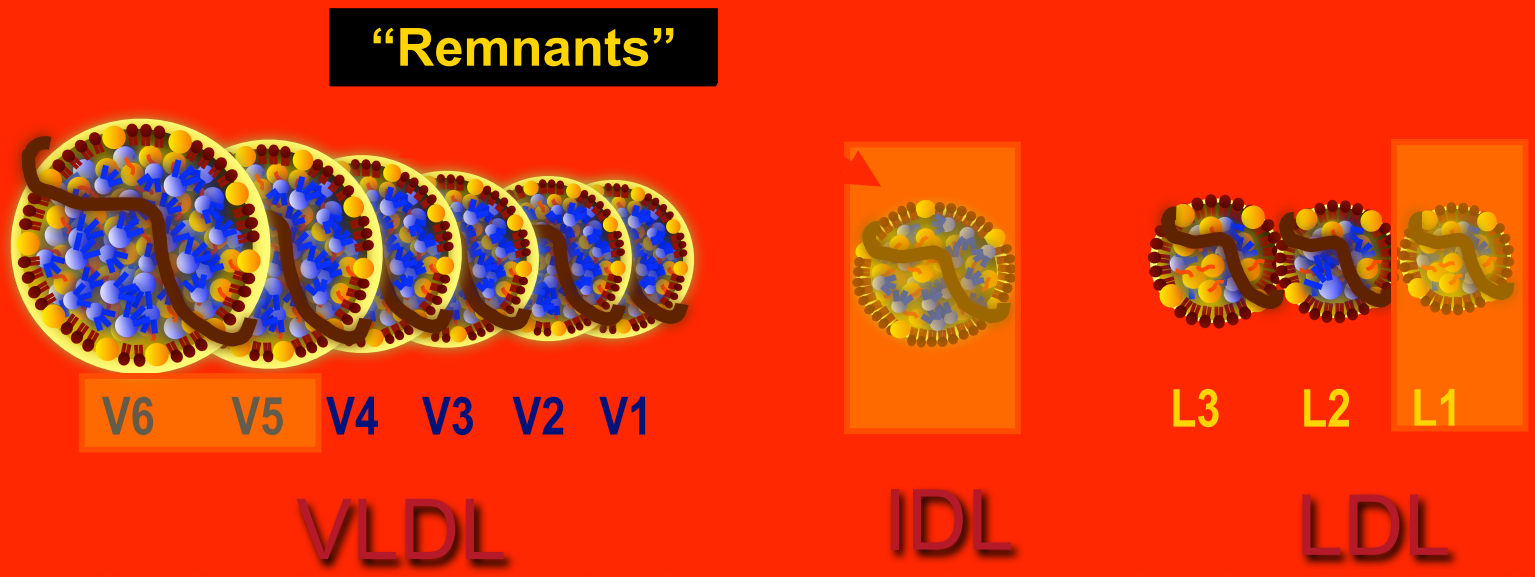
Beta-lipoprotein Concentration = Apo B or NMR LipoProfile



Beta-lipoprotein Estimate = VLDL-C + IDL-C + LDL-C

Beta-lipoprotein Estimate = Non HDL-C

Beta-Lipoprotein Size or Subclass



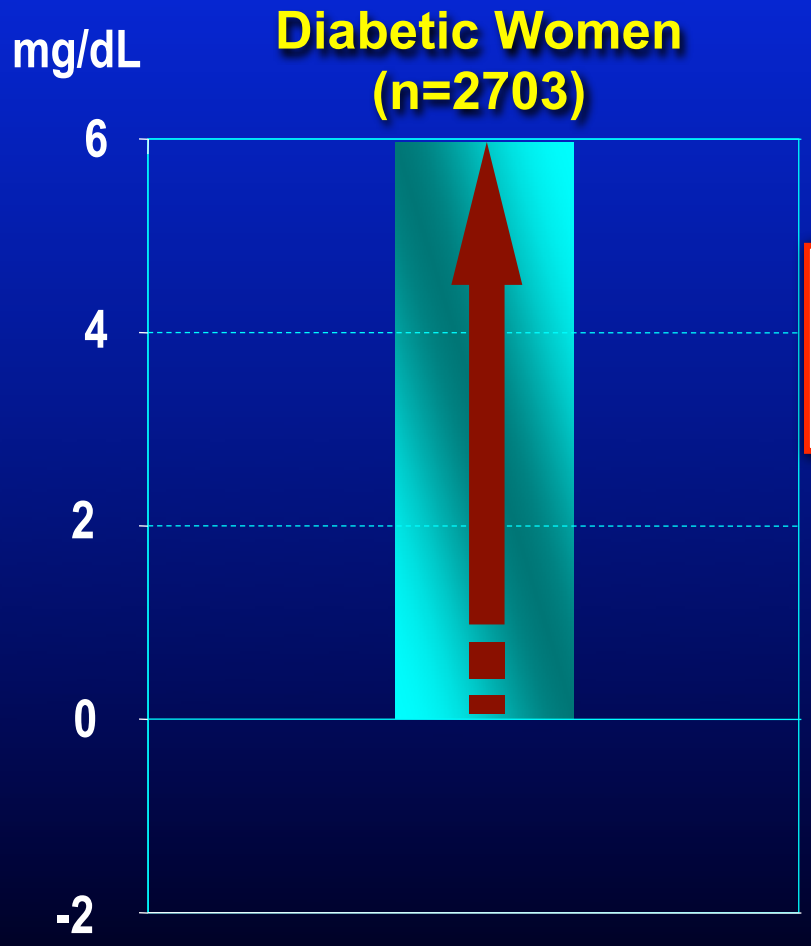
Lipoproteins are heterogeneous and come in various sizes and densities: each patient has all sizes of lipoproteins, but each has a predominant particle size or phenotype

Arterioscler Thromb Vasc Biol 1998;18:1046-1053

Handbook of lipoprotein Testing 1997 AACC Press

www.lipoprofile.com

Strong Heart Study
Mean Apo B in Diabetics



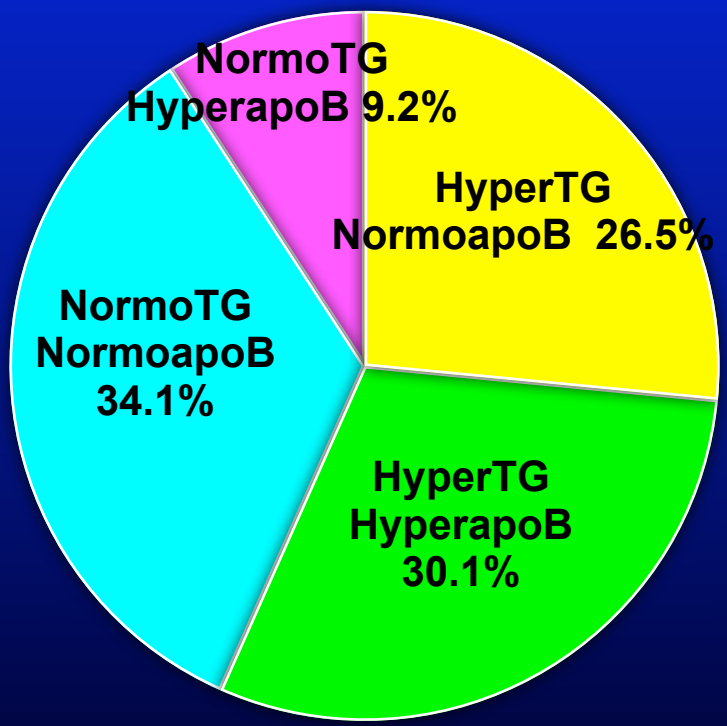
Difference between participants with and without diabetes mg/dl

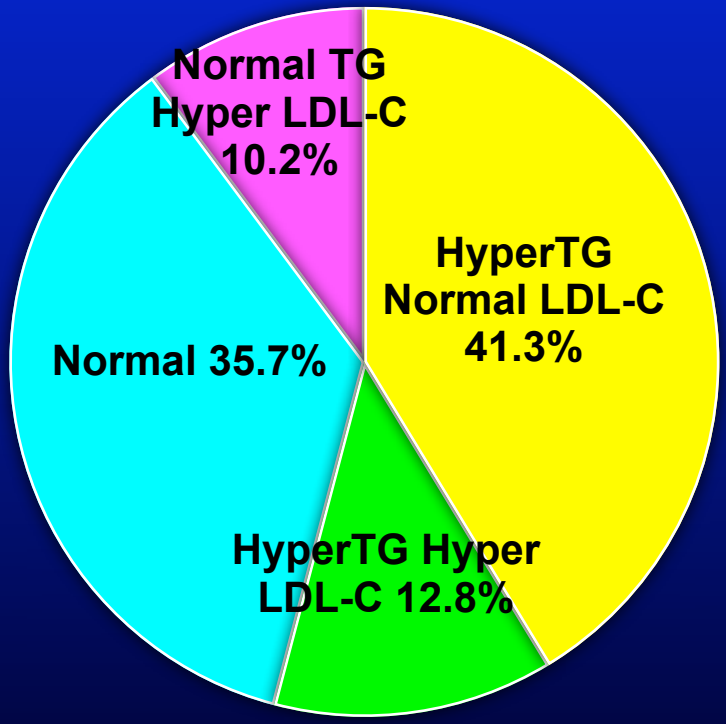
P = 0.0005

Howard BV, et al. *Diabetes Care.* 1998;21:1258-65.

Diabetes and apoB

Phenotype Frequencies based on TG and apoB or TG and LDL-C





Sniderman et al. Diabetes Care 25:579–582, 2002

Diabetes and apoB

CONCLUSIONS: The dyslipidemic profile of patients with type 2 diabetes is not uniform.

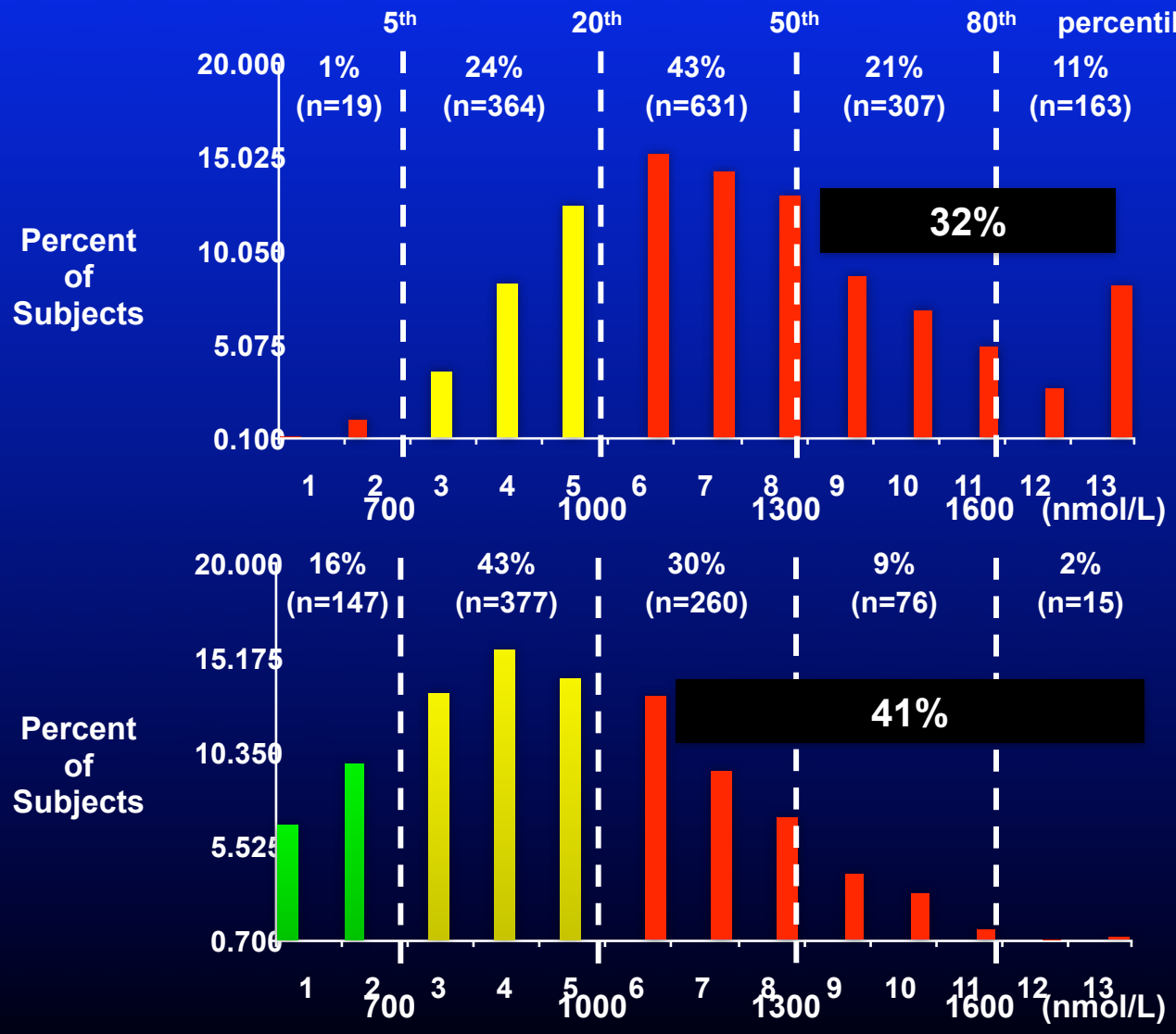
A substantial group have normal lipids and normal LDL particle number and size whereas others have markedly abnormal profiles.

Diagnosis based on triglycerides and apoB rather than triglycerides and LDL cholesterol revealed that more than one in five had hypertriglyceridemic hyper-apoB, which is characterized by hypertriglyceridemia, marked elevation of LDL particle number, small dense LDL, and low HDL.

This constellation of abnormalities that is associated with markedly accelerated atherogenesis and therefore justifies intensive medical therapy.

Sniderman et al. Diabetes Care 25:579–582, 2002

LDL Particle Number Distribution in T2DM Subjects with Normal, at Goal LDL-C



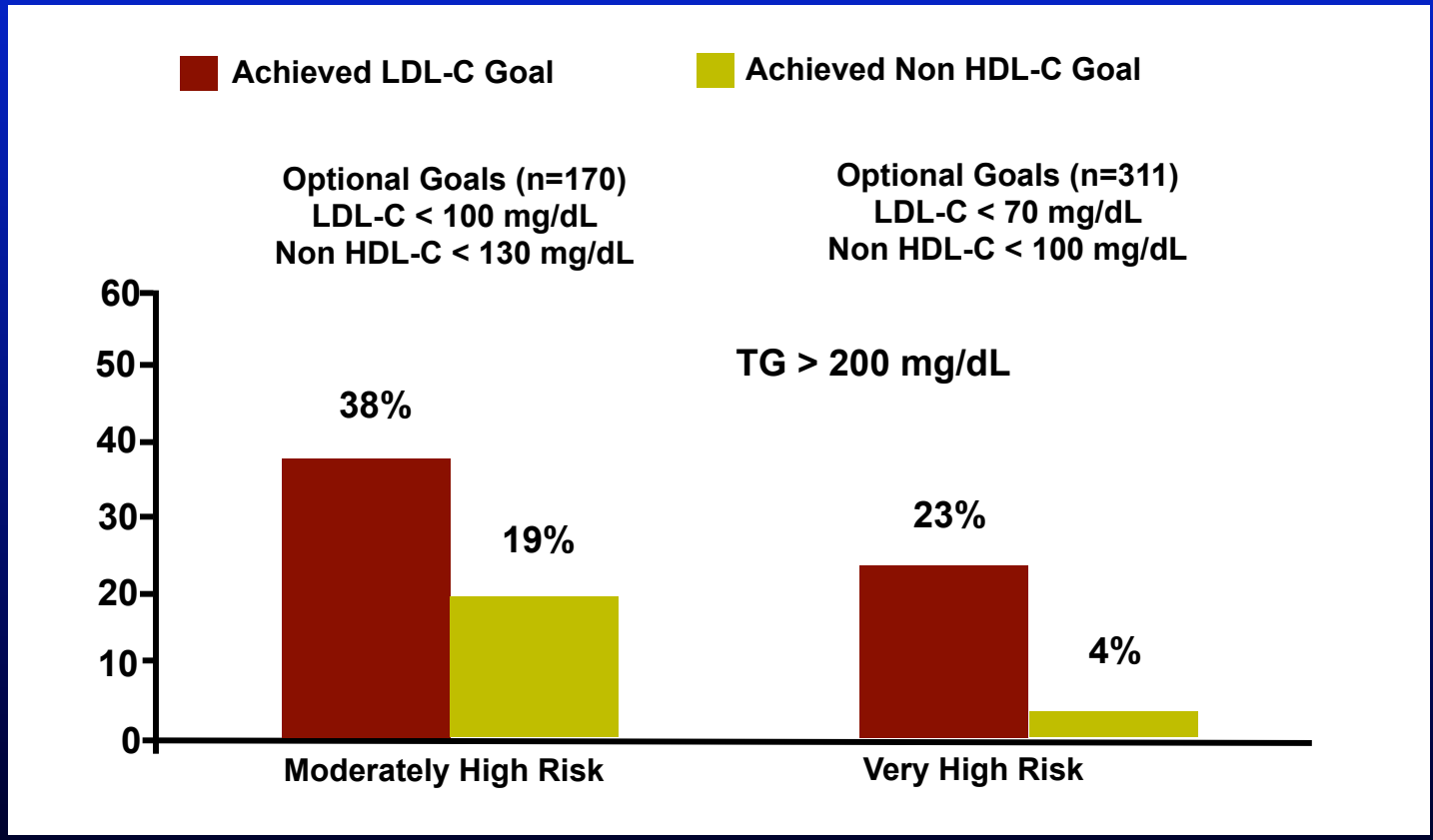
LDL-C
71-99 mg/dL
(n=1,484)

LDL-C
≤ 70 mg/dL
(n=871)

Cromwell W & Otvos J (Am J Cardiol 2006;98:1599 –1602

NEPTUNE II Survey Non HDL-C Goal

NCEP Evaluation ProjecT Utilizing Novel E-technology



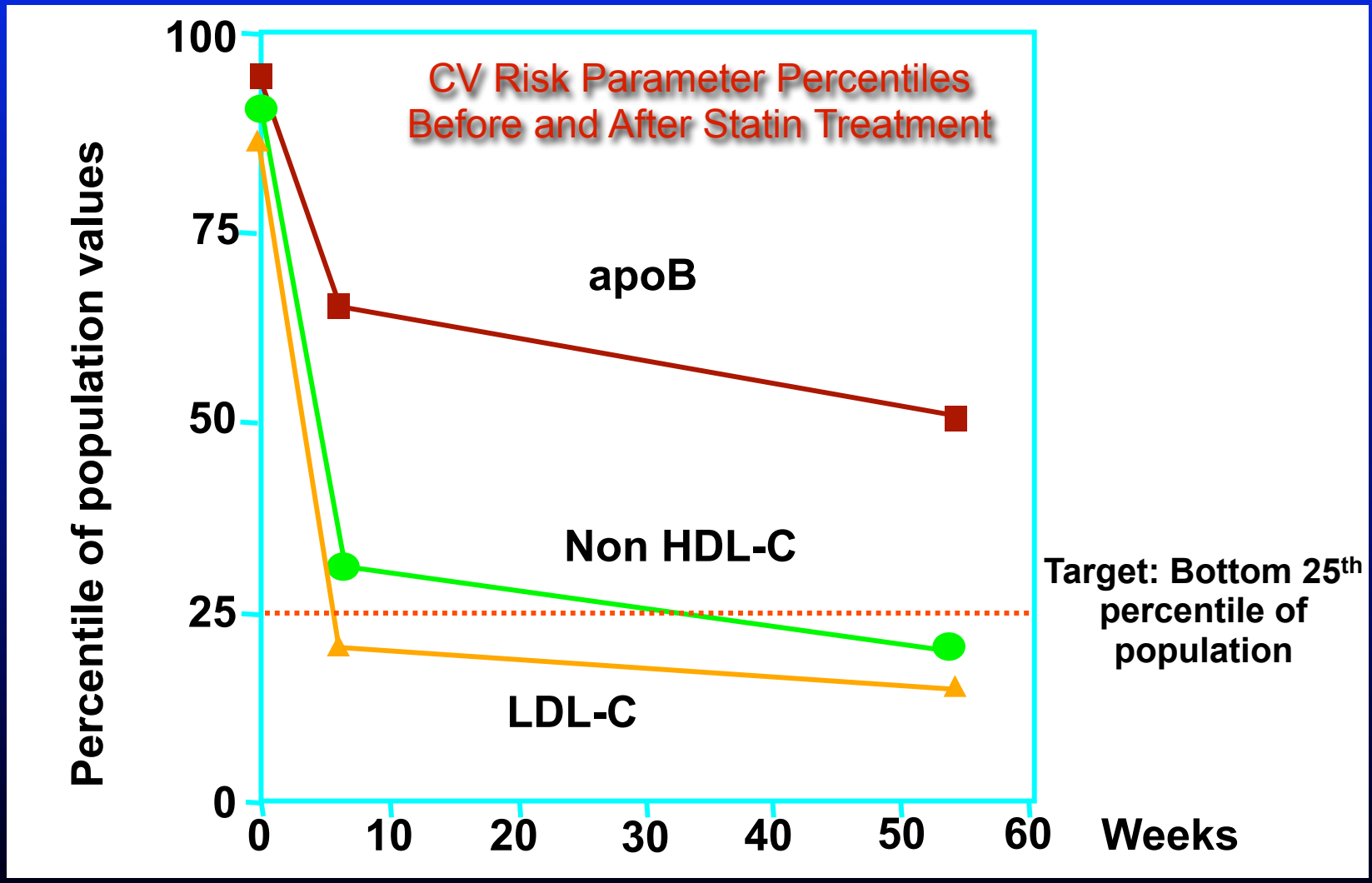
Am J Cardiol 2005;96:556-563

Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS)

- Baseline and on-treatment Non HDL-C levels correlated better with apoB than did LDL-C
- Baseline TG levels did not greatly influence the strength of this correlation
- Unlike LDL-C, non HDL-C is not affected by rising TG concentrations
- Using non HDL-C may provide **superior guidance** as to how aggressively dyslipidemic patients should be treated
- This would require treating patients more aggressively than is current practice, particularly in those with highest risk

Ballantyne C, Amer J Cardiol. 2001;88:265-269

Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS)



Sniderman. *Curr Opin Lipid*. 2004;15:433-438.

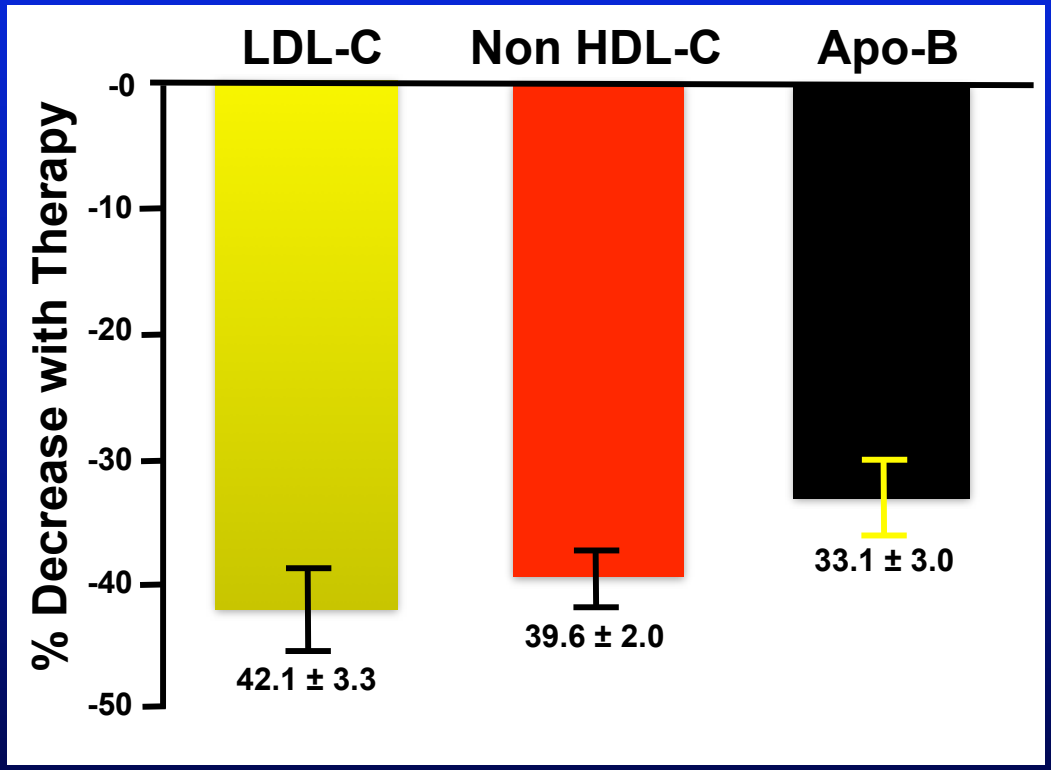
LDL-C vs Non HDL-C vs ApoB

- ApoB and Non HDL-C are highly correlated but only moderately concordant—that is, for any given value of one, there is a substantial range of values for the other.
- Agreement, not surprisingly, is greater in normotriglyceridemic compared to hypertriglyceridemic subjects. However, even within the normotriglyceridemic group, there is only moderate concordance between the two methods.
- The net result is that for individuals, the value of ApoB is not accurately predictable from the value for non HDL-C. atherosclerosis

Sniderman AD Journal of Clinical Lipidology (2008) 2, 36–42

On Therapy LDL-C vs Non HDL-C vs ApoB

N = 17,035



Average achieved LDL-C percentile was the 27th %tile. In contrast, average on-treatment LDL-P only was reduced to the 51st percentile (P 0.007). Thus, the reduction in LDL-P was significantly less than LDL-C.

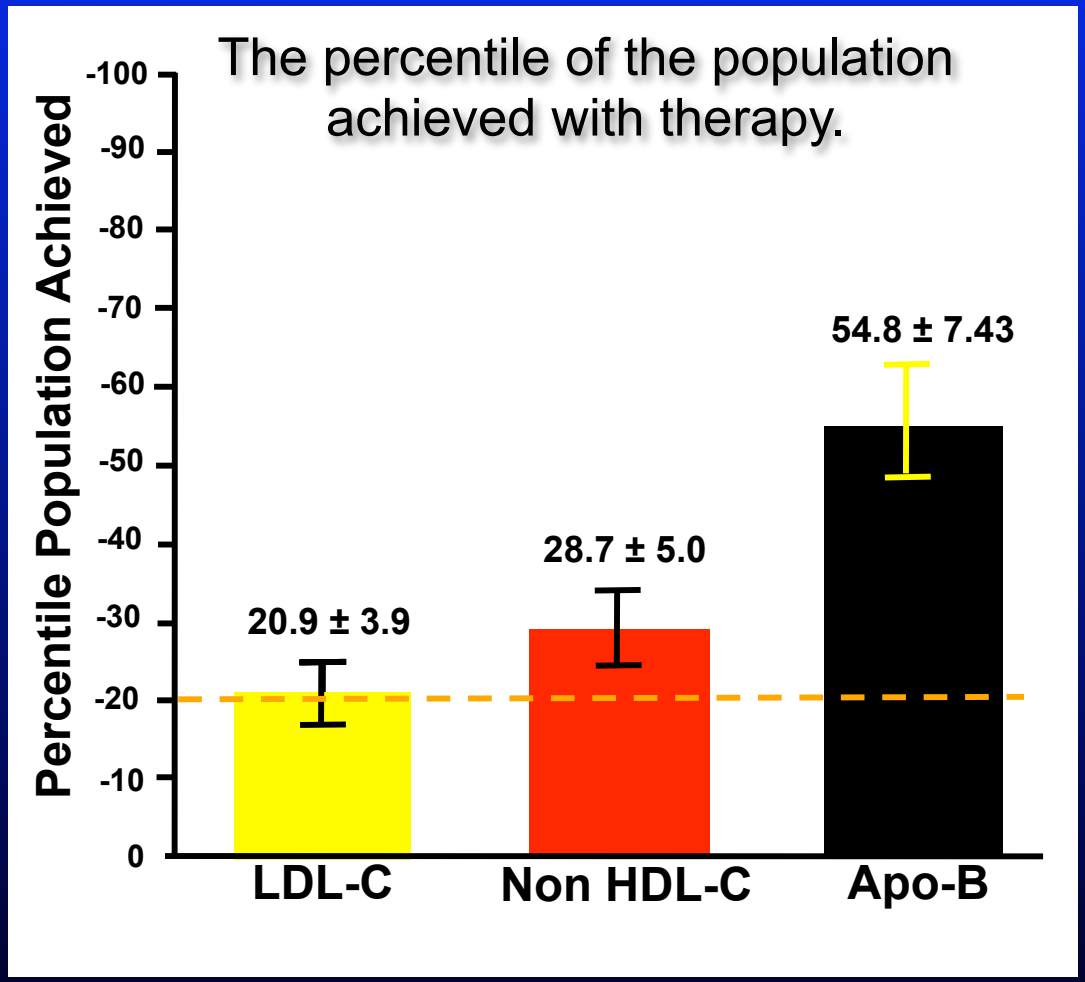
The decrease in non–HDL-C was significantly less (P 0.001) than the decrease in LDL-C, whereas the decrease in ApoB was significantly less than the decrease in either LDL-C or non–HDL-C (P 0.001).

Findings in the eight studies with 889 subjects in which LDL-P was measured by nuclear magnetic resonance are very similar to those obtained with ApoB, and are equally consistent.

Average percent decreases in LDL-C and LDL-P were 35.9 3.5% and 30.6 2.8%, respectively.

Sniderman, AD Journal of Clinical Lipidology (2008) 2, 36–42

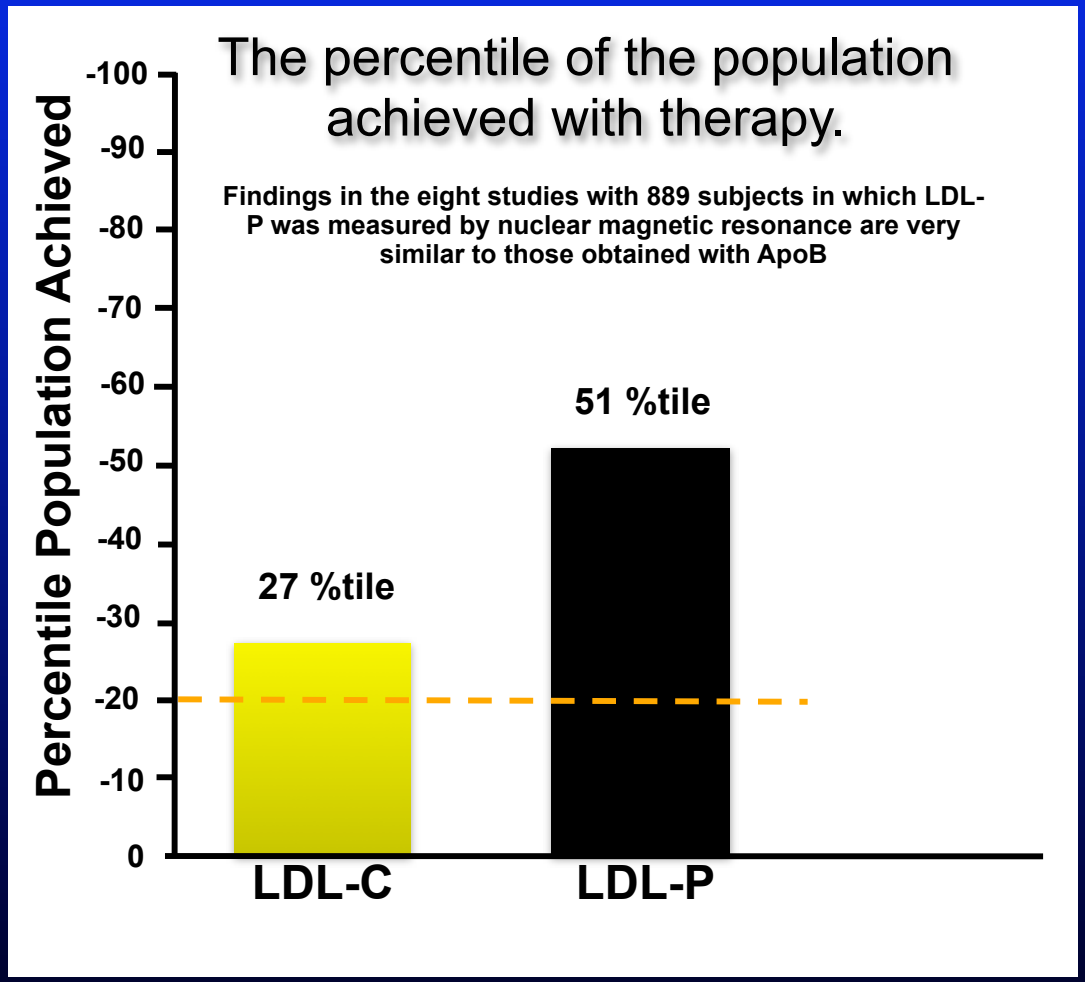
On Therapy LDL-C vs Non HDL-C vs ApoB



LDL-C, on average, was reduced to a level equal to the 22nd percentile of the reference population. The corresponding average concentration achieved for non–HDL-C was the 29th percentile value, which was a significantly lesser change than achieved with LDL-C (P 0.001). Both differ substantially with the findings obtained for ApoB. ApoB was only decreased to the 55th percentile of the population, a drop that is significantly less than achieved with LDL-C or non HDL-C (P 0.001 in both comparisons).

Sniderman, AD Journal of Clinical Lipidology (2008) 2, 36–42

On Therapy LDL-C vs LDL-P



Very similar results were obtained in eight studies of LDL lowering in 889 subjects in which the responses of LDL-C and LDL particle number (LDL-P) assessed by nuclear magnetic resonance spectroscopy were compared.

LDL-C was reduced to the 27th percentile of the population, whereas LDL-P was only reduced to the 51st percentile of the population ($P<0.007$).

Thus, the reduction in LDL-P was significantly less than LDL-C.

Sniderman, AD Journal of Clinical Lipidology (2008) 2, 36–42

LDL-C vs Non HDL-C vs ApoB

- The decrease in LDL-C to LDL-lowering therapy was significantly greater than the decrease in non HDL-C. However, the decrease in ApoB and LDL-P was significantly less than either, whether expressed as percent decrease or percentile of the population achieved.
  - Given that LDL particles make up the vast majority of total plasma ApoB, agreement between ApoB and LDL-P is anticipated.
- Nevertheless, the concordance of the responses of ApoB and LDL-P to LDL-lowering therapy provides powerful confirmation of the principal findings— the discordance between the extent of the response of the cholesterol measures on the one hand, and the atherogenic particle number measures on the other.

Sniderman AD Journal of Clinical Lipidology (2008) 2, 36–42

LDL-C vs Non HDL-C vs ApoB

- There are two explanations for the discordance between the response of cholesterol and particle number to statins.
  - The first relates to changes in LDL composition, but not size, with statin therapy.
  - LDL particle size is generally unchanged by statin therapy, but that does not mean LDL composition remains fixed.
- A recent Framingham report showed that there were 10% to 25% fewer cholesterol molecules per LDL particle in individuals with LDL-C 100 mg/dL compared to those with LDL-C 160 mg/dL.
  - This was independent of plasma triglyceride and was not associated with any difference in LDL particle size. It was postulated that LDL particles of individuals with low LDL-C become relatively cholesterol-depleted and triglyceride- enriched as a result of core lipid exchange mediated by cholesterol ester transfer protein.

Sniderman AD Journal of Clinical Lipidology (2008) 2, 36–42

LDL-C vs Non HDL-C vs ApoB

- Therefore, statin therapy results in triglyceride enrichment and cholesterol depletion of LDL particles. Because triglycerides persist within the particle core, LDL composition, but not LDL size, changes.
- Changes in core lipid composition of LDL can, therefore, be driven not only by very LDL triglyceride elevation, ie, the usual model, but also by LDL-C reduction, ie, the statin model.
- These data establish that basing LDL-lowering therapy only on the cholesterol indexes results in a treatment gap in a large group of patients: a treatment gap that can be recognized and closed with more intensive therapy only if the atherogenic particle number is measured.

Sniderman AD Journal of Clinical Lipidology (2008) 2, 36–42

LDL-C vs Non HDL-C vs ApoB

Many patients who achieve LDL-C and non–HDL-C target levels will not have achieved correspondingly low population-equivalent ApoB or LDL-P targets. Reliance on LDL-C and non–HDL-C can create a treatment gap in which the opportunity to give maximal LDL-lowering therapy is lost.

Sniderman AD Journal of Clinical Lipidology (2008) 2, 36–42

Journal of the American College of Cardiology

Published by Elsevier Inc.

EDITORIAL COMMENT

We Must Prevent Disease, Not Predict Events*

Allan D. Sniderman, MD

Montreal, Quebec, Canada

We KNOW what causes disease within our arteries but can only guess at what precipitates clinical events.

It follows that prevention of coronary disease would be much more effective if we focused on PREVENTING disease developing within our arteries rather than trying to predict who is just about to become a victim and then trying frantically, at what may be just one minute before their final midnight, to rescue them

If we prevent the disease, we will prevent the events.

Take away the apoB particles and

JACC, 52(4) 2008. 300-301.