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Apolipoprotein B and Cardiovascular Disease Risk: Position Statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

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Contois JH, et al. Clinical Chemistry 2009; 55:407-419

Recommendations from AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

- "LDL particles, not simply LDL-C, play a central role in atherogenesis."
- "LDL particles move into the arterial intima through a gradient-driven process, and the rate of passive diffusion is increased when the concentration of circulating LDL particles is increased."
- "Once inside the intima, the LDL particles bind to proteoglycans and initiate a process whereby the LDL particles become oxidized or other wise modified and are taken up by monocytes or macrophages to form foam cells or macrophages."
- "The cholesterol molecules contained in the LDL are "passengers," but the intact particles drive the atherosclerotic process."

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- Programs to standardize LDL-C, HDL-C, and triglycerides have met with only modest success, despite the widespread belief that these assays are accurate and reliable.
- ApoB standardization has fared much better with the success of the IFCC standardization project to improve apoA-I and apoB measurements

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- "LDL-C, non-HDL-C, LDL-P, and total apoB are all, to varying degrees, measures of LDL related risk."
- "These cholesterol and particle measures are highly intercorrelated, which explains why they have all been implicated as predictors of CVD risk in epidemiologic studies, but biologically they reflect different entities."
- "Despite a high correlation, these markers are only modestly concordant, indicating that one cannot simply substitute for another in classifying patients into risk categories."
- "We believe that the medical decision cutpoints should be set so that the apoB and LDL-P cutpoints are equivalent to those for LDL-C in terms of population percentiles."

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Suggested Treatment Goals

ApoB, mg/dL	LDL-C, mg/dL	Non-HDL-C, mg/dL	LDL-P, nmol/L
	< 70	< 80	
< 80	< 100	< 120	< 1100
< 100	< 130	< 150	< 1400

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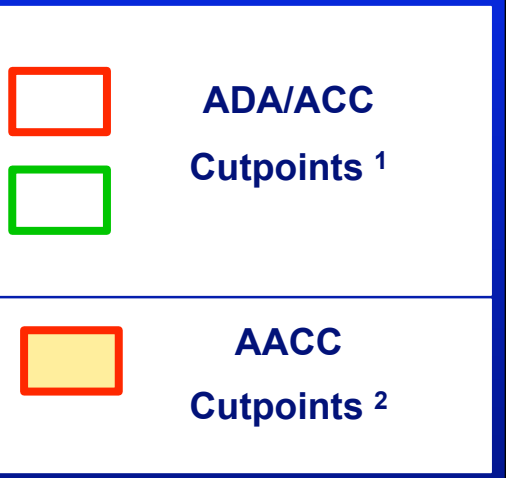
Population Distributions of LDL-C, non-HDL-C, ApoB and LDL-P in Framingham Offspring Study

Percentile	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	LDL-P (nmol/L)	ApoB (mg/dL)
2	70	83	720	54
5	78	94	850	62
10	88	104	940	69
20	100	119	1100	78
30	111	132	1220	85
40	120	143	1330	91
50	130	153	1440	97
60	139	163	1540	103
70	149	175	1670	110
80	160	187	1820	118
90	176	205	2020	130
95	191	224	2210	140



The medical decision cutpoints should be set so that the apoB and LDL-P cutpoints are equivalent to those for LDL-C in terms of population percentiles.

[1] Brunzell, et al. Diabetes Care 2008;31(4):811-822.
[2] Contois JH, et al. Clinical Chemistry 2009; 55:407-419

Recommendations from AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices

Use of ApoB and LDL Particle Number in Clinical Management

- We do not believe that an apoB cutpoint equivalent to an LDL-C of 70 mg/dL (1.81 mmol/L) is necessary at this time.
- We believe that a focus on reduction of LDL particles in very-high-risk patients is appropriate, and data are needed to determine optimal apoB and LDL-P target concentrations.
- However, a goal that is less than the 5th percentile of the population, as is an LDL-C 70 mg/dL (1.81 mmol/L), may be unreasonable or unnecessary.

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- There are certain flaws with using the cycle 4 dataset from the Framingham Offspring Study to determine population equivalent cutpoints. The specimens were collected between 1988 and 1991, the vast majority of Framingham subjects were white, and the dataset excludes subjects with triglycerides 400 mg/dL (4.52 mmol/L) to calculate LDL-C.
- There has likely been a shift in the distribution of lipids and lipoproteins over time so that what was once the 20th percentile is now the 30th percentile; however, the equivalence between a given percentile of apoB and LDL-C is unlikely to shift significantly.
- Also, although the relative risk associated with a given concentration of apoB or LDL-C may vary somewhat with race, the relationship between apoB and LDL-C with CVD risk is strong for all racial groups. Therefore, we believe that these recommended cutpoints remain valid.

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- We agree that a greater emphasis on non–HDL-C rather than LDL-C will improve patient care. Data from several prospective studies show non–HDL-C to be a better predictor of cardiovascular events than LDL-C.
- In terms of relative risk, non–HDL-C is consistently stronger than LDL-C and, in many studies, equivalent to apoB or LDL-P.
- However, apoB has been more extensively validated in epidemiological studies and clinical trials than non–HDL-C, and non–HDL-C, like LDL-C, reflects the cholesterol content of atherogenic particles and **not the number of atherogenic particles**.
- Importantly, on-treatment non–HDL-C concentrations may not reflect residual risk associated with increased LDL particle number

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Use of LDL Particle Number in Clinical Management

- "Statins are highly effective in reducing serum cholesterol through inhibition of HMG-CoA reductase, which upregulates LDL receptors and leads to increased clearance of LDL particles from the circulation."
- "However, the reduction in serum apoB or LDL-P concentration is not as dramatic as the reduction in LDL-C or non HDL-C."
- "As a result, patients treated to goal for LDL-C may not have achieved correspondingly low LDL particle concentrations, leading them with potential residual risk."

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- "Because therapies with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors reduce LDL-C to a greater extent than they do LDL particles, apoB or LDL-P appear to provide a better assessment of on-treatment residual risk than LDL-C measurement."
- "Importantly, on-treatment non-HDL-C concentrations may not reflect residual risk associated with increased LDL particle number."
- "In light of the mounting evidence, the members of this working group of the Lipoproteins and Vascular Diseases Division of the AACC believe that apoB and alternate measures of LDL particle concentration should be recognized and included in guidelines, rather than continuing to focus solely on LDL-C."

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Is Cholesterol a Reliable Measure of LDL Particle Concentration?

- "Cholesterol has served as a useful surrogate for estimating LDL-related risk, but LDL-C concentration can vary widely between individuals with the same LDL particle concentration."
- "LDL-C content does not reflect LDL particle concentration because metabolic reactions involving lipid can alter both lipoprotein size and lipid composition."
- "Any measure of LDL-C, including the β-quantification reference method, suffers from the fact that measurement of the cholesterol component of LDL does not consistently reflect the concentration of LDL particles in serum/plasma."

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Alternate Measures of LDL Quantity

Options for Measurement of LDL Particle Concentration

- "Although it is often considered to be a distinct risk factor, apoB is better considered an alternate measure of LDL-related risk because it largely reflects LDL particle concentration."
- "Nuclear magnetic resonance (NMR) has more recently been introduced as another means of quantifying LDL particle number (LDL-P) concentration."

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Prospective Studies of LDL-P in Comparison to LDL-C

Study	Comparison	LDL-P	LDL-C	Matching and/or adjustment variables
Blake et al. 2002	Quartile 4 vs 1	4.17 (1.96-8.87)	2.06 (1.03-4.12)	Age, smoking, Rx group
	Quartile 4 vs 1	M, NS; W, 2.59	M, NS, W, 3.34	Age, race
Kuller et al. 2002 Rosenson et al. 2002	Above vs. below median	2.1 (0.7-5.8)	1.4 (0.5-3.9)	Age, race, baseline lumen diameter
El Harchaoui et al. 2007	Quartile 4 vs 1	1.78 (1.34-2.37)	1.22 (0.92-1.61)	Smoking, SBP, LDL-C or LDL-P
Otvos et al 2007	Baseline, 1 SD	1.29 (1.05-1.37)	1.10 (0.92-1.61)	Treatment group, age, hypertension, smoking, BMI, diabetes
	On-trial, 1 SD	1.28 (1.12-1.47)	1.08 (0.95-1.23)	
Cromwell et al. 2007	1 SD	M, 1.24 (1.10-1.39), W, 1.33 (1.17-1.50)	M, 1.06 (0.94-1.20); 1.18 (1.02-1.37)	W, Age, SBP, DBP, smoking, medications
Mora et al 2007	Quintile 5 vs 1	2.51 (1.91-3.30)	1.74 (1.40-2.16)	

Abbreviations: NS ,not significant;SBP, systolic BP; BMI ,body mass index; DBP, diastolic BP

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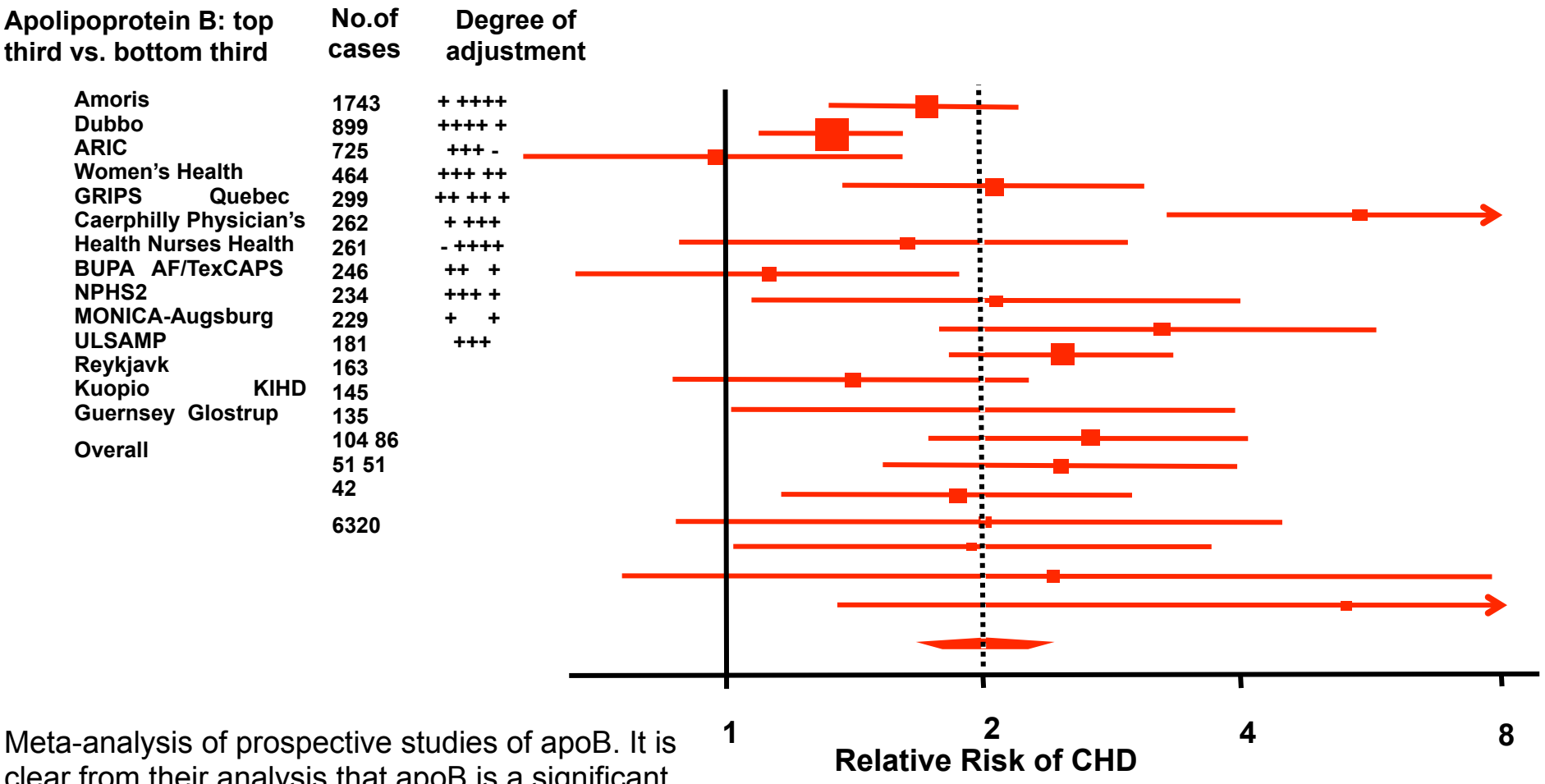
Prospective Studies of Apolipoprotein B



Meta-analysis of prospective studies of apoB. It is clear from their analysis that apoB is a significant predictor of CHD, with an overall relative risk of about 2.0 for the upper vs the lower tertile. J Intern Med 2006;259:481–92.

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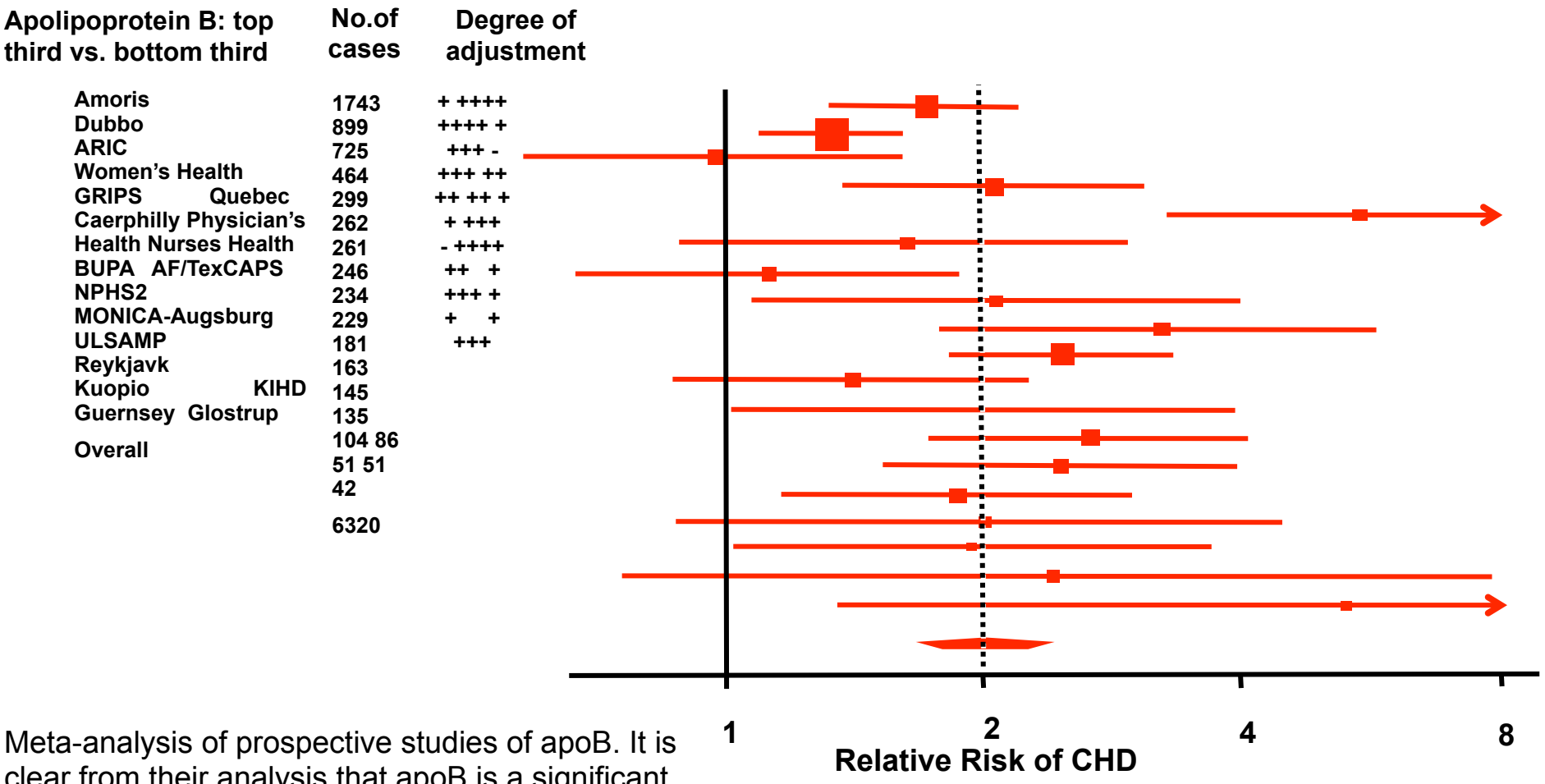

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LDL Particle Concentration (LDL-P)

LDL-P is consistently more predictive of cardiovascular disease than is LDL-C, most noticeably in VAHIT, the Women's Health Study, and the Framingham Heart Study, where LDL-P was more strongly predictive of cardiovascular events than other lipid parameters. In the Multi-Ethnic Study of Atherosclerosis (MESA), LDL-P was associated with preclinical atherosclerosis (carotid intima-media thickness), even in subjects with LDL-C 100 mg/dL .

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LDL Particle Concentration (LDL-P)

Effectiveness of statin treatment at reducing LDL-C, non-HDL-C, apoB and LDL-P

	Reduction on therapy (%)	Mean on-treatment concentration	Mean on-treatment percentile
ApoB Studies (n- 17,035			
LDL-C	42.1	99.2 mg/dL	21
Non-HDL-C	39.6	127.0 mg/dL	29
ApoB	33.1	101.6 mg/dL	55
LDL-P Studies (n- 889)			
LDL-C	35.9	105.2 mg/dL	27
LDL-P	30.6	1459 nmol/L	51

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A wealth of evidence has now accumulated demonstrating the superiority of apoB measurement over that of LDL cholesterol for assessment of CVD risk and events.

Accordingly, addition of apoB to the routine lipid panel for assessing and monitoring patients at risk for adverse outcomes should enhance patient management.

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Call to Action

- "The next logical step is the addition of apoB to NCEP and other guidelines in the US."
- Deferring action, in spite of the accumulating evidence that apoB is the superior measure of LDL-related risk, does increase risk of eventually losing public trust."

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