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Weighing in Before the Fight
Low-Density Lipoprotein Cholesterol and Non–High-Density Lipoprotein Cholesterol Versus Apolipoprotein B as the Best Predictor for Coronary Heart Disease and the Best Measure of Therapy

Margo A. Denke, MD

In this issue of Circulation, Pischon and colleagues1 present provocative data pitting the power of non–high-density lipoprotein cholesterol (non-HDL-C) versus apolipoprotein (apo) B to predict coronary heart disease (CHD) development in healthy men. They conclude not only that apoB is a superior predictor of CHD risk but, in addition, that “the practical application of our findings would be the substitution of apoB for LDL-C and non-HDL-C for screening and treatment of CHD risk.”

Round 2: Biological Variation
Interindividual day-to-day variation in apoB is similar to that found for TC (5% to 7%); calculated LDL-C is higher at 9% and non-HDL-C is probably in a similar range.4 Variation from race and gender finds higher mean non-HDL-C in men than in women (160 versus 154 mg/dL) and lower non-HDL-C in blacks as compared with Mexican Americans and whites (eg, 149 versus 160 versus 162 mg/dL in men, respectively).5 With regard to apoB, there are no significant differences in the age-adjusted mean apoB between men and women; black men have a slight but significantly lower age-adjusted mean apoB than whites or Mexican Americans (98 mg/dL versus 99 mg/dL versus 101 mg/dL, respectively).6

Round 2 Score: 10:10
Variations in measurement resulting from biological factors including gender and race are minimal.

Round 3: Availability of Measurements
Non-HDL-C is now calculated from TC and HDL-C using software set up in chemistry autoanalyzers. Several companies make a commercial assay autoanalyzer kit for apoB. The Roche Diagnostics ApoB ver 2 Kit (Catalog No. 3032639), likely used by Pischon et al, has an assay range of 20 to 400 mg/dL and an expected CV ≤4% for apoB levels >40 mg/dL.

Round 3 Score: 10:7
ApoB measurements would require some effort to be added to every autoanalyzer panel; in-office Clinical Laboratory Improvement Act–waived determinations would not immediately have the capability to quantify apoB. With time, this could be corrected.

Round 4: Expense
A single determination (2001 Canadian dollars) of apoB costs $22.99 compared with TC and HDL-C plus triglycerides (TG) $32.97.

Round 4 Score: 6:8
Costs for apoB are less than a lipid profile; the profile, however, contains TG and HDL-C which still add value.

Round 5: Population Distribution
The Lipid Research Clinics Prevalence Study data from the 1970s oversampled lipid disorders to provide reasonable estimates of dyslipidemias; apolipoproteins were not measured. The later National Health and Nutrition Examination Survey (NHANES) databases have published accurate population estimates for lipid and lipoprotein distributions in the US population; this recurrent survey has permitted population tracking of...
changes in lipid values over time. Added to case-control data from populations with and without coronary disease, these databases have been vital for selecting reasonable treatment cutpoints considering not only a marker’s sensitivity and specificity but also the potential exposure of the population to treatment recommendations. ApoB measurements, standardized with the World Health Organization–International Federation of Clinical Chemistry and Laboratory Medicine reference material, are available from the 11 483 examinees of NHANES III. NHANES III included oversampling of blacks, Hispanics, and older adults to allow adequate percentile descriptions in these subgroups. Additional databases are available from other countries.

**Round 5 Score: 10:8**

Far more information is available about the cholesterol content of serum, and specific lipoproteins, than the apoB content. Cutpoints for apoB as a target cannot be readily defined.

**Round 6: Independence of Measurements**

Technically the measurements are independent: ApoB represents the number of non-HDL particles and non-HDL-C represents the cholesterol content of these particles. Separating their independent identities is another matter. In the Quebec Cardiovascular Study of 2103 men without coronary disease, the correlation between non-HDL-C and apoB was \( r = 0.87 \), \( P < 0.001 \). A detailed concordance evaluation found that 76.4% of participants in the first quintile of apoB (<91 mg/dL) were also in the first quintile of non-HDL-C (<147 mg/dL). Of the participants in the fifth quintile of apoB (>142 mg/dL), 72.8% were also in the fifth quintile of non-HDL-C (>213 mg/dL). Participants in the second, third, and fourth quintiles had a 43.1% to 53.3% concordance.

NHANES III also documents the high correlation between non-HDL-C and apoB of \( r = 0.92 \). Concordance was assessed according to calculated LDL-C cutpoints. An LDL-C <130 corresponded to a mean apoB concentration of 88 mg/dL (95% CI 61 to 116 mg/dL). For LDL-C 130 to 159 mg/dL, the mean apoB was 115 mg/dL (95% CI 94 to 138 mg/dL); for LDL-C 160 to 189 mg/dL, mean apoB was 132 mg/dL (95% CI 112 to 157 mg/dL). Declaring an apoB cutoff of 107 mg/dL equivalent to an LDL-C ≥130 mg/dL, apoB had a sensitivity of 82.6% and a specificity of 85.6%; 15.7% of subjects were misclassified. Declaring an apoB cutoff of 127 mg/dL for an LDL-C ≥160 mg/dL, the sensitivity and specificity improved (71.2% and 93.6%, respectively), resulting in a misclassification of only 5.2%.

In the Insulin Resistance Atherosclerosis Study, a special population of 1522 men and women, half of whom had normal glucose tolerance, one third with diabetes, and the remainder with impaired glucose tolerance, 10% of subjects had an apoB >120 mg/dL but did not have elevated LDL-C or non-HDL-C. In data from 215 patients undergoing treatment in a Canadian lipid clinic, elevated apoB remained in only 4% of the patients who had met their lipid targets.

**Round 6 Score: 8:8**

No measure is perfect. Misclassification using the NHANES database suggests the present guidelines may be missing 8% of high-risk patients who have high apoB. A similar percent-age of hypercholesterolemic patients who do not have apoB elevations would be missed by apoB.

**Round 7: Superior Epidemiological Correlation With Disease**

Besides the analysis of Pischon et al., 5 other analyses weigh in. Colleagues working on the Nurses Health Study found that apoB did not add information to LDL-C in a multivariable-adjusted model. The Apolipoprotein-related Mortality Risk (AMORIS) study measured levels of TC, TG, apoB, and apoA1 in 175 553 Swedish men and women; during the next 5 years 1223 died of myocardial infarctions. Other than gender and age, no other risk factor data were collected. AMORIS used trial-derived formulas to estimate LDL-C and HDL-C. Not all of the statistics for primary comparisons were reported. Similar linear graphs for quartiles of apoB and calculated LDL-C are shown; the text states the risk ratio (RR) for apoB increased from the first to the fourth quartile by 2.7 for both men (\( P < 0.0001 \)) and women (\( P < 0.0001 \)) as compared with the RR for LDL-C, which increased 3-fold for men (\( P < 0.0001 \)) and just under 2-fold for women (\( P < 0.01 \)). Two models pertinent to this competition were presented. The first enters only calculated LDL-C, showing an RR of 1.4 (95% CI 1.33 to 1.48; \( P = 0.0001 \)) for men and 1.24 (95% CI 1.12 to 1.37; \( P < 0.0001 \)) for women. An apoB-only model was not reported; a model considering both apoB and calculated LDL-C found that men had RR of 1.22 (95% CI 1.17 to 1.51 \( P < 0.0001 \)) and 1.14 (95% CI 1.01 to 1.28; \( P = 0.032 \)) and women had RR of 1.53 (95% CI 1.25 to 1.88; \( P < 0.0001 \)) and 0.85 (95% CI 0.69 to 1.05; \( P = 0.139 \)). ApoB markedly attenuated the risk attributable to LDL; consideration for how much the predictive power of non-HDL-C would be attenuated was not included.

In the Atherosclerosis Risk In Communities (ARIC) study, 13 725 CHD events were observed at the 10-year follow-up of 12 339 men and women. LDL-C and apoB were associated with a similar top quintile RR of 2.4 and 2.5 in men and 2.7 and 2.8 in women. ApoB measurements did not contribute to risk prediction in subgroups with elevated TG, lower LDL-C, or high apoB relative to LDL-C.

In the Northwick Park Heart Study, 2508 men ages 50 to 61 residing in the United Kingdom were studied for 5 years; 163 fatal and nonfatal coronary events were observed. 14 TG, TC, calculated LDL-C, and apoB all provided similar RRs for disease prediction, with univariate RRs for an LDL-C of 2.67 (95% CI 1.62 to 4.41; \( P < 0.0005 \)) and apoB of 2.90 (95% CI 1.82 to 4.64; \( P < 0.005 \)). Non-HDL-C was not evaluated. In multivariate analyses, the better predictors of risk included the combination of apoB and HDL-C (RR 8.38, 95% CI 3.21 to 21.92) or apoB and TG (RR 4.05, 95% CI 1.57 to 6.23).

In the Quebec Cardiovascular study, 2155 men ages 45 to 76 were studied for 5 years; 116 fatal and nonfatal coronary events were observed. Measurements of TC, TG, HDL, apoB, and apoA1 were made; LDL-C was calculated. The analysis was limited with regard to the direct comparison of apoB and LDL-C and the statistical issues of colinearity. In the multivariate analyses reported, apoB had an RR of 1.44 (95% CI 1.22 to 1.67) and TC had an RR of 1.46 (1.23 to 1.74). The
RR for LDL-C was not reported, and non-HDL-C calculations were not performed.

**Round 7 Score: 10:8**
The cholesterol content of serum or particles continues to predict disease in all datasets. ApoB did not consistently add to the prediction.

**Round 8: Superior Prediction of Disease From Randomized Clinical Trials of Cholesterol-Lowering Therapies**
Statins lower LDL-C and apoB. In patients with hypercholesterolemia, reductions in apoB are more highly correlated with reductions in non-HDL-C \((r=0.938; P<0.0001)\) than reduction in LDL-C \((r=0.849; P<0.001)\), but both correlations are highly significant.16 In the Air Force Coronary/Texas Atherosclerosis Prevention Study (AFCAPS/TexCAPS), apoB predicted risk both at baseline \((P=0.002)\) and on therapy \((P<0.001)\), whereas LDL-C did not.17 In the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, a secondary prevention trial in which the lowest LDL-C corresponded to the mean LDL-C in AFCAPS/TexCAPS, the proportion of the treatment effect explained by reductions in LDL-C was 52% (95% CI 10 to 94; \(P=0.094\)) compared with 67% (95% CI 24 to 110; \(P=0.233\)) for apoB.18

**Round 8 Score: 5:6**
This is a new area of post hoc data analysis. The AFCAPS/TexCAPS data are impressive. Better statistical methods and the addition of this analysis to more trial data are needed.

**Round 9: Conjecture About the Role of ApoB in National Cholesterol Education Program IV**
A tenet of the recurring National Cholesterol Education Program guidelines is to use new knowledge to build onto the existing guidelines.

**Round 9 Score: KO of ApoB**
The guidelines are named for cholesterol. Extensive campaigns to educate health professionals and the public have taken place since the 1980s. Obliterating the cholesterol measurement, as proposed by Pischon et al, would create confusion.

**After the Fight**
This, of course, does not end the competition. ApoB identifies individuals with small, dense LDL who may now be missed by the present guidelines. On the basis of the scores, apoB is not in the same weight class as NCEP’s primary target, LDL-C. New contests can be proposed in which apoB is pitted against an appropriate contender: ApoB measurement as a secondary target, replacing non-HDL-C? ApoB as an emerging risk factor? Optional measurements to be used in the identification of risk and assessment of therapy? Or in a second treatment algorithm, using TG/apoB?29

While you muse over the next apoB competition, have a look in the locker room for high-sensitivity C-reactive protein. Care to watch another fight?

**References**

Key Words: Editorials ■ cholesterol ■ lipids ■ lipoproteins ■ patients