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EDITORIAL COMMENT

Integrated Measure for Atherogenic Lipoproteins in the Modern Era

Risk Assessment Based on Apolipoprotein B*

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Disorders of insulin resistance (obesity, metabolic syndrome, and type 2 diabetes) have resulted in global demographic shifts in circulating lipid levels characterized by declining levels of low-density lipoprotein cholesterol (LDL-C). We advocate that apolipoprotein B (apoB) is a superior measure of cardiovascular disease (CVD) risk in the modern era, during which an increasing proportion of society manifests obesity, pre-diabetes, and type 2 diabetes. Our specific arguments derive from genetics, population studies, and clinical trials.

CLINICAL MEASURES OF ATHEROGENIC LIPIDS AND LIPOPROTEINS

The standard lipid measure for atherosclerotic CVD risk assessment LDL-C guides therapeutic interventions directed at reducing cardiovascular (CV) events. However, several lines of evidence now argue against the continued use of LDL-C as a first-line measure of lipid-related risk.

LDL-C is a calculated value that depends on the analytic variability of other directly measured components, namely total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs). Specifically, LDL-C concentration is calculated as TC minus very low-density lipoprotein cholesterol (VLDL-C) (estimated as 20% of the TGs obtained after an overnight fast) minus HDL-C. In clinical laboratories, commercially available direct methods for HDL-C have a coefficient of variation in hyperlipidemia and CVD patients ranging from −19.8% to 36.3% for HDL-C and from −26.6% to 31.9% for LDL-C (1).

Additionally, the biological variability in TGs introduces another source of variation in the estimation of VLDL-C. Although, the LDL-C calculation is considered "valid" when TGs are <400 mg/dl, a comparison of directly measured LDL-C by ultracentrifugation demonstrates diminished accuracy of the LDL-C calculation for TGs >200 mg/dl (2). Thus, measurement variability in LDL-C impacts risk assessment and treatment decisions. Non-HDL-C (TC minus HDL-C) represents a measure of the cholesterol content in atherogenic lipoproteins, but is not a measure of particle concentration.

Measurement of apoB, the major structural protein on the surface of a heterogeneous pool of atherogenic lipoproteins with varying content of cholesterol and TGs, represents the concentration of atherogenic lipoproteins that encompass VLDL, intermediate-density lipoprotein, LDL, and lipoprotein (a) particles (**Figure 1**). Because 1 apoB is present on a single atherogenic lipoprotein particle, this measure is not dependent on compositional changes in the core neutral lipid content that may impact risk assessment with LDL-C and non-HDL-C. Due to these limitations of LDL-C, several professional societies proposed measuring apoB or LDL particle concentration as an additional measure for risk assessment after consideration of LDL-C and non-HDL-C (3).

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EPIDEMIOLOGY

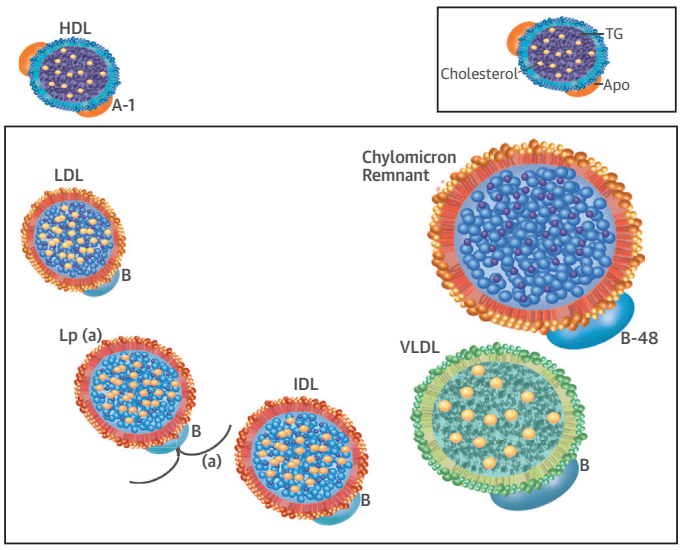
Population-based studies have identified differences in CVD risk prediction between LDL-C, non-HDL-C, and apoB. A meta-analysis that included 233,455 participants and 22,950 events from 12 independent studies reported that relative risk (RR) ratios were lowest for LDL-C (RR: 1.25), intermediate for non-HDL-C (RR: 1.34), and highest for apoB (RR: 1.43) (4). Based on differences in CVD events at 10 years, a treatment strategy that used non-HDL-C would potentially prevent 300,000 more events than an LDL-C strategy, and an apoB strategy 500,000 more than a non-HDL-C strategy.

Discordance analysis is a technique for evaluating biologically linked variables that are analyzed by groups of concordance or discordance in their relative distributions. In the Women's Health Study, which included 27,533 healthy women who had 1,070 incident coronary heart disease (CHD) events after an average 17.2 years, the prevalence of LDL discordance defined by medians for non-HDL-C, apoB, and LDL particle number (LDL-P) was 11.6%, 18.9%, and 24.3%, respectively (5). Among women with low LDL-C, CHD events were underestimated compared with non-HDL-C (age-adjusted hazard ratio [HR]: 2.92), apoB (HR: 2.48) or LDL-P (HR: 2.32). After multivariable analysis that included potentially confounding factors (body mass index, TGs, HDL-C, and diabetes), CHD risk was underestimated by 30% to 50% for

SEE PAGE 193

women with discordant levels. In this issue of the *Journal*, Wilkins et al. (6) use discordance analysis to investigate the association between LDL-C, non-HDL-C, and apoB on the long-term risk of developing biomarkers of insulin resistance and coronary artery calcification (CAC). Their analysis of the CARDIA (Coronary Artery Disease in Young Adults) study classified 2,794 participants into low or high apoB, LDL-C, and non-HDL-C groups defined by the median of the distribution: apoB (88 mg/dl), LDL-C (107 mg/dl), and non-HDL-C (121 mg/dl). At year 25, the odds ratios for CAC (Agatston score >0) were higher for groups with high apoB regardless of whether the LDL-C or non-HDL-C was high or low in multivariable adjusted models that include age, race, sex and baseline smoking status, systolic blood pressure, antihypertensive medication use, body mass index, and diabetes. This discordance analysis showed that measurement of apoB at a mean age of 25 years was more predictive of CAC in 18% of these young adults than LDL-C or non-HDL-C. The high apoB groups included higher proportions of participants with high glucose, high triglycerides, and diabetes.

FIGURE 1 Spectrum of Lipoproteins



Non–high-density lipoprotein cholesterol (HDL-C), a derived variable, is the sum of all cholesterol carried within atherogenic lipoproteins. One molecule of full-length apolipoprotein B (known as apoB-100) is present on all atherogenic lipoproteins, except for chylomicron remnants, whose defining shorter B-48 isoform is undetectable by common laboratory methods. Given these biochemical interconnections, concentrations of apoB and non-HDL-C are highly correlated. ApoB reflects the total particle number, whereas non-HDL-C integrates their total cholesterol content. However, correlation of both apoB and non-HDL-C with a third variable, namely low-density lipoprotein cholesterol (LDL-C), is more erratic. **Box in upper right** shows a "generic lipoprotein." (a) = apo(a); A-1 = apo A-1; Apo = apolipoprotein; B = apo B-100; IDL = intermediate-density lipoprotein; Lp(a) = lipoprotein(a); TG = triglyceride; VLDL = very low-density lipoprotein.

GENETICS

Population studies employing genome-wide association and next-generation sequencing consistently implicate loci that govern plasma LDL-C and TG levels as among the strongest determinants of CVD risk (7). Furthermore, aggregated human genetic evidence supports the clustering of CVD, obesity, and risk factors such as abnormal lipids and hypertension, with dozens of genomic regions exerting pleiotropic effects on these highly interrelated traits (8). ApoB metabolism is central to the genetic mechanisms underlying risk, as evidenced in family-based studies (8). Yet, despite being so inextricably linked, apoB levels and related traits such as LDL particle size have yet to undergo large-scale genome-scale analysis, using such tools as Mendelian randomization or next-generation deoxyribonucleic acid sequencing.

Such studies are needed to definitively implicate genetic determinants of apoB levels as superior predictors of CVD risk and of other deleterious outcomes such as diabetes.

CLINICAL TRIALS

The placebo-controlled AFCAPS/TexCAPS study (Air Force/Texas Coronary Atherosclerosis Prevention Study) was the first major statin trial to report that apoB may be a better predictor of risk for major CV events than LDL-C. It found that on-treatment apoB significantly predicted risk, whereas LDL-C did not (9). Subsequent meta-analyses have generated divergent findings. One analysis of 8 statin trials, which included both placebo-controlled studies and trials of intensive versus standard therapy, found that the predictive value of on-treatment non-HDL-C was greater than that of both apoB and LDL-C (10). A subsequent meta-analysis of 7 placebo-controlled statin trials found that RR reduction was more closely related to reductions in apoB than to reductions in either non-HDL-C or LDL-C (11). Another meta-analysis reported that among statin trials, decreases in apoB improved CHD prediction, but this observation did not extend to all cholesterol-lowering drug classes (12). Due to the heterogeneity in obesity and insulin resistance in these meta-analyses, it is difficult to make a definitive statement about whether apoB more accurately predicts CV risk than LDL-C or non-HDL-C.

In the modern era of overweight and sedentary individuals with insulin resistance disorders, multiple sources of evidence warrant the transition from LDL-C and non-HDL-C to more stable and proximal measures of atherogenic lipoproteins for risk assessment and therapeutic targets (**Figure 1**). Although some consensus statements argue that new prospectively designed clinical trials must be performed to validate a biomarker, the conduct of trials using therapies already proven to reduce CVD events is neither ethical nor practical. From our perspective, evaluation of innovative biomarkers that can be analyzed from stored specimens is an efficient, cost-effective, and scientifically rigorous approach to evaluating related measures of atherogenic lipoproteins, with dual goals of improving risk assessment calibration and refining targets of therapy. ApoB is an excellent example of such a biomarker that may be "ready for prime time" for numerous reasons, including those outlined by Wilkins et al. (6).

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