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Role of apolipoprotein B in the clinical management of cardiovascular risk in adults: An expert clinical consensus from the national lipid association

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KEYWORDS
Apolipoprotein B;
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Abstract: This National Lipid Association (NLA) Expert Clinical Consensus provides an overview of the physiologic and clinical considerations regarding the role of apolipoprotein B (apoB) measurement to guide clinical care based on the available scientific evidence and expert opinion. ApoB represents the

Abbreviations: apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; C, cholesterol; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); Non-HDL, non-high-density lipoprotein; RCT, randomized controlled trial; TG, triglycerides; VLDL, very low-density lipoprotein.

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Discordance;
Low-density lipoprotein cholesterol;
Non-high-density lipoprotein cholesterol

total concentration of atherogenic lipoprotein particles in the circulation and more accurately reflects the atherogenic burden of lipoproteins when compared to low-density lipoprotein cholesterol (LDL-C). ApoB is a validated clinical measurement that augments the information found in a standard lipoprotein lipid panel; therefore, there is clinical value in using apoB in conjunction with a standard lipoprotein lipid profile when assessing risk and managing lipid-lowering therapy (LLT). ApoB has been shown to be superior to LDL-C in risk assessment both before and during treatment with LLT. In individuals, there can be discordance between levels of LDL-C and apoB, as well as LDL-C and non-high-density lipoprotein cholesterol (non-HDL-C), despite high levels of population-wide correlation. When there is discordance between LDL-C and apoB, or LDL-C and non-HDL-C, atherosclerotic cardiovascular disease risk generally aligns better with apoB or non-HDL-C. Additionally, apoB can be used in tandem with standard lipoprotein lipid measurements to diagnose distinct lipoprotein phenotypes. ApoB testing can inform clinical prognosis and care, as well as enable family cascade screening, when an inherited lipoprotein syndrome is identified. The NLA and other organizations will continue to educate clinicians about the role of apoB measurement in improving clinical risk assessment and dyslipidemia management. An urgent need exists to improve access and reimbursement for apoB testing.

Summary of key points

1. Apolipoprotein (apo)B is the main structural protein found on all atherogenic lipoproteins and it is the principal ligand for the low-density lipoprotein (LDL) receptor.
2. There is a single apoB molecule found on each atherogenic lipoprotein: apoB-100 for LDL, intermediate-density lipoprotein (IDL), very-low-density lipoprotein (VLDL), and lipoprotein(a) [Lp(a)], and apoB-48 for chylomicron and chylomicron remnant particles. Thus, the apoB concentration is a direct measure of the circulating burden of atherogenic lipoprotein particles.
3. ApoB is a precise, accurate, and well-validated measurement.
4. On a population level, LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), and apoB concentrations are highly correlated, with the relationship being somewhat stronger between non-HDL-C and apoB than for LDL-C and apoB.
5. ApoB and non-HDL-C stratify atherosclerotic cardiovascular disease (ASCVD) risk more accurately than LDL-C before and during treatment with lipid-lowering therapy (LLT).
6. Discordance between apoB and LDL-C, apoB and non-HDL-C, as well as non-HDL-C and LDL-C, is common. When discordance is present, apoB is the strongest predictor of ASCVD risk, followed by non-HDL-C, with LDL-C being the least predictive of the three measures.
7. Lowering apoB and non-HDL-C can be achieved with nutritional interventions, other lifestyle interventions, and pharmacotherapy.
8. Thresholds for initiating or intensifying pharmacotherapy for apoB levels are not as well-established compared to LDL-C and non-HDL-C levels. However, based on evidence from untreated populations and from randomized controlled trials of individuals treated with LLTs, apoB thresholds for patients who are at very high, high, and borderline to intermediate risk for ASCVD are suggested to be 60, 70, and 90 mg/dL, respectively, to correspond with the current treatment thresholds for LDL-C and non-HDL-C.
9. ApoB is an important clinical measurement that enables lipid specialists to identify some lipid and lipoprotein syndromes, thus providing information relevant to prognosis, treatment expectations, and the need for family cascade screening.
10. Barriers for apoB testing should be addressed and minimized to enable equitable access to optimize care aimed at minimizing ASCVD risk.

Preamble

The following is a National Lipid Association (NLA) Expert Clinical Consensus on the role of apolipoprotein (apo)B in adult patient care. This document is meant to clarify the role of apoB testing for clinicians who manage cardiovascular risk and lipid disorders, as well as health systems, payers, and medical associations. The 2021 NLA Scientific Statement, *Lipid Measurements in the Management of Cardiovascular Diseases*,[1] outlined the clinical chemistry of apoB measurement and suggested a rationale for the use of apoB within a comprehensive review of all the clinical lipid and lipoprotein measures. We invite readers to review that document and refer to this Expert Clinical Consensus as its companion. This Expert Clinical Consensus summarizes the evidence for apoB measurement in routine and specialty clinic lipid management to inform ASCVD risk assessment and decisions regarding initiation or intensification of therapies for lowering atherogenic lipoprotein burden.

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Introduction: what is apoB?

ApoB is the main structural and singular nonexchangeable apolipoprotein on atherogenic lipoproteins. In addition to providing a scaffold for lipoproteins, it is also the principal ligand for the hepatic LDL receptor. The strong ionic charge of the apoB molecule contributes to the entrapment of apoB-containing lipoproteins in the subendothelial space where atherosclerosis develops. Atherogenic lipoproteins have other features that affect their atherogenic potential (e.g., lipid content, oxidized phospholipids, other apolipoproteins, and size); however, they all have in common the presence of a single apoB molecule per particle.

Chylomicron particles and their remnants contain apoB-48, the intestinally derived truncated form of the apolipoprotein, which lacks the LDL receptor binding domain. Thus, clearance of chylomicron remnants is primarily mediated by the interaction between apoE binding to hepatic LDL receptor-related protein 1 or related receptors. Conversely, hepatically derived apoB-100, which is on VLDL, IDL, LDL, and Lp(a) particles, is the principal ligand for the hepatic LDL receptor. Lp(a) also has apo(a) bound covalently to apoB-100, which may interfere with its interaction with the LDL receptor and circulatory clearance.[2,3] Routine diagnostic assays for apoB do not distinguish between apoB-48 and apoB-100; however, after a 12-hour fast under normal physiologic circumstances, it is mostly apoB-100 that is present in the circulation. Even postprandially, more than 95 % of apoB in circulation is apoB-100 in individuals without severe hypertriglyceridemia.[4] Therefore, there is minimal change in apoB levels in the fasting compared to the non-fasting state.[5]

ApoB-100 is a large protein, the primary structure of which contains more than 4500 amino acid residues.[6] Unlike the other apolipoproteins, apoB contains large sections of beta sheets, which bind tightly to lipids and account for the non-exchangeability of apoB.[7] Because there is a single apoB present on each atherogenic lipoprotein, the measured apoB level represents the serum concentration of atherogenic lipoproteins. The lipid content of lipoproteins (e.g., cholesterol and triglycerides [TGs]) and the lipoprotein particle concentration have different physiologic impacts; therefore, LDL-C, non-HDL-C, and apoB measure different aspects of the atherogenic lipoprotein concentration.

By far the most abundant apoB-containing lipoprotein particle in the circulation is LDL. ApoB and LDL-C levels correlate closely in populations; however, the lipid composition and size of LDL particles can vary greatly between individuals and even within an individual from one measurement to another.[8,9] While there is a high degree of correlation between these levels in the population, there can be discordance between LDL-C and apoB measurements in individuals, especially in those treated with statins and in those with cholesterol-depleted and cholesterol-enriched LDL.[10–13] This discordance can lead to both undertreatment with LLT and potential misclassification of ASCVD risk, if the cholesterol content of LDL rather than the protein measurement is relied upon exclusively. Non-HDL-C (total cholesterol minus HDL-C) represents the cholesterol carried by all apoB-containing lipoproteins in circulation. Compared to LDL-C, non-HDL-C correlates more closely with the apoB concentration and is also a stronger predictor of ASCVD risk.[9,14,15] However, like LDL-C, discordance can exist between non-HDL-C and apoB, resulting in similar issues of ASCVD risk misclassification and undertreatment with LLT, albeit to a lesser degree than for LDL-C.[9] Thus, apoB measurement can be useful to identify patients with borderline ASCVD risk who have a discordantly low apoB relative to LDL-C and/or non-HDL-C and the absence of risk-enhancing factors. An apoB measurement can assist in the shared decision-making discussion about whether pharmacotherapy can be deferred in these patients.

LDL-C can be measured with beta-quantification after ultracentrifugation (the "gold standard" for lipoprotein lipid measurement), which is the most accurate but also a cumbersome and time-consuming method. It is used for the standardization of LDL-C methods by the Centers for Disease Control and Prevention[16] but is not widely available for clinical use. In routine clinical practice, LDL-C is usually estimated by a mathematical equation. Until recently, most clinical laboratories used the Friedewald formula to calculate LDL-C: LDL-C (mg/dL) = total cholesterol − HDL-C − (TG/5). The equation assumes a fasting blood sample and the TG/5 component represents an estimate of VLDL cholesterol based on the expected average of TG:cholesterol content in VLDL particles.[17] Because the lipid content of VLDL is variable, LDL-C calculations that rely on a fixed TG: cholesterol ratio, such as the Friedewald formula, can be unreliable, especially in individuals with hypertriglyceridemia and/or low LDL-C.[18–21] Thus, novel LDL-C calculations have been developed that improve the estimated LDL-C level compared to the Friedewald equation, including the Martin–Hopkins[19] and Sampson-National Institutes of Health (NIH) equations.[22]

With the Martin–Hopkins approach, LDL-C is calculated as total cholesterol − HDL-C − (TG/adjustable factor).[19,23] The adjustable factor varies by TG and non-HDL-C concentration. With the Sampson-NIH equation, LDL-C is calculated as total cholesterol/0.948 − HDL-C/0.971 − (TG/8.56 + TG × non × HDL-C/2140 − TG^2/16,100) − 9.44.[22,23] Using an LDL-C estimate with the Martin–Hopkins equation[19] resolves some of the discordance between apoB and a Friedewald calculated LDL-C by correcting the underestimation that can occur with the Friedewald equation.[24-26] Regardless of which equation is used to estimate LDL-C, discordance between apoB and LDL-C still frequently occurs.[27] In these cases, the addition of an apoB measurement may improve risk stratification and thus help to guide therapy.

ApoB has an advantage over LDL-C in that it also allows hyperlipoproteinemia phenotype diagnosis by the Fredrickson-Levy-Lees classification scheme.[28,29] In 2007, Sniderman and colleagues proposed an algorithm that en-

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ables lipoprotein phenotypic classification based upon inputs of total cholesterol, TG, and apoB levels. Once the lipoprotein phenotype has been characterized, a medical syndrome can be identified.[30] Characterization of the lipoprotein phenotype and syndrome can thus enable better risk stratification, targeted therapy, and optimal cascade screening of family members.

ApoB measurement: are apoB assays available and accurate for clinical use?

Commercial assays for apoB are based on either immunoturbidometric or immunonephelometric testing,[1] which use antibodies that recognize both apoB-100 and apoB-48 and have been available for many years. These tests can be completed on high-throughput automated analyzers that are commonly used by clinical laboratories for other types or routine diagnostic testing, such as the lipid measurements in the standard lipid panel. As such, the cost of performing the test is low and its accuracy is high.[27] The current diagnostic assays for apoB are sufficiently accurate for routine diagnostic testing, based upon assessment of both bias and precision. Bias (deviation from "true" value based on a reference method) and precision (measure of reproducibility) are commonly expressed as the percent coefficient of variation for which the equation is 100 x standard deviation/sample mean.[31–33]

Results from the College of American Pathologist Accuracy Based Lipid Survey indicates that bias for most apoB tests is below 4 mg/dL, and the coefficient of variation usually ranges between 5 % and 6 % (Supplemental Fig. 1). These accuracy metrics are comparable to other lipid and lipoprotein tests[1] and, in fact, are better compared to some direct LDL-C tests, which can show a significant positive bias with hypertriglyceridemic samples.[34]

The reference method for apoB is based on measuring the total protein content of LDL purified by ultracentrifugation, which was produced by the International Federation of Clinical Chemistry and the World Health Organization.[32,35] This same purified LDL material is also used by diagnostic companies to calibrate their apoB assays. There is an ongoing effort by the International Federation of Clinical Chemistry, which is close to completion, to better standardize apoB by developing a new mass spectrometry reference method that detects a specific apoB peptide.[36] The current reference method for LDL-C is beta-quantification, an ultracentrifugation/precipitation method that includes not only cholesterol on LDL but also cholesterol on Lp(a) and IDLs.[16] Future standardization of apoB tests by mass spectrometry will likely make it even more accurate than LDL-C tests and could also further improve its performance as a cardiovascular biomarker. In summary, apoB assays are sufficiently accurate for routine clinical use and clinical laboratories could easily accommodate increased apoB testing. However, there are other barriers to its widespread use, such as reimbursement and clinician acceptance, which will be discussed below.

Correlation and discordance of apoB, non-HDL-C, and LDL-C: can apoB or non-HDL-C levels reflect ASCVD risk better than LDL-C levels?

Historically, LDL-C has been accepted as the primary target for lipid management to lower ASCVD risk. However, results from recent studies suggest that LDL-C may be an inadequate measure when discordant from apoB and/or non-HDL-C levels. A variety of conditions, such as hypertriglyceridemia, obesity, and insulin resistance, can lead to smaller cholesterol-depleted LDL particles and result in lower LDL-C but still elevated apoB levels.[37] For that reason, other metrics have been considered, especially non-HDL-C, apoB, LDL particle concentration, and improved methods for calculating or measuring LDL-C (e.g., Martin–Hopkins equation, Sampson-NIH equation, small dense LDL-C, or directly measured LDL-C). Because these alternative ASCVD risk biomarkers use different methodologies and measure different lipoprotein properties, the results may be discordant. The focus in the discussion below will be on the relationships between calculated LDL-C and non-HDL-C levels with apoB concentration.

It is well-established that there exists discordance in LDL-C and non-HDL-C for any given value of apoB. Recent data from the United Kingdom indicate that, despite high correlations of ≥0.95 between apoB and non-HDL-C at the population level, and a slightly lower degree of correlation between apoB and LDL-C, there is a wide variation in apoB concentration for any given non-HDL-C or LDL-C value.[9] For example, using the population percentiles for LDL-C, non-HDL-C, and apoB for untreated adults in the National Health and Nutrition Examination Survey (NHANES) 2005–2016 (Table 1), for a non-HDL-C of 100 mg/dL (∼10–20th percentile in the NHANES population), the range of apoB that covered 95 % of the values was 52–78 mg/dL (∼5–30th percentile in NHANES). Similarly, for a non-HDL-C of 160 mg/dL (∼70–80th percentile in NHANES), 95 % of the apoB values were in the range of 88–112 mg/dL (∼40–80th percentile in NHANES). Similar findings were observed for LDL-C compared to apoB.[9]

Discordance analyses have been performed using a variety of approaches and cohorts, including comparisons of below vs. above population median levels, quintile differences, percentile differences, and the simple discrepancy between expected and measured levels (residual analysis). Regardless of the cohort examined or analysis used, it has been consistently demonstrated that apoB and non-HDL-C are more closely associated with ASCVD risk than LDL-C, and apoB concentration predicts risk better than non-HDL-C.[9,12,14,37–46] Results from analyses using data from statin-treated subjects in the Copenhagen General Population Study[14] indicated that, when there is discordance between apoB and LDL-C, risk follows apoB (Table 2). ApoB above the median and LDL-C below the median was associated with an increased risk for all-cause mortality, whereas

Table 1 Population percentiles of LDL-C, non-HDL-C, and apoB levels in untreated U.S. adults* (NHANES 2005–2016, $n = 12{,}696$).

Percentiles in the untreated population	LDL-C† (mg/dL)	Non-HDL-C (mg/dL)	ApoB (mg/dL)
1	45	59	41
5	63	79	54
10	72	88	61
20	85	103	70
30	95	114	77
40	104	125	84
50	112	135	90
60	121	145	97
70	131	156	104
80	143	170	113
90	161	191	125
95	176	208	137
99	211	247	160

*Adults 18–85 years of age not receiving lipid-modifying therapy.
†Calculated using the Friedewald equation. TG levels in the participants were 12–400 mg/dL.
Abbreviations: ApoB, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; non-HDL-C, non-high-density lipoprotein cholesterol; TG, triglyceride.

Table 2 Association between concordant or discordant apoB and LDL-C and apoB and non-HDL-C and all-cause mortality in statin-treated patients.[14]

Lipoprotein lipid level, median split	Hazard ratio (95 % CI)
ApoB vs. LDL-C	
ApoB and LDL-C < median	Referent
ApoB < median, LDL-C ≥ median	0.86 (0.75–0.99)
ApoB ≥ median, LDL-C < median	1.21 (1.07–1.36)
ApoB and LDL-C ≥ median	1.10 (1.00–1.21)
ApoB vs. non-HDL-C	
ApoB and non-HDL-C < median	Referent
ApoB < median, non-HDL-C ≥ median	0.75 (0.62–0.92)
ApoB ≥ median, non-HDL-C < median	1.21 (1.03–1.41)
ApoB and non-HDL-C ≥ median	1.13 (1.03–1.23)

Abbreviations: ApoB, apolipoprotein B; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

an apoB below the median and LDL-C above the median was associated with reduced risk for all-cause mortality. Similar results were observed for discordance between apoB and non-HDL-C[14] (Table 2 and Fig. 1).

Results of Mendelian randomization analyses indicate that, when genetic variants result in discordance between apoB and LDL-C, cardiovascular risk aligns more closely with apoB than LDL-C.[39,47] For example, Ference et al. conducted Mendelian randomization analyses to examine the association between scores for the cholesteryl ester transfer protein (*CETP*) and 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*) genes, differences in LDL-C and apoB levels, and the risk of cardiovascular events using data from participants in 14 cohort studies.[39] The results of the analyses indicated that, when combined exposure to genetic variants of the *CETP* and *HMGCR* genes were associated with discordant reductions in LDL-C and apoB levels, the reduction in cardiovascular events was more closely associated with the reduction in apoB levels compared to the reduction in LDL-C levels.[39,48]

Furthermore, Mendelian randomization studies have shown that genetically determined differences in both LDL-C and VLDL-C, the two main components of non-HDL-C, are associated with similar differences per mg/dL in ASCVD event risk. For example, genetic variants associated with 10 mg/dL reductions in LDL-C and VLDL-C (equivalent to ~50 mg/dL reduction in TG) were each associated with 23 % lower odds for incident coronary heart disease.[49] In multivariate analyses, both LDL-C and VLDL-C were reduced to non-significance after adjustment for differences in apoB, consistent with the view that the clinical benefits of lowering LDL-C and VLDL-C levels may be mostly driven by changes in apoB (i.e., atherogenic lipoprotein particle) concentration.[49]

Evidence from RCTs: what is the apoB response in RCTs compared to LDL-C (or non-HDL-C)?

RCTs investigating LLTs and cardiovascular outcomes have typically enrolled patients based on levels of cardiovascular risk and threshold LDL-C levels. Non-HDL-C and apoB have been measured or reported for some, but not all, of these trials. Also, apoB measurements were often not completed as frequently during the follow-up period as LDL-C, and/or only for a subset of the entire trial population. Consequently, the available data from RCTs supporting the targeting of non-HDL-C and apoB is limited compared to that for LDL-C.

RCTs have been conducted that examined the effects of statin monotherapy vs. placebo, more vs. less intense therapy, and/or combination therapy with a new agent on a background of standard of care (background statin) vs. standard

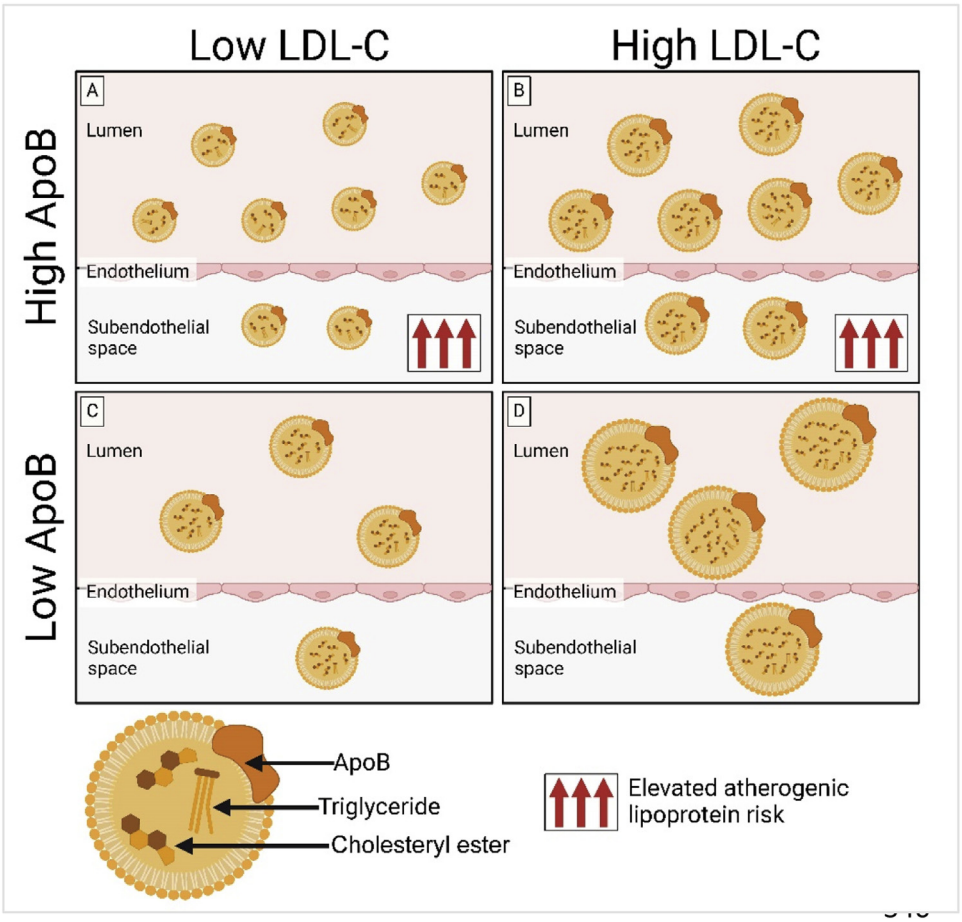

Fig. 1 Association between concordant or discordant apoB and LDL-C and corresponding atherogenic lipoprotein risk.[14] When apoB and LDL-C are concordantly low (Panel A), atherogenic lipoprotein risk is not elevated. When apoB and LDL-C are concordantly elevated (Panel D), atherogenic lipoprotein risk is elevated. When apoB and LDL-C are discordant (Panels B and C), lipoprotein risk follows apoB. Image created with BioRender.
Abbreviations: ApoB, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol.

of care alone. Some of these studies have reported effects of these therapies on LDL-C, non-HDL-C, and apoB levels along with cardiovascular outcomes.[50–52] It is uncommon for LLT to have been adjusted during the RCTs based on achieved LDL-C levels, and LLT was never adjusted based upon non-HDL-C or apoB concentrations. There have been no RCTs conducted in which participants at risk of ASCVD were randomized to treatment strategies based on achieving non-HDL-C or apoB therapeutic objectives to determine which strategy results in the best cardiovascular outcomes. The results of analyses of RCTs (often *post hoc*) and meta-analyses that compared outcomes based on achieved LDL-C, non-HDL-C, and apoB levels are summarized below.

Statin monotherapy

In the Scandinavian Simvastatin Survival Study (4S), which was a secondary prevention trial among individuals with very high baseline cholesterol (total cholesterol at entry = 213–310 mg/dL), Pedersen et al. compared the impacts of changes in LDL-C, non-HDL-C, and apoB on major coronary events in the simvastatin group. A 1 % reduction resulted in a decrease of major coronary events of 1.7 % for LDL-C, 1.7 % for non-HDL-C, and 1.1 % for apoB.[53] In the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial, both non-HDL-C and apoB changes were better predictors of coronary events than LDL-C in an analysis starting at month 6, with a one standard deviation change in non-HDL-C and apoB associated with relative risk reductions of 14.1 % and 14.3 %, respectively, compared to 11.8 % for LDL-C.[54] Using combined data from the Treating to New Targets (TNT) and IDEAL trials, Kastelein et al.[55] evaluated the associations between indicators of atherogenic lipoprotein burden and major cardiovascular events (MACE). Non-HDL-C (HR: 1.19; 95 % CI: 1.14–1.25) and apoB (HR: 1.19; 95 % CI: 1.14–1.24) had the strongest relationships to MACE for each standard deviation increase in value. The association between each standard deviation increment in LDL-C and MACE was numerically smaller (HR: 1.15; 95 % CI: 1.10–1.20), although confidence intervals for all three variables overlapped.[55] An analysis of the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial found that on-treatment LDL-C, non-HDL-C, and apoB were

similarly predictive of subsequent cardiovascular events.[56] The same conclusion was reached in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT TIMI22) trial, which compared pravastatin and atorvastatin in patients with acute coronary syndrome; one standard deviation differences in LDL-C, non-HDL-C, and apoB was similarly predictive of risk of death or acute coronary events.[57]

Combination therapy

The Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY OUTCOMES) trial compared the impact of adding alirocumab compared to placebo to a background of maximally tolerated statin therapy in a sample of >18,000 individuals who had experienced a recent acute coronary syndrome.[52] Hagstrom et al. assessed the relationship between apoB and MACE in this trial for both baseline apoB and on-treatment apoB.[58] Achieved LDL-C (<25, 25–50, and >50 mg/dL) and apoB (≤35 mg, >35–<50, and ≥50 mg/dL) strata were prespecified for the *post hoc* analysis. The strata for apoB were defined by the lower limit of detection (35 mg/dL) and a boundary level that was approximately the median of samples with an apoB concentration above the lower limit of detection (50 mg/dL).

MACE incidence increased with increasing baseline apoB and remained predictive after adjustment for baseline LDL-C. Higher baseline apoB was associated with greater relative and absolute risk reduction for MACE when comparing the alirocumab and placebo groups. Lower on-treatment apoB concentration was associated with lower incidence of MACE in the alirocumab group and remained predictive of MACE after adjustment for on-treatment LDL-C or non-HDL-C level. Achieved LDL-C and non-HDL-C levels were individually predictive of MACE, but not after adjustment for on-treatment apoB concentration. The authors also demonstrated that 18.2 % of individuals who achieved an LDL-C level <22 mg/dL did not achieve an apoB level ≤35 mg/dL, while only 4 % of those who achieved a non-HDL-C level <40.9 mg/dL did not achieve an apoB level ≤35 mg/dL, suggesting that on-treatment non-HDL-C and apoB are better markers to assess the risk of MACE than LDL-C when monitoring alirocumab-statin combination therapy.

Marston and colleagues assessed whether achieved apoB, non-HDL-C, and TG levels were associated with fatal and non-fatal myocardial infarction[46] in analyses using combined datasets from the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial[51] (starting at month 4) and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)[50] (starting at month 3). The authors showed that achieved apoB was the best predictor of myocardial infarction risk and that it remained predictive even when adjusted for non-HDL-C and TG concentrations.[46]

Meta-analyses

Meta-analyses of RCTs comparing apoB and non-HDL-C as predictors of cardiovascular outcomes have produced heterogeneous results. Boekholdt et al. completed a meta-analysis of 8 statin RCTs using individual patient level data, and computed hazard ratios for the risk of major cardiovascular events for a one standard deviation higher on-treatment level of LDL-C, non-HDL-C, and apoB.[59] The results indicated that, for every one standard deviation increase, the hazard ratio was higher for non-HDL-C (HR: 1.16; 95 % CI: 1.12–1.19) compared to LDL-C (HR: 1.13; 95 %: CI 1.10–1.17) and apoB (HR: 1.14; 95 % CI: 1.11–1.18). In a separate analysis, change in LDL-C level explained 50 % of the treatment effect, compared to 64 % for non-HDL-C and 54 % for apoB. Non-HDL-C was significantly better as a predictor than apoB or LDL-C in both types of analyses, whereas the difference between apoB and LDL-C did not achieve statistical significance.[59]

Thanassoulis et al. included 7 placebo-controlled statin trials in a study-level meta-analysis using both a frequentist and a Bayesian approach. The mean coronary heart disease risk reduction per standard deviation (95 % confidence interval [CI]) decrease was 20.1 % (15.6–24.3 %) for LDL-C, 20.0 % (15.2–24.7 %) for non-HDL-C, and 24.4 % (19.2–29.2 %) for apoB across trials.[60] It is unclear whether the varying results from these two meta-analyses are related to differences such as analysis of patient versus trial level data, populations with differing lipid and lipoprotein distributions, or differences in the meta-analytic statistical methods employed.

In summary, based on the evidence discussed above, changes from baseline and on-treatment levels of LDL-C, non-HDL-C, and apoB, individually predict ASCVD risk in patients treated with statin monotherapy and statin + nonstatin therapy. Non-HDL-C and apoB are generally stronger predictors of residual risk than LDL-C, and apo B is sometimes, but not universally, a stronger predictor than non-HDL-C, albeit with considerable heterogeneity in the results.

ApoB management and therapeutic objectives: are there specific apoB thresholds for treatment decision-making?

Recent guidelines and recommendations for the management of cholesterol levels to lower ASCVD risk have emphasized treatment thresholds for LDL-C and non-HDL-C.[61,62] These are values where, if a patient's level remains at or above the threshold, consideration should be given to intensification of therapy. The conclusions from the 2018 American Heart Association (AHA)/American College of Cardiology (ACC)/Multisociety Guideline on the Management of Blood Cholesterol (2018 AHA/ACC/Multisociety Blood Cholesterol Guideline)[61] are derived from the strongest level of evi-

dence from RCTs (and meta-analyses of those trials) supporting the role of LDL-C thresholds for intensification of pharmacotherapy to reduce ASCVD risk. None of the RCTs considered in the 2018 Blood Cholesterol Guideline used apoB as a primary enrollment criterion. However, some RCTs did measure apoB levels at baseline and during treatment. In IMPROVE-IT, FOURIER, and ODYSSEY OUTCOMES, LDL-C and apoB levels were measured at baseline and at various timepoints over the duration of the trials. In IMPROVE-IT, the addition of ezetimibe to simvastatin in patients with a history of acute coronary syndrome reduced apoB by an additional 15 % compared to simvastatin monotherapy, which resulted in a median apoB level of 67 mg/dL and LDL-C level of 54 mg/dL. This produced a 6.4 % relative risk reduction for MACE during a median follow-up period of 6 years[50] (Table 3). Results from IMPROVE-IT have supported a recommended LDL-C treatment intensification threshold of 55 mg/dL for very high-risk patients, even though it was not an a priori determined inclusion threshold for initiating therapy in any RCT.[62] Evolocumab or alirocumab added to moderate- to high-intensity statin ± ezetimibe in patients with ASCVD resulted in >40 % reduction in apoB. In FOURIER, at 48 weeks, the median apoB level was 38 mg/dL with a corresponding median LDL-C level of 30 mg/dL with evolocumab in patients with stable ASCVD.[51] In ODYSSEY OUTCOMES, after 12 months of treatment, the mean apoB level was 49 mg/dL and the mean LDL-C level was 48 mg/dL in patients with a history of acute coronary syndrome.[52] A 15 % relative risk reduction in MACE was found in both FOURIER and ODYSSEY OUTCOMES over median follow-up periods of 2.2 years and 2.8 years, respectively (Table 3).

Recommended thresholds for apoB to inform treatment decisions

The population-based relationships between LDL-C (Friedewald calculated) and apoB from an untreated NHANES 2005–2016 sample (Panel A; ≥18 years old; $n = 12{,}696$) and the on-treatment samples from IMPROVE-IT ($n = 13{,}729$) and FOURIER ($n = 25{,}239$); Panel B) are illustrated in Fig. 2. The green line for NHANES and the red line for the treated populations show the least squares linear regression relationships for LDL-C vs. apoB in the untreated and treated groups, respectively. Panel C shows both sets of data and the corresponding regression lines on the same graph. These results demonstrate the strong linear relationship between LDL-C and apoB, as well as the range of values above and below the regression lines (discordance).

In the NHANES sample in Panels A and C (green points), there is even distribution of individuals above and below the line, whereas in the treated samples from IMPROVE-IT and FOURIER, there is a larger population of individuals (red points in Panels B and C) above the NHANES (green) line indicating more cholesterol-depleted LDL. Notably, the average level of apoB is higher for any given level of LDL-C in treated groups. The difference in the relationship between LDL-C and apoB in untreated and treated groups is likely the consequence of relatively less apoB reduction compared to LDL-C reduction during treatment with statins, ezetimibe, and proprotein convertase subtilisin-kexin type 9 (PCSK9) monoclonal antibodies as a consequence of the selective clearance of larger, more cholesterol-enriched LDL particles compared to smaller, more cholesterol-depleted LDL particles.[63] This is illustrated by results from an analysis

Table 3 Median or mean[a] achieved LDL-C, non-HDL-C, and apoB levels in high-risk ASCVD patients on statin therapy and statin therapy plus nonstatin therapy.

RCT	Treatment	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	ApoB (mg/dL)	Primary Outcome vs. Placebo[b] (RRR)
IMPROVE-IT[50] [c]	Statin[d]	70	93	79	6.4 %
	Statin + EZE[d]	54	72	67	
FOURIER[51] [c]	Statin[e,f]	92	121	83	15 %
	Statin + EVO[f,g]	30	49	38	
ODYSSEY OUTCOMES[52]	Statin[e,f]	92	122	83	15 %
	Statin + ALI[f,g]	48	74	49	

[a]Values presented are medians for IMPROVE-IT and FOURIER and means for ODYSSEY OUTCOMES.
[b]Median duration of follow-up: IMPROVE-IT, 6 years; FOURIER, 2.2 years; ODYSSEY OUTCOMES, 2.8 years.
[c]Data courtesy of the Thrombolysis in Myocardial Infarction (TIMI) Study Group.
[d]LDL-C values for IMPROVE-IT are median time-averaged over the course of the study, as presented in the primary publication.[50] Non-HDL-C and apoB values are medians at 1 year.
[e]LDL-C, non-HDL-C, and apoB for statin monotherapy are baseline values in FOURIER and ODYSSEY OUTCOMES.
[f]A small percentage of participants in the treatment and placebo groups in FOURIER and ODYSSEY OUTCOMES were taking ezetimibe at baseline and during the trials.
[g]LDL-C, non-HDL-C, and apoB for statin + PCSK9 mAbs are 48-week values for FOURIER and 12-month values for ODESSEY-OUTCOMES.
Abbreviations: ALI, alirocumab; apoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; EVO, evolocumab; EZE, ezetimibe; FOURIER, further cardiovascular outcomes research with PCSK9 Inhibition in Subjects with Elevated Risk; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab; PCSK9 mAbs, proprotein convertase subtilisin-kexin type 9 monoclonal antibodies; RCT, randomized controlled trial; RRR=relative risk reduction.

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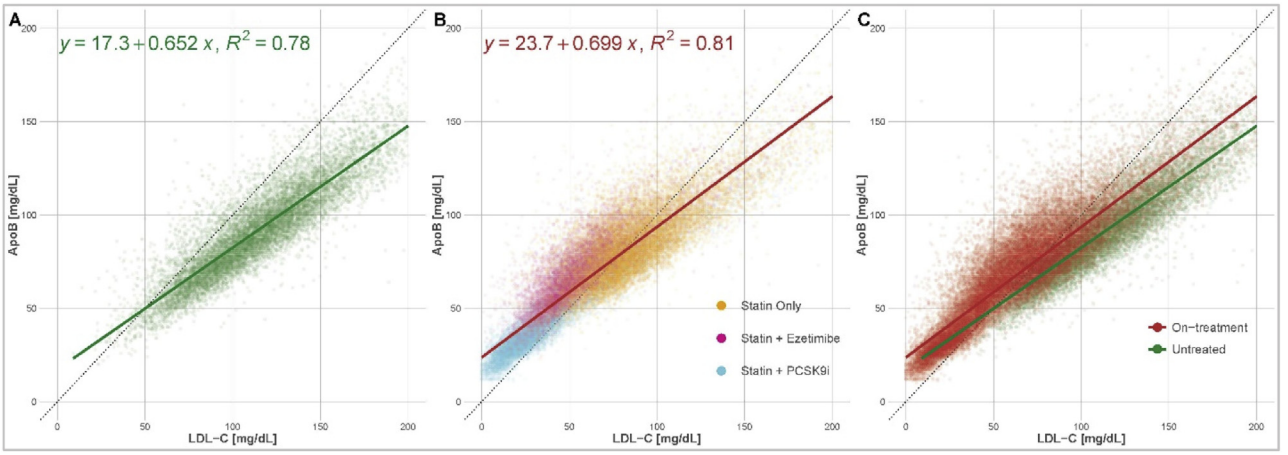

Fig. 2 Population-based relationship between LDL-C (Friedewald calculated) and apoB from an untreated sample (NHANES 2005–2016) and two on-treatment samples (IMPROVE-IT and FOURIER). Panel A is the untreated NHANES sample ($n = 12{,}696$, 18–85 years of age). Panel B is the achieved 1-year values for IMPROVE-IT or 48-week values for FOURIER, separated into statin monotherapy ($n = 18{,}812$ [6878 in IMPROVE-IT and 11,934 in FOURIER]), statin + ezetimibe ($n = 7475$ [6851 in IMPROVE-IT and 660 in FOURIER]), and statin + PCSK9i ($n = 12{,}645$, all in FOURIER). Panel C is both the untreated and on-treatment scatterplots on the same graph. The solid grey line in each graph represents the line of identity.
Abbreviations: ApoB, apolipoprotein B; FOURIER, Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; NHANES, National Health and Nutrition Examination Survey; PCSK9i, proprotein convertase subtilisin-kexin type 9 inhibitor.

of 11 clinical trials using statin monotherapy ($n = 9$) or statin + ezetimibe ($n = 2$) showing that LDL-lowering therapy reduced apoB by a mean of 33 % compared with 42 % for LDL-C.[64] Similar results have been observed with other LDL-lowering medications, e.g., see Table 3.

Using the regression equations in Fig. 2, the predicted average apoB concentration corresponding to LDL-C threshold levels of 55, 70, and 100 mg/dL are 62, 73, and 94 mg/dL, respectively, for treated individuals, and 53, 63, and 83 mg/dL, respectively, for untreated individuals. Based on the average of the predicted apoB concentrations for the corresponding LDL-C threshold in the treated and untreated groups, rounded to the nearest integer ending in zero, apoB thresholds are recommended for consideration of intensification of LLT (Table 4). NHANES data for untreated individuals are also presented in Table 1 with population percentiles for comparison. The use of apoB thresholds is supported by results from an analysis reported by Johannesen et al. using data from 95,108 men and women not on statin therapy from the Copenhagen General Population Study.[65] Their findings indicate that excess apoB, i.e., the excess above the predicted concentration based on the level of LDL-C using linear regression, was associated in a dose-dependent manner with higher risk for incident ASCVD in men and women. This increase in risk associated with discordantly high apoB was present across the spectrum of LDL-C concentrations.

Table 4 Treatment thresholds for intensification of care.* Recommended treatment thresholds for LDL-C and non-HDL-C[61,62,66] and NLA suggested apoB treatment thresholds.

ASCVD risk category	Treatment threshold (mg/dL)		
	LDL-C	Non-HDL-C	ApoB
Very high risk[a]	55	85	60
High risk[b]	70	100	70
Borderline to intermediate risk[c]	100	130	90

*The tables provides a simplified summary of the risk categories and treatment thresholds outlined by Arnett et al.,[66] Grundy et al.,[61] and Lloyd-Jones et al.[62]
[a]Very high risk includes a history of multiple major ASCVD events (e.g., recent ACS, MI, ischemic stroke, symptomatic PAD) or 1 major ASCVD event and multiple high-risk conditions (e.g., ≥65 years of age, heterozygous FH, history of CABG or PCI, diabetes mellitus, HTN, CKD, current smoking, persistently elevated LDL-C ≥100 mg/dL despite statin + ezetimibe, history of HF).
[b]High risk refers to the presence of clinical ASCVD with or without severe hypercholesterolemia (LDL-C ≥190 mg/dL), diabetes mellitus, or an estimated 10-year risk for ASCVD of ≥20 %.
[c]Borderline risk refers to an estimated 10-year risk for ASCVD of 5 % to <7.5 %. Intermediate risk refers to the presence of severe primary hypercholesterolemia (LDL-C ≥190 mg/dL) or an estimated 10-year risk for ASCVD of 7.5 % to <20 %.*Abbreviations*: ACS, acute coronary syndrome; ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CKD, chronic kidney disease; FH, familial hypercholesterolemia; HF, heart failure; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; non-HDL-C, non-high-density lipoprotein cholesterol; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

ApoB-lowering medications: options for intensification of therapy

The foundation of ASCVD risk reduction is a healthful lifestyle. Nutrition interventions can be effective in reducing LDL-C, non-HDL-C, and apoB levels. A detailed discussion of nutrition interventions for addressing elevated atherogenic lipoprotein levels is beyond the scope of this ECC. Interested readers are encouraged to read the "Nutrition Interventions

for Adults with Dyslipidemia" NLA Clinical Perspective.[67] Statins remain guideline-directed first line pharmacotherapy, which is based on decades of supportive clinical trial data, population accessibility, tolerability, affordability, and beneficial effects for multiple clinical categories.

Contemporary treatment recommendations outline the importance of nonstatin medications. Their clinical role has been described most recently in the 2022 ACC Expert Consensus Pathway (ECDP) on the Role of Nonstatin Therapies for LDL-Cholesterol Lowering in the Management of ASCVD (2022 ACC ECDP on Nonstatin Therapies).[62] ApoB-lowering is a U.S. Food and Drug Administration-approved indicated use for rosuvastatin, atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, ezetimibe, mipomersen, and lomitapide, but is not included in prescribing information for pitavastatin, alirocumab, evolocumab, inclisiran, bempedoic acid, cholestyramine, colesevelam, or evinacumab (package inserts accessed June 2024). Nonetheless, given that the mechanism of action for the LLTs that lack the labeled indication of lowering apoB is upregulation of LDL receptors, there is no reason to expect clinically relevant differences in the degree of apoB-lowering relative to the corresponding reductions in LDL-C by these medications. The 2022 ACC ECDP on Nonstatin Therapies suggested an order of operations based upon ASCVD risk, reference LDL-C thresholds for intensification of therapy, RCT outcomes, and Food and Drug Administration-approved indications of therapy and there is no reason to suggest a different approach for apoB reduction.

In the U.S., the 2018 AHA/ACC/Multisociety Blood Cholesterol Guideline suggests LDL-C thresholds of 100 mg/dL and 70 mg/dL for consideration of intensification of therapy depending on ASCVD risk category.[61] While there are no RCTs that used LDL-C 55 mg/dL as a treatment threshold, this was the approximate level achieved in the IMPROVE-IT trial.[50] Therefore, the 2022 ACC ECDP for Use of Nonstatin Therapies recommended an LDL-C threshold of 55 mg/dL for patients at very high risk.[62]

At present, the use of apoB to assess the effectiveness of LLTs remains a matter of clinical judgement. Nonetheless, U.S., European, and Canadian guidelines and recommendations advocate measurement of apoB for cardiovascular risk assessment and/or treatment effectiveness, particularly in subgroups, such as patients with hypertriglyceridemia, diabetes mellitus, visceral adiposity, insulin resistance/metabolic syndrome, low HDL-C, or very low LDL-C levels.[61,68–70]

Specific apoB thresholds have not been suggested in U.S. guidelines and recommendations, but corresponding non-HDL-C values were suggested by the 2015 NLA Recommendations for Patient-Centered Management of Dyslipidemia,[71] the 2018 AHA/ACC/Multisociety Blood Cholesterol Guideline,[61] and the 2022 ACC ECDP on Nonstatin Therapies.[62] The treatment thresholds for apoB suggested in Table 2 can be employed by clinicians to assess whether initiation or intensification of LLT should be considered. An LDL-C level of 160 mg/dL and an apoB level of 130 mg/dL correspond to approximately the 90th percentiles of the untreated adult population (Table 1), both of which are risk-enhancing factors and warrant a clinician-patient discussion regarding initiation or intensification of LLT.[61,62,66]

Limitations for use of apoB to identify lipoprotein-associated ASCVD risk

It should be noted that there are some conditions for which apoB will not provide a complete assessment regarding lipoprotein-associated ASCVD risk. Examples include: 1) severe hypertriglyceridemia with chylomicronemia, where the primary objective is reducing chylomicronemia/TGs to lower the risk of pancreatitis[72]; 2) dysbetalipoproteinemia (type III hyperlipoproteinemia), in which there is increased cardiovascular risk due to elevations in chylomicron- and VLDL-remnant cholesterol, despite levels of apoB that are often normal or low[73]; 3) elevated Lp(a), which is not always accompanied by apoB elevation[74]; and 4) certain other lipid disorders, such as the presence of lipoprotein X[75] or very low levels of HDL-C.[68,76] Patient case scenarios that illustrate situations where apoB measurement may improve clinician decision-making are presented in the Supplemental Materials.

Putting it all together: how can this information about apoB influence patient care?

LDL-C and apoB are both meant to represent the relative contribution of atherogenic lipoproteins to ASCVD risk. While the two are strongly correlated, the relationship differs depending on the specific patient population and circumstances.

As discussed above, significant discordance can exist in individuals and is amplified in treated patients because of the larger relative reduction in LDL-C compared to apoB. This discordance may impact optimal clinical decision-making if we do not have apoB results for an individual. The analysis results illustrated in Fig. 2 enable a clear way to conceptualize discordance by observing the guideline-based LDL-C thresholds for intensification of therapy (55, 70, and 100 mg/dL, respectively) on the graph and noting the wide variance of apoB around each of those levels above and below the regression line. For a treated individual whose apoB is below the regression line, intensification of therapy may be at the discretion of the clinician and patient at that level of LDL-C. However, for a treated individual who has an apoB level above the line, especially if far above, there is a stronger rationale for intensification of treatment. Similarly, in untreated patients, the degree of discordance relative to the regression line may be used to assess risk to inform clinical judgement about the need for pharmacotherapy.

It is important to recognize discordance between apoB and LDL-C in patients and, when present, consider apoB

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Table 5 Scenarios in which clinicians may consider measuring apoB.

Clinical scenario	Rationale
Initial evaluation	• Assess for discordance between LDL-C, non-HDL-C, and apoB • Identify an elevated apoB level as a potential risk-enhancing factor or a marker of severe hyperlipoproteinemia[61,66,77]
4–12 weeks after changes in LLT (initiation, escalation, or de-escalation)	• Determines whether LDL-C, non-HDL-C, and apoB levels are above therapeutic thresholds on treatment
Clinical or metabolic change	• Determine the effect of a newly diagnosed health condition, such as a significant weight change, new medical diagnosis (e.g., kidney, liver, thyroid diseases), new onset or worsening of hyperglycemia, or development of an endocrine disorder or inflammatory disease • Determine whether the initiation of a new medication affecting lipid/lipoprotein metabolism has affected LDL-C, non-HDL-C, and apoB levels (e.g., sex hormone therapy, thiazide diuretics, antiretroviral therapy, and immunosuppressive drugs[71])
Cascade screening	• Assist in clarifying a potential genetic lipoprotein disorder in family members of patients with elevated apoB levels[78]

Abbreviations: apoB, apolipoprotein B; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; non-HDL-C, non-high-density lipoprotein cholesterol.

as an additional therapeutic target (along with non-HDL-C). It is important to have a clinician-patient discussion about the utility and potential expense to the patient of measuring apoB. Table 5 summarizes situations in which clinicians should consider measuring apoB to enhance care.

As discussed above and summarized in Table 4, the results from the untreated and treated regression equations illustrated in Fig. 2 indicate apoB thresholds to consider for intensification of therapy. Guideline LDL-C thresholds were mainly defined based upon clinical trial entry criteria. The same approach is not possible with apoB because the completed RCTs were not designed using apoB entry criteria. However, given the observed benefits from both LDL-C and apoB reduction with lifestyle modification and lipid-lowering pharmacotherapies, it is reasonable to consider the suggested apoB equivalents from the results of the regression analysis.

In addition to using apoB levels to determine which patients would benefit from intensification of therapy or in whom pharmacotherapy might be deferred, apoB measurement can be helpful for classification of lipoprotein phenotypes. Hyperlipidemia can be classified by lipid characteristics (e.g., hypercholesterolemia, hypertriglyceridemia, combined hyperlipidemia) or by lipoproteins as suggested by the classification scheme of Fredrickson, Levy, and Lees developed at the NIH in the 1960s,[28] by clinical syndrome, and/or by use of genetic testing. Using the laboratory techniques devised by Goffman and colleagues in the prior decade, Fredrickson and colleagues classified disorders from analysis of electrophoresis patterns after ultracentrifugation into five phenotypes (types I–V). Each phenotype is characterized by either one or two different lipoprotein species in excess: chylomicrons (type I), LDL (type IIa), VLDL and LDL (type IIb), remnant particles (type III), VLDL (type IV), or chylomicrons and VLDL (type V).[28] This lipoprotein phenotypical classification scheme was adopted by the WHO in 1972. However, it is not typically utilized in contemporary clinical practice because some of the diagnoses would require testing beyond what is reported on a standard lipoprotein lipid profile. Nevertheless, because it is sometimes necessary to characterize the lipoprotein phenotype to diagnose a clinical syndrome and clarify lipoprotein treatment target(s), this classification still has clinical utility. The diagnosis of the individual patient with a clinical syndrome can enable more accurate patient prognosis, tailoring of treatment strategies, and facilitation of cascade screening. Genetic testing can be particularly useful to assist with the characterization of clinical syndromes, but it cannot stand alone in the process. The NLA Scientific Statement on Genetic Testing in Dyslipidemia provides recommendations and applications for genetic testing in patients with dyslipidemia.[78]

Because electrophoresis and ultracentrifugation are no longer performed by most clinical laboratories, alternative approaches for lipoprotein characterization are needed. In 2007, an algorithm was described by de Graaf, Couture, and Sniderman that incorporated total cholesterol, TG, and apoB levels[79] and is available as an online application (https://apob.app/). Use of apoB alongside total cholesterol and TG levels allows converting the descriptive lipid condition to the expected lipoprotein phenotype per Fredrickson-Levy-Lees.[80,81] Other approaches for estimating lipoprotein phenotypes have been described such as one by Sampson et al.[82] However, neither the *apoB.app* nor the phenotypic classification system described by Sampson et al. have been validated across multiple databases against the gold standard of beta-quantification after ultracentrifugation, which would be needed for thorough validation. However, given the potential prognostic and therapeutic importance of making specific diagnoses, the *apoB.app* (and other simplified approaches) can add value in clinical care, especially for individuals with mixed hyperlipidemia and severe hypertriglyceridemia. Once the lipoprotein abnormality is known, the

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Table 6 Categories of dyslipidemia with corresponding TG and apoB levels and TG:apoB and TC:apoB ratios.[28,29,80,81]

Categories of dyslipidemia	Fredrickson-levy-lee lipoprotein phenotype	TG; TG:apoB; TC:apoB (mg/dL)	ApoB (mg/dL)	Syndrome
Hypercholesterolemia	IIa: LDL	TG <133	≥120	Familial hypercholesterolemia
Combined or mixed hyperlipidemia	IIb: LDL + VLDL	TG ≥133	≥120	Familial combined hyperlipidemia
	III: chylomicron + VLDL remnants	TG ≥133; TG:apoB <8.8; TC:apoB ≥2.4	<120	Familial dysbetalipoproteinemia
Hypertriglyceridemia	IV: VLDL	TG ≥133; TG:apoB <8.8; TC:apoB <2.4	<120	Familial hypertriglyceridemia
Severe hypertriglyceridemia	I: chylomicrons	TG ≥133; TG:apoB ≥8.8	<75	Familial chylomicronemia syndrome
	V: VLDL + chylomicrons	TG ≥133; TG:apoB ≥8.8	≥75	Multifactorial chylomicronemia syndrome

Abbreviations: apoB, apolipoprotein B; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides; VLDL, very-low-density lipoprotein.

clinical syndrome can be properly defined, guiding prognosis, treatment, family cascade screening. Table 6 outlines diagnostic dilemmas that can be addressed with this approach.

Addressing payer concerns: is apoB an "experimental" test?

Despite national and international guidelines that outline the important role of apoB measurement in ASCVD risk assessment and evaluation of response to treatment, it is not an explicit target of therapy recommended by the 2018 AHA/ACC/Multisociety Blood Cholesterol Guideline. As such, payers often refer to the measurement as "experimental," which is an assertion that is not supported given the current evidence.

Routine diagnostic tests for apoB were first developed in the 1980s and have been steadily improved and standardized.[83] ApoB testing is readily available for clinicians to order at major commercial laboratories (e.g., LabCorp, Quest Diagnostics), but may not be available at local or hospital laboratories. "Outside testing" increases turnaround time for test results and inflates the cost of testing. In addition, health insurance payment denials or prior authorization requirements often occur for apoB testing in routine practice, and/or demand excessive co-payments partly because of lack of guideline recommendations, low demand, and system inefficiencies. The mischaracterization of apoB as experimental and subsequent payment denials are harmful to patient care and can lead to patient mistrust of clinicians by patients whose insurance provider denies coverage or requires a large co-payment. Given the critical importance of apoB for discerning risk both before and during LLT, and its usefulness in making a proper diagnosis, an important goal of this Expert Clinical Consensus is to alert both clinicians and payers about the role of apoB in cardiovascular risk assessment and management. Furthermore, by documenting the value of apoB testing in routine medical care of adults, this statement can be used as a reference in supporting payment authorization requests should the need arise.

Conclusions

ApoB represents the concentration of atherogenic lipoprotein particles in the circulation, and non-HDL-C represents all the cholesterol carried by apoB-containing lipoproteins. Compared to LDL-C, apoB more accurately reflects the atherogenic impact of lipoproteins before and during lipid-altering treatment. There can be discordance between LDL-C and apoB in the individual, despite a high level of population-wide correlation. When there is discordance between apoB and LDL-C, or non-HDL-C and LDL-C, apoB and non-HDL-C provide more accurate indications of lipoprotein-associated ASCVD risk to guide therapy.[46,61,68,70]

ApoB measurement is particularly useful to improve risk assessment at both the lower and higher ends of the LDL-C range. When apoB levels are very high, it can be a confirmatory marker of high risk for ASCVD and is a risk-enhancing factor. When apoB is not as high as expected in a patient with elevated LDL-C, it can be a source of reassurance in a low-risk patient that prescription of LLT is not as urgent. In contrast, when apoB remains elevated despite LDL-C lowering, especially in high- or very-high-risk patients, treatment intensification should be considered.

ApoB, along with total cholesterol and TG, can be used to diagnose lipoprotein phenotypes without the need for specialized testing. This will help inform clinical prognosis and care and enable family cascade screening when a lipoprotein syndrome is diagnosed.

ApoB is a well-validated clinical measurement that augments the information provided by a standard lipoprotein lipid panel. Ideally, it would be included in every lipid panel, but there are presently practical limitations to doing so, in-

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cluding gaps in understanding its role in care and the present high charges for performing the test. The NLA and other organizations will continue to educate healthcare professionals and the public about the role of apoB in cardiovascular risk management.

The Writing Committee hopes this NLA Expert Clinical Consensus can serve as an educational tool and resource for clinicians. We support the view that apoB testing is underutilized in clinical practice, and that it should be reclassified by payers as a routine (non-experimental) test to improve access. Finally, we strongly recommend that RCTs that are conducted to evaluate lipid-altering interventions for lowering ASCVD risk include measurement of apoB to further elucidate its role in patient care.

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Artificial intelligence was not used in the writing of the text nor creation of its figures.

Disclaimers and limitations

This Expert Clinical Consensus is intended to be an educational tool that incorporates the current medical science and the clinical experiences of lipid specialists and others with expertise in various aspects of medical and/or laboratory science. The intent is to facilitate and improve the clinical care and management of patients. This Expert Clinical Consensus should not be interpreted as "rules" and/or directives regarding the medical care of an individual patient. The decision regarding the optimal care of the patient is best facilitated with a patient-centered approach, managed by the clinician tasked with directing an individual treatment plan. In areas regarding inconclusive or insufficient scientific evidence, the authors used their professional judgment. This Expert Clinical Consensus is not a substitute for maintaining awareness of emerging science. Finally, decisions by clinicians and healthcare professionals to apply the principles in this Expert Clinical Consensus are best made by considering local resources, individual patient circumstances, patient agreement, and knowledge of federal, state, and local laws and guidance.

Updating

This Expert Clinical Consensus may require future updates. The timing of such an update will be determined by the NLA.

CRediT authorship contribution statement

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2024.08.013.

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