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Medical Policy Manual

Laboratory, Policy No. 78

Biomarkers for Cardiovascular Disease

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Numerous lipid and non-lipid biomarkers have been proposed as potential risk markers for cardiovascular disease, including high-density lipoprotein (HDL) subclass and low-density lipoprotein (LDL) subclass. These biomarkers have been studied as alternatives or additions to standard lipid panels for risk stratification in cardiovascular disease or as treatment targets for lipid-lowering therapy.

MEDICAL POLICY CRITERIA

Measurement or quantitation of lipoprotein subclasses as biomarkers for cardiovascular disease is considered **investigational**.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. [Apolipoprotein E for Risk Assessment and Management of Cardiovascular Disease](#), Genetic Testing, Policy No. 05
2. [Genotyping for 9p21 Single Nucleotide Variants to Predict Risk of Cardiovascular Disease or Aneurysm](#), Genetic Testing, Policy No. 62

3. [Measurement of Lipoprotein-Associated Phospholipase A2 \(LpPLA2\) in the Assessment of Cardiovascular Risk](#), Laboratory, Policy No. 63
4. [Investigational Gene Expression, Biomarker, and Multianalyte Testing](#), Laboratory, Policy No. 77
5. [Screening Laboratory Testing](#), Laboratory, Policy No. 80

BACKGROUND

LIPID PANELS

Standard lipid panel testing generally consists of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride measurement.

LOW-DENSITY LIPOPROTEINS AND CARDIOVASCULAR DISEASE

Low-density lipoproteins (LDLs) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project as the primary target of cholesterol-lowering therapy. An LDL particle consists of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins surrounding an inner lipid core composed of cholesterol ester and triglycerides. Traditional lipid risk factors such as LDL cholesterol (LDL-C), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of subjects with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of coronary artery disease (CAD) occur in subjects with “normal” levels of total cholesterol and LDL-C. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

Other non-lipid markers have been identified as being associated with cardiovascular disease (CVD), including B-type natriuretic peptide, cystatin C, fibrinogen, and leptin. These biomarkers may have a predictive role in identifying CVD risk or in targeting therapy. In the United States, social, biological, and environmental disparities exist in the prevalence, morbidity, and mortality rates that are associated with CVD.^[1] Population subgroups that are most significantly adversely affected by such disparities included Black and Hispanic Americans, individuals with low socioeconomic status, and individuals who live in rural settings.

LIPID MARKERS

High-Density Lipoprotein Subclass

High-density lipoprotein particles exhibit considerable heterogeneity, and it has been proposed that various subclasses of HDL may have a greater role in protection from atherosclerosis. Particles of HDL can be characterized based on size or density and/or on apolipoprotein composition. Using size or density, HDL can be classified into HDL₂, the larger, less dense particles that may have the greatest degree of cardioprotection, and HDL₃, which are smaller, denser particles.

An alternative to measuring the concentration of subclasses of HDL (e.g., HDL₂, HDL₃) is a direct measurement of HDL particle size and/or number. Particle size can be measured by nuclear magnetic resonance spectroscopy or by gradient-gel electrophoresis. High-density lipoprotein particle numbers can be measured by nuclear magnetic resonance spectroscopy. Several commercial labs offer these measurements of HDL particle size and number. Measurement of apo AI has used HDL particle number as a surrogate, based on the premise that each HDL particle contains a single apo AI molecule.

Low-Density Lipoprotein Subclass

Two main subclass patterns of LDL, called A and B, have been described. In subclass pattern A, particles have a diameter larger than 25 nm and are less dense, while in subclass pattern B, particles have a diameter less than 25 nm and a higher density. Subclass pattern B is a common inherited disorder associated with a more atherogenic lipoprotein profile, also termed “atherogenic dyslipidemia.” In addition to small, dense LDL, this pattern includes elevated levels of triglycerides, elevated levels of apo B, and low levels of HDL. This lipid profile is commonly seen in type 2 diabetes and is a component of the “metabolic syndrome,” defined by the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) to also include raised blood pressure, insulin resistance, increased levels of inflammatory markers such as C-reactive protein, and a prothrombotic state. The presence of the metabolic syndrome is considered by Adult Treatment Panel III to be a substantial risk-enhancing factor for CAD.

Low-density lipoprotein size has also been proposed as a potentially useful measure of treatment response. Lipid-lowering treatment decreases total LDL and may also induce a shift in the type of LDL, from smaller, dense particles to larger particles. It has been proposed that this shift in lipid profile may be beneficial in reducing the risk for CAD independent of the total LDL level. Also, some drugs may cause a greater shift in lipid profiles than others. Niacin and/or fibrates may cause a greater shift from small to large LDL size than statins. Therefore, measurement of LDL size may potentially play a role in drug selection or may be useful in deciding whether to use a combination of drugs rather than a statin alone.

In addition to the size of LDL particles, interest has been shown in assessing the concentration of LDL particles as a distinct cardiac risk factor. For example, the commonly performed test for LDL-C is not a direct measure of LDL, but, chosen for its convenience, measures the amount of cholesterol incorporated into LDL particles. Because LDL particles carry much of the cholesterol in the bloodstream, the concentration of cholesterol in LDL correlates reasonably well with the number of LDL particles when examined in large populations. However, for an individual patient, the LDL-C level may not reflect the number of particles due to varying levels of cholesterol in different sized particles. It is proposed that the discrepancy between the number of LDL particles and the serum level of LDL-C represents a significant source of unrecognized atherogenic risk. The size and number of particles are interrelated. For example, all LDL particles can invade the arterial wall and initiate atherosclerosis. However, small, dense particles are thought to be more atherogenic than larger particles. Therefore, for patients with elevated numbers of LDL particles, the cardiac risk may be further enhanced when the particles are smaller versus larger.

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Lipid and non-lipid biomarker tests are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

EVIDENCE SUMMARY

LIPID BIOMARKERS

A large body of literature has accumulated on the utility of novel lipid risk factors in the prediction of future cardiac events. The evidence reviewed herein consists of systematic reviews, meta-analyses, and large, prospective cohort studies that have evaluated the association between these lipid markers and cardiovascular outcomes. A smaller amount of literature is available on the utility of these markers as a marker of treatment response. Data on treatment responses are taken from randomized controlled trials (RCTs) that use one or more novel lipid markers as a target of lipid-lowering therapy.

The Adult Treatment Panel III (ATP III) guidelines noted that to determine their clinical significance, emerging risk factors should be evaluated against the following criteria:^[2]

- Significant predictive power that is independent of other major risk factors
- A relatively high prevalence in the population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population reference values, and be relatively stable biologically

It is preferable, but not necessary, that modification of the risk factor in clinical trials will have shown a reduction in risk.

Representative Systematic Reviews

A 2015 health technology assessment conducted for the National Institute for Health Research assessed strategies for monitoring lipid levels in patients at risk or with cardiovascular disease (CVD).^[3] The assessment included a systematic review of predictive associations for CVD events. Studies were included if they had at least 12 months of follow-up and 1,000 participants. Results were stratified by the use of statins and primary versus secondary prevention. For populations not taking statins, 90 publications reporting 110 cohorts were included and, for populations taking statins, 25 publications reporting 28 cohorts were included. In populations not taking statins, the ratio of apolipoprotein B (apo B) to apolipoprotein AI (apo AI) was most strongly associated with the outcome of CVD events (hazard ratio [HR] 1.35, 95% confidence interval [CI] 1.22 to 1.5) although the HRs for apo B, total cholesterol (TC)/HDL, and LDL/HDL all had overlapping CIs with the HR for apo B/apo AI. In populations taking statins, insufficient data were available to estimate the association between apo B or apo AI and CVD events.

Tzoulaki (2013) reported on meta-analyses of biomarkers for CVD risk to examine potential evidence of bias and inflation of results in the literature.^[4] Included in the evaluation were 56 meta-analyses, with 49 reporting statistically significant results. Very large heterogeneity was seen in nine meta-analyses, and small study effects were seen in 13 meta-analyses. Significant excess of studies with statistically significant results was found in 29 (52%) meta-analyses. Reviewers reported only 13 meta-analyses with statistically significant results that had more than 1000 cases and no evidence of large heterogeneity, small-study effects, or excess significance.

In a systematic review, Willis (2012) evaluated whether validated CVD risk scores could identify patients at risk for CVD for participation in more intensive intervention programs for primary prevention.^[5] Sixteen articles on five studies were selected. Reviewers were unable to perform a meta-analysis due to the heterogeneity of studies. The evidence was not considered strong enough to draw definitive conclusions, but reviewers noted that lifestyle interventions

with higher intensity might have the potential for lowering CVD risk.

ASYMPTOMATIC INDIVIDUALS WITH RISK OF CARDIOVASCULAR DISEASE

High-Density Lipoprotein Particle Size and Concentration

Systematic Review

Singh (2020) reported the results for a pooled analysis examining the association between HDL particle concentration and stroke and myocardial infarction (MI) in patients without baseline atherosclerotic disease.^[6] The analysis included 15,784 patients from four prospective cohort studies, which included the ARIC study. A significant inverse association was reported between HDL particle concentration and stroke and MI, when comparing patients with HDL particle concentration in the fourth quartile and the first quartile (HR 0.64, 95% CI 0.52 to 0.78). When comparing the individual components of the primary endpoint at quartile 4 with quartile 1, a significant reduction in both MI (HR 0.63, 95% CI 0.49 to 0.81) and stroke (HR 0.66, 95% CI 0.48 to 0.93) was reported. There was significant heterogeneity between studies regarding patient ethnicity and geographic location. Sub-analysis by race revealed that the significant inverse association between HDL particle concentration and stroke and MI was not seen in black populations. When comparing quartile 4 with quartile 1 among black patients, HDL particle concentration did not have an inverse association with MI (HR 1.22, 95% CI 0.76 to 1.98). However, the heterogeneity and uneven distribution of patients may have contributed to subgroup analyses being underpowered and the possibility of type 2 error.

Randomized Controlled Trial

In the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER RCT) (2013), 10,886 patients without CVD were randomized to rosuvastatin or placebo and followed for a median of two years.^[7] Before randomization and one year after, levels of LDL-C, HDL-C, apo AI, and nuclear magnetic resonance (NMR)-measured HDL size and HDL particle numbers were evaluated. Statistically significant changes in the median and 25th and 75th percentile values of HDL levels between baseline and one-year values occurred in the rosuvastatin and placebo groups for all levels ($p < 0.001$), except for apo AI and HDL particle size in the placebo group, which did not differ significantly ($p = 0.09$ and $p = 0.74$, respectively). Changes in the rosuvastatin group were also statistically significant compared with placebo for LDL-C, HDL-C, apo AI, and HDL particle size and number (all $p < 0.001$). In the placebo group, inverse associations with CVD and HDL-C, apo AI, and HDL particles were reported. High-density lipoprotein particle number in the rosuvastatin group had a greater association with CVD (HR 0.73, 95% CI 0.57 to 0.93, $p = 0.01$) than HDL-C (HR 0.82, 95% CI 0.63 to 1.08, $p = 0.16$) or apo AI (HR 0.86, 95% CI 0.67 to 1.10, $p = 0.22$). This association remained after adjusting for HDL-C (HR 0.72, 95% CI 0.53 to 0.97, $p = 0.03$). Size of HDL was not significantly associated with CVD in risk factor-adjusted models.

Low-Density Lipoprotein Subclass and Low-Density Lipoprotein Particle Size and Concentration

Observational Studies

A nested case-control study (1996) from the Physician's Health Study, a prospective cohort study of approximately 15,000 men, investigated whether LDL particle size is an independent predictor of CAD risk, particularly compared to triglyceride levels.^[8] The authors concluded that while LDL particle diameter was associated with the risk of MI, this association was not present

after adjustment for triglyceride level. Only the triglyceride level was independently significant.

The Quebec Cardiovascular Study evaluated the ability of “nontraditional” lipid risk factors, including LDL size, to predict subsequent CAD events in a prospective cohort of 2,155 men followed for five years.^[9, 10] The presence of small LDL particles was associated with a 2.5-fold increased risk for ischemic heart disease after adjustment for traditional lipid values, indicating a level of risk similar to total LDL. This study also suggested an interaction in atherogenic risk between LDL size and apo B levels. In the presence of small LDL particles, elevated apo B levels were associated with a six-fold increased risk of CAD, whereas when small LDL particles were not present, elevated apo B levels were associated with only a two-fold increase in risk.

Tzou (2005) examined the clinical value of “advanced lipoprotein testing” in 311 randomly selected adults participating in the Bogalusa Heart Study.^[11] Advanced lipoprotein testing consisted of subclass patterns of LDL (i.e., presence of large buoyant particles, intermediate particles, or small dense particles). These measurements were used to predict the presence of subclinical atherosclerosis, as measured ultrasonographically by carotid intimal-media thickness. In multivariate logistic regression models, substituting advanced lipoprotein testing for corresponding traditional lipoprotein values did not improve prediction of the highest quartile of carotid intimal-media thickness.

Low-Density Lipoprotein Particle Size and Concentration Measured by Nuclear Magnetic Resonance

Similar to small dense lipoprotein particles, several epidemiologic studies have shown that the lipoprotein particle size and concentration measured by NMR are also associated with cardiac risk. For example, data derived from the Women’s Health Study, Cardiovascular Health Study, and Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-1) trial have suggested that the number of LDL particles is an independent predictor of cardiac risk.^[12-14] Translating these findings into clinical practice requires setting target values for lipoprotein numbers. Proposed target values have been derived from the same data set (i.e., Framingham study) used to set the ATP III target goals for LDL-C. For example, the ATP III targets for LDL-C correspond to the 20th, 50th, and 80th percentile values in the Framingham Offspring Study, depending on the number of risk factors present. Proposed target goals for lipoprotein numbers correspond to the same percentile values, and LDL particle concentrations corresponding to the 20th, 50th, and 80th percentile are 1100, 1400, and 1800 nmol/L, respectively.^[15]

Systematic Review

Rosenson and Underberg (2013) conducted a systematic review of studies on lipid-lowering pharmacotherapies to evaluate changes in LDL particles pre- and post-treatment.^[16] Reductions in mean LDL particles occurred in 34 of the 36 studies evaluated. Percentage reductions of LDL particles in several statin studies were smaller than reductions in LDL-C. Low-density lipoprotein particles and apo B changes were comparable. Reviewers suggested the differences in LDL particle reductions with different lipid-lowering therapies demonstrated potential areas of residual cardiovascular risk that could be addressed with LDL particle monitoring.

Observational Studies

Mora (2009) evaluated the predictive ability of LDL particle size and number measured by NMR in participants of the Women's Health Study, a prospective cohort trial of 27,673 women followed over an 11-year period.^[17] After controlling for non-lipid factors, LDL particle number was a significant predictor of incident CVD, with an HR of 2.51 (95% CI 1.91 to 3.30) for the highest compared with the lowest quintile. Low-density lipoprotein particle size was similarly predictive of cardiovascular risk, with an HR of 0.64 (95% CI 0.52 to 0.79). Compared with standard lipid measures and apolipoproteins, LDL particle size and number showed similar predictive ability but were not superior in predicting cardiovascular events.

Toth (2014) analyzed LDL-C and LDL particle levels and cardiovascular risk using commercial insurance and Medicare claims data on 15,569 high-risk patients from the HealthCore Integrated Research Database.^[18] For each 100 nmol/L increase in LDL particle level, there was a 4% increase in the risk of a CHD event (HR 1.04, 95% CI 1.02 to 1.05, $p < 0.0001$). A comparative analysis, using 1:1 propensity score matching of 2,094 patients from the LDL-C target cohort (LDL-C level < 100 mg/dL without a LDL particle level) and a LDL particle target cohort (LDL particle < 1000 nmol/L and LDL-C of any level) found a lower risk of CHD or stroke in patients who received LDL-C measurement and were presumed to have received more intensive lipid-lowering therapy (HR 0.76, 95% CI 0.61 to 0.96, at 12 months). A comparison of smaller LDL particle target groups at 24 ($n = 1,242$) and 36 ($n = 705$) months showed similar reductions in CHD (HR 0.78, 95% CI 0.62 to 0.97) and stroke (HR 0.75, 95% CI 0.58 to 0.97).

Section Summary: Asymptomatic Individuals with Risk of Cardiovascular Disease

The evidence for asymptomatic individuals with risk of CVD who receive lipoprotein subclass testing includes systematic reviews, meta-analyses, and large, prospective cohort studies. The evidence from cohort studies and meta-analyses of these studies has suggested that some of these markers are associated with increased cardiovascular risk and may provide incremental accuracy in risk prediction. However, it has not been established whether the incremental accuracy provides clinically important information beyond that of traditional lipid measures. Furthermore, no study has provided high-quality evidence that measurement of markers leads to changes in management that improve health outcomes.

INDIVIDUALS WITH HYPERLIPIDEMIA MANAGED WITH LIPID-LOWERING THERAPY

Low-Density Lipoprotein Subclass and Low-Density Lipoprotein Particle Size and Concentration

Patients with subclass pattern B have been reported to respond more favorably to diet therapy than those with subclass pattern A.^[19] Subclass pattern B has also been shown to respond more favorably to gemfibrozil and niacin, with a shift from small, dense LDL particles to larger LDL particles. While statin drugs lower the overall concentration of LDL-C, there is no shift to the larger LDL particles.

Randomized and Nonrandomized Controlled Trials

Superko (2005) reported that the response to gemfibrozil differed in patients who had LDL subclass A compared with those who had LDL subclass B.^[20] There was a greater reduction in the small, LDL levels for patients with subclass B, but this did not correlate with clinical outcomes. Another study has reported that atorvastatin treatment led to an increase in mean LDL size, while pravastatin treatment led to a decrease in LDL size.^[21]

Various studies have generally confirmed that small, dense LDL is impacted preferentially by

fibrate treatment^[22-24] and possibly also by statin therapy.^[22, 24] However, none demonstrated that preferentially targeting small, dense LDL leads to improved outcomes, compared with standard LDL targets widely used in clinical care.

Several trials with angiographic outcomes have examined the change in LDL particle size in relation to the angiographic progression of CAD. The 1996 Stanford Coronary Risk Intervention Project trial studied the relation between small, dense LDL and the benefit of diet, counseling, and drug therapy in patients with CAD, as identified by initial coronary angiogram.^[25] Patients with subclass pattern B showed a significantly greater reduction in CAD progression than those with subclass pattern A. The 1990 Familial Atherosclerosis Treatment Study randomized patients from families with premature CAD and elevated apo B levels.^[26] Change in LDL particle size correlated significantly with the angiographic progression of CAD in this study.

Fewer studies have evaluated clinical outcomes in relation to LDL particle size. In the 2001 Cholesterol and Recurrent Events trial, survivors of MI with normal cholesterol levels were randomized to lipid-lowering therapy or placebo.^[27] A post hoc analysis from this trial failed to demonstrate a correlation between change in particle size and treatment benefit.

Section Summary: Low-Density Lipoprotein Subclass and Low-Density Lipoprotein Particle Size and Concentration

The direct clinical application of measuring small, dense lipoprotein particles is still unclear. To improve outcomes, clinicians must have the tools to translate this information into clinical practice. Such tools for linking levels of small, dense LDL to clinical decision making are currently not available. Published data are inadequate to determine how such measurements should guide treatment decisions and whether these treatment decisions result in beneficial patient outcomes.

PRACTICE GUIDELINE SUMMARY

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

In 2013, the National Heart, Lung, and Blood Institute published a systematic evidence review on managing blood cholesterol in adults.^[28] The review was used to develop joint guidelines by the American College of Cardiology (ACC) and American Heart Association (AHA) on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults (see below).^[29]

AMERICAN COLLEGE OF CARDIOLOGY AND AMERICAN HEART ASSOCIATION

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) published guidelines for the assessment of cardiovascular risk.^[29] Pooled cohort equations for estimating atherosclerotic cardiovascular disease (ASCVD) were developed from sex- and race-specific proportional hazards models that included covariates of age, treated or untreated systolic blood pressure level, total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels, current smoking status, and history of diabetes. Additional risk factors evaluated included diastolic blood pressure, family history of ASCVD, moderate or severe chronic kidney disease, and body mass index. None of the variables significantly improved discrimination for 10-year hard ASCVD risk prediction. The ACC and AHA recommended that further research using state-of-the-art statistical techniques (including net reclassification improvement and

integrative discrimination index) examine the utility of novel biomarkers when added to these new pooled cohort equations in different populations and patient subgroups. The guidelines stated that future updates might include guidance on whether on-treatment markers such as apo B, Lp(a), or low-density lipoprotein (LDL) particles are useful for guiding treatment decisions.

The ACC/AHA (2019) guidelines on primary prevention of cardiovascular disease did not include any discussion of lipoprotein subclasses.^[30]

AMERICAN DIABETES ASSOCIATION AND AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

In 2008, a consensus statement from the American Diabetes Association and the ACC Foundation addressed lipoprotein management in patients with cardiometabolic risk.^[31] This consensus statement commented on the use of LDL particle number in patients with cardiometabolic risk and on the limitations of the clinical utility of nuclear magnetic resonance measurement of LDL particle number or size, including lack of widespread availability. The statement also noted that there is a need for more independent data confirming the accuracy of the method and whether its predictive power is consistent across various patient populations.

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN COLLEGE OF ENDOCRINOLOGY

In 2017, the American Association of Clinical Endocrinology (AACE) and the American College of Endocrinology (ACE) published joint guidelines on the management of dyslipidemia and the prevention of cardiovascular diseases.^[32] The guidelines recommended that, among patients with “triglyceride (TG) concentration of greater than 150 mg/dL or HDL-C concentration of less than 40 mg/dL, the apo B or the apo B to apo AI ratio may be useful in assessing residual risk in individuals at risk for ASCVD (even when the LDL-C levels are controlled).”

In 2020, the AACE published an updated consensus statement on dyslipidemia and prevention of cardiovascular disease.^[33] Recommendations included consideration LDL particle measurement “based on individual patient clinical circumstances.”

NATIONAL LIPID ASSOCIATION

National Lipid Association (NLA) recommendations for patient-centered management of dyslipidemia were published in 2015.^[34] These recommendations stated that non-HDL-C and LDL-C should be primary targets for therapy.

In 2021, the NLA issued a scientific statement on lipid measurements in cardiovascular disease including information on apo B, small dense LDL, and Lp(a).^[35] The authors recommend that measurements of apo B and small dense LDL “may be reasonable at initial evaluation,” and that small dense LDL measurement is “not recommended” for patients receiving lipid lowering therapy.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

The U.S. Preventive Services Task Force (2018) issued updated recommendations on the use of nontraditional risk factors for the assessment of coronary heart disease (CHD).^[36] The recommendations concluded that the evidence was insufficient to assess the benefits and

harms of novel testing methods to diagnose CVD. However, the nontraditional risk factors included in this recommendation were different than those in this evidence review.

SUMMARY

There is not enough research to show that measurement or quantitation of lipoprotein subclasses can improve health outcomes for individuals who are asymptomatic with risk of cardiovascular disease or those with hyperlipidemia managed with lipid-lowering therapy. Studies have suggested that some of these markers are associated with increased cardiovascular risk and may provide incremental accuracy in risk prediction. However, it has not been established whether the incremental accuracy provides clinically important information beyond that of traditional lipid measures. In addition, evidence-based clinical practice guidelines do not recommend these measurements. Therefore, this testing is considered investigational for the assessment of cardiovascular risk.

REFERENCES

1. Mensah GA, Mokdad AH, Ford ES, et al. State of disparities in cardiovascular health in the United States. *Circulation*. 2005;111(10):1233-41. PMID: 15769763
2. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285(19):2486-97. PMID: 11368702
3. Perera R, McFadden E, McLellan J, et al. Optimal strategies for monitoring lipid levels in patients at risk or with cardiovascular disease: a systematic review with statistical and cost-effectiveness modelling. *Health Technol Assess*. 2015;19(100):1-401, vii-viii. PMID: 26680162
4. Tzoulaki I, Siontis KC, Evangelou E, et al. Bias in associations of emerging biomarkers with cardiovascular disease. *JAMA Intern Med*. 2013;173(8):664-71. PMID: 23529078
5. Willis A, Davies M, Yates T, et al. Primary prevention of cardiovascular disease using validated risk scores: a systematic review. *J R Soc Med*. 2012;105(8):348-56. PMID: 22907552
6. Singh K, Chandra A, Sperry T, et al. Associations Between High-Density Lipoprotein Particles and Ischemic Events by Vascular Domain, Sex, and Ethnicity: A Pooled Cohort Analysis. *Circulation*. 2020;142(7):657-69. PMID: 32804568
7. Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. *Circulation*. 2013;128(11):1189-97. PMID: 24002795
8. Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA*. 1996;276(11):882-8. PMID: 8782637
9. Lamarche B, Moorjani S, Lupien PJ, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec cardiovascular study. *Circulation*. 1996;94(3):273-8. PMID: 8759066
10. Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. *Circulation*. 1997;95(1):69-75. PMID: 8994419

11. Tzou WS, Douglas PS, Srinivasan SR, et al. Advanced lipoprotein testing does not improve identification of subclinical atherosclerosis in young adults: the Bogalusa Heart Study. *Ann Intern Med.* 2005;142(9):742-50. PMID: 15867406
12. Blake GJ, Otvos JD, Rifai N, et al. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. *Circulation.* 2002;106(15):1930-7. PMID: 12370215
13. Kuller L, Arnold A, Tracy R, et al. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the cardiovascular health study. *Arterioscler Thromb Vasc Biol.* 2002;22(7):1175-80. PMID: 12117734
14. Rosenson RS, Otvos JD, Freedman DS. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial. *Am J Cardiol.* 2002;90(2):89-94. PMID: 12106834
15. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol.* 2002;90(8A):22i-29i. PMID: 12419478
16. Rosenson RS, Underberg JA. Systematic review: Evaluating the effect of lipid-lowering therapy on lipoprotein and lipid values. *Cardiovasc Drugs Ther.* 2013;27(5):465-79. PMID: 23893306
17. Mora S, Otvos JD, Rifai N, et al. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation.* 2009;119(7):931-9. PMID: 19204302
18. Toth PP, Grabner M, Punekar RS, et al. Cardiovascular risk in patients achieving low-density lipoprotein cholesterol and particle targets. *Atherosclerosis.* 2014;235(2):585-91. PMID: 24956532
19. Kwiterovich PO, Jr. Clinical relevance of the biochemical, metabolic, and genetic factors that influence low-density lipoprotein heterogeneity. *Am J Cardiol.* 2002;90(8A):30i-47i. PMID: 12419479
20. Superko HR, Berneis KK, Williams PT, et al. Gemfibrozil reduces small low-density lipoprotein more in normolipemic subjects classified as low-density lipoprotein pattern B compared with pattern A. *Am J Cardiol.* 2005;96(9):1266-72. PMID: 16253595
21. Sirtori CR, Calabresi L, Pisciotto L, et al. Effect of statins on LDL particle size in patients with familial combined hyperlipidemia: a comparison between atorvastatin and pravastatin. *Nutr Metab Cardiovasc Dis.* 2005;15(1):47-55. PMID: 15871851
22. Arca M, Montali A, Pigna G, et al. Comparison of atorvastatin versus fenofibrate in reaching lipid targets and influencing biomarkers of endothelial damage in patients with familial combined hyperlipidemia. *Metabolism.* 2007;56(11):1534-41. PMID: 17950105
23. Rosenson RS, Wolff DA, Huskin AL, et al. Fenofibrate therapy ameliorates fasting and postprandial lipoproteinemia, oxidative stress, and the inflammatory response in subjects with hypertriglyceridemia and the metabolic syndrome. *Diabetes Care.* 2007;30(8):1945-51. PMID: 17483155
24. Tokuno A, Hirano T, Hayashi T, et al. The effects of statin and fibrate on lowering small dense LDL- cholesterol in hyperlipidemic patients with type 2 diabetes. *J Atheroscler Thromb.* 2007;14(3):128-32. PMID: 17587764
25. Miller BD, Alderman EL, Haskell WL, et al. Predominance of dense low-density lipoprotein particles predicts angiographic benefit of therapy in the Stanford Coronary Risk Intervention Project. *Circulation.* 1996;94(9):2146-53. PMID: 8901665
26. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med.* 1990;323(19):1289-98. PMID: 2215615

27. Campos H, Moye LA, Glasser SP, et al. Low-density lipoprotein size, pravastatin treatment, and coronary events. *JAMA*. 2001;286(12):1468-74. PMID: 11572739
28. National Heart Lung and Blood Institute. Managing Blood Cholesterol in Adults: Systematic Evidence Review From the Cholesterol Expert Panel, 2013. Bethesda, MD: National Heart, Lung, and Blood Institute; 2013. [cited 1/26/2026]. 'Available from:' <https://www.nhlbi.nih.gov/sites/default/files/media/docs/cholesterol-in-adults.pdf>.
29. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(25 Pt B):2889-934. PMID: 24239923
30. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646. PMID: 30879355
31. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care*. 2008;31(4):811-22. PMID: 18375431
32. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocr Pract*. 2017;23(Suppl 2):1-87. PMID: 28437620
33. Handelsman Y, Jellinger PS, Guerin CK, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Management of Dyslipidemia and Prevention of Cardiovascular Disease Algorithm - 2020 Executive Summary. *Endocr Pract*. 2020;26(10):1196-224. PMID: 33471721
34. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. *J Clin Lipidol*. 2014;8(5):473-88. PMID: 25234560
35. Wilson PW, Jacobson TA, Martin SS, et al. Lipid measurements in the management of cardiovascular diseases: Practical recommendations a scientific statement from the national lipid association writing group. *J Clin Lipidol*. Published online: September 24, 2001.
36. Force USPST, Curry SJ, Krist AH, et al. Risk Assessment for Cardiovascular Disease With Nontraditional Risk Factors: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2018;320(3):272-80. PMID: 29998297

CODES

Codes	Number	Description
CPT	0052U	Lipoprotein, blood, high resolution fractionation and quantitation of lipoproteins, including all five major lipoprotein classes and subclasses of HDL, LDL, and VLDL by vertical auto profile ultracentrifugation
	0541U	Cardiovascular disease (HDL reverse cholesterol transport), cholesterol efflux capacity, LC-MS/MS, quantitative measurement of 5 distinct HDL-bound apolipoproteins (apolipoproteins A1, C1, C2, C3, and C4), serum, algorithm reported as prediction of coronary artery disease (pCAD) score
	83700	Lipoprotein, blood; electrophoretic separation and quantitation

Codes	Number	Description
	83701	Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation)
	83704	Lipoprotein, blood; quantitation of lipoprotein particle number(s) (eg, by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed
	83722	Lipoprotein, direct measurement; small dense LDL cholesterol
HCPCS	None	

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