Cardiovascular Disease Risk Tests

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➲ Instructions for Use

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Related Policy

- Genetic Testing for Cardiac Disease

Coverage Rationale

The following are unproven and not medically necessary due to insufficient evidence of efficacy:

- Arterial compliance testing, using waveform analysis as a method to determine risk for cardiovascular disease
- Carotid intima-media thickness measurement as an effective screening tool for the management of cardiovascular disease
- Subfractions or particle size advanced lipoprotein analysis as a method to determine risk for cardiovascular disease
- Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) enzyme as a method to determine risk for cardiovascular disease or ischemic stroke
- Multiprotein diagnostic biomarker:
  - Analysis of protein biomarkers by aptamer-based microarray and algorithm
  - Cardiovascular disease [high-density lipoprotein (HDL) reverse cholesterol transport], cholesterol efflux capacity, liquid chromatography–tandem mass spectrometry, and quantitative measurement of five distinct HDL-bound apolipoproteins (apolipoproteins A1, C1, C2, C3, and C4), with algorithm and reported as a risk score
  - Three proteins [high-sensitivity troponin, adiponectin, and kidney injury molecule-1 (KIM-1)], with algorithm and reported as a risk score
  - Four proteins [NT-proBNP, osteopontin, tissue inhibitor of metalloproteinase-1 (TIMP-1), and KIM-1], with algorithm and reported as a risk score
  - Seven proteins (IL-16, FAS, FASLigand, HGF, CTACK, EOTAXIN, and MCP-3), with algorithm and reported as a risk score

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other policies and guidelines may apply.

CPT Code	Description
0019M	Cardiovascular disease, plasma, analysis of protein biomarkers by aptamer-based microarray and algorithm reported as 4-year likelihood of coronary event in high-risk populations
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

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CPT Code	Description
0308U	Cardiology (coronary artery disease [CAD]), analysis of 3 proteins (high sensitivity [hs] troponin, adiponectin, and kidney injury molecule-1 [KIM-1]) with 3 clinical parameters (age, sex, history of cardiac intervention), plasma, algorithm reported as a risk score for obstructive CAD
0309U	Cardiology (cardiovascular disease), analysis of 4 proteins (NT-proBNP, osteopontin, tissue inhibitor of metalloproteinase-1 [TIMP-1], and kidney injury molecule-1 [KIM-1]), plasma, algorithm reported as a risk score for major adverse cardiac event
0377U	Cardiovascular disease, quantification of advanced serum or plasma lipoprotein profile, by nuclear magnetic resonance (NMR) spectrometry with report of a lipoprotein profile (including 23 variables)
0415U	Cardiovascular disease (acute coronary syndrome [ACS]), IL-16, FAS, FASLigand, HGF, CTACK, EOTAXIN, and MCP-3 by immunoassay combined with age, sex, family history, and personal history of diabetes, blood, algorithm reported as a 5-year (deleted risk) score for ACS
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
1104T	Noninvasive cardiopulmonary assessment, including quantitative parameters, respectively predictive of significant epicardial coronary artery disease, pulmonary hypertension, and/or elevated pulmonary capillary wedge pressure, derived by augmentative algorithmic analysis of orthogonal voltage gradient and photoplethysmography signals, with automated report
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)
83701	Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (e.g., electrophoresis, ultracentrifugation)
83704	Lipoprotein, blood; quantitation of lipoprotein particle number(s) (e.g., by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed
93050	Arterial pressure waveform analysis for assessment of central arterial pressures, includes obtaining waveform(s), digitization and application of nonlinear mathematical transformations to determine central arterial pressures and augmentation index, with interpretation and report, upper extremity artery, non-invasive
93895	Quantitative carotid intima media thickness and carotid atheroma evaluation, bilateral

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Description of Services

Cardiovascular diseases, including coronary artery disease, stroke, and hypertension, are the leading causes of morbidity and mortality in the United States. Vascular disease is the major contributor to cardiovascular morbid events and ideally is identified early before symptoms are detected or irreversible damage has occurred. Arterial compliance (elasticity), carotid intima-media thickness (CIMT), and advanced lipoprotein analysis are tests that have been proposed to measure and monitor atherosclerosis.

Measurement of CIMT for the screening or management of cardiovascular diseases is based on the theory that the extent of carotid atherosclerosis correlates positively with the severity of coronary atherosclerosis. CIMT is a noninvasive test using ultrasound to capture images of the carotid artery and computer software to analyze the measurements.

Cholesterol is a fat-like substance (lipid) that is present in cell membranes and travels in the blood in distinct particles containing both lipid and proteins (lipoproteins). The two main types of lipoproteins include low-density lipoprotein and high-density lipoprotein. Low-density lipoprotein cholesterol typically makes up 60% to 70% of the total serum cholesterol and contains a single apolipoprotein, namely apo B-100. High-density lipoprotein cholesterol normally makes up 20% to 30% of the total serum cholesterol. The major apolipoproteins of high-density lipoprotein are apo A-I and apo A-II. Apolipoprotein and lipoprotein-associated phospholipase A_2 (Lp-PLA_2) are risk factors that are being evaluated for their ability to predict cardiovascular disease or ischemic stroke. (National Heart, Lung, and Blood Institute, 2002; updated 2024)

Lp-PLA_2, a vascular inflammatory enzyme, has been investigated as a surrogate biomarker of increased coronary heart disease and stroke risk. Lp-PLA_2 testing has been used as an adjunct to conventional risk assessment in healthy or asymptomatic adults to determine who might benefit from specific risk-reducing interventions, such as pharmacological therapies and behavior modification strategies. (Huang and Zhu, 2025)

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The HART CADhs® is a multiprotein diagnostic test for determining whether an individual has heart disease and may be at imminent risk of a heart attack. HART CVE® is a multiprotein risk test for an individual's 1-year risk of heart attack, stroke, or cardiac death. Artificial intelligence is used to interrogate well-characterized clinical datasets to produce novel, multiprotein, algorithmically scored tests. (Prevencio Inc., 2022)

Clinical Evidence

Arterial Compliance

There is insufficient evidence to conclude that noninvasive arterial compliance testing is clinically effective for the management of cardiovascular disease (CVD). There is inadequate clinical evidence from prospective studies that the use of this technology alters individuals' management and improves clinical outcomes. The identified literature is limited by the cross-sectional design of some of the studies and lack of assessment of the clinical utility of the test.

Li et al. (2025) conducted a systematic review and meta-analysis of 20 studies that involved 381,303 individuals aged 18 years and above assessing the correlation of estimated pulse wave velocity (ePWV) with the likelihood of cardiovascular events and all-cause mortality. Individuals with higher ePWV had significantly increased risks of cardiovascular events, cardiovascular mortality, and all-cause mortality. Specifically, for each 1-m/s increase in ePWV, the risks of the outcomes increased by 36%, 41%, and 37%, respectively. The authors concluded that higher ePWV correlated with an increased rate of cardiovascular events and all-cause mortality. For individuals with CVD, the authors concluded that ePWV can be used as an important risk stratification tool and as a critical indicator for screening individuals who are at a high risk for cardiovascular and other adverse events. The findings are limited by publication bias and uneven regional distribution, which may affect the generalizability of the results. The authors also acknowledged that there is no current established standard cutoff value for ePWV to predict specific outcomes in specific populations. Larger, prospective studies are required to reinforce the predictive capacity of ePWV and define reference values more conclusively. Furthermore, the clinical utility of the test to improve individuals' outcomes was not assessed.

Claessens et al. (2023) studied 1,066 participants according to age brackets. Four cohorts were investigated: healthy participants, hypertensive participants, those with ischemic heart disease, and participants with valvular heart disease. PWV analysis measured arterial distensibility. The aim of this study was to evaluate the clinical importance and usefulness of pulse wave analysis. Arterial stiffness was analyzed through the SphygmoCor XCEL Central Blood Pressure Measurement System and SphygmoCor XCEL PWV Measurement System. There were statistically significant differences between the healthy participant and hypertensive participant cohorts in nearly all age brackets. Central aortic blood pressure systolic seemed to be a determining factor. In conclusion, a significant determining factor in problems of arterial stiffness appears to be central aortic blood pressure systolic. According to the authors, pulse wave analysis and PWV are important measures in the evaluation and measurement of arterial hypertension but do not yield definitive results. The authors noted that further investigation is needed. Additionally, medication therapy was not a contraindication for study inclusion, although certain medications such as β-blockers, angiotensin-converting enzyme inhibitors, and statins could influence pulse wave analysis measurements. The findings are limited by the cross-sectional design and lack of assessment of the clinical utility of the test.

Piko et al. (2021) performed a cross-sectional study, single-center evaluation of the ankle-brachial index (ABI), mean carotid-femoral PWV (cfPWV), and pulse wave analysis parameters. Data were obtained in a 2-year period. Overall, 123 participants who underwent elective coronary angiography were included. The ABI was measured, and arterial stiffness parameters were derived with applanation tonometry of the radial, carotid, and femoral arteries. The mean ABI was 1.04 ±0.12, mean subendocardial viability ratio (SEVR) was 166.6% ±32.7%, and mean cfPWV was 10.3 ±2.4 m/s. Most of the study participants [n = 81 (65.9%)] had coronary artery disease (CAD). There was no difference in the ABI among different degrees of CAD. Participants with zero- and three-vessel CAD had significantly lower values of SEVR compared with study participants with one- and two-vessel CAD. No significant difference was observed in cfPWV values. A Spearman correlation test showed a correlation between the ABI and SEVR and between the ABI and cfPWV. A multiple regression analysis confirmed an association between cfPWV and the ABI, cfPWV and mean arterial pressure, cfPWV and age, and cfPWV and body mass index but not with arterial hypertension, dyslipidemia, diabetes, or smoking status. SEVR was not statistically significantly associated with the ABI using the same multiple regression model. The authors concluded that a reduced ABI was associated with increased cfPWV but not with advanced CAD or decreased SEVR. Limitations of the study include the cross-sectional design, small sample size, and inclusion of only Caucasian participants.

Sequí-Domínguez et al. (2020) conducted a systematic review and meta-analysis to estimate PWV and cfPWV performance and predict cardiovascular and all-cause mortality. In addition, the authors compared the results of cfPWV thresholds with already established values to increase its validity. Nine studies (n = 3,170) were included in the systematic

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review, and due to the limited studies measuring brachial-ankle PWV, only studies that measured cfPWV were incorporated in the main quantitative data synthesis. All included studies were of longitudinal nature, and two of them were cross-sectional analyses from longitudinal studies. The predictive performance of the cfPWV pooled diagnostic odds ratio (OR) values was 11.23 (95% CI, 7.29-17.29) for cardiovascular mortality and 6.52 (95% CI, 4.03-10.55) for all-cause mortality. The area under the hierarchical summary receiver operating characteristic curve for cfPWV was 0.75 (95% CI, 0.69-0.81) for cardiovascular mortality and 0.78 (95% CI, 0.74-0.83) for all-cause mortality, and the closest cutoff points to the summary point were 10.7 and 11.5, respectively. The authors concluded that cfPWV is a useful cardiovascular and all-cause mortality predictor; a feasible, noninvasive, and replicable method for estimating risk; and applicable in high-risk populations. Limitations of the study include the publication bias, small sample size, specific population characteristics, and cfPWV measurement technique differences. Additionally, the incremental value and clinical utility of this test were not reported.

Hitsumoto (2017) conducted a study that evaluated the impact of the arterial velocity pulse index (AVI) as a novel marker of atherosclerosis using pulse wave analysis on high-sensitivity troponin T (hs-cTnT) in participants with hypertension. The study enrolled 455 participants without a history of cardiovascular events. The AVI and hs-cTnT levels were measured. Hs-cTnT was detected in 405 participants (89.0%). The AVI was significantly higher in study participants with detectable hs-cTnT than in those without. In participants with detectable hs-cTnT, there was a significant positive correlation between the AVI and hs-cTnT. The authors concluded that the significant relationship between the AVI and hs-cTnT, as determined by a multivariate analysis, indicated that arterial wave reflection is an important factor for the progression of subclinical myocardial damage in hypertensive individuals. They identified some study limitations. First, treatment with antihypertensive drugs was stopped 24 hours or more before measurement to avoid influencing the AVI. This time was not sufficient to mitigate the effects of long-acting drugs. Second, ultrasonic echocardiography, coronary angiography, and computed tomography angiography were not performed. CVDs such as heart failure or CAD may have gone undetected. Third, the sample size was relatively small. Prospective studies are required to clarify the clinical significance of the AVI as a risk factor for CVD in study participants with hypertension. The study did not address the clinical utility of the test or its incremental value to standard cardiovascular risk markers.

Carotid Intima-Media Thickness

The clinical evidence is insufficient to show an added benefit of carotid intima-media thickness (CIMT) testing beyond traditional risk assessment. There is inadequate clinical evidence from prospective studies that shows that the use of this technology alters individuals' management and improves clinical outcomes. Additional research that involves larger, well-designed studies is needed to establish the role of arterial compliance in the early identification, prevention, and management of CVD.

Mitra et al. (2025) conducted a prospective cohort study using data from the UK Biobank, with a mean follow-up of 4.3 years, to assess the association between CIMT and the risk of major adverse cardiovascular events (MACEs) and improve prevention strategies. Overall, 29,292 participants who were aged 40 to 69 years from the UK Biobank and free from CVD at baseline were involved in this population-based study. CIMT was measured at baseline, and a composite cardiometabolic risk biomarker index (CRBI) was developed using hemoglobin A_{1c}, total cholesterol ratio, and blood pressure. The association between CIMT, the CRBI, and the risk of these events was evaluated using hazard ratios (HRs) and adjusted for confounders. Lifestyle factors such as smoking and physical activity were also correlated with higher CIMT, particularly in male participants. An increased CIMT was significantly associated with the cumulative burden of cardiometabolic risk factors, as measured by the CRBI score. The authors concluded that CIMT is a strong predictor of coronary heart disease (CHD) and myocardial infarction but not stroke, dementia, peripheral vascular disease, or aortic aneurysm. Additionally, the CRBI offers additional predictive value for subclinical atherosclerosis and future cardiovascular events. Although the large sample size is a study strength, the findings are limited by the observational design and a study population that was predominantly Caucasian and drawn from a single country, which may limit generalizability and leave certain environmental, genetic, and cultural confounders unaccounted for, causing a lack of generalizability to the U.S. population. Furthermore, the clinical utility of the measurements and how the measurements impact individuals' care are not addressed.

Ling et al. (2023) completed a systematic review of the different definitions of CIMT used in prospective cohort studies. Of the 2,287 articles, 18 articles (14 studies), with > 10 different CIMT definitions, were identified and included in the meta-analysis. CIMT has been used as a predictor of future CVD; however, various definitions of CIMT exist. The authors concluded that combined IMT is more strongly associated with CVD events than single-segment CIMT definitions. Limitations of the systematic review include the limited available research, as well as the differences in CIMT measurements across the studies, which could affect the associations. Further studies are needed to draw a final conclusion on the strength of associations of the different definitions of CIMT with future CVD. Furthermore, the study does not address the incremental value or clinical utility of the test for the management of CVD.

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Tschiderer et al. (2023) conducted a meta-analysis on the relationship between CIMT and incident carotid plaque. The study included 21,494 individuals without a history of CVD and without preexisting carotid plaque at baseline from 20 prospective studies in the Proof-ATHERO (Prospective Studies of Atherosclerosis) consortium. The overall mean of baseline common carotid artery IMT (CCA-IMT) values was 0.71 mm, with 15 studies reporting mean CCA-IMT values and five studies reporting maximum CCA-IMT values. Over a median follow-up of 5.9 years, 8,278 individuals developed first-ever carotid plaque. The authors combined study-specific ORs for incident carotid plaque using a random-effects meta-analysis. In subgroup analyses, there was no significant effect modification across clinically relevant subgroups. Baseline CCA-IMT was approximately log-linearly associated with the odds of developing carotid plaque. The age-, sex-, and trial arm–adjusted OR for carotid plaque per SD higher baseline CCA-IMT was 1.40. The corresponding OR that was further adjusted for ethnicity, smoking, diabetes, body mass index, systolic blood pressure, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), and lipid-lowering and antihypertensive medication was 1.34. A sensitivity analysis, restricted to studies defining plaque as focal thickening, yielded a comparable OR (1.38; 14 studies; 17,352 study individuals; 6,991 incident plaques). The authors concluded that the large-scale meta-analysis, based on individual-level data, showed that CCA-IMT is associated with the long-term risk of developing first-ever carotid plaque, independent of traditional cardiovascular risk factors. Limitations in the study were identified: the differences in how individual studies were defined and how CCA-IMT and carotid plaque were measured; exact time point of plaque development; inclusion of long-term studies from the 1990s to 2000s, which used older ultrasound devices; and use of two-dimensional carotid plaque data vs three-dimensional carotid plaque data. Furthermore, the study did not address the clinical utility of the test or how this technology alters individuals' management and improves clinical outcomes.

Nonterah et al. (2022) compared the association of established cardiovascular risk factors with CIMT, a subclinical marker of atherosclerosis, between African, African American, Asian, European, and Hispanic populations. A cross-sectional analysis of 15 cohorts that were drawn from Africa, Asia, Europe, and North America, with a total of 34,025 participants and a mean ±SD age of 52 ±5 years and crude CIMT of 0.69 ±0.14 mm, was conducted. The greatest CIMT adjusted for risk factors was among the African American populations, followed by the Asian, European, and Hispanic populations, with African populations having the lowest mean CIMT. Men had higher CIMT levels than women. Age, sex, body mass index, and systolic blood pressure had a significant positive association with CIMT in all races and ethnicities at varying magnitudes. Compared with European populations, the association of age, sex, and systolic blood pressure with CIMT was weaker in all races and ethnicities. In the Asian population, smoking, body mass index, and glucose had the strongest positive association with CIMT compared with all other racial and ethnic groups. In the African American and African populations only, HDL-C had significant protective effects. The authors concluded that the magnitude of the associations of CVD risk factors with CIMT has implications for ethnic-specific primary prevention strategies and can offer insights into racial- and ethnic-specific mechanisms involved in the pathogenesis of CVD. Limitations in the study include the small sample size of the Asian and Hispanic population, dietary intake data, and unavailability of medication use across all the studies. Furthermore, the incremental value of CIMT and its clinical utility in participants' care was not addressed.

Azcui Aparicio et al. (2021) conducted a systematic review to compare the predictive value of CIMT, carotid plaque identification, and coronary artery calcium (CAC) scoring for identifying subclinical atherosclerosis and assessing the future risk of CVD in asymptomatic, low- to intermediate-risk individuals. Overall, 30 studies (23 prospective cohort studies, one retrospective cohort study, one case-control study, and five cross-sectional studies) were included in the review, with 92,498 individuals. The follow-up duration in 11 studies was an average of 10.3 ±4.8 years, with a median duration of 6.0 years. The inclusion of CAC scores yielded the highest HR, ranging from 1.45 (95% CI, 1.11-1.88; p = 0.006) to 3.95 (95% CI, 2.97-5.27; p < 0.001), followed by maximum CIMT (HR, 1.08, 95% CI, 1.06-1.11, p < 0.001 to 2.58, 95% CI, 1.83-3.62, p < 0.001) and carotid plaque presence (HR, 1.21, 95% CI, 0.5-1.2, p = 0.39 to 2.43, 95% CI, 1.7-3.47, p < 0.001). The net reclassification index ranked higher with CAC (≥ 11.2%), followed by carotid plaque (≥ 2%) and CIMT (3%). The authors concluded that CAC scoring was superior compared with carotid plaque and CIMT measurements in asymptomatic study individuals who were classified as being at low to intermediate risk. A limitation that was identified in this systematic review is the heterogeneity of ultrasound markers used in different papers, especially those for CIMT. Additionally, this study did not address how CIMT alters individuals' management and improves clinical outcomes.

Liu et al. (2020) conducted a meta-analysis to confirm whether CIMT could serve as an accurate diagnostic method for CAD. Overall, 22 articles were included in the study. The sensitivity and specificity of IMT for diagnosing CAD were 0.68 (0.57-0.77) and 0.70 (0.64-0.75), respectively. The area under the curve was 0.74 (0.70-0.78). Subgroup analyses based on the cutoff value of IMT demonstrated a cutoff value of 1 mm to be a more accurate diagnostic criterion for CAD (sensitivity, 0.66; specificity, 0.79; area under the curve, 0.80). The pooled results for the sensitivity analysis were robust. A Deeks funnel plot indicated no significant publication bias (p = 0.195). The authors concluded that CIMT is a suggestable screening tool for CAD. Limitations in the study are the inclusion of less Asian population studies in

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comparison to the Caucasian population and significant heterogeneity in the sensitivity and specificity analyses. Additionally, the analyses did not address the clinical utility of the test in improving individuals' outcomes.

Willeit et al. (2020) conducted a meta-analysis of randomized clinical trials that explored CIMT progression as a surrogate marker for different types of CVD end points, defined as myocardial infarction, stroke, revascularization procedures, or fatal CVD. The study included 119 randomized controlled trials that involved 100,667 study individuals, with a mean follow-up of 3.7 years. Of those individuals, 12,038 developed the combined CVD end point. A 10-µm/y slower CIMT progression was associated with a relative risk (RR) of 0.91 (95% CI, 0.87-0.94) for the principal outcome of CVD. The interventions reduced the CVD risk and resulted in an RR of 0.92 (95% CI, 0.87-0.97), independent of their effects on CIMT progression. The authors estimated that interventions reducing CIMT progression by 10, 20, 30, or 40 µm/y would yield RRs of 0.84 (0.75-0.93), 0.76 (0.67-0.85), 0.69 (0.59-0.79), or 0.63 (0.52-0.74), respectively. The authors concluded that the effects of interventions on CIMT progression and on CVD risk are associated. Study limitations were identified. The type of therapeutic intervention was different across the included trials, which may affect the CIMT surrogate value, and the individuals had different comorbidities. However, this study did not address how integrating the measurement of CIMT into clinical care alters individuals' management and improves clinical outcomes.

Kumar et al. (2020) conducted a meta-analysis to clarify the association between CCA-IMT and the risk of stroke. The study included 19 studies, with 16 studies involving 3,475 ischemic stroke (IS) cases and 11,826 controls; six studies with 902 large-vessel disease and 548 small-vessel disease of IS subtypes; and five studies with 228 intracerebral hemorrhage and 1,032 IS cases. The authors reported that the results showed an association between increased CCA-IMT with the risk of IS compared with control individuals [standardized mean difference (SMD), 1.46; 95% CI, 0.90-2.02]. There was an increased risk of large-vessel disease compared with the small-vessel disease subtype of IS (SMD, 0.36; 95% CI, 0.19-0.52) and more chance of occurrence of IS rather than intracerebral hemorrhage (SMD, 0.71; 95% CI, 0.28-1.41). The authors concluded that carotid intima thickness measurements are associated with the risk of stroke and may be used as a diagnostic marker for predicting the risk of stroke events. Prospective studies, embedded with a larger sample size, are needed to validate the findings.

Advanced Lipoprotein Analysis

Studies report inconsistent results regarding the incremental benefit of advanced lipoprotein testing over conventional risk factors or its clinical utility in changing management and improving clinical outcomes. Research has shown a lack of universal, standardized testing modalities and selection criteria for individuals. Additional large, prospective studies are needed to establish whether measurement of these markers will be more predictive of CVD than conventional lipid risk factors.

The Emerging Risk Factors Collaboration assessed whether adding various emerging lipid markers to total cholesterol and HDL-C improved CVD risk prediction. Records were evaluated from 165,544 individuals without baseline CVD from 37 cohort studies in which apolipoprotein B (apoB) and apoA1, lipoprotein(a), or lipoprotein-associated phospholipase A_2 (Lp-PLA_2) was measured. Individuals received follow-up for 10 years, during which 15,126 CVD-related fatal and nonfatal outcomes occurred. The main outcome measures were CVD outcomes and low- (< 10%), intermediate- (10% to < 20%), and high-risk (≥ 20%) prediction. The authors concluded that replacing total lipid panels with various lipid biomarkers did not significantly improve CVD risk prediction. (Di Angelantonio et al., 2012)

Lipoprotein-Associated Phospholipase A_2

Given the low-quality evidence, no conclusions can be drawn regarding the clinical utility of Lp-PLA_2 alone or in combination with other traditional biomarkers and/or risk assessments to determine the risk of CHD events in healthy or asymptomatic individuals. Additional well-designed clinical trials are necessary to establish the clinical utility of Lp-PLA_2 and sPLA_2-IIA for cardiovascular risk assessment and to determine the role of Lp-PLA_2 as a potential adjunct to traditional risk assessment in the management of CVD or stroke in adults.

Huang and Zhu (2025) conducted a meta-analysis of studies to analyze the diagnostic value of Lp-PLA_2 as a biomarker of atherosclerotic plaque stability. A total of 22 articles (containing 1,110 stable plaque cases and 1,298 unstable plaque cases) met the meta-analysis criteria. The primary study focuses included CAD (n = 5), acute IS (n = 6), anterior circulation cerebral infarction (n = 2), carotid atherosclerosis (n = 8), and cerebral infarction (n = 1). By evaluating pooled data from diverse individual cohorts and vascular territories, the authors sought to clarify the data's clinical relevance, address discrepancies in the existing literature, and explore sources of heterogeneity, such as comorbid conditions and methodological variations. The findings could influence future guidelines for risk assessment and therapeutic targeting in high-risk populations. The authors concluded that this meta-analysis synthesizes the current evidence on the diagnostic value of Lp-PLA_2 for atherosclerotic plaque stability, providing a comprehensive evaluation of its clinical relevance across diverse individual cohorts and vascular territories, to ensure better stratification of intermediate-risk individuals for targeted

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treatment. The pooled results from 22 studies (1,110 stable plaque cases and 1,298 unstable plaque cases) demonstrate that Lp-PLA_2 exhibits significant diagnostic accuracy for plaque stability assessment. These findings suggest that Lp-PLA_2 is a promising biomarker for identifying vulnerable plaques, which are critical in predicting acute cardiovascular events. Limitations of the study include substantial heterogeneity across studies, necessitating future large-scale studies that use consistent techniques and diagnostic thresholds. More prospective studies, with well-defined criteria and long-term follow-up, are essential to solidify the findings and address the clinical utility of the test. The clinical utility of the test and how it impacts individuals' care were not addressed in this publication.

Zhang et al. (2021) performed a prospective study to investigate the association between CVD and Lp-PLA_2. Overall, 823 participants who were at a high risk of stroke were screened and followed up at 3, 6, 12, and 24 months. Among the 823 participants, 286 had varying degrees of carotid artery stenosis, and 18 had cerebrovascular events. The level of Lp-PLA_2 was higher in the group with cerebrovascular events than in the group without cerebrovascular events (662.81 ±111.25 vs 559.86 ±130.05; $p < 0.001$). No statistical difference was found between the other parameters of the event group, such as HDL and LDL, and the no-event group. The incidence of cerebrovascular events in the stenosis group was higher than that in the no-stenosis group, but no statistically significant difference was noted. The authors concluded that the level of Lp-PLA_2 was positively correlated with the degree of carotid artery stenosis and predicted cerebrovascular events. There were some limitations of the study that were noted by the authors. The sample size was not large, the follow-up time was only 2 years, and the number of cerebrovascular events that eventually occurred was relatively small. The study was conducted at a single center, and the study population mainly included people aged > 40 years at a high risk of stroke, so the results of the study only represented a small part of the population. Furthermore, the study did not address how integrating measurements of Lp-PLA_2 into clinical care alters individuals' management and improves clinical outcomes.

Hu et al. (2019) conducted a meta-analysis to determine whether elevated Lp-PLA_2 is a risk factor for stroke. Overall, 22 studies, involving 157,693 individuals, were included for analysis. The RRs for overall stroke with 1 SD higher Lp-PLA_2 activity and mass were 1.07 (95% CI, 1.02-1.13) and 1.11 (95% CI, 1.04-1.19), respectively. The RRs for IS with 1 SD higher Lp-PLA_2 activity and mass were 1.08 (95% CI, 1.01-1.15) and 1.11 (95% CI, 1.02-1.22), respectively. When comparing the highest and lowest levels of Lp-PLA_2, the RRs for stroke for Lp-PLA_2 activity and mass were 1.26 (95% CI, 1.03-1.54) and 1.56 (95% CI, 1.21-2.00), respectively. When comparing the highest and lowest levels of Lp-PLA_2, the pooled RRs for IS for Lp-PLA_2 activity and mass were 1.29 (95% CI, 1.07-1.56) and 1.68 (95% CI, 1.12-2.53), respectively. The authors concluded that elevated Lp-PLA_2 levels are associated with a higher stroke risk. The authors identified some study limitations. The test methods for Lp-PLA_2 were not uniform in the included studies, which is a potential source of bias, and there was a lack of studies in individuals who were aged ≥ 65 years. Lp-PLA_2, as a therapeutic target to prevent stroke, requires further investigation. Furthermore, the study did not address how integrating measurements of Lp-PLA_2 into clinical care alters individuals' management and improves clinical outcomes.

Benderly et al. (2017) performed a study to evaluate the relevance of Lp-PLA in risk prediction among individuals with CHD. Lp-PLA activity was measured in 2,538 individuals with CHD who were included in the Bezafibrate Infarction Prevention study. With adjustment for study individuals' characteristics and traditional risk factors, 1 SD of Lp-PLA was associated with an HR of 1.12 (95% CI, 1.00-1.25) for mortality and 1.03 (0.93-1.14) for cardiovascular events. The authors concluded that Lp-PLA did not significantly improve model discrimination or calibration and that the results do not support the added value of Lp-PLA for predicting cardiovascular events or mortality among individuals with CHD beyond the traditional risk factor.

Younus et al. (2017) performed a systematic review to clarify the relationship between Lp-PLA_2 and subclinical CVD, as defined by CAC, CIMT, and endothelial function. Overall, 13 studies were included in the review; six examined the relationship between Lp-PLA_2 and coronary artery calcification, of which three showed a significant correlation. Two studies examined the relationship between Lp-PLA_2 and endothelial dysfunction, and one reported a significant relationship. Five studies investigated the association of Lp-PLA_2 with CIMT, and three reported a significant relationship. The authors concluded that this review showed a variable association between Lp-PLA_2 and subclinical disease and that the results do not conclusively support the use of Lp-PLA_2 in the diagnosis and management of subclinical CVD. Future research is needed to clarify what role Lp-PLA_2 has in guiding treatment.

Li et al. (2017a) conducted a systematic review with meta-analysis to investigate the associations between Lp-PLA_2 and the long-term risks of CHD and IS in the general population. Overall, 12 prospective cohort studies were included. Combined HRs for CHD and IS risks for the highest category referring to the lowest category of Lp-PLA_2 were 1.46 and 1.58, respectively. The same patterns were observed for both mass and activity, with the exception of those for CHD. For every 1 SD increase in Lp-PLA_2 activity, CHD risk increased by 12%; no association between 1 SD increases in Lp-PLA_2 activity and IS was observed. Lp-PLA_2 mass was associated with CHD risk. Lp-PLA_2 mass per 1 SD increase was not associated with IS risk. The authors concluded that greater Lp-PLA_2 activity or mass was associated with an increased risk of CHD and IS; however, additional well-designed trials are warranted to confirm this association.

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Tian et al. (2017) conducted a systematic review and meta-analysis to assess the associations of Lp-PLA_2 levels (mass and activity) with recurrent vascular events in individuals with TIA and/or first IS and with stroke in the general population. Overall, 11 studies that comprised 20,284 individuals (4,045 were individuals with TIA and/or first IS, and 16,239 were residents in the general population) were identified. The pooled RR for recurrent vascular events (467 cases) in the TIA and/or first ischemic group was 2.24, whereas the pooled RR for stroke (1,604 cases) in the general population was 1.47. The pooled RRs for Lp-PLA_2 mass and activity levels with the risk of stroke in the general population were 1.69 and 1.28, respectively. The authors concluded that in individuals with TIA and first IS, elevated Lp-PLA_2 activity levels were associated with recurrent vascular events; in the general population, elevated Lp-PLA_2 levels were associated with the risk of stroke.

Multiprotein Blood Test With Algorithm and Reported as a Risk Score

There is a lack of quality clinical evidence to conclude that multiprotein blood tests with algorithm and reported as a risk score are effective for the screening or management of CVD. While existing studies suggest correlations between scores and risks, the clinical utility of the tests has not been addressed convincingly.

Neumann et al. (2024) conducted an individual-level analysis of cardiovascular biomarker data from 28 general population cohorts from 12 countries and four continents. The analysis included 164,054 individuals, with a median age of 53.1 years; 52.4% were women. The median follow-up was 11.8 years. Measurement of high-sensitivity cardiac troponin I (hs-cTnI), high-sensitivity cardiac troponin T, N-terminal pro B-type natriuretic peptide (NT-proBNP), BNP, or high-sensitivity C-reactive protein was analyzed for the primary outcome of incident atherosclerotic CVD (ASCVD) and secondary outcomes, including heart failure, IS, and myocardial infarction. The authors concluded that cardiovascular biomarkers were strongly associated with the secondary outcomes of nonfatal and fatal cardiovascular events and mortality. However, the addition of biomarkers to established risk factors led to only a minimal improvement in risk prediction metrics for ASCVD. Five established biomarkers that are widely available in clinical practice were analyzed; however, the absolute measurements for high-sensitivity cardiac troponin T and BNP were limited. Limitations of the study include its lack of addressing the clinical utility of the test to improve clinical outcomes.

A Hayes (2023) Evidence Analysis Research Brief on the HART CADhs blood test (Prevencio Inc.) was used to predict the risk of obstructive CAD and sought to summarize the volume of publications to determine whether there is adequate published, peer-reviewed literature to evaluate the HART CADhs blood test (Prevencio Inc.). Hayes's findings suggest that there currently is not enough published, peer-reviewed literature to evaluate the evidence related to the HART CADhs blood test (Prevencio Inc.) to predict the risk of obstructive CAD in a full assessment. One cross-sectional study was identified, but no clinical utility studies evaluating HART CADhs for the prognosis of obstructive CAD were identified.

Mohebi et al. (2023) conducted a study using a panel of biomarkers developed via targeted proteomics to stratify the risk of developing a cardiovascular event (cardiovascular event: incident myocardial infarction, stroke, or cardiovascular death) following coronary angiography. The inclusion criteria included 446 individuals with chronic kidney disease (CKD) over a 2-year follow-up period. The four biomarkers (kidney injury molecule-1, NT-proBNP, osteopontin, and tissue inhibitor of metalloproteinase-1) were integrated into a prognostic algorithm to predict cardiovascular events. Overall, 74 cardiovascular events were discovered; 51 events occurred in stage 1 to 2 CKD, and 23 events occurred in stage 3 to 5 CKD. The C statistic for predicting 2-year cardiovascular events in all 446 individuals was 0.77. Individuals at cardiovascular event lower risk in each CKD staging group were used as a reference, and the HR (95% CI) of cardiovascular events was 2.82 for CKD stage 1 to 2/cardiovascular event higher risk and 8.32 for CKD stage 3 to 5/cardiovascular event higher risk. The authors concluded that biomarker panels prior to coronary catheterization may be useful to individualize cardiovascular event risk assessment among individuals with CKD. A limitation of the study is its failure to address the clinical utility of the test to improve clinical outcomes.

Cheng et al. (2022) conducted a systematic review and meta-analysis of studies that evaluated the relationship of cholesterol efflux capacity (CEC) with CAD and cardiovascular mortality in a general population. Overall, 18 observational studies were included. Compared with the non-CAD group, the CAD group (SMD, -0.48; 95% CI, -0.66 to -0.30; I^2 = 88.9%) had significantly lower CEC. In the high-CEC population, the risks of CAD (OR, 0.52; 95% CI, 0.37-0.71; I^2 = 81%) significantly decreased, and a linear negative dose response was detected. However, an association between CEC and the risk of cardiovascular mortality was not found (OR, 0.44; 95% CI, 0.18-1.06; I^2 = 83.2%). The authors concluded that first, CEC values were significantly lower in the CAD group than in the non-CAD group; second, the reduced CEC values were significantly associated with the risk of CAD; and third, there was not a significant correlation between CEC values and the risk of cardiovascular mortality. In conclusion, the authors stated that decreased CEC is strongly associated with a risk for CAD, independent of HDL-C level. However, decreased CEC did not seem to be related to cardiovascular mortality. Additionally, the authors concluded that CEC is negatively correlated with the risk of CAD in a linear manner. The researchers noted that most of the cohorts included U.S. and Asian individuals, with the inclusion of only a few European individuals and no individuals from other regions, which was a limitation of the study. Additional study limitations

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include failure to assess the incremental value of the test, its clinical utility to improve patient-centered outcomes, and its combination with other risk factors to derive a score.

Lee et al. (2021) conducted a systematic review and meta-analysis of studies that evaluated the association of CEC and adverse cardiovascular events. The researchers stated that serum HDL-C levels are inversely associated with CVD events but that emerging evidence suggests that it is the functional properties of HDL, particularly reverse cholesterol transport, that are an important protective mechanism mediating cholesterol removal from macrophage cells and reducing plaque lipid content. CEC measures the capacity of HDL to perform this function. The authors included a total of 20 trials. Ten studies included individuals with cardiovascular risk factors, four studies included individuals with CKD, and six studies included general populations without cardiovascular risk factors or CKD. The researchers stated that increased CEC was significantly associated with reduced adverse cardiovascular events. A significant CEC adverse cardiovascular RR relationship was observed ($p = 0.024$), such that for every 0.1-unit increase in CEC, there was a 5% reduced risk for adverse cardiovascular events (RR, 0.95; 95% CI, 0.91-0.99). In this meta-analysis study, higher CEC levels were associated with favorable cardiovascular outcomes. Compared with the lowest CEC group, the highest CEC group had a 37% and 34% reduced risk of adverse cardiovascular events and ASCVD, respectively. Although the association of CEC with mortality was not statistically significant, the analysis demonstrated that there may be a trend toward lower mortality with higher CEC. With the possibility that the choice of CEC assay may influence its association with adverse cardiovascular outcomes, the gold standard for measuring CEC in individuals has not yet been established. Limitations in this meta-analysis include the follow-up duration, as well as case definitions for adverse cardiovascular events and ASCVD, as they varied in the reviewed studies. Therefore, this analysis was unable to determine the association of CEC with specific components of the composite end points. Additionally, the cutoff value for defining high vs low CEC varied across the included few studies that were available for review. The study demonstrated an inverse relationship between CEC levels, quantitative measure of HDL functionality, and risk of adverse cardiovascular events or ASCVD. The study limitations include its failure to investigate the incremental value of the test or its clinical utility to improve outcomes or combination with other risk factors to derive a score.

McCarthy et al. (2020) conducted an observational study in participants referred for coronary angiography; predictors of ≥ 70% coronary stenosis were identified from six clinical variables and 109 biomarkers. The study population included CASABLANCA (Catheter Sampled Blood Archive in Cardiovascular Diseases) derivation (n = 636) and internal validation (n = 275) cohorts. An externally validated cohort in the BACC (Biomarkers in Acute Cardiac Care) study included 241 study participants presenting to the emergency department with suspected acute myocardial infarction; ≥ 50% coronary stenosis was considered significant. The resulting model consisted of three clinical variables (male sex, age, and previous PCI) and three biomarkers (hs-cTnI, adiponectin, and kidney injury molecule-1). In the internal validation cohort, the model yielded an area under the receiver operating characteristic curve (AUC) of 0.85 for coronary stenosis of ≥ 70%. Dividing the risk score result into five levels resulted in a positive predictive value of 97% and a negative predictive value of 89% at the highest and lowest levels, respectively. In the external validation cohort, the score performed was similar, with an AUC of 0.86. In participants who had myocardial infarction neither ruled out nor ruled in via hs-cTnI testing (indeterminate zone; n = 65), the score had an AUC of 0.88. The authors concluded that a model inclusive of hs-cTnI can predict the presence of obstructive CAD across a wide variety of individuals with high accuracy, including those with indeterminate hs-cTnI concentrations. Limitations include single-point-in-time measurements of biomarkers and obstructive CAD definitions that differed in each cohort; additionally, the study did not address how the use of this model improves clinical outcomes or the management of CVD. (This review is included in the Hayes, 2023, Evidence Analysis Research Brief.)

Neumann et al. (2020) performed a retrospective review to apply a novel risk prediction model in a cohort of patients who presented to the emergency department with symptoms that were suggestive of myocardial infarction. Four biomarkers (NT-proBNP, kidney injury molecule-1, osteopontin, and tissue inhibitor of metalloproteinase-1) were tested in 750 patients. The end point was a composite of incident myocardial infarction or cardiovascular mortality. Overall, 22 study patients had a MACE within 1 year. The median concentration of kidney injury molecule-1 was 0.075 ng/mL compared with 0.024 ng/mL in patients with or without a MACE, respectively; the median concentration of NT-proBNP was 8,500 pg/mL compared with 870 pg/mL in patients with or without a MACE; the median concentration of osteopontin was 62 ng/mL compared with 30 ng/mL in patients with or without a MACE; and the median concentration of tissue inhibitor of metalloproteinase-1 was 152 ng/mL compared with 90 ng/mL in patients with or without a MACE. The authors concluded that the study validated the high accuracy of a multiple-biomarker panel to predict incident cardiovascular events in patients with suspected myocardial infarction. Study limitations include a small absolute number of observed cardiovascular events and an overall sample size that was limited to 750 patients, which could impact the significance of the findings. The study is limited by its retrospective observations, and the design did not allow for assessment of whether the use of the score impacted care or patients' outcomes.

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Clinical Practice Guidelines

American Association of Clinical Endocrinology (AACE)

A 2025 AACE updated consensus statement of the algorithm for the management of adults with dyslipidemia makes the following recommendation:

- For primary ASCVD prevention, individuals with dyslipidemia should be assessed using a validated risk assessment tool.
- Individuals for both primary and secondary prevention should be counseled on enduring lifestyle changes to address lipid and nonlipid ASCVD risk factors.
- The routine use of nontraditional risk markers, including apoB, does not provide meaningful improvement in risk prediction; however, the use of nontraditional risk markers in young adults with a family history of premature ASCVD may be beneficial in risk prediction.

(Patel et al., 2025)

The 2017 AACE guidelines for the management of dyslipidemia and prevention of CVD make the following recommendations:

- CIMT: CIMT may be considered to refine risk stratification to determine the need for more aggressive ASCVD preventive strategies (intermediate level of evidence and recommendation grade).
- ApoB: For individuals at an increased risk of ASCVD, including those with diabetes, an optimal apoB goal is < 90 mg/dL, while for individuals with established ASCVD or diabetes plus one or more additional risk factor(s), an optimal apoB goal is < 80 mg/dL; for individuals at extreme risk, an optimal apoB goal is < 70 mg/dL (strong level of evidence and recommendation grade).
- Lp-PLA_2: Measuring Lp-PLA_2 in some studies has demonstrated more specificity than high-sensitivity C-reactive protein when it is necessary to further stratify an individual's ASCVD risk, especially in the presence of high-sensitivity C-reactive protein elevations (strong level of evidence and recommendation grade).

American College of Cardiology (ACC)/American Heart Association (AHA)

A 2019 ACC/AHA guideline on the primary prevention of CVD identifies the following risk-enhancing factors for clinician-individual risk discussion:

- Lipids/biomarkers associated with increased ASCVD risk:
  - Persistently elevated primary hypertriglyceridemia (≥ 175 mg/dL, nonfasting)
  - If measured:
    - Elevated high-sensitivity C-reactive protein (≥ 2.0 mg/L)
    - Elevated apoB (≥ 130 mg/dL): A relative indication for its measurement would be triglyceride of ≥ 200 mg/dL; a level of ≥ 130 mg/dL corresponds to an LDL-C of > 160 mg/dL and constitutes a risk-enhancing factor
    - ABI (< 0.9)

A 2013 ACC/AHA guideline on the assessment of initial CVD event risk states that CIMT is not recommended for routine measurement in clinical practice for initial CVD event risk assessment.

The 2010 ACC/AHA Task Force made the following recommendations on assessing cardiovascular risk in asymptomatic adults:

- Arterial compliance: The ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that measures of arterial stiffness outside of research settings are not recommended (class III; level of evidence C recommendation, no benefit; limited populations evaluated).
- CIMT: The ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that measurement of carotid artery IMT is reasonable for asymptomatic adults at an intermediate risk. Published recommendations on the required equipment, technical approach, operator training, and experience for performance of the test must be carefully followed to achieve high-quality results (class IIa; level of evidence B recommendation, conflicting evidence), but the panel recommends in favor of testing.
- Advanced lipoprotein analysis: The ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that the measurement of lipid parameters, including lipoproteins and apolipoproteins beyond a standard fasting lipid profile, is not recommended (class III; level of evidence C recommendation, no benefit; limited populations evaluated).
- Lp-PLA_2: The ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that Lp-PLA_2 might be reasonable for cardiovascular risk assessment in intermediate-risk, asymptomatic adults. The report also states that at this time, there is no information indicating that Lp-PLA_2 levels are clinically effective for motivating

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individuals, guiding treatment, or improving outcomes (class IIb; level of evidence B, conflicting evidence), and the usefulness/efficacy of the test are less well established.
(Greenland et al., 2010)

American Diabetes Association (ADA)

A 2024 update to the ADA 2022 guideline on CVD and risk management states that risk scores and other cardiovascular biomarkers have been developed for risk stratification of secondary prevention individuals (i.e., those who are already high risk because they have ASCVD) but are not yet in widespread use. Individuals with diabetes are at an increased risk of the development of asymptomatic cardiac structural or functional abnormalities. Screening asymptomatic adults with diabetes by measurement of natriuretic peptides, including BNP or NT-proBNP levels, may facilitate comprehensive cardiovascular risk reduction. The biomarker threshold for abnormal values is a BNP level of ≥ 50 pg/mL and NT-proBNP level of ≥ 125 pg/mL. Abnormal levels of natriuretic peptide will need to be evaluated in the context of each person using clinical judgment, as various comorbidities can increase or decrease natriuretic peptide levels, thus impairing sensitivity of testing. With newer, more expensive lipid-lowering therapies now available, use of these risk assessments may help target these new therapies to higher-risk individuals with ASCVD in the future.

American Heart Association (AHA)/American College of Cardiology (ACC)/American Association of Cardiovascular & Pulmonary Rehabilitation (AACVPR)/American Academy of Physician Associates (AAPA)/Association of Black Cardiologists (ABC)/American College of Preventive Medicine (ACPM)/American Diabetes Association (ADA)/American Geriatrics Society (AGS)/American Pharmacists Association (APhA)/American Society for Preventive Cardiology (ASPC)/National Lipid Association (NLA)/Preventive Cardiovascular Nurses Association (PCNA)

A 2026 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of dyslipidemia has made new practice-changing recommendations since the last iteration of the guideline on the measurement of apoB. The recommendations state that apoB measurement may be useful to improve risk assessment and guide therapy once LDL-C and non–HDL-C goals are met, particularly in individuals with elevated triglycerides of ≥ 200 mg/dL, diabetes, or low achieved LDL-C (< 70 mg/dL). A persistent elevation of apoB can be considered a risk-enhancing factor.

American Heart Association (AHA)/American Stroke Association (ASA)

The 2024 AHA/ASA guidelines on the primary prevention of stroke recommend the following:

- Screening and addressing adverse social determinants to identify and treat stroke risk factors
- Adults with no prior CVD and those with high or intermediate risk adhere to the Mediterranean diet
- Physical activity is essential for cardiovascular health and stroke risk reduction
- Use of glucagon-like protein-1 receptor agonists in individuals with diabetes and high cardiovascular risk or established CVD
- Combination of at least two antihypertensive medications for most individuals who require pharmacological treatment of hypertension
- Antiplatelet therapy in individuals with antiphospholipid syndrome or systemic lupus erythematosus without a history of stroke or unprovoked venous thromboembolism
- Screening and management of hypertension during pregnancy
- Evaluation and management of vascular risk factors in individuals with endometriosis, premature ovarian failure, and early-onset menopause
- Evaluation and modification of risk factors in transgender women taking estrogens could be beneficial

Additionally, the 2024 AHA/ASA guidelines on the primary prevention of stroke state that the following risk-enhancing factors qualify for treatment with lipid therapy for primary stroke prevention:

- Primary hypertriglyceridemia
- Elevated high-sensitivity C-reactive protein
- Elevated apoB
- ABI of < 0.9

(Bushnell et al., 2024)

American Society for Clinical Pathology (ASCP)

The ASCP recommends against routinely ordering expanded lipid panels (particle sizing or nuclear magnetic resonance) as screening tests for CVD. (ASCP, 2020)

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Canadian Society of Clinical Chemists (CSCC)/Canadian Cardiovascular Society (CCS)

The 2022 CSCC clinical laboratory lipid-reporting recommendations, based on the 2021 CCS guidelines on the management of dyslipidemia for the prevention of CVD in the adult, state the following:

- Recommend that laboratories offer nonfasting and fasting lipid assessment
- Recommend that laboratories offer a lipid panel that consists of total cholesterol, LDL-C, HDL-C, non–HDL-C, and triglycerides; apoB should be offered only as an individually orderable test
- Recommend that laboratories adopt a lipid-reporting format that includes lipid decision thresholds on the basis of lipid screening in primary prevention individuals
- Include minimal interpretive comments on the lipid report with reference to the 2021 CCS guidelines, where applicable
- Recommend implementation of the new National Institutes of Health equation, rather than the Friedewald equation, for calculating LDL-C in all individuals

(White-Al Habeeb et al., 2022)

Endocrine Society (ES)

In a clinical guideline on lipid management in individuals with endocrine disorders, the ES states that advanced lipid testing may be helpful in further characterizing lipid abnormalities, but studies have not provided conclusive evidence that measurement of particle size or density adds to CVD prediction beyond the standard lipid risk factors. (Newman et al., 2020)

National Lipid Association (NLA)

An expert clinical consensus was issued in 2024 regarding the role of apoB measurement in the clinical management of cardiovascular risk in adults. ApoB has been shown to be superior to LDL-C in risk assessment, both before and during treatment with lipid-lowering treatment. In individuals, there can be discordance between levels of LDL-C and apoB, as well as LDL-C and 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, ASCVD risk generally aligns better with apoB or non–HDL-C. ApoB measurement is particularly useful to improve risk assessment at both the lower and higher ends of the LDL-C range. ApoB, along with total cholesterol and triglycerides, 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. (Soffer et al., 2024)

A 2021 scientific statement from the NLA on lipid measurements in the management of CVDs, practical recommendations, notes the following key points:

- LDL-C and non–HDL-C have benefits in assessing ASCVD risk and residual risk.
- LDL particle number assays are not standardized but may help guide treatment in persons after initial lipid evaluation in select individuals.
- Further research is needed for advanced lipoprotein tests (e.g., LDL particle number, small dense LDL-C, remnant cholesterol) due to the lack of appropriate standardization, and cross-comparison of these tests using different measurement techniques is difficult.

(Wilson et al., 2021)

U.S. Preventive Services Task Force (USPSTF)

The USPSTF 2018 recommendation statement on screening for peripheral artery disease and CVD risk assessment with the ABI concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for peripheral artery disease and CVD risk with the ABI in asymptomatic adults.

Department of Veterans Affairs/Department of Defense (VA/DOD)

The VA/DOD 2025 clinical practice guidelines on the management of dyslipidemia for cardiovascular risk reduction in individuals who are 18 years or older and have or are at risk for CVD note that for the management of dyslipidemia for cardiovascular risk reduction, the routine measurement of high-sensitivity C-reactive protein, apoB, polygenic risk scores, total carotid plaque area, or ABI is not useful to refine cardiovascular risk.

U.S. Food and Drug Administration (FDA)

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Noninvasive blood pressure measurement system products such as the CVProfilor are numerous. Search by product code DXN to view devices: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed June 23, 2026)

Measurement of carotid intima-media thickness is a procedure and not subject to FDA regulation. B-mode ultrasound equipment used to measure carotid intima-media thickness is regulated by the FDA, but products are too numerous to list. Refer to the following website for more information (use product code IYO): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed June 23, 2026)

Advanced lipoprotein analysis must be performed in accordance with the quality standard established in 1988 by the Clinical Laboratory Improvement Amendments.

Products used to measure lipoprotein(a) are too numerous to list. Refer to the following website for more information (use product code DFC): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed June 23, 2026)

Products for the measurement of lipoprotein-associated phospholipase A_2 can be found with product codes NOE and JJX at the following site: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed June 23, 2026)

The SphygmoCor System (ATCOR Medical) is a series of noninvasive blood pressure monitoring devices that are intended to help clinicians manage hypertensive and prehypertensive patients by providing central arterial pressure waveform analysis and calculations of central arterial blood pressure and arterial stiffness. The SphygmoCor XCEL system was cleared by the FDA in November 2012 (K122129). Several additional 510(k) clearances had been granted earlier by the FDA. The predicate device was the SphygmoCor CVMS, which was cleared in August 2007 (K070795). Refer to the following website for more information: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K122129. (Accessed June 23, 2026)

The CorVista System is a coronary artery disease machine learning–based notification software system consisting of one or more noninvasive physiological inputs for coronary artery disease detection or classification. The CorVista System (K232686) was cleared by the FDA on September 8, 2023. Search by product code QXX. Refer to the following website for more information: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K232686. (Accessed June 23, 2026)

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Policy History/Revision Information

Date	Summary of Changes
11/01/2026	**Coverage Rationale** • Updated list of unproven and not medically necessary indications; replaced “advanced lipoprotein analysis [*e.g., lipoprotein(a),* subfractions, or particle size] as a method to determine risk for cardiovascular disease” with “subfractions or particle size advanced lipoprotein analysis as a method to determine risk for cardiovascular disease” **Applicable Codes** • Removed CPT code 83695 **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information • Archived previous policy version SRST2026T0389FF

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