Cardiovascular Disease Risk Tests

Policy Number: 2026T0389EE
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➲ Instructions for Use

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Related Commercial/Individual Exchange Policy

- Genetic Testing for Cardiac Disease

Community Plan Policy

- Cardiovascular Disease Risk Tests

Application

UnitedHealthcare Commercial

This Medical Policy applies to UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans.

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
- Advanced lipoprotein analysis [e.g., lipoprotein(a), subfractions, or particle size] 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
- Endothelial function assessment using tools such as peripheral arterial tonometry (PAT) or brachial artery pressure ultrasound as a prognostic indicator to determine risk of cardiovascular disease
- 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
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
83695	Lipoprotein (a)
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
93799	Unlisted cardiovascular service or procedure
93895	Quantitative carotid intima media thickness and carotid atheroma evaluation, bilateral
93998	Unlisted noninvasive vascular diagnostic study

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.

Arterial endothelial dysfunction and endothelial damage, which play an important role in the atherosclerotic process, may result in reduced arterial compliance (elasticity) or increased arterial stiffness, especially in the smaller arteries. Arterial compliance can be measured by several techniques, many of which are invasive or clinically inappropriate. Direct methods include magnetic resonance imaging and ultrasound. Indirect methods include pulse wave velocity and

augmentation index. At this time, there is no gold standard for arterial compliance measurement. Cardiovascular profiling using blood pressure waveform analysis (the rate at which pressure rises and falls during the cardiac cycle) provides a noninvasive assessment of arterial compliance. It is used for both large and small arteries by calculating pulse pressure, body surface area, and body mass index to determine arterial compliance indices. These indices have been proposed as early indicators of cardiovascular disease. Other noninvasive prognostic tools to assess endothelial functioning have been introduced as adjuncts to standard cardiovascular disease risk assessments (Roman et al., 2006). Specifically, these tools attempt to further stratify the risk of cardiovascular morbidity while refining disease prevention measures. Two such assessment approaches involve the use of artery ultrasound testing and peripheral arterial tonometry using a fingertip pulse amplitude tonometry device. Brachial artery ultrasound uses high-resolution ultrasound to assess changes in vascular dimensions, while pulse amplitude tonometry records finger arterial pulse wave amplitude in response to reactive hyperemia. Increased finger pulse amplitude is posited to be a complex response to ischemia and reflects changes in digital flow and digital vessel dilation (Kuvin et al., 2007; Hamburg et al., 2008).

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). Three major classes of lipoproteins are found in the serum of a fasting individual: low-density lipoproteins, high-density lipoproteins (HDLs), and very low-density lipoproteins. Low-density lipoprotein cholesterol typically makes up 60% to 70% of the total serum cholesterol and contains a single apolipoprotein, namely apo B-100. HDL cholesterol normally makes up 20% to 30% of the total serum cholesterol. The major apolipoproteins of HDL are apo A-I and apo A-II. The very low-density lipoproteins are triglyceride-rich lipoproteins but contain 10% to 15% of the total serum cholesterol. Apolipoprotein, lipoprotein(a), and lipoprotein-associated phospholipase A_2 (Lp-PLA_2) are risk factors being evaluated for their ability to predict cardiovascular disease or ischemic stroke (National Heart, Lung, and Blood Institute, 2002).

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 (Holmes et al., 2013).

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, 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.

In a systematic review and meta-analysis of 20 studies involving 381,303 individuals aged 18 years and above, Li et al. (2025) assessed 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 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, 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.

In a systematic review and meta-analysis, Sequí-Domínguez et al. (2020) sought to estimate PWV and cfPWV performance, predicting 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 review, and due to the limited studies measuring brachial-ankle PWV, only studies measuring 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 point to the summary point was 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 evaluating 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.

Cheng et al. (2016) evaluated the prognostic value and clinical utilities of pulse wave analysis–derived mechanical biomarkers in two independent, population-based cohorts. Pulse wave analysis on central arterial pressure waveforms were obtained from participants without a prior history of CVDs. The two studies were the Kinmen study (1,272 participants; median follow-up of 19.8 years) and the CVDFACTS (Cardiovascular Disease Risk Factors Two-Township Study; 2,221 participants; median follow-up of 10 years). In the Kinmen study, right carotid artery pressure waveforms, which have been demonstrated to closely resemble central aortic pressure waveforms, were registered noninvasively with a tonometer. In the CVDFACTS study, central aortic pressure waveforms were obtained with a SphygmoCor device using radial arterial pressure waveforms. The associations between all mechanical biomarkers derived from pulse wave analysis and cardiovascular mortality were then examined in the multivariate Cox proportional hazards models that took into account cardiovascular risk factors, including age, sex, systolic blood pressure, body mass index, fasting glucose, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and smoking. Only the systolic and diastolic rate constant of reservoir pressure could independently and consistently predict cardiovascular mortality in both cohorts. Cardiovascular mortality was higher in the Kinmen study due to higher hypertension prevalence and more male participants. During a median follow-up of 19.8 years, 315 deaths (26.9%) occurred (84 of cardiovascular origin). In the CVDFACTS study, a total of 171 deaths occurred (34 of cardiovascular origin) during a median follow-up of 10 years. Increased brachial systolic blood pressure, pulse pressure, backward wave amplitudes (Pb), and augmentation index (AIx) were significantly associated with increased cardiovascular mortality in both studies. Biomarkers derived from reservoir pressure wave analysis were positively associated with cardiovascular mortality in the Kinmen study, and in the CVDFACTS study, only peak of reservoir pressure and diastolic rate constant remained significant in predicting cardiovascular mortality. The authors concluded that these findings suggest that mechanical biomarkers derived from pulse wave analysis could not only independently predict the long-term cardiovascular risks beyond the traditional risk factors but also provide more accurate risk stratification by incorporating these mechanical biomarkers into the risk prediction models. It is not clear how this information will affect individuals' management.

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 the use of this technology alters individuals' management and improves clinical outcomes. Additional research involving 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. A total of 29,292 participants aged 40 to 69 years from the UK Biobank who were 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.

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, LDL-C and 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 the 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 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 not having medication use available 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. A total of 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 classified as being at low to intermediate risk. A limitation 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. A total of 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 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.

A meta-analysis of randomized clinical trials was performed by Willeit et al. (2020) and 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 (ICH) 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 as 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 ICH (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.

The Jackson Heart Study is the largest single-site, epidemiological, population-based study in African American individuals and was designed to better understand the etiology of cardiovascular, renal, and respiratory diseases in a community-based cohort. At the baseline examination (2000 to 2004), adults 21 to 94 years of age underwent bilateral far-wall CIMT measurement (mean, 0.76 mm). Incident CVD events were then assessed over 7 to 11 years of follow-up. The study included 2,463 women and 1,338 men who were free of clinical CVD at baseline. Risk reclassification was only mildly improved by adding CIMT: a net reclassification index of 0.13 and 0.05 for women and men, respectively, and an integrated discrimination improvement of 0.02 and 0.01 for women and men. The authors concluded that CIMT was associated with incident CVD but provided modest incremental improvement in risk reclassification beyond traditional risk factors. They identified limitations of the study. First, the study was performed in a single geographic area, which may limit generalizability. Second, although the follow-up period was relatively long, 9 years is shorter than the 10-year period in which the Framingham Risk Score is calculated, and this may decrease the overall power of the observations. Third, carotid plaque was not systemically assessed. Finally, the impact of statins and antihypertensive and antiplatelet medications during the ascertainment period is unknown (Villines et al., 2017).

Geisel et al. (2017) performed a study to compare the predictive value of coronary artery calcification, CIMT, and the ABI in a primary prevention cohort to determine which of the three markers improves cardiovascular risk discrimination best. The study included 3,108 participants without prevalent CVDs from the population-based Heinz Nixdorf Recall study. Associations with incident major cardiovascular events (coronary event, stroke, or cardiovascular death; n = 223) were assessed during a follow-up period of 10.3 ±2.8 years, with Cox proportional regressions in the total cohort, and stratified by Framingham Risk Score. All three markers were associated with cardiovascular events. The authors concluded that coronary artery calcification provides the best discrimination of risk compared with CIMT and the ABI, particularly in the intermediate-risk group, whereas CIMT may be an alternative measure for reassurance in the low-risk group.

A systematic review was conducted by Day et al. (2017) to investigate the association in children and young people between blood pressure and CIMT. A total of 28 studies were included. The results were mixed, with the largest and highest-quality studies suggesting an independent positive association between blood pressure and CIMT, even after adjustment for other cardiovascular risk factors. There was no indication of a clear threshold level for the effect of blood pressure on CIMT. There were insufficient data to support a pharmacological treatment threshold for the treatment of high blood pressure to prevent future CVD. The studies that were included varied widely in terms of quality and design, and it was not possible to combine the data in a meta-analysis. The authors concluded that there is likely to be an independent association between blood pressure and CIMT in childhood, but it is not clear at what point this should be treated.

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) [Lp(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 information on total cholesterol and HDL-C with various lipid parameters did not significantly improve CVD risk prediction (Di Angelantonio et al., 2012).

Lipoprotein(a)

While identified research shows that Lp(a) is associated with increased risks of cardiovascular events, the clinical utility of its measurement to improve clinical decision-making or improve individuals' outcomes has not been established.

Bhatia et al. (2025) conducted an individual-level meta-analysis in 27,658 individuals enrolled in six placebo-controlled statin trials to assess the association of LDL-C and Lp(a) levels with nonfatal or fatal CHD events, stroke, or atherosclerotic CVD (ASCVD). The multivariable-adjusted association between baseline Lp(a) level and ASCVD risk was modeled continuously using generalized additive models, and the association between baseline LDL-C level and ASCVD risk by baseline Lp(a) level was modeled using Cox proportional hazards models with random effects. In this large, individual-level meta-analysis of statin trials, it was observed that baseline Lp(a) level was associated with cardiovascular risk continuously and independently of baseline LDL-C; an elevated Lp(a) level was associated with increased risk, even when LDL-C was treated to low levels with statin therapy; and the greatest risk occurred when both Lp(a) and LDL-C levels were elevated. Together, these findings demonstrate that Lp(a) and LDL-C are independent and additive for cardiovascular risk, even on statin treatment, and LDL-C reduction does not completely offset Lp(a)-mediated risk. The authors concluded that the study has important implications for the management of individuals with elevated Lp(a) levels, stating that Lp(a) and LDL-C levels were independent and that potent LDL-C level reduction did not offset Lp(a)-mediated risk. First, there does not appear to be sufficient evidence that reducing LDL-C can fully offset the risk associated with Lp(a), both when assessed by achieved levels and absolute change, emphasizing that both are important targets for risk reduction requiring tailored management approaches, especially with the advent of targeted therapies. Second, their findings suggest that both LDL-C and Lp(a) levels are important and independent targets for reducing cardiovascular risk. The authors stated that it has well been established that the prevalence of an elevated Lp(a) level differs by race and ethnicity, so using a single cutoff may not be broadly representative globally. Limitations within the study include findings that are limited by a lack of comparison to a reference standard, being that Lp(a) levels differ among ethnicity and race, as the majority of individuals were White. Additionally, the authors' interpretation of the findings may have been biased due to financial conflicts of interest. Further studies are necessary for testing and incorporating Lp(a) into cardiovascular risk assessment and verifying the clinical utility of the measurements and how they impact individuals' care.

Palaiodimou et al. (2025) conducted a systematic review and meta-analysis of a total of 12 studies, including one randomized controlled trial post hoc analysis and 11 observational studies comprised of 17,903 individuals (mean age, 63 years; 38% female) with IS or transient ischemic attack (TIA), that reported Lp(a) levels. Pooled ORs were calculated using a random-effects model. Elevated Lp(a) levels were significantly associated with increased stroke recurrence (OR, 1.69; 95% CI, 1.09-2.63; p = 0.020) and poor functional outcome (OR, 2.09; 95% CI, 1.40-3.11; p < 0.001). No significant associations were found between Lp(a) levels and all-cause mortality (OR, 2.20; 95% CI, 0.89-5.43; p = 0.088) or recurrent vascular events (OR, 2.66; 95% CI, 0.95-7.44; p = 0.063). The authors concluded that elevated Lp(a) levels are linked to increased stroke recurrence and poor functional outcomes in individuals who previously had an initial stroke and may represent a novel therapeutic target in secondary stroke prevention in addition to a promising biomarker. Limitations of the study include that the majority of the included studies were observational studies. Further studies, including well-designed randomized controlled trials, are necessary to address the clinical utility of the measurements and how they could impact individuals' care and improve outcomes.

Berman et al. (2024) performed a retrospective cohort study to assess the association between Lp(a) and MACEs in patients with or without baseline ASCVD. Lp(a) in the cohort of patients was measured between 2000 to 2019. Cox proportional hazards modeling was used to assess the association of Lp(a) percentile group with MACEs. A total of 16,419 patients were analyzed, with the median follow-up being 11.9 years. Among the 10,181 study patients (62%) with baseline ASCVD, patients in the 71st to 90th percentile group had a 21% increased hazard of MACEs (adjusted HR, 1.21; p < 0.001), which was similar to that in patients in the 91st to 100th group (adjusted HR, 1.26; p < 0.001). The authors concluded that per this large, U.S.-based cohort, elevated Lp(a) is independently linked with long-term MACEs in individuals with or without baseline ASCVD. The study did not address the clinical utility of measuring Lp(a) to improve clinical outcomes.

Leistner et al. (2024) conducted the noninterventional, cross-sectional LipidCardio study that included participants aged ≥ 21 years who underwent angiography from October 2016 to March 2018 and had at least one Lp(a) measurement. The

authors aimed to quantitatively study the association of increasing Lp(a) levels and the severity of CAD. The association between Lp(a) and CAD severity was determined by synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX)-I and Gensini scores and angiographic characteristics. A total of 975 study participants were included, with a mean age of 69.5 years. Overall, 70.1% were male, 97.5% had Caucasian ancestry, and 33.2% had a family history of premature ASCVD. The authors concluded that elevated Lp(a) was associated with a more significant presentation of CAD. The study did not address the incremental value over standard CVD risk factors of measuring Lp(a) or its clinical utility to improve clinical outcomes.

Ridker et al. (2024) analyzed data from a prospective cohort study to address the utility of high-sensitivity C-reactive protein, LDL-C, and Lp(a) biomarkers as a risk-reduction method in predicting cardiovascular risk in women. In the Women's Health Study, the biomarkers of 27,939 initially healthy American women were measured at baseline and followed over 30 years for the primary end point of a first MACE, a composite of myocardial infarction, coronary revascularization, stroke, or cardiovascular death. Adjusted HRs for the primary end point comparing the top to bottom quintile were 1.70 (95% CI, 1.52-1.90) for high-sensitivity C-reactive protein, 1.36 (95% CI, 1.23-1.52) for LDL-C, and 1.33 (95% CI, 1.21-1.47) for Lp(a). Each biomarker displayed independent contributions to overall risk. The authors stated that Lp(a) levels are genetically determined and stable over time; thus, the measurement is recommended once, without the need for repeat evaluation. Additionally, the authors hypothesized that bundling the three biomarkers [high-sensitivity C-reactive protein, LDL-C, and Lp(a)] at a single point could provide a useful method for lifetime biomarker risk assessment. The authors stated that their data are consistent with the hypothesis that adjunctive interventions addressing a diverse set of biological targets may ultimately be needed for optimal atherosclerotic protection. Limitations of the study include that the proportion of non-Caucasian women was 5.1%; therefore, the findings may not be generalizable to the U.S. population. Additionally, the study focused on solely women, and long-term data in men are needed to generalize the findings. The analysis did not address the clinical utility of the test to improve clinical outcomes.

Orfanos et al. (2023) conducted a systematic review to report the burden of clinically relevant elevated Lp(a) in the secondary prevention ASCVD population. Overall, 61 studies met the inclusion criteria. Of the included studies, 25 were observational studies, and one clinical trial reported the clinical burden of clinically relevant elevated Lp(a) levels. The major clinical outcomes included MACEs (n = 20), myocardial infarction (n = 11), revascularization (n = 10), stroke (n = 10), cardiovascular mortality (n = 9), and all-cause mortality (n = 10). The authors identified that the evidence showed a significant association between elevated Lp(a) levels and an increased risk of MACEs (n = 15) as well as revascularization (n = 8), while a trend for positive association was observed with remaining cardiovascular outcomes. A meta-analysis was not feasible for the included studies due to the heterogeneity in Lp(a) thresholds, outcome definitions, and individuals' characteristics. Three studies reported humanistic burden. The authors' findings showed that individuals with elevated Lp(a) levels had higher odds of manifesting cognitive impairment and disability related to stroke. Elevated Lp(a) levels negatively correlated with health-related quality of life (R = -0.166; p = 0.014; n = 1). A single study reported no association between elevated Lp(a) levels and economic burden. The authors concluded that the systematic literature review demonstrated a significant association of elevated Lp(a) levels with major cardiovascular outcomes and increased humanistic burden in the secondary prevention ASCVD population. The authors concluded that these results reinforce the need to quantify and manage Lp(a) for cardiovascular risk reduction and to perform further studies to characterize the economic burden. Limitations in the study were identified. None of the included studies reported the association between Lp(a) levels and cardiovascular outcomes in different ethnic subpopulations. The heterogeneity in the population of individuals, reference thresholds [or low Lp(a) levels], comorbidities, biomarkers, gender distribution, risk factors for ASCVD, and definition of outcomes are additional limitations. Finally, limited studies evaluating the economic and humanistic burden of elevated Lp(a) was another key gap. The study did not address the clinical utility of measuring Lp(a) levels in changing management and improving clinical outcomes. (Sang et al., 2021, previously cited in this policy, is included in this systematic review.)

Kumar et al. (2021) conducted a systematic review and meta-analysis to investigate the association of Lp(a) levels with the risks of stroke and its subtypes. The study included 41 observational studies that involved 7,874 individuals with IS and 32,138 controls; 13 studies for the IS subtypes based on TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification and seven studies, with 871 ICH cases and 2,865 control individuals, were included. The findings exhibited a significant association between increased levels of Lp(a) and the risk of IS compared with that in control individuals (SMD, 0.76; 95% CI, 0.53-0.99). Lp(a) levels were also found to be significantly associated with the risk of the large artery atherosclerosis subtype of IS (SMD, 0.68; 95% CI, 0.01-1.34) and the risk of ICH (SMD, 0.65; 95% CI, 0.13-1.17) compared with controls. The authors concluded that increased Lp(a) levels could be a predictive marker for identifying individuals who are at risk of developing IS, large artery atherosclerosis, and ICH. The meta-analysis revealed that increased levels of Lp(a) are significantly associated with the risk of IS in Asian as well as Caucasian populations. Limitations in the study comprise the wide range of variables of age, ethnicity, sample size, and study design; lack of original mean and SD values of Lp(a) levels; nonavailability of cutoff values for Lp(a); and the random-effects model used

to account for the significant heterogeneity arising out of the studies. Furthermore, the study did not address the incremental value of Lp(a) to conventional risk factors or its clinical utility in improving outcomes.

Shah et al. (2020) analyzed data from a randomized clinical trial to see the impact of elevated Lp(a) in a high-risk secondary prevention cohort of participants with diabetes on optimal medical treatment who were enrolled in the ACCELERATE (Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes) trial, with the aim of identifying study participants who could potentially benefit from Lp(a)-targeted treatment. Participants who met eligibility to enroll in the trial were divided into participants with and without diabetes to assess the impact of Lp(a) tertiles in each group. Baseline Lp(a) levels were measured. Participants were chosen from the placebo arm of the trial to limit any potential drug effect on the outcomes. The primary end point of this analysis was the first occurrence of any component of the composite cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina. Participants were followed up every 3 months after randomization, with a median duration of 28 months. Overall, 5,121 study participants (3,482 participants with diabetes; 1,639 without diabetes) in the placebo arm of ACCELERATE had baseline Lp(a) levels evaluated. A total of 3,426 had a diagnosis of type 2 diabetes, and 56 had a diagnosis of type 1 diabetes. The majority of the study participants were Caucasian and male, and the average age of the entire study population was 64 ±10 years. The baseline mean LDL-C, mean HDL-C, and median triglyceride levels were 81.6 ±27.9 mg/dL, 45.6 ±11.8 mg/dL, and 128.0 (93.0, 178.0) mg/dL, respectively. The median Lp(a) was 29.1 (10.8, 108.1) nmol/L. African American participants had a higher median Lp(a) than Caucasian participants and Asian participants (118.4 vs. 28.9 vs. 26.0 nmol/L, respectively). Participants without diabetes had higher median Lp(a) values than their counterparts with diabetes. The event rates for the composite end point were significantly higher in the highest tertile of Lp(a). The authors concluded that in a contemporary population of participants with high-risk established CVD on optimal medical treatment, higher tertiles of Lp(a) were associated with increased cardiovascular events. This relationship of cardiovascular events was similar in participants with or without diabetes. They further stated that based on their findings, at least one-third of contemporary high-risk individuals with diabetes on optimal medical treatment have high Lp(a) levels and increased risk for new cardiovascular events and might benefit from pharmacological intervention aimed at significantly reducing Lp(a) levels. This study did not address how integrating these measurements into clinical care alters individuals' management and improves clinical outcomes.

Kouvari and Panagiotakos (2019a) conducted a systematic review that outlined the current state of knowledge regarding the role of Lp(a) in primary and secondary CVD prevention. Searches resulted in the selection of 19 studies. In the context of primary CVD prevention, nine cohorts, two case cohorts, and two retrospective studies were identified, the majority of which suggested a significant positive association between Lp(a) and CVD onset. In terms of secondary CVD prevention, five cohorts and one case cohort were considered eligible, highlighting from a positive to a neutral association between Lp(a) and CVD progression. The authors concluded that a positive association between Lp(a) and CVD seemed to be supported by a large body of evidence, yet it is comparatively moderate in magnitude and differentiates according to study individuals and the examined end points. This fact, along with the lack of a definitive functional mechanism, limits the potential connotation of Lp(a) in daily clinical practice.

The ATTICA prospective, longitudinal cohort study was conducted during 2001 to 2012 and included 1,514 men and 1,528 women who were free of CVD from the greater Athens, Greece, area (Kouvari et al., 2019b). Follow-up CVD assessment was achieved in 2,020 participants; baseline Lp(a) was measured in 1,890 participants. The recommended threshold of 50 mg/dL was used to define abnormal Lp(a) status. The 10-year CVD event rate was 14% and 24% in participants with an Lp(a) of < 50 and Lp(a) of ≥ 50 mg/dL, respectively. A multivariate analysis revealed that participants with an Lp(a) of ≥ 50 mg/dL vs. Lp(a) of < 50 mg/dL had approximately a two times higher CVD risk (HR, 2.18; 95% CI, 1.11-4.28). The sex-based analysis revealed that the independent Lp(a) effect was retained only in men; in women, significance was lost after adjusting for lipid markers. Sensitivity analyses revealed that Lp(a) increased CVD risk only in case of abnormal HDL-C, apolipoprotein A1, and triglycerides as well as low adherence to a Mediterranean diet. The authors concluded that certain characteristics of individuals may be relevant when considering Lp(a) as a therapeutic or risk-prediction target.

Based on the BiomarCaRE (Biomarker for Cardiovascular Risk Assessment in Europe) project, Waldeyer et al. (2017) analyzed data from 56,804 participants from seven prospective population-based cohorts. The three end points considered were incident major coronary events (MCEs), incident CVD events, and total mortality. Kaplan-Meier curves showed the highest event rate of MCEs and CVD events for Lp(a) levels in the ≥ 90th percentile. Cox regression models revealed a significant association of Lp(a) levels with MCEs and CVD, with an HR of 1.30 for MCEs and 1.25 for CVD for Lp(a) levels in the 67th to 89th percentile, and an HR of 1.49 for MCEs and 1.44 for CVD for Lp(a) levels in the > 90th percentile vs. Lp(a) levels in the lowest third. There was no significant association between Lp(a) levels and total mortality. A subgroup analysis identified the highest Lp(a)-associated risk in participants with diabetes, with an HR for MCEs of 1.31 and for CVD of 1.22, compared with those without diabetes, with an HR for MCEs of 1.15. No difference in the Lp(a)-associated risk was seen for other cardiovascular high-risk states. Overall, 2,452 incident MCEs were observed during a

median follow-up time of 8.8 years, 2,966 incident CVD events were observed after a median of 8.7 years, and 4,877 deaths occurred after a median of 9.2 years. The authors concluded that elevated Lp(a) was associated with an increased risk for MCEs and CVD in study participants with diabetes and that these results may lead to better identification of target populations that might benefit from future Lp(a)-lowering therapies. Some limitations were identified. Differences in storage duration among the included cohorts may have contributed to differences in the Lp(a) levels across populations. Further, Lp(a) measurements were not performed consecutively, so they could not correct for regression dilution bias.

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 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 was not addressed in this publication.

Zhang et al. (2021) performed a prospective study to investigate the association between CVD and Lp-PLA_2. A total of 823 participants 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 one 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 one 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 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 included in the Bezafibrate Infarction Prevention study. With adjustment for study individuals' characteristics and traditional risk factors, one 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.

A systematic review with meta-analysis was conducted by Li et al. (2017a) 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 one SD increase in Lp-PLA_2 activity, CHD risk increased by 12%; no association between one 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 one 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.

A systematic review and meta-analysis was conducted by Tian et al. (2017) 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. A total of 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.

Garg et al. (2015) evaluated the associations of Lp-PLA_2 and first-time cardiovascular events in a healthy, multiethnic cohort characterized by the presence or absence of baseline subclinical atherosclerosis. Lp-PLA_2 mass and activity were measured at baseline in 5,456 participants in MESA (Multi-Ethnic Study of Atherosclerosis). Participants were characterized for the presence of baseline subclinical disease (CAC score > 0 or CIMT value > 80th percentile) and followed up prospectively for the development of CVD events. At 9- to 12-month intervals, participants or family members were contacted regarding interim hospital admissions, outpatient diagnoses of CVD, and deaths. Overall, 516 CVD events occurred over a median follow-up of 10.2 years; 358 were due to CHD. Higher Lp-PLA_2 mass and activity were both associated with an increased incidence of CVD and CHD risk in participants with or without baseline subclinical disease, defined by the presence of calcified CAD or a thickened carotid intima-media. Both Lp-PLA_2 mass and activity were weakly correlated with CIMT and CAC. In the subset of participants on baseline statin therapy (n = 879), higher Lp-PLA_2 mass was not associated with an increased risk of incident CVD or CHD. The authors concluded that Lp-PLA_2 was positively associated with CVD and CHD risk, regardless of the presence of CAC or a thickened carotid-intima media. They did identify study limitations. The population included participants with no known baseline clinical CVD, and findings cannot be generalized to dissimilar populations. The number of CVD events was low for some strata in their stratified analyses. Other studies or longer-term follow-up is required to further investigate these questions. Lastly, their detection of atherosclerosis was based on surrogate measures and did not capture all participants with evidence of subclinical disease.

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 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 information on total

cholesterol and HDL-C with various lipid parameters did not significantly improve CVD risk prediction (Di Angelantonio et al., 2012).

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 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. The study did not address 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. However, the study did not address the clinical utility of the test to improve clinical outcomes.

Cheng et al. (2022) conducted a systematic review and meta-analysis of studies evaluating the relationship of cholesterol efflux capacity (CEC) with CAD and cardiovascular mortality in a general population. A total of 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. Furthermore, 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 were not assessed.

Lee et al. (2021) conducted a systematic review and meta-analysis of studies evaluating the association of CEC and adverse cardiovascular events. The researchers stated that serum HDL-C levels are inversely associated with CVD events, but emerging evidence suggests that it is the functional properties of HDL, particularly reverse cholesterol transport, which is 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 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. However, the study did not 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 percutaneous coronary intervention) 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 in those with indeterminate hs-cTnI concentrations. Limitations include that the single point in time measurements of biomarkers and obstructive CAD definitions differed in each cohort. 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 presenting with symptoms suggestive of myocardial infarction to the emergency department. 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, respectively; the median concentration of osteopontin was 62 ng/ml compared with 30 ng/ml in patients with or without a MACE, respectively; 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, respectively. 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. The absolute number of observed cardiovascular events was small, and the overall sample size was limited to 750 patients, which could impact the significance of the findings. The study is limited by its retrospective observations. Furthermore, the design did not allow assessment of whether the use of the score impacted care or patients' outcomes.

Endothelial Function Assessment

There is insufficient evidence in the peer-reviewed, medical literature to support the effectiveness and clinical utility of endothelial function assessment to establish the risk of CVD. The majority of the identified studies reported some measure of statistical association of either peripheral arterial tonometry (PAT) or brachial artery ultrasound with CVD, but the findings are conflicting. Furthermore, these associations are insufficient to demonstrate their clinical utility to effectively predict cardiovascular morbidity or change individuals' management and outcomes. Well-designed studies that extend beyond measures of simple statistical association are needed to demonstrate the clinical usefulness of such assessment tools to effectively predict cardiovascular events and classify individuals according to their individual cardiovascular risk.

Cooper et al. (2021) performed a prospective observational study to assess the associations between digital PAT measures and first-onset major CVD events in a sample of Framingham Heart Study participants. Using a fingertip PAT device, the pulse amplitude in Framingham Offspring and Third Generation participants (n = 3,865) was assessed at baseline and in 30-second intervals for 4 minutes during reactive hyperemia. The PAT ratio (relative hyperemia index) was calculated as the post-to-preocclusion pulse signal ratio in the occluded arm, relative to the same ratio in the control (nonoccluded) arm. A Cox proportional hazards regression was used to relate PAT measures in the fingertip to incident CVD events. During follow-up (median, 9.2 years), 270 participants experienced new-onset CVD events. In multivariable models adjusted for cardiovascular risk factors, baseline pulse amplitude (HR per one SD, 1.04; 95% CI, 0.90-1.21; p = 0.57) and PAT ratio (HR, 0.95; 95% CI, 0.84-1.08; p = 0.43) were not significantly related to incident composite CVD events. A higher PAT ratio (HR, 0.76; 95% CI, 0.61-0.94; p = 0.013) but not baseline pulse amplitude (HR, 1.15; 95% CI, 0.89-1.49; p = 0.29) was related to a lower risk for incident stroke. In a sensitivity analysis by stroke subtype, a higher PAT ratio was related to a lower risk of incident IS events (HR, 0.68; 95% CI, 0.53-0.86; p = 0.001). The authors concluded that PAT measures were not associated with composite CVD events; a lower PAT ratio, which is a measure of microvascular structure and function in the finger, was associated with a greater risk of incident stroke. Further quality-controlled studies are needed to evaluate the association of PAT measures with cerebrovascular function and cognition.

Schnabel et al. (2021) evaluated the associations of noninvasive measures of flow-mediated dilation and PAT with incident CVD and mortality in a cohort study. In a post hoc analysis of the community-based Gutenberg Health Study, the brachial artery flow-mediated dilation (n = 12,599) and fingertip PAT (n = 11,125) were measured. After a follow-up of up to 11.7 years, there were 595 incident CVD events, 106 cardiac deaths, and 860 deaths in total. Noninvasive measures of peripheral vascular structure and function did not reveal clinically relevant associations with incident CVD or mortality. The authors concluded that the routine measurement of flow-mediated dilation or PAT in the community cohort to screen for a high risk of CVD or mortality was not effective, and whether determination of pulse amplitude by PAT improves clinical decision-making in primary prevention needs to be demonstrated.

A study by Venuraju et al. (2019) aimed to determine the prognostic factors for endothelial dysfunction and identify relationships between reactive hyperemia index (RHI) score, clinically relevant CAD (> 50% stenosis), and MACEs in study individuals with type 2 diabetes. Endothelial function was assessed using PAT and correlated with individuals' characteristics and cardiovascular outcomes during a median follow-up of 22.8 months. Among 235 individuals, with a median duration of type 2 diabetes of 13 years, the mean (SD) RHI score was 2.00. Serum LDL-C and HDL-C levels positively and negatively predicted RHI score, respectively. The median CAC score was 109 Agatston units, but no correlation between CAC and RHI scores was observed. The RHI score did not predict the number or severity of coronary plaques identified using computed tomography coronary angiography. Additionally, there was no association between RHI score and the risk of a MACE during follow-up. Overall, endothelial function was not predictive of CAC score or the extent and severity of coronary plaque or MACEs and did not demonstrate utility in cardiovascular risk stratifying individuals with type 2 diabetes.

Van den Heuvel et al. (2015) examined the applicability of PAT to detect a low risk of CAD in a chest pain clinic. In 93 participants, PAT was performed, resulting in the RHI and AIx. Participants were risk classified according to HeartScore, Diamond and Forrester pretest probability, exercise testing (X-ECG), and computed tomography calcium scoring and angiography. Correlations, risk-group differences, and prediction of revascularization within 1 year were calculated. The RHI correlated with HeartScore and AIx with Diamond and Forrester pretest probability, but both were not significantly different between the normal and ischemic X-ECG groups. The RHI and AIx were similar between low risk compared with intermediate to high risk and failed to predict revascularization. The authors concluded that PAT cannot detect a low risk of CAD, possibly because the RHI and AIx vs. X-ECG, computed tomography calcium scoring, and computed tomography angiography represent independent processes.

In a correlation study in Framingham Heart Study participants (n = 1,957), Hamburg et al. (2008) evaluated the relationship between digital pulse amplitude using a fingertip PAT device and CVD risk factors. The initial findings demonstrated that manually induced, reactive hyperemia resulted in a time-dependent increase in fingertip pulse amplitude. Based on a stepwise, multivariate, linear regression model, a number of risk factors were inversely related to the hyperemic response (PAT ratio), including male sex, body mass index, total cholesterol/HDL-C, diabetes, smoking, and lipid-lowering treatment. Conversely, increasing age was positively correlated with PAT ratio ($p < 0.01$). These results may suggest a link between certain risk factors and lower digital hyperemic response. However, a causal relationship between these risk factors and digital vascular function could not be established. Given the homogenous nature of the study participants (Caucasian participants of European descent), the preliminary results are also not generalizable to different ethnic or racial groups. Despite these positive preliminary findings, the clinical utility and predictive value of digital pulse amplitude have yet to be established.

Clinical Practice Guidelines

American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)

A 2020 consensus statement by the AACE and ACE on the management of dyslipidemia and prevention of CVD algorithm makes the following recommendation:
Measurement of Lp(a) in individuals should be considered in the following settings:

- All individuals with clinical ASCVD, especially premature or recurrent ASCVD, despite LDL-C lowering
- Individuals with a family history of premature ASCVD and/or increased Lp(a)
- Individuals with South Asian or African ancestry, especially with a family history of ASCVD or increased Lp(a)
- Individuals with a 10-year ASCVD risk of ≥ 10% (primary prevention setting), in order to stratify risk
- Individuals with a personal or family history of aortic valve stenosis
- Individuals with refractory elevations of LDL-C, despite aggressive LDL-C–lowering therapy (i.e., statin resistance)

(Handelsman et al., 2020)

American Association of Clinical Endocrinologists (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 and Lp(a), 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(a): Testing for Lp(a) is not generally recommended, although it may provide useful information to assign risk in Caucasian individuals with ASCVD, those with an unexplained family history of early ASCVD, or those with unknown family history such as adopted individuals.
- 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 Lp(a): A relative indication for its measurement is family history of premature ASCVD. An Lp(a) of ≥ 50 mg/dL or ≥ 125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a)
    - 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 makes the following recommendations on the assessment of initial CVD event risk:

- CIMT: 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; very 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; very 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 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.
- Brachial/peripheral flow-mediated dilation: The ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that peripheral arterial flow-mediated dilation studies are not recommended for cardiovascular risk assessment in asymptomatic adults. Class III, level of evidence B – no benefit. The guideline also states that it is unclear whether measures of peripheral endothelial health provide incremental predictive information when controlling for traditional risk factors.

(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)

A 2022 scientific statement from the AHA on the clinical use of Lp(a) states the following:

- Elevated Lp(a) is causal for ASCVD and could inform clinical decision-making regarding risk management.
- Lp(a) levels are largely determined by genetic factors.
- Screening for Lp(a) is the strongest for those with a family or personal history of ASCVD, although various organizations have proposed to obtain a level once in every adult.

(Reyes-Soffer et al., 2022)

American Heart Association (AHA)/American College of Cardiology (ACC)/American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR)/American Academy of Physician Assistants (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 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol makes the following statements on the measurements of apoB and Lp(a):

- A relative indication for apoB measurement would be triglyceride of ≥ 200 mg/dL. A persistent elevation of apoB can be considered a risk-enhancing factor.

- Indications for Lp(a) measurement are a family history of premature ASCVD or a personal history of ASCVD that is not explained by major risk factors. An elevation of Lp(a) is considered to be a risk-enhancing factor, especially in those with higher Lp(a) values and, if used in women, only in the presence of hypercholesterolemia.

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 Lp(a)
- 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).

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 consisting of total cholesterol, LDL-C, HDL-C, non–HDL-C, and triglycerides. ApoB and Lp(a) should be offered only as individually orderable tests
- 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).

European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS)

A 2025 focused update of the 2019 guidelines for the management of dyslipidemias was issued, as the publication of new evidence could influence clinical practice; the update included the following recommendations on Lp(a):

- Epidemiological and genetic studies strongly support a likely causal and direct continuous association between high plasma levels of Lp(a) and a higher risk of ASCVD and aortic valve stenosis.

- Lp(a) measurement should be considered at least once in every adult's lifetime, either at the first lipid profile or at the next one, if lipid profiles have previously been performed.
- It is reasonable to consider elevated Lp(a) levels of > 50 mg/dL (≥ 105 nmol/L) (affecting at least 20% of the population) to refine cardiovascular risk estimation across the spectrum of cardiovascular risk; moreover, this cutoff level should be considered as a risk modifier to potentially reclassify the cardiovascular risk category, specifically in individuals at moderate risk or individuals close to treatment decision thresholds.

(Mach et al., 2025)

The ESC/EAS 2019 Dyslipidemia Clinical Practice Guideline recommendations include the following:

- Measurement of Lp(a) at least once in each adult's lifetime to identify those with very high inherited Lp(a) levels of above 180 mg/dL (> 430 nmol/L) who may have a lifetime risk of ASCVD that is equivalent to the risk associated with heterozygous familial hypercholesterolemia.
- Lp(a) should be considered in selected individuals with a family history of premature CVD and for reclassification in people who are borderline between moderate and high risk.
- ApoB analysis is recommended for risk assessment, particularly in people with high triglycerides, diabetes, obesity or metabolic syndrome, or very low LDL-C (Mach 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 2024 focused update to the 2019 scientific statement on the use of Lp(a) in clinical practice was issued, as accumulating epidemiological data have clarified the relationship between Lp(a) levels and CVD risk and cardiovascular risk reduction. This update was made to help guide clinicians in applying the emerging evidence in clinical practice. Sufficient evidence supports the recommendation to measure Lp(a) levels at least once in all adults for risk stratification. Individuals with Lp(a) levels of < 75 nmol/L (30 mg/dL) are considered low risk; individuals with Lp(a) levels of ≥ 125 nmol/L (50 mg/dL) are considered high risk; and individuals with Lp(a) levels between 75 and 125 nmol/L (30-50 mg/dL) are at intermediate risk. Cascade screening of first-degree relatives of individuals with elevated Lp(a) can identify those at risk and who require intervention. Individuals with elevated Lp(a) should receive early, more intensive risk factor management such as lifestyle modification and lipid-lowering medication therapy to reduce LDL-C. Lp(a) is an established independent causal risk factor for CVD, and despite the high prevalence of Lp(a) elevation (approximately one of five individuals), measurement rates are low, warranting improved screening strategies for CVD prevention (Koschinsky 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 for select individuals.
- Lp(a) can help to guide therapy in persons with primary hypercholesterolemia or those at very high risk to develop ASCVD events.
- 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)

A 2019 scientific statement from the NLA on the use of Lp(a) in clinical practice notes the following key points:

- The measurement of Lp(a) is reasonable in adults with:
  - Premature ASCVD (< 55 years of age in men; < 65 years of age in women)
  - Recurrent or progressive ASCVD, despite optimal lipid lowering
  - Calcific valvular aortic disease
- Individuals with high Lp(a) levels may have less-than-expected LDL-C lowering on statin therapy

- There is a lack of current evidence demonstrating that lowering Lp(a), independently of LDL-C, reduces ASCVD events in individuals with established ASCVD. It appears that large absolute reductions in Lp(a) may be needed to demonstrate a significant clinical benefit

(Wilson et al., 2019)

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 concluded 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.

Veterans Affairs and Department of Defense (VA/DoD)

The VA/DoD 2020 clinical practice guidelines on the management of dyslipidemia for cardiovascular risk reduction suggest against the routine use of additional risk markers (e.g., high-sensitivity C-reactive protein, ABI, CAC) when assessing cardiovascular risk.

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Noninvasive blood pressure measurement system products such as the CVProfilor are numerous. Search by product code DXN to view devices. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 5, 2025)

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). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 5, 2025)

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). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed November 5, 2025)

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 November 5, 2025)

The Endo PAT 2000 received FDA 510(k) clearance (K032519) on November 12, 2003. According to the clearance summary, the Endo PAT 2000 device is a noninvasive device intended for use as a diagnostic aid in the detection of coronary artery endothelial dysfunction (positive or negative) using a reactive hyperemia procedure. The Endo PAT 2000 has been shown to be predictive of coronary artery endothelial dysfunction in the following patient population: patients with signs or symptoms of ischemic heart disease, who are indicated for coronary artery angiography, but who lack angiographic evidence of obstructive coronary artery disease. The Endo PAT 2000 device is not intended for use as a screening test in the general patient population. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K032519. (Accessed November 5, 2025)

The Endo PAT 2000 510(k) clearance summary lists the PAT 1000 RD [Itamar Medical Ltd.; (K001852)] as a predicate device. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K001852. (Accessed November 5, 2025)

The SphygmoCor System (ATCOR Medical) is a series of noninvasive blood pressure monitoring devices 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, cleared in August 2007 (K070795). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=K122129. (Accessed November 5, 2025)

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Policy History/Revision Information

Date	Summary of Changes
04/01/2026	**Supporting Information** • Updated *Clinical Evidence* and *References* sections to reflect the most current information • Archived previous policy version 2026T0389DD

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.