Cardiovascular Disease Risk Tests

Policy Number: CS015.U
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➲ Instructions for Use

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Related Community Plan Policy
- Genetic Testing for Cardiac Disease

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Application

This Medical Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

State	Policy/Guideline
Idaho	Cardiovascular Disease Risk Tests (for Idaho Only)
Indiana	None
Kansas	Cardiovascular Disease Risk Tests (for Kansas Only)
Kentucky	Cardiovascular Disease Risk Tests (for Kentucky Only)
Louisiana	Cardiovascular Disease Risk Tests (for Louisiana Only)
New Jersey	Cardiovascular Disease Risk Tests (for New Jersey Only)
New Mexico	Cardiovascular Disease Risk Tests (for New Mexico Only)
North Carolina	Cardiovascular Disease Risk Tests (for North Carolina Only)
Ohio	Cardiovascular Disease Risk Tests (for Ohio Only)
Pennsylvania	Cardiovascular Disease Risk Tests (for Pennsylvania Only)
Tennessee	Cardiovascular Disease Risk Tests (for Tennessee Only)

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 (CIMT) measurement as an effective screening tool for the management of cardiovascular disease
- Advanced lipoprotein analysis [e.g., lipoprotein(a), subfractions, or particle size] as method to determine risk for cardiovascular disease
- Lipoprotein-associated phospholipase A2 (Lp-PLA2) 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
- Multi-protein diagnostic biomarker:
  - Analysis of protein biomarkers by aptamer-based microarray and algorithm

- 3 proteins [high sensitivity (hs) troponin, adiponectin, and kidney injury molecule-1 (KIM-1)] with algorithm and reported as a risk score
- 4-proteins [NT-proBNP, osteopontin, tissue inhibitor of metalloproteinase-1 (TIMP-1), and KIM-1] with algorithm and reported as a risk score
- 7 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 federal, state, or contractual requirements 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
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 (CVD), 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 (BSA) and body mass index (BMI) to determine arterial compliance indices. These indices have been proposed as early indicators of CVD. 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 (PAT) device. Brachial artery ultrasound uses high-resolution ultrasound to assess changes in vascular dimensions, while the PAT 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 carotid intima-media thickness (CIMT) for 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 (LDL), high density lipoproteins (HDL), and very low density lipoproteins (VLDL). LDL cholesterol typically makes up 60-70 percent of the total serum cholesterol and contains a single apolipoprotein, namely apo B-100 (apo B). HDL cholesterol normally makes up 20-30 percent of the total serum cholesterol. The major apolipoproteins of HDL are apo A-I and apo A-II. The VLDL are triglyceride-rich lipoproteins, but contain 10-15 percent of the total serum cholesterol. Apolipoprotein, lipoprotein (a) and lipoprotein-associated phospholipase A2 are risk factors being evaluated for their ability to predict cardiovascular disease or ischemic stroke (NHLBI, 2002).

Lipoprotein-associated phospholipase A2 (Lp-PLA2), a vascular inflammatory enzyme, has been investigated as a surrogate biomarker of increased coronary heart disease and stroke risk. Lp-PLA2 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 multi-protein diagnostic test for determining whether a patient has heart disease and may be at imminent risk of a heart attack. HART CVE® is a multi-protein risk test for a patient's one-year risk of heart attack, stroke, or cardiac death. Artificial intelligence is employed to interrogate well-characterized clinical data sets to produce novel, multi-protein, 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 patient 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.

Claessens et al. (2023) studied one thousand sixty-six participants according to age brackets. Four cohorts were investigated-healthy subjects (NL), hypertensive participants (HP), ischemic heart disease (IHD) and valvular heart disease (VHD) participants. Pulse wave velocity (PWV) analysis measure arterial distensibility. The aim of this study was to evaluate the clinical importance and usefulness of pulse wave analysis. Arterial stiffness was analyzed through Sphygmocor XCEL Central Blood Pressure Measurement System and Sphygmocor XCEL PWV Measurement System. There were found to be statistically significant differences between NL and HP cohorts in nearly all age brackets. Central aortic blood pressure systolic (CABPS) seemed to be a determining factor. In conclusion, a significant determining factor in problems of arterial stiffness appears to be CABPS. 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 further investigation is needed. Additionally, medication therapy was not a contra-indication for study inclusion although certain

medications such as beta blockers, ACE 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-section study, single-center evaluation of ankle-brachial index (ABI), mean carotid-femoral pulse wave velocity (cfPWV) and pulse wave analysis (PWA) parameters. Data was obtained in a 2-year period. One hundred and twenty-three participants who underwent elective coronary angiography were included. Ankle-brachial index (ABI) was measured, and arterial stiffness parameters were derived with applanation tonometry of the radial, carotid and femoral artery. Mean ABI was 1.04 ±0.12, mean subendocardial viability ratio (SEVR) 166.6 ±32.7% and mean cfPWV 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 ABI among different degrees of CAD. Participants with zero- and three-vessel CAD had significantly lower values of SEVR, compared to study participants with one- and two-vessel CAD. No significant difference was observed in cfPWV values. Spearman's correlation test showed a correlation between ABI and SEVR and between ABI and cfPWV. Multiple regression analysis confirmed an association between cfPWV and ABI, cfPWV and mean arterial pressure, cfPWV and age and between cfPWV and body mass index, but not with arterial hypertension, dyslipidemia, diabetes mellitus or smoking status. SEVR was not statistically significantly associated with ABI using the same multiple regression model. The authors concluded that reduced ABI was associated with increased cfPWV, but not with advanced CAD or decreased SEVR. Limitations of the study included the cross-sectional design, small sample size and inclusion of only Caucasian individuals.

In a systematic review and meta-analysis, Sequí -Dominguez et al. (2020) sought to estimate PWV and carotid femoral PWV 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 pulse wave velocity (baPWV), only studies measuring cfPWV were incorporated in the main quantitative data synthesis. All included studies were of longitudinal nature two of them were cross-sectional analyses from longitudinal studies. The predictive performance of cfPWV pooled diagnostic odds ratio (dOR) values were 11.23 (95% CI, 7.29-1.29) 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 (HSROC) 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, where the closest cut-off 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 and it is a feasible, non-invasive and replicable method for estimating risk, and applicable in high-risk populations. Limitations of the study include 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 arterial velocity pulse index (AVI) as a novel marker of atherosclerosis using pulse wave analysis on high-sensitivity troponin T (hs-cTnT) in individuals with hypertension. The study enrolled 455 individuals without a history of cardiovascular events. AVI and hs-cTnT levels were measured. Hs-cTnT was detected in 405 participants (89.0%). AVI was significantly higher in study participants with detectable hs-cTnT than in those without. In individuals with detectable hs-cTnT, there was a significant positive correlation between AVI and hs-cTnT. The authors concluded that the significant relationship between AVI and hs-cTnT, as determined by 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 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. Cardiovascular diseases such as heart failure or coronary artery disease may have gone undetected. Third, the sample size was relatively small. Prospective studies are required to clarify the clinical significance of AVI as a risk factor for cardiovascular disease in study participants with hypertension. The study does 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 (PWA) derived mechanical biomarkers in two independent population-based cohorts. PWA on central arterial pressure waveforms were obtained from subjects without a prior history of cardiovascular diseases. The two studies were the Kinmen study (1,272 participants, a median follow-up of 19.8 years); and the Cardiovascular Disease Risk Factors Two-Township Study (CVDFACTS) (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 BP, body mass index, fasting glucose, triglycerides, low-density-lipoprotein cholesterol, and high-density-lipoprotein cholesterol, and smoking. Only

systolic (SC) and diastolic rate constant (DC) 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 (26.9%) deaths 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 BP, pulse pressure, backward wave amplitudes (Pb), and augmentation index (AI) 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 DC remained significant in predicting cardiovascular mortality. The authors concluded that these findings suggested 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 patient management.

Carotid Intima-Media Thickness (CIMT)

The clinical evidence is insufficient to show an added benefit of CIMT testing beyond traditional risk assessment. There is inadequate clinical evidence from prospective studies that the use of this technology alters patient 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.

Ling et al. (2023) completed a systematic review of the different definitions of carotid intima-media thickness (cIMT) utilized 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 utilized as a predictor of future cardiovascular disease (CVD); however, various definitions of cIMT exist. The authors concluded that Combined-IMT is more strongly associated with CVD events compared to single-segment cIMT definitions. Limitations of the systematic review include 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 the 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 cardiovascular disease and without preexisting carotid plaque at baseline from twenty prospective studies within the Proof-ATHERO (Prospective Studies of Atherosclerosis) consortium. The overall mean of baseline common carotid artery intima-media thickness (CCA-IMT) values was 0.71 mm, with 15 studies reporting mean CCA-IMT values and 5 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 odds ratios (ORs) for incident carotid plaque using random-effects meta-analysis. In subgroup analyses, there was no significant effect modification across clinically relevant subgroups. Baseline CCA-IMT was approximately log-linearly associated with the odds of developing carotid plaque. The age-, sex-, and trial arm–adjusted OR for carotid plaque per SD higher baseline CCA-IMT was 1.40. The corresponding OR that was further adjusted for ethnicity, smoking, diabetes, body mass index, systolic blood pressure, low-and high-density lipoprotein cholesterol, and lipid-lowering and antihypertensive medication was 1.34. Sensitivity analysis restricted to studies defining plaque as focal thickening yielded a comparable OR (1.38; 14 studies; 17,352 study participants; 6,991 incident plaques). The authors concluded the large-scale meta-analysis based on participant-level data, 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. Differences in how individual studies were defined and measured CCA-IMT and carotid plague. The exact time point of plaque development. The long-term studies from 1990s to 2000s which use older ultrasound devices. The usage of 2-dimensional carotid plaque data versus 3-deminsional carotid plaque data. Furthermore, the study doesn't address the clinical utility of the test or how this technology alters patient management and improves clinical outcomes.

Nonterah et al. (2022) compared the association of established cardiovascular risk factors with carotid-intima media thickness (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 with 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 the among African American populations followed by Asian, European, and Hispanic populations with African populations having the lowest mean CIMT. Men had higher CIMT levels in comparison with 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. In comparison to 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 when compared with all other racial and ethnic groups. In the African American and African populations only, high-density lipoprotein-cholesterol had significant

protective effects. The authors concluded the magnitude of the associations of CVD risk factors with CIMT has implications for ethnic specific primary prevention strategies and offer insights into racial-and ethnic-specific mechanisms involved in the pathogenesis of CVD. Limitations in the study included the small sample size of the Asian and Hispanic population, the dietary intake data and not having medication use was not available across all the studies. Furthermore, the incremental value of CIMT and its clinical utility on patient care was not addressed.

Azcui Aparicio et al. (2021) conducted a systematic review to compare the predictive value of CIMT, carotid plaque identification, and CAC scoring for identifying sub-clinical atherosclerosis and assessing future risk of CVD in asymptomatic, low-to-intermediate risk individuals. A total of 30 studies (23 prospective cohort studies, 1 retrospective cohort study, 1 case-control study, and 5 cross-sectional studies) were included in the review with 92, 498 participants. Follow-up duration in 11 studies was an average of 10.3 ±4.8 years and a median duration of 6.0 years. 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 to carotid plaque and CIMT measurements in asymptomatic study participants classified as being at low-to-intermediate risk. A limitation identified in this systematic review was the heterogeneity of ultrasound markers used in different papers, especially those for CIMT. Additionally, this study did not address how CIMT alters patients' management and improves clinical outcomes.

Liu et al. (2020) conducted a meta-analysis to confirm whether carotid intima-media thickness (IMT) could serve as an accurate diagnostic method for coronary artery disease (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 (AUC) was 0.74 (0.70-0.78). Subgroup analyses based on cutoff value of IMT demonstrated a cutoff value of 1 mm to be a more accurate diagnostic criteria for CAD (sensitivity: 0.66; specificity: 0.79; AUC: 0.80). The pooled results for sensitivity analysis were robust. Deek's funnel plot indicated no significant publication bias (p = 0:195). The authors concluded carotid IMT to be a suggestable screening tool for CAD. Limitations in the study were less Asian population studies in comparison to 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) exploring 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 participants 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 of 0.91 (95% CI, 0.87-0.94) for the principal outcome of CVD. The interventions reduced the CVD risk and resulted in relative risk 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 relative risks 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. This study did not however address how integrating measurement of CIMT to clinical care alters patient management and improves clinical outcomes.

Kumar at al. (2020) conducted a meta-analysis to clarify the association between CCA-IMT with the risk of stroke. The study included 19 studies; sixteen studies involving 3,475 ischemic stroke (IS) cases and 11,826 controls; six studies with 902 large vessel disease (LVD) and 548 small vessel disease (SVD) of IS subtypes; five studies with 228 intracerebral hemorrhage (ICH) and 1,032 IS cases. The authors reported the results noted an association between increased CCA-IMT with risk of IS as compared to control subjects (SMD = 1.46, 95% CI = 0.90-2.02). There was an increased risk of LVD as compared to the SVD 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 larger sample size are needed to validate the findings.

The Jackson Heart Study (JHS) is the largest single-site, epidemiologic population-based study of African-Americans 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 cardiovascular disease (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: Net Reclassification Index 0.13 and 0.05 for women and men, respectively; Integrated Discrimination Improvement 0.02 and 0.01 for women and men, respectively. 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 within a single geographical area, which may limit generalizability. Second, although the follow-up period was relatively long, 9.0 years is shorter than the 10-year period for 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, 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 (CAC), carotid intima-media thickness (CIMT) and ankle-brachial index (ABI) in a primary prevention cohort to determine which of the three markers improves cardiovascular (CV) risk discrimination best. The study included 3,108 participants without prevalent CV diseases from the population-based Heinz Nixdorf Recall study. Associations with incident major CV events (coronary event, stroke, CV 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 CV events. The authors concluded that coronary artery calcification provides the best discrimination of risk compared with CIMT and 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 carotid intima-media thickness. 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 carotid intima-media thickness, even after adjustment for other cardiovascular risk factors. There was no indication of a clear threshold level for the effect of blood pressure on carotid intima-media thickness. There was insufficient data to support a pharmacological treatment threshold for the treatment of high blood pressure to prevent future cardiovascular disease. The studies 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 carotid intima-media thickness in childhood, but it is not clear at what point this should be treated.

Den Ruijter et al. (2012) conducted a meta-analysis to determine whether the addition of CIMT measurements to the Framingham Risk Score added value in 10-year risk prediction of first-time myocardial infarctions or strokes. Individual data from studies were combined into one data set and a meta-analysis was performed on individuals without existing cardiovascular disease. Fourteen population-based cohorts of 45,828 individuals were included. During a median follow-up of 11 years, 4,007 first-time myocardial infarctions or strokes occurred. The authors concluded that adding CIMT measurements to the Framingham Risk Score was associated with a small improvement in 10-year risk prediction of first-time myocardial infarction or stroke, but this improvement is unlikely to be of clinical importance.

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 improve clinical outcomes. Research has shown a lack of universal, standardized testing modalities and patient selection criteria. 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 high-density lipoprotein cholesterol (HDL-C) improved cardiovascular disease (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 A2 (Lp-PLA2) were measured. Participants received follow- up for 10 years, during which 15,126 CVD-related fatal and nonfatal outcomes occurred. 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) [Lp(a)]

Berman et al. (2024) performed a retrospective cohort study to assess the association between Lipoprotein(a) [Lp(a)] and major adverse cardiovascular disease events (MACE) of individuals with and without baseline atherosclerotic cardiovascular disease (ASCVD). The Lp(a) of the cohort of individuals was measured between 2000 to 2019. Cox proportional hazards modeling was utilized to assess the association of Lp(a) percentile group with MACE. A total of 16,419 participants were analyzed with the median follow-up being 11.9 years. Among the 10,181 (62%) study participants with baseline ASCVD, participants in the 71st to 90th percentile group had a 21% increased hazard of MACE (adjusted HR: 1.21; $p < 0.001$), which was similar to that of participants in the 91st to 100th group (adjusted HR: 1.26; $p < 0.001$). The authors concluded per this large U.S. based cohort, that elevated Lp(a) is independently linked with long-term

MACE in participants with and without baseline ASCVD. The study does not address the clinical utility of measuring Lp(a) to improve clinical outcomes.

Leistner et al. (2024) conducted a non-interventional, cross-sectional, LipidCardio study including participants aged ≥ 21 years old undergoing angiography from October 2016 – March 2018 who have had at least one lipoprotein(a) [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 PCI 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 of age. 0.1% were male, 97.5% had Caucasian ancestry, and 33.2% had a family history of premature atherosclerotic cardiovascular disease. The authors concluded elevated Lp(a) was associated with a more significant presentation of CAD. The study does not address the incremental value over standard CVD risk factors of measuring Lp(a) or its clinical utility to improve clinical outcomes.

Orfanos et al. (2023) conducted a systematic review to report the burden of clinically relevant elevated lipoprotein (a) [Lp(a)] in secondary prevention atherosclerotic cardiovascular disease (ASCVD) population. Sixty-one studies met inclusion criteria. Of the included studies, 25 were observational studies and one clinical trial reported clinical burden of clinically relevant elevated Lp(a) levels. Major clinical outcomes included major adverse cardiovascular event (MACE; n = 20), myocardial infarction (MI; n = 11), revascularization (n = 10), stroke (n = 10), cardiovascular (CV) mortality (n = 9), and all-cause mortality (n = 10). The authors identified that the evidence showed significant association between elevated Lp(a) levels and an increased risk of MACE (n = 15) as well as revascularization (n = 8), while they demonstrated a trend for positive association with remaining CV outcomes. Meta-analysis was not feasible for included studies due to heterogeneity in Lp(a) thresholds, outcome definitions, and participant characteristics. Three studies reported humanistic burden. The authors findings deduced participants 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 the systematic literature review demonstrated a significant association of elevated Lp(a) levels with major CV outcomes and increased humanistic burden in secondary prevention ASCVD population. The authors concluded that these results reinforce the need to quantify and manage Lp(a) for CV 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 CV outcomes in different ethnic subpopulations. The heterogeneity in participant population; reference thresholds (or low Lp(a) levels); comorbidities; biomarkers; gender distribution, risk factors for ASCVD; and definition of outcomes were 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 improve clinical outcomes (Sang 2021 which was 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 involving 7,874 participants with ischemic stroke (IS) and 32,138 controls; 13 studies for the IS subtypes based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification and 7 studies with 871 Intracerebral hemorrhage (ICH) cases and 2,865 control subjects were included. The findings exhibited a significant association between increased levels of Lp(a) and risk of IS as compared to control subjects [standardized mean difference (SMD) 0.76; 95% confidence interval (CIs) 0.53-0.99]. Lp(a) levels were also found to be significantly associated with the risk of large artery atherosclerosis (LAA) 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) as compared to controls. The authors concluded increased Lp(a) levels could be a predictive marker for identifying individuals who are at risk of developing IS, LAA 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 population. Limitations in the study comprised of wide range variables of age, ethnicity, sample size, study-design; lack of original mean and standard deviation values of Lp(a) levels; non-availability of cut-of values of Lp(a); and the random-effects model used to account for the significant heterogeneity arising out of the studies. Furthermore, the study does 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 patients with diabetes on optimal medical treatment enrolled in the Assessment of Clinical Effects of Cholesteryl Ester Transfer Protein Inhibition with Evacetrapib in Patients at a High Risk for Vascular Outcomes (ACCELERATE) trial to identify patients who could potentially benefit from Lp(a)-targeted treatment. Participants who met eligibility to enroll in the trial were divided into patients 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 for this analysis was the first occurrence of any component of the composite cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for

unstable angina. Patients were followed every 3 months after randomization with a median duration of 28 months. Overall, 5,121 patients (3,482 patients 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. A majority of patients were Caucasian males, and the average age of the entire study population was 64 ±10 years. Baseline mean LDL cholesterol, mean HDL cholesterol, 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 Americans had a higher median Lp(a) compared with Caucasians and Asians (118.4 vs. 28.9 vs. 26.0 nmol/L, respectively). Participants without diabetes had higher median Lp(a) values compared with their counterparts with diabetes. 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 patients with high-risk established cardiovascular disease on optimal medical treatment, higher tertiles of Lp(a) were associated with increased cardiovascular events. This relationship of cardiovascular events was similar in patients with and without diabetes. They further recommended that based on their findings, at least a third of contemporary high-risk patients 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 to clinical care alters patient management and improves clinical outcomes.

Kouvari and Panagiotakos (2019a) conducted a systematic review which outlined the current state of knowledge regarding the role of Lp(a) in primary and secondary CVD prevention. Searches resulted in the selection of n = 19 studies. In the context of primary CVD prevention, n = 9 cohorts, n = 2 case-cohorts, and n = 2 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, n = 5 cohorts and n = 1 case-cohort were considered as 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 participants and the examined endpoints. 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 2001-2012 and included 1,514 men and 1,528 women free of cardiovascular disease (CVD) from the greater Athens area, Greece (Kouvari et al., 2019b). Follow-up CVD assessment was achieved in 2020 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. Ten-year CVD-event rate was 14% and 24% in participants with Lp(a) < 50 and Lp(a) ≥ 50 mg/dL, respectively. Multivariate analysis revealed that participants with Lp(a) ≥ 50 mg/dL versus Lp(a) < 50 mg/dL had about 2 times higher CVD risk [hazard ratio (HR) = 2.18, 95% confidence interval (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 high-density lipoprotein cholesterol, apolipoprotein A1, and triglycerides as well as low adherence to Mediterranean diet. The authors concluded that certain participant characteristics may be relevant when considering Lp(a) as a therapeutic or risk-prediction target.

Based on the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE)-project, Waldeyer et al. (2017) analyzed data of 56,804 participants from 7 prospective population-based cohorts. The three endpoints considered were incident major coronary events (MCE), incident cardiovascular disease (CVD) events, and total mortality. Kaplan-Meier curves showed the highest event rate of MCE and CVD events for Lp(a) levels ≥ 90th percentile. Cox regression models revealed a significant association of Lp(a) levels with MCE and CVD with a hazard ratio (HR) of 1.30 for MCE and of 1.25 for CVD for Lp(a) levels in the 67-89th percentile and a HR of 1.49 for MCE and 1.44 for CVD for Lp(a) levels > 90th percentile vs. Lp(a) levels in the lowest third. There was no significant association between Lp(a) levels and total mortality. Subgroup analysis identified the highest Lp(a)-associated risk in participants with diabetes HR for MCE 1.31 and for CVD 1.22 compared to those without diabetes, HR for MCE 1.15. No difference of the Lp(a)- associated risk were seen for other cardiovascular high-risk states. Two thousand four hundred and fifty-two incident MCE were observed during a median follow-up time of 8.8 years, 2,966 incident CVD events after a median of 8.7 years, and 4,877 deaths after a median of 9.2 years. The authors concluded that elevated Lp(a) was associated with an increased risk for MCE and CVD in study participants with diabetes and that these results may lead to better identification of target populations who 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 A2 (Lp-PLA2)

Given the low-quality evidence, no conclusions can be drawn regarding the clinical utility of Lp-PLA2 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 sPLA2-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 cardiovascular disease or stroke in adults.

Zhang et al. (2021) performed a prospective study to investigate the association between cardiovascular disease and Lp-PLA2. A total of 823 participants at a high risk of stroke were screened and followed 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-PLA2 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, 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-PLA2 was positively correlated with the degree of carotid artery stenosis and predicted cerebrovascular events. There were some limitations of the study 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-PLA2 to clinical care alters patient management and improves clinical outcomes.

Hu et al. (2019) conducted a meta-analysis to determine whether elevated Lp-PLA2 is a risk factor for stroke. Twenty-two studies involving 157,693 participants were included for analysis. The RRs for overall stroke with 1 SD higher Lp-PLA2 activity and mass were 1.07 (95% CI 1.02-1.13) and 1.11 (95% CI 1.04-1.19), respectively. The RRs of ischemic stroke with 1 SD higher Lp-PLA2 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-PLA2, the RRs of stroke for Lp-PLA2 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-PLA2, the pooled RRs of ischemic stroke for Lp-PLA2 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-PLA2 levels are associated with higher stroke risk. The authors identified some study limitations. The test methods for Lp-PLA2 were not uniform in the included studies, which is a potential source of bias and there was a lack of studies in individuals ≥ 65 years. Lp-PLA2 as a therapeutic target to prevent stroke requires further investigation. Furthermore, the study did not address how integrating measurements of Lp-PLA2 to clinical care alters patient management and improves clinical outcomes.

Benderly et al. (2017) performed a study to evaluate the relevance of Lp-PLA to risk prediction among patients with coronary heart disease (CHD). Lp-PLA activity was measured in 2538 CHD participants included in the Bezafibrate Infarction Prevention (BIP) study. Adjusting for study participant characteristics and traditional risk factors, 1 standard deviation of Lp-PLA was associated with a hazard ratio (HR) of 1.12 [95% confidence interval (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 the results did not support added value of Lp-PLA for predicting cardiovascular events or mortality among CHD patients beyond traditional risk factor.

Younus et al. (2017) performed a systematic review to clarify the relationship between lipoprotein-associated phospholipase A2 (Lp-PLA2) and subclinical cardiovascular disease (CVD) as defined by coronary artery calcium (CAC), carotid intima-media thickness (CIMT) and endothelial function. Thirteen studies were included in the review, 6 examined the relationship between Lp-PLA2 and coronary artery calcification, of which 3 showed a significant correlation. Two studies examined the relationship between Lp-PLA2 and endothelial dysfunction, and 1 reported a significant relationship. Five studies investigated the association of Lp-PLA2 with carotid intima-media thickness, and 3 reported a significant relationship. The authors concluded that this review showed a variable association between Lp-PLA2, and subclinical disease and the results do not conclusively support the use of Lp-PLA2 in the diagnosis and management of subclinical CVD. Future research is needed to clarify what role Lp-PLA2 has in guiding treatment.

A systematic review with meta-analysis was conducted by Li et al. (2017a) to investigate the associations between lipoprotein-associated phospholipase A2 (Lp-PLA2) and the long-term risks of coronary heart disease (CHD) and ischemic stroke (IS) in the general population. Twelve prospective cohort studies were included. Combined hazard ratios for CHD and IS risks for the highest category referring to lowest category of Lp-PLA2 were 1.46 and 1.58, respectively. The same patterns were observed for both mass and activity, with the exception of those for CHD. For every 1-standard deviation (SD) increase in Lp-PLA2 activity, CHD risk increased by 12%; no association between 1-SD increases in Lp-PLA2 activity and IS was observed. Lp-PLA2 mass was associated with CHD risk. Lp-PLA2 mass per 1-SD increase was not associated with IS risk. The authors concluded that greater Lp-PLA2 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-PLA2 levels (mass and activity) with recurrent vascular events in participants with transient ischemic attack (TIA) and/or first ischemic

stroke and with stroke in the general population. A total of 11 studies that comprised 20,284 participants (4,045 were participants with TIA and/or first ischemic stroke and 16,239 were residents in general population) were identified. The pooled relative risk (RR) of recurrent vascular events (467 cases) in TIA and/or first ischemic group was 2.24, whereas the pooled RR of stroke (1,604 cases) in the general population was 1.47. The pooled RRs of Lp-PLA2 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 participants with TIA and first ischemic stroke, elevated Lp-PLA2 activity levels were associated with recurrent vascular events and in the general population elevated Lp-PLA2 levels were associated with the risk of stroke.

Li et al. (2017b) conducted a meta-analysis to investigate the association between Lp-PLA2 and the prognosis of coronary heart disease (CHD). Fifteen studies with 30,857 participants were included. Overall, higher Lp-PLA2 activity or mass was not significantly related to increased risk of long-term all-cause mortality but was independently associated with an increased risk of long-term cardiovascular events. The prognostic value of Lp-PLA2 in predicting cardiovascular events was observed in study participants with stable CHD who were not receiving therapies for inhibiting Lp-PLA2. The authors concluded that greater Lp-PLA2 activity or mass was independently associated with cardiovascular events in participants with CHD, particularly in participants with stable CHD who were not receiving therapies for inhibiting Lp-PLA2.

Garg et al. (2015) evaluated associations of Lp-PLA2 and first-time cardiovascular events in a healthy multi-ethnic cohort characterized by presence or absence of baseline subclinical atherosclerosis. Lp-PLA2 mass and activity were measured at baseline in 5,456 participants in the Multi-Ethnic Study of Atherosclerosis. Individuals were characterized for presence of baseline subclinical disease (coronary artery calcium score > 0 or carotid intima-media thickness value > 80th percentile) and followed prospectively for development of cardiovascular disease (CVD) events. At 9-12-month intervals, participants or family members were contacted regarding interim hospital admissions, outpatient diagnoses of CVD, and deaths. Five hundred and sixteen CVD events occurred over a median follow-up of 10.2 years; 358 were due to coronary heart disease (CHD). Higher Lp-PLA2 mass and activity were both associated with increased incidence of CVD and CHD risk in individuals with or without baseline subclinical disease, defined by the presence of calcified coronary artery disease or a thickened carotid intima-media. Both Lp-PLA2 mass and activity were weakly correlated with carotid IMT and CAC. In the subset of participants on baseline statin therapy (n = 879), higher Lp-PLA2 mass was not associated with an increased risk of incident CVD or CHD. The authors concluded that Lp-PLA2 was positively associated with CVD and CHD risk, regardless of the presence of coronary artery calcium or a thickened carotid-intimal 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 is based on surrogate measures and does 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 high-density lipoprotein cholesterol (HDL-C) improved cardiovascular disease (CVD) risk prediction. Records were evaluated from 165,544 individuals without baseline CVD from 37 cohort studies in which Lp-PLA_2 was measured. Participants received follow- up for 10 years, during which 15,126 CVD-related fatal and nonfatal outcomes occurred. 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).

Multi-Protein Blood Test With Algorithm and Reported as a Risk Score

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

A Hayes (2023) Evidence Analysis Research Brief on HART CADhs blood test (Prevencio Inc.,) used to predict risk of obstructive coronary artery disease, sought to summarize the volume of publications to determine whether there is adequate published peer-reviewed literature to evaluate HART CADhs blood test (Prevencio Inc.). Hayes findings suggests that there currently is not enough published peer-reviewed literature to evaluate the evidence related to HART CADhs blood test (Prevencio Inc.) to predict risk of obstructive coronary artery disease (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 CVE (CVE: incident myocardial infarction [MI], stroke, or cardiovascular death) following coronary angiography. The inclusion criteria included 446 participants with chronic kidney disease (CKD) over a 2-year follow up period. The 4 biomarkers (kidney injury molecule-1, N-terminal pro B-type natriuretic peptide, osteopontin, and tissue inhibitor of metalloproteinase-1) were integrated into a prognostic algorithm to predict CVE. 74 CVE were discovered; 51

events occurred in stage 1-2 CKD and 23 events occurred in stage 3-5 CKD. The C-statistic for predicting 2-years cardiovascular events in all 446 participants was 0.77. Considering participants at CVE lower-risk within each CKD staging group as a reference, the hazard ratio (95% confidence interval) of cardiovascular events was 2.82 for CKD stage 1-2/CVE higher-risk, and 8.32 for CKD stage 3-5/CVE higher-risk. The authors concluded biomarker panels prior to coronary catheterization may be useful to individualize CVE risk assessment among participants with CKD. The study however doesn't address the clinical utility of the test to improve clinical outcomes.

McCarthy et al. (2020) conducted an observational study of participants referred for coronary angiography, predictors of = 70% coronary stenosis were identified from 6 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 ED with suspected acute myocardial infarction where = 50% coronary stenosis was considered significant. The resulting model consisted of 3 clinical variables (male sex, age, and previous percutaneous coronary intervention) and 3 biomarkers (hs-cTnI [high-sensitivity cardiac troponin I], 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 = 70%. Dividing the risk score result into 5 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 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 a model inclusive of hs-cTnI can predict the presence of obstructive CAD across a wide variety of participants with high accuracy including in those with indeterminate hs-cTnI concentrations. Limitations included single point in time measurements of biomarkers and obstructive CAD definitions differed in each cohort. The study doesn't 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 participants presenting with symptoms suggestive of MI to the emergency department. Four biomarkers (N-terminal pro B-type natriuretic peptide [NT-proBNP], kidney injury molecule-1 [KIM-1], osteopontin [OPN] and tissue inhibitor of metalloproteinase-1 [TIMP-1]) were tested on 750 participants. The end point was a composite of incident MI or cardiovascular mortality. Twenty-two study participants had a major adverse cardiovascular event (MACE) within 1 year. The median concentration of KIM-1 was 0.075 ng/ml compared with 0.024 ng/ml, in participants with and without a MACE, respectively; the median concentration of NT-proBNP 8,500 pg/ml compared with 870 pg/ml, in participants with and without a MACE, respectively; the median concentration of OPN was 62 ng/ml compared with 30 ng/ml, in participants with and without a MACE, respectively; and the median concentration of TIMP-1 was 152 ng/ml compared with 90 ng/ml, in participants with and 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 participants with suspected MI. The absolute number of observed cardiovascular events was small and the overall sample size was limited to 750 individuals, which could impact the significance of findings. The study is limited by its retrospective observations. Furthermore, the design did not allow to assess 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 cardiovascular disease. The majority of the identified studies reported some measure of statistical association of either peripheral arterial tonometry (PAT) or brachial artery ultrasound with cardiovascular disease, but findings are conflicting. Furthermore, these associations are insufficient to demonstrate their clinical utility to effectively predict cardiovascular morbidity or change patient 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 patients according to their individual cardiovascular risk.

Cooper et al. (2021) performed a prospective observational study to assess associations between digital PAT measures and first-onset major cardiovascular disease events in a sample of FHS (Framingham Heart Study) participants. Using a fingertip PAT device, the pulse amplitude in Framingham Offspring and Third Generation participants (n = 3,865) were 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-pre occlusion pulse signal ratio in the occluded arm, relative to the same ratio in the control (nonoccluded) arm. The 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 (hazard ratio [HR] per 1 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. 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 lower risk for incident stroke. In a sensitivity analysis by stroke subtype, higher PAT ratio was related to lower risk of incident ischemic stroke 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, lower PAT ratio − a measure of microvascular structure and function in the finger − was associated with 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 dilatation and peripheral arterial tonometry 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 dilatation (n = 12,599) and fingertip peripheral arterial tonometry (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 cardiovascular disease or mortality. The authors concluded that routine measurement of flow-mediated dilation or peripheral arterial tonometry in the community cohort to screen for high risk of cardiovascular disease or mortality was not effective and whether determination of pulse amplitude by peripheral arterial tonometry improves clinical decision-making in primary prevention needs to be demonstrated.

A study by Venuraju et al. (2019) aimed to determine prognostic factors for endothelial dysfunction and identify relationships between reactive hyperemia index (RHI) score, clinically relevant coronary artery disease (> 50% stenosis), and major adverse cardiovascular events (MACEs) in study participants with type 2 diabetes mellitus (T2DM). Endothelial function was assessed using peripheral arterial tonometry and correlated with participant characteristics and cardiovascular outcomes during a median follow-up of 22.8 months. Among 235 participants with a median duration of T2DM of 13 years, mean (standard deviation) RHI score was 2.00. Serum low- and high-density lipoprotein cholesterol levels positively and negatively predicted RHI score, respectively. Median coronary artery calcium (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, extent, and severity of coronary plaque or MACEs and did not demonstrate utility in cardiovascular risk stratifying participants with T2DM.

Van den Heuvel et al. (2015) examined the applicability of PAT to detect a low risk of coronary artery disease (CAD) in a chest pain clinic. In 93 participants, PAT was performed resulting in RHI and augmentation (AIx) indices. Participants were risk classified according to HeartScore, Diamond and Forrester pretest probability (DF), exercise testing (X-ECG), and computed tomography calcium scoring (CCS) and angiography (CTA). Correlations, risk group differences and prediction of revascularization within 1 year were calculated. RHI correlated with HeartScore, AIx with DF but both were not significantly different between normal and ischemic X-ECG groups. RHI and AIx were similar between low risk as 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 RHI and Aix versus X-ECG, CCS and CTA represent independent processes.

Rubinshtein et al. (2010) examined whether endothelial dysfunction, as detected by non-invasive peripheral arterial tonometry (EndoPAT), can predict late cardiovascular events (n = 270). Once reactive hyperemia (RH) was manually induced, participants were evaluated over a 7-year follow-up period for subsequent cardiovascular adverse events, such as cardiac death, myocardial infarction, revascularization or cardiac hospitalization. Cox regression models were used to estimate the association of EndoPAT results with adverse events, adjusted for age. Univariate predictors of adverse events were natural logarithmic scaled RH index (LRHI), advancing age, and prior coronary bypass surgery. Multivariate analysis identified LRHI value of less than 0.4 as an independent predictor of cardiovascular events.

In a correlation study of Framingham Heart Study participants (n = 1,957), Hamburg et al. (2008) evaluated the relationship between digital pulse amplitude using a fingertip PAT device and cardiovascular disease risk factors. 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 being male, body mass index (BMI), total/high density lipoprotein (HDL) cholesterol, 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 individuals 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 cardiovascular disease 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 ≥ 10% (primary prevention setting), in order to stratify risk
- Patients with a personal or family history of aortic valve stenosis
- Patients 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)

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

- Carotid intima media thickness: CIMT may be considered to refine risk stratification to determine the need for more aggressive atherosclerotic cardiovascular disease (ASCVD) preventive strategies (intermediate level of evidence and recommendation grade).
- Apolipoprotein B: For individuals at increased risk of ASCVD, including those with diabetes, an optimal apolipoprotein B (apo B) goal is < 90 mg/dL, while for individuals with established ASCVD or diabetes plus 1 or more additional risk factor(s), an optimal apo B goal is < 80 mg/dL, and for individuals at extreme risk, an optimal apo B goal is < 70 mg/dL (strong level of evidence and recommendation grade).
- Lipoprotein(a): Testing for lipoprotein(a) is not generally recommended, although it may provide useful information to assign risk in Caucasians with ASCVD, those with an unexplained family history of early ASCVD, or those with unknown family history such as adopted individuals.
- Lipoprotein-associated phospholipase A2: Measuring lipoprotein-associated phospholipase A2 (Lp-PLA2) in some studies has demonstrated more specificity than hsCRP, when it is necessary to further stratify an individual's ASCVD risk, especially in the presence of hsCRP 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 cardiovascular disease identifies the following risk enhancing factors for clinician–patient 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 lipoprotein(a): A relative indication for its measurement is family history of premature ASCVD. A lipoprotein(a) ≥ 50 mg/dL or ≥ 125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of lipoprotein(a)
    - Elevated apolipoprotein B (≥ 130 mg/dL): A relative indication for its measurement would be triglyceride ≥ 200 mg/dL. A level ≥ 130 mg/dL corresponds to an LDL-C > 160 mg/dL and constitutes a risk-enhancing factor
    - Ankle-brachial index (< 0.9)

A 2013 ACC/AHA guideline makes the following recommendations on the assessment of initial CVD event risk:

- Carotid intima-media thickness: CIMT is not recommended for routine measurement in clinical practice for initial CVD event risk assessment.

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

- Arterial compliance: 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.
- Carotid intima media thickness: 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 intermediate risk. Published recommendations on required equipment, technical approach and 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: ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that 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.
- Lipoprotein-associated phospholipase A2: ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that lipoprotein-associated phospholipase A_2 (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 patients, guiding treatment or improving outcomes. Class IIb, Level of Evidence B – conflicting evidence and usefulness/efficacy of test is less well established.
- Brachial/peripheral flow-mediated dilation: ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that peripheral arterial flow-mediated dilation (FMD) 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.

American Diabetes Association (ADA)

ADA 2022 guideline on cardiovascular disease and risk management states that risk scores and other cardiovascular biomarkers have been developed for risk stratification of secondary prevention patients (i.e., those who are already high risk because they have ASCVD) but are not yet in widespread use. With newer, more expensive lipid-lowering therapies now available, use of these risk assessments may help target these new therapies to “higher risk” ASCVD patients in the future.

American Heart Association (AHA)

A 2022 scientific statement from the American Heart Association on clinical use of lipoprotein(a) stated 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.
- Further studies are necessary to understand the mechanistic links between apo(a) isoforms and risk for ASCVD; pathways for Lp(a) synthesis, regulation, and metabolism; and Lp(a) - associated risk in diverse genetic and environmental contexts (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 apolipoprotein B and lipoprotein(a):

- A relative indication for apolipoprotein B measurement would be triglyceride ≥ 200 mg/dL. A persistent elevation of apoB can be considered a risk-enhancing factor.
- Indications for Lp(a) measurement are family history of premature atherosclerotic cardiovascular disease (ASCVD) or personal history of ASCVD not explained by major risk factors. An elevation of Lp(a) is considered to be a risk-enhancing factor. This is 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 Stroke Council (ASA)

The 2014 AHA/ASA guideline on primary prevention of stroke states the following:

- Measurement of inflammatory markers such as Lp-PLA2 in patients without cardiovascular disease may be considered to identify patients who may be at increased risk of stroke, although their usefulness in routine clinical practice is not well established.
- The clinical benefit of using Lp(a) in stroke risk prediction is not well established.

American Society for Clinical Pathology (ASCP)

The ASCP recommends against routinely ordering expanded lipid panels (particle sizing, nuclear magnetic resonance) as screening tests for cardiovascular disease (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 cardiovascular disease in the adult states the following:

- Recommend laboratories offer non fasting and fasting lipid assessment
- Recommend 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 laboratories adopt a lipid reporting format that includes lipid decision thresholds on the basis of lipid screening in primary prevention patients
- Include minimal interpretive comments on the lipid report with reference to the 2021 CCS guidelines, where applicable
- Recommend implementation of the new NIH equation, rather than the Friedewald equation, for calculating LDL-C in all patients (White-Al Habeeb, 2022)

Endocrine Society (ES)

In a clinical guideline on lipid management in patients with endocrine disorders, the Endocrine Society 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, 2020).

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

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

- Measurement of lipoprotein(a) [Lp(a)] at least once in each adult's lifetime to identify those with very high inherited Lp(a) levels above 180 mg/dL (> 430 nmol/L) who may have a lifetime risk of atherosclerotic CV disease (ASCVD) that is equivalent to the risk associated with heterozygous familial hypercholesterolemia.
- Lp(a) should be considered in selected patients 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 (TG), DM, obesity or metabolic syndrome, or very low LDL-C (Mach, 2020).

National Lipid Association (NLA)

A focused update to the 2019 scientific statement was issued as accumulating epidemiological data has clarified the relationship between lipoprotein(a) [Lp(a)] levels and cardiovascular disease risk and cardiovascular risk reduction. This update to guide clinicians in applying the emerging evidence in clinical practice. There is now sufficient evidence to support the recommendation to measure Lp(a) levels at least once in every adult for risk stratification. Individuals with Lp(a) levels < 75 nmol/L (30 mg/dL) are considered low risk, patients with Lp(a) levels ≥ 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 require intervention. Patients with elevated Lp(a) should receive early, more-intensive risk factor management such as lifestyle modification and lipid-lowering medication therapy to reduce low-density lipoprotein cholesterol (LDL-C). Although Lp(a) is an established independent causal risk factor for cardiovascular disease, and despite the high prevalence of Lp(a) elevation (approximately 1 of 5 individuals), measurement rates are low, warranting improved screening strategies for cardiovascular disease prevention (Koschinsky et al., 2024).

A 2021 scientific statement from the National Lipid Association on lipid measurements in the management of cardiovascular diseases: practical recommendations noted the following key points:

- LDL-C and non-HDL-C have benefits in assessing ASCVD risk and residual risk.
- LDL-P assays are not standardized but may help guide treatment in persons after initial lipid evaluation for select patients.
- 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, or remnant cholesterol) due to lack of appropriate standardization and cross comparison of these tests utilizing different measurement techniques is difficult (Wilson et al., 2021).

A 2019 a scientific statement from the National Lipid Association on the use of lipoprotein(a) in clinical practice noted the following key points:

- The measurement of Lp(a) is reasonable in adults with:
  - Premature ASCVD (< 55 y of age in men, < 65 y of age in women)
  - Recurrent or progressive ASCVD, despite optimal lipid lowering
  - Calcific valvular aortic disease
- Patients 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 cardiovascular disease risk assessment with the ankle-brachial index concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for PAD 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 suggested against the routine use of additional risk markers (e.g., high-sensitivity C-reactive protein, ankle-brachial index, coronary artery calcium) 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.

Non-invasive 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 October 9, 2024)

Measurement of CIMT is a procedure, and not subject to FDA regulation. B-mode ultrasound equipment used to measure CIMT 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 October 9, 2024)

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

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 October 9, 2024)

Products for the measurement of Lp-PLA2 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 October 9, 2024)

The EndoPAT 2000 received FDA 510(k) clearance (K032519) on November 12, 2003. According to the clearance summary, the EndoPAT 2000 device is a non-invasive 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 October 9, 2024)

The EndoPAT 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 October 9, 2024)

The SphygmoCor System (AtCor Medical) is a series of noninvasive BP monitoring devices intended to help clinicians manage hypertensive and pre-hypertensive patients by providing central arterial pressure waveform analysis and

calculations of central arterial BP and arterial stiffness. SphygmoCor XCEL System was cleared by the FDA in November 2012 (K122129). Several additional 510(k) clearances had been granted earlier by 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 October 9, 2024)

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Policy History/Revision Information

Date	Summary of Changes

06/01/2025	**Application**
	Idaho and ***Kansas***
	• Added language to indicate this Medical Policy does not apply to the states of Idaho and Kansas; refer to the state-specific policy versions
	Coverage Rationale
	• Revised list of unproven and not medically necessary services:
	  ○ Removed "long-chain omega-3 fatty acids as method to determine risk for cardiovascular disease"
	  ○ Replaced "lipoprotein-associated phospholipase A2 (Lp-PLA2) enzyme *and other human A2 phospholipases such as secretory phospholipase A2 (sPLA2-IIA)* as method to determine risk for cardiovascular disease or ischemic stroke" with "lipoprotein-associated phospholipase A2 (Lp-PLA2) enzyme as *a* method to determine risk for cardiovascular disease or ischemic stroke
	  ○ Updated list of examples of advanced lipoprotein analysis; removed "apolipoproteins"
	Applicable Codes
	• Removed CPT codes 82172 and 84999
	Supporting Information
	• Updated *Description of Services*, *Clinical Evidence*, *FDA*, and *References* sections to reflect the most current information
	• Archived previous policy version CS015.T

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state, or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state, or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state, or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state, or contractual requirements for benefit plan coverage. 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.

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