United Healthcare® Community Plan

UnitedHealthcare® Community Plan
Medical Policy

Cardiovascular Disease Risk Tests (for Louisiana Only)

Policy Number: CS015LA.~~J~~**K**
Effective Date: ~~January 1~~**TBD**, 2022

⮒ Instructions for Use

Application

This Medical Policy only applies to the state of Louisiana.

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., apolipoproteins, lipoprotein(a), subfractions or particle size) as method to determine risk for cardiovascular disease
- 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
- Long-chain omega-3 fatty acids as method to determine risk for cardiovascular disease
- 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, such as 3 proteins (high sensitivity [hs] troponin, adiponectin, and kidney injury molecule-1 [KIM-1]) or 4 proteins (NT-proBNP, osteopontin, tissue inhibitor of metalloproteinase-1 [TIMP-1], and KIM-1) with algorithm and reported as a risk score**
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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
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]), 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**
~~0111T~~	~~Long-chain (C20-22) omega-3 fatty acids in red blood cell (RBC) membranes~~
~~0126T~~	~~Common carotid intima-media thickness (IMT) study for evaluation of atherosclerotic burden or coronary heart disease risk factor assessment~~
*82172	Apolipoprotein, each
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
84999	**Unlisted chemistry procedure**
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

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Codes labeled with an asterisk(*) are not on the state of Louisiana Fee Schedule and therefore not covered by the State of Louisiana Medicaid Program.

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 ~~used~~ **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** ~~its~~ 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 ~~may be used~~ **have been proposed** as ~~an~~ early ~~indication~~ **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, whi~~t~~le 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).

~~Carotid~~ **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 emerging 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. Secretory phospholipase A2-IIa (sPLA2) is a member of the PLA2 enzymes superfamily of pro-inflammatory enzymes. sPLA2 enzymes have been identified as potential risk markers for congestive heart disease (CHD) both from animal studies and observational analyses (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 effective as a screening tool for the early detection 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. 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.

Cheng et al. (2016) systematically and comprehensively 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 (1272 individuals, a median follow-up of 19.8 years); and the Cardiovascular Disease Risk Factors Two-Township Study (CVDFACTS) (2221 individuals, 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.~~

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. All data was obtained in a 2 year period. One hundred and twenty-three patients 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 patients (n = 81, 65.9%) had coronary artery disease (CAD). There was no difference in ABI among different degrees of CAD. Patients with zero- and three-vessel CAD had significantly lower values of SEVR, compared to patients 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 patients.

Hitsumoto (2017) conducted a study to evaluate 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 hypertensive patients. The study enrolled 455 patients without a history of cardiovascular events. AVI and hs-cTnT levels were measured. Hs-cTnT was detected in 405 patients (89.0%). AVI was significantly higher in patients with detectable hs-cTnT than in those without. In patients 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 patients. 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 hypertensive patients.

Cheng et al. (2016) ~~systematically and comprehensively~~ **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 (1272 individuals, a median follow-up of 19.8 years); and the Cardiovascular Disease Risk Factors Two-Township Study (CVDFACTS) (2221 individuals, 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**

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In a prospective, single-center study of moderate size (n=298), Duprez et al. (2004) studied 206 male and 92 female healthy subjects with a mean age of 50 +/- 12 years. Noninvasive radial artery pressure waveforms were acquired with a piezoelectric transducer and analyzed for 1) diastolic indices of C1 and C2 from the CR-2000 CVProfilor, and 2) systolic indices of augmentation as defined by augmentation pressure (AP), augmentation index (AIx), and systolic reflective index (SRI = P2/P1). These indices were then correlated to each other as well as to individual traditional risk factors and the Framingham Risk Score. The results indicate that the diastolic indices were significantly and inversely correlated to systolic indices with C2 showing a stronger inverse association than C1. C2 and AIx were significantly correlated with height, weight, and body mass index in men but not in women. All indices correlated better to blood pressure in women than men. In women, only systolic indices were significantly correlated to HDL cholesterol and only diastolic indices were significantly correlated to LDL cholesterol. All indices were significantly correlated to the Framingham Risk Score, which was stronger in women than men, but when adjusted for age only diastolic indices remained significant in women. The authors concluded that diastolic and systolic indices of pulse contour analysis correlate differently with traditional risk factors in men and women.

Three prospective, multicenter studies, of moderate sample size (n=212, n=230 and n=178), were conducted by the same research group and used the same study population of normotensive and hypertensive individuals. In these groups of individuals, blood pressure was measured using a mercury manometer and arterial compliance or elasticity was determined using the CVProfilor CardioVascular Profiling System. These parameters were measured in triplicate 3 minutes apart in a random sequence, with the patient in a supine position.

Carotid Intima-Media Thickness (CIMT)

The clinical evidence is insufficient to show an added benefit of CIMT testing beyond traditional ~~lipid~~ 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.

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 individuals 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 patient management and improves clinical outcomes.

A meta-analysis of randomized clinical trials was performed by Willeit et al. (2020) to explore 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 patients with a mean follow-up of 3.7 years. Of those patients, 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 3475 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 1032 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 3108 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. ~~The findings of this study need to be validated by well-designed studies.~~

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.

~~van den Oord et al. (2013) conducted a systematic review and meta-analysis of the published evidence on the association of CIMT with future cardiovascular events and its additional value to traditional cardiovascular risk prediction models. Fifteen studies~~

were included in the analysis. The authors concluded that CIMT was associated with future cardiovascular events. However, the addition of CIMT to traditional cardiovascular risk prediction models did not lead to a statistically significant increase in performance of those models.

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, 4007 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.

Costanzo et al. (2010) performed a meta-analysis to verify whether CIMT regression is associated with reduced incidence of cardiovascular events. CIMT increase is associated with a raised risk of coronary heart disease (CHD) and cerebrovascular (CBV) events; however, it is undetermined whether favorable changes of CIMT reflect prognostic benefits. Forty-one trials enrolling 18,307 participants were included. Despite significant reduction in CHD, CBV events and all-cause death induced by active treatments, there was no significant relationship between CIMT regression and CHD events, CBV events and all-cause death. In addition, subjects' baseline characteristics, cardiovascular risk profile, CIMT at baseline, follow-up, and quality of the trials did not significantly influence the association between CIMT changes and clinical outcomes. The authors concluded that regression or slowed progression of CIMT, induced by cardiovascular drug therapies; do not reflect reduction in cardiovascular events.

Jeevarethinam et al. (2015) wanted to determine whether increased carotid intima-media thickness (cIMT) and prevalence of carotid plaque (CP) are predictive of prevalence and severity of coronary atherosclerosis. Consecutive patients (n = 150) with no history of coronary artery disease (CAD), who underwent both carotid ultrasound and computed tomographic coronary angiography, were included in the analysis. The mean cIMT was higher in patients with CAD than in those without CAD (0.76 vs 0.66 mm). A total of 101 (67.3%) patients were found to have coronary plaque. Backward selection analysis (starts with all variables and removes nonsignificant variables one at a time, until all remain significant) showed higher mean cIMT measurement correlated well with prevalence of coronary plaque and obstructive coronary plaque disease. The prevalence of CP in patients with CAD was 45.5%. The authors concluded that the mean cIMT measurement and CP correlated well with the prevalence of any coronary plaque. They acknowledge that there is no consensus whether measuring cIMT and identifying CP is beneficial in an asymptomatic population in predicting cardiovascular disease. The study was limited by small sample size, predominantly middle-aged males, and its retrospective nature.
Roy et al (2015) performed a prospective study to assess the utility of carotid intima-media thickness (CIMT) and computed tomographic coronary artery calcium score (CACS) to detect subclinical atherosclerosis in younger women. Asymptomatic women aged 50 to 65 years with at least one cardiovascular (CV) risk factor and low Framingham risk scores (FRS) were identified prospectively at primary care and cardiology clinics. Mean intimal thickness, plaque on CIMT, and Agatston calcium score for CACS were obtained. Of 86 women, 62% had high-risk CIMT. In contrast, 3.5% had CACS > 100, all of whom had plaque by CIMT. Of the 58 women with CACS of 0, 55% had high-risk CIMT. Six month follow-up was available on 84 of the 86 subjects. The authors concluded that the results demonstrated

that 51.2% of women classified at low risk by the FRS had carotid plaque and CIMT appeared to identify those at a higher CV risk. They suggest that CIMT may be a more sensitive method for CV risk assessment than CACS or traditional risk tools in this population. Further studies are needed to determine if earlier detection would be of clinical benefit. The significance of this study is limited by a small sample size and short follow-up period.

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, 4007 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.

CIMT is being used as a surrogate end point in randomized control trials (RCTs) of novel cardiovascular therapies. However, it remains unclear whether changes in CIMT that result from these therapies correlate with nonfatal myocardial infarction (MI). Goldberger et al. (2010) performed a meta-analysis of 28 randomized controlled trials (RCT) with 15,598 patients. Differences in mean change in CIMT over time between treatment and control groups correlated with developing nonfatal MI during follow-up. However, there was no significant relationship between mean change in CIMT and nonfatal MI in RCTs evaluating statin therapy or those with high CIMTs at baseline. The authors concluded that less progression in CIMT over time is associated with a lower likelihood of nonfatal MI in selected RCTs; however, these findings were inconsistent at times, suggesting caution in using CIMT as a surrogate end point.

In a multicenter, comparative study, Nambi et al. (2010) evaluated whether CIMT and the presence or absence of plaque improved CHD risk prediction when added to traditional risk factors (TRF). Risk prediction models considered included TRF only, TRF plus CIMT, TRF plus plaque and TRF plus CIMT plus plaque. Of 13,145 eligible subjects (5,682 men, 7,463 women), approximately 23% were reclassified by adding CIMT plus plaque information. The authors concluded by stating that traditional CHD risk prediction schemes need further improvement as the majority of the CHD events occur in the "low" and "intermediate" risk groups. Adding plaque and CIMT to TRF improved CHD risk prediction in the ARIC (Atherosclerosis Risk In Communities) study.

Folsom et al. (2008) assessed whether maximum CIMT or coronary artery calcium (CAC) is the better predictor of incident CVD in a prospective cohort study of subjects aged 45 to 84 years who were initially free of CVD (n = 6698). The main outcome measure was the risk of incident CVD events (coronary heart disease, stroke and fatal CVD) over a maximum of 5.3 years of follow-up. The investigators found that there were 222 CVD events during follow-up. CAC was associated more strongly than CIMT with the risk of incident CVD. The hazard ratio was only 1.2 for the association between CIMT and risk of incident CVD. A receiver operating characteristic curve analysis also suggested that CAC score was a better predictor of incident CVD than was CIMT. The investigators reported that CAC score is a better predictor of subsequent CVD events than CIMT.

Advanced Lipoprotein Analysis

Studies report inconsistent results regarding the usefulness of advanced lipoprotein testing. 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 emerging markers will be more predictive of CVD than conventional lipid risk factors.

Sang et al. (2021) conducted a study to investigate the association of lipoprotein(a) with long-term poor prognosis following acute coronary syndromes (ACS) in advanced-age patients. The study included 536 patients aged ≥80 years hospitalized for ACS. The primary outcomes were hard CHD events (a composite of fatal or non-fatal myocardial infarction, and CHD death). The secondary outcomes included major adverse cardiovascular events (MACEs), all-cause death and cardiac death. During a median 66-month follow-up, 89 hard CHD events occurred. Kaplan-Meier curves showed higher cumulative incidence of hard CHD events, MACEs, all-cause death and cardiac death in high lipoprotein(a) group than that in low lipoprotein(a) group. Multivariate Cox proportional hazards analyses revealed that elevated lipoprotein(a) levels were independently associated with an increased risk of hard CHD events [hazard ratio (HR): 1.714, 95% confidence interval (95%CI): 1.114-2.638], MACEs (HR 1.354, 95%CI: 1.024-1.790), all-cause death (HR 1.804, 95%CI: 1.286-2.532) and cardiac death (HR 1.891, 95%CI: 1.112-3.217). The authors concluded that elevated lipoprotein(a) levels were associated with an increased risk of hard CHD events, MACEs, all-cause death and cardiac death in the advanced-age patients with ACS, which indicated that routine screening for lipoprotein(a) might aid prognosis and risk assessment. This study did not address how integrating these measurements to clinical care alters patient management and improves clinical outcomes.

Shah et al. (2020) ~~conducted~~ **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. ~~All events were centrally adjudicated by a blinded clinical end point committee.~~ 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 ±6 10 years. Baseline mean LDL cholesterol, mean HDL cholesterol, and median triglyceride levels were 81.6 ±6 27.9 mg/dL, 45.6 ±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 population 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 1514 men and 1528 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 1890 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 patient 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 individuals 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, 2966 incident CVD events after a median of 8.7 years, and 4877 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 individuals with diabetes. T **and that t**hese 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.

~~Zhu et al. (2017) conducted a study to investigate the relationship between apoA-1, apoB, and measures of vascular function, as well their relationship to adverse cardiovascular events. They evaluated whether apoB or the apoB/apoA-1 ratio was more closely related to vascular markers than was low-density lipoprotein cholesterol (LDL-C) or non-high-density lipoprotein cholesterol (non-HDL-C). One thousand five hundred twenty-two healthy middle-aged men of the Firefighters and Their Endothelium (FATE) cohort were assessed for risk factors and flow-mediated dilatation (FMD), hyperemic velocity (VTI), and carotid intima-media thickness (CIMT). Participants were then followed for 7.2 years. ApoA-1 and apoB levels were measured at baseline. The authors found that apoA-1 was not correlated with VTI, FMD, or CIMT, and apoB was significantly related to VTI and CIMT. In substituted models, LDL-C and non-HDL-C levels appeared to have the same degree of association as apoB for VTI but were not associated with CIMT. ApoB and the apoB/apoA-1 ratio appeared to offer little to no advantage compared with LDL-C or non-HDL-C in the prediction of vascular function. ApoB was found to be a positive predictor of cardiovascular events. The authors concluded that when compared with LDL-C and HDL-C, neither apoB nor the apoB/apoA ratio appeared to confer any significant advantage in the prediction of the vascular markers examined.~~

Benderly et al. (2017) performed a study to evaluate the relevance of Lp-PLA to risk prediction among coronary heart disease (CHD) patients. Lp-PLA activity was measured in 2538 CHD patients included in the Bezafibrate Infarction Prevention (BIP) study. Adjusting for patient 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.

Forbes et al. (2016) conducted a systematic review which assessed the relationship between lipoprotein(a) (Lp(a)) and cardiovascular disease (CVD) outcomes. The 60 studies included ten randomized control trials, 37 prospective cohort studies and 13 nested case control studies. Twenty out of 39 studies (52.3 %) had a follow-up of 5 to ≤ 10 years and 11 out of 39 studies (28.2 %) followed participants for over 10 yrs. The longest follow-up period was 20 years. The authors concluded that their review suggested that evidence is available to support an independent positive association between Lp(a) and the risk of future CVD events both in the general population and in high risk populations, such as those with diabetes, hypertension, or on dialysis. Evidence also exists to support the positive independent association of Lp(a) mass with CVD events in secondary prevention populations. The number of studies for high risk primary prevention populations and secondary prevention populations was limited. The analysis was limited by the inability to carry out statistical pooling/meta-analysis and the methods used to measure Lp(a) mass were poorly reported.

~~A cardiovascular disease (CVD) case-control study to compare standard lipid profile testing with advanced lipid and inflammatory marker analysis was conducted by Stock et al. (2016). All analyses were run in a blinded fashion. Serum direct LDL-C, small dense LDL-C (sdLDL-C), very low density lipoprotein cholesterol (VLDL-C), apolipoprotein (apo) B, apoA-I, lipoprotein(a), Lp(a), apoA-I immunoblotting, high sensitivity C reactive protein (hsCRP), and serum amyloid A (SAA) were measured in 298 documented CVD cases and 609 age and gender matched controls. All cases were sampled more than 4 weeks after any CVD event. In male and female cases, direct LDL-C median levels were 2% and 17% higher, sdLDL-C 46% and 46% higher, VLDL-C 22% and 4% higher, apoB 6% and 17% higher, and Lp(a) 26% and 70% higher, respectively, than in matched controls. Median HDL-C levels were 25% and 26% lower, apoA-I 9% and 7% lower, while apoA-I values in HDL particles were 30% and 26% lower in very large a-1 HDL, 9% and 11% lower in large a-2 HDL, 4% and 4% lower in medium a-3 HDL, 13% and 6% lower in small a-4 HDL, and 16% and 15% higher in very small preb-1 HDL as compared to matched controls. Median hsCRP levels were 113% and 178% higher, and SAA levels were 41% and 43% higher than in matched controls. The authors concluded that the results indicated that advanced lipid and inflammatory marker testing provides significantly more information distinguishing CVD cases from controls than does standard lipid testing and supports the use of advanced testing in CVD prevention. The short terms follow-up did not allow for assessment of intermediate and long term outcomes.~~

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-Associated Phospholipase A2 (Lp-PLA2)

Given the low-quality evidence and absence of important 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 individuals 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.**

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 and meta-analysis was conducted by Li et al. (2017**a**) 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 patients 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 TIA and/or first ischemic stroke patients 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 (1604 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 patients 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. (2017**b**) 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 patients 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 patients with CHD, particularly in patients with stable CHD who were not receiving therapies for inhibiting Lp-PLA2.

~~Wei et al. (2017) performed a study to investigate the role of Lp-PLA2 in ischemic stroke. The study included 328 hospitalized patients, including 179 cases of acute cerebral infarction (ACI) and 149 non-ACI controls. The serum level of Lp-PLA2 in ACI was significantly higher than non-ACI. The serum level of Lp-PLA2 in the recurrence of ACI was significantly higher than the nonrecurrence. The serum levels of Lp-PLA2 in large-artery atherosclerosis subtype were the highest among the subtypes of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) and non-ACI controls. The level of Lp-PLA2 in large-artery atherosclerosis and the cardioembolism group was statistically significantly higher than that of the control cases. There was no statistically significant difference between the small-vessel occlusion group and the control cases. The authors concluded that the study confirmed that the elevated Lp-PLA2 level can be a risk factor for ischemic stroke in the Chinese population and the serum level of Lp- PLA2 may be a predictive factor for the recurrence of ACI. This was a non-randomized study. The findings may not be generalizable to other ethnicities and races.~~

Liu et al. (2015) conducted a systematic review of the epidemiological studies on the relationship between Lp-PLA2 and atherosclerotic cardiovascular disease (CVD), to evaluate the relationship between Lp-PLA2 and the different stages of atherosclerosis. Thirty-three studies were included in the final analysis with 49,260 subjects. Among the 33 studies, 31 showed a positive association between increased Lp-PLA2 and high risk for incidence or mortality of total CVD, coronary heart disease (CHD) or stroke. The majority of the published studies suggest that Lp-PLA2 is closely associated with CVD events. High Lp-PLA2 was associated with increased risk for both first and recurrence of total CVD, CHD, and ischemic stroke. To understand the role of Lp-PLA2 in the early prevention and treatment of CVD, it is important to clarify the relationship between Lp-PLA2 and subclinical atherosclerosis. Studies on this relationship are limited. Most of previous studies were cross-sectional or case-control in nature and often showed conflicting results. The authors concluded that high Lp-PLA2 is associated with increased risk of

clinical CVD events, while the association between Lp-PLA2 and subclinical atherosclerosis remains uncertain. Further prospective cohort studies on the relationship between Lp-PLA2 and subclinical atherosclerosis are warranted to determine whether Lp-PLA2 may only play a role in the progression of subclinical atherosclerosis to clinical events or both the initiation of the atherosclerosis and the progression.

Garg~a~ 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 5456 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 patients 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 individuals 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).

An expert consensus panel (Davidson et al., 2008), evaluated how Lp-PLA2 might be used for determining CVD risk and concluded that testing is not recommended for the general population or for persons who are at low risk. The panel defined a simplified approach to determining criteria for testing of persons who are at least moderate-risk for CHD and includes the following individuals:
- Any age with two major risk factors
- Age greater than or equal to 65 years with one major risk factor
- Cigarette smoking
- Fasting blood glucose greater than or equal to 100 mg/dl
- Metabolic syndrome

~~Lp-PLA$_2$ levels greater than 200 mg/dl warrants risk reclassification and reduction of LDL levels. The authors suggest annual testing for individuals with levels greater than 200 mg/dl. The evidence reviewed by the panel lends some support to further stratify risk in select individuals and there is some evidence in the published medical literature that statin drugs and fibrates may reduce Lp-PLA$_2$ levels. It is not presently known whether lowering Lp-PLA$_2$ levels will decrease the incidence of CHD or stroke and improve clinical health outcomes. Treatment for elevated Lp-PLA$_2$ is targeted at lowering LDL levels.~~

In a prospective case-cohort (n=949), using a subset of participants in the Atherosclerosis Risk in Communities (ARIC) study, Nambi et al. (2009) found that Lp-PLA$_2$ improved ischemic stroke risk prediction. The improvement was most enhanced when Lp-PLA$_2$ was combined with high sensitivity C-reactive protein levels and provided the most benefit in individuals at intermediate risk of ischemic stroke. The authors state that it would be ideal to validate these findings in other cohorts and conduct studies to examine if changes in therapy based on such risk stratification improve ischemic stroke prevention.

Secretory Phospholipase A2 (sPLA2)-IIA

It has been suggested that higher circulating levels of sPLA2 enzyme activity ~~have been~~ **are** associated with increased risk of cardiovascular events. However, it is not clear if this association is **causal or how measurement of this marker improves clinical care or outcomes**.

A nested case–control study was conducted by Smith et al. (2021) using data from the European Prospective Investigation into Cancer—Norfolk study. Cases (n = 145) in the current study were participants who developed ischemic stroke during follow-up, with controls (n = 290) matched in a 2:1 ratio based on age and sex. The aim of the study was to evaluate the association between both sPLA2 concentration and activity as continuous variables with risk of future ischemic stroke. The authors found that PLA2 activity levels were higher in cases than controls (4.6 nmol/min/ml, IQR 4.1–5.4 vs. 4.3 nmol/min/ml, IQR 3.7–4.9; p = 0.001). The differences in sPLA2 concentration were not found to be statistically significant. After adjusting for all confounding factors, sPLA2 concentration was again found not to be associated with risk of ischemic stroke: OR 1.02 (95% CI 0.99–1.04). However, sPLA2 activity was found to be associated with an increased risk: OR 1.23 (95% CI 1.01–1.49). The authors concluded that the activity of sPLA2, but not sPLA2 concentration, is associated with an increased risk of future ischemic stroke. The current study had some limitations. The participants were drawn from an EPIC-Norfolk CAD case–control study and the prevalence of cardiovascular risk factors in both cases and controls may be higher than in the general population. This was an observational study and further research with larger control trials is required. Furthermore, this study did not test how use of this marker improves clinical care or outcomes.

Guardiola et al. (2015) used genetic variants of PLA2G10, encoding sPLA2-X, to investigate the contribution of sPLA2-X to the measure of secretory phospholipase A2 (sPLA2) activity and coronary heart disease (CHD) risk traits and outcome. Three PLA2G10 tagging single-nucleotide polymorphisms (rs72546339, rs72546340, and rs4003232) and a previously studied PLA2G10 coding single-nucleotide polymorphism rs4003228, R38C, were genotyped in a nested case: control cohort drawn from the prospective EPIC-Norfolk Study (2175 cases and 2175 controls). Meta-analysis of rs4003228 (R38C) and CHD was performed using data from the Northwick Park Heart Study II and 2 published cohorts AtheroGene and SIPLAC, providing in total an additional 1884 cases and 3119 controls. EPIC-Norfolk subjects in the highest tertile of sPLA2 activity were older and had higher inflammatory

markers compared with those in the lowest tertile for sPLA2 activity. None of the PLA2G10 tagging single-nucleotide polymorphism nor R38C, a functional variant, were significantly associated with sPLA2 activity, intermediate CHD risk traits, or CHD risk. The authors concluded that PLA2G10 variants are not significantly associated with plasma sPLA2 activity or with CHD risk.

Holmes et al (2013) investigated the role of secretory phospholipase A2 (sPLA2)-IIA in cardiovascular disease. The authors conducted a Mendelian randomization meta-analysis of 19 general population and 10 studies in patients with acute coronary syndrome (ACS). They identified a single nucleotide polymorphism (SNP) in PLA2G2A (rs11573156) that had a large and specific effect on circulating sPLA2-IIA mass and a small-to-modest effect on sPLA2 enzyme activity, but found no association between rs11573156 and incident, prevalent or recurrent major vascular event (MVE). The odds ratio (OR) for a major vascular event [MVE] was 1.02 in general populations and 0.96 in ACS cohorts. Instrumental variable analysis failed to show associations between sPLA2 enzyme activity and MVE. Higher sPLA2-IIA mass or sPLA2 enzyme activity may be a consequence not a cause of atherosclerosis. The authors concluded that reducing sPLA2-IIA mass is unlikely to be a useful therapeutic goal for preventing cardiovascular events.

Xin et al (2013) investigated the potential association between serum sPLA2-IIa and prognosis in post-acute myocardial infarction (post-AMI) patients (n=964). Elevated serum sPLA2-IIa during the convalescent stage of AMI predicted long-term mortality and readmission for heart failure (HF) after survival discharge in the post-AMI patients. Clinical data after discharge was obtained at 3 and 12 months after the onset of AMI, and annually thereafter up to 5 years. Patients with elevated serum sPLA2-IIa > 360 ng/dl (n=164) were more likely to have diabetes mellitus, hypertension, HF, and multivessel disease compared to those with serum sPLA2-IIa ≤ 360 ng/dl. In addition, patients with elevated serum sPLA2-IIa had significantly lower HDL-cholesterol and higher LDL-cholesterol levels, compared to sPLA2-IIa ≤ 360 ng/dl subjects. During a median follow-up period of 1,462 days, 52 patients died, 31 had non-fatal reinfarction, and 40 were rehospitalized for heart failure. Patients with elevated sPLA2-IIa had a significantly higher incidence of death (18.3% vs. 2.75%) and readmission for HF (14% vs. 2.1%) than those without, although no significant differences in the rate of nonfatal MI was detected between the 2 groups (4.88% vs. 2.87%). The authors concluded that elevated serum sPLA2-IIa served as an accurate predictor of long-term outcome and those patients with sPLA2-IIa > 360 ng/dl during the convalescent stage of AMI may be treated as at high risk for subsequent adverse events. This study did not ~~confirm~~ **address** the benefits of **using** sPLA2 findings on health outcomes in patients with cardiovascular disease.

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 as a screening tool for the early detection of cardiovascular disease (CVD).

Neumann et al. (2020) performed a retrospective review to apply a novel risk-prediction model in a cohort of patients presenting with symptoms suggestive of 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 patients. The end point was a composite of incident myocardial infarction or cardiovascular mortality. Twenty two patients 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 patients with and without a MACE,

respectively; the median concentration of NT-proBNP 8500 pg/ml compared with 870 pg/ml, in patients with and without a MACE, respectively; the median concentration of OPN was 62 ng/ml compared with 30 ng/ml, in patients with and without a MACE, respectively; and the median concentration of TIMP-1 was 152 ng/ml compared with 90 ng/ml, in patients 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 patients with suspected myocardial infarction. 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.

There are two clinical trials underway to evaluate new cardiac biomarkers; The CASABLANCA Study: Catheter Sampled Blood Archive in Cardiovascular Diseases. ClinicalTrials.gov Identifier: NCT00842868 and Biomarkers in Acute Cardiac Care (BACC). ClinicalTrials.gov Identifier: NCT02355457.

Long-Chain Omega-3 Fatty Acids

There is insufficient evidence to conclude that measuring long-chain omega-3 fatty acids is effective as a screening tool for the early detection 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. 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.

In a multiethnic population-based cross-sectional study of 998 asymptomatic men aged 40–49 years (300 US-White, 101 US-Black, 287 Japanese American, and 310 Japanese in Japan), Mahajan et al. (2019) examined the relationship of serum LCn-3PUFAs to aortic calcification (measured by electron-beam computed tomography. Overall, 56.5% participants had an aortic calcification score (AoCaS) > 0. The means (SD) of total LCn-3PUFAs, EPA, and DHA were 5.8% (3.3%), 1.4% (1.3%), and 3.7% (2.1%), respectively. In multivariable-adjusted Tobit regression, a 1-SD increase in total LCn-3PUFAs, EPA, and DHA was associated with 29% (95% CI Z 0.51, 1.00), 9% (95% CI Z 0.68, 1.23), and 35% (95% CI Z 0.46, 0.91) lower AoCaS, respectively. There was no significant interaction between race/ethnicity and total LCne3PUFAs, EPA or DHA on aortic calcification. The authors concluded that this study showed the significant inverse association of LCn-3PUFAs with aortic calcification independent of conventional cardiovascular risk factors among men in the general population. This association appeared to be driven by DHA but not EPA. The study had limitations. First, the serum fatty acids composition has a lot of day-to-day variations and reflect recent intake of fat and thus more likely to lead to misclassification bias than more stable markers of intake such as red blood cell fatty acids or adipose tissue fatty acids. Second, the study examined healthy men aged 40-49 years in Japan and the US; therefore, the results of the study cannot be generalized to females, other populations, or age groups. Follow-up population-based studies are needed to further clarify the effect of LCn-3PUFAs on the incidence and progression of atherosclerosis.

Endothelial Function Assessment

There is insufficient evidence in the peer-reviewed medical literature to support the effectiveness and prognostic 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) ~~PAT~~ or brachial artery ultrasound with cardiovascular disease. However, these associations are insufficient to ~~directly~~ 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=3865) 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 patients with T2DM. Endothelial function was assessed using peripheral arterial tonometry and correlated with patient characteristics and cardiovascular outcomes during a median follow-up of 22.8 months. Among 235 patients 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 an 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 patients with T2DM.

~~A retrospective cross-sectional analysis was performed by Sara et al. (2019) on patients who were referred to Mayo Clinic between 2006 and 2014 for routine clinical evaluation of chest pain and/or assessment of baseline cardiovascular disease risk that included an assessment of peripheral endothelial dysfunction (PED) using EndoPAT. Individuals included in this study underwent clinically indicated routine echocardiography within 2 months of assessment of PED. Patients with clinical heart failure were excluded. Three hundred fifty-five patients were included. Patients with PED (n=160) had a higher percentage of males, a higher body mass index, a higher percentage of any documented coronary artery disease (CAD), and a lower ejection fraction compared to patients without PED. In a univariate analysis, there was a significant association between PED and asymptomatic left ventricular systolic dysfunction (ALVSD), as well as after stratifying by sex and presence of CAD. In a multivariate analysis adjusting for age, sex, BMI and CAD status, ALVSD was significantly associated with PED. The authors concluded that the study demonstrated that ALVSD is associated with PED, regardless of confounding variables including the presence of CAD. Assessing PED noninvasively using EndoPAT could be a useful tool in detecting asymptomatic cardiac disease in low risk patients. The prognostic value of these findings should be further investigated.~~

Van den Heuvel et al. (2015) examined the applicability of ~~peripheral arterial tonometry (~~PAT~~)~~ to detect a low risk of coronary artery disease (CAD) in a chest pain clinic. In 93 patients, PAT was performed resulting in ~~reactive hyperaemia (~~RHI~~)~~ and augmentation (AIx) indices. Patients 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.

Rubenstein 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 hyperaemia (RH) was manually induced, patients were evaluated over a 7-year follow-up period for subsequent cardiovascular adverse events, such as cardiac death, myocardial infarction ~~(MI)~~, 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)**~~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=1957), Hamburg et al. (2008) evaluated the relationship between digital pulse amplitude using a fingertip ~~peripheral arterial tonometry (~~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)

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 (Aa): 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 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.~~
- ~~**Advanced Lipoprotein Analysis:** The contribution to initial CVD event risk assessment using apolipoprotein B is uncertain.~~

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:
  o Persistently elevated primary hypertriglyceridemia (≥175 mg/dL, nonfasting)
  o 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.**
- **Advanced Lipoprotein Analysis: The contribution to initial CVD event risk assessment using apolipoprotein B is uncertain.**

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.

- **Long-Chain Omega-3 Fatty Acids**: ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults do not address this test as a measure of cardiovascular risk.
- **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 2021 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)/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~~ **B** and lipoprotein (a):

- A relative indication for apolipoprotein ~~b~~ **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)** ~~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~~ **The ASCP recommends against routinely** ordering expanded lipid panels (particle sizing, nuclear magnetic resonance) as screening tests for cardiovascular disease (ASCP, 2020).

Endocrine Society

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

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)**

US 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.

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): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed January 18, 2020)

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): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm. (Accessed January 18, 2020)

Products used to measure apoliproteins are too numerous to list. Refer to the following website for more information (use product code DER or MSJ): http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.

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.

The EndoPAT 2000 received FDA 510(k) clearance (K032519) on November 12, 2003. According to the clearance summary, the Endo PAT 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.

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.

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 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.

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Policy History/Revision Information

Date	Summary of Changes
TBD	**Coverage Rationale** • Added language to indicate multi-protein diagnostic biomarkers, such as 3-proteins [high sensitivity (HS) troponin, adiponectin, and kidney injury molecule-1 (KIM-1)] or 4-proteins [NT-proBNP, osteopontin, tissue inhibitor of metalloproteinase-1 (TIMP-1), and KIM-1] with algorithm and reported as a risk score, are unproven and not medically necessary **Applicable Codes** • Added CPT codes 0308U, 0309U and 84999 • Removed CPT codes 0111T and 0126T • Added language "Codes labeled with an asterisk(*) are not on the state of Louisiana Fee Schedule and therefore not covered by the State of Louisiana Medicaid Program." **Supporting Information** • Updated *Description of Services*, *Clinical Evidence*, and *References* sections to reflect the most current information • Archived previous policy version CS015LA.J

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.

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