Cardiovascular Disease Risk Tests

Policy Number: 2021T0389R
Effective Date: January 1, 2021

Instructions for Use

Table of Contents Page

Related Commercial Policy
• Genetic Testing for Cardiac Disease

Community Plan Policy
• Cardiovascular Disease Risk Tests

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

Applicable Codes

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

CPT Code	Description
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
0423T	Secretory type II phospholipase A2 (sPLA2-IIA)
82172	Apolipoprotein, each
83695	Lipoprotein (a)
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)

CPT Code	Description
83701	Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (e.g., electrophoresis, ultracentrifugation)
83704	Lipoprotein, blood; quantitation of lipoprotein particle number(s) (e.g., by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed
93050	Arterial pressure waveform analysis for assessment of central arterial pressures, includes obtaining waveform(s), digitization and application of nonlinear mathematical transformations to determine central arterial pressures and augmentation index, with interpretation and report, upper extremity artery, non-invasive
93799	Unlisted cardiovascular service or procedure
93895	Quantitative carotid intima media thickness and carotid atheroma evaluation, bilateral
93998	Unlisted noninvasive vascular diagnostic study

Description of Services

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

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.

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.

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.

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.

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.

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.

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.

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.

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.

Shah et al. (2020) conducted 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.

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. These results may lead to better identification of target populations who might benefit from future Lp(a)-lowering therapies. Some limitations were identified. Differences in storage duration among the included cohorts may have contributed to differences in the Lp(a) levels across populations. Further, Lp(a) measurements were not performed consecutively so they could not correct for regression dilution bias.

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).

Higher LDL particle number has been associated with cardiovascular disease incidence, but studies have not determined whether any measures of LDL subfractions add incremental benefit to traditional risk factor assessment. Routine use of clinically available LDL subfraction tests to estimate cardiovascular disease risk is premature (Ip et al., 2009).

Lipoprotein-Associated Phospholipase A2 (Lp-PLA2)

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 stroke in adults.

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) 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) 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.

Evidence from a number of large prospective group and case-control studies consistently demonstrate a positive association of lipoprotein-associated phospholipase A2 (Lp-PLA2) with coronary heart disease (CHD) events. This association appears to be independent of most other risk factors. Increasing levels of Lp-PLA2 indicate increasing risk of CHD events. However, the overall magnitude of these associations varied considerably and the evidence was weakened by several methodological limitations, such as heterogeneity across trials, varying approaches to measuring levels of Lp-PLA2, differences in patient populations and variability in length of follow-up.

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-PLA2 and to determine the role of Lp-PLA2 as a potential adjunct to traditional risk assessment in the overall management of CHD in adults).

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.

Garga 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.

While these studies suggest that Lp-PLA_2 is an independent risk factor for CHD, there is a lack of agreement on how this information would be used in clinical decision-making. The key outcome of risk assessment for coronary heart disease (CHD) or ischemic stroke prediction is an improvement in health outcomes, i.e., reduced morbidity and mortality. Improved risk prediction does not by itself result in improved health outcomes. At the present time, measurements of Lp-PLA_2 are not a component of the guidelines developed by the National Cholesterol Education Program Adult Treatment Panel III. While studies have suggested that statin drugs and fibrates may reduce levels of Lp-PLA_2, it is not known whether such drug therapy in patients not already considered candidates based on other well established risk factors will ultimately decrease the incidence of coronary heart disease or ischemic stroke.

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 associated with increased risk of cardiovascular events. However, it is not clear if this association is causal.

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 the benefits of sPLA2 findings on health outcomes in patients with cardiovascular disease.

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.

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 PAT or brachial artery ultrasound with cardiovascular disease. However, these associations are insufficient to directly demonstrate their clinical utility to effectively predict cardiovascular morbidity. 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.

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.

The US Preventive Services Task Force (USPSTF) concludes that the current evidence is insufficient to assess the balance of benefits and harms of adding the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hsCRP) level, or coronary artery calcium (CAC) score to traditional risk assessment for cardiovascular disease (CVD) in asymptomatic adults to prevent CVD events (July 2018).

A 2019 Hayes report on noninvasive peripheral arterial tonometry states that the ”evidence evaluating the clinical validity of reactive hyperemia peripheral arterial tonometry (RH-PAT) is insufficient to determine its value in the evaluation of coronary artery disease or to predict cardiovascular adverse events” (Hayes, 2019).

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 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.

Professional Societies

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

The 2017 AACE guidelines for management of dyslipidemia and prevention of cardiovascular disease (Jellinger et al, 2017) make the following recommendations:

- Carotid Intima Media Thickness: CIMT may be considered to refine risk stratification to determine the need for more aggressive atherosclerotic cardiovascular disease (ASCVD) preventive strategies (Intermediate level of evidence and recommendation grade).
- Apolipoprotein B: For individuals at increased risk of ASCVD, including those with diabetes, an optimal apolipoprotein B (apo B) goal is <90 mg/dL, while for individuals with established ASCVD or diabetes plus 1 or more additional risk factor(s), an optimal apo B goal is <80 mg/dL, and for individuals at extreme risk, an optimal apo B goal is <70 mg/dL (Strong level of evidence and recommendation grade).
- Lipoprotein (A): Testing for lipoprotein(a) is not generally recommended, although it may provide useful information to assign risk in caucasians with ASCVD, those with an unexplained family history of early ASCVD, or those with unknown family history such as adopted individuals.
- Lipoprotein-Associated Phospholipase A2: Measuring lipoprotein-associated phospholipase A2 (Lp-PLA2) in some studies has demonstrated more specificity than hsCRP, when it is necessary to further stratify an individual's ASCVD risk, especially in the presence of hsCRP elevations (Strong level of evidence and recommendation grade).

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

A 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 (Arnett et al., 2019) identifies the following risk enhancing factors for clinician–patient risk discussion:

- Lipids/biomarkers associated with increased ASCVD risk:
  - Persistently elevated primary hypertriglyceridemia (≥175 mg/dL, nonfasting)
  - If measured:
    - Elevated high-sensitivity C-reactive protein (≥2.0 mg/L)
    - Elevated lipoprotein(a): A relative indication for its measurement is family history of premature ASCVD. A lipoprotein(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of lipoprotein(a)
    - Elevated apolipoprotein B (≥130 mg/dL): A relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor
    - Ankle-brachial index (<0.9)

The following guidelines are still listed as active on the ACC website. An ACC/AHA Task Force makes the following recommendations on assessing cardiovascular risk in asymptomatic adults (Greenland et al., 2010):

- 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. See Goff et al. (2013) for updated information.
- 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 2020 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 and lipoprotein (a):

- A relative indication for apolipoprotein b measurement would be triglyceride ≥200 mg/dL. A persistent elevation of apoB can be considered a risk-enhancing factor.
- Indications for Lp(a) measurement are family history of premature atherosclerotic cardiovascular disease (ASCVD) or personal history of ASCVD not explained by major risk factors. An elevation of Lp(a) is considered to be a risk-enhancing factor. This is especially in those with higher Lp(a) values and, if used in women, only in the presence of hypercholesterolemia (Grundy et al., 2019)

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 (Meschia et al., 2014)

Endocrine Society

In a clinical guideline on the evaluation and treatment of hypertriglyceridemia, the Endocrine Society recommends against the routine measurement of lipoprotein subclasses and particle concentration. Studies have not provided conclusive evidence that measurement of particle size or density adds to CVD prediction beyond the standard lipid risk factors. These recommendations are based on low quality evidence (Berglund et al., 2012).

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 (ESC National Cardiac Societies, 2019)

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. See the following website for more information (use product code IYO). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.

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. See the following website for more information (use product code DFC). Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.

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

Products for the measurement of Lp-PLA_2 can be found with product codes NOE and JJX at the following site: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm.

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.

Centers for Medicare and Medicaid Services (CMS)

Medicare does not have a National Coverage Determination (NCD) for arterial compliance testing, using waveform analysis used to determine risk for cardiovascular disease. Local Coverage Determinations (LCDs) exist; see the LCDs for Noncovered Services and Services That Are Not Reasonable and Necessary.

Medicare does not have an NCD for carotid intima-media thickness (CIMT) testing used as a screening tool for the management of cardiovascular disease LCDs exist; see the LCDs for Non-Invasive Cerebrovascular Studies.

Medicare does not have an NCD for advanced lipoprotein analysis (e.g., apolipoproteins, lipoprotein (a), subfractions or particle size) used to determine risk for cardiovascular disease. LCDs exist; see the LCDs for MolDX: Biomarkers in Cardiovascular Risk Assessment and Noncovered Services.

Medicare does not have an NCD for lipoprotein-associated phospholipase A2, (Lp-PLA_2) enzyme and other human A2 phospholipases such as secretory phospholipase A2 (sPLA2-IIA) testing used to determine risk for cardiovascular disease or ischemic stroke. LCDs exist; see the LCDs for MolDX: Biomarkers in Cardiovascular Risk Assessment, Assays for Vitamins and Metabolic Function and Non-covered Services.

Medicare does not have an NCD for measurement of long-chain omega-3 fatty acids testing used to determine cardiovascular disease risk. LCDs exist; see the LCDs for Category III CPT Codes, Noncovered Services and Services That Are Not Reasonable and Necessary.

Medicare does not have an NCD for endothelial function assessment using tools such as peripheral arterial tonometry (PAT) or brachial artery pressure ultrasound as prognostic indicators to determine risk of cardiovascular disease LCDs exist; see LCDs for Noncovered Services and Services That Are Not Reasonable and Necessary.
(Accessed February 14, 2020)

References

American Diabetes Association. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020 Jan;43(Suppl 1):S111-S134.

Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Sep 10;140(11):e596-e646.

Bays HE, Jones PH, Orringer CE, et al. National Lipid Association Annual Summary of Clinical Lipidology 2016. J Clin Lipidol. 2016 Jan-Feb;10(1 Suppl):S1-43.

Benderly M, Sapir B, Kalter-Leibovici O, et al. Lipoprotein-associated phospholipase A and subsequent cardiovascular events and mortality among patients with coronary heart disease. Biomarkers. 2017 May - Jun;22(3-4):219-224.

Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012 Sep;97(9):2969-89.

Caslake MJ, Packard CJ, Robertson M, et al. PROSPER Study Group. Lipoprotein-associated phospholipase A(2), inflammatory biomarkers, and risk of cardiovascular disease in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER). Atherosclerosis. 2010;210(1):28-34.

Cheng Hao-Min, Chuang Shao-Yuan, Wang J, et al. Prognostic significance of mechanical biomarkers derived from pulse wave analysis for predicting long-term cardiovascular mortality in two population-based cohorts. International Journal of Cardiology 215 (2016) 388–395.

Costanzo P, Perrone-Filardi P, Vassallo E, et al. Does carotid intima-media thickness regression predict reduction of cardiovascular events? A meta-analysis of 41 randomized trials. J Am Coll Cardiol. 2010 Dec 7;56(24):2006-20.

Davidson MH, Corson MA, Alberts MJ, et al. Consensus panel recommendation for incorporating lipoprotein-associated phospholipase A2 testing into cardiovascular disease risk assessment guidelines. Am J Cardiol. 2008 Jun 16;101(12A):51F-57F.

Day TG, Park M, Kinra S. The association between blood pressure and carotid intima-media thickness in children: a systematic review. Cardiol Young. 2017 Sep;27(7):1295-1305.

Den Ruijter HM, Peters SA, Anderson TJ, et al. Common carotid intima-media thickness measurements in cardiovascular risk prediction: a meta-analysis. JAMA. 2012 Aug 22;308(8):796-803.

Di Angelantonio E, Gao P, Pennells L, et al.; Emerging Risk Factors Collaboration. Lipid-related markers and cardiovascular disease prediction. JAMA. 2012 Jun 20;307(23):2499-506.

Duprez, D. A., Kaiser, D. R., Whitwam, W., et al. Determinants of radial artery pulse wave analysis in asymptomatic individuals. Am J Hypertens. 2004;17(8):647-53.

European Society of Cardiology (ESC), European Atherosclerosis Society (EAS). Dyslipidemia Clinical Practice Guidelines (2019). *Medscape* - Oct 08, 2019.

Folsom, AR, Kronmal, RA, Detrano, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med. 2008;168(12):1333-1339.

Forbes CA, Quek RG, Deshpande S, et al. The relationship between Lp(a) and CVD outcomes: a systematic review. Lipids Health Dis. 2016; 15(1):95.

Garg, PK, McClellandb, RL, Jenny, NS, et al. Lipoprotein-associated phospholipase A2 and risk of incident cardiovascular disease in a multi-ethnic cohort: The multi ethnic study of atherosclerosis. Atherosclerosis. 2015 July ; 241(1): 176–182.

Geisel MH, Bauer M, Hennig F, et al. Comparison of coronary artery calcification, carotid intima-media thickness and ankle-brachial index for predicting 10-year incident cardiovascular events in the general population. Eur Heart J. 2017 Jun 14;38(23):1815-1822.

Goldberger ZD, Valle JA, Dandekar VK, et al. Are changes in carotid intima-media thickness related to risk of nonfatal myocardial infarction? A critical review and meta-regression analysis. Am Heart J. 2010 Oct;160(4):701-14.

Goldstein LB, Bushnell CD, Adams RJ, et al. American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research; Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011 Feb;42(2):517-84. Erratum in: Stroke. 2011 Feb;42(2):e26.

Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2010 Dec 21;122(25):e584-636.

Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019 Jun 18;139(25):e1082-e1143.

Guardiola M, Exeter HJ,Perret C, et al. PLA2G10 gene variants, sPLA2 activity, and coronary heart disease risk. Circ Cardiovasc Genet. 2015 Apr;8(2):356-62.

Hamburg NM, Keyes MJ, Larson MG, et al. Cross-sectional relations of digital vascular function to cardiovascular risk factors in The Framingham Heart Study. Circulation. 2008; 117(19):24676-2474.

Hayes, Inc. Hayes Medical Technology Directory Report. Noninvasive Peripheral Arterial Tonometry. Lansdale, PA: Hayes Inc. December 11, 2014. Updated March 22, 2019.

Hitsumoto, Takashi. Arterial velocity pulse index as a novel marker of atherosclerosis using pulse wave analysis on high sensitivity troponin T in hypertensive patients. Cardiol Res. 2017;8(2):36-43.

Holmes MV, Simon T, Exeter HJ, et al. Secretory phospholipase A(2)-IIA and cardiovascular disease: a mendelian randomization study. J Am Coll Cardiol. 2013 Nov 19;62(21):1966-76.

Ip S, Lichtenstein AH, Chung M, et al. Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes. Ann Intern Med. 2009 Apr 7;150(7):474-84.

Jeevarethinam A, Venuraju S, Weymouth M, et al. Carotid intimal thickness and plaque predict prevalence and severity of coronary atherosclerosis: a pilot study. Angiology. 2015 Jan;66(1):65-9.

Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. Endocr Pract. 2017;23(Suppl 2).

Kouvari M, Panagiotakos DB. The role of lipoprotein (a) in primary and secondary cardiovascular disease prevention: a systematic review of epidemiological studies. Curr Opin Cardiol. 2019a Jul;34(4):424-434.

Kouvari M, Panagiotakos DB, Chrysohoou C, et al. Lipoprotein (a) and 10-year cardiovascular disease incidence in apparently healthy individuals: a sex-based sensitivity analysis from ATTICA cohort study. Angiology. 2019b Oct;70(9):819-829.

Kuvin JT, Mammen A, Mooney P, et al. Assessment of peripheral vascular endothelial function in the ambulatory setting. Vasc Med. 2007; 12: 13-16.

Li D, Wei W, Ran X, et al. Lipoprotein-associated phospholipase A2 and risks of coronary heart disease and ischemic stroke in the general population: A systematic review and meta-analysis. Clin Chim Acta. 2017 Aug;471:38-45.

Li D, Zhao L, Yu J, et al. Lipoprotein-associated phospholipase A2 in coronary heart disease: Review and meta-analysis. Clin Chim Acta. 2017 Feb;465:22-29.

Liu, Jing, Hong, Yuling, Qi, Yue, et al. Systematic review of the association between lipoprotein-associated phospholipase A2 and atherosclerosis. N Am J Med Sci (Boston). 2015 September 01.

Mahajan H, Choo J, Masaki K, et al. Serum long-chain n-3 polyunsaturated fatty acids and aortic calcification in middle-aged men: the population-based cross-sectional ERA-JUMP study. Nutr Metab Cardiovasc Dis. 2019 Aug;29(8):837-846.

Meschia JF, Bushnell C, Boden-Albala B, et al. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:3754–3832.

Nambi V, Chambless L, Folsom AR, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am Coll Cardiol. 2010 Apr 13;55(15):1600-7.

Nambi V, Hoogeveen RC, Chambless L, et al. Lipoprotein-associated phospholipase A2 and high-sensitivity C-reactive protein improve the stratification of ischemic stroke risk in the Atherosclerosis Risk in Communities (ARIC) study. Stroke. 2009 Feb;40(2):376-81.

National Heart, Lung and Blood Institute (NHLBI). Third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III): Final report. NIH Publication No. 02-5215. September 2002.

Olson N, O'Meara ES, Jenny NS, et al. Lipoprotein-associated phospholipase A2 and risk of venous thrombosis in older adults. Am J Hematol. 2008;83(7):524-527.

Roman MJ, Naqvi TZ, Gardin JM, et al. American Society of Echocardiography Report. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society for Vascular Medicine and Biology. Vasc Med. 2006; 11: 201-211.

Roy RR, Hurst RT, Lester SJ, et al. Risk stratification for cardiovascular disease in women in the primary care setting. J Am Soc Echocardiogr. 2015 Oct;28(10):1232-9.

Rubinshtein R., Kuvin J.T., Soffler M., Lennon R.J., Lavi S., Nelson R.E., Pumper G.M., Lerman L.O., Lerman A. Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. European Heart Journal. 31 (9) (pp 1142-1148), 2010.

Sara JD, Taher R, Lerman L and Lerman A. Asymptomatic left ventricle systolic dysfunction is associated with peripheral endothelial dysfunction in patients without coronary artery disease. Journal of the American College of Cardiology. Volume 73, Issue 9 Supplement 1, March 2019.

Shah NP, Wang Q, Wolski KE, et al. The role of lipoprotein (a) as a marker of residual risk in patients with diabetes and established cardiovascular disease on optimal medical therapy: post hoc analysis of ACCELERATE. Diabetes Care. 2020 Feb;43(2):e22-e24.

Stock, Eveline, Maddalena, Julia, Schaefer, Ernst, et al. Advanced lipid testing uncovers hidden cardiovascular disease risk: A case control analysis. Journal of Clinical Lipidology, Vol 10, No 3, June 2016.

Task Force Members; ESC National Cardiac Societies; ESC Committee for Practice Guidelines (CPG). Corrigendum to "2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk" Atherosclerosis 290 (2019) 140-205.

Tian Y, Jia H, Li S, et al. The associations of stroke, transient ischemic attack, and/or stroke-related recurrent vascular events with lipoprotein-associated phospholipase A2: A systematic review and meta-analysis. Medicine (Baltimore). 2017 Dec;96(51):e9413.

US Preventive Services Task Force (USPSTF). Recommendation Statement. Risk assessment for cardiovascular disease with nontraditional risk factors. July 2018.

van den Heuvel M, Sorop O, Musters PJ, et al. Peripheral arterial tonometry cannot detect patients at low risk of coronary artery disease. Neth Heart J. 2015 Sep;23(10):468-74.

van den Oord SC, Sijbrands EJ, ten Kate GL, et al. Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis. Atherosclerosis. 2013 May;228(1):1-11.

Venuraju S, Jeevarethinam A, Mehta VS, et al. Predicting severity of coronary artery disease in patients with diabetes using endothelial function measured with peripheral arterial tonometry: PROCEED study. Angiology. 2019 Aug;70(7):613-620.

Villines T, Hsu L, Blackshear C, et al. Cardiovascular events in black Americans (From the Jackson Heart Study). Am J Cardiol 2017;120:1528–1532.

Waldeyer C, Makarova N, Zeller T, et al., Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. Eur Heart J. 2017 Apr 24.

Wei L, Ke Z, Zhao Y, et al. The elevated lipoprotein-associated phospholipase A2 activity is associated with the occurrence and recurrence of acute cerebral infarction. Neuroreport. 2017 Apr 12;28(6):325-330.

Xin H, Chen ZY, Lv XB, et al. Serum secretory phospholipase A2-IIa (sPLA2-IIA) levels in patients surviving acute myocardial infarction. Eur Rev Med Pharmacol Sci. 2013 Apr;17(8):999-1004.

Younus A, Humayun C, Ahmad R et al. Lipoprotein-associated phospholipase A2 and its relationship with markers of subclinical cardiovascular disease: A systematic review. Journal of Clinical Lipidology, Vol 11, No 2, April 2017.

Zhu YM, Verma S, Fung M, et al. Association of apolipoproteins b and a-1 with markers of vascular health or cardiovascular events. Can J Cardiol. 2017 Oct;33(10):1305-1311.

Policy History/Revision Information

Date	Summary of Changes
01/01/2021	Applicable Codes • Updated list of applicable CPT codes to reflect annual code edits; removed 0111T and 0126T Supporting Information • Archived previous policy version 2020T0389Q

Instructions for Use

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

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

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