

# CARDIOVASCULAR DISEASE RISK TESTS

Policy Number: 2019T0389P

Effective Date: January 1, 2019

[Instructions for Use](#) ⓘ

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## Related Commercial Policy

- [Gene Expression Tests](#)

## 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 Coverage Determination 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
0111T	Long-chain (C20-22) omega-3 fatty acids in red blood cell (RBC) membranes
0126T	Common carotid intima-media thickness (IMT) study for evaluation of atherosclerotic burden or coronary heart disease risk factor assessment
0423T	Secretory type II phospholipase A2 (sPLA2-IIA)
82172	Apolipoprotein, each
83695	Lipoprotein (a)
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA <sub>2</sub> )
83701	Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (e.g., electrophoresis, ultracentrifugation)

CPT Code	Description
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

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## 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, while the PAT records finger arterial pulse wave amplitude in response to reactive hyperemia. Increased finger pulse amplitude is posited to be a complex response to ischemia and reflects changes in digital flow and digital vessel dilation (Kuvin et al., 2007; Hamburg et al., 2008).

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).

**Arterial Compliance**

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 small, randomized, controlled trial (n=30), Woodman et al. (2005) compared large and small artery compliance (C1 and C2, respectively), stroke volume/pulse pressure (SV/PP), augmentation index (AIx), central pulse pressure (CPR), stiffness index (SI), systemic arterial compliance (SAC) and brachial pulse pressure to central pulse wave velocity (PWV). The authors concluded that C1, C2, SV/PP, and SAC showed poor agreement with central PWV, an established measure of central arterial stiffness. In comparison, SI, AIx, and CPP are more closely related to central arterial stiffness.

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.

Wilson et al. (2004) compared small and large arterial elasticity (SAE/C2, LAE/C1), endothelial function as measured by flow mediated dilation (FMD), carotid intima-medial thickness (IMT), ankle brachial index (ABI), pulse pressure (PP) and pulse wave velocity (PWV) for assessing arterial function in low and high vascular disease risk groups. Twenty healthy subjects (HS) and 20 older subjects with type 2 diabetes mellitus (DM) were studied with all techniques at a single sitting by a single operator. C2 assessed by pulse wave analysis correlated with endothelial function measured by FMD in young apparently healthy subjects and older subjects with type 2 diabetes. Systolic BP and PP correlated with C2 and FMD in older diabetic subjects but not healthy subjects. The interrelationships between arterial function measures are different in high and low risk populations. This variability needs to be considered when applying these techniques to individuals in different populations.

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.

The objective of the first study was to determine arterial elasticity in normotensive and hypertensive individuals using the CVProfilor. An evaluation of large artery and small artery elasticity in 212 normotensives (with and without a family history of hypertension) and hypertensives (treated and controlled or untreated and uncontrolled) demonstrated that both large artery and small artery elasticity indices were significantly higher ( $P<0.0001$ ) in normotensives without a family history compared with untreated and uncontrolled hypertensives. After controlling for age and BSA, there was a significant linear trend ( $P=0.0001$ ) across the four groups in these elasticity indices. As hypertension status worsened, large and small artery elasticity decreased, suggesting a potential for the diagnostic use of arterial elasticity determinations (Prisant et al., 2001a).

The aim of the second study was to assess and compare the accuracy of sequential same arm blood pressure measurement by the mercury sphygmomanometer with oscillometric blood pressure measurements using the CVProfilor, which also determines arterial elasticity. Sequential single-arm blood pressure measurements performed in 230 normotensives and hypertensives (in which the sequence of testing was randomized) showed that the CVProfilor, which uses a dynamic linear deflation oscillometric method, measures blood pressure with reasonable agreement to that obtained manually using a mercury sphygmomanometer as reference method. For systolic and diastolic blood pressure, 60.9% and 70.4% of sequential measurements were within mm Hg, respectively, and 85.2% of systolic and 92.6% of diastolic blood pressure measurements were within mm Hg agreement (Prisant et al., 2001b).

The third study examined arterial elasticity by ethnicity in normotensive and hypertensive individuals to determine whether there were racial differences. An evaluation of large and small artery elasticity indices in 178 normotensives and hypertensives confirmed that these are reduced as hypertension status worsens. While age and height were important covariates of small and large artery elasticity, and hypertension status was a significant predictor of small and large artery elasticity, race was not found to be a significant predictor of either small or large artery elasticity. That is, large and small artery elasticity indices do not differ between white and black individuals with varying degrees of hypertension after adjusting for covariates (Prisant et al., 2002).

### **Carotid Intima-Media Thickness (CIMT)**

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  $10.3 \pm 2.8$  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.

The 2016 European Guidelines on cardiovascular disease prevention in clinical practice concluded that routine screening with imaging modalities to predict future cardiovascular (CV) events is generally not recommended in clinical practice. Imaging methods may be considered as risk modifiers in CV risk assessment, i.e., in individuals with calculated CV risks. Currently, most imaging techniques have not been rigorously tested as screening tools in CV risk assessment; more evidence on calibration, reclassification and cost-effectiveness is still needed.

### **Advanced Lipoprotein Analysis**

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  $\leq$  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 A<sub>2</sub> (Lp-PLA<sub>2</sub>) 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 ( $\geq$ 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)***

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-PLA<sub>2</sub>) 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-PLA<sub>2</sub> 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-PLA<sub>2</sub> activity, CHD risk increased by 12%; no association between 1-SD increases in Lp-PLA<sub>2</sub> activity and IS was observed. Lp-PLA<sub>2</sub> mass was associated with CHD risk. Lp-PLA<sub>2</sub> mass per 1-SD increase was not associated with IS risk. The authors concluded that greater Lp-PLA<sub>2</sub> activity or mass was associated with an increased risk of CHD and IS; however, additional well-designed trials are warranted to confirm this association.

A systematic review and meta-analysis was conducted by Tian et al. (2017) to assess the associations of Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub> 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-PLA<sub>2</sub> activity levels were associated with recurrent vascular events and in the general population elevated Lp-PLA<sub>2</sub> levels were associated with the risk of stroke.

Li et al. (2017) conducted a meta-analysis to investigate the association between Lp-PLA<sub>2</sub> and the prognosis of coronary heart disease (CHD). Fifteen studies with 30,857 participants were included. Overall, higher Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub> in predicting cardiovascular events was observed in patients with stable CHD who were not receiving therapies for inhibiting Lp-PLA<sub>2</sub>. The authors concluded that greater Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub>.

Wei et al. (2017) performed a study to investigate the role of Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub> in ACI was significantly higher than non-ACI. The serum level of Lp-PLA<sub>2</sub> in the recurrence of ACI was significantly higher than the nonrecurrence. The serum levels of Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub> 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-PLA<sub>2</sub> level can be a risk factor for ischemic stroke in the Chinese population and the serum level of Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub>) with coronary heart disease (CHD) events. This association appears to be independent of most other risk factors. Increasing levels of Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub>, 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-PLA<sub>2</sub> alone or in combination with other traditional biomarkers and/or risk assessments to determine the risk of CHD events in healthy or asymptomatic individuals. Additional well-designed clinical trials are necessary to establish the clinical utility of Lp-PLA<sub>2</sub> and to determine the role of Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub> and atherosclerotic cardiovascular disease (CVD), to evaluate the relationship between Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub> 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-PLA<sub>2</sub> is closely associated with CVD events. High Lp-PLA<sub>2</sub> was associated with increased risk for both first and recurrence of total CVD, CHD, and ischemic stroke. To understand the role of Lp-PLA<sub>2</sub> in the early prevention and treatment of CVD, it is important to clarify the relationship between Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub> is associated with increased risk of clinical CVD events, while the association between Lp-PLA<sub>2</sub> and subclinical atherosclerosis remains uncertain. Further prospective cohort studies on the relationship between Lp-PLA<sub>2</sub> and subclinical atherosclerosis are warranted to determine whether Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub> and first-time cardiovascular events in a healthy multi-ethnic cohort characterized by presence or absence of baseline subclinical atherosclerosis. Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub> 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-PLA<sub>2</sub> mass and activity were weakly correlated with carotid IMT and CAC. In the subset of patients on baseline statin therapy (n=879), higher Lp-PLA<sub>2</sub> mass was not associated with an increased risk of incident CVD or CHD. The authors concluded that Lp-PLA<sub>2</sub> 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<sub>2</sub> 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).

The 2016 European Guidelines on cardiovascular disease prevention in clinical practice concluded the following regarding biomarkers:

- Not all potentially useful circulatory biomarkers have undergone state-of-the-art assessment of their added value in CV risk prediction on top of conventional risk factors.
- Biomarkers may be useful in specific subgroups, but this has been addressed in only a limited number of studies.
- The role of metabolomics as risk factors for CVD and to improve CV risk prediction beyond conventional risk factors should be further assessed.

An expert consensus panel (Davidson et al., 2008), evaluated how Lp-PLA<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> levels. It is not presently known whether lowering Lp-PLA<sub>2</sub> levels will decrease the incidence of CHD or stroke and improve clinical health outcomes. Treatment for elevated Lp-PLA<sub>2</sub> is targeted at lowering LDL levels.

While these studies suggest that Lp-PLA<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub>, 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<sub>2</sub> improved ischemic stroke risk prediction. The improvement was most enhanced when Lp-PLA<sub>2</sub> 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**

While there are many published studies addressing the potential benefits of adding omega-3 fatty acids to one's diet, no studies were identified evaluating the clinical application of measuring long-chain omega-3 fatty acids to determine risk of cardiovascular disease.

### **Endothelial Function Assessment**

A 2017 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, 2017).

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.

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<sub>2</sub> (Lp-PLA<sub>2</sub>) 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<sub>2</sub> 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 Dilatation:** ACC/AHA guidelines for the assessment of cardiovascular risk in asymptomatic adults state that peripheral arterial flow-mediated dilatation (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 guidelines state that some experts recommend a greater focus on non-HDL cholesterol, apolipoprotein B (apoB) or lipoprotein particle measurements to assess residual CVD risk in statin-treated patients who are likely to have small LDL particles, such as people with diabetes, but it is unclear whether clinical management would change with these measurements (ADA, 2014).

ADA 2018 guideline 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 Stroke Association Stroke Council (ASA)**

The AHA/ASA updated the guideline on primary prevention of stroke in 2011. The guideline states that measurement of inflammatory markers such as Lp-PLA<sub>2</sub> in patients without cardiovascular disease may be considered to identify patients who may be at increased risk of stroke, although their effectiveness (i.e., usefulness in routine clinical practice) is not well established (Goldstein et al., 2011).

### **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).

### **U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

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<sub>2</sub> can be found with product codes NOE and JJX at the following site:  
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmnm.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/pmnm.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/pmnm.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/pmnm.cfm?ID=K122129>.  
(Accessed October 12, 2018)

## CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not have a National Coverage Determination (NCD) for arterial compliance testing, using waveform analysis. 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. 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). LCDs exist; see the LCDs for [MoIDX: Biomarkers in Cardiovascular Risk Assessment](#).

Medicare does not have an NCD for lipoprotein-associated phospholipase A<sub>2</sub>, (Lp-PLA<sub>2</sub>) enzyme and other human A<sub>2</sub> phospholipases such as secretory phospholipase A<sub>2</sub> (sPLA<sub>2</sub>-IIA) testing. LCDs exist; see the LCDs for [MoIDX: 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 as a tool for determining 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. LCDs exist; see LCDs for [Noncovered Services](#) and [Services That Are Not Reasonable and Necessary](#).  
(Accessed November 9, 2018)

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#### POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
01/01/2019	<ul style="list-style-type: none"> <li>• Reorganized policy template:               <ul style="list-style-type: none"> <li>○ Simplified and relocated <i>Instructions for Use</i></li> <li>○ Removed <i>Benefit Considerations</i> section</li> </ul> </li> <li>• Simplified coverage rationale (no change to guidelines)</li> <li>• Updated list of applicable CPT codes:               <ul style="list-style-type: none"> <li>○ Added 93998</li> <li>○ Removed 0337T (<i>annual code edit</i>)</li> </ul> </li> <li>• Updated supporting information to reflect the most current clinical evidence, CMS information, and references</li> <li>• Archived previous policy version 2018T03890</li> </ul>

#### 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.

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.