



Medical Coverage Policy

Effective Date08/15/2023

Next Review Date08/15/2024

Coverage Policy Number..... 0137

Atherosclerotic Cardiovascular Disease Risk Assessment: Emerging Laboratory Evaluations

Table of Contents

Overview	2
Coverage Policy.....	2
General Background	4
Medicare Coverage Determinations	25
Coding Information.....	25
References	27

Related Coverage Resources

- [Cardiac Imaging Guidelines](#)
- [Carotid Intima-Media Thickness Measurement](#)
- [Genetic Testing for Hereditary and Multifactorial Conditions](#)
- [Genetic Testing for Hereditary Cardiomyopathies and Arrhythmias](#)
- [Plasma Brain Natriuretic Peptide in the Outpatient Setting](#)
- [Recurrent Pregnancy Loss: Diagnosis and Treatment](#)

INSTRUCTIONS FOR USE

The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer’s particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer’s benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer’s benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment and have discretion in making individual coverage determinations. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not

recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This Coverage Policy addresses emerging laboratory tests performed for atherosclerotic cardiovascular disease risk assessment.

Coverage Policy

Lipoprotein-associated phospholipase A2 (Lp-PLA₂) testing (CPT® 83698) is considered medically necessary for ANY of the following individuals who are at intermediate- or high-risk for developing coronary heart disease (CHD):

- any age with at least two or more major risk factors (e.g., smoking, hypertension, family history of premature CHD, diabetes mellitus, low levels of HDL cholesterol)
- age ≥ 65 years with one major risk factor
- cigarette smoking
- fasting blood glucose level of ≥ 100 mg/dl
- metabolic syndrome

Lipoprotein-associated phospholipase A2 (Lp-PLA₂) testing for ANY other indication is considered experimental, investigational or unproven.

Apolipoprotein B testing (CPT® 82172) is considered medically necessary when the individual is undergoing management for lipoprotein abnormalities and ANY of the following conditions is met:

- established coronary heart disease (CHD), as evidenced by ANY of the following:
 - previous history of myocardial infarction (MI)
 - stable or unstable angina
 - revascularization with coronary artery bypass grafting
 - percutaneous coronary angioplasty
- diabetes mellitus
- two or more major risk factors (i.e., tobacco smoking, hypertension, family history of premature CHD, low levels of HDL cholesterol, age [men ≥ 45 years, women ≥ 55 years])

Apolipoprotein B testing for ANY other indication is considered experimental, investigational or unproven.

Lipoprotein(a) enzyme immunoassay (Lp[a]) testing (CPT® 83695) is considered medically necessary for ANY of the following at-risk groups, when used to assess risk and guide treatment of lipoprotein abnormalities:

- family history of premature CHD
- genetic predisposition for hypercholesterolemia
- established atherosclerotic heart disease with a normal routine lipid profile
- hyperlipidemia refractory to therapy
- history of recurrent arterial stenosis

Lipoprotein(a) enzyme immunoassay (Lp[a]) testing for ANY other indication is considered experimental, investigational or unproven.

The following testing is considered experimental, investigational or unproven for screening, diagnosing or management of coronary heart disease:

- apolipoprotein A-1
- circulating micro RNAs
- CoEnzyme Q10
- cystatin C
- fatty acids (e.g., Omega-3, Omega-6, saturated, monounsaturated [e.g., Boston Heart Fatty Acid Balance™ test])
- GlycA (glycosylated acute phase proteins)
- growth stimulation expressed gene 2 (ST2)
- leptin and other similar type tests (e.g., adiponectin, apelin, galectin 3, resistin, retinol binding protein, visfatin)
- lipoprotein remnants, including very low density lipoprotein (VLDL) and intermediate dense lipoprotein (IDL)
- long-chain omega-3 fatty acids
- molecular lipid and/or metabolic profiling (e.g., lipidomics, metabolomics)
- osteoprotegerin
- oxidized phospholipids
- peroxisome proliferator activated receptor
- protein C
- plasma ceramides (e.g., MI-Heart Ceramides)
- plasma myeloperoxidase (MPO)
- pregnancy-associated plasma protein-A (PAPP-A)
- prothrombotic factors (e.g., plasminogen activator inhibitor [PAI-1], activated factor VII, tissue plasminogen activator [tPA], von Willebrand factor, factor V Leiden, protein C, antithrombin III, fibrinogen)
- quantification of lipoproteins, including any of the following:
 - VLDL subclasses
 - IDL subclasses
 - high-density lipoprotein (HDL) subclasses (LpAI, LpAI/AII and/or HDL3, HDL2)
 - low-density lipoprotein (LDL) subclass size and concentration (small and large LDL particles)
- secretory type II phospholipase A2 (sPLA₂), including isoenzymes (e.g., sPLA₂-IIA)
- serum sterols (e.g., Boston Heart Cholesterol Balance® test)
- skin cholesterol testing
- test panels/profiles that include non-standard lipoprotein and/or other emerging cardiac disease risk markers (e.g., HART CADhs, HART CVE, vertical auto profile [VAP], NMR LipoProfile®, TruRisk™ Lipoprotein Particle Profile™, MIRISK VP™, Singulex® Cardiac/Inflammatory Biomarkers, Boston Heart HDL Map®, Cholesterol Balance® and Fatty Acid Balance™ Test)
- thromboxane metabolite(s) testing
- total cholesterol content in red blood cell membranes
- tumor necrosis factor alpha
- Troponin*
- homocysteine testing*

***Note: The measurement of troponin levels to assess for acute cardiac injury or homocysteine testing for evaluation of folate deficiency, homocystinuria or venous**

thromboembolism (i.e., unexplained thrombotic disorders) does not fall within the scope of this Cigna Medical Coverage Policy.

General Background

Cholesterol has been proven to play a major role in the development of heart disease and contains both lipids and proteins (lipoproteins). Low density lipoprotein (LDL) is considered the primary target for lipid lowering therapy.

Determination of cardiac disease risk is based on standard, accepted risk-stratification approaches, involving determination of standard lipid profiles consisting of total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides levels.

Scientific evidence illustrates that therapies aimed at reducing LDL cholesterol levels reduce cardiovascular risk and historically various guidelines have recommended treating to LDL-cholesterol target levels. However, in 2013, American College of Cardiology (ACC) and American Heart Association (AHA) no longer recommended treating to specific LDL and non-HDL targets. According to the ACC/AHA guidelines (Goff, et al., 2013), evidence from randomized controlled clinical trials supporting treatment to specific targets is lacking. The emphasis for management of cardiovascular risk, in addition to a healthy lifestyle and diet, is the intensity of statin use (i.e., appropriate and maximum-tolerated statin therapies). Once an individual is placed on statin therapy, follow-up LDL testing may be considered on an individual basis to monitor adherence to therapy and efficacy. Similarly, the Department of Veterans Affairs and Department of Defense (Va/DOD) Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction (2020) supports the use of statin therapy, adoption of healthy lifestyles, and a healthy diet for individuals with elevated cardiovascular risk. With regards to secondary prevention the guideline does not identify any LDL-C threshold for statin therapy with subjects with known atherosclerotic cardiovascular disease (ASCVD) and strongly recommends against the routine monitoring of LDL-C and non-HDL-C goals. According to the guidelines, patients with known ASCVD should be offered treatment with a moderate dose statin, regardless of lipid levels.

While it remains that some individuals continue to have significant risk despite lowering LDL cholesterol levels, some authors contend that evaluating lipoproteins other than LDL (or non-HDL) levels may provide significant additional information regarding cardiovascular disease (CVD) risk for a subset of patients (e.g., those identified as "high risk" or with multiple risk factors). Risk factors other than LDL cholesterol are referred to as "emerging/novel risk factors" and include a variety of tests such as serum inflammatory markers, comprehensive lipoprotein testing, angiotensin gene testing, prothrombotic factors and other types of gene testing. Several clinical trials are underway to evaluate methods aimed at cardiovascular risk reduction; however, evidence in the form of randomized controlled trials supporting that treating to target levels of emerging risk factors lowers risk is lacking. Recent textbook literature (Ridker, et al., 2019) states that although data for advanced lipid testing continue to accrue, it remains unclear whether novel methods of lipid evaluation add to standard lipid screening in routine practices or should remain specialized tools for research and lipid clinics.

Determining Cardiac Risk

Pooled Cohort Equation: In 2013, the ACC/AHA published new guidelines on the assessment of cardiovascular risk (Goff, et al., 2013). Within these guidelines the ACC/AHA work group developed new equations to estimate 10-year risk and lifetime risk for developing a first ASCVD event (i.e., nonfatal myocardial infarction, CHD death, or fatal or nonfatal stroke). The Pooled Cohort Equation is designed to assess risk and include subjects from diverse cohorts such as the Framingham Heart Study, Atherosclerosis Risk in Communities (ARIC) study, the Coronary Artery

Risk Development in Young Adults (CARDIA) and the Cardiovascular Health Study (CHS), and provides sex and race specific estimates for 10-year risk for ASCVD in non-Hispanic African-American and non-Hispanic white men and women age 40-79 years. The variables included in the risk assessment include age, sex, race, total and HDL-cholesterol, systolic blood pressure (BP), use of blood pressure lowering medication, diabetes, and smoking status (Goff, et al 2013). Based on the results of the assessment tool, a 10-year risk of < 7.5% is considered low and a 10-year risk of $\geq 7.5\%$ is considered elevated.

An electronic version of the CV Risk Calculator using the Pooled Cohort Equation is available at: <https://static.heart.org/riskcalc/app/index.html#!/baseline-risk>

Framingham Risk Score: When utilizing the Framingham risk scoring tool, point scores are assigned to various risk factors and totaled. These risk factors are considered major independent cardiovascular risk factors and include the following:

- cigarette smoking
- hypertension (BP $\geq 140/90$ mm/Hg or on antihypertensive medication)
- low HDL cholesterol (< 40mg/dL)
- family history of premature CHD (CHD in male first-degree relative < 55 years, CHD in female first-degree relative < 65 years)
- age (men ≥ 45 years, women ≥ 55 years)

Ten-year risk percent is then determined by a point total. Framingham risk scoring divides persons with multiple risk factors into categories of 10-year risk for CHD, which are > 20%, 10-20%, or < 10%.

Low cardiac risk is described as having one risk factor or less; moderate cardiac risk is defined as having two risk factors and a 10-year Framingham risk of less than 10%; moderate high risk is defined as having more than two risk factors and a 10-year Framingham risk of 10–20%; persons in the high risk category have existing CHD (previous history of MI, stable or unstable angina, or revascularization with coronary artery bypass grafting or percutaneous coronary angioplasty) or a CHD risk equivalent (e.g., diabetes mellitus, abdominal aortic aneurysm, peripheral vascular disease, significant coronary artery disease, a 10-year Framingham risk that exceeds 20%) (Toth, et al., 2004). The American Heart Association also includes chronic kidney disease as a risk equivalent.

Reynolds Risk Score: The Reynolds risk score may also be used to predict risk of future heart attack, stroke, or other major heart disease in the next ten years. In addition to age, blood pressure, cholesterol levels, and whether an individual smokes or not, the Reynolds Risk Score includes high-sensitivity C-reactive protein (hs-CRP) level and parental history of heart attack before age 60. The Reynolds Risk Score is based on information collected from 24,558 initially healthy women for a median of 10.2 years, and stratified risk, as well the Framingham model, for women at high and low risk. For women at intermediate risk, the Reynolds Risk Score more accurately reclassified women into higher or lower risk categories (Ridker, et al., 2007).

An electronic version of the Reynolds Risk Score is available at: <http://www.reynoldsriskscore.org/>.

Standard Lipoprotein Profile

A standard lipoprotein profile includes total cholesterol, HDL cholesterol, and triglyceride levels in addition to a calculated LDL cholesterol level and calculated non-HDL levels. Calculation of the LDL level is usually an indirect measurement and is estimated from measurements of total cholesterol, total triglycerides and HDL cholesterol. Guidelines and recommendations for standard lipid screening in the general population are well-established.

In some clinical situations, direct LDL calculations may be considered more accurate (e.g., presence of chylomicrons, elevated triglycerides [>400 mg/dl]). However, the methods available to specifically measure LDL cholesterol have not been standardized (Brunzell, et al., 2008). In addition, the National Cholesterol Education Program Adult Treatment Panel III (ATP III) recommendations do not recommend replacing calculated LDL levels for direct LDL. Calculated LDL levels are recommended for those individuals without hypertriglyceridemia.

Non-HDL cholesterol represents total cholesterol minus the HDL cholesterol. It may also be referred to as the sum of all the apolipoprotein B containing lipoprotein (i.e., very low density lipoprotein [VLDL], LDL, intermediate density lipoprotein [IDL], lipoprotein [a]) levels. Among individuals with hypertriglyceridemia (i.e., triglycerides of at least 200 mg/dl), the ATP III guidelines suggest non-HDL as a secondary target of therapy, after targeting LDL cholesterol levels. Individuals with hypertriglyceridemia typically include those individuals with cardio-metabolic risk (CMR) or diabetes. The targeted level for non-HDL cholesterol is the LDL cholesterol target plus 30. Authors contend that measuring non-HDL cholesterol is more practical than directly measuring apo B, and furthermore that non-HDL is predictive of heart disease in individuals who have high triglycerides (as the triglycerides rise, so do the VLDLs). A consensus statement from the American Diabetes Association and American College of Cardiology Foundation (ADA/ACC) (Brunzell, et al., 2008) recommends the calculation of non-HDL cholesterol on all lab reports to determine cardiovascular disease risk in CMR individuals with low to moderate LDL levels. Consequently, non-HDL cholesterol may be considered an additional tool to assess cardiovascular risk in individuals whose risk is not adequately defined by LDL cholesterol alone (e.g., diabetics).

Advanced Laboratory Evaluation

Factors considered in the evaluation of emerging risk factors include determining the predictive power, population prevalence, and availability of laboratory testing, the standardization methods, reference values, stability, and evidence confirming whether or not modification of these markers will reduce risk and ultimately lead to improved clinical outcomes for patients with cardiac risk factors. Furthermore, the clinical utility of emerging risk factor testing relies on conclusive evidence the test predicts risk beyond that of current risk prediction methods (considered standard of care) and evidence supporting improved clinical outcomes, such as a reduction in CVD or events, as a result of specific management strategies.

Evidence in the existing literature indicates most emerging risk factors are not independently related to the risk of recurrent CVD (Wattanakit, et al., 2005). However, some of these risk factors may be associated with increased risk of cardiac disease in patients already at risk. Even so, it has not been proven that lowering levels is associated with a significant decrease in the incidence or mortality of heart disease. Many of the assays/tests used to determine these levels are not standardized and accuracy, sensitivity, specificity and predictive values have not been firmly established in the medical literature. Overall, when comparing predictive values of the emerging risk factors with traditional measurements, some of the emerging risk factors have predictive value that are considered comparable, although some are not as predictive. For a majority of the emerging risk factors, there is no consensus among authors towards identifying targeted therapy and if targeted therapy reduces risk and improves clinical outcomes when compared to the traditional evaluation and therapy. As a result, there is little agreement among authors regarding recommendations for performing any of the emerging cardiac risk factors as part of the routine risk assessment for the general population or as part of advanced lipid testing for those who may be at increased risk. Additionally, the 2013 ACC/AHA guidelines for cardiovascular risk indicate measuring ApoB, albuminuria, glomerular filtration rate, or cardiorespiratory fitness is of uncertain value for reclassification or determining contribution to risk assessment due to either no proven utility or insufficient evidence to determine any additional

value (Goff, et al., 2013). High sensitivity C-reactive protein may be considered to inform treatment decision making if after initial assessment risk-based treatment is uncertain.

Comprehensive lipoprotein panels have been developed which include standard lipid tests such as total cholesterol, HDL, LDL and triglycerides in addition to several other emerging lipid measurements. Panel tests such as vertical auto profile (VAP) (VAP Diagnostics Lab, Birmingham, AL), Lipoprotein Particle Profile™ (SpectraCell Laboratories, Inc. Houston, TX), TruRisk™ (Aviir, Inc., Irvine, CA) and NMR LipoProfile® (LipoScience Inc, Raleigh, NC) are panels that include cholesterol, lipids, triglycerides, lipoproteins and various lipoprotein subclass measurements.

Other test panels or test profiles being developed and proposed for determining cardiac risk include panels for various biomarkers. MIRISK VP™ (Aviir Inc., Irvine, CA) is a panel of tests which includes seven protein biomarkers used to evaluate risk in individuals who are intermediate or high risk based on results of a baseline cardiac risk assessment test (MIRISK). MIRISK VP™ involves application of an algorithm that includes four clinical risk factors in addition to seven protein biomarkers to obtain a risk score which is then used to estimate cardiac risk in the next five years. PULS (Protein Unstable Lesion Signature) Cardiac Test™ (GD Biosciences, Irvine, CA) is a panel of biomarkers proposed aimed at detecting an individual's risk of coronary heart disease. According to the manufacturer, this test panel purportedly measures nine protein biomarkers used to measure the body's immune response to coronary endothelial damage, ultimately resulting in unstable lesion rupture. However, similar to other emerging cardiac risk laboratory evaluations, scientific evidence supporting clinical efficacy is lacking for panel testing of these and other various biomarkers, and improvement in health outcomes as a result of testing has not been proven in the published scientific literature. Although comprehensive lipid panels and other test panels/profiles for assessing cardiovascular disease risk are currently available, the clinical utility of adding these laboratory tests to a standard lipid profile has not been established.

Apolipoproteins: Lipoproteins are large complexes of molecules that transport lipids (primarily triglycerides and cholesterol) through the blood. Apolipoproteins are proteins on the surface of the lipoprotein complex that bind to specific enzymes or transport proteins on the cell membranes. This directs the lipoprotein to the proper site of metabolism.

- Apolipoprotein A-1 (apo A-1) is a lipid-binding protein that forms complexes with other proteins and lipids to form HDL particles. It is the major protein component of HDL and is usually reduced when the HDL level is low. Together, apo A-1 and apo A-2 constitute 90% of total HDL protein. Low levels of apo A-1 may be associated with an increased risk for CVD. However, testing of apo A-1 does not add any additional predictive power above a traditional HDL level. Testing for apo A-1 is often performed with apolipoprotein B and reported as a ratio (apo B: apo A-1) which may provide information regarding the cholesterol transport to and from the peripheral tissues, including the walls of arteries. Researchers suggest that the apo B: apo A-1 ratio provides a measure of atherogenic to antiatherogenic lipoprotein particles similar to that of total cholesterol to HDL cholesterol ratios and may be a better discriminator of CVD.
- Apolipoprotein B (apo B) has two forms found in humans. The most abundant form is known as large B or B-100. It is the major protein found in LDL and VLDL. While lipoprotein particles vary in their cholesterol content, each lipoprotein particle (i.e., LDL, IDL, VLDL, Lp[a]) carries one molecule. It has been suggested that apo B is a better marker of atherogenic particles than total LDL and even non-HDL levels. The assay for measuring apo B has become standardized (Brunzell, et al., 2008).

Evidence supporting apolipoprotein measurements improve overall risk prediction compared to standard lipid testing remains mixed and the clinical utility of apolipoprotein testing in the general

population is debatable. For some measurements, universal standardized testing modalities are not widely available. In addition, patient-selection criteria have not been clearly established. Numerous studies have been conducted and consist of both retrospective and prospective case series, cohort studies, and randomized controlled clinical trials, including a few systematic reviews and meta-analyses. Many study populations involve large subsets of patients evaluating outcomes over several years. Some proponents report the predictive power of apolipoprotein testing (apo A-1 and apo B) is comparable to or better than traditional measurements (Benderly, et al., 2009; Khadem-Ansari, et al., 2009; Kastelein, et al., 2008; Sniderman, et al., 2003a; Luc, et al., 2002; Gotto, et al., 2000) although in other studies testing was not found advantageous (Ray, et al., 2009; Ingelsson, et al., 2007; Sharrett, et al., 2001; Stampfer, et al., 1991). Additionally, some studies strongly support the association of apo B with CVD and provide evidence that apo B may have more clinical utility than conventional measurements, including LDL (Gigante, et al., 2012; Khadem-Ansari, et al., 2009; Sierra-Johnson, et al., 2009; Gotto, et al., 2000; Lamarche, et al., 1996). The literature also lends some support that the ratios of total cholesterol to HDL and of apo B: apo A-1 (atherogenic to antiatherogenic particles) are more highly correlated with severity and extent of CVD (Song, et al., 2015; Lau and Smith, 2009; Sierra-Johnson, et al., 2009; Wallach, et al., 2007). Wallach et al. (2007), however, noted that the apo B: apo A-1 ratio showed greater sensitivity/specificity for CVD than LDL-C: HDL-C ratio, HDL-C: triglyceride ratio, or any of the individual components. Although few studies have evaluated the effect of lipid lowering agents on apolipoproteins, there is some evidence to suggest a positive effect (Tani, et al., 2010; Ray, et al., 2009; Holme, et al., 2008). A meta-analysis of 25 clinical trials (12 statin, four fibrates, five niacin, two comparative trials, one ileal bypass) supports statins lower apo B more than nonstatin therapies, suggesting that intensifying statins may be a preferred method to lower apo B levels compared to other treatments (Robinson, et al., 2012). Across all drug trials evaluated in this meta-analysis, apo B did not consistently improve risk prediction, although in the statin trials specifically, apo B decrease did add information to LDL and non-HDL for predicting coronary risk heart disease.

The ATP III guidelines do not recommend apo A-1 for routine risk assessment, and according to the guideline, non-HDL serves as a surrogate for apo B. The guidelines do not define the total cholesterol: HDL ratio as a specified target of therapy; LDL remains the primary lipid lowering target.

A consensus statement from the ADA/ACC (Brunzell, et al., 2008) suggests that measurements of apo A-1 provide little clinical value beyond measurements of HDL cholesterol level. The authors also report that although not all studies agree, once LDL cholesterol is lowered, testing for apo B may more accurately identify those still at risk for cardiovascular events and to determine the need for medication.

The National Academy of Clinical Biochemistry Laboratory (the Academy of the American Association for Clinical Chemistry) established medical practice guidelines for emerging biomarkers for primary prevention of cardiovascular disease (Myers, et al., 2009). These guidelines support apo B testing and apo B: apo A-1 ratio measurement as alternatives to non-HDL cholesterol and total cholesterol: HDL cholesterol ratio. However, the workgroup acknowledged manufacturers of the assays should establish traceability to accepted standards to assure reliable and comparable results.

The College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines on assessment of cardiovascular risk do not support advanced lipid testing of apo B. According to the guideline recommendations, the contribution of apo B to risk assessment for a first ASCVD event is uncertain at present (Goff, et al., 2013).

The ACC/AHA recommendations published in 2013 considered Apo-B as a new risk marker. However, the workgroup concluded that the contribution of Apo B to risk assessment for first ASCVD event is uncertain (Goff, et al., 2013).

Guidelines for the management of dyslipidemias published by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) (Mach, et al., 2020) recommend ApoB analysis for risk assessment, particularly in people with high triglycerides (TG), diabetes mellitus (DM), obesity or metabolic syndrome, or very low density lipoprotein cholesterol (LDL-C). It can be used as an alternative to LDL-C, if available, as the primary measurement for screening, diagnosis, and management, and may be preferred over non-high-density lipoprotein cholesterol (HDL-C) in people with high TG, DM, obesity, or very low LDL-C.

The 2016 National Lipid Association (NLA) published "Recommendations for Patient Centered Management of Dyslipidemia". Within these recommendations, the NLA notes Apo-B is an optional, secondary lipid target for treatment. However, the NLA Expert Panel favors non-HDL over Apo-B because it is universally available, does not require any additional expense, and because apo-B has not consistently been superior to non-HDL in predicting risk. Regarding biomarkers for "on-treatment," the NLA panel notes the following (Bays, et al., 2016):

- Apo B is a potential marker of residual ASCVD risk because apo B may remain elevated in some individuals who have attained their treatment goals for non-HDL-C and LDL-C, as may occur in patients with elevated triglyceride and lower HDL-C levels.
- If apo B is used as an optional target for treatment, goals are < 90 mg/dL for primary prevention and
- < 80 mg/dL for those with very high risk.
- Measurement of apo B is generally not recommended until the patient has been treated to his or her goal levels for atherogenic cholesterol.

The American Association of Clinical Endocrinologists (AACE) supports performance of apo B levels to assess the success of LDL-C-lowering therapy (Jellinger, et al., 2017).

High Density Lipoprotein (HDL) Subclass/Particle (LpAI, LpAI: AII): HDL can be classified by the apolipoprotein content (LpAI, LpAII), by size (small and large), by density (HDL2, HDL3), and by surface charge (pre-beta, alpha and pre-alpha). For example, regarding apolipoprotein content, HDL particles containing apo AI (LpAI) carries only apo AI on its surface whereas apo AII (LpAI:LpAII) carries both apo AI and apo AII on its surface. Total HDL (HDL-C) reflects the cholesterol content within all HDL subclass particles and is the risk indicator most commonly used in cardiac risk assessment. Various types of HDL subclass tests are being proposed to provide information regarding CVD risk in addition to total cholesterol, HDL cholesterol and low-density lipoprotein cholesterol. It has been suggested that HDL subclasses may be more closely associated with risk than total HDL and may provide additional risk information for those individuals identified as low- or intermediate-risk by standard lipoprotein tests.

HDL subclass testing may be performed by methods using various separation techniques such as nuclear magnetic resonance (NMR), gradient gel electrophoresis (GGE) and ultracentrifugation.

Consistent with the ATP III panel, the literature does not support improved clinical outcomes with the use of HDL subclass testing, and it has not been recommended as a routine measurement of cardiac risk. A consensus statement by the ACC and the ADA (Brunzell, et al., 2008) indicates that measurements of HDL subfractions (or apo A-1) appear to provide little clinical value beyond measurements of HDL cholesterol. Currently, there is lack of evidence to support HDL subclass testing in the screening, diagnosis or management of dyslipidemia and/or CVD.

Lipoprotein Remnants: According to the ATP III publication, lipoprotein remnants, including intermediate density lipoproteins (IDLs) and VLDLs, have been shown to be atherogenic. They are triglyceride-rich lipoproteins, and elevated triglycerides have been identified as an independent risk factor of CVD. The lipoprotein remnant particles may penetrate the arterial wall more easily than larger lipoproteins. The panel concluded that studies are limited, and measurement with specific assays for lipoprotein remnants cannot be recommended for routine practice.

Lipoprotein(a) Enzyme Immunoassay (Lp[a]): Lipoprotein(a) is a low-density, lipoprotein-like particle that may have atherogenic potential. It has been proposed by several authors to represent a link between atherosclerosis and atherothrombosis. Structurally, it is very similar to plasminogen, and may specifically compete with plasminogen in fibrinolysis by inhibiting the activation of plasminogen to plasmin, increasing the potential of plaque development and possible blockage. Research has shown it accumulates in atherosclerotic lesions; however, the actual process remains unclear. Lp(a) concentrations are genetically determined and not influenced by age, physical activity or diet. A standardized international reference material has been developed and is accepted by the World Health Organization Expert Committee on Biological Standardization and the International Federation of Clinical Chemistry and Laboratory Medicine. In general, lipoprotein(a) levels above 30mg/dl are considered elevated with levels > 50 considered high risk. Treatments specifically aimed at reducing lipoprotein(a) levels are not widely available (Grundey, et al., 1999) although therapy generally includes more aggressive management. Niacin and estrogen have been shown to lower blood levels of Lp(a). Guidelines recommending intervention based on Lp(a) levels are limited, although according to the National Academy of Clinical Biochemistry Laboratory Practice Guidelines (Myers, et al., 2009) when both Lp(a) and LDL cholesterol are highly increased an attempt can be made to lower the Lp(a) value by lowering the increased LDL cholesterol.

While screening in the general population for routine risk assessment is not recommended, testing may be helpful for those individuals already known to be at high risk. There are some advocates for Lp(a) who recommend assessment for persons with a strong family history of premature CVD or those with genetic causes of hypercholesterolemia (e.g., familial hypercholesterolemia). According to the ATP III, an elevation of Lp(a) may raise an individual's risk to a higher level and the ATP III accepts testing for Lp(a) as an option for these selected persons. The consensus statement from the ADA/ACC (Brunzell, et al., 2008) also supports testing of Lp(a) in select individuals. Brunzell et al. reported that lipoprotein(a) predicts CVD and there is little evidence that insulin resistance or diabetes influences lipoprotein(a) concentrations. According to the consensus statement, the clinical utility of routine measurement of Lp(a) is unclear, although more aggressive control of other lipoprotein parameters may be warranted in those with high concentrations of Lp(a).

The National Lipid Association (Wilson, et al., 2019) stated evidence supports elevated lipoprotein(a) as an independent risk factor for ASCVD. They acknowledge there is no global standardization of Lp(a) measurement, and the preferred measurement unit is nmol/L. While nmol/L cannot be converted directly to mg/dL, levels ≥ 50 mg/dL and ≥ 100 nmol/L each suggest increased risk of ASCVD. The NLA added that repeat measurement of Lp(a) is not recommended as the clinical value of serial measurements has not been established.

The Endocrine Society's Lipid Management in Patients with Endocrine Disorders: An Endocrine Society Clinical Practice Guideline recommends Lp(a) testing in adult patients with a family history of premature ASCVD, or a personal history of ASCVD or a family history of high Lp(a) for better decision-making about short-term and lifetime ASCVD risk and need to intensify LDL-C lowering therapy (Newman, et al., 2020).

The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidemias address lipid analyses for CVD risk estimation. The guideline recommendations state:

- Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolaemia
- 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 (Mach et al., 2020).

The American Association of Clinical Endocrinologists (AACE) 2020 guidelines for management of dyslipidemia and prevention of cardiovascular disease recommended measuring lipoprotein (a) [Lp(a)] in the following individuals: patients with family history of premature atherosclerotic cardiovascular disease (ASCVD) and/or increased Lp(a), or in those with premature or recurrent ASCVD despite LDL-C lowering (Handelsman, et al., 2020).

The College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (Greenland, et al., 2010) did not find Lp(a) testing to be of benefit in cardiovascular risk assessment in asymptomatic individuals.

The American Association of Clinical Chemistry (AACC) guidelines (Myers, et al., 2009) support Lp(a) testing if the risk is intermediate and there is uncertainty regarding management with statins or aspirin, or if there is a strong family history of premature CVD/genetic predisposition.

Lipoprotein-Associated Phospholipase A₂ (Lp-PLA₂): Lp-PLA₂ belongs to the family of phospholipase A₂ enzymes. Evidence has suggested Lp-PLA₂ plays a role in atherosclerosis, and it has been proposed that Lp-PLA₂ testing may aid in detecting CVD risk. Lp-PLA₂ is a marker of inflammation produced primarily in macrophages and bound to LDL. Lp-PLA₂ is commonly measured by the diaDexus PLAC™ test (diaDexus, Inc., South San Francisco, CA) an enzyme-linked immunoabsorbant assay (ELISA) test, and must be run in a CLIA (Clinical Laboratory Improvement Act) certified high-complexity laboratory.

It has been identified in some clinical trials (West of Scotland Coronary Prevention Study [Packard, et al., 2000] and Atherosclerosis Risk in Communities Study [Ballantyne and Hoogeveen, 2003]) that patients with elevated levels of Lp-PLA₂ had increased risk of cardiovascular disease (Moriarty and Gibson, 2005). Wallach (2007) suggests increased Lp-PLA₂ with low LDL-C increases risk of heart disease by two times and that increased Lp-PLA₂ with high CRP increases risk of heart disease by three times. The ATP III guidelines do not include measurement of Lp-PLA₂, although several studies have been published since the initial recommendations. Corson et al. (2008) reported that Lp-PLA₂ should be considered an important cardiovascular risk marker whose utility is as an adjunct to the major risk factors to adjust absolute risk status and thereby modify low-density lipoprotein cholesterol goals. The ADA/ACC consensus statement (Brunzell, et al., 2008) does not address the use of Lp-PLA₂ levels for determining CVD risk. Davidson et al. (2008), an expert consensus panel, 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. However, the panel does recommend testing in moderate- or high-risk persons to further stratify risk. In the authors' opinion, many high-risk persons taking statins have significant residual risk identifiable with Lp-PLA₂ testing. Therefore, 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 \geq 65 years with one major risk factor
- cigarette smoking
- fasting blood glucose \geq 100 mg/dl
- metabolic syndrome

Lp-PLA₂ 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-PLA₂ levels. Treatment for elevated Lp-PLA₂ is targeted at lowering LDL levels.

The College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (Greenland, et al., 2010) reported lipoprotein-associated phospholipase A₂ (Lp-PLA₂) might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults.

The American Association of Clinical Endocrinologists (AACE) guidelines for management of dyslipidemia and prevention of atherosclerosis (Jellinger, et al., 2017) supports measuring Lp-PLA₂ when it is necessary to further stratify a patient's CVD risk, especially in the presence of systemic highly sensitive CRP elevations.

Secretory Type II Phospholipase A₂: Secretory type II phospholipase A₂ also belongs to the family of phospholipase A₂ enzymes, distinct from Lp-PLA₂, and is purported to be associated with increased risk of CAD, similar to CRP when sPLA₂ levels are elevated. It is an acute phase protein for which plasma levels rise during inflammatory conditions such as infection, septic shock and Rheumatoid Arthritis (RA) (Niessen, et al., 2003). Theoretically the atherogenic mechanism of sPLA₂ consists of the release of various lipid mediators at the site of lipoprotein retention in the arterial wall which may subsequently trigger a local inflammatory cellular response. In addition, in arterial tissue it may directly modify the LDL particles to become more atherogenic. While there are different forms of the enzyme (e.g., sPLA₂-IIA, sPLA₂-III, sPLA₂-V and sPLA₂-X) that may promote atherosclerosis, the assay for sPLA₂ activity does not distinguish between isoenzyme types (Holmes, et al., 2013). A small number of studies have evaluated the utility of sPLA₂ and consist mainly of published reviews, case series, observational studies, a prospective case-control study, and few randomized controlled trials (Lind, et al., 2012; O'Donoghue, et al, 2011; Boekholdt, et al., 2005; Liu, et al., 2003; Kovanen and Pentikäinen, 2000; Kugiyama, et al., 1999). The results of some studies tend to support an association of increased cardiovascular risk when sPLA₂ levels are elevated in individuals with stable CAD (O'Donoghue, et al., 2011; Koenig, et al., 2009; Liu, et al., 2003; Kugiyama, et al., 1999). Published evidence also lends some support that the magnitude of the association is similar to hsCRP and CAD risk (O'Donoghue, et al, 2011; Boekholdt, et al., 2005). Holmes et al. (2013) conducted a Mendelian randomization meta-analysis of 19 general population studies and 10 acute coronary syndrome cohorts to evaluate a causal relationship of sPLA₂ enzyme activity or sPLA₂-IIA mass to cardiovascular events. The authors 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, although no association was found between rs11573156 and incident, prevalent or recurrent major vascular events (MVE). In the authors opinion higher sPLA₂-IIA mass or sPLA₂ enzyme activity may be a consequence and 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. While some evidence suggests sPLA₂ may play a role in the development of CAD additional clinical studies are needed to firmly establish a causal relationship in the pathogenesis of CAD, how it compares with other established markers of risk, and the clinical utility for predicting CAD risk and reducing morbidity.

Low Density Lipoprotein (LDL) Subclass (Small and Large LDL Particles): LDL subclass testing has been proposed as a source of quantitative and qualitative LDL information. These tests provide the number of LDL particles, measure of particle size and concentrations of subclasses including IDL, subclasses of HDL, and subclasses of VLDL. It has been reported that a discrepancy between the quantity of LDL particles and the serum level of total LDL may represent a significant source of unrecognized cardiovascular risk. While the underlying mechanism of how LDL subclass particles relate to CVD has not been established, one theory is that although small LDL particles carry less cholesterol compared to large LDL particles, the small LDL particles can be more easily deposited into the intima and lead to atherosclerosis. Even though LDL cholesterol levels may be normal, an elevation of small, dense LDL particles may be associated with CVD, and is commonly seen in individuals with elevated triglycerides levels and low HDL cholesterol levels (also reflective of conditions such as obesity and insulin-resistance-related cardiometabolic risk) (Brunzell, et al., 2008).

Determining LDL particle concentration has been the focus of recent research; authors propose determining LDL particle concentration (i.e., number of LDL particles) would be the more precise marker for determining risk, particularly when the LDL cholesterol and LDL particle concentration are not concordant.

LDL particles can be measured by several techniques, including ultracentrifugation, gradient gel electrophoresis, nuclear magnetic resonance spectroscopy (NMR) and high pressure liquid chromatography (HPLC).

The ATP III guidelines do not support measurement of small LDL particles in routine practice, although if particles are evaluated their use is best indicated for atherogenic dyslipidemia and metabolic syndrome. In combination with elevated triglycerides or low HDL, increased small LDL particles in high risk persons may be treated with nicotinic acid or fibric acid as part of lipid lowering therapy.

The Endocrine Society Clinical Guidelines (Rosenzweig, et al., 2008) for primary prevention of cardiovascular disease and type 2 diabetes mellitus in patients at metabolic risk does not support LDL particle measurement for evaluating cardiovascular risk. According to the Endocrine Society, LDL cholesterol is the primary target of lipid lowering therapy and non HDL is considered a secondary target.

According to the ADA/ACC consensus statement (Brunzell, et al., 2008), measuring LDL particles using NMR may be more accurate, and "many cross sectional and prospective studies show LDL particle number is a better discriminator of risk than is LDL cholesterol." However, the authors state there is a lack of data confirming the accuracy of the method and question whether its CVD predictive power is consistent across various ethnicities, ages, and conditions that affect lipid metabolism. Consistent with the ADA/ACC consensus, Ip et al. (2009) reported that even with evidence to support a higher LDL particle number predicts incident CVD, evidence is lacking to support the clinical utility of adding LDL subfractions to the traditional risk factors. Furthermore, the authors noted that LDL subfraction testing will only be clinically useful if treatments, based on the results of testing, improve clinical outcomes.

According to a report from the Agency for Healthcare Research and Quality (AHRQ) regarding LDL subfraction (subclass) measurement, it has yet to be determined if cardiac disease risk assessment and treatment decisions would be improved by adding LDL subclass measurements (AHRQ, 2008). Furthermore, the AHRQ report states that there is not yet a standard method subfraction measurement that can be used as a reference standard, has been demonstrated to be superior to other methods, or has been demonstrated to be accurate and reliable.

The American Association of Clinical Chemistry (AACC) guidelines (Myers, et al., 2009) do not support LDL subclass testing; according to the guideline the analyses of the existing studies are generally not adequate to show added benefit when compared to standard risk assessment for primary prevention.

In 2009, the Lipoproteins and Vascular Diseases Division of the American Association for Clinical Chemistry (AACC) published a report in which they reviewed the studies for apoB and LDL particle measurement. The authors noted that superiority of apoB or LDL particle measurement has been demonstrated in prospective studies when compared to LDL cholesterol measurement for the assessment of risk. As a result, the group recommends that apoB and alternate measures of LDL particle concentration be included in future NCEP and other various guidelines for cardiac risk. Until that time however it is reasonable to include both apoB (and LDL particle concentration) and LDL to assess related risk until apoB becomes more widely recognized. The authors acknowledged although measuring LDL particle concentration is appropriate in high risk individuals, target concentrations need to be determined through additional data. Until that time, they recommend using cutoff points similar to that of LDL (i.e., 20th percentile according to Framingham). A result of < 1100 nmol/L would equate to LDL < 100 mg/dL and a particle concentration of <1400 nmol/L would equate to an LDL < 130 (Contois, et al., 2009).

The College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (Greenland, et al., 2010) indicate evidence that more advanced lipid testing such as LDL-P concentration has predictive capacity beyond standard lipid measurements in asymptomatic individuals is lacking (Greenland, et al., 2010).

Otvos et al. (2011) used data from the Multi-Ethnic Study of Atherosclerosis (MESA) (n=6814) to evaluate differences between LDL cholesterol and particle concentration and their relationship to incident cardiac events among those with concordant and discordant levels. Individuals were followed for an average of 5.5 years; incident cardiac disease included myocardial infarction, coronary heart disease death, angina, stroke, stroke death, other atherosclerotic or cardiovascular death. Both LDL and LDL particles were associated with incident disease overall; when the levels disagreed only the LDL particle was associated with incident CVD. A consistent relationship was noted with intima media thickness and LDL particle rather than with LDL.

The National Lipid Association (Davidson, et al., 2011) evaluated the clinical utility of inflammatory markers and advanced lipoprotein testing (i.e., C-reactive protein, lipoprotein associated phospholipase A₂, apolipoprotein B, LDL particle concentration, lipoprotein (a), and LDL and HDL subfractions) to improve cardiovascular risk prediction and for use as potential targets of therapy. The consensus panel identified four categories of recommendations based on their review of current published evidence and testimony from other experts in the field: recommended for routine measurement, reasonable for many patients, considered in selected patients, or not recommended. Regarding LDL particle measurement specifically, the recommendations were as follows:

- For low risk patients testing is "not recommended."
- The panel concluded that subjects at intermediate risk (5-20%), those with a family history of CHD, and those with recurrent events all had potential for discordantly elevated LDL particles; the recommendation for testing is "reasonable for many patients." When LDL particle concentration is discordant despite LDL or non HDL goals, consideration should be given to intensify lipid lowering therapy.
- For individuals with high risk, with known CHD, or CHD high risk equivalent the recommendation is that "testing is considered for select patients" and to treat to LDL or non HDL levels on lipid lowering therapy.

The American College of Cardiology (ACC) and American Heart Association (AHA) in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) published guidelines for cardiovascular risk classification (Goff, et al., 2013) and recommendations for management of blood cholesterol levels in adults (Stone, et al., 2014). While these guidelines did include evaluation of some new risk markers (e.g., hs-CRP, ApoB, creatinine) they did not include evaluation of LDL-P as a risk marker, noting that other novel potential screening tools may be considered in future guidelines.

In 2022, AACE published a clinical practice guideline on developing a comprehensive plan for diabetes mellitus (Blonde, et al., 2022). The algorithm includes a CVD risk factor algorithm which addresses dyslipidemia and hypertension management. Dyslipidemia management includes therapeutic lifestyle changes and CVD risk assessment using lipid evaluations; desirable values for LDL-C, Non-HDL-C, TG, TC/HDL-C, Apo B and LDL-P have been established for moderate and high risk individuals. The algorithm also includes methods to lower levels if desirable levels are not achieved. If desirable levels are not reached, the AACE recommends intensifying therapeutic lifestyle changes, and in particular for lowering Apo B and LDL-P the algorithm includes intensifying statin and/or ezetimibe and/or colesvelam and/or niacin therapy. They conclude that sequential monitoring of some biomarkers is not recommended at this time; high-sensitivity CRP is not mechanistically linked to the pathophysiology of atherosclerosis, coronary artery calcium changes are unlikely to be reversed, and lipoprotein(a) as a targetable marker requires validation by future outcome trials.

Guidelines for the management of dyslipidemias published by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) do not support testing of LDL subclasses. According to the guidelines small dense LDL may be considered and emerging risk factor however it is not currently recommended for risk estimation (Catapano, et al., 2016). LDL particle subclasses are not included in the guidelines "European Consensus of Cardiovascular Disease Prevention" (Piepoli, et al., 2016).

The NLA Recommendations for Patient-Centered Management of Dyslipidemia (Bays, et al., 2016) do not recommend LDL-P testing for individuals at low risk of ASCVD. For patients at higher risk, particularly those suspected of having discordant levels, it remains unclear if LDL-P would alter initial treatment decisions. LDL-P may be considered for select patients, including those with family history of premature ASCVD, elevated triglycerides, low HDL-levels, metabolic syndrome, DM, or recurrent ASCVD events despite disease management. Regarding biomarkers for "on-treatment," LDL-P may be useful in some cases to monitor the course of lipid-lowering therapy.

The American Association of Clinical Endocrinologists (AACE) published guidelines for management of dyslipidemia and prevention of atherosclerosis (Jellinger, et al., 2017). Within these guidelines the panel identifies major risk factors (i.e., advanced age, high total cholesterol, high non HDL, high LDL, low HDL, DM, hypertension, cigarette smoking, family history of CAD) and those risk factors that are considered additional risk factors (i.e., obesity/abdominal obesity, family history of hyperlipidemia, small dense LDL, elevated apo B, elevated LDL particle number, fasting/postprandial hypertriglyceridemia, polycystic ovarian syndrome, dyslipidemic triad). Once initial screening for detection of cardiovascular risk has been performed utilizing lipid screening tests (fasting lipid profile, LDL, HDL, non HDL, triglycerides, apolipoproteins [apo B and/or apo B/apo A1 RATIO]) secondary causes of dyslipidemia should be excluded (i.e., glucose, thyroid, renal, liver). Additional risk factor testing may be indicated using hs CRP, Lp-PLA₂, coronary artery calcification and ultrasound measurement of carotid intima media thickness for some individuals. Once initial cardiac risk has been determined, and treatment has been recommended, follow-up and monitoring of post-treatment status should include a periodic full fasting lipid panel. If optimal lipid levels are not reached following lipid lowering treatment, or if ASCVD progresses despite optimal lipid levels, advanced lipoprotein testing may be performed including nuclear magnetic resonance, gradient gel electrophoresis, ultracentrifugation, and apo B and A levels, and/or

lipoprotein(a) levels to determine the size or numbers of certain lipoproteins. The guideline additionally supports the use of apolipoprotein (apo) B level and/or LDL particle concentration to refine efforts to achieve effective LDL-C lowering. However, the guidelines indicate that consistency between methods for LDL particle testing has not been established.

Evidence in the medical literature lends support that LDL particle size and concentration is associated with atherosclerosis and coronary artery disease (Mora, et al., 2009; Biswas, et al., 2008; Koba, et al., 2008; Cromwell, et al., 2007; Mora, et al., 2007; Cromwell and Otvos, 2006; Otvos, et al., 2006). Mora and colleagues (2009) reported however that risk prediction is comparable but not superior to standard lipids or immunoassay-measured apolipoproteins. When adding LDL particle concentration or apoB to a panel that already included a total/HDL cholesterol ratio the authors noted there was no change in classification of risk. More recently, Steffen et al. (2015) published the results of cox-regression analysis of a multicenter study (MESA) evaluating associations between lipids and lipoproteins (Apo-B, ApoB/ApoA-1, LDL-PDL-P/HDL-p) to primary CHD event (n=4679). Associations between lipoprotein particle measures and CHD were attenuated after adjustment for standard lipid panel variables. Using the ACC/AHA risk calculator, ApoB/ApoA-1, and LDL-P/HDL-P were found to moderately improve the prediction of risk for future CHD events. The attenuated associations of lipoprotein particle measures however did not detect risk that was unaccounted for by the standard lipid panel, after adjustment for the lipids. The authors acknowledged additional studies are needed to confirm or refute the significance of their results.

While standards for LDL subclass categorization and optimal levels of the LDL subclasses have not yet been firmly established (Chung, et al., 2009; AHRQ, 2008), it has been suggested that when determining risk categories low risk is defined as <1000 nmol/L, intermediate risk is 1000-1599 nmol/L, and high risk is \geq 1600 nmol/L (Contois, et al., 2009). LDL particle concentration evaluation is not recommended for low risk individuals. Whether the use of LDL particle testing in addition to LDL cholesterol testing has clinical utility, resulting in a reduction of CVD and associated events for individuals has not been demonstrated in the published literature. However, when discordant, LDL particle concentration has been shown to be the better predictor of risk. Theoretically treatment aimed at lowering LDL will lower LDL particle concentration and cholesterol content, hypothetically reducing the occurrence of adverse cardiac events. Some studies have shown that pharmacologic treatment lowers particle concentration (Le, et al., 2013; Rosenson and Underberg, 2013).

Although LDL particle concentration is associated with cardiac risk and published evidence lends support that for some individuals testing may be considered a more precise method of risk assessment compared with total LDL, there is insufficient published evidence that treatment aimed at lowering LDL particle concentration changes cardiac outcomes. In addition, recommendations, consensus statements and guidelines from several professional society organizations are mixed. There is insufficient evidence in the published scientific literature to support strong evidence based conclusions regarding clinical utility and the impact on net health outcomes cannot be determined at this time.

Homocysteine: Homocysteine is an amino acid that is normally found in the body. Several vitamins, including folic acid, B₆, and B₁₂ aid in the metabolism of homocysteine. Total homocysteine concentration (plasma and urine) is indicated and well accepted in the medical literature for diagnosing conditions such as folate, B₆, and B₁₂ deficiencies. For these conditions levels are generally elevated. Patients with homocystinuria, a rare recessive disease, may develop accelerated premature vascular disease. Clinical manifestations of homocystinuria generally include disorders of the optical lens, osteoporosis and associated skeletal abnormalities, intellectual disabilities, psychiatric disturbances and thromboembolic disease. Treatment to normal homocysteine levels improves outcomes in individuals with homocystinuria.

Elevated levels of homocysteine may result in damage to the walls of the artery and leads to thrombus formation. Thrombus formation results in conditions such as cerebrovascular accidents, heart attacks and pulmonary embolism. Replacement of the deficient vitamins achieves normal levels. Evaluation of homocysteine levels may also be performed as part of the diagnostic work-up for dementia and other related conditions; however while in some cases levels may be elevated, testing for homocysteine levels is not generally recommended (Gingrich and Carroll, 2011; Noel, et al., 2011) and is not included in the standard evaluation of dementia (Reichman and Cummings, 2007).

The mechanisms of action for increasing an individual's risk of CVD related to elevated levels of homocysteine is inflammatory response in the arteries, increased levels of LDL, and increased potential for thrombosis. Elevated plasma levels have been demonstrated in patients with CVD and have also been shown to increase risk even in the presence of desirable lipids and lipid subfractions (Daly, et al., 2009).

Elevated homocysteine levels are not classified as major cardiac disease risk factors according to the AHA, and published recommendations for homocysteine testing as a cardiac risk factor are not consistent. In 2008, Davidson et al. (2008) reported the predictive power and clinical utility of biomarkers, including homocysteine, in the evaluation of persons with lipoprotein abnormalities is unclear. According to the ATP III guidelines, homocysteine testing may be considered an option only in selected cases (e.g., for patients with a strong family history of premature coronary heart disease [CHD] in an otherwise low-risk patient). Furthermore, while it has been suggested lowering high levels of homocysteine with diet or vitamin supplements can decrease one's cardiac risk, routine testing is not recommended (Cesari, et al., 2005; Giacobbe and Murray, 2004; Splaver, et al., 2004; Linton and Fazio, 2003) and it is not known if lowering homocysteine levels will reduce cardiovascular morbidity and mortality (Mangoni and Jackson, 2002; Grundy, et al., 1999).

Some evidence in the form of randomized controlled trials do not support a treatment effect when homocysteine levels are reduced. Lonn et al. (2006) conducted a randomized controlled clinical trial to assess whether the supplementation of folic acid, vitamins B₆, and B₁₂ reduced the risk of cardiovascular disease in patients with vascular disease; the authors concluded supplementation did not reduce cardiovascular risk. Ebbing et al. (2008) conducted a randomized double-blind, controlled clinical trial to evaluate the effect of treatment with folic acid, vitamin B₁₂, and vitamin B₆ as secondary prevention in patients with coronary artery disease or aortic valve stenosis. The primary endpoint was a composite of all-cause death, nonfatal acute myocardial infarction, acute hospitalization for unstable angina and nonfatal thromboembolic stroke. Mean plasma homocysteine concentration was reduced by 30% after one year of treatment, however the trial did not support a treatment effect from folic acid/vitamin B₁₂ or vitamin B₆ on total mortality or cardiovascular events among the patients. The authors of a double-blind RCT evaluated the potential benefits and hazards of lowering homocysteine with folic acid and vitamin B₁₂ supplementation in survivors of myocardial infarction (n=12,064) and reported that in high risk patients supplementation had no beneficial effect on major vascular events (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine [SEARCH] Collaborative Group, 2010). The authors of a recent Cochrane review concluded that the results from available published trials suggest that there is no evidence to support the use of homocysteine lowering interventions, in the form of vitamins B₆, B₉ or B₁₂, given alone or in combination, at any dosage compared with placebo or standard care, prevented cardiovascular events in participants at risk or with established CVD (Marti-Carvajal, et al., 2009).

According to 2022 test utilization guidelines established by the American Association of Clinical Chemistry (AACC) there is still a need for standardization of homocysteine assays and there is

still no convincing evidence to recommend screening in the general population. They further state while homocysteine may be used to assess risk of cardiovascular disease in high-risk individuals for heart attack or stroke without traditional risk factors, this clinical utility is uncertain and controversial.

A meta-analysis of 30 RCTs (n=82,334) was conducted to assess the overall effect of folic acid supplementation on the risk of CVD, CHD or stroke (Li, et al., 2016). The average folic acid supplementation was 3.2 years, the dosage ranged from .5 to 15 mg/day, with the exception of one trial of end-stage renal disease with a dosage of 40 mg/day. Subjects had pre-existing conditions including prior CVD, renal disease, hypertension, atherosclerosis, esophageal dysplasia, and colorectal adenomas. The incident rate for stroke (20 RCTs) was 3.8% in the folic acid group compared to 4.4% in the control group, for CHD (25 RCTs) it was 7.7% in the folic acid group compared to 7.4% in the control group, and for risk of CVD (22 RCTs) it was 12.8% in the folic acid group compared to 13.4% in the control group. The authors concluded there was a 10% reduced risk of stroke and a 4% reduced risk of overall CVD with folic acid supplementation. A greater benefit for CVD was observed among participants without preexisting CVD or with lower plasma folate levels at baseline and in studies with a larger decrease in homocysteine levels. Limitations of the analysis acknowledged by the authors included the inability to completely exclude publication bias, variation in trial design, and heterogeneous definitions of CVD outcomes which may influence interpretation of results.

Evidence suggesting improved clinical outcomes of reduced cardiac risk and adverse events as a result of lowering homocysteine levels with treatment is lacking. Patient selection criteria and target levels or safe levels of homocysteine for determining cardiac risk have not been clearly defined. While there is some clinical utility for homocysteine evaluation to confirm folate deficiency there is insufficient evidence in the peer-reviewed, published scientific literature to support routine measurement of homocysteine testing for screening, diagnosing and management of CVD, for evaluation of dementia, for hypertension, or for other non-specific symptoms in general, such as shortness of breath, malaise and fatigue. Further randomized controlled clinical trials are needed to support the potential clinical utility of lowering homocysteine levels.

Long-chain Omega-3 Fatty Acids: Long-chain omega-3 fatty acids may be detected in the red cell membrane using gas chromatography. It has been suggested this measurement may be clinically useful as a cardiac risk factor for sudden cardiac death. Omega-3 fatty acids have been linked to various health conditions including, but not limited to, heart disease, dementia and visual performance. Furthermore, it has been reported that omega-3 fatty acid consumption, primarily eicosapentaenoic acid and docosahexaenoic acid found in fish, may have beneficial effects on several cardiovascular outcomes, including sudden death, cardiac death and stroke. Additionally, some data suggest these fatty acids have antiarrhythmic properties.

Omega-3 fatty acids benefit the heart of healthy people and those at high risk of or who have cardiovascular disease (AHA, 2006). The AHA recommends inclusion of omega-3 fatty acids in patients with stable coronary artery disease because of evidence from randomized controlled trials that omega-3 fatty acids decrease the risk of arrhythmias, decrease triglyceride levels, decrease growth rate of atherosclerotic plaque and slightly lowers blood pressure. However, more studies are needed to confirm and further define the health benefits of omega-3 fatty acid supplements for preventing a first or subsequent cardiovascular event.

Evidence in the peer reviewed published literature examining the relationship between fish consumption and risk of coronary disease or stroke consist mainly of observational studies and meta-analyses (Mozaffarian, et al., 2005; He, et al., 2004; Whelton, et al., 2004; Hu, et al., 2003; Albert, et al., 2002) and demonstrate that the n-3 fatty acids found in fish are associated with a reduced risk of CVD. The results of one meta-analysis demonstrate that dietary supplements with

omega-3 fatty acids for one year or longer significantly reduced the risk of cardiovascular deaths, including sudden cardiac death, all-cause mortality, and nonfatal cardiovascular events (Marik and Varon, 2009). According to the authors the benefit appeared to depend on the patient's risk stratification; a reduction in death was associated with high risk patients and a reduction of nonfatal events was associated with moderate risk patients. Meta-regression failed to demonstrate an association between treatment effect and dose of fish oil. Based on the results of a systematic review, Hartweg et al. (2009) concluded that the main mechanism by which omega-3 may lower CVD risk in type 2 diabetic patients is by reducing thrombogenesis and improving triglyceride levels. The authors reviewed 24 trials involving 1533 participants and noted that long-term supplementation reduced CVD risk factors (i.e., triglycerides, fibrinogen, and platelet aggregation) safely, and may be added to conventional therapy while maintaining good glycemic and lipid control for this subset of individuals. However the authors acknowledged that three large clinical outcome trials evaluating omega-3 supplementation in diabetic patients have yet to publish results and therefore, the potential benefits of omega-3 supplementation in CVD risk reduction for patients with type 2 diabetes remains inconclusive.

The Agency for Healthcare Research and Quality (AHRQ) reported that a large, consistent, beneficial effect of omega-3 fatty acids was found only for triglyceride levels, and little or no effect was found for a variety of other cardiovascular risk factors and markers of cardiovascular disease (Balk, et al., 2004).

Despite a correlation with cardiac risk, there is insufficient scientific evidence in the published literature regarding how measurements of omega-3 fatty acid composition would affect management and improve clinical outcomes of individuals at risk for or patients with CHD.

Plasma Myeloperoxidase: Plasma myeloperoxidase (MPO), an enzyme secreted by white blood cells (inflammatory marker), may contribute to tissue injury during inflammation and promote plaque buildup in coronary arteries; preliminary research suggests a link between myeloperoxidase and both inflammation and cardiovascular disease risk. MPO can be measured by spectrophotometric assays, counter and flow cytometry as well as with other commercial methods being proposed. Although studies of MPO testing indicate a possible relationship between elevated levels and cardiac risk, its ability to improve on existing risk stratification methods is unclear (Roman, et al., 2008; Stefanescu, et al., 2008; Apple, et al., 2007). Furthermore, in the studies evaluating MPO various methods of testing were used, making comparisons difficult and reference standards have not yet been identified. The body of evidence evaluating MPO as a potential cardiac biomarker is insufficient to support an increased predicative value as compared to traditional testing or for recommending medical management based on MPO values that would improve clinical outcomes.

Prothrombotic Factors: Prothrombotic factors such as plasminogen activator inhibitor (PAI-1), activated factor VII, tissue plasminogen activator (tPA), von Willebrand factor, factor V Leiden, protein C, antithrombin III, and fibrinogen have been proposed as risk factors of cardiovascular disease (Linton and Fazio, 2003). Evidence supporting clinical utility in the published peer reviewed scientific literature is lacking; measurement of prothrombotic factors as part of the routine assessment for cardiovascular risk has not been shown to improve patient outcomes. In addition, testing is not recommended by the ATP III guidelines.

Growth Stimulation Expressed Gene 2: Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1) (e.g., Presage® ST2 Assay, Critical Diagnostics, San Diego, CA) is a biomarker being investigated for several medical conditions, including cardiovascular disease. Authors suggest plasma ST2 is thought to identify which chronic heart failure subjects are progressing towards worsening heart failure. It has been purported testing may be indicated to establish a prognosis for congestive heart failure subjects, to guide chronic heart failure therapies, and to

predict cellular rejection post cardiac transplantation. There is some evidence in the peer-reviewed scientific literature to support a correlation between elevated ST2 (i.e., >35 ug/L) and adverse cardiac outcomes (e.g., higher risk of heart failure, sudden cardiac death, and all-cause death) (Wang, et al., 2012; Kohli, et al., 2012; Shimpo, et al., 2004). However, evidence demonstrating how growth stimulation expressed gene-2 testing impacts the clinical management of subjects with congestive heart failure, the recommended frequency of testing, and resulting clinical outcomes is lacking. Furthermore, in comparison to other established measures of heart failure the published evidence is insufficient to support ST2 provides predictive information, alone or in combination, above that of conventional measures (e.g., standard clinical exam combined with BNP levels). Further research is needed to firmly establish the clinical utility for growth stimulation expressed gene 2 (ST2) in the management of patients with heart failure.

Pregnancy Associated Plasma Protein-A (PAPP-A): Pregnancy associated plasma protein-A is a circulating protein found in the serum of pregnant women. Recently, authors have asserted PAPP-A is an emerging biomarker of inflammation and plaque instability, linked to coronary artery disease and acute coronary syndrome. Evidence in the peer-reviewed published literature evaluating PAPP-A as a cardiac biomarker consists primarily of observational studies and systematic reviews (Li, et al., 2017; Gutiérrez-Leonard, et al., 2016; Nichenametla and Thomas, 2016; Wu, et al., 2016; Parveen, et al., 2015; Li, et al., 2013; von Haeling, et al., 2013; Wlazel, et al., 2013; Gururajan, et al., 2012). It has been reported standardization of assays has not yet been established and optimal cut-off values have yet to be determined. While some trials support a positive correlation to acute coronary events, others do not. The clinical utility of PAPP-A is unproven and additional studies are needed to validate PAPP-A as a biomarker for predicting cardiovascular events.

GlycA (Glycosylated Acute Phase Proteins): GlycA is a composite biomarker of systemic inflammation that integrates both the protein levels and glycosylation states of several acute phase proteins in serum or plasma. GlycA is hypothesized to be a clinical marker of systemic inflammation and may also be a biomarker of cardiovascular risk. Evidence in the peer-reviewed published literature evaluating GlycA as a biomarker consists primarily of cross-sectional, observational and interventional studies. It has been reported that GlycA test results may have clinical utility similar or complementary to high sensitivity C-reactive protein, fibrinogen and other biomarkers; however, additional studies are needed to validate GlycA as a biomarker of cardiovascular risk (Otvos, et al., 2018; Connelly, et al., 2017; Akinkuolie, et al., 2016; Otvos, et al., 2015; Akinkuolie, et al., 2014).

Other Cardiac Risk Assessment Tests

Several other tests, performed either alone or as part of panels, are under investigation for assessing cardiovascular and atherosclerotic risk (Peterson, et al., 2018; Hoff, et al., 2016; Laaksonen, 2016; Rankin, et al., 2014; Stegemann, et al., 2014; Kramer, 2013; Salgado, et al., 2013; Tashakkor and Mancini, 2013; Creemers, et al., 2012; Pala, et al., 2012; Røysland, et al., 2012; Shah, et al., 2012; Berliner, et al., 2009). How the results of these various tests impact risk stratification and disease management has yet to be determined. At present professional society recommendations and evidence in the published peer-reviewed scientific literature is insufficient to support clinical utility for performance of any of the following tests for the screening, diagnosing or management of coronary heart disease:

- Adiponectin
- Apelin
- Circulating micro RNAs
- Coenzyme Q10 (CoQ10)
- Cystatin C
- Fatty acid levels (e.g., Omega-3, Omega-6, monounsaturated, saturated)

- Galectin 3
- Leptin
- Osteoprotegerin
- Oxidized phospholipids
- Molecular lipid and/or metabolic profiling (e.g., lipidomics, metabolomics)
- Peroxisome proliferator activated receptor
- Plasma ceramides (e.g., MI-Heart Ceramides)
- Protein C
- Resistin
- Retinol binding protein
- Serum sterols
- Skin cholesterol testing
- Thromboxane metabolite(s) testing
- Total cholesterol content in red blood cell membranes
- Tumor necrosis factor alpha
- Troponin, (for other than acute myocardial injury)
- Visfatin

Professional Societies/Organizations

A 2022 American Diabetes Association (ADA) guideline on cardiovascular disease and risk management stated 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.

A 2022 scientific statement from the American Heart Association (AHA) on clinical use of lipoprotein(a) stated the following:

- Elevated Lp(a) is causal for ASCVD and could inform clinical decision-making regarding risk management.
- Lp(a) levels are largely determined by genetic factors.
- Further studies are necessary to understand: links between apo(a) and risk for ASCVD; pathways for Lp(a) synthesis, regulation, and metabolism; and Lp(a) associated risk in diverse genetic and environmental contexts (Reyes-Soffer et al., 2022).

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

A 2018 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) guideline on the management of blood cholesterol, Grundy et al. (2019), 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.

In October 2018, the U.S. Preventive Services Task Force (USPSTF) published updated recommendations for using nontraditional risk factors in coronary heart disease assessment (USPSTF, 2018). The recommendation states: The 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. The current recommendation focuses on three nontraditional risk factors—the ABI, hsCRP level, and CAC score. The USPSTF chose these risk factors because they have the most promising evidence base, are reliably measured, are independently associated with CVD risk or CVD events, and the prevalence and distribution of abnormal and normal values have been described in the target population.

In 2016 the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice were updated (Piepoli, et al., 2016). Within these guidelines the committee classifies biomarkers into those that are inflammatory (e.g., high sensitivity C-reactive protein [hsCRP, fibrinogen]), thrombotic (e.g., homocysteine, lipoprotein-associated phospholipase A2), glucose and lipid-related (e.g., apolipoproteins) and organ-specific (e.g., renal, cardiac). According to the guidelines:

- Not all potentially useful circulatory and urinary 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.

The American College of Cardiology (ACC) and American Heart Association (AHA) in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) published guidelines for cardiovascular risk classification (Goff, et al., 2013) and recommendations for management of blood cholesterol levels in adults (Stone, et al., 2014). Regarding cardiovascular risk classification the ACC/AHA recommends the use of a Pooled Cohort Equation which takes into consideration additional variables such as age and race, in contrast to the ATP III risk classification. As part of risk factor management the ACC/AHA also considered newer risk factors such as hs- CRP, ApoB, glomerular filtration rate (GFR), microalbuminuria, family history, cardiorespiratory fitness, ankle brachial index (ABI), coronary artery calcium (CAC) scoring, or carotid intima media thickness (CIMT) and the impact of each on reclassification or contribution to risk assessment. The work group noted that none of these markers has been evaluated as a screening test in randomized controlled trials

monitoring clinical events as measured outcomes. The evidence available and reviewed either did not support clinical utility or was insufficient to support any additional value for these markers. Within the management of blood cholesterol guidelines, the ACC/AHA does not define LDL cholesterol target goals and notes there were no randomized controlled trials supporting the previously recommended targets. This work group recommends using the Pooled Cohort Equation to more accurately determine risk and then initiating statin therapy to those most likely to benefit. As a result four major statin benefit groups have been identified for which statin therapy is recommended and for which the risk reduction benefit exceeds potential adverse events: individuals with clinical ASCVD, individuals with primary elevations of LDL > 190mg/d/L, individuals with diabetes aged 40-75 years and LDL 70-189 mg/dL and without clinical ASCVD, or those without clinical ASCVD or diabetes with LDL 70-189 mg/dL and estimated 10-year risk of ASCVD \geq 7.5%. In the new guidelines statin therapy is graded as either high intensity or moderate intensity. High intensity statin therapy is defined as that which is intended to reduce LDL by \geq 50% and moderate intensity statin therapy is intended to reduce LDL by 30-50% (Stone, et al., 2014).

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published guidelines for assessment of cardiovascular risk in asymptomatic individuals (i.e., apparently healthy adult) (Greenland, et al., 2010). The task force conducted a systematic review of the current scientific evidence (March 2008 – April 2010) and used evidence based methodologies to weigh the evidence which was reviewed. Level A evidence represented data from multiple randomized controlled trials or meta-analyses, level B evidence was data from a single RCT or nonrandomized trial, and level C evidence represented consensus opinion, case studies or standard of care. The recommendations were approved and endorsed by the ACCF, AHA, American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. The guidelines support global risk assessment in all asymptomatic adults without a clinical history of CVD (level B evidence) and obtaining a family history of atherothrombotic CVD (level B evidence). Regarding laboratory studies specifically, the guidelines recommend hs C-reactive protein (level B evidence), hemoglobin A1C (level B evidence), and Lp-PLA2 (level B evidence). The guidelines do not support genotype testing (level B evidence) or measurement of lipid parameters such as lipoproteins, apolipoproteins, particle size and density, beyond the standard fasting lipid profile (level C evidence), or natriuretic peptide testing (level B evidence).

The American Association of Clinical Chemistry (AACC) issued guidelines (Myers, et al., 2009) titled "The National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guidelines", for emerging biomarkers for primary prevention of cardiovascular disease. The guidelines were developed by a multidisciplinary expert panel after systematically reviewing available evidence and evaluating criteria of clinical usefulness, consistency of epidemiologic data, improved predictive value, independence from other factors, and available analytical methods. When possible, the recommendations were based on prospective observational studies of healthy populations. Retrospective studies or studies consisting of populations with vascular disease were only considered for secondary prevention. The strength of data was characterized using the criteria from the AHA/ACC. The guidelines supported testing of hs-CRP, Lp(a), apo B, apo B/apo A-I ratio, and chronic kidney disease including serum creatinine and microalbuminuria in specific patient populations as identified by the expert panel. The guidelines state that as a result of analytical concerns, insufficient assay standardization, and uncertainty in identifying treatment strategies testing for fibrinogen is not recommended; existing studies are not adequate to show benefit over standard risk assessment for lipoprotein subclass testing; population routine testing for small size apo A is not warranted, apo B should not be routinely measured for use in global risk assessment, the clinical application for homocysteine is uncertain, and more research should

be performed to determine if BNP and NT-proBNP are useful in identifying individuals who are at increased risk of developing heart failure and might benefit from therapies for prevention.

The AACC also published a position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices for apo B testing and cardiovascular disease risk (Contois, et al., 2009). Based on the working group’s review of the available studies, rather than solely focus on LDL cholesterol, the working group supports that apo B along with LDL cholesterol is beneficial for assessing LDL-related risk until the superiority of apo B is generally recognized. The working group also stressed the need for future NCEP guidelines to address apo B and LDL particle measurement.

A consensus statement from the American Diabetes Association and the American College of Cardiology Foundation (Brunzell, et al., 2008) addressed issues surrounding the concept of global cardiometabolic risk (CMR), treatment targets, and the best approach for CVD risk reduction. The consensus panel recommended that because apo B appears to be a more sensitive index of residual CVD risk when LDL cholesterol or non-HDL cholesterol (i.e., total cholesterol minus HDL cholesterol) are < 130 mg/dl or <160 mg/dl respectively, measuring apo B using a standardized assay is warranted in patients with CMR on pharmacologic treatment; in particular, apo B levels should be used to guide adjustments of therapy.

The recommended suggested treatment goals for individuals with CMR and lipoprotein abnormalities now include apolipoprotein B levels, and are as follows:

Table 1: Suggested treatment goals in patients with CMR and lipoprotein abnormalities (based on the panel’s consensus of evaluation of available evidence):

	LDL cholesterol goal (mg/dl)	Non-HDL cholesterol goal (mg/dl)	Apo B goal (mg/dl)
High-risk patients, including those with 1) known CVD or 2) diabetes plus one or more additional major CVD risk factor*	< 70	< 100	< 80
High-risk patients, including those with 1) no diabetes or known clinical CVD but two or more additional major CVD risk factors* or 2) diabetes but no other major CVD risk factors*	<100	<130	<90

*Other major risk factors (beyond dyslipoproteinemia) include: smoking, hypertension, and family history of premature CAD.

The National Cholesterol Education Program Adult Treatment Panel (Adult Treatment Panel III [ATP III]) guidelines do not recommend routine measurement of any of the emerging risk factors for the purpose of risk assessment; these tests should be used in selected persons, and only on the basis of considered clinical judgment (National Cholesterol Education Program, 2002).

Regarding the use of conditional and predisposing risk factors in risk assessment, in 1999 the AHA and ACC reported conditional risk factors included: elevated serum triglycerides, small LDL particles, elevated serum homocysteine, elevated serum lipoprotein(a), prothrombotic factors (e.g., fibrinogen), and inflammatory markers (e.g., C-reactive protein). However, their quantitative contribution and independence of contribution to risk are not well defined, and they are not usually included in global risk assessment (ACC, 1999). Furthermore, the AHA and ACC concluded a high serum concentration of homocysteine is associated with increased risk for CHD; however, it remains to be proved in controlled clinical trials that a reduction in serum homocysteine levels will reduce the risk for CHD. Routine measures of lipoprotein (a), fibrinogen, and C-reactive protein currently are not recommended. An elevated serum lipoprotein(a) correlates with a higher incidence of CHD in some studies but not in others, and specific therapeutics to reduce lipoprotein(a) levels are not available. Additionally, the AHA and ACC stated that some investigators have suggested that an elevated lipoprotein(a) level justifies a more aggressive lowering of LDL-C. An elevated fibrinogen level is also correlated with a higher CHD incidence; however, again, no specific therapies are available, except that in smokers, smoking cessation may reduce fibrinogen concentrations. Finally, C-reactive protein is promising as a risk predictor. The preferred method for measurement appears to be a high-sensitivity test. C-reactive protein appears to be related to systemic inflammation; however, its causative role in atherogenesis is uncertain.

Use Outside of the US

No relevant information.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	Lipid Testing (190.23)	1/1/2005
LCD	CGS Administrators, LLC	MoIDX: Biomarkers in Cardiovascular Risk Assessment (L36139)	3/2/2023
LCD	Noridian Healthcare Solutions, LLC	MoIDX: Biomarkers in Cardiovascular Risk Assessment (L36358 & L36362)	4/22/2021
LCD	Palmetto GBA	MoIDX: Biomarkers in Cardiovascular Risk Assessment (L36129)	4/22/2021
LCD	Wisconsin Physicians Service Insurance Corporation	MoIDX: Biomarkers in Cardiovascular Risk Assessment (L36523)	3/30/2023

Note: Please review the current Medicare Policy for the most up-to-date information. (NCD = National Coverage Determination; LCD = Local Coverage Determination)

Coding Information

Notes:

1. This list of codes may not be all-inclusive.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

Lipoprotein-associated phospholipase A2 (Lp-PLA2) testing

CPT®* Codes	Description
83698	Lipoprotein-associated phospholipase A2 (Lp-PLA2)

Apolipoprotein B testing

CPT®* Codes	Description
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) APOB (apolipoprotein B)(eg, familial hypercholesterolemia type B) common variants (eg, R3500Q, R3500W)
82172	Apolipoprotein, each

Lipoprotein(a) enzyme immunoassay (Lp[a]) testing

CPT®* Codes	Description
83695	Lipoprotein (a)

Other Emerging Cardiac Disease Risk Factor Laboratory Tests

Considered Experimental, investigational, or unproven when performed for screening, diagnosing or management of coronary heart disease:

CPT®* Codes	Description
82163	Angiotensin II
82172	Apolipoprotein, each
82542	Column chromatography, include mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen
82610	Cystatin C
82777	Galectin-3
83006	Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)
83090	Homocysteine
83519	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (eg, RIA)
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
83700	Lipoprotein, blood; electrophoretic separation and quantitation
83701	Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation)

CPT®* Codes	Description
83704	Lipoprotein, blood; quantitation of lipoprotein particle number(s) (eg, by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed
83719	Lipoprotein, direct measurement; VLDL cholesterol
83876	Myeloperoxidase (MPO)
84163	Pregnancy-associated plasma protein-A (PAPP-A)
84431	Thromboxane metabolite(s), including thromboxane if performed, urine
84484	Troponin, quantitative
84999 [†]	Unlisted chemistry procedure
85230	Clotting; factor VII (proconvertin, stable factor)
85247	Clotting; factor VIII, von Willebrand factor, multimeric analysis
85300	Clotting inhibitors or anticoagulants; antithrombin III, activity
85303	Clotting inhibitors or anticoagulants; protein C, activity
85384	Fibrinogen; activity
85385	Fibrinogen; antigen
85415	Fibrinolytic factors and inhibitors; plasminogen activator
0024U	Glycosylated acute phase proteins (GlycA), nuclear magnetic resonance spectroscopy, quantitative
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
0119U	Cardiology, ceramides by liquid chromatography-tandem mass spectrometry, plasma, quantitative report with risk score for major cardiovascular events
0308U	Cardiology (coronary artery disease [CAD]), analysis of 3 proteins (high sensitivity [hs] troponin, adiponectin, and kidney injury molecule-1 [KIM-1]), plasma, algorithm reported as a risk score for obstructive CAD
0309U	Cardiology (cardiovascular disease), analysis of 4 proteins (NT-proBNP, osteopontin, tissue inhibitor of metalloproteinase-1 [TIMP-1], and kidney injury molecule-1 [KIM-1]), plasma, algorithm reported as a risk score for major adverse cardiac event
0377U	Cardiovascular disease, quantification of advanced serum or plasma lipoprotein profile, by nuclear magnetic resonance (NMR) spectrometry with report of a lipoprotein profile (including 23 variables)

[†] **Note:** Experimental, investigational, unproven and not covered when used to report any non-covered service outlined as such in this document (e.g., Long-chain [C20-22] omega-3 Fatty acids in RBC membranes, MIRISK VP™, PULS Cardiac Test™).

***Current Procedural Terminology (CPT®) ©2022 American Medical Association: Chicago, IL.**

References

1. Agency for Healthcare Research and Quality (AHRQ). Low density lipoprotein subfractions: Systematic review of measurement methods and association with cardiovascular outcomes. Jun 2008 (archived). Accessed Jun 26, 2023. Available at URL address: <https://www.ncbi.nlm.nih.gov/books/NBK248379/>
2. AHA; ACC; National Heart, Lung, and Blood Institute, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease:

2006 update endorsed by the National Heart, Lung, and Blood Institute. *J Am Coll Cardiol.* 2006;47(10):2130-2139.

3. Ahmed MS, Ji JZ, Meng QH. Lipoprotein-associated phospholipase A2: how effective as a risk marker of cardiovascular disease and as a therapeutic target? *Inflamm Allergy Drug Targets.* 2011 Aug 1;10(4):236-46.
4. Akinkuolie AO, Buring JE, Ridker PM, Mora S. A novel protein glycan biomarker and future cardiovascular disease events. *J Am Heart Assoc.* 2014 Sep 23;3(5):e001221.
5. Akinkuolie AO, Glynn RJ, Padmanabhan L, Ridker PM, Mora S. Circulating N-Linked Glycoprotein Side-Chain Biomarker, Rosuvastatin Therapy, and Incident Cardiovascular Disease: An Analysis From the JUPITER Trial. *J Am Heart Assoc.* 2016 Jul 13;5(7). pii: e003822.
6. Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC, Ma J. Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med.* 2002 Apr 11;346(15):1113
7. American Association for Clinical Chemistry Academy. AACC. Optimal Testing AACC's Guide to Lab Test Utilization: Homocysteine Optimal Testing Recommendations. 2022. Available at URL address: <https://www.aacc.org/advocacy-and-outreach/optimal-testing-guide-to-lab-test-utilization/g-s/homocysteine>
8. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. *Diabetes Care.* 2022 Jan 1;45(Suppl 1):S144-S174. doi: 10.2337/dc22-S010. Erratum in: *Diabetes Care.* 2022 Mar 07; Erratum in: *Diabetes Care.* 2022 Sep 1;45(9):2178-2181. PMID: 34964815.
9. American Diabetes Association. Professional Practice Committee: Standards of Medical Care in Diabetes-2018. *Diabetes Care.* 2018 Jan;41(Suppl 1):S3.
10. Anuurad E, Boffa MB, Koschinsky ML, Berglund L. Lipoprotein(a): a unique risk factor for cardiovascular disease. *Clin Lab Med.* 2006 Dec;26(4):751-72.
11. Apple FS, Pearce LA, Chung A, Ler R, Murakami MM. Multiple biomarkers use for detection of adverse events in patients presenting with symptoms suggestive of acute coronary syndrome. *Clin Chem.* 2007 May;53(5):874-81.
12. 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 [published correction appears in *Circulation.* 2019 Sep 10;140(11):e649-e650] [published correction appears in *Circulation.* 2020 Jan 28;141(4):e60] [published correction appears in *Circulation.* 2020 Apr 21;141(16):e774].*Circulation.* 2019;140(11):e596-e646.
13. Balk E, Chung M, Lichtenstein A, et al. Effects of Omega-3 Fatty Acids on Cardiovascular Risk Factors and Intermediate Markers of Cardiovascular Disease. Summary, Evidence Report/Technology Assessment: Number 93. AHRQ Publication Number 04-E010-1, Mar 2004. Agency for Healthcare Research and Quality, Rockville, MD. Accessed Jun 26, 2023. Available at URL address: <https://www.ncbi.nlm.nih.gov/books/NBK11935/>

14. Ballantyne CM, Hoogeveen RC. Role of lipid and lipoprotein profiles in risk assessment therapy. *Am Heart J*. 2003 Aug;146(2):227-33.
15. Bays HE, Jones PH, Brown WV, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2015. *J Clin Lipidol*. 2014 Nov-Dec;8(6 Suppl):S1-36.
16. Bays HE, Jones PH, Orringer CE, Brown WV, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2016. *J Clin Lipidol*. 2016 Jan-Feb;10(1 Suppl):S1-43.
17. Benderly M, Boyko V, Goldbourt U. Apolipoproteins and long-term prognosis in coronary heart disease patients. *Am Heart J*. 2009 Jan;157(1):103-10.
18. Berglund L, Anuurad E. Role of Lipoprotein(a) in Cardiovascular Disease Current and Future Perspectives. *J Am Coll Cardiol*. 2008 Jul 8;52(2):132-134.
19. Berliner JA, Leitinger N, Tsimikas S. The role of oxidized phospholipids in atherosclerosis. *J Lipid Res*. 2009;50 Suppl(Suppl):S207-S212.
20. Biswas S, Ghoshal PK, Mandal SC, Mandal N. Association of low-density lipoprotein particle size and ratio of different lipoproteins and apolipoproteins with coronary heart disease. *J Cardiol*. 2008 Oct;52(2):118-26.
21. Blonde L, Umpierrez GE, Reddy SS, McGill JB, Berga SL, Bush M, Chandrasekaran S, DeFronzo RA, Einhorn D, Galindo RJ, Gardner TW, Garg R, Garvey WT, Hirsch IB, Hurley DL, Izuora K, Kosiborod M, Olson D, Patel SB, Pop-Busui R, Sadhu AR, Samson SL, Stec C, Tamborlane WV Jr, Tuttle KR, Twining C, Vella A, Vellanki P, Weber SL. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. *Endocr Pract*. 2022 Oct;28(10):923-1049. doi: 10.1016/j.eprac.2022.08.002. Epub 2022 Aug 11. Erratum in: *Endocr Pract*. 2023 Jan;29(1):80-81. PMID: 35963508; PMCID: PMC10200071.
22. Boekholdt SM, Keller TT, Wareham NJ, Luben R, Bingham SA, Day NE, Sandhu MS, Jukema JW, Kastelein JJ, Hack CE, Khaw KT. Serum levels of type II secretory phospholipase A2 and the risk of future coronary artery disease in apparently healthy men and women: the EPIC-Norfolk Prospective Population Study. *Arterioscler Thromb Vasc Biol*. 2005 Apr;25(4):839-46.
23. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, Witztum JL. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2008 Apr 15;51(15):1512-24.
24. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis*. 2016 Oct;253:281-344.
25. Centers for Medicare and Medicaid Services (CMS). Local Coverage Determinations (LCDs) alphabetical index. Accessed Mar 6, 2023. Available at URL address: <https://www.cms.gov/medicare-coverage-database/reports/local-coverage-proposed-lclds-alphabetical-report.aspx?proposedStatus=A&sortBy=title>

26. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed Mar 6, 2023. Available at URL address: <https://www.cms.gov/medicare-coverage-database/reports/national-coverage-ncd-report.aspx?chapter=all&sortBy=title>
27. Cesari M, Rossi GP, Pessina AC. Homocysteine-lowering treatment in coronary heart disease. *Curr Med Chem Cardiovasc Hematol Agents*. 2005 Oct;3(4):289-95.
28. Chamberlain JJ, Johnson EL, Leal S, Rhinehart AS, Shubrook JH, Peterson L. Cardiovascular Disease and Risk Management: Review of the American Diabetes Association Standards of Medical Care in Diabetes 2018. *Ann Intern Med*. 2018 May 1;168(9):640-650.
29. Chung M, Lichtenstein AH, Ip S, Lau J, Balk EM. Comparability of methods for LDL subfraction determination: A systematic review. *Atherosclerosis*. 2009 Aug;205(2):342-8.
30. Cole TG, Contois JH, Csako G, McConnell JP, Remaley AT, Devaraj S, Hoefner DM, Mallory T, Sethi AA, Warnick GR. Association of Apolipoprotein B and Nuclear Magnetic Resonance Spectroscopy-Derived LDL Particle Number with Outcomes in 25 Clinical Studies: Assessment by the AACC Lipoprotein and Vascular Diseases Division Working Group on Best Practices. *Clin Chem*. 2013 May;59(5):752-70.
31. Connelly MA, Otvos JD, Shalaurova I, Playford MP, Mehta NN. GlycA, a novel biomarker of systemic inflammation and cardiovascular disease risk. *J Transl Med*. 2017 Oct 27;15(1):219.
32. Contois JH, McConnell JP, Sethi AA, Csako G, Devaraj S, Hoefner DM, Warnick GR; AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. Apolipoprotein B and cardiovascular disease risk: position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. *Clin Chem*. 2009 Mar;55(3):407-19.
33. Corson MA, Jones JH, Davidson MH. Review of the evidence for the clinical utility of lipoprotein-associated phospholipase A2 as a cardiovascular risk marker. *Am J Cardiol*. 2008 Jun;101(12):Suppl.
34. Crea F, Morrow DA. C-reactive protein in cardiovascular disease. Last updated Aug 20, 2020. In: *UpToDate*, Kaski JC (Ed), *UpToDate*, Waltham, MA
35. Creemers EE, Tijssen AJ, Pinto YM. Circulating microRNAs: novel biomarkers and extracellular communicators in cardiovascular disease. *Circ Res*. 2012;110(3):483-495.
36. Critical Diagnostics. Presage® ST2 Assay - Instructions for Use. Accessed Jun 26, 2023. Available at URL address: <http://criticaldiagnostics.com/US/products/index.htm>
37. Cromwell WC, Otvos JD. Heterogeneity of low-density lipoprotein particle number in patients with type 2 diabetes mellitus and low-density lipoprotein cholesterol <100 mg/dl. *Am J Cardiol*. 2006 Dec 15;98(12):1599-602.
38. Cromwell WC, Otvos JD, Keyes MJ, Pencina MJ, Sullivan L, Vasan RS, Wilson PW, D'Agostino RB. LDL Particle Number and Risk of Future Cardiovascular Disease in the Framingham Offspring Study - Implications for LDL Management. *J Clin Lipidol*. 2007 Dec;1(6):583-92.

39. Daly C, Fitzgerald AP, O'Callaghan P, Collins P, Cooney MT, Graham IM; COMAC Group. Homocysteine increases the risk associated with hyperlipidaemia. *Eur J Cardiovasc Prev Rehabil*. 2009 Apr;16(2):150-5.
40. Davidson MH, Ballantyne CM, Jacobson TA, Bittner VA, Braun LT, Brown AS, et al. Clinical utility of inflammatory markers and advanced lipoprotein testing: advice from an expert panel of lipid specialists. *J Clin Lipidol*. 2011 Sep-Oct;5(5):338-67.
41. Davidson MH, Corson MA, Alberts MJ, Anderson JL, Gorelick PB, Jones PH, et al. Consensus Panel Recommendation for Incorporating Lipoprotein-Associated Phospholipase A₂ Testing into Cardiovascular Disease Risk Assessment Guidelines. *Am J Cardiol*. 2008 Jun;101(12A Supp).
42. Delgado-Lista J, Perez-Martinez P, Lopez-Miranda J, Perez-Jimenez F. Long chain omega-3 fatty acids and cardiovascular disease: a systematic review. *Br J Nutr*. 2012 Jun;107 Suppl 2:S201-13.
43. Dembic M, Hedley PL, Torp-Pedersen C, Kober L, Christiansen M. Pregnancy-associated plasma protein-A (PAPP-A) and the proform of the eosinophil major basic protein (ProMBP) are associated with increased risk of death in heart failure patients. *Scand J Clin Lab Invest*. 2017 May 24:1-6.
44. Diabetes Prevention Program Research Group. Strategies to identify adults at high risk for type 2 diabetes: the Diabetes Prevention Program. *Diabetes Care*. 2005 Jan;28(1):138-44.
45. Ebbing M, Bleie Ø, Ueland PM, Nordrehaug JE, Nilsen DW, Vollset SE, Refsum H, Pedersen EK, Nygård O. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. *JAMA*. 2008 Aug 20;300(7):795-804.
46. El Harchaoui K, Arsenault BJ, Franssen R, Després JP, Hovingh GK, Stroes ES, Otvos JD, Wareham NJ, Kastelein JJ, Khaw KT, Boekholdt SM. High-density lipoprotein particle size and concentration and coronary risk. *Ann Intern Med*. 2009 Jan 20;150(2):84-93.
47. El Harchaoui K, van der Steeg WA, Stroes ES, Kuivenhoven JA, Otvos JD, Wareham NJ, Hutten BA, Kastelein JJ, Khaw KT, Boekholdt SM. Value of low-density lipoprotein particle number and size as predictors of coronary artery disease in apparently healthy men and women: the EPIC-Norfolk Prospective Population Study. *J Am Coll Cardiol*. 2007 Feb 6;49(5):547-53.
48. Elashoff MR, Wingrove JA, Beineke P, et al. Development of a Blood-Based Gene Expression Algorithm for Assessment of Obstructive Coronary Artery Disease in Non-Diabetic Patients. *BMC Med Genomics* 2011; 4(1):26doi: 10.1186/1755-8794-4-26.
49. Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P, Pennells L, Kaptoge S, Caslake M, et al. Lipid-related markers and cardiovascular disease prediction. *JAMA*. 2012 Jun 20;307(23):2499-506.
50. Emerging Risk Factors Collaboration, Erqou S, Kaptoge S, Perry PL, Di Angelantonio E, Thompson A, White IR, Marcovina SM, Collins R, Thompson SG, Danesh J. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. 2009 Jul 22;302(4):412-23.

51. Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Pennells L, Wood AM, White IR, et al. C-reactive protein, fibrinogen, and cardiovascular disease prediction. *N Engl J Med*. 2012 Oct 4;367(14):1310-20.
52. Felker GM, Fiuzat M, Thompson V, et al. Soluble ST2 in ambulatory patients with heart failure: Association with functional capacity and long-term outcomes. *Circ Heart Fail*. 2013;6(6):1172-1179.
53. Folsom AR, Nambi V, Pankow JS, Tang W, Farbaksh K, Yamagishi K, Boerwinkle E. Effect of 9p21 genetic variation on coronary heart disease is not modified by other risk markers. The Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis*. 2012 Oct;224(2):435-9.
54. 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.
55. Frontini MG, Srinivasan SR, Xu JH, Tang R, Bond MG, Berenson G. Utility of non-high-density lipoprotein cholesterol versus other lipoprotein measures in detecting subclinical atherosclerosis in young adults (The Bogalusa Heart Study). *Am J Cardiol*. 2007 Jul 1;100(1):64-8.
56. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. AACE comprehensive diabetes management algorithm 2015. *Endocr Pract*. 2015 Apr;21(4):438-47.
57. Garg PK, McClelland RL, Jenny NS, Criqui M, Liu K, Polak JF, Jorgensen NW, Cushman M. Association of Lipoprotein-associated Phospholipase A2 and Endothelial Function in the Multi-Ethnic Study of Atherosclerosis (MESA). *Vasc Med*. 2011 Jun 27.
58. Garga, 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.
59. Garvey WT, Kwon S, Zheng D, Shaughnessy S, Wallace P, Hutto A, Pugh K, Jenkins AJ, Klein RL, Liao Y. Effects of insulin resistance and type 2 diabetes on lipoprotein subclass particle size and concentration determined by nuclear magnetic resonance. *Diabetes*. 2003 Feb;52(2):453-62.
60. Genest J, Frohlich J, Fodor G, McPherson R (the Working Group on Hypercholesterolemia and Other Dyslipidemias). Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: 2003 update. *CMAJ*. 2003 Oct;169(9). Accessed Jun 26, 2023. Available at URL address: <http://www.cmaj.ca/cgi/content/full/169/9/921>
61. Giacobbe DT, Murray MJ. Vascular disease and inflammation. *Anesthesiology Clin N Am*. 2004 Jun;22(2):183-97v.
62. Gigante B, Leander K, Vikstrom M, Frumento P, Carlsson AC, Bottai M, de Faire U. Elevated ApoB serum levels strongly predict early cardiovascular events. *Heart*. 2012 Aug;98(16):1242-5.
63. Gingrich C, Carroll WE. Neurology. Chapter 42. In: *Rakel: Textbook of Family Medicine*, 8th ed. Copyright © 2011.

64. Goff DC Jr, D'Agostino RB Jr, Haffner SM, Otvos JD. Insulin resistance and adiposity influence lipoprotein size and subclass concentrations. Results from the Insulin Resistance Atherosclerosis Study. *Metabolism*. 2005 Feb;54(2):264-70.
65. Goff DC Jr, Lloyd-Jones DM, Bennett G, O'Donnell CJ, Coady S, Robinson J, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013 Nov 12. pii: S0735-1097(13)06031-2.
66. Gotto AM Jr, Whitney E, Stein EA, Shapiro DR, Clearfield M, Weis S, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation*. 2000 Feb;101(5):477-84.
67. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, 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. *J Am Coll Cardiol*. 2010 Dec 14;56(25):e50-103.
68. Grundy SM. Cardiovascular and Metabolic Risk Factors: How Can We Improve Outcomes in the High-Risk Patient? *Am J Med*. 2007 Sep;120(9 Supp 1):S3-8; discussion S9.
69. Grundy SM, Cleeman JI, Baird Merz CN, Brewer HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *Circulation*. 2004 Jul;110: 227-39.
70. Grundy SM, Pasternak R, Greenland P, Smith S, Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor equations. A Statement for Healthcare Professionals From the American Heart Association and the American College of Cardiology. *AHA/ACC Scientific Statement*. *J Am Coll Cardiol*. 1999 Oct;34(4):1348-59.
71. 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 [published correction appears in *J Am Coll Cardiol*. 2019 Jun 25;73(24):3237-3241]. *J Am Coll Cardiol*. 2019;73(24):e285-e350.
72. 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.
73. Gururajan P, Gurumurthy P, Nayar P, Rao GS, Babu RS, Sarasabharati A, Cherian KM. Pregnancy associated plasma protein-A (PAPP-A) as an early marker for the diagnosis of acute coronary syndrome. *Indian Heart J*. 2012 Mar-Apr;64(2):141-5.
74. Gutiérrez-Leonard H, Martínez-Lara E, Fierro-Macías AE, et al. Pregnancy-associated plasma protein-A (PAPP-A) as a possible biomarker in patients with coronary artery disease. *Ir J Med Sci*. 2016 Oct 11.
75. Halle DA, Loscalzo J. Lipid disorders: Diagnosis, management and controversy. In: Noble, J, editor. *Textbook of Primary Care Medicine*, 3rd edition. Copyright © 2001 Mosby, Inc. Ch. 71.

76. Handelsman Y, Bloomgarden Z, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology – Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan. Updated 2022. Accessed Jun 26, 2023. Available at URL address: 2022 Clinical Practice Guideline for Development of a Diabetes Mellitus Comprehensive Care Plan | American Association of Clinical Endocrinology (aace.com)
77. Handelsman Y, Jellinger PS, Guerin CK, Bloomgarden ZT, Brinton EA, Budoff MJ, Davidson MH, Einhorn D, Fazio S, Fonseca VA, Garber AJ, Grunberger G, Krauss RM, Mechanick JI, Rosenblit PD, Smith DA, Wyne KL. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Management of Dyslipidemia and Prevention of Cardiovascular Disease Algorithm - 2020 Executive Summary. *Endocr Pract.* 2020 Oct;26(10):1196-1224. doi: 10.4158/CS-2020-0490. PMID: 33471721.
78. Hartweg J, Farmer AJ, Holman RR, Neil A. Potential impact of omega-3 treatment on cardiovascular disease in type 2 diabetes. *Curr Opin Lipidol.* 2009 Feb;20(1):30-8.
79. He K, Song Y, Daviglius ML, Liu K, Van Horn L, Dyer AR, Greenland P. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation.* 2004 Jun 8;109(22):2705-11.
80. Heart Protection Study Collaborative Group, Bulbulia R, Bowman L, Wallendszus K, Parish S, Armitage J, Peto R, Collins R. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. *Lancet.* 2011 Dec 10;378(9808):2013-20.
81. Herman L, Froelich J, Kanelos D, et al. Utility of a genomic-based, personalized medicine test in patients presenting with symptoms suggesting coronary artery disease. *J Am Board Fam Med.* 2014;27(2):258-267.
82. Hilvo M, Wallentin L, Ghukasyan Lakic T, et al. Prediction of Residual Risk by Ceramide-Phospholipid Score in Patients With Stable Coronary Heart Disease on Optimal Medical Therapy. *J Am Heart Assoc.* 2020;9(10):e015258.
83. Hochheiser LI, Juusola JL, Monane M, Ladapo JA. Economic utility of a blood-based genomic test for the assessment of patients with symptoms suggestive of obstructive coronary artery disease. *Popul Health Manag.* 2014 Feb 25.
84. Hoff J, Wehner W, Nambi V. Troponin in Cardiovascular Disease Prevention: Updates and Future Direction. *Curr Atheroscler Rep.* 2016 Mar;18(3):12.
85. Holme I, Cater NB, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Larsen ML, Lindahl C, Pedersen TR; Incremental Decrease in End-Points Through Aggressive Lipid-Lowering (IDEAL) Study Group. Lipoprotein predictors of cardiovascular events in statin-treated patients with coronary heart disease. Insights from the Incremental Decrease In End-points Through Aggressive Lipid-lowering Trial (IDEAL). *Ann Med.* 2008;40(6):456-64.
86. 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.

87. Hopewell JC¹, Clarke R, Parish S, Armitage J, Lathrop M, Hager J, Collins R; Heart Protection Study Collaborative Group. Lipoprotein(a) genetic variants associated with coronary and peripheral vascular disease but not with stroke risk in the Heart Protection Study. *Circ Cardiovasc Genet*. 2011 Feb;4(1):68-73.
88. Hsia J, Otvos JD, Rossouw JE, Wu L, Wassertheil-Smoller S, Hendrix SL, Robinson JG, Lund B, Kuller LH; Women's Health Initiative Research Group. Lipoprotein particle concentrations may explain the absence of coronary protection in the women's health initiative hormone trials. *Arterioscler Thromb Vasc Biol*. 2008 Sep;28(9):1666-71.
89. Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE. Fish and long-chain omega-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. *Circulation*. 2003 Apr 15;107(14):1852-7.
90. Huang YC. Lowering homocysteine levels does not reduce rates of stroke, coronary heart disease or death in people with ischaemic stroke. *Evidence-based public health*. 2004;8(4):210-12.
91. Humphrey LL, Fu R, Rogers K, Freeman M, Helfand M. Homocysteine level and coronary heart disease incidence: a systematic review and meta-analysis. *Mayo Clin Proc*. 2008 Nov;83(11):1203-12.
92. Iakoubova OA, Sabatine MS, Rowland CM, Tong CH, Catanese JJ, Ranade K, Simonsen KL, Kirchgessner TG, Cannon CP, Devlin JJ, Braunwald E. Polymorphism in KIF6 gene and benefit from statins after acute coronary syndromes: results from the PROVE IT-TIMI 22 study. *J Am Coll Cardiol*. 2008 Jan 29;51(4):449-55.
93. Ikewaki K, Terao Y, Ozasa H, Nakada Y, Tohyama J, Inoue Y, Yoshimura M. Effects of atorvastatin on nuclear magnetic resonance-defined lipoprotein subclasses and inflammatory markers in patients with hypercholesterolemia. *J Atheroscler Thromb*. 2009 Mar;16(1):51-6.
94. Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, Keyes MJ, Pencina MJ, Schoonmaker C, Wilson PW, D'Agostino RB, Vasan RS. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA*. 2007 Aug 15;298(7):776-85.
95. Ip S, Lichtenstein AH, Chung M, Lau J, Balk EM. Systematic review: association of low-density lipoprotein subfractions with cardiovascular outcomes. *Ann Intern Med*. 2009 Apr 7;150(7):474-84.
96. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, et al., National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 1-Full Report. March-April 2015, Volume 9, Issue 2, Pages 129-169.
97. Jafri H, Alsheikh-Ali A, Mooney P, Kimmelstiel C, Karas R, Kuvin J. Extended-release niacin reduces LDL particle number without changing total LDL cholesterol in patients with stable CAD. *Journal of Clinical Lipidology*. 2009 Feb;3(1):45-50.
98. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al., American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. AACE 2017. Updated 2020. Accessed Jun 26, 2023. Available at URL address: 2020

99. Jellinger PS, Smith DA, Mehta AE, Ganda O, Handelsman Y, Rodbard HW, Shepherd MD, Seibel JA; AACE Task Force for Management of Dyslipidemia and Prevention of Atherosclerosis, Kreisberg R, Goldberg R. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. *Endocr Pract.* 2012 Mar-Apr;18 Suppl 1:1-78.
100. Jialal I, Devaraj S. Role of C-reactive protein in the assessment of cardiovascular risk. *The Am J Cardiol.* 2003 Jan;91(2):200-2.
101. Kappelle PJ, Dallinga-Thie GM, Dullaart RP; Diabetes Atorvastatin Lipid Intervention (DALI) study group. Atorvastatin treatment lowers fasting remnant-like particle cholesterol and LDL subfraction cholesterol without affecting LDL size in type 2 diabetes mellitus: Relevance for non-HDL cholesterol and apolipoprotein B guideline targets. *Biochim Biophys Acta.* 2010 Jan;1801(1):89-94.
102. Kastelein JJ, van der Steeg WA, Holme I, Gaffney M, Cater NB, Barter P, Deedwania P, Olsson AG, Boekholdt SM, Demicco DA, Szarek M, LaRosa JC, Pedersen TR, Grundy SM; TNT Study Group; IDEAL Study Group. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation.* 2008 Jun 10;117(23):3002-9.
103. Khadem-Ansari MH, Rasmi Y, Rahimi-Pour A, Jafarzadeh M. The association between serum apolipoprotein A-I and apolipoprotein B and the severity of angiographical coronary artery disease. *Singapore Med J.* 2009 Jun;50(6):610-3.
104. Khera AV, Demler OV, Adelman SJ, Collins HL, Glynn RJ, Ridker PM, et al. Cholesterol Efflux Capacity, High-Density Lipoprotein Particle Number, and Incident Cardiovascular Events: An Analysis From the JUPITER Trial (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin). *Circulation.* 2017 Jun 20;135(25):2494-2504.
105. Knopp RH, Paramsothy P, Atkinson B, Dowdy A. Comprehensive lipid management versus aggressive low-density lipoprotein lowering to reduce cardiovascular risk. *Am J Cardiol.* 2008 Apr 17;101(8A):48B-57B.
106. Koba S, Yokota Y, Hirano T, Ito Y, Ban Y, Tsunoda F, Sato T, Shoji M, Suzuki H, Geshi E, Kobayashi Y, Katagiri T. Small LDL-cholesterol is superior to LDL-cholesterol for determining severe coronary atherosclerosis. *Atheroscler Thromb.* 2008 Oct;15(5):250-60.
107. Koenig W, Vossen CY, Mallat Z, Brenner H, Benessiano J, Rothenbacher D. Association between type II secretory phospholipase A2 plasma concentrations and activity and cardiovascular events in patients with coronary heart disease. *Eur Heart J.* 2009 Nov;30(22):2742-8.
108. Kohli P, Bonaca MP, Kakkar R, et al. Role of ST2 in non-ST-elevation acute coronary syndrome in the MERLIN-TIMI 36 trial. *Clin Chem.* 2012 Jan;58(1):257-66.
109. Kopecky ST, Halkar MG. Screening for coronary heart disease. Last updated Sep 14, 2021. In: UpToDate, Pellikka PA (Ed), UpToDate, Waltham, MA

110. 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*. 2019;70(9):819-829.
111. 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*. 2019;34(4):424-434.
112. Kovanen PT, Pentikäinen MO. Secretory group II phospholipase A(2) : a newly recognized acute-phase reactant with a role in atherogenesis. *Circ Res*. 2000 Mar 31;86(6):610-2.
113. Kramer CK, Zinman B, Gross JL, et al. Coronary artery calcium score prediction of all cause mortality and cardiovascular events in people with type 2 diabetes: systematic review and meta-analysis. *BMJ*. 2013;346:f1654. Published 2013 Mar 25.
114. Kugiyama K, Ota Y, Takazoe K, Moriyama Y, Kawano H, Miyao Y, Sakamoto T, Soejima H, Ogawa H, Doi H, Sugiyama S, Yasue H. Circulating levels of secretory type II phospholipase A(2) predict coronary events in patients with coronary artery disease. *Circulation*. 1999 Sep 21;100(12):1280-4.
115. Kulkarni KR. Cholesterol profile measurement by vertical auto profile method. *Clin Lab Med*. 2006 Dec;26(4):787-802.
116. Kuller L, Arnold A, Tracy R, Otvos J, Burke G, Psaty B, Siscovick D, Freedman DS, Kronmal R. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the cardiovascular health study. *Arterioscler Thromb Vasc Biol*. 2002 Jul 1;22(7):1175-80.
117. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. *Am J Epidemiol* 1996 Sep;144(6):537-47.
118. Kullo IJ, Li G, Bielak LF, Bailey KR, Sheedy PF 2nd, Peyser PA, Turner ST, Kardina SL. Association of plasma homocysteine with coronary artery calcification in different categories of coronary heart disease risk. *Mayo Clin Proc*. 2006 Feb;81(2):177-82.
119. Kwon SW, Lee BK, Hong BK, Kim JY, Choi EY, Sung JM, Rhee JH, Park YM, Ma DW, Chung H, Mun HS, Lee SJ, Park JK, Min PK, Yoon YW, Rim SJ, Kwon HM. Prognostic significance of elevated lipoprotein(a) in coronary artery revascularization patients. *Int J Cardiol*. 2012 May 23.
120. Ky B, French B, McCloskey K, et al. High-sensitivity ST2 for prediction of adverse outcomes in chronic heart failure. *Circ Heart Fail*. 2011 Mar;4(2):180-7.
121. Laaksonen R. Identifying new Risk Markers and Potential Targets for Coronary Artery Disease: The Value of the Lipidome and Metabolome. *Cardiovasc Drugs Ther*. 2016 Feb;30(1):19-32.
122. LabCorp. GlycA. Accessed Jun 26, 2023. Available at URL address: <https://www.labcorp.com/test-menu/26131/glyca#>

123. Lamarche B, Moorjani S, Lupien PJ, Cantin B, Bernard PM, Dagenais GR, Despres JP. Apolipoprotein A-I and B Levels and the Risk of Ischemic Heart Disease During a Five-Year Follow-up of Men in the Quebec Cardiovascular Study. *Circulation*. 1996;94:273-78.
124. Lansky A, Elashoff MR, Ng V, et al. A gender-specific blood-based gene expression score for assessing obstructive coronary artery disease in nondiabetic patients: results of the Personalized Risk Evaluation and Diagnosis in the Coronary Tree (PREDICT) trial. *Am Heart J*. 2012 Sep;164(3):320-6.
125. Lau JF, Smith DA. Advanced lipoprotein testing: recommendations based on current evidence. *Endocrinol Metab Clin North Am*. 2009 Mar;38(1):1-31.
126. Le NA, Jin R, Tomassini JE, Tershakovec AM, Neff DR, Wilson PW. Changes in lipoprotein particle number with ezetimibe/simvastatin coadministered with extended-release niacin in hyperlipidemic patients. *J Am Heart Assoc*. 2013 Aug 7;2(4):e000037.
127. Lee KW, Hill JS, Walley KR, Frohlich JJ. Relative value of multiple plasma biomarkers as risk factors for coronary artery disease and death in an angiography cohort. *CMAJ*. 2006 Feb 14;174(4):461-6.
128. Li D, Wei W, Ran X, Yu J, Li H, Zhao L, Zeng H, Cao Y, Zeng Z, Wan Z. 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.
129. Li WP, Neradilek MB, Gu FS, et al. Pregnancy-associated plasma protein-A is a stronger predictor for adverse cardiovascular outcomes after acute coronary syndrome in type-2 diabetes mellitus. *Cardiovasc Diabetol*. 2017 Apr 5;16(1):45.
130. Li Y, Huang T, Zheng Y, Muka T, Troup J, Hu FB. Folic Acid Supplementation and the Risk of Cardiovascular Diseases: A Meta-Analysis of Randomized Controlled Trials. *J Am Heart Assoc*. 2016 Aug 15;5(8).
131. Li Y, Zhou C, Zhou X, Li L, Hui R. Pregnancy-associated plasma protein A predicts adverse vascular events in patients with coronary heart disease: a systematic review and meta-analysis. *Arch Med Sci*. 2013 Jun 20;9(3):389-97.
132. Li ZG, Li G, Zhou YL, Chen ZJ, Yang JQ, Zhang Y, Sun S, Zhong SL. Lack of association between lipoprotein(a) genetic variants and subsequent cardiovascular events in Chinese Han patients with coronary artery disease after percutaneous coronary intervention. *Lipids Health Dis*. 2013 Aug 27;12:127.
133. Lind L, Simon T, Johansson L, et al. Circulating Levels of Secretory- and Lipoprotein-Associated Phospholipase A2 Activities: Relation to Atherosclerotic Plaques and Future All-Cause Mortality. *Eur Heart J*. 2012 Dec;33(23):2946-54.
134. Linton MF, Fazio S. A practical approach to risk assessment to prevent coronary artery disease and its complications. *Am J Cardiol*. 2003 Jul;92(1A)19i-26i.
135. Liu PY, Li YH, Tsai WC, Chao TH, Tsai LM, Wu HL, Chen JH. Prognostic value and the changes of plasma levels of secretory type II phospholipase A2 in patients with coronary artery disease undergoing percutaneous coronary intervention. *Eur Heart J*. 2003 Oct;24(20):1824-32.

136. Lloyd-Jones DM. Epidemiology of cardiovascular disease. In: Goldman L, Schafer AI. Goldman-Cecil Medicine. 25th Ed. Philadelphia, PA: Saunders; 2016:257-262.e1
137. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, McQueen MJ, Probstfield J, Fodor G, Held C, Genest J Jr; Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med*. 2006 Apr 13;354(15):1567-77.
138. Lp-PLA(2) Studies Collaboration, Thompson A, Gao P, Orfei L, Watson S, Di Angelantonio E, Kaptoge S, Ballantyne C, Cannon CP, Criqui M, Cushman M, Hofman A, Packard C, Thompson SG, Collins R, Danesh J. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet*. 2010 May 1;375(9725):1536-44.
139. Luc G, Bard JM, Ferrières J, Evans A, Amouyel P, Arveiler D, Fruchart JC, Ducimetière P. Value of HDL cholesterol, apolipoprotein A-I, lipoprotein A-I, and lipoprotein A-I/A-II in prediction of coronary heart disease: the PRIME Study. Prospective Epidemiological Study of Myocardial Infarction. *Arterioscler Thromb Vasc Biol*. 2002 Jul 1;22(7):1155-61.
140. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188.
141. Mackey RH, Greenland P, Goff DC Jr, Lloyd-Jones D, Sibley CT, Mora S. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (multi-ethnic study of atherosclerosis). *J Am Coll Cardiol*. 2012 Aug 7;60(6):508-16.
142. Malave H, Castro M, Burkle J, Voros S, Dayspring T, Honigberg R, Pourfarzib R. Evaluation of Low-Density Lipoprotein Particle Number Distribution in Patients With Type 2 Diabetes Mellitus With Low-Density Lipoprotein Cholesterol <50 mg/dl and Non-High-Density Lipoprotein Cholesterol <80 mg/dl. *Am J Cardiol*. 2012 May 21.
143. Mangoni AA, Jackson SHD. Homocysteine and cardiovascular disease: current evidence and future prospects. *Am J Med*. 2002 May;112(7):556-65.
144. Manickam P, Rathod A, Penaich S, Hari P, Veeranna V, Badheka A, et al. Comparative prognostic utility of conventional and novel lipid parameters for cardiovascular disease risk prediction: do novel lipid parameters offer an advantage? *J Clin Lipidol* 2011;5:82-90.
145. Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. *Clin Cardiol*. 2009 Jul;32(7):365-72.
146. Martí-Carvajal AJ, Solà I, Lathyris D, Salanti G. Homocysteine lowering interventions for preventing cardiovascular events. *Cochrane Database Syst Rev*. 2009 Oct 7;(4):CD006612.
147. Martin SS, Qasim AN, Wolfe M, St Clair C, Schwartz S, Iqbal N, Schutta M, Bagheri R, Mehta NN, Rader DJ, Reilly MP. Comparison of high-density lipoprotein cholesterol to apolipoprotein A-I and A-II to predict coronary calcium and the effect of insulin resistance. *Am J Cardiol*. 2011 Feb 1;107(3):393-8.

148. Meeusen JW, Donato LJ, Kopecky SL, Vasile VC, Jaffe AS, Laaksonen R. Ceramides improve atherosclerotic cardiovascular disease risk assessment beyond standard risk factors. *Clin Chim Acta*. 2020;511:138-142.
149. Memon L, Spasojevic-Kalimanovska V, Bogavac-Stanojevic N, Kalimanovska-Ostic D, Jelic-Ivanovic Z, Spasic S, Topic A. Association of C-reactive protein with the presence and extent of angiographically verified coronary artery disease. *Tohoku J Exp Med*. 2006 Jul;209(3):197-206.
150. Miller M, Ginsberg HN, Schaefer EJ. Relative atherogenicity and predictive value of non-high-density lipoprotein cholesterol for coronary heart disease. *Am J Cardiol*. 2008 Apr 1;101(7):1003-8.
151. Mora S, Buring JE, Ridker PM. Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events. *Circulation*. 2014 Feb 4;129(5):553-61.
152. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation*. 2009 Feb 24;119(7):931-9.
153. Mora S, Otvos JD, Rosenson RS, Pradhan A, Buring JE, Ridker PM. Lipoprotein particle size and concentration by nuclear magnetic resonance and incident type 2 diabetes in women. *Diabetes*. 2010 May;59(5):1153-60.
154. Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC Jr, O'Leary DH, Saad MF, Tsai MY, Sharrett AR. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007 May;192(1):211-7.
155. Mora S, Wenger NK, Demicco DA, Breazna A, Boekholdt SM, Arsenault BJ, Deedwania P, Kastelein JJ, Waters DD. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. *Circulation*. 2012 Apr 24;125(16):1979-87.
156. Moriarty PM, Gibson CA. Effect of low-density lipoprotein apheresis on lipoprotein - associated phospholipase A₂. *Am J Cardiol*. 2005 May;95(10):1246-47.
157. Morrow DA, Sabatine MS, Brennan ML, de Lemos JA, Murphy SA, Ruff CT, Rifai N, Cannon CP, Hazen SL. Concurrent evaluation of novel cardiac biomarkers in acute coronary syndrome: myeloperoxidase and soluble CD40 ligand and the risk of recurrent ischaemic events in TACTICS-TIMI 18. *Eur Heart J*. 2008 May;29(9):1096-102.
158. Moyad MA. Introduction to risk assessment and serum risk markers for the prevention of coronary heart disease and other potential conditions that impact men's health, part II: what do I tell my patients? *Urol Clin North Am*. 2004 May;31(2):199-205.
159. Mozaffarian D, Longstreth WT Jr, Lemaitre RN, Manolio TA, Kuller LH, Burke GL, Siscovick DS. Fish consumption and stroke risk in elderly individuals: the cardiovascular health study. *Arch Intern Med*. 2005 Jan 24;165(2):200-6.
160. Myers GL, Christenson RH, Cushman M, Ballantyne CM, Cooper GR, Pfeiffer CM, et al.; NACB LMPG Committee Members. National Academy of Clinical Biochemistry Laboratory

Medicine Practice guidelines: emerging biomarkers for primary prevention of cardiovascular disease. 2009. Accessed Jun 26, 2023. Available at URL address: <https://www.aacc.org/science-and-practice/practice-guidelines/emerging-cv-risk-factors>

161. Naghavi M, Falk E, Hecht HS, Jamieson MJ, Kaul S, Berman D, et al.; SHAPE Task Force. From vulnerable plaque to vulnerable patient--Part III: Executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. *Am J Cardiol.* 2006 Jul 17;98(2A):2H-15H. Epub 2006 Jun 12.
162. National Cholesterol Education Program. Third report of the panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Sept 2002. Risk assessment tool for estimating 10-year risk of developing hard CHD (myocardial infarction and coronary death). Accessed Jun 26, 2023. Available at URL address: <http://circ.ahajournals.org/content/106/25/3143.long>
163. Ndrepepa G, Braun S, King L, Fusaro M, Keta D, Cassese S, Tada T, Schömig A, Kastrati A. Relation of fibrinogen level with cardiovascular events in patients with coronary artery disease. *Am J Cardiol.* 2013 Mar 15;111(6):804-10.
164. Newman CB, Blaha MJ, Boord JB, et al. Lipid Management in Patients with Endocrine Disorders: An Endocrine Society Clinical Practice Guideline [published correction appears in *J Clin Endocrinol Metab.* 2021 May 13;106(6):e2465]. *J Clin Endocrinol Metab.* 2020;105(12):dga674.
165. Nichenametla G, Thomas VS. Evaluation of Serum Pregnancy Associated Plasma Protein-A & Plasma D-Dimer in Acute Coronary Syndrome. *J Clin Diagn Res.* 2016 Jan;10(1):BC01-3.
166. Niessen HW, Krijnen PA, Visser CA, Meijer CJ, Erik Hack C. Type II secretory phospholipase A2 in cardiovascular disease: a mediator in atherosclerosis and ischemic damage to cardiomyocytes? *Cardiovasc Res.* 2003 Oct 15;60(1):68-77.
167. Nishikura T1, Koba S, Yokota Y, Hirano T, Tsunoda F, Shoji M, et al. Elevated Small Dense Low-Density Lipoprotein Cholesterol as a Predictor for Future Cardiovascular Events in Patients with Stable Coronary Artery Disease. *J Atheroscler Thromb.* 2014 Apr 8.
168. Noel MB, Thompson M, Wadland C, Holtrop JS. Nutrition and family medicine. CH 37. Rakel: Textbook of Family Medicine, 8th ed. Copyright© 2011.
169. O'Callaghan PA, Fitzgerald A, Fogarty J, Gaffney P, Hanbidge M, Boran G, Enright H, Murphy J, McCarthy B, Graham IM. New and old cardiovascular risk factors: C-reactive protein, homocysteine, cysteine and von Willebrand factor increase risk, especially in smokers. *Eur J Cardiovasc Prev Rehabil.* 2005 Dec;12(6):542-7.
170. O'Donoghue ML, Mallat Z, Morrow DA, Benessiano J, Sloan S, Omland T, Solomon SD, Braunwald E, Tedgui A, Sabatine MS. Prognostic utility of secretory phospholipase A(2) in patients with stable coronary artery disease. *Clin Chem.* 2011 Sep;57(9):1311-7.
171. Oei HH, van der Meer IM, Hofman A, Koudstaal PJ, Stijnen T, Breteler MM, Witteman JC. Lipoprotein-associated phospholipase A2 activity is associated with risk of coronary heart disease and ischemic stroke: the Rotterdam Study. *Circulation.* 2005 Feb 8;111(5):570-5.
172. Otvos JD, Collins D, Freedman DS, Shalaurava I, Schaefer EJ, McNamara JR, Bloomfield HE, Robins SJ. Low-density lipoprotein and high-density lipoprotein particle subclasses

- predict coronary events and are favorably changed by gemfibrozil therapy in the Veterans Affairs High-Density Lipoprotein Intervention Trial. *Circulation*. 2006 Mar 28;113(12):1556-63.
173. Otvos JD, Guyton JR, Connelly MA, Akapame S, Bittner V, Kopecky SL, et al. Relations of GlycA and lipoprotein particle subspecies with cardiovascular events and mortality: A post hoc analysis of the AIM-HIGH trial. *J Clin Lipidol*. 2018 Mar - Apr;12(2):348-355.e2.
 174. Otvos JD, Mora S, Shalaurova I, Greenland P, Mackey RH, Goff DC Jr. Clinical implications of discordance between low-density lipoprotein cholesterol and particle number. *J Clin Lipidol*. 2011 Mar-Apr;5(2):105-13.
 175. Otvos JD, Shalaurova I, Wolak-Dinsmore J, Connelly MA, Mackey RH, Stein JH, Tracy RP. GlycA: A Composite Nuclear Magnetic Resonance Biomarker of Systemic Inflammation. *Clin Chem*. 2015 May;61(5):714-23.
 176. Packard CJ, O'Reilly DS, Caslake MJ, McMahon AD, Ford I, Cooney J, Macphee CH, Suckling KE, Krishna M, Wilkinson FE, Rumley A, Lowe GD. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. West of Scotland Coronary Prevention Study Group. *N Engl J Med*. 2000 Oct 19;343(16):1148-55.
 177. Pala L, Monami M, Ciani S, et al. Adipokines as possible new predictors of cardiovascular diseases: a case control study. *J Nutr Metab*. 2012;2012:253428.
 178. Papanastasiou CA, Kokkinidis DG, Oikonomou EK, Mantziaris VG, Foley TR, Karamitsos TD, et al. Pregnancy associated plasma protein-A as a prognostic biomarker of all-cause mortality and cardiovascular events in patients presenting with chest pain: a systematic review. *Biomarkers*. 2018 Feb;23(1):1-9.
 179. Parish S, Offer A, Clarke R, Hopewell JC, Hill MR, Otvos JD, Armitage J, Collins R; on behalf of the Heart Protection Study Collaborative Group. Lipids and Lipoproteins and Risk of Different Vascular Events in the MRC/BHF Heart Protection Study. *Circulation*. 2012 May 22;125(20):2469-2478.
 180. Parveen N, Subhakumari KN, Krishnan S. Pregnancy Associated Plasma Protein-A (PAPP-A) Levels in Acute Coronary Syndrome: A Case Control Study in a Tertiary Care Centre. *Indian J Clin Biochem*. 2015 Apr;30(2):150-4.
 181. Paynter NP, Sesso HD, Conen D, Otvos JD, Mora S. Lipoprotein subclass abnormalities and incident hypertension in initially healthy women. *Clin Chem*. 2011 Aug;57(8):1178-87.
 182. Pearson TA. New tools for coronary risk assessment: what are their advantages and limitations? *Circulation*. 2002;105(7):886-92.
 183. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon III RO, Criqui M, Yazid YF, Fortmann SP, Hong y, Myers GL, Rifai N, Smith Jr SC, Taubert K, Tracy RP, Vinicor F. Markers of inflammation and cardiovascular disease. Application to clinical and public health practice. A statement for healthcare professionals from the Centers For Disease Control and Prevention and the American Heart Association (AHA/CDC) Scientific Statement. *Circulation*. 2003;107:499-511.
 184. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *The*

Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012 Jul;33(13):1635-701.

185. Piepoli F, Hoes AW, Agewall S, Albus C, Brotons, Catapano AL, et al. 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (Constituted by Representatives of 10 Societies and by Invited Experts): Developed With the Special Contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur J Prev Cardiol* 23 (11), NP1-NP96. 2016 Jun 27.
186. Rankin NJ, Preiss D, Welsh P, Burgess KE, Nelson SM, Lawlor DA, Sattar N. The emergence of proton nuclear magnetic resonance metabolomics in the cardiovascular arena as viewed from a clinical perspective. *Atherosclerosis*. 2014 Nov;237(1):287-300.
187. Ray KK, Cannon CP, Cairns R, Morrow DA, Ridker PM, Braunwald E. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. *Arterioscler Thromb Vasc Biol*. 2009 Mar;29(3):424-30.
188. Reichman WE, Cummings JL. Dementia. Ch 25. In: Duthie: Practice of Geriatrics, 4th ed. Copyright © 2007.
189. Reyes-Soffer G, Ginsberg HN, Berglund L, et al. Lipoprotein(a): A genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2022 Jan;42(1):e48-e60.
190. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. *J Am Coll Cardiol*. 2007 May 29;49(21):2129-38.
191. Ridker PM. High sensitivity c-reactive protein, inflammation, and cardiovascular risk: from concept to clinical benefit. *Am Heart J*. 2004 Jul;148(1 Supp):S19-26.
192. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA*. 2007 Feb 14;297(6):611-9.
193. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. C-reactive protein levels and outcomes after statin therapy. *N Engl J Med*. 2005 Jan;352:20-8.
194. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med*. 1997;336:973-79.
195. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008 Nov 20;359(21):2195-207.

196. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000 Mar; 342(12):836-43.
197. Ridker PM, Libby P. Risk factors for atherothrombotic disease. In: Libby: Braunwald's heart disease: a textbook of cardiovascular medicine, 8th ed. Copyright © 2007.
198. Ridker PM, Libby P. Risk markers and the primary prevention of cardiovascular disease. In: Libby: Braunwald's heart disease: a textbook of cardiovascular medicine, 11th ed. Copyright © 2019; 876-909.
199. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of c-reactive protein and low density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002 Nov;347(20):1157-1565.
200. Ridker PM, Wilson PWF, Grundy SM. Should c-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? American Heart Association. Reviews: Current perspectives. *Circulation*. 2004;109:2818-25.
201. Rizzo JA1, Mallow PJ, Waters HC, Pokrywka GS. Managing to low-density lipoprotein particles compared with low-density lipoprotein cholesterol: a cost-effectiveness analysis. *J Clin Lipidol*. 2013 Nov-Dec;7(6):642-52.
202. Robinson JG, Wang S, Jacobson TA. Meta-analysis of comparison of effectiveness of lowering apolipoprotein B versus low-density lipoprotein cholesterol and nonhigh-density lipoprotein cholesterol for cardiovascular risk reduction in randomized trials. *Am J Cardiol*. 2012 Nov 15;110(10):1468-76.
203. Roman RM, Wendland AE, Polanczyk CA. Myeloperoxidase and coronary arterial disease: from research to clinical practice. *Arq Bras Cardiol*. 2008 Jul;91(1):e11-9.
204. Rosenson RS. Lipoprotein classification, metabolism, and role in atherosclerosis. Last updated Jan 18, 2022. In: UpToDate, Freeman M (Ed), UpToDate, Waltham, MA.
205. Rosenson RS. Management of non-high-density lipoprotein abnormalities. *Atherosclerosis*. 2009 Dec;207(2):328-35.
206. Rosenson RS. Measurement of blood lipids and lipoproteins. Last updated Nov 4, 2021. In: UpToDate, Freeman M (Ed), UpToDate, Waltham, MA.
207. Rosenson RS, Otvos JD, Hsia J. Effects of rosuvastatin and atorvastatin on LDL and HDL particle concentrations in patients with metabolic syndrome: a randomized, double-blind, controlled study. *Diabetes Care*. 2009 Jun;32(6):1087-91.
208. Rosenson RS, Smith CC, Bauer KA. Overview of homocysteine. Last updated Dec 6, 2021. In: UpToDate, Freeman M (Ed), UpToDate, Waltham, MA.
209. Rosenson RS, Stein JH, Durrington P. Lipoprotein(a). Last updated Jan 31, 2022. In: UpToDate, Freeman M (Ed), UpToDate, Waltham, MA.
210. Rosenson RS, Underberg JA. Systematic review: Evaluating the effect of lipid-lowering therapy on lipoprotein and lipid values. *Cardiovasc Drugs Ther*. 2013 Oct;27(5):465-79.

211. Rosenzweig JL, Ferrannini E, Grundy SM, Haffner SM, Heine RJ, Horton ES, Kawamori R; Endocrine Society. Primary prevention of cardiovascular disease and type 2 diabetes in patients at metabolic risk: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2008 Oct;93(10):3671-89.
212. Røysland R, Kravdal G, Høiseth AD, et al. Cardiac troponin T levels and exercise stress testing in patients with suspected coronary artery disease: the Akershus Cardiac Examination (ACE) 1 study. *Clin Sci (Lond).* 2012;122(12):599-606.
213. Sabatine MS, Morrow DA, O'Donoghue M, Jablonski KA, Rice MM, Solomon S, Rosenberg Y, Domanski MJ, Hsia J; PEACE Investigators. Prognostic utility of lipoprotein-associated phospholipase A2 for cardiovascular outcomes in patients with stable coronary artery disease. *Arterioscler Thromb Vasc Biol.* 2007 Nov;27(11):2463-9.
214. Sacks FM, Campos H. Clinical review 163: cardiovascular endocrinology: low-density lipoprotein size and cardiovascular disease: a reappraisal. *J Clin Endocrinol Metab.* 2003 Oct;88(10):4525-32.
215. Salgado JV, Souza FL, Salgado BJ. How to understand the association between cystatin C levels and cardiovascular disease: Imbalance, counterbalance, or consequence? *J Cardiol.* 2013;62(6):331-335.
216. Shah SH, Kraus WE, Newgard CB. Metabolomic profiling for the identification of novel biomarkers and mechanisms related to common cardiovascular diseases: form and function. *Circulation.* 2012 Aug 28;126(9):1110-20.
217. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, Patsch W. Atherosclerosis Risk in Communities Study Group. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* 2001 Sep;104(10):1108-13.
218. Shimpo M, Morrow DA, Weinberg EO, et al. Serum levels of the interleukin-1 receptor family member ST2 predict mortality and clinical outcome in acute myocardial infarction. *Circulation.* 2004;109(18):2186-2190.
219. Sierra-Johnson J, Fisher RM, Romero-Corral A, Somers VK, Lopez-Jimenez F, Ohrvik J, et al. Concentration of apolipoprotein B is comparable with the apolipoprotein B/apolipoprotein A-I ratio and better than routine clinical lipid measurements in predicting coronary heart disease mortality: findings from a multi-ethnic US population. *Eur Heart J.* 2009 Mar;30(6):710-7.
220. Singh IM, Shishehbor MH, Ansell BJ. High-density lipoprotein as a therapeutic target: a systematic review. *JAMA.* 2007 Aug 15;298(7):786-98.
221. Sniderman A, Couture P, de Graaf J. Diagnosis and treatment of apolipoprotein B dyslipoproteinemias. *Nat Rev Endocrinol.* 2010 Jun;6(6):335-46.
222. Sniderman AD, Furberg CD, Keech A, Roeters van Lennep JE, Frohlich J, Jungner I, Walldius G. Apolipoproteins versus lipids as indices of coronary risk and as targets for statin treatment. *Lancet.* 2003a Mar 1;361(9359):777-80.

223. Sniderman AD, Kwiterovich PO. Update on the detection and treatment of atherogenic low-density lipoproteins. *Curr Opin Endocrinol Diabetes Obes.* 2013 Apr;20(2):140-7.
224. Sniderman AD, St-Pierre AC, Cantin BC, Dagenias GR, Despres JP, Lamarche B. Concordance/discordance between plasma apolipoprotein B levels and the cholesterol indexes of atherosclerotic risk. *Am J Cardiol.* 2003b May;91(10):1173-7.
225. Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, Furberg CD. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. *Circ Cardiovasc Qual Outcomes.* 2011 May;4(3):337-45.
226. Son JW, Kim DJ, Lee CB, Oh S, Song KH, Jung CH, et al., Effects of patient-tailored atorvastatin therapy on ameliorating the levels of atherogenic lipids and inflammation beyond lowering low-density lipoprotein cholesterol in patients with type 2 diabetes. *J Diabetes Investig.* 2013 Sep 13;4(5):466-74.
227. Song Y, Yang Y, Zhang J, et al. The apoB100/apoAI ratio is independently associated with the severity of coronary heart disease: a cross sectional study in patients undergoing coronary angiography. *Lipids Health Dis.* 2015 Nov 18;14:150.
228. Splaver A, Lamas GA, Hennekens CH. Homocysteine and cardiovascular disease: biological mechanisms, observational epidemiology, and the need for randomized trials. *Am Heart J.* 2004 Jul;148(1):3440.
229. Stampfer MJ, Sacks FM, Salvini S, Willett WC, Hennekens CH. A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *N Engl J Med.* 1991 Aug;325-6:373-81.
230. Stefanescu A, Braun S, Ndrepepa G, Koppa T, Pavaci H, Mehilli J, Schömig A, Kastrati A. Prognostic value of plasma myeloperoxidase concentration in patients with stable coronary artery disease. *Am Heart J.* 2008 Feb;155(2):356-60.
231. Steffen BT, Guan W, Remaley AT, et al. Use of lipoprotein particle measures for assessing coronary heart disease risk post-American Heart Association/American College of Cardiology guidelines: the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2015 Feb;35(2):448-54.
232. Stegemann C, Pechlaner R, Willeit P, Langley SR, Mangino M, Mayr U, Menni C, Moayyeri A, Santer P, Rungger G, Spector TD, Willeit J, Kiechl S, Mayr M. Lipidomics profiling and risk of cardiovascular disease in the prospective population-based Bruneck study. *Circulation.* 2014 May 6;129(18):1821-31.
233. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2014 Jul 1;63(25 Pt B):2889-934.
234. Straczek C, Marti-Soler H, Tafflet M, Perier MC, Dupuy AM, Tzourio C, Barberger-Gateau P, Empana JP. Comparable incremental value of standard and nonstandard lipids for coronary

heart disease risk assessment in elderly adults: the Three City Study. *J Am Geriatr Soc*. 2013 Jul;61(7):1234-6.

235. Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage JM, Bowman L, Clarke RJ, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Sleight P, Peto R, Collins R. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial. *JAMA*. 2010 Jun 23;303(24):2486-94.
236. Suh S, Park HD, Kim SW, Bae JC, Tan AH, Chung HS, Hur KY, Kim JH, Kim KW, Lee MK. Smaller Mean LDL Particle Size and Higher Proportion of Small Dense LDL in Korean Type 2 Diabetic Patients. *Diabetes Metab J*. 2011 Oct;35(5):536-42.
237. Sukhija R, Fahdi I, Garza L, Fink L, Scott M, Aude W, Pacheco R, Bursac Z, Grant A, Mehta JL. Inflammatory markers, angiographic severity of coronary artery disease, and patient outcome. *Am J Cardiol*. 2007 Apr 1;99(7):879-84.
238. Tani S, Nagao K, Anazawa T, Kawamata H, Furuya S, Takahashi H, Iida K, Matsumoto M, Washio T, Kumabe N, Hirayama A. Relation of change in apolipoprotein B/apolipoprotein A-I ratio to coronary plaque regression after Pravastatin treatment in patients with coronary artery disease. *Am J Cardiol*. 2010 Jan 15;105(2):144-8.
239. Tashakkor AY, Mancini GB. The relationship between skin cholesterol testing and parameters of cardiovascular risk: a systematic review. *Can J Cardiol*. 2013 Nov;29(11):1477-87.
240. Tian L, Long S, Li C, Liu Y, Chen Y, Zeng Z, Fu M. High-density lipoprotein subclass and particle size in coronary heart disease patients with or without diabetes. *Lipids Health Dis*. 2012 May 15;11(1):54.
241. Tighe DA, Ockene IS, Reed G, Nicolosi R. Calculated low density lipoprotein cholesterol levels frequently underestimate directly measured low density lipoprotein cholesterol determinations in patients with serum triglyceride levels ≤ 4.52 mmol/l: an analysis comparing the LipiDirect magnetic LDL assay with the Friedewald calculation. *Clin Chim Acta*. 2006 Mar;365(1-2):236-42.
242. Toth PP, Grabner M, Punekar RS, Quimbo RA, Cziraky MJ, Jacobson TA. Cardiovascular risk in patients achieving low-density lipoprotein cholesterol and particle targets. *Atherosclerosis*. 2014 May 22;235(2):585-591.
243. Toth PP. High-density lipoprotein and cardiovascular risk. *Circulation*. 2004 Apr 20;109(15):1809-12.
244. Toth PP, Shammas NW, Dipel EJ, Foreman B. Dyslipidemia. In: *Rakel: Textbook for Family Medicine*, 8th ed. Ch 27 Copyright © 2008 Saunders.
245. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, Boehme AK, Buxton AE, Carson AP, Commodore-Mensah Y, Elkind MSV, Evenson KR, Eze-Nliam C, Ferguson JF, Generoso G, Ho JE, Kalani R, Khan SS, Kissela BM, Knutson KL, Levine DA, Lewis TT, Liu J, Loop MS, Ma J, Mussolino ME, Navaneethan SD, Perak AM, Poudel R, Rezk-Hanna M, Roth GA, Schroeder EB, Shah SH, Thacker EL, VanWagner LB, Virani SS, Voecks JH, Wang NY, Yaffe K, Martin SS. Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. *Circulation*. 2022 Feb 22;145(8):e153-e639.

doi: 10.1161/CIR.0000000000001052. Epub 2022 Jan 26. Erratum in: Circulation. 2022 Sep 6;146(10):e141. PMID: 35078371.

246. Underbakke G, McBride PE. Dyslipidemias. Ch 40. In: Rakel: Integrative Medicine, 2nd. Copyright © 2007 Saunders.
247. U.S. Preventive Services Task Force (USPSTF). *Screening for Lipid Disorders in Children: Recommendation Statement*. Updated August 9, 2016. Agency for Healthcare Research and Quality, Rockville, MD. Accessed Jun 26, 2023. Available at URL address: <http://jamanetwork.com/journals/jama/fullarticle/2542642>
248. US Preventive Services Task Force, Curry SJ, Krist AH, et al. Risk Assessment for Cardiovascular Disease With Nontraditional Risk Factors: US Preventive Services Task Force Recommendation Statement. JAMA. 2018;320(3):272-280.
249. van Capelleveen JC, Bochem AE, Boekholdt SM, Mora S, Hoogeveen RC, Ballantyne CM, Ridker PM, Sun W, Barter PJ, Tall AR, et al. Association of High-Density Lipoprotein-Cholesterol Versus Apolipoprotein A-I With Risk of Coronary Heart Disease: The European Prospective Investigation Into Cancer-Norfolk Prospective Population Study, the Atherosclerosis Risk in Communities Study, and the Women's Health Study. J Am Heart Assoc. 2017 Aug 3;6(8).
250. van Holten TC, Waanders LF, de Groot PG, Vissers J, Hoefler IE, Pasterkamp G, Prins MW, Roest M. Circulating biomarkers for predicting cardiovascular disease risk; a systematic review and comprehensive overview of meta-analyses. PLoS One. 2013 Apr 22;8(4):e62080.
251. Vargas J, Lima JA, Kraus WE, et al. Use of the Corus® CAD gene expression test for assessment of obstructive coronary artery disease. Likelihood in symptomatic non-diabetic patients. PLoS Curr. 2013 Aug 26;5.
252. Veterans Affairs and Department of Defense (VA/DoD) Clinical Practice Guidelines: The Management of Dyslipidemia for Cardiovascular Risk Reduction (Lipids) (2020). Accessed Jun 26, 2023. Available at URL address: <http://www.healthquality.va.gov/guidelines/CD/lipids/>
253. Vijan S. Screening for lipid disorders in adults. Last updated Aug 2, 2021. In: UpToDate, Freeman M (Ed), UpToDate, Waltham, MA.
254. von Haehling S, Doehner W, Jankowska EA, et al. Value of serum pregnancy-associated plasma protein A for predicting cardiovascular events among patients presenting with cardiac chest pain. CMAJ. 2013 Apr 16;185(7):E295-303.
255. Voros S, Elashoff MR, Wingrove JA, et al. A peripheral blood gene expression score is associated with atherosclerotic plaque burden and stenosis by cardiovascular CT-angiography: Results from the PREDICT and COMPASS studies. Atherosclerosis. 2014;233(1):284-290.
256. 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.

257. Wallach J. Serum apolipoproteins. In: Seigafuse S, Winter N, Konstant D, Schonberger K, Walz N, Brown K, et al. editors. Interpretation of diagnostic tests. Cardiovascular diseases. Diseases principally of endocardium. © 2007 by Lippincott Williams & Wilkins.
258. Wallentin L, Held C, Armstrong PW, et al., Lipoprotein-Associated Phospholipase A2 Activity Is a Marker of Risk But Not a Useful Target for Treatment in Patients With Stable Coronary Heart Disease. *J Am Heart Assoc.* 2016 Jun; 5(6): e003407.
259. Wang J, Tan GJ, Han LN, Bai YY, He M, Liu HB. Novel biomarkers for cardiovascular risk prediction. *J Geriatr Cardiol.* 2017 Feb;14(2):135-150.
260. Wang TJ, Wollert KC, Larson MG, et al. Prognostic utility of novel biomarkers of cardiovascular stress: The Framingham Heart Study. *Circulation.* 2012;126(13):1596-1604.
261. Wattanakit K, Folsom AR, Chambless LE, Nieto FJ. Risk factors for cardiovascular event recurrence in the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J.* 2005 Apr;149(4):606-12.
262. Whelton SP, He J, Whelton PK, Muntner P. Meta-analysis of observational studies on fish intake and coronary heart disease. *Am J Cardiol.* 2004 May 1;93(9):1119-23.
263. Williams PT, Zhao XQ, Marcovina SM, Brown BG, Krauss RM. Levels of cholesterol in small LDL particles predict atherosclerosis progression and incident CHD in the HDL-Atherosclerosis Treatment Study (HATS). *PLoS One.* 2013;8(2):e56782.
264. Wilson DP, Jacobson TA, Jones PH, Koschinsky ML, McNeal CJ, Nordestgaard BG, Orringer CE. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. *J Clin Lipidol.* 2019 May-Jun;13(3):374-392. doi: 10.1016/j.jacl.2019.04.010. Epub 2019 May 17. Erratum in: *J Clin Lipidol.* 2022 Sep-Oct;16(5):e77-e95. PMID: 31147269.
265. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-47.
266. Wilson P. Cardiovascular disease risk assessment for primary prevention: Risk calculators. Last updated Sep 1, 2021. In: UpToDate, Gersh BJ (Ed), UpToDate, Waltham, MA.
267. Wilson P. Cardiovascular disease risk assessment for primary prevention: Our approach. Last updated Oct 17, 2022. In: UpToDate, Downey BC (Ed), UpToDate, Waltham, MA.
268. Wilson P. Overview of established risk factors for cardiovascular disease. Last updated Jan 11, 2023. In: UpToDate, Downey BC (Ed), UpToDate, Waltham, MA.
269. Wilson P. Overview of possible risk factors for cardiovascular disease. Last updated Jun 7, 2022. In: UpToDate, Downey BC (Ed), UpToDate, Waltham, MA.
270. Wlazeł RN, Rysz J, Paradowski M. Examination of serum pregnancy-associated plasma protein A clinical value in acute coronary syndrome prediction and monitoring. *Arch Med Sci.* 2013 Feb 21;9(1):14-20.
271. Wu XF, Yang M, Qu AJ, et al. Level of Pregnancy-associated Plasma Protein-A Correlates With Coronary Thin-cap Fibroatheroma Burden in Patients With Coronary Artery Disease:

Novel Findings From 3-Vessel Virtual Histology Intravascular Ultrasound Assessment. *Medicine (Baltimore)*. 2016 Jan;95(3):e2563.

272. Xin H, Chen ZY, Lv XB, Liu S, Lian ZX, Cai SL. 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.
273. Xu RX1, Guo YL, Li XL, Li S, Li JJ. Impact of short-term low-dose atorvastatin on LDL and HDL subfraction phenotype. *Clin Exp Pharmacol Physiol*. 2014 Apr 17.
274. Yin WH, Chen JW, Jen HL, Chiang MC, Huang WP, Feng AN, Young MS, Lin SJ. Independent prognostic value of elevated high-sensitivity C-reactive protein in chronic heart failure. *Am Heart J*. May 01, 2004;147(5):931-8.
275. Ying X, Qian Y, Jiang Y, Jiang Z, Song Z, Zhao C. Association of the apolipoprotein B/apolipoprotein A-I ratio and low-density lipoprotein cholesterol with insulin resistance in a Chinese population with abdominal obesity. *Acta Diabetol*. 2012 Dec;49(6):465-72.
276. Zhu YM, Verma S, Fung M, McQueen MJ, Anderson TJ, Lonn EM. Association of Apolipoproteins B and A-1 With Markers of Vascular Health or Cardiovascular Events. *Can J Cardiol*. 2017 Oct;33(10):1305-1311.

“Cigna Companies” refers to operating subsidiaries of Cigna Corporation. All products and services are provided exclusively by or through such operating subsidiaries, including Cigna Health and Life Insurance Company, Connecticut General Life Insurance Company, Evernorth Behavioral Health, Inc., Cigna Health Management, Inc., and HMO or service company subsidiaries of Cigna Health Corporation. © 2023 Cigna.