

DRAFT Medical Coverage Policy | Biomarker Testing in Risk Assessment and Management of Cardiovascular Disease



EFFECTIVE DATE: 12|01|2024

POLICY LAST REVIEWED: 08|07|2024

OVERVIEW

Numerous lipid and non-lipid biomarkers have been proposed as potential risk markers for cardiovascular disease (CVD). Biomarkers assessed herein include, B-type natriuretic peptide, cystatin C, fibrinogen, high-density lipoprotein subclass, leptin, low-density lipoprotein subclass, lipoprotein(a), and lipoprotein-associated phospholipase A2 (Lp-PLA2). These biomarkers have been studied as alternatives or additions to standard lipid panels for risk stratification in CVD or as treatment targets for lipid-lowering therapy. Cardiovascular risk panels refer to different combinations of cardiac markers that are intended to evaluate the risk of CVD. There are numerous commercially available risk panels that include different combinations of lipids, noncardiac biomarkers, measures of inflammation, metabolic parameters, and/or genetic markers. Risk panels report the results of multiple individual tests, as distinguished from quantitative risk scores that combine the results of multiple markers into a single score.

This policy does not address the use of a simple lipid panel, which includes a total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides. Certain calculated ratios (eg, total/high-density lipoprotein cholesterol) may also be reported as part of a simple lipid panel. Other types of lipid testing (ie, apolipoproteins, lipid particle number or particle size, lipoprotein [a]) are not considered components of a simple lipid profile.

This policy also does not address the use of panels of biomarkers in the diagnosis of acute myocardial infarction.

For coverage of tests filed with PLA codes (0119U-MI-HEART Ceramides, Plasma and 0052U-VAP Cholesterol Test), please refer to the related policy “Proprietary Laboratory Analyses (PLA) and Multianalyte Assays with Algorithmic Analyses (MAAA)”

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

CPT Codes 82610, 83700, 83701 and 83704

Measurement of the following nontraditional lipid and non-lipid biomarkers are medically necessary when filed with a covered diagnosis. See the Coding section for details.

- Lipoprotein, blood; electrophoretic separation and quantitation (CPT Code 83700)
- Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation) (CPT Code 83701)
- Lipoprotein, blood; quantitation of lipoprotein particle number(s) (eg, by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed (CPT Code 83704)

- Cystatin C (CPT Code 82610)

CPT Codes 83695, 83722, 85384 and 85385

Measurements of the following nontraditional lipid and non-lipid biomarkers are not covered for Medicare Advantage Plans and not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

- Lipoprotein (a) (CPT Code 83695)
- Lipoprotein, direct measurement; small dense LDL cholesterol (CPT Code 83722)
- Fibrinogen; activity (CPT Code 85384)
- Fibrinogen; antigen (CPT Code 85385)

CPT Code 83698

Measurement of lipoprotein-associated phospholipase A2 is considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine the effects of the technology on health outcomes.

CPT Code 83880

B type natriuretic peptide testing is covered but not separately reimbursed when used in conjunction with standard diagnostic tests, medical history and clinical findings during an evaluation of heart failure in an acute care setting or other setting (i.e. emergency department) where test results are immediately determined.

Other Cardiovascular Disease Testing

Cardiovascular disease risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels), are considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine the effects of the technology on health outcomes.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary.

BACKGROUND

Simple Lipid Panel

A simple lipid panel is generally composed of the following lipid measures:

- Total cholesterol
- Low-density lipoprotein cholesterol
- High-density lipoprotein cholesterol
- Triglycerides

Certain calculated ratios (eg, total/high-density lipoprotein cholesterol) may also be reported as part of a simple lipid panel.

Other types of lipid testing (ie, apolipoproteins, lipid particle number or particle size, lipoprotein [a]) are not considered components of a simple lipid profile.

Cardiovascular Disease

Cardiovascular disease (CVD) remains the single largest cause of morbidity and mortality in the developed world. Mortality from CVD has accounted for 1 in 4 deaths in the United States, and there are numerous socio-economic factors that affect CVD mortality rates. Lower-income, race, age, and behavioral factors all have a significant impact on health outcome disparities associated with CVD.

As a result, accurate prediction of CVD risk is a component of medical care that has the potential to focus on and direct preventive and diagnostic activities. Current methods of risk prediction in use in general clinical care are not highly accurate and, as a result, there is a potential unmet need for improved risk prediction instruments.

Experts recommend formal genetic counseling for individuals who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some individuals; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Risk Assessment

Although treatment for elevated coronary disease risk with statins targets cholesterol levels, selection for treatment involves estimation of future coronary artery disease (CAD) risk using well-validated prediction models that use additional variables.

Components of CVD risk include family history, cigarette smoking, hypertension, and lifestyle factors such as diet and exercise. Also, numerous laboratory tests have been associated with CVD risk, most prominently lipids such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL). These clinical and lipid factors are often combined into simple risk prediction instruments, such as the Framingham Risk Score. The Framingham Risk Score provides an estimate of the 10-year risk for developing cardiac disease and is currently used in clinical care to determine the aggressiveness of risk factor intervention, such as the decision to treat hyperlipidemia with statins.

Many additional biomarkers, genetic factors, and radiologic measures have been associated with an increased risk of CVD. Over 100 emerging risk factors have been proposed as useful for refining estimates of CVD risk. Some general categories of these potential risk factors are as follows:

Lipid Markers. In addition to LDL and HDL, other lipid markers may have predictive ability, including the apolipoproteins, lipoprotein (a) (Lp[a]), lipid subfractions, and/or other measures.

Inflammatory Markers. Many measures of inflammation have been linked to the likelihood of CVD. High-sensitivity C-reactive protein (hs-CRP) is an example of an inflammatory marker; others include fibrinogen, interleukins, and tumor necrosis factor.

Metabolic Syndrome Biomarkers. Measures associated with metabolic syndromes, such as specific dyslipidemic profiles or serum insulin levels, have been associated with an increased risk of CVD.

Genetic markers. A number of variants associated with increased thrombosis risk, such as the 5,10-methylene tetrahydrofolate reductase (MTHFR) variant or the prothrombin gene variants, have been associated with increased CVD risk. Also, numerous single nucleotide variants have been associated with CVD in large genome-wide studies.

Risk Panel Testing

CVD risk panels may contain measures from 1 or all of the previous categories and may include other measures not previously listed such as radiologic markers (carotid medial thickness, coronary artery calcium score). Some CVD risk panels are relatively limited, including a few markers in addition to standard lipids. Others include a wide variety of potential risk factors from a number of different categories, often including both genetic and nongenetic risk factors. Other panels are composed entirely of genetic markers.

Some examples of commercially available CVD risk panels are as follows:

CV Health Plus Genomics™ Panel (Genova Diagnostics): prothrombin; factor V Leiden; fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; Lp(a); lipoprotein-associated phospholipase A2 (Lp-PLA2); MTHFR gene; triglycerides; very-low-density lipoprotein (VLDL); VLDL size; vitamin D; hs-CRP.

CV Health Plus™ Panel (Genova Diagnostics): fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; lipid panel; Lp(a); Lp-PLA2; triglycerides; VLDL; VLDL size; vitamin D; hs-CRP.

CVD Inflammatory Profile (Cleveland HeartLab): hs-CRP, urinary microalbumin, myeloperoxidase, Lp-PLA2, F2 isoprostanes.

Applied Genetics Cardiac Panel: genetic variants associated with CAD: cytochrome p450 variants associated with the metabolism of clopidogrel, ticagrelor, warfarin, beta-blockers, rivaroxaban, prasugrel (2C19, 2C9/VKORC1, 2D6, 3A4/3A5), factor V Leiden, prothrombin gene, MTHFR gene, APOE gene.

Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel: factor V Leiden, factor V R2, prothrombin gene, factor XIII, fibrinogen-455, plasminogen activator inhibitor-1, platelet glycoprotein (GP) IIIA variant human platelet antigen (HPA)-1 (PLA1/2), MTHFR gene, angiotensin-converting enzyme insertion/deletion, apo B, apo E.

In addition to panels that are specifically focused on CVD risk, a number of commercially available panels include markers associated with cardiovascular health, along with a range of other markers that have been associated with inflammation, thyroid disorders and other hormonal deficiencies, and other disorders. An example of these panels is:

Advanced Health Panel (Thorne): total cholesterol, HDL, LDL, triglycerides, HDL ratios, non-HDL cholesterol, LDL particle number, small LDL, medium LDL, LDL pattern, LDL peak size, large HDL, apo A1, apo B, Lp(a), cortisol, hs-CRP, homocysteine, glucose, hemoglobin A1c, insulin, homeostatic model assessment for insulin resistance, free T4, free T3, thyroid-stimulating hormone, reverse T3, dehydroepiandrosterone sulfate, estradiol, follicle stimulating hormone, luteinizing hormone, sex hormone binding globulin, total testosterone, free testosterone, albumin, globulin, albumin/globulin ratio, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gammaglutamyl transferase, total bilirubin, total serum protein, blood urea nitrogen, creatinine, blood urea nitrogen/creatinine ratio, estimated glomerular filtration rate from creatinine, estimated glomerular filtration rate from cystatin C, cystatin C, fibrinogen, platelet count, white cell count, absolute neutrophils, lymphocytes, absolute lymphocytes, monocytes, absolute monocytes, eosinophils, absolute eosinophils, basophils, absolute basophils, red blood cell count, hemoglobin, hematocrit, mean platelet volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distribution width, folate, vitamin B12, vitamin D, red blood cell magnesium, calcium, carbon dioxide, chloride, potassium, sodium, ferritin, iron total iron binding capacity, omega-3 index, omega-6 to omega-3 ratio, arachidonic acid, eicosapentaenoic acid, eicosapentaenoic acid/arachidonic acid ratio, docosahexaenoic acid, free fatty acids.

Low-density Lipoproteins (LDLs) and Cardiovascular Disease

Low-density lipoproteins (LDLs) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project as the primary target of cholesterol-lowering therapy. An LDL particle consists of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins surrounding an inner lipid core composed of cholesterol ester and triglycerides. Traditional lipid risk factors such as LDL cholesterol (LDL-C), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of subjects with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of CAD occur in subjects with "normal" levels of total cholesterol and LDL-C. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

Other non-lipid markers have been identified as being associated with CVD, including B-type natriuretic peptide, cystatin C, fibrinogen, and leptin. These biomarkers may have a predictive role in identifying CVD risk or in targeting therapy.

Lipid Markers

High-Density Lipoprotein (HDL) Subclass

HDL particles exhibit considerable heterogeneity, and it has been proposed that various subclasses of HDL may have a greater role in protection from atherosclerosis. Particles of HDL can be characterized based on size or density and/or on apolipoprotein composition. Using size or density, HDL can be classified into HDL2, the larger, less dense particles that may have the greatest degree of cardioprotection, and HDL3, which are smaller, denser particles.

An alternative to measuring the concentration of subclasses of HDL (eg, HDL2, HDL3) is a direct measurement of HDL particle size and/or number. Particle size can be measured by nuclear magnetic resonance (NMR) spectroscopy or by gradient-gel electrophoresis. HDL particle numbers can be measured by NMR spectroscopy. Several commercial labs offer these measurements of HDL particle size and number. Measurement of apo AI has used HDL particle number as a surrogate, based on the premise that each HDL particle contains a single apo AI molecule.

Low-Density Lipoprotein (LDL) Subclass

Two main subclass patterns of LDL, called A and B, have been described. In subclass pattern A, particles have a diameter larger than 25 nm and are less dense, while in subclass pattern B, particles have a diameter less than 25 nm and a higher density. Subclass pattern B is a common inherited disorder associated with a more atherogenic lipoprotein profile, also termed "atherogenic dyslipidemia." In addition to small, dense LDL, this pattern includes elevated levels of triglycerides, elevated levels of apo B, and low levels of HDL. This lipid profile is commonly seen in type 2 diabetes and is a component of the "metabolic syndrome," defined by the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) to also include high normal blood pressure, insulin resistance, increased levels of inflammatory markers such as C-reactive protein, and a prothrombotic state. The presence of the metabolic syndrome is considered by Adult Treatment Panel III to be a substantial risk-enhancing factor for CAD.

LDL size has also been proposed as a potentially useful measure of treatment response. Lipid-lowering treatment decreases total LDL and may also induce a shift in the type of LDL, from smaller, dense particles to larger particles. It has been proposed that this shift in lipid profile may be beneficial in reducing the risk for CAD independent of the total LDL level. Also, some drugs may cause a greater shift in lipid profiles than others. Niacin and/or fibrates may cause a greater shift from small to large LDL size than statins. Therefore, measurement of LDL size may potentially play a role in drug selection or may be useful in deciding whether to use a combination of drugs rather than a statin alone.

In addition to the size of LDL particles, interest has been shown in assessing the concentration of LDL particles as a distinct cardiac risk factor. For example, the commonly performed test for LDL-C is not a direct measure of LDL, but, chosen for its convenience, measures the amount of cholesterol incorporated into LDL particles. Because LDL particles carry much of the cholesterol in the bloodstream, the concentration of cholesterol in LDL correlates reasonably well with the number of LDL particles when examined in large populations. However, for an individual patient, the LDL level may not reflect the number of particles due to varying levels of cholesterol in different sized particles. It is proposed that the discrepancy between the number of LDL particles and the serum level of LDL represents a significant source of unrecognized atherogenic risk. The size and number of particles are interrelated. For example, all LDL particles can invade the arterial wall and initiate atherosclerosis. However, small, dense particles are thought to be more atherogenic than larger particles. Therefore, for patients with elevated numbers of LDL particles, the cardiac risk may be further enhanced when the particles are smaller versus larger.

Lipoprotein (a)

Lp (a) is a lipid-rich particle similar to LDL. The major apolipoprotein associated with LDL is Apo B; in Lp(a), however, there is an additional apo A covalently linked to apo B. The apo A molecule is structurally similar to plasminogen, suggesting that Lp(a) may contribute to the thrombotic and atherogenic basis of CVD. Levels of Lp(a) are relatively stable in individuals over time but vary up to 1000-fold between individuals, presumably on a genetic basis. The similarity between Lp(a) and fibrinogen has stimulated intense interest in Lp(a) as a link between atherosclerosis and thrombosis. In addition, approximately 20% of patients with CAD have elevated Lp(a) levels. Therefore, it has been proposed that levels of Lp(a) may be an independent risk factor for CAD.

Non-Lipid Markers

B-type or Brain Natriuretic Peptide

Brain natriuretic peptide (BNP, also called B-type natriuretic peptide) is an amino acid polypeptide secreted primarily by the ventricles of the heart when the pressure to the cardiac muscles increases or there is myocardial ischemia. Elevations in BNP levels reflect deterioration in cardiac loading levels and may predict adverse events. Brain natriuretic peptide has been studied as a biomarker for managing heart failure and predicting cardiovascular and heart failure risk.

Cystatin C

Cystatin C is a small serine protease inhibitor protein secreted from all functional cells in the body. It has primarily been used as a biomarker of kidney function. Cystatin C has also been studied to determine whether it may serve as a biomarker for predicting cardiovascular risk. Cystatin C is encoded by the CST3 gene.

Fibrinogen

Fibrinogen is a circulating clotting factor and precursor of fibrin. It is important in platelet aggregation and a determinant of blood viscosity. Fibrinogen levels have been shown to be associated with future risk of CVD and all-cause mortality.

Leptin

Leptin is a protein secreted by fat cells that have been found to be elevated in heart disease. Leptin has been studied to determine if it has any relation to the development of CVD.

Lipoprotein-associated Phospholipase A2

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with LDLs. Accumulating evidence has suggested that Lp-PLA2 is a biomarker of CAD and may have a proinflammatory role in the progression of atherosclerosis. Recognition that atherosclerosis represents, in part, an inflammatory process has created considerable interest in the measurement of proinflammatory factors as part of cardiovascular disease risk assessment.

Interest in Lp-PLA2 as a possible causal risk factor for CAD has generated the development and testing of Lp-PLA2 inhibitors as a new class of drugs to reduce the risk of CAD. However, clinical trials of Lp-PLA2 inhibitors have not shown significant reductions in CAD endpoints. Furthermore, assessment of Lp-PLA2 levels has not been used in the selection or management of subjects in the clinical trials.

Regulatory Status

Multiple assay methods for cardiac risk marker components, such as lipid panels and other biochemical assays, have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process.

In December 2014, the PLAC® Test (diaDexus), a quantitative enzyme assay, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for Lp-PLA2 activity. It was considered substantially equivalent to a previous version of the PLAC® Test (diaDexus), which was cleared for marketing by the FDA in July 2003.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Components of testing panels, lipid, and non-lipid biomarker tests are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of these tests.

There is a Local Coverage Determination (LCD) for B-type Natriuretic Peptide (BNP) Testing that indicates: BNP measurements may be considered reasonable and necessary when used in combination with other medical data such as medical history, physical examination, laboratory studies, chest x-ray, and electrocardiography:

- To distinguish cardiac cause of acute dyspnea from pulmonary or other non-cardiac causes. Plasma BNP levels are significantly increased in patients with CHF (Congestive Heart Failure) presenting with acute dyspnea compared with patients presenting with acute dyspnea due to other causes.
- To distinguish decompensated CHF from exacerbated chronic obstructive pulmonary disease (COPD) in a symptomatic patient with combined chronic CHF and COPD. Plasma BNP levels are significantly increased in patients with CHF with or without concurrent lung disease compared with patients who have primary lung disease.
- To establish prognosis or disease severity in chronic CHF when needed to guide therapy
- To achieve optimal dosing of guideline-directed medical therapy (GDMT) in select clinically euvolemic patients followed in a well-structured heart failure (HF) disease management program
- To guide therapeutic decision-making in individuals who have amyloidosis

BNP measurements must be analyzed in conjunction with standard diagnostic tests, medical history and clinical findings. The efficacy of BNP measurement as a stand-alone test has not yet been established. Clinicians should be aware that certain conditions such as ischemia, infarction and renal insufficiency, may cause elevation of circulating BNP concentration and require alterations of the interpretation of BNP results. Therefore, B type natriuretic peptide testing is covered but not separately reimbursed when used in conjunction with standard diagnostic tests, medical history and clinical findings during an evaluation of heart failure in an acute care setting or other setting (i.e. emergency department) where test results are immediately determined.

For individuals who are asymptomatic with risk of cardiovascular disease (CVD) who receive nontraditional cardiac biomarker testing (eg, apo B, apo AI, apo E, high-density lipoprotein [HDL] subclass, low-density lipoprotein [LDL] subclass, lipoprotein[a], B-type natriuretic peptide [BNP], cystatin C, fibrinogen, leptin), the evidence includes systematic reviews, meta-analyses, and large, prospective cohort studies. Relevant

outcomes are overall survival (OS), other test performance measures, change in disease status, morbid events, and medication use. The evidence from cohort studies and meta-analyses of these studies has suggested that some of these markers are associated with increased cardiovascular risk and may provide incremental accuracy in risk prediction. In particular, apo B and apo AI have been identified as adding some incremental predictive value. However, it has not been established whether the incremental accuracy provides clinically important information beyond that of traditional lipid measures. Furthermore, no study has provided high-quality evidence that measurement of markers leads to changes in management that improve health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with hyperlipidemia managed with lipid-lowering therapy who receive nontraditional cardiac biomarker testing (eg, apo B, apo AI, apo E, lipoprotein [a], BNP, cystatin C, fibrinogen, leptin), the evidence includes analyses of the intervention arm(s) of lipid-lowering medication trials. Relevant outcomes are OS, change in disease status, morbid events, and medication use. In particular, apo B, apo AI, and apo E have been evaluated as markers of lipid-lowering treatment success, and evidence from the intervention arms of several randomized controlled trials (RCTs) has suggested that these markers are associated with treatment success. However, there is no direct evidence that using markers other than LDL and HDL as a lipid-lowering treatment target leads to improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Therefore, these services are considered not medically necessary for Commercial products.

For individuals who have a risk of CVD who receive Lp-PLA2 testing, the evidence includes studies of the association between Lp-PLA2 and various coronary artery disease (CAD) outcomes. Relevant outcomes are OS, disease-specific survival, and test validity. The studies have demonstrated that Lp-PLA2 levels are an independent predictor of CVD. Although Lp-PLA2 levels are associated with CVD risk, changes in patient management that would occur as a result of obtaining Lp-PLA2 levels in practice are not well-defined. To demonstrate clinical utility, clinicians must have the tools to incorporate Lp-PLA2 test results into existing risk prediction models that improve classification into risk categories, alter treatment decisions, and lead to improved health outcomes. Direct evidence for such improved health outcomes with Lp-PLA2 testing in clinical practice is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes. Therefore, this service is not covered for Medicare Advantage Plans and not medically necessary for Commercial products.

For individuals who have risk factors for CVD who receive CVD risk panels, the evidence includes multiple cohorts and case-control studies and systematic reviews of these studies. Relevant outcomes are test validity, other test performance measures, change in disease status, and morbid events. The available evidence from cohort and case-control studies indicates that many of the individual risk factors included in CVD risk panels are associated with an increased risk of CVD. However, it is not clear how the results of individual risk factors impact management changes, so it is also uncertain how the panels will impact management decisions. Given the lack of evidence for the clinical utility of any individual risk factor beyond simple lipid measures, it is unlikely that the use of CVD risk panels improves outcomes. Studies that have evaluated the clinical validity of panels of multiple markers have not assessed management changes that would occur as a result of testing or demonstrated improvements in outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT codes are medically necessary when filed with one of the covered ICD-10-CM codes, below:

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)

83704 Lipoprotein, blood; quantitation of lipoprotein particle number(s) (eg, by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed

Covered ICD-10-CM

The following CPT code(s) are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

- 83695** Lipoprotein (a)
- 83698** Lipoprotein-associated phospholipase A2, (Lp-PLA2)
- 83722** Lipoprotein, Direct Measurement; Small Dense LDL Cholesterol
- 85384** Fibrinogen; activity
- 85385** Fibrinogen; antigen

The following CPT code(s) are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products **EXCEPT** when utilized for evaluating renal function and filed with one of the covered ICD-10-CM codes, below:

- 82610** Cystatin C

Covered ICD-10-CM codes:

- N18.30 – N18.32
- T50.904A - T50.905S
- T50.994A - T50.995S
- T65.94XA - T65.94XS
- Z52.4

*When there is no specific CPT code for a cardiovascular risk panel, the following Unlisted CPT code should be filed:

- 81479** Unlisted molecular pathology procedure

The following CPT code is covered but not separately reimbursed for Medicare Advantage Plans and Commercial Products:

- 83880** Natriuretic peptide

RELATED POLICIES

- Biomarker Testing Mandate
- Medicare Advantage Plans National and Local Coverage Determinations Policy
- Non-Reimbursable Health Service Codes

PUBLISHED

- Provider Update: February 2024, October 2024
- Provider Update, March 2023, November 2023
- Provider Update, April 2022
- Provider Update, April 2021
- Provider Update, April 2020

REFERENCES

1. CMS.gov, Centers for Medicare and Medicaid Services Local Coverage Determination (LCD): B-type Natriuretic Peptide (BNP) Testing (L33573)
2. Niakouei A, Tehrani M, Fulton L. Health Disparities and Cardiovascular Disease. Healthcare (Basel). Mar 22 2020; 8(1). PMID 32235705
3. D'Agostino RB, Grundy S, Sullivan LM, et al. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA. Jul 11 2001; 286(2): 180-7. PMID 11448281
4. Helfand M, Buckley DI, Freeman M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med. Oct 06 2009; 151(7): 496-507. PMID 19805772

5. Brotman DJ, Walker E, Lauer MS, et al. In search of fewer independent risk factors. *Arch Intern Med.* Jan 24 2005; 165(2): 138-45. PMID 15668358
6. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* Dec 14 2010; 56(25): e50-103. PMID 21144964
7. Thorne. Advanced Health Panel. <https://www.thorne.com/products/dp/advanced-health-panel>. Accessed October 16, 2023.
8. Mensah GA, Mokdad AH, Ford ES, et al. State of disparities in cardiovascular health in the United States. *Circulation.* Mar 15 2005; 111(10): 1233-41. PMID 15769763
9. White HD, Held C, Stewart R, et al. Darapladib for preventing ischemic events in stable coronary heart disease. *N Engl J Med.* May 01 2014; 370(18): 1702-11. PMID 24678955
10. O'Donoghue ML, Braunwald E, White HD, et al. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. *JAMA.* Sep 10 2014; 312(10): 1006-15. PMID 25173516
11. Nicholls SJ, Kastelein JJ, Schwartz GG, et al. Varespladib and cardiovascular events in patients with an acute coronary syndrome: the VISTA-16 randomized clinical trial. *JAMA.* Jan 15 2014; 311(3): 252-62. PMID 24247616
12. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA.* May 16 2001; 285(19): 2486-97. PMID 11368702
13. Perera R, McFadden E, McLellan J, et al. Optimal strategies for monitoring lipid levels in patients at risk or with cardiovascular disease: a systematic review with statistical and cost-effectiveness modelling. *Health Technol Assess.* Dec 2015; 19(100): 1-401, vii-viii. PMID 26680162
14. Thanassoulis G, Williams K, Ye K, et al. Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials. *J Am Heart Assoc.* Apr 14 2014; 3(2):e000759. PMID 24732920
15. van Holten TC, Waanders LF, de Groot PG, et al. Circulating biomarkers for predicting cardiovascular disease risk; a systematic review and comprehensive overview of meta-analyses. *PLoS One.* 2013; 8(4): e62080. PMID 23630624
16. Tzoulaki I, Siontis KC, Evangelou E, et al. Bias in associations of emerging biomarkers with cardiovascular disease. *JAMA Intern Med.* Apr 22 2013; 173(8): 664-71. PMID 23529078
17. Willis A, Davies M, Yates T, et al. Primary prevention of cardiovascular disease using validated risk scores: a systematic review. *J R Soc Med.* Aug 2012; 105(8): 348-56. PMID 22907552
18. 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.* Nov 15 2012; 110(10): 1468-76. PMID 22906895
19. Di Angelantonio E, Gao P, Pennells L, et al. Lipid-related markers and cardiovascular disease prediction. *JAMA.* Jun 20 2012; 307(23): 2499-506. PMID 22797450
20. Sharrett AR, Ballantyne CM, Coady SA, et al. 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.* Sep 04 2001; 104(10): 1108-13. PMID 11535564
21. Rasouli M, Kiasari AM, Mokhberi V. The ratio of apoB/apoAI, apoB and lipoprotein(a) are the best predictors of stable coronary artery disease. *Clin Chem Lab Med.* 2006; 44(8): 1015-21. PMID 16879071
22. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA.* Feb 14 2007; 297(6): 611-9. PMID 17299196
23. Ingelsson E, Schaefer EJ, Contois JH, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA.* Aug 15 2007; 298(7): 776-85. PMID 17699011

24. Clarke R, Emberson JR, Parish S, et al. Cholesterol fractions and apolipoproteins as risk factors for heart disease mortality in older men. *Arch Intern Med.* Jul 09 2007; 167(13): 1373-8. PMID 17620530
25. Gotto AM, Whitney E, Stein EA, 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.* Feb 08 2000; 101(5): 477-84. PMID 10662743
26. Simes RJ, Marschner IC, Hunt D, et al. Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels?. *Circulation.* Mar 12 2002; 105(10): 1162-9. PMID 11889008
27. Kastelein JJ, van der Steeg WA, Holme I, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation.* Jun 10 2008; 117(23): 3002-9. PMID 18519851
28. Mora S, Wenger NK, Demicco DA, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. *Circulation.* Apr 24 2012; 125(16): 1979-87. PMID 22461416
29. Schmitz F, Mevissen V, Krantz C, et al. Robust association of the APOE epsilon4 allele with premature myocardial infarction especially in patients without hypercholesterolaemia: the Aachen study. *Eur J Clin Invest.* Feb 2007; 37(2): 106-8. PMID 17217375
30. Singh K, Chandra A, Sperry T, et al. Associations Between High-Density Lipoprotein Particles and Ischemic Events by Vascular Domain, Sex, and Ethnicity: A Pooled Cohort Analysis. *Circulation.* Aug 18 2020; 142(7): 657-669. PMID 32804568
31. Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. *Circulation.* Sep 10 2013; 128(11): 1189-97. PMID 24002795
32. Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA.* Sep 18 1996; 276(11): 882-8. PMID 8782637
33. Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Québec Cardiovascular Study. *Circulation.* Jan 07 1997; 95(1): 69-75. PMID 8994419
34. Tzou WS, Douglas PS, Srinivasan SR, et al. Advanced lipoprotein testing does not improve identification of subclinical atherosclerosis in young adults: the Bogalusa Heart Study. *Ann Intern Med.* May 03 2005; 142(9): 742-50. PMID 15867406
35. Blake GJ, Otvos JD, Rifai N, et al. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. *Circulation.* Oct 08 2002; 106(15): 1930-7. PMID 12370215
36. Kuller L, Arnold A, Tracy R, et al. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the cardiovascular health study. *Arterioscler Thromb Vasc Biol.* Jul 01 2002; 22(7): 1175-80. PMID 12117734
37. Rosenson RS, Otvos JD, Freedman DS. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial. *Am J Cardiol.* Jul 15 2002; 90(2): 89-94. PMID 12106834
38. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol.* Oct 17 2002; 90(8A): 22i-29i. PMID 12419478
39. Rosenson RS, Underberg JA. Systematic review: Evaluating the effect of lipid-lowering therapy on lipoprotein and lipid values. *Cardiovasc Drugs Ther.* Oct 2013; 27(5): 465-79. PMID 23893306
40. Mora S, Otvos JD, Rifai N, et al. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation.* Feb 24 2009; 119(7): 931-9. PMID 19204302
41. Toth PP, Grabner M, Punekar RS, et al. Cardiovascular risk in patients achieving low-density lipoprotein cholesterol and particle targets. *Atherosclerosis.* Aug 2014; 235(2): 585-91. PMID 24956532
42. Bennet A, Di Angelantonio E, Erqou S, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. *Arch Intern Med.* Mar 24 2008; 168(6): 598-608. PMID 18362252
43. Smolders B, Lemmens R, Thijs V. Lipoprotein (a) and stroke: a meta-analysis of observational studies. *Stroke.* Jun 2007; 38(6): 1959-66. PMID 17478739

44. Khera AV, Everett BM, Caulfield MP, et al. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *Circulation*. Feb 11 2014; 129(6): 635-42. PMID 24243886
45. Albers JJ, Slee A, O'Brien KD, et al. Relationship of apolipoproteins A-1 and B, and lipoprotein(a) to cardiovascular outcomes: the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes). *J Am Coll Cardiol*. Oct 22 2013; 62(17): 1575-9. PMID 23973688
46. 66. Kamstrup PR, Benn M, Tybjaerg-Hansen A, et al. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation*. Jan 15 2008; 117(2): 176-84. PMID 18086931
47. Tzoulaki I, Murray GD, Lee AJ, et al. Relative value of inflammatory, hemostatic, and rheological factors for incident myocardial infarction and stroke: the Edinburgh Artery Study. *Circulation*. Apr 24 2007; 115(16): 2119-27. PMID 17404162
48. Zakai NA, Katz R, Jenny NS, et al. Inflammation and hemostasis biomarkers and cardiovascular risk in the elderly: the Cardiovascular Health Study. *J Thromb Haemost*. Jun 2007; 5(6): 1128-35. PMID 17388967
49. 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*. Aug 21 2017; 38(32): 2490-2498. PMID 28449027
50. Lee SR, Prasad A, Choi YS, et al. LPA Gene, Ethnicity, and Cardiovascular Events. *Circulation*. Jan 17 2017; 135(3): 251-263. PMID 27831500
51. Rigal M, Ruidavets JB, Viguier A, et al. Lipoprotein (a) and risk of ischemic stroke in young adults. *J Neurol Sci*. Jan 15 2007; 252(1): 39-44. PMID 17113602
52. Suk Danik J, Rifai N, Buring JE, et al. Lipoprotein(a), hormone replacement therapy, and risk of future cardiovascular events. *J Am Coll Cardiol*. Jul 08 2008; 52(2): 124-31. PMID 18598891
53. 73. Genser B, Dias KC, Siekmeier R, et al. Lipoprotein (a) and risk of cardiovascular disease--a systematic review and meta analysis of prospective studies. *Clin Lab*. 2011; 57(3-4): 143-56. PMID 21500721
54. Erqou S, Kaptoge S, Perry PL, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA*. Jul 22 2009; 302(4): 412-23. PMID 19622820
55. Schaefer EJ, Lamon-Fava S, Jenner JL, et al. Lipoprotein(a) levels and risk of coronary heart disease in men. The lipid Research Clinics Coronary Primary Prevention Trial. *JAMA*. Apr 06 1994; 271(13): 999-1003. PMID 8139085
56. Nestel PJ, Barnes EH, Tonkin AM, et al. Plasma lipoprotein(a) concentration predicts future coronary and cardiovascular events in patients with stable coronary heart disease. *Arterioscler Thromb Vasc Biol*. Dec 2013; 33(12): 2902-8. PMID 24092750
57. Bostom AG, Cupples LA, Jenner JL, et al. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger. A prospective study. *JAMA*. Aug 21 1996; 276(7): 544-8. PMID 8709403
58. Ohira T, Schreiner PJ, Morrisett JD, et al. Lipoprotein(a) and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. Jun 2006; 37(6): 1407-12. PMID 16675734
59. Fogacci F, Cicero AF, D'Addato S, et al. Serum lipoprotein(a) level as long-term predictor cardiovascular mortality in a large sample of subjects in primary cardiovascular prevention: data from the Brisighella Heart Study. *Eur J Intern Med*. Jan 2017; 37: 49-55. PMID 27553697
60. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA*. Nov 10 1993; 270(18): 2195-9. PMID 8411602
61. Bolibar I, von Eckardstein A, Assmann G, et al. Short-term prognostic value of lipid measurements in patients with angina pectoris. The ECAT Angina Pectoris Study Group: European Concerted Action on Thrombosis and Disabilities. *Thromb Haemost*. Dec 2000; 84(6): 955-60. PMID 11154140
62. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med*. Dec 24 2009; 361(26): 2518-28. PMID 20032323
63. Shaw LJ, Polk DM, Kahute TA, et al. Prognostic accuracy of B-natriuretic peptide measurements and coronary artery calcium in asymptomatic subjects (from the Early Identification of Subclinical

- Atherosclerosis by Noninvasive Imaging Research [EISNER] study). *Am J Cardiol.* Nov 01 2009; 104(9): 1245-50. PMID 19840570
64. Wu Z, Pilbrow AP, Liew OW, et al. Circulating cardiac biomarkers improve risk stratification for incident cardiovascular disease in community dwelling populations. *EBioMedicine.* Aug 2022; 82: 104170. PMID 35850010
 65. Melander O, Newton-Cheh C, Almgren P, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *JAMA.* Jul 01 2009; 302(1): 49-57. PMID 19567439
 66. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med.* Feb 12 2004; 350(7): 655-63. PMID 14960742
 67. Ito H, Pacold IV, Durazo-Arvizu R, et al. The effect of including cystatin C or creatinine in a cardiovascular risk model for asymptomatic individuals: the multi-ethnic study of atherosclerosis. *Am J Epidemiol.* Oct 15 2011; 174(8): 949-57. PMID 21880578
 68. Lee M, Saver JL, Huang WH, et al. Impact of elevated cystatin C level on cardiovascular disease risk in predominantly high cardiovascular risk populations: a meta-analysis. *Circ Cardiovasc Qual Outcomes.* Nov 2010; 3(6): 675-83. PMID 20923994
 69. Luo J, Wang LP, Hu HF, et al. Cystatin C and cardiovascular or all-cause mortality risk in the general population: A meta-analysis. *Clin Chim Acta.* Oct 23 2015; 450: 39-45. PMID 26192218
 70. Kengne AP, Czernichow S, Stamatakis E, et al. Fibrinogen and future cardiovascular disease in people with diabetes: aetiological associations and risk prediction using individual participant data from nine community-based prospective cohort studies. *Diab Vasc Dis Res.* Mar 2013; 10(2): 143-51. PMID 22786872
 71. Willeit P, Thompson SG, Agewall S, et al. Inflammatory markers and extent and progression of early atherosclerosis: Meta-analysis of individual-participant-data from 20 prospective studies of the PROG-IMT collaboration. *Eur J Prev Cardiol.* Jan 2016; 23(2): 194-205. PMID 25416041
 72. Ahmadi-Abhari S, Luben RN, Wareham NJ, et al. Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study. *Eur J Epidemiol.* Jul 2013; 28(7): 541-50. PMID 23821244
 73. Danesh J, Lewington S, Thompson SG, et al. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA.* Oct 12 2005; 294(14): 1799-809. PMID 16219884
 74. Kaptoge S, White IR, Thompson SG, et al. Associations of plasma fibrinogen levels with established cardiovascular disease risk factors, inflammatory markers, and other characteristics: individual participant meta-analysis of 154,211 adults in 31 prospective studies: the fibrinogen studies collaboration. *Am J Epidemiol.* Oct 15 2007; 166(8): 867-79. PMID 17785713
 75. 95. Sattar N, Wannamethee G, Sarwar N, et al. Leptin and coronary heart disease: prospective study and systematic review. *J Am Coll Cardiol.* Jan 13 2009; 53(2): 167-75. PMID 19130985
 76. 96. Zeng R, Xu CH, Xu YN, et al. Association of leptin levels with pathogenetic risk of coronary heart disease and stroke: a meta-analysis. *Arq Bras Endocrinol Metabol.* Nov 2014; 58(8): 817-23. PMID 25465603
 77. 97. Yang H, Guo W, Li J, et al. Leptin concentration and risk of coronary heart disease and stroke: A systematic review and meta-analysis. *PLoS One.* 2017; 12(3): e0166360. PMID 28278178
 78. 98. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA.* Mar 28 2012; 307(12): 1302-9. PMID 22453571
 79. 99. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol.* Aug 05 2014; 64(5): 485-94. PMID 25082583

88. 100. Ballantyne CM, Pitt B, Loscalzo J, et al. Alteration of relation of atherogenic lipoprotein cholesterol to apolipoprotein
89. B by intensive statin therapy in patients with acute coronary syndrome (from the Limiting Undertreatment of lipids in
90. ACS With Rosuvastatin [LUNAR] Trial). *Am J Cardiol.* Feb 15 2013; 111(4): 506-9. PMID 23237107
91. Ray KK, Cannon CP, Cairns R, et al. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-
92. 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.* Mar 2009; 29(3): 424-30. PMID 19122170
93. Ordovas JM, Mooser V. The APOE locus and the pharmacogenetics of lipid response. *Curr Opin Lipidol.* Apr 2002; 13(2): 113-7. PMID 11891412
94. Vossen CY, Hoffmann MM, Hahmann H, et al. Effect of APOE genotype on lipid levels in patients with coronary heart disease during a 3-week inpatient rehabilitation program. *Clin Pharmacol Ther.* Aug 2008; 84(2): 222-7. PMID 18388879
95. Kwiterovich PO. Clinical relevance of the biochemical, metabolic, and genetic factors that influence low-density lipoprotein heterogeneity. *Am J Cardiol.* Oct 17 2002; 90(8A): 30i-47i. PMID 12419479
96. Superko HR, Berneis KK, Williams PT, et al. Gemfibrozil reduces small low-density lipoprotein more in normolipemic subjects classified as low-density lipoprotein pattern B compared with pattern A. *Am J Cardiol.* Nov 01 2005; 96(9): 1266-72. PMID 16253595
97. Sirtori CR, Calabresi L, Pisciotto L, et al. Effect of statins on LDL particle size in patients with familial combined hyperlipidemia: a comparison between atorvastatin and pravastatin. *Nutr Metab Cardiovasc Dis.* Feb 2005; 15(1): 47-55. PMID 15871851
98. Arca M, Montali A, Pigna G, et al. Comparison of atorvastatin versus fenofibrate in reaching lipid targets and influencing biomarkers of endothelial damage in patients with familial combined hyperlipidemia. *Metabolism.* Nov 2007; 56(11): 1534-41. PMID 17950105
99. Rosenson RS, Wolff DA, Huskin AL, et al. Fenofibrate therapy ameliorates fasting and postprandial lipoproteinemia, oxidative stress, and the inflammatory response in subjects with hypertriglyceridemia and the metabolic syndrome. *Diabetes Care.* Aug 2007; 30(8): 1945-51. PMID 17483155
100. Tokuno A, Hirano T, Hayashi T, et al. The effects of statin and fibrate on lowering small dense LDL-cholesterol in hyperlipidemic patients with type 2 diabetes. *J Atheroscler Thromb.* Jun 2007; 14(3): 128-32. PMID 17587764
101. Miller BD, Alderman EL, Haskell WL, et al. Predominance of dense low-density lipoprotein particles predicts angiographic benefit of therapy in the Stanford Coronary Risk Intervention Project. *Circulation.* Nov 01 1996; 94(9): 2146-53. PMID 8901665
102. Campos H, Moye LA, Glasser SP, et al. Low-density lipoprotein size, pravastatin treatment, and coronary events. *JAMA.* Sep 26 2001; 286(12): 1468-74. PMID 11572739
103. Bays HE, Dujovne CA, McGovern ME, et al. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADVICOR Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol.* Mar 15 2003; 91(6): 667-72. PMID 12633795
104. van Wissen S, Smilde TJ, Trip MD, et al. Long term statin treatment reduces lipoprotein(a) concentrations in heterozygous familial hypercholesterolaemia. *Heart.* Aug 2003; 89(8): 893-6. PMID 12860867
105. National Institutes of Health, National Heart Lung and Blood Institute. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (NIH Publication No. 01-3670). 2001; <http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf>. Accessed November 17, 2023.
106. Thompson A, Gao P, Orfei L, et al. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet.* May 01 2010; 375(9725): 1536-44. PMID 20435228

107. Garza CA, Montori VM, McConnell JP, et al. Association between lipoprotein-associated phospholipase A2 and cardiovascular disease: a systematic review. *Mayo Clin Proc.* Feb 2007; 82(2): 159-65. PMID 17290721
108. Antonopoulos AS, Angelopoulos A, Papanikolaou P, et al. Biomarkers of Vascular Inflammation for Cardiovascular Risk Prognostication: A Meta-Analysis. *JACC Cardiovasc Imaging.* Mar 2022; 15(3): 460-471. PMID 34801448
109. Gottlieb SS, Harris K, Todd J, et al. Prognostic significance of active and modified forms of endothelin 1 in patients with heart failure with reduced ejection fraction. *Clin Biochem.* Mar 2015; 48(4-5): 292-6. PMID 25541019
110. Patterson CC, Blankenberg S, Ben-Shlomo Y, et al. Which biomarkers are predictive specifically for cardiovascular or for non-cardiovascular mortality in men? Evidence from the Caerphilly Prospective Study (CaPS). *Int J Cardiol.* Dec 15 2015; 201: 113-8. PMID 26298350
111. Malachias MVB, Jhund PS, Claggett BL, et al. NT-proBNP by Itself Predicts Death and Cardiovascular Events in High-Risk Patients With Type 2 Diabetes Mellitus. *J Am Heart Assoc.* Oct 20 2020; 9(19): e017462. PMID 32964800
112. Schoe A, Schippers EF, Ebmeyer S, et al. Predicting mortality and morbidity after elective cardiac surgery using vasoactive and inflammatory biomarkers with and without the EuroSCORE model. *Chest.* Nov 2014; 146(5): 1310-1318. PMID 24992322
113. Şaylık F, Akbulut T. Temporal relationship between serum calcium and triglyceride-glucose index and its impact on the incident of the acute coronary syndrome: a cross-lagged panel study. *Acta Cardiol.* Jul 2023; 78(5): 586-593. PMID 35969239
114. Mohebi R, van Kimmenade R, McCarthy CP, et al. Performance of a multi-biomarker panel for prediction of cardiovascular event in patients with chronic kidney disease. *Int J Cardiol.* Jan 15 2023; 371: 402-405. PMID 36202172
115. Safo SE, Haine L, Baker J, et al. Derivation of a Protein Risk Score for Cardiovascular Disease Among a Multiracial and Multiethnic HIV+ Cohort. *J Am Heart Assoc.* Jul 04 2023; 12(13): e027273. PMID 37345752
116. Wallentin L, Eriksson N, Olszowka M, et al. Plasma proteins associated with cardiovascular death in patients with chronic coronary heart disease: A retrospective study. *PLoS Med.* Jan 2021; 18(1): e1003513. PMID 33439866
117. Wuopio J, Hilden J, Bring C, et al. Cathepsin B and S as markers for cardiovascular risk and all-cause mortality in patients with stable coronary heart disease during 10 years: a CLARICOR trial sub-study. *Atherosclerosis.* Nov 2018; 278: 97-102. PMID 30261474
118. Winkel P, Jakobsen JC, Hilden J, et al. Prognostic value of 12 novel cardiological biomarkers in stable coronary artery disease. A 10-year follow-up of the placebo group of the Copenhagen CLARICOR trial. *BMJ Open.* Aug 20 2020; 10(8): e033720. PMID 32819979
119. Welsh P, Kou L, Yu C, et al. Prognostic importance of emerging cardiac, inflammatory, and renal biomarkers in chronic heart failure patients with reduced ejection fraction and anaemia: RED-HF study. *Eur J Heart Fail.* Feb 2018; 20(2): 268-277. PMID 28960777
120. Harari G, Green MS, Magid A, et al. Usefulness of Non-High-Density Lipoprotein Cholesterol as a Predictor of Cardiovascular Disease Mortality in Men in 22-Year Follow-Up. *Am J Cardiol.* Apr 15 2017; 119(8): 1193-1198. PMID 28267961
121. Kunutsor SK, Bakker SJ, James RW, et al. Serum paraoxonase-1 activity and risk of incident cardiovascular disease: The PREVEND study and meta-analysis of prospective population studies. *Atherosclerosis.* Feb 2016; 245: 143-54. PMID 26724525
122. Keller T, Boeckel JN, Groß S, et al. Improved risk stratification in prevention by use of a panel of selected circulating microRNAs. *Sci Rep.* Jul 03 2017; 7(1): 4511. PMID 28674420
123. de Lemos JA, Ayers CR, Levine BD, et al. Multimodality Strategy for Cardiovascular Risk Assessment: Performance in 2 Population-Based Cohorts. *Circulation.* May 30 2017; 135(22): 2119-2132. PMID 28360032
124. Greisenegger S, Segal HC, Burgess AI, et al. Biomarkers and mortality after transient ischemic attack and minor ischemic stroke: population-based study. *Stroke.* Mar 2015; 46(3): 659-66. PMID 25649803

125. Cho S, Lee SH, Park S, et al. The additive value of multiple biomarkers in prediction of premature coronary artery disease. *Acta Cardiol.* Apr 2015; 70(2): 205-10. PMID 26148381
126. Wilsgaard T, Mathiesen EB, Patwardhan A, et al. Clinically significant novel biomarkers for prediction of first ever myocardial infarction: the Tromsø Study. *Circ Cardiovasc Genet.* Apr 2015; 8(2): 363-71. PMID 25613532
127. Guarrera S, Fiorito G, Onland-Moret NC, et al. Gene-specific DNA methylation profiles and LINE-1 hypomethylation are associated with myocardial infarction risk. *Clin Epigenetics.* 2015; 7: 133. PMID 26705428
128. Lara J, Cooper R, Nissan J, et al. A proposed panel of biomarkers of healthy ageing. *BMC Med.* Sep 15 2015; 13:222. PMID 26373927
129. Paynter NP, Chasman DI, Paré G, et al. Association between a literature-based genetic risk score and cardiovascular events in women. *JAMA.* Feb 17 2010; 303(7): 631-7. PMID 20159871
130. Zethelius B, Berglund L, Sundström J, et al. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med.* May 15 2008; 358(20): 2107-16. PMID 18480203
131. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* Jul 13 2004; 110(2): 227-39. PMID 15249516
132. National Heart Lung and Blood Institute. Managing Blood Cholesterol in Adults: Systematic Evidence Review From the Cholesterol Expert Panel, 2013. Bethesda, MD: National Heart, Lung, and Blood Institute; 2013. <https://www.nhlbi.nih.gov/sites/default/files/media/docs/cholesterol-in-adults.pdf>. Accessed November 3, 2023.
133. Stone NJ, Robinson JG, Lichtenstein AH, et al. 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.* Jul 01 2014; 63(25 Pt B): 2889-934. PMID 24239923
134. Goff DC, Lloyd-Jones DM, Bennett G, 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. *Circulation.* Jun 24 2014; 129(25 Suppl 2): S49-73. PMID 24222018
135. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* Sep 10 2019; 140(11): e596-e646. PMID 30879355
136. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care.* Apr 2008; 31(4): 811-22. PMID 18375431
137. ElSayed NA, Aleppo G, Aroda VR, et al. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2023. *Diabetes Care.* Jan 01 2023; 46(Suppl 1): S158-S190. PMID 36507632
138. Jellinger PS, Handelsman Y, Rosenblit PD, et al. AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE. *Endocr Pract.* Apr 2017; 23(Suppl 2): 1-87. PMID 28437620
139. Handelsman Y, Jellinger PS, Guerin CK, et al. 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.* Oct 2020; 26(10): 1196-1224. PMID 33471721
140. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. *Endocr Pract.* Oct 2022; 28(10): 923-1049. PMID 35963508
141. 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.* Jan 01 2020; 41(1): 111-188. PMID 31504418
142. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J.* Sep 07 2021; 42(34): 3227-3337. PMID 34458905

143. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. *J Clin Lipidol*. 2014; 8(5): 473-88. PMID 25234560
144. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. Jun 18 2019; 139(25): e1082-e1143. PMID 30586774
145. Wilson DP, Jacobson TA, Jones PH, et al. 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; 13(3): 374-392. PMID 31147269
146. Wilson PW, Jacobson TA, Martin SS, et al. Lipid measurements in the management of cardiovascular diseases: Practical recommendations a scientific statement from the national lipid association writing group. *J Clin Lipidol*. Published online: September 24, 2021
147. National Institute for Health and Care Excellence (NICE). Cardiovascular disease: risk assessment and reduction, including lipid modification [CG181]. updated May 2023; <https://www.nice.org.uk/guidance/cg181>. Accessed November 3, 2023.
148. Curry SJ, Krist AH, Owens DK, et al. Risk Assessment for Cardiovascular Disease With Nontraditional Risk Factors: US Preventive Services Task Force Recommendation Statement. *JAMA*. Jul 17 2018; 320(3): 272-280. PMID 29998297

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