Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

Description/Background

Numerous lipid and nonlipid biomarkers have been proposed as potential risk markers for cardiovascular disease (CVD). The biomarkers assessed here are those that have the most evidence in support of their use in clinical care, including apolipoprotein B (apo B), apolipoprotein A1 (apo A1), apolipoprotein E (apo E), B-type natriuretic peptide, cystatin C, fibrinogen, high-density lipoprotein (HDL) subclass, leptin, low-density lipoprotein (LDL) subclass, lipoprotein(a), high sensitivity C-reactive protein (hs-CRP), and genetic biomarkers. These biomarkers have been studied as an alternative or addition to standard lipid panels for risk stratification in CVD or as treatment targets for lipid-lowering therapy.

LOW-DENSITY LIPOPROTEINS 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 (NCEP) as the primary target of cholesterol- lowering therapy. LDL particles consist 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 individuals with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of coronary artery disease (CAD) occur in those 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 having an association with cardiovascular disease (CVD), including high sensitivity C-reactive protein, B-type natriuretic peptide, cystatin C, fibrinogen, and leptin. These biomarkers may have a predictive role in identifying cardiovascular disease risk or in targeting for therapy.

Lipid Markers

Apolipoprotein B

Apolipoprotein (Apo) B is the major protein moiety of all lipoproteins except for high-density lipoprotein (HDL). The most abundant form of apo B, large B or B_{100}, constitutes the apo B found in LDL and very-low density LDL. Because LDL and very-low density LDL each contain 1 molecule of apo B, the measurement of apo B reflects the total number of these atherogenic particles, 90% of which are LDL. Because LDL particles can vary in size and in cholesterol content, for a given concentration of LDL-C, there can be a wide variety in size and numbers of LDL particles. Thus, it has been postulated that apo B is a better measure of the atherogenic potential of serum LDL than the LDL concentration.

Apolipoprotein AI

High-density lipoprotein contains 2 associated apolipoproteins: (ie, apo AI, apo AII). High-density lipoprotein particles can also be classified by whether they contain apo AI only or they contain both apo AI and apo-AII. Because all HDL particles contain apo AI, this lipid marker can be used as an approximation for HDL number, similar to the way apo B has been proposed as an approximation of the LDL number.

Direct measurement of apo AI concentrations has been proposed as more accurate than the traditional use of HDL level in the evaluation of cardioprotective, or “good,” cholesterol. In addition, the ratio of apo B/apo AI has been proposed as a superior measure of the ratio of proatherogenic (ie, “bad”) cholesterol to anti-atherogenic (ie, “good”) cholesterol.

Apolipoprotein E

Apolipoprotein E is the primary apolipoprotein found in very-low density LDLs and chylomicrons. Apolipoprotein E is the primary binding protein for LDL receptors in the liver and is thought to play an important role in lipid metabolism. The Apolipoprotein E (*APOE)* gene is polymorphic, consisting of 3 epsilon alleles (e2, e3, and e4) that code for 3 protein isoforms, known as E2, E3, and E4, which differ from one another by 1 amino acid. These molecules mediate lipid metabolism through their different interactions with LDL receptors. The genotype of apo E alleles can be assessed by gene amplification techniques, or the *APOE* phenotype can be assessed by measuring plasma levels of apo E.

It has been proposed that various *APOE* genotypes are more atherogenic than others and that *APOE* measurement may provide information on risk of CAD beyond traditional risk factor measurement. It has also been proposed that the *APOE* genotype may be useful in the selection of specific components of lipid-lowering therapy, such as drug selection. In the major lipid-lowering intervention trials, including trials of statin therapy, there is considerable variability in response to therapy that cannot be explained by factors such as compliance. *APOE* genotype may be one factor that determines an individual’s degree of response to interventions such as statin therapy.

High-Density Lipoprotein Subclass

High-density lipoprotein 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 HDL_2, the larger, less dense particles that may have the greatest degree of cardioprotection, and HDL_3, which are smaller, denser particles.

An alternative to measuring the concentration of subclasses of HDL (eg, HDL_2 and HDL_3) is 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. High-density lipoprotein 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 Subclass

Two main subclass patterns of LDL, called A and B, have been described. In subclass pattern A, the particles have a diameter larger than 25 nm and are less dense, while in subclass pattern B, the particles have a diameter less than 25 nm and a higher density. Subclass pattern B is a commonly 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 one 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; ATP 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.

Low-density lipoprotein 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 risk for CAD independent of the total LDL level. Also, some drugs may cause a greater shift in lipid profile 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 to use a combination of 2 or more 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, 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-C 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-C 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, cardiac risk may be further enhanced when the particles are smaller versus larger.

Lipoprotein (a)

Lipoprotein (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 1,000-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

Brain Natriuretic Peptide
Brain natriuretic peptide (BNP) 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 cardiovascular risk and all-cause mortality.

High-Sensitivity C-Reactive Protein (hs-CRP)
High sensitivity C-reactive protein (hs-CRP) is produced in response to inflammation in the body. It is a systemic marker of inflammation that has been extensively studied and identified as an independent risk factor for coronary artery disease (CAD). A high sensitivity CRP assay can detect low levels of chronic inflammation associated with heart disease.

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

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Improvement Act of 1988 (CLIA). 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 U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Medical Policy Statement

The safety and effectiveness of measuring apolipoprotein B concentrations have been established. It may be a useful diagnostic option when indicated for individuals at intermediate- or high-risk for a cardiovascular event.

The safety and effectiveness of high sensitivity C-reactive protein (hs-CRP) measurement have been established. It may be a useful diagnostic option when indicated for individuals at intermediate-risk for a cardiovascular event.

The safety and effectiveness of lipoprotein(a) measurement have been established. It may be a useful diagnostic option in those who meet criteria.

The peer reviewed medical literature has not demonstrated the clinical utility of laboratory testing of other novel biomarkers to assess cardiovascular risk, including but not limited to apolipoprotein AI, apolipoprotein E or *APOE* genotypes, brain natriuretic peptide (BNP), cystatin C, fibrinogen, leptin, LDL subclass, HDL subclass, and PULS cardiac. Therefore, these services are experimental/investigational.

Inclusionary and Exclusionary Guidelines

Inclusions:

Apolipoprotein B (apo B)
Apolipoprotein B measurement is established for individuals who meet **at least one** of the following criteria:

- Hypertriglyceridemia
- Diabetes mellitus
- Obesity
- Metabolic syndrome
- Other dyslipidemias (eg, very low LDL-C)
- On lipid therapy
- To facilitate diagnosis of Familial Dysbetalipoproteinemia
- To facilitate diagnosis of Familial Combined Hyperlipidemia

High-sensitivity C-reactive protein (hs-CRP)
High-sensitivity C-reactive protein testing is established for individuals who meet the following:

- After quantitative risk assessment using ACC/AHA Pooled Cohort Equations to calculate 10-year risk of CVD events*, a risk-based treatment decision is uncertain

*Several tools are available to calculate 10-year risk of atherosclerotic cardiovascular disease (ASCVD). The following are examples:
ACC/AHA: https://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calulate/estimator/
ClinCalc.com: https://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx

Lipoprotein(a) (Lp[a])
Lipoprotein(a) measurement is established for individuals meet at least one of the following criteria:

- Individuals with primary severe hypercholesterolemia (LDL cholesterol greater than or equal to 190 mg/dL) or suspected familial hypercholesterolemia, OR

- Individuals with premature atherosclerotic cardiovascular disease (ASCVD) (ie, diagnosis of ASCVD in men younger than 55 years of age; and in women younger than 65 years of age), OR
- Family history of first-degree relatives with premature (ASCVD) (ie, first-degree male relative diagnosed with ASCVD before reaching 55 years of age; first-degree female relative diagnosed with ASCVD before reaching 65 years of age), OR
- Family history of first-degree relative with elevated Lp(a), OR
- Individuals at very high-risk* of ASCVD to better define those who are more likely to benefit from PCSK9 (proprotein convertase subtilisin/kexin type 9 serine protease) inhibitor therapy

*Very high-risk includes a history of more than one major ASCVD events (eg, history of myocardial infarction, history of ischemic stroke, recent acute coronary syndrome) or one major ASCVD even and multiple high-risk conditions (eg, over 65 years of age, family history of hypercholesterolemia, diabetes mellitus, hypertension, chronic kidney disease, history of congestive heart failure, current smoker, etc.)

Exclusions:

- Measurement of apolipoprotein B, high-sensitivity C-reactive protein, and lipoprotein(a) is excluded for all other indications, including use as a routine screening test and for monitoring response to therapy
- Laboratory testing of other novel biomarkers to assess cardiovascular risk, including but not limited to apolipoprotein AI, apolipoprotein E or *APOE* genotypes, brain natriuretic peptide (BNP), cystatin C, fibrinogen, leptin, LDL subclass, HDL subclass, and PULS cardiac

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CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81401	81405	81406	82172	83695
84999	86141			

Other codes (investigational, not medically necessary, etc.):

82397	82610	82664	83520	83700	83701
83704	83718	83719	83721	83722	83880
84181	85384	85385	0052U		

Note: The above code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

NOVEL BIOMARKERS

A large body of literature has accumulated on the utility of novel lipid risk factors in the prediction of future cardiac events. The evidence reviewed for this policy consists of systematic

reviews, meta-analyses and large, prospective cohort studies that have evaluated the association between these lipid markers and cardiovascular outcomes. A smaller amount of literature is available on the utility of these markers as a measure of treatment response. Data on treatment response is taken from randomized controlled trials (RCTs) that use 1 or more novel lipid markers as a target of lipid-lowering therapy.

The Adult Treatment Panel III (ATP III) guidelines noted that, to determine their clinical significance, the emerging risk factors should be evaluated against the following criteria:(1)

- Significant predictive power that is independent of other major risk factors
- A relatively high prevalence in the population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population reference values, and be relatively stable biologically
- It is preferable, but not necessarily, that modification of the risk factor in clinical trials will have shown reduction in risk.

Representative Systematic Reviews

A 2015 health technology assessment, conducted for the National Institute for Health Research, assessed strategies for monitoring lipid levels in patients at risk or with cardiovascular disease (CVD).(2) The assessment included a systematic review of predictive associations for CVD events. Studies were included if they had at least 12 months of follow-up and 1000 participants. Results were stratified by the use of statins and primary versus secondary prevention. For populations not taking statins, 90 publications reporting 110 cohorts were included and, for populations taking statins, 25 publications reporting 28 cohorts were included. In populations not taking statins, the ratio of apolipoprotein B (apo B) to apolipoprotein AI (apo AI) was most strongly associated with the outcome of CVD events (hazard ratio [HR], 1.35; 95% confidence interval [CI], 1.22 to 1.5) although the HRs for apo B, total cholesterol (TC)/high-density lipoprotein (HDL), and low-density lipoprotein (LDL)/HDL all had overlapping CIs with the HR for apo B/apo AI. In populations taking statins, insufficient data were available to estimate the association between apo B or apo AI and CVD events.

Thanassoulis et al (2014) reported on a meta-analysis of 7 placebo-controlled statin trials evaluating the relation between statin-induced reductions in lipid levels and reduction of coronary heart disease (CHD) risk.(3) Each trial included low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (HDL-C), and apo B values assessed at baseline and 1-year follow-up. In both Frequentist and Bayesian meta-analyses, reductions in apo B were more closely related to CHD risk reduction from statins than LDL-C or non-HDL-C.

Van Holten et al (2013) reported on a systematic review of 85 articles with 214 meta-analyses to compare serological biomarkers for risk of CVD.(4) Predictive potential for primary CVD events was strongest with lipids with a ranking from high to low found with: C-reactive protein, fibrinogen, cholesterol, apolipoprotein B, the apolipoprotein A/apolipoprotein B ratio, high density lipoprotein, and vitamin D. Markers associated with ischemia were more predictive of secondary cardiovascular events and included from high to low result: cardiac troponins I and T, C-reactive protein, serum creatinine, and cystatin C. A strong predictor for stroke was fibrinogen.

Tzoulaki et al (2013) reported on meta-analyses of biomarkers for CVD risk to examine potential evidence of bias and inflation of results in the literature.(5) Included in the evaluation

were 56 meta-analyses, with 49 reporting statistically significant results. Very large heterogeneity was seen in 9 meta-analyses, and small study effects were seen in 13 meta-analyses. Significant excess of studies with statistically significant results was found in 29 (52%) meta-analyses. Reviewers reported only 13 meta-analyses with statistically significant results that had more than 1000 cases and no evidence of large heterogeneity, small-study effects, or excess significance.

In a systematic review, Willis et al (2012) evaluated whether validated CVD risk scores could identify patients at risk for CVD for participation in more intensive intervention programs for primary prevention.(6) Sixteen articles on 5 studies were selected. Reviewers were unable to perform a meta-analysis due to the heterogeneity of studies. The evidence was not considered strong enough to draw definitive conclusions, but reviewers noted that lifestyle interventions with higher intensity might have the potential for lowering CVD risk.

ASYMPTOMATIC INDIVIDUALS WITH RISK OF CARDIOVASCULAR DISEASE

Clinical Context and Test Purpose

The purpose of novel cardiac biomarker testing in individuals who are asymptomatic with risk of CVD is to inform a decision whether novel cardiac biomarker testing improves CVD diagnosis and treatment decisions.

The question addressed in this evidence review is: Does novel cardiac biomarker testing improve the net health outcome in asymptomatic individuals at risk of CVD?
The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are asymptomatic with risk of cardiovascular disease.

Interventions

The therapy being considered is novel cardiac biomarker testing.

Comparators

Comparators of interest include routine care without biomarker testing.

Outcomes

The general outcomes of interest are overall survival (OS), other test performance measures, change in disease status, morbid events, and medication use.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- The study population represents the population of interest. Eligibility and selection are described.
- The test is compared with a credible reference standard.
- If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.

- Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (eg, receiver operating characteristic, area under operating characteristic, c-statistic, likelihood ratios) may be included but are less informative.
- Studies should also report reclassification of the diagnostic or risk category.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

APOLIPOPROTEIN B

Apo B as a Predictor of Cardiovascular Risk
The following organizations have issued statements and/or guidelines in support of apolipoprotein B testing for individuals with increased risk factors for CVD:

- The American Association for Clinical Chemistry (AACC)
- The American Association of Clinical Endocrinologists (AACE)
- The American Diabetes Association
- The American College of Cardiology Foundation
- The National Lipid Association
- The Canadian Cardiovascular Society
- The British Columbia Medical Services Commission
- The European Society of Cardiology/European Atherosclerosis Society

A publication from a consensus conference of the American Diabetes Association and the American College of Cardiology Foundation includes specific recommendations for incorporating apo B testing into clinical care for high-risk patients. It is recommended that for patients with metabolic syndrome who are being treated with statins, both LDL-C and apo B should be used as treatment targets, with an apo B target of less than 90 mg/dL. This consensus statement also commented on the use of LDL particle number in patients with cardiometabolic risk and the limitations of the clinical utility of NMR measurement of LDL particle number or size, including lack of widespread availability. Also mentioned was the need for more independent data confirming the accuracy of the method and whether its predictive power is consistent across various patient populations.(7)

The American Association for Clinical Chemistry (2013) conducted a review of 25 clinical studies containing 85 outcomes for which both biomarkers apolipoprotein B (apo B) and LDL particle number (LDL-P) were determined. In 21 of 25 (84.0%) studies, both apo B and LDL-P were significant for at least 1 outcome. Neither was significant for any outcome in only 1 study (4.0%). In 50 of 85 comparisons (58.8%), both apo B and LDL-P had statistically significant associations with the clinical outcome, whereas in 17 comparisons (20.0%) neither was significantly associated with the outcome. In 18 comparisons (21.1%) there was discordance between apo B and LDL-P. The AACC concluded “in most studies, both apo B and LDL-P were comparable in association with clinical outcomes. The biomarkers were nearly equivalent in their ability to assess risk for CVD and both have consistently been shown to be stronger risk factors than LDL-C. We support the adoption of apo B and/or LDL-P as indicators of atherogenic particle numbers into CVD risk screening and treatment guidelines. Currently, in the opinion of this Working Group on Best Practices, apo B appears to be the preferable biomarker for guideline adoption because of its availability, scalability, standardization, and relatively low cost.”(8)

The American Association of Clinical Endocrinologists (2017) published clinical practice guidelines for the diagnosis and treatment of dyslipidemia and prevention of atherosclerosis. The ACCE states “when the triglyceride concentration is greater than 150 mg/dL or the HDL-C concentration is less than 40 mg/dL, the apo B or the apo B to apo AI ratio may be particularly useful in assessing residual risk in patients at risk for CAD (even when LDL-C levels are controlled); this includes patients with established CAD, type 2 diabetes, or the insulin resistance syndrome who are at high risk for CAD. AACE therefore recommends apo B testing in such patients.” The guidelines support the use of apolipoprotein B or LDL particle number measurements to refine efforts to achieve effective LDL-C lowering, provide screening recommendations for persons of different ages, and identify special issues for pediatric patients. AACE recommends the goals set by the American College of Cardiology and the American Diabetes Association that optimal apo B levels for patients at risk of CAD, including those with diabetes, are less than 90 mg/dL, while patients with established CAD or diabetes plus 1 or more additional risk factor should have an apo B goal of less than 80 mg/dL.(9)

The National Lipid Association (2014) convened a panel of clinical experts to evaluate the use of selected biomarkers in clinical practice as either tools to improve risk assessment or as markers to adjust therapy once a decision to treat had been made. The summary of recommendations is as follows:(10)

Apo B: initial clinical assessment

1. In patients at low risk, < 5% 10-year CHD event risk, the likelihood of markedly elevated Apo B is low. Hence, use of Apo B is not recommended in this category (rating: ‘‘not recommended’’).
2. In patients at intermediate risk, those with premature family history, and those with recurrent events, measurement of Apo B would enable the best possible management of modifiable factors for vascular risk (rating: ‘‘reasonable for many patients’’).
3. Once a patient with CHD or CHD risk equivalent has achieved his or her LDL-C and/or non-HDL-C goals, obtaining an Apo B measurement might be useful for determining whether further intensification of lipid lowering therapy should be considered, as might be the case for discordant individuals with residual Apo B elevation (rating: ‘‘consider for selected patients’’).

Apo B: on-treatment management decisions

1. There is no clear benefit of measuring Apo B in patients at low risk receiving lipid-altering therapy, and therefore it is not recommended in this group of patients (rating: ‘‘not recommended’’).
2. In patients at intermediate risk, with CHD or CHD risk equivalent, and in those with recurrent events, measurement of Apo B is reasonable for many patients (rating: ‘‘reasonable for many patients’’)
3. In patients with a family history of premature CHD, measurement of Apo B should be considered for selected patients (rating: ‘‘consider for selected patients’’).

The Emerging Risk Factors Collaboration (2012) published a patient-level meta-analysis of 37 prospective cohort studies enrolling 154,544 individuals.(11) Risk prediction was examined for a variety of traditional and nontraditional lipid markers. For apolipoprotein B (apo B), evidence from 26 studies on 139,581 individuals reported that apo B was an independent risk factor for cardiovascular events, with an adjusted hazard ratio of 1.24 (95% confidence interval [CI], 1.19 to 1.29).

Canadian Cardiovascular Society guidelines (2009, 2013) recommend apoB as the primary alternate target to LDL-C.(12) The guidelines explain that, based on the available evidence, many experts have concluded that apoB is a better marker than LDL-C for the risk of vascular disease and a better index of the adequacy of LDL-lowering therapy than LDL-C. The guidelines also note that there now appears to be less laboratory error in the determination of apoB than LDL-C, particularly in patients with hypertriglyceridemia, and all clinical laboratories could easily and inexpensively provide standardized measurements of apoB. The guidelines state, however, that not all experts are fully convinced that apoB should be measured routinely and, in any case, apoB is not presently being measured in most clinical laboratories. Consequently, a substantial educational effort for patients and physicians would be required for the most effective introduction of apoB into widespread clinical practice. The guidelines conclude that, despite these reservations, all would agree that physicians who wish to use apoB in their clinical care should be encouraged to do so. Furthermore, the present compromise approach represents a positive transitional phase in the assessment of lipid parameters to improve the prevention of CVD through the clinical measurement of apoB. The guidelines state that apoB target for high-risk subjects is less than 0.80 g/L.

Guidelines from the British Columbia Medical Services Commission (2008) states that apolipoprotein B (apoB) should be considered for follow-up testing in high-risk patients who are undergoing treatment for hypercholesterolemia (but not for other dyslipidemias).(13) The guidelines state that other lipid tests are not required if using apoB for follow-up.
A cohort study (2005) of 15,632 participants from the Women's Health Initiative provided similar information in women.(14) In this analysis, the hazard ratio for developing coronary heart disease in the highest versus the lowest quintiles was greater for apo B (2.50; 95% CI, 1.68 to 3.72) compared to LDL-C (1.62; 95% CI, 1.17 to 2.25), after adjustment for traditional cardiovascular risk factors.

Guidelines from the European Society of Cardiology/European Atherosclerosis Society (2019) states that apolipoprotein B (apoB) was a more accurate marker of cardiovascular risk than low-density lipoprotein cholesterol (LDL-C) and non–high-density lipoprotein cholesterol.(138)

The Copenhagen City Heart Study (2007) prospectively evaluated a cohort of 9,231 asymptomatic persons from the Danish general population followed for 8 years.(15) Subjects with total apo B levels in the top one-third (top tertile) had a significantly increased relative risk of cardiovascular events than patients in the lowest one-third, after controlling for LDL-C and other traditional cardiovascular risk factors (risk ratio [RR], 1.4; 95% CI, 1.1 to 1.8 for men; RR=1.5; 95% CI, 1.1 to 2.1 for women). This study also compared the discriminatory ability of apo B with that of traditional lipid measures, by using the area under the curve (AUC) for classifying cardiovascular events. Total apo B levels had a slightly higher AUC (0.58) than LDL-C (0.57).

Robinson et al (2012) published results of a Bayesian random-effects meta-analysis of RCTs to compare the effectiveness of lowering apo B versus LDL-C and non-HDL-C for reducing CVD, CHD, and stroke risk.(16) Selected for analysis were 131,134 patients from 25 RCTs including 12 trials on statins, 5 on niacins, 4 on fibrates, 1 on simvastatin plus ezetimibe, 1 on aggressive versus standard LDL and blood pressure targets, and 1 on ileal bypass surgery. In the analysis of all trials, each apo B decrease of 10 mg/dL resulted in a 6% decrease in major CVD risk and a 9% decrease in CHD risk prediction.

The INTERHEART study compared apo B:apo A-1 with other cholesterol ratios as markers for the risk of acute myocardial infarction in all the major ethnic groups of the world. In this study, 12,461 patients with acute MI from the world's major regions and ethnic groups were compared with 14,637 age- and sex-matched controls to assess the contributions of various cardiovascular risk factors. Investigators obtained non-fasting blood samples from 9,345 cases and 12,120 controls and measured cholesterol fractions and apolipoproteins to determine their respective predictive values. Ratios were stronger predictors of MI than were individual components, and apolipoproteins were better predictors than their cholesterol counterparts. The apo B:apo A-1 ratio was the strongest predictor, with a population-attributable risk of 54%, compared with risks of 37% for LDL/HDL and 32% for total cholesterol/HDL. A 1-standard-deviation increase in apo B:apo A-1 was associated with an odds ratio of 1.59 for MI, compared with 1.17 for an equivalent increase in total cholesterol/HDL. The results were similar for both sexes and across all ethnic groups and ages.(17)

Sniderman et al (2012) reported on 9,345 acute myocardial infarction patients compared with 12,120 controls in the INTERHEART study to determine whether apo B or non-HDL-C are equivalent markers of risk when the two markers are discordant. The authors reported discordance in the levels of cholesterol contained in apo B and non-HDL-C. Apo B was found to be more accurate than non-HDL-C as a marker for cardiovascular risk.(18)

Sniderman et al (2011) performed a meta-analysis of all published reports containing apo B, LDL-C, and non-HDL-C cardiovascular relative risk ratios (RRRs). Fifteen independent published analyses identified for this meta-analysis provided a total of 233,455 subjects and 22,950 events. The objectives were "to determine the overall balance of the evidence comparing the standardized RRRs of all 3 markers and, if possible, to identify any factors associated with the variance among the studies." The researchers concluded that whether analyzed individually or head to head, apo B was the most potent marker of risk, LDL-C was the least, and non-HDL-C was intermediate. The study indicates that apo B is superior to LDL-C and non-HDL-C as a predictor of cardiovascular risk.(19)

The 2000 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) evaluated lipid parameters among 6,605 men and women with average LDL- and low HDL-cholesterol levels who were randomly assigned to receive either lovastatin or placebo.(22) Baseline LDL- and HDL-cholesterol, as well as levels of apo B, were predictive of future coronary events. However, in the treatment group, post-treatment levels of LDL-C and HDL-C were not predictive of subsequent risk, while post-treatment apo-B levels were predictive. Kastelein et al (2008) combined data from 2 RCTs, the Treating to New Targets (TNT) and Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) trials, to compare the relationship between response to lipids, apo B levels, and other lipid measures.(19) This analysis included 18,889 patients with established coronary disease randomly assigned to low- or high-dose statin treatment. In pairwise comparisons, the on-treatment apo B level was a significant predictor of cardiovascular events (HR=1.24; 95% CI, 1.13 to 1.36; $p<0.001$), while LDL level was not. Similarly, the ratio of apo B/apo AI was a significant predictor of events (HR=1.24; 95% CI, 1.17 to 1.32), while the total/HDL-C was not. In another publication that reported on the TNT study, the on-treatment apo B level was also a significant predictor of future events (adjusted HR=1.19; 95% CI, 1.11 to 1.28).(23)

Section Summary: Apolipoprotein B

The evidence has suggested that apo B provides independent information on risk assessment for CVD and that apo B may be superior to LDL-C in predicting cardiovascular risk. Numerous

large prospective cohort studies and nested case-control studies have compared these measures, and most have concluded that apo B is a better predictor of cardiac risk than LDL-C.

LDL-C is not the best indicator of the risk associated with LDL, as risk correlates more closely with the number of circulating atherogenic particles than with the quantity of cholesterol transported by LDL particles. In individuals whose LDL particles contain less cholesterol than normal, the LDL-C concentration may underestimate the number of LDL particles. In these individuals, the apo B concentration will more accurately reflect the number of LDL particles and LDL-related CVD risk. Likewise, in individuals whose LDL particles contain more cholesterol than normal, the LDL-C concentration will overestimate the number of LDL particles. In these patients, the apo B concentration will more accurately reflect the number of LDL particles than will the LDL-C concentration.(9) A high proportion of patients with diabetes, metabolic syndrome, obesity, hypertriglyceridemia, or low HDL-C, but otherwise-normal lipids, will have increased numbers of LDL particles that contain less cholesterol than average. The LDL-C concentration is often normal in these patients, despite an elevated level of LDL particles, and accordingly, an elevated circulating concentration of apo B.(10)

As a marker of response to cholesterol-lowering treatment, apo B may be more accurate than LDL-C and may provide a better measure of the adequacy of anti–lipid therapy than does LDL-C. Post hoc analyses of RCTs of statin treatment have reported that on-treatment levels of apo B are more highly correlated with clinical outcomes than standard lipid measures.

The evidence is sufficient to warrant the clinical use of apo B levels as a replacement for LDL-C levels in select patient populations – those with hypertriglyceridemia, abdominal obesity, metabolic syndrome or insulin resistance, and patients with otherwise-normal lipids but low HDL-C. Apo B is not recommended in patients who are considered “low risk” because it is unlikely that an elevated apo B level would be a finding in this group. “Low risk” is defined as 10-year CHD event risk < 5% on the basis of Framingham scoring.(10)

APOLIPOPROTEIN AI

Systematic Review

In the Emerging Risk Factors Collaboration meta-analysis (2012) described above, apo AI was also examined as an independent risk factor.(11) For apo AI, evidence from 26 studies (n=139,581) reported that apo AI was an independent risk factor for reduced cardiovascular risk. However, as with apo B, when apo AI was substituted for traditional lipids, there was no improvement in risk prediction. In fact, there was a slight worsening in the predictive ability, evidenced by a -0.0028 decrease in the C-statistic (p<.001) and a -1.08% decrease in the net reclassification improvement of (p<.01).

Observational Studies

Clarke et al (2007) published a prospective cohort study of 7044 elderly men enrolled in the Whitehall Cardiovascular Cohort from England.(24) Measurements of apolipoprotein levels were performed on 5344 of these men, and they were followed up for a mean of 6.8 years. The

authors reported that the apo B/apo AI ratio was a significant independent predictor (Table 1) with similar predictive ability as the TC/HDL ratio (HR=1.57; 95% CI, 1.32 to 1.86).

Ridker et al (2007) described above, compared the predictive ability of apo AI and the apo B/apo AI ratio with standard lipid measurements.(25) Both ratios had similar predictive ability to standard lipid measurements but were no better. The HR for future cardiovascular events was 1.75 (95% CI, 1.30 to 2.38) for apo AI compared with 2.32 (95% CI, 1.64 to 3.33) for HDL-C (Table 1). The HR for the apo B/apo AI ratio was 3.01 (95% CI, 2.01 to 4.50), compared with 3.18 (95% CI, 2.12 to 4.75) for the LDL-C/HDL-C ratio.

A nested case-control study (2007) performed within the larger European Prospective Investigation into Cancer and Nutrition-Norfolk cohort study, evaluated the predictive ability of the apo B/apo AI ratio in relation to traditional lipid measures in 25,663 patients.(26) The case-control substudy enrolled 869 patients who had developed CAD during a mean follow-up of 6 years and 1511 control patients without CAD. The authors reported that the apo B/apo AI ratio was an independent predictor of cardiovascular events after controlling for traditional lipid risk factors and the Framingham risk score (Table 1). However, the authors also reported that this ratio was no better than the TC/HDL ratio in discriminating between cases (AUC 0.673) and controls (AUC, 0.670; p=.38).

Table 1. Results of Diagnostic Apolipoprotein AI Studies

Study	Study Type	N	Efficacy of Apolipoprotein AI in Determining CVD Risk	
			HR (95% CI)	OR (95% CI)
ERFC (2012)8,	Review of prospective cohorts	139,581	0.87 (0.84 to 0.90)	-
Clarke et al (2007)21,	Prospective cohort	7044	1.54 (1.27 to 1.87)	-
Ridker et al (2007)18,	Prospective cohort	2966	2.32 (1.64 to 3.33)	-
van der Steeg et al (2007)22,	Case-control	25,663	-	1.85 (1.15 to 2.98)

CI: confidence interval; CVD: cardiovascular disease; ERFC: Emerging Risk Factors Collaboration; HR: hazard ratio; OR: odds ratio.

The Apolipoprotein-Related Mortality Risk Study (2001) followed 175,000 Swedish men and women for 5.5 years and reported that decreased apo AI was an independent predictor of CAD events.(13) The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) investigated lipid parameters among 6,605 men and women with average LDL-C and low HDL-C who were randomized to lovastatin or placebo.(22) This study reported that apo AI levels and the apo B/apo AI ratio were strong predictors of CAD events.

The Copenhagen City Heart Study (2007) was a prospective cohort study of 9,231 asymptomatic persons from the Danish general population.(15) The apo B/apo AI ratio was reported as an independent predictor of cardiovascular events, with a hazard ratio similar to that for TC/HDL-C. This study also compared the discriminatory ability of the apo B/apo AI ratio with that of traditional lipid measures, using the AUC for classifying cardiovascular events. The apo B/apo AI ratio had a slightly higher AUC (0.59) than the TC/HDL-C ratio (0.58), but this difference was not statistically significant.

Section Summary: Apolipoprotein AI

The current evidence has generally indicated that measurement of apo AI, and the apo B/apo AI ratio are as good as, or better than currently used lipid measures such as LDL and HDL. Some experts argue that the apo B/apo AI ratio is superior to the LDL/HDL ratio as a predictor of cardiovascular risk and should supplement or replace traditional lipid measures as both a risk marker and a treatment target.(22,27) However, there is substantial uncertainty regarding the degree of improvement that these measures provide. The evidence suggests that any incremental improvement in predictive ability over traditional measures is likely to be small and of uncertain clinical significance.

APOLIPOPROTEIN E

A large body of research has established a correlation between lipid levels and the underlying *APOE* genotype. For example, in population studies, the presence of an apo e2 allele is associated with the lowest cholesterol levels and the apo e4 allele is associated with the highest levels.(23,28)

Systematic Reviews

A meta-analysis published by Bennet et al (2007) summarized the evidence from 147 studies on the association of APOE genotypes with lipid levels and cardiac risk.(29) Eighty-two studies included data on the association of APOE with lipid levels, and 121 studies reported the association with clinical outcomes. Authors estimated that patients with the apo e2 allele had LDL levels that were approximately 31% less compared to patients with the apo e4 allele. When compared to patients with the apo e3 allele, patients with apo e2 had an approximately 20% decreased risk for coronary events (OR=0.80; 95% CI, 0.70 to 0.90). Patients with the apo e4 had an estimated 6% higher risk of coronary events that was of marginal statistical significance (OR=1.06; 95% CI, 0.99 to 1.13).

Sofat et al (2016) published a meta-analysis of 3 studies of circulating apo E and CVD events.(30) The method for selecting the studies was not described. The 3 studies included 9587 participants and 1413 CVD events. In pooled analysis, there was no association between apo E and CVD events. The unadjusted odds ratio for CVD events for a standard deviation increase in apo E concentration was 1.02 (95% CI, 0.96 to 1.09). After adjustment for other cardiovascular risk factors, the odds ratio for CVD for a standard deviation increase in apo E concentration was 0.97 (95% CI, 0.82 to 1.15).

Observational Studies

Numerous studies have focused on the relation between genotype and physiologic markers of atherosclerotic disease. A number of small- to medium-sized cross-sectional and case-control studies have correlated apo E with surrogate outcomes such as cholesterol levels, markers of inflammation, or carotid intima-media thickness.(—31,32,33,34,35,36) These studies have generally shown a relationship between APOE and these surrogate outcomes. Other studies have suggested that carriers of apo e4 are more likely to develop signs of atherosclerosis independent of total and LDL-cholesterol levels.(37,38,39,40)

Some larger observational studies have correlated *APOE* genotype with clinical disease. The Atherosclerosis Risk in Communities (ARIC) study (2001) followed up 12,000 middle-aged subjects free of CAD at baseline for 10 years.(41) This study reported that the e3/2 genotype was associated with carotid artery atherosclerosis after controlling for other atherosclerotic risk factors. Volcik et al (2006), also analyzing ARIC study data, reported that *APOE*

polymorphisms were associated with LDL levels and carotid intima-media thickness but were not predictive of incident CAD.(42)

Section Summary: Apolipoprotein E

The evidence has suggested that *APOE* genotype may be associated with lipid levels and CAD but, is probably not useful in providing additional clinically relevant information beyond established risk factors. Apo E is considered a relatively poor predictor of CAD, especially when compared to other established and emerging clinical variables and does not explain a large percent of the inter-individual variation in TC and LDL levels. Moreover, apo E has not been incorporated into standardized cardiac risk assessment models and was not identified as an important “emerging risk factor” in the most recent ATP III recommendations.

HIGH-DENSITY LIPOPROTEIN PARTICLE SIZE AND CONCENTRATION

Systematic review

Singh et al (2020) reported the results for a pooled analysis examining the association between HDL particle concentration and stroke and MI in patients without baseline atherosclerotic disease.(43) The analysis included 15,784 patients from 4 prospective cohort studies, which included the ARIC study. A significant inverse association was reported between HDL particle concentration and stroke and MI, when comparing patients with HDL particle concentration in the fourth quartile and the first quartile (HR, 0.64; 95% CI, 0.52 to 0.78). When comparing quartile 4 with quartile 1 with regard to the individual components of the primary endpoint, a significant reduction in both MI (HR, 0.63; 95%, 0.49 to 0.81) and stroke (HR, 0.66; 95% CI, 0.48 to 0.93) was reported. There was significant heterogeneity between studies with regard to patient ethnicity and geographic location. Sub-analysis by race revealed that the significant inverse association between HDL particle concentration and stroke and MI was not seen in black populations. When comparing quartile 4 with quartile 1 among black patients, HDL particle concentration did not have an inverse association with MI (HR, 1.22;95% CI, 0.76 to 1.98). However, the heterogeneity and uneven distribution of patients may have contributed to subgroup analyses being underpowered and the possibility of type 2 error.

Randomized controlled Trial

In the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER RCT) (2013), 10,886 patients without CVD were randomized to rosuvastatin or placebo and followed for a median of 2 years.(44) Before randomization and 1 year after, levels of LDL-C, HDL-C, apo AI, and nuclear magnetic resonance (NMR)–measured HDL size and HDL particle numbers were evaluated. Statistically significant changes in the median and 25th and 75th percentile values of HDL measures between baseline and year 1 values occurred in the rosuvastatin and placebo groups for all levels ($p<.001$), except for apo AI and HDL particle size in the placebo group, which did not differ significantly ($p=.09$ and 0.74, respectively). Changes in the rosuvastatin group were all statistically significant compared with placebo for LDL-C, HDL-C, apo AI, and HDL particle size and number (all $p<.001$). In the placebo group, inverse associations with CVD and HDL-C, apo AI, and HDL particle were seen. High-density lipoprotein particle number in the rosuvastatin group had a greater association with CVD (HR, 0.73; 95% CI, 0.57 to 0.93; $p=.01$) than HDL-C (HR, 0.82; 95% CI, 0.63 to 1.08; $p=.16$) or apo AI (HR, 0.86; 95% CI, 0.67 to 1.10; $p=.22$). This association remained after adjusting for HDL-C (HR, 0.72; 95% CI, 0.53 to 0.97; $p=.03$). Size of HDL was not significantly associated with CVD in risk factor–adjusted models.

Section Summary: High-Density Lipoprotein Particle Size and Concentration
One RCT and a pooled analysis have evaluated the association of HDL particle size and number as measured by NMR. While these studies found an association with HDL particle concentration (but not HDL size) and CVD, it is uncertain how NMR-measured HDL particle number would be used to change clinical management beyond the information provided by traditional lipid measures. It is also unclear whether the association between HDL particle concentration and cardiovascular events is seen in all patient populations.

LOW-DENSITY LIPOPROTIEN SUBCLASS AND LOW-DENSITY LIPOPROTEIN PARTICLE SIZE AND CONCENTRATION

Observational Studies
A nested case-control study (1996) from the Physician's Health Study, a prospective cohort study of approximately 15,000 men, investigated whether LDL particle size was an independent predictor of CAD risk, particularly in comparison to triglyceride levels.(45) The authors concluded that while LDL particle diameter was associated with risk of MI, this association was not present after adjustment for triglyceride level. Only the triglyceride level was independently significant.

The Quebec Cardiovascular Study evaluated the ability of "nontraditional" lipid risk factors, including LDL size, to predict subsequent CAD events in a prospective cohort of 2155 men followed for 5 years.(12,46) The presence of small LDL was associated with a 2.5-fold increased risk for ischemic heart disease after adjustment for traditional lipid values, indicating a level of risk similar to total LDL. This study also suggested an interaction in atherogenic risk between LDL size and apoB levels. In the presence of small LDL particles, elevated apolipoprotein B levels were associated with a 6-fold increased risk of CAD, whereas when small LDL particles were not present, elevated apoB levels were associated with only a 2-fold increase in risk.

Tzou et al (2005) examined the clinical value of "advanced lipoprotein testing" in 311 randomly selected adults participating in the Bogalusa Heart Study.(47) Advanced lipoprotein testing consisted of subclass patterns of LDL (ie, presence of large buoyant particles, intermediate particles, or small dense particles). These measurements were used to predict the presence of subclinical atherosclerosis, as measured ultrasonographically by carotid intimal-media thickness. In multivariate logistic regression models, substituting advanced lipoprotein testing for corresponding traditional lipoprotein values did not improve prediction of the highest quartile of carotid intimal-media thickness.

LDL PARTICLE SIZE AND CONCENTRATION MEASURED BY NUCLEAR MAGNETIC RESONANCE
Similar to small dense lipoprotein particles, several epidemiologic studies have shown that the lipoprotein particle size and concentration measured by nuclear magnetic resonance (NMR) are also associated with cardiac risk. For example, the data derived from the Women's Health Study, Cardiovascular Health Study, and Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-1) trial have suggested that the number of LDL particles is an independent predictor of cardiac risk.(48,49,50) Translating these findings into clinical practice requires setting target values for lipoprotein number. Proposed target values have been derived from the same data set (ie, Framingham study) used to set the ATP III target goals for LDL-C. For example, the ATP III targets for LDL-C correspond to the 20th, 50th, and 80th

percentile values in the Framingham Offspring Study, depending on the number of risk factors present. Proposed target goals for lipoprotein number correspond to the same percentile values, and LDL particle concentrations corresponding to the 20th, 50th, and 80th percentile are 1100, 1400, and 1800 nmol/L, respectively.(51)

Systematic Review

Rosenson and Underberg (2013) conducted a systematic review of studies on lipid-lowering pharmacotherapies to evaluate changes in LDL particles pre- and post-treatments.(52) Reductions in mean LDL particles occurred in 34 of the 36 studies evaluated. Percentage reductions of LDL particles in several statin studies were smaller than reductions in LDL-C. LDL particles and apo B changes were comparable. Reviewers suggested the differences in LDL particle reductions with different lipid-lowering therapies demonstrated potential areas of residual cardiovascular risk that could be addressed with LDL particle monitoring.

Observational Studies

Mora et al (2009) evaluated the predictive ability of LDL particle size and number measured by NMR in participants of the Women's Health Study, a prospective cohort study of 27,673 women followed over an 11-year period.(53) After controlling for nonlipid factors, LDL particle number was a significant predictor of incident cardiovascular disease, with a hazard ratio of 2.51 (95% CI, 1.91 to 3.30) for the highest, compared to the lowest quintile. LDL particle size was similarly predictive of cardiovascular risk, with a hazard ratio of 0.64 (95% CI, 0.52 to 0.79). Compared with standard lipid measures and apolipoproteins, LDL particle size and number showed similar predictive ability but were not superior in predicting cardiovascular events.

Toth et al (2014) analyzed LDL-C and LDL particle levels and cardiovascular risk using commercial insurance and Medicare claims data on 15,569 high-risk patients from the HealthCore Integrated Research Database.(54) For each 100 nmol/L increase in LDL particle level, there was a 4% increase in risk of a CHD event (HR=1.04; 95% CI, 1.02 to 1.05; p<0.000). A comparative analysis, using 1:1 propensity score matching of 2094 patients from the LDL-C target cohort (LDL-C level <100 mg/dL without a LDL particle level) and a LDL particle target cohort LDL particle <1000 nmol/L and LDL-C of any level) found a lower risk of CHD or stroke in patients who received LDL-C measurement and were presumed to have received more intensive lipid-lowering therapy (HR=0.76; 95% CI, 0.61 to 0.96; at 12 months). A comparison of smaller LDL particle target groups at 24 (n=1242) and 36 (n=705) months showed similar reductions in CHD (HR=0.78; 95% CI, 0.62 to 0.97) and stroke (HR=0.75; 95% CI, 0.58 to 0.97).

Section Summary: LDL Subclass and LDL Particle Size and Concentration

Small LDL size is a component of an atherogenic lipid profile; other components include increased triglycerides, increased apo B, and decreased HDL. Some studies have reported that LDL size is an independent risk factor for CAD, while others have reported that a shift in LDL size may be a useful marker of treatment response.

A relatively small number of studies have evaluated the predictive ability of LDL particle size and number as measured by NMR. These studies do not demonstrate that NMR-measured particle size and/or number offer additional predictive ability beyond that provided by traditional lipid measures. Measures by NMR have been proposed as indicators of residual cardiovascular risk in patients treated with statins who have met LDL goals, but there is no evidence that these measures improve health outcomes when used for this purpose.

LIPOPROTEIN (A)

Numerous prospective RCTs, cohort studies and systematic reviews have evaluated lipoprotein (a) (Lp[a]) as a cardiovascular risk factor. The following are representative prospective trials drawn from the relevant literature. Table 2 summarizes the results of diagnostic Lp(a) studies that assess the HR or of the efficacy of Lp(a) in determining CVD risk.

Systematic Review

The Emerging Risk Factors Collaboration (2012) published a patient-level meta-analysis assessing 37 prospective cohort studies enrolling 154,544 individuals.(11) Risk prediction was examined for a variety of traditional and nontraditional lipid markers. For Lp(a), evidence from 24 studies on 133,502 individuals reported that Lp(a) was an independent risk factor for reduced cardiovascular risk (Table 2). The addition of Lp(a) to traditional risk factors resulted in a small improvement in risk prediction, with a 0.002 increase in the C-statistic. A reclassification analysis, found no significant improvement in the net reclassification index (0.05%; 95% CI, -0.59 to 0.70).

Several meta-analyses have also examined the relation between Lp(a) levels and cardiovascular risk. Bennet et al (2008) synthesized the results of 31 prospective studies with at least 1 year of follow-up and that reported data on cardiovascular death and nonfatal MI. (55) The combined results revealed a significant positive relationship between Lp(a) and cardiovascular risk (Table 2). This analysis reported a moderately high degree of heterogeneity in selected studies (I^2=43%), reflecting the fact that not all reported a significant positive association.

Smolders et al (2007) summarized evidence from observational studies on the relation between Lp(a) and stroke.(56) Five prospective cohort studies and 23 case-control studies were included in this meta-analysis. Results from prospective cohort studies showed that Lp(a) level added only incremental predictive information (combined RR for the highest one-third of Lp[a], 1.22; 95% CI, 1.04 to 1.43). Results from case-control studies showed an elevated Lp(a) level was associated with an increased risk of stroke (Table 2).

Randomized Controlled Trials

Several RCTs on lipid-lowering therapies have found Lp(a) is associated with residual cardiovascular risk. In a subgroup analysis of 7746 white patients from the JUPITER study (2014), median Lp(a) levels did not change in either group of patients randomized to treatment with rosuvastatin or placebo during a median 2-year follow-up.(57) Lp(a) was independently associated with a residual risk of CVD despite statin treatment. In the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes study (2013), Lp(a) levels in 1440 patients at baseline and on simvastatin plus placebo or simvastatin plus extended-release niacin were significantly predictive of cardiovascular events (Table 2).(58)

Observational Studies

Kamstrup et al (2008) analyzed data from the Copenhagen City Heart Study, which followed 9330 subjects from the Copenhagen general population over 10 years.(59) This study reported on a graded increase in the risk of cardiac events with increasing Lp(a) levels. At extreme levels of Lp(a) above the 95th percentile, the aHR for MI was slightly higher for women than for men (Table 4). Tzoulaki et al (2007) reported on data from the Edinburgh Artery Study, a

population cohort study that followed 1592 subjects for a mean of 17 years.(60) They reported that Lp(a) was an independent predictor of MI (Table 2).

Zakai et al (2007) evaluated 13 potential biomarkers for independent predictive ability compared with established risk factors, using data from 4510 subjects followed for 9 years in the Cardiovascular Health Study.(61) Lipoprotein (a) was 1 of 7 biomarkers that had incremental predictive ability above the established risk factors (Table 2).

Waldeyer et al (2017) analyzed data of 56,084 participants from Biomarkers for Cardiovascular Risk Assessment in Europe project, which followed 7 prospective population-based cohorts across Europe, with a maximum follow-up of 24 years, to characterize the association of Lp(a) concentration with major coronary events, incident CVD, and total mortality.(62) The highest event rate of major coronary events and CVD was observed for Lp(a) levels at the 90th percentile or higher (p<.001 for major coronary events and CVD). Adjusting for age, sex, and cardiovascular risk factors, compared with Lp(a) levels in the lowest third in the 67th to 89th percentile, there were significant associations between Lp(a) levels and major coronary events (HR, 1.3; 95% CI, 1.15 to 1.46) and CVD (HR, 1.25; 95% CI, 1.12 to 1.39) (Table 2). For Lp(a) levels at the 90th percentile or higher, the aHR for the association between Lp(a) and major coronary events was 1.49 (95% CI, 1.29 to 1.73) and for the association between Lp(a) and CVD, it was 1.44 (95% CI, 1.25 to 1.65) compared with Lp(a) levels in the lowest third. There was no significant association between Lp(a) levels and total mortality.
Lee et al (2017) investigated whether elevated circulating Lp(a) level was a key determinant in predicting the incidence of major adverse cardiovascular events among the participants of the Dallas Health Study, a multiethnic prospective cohort with a median follow-up of 9.5 years (N=3419 patients).(63) Quartiles 4 of Lp(a) and oxidized phospholipid on apo B-100 were associated with HRs for time to major adverse cardiovascular events of 2.35 (95% CI, 1.50 to 3.69) and 1.89 (95%CI, 1.26 to 2.84), respectively, adjusting for age, sex, body mass index (BMI), diabetes, smoking, LDL, HDL-C, and triglycerides (Table 2). The addition of major apolipoprotein(a) isoform and 3 *LPA* single nucleotide variants prevalent among white, black, and Hispanic subjects in the model attenuated the risk, but significance was maintained for both Lp(a) and oxidized phospholipid on apo B-100.

Some researchers have hypothesized that there is a stronger relation between Lp(a) and stroke than CHD. Similar to the situation with cardiac disease, most prospective studies have indicated that Lp(a) level is an independent risk factor for stroke. In a prospective cohort study, Rigal et al (2007) reported that an elevated Lp(a) level was an independent predictor of ischemic stroke in men (Table 2).(64)

There also may be a link between Lp(a) level as a cardiovascular risk factor and hormone status in women. Suk Danik et al (2008) reported on the risk of a first cardiovascular event over a 10-year period in 27,736 women enrolled in the Women's Health Study.(65) After controlling for standard cardiovascular risk factors, Lp(a) levels were an independent predictor of risk in women not taking hormone replacement therapy (Table 2). However, for women who were taking hormone replacement therapy, Lp(a) levels were not a significant independent predictor of cardiovascular risk (HR, 1.13; 95% CI, 0.84 to 1.53; p=.18).

Table 2. Results of Diagnostic Lipoprotein(a) Studies

Study	Study Type	N	Efficacy of Lp(a) in Determining CVD Risk	
			HR (95% CI)	OR (95% CI)

ERFC (2012)8,	SR/MA	154,544	1.13 (1.09 to 1.18)	-
Khera et al (2014)54,	RCT	7746	1.27 (1.01 to 1.59) p=.04	-
Albers et al (2013)55,	RCT	1440	1.18-1.25	-
Kamstrup et al (2008)56,	Post hoc analysis	9330	Men: 3.6 (1.7 to 7.7) Women: 3.7 (1.7 to 8.0)	-
Tzoulaki et al (2007)57,	Prospective cohort	1592	1.49 (1.0 to 2.2)	-
Zakai et al (2007)58,	Prospective cohort	4510	1.07 (1.0 to 1.12)	-
Waldeyer et al (2017)59,	Post hoc analysis	56,084	1.3 (1.15 to 1.46)	-
Lee et al (2017)60,	Prospective cohort	3419	2.35 (1.50 to 3.69)	-
Rigal et al (2007)61,	Prospective cohort	100	-	Men: 3.55 (1.33 to 9.48) Women: 0.42 (0.12 to 1.26)
Suk Danik et al (2008)62,	Prospective cohort	27,736	1.77 (1.36 to 2.30) p<.001	-
Bennet et al (2008)52,	SR/MA	2047	-	1.45 (1.32 to 1.58)
Smolders et al (2007)53,	SR/MA of Observational	56,010	-	2.39 (1.57 to 3.63)

CI: confidence interval; CVD: cardiovascular disease; ERFC: Emerging Risk Factors Collaboration; HR: hazard ratio; MA: meta-analysis; Lp(a): lipoprotein(a); OR: odds ratio; RCT: randomized control trial; SR: systematic review.

Additional Studies

Beyond the studies describing the HR or for the efficacy of Lp(a) and CVD summarized in Table 3, additional key studies have examined the relation between Lp(a) and CVD risk, which are summarized below.

Additional Systematic Reviews

A systematic review by Genser et al (2011) included 67 prospective studies (N=181,683 subjects) that evaluated the risk of CVD associated with Lp(a).(66) Pooled analysis was performed on 37 studies that reported the endpoints of cardiovascular events. When grouped by design and populations, the RRs for these studies, comparing the uppermost and lowest strata of Lp(a), ranged from 1.64 to 2.37. The RR for cardiovascular events was higher in patients with previous CVD than with patients without the previous disease. There were no significant associations found between Lp(a) levels, overall mortality, or stroke.

A patient-level meta-analysis (2009) of 36 prospective studies published between 1970 and 2009 included 126,634participants.(67) Overall, the independent association between Lp(a) level and vascular disease was consistent across studies but modest in size. The combined RR, adjusted for age, sex, and traditional lipid risk factor, was 1.13 (95% CI, 1.09 to 1.18) for

CHD and 1.10 (95% CI, 1.02 to 1.18) for ischemic stroke. There was no association between Lp(a) levels and mortality.

Additional Randomized Controlled Trials
The Lipid Research Clinics Coronary Primary Prevention Trial (1994), one of the first large-scale RCTs of cholesterol-lowering therapy, measured initial Lp(a) levels and reported that Lp(a) was an independent risk factor for CAD when controlling for other lipid and non-lipid risk factors.(68)

The LIPID RCT (2013) randomized 7863 patients to pravastatin or placebo.(69) Patients were followed for a median of 6years. Lipoprotein (a) concentrations did not change significantly at 1 year. Baseline Lp(a) concentration was associated with total CHD events (p<.001), total CVD events (p=.002), and coronary events (p=.03).

Additional Observational Studies
As part of the Framingham Offspring Study, Lp(a) levels were measured in 2191 asymptomatic men between the ages of 20 and 54 years.(70) After a mean follow-up of 15 years, there were 129 CHD events, including MI, coronary insufficiency, angina, or sudden cardiac death. Comparing the Lp(a) levels of these patients with the other participants, the authors concluded that elevated Lp(a) was an independent risk factor for the development of premature CHD (ie, before age 55 years). The ARIC study (2001) evaluated the predictive ability of Lp(a) in 12,000 middle-aged subjects free of CAD at baseline who were followed for 10 years.(41) Lipoprotein (a) levels were significantly higher among patients who developed CAD than among those who did not, and Lp(a) levels were an independent predictor of CAD above traditional lipid measures.

In the ARIC prospective cohort study of 14,221 participants, elevated Lp(a) was a significant independent predictor of stroke in black women (RR, 1.84; 95% CI, 1.05 to 3.07) and white women (RR, 2.42; 95% CI, 1.30 to 4.53) but not in black men (RR, 1.72; 95% CI, 0.86 to 3.48) or white men (RR, 1.18; 95% CI, 0.47 to 2.90).(71)

Fogacci et al (2017) examined whether serum Lp(a) levels could predict long-term survival in 1215 adults with no CVD at enrollment and similar general cardiovascular risk profiles from Brisighella Heart Study cohort in Italy.(72) Subjects were stratified into a low (n=865), intermediate (n=275), and high (n=75) cardiovascular risk groups using an Italian-specific risk chart. Subjects at high and intermediate cardiovascular risk ages 56 to 69 years (regardless of sex) and women ages 40 to 55 years with a low cardiovascular risk profile who had lower Lp(a) levels showed statistically significant lower cardiovascular mortality (p<.05) and longer survival time (p<.05) during the 25-year follow-up. The authors constructed a receiver operating characteristic curve for each cardiovascular risk group using Lp(a) as a test variable and death as a state variable and identified serum Lp(a) as an independent long-term cardiovascular mortality prognostic indicator for subjects at high cardiovascular risk (AUC, 0.63; 95% CI, 0.50 to 0.76; p=.049) and for women at intermediate cardiovascular risk (AUC, 0.7; 95% CI, 0.52 to 0.79; p=.034).

Some studies, however, have failed to demonstrate such predictive ability. In the Physicians' Health Study (1993), initial Lp(a) levels in the 296 participants who subsequently experienced MI were compared with Lp(a) levels in matched controls who remained free from CAD.(73) Authors found that the distribution of Lp(a) levels between the groups was identical. The European Concerted Action on Thrombosis and Disabilities study (2000), a trial of secondary

prevention, evaluated Lp(a) as a risk factor for coronary events in 2800 patients with known angina pectoris.(74) In this study, Lp(a)levels did not differ significantly among patients who did and did not have subsequent events, suggesting that Lp(a) levels were not useful risk markers in this population.

Genetic studies have examined the association between various genetic loci and Lp(a) levels, and Mendelian randomization studies have examined whether Lp(a) level is likely to be causative for CAD. In a 2009 study, 3 separate loci were identified for increased Lp(a) levels.(75) Genetic variants identified at 2 of these loci that were independently associated with coronary disease (OR, 1.70; 95% CI, 1.49 to 1.95; OR, 1.92; 95% CI, 1.48 to 2.49). This finding strongly implies that elevated Lp(a) levels are causative of coronary disease, as opposed to simply being associated.

Lipoprotein(a) is recognized as a genetically determined, causal and prevalent risk factor for atherosclerotic cardiovascular disease. The American Heart Association performed an expert peer review of epidemiologic and genetic data in development of their scientific statement in 2022. Evidence revealed elevated levels of La(a) are prevalent in approximately 20% of the population. Observational and genetic data strongly supported an independent and causal relationship between high plasma concentrations of Lp(a) and increased risk of atherosclerotic cardiovascular disease-related events, such as myocardial infarction, stroke, and valvular stenosis. In the largest single study to date, a multiethnic population of 460,506 participants of the UK Biobank were examined. Concentrations of Lp(a) were variable across all racial subgroups and the associated risk were found to be similar. Awareness of the presence of elevated Lp(a) is important because it could inform clinical decision making. Presently the group states the evidence is in favor of performing targeted screening in selected individuals and to consider cascade screening when appropriate to identify those with high Lp(a). To lower overall ASCVD risk it is recommended to target LDL-C with statin and adjunctive medications as initial therapy.(135,136)

Section Summary: Lipoprotein (a)
A large amount of epidemiologic evidence has determined that Lp(a) is an independent risk factor for cardiovascular disease. The overall degree of risk associated with Lp(a) levels appears to be modest, and the degree of risk may be mediated by other factors such as LDL levels and/or hormonal status.

B-TYPE OR BRAIN NATRIURETIC PEPTIDE

Observational Studies
The use of B-type or brain natriuretic peptide (BNP) levels for monitoring and managing established heart failure patients has been frequently studied and has demonstrated value. Studies on the use of BNP for determining cardiovascular risk in the asymptomatic population, however, are limited. In the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research study, Shaw et al (2009) evaluated BNP and coronary artery calcium levels in 2458 asymptomatic adults.(76) Levels of BNP ranging from 40 to 99.9 and 100 pg/m or higher had a 2.2 to 7.5 relative hazard for a cardiovascular event compared to BNP levels of less than 40 pg/ml ($p<.001$). Other large population cohort studies have shown a relationship between elevations in BNP levels and future risks of cardiovascular events or heart failure. Wu et al (2022) assessed the value of cardiac troponins and amino terminal B type cardiac natriuretic peptide (NT-proBNP) in 2 different cohorts of asymptomatic patients (n=4102; n=2538).(137) Study investigators found that cardiac marker data correctly reclassified risk

upwards in 6.7% of patients and downwards in 3.3% of patients; the overall C statistic for discrimination of the primary endpoint (composite of all first CV events) increased from 0.755 to 0.771 (+0.016, p=.01).In a cohort study (N=5067), Melander et al found adding C-reactive protein and BNP to a risk model of conventional factors increased the C-statistic for cardiovascular events by 0.007 (p=.04) and for coronary events by 0.009 (p=.08).(77) In a cohort study of 3346 patients without heart failure, Wang et al found BNP levels above the 80th percentile (20.0 pg/mL for men, 23.3 pg/mL for women) were associated with multivariable-adjusted hazard ratios of 1.62 for death (p=.02), 1.76 for a first major coronary event, (p=.03), 1.91 for atrial fibrillation (p=.02), 1.99 for stroke or transient ischemic attack (p=.02), and 3.07 for heart failure (p=.002).(78) However, any gains over use of conventional risk factors appear to be minimal.

Section Summary: B-Type or Brain Natriuretic Peptide
Levels of BNP appear to be associated with cardiovascular risks. However, no evidence was identified demonstrating that the use of BNP testing in clinical care improves outcomes.

CYSTATIN C
Ito et al (2011) evaluated the value of adding cystatin C to Framingham Risk Score variables to predict cardiovascular disease risk in 6653 adults without CVD from the Multi-Ethnic Study of Atherosclerosis.(79) Cardiovascular risk prediction did not improve with the addition of cystatin C to Framingham Risk Score variables. Lee et al (2010) conducted a meta-analysis of 14 studies (N=22,509) with predominantly high-cardiovascular-risk patients to evaluate the relation between elevated cystatin C levels and CVD risk.(80) Higher levels of cystatin C were associated with greater risk of CVD (RR=2.62; 95% CI, 2.05 to 3.37; p<0.001), coronary heart disease (RR, 1.72; 95% CI, 1.27 to 2.34; p<.001), and stroke (RR, 1.83; 95% CI, 1.12 to 3.00; p=.02) after adjustment for known cardiovascular risk factors. Luo et al (2015) reported on a meta-analysis of studies evaluating the relation between cystatin C and cardiovascular and all-cause mortality in the general population.(81) Reviewers included 9 prospective studies (N=39,854). Across the 6 studies reporting cardiovascular mortality-specific outcomes, the pooled adjusted HR of cardiovascular mortality, comparing the highest and lowest cystatin C categories, was 2.74 (95% CI, 2.04 to 3.68, p=.021).

Section Summary: Cystatin C
Several meta-analyses have reported that higher levels of cystatin C are associated with higher cardiovascular risk and higher risk of cardiovascular death. In contrast, in a large cohort, cystatin C did not improve risk prediction of CVD. No evidence was identified demonstrating that the use of cystatin C testing in clinical care improves outcomes.

FIBRINOGEN

Systematic Reviews
Kengne et al (2013) evaluated data from 9 prospective, community-based cohorts from the British and Scottish general population-based health surveys.(82) In the analysis of 33,091 adults, 1006 of whom had diabetes, fibrinogen was positively associated with a higher risk of CVD by 34% (95% CI, 26% to 42%) and all-cause mortality by 30% (95% CI, 26% to 35%). The relation between cardiovascular mortality and higher fibrinogen produced HRs of 1.48 (95% CI, 1.21 to 1.81) in subjects with diabetes and 1.31 (95% CI, 1.23 to 1.39) in those without diabetes. The interaction between fibrinogen and CVD risk did not differ significantly between the diabetic and nondiabetic populations (p=.47). Despite improved predictive

accuracy, the addition of fibrinogen to established risk factors was reported to not be clinically important.

Willeit et al (2016) reported results of a patient-level meta-analysis from 20 prospective studies to assess the association between a number of inflammatory markers (including fibrinogen) and atherosclerosis among patients without preexisting CVD.(83) Selected were prospective cohort studies from the PROG-IMT collaboration, which included participants from the general population and reported at least 2 visits with measurements of common carotid artery intima-media thickness as a marker of preclinical atherosclerosis, along with at least 1 inflammatory marker (high-sensitivity-CRP, leukocyte count, and/or fibrinogen). Overall, reviewers included 20 studies (N=49,087), of which 13 studies (n=35,096) reported fibrinogen levels. In a cross-sectional analysis, a 1 SD higher baseline fibrinogen level was associated with common carotid artery intima-media thickness (mean, 0.0073 mm; 95% CI, 0.0047 to 0.0097; p<.001). However, in longitudinal analysis, neither the baseline level of any of the inflammatory markers evaluated nor their progression was associated with progression of common carotid artery intima-media thickness.

Observational Studies
Other studies have found an association between fibrinogen and cardiovascular risk including the EPIC-Norfolk cohort study (84) and the Fibrinogen Studies Collaboration.(85,86) In a report from the Fibrinogen Studies Collaboration, it was noted that fibrinogen levels increased with age and were linked to established risk factors such as triglycerides, smoking and body mass index.(86)

Section Summary: Fibrinogen
Reports from a number of cohort studies suggest that fibrinogen levels are associated with cardiovascular risk. However, no evidence was identified demonstrating that the use of fibrinogen testing in clinical care improves outcomes.

LEPTIN

Systematic Reviews
Sattar et al (2009) reported on a prospective study of 5661 men and a systematic review of 7 prospective studies to evaluate the relationship between leptin and CVD.(87) Leptin levels in the top third had an odds ratio for coronary heart disease of 1.25 (95% CI, 0.96 to 1.62) compared with the bottom third. After adjusting for body mass index (BMI), the odds decreased to 0.98 (95% CI, 0.72 to 1.34) suggesting an association of leptin with CVD disease is largely dependent on BMI.

Zeng et al (2014) conducted a meta-analysis of studies reporting the association between leptin levels and risk of CHD or stroke.(88) The meta-analysis included 8 nested case-control studies with 1980 patients and 11,567 controls. In a pooled analysis, leptin levels were significantly associated with pathogenic risk of CHD (OR, 1.90; 95% CI, 1.06 to 3.43; p=.032) and pathogenic risk of stroke (OR, 2.14; 95% CI, 1.48 to 3.08; p<.001).

Yang et al (2017) conducted a systematic review of case-control and cohort studies that assessed leptin concentration and CHD risk.(89) Thirteen epidemiologic studies totaling 4257 CVD patients and 26710 controls were included. Adjusting for cardiovascular risk factors, there was no statistically significant association between leptin concentration and CHD risk (OR, 1.16; 95% CI, 0.97 to 1.40). The association did not change when analyses were restricted to

high-quality studies (OR, 1.07; 95% CI, 0.96 to 1.19) for CHD. In a subgroup meta-analysis, a high leptin level was not independently associated with CHD in both females (OR, 1.03; 95% CI, 0.86 to 1.23) and male patients (OR, 1.09; 95% CI, 0.95 to 1.26).

Section Summary: Leptin
Two meta-analyses suggest that leptin levels are associated with CHD and stroke, although this association may depend on BMI. Another meta-analysis suggested no significant association between leptin concentration and CHD risk. No evidence was identified demonstrating that the use of leptin testing in clinical care improves outcomes.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Asymptomatic Individuals with Risk of Cardiovascular Disease
The evidence for asymptomatic individuals with risk of CVD who receive novel cardiac biomarker testing includes systematic reviews, meta-analyses, and large, prospective cohort studies. 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. Several biomarkers 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.

INDIVIDUALS WITH HYPERLIPIDEMIA MANAGED WITH LIPID-LOWERING THERAPY

Clinical Context and Test Purpose
The purpose of novel cardiac biomarker testing in individuals with hyperlipidemia managed with lipid-lowering therapy is to inform a decisions to proceed with appropriate treatment.

The question addressed in this evidence review is: Does novel cardiac biomarker testing improve the net health outcome in individuals with hyperlipidemia?

The following PICO was used to select literature to inform this review.

Patients
The relevant population of interest is individuals with hyperlipidemia managed with lipid-lowering therapy.

Interventions

The therapy being considered is novel cardiac biomarker testing.

Comparators
Comparators of interest include routine care without biomarker testing.

Outcomes
The general outcomes of interest are overall survival (OS), change in disease status, morbid events, and medication use.

Study Selection Criteria
Methodologically credible studies were selected using the principles described in the first indication.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

APOLIPOPROTEIN B

Systematic Reviews
A number of RCTs of statin therapy have examined the change in apo B on-treatment in relation to clinical CAD outcomes and assessed whether apo B predicted outcomes better than LDL-C.

Boekholdt et al (2012) published a patient-level meta-analysis of on-treatment levels of traditional and nontraditional lipids as a measure of residual risk.(90) Eight studies enrolling 62,154 participants were included. The aHR for each 1 SD increase in apo B was 1.14 (95% CI, 1.11 to 1.18), which did not differ significantly from LDL-C (aHR, 1.13; 95% CI, 1.10to 1.17; p=.21). The aHR for HDL-C was 1.16 (95% CI, 1.12 to 1.19), which was significantly greater than LDL-C or apo B (p=.002). In a subsequent report from this meta-analysis, Boekholdt et al (2014) evaluated the LDL-C, non-HDL-C, and apo B levels of 38,153 patients allocated to the statin therapy groups.(91) Despite statin therapy, reductions in levels of LDL-C, non-HDL-C, and apo B from baseline to 1 year showed large interindividual variations.

Randomized Controlled Trials
Ballantyne et al (2013) reported on a post hoc analysis of 682 patients with acute coronary syndrome from the randomized, phase 3 Limiting Undertreatment of Lipids in Acute coronary syndrome with Rosuvastatin trial.(92) The Limiting Undertreatment of Lipids in Acute coronary syndrome with Rosuvastatin subgroup analysis examined apo B in relation to LDL-C and non-HDL-C under intensive statin therapy with rosuvastatin or atorvastatin. The treatment target level for apo B of 80 mg/dL correlated with an LDL-C level of 90 mg/dL and a non-HDL-C level of 110 mg/dL at baseline and with an LDL-C of 74 mg/dL and a non-HDL-C of 92 mg/dL with statin therapy. Independent of triglyceride status, non-HDL-C was found to have a stronger correlation with apo B than with LDL-C and could be an adequate surrogate for apo B during statin therapy.

The AFCAPS/TexCAPS (2000) evaluated lipid parameters among 6605 men and women with average LDL-C and low HDL-C levels who were randomized to lovastatin or placebo.(22) Baseline LDL-C, HDL-C, and apo B levels were predictive of future coronary events. However, in the treatment group, post-treatment levels of LDL-C and HDL-C were not predictive of subsequent risk, while post-treatment apo B levels were.

In the Long-term Intervention with Pravastatin in Ischemic Disease trial (2002), the relation between on-treatment apo B levels and clinical outcomes was examined in 9140 patients randomized to pravastatin or placebo and followed for a mean of 6.1 years.(27) The aHR for apo B levels (2.10; 95% CI, 1.21 to 3.64, p=.008) was higher than that for LDL-C (1.20;95% CI, 1.00 to 1.45; p=.05). Also, the proportion of the treatment effect explained by on-treatment apo B levels (67%) was higher than that for LDL-C levels (52%).

Kastelein et al (2008) combined data from 2 RCTs, the Treating to New Targets (TNT) and Incremental Decrease in End Points through Aggressive Lipid Lowering trials, to compare the relation between response to lipids, apo B levels, and other lipid measures.(23)
The analysis included 18,889 patients with established coronary disease randomized to low- or high-dose statin treatment. In pairwise comparisons, the on-treatment apo B level was a significant predictor of cardiovascular events (HR=1.24; 95% CI, 1.13 to 1.36; p<.001), while LDL level was not. Similarly, the ratio of apo B/apo AI was a significant predictor of events (HR, 1.24; 95% CI, 1.17 to 1.32), while the TC/HDL-C ratio was not. In another publication that reported on the TNT study (2012), the on-treatment apo B level was also a significant predictor of future events (aHR, 1.19; 95% CI, 1.11 to 1.28).(28) In this study, the known baseline variables performed well in discriminating future cases from non-cases, and the addition of apo B was not associated with additional risk.

Mora et al (2012) measured on-treatment lipid levels to assess the prediction of residual risk while on statin therapy.(93) Using data from the JUPITER trial, on-treatment levels of LDL-C, non-HDL-C, high-sensitivity CRP, apo B, and apo AI were used to predict subsequent cardiovascular events. The HRs for cardiovascular events were similar among the lipid measures, ranging from 1.22 to 1.31, with no significant differences between them. The residual risk declined overall with a decreasing level of LDL-C, with the lowest risk seen in subjects achieving an LDL-C level of less than 70 mg/dL.

Section Summary: Apolipoprotein B
As a marker of response to cholesterol-lowering treatment, apo B may be more accurate than LDL-C and may provide a better measure of the adequacy of antilipid therapy than LDL-C. Post hoc analyses of RCTs of statin treatment have reported that on-treatment levels of apo B are more highly correlated with clinical outcomes than standard lipid measures.

APOLIPOPROTEIN AL

Randomized Controlled Trials
A number of studies have evaluated the utility of the apo B/apo AI ratio as a marker of treatment response in RCTs of statin treatment. For example, in the Kastelein et al (2008) study (described above), authors combined data from 2 RCTs, the TNT and Incremental Decrease in End Points Through Aggressive Lipid Lowering trials, to compare

the relation between response to lipids, apo B/apo AI ratio, and other lipid measures.(23) The apo B/apo AI ratio was a significant predictor of events (HR, 1.24; 95% CI, 1.17 to 1.32) while the TC/HDL-C was not.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in MI (PROVE-IT TIMI) study (2009) randomized 4162 patients with an acute coronary syndrome to standard statin therapy or intensive statin therapy.(94) While the on-treatment apo B/apo AI ratio was a significant predictor of cardiac events (HR for each SD increment, 1.10; 95% CI, 1.01 to 1.20) ; it was not superior to LDL-C (HR, 1.20; 95% CI, 1.07 to 1.35) or the TC/HDL ratio (HR, 1.12; 95%CI, 1.01 to 1.24) as a predictor of cardiac events.

Preliminary studies of infusions of reconstituted apo AI have demonstrated plaque regression in a small number of patients with acute coronary syndrome.(95) Based on this research, there has been interest in developing synthetic apo AI mimetic proteins, and such agents are in the drug development stage. These types of agents would likely target patients with residual cardiac risk following maximal statin therapy, especially patients with low HDL levels.

Section Summary: Apolipoprotein AI
The use of apo AI and the apo B/apo AI ratio as a target of treatment response to statins may also be as good as or better than the traditional measure of LDL. However, to improve outcomes, clinicians must have the tools to translate this information into clinical practice. Such tools for linking apo AI to clinical decision making, both in risk assessment and treatment response, are currently not available. Apolipoprotein AI has not been incorporated into quantitative risk assessment models or treatment guidelines that can be used in clinical practice (eg, the ATP III).(1) The ATP III practice guidelines continue to tie clinical decision making to conventional lipid measures, such as TC, LDL-C, and HDL-C. Therefore, it is not yet possible to conclude that these measures improve outcomes or that they should be adopted in routine clinical care. There is continued interest in developing new therapeutic agents that raise HDL, and apo AI mimetics are currently in development for this purpose.

APOLIPOPROTEIN E

Randomized Controlled Trials
Apolipoprotein E has been investigated as a predictor of response to therapy by examining apo E alleles in the intervention arm(s) of lipid-lowering trials. Some data have suggested that patients with an apo e4 allele may respond better to diet-modification strategies.(96,97) Other studies have suggested that response to statin therapy may vary by *APOE* genotype and that the e2 allele indicates greater responsiveness to statins.(96,98)

Chiodini et al (2007) examined differential response to statin therapy by *APOE* genotype in a reanalysis of data from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto-Prevenzione (GISSI-P) study.(99) The GISSI-P was an RCT comparing pravastatin with placebo in 3304 Italian patients with previous MI. Patients with the apo e4 allele treated with statins had a greater response to treatment as evidenced by lower overall mortality (1.85% vs 5.28%, respectively, p=.023), while there was no difference in mortality for patients who were not treated with statins (2.81% vs 3.67%, respectively, p=d.21). This study corroborated results reported in previous studies but did not provide evidence to suggest that changes in treatment should be made as a result of *APOE* genotype.

Observational Studies

Other studies have evaluated *APOE* genetic status as a predictor of response to lipid-lowering therapy. Donnelly et al (2008) reported on 1383 patients treated with statins from the Genetics of Diabetes Audit and Research in Tayside, Scotland (Go-DARTS) database.(100) Researchers reported on final LDL levels and percentages of patients achieving target LDL by *APOE* genetic status. LDL levels following treatment were lower for patients who were homozygous for apo e2 (0.6 mmol/L), than for patients homozygous for apo e4 (1.7 mmol/L, p<.001). All patients who were homozygous for apo e2 reached their target LDL level, compared to 68% of patients homozygous for apo e4 (p<.001).

Vossen et al (2008) evaluated response to diet and statin therapy by apo E status in 981 patients with CAD who were enrolled in a cardiac rehabilitation program.(101) They reported that patients with an apo e4 allele were more responsive to both diet and statin therapy than were patients with an apo e2 allele. The overall response to treatment was more dependent on baseline LDL levels than *APOE* genetic status, with 30% to 47% of the variation in response to treatment explained by baseline LDL, compared with only 1% of the variation explained by *APOE* status.

Section Summary: Apolipoprotein E
The evidence on response to treatment indicates that *APOE* genotype may be a predictor of response to statins and may allow clinicians to better gauge a patient's chance of successful treatment, although not all studies have consistently reported this relation. At present, it is unclear how this type of information would change clinical management. Dietary modifications are a universal recommendation for those with elevated cholesterol or LDL levels, and statin drugs are the overwhelmingly preferred agents for lipid-lowering therapy. It is unlikely that a clinician would choose alternative therapies, even in the presence of an *APOE* phenotype that indicates diminished response.

None of the available evidence has provided adequate data to establish that *APOE* genotype or phenotype improves outcomes when used in clinical care.

LOW-DENSITY LIPOPROTEIN SUBCLASS AND LOW-DENSITY LIPOPROTEIN PARTICLE SIZE AND CONCENTRATION

Patients with subclass pattern B have been reported to respond more favorably to diet therapy than those with subclass pattern A.(102) Subclass pattern B has also been shown to respond more favorably to gemfibrozil and niacin, with a shift from small, dense LDL particles to larger LDL particles. While statin drugs lower the overall concentration of LDL cholesterol, there is no shift to the larger LDL particles.

Randomized and Nonrandomized Controlled Trials
Superko et al (2005) reported that the response to gemfibrozil differed in patients who had LDL subclass A compared to those who had LDL subclass B.(103) There was a greater reduction in the small, LDL levels for patients with subclass B, but this did not correlated with clinical outcomes. Another study reported that atorvastatin treatment led to an increase in mean LDL size, while pravastatin treatment led to a decrease in LDL size.(104)

Various studies have generally confirmed that small, dense LDL is impacted preferentially by fibrate treatment (105,106,107) and possibly also by statin therapy.(105,107) However, none demonstrated that preferentially targeting small, dense LDL leads to improved outcomes, compared with standard LDL targets widely used in clinical care.

Several trials with angiographic outcomes have examined the change in LDL particle size in relation to angiographic progression of CAD. The 1996 Stanford Coronary Risk Intervention Project trial studied the relation between small, dense LDL and the benefit of diet, counseling, and drug therapy in patients with CAD, as identified by initial coronary angiogram.(108) Patients with subclass pattern B showed a significantly greater reduction in CAD progression than those with subclass pattern A. The 1990 Familial Atherosclerosis Treatment Study randomized patients from families with premature CAD and elevated apo B levels.(109) Change in LDL particle size correlated significantly with angiographic progression of CAD in this study.

Fewer studies have evaluated clinical outcomes in relation to LDL particle size. In the 2001Cholesterol and Recurrent Events trial, survivors of MI with normal cholesterol levels were randomized to lipid-lowering therapy or placebo.(110) A post hoc analysis from this trial failed to demonstrate a correlation between change in particle size and treatment benefit.

Section Summary: Low-Density Lipoprotein Subclass and Low-Density Lipoprotein Particle Size and Concentration
The direct clinical application of measuring small, dense lipoprotein particles is still unclear. To improve outcomes, clinicians must have tools to translate this information into clinical practice. Such tools for linking levels of small, dense LDL to clinical decision making are currently not available. Published data are inadequate to determine how such measurements should guide treatment decisions and whether these treatment decisions result in beneficial patient outcomes.

LIPOPROTEIN (A)
There is a lack of evidence to determine whether Lp(a) can be used as a target of treatment. Several randomized studies of lipid lowering therapy have included Lp(a) measurements as an intermediate outcome. While these studies have demonstrated that Lp(a) levels are reduced in patients receiving statin therapy, the data are inadequate to demonstrate how this laboratory test can be used to improve patient management.(111,112)

Section Summary: Lipoprotein (a)
There is limited evidence on the use of Lp(a) as a treatment target for patients with hyperlipidemia. The available evidence is insufficient related to impact on clinical outcomes.

HIGH SENSITIVITY C-REACTIVE PROTEIN (HS-CRP)
The following organizations have statements and/or guidelines in support of hs-CRP testing for individuals with increased risk factors for CVD:

- American College of Cardiology
- American Heart Association
- American Association of Clinical Endocrinologists
- National Lipid Association
- Centers for Disease Control and Prevention
- Canadian Cardiovascular Society
- European Society of Cardiology

High sensitivity C-reactive protein (hs-CRP) as a Predictor of Cardiovascular Disease
The most recent guidelines from the American College of Cardiology /American Heart Association (ACC/AHA) for the assessment of cardiovascular risk state “after quantitative risk

assessment, a risk-based treatment decision is uncertain, assessment of 1 or more of the following— family history, hs-CRP, CAC score, or ABI—may be considered to inform treatment decision making." The level of evidence is rated a "B", indicating a moderate recommendation in which certainty is based on evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate.(113)

A Writing Group convened by the AHA and the Centers for Disease Control and Prevention (2003) endorsed the optional use of hs-CRP to identify persons without known cardiovascular disease who are at intermediate risk (10 to 20% risk of coronary heart disease over the next 10 years). For these patients, the results of hs-CRP testing may help guide considerations of further evaluation (e.g. imaging, exercise testing) or therapy (e.g., drug therapies with lipid-lowering, anti-platelet, or cardio-protective agents). High-sensitivity CRP testing is not necessary in high-risk patients who have a 10-year risk of greater than 20%, as these patients already qualify for intensive medical interventions. Individuals at low-risk (less than 10% per 10 years) will be unlikely to have a high-risk (greater than 20%) identified through hs-CRP testing. The Writing group recommended screening average risk (10-year risk less than 10 %) for hs-CRP for purposes of cardiovascular risk assessment.(114)

Additionally, the Writing Group recommended that hs-CRP be performed twice, optimally 2 weeks apart, fasting or non-fasting in metabolically stable patients. Patients with an average hs-CRP level greater than 3.0 mg/dL are considered to be at high relative risk of CHD. Patients with an average hs-CRP level less than 1 mg/L are at low relative risk, and patients with an hs-CRP level between 1.0 and 3.0 mg/L are at average relative risk. If hs-CRP level is greater than 10 mg/dL, the Writing Group recommended that testing should be repeated and the patient examined for sources of infections or inflammation. The Writing group recommended against the measurement of inflammatory markers other than hs-CRP (cytokines, other acute-phase reactants) for determination of coronary risk in addition to hs-CRP.

The AHA/CDC Writing Group Statement Summary:

- hsCRP is a global indicator of future vascular events in adults without any previous history of cardiovascular disease (CVD), with acceptable precision levels down to or below 0.3 mg/L
- hsCRP enhances risk assessment and therapeutic outcomes in primary CVD prevention
- hsCRP is particularly advantageous for assessing the risk in patients with:
    - Framingham 10-year risk scores of 10%-20% and/or
    - LDL levels of <160 mg/dL
- hsCRP acts as an independent marker for evaluating the possibility of recurrent cardiac events, such as myocardial infarction or restenosis, after percutaneous coronary intervention

The National Lipid Association convened a panel of clinical experts to evaluate the use of selected biomarkers in clinical practice as either tools to improve risk assessment or as markers to adjust therapy once a decision to treat had been made.(10) The summary of recommendations is as follows:

CRP: Initial Clinical Assessment

1. In patients with low risk (10-year CHD event risk < 5% on the basis of Framingham scoring), CRP measurement is not recommended for routine use but may be of value in

selected patients, particularly those who have multiple mild disturbances, including those with the metabolic syndrome (rating: ‘‘not recommended’’).
2. In patients with intermediate risk (5%–20% 10-year risk), it is recommended that CRP be measured routinely in men > 50 years of age and women > 60 years of age given its capacity to enhance risk prediction, especially when used with Reynolds risk scoring (rating: ‘‘recommended for routine measurement’’).
3. In certain patients with CHD and risk equivalents, CRP measurement may be considered (rating: ‘‘consider for selected patients’’).
4. In patients with a premature family history of CHD or in patients with established CHD with a history of recurrent events despite appropriate therapy, CRP measurement is a reasonable option to help determine if therapy should be: (1) started in the case of premature family history; or (2) intensified, or effort be made to identify other ancillary risk factors that may be impacting the progression or stability of established atherosclerotic plaque (rating: ‘‘reasonable for many patients’’).

CRP: On-Treatment Management Decisions

1. Among patients on treatment, there is insufficient evidence to support CRP measurement in patients with low risk and it is not recommended (rating: ‘‘not recommended’’).
2. In patients with intermediate risk, CHD (or a CHD risk equivalent), or a history of recurrent coronary events, CRP measurement is reasonable and can help to guide the intensity of therapy (rating: ‘‘reasonable for many patients’’).
3. Among patients with family history of premature CHD, CRP measurement can be considered and may have value, but its clinical utility in guiding therapy in this setting is less certain pending further investigation (rating: ‘‘consider for selected patients’’).

Buckley et al (2009) conducted a systematic review and meta-analyses of epidemiologic studies to help the U.S. Preventive Services Task Force (USPSTF) determine whether CRP level should be incorporated into guidelines for coronary and cardiovascular risk assessment in primary care. It was concluded that there is strong evidence that CRP has predictive value for cardiovascular events independent of other risk factors and that moderate evidence suggests that may improve risk stratification for those at intermediate risk.(115)

High sensitivity CRP has been added to the European Society of Cardiology’s guidelines for risk stratification of patients with acute coronary syndrome (2011). The guidelines state “There is solid evidence that even among patients with troponin-negative NSTE-ACS, elevated levels of hsCRP (>10 mg/L) are predictive of long-term mortality (>6 months up to 4 years). The FRISC study confirmed that elevated hsCRP levels are associated with increased mortality at the time of the index event and continuously increase over 4 years.”(116)

Cook et al (2006) compared risk-prediction models that include or do not include hs-CRP. The models were applied to 15,048 Women’s Health Study participants who were age 45 or older and free of cardiovascular disease and cancer at baseline. During a mean follow-up of 10 years, 390 women developed CVD. For accurately predicting CVD events, hs-CRP was out-matched only by older age, current smoking, and high blood pressure among traditional Framingham variables. Non-diabetic women were classified according to their 10-year risk for CVD in a model without CRP. Adding CRP to the model substantially improved predictive

accuracy for women with an initial 10-year CVD risk of at least 5%. The gain in accuracy was greatest among women who were initially classified in the 5% to 9.9% risk range: 21.3 % of those women were reclassified in a more accurate risk category when CRP was included in the risk prediction model (11.9% moved down a risk category (to less than 5 %) and 9.5 % moved up a risk category (to 10 % to 19.9%)). Accounting for the predictive value of older age, smoking, and high BP lessened the predictive contribution of CRP but still left CRP ahead of any cholesterol parameter (total, LDL, or HDL).(117)

Evidence from the JUPITER trial (2009) suggests that, for people choosing to start statin therapy, reduction in both LDL cholesterol and hs-CRP are indicators of successful treatment with statins. In an analysis of 15,548 initially healthy men and women participating in the JUPITER trial (87 % of full cohort), investigators prospectively assessed the effects of rosuvastatin versus placebo on rates of non-fatal myocardial infarction, non-fatal stroke, admission for unstable angina, arterial revascularization, or cardiovascular death during a maximum follow-up of 5 years (median of 1.9 years). Compared with placebo, participants allocated to rosuvastatin who achieved LDL cholesterol less than 1.8 mmol/L had a 55 % reduction in vascular events, and those achieving hs-CRP less than 2 mg/L a 62 % reduction. Although LDL cholesterol and hs-CRP reductions were only weakly correlated in individual patients (r values < 0.15), the investigators reported a 65 % reduction in vascular events in participants allocated to rosuvastatin who achieved both LDL cholesterol less than 1.8 mmol/L and hs-CRP less than 2 mg/L, versus a 33 % reduction in those who achieved 1 or neither target. In participants who achieved LDL cholesterol less than 1.8 mmol/L and hs-CRP less than 1 mg/L, the investigators found a 79 % reduction. The investigators reported that achieved hs-CRP concentrations were predictive of event rates irrespective of the lipid endpoint used, including the apolipoprotein B to apolipoprotein AI ratio.(118)

A meta-analysis found that hs-CRP concentration has continuous associations with the risk of coronary heart disease, ischemic stroke, and vascular mortality (Emerging Risk Factors Collaboration, 2010). Investigators assessed the associations of hs-CRP concentration with risk of vascular and non-vascular outcomes under different circumstances. Investigators meta-analyzed individual records of 160,309 people without a history of vascular disease from 54 long-term prospective studies. Within-study regression analyses were adjusted for within-person variation in risk factor levels. The investigators found that log(e) hs-CRP concentration was linearly associated with several conventional risk factors and inflammatory markers, and nearly log-linearly with the risk of ischemic vascular disease and non-vascular mortality. Risk ratios (RRs) for coronary heart disease per 1 standard deviation higher log(e) hs-CRP concentration (3 -fold higher) were 1.63 (95 % confidence interval (CI): 1.51 to 1.76) when initially adjusted for age and sex only, and 1.37 (1.27 to 1.48) when adjusted further for conventional risk factors; 1.44 (1.32 to 1.57) and 1.27 (1.15 to 1.40) for ischemic stroke; 1.71 (1.53 to 1.91) and 1.55 (1.37 to 1.76) for vascular mortality; and 1.55 (1.41 to 1.69) and 1.54 (1.40 to 1.68) for non-vascular mortality. The investigators noted that RRs were largely unchanged after exclusion of smokers or initial follow-up. After further adjustment for fibrinogen, the corresponding RRs were 1.23 (1.07 to 1.42) for coronary heart disease; 1.32 (1.18 to 1.49) for ischemic stroke; 1.34 (1.18 to 1.52) for vascular mortality; and 1.34 (1.20 to 1.50) for non-vascular mortality. The investigators concluded that hs-CRP concentration has continuous associations with the risk of coronary heart disease, ischemic stroke, vascular mortality, and death from several cancers and lung disease that are each of broadly similar size. The investigators noted that the relevance of hs-CRP to such a range of disorders is unclear. The investigators found that associations with ischemic vascular disease depend considerably on conventional risk factors and other markers of inflammation.(119)

The 2009 Guidelines from the Canadian Cardiovascular Society state the measurement of hs-CRP is recommended in men older than 50 years and women older than 60 years of age who are at intermediate risk (10% to 19%) according to their Framingham risk score and who do not otherwise qualify for lipid-lowering therapy (i.e., if their LDL-C is less than 3.5 mmol/L). The guidelines explain that the rationale for measuring hs-CRP specifically in these individuals is that there is now class I evidence for the benefit of statin therapy in such individuals with hs-CRP greater than 2.0 mg/L. The guidelines found that data from the JUPITER study show that statin therapy reduces cardiovascular events (hazard ratio 0.56 [95% CI 0.46 to 0.69]; P<0.00001). The guidelines note that because hs-CRP can be elevated during acute illness, clinical judgment should be exercised in the interpretation of any single measurement of hs-CRP. The 2012 Canadian Cardiovascular Society guidelines state that those individuals who meet JUPITER criteria (men > than 50 years and women > than 60 years of age and CRP greater than or equal to 2 mg/L and LDL greater than 3.5 mmol/L) could be considered for treatment based on the results of that study.(120)

An American Heart Association (AHA) statement on nontraditional risk factors and biomarkers in cardiovascular disease in youth states:(121) "There currently is no clinical role for measuring CRP routinely in children when assessing or considering therapy for CVD risk factors." The AHA statement explains that, although numerous studies suggest that CRP is elevated in children with higher CVD risk, correlates with the progression of atherosclerotic changes, and tracks, albeit weakly, over 21 years from childhood to adulthood independently of other metabolic and conventional cardiovascular risk factors, it is not yet clear whether high CRP levels during childhood and adolescence lead to an increased risk of CVD in later life. The AHA stated that lifestyle interventions have been shown to decrease CRP in children, and statins reduce CRP in adults. "However, minimal information is available on the effect of statins on CRP in children and youth and, importantly whether lowering CRP in children per se would modify preclinical disease or CVD outcomes."

The American Association of Clinical Endocrinologists (AACE) (2012) issued a 2b recommendation for the use of hs-CRP to stratify CVD risk in patients with a standard risk assessment that is borderline, or in those with an LDL-C concentration less than 130 mg/dL.(122)

Section Summary: hs-CRP
Several studies have shown that hs-CRP adds to the predictive capability of other established risk factors for CVD. The best evidence to date supports hs-CRP as an independent factor in predicting increased CVD risk. Although evidence for benefit or harm is not decidedly conclusive (Quality of Evidence IIb, Level C) for using hs-CRP as a marker in all patient groups as part of a global risk assessment, the AHA/CDC Writing Group endorses (at Evidence Level B) the use of hs-CRP as an adjunct to the major risk factors to assess and identify patients who may be at higher risk for CVD than estimated by major risk factors.

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

For individuals with hyperlipidemia managed with lipid-lowering therapy who receive novel cardiac biomarker testing (eg, apo B, apo AI, apo E, apo E, HDL subclass, LDL subclass, Lp[a], BNP, cystatin C, fibrinogen, leptin), the evidence includes analyses of the intervention arm(s) of lipid-lowering medication trials. Relevant outcomes are overall survival, 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 RCTs has suggested that these markers are associated with treatment success. There is evidence that some of these markers may provide increment accuracy in risk prediction, specifically, apo B, hs-CRP, Lp(a), and genes *LDLR, APOB, PCSK9* and ARH receptor protein.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Heart, Lung, and Blood Institute

In 2001, the National Heart, Lung, and Blood Institute’s National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) issued a position statement.(1) Apo lipoprotein B (apo B), apolipoprotein AI (apo AI), lipid subclass, and lipoprotein(a) (Lp[a]) were listed as “emerging risk factors” for cardiovascular risk assessment, without specific recommendations for how these measures should be used in clinical practice. A 2004 update to these guidelines discussed the result of clinical trials of statin therapy.(123)

In 2013, the Institute published a systematic evidence review on managing blood cholesterol in adults.(124) The review was used to develop joint guidelines by the American College of Cardiology (ACC) and American Heart Association (AHA) on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults (see below).(125)

American College of Cardiology and American Heart Association

In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) published guidelines for the assessment of cardiovascular risk.(125) Pooled cohort equations for estimating arteriosclerotic cardiovascular disease (ASCVD) were developed from sex- and race-specific proportional hazards models that included covariates of age, treated or untreated systolic blood pressure level, total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels, current smoking status, and history of diabetes. Additional risk factors evaluated included diastolic blood pressure, family history of ASCVD, moderate or severe chronic kidney disease, and body mass index. None of the variables significantly improved discrimination for

10-year hard ASCVD risk prediction. The ACC and AHA recommended that further research using state-of-the-art statistical techniques (including net reclassification improvement and integrative discrimination index) examine the utility of novel biomarkers when added to these new pooled cohort equations in different populations and patient subgroups. The guidelines stated that future updates might include guidance on whether on-treatment markers such as apo B, Lp(a), or low-density lipoprotein (LDL) particles are useful for guiding treatment decisions.

The ACC/AHA (2019) guidelines on primary prevention of cardiovascular disease include information on appropriateness of Lp(a) level measurement stating, “a relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a).”(126) The Guidelines also include recommendations for apo B measurement stating, “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.”

American Diabetes Association and American College of Cardiology Foundation
In 2008, a consensus statement from the American Diabetes Association and the ACC Foundation addressed lipoprotein management in patients with cardiometabolic risk.(127) The statement included specific recommendations for incorporating apo B testing into clinical care for high-risk patients and recommended that, for patients with metabolic syndrome being treated with statins, both LDL-C and apo B should be used as treatment targets, with an apo B target of less than 90 mg/dL, even if target LDL has been achieved.

This consensus statement also commented on the use of LDL particle number in patients with cardiometabolic risk and on the limitations of the clinical utility of nuclear magnetic resonance measurement of LDL particle number or size, including lack of widespread availability. it also mentioned that there is a need for more independent data confirming the accuracy of the method and whether its predictive power is consistent across various patient populations.

The American Diabetes Association 2022 Standards of Care do not discuss the use of specific novel biomarkers for cardiovascular disease and risk management.(128)

American Association of Clinical Endocrinologists and American College of Endocrinology
In 2017, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) published joint guidelines on the management of dyslipidemia and the prevention of cardiovascular diseases.(129) The guidelines recommended that, among patients with “triglyceride (TG) concentration of greater than 150 mg/dL or HDL-C concentration of less than 40 mg/dL, the apo B or the apo B to apo AI ratio may be useful in assessing residual risk in individuals at risk for ASCVD (even when the LDL-C levels are controlled).”

In 2020, the AACE published an updated consensus statement on dyslipidemia and prevention of cardiovascular disease.(130) They recommended measurement of Lp(a) in several patient populations including those with ASCVD, those with a family history of premature ASCVD and/or increased Lp(a), and individuals with a 10-year ASCVD risk of 10% or greater. Recommendations also included consideration of apo B or LDL particle measurement "based on individual patient clinical circumstances."

National Lipid Association
In 2019, the National Lipid Association issued a scientific statement on the use of Lp(a), which notes that Lp(a) measurement "is reasonable" to refine risk assessment for ASCVD events in the following populations: patients with first-degree relatives with premature ASCVD (<55 years of age for men; <65 years of age for women), patients with premature ASCVD without traditional risk factors, patients with severe hypercholesterolemia (LDL-C ≥190 mg/dL) or familial hypercholesterolemia, and patients with very-high risk of ASCVD that may be candidates for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy.(131) Additionally Lp(a) "may be reasonable" to measure in patients with the following: intermediate (7.5 to 19.9%) or borderline (5 to 7.4%) ASCVD risk when statin initiation is uncertain for primary prevention, inadequate response to LDL-C lowering therapy despite adherence, family history of elevated Lp(a), calcific valvular aortic stenosis, or recurrent or progressive ASCVD despite lipid-lowering therapy.

In 2021, the National Lipid Association issued a scientific statement on lipid measurements in cardiovascular disease including information on apo B, small dense LDL, and Lp(a).(132) The authors refer to the 2019 statement for information on Lp(a), and they recommend that measurements of apo B and small dense LDL "may be reasonable at initial evaluation." Additionally, apo B measurement "is reasonable" for patients receiving lipid lowering therapy while small dense LDL measurement is "not recommended" for these patients.

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
The U.S. Preventive Services Task Force (2009) issued recommendations on the use of nontraditional risk factors for the assessment of coronary heart disease (CHD).(133) The Task Force included lipoprotein (a) in its summary statement: “The evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors discussed in this statement to screen asymptomatic men and women with no history of CHD to prevent CHD events.”

The recommendation was updated in 2018 and came to the same conclusion: evidence is insufficient to assess the benefits and harms of novel testing methods to diagnose CVD. However, the nontraditional risk factors included in this recommendation were different than those in this evidence review.(134)

Government Regulations
National:
No NCD specifically addresses novel biomarkers for cardiovascular disease.

National Coverage Determination (NCD) for Lipid Testing (190.23), Effective Date of this Version 1/1/05, Implementation Date 3/11/05
Indications and Limitations of Coverage
The medical community recognizes lipid testing as appropriate for evaluating atherosclerotic cardiovascular disease. Conditions in which lipid testing may be indicated include:
- Assessment of patients with atherosclerotic cardiovascular disease.
- Evaluation of primary dyslipidemia.
- Any form of atherosclerotic disease, or any disease leading to the formation of atherosclerotic disease.
- Diagnostic evaluation of diseases associated with altered lipid metabolism, such as: nephrotic syndrome, pancreatitis, hepatic disease, and hypo and hyperthyroidism.

- Secondary dyslipidemia, including diabetes mellitus, disorders of gastrointestinal absorption, chronic renal failure.
- Signs or symptoms of dyslipidemias, such as skin lesions.
- As follow-up to the initial screen for coronary heart disease (total cholesterol + HDL cholesterol) when total cholesterol is determined to be high (>240 mg/dL), or borderline-high (200-240 mg/dL) plus two or more coronary heart disease risk factors, or an HDL cholesterol, <35 mg/dl.

To monitor the progress of patients on anti-lipid dietary management and pharmacologic therapy for the treatment of elevated blood lipid disorders, total cholesterol, HDL cholesterol and LDL cholesterol may be used. Triglycerides may be obtained if this lipid fraction is also elevated or if the patient is put on drugs (for example, thiazide diuretics, beta blockers, estrogens, glucocorticoids, and tamoxifen) which may raise the triglyceride level.
When monitoring long term anti-lipid dietary or pharmacologic therapy and when following patients with borderline high total or LDL cholesterol levels, it may be reasonable to perform the lipid panel annually. A lipid panel at a yearly interval will usually be adequate while measurement of the serum total cholesterol or a measured LDL should suffice for interim visits if the patient does not have hypertriglyceridemia.

When monitoring long term anti-lipid dietary or pharmacologic therapy and when following patients with borderline high total or LDL cholesterol levels, it may be reasonable to perform the lipid panel annually. A lipid panel at a yearly interval will usually be adequate while measurement of the serum total cholesterol or a measured LDL should suffice for interim visits if the patient does not have hyper-triglyceridemia.

Any one component of the panel or a measured LDL may be reasonable and necessary up to six times the first year for monitoring dietary or pharmacologic therapy. More frequent total cholesterol HDL cholesterol, LDL cholesterol and triglyceride testing may be indicated for marked elevations or for changes to anti-lipid therapy due to inadequate initial patient response to dietary or pharmacologic therapy. The LDL cholesterol or total cholesterol may be measured three times yearly after treatment goals have been achieved.

Electrophoretic or other quantitation of lipoproteins may be indicated if the patient has a primary disorder of lipoid metabolism.

Effective January 1, 2005, the Medicare law expanded coverage to cardiovascular screening services. Several of the procedures included in this NCD may be covered for screening purposes subject to specified frequencies. See 42 CFR 410.17 and section 100, chapter 18, of the Claims Processing Manual, for a full description of this benefit.

Limitations
Lipid panel and hepatic panel testing may be used for patients with severe psoriasis which has not responded to conventional therapy and for which the retinoid etretinate has been prescribed and who have developed hyperlipidemia or hepatic toxicity. Specific examples include erythrodermia and generalized pustular type and psoriasis associated with arthritis.

Routine screening and prophylactic testing for lipid disorder are not covered by Medicare. While lipid screening may be medically appropriate, Medicare by statute does not pay for it.

Lipid testing in asymptomatic individuals is considered to be screening regardless of the presence of other risk factors such as family history, tobacco use, etc.
Once a diagnosis is established, one or several specific tests are usually adequate for monitoring the course of the disease. Less specific diagnoses (for example, other chest pain) alone do not support medical necessity of these tests.

When monitoring long term anti-lipid dietary or pharmacologic therapy and when following patients with borderline high total or LDL cholesterol levels, it is reasonable to perform the lipid panel annually. A lipid panel at a yearly interval will usually be adequate while measurement of the serum total cholesterol or a measured LDL should suffice for interim visits if the patient does not have hypertriglyceridemia.
Any one component of the panel or a measured LDL may be medically necessary up to six times the first year for monitoring dietary or pharmacologic therapy. More frequent total cholesterol HDL cholesterol, LDL cholesterol and triglyceride testing may be indicated for marked elevations or for changes to anti-lipid therapy due to inadequate initial patient response to dietary or pharmacologic therapy. The LDL cholesterol or total cholesterol may be measured three times yearly after treatment goals have been achieved.

If no dietary or pharmacological therapy is advised, monitoring is not necessary.
When evaluating non-specific chronic abnormalities of the liver (for example, elevations of transaminase, alkaline phosphatase, abnormal imaging studies, etc.), a lipid panel would generally not be indicated more than twice per year.

Local:

Wisconsin Physician Services Local Coverage Determination
LCD Title: Modi: Biomarkers in Cardiovascular Risk Assessment (L36523)
Effective Date: For services performed on or after 03/30/2023

Under preventative services, Medicare Part B covers the basic lipid panel (total cholesterol, high density lipoprotein-cholesterol (HDL-C), triglycerides, and low density lipoprotein-cholesterol (LDL-C) for cardiovascular (CV) disease screening, every 5 years when ordered by a doctor.

NCD 190.23 covers lipid panel testing for symptomatic patients for evaluating atherosclerotic CV disease, to monitor the progress of patients on anti-lipid dietary management and pharmacologic therapy for various lipid disorders.

This policy denies coverage for all CV risk assessment panels, except the basic lipid panel, for symptomatic (with signs and symptoms) patients with suspected or documented CV disease because panel testing is not specific to a given patient’s lipid abnormality or disease. The policy indicates the medical indication(s) based on published scientific articles and consensus guidelines for individual lipid biomarkers that may be covered to characterize a given lipid abnormality or disease, to determine a treatment plan or to assist with intensification of therapy. Each individual lipid biomarkers must be specifically ordered and the reason for the test order documented in the patient’s medical record. The policy denies coverage for all non-lipid biomarkers when used for CV risk assessment including but not limited to, biochemical, immunologic, hematologic, and genetic biomarkers for CV risk assessment regardless of whether ordered in a panel or individually.

The following biomarkers, when they are included in a CV risk assessment panel, are non-covered:

- Lipoprotein subclasses;
- LDL particles;
- Intermediate density lipoproteins;
- High density lipoprotein AI9LpAI and AI/AII;
- Lipoprotein(a);
- Apolipoprotein B (Apo B), apo A-I and apo E;
- Lipoprotein-associated phospholipase A2 (Lp-PLA2)
- BNP
- Cystatin C
- Thrombogenic/hematologic actors
- Interleukin-6 (IL-6), tissue necrosis factor- a (TNF- a), plasminogen activator inhibitor-1 (PAI-1) and IL-6 promoter polymorphism
- Free fatty acids
- Vastatin, angiotensin-converting enzyme 1 (ACE2) and serum amyloid A
- Microalbumin
- Myeloperoxidase (MPO)
- Homocysteine and methylenetetrahydrofolate reductase (MTHFR) mutation testing
- Uric acid
- Vitamin D
- White blood cell count
- Long-chain omega-3 fatty acids in red blood cell membranes
- Gamma-glutamyltransferase (GGT)
- Genomic profiling including CardiaRisk angiotensin gene
- Leptin, ghrelin, adiponectin and adipokines including retinol binding protein 4 (RBP4) and resistin
- Inflammatory markers including VCAM-1, P-selectin (PSEL) and E-selectin (ESEL)
- Cardiovascular risk panels

Note #1: There is no Medicare benefit for screening CV risk assessment testing for asymptomatic (without signs or symptoms of disease) patients. Screening asymptomatic patients for cardiovascular risk is statutorily excluded by Medicare and will not be addressed in this policy.

Note #2: FDA approval/clearance means that a test/assay has analytical and clinical validity. The FDA does not review clinical utility (that the test/assay demonstrates improved patient outcomes). To meet Medicare's "reasonable and necessary" criteria for coverage, a test/assay must have proven clinical utility.

High-sensitivity C-reactive protein (hs-CRP)

In summary, this contractor expects testing to be limited to the following criteria:

1. Patient has intermediate CV risk (10-20% risk of CVD per 10 years using the Framingham point score);and
2. Patient has LDL-C between 100-130 mg/dL; and
3. Patient has two or more CHD major risk factors, including
    - Age (Men > 50 years; Women > 60 years)
    - Current cigarette smoking
    - Family history of premature CHD (CHD in male first degree relative <55; CHD in female fist degree relative <65 years of age)

- Hypertension (Systolic > 140 mm Hg, or on anti-hypertensive medication)
- Low HDL-C (<40 mg/dL)

The use of hs-CRP testing to evaluate the effects of treatment or to motivate patients to improve lifestyle behaviors are not considered medically reasonable and necessary, and therefore not covered by Medicare.

There are fees found on the 2023 3rd Quarter CMS Clinical Laboratory Fee Schedule for codes 82172, 83695 and 86141. An assigned fee is not a guarantee of payment.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Cardiovascular Risk Panels
- Genetic Testing – Gene Expression Testing in the Evaluation of Patients with Stable Ischemic Heart Disease
- Measurement of Lipoprotein-associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk
- Myeloperoxidase Immunoassay for Cardiac Disease Risk

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/12	10/11/11	11/9/11	Joint policy established. Consolidated previous policies, "Low Density Lipoprotein (LDL) Particle Size" and "High Density Lipoprotein Subclass Testing in the Diagnosis and Management of Cardiovascular Disease". These two policies will be moved out of the active policies queue.
3/1/13	12/11/12	12/31/12	Routine maintenance. Added new code, 81401; Revised language in policy statement. Policy title changed from "Lipid Risk Factors in the Assessment and Management of Cardiovascular Disease" to "Novel Lipid Risk Factors in the Risk Assessment and Management of Cardiovascular Disease".
7/1/14	4/8/14	4/15/14	Policy extensively rewritten and intent changed; added apo B and hs-CRP as established; title changed from "Novel Lipid Risk Factors in the Risk Assessment and Management of Cardiovascular Disease" to current title; references updated
11/1/15	8/18/15	9/16/15	Added description and rationale information on genetic biomarkers for CVD, FH (heterozygous and homozygous) Added code 81401, as this describes *APOB* molecular testing Added code 81405, as this describes *LDLR* molecular testing Added code 81406, used for *PCSK9* molecular testing Added 84999, may be used for *ARH* adaptor protein testing Added *LDLR, APOB, PCSK9* and *ARH* adaptor protein (*LDLRAP1*) to genetic tests established for FH. Added to MPS: "The safety and effectiveness of genetic testing of *LDLR, APOB, PCSK9* and *ARH* adaptor protein (*LDLRAP1*) have been established. It may be a useful

			diagnostic option for individuals with suspected homozygous familial hypercholesterolemia, in whom the diagnosis is uncertain." Revised MPS to include all biomarkers noted in policy. Added "*APOE* genotyping" to exclusions and MPS (literature does not support) Added to Exclusions: "Laboratory testing of other novel biomarkers to assess cardiovascular risk, including but not limited to apolipoprotein AI, apolipoprotein E or APOE genotypes, LDL subclass, HDL subclass, lipoprotein[a]), Cystatin C, brain natriuretic peptide (BNP), fibrinogen, and leptin."
11/1/16	8/16/16	8/16/16	Routine maintenance Literature review Added code 82397, may be used for leptin testing Added code 82664, may be used for HDL subclass Added code 83520, may be used for leptin testing Added code 83700, classified for lipoprotein, blood; electrophoretic separation and quantitation Added code 83721, classified for Lipoprotein, direct measurement; LDL cholesterol Added code 84181, may be used for APOE phenotyping or genotyping Added code 85385, classified for Fibrinogen, antigen LCD update PULS cardiac testing added to MPS
11/1/17	8/15/17	8/15/17	Routine maintenance
11/1/18	8/21/18	8/21/18	• Routine maintenance • Removed homozygous familial hypercholesterolemia from policy • 0055U added to EI
1/1/19	10/16/18	10/16/18	• 0055U removed • 0052U added
1/1/20	10/15/19		• Routine maintenance • 83722 added per code update EI
11/1/20	8/18/20		• Routine maintenance
11/1/21	8/17/21		• Routine maintenance

11/1/22	8/16/22		• Routine maintenance • Lipoprotein(a) (83695) moved from E/I to EST • Apo B and hs-CRP criteria aligned with avalon policy • Ref added 135,136
11/1/23	8/15/23		• Routine maintenance • Vendor: Avalon (ky)

Next Review Date: 3rd Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: NOVEL BIOMARKERS IN RISK ASSESSMENT AND MANAGEMENT OF CARDIOVASCULAR DISEASE

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, policy criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.