

Medical Policy



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

Professional

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Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are asymptomatic with risk of cardiovascular disease 	Interventions of interest are: <ul style="list-style-type: none"> Novel cardiac biomarkers testing 	Comparators of interest are: <ul style="list-style-type: none"> Routine care without biomarker testing 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Other test performance measures Change in disease status Morbid events Medication use
Individuals: <ul style="list-style-type: none"> With hyperlipidemia managed with lipid-lowering therapy 	Interventions of interest are: <ul style="list-style-type: none"> Novel cardiac biomarkers testing 	Comparators of interest are: <ul style="list-style-type: none"> Routine care without biomarker testing 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Change in disease status Morbid events Medication use

DESCRIPTION

Numerous lipid and non-lipid biomarkers have been proposed as potential risk markers for cardiovascular disease. Biomarkers assessed herein are those that have the most evidence in support of their use in clinical care, including apolipoprotein B (apo B), apolipoprotein AI (apo AI), apolipoprotein E (apo E), high-density lipoprotein (HDL) subclass, low-density lipoprotein (LDL) subclass, lipoprotein (a), B-type natriuretic peptide, cystatin C, fibrinogen, and leptin. These biomarkers have been studied as alternatives or additions to standard lipid panels for risk stratification in cardiovascular disease or as treatment targets for lipid-lowering therapy.

Objective

The objective of this evidence review is to determine whether novel cardiac biomarker testing in asymptomatic patients or patients with hyperlipidemia improves the net health outcome.

Background

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

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

LIPID MARKERS

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 B₁₀₀, constitutes the apo B found in LDL and very-LDL. Because LDL and very-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 LDL concentration.

Apolipoprotein AI

High-density lipoprotein contains 2 associated apolipoproteins (ie, AI, AII). High-density lipoprotein particles can also be classified by whether they contain apo AI only or they contain apo AI and apo AII. All lipoproteins contain apo AI, and some also contain 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 has been proposed as more accurate than the traditional use of HDL level in the evaluation of the 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-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, 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 the risk of CAD above 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. The *APOE* genotype may be a 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 HDL₂, the larger, less dense particles that may have the greatest degree of cardioprotection, and HDL₃, which are smaller, denser particles.

An alternative to measuring the concentration of subclasses of HDL (eg, HDL₂, HDL₃) is a direct measurement of HDL particle size and/or number. Particle size can be measured by nuclear magnetic resonance spectroscopy or by gradient-gel electrophoresis. High-density lipoprotein particle numbers can be measured by nuclear magnetic resonance 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, particles have a diameter larger than 25 nm and are less dense, while in subclass pattern B, particles have a diameter less than 25 nm and a higher density. Subclass pattern B is a common inherited disorder associated with a more atherogenic lipoprotein profile, also termed “atherogenic dyslipidemia.” In addition to small, dense LDL, this pattern includes elevated levels of triglycerides, elevated levels of apo B, and low levels of HDL. This lipid profile is commonly

seen in type 2 diabetes and is a component of the “metabolic syndrome,” defined by the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) to also include high normal blood pressure, insulin resistance, increased levels of inflammatory markers such as C-reactive protein, and a prothrombotic state. The presence of the metabolic syndrome is considered by Adult Treatment Panel III to be a substantial risk-enhancing factor for CAD.

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 the risk for CAD independent of the total LDL level. Also, some drugs may cause a greater shift in lipid profiles than others. Niacin and/or fibrates may cause a greater shift from small to large LDL size than statins. Therefore, measurement of LDL size may potentially play a role in drug selection or may be useful in deciding whether to use a combination of drugs rather than a statin alone.

In addition to the size of LDL particles, interest has been shown in assessing the concentration of LDL particles as a distinct cardiac risk factor. For example, the commonly performed test for LDL-C is not a direct measure of LDL, but, chosen for its convenience, measures the amount of cholesterol incorporated into LDL particles. Because LDL particles carry much of the cholesterol in the bloodstream, the concentration of cholesterol in LDL correlates reasonably well with the number of LDL particles when examined in large populations. However, for an individual patient, the LDL-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, the 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 the apo B. The apo A molecule is structurally similar to plasminogen, suggesting that Lp(a) may contribute to the thrombotic and atherogenic basis of CVD. Levels of Lp(a) are relatively stable in individuals over time but vary up to 1000-fold between individuals, presumably on a genetic basis. The similarity between Lp(a) and fibrinogen has stimulated intense interest in Lp(a) as a link between atherosclerosis and thrombosis. In addition, approximately 20% of patients with CAD have elevated Lp(a) levels. Therefore, it has been proposed that levels of Lp(a) may be an independent risk factor for CAD.

NON-LIPID MARKERS

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 CVD and all-cause mortality.

Leptin

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

REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). 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 this test.

POLICY

Measurement of novel lipid and non-lipid risk factors (ie, apolipoprotein B, apolipoprotein AI, apolipoprotein E, low-density lipoprotein subclass, high-density lipoprotein subclass, lipoprotein[a], B-type natriuretic peptide, cystatin C, fibrinogen, leptin) is considered **experimental/ investigational** as an adjunct to low-density lipoprotein cholesterol in the risk assessment and management of cardiovascular disease.

Policy Guidelines

Genetic Counseling

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

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through October 30, 2020.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function^{3/4}including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

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 herein 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 marker of treatment response. Data on treatment responses are taken from 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, 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 necessary, that modification of the risk factor in clinical trials will have shown a 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 LDL 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 serologic 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 (CRP), fibrinogen, cholesterol, apo B, the apo A/apo B ratio, HDL, 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, CRP, 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 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 is to provide an alternative or superior method for diagnosing CVD to inform a decision to proceed with appropriate treatment for patients who are asymptomatic with a risk of CVD .

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

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

Populations

The relevant population of interest is individuals who are asymptomatic with a risk of CVD

Interventions

The intervention being considered is novel cardiac biomarker testing, which would be managed by cardiologists and primary care providers in an outpatient clinical setting.

Comparators

Comparators of interest include routine care without biomarker testing.

Patients who are asymptomatic with a risk of CVD are actively managed by cardiologists and primary care providers in an outpatient clinical setting.

Outcomes

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

Follow-up at 1 and 6 years are of interest for novel cardiac biomarker testing for 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.

APOLIPOPROTEIN B

Systematic Review

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.⁷ Selected for analysis were 131 134 patients from 25 RCTs including 12 trials on statins, 5 on niacin, 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, but stroke risk was not decreased. Decreased apo B levels were not superior to decreased non-HDL levels in decreasing CVD (Bayes factor [BF] =2.07) and CHD risk (BF=1.45) prediction. When non-HDL-C plus LDL-C decrease were added to apo B decrease, CVD risk prediction improved slightly (BF=1.13) but not CHD risk prediction (BF=1.03) and stroke risk prediction worsened (BF=0.83). In summary, any apo B decrease did not consistently add information to LDL, non-HDL, or LDL/non-HDL decreases to improve CVD risk prediction when analyzed across lipid-modifying treatments of all types.

The Emerging Risk Factors Collaboration (2012) published a patient-level meta-analysis of 37 prospective cohort studies enrolling 154 544 patients.⁸ Risk prediction was examined for a variety of traditional and nontraditional lipid markers. For apo B, evidence from 26 studies (n=139,581 subjects) reported that apo B was an independent risk factor for cardiovascular events (Table 1; study 1). On reclassification analysis, when apo B and apo AI were substituted for traditional lipids, there was no improvement in risk prediction. In fact, there was a slight worsening in the predictive ability, as evidenced by a -0.0028 decrease in the C statistic (p<0.001), and a -1.08% decrease in the net reclassification improvement (p<0.01).

Observational Studies

The Quebec Cardiovascular Study (1996) evaluated the ability of levels of apo B and other lipid parameters to predict subsequent coronary artery disease (CAD) events in a prospective cohort study of 2155 men followed for 5 years.⁹ Elevated levels of apo B were found to be an independent risk factor for ischemic heart disease after adjustment for other lipid parameters

(Table 1; study 2). In patients with an apo B level of greater than 120 mg/dL, there was a 6.2-fold increase in the risk of cardiovascular events.

The Apolipoprotein Mortality Risk Study was another prospective cohort study (2001) that followed 175 000 Swedish men and women presenting for routine outpatient care over a mean of 5.5 years.¹⁰ This study found that apo B was an independent predictor of CAD events and was superior to LDL-C levels in predicting risk, not only for the entire cohort but also for all subgroups examined. Relative risks (RR) for the highest quartile of apo B levels were 1.76 in men ($p < 0.001$) and 1.69 in women ($p < 0.001$) (Table 1; study 3).

A cohort study (2005) of 15 632 participants from the Women's Health Initiative provided similar information in women.¹¹ In this analysis, the HR for developing CHD in the highest versus the lowest quintiles was greater for apo B (2.50; 95% CI, 1.68 to 3.72) than LDL-C (1.62; 95% CI, 1.17 to 2.25), after adjusting for traditional cardiovascular risk factors (Table 1; study 4).

The Copenhagen City Heart Study (2007) prospectively evaluated a cohort of 9231 asymptomatic persons from the Danish general population followed for 8 years.¹² Subjects with total apo B levels in the top one-third (top tertile) had a significantly increased RR of cardiovascular events than patients in the lowest one-third, after controlling for LDL-C and other traditional cardiovascular risk factors (Table 1; study 5). 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); however, this difference in AUC was not statistically significant.

Kappelle et al (2011) used data from the prospective Prevention of Renal and Vascular End-stage Disease trial (PREVEND) cohort to evaluate the predictive value of the apo B/apo AI ratio independent of other traditional risk factors, including albuminuria and CRP.¹³ Among 6948 subjects without previous heart disease and who were not on lipid-lowering drugs, the adjusted hazard ratio (aHR) for a high apo B/apo AI ratio (Table 1; study 6) did not differ significantly from the TC/HDL-C ratio of 1.24 (95% CI, 1.18 to 1.29), and did not change significantly after further adjustment for triglycerides.

Pencina et al (2015) used data from 2966 participants of the Framingham Offspring Study cohort who were aged 40 to 75 years in the fourth examination cycle and did not have CVD, triglyceride levels greater than 400 mg/dL, or missing data on model covariates.¹⁴ They calculated the differences between observed apo B and expected apo B based on linear regression models of LDL-C and non-HDL-C levels. These differences were added to a Cox model to predict new-onset CHD, adjusting for standard risk factors (age, sex, systolic blood pressure, antihypertensive treatment, smoking, diabetes, HDL-C, and LDL-C or non-HDL-C). The difference between observed and expected apo B was associated with future CHD events. The aHR for the difference based on the apo B and LDL-C model was 1.26 (95% CI, 1.15 to 1.37) for each standard deviation (SD) increase beyond expected apo B levels (Table 1; study 7). For the difference based on the apo B and non-HDL-C model, the HR was 1.20 (95% CI, 1.11 to 1.29). The discrimination C statistic for predicting new-onset CHD from a model with standard risk factors was 0.72 (95% CI, 0.70 to 0.75). The C statistic improved very slightly but with overlapping CIs to 0.73 (95% CI, 0.71 to 0.76) after adding the difference based on the apo B and LDL-C model to the standard risk factors and increased to 0.73 (95% CI, 0.71 to 0.75) after adding the difference based on the apo B and non-HDL-C model.

Table 1 summarizes the results of the above apolipoprotein B studies.

Table 1. Results of Diagnostic Apolipoprotein B Studies

Study	Study Type	N	Efficacy of Apo B in Determining CVD Risk	
			HR (95% CI)	RR (95% CI)
Study 1: ERFC (2012) ⁸ ,	MA of prospective cohorts	154,544	1.24 (1.19 to 1.29)	-
Study 2:Lamarche et al (1996) ⁹ ,	Prospective cohort	2155	-	1.40 (1.2 to 1.7)
Study 3:Walldius et al (2001) ¹⁰ ,	Prospective cohort	175,000	-	Men: 1.76 (p<0.001) Women: 1.69 (p<0.001)
Study 4: Ridker et al (2005) ¹¹ ,	Prospective cohort	15,632	2.50 (1.68 to 3.72)	-
Study 5: Benn et al (2007) ¹² ,	Prospective cohort	9231	-	Men: 1.4 (1.1 to 1.8) Women: 1.5 (1.1 to 2.1)
Study 6:Kappelle et al (2011) ¹³ ,	Prospective cohort	6948	1.37 (1.26 to 1.48)	-
Study 7:Pencina et al (2015) ¹⁴ ,	Prospective cohort	2966	1.26 (1.15 to 1.37)	-

APO B: apolipoprotein B; CI: confidence interval; CVD: cardiovascular disease; ERFC: Emerging Risk Factors Collaboration; HR: hazard ratio; MA: meta-analysis; RR: relative risk

The Atherosclerosis Risk in Communities (ARIC) study (2001), concluded that apo B did not add additional predictive information above standard lipid measures.¹⁵ The ARIC study followed for 10 years, 12000 middle-aged adults free of CAD at baseline. While apo B was a strong univariate predictor of risk, it did not add independent predictive value above traditional lipid measures in multivariate models.

The ratio of apo B/apo AI has also been proposed as a superior measure of the ratio of proatherogenic (ie, "bad") cholesterol to anti-atherogenic (ie, "good") cholesterol. This ratio may be a more accurate measure of this concept, compared with the more common TC/HDL ratio. A number of epidemiologic studies have reported that the apo B/apo AI ratio is superior to other ratios, such as TC/HDL-C and non-HDL-C/HDL-C.^{16,17}Other representative studies of the apo B/apo AI ratio are discussed next.

Some studies have tested the use of apo B in a multivariate risk prediction model with both traditional risk factors and apolipoprotein measures included as potential predictors. Ridker et al (2007) published the Reynolds Risk Score, based on data from 24558 initially healthy women

enrolled in the Women's Health Study and followed for a median of 10.2 years.¹⁸ Thirty-five potential predictors of CVD were considered as potential predictors, and 2 final prediction models were derived. The first was the best-fitting model statistically and included both apo B and the apo B/apo AI ratio as 2 of 9 final predictors. The second called the "clinically simplified model" substituted LDL-C for apo B and TC/HDL-C for apo B/apo AI. The authors developed this simplified model "for the purpose of clinical application and efficiency" and justified replacing the apo B and apo B/apo AI measures as a result of their high correlation with traditional lipid measures ($r=0.87$ and 0.80 , respectively). The predictor has not been evaluated in clinical care.

Ingelsson et al (2007) used data from 3322 subjects in the Framingham Offspring Study to compare prediction models using traditional lipid measures with models using apolipoprotein and other nontraditional lipid measures.¹⁹ This study reported that the apo B/apo AI ratio had a similar predictive ability as traditional lipid ratios with respect to model discrimination, calibration, and reclassification. The authors also reported that the apo B/apo AI ratio did not provide any incremental predictive value over traditional measures.

Sniderman et al (2012) reported on 9345 acute myocardial infarction (MI) patients who were compared with 12120 controls in the standardized case-control INTERHEART study.²⁰ The authors reported discordance in the levels of cholesterol contained in apo B and non-HDL-C. Unlike the Robinson et al (2012) study, apo B was found to be more accurate than non-HDL-C as a marker for cardiovascular risk.

Subsection 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. However, some meta-analyses have concluded that apo B is not a better predictor of cardiac risk than HDL or non-HDL combined with LDL. There is also greater uncertainty about the degree of improvement in risk prediction and whether the magnitude of improvement is clinically significant. While there have been attempts to incorporate apo B into multivariate risk prediction models, at present, apo B is not included in the models most commonly used in routine clinical care, such as the Framingham risk model and the Prospective Cardiovascular Munster Study Score.

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.⁸ For apo AI, evidence from 26 studies ($n=139\ 581$ subjects) reported that apo AI was an independent risk factor for reduced cardiovascular risk (Table 2; study 1). 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 ($p<0.001$) and a -1.08% decrease in the net reclassification improvement ($p<0.01$).

Observational Studies

Clarke et al (2007) published a prospective cohort study of 7044 elderly men enrolled in the Whitehall Cardiovascular Cohort from England.²¹ Measurements of apolipoprotein levels were

performed on 5344 of these men, and they were followed for a mean of 6.8 years. The authors reported that the apo B/apo AI ratio was a significant independent predictor (Table 2; study 2) 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.¹⁸ 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 2; study 3). 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 25663 patients.²² The case-control subgroup study 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 2; study 4). 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=0.38).

Table 2. Results of Diagnostic Apolipoprotein AI Studies

Study	Study Type	N	Efficacy of Apolipoprotein AI in Determining CVD Risk	
			HR (95% CI)	OR (95% CI)
Study 1: ERFC (2012) ⁸	Review of prospective cohorts	139,581	0.87 (0.84 to 0.90)	-
Study 2: Clarke et al (2007) ²¹	Prospective cohort	7044	1.54 (1.27 to 1.87)	-
Study 3: Ridker et al (2007) ¹⁸	Prospective cohort	2966	2.32 (1.64 to 3.33)	-
Study 4: van der Steeg (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 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.¹⁰ The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS [2000]) investigated lipid parameters among 6605 men and women with average LDL-C and low HDL-C levels who were randomized to lovastatin or placebo.²³ 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 9231 asymptomatic persons from the Danish general population.¹² The apo B/apo AI ratio was reported as an independent predictor of cardiovascular events, with an HR 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 the 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 have argued 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.^{23,24} 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.^{25,26}

Systematic Reviews

A meta-analysis published by Bennet et al (2007) summarized the evidence from 147 studies on the association between *APOE* genotypes using lipid levels and cardiac risk.²⁷ Eighty-two studies with a total of 86 067 participants included data on the association between apo E and lipid levels and 121 studies reported on the association with clinical outcomes. The authors estimated that patients with the apo e2 allele had LDL levels that were approximately 31% lower than those in patients with the apo e4 allele. Compared with patients with the apo e3 allele, patients with apo e2 had an approximately 20% lower risk for coronary events (odds ratio [OR]=0.80; 95% CI, 0.70 to 0.90). Patients with the apo e4 had an estimated 6% higher risk of coronary events, which 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.²⁸ The method for selecting the studies was not described. The 3 studies included 9587 participants and 1413 CVD events. In a pooled analysis, there was no association between apo E and CVD events. The unadjusted OR for CVD events for each SD increase in apo E concentration was 1.02 (95% CI, 0.96 to 1.09). After adjustment for other cardiovascular risk factors, the OR for CVD for each SD 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.^{29,30,31,32,33,34} These studies have generally shown a relationship between apo E and these surrogate outcomes. Other studies have suggested that carriers of apo e4 are more likely to develop signs of atherosclerosis independent of TC and LDL-C levels.^{35,36,37,38}

Some larger observational studies have correlated *APOE* genotype with clinical disease. The ARIC study (2001) followed 12000 middle-aged subjects free of CAD at baseline for 10 years.¹⁵ This study reported that the apo 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.³⁹

Subsection 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 compared with other established and emerging clinical variables, and does not explain a large percentage of the interindividual 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.⁴⁰ 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), 10886 patients without CVD were randomized to rosuvastatin or placebo and followed for a median of 2 years.⁴¹ 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 levels between baseline and year 1 values occurred in the rosuvastatin and placebo groups for all levels (p<0.001), except for apo AI and HDL particle size in the placebo group, which did not differ significantly (p=0.09 and 0.74, respectively). Changes in the rosuvastatin group were also statistically significant compared with placebo for LDL-C, HDL-C, apo AI, and HDL particle size and number (all p<0.001). In the placebo group, inverse associations with CVD and HDL-C, apo AI, and HDL particles were reported. 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=0.01) than HDL-C (HR=0.82; 95% CI, 0.63 to 1.08; p=0.16) or apo AI (HR=0.86; 95% CI, 0.67 to 1.10; p=0.22). This association remained after adjusting for HDL-C (HR=0.72; 95% CI, 0.53 to 0.97; p=0.03). Size of HDL was not significantly associated with CVD in risk factor-adjusted models.

Subsection Summary: High-Density Lipoprotein Particle Size and Concentration

One RCT and a pooled analysis has evaluated the association of HDL particle size and number as measured by NMR. While these studies found an association with HDL particle (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 LIPOPROTEIN 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 15000 men, investigated whether LDL particle size is an independent predictor of CAD risk, particularly compared with triglyceride levels.⁴² The authors concluded that while LDL particle diameter was associated with the 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.^{9,43} The presence of small LDL particles 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 apo B levels. In the presence of small LDL particles, elevated apo B levels were associated with a 6-fold increased risk of CAD, whereas when small LDL particles were not present, elevated apo B 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.⁴⁴ 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 ultra sonographically 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.

Low-Density Lipoprotein 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 NMR are also associated with cardiac risk. For example, 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.^{45,46,47} Translating these findings into clinical practice requires setting target values for lipoprotein numbers. 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 numbers 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.⁴⁸

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-treatment.⁴⁹ 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. Low-density lipoprotein 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 trial of 27 673 women followed over an 11-year period.⁵⁰ After controlling for non-lipid factors, LDL particle number was a significant predictor of incident CVD, with an HR of 2.51 (95% CI, 1.91 to 3.30) for the highest compared with the lowest quintile. Low-density lipoprotein particle size was similarly predictive of cardiovascular risk, with an HR 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.⁵¹ For each 100 nmol/L increase in LDL particle level, there was a 4% increase in the 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).

Subsection Summary: Low-Density Lipoprotein Subclass and Low-Density Lipoprotein 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 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 Lp(a) as a cardiovascular risk factor. The following are representative prospective trials drawn from the relevant literature. Table 3 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.⁸ Risk prediction was examined for a variety of traditional and nontraditional lipid markers. For Lp(a), evidence from 24 studies on 133,502 subjects reported that Lp(a) was an independent risk factor for reduced cardiovascular risk (Table 3; study 1). 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.⁵² The combined results revealed a significant positive relationship between Lp(a) and cardiovascular risk (Table 3; study 11). 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.⁵³ 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 3; study 12).

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.⁵⁴ Lp(a) was independently associated with a residual risk of CVD despite statin treatment (Table 5; study 2). 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 3; study 3).⁵⁵

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.⁵⁶ 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 5; study 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.⁵⁷ They reported that Lp(a) was an independent predictor of MI (Table 3; study 5).

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.⁵⁸ Lipoprotein (a) was 1 of 7 biomarkers that had incremental predictive ability above the established risk factors (Table 3; study 6).

Waldeyer et al (2017) analyzed data of 56084 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.⁵⁹ The highest event rate of major coronary events and CVD was observed for Lp(a) levels at the 90th percentile or higher ($p < 0.001$ 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 3; study 7). 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 Dallas Health Study, a multiethnic prospective cohort with a median follow-up of 9.5 years ($n=3419$ patients).⁶⁰ 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 3; study 8). 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 3; study 9).⁶¹

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 27736 women enrolled in the Women's Health Study.⁶² After controlling for

standard cardiovascular risk factors, Lp(a) levels were an independent predictor of risk in women not taking hormone replacement therapy (Table 3; study 10). 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=0.18).

Table 3. Results of Diagnostic Lipoprotein(a) Studies

Study	Study Type	N	Efficacy of Lp(a) in Determining CVD Risk	
			HR (95% CI)	OR (95% CI)
Study 1: ERFC (2012) ⁸ ,	SR/MA	154,544	1.13 (1.09 to 1.18)	-
Study 2:Khera et al (2014) ⁵⁴ ,	RCT	7746	1.27 (1.01 to 1.59) p=0.04	-
Study 3:Albers et al (2013) ⁵⁵ ,	RCT	1440	1.18-1.25	-
Study 4: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)	-
Study 5:Tzoulaki et al (2007) ⁵⁷ ,	Prospective cohort	1592	1.49 (1.0 to 2.2)	-
Study 6:Zakai et al (2007) ⁵⁸ ,	Prospective cohort	4510	1.07 (1.0 to 1.12)	
Study 7: Waldeyer et al (2017) ⁵⁹ ,	Post hoc analysis	56,084	1.3 (1.15 to 1.46)	
Study 8:Lee et al (2017) ⁶⁰ ,	Prospective cohort	3419	2.35 (1.50 to 3.69)	
Study 9: Rigal et al (2007) ⁶¹ ,	Prospective cohort	100	-	Men: 3.55 (1.33 to 9.48) Women: 0.42 (0.12 to 1.26)
Study 10:Suk Danik et al (2008) ⁶² ,	Prospective cohort	27,736	1.77 (1.36 to 2.30) p<0.001	-
Study 11:Bennet et al (2008) ⁵² ,	SR/MA	2047	-	1.45 (1.32 to 1.58)
Study 12: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 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).⁶³ 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 126,634 participants.⁶⁴ 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.⁶⁵ The LIPID RCT (2013) randomized 7863 patients to pravastatin or placebo.⁶⁶ Patients were followed for a median of 6 years. Lipoprotein (a) concentrations did not change significantly at 1 year. Baseline Lp(a) concentration was associated with total CHD events ($p<0.001$), total CVD events ($p=0.002$), and coronary events ($p=0.03$).

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.⁶⁷ 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.¹⁵ 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 14221 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).⁶⁸

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.⁶⁹ 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 ($p<0.05$) and longer survival time ($p<0.05$) 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; $p=0.049$) and for women at intermediate cardiovascular risk (AUC=0.7; 95% CI, 0.52 to 0.79; $p=0.034$).

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.⁷⁰ 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.⁷¹ 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.⁷² 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.

Subsection Summary: Lipoprotein (a)

A large amount of epidemiologic evidence has determined that Lp(a) is an independent risk factor for CVD. 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.⁷³ Levels of BNP ranging from 40 to 99.9 pg/mL and from 100 pg/mL or higher had a 2.2 to 7.5 relative hazard for a cardiovascular event compared with BNP levels less than 40 pg/mL ($p<0.001$). Other large population cohort studies have shown a relationship between elevations in BNP levels and future risks of cardiovascular events or heart failure. In a cohort study of 5067, Melander et al (2009) found adding CRP and BNP to a risk model of conventional factors increased the C statistic for cardiovascular events by 0.007 ($p=0.04$) and for coronary events by 0.009 ($p=0.08$).⁷⁴ In a cohort study of 3346 patients without heart failure,

Wang et al (2004) found BNP levels above the 80th percentile (20.0 pg/mL for men, 23.3 pg/mL for women) were associated with multivariable aHRs of 1.62 for death ($p=0.02$), 1.76 for a first major coronary events, ($p=0.03$), 1.91 for atrial fibrillation ($p=0.02$), 1.99 for stroke or transient ischemic attack ($p=0.02$), and 3.07 for heart failure ($p=0.002$).⁷⁵ However, any gains over the use of conventional risk factors appear to be minimal.

Subsection 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 CVD risk in 6653 adults without CVD from the Multi-Ethnic Study of Atherosclerosis.⁷⁶ 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 participants) with predominantly high cardiovascular risk patients to evaluate the relation between elevated cystatin C levels and CVD risk.⁷⁷ Higher levels of cystatin C were associated with greater risk of CVD (RR=2.62; 95% CI, 2.05 to 3.37; $p<0.001$), CHD (RR=1.72; 95% CI, 1.27 to 2.34; $p<0.001$), and stroke (RR=1.83; 95% CI, 1.12 to 3.00; $p=0.02$) after adjusting 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.⁷⁸ Reviewers included 9 prospective studies (N=39 854 subjects). Across the 6 studies reporting cardiovascular mortality-specific outcomes, the pooled aHR of cardiovascular mortality, comparing the highest and lowest cystatin C categories, was 2.74 (95% CI, 2.04 to 3.68; $p=0.021$).

Subsection Summary: Cystatin C

Several meta-analyses have reported that higher levels of cystatin C are associated with higher cardiovascular risk and a higher risk of cardiovascular death. In contrast, in a large cohort, cystatin C did not improve the 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.⁷⁹ 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 levels and CVD risk did not differ significantly between the diabetic and nondiabetic populations ($p=0.47$). Despite improved predictive accuracy, the addition of fibrinogen to established risk factors was not reported to be clinically important.

Willeit et al (2016) reported on 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.⁸⁰ 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 participants), of which 13 studies (35,096 participants) 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 mm; $p < 0.001$). However, in longitudinal analysis, neither the baseline level of any of the inflammatory markers evaluated nor their progression was associated with the progression of common carotid artery intima-media thickness.

Observational Studies

Other studies have found an association between fibrinogen and cardiovascular risk, including the European Prospective Investigation into Cancer and Nutrition-Norfolk cohort study⁸¹, and the Fibrinogen Studies Collaboration.^{82,83} In a 2007 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 BMI.⁸³

Subsection Summary: Fibrinogen

Reports from a number of cohort studies and subsequent systematic review/meta-analysis, have suggested 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.⁸⁴ Leptin levels in the top third had an odds for CHD of 1.25 (95% CI, 0.96 to 1.62) compared with the bottom third. After adjusting for BMI, the odds decreased to 0.98 (95% CI, 0.72 to 1.34), suggesting an association of leptin with CVD is largely dependent on BMI.

Zeng et al (2014) conducted a meta-analysis of studies reporting on the association between leptin levels and risk of CHD or stroke.⁸⁵ The meta-analysis included 8 nested case-control studies with 1980 patients and 11567 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; $p=0.032$) and pathogenic risk of stroke (OR=2.14; 95% CI, 1.48 to 3.08; $p < 0.001$).

Yang et al (2017) conducted a systematic review of case-control and cohort studies that assessed leptin concentration and CHD risk.⁸⁶ 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).

Subsection Summary: Leptin

Two meta-analyses have suggested 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. Individuals with hyperlipidemia managed with lipid-lowering therapy.

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. In particular, apo B and apo AI have been identified as adding some incremental predictive value. However, it has not been established whether the incremental accuracy provides clinically important information beyond that of traditional lipid measures. Furthermore, no study has provided high-quality evidence that measurement of markers leads to changes in management that improve health outcomes.

INDIVIDUALS WITH HYPERLIPIDEMIA MANAGED WITH LIPID-LOWERING THERAPY

Clinical Context and Test Purpose

The purpose of novel cardiac biomarker testing is to provide an alternative or superior method for diagnosing CVD to inform a decision to proceed with appropriate treatment in patients with hyperlipidemia managed with lipid-lowering therapy.

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

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

Populations

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

Interventions

The therapy being considered is novel cardiac biomarker testing, which is performed by cardiologists and primary care providers in an outpatient clinical setting.

Comparators

Comparators of interest include routine care without biomarker testing.

Patients with hyperlipidemia managed with lipid-lowering therapy are actively managed by cardiologists and primary care providers in an outpatient clinical setting.

Outcomes

The general outcomes of interest are OS, change in disease status, morbid events, and medication use.

Follow-up at 1, 2, 15, and 25 years is of interest for novel cardiac biomarker testing for OS, 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.

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.⁸⁷ Eight studies enrolling 62154 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, 1.10 to 1.17; p=0.21). 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=0.002). In a subsequent report from this meta-analysis, Boekholdt et al (2014) evaluated the LDL-C, non-HDL-C, and apo B levels of 38153 patients allocated to the statin therapy groups.⁸⁸ 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.⁸⁹ 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.²³ Baseline LDL-C, HDL-C, and apo B levels were predictive of future coronary events. However, in the

treatment group, posttreatment levels of LDL-C and HDL-C were not predictive of subsequent risk, while posttreatment 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.²⁴ The aHR for apo B levels (2.10; 95% CI, 1.21 to 3.64, $p=0.008$) was higher than that for LDL-C (1.20; 95% CI, 1.00 to 1.45; $p=0.05$). 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.²⁵ The analysis included 18889 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; $p<0.001$), 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 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).²⁶ In this study, the known baseline variables performed well in discriminating future cases from noncases, 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.⁹⁰ 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.

Subsection 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. Whether the degree of improvement in assessing treatment response is clinically significant has yet to be determined.

Currently, it is not possible to conclude that the use of apo B levels will improve outcomes in routine clinical care. Improved ability to predict risk and/or treatment response does not by itself result in better health outcomes. To improve outcomes, clinicians must have the tools to translate this information into clinical practice. No studies have demonstrated improved health outcomes by using apo B in place of LDL-C for risk assessment and/or treatment response. The most widely used risk assessment models (eg, the Framingham prediction model) and the most widely used treatment guidelines (eg, the ATP III guidelines) do not provide the tools necessary for clinicians to incorporate apo B measurements into routine assessment and management of hyperlipidemic patients. This lack creates difficulties in interpreting and applying the results of apo B and/or apo B/apo AI measurements to routine clinical care.

APOLIPOPROTEIN AI

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 the 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.²⁵ 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.⁹¹ 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 the acute coronary syndrome.⁹² Based on this research, there has been an 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.

Subsection 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.^{93,94} Other studies have suggested that response to statin therapy may vary by *APOE* genotype and that the e2 allele indicates greater responsiveness to statins.^{93,95}

Chiodini et al (2007) examined the 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.⁹⁶ The GISSI-P study 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 better treatment response as evidenced by lower overall mortality rates (1.85% vs 5.28%, respectively, $p=0.023$), while there was no difference in mortality rates for patients not treated with statins (2.81% vs 3.67%, respectively, $p=0.21$). This study corroborated results reported previously but did not provide evidence that changes in treatment should be made as a result of the *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.⁹⁷ Researchers reported on final LDL levels and percentages of patients achieving target LDL by *APOE* genetic status. Low-density lipoprotein 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; $p<0.001$). All patients who were homozygous for apo e2 reached their target LDL level compared with 68% of patients homozygous for apo e4 ($p<0.001$).

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.⁹⁸ They reported that patients with an apo e4 allele were more responsive to 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.

Subsection Summary: Apolipoprotein E

The evidence on the response to treatment indicates that *APOE* genotype may be a predictor of response to statins and may allow clinicians to better gage 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 a diminished response.

None of the available evidence has provided adequate data to establish that the *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.⁹⁹ 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-C, 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 with those who had LDL subclass B.¹⁰⁰ There was a greater reduction in the small, LDL levels for patients with subclass B, but this did not correlate with clinical outcomes. Another study has reported that atorvastatin treatment led to an increase in mean LDL size, while pravastatin treatment led to a decrease in LDL size.¹⁰¹

Various studies have generally confirmed that small, dense LDL is impacted preferentially by fibrate treatment^{102,103,104}, and possibly also by statin therapy.^{102,104} 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 the 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.¹⁰⁵ 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.¹⁰⁶ Change in LDL particle size correlated significantly with the angiographic progression of CAD in this study.

Fewer studies have evaluated clinical outcomes in relation to LDL particle size. In the 2001 Cholesterol and Recurrent Events trial, survivors of MI with normal cholesterol levels were randomized to lipid-lowering therapy or placebo.¹⁰⁷ A post hoc analysis from this trial failed to demonstrate a correlation between change in particle size and treatment benefit.

Subsection 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 the 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.^{108,109}

Subsection Summary: Lipoprotein(a)

There is considerable uncertainty regarding the clinical utility of measuring Lp(a), specifically how knowledge of Lp(a) levels can be used in the clinical care of patients being evaluated for lipid disorders. There is scant evidence on the use of Lp(a) as a treatment target for patients with hyperlipidemia. The available evidence is insufficiently related to the impact on clinical outcomes.

Section Summary: Individuals with Hyperlipidemia Managed with Lipid-Lowering Therapy

Evidence for individuals with hyperlipidemia managed with lipid-lowering therapy who receive novel cardiac biomarker testing includes analyses of the intervention arm(s) of lipid-lowering medication trials. 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. However, there is no direct evidence that using markers other than LDL and HDL as a lipid-lowering treatment target leads to improved health outcomes.

Summary of Evidence

For individuals who are asymptomatic with risk of cardiovascular disease who receive novel cardiac biomarker testing (eg, apo B, apo AI, apo E, HDL subclass, LDL subclass, lipoprotein[a], B-type natriuretic peptide, cystatin C, fibrinogen, leptin), 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 and may provide incremental accuracy in risk prediction. In particular, apo B and apo AI have been identified as adding some incremental predictive value. However, it has not been established whether the incremental accuracy provides clinically important information beyond that of traditional lipid measures. Furthermore, no study has provided high-quality evidence that measurement of markers leads to changes in management that improve health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

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, lipoprotein[a], B-type natriuretic peptide, 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 randomized controlled trials has suggested that these markers are associated with treatment success. However, there is no direct evidence that using markers other than LDL and HDL as a lipid-lowering treatment target leads to improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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 Apolipoprotein 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.¹¹⁰

In 2013, the Institute published a systematic evidence review on managing blood cholesterol in adults.¹¹¹ 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).¹¹²

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.¹¹² Pooled cohort equations for estimating atherosclerotic 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) guideline on primary prevention of cardiovascular disease state regarding elevated Lp(a) that “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).”¹¹³ The guideline further states regarding elevated apo B (≥ 130 mg/dL) that “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.¹¹⁴ This 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. The statement also noted 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 2020 Standards of Care do not discuss the use of novel biomarkers for cardiovascular disease and risk management.¹¹⁵

American Association of Clinical Endocrinologists and the American College of Endocrinology

In 2017, the American Association of Clinical Endocrinologists and the American College of Endocrinology published joint guidelines on the management of dyslipidemia and the prevention of cardiovascular diseases.¹¹⁶ 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).”

National Lipid Association

National Lipid Association (NLA) recommendations for patient-centered management of dyslipidemia were published in 2015.¹¹⁷ These recommendations stated that non-HDL-C and LDL-C should be primary targets for therapy and that apo B is an optional, secondary target for therapy. The Association favored non-HDL-C over apo B because the former is universally available and because apo B has not consistently shown superiority in predicting ASCVD risk.

In 2018, the NLA published a guideline on the management of blood cholesterol in conjunction with 11 other organizations, which discussed the measurement of apo B and Lp(a).¹¹⁸ A triglyceride level ≥ 200 mg/dL was mentioned as a relative indication of apo B measurement. Relative indications for measurement of Lp(a) include family history of premature ASCVD or ASCVD without traditional risk factors.

In 2019, the NLA 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 PCSK9 inhibitor therapy.¹¹⁹ 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.

National Institute for Health and Care Excellence

In 2016, the National Institute for Health and Care Excellence updated its guidance on risk assessment and reduction, including lipid modification of CVD.¹²⁰ The guidance recommended measuring a full lipid profile including total cholesterol, HDL, non-HDL, and triglycerides before starting lipid-lowering therapy for primary prevention of CVD. The guidance also recommended measurement of total cholesterol, HDL, non-HDL, and triglycerides for primary and secondary prevention in people on high-intensity statins at 3 months of treatment, aiming for a 40% reduction in non-HDL. Nontraditional risk factors, including ApoB, were not discussed as part of risk assessment or treatment targets.

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).¹²¹ The Task Force included Lp(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 2019 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.^{122,}

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in November 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

- | | |
|-------|--|
| 81401 | Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) |
| 82172 | Apolipoprotein, each |
| 82397 | Chemiluminescent assay |
| 82610 | Cystatin C |
| 82664 | Electrophoretic technique, not elsewhere specified |
| 83695 | Lipoprotein (a) |
| 83700 | Lipoprotein, blood; electrophoretic separation and quantitation |
| 83701 | Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation) |
| 83704 | Lipoprotein, blood; quantitation of lipoprotein particle number(s) by nuclear magnetic resonance spectroscopy), includes and lipoprotein particle subclasses |
| 83721 | Lipoprotein, direct measurement; LDL cholesterol |
| 83722 | Lipoprotein, direct measurement; small dense LDL cholesterol |
| 83880 | Natriuretic peptide |
| 84181 | Protein; Western Blot, with interpretation and report, blood or other body fluid |
| 85384 | Fibrinogen; activity |
| 85385 | Fibrinogen; antigen |
| 0052U | Lipoprotein, blood, high resolution fractionation and quantitation of lipoproteins, including all five major lipoprotein classes and subclasses of HDL, LDL, and VLDL by vertical auto profile ultracentrifugation |

DIAGNOSES

Experimental / investigational for all diagnoses related to this policy.

REVISIONS	
02-10-2011	<ul style="list-style-type: none"> ▪ Created a new medical policy entitled Novel Lipid Risk Factors in Risk Assessment and Management of Cardiovascular Disease which replaced the following medical policies: <ol style="list-style-type: none"> 1. Apolipoprotein B in the Risk Assessment and Management of Cardiovascular Disease 2. Apolipoprotein E Genotype or Phenotype in the Management of Cardiovascular Disease 3. High-Density Lipoprotein Subclass Testing in the Diagnosis and Management of Cardiovascular Disease 4. Lipoprotein(a) Enzyme Immunoassay in the Management of Cardiovascular Disease 5. Small Low-Density Lipoprotein (LDL) Particles and concentration of LDL Particles in Cardiac Risk Assessment and Management ▪ No policy language changes were made. Services in the previous medical policies were considered experimental / investigational and continue to be experimental / investigational in the new policy.
09-20-2011	Description section updated.
	Rationale section added.
	References section updated.
09-18-2012	Description section updated.
	Rationale section added.
	References section updated.
04-25-2016	Published 03-24-2016. Effective 04-25-2016.
	Title revised to "Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease" from "Novel Lipid Risk Factors in Risk Assessment and Management of Cardiovascular Disease"
	Description section updated
	In Policy section: <ul style="list-style-type: none"> ▪ Added "and non-lipid" and "B-type natriuretic peptide, cystatin C, fibrinogen, leptin," to read "Measurement of novel lipid and non-lipid risk factors (ie, apolipoprotein B, apolipoprotein AI, apolipoprotein E, B-type natriuretic peptide, cystatin C, fibrinogen, leptin, LDL subclass, HDL subclass, lipoprotein[a]) is considered experimental/ investigational as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease."
	Rationale section updated
	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT codes: 81401, 82610, 83721, 83880, 85384, 85385 ▪ Updated Coding notations
	References updated
03-28-2018	Description section updated.
	In Policy section: <ul style="list-style-type: none"> ▪ Revised "LDL" to "low-density lipoprotein" and "HDL" to "high-density lipoprotein" from abbreviations to specific meaning to read "Measurement of novel lipid and non-lipid risk factors (ie, apolipoprotein B, apolipoprotein AI, apolipoprotein E, low-density lipoprotein subclass, high-density lipoprotein subclass, lipoprotein[a], B-type natriuretic peptide, cystatin C, fibrinogen, leptin) is considered experimental/ investigational as an adjunct to low-density lipoprotein cholesterol in the risk assessment and management of cardiovascular disease."
	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT Codes: 82397, 83520 ▪ Revised CPT Code nomenclature: 83704 ▪ Updated Coding notations
	Rationale section added.
	References section updated.

REVISIONS	
07-01-2018	In Coding section: <ul style="list-style-type: none"> ▪ Added PLA Code: 0052U
01-01-2019	In Coding section: Added CPT Code: 83722
03-13-2019	Description section updated.
	Rationale section added.
	References section updated.
03-11-2021	Updated Description section
	Updated Rationale section
	In the coding section: <ul style="list-style-type: none"> • Removed CPT codes 83520 and 84999
	Updated Reference section

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