

Medical Policy



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

Professional

Original Effective Date: March 13, 2009
 Revision Date(s): February 10, 2011;
 September 20, 2011; September 18, 2012;
 April 25, 2016; March 28, 2018
 July 1, 2018; January 1, 2019;
 March 13, 2019
 Current Effective Date: March 28, 2018

Institutional

Original Effective Date: March 13, 2009
 Revision Date(s): February 10, 2011;
 September 20, 2011; September 18, 2012;
 April 25, 2016; March 28, 2018;
 July 1, 2018; January 1, 2019;
 March 13, 2019
 Current Effective Date: March 28, 2018

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member's benefits, contact [Blue Cross and Blue Shield of Kansas Customer Service](#).

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are asymptomatic with risk of cardiovascular disease	Interventions of interest are: • Novel cardiac biomarkers testing	Comparators of interest are: • Routine care without biomarker testing	Relevant outcomes include: • Overall survival • Other test performance measures • Change in disease status • Morbid events • Medication use
Individuals: • With hyperlipidemia managed with lipid-lowering therapy	Interventions of interest are: • Novel cardiac biomarkers testing	Comparators of interest are: • Routine care without biomarker testing	Relevant outcomes include: • 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 (CVD). 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 CVD 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. LDL particles consist of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins surrounding an inner lipid core composed of cholesterol ester and triglycerides. Traditional lipid risk factors such as LDL cholesterol (LDL-C), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of 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 for therapy.

Lipid Markers

Apolipoprotein B

Apolipoprotein B (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-low-density lipoproteins (VLDL). Because LDL and VLDL each contains 1 molecule of apo B, 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

HDL contains 2 associated apolipoproteins (ie, AI, AII). HDL 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 (apo E) is the primary apolipoprotein found in VLDLs and chylomicrons. Apo 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 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. *APOE* genotype may be a factor that determines an individual’s degree of response to interventions such as statin therapy.

HDL Subclass

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

An alternative to measuring the concentration of subclasses of HDL (eg, HDL₂, HDL₃) is direct measurement of HDL particle size and/or number. Particle size can be measured

by nuclear magnetic resonance spectroscopy or by gradient-gel electrophoresis. HDL 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.

LDL Subclass

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

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

Lipoprotein (a)

Lipoprotein (a) (Lp[a]) is a lipid-rich particle similar to LDL. Apo B is the major apolipoprotein associated with LDL; 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 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. BNP 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 has been found to be elevated in heart disease. Leptin has been studied to determine if it has any relation to the development of CVD.

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 with searches of the MEDLINE database. The most recent literature update was performed through October 6, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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 response are taken from RCTs that use one 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 criteria¹:

- 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
- Preferable, but not necessarily, modification of the risk factor in clinical trials will have shown

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).³ 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 use of statins and primary vs 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.⁴ 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.⁵ 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.⁶ 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.⁷ 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 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 a treatment option that is an alternative to or an improvement on existing therapies in patients who are asymptomatic with risk of cardiovascular disease.

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 PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The therapy being considered is novel cardiac biomarker testing.

Comparators

Comparators of interest include routine care without biomarker testing.

Outcomes

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

Timing

Follow-up at 1- and 6- years is of interest for novel cardiac biomarker testing for overall survival, other test performance measures, change in disease status, morbid events, and medication use.

Setting

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- a) The study population represents the population of interest. Eligibility and selection are described.
- b) The test is compared with a credible reference standard.
- c) If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
- d) Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (eg, ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
- e) Studies should also report reclassification of diagnostic or risk category.

Apolipoprotein B

Table 1. Results of Diagnostic Apolipoprotein B Studies

Study	N	Efficacy of Apolipoprotein B in Determining CVD Risk	
		HR (95% CI)	RR (95% CI)
Study 1: UK MA trial	154,544	1.24 (1.19 to 1.29)	
Study 2: Canadian prospective cohort study	2155		1.40 (1.2 to 1.7)
Study 3: European prospective cohort study	175,000		Men: 1.76 (p<0.001) Women: 1.69 (p<0.001)
Study 4: European cohort study	15,632	2.50 (1.68 to 3.72)	
Study 5: European prospective cohort study	9231		Men: 1.4 (1.1 to 1.8) Women: 1.5 (1.1 to 2.1)
Study 6: US prospective cohort study	6948	1.37 (1.26 to 1.48)	
Study 7: US, Canadian, European prospective cohort study	2966	1.26 (1.15 to 1.37)	

CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio; MA: meta-analysis; RR: relative risk

Robinson et al (2012) published results of a Bayesian random-effects meta-analysis of RCTs to compare the effectiveness of lowering apo B vs LDL-C and non-HDL-C for reducing CVD, CHD, and stroke risk.⁸ Selected for analysis were 131,134 patients from 25 RCTs including 12 trials on statins, five on niacins, four on fibrates, one on simvastatin plus ezetimibe, one on aggressive vs standard LDL and blood pressure targets, and one 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.

Sniderman et al (2012) reported on 9345 acute myocardial infarction (MI) patients who were compared with 12,120 controls in the standardized case-control INTERHEART study.⁹ The authors reported discordance in the levels of cholesterol contained in apo B and non-HDL-C. Unlike the Robinson study, apo B was found to be more accurate than non-HDL-C as a marker for cardiovascular risk.

The Emerging Risk Factors Collaboration (2012) published a patient-level meta-analysis of 37 prospective cohort studies enrolling 154,544 patients.¹⁰ 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, with an adjusted HR (AHR) of 1.24 (95% CI, 1.19 to 1.29). 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).

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.¹¹ Elevated levels of apo B were found to be an independent risk factor for ischemic heart disease after adjustment for other lipid parameters (relative risk [RR], 1.40; 95% CI, 1.2 to 1.7). 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 (AMORIS) 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.¹² 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 for the highest quartile of apo B levels were 1.76 in men (p<0.001) and 1.69 in women (p<0.001).

A cohort study (2005) of 15,632 participants from the Women's Health Initiative provided similar information in women.¹³ In this analysis, the HR for developing CHD in the highest vs 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.

The Copenhagen City Heart Study (2007) prospectively evaluated a cohort of 9231 asymptomatic persons from the Danish general population followed for 8 years.¹⁴ Subjects with total apo B levels in the top one-third (top tertile) had a significantly increased relative risk of cardiovascular events than patients in the lowest one-third, after controlling for LDL-C and other traditional cardiovascular risk factors (RR=1.4; 95% CI, 1.1 to 1.8 for men; RR=1.5; 95% CI, 1.1 to 2.1 for women). This study also compared the discriminatory ability of apo B with that of traditional lipid measures, by using the area under the curve (AUC) for classifying cardiovascular events. Total apo B levels had a slightly higher AUC (0.58) than LDL-C (0.57); however, this difference in AUC was not statistically significant.

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 12,000 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 are discussed next. Kappelle et al (2011) used data from the prospective Prevention of Renal and Vascular End-stage Disease trial cohort to evaluate the predictive value of the apo B/apo AI ratio independent of other traditional risk factors, including albuminuria and CRP.^{18,} Among 6948 subjects without previous heart disease and who were not on lipid-lowering drugs, the AHR for a high apo B/apo AI ratio was 1.37 (95% CI, 1.26 to 1.48). This HR 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.

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 24,558 initially healthy women enrolled in the Women's Health Study and followed for a median of 10.2 years.^{19,} 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.^{20,} This study reported that the apo B/apo AI ratio had similar predictive ability as traditional lipid ratios with respect to model discrimination, calibration, and reclassification. Authors also reported that the apo B/apo AI ratio did not provide any incremental predictive value over traditional measures.

Pencina et al (2015) used data from 2966 participants of the Framingham Offspring Study cohort who were ages 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.^{21,} 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 increase beyond expected apo B levels. 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.

Section Summary: Apolipoprotein B

The evidence has suggested that apo B provides independent information on risk assessment for CVD and that apo B may be superior to LDL-C in predicting cardiovascular risk. Numerous large prospective cohort studies and nested case-control studies have compared these measures, and most have concluded that apo B is a better predictor of cardiac risk than LDL-C. 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

Table 2. Results of Diagnostic Apolipoprotein AI Studies

Study	N	Efficacy of Apolipoprotein B in Determining CVD Risk	
		HR (95% CI)	OR (95% CI)
Study 1: UK MA trial	139,581	0.87 (0.84 to 0.90)	-
Study 2: UK prospective cohort study	7044	1.54 (1.27 to 1.87)	-
Study 3: US prospective cohort study	2966	2.32 (1.64 to 3.33)	-
Study 4: European and Japanese prospective cohort study	25,663	-	1.85 (1.15 to 2.98)

CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio; MA: meta-analysis; OR: odds ratio

In the Emerging Risk Factors Collaboration meta-analysis (2012) described above, apo AI was also examined as an independent risk factor.¹⁰ For apo AI, evidence from 26 studies (total N=139,581 subjects) reported that apo AI was an independent risk factor for reduced cardiovascular risk, with an AHR for cardiovascular events of 0.87 (95% CI, 0.84 to 0.90). 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).

AMORIS (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.¹² AFCAPS/TexCAPS investigated lipid parameters among 6605 men and women with average LDL-C and low HDL-C levels who were randomized to lovastatin or placebo.²² This study reported that apo AI levels and the apo B/apo AI ratio were strong predictors of CAD events.

The Copenhagen City Heart Study (2007) was a prospective cohort study of 9231 asymptomatic persons from the Danish general population.¹⁴ 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.

Clarke et al (2007) published a prospective cohort study of 7044 elderly men enrolled in the Whitehall Cardiovascular Cohort from England.²³ Measurements of apolipoprotein levels were performed on 5344 of these men, and they were followed for a mean of 6.8 years. Authors reported that the apo B/apo AI ratio was a significant independent predictor (HR=1.54; 95% CI, 1.27 to 1.87), with similar predictive ability as the TC/HDL ratio (HR=1.57; 95% CI, 1.32 to 1.86).

Ridker et al (2007) compared the predictive ability of apo AI and the apo B/apo AI ratio with standard lipid measurements.¹⁹ 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. 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 (EPIC-Norfolk) cohort study, evaluated the predictive ability of the apo B/apo AI ratio in relation to traditional lipid measures in 25,663 patients.²⁴ 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. 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 (adjusted OR=1.85; 95% CI, 1.15 to 2.98). However, 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).

Section Summary: Apolipoprotein AI

The current evidence has generally indicated that measurement of apo AI and the apo B/apo AI ratio are as good as or better than currently used lipid measures such as LDL and HDL. Some experts 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.^{25,26} 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

Table 3. Results of Diagnostic Apolipoprotein E Trials

Trial	N	Efficacy of Apolipoprotein B in Determining CVD Risk
		OR (95% CI)
Trials 1: US and Canada MA trial	86,067 from 82 studies	0.80 (0.70 to 0.90)
Trials 2: UK MA trial	9587 from 3 studies	0.97 (0.82 to 1.15)

CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio; MA: meta-analysis; OR: odds ratio

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.^{27,28,}

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 relation 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 12,000 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,}

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.^{40,} Eighty-two studies included data on the association between apo E and lipid levels, and 121 studies reported on the association with clinical outcomes. 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 (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.^{41,} The method for selecting the studies was not described. The 3 studies included 9587 participants and 1413 CVD events. In pooled analysis, there was no association between apo E and CVD events. The unadjusted odds ratio (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 odds for CVD for each SD increase in apo E concentration was 0.97 (95% CI, 0.82 to 1.15).

Section Summary: Apolipoprotein E

The evidence have 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.

HDL Particle Size and Concentration

In the JUPITER RCT (2013), 10,886 patients without CVD were randomized to rosuvastatin or placebo and followed for a median of 2 years.^{42,} 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 particle were reported. HDL 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; $p = 0.03$). HDL size was not significantly associated with CVD in risk factor-adjusted models.

The purpose of the gaps tables (see Tables X and X) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table X. Relevance Gaps

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
JUPITER (2013)	4. Individuals with CVD, diabetes, high LDL cholesterol, or high triglycerides excluded				
LIPID (2013)					
AIM-HIGH (2013)					

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table X. Study Design and Conduct Gaps

Study	Allocation ^a	Blinding ^b	Selective Reporting ^c	Follow-Up ^d	Power ^e	Statistical ^f
JUPITER (2013)	3. Allocation concealment unclear					
LIPID (2013)	3. Allocation concealment unclear					
AIM-HIGH (2013)		2. Blinding protocol unclear				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Follow-Up key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: HDL Particle Size and Concentration

One RCT has evaluated the association of HDL particle size and number as measured by NMR with residual CVD risk. While this study 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 information provided by traditional lipid measures.

LDL Subclass and LDL Particle Size and Concentration

A nested case-control study (1996) from the Physician's Health Study, a prospective cohort study of approximately 15,000 men, investigated whether LDL particle size is an independent predictor of CAD risk, particularly compared with triglyceride levels.⁴³ Authors concluded that while LDL particle diameter was associated with risk of MI, this association was not present after adjustment for triglyceride level. Only 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.^{11,44} 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.⁴⁵ Advanced lipoprotein testing consisted of subclass patterns of LDL (ie, presence of large buoyant particles, intermediate particles, or small dense particles). These measurements were used to predict the presence of subclinical atherosclerosis, as measured ultrasonographically by carotid intimal-media thickness. In multivariate logistic regression models, substituting advanced lipoprotein testing for corresponding traditional lipoprotein values did not improve prediction of the highest quartile of carotid intimal-media thickness.

LDL Particle Size and Concentration Measured by NMR

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 PLAC-1 trial have suggested that the number of LDL particles is an independent predictor of cardiac risk.^{46,47,48} Translating these findings into clinical practice requires setting target values for lipoprotein number. Proposed target values have been derived from the same data set (ie, Framingham study) used to set the ATP III target goals for LDL-C. For example, the ATP III targets for LDL-C correspond to the 20th, 50th, and 80th percentile values in the Framingham Offspring Study, depending on the number of risk factors present. Proposed target goals for

lipoprotein number correspond to the same percentile values, and LDL particle concentrations corresponding to the 20th, 50th, and 80th percentile are 1100, 1400, and 1800 nmol/L, respectively.⁴⁹

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. LDL 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.

Rosenson and Underberg (2013) conducted a systematic review of studies on lipid-lowering pharmacotherapies to evaluate changes in LDL particles pre- and posttreatment.⁵¹ Reductions in mean LDL particles occurred in 34 of the 36 studies evaluated. Percentage reductions of LDL particles in several statin studies were smaller than reductions in LDL-C. LDL particles and apo B changes were comparable. Reviewers suggested the differences in LDL particle reductions with different lipid-lowering therapies demonstrated potential areas of residual cardiovascular risk that could be addressed with LDL particle monitoring.

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.⁵² For each 100 nmol/L increase in LDL particle level, there was a 4% increase in risk of a CHD event (HR=1.04; 95% CI, 1.02 to 1.05; $p < 0.000$). A comparative analysis, using 1:1 propensity score matching of 2094 patients from the LDL-C target cohort (LDL-C level < 100 mg/dL without a LDL particle level) and a LDL particle target cohort (LDL particle < 1000 nmol/L and LDL-C of any level) found a lower risk of CHD or stroke in patients who received LDL-C measurement and were presumed to have received more intensive lipid-lowering therapy (HR=0.76; 95% CI, 0.61 to 0.96; at 12 months). A comparison of smaller LDL particle target groups at 24 ($n=1242$) and 36 ($n=705$) months showed similar reductions in CHD (HR=0.78; 95% CI, 0.62 to 0.97) and stroke (HR=0.75; 95% CI, 0.58 to 0.97).

Section Summary: LDL Subclass and LDL Particle Size and Concentration

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

A relatively small number of studies have evaluated the predictive ability of LDL particle size and number as measured by NMR. These studies do not demonstrate that NMR-measured particle size and/or number offer predictive ability beyond that provided by traditional lipid measures. NMR measures 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)

Table 4. Results of Diagnostic Lipoprotein (A) Studies

Study	N	Efficacy of Apolipoprotein B in Determining CVD Risk	
		HR (95% CI)	OR (95% CI)
Study 1: UK MA	154,544	1.13 (1.09 to 1.18)	-
Study 2: US RCT	7746	1.27 (1.01 to 1.59) p=0.002	-
Study 3: US RCT	1440	1.18-1.25	-
Study 4: European post hoc	9330	Men: 3.6 (1.7 to 7.7) Women: 3.7 (1.7 to 8.0)	-
Study 5: UK prospective cohort	1592	1.49 (1.0 to 2.2)	-
Study 6: US prospective cohort	4510	1.07 (1.0 to 1.12)	-
Study 7: European post hoc	56,084	1.3 (1.15 to 1.46)	-
Study 8: US/Korea prospective cohort	3419	2.35 (1.50 to 3.69)	-
Study 9: European prospective cohort	100	-	Men: 3.55 (1.33 to 9.48) Women: 0.42 (0.12 to 1.26)
Study 10: US prospective cohort	27,736	1.77 (1.36 to 2.30) p<0.001	-
Study 11: UK MA	2047	-	1.45 (1.32 to 1.58)
Study 12: European observational	56,010	-	2.39 (1.57 to 3.63)

CI: confidence interval; CVD: cardiovascular disease; HR: hazard ratio; MA: meta-analysis; OR: odds ratio; RCT: randomized control trial; RR: relative risk

Numerous prospective RCTs, cohort studies, and systematic reviews have evaluated lipoprotein (a) (Lp[a]) as a cardiovascular risk factor. The following are representative prospective trials drawn from the relevant literature.

The Emerging Risk Factors Collaboration (2012) published a patient-level meta-analysis assessing 37 prospective cohort studies enrolling 154,544 individuals.¹⁰ 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, with an AHR for cardiovascular events of 1.13 (95% CI, 1.09 to 1.18). 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%).

A systematic review by Genser et al (2011) included 67 prospective studies (total N=181,683 subjects) that evaluated the risk of CVD associated with Lp(a).⁵³ Pooled analysis was performed on 37 studies that reported the end points of cardiovascular events. When grouped by design and populations, the relative risks for these studies, comparing the uppermost and lowest strata of Lp(a), ranged from 1.64 to 2.37. The relative risk for cardiovascular events was higher in patients with previous CVD than with patients without previous disease. There were no significant associations found between Lp(a) levels, overall mortality, or stroke.

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.⁵⁴ As

part of the Framingham Offspring Study, Lp(a) levels were measured in 2191 asymptomatic men between ages of 20 and 54 years.⁵⁵ 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 Lp(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.

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.⁵⁶ Lp(a) was independently associated with a residual risk of CVD despite statin treatment (AHR=1.27; 95% CI, 1.01 to 1.59; $p=0.04$). The LIPID RCT (2013) randomized 7863 patients to pravastatin or placebo.⁵⁷ Patients were followed for a median 6 years. Lp(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 ($p=0.03$). In the AIM-HIGH 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 (HR range, 1.18-1.25).⁵⁸

Kamstrup et al (2008) analyzed data from the Copenhagen City Heart Study, which followed 9330 subjects from the Copenhagen general population over 10 years.⁵⁹ This study reported on a graded increase in risk of cardiac events with increasing Lp(a) levels. At extreme levels of Lp(a) above the 95th percentile, the AHR for MI was 3.6 (95% CI, 1.7 to 7.7) for women and 3.7 (95% CI, 1.7 to 8.0) for men. Tzoulaki et al (2007) reported on data from the Edinburgh Artery Study, a population cohort study that followed 1592 subjects for a mean of 17 years.⁶⁰ They reported that Lp(a) was an independent predictor of MI, with an odds of 1.49 (95% CI, 1.0 to 2.2) for the highest one-third vs the lowest one-third.

Zakai et al (2007) evaluated 13 potential biomarkers for independent predictive ability compared with established risk factors, using data from 4510 subjects followed for 9 years in the Cardiovascular Health Study.⁶¹ Lp(a) was 1 of 7 biomarkers that had incremental predictive ability above established risk factors. The AHR for each SD increase in Lp(a) was 1.07 (95% CI, 1.0 to 1.12).

Waldeyer et al (2017) analyzed data of 56,084 participants from Biomarkers for Cardiovascular Risk Assessment in Europe project, which followed 7 prospective population-based cohorts across Europe, with a maximum follow-up of 24 years, to characterize the association of Lp(a) concentration with major coronary events (MCE), incident CVD, and total mortality.⁶² The highest event rate of MCE and CVD was observed for Lp(a) levels at the 90th percentile or higher ($p<0.001$ for MCE 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 MCE (HR=1.3; 95% CI, 1.15 to 1.46) and CVD (HR=1.25; 95% CI, 1.12 to 1.39). For Lp(a) levels at the 90th percentile or higher, the AHR for the association between Lp(a) and MCE 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 (DHS), a multiethnic prospective cohort with a median follow-up of 9.5 years (N=3419 patients).⁶³ Quartiles 4 of Lp(a) and oxidized phospholipid on apo B-100 (OxPL-apoB) 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. 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 OxPL-apoB.

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.⁶⁴ 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.⁶⁵ 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.⁶⁶ 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.

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 (OR=3.55; 95% CI, 1.33 to 9.48) but not in women (OR=0.42; 95% CI, 0.12 to 1.26).⁶⁷ In the ARIC prospective cohort study of 14,221 participants, elevated Lp(a) was a significant independent predictor of stroke in black women (RR=1.84; 95% CI, 1.05 to 3.07) and white women (RR=2.42; 95% CI, 1.30 to 4.53) but not in black men (RR=1.72; 95% CI, 0.86 to 3.48) or white men (RR=1.18; 95% CI, 0.47 to 2.90).⁶⁸

There also may be a link between Lp(a) level as a cardiovascular risk factor and hormone status in women. Suk Danik et al (2008) reported on the risk of a first cardiovascular event over a 10-

year period in 27,736 women enrolled in the Women's Health Study.⁶⁹ After controlling for standard cardiovascular risk factors, Lp(a) levels were an independent predictor of risk in women not taking hormonal replacement therapy (HR=1.77; 95% CI, 1.36 to 2.30; $p < 0.001$). However, for women who were taking hormonal replacement therapy, Lp(a) levels were not a significant independent predictor of cardiovascular risk (HR=1.13; 95% CI, 0.84 to 1.53; $p = 0.18$).

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.⁷⁰ The combined results revealed a significant positive relation between Lp(a) and cardiovascular risk, with an odds for patients with an Lp(a) level in the top-third compared with those in the bottom-third of 1.45 (95% CI, 1.32 to 1.58). 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.⁷¹ 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 (combined OR=2.39; 95% CI, 1.57 to 3.63).

A patient-level meta-analysis (2009) of 36 prospective studies published between 1970 and 2009 included 126,634 participants.⁷² Overall, the independent association between Lp(a) level and vascular disease was consistent across studies but modest in size. The combined relative risk, 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.

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.⁷³ Genetic variants identified at two 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.

Section 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

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.⁷⁴ BNP levels 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 relation 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 ($p = 0.08$).⁷⁵ 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 MCE, ($p = 0.03$), 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 ($p = 0.002$).⁷⁶ However, any gains over use of conventional risk factors appear to be minimal.

Section Summary: B-Type or Brain Natriuretic Peptide

BNP levels 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.⁷⁷ 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 (total $N = 22,509$ participants) with predominantly high cardiovascular risk patients to evaluate the relation between elevated cystatin C levels and CVD risk.⁷⁸ 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.⁷⁹ Reviewers included 9 prospective studies (total $N = 39,854$ 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; $p = 0.021$).

Section Summary: Cystatin C

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

Fibrinogen

Kengne et al (2013) evaluated data from 9 prospective, community-based cohorts from the British and Scottish general population-based health surveys.⁸⁰ 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 a 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.⁸¹ 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 (hs-CRP, leukocyte count, and/or fibrinogen). Overall, reviewers included 20 studies (total N=49,087 participants), of which 13 studies (35,096 participants) reported fibrinogen levels. In 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 progression of common carotid artery intima-media thickness.

Other studies have found an association between fibrinogen and cardiovascular risk, including the EPIC-Norfolk cohort study⁸², and the Fibrinogen Studies Collaboration.^{83,84} 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

Section Summary: Fibrinogen

Reports from a number of cohort studies 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

Sattar et al (2009) reported on a prospective study of 5661 men and a systematic review of 7 prospective studies to evaluate the relation between leptin and CVD.⁸⁵ 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 any 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.⁸⁶ The meta-analysis included 8 nested case-control studies with 1980 patients and 11,567 controls. In 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.⁸⁷ Thirteen epidemiologic studies totaling 4257 CVD patients and 26710 controls were included. Adjusting for cardiovascular risk factors, there was no statistically significant association between leptin concentration and CHD risk (OR=1.16; 95% CI, 0.97 to 1.40). The association did not change when analyses were restricted to high-quality studies (OR=1.07; 95% CI, 0.96 to 1.19) for CHD. In a subgroup meta-analysis, a high leptin level was not independently associated with CHD in both females (OR=1.03; 95% CI, 0.86 to 1.23) and male patients (OR=1.09; 95% CI, 0.95 to 1.26).

Section Summary: Leptin

Two meta-analyses 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

Individuals with Hyperlipidemia managed with lipid-lowering therapy

Clinical Context and Test Purpose

The purpose of novel cardiac biomarker testing is to provide a treatment option that is an alternative to or an improvement on existing therapies 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 PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The therapy being considered is novel cardiac biomarker testing.

Comparators

Comparators of interest include routine care without biomarker testing.

Outcomes

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

Timing

Follow-up at 1-, 2-, 15-, and 25- years is of interest for novel cardiac biomarker testing for overall survival, change in disease status, morbid events, and medication use.

Setting

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

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

Apolipoprotein B

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.⁸⁸ Eight studies enrolling 62,154 participants were included. The AHR for each 1 standard deviation (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 38,153 patients allocated to the statin therapy groups.⁸⁹ Despite statin therapy, reductions in levels of LDL-C, non-HDL-C, and apo B from baseline to 1 year showed large interindividual variations.

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 (LUNAR) trial.⁹⁰ The LUNAR 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 Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS [2000]) evaluated lipid parameters among 6605 men and women with average LDL-C and low HDL-C levels who were randomized to lovastatin or placebo.²² Baseline LDL-C, HDL-C, and apo B levels were predictive of future coronary events. However, in the treatment group, 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.⁹¹ 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 (IDEAL) trials, to compare the relation between response to lipids, apo B levels, and other lipid measures.⁹² The analysis included 18,889 patients with established coronary disease randomized to low- or high-dose statin treatment. In pairwise comparisons, the on-treatment apo B level was a significant

predictor of cardiovascular events (HR=1.24; 95% CI, 1.13 to 1.36; $p<0.001$), 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).⁹³ 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.⁹⁴ Using data from the JUPITER trial, on-treatment levels of LDL-C, non-HDL-C, high-sensitivity CRP (hs-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 less than 70 mg/dL.

Section Summary: Apolipoprotein B

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

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 2008 Kastelein study (described above), authors combined data from 2 RCTs, the TNT and IDEAL trials, to compare the relation between response to lipids, apo B/apo AI ratio, and other lipid measures.⁹² 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 PROVE-IT TIMI study (2009) randomized 4162 patients with acute coronary syndrome to standard statin therapy or intensive statin therapy.⁹⁵ While the on-treatment apo B/apo AI ratio was a significant predictor of cardiac events (HR for each SD increment, 1.10; 95% CI, 1.01 to 1.20), it was not superior to LDL-C (HR=1.20; 95% CI, 1.07 to 1.35) or the TC/HDL ratio (HR=1.12; 95% CI, 1.01 to 1.24) as a predictor of cardiac events.

Preliminary studies of infusions of reconstituted apo AI have demonstrated plaque regression in a small number of patients with acute coronary syndrome.⁹⁶ Based on this research, there has been interest in developing synthetic apo AI mimetic proteins, and such agents are in the drug development stage. These types of agents would likely target patients with residual cardiac risk following maximal statin therapy, especially patients with low HDL levels.

Section Summary: Apolipoprotein AI

The use of apo AI and the apo B/apo AI ratio as a target of treatment response to statins may also be as good as or better than the traditional measure of LDL. However, to improve outcomes, clinicians must have the tools to translate this information into clinical practice. Such tools for linking apo AI to clinical decision making, both in risk assessment and treatment response, are currently not available. Apo 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

Apo 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.^{97,98} Other studies have suggested that response to statin therapy may vary by *APOE* genotype and that the e2 allele indicates greater responsiveness to statins.^{97,99}

Chiodini et al (2007) examined differential response to statin therapy by *APOE* genotype in a reanalysis of data from the GISSI study.¹⁰⁰ GISSI 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 *APOE* genotype.

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.¹⁰¹ Researchers reported on final LDL levels and percentages of patients achieving target LDL by *APOE* genetic status. LDL levels following treatment were lower for patients who were homozygous for apo e2 (0.6 mmol/L) than for patients homozygous for apo e4 (1.7 mmol/L; $p<0.001$). 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.¹⁰² 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.

Section Summary: Apolipoprotein E

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

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

LDL Subclass and LDL 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.¹⁰³ 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.¹⁰⁴

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.¹⁰⁵ 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.¹⁰⁶

Various studies have generally confirmed that small, dense LDL is impacted preferentially by fibrate treatment^{107,108,109}, and possibly also by statin therapy.^{107,109} However, none demonstrated that preferentially targeting small, dense LDL leads to improved outcomes, compared with standard LDL targets widely used in clinical care.

Several trials with angiographic outcomes have examined the change in LDL particle size in relation to angiographic progression of CAD. The 1996 Stanford Coronary Risk Intervention Project trial studied the relation between small, dense LDL and the benefit of diet, counseling, and drug therapy in patients with CAD, as identified by initial coronary angiogram.¹¹⁰ 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.¹¹¹ Change in LDL particle size correlated significantly with angiographic progression of CAD in this study.

Fewer studies have evaluated clinical outcomes in relation to LDL particle size. In the 2001 Cholesterol and Recurrent Events trial, survivors of MI with normal cholesterol levels were randomized to lipid-lowering therapy or placebo.¹¹² A post hoc analysis from this trial failed to demonstrate a correlation between change in particle size and treatment benefit.

Section Summary: LDL Subclass and LDL Particle Size and Concentration

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

Lipoprotein (a)

There is a lack of evidence to determine whether Lp(a) can be used as a target of treatment. Several randomized studies of lipid-lowering therapy have included Lp(a) measurements as an intermediate outcome. While these studies have demonstrated that Lp(a) levels are reduced in patients receiving statin therapy, the data are inadequate to demonstrate how this laboratory test can be used to improve patient management.^{113,114}

Section 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 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 insufficient related to impact on clinical 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 the effects of the technology on 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 the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Heart, Lung, and Blood Institute

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 in 2001.¹ 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.¹¹⁵

In 2013, the Institute published a systematic evidence review on managing blood cholesterol in adults.¹¹⁶ 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).¹¹⁷

ACC and AHA

ACC and AHA published guidelines in 2013 for the assessment of cardiovascular risk.¹¹⁷ 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. 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.

European Society of Cardiology et al

The 2012 guidelines from the European Society of Cardiology and other societies on cardiovascular disease (CVD) prevention in clinical practice indicated that apo B can be a substitute for low-density lipoprotein cholesterol (LDL-C), but its use does not improve risk assessment and apo B is not readily available.¹¹⁸ The use of Lp(a) was not justified as a treatment target or for screening the general population.

In 2016, the Society and other societies issued guidelines on cardiovascular risk prevention in clinical practice, which included recommendations for lipid control based on LDL-C levels and targets.¹¹⁹ The guidelines indicated that "there is no evidence that apo B is a better predictor of CVD than LDL-C." They also stated that while the apo B/apo AI ratio is one of the strongest predictors of CVD, there is insufficient evidence to support its use as a treatment goal.

American Diabetes Association and ACC Foundation

In 2008, a consensus statement from the American Diabetes Association and the ACC Foundation addressed lipoprotein management in patients with cardiometabolic risk.¹²⁰ 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.

American Association of Clinical Endocrinologists and American College of Endocrinology

In 2017, American Association of Clinical Endocrinologists and American College of Endocrinology published joint guidelines on the management of dyslipidemia and prevention of CVDs.¹²¹ 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 recommendations for patient-centered management of dyslipidemia were published in 2015.¹²² 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.

Canadian Cardiovascular Society

The Canadian Cardiovascular Society (2003) endorsed use of apo B as a treatment target and proposed a target apo B level of 90 mg/dL.¹²³ These guidelines also recommended that a Lp(a) concentration greater than 30 mg/dL with elevated LDL or other major risk factors may indicate the need for earlier and more intensive therapy to lower the LDL-C level. These guidelines were updated in 2006¹²⁴, and 2016.

National Institute for Health and Care Excellence

The National Institute for Health and Care Excellence updated its guidance on risk assessment and reduction, including lipid modification, of CVD in 2016.¹²⁵ The guidance recommended measuring a full lipid profile including total cholesterol, high-density lipoprotein (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 40% reduction in non-HDL. Apo B and other nontraditional risk factors 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 issued recommendations in 2009 on the use of nontraditional risk factors for the assessment of coronary heart disease (CHD).¹²⁶ 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.”

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in October 2017 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
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise 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
84999	Unlisted chemistry procedure
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

- There is no specific CPT code for measurement of apolipoprotein B. CPT code 82172 might be used.
- There is no specific code for apo E phenotyping or genotyping. For phenotyping, CPT code 84181 may be used. Testing for *APOE* common variants can be reported using CPT code 81401.

- There is no CPT code for subclassification that is specific to low-density lipoprotein (LDL) subclass but code 83721 is available for LDL cholesterol.
- There is no CPT code for subclassification specific to high-density lipoprotein (HDL). CPT code 82664 or 83701 may be used.
- There is a CPT code for lipoprotein particle number and subclass quantification by nuclear magnetic resonance spectroscopy that is also not specific to HDL 83704.
- The following CPT codes for quantitation of lipoprotein levels are available: 83700, 83701, and 83704.
- There is a specific CPT code for lipoprotein (a) testing: 83695.
- There is a specific CPT code for B-type natriuretic peptide testing: 83880.
- Testing for cystatin C is reported with CPT code: 82610.
- There are 2 CPT codes for fibrinogen testing: 85384, 85385.
- There is no specific CPT code for leptin testing. According to laboratory websites, CPT codes such as 82397 (Chemiluminescent assay) or 83520 (Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified) might be used.
- A new PLA CPT code was effective 7/1/18: 0052U.
- A new Category 1 code was effective 1/1/19 that is a direct single step method, for the quantification of small dense low-density lipoprotein cholesterol: 83722.

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:

REVISIONS	
	<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.
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.

REFERENCES

1. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. May 16 2001;285(19):2486-2497. PMID 11368702
2. BlueCross and BlueShield Technology Evaluation Center. C-Reactive Protein as a Cardiac Risk Marker (Special Report). TEC Assessment. 2002;Volume 17:Tab 23. PMID
3. Perera R, McFadden E, McLellan J, et al. Optimal strategies for monitoring lipid levels in patients at risk or with cardiovascular disease: a systematic review with statistical and cost-effectiveness modelling. Health Technol Assess. Dec 2015;19(100):1-401, vii-viii. PMID 26680162
4. Thanassoulis G, Williams K, Ye K, et al. Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials. J Am Heart Assoc. Apr 14 2014;3(2):e000759. PMID 24732920
5. van Holten TC, Waanders LF, de Groot PG, et al. Circulating biomarkers for predicting cardiovascular disease risk; a systematic review and comprehensive overview of meta-analyses. PLoS One. May 2013;8(4):e62080. PMID 23630624

6. Tzoulaki I, Siontis KC, Evangelou E, et al. Bias in associations of emerging biomarkers with cardiovascular disease. *JAMA Intern Med.* Apr 22 2013;173(8):664-671. PMID 23529078
7. Willis A, Davies M, Yates T, et al. Primary prevention of cardiovascular disease using validated risk scores: a systematic review. *J R Soc Med.* Aug 2012;105(8):348-356. PMID 22907552
8. Robinson JG, Wang S, Jacobson TA. Meta-analysis of comparison of effectiveness of lowering apolipoprotein B versus low-density lipoprotein cholesterol and nonhigh-density lipoprotein cholesterol for cardiovascular risk reduction in randomized trials. *Am J Cardiol.* Nov 15 2012;110(10):1468-1476. PMID 22906895
9. Sniderman AD, Islam S, Yusuf S, et al. Discordance analysis of apolipoprotein B and non-high density lipoprotein cholesterol as markers of cardiovascular risk in the INTERHEART study. *Atherosclerosis.* Dec 2012;225(2):444-449. PMID 23068583
10. Emerging Risk Factors Collaboration, Di Angelantonio E, Gao P, et al. Lipid-related markers and cardiovascular disease prediction. *JAMA.* Jun 20 2012;307(23):2499-2506. PMID 22797450
11. Lamarche B, Moorjani S, Lupien PJ, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec Cardiovascular Study. *Circulation.* Aug 1 1996;94(3):273-278. PMID 8759066
12. Walldius G, Jungner I, Holme I, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet.* Dec 15 2001;358(9298):2026-2033. PMID 11755609
13. Ridker PM, Rifai N, Cook NR, et al. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA.* Jul 20 2005;294(3):326-333. PMID 16030277
14. Benn M, Nordestgaard BG, Jensen GB, et al. Improving prediction of ischemic cardiovascular disease in the general population using apolipoprotein B: the Copenhagen City Heart Study. *Arterioscler Thromb Vasc Biol.* Mar 2007;27(3):661-670. PMID 17170368
15. Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* Sep 4 2001;104(10):1108-1113. PMID 11535564
16. Rasouli M, Kiasari AM, Mokhberi V. The ratio of apoB/apoAI, apoB and lipoprotein(a) are the best predictors of stable coronary artery disease. *Clin Chem Lab Med.* Aug 2006;44(8):1015-1021. PMID 16879071
17. Walldius G, Jungner I. Apolipoprotein B and apolipoprotein A-I: risk indicators of coronary heart disease and targets for lipid-modifying therapy. *J Intern Med.* Feb 2004;255(2):188-205. PMID 14746556
18. Kappelle PJ, Gansevoort RT, Hillege JL, et al. Apolipoprotein B/A-I and total cholesterol/high-density lipoprotein cholesterol ratios both predict cardiovascular events in the general population independently of nonlipid risk factors, albuminuria and C-reactive protein. *J Intern Med.* Feb 2011;269(2):232-242. PMID 21129046
19. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA.* Feb 14 2007;297(6):611-619. PMID 17299196
20. Ingelsson E, Schaefer EJ, Contois JH, et al. Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. *JAMA.* Aug 15 2007;298(7):776-785. PMID 17699011
21. Pencina MJ, D'Agostino RB, Zdrojewski T, et al. Apolipoprotein B improves risk assessment of future coronary heart disease in the Framingham Heart Study beyond LDL-C and non-HDL-C. *Eur J Prev Cardiol.* Oct 2015;22(10):1321-1327. PMID 25633587
22. Gotto AM, Jr., Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). *Circulation.* Feb 8 2000;101(5):477-484. PMID 10662743
23. Clarke R, Emberson JR, Parish S, et al. Cholesterol fractions and apolipoproteins as risk factors for heart disease mortality in older men. *Arch Intern Med.* Jul 9 2007;167(13):1373-1378. PMID 17620530

24. van der Steeg WA, Boekholdt SM, Stein EA, et al. Role of the apolipoprotein B-apolipoprotein A-I ratio in cardiovascular risk assessment: a case-control analysis in EPIC-Norfolk. *Ann Intern Med.* May 1 2007;146(9):640-648. PMID 17470832
25. Mudd JO, Borlaug BA, Johnston PV, et al. Beyond low-density lipoprotein cholesterol: defining the role of low-density lipoprotein heterogeneity in coronary artery disease. *J Am Coll Cardiol.* Oct 30 2007;50(18):1735-1741. PMID 17964036
26. Sniderman AD, Kiss RS. The strengths and limitations of the apoB/apoA-I ratio to predict the risk of vascular disease: a Hegelian analysis. *Curr Atheroscler Rep.* Oct 2007;9(4):261-265. PMID 18173952
27. Davignon J, Gregg RE, Sing CF. Apolipoprotein E polymorphism and atherosclerosis. *Arteriosclerosis.* Jan-Feb 1988;8(1):1-21. PMID 3277611
28. Hallman DM, Boerwinkle E, Saha N, et al. The apolipoprotein E polymorphism: a comparison of allele frequencies and effects in nine populations. *Am J Hum Genet.* Aug 1991;49(2):338-349. PMID 1867194
29. Koch W, Hoppmann P, Schomig A, et al. Apolipoprotein E gene epsilon2/epsilon3/epsilon4 polymorphism and myocardial infarction: case-control study in a large population sample. *Int J Cardiol.* Mar 28 2008;125(1):116-117. PMID 17433475
30. Kulminski AM, Ukraintseva SV, Arbeev KG, et al. Health-protective and adverse effects of the apolipoprotein E epsilon2 allele in older men. *J Am Geriatr Soc.* Mar 2008;56(3):478-483. PMID 18179501
31. Schmitz F, Mevissen V, Krantz C, et al. Robust association of the APOE epsilon4 allele with premature myocardial infarction especially in patients without hypercholesterolaemia: the Aachen study. *Eur J Clin Invest.* Feb 2007;37(2):106-108. PMID 17217375
32. Vaisi-Raygani A, Rahimi Z, Nomani H, et al. The presence of apolipoprotein epsilon4 and epsilon2 alleles augments the risk of coronary artery disease in type 2 diabetic patients. *Clin Biochem.* Oct 2007;40(15):1150-1156. PMID 17689519
33. Ciftdogan DY, Coskun S, Ulman C, et al. The association of apolipoprotein E polymorphism and lipid levels in children with a family history of premature coronary artery disease. *J Clin Lipidol.* Jan-Feb 2012;6(1):81-87. PMID 22264578
34. Vasunilashorn S, Gleib DA, Lan CY, et al. Apolipoprotein E is associated with blood lipids and inflammation in Taiwanese older adults. *Atherosclerosis.* Nov 2011;219(1):349-354. PMID 21840004
35. de Andrade M, Thandi I, Brown S, et al. Relationship of the apolipoprotein E polymorphism with carotid artery atherosclerosis. *Am J Hum Genet.* Jun 1995;56(6):1379-1390. PMID 7762561
36. Eichner JE, Kuller LH, Orchard TJ, et al. Relation of apolipoprotein E phenotype to myocardial infarction and mortality from coronary artery disease. *Am J Cardiol.* Jan 15 1993;71(2):160-165. PMID 8421977
37. Wilson PW, Myers RH, Larson MG, et al. Apolipoprotein E alleles, dyslipidemia, and coronary heart disease. The Framingham Offspring Study. *JAMA.* Dec 7 1994;272(21):1666-1671. PMID 7966894
38. Wilson PW, Schaefer EJ, Larson MG, et al. Apolipoprotein E alleles and risk of coronary disease. A meta-analysis. *Arterioscler Thromb Vasc Biol.* Oct 1996;16(10):1250-1255. PMID 8857921
39. Volcik KA, Barkley RA, Hutchinson RG, et al. Apolipoprotein E polymorphisms predict low density lipoprotein cholesterol levels and carotid artery wall thickness but not incident coronary heart disease in 12,491 ARIC study participants. *Am J Epidemiol.* Aug 15 2006;164(4):342-348. PMID 16760224
40. Bennet AM, Di Angelantonio E, Ye Z, et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. *JAMA.* Sep 19 2007;298(11):1300-1311. PMID 17878422
41. Sofat R, Cooper JA, Kumari M, et al. Circulating apolipoprotein E concentration and cardiovascular disease risk: meta-analysis of results from three studies. *PLoS Med.* Oct 2016;13(10):e1002146. PMID 27755538
42. Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. *Circulation.* Sep 10 2013;128(11):1189-1197. PMID 24002795
43. Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA.* Sep 18 1996;276(11):882-888. PMID 8782637

44. Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. *Circulation*. Jan 7 1997;95(1):69-75. PMID 8994419
45. Tzou WS, Douglas PS, Srinivasan SR, et al. Advanced lipoprotein testing does not improve identification of subclinical atherosclerosis in young adults: the Bogalusa Heart Study. *Ann Intern Med*. May 3 2005;142(9):742-750. PMID 15867406
46. Blake GJ, Otvos JD, Rifai N, et al. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. *Circulation*. Oct 8 2002;106(15):1930-1937. PMID 12370215
47. Kuller L, Arnold A, Tracy R, et al. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the Cardiovascular Health Study. *Arterioscler Thromb Vasc Biol*. Jul 1 2002;22(7):1175-1180. PMID 12117734
48. Rosenson RS, Otvos JD, Freedman DS. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial. *Am J Cardiol*. Jul 15 2002;90(2):89-94. PMID 12106834
49. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. *Am J Cardiol*. Oct 17 2002;90(8A):22i-29i. PMID 12419478
50. Mora S, Otvos JD, Rifai N, et al. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation*. Feb 24 2009;119(7):931-939. PMID 19204302
51. Rosenson RS, Underberg JA. Systematic review: Evaluating the effect of lipid-lowering therapy on lipoprotein and lipid values. *Cardiovasc Drugs Ther*. Jul 28 2013;27(5):465-479. PMID 23893306
52. Toth PP, Grabner M, Punekar RS, et al. Cardiovascular risk in patients achieving low-density lipoprotein cholesterol and particle targets. *Atherosclerosis*. Aug 2014;235(2):585-591. PMID 24956532
53. Genser B, Dias KC, Siekmeier R, et al. Lipoprotein (a) and risk of cardiovascular disease--a systematic review and meta analysis of prospective studies. *Clin Lab*. Apr 2011;57(3-4):143-156. PMID 21500721
54. Schaefer EJ, Lamon-Fava S, Jenner JL, et al. Lipoprotein(a) levels and risk of coronary heart disease in men. The Lipid Research Clinics Coronary Primary Prevention Trial. *JAMA*. Apr 6 1994;271(13):999-1003. PMID 8139085
55. Bostom AG, Cupples LA, Jenner JL, et al. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger. A prospective study. *JAMA*. Aug 21 1996;276(7):544-548. PMID 8709403
56. Khera AV, Everett BM, Caulfield MP, et al. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). *Circulation*. Feb 11 2014;129(6):635-642. PMID 24243886
57. Nestel PJ, Barnes EH, Tonkin AM, et al. Plasma lipoprotein(a) concentration predicts future coronary and cardiovascular events in patients with stable coronary heart disease. *Arterioscler Thromb Vasc Biol*. Dec 2013;33(12):2902-2908. PMID 24092750
58. Albers JJ, Slee A, O'Brien KD, et al. Relationship of apolipoproteins A-1 and B, and lipoprotein(a) to cardiovascular outcomes: the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes). *J Am Coll Cardiol*. Oct 22 2013;62(17):1575-1579. PMID 23973688
59. Kamstrup PR, Benn M, Tybjaerg-Hansen A, et al. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. *Circulation*. Jan 15 2008;117(2):176-184. PMID 18086931
60. Tzoulaki I, Murray GD, Lee AJ, et al. Relative value of inflammatory, hemostatic, and rheological factors for incident myocardial infarction and stroke: the Edinburgh Artery Study. *Circulation*. Apr 24 2007;115(16):2119-2127. PMID 17404162

61. Zakai NA, Katz R, Jenny NS, et al. Inflammation and hemostasis biomarkers and cardiovascular risk in the elderly: the Cardiovascular Health Study. *J Thromb Haemost.* Jun 2007;5(6):1128-1135. PMID 17388967
62. Waldeyer C, Makarova N, Zeller T, et al. Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. *Eur Heart J.* Aug 21 2017;38(32):2490-2498. PMID 28449027
63. Lee SR, Prasad A, Choi YS, et al. LPA gene, ethnicity, and cardiovascular events. *Circulation.* Jan 17 2017;135(3):251-263. PMID 27831500
64. Fogacci F, Cicero AF, D'Addato S, et al. Serum lipoprotein(a) level as long-term predictor of cardiovascular mortality in a large sample of subjects in primary cardiovascular prevention: data from the Brisighella Heart Study. *Eur J Intern Med.* Jan 2017;37:49-55. PMID 27553697
65. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. *JAMA.* Nov 10 1993;270(18):2195-2199. PMID 8411602
66. Bolibar I, von Eckardstein A, Assmann G, et al. Short-term prognostic value of lipid measurements in patients with angina pectoris. The ECAT Angina Pectoris Study Group: European Concerted Action on Thrombosis and Disabilities. *Thromb Haemost.* Dec 2000;84(6):955-960. PMID 11154140
67. Rigal M, Ruidavets JB, Viguier A, et al. Lipoprotein (a) and risk of ischemic stroke in young adults. *J Neurol Sci.* Jan 15 2007;252(1):39-44. PMID 17113602
68. Ohira T, Schreiner PJ, Morrisett JD, et al. Lipoprotein(a) and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. *Stroke.* Jun 2006;37(6):1407-1412. PMID 16675734
69. Suk Danik J, Rifai N, Buring JE, et al. Lipoprotein(a), hormone replacement therapy, and risk of future cardiovascular events. *J Am Coll Cardiol.* Jul 8 2008;52(2):124-131. PMID 18598891
70. Bennet A, Di Angelantonio E, Erqou S, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. *Arch Intern Med.* Mar 24 2008;168(6):598-608. PMID 18362252
71. Smolders B, Lemmens R, Thijs V. Lipoprotein (a) and stroke: a meta-analysis of observational studies. *Stroke.* Jun 2007;38(6):1959-1966. PMID 17478739
72. Erqou S, Kaptoge S, Perry PL, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA.* Jul 22 2009;302(4):412-423. PMID 19622820
73. Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med.* Dec 24 2009;361(26):2518-2528. PMID 20032323
74. Shaw LJ, Polk DM, Kahute TA, et al. Prognostic accuracy of B-natriuretic peptide measurements and coronary artery calcium in asymptomatic subjects (from the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research [EISNER] study). *Am J Cardiol.* Nov 1 2009;104(9):1245-1250. PMID 19840570
75. Melander O, Newton-Cheh C, Almgren P, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. *JAMA.* Jul 1 2009;302(1):49-57. PMID 19567439
76. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med.* Feb 12 2004;350(7):655-663. PMID 14960742
77. Ito H, Pacold IV, Durazo-Arvizu R, et al. The effect of including cystatin C or creatinine in a cardiovascular risk model for asymptomatic individuals: the multi-ethnic study of atherosclerosis. *Am J Epidemiol.* Oct 15 2011;174(8):949-957. PMID 21880578
78. Lee M, Saver JL, Huang WH, et al. Impact of elevated cystatin C level on cardiovascular disease risk in predominantly high cardiovascular risk populations: a meta-analysis. *Circ Cardiovasc Qual Outcomes.* Nov 2010;3(6):675-683. PMID 20923994
79. Luo J, Wang LP, Hu HF, et al. Cystatin C and cardiovascular or all-cause mortality risk in the general population: A meta-analysis. *Clin Chim Acta.* Jul 17 2015;450:39-45. PMID 26192218
80. Kengne AP, Czernichow S, Stamatakis E, et al. Fibrinogen and future cardiovascular disease in people with diabetes: aetiological associations and risk prediction using individual participant data from nine community-based prospective cohort studies. *Diab Vasc Dis Res.* Mar 2013;10(2):143-151. PMID 22786872

81. Willeit P, Thompson SG, Agewall S, et al. Inflammatory markers and extent and progression of early atherosclerosis: Meta-analysis of individual-participant-data from 20 prospective studies of the PROG-IMT collaboration. *Eur J Prev Cardiol.* Jan 2016;23(2):194-205. PMID 25416041
82. Ahmadi-Abhari S, Luben RN, Wareham NJ, et al. Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study. *Eur J Epidemiol.* Jul 3 2013;28(7):541-550. PMID 23821244
83. Fibrinogen Studies Collaboration, Kaptoge S, White IR, et al. Associations of plasma fibrinogen levels with established cardiovascular disease risk factors, inflammatory markers, and other characteristics: individual participant meta-analysis of 154,211 adults in 31 prospective studies: the fibrinogen studies collaboration. *Am J Epidemiol.* Oct 15 2007;166(8):867-879. PMID 17785713
84. Fibrinogen Studies Collaboration, Danesh J, Lewington S, et al. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. *JAMA.* Oct 12 2005;294(14):1799-1809. PMID 16219884
85. Sattar N, Wannamethee G, Sarwar N, et al. Leptin and coronary heart disease: prospective study and systematic review. *J Am Coll Cardiol.* Jan 13 2009;53(2):167-175. PMID 19130985
86. Zeng R, Xu CH, Xu YN, et al. Association of leptin levels with pathogenetic risk of coronary heart disease and stroke: a meta-analysis. *Arq Bras Endocrinol Metabol.* Nov 2014;58(8):817-823. PMID 25465603
87. Yang H, Guo W, Li J, et al. Leptin concentration and risk of coronary heart disease and stroke: A systematic review and meta-analysis. *PLoS One.* Mar 9 2017;12(3):e0166360. PMID 28278178
88. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. *JAMA.* Mar 28 2012;307(12):1302-1309. PMID 22453571
89. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol.* Aug 5 2014;64(5):485-494. PMID 25082583
90. Ballantyne CM, Pitt B, Loscalzo J, et al. Alteration of relation of atherogenic lipoprotein cholesterol to apolipoprotein B by intensive statin therapy in patients with acute coronary syndrome (from the Limiting UNderreatment of lipids in ACS With Rosuvastatin [LUNAR] Trial). *Am J Cardiol.* Feb 15 2013;111(4):506-509. PMID 23237107
91. Simes RJ, Marschner IC, Hunt D, et al. Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? *Circulation.* Mar 12 2002;105(10):1162-1169. PMID 11889008
92. Kastelein JJ, van der Steeg WA, Holme I, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. *Circulation.* Jun 10 2008;117(23):3002-3009. PMID 18519851
93. Mora S, Wenger NK, Demicco DA, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. *Circulation.* Apr 24 2012;125(16):1979-1987. PMID 22461416
94. Mora S, Glynn RJ, Boekholdt SM, et al. On-treatment non-high-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and lipid ratios in relation to residual vascular risk after treatment with potent statin therapy: JUPITER (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin). *J Am Coll Cardiol.* Apr 24 2012;59(17):1521-1528. PMID 22516441
95. Ray KK, Cannon CP, Cairns R, et al. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, or hs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. *Arterioscler Thromb Vasc Biol.* Mar 2009;29(3):424-430. PMID 19122170
96. Osei-Hwedieh DO, Amar M, Sviridov D, et al. Apolipoprotein mimetic peptides: Mechanisms of action as anti-atherogenic agents. *Pharmacol Ther.* Apr 2011;130(1):83-91. PMID 21172387
97. Ordovas JM, Mooser V. The APOE locus and the pharmacogenetics of lipid response. *Curr Opin Lipidol.* Apr 2002;13(2):113-117. PMID 11891412

98. Sarkkinen E, Korhonen M, Erkkila A, et al. Effect of apolipoprotein E polymorphism on serum lipid response to the separate modification of dietary fat and dietary cholesterol. *Am J Clin Nutr.* Dec 1998;68(6):1215-1222. PMID 9846849
99. Carmena R, Roederer G, Mailloux H, et al. The response to lovastatin treatment in patients with heterozygous familial hypercholesterolemia is modulated by apolipoprotein E polymorphism. *Metabolism.* Jul 1993;42(7):895-901. PMID 8345800
100. Chiodini BD, Franzosi MG, Barlera S, et al. Apolipoprotein E polymorphisms influence effect of pravastatin on survival after myocardial infarction in a Mediterranean population: the GISSI-Prevenzione study. *Eur Heart J.* Aug 2007;28(16):1977-1983. PMID 17567623
101. Donnelly LA, Palmer CN, Whitley AL, et al. Apolipoprotein E genotypes are associated with lipid-lowering responses to statin treatment in diabetes: a Go-DARTS study. *Pharmacogenet Genomics.* Apr 2008;18(4):279-287. PMID 18334912
102. Vossen CY, Hoffmann MM, Hahmann H, et al. Effect of APOE genotype on lipid levels in patients with coronary heart disease during a 3-week inpatient rehabilitation program. *Clin Pharmacol Ther.* Aug 2008;84(2):222-227. PMID 18388879
103. Kwiterovich PO, Jr. Clinical relevance of the biochemical, metabolic, and genetic factors that influence low-density lipoprotein heterogeneity. *Am J Cardiol.* Oct 17 2002;90(8A):30i-47i. PMID 12419479
104. Superko HR. Beyond LDL cholesterol reduction. *Circulation.* Nov 15 1996;94(10):2351-2354. PMID 8921770
105. Superko HR, Berneis KK, Williams PT, et al. Gemfibrozil reduces small low-density lipoprotein more in normolipemic subjects classified as low-density lipoprotein pattern B compared with pattern A. *Am J Cardiol.* Nov 1 2005;96(9):1266-1272. PMID 16253595
106. Sirtori CR, Calabresi L, Pisciotta L, et al. Effect of statins on LDL particle size in patients with familial combined hyperlipidemia: a comparison between atorvastatin and pravastatin. *Nutr Metab Cardiovasc Dis.* Feb 2005;15(1):47-55. PMID 15871851
107. Arca M, Montali A, Pigna G, et al. Comparison of atorvastatin versus fenofibrate in reaching lipid targets and influencing biomarkers of endothelial damage in patients with familial combined hyperlipidemia. *Metabolism.* Nov 2007;56(11):1534-1541. PMID 17950105
108. Rosenson RS, Wolff DA, Huskin AL, et al. Fenofibrate therapy ameliorates fasting and postprandial lipoproteinemia, oxidative stress, and the inflammatory response in subjects with hypertriglyceridemia and the metabolic syndrome. *Diabetes Care.* Aug 2007;30(8):1945-1951. PMID 17483155
109. Tokuno A, Hirano T, Hayashi T, et al. The effects of statin and fibrate on lowering small dense LDL-cholesterol in hyperlipidemic patients with type 2 diabetes. *J Atheroscler Thromb.* Jun 2007;14(3):128-132. PMID 17587764
110. Miller BD, Alderman EL, Haskell WL, et al. Predominance of dense low-density lipoprotein particles predicts angiographic benefit of therapy in the Stanford Coronary Risk Intervention Project. *Circulation.* Nov 1 1996;94(9):2146-2153. PMID 8901665
111. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med.* Nov 8 1990;323(19):1289-1298. PMID 2215615
112. Campos H, Moye LA, Glasser SP, et al. Low-density lipoprotein size, pravastatin treatment, and coronary events. *JAMA.* Sep 26 2001;286(12):1468-1474. PMID 11572739
113. Bays HE, Dujovne CA, McGovern ME, et al. Comparison of once-daily, niacin extended-release/lovastatin with standard doses of atorvastatin and simvastatin (the ADVICOR Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). *Am J Cardiol.* Mar 15 2003;91(6):667-672. PMID 12633795
114. van Wissen S, Smilde TJ, Trip MD, et al. Long term statin treatment reduces lipoprotein(a) concentrations in heterozygous familial hypercholesterolaemia. *Heart.* Aug 2003;89(8):893-896. PMID 12860867

115. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. Jul 13 2004;110(2):227-239. PMID 15249516
116. National Heart Lung and Blood Institute. *Managing Blood Cholesterol in Adults: Systematic Evidence Review From the Cholesterol Expert Panel, 2013*. Bethesda, MD: National Heart, Lung, and Blood Institute; 2013.
117. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. Jul 1 2014;63(25 Pt B):2889-2934. PMID 24239923
118. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. Jul 2012;33(13):1635-1701. PMID 22555213
119. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. Aug 1 2016;37(29):2315-2381. PMID 27222591
120. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. *Diabetes Care*. Apr 2008;31(4):811-822. PMID 18375431
121. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract*. Apr 2017;23(Suppl 2):1-87. PMID 28437620
122. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 1 - executive summary. *J Clin Lipidol*. Sep-Oct 2014;8(5):473-488. PMID 25234560
123. Genest J, Frohlich J, Fodor G, et al. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the 2003 update. *CMAJ*. Oct 28 2003;169(9):921-924. PMID 14581310
124. McPherson R, Frohlich J, Fodor G, et al. Canadian Cardiovascular Society position statement-- recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. *Can J Cardiol*. Sep 2006;22(11):913-927. PMID 16971976
125. National Institute for Health and Care Excellence (NICE). *Cardiovascular disease: risk assessment and reduction, including lipid modification [CG181]*. 2016; <https://www.nice.org.uk/guidance/cg181>. Accessed January 25, 2018.
126. Helfand M, Buckley DI, Freeman M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. *Ann Intern Med*. Oct 6 2009;151(7):496-507. PMID 19805772