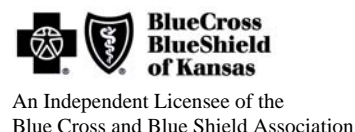


## Medical Policy



### **Title: Apolipoprotein B in the Risk Assessment and Management of Cardiovascular Disease**

#### **Professional**

Original Effective Date: March 13, 2009

Revision Date(s):

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#### **DESCRIPTION**

Low-density lipoproteins (LDL) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project (NCEP) as the primary target of cholesterol-lowering therapy. LDL particles consist of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins, surrounding an inner lipid core composed of cholesterol ester and triglycerides. LDL particles can vary both in size and in cholesterol content, and for a given level of LDL-C, there can be a wide variety of both size and numbers of LDL particles. Traditional lipid risk factors such as 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 occur in subjects with 'normal' levels of total and LDL cholesterol. Thus there is considerable potential to improve the accuracy of current cardiovascular risk prediction models. Recently there has been interest in investigating the concentration of LDL particles and their size as an independent risk factor.

Two basic techniques are used for measuring LDL particle concentration, the surrogate measurement of apolipoprotein B (apo B) or direct measurement of the number of particles using nuclear magnetic spectroscopy. Apo B is the major protein moiety of all lipoproteins except for high-density lipoprotein (HDL). The most abundant form of apo B, large B or B-100, constitutes the apo B found in low-density lipoproteins (LDL) and very-low-density lipoproteins (VLDL). Since both LDL and VLDL each contain 1 molecule of apolipoprotein B, measurement of apo B reflects the total number of these atherogenic particles, 90% of which are LDL. Nuclear resonance spectroscopy (NMR) is based on the fact that lipoprotein subclasses of different size broadcast distinguishable NMR signals. Thus NMR can quantify the number of LDL particles of a specific size (i.e., small dense LDL) and can provide a measurement of the total number of particles

## **POLICY**

Measurement of apolipoprotein B is considered **investigational** as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease.

Determination of apolipoprotein B may be offered as a component of a comprehensive cardiovascular risk assessment offered by reference laboratories. Comprehensive risk assessment may include evaluation of small low-density lipoproteins, subclassification of high-density lipoproteins, evaluation of apolipoprotein E genotype or phenotype, total plasma homocysteine, lipoprotein(a), high-sensitivity C-reactive protein, and homocysteine levels.

## **RATIONALE**

The use of apo B levels has been evaluated both for risk assessment and as a marker of treatment response. A representative review of the most salient studies follows.

A number of epidemiologic studies have evaluated the ability of apo B levels to predict future cardiovascular risk, while controlling for established risk factors. The majority of these studies have reported that apo B provides independent predictive information above that of traditional lipid markers. The Quebec Cardiovascular Study (1) 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 2,155 men followed up for 5 years. Elevated levels of apo B were found to be an independent risk factor for ischemic heart disease after adjustment for other lipid parameters. In patients with an apo B level of >120 mg/dL, there was a 6.2-fold increase in the risk of cardiovascular events. The Apolipoprotein-Related Mortality Risk Study (ARMORIS) was another prospective cohort study that followed 175,000 Swedish men and women for 5.5 years. (2) This study also found that apo B was an independent predictor of CAD events and was superior to LDL-C in predicting risk, both for the entire cohort and in all subgroups examined. A third, large prospective cohort study, the Atherosclerosis Risk in Communities (ARIC) followed 12,000 middle-aged individuals free of CAD at baseline for 10 years, and reported results that differed from the other 2 studies. (3) While apo B was a strong univariate predictor of risk, it did not add independent predictive value above traditional lipid measures in multivariate models.

A literature update in 2005 found further evidence for apo B as an independent predictor of cardiac disease, and for apo B as a stronger predictor of cardiovascular outcomes when compared with LDL-C. (4, 5) A literature search performed in December 2006 found evidence that corroborates these conclusions. In a nested case-control study performed among the 18,225 male participants in the Health Professionals Follow-up Study, the relative risk for the development of coronary heart disease in the highest versus lowest quintiles was greater for apo B (3.01, 95% confidence interval [CI]: 1.81–5.00) compared to LDL-C (1.81, 95% CI: 1.12–2.93) (6). A cohort study of 15,632 participants from the Women's Health Initiative provided similar information in women.

In this analysis, the hazard ratio for developing coronary heart disease in the highest versus the lowest quintiles was greater for apo B (2.50, 95% CI: 1.68–3.72) compared to LDL-C (1.62, 1.17–2.25) (7).

The ratio of apo B/apo A-I has also been proposed as a superior measure of the ratio of pro-atherogenic (i.e., “bad”) cholesterol to anti-atherogenic (i.e., “good”) cholesterol. This ratio may be a more accurate measure of this concept, compared to the more common total cholesterol (TC)/HDL ratio. A number of epidemiologic studies have reported that the apo B/apo A-I ratio is superior to other ratios, such as TC/HDL-C, or non-HDL chol/HDL-C. (8, 9) However, in the Women’s Health Study analysis (7), the ratio of apo B/apo-AI was not superior as a risk factor for future cardiovascular events (HR 3.01, 95% CI: 2.01–4.50) compared to TC/HDL-C (HR 3.81, 95% CI: 2.47–5.86).

The use of apo B as a marker of treatment response has been evaluated in a number of randomized controlled trials of statin therapy. Several randomized interventional studies of statin therapy using angiographic outcomes have demonstrated that lipid-lowering therapy is associated with a reduction in apo B levels and that angiographic treatment benefit is correlated with decreases in apo B. (10-12) However, the principal outcome of these studies focused on reduction in other lipid parameters, such as total cholesterol or LDL-C, and apo B levels were not used as a tool in clinical decision making. (10-12)

Fewer intervention trials have examined the change in apo B on treatment in relation to clinical CAD outcomes. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) evaluated lipid parameters among 6,605 men and women with average LDL and low HDL cholesterol who were randomized to receive either lovastatin or placebo. (13) Baseline LDL and HDL cholesterol as well as levels of apo B were predictive of future coronary events. However, in the treatment group, post-treatment levels of LDL-C and HDL-C were not predictive of subsequent risk, while post-treatment apo-B levels were predictive.

In a small treatment study, Zambon and colleagues (14) reported that response to statin therapy may vary by type of hyperlipidemia class, defined partly by apo B levels. Patients with elevated apo B levels had a superior response compared to patients with elevated lipoprotein a levels. Other authors have proposed target levels for the use of apo B as a marker of adequacy of therapy. A Canadian task force has proposed an apo B level of 90 mg/dL (15), while others have proposed using a lower target of 80 mg/dL. (16) However, none of the major guideline bodies in the United States, such as National Cholesterol Education Adult Treatment Panel III (NCEP ATP III), have incorporated apo B targets as part of their formal recommendations.

In summary, the evidence suggests that apo B may provide independent information on risk assessment for CAD. There is a substantial body of evidence currently to suggest that apo B is a better predictor of cardiac risk compared to LDL-C. Furthermore, as a marker of response to cholesterol-lowering treatment, apo B may be more accurate than

LDL-C, and may provide a better measure of the adequacy of anti-lipid therapy than does LDL-C.

However, the level of apo B has not been incorporated into quantitative risk assessment models or treatment guidelines, such as ATP III (17), which can be used in clinical practice. The complete text of the ATP-III guidelines identifies apo B as an “emerging risk factor.” The document notes that to determine their clinical significance, the emerging risk factors must be evaluated against the following criteria:

- 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 reduction in risk.

In their discussion of apo B, the guidelines state that the apo B level typically is disproportionately higher in persons with hypertriglyceridemia, and that “ATP III takes this difference into account and sets a secondary target, non HDL cholesterol, in persons with hypertriglyceridemia. Non HDL cholesterol is significantly correlated with apolipoprotein B and can serve as a ‘surrogate’ for it. The non-HDL cholesterol measure is readily available in clinical practice, whereas standardized apolipoprotein B measures are not widely available.” The ATP III guidelines do not identify direct measure of LDL particle concentration as an “emerging risk factor.”

Moreover, improved ability to predict risk and/or treatment response does not by itself result in better health outcomes. (18,19) 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 either risk assessment and/or treatment response. The current ATP III guidelines for management do not provide the tools necessary for clinicians to incorporate these measurements into routine assessment and management of hyperlipidemic patients.

In 2004, the American College of Physicians published clinical practice guidelines regarding lipid control in the management of type 2 diabetes. (20) These guidelines do not address the role of measurement of either apo-B or direct measurements of lipid particle concentration. In July 2004, Grundy and colleagues published an article outlining the implications of recent clinical trials of statin therapy. (21) The authors recommended a further lowering of the target LDL-C for some populations of patients. For example, the LDL-C target of 100 mg/dL in high-risk patients was lowered to 70 mg/dL. In addition, the authors recommended that consideration be given to combining a fibrate or nicotinic acid with an LDL-lowering drug in patients with high triglycerides or low HDL-C concentration. For moderately high-risk patients, the target LDL-C has been lowered

from 130 mg/dL to 100 mg/dL. While not an explicit update of the ATP III recommendations, the conclusions were endorsed by the National Heart, Lung, and Blood Institute, the American College of Cardiology Foundation, and the American Heart Association. These new more aggressive targets of therapy create additional questions of how measurements of apo B can be used to improve patient management.

Some experts currently believe that the evidence is sufficient to warrant the routine clinical use of apo B levels as a replacement for LDL-C levels, and the use of the apo B/apo A-I ratio as a replacement for the TC/HDL-C ratio. (16) These experts argue that the use of apo B in place of LDL-C will allow better targeting of anti-lipid therapy, and avoid undertreatment in a substantial number of patients with low or normal LDL levels and small, dense subtype (high apo B). However, as of the current time, none of the major guidelines, such as NCEP ATP III, have yet to formally incorporate the measurement of apo B into their recommendations.

### **2008 Update**

A literature search was conducted for the period of January 2007 through March 2008. New literature identified during this period continued to focus on the utility of apo B and apo B/apo A-I as additional predictors of cardiovascular risk, and on the relationship of these apolipoprotein measures to traditional lipid risk factors. A smaller amount of literature focused on using apo B as a target of lipid-lowering therapy.

The Copenhagen City Heart Study (22) was a prospective cohort study of 9,231 asymptomatic persons from the Danish general population. This study followed up patients for 8 years and evaluated the incremental predictive value of apo B compared to traditional lipid risk factors. Individuals with total apo B levels in the top one-third (top tertile) had a significantly increased relative risk of cardiovascular events compared to patients in the lowest one-third, after controlling for LDL-C and other traditional cardiovascular risk factors (RR 1.4, 95% CI: 1.1–1.8 for men; RR 1.5, 95% CI: 1.1–2.1 for women). The apo B/apo A-I ratio was also examined as an independent predictor of cardiovascular events, with similar results reported. This study also compared the discriminatory ability of apo B and the apo B/apo A-I ratio 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 compared to LDL-C (0.58 vs. 0.57), and the apo B/apo A-I ratio had a slightly higher AUC when compared to total cholesterol/HDL cholesterol ratio (0.59 vs. 0.58). Neither of these differences in AUC was statistically significant.

Clarke and co-workers (23) published a prospective cohort study of 7,044 elderly males enrolled in the Whitehall Cardiovascular Cohort from London, England. Measurements of apolipoprotein levels were performed on 5,344 of these individuals, and patients were followed up for a mean of 6.8 years. The authors reported that apo B was a significant independent predictor of ischemic heart disease mortality (HR for a 2 standard deviation change in apo B; 1.34, 95% CI: 1.08–1.65), while LDL cholesterol was not a significant

independent predictor (HR 1.19, 95% CI: 0.96–1.47). The apo B/apo A-I ratio was also a significant independent predictor (HR 1.54, 95% CI: 1.27–1.87), with similar predictive ability compared to the total cholesterol/HDL ratio (HR 1.57, 95% CI: 1.32–1.86). A nested case-control study (24), performed within the larger EPIC-Norfolk cohort study, evaluated the predictive ability of apo B in relation to traditional lipid measures. The EPIC-Norfolk (European Prospective Investigation into Cancer and Nutrition-Norfolk) study is a cohort study of 25,663 patients from Norfolk, UK. The case control substudy enrolled 869 patients who had developed CAD during a mean follow-up of 6 years, and 1,511 control patients without CAD. The authors reported that the apo B/apo A-I ratio was an independent predictor of cardiovascular events after controlling for traditional lipid risk factors and the Framingham risk score (adjusted odds ratio 1.85, 95% CI: 1.15–2.98). However, the authors also reported that this ratio was no better than total cholesterol/HDL ratio for discriminating between cases and controls (AUC 0.673 vs. 0.670,  $p=0.38$ ). The addition of the apo B/apo A-I ratio to the Framingham risk model resulted in a statistically significant improvement in predictive value (AUC 0.594 vs. AUC 0.613,  $p<0.001$ ), but the authors concluded that this increment in predictive value was likely to be of little clinical value.

Two studies developed a multivariate risk prediction model in which both traditional risk factors and apolipoprotein measures were included as potential predictors. Ridker and co-workers (25) published the Reynolds Risk Score, based on data from 24,558 initially healthy women enrolled in the Women's Health Study and followed up for a median of 10.2 years. A total of 35 potential predictors of cardiovascular disease were considered as potential predictors, and 2 final prediction models were derived. The first model was the best fitting model statistically, and included both apo B and the apo B/apo A-I ratio as 2 of 9 final predictors. The second model, called the "clinically simplified model," substituted LDL-C for apo-B and total/HDL cholesterol for apo B/apo A-I. The authors developed this simplified model "for the purpose of clinical application and efficiency," and justified replacing the apo-B and apo B/apo A-I measures as a result of their high correlation with traditional lipid measures ( $r=0.87$  and  $0.80$  respectively). Ingelsson and co-workers (26) used data from 3,322 individuals in the Framingham Offspring Study to compare prediction models with traditional lipid measures to models that include apolipoprotein and other nontraditional lipid measures. This study reported that the apo B/apo A-I ratio had similar predictive ability to traditional lipid ratios with respect to model discrimination, calibration, and reclassification. The authors also reported that the apo B/apo A-I ratio did not provide any incremental predictive value over traditional measures.

A smaller number of studies evaluated apo-B as a treatment target for antilipid therapy. Liem and co-workers (27) evaluated the changes the apo B/apo A-I ratio for 593 patients on statin therapy, and correlated the change in this ratio with the occurrence of cardiovascular events. The authors reported that the apo B/apo A-I ratio was associated with clinical outcomes even after controlling for standard risk factors. Also, the LDL-C/HDL-C was not significantly correlated with clinical events. However, there was no

increase in the AUC for clinical events when the apo B/apo A-I level was added to traditional lipid targets. Holme and colleagues (28) measured changes in total apo B levels and the apo B/apo A-I ratio as a result of exercise training in 219 obese, Norwegian men. There were significant decreases in total apo B levels but not in total LDL-C. Both the apo B/apo A-I and the total cholesterol/HDL ratios were improved, but the apo B/apo A-I ratio was affected to a greater degree compared with the total cholesterol/HDL ratio.

Some experts continue to argue that apo B is superior to LDL cholesterol, and that the apo B/apo A-I ratio is superior to the LDL/HDL ratio, as predictors of cardiovascular risk, and that these apolipoprotein measures should supplement or replace traditional lipid measures (22, 29- 31). Furthermore, a publication from a recent consensus conference (31) included specific recommendations for incorporating apo B testing into clinical care for high-risk patients. This expert panel stated that "ApoB and LDL particle number also appear to be more discriminating measures of the adequacy of LDL lowering therapy than are LDL cholesterol or non-HDL cholesterol." They therefore recommend that for patients with metabolic syndrome who are being treated with statins, both LDL cholesterol and apo B should be used as treatment targets, with an apo B target of less than 90mg/dl. Treatment should be intensified for patients with apoB above this level even if target LDL has been achieved.

The current evidence does, in general, support the contention that apo B and apo B/apo A-I are as good as or better than currently used lipid measures as predictors of cardiovascular risk. Also, tools for assisting clinicians in applying apo B measurements to clinical care are being developed. However, it is not yet possible to conclude that the use of apo B levels will improve outcomes when used in routine clinical care. First, the evidence suggests that any incremental improvement in predictive ability over traditional measures is likely to be small and of uncertain clinical significance. Second, none of the major lipid treatment guidelines, such as NCEP ATP III, have yet to formally incorporate the measurement of apolipoproteins into their recommendations. This creates difficulties in interpreting and applying the results of apo B and/or apo B/apo A-I measurements to routine clinical care. As a result, it does not appear likely that in the near future apolipoprotein measures will replace traditional lipid measurements for cardiovascular risk prediction in routine clinical care.

### **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**

82172 Apolipoprotein, each

There is no specific CPT code for measurement of apolipoprotein B. CPT code 82172 (apolipoprotein, each) might be used.

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