

## Medical Policy



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### **Title: High-Density Lipoprotein Subclass Testing in the Diagnosis and Management of Cardiovascular Disease**

#### **Professional**

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#### **DESCRIPTION**

A large body of epidemiologic literature has demonstrated an inverse relationship between levels of high-density lipoprotein (HDL) and cardiovascular risk, indicating that HDL may have a protective role against cardiovascular disease. 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/density, and/or on the apolipoprotein composition. Using size/density, HDL can be classified into HDL<sub>2</sub>, the larger, less dense particles that may have the greatest degree of cardioprotection, and HDL<sub>3</sub>, which are smaller, more dense particles. HDL contains 2 associated apolipoproteins, i.e., A-I and A-II. HDL particles can also be classified by whether they contain apolipoprotein A-I (apo A-I) only or whether they contain both apo A-I and A-II. There has been substantial interest in determining whether subclasses of HDL can be used to provide additional information on cardiovascular risk compared to HDL alone.

Traditional lipid risk factors such as total HDL and 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 cholesterol. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

More recently, measurement of apo A-I has become the preferred method for HDL subclass type. Direct measurement of apo A-I has been proposed as more accurate than the traditional use of HDL level in evaluation of the cardioprotective, or "good," cholesterol. In addition, the ratio of apo B/apo A-I has been proposed as a superior measure of the ratio of pro-atherogenic (i.e., "bad") cholesterol to anti-atherogenic (i.e., "good") cholesterol. Some, but not all, 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.

## **POLICY**

Subclassification of high-density lipoproteins is considered **investigational** in the screening, diagnosis, and management of cardiovascular disease.

HDL subclassification may be included as a component of a comprehensive cardiovascular risk assessment offered by reference laboratories. Comprehensive risk assessment may include evaluation of small low-density lipoproteins, high-sensitivity C-reactive protein, evaluation of apolipoprotein E genotype or phenotype, total plasma homocysteine, apolipoprotein B, and lipoprotein(a). The lack of a specific CPT code may make identification of claims for HDL subclassification difficult. However, HDL subclassification as part of cardiovascular risk assessment is likely when CPT code 82664 is submitted from a reference laboratory in conjunction with CPT codes 82172 (used to code for apolipoprotein B), CPT code 83695 (used to code for lipoprotein a), CPT code 84181 (used to code for apolipoprotein E phenotyping), CPT code 86141 (used to code for high-sensitivity C-reactive protein), CPT code 83090 (homocysteine), and CPT code 83701 (used to code for small, low-density LDL).

## **RATIONALE**

Results of retrospective cross-sectional studies have suggested that the protective effect of HDL was associated primarily with the HDL-2 subclass. (1, 2) These studies, however, could not determine whether decreased HDL-2 preceded the development of cardiovascular disease or was its result. A number of large, prospective studies designed to answer this question have reported mixed results. The Apolipoprotein-Related Mortality Risk Study (ARMORIS) followed up 175,000 Swedish men and women for 5.5 years (3) and reported that decreased apo-A1 was an independent predictor of CAD events. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) studied lipid parameters among 6,605 men and women with average LDL-C and low HDL cholesterol who were randomized to receive either lovastatin or placebo. (4) This study also reported that levels of apo A-I, as well as the ratio of apo B/apo A-I, were strong predictors of CAD events. In the Kuopio Ischemic Heart Disease Risk Factor Study, both total HDL-C and levels of HDL-2 had significant independent associations with risk of acute myocardial infarction. (5) The Quebec Cardiovascular Study investigated the association of HDL-2 and HDL-3 subclasses with ischemic heart disease in a subsample of 944 French-Canadian men participating in the larger trial. (6) During the 10-year follow-up, levels of HDL-2 were statistically significant as independent predictors of CAD events, but the difference in predictive value with and without HDL subclasses was not considered clinically significant.

In contrast, some studies have not reported HDL subclassification to be an independent predictor of CAD. A large prospective cohort study, the Atherosclerosis Risk in Communities (ARIC) study, followed 12,000 middle-aged individuals free of CAD at baseline for 10 years (7). In this study, prediction of CAD was not improved by addition of either apo A-I levels or HDL density. Similarly, in the Physicians' Health Study (8) and

the Caerphilly and Speedwell Collaborative Heart Disease Studies (9), both of which were studies of middle-aged men, risk prediction based on HDL-C was also not improved by HDL subclassification.

HDL subclasses have also been investigated in patients with known ischemic heart disease. The Monitored Atherosclerosis Regression Study (MARS) was a randomized placebo-controlled trial examining the angiographically determined progression of known atherosclerosis among those randomized to receive either lovastatin or placebo. (10) HDL-3 mass was found to be an independent correlate of coronary artery lesion progression in the combined treatment group analysis.

In summary, while a number of studies suggest that HDL subclassification provides independent information on risk assessment for CAD, this finding has not been reported consistently in all studies. HDL subclassification has not been incorporated into quantitative risk assessment models or treatment guidelines, such as ATP III, (11) that can be used in clinical practice. Moreover, improved risk prediction does not by itself result in better health outcomes. (12) To improve outcomes, clinicians must have the tools to translate this information into clinical practice. Such tools for linking HDL subclasses to clinical decision making, both in risk assessment and treatment response, are currently not available. The ATP-III practice guidelines continue to tie clinical decision making to conventional lipid measures, such as total cholesterol, LDL-C, and HDL-C. As a result, there is a lack of recommendations from this body regarding how the additional information from HDL subclass levels might be used in clinical practice.

### **2005 Update**

A search of the literature from 2003 through June 2005 did not identify any published studies that would prompt reconsideration of the policy statement. While controlled studies have included measurement of HDL subclasses as an intermediate outcome (13), there are still inadequate data to show how this laboratory test can be used to improve patient management. In 2005, Tzou and colleagues examined the clinical value of “advanced lipoprotein testing” in 311 randomly selected adults participating in the Bogalusa Heart Study. (14) Advanced lipoprotein testing included high density lipoprotein cholesterol subclasses, among other measures. These measurements were used to predict the presence of subclinical atherosclerosis, as measured ultrasonographically by carotid intima-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 intima-media thickness.

### **2006-2007 Update**

A literature search was conducted for July 2005 through December 2006. Ridker and colleagues (15) compared the predictive ability of apo A-I and the ratio of apo B/apo A-I to standard lipid measurements. Measurements of apo A-I and the apo B/apo A-I ratio had similar predictive ability to standard lipid measurements, but were no better. The hazard ratio (HR) for future cardiovascular events was 1.75 (95% confidence interval

[CI]: 1.30–2.38) for apo A-I, compared to 2.32 (95% CI: 1.64–3.33) for HDL-C. The HR for the ratio of apo B/apo A-I was 3.01 (95% CI: 2.01–4.50), compared with a HR of 3.18 (95% CI: 2.12–4.75) for the ratio of LDL-C/HDL-C. While some controlled studies have included measurement of HDL subclasses as an intermediate outcome (13, 16), data are still inadequate to show how this result can be used to improve management and outcomes.

### **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 A-I and the apo B/apo A-I ratio as additional predictors of cardiovascular risk, and on the relationship of these apolipoprotein measures to traditional lipid risk factors.

Several large cohort studies reported on the predictive ability of the apo B/apo A-I ratio in predicting cardiovascular disease. The Copenhagen City Heart Study (17) was a prospective cohort study of 9,231 asymptomatic persons from the Danish general population. The apo B/apo A-I ratio was reported to be an independent predictor of cardiovascular events, with a hazard ratio similar to that for total/HDL cholesterol. This study also compared the discriminatory ability of the apo B/apo A-I ratio with that of traditional lipid measures, by use of the area under the curve (AUC) for classifying cardiovascular events. 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), but this difference was not statistically significant. Clarke and colleagues (18) published a prospective cohort study of 7,044 elderly men 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 the apo B/apo A-I ratio was also a significant independent predictor (hazard ratio [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 (19), performed within the larger EPIC-Norfolk cohort study, evaluated the predictive ability of apo B/apo A-I 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 [OR] 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,  $p<0.01$ ), but the authors concluded that this increment in predictive value was likely to be of little clinical value. This same study also reported the predictive ability of

apo A-II in a separate publication. (20) In this analysis, individuals with apo A-II levels in the highest quartile had a decreased risk of cardiovascular events compared to those in the lowest quartile (adjusted OR 0.62, 95% CI: 0.43-0.90).

Two studies developed a multivariate risk prediction model in which both traditional risk factors and apolipoprotein measures were included as potential predictors. Ridker and colleagues (21) 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 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 colleagues (22) 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.

Some experts continue to argue that the apo B/apoA-I ratio is superior to the LDL/HDL ratio as a predictor of cardiovascular risk, and should supplement or replace traditional lipid measures (17, 23, 24). While the current evidence, in general, supports the contention that apo B/apo A-I is as good or better than currently used measures, it is not yet possible to conclude that these measures should be adopted 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 the National Cholesterol Education Program (NCEP) ATP III, have formally incorporated 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

82664 Electrophoretic technique, not elsewhere specified

There is no specific code for subclassification of HDL. CPT code 82664 (electrophoretic technique, not otherwise specified) may be used.

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